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Therapeutic Decision-making around Stroke Prevention in Atrial Fibrillation

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Certificate of Original Authorship

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and in the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are appropriately acknowledged within the thesis.

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Yishen Wang

Table 1: Abbreviations

ACCP	American College of Cardiology Physicians
ADRs	adverse drug reactions
AHA	American Heart Association
AF	atrial fibrillation
ALP	alkaline phosphatase
ALT	alanine transaminase
APSA	Australasian Pharmaceutical Science Association
ASCEPT	Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CARATV2.0	Computerised Antithrombotic Risk Assessment Tool Version 2.0
CCS	Canadian Cardiovascular Society
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CrCL	creatinine clearance
CVD	cardiovascular disease
CYP2C9	cytochrome P450 enzyme
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
FDA	U.S. Food and Drug Administration
GI	gastrointestinal
GPs	general practitioners
HF	heart failure
HMR	Home Medicines Review
HTN	hypertension
ICH	intracranial haemorrhage
INR	International Normalised Ratio
NPS	National Prescribing Service
NOACs	novel oral anticoagulants
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
OR	odds ratio
PBS	Pharmaceutical Benefits Scheme

PIM	potentially inappropriate medication
RA	rheumatoid arthritis
SF-36	Short Form (36) Health Survey
TIA	transient ischaemic attack
TGA	Therapeutic Goods Administration
TTR	time in therapeutic range

List of Original Peer-Reviewed Publications Generated Through This PhD Research

The follow people and institutions contributed to the publication of work undertaken as part of this thesis:

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Thesis Abstract

Background

The decision-making around antithrombotic therapy in patients with atrial fibrillation (AF) is complex because it requires careful and systematic assessment of the risk versus the benefit of therapy and must consider the characteristics of both the therapy and patients. The unpredictable pharmacological action of the traditionally used anticoagulant warfarin, together with the advanced age, multiple comorbidities and polypharmacy in patients with AF, may increase the risk of adverse drug events. Concern about these factors makes clinicians hesitant to prescribe warfarin, and they therefore underuse antithrombotics in many 'eligible' patients (i.e., those for whom the benefits of anticoagulation outweigh its risks) (1-4).

Three novel oral anticoagulants (NOACs; also called non-vitamin K antagonist oral anticoagulants)—dabigatran, rivaroxaban and apixaban—have been approved to try to overcome the limitations of warfarin, such as the need for regular monitoring and numerous drug–drug interactions. However, these NOACs have different pharmacological features and other risks; for example, NOACs are contraindicated in patients with severe liver or renal impairment. The increased number of antithrombotic agents further complicates the decision-making around antithrombotic treatment selection. Feedback from health professionals highlights their need for intervention and support in this aspect (5, 6). Decision support tools have been developed to help health professionals optimise the use of antithrombotics. One example is the Computerised Antithrombotic Risk Assessment Tool

(CARAT), which can be used to obtain a systematic review of individual patients and to decide on the most appropriate antithrombotic therapy. In view of the recently expanded range of treatment options, the original CARAT has been modified into a second version (CARATV2.0), which now considers both warfarin and NOACs as treatment options.

Aim

The aim of this doctoral research was to evaluate the potential role, usability and impact of CARATV2.0 on decision-making around antithrombotic therapy in clinical practice.

Methods

The evaluation of CARATV2.0 was conducted in three stages. In the first stage, CARATV2.0 was pre-tested using a database of primary care patients with AF to assess its potential for optimising the use of antithrombotic therapy. Concurrently, it was piloted in a real-world cohort of patients with AF in a tertiary hospital to evaluate the tool's impact on the prescription of antithrombotics. In the second stage, CARATV2.0 was evaluated through qualitative interviews of a range of health professionals to better understand the suitability of its content and its role in clinical practice. CARAT2.0 was modified further by incorporating the feedback received in the second stage. In the third stage, the factors affecting health professionals' decision-making were explored to understand how health professionals select and prescribe antithrombotics. The use of polypharmacy and how this may contribute to patients'overall risk of medication misadventure were also explored in patients with AF being treated in the general practice setting.

Results

The pre-test study of 395 patients showed that there was scope for better rationalisation of antithrombotic use in the general practice setting, such that CARATV2.0 could assist in identifying patients' suitable for oral anticoagulants based on risk versus benefit assessment. According to CARATV2.0, 96.7% patients were deemed to be eligible for anticoagulant therapy. More importantly, CARATV2.0 was able to recommend an appropriate anticoagulant (i.e., warfarin or NOACs) for individual patients, taking into account any contraindications.

The potential usefulness of CARATV2.0 was recognised by health professionals interviewed (n=26) in the qualitative study, with most expressing an interest in using this tool in clinical practice, particularly in their decision-making around choosing specific agents (i.e., selecting between warfarin and NOACs). Health professionals also acknowledged that comprehensive assessment of patients was important in improving clinical outcomes from treatment, however, in clinical practice, they did not routinely do this; instead, their decision-making was influenced by very specific factors. Patient-related factors, including a high risk of bleeding, a high risk of falls, and advanced age, were found to be associated with health professionals' reluctance to prescribe anticoagulants. Non-patient related factors, such as the health professionals' preference for a particular agent (warfarin or NOACs), practical management issues (e.g., convenience of NOACs), and practice-culture issues (e.g., prescribers' desire to "continue existing therapy", time pressure in clinical practice) also affect decision-making.

The ability of CARATV2.0 to address patient-related factors and to improve the use of therapy in real-world patients was shown in the pilot study of 251 patients. Post-

intervention, the prescription of oral anticoagulants (warfarin and NOACs) increased significantly from 50.5% (at admission) to 71.7% (at discharge). Among the 58.2% patients who were recommended therapy changes by CARATV2.0, 24.7% were adopted by prescribers prior to the patient discharge from hospital. Moreover, prescribers agreed with CARATV2.0's recommendations on whether a patient was eligible for anticoagulants in 79.3% of cases and agreed with the specific therapy selected (including specific oral anticoagulant agents) in 52.6% patients. To facilitate the implementation of CARATV2.0 into practice, many health professionals suggested integrating CARATV2.0 into existing systems to enable the auto-population of patient data (e.g., electronic medical systems), and/or involving nurses and pharmacists in the decision-making process via existing medicines review processes.

Conclusion

Although health professionals' decision-making around antithrombotics is influenced by many factors, this research shows that CARATV2.0 is a useful tool for assisting the systematic assessment of risk versus benefit and for rationalising the use of antithrombotic therapy. Future research should evaluate CARATV2.0 in a multicentre randomised control trial with long-term follow-up and investigate the integration of CARATV2.0 into existing systems and processes such as electronic medical records.

Chapter One

Introduction

Chapter One

1.1 Introduction

1.1.2 Suboptimal use of antithrombotics for stroke prevention in atrial fibrillation

Atrial fibrillation (AF) is one of the most prevalent cardiac arrhythmias globally, particularly in the elderly (7). The haemodynamic changes associated with AF can substantially increase the risk of thrombus formation in the heart, leading to stroke. A previous study by Wolf et al. (1991) showed that people with the non-valvular form of AF have about a five-times higher risk of stroke than people without AF (8). As the prevalence of AF increases with age, the risk of stroke related to AF also increases. According to a U.S. study by Wang et al. (2003), the percentage of strokes attributable to AF increases markedly from 1 in 67 for people aged 50–59 years to 1 in 4 for people aged 80–89 years (9).

Compared with strokes not related to AF, AF-related strokes are associated with higher mortality, morbidity, longer hospitalisation and poorer functional outcomes (10, 11). A longitudinal study of 5070 patients conducted over 40 years and reported by Lin et al. (1999) found that ischaemic stroke associated with AF was nearly twice as likely to be fatal than was non-AF stroke (11). One possible reason why strokes are more serious in patients with AF is the reduced regional cerebral blood flow because of the higher prevalence of ischaemic heart disease and congestive heart failure. Moreover, AF patients have a less developed collateral circulation in the brain, which further compromises the brain circulation and can increase the infarction size and delay the recovery of functional status after embolism associated with AF (11). Due to the ageing

population, AF and stroke have become major public health issues and pose an economic burden on the healthcare system (12).

Many international and national clinical guidelines advocate the use of antithrombotic therapy, especially oral anticoagulants, in patients with AF (13-19) because this therapy can significantly decrease the risk of stroke and stroke-related mortality (20). Hence, current stroke prevention relies on the use of antithrombotic therapy such as oral anticoagulants, although these agents carry an inherently high risk of adverse events such as haemorrhage. For decades, warfarin was the only oral anticoagulant available for long-term therapy. However, because of its unpredictable therapeutic effects, narrow therapeutic window, genetic heterogeneity in the pharmacokinetic response, and numerous food and drug interactions, warfarin requires regular monitoring via blood tests such as measurement of the International Normalized Ratio (INR) (21). Warfarin's complex pharmacological features contribute to the difficulty in its management by patients and the increased risk of adverse drug reactions (e.g., bleeding), which have led to a reluctance by clinicians to prescribe it (3, 5, 22-25). In an Australian study by Bajorek et al. (2005), around 25% of the patients who were eligible for anticoagulants (at least at moderate stroke risk and no contraindications for oral anticoagulants) were not prescribed warfarin (1).

Many barriers to the prescription of oral anticoagulants in patients with AF have been identified. These include patient characteristics (e.g., medical conditions, fall risk, age, preference for therapy, capability in managing therapy) (26); factors related to healthcare professionals (e.g., limited information or experience in managing antithrombotics, lack of awareness of stroke risk) (5); and limited efforts by the health

system to improve the quality of care for AF patients (27). The contribution of these barriers to the significant under-treatment of patients with AF with oral anticoagulants in both general practice and hospital settings has been reported in many countries (1, 26, 28-30). According to an Australian study by Bajorek et al. (2002), AF patients aged ≥ 80 were 5.46 times less likely to be prescribed warfarin than were patients aged < 80 years (25.5% versus 61.5%, respectively, odds ratio (OR) = 5.46, P < 0.0001) (22).

1.1.3 Complex decision-making for stroke prevention in patients with atrial fibrillation

Three novel oral anticoagulants (NOACs)—dabigatran, rivaroxaban and apixaban—have been developed recently to overcome the problems with warfarin use and are currently indicated for the prevention of stroke in people with AF (31). In Australia, these three NOACs have been approved by the Therapeutic Goods Administration (TGA) and are listed on the Australian Pharmaceutical Benefits Scheme (PBS).

NOACs are more predictable than warfarin in terms of their pharmacodynamic and pharmacokinetic properties, and they do not require routine monitoring of coagulation parameters. The NOACs are also less likely to interact with other medications, herbal preparations and dietary constituents, which simplifies the management of these medications for both patients and health professionals (32, 33). In addition, the associated intracranial bleeding risk is lower with all the NOACs than with warfarin (34, 35). Treatment with NOACs, however, is not without risks. Some NOACs, such as high-dose dabigatran and rivaroxaban, pose a higher risk of gastrointestinal (GI) bleeding and adverse GI effects than does warfarin treatment (34, 35). A meta-analysis

by Ruff et al. (2013) demonstrated that, compared with warfarin, NOACs significantly reduce the risk of intracranial haemorrhage (OR = 0.48, P < 0.0001) but increase the risk of GI bleeding (OR = 1.25, P = 0.04) (34). In addition, most NOAC dosages need to be adjusted in patients with renal impairment and are contraindicated in those with severe renal or liver impairment (31). Moreover, the higher dosing frequency of NOACs and the lack of regular monitoring may reduce medication adherence, especially in elderly patients with polypharmacy. To treat over-coagulation caused by NOACs, only dabigatran currently has an antidote approved by the Food and Drug Administration (FDA) (36). Therefore, the decision-making around antithrombotic therapy in patients with AF is further complicated by the availability of NOACs.

Patients with AF are generally older, and their advanced age presents further challenges in the selection and management of medicines because of age-related physiological changes and functional and cognitive impairments (25). These patients may require other medications such as those for accompanying cardiovascular conditions (e.g., arrhythmia) and stroke risk factors (e.g., hypertension, diabetes, hyperlipidaemia), or other comorbidities (37, 38). However, some of the therapies indicated for AF (e.g., amiodarone and digoxin) are regarded high risk in regard to causing medication misadventure (e.g., bradyarrhythmias) and are considered potentially inappropriate medicines (PIMs) for older people as per internationally recognised guidelines such as the Beers Criteria (39, 40). The use of these multiple medications concomitantly with antithrombotics can complicate medication management and increase the risk of medication misadventure. These issues can manifest as medication nonadherence, adverse drug reactions (ADRs) and drug interactions, any of which may lead to poor clinical outcomes (18, 41, 42).

Collectively, factors such as the unpredictable pharmacological features of warfarin, the specific characteristics of NOACs, and the physiological changes in older patients with AF and their multiple comorbidities and polypharmacy complicate the decision-making around antithrombotic therapy. Even with the availability of NOACs, the current use of antithrombotics remains suboptimal, as reported by Lip et al. (2014) in a European registry study (4). Given the complexity of decision-making, to optimise the use of antithrombotics for stroke prevention in patients with AF, support for the prescription and management of these patients should be provided to those health professionals making these therapeutic decisions. Indeed, an Australian study by Bajorek et al. (2005) confirms that clinicians feel they need support in this area. For example, they would like to receive better tailored information for assessing the risk versus benefit for individual patients (5). This type of support should aim to help the clinicians choose the appropriate therapy based on the assessment of risk (haemorrhage) versus the benefit (reduction of stroke risk) and medication safety considerations.

1.1.4 Risk assessment tools

Numerous risk assessment tools have been developed to help the decision-making around antithrombotic use in patients with AF (23). $CHADS_2$ (43) and CHA_2DS_2VASc (44) are the most widely used tools for assessing stroke risk, and HAS-BLED (45) and $HEMORR_2HAGES$ (46) are the most widely used tools for assessing bleeding risk. These tools differ in both their development and predictive value, which must be considered before their application in decision-making. Moreover, these separate risk assessment tools need to be integrated to estimate the relative risk (e.g., bleeding) versus benefit (e.g., stroke prevention) of using antithrombotics in individual patients.

Furthermore, the decision-making around antithrombotic therapy in patients with AF involves more than an assessment of stroke risk versus bleeding risk; that is, the main barriers to the use of anticoagulants often relate to medication safety issues (e.g., patients' adherence, falls risk and capability in managing therapy), which may increase the risk of medication misadventure (5, 47). Hence, a comprehensive therapeutic decision-making algorithm that synthesises both stroke and bleeding risk assessment tools and integrates key medication safety issues is needed to improve the therapeutic decision-making process for stroke prevention in patients with AF.

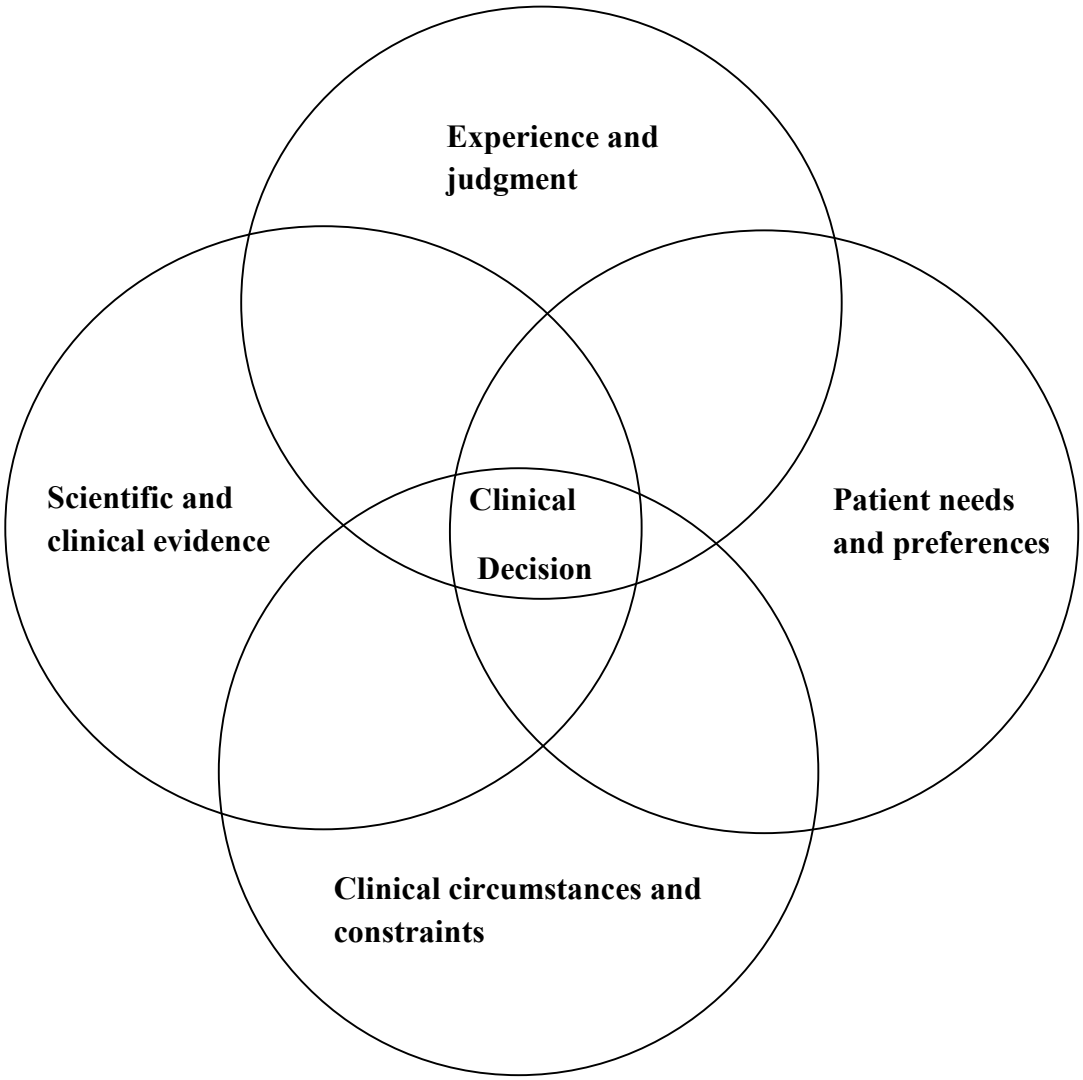
1.1.5 Therapeutic decision-making

Therapeutic decision-making involves integrating evidence-based clinical and scientific information, weighing of the probabilities and various outcomes, and balancing the risk versus benefit to select the most appropriate treatment for individual patients. Generally, the therapeutic decision-making model comprises four main aspects: a) clinical evidence (e.g., clinical trials, systematic review); b) clinicians' experience and judgement (e.g., doctors' clinical experience and preferences); c) patients' needs and preferences (e.g., cultural beliefs, personal values); and d) clinical circumstances and constraints (e.g., hospital/clinic, time, funding, policy, facilities) (Figure 1) (48, 49).

This complex decision model is also applicable in therapeutic decision-making for stroke prevention in people with AF. Decision-making can be an emotive process (5), and any of the four aspects of the decision-making model, especially the subjective aspects (i.e., experience, judgement, patient needs and preferences), may underpin the

suboptimal use of antithrombotics, particularly oral anticoagulants, in people with AF. Therefore, treatment selection should consider all four of the model's aspects.

Figure 1. Clinical decision-making model for stroke prevention in atrial fibrillation



Adapted from Borislav D Dimitrov, et al. *Kidney International* (2003) 63, 1924–1933.

1.1.6 Interventions to improve prescribing

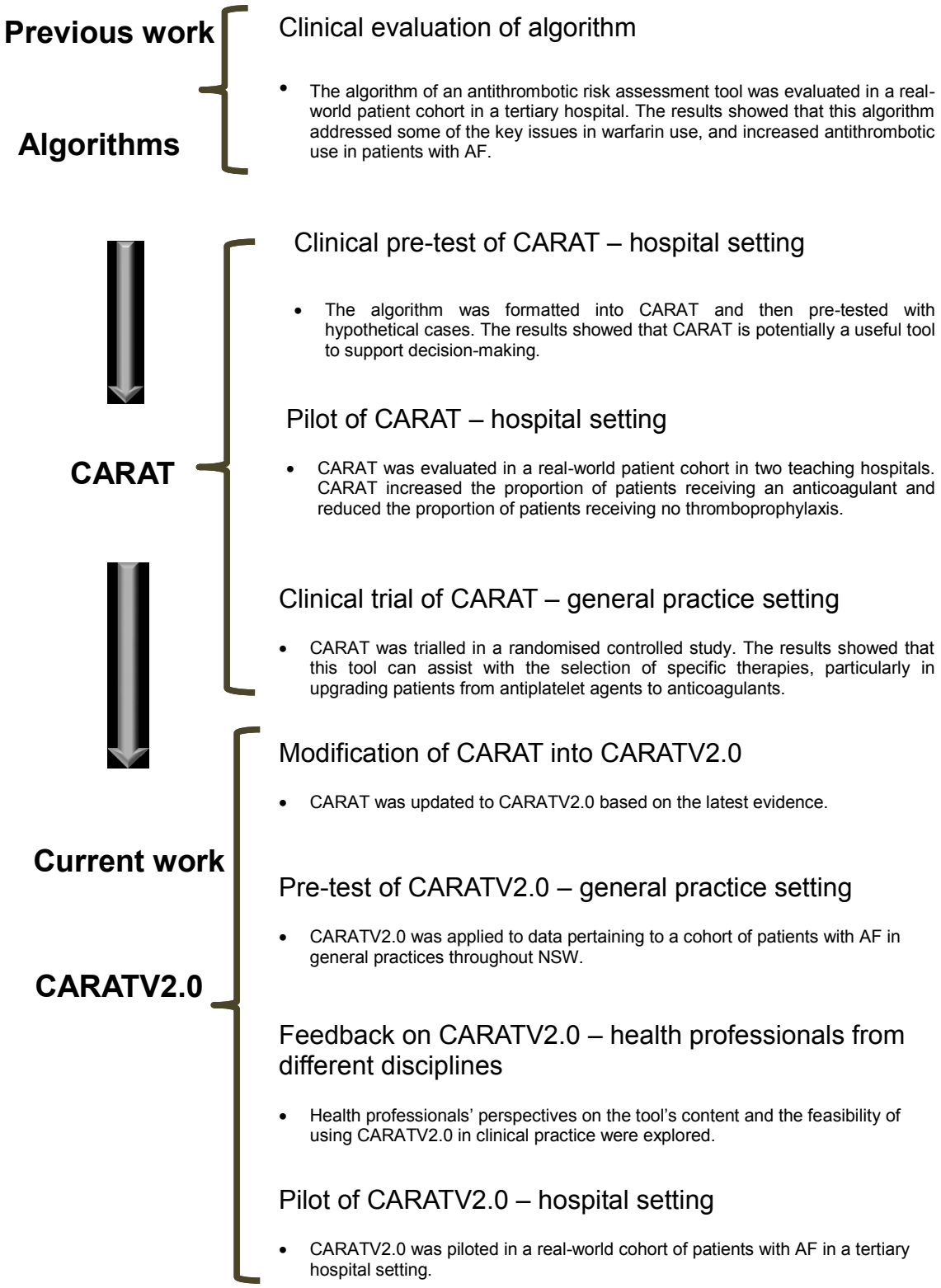
Optimal and evidence-based use of pharmacotherapy is critical for improving the outcomes of patients and reducing the healthcare burden (50). Various interventions

such as education, audit, pharmacy-led intervention, and clinical decision support tools are effective in optimising therapeutic decision-making (4, 51). However, compared with other interventions, clinical decision support tools provide evidence-based recommendations and offer instant information, point-of-care support, easy access to support for clinical decisions, and savings on healthcare expenditure (52-54). Clinical decision support tools can help improve health care by offering assistance (e.g., therapy recommendations, diagnostic support) to health professionals and patients. These tools include computerised reminders, condition-specific order sets and diagnostic support (55). Some can assist the processes of drug prescription and management in clinical practice; examples include the statin prescription reminder (56) and the prescription system for anti-asthmatic drugs (57).

A powerful clinical decision support tool can offer an explicit and systematic approach to decision-making that is based on the integration of the best research evidence with patients' medical history, patient preferences, and clinical evidence (58, 59). Hence, a clinical decision support tool is able to decrease the risk of errors and increase safety.

In the context of stroke prevention in people with AF, to optimise the therapeutic decision-making around antithrombotics, an antithrombotic risk assessment algorithm was developed previously (1, 6). This algorithm was created as part of a collaborative and multidisciplinary review process (1, 6). After a successful trial in patient cohort, it was then formatted into an electronic web-based tool, the Computerised Antithrombotic Risk Assessment Tool (CARAT) (6) (Figure 2).

Figure 2 Development of Computerised Antithrombotic Risk Assessment Tool



CARAT facilitates a systematic review of individual patients' risk factors. The review includes assessment of stroke and bleeding risk, as well medication safety issues, such as drug–drug interactions, renal and hepatic function, cognitive function, medication management capabilities and relevant social factors. The decision support tool generates a treatment recommendation for antithrombotic therapy based on a comprehensive risk versus benefit assessment of individual patients. The findings from previous studies have demonstrated CARAT's potential to optimise the use of antithrombotics in clinical practice (6, 23, 60).

1.1.7 Aims and objectives of this research

This doctoral research was conducted after consideration of the recent availability of NOACs, the complexity of the decision-making around antithrombotics, and the limited support for clinicians when making decisions to optimise the use of antithrombotic therapy in people with AF. The aim of this research was to explore decision-making around antithrombotics for stroke prevention in patients with AF. The first objective was to modify and update the CARAT decision support tool to create a second version (CARATV2.0). This second version considers both warfarin and the NOACs (dabigatran, rivaroxaban and apixaban) as treatment options and is based on the latest clinical evidence, aligning with guidelines and systematic reviews (13, 16, 18, 31, 61-63) and health professionals' feedback. The second objective was to evaluate the tool's usability and potential impact on the use of antithrombotic therapy in clinical practice. The third objective was to identify the factors that influence clinicians' decision-making around antithrombotic prescription for stroke prevention in patients with AF.

The significance of this research lies in the ability of the CARATV2.0 decision support tool to provide a comprehensive assessment of individual patients, to generate evidence-based therapy recommendations and to offer point-of-care support for clinical decisions through the use of information technology. If implemented in clinical practice, the tool may also help to reduce the considerable economic and healthcare burden of stroke on individuals and the global community given the increasingly ageing population.

1.2 Overview of the thesis

Chapter 1 Introduction

This chapter provides an introduction and overview of the thesis.

Chapter 2 Literature review

This chapter reviews the literature and focuses on two key aspects of contemporary decision-making around stroke prevention in AF, as presented in the following two papers:

- Paper 1 Safe use of antithrombotics for stroke prevention in atrial fibrillation: considerations of risk assessment tools to support decision-making.
- Paper 2 New oral anticoagulants in practice: pharmacological and practical considerations.

Paper 1 reviewed the risk assessment tools available to assist clinicians prescribing antithrombotics in people with AF. The major electronic databases PubMed, Ovid and

Embase, and other online resources such as Google and Google Scholar, were searched to identify all relevant publications. This literature review summarised the essential features of available risk assessment schemes for the decision-making around antithrombotics in people with AF. CARAT was modified to CARATV2.0 using the latest validated stroke risk assessment schemes, $CHADS_2$ (43) and CHA_2DS_2VASc (44), and the bleeding risk assessment schemes, HAS-BLED (45) and $HEMORR_2HAGES$ (46).

After the update of the risk assessment schemes, another review with a focus on the pharmacological features of the available oral anticoagulants was conducted and is reported in Paper 2. Relevant publications were identified via a search of key databases and resources mentioned above. Product information and other information resources were also reviewed to extract key information about the four oral anticoagulants available in Australia ─ warfarin, dabigatran, rivaroxaban and apixaban. This review comprehensively summarised the pharmacological and practical considerations around the use of these anticoagulants, which were integrated into the updated decision support tool.

Chapter 3 Pre-test of CARATV2.0

This chapter comprises:

- Paper 3 Clinical pre-test of a Computerised Antithrombotic Risk Assessment Tool for stroke prevention in atrial fibrillation patients: giving consideration to NOACs.

After CARATV2.0 was developed, the tool was evaluated using both quantitative and qualitative research methods. The findings of the first quantitative study are presented in Chapter 3. In this study, CARATV2.0 was pre-tested in a cohort of 393 patients with AF who were recruited for a previous study (60) from general practices in New South Wales, Australia. The data for the patients were used to populate CARATV2.0 to assess each patient's risk of stroke (44, 64), risk of bleeding (45, 46), the presence of any relevant contraindications to antithrombotic therapy, and major medication safety issues. The findings showed that use of CARATV2.0 may improve the selection of antithrombotic treatment for patients with AF. This finding provided the evidence for the next phase of this thesis.

Chapter 4 Feedback on CARATV2.0

Chapter 4 comprises:

- Paper 4: Selecting antithrombotic therapy for stroke prevention in atrial fibrillation (AF): health professionals' feedback on a decision support tool

After CARATV2.0 was pre-tested, it was then evaluated by a range of health professionals in a qualitative study. In this study, 26 health professionals were interviewed (face-to-face, semi-structured interviews) to canvas their feedback on CARATV2.0. The interview transcripts were analysed for themes using standard thematic analysis techniques (manual inductive coding), inter-researcher validation and participant verification. The health professionals interviewed expressed interest in using

this tool in clinical practice and believed that the tool could optimise antithrombotic use. The health professionals' feedback on CARATV2.0 was then used to improve the tool.

Chapter 5 Decision-making around antithrombotics

Chapter 5 comprises:

- Paper 5: Decision-making around antithrombotics for stroke prevention in atrial fibrillation: the health professionals' views

Current practice for prescribing antithrombotics often involves initiation of therapy by specialists in the acute care setting (hospital), but the long-term management is provided by general practitioners (GPs), nurses and pharmacists. Therefore, to optimise the use of antithrombotics, it was important to explore health professionals' perspectives on the decision-making around antithrombotics. The data for Chapter 5 were collected as part of the large qualitative study canvassing health professionals' feedback on CARATV2.0. Using similar methods as those used in Paper 4, this study explored in depth health professionals' perspectives of the decision-making around antithrombotics for stroke prevention in people with AF. The results showed that antithrombotic decision-making is at least partially preference based rather than systematic and that health professionals from different disciplines focus on different aspects of the decision-making process.

Chapter 6 Pilot of CARATV2.0 in clinical practice

This chapter 6 comprises:

- Paper 6: Pilot of a Computerised Antithrombotic Risk Assessment Tool Version 2 (CARATV2.0) for stroke prevention in atrial fibrillation

Finally, to facilitate the implementation of this tool in clinical practice, a prospective pilot study in a cohort of real-world patients was conducted in a major teaching hospital. Data from eligible patients were collected from medical records, admission notes and patient interviews in cardiology, neurology, aged care and general medicine departments. The information collected was used to populate CARATV2.0 to generate a treatment recommendation for antithrombotic therapy. Prescribers' agreement or disagreement with the CARATV2.0 recommendations and their reasons for treatment selection were recorded. The antithrombotic therapy used throughout patients' admission was followed up until discharge, and the antithrombotic therapy prescribed at discharge was recorded. The findings showed that CARATV2.0 was helpful to the decision-making for therapy selection and significantly affected the use of antithrombotic therapy.

Chapter 7 Additional information

This chapter comprises two additional papers authored or co-authored during the doctoral research relating to the thesis topic:

- Paper 7 Old age, high risk medication, polypharmacy — a 'trilogy' of risks in older patients with atrial fibrillation

- Paper 8 Stroke prevention in atrial fibrillation: impact of a Computerised Risk Assessment Tool (CARAT) on the prescription of thromboprophylaxis in the hospital setting.

Paper 7 reports a study that investigated the degree of polypharmacy in people with AF and how polypharmacy may contribute to their overall risk of medication misadventure. Information for this study was collected from a database characterising a cohort of patients with AF treated in general practices. The study showed that most older patients with AF used polypharmacy and that many of the medications were potentially inappropriate medications (PIMs) which carry an increased risk of adverse drug events. Compared with AF patients who had a high risk of bleeding, patients with a lower risk of bleeding were more likely to use polypharmacy. Given that patients with a lower risk of bleeding are generally deemed to be more eligible for anticoagulants (e.g., warfarin), the risk of medication misadventure in these patients was increased by the concomitant use of polypharmacy and anticoagulants. These findings demonstrate the complexity of therapeutic decision-making for stroke prevention in people with AF. The findings also reinforce the need to undertake regular medication reviews alongside risk assessment to reduce the potential for medication misadventure and optimising medication use.

Paper 8 describes a study that evaluated the potential impact of CARAT on antithrombotic prescription for patients with AF. CARAT was applied to a cohort of patients recruited from two teaching hospitals. CARAT generated treatment recommendations based on patients' medical history; recommendations were provided to prescribers for consideration. The intervention with CARAT significantly increased

the use of anticoagulants in patients with AF, which supported its modification to CARATV2.0.

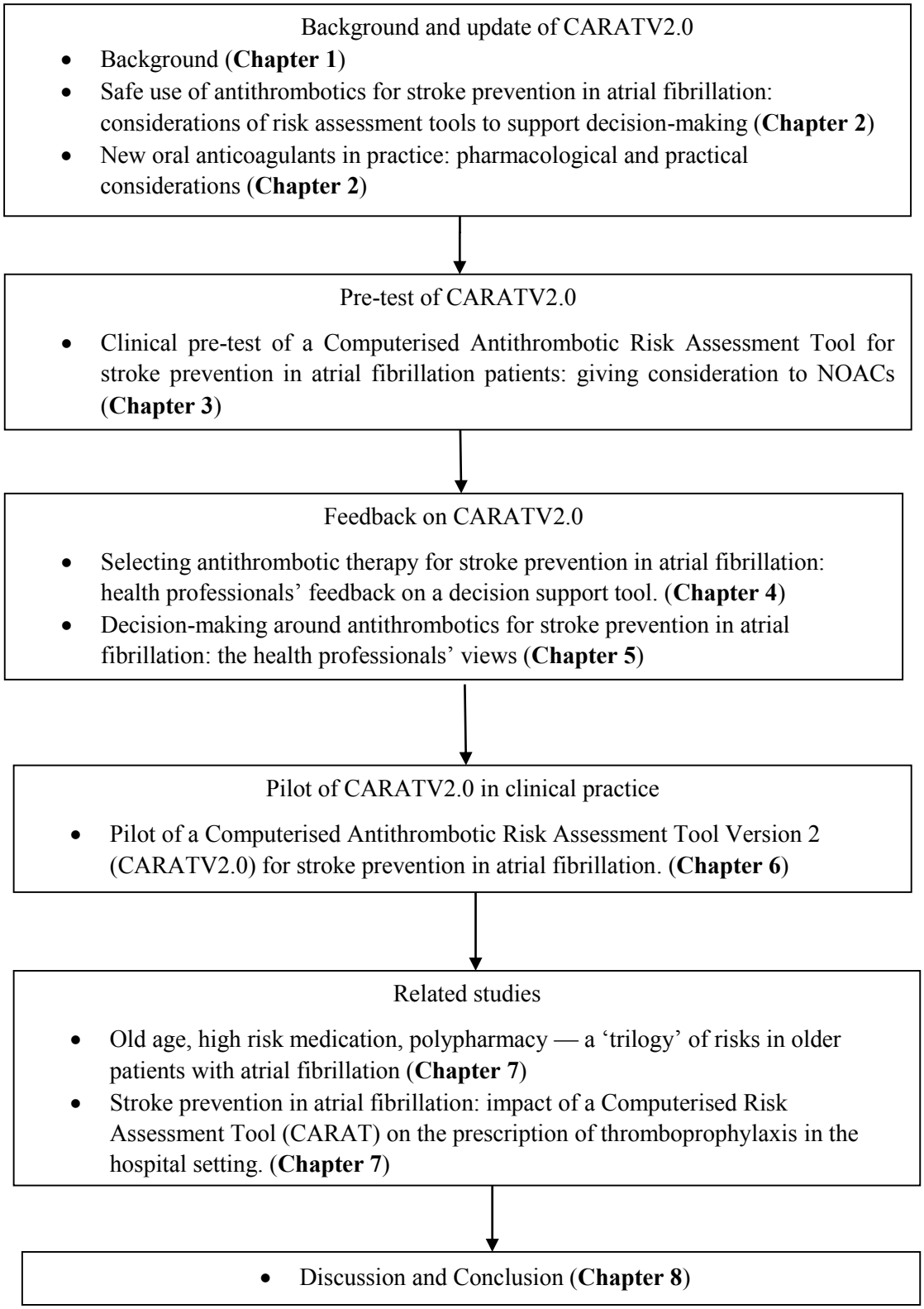
Chapter 8 Discussion

This chapter synthesises the findings from each chapter, reflecting an implications for practice, whilst acknowledging some of the limitations of the research and presenting recommendations for future research.

Chapter 9 Conclusion

This chapter presents the summary conclusions of the research.

Figure 3 Thesis overview



Chapter Two

Literature review

2.1 Safe use of antithrombotics for stroke prevention in atrial fibrillation: considerations of risk assessment tools to support decision-making

Yishen Wang, Beata V. Bajorek.

Therapeutic Advances in Drug Safety. 2014;5(1):21 – 37

Published version attached in Appendix

Safe use of antithrombotics for stroke prevention in atrial fibrillation: consideration of risk assessment tools to support decision-making

Ther Adv Drug Saf
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Yishen Wang and Beata Bajorek

Abstract: Clinical guidelines advocate stroke prevention therapy in atrial fibrillation (AF) patients, specifically anticoagulation. However, the decision to initiate treatment is based on the risk (bleeding) *versus* benefit (prevention of stroke) of therapy, which is often difficult to assess. This review identifies available risk assessment tools to facilitate the safe and optimal use of antithrombotic therapy for stroke prevention in AF. Using key databases and online clinical resources to search the literature (1992–2012), 19 tools have been identified and published to date: 11 addressing stroke risk, 7 addressing bleeding risk and 1 integrating both risk assessments. The stroke risk assessment tools (e.g. $CHADS_2$, CHA_2DS_2-VASc) share common risk factors: age, hypertension, previous cerebrovascular attack. The bleeding risk assessment tools (e.g. $HEMORR_2HAGES$, HAS-BLED) share common risk factors: age,

Abstract: Clinical guidelines advocate stroke prevention therapy in atrial fibrillation (AF) patients, specifically anticoagulation. However, the decision to initiate treatment is based on the risk (*bleeding*) versus benefit (*prevention of stroke)* of therapy, which is often difficult to assess. This review identifies available risk assessment tools to facilitate the safe and optimal use of antithrombotic therapy for stroke prevention in AF. Using key databases and online clinical resources to search the literature (1992-2012), 19 tools have been identified and published to date: 11 addressing stroke risk, 7 addressing bleeding risk, 1 integrating both risk assessments. The stroke risk assessment tools (e.g., $CHADS_2$, CHA_2DS_2-VASc) share common risk factors: age, hypertension, previous cerebrovascular attack. The bleeding risk assessment tools (e.g., $HEMORR_2HAGES$, HAS-BLED) share common risk factors: age, previous bleeding, renal and liver impairment. In terms of their development, 6 of the stroke risk assessment tools have been derived from clinical studies, whilst 5 are based on refinement of existing tools or expert consensus. Many have been evaluated by prospective application to data from real patient cohorts. Bleeding risk assessment tools have been derived from trials, or generated from patient data and then validated via further studies. One identified tool (i.e., Computerised Antithrombotic Risk Assessment Tool-CARAT) integrates both stroke and bleeding, and specifically considers other key factors in decision-making regarding antithrombotic therapy, particularly those increasing the risk of medication misadventure with treatment (e.g., function, drug interactions, medication adherence). This highlights that whilst separate tools are available to assess stroke and bleeding risk, they do not estimate the relative *risk versus benefit* of treatment in an individual patient nor consider key medication safety aspects. More effort is needed to synthesise these separate risk assessments and integrate key

medication safety issues, particularly since the introduction of new anticoagulants into practice.

Introduction

The increasing incidence of stroke is due to an increase in the prevalence of key risk factors such as advancing age and other underlying cardiovascular conditions, particularly atrial fibrillation (AF). In Europe, the prevalence of stroke is about 2% and increasing (1). In the U.S., the prevalence of stroke is approximately 3% of the adult population (approximately 7 million individuals), and it is estimated that by 2030, the prevalence of stroke will increase by 24.9% to 4.0%, affecting an additional 4 million people (2, 3). In Australia, recent health reports (2009) have estimated that 375,800 Australians (205,800 males and 170,000 females) have suffered a stroke at some time in their lives, which makes it the third leading cause of death for men and the second cause of death for women (4).

Among persons with AF (non-valvular form), the risk of stroke is approximately five times higher than that in persons without AF (2, 5, 6). The relationship between advancing age and AF and stroke is also important, as AF is the commonest irregular heart rhythm encountered in clinical practice and is most prevalent in the elderly (5, 6). Aging itself is a strong risk factor of stroke (6); around half of all strokes occur in people over the age of 75 years. In the US, the incidence of stroke increases dramatically from around 30–120 per 100,000 persons per year in the age group 35–44 years old, rising to 670–970 per 100,000 persons per year for those aged 65–74 years (7). It is estimated that the risk of hospitalisation for stroke in people aged 75–84 years is more than 10 times the risk for those in the 55–64 year age group (4). As the population ages, the number of stroke incidents is expected to increase; for example, in Australia, there were approximately 60,000 new or recurrent strokes in the year 2010 (8)

compared with 50,000 in 2008 (AIHW 2008) (9). Overall, because the prevalence of AF rises with age, the risk of stroke due to AF is highest in the very elderly, such that the percentage of strokes attributable to AF increases dramatically from 1 in 67 persons in the 50–59 year age group to 1 in 4 for persons in the 80–89 year age group (2).

Clinical guidelines (8, 10-13) advocate stroke prevention therapy in persons with AF, recommending the use of antithrombotic agents (e.g., warfarin, aspirin). Pooled analyses of many clinical trials have provided strong evidence that antithrombotics (anti-clotting agents) can prevent stroke in patients with AF; warfarin (anticoagulant) reduces the risk of stroke by approximately 60%, while aspirin (antiplatelet) is less effective, reducing the risk by about one-fifth (14, 15). Prevention of stroke therefore currently relies on the use of antithrombotic therapy (anticoagulants as first line), although these agents inherently carry risks of adverse events (e.g., haemorrhage). For this reason, much attention has been focused on the research and development of alternative drugs (e.g., new antithrombotics such as dabigatran, rivaroxaban, apixaban). Unfortunately, none of these agents are devoid of significant risks to the patient. Therefore, the decision-making regarding stroke prevention relies on a risk versus benefit assessment for each individual patient (i.e., an assessment of the potential risk of haemorrhage in the patient versus the benefit of the treatment in terms of reduction in the risk of stroke).

To this end, much emphasis has been placed on the development of tools to facilitate these risk assessments and support decision-making. In particular, there is a need to address a range of factors that contribute to medication safety in this clinical context, including patients' age, cognition, function, falls risk, and medication adherence (16-18).

Therefore, the decision-making process should necessarily consider both the stroke risk and bleeding risk as well as other medication safety issues. This narrative review focuses on the contemporary issues surrounding decision-making for stroke prevention in AF, specifically identifying the available risk assessment tools that help facilitate the safe selection of therapy in at-risk elderly persons. This review describes the features of the various tools developed to date and their relevance and potential application to clinical practice.

Methods

A review of the literature was undertaken via key electronic databases (PUBMED, OVID, EMBASE) and other online resources (e.g., Google, Google scholar) using the search terms "atrial fibrillation", "stroke risk factors", "stroke risk assessment", "stroke risk stratification", "bleeding risk factors", "bleeding risk assessment", and "bleeding risk stratification". The search was limited to peer-reviewed, English language publications (journal articles, reviews, consensus statements, published guidelines) within the 20-year period 1992 to 2012 (the period immediately following the publication of the pivotal clinical trials of stroke prevention in AF (19-24)). In regard to guidelines and consensus statements, only the latest (current) versions were included for review. Each publication was searched to identify risk assessment or risk stratification tools/schemes to support decision-making. Overall, 19 tools were identified: 11 addressing stroke risk, 7 addressing bleeding risk, and 1 tool addressing both stroke and bleeding risk.

Stroke risk assessment tools

A number of tools have been developed to assess stroke risk (Table 1), although few guidelines to date specifically include a stroke risk stratification scheme alongside recommendations for antithrombotic therapy (e.g., guidelines published by the American College of Cardiology Foundation/American Heart Association/ European Society of Cardiology (ACC/AHA/ESC; updated 2011) (25). Overall, among the available stroke risk assessment tools, the $CHADS_2$ (26) and CHA_2DS_2-VASc (27) have been the most frequently advocated tools, sharing the following common risk factors: age, hypertension, diabetes mellitus (DM), previous stroke/transient ischaemic attack. Stroke risk schemes all vary significantly in complexity with the number of variables included ranging from 4 to 7, with a median of 5 (Table 1). The most frequently mentioned inputs across all of the stroke risk tools are previous stroke/transient ischaemic attack (TIA) (11 out of 11 tools), followed by age (10 out of 11), hypertension (HTN) (10 out of 11), and DM (9 out of 11). Heart failure (HF) (5 out of 11), left ventricular (LV) systolic dysfunction (4 out of 11) and female gender (4 out of 11) are also often considered. Other risk factors incorporated into some tools relate to cardiovascular diseases (e.g., coronary heart disease, myocardial infarction (MI), peripheral vascular disease, aortic plaque). Most of these schemes are based on scoring systems (e.g., $CHADS_2$, Framingham Heart Study (2003), Modified $CHADS_2$ score (2008) and CHA_2DS_2-VASc), where the included risk factors have been weighted (i.e., assigned different amounts of points) according to their relative contribution (i.e., relative risks) in causing stroke; the overall stroke risk is then estimated by summing the scores (Table 1). This means that these schemes are not mere check-lists, but rather provide some indication of the level of predicted risk in an individual patient.

Age is an important risk factor for stroke, particularly in the context of AF management. These stroke risk schemes vary in how age is considered within the risk assessment, with different age categories used in various schemes. For example, the $CHADS_2$ uses age 75 years as a cut-off to denote risk associated with advancing age, while with the Modified $CHADS_2$ score (2008) different age categories are used to better reflect increasing stroke risk with increasing age, such that a score of 1 is assigned to persons aged 40 to 64 years and a score of 6 is assigned to those persons aged 85 years and older.

TOOLS FROM THE 'ATRIAL FIBRILLATION INVESTIGATORS'

1) Atrial Fibrillation Investigators (AFI) (1994) (28)

This stroke assessment tool was derived from the pooled analysis of five clinical studies (AFASAK (21), SPAF (23), BAATAF (20), CAFA (19), and SPINAF (24)) of stroke prevention therapies in AF; CAFA, BAATAF, and SPINAF trialled warfarin versus placebo, whereas AFASAK and SPAF participants were treated with aspirin or warfarin versus placebo. Collectively, over 1,800 patients received warfarin or placebo while over 1,130 patients received aspirin or placebo; the mean age of patients was 69 years (range 38-91 years). BAATAF, AFASAK and SPAF excluded patients with previous thromboembolism or cerebrovascular diseases. All studies, except CAFA, sought to identify stroke risk factors (such as history of stroke/transient ischaemic, age) according to their relative risks via univariate and multivariate analyses. These factors were then evaluated using the data from all of these studies (BAATAF, AFASAK, SPINAF, SPAF and CAFA) to derive a risk assessment tool which categorises patients into different

levels of stroke risk (ranging from 1.0% relative risk in the low risk group to 8.1% in the high risk group)(Table 1).

2) Atrial Fibrillation Investigators (AFI) (1998) (29)

Following from the development of the first tool (1994), this risk assessment tool was based on a further pooled analysis of 3 randomized trials: BAATAF (20), SPAF I (23) and SPINAF (24). Here, data was analysed for the control group patients only; over 1,060 patients (mean age 67±10.4 years) were followed up for an average of 1.6 years. The patients' echocardiograms as well as clinical parameters were reviewed and then analysed (using univariate and multivariate analyses) with regard to their impact on the relative risk of stroke. Age, previous stroke, and hypertension were identified as key predictors of stroke in AF (Table 1). The annual stroke rate ranged from 0.8% in those patients less than 65 years old with no additional risk factors and normal left ventricular function, up to 19.7% in those patients more than 75 years old with 1 or more additional risk factors and abnormal left ventricular function.

3) Birmingham/NICE (UK) (2006) (30)

In another analysis of the data from the AFI (1995) study, this assessment tool (Table 1) was based on the refinement of the AFI (1995) risk stratification tool and subsequently incorporated within the UK National Institute for Health and Clinical Excellence (NICE) guidelines for AF management. The tool itself was evaluated using data from over 990 patients from the SPAF III trial, who received treatment with either aspirin alone or aspirin combined with low dose warfarin (target international normalized ratio (INR)

1.2-1.5), and followed up for a mean 2 years (including blood sampling for von Willebrand factor-vWf). The evaluation of this tool included a comparison with $CHADS_2$ (described later). Cox modelling and multivariate analyses were used to determine the association of vWf with ischaemic and vascular events. The annual stroke and vascular event rates ranged from 0.0% in the low risk group up to 5.75% in the high risk group. This Birmingham scheme was shown to have a similar predictive value to the $CHADS_2$ scheme for both ischaemic stroke and vascular events. Also, vWf was shown to be an independent risk factor for vascular events.

TOOLS FROM THE 'STROKE PREVENTION IN ATRIAL FIBRILLATION INVESTIGATORS'

1) Stroke Prevention in Atrial Fibrillation Investigators (SPAF) (1995) (31)

Since aspirin was shown to be less effective than warfarin in the Atrial Fibrillation Investigators Study (1994), data from a large cohort of AF patients in SPAF I and II were analysed to identify patient characteristics related to arterial thromboembolism occurring during aspirin therapy. It was hypothesized that thromboembolism risk factors were different in AF patients receiving aspirin compared to those who were untreated. Over 850 patients receiving aspirin (mean age 69 ±11 years) were followed for 1,987 patient-years (range 4 days to 5.3 years) and risk factors (such as age, hypertension, impaired LV function) were identified according to their relative risks via multivariate analysis. The annual risk of stroke and systemic thromboembolism in patients ranged from 1.9% in the low risk group to 5.9% in the high risk group (Table 1).

2) Stroke Prevention in Atrial Fibrillation Investigators (SPAF I) (1999) (32)

Following from the 1995 tool, over 2,010 patients (69±10 years) from the series of Stroke Prevention in Atrial Fibrillation trials (trials I to III) who received either aspirin alone or low-dose warfarin were followed up for an average 2.0 years to explore potential stroke risk factors. SPAF I and II trials excluded patients with previous stroke or TIA, whereas SPAF III included patients with previous stroke or TIA. Risk factors were explored using multivariate logistic regression analysis to determine their relative risks, from which a risk stratification scheme was then developed for patients without a previous stroke or TIA (Table1). When applied to patient data, the scheme showed a statistically significant difference in stroke prevalence among low (0.9%), moderate (2.6%) and high risk groups (7.1%).

THE "CHADS"-BASED TOOLS

1) $CHADS_2$ (2001) (26)

This risk assessment tool is currently one of the most widely used, despite the development of others since it was first introduced to practice. Two previous stroke risk stratification schemes (from the Atrial Fibrillation Investigators (1994) and Stroke Prevention in Atrial Fibrillation Investigators (SPAF) (1995) were combined to derive this new scheme. Independent risk factors identified in the two schemes (such as prior cerebral stroke, hypertension, DM, age) were selectively included. In the scoring process, 1 point was assigned to all risk factors except stroke/TIA history (assigned two points) (Table 1). To validate this new scheme, the tool was applied to data from the

National Registry of AF (NRAF in the USA), which included over 1,700 non-rheumatic AF medicare beneficiaries (aged 65 to 95 years) not receiving warfarin at hospital discharge. The stroke risk ranged from 1.9 per 100 patient years (score of 0) to 18.2 per 100 patient years (score of 6). Overall $CHADS_2$ has shown high and better predictive value than either AFI or SPAF.

2) Modified $CHADS_2$ score (2008) (33)

A limitation of the original $CHADS_2$ tool is regarded to be its inability to clearly distinguish patients with high stroke risk from those with a moderate risk (34). Thus, the modified $CHADS_2$ score (Table 1) was proposed and tested against the original $CHADS_2$ score by using data from over 51,800 chronic AF patients aged 40 years or older from the General Practice Research Database (GPRD; i.e., the computerised medical records of general practitioners in the UK). The investigators evaluated the inclusion of additional factors such as sex, extension of age categories, and also re-weighting the previously included risk factors. Overall, the stroke risk was found to range from 0.72% for a risk score of 1 up to 15.64% for a risk score of 14. The revised $CHADS_2$ was shown to have better classification and predictive value than the original $CHADS_2$.

3) CHA_2DS_2-VASc (2010) (27)

This tool is a further evolution of the modified-$CHADS_2$ tool and refinement of the Birmingham (2006) scheme, to include risk factors such as female gender and vascular disease (Table 1). It has been evaluated by application to a cohort of real AF patients

from the Euro Heart Survey (35), and compared against several other schemes such as AFI (1994), SPAF (1999), $CHADS_2$, $CHADS_2$ modified, Framingham (2003), and Birmingham (2006) tools. In this tool, the hospital and death annual rate due to stroke and other thromboembolism ranges from 0.78% for a score of 0 up to 23.64% for a score of 9 (36). CHA_2DS_2-VASc (2010) has been shown to have a modest predictive value and to be better than either $CHADS_2$ or the modified $CHADS_2$ for predicting the risk of stroke and systemic thromboembolism.

OTHER TOOLS

1) European Atrial Fibrillation Trial Study Group (EAFT) (1995) (37)

This assessment tool was based on the analysis of data from over 370 patients (mean age 71±8 years, with the majority over 60 years) enrolled in the European Atrial Fibrillation Trial. In EAFT, patients with one or more non-disabling episodes of cerebral ischaemia and concomitant non-rheumatic AF (NRAF) were randomised to receive anticoagulant therapy, aspirin or placebo, and followed up for an average 1.5 years (22). The data pertaining to those in the placebo-treated group was used to derive this risk tool; clinical predictors (including previous stroke/TIA, systolic blood pressure (BP) >160 mm Hg were selected according to their relative risks via multivariate analysis (Table 1). Unlike other tools, age was not included as an independent risk factor because of the relatively higher average age of this subgroup of placebo-treated patients, although age was identified as risk factor in the broader EAFT trial (37). The annual event rate of stroke and other major vascular events ranged from 0.0% in those

aged more than 75 years with no risk factors up to 37% in those more than 75 years old with 3 or more additional risk factors.

2) Framingham Heart Study (2003) (38)

This tool was based on observational data from the Framingham Heart Study, pertaining to a cohort of over 700 patients (aged from 55 to 94 years). The selected patients had a diagnosis of new on-onset AF, were not receiving warfarin, and were followed up for mean 4.0 years. A Cox model was used to identify risk factors and points were assigned to each to derive an overall risk score. A linear function was computed for each score to produce an estimation of 5 year stroke risk, ranging from 5% for a calculated score of 0-1 points, up to 75% for a score of 31 points. This risk assessment tool was shown to have modest predictive value for 5 year risk of a stroke event in individuals with AF (Table 1) as well as the 5 year risk of stroke or death.

3) ACC/AHA/ESC Guidelines updated (2011) (25)

This tool has been proposed by expert consensus, to not only stratify stroke risk in AF patients, but also recommend antithrombotic therapy for patients in each risk category (Table 1). It was derived by expert review of several risk stratification schemes such as the AFI (1994) (1998), SPAF (1995) (1999), Framingham Heart Study (2003), and $CHADS_2$ tools, but has not yet been evaluated via application to data from patient cohorts or clinical databases.

Summary of Features of Stroke Risk Assessment Tools

Overall, a history of stroke or TIA is the most frequently included risk factor in these stroke risk assessment tools followed by age, hypertension and DM. Many of the stroke risk assessment tools have been generated by review of previous risk factors but have not specifically sought to investigate or identify any new risk factors. Six of the stroke risk assessment tools (28, 29, 31, 32, 37, 38) have been derived from clinical or epidemiological studies of AF patients, while five are largely based on expert consensus. Furthermore, several tools have been based on selected patient cohorts or databases (where verification of data was not possible), and are potentially not representative of the broader target population (selection bias). Since each trial has defined risk factors differently, and risk factors were only assessed at the time of randomization, the true magnitude of impact of each factor (according to their relative risk) may be underestimated. Overall, CHA_2DS_2-VASc has been reported to have a better predictor than the AFI (1994, 1998), SPAF (1995), $CHADS_2$ modified, $CHADS_2$, Framingham (2003), and NICE (2006) tools in AF patients (39, 40).

Bleeding risk assessment tools

Altogether, seven bleeding risk tools have been developed and employed in evaluating bleeding risk among AF patients (Table 2), although not all have been specifically developed for patients with AF. All of these bleeding risk tools stratify patients into low, intermediate and high bleeding risk categories. Among them, $HEMORR_2HAGES$ (41) and HAS-BLED (42) have been the most commonly advocated, both sharing common risk factors such as age, previous bleeding, renal and liver impairment. Although each scheme uses different age cut-offs, ‘increased age’ *per se* is the only risk parameter common to all seven risk tools. The other most frequently mentioned inputs in these

tools are age history of bleeding/prior bleeding (six out of seven tools), followed by anaemia/thrombocytopenia (five out of seven), renal dysfunction (five out of seven), previous stroke (three out of seven), hypertension (three out of seven), alcohol (three out of seven), DM (two out of seven), prior MI or ischaemic heart disease (two out of seven), liver dysfunction (two out of seven), malignancy (three out of seven), and female gender (two out of seven). Antiplatelet drug use, genetic factors, and excessive falls risk, are also considered in certain tools. To account for the different levels of risk attributed to various factor, different points have been assigned to each to derive an overall summative score (Table 2).

OBRI (Beyth et al. 1998) (43)

This bleeding risk tool (Table 2) was refined from the bleeding index developed by Landefeld and Goldman in 1989 (44), and designed for application to all types of patients at risk of haemorrhage, not specifically for AF patients. Development of the tool was based on the records of over 560 patients aged 18 to 92 years (mean age 61±14) who were discharged from hospital on long-term warfarin therapy for indications such as AF, stroke, and other thromboembolism. Four risk factors (age ≥65 years, history of gastrointestinal bleeding, history of stroke, and severe comorbid conditions such as recent myocardial infarction, renal insufficiency, severe anaemia) were identified by their relative risks as calculated in univariate and multivariate analyses. This OBRI scheme was then further tested on 264 outpatients who were commenced on warfarin after hospital discharge, and who were followed for a period of up to seven years. The major bleeding incidence reportedly ranged from 3% in low risk group to 53% in high risk group, yielding modest predictive value for the tool.

Kuijer et al. (1999) *(45)*

A literature review (comprising 15 papers) was conducted to identify risk factors for bleeding in a range of patients using anticoagulant therapy. The risk stratification scheme (Table 2) was constructed according to the odd ratios of the various risk factors, and then initially evaluated in a subset of over 240 patients, followed by more extensive testing in an independent cohort of 780 patients (all from the database of the Columbus Investigators Study (46)); in the Columbus Investigators study over 1,020 patients with venous thromboembolism (VTE) were allocated to receive heparin-based therapy plus an oral anticoagulant. In the initial subgroup of 240 patients, this tool was shown to have modest predictive value for all bleeding complications and major bleeding complications. Then, in the subsequent patient cohort, the tool was able to categorise one-fifth of the patients as high risk, where the absolute risk of bleeding was found to be significantly higher than the low-risk group (10% compared versus 1%).

HEMORR$_2$HAGES (2006) *(41)*

This tool was derived from 3 previous risk schemes (the OBRI (1998) (43); the scheme of Kuijer et al. (1999) (45), Kearon et al, (2003) (47)), a systematic review (48), and results from a literature (i.e., PubMed) search. Overall, 11 risk factors (Table 2) were selected, with prior bleeding assigned two points (a higher weighting) and all other risk factors assigned one point, according to expert consensus. The scheme was then tested and compared with the other three schemes using data from over 3,790 medicare beneficiaries (mean age 80.2 years) listed in the National Registry of Atrial Fibrillation database (the same database used for validation of the CHADS$_2$). The bleeding risk

ranged from 1.9 for a score of 0 up to 12.3 per 100 patient year for a score over 4. Among patients prescribed warfarin, $HEMORR_2HAGES$ was shown to predict major bleeding better than the schemes by Kearon et al (2003), Kuijer et al. (1999) or OBRI (1998).

Shireman et al. (2006) *(49)*

This tool was developed and validated via a retrospective analysis of data from a cohort of over 26,300 AF patients who were aged over 65 years (identified in a national registry), and followed up for 90 days (NB/ the same database that was used for validation of $CHADS_2$). Eighteen variables (such as age, gender, stroke) (Table 2) were initially explored in multivariate modelling, and eight were finally selected into the risk scheme. The major bleeding rate ranged from 0.9% in low risk group up to 5.4% in high risk group. Overall, this tool was shown to have better predictive value than the OBRI and Kuijer et al (1999) schemes.

RIETE risk scheme (2008)(50)

This tool was based on the RIETE Registry of patients (mean age 66±17 years) with acute VTE, who were receiving anticoagulant therapy and followed up for three months. Over 13,000 patients were used as the derivation sample and over 6500 patients were used as the validation sample. Risk factors such as recent major bleeding, anaemia, malignancy, clinically overt pulmonary embolism, age were identified based on their odds ratio in multivariate analysis (Table 2). During validation, the scheme was able to identify significant differences in the risk of major bleeding, ranging from 0.1% in low

risk patients to 6.2% in high risk patients. Since this tool was developed using data from patients with VTE, its application to patients with AF or at risk of stroke is uncertain.

HAS-BLED (2010) *(42)*

This scheme was developed by using data from a real-world cohort of 3,450 AF patients (mean age 66.8±12.8 years) receiving antithrombotic therapy: oral anticoagulant (OAC), antiplatelet only, OAC plus antiplatelet combined, or no therapy at all. The patient data came from the prospective Euro Heart Survey (35) on AF, where patients were followed up for up to one year. The risk factors (such as age, female, hypertension, renal failure, prior major bleeding episode) (Table 2) were identified from univariate and multivariate analysis, with the resultant tool shown to have better predictive value than $HEMORR_2HAGES$. The yearly major bleeding rate varied from 1.13% for a score of zero up to 12.5% for a score of five.

ATRIA (2011) *(51)*

ATRIA was developed by obtaining the clinical data from over 13,559 non-valvular AF patients taking warfarin therapy (mean age 71 years), and enrolled and followed-up for up to 3.5 years in the ATRIA study (52, 53). This cohort was separated into "derivation" and "validation" groups. Risk factors were initially selected from six previous published risk stratification schemes (41, 43, 45, 47, 49, 50), evaluated by univariate and multivariate analyses of data from the derivation group of patients. Five risk factors (Table 2) were finally selected and assigned scores based on their regression coefficients. The scheme was then tested in the validation group of patients from the

ATRIA study and compared with other risk stratification schemes. The risk of major bleeding ranged from 0.4% (0 points) to 17.3% (10 points). The predictive value for major bleeding of this tool was shown to be higher than OBRI, Kuijer et al. (1999), Kearon et al. (2003), HEMORR$_2$HAGES (2006), Shireman et al. (2006) and RIETE risk schemes (2008).

Features of Bleeding Risk Assessment Tools

In reviewing these tools, it is important to note their origins and therefore their relevance in the context of AF management. Three of these bleeding risk assessment tools were derived via refinement of previous risk assessment schemes (41, 43) or literature review (45). One was derived from retrospective data extraction from clinical databases (49). Only HAS-BLED, RIETE risk scheme, ATRIA were derived from prospective studies of selected patient cohorts and all of them excluded patients who were not able to be followed up (selection bias). Although most of the data from which the tools were derived included a follow-up period of approximately 1 year, the schemes by Shireman et al. (2006) and RIETE (2008) had relatively minimal follow-up (only 90 days) and did not include review of the international normalized ratio (INR) during follow-up. Furthermore, among these tools, only HAS-BLED, ATRIA, and Shireman et al (2006) were specifically derived from AF patients, whilst HAS-BLED, ATRIA, HEMORR$_2$HAGES and Shireman et al have all been validated in AF patients. The schemes by Kuijer et al. (1999) and RIETE (2008) are limited in their application by the fact that they were based on VTE patients, whilst ORBI was based on a broad range of patients discharged from hospital using antithrombotics. Indeed, these non-AF specific tools have been shown to be inferior in their application to the target patient population

compared to those tools which were validated in AF patients (41, 51). In some recent reports (e.g., Apostolakis et al JACC 2012, Roldan et al 2012, Lip et al 2012, Apostolakis et al JACC 2013) HAS-BLED has been shown to perform better in predicting bleeding risk than the ATRIA, HEMORR$_2$HAGES, Shireman et al, Kuijer et al. (1999) and OBRI tools in AF patients (54-57).

Overall, in considering the inputs in these tools, advancing age has been the most frequently cited risk factor for bleeding, followed by a history of bleeding/prior bleeding, anaemia/thrombocytopenia, and renal dysfunction. The impact of age in the risk assessment process is highlighted again, and highlights the need to carefully assess the medication safety aspects of the decision-making process.

Assessment of Medication Safety in Elderly Patients

When exploring the utilisation of anticoagulant therapy for stroke prevention in AF, issues impacting on medication safety must necessarily be explored. Age *per se* has often been cited as a key consideration in decision-making and a major barrier to the use of warfarin, reflecting the challenges of using high-risk anticoagulant therapies in the at-risk elderly population. However, a patient's age *per se* is not a contraindication to therapy, but rather it represents an over-arching marker of other age-related factors that impact on their ability to manage complex regimens and/or which may increase their risk of adverse clinical outcomes. These factors include: impaired cognitive function (e.g., dementia), frailty (e.g., falls risk), co-morbidities, decreased renal function, polypharmacy and poor medication adherence (16-18, 58-61). Therefore, it is important to consider medication safety assessments alongside stroke and bleeding risk.

In reviewing the spectrum of risk assessment tools developed to date, only one has been identified that purposefully considers medication safety. The CARAT (Computerised Antithrombotic Risk Assessment Tool) is a web-based tool, which comprises both stroke and bleeding risk assessments (the $CHADS_2$ and $HEMMORR_2HAGES$ schemes, respectively) alongside medication safety issues. The tool evolved from an earlier risk assessment process that was paper-based (62), and which had been shown to be effective, as part of a collaborative and multidisciplinary review process, in optimising the use of antithrombotic therapy in older persons with AF (62, 63). The utility of the tool lies in integrating the risk: benefit assessment and systematically reviewing key medication safety issues such as the individual's function, cognition, drug interactions, medication adherence, medication management capabilities, and relevant social factors. In applying this tool, the clinician can calculate the estimated risk of stroke, risk of bleeding, and identifies any key contraindications to the use of treatment options, before providing a treatment recommendation for an individual patient (62, 63).

Whereas previous risk assessment tools for stroke and bleeding have been principally evaluated for their ability to predict risk, evaluation of the CARAT has focused on canvassing clinicians' application of this tool in decision-making. In an initial scenario-based survey, four cases (patient profiles describing different levels of risk) were used to test the agreement between clinicians' independent treatment recommendations and those generated by CARAT. The majority of clinicians (71%, n = 77) 'Agreed' with CARAT's treatment recommendations (four questions; n = 108 responses), and importantly 'Agreed' with its estimation of bleeding risk (three questions on bleeding risk; n = 81 responses). Regarding the overall usefulness and applicability of CARAT to clinical practice, out of 189 responses, 51% were "agree" or "somewhat agree" and 25%

were neutral or undecided with CARAT. In their feedback, clinicians provided commentary on the CARAT to identify it's potential role in decision-making:

'Rapid calculation of risks is very useful' (Cardiologist)

'Bleeding risk assessment section is very useful' (Cardiologist)

'Warfarin is not a lifelong decision; people can fail a trial of anticoagulation but embolic stroke is irreversible [this tool helps re-focus away from bleeding risk, highlighting stroke risk]' (Neurologist)

'This tool should ideally be applied in ED and result should go to Local Medical officer' (Cardiologist)

Discussion

What this review highlights is that there are indeed a number of tools to assess either stroke risk or bleeding risk in patients with AF. However, the tools are not uniform and their differences (including their limitations) need to be considered prior to application in decision-making. It is important to consider the development of these tools, and how their inputs were derived, acknowledging that not all risk factors can be treated equally since they present different relative risks. Indeed, each of the tools presented in this review does weight their input factors differently, and this is particularly reflective in the evolution of the $CHADS_2$ to the CHA_2DS_2-VASc, where different age groups are assigned different points (i.e., the older age group is assigned more points).

In relation to the inclusion of 'age' as an important risk factor in both stroke and bleeding risk assessment needs examination. The age "cut-off" to define an 'older'

person differs across tools, ranging from 60 years up to 75 years, often below the average age (approximately 75 years old) of most AF patients. Whilst a few tools use cohort data to derive the age groupings in tools, some have been determined by expert consensus only. The inclusion of 'age' as a risk factor is not unexpected, given what is known about the increasing prevalence of AF and risk of stroke with advancing age. However, care must be taken about selecting arbitrary age 'cut-offs', noting that age per se is often an over-arching marker of other risk factors such as key comorbidities that are more prevalent with age (e.g., cardiovascular disease, diabetes, hypertension) and/or measures of frailty (e.g., falls risk), medication management ability (e.g., adherence), as well as cognition and function (e.g., dementia), although, being elderly does not necessarily imply that these risks are present.

Overall, this review shows that most effort to date has focused on the development of tools to predict the risk of stroke, and less so on predicting the risk of bleeding. For stroke risk assessment, current guidelines recommend either that CHA_2DS_2-VASc be used for stroke risk assessment (e.g., European Society of Cardiology (ESC) (13), or $CHADS_2$ (e.g., American College of Chest Physicians (ACCP) (10), Canadian Cardiovascular Society (CCS) (12)). The use of CHA_2DS_2-VASc may increase over time, since it is reported to better predict stroke risk than AFI (1994, 1998), SPAF (1995), $CHADS_2$ modified, $CHADS_2$, Framingham (2003), and NICE (2006) tools in AF patients (39, 40).

The availability of bleeding risk tools has certainly assisted clinicians in decision-making, enabling a balanced risk versus benefit assessment. Tools such as the HAS-BLED have now been incorporated in some guidelines (e.g., ESC guideline), where a

score of 3 or more is considered to be an indicator of a high bleeding risk. However, it is important to note that the use of these bleeding risk tools is not to identify patients in whom treatment should be excluded; rather, these tools should be used to identify the potential for bleeding in an individual and identify appropriate risk reduction measures, i.e., treating modifiable risk factors (e.g., anaemia, drug use, alcohol use, uncontrolled hypertension, labile INRs, reduced platelet count), and providing support services to ensure close monitoring and regular review. In other words, a high bleeding risk score indicates the need to correct reversible risk factors and provide additional follow-up services, rather than providing a reason not to prescribe anticoagulants (13, 58).

In reviewing the available risk tools collectively, it can been seen that there is a certain level of overlap between bleeding risk factors and stroke risk factors, specifically age, hypertension, previous stroke, and diabetes. Indeed, some studies using the $CHADS_2$ and CHA_2DS_2-VASc tools have reported that patients with high bleeding risk have also been shown to have high stroke risk. Over 90% and over 99% of patients with high bleeding risk (HAS-BLED 3 or more) were categorized as high stroke risk by $CHADS_2$ and CHA_2DS_2-VASc respectively (55, 64). Whether it is sufficient to use tools such as $CHADS_2$ and CHA_2DS_2-VASc to predict both stroke risk and bleeding risk needs further exploration, but would certainly help to simplify the risk assessment.

Integrating Bleeding and Stroke Risks

The simplification of decision-making through the use of such tools is an important goal in this context, recognising that the initiation of antithrombotic therapy is always complex for clinicians, since it involves weighing the risk (*e.g., bleeding*) versus benefit

(*prevention of stroke)* of therapy, as well as other clinical characteristics of the patients, and these may vary widely among patients (61, 65). This review highlights that a number of tools are available to assess stroke risk or bleeding risk separately, and thus provide some information for antithrombotic therapy decision-making. In this regard, they are all helpful in identifying reversible risk factors (e.g., anaemia, uncontrolled hypertension) that can be modified through targeted intervention. However, the two assessments need to be brought together to complete the decision-making process for the selection of appropriate treatment, and ideally should estimate the relative risk versus benefit of available treatment options in an individual AF patient. Furthermore, the decision-making in AF is not solely based on stroke risk versus bleeding risk. Previous studies have highlighted that key barriers to the use of anticoagulants often relate to other patient factors that potentially increase the risk of medication misadventure (65, 66). Assuring medication safety is especially important for anticoagulants (e.g. warfarin) because they maintain a higher potential for adverse events due to their inherent risk of haemorrhage and/or complex pharmacology. Few of the available tools have provided this functionality (except CARAT), yet it is important to the whole process (Table 3) (67).

Integration of risk schemes and consideration of additional factors does provide a more comprehensive assessment of an individual's suitability for specific antithrombotic therapies. However, this potentially increases the complexity of the risk assessment process; in considering the usability of any of these tools, the critical issue relates to simplicity and practicality, so that it can be readily applied in everyday clinical practice. Compounding this is the need for regular review of risk, as these can change over time (e.g., increasing age). Although electronic and digital resources are increasingly

available (including smartphones, portable computers, iPads) in the health setting, the ability to calculate a score easily and simply in the midst of a busy practice is paramount. The need for a meaningful, individualised risk assessment must be balanced against the need for usability by clinicians. This aspect has been specifically explored for one of the tools described in this review, where clinicians' opinions have been gauged regarding the overall usefulness and applicability of the CARAT to clinical practice. Whilst the CARAT is web-based, it integrates a number of separate assessments (i.e., stroke risk, bleeding risk, medication safety considerations), and therefore requires more input from the clinicians at the time of decision-making. This may potentially affect it's usability in some settings, and for this reason such tools might be best incorporated into clinical services that specifically review a person's pharmacotherapy (e.g., accredited Medication Review services; pharmacy-based medicines checks, such as the MedsCheck program in Australia). There is a need to explore the role of support services provided by suitably trained and accredited health professionals (e.g., nurse practitioners, practice nurses, accredited pharmacists, consultant pharmacists) in using these tools within dedicated services, to help support clinicians in decision-making.

Therefore, more effort is needed to synthesise these separate risk assessments and integrate key medication safety issues, particularly in view of the introduction of new anticoagulants into practice. The introduction of these new drugs (e.g., rivaroxaban, dabigatran, apixaban) has been based on data from clinical trials which have included limited numbers of patients and which have applied strict exclusion criteria (e.g., a severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, creatinine clearance of less than 30 ml per minute, active liver disease) (68-70). To date, there are no assessment tools available to predict and/or stratify the

risk of bleeding in regard to new anticoagulants. Although there is a perception that these new drugs are significantly safer than traditional antithrombotic options, they are not without risk, and risk versus benefit assessments remains critically important.

Summary

Although, separate tools are available to assess stroke risk and bleeding risk independently, they do not estimate the relative risk versus benefit of available treatment options in an individual patient, and seldom consider key medication safety aspects of prescribing treatment. More effort is needed to synthesise these separate risk assessments, integrate key medication safety issues, and incorporate them into daily clinical practice, particularly in view of the introduction of new anticoagulants into practice. Among the many factors contributing to risk, age is an important risk factor, but its definition and categorisation need further clarification and validation.

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None to declare.

Table 1. Stroke Risk Schema

Stroke Risk Schema Study (year)	Low risk	Intermediate risk	High risk	C-statistic
Atrial Fibrillation Investigators (1994) (28)	Age <65 year with no high risk factors	Age 65-75 year with no high risk factors	Any age with HTN, DM, previous stroke /TIA; age >75 year with or without risk factors	N/A
Stroke Prevention in Atrial Fibrillation Investigators (SPAF) (1995) (31)	No high or moderate risk features	HTN, no high risk features	Previous thromboembolism, systolic BP >160 mm Hg, LV dysfunction*, Women >75 year	N/A
European Atrial Fibrillation Trial Study Group (EAFT) (1995) (37)	No risk factors†	1–2 risk factors †	≥ 3 risk factors †	N/A
Atrial Fibrillation Investigators (1998)(29)	Age <65 year, no clinical risk actors (including previous stroke/TIA, history of HTN, and DM), normal LV (normal or mild LV dysfunction)	Age 65-75 year, no clinical factors, normal LV	Age >75 year; age ≤ 75 with either clinical risk factors or abnormal LV; age ≤ 75 and ≥ 1 clinical risk factors with or without abnormal LV‡	N/A
Stroke Prevention in Atrial Fibrillation Investigators (1999)(32)	No high/moderate risk features§	No high risk features, either of HTN, DM	Women >75 year old, men >75 year old +HTN, systolic BP>160 mm Hg	N/A
$CHADS_2$(2001)(26)	Score 0‖	Score 1–2‖	Score 3–6‖	0.68 (Ischemic stroke)
Framingham Heart Study (2003)(38)	Score 0–7 ¶	Score 8–15 ¶	Score 16–31 ¶	0.66 (Stroke excludes TIA)
Birmingham/NICE (UK) (2006) (30)	Age<65 year with no moderate or high risk features	Age≥ 65 year, no high risk features; age <75 year with DM, HTN, or vascular disease	Previous stroke, TIA or thromboembolism; age ≥ 75 year with DM, HTN or vascular disease; HF or abnormal LV function by echocardiography	0.64 (Ischemic stroke)
Modified CHADS2 score (2008) (33)	Score 0**	Score 1–5**	Score >6**	0.72 (All kinds of stroke)
CHA_2DS_2-VASc (2010) (27)	Score= 0 ††	Score =1††	Score ≥ 2††	0.61 (Ischemic stroke, peripheral embolism or pulmonary embolism)
ACC/AHA/ESC Guidelines updated (2011) (25)	No risk factors§§	One moderate-risk factor (age≥ 75 year, HTN, HF, LV ejection fraction 35% or less, DM)	Any high-risk factor (previous stroke, TIA or embolism, mitral stenosis, prosthetic heart valve) or more than 1 moderate-risk factor	N/A

*Recent (3 months) clinical congestive heart failure or left ventricular fractional shortening 25% by M-mode echocardiography.
†Risk factors: Previous stroke/TIA, ischaemic heart disease, systolic BP >160 mm Hg, duration of AF >1 year, ≥1 infarcts on brain CT, cardiothoracic ratio enlargement on chest roentgenogram.
‡Abnormal LV: moderate-to-severe systolic dysfunction by 2-dimensional echocardiocardiography.
§High risk features: women >75 year old, men >75 year old+HTN, systolic BP>160 mm Hg (any age). Moderate risk features: HTN (age≤ 75), DM.
‖Risk factors: congestive heart failure, HTN, age ≥ 75 year, DM 1 point each; previous stroke/TIA 2 points.
¶Age (0–10 points; 55-59, 0 point; 60-62 year, 1 points ;63-66 year, 2points ; 67-71 year, 3 points; 72-74year, 4 points; 75-77 year, 5 points; 78-81 year, 6 points; 82-85 year, 7points; 86-90 year, 8 points, 91-93year, 9 points; >93 year 10 points), gender (6 points for women), systolic BP (<120mmHg, 0 point; 120-139 mmHg, 1 point; 140-159mmHg, 2point; 160-179 mmHg, 3point; >179mmHg, 4 points), DM (5 points), previous stroke/TIA (6 points).
** Age 40-64 year, 1 point; 65-69 year, 2 points; 70-74 year , 3points; 75-79 year, 4 points; 80-84year, 5 points; 85-115, 6 points; female, 1 point; DM, 1 point; history of stroke /TIA, 6 points.
†† Major risk factors are age ≥ 75 years and previous stroke/TIA/thromboembolism (2 points each); clinically relevant non-major risk factors are heart failure, hypertension, diabetes, age 65–74 years, female gender and vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), 1 point each.

§§"Less well-validated" risk factors are female sex, coronary artery disease and age 65 to 75 years. It is unclear whether patient with ≥ 1 of these should be categorized as moderate risk.
HTN: hypertension, DM: diabetes mellitus, LV: left ventricle, TIA: transient ischemic attack, HF: heart failure, BP: blood pressure,

Table 2. Bleeding risk schema

Bleeding Risk Schema (year)	Risk factors recruited in score calculation	Low risk	Intermediate risk	High risk	C-statistic*
OBRI (Beyth *et* al. 1998 (43) modification of bleeding index developed by Landefeld and Goldman (44))	Age ≥ 65 years, GI bleeding in last 2 weeks, previous stroke, comorbidities (≥ 1 of the following: recent MI, hematocrit <30%, diabetes mellitus or creatinine >1.5 mg/dl),1 point for each above risk factor	0	1-2	3-4	0.78
Kuijer *et al.* (1999) (45)	Age≥ 60 years old (1.6 point), female sex (1.3 point), malignancy (2.2 point)	0	>0 and <3	≥ 3	0.72
HEMORR$_2$HAGES (2006) (41)	Hepatic and/or renal disease, ethanol abuse, malignancy, older (age >75 years), low platelet count or function, rebleeding risk, uncontrolled hypertension, anaemia, genetic factor(s) (e.g., CYP2C9 single-nucleotide polymorphisms), excessive fall risk and stroke (1 point for each risk factor, 2 points for previous bleeding)	0-1	2-3	≥ 4	0.67
Shireman *et al*. (2006) (49)	Risk score = (0.49 × aged >70 years) + (0.32 × female) + (0.58 × remote bleed) + (0.62 × recent bleed) + (0.71 × alcohol/drug abuse) + (0.27 × diabetes) + (0.86 × anaemia) + (0.32 × antiplatelet drug use), 1 point for each existing condition, 0 if absent	≤ 1.07	> 1.07 and < 2.19	≥ 2.19	0.63
RIETE risk scheme (Ruiz- Gimenez et al, 2008) (50)	Recent major bleeding (<15 days prior to thrombotic event) (2 points), creatinine > 1.2 mg/dL (1.5 points), anaemia (1.5 points), malignancy (1 point), clinically overt pulmonary embolism (1 point), age > 75 years (1 point)	0	1-4	> 4	N/A
HAS-BLED (2010) (42)	Hypertension (systolic blood pressure >160 mmHg), abnormal renal (presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 μmol/l), abnormal liver function (chronic hepatic disease [cirrhosis] or bilirubin >2× upper limit of normal, AST/ALT/ALP >3× upper limit of normal), stroke, previous bleeding history or bleeding diathesis or anaemia, labile INRs (high INRs and poor time in therapeutic range), elderly (e.g., age >65 years), drugs (concomitant use of antiplatelet agents or NSAID), alcohol, 1 point each risk factor	0	1-2	≥3	0.72
ATRIA (2011) (51)	Anaemia (3 points), severe renal disease (e.g., glomerular filtration rate < 30 ml/min or dialysis dependent, 3 points), age ≥ 75 years (2 points), prior bleeding (1 point), and hypertension (1 point)	0-3	4	5-10	0.74

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CYP: Cytochrome P; GI: Gastrointestinal; INR: International normalized ratio; MI: Myocardial infarction; OBRI: Outpatient bleeding risk index.
*C-statistic: major bleeding (slightly different definition in each scheme, refer to each scheme for exact definition) in validation or testing groups

Table 3. Contraindications of antithrombotic therapy (adapted from Bajorek et al (67))

	Absolute contraindications	Relative contraindications
Medical	• Bleeding disorder • Complicated liver disease • Active gastrointestinal ulceration or bleeding in past 3 months • Previous intracranial haemorrhage/surgery • Previous intracerebral aneurysm/tumour • Ophthalmic surgery in past 3 months • Diabetic proliferative retinopathy	• Uncomplicated liver disease • Previous gastrointestinal bleeding or ulceration
Functional	• Fall in past 6 months associated with major • Bleeding	• High risk of falls • No medication supervision and either visual or colour blindness, deaf, or • Language barrier
Cognitive	• Uncontrolled psychosis; dementia	• No medication supervision and mild • Cognitive impairment (Mini Mental State Examination score 15-24/30)
Social	• Current alcoholism (male > 60gm alcohol / day, female >40g alcohol / day)	• Nursing home resident, socially isolated
Iatrogenic	• No medication supervision and poor compliance likely • Unable to self-medicate • High risk drug interactions • Previous adverse drug reaction to warfarin	• Frequent use of non-steroidal anti-inflammatory • Drugs

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2.2 New oral anticoagulants in practice: pharmacological and practical considerations

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REVIEW ARTICLE

New Oral Anticoagulants in Practice: Pharmacological and Practical Considerations

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Abstract Although highly effective, warfarin use is complicated by its unpredictable narrow therapeutic window, genetic heterogeneity in pharmacokinetic response, numerous food and drug interactions, and the need for regular international normalized ratio (INR) monitoring. Currently, several novel oral anticoagulant (NOAC) drugs (dabigatran, rivaroxaban, apixaban) are available on the market as alternatives to warfarin. These agents all feature the NOACs, their limited range of indications, and their cost, the characteristics of each anticoagulant must be carefully considered to carefully select the agent that will provide the optimal risk/benefit profile in the individual patient.

1 Introduction

Abstract

Although highly effective, warfarin use is complicated by its unpredictable narrow therapeutic window, genetic heterogeneity in pharmacokinetic response, numerous food and drug interactions, and the need for regular international normalized ratio (INR) monitoring. Currently, several novel oral anticoagulant (NOAC) drugs (dabigatran, rivaroxaban, apixaban) are available on the market as alternatives to warfarin. These agents all feature more predictable pharmacodynamic and pharmacokinetic properties than warfarin. Additionally, the NOACs do not require routine monitoring of coagulation parameters, and have a relatively lower potential for interactions with drug, herb, and dietary constituents, which enhances the convenience of management for both patients and health professionals alike. However, there are other considerations regarding the use of NOACs that must be taken into account during management of therapy. In contrast to warfarin, most NOACs need dosage adjustments in renal impairment and are contraindicated in severe liver impairment, and there are no specific antidotes for treating NOAC-related over-anticoagulation. The more frequent dosing needed for NOACs may reduce adherence especially in elderly patients with polypharmacy. Furthermore, NOACs, especially dabigatran, are not as well tolerated as warfarin in patients with gastrointestinal diseases. Overall, the availability of the NOACs has expanded the treatment armamentarium, but they are not without risk. Given the limited experience with the NOACs, their limited range of indications, and cost, the characteristics of each anticoagulant must be carefully considered to carefully select the agent that will provide the optimal risk/benefit profile in the individual patient.

Introduction

Until very recent times, warfarin (a vitamin K antagonist) has historically been the only anticoagulant available as an oral formulation for long-term therapy. Although it is highly effective, its complex pharmacology has always been associated with a greater difficulty of use, leading to a potential increase in adverse events and/or reluctance by clinicians to prescribe it (1). The specific challenges of warfarin include its unpredictable effects, a narrow therapeutic window, genetic heterogeneity in pharmacokinetic response, numerous food and drug interactions, and the need for regular monitoring via blood tests [i.e., international normalized ratio – (INR)] (2). A great amount of effort has been expended to devise guidelines and services to address these challenges and support clinicians in managing warfarin therapy. However, the increasing burden of use, particularly in the elderly who are both susceptible to thromboembolic complications and medication misadventure, means that some of these strategies are not applicable and/or unsustainable in this at-risk patient population.

For this reason, three main novel oral anticoagulants (NOACs) have recently entered the practice arena, and are currently indicated for the prevention of stroke in atrial fibrillation (AF): dabigatran, rivaroxaban and apixaban (rivaroxaban is also indicated in the prevention and management of venous thromboembolism) in North America and Australia. All three agents have been shown to be effective, with potential advantages over warfarin. However, some of these so-called advantages may be regarded as potential disadvantages in specific situations. It should be acknowledged that NOACs are not without risk and there are differences among the individual agents which need to be considered. Furthermore, these agents are relatively more expensive than warfarin

(3). Pharmacoeconomic studies to date have highlighted that these agents might only be cost-effective at certain doses in specific situations; a Markov decision model suggested that dabigatran 150mg twice daily was more cost-effective than warfarin only in those patients at highest stroke risk ($CHADS_2 \geq 3$) with suboptimal levels of anticoagulation control (i.e., clotting parameters reported as being less than 72.6% time in therapeutic INR range (TTR) (4).

Therefore, there is emphasis on the need to individualise risk/benefit assessments to identify those patients who are most likely to benefit in changing from warfarin to NOACs. This review aims to describe pharmacokinetic and pharmacodynamic differences among these new oral anticoagulant drugs and warfarin, to help inform decision-making approaches.

1) Pharmacological characteristics of the anticoagulants: Pharmacokinetic Parameters

Absorption

Both warfarin and the NOACs are available for oral administration. Warfarin is additionally available for intravenous administration, although this is rarely used given the availability of effective parenteral anticoagulants such as heparin (2). In relation to the oral formulations of these anticoagulants, warfarin and rivaroxaban have the highest bioavailability (>80%) (5, 6), whilst dabigatran has the lowest (6.5%) (Table 1) (7). For this reason, some attention should be paid to the administration of dabigatran and factors that might significantly affect its bioavailability. For example, patients should be

counseled not to break the hydroxypropyl methylcellulose (HPMC) shell that encapsulates dabigatran (i.e., dabigatran capsules) which helps to stabilise the drug; removing the capsule may significantly increase (by 75%) its bioavailability (8). All of these NOACs are quickly absorbed with a maximal plasma concentration (C_{max}) within 2 - 4 hours of oral administration. For warfarin, its absorption is generally not affected by food; however the concomitant, large intake of specific foods (i.e., butternut, marshmallow) with high fiber content and/or which have a laxative effect may decrease its absorption (9) (see Drug Interactions). For rivaroxaban, the impact of food on drug absorption is dose-dependent; while concomitant intake of food increases the absorption of rivaroxaban at the 15mg and 20mg doses, it does not affect rivaroxaban at the lower 10 mg dose. Therefore, rivaroxaban 15mg and 20mg doses should be taken with food (6). In contrast, food intake does not affect the plasma drug concentrations following dabigatran and apixaban absorption, and therefore can be taken with or without food (8, 10). Changes in gastric pH (e.g., following the use of ranitidine, famotidine, omeprazole) have no clinically significant impact on the absorption of warfarin, dabigatran, rivaroxaban and apixaban (6, 8, 10, 11).

Distribution

Dabigatran has the highest volume of distribution (70L) reflecting its moderate tissue distribution and low plasma protein binding (approximately 35%) (8) (Table 1), while warfarin has the lowest volume of distribution (8L) reflecting its very high degree of plasma protein binding (99%) (5). For this reason, patients with low serum albumin (e.g., liver failure) may require lower dosages of warfarin due to the increase in the unbound (free) fraction of warfarin (which is responsible for its clinical effects).

Conversely, high protein diets (e.g., some powdered protein supplements) have been reported to increase serum albumin levels leading to increased plasma protein binding, thereby increasing warfarin dose requirements (12, 13). Drugs that are also highly protein bound may interact with warfarin via competitive displacement from proteins, increasing the unbound (free) fraction of the drug (9). Although apixaban and rivaroxaban also have relatively high plasma protein binding (87% and 92–95%, respectively) (6, 10), there is a lack of data on interactions between these NOACs and any other drug, dietary supplements, or health states that might alter plasma protein levels and/or protein binding (see Pharmacokinetic interactions (Table 2)).

There is some variation in dosing of these agents according to patient weight, especially for warfarin (i.e., patients with lower body weights generally need lower doses of warfarin to achieve similar therapeutic effects) (14). It is generally regarded that female patients may need a lower warfarin dosage than male patients due to generally lower body weights (15). For NOACs, body weights of greater than 120 kg may result in lower area under the curve (AUC) (i.e., lower plasma levels of the drugs), whereas body weights less than 50 kg may result in higher AUC (i.e., higher plasma levels of the drugs), compared to that in adults with average weights (between 65 and 85 kg). However, no dose adjustments are currently indicated on the basis of weight alone (see Table 3).

Metabolism

All four oral anticoagulants are metabolized prior to excretion, so attention must be paid to enzyme capacity and function. Warfarin is almost totally metabolized by hepatic

microsomal enzymes (cytochrome P (CYP)-450 - the metabolic pathway of many commonly used drugs) to inactive hydroxylated metabolites (predominant route) and by reductases to warfarin alcohols. Warfarin should therefore be used with caution in patients with significant liver impairment, as this may lead to increased plasma concentrations; a reduced dosage and more frequent monitoring (e.g., INR) should be considered. The S-enantiomer of warfarin (i.e., the component most responsible for warfarin's main effects) is specifically metabolized by CYP2C9 enzymes, whose polymorphisms significantly affect warfarin metabolism (see Pharmacogenetics (Table 2) (16). Dabigatran etexilate, the only pro-drug among the oral anticoagulants, must be converted to dabigatran (active form) via esterase-catalysed hydrolysis in plasma and in the liver, with around 20% of dabigatran conjugated by glucuronosyltransferases to active acylglucuronides (17). In persons with significant liver impairment, the bioconversion of dabigatran etexilate into the active form may be slower and this may subsequently delay the onset of effect (18). Rivaroxaban is mostly (approximately two-thirds) hepatically metabolised to inactive forms (via CYP3A4 enzymes). For apixaban, about one-quarter is metabolized into inactive forms via CYP3A4/5 enzymes. Therefore, in all patients, liver function should be assessed prior to and during therapy with these oral anticoagulants (6, 10). Furthermore, drugs that inhibit or induce any of the metabolising enzymes, as well as any gene variances of these enzymes, may affect the metabolism of these anticoagulants (5) (see Drug-drug interactions).

Excretion

Warfarin is excreted mostly by urine but in the form of inactive metabolites, such that renal function does not have a significant impact on its plasma concentration. For this

reason, warfarin may be a preferred oral anticoagulant in persons with major renal impairment. Among the NOACs, dabigatran is excreted mostly (85%) in active form in the urine (17); it is contraindicated in patients with creatinine clearances (CrCL) of <30mL/min. In those patients with CrCl of 30-50 mL/min, it should be used cautiously with regular (at least annual) monitoring of renal function; dosage adjustment (i.e., reduced dose) is recommended (Table 3) (8). Urine excretion accounts for two-thirds of rivaroxaban excretion (one-third as the inactive metabolite and one-third as the active form) (6). Rivaroxaban at the 10mg dosage should be used with caution in patients with severe renal impairment (CrCl 15-29mL/min), while the 15mg and 20mg dosages are contraindicated in patients with CrCl ≤ 30mL/min (Table 3) (6). In contrast, urine excretion accounts for only 27% of apixaban excretion (active form) (5). Apixaban should be used with caution in patients with a CrCl 15-29mL/min; a dosage adjustment is also recommended (Table 3) (10). Both rivaroxaban and apixaban are contraindicated for use in patients with CrCl<15mL/min given the lack of data currently for their use in such patients (see Renal Impairment). In summary, the dosing of NOACs is renal-dependant, particularly for dabigatran users, so it is important to monitor the patients' renal function.

In regard to the elimination of these drugs, as well as time to reach therapeutic effect, it is important to note the varying half-lives of the oral anticoagulants. Warfarin has the longest half-life (range of 20-60 hours; mean 40 hours), reflecting the different half-lives of the clotting factors it targets in the coagulation cascade (factor II: 42–72 hours, VII: 4–6 hours, IX: 21–30 hours, X: 27–48 hours). The long half-life results in a time-lag between the initiation or dosage change of warfarin and its anticoagulant effect (19). The NOACs all have shorter half- lives (ranging from 5-14 hours; Table 1) (6, 10, 20),

affecting the frequency of dosing of these agents, such that dabigatran and apixaban are administered twice daily. Rivaroxaban, despite having a similar half-life to the other NOACs, is recommended for use at a once daily dosage (except for the initial treatment of deep venous thromboembolism (DVT) and pulmonary embolism (PE)). This is based on the findings from Phase I and II studies which have shown that the pharmacokinetic and pharmacodynamics characteristics of rivaroxaban are similar and predictable whether given once or twice daily for stroke prevention in AF, and are supported by the findings from Phase III clinical trials using rivaroxaban once daily (21-26). This maintains certain advantages over other agents, as the frequency of administration may be an important consideration for persons with polypharmacy and/or problems with medication adherence.

Furthermore, it takes between 3 and 5 half-lives to reach steady state plasma concentrations in most patients taking pharmacotherapy. The difference in half-lives between warfarin and the NOACs has a major impact on the time it takes to reach steady-state (full therapeutic effect), such that warfarin does not start to approach steady-state levels until 3 to 5 days after the initiation of therapy, and may take about a week or even longer to reach full steady state. In contrast, the NOACs approach steady-state levels after 2 days of therapy, taking around 2-5 days to reach full therapeutic effect. The time to therapeutic effect is important when initiating anticoagulant therapy acutely for immediate prevention; in the treatment of acute thromboembolism, the initiation of warfarin may require overlapping administration of parenteral anticoagulants (i.e., heparins, enoxaparin) to ensure adequate anticoagulation in the period prior to reaching steady-state.

Similar time frames (i.e., 3 to 5 half-lives) are required to reverse the therapeutic effects of the anticoagulants after cessation of therapy. For this reason, warfarin must be ceased earlier than the NOACs prior to any major surgical interventions that carry a high risk of bleeding.

2) Pharmacological characteristics of the anticoagulants: Pharmacodynamic Aspects

All four oral anticoagulants target the coagulation cascade (secondary haemostasis: extrinsic and intrinsic pathway). In the extrinsic pathway, external triggers (such as damage to blood vessels) activate tissue factor (clotting factor III), which in turn activates clotting factors X and II, and converts prothrombin to thrombin. In the intrinsic pathway, internal physiological triggers prompt kininogen (HMWK), prekallikrein, and activated clotting factor XII to sequentially activate factors XI, IX, VIII, X and convert prothrombin (clotting factor II) to thrombin. The activation of either the extrinsic or intrinsic pathway ultimately leads to the generation of thrombin and then fibrin, which underpins thrombus formation in the body (Figure 1).

Warfarin reduces the regeneration of vitamin K through inhibition of the hydroquinone vitamin K epoxide reductase (VKORC1) enzymes, thereby inhibiting the synthesis of vitamin K dependent coagulation factors II, VII, IX, and X. The variability in its effects are in some part due to the different half-lives of these clotting factors, causing a time lag between the initiation of, or changes in, warfarin dose and its anticoagulant effect (see Excretion) (19).

Among the NOACs, rivaroxaban and apixaban are direct Factor Xa inhibitors whereas dabigatran is a direct thrombin inhibitor (Fig. 1). Since these agents have more specific targets in the coagulation cascade, they have fairly predictable individual dose-response effects, i.e., a dose-dependent prolongation in partial thromboplastin time (aPTT) and prothrombin time (PT) (27). However, when NOACs are used in population, substantial variation in dose-response may be seen (i.e., variability in peak and trough levels after fixed dose NOAC ingestion). Therefore, although routine monitoring of clotting times to guide dosage adjustment is regarded to be unnecessary for the NOACs, patient follow-up and review is still required.

3) Considerations in Special Patient Populations

Liver Impairment

Given that all of the oral anticoagulants are hepatically metabolised to some extent, liver function should be determined: prior to the initiation of therapy; periodically during therapy; and at any time when liver function may be acutely compromised. Liver impairment potentially increases the anticoagulant effect of warfarin in two ways; first, the synthesis of clotting factors may be reduced, and second, the metabolism of warfarin may be reduced. Therefore, close monitoring of clotting times and liver function is needed for patients with liver impairment who are taking warfarin (2). All NOACs are contraindicated in severe liver impairment (i.e. Child-Pugh C) given that the plasma drug concentrations are known to increase as liver function deteriorates (these patients were also excluded in clinical trials due to heightened risks of over-anticoagulation). In addition, dabigatran and rivaroxaban are also contraindicated in moderate liver

impairment (i.e. Child-Pugh B) (6, 8, 10).

Renal Impairment

As warfarin is mostly converted to inactive metabolites before urinary excretion, renal impairment does not increase the overall exposure to warfarin and no dosage adjustment is necessary for such patients (5). Among the NOACs, significant increases in plasma concentrations of dabigatran have been observed in patients with moderate renal impairment (creatinine clearance (CrCl) 30-50 mL/min) as well as in severe renal impairment (CrCL<30mL/min). Therefore, dabigatran is contraindicated in patients with CrCL<30mL/min, while for patients with CrCl 30-50 mL/min annual renal function assessment and reduced dose is recommended (Table 3) (8).

The plasma concentrations of rivaroxaban and apixaban are also inversely correlated with a decrease in renal function (CrCl). Rivaroxaban at the 10mg dosage should be used with caution in patients with severe renal impairment (CrCl 15-29mL/min), while 15mg and 20mg dosages are contraindicated in patients with CrCl less than 30mL/min (Table 3) (6). Dosage adjustment of apixaban is recommended for patients with CrCl 15-29mL/min (Table 3) (10). Both rivaroxaban and apixaban are contraindicated for use in patients with CrCl<15mL/min given the lack of data currently.

In addition to monitoring clotting times and renal function, it is also important to review a person's medication regimen to identify the concomitant use of any agents that may alter renal function and/or the renal excretion of the NOACs (e.g., frusemide, hydrochlorothiazide, gentamicin, ranitidine) (6,8,10).

Pharmacogenetics and Pharmacogenomics

In regard to the pharmacogenomics and pharmacogenetics of the oral anticoagulants, most of the available data pertain to warfarin therapy (28). For NOACs, to date, some limited data is available for dabigatran, with reports showing that the CES1 rs2244613 minor allele (occurring in 32.8% of patients in the RE-LY trial via genome-wide association analysis) is associated with a lower exposure to the active dabigatran metabolite and a lower risk of bleeding (29). For the other NOACs, no particular gene type has yet been implicated in any inter-patient (e.g., White/Caucasian, Asian and Black/African American subjects) variability in response to therapy (30, 31).

As warfarin is mainly metabolized to 7-hydroxywarfarin by CYP2C9, the variant alleles CYP2C9*2 and CYP2C9*3 can cause decreased CYP2C9 enzymatic 7-hydroxylation of warfarin. In addition, as warfarin reduces the regeneration of vitamin K through inhibition of vitamin K epoxide reductase complex (VKORC), certain single nucleotide polymorphisms in the VKORC1 gene (e.g., –1639G>A) have been associated with reduced warfarin dose requirements. Therefore, patients with a high bleeding risk (e.g., elderly, prior bleeding history) and/or inexplicable problems with over-anticoagulation, may be screened for CYP2C9 and VKORC1 gene variants to determine the optimal dosage; patients with CYP2C9*2 or CYP2C9*3 alleles and polymorphisms of the VKORC1 gene (e.g., -1639G>A allele) will generally require a lower dose (2, 5).

Ethnic (racial) differences may also lead to different therapeutic effects of warfarin. Asian patients have been shown to need lower doses of warfarin than other races to

achieve similar therapeutic effects (2, 14). Reasons for this include genetic differences in drug metabolizing capacity. For example, VKORC1 AA allele is more prevalent in Asians (32) and there is relatively low body weight in Asian patients. The VKORC1 AA allele has been associated with a 2- to 4-fold increase in the INR and increased risk of over-anticoagulation; overall, its effect on warfarin dosage adjustment is 2-fold greater effect than CYP2C9 alleles (CYP2C9*2 or CYP2C9*3 alleles are more common in Caucasian patients) (33). Other contributing factors include the differences in dietary habits and use of complementary medicines among various ethnic groups (see Interactions involving complementary and alternative medicines, supplements and food).

Elderly

Various physiological changes associated with advancing age have been shown to increase the exposure of patients to all of these oral anticoagulants (Table 2). Although for warfarin, no overall differences in key effectiveness or safety outcomes have been observed between elderly patients and their younger counterparts in clinical trials, older patients (60 years or older) appear to exhibit greater than expected PT/INR responses to this agent (5). For this reason, in elderly patients, lower initiation and maintenance dosages may be considered (2). Among the NOACs, dabigatran exposure is 28% higher in elderly patients (65–75 years old) and 68% higher in patients ≥75 years old, compared to younger subjects (<65) (8). For rivaroxaban, elderly patients (>65 years old) have a reported 1.5-fold higher exposure plasma AUC values than younger patients (6), while apixaban has a 32% higher AUC in elderly patients (≥65 years old) than in younger patients (18-40 years old) (10). All of these observed increases are generally attributed to age-related physiological decline in organ function. For this reason, renal

function should be assessed (i.e., creatinine clearance – CrCL – tested at least annually) in older persons before initiating treatment with NOACs, especially for patients over 75 years old who are prescribed dabigatran and for patients over 80 years old who are prescribed apixaban. The Product Information for individual NOACs specifies age-based dosing recommendations (Table 3).

Pediatric and Adolescents

Warfarin use in children is particularly complex, compounded by a physiological deficiency in Vitamin K dependent clotting factors in the newborn, including low concentrations of Vitamin K being transferred from the mother's breast milk; in contrast, formula-fed babies may be exposed to high levels of Vitamin K in formula milk (34). Additional challenges are presented by the limited evidence-base to guide warfarin use in children less than 3 months old, and not forgetting the practical considerations of dosage administration where a commercially-prepared liquid formulation is not available. Furthermore, therapeutic monitoring is more difficult to achieve in children, due to poor tolerability as well as the frequent monitoring lack of pediatric-specific INR therapeutic ranges (34). The latter is important to note, as limited data from observational studies and patient registries shows that therapeutic anticoagulation (i.e., INR) is difficult to achieve and maintain in pediatric and adolescent (from birth to 18 years of age) patients, hence more frequent INR monitoring is recommended (2, 35). In regard to dosing, current guidelines (34) recommend an initial dose of 0.2 mg/kg, with subsequent dose adjustments made according to INR (average dosage 0.33 mg/kg for infants and 0.09 mg/kg for teenagers to maintain an INR of 2.5; target range 2.0 to 3.0)

(34). Due to the exclusion of these patients from the clinical trials, NOACs are not currently recommended for pediatric patients (Table 2).

Pregnancy and Lactation

Warfarin is contraindicated for use in pregnant women because it passes through the placental barrier and may cause fatal haemorrhage to the foetus (in utero) and birth malformations (e.g., chondrodysplasia punctata, mental retardation) (5). Given their absorption characteristics, NOACs are expected to diffuse across the placenta, and thus are also contraindicated in pregnancy(6, 8, 10) (Table 2). Although there have not been any studies of NOACs in pregnant women, and therefore there are no data to support their use, the prescribing information for these products states that they "should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus (30). Low-molecular-weight heparins (LMWHs) are recommended for pregnant women as these do not cross the placenta to affect the fetus (36).

Warfarin is generally regarded to be relatively safe for breast feeding women, given that it is clinically undetectable in breast milk and because studies to date have shown normal PT results in infants nursed by warfarinised mothers with standard dose (2). However, as effects in premature infants have not been evaluated, caution should be taken when prescribing warfarin to their breastfeeding mothers (35). Data from animal studies suggest that NOACs are excreted via lactation, and in the absence of specific human data to demonstrate safety, their use in breast feeding women is not recommended (6, 8, 10).

Gender

There are no specific differences reported in the effects of the oral anticoagulants between males and females, other than effects during menstruation. Warfarin has been reported to increase the amount of menstrual blood loss in women of reproductive age, and therefore should be closely monitored and managed with tranexamic acid and/or oral contraceptive pills if menorrhagia persists (37, 38). For NOACs, there is no data regarding use in menstruating females (Table 2).

4) Medication Safety Considerations: Interactions

Drug-Drug Interactions

Pharmacokinetics Interactions

Due to its complex pharmacology, warfarin has a higher potential for drug interactions compared to the NOACs, and this is an important consideration for use in the at-risk elderly population which is likely to be taking polypharmacy. Drugs such as cholestyramine and sucralfate affect the bioavailability of warfarin by inhibiting its absorption (see Absorption). Noting the high protein binding of warfarin, the concomitant use of other agents which are also highly protein bound (e.g., commonly used agents such as ibuprofen, quinidine, fenofibrates, losartan, valsartan, amlodipine, felodipine) may necessitate a dose reduction for warfarin, as well as close monitoring (9, 39). Since CYP450 isozymes, CYP2C9 (principle), CYP1A2, and 3A4, enzymes are all involved in the metabolism of warfarin, inhibitors of these enzymes (e.g., amiodarone, fluconazole) have the potential to increase the effect of warfarin; conversely, inducers

of CYP2C9, and/or 1A2, and/or 3A4 enzymes (e.g., carbamazepine, phenobarbital) have the potential to decrease the effect of warfarin (2, 39). Interactions between warfarin and other drugs can be managed through more frequent therapeutic drug monitoring. However, given that any dosage adjustment will not be reflected in coagulation tests (i.e. INR) for at least 3 days (due to the long half-life and time to reach steady-state levels) (2,14), dosage adjustments should be anticipated in advance once a potential drug interaction has been identified (2). This is particularly important for agents that are used acutely over the short-term, such as anti-infectives. Several anti-infective agents, such as co-trimoxazole, fluconazole, azithromycin, ciprofloxacin, have been reported to increase the risk of bleeding when concomitantly administered with warfarin, due to the inhibition of the CYP isoform, alteration of gastrointestinal flora, or competitive protein binding (40).

Among all of the oral anticoagulants, dabigatran is the only one that is not metabolised by the cytochrome P450 enzymes, and therefore has a lower potential for drug interactions. However, dabigatran etexilate (the pro-drug of dabigatran) is a substrate of the efflux transporter P-glycoprotein (P-gp), and therefore co-administration with P-gp *inhibitors* (e.g., dronedarone, ketoconazole, verapamil) can ultimately increase its plasma concentrations. For this reason, dabigatran etexilate should be administered at least 2 hours apart from doses of any P-gp inhibitor agents during the first 3 days of concurrent therapy. The co-administration of dabigatran etexilate with P-gp *inducers* (e.g., rifampicin, carbamazepine, phenytoin) should be avoided, as these agents may decrease the plasma concentration of dabigatran, leading to loss of effect (Table 2) (8).

Both rivaroxaban and apixaban are eliminated mainly via cytochrome P450-mediated (CYP 3A4, CYP 2J2) hepatic metabolism, but are also substrates of P-glycoprotein (P-gp). Therefore, co-administration of drugs with both CYP 3A4 and/ P-gp inhibition properties (e.g., ketoconazole, ritonavir) with rivaroxaban or apixaban should be avoided as this may reduce their elimination and significantly increase systemic exposure (6, 10), leading to over-anticoagulation. Less potent CYP 3A4 and/P-gp inhibitors (e.g., amiodarone, diltiazem, verapamil) should be used with caution.

Pharmacodynamic Interactions

All of the oral anticoagulants should be used cautiously with any other agents that possess antithrombotic activity. For patients taking warfarin, practice guidelines generally recommend avoiding the concurrent use of NSAIDs or other platelet aggregation inhibitors, unless the benefit is likely to be greater than any harm from bleeding such as may be the case in patients with mechanical heart valves, acute coronary syndrome, or recent coronary stents or bypass surgery (41). For apixaban and rivaroxaban, co-administration with other anticoagulants (e.g., enoxaparin) is associated with additive effects on anti-Factor Xa activity. For dabigatran, co-administration with the LMWH anticoagulant enoxaparin also reportedly results in higher anti-FXa/FIIa activity. Co-administration of more than one oral anticoagulant should be avoided, and co-administration of any oral anticoagulant with platelet aggregation inhibitors or NSAIDs should be undertaken cautiously (6, 8, 10, 11).

Interactions Involving Complementary and Alternative Medicines, Supplements, and Food

Warfarin has been reported to interact with several herbs and/or foods (Table 2), which may impact adversely on the patient's daily life and may be a cause of non-adherence to the therapy. St. John's Wort induces CYP 2C9 and 1A2 enzymes, and thus decreases the therapeutic effect of warfarin (42). Garlic has antiplatelet functions and may also inhibit CYP enzymes 2C9, 2C19 and 3A4, thereby increasing the therapeutic effect of warfarin (43). Cranberry has also been reported to increase warfarin's effect via two mechanisms; first, it contains flavonoids which can inhibit CYP enzymes, and second it contains salicylic acid which possesses some antiplatelet effects (44, 45). Fish oil has also been reported to increase the INR (46) via inhibition of platelet aggregation and vitamin K-dependent coagulation factors (decreased thromboxane A2 and factor VII levels) (47).

Given that warfarin's main mechanism of action relies on its inhibition of vitamin-K dependent clotting factors, the excessive and/or inconsistent intake of vitamin K (diet or supplementation) may lead to suboptimal anticoagulation (evident in poorly controlled INRs). For this reason, patients taking warfarin therapy should be counseled about the importance of a balanced diet (consistent vitamin K intake); referral to a dietician may be warranted. Furthermore, the use of any supplements (e.g., multivitamins) should be reviewed to identify any vitamin K content. In addition, the use of herbal medicines (e.g., dansen, quilingao), which are commonly used in Asian people, should be monitored, as they may possess antithrombotic effects and/or affect the metabolism of warfarin (47).

For NOACs, the potential for herb/supplement/food interactions is significantly lower. However, herbal compounds that are also strong CYP3A4 and P-gp inducers (e.g., St.

John Wort) can decrease plasma concentration of these agents and should be used with caution or avoided altogether (6, 10, 40).

5) Medication Safety Considerations: Prevention and Treatment of Adverse Reactions

Reported Adverse Drug Reactions

Haemorrhage is inherently the most important adverse reaction of oral anticoagulants, and may present as minor or major (including life-threatening) bleeds, as well as in less obvious ways such as headache, paralysis, and/or pain in the chest, abdominal, joints or muscles. All oral anticoagulants are contraindicated in patients with significant active bleeding (e.g., intracranial, intraocular, gastrointestinal bleeding). In regard to specific types of bleeds, intracranial haemorrhage (ICH) is relatively rare (incident 0.7-0.8%) although it is the most feared complication of anticoagulation (48). In comparison, all of the NOACs have been reported to cause less ICH than warfarin, and therefore are the preferred options for patients with a history of previous ICH or who are at a higher risk of ICH (48). A more common type of haemorrhage is gastrointestinal bleeding, and this is more commonly reported for some of the NOACs; dabigatran 150mg (but not the 110mg dose) has higher rates of gastrointestinal bleeding compared to warfarin. Rivaroxaban (but not apixaban) is also associated with higher rates of GI bleeding. Therefore, dabigatran and rivaroxaban should be avoided in patients with a history of major gastrointestinal disease, particularly where bleeding has previously occurred (19, 49).

On a day-to-day basis, warfarin is generally well tolerated. However, serious but rare complications of therapy include necrosis and/or gangrene of the skin and other tissues (requiring debridement or amputation), hypersensitivity/allergic reactions and systemic cholesterol microembolization. For NOACs, gastrointestinal irritation (e.g., gastrointestinal bleeding, upper abdominal pain, gastritis) is commonly reported, particularly for dabigatran (both 110 and 150 mg doses) where gastrointestinal reactions have been cited as one of the most common reasons for treatment cessation (8). After initiating treatment, the incidence of dyspepsia with dabigatran is reportedly 11.3%–11.8% (RE-LY trial) (50), resulting from either a direct injurious effect of the medication on the esophageal mucosa, or as an indirect effect that promotes the reflux of gastric contents, Although the specific mechanism is unknown, risk factors that have been associated with the dabigatran-induced dyspepsia include: being female, aged 75 years and older, non-white ethnicity, and concomitant use of specific medication i.e., proton pump inhibitor (PPIs), H2 receptor antagonist (H2RAs), Non-Steroidal Anti-Inflammatory Drug (NSAIDs) (51). Although administration of doses with food and/or use of proton pump inhibitors may ameliorate the gastrointestinal effects to some extent, dabigatran is not recommended for use in patients with gastrointestinal disease or in those using NSAIDs and/or other drugs that cause gastrointestinal discomfort. For apixaban and rivaroxaban, anaemia (posthaemorrhagic) and nausea are the most frequently reported adverse reactions. However, as these complaints are from major hip/knee replacement clinical trials, they may be acutely due to the effects of surgery rather than the drug itself.

The decision to initiate anticoagulant treatment is based on the risk (e.g., *bleeding*) versus benefit (e.g., *prevention of stroke)* of therapy. Since the risk of adverse reactions,

specifically haemorrhage, is integral to this, several approaches are important in reducing the risk of bleeding and related outcomes: assessment of risk, therapeutic drug monitoring, and management of over-anticoagulation.

Assessment of Risk

For use on atrial fibrillation, a number of stroke risk assessment tools (e.g., $CHADS_2$ (52) and CHA_2DS_2-VASc (53)) and bleeding risk assessment tools (e.g., $HEMORR_2HAGES$ (54) and HAS-BLED (55)) have been proposed for clinical use (56). In regard to the assessment of risk, guidelines are used for the prevention (57-59) versus treatment of venous thromboembolism (VTE) (60). For prevention of VTE, anticoagulants such as low-molecular weight heparin (LMWH) are recommended for patients undergoing major orthopaedic surgery, and for those patients with increased risk (e.g., Padua Prediction Score≥4, Caprini score≥3 or Rogers score>10) (57-59) of VTE without high bleeding risk. For the treatment of VTE, initial parenteral anticoagulant therapy (e.g., LMWH) is recommended followed by warfarin (60), Bleeding assessment tools include those developed by Kuijer et al. (1999) (61) and the RIETE risk scheme (2008) (62).

Therapeutic Drug Monitoring (TDM)

Monitoring of therapeutic response has been critically important in the management of therapy as it has historically guided warfarin dosing regimens. TDM for warfarin has relied on measurement of clotting time (blood test), specifically prothrombin time (PT), which is then calibrated according to the international sensitivity index (ISI accounting for variability in reagents across different laboratories) to generate the International

Normalized Ratio (INR). The INR provides a measure of the degree of anticoagulation observed in the individual patient, rather than measuring plasma drug concentrations (which do not correlate well with therapeutic effect). For this reason, warfarin is dosed according to INR, with target INRs ranging from 2.0 to 3.5 for various indications (e.g., the target INR range for patients with AF is 2 to 3). An INR of 2.0 means that it takes twice the time to form a clot in that patient, compared to a normal (not anticoagulated) person; low INRs indicate a higher propensity to form clots, whereas a higher INR indicates a higher propensity to bleed.

The challenge of INR testing is the frequency at which it needs to be done. When initiating warfarin therapy, the INR should generally be measured 15 hours or more (usually 2 -3 days) after the first dose, and then measured every few days until optimal therapeutic INR has been achieved. During maintenance therapy, the INR is measured every 1-2 weeks in the early weeks of therapy until the INR remains stable, after which the frequency of testing can be reduced to every 4 weeks (2, 39). However, more frequent INR monitoring may be needed in patients at a higher risk of bleeding, and at any time when warfarin's effect may be altered by acute illness, drug or food interactions.

For the NOACs, the issue of TDM is not fully elucidated as yet. Pharmacodynamically, there is a close correlation between the plasma concentrations and anticoagulant effects of these agents, and therefore variability in anticoagulation levels is less likely (see Pharmacological characteristics of the anticoagulants: Pharmacodynamics aspects). Therefore, dosage adjustments are not generally required, and TDM is not currently advocated. However, in acute situations where there is a need to determine the level of

anticoagulation in an individual patient (e.g., prior to emergency surgery, treatment of major haemorrhage), the INR is not useful for the NOACs and there are limited alternative options currently. For dabigatran, a range of parameters have been explored to enable therapeutic monitoring when required; the aPTT, thrombin time (TT) and ecarin clotting time (ECT) (not widely available in clinical practice) may all be useful in determining the level of anticoagulation activity. The aPTT offers a quantitative assessment of dabigatran anticoagulant effect and an aPTT over 2.5 times of the control suggests excessive anticoagulation (8). The TT can be used to determine the presence or absence of anticoagulant effect and is too sensitive be used to monitor the anticoagulant effect of dabigatran as it may remain prolonged for days after the last dose is taken (63, 64). The ECT approach appears to be more reliable at lower dabigatran concentrations (65). More recently, a commercially available direct thrombin inhibitor assay, i.e., the HEMOCLOT™ test, has been extensively tested to quantitatively determine plasma concentrations (range 100-2000nmol/l) and related anticoagulant activity of dabigatran (66). For apixaban, PT and aPTT tests appear to be not sensitive enough to determine the level of anticoagulation achieved by the agent, although plasma concentrations and anti-FXa activity have a linear relationship over a wide dose range; the anti-FXa assay can reliably quantify a wide range of apixaban concentrations (10, 67). For rivaroxaban, PT can be used as as a screening test of bleeding risk and the more specific and sensitive chromogenic anti-Factor Xa assay (using validated rivaroxaban calibrators and controls) can be used to assess the drugs plasma concentrations gravimetrically (ng/mL or ug/L) (6) (Table 1).

The process of INR testing inherently makes patients more adherent to warfarin therapy (or at least, it enables clinicians to verify adherence to therapy); with NOACs,

adherence may be potentially reduced for this reason.

Treatment of Over-anticoagulation

In the event of excessive anticoagulation, appropriate measures must be taken to reverse the effects of the agent and prevent further complications. For warfarin, there are guidelines for the management of over-anticoagulation, which are based on INR results as well as the patient's clinical presentation (i.e., with or without active bleeding). Simple measures range from withholding and reducing warfarin doses until the INR returns to a safe range, through to administering vitamin K1, and for more severe cases, the use of fresh whole blood or fresh frozen plasma and/or the administration of Prothrombin Complex Concentrate (PCC) or activated Factor VII (there is some concern about the increased risk of arterial events associated with activated Factor VII use (68)) (2, 5, 69).

For NOACs, specific antidotes are not yet available for reversing their anticoagulant effects; vitamin K or protamine sulphate (for heparins) are ineffective here. For this reason, over-anticoagulation with the NOACs currently relies on cessation of therapy (noting the relatively shorter half-life of the NOACs compared to warfarin), and/or general supportive measures particularly where severe bleeding is present (e.g., blood transfusion, intensive care) (70). Concentrates of coagulation factors II, IX, or X, PCC, fresh frozen plasma (FFP), or hemodialysis (for dabigatran only, because of its relatively low plasma protein binding) can be considered in cases of severe bleeding (8, 71). For apixaban and rivaroxaban, activated charcoal can be used within 3 hours and 8 hours, respectively, of taking a dose to reduce further drug absorption (6, 10). For dabigatran, given that it is mostly excreted in the urine, pharmacologically-induced

diuresis may assist drug clearance (72), but may not be appropriate where fluid loss might lead to haemodynamic deterioration (Table 1).

Pre-operative Reversal of Anticoagulation

Because of its long and variable half-life (20-60 hours), warfarin should be at least stopped 5 days (73) before major surgery to allow sufficient time for regeneration of vitamin K-dependent coagulant factors to achieve normal coagulation status. For the NOACs, since the elimination half-life is relatively shorter (5-14 hours), these agents can generally be stopped around 1-2 days before major surgery (74). Consideration should, however, be given to the main routes of elimination of each NOAC and any impairments to this that may delay the elimination of the drug. For example, dabigatran, whose elimination is mostly affected by renal function (see Excretion), must be stopped at least 2-4 days prior to surgery in patients with renal impairment (CrCL $\leq$50 mL/min) (8, 74, 75), or in those undergoing high bleeding-risk surgical procedures (e.g., neurosurgery, cardiovascular surgery), or those using spinal anesthesia (76). Similar consideration regarding earlier discontinuation may also be needed for patients with renal impairment who are taking rivaroxaban and apixaban (70, 74) (Table 1). Minor procedures, such as dental surgery, can usually be safely performed without discontinuation of warfarin if the INR is less than 4.0 (optimally 2.5) (77); the NOACs do not need to be ceased either in these cases (78).

In emergency surgery or intervention, immediate discontinuation of all oral anticoagulants is necessary. For warfarin, the procedure should be delayed for 6-24 hours and vitamin K (5-10 mg by intravenous injection or orally) administered; further doses should be repeated in 6-12 hours if the INR remains and/or if sustained reversal is

desired. If the surgery or intervention cannot be feasibly delayed, FFP and/or PCC should be administered prior to procedure (79). For NOACs, procedures should be delayed until at least 12 hours after the last dose. Where delaying the procedure is not possible, and the potential risk of bleeding has to be assessed against the urgency of procedure, the treatment methods currently advocated for severe bleeding (mentioned earlier) should be made available.

Summary

Compared with warfarin, the novel oral anticoagulant drugs maintain certain advantages, given their pharmacokinetic and pharmacodynamics characteristics. In particular, the reduced dependence on regular monitoring of clotting times may assist with day-to-day management of patients and adherence. However, most NOACs require monitoring of renal function, unlike warfarin, and these may inform dosage adjustments. In addition, NOACs are contraindicated in patients with moderate and severe liver impairment while warfarin may be used with caution in these patients groups. Although NOACs have fewer reported interactions with drugs or complementary medicines, they are not devoid of interactions. Furthermore, while warfarin has an available antidote for treating over-anticoagulation and bleeding events, the NOACs currently lack specific antidotes. The characteristics of each anticoagulant must be carefully considered during decision-making, to select the agent that will provide the optimal risk/benefit profile in the individual patient.

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Table 1. Pharmacological properties of the oral anticoagulants

	Warfarin	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
Drug Class	Vitamin K antagonist	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Pharmacokinetics Absorption	Within 4hrs	0.5-2hrs absorbed as pro-drug dabigatran etexilate	2 - 4 hrs	3-4hrs
Bioavailability	98%	6.5%	80-100%	50%
Peak action (Tmax)	72-120hrs	1.25-3hrs	2-4hrs	1-4hrs
Distribution (volume of distribution)	8L (0.14/kg)	60-70L	50L	21L
Metabolism	Hepatic CYP-450 (R-enantiomer is metabolized by CYP1A2, CYP2C19 and 3A4, S-enantiomer is metabolized by CYP2C9) and reductases.	Activated by esterase-catalysed hydrolysis (hepatic or plasma). CYP450 independent. conjugation forming pharmacologically active acylglucuronides.	Hepatic CYP3A4, CYP2J2 and CYP-independent mechanisms.	Mostly hepatic CYP3A4/5, also CYP1A2, 2C8, 2C9, 2C19, and 2J2.
Liver impairment	Impaired synthesis of coagulant factors and decreased metabolism of warfarin, use with caution	Contraindicated in moderate and severe hepatic impairment (i.e. Child-Pugh B and C)	Contraindicated in moderate and severe hepatic impairment (i.e. Child-Pugh B and C)	Contraindicated in severe hepatic impairment (i.e. Child-Pugh C)
Excretion	Mostly urine, lesser bile	85% unchanged via urine, conjugated via bile	2/3 metabolic degradation(1/3 kidney, 1/3 feces), 1/3 unchanged excretion in urine	27% urine, else via biliary direct intestinal excretion.
Elimination Elimination half-life	20-60hrs (R enantiomer-29 hours, S-enantiomer half-life 45 hours)	7-17 hours	7-13 hours	8-15 hours
Preoperative Phase	Adjust or stop 5 days before surgery	Stop at least 24 hrs before surgery; if high bleeding risk procedure[a] and/ CrCL≤ 50 mL/min:stop 2-4 days before surgery[b]	Stop 24hrs before surgery; if CrCL<50mL/min: stop 2-4 days before surgery[c].	Stop 24hrs before surgery; if CrCL<50mL: stop 2-4 days before surgery[c].
Renal impairment	Minor effect, no dosage adjustment	Contraindicated in CrCl<15ml/min[d].	Contraindicated in CrCl<15ml/min[d].	Contraindicated in CrCl<15ml/min[d].
Pharmacodynamics	Anticoagulant effect depends on dosage and patient's genotype. Monitor INR	Close correlation between anticoagulant effect and plasma concentrations [e]	Close correlation between anti-FXa activity and plasma concentrations [e].	Close correlation between anti-FXa activity and plasma concentrations [e].
Monitoring tests	INR	aPTT, TT, HEMOCLOT test	PT, chromogenic anti-FXa assay	anti-FXa assay
Antidotes for reversal of over-anticoagulation	Vitamin K1. Severe cases FFP, PCC, fresh whole blood.	Diuresis. Severe cases: FFP, PCC, haemodialysis[f]	Activated charcoal within 8 hour of last dose. Severe cases: FFP, PCC [f]	Activated charcoal within 3 hours of last dose. Severe cases: FFP, PCC [f]

[a] e.g., Neurosurgery, cardiovascular surgery, or with spinal anesthesia.

[b] If CrCl<30ml/min, stop over 2-5 days before surgery. If high bleeding risk procedure and CrCl<30ml/min: stop over 5 days before surgery.
[c] If high bleeding risk procedure: stop 3-4 days before surgery.
[d]Plasma concentration increases as renal function deteriorates,
[e] No need for monitoring of clotting times
[f]No specific antidote.

Table 2. Key factors affecting the use of oral anticoagulants

Special population	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Elderly persons	Elderly patients (≥ 60 yrs) need lower dosage to achieve therapeutic effect	Higher plasma concentrations in elderly patients (≥ 65 yrs), may need dose adjustment	Higher plasma concentrations in elderly patients (≥ 65 yrs), may need dose adjustment	Higher plasma concentrations in elderly patients (≥ 65 yrs), may need dose adjustment
Gender differences	Female may need lower dosage	No need for dosage adjustment	No need for dosage adjustment	No need for dosage adjustment
Body weight	May need less dosage for lower body weight	No need for dosage adjustment	No need for dosage adjustment	Body weight > 120 kg and < 50 kg may need dose adjustment
Children and adolescents (from birth to 18 years)	Limited data, more frequent INR monitoring is needed	No data	No data	No data
Pregnancy	Contraindication (Category D/X*)	Category C*	Category C*	Category B*
Interethnic difference	Asian patients may require lower dosage	No need for dosage adjustment	No need for dosage adjustment	No need for dosage adjustment
Pharmacogenetics	Lower dosage required for patients with CYP2C9*2 or CYP2C9*3 alleles, or VKORC1 gene (especially the 1639G>A allele)	No data	No data	No data
Pharmacokinetic (PK) Interactions	Inhibitors of CYP2C9, 1A2, and/or 3A4; Inducers of CYP2C9, 1A2, and/or 3A4 e.g., ibuprofen, losartan, amiodarone, phenobarbital	P-gp inducers and inhibitors e.g., dronedarone, amiodarone, verapamil, rifampicin, carbamazepine	Inhibitors of CYP 3A4, CYP 2J2 and P-glycoprotein (P-gp) e.g., amiodarone, diltiazem, ritonavir, ketoconazole	Inhibitors of CYP3A4 and P-gp e.g., amiodarone, diltiazem, ritonavir, ketoconazole
Pharmacodynamic (PD) Interactions	Anticoagulants, platelet aggregation inhibitors and NSAIDs**	Anticoagulants, platelet aggregation inhibitor and NSAIDs**	Anticoagulants, platelet aggregation inhibitors and NSAIDs**	Anticoagulants, platelet aggregation inhibitors and NSAIDs**
Complementary medicines and food example	St. John's wort, danshen, cranberry, grapefruit juice	St John's wort	St John's wort, grapefruit juice	St John's wort, grapefruit juice

* FDA Pharmaceutical Pregnancy Categories (65): **Category B:** Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. **Category C:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category D:** There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category X:** Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use.

** e.g., alteplase , aspirin, clopidogrel

Table 3. Dosing recommendations by indication

Indications for therapy	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Venous Thromboembolism Prevention in total hip and knee replacement	2 to 10 mg daily, INR of 2.5 (INR range, 2.0-3.0) within 12-24hours of surgery for minimum 10-14 days (recommended to be extended to 35 days in outpatient) [81]	220mg daily (CrCl>50mL/min) /150mg daily (CrCL 30–50 mL/min or with P-gp inhibitors) within 1-4 hours after surgery for knee replacement (10days), hip replacement (28-35 days)	10 mg daily (CrCl ≥ 15 mL/min) 6-10hours after surgery (2 weeks for knee replacement, 5 weeks for hip replacement)	2.5 mg twice daily (CrCl>15ml/min) 12-24 hours after surgery, knee replacement (10-14 days), hip replacement (32-38 days)
Deep venous thrombosis [DVT] and pulmonary embolism (PE) treatment and prevention	2 to 10 mg daily (overlapping with LMWH or fondaparinux for 5 days), INR of 2.5 (INR range, 2.0-3.0) for 3 months or more (depends on individual risk versus benefit) [60]	RE-COVER Clinical trial completed [82]: 150 mg twice daily for 6 months	15 mg twice daily for 3 weeks, followed by 20 mg daily continue as long as risk exists	Clinical trial of treating venous thromboembolism completed [83]: 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months
Stroke Prevention in Atrial Fibrillation/ cardiac valve replacement [a]	2 to 10 mg daily, INR 2.5 (range, 2.0-3.0)[b]/ 3.0 (range, 2.5-3.5)[c]	150mg twice daily (CrCl>30mL/min)/75mg twice daily [d]	15 mg daily (CrCl 15 – 50 mL/min)/ 20 mg daily (CrCl > 50 mL/min)	5mg twice daily (CrCl>30ml/min) /2.5mg [e] twice daily
Thromboembolic events prevention Post-Myocardial Infarction	2 to 10 mg daily, (INR, 2.0-3.0) plus low-dose aspirin (≤ 100 mg/day) [f]	N/A	N/A	N/A
Cardiovascular events prevention after Recent acute coronary syndrome (adjunctive therapy)	N/A	N/A	ATLAS ACS-2-TIMI-51[g] clinical trial completed[84]: 2.5/5mg twice daily	N/A

[a] Cardiac valve replacement only indicted for warfarin

[b] Non-valvular AF, bioprosthetic valve in the mitral position or bileaflet mechanical valve or a Medtronic Hall (Minneapolis, MN) tilting disk valve in the aortic position who are in sinus rhythm and without left atrial enlargement

[c] INR 3.0 (range, 2.5-3.5)[b] for tilting disk valves, bileaflet mechanical valves, caged ball or caged disk valves, bioprosthetic valve

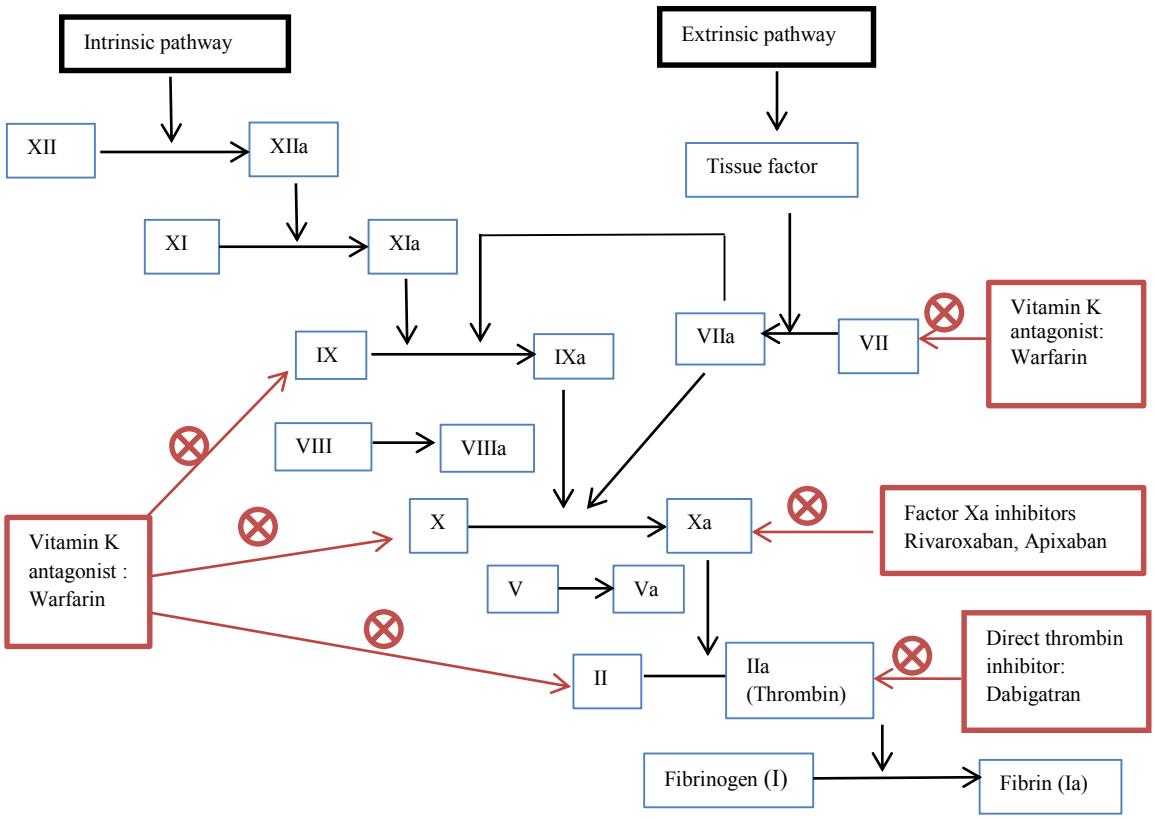
[d] CrCL: 15–29 mL /min, or if concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole and CrCl 30-50mL/min.

[e] Any2 of these age ≥ 80 years body weight≤ 60 kg serum creatinine ≥ 1.5 mg/dL. Or strong inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)

[f] Patients with high risk of thromboembolism. e.g., those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on transthoracic echocardiography, those with AF, and those with a history of a thromboembolic event) [2]

[g] Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction-51

Figure 1. Description of coagulation cascade and the sites targeted by old and new oral anticoagulants



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Chapter Three

3.1 Clinical pre-test of a Computerised Antithrombotic Risk Assessment Tool for stroke prevention in atrial fibrillation patients: giving consideration to NOACs

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Clinical pre-test of a computerised antithrombotic risk assessment tool for stroke prevention in atrial fibrillation patients: giving consideration to NOACs

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Keywords
atrial fibrillation, computer-assisted, decision making, decision support, novel oral anticoagulant, novel oral anticoagulant, stroke prevention, warfarin

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Abstract

Rationale, aims and objectives The decision-making around antithrombotics in atrial fibrillation requires comprehensive risk versus benefit assessment. In view of the availability of novel oral anticoagulants (NOACs) including dabigatran, rivaroxaban and apixaban, a decision support tool designed to assist the selection of antithrombotics has been modified to consider both warfarin and NOACs. This study aims to pre-test this modified decision support tool.

Methods The decision support tool was modified to consider either warfarin or NOACs as first-line therapy and applied to data pertaining to a cohort of 393 patients in New South Wales.

Rationale, aims and objectives

The decision-making around antithrombotics in atrial fibrillation (AF) requires comprehensive risk versus benefit assessment. In view of the availability of novel oral anticoagulants (NOACs) including dabigatran, rivaroxaban, and apixaban, a decision support tool designed to assist the selection of antithrombotics, has been modified to consider both warfarin and NOACs. This study aims to pre-test this modified decision support tool.

Methods

The decision support tool was modified to consider either warfarin or NOACs as first-line therapy and applied to data pertaining to a cohort of 393 patients in New South Wales.

Results

Overall, 380 (96.7%) patients were eligible for oral anticoagulants. In the scenario of warfarin being recommended as first-line therapy, the Computerised Antithrombotic Risk Assessment Tool version 2.0 (CARATV2.0) recommended warfarin for 360 (91.6%) patients, any NOAC for 5 (1.3) patients, either rivaroxaban or apixaban for 6 (1.5%) patients, and apixaban for 9 (2.2%) patients. In the scenario of NOACs as first-line therapy, CARATV2.0 recommended any NOAC for 279 (70.9%) patients, either rivaroxaban or apixaban for 80 (20.4%) patients, apixaban for 9 (2.3%) patients, and warfarin for 12 (3.1%) patients. Key reasons for CARATV2.0 to recommend a change from warfarin (patients' current therapy) to NOACs included: known warfarin

allergy/adverse reaction, a history of intracranial bleeding, and previous gastrointestinal bleeding. Key predictors for CARATV2.0 to consider that patients are more suitable for NOACs over warfarin were: a diagnosis of other gastrointestinal diseases, more comorbidities and high risk of falls.

Conclusions

According to this decision support tool, both warfarin and NOACs are viable treatment options in majority of the patients, but there is a scope for better rationalisation of therapy.

Introduction

The use of antithrombotic therapy (e.g., anticoagulant, antiplatelet) to prevent stroke in older patients with atrial fibrillation (AF) is widely recognised (1). As a traditional anticoagulant, warfarin is highly effective, but its unpredictable therapeutic effects, various food and drug interactions, and the need for regular monitoring have been associated with a greater difficulty of use, leading to a potential increase in adverse events and/or reluctance by clinicians to prescribe it (2, 3), especially in older AF patients (3, 4).

To overcome these limitations, three novel oral anticoagulants (NOAC) have been introduced into practice: dabigatran, rivaroxaban, and apixaban. The availability of these new anticoagulants for stroke prevention in AF has substantially expanded the treatment armamentarium, however, this has also rendered decision-making around therapy selection more complex. Furthermore, concerns about the cost implications of the newer, more expensive agents has led to recommendations for a more considered approach to the selection of therapy (5). A Computerised Antithrombotic Risk Assessment Tool (CARAT) for selecting antithrombotic agents in AF developed by our team for Australian clinical practice was shown to significantly improve the use of antithrombotic therapy (6). This tool is unique in that it comprehensively reviews stroke risk, bleeding risk and major issues around medication safety (e.g. adherence, falls risk, cognitive function), and additionally calculates the estimated risk versus benefit of therapy for individual patients (7). Although there are other risk assessment tools that synthesise assessment of stroke and bleeding risks to recommend antithrombotic therapy—for example, the clinical decision aid developed by LayHaye et al. (8) and the

decision model developed by Casciano et al. (9)—none consider medication safety issues that affect the selection of therapy (8, 9). In addition, none of these tools have been shown to improve the use of antithrombotic therapy in practice (8, 9), unlike CARAT. Thus, the CARAT is a novel and useful way of assisting the decision-making around antithrombotic therapy.

In view of the recent availability of the NOACs, CARATV2.0 has been updated into Computerised Antithrombotic Risk Assessment Tool version 2.0 (CARATV2.0) based on the current clinical evidence (5, 10, 11). Therefore, the aim of this study was to pre-test CARATV2.0 and identify its treatment recommendations for a cohort of patients with AF. Specifically, the recommendations of CARATV2.0 were compared against patients' current treatment, and the factors associated with treatment selection were identified.

Method

Study design and data collection

The study was cross-sectional in design. Data pertaining to a cohort of 393 patients with AF who were recruited from general practices for a previous study in 2012 (12) were extracted for this study. Only the baseline data of these patients were available at the time of this study. All the patients were aged ≥ 65 years with a confirmed diagnosis of AF and dwelling in urban and rural New South Wales. The lead researcher extracted key patient information (e.g., medical history, medication use,

functional/cognitive/social status) from the previous trial database (baseline patient data before any intervention was given).

Application of CARATV2.0

The extracted data were then used to populate the CARATV2.0 and assess each patient's risk of stroke, bleeding, and medication misadventure. The CARATV2.0 inputs were reviewed and verified by a second researcher. After populating the tool, a treatment recommendation for each patient was generated and compared to the current pharmacotherapy prescribed for the patient.

Risk Assessment in CARATV2.0

To assess the stroke risk, $CHADS_2$.(13) and CHA_2DS_2VASc (14) scores of 0, 1, ≥ 2 were classified as low, intermediate and high stroke risk, respectively. To assess the bleeding risk, HAS-BLED (15) scores of 0, 1-2, ≥ 3 were classified as low, intermediate and high bleeding risk and $HEMORR_2HAGES$ (16) scores of 0-1, 2-3, ≥ 4 were classified as low, intermediate and high bleeding risk, respectively. The presence of any relevant contraindications to antithrombotic therapy (both warfarin and NOACs) and major medication safety issues (e.g. renal and liver impairement, non-adherence, falls risk, cognitive impairment, significant drug interactions) that may affect treatment choice were also assessed.

Algorithm of CARATV2.0

Two sets of scores (stroke risk using $CHADS_2$ (13) and CHA_2DS_2VASc (14); bleeding risk using HAS-BLED (15) and $HEMORR_2HAGES$ (16)) were used to verify the risk assessment within CARATV2.0; if there was discrepancy in scores, the highest level of risk was used, regardless of scoring tool. A patient was considered to be eligible for oral anticoagulants, whenever the risk of stroke (assessed by $CHADS_2$ (13) or CHA_2DS_2VASc (14)) was equal or more than the risk of bleeding (assessed by HAS-BLED (15) or $HEMORR_2HAGES$ (16)). When the bleeding risk of using oral anticoagulants in the patient exceeded the benefit of stroke prevention, the patient was deemed to be unsuitable for oral anticoagulants by CARATV2.0; alternative treatment (e.g. an oral antiplatelet) and specialist consultation were recommended instead. In cases, where the patient was eligible for oral anticoagulants and had no contraindications to any of the oral anticoagulants (i.e. eligible for either warfarin or NOACs) two scenarios were considered:

Scenario one

In the first scenario, warfarin was considered first-line therapy by CARATV2.0 with NOACs as second-line therapy, as per the government review (5) and Australian Therapeutic Guidelines (17).

Scenario two

NOACs were assumed as the first-line therapy and warfarin as the second-line therapy, as per international guidelines (10, 11).

Where the patient had contraindications to the first-line therapy, the second-line therapy was recommended, provided there were no known contraindications. Specific contraindications included renal impairment, liver impairment, drug allergies, and previous adverse events (e.g. bleeding) (6, 18, 19). Renal impairment was defined as a creatinine clearance (CrCl) of <30 ml/min (for dabigatran and rivaroxaban), a CrCl of <25 ml/min (for apixaban), and for patients on maintenance haemodialysis a CrCl of <15 ml/min (for all NOACs) (6, 18, 19). Liver impairment was defined as moderate and severe hepatic impairment (i.e. Child-Pugh B and C, for dabigatran and rivaroxaban) and severe hepatic impairment (i.e. Child-Pugh C, for apixaban) (6, 18, 19).

Data analysis

Computerised data analysis employed SPSS (Statistical Package for the Social Sciences Version 19). The chi-square test examined differences in independent proportions or categories; multivariate logistic regression analysis (Forward Wald) identified predictors of the likelihood for specific treatment recommendations derived from CARATV2.0. $P < 0.05$ was considered statistically significant.

Results

Sample Characteristics

For the 393 patients reviewed (mean age 78.0 (± 7.0) years), 54.5% were male and 45.8% (n = 180) were aged ≥ 80 years (Table 1).

Treatment Recommendations

Eligibility for oral anticoagulants according to CARATV2.0

On application of the tool, 380 (96.7%) patients were deemed eligible for oral anticoagulants. Of the 13 patients deemed unsuitable for any oral anticoagulants, all had at least an intermediate stroke risk (as per $CHADS_2$, CHA_2DS_2-VASc) but with a high bleeding risk (as per $HEMORR_2HAGES$, HAS-BLED) (Table 1). Among the remaining 380 patients, 274 had no apparent contraindications to any oral anticoagulant and were, therefore, eligible for either warfarin or NOACs.

Scenario one: warfarin as first line therapy

Overall, 360 (91.6%) patients were recommended warfarin, 5 (1.3%) any NOAC (dabigatran or rivaroxaban or apixaban), 6 (1.5%) either rivaroxaban or apixaban, 9 (2.3%) apixaban only, and 13 (3.3%) were unsuitable for anticoagulants (Table 2, Figure 1).

Scenario two: NOACs as first line therapy

Overall, 279 (70.9%) patients were recommended any NOAC (dabigatran, rivaroxaban, or apixaban), 80 (20.4%) either rivaroxaban or apixaban (i.e., dabigatran contraindicated), and 9 (2.3 %) apixaban only (Figure 1). Twelve patients with renal impairment (9 unknown stage of chronic kidney disease (CKD), 1 severe CKD, 2 end-stage renal disease (ESRD)) were recommended warfarin. Thirteen (3.3%) were unsuitable for oral anticoagulants (Table 2).

Comparison with actual therapies received by the patients

The actual therapies received by patients, as prescribed by their general practitioners (GPs) at baseline, were warfarin (± aspirin) for 316 (80.4%) patients; aspirin only for 23 (5.9%) patients; dabigatran for 45 (11.4%) patients; clopidogrel for 3 (0.7%) patients; and nil therapy for 6 (1.6%) patients. Among the patients receiving aspirin and clopidogrel, 25 (96.2%) were deemed to be eligible for oral anticoagulants per CARATV2.0 (Figure 1).

More patients were recommended anticoagulants by CARATV2.0 than currently prescribed by GPs (96.7% versus 91.9%, P=0.004), while more patients were prescribed antiplatelets by GPs than recommended by CARATV2.0 (6.6% versus 0.0%, P<0.001).

Change in therapy

Overall, CARATV2.0 recommended the initiation of an anticoagulant in 30 (93.8%) of the 32 patients who were not currently receiving an anticoagulant (i.e., patients were currently prescribed aspirin only, clopidogrel only, or nil therapy).

Scenario one: warfarin as first line therapy

A total of 103 patients were recommended a change to their current antithrombotic therapy by CARATV2.0 (Table 3). Among those currently on nil therapy (n=6), 4 patients were recommended warfarin and 1 any NOAC (i.e., dabigatran or rivaroxaban or apixaban), whilst among those using antiplatelet therapy only (aspirin or clopidogrel only; n=26), 23 were recommended warfarin, whilst 2 were recommended rivaroxaban or apixaban. Among the 316 patients who were currently on warfarin, 16 (5.1%) were specifically recommended a change to alternative therapy by CARATV2.0 including:

any NOAC (n=4), rivaroxaban or apixaban (n=4), apixaban only (n=8); 10 were deemed unsuitable for any oral anticoagulant. The most common reasons for changing from warfarin to a NOAC included: documented warfarin allergy/adverse reaction (n=9 patients), a history of intracranial bleeding (n=5), and previous gastrointestinal (GI) bleeding/ulcer (n=8).

The only NOAC actually prescribed at the time of this study was dabigatran (n=45 patients, available via the sponsoring company's Product Familiarisation Program (20). Among these 45 patients, CARATV2.0 recommended warfarin therapy for 43 patients (95.6%) due to the lack of specific contraindications, apixaban in 1 patient due to a history of GI bleeding, and 1 patient was identified as unsuitable for any oral anticoagulants.

Scenario two: NOACs as first line therapy

A total of 385 patients were recommended a change to their current antithrombotic therapy by CARATV2.0 (Table 3). Among those currently on nil therapy (n=6), 1 patient was recommended warfarin, 3 any NOAC (i.e., dabigatran or rivaroxaban or apixaban) and 1 rivaroxaban or apixaban. Among those using antiplatelet therapy only (aspirin or clopidogrel only; n=26), 14 were recommended any NOAC, 10 rivaroxaban or apixaban, and 1 warfarin. Among the 316 patients who were currently on warfarin, 308 (97.7%) were specifically recommended a change to alternative therapy by CARATV2.0 including: any NOAC (n=228), rivaroxaban or apixaban (n=62), apixaban only (n=8); 10 were deemed unsuitable for any oral anticoagulants.

Among the patients who were actually prescribed a NOAC (n=45 patients (20), CARATV2.0 recommended a change to alternative therapy for 10 patients (22.2%), including warfarin for 2 patients due to end-stage renal disease (ESRD) (GFR <15 mL/min/1.73 m^2), apixaban for 1 patient due to a history of GI bleeding (rendering them potentially unsuitable candidates for dabigatran therapy and rivaroxaban therapy), rivaroxaban or apixaban in 7 due to a history of GI disease (rendering them potentially unsuitable candidates for dabigatran therapy), and 1 patient was identified as unsuitable for any oral anticoagulants.

Factors predicting suitability for oral anticoagulants

Following the re-distribution of therapy according to CARATV2.0 recommendations and exploring factors predicting that a patient is more suitable for NOACs than warfarin, univariate analysis identified that the likelihood of being recommended a NOAC over warfarin was 7.77 times higher in patients with a high risk of falls (previous fall) (95%CI=1.89-31.91, P=0.004), 3.73 times higher in patients with other GI diseases (95%CI=1.50-9.31, P=0.005) and 1.19 times higher in patients with increasing number of comorbidities (95%CI=1.02-1.39, P=0.03). In multivariate logistic analysis to identify factors affecting the likelihood of receiving a NOAC over warfarin, only a history of other GI diseases (adjusted OR=3.26, 95%CI=1.28-8.32, P=0.01) and a high risk of fall (previous fall) (adjusted OR=5.51, 95%CI=1.26-23.97, P=0.02) remained as significant predictors in the final model (Cox&Snell R square=0.03, Nagelkerke R square=0.09, 94.7% correctly predicted).

Discussion

In this study, we pre-tested a customised decision support tool (CARATV2.0) that considers both NOACs and warfarin as treatment options. Although previous studies have described tools that consider both stroke and bleeding risk for decision-making regarding antithrombotic therapy (8, 9), none have considered major issues relating to medication safety and medication management. Also, none of these tools, except the previous version of CARATV2.0 (6), have been shown to improve the use of antithrombotic therapy in actual clinical practice. Overall, this study has shown that CARATV2.0 has potential utility in the decision-making around the selection of antithrombotic therapy for AF patients. The proportion of patients prescribed anticoagulants was already very high compared to many international studies (21), likely due to increased awareness among clinicians, and improved information and education about using antithrombotic therapy in Australia. However, there is room to further optimise the utilisation of therapy in practice with more patients recommended an anticoagulant by CARATV2.0 than actually prescribed by GPs, and better rationalisation of therapies based on individual risk factors.

Stroke and bleeding risk assessment

Although it is recognised that the risk of ischemic stroke in the absence of anticoagulation is higher than the risk of bleeding from anticoagulant treatment in almost all AF patients (except those with low stroke risk or extremely high bleeding risk) (22), previous studies have shown that the fear of bleeding is the most influential factor for the underutilisation of oral anticoagulants (3, 4), especially in older patients (2). Therefore, both stroke risk and bleeding risk assessment schemes were integrated into

CARATV2.0 to assist the risk versus benefit assessment, and help to explicitly confirm that the risk of stroke outweighs the risk of bleeding in most patients.

Two stroke risk assessment schemes ($CHADS_2$ and CHA_2DS_2-VASc) and two bleeding risk assessment schemes (HAS-BLED $HEMORR_2HAGES$) have been incorporated in CARATV2.0 to achieve a higher sensitivity and specificity in the risk assessment. CHA_2DS_2-VASc possesses better specificity in identifying low-risk patients who genuinely do not need antithrombotic therapy, although some of the CHA_2DS_2-VASc intermediate-high risk patients may not need antithrombotic therapy either. $CHADS_2$, by contrast, has a better sensitivity in identifying low-risk patients and tends to stratify more patients as low risk, although some of the $CHADS_2$ low-risk patients may benefit from antithrombotic therapy (23). Regarding the bleeding risk assessment, HAS-BLED has shown poor discriminatory value in this study (identifying 98.7% patients as at intermediate to high bleeding risk with only 1.3% of population at low risk), but it has better sensitivity in identifying "any clinically relevant bleeding" in anticoagulated patients with AF (24). On the contrary, $HEMORR_2HAGES$ has a higher specificity (24) and identified only around half of the patients at intermediate to high bleeding risk compared with HAS-BLED.

Selection among anticoagulants: Scenario one

In scenario one, the treatment recommendations were aligned with the government review (5) and Australian Therapeutic Guidelines (17), which points out that none of the major NOACs randomised controlled trials (25-27) provides evidence to support the superiority of the NOACs over well-managed warfarin (time in therapeutic range

(TTR)>64%) (28). Since the Australian patients in the RE-LY and ARISTOTLE trials had a TTR of approximately 74% (5), the preference for therapy may be different in the Australian setting when warfarin can be well-controlled. However, in real-world practice, the TTR may fluctuate without appropriate monitoring and dosage adjustment, which can negatively affect the efficacy of warfarin. Therefore, it is important to ensure the regular monitoring and high TTR if warfarin is chosen for the patients.

The low proportion of patients specifically recommended a NOAC when warfarin was chosen as the first-line therapy is an important consideration in view of the concerns outlined in the Pharmaceutical Benefits Advisory Committee report (adverse events of NOACs e.g., major GI bleeding with the higher dose of dabigatran, major bleeding with rivaroxaban) (5). By February 2013, the Therapeutic Goods Administration (TGA) had reported 1,054 adverse events, including 361 serious bleeding events and 192 serious GI bleeding events. with dabigatran (29). As per CARATV2.0 (scenario one), most patients who were prescribed dabigatran were principally eligible for warfarin and it is these patients in whom the risk of GI bleeding can be minimised through careful treatment selection (HR=1.5, 95%CI 1.19-1.89) (30). Admittedly, the major GI bleeding associated with warfarin use could have been underreported as compared with dabigatran. According to a meta-analysis, dabigatran causes more GI bleeding than warfarin or other NOACs (OR=1.58, 95%CI, 1.29-1.93), whilst rivaroxaban reportedly causes more GI bleeding (OR=1.48, 95%CI, 1.21-1.82) than apixaban (OR=1.23, 95%CI, 0.56-2.73) (18). However, it is also important to note that the increased incidence of GI bleeding with dabigatran may be primarily driven by the use of the higher 150mg dose in those aged over 75 years (31). Since the lower (110mg) dose is

recommended for those aged 75 years and above in Australia, the risk of GI bleeding with dabigatran may be much lower.

Selection among oral anticoagulants: Scenario two

In scenario two, the treatment recommendations were aligned with international guidelines (10, 11), informed by those studies reporting that NOACs outperform warfarin in the risk reduction of both stroke and bleeding risk (32). Systematic reviews and meta-analyses have demonstrated the superiority of NOACs (as a class) over warfarin, in reducing- intracranial bleeding risk (OR=0.48, 95%CI 0.39-0.59) (32). However, the high-dose NOACs (except high-dose apixaban), although more effective in reducing the stroke risk than warfarin, are associated with increased GI bleeding (OR=1.25, 95%CI 1.01-1.55). In contrast, low-dose NOACs (recommended for elderly patients) have a similar risk of GI bleeding risk as warfarin, but are associated with a higher risk of ischemic stroke risk (32). Therefore, although the NOACs are suitable alternatives to warfarin in most patients, caution is needed in selecting among different NOACs and different dosages regimens, especially in older patients.

Factors predicting the suitability for oral anticoagulants

As reported in other studies (30), there is an increased GI bleeding risk in patients with GI diseases, and an increased the intracranial bleeding risk in patients with a high risk of falls. Also, a higher number of comorbidities is associated with more drug-drug interactions, and adverse drug events (ADRs) (e.g., bleeding), especially if the patient is on warfarin rather than NOACs. The predictors identified in this study show the

appropriateness of CARATV2.0 in selecting among different anticoagulants. This finding reinforces the need to regularly review a patient to identify changes in both bleeding and stroke risk with advancing age over time.

In considering the findings of this study, the limitations must be acknowledged. Being a retrospective study, it may not fully account for patient preferences for any of these therapies. Furthermore, this study was not designed to explore the cost-effectiveness of using different anticoagulants for two reasons. First, previous studies have identified that the key barriers to the optimal use of anticoagulants are prescribers' concerns about bleeding risk and medication safety issues (e.g., falls risk, medication adherence) in individual patients (3, 33), rather than treatment costs, and the CARATV2.0 was specifically developed to address these. Second, in Australia, the cost of the treatments plays a very limited role in the decision-making by clinicians, or in determining patient preferences, given that the Australian government subsidises the costs of the NOACs via its Pharmaceutical Benefits Scheme (PBS) (34). Therefore, the issue of cost-effectiveness is only relevant from the Australian health-system perspective (i.e., government health budget) (5). In taking a broader perspective regarding the cost-effectiveness of NOACs versus warfarin, international studies have reported that among the NOACs, high-dose dabigatran (150 mg twice daily) is a cost-effective alternative in terms of stroke prevention in patients with AF (35), however, this regimen comes at a 'clinical cost' in terms of a higher risk of bleeding, especially in older persons (36, 37). Compared to NOACs, the cost-effectiveness of warfarin increases as the quality of anticoagulation control improves (as measured by TTR) (38). Therefore, NOACs may not be cost-effective alternatives in all patients (such as older AF patients with well-controlled TTRs). Wider application of tools such as CARATV2.0 needs to consider the

specific health-systems where these treatment options are used. Third, CARATV2.0 was not designed to recommend the appropriate combination use of antiplatelet therapy with oral anticoagulants. However, increased bleeding risk with the use of antiplatelet is assessed in the bleeding risk assessment scheme (HEMORR$_2$HAGES). Finally, the study did not investigate whether CARATV2.0 performs better than clinicians' use of stroke risk schemes (CHADS$_2$ and CHA$_2$DS$_2$-VASc) and bleeding risk schemes (HEMORR$_2$HAGES and HAS-BLED) alone. The comparison with GPs' prescribing may not be reliable and the accuracy of CARATV2.0's recommendations depends on its modelling assumptions. Nevertheless, this study provides insights into the selection of antithrombotics in Australian clinical practice.

Conclusion

According to this decision support tool, both warfarin and NOACs appear to be viable treatment options in most patients, but there is scope for rationalising the selection of antithrombotic therapy for individual patients. Further study is needed to evaluate the impact of this tool on the use of antithrombotics and the outcomes of AF patients.

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Declaration of Conflicting Interests

None to declare.

Ethical approval

Ethical approval for the initial CARAT clinical trial study was obtained from the participating institutions (12).

The authors had full access to all of the data (including statistical reports and tables) pertaining to this study.

Table 1. Patient characteristics

Patient characteristics	Overall	% of total (N = 393)
Age (mean ±SD)	78.0 ± 7.0	
Age group		
< 80 years	213	54.2
≥ 80 years	180	45.8
Gender		
Male	214	54.5
Female	179	45.5
Current cardiac rhythm		
Normal sinus rhythm	45	11.5
Controlled AF	347	88.3
Uncontrolled AF	1	0.3
Type of AF		
Paroxysmal	139	35.4
Persistent	224	57.0
New onset	22	5.6
Unknown	8	2.0
$CHADS_2$ score:		
Low	27	6.9
Intermediate	88	22.4
High	278	70.7
CHA_2DS_2-VASc score:		
Intermediate	41	10.4
High	352	89.6
HAS-BLED score		
Low	5	1.3
Intermediate	341	86.7
High	47	12.0
$HEMORR_2HAGES$ score		
Low	187	46.7
Intermediate	193	49.1
High	13	3.3
Previous hospital admission for AF	135	36.6
History of AF		
< 1 year	49	12.5
≥ 1 year	344	87.5
History of cardio-version		
Not attempted	315	80.2
Direct current	78	19.8
Manager of antithrombotic therapy		
GP	336	85.5
GP + specialist	57	14.5
Medication safety issues		
Number of comorbidities (mean ±SD)	5.81 ±2.56	
Prior intracranial haemorrhage	5	1.4
Previous cerebrovascular accident	50	13.6
Prior gastrointestinal bleeding or ulcer	9	2.4
Other gastrointestinal disease†	91	24.6
Chronic kidney disease	17	1.6
Allergy/adverse reaction to warfarin	14	3.8
Prescription medications (mean ±SD)	9.21 ± 4.04	
Non-prescription medications (mean ±SD)	1.52 ±1.31	
Polypharmacy (≥ 4 kinds of drugs)	371	94.4
Poor medication adherence (39)	22	5.6
Cognitive impairment	18	4.6
Visual impairment	24	6.1
Hearing impairment	34	8.7
Language barrier	4	1.0
Previous history of falls	22	5.6
Mobility disorder	17	4.3
Residential facility (nursing home)	4	1.0
Difficulty accessing medical care	3	0.8
Needs assistance with medication	161	41.0

Note: AF = atrial fibrillation; † Includes gastroesophageal reflux disease, gastritis and other gastrointestinal diseases (except malignancy) without bleeding or ulcer.
Non-prescription medications: over-the-counter medications and supplements.
Poor medication adherence: Morisky score (4 items) ≥ 3 (39).
Needs assistance with medication: needs assistance with administration of medicines and/or daily management of the treatment (e.g. follow-up for blood tests, adherence to regimen).
Difficulty accessing medical care: patients do not have ready access to health/medical services due to geography (e.g. remote or rural area), poor mobility or lack of transport.

Table 2. Antithrombotic therapy recommended by CARATV2.0

Scenario one: warfarin as first line therapy					
Mean (SD) or *N* (% of row)	**Warfarin n = 360 [91.6]**	**Any NOAC n = 5 [1.3]**	**Rivaroxaban or Apixaban n = 6 [1.5]**	**Apixaban n = 9 [2.3]**	**Unsuitable for oral anticoagulants † n=13 [3.3]**
Age group					
< 80 years	195 [90.0]	2[1.0]	4[2.0]	8 [4.0]	4 [2.0]
≥ 80 years	165 [91.2]	3[1.8]	2[1.2]	1 [0.6]	9 [5.3]
P*	0.15				
P**	0.09				
$CHADS_2$ score:					
Low	26 [96.3]	0 [0.0]	0 [0.0]	1 [3.7]	0 [0.0]
Intermediate	83 [94.3]	0 [0.0]	0 [0.0]	3 [3.4]	2 [2.3]
High	251 [90.3]	5 [1.8]	6 [2.2]	5 [1.8]	11 [4.0]
P*	0.43				
P**	0.27				
CHA_2DS_2-VASc score:					
Intermediate	40 [97.6]	0 [0.0]	0 [0.0]	1 [2.4]	0 [0.0]
High	320 [90.9]	5 [1.4]	6[1.7]	8 [2.3]	13 [3.7]
P*	0.38				
P**	0.54				
HAS-BLED score					
Low	5 [100.0]	0[0.0]	0 [0.0]	0 [0.0]	0 [0.0]
Intermediate	324 [95.0]	4[1.2]	5 [1.5]	8 [2.3]	0 [0.0]
High	31 [66.0]	1[2.1]	1 [2.1]	1 [2.1]	13 [27.7]
P*	<0.001				
P**	0.51				
$HEMORR_2HAGES$ score					
Low	181 [96.8]	0 [0.0]	2 [1.1]	4 [2.1]	0 [0.0]
Intermediate	179 [92.7]	5 [2.6]	4 [2.1]	5 [2.6]	0 [0.0]
High	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	13 [100.0]
P*	<0.001				
P**	0.31				
Medication safety issues present					
Allergy/adverse reaction to warfarin (yes)	0 [0.0]	3 [21.4]	6 [42.9]	3 [21.4]	2 [14.3]
Cognitive impairment (yes)	17 [94.4]	0 [0.0]	0 [0.0]	0 [0.0]	1 [5.6]
Previous history of falls	8 [61.5]	1 [7.7]	2 [15.4]	0 [0.0]	2 [15.4]
Poor adherence (yes)	20 [90.5]	0 [0.0]	1 [4.5]	0 [0.0]	1 [4.5]
Scenario two: NOACs as first line therapy					
Mean (SD) or *N* (% of row)	**Warfarin n = 12 [3.1]**	**Any NOACs n = 279 [70.9]**	**Rivaroxaban or Apixaban n = 80 [20.4]**	**Apixaban n = 9 [2.3]**	**Unsuitable for oral anticoagulants † n=13 [3.3]**
Age group					
< 80 years	7 [3.5]	158 [72.2]	36 [18.2]	8 [4.0]	4 [2.0]
≥ 80 years	5 [2.9]	121 [65.5]	44 [25.7]	1 [0.6]	9 [5.3]
P*	0.86				
P**	0.65				
$CHADS_2$ score:					
Low	0 [0.0]	21 [77.8]	5 [18.5]	1 [3.7]	0 [0.0]
Intermediate	2 [2.3]	66 [75.0]	15 [17.0]	3 [3.4]	2 [2.3]
High	10 [3.6]	192 [69.1]	60 [21.6]	5 [1.8]	11 [4.0]
P*	0.38				
P**	0.56				
CHA_2DS_2-VASc score:					
Intermediate	0 [0.0]	34 [82.9]	6 [14.6]	1 [2.4]	0 [0.0]
High	12 [3.6]	245 [69.6]	74 [21.0]	8 [2.3]	13 [3.7]
P*	0.52				
P**	0.48				
HAS-BLED score					
Low	0 [0.0]	5 [100.0]	0 [0.0]	0 [0.0]	0 [0.0]
Intermediate	9 [2.6]	251 [73.6]	73 [21.4]	8 [2.3]	0 [0.0]
High	3 [6.4]	23 [48.9]	7 [14.9]	1 [2.1]	13 [27.7]
P*	<0.001				
P**	0.24				
$HEMORR_2HAGES$ score					
Low	5 [2.7]	146 [78.1]	32 [17.1]	4 [2.1]	0 [0.0]
Intermediate	7 [3.6]	133 [68.9]	48 [24.9]	5 [2.6]	0 [0.0]
High	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	13[100.0]
P*	<0.001				

P**	0.83				
Medication safety issues present					
Allergy/adverse reaction to warfarin (yes)	0 [0.0]	5 [35.7]	7 [50.0]	1 [7.1]	1 [7.1]
Cognitive impairment (yes)	0 [0.0]	9 [50.0]	8 [44.4]	0 [0.0]	1 [5.6]
Previous history of falls (yes)	0 [0.0]	4 [30.8]	7 [53.8]	0 [0.0]	2 [15.4]
Poor adherence (yes)	1 4.5]	16 [72.7]	4 [18.2]	0 [0.0]	1 [4.5]

†Unsuitable for oral anticoagulants: consideration should be given to addressing modifiable risk factors for bleeding, and/or using alternative agents (e.g. aspirin, clopidogrel) with specialist advice.

P*: patients deemed eligible for oral anticoagulants versus patients deemed unsuitable for oral anticoagulants by CARATV2.0.

P**: patients recommended warfarin versus patients recommended NOACs by CARATV2.0.

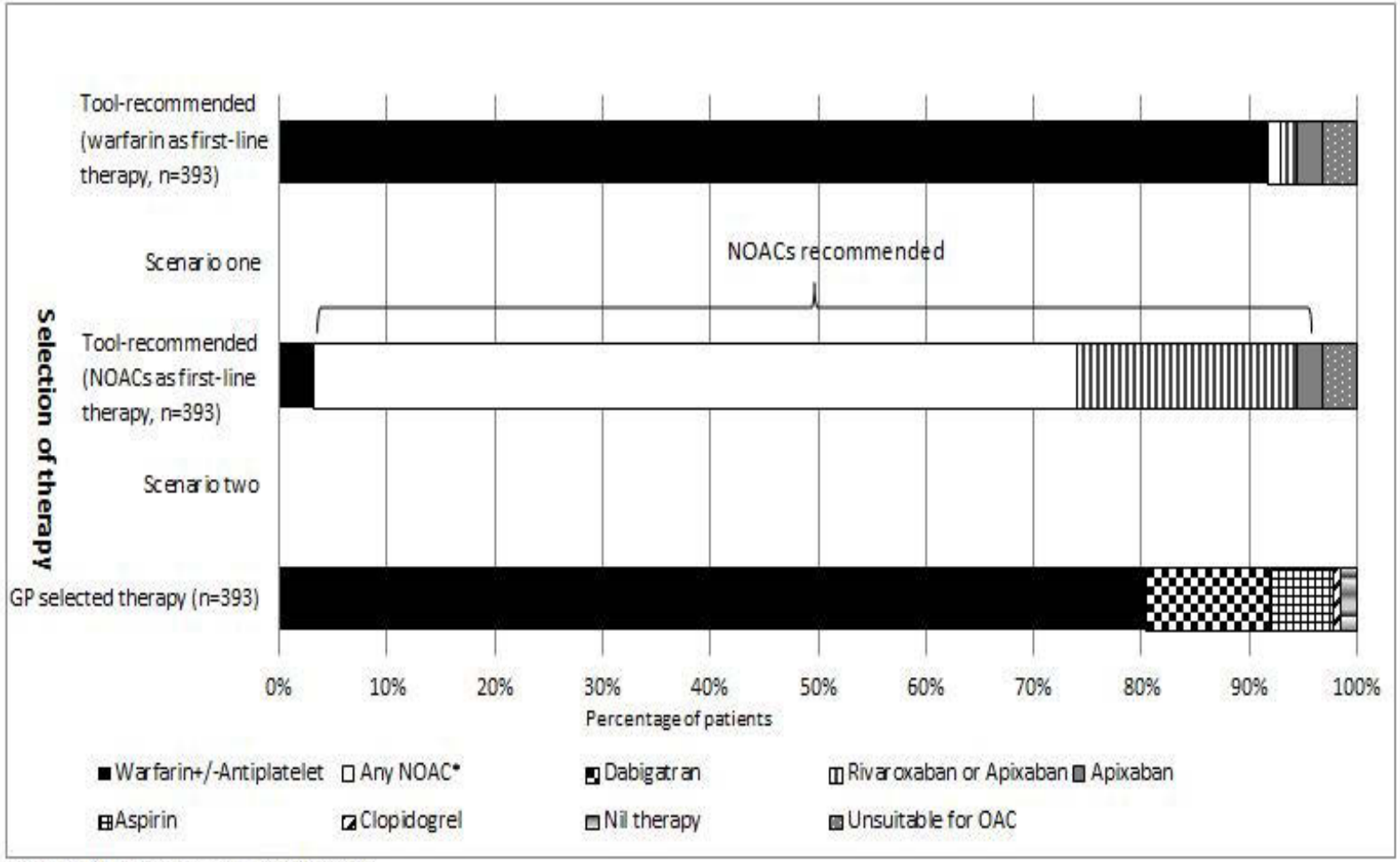
Table 3. Recommended change of anticoagulant by CARATV2.0

Patient number	Currently prescribed by general practitioners	Recommended by CARATV2.0 (warfarin as first line) Scenario one	Nature of recommended change in therapy*
4	Warfarin +/- aspirin	Rivaroxaban or Apixaban	sidestepping
10	Warfarin +/- aspirin	Unsuitable for oral anticoagulants †	N/A
4	Warfarin +/- aspirin	Rivaroxaban or Apixaban or Dabigatran	sidestepping
8	Warfarin +/- aspirin	Apixaban	sidestepping
20	Aspirin only	Warfarin	upgrade
1	Aspirin only	Unsuitable for oral anticoagulants	N/A
2	Aspirin only	Rivaroxaban or Apixaban	upgrade
3	Clopidogrel	Warfarin	upgrade
4	Nil	Warfarin	upgrade
1	Nil	Rivaroxaban or Apixaban or Dabigatran	upgrade
1	Nil	Unsuitable for oral anticoagulants	N/A
43	Dabigatran	Warfarin	sidestepping
1	Dabigatran	Apixaban	sidestepping
1	Dabigatran	Unsuitable for oral anticoagulants	N/A
Patient number	**Currently prescribed by general practitioners**	**Recommended by CARATV2.0 (NOACs as first line) Scenario two**	**Nature of recommended change in therapy***
1	Nil	Warfarin	upgrade
1	Nil	Rivaroxaban or Apixaban	upgrade
3	Nil	Rivaroxaban or Apixaban or Dabigatran	upgrade
1	Nil	Unsuitable for oral anticoagulants	N/A
8	Warfarin +/- aspirin	Apixaban	sidestepping
62	Warfarin +/- aspirin	Rivaroxaban or Apixaban	sidestepping
228	Warfarin +/- aspirin	Rivaroxaban or Apixaban or Dabigatran	sidestepping
10	Warfarin +/- aspirin	Unsuitable for oral anticoagulants	N/A
2	Dabigatran	Warfarin	sidestepping
1	Dabigatran	Apixaban	sidestepping
7	Dabigatran	Rivaroxaban or Apixaban	sidestepping
34	Dabigatran	Rivaroxaban or Apixaban or Dabigatran	sidestepping
1	Dabigatran	Unsuitable for oral anticoagulants	N/A
1	Aspirin only	Warfarin	upgrade
8	Aspirin only	Rivaroxaban or Apixaban	upgrade
13	Aspirin only	Rivaroxaban or Apixaban or Dabigatran	upgrade
1	Aspirin only	Unsuitable for oral anticoagulants	N/A
2	Clopidogrel	Rivaroxaban or Apixaban	upgrade
1	Clopidogrel	Rivaroxaban or Apixaban or Dabigatran	upgrade

*Upgrade means "Upgrades" to a more effective prophylactic therapy (i.e., from no therapy to any agent, or from aspirin to warfarin/dabigatran). Sidestepping means patients remain in the same level of treatment (i.e., from one anticoagulant to another anticoagulant, one antiplatelet to another antiplatelet).

† Unsuitable for oral anticoagulants: consideration should be given to addressing modifiable risk factors for bleeding, and/or using alternative agents (e.g., aspirin, clopidogrel) with specialist advice

Figure. 1 Recommendation of CARATV2.0 versus GP's selection



*include dabigatran, rivaroxaban and apixaban.

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Chapter Four

4.1 Selecting antithrombotic therapy for stroke prevention in atrial fibrillation (AF): health professionals' feedback on a decision support tool

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Abstract
A Computerised Antithrombotic Risk Assessment Tool was developed for assisting the selection of antithrombotic therapy based on the risk versus benefit assessment. In view of the recent availability of the novel oral anticoagulants, this tool has been updated to CARATV2.0. To explore health professionals' perspectives on the tool, semi-structured interviews were conducted in seven pharmacists, seven specialists

Supporting documents located in:
• Appendix I Data Collection Form
• Appendix II Participant Information Sheet
• Appendix III Participant Consent Form
• Appendix IV Flyers and Fax-back Form
• Appendix V Ethics Approval

Abstract

A Computerised Antithrombotic Risk Assessment Tool (CARAT) was developed for assisting the selection of antithrombotic therapy based on the risk versus benefit assessment. In view of the recent availability of the novel oral anticoagulants, this tool has been updated to CARATV2.0. To explore health professionals' perspectives on the tool, semi-structured interviews were conducted with seven pharmacists, seven specialists, six general practitioners and six nurses, who were involved in management of antithrombotic therapy for AF. Three overarching themes emerged: (1) CARATV2.0 provides comprehensive structured assessment of patients and could assist with the prescription and review of antithrombotic therapy; (2) subjective issues such as health professionals' and patients' preference for a particular antithrombotic therapy may affect the usefulness of CARATV2.0; (3) CARATV2.0 requires integration into existing systems and processes. Overall, the majority of health professionals surveyed would like to use CARATV2.0 in practice, believing it would improve antithrombotic use and might reduce stroke incidence.

Key words: decision making, computer-assisted, anticoagulant agents, atrial fibrillation, decision support

Introduction

The decision making around antithrombotic therapy (e.g. anticoagulant and antiplatelet therapy) in atrial fibrillation (AF) is complex because it involves assessment of risks versus benefits.(1) For many years warfarin was the only available oral anticoagulant, but its unpredictable therapeutic effects, various food and drug interactions, and the need for regular monitoring have been associated with great difficulties in its use. Such difficulties have led to a potential increase in adverse events and reluctance by clinicians to prescribe the medication.(2-4) The recently marketed novel oral anticoagulants (NOACs)—dabigatran, rivaroxaban and apixaban—have substantially expanded the treatment armamentarium and are intended to overcome the limitations of warfarin. However, these new anticoagulants are not without risk because some of their so-called advantages can be regarded as potential disadvantages in specific situations. (5)

To optimise the use of antithrombotic therapy in patients with AF, and specifically assist health professionals in selecting appropriate agents, an electronic decision support tool ─ the original Computerised Antithrombotic Risk Assessment Tool (CARAT) ─ was developed (6). Its decision-making algorithm was computerised by first preparing a prototype in Microsoft Excel™ and then formatting it as a web-based interface for online access (6). The tool generated treatment recommendations (e.g., warfarin versus aspirin therapy) for individual patients based on their risk (bleeding) versus benefit (stroke prevention) estimation, as well as the relevant medication safety considerations (e.g. drug–drug interactions, renal function, medication adherence). The original CARAT has been

trialed in real world hospital patients (7) and general practice patients (8), and evaluated by specialist clinicians for its potential clinical application in a vignette-based study (6). CARAT has demonstrated its potential utility in practice (6, 7). Although other risk assessment tools have been developed to synthesise the assessment of stroke and bleeding risks— for example, the clinical decision aid developed by LaHaye et al. (9) and the decision model developed by Casciano et al. (10) — none consider the broader medication safety issues that particularly affect the selection of therapy in the target at-risk patient population (9, 10). Thus, the CARAT provides a novel, more holistic, and pragmatic approach to the decision-making around antithrombotic therapy.

Our previous (i.e., original) version of CARAT was designed to address the complexity in decision-making by integrating the relevant assessments around stroke risk, bleeding risk, and medication safety for individual patients (6); at that time, the tool was able to assist in selecting among two main treatment options – warfarin and aspirin. Now that we have moved forward in time, there are additional issues to consider in the decision-making process which need to be factored into the CARAT. First, the expanded range of treatment options incorporating the NOACs (dabigatran, rivaroxaban and apixaban) has increased the number of parameters (e.g., drug-drug interactions, side-effects, doses and frequency of administration) that need to be considered, further complicating decision-making (11). Second, the range of risk assessment tools for stroke risk (e.g., $CHADS_2$, CHA_2DS_2VASc (12)) and bleeding risk (HAS-BLED (13), $HEMORR_2HAGES$ (14)) has evolved. Third, the evidence-base around the effectiveness and safety of available treatment options has grown; for example, aspirin is no longer recommended for stroke prevention in AF (15). Fourth, a

broader range of health professionals are now involved in therapeutic recommendations and decision-making around antithrombotics therapy, whereby hospital specialists and general practitioners (GPs) are able to draw upon the services of nurse practitioners (16) and consultant pharmacists (e.g., as part of the medicines review process (17)). Collectively, these issues have warranted a revision of the original CARAT, into its second version CARATV2.0, which considers the latest clinical evidence (e.g., guidelines (18-20), practice reviews (5, 21, 22)) and available treatments (warfarin and NOACs).

As an initial evaluation of this revised (prototype) CARATV2.0 tool, the aim of this study was to obtain feedback from a wide range of health professionals who are involved in the decision-making around antithrombotics in AF (specialist clinicians, general practitioners, nurses, pharmacists) , to help inform the future implementation of this tool in practice. Specific topics explored were the: (a) strengths and weaknesses of this tool; (b) appropriateness and relevance of the content of this tool; (c) usefulness of this tool for selecting appropriate antithrombotics, especially between warfarin and NOACs; (d) feasibility of using this tool in clinical practice; and (e) suggestions for further improvement.

Method:

Design and setting:

This qualitative study was based on face-to-face interviews. From August to October 2014, health professionals (subgroups: specialist clinicians, general practitioners, nurses,

pharmacists) practising in the Sydney metropolitan area were involved in this study (Figure 1).

Ethics approval for conducting this study was given by University of Technology Sydney (REF NO. 2013000338).

Participant recruitment:

Purposive sampling was used to identify and recruit health professionals with experience in prescribing antithrombotics and managing antithrombotic therapy for patients with AF (23). Specialist clinicians, hospital-based pharmacists and nurses were recruited via an invitational flyer emailed or faxed to the network of hospitals affiliated with the university. Community-based pharmacists accredited for Home Medicines Review were recruited through an emailed flyer (using contact details from the Australian Association of Consultant Pharmacy). Flyers were also emailed to community-based nurses in community health services affiliated with the university network of hospitals. By visiting family practices and medical centres in the Sydney metropolitan area, the researcher also distributed invitational flyers to general practitioners (GPs). Emails and faxes were also sent to GPs listed on the internet. Eligible health professionals who agreed to participate provided written consent.

An estimated 24–40 participants (6–10 participants per group) were needed to achieve theme saturation within each subgroup of health professionals (specialist clinicians, general practitioners, nurses, pharmacists) (23). As this tool was developed to support a broad range

of health professionals who are involved in the day-to-day management of older persons taking antithrombotics, in particular those who had previously expressed a need for assistance in decision-making (3, 24), the study largely focused on canvassing feedback from GPs, nurses, and pharmacists, in preference to experienced cardiologists. For this reason, relatively few cardiologists were recruited to this study.

Data collection:

Semi-structured interviews (20–30 minutes each) were conducted by the researcher at a location convenient to each participant. At the beginning of each interview, demographic data for each participant were collected using a predesigned questionnaire. Then, the researcher presented CARATV2.0 (on the researcher's laptop) to the participant. After this familiarisation with the tool, the participant was given the opportunity to explore CARATV2.0. Finally, the researcher used a set of open-ended questions to explore the participant's feedback on the content of the tool and the feasibility of using CARATV2.0 in clinical practice. All questions were pretested in mock individual interviews with nonparticipants.

Prototype of CARATV2.0

The underpinning algorithm of this revised tool has been developed as a Microsoft Excel™-based prototype for pretesting, with the intention of subsequently formatting the tool into an online (web-based) platform or mobile application that will enable the integration of this tool into prescribing software and/or electronic health data management

systems. The prototype comprises 4 distinct sections: (1) stroke risk assessment, i.e., $CHADS_2$ (25), CHA_2DS_2VASc (12); (2) bleeding risk assessment, i.e., HAS-BLED (13), $HEMORR_2HAGES$ (14); (3) medication safety issues, e.g., mini–mental state examination (26) for cognition, eGFR (MDRD and Cockcroft and Gault equations (27)) for renal function, Child-Pugh score (28) for liver function); (4) therapy recommendations and advice. The application of the tool requires the user to input relevant data into the cells, which auto-populates the formulae underpinning the decision-making algorithm, and which, in turn, generates a treatment recommendation. A patient is considered to be eligible for oral anticoagulants whenever the risk of stroke is equal to or more than the risk of bleeding, otherwise the patient is deemed to be unsuitable for oral anticoagulants. CARATV2.0 also provides initial advice around any identified medication safety issues which need to be addressed by the clinician. This study explores feedback on the data inputs and usability of CARATV2.0.

Data analysis:

The interviews were digitally recorded (audio) and transcribed verbatim by the researcher. The accuracy of the transcripts was confirmed by listening to the digital records and reviewing the transcripts. The transcripts were analysed for themes, using standard thematic analysis techniques (manual inductive coding).(29) The two authors independently reviewed the transcripts and identified themes before reaching a consensus through discussion. The accuracy and reliability of the analysis was confirmed by inter-researcher validation (with three other independent researchers).

Results

Overall, 26 participants comprising 7 specialist clinicians, 6 GPs, 7 pharmacists and 6 nurses were interviewed (Table 1). Similar themes were identified among the four subgroups, with three overarching themes emerging (Tables 2–4, Figure 1).

Theme 1: Need for comprehensive structured assessment of patients to assist with the prescription and review of antithrombotic therapy

The most highly appreciated feature of CARATV2.0 was that it provides comprehensive assessment of a patient's risk versus benefit of using antithrombotics. Perhaps more importantly, the ability of CARATV2.0 to provide guidance and assistance in selecting among oral anticoagulants, especially between warfarin and the NOACs, was highlighted by health professionals. Overall, health professionals considered this tool helpful in the decision making for antithrombotic therapy, and hoped that it could help reduce the incidence of strokes.

Specifically, many GPs and specialists felt that CARATV2.0 validated or organised their own decision-making process. Interested in using this tool for the prescription of antithrombotics, GPs and specialists tended to see the tool as most useful in those cases in which there are clinical dilemmas (i.e. where the risk versus benefit of using oral anticoagulants is not clear-cut). With regard to selection among oral anticoagulants, both GPs and specialists appreciated that the tool offered a specific recommendation among the oral anticoagulants (especially either warfarin or a NOAC). The doctors considered this

useful because they perceived that the differences in the benefits and risks of individual anticoagulant agents was not clear to many doctors. One GP mentioned that this tool could be useful for the initiation of therapy.

Similarly, the senior accredited and hospital-based pharmacists (with ≥ 40 years of experience) also stated that CARATV2.0 validated or organised their own decision-making process. In contrast, nurses and the junior accredited pharmacists felt that they could use this tool as a reference for their medication reviews and patient assessments, especially when choosing among oral anticoagulants. Pharmacists and nurses also emphasised that patients' risk factors associated with antithrombotic therapy were not static; therefore, they tended to see this tool as most useful for regular reviews of patients. This aspect of tool use seemed to be overlooked by the GPs and specialists.

Theme 2: Health professionals' and patients' preference for a particular antithrombotic therapy

Health professionals' opinions on CARATV2.0's recommendations were underpinned by whether they perceived the tool as preferring any particular antithrombotic therapy and whether this therapy was the one they preferred to use. While warfarin was preferred by the majority of health professionals, one neurologist, two haematologists, one GP and one nurse stated that they preferred using NOACs. Some pro-NOAC health professionals perceived that CARATV2.0 was biased towards warfarin and thus distrusted CARATV2.0's recommendation when it did not recommend their preferred therapy. Similarly, several pro-warfarin health professionals questioned and disliked CARATV2.0's

recommendations because it did not allow negotiation with their preference. Because patients were routinely referred to either GPs (in remote and regional areas) or specialists (in metropolitan areas) for the prescription of antithrombotic therapy, many health professionals believed that the usefulness of CARATV2.0 in improving antithrombotic selection would depend on whether the tool's recommendations are followed by the GPs and hospital doctors.

Some GPs believed that CARATV2.0 might be able to assist in negotiations with patients by providing evidence (e.g. stroke risk score) for explanations. However, one GP argued that CARATV2.0 could not help in persuading patients to take certain oral anticoagulants, because the negotiation to persuade or convince patients to take antithrombotic therapy involves managing individualised health expectations, rather than only presenting scientific evidence about this form of therapy.

Pharmacists' and nurses' perspectives on the usefulness of CARATV2.0 was largely determined by whether they thought this tool considered important issues in medication management when selecting antithrombotic therapy for individual patients. While pharmacists focused more on the medication safety issues (e.g. drug–drug interactions, adherence and international normalised ratio [INR]) when using this tool, nurses paid more attention to the tool's assessment of patients' capability to manage their medications (e.g. mobility, cognitive function, lifestyle). Although pharmacists and nurses believed that CARATV2.0 comprehensively assessed the major medication management issues, they also pointed out that CARATV2.0 did not consider every issue, for example, use of fish oil

supplements or binge drinking. But they also admitted that the selective inclusion of the most important medication management issues ensured the simplicity and ease of use of this tool.

Theme 3: Integration into existing systems and processes

Hospital-based health professionals (including specialists, nurses and pharmacists) and GPs suggested integration of CARATV2.0 into existing systems and processes due to the limited time available for making clinical decisions. Most hospital-based health professionals and GPs recommended that the tool's usefulness could be improved if it was integrated into or linked with electronic medical records or the electronic prescribing software used in hospitals and general practices. They recommended it be accessible through mobile phones, computers and tablets in order to self-populate the medical records and databases, and to make the tool easily accessible and portable. However, both GPs and hospital-based health professionals were worried that some of the practice computer software might not interact well with CARATV2.0. They were also concerned that some of the information required by CARATV2.0 might not be available in the electronic health system, which would mean that such information would require manual entering. To solve this problem, some suggested that pharmacists, junior medical residents, medical students or practice staff (e.g. nurses) could populate CARATV2.0 manually, allowing senior clinicians more time to review CARATV2.0's recommendations.

In contrast to hospital-based health professionals, the time needed for populating CARATV2.0 was not raised as a major issue by community-based pharmacists and

community-based nurses. Some of these practitioners actually thought that CARATV2.0 would save them time because it considers all the antithrombotics indicated for AF and integrates many relevant risk assessment tools into one tool. They paid more attention to how the tool's usability could be improved by incorporation into their medication review and patient assessment processes within an electronic format (e.g. 'apps', websites or software).

Discussion

The results from this study show that CARATV2.0 is generally welcomed by health professionals and that they consider it can potentially improve prescription of oral anticoagulants and clinical outcomes of patients. This is consistent with evidence that computerised decision support tools can significantly improve prescription among clinicians, and can improve the quality and safety of care provided.(30, 31) Although decision support tools that focus on the assessment of stroke and bleeding risk are widely available,(32) so far CARATV2.0 is the only tool that integrates stroke risk assessment, bleeding risk assessment and medication safety assessment, and that considers both the traditional antithrombotic agent, warfarin, and the NOACs.

Since decision making is an emotive process, comprehensive risk versus benefit assessment, systematic documentation, and communication of decisions can assist in the selection of optimal therapy for individual patients.(3) However, due to limited experience with use of the newly available NOACs, especially NOAC use in elderly patients, the risk versus benefit assessment of using oral anticoagulants in these, and other, patients is a complex

task for many health professionals. CARATV2.0's comprehensive risk versus benefit assessment of individual patients provides guidance and a reference for, and confidence in, not only the decision on whether a patient should be treated with antithrombotics, but also choosing the appropriate therapy among various oral anticoagulants. Furthermore, because CARATV2.0 is based on the latest clinical guidelines, the tool can also reinforce the use of clinical guidelines by health professionals.

The study found that subjective issues, including clinician and patient preferences for particular antithrombotic therapies, can have a substantial impact on the clinical decision-making process.(33) Studies have shown that clinicians tend to override recommendations made by a decision support tool if they have a strong preference for a particular medication.(34) Also, patients' preference of therapy has been reported to substantially affect the clinical decision making for therapy.(35) Although it is widely recognised that computerised decision support tools have the potential to improve the behaviour of clinicians in terms of prescription and consistency of decision making, evidence supporting the long-term impact of decision support tools on clinicians' prescribing behaviour is lacking.(36) Given these subjective issues, the impact of CARATV2.0 on decision making for antithrombotic therapy in AF needs to be further explored.

The suggestion of integrating CARATV2.0 into existing systems and processes shows that the health professionals valued the tool as an effective support for clinical decision making.(34) According to a systematic review by Kawamoto K et al., a successful decision support tool needs to be computer-based, to have automatic provision of decision support

as part of clinician workflow, to provide recommendations rather than just assessments, and to provide decision support at the time and location of decision making.(37) However, this suggestion also reflects that clinicians are reluctant to prioritise and allocate time for the initial decision making around antithrombotics, which contrasts with the time spent in managing the adverse outcomes of poor or suboptimal prescription. Also, 'pharmacotherapy' as an intervention follows a less structured decision-making process than other interventions such as surgery.

Some limitations of the study need to be acknowledged. The participating specialist clinicians, GPs, pharmacists and nurses in this study were volunteers who showed interest in the study. This could have biased their feedback on CARATV2.0. Also, the sampling strategy affects to some extent the generalisability of the study findings beyond these participants. Furthermore, CARATV2.0 inputs are based on available evidence from guidelines and reviews, which may not be relevant to all patient populations and may change over time as new evidence emerges. Since the findings from this research are restricted to the content and feasibility of this tool, the potential clinical and economic impact of the tool, and the feasibility of using the tool in real-world clinical practice require further evaluation.

Overall, the feedback from health professionals identifies that the only drawback of this tool is the time needed to complete the assessment (i.e., input the relevant data). To address this issue for future application in practice, CARATV2.0 may be integrated into other systems (e.g., electronic medical records) to enable the auto-population of patient data into

the tool. Furthermore, the tool may be used by other health professionals (e.g., nurse practitioners, consultant pharmacists) where comprehensive patient assessment and medication review are part of their targeted services (17, 38). .

Conclusion

CARATV2.0 was regarded by a variety of health professionals as a potentially useful tool that provided a systematic assessment around the decision making for antithrombotic therapy in patients with AF. The tool also shows potential for rationalising the use of antithrombotics and for improving the clinical outcomes of patients with AF. Future research should evaluate the impact of this tool on the prescription of antithrombotics in clinical practice. The main drawback of this prototype tool is that it requires the manual input of data, which may not be time-efficient for busy health professionals. Therefore, processes for the auto-population of the tool with relevant patient data need to be explored, for example, the integration of CARATV2.0 into electronic databases or prescribing software or/and re-formatting it into a mobile online application.

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Declaration of Conflicting Interests

None to declare.

Ethical approval

Ethics approval was given by University of Technology Sydney (UTS HREC REF NO. 2013000338).

Authors contribution

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Table 1 Participant Characteristics

Participant characteristics	Mean years of experience in managing patients with AF ±SD (range)	Mean number of patients with AF managed annually±SD (range) (self-reported)
Specialist clinicians (n=6) • 3 geriatricians • 2 haematologists • 1 cardiologist • 1 neurologist	23.4 ± 13.1 (5-40)	117.5 ± 109.3 (5-300)
General practitioners (n=6)	22.3 ± 10.1 (12-40)	21.5 ± 12.4 (4-35)
Pharmacists (n=7)* • 6 accredited pharmacists • 1 hospital pharmacist	20.4 ± 17.7 (5-50)	46.9 ± 39.4 (5-100)
Nurses (n=6) † • 3 nurse practitioners (NP) (2 cardiology, 1 neurology) • 3 clinical nurse consultants (neurology)	20.2 ± 9.5 (8-30)	145 ± 77.8 (100-300)

*All six accredited pharmacists (home medication review and/or residential medication management review) were community-based

†Among them, the two cardiology nurses were community-based, while the others were hospital-based.

Table 2. Theme 1: Need for comprehensive structured assessment of patients to assist with the prescription and review of antithrombotic therapy

General practitioners	Pharmacists	Nurses	Specialists clinicians
It (CARATV2.0) is very thorough. It has everything there that we should definitely take into account. When I see a patient … there may be aspects that I wouldn't have thought about that I should have thought about that wasn't there. So it is a very good tool that has everything on it. (G03) *You (CARATV2.0) have all renal liver function, gastrointestinal problem and other illnesses. You seem to cover everything that a good clinician would have to take into consideration anyway… As a doctor you think along these lines anyway, so all you (CARATV2.0) are doing is to put them into a chart or table or tool that gives you a visual and a check list, I suppose. (G05)* *The strength is that it is very important that as clinicians whether we still use the warfarin or the newer agents. I think if the prescribers have got a tool that would help them… Having it as a rigid module, I think it is a good idea. (G06)* *I can see it (CARATV2.0) would be useful for GPs that don't have access to a cardiologist… It is good for doctors who are not certain or don't have access to cardiologist … The new doctors love to have something like that, because it gives them the confidence to manage the patient and to be able to assess the patient to know what they should be doing. (G02)*	*I will definitely use it (CARATV2.0)… if I have a patient that I wasn't sure whether or not they should be on say warfarin…All of these criteria that you have got listed here, taken into account with the choices basically they will go. Ok this person had an event and he need to be on kind of anticoagulant. Ok then let's put him on warfarin. Maybe there are $CHADS_2$ score and HES-BLAD score… but they (CHADS2 score and HES-BLAD) are not looking at such comprehensive criteria, so this (CARATV2.0) is much more specific. (P02)* *The strength would be that it (CARATV2.0) considers all the factors of a patient which I usually consider when I am recommending an anticoagulant or checking what they are already taking, so I will look at the safety issues I look at the drugs that they are taking. I look at their actual medical condition as well so it has got all those things covered. And having that universal tool would be a big strength because as I said I can refer to a doctor what I am referring to.(P06)* *I think it (CARATV2.0) is good for pharmacist. It looks good to show this to doctor to say this is my recommendation. You have got something to back it up. So decision-making tool to back it up. (P04)* *Comprehensive. All the factors that I would consider starting someone on anticoagulant is in this tool.(P07)*	*I think that (CARATV2.0) offers a global assessment around anticoagulation not just simply risk stratification tool but a global assessment tool. It takes into consideration other factors that are above and beyond stroke and bleeding risk, such as adherence. (N01)* *… we might be in a situation especially with patients in nursing homes things like that. I would not feel confident without a pharmacist's recommendation, but with that tool (CARATV2.0) I can possibly. (N02)* *I think it (CARATV2.0) is good because one again it makes you look at the patient as a whole … It (CARATV2.0) brings in all those other factors like their cognition their function and those sorts of things. I think that gets forgotten when people are prescribing. They forget the whole patient … I think that is what is good about being able to select or being able to choose between warfarin and other OACs. (N05)* *I think it (CARATV2.0) is good because it would make you also think about things that you might not think about when prescribing these medications that you might forget about the drug interactions and things like that. (N06)*	*For me it (CARATV2.0) might be useful but I imagine that I would most likely be using it in patients where it is not certain either way. Like I probably wouldn't use it if it clear in my mind that there is high risk of stroke and low risk of bleeding … Whereas for patients who a bit equivocal then I may use this tool to help me choose one or the other. (S01)* *The benefit is that you (CARATV2.0) are assessing both the risk of stroke and the risk of haemorrhage, and you have also got some aged care risk factors in there, which a lot of other tools don't have. (S03)* *One of the first thing that is good is that if a doctor who has not treated many patients with AF is that by going through this (CARATV2.0) they see a lot to consider and it also makes them to think the patient a little bit more thoroughly. I think that is good… It is good that these scores ($CHADS_2$ and CHA_2DS_2-VASc, and HAS-BLED and $HEMORR_2HAGE$) are included and the scores are also given at the end. (S05)* *All the components (in CARATV2.0) are the same as the experienced clinicians would use and make a judgement about whether to use or not to use anticoagulant therapy. So the use of CHA_2DS_2-VASc and HAS-BLED scores, the differentiation between warfarin and NOACs are all quite appropriate. (S04)*

$CHADS_2$: congestive heart failure, hypertension, age =75 years, diabetes mellitus, stroke. CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75, diabetes, prior stroke or transient ischaemic attack, vascular disease, age 65–74, and sex. $HEMORR_2HAGE$: hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, re-bleeding, hypertension, anaemia, genetic factors, excessive fall risk and stroke. HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol.

Table 3. Theme 2: Health professionals' and patients' preference for a particular antithrombotic therapy

General practitioners	Pharmacists	Nurses	Specialists clinicians
I think traditionally that people with high risk score of $CHADS_2$ should be a candidate to warfarin. That is the decision that I always made, so I would need be shown why I should be changing my decision. Why somebody might not be given warfarin but given NOACs instead. (G01) *My only concern is that I am always very aware of warfarin, so if it (CARATV2.0) does recommend warfarin I may not take the recommendation, I would have to looking closely to see why it recommends warfarin instead of NOACs. (G03)* *The difficulty is to negotiate with the patients about their degree of risk. The meaning behind not being on an anticoagulant. What it would mean in terms of follow-up for it to be safe, if they are on anticoagulant. And the management around that… A lot of patient, where warfarin is appropriate have bad stories. Maybe the parents have been on it or the relatives, then they had a bleeding and regular blood test. So for lots of GPs, to address these issues is in fact the main task… So to manage the people´s expectation of health is the most important part of the consultation about anticoagulants. So I suppose with this tool it is really more about the technical decision. (G04)* *One of the difficulties in general practice is the cardiologist does something different from what you do. That becomes quite complicated, because I have been quite surprised that some of my patients are under cardiology care who are not on medication.(G02)*	*Well, you (CARATV2.0) have got all these you have listed all possible risk factors. As much as you can, of course sometimes these risk factors might vary or might be severe than in other situations. Like anaemia for instance, that might not be present might later be present. So it is just you would have to constantly measure these from time to time. (P03)* *Because some people do not like to go to their doctor to get the blood check, I don´t think it (CARATV2.0) addresses this problem, but otherwise it is pretty good.(P04)* *It is good tool. A lot depends on the patient… the doctor may evaluate the patient according to this tool. But the outcome does not depend on that they recommend warfarin or NOACs, it really depends on the patient´s cognitive function. Because sometimes, they (patients) don´t understand this situation very well and they don´t know how to ask questions. And even Webster pack is not always suitable. (P05)* *If there is an option to include all the drugs that the patient is on or if they want to do a little drug interactions…put the drug that they (patients) are on you might come up with some extra interactions. But that is probably going take away the simpleness of this tool, which is a big plus to it. So obviously it (CARATV2.0) is very very good but there still be a few little drugs that might interact that might be missed. (P06)*	*I think the nurses have limited input into choices and decision-makings. I think the decision of anticoagulant actually come from the cardiologist in the end. Nurses may fill it (CARATV2.0) in and the pharmacist can fill it in. Is cardiologist going to look at it and follow? …I think still a lot of clinicians are hesitant to use NOACs …if you have cardiologist who have been using warfarin for the last 40 yrs and why they are going to change to NOACs? No. If they have someone who is on warfarin and adherent why change it… So it (CARATV2.0) doesn´t really consider the clinicians preference…Well it is nice to give a recommendation based on international guidelines validated risk assessment tools, I think it doesn´t consider the clinicians previous experience of the agents and that is going to influence their decision-making. But I think this is still useful tool. (N01)* *I think it is good that it (CARATV2.0) makes you think about other things from a nursing point of view. I think it makes you think very much the cognition the falls risk visual deficit…that is good. Because all these things can be difficult for patients to actually overcome. So by taking that into consideration I think that is good…I like that. (N04)* *I think that is what is good about being able to select or being able to choose between warfarin and the NOACs. Because warfarin is a really hard medication to manage whether we can actually say this patient would definitely benefit from one the NOACs, because of their cognition bla bla then I think this tool is helpful in that respect. (N05)*	*I do not believe you should use warfarin as first line. It is a choice and some patients who we would prefer them to be on warfarin typically with renal impairment and maybe noncompliance. And certainly people who are well established on warfarin, they do not need to switch them. But for anyone who is new, I do not see there is any justification for saying warfarin first and then the new drugs. (S06)* *The other thing that I am not totally convinced by it yet, is whether there is enough data in older patients for the NOACs. That is the other thing that I am not sure about given that they have been safety signals for things like gastrointestinal bleeding. You know I probably want more data in older patients. (S01)* *One of the clinical concerns that we all face now with the NOACs is what happen to people who are elderly and who are around NOACs because of AF and happened to get gastrointestinal disturbance get diarrhea, vomiting, dehydration, renal impairment. And suddenly get an eGFR that drops down to 30 and they are on a NOACs. Unless they are aware of the risk. They are going to have increased risk of bleeding. So I think as an educational tool it is useful and that is going to be one of the main clinical concerns that I have in the use of NOACs. (S04)*

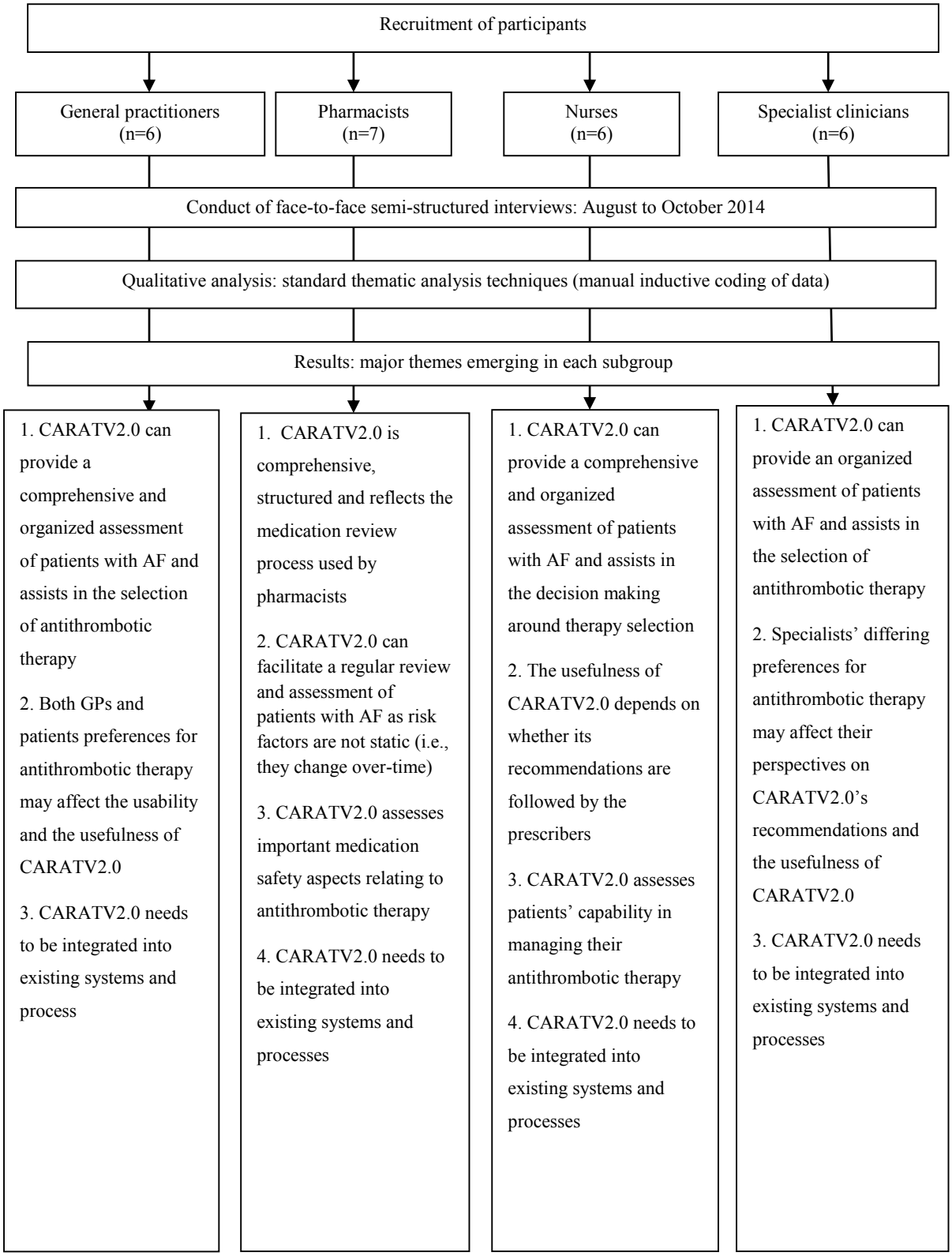
NOACs: novel Oral Anticoagulants. eGFR: Estimated Glomerular Filtration Rate

Table 4. Theme 3: Integration into existing systems and processes

General practitioners	Pharmacists	Nurses	Specialists clinicians
I think if you can incorporate it (CARATV2.0) into the (practice) software and the software would populate as much as the data from our file as much as possible that would be very good. (G03) *The weakness will be if this tool is not in cooperated in the practice software, so it must be integrated. Because it would be very difficult for a doctor to go somewhere else or another website. It is going be there as you are prescribing and also in a hospital situation it has to be accessible. So you know in the patient's file it is going to be part of that medical record and accessible to people. (G06)* *I think if you can incorporate it (CARATV2.0) into the software and the software would populate as much as the data from our file as much as possible that would be very good. Also, we have got a chronic disease nurse, and she could administer it and fill the answer then that could also make it quite easier for us.(G02)*	*If you are doing a medication review, you look at the pathology first before you went out... It will be better your renal function and liver function altogether, because that will be the pathology that the patients wouldn't know those answers. So it will be better if they are together at the beginning or at the end (of CARATV2.0)... I think it (CARATV2.0) will work really well within HMR or RMMR ... mean a lot of questions you going to ask anyway. (P01)* *I usually not initiating treatment, so in my practice it would be basically just check what the patient is taking is best for them. And particularly if they are recently being changed or initiated a drug, I will be checking that it is the right drug that they should be on. So for me it (CARATV2.0) is a good checking mechanism.(P06)* *I think it is good as well. In a community would be useful. For annual review or something, they (patients) can not reach therapeutic level they have a labile INR... using this tool to determine whether warfarin still the therapeutic choice for this patient or not. (P07)*	*I think the mobility thing is important to have. Like to have it (CARATV2.0) with the patient. Like explaining to the patient about the things. And have it portable not on a desktop. I guess there is access issues around if it is something like internet based.(N01)* *Maybe you can get an app. If you can get it (CARATV2.0) into an app, maybe everyone would use it because it would be easy to carry around and ask patients questions. (N06)* *I think that (integration into electronic health system) will be useful. Because there is a lot of things there that you don't need to do it again ... A lot of that stuff whether the patient has AF or not could then go into that system. (N05)*	*I think easy to use is the main thing. If you do turn it (CARATV2.0) into an app make it simple to enter things so you don't have to enter a lot of text more than that you have tick box to make it bit easier. Might be useful to have section of patient information, so you know based on this tool your doctor has recommended XYZ, these are precaution whenever using this agent is. So if you use a website or something that it can generate patient information sheet.(S01)* *I think we probably need it (CARATV2.0) as an app and need it to be electronic and need to be touch screen if we can have that. And then we just need to practice. (S03)* *It (CARATV2.0) will be much more acceptable on an app... Because you can just have it in your phone and download the things and much quicker than finding a computer and calling it up in computer and excel file to type it in for me. (S02)*

HMR: Home Medicines Review. RMMR: Residential Medication Management Review

Figure 1: Key stages in eliciting feedback from health professionals about the decision-support tool



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Chapter Five

5.1 Decision-making around antithrombotics for stroke prevention in atrial fibrillation: the health professionals' views

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RESEARCH ARTICLE

Decision-making around antithrombotics for stroke prevention in atrial fibrillation: the health professionals' views

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Abstract *Background* For stroke prevention in patients with atrial fibrillation (AF), the decision-making around antithrombotic therapy has been complicated by older age, multiple comorbidities, polypharmacy and the different pharmacological properties of warfarin and the nonvitamin K antagonist oral anticoagulants (NOACs). The complexity of decision-making has been associated with a reluctance by health professionals to use antithrombotic therapy, leading to poor clinical outcomes. In order to improve

themes emerged. (1) Comprehensive assessment is necessary for decision-making but is not always implemented. Health professionals mostly focused on stroke risk assessment, not on the bleeding risk and medication safety issues. (2) Health professionals from different disciplines have different preferences for antithrombotic therapies. Although the majority of health professionals considered warfarin as the first-line therapy, NOACs were preferred by neurologists and haematologists. (3) Health professionals

Supporting documents located in:
• Appendix I Data Collection Form
• Appendix II Participant Information Sheet
• Appendix III Participant Consent Form
• Appendix IV Flyers and Fax-back Form
• Appendix V Ethics Approval

Abstract

Background

For stroke prevention in patients with atrial fibrillation (AF), the decision-making around antithrombotic therapy has been complicated by older age, multiple comorbidities, polypharmacy and the different pharmacological properties of warfarin and the non-vitamin K antagonist oral anticoagulants (NOACs). The complexity of decision-making has been associated with a reluctance by health professionals to use antithrombotic therapy, leading to poor clinical outcomes. In order to improve stroke prevention in patients with AF, the contemporary perspectives of health professionals on the decision-making around antithrombotic therapy needs exploration.

Objective

To elicit emerging themes describing health professionals' perspectives on the decision-making around antithrombotic therapy for stroke prevention in patients with AF.

Setting

Sydney metropolitan area of New South Wales, Australia.

Method

A qualitative study based on face-to-face interviews was conducted from August to October 2014. Seven pharmacists, seven specialists, six general practitioners and six nurses practising in the Sydney metropolitan area and managing antithrombotic therapy for AF were interviewed until theme saturation was achieved in each subgroup. Interview transcripts were analysed using manual inductive coding.

Main outcome measure

Emerging themes describing health professionals' perspectives on the decision-making around antithrombotic therapy for stroke prevention in patients with AF.

Results

Three overarching themes emerged. (1) Comprehensive assessment is necessary for decision-making but is not always implemented. Health professionals mostly focused on stroke risk assessment, not on the bleeding risk and medication safety issues. (2) Health professionals from different disciplines have different preferences for antithrombotic therapies. Although the majority of health professionals considered warfarin as the first-line therapy, NOACs were preferred by neurologists and haematologists. (3) Health professionals focused on different aspects of the decision-making process: GPs and specialists were concerned about the appropriate prescription of antithrombotics, while pharmacists and nurses focused on daily medication management by patients.

Conclusion

The decision-making process appears to be partially preference based rather than systematic, and health professionals from various disciplines focus on different parts of the decision-making process.

Introduction

Preventing strokes in patients with atrial fibrillation (AF) relies on the use of antithrombotic therapy (1). However, for patients with AF, the decision-making around treatment selection has been complicated by their (generally) older age and multiple comorbidities, the polypharmacy used by many patients, and the unpredictable therapeutic effects of the traditional oral anticoagulant, warfarin. The complexity of decision-making underpins the well-reported suboptimal use of antithrombotics in practice (2, 3).

Recently, three non-vitamin K antagonist oral anticoagulants (NOACs) - dabigatran, rivaroxaban, apixaban - were marketed in various countries for clinical use, as alternatives to warfarin. Although these novel agents overcome some of the limitations of traditional anticoagulants, they are not without risk. In contrast to warfarin, most NOACs need dosage adjustment in renal impairment, are contraindicated in severe liver impairment and, to date, only dabigatran has a specific antidote available for reversal of its anticoagulant effects (4, 5). Aside from the clinical differences, the NOACs are significantly more expensive (in terms of absolute drug costs) than warfarin, impacting on prescribers' decisions and on patient preferences for treatments (6, 7). Fortunately in countries such as Australia the costs of treatment play a limited role in decision-making because subsidy schemes (e.g., Pharmaceutical Benefit Scheme (PBS) (8)) make high-cost medication affordably accessible. In this regard, the cost of treatment becomes largely an issue for the health-system (i.e., the government's health-budget), and this may underpin initial recommendations to restrict access to certain treatments (9). Indeed, in Australia, a

government review has recommended that the use of NOACs is rationalised, such that warfarin is considered a first-line therapy in those who are able to take it, reserving NOACs as an alternative for those unable to use warfarin (9). Collectively, the above issues make decision-making around the selection of anticoagulant therapy challenging.

Historically, guidelines have emphasised the benefits of stroke prevention (10, 11), while health professionals have been more concerned about the risks (e.g. bleeding) (12). Currently, both international and Australian guidelines give consideration to the risk of bleeding and anticoagulant control (e.g. time in therapeutic range) in addition to the benefit of therapy in terms of stroke prevention (13-15). However, in practice, the decision-making by clinicians tends to focus on the risks (16).

Currently, the use of antithrombotics remains suboptimal, despite the availability of both NOACs and warfarin as treatment options (17). Furthermore, some health professionals are concerned about the safety of NOACs (especially in elderly patients), while others advocate the benefits of NOACs and prefer to use them rather than other antithrombotics for most patients (18, 19). Globally, disparity also exists among recommendations for therapy selection in clinical guidelines. Some international guidelines, particularly those of the European Society of Cardiology (2012) and the European Heart Rhythm Association (2015), recommend the use of NOACs rather than warfarin (14, 18). In contrast, Australian guidelines, for example, the National Prescribing Service guidelines (2013) (20), the Therapeutic Guidelines (2012) (13) and an Australian Government Review (2012) (9) recommend warfarin as the first-line therapy and NOACs as second-line therapy.

In prescribing antithrombotics, current practice often involves initiation of therapy in the acute care setting (hospital) by specialists, with long-term management provided by general practitioners (GPs), nurses and pharmacists. Therefore, to optimise the use of antithrombotics, health professionals' perspectives on the decision-making around antithrombotics should be explored, especially their perspectives on using NOACs and warfarin.

Aim of the study

The aim of this study was to explore health professionals' perspectives on the use of antithrombotic therapy for stroke prevention in patients with AF. Specific objectives were to explore (a) how health professionals make decisions to use antithrombotics in patients, (b) how they select from the range of antithrombotic therapies (e.g. selecting between warfarin and NOACs), and (c) their primary focus in the decision-making process.

Ethical approval

Ethics approval for conducting this study was obtained from the University of Technology Sydney (UTS) (REF NO. 2013000338).

Method

Design and setting:

This was a qualitative study based on face-to-face interviews concluded between August and October 2014. Health professionals practising in the Sydney metropolitan area were invited to participate [subgroups: specialist clinicians (S), general practitioners (G), nurses (N) and pharmacists (P)]. The data were collected as a part of a larger study canvassing health professionals' feedback on a decision support tool designed for antithrombotic risk assessment (21).

Participant recruitment:

Using purposive sampling, only health professionals with experience in prescribing and managing antithrombotics for stroke prevention in AF were recruited. Specialist clinicians, hospital-based pharmacists and nurses were recruited by voluntary response to invitational flyers sent through email or fax within the UTS network of hospitals. Flyers were also emailed to community-based pharmacists accredited for Home Medicines Review (publicly listed email addresses obtained from the Australian Association of Consultant Pharmacy) and to community-based nurses in community health services affiliated with the university network of hospitals. The researcher visited family practices and medical centres in the Sydney metropolitan area to distribute flyers to GPs, and sent flyers via email or fax to GPs or general practices listed on the internet. Written consent was sought from eligible participants.

To achieve theme saturation within each subgroup of health professionals, an estimated 24–40 participants overall (6–10 participants for each subgroup) were needed (22).

Data collection:

Semi-structured, face-to-face interviews (20–30 minutes each) were conducted by the researcher at a location convenient to each participant. Using a predesigned interview guide and questionnaire, demographic information on participants was collected before each interview. The researcher interviewed participants with open-ended questions about their perspectives on decision-making around antithrombotics for stroke prevention in patients with AF. All questions were pretested in mock individual interviews with nonparticipants. Interviews were conducted until theme saturation was achieved within each subgroup.

Data analysis:

The audiotaped interviews were transcribed verbatim by the researcher. The transcripts were compared with the recordings to ensure accuracy and then manually coded by the two authors independently, using standard thematic analysis techniques (22). The two authors reached a consensus through discussion, after independently reviewing the transcripts and identifying relevant themes. Three other independent researchers validated the accuracy of the analysis.

Results

Overall, 26 health professionals were interviewed, including 7 specialist clinicians, 6 GPs, 7 pharmacists and 6 nurses (Table 1). Similar themes were identified among the four subgroups, with three overarching themes emerging (Tables 2–5).

Theme 1: Comprehensive assessment is necessary for the decision-making but not always implemented

According to the majority of health professionals**,** the decision-making around antithrombotics is complex. Therefore, they indicated that the decision-making should include comprehensive assessment of patients' stroke risk, bleeding risk and medication management issues (e.g. adherence, cognitive function, renal function, drug interactions).

> If you are going to [be] prescribing it and you haven't documented that you have gone through all that (stroke, bleeding risk and medication safety), if something happens and they have a big GI [gastrointestinal] bleed, or the patient dies and you have been shown to prescribe the medication for which you haven't made adequate risk assessment, I would imagine you would be liable the same as we [are when] prescribing anything. (G05)

Any tools or assistance that could help with this comprehensive assessment were considered beneficial by health professionals: they perceived that sometimes health professionals were unconfident in using oral anticoagulants, especially NOACs. They also noted that practitioners had limited access to specialists for advice if they worked in regional and remote areas.

However, the real-world implementation of this comprehensive assessment was not ideal. Compared with stroke risk assessment, bleeding risk assessment was seldom raised by the health professionals as an important step in their own decision-making process. Two GPs

and two haematologists revealed that many GPs and hospital doctors usually only consider stroke risk assessment (using for example, $CHADS_2$ and/or CHA_2DS_2-VASc) in the decision-making around antithrombotic therapy. Moreover, they indicated that sometimes GPs and hospital doctors did not even use $CHADS_2$ or CHA_2DS_2-VASc due to the time pressure in clinical practice, a lack of awareness of stroke risk in patients with AF, or routine referral to cardiologists. Furthermore, the haematologists considered assessment of bleeding risk unnecessary because they said it would not affect their choice of therapy.

> Cardiologists do these scores (CHA_2DS_2-VASc and HAS-BLED) routinely, but they've got them on their phones and they do that every day. But that is all they do. They just do the CHA_2DS_2-VASc and HAS-BLED and that is all they do. If we are lucky, they may think about eGFR and creatinine clearance, but that is it. (S06)

In contrast to GPs and specialists, pharmacists and nurses frequently stressed the necessity of considering medication safety and management issues (e.g. patients' cognitive function, drug interactions, adherence) as an important part of the decision-making process. The NOACs are relatively new treatment options (there is limited evidence about safety considerations) and patients' risk factors around antithrombotic therapy are not static. Thus, the pharmacists and nurses considered that medication safety and management issues should be an important part of the decision-making process in order to reduce the risk of medication misadventure (e.g. adverse events, drug interactions).

> So I would work out my CHA_2DS_2-VASc, creatinine clearance and other things in different tools. And, like, patient history is just talking to [the] patient—that is

> something that are (*sic*) separate completely … All those factors together, to me, [I] would base my decision on whether or not I would recommend anticoagulation for a patient or not. (P07)

Theme 2: Health professionals have their own preferences for antithrombotic therapy

The majority of health professionals preferred warfarin to NOACs for antithrombotic therapy, with two pharmacists (accredited) and two GPs expressing a strong preference for using warfarin as first-line therapy. To explain the reasons for their preference, the two GPs stressed that warfarin was recommended by specific guidelines as the first-line therapy and that clinicians had long-term experience with warfarin. The two pharmacists stressed that clinicians' long-term experience with warfarin, together with the regular monitoring requirement for warfarin therapy, could help to ensure the regular review of patients and thus increase the safety of the therapy.

> I was always pro-warfarin; like, I am quite keen to use warfarin in non-valvular AF, because I tend to think it is the best way of preventing stroke. And I have not been using many of the new drugs, partly for the fact that they are new and I am nervous about … I am worried about the lack of reversibility, for example, [with] the NOACs. (G01)

Among specialist clinicians, geriatricians and cardiologists were very concerned about the risk of using NOACs in very elderly patients due to the limited data and the risk of acute renal impairment, and also because there were no antidotes for NOACs at the time of the interviews.

> The other thing that I am not totally convinced [about] … is whether there is enough data in older patients for the NOACs. That is the other thing that I am not sure about, given that they have been safety signals for things like gastrointestinal bleeding. (S01)

The other pro-warfarin health professionals were either uncertain about the efficacy and bleeding risks of NOACs compared with the risks associated with warfarin, or followed specific guidelines and information from continuing medical education that favoured warfarin.

Compared with cardiologists and geriatricians, who were cautious about using NOACs, a neurologist and the haematologists had strong opinions about using NOACs as first-line therapy. To explain the reasons for their preference, they cited different evidence (including clinical guidelines, clinical trials and clinical registry data) that supported the better efficacy and safety of NOACs compared with warfarin. They also highlighted the poor international normalised ratio (INR) control in patients on warfarin. One GP and one neurology nurse also preferred NOACs. For them, the convenience of NOACs (fixed daily dosage, no need for regular blood tests) and the fluctuation of the INR in patients on warfarin therapy were the reasons for preferring NOACs. Pro-NOAC clinicians, although recognising that NOACs pose a high bleeding risk in patients with severe renal impairment, argued that NOACs should be the first-line treatment, or at least that NOAC and warfarin therapy should be equally considered for most patients.

> We would give the patients NOACs unless they are not suitable, usually with [a] renal problem … Otherwise, we would give them NOACs … If a patient has a reduced renal

problem, then you can consider 110 mg dabigatran or apixaban 2.5 mg, which can go to a creatinine clearance of 30. It might be if the patient has ischaemic heart disease, rivaroxaban might be of more benefit … if it [is] not suitable, then we consider warfarin. (S05)

In addition, many health professionals, especially GPs and nurses, stressed that the preferences of patients substantially influenced decision-making around antithrombotic therapy. According to some, patients were fearful of warfarin therapy due to their own previous negative experiences (e.g. bleeding, regular need for INR tests), or because of negative stories about warfarin therapy relayed by relatives, friends or the media. Therefore, these health professionals perceived that the advantages of NOACs (e.g. no monitoring and fewer dietary restrictions) had caused patients to be somewhat pro-NOACs. This therapy preference among patients presented a challenge to health professionals, especially to GPs. Some GPs stressed that they often had to negotiate with and convince patients to take warfarin; they considered these interactions more difficult than the technical decision-making around the therapy.

Theme 3: Health professionals focused on different aspects of the decision-making process

The different focus of the four subgroups of health professionals might be explained by their roles in clinical practice. Specialists and GPs were more concerned about the prescription of antithrombotics, because they believed that the clinical outcomes substantially depended on the therapy chosen. Both GPs and specialists highlighted

significant under-treatment with antithrombotic therapy in patients with AF, especially elderly patients with AF, in general practice. The GPs and specialists believed that possible reasons for this underuse of antithrombotic therapy were (a) the significant proportion of patients in whom AF remains undiagnosed, (b) the waiting time before seeing a specialist (cardiologist), (c) the limited experience and knowledge of some primary care prescribers (GPs) in managing patients with AF (e.g. selecting appropriate antithrombotic therapy), (d) prescribers' fear of patients having adverse drug events (e.g. bleeding), and (e) some patients' preferences for or fear of antithrombotics. The prescribers' fear of using antithrombotics was considered unjustifiable by some GPs and specialists: they emphasised that the bleeding risk can be managed and that the risk of bleeding with oral anticoagulants is much lower than the risk of patients without anticoagulants having a stroke.

> There are still many patients with AF who are not on [an] oral anticoagulant who should be on [one], and there are many who are on aspirin [and the doctor] think[s] it is an appropriate therapy, which evidence now suggests that it is not … there is still under-prescription in AF. (S04)

Furthermore, the perceived inconsistencies in antithrombotic decision-making among GPs, between GPs and specialists, and between urban and rural areas were raised by some GPs as an issue in antithrombotic use. Since patients are routinely referred to cardiologists for the decision to initiate anticoagulants, GPs admitted that they usually would not challenge a hospital doctor's judgement, even if they considered that a patient should receive antithrombotic therapy but had not been prescribed the therapy on discharge from hospital.

> One of the difficulties in general practice is the cardiologist does something different from what you do. That becomes quite complicated, because I have been quite surprised that some of my patients [who] are under cardiology care [but] who are not on medication … The problem with the GP is that you are in competition with [the] cardiologist, who doesn't believe that they (patients) need it. So you [are] then overriding the specialist management of that person's cardiac problem (G02)

In contrast, in nurses and pharmacists' opinions, the outcomes for patients depend not only on the therapy but also on how the patients manage the therapy in daily life. Therefore, patients' capability in medication management, associated with factors such as adherence, lifestyle (e.g. binge drinking) and cognitive function, was the focus of nurses and pharmacists. Pharmacists were also concerned about medication safety issues such as drug–drug interactions, drug–food interactions, complementary medicine use, and time in therapeutic INR range (TTR). Nurses' and pharmacists' preferences for antithrombotic agents was, therefore, somewhat determined by whether they perceived one agent could be more easily managed by the patient than another agent.

> If someone is coming with AF, dementia, decreasing function, multiple falls. Is warfarin still ok for this patient? (N02)

In addition, some nurses stated that, although they might have certain input in the decision-making around antithrombotic therapy, the final decision was usually made by doctors, which somewhat discouraged nurses from making recommendations.

Discussion

This study concurrently explored the perspectives of four groups of health professionals on decision-making around antithrombotic therapy in patients with AF, particularly concerning warfarin and NOACs as treatment options (24-27). At the time of the study, in the decision-making around antithrombotic therapy, assessment of bleeding risk and measures of anticoagulant control (e.g. time in therapeutic range) were considered alongside assessment of stroke risk by both international and Australian guidelines (13-15). However, although most health professionals interviewed in this study recognised the importance of a comprehensive assessment of risk versus benefit when deciding which antithrombotic to use, few of them actually discussed a wide range of issues around bleeding risk and medication safety in relation to their decision-making process; instead, they focused primarily on risk factors for stroke. Thus, it appears that, when selecting antithrombotic therapy, assessment of risk versus benefit in individual patients is not routinely undertaken in clinical practice.

Health professionals' differing preferences for particular antithrombotic therapies have been reported previously (21). In this study, the preferences of most health professionals when selecting among antithrombotic therapies were consistent with an Australian Government review (8) and the Australian Therapeutic Guidelines (13); both guidelines recommend warfarin as first-line therapy and NOACs as the second choice. However, these recommendations differ from those in international guidelines, such as the European Heart Rhythm Association guidelines (14), which recommend NOACs as first-line therapy. The

health professionals in this study did not express an overt awareness of any differences between their prescription choices and the recommendations in the guidelines. However, some were aware of differences between their prescription choices and those of specialist doctors. Similar to findings in previous reports (28), this study identified an inter-specialty difference in therapy selection between cardiologists and geriatricians on the one hand, and neurologists and haematologists on the other. While the approach taken by neurologists and haematologists is more aligned with international guidelines (14), cardiologists and geriatricians appear to be more cautious about using NOACs. This difference might be explained by the characteristics of the patients treated in these specialties, leading cardiologists and geriatricians to focus on the safety of the medications, neurologists to focus on preventing further adverse events (i.e. stroke due to therapeutic failure of the antithrombotic medications), and haematologists to focus on the practicalities of medication management and anticoagulant control. These inter-specialty differences in therapy selection can explain variation in the prescription of antithrombotics, with previous studies showing that cardiologists are more likely to prescribe appropriate oral anticoagulants for patients with AF than are other specialist clinicians and GPs (29, 30). Moreover, studies have shown that differences in therapy selection can lead to a range of outcomes for patients, with better outcomes for patients receiving antithrombotic treatment consistent with guidelines (31).

Previous studies have reported that patients prefer a particular antithrombotic therapy, and indicate that patients have a negative opinion of warfarin derived from either their own experience or the experience from others (32, 33). In this study, although patients'

preference was not directly investigated, according to the health professionals interviewed, patients generally preferred NOACs over warfarin. This finding is unsurprising, given that a previous study found a 'hypothetical oral anticoagulant', which had no monitoring requirement and no interactions with food, alcohol or concomitant medications, was preferred over warfarin by more than half of the patients; the 'no monitoring' was considered the primary advantage by the patients (34). Therefore, the preferences of patients present a significant challenge in antithrombotic prescription in general practice (35), and may contribute to the under-treatment of patients.

In understanding the reasons for underuse of antithrombotics, factors influencing the health professionals' decision-making are important. Many factors, such as guidelines, the opinions of specialist clinicians, access to reliable INR monitoring, prescribers' experience (or lack of it) with oral anticoagulants, patient characteristics (e.g. dementia, risk of falls) and patient preferences, have been reported to affect health professionals' decision-making (1, 24, 35-37). In addition to factors identified in previous reports, this study found that the roles of health professionals from different disciplines affected their focus in the decision-making process, which in turn may affect their selection of treatment options. This finding suggests that, in order to comprehensively assess patients' suitability for antithrombotics, and to select the appropriate medication for individual patients, it may be necessary to encourage communication and collaboration among health professionals from different disciplines.

In this study, cost was not mentioned by health professionals as an issue affecting decision-

making around antithrombotic therapy. This is likely due to the fact that the NOACs are subsidised by the Australian Pharmaceutical Benefits Scheme (PBS), making these medicines affordable for patients, albeit costly for the government. Concerns about the cost-implications to the government of the widespread use of the newer, more expensive, agents has led the Australian government to take a more considered approach to the selection of therapy (9). Therefore, compared to international guidelines (14, 18), Australian local guidelines tend to give equal or greater consideration to the use of warfarin as the first-line therapy, compared to NOACs (13, 20). This may have been reflected in the views of these participating Australian health professionals', noting the expressed preferences for warfarin over NOACs.

Uniquely, this study also revealed GPs' reluctance to challenge a hospital doctor's decision, and their routine referral of patients to hospital for initiation of warfarin therapy (38). Possible solutions include improving GPs' knowledge of evidence-based medicine about the prescription of antithrombotics; studies have shown that GPs with experience in practising evidence-based medicine are more likely to challenge the decisions of hospital doctors (38).

In considering the findings of this study, some limitations are acknowledged. The study design may have affected the representativeness of the participants and, therefore, the generalisability of the study's findings to a broader population. Although some participants interviewed had substantial experience working in rural and regional areas, most of the participants were practising in the Sydney metropolitan area; therefore, their perspectives

may differ from those of their counterparts in rural and regional areas. Furthermore, health professionals' perspectives on decision-making around antithrombotic therapy may change over time as new evidence emerges. Exploring the perspectives on decision-making around antithrombotic therapy of health professionals from a broader geographic area would be useful.

Conclusion

The decision-making process appears to be partially preference based rather than systematic, and health professionals from various disciplines focused on different aspects of the decision-making process.

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Declaration of Conflicting Interests

None to declare.

Ethical approval

Ethics approval was given by University of Technology Sydney (REF NO. 2013000338).

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Table 1 Participant Characteristics

Participant characteristics	Median number of years of experience in managing patients with AF (IQR) (absolute range)	Median number of patients with AF managed annually (IQR) (absolute range) (self-reported)
Specialist clinicians (n=6) • 3 geriatricians • 2 haematologists • 1 cardiologist • 1 neurologist	28 (13-32.5) (5-40)	100 (25-225) (5-300)
General practitioners (n=6)	22 (15-24.5) (12-40)	25 (12.5-30) (4-35)
Pharmacists (n=7)* • 6 accredited pharmacists • 1 hospital pharmacist	12 (8-30) (5-50)	50 (17.5-75) (5-100)
Nurses (n=6) † • 3 nurse practitioners (2 cardiology, 1 neurology) • 3 clinical nurse consultants (neurology)	21.5 (12.5-28.3) (8-30)	116 (100-132) (100-300)

IQR: interquartile range; Accredited pharmacists: accredited for Home Medicines Review and/ or Residential Medication Management Review (39)

*All six accredited pharmacists (home medication review and/or residential medication management review) were community-based

†Among them, the two cardiology nurses were community-based, while the others were hospital-based.

Table 2. Selected major themes in each subgroup

General practitioners	Pharmacists	Nurses	Specialists clinicians
1. Comprehensive assessment of patients is needed but not always implemented	1. Comprehensive assessment of patients especially the medication safety and management issues is needed	1. Comprehensive assessment of patients especially the practical management issues was needed	1. Comprehensive assessment of patients is needed but not always implemented
2. Decision-making around antithrombotics is a negotiation between the prescribers' preference and the patients' preference	2. Some focus on the medication safety issues of the AF management when selecting among antithrombotic agents	2. Culture (subjective) issues in clinical affect the decision-making around antithrombotic therapy	2. Therapy preference and clinical experience affects the decision-making process
3. Focus on the under prescription of antithrombotics and the inconsistency in prescribing	3. Regular review is needed for patients with AF as risk factors of antithrombotic management are not static	3. Focus more on the practical management of the therapy	3. Focus on the under prescription of antithrombotics in patients with AF

Table 3 Theme 1: Comprehensive assessment is necessary for the decision-making but not always implemented

General practitioners	Pharmacists	Nurses	Specialists clinicians
When I see a patient, I would look up some of the information but I would rely on my memory for lot of it and there may be aspects that I wouldn't have thought about that I should have thought about that wasn't there. (G03) *If you are going to prescribing it and you haven't documented that you have gone through all that (stroke, bleeding risk, and medication safety) if something happens and they have a big GI bleeding, or the patient dies and you have been shown to prescribe the medication for which you haven't made adequate risk assessment I would imagine you would be liable the same as we prescribing anything. (G05)* *But I have always just used $CHADS_2$ and like I just do a $CHADS_2$ score if they are 0 or 1, I would suggest aspirin if they are greater than that I would give them warfarin. You know that is how I have been working up till now, which is basically this. (G01)* *... things like $CHADS_2$ and CHA_2DS_2-VASc and those bleeding risk assessment tools. Some individual use. Again the reality is most GP would not use. (G04)*	*When I am recommending an anticoagulant or checking what they are already taking, I will look at the safety issues. I look at the drugs that they are taking. I look at their actual medical condition as well. (P06)* *Obviously you want the best outcome of your patients, you do not want them to be on something that going to be hard for them to manage. Say for example, you take MMSE and you want to make sure that they are able to manage. This is very important. (P02)* *So I would work out my CHA_2DS_2-VASc, creatinine clearance and other things in different tools. And like patient history is just talking to patient that is something that are separate completely. All those factors together to me would base my decision on whether or not I would recommend anticoagulation for a patient or not. From a pharmacist point of view, we look at this anyway prior to making a recommendation. Everything that we go through, we go through CHA_2DS_2-VASc history of valvular or non-valvular AF, weight creatinine clearance, history of bleeding, tendency for fall diet intake. (P07)*	*I think we need something that is more comprehensive than just doing CHA_2DS_2-VASc. (N01)* *It is not just like this is someone who had a stroke or risk of stroke, who has AF so let's put them on OACs but it brings in all those other factors like their cognition their function and those sorts of things. I think that get forgotten when people are prescribing. They forget the whole patient can this patient actually copes with that. I think that is what is good about being able to select or being able to choose between warfarin and other OAC. (N05)* *I think especially because the drugs are so new we do not know so much about them and we do need to be prompted about thinking about all these components (stroke, bleeding risk, and medication safety) until we get a bit more a grip on what we are dealing with. (N06)*	*All the components are the same as the experienced clinicians would use and make a judgement about whether to use or not to use anticoagulant therapy, so the use of CHA_2DS_2-VASc and HAS-BLED scores, the differentiation between warfarin and NOACs is all quite appropriate.(S04)* *I am much more familiar with the HAS-BLED score than with the other score ($HEMORR_2HAGE$). But a lot of data says that we probably over estimate the risk of bleeding in a lot of patients anyway and they are also working on other scores, better than HAS-BLED score really telling us how big is the risk of bleeding for patients. And I think that is important. Because that is the main factor why doctors don't put patients on oral anticoagulation, because they think they will bleed. (S05)* *Cardiologists do these scores (CHA_2DS_2-VASc and HAS-BLED) routinely but they got them on their phones and they do that every day. But that is all they do. They just do the CHA_2DS_2-VASc and HAS-BLED and that is all they do. If we are lucky they may think about eGFR and creatinine clearance but that is it. (S06)* *Bleeding risk schemes doesn't help, because even if the score is high they should be on anticoagulation anyway. And some studies have proved that high HAS-BLE and high CHA_2DS_2-VASc, they (patients) benefit just as much as with the low HAS-BLED. (G06)*

$CHADS_2$: congestive heart failure, hypertension, age =75 years, diabetes mellitus, stroke. CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75, diabetes, prior stroke or transient ischaemic attack, vascular disease, age 65–74, and sex. $HEMORR_2HAGE$: hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, re-bleeding, hypertension, anaemia, genetic factors, excessive fall risk and stroke. HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol. NOACs: novel Oral Anticoagulants. eGFR: Estimated Glomerular Filtration Rate

Table 4 Theme 2: Health professionals have their own preferences for antithrombotic therapy

General practitioners	Pharmacists	Nurses	Specialists clinicians
I was always pro-warfarin, like I am quite keen to use warfarin in non-valvular AF, because I tend to think it is the best way of preventing stroke. And I have not been using many of the new drugs, partly for the factor that they are new and I am nervous about... I am worried about the lack of reversibility for example the NOACs, all my patients want them,, because they like the idea of not having to use warfarin. Everybody is scared of warfarin, And it is often very hard to convince patients to take warfarin ... Also there is the anxiety of having to have bleed test monitored the dose and those sort of things. (G01) *The convenience factor in the NOACs is particularly the once a day dosage and no blood test. Patients prefer them.... I still always concern that warfarin is always a risk as it is bit unpredictable... But in the real world warfarin is not taken well, a lot of people forget. So it is not useful as they are not in the range. (G03)* *The difficulty is not the decision-making. The difficulty is to negotiate with the patients about their degree of risk. The meaning behind not being on an anticoagulant. What if it would mean in terms of follow-up for it to be safe, if they are on anticoagulant ... Warfarin is going around for quite a long time. A lot of patient, where warfarin is appropriate they have bad stories... So for lots of GPs, to address these issues is in fact the main task. (G04)*	*Someone who is not able to manage warfarin for whatever reason. You have got the three new agents .... To my understanding some of them only recently have their use extended to AF in the past was just for post- surgery for replacement or sort of thing... I guess you would base that which has been around the longest and has the most the sort of data available to use, monitoring type thing.(P02)* *I had a patient who was only in her 40s but she was a king sailor... And she would be suitable for NOACs... But there are exceptions like that, but would be very few. I would not encourage the new ones at this stage ... And how you going to measure it (NOACs therapeutic level), you don't know whether they are in range. You could still bleed ...we have heard of cases where there has been death. I think was in Lancent. The other thing people use it for convenience for elderly and they are the ones that have it in the Webster pack and it is not stable in the Webster pack. It has to be kept in the foil. And there is no antidote. So that is very important factor to tell the patient when they make choices like that... So again as I said we all to stick to the one that is well-known. You know elderly patients whether they are on warfarin or not. They seem to go the doctor at least once a month and they can be monitored. (P05)*	*I think the nurses have limited input into choices and decision-makings. I think the decision of anticoagulant actually come from the cardiologist in the end...A lot of the cardiologists are hesitant to change ... I think still a lot of clinicians are hesitant to use NOACs... It goes back to the culture thing, if you have cardiologist who have been using warfarin for the last 40 years and why they are going to change to NOACs? ...Cardiologists as opposed to neurologists are more reluctant to change to NOACs... But neurologist if they have a newly diagnosed AF, they would start them on NOACs. I think there some underlying issues like renal or other cardiac conditions that may influence the choices. (N01)* *..because especially with the NOACs it is sort of just the choice really of the doctor. And there is not lot of factors that go into making that decision often just someone's favourite you know what they used to or something like that because there isn't that much sort of difference between them that we know of so this might be good as it takes quite a lot of that guess work make it a bit more individualized decision as opposed to just picking up because you are used to it. (N06)* *I suppose if they have some issues with their cognitive most likely would recommend once a day OACs than twice a day. (N04)*	*Of course some of the doctors like warfarin because it has been around for such a long time. But the risk of ischaemic stroke is higher with warfarin and the risk for bleeding is higher with warfarin ... We would give the patients NOACs unless they are not suitable usually with renal problem ... Otherwise, we would give them NOACs. And for the NOAC, if it is a young patient <65 and no other issues, we would give dabigatran 150mg bid because it has the best date for effectiveness. If a patient has a reduced renal problem then you can consider 110mg dabigatran or apixaban 2.5mg which can go creatinine clearance of 30. It might be if the patient has ischaemic heart disease, rivaroxabna might be of more benefit ... if it not suitable then we consider warfarin.(S05)* *The other thing that I am not totally convinced ... is whether there is enough data in older patients for the NOACs. That is the other thing that I am not sure about given that they have been safety signals for things like gastrointestinal bleeding. (S01)* *There is no evidence to tell us, which treatment is better. All we know from the three randomized control trial is that all the NOACs are as good as warfarin in preventing thromboembolism and that the NOACs are slightly less likely to cause intracranial bleeding and slightly more likely to cause gastrointestinal bleeding... One of the clinical concerns that we all face now with the NOACs is what happen to people who are elderly and who around NOACs because of AF and happened to get GI disturbance get diarrheal, vomiting, dehydration, renal impairment. And suddenly get an eGFR that drops down to 30 and they are on a NOACs. Unless they are aware of the risk. They are going to have increased risk of bleeding. (S04)*

Table 5 Theme 3: Health professionals focused on different aspects of the decision-making process.

General practitioners	Pharmacists	Nurses	Specialists clinicians
I think doctors are anxious about avoiding risks of medications, we worried about causing bleeding. But because of our fear of that we massive under treat patients with AF and we don't prevent stroke when we should be… because our failing as a medical profession is about not using these drugs enough…. I think the disaster is that the patient has a stroke because they had an untreated AF. (G01) *One of the difficulties in general practice is the cardiologist does something different from what you do. That becomes quite complicated, because I have been quite surprised that some of my patients are under cardiology care who are not on medication. So I have been here 2.5 yrs. I have picked a lot of pts that got AF and probably 1/3 of them attending cardiology at least once a year and not on any medication … The problem with the GP is that you are in competition with cardiologist who doesn't believe that they (patients) need it. So you then overriding the specialist management of that person's cardiac problem, if they have got a cardiologist that they go to who doesn't think that it is appropriate that they have to go on to one of the antithrombotic medications and you step in and said that I think you should. (G02)*	*Because it (adherence) is self-reporting, they say "oh I do everything the doctor told me,""yes I take it every day". And you look at the pharmacy history they are not taking it every day. It is not reliable. The pharmacy history is much more reliable.(P01)* *Well, you have got all these you have listed all possible risk factors (stroke, bleeding and medication safety risk factors), as much as you can. Of course sometimes these risk factors might vary or might be severe than in other situations. Like anaemia for instance, that might not be present might later be present. So it is just you would have to constantly measure these from time to time. It is time consuming and detailed and maybe doesn't warrant maybe because of the patient health illiteracy. (P05)*	*Patient in practice particularly for someone on warfarin you get the patient on warfarin and the INR is between 2-3 and their INR is easy to control that is fine and then you get other patient and their INR is all over the place. So it maybe because of life factors like if someone has a few glass of wine and it affects the INR or if they binge drink on the weekend, they have fluctuation of INR. (N01)* *You know that is the good thing about the NOACs because you don't have to change the dose like warfarin. You can put them in Webster-paks and therefore you can make sure the patient, even if they don't have to work out what to take as long as you remind them have you look at your Webster-pak and taking you tablet then you are going to get compliance that way. Even if their cognition is not 100%.(N05)* *If someone is coming with AF, dementia, decreasing function, multiple falls. Is warfarin still ok for this patient? (N02)* *…they (GPs) just give aspirin which for someone with AF is not recommended in the guidelines. So sometimes I see them (patients) in our TIA clinic or our stroke clinic and they had their stroke because they had AF which is either never been treated or under treated just with aspirin and that is why they have their stroke…And that is the same with warfarin even before the NOACs patients still were not put on to warfarin who had AF, just because they (GPs) thought the risk of bleeding is far too high. However, the risk of stroke far out weights and we have seen that in our clinic all the time.(N05)*	*There are still many patients with AF who are not on oral anticoagulant who should be on and there are many who are on aspirin think it is an appropriate therapy which evidence now suggests that it is not… there is still under prescription in AF… Probably worse in general practice, would vary depending on the part of Sydney that you deal with in terms of patients their risk profile, their education, access to general practice, access to specialists. In this region here every one has access to specialist, while in other areas they can be very long waiting time to see cardiologist. And GPs would often not initiate therapy. (S04)* *…from our point of view, patients are usually are under treated, so very often GPs because they think the patient has risk of fall or so, would not treat the patient, so very frequently pts that we are treating are not treated. (G05)* *…CHA_2DS_2-VASc is the only way to really pull out the set of people at very low risk who do not need anticoagulation And $CHADS_2$ had quite a wide range of risk, so if you use CHA_2DS_2-VASc you can arrive at a set of people who definitely do not need any drug and leave them out, but that is probably <5%. (S06)*

TIA : *transient ischaemic attack*

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Chapter Six

6.1 Pilot of a Computerised Antithrombotic Risk Assessment Tool Version 2 (CARATV2.0) for stroke prevention in atrial fibrillation

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Supporting documents located in:
• Appendix VI Data Collection Form
• Appendix VII Participant Information Sheet and Participant Consent Form (Patients)
• Appendix VIII Participant Information Sheet and Participant Consent Form (Person Responsible)
• Appendix IX Participant Information Sheet and Participant Consent Form (Prescribers)
• Appendix X Flyers
• Appendix XI RNSH Ethics Approval
• Appendix XII RNSH Governance Authorisation
• Appendix XIII UTS Ethics Approval

Abstract

Background

The decision-making around stroke prevention in atrial fibrillation (AF) requires comprehensive assessment of risk versus benefit and appropriate selection among antithrombotic agents [e.g., warfarin, non-vitamin K antagonist oral anticoagulants (NOACs)]. Therefore, we aim to pilot-test the impact of a customised decision support tool—the Computerised Antithrombotic Risk Assessment Tool (CARATV2.0) on use of antithrombotic therapy in a cohort of patients with AF.

Method

In this prospective interventional study, 251 patients with AF aged ≥65 years, admitted to a teaching hospital in Australia were recruited. CARATV2.0 generated treatment recommendations based on patients' medical history; recommendations were provided to prescribers for consideration.

Results

At baseline (admission), 30.3% of patients were prescribed warfarin, 26.7% an antiplatelet, 8.4% apixaban, 8.0% rivaroxaban, 3.6% dabigatran. CARATV2.0 recommended a change of therapy for 146 (58.2%) patients. Through recommendations of CARATV2.0, at discharge, 40.2% of patients were prescribed warfarin, 17.7% antiplatelet, 14.3% apixaban,

10.4% rivaroxaban, 5.6% dabigatran. Overall, the proportion of patients receiving an antithrombotic on discharge increased significantly (baseline 77.2% versus 89.2% (*P* <.001). Prescribers moderately agreed with CARATV2.0's recommendations (kappa = 0.275, *P* <.001). The desire to continue therapy and practical medication safety issues were the major reasons for not accepting CARATV2.0's recommendations. Factors predicting the prescription of antiplatelets rather than anticoagulants included higher bleeding risk and high risk of falls. An inter-speciality difference in therapy selection was detected.

Conclusions

This decision support tool can help optimise the use of antithrombotic therapy in patients with AF by considering risk versus benefit profiles and rationalising treatment selection.

Key words: decision-making, computer-assisted, anticoagulant agents, warfarin, atrial fibrillation, stroke, clinical decision support

Introduction

The decision-making around antithrombotic therapy for stroke prevention in atrial fibrillation (AF) is complicated by therapy options and risk versus benefit assessment. Three non-vitamin K antagonist oral anticoagulants (NOACs)—dabigatran, rivaroxaban and apixaban—have been developed and approved to overcome the limitations of warfarin, but they are not without risk and have different pharmacological profiles (1, 2). Compared with warfarin, the NOACs do not require routine monitoring of coagulation parameters and have fewer interactions with other drugs and food, which enhances the convenience of therapy management. However, in contrast to warfarin, most NOACs need dosage adjustment in patients with renal impairment and are contraindicated in severe liver impairment. For patients with gastrointestinal disease, some NOACs (such as dabigatran) are not as well tolerated as warfarin. More frequent dosing is needed for some NOACs (e.g., twice daily for dabigatran and apixaban) compared to warfarin (once daily), which may reduce patients' adherence, especially in older patients who are already using polypharmacy (1). Additionally, they are more expensive, which underpins recent recommendations to prioritise the use of warfarin for those patients in whom it is appropriate (3). Regarding the risk versus benefit assessment of using antithrombotics, currently both international (e.g. the ESC and AHA/ACC/HR guidelines) and Australian guidelines (e.g. the Therapeutic and NPS guidelines) recommend consideration of both the risk of bleeding and anticoagulation control (e.g. INR, time in therapeutic range) in addition to the risk of stroke (4-7). Therefore, health professionals needed a more tailored evaluation

for the complete assessment of patients with AF for both initiation of therapy and follow-up (8, 9).

To assist clinicians in selecting appropriate antithrombotic therapy for patients with AF, the Computerised Antithrombotic Risk Assessment Tool (CARAT) was previously developed and successfully trialled (10). This decision support tool facilitates a comprehensive review of risk factors and calculates the estimated risk versus benefit of therapy for individual patients, taking into account any relevant medication safety issues (e.g. renal function, falls risk). In view of the recent availability of NOACs and further evidence from clinical trials (3, 11, 12), the tool has been updated (CARATV2.0) (13), in-line with current guidelines (e.g. the Australian Therapeutic Guidelines (4), NPS MedicineWise guidelines (14), AHA/ACC/HR guideline (6), American Chest Physician Guidelines (15), and the ESC Guidelines (7)), and the broader literature (1, 3, 16, 17).

As a pre-test of its underpinning algorithm and data inputs, CARATV2.0 was piloted in a cohort of patients admitted to a Sydney hospital for management of their AF. The main aim of this study was to evaluate the potential impact of CARATV2.0 on the use of antithrombotic therapy, to ensure that CARATV2.0 included all of the appropriate inputs for decision-making around antithrombotics from the clinicians' perspective, before evaluating it in a randomised controlled trial. Specifically, CARATV2.0's inputs were confirmed by seeking clinicians' opinions on the reasons for agreeing or disagreeing with the tool's assessment of patients and its recommendations for antithrombotic therapy. The proportion of patients receiving antithrombotic therapy at admission versus at discharge

(pre versus post application of the decision support tool) was compared to evaluate the impact of this tool. Factors associated with treatment selection (at discharge) were also identified.

Method

Design and setting

This prospective cohort study was conducted in a tertiary teaching hospital in Sydney, Australia, from August 2015 until October 2015. CARATV2.0 was used to review patients with AF admitted to the hospital and to generate recommendations for antithrombotic therapy.

Ethics approval for the study was obtained from the respective institutions' human research and ethics committees (REF NO. HREC/15/HAWKE/103).

Participant recruitment

Both patients and prescribers were recruited as participants. Prescribers were recruited through initial contact at seminars and at clinical meetings in the target wards where patients with AF were likely to be admitted (i.e. cardiology, neurology, aged care and general medicine). Subsequently, prescribers were approached directly to obtain their informed written consent to participate.

Patients with AF were identified by the principal researcher (a medical doctor) through screening of admissions to the hospital wards. Patients were selected if they satisfied the following criteria: aged 65 years or older; could speak English; had a principal diagnosis of non-valvular AF or a secondary diagnosis of AF regarded as contributory to the admission; and were able to (or had a person responsible who was able to) provide informed written consent to participate in the study. Patients were recruited through face-to-face contact by the principal researcher on wards.

Data collection (trial scenario)

The researcher visited target wards daily and liaised with the ward staff to identify patients with AF. The medical records of each eligible consenting patient were then reviewed to extract relevant data (e.g. medical history). Where key data needed specific clarification, the relevant health professionals, the patients, or both, were approached directly.

The extracted data were used by the researcher to populate CARATV2.0 in order to generate a treatment recommendation for each patient. CARATV2.0's recommendations were then presented to the prescribers as follows: documented clinical notes, discussed during ward rounds, or discussed via phone (after paging the doctor). Prescribers' agreement or disagreement with CARATV2.0's recommendations, and the reasons for alternative treatment selection, were recorded. Each patient's management was followed until hospital discharge.

Algorithm of CARATV2.0

CARATV2.0 (currently an Excel prototype) is an electronic tool that canvases a range of factors to determine a patient's risk of stroke versus risk of bleeding. Stroke risk is assessed with $CHADS_2$ (18) and CHA_2DS_2VASc (19); bleeding risk is assessed with HAS-BLED (20) and $HEMORR_2HAGES$ (21). The two sets of scores verify each assessment, giving weight to the highest score (level of risk). The four scores are each categorised into low, intermediate or high risk. CARATV2.0 additionally considers major medication safety issues that may affect treatment choice (e.g. renal and liver function, drug interactions, falls risk and cognitive function) (10).

When applying CARATV2.0, a patient is considered eligible for oral anticoagulants when the risk of stroke (assessed by $CHADS_2$ (18) or CHA_2DS_2VASc (19)) is equal to or higher than the risk of bleeding (assessed by HAS-BLED (20) or $HEMORR_2HAGES$ (21)). When the bleeding risk of using oral anticoagulants in the patient outweighs the benefit of stroke prevention, CARATV2.0 considers the patient unsuitable for oral anticoagulants; alternative treatment (e.g. an oral antiplatelet) and specialist consultation are recommended instead. Given that CARATV2.0 was developed primarily for the Australian setting, its treatment recommendations followed the Australian Therapeutic Guidelines (4) and were aligned with the Australian Government Review (3). Whenever the patient was deemed to be eligible for oral anticoagulants (either warfarin or NOACs) and has no contraindications to warfarin or NOACs, CARATV2.0 considered warfarin as the first-line therapy and NOACs as alternative therapy. However, it should be noted that the Australian guidelines differ slightly from international guidelines (e.g., European Society of Cardiology (2012)

and the European Heart Rhythm Association (2015)) in that the international guidelines advocate the use of NOACs over warfarin (7, 22).

The primary function of CARATV2.0 is to assess the need for antithrombotic therapy in patients who have AF as the primary indication. It does not make specific recommendations about combination therapies in the presence of multiple indications (e.g., an anticoagulant plus an antiplatelet), given the lack of evidence about the safety of using multiple agents. However, the tool does screen for other indications, such as ischemic heart disease (with or without stent) and valvular AF, which may also require antithrombotics and which may lead to the need for combination therapy, as identified by the American Chest Physician Guidelines (15). Thereby, CARATV2.0 brings to the attention of prescribers that their patients may have other indications requiring additional antithrombotic therapy that may need to be carefully managed. CARATV2.0 does not make any recommendations about deprescribing any antithrombotic therapy that the patient may be taking for other indications.

Post hoc analysis

Post hoc analysis of CARATV2.0's recommendations was conducted after data collection was completed. This analysis assumed that CARATV2.0 considered NOACs as the first-line therapy and warfarin as the second-line therapy (i.e. reversal of first versus second – line therapies, in line with international guidelines (6, 7)). The patient data collected in the pilot study (trial scenario) were applied to CARATV2.0 to generate treatment recommendations. Finally, the therapy recommended by CARATV2.0 (NOACs as first-line)

was compared with the therapy received by patients in the trial scenario on discharge. The purpose of this post hoc analysis was to demonstrate the adaptability of CARATV2.0 to the international guidelines and to review the recommendations when international guidelines were adopted.

Data analysis

Computerised data analysis employed SPSS (Statistical Package for the Social Sciences) Version 19. T-tests, ANOVA, and Mann-Whitney U and Kruskal-Wallis tests were used to explore continuous variables. The Chi-square test examined differences in independent proportions. Kappa analysis assessed the level of agreement between CARATV2.0's recommendations and the antithrombotic therapy actually prescribed at discharge. Logistic regression analysis identified predictors for the use of antithrombotic therapy. All the relevant patient data (all variables listed in Table 1 and Table 2), including age, gender, admission department, risk of stroke (assessed by $CHADS_2$ (18) or CHA_2DS_2VASc (19)), risk of bleeding (assessed by HAS-BLED (20) or $HEMORR_2HAGES$ (21)), medical conditions (e.g., renal impairment, liver impairment. gastrointestinal bleeding, intracranial bleeding), medication safety issues (e.g., adherence, cognition, falls risk), number of medications were included in the univariate analysis. All variables showing a significant association in the univariate analysis were then considered in the multivariate logistic regression modeling (Forward Wald). Although age and gender were not significant in the univariate analysis, they were also further explored in the multivariate analysis. The significance level for all analyses, univariate and multivariate, was set at $P < 0.05$.

Results

Patient characteristics

Of the 253 patients recruited to the study, 2 were excluded from analysis due to incomplete data (death during hospitalisation). The average age of the 251 patients (51.0% females) was 82.3 ± 8.2 years (Table 1).

Baseline therapy at admission (pre-CARATV2.0)

At admission, 194 (77.2%) patients were using antithrombotics: 126 (50.5%) were using anticoagulants and 67 (26.7%) were using antiplatelets (Figure 1). Warfarin (± antiplatelet) was most commonly used 76 (30.3%), followed by aspirin (± other antiplatelet; 54, 21.5%), clopidogrel (13, 5.2%), apixaban (21, 8.4%), rivaroxaban (± antiplatelet; 20, 8.0%), dabigatran (9, 3.6%). Among the 57 patients on no antithrombotic therapy, 56 (98.2%) were categorised as high stroke risk by CHA_2DS_2VASc, and 37 (64.9%) as high risk by $CHADS_2$).

CARATV2.0's recommendations

Overall, CARATV2.0 recommended a change of therapy in 146 (58.2%) patients (Supplememt Table 1). Among the 124 patients who were receiving an oral anticoagulant at admission, only 102 (82.3%) patients were assessed as eligible for therapy by CARATV2.0. Among the 76 patients who were taking warfarin on admission, 8 (9.5%) were specifically

recommended an alternative therapy. Among the 50 patients who were taking one of the NOACs on admission, 32 (64.0%) were specifically recommended an alternative therapy by CARATV2.0 (Supplememt Table 1).

After the review of treatment using CARATV2.0, 167 (66.5%) patients were recommended warfarin; 21 (8.0%) any NOAC (dabigatran, rivaroxaban or apixaban); 12 (4.8%) either rivaroxaban or apixaban; 20 (8.0%) apixaban only; 2 (0.8%) either dabigatran or rivaroxaban; and 1 (0.4%) either dabigatran or apixaban. Twenty-eight (11.3%) patients were identified as unsuitable for any oral anticoagulant (Figure 1).

Discharge therapy (post-CARATV2.0)

At discharge, the proportion of patients receiving antithrombotics (Table 1) significantly increased to 89.2% (from 77.2% at baseline; P <.001) (Figure 1). More than 40% of patients were prescribed warfarin, while more than one-third were prescribed one of the NOACs. Among the 146 (58.2%) patients who were recommended therapy changes by CARATV2.0, 36 (24.7%) were adopted by the prescribers before discharge.

Among the factors affecting the selection of antithrombotics (at discharge), falls risk, bleeding risk, chronic kidney disease and being admitted to the neurology department had the greatest impact. Patients with a high risk of falls or a high risk of bleeding were more likely to receive antiplatelets than anticoagulants. Notably, patients with chronic kidney disease and those admitted to the neurology department were more likely to receive NOACs than warfarin (Table 2).

Prescribers' reasons for disagreement with CARATV2.0's recommendations

Prescribers agreed with CARATV2.0's recommendations on whether a patient was eligible for anticoagulants in 199 (79.3%) patients, and agreed with the specific therapy selected (including specific oral anticoagulant agents) in 132 (52.6%) patients. There was a moderate level of agreement between prescribers and CARATV2.0 regarding the use of anticoagulants versus other therapy (kappa = 0.275, P <0.001).

However, at discharge, prescribers did not follow the specific therapy recommendations of CARATV2.0 in 119 cases (Supplemental Table 2). Most common reasons given were (a) desire to continue existing therapy (e.g. "continue pre-admission therapy"), (b) practical management issues (e.g. "NOACs better/easier to manage/no need for monitoring") and (c) perceived issues of medication safety associated with potential risk of bleeding (e.g. "falls risk", "old age", "dementia") (Figure 2). In contrast, the benefit of treatment (e.g. "stroke risk") and specific bleeding events (e.g. "history of gastrointestinal bleeding") were among the least common reasons for not taking CARATV2.0's recommendations.

Post hoc analysis: consideration of NOACs as first-line therapy

In the post hoc analysis, patients who were identified as unsuitable for any oral anticoagulant in the trial scenario also remained ineligible for any oral anticoagulant. Among those who were eligible for oral anticoagulants, 119 (47.4%) patients were recommended any NOAC (dabigatran, rivaroxaban or apixaban); 50 (19.9%) were recommended either rivaroxaban or apixaban; 29 (11.6%) apixaban only; 3 (1.2%) either

dabigatran or rivaroxaban; and 1 (0.4%) either dabigatran or apixaban. Only 21 (12.6%) patients were recommended warfarin, 17 due to severe renal impairment (creatinine clearance <25 min/1.73 m^2) and 4 due to hepatic impairment. When examining the distribution of therapy, CARATV2.0's recommendations in the trial scenario better aligned with the treatment prescribed to patients at discharge in 132 (52.6%) patients, while CARATV2.0's recommendations in the post hoc analysis (NOACs as first-line therapy) only aligned with treatment prescribed to patients at discharge in 98 (39.0%) patients (*P* = .002).

Discussion

In this study, a novel decision support tool (CARATV2.0), which considers warfarin as first-line therapy and NOACs as alternative treatment options, was pilot-tested in a tertiary hospital. Results showed that CARATV2.0 assisted treatment selection and optimised the use of antithrombotic therapy in this patient population. More importantly, CARATV2.0 significantly increased the use of anticoagulants (warfarin and NOACs) in patients identified as eligible for oral anticoagulant therapy by this decision support tool. Moreover, since the average age of the patient population in this study was older than that of the general population of patients with AF (23), antithrombotic use in the general population may be further increased by the application of CARATV2.0. Because both national and international guidelines indicate the superiority of anticoagulants over antiplatelets for stroke prevention in patients with AF, the ability of CARATV2.0 to improve the use of anticoagulants has a valuable role in clinical practice.

Among factors affecting the selection of antithrombotics, bleeding risk and falls risk were the major barriers to prescribing anticoagulants (24). The perceived association between a high risk of falls and intracranial bleeding (ICH) may have driven prescribers to avoid prescribing oral anticoagulants in those patients with a high fall risk (25). However, a patient needs to fall about 300 times per year before their risk of ICH exceeds the benefits of using anticoagulation (26). Moreover, there is no significant difference in the risk of ICH between therapy with NOACs such as apixaban and therapy with antiplatelets (27). Therefore, for most patients, falls risk should not be a major barrier to prescribing an anticoagulant.

In contrast, prescribers' preference for prescribing warfarin to patients with chronic kidney disease is understandable, as studies have shown that NOACs should be used with caution in patients with renal impairment, and are contraindicated in patients with severe renal impairment (1). Interestingly, compared with admission to the other departments, patients admitted to the neurology department were more likely to be prescribed NOACs than prescribed warfarin. Possibly, neurologists have a different approach to selecting an antithrombotic therapy that is more aligned with international guidelines (28).

The treatment received by patients at discharge better aligned with CARATV2.0's recommendations when warfarin was considered as the first-line therapy, which suggests that most prescribers are still cautious of using NOACs as the first-line therapy. Although the majority of prescribers agreed with CARATV2.0's recommendations to prescribe anticoagulants, some cited reasons for not taking CARATV2.0's recommendations for

specific antithrombotic agents. The desire to continue therapy, and issues of practical management and medication safety were cited as the major reasons for not accepting CARATV2.0's recommendations. Among these reasons, the desire to "continue pre-admission therapy" was commonly cited, which indicates that prescribers are reluctant to change therapy once initiated (29). Although important issues of medication safety (e.g. falls risk, advanced age and dementia) and bleeding risk are considered by CARATV2.0 when making recommendations, some prescribers still cited these reasons for not prescribing anticoagulants. Thus, prescribers apparently perceived some factors as more risky than the evidence suggests. The concerns about issues of practical management and medication safety indicate that hospital prescribers are still worried about the long-term management of antithrombotic therapy by GPs, and about the risk of adverse events. However, studies have shown that GPs are more focused on the benefits of antithrombotic therapy for patients (30).

In the post hoc analysis, we have also shown that CARATV2.0 can be adapted to the international setting, where there may be differences in guideline recommendations (in terms of whether NOACs or warfarin are used first-line). The assessment process of CARATV2.0 may be adjusted in terms of which agent is advocated as the first-line therapy. Therefore, for international users, CARATV2.0 can be customised to align with the local guidelines of each country. The tool's adaptability to other settings may be important, not only in terms of what the local guidelines advocate, but also in terms of cost implications. In Australia, both warfarin and NOACs are cost-subsidised by the Australian government

(31), whereas in other countries the high-cost of NOACs may be borne by the patients, and these cost implications may impact treatment preferences.

In considering the findings, some limitations of the study need to be acknowledged. Although CARATV2.0 was developed with the latest evidence and treatment options available at the time, its algorithm may need to change as new evidence and therapies arise. Furthermore, one of the current limitations of CARATV2.0 is that it does not make recommendations around the use of combination therapy (e.g., an anticoagulant plus an antiplatelet) in patients with multiple indications. Future work needs to consider how this can be addressed. In addition, this study focused on patients with AF who were admitted to one hospital. Therefore, the results might not be generalisable to the broader AF population. Due to the lack of a control group in this study, it is uncertain whether changes to therapy might have occurred without the intervention of CARATV2.0. Finally, this pilot study did not explore the clinical outcomes of patients. Clinical trials in a broader patient population, involving comparisons to a control group, and with long-term follow-up, are needed to further evaluate this decision support tool.

Conclusion

In this study, CARATV2.0 successfully increased the use of anticoagulants in patients with AF and, by taking risk versus benefit profiles into account, demonstrated its potential in the selection of appropriate antithrombotic therapy. In the decision-making around antithrombotic therapy, there is inter-speciality difference in therapy selection. In addition,

prescribers were reluctant to change therapy once initiated and perceived some factors (e.g. falls risk and age) as more risky than the evidence would suggest.

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Declaration of Conflicting Interests

None to declare.

Ethical approval

Ethical approval for the study was obtained from the respective institutions' human research and ethics committees (REF NO. HREC/15/HAWKE/103).

The authors had full access to all of the study data (including statistical reports and tables).

Table 1 Utilisation of antithrombotic therapy (at discharge)

Characteristics (at discharge) Mean (SD) or N (%) N=251	Total N=251 [100]	Nil n = 27 [10.8]	Warfarin(±antiplatelet) n=101 [40.2]	Aspirin (±antiplatelet) †n=37 [14.7]	Dabigatran n = 14 [5.6]	Rivaroxaban (±antiplatelet) n = 26 [10.4]	Apixaban(±antiplatelet) n=36 [14.3]	Clopidogrel n=10 [4.0]
	Part 1 - Sociodemographics and risk stratification							
Age (years)	82.3± 8.2	85.7±8.4	81.7±7.8	84.1±8.6	81.9±8.2	79.3±8.7	82.1±7.1	82.2±9.1
Type of AF*								
Paroxysmal	97[38.6]	11[11.3]	36[37.1]	13[13.4]	3[3.1]	13[13.4]	17[17.5]	4[4.1]
Persistent	106[42.2]	9[8.5]	44[41.5]	19[17.9]	7[6.6]	10[9.4]	14[13.2]	3[2.8]
New Onset	9[3.6]	2[22.2]	3[33.3]	2[22.2]	1[11.1]	1[11.1]	0[0.0]	0[0.0]
Unknown	39[15.5]	5[12.8]	18[46.2]	3[7.7]	3[7.7]	2[5.1]	5[12.8]	4[7.7]
Current Cardiac Rhythm								
Normal Sinus Rhythm	108[43.0]	14[13.0]	44[40.7]	11[10.2]	3[2.8]	12[11.1]	18[16.7]	6[5.6]
Controlled AF	109[43.4]	9[8.3]	45[41.3]	17[15.6]	9[8.3]	13[11.9]	14[12.8]	2[1.8]
Paced	34[13.5]	4[11.8]	12[35.3]	9[26.5]	2[5.9]	1[2.9]	4[11.8]	2[5.9]
Gender								
Female, n [%]	128[51.0]	14[10.9]	47[36.7]	17[13.3]	6[4.7]	17[13.3]	20[15.6]	7[5.5]
Principle managers of antithrombotics								
GP	207[82.5]	21[12.0]	70[40.0]	33[18.9]	7[4.0]	15[8.6]	22[12.6]	7[4.0]
GP+ specialist	32[12.7]	3[7.3]	14[34.1]	4[9.8]	6[14.6]	6[14.6]	8[19.5]	0[0.0]
Specialist	41[16.3]	2[6.3]	16[50.0]	0[0.0]	1[3.1]	5[15.6]	5[15.6]	3[9.4]
None	3[1.2]	1[33.3]	1[33.3]	0[0.0]	0[0.0]	0[0.0]	0[0.0]	0[0.0]
Department								
General medicine	77[30.7]	8[10.4]	33[42.9]	9[11.7]	6[7.8]	6[7.8]	10[13.0]	5[6.5]
Cardiology	85[33.9]	6[7.1]	39[45.9]	12[14.1]	2[2.4]	12[14.1]	12[14.1]	2[2.4]
Aged care	51[20.3]	11[21.6]	19[37.3]	12[23.5]	1[2.0]	4[7.8]	3[5.9]	1[2.0]
Neurology	38[15.1]	2[5.3]	10[26.3]	4[10.5]	5[13.2]	4[10.5]	11[28.9]	2[5.3]
Other indications for antithrombotics								
History of PE/DVT†	20[8.0]	2[10.0]	10[50.0]	5[25.0]	0[0.0]	3[15.0]	0[0.0]	0[0.]
Coronary heart disease	92[35.1]	10[10.9]	40[43.5]	12[13.0]	5[5.4]	10[10.9]	13[14.1]	2[2.2]
CABG‡	26 [10.4]	1.[3.8]	16[61.5]	2[7.7]	0[0.0]	5[19.2]	0[0.0]	2[7.7]
Stent	14[5.6]	1[7.1]	6[42.9]	0[0.0]	0[0.0]	3[21.4]	4[28.6]	0[0.0]
CABG+stent	4[1.6]	[0.0]	2[50.0]	0[0.0]	1[25.0]	0[0.0]	0[0.0]	1[25.0]
$CHADS_2$ score:								
Low	10[4.0]	1[10.0]	5 [50.0]	1[10.0]	0 [0.0]	2 [20.0]	0[0.0]	1[10.0]
Intermediate	55[21.9]	8[14.5]	18 [32.7]	10[18.2]	3 [5.5]	9[16.4]	6[10.9]	1[1.8]
High	186[74.1]	18[9.7]	78 [41.9]	26[14.0]	11[5.9]	15[8.1]	30[16.1]	8[4.3]
CHA_2DS_2-VASc score:								
Intermediate	2[0.8]	0[0.0]	1[50.0]	0[0.0]	0 [0.0]	1 [50.0]	0[0.0]	0[0.0]
High	249[99.2]	27[10.8]	100[40.2]	37[14.9]	14[5.6]	25[10.0]	36[14.5]	10[4.0]
HAS-BLED score								
Low	3[1.2]	0[0.0]	2 [66.7]	0[0.0]	0[0.0]	1[33.3]	0[0.0]	0[0.0]
Intermediate	199[79.3]	22[11.1]	86 [43.2]	25[12.5]	10[5.0]	22[11.1]	29[14.6]	5[2.5]
High	49[19.5]	5[10.2]	13[26.5]	12[24.5]	4[8.2]	3[6.1]	7[14.3]	5[10.2]
$HEMORR_2HAGES$ score								
Low	86[34.3]	8[9.3]	38[44.2]	9[10.5]	5[6.0]	13[15.1]	12[14.0]	1[1.2]
Intermediate	126[50.2]	12[9.5]	56[44.4]	14[11.1]	7[5.6]	10[7.9]	22[17.5]	5[4.0]
High	39[15.5]	7[17.9]	7[17.9]	14[35.9]	2[5.1]	3[7.7]	2[5.1]	4[10.3]
	Part 2 - Clinical and medication safety considerations							
Disease condition								
Previous cerebrovascular accident (yes)	74[30.0]	6[7.9]	26[34.2]	13[17.1]	8[10.5]	3[3.9]	15[19.7]	5[6.6]
Previous intracranial haemorrhage§ (yes)	11[4.4]	0[0.0]	3[27.3]	6[54.5]	0[0.0]	0[0.0]	0[0.0]	2[18.2]
Prior gastrointestinal bleeding or ulcer (yes)	16[6.4]	2[12.5]	2[12.5]	3[18.8]	1[6.3]	3[18.8]	4[25.0]	1[6.3]
Other gastrointestinal	11[4.4]	10[14.3]	26[37.1]	8[11.4]	2[2.9]	10 [14.3]	12[17.1]	2[2.9]

disease‖ (yes)								
Chronic kidney disease (yes)	44[17.5]	9[20.5]	22[50.2]	3[6.8]	0[0.0]	2[4.5]	4[9.1]	4[9.1]
Liver impairment¶ (yes)	10[4.0]	2[20.0]	4[40.0]	3[30.0]	0[0.0]	0[0.0]	1[10.0]	0[0.0]
Medication safety issue								
Allergy/ADR ** to warfarin (yes)	14[5.6]	6[42.9]	2[14.3]	1[7.1]	0[0.0]	3[21.4]	1[7.1]	1[7.1]
ADR to dabigatran (yes)	6[2.4]	0[0.0]	4[66.7]	0[0.0]	1[16.7]	0[0.0]	1[16.7]	0[0.0]
ADR to rivaroxaban (yes)	5[2.0]	0[0.0]	1[20.0]	2[40.0]	0[0.0]	1[20.0]	1[20.0]	0[0.0]
Allergy/ADR to apixaban (yes)	3[1.2]	1[33.3]	1[33.3]	0[0.0]	0[0.0]	1[33.3]	0[0.0]	0[0.0]
Allergy/ADR to aspirin (yes)	4[1.6]	1[20.0]	3[60.0]	0[0.0]	0[0.0]	1[20.0]	0[0.0]	0[0.0]
ADR to clopidogrel (yes)	2[0.8]	2[100.0]	0[0.0]	0[0.0]	0[0.0]	0[0.0]	0[0.0]	0[0.0]
Cognitive impairment (yes)	32[12.7]	8[25.0]	5[15.6]	10[31.2]	1[3.1]	1[3.1]	7[21.9]	0[0.0]
Visual impairment (yes)	63[25.1]	3[7.0]	19[44.2]	9[20.9]	2[4.7]	2[4.7]	5[11.6]	3[7.0]
Hearing impairment (yes)	63[25.1]	7[11.1]	31[49.2]	10[15.9]	2[3.2]	2[3.2]	8[12.7]	3[4.8]
Mobility disorder (yes)	58[23.1]	8[13.8]	22[37.9]	13[22.4]	3[5.2]	2[3.4]	10[17.2]	0[0.0]
Language barrier (yes)	10[4.0]	1[10.0]	1[10.0]	6[60.0]	0[0.0]	0[0.0]	2[20.0]	0[0.0]
High fall risk/history of frequent falls (yes)	74[29.5]	8[10.8]	26[35.1]	20[27.0]	3[4.1]	5[6.8]	7[9.5]	5[6.8]
Poly pharmacy (≥ 4 kinds of medications) (yes)	239[95.2]	25[10.5]	96[40.2]	36[15.1]	12[5.0]	25[10.5]	35[14.6]	10[4.2]
Needs assistance with medication (yes)	120[47.8]	15[12.5]	49[40.8]	17[14.2]	8[6.7]	11[9.2]	15[12.5]	5[4.2]
Poor adherence (Morisky score >2) **(32)** (yes)	10[4.0]	1[12.5]	2[25.0]	3[37.5]	1[12.5]	1[25.0]	1[12.5]	1[0.0]
Medications that interact with antithrombotics								
Verapamil (yes)	4[1.6]	0[0.0]	3[75.0]	0[0.0]	0[0.0]	0[0.0]	1[25.0]	0[0.0]
Diltiazem (yes)	3[1.2]	0[0.0]	2[66.7]	0[0.0]	0[0.0]	0[0.0]	1[33.3]	0[0.0]
Amiodarone (yes)	33[13.1]	4[12.1]	14[42.4]	4[12.1]	2[6.1]	3[9.1]	5[15.2]	1[3.0]
Flecainide (yes)	12[4.8]	1[8.3]	6[50.0]	0[0.0]	0[0.0]	1[8.3]	2[16.7]	2[16.7]
Propranolol (yes)	4[1.6]	0[0.0]	3[75.0]	1[25.0]	0[0.0]	0[0.0]	0[0.0]	0[0.0]
Digoxin (yes)	56[22.3]	6[10.7]	18[32.1]	8[14.3]	6[10.7]	9[16.1]	6[10.7]	3[5.4]
Beta Blocker (yes)	113[45.0]	12[10.6]	48[42.4]	15[13.3]	7[6.2]	12[10.6]	14[12.4]	5[4.4]
Oral corticosteroid (yes)	32[12.7]	6[18.8]	8[25.0]	6[18.8]	2[6.3]	3[9.4]	7[21.9]	0[0.0]

Morisky score: the Morisky Medication Adherence Scale-MMAS-4 (32). Need assistance with medication: patients need carers, home nursing service, dosing aid, blister pack or acute post-acute care service to help with daily medication management.
* AF: atrial fibrillation
† PE: pulmonary embolism; DVT: deep venous thrombosis
‡ CABG: coronary artery bypass grafting
§ Including prior haemorrhagic stroke, subdural or subarachnoid haemorrhage
‖ Including gastroesophageal reflux disease, gastritis and other gastrointestinal diseases (except malignancy) without bleeding or ulcer
¶ Liver impairment is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin 2 to 3 times the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 times the upper limit normal, etc.) (Baseline INR ≥ 1.3)
**ADR: adverse drug event

Table 2. Predictors of antithrombotic therapy choice

Likelihood of receiving antiplatelets over anticoagulants†	**Univariate Analysis Odds Ratio (95%CI)**	**P**	**Multivariate logistic regression Odds Ratio (95%CI)***	**P**
High risk of fall (previous frequent falls)				
Yes	3.77 (1.93-7.37)	<0.001	2.25 (1.01-5.01)	0.04
No (Reference)	1			
Prior history of intracranial bleeding				
Yes	3.45 (1.74-6.85)	<0.001	-	-
No (Reference)	1			
Cognitive impairment				
Yes	3.15 (1.30-7.64)	0.01	-	-
No (Reference)	1			
Bleeding risk‡				
Low bleeding risk	0.11 (0.04-0.30)	<0.001	0.20 (0.07-0.60)	0.004
Intermediate bleeding risk	0.16 (0.07-0.37)	<0.001	0.21 (0.08-0.51)	0.001
High bleeding risk (Reference)	1			
Higher number of total medications				
Yes	1.11 (1.02-1.20)	0.02	-	-
No (Reference)	1			
* Cox&Snell R2 =0.12, Nagelkerke R2=0.18, 80.8% correctly predicted				
Likelihood of receiving warfarin over NOACs §	**Univariate Analysis OR (95%CI)**	**P**	**Multivariate logistic regression OR (95%CI)****	**P**
Systolic BP>160mmHg				
Yes	0.23 (0.06-0.87)	0.03	0.18 (0.04-0.92)	0.04
No (Reference)	1			
Chronic kidney disease				
Yes	3.25 (1.25-8.47)	0.02	3.96 (1.25-12.51)	0.02
No (Reference)	1			
Prior GI bleeding/ulcer				
Yes	0.41 (0.19-0.91)	0.03	0.29 (0.09-0.94)	0.04
No (Reference)	1			
Patients admitted to departments‖				
General medicine department	3.00 (1.18-7.61)	0.02	4.67 (1.52-14.39)	0.01
Cardiology department	3.00 (1.21-7.43)	0.02	3.80 (1.26-11.47)	0.02
Aged care department	4.75 (1.54-14.58)	0.006	5.81 (1.42-23.81)	0.02
Neurology department (Reference)	1			
** Cox&Snell R2=0.20, Nagelkerke R2=0.27, 71.2% correctly predicted.				

† Antiplatelets (including aspirin+clopidogrol, aspirin+dipyramidole, aspirin, clopidogrol) anticoagulants include warfarin and NOACs
‡ As assessed by $HEMORR_2HAGES$
§ Including dabigatran or rivaroxaban or apixaban
‖ Patients admitted to the department
High risk of fall: previous frequent falls or high risk of fall as documented in clinical notes
Prior intracranial haemorrhage: all type of haemorrhagic stroke and subdural or subarachnoid haemorrhage
Cognitive impairment: all types of dementia and other cognitive impairment as documented in clinical notes
Chronic kidney disease: all types of chronic renal impairment as documented in clinical notes
Prior GI bleeding/ulcer: all types of gastrointestinal bleeding and ulcer as documented in clinical notes

Supplemental Table 1. Documented changes to antithrombotic therapy

Total patient number	Antithrombotic therapy on admission	Recommended by CARATV2.0	Antithrombotic prescribed at discharge	Nature of change in therapy*
Patients recommended a specific change by CARATV2.0 (N=146)				
4	Antiplatelet (±antiplatelet)‖	NOACs†	Nil antithrombotics	Downgrade
1	Antiplatelet (±antiplatelet)	NOACs	Warfarin (±antiplatelet)	Upgrade
8	Antiplatelet (±antiplatelet)	NOACs	Antiplatelet (±antiplatelet)	Sidestepping
3	Antiplatelet (±antiplatelet)	NOACs	NOACs (±antiplatelet) §	Upgrade
18	Antiplatelet (±antiplatelet)	Warfarin	Antiplatelet (±antiplatelet)	Sidestepping
10	Antiplatelet (±antiplatelet)	Warfarin	Warfarin (±antiplatelet)	Upgrade
8	Antiplatelet (±antiplatelet)	Warfarin	NOACs (±antiplatelet)	Upgrade
2	NOACs (±antiplatelet)	Warfarin	Warfarin (±antiplatelet)	Sidestepping
25	NOACs (±antiplatelet)	Warfarin	NOACs (±antiplatelet)	Sidestepping
1	NOACs (±antiplatelet)	Warfarin	Nil antithrombotics	Downgrade
2	NOACs (±antiplatelet)	Unsuitable for oral anticoagulants‡	NOACs (±antiplatelet)	Sidestepping
11	Nil antithrombotics	Warfarin	Nil antithrombotics	Sidestepping
15	Nil antithrombotics	Warfarin	Warfarin (±antiplatelet)	Upgrade
13	Nil antithrombotics	Warfarin	NOACs (±antiplatelet)	Upgrade
5	Nil antithrombotics	NOACs	Nil antithrombotics	Sidestepping
1	Nil antithrombotics	NOACs	Warfarin (±antiplatelet)	Upgrade
3	Nil antithrombotics	NOACs	NOACs (±antiplatelet)	Upgrade
2	Nil antithrombotics	NOACs	Antiplatelet (±antiplatelet)	Upgrade
7	Warfarin (±antiplatelet)	NOACs	Warfarin (±antiplatelet)	Sidestepping
1	Warfarin (±antiplatelet)	NOACs	NOACs (±antiplatelet)	Sidestepping
1	Warfarin (±antiplatelet)	Unsuitable for oral anticoagulants	Nil antithrombotics	Downgrade
2	Warfarin (±antiplatelet)	Unsuitable for oral anticoagulants	Antiplatelet (±antiplatelet)	Downgrade
1	Warfarin (±antiplatelet)	Unsuitable for oral anticoagulants	Warfarin (±antiplatelet)	Sidestepping
1	Rivaroxaban (±antiplatelet)	Apixaban	Rivaroxaban (±antiplatelet)	Sidestepping
1	Rivaroxaban (±antiplatelet)	Apixaban	Apixaban (±antiplatelet)	Sidestepping
Patients not recommended a specific change by CARATV2.0 but changed therapy by prescribers at discharge (N=11)				
1	Antiplatelet (±antiplatelet)	Unsuitable for oral anticoagulants	Nil antithrombotics	Downgrade
2	Antiplatelet (±antiplatelet)	Unsuitable for oral anticoagulants	NOACs (±antiplatelet)	Upgrade
1	Nil antithrombotics	Unsuitable for oral anticoagulants	NOACs (±antiplatelet)	Upgrade
2	Nil antithrombotics	Unsuitable for oral	Warfarin (±antiplatelet)	Upgrade

		anticoagulants		
1	Nil antithrombotics	Unsuitable for oral anticoagulants	Antiplatelet (±antiplatelet)	Upgrade
1	Warfarin (±antiplatelet)	Warfarin	NOACs (±antiplatelet)	Sidestepping
1	Warfarin (±antiplatelet)	Warfarin	Nil antithrombotics	Downgrade
1	Warfarin (±antiplatelet)	Warfarin	Antiplatelet (±antiplatelet)	Downgrade
1	NOACs (±antiplatelet)	NOACs	Warfarin (±antiplatelet)	Sidestepping

* Discharge compared with admission. Upgrade means "Upgrades" to a more effective prophylactic therapy (i.e., from no therapy to any agent, or from aspirin to warfarin/dabigatran). Sidestepping means patients remain in the same level of treatment (i.e., from one anticoagulant to one anticoagulant, one antiplatelet to one antiplatelet). "Downgrade" to a less effective prophylactic therapy (i.e. from one anticoagulant to one antiplatelet, from one antiplatelet to nil antithrombotic therapy)

† Including: any NOAC (dabigatran or rivaroxaban or apixaban), either rivaroxaban or apixaban, apixaban only, either dabigatran or rivaroxaban, either dabigatran or apixaban

‡ Unsuitable for oral anticoagulants: if non-modifiable risk factors, consider alternative antithrombotics (e.g., aspirin, clopidogrel) or seek specialists' advice

§ Including dabigatran or rivaroxaban or apixaban

‖ Antiplatelet (±antiplatelet) including: apirin, aspirin+dipyramidole, aspirin+clopidorel or clopidorel.

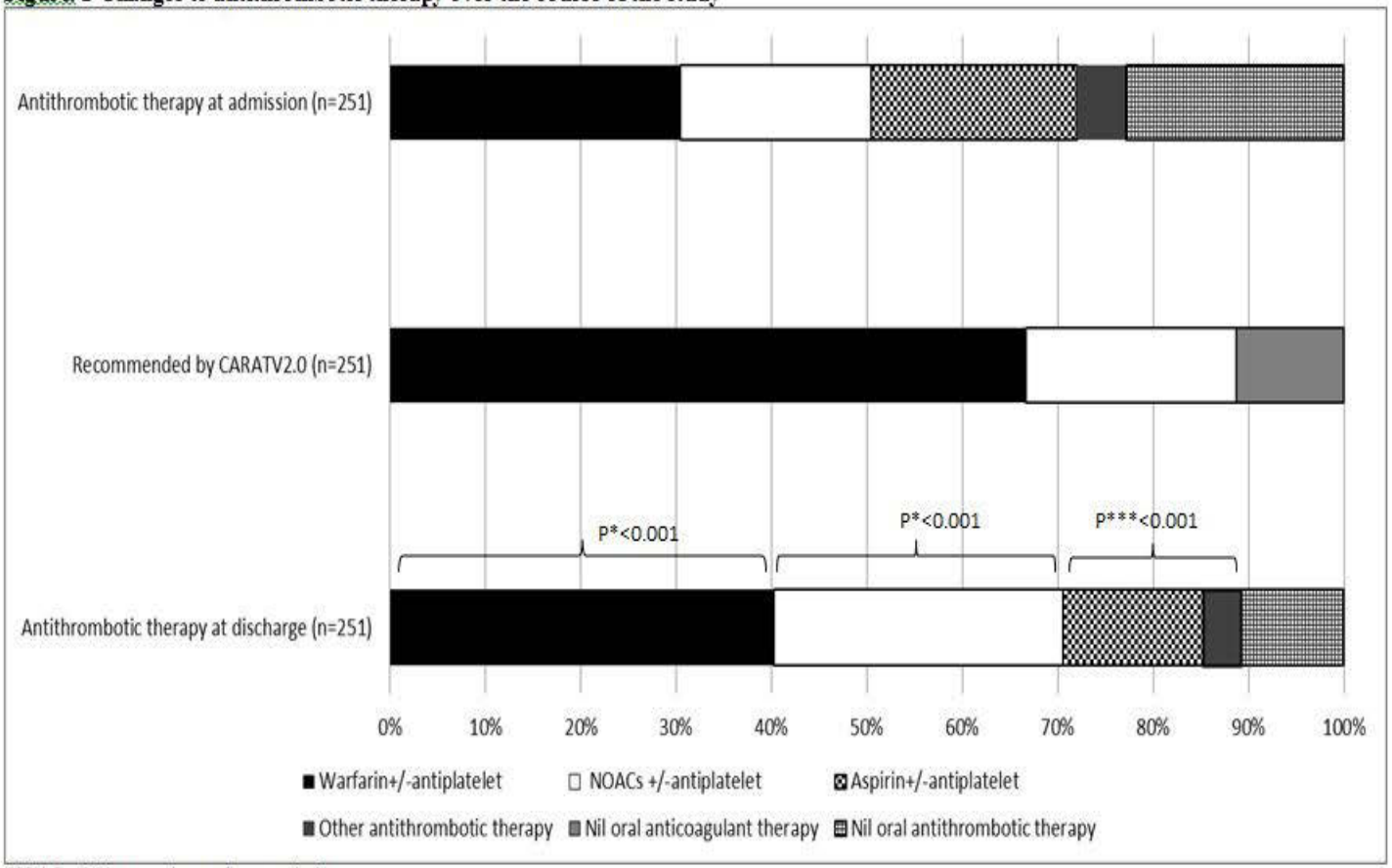
Supplemental Table 2 Prescribers' reasons for not following CARATV2.0's recommendations

Therapy recommended by CARATV2.0 (n=119)	Therapy prescribed by prescribers at discharge (n=119)	Prescribers' reasons for not following CARATV2.0's recommendations
Warfarin (n=79)	NOACs (±antiplatelet) (n=44)	• NOACs better/easier to manage/no need for monitoring (n=19) • continue pre-admission therapy (n=16) • consultant/specialist's opinion (n=6) • patient not reliable on INR check (n=1) • high fall risk (may leads to bleeding) (n=1) • dementia (hard to manage warfarin) (n=1)
	Antiplatelet (±antiplatelet) n=22	• high fall risk (may leads to bleeding) (n=6) • couple of AF episodes (follow-up to consider OAC) (n=5) • continue pre-admission therapy (n=3) • bleeding risk (history of GI or urinary bleeding) (n=3) • anemia (n=1) • cognitive impairment and high fall risk (n=1) • dementia (n=1) • GP's opinion (n=1) • older age (palliative care) (n=1)
	Nil antithrombotic therapy (n=13)	• New onset of AF (follow-up to consider OAC) (n=5) • risk of bleeding due to comorbidities (n=2) • GP to start warfarin (n=1) • older age (palliative care) (n=1) • older age and comorbidities (n=1) • older age and high fall risk (n=1) • older age and dementia (n=1) • dementia and wheel chair bound (n=1)
NOACs* (n=29)	Warfarin (±antiplatelet) (n=10)	• continue pre-admission therapy (n=5) • warfarin works well and can be monitored (n=3) • specialist's opinion (n=1) • ADR with rivaroxban so back to warfarin (n=1)
	Antiplatelet (±antiplatelet) (n=10)	• continue pre-admission therapy (n=2) • bleeding risk>stroke risk (n=1) • bleeding risk due to previous trauma and current cancer status (n=1) • older age and high fall risk (n=1) • dementia and high fall risk (n=1) • specialist's opinion (n=1) • GP's opinion (worried about fall risk) (n=1) • GP and specialist' opinion (fall risk and prior subdural bleeding) (n=1) • couple of AF episodes (follow-up to consider OAC) (n=1)
	Nil antithrombotic therapy (n=9)	• low platelet and anemia (n=2) • multiple myeloma and anemia baseline INR 1.6 (n=1) • recent bleeding (follow-up to consider OAC) (n=1) • older age (n=1)

		• older age and comorbidities (n=1) • fall risk (may leads to bleeding) (n=1) • GP and specialist's opinion (n=1) • GP's opinion (n=1)
Unsuitable for OAC† (n=8)	Warfarin (±antiplatelet) (n=3)	• stroke risk (need OAC) (n=2) • continue pre-admission therapy (n=1)
	NOACs ‡ (±antiplatelet) (n=5)	• stroke risk (need OAC) (n=2) • continue pre-admission therapy (n=2) • specialist's opinion (n=1)
Apixaban (n=3)	Rivaroxaban (±antiplatelet) (n=3)	• Rivaroxaban better /easier to manage (n=2) • continue pre-admission therapy (n=1)

Antiplatelet (±antiplatelet) including: aspirin, aspirin+dipyramidole, aspirin+clopidogrel or clopidogrel.
OAC: oral anticoagulants
* Including: any NOAC (dabigatran or rivaroxaban or apixaban), either rivaroxaban or apixaban, apixaban only, either dabigatran or rivaroxaban, either dabigatran or apixaban
†Unsuitable for oral anticoagulants: if non-modifiable risk factors, consider alternative antithrombotics (e.g., aspirin, clopidogrel) or seek specialists' advice
‡ Including dabigatran or rivaroxaban or apixaban

Figure. 1 Changes to antithrombotic therapy over the course of the study



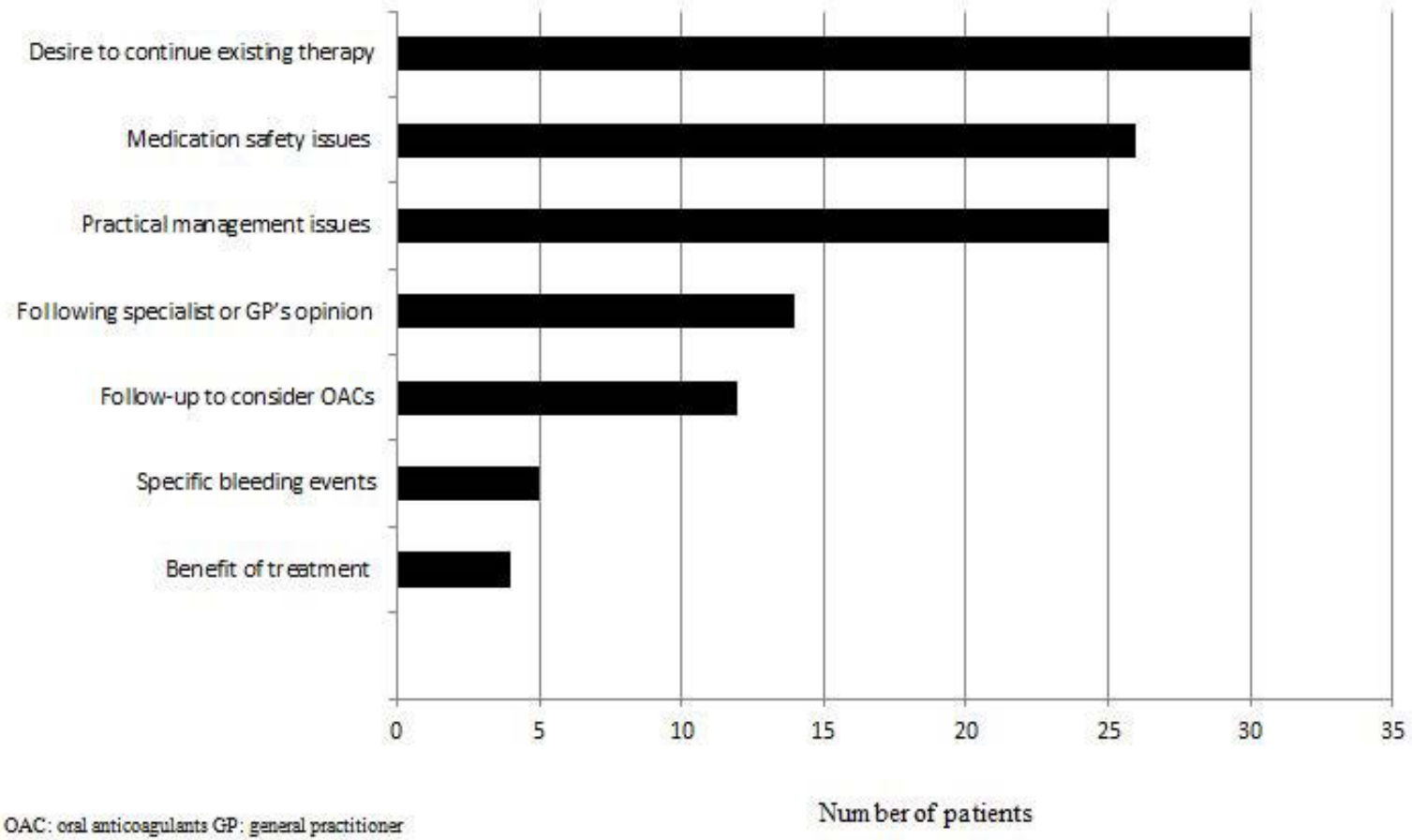
NOACs: dabigatran, rivaroxaban or apixaban.

* P-value (significance) use of therapy (proportion of patients receiving warfarin (±antiplatelet) at discharge compares with use of therapy (proportion of patients receiving warfarin (±antiplatelet) on admission.

** P-value (significance) use of therapy (proportion of patients receiving NOACs) at discharge compares with use of therapy (proportion of patients receiving NOACs) on admission

***P-value (significance) use of therapy (proportion of patients receiving antiplatelet (±antiplatelet) at discharge compares with use of therapy (proportion of patients receiving antiplatelet (±antiplatelet) on admission.

Figure. 2 Main reasons for not taking CARATV2.0's recommendations



OAC: oral anticoagulants GP: general practitioner

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Chapter Seven

7.1 Old age, high risk medication, polypharmacy—a 'trilogy' of risks associated with medication use in the elderly with atrial fibrillation.

Yishen Wang, Shamsher Singh and Beata Bajorek

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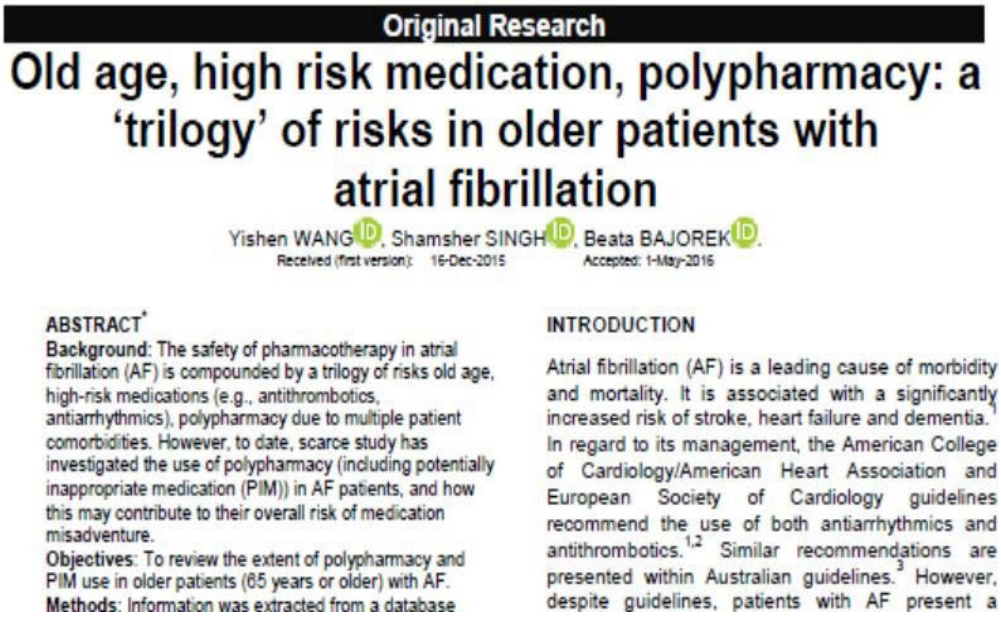
Published version attached in Appendix



Original Research

Old age, high risk medication, polypharmacy: a 'trilogy' of risks in older patients with atrial fibrillation

Yishen WANG, Shamsher SINGH, Beata BAJOREK.

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ABSTRACT*

Background: The safety of pharmacotherapy in atrial fibrillation (AF) is compounded by a trilogy of risks old age, high-risk medications (e.g., antithrombotics, antiarrhythmics), polypharmacy due to multiple patient comorbidities. However, to date, scarce study has investigated the use of polypharmacy (including potentially inappropriate medication (PIM)) in AF patients, and how this may contribute to their overall risk of medication misadventure.

Objectives: To review the extent of polypharmacy and PIM use in older patients (65 years or older) with AF.

Methods: Information was extracted from a database

INTRODUCTION

Atrial fibrillation (AF) is a leading cause of morbidity and mortality. It is associated with a significantly increased risk of stroke, heart failure and dementia.[1] In regard to its management, the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend the use of both antiarrhythmics and antithrombotics.[1,2] Similar recommendations are presented within Australian guidelines.[3] However, despite guidelines, patients with AF present a

Abstract

Background: The safety of pharmacotherapy in atrial fibrillation (AF) is compounded by a trilogy of risks including old age, high-risk medications (e.g., antithrombotics, antiarrhythmics) and polypharmacy due to multiple patient comorbidities. However, to date, scarce study has investigated the use of polypharmacy (including potentially inappropriate medication (PIM)) in AF patients, and how this may contribute to their overall risk of medication misadventure.

Objectives: To review the extent of polypharmacy and PIM use in older patients (≥ 65 years) with AF.

Methods: Information was extracted from a database characterising a cohort of older AF patients treated in general practice in New South Wales, Australia. Patient characteristics, number and types of drugs, the degree of PIM use were recorded. The predictors for the use of polypharmacy in older AF patients were identified.

Results: Overall, 367 patients (mean age 77.8 years) were reviewed, among which 94.8% used ≥ 5 medications and over half used ≥ 10 medications. Cardiovascular agents were most commonly used (98.9%), followed by antithrombotics (90.7%). Among agents deemed PIMs, digoxin (30.2%) was the most frequently used, followed by benzodiazepines (19.6%), and sotalol (9.8%). AF patients using polypharmacy (use of five or more regular medications) were more likely to have low bleeding risk (OR=10.97), representing those patients in whom high-risk antithrombotics are mostly indicated. Patients with major-

polypharmacy (≥ 10 medications) are more likely to have obstructive pulmonary diseases (OR=2.32), upper gastrointestinal diseases (OR=2.02) and poor physical function (OR=1.04), but less likely to have cognitive impairment (OR=0.27).

Conclusion: Polypharmacy affects most older AF patients, comprising medications that are indicated for AF, yet regarded as PIMs. Patients with lower risk of bleeding, obstructive pulmonary diseases, upper gastrointestinal diseases and poor physical function are also at higher risk of using higher number of medications. This may lead to an increased risk for medication misadventure due to the concomitant use of polypharmacy and medications for AF.

Introduction

Atrial fibrillation (AF) is a leading cause of morbidity and mortality. It is associated with a significantly increased risk of stroke, heart failure and dementia (1). In regard to its management, the American College of Cardiology/American Heart Association and European Society of Cardiology (1, 2) guidelines recommend the use of both antiarrhythmics and antithrombotics. Similar recommendations are presented within Australian guidelines (3). However, despite guidelines, patients with AF present a quandary for health care professionals. First, their age (i.e., being older persons) presents specific challenges in the selection of medicines and associated management, due to age-related physiological changes as well as functional and cognitive impairments (4). Second, the need to use high-risk medications (e.g., antithrombotics and antiarrhythmics), as indicated by clinical guidelines, increases their risk for medication misadventure (e.g., bleeding, bradyarrhythmias) (1).

However, the risks do not stop here. In fact, patients with AF are exposed to a trilogy of risks, inherent to their overall disease presentation and management. Aside from their advancing age and the use of high-risk medicines, there is an additional risk factor: polypharmacy. A multitude of agents may be prescribed to AF patients for stroke prevention, management of the arrhythmia, treatment of accompanying cardiovascular and stroke risk factors, as well as therapies for other comorbidities. Collectively, these complicate medication management and increase the risk of medication misadventure, manifesting as non-adherence, adverse drug reactions (ADRs), and drug interactions, all of

which can lead to poor clinical outcomes (5). In turn, this complicates health professionals' decision-making, particularly in relation to prescribing anticoagulation for stroke prevention (6).

Aim of the study

International studies have shown that polypharmacy is common in patients with AF (7, 8) and in patients using anticoagulants (3). However, in Australia, little attention has been paid to the degree of polypharmacy in elderly AF patients and how this may contribute to their overall risk of medication misadventure. Therefore, the aim of this study was to characterise AF patients in the Australian primary care setting in terms of this 'trilogy' of risks, and to specifically: 1) describe the extent of use of polypharmacy in older AF patients; 2) determine the degree to which these medications may be potentially inappropriate; 3) identify factors associated with the use of polypharmacy; and 4) identify factors associated with major polypharmacy versus minor polypharmacy in older AF patients.

Ethical approval

Ethics approval was obtained from the participating institutions (9). Patient data were coded and de-identified prior to analysis.

Method

Design

In this cross-sectional study, information was extracted from a database pertaining to a cohort of AF patients (≥ 65 years) recruited for a previous study conducted in general practices within metropolitan and regional areas of New South Wales, Australia (detailed description of the study recruitment/data collection methods is reported elsewhere (9)). Patients with a confirmed diagnosis of AF were recruited by their general practitioners (GPs) during routine care.

Data Collection

Purpose-designed data collection instruments were used to extract and record data from medical notes, patient interviews, and a brief patient survey (e.g., medical history, medication use). All collected data were verified by the patients' GPs.

Definitions and Measures

Polypharmacy is most commonly defined as the use of five or more regular medications (10). For the purposes of this study, polypharmacy was categorised as follows (11):

- Non-Polypharmacy: four or less medications
- Minor-Polypharmacy: use of five to nine medications
- Major-Polypharmacy: concomitant use of ten or more medications

Diagnoses were coded using the World Health Organization (WHO) *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) (12). $CHADS_2$ (13) and CHA_2DS_2VASc (14) scores 0, 1, ≥ 2 were classified as low, intermediate and high stroke risk, respectively. HAS-BLED (15) scores 0, 1-2, ≥ 3 were classified as low, intermediate and high bleeding risk, respectively. $HEMORR_2HAGES$ (16) scores 0-1, 2-3, ≥ 4 were classified as low, intermediate and high bleeding risk, respectively. In this study, CHA_2DS_2VASc and HAS-BLED were used as they are commonly recommended by international guidelines (14, 15). Although CHA_2DS_2VASc and HAS-BLED are advocated in more recent European Society of Cardiology guidelines, $CHADS_2$ was additionally used in this study because it is included in Australian local guidelines (e.g., National Prescribing Service guideline (2013) (17), Therapeutic Guidelines (2012) (18)), while $HEMORR_2HAGES$ was used because it is recommended by National Clinical Guideline Centre (UK) and American College of Cardiology/American Heart Association guidelines (19, 1). Moreover, since these scoring tools have different sensitivities and specificities, the use of four scores assisted in reducing any false positives and false negatives in the risk assessment. SF-36, a survey, which provides psychometrically-based physical and mental health summary measures and a preference-based health utility index, was also used (20).

Recorded medications included both over-the-counter and prescription medicines used by patients (as documented in their medication histories), regardless of short-term or long-term use. All medications were classified according to Anatomical Therapeutic Chemical (ATC) classification system (21). The medications used by patients were then assessed to whether they were 'potentially inappropriate medicines' (PIMs) for older patients, according to two

explicit criteria, i.e. Beers criteria 2012 (22) and PRISCUS criteria (23). Both Beers criteria and PRISCUS criteria were selected because of slight variations in defining certain medications as potentially inappropriate based on the dosage (e.g., digoxin).

Statistical Analysis

Computerised data analysis employed SPSS (Statistical Package for the Social Sciences Version 19). To explore relationships involving continuous variables, ANOVA (parametric distribution) and Kruskal-Wallis (non-parametric distribution) were used. The Chi-square test examined differences in independent proportions. Multivariate logistic regression (Forward Wald) analysis was used to assess the influence of the predictors on polypharmacy. $P<0.1$ was used in multivariate logistic regression. $P<0.05$ was considered statistically significant for all other analysis.

Results

Patient characteristics

The mean age of patients (N=367) was 77.8 years; two-thirds were less than 75 years old. The age categories were based on those used by clinical guidelines for anticoagulant treatment, as well as the apparent distribution of polypharmacy by age in the cohort (Table 1). In terms of their AF history, most (87.5%) patients had AF for at least 1 year, with over half (57.5%) diagnosed as having persistent AF. Most patients were categorised as being at least at intermediate risk of stroke (92.1% by $CHADS_2$ and 100% by CHA_2DS_2VASc).

Over half of the patients (53.4%) were identified to have 'intermediate' or 'high' bleeding risk as per HEMORR2HAGS and 93.9% patients were identified to have 'intermediate' or 'high' as per HAS-BLED scores.

Extent of polypharmacy

Overall, 348 (94.9%) patients were using some degree of polypharmacy, whilst just over half (55.9%; n=205) of the patients were using major-polypharmacy (Table 1). Compared to patients in the non-polypharmacy group (5.1% of patients), those with minor-polypharmacy and major-polypharmacy had more comorbidities (P<0.01) (Table 2). In terms of major diseases (excluding AF), patients in the major-polypharmacy group had a higher incidence of diabetes (P<0.01), upper gastrointestinal (GI) discomfort (P<0.01), and asthma or chronic obstructive pulmonary disease (P<0.01). Patients in the major-polypharmacy group had a significantly lower SF-36 physical score than those with minor-polypharmacy or non-polypharmacy (P=0.01).

Polypharmacy in AF patients according to 'risk category'

When comparing the use of polypharmacy by stroke risk (per $CHADS_2$), a higher proportion of patients used polypharmacy among those at high risk of stroke, compared to those at low risk of stroke (98.4% vs. 84.6%, P=0.002). When compared by bleeding risk (per $HEMORR_2HAGS$), a higher proportion of patients used polypharmacy among those at intermediate risk of bleeding, compared to those at high risk of bleeding (96.5% vs. 86.2%,

P=0.013) (Table 1). When comparing the use of polypharmacy across various risk categories per CHA_2DS_2VASc and HAS-BLED scores, no significant difference was found.

A number of patients were identified as having specific medication safety issues that might affect a patient's medication management ability and/or put them at a risk of medication misadventure. Among those patients with documented cognitive impairment (n=18), 83.3% had major-polypharmacy and the remainder had minor-polypharmacy. Among all of the patients who reportedly needed assistance with medication management, 46.3% had major-polypharmacy and the remainder had minor-polypharmacy. All patients with poor medication adherence (self-reported) had some degree of polypharmacy; almost three quarters (72.7%) of these patients had major-polypharmacy (Table 2).

Number and types of drugs

Patients with major-polypharmacy used almost two and half times the mean number of medications (mean=2.5, SD=1.0) per diagnosed disease, compared to non-polypharmacy patients (mean=1.1, SD=0.5, P<0.01). Unsurprisingly, drugs acting on the cardiovascular system, as well as blood and blood forming agents, were the most commonly used medications (Table 3). Since all patients had at least an intermediate stroke risk (as per CHA_2DS_2VASc), most were taking warfarin±aspirin (79.8%) and around one in ten were on dabigatran (11.7%). Around one in twenty patients were using aspirin or clopidogrel (6.8%) (Table 4). Among all patients, nearly two-thirds were using beta blockers (59.4%), while around one in ten patients were using sotalol (9.8%) or nondihydropyridine calcium channel blockers (10.3%). Surprisingly, 30.2% patients were using digitalis glycosides

(digoxin), despite it not being indicated as a first-line therapy by clinical guidelines (24) and noting that it is identified as a PIM. Among "non-cardiovascular" medications, analgesics (N02) and drugs for acid-related disorders were most commonly used (taken by over half of the patients). Among these, 55.3% of patients were using analgesics in combination with antithrombotics, comprising 137 (37.3%) patients using warfarin concurrently with paracetamol, 32 (8.7%) patients using warfarin concurrently with opioids, and 9 (2.5%) patients using warfarin concurrently with nonsteroidal anti-inflammatory drugs (NSAIDs).

Factors associated with polypharmacy versus non-polypharmacy

Univariate analysis was used to identify the factors associated with polypharmacy (≥5 medications) versus non-polypharmacy. Univariate analysis identified that patients using polypharmacy were more likely to have a higher stroke risk, per $CHADS_2$ (OR 4.40, 95%CI 1.23-15.66, P=0.03 compared with low stroke risk) and a lower bleeding risk, per $HEMORR_2HAGS$ (OR 10.97, 95%CI 1.66-72.60, P=0.01 compared with high bleeding risk). In multivariate analysis, only a lower bleeding risk ($HEMORR_2HAGS$) remained a significant predictor of polypharmacy (OR 10.97, 95%CI 1.66-72.60, P=0.01) (Model: Cox&Snell R^2 =0.03, Nagelkerke R^2=0.09, 94.8% correctly predicted). CHA_2DS_2VASc and HAS-BLED were not found to be significantly associated with polypharmacy.

Univariate analysis was used to identify the factors associated with major-polypharmacy versus minor-polypharmacy. Univariate analysis identified that patients using major-polypharmacy were more likely to have higher number of comorbidities (OR 1.28, 95%CI

1.15-1.42, P<0.001), upper gastrointestinal disease (includes gastric ulcer, gastritis, oesophagitis/ulcer, duodenal ulcer or gastroesophageal reflux disease, OR 2.51, 95%CI 1.56-4.04, P<0.001), obstructive pulmonary disease (asthma or chronic obstructive pulmonary disease (COPD), OR 2.89, 95%CI 1.47-5.72, P=0.002), and poor physical function (as measured by SF-36 physical score, OR 1.05, 95%CI 1.02-1.08, P=0.003), but less likely to have cognitive impairment (OR 0.27, 95%CI 0.07-0.96, P=0.04). In multivariate analysis, obstructive pulmonary disease (adjusted OR 2.32, 95%CI 1.14-4.71, P=0.02), upper gastrointestinal disease (adjusted OR 2.02, 95%CI 1.23-3.34, P=0.006), cognitive impairment (adjusted OR 0.27, 95%CI 0.07-0.97, P=0.04), and poor physical function (as measured by SF-36 physical score, adjusted OR 1.04, 95%CI 1.00-1.07, P=0.01) remained significant predictors of major-polypharmacy (Model: Cox&Snell R^2 =0.10, Nagelkerke R^2=0.13, 63.5% correctly predicted).

Inappropriate use of medications

Overall, 250 (68%) patients (mean age 77.9 years) were using at least 1 PIM (Table 3). Among the most frequently identified PIMs (Table 4), four agents were for rhythm and/or rate control: digoxin (30.2%), sotalol (9.8%), amiodarone (7.9%), and flecainide (2.2%). Among those on digoxin, only 24 (21.6%) patients had a documented diagnosis of chronic heart failure, as required by guidelines (24).

The most commonly used "non-AF" PIMs were benzodiazepines (long, short and intermediate acting) (19.1%), followed by spironolactone (9.3%) and tricyclic antidepressants (TCA) (amitriptyline, imipramine) (7.6%).

Discussion

Our study presents some initial findings on the use of high-risk medications and polypharmacy, including PIMs, among older AF patients in a primary care setting. The study has identified a high prevalence of polypharmacy in older patients with AF (94.8%). This rate of polypharmacy is higher than reported in a study of older patients (aged ≥70 years, including AF and non-AF patients), treated in the general practice setting in Germany (25) and higher than in an Australian study of older patients (aged ≥ 70 years) admitted to general medical units in acute care hospitals (10). Not unexpectedly, the most frequently prescribed medications included cardiovascular agents, consistent with other studies (26), followed by antithrombotics. The significance of this is that these commonly used medications not only contribute to the burden of polypharmacy in AF patients, but they are also regarded to be high risk medicines and, in some cases, PIMs. Since these are guideline-indicated therapies for AF patients (1), this polypharmacy comprising PIMs creates a particularly high-risk situation for patients, further increasing the likelihood of adverse drug reactions and medication misadventure (27). Regarding the use of aspirin as a monotherapy, evidence-based clinical practice guidelines suggest that aspirin alone is insufficient to reduce stroke risk. In our study, since the stroke risk in this patient sample was at least intermediate (as per CHA_2DS_2VASc), the observed use of aspirin monotherapy was potentially not aligned with evidence-based guidelines (14).

It is important to note that among the most commonly used AF therapies in this study, several (i.e., antiarrhythmics) were identified as PIMs according to Beers criteria or the

PRISCUS list. In particular, the use of digoxin was surprisingly high in this study population and consistent with other studies (28, 29). Given that digoxin is no longer recommended as a mainstay therapy, being reserved for those AF patients who have congestive heart failure unresponsive to first-line therapy, this possible overuse in patients with AF raises concerns about the safety and necessity of its use (28).

Medication safety in AF patients is further compounded when patients require pharmacotherapy for other non-AF conditions. As also reported in earlier studies, a surprisingly high number of patients used analgesics, suggesting that in older patients with AF there is a high prevalence of pain conditions (e.g., arthritis) (30). The concurrent use of analgesics with AF pharmacotherapy may lead to drug interactions and/or GI (gastrointestinal) adverse drug reactions which may increase the risk of bleeding, especially GI bleeding. Noting that the prevalence of NSAIDs use in our study was only 4.3%, much lower than other studies of AF patients (33) and the use of NSAIDs in combination with warfarin only 2.5%, the rate of such interactions might be relatively low. Nevertheless, the episodic nature of pain can complicate AF management, because pain is symptomatic and therefore patients may prioritise analgesic use over AF therapy (34). However, this study found that the use of paracetamol in combination with warfarin is relatively common. As reported by other studies, the interaction between warfarin and paracetamol is often underestimated, but is important because it can potentiate the anticoagulant effect of warfarin and increase the rate of fatal bleeding 2.7 times (compared to warfarin use alone) (19, 20). The mechanism of this interaction is not fully understood but some studies support the hypothesis that paracetamol (or its metabolites) interact with certain enzymes

responsible for the synthesis of vitamin K dependent coagulation factors (vitamin K-dependent γ-carboxylase and vitamin K epoxide reductase) (19).

Although proton pump inhibitors (PPIs) are commonly used medications, this study shows that the use of PPIs is higher than that in other studies of general older patients in nursing homes (35) and those admitted to hospitals (36). The frequent use of PPIs for GI conditions in our study raises concerns that many AF patients may potentially suffer from drug-induced GI adverse drug reactions, since a number of AF pharmacotherapies (e.g., antiarrhythmics, antithrombotics) are reported to cause GI symptoms, including upper GI bleeding. Separate to GI adverse drug reactions, according to the approved product information, acid-minimising/suppressing agents (e.g., omeprazole (37)) may also interact with prescribed AF medications (e.g., warfarin, digoxin), increasing the potential for side effects (e.g. bleeding, arrhythmia) leading to suboptimal clinical outcomes (38).

In relation to the over-use of therapies, a surprisingly high proportion of patients were found to be taking benzodiazepines in this study, which are recognised as a major cause of adverse drug reactions in the older patients (39). A previous study pertaining to general older patients (aged >65 years) in the Australian general practice setting reported that 45% of patients using benzodiazepines experienced two to six adverse drug reactions, whilst 15% of patients had seven or more reactions during the study period (39). Benzodiazepines, as well as other psycholeptics, psychoanaleptics, diuretics, antihypertensive agents, anti-inflammatory and anti-rheumatic products (e.g., NSAIDs) are regarded as PIMs in older persons; many of these may lead to a high risk of falls, and/or increased risk of intracranial

bleeding, whilst others can cause GI bleeding, exacerbating the background risks already posed by specific AF therapies (40).

Regarding the different classifications of bleeding risk assessment, two tools were used: HAS-BLED, which is widely incorporated into international treatment guidelines (1, 2), and HEMORR$_2$HAGES, as recommended by National Clinical Guideline Centre (UK) and American College of Cardiology/American Heart Association guidelines (1, 19). Compared with HAS-BLED, HEMORR$_2$HAGES uniquely includes a wider range of risk factors namely: malignancy, anemia, genetic factors, reduced platelet count or function, excessive falls risk, in addition to the common bleeding risk factors (e.g., hypertension, abnormal renal/liver function, stroke, bleeding predisposition, age, alcohol use). HAS-BLED has better sensitivity than HEMORR$_2$HAGES in identifying any clinically relevant bleeding in anticoagulated patients with AF (41). However, HEMORR$_2$HAGES has a higher diagnostic accuracy due to its higher specificity (41). The association between a lower HEMORR$_2$HAGES (but not HAS-BLED) score and polypharmacy may be explained by the wider range of risk factors included in it, although none of the individual risk factors were found to be significantly associated with polypharmacy in this study. In this regard, decision support tools (such as CARAT (42)) can help assess these risk factors when recommending antithrombotic therapy, and therefore may be useful in identifying the potential for polypharmacy (and therefore any medication safety issues).

This study has identified that patients using polypharmacy are also more likely to have a low risk of bleeding. Given that the decision-making around the use of antithrombotics in

AF focuses on weighing the risk of stroke versus the risk of bleeding, in this equation these "low risk" patients (low bleeding risk) are generally deemed to be more eligible for anticoagulants (e.g., warfarin) than patients at a higher bleeding risk. However, these same low-risk patients are also more likely to have polypharmacy (as identified here), thereby increasing the risk of drug-drug interactions, adverse drug reactions and treatment non-adherence. Therefore, in prescribing antithrombotics for AF patients, clinicians must consider both the stroke versus bleeding risks alongside the relevant medication safety considerations (i.e., the implications of polypharmacy), to ensure that in optimising antithrombotic therapy they are not inadvertently putting "low risk" patients at high risk of medication misadventure. Whilst this should not stop the use of antithrombotics, it does reinforce the need for comprehensive patient assessment with regular review and follow-up to monitor for medication misadventure in all patients including those apparently at "low risk".

In this study, patients with major-polypharmacy were more likely to have obstructive pulmonary disease (asthma or COPD), upper gastrointestinal disease and poor physical function (as per SF-36), but less likely to have cognitive impairment. This is consistent with other studies showing that asthma or COPD and gastrointestinal disease (43, 44) are associated with excessive polypharmacy (≥ 10 drugs) (45). Possible reasons include that obstructive pulmonary disease can cause a range of different comorbidities, including heart disease (e.g., heart failure, arrhythmias), chronic kidney disease, cancer, metabolic disease (e.g., osteoporosis, diabetes) and pulmonary embolism (46). Since patients with upper gastrointestinal disease have a higher risk of gastrointestinal bleeding (38), the association

of upper gastrointestinal diseases with major-polypharmacy in patients with AF needs some vigilance; the concomitant use of oral antithrombotics (e.g., dabigatran, aspirin) and NSAIDs in the presence of polypharmacy and gastrointestinal disease may predispose patients to an increased risk of GI haemorrhage and associated morbidity and mortality. Similarly, poor physical function (measured by SF-36), as reported by previous studies was found to be associated with the use of an increased number of medications (47). Since patients with polypharmacy are at higher risk of adverse reactions (5), it is important to balance the need for multiple medications with patients' desired quality of life. In contrast, cognitive impairment has been shown to be associated with a reduced use of medications (43, 44). This may be due to prescribers' concerns about using multiple medications in those patients, as studies have shown that cognitive impairment may cause lower adherence and communication difficulties, including a decreased ability to report adverse effects (48, 49).

The 'trilogy' of risks in older AF patients warrants specific attention when managing their medication regimens. Services such as Home Medicines Review (HMR) (50) can help to assess the medication regimens of such patients, and have been shown to reduce the use of PIMs (51). Other services such as MedsCheck (medicines use review) and Diabetes MedsCheck (diabetes medication management) are structured pharmacy services, involving face-to-face consultations between the pharmacist and consumer (52). These services are designed to enhance the quality use of medicines through patient education, self-management and medication adherence strategies, and may help to reduce the medication misadventure experienced by patients (53). Some available risk assessment tools, such as

CHA_2DS_2VASc (14) and HAS-BLED (15), can assist in quantifying the stroke or bleeding risk for an individual patient. However, medication management in AF patients requires a more careful balance of risks and benefits to ensure optimal therapy that not only minimises the stroke and bleeding risks, but also reduces the risk for medication misadventure from any cause.

Targeted decision support tools, which systematically assess a patient's medical history, stroke and bleeding risk and which consider pertinent medication safety issues (e.g. polypharmacy, drug-drug interactions), may assist here (42); these tools can support prescribing as well as facilitate the regular review of medication regimens. Regular medication review services using risk assessment tools may help reduce the risk and optimise medication use. However, there are still some gaps in implementing these tools and services in the medication management of AF patients. Designed for specific contexts (e.g., stroke, bleeding) or certain types of medication (e.g., antithrombotics), these tools (CHA_2DS_2VASc (14), HAS-BLED (15) and CARAT (42)) alone may not be completely useful in the comprehensive review and management of AF patients' overall medication regimen (as opposed to just their antithrombotic therapy). Also, these tools and services have not yet been evaluated in large-scale studies involving older AF patients. Therefore, given that the use of pharmacotherapy in this specific context (older persons with AF) is complex, further research needs to more comprehensively investigate the risk factors and explore the impact of targeted interventions on managing the 'trilogy' of risks.

In considering the findings of this study, some limitations need to be acknowledged. The retrospective nature of the study, and the limited number of AF patients in the cohort reviewed, result in relatively wide confidence intervals, requiring that the findings to be interpreted with caution. A prospective study using a matched control design would perhaps provide more robust findings. The logistic regression analysis for the outcome "major-polypharmacy versus minor polypharmacy" has limited prediction value, which means that there may be other risk factors associated with major-polypharmacy which need to be explored in future studies. However, the selection of these patients is representative of older patients with AF encountered in the Australian general practice setting, providing an important insight into the specific challenges of using pharmacotherapy in this patient cohort. Furthermore, although there is uncertainty around the reliability of GPs' medication records as the primary source of medication histories, the medication lists recorded in this study were verified by the GPs. Due to the cross-sectional design of this study, only explicit criteria were used to identify PIMs. Though many of the results of this study confirm the previous findings in the literature, this study is first to demonstrate the relationship between low-bleeding risk and polypharmacy.

Conclusion

Polypharmacy affects most older AF patients, comprising medications that are indicated for AF, yet regarded as PIMs. Patients with a lower risk of bleeding, obstructive pulmonary disease, upper gastrointestinal disease and poor physical function are significantly more likely to use multiple medications. This may lead to an increased risk of medication

misadventure due to the concomitant use of polypharmacy and high-risk medications indicated for AF.

Conflicts of interest

None to declare.

Table 1 Patient characteristics

Characteristics **N (%) of patients** 367 (100)	**Non-polypharmacy** **(0-4 drugs)** (% of total) 19 (5.2)	**Minor-polypharmacy** **(5-9 drugs)** (% of total) 143 (39.0)	**Major-polypharmacy** **(≥10 drugs)** (% of total) 205 (55.9)	**P**[*]
Gender male	13 (3.5)	87 (23.7)	103 (28.1)	0.07
female	6 (1.6)	56 (15.3)	102 (27.8)	
Age μ (SD)	75.5 (6.8)	77.5 (6.9)	78.2 (7.1)	0.17
Age group				
≥75 years	9 (2.4)	91 (24.8)	129 (24.6)	0.38
<75 years	10 (2.7)	52 (14.2)	76 (20.7)	
Type of AF				
Paroxysmal	5 (1.4)	49 (13.3)	73 (19.9)	0.56 †
Persistent	12 (3.3)	86 (23.4)	113 (30.8)	
New Onset	1 (0.3)	6 (1.6)	14 (3.8)	
Unknown	1 (0.3)	2 (0.6)	5 (1.4)	
History of AF <1 year ≥ 1 year	 3 (0.8) 16 (4.4)	 16 (4.4) 127 (34.6)	 27 (7.4) 178 (48.5)	0.78
Current Cardiac Rhythm				
Normal Sinus Rhythm	2 (0.8)	11 (3.0)	28 (7.6)	0.22‡
Controlled AF	17 (4.6)	131 (8.4)	177 (48.2)	
Uncontrolled AF	0 (0.0)	1 (0.3)	0 (0.0)	
$CHADS_2$ score§				
Low	4 (1.2)	11 (3.0)	14 (3.8)	0.004
Intermediate	7 (1.9)	53 (14.4)	48 (13.1)	
High	8 (2.4)	77 (20.9)	143 (38.9)	
CHA_2DS_2-VASc score§				
Intermediate	2 (0.6)	6 (1.6)	6 (1.6)	0.24
High	17 (4.6)	137 (37.3)	199 (54.2)	
$HEMORR_2HAGS$ score¶				
Low	14 (3.8)	75 (20.4)	81 (22.1)	0.04
Intermediate	3 (0.8)	65 (17.7)	116 (31.6)	
High	2 (0.6)	3 (0.8)	8 (2.4)	
HAS-BLED score#				
Low	1 (0.3)	2 (0.6)	2 (0.6)	0.51
Intermediate	15 (4.1)	124 (33.8)	177 (48.2)	
High	3 (0.8)	17 (4.6)	26 (7.1)	

***** Difference among non-polypharmacy, minor-polypharmacy and major-polypharmacy

† P value: persistent compared with all other

‡ P value: sinus rhythm compared with all other

§ $CHADS_2$ (13) and CHA_2DS_2VASc (14) scores of 0, 1, ≥ 2 were classified as low, intermediate and high stroke risk, respectively.

¶ $HEMORR_2HAGES$ (16) scores of 0-1, 2-3, ≥ 4 were classified as low, intermediate and high bleeding risk, respectively.

HAS-BLED (15) scores of 0, 1-2, ≥ 3 were classified as low, intermediate and high bleeding risk, respectively.

Table 2 Medication safety considerations

Characteristics **N (%) of patients** 367 (100)	**Non-polypharmacy (0-4 drugs)** (% of total) 19 (5.2)	**Minor-polypharmacy (5-9 drugs)** (% of total) 143 (39.0)	**Major-polypharmacy (≥10 drugs)** (% of total) 205 (55.9)	**P***
Comorbidities μ (SD)	4.7 (3.3)	5.0 (2.4)	6.3 (2.4)	<0.01
Number of drugs (both prescription and non-prescription) μ (SD)	3.9 (0.6)	7.4 (1.4)	13.9 (3.4)	<0.01
Prescription drugs μ (SD)	3.47 (0.6)	6.3 (1.5)	12.0 (3.3)	<0.01
Non-prescription drugs (e.g., OTC, supplements) μ (SD)	0.21 (0.4)	1.08 (1.0)	1.9 (1.4)	<0.01
Cognitive impairment	0 (0.0)	3 (0.8)	15 (4.1)	0.07
Visual impairment	0 (0.0)	8 (2.2)	14 (3.8)	0.70
Hearing impairment	2 (0.6)	9 (7.9)	20 (6.2)	0.48
Language barrier	0 (0.0)	1 (0.3)	3 (0.8)	0.71
Mobility impairment	1 (0.3)	4 (1.1)	12 (3.3)	0.34
Residential care facility	0 (0.0)	1 (0.3)	3 (0.8)	0.71
Difficulty access medical care	0 (0.0)	2 (0.6)	1 (0.3)	0.63
Need assistance with medication	4 (1.1)	51 (13.9)	95 (25.9)	0.03
Poor adherence (self-reported)	0 (0.0)	6 (1.6)	16 (4.4)	0.27
Other major diseases				
Chronic heart failure	3 (0.8)	38 (10.3)	51 (13.9)	0.65
Hypertension	12 (3.7)	97 (26.4)	140 (38.1)	0.88
Diabetes	1 (0.3)	37 (10.1)	35 (9.5)	0.03
Prior stroke or TIA	5 (7.5)	27 (7.3)	35 (9.5)	0.52
Coronary heart disease	3 (0.8)	43 (11.7)	64 (16.9)	0.40
Asthma or COPD	4 (1.1)	12 (3.7)	43 (11.7)	<0.01
Arthritis (OA, RA, Psoriasis Arthritis)	3 (0.8)	32 (8.7)	62 (16.9)	0.16
Upper GI discomfort †	3 (0.8)	33 (8.9)	88 (24.0)	<0.01
Renal disease	0 (0.0)	7 (1.9)	9 (2.3)	0.92
Previous fall	0 (0.0)	4 (1.2)	7 (1.2)	1.00
Self-reported Health SF-36 ‡				
Physical μ (SD)	46.5 (5.9)	45.1 (8.2)	42.4 (7.4)	<0.01
Mental μ (SD)	58.2 (3.8)	55.4 (7.1)	54.8 (7.4)	0.10

TIA =transient ischaemic attack, COPD =chronic obstructive pulmonary disease, OA =osteoarthritis, RA= rheumatoid arthritis, GI= gastrointestinal, SF-36 =The Short Form (36) Health Survey is a patient-reported survey of patient health.

* Difference between non-polypharmacy, minor-polypharmacy and major-polypharmacy

† Upper GI diseases include gastric ulcer, gastritis, esophagitis/ulcer, duodenal ulcer or gastroesophageal reflux disease

‡ SF-36, a survey, which provides psychometrically-based physical and mental health summary measures and a preference-based health utility index (54). A high score of SF-36 means better health. Physical includes: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning. Mental includes: Role-Emotional, Mental Health

Table 3 Pharmacotherapy use and potentially inappropriate medicines (PIM)

Main therapeutic classes and most common subclasses † **N (%) of patients** 367 (100)	**Overall** (% of total) N (%) 367 (100)	**Non-polypharmacy (0-4 drugs)** (% of total) N (%) 19 (5.2)	**Minor-polypharmacy (5-9 drugs)** (% of total) 143 (39.0)	**Major-polypharmacy (≥10 drugs)** (% of total) 205 (55.9)	**P***
Cardiovascular agents					
Blood and blood forming agents (B)	361 (98.4)	19 (5.2)	140 (38.1)	202 (55.0)	<0.01
Antithrombotic agents (B01)	361 (98.4)	19 (5.24)	140 (38.1)	202 (55.0)	<0.01
Vitamin K antagonists (B01AA) Direct thrombin inhibitors (dabigatran) (B01AE)	293 (79.8) 43 (11.7)	14 (3.8) 3 (0.8)	122 (33.3) 12 (3.3)	157 (42.8) 28 (7.6)	<0.01 <0.01
Platelet aggregation inhibitors (B01AC)	38 (10.4)	2 (0.6)	7 (1.7)	29 (7.9)	<0.01
Cardiovascular system (C)	363 (98.9)	17 (4.6)	142 (38.7)	204 (55.6)	0.01
Lipid modifying agents (C10)	228 (62.1)	10 (2.7)	85 (23.2)	133 (36.2)	0.42
HMG CoA reductase inhibitors (C10AA)	220 (59.9)	9 (2.5)	84 (22.9)	127 (34.1)	0.42
Antihypertensive agents (C02) Prazosin‡ (C02CA01)	19 (5.2)	1 (0.3)	9 (2.5)	9 (2.5)	0.73
Methyldopa ‡ (C02AB)	6 (1.6)	0 (0.0)	1 (0.3)	5 (1.4)	0.31
Agents acting on the renin-angiotensin system (C09)	241 (65.7)	10 (2.7)	92 (25.1)	139 (37.9)	0.36
ACE inhibitors, plain (C09AA)	144 (39.2)	1 (0.3)	53 (14.4)	90 (24.5)	<0.01
Angiotensin II antagonists (C09CA)	119 (32.4)	4 (1.1)	47 (12.8)	68 (18.5)	0.56
Calcium channel blockers (C08)	95 (25.9)	5 (1.4)	30 (8.2)	60 (16.3)	0.03
Dihydropyridine derivatives (C08CA)	67 (18.3)	2 (0.6)	17 (4.6)	48 (13.1)	0.02
Benzothiazepine derivatives (diltazem) (C08DB)	17 (4.6)	0 (0.0)	7 (1.9)	10 (2.7)	1.00
Phenylalkylamine derivatives (verapamil) (C08DA)	21 (5.7)	3 (0.8)	6 (1.6)	12 (3.7)	0.12
Diuretics (C03)	162 (44.1)	3 (0.8)	53 (14.4)	106 (28.8)	<0.01
Sulfonamides (C03CA)	140 (38.1)	3 (0.8)	43 (11.7)	94 (25.6)	<0.01
Aldosterone antagonists (spironolactone¶) (C03DA)	34 (9.3)	0 (0.0)	11 (3.0)	23 (33.5)	0.22
Beta Blocker agents (C07)	218 (59.4)	8 (2.2)	87 (23.7)	123 (3.5)	0.28
Beta blocking agents, non-selective (C07AA) Sotalol (C07AA07)	55 (14.9) 30 (9.8)	2 (0.6) 1 (0.3)	26 (7.1) 19 (5.2)	27 (7.3) 16 (4.4)	0.40 0.18
Beta blocking agents, selective (C07AB)	154 (41.9)	10 (2.7)	51 (13.9)	93 (25.4)	0.12
Cardiac therapy (C01)	175 (47.7)	10 (2.7)	71 (19.3)	94 (25.6)	0.74
Antiarrhythmics, class III (C01BD) (amiodarone) ¶	29 (7.1)	1 (0.3)	11 (3.0)	17 (4.6)	0.90
Digitalis glycosides (digoxin) § (C01AA)	111 (30.2)	8 (2.2)	30 (8.2)	73 (19.9)	<.0.01
Flecainide ‡ (C01BC04)	8 (2.2)	1 (0.3)	3 (0.8)	4 (1.1)	0.67
Organic nitrates (C01DA)	71 (19,3)	1 (0.3)	17 (4.6)	53 (14.4)	<0.01
Non-cardiovascular agents					
Drugs for acid related disorders (A02)	198 (53.9)	6 (1.6)	55 (14.9)	137 (37.3)	<0.01
Proton pump inhibitor (A02BC)	156 (42.5)	6 (1.6)	43 (11.7)	107 (29.2)	<0.01
Drugs for functional gastrointestinal disorders (A03)					

Metoclopramide¶ (A03FA01)	8 (2.2)	0 (0.0)	2 (0.6)	6 (1.6)	<0.01
Psycholeptics (N05)	73 (19.9)	1 (0.3)	17 (4.6)	55 (14.9)	0.01
Benzodiazepine derivatives (N05CD) Short and intermediate acting ‡ Long acting ‡	70 (19.1) 54 (14.7) 18 (4.9)	1 (0.3) 1 (0.3) 0 (0.0)	17 (4.6) 14 (3.8) 3 (0.8)	52 (14.2) 39 (10.6) 15 (4.1)	0.002 0.02 0.27
Psychoanaleptics (N06)	70 (19.1)	1 (0.3)	13 (3.5)	56 (15.2)	<0.01
Antidepressant (N06A)	68 (18.5)	1 (0.3)	12 (3.3)	55 (14.9)	<0.01
TCA (N06AA) (amitriptyline, imipramine)	28 (7.6)	1 (0.3)	4 (1.1)	23 (6.2)	<0.01
SSRI (N06AB) (fluoxetine) ‡	24 (6.5)	0 (0.0)	5 (1.6)	19 (5.2)	0.03
Analgesics(N02)	207 (56.4)	5 (1.4)	59 (16.2)	143 (39.0)	<0.01
Anilides (paracetamol) (N02BE) Opioids (N02A)	196 (53.4) 42 (11.4)	5 (1.4) 0 (0.0)	56 (16.1) 5 (1.4)	135 (36.8) 37 (10.1)	<0.01 <0.01
Corticosteroids, dermatological preparations (D07) Corticosteroid for systemic use (H02)	93 (25.3) 27 (7.4)	5 (1.4) 0 (0.0)	26 (28.0) 5 (1.4)	62 (16.9) 22 (6.0)	0.04 0.02
Drugs for obstructive airway diseases (R03)	89 (24.3)	5 (1.4)	20 (5.4)	64 (17.4)	<0.01
Selective beta-2-adrenoreceptor agonists (R03AC)	51 (13.9)	4 (1.1)	8 (2.2)	39 (10.6)	<0.01
Corticosteroids inhaler (R03BA)	61 (16.6)	4 (1.1)	14 (3.8)	43 (11.8)	0.02
Drugs used in Diabetes (A10)	62 (16.9)	4 (1.1)	14 (3.8)	44 (12.0)	0.02
Insulin and analogues (A10A)	14 (3.8)	0 (0.0)	3 (0.8)	11 (3.0)	0.19
Blood glucose lowering drugs excl. insulin (A10B)	56 (15.3)	4 (1.1)	13 (3.5)	39 (10.6)	0.03
Anti-inflammatory and anti-rheumatic products (M01)					
Non-selective NSAID (M01AB) (diclofenac¶, ibuprofen¶, naproxen¶, indomethacin‡, piroxiacam‡)	16 (4.3)	0 (0.0)	5 (1.4)	11 (3.0)	0.29
Sex hormones and modulators of the genital system (G03) Estrogen with or without progestin¶ (G03CA)	23 (6.3)	1 (0.3)	4 (1.1)	18 (4.9)	0.59
Urologicals (G04)					
Urological spasmolytic agents (G04BD) (oxybutynine, tolterodine, solifenacin) ‡	9 (2.5)	1 (0.3)	1 (0.3)	7 (1.9)	0.16
Use of potentially inappropriate medications (PIMs)					
Overall use of PIMs	250 (68.2)	12 (3.3)	79 (21.5)	159 (43.3)	<0.001
One PIM (mean age =77.9 years)	144 (40.3)	9 (2.5)	56 (15.3)	84 (22.9)	-
Two PIMs(mean age =76.4 years)	68 (18.5)	2 (0.5)	15 (4.1)	51 (13.9)	-
Three PIMs (mean age =77.0 years)	38 (7.6)	1 (0.3)	7 (1.9)	20 (5.4)	-
Four PIMs (mean age =75.8 years).	5 (1.4)	0 (0.0)	1 (0.3)	4 (1.1)	-

NSAID: nonsteroidal anti-inflammatory drugs; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors

* Difference between non-polypharmacy, minor-polypharmacy and major-polypharmacy.

†All medications were classified according to Anatomical Therapeutic Chemical (ATC) classification system.

‡ Potentially inappropriate medicines (PIMs) according to both Beers criteria and PRISCUS criteria

§ Within these 111 patients, 22 patients met Beers criteria for potentially inappropriate use of digoxin (i.e. digoxin >0.125mg/d).

¶ Only included in Beers criteria.

Table 4 Antithrombotic therapy use stratified according to stroke risk

Stroke risk N (% of total)	**Warfarin** 279 (76.0)	**Warfarin+aspirin** 14 (3.8)	**Dabigatran** 43 (11.7)	**Clopidogrel** 3 (0.8)	**Aspirin** 22 (6.0)	**Nil therapy** 6 (1.6)
$CHADS_2$ score§						
Low	25 (6.8)	1 (0.3)	2 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Intermediate	87 (23.7)	1 (0.3)	14 (3.8)	0 (0.0)	7 (1.9)	1 (0.3)
High	167 (45.5)	12 (3.3)	27 (7.4)	3 (0.8)	14 (3.8)	5 (1.4)
CHA_2DS_2-VASc score§						
Intermediate	11 (3.0)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.00
High	268 (73.0)	21 (5.7)	42 (11.4)	3 (0.8)	21 (5.7)	6 (1.6)

§ $CHADS_2$ (13) and CHA_2DS_2VASc (14) scores of 0, 1, ≥ 2 were classified as low, intermediate and high stroke risk, respectively.

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7.2 Stroke prevention in atrial fibrillation: impact of a Computerised Risk Assessment Tool (CARAT) on the prescription of thromboprophylaxis in the hospital setting.

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Original Article

Impact of a Computerized Antithrombotic Risk Assessment Tool on the Prescription of Thromboprophylaxis in Atrial Fibrillation: Hospital Setting

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Abstract

The computerized antithrombotic risk assessment tool (CARAT) is an online decision-support algorithm that facilitates a systematic review of a patient's stroke risk, bleeding risk, and pertinent medication safety considerations, to generate an individualized treatment recommendation. The CARAT was prospectively applied across 2 hospitals in the greater Sydney area. Its impact on antithrombotics utilization for thromboprophylaxis in patients with nonvalvular atrial fibrillation was evaluated. Factors influencing prescribers' treatment selection were identified. The CARAT recommended a change in baseline therapy for 51.8% of patients. Among anticoagulant-eligible patients (ie, where the risk of stroke outweighed the risk of bleeding) using "nil therapy" or antiplatelet therapy at baseline, the CARAT recommended an upgrade to warfarin in 60 (30.8%) patients. For those in whom the bleeding risk outweighed the stroke risk, the CARAT recommended a downgrade from warfarin to safer alternatives (eg, aspirin) in 37 (19%) patients. Among the "most eligible" (ie, high stroke risk, low bleeding risk, no contraindications; n = 75), the CARAT recommended warfarin for all cases. Discharge therapy observed a marginal increase in anticoagulation prescription in eligible patients (n = 116; 57.8% vs 64.7%, $P = .35$) compared to baseline. Predictors of warfarin use (vs antiplatelets) included congestive cardiac failure, diabetes mellitus, and polypharmacy. The CARAT was able to optimize the selection of therapy, increasing anticoagulant use among

ABSTRACT

The computerised antithrombotic risk assessment tool (CARAT) is an online decision-support algorithm that facilitates a systematic review of a patient's stroke risk, bleeding risk, and pertinent medication safety considerations, to generate an individualised treatment recommendation. CARAT was prospectively applied across two hospitals in the greater Sydney area. Its impact on antithrombotics utilisation for thromboprophylaxis in nonvalvular atrial fibrillation patients was evaluated. Factors influencing prescribers' treatment selection were identified. CARAT recommended a change in baseline therapy for 51.8% patients. Among anticoagulant-eligible patients (i.e., where risk of stroke outweighed risk of bleeding) using 'nil therapy' or antiplatelet therapy at baseline, CARAT recommended an upgrade to warfarin in 60 (30.8%) patients. For those in whom the bleeding risk outweighed stroke risk, CARAT recommended a downgrade from warfarin to safer alternatives (e.g., aspirin) in 37 (19%) patients. Among the 'most eligible' (i.e., high stroke risk, low bleeding risk, no contraindications; n=75), CARAT recommended warfarin for all cases. Discharge therapy observed a marginal increase in anticoagulation prescription in eligible patients (n = 116) (57.8% versus 64.7%, P = 0.35) compared to baseline. Predictors of warfarin use (versus antiplatelets) included congestive cardiac failure, diabetes mellitus, and polypharmacy. CARAT was able to optimise the selection of therapy, increasing anticoagulant use among eligible patients. With the increasing complexity of decision-making, such tools may be useful adjuncts in therapy selection in AF. Future studies should explore the utility of such tools in selecting therapies from within an expanded treatment armamentarium comprising the non-vitamin K antagonist oral anticoagulants.

Introduction

Decision-making around the selection of antithrombotic therapies for stroke prevention in patients with atrial fibrillation (AF) is relatively complex, underpinning the suboptimal use of anticoagulants (particularly warfarin) in the target elderly population.(1-6) Prescribers are understandably concerned about the potential for bleeding, especially in older patients, (7, 8) given that multiple comorbidities, polypharmacy, frailty, risk of falls, and cognitive impairment, may all contribute to adverse drug events. (9, 10) Therefore, the assessment of the risk versus benefit of therapy is not straightforward, (11, 12) and has more recently been further challenged by the availability of additional treatment options (i.e., non-vitamin K antagonist oral anticoagulants - NOACs), none of which are risk-free.

There is a need to support clinicians in their decision-making, to help canvas the range of treatment options and to ensure a robust assessment of the risk versus benefit of therapy in an individual patient. Decision-support tools represent one such strategy, and the computerised antithrombotic risk assessment tool (CARAT) is one example. (13) Derived from hospital-based risk assessment algorithms, (14) the CARAT facilitates a systematic review of the patient's stroke and bleeding risk factors, as well as pertinent medication safety considerations, and subsequently generates a treatment recommendation. As a prototype, the tool has received positive feedback from clinicians regarding its applicability in practice, particularly in helping to differentiate among treatment options whilst also emphasising the need to consider anticoagulant therapy as first-line treatment. (13, 15) At the time of this study, the NOACs were not widely available, and as such the tested version

of this tool considered warfarin as the first-line treatment option, and indeed – to a large extent – this still reflects current practice in Australia; following the recent introduction of the new agents, the practice is largely to continue existing patients on warfarin, and consider the introduction of NOACs in newly diagnosed patients (16). However, this will likely change over time, adding to the complexity of treatment selection.

In view of the need to support decision-making in practice, the aim of this study was to evaluate the impact of the CARAT on the utilisation of antithrombotic therapy in patients with AF. Specifically, the objectives were to: determine the proportion of patients prescribed antithrombotic therapy at baseline (pre-CARAT) and at discharge (post-CARAT); to compare the treatment recommendations generated by CARAT with the antithrombotic therapies actually prescribed by clinicians (post-CARAT); and to identify the factors influencing prescribers' choice of therapy.

PATIENTS & METHOD

Study design

A prospective cohort study was conducted across two hospitals in the wider Sydney area (one large metropolitan hospital, one regional hospital NSW, Australia), over a period of 12 months, prior to the listing of the first NOAC in pharmaceutical benefits scheme (PBS) (between 2011-13) for thromboprophylaxis in AF (17). Essentially, the treatment regimens of hospital inpatients were reviewed before applying the CARAT to generate patient specific treatment recommendations; the recommendations were presented to the treating

clinicians for consideration during their decision-making. The review of therapy, application of CARAT, and liaison with clinicians was undertaken by a designated project pharmacist at each hospital. The final antithrombotic treatment decisions (at discharge) were recorded to identify any changes to therapy. Approval for the conduct of the study was obtained from the respective institutions' human research and ethics committees.

Patient recruitment

Patients with AF were identified through screening of admissions to the target hospital wards (i.e., cardiology, aged care, and stroke units). Patients were recruited if they fulfilled the following criteria: diagnosed with nonvalvular AF (new-onset or pre-existing); aged ≥ 18 years; able to communicate in English (or had a carer who was able to do so on their behalf); and able to provide written consent to participate in the study.

Baseline data collection (Pre-CARAT)

A purpose-designed data collection form was used to extract relevant patient information to populate the CARAT tool, including the patient's: medical history including stroke and bleeding risk factors; medication regimen including antithrombotic therapy; functional and/or cognitive impairments; medication management issues; and current social situation) (Table 1). These data were extracted from the medical notes and medication charts; where specific information or further clarification was needed, the patient/ carer was interviewed at the bed-side. All collected data were used to populate the CARAT tool to generate an individualised treatment recommendation. The baseline antithrombotic therapy was also documented at this stage.

Application of CARAT (intervention phase)

The CARAT is a custom-designed online decision support tool (13, 14) which recommends antithrombotic therapy based on patients' estimated risk (bleeding) versus benefit (stroke prevention) assessment, potential contraindications (medication safety issues), and evidence-based guidelines (18-21). At the first level, the stroke risk assessment is based on the validated $CHADS_2$ score (18) and CHA_2DS_2-VASc score (19), and the bleeding risk estimated using the $HEMORR_2HAGES$ score (21) and HAS-BLED score (20); both stratification schemes categorise patients as being at low, intermediate or high risk.

- The patients' level of risk (for both stroke and bleeding) was ascertained by calculating the number of points accrued using the available risk assessment tools as follows:
- $CHADS_2$ stroke risk 0 points = low risk, 1 point = intermediate risk, and ≥ 2 points = high risk (18)
- CHA_2DS_2-VASc stroke risk: 0 points = low risk, 1 point = intermediate risk, and ≥ 2 points= high risk (22)
- HAS-BLED bleeding risk: 0= low risk, 1= intermediate risk, ≥ 2= high risk (20)
- $HEMORR_2HAGES$ bleeding risk: 0-1= low risk, 2-3= intermediate risk, and $\geqslant 4$= high risk (23)

Both sets of scoring tools were applied to all patients; where a discrepancy between the scores was observed, the highest level of risk was recorded for that patient regardless of the

tool used (using the most conservative approach). Patients were considered eligible for anticoagulation if their stroke risk was equal to, or more than, the bleeding risk. Likewise, if the risk of bleeding was higher than the risk of stroke, the patients were considered to be ineligible for oral anticoagulants by the tool; alternative therapies (i.e., antiplatelets) or specialist review was recommended instead. Patients who were at intermediate or high risk of stroke AND at low risk of bleeding were determined by CARAT to be eligible for anticoagulation with warfarin therapy. At the second level of assessment, CARAT considered any medication safety issues that may act as contraindications to the use of therapy; these included medical, functional, cognitive, social and iatrogenic factors such as drug allergies, clinically significant (major) drug interactions, medication nonadherence, and medication management support difficulties (14). Where these factors were present and were considered to be non-modifiable, they were regarded as contraindications to therapy. Patients who were deemed to be 'most eligible' for anticoagulant therapy were those assessed to have a high stroke risk, low bleeding risk, and without any contraindications to therapy. Once the tool was populated with the patient's data, the risks were assessed, and then a treatment recommendation (for warfarin, aspirin, other, or 'nil therapy') was generated. CARAT recommends 'nil therapy' only in two particular scenarios: 1) where patients are assessed to have low risk of stroke with a high risk of bleeding; or 2) when both anticoagulant therapy and antiplatelet therapy are contraindicated (most likely due to a specific history of bleeding events)

In this study, utilising the patient data extracted at baseline, the project pharmacist populated the tool to generate an individualised assessment and treatment recommendation,

which was documented (printed and attached to the patient's medication chart) and presented to the treating medical team for consideration. The project pharmacist liaised directly with the medical teams (e.g., on the ward, during rounds or case conferences) to ascertain their final treatment decisions, and the reasons for their choice. The antithrombotic therapy prescribed to each patient on discharge was subsequently recorded, noting any changes (compared to baseline).

Patient follow-up

Patients, who consented to follow-up were contacted by the project pharmacist approximately 12 months after discharge from hospital. In a brief telephone interview, guided by a semi-structured questionnaire (open and closed ended questions), the project pharmacist confirmed the patient's antithrombotic therapy post-discharge to identify any subsequent changes to treatment.

Data analysis

The Statistical Package for the Social and Sciences (SPSS 21.0) software was used for data analysis. Descriptive statistics were used to characterise the patients and to describe the utilisation of therapy. The chi-square test was applied to determine the relationship between categorical variables. Cohen's kappa was applied to calculate inter-rater agreement between clinicians' choice and CARAT recommendation. Multivariate logistic regression (Forward Wald) identified factors affecting prescribers' preferences for antithrombotic therapy. P-values of ≤ 0.05 were considered statistically significant in all analyses.

RESULTS

Of the 205 patients who participated in the study, 10 were excluded from the analysis due to incomplete data. On average, the remaining 195 patients (51.8% females) had 2.97 ± 1.56 co-existing chronic conditions. Eight patients were on medications that reportedly had minor-moderate interactions with warfarin (paracetamol, prednisolone, amiodarone) (Table 1).

Baseline utilisation of therapy

Overall, 87.7% of patients were using some type of antithrombotic therapy at baseline (pre-CARAT application). Warfarin was the most frequently prescribed therapy in 53.3% of patients (44.1% on warfarin alone, and the remaining 9.2% using combination therapy involving an antiplatelet agent) (Table 2 and 3). Among patients eligible for warfarin (i.e., risk of stroke outweighed bleeding risk; n = 116), an anticoagulant was used only in 57.8% of patients. At baseline, patients with a low risk of stroke (n=8) were more frequently prescribed 'nil therapy' compared to patients with a high risk of stroke (n=146) (25.0% versus 10.9%, $P < 0.01$) (Table 3).

Among the 75 (38.4%) patients deemed to be 'most eligible' for anticoagulant therapy (i.e., high risk of stroke, low bleeding risk', no contraindications to therapy), only two thirds (66.6%) of patients received warfarin, whilst the remaining 33.3% were not anticoagulated (22.7% of these patients were on aspirin, and the remaining 10.7% were on 'nil therapy') (Table 3).

CARAT recommended therapy

CARAT recommended antithrombotic therapy in all 195 patients, with warfarin the most commonly recommended option (59.4% patients); no patient was recommended 'nil therapy' (Table 3). In only 5 cases did CARAT recommend 'other therapy' (i.e., clopidogrel) because 4 patients were allergic to aspirin, and 1 patient was allergic to both warfarin and aspirin. Among those deemed to be 'most eligible' for warfarin therapy (n = 75), CARAT expectedly recommended warfarin in all patients (Table 3).

Baseline versus CARAT recommended therapy

CARAT recommended a change in baseline therapy for 101 (51.8%) patients, with 60 (30.8%) considered upgrades in therapy (i.e., change to a more effective therapy) (Table 4). Among these upgrades, 49 patients were deemed to be at high risk of stroke and were recommended an upgrade to warfarin. In contrast, 37 (19%) patients were recommended 'downgrades' because their risk of bleeding outweighed their stroke risk. The net effect of the upgrades and downgrades in therapy was an overall increase (from baseline) in the potential use of any antithrombotic therapy (87.7% versus 100%, $P < 0.01$) and in the potential use of warfarin therapy specifically (53.3% versus 59.4%, $P = 0.02$) (Table 3). Among those patients with a low risk of bleeding (n=118), the net effect of CARAT recommendations was also a significant increase in the potential use of antithrombotic therapy (88.1% versus 100%, $P < 0.01$) (Table 3). Among those assessed as being 'most eligible' for anticoagulation (n = 75), CARAT recommended an upgrade to therapy in all cases with an overall increase (from baseline) in the potential use of any antithrombotic

therapy (89.3% versus 100%, P = 0.01), as well as an increase in the use of warfarin (66.6% versus 100%, P < 0.01).

Discharge therapy (post-CARAT)

At discharge there was an overall increase in the prescription (actual use) of antithrombotic therapy, compared to baseline (87.7% versus 93.8%, P = 0.05). The proportion of patients prescribed CARAT-recommended therapy increased significantly compared to that at baseline (48.2% versus 57.9%, P < 0.01). Among the patients deemed to be eligible for anticoagulant therapy (i.e. in whom the risk of stroke was outweighed by the risk of bleeding) as per CARAT (n=116), there was a slight increase in anticoagulant therapy prescription during discharge, compared to that observed at baseline (57.8% versus 64.7%, P = 0.35).

Among those deemed to be 'most eligible' for anticoagulation (n=75), there was a marginal (non-significant) increase in the actual use of warfarin (73.3% at discharge versus 66.6% at baseline, P = 0.47) (Table 3). More than one quarter (26.7%) of the 'most eligible' patients were not prescribed anticoagulant therapy at discharge: 20% of these patients were discharged on aspirin whilst the remaining 6.7% were discharged on 'nil therapy' (Table 3).

Factors influencing selection of antithrombotic therapy

Following multivariate analysis (logistic regression, stepwise Forward Wald), congestive cardiac failure (adjusted odds ratio (OR) = 3.748, 95% confidence interval (CI) = 1.79-7.84, P < 0.001), polypharmacy (≥ 4 medications) (adjusted OR = 2.433, 95%CI = 1.06-

5.56, P = 0.035), and diabetes mellitus (adjusted OR = 2.812, 95%CI = 1.07-7.33, P = 0.034) were significant predictors of the likelihood of a patient receiving warfarin in preference to antiplatelet therapy at discharge (Cox and Snell R^2 =0.15, Nagelkerke R^2 = 0.10, 67.8% correctly predicted).

Prescribers' reasons for therapy selected

Among the 81 patients who were prescribed (at discharge) a therapy different to that recommended by CARAT, a specific reason was provided by the prescriber in 34 cases. In 25 of these cases CARAT had recommended warfarin therapy; clinicians' reasons for not prescribing warfarin in 17 of these cases were perceived excessive falls risk (6 cases), dementia (4 patients), previous history of bleeding (4 cases), patients to be referred for palliative care (2 cases), and patient and carer reluctant to be on warfarin (1 case). In the other 8 patients, who were deemed to be the most eligible candidates for anticoagulation, the documented reasons for not prescribing warfarin therapy were: patient and carer reluctant to use warfarin (5 cases), and concerns about non-adherence (3 cases).

In 6 patients, CARAT had recommended antiplatelet therapy (rather than anticoagulation) because of a high risk of bleeding. However, these patients were all prescribed warfarin at discharge, with clinicians citing the following reasons: history of previous stroke (1 patient); concomitant deep vein thrombosis (1 patient); concurrent renal embolism (1 case); reluctance to change current therapy since patient had been using warfarin for 'years' (2 patients); and patient wished to continue warfarin therapy (1 patient). While for the remaining 3 patients who were not prescribed aspirin therapy as recommended by CARAT

but were discharged on 'nil therapy' instead, clinicians cited the following reasons: previous history of gastrointestinal bleeding (2 cases) and anaemia (1 case). Overall, the level of agreement between CARAT and clinicians' choice of therapy was relatively low (Kappa = 0.193).

Patient follow-up post-discharge

Among the 56 patients who consented to, and were available for, follow-up 36 patients were discharged on the therapy recommended by CARAT and the majority (85%) were maintained on this until the point of follow-up (32 patients on warfarin, 3 on aspirin, 1 on clopidogrel). In another 5 patients, the therapy had changed post-discharge due to: 'bleeding in the brain' (1 on aspirin); 'not happy with the therapy' (1 on clopidogrel); 'therapy too complicated' (2 on warfarin who reported that the international normalised ratio (INR) was often out of range, requiring frequent dose adjustments); 1 patient experienced a transient ischaemic attack (TIA) requiring a change of antithrombotic therapy (patient was on warfarin at time of hospital discharge).

For the 28 patients discharged on a therapy not recommended by CARAT, all remained on that therapy at the time of follow-up. Of the 8 patients on warfarin, 2 patients expressed that they found INR monitoring complicated. Among the 19 patients on aspirin, 1 complained about 'stomach upsets' from the therapy.

DISCUSSION

Overall, in this study a decision support tool (CARAT) was able to facilitate a comprehensive assessment of individual patients according to their stroke and bleeding risks, and relevant medication safety issues, to generate treatment recommendations. The net effects of this are that the overall use of antithrombotics increased. Recent studies have reported that antithrombotic therapy is not always utilised in accordance with the individualised stroke risk-benefit assessment for a patient (24, 25). In this study, a comprehensive decision-making support tool was able to optimise the use of therapy in eligible "at-risk" patients, especially anticoagulation. International studies have shown that basing treatment selection on risk-benefit assessment and guidelines successfully increase the use of anticoagulants in at-risk patients (26, 27). However, in our study, the tool additionally included an assessment of medication safety considerations, improving the overall utilisation of antithrombotics.

However, not all patients were discharged on tool-recommended therapy, as reported in other studies (26). Prescribers sometimes disagreed with CARAT due to isolated risk factors, such as perceived risk of falls, history of bleeding (28), even though these were already factored into the tool's risk-benefit assessment. This perhaps reflects clinicians' reluctance to prescribe antithrombotics to some patients, leading them to focus on specific issues. Although the recent availability of the NOACs may help overcome certain barriers to anticoagulation, they are not without risk, such that individualised risk assessment remains an important component of decision-making. Thus, there is a need for clinicians to holistically assess individual patients when prescribing antithrombotic therapy, especially,

the need to account patient preferences and likely adherence as reflected in clinicians' feedback.

On follow-up, discharge therapy was retained in most without any major problems. Some patients, however, were challenged by the need for regular INR monitoring; in such cases NOACs may offer advantages. Indeed the practical difficulties of warfarin therapy (e.g., time and inconvenience involved in attending the anticoagulation clinics, inconvenience when travelling, and challenges in educating patients about INR testing) contribute to patients' dissatisfaction (29). This study also identified clinicians' perceptions about patients' nonadherence as a deterrent to warfarin use (30). However, in regard to NOACs, the absence of therapeutic monitoring to identify medication nonadherence is also of concern for clinicians (31). This study, akin to other studies (14, 27), highlights the need for patient and family involvement in shared decision-making, factoring individual perspectives which may underpin adherence to therapy.

In considering the findings of this study, the limitations must be acknowledged. First, this study was conducted in the local Australian hospital setting and the results might not be generalisable to other health setting. Second, the NOACs were not available under the Pharmaceutical Benefits Scheme (PBS) at the time of study, hence they were not considered as core treatment options in CARAT. However, the decision-making around treatment selection (warfarin versus NOACs) is still based on individualised risk versus benefit assessments involving similar risk factors, alongside relevant medication-safety

issues (including those specific to NOACs). Lastly, only a limited number of patients gave their consent for the follow-up.

Overall, this tool has assisted prescribers in the rational selection of antithrombotic therapy in at-risk AF patients. Anticoagulants appear to be a viable option for most patients even, when the risk-benefit assessment is considered. A proportion of eligible patients are potentially undertreated, despite the risk-benefit assessment. A computerised antithrombotic risk assessment tool was able to optimise the selection of therapy in patients with AF, increasing the proportion of patients receiving an anticoagulant and reducing the proportion receiving no thromboprophylaxis at all. Given the increasing complexity of decision-making in the clinical context, such a tool may be a useful adjunct in selecting appropriate therapies for AF patients. Although the recommendations generated by CARAT were based on validated stroke risk and bleeding risk assessment scores, as well as evidence-base clinical guidelines, (18-21) future studies need to explore the utility of such a tool in selecting therapies from within an expanded treatment armamentarium comprising the NOACs. Furthermore, future studies need to validate this tool with regard to the prediction of clinical outcomes (i.e., stroke and bleeding events) to confirm the full benefits of CARAT following the optimisation of stroke prevention among 'at-risk' patients.

Declaration of conflicting interests

No conflicts of interest to declare.

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Table 1: Patient characteristics

Characteristics (N = 195)	**Number of patients (% of total patients)**
Age (≥ 75 years)	133 (62.8%)
Gender (N=195)	
Male	94 (46.6%)
Female	101 (51.8%)
Type of AF (N=195)	
New onset	24 (12.3%)
Paroxysmal	48 (24.6%)
Persistent	82 (42.1%)
Not known	41 (21%)
Clinical history (N = 195)	
Congestive cardiac failure (CCF)	68 (34.9%)
Diabetes Mellitus	32 (16.4%)
Hypertension	140 (71.8%)
Uncontrolled hypertension	23 (11.8%)
History of Stroke	39 (20%)
History of Transient Ischaemic attack (TIA)	27 (13.8%)
History of Bleeding	29 (14.9%)
Malignancy	40 (20.5%)
Hepatic-renal disease	24 (12.3%)
Alcohol abuse	7 (3.6%)
Low platelet count	14 (7.2%)
Anaemia	35 (17.9%)
Dementia	17 (8.7%)
Excessive fall risk	71 (36.4%)
Using poly-pharmacy(>4 medications)	160 (82.1%)
Using medications with major drug interactions with warfarin	8 (4.1%)
Allergic to warfarin	7 (3.6%)
Allergic to warfarin AND aspirin	1 (0.5%)
Allergic to aspirin	8 (4.1%)
Allergic to aspirin and clopidogrel	1 (.5%)
Estimated Stroke Risk* (N = 195)	
High	148 (75.9%)
Intermediate	39 (20%)
Low	8 (4.1%)
Estimated Bleeding Risk* (N = 195)	
High	11 (5.6%)
Intermediate	56 (28.7%)
Low	128 (65.6%)

* stroke risk based on $CHADS_2$ score; bleeding risk based on $HEMORR_2HAGES$ score

* Uncontrolled hypertension defined as systolic blood pressure (SBP) > 160 mm hg [(1)]

Table 2: Indications for the use of combination antithrombotic therapy

Combination antithrombotic therapy prescribed at discharge (N = 195)	**Indication/s cited in the patients' medical notes**	**Number of patients (%)**
aspirin + clopidogrel	Post-coronary artery bypass graft (CABG) Coronary artery stent Ischaemic heart disease (IHD)	6 (3%)
aspirin + dipyramidole	Transient Ischaemic Attack (TIA)	4 (2%)
warfarin + clopidogrel	Post-coronary artery bypass graft (CABG) Coronary artery stent	2 (1%)
warfarin + aspirin	Post-coronary artery bypass graft (CABG)	4 (2%)
warfarin + dipyramidole	Not specified	1 (1%)
aspirin + enoxaparin	Bridging therapy	1 (1%)

Table 3: Distribution of antithrombotic therapy according to patients' stroke and bleeding risk

Stage of study	Risk (per scoring tool*)	Warfarin (± antiplatelet)	Aspirin (± other antiplatelet)	Clopidogrel	Nil therapy	Total number of patients (% of total)
PART A: ANTITHROMBOTIC THERAPY ACCORDING TO STROKE RISK						**(N = 195)**
Baseline therapy	Low	2 (1%)	4 (2.1%)	0 (0%)	2 (1%)	**8 (4.1%)**
	Intermediate	22 (11.2%)	12 (6.1%)	1 (0.5%)	6 (3.1%)	**41 (21%)**
	High	80 (41%)	42 (21.5%)	8 (4.1%)	16 (8.2%)	**146 (74.9%)**
	Total	**104 (53.3%)**	**58 (29.7%)**	**9 (4.6%)**	**24 (12.3%)**	**195 (100%)**
CARAT recommendation	Low	0 (0%)	8 (4.1%)	0 (0%)	0 (0%)	**8 (4.1%)**
	Intermediate	4 (2.1%)	35 (17.9%)	2 (1%)	0 (0%)	**41 (21%)**
	High	112 (57.4%)	32 (16.4%)	2 (1%)	0 (0%)	**146 (74.9%)**
	Total	**116 (59.4%)**	**75 (38.4%)**	**4 (2%)**	**0 (0%)**	**195 (100%)**
Discharge Therapy	Low	0 (0%)	7 (3.6%)	0 (0%)	1 (0.5%)	**8 (4.1%)**
	Intermediate	21 (10.8%)	18 (9.2%)	1 (0.5%)	1 (0.5%)	**41 (21%)**
	High	86 (44.1%)	43 (22.1%)	7 (3.6%)	10 (5.1%)	**146 (74.9%)**
	Total	**107 (54.8%)**	**68 (34.8%)**	**8 (4.1%)**	**12 (6.1%)**	**195 (100%)**
Change in therapy (baseline versus CARAT)	*P-value*	*<0.01*	*<0.01*	*<0.75*	*0.03*	*<0.01*
PART B: ANTITHROMBOTIC THERAPY ACCORDING TO BLEEDING RISK						**(N = 195)**
Baseline therapy	Low	71 (36.4%)	29 (14.8%)	4 (2.1%)	14 (7.1%)	**118 (60.5%)**
	Intermediate	27 (13.8%)	27 (13.8%)	4 (2.1%)	6 (3%)	**64 (32.8%)**
	High	6 (3%)	2 (1%)	1 (0.5%)	4 (2.1%)	**13 (6.6%)**
	Total	**104 (53.3%)**	**58 (29.7%)**	**9 (4.6%)**	**24 (12.3%)**	**195 (100%)**
CARAT recommendation	Low	79 (40.5%)	38 (19.4%)	1 (0.5%)	0 (0%)	**118 (60.5%)**
	Intermediate	35 (17.9%)	26 (13.3%)	3 (1.5%)	0 (0%)	**64 (32.8%)**
	High	2 (1%)	11 (5.6%)	0 (0%)	0 (0%)	**13 (6.6%)**
	Total	**116 (59.4%)**	**75 (38.4%)**	**4 (2%)**	**0 (0%)**	**195 (100%)**
Discharge therapy	Low	73 (37.4%)	35 (17.9%)	4 (2.1%)	6 (3%)	**118 (60.5%)**
	Intermediate	28 (14.3%)	29 (14.8%)	3 (1.5%)	4 (2.1%)	**64 (32.8%)**
	High	6 (3%)	4 (2.1%)	1 (0.5%)	2 (1%)	**13 (6.6%)**
	Total	**107 (54.8%)**	**68 (34.8%)**	**8 (4.1%)**	**12 (6.1%)**	**195 (100%)**
Change in therapy (baseline versus CARAT)	*P-value*	***0.02****	*0.30*	*0.22*	*0.12*	***<0.01****
PART C: ANTITHROMBOTIC THERAPY AMONG THE 'MOST ELIGIBLE' PATIENTS'**						**(N = 75)**
Baseline therapy	The most eligible patients**	50 (25.6%) *(66.6%)*	17 (8.7%) *(22.7%)*	0 (0%)	8 (4.1%) *(10.7 %)*	**75 (38.4%)/ (100%)**
CARAT recommendation		75 (38.4%) *(100%)*	0 (0%)	0 (0%)	0 (0%)	**75 (38.4%)/ (100%)**
Discharge therapy		55 (28.2%) *(73.3%)*	15 (7.6%) *(20%)*	0 (0%)	5 (2.5%) *(6.7%)*	**75 (38.4%)/ (100%)**
Change in therapy (baseline versus CARAT)	*P-value*	*0.15*	*0.06*	-	*<0.01**	

* stroke risk based on $CHADS_2$ score; bleeding risk based on $HEMORR_2HAGES$ score

** '*most eligible'* candidates are defined as those at HIGH risk of bleeding, LOW risk of haemorrhage, and without any medication safety considerations (nil contraindications).

Table 4: Changes in antithrombotic therapy pre-and post-intervention (N = 195)

Change in therapy (number of patients, % within group)	**Baseline (N = 101)**	**Discharge (N = 82)**	**P-value**
Upgrade in therapy			
Nil therapy to warfarin	13 (6.6%)	7 (3.5%)	0.02*
Aspirin/clopidogrel to warfarin	36 (18.4%)	34 (17.4%)	
Nil to aspirin/clopidogrel	11 (5.6%)	5 (2.5%)	
Total	**60 (30.8%)**	**46 (23.5%)**	
Downgrade in therapy			
Warfarin to aspirin	37 (19%)	32 (16.4%)	0.29
Total	**37 (19%)**	**32 (16.4%)**	
Side-stepping			
Aspirin to clopidogrel	2 (1%)	2 (1%)	0.5
Clopidogrel to aspirin	2 (1%)	2 (1%)	
Total	**4 (2%)**	**4 (2%)**	

***Upgrade:** Patients requiring a change from less effective to more effective stroke prevention therapy (e.g., from nil therapy to anticoagulant or antiplatelet therapy, or from antiplatelet therapy to anticoagulant therapy)

***Downgrade:** Patients requiring change to less effective, albeit safer, therapy (e.g., from anticoagulant to antiplatelet, or from antiplatelet or anticoagulant to nil therapy)

***Side-stepping:** Patients requiring change within the same class of treatment (e.g., changing from one anticoagulant to another anticoagulant, or from one antiplatelet to another antiplatelet).

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Chapter Eight

Discussion

Chapter Eight

8.1 Discussion

This doctoral research focused on evaluating a customised decision support tool (CARATV2.0) designed to assist prescribers in their decision-making around antithrombotic therapy in patients with atrial fibrillation (AF). Clinical decision support tools are increasingly recognised as a valuable way to assist health professionals in daily practice to support their diagnostic and prescribing process, and to improve the quality of care, especially in complex cases (66, 67).

In this research, the original CARAT was modified into CARATV2.0 and subsequently tested. The constructive feedback from health professionals (Chapters 4 and 5) and findings from the pre-test and pilot studies (Chapters 3 and 6) were used to improve this tool to ensure its usefulness in clinical practice. This decision support tool has been designed to support the decision-making on two levels. First, it assesses the risks in individual patients, thereby identifying those most eligible for anticoagulation. Second, it helps the clinician select an appropriate antithrombotic agent from an expanded range of options. This research evaluated the tool's usability and potential impact on the use of antithrombotic therapy in clinical practice, and identified the factors influencing health professionals' decision-making around antithrombotics for stroke prevention in patients with AF. The research was conducted in three stages:

- Stage 1: modification and clinical testing of CARATV2.0
- Stage 2: eliciting feedback on CARATV2.0 from health professionals
- Stage 3: exploring key issues in the decision-making around antithrombotics.

A detailed discussion of the key results arising from these three stages is now presented.

8.1.1 Comprehensive risk assessment in antithrombotic decision-making

Comprehensive decision support tools are needed

Risk assessment tools are designed to evaluate patients' risk of developing certain medical conditions or health outcomes (e.g., fall, stroke, bleeding, cardiovascular diseases, dementia), and to identify the need for treatment to manage these risks (23, 68). In the context of anticoagulant use, a literature review by Wang et al. (Australia) found that about 20 tools are available to assess stroke risk and bleeding risk separately. However, few of these tools synthesise the stroke risk and bleeding risk as part of a single decision-making process (23) (Chapter 2). Those tools that do synthesise the two risk assessments include the clinical decision aid developed by LaHaye et al. (Canada) (69), the decision model developed by Casciano et al. (USA) (70), the anticoagulant decision support tool developed by Wess et al. (USA) (71), and the shared decision-making tool developed by Kaiser et al. (USA) (72). However, none meet health professionals' expressed need for a comprehensive assessment tool to address the spectrum of factors and medication safety issues that are prevalent in the target population (i.e., older persons).

The health professionals interviewed highlighted the need for a more comprehensive assessment tool that includes stroke risk, bleeding risk and medication safety issues (e.g., medication adherence, cognitive function, renal function, drug interactions) in decision-making around antithrombotics (Stage 2: Qualitative study, Chapters 4 and 5). This finding is consistent with a qualitative study by Bajorek et al. (Australia) (5). The authors interviewed hospital specialists, general practitioners (GPs), pharmacists and nurses. They found that in addition to a means of assessing stroke risk, health professionals needed a more tailored method to perform a complete assessment of patients (e.g., the contraindications for antithrombotics, medication management issues, pharmacology of antithrombotics, social issues, iatrogenic issues) for both initiation of therapy and follow-up of patients (5).

CARATV2.0 versus other tools

Compared with other available tools, CARATV2.0 provides a more comprehensive assessment by addressing several aspects. The first aspect is the appropriate risk assessment of individual patients' suitability for oral anticoagulants. CARATV2.0 uses two sets of risk assessment scores, both of which are recommended for use by major clinical guidelines (16, 19, 73-75), to achieve a higher sensitivity and specificity in the assessment (of both the stroke and bleeding risks) than those achieved by other tools (Stage 1: Pre-test, Chapter 3). The tool uses scores from CHA_2DS_2-VASc and CHA_2DS_2-VASc, and from HAS-BLED and $HEMORR_2HAGES$. The paired stroke and bleeding risk assessment scores have different sensitivities and specificities (76, 77). CHA_2DS_2-VASc has better specificity in

identifying low-risk patients who do not need antithrombotic therapy, but $CHADS_2$ has better sensitivity for stratifying patients who have a low stroke risk (76). For the assessment of bleeding risk, HAS-BLED has better sensitivity in identifying "any clinically relevant bleeding" (77), whereas $HEMORR_2HAGES$ has higher specificity for identifying patients who have an intermediate or high risk of bleeding (77). By contrast, the shared decision-making tool of Kaiser et al. (USA) (72) includes assessment scores from only $CHADS_2$ and ATRIA in its algorithm; the latter is not recommended in current clinical guidelines (16, 19, 73-75). The decision model developed by Casciano et al. (USA) (70) includes only assessment scores from CHA_2DS_2-VASc and HAS-BLED in its algorithm. The anticoagulant decision support tool of Wess et al. (USA) (71) does not use risk assessment scores as recommended by current guidelines. Rather, it assesses the stroke and bleeding risk by calculating the number of quality-adjusted life years gained through treatment with warfarin, based on risk factors such as age, sex, hypertension, congestive heart failure, diabetes, myocardial infarction, prior stroke/transient ischaemic attack (TIA), gastrointestinal (GI) bleeding, renal insufficiency and anaemia. Therefore, compared with CARATV2.0, the ability (sensitivity and specificity) of the other tools to identify patients eligible for oral anticoagulants may be limited by the risk ssessment methods used (1, 5, 6).

The second aspect is CARATV2.0's consideration of medication safety issues (e.g., adherence, drug–drug interaction, practical management issues, renal function) relating to the use of warfarin, aspirin and novel oral anticoagulants (NOACs). This research found that CARATV2.0's approach can indeed identify patients suitable for specific antithrombotic agents (e.g., warfarin, NOACs), assisting the clinician's selection of

appropriate therapy (23, 31) (Chapters 2 – 4 and 6). By contrast, the decision support tools of Casciano et al. and Wess et al. consider only warfarin and aspirin as treatment options, and the shared decision-making tool of Kaiser et al. (72) focuses on the risk assessment rather than treatment recommendations. Although the clinical decision aid developed by LaHaye et al. considers both NOACs and warfarin in its algorithm, it generates recommendations based on mainly the relative risks of stroke and major bleeding associated with antithrombotic therapies (69).

The third aspect is that CARATV2.0 is the only tool that follows the Australian Therapeutic Guidelines (19) and considers the unique features of Australian patients with AF, such as the better international normalized ratio (INR) control observed in Australian patients (63, 78-80), as highlighted in the Australian Government review of anticoagulation therapy in AF (63). The better INR control in Australian patients may reflect the support offered to patients through the Australian health care system, which subsidises the cost of INR testing and patient consultations by general practitioners (GP). The Australian Government review also notes that, in the major clinical trials of NOACs (RE-LY for dabigatran (81), ARISTOTLE for apixaban (82)), the average time in therapeutic range (TTR) for Australian patients receiving comparator treatment warfarin was about 74%. This suggests that warfarin is better controlled in Australian patients than those participating in these major international trials (TTR approximately 63%). Moreover, the incident of stroke was not lower in patients receiving NOAC therapy than for those receiving well-controlled warfarin therapy (TTR >64%) (83). Therefore, considering that warfarin is non-inferior to NOACs for stroke prevention, and that NOACs are more expensive to the Australian

Government (i.e., the cost of warfarin and NOACs to patients are subsidised by the government), both the Government review (63) and the Therapeutic Guidelines (19) recommend warfarin as a first-line therapy. For this reason, CARATV2.0 currently recommends warfarin as a first-line therapy, reflecting local practice guidelines (19).

Health professionals' awareness of comprehensive assessment

Previous studies have shown that health professionals focus primarily on bleeding risk in their decision-making around antithrombotics. For example, in a survey of cardiologists, neurologists, internists and family physicians in Alberta (Canada), Bungard et al. (2003) found that the potential for bleeding (e.g., ongoing history of falls, history of bleeding) was the key determinant in prescribing anticoagulants (84). However, this doctoral research found different health professionals' perspectives on the decision-making around antithrombotic therapy; that is, the health professionals interviewed in this research considered that a comprehensive assessment of risk versus benefit (e.g., stroke risk, bleeding risk, medication adherence, cognitive function, renal function, drug interactions) in individual patients is necessary when choosing an antithrombotic (Stage 2: Qualitative study, Chapters 4 and 5). This increased awareness of the need for comprehensive assessment may relate to the changes in clinical guidelines over time. For example, at the beginning of the century, key treatment guidelines (e.g., ACCP 2001 and ACC/AHA/ESC 2011 guidelines (85)) emphasised the benefit of stroke prevention (e.g., in regard to use of warfarin) with less attention to formal assessment of bleeding risk. However, current international (e.g., ESC and AHA/ACC/HR guidelines) and Australian guidelines (e.g.,

Therapeutic Guidelines and National Prescribing Service (NPS) MedicineWise) stress the importance of assessing both the risk of stroke and bleeding using validated tools such as CHA_2DS_2-VASc, HAS-BLED) alongside a consideration of anticoagulation control (e.g., INR, TTR), renal function and drug interactions (16, 19, 74, 86).

Lack of comprehensive assessment

Although a full assessment of risk versus benefit in the decision-making was acknowledged as critical by health professionals in this doctoral research (Stage 2: Qualitative study, Chapters 4 and 5), in practice their daily decision-making tends to focus on only one aspect of assessment (e.g., stroke prevention or bleeding risk). A few clinicians noted that bleeding risk and medication safety assessment were not undertaken routinely in their clinical practice (Stage 2: Qualitative study, Chapters 4 and 5). These clinicians revealed that sometimes GPs and hospital doctors did not even assess stroke risk due to time pressures in clinical practice, not being aware of the need for anticoagulation to prevent stroke, and routine referral to cardiologists for decision-making (Stage 2: Qualitative study, Chapters 4 and 5) (18, 87, 88).

This focus on stroke prevention and the lack of comprehensive assessment by health professionals are consistent with the findings of other studies. A survey of 50 Australian GPs by Bajorek et al. (Australia) found that GPs focus more on the benefit of antithrombotics (i.e., stroke prevention) than on the risk of bleeding. The stroke risk ($CHADS_2$ score) was identified as the most important determinant of GPs' initiation of antithrombotic therapy, whereas assessment of bleeding risk was seldom raised as a key

factor in their decision-making (89). A study by Patel et al. (Canada) retrospectively reviewed the records of 6346 patients with AF. The authors reported that an annual assessment of stroke risk was not undertaken for 15% of patients and assessment of major bleeding risk was not undertaken for 25% of patients mainly because of the lack of a systematic approach towards decision-making (90).

Failure to perform a comprehensive assessment may increase the risk of medication misadventure, especially in older patients with AF (91). For instance, this doctoral research found that older patients with AF with a low risk of bleeding were more likely to be prescribed multiple medications (polypharmacy) (Chapter 7). Because of their low bleeding risk, these patients were also more likely to be prescribed antithrombotics. Thus, in effect, the low-risk patients were exposed to a higher risk of medication misadventure because of the concomitant use of polypharmacy and antithrombotics (Chapter 7).

Measures to improve comprehensive assessment

The lack of comprehensive assessment of patients with AF in clinical practice needs to be addressed. One possible way is to provide decision support tools to assist in the assessment, particularly where they can be incorporated into practice software, mobile applications or websites, and integrated into existing systems and processes such as electronic medical records (Stage 2: Qualitative study, Chapter 4). The tool could then be used to populate data automatically, or to facilitate more efficient data entry by a health professional. Thus, CARATV2.0 would meet the criteria for an effective decision support tool as outlined by Kawamoto et al. (USA) (20):

- computer based
- provides decision support automatically as part of the clinician workflow
- provides both recommendations and assessments
- provides decision support at the same time and location of the decision-making (point of care)

Where time restrictions in clinical practice preclude a comprehensive assessment by doctors, alternative models of practice should be considered. For example, pharmacists and practice nurses could assist in the evaluation of patients using risk assessment tools. In this alternative model, patients could be evaluated systematically using CARATV2.0 by pharmacists (e.g., hospital pharmacists, accredited pharmacists conducting home medication reviews, prescribing pharmacists) or nurses (e.g., practice nurses, clinical nurse specialists), as part of the medicines review or patient review process, at both the initiation and follow-up stages of antithrombotic therapy. The recommendations could then be discussed with doctors to collaboratively manage the therapy. This approach to decision-making would be time efficient for medical doctors, while at the same time ensuring that patients can receive comprehensive assessment (Stage 2: Qualitative study, Chapters 4 and 5).

The success of this type of model in a hospital setting has been previously reported. In a study by Jackson et al. (Australia), pharmacists used Australian clinical guidelines to assess stroke risk in 134 hospital inpatients and presented the recommendations for antithrombotic therapy to the medical team. This model of practice significantly increased the use of

appropriate antithrombotics to 98% at discharge versus 74% at admission (92). Another pharmacist-led multidisciplinary interventional study of 218 patients with AF by Bajorek et al. (Australia) investigated a decision-making review process using evidence-based algorithms (1). It was the first time that such a pharmacist-led multidisciplinary review process had been successfully trialled in a hospital setting to optimise treatment in this context. The pharmacist reviewed and assessed patients' stroke risk, bleeding risk, and medication safety issues, and subsequently made a recommendation about antithrombotic therapy to the prescribers. The study reported a significant increase in antithrombotic use in treatment eligible patients (59.6% vs 81.2%, $P < 0.001$). More importantly, this review process reported a small net decrease (20.7% vs 17.4%) in the proportion of patients receiving warfarin, after some of the already warfarinised patients were subsequently identified as being no longer eligible for oral anticoagulants; in other words, the review process identified the changing risk:benefit ratio over time (1). Therefore, this review process optimised the use of antithrombotic therapy by not only recommending the initiation of antithrombotics in eligible patients, but also facilitated deprescribing in patients no longer eligible for antithrombotics. Through comprehensive assessment of patients and addressing the major barriers to treatment changes (e.g., clinicians' being uncertain about the relative risk and benefit of therapy in individuals, a reluctance to discontinue medications for fear of stroke) (93), this process supported doctors in the deprescribing of antithrombotics in ineligible patients. In this regard, the process (and its underpinning algorithms) has demonstrated its ability to facilitate the appropriate use of antithrombotics, rather than simply increase use, in an objective way. This intervention demonstrated an enhanced use of available resources and the application of existing professional skills of

pharmacists to a specific drug and disease state (1). The success of this study highlights the important role that a pharmacist can play in a multidisciplinary team to proactively affect the decision-making around antithrombotics to potentially improve patient outcomes. Moreover, this algorithm may also be used by other properly trained health professionals to provide time-efficient and accurate recommendations to doctors in the decision-making around antithrombotics.

Existing services provided by pharmacists in primary care can also be used to support the decision-making around antithrombotics. In the community setting, pharmacist-led Home Medicines Reviews (HMR) incorporating decision support tools (such as CARATV2.0) may have the potential to improve patient outcomes. The ability of an appropriately trained accredited pharmacist, working within the Australian HMR framework, to reduce adverse events and improve patient outcomes has already been demonstrated. A prospective cohort study of patients with AF receiving a home-based, post-discharge service for warfarin management (involving HMR with home-based point-of-care INR monitoring and patient education about warfarin) was conducted by Stafford et al. (Australia). Compared with usual care, this intervention significantly decreased the rates of both combined major and minor haemorrhagic events (14.7% vs 5.3%; P = 0.03) and combined haemorrhagic and thrombotic events to day 90 (19.0% vs 6.4%; P = 0.008) (94). Using the existing HMR framework, pharmacists may be able to optimise treatment recommendations in this context, particularly if enhanced by targeted decision-aids.

Nurses (e.g., clinical nurse specialists, practice nurses) can also play a role in assisting the decision-making around antithrombotics in patients with AF by providing comprehensive assessment, coordinating diagnostic work-up, developing a treatment plan, and setting up appropriate follow-up and patient education (95). A study by Hendriks et al. of patients with AF (The Netherlands) reported fewer cardiovascular-associated deaths and lower mortality (14.3% of 356 patients; hazard ratio: 0.65) in those receiving nurse-led care (comprising guidelines-based, software-supported, integrated chronic care supervised by a cardiologist) than in patients receiving usual care (20.8% of 356 patients) (96). Hence, alternative models using multidisciplinary approaches (pharmacist, nurses, doctors) may improve the use of antithrombotics and patient outcomes.

8.1.2 Role and impact of CARATV2.0 in clinical practice

To evaluate its role and usability, CARATV2.0 was pre-tested using patient data. Health professionals' feedback on CARATV2.0 was explored in a qualitative interview study. The impact of this tool on clinical practice was later assessed using a prospective real-world patient cohort. This articulated evaluation process has explored CARATV2.0's application in real-world patients and its ability to select appropriate antithrombotic agents for individual patients, thus clarifying the usability and validity of this tool. By contrast, other synthesised risk assessment tools, such as the clinical decision aid of LaHaye et al. and the decision model developed by Casciano et al. were only retrospectively tested using patient databases (69, 70). The anticoagulant decision support tool of Wess et al. and the shared

decision-making tool of Kaiser et al. were evaluated only through a survey of the potential users (e.g., doctors, patients) (71, 72).

The pre-test showed that the tool can be useful for optimising the selection of antithrombotics by identifying the suitability of individual patients for therapy (Stage 1: Pre-test, Chapter 3), as also reflected in the health professionals' feedback (Stage 2: Qualitative study, Chapter 4). Some health professionals welcomed CARATV2.0 because it can help them decide whether a patient is suitable for anticoagulation therapy and can validate their decision-making process. This assistance is especially valuable in cases in which the risk versus benefit of using oral anticoagulants is not straightforward. They also appreciated that this tool offered an evidence-based evaluation of patients to help them select the appropriate anticoagulant agent, especially between warfarin and NOACs (Chapter 4).

Since the NOACs are relatively new therapeutic options and their benefits and risks are not very clear, health professionals interviewed in this research thought that they sometimes lacked the confidence to make decisions when selecting specific therapy, especially when choosing between warfarin and NOACs (Stage 2: Qualitative study, Chapters 4 and 5). Other studies have also reported on health professionals' uncertainty and lack of confidence in selecting an antithrombotic agent (97, 98). In a qualitative study by Anderson et al. (UK), physicians in cardiology, general medicine and geriatric medicine individually reviewed five clinical vignettes, and then recommended antithrombotic treatment for each. Certainty was expressed by fewer than one in five of physicians for each vignette. Moreover, the

treatment decisions of those physicians who were more certain in their narratives were inconsistent across all vignettes and were often incorrect in the selection of an appropriate antithrombotic agent (99).

An evaluation of the impact of CARATV2.0 on the use of antithrombotic therapy showed that the overall use of antithrombotics increased significantly (12% net) after clinical intervention with the tool (Stage 1: Pilot study, Chapter 6). This finding is consistent with that of a study that showed that the use of evidence-based computer software by health professionals in practice can improve the care of patients with AF. In an interventional study by Nieuwlaat et al. (The Netherlands), the antithrombotic treatment prescribed by clinicians using a guideline-based, computer-supported care program elicited better adherence to the guideline-recommended treatment than did the treatment prescribed by the control group (antithrombotic therapy in 90% vs 78% patients) (100). Interestingly, in this doctoral research, the percentage of patients using anticoagulants (warfarin or NOACs) increased significantly (by 20%) and the percentage using antiplatelets decreased (by 8%) in the pilot study of CARATV2.0 (Chapter 6). In contrast, in the study of the original CARAT (1), the corresponding percentages decreased by 4% and increased by 23%. The increase in antiplatelet use occured because a proportion of the patients who were not prescribed any antithrombotic therapy at admission were identified by CARAT as eligible for at least an antiplatelet agent. The decrease in anticoagulant use in the original CARAT study occurred because a proportion of the patients who were already on warfarin at admission were subsequently identified by CARAT as ineligible for oral anticoagulants because the risk of therapy had increased over time. The net effect of the changes made was

a significant decrease in the proportion of ‘‘unprotected’’ patients (those receiving no antithrombotics at all) (40.4.% vs18.8%, P < 0.001). These findings highlight the ability of this tool to identify patients who are suitable or unsuitable for oral anticoagulant therapy, to rationalise the use of antithrombotics for individual patients, and thereby improve both efficacy and safety.

The difference between the impact on therapy prescription of the new version and the original CARAT tool may relate to several factors. These factors include the different characteristic profiles of patients in the study of the original CARAT (1) and the pilot study of CARATV2.0 (Chapter 6), the availability of NOACs, and the modification of the tool's algorithm to reflect the latest guidelines and clinical evidence (e.g., Australian Government review) (13, 16, 18, 63). These factors may have concomitantly contributed to the increased anticoagulant use in the pilot study. Furthermore, CARAT considered mainly warfarin and aspirin in its algorithm, since NOACs were not available at the time; however, by the time the pilot study of CARATV2.0 was conducted, the NOACs were available and were subsidised by the PBS (101). Since both international and Australian guidelines recommend NOACs as treatment options, CARATV2.0 considered both warfarin and NOACs in its algorithm. This change in treatment options may have led to the increased use of anticoagulants in patients who were previously considered unsuitable for warfarin therapy (and for whom there were previously no alternative options).

This doctoral research also found that more prescribers agreed with the original CARAT's recommendations for the use of specific antithrombotic agents than with the

recommendations of CARATV2.0 (94% vs 53%) (Stage 1: Pilot study, Chapter 6) (25). This finding may be explained by the divergence in treatment recommendations between international and local guidelines regarding first-line therapy as well as the increased number of anticoagulant agents (from one to four) available in practice, at the time of CARATV2.0 testing (Chapter 6). Some international guidelines, such as those of the European Society of Cardiology and the European Heart Rhythm Association, recommend the use of NOACs over warfarin (16, 102), whereas Australian guidelines and reviews (e.g., National Prescribing Service Guidelines, Therapeutic Guidelines) (19, 63, 73) recommend warfarin over NOACs. This disparity may lead to a wider range of opinions among health professionals about the specific agent most appropriate for treatment.

Limitations of CARATV2.0

In considering the role and impact of CARATV2.0, it is also important to recognise its limitations. Firstly, relatively limited information is available about the characteristics of the newer NOACs (compared to warfarin), and this precludes confirmation of risk versus benefit in some patient groups. Therefore, CARATV2.0 sometimes identifies that the patient is suitable for more than one of the available NOACs (e.g., "suitable for any NOAC" or "suitable for either rivaroxaban and apixaban"). A second limitation is that the tool recommends antithrombotics for stroke prevention in patients with AF as a single indication, given the absence of robust data around the risk of bleeding with multiple agents (e.g., use of an anticoagulant plus an antiplatelet). However, the tool does screen for other indications, such as ischaemic heart disease (with or without stent) and valvular AF, which

may also require antithrombotics and which may lead to the need for combination therapy, as identified by the American Chest Physician Guidelines (13). In addition, this tool was developed for an Australian practice setting according to Australian guidelines, such as the National Prescribing Service guidelines (2013) (73) and the Therapeutic Guidelines (2012) (19). It should be noted that the Australian guidelines differ slightly from international guidelines (e.g., European Society of Cardiology (2012) and the European Heart Rhythm Association (2015)) in that the international guidelines advocate the use of NOACs over warfarin (16, 88). However, since our post hoc analysis in the trial study shows that CARATV2.0 can be adapted to international settings, where there may be differences in guideline recommendations (in terms of whether NOACs or warfarin are used first-line) (Chapter 6); the assessment process of CARATV2.0 may be adjusted in terms of which agent is advocated as the first-line therapy. Therefore, for international users, CARATV2.0 can be customised to align with the local guidelines of each country. To date, there are no specific assessment tools available to predict and/or stratify the risk of bleeding in regard to the new anticoagulants. In our studies (Chapter 4 and 5), we received feedback from clinicians and health professionals about CARATV2.0 inputs and appropriateness of the bleeding risk assessment. They were all satisfied that CARATV2.0 used HEMORR$_2$HAGES and HAS-BLED for bleeding risk assessment and acknowledged that there were no other tools available at present (Chapter 4 and 5).

8.1.3 Issues affecting the decision-making around antithrombotics

This doctoral research also explored the issues affecting the decision-making around antithrombotics (Chapters 3, 5 and 6). The key factors identified include: bleeding risk; medication safety issues (e.g., older age, falls risk, renal impairment); health professionals' and patients' preferences for therapy; practical management issues (e.g., convenience of NOACs); and cultural issues in clinical practice (e.g., time pressures, reluctance to change therapy).

8.1.3.1 Bleeding risk

The findings of this doctoral research suggest that prescribers perceive the bleeding risk of anticoagulants to be more severe than supported by the available evidence (Chapter 6). This finding is consistent with that of a study by Peterson et al. (Australia). In their survey of 818 physicians (including cardiologists, other specialists and GPs), Peterson et al. (Australia) reported that physicians often overestimated the risk of major bleeding with warfarin use in patients with AF compared with the risk reported in the literature (103).

The health professionals interviewed in our qualitative study seldom noted assessment of bleeding risk as an important part of their decision-making process and did not routinely assess bleeding risk in their daily practice (Chapter 5). This is consistent with the finding of a study by Bajorek et al. (Australia), which canvassed the perspectives of 50 GPs on antithrombotic management. The study found that GPs did not specifically mention bleeding risk assessment as a necessary step in their decision-making around antithrombotics in patients with AF (89). Collectively, these findings suggest that, despite their concern about bleeding risk and their overestimation of bleeding risk compared with

the evidence, few clinicians actually assess bleeding risk as recommended by treatment guidelines.

It appears that other measures may be needed to encourage health professionals to perform guideline recommended bleeding risk assessments alongside stroke risk assessments. Such measures could include providing ongoing medical education (104) (e.g., workshops, lectures) about risk assessment. A previous study by McNulty et al. (UK) has shown the value of medical education in influencing the prescribing of antithrombotics in the hospital setting. The authors retrospectively audited the medical records of patients with AF admitted to a 1000 bed acute hospital. Overall, 185 patients were studied in the first audit. Following an extensive education programme targeting medical officers (tutorials comprising problem-based learning, case studies, and an antithrombotic management algorithm), the authors conducted a second audit on another 185 patients. Compared with the first audit, the education programme increased warfarin use in patients at high risk stroke of by 11% (38% to 49%, $P < 0.05$). (105). Education of community-based prescribers has likewise been shown as effective in improving prescribing. In a study by Gadzhanova et al. (Australia), the authors conducted a time-series analysis using the Department of Veterans' Affairs (DVA) claims dataset to evaluate the impact of medical educational programs (e.g., written education materials, one-on-one educational visits, case studies) provided by NPS MedicineWise on the use of antithrombotics in AF. According to the authors, these programs resulted in increases of 1.27% and 0.63% in the use of antithrombotics (aspirin or warfarin) at 6 months and 12 months, respectively, after the intervention (104). Although these increases are small to moderate in effect, such changes

may build their impact over a longer period of time, and may be potentially important when thousands of patients are affected. A study by Jackson et al. (Australia) trialled a comprehensive educational program (e.g., locally produced guidelines followed by practice visits by a research pharmacist) for rationalising prescribing of antithrombotics among 162 GPs (106). This intervention significantly increased the use of warfarin in patients at high risk of stroke (from 33% to 46%, $P < 0.05$). Dispensing data for antithrombotics revealed a much greater increase in the use of warfarin for the intervention group than for the control group ($Z = 6.48$, $P < 0.001$) (106). All three studies highlight the importance of prescriber education, with the greatest impact provided by programmes incorporating practice-based practical guidelines and problem-solving.

8.1.3.2 Medication safety issues

In our qualitative interviews, health professionals commented that medication safety issues (e.g. age, falls risk, renal function) are key considerations in decision-making and treatment selection (Chapters 4 and 5). The pilot study likewise showed that medication safety issues (e.g. age, falls risk) were among the most commonly cited reasons by prescribers for not accepting CARATV2.0's recommendations (Chapter 6). This is consistent with the findings of a systematic review and meta-analysis by Baczek et al. (USA), which pooled the multivariate analyses of 28 observational studies to calculate the odds ratios (ORs) for the predictors of warfarin use. Compared with their younger counterparts, older patients with AF (per 10-year increase; OR = 0.78) and those with a risk of falls (OR = 0.60) were less likely to receive warfarin (107). In addition to age and falls risk, we also found that

patients' renal function influences prescribers' selection of specific agents (Chapter 6), reflecting the fact that NOACs are contraindicated in patients with severe renal impairment (31).

Age

Advancing age is associated with suboptimal use of antithrombotics (107). According to an Australian study by Bajorek et al. (2002), AF patients aged ≥ 80 were 5.46 times less likely to be prescribed warfarin than were patients aged <80 years (25.5% versus 61.5%, respectively, $P < 0.0001$) (108). This doctoral research also found that older age is a barrier to clinicians' prescribing of oral anticoagulants (Chapter 5). CARATV2.0 incorporates age (as a risk factor for stroke) and other age-related risk factors (e.g., comorbidities, renal impairment, adherence, falls risk) into its therapy recommendations. Despite these inclusions, in the pilot study, older age remained one of the prime reasons for physicians' not adopting the CARATV2.0 recommendation to initiate anticoagulant therapy (n = 8 out of 119 patients) (Chapter 6). This finding is consistent with that of a systematic review of 30 cross-sectional surveys by Pugh et al. (UK), which showed that physicians were less likely to prescribe anticoagulants for patients >70 years of age than for those <70 years of age (87). The systematic review also found that, when asked about the risk versus benefit of using anticoagulants, only 56% of physicians agreed that the benefits of anticoagulation therapy outweighed the risks in elderly patients when an "elderly" person was defined as >75 years of age. However, more (63%) physicians agreed that the benefits of

anticoagulation therapy outweighed the risks when an "elderly" person was defined as a younger age group (>65 years) (87).

However, age per se should not be regarded as an absolute contraindication for therapy. Age is a composite marker of other factors whose prevalence or risk increases with age (e.g., comorbidities, renal impairment, poor adherence, falls risk). It is these factors, and not age itself, that affect the pharmacological handling of medications and patients' ability to manage complex regimens, which has the potential to subsequently increase their risk of medication misadventure (23, 31) (Chapter 2). Therefore, in clinical practice, these individual age-related issues should be purposefully assessed and mitigated when possible, rather than broadly excluding patients from oral anticoagulant therapy on the basis of age alone.

This doctoral research also found that patient age affected the selection of specific anticoagulant agents. Geriatricians and cardiologists interviewed in the qualitative study were concerned about the risk of using NOACs in very elderly patients because of the limited data on using NOACs in this patient group and the higher risk of acute renal impairment in elderly patients (Chapter 5). Other studies have reported similar concerns among prescribers about using NOACs in older patients. In a retrospective claim analysis of 20,320 patients by Azza et al. (USA), those aged ≥65 years were less likely to be prescribed dabigatran than warfarin compared to younger patients (OR = 0.44, $P < 0.0001$) (109). This finding may reflect prescribers' initial concerns about the increased incidence of bleeding events associated with dabigatran use, especially in elderly patients with

impaired renal function; this risk is not completely eliminated by dosage adjustment (110). Although renal function is somewhat important to warfarin use, its anticoagulant effects are more readily measured and monitored through INR testing. The important role of monitoring in mitigating the risk associated with the specific agents has also been reinforced by the findings from our qualitative interviews; not only can regular monitoring reduce the risk of bleeding in older patients (Chapter 5), it can also identify a patient's adherence to the regimen, thereby allowing health professionals to fully understand the potential risks and benefits in an individual.

Falls risk

In the qualitative study, in addition to age, falls risk was also considered to be an important medication safety issue by health professionals (Chapter 5). Although CARATV2.0 considers falls risk within the calculation of the HEMORR$_2$HAGES score as well as within the broader assessment of medication safety issues in its algorithm, the pilot study showed that, when recommending therapy, prescribers remained fearful of the bleeding risk associated with falls (Chapter 6). Falls risk was identified as the major predictor of prescribing antiplatelet agents instead of anticoagulant therapy (OR = 2.25, P = 0.04; Chapter 6). This shows that prescribers placed a higher value on falls risk than is supported by the evidence, and may reflect prescribers' concerns about the association between falls risk and a high risk of intracranial bleeding, especially in patients taking warfarin. In a study by Gage et al. (USA) that prospectively followed up 19,506 patients with AF for 1

year, a high falls risk was associated with a higher rate of intracranial haemorrhage (ICH) (OR = 2.0, 95% CI 1.3–3.1) (111).

However, the benefit of anticoagulants greatly outweighs the relative risk of ICH. For example, using a Markov decision analytic model, Man-Son-Hing et al. (Canada) estimated that the benefit of anticoagulants for stroke prevention far exceeds the risk of ICH unless a patient falls about 300 times per year (112). In addition, a review by Hankey et al. (Australia) showed that the risk of ICH does not differ significantly between NOACs (such as apixaban) and antiplatelets (risk ratio = 0.84; 95% CI, 0.38–1.87) (113).

Renal function

The pilot study found that patients with renal impairment were more likely to be prescribed warfarin than NOACs (Chapter 6), consistent with the findings from the qualitative interviews. Health professionals are cautious about using NOACs in patients with renal impairment (Chapter 5), because they are associated with a higher risk of bleeding (88). Furthermore, renal function is important in the decision-making process because it can deteriorate acutely in elderly patients with AF. In a cohort study of 437 patients by Pascual et al. (Spain), the incidence of acute kidney injury (AKI) was 3.5 times higher in patients aged >70 years than in their younger counterparts (114, 115). More importantly, in a study by Jun et al. (Canada) of 12,403 patients with AF who were taking warfarin, reduced renal function was associated with a higher risk of major bleeding. Bleeding rates increased from 6.1 per 100 person years in patients with an estimated glomerular filtration rate (eGFR) > 90 mL/min/1.73 m^2 to 63.4 per 100 person-years in those with an eGFR < 15 mL/min/1.73

m^2 (adjusted incidence rate ratio 10.3, 95% CI 2.3–45.5) (116). Unlike the NOACs, warfarin may be used in patients with severe renal impairment and its anticoagulant effects can be monitored through INR testing (23), and therefore is potentially a safer choice for such patients. An assessment of renal function, both before the initiation of antithrombotic therapy and regularly thereafter, with tools such as CARATV2.0, may help in the early detection of increased bleeding risk related to renal impairment.

8.1.3.3 Health professionals' and patients' preferences for therapy

This doctoral research explored for the first time Australian health professionals' preferences for therapy, specifically in choosing between warfarin and NOACs. The qualitative study found that, overall, most health professionals (pharmacists, cardiology nurses, cardiologists, geriatricians, GPs) preferred to use warfarin as the first-line therapy, which is consistent with Australian local guidelines (19, 86). However, the neurologists and haematologists advocated the use of NOACs over warfarin as the first-line therapy, which is aligned more closely with international guidelines (102, 117) (Chapters 4 and 5). This difference in therapy preferences was also reflected in the pilot study, which showed that patients managed in neurology departments were more likely to be prescribed NOACs instead of warfarin (general medicine OR = 4.67, aged care OR = 5.81, cardiology OR = 3.80). This difference occurred even though prescribers in the general medicine, neurology, aged care and cardiology departments used the same intervention (CARATV2.0) (Chapter 6). By contrast, a retrospective claims analysis of 20,320 patients by Abudagga et al. (USA) found that patients managed by cardiologists (adjusted OR = 3.12) were more likely to be

prescribed dabigatran than were patients managed by primary care, family, or internal medicine physicians (109). The preference for therapy among different specialists between Australian and U.S. health professionals might relate to the recommendations of the Australian local guidelines (i.e., warfarin as first-line therapy) (118). This preference might also relate to the characteristics of patients treated in these specialties, which may lead physicians to focus on different aspects of decision-making. For example, geriatricians may focus on patients' fragility (e.g., falls risk, cognitive function) and how to prevent medication misadventure (e.g., bleeding), cardiologists on managing coexisting heart disease (e.g., coronary heart disease), neurologists on reducing stroke incidents, and general medicine specialists on managing comorbidities.

Vasishta et al. (UK) found that geriatricians' decision-making around warfarin was influenced by patients' disability, history of cerebrovascular disease, and falls, more so than the decisions of other specialists (in cardiology, gastroenterology, diabetes and endocrinology, nephrology and neurology) (119). In a survey of clinicians, Bajorek et al. (Australia) also found differences between specialists in decision-making around antithrombotics. Geriatricians perceived the risk of bleeding with therapy to be greater than that perceived by cardiologists, particularly for patients with functional and/or cognitive impairment. Thus, the geriatricians disagreed with cardiologists about therapy recommendations for some patients (6). This variation in prescribing behaviour among health professionals may lead to suboptimal outcomes for some patients. Lip et al. (UK) followed 2634 patients with AF for 1 year and observed that a higher rate of stroke, bleeding and mortality among patients not receiving guideline-based treatment (120).

Although this research did not specifically explore the impact of patients' needs and preferences on the decision-making around antithrombotic therapy, health professionals interviewed in this doctoral research, especially GPs, stressed that patient preference plays an important role in their therapy selection (Chapters 4 and 5). This is consistent with the findings of previous studies (121). According to a survey of 137 patients with AF by Palacio et al. (USA), 98% of patients wanted to actively participate in the decision-making process. More than one-third of AF patients preferred an anticoagulant that had an antidote (e.g., warfarin) even if the risk of bleeding was very small, and one-fifth preferred an agent that provided the best quality of life (e.g., NOACs) (33). Another survey of 201 patients by Shafrin et al. (USA) reported that patients currently using warfarin preferred NOACs to warfarin (73.0%), whereas non-warfarinised patients preferred warfarin over NOACs (78.2%) (122). This finding suggests that patients have strong preferences for specific antithrombotic agents, which may be influenced by their experiences of therapy to date, and/or may differ from clinicians' perspectives.

Therefore, in order to optimise the use of antithrombotic therapy, it is important that health professionals engage patients in shared decision-making. The benefits of shared decision-making include improving patient understanding of treatment, facilitating patient–clinician communication, and reducing decisional conflict between patients and clinicians. Patients' better understanding of treatment may also lead to better adherence to their medications. Decision support tools must also consider patient preferences alongside the risk versus benefit assessment to support shared decision-making for stroke prevention in AF (123).

8.1.3.4 Practical issues around medication management

A patient's ability to practically manage their medication on a day-to-day basis is an important consideration in decision-making, and is affected by their capability to adhere to the medication regimen (e.g., cognitive function), access to healthcare facilities, and monitoring requirements of the medications (5, 124) (Chapters 4 and 5). In contrast to warfarin, NOACs have a fixed daily dosage regimen and do not need frequent monitoring. NOACS also have fewer interactions with drugs and food (Chapter 2). Unsurprisingly, the convenience of NOACs has been highlighted by some of the "pro-NOAC" health professionals in our qualitative interviews. These participants perceived that NOACs are managed more easily by patients and that patients would prefer this convenience (Chapters 4 and 5). The pilot study also found that hospital prescribers cited "NOACs better", "easier to manage", "no need for monitoring" as the reasons for not following the CARATV2.0's recommendations to use warfarin (n= 20 out of 119 patients) (Chapter 6). This finding is consistent with a previous study by Wild et al. (UK) (125). In that study, the authors interviewed 60 patients and found that a "hypothetical oral anticoagulant" with no monitoring requirement and no interactions with food, alcohol or concomitant medications was preferred over warfarin by more than half of the patients; the "no monitoring requirement" was considered the primary advantage by these patients (125). Aside from the convenience, there are also drawbacks for NOACs. The twice-daily dosage of NOACs (except for rivaroxaban), together with the lack of monitoring, may negatively affect patient adherence. For example, a survey of 266 patients by Andrade et al. (Canada) found that patients taking once-daily anticoagulants (rivaroxaban or warfarin) had better adherence.

Non-adherence occurred in only 6% and 14% of patients who received rivaroxaban and warfarin, respectively, compared with non-adherence in about 30% of patients who received twice daily dabigatran or apixaban ($P < 0.01$) (126). The potential for non-adherence is important to note, since it underpins the effectiveness of treatment, and the subsequent risk:benefit ratio of therapy. Furthermore, the absence of regular monitoring regarding NOACs use also means that it is harder for clinicians to identify non-adherence in their patients (31).

Cognitive function affects a patient's ability to manage their daily medication regimen. Therefore, in addition to the practical convenience of treatment, health professionals, especially nurses and pharmacists, also consider patients' cognitive function to be important in the decision-making around antithrombotics (Chapters 4 and 5). In the pilot study, significant cognitive impairment (i.e., dementia) was also one of the reasons for not prescribing warfarin as recommended by CARATV2.0 ($n = 5$ out of 119 patients) (Chapter 6). This finding is consistent with a meta-analysis of 28 studies by Baczek et al. (USA), who found that AF patients with cognitive impairment (i.e., dementia) were less likely to receive warfarin over antiplatelets (OR = 0.32, P = 0.01) (127). This suggests that prescribers are worried about the long-term management of warfarin in such patients given that those with poor cognitive function may have difficulty in managing their daily medications leading to poor adherence and medication misadventure (128). This is not an insignificant consideration in decision-making, given the correlation between advancing age, prevalence of AF, and increasing risk of stroke alongside the age-related decline in cognitive function.

8.1.3.5 Cultural issues in clinical practice

Cultural issues refer to the values, beliefs, underlying assumptions, attitudes, and behaviours shared by the people who work in the practice that affect health professionals' decision-making (129, 130). This doctoral research is the first to identify time pressure and reluctance to change existing therapy as major cultural issues in the decision-making around antithrombotics (Chapters 4 and 5). The limited time available for decision-making around antithrombotics was mentioned consistently by many health professionals as the key reason for not performing comprehensive risk versus benefit assessments of patients, and sometimes for not assessing stroke risk, despite guidelines recommendations (Chapters 4 and 5).

Time pressure was also cited by GPs, specialist clinicians and hospital pharmacists in the qualitative study as a key reason for suggesting the integration of CARATV2.0 into existing systems (e.g., electronic medical records) (Chapter 4). This finding is consistent with both international and local studies showing that time pressures can interfere practice. A survey by Scott et al. (Australia) of 545 physicians identified time limitations as one of the most important barriers to the daily application of evidence-based medicine (across all therapeutic areas) (131). Similarly, in qualitative interviews with 26 nurses, Adib-Hajbaghery et al. (Iran) found that time pressures affected nurses' general clinical decision-making and the implementation of evidence-based nursing practice (132).

However, the finding of this doctoral research also indicates that clinicians appear reluctant to prioritise and to allocate time for decision-making around antithrombotics, which

paradoxically may increase the time spent in managing the adverse outcomes of poor or suboptimal prescribing. A review by Dugdale et al (USA) reported that physicians' risk of malpractice claims is associated with the length of time they spend on each patient consultation and that spending less than 15 minutes was a risk factor for inappropriate prescribing (133). Hence, as an intervention, 'pharmacotherapy' should also follow a comprehensive decision-making process, similar to that applied in other medical interventions (e.g., surgery).

Decision support tools can help with time pressure issues. Such tools can be re-formatted into practice software, mobile applications or websites, and be integrated into existing systems and processes (e.g., electronic medical records) (Chapter 4), to auto-populate patient data and to provide time-efficient recommendations. In their expert opinion, Payne et al. (USA) concluded that a successful decision support tool (e.g., electronic HIV Guidelines at Boston Beth Israel, computer decision support system for antimicrobial use) could both save time in clinical practice and provide patient-specific recommendations (134). To both ensure comprehensive assessment and save time for prescribers, alternative models of care may also be considered to support doctors' decision-making. For example, hospital pharmacists or nurses could systematically assess patients with CARATV2.0 and present the recommendations to the prescriber for consideration (Chapters 4 and 5). It is not unrealistic that a hospital pharmacist undertakes this sort of review and conveys the outcome to prescribers, so in this regard, the CARAT study described in Chapter 7 does replicate practice. This model of practice has been reported previously; a pharmacist-led review process was successfully trialled by Bajorek et al. (Australia) in a hospital setting.

This process generated recommendations for antithrombotic therapy for stroke prevention based on individual patients' information, and these recommendations were presented to the patients' healthcare team by a pharmacist, significantly improving the use of antithrombotic therapy (1). The clinicians interviewed in this doctoral study (Chapter 4) also suggested that pharmacists, junior medical residents, medical students or practice staff (e.g. nurses) could populate CARATV2.0 manually, for subsequent review by clinicians (135). In the community setting, pharmacists and nurses could also help review patients using CARATV2.0, performing INR monitoring and adjusting dosages (136). According to a review by Ackermann et al. (Australia), pharmacists situated in GP clinics can assist by conducting medicines review for vulnerable patients (e.g., elderly), managing chronic diseases (e.g., atrial fibrillation) and monitoring high risk medications (e.g., warfarin) (137)..

In addition to time pressure, this doctoral research found that both hospital-based doctors and GPs were reluctant to change therapy. In the pilot study, many prescribers (30) tended to continue the existing therapy for patients despite an alternative recommendation being provided by CARATV2.0, i.e., a recommendation to change the patients' therapy (Chapter 6). The GPs interviewed said they usually would not change the antithrombotic therapy initiated by the hospital doctors, nor would they initiate new therapy if the patient was discharged from hospital with no therapy (Chapters 4 and 5). The desire to continue existing therapy was cited as the reason for not following the CARATV2.0 recommendations for 30 out of 119 patients in the pilot study but was cited by clinicians as

the reason for not following for the tool's recommendations for only 3 out of 13 patients in the original CARAT study (1) (Chapter 6).

This reluctance to change therapy among prescribers in both hospital and community settings is consistent with previous studies. In a qualitative study of 12 GPs' decision-making around antithrombotics by Lipman et al. (UK), many expressed a reluctance to change the antithrombotic therapy prescribed by hospital doctors (138). One possible solution is to provide prescribers a framework to document treatment changes, to rationalise their treatment selection.

8.1.4 Current use of antithrombotic therapy in Australia

In addition to the evaluation of CARATV2.0 and identification of key issues in the decision-making around antithrombotics in patients with AF, the current use of antithrombotic therapy in an Australian hospital setting was explored as part of the pilot study (Chapter 6). Overall, the use of antithrombotics in Australian patients with AF in this setting has increased over the past decade, from 78.9% to 89.2% (1). The increase in antithrombotic use may reflect both the availability of NOACs (139) and the promotion of the use of antithrombotics in patients with AF in current guidelines (e.g., ESC, AHA/ACC/HRS, NPS)(13, 16, 18, 86).

Compared with recent international studies, our Australian pilot study found that the percentage of patients with AF receiving antithrombotics overall (89.2%) is lower than that reported in European studies (95.2% and 95.9%) (4, 140) and North American studies

(92.4%) (140) but higher than that reported in Asian studies (85.9% and 89.0%) (141, 142) (Chapters 3 and 6). Regarding the use of oral anticoagulants (i.e., warfarin or NOACs), the pilot study identified a much lower percentage of patients receiving anticoagulants (70.5%) than reported in European (80.0% and 90.2%) and North American studies (78.2%) (Chapter 6). In terms of specific agents, the absolute percentage of patients with AF using NOACs in our Australian pilot study was over 15% higher than reported in a European study (patients with either existing or newly diagnosed AF) (2013) (4). However, the absolute percentage of patients using NOACs in our pilot study was about 15% lower than reported in a more recent European and North American study (2015) of patients with newly diagnosed AF (140) (Chapter 6).

These differences in the proportion of patients receiving oral anticoagulants may be related to several factors. First, the patients in our pilot study were older than patients in the European and North American studies (4, 140) (mean age 82.3 years vs 68.8 years and 71.0 years, respectively). Other possible explanations are the wider availability of NOACs in North America and Europe, and the influence of international guidelines (e.g., ESC, European Heart Rhythm Association) (16, 88) promoting the use of NOACs. By contrast, NOACs have only recently become available in Australia (year 2011), and local guidelines currently promote the use of warfarin as first-line therapy (Therapeutic Guideline (19)), reflecting a more cautious approach to using NOACs and/or a reluctance to switch therapy in patients stable on warfarin. In addition, some Australian prescribers (e.g., geriatricians, GPs, cardiologists) remain concerned about the safety of using NOACs, especially in elderly patients (Chapters 4 and 5).

8.1.5 Recommendations and future directions for research

Overall, the findings of this research indicate that CARATV2.0 may be helpful for optimising the use of antithrombotic therapy in patients with AF. For this tool to be implemented in clinical practice, further evaluation and modification are needed. Multicentre randomised controlled trials with follow-up (60) should be conducted with real patient cohorts in primary care settings (e.g., general practice, community pharmacies) and hospital settings (e.g., tertiary hospitals, community hospitals), and with a wide range of potential user groups (e.g., doctors, pharmacists, nurses). Future trials should also investigate the long-term impact of the use of this tool on the application of therapy and patient outcomes, and the cost-effectiveness of using this tool in clinical practice. Moreover, alternative management models should be explored in future studies to help improve comprehensive assessment in the decision-making around antithrombotics, to ensure cooperation between different disciplines and specialties in this process process, to redress clinical constraints (e.g., time pressure), and to improve medication safety and practical medication management.

Considering the unique features of Australian clinical practice, in the future, this tool could be used in a number of settings (137):

- as part of HMR services provided by accredited pharmacists
- by community pharmacists when dispensing medications

- by hospital pharmacists or nurses as part of anticoagulant clinics and clinical review of patients
- by pharmacists in GP clinics as part of chronic disease management
- by GPs in their surgeries for the initial prescription and follow-up of antithrombotics

8.2 Conclusion

Therapeutic decision-making around antithrombotics in AF is complex and requires an assessment of risk versus benefit. This research examined a modified decision support tool to facilitate this, and evaluated its usability and role in clinical practice.

When evaluated using patient data (database) and a real-world patient cohort, CARATV2.0 was able to help rationalise antithrombotic prescription in clinical practice, demonstrating its potential to improve the clinical outcomes of patients with AF. Importantly, the intervention with CARATV2.0 achieved a significant increase in the proportion of treatment in eligible patients using anticoagulants (warfarin and NOACs) compared with use at baseline (admission).

According to the health professionals interviewed in this research, CARATV2.0 is useful in assisting the decision-making around antithrombotic therapy for patients with AF. Both health professionals' preference for therapy and interdisciplinary differences in antithrombotic decision-making might have affected the professionals' opinions on the tool's recommendations. However, most of the health professionals were interested in using

this tool in clinical practice to help them select appropriate anticoagulant agents following an evidence-based evaluation of patients.

This research also shows that the current use of antithrombotics for stroke prevention in patients with AF is still potentially not optimal. The research identified key factors that affect decision-making around antithrombotics: practice-culture issues (e.g., time pressure, reluctance to change therapy); health professionals' perceptions about patient preferences for therapy; perceptions about bleeding risk; medication safety issues (e.g., older age, falls risk, renal impairment); and practical management issues (e.g., convenience of NOACs).

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Appendices

I. Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

Data Collection Form

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INTERVIEW QUESTIONS

Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

Interview Questions (will be asked by researcher)

1a) General Characteristics of Participants

Tick one: ☐ Specialist Clinician, ☐ GP, ☐ Nurse Consultants, ☐ Nurse Practitioner, ☐ Accredited Pharmacist☐ Hospital Pharmacist

1b) Years of experience in Practice_____

1c) Practice region_____ 1d) Type of specialization_____

1e) How many AF patients you manage annually?_____

1f) How many years have you been managing AF patients?_____

2. Perspective about CARATV2.0 tool

(Provide demonstration of this tool first) Audio (digitally) record response.

1. What is your overall impression of this tool?

What is the benefit or strength of this tool?

What is the weakness or limitation of this tool?

2. How relevant and appropriate is the content of this tool?

How well does the tool assess stroke and bleeding risk? (e.g., provide up-to-date and sufficient information, systematic assessment)

How well does the tool consider medication safety issues (e.g., drug interactions)?

3. How useful is this tool in assisting the decision-making in selecting appropriate antithrombotics for your AF patients?

Strength and weakness in recommending therapy? (e.g., provide up-to-date recommendation, individualized therapy)

How useful is this tool in identifying suitable candidates for warfarin?

How useful is this tool in identifying suitable candidates for new oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban)? (e.g., specific NOACs for specific patient)

4. How feasible might this tool be in practice?

What is the role of this tool in practice?

How might this tool improve the clinical outcomes of AF patients? (e.g., reducing adverse drug events)

5. What suggestions do you have for the further development of this tool?

II. Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

Participant Information Sheet

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Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

PARTICIPANT INFORMATION SHEET

Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool
UTS HREC REF NO. 2013000338

YOUR INVITATION TO PARTICIPATE

You are invited to take part in a study "Selecting Antithrombotic Therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool".

WHO IS DOING THE RESEARCH?

This study is conducted by Dr. Yishen Wang (PhD student at University of Technology Sydney) and A/Prof Beata Bajorek (University of Technology Sydney)

WHAT IS THIS RESEARCH ABOUT?

In this study, we will canvas feedback from health professionals about the content and feasibility of using a novel decision-making tool, as well as seeking suggestions for further improvement.

This tool has been designed to assist clinicians in deriving a treatment recommendation, based on risk assessment and the features of available anticoagulants (warfarin and novel oral anticoagulants (NOACs): dabigatran, rivaroxaban, and apixaban) for stroke prevention in AF patients.

Who is invited to take part?

Health professionals (e.g., specialist clinicians, general practitioners, nurse consultants and practitioners, accredited pharmacists, hospital pharmacists) who are practicing in the Sydney metropolitan region, and involved in the management and care of patients taking antithrombotic therapy for AF.

IF I SAY YES, WHAT WILL IT INVOLVE?

We will conduct a brief interview (about 20-30 minutes maximum in total) at a location convenient to you. The researcher (Dr. Yishen Wang) will come to do this interview with you when you are available. First, this tool will be introduced to you by the researcher. Then you will be interviewed about your opinions of the content, feasibility of use in clinical practice, and any suggestions for further improvement. The interview response will be digitally-recorded (audio) and transcribed (de-identified).

ARE THERE ANY RISKS/INCONVENIENCE?

There are no risks from participating in this interview. We will simply invite you to provide feedback on this tool at a time and location convenient to you. All feedback is treated confidentially. No response will be identifiable.

WHY HAVE I BEEN ASKED?

Your expertise in management and care of patients taking antithrombotic therapy for AF will help inform the development of a practice tool.

DO I HAVE TO SAY YES?

No. You don't have to say yes.

WHAT WILL HAPPEN IF I SAY NO?

Nothing. I will thank you for your time so far and won't contact you about this research again.

IF I SAY YES, CAN I CHANGE MY MIND LATER?

Participation in this study is voluntary. You can change your mind at any time and you don't have to say why. I will thank you for your time so far and won't contact you about this research again. Any information if collected from you during the study will then be destroyed and the information provided will not be included in the study.

WHAT IF I HAVE CONCERNS OR A COMPLAINT?

If you have concerns about the research that you think I or my supervisor can help you with, please feel free to contact me (us) on:

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This study has been approved b the University of Technology Sydney, Sydney Human Research Ethics Committee. If you would like to talk to someone who is not connected with the research, you may contact the Research Ethics Officer on 02 9514 9772, and quote this number *(UTS HREC REF NO. 2013000338)*

III. Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

Participant Consent Form

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Associate Professor Beata Bajorek

Graduate School of Health Faculty of Pharmacy

University of Technology Sydney NSW 2007

AUSTRALIA

Telephone: +61 2 9514 8301

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Participant Consent Form

Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

PARTICIPANT CONSENT FORM

"Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool"

I _____ (participant's name) agree to participate in the research project

"**Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool**"

I understand that the purpose of this study is to canvas feedback from health professionals about the content and feasibility of using a novel decision-making tool, as well as seeking suggestions for further improvement.

In giving my consent I acknowledge that:

- The procedures required for the project, the time involved (20-30mins maximum in total), any inconvenience or risk, and their implications have been explained to me, and any questions I have about the project have been answered to my satisfaction.
- I have read the Participant Information Sheet and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.
- I understand that my involvement is strictly confidential and no information about me, my practice, will be used in any way that reveals my identity.
- I understand that being in this study is completely voluntary.
- I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher(s) or their affiliated institutions now or in the future.
- I understand that I can stop the interview at any time if I do not wish to continue, the audio recording and any notes will then be destroyed and the information provided will not be included in the study.
- I am aware that I can contact Dr. Yishen Wang (PhD student) or her supervisor A/Prof Beata Bajorek, if I have any concerns about the research. I also understand that I am free to withdraw my participation from this research project at any time I wish, without consequences, and without giving a reason.
- I agree that Dr. Yishen Wang has answered all my questions fully and clearly.

_____ Date____/____/2014
Signature (participant)

_____ Date ____/____/2014
Signature (witness)

NOTE:
This study has been approved by the University of Technology, Sydney Human Research Ethics Committee. If you have any complaints or reservations about any aspect of your participation in this research which you cannot resolve with the researcher, you may contact the Ethics Committee through the Research Ethics Officer

(ph: +61 2 9514 9772 Research.Ethics@uts.edu.au) and quote the UTS HREC REF NO. 2013000338. Any complaint you make will be treated in confidence and investigated fully and you will be informed of the outcome. Version1 (300514)

IV. Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

Flyers and Fax-back Form

ANTITHROMBOTIC THERAPY FOR STROKE PREVENTION IN AF (STUDY)

Q/ do you provide care to patients with Atrial Fibrillation (AF) who require antithrombotic therapy for stroke prevention?

Q/ do you contribute to the decision-making / recommendations regarding the selection of specific antithrombotic therapy for individual patients?

If YES, we would like to canvas your opinions on a decision support tool to assist clinicians and practitioners in deriving treatment recommendations for persons with AF.

These opinions are being sought as part of study being conducted by Dr Yishen Wang (PhD student) from the Graduate School of Health – University of Technology.

Further information is attached. We look forward to hearing from you. Please contact: [redacted] OR (02) 9514-9226

Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

Are you involved in the management and care of patients taking antithrombotic prescription for atrial fibrillation?

If YES, we would like you to invite you to participate in a study "Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool".

If you would like more information, please complete and return the section below.

Fax-back Form to +61 2 9514 8300 (Dr. Yishen Wang)

Please tick one:	☐ Specialist Clinician ☐ GP ☐ Nurse Consultant ☐ Nurse Practitioner ☐ Accredited Pharmacist ☐ Hospital Pharmacist
Name of Health Professional	
Practice Site (Organization)	
Telephone	
Mobile	
Fax number	
Email	
Address	
	(Number) (Street name)
	(Suburb) (Postcode)

We will contact you shortly. Thank you.

V. Project Title: Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool

Ethics Approval

UTS HREC Approval

Research.Ethics@uts.edu.au

Wed 2/07/2014 16:22

收件箱

To: Yishen Wang < [redacted] >; Beata.Bajorek@uts.edu.au <Beata.Bajorek@uts.edu.au>; Research.Ethics@uts.edu.au <Research.Ethics@uts.edu.au>;

Dear Applicant

The UTS Human Research Ethics Committee reviewed your application titled, "(ERC) Selecting Antithrombotic therapy for Stroke Prevention in Atrial Fibrillation (AF): Health Professionals' Feedback on a Decision Support Tool", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research (2007). I am pleased to inform you that ethics approval is now granted.

Your approval number is UTS HREC REF NO. 2013000338
Your approval is valid five years from the date of this email.

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually from the date of approval, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: http://rmprod.itd.uts.edu.au/RMENet/HOM001N.aspx
* if accessing outside of UTS network: https://remote.uts.edu.au , and click on "RMENet - ResearchMaster Enterprise" after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to: http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

Professor Marion Haas
Chairperson
UTS Human Research Ethics Committee
C/- Research & Innovation Office
University of Technology, Sydney
T: (02) 9514 9645
F: (02) 9514 1244
E: Research.Ethics@uts.edu.au
I: http://www.research.uts.edu.au/policies/restricted/ethics.html
P: PO Box 123, BROADWAY NSW 2007
[Level 14, Building 1, Broadway Campus]
CB01.14.08.04

VI. Project Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

Data Collection Form

Dr. Yishen Wang
Graduate School of Health-Pharmacy
University of Technology Sydney NSW 2007
AUSTRALIA
Telephone: +61 2 9514 9226
Email: [redacted]

Associate Professor Beata Bajorek
Graduate School of Health-Pharmacy
University of Technology Sydney NSW 2007
AUSTRALIA
Telephone: +61 2 9514 8301
Facsimile: +61 2 9514 8300
Email: Beata.Bajorek@uts.edu.au

DATA COLLECTION FORM

Project Title: Pilot of a Decision Support Tool for stroke prevention in atrial fibrillation (AF)

Step 1	Step 2	Step 3	Step 4	Step 5
Screen to identify eligible patients	Review patient's medical record	Interview patients	Apply the decision support tool to the extracted data	Present recommendations to prescribers

Acknowledgement: This form is adopted from Bajorek B, Magin P, Hilmer S, Krass I. A cluster-randomized controlled trial of a computerized antithrombotic risk assessment tool to optimize stroke prevention in general practice: a study protocol. BMC Health Serv Res. 2014;14(1):55.

Step1 screening patients

❑Are aged 65 or older

❑Have a principal diagnosis of AF (ICD-10-CM code I48.91, I48.0, I48.1, I48.2), whether new or pre-existing

❑OR have a secondary diagnosis of AF regarded to be contributory to the admission (e.g., stroke, heart failure, cardiac shock)

❑Have non-valvular AF i.e., excluding those with a documented history of 'rheumatic' heart disease, 'valvular' disease, or 'valvular' AF.

❑Are admitted to Royal North Shore Hospital (cardiology, neurology, aged care, general medicine) during the data collection period, irrespective of the antithrombotic therapy prescribed at the time of recruitment

❑The patients (or the carers) are able to provide informed written consent to participate in the study.

❑For patients who will be admitted more than once during the data collection period, CARATV2.0 will be performed on the first admission only.

❑Patients who speak English.

Step 2 Reviewing patient's medical record

Patient characteristics:

Age:_____ years, Gender: ❑F (1)❑ M(2)) Ethnicity ❑Caucasian (1)❑Asian (2) African ❑ (3) Aboriginal or island people❑(4)

• Medical history: Patient Characteristics (from medical record):

1. Co-morbidities:

Cardiovascular

1. ❑Ischaemic Heart Disease (IHD)
2. ❑Cardiomyopathy
3. ❑Prosthetic heart valve
4. ❑Hyperlipidemia
5. ❑Previous Stroke: …….. Type: ❑ Ischaemic
   ❑ Embolic
   ❑ Haemorrhagic
   Date/s: ……
   ……..
6. ❑Hypertension (treated or untreated)

Systolic_____mmHg Diastolic_____ mmHg

7. ❑ Congestive Heart Failure/LV dysfunction
8. ❑ Vascular Disease (PAD, aortic plaque)
9. ❑ Dissecting aorta
10. ❑Intracranial aneurysm
11. ❑Intracranial hemorrhage
12. ❑ other

_____
_____

Neurological

13. ❑Parkinson's Disease (PD)
14. ❑Alzheimer's / Dementia
15. ❑ Other

_____
_____

Hepatic

16. ❑Encephalopathy
17. ❑ Other

_____
_____

Renal

18. ❑Chronic Renal Failure (CRF)
19. ❑Acute renal failure
20. ❑ Other

_____
_____

Weight_____kg

Endocrine

24. ❑Thyroid
25. ❑Diabetes
26. ❑ Other

_____
_____

Haematological

27. ❑Anaemia
28. ❑Thrombocytopenia
29. ❑Thromboembolism (outside brain, heart, eyes, and lungs)
30. ❑ Other

_____
_____

Gastrointestinal

31. ❑Gastro-esophageal Reflux Disease (GORD)
32. ❑ gastrointestinal Ulcer Disease
33. ❑ gastrointestinal bleeding
34. ❑ Liver disease
35. ❑Other gastrointestinal disease
36. ❑ other

_____
_____

37. ❑ Malignancy_____
38. Other

_____
_____
_____

2. Lab result:

39. kidney function: creatinine _____ (µmol/L)
    eGFR_____
    CrCl_____
40. Liver function: AST_____

Visual

21. ❑Macular Degeneration(MD)
22. ❑Glaucoma
23. ❑ Other

_____
_____

ALT_____

Bilirubin (umol/l)_____Albumin (g/dl)_____

Encephalopathy_____Ascites_____

_____

Prothromin time (sec>control)_____CHILD _____

50. Coagulant parameters: INR_____ APTT_____s PT_____s TT_____ s RBC_____ x 10^{12} / l Platelet_____ x 10^{9} / l INR_____

51. Labile INRs (if on warfarin) TTR_____

• Medication history (from medical record):

3. Current Medication Regimen (from medical record):

Name & Dosage	Indication

*NON - Prescription Medications (eg OTC, supplements):number*_____

Name & Dosage	Indication

Medication classes prescribed

1. ❑Antithrombotic agents (B01) (at admission)

Nil therapy ❑ (1)
Warfarin ❑ (2)
Aspirin ❑ (3)
Dosage……
Dabigatran ❑ (4)
Rivaroxaban ❑ (5) When started_____(months)
Apixaban ❑ (6)
Warfarin+Aspirin ❑ (7)
Warfarin+clopidogrel ❑ (8)
Warfarin+Aspirin+clopidogrel ❑ (9)

2. ❑Antiarrhythmics

❑Dronedarone ❑ (1)
❑Amiodarone ❑ (2)
❑ Verapamil ❑ (3)
❑ Quinidine ❑ (4)
❑Propafenone ❑ (5)
❑Digoxin ❑ (6)
❑Sotalol ❑ (7)

3. ❑Beta Blocker
4. ❑Calcium Channel blocker
5. ❑Alpha Blockers
6. ❑Nitrates
7. ❑Other Antihypertensive: _____
8. ❑Sedatives
9. ❑Cholesterol lowering

❑Antilipid agents (statins) ❑ (1)
❑ Fibrate ❑ (2)
❑Paracetamol

10. ❑regular NSAIDs (including low dose aspirin)
11. ❑Opioid
12. ❑PPI/H2 Antagonists

	13. ❑Asthma therapy 14. ❑Diuretics 15. ❑Tricyclic Antidepressants 16. ❑SSRIs 17. ❑Antipsychotic 18. ❑Anti-dementia drugs 19. ❑Anti-parkinson's drugs 20. ❑Hypoglycaemics 21. ❑Regular Corticosteroids (long term and high dosage) 22. ❑Hormone Replacement Therapy (HRT) 23. ❑Bisphosphonates 24. Total number of medication_____ POLYPHARMACY≥ 4 medications Yes ❑ (1) No ❑ (2) 25. Ethanol abuse Yes ❑ (1) No ❑ (2)

• AF history (from medical record):

4. Prior History of AF: Yes ❑(1) (prior to THIS consultation) No ❑(2)	→ 4.a If YES, time since first diagnosed: _____ months

5. Type of AF

Paroxysmal ❑ (1) **5.a** Episodes in last 12 months: ≤2 ❑ (1) >2 ❑ (2)	**Persistent** ❑ (2) **5.b** Duration: _____	**New onset** ❑ (3) **5.c** Date of onset: <48 hours ❑ (1) ≥ 48 hours ❑ (2) Unknown ❑ (3)	**Unknown** ❑ (4) (not yet confirmed)

6. a Primary reason for admission: Acute AF management ❑ (1) Stroke / CVA due to AF ❑ (2) Elective Cardioversion ❑ (3) Other …… ❑ (4)	**6.b Secondary reason for admission:** Acute AF management ❑ (1) Stroke / CVA due to AF ❑ (2) Elective Cardioversion ❑ (3) Other …… ❑ (4)

7. Current cardiac rhythm (from the latest EKG before discharge):

Normal Sinus Rhythm (NSR) ❑ (1)	**Controlled AF** ❑ (2)	**Uncontrolled AF** ❑ (3)

8. Indications for antithrombotics

AF only	❑ (1)
AF+PCI (after 12months)	❑ (2)
AF+Stable CAD (ACS after 12months)	❑ (3)
AF+ACS without sent (within 12months)	❑ (4)
AF+PCI (bare-metal stent over 1 month and less than 12 months)	❑ (5)
AF+PCI (drug-eluting stent over 6 months and less than 12 months)	❑ (6)

AF+PCI (bare-metal stent in 1 month) ❑ (7) AF+PCI (drug-eluting stent within 6months) ❑ (8) AF+DVT ❑ (9) AF+PE ❑ (10) AF+Other ❑ (11)		
9. Who is principally managing AF therapy / antithrombotics:	GP ❑ **(1)** Specialist ❑ **(2)** →	Cardiologist ❑ **(3)** Stroke Neurologist ❑ **(4)** Aged care ❑ **(5)** General medicine ❑ **(6)**
• History of Antithrombotic (anti-clotting) medication use (from medical record/patient interview):		
10. Patient is ALLERGIC to any oral antithrombotics?	Yes ❑ (1) No ❑ (2)	Allergic to: Warfarin ❑ (1) Dabigatran ❑ (2) Rivaroxaban ❑ (3) Apixaban ❑ (4) Aspirin ❑ (5) Clopidogrel ❑ (6) Reaction:
11. Patient has had previous ADVERSE REACTIONS to antithrombotics:	Yes ❑ (1) No ❑ (2)	Agent : Warfarin ❑ (1) Dabigatran ❑ (2) Rivaroxaban ❑ (3) Apixaban ❑ (4) Aspirin ❑ (5) Clopidogrel ❑ (6) Reaction:
12. Patient has REFUSED / DECLINED antithrombotics:	Yes ❑ (1) No ❑ (2)	Refused Warfarin ❑ (1) Dabigatran ❑ (2) Rivaroxaban ❑ (3) Apixaban ❑ (4) Aspirin ❑ (5) Clopidogrel ❑ (6) Reason provided:
13. Patient has CONTRAINDICATIONS to antithrombotics *:*	Yes ❑ (1) No ❑ (2)	Reason:
14. Patient has previously FAILED antithrombotic therapy:	Yes ❑ (1) No ❑ (2)	→ Adverse effects ❑ (1) Thromboembolism ❑ (2) Unstable therapy (INR) ❑ (3) Non-compliance ❑ (4) Other ❑ (5)
15. Documented reasons for use or non-use of antithrombotic therapy:		

• Medication Management Issues (from medical record/patient interview):		
16. Cognitive function (MMSE) < 24 (dementia):	Yes ❑ (1) No ❑ (2)	
17. Patient has a history of NON-COMPLIANCE with medication (documented in medical record/medication review):	Yes ❑ (1) No ❑ (2)	
18. Do you ever forget to take your antithrombotic medicine?	Yes ❑ (1) No ❑ (2)	
19. Do you ever have problems remembering to take your antithrombotic medication?	Yes ❑ (1) No ❑ (2)	
20. When you feel better, do you sometimes stop taking your antithrombotic medicine?	Yes ❑ (1) No ❑ (2)	
21. Sometimes if you feel worse when you take your antithrombotic medicine, do you stop taking it?	Yes ❑ (1) No ❑ (2)	
22. Patient utilises ASSISTANCE for medication management (e.g., assistance by carer or family member):	Yes ❑ (1) No ❑ (2)	→ Carer / Family ❑ (1) Home Nursing service ❑ (2) Dosing Aids / Blister packs ❑ (3) APAC service ❑ (4) Other ❑ (5)
23. Patient has major VISION IMPAIRMENT (e.g., severe glaucoma, macular degeneration, color blindness or best-corrected vision acuity 6/60, or documented diagnosis) :	Yes ❑ (1) No ❑ (2)	
24.Patient has major HEARING IMPAIRMENT (sensorineural and/ conductive hearing loss unaided hearing threshold for the better ear of 91 dB or greater, or where the individual may hear loud sounds but does not rely on hearing as a primary form of communication; documented diagnosis by audiogram or medical record):	Yes ❑ (1) No ❑ (2)	
25. Patient has major LANGUAGE / COMMUNICATION BARRIER (any documented difficulty of communication):	Yes ❑ (1) No ❑ (2)	
26. Poor comprehension of antithombotic therapy (documented in medical record/medication review):	Yes ❑ (1) No ❑ (2)	
27.Patient is at a Residential Care facility (nursing home):	Yes ❑ (1) No ❑ (2)	
28. Patient has difficulty accessing medical care and INR monitoring:	Yes ❑ (1) No ❑ (2)	
29. Patient has poor diet and extremely low vitamin K intake:	Yes ❑ (1) No ❑ (2)	

30. Patient has major MOBILITY DISORDER (e.g., severe arthritis, Parkinson's disease, wheelchair bound or other mobility disorder documented in medical record):	Yes ❑ (1) No ❑ (2)	Detail:
31. Patient has other FUNCTIONAL IMPAIRMENT (e.g., unable to manage social and personal business, or other functional disorder documented in medical record):	Yes ❑ (1) No ❑ (2)	Detail:
32. Excessive Fall Risk: Definition: history of frequent falls. Use of medications such as Antihypertensives, Antiparkinsons, Antipsychotics, Tricyclic antidepressants, benzodiazepines. History of gait disorder.	Yes ❑ (1) No ❑ (2)	

• Application of CARATV2.0 (after applying the above information to CARATV2.0)	
33. STROKE RISK Assessment:	CHADS2 score____ CHA2DS2-VASc score_____
34. BLEEDING RISK Assessment:	HEMORR2HAGES score_____ HAS-BLED score_____
35. Antithrombotic therapy prescribed by clinicians pre CARATV2.0:	Nil therapy ❑ (1) Warfarin ❑ (2) Aspirin ❑ (3) Dabigatran/Rivaroxaban/Apixaban ❑ (4) Dosage_____ Rivaroxban/Apixban ❑ (5) Apixaban ❑ (6) Warfarin+Aspirin ❑ (7) Warfarin+clopidogrel ❑ (8) Warfarin+Aspirin+clopidogrel ❑ (9) Heparin ❑ (10) LMWH ❑ (11)
36. Antithrombotic therapy recommended by CARATV2.0:	Nil therapy ❑ (1) Warfarin ❑ (2) Aspirin ❑ (3) Dabigatran/Rivaroxaban/Apixaban ❑ (4) Dosage_____ Rivaroxban/Apixban ❑ (5) Apixaban ❑ (6) Warfarin+Aspirin ❑ (7) Warfarin+clopidogrel ❑ (8) Warfarin+Aspirin+clopidogrel ❑ (9)
• Present recommendation to prescribers:	
37. Antithrombotic therapy selected by clinician post CARATV 2.0:	Nil therapy ❑ (1) Warfarin ❑ (2) Aspirin ❑ (3) Dabigatran ❑ (4) Dosage_____ Rivaroxban ❑ (5) Apixaban ❑ (6) Warfarin+Aspirin ❑ (7) Warfarin+clopidogrel ❑ (8) Warfarin+Aspirin+clopidogrel ❑ (9)
38. Do prescribers agree with CARATV2.0 recommendation:	Yes ❑ (1) No ❑ (2)
39. Reason for prescribers disagreement with CARATV2.0 recommendation	
40. How has patient's therapy changed overall:	No change ❑ (1) Change ❑ (2) details_____

VII. Project Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

Participant Information Sheet and Consent Form (Patients)

Royal North Shore Hospital

PARTICIPANT INFORMATION SHEET---PATIENTS

Anti-clotting Medication Use for Stroke Prevention

(Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF))

Invitation

You are invited to participate in a research study:

Anti-clotting Medication Use for Stroke Prevention

(Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF))

The purpose of the study is to find out how useful a newly developed 'decision support tool' might be in assisting doctors when they are prescribing anti-clotting medications. A decision support tool is a checklist that helps health professionals assess a person's medical history and medications to help make decisions about the most suitable medications to use in particular patients.

The study is being conducted by Yishen Wang (PhD student) and her supervisor A/Prof Beata Bajorek from Graduate School of Health-Pharmacy, University of Technology Sydney, Department of Pharmacy, Royal North Shore Hospital (Northern Local Health District).

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. ‘What is the purpose of this study?’

The decision support tool used in this study is a computer program that will be used to review your anti-clotting medications with this tool (program) and ask doctors how useful the tool is in helping them to confirm your treatment. The study does not involve changing your medications. .

2. ‘Why have I been invited to participate in this study?’

You are invited to participate in this study because you have an irregular heartbeat, are taking anti-clotting medicines, and are currently admitted at Royal North Shore Hospital.

3. ‘What if I don’t want to take part in this study, or if I want to withdraw later?’

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. Any data already collected will be destroyed.

4. ‘What does this study involve?’

If you agree to participate in this study, you will be asked to

- Allow the research team to access your medical records and notes to obtain information relevant to the study.
- We may also ask you some questions about your medicines use. We are most interested in asking you about your anti-clotting medications (such as warfarin, aspirin, Coumadin™, Marevan™, Astrix™, Cartia™, Cardiprin™, Asasantin SR™, CoPlavix™, DuoCover™, Solprin™, Pradaxa™, Xarelto™, Eliquis™).

5. 'What are the alternatives to participating in this study?'

You will still experience the same medical care, whether or not you participate in this study. We will simply look at your medication chart and clinical notes during your hospital stay and may also ask you some questions about your medicines.

6. 'Are there risks to me in taking part in this study?'

There are no known risks associated with taking part in this study. Your participation in the study will involve only the researchers reviewing your medical notes, and possibly asking you some questions about your medications. Taking part in the study will not result in any changes being made to your medications.

7. 'Will I benefit from the study?'

You will not directly benefit from this study. We hope that, in the future, the decision support tool can be used in hospitals to assist doctors in making decisions about the most suitable anti-clotting medications to use for particular patients.

8. 'Will taking part in this study cost me anything, and will I be paid?

No, there is no cost to you in participating in this study.

9. 'How will my confidentiality be protected?'

Of the people treating you, only the doctors who are responsible for the management of your anti-clotting medication will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers Yishen Wang and Beata Bajorek will have access to the information and the results. All paper files will be stored in locked desk drawers at the Graduate School of Health-Pharmacy. All electronic files (except the master list) will be saved on computer drives with password protection for a minimum of 5 years in the researcher's office at the Graduate School of Health-Pharmacy, University of Technology Sydney. The master list which links the code to any identifiable data will be stored in the principal

researcher's office at the Department of Pharmacy, Royal North Shore Hospital, separate from the main data set stored at the Graduate School of Health-Pharmacy, University of Technology Sydney.

10. 'What happens with the results?'

The findings of this study may be presented in journals, research reports and conference presentation or other professional forums. But you will never be identified in the results.

11. How is this study paid for?

This study is not sponsored by any grants, sponsors, departments or organizations. The study is paid by the Graduate School of Health, University of Technology Sydney.

12. 'What should I do if I want to discuss this study further before I decide?'

If you would like to know more at any stage, please do not hesitate to contact Dr Yishen Wang on Yishen.Wang@student.uts.edu.au OR (02) 9514-9226.

13. 'Who should I contact if I have concerns about the conduct of this study?'

This study has been approved by the Northern Sydney Local Health District Human Research Ethics Committee (HREC). Any person with concerns or complaints about the conduct of this study should contact the Research Office who is nominated to receive complaints from research participants. You should contact them on 02 9926 4590 and quote HREC reference number HREC/15/HAWKE/103.

Thank you for taking the time to consider this study.

If you wish to take part in it, please sign the attached consent form.

This information sheet is for you to keep.

Royal North Shore Hospital

CONSENT FORM---PATIENTS

Anti-clotting Medication Use for Stroke Prevention

(Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF))

1. ..... agree to participate as a subject in the study described in the Participant Information Sheet **(attached to this form).**

2. I acknowledge that I have read the Participant Information Sheet, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.

3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.

4. I understand that I can withdraw from the study at any time without prejudice to my relationship to the investigators or Royal North Shore Hospital or University of Technology Sydney.

5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.

6. I understand that if I have any questions relating to my participation in this research, I may contact Yishen Wang on Yishen.Wang@student.uts.edu.au OR (02) 9514-9226. who will be happy to answer them.

7. I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet.

Complaints may be directed to the Research Office on Level 13, Kolling Building, Royal North Shore Hospital, St Leonards NSW 2065
Phone 02 9926 4590 | email NSLHD-research@health.nsw.gov.au

Signature of participant (or legal guardian) Please PRINT name Date

_____

Signature of witness Please PRINT name Date

_____

Signature of investigator Please PRINT name Date

_____

Royal North Shore Hospital
REVOCATION OF CONSENT

Anti-clotting Medication Use for Stroke Prevention

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with Royal North Shore hospital or University of Technology Sydney.

Signature Date

Please PRINT Name

The section for Revocation of Consent should be forwarded to:

Name	Beata BAJOREK
Title	A/Prof.
Qualifications	PhD BPharm DipHospPharm GradCertEdStud(HigherEd)
Positions held: employed,	Associate Professor, University of Technology Sydney Academic Pharmacist, Department of Pharmacy, RNS Hospital (Northern LHD)
Full mailing address (including building number)	Graduate School of Health-Pharmacy, Building 7 level 4 University of Technology Sydney NSW 2007 Level 1 Pharmacy Department, RNS Hospital (Northern LHD) NSW 2065
Telephone	+61 2 9514 8301
Fax	61-2-9514-8300
E-mail	Beata.Bajorek@uts.edu.au.

VIII. Project Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

Participant Information Sheet and Consent Form (Person responsible)

Royal North Shore Hospital

PARTICIPANT INFORMATION SHEET---PERSON RESPONSIBLE

Anti-clotting Medication Use for Stroke Prevention

(Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF))

Invitation

The person that you are responsible for (him/her) is invited to participate in a research study:

Anti-clotting Medication Use for Stroke Prevention

(Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF))

The purpose of the study is to find out how useful a newly developed 'decision support tool' might be in assisting doctors when they are prescribing anti-clotting medications. A decision support tool is a checklist that helps health professionals assess a person's medical history and medications to help make decisions about the most suitable medications to use in particular patients.

The study is being conducted by Yishen Wang (PhD student) and her supervisor A/Prof Beata Bajorek from Graduate School of Health-Pharmacy, University of Technology Sydney, Department of Pharmacy, Royal North Shore Hospital (Northern Local Health District).

Before you decide whether or not you wish for the person you are responsible for to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

14. 'Why have I been invited to participate in this study?'

The person you are responsible for has been invited to participate in this study because he/she has an irregular heartbeat, is taking anti-clotting medicines, as is currently admitted at Royal North Shore Hospital.

15. 'What if I don't want to take part in this study, or if I want to withdraw later?'

Participation in this study is voluntary. It is completely up to you whether or not you decide that you are happy for the person you are responsible for to participate. Choosing not to participate will have no effect the treatment he/she receives now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for the person you are responsible for.

If you wish to withdraw the person from the study once it has started, you can do so at any time without having to give a reason and any data already collected will be destroyed.

16. 'What does this study involve?'

If you agree to participate in this study, you will be asked to

- Allow the research team to access medical records and notes of the person you are responsible for to obtain information relevant to the study.

We may also ask you some questions about his/her medicines. We are most interested in asking you about his/her anti-clotting medicines (such as warfarin, aspirin, Coumadin™, Marevan™, Astrix™, Cartia™, Cardiprin™, Asasantin SR™, CoPlavix™, DuoCover™, Solprin™, Pradaxa™, Xarelto™, Eliquis™).

5 'What are the alternatives to participating in this study?'

The person you are responsible for for will still experience the same medical care, whether or not you decide to include them in this study. We will simply look at his/her medication chart and clinical notes during his/her hospital stay and may also ask you some questions about his/her medicines.

6 **'Are there risks to me in taking part in this study?'**

There are no known risks associated with taking part in this study. Participation in the study will involve only the researchers reviewing medical notes of the person you are responsible for, and possibly asking you some questions about his/her medications. Taking part in the study will not result in any changes being made to their medications.

7 'Will I benefit from the study?'

Neither you nor the person you care for will directly benefit from this study. We hope that in the future, the decision-making support tool can be used in hospitals to assist doctors in making decisions about the most suitable anti-clotting medicines to use for different patients.

8 'Will taking part in this study cost me anything, and will I be paid?

No, there is no cost to you, or the person you are responsible for, in participating in this study.

9 'How will my confidentiality be protected?'

Of the people treating the person you are responsible for, only the doctors who are responsible for the management for his/her anti-clotting medicine will know whether or not he/she is participating in this study. Any identifiable information that is collected about him/her in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers Yishen Wang and Beata Bajorek will have access to the information and the results. All paper files will be stored and in the locked desk drawers at the Graduate School of Health-Pharmacy. All the electronic files (except the master list) will be saved on computer drives with password protection for a minimum of 5 years in the researcher's office at the Graduate School of Health-Pharmacy, University of Technology Sydney. The master list which links the code to any identifiable data will be stored in the principal researcher's office at the Department of Pharmacy, Royal North Shore Hospital, separate from the main data set stored at the Graduate School of Health-Pharmacy, University of Technology Sydney.

10 'What happens with the results?'

The findings of this study may be presented in journals, research reports and conference presentation or other professional forums. But the person that you care for will never be identified in the results.

11 'How is this study paid for?'

This study is not sponsored by any grants, sponsors, departments or organizations. The study is paid by the Graduate School of Health, University of Technology Sydney.

12 'What should I do if I want to discuss this study further before I decide?'

If you would like to know more at any stage, please do not hesitate to contact Dr Yishen Wang on Yishen.Wang@student.uts.edu.au OR (02) 9514-9226.

13 'Who should I contact if I have concerns about the conduct of this study?'

This study has been approved by the Northern Sydney Local Health District Human Research Ethics Committee (HREC). Any person with concerns or complaints about the conduct of this study should contact the Research Office who is nominated to receive complaints from research participants. You should contact them on 02 9926 4590 and quote HREC reference number HREC/15/HAWKE/103.

Thank you for taking the time to consider this study.

If you wish to take part in it, please sign the attached consent form.

This information sheet is for you to keep.

Royal North Shore Hospital

CONSENT FORM--- PERSON RESPONSIBLE

Anti-clotting Medication Use for Stroke Prevention

Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

3. ..... agree to participate as a subject in the study described in the Participant Information Sheet **(attached to this form).**

4. I acknowledge that I have read the Participant Information Sheet, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.

8. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.

9. I understand that I can withdraw from the study at any time without prejudice to my relationship to the investigators or Royal North Shore Hospital or University of Technology Sydney.

10. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.

11. I understand that if I have any questions relating to my participation in this research, I may contact Yishen Wang on Yishen.Wang@student.uts.edu.au OR (02) 9514-9226. who will be happy to answer them.

12. I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet.

Complaints may be directed to the Research Office on Level 13, Kolling Building, Royal North Shore Hospital, St Leonards NSW 2065
Phone 02 9926 4590 | email NSLHD-research@health.nsw.gov.au

Signature of participant (or legal guardian) Please PRINT name Date

_____

Signature of witness Please PRINT name Date

_____

Signature of investigator Please PRINT name Date

_____

Royal North Shore Hospital

REVOCATION OF CONSENT

Anti-clotting Medication Use for Stroke Prevention

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with Royal North Shore hospital or University of Technology Sydney.

Signature Date

Please PRINT Name

The section for Revocation of Consent should be forwarded to:

Name	Beata BAJOREK
Title	A/Prof.
Qualifications	PhD BPharm DipHospPharm GradCertEdStud(HigherEd)
Positions held: employed,	Associate Professor, University of Technology Sydney Academic Pharmacist, Department of Pharmacy, RNS Hospital (Northern LHD)
Full mailing address (including building number)	Graduate School of Health-Pharmacy, Building 7 level 4 University of Technology Sydney NSW 2007 Level 1 Pharmacy Department, RNS Hospital (Northern LHD) NSW 2065
Telephone	+61 2 9514 8301
Fax	61-2-9514-8300
E-mail	Beata.Bajorek@uts.edu.au.

IX. Project Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

Participant Information Sheet and Consent Form (Prescribers)

Royal North Shore Hospital

PARTICIPANT INFORMATION SHEET--- PRESCRIBERS

Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

(Anti-clotting Medication Use for Stroke Prevention)

Invitation

You are invited to participate in a research study:

Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)
(Anti-clotting Medication Use for Stroke Prevention)

This decision support tool has been designed to assist clinicians in deriving a treatment recommendation for antithrombotic therapy in AF patients that is based on a risk versus benefit assessment of individual patients. The tool considers the novel oral anticoagulants (NOACs)—dabigatran, rivaroxaban and apixaban—as alternatives to warfarin for stroke prevention in AF, reflecting the latest guidelines [1-5]. In order to evaluate this tool in clinical practice, we are pilot-testing this tool in RNSH.

You should maintain your usual practice, whether or not you participate in this study. We are simply seeking your perspective on the tool's recommendations in comparison with your usual practice.The study is being conducted by Yishen Wang (PhD student) and her supervisor A/Prof Beata Bajorek from Graduate School of Health-Pharmacy, University of Technology Sydney, Department of Pharmacy, RNS Hospital (Northern LHD).

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will

involve. Please take the time to read the following information carefully and discuss it with others if you wish.

17. 'What is the purpose of this study?'

To pilot test this decision support tool in a cohort of AF patients in a hospital setting. The feasibility of using this tool in the hospital setting will be evaluated.

18. 'Why have I been invited to participate in this study?'

You are invited to participate in this study because you are central to the decision-making regarding the selection of specific antithrombotic therapy for AF patients. We are interested in seeing to what extent such a decision support tool may assist treatment selection in the type of patients that you treat.

19. 'What if I don't want to take part in this study, or if I want to withdraw later?'

Participation in this study is voluntary. It is completely up to you whether or not you participate. Whatever your decision, it will not affect your relationship with the researchers of the study and their affiliated institutions.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. Any data already collected will be destroyed.

20. 'What does this study involve?'

If you agree to participate in this study, you will be asked to

- Allow the researchers to access your patients' medical records to obtain information relevant to the study (medical history, history of antithrombotic therapy, medication management issues).
- Indicate your level of agreement and disagreement with the antithrombotic therapy recommendations generated by the decision support tool.

Please note that the tool will only generate treatment recommendations for your consideration; you maintain complete authority for the selection of therapy based on your own clinical judgement. You are not required to accept the tool's recommendations. We will simply populate this tool with patients' data and then present the generated recommendations to you during your ward rounds.

21. 'What are the alternatives to participating in this study?'

You should maintain your usual practice, whether or not you participate in this study. We are simply seeking your perspective on the tool's recommendations alongside your usual practice.

22. 'Are there risks to me in taking part in this study?'

There are no known risks associated with taking part in this study. The study involves only a review of medical notes to populate the decision support tool by the researcher, and asking your opinion on the recommendations generated by the tool..

23. 'Will I benefit from the study?'

You will not directly benefit from this study. However, your participation will help inform the need for, and development of, a decision support tool.

24. 'Will taking part in this study cost me anything, and will I be paid?

No, there is no cost to you in participating in this study.

25. 'How will my confidentiality be protected?'

A unique code will be used to represent each participant on study documents or data files. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers Yishen Wang and Beata Bajorek will have access to the information and the results. All paper files will be

stored in locked desk drawers in the researcher's office at the Graduate School of Health-Pharmacy. All the electronic files (except the master list) will be saved on computer drives with password protection for a minimum of 5 years in the researcher's office at the Graduate School of Health-Pharmacy, University of Technology Sydney. The master list which links the code to any identifiable data will be stored in the principal researcher's office at the Department of Pharmacy, Royal North Shore Hospital, separate from the main data set stored at the Graduate School of Health-Pharmacy, University of Technology Sydney.

26. 'What happens with the results?'

The findings of this study may be presented in journals, research reports and conference presentation or other professional forums. No personally-identifiable information will be presented.

27. How is this study paid for?

This study is not sponsored by any grants, sponsors, departments or organizations. The study is paid by the Graduate School of Health, University of Technology Sydney.

28. 'What should I do if I want to discuss this study further before I decide?'

If you would like to know more at any stage, please do not hesitate to contact Dr Yishen Wang on Yishen.Wang@student.uts.edu.au OR (02) 9514-9226.

29. 'Who should I contact if I have concerns about the conduct of this study?'

This study has been approved by the Northern Sydney Local Health District Human Research Ethics Committee (HREC). Any person with concerns or complaints about the conduct of this study should contact the Research Office who is nominated to receive complaints from research participants. You should contact them on 02 9926 4590 and quote HREC reference number HREC/15/HAWKE/103.

Thank you for taking the time to consider your participation in this study.

If you wish to take part, please sign the attached consent form.

This information sheet is for you to keep.

Reference

1. Bajorek, B.V., et al., Optimizing the use of antithrombotic therapy for atrial fibrillation in older people: A pharmacist-led multidisciplinary intervention. Journal of the American Geriatrics Society, 2005. 53(11): p. 1912-1920.
2. Bajorek, B.V., N. Masood, and I. Krass, Development of a Computerised Antithrombotic Risk Assessment Tool (CARAT) to optimise therapy in older persons with atrial fibrillation. Australas J Ageing, 2012. 31(2): p. 102-9.
3. You, J.J., et al., Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 2012. 141(2 Suppl): p. e531S-75S.
4. Skanes, A.C., et al., Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control. Canadian Journal of Cardiology, 2012. 28(2): p. 125-136.
5. Heidbuchel, H., et al., European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace, 2013. 15(5): p. 625-651.
6. Camm, A.J., et al., 2012 focused update of the ESC Guidelines for the management of atrial fibrillation An update of the 2010 ESC Guidelines for the management of atrial fibrillationDeveloped with the special contribution of the European Heart Rhythm Association. Europace, 2012. 14(10): p. 1385-1413.
7. January, C.T., et al., AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology, 2014.

Royal North Shore Hospital

CONSENT FORM--- PRESCRIBERS

Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)
(Anti-clotting Medication Use for Stroke Prevention)

5. I,..... agree to participate as a subject in the study described in the Participant Information Sheet **(attached to this form).**

6. I acknowledge that I have read the Participant Information Sheet, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.

13. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.

14. I understand that I can withdraw from the study at any time without prejudice to my relationship to the investigators or Royal North Shore Hospital or University of Technology Sydney.

15. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.

16. I understand that if I have any questions relating to my participation in this research, I may contact Yishen Wang on Yishen.Wang@student.uts.edu.au OR (02) 9514-9226. who will be happy to answer them.

17. I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet.

Complaints may be directed to the Research Office on Level 13, Kolling Building, Royal North Shore Hospital, St Leonards NSW 2065
Phone 02 9926 4590 | email NSLHD-research@health.nsw.gov.au

Signature of participant **Please PRINT name** **Date**

_____

Signature of witness **Please PRINT name** **Date**

_____

Signature of investigator **Please PRINT name** **Date**

_____

Royal North Shore Hospital

REVOCATION OF CONSENT

Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

(Anti-clotting Medication Use for Stroke Prevention)

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with Royal North Shore hospital or University of Technology Sydney.

Signature Date

Please PRINT Name

The section for Revocation of Consent should be forwarded to:

Name	Beata BAJOREK
Title	A/Prof.
Qualifications	PhD BPharm DipHospPharm GradCertEdStud(HigherEd)
Positions held: employed,	Associate Professor, University of Technology Sydney Academic Pharmacist, Department of Pharmacy, RNS Hospital (Northern LHD)
Full mailing address (including building number)	Graduate School of Health-Pharmacy, Building 7 level 4 University of Technology Sydney NSW 2007 Level 1 Pharmacy Department, RNS Hospital (Northern LHD) NSW 2065
Telephone	+61 2 9514 8301
Fax	61-2-9514-8300
E-mail	Beata.Bajorek@uts.edu.au.

X. Project Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

Flyers

PILOT OF A DECISION SUPPORT TOOL FOR STROKE PREVENTION IN ATRIAL FIBRILLATION (AF) (STUDY)

(Anti-clotting Medication Use for Stroke Prevention)

Research Project Taking Place in Ward

This pilot study is being conducted by Dr Yishen Wang (PhD student) from the Graduate School of Health – University of Technology (August until December 2015). It involves:

- **Visits to the ward (during working hours Monday to Friday)**
- **Collecting data from medical records/ patient notes**
- **Asking AF patients some simple questions regarding medication use**
- **Applying collected data to a decision support tool**
- **Conveying treatment recommendations to prescribers, and recording their opinion on this tool's treatment recommendation for antithrombotic therapy (i.e. agreement, disagreement, reasons for treatment preference)**

Please contact: [redacted] OR (02) 9514-9226, for further information.

This study has been approved by the NSLHD HREC, reference number HREC/15/HAWKE/103.

XI. Project Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

Ethics Approval

Research Office
Kolling Building, Level 13
Royal North Shore Hospital
St Leonards NSW 2065
Tel (02) 9926 4590 Fax (02) 9926 6179

Health
Northern Sydney
Local Health District

23 July 2015

A/Prof Beata Bajorek
Graduate School of Health – Pharmacy
University of Technology
Sydney NSW 200

Dear Beata

NSLHD reference: RESP/15/59
Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)
HREC reference: HREC/15/HAWKE/103

Thank you for your letter, dated **July 2015 (received 16 July 2015)**, responding to the Northern Sydney Local Health District HREC's request for additional information/modification for the above project, which was first considered by the HREC at its meeting held on **13 April 2015.** This HREC has been accredited by NSW Ministry of Health as a Lead HREC under the model for single ethical and scientific review and Certified by the NHMRC under the National model for Harmonisation of Multicentre Ethical Review (HoMER). This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. No HREC members with a conflict of interest were present for review of this project.

I am pleased to advise that the Committee at an Executive meeting on **22 July 2015** has granted ethical and scientific approval of the above **single centre** project.

You are reminded that this letter constitutes *ETHICAL* and *SCIENTIFIC* approval only. You must not commence this research project at a site until a completed Site Specific Assessment Form/Access Request and associated documentation have been submitted to the site Research Governance Officer and Authorised. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The project is approved to be conducted at:
- **Royal North Shore Hospital**

If a new site(s) is to be added please inform the HREC in writing and submit a Site Specific Assessment Form (SSA) to the Research Governance Officer at the new site.

The following documentation has been reviewed and approved by the HREC:

Document	Version	Date
Study Protocol	3	10 July 2015
Participant Information Sheet and Consent Form - Prescribers	3	10 July 2015
Participant Information Sheet and Consent Form – Patients	3	10 July 2015
Participant Information Sheet and Consent Form – Person Responsible	3	10 July 2015
Flyer	2	20 June 2015
Data collection sheet	2	20 June 2015

The National Ethics Application Form reviewed by the HREC was **NEAF AU/1/2FFD116**

Please note the following conditions of approval:

- HREC approval is valid for **5 years** from the date of approval and expires on **22 July 2020.** The Co-ordinating Investigator is required to notify the HREC 6 months prior to this date if the project is

expected to extend beyond the original approval date at which time the HREC will advise of the requirements for ongoing approval of the study.

- The Co-ordinating Investigator will provide an annual progress report beginning in **August 2015**, to the HREC as well as a final study report at the completion of the project in the specified format. An annual report is due **every year on 30 August**.
- The Co-ordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project and any complaints made by study participants regarding the conduct of the study.
- Proposed changes to the research protocol, conduct of the research, or length of HREC approval will be provided to the HREC for review, in the specified format.
- The HREC will be notified, giving reasons, if the project is discontinued before the expected date of completion.
- Investigators holding an academic appointment (including conjoint appointments) and students undertaking a project as part of a university course are advised to contact the relevant university HREC regarding any additional requirements for the project.

Please note it is the responsibility of the sponsor or the co-ordinating investigator of the project to register this study on a publicly available online registry (eg Australian Clinical Trial Registry www.actr.org.au) if applicable.

Should you have any queries about your project please contact the Research Office, Tel: 9926 4590, email: NSLHD-Research@health.nsw.gov.au.

Please quote **NSLHD reference RESP/15/59** in all correspondence.

The HREC wishes you every success in your research.

Yours sincerely

Ellie Pratt
Research Ethics Manager
NORTHERN SYDNEY LOCAL HEALTH DISTRICT

cc. Yishen Wang
RESP/15/4024

XII. Project Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)
Governance Authorization

Research Office
Kolling Building, Level 13
Royal North Shore Hospital
St Leonards NSW 2065
Tel (02) 9926 4990 Fax (02) 9926 6179

Health
Northern Sydney
Local Health District

29 July 2015

A/Prof Beata Bajorek
Graduate School of Health – Pharmacy
University of Technology
Sydney NSW 200

Dear Beata

NSLHD reference: RESP/15/59
Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)
HREC reference: HREC/15/HAWKE/10
SSA reference: SSA/15/HAWKE/228

Thank you for submitting an application for authorisation of this project. I am pleased to advise that the delegate of the Chief Executive for Northern Sydney Local Health District on **24 July 2015** has granted authorisation for the above project to commence at **Royal North Shore Hospital**.

The version of the SSA reviewed by NSLHD RGO was: **AU/2/FE2E117**.

Ethical approval for this study was granted by the **Northern Sydney Local Health District** HREC at a meeting of the Executive Committee **held** on **22 July 2015.**

The documents authorised for use at this site are:

Document	Version	Date
Study Protocol	3	10 July 2015
Participant Information Sheet and Consent Form – Prescribers	3	10 July 2015
Participant Information Sheet and Consent Form – Patients	3	10 July 2015
Participant Information Sheet and Consent Form – Person Responsible	3	10 July 2015
Flyer	2	20 June 2015
Data Collection Sheet	2	20 June 2015

Site authorisation will cease on the date of HREC expiry **22 July 2020**

You are reminded that, in order to comply with the Guidelines for Good Clinical Research Practice (GCRP) in Australia, and in accordance with additional requirements of NSLHD, the Chief Investigator is responsible for ensuring the following:

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.
3. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and are submitted to the lead HREC for review, are copied to the Research Governance Officer.
4. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted to the Research Governance Officer.
5. The annual report acknowledgment from the Lead HREC should be submitted to the Research Governance Officer.

Standard forms and additional guidance documents are available on the Research Office Website: http://www.nslhd.health.nsw.gov.au/Research/Pages/default.aspx

Yours sincerely

Kylie Becker
Research Governance Officer and Compliance Manager
Research Office
Northern Sydney Local Health District

cc.Yishen Wang
RESU/15/49/2

XIII. Project Title: Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)

UTS HREC Ethics Approval

Research.Ethics@uts.edu.au

Tue 4/08/2015 14:57

To: Yishen Wang < >; Beata.Bajorek@uts.edu.au <Beata.Bajorek@uts.edu.au>; Research.Ethics@uts.edu.au <Research.Ethics@uts.edu.au>;

Dear Applicant

[External Ratification: North Sydney Local Health District - HREC/15/HAWKE/103 - 22/07/15 to 22/07/20]

The UTS Human Research Ethics Expedited Review Committee reviewed your application titled, "A Pilot of a Decision Support Tool for Stroke Prevention in Atrial Fibrillation (AF)", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct In Human Research (2007). I am pleased to inform you that your external ethics approval has been ratified.

Your approval number is UTS HREC REF NO. 2015000518

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

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Safe use of antithrombotics for stroke prevention in atrial fibrillation: consideration of risk assessment tools to support decision-making

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Abstract: Clinical guidelines advocate stroke prevention therapy in atrial fibrillation (AF) patients, specifically anticoagulation. However, the decision to initiate treatment is based on the risk (bleeding) *versus* benefit (prevention of stroke) of therapy, which is often difficult to assess. This review identifies available risk assessment tools to facilitate the safe and optimal use of antithrombotic therapy for stroke prevention in AF. Using key databases and online clinical resources to search the literature (1992–2012), 19 tools have been identified and published to date: 11 addressing stroke risk, 7 addressing bleeding risk and 1 integrating both risk assessments. The stroke risk assessment tools (e.g. $CHADS_2$, CHA_2DS_2-VASc) share common risk factors: age, hypertension, previous cerebrovascular attack. The bleeding risk assessment tools (e.g. $HEMORR_2HAGES$, HAS-BLED) share common risk factors: age, previous bleeding, renal and liver impairment. In terms of their development, six of the stroke risk assessment tools have been derived from clinical studies, whilst five are based on refinement of existing tools or expert consensus. Many have been evaluated by prospective application to data from real patient cohorts. Bleeding risk assessment tools have been derived from trials, or generated from patient data and then validated via further studies. One identified tool (i.e. Computerised Antithrombotic Risk Assessment Tool [CARAT]) integrates both stroke and bleeding, and specifically considers other key factors in decision-making regarding antithrombotic therapy, particularly those increasing the risk of medication misadventure with treatment (e.g. function, drug interactions, medication adherence). This highlights that whilst separate tools are available to assess stroke and bleeding risk, they do not estimate the relative risk *versus* benefit of treatment in an individual patient nor consider key medication safety aspects. More effort is needed to synthesize these separate risk assessments and integrate key medication safety issues, particularly since the introduction of new anticoagulants into practice.

Keywords: atrial fibrillation, bleeding, decision making, risk assessment, risk versus benefit, stroke, stroke prevention

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Introduction

The increasing incidence of stroke is due to an increase in the prevalence of key risk factors such as advancing age and other underlying cardiovascular conditions, particularly atrial fibrillation (AF). In Europe, the prevalence of stroke is about 2% and increasing [Kirchhof *et al.* 2007]. In the US, the prevalence of stroke is approximately 3% of the adult population (approximately 7 million individuals), and it is estimated that by 2030, the prevalence of stroke will increase by 24.9% to 4.0%, affecting an additional 4 million people [Heidenreich *et al.* 2011; Roger *et al.* 2012]. In Australia, recent health reports (2009) have estimated that 375,800 Australians (205,800 men and 170,000 women) have suffered a stroke at some time in their lives, which makes it the third leading cause of death for men and the second

leading cause of death for women [Australian Institute of Health and Welfare, 2012].

Among persons with AF (nonvalvular form), the risk of stroke is approximately five times higher than that in persons without AF [Benjamin *et al.* 1994; Roger *et al.* 2012; Wolf *et al.* 1991]. The relationship between advancing age and AF and stroke is also important, as AF is the most common irregular heart rhythm encountered in clinical practice and is most prevalent in the elderly [Benjamin *et al.* 1994; Wolf *et al.* 1991]. Aging itself is a strong risk factor for stroke [Benjamin *et al.* 1994]; around half of all strokes occur in people over the age of 75 years. In the US, the incidence of stroke increases dramatically from around 30–120 per 100,000 persons per year in the age group 35–44 years old, rising to 670–970 per 100,000 persons per year for those aged 65–74 years [Roger *et al.* 2011]. It is estimated that the risk of hospitalization for stroke in people aged 75–84 years is more than 10 times the risk for those in the 55–64 year age group [Australian Institute of Health and Welfare]. As the population ages, the number of stroke incidents is expected to increase; for example, in Australia, there were approximately 60,000 new or recurrent strokes in the year 2010 [Boddice *et al.* 2010] compared with 50,000 in 2008 (AIHW 2008) [Australian Institute of Health and Welfare, 2008]. Overall, because the prevalence of AF rises with age, the risk of stroke due to AF is highest in the very elderly, such that the percentage of strokes attributable to AF increases dramatically from 1 in 67 persons in the 50–59 year age group to 1 in 4 for persons in the 80–89 year age group [Roger *et al.* 2012].

Clinical guidelines [Boddice *et al.* 2010; Camm *et al.* 2012; Skanes *et al.* 2012; Wann *et al.* 2011; You *et al.* 2012] advocate stroke prevention therapy in persons with AF, recommending the use of antithrombotic agents (e.g. warfarin, aspirin). Pooled analyses of many clinical trials have provided strong evidence that antithrombotics (anticlotting agents) can prevent stroke in patients with AF; warfarin (anticoagulant) reduces the risk of stroke by approximately 60%, while aspirin (antiplatelet) is less effective, reducing the risk by about one-fifth [Hart *et al.* 2007; van Walraven *et al.* 2002]. Prevention of stroke therefore currently relies on the use of antithrombotic therapy (anticoagulants as first line), although these agents inherently carry risks of adverse events (e.g. haemorrhage). For this reason, much attention has been focused on the research and development of alternative drugs (e.g. new antithrombotics such as dabigatran, rivaroxaban, apixaban). Unfortunately, none of these agents are devoid of significant risks to the patient. Therefore, the decision-making process regarding stroke prevention relies on a risk *versus* benefit assessment for each individual patient (i.e. an assessment of the potential risk of haemorrhage in the patient *versus* the benefit of the treatment in terms of reduction in the risk of stroke).

To this end, much emphasis has been placed on the development of tools to facilitate these risk assessments and support the decision-making process. In particular, there is a need to address a range of factors that contribute to medication safety in this clinical context, including patients' age, cognition, function, falls risk, and medication adherence [Bajorek *et al.* 2007; De Breucker *et al.* 2010; Tulner *et al.* 2010]. Therefore, the decision-making process should necessarily consider both the stroke risk and bleeding risk as well as other medication safety issues. This narrative review focuses on the contemporary issues surrounding decision-making for stroke prevention in AF, specifically identifying the available risk assessment tools that help facilitate the safe selection of therapy in at-risk elderly persons. This review describes the features of the various tools developed to date and their relevance and potential application to clinical practice.

Methods

A review of the literature was undertaken via key electronic databases (PUBMED, OVID, EMBASE) and other online resources (e.g. Google, Google Scholar) using the search terms 'atrial fibrillation', 'stroke risk factors', 'stroke risk assessment', 'stroke risk stratification', 'bleeding risk factors', 'bleeding risk assessment', and 'bleeding risk stratification'. The search was limited to peer-reviewed, English language publications (journal articles, reviews, consensus statements, published guidelines) within the 20-year period 1992 to 2012 (the period immediately following the publication of the pivotal clinical trials of stroke prevention in AF [Connolly *et al.* 1991; European Atrial Fibrillation Trial Study Group, 1993; Ezekowitz *et al.* 1992; Petersen *et al.* 1989; Poller *et al.* 1991; The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990]). With regard to guidelines and consensus statements, only the latest

(current) versions were included for review. Each publication was searched to identify risk assessment or risk stratification tools/schemes to support decision-making. Overall, 19 tools were identified: 11 addressing stroke risk, 7 addressing bleeding risk, and 1 tool addressing both stroke and bleeding risk.

Stroke risk assessment tools

A number of tools have been developed to assess stroke risk (Table 1) although few guidelines to date specifically include a stroke risk stratification scheme alongside recommendations for antithrombotic therapy (e.g. guidelines published by the American College of Cardiology Foundation/ American Heart Association/ European Society of Cardiology (ACC/AHA/ESC; updated 2011) [Fuster *et al.* 2011]. Overall, among the available stroke risk assessment tools, the $CHADS_2$ [Gage *et al.* 2001] and CHA_2DS_2-VASc [Lip *et al.* 2010b] have been the most frequently advocated tools, sharing the following common risk factors: age, hypertension, diabetes mellitus (DM), previous stroke/transient ischaemic attack (TIA). Stroke risk schemes all vary significantly in complexity with the number of variables included ranging from 4 to 7, with a median of 5 (Table 1). The most frequently mentioned inputs across all of the stroke risk tools are previous stroke/TIA (11 out of 11 tools), followed by age (10 out of 11), hypertension (HTN; 10 out of 11), and DM (9 out of 11). Heart failure (HF; 5 out of 11), left ventricular (LV) systolic dysfunction (4 out of 11), and female gender (4 out of 11) are also often considered. Other risk factors incorporated into some tools relate to cardiovascular diseases (e.g. coronary heart disease, myocardial infarction [MI], peripheral vascular disease, aortic plaque). Most of these schemes are based on scoring systems (e.g. $CHADS_2$, Framingham Heart Study (2003), Modified $CHADS_2$ score (2008) and CHA_2DS_2-VASc), where the included risk factors have been weighted (i.e. assigned different amounts of points) according to their relative contribution (i.e. relative risks) in causing stroke; the overall stroke risk is then estimated by summing the scores (Table 1). This means that these schemes are not mere checklists, but rather provide some indication of the level of predicted risk in an individual patient.

Age is an important risk factor for stroke, particularly in the context of AF management. These stroke risk schemes vary in how age is considered within the risk assessment, with different age categories used in various schemes. For example, the $CHADS_2$ uses age 75 years as a cut-off to denote risk associated with advancing age, while the Modified $CHADS_2$ score (2008) employs a range of age categories to better reflect increasing stroke risk over time, such that a score of 1 is assigned to persons aged 40–64 years and a score of 6 is assigned to those persons aged 85 years and older.

Tools from the 'Atrial fibrillation investigators'

Atrial Fibrillation Investigators (1994). The Atrial Fibrillation Investigators (AFI) (1994) [Laupacis *et al.* 1994] stroke assessment tool was derived from the pooled analysis of five clinical studies (AFASAK [Petersen *et al.* 1989], SPAF [Poller *et al.* 1991], BAATAF [The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990], CAFA [Connolly *et al.* 1991], and SPINAF [Ezekowitz *et al.* 1992]) of stroke prevention therapies in AF; CAFA, BAATAF, and SPINAF trialled warfarin *versus* placebo, whereas AFASAK and SPAF participants were treated with aspirin or warfarin *versus* placebo. Collectively, over 1800 patients received warfarin or placebo while over 1130 patients received aspirin or placebo; the mean age of patients was 69 years (range 38–91 years). BAATAF, AFASAK, and SPAF excluded patients with previous thromboembolism or cerebrovascular diseases. All studies, except CAFA, sought to identify stroke risk factors (such as history of stroke/TIA, age) according to their relative risks via univariate and multivariate analyses. These factors were then evaluated using the data from all of these studies (BAATAF, AFASAK, SPINAF, SPAF, and CAFA) to derive a risk assessment tool which categorizes patients into different levels of stroke risk (ranging from 1.0% relative risk in the low-risk group to 8.1% in the high-risk group; see Table 1).

Atrial Fibrillation Investigators (1998). Following from the development of the first tool (1994), this risk assessment tool was based on a further pooled analysis of three randomized trials [Atrial Fibrillation Investigators, 1998]: BAATAF [The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990], SPAF I [Poller *et al.* 1991], and SPINAF [Ezekowitz *et al.* 1992]. Here, data was analysed for the control group patients only; over 1060 patients (mean age 67 ± 10.4 years) were followed up for an average of 1.6 years. The patients' echocardiograms as well as

Table 1. Stroke risk schema.

Stroke Risk Schema Study (year)	Low risk	Intermediate risk	High risk	*C*-statistic
Atrial Fibrillation Investigators (1994) [Laupacis *et al.* 1994]	Age <65 years with no high-risk factors	Age 65–75 years with no high-risk factors	Any age with HTN, DM, previous stroke/TIA; age >75 years with or without risk factors	N/A
Stroke Prevention in Atrial Fibrillation Investigators [SPAF] (1995) [Stroke Prevention in Atrial Fibrillation Investigators, 1995]	No high- or moderate-risk features	HTN, no high-risk features	Previous thromboembolism, systolic BP >160 mmHg, LV dysfunction*, Women >75 years	N/A
European Atrial Fibrillation Trial Study Group [EAFT] (1995) [Van Latum *et al.* 1995]	No risk factors†	1–2 risk factors †	≥ 3 risk factors †	N/A
Atrial Fibrillation Investigators (1998) [Atrial Fibrillation Investigators, 1998]	Age <65 years, no clinical risk actors (including previous stroke/TIA, history of HTN, and DM), normal LV (normal or mild LV dysfunction)	Age 65–75 years, no clinical factors, normal LV	Age >75 years; age ≤75 with either clinical risk factors or abnormal LV; age ≤ 75 and ≥1 clinical risk factors with or without abnormal LV‡	N/A
Stroke Prevention in Atrial Fibrillation Investigators (1999) [Hart *et al.* 1999]	No high/moderate-risk features§	No high-risk features, either of HTN, DM	Women >75 years old, men >75 years old +HTN, systolic BP >160 mmHg	N/A
CHADS$_2$ 2001) [Gage *et al.* 2001]	Score 0‖	Score 1–2‖	Score 3–6‖	0.68 (ischaemic stroke)
Framingham Heart Study (2003) [Wang *et al.* 2003]	Score 0–7 ¶	Score 8–15 ¶	Score 16–31 ¶	0.66 (stroke excludes TIA)
Birmingham/ NICE (UK) (2006) [Lip *et al.* 2006]	Age <65 years with no moderate- or high-risk features	Age ≥65 years, no high risk features; age <75 years with DM, HTN, or vascular disease	Previous stroke, TIA or thromboembolism; age ≥75 years with DM, HTN or vascular disease; HF or abnormal LV function by echocardiography	0.64 (ischaemic stroke)

(Continued)

Table 1. (Continued)

Stroke Risk Schema Study (year)	Low risk	Intermediate risk	High risk	C-statistic
Modified CHADS2 score (2008) [Rietbrock *et al.* 2008]	Score 0**	Score 1–5**	Score >6**	0.72 (all kinds of stroke)
CHA_2DS_2-VASc (2010) [Lip *et al.* 2010b]	Score = 0 ††	Score = 1 ††	Score ≥2††	0.61 (ischaemic stroke, peripheral embolism or pulmonary embolism)
ACC/AHA/ESC Guidelines updated (2011) [Fuster *et al.* 2011]	No risk factors§§	One moderate-risk factor (age ≥75 years, HTN, HF, LV ejection fraction 35% or less, DM)	Any high-risk factor (previous stroke, TIA or embolism, mitral stenosis, prosthetic heart valve) or more than 1 moderate-risk factor	N/A

*Recent (3 months) clinical congestive heart failure or left ventricular fractional shortening 25% by M-mode echocardiography.
†Risk factors: Previous stroke/TIA, ischaemic heart disease, systolic BP >160 mmHg, duration of AF >1 year, ≥1 infarcts on brain CT, cardiothoracic ratio enlargement on chest roentgenogram.
‡Abnormal LV: moderate-to-severe systolic dysfunction by two-dimensional echocardiography.
§High-risk features: women >75 years old, men >75 years old + HTN, systolic BP >160 mmHg (any age). Moderate risk features: HTN (age ≤75), DM.
¶Risk factors: congestive heart failure, HTN, age ≥75 years, DM (1 point each; previous stroke/TIA (2 points).
‖Age (0–10 points; 55–59 years, 0 point; 60–62 years, 1 points; 63–66 years, 2 points; 67–71 years, 3 points; 72–74 years, 4 points; 75–77 years, 5 points; 78–81 years, 6 points; 82–85 years, 7 points; 86–90 years, 8 points, 91–93 years, 9 points; >93 years, 10 points), gender (6 points for women), systolic BP (<120 mmHg, 0 point; 120–139 mmHg, 1 point; 140–159 mmHg, 2 points; 160–179 mmHg, 3 points; >179 mmHg, 4 points), DM (5 points), previous stroke/TIA (6 points).
**Age 60–64 years, 1 point; 65–69 years, 2 points; 70–74 years, 3 points; 75–79 years, 4 points; 80–84 years, 5 points; 85–115 years, 6 points; female, 1 point; DM, 1 point; history of stroke/TIA, 6 points.
††Major risk factors are age ≥75 years and previous stroke/TIA/thromboembolism (2 points each); clinically relevant nonmajor risk factors are heart failure, hypertension, diabetes, age 65–74 years, female gender and vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), 1 point each.
§§Less well-validated risk factors are female sex, coronary artery disease and age 65–75 years. It is unclear whether patient with ≥1 of these should be categorized as moderate risk.
HTN, hypertension; DM, diabetes mellitus; LV, left ventricle; TIA, transient ischaemic attack; HF, heart failure; BP, blood pressure.

clinical parameters were reviewed and then analysed (using univariate and multivariate analyses) with regard to their impact on the relative risk of stroke. Age, previous stroke, and hypertension were identified as key predictors of stroke in AF (Table 1). The annual stroke rate ranged from 0.8% in those patients less than 65 years old with no additional risk factors and normal left ventricular function, up to 19.7% in those patients more than 75 years old with one or more additional risk factors and abnormal left ventricular function.

Birmingham/NICE (UK) (2006). In another analysis of the data from the AFI (1995) study, the Birmingham/NICE (UK) (2006) [Lip *et al.* 2006] assessment tool (Table 1) was based on the refinement of the AFI (1995) risk stratification tool and subsequently incorporated within the UK National Institute for Health and Clinical Excellence (NICE) guidelines for AF management. The tool itself was evaluated using data from over 990 patients from the SPAF III trial, who received treatment with either aspirin alone or aspirin combined with low-dose warfarin (target international normalized ratio [INR] 1.2–1.5), and followed up for a mean of 2 years (including blood sampling for von Willebrand factor [vWf]). The evaluation of this tool included a comparison with $CHADS_2$ (described later). Cox modelling and multivariate analyses were used to determine the association of vWf with ischaemic and vascular events. The annual stroke and vascular event rates ranged from 0.0% in the low-risk group up to 5.75% in the high-risk group. This Birmingham scheme was shown to have a similar predictive value to the $CHADS_2$ scheme for both ischaemic stroke and vascular events. Also, vWf was shown to be an independent risk factor for vascular events.

Tools from the 'Stroke prevention in atrial fibrillation investigators'

Stroke Prevention in Atrial Fibrillation Investigators (1995). Since aspirin was shown to be less effective than warfarin in the Atrial Fibrillation Investigators Study (1994), data from a large cohort of AF patients (Stroke Prevention in Atrial Fibrillation Investigators [SPAF] (1995) [Stroke Prevention in Atrial Fibrillation Investigators, 1995]) in SPAF I and II were analysed to identify patient characteristics related to arterial thromboembolism occurring during aspirin therapy. It was hypothesized that thromboembolism risk factors were different in AF patients receiving aspirin compared to those who were untreated. Over 850 patients receiving aspirin (mean age 69 ± 11 years) were followed for 1987 patient-years (range 4 days to 5.3 years) and risk factors (such as age, hypertension, impaired LV function) were identified according to their relative risks via multivariate analysis. The annual risk of stroke and systemic thromboembolism in patients ranged from 1.9% in the low-risk group to 5.9% in the high-risk group (Table 1).

SPAF I (1999). Following from the 1995 tool, over 2010 patients (69±10 years) from the series of Stroke Prevention in Atrial Fibrillation trials (trials I to III) who received either aspirin alone or low-dose warfarin were followed up for an average 2.0 years to explore potential stroke risk factors [Hart *et al.* 1999]. SPAF I and II trials excluded patients with previous stroke or TIA, whereas SPAF III included patients with previous stroke or TIA. Risk factors were explored using multivariate logistic regression analysis to determine their relative risks, from which a risk stratification scheme was then developed for patients without a previous stroke or TIA (Table 1). When applied to patient data, the scheme showed a statistically significant difference in stroke prevalence among low- (0.9%), moderate- (2.6%), and high-risk groups (7.1%).

The 'CHADS'-based tools

$CHADS_2$ (2001). The $CHADS_2$ (2001) [Gage *et al.* 2001] risk assessment tool is currently one of the most widely used, despite the development of others since it was first introduced into practice. Two previous stroke risk stratification schemes (from the AFI (1994) and SPAF (1995)) were combined to derive this new scheme. Independent risk factors identified in the two schemes (such as prior cerebral stroke, hypertension, DM, age) were selectively included. In the scoring process, one point was assigned to all risk factors except stroke/TIA history (assigned two points) (Table 1). To validate this new scheme, the tool was applied to data from the National Registry of AF (NRAF in the USA), which included over 1700 nonrheumatic AF Medicare beneficiaries (aged 65–95 years) not receiving warfarin at hospital discharge. The stroke risk ranged from 1.9 per 100 patient years (score of 0) to 18.2 per 100 patient years (score of 6). Overall $CHADS_2$ has shown high and better predictive value than either AFI or SPAF.

Modified $CHADS_2$ score (2008). A limitation of the original $CHADS_2$ tool is regarded to be its

inability to clearly distinguish patients with high stroke risk from those with a moderate risk [Baruch *et al.* 2007]. Thus, the modified $CHADS_2$ score (2008) [Rietbrock *et al.* 2008] (Table 1) was proposed and tested against the original $CHADS_2$ score by using data from over 51,800 chronic AF patients aged 40 years or older from the General Practice Research Database (GPRD; the computerized medical records of general practitioners in the UK). The investigators evaluated the inclusion of additional factors such as sex, extension of age categories, and also reweighting the previously included risk factors. Overall, the stroke risk was found to range from 0.72% for a risk score of 1 up to 15.64% for a risk score of 14. The revised $CHADS_2$ was shown to have better classification and predictive value than the original $CHADS_2$.

CHA_2DS_2-VASc (2010). The CHA_2DS_2-VASc (2010) [Lip *et al.* 2010b] tool is a further evolution of the modified-$CHADS_2$ tool and refinement of the Birmingham (2006) scheme, to include risk factors such as female gender and vascular disease (Table 1). It has been evaluated by application to a cohort of real AF patients from the Euro Heart Survey [Nieuwlaat *et al.* 2008], and compared against several other schemes such as the AFI (1994), SPAF (1999), $CHADS_2$, $CHADS_2$ modified, Framingham (2003), and Birmingham (2006) tools. In this tool, the hospital and death annual rate due to stroke and other thromboembolism ranges from 0.78% for a score of 0 up to 23.64% for a score of 9 [Olesen *et al.* 2011]. CHA_2DS_2-VASc (2010) has been shown to have a modest predictive value and to be better than either $CHADS_2$ or the modified $CHADS_2$ for predicting the risk of stroke and systemic thromboembolism.

Other tools

European Atrial Fibrillation Trial Study Group (1995). The European Atrial Fibrillation Trial (EAFT) (1995) [Van Latum *et al.* 1995] assessment tool was based on the analysis of data from over 370 patients (mean age 71 ± 8 years, with the majority over 60 years) enrolled in the EAFT. In EAFT, patients with one or more nondisabling episodes of cerebral ischaemia and concomitant nonrheumatic AF (NRAF) were randomized to receive anticoagulant therapy, aspirin or placebo, and followed up for an average 1.5 years [European Atrial Fibrillation Trial Study Group, 1993]. The data pertaining to those in the placebo-treated group was used to derive this risk tool; clinical predictors (including previous stroke/TIA, systolic blood pressure (BP) >160 mmHg) were selected according to their relative risks via multivariate analysis (Table 1). Unlike other tools, age was not included as an independent risk actor because of the relatively higher average age of this subgroup of placebo-treated patients, although age was identified as risk factor in the broader EAFT trial [Van Latum *et al.* 1995]. The annual event rate of stroke and other major vascular events ranged from 0.0% in those aged more than 75 years with no risk factors up to 37% in those more than 75 years old with 3 or more additional risk factors.

Framingham Heart Study (2003). The Framingham Heart Study (2003) [Wang *et al.* 2003] tool was based on observational data from the Framingham Heart Study, pertaining to a cohort of over 700 patients (aged from 55 to 94 years). The selected patients had a diagnosis of new on-onset AF, were not receiving warfarin, and were followed up for mean 4.0 years. A Cox model was used to identify risk factors and points were assigned to each to derive an overall risk score. A linear function was computed for each score to produce an estimation of 5 year stroke risk, ranging from 5% for a calculated score of 0–1 points, up to 75% for a score of 31 points. This risk assessment tool was shown to have modest predictive value for 5-year risk of a stroke event in individuals with AF (Table 1) as well as the 5-year risk of stroke or death.

ACC/AHA/ESC Guidelines updated (2011). The ACC/AHA/ESC Guidelines updated (2011) [Fuster *et al.* 2011] tool has been proposed by expert consensus, to not only stratify stroke risk in AF patients, but also recommend antithrombotic therapy for patients in each risk category (Table 1). It was derived by expert review of several risk stratification schemes such as the AFI (1994) (1998), SPAF (1995, 1999), Framingham Heart Study (2003), and $CHADS_2$ tools, but has not yet been evaluated via application to data from patient cohorts or clinical databases.

Summary of features of stroke risk assessment tools

Overall, a history of stroke or TIA is the most frequently included risk factor in these stroke risk assessment tools followed by age, hypertension, and DM. Many of the stroke risk assessment tools have been generated by review of previous risk factors but have not specifically sought to investigate or identify any new risk factors. Six of the

stroke risk assessment tools [Atrial Fibrillation Investigators, 1998; Hart *et al.* 1999; Laupacis *et al.* 1994; Stroke Prevention in Atrial Fibrillation Investigators, 1995; Van Latum *et al.* 1995; Wang *et al.* 2003] have been derived from clinical or epidemiological studies of AF patients, while five are largely based on expert consensus. Furthermore, several tools have been based on selected patient cohorts or databases (where verification of data was not possible), and are potentially not representative of the broader target population (selection bias). Since each trial has defined risk factors differently, and risk factors were only assessed at the time of randomization, the true magnitude of impact of each factor (according to their relative risk) may be underestimated. Overall, CHA_2DS_2-VASc has been reported to have a better predictor than the AFI (1994, 1998), SPAF (1995), $CHADS_2$ modified, $CHADS_2$, Framingham (2003), and NICE (2006) tools in AF patients [Lip *et al.* 2010a; Van Staa *et al.* 2011].

Bleeding risk assessment tools

Altogether, seven bleeding risk tools have been developed and employed in evaluating bleeding risk among AF patients (Table 2), although not all have been specifically developed for patients with AF. All of these bleeding risk tools stratify patients into low, intermediate, or high bleeding risk categories. Among them, $HEMORR_2HAGES$ [Gage *et al.* 2006] and HAS-BLED [Pisters *et al.* 2010] have been the most commonly advocated, both sharing common risk factors such as age, previous bleeding, renal, and liver impairment. Although each scheme uses different age cut-offs, 'increased age' *per se* is the only risk parameter common to all seven risk tools. The other most frequently mentioned inputs in these tools are age history of bleeding/prior bleeding (six out of seven tools), followed by anaemia/thrombocytopenia (five out of seven tools), renal dysfunction (five out of seven tools), previous stroke (three out of seven tools), hypertension (three out of seven tools), alcohol (three out of seven tools), DM (two out of seven tools), prior MI or ischaemic heart disease (two out of seven tools), liver dysfunction (two out of seven tools), malignancy (three out of seven tools), and female gender (two out of seven tools). Antiplatelet drug use, genetic factors, and excessive falls risk, are also considered in certain tools. To account for the different levels of risk attributed to various factor, different points have been assigned to each to derive an overall summative score (Table 2).

OBRI

The OBRI [Beyth *et al.* 1998] bleeding risk tool (Table 2) was refined from the bleeding index developed by Landefeld and Goldman in 1989 [Landefeld and Goldman, 1989], and designed for application to all types of patients at risk of haemorrhage, not specifically for AF patients. Development of the tool was based on the records of over 560 patients aged 18–92 years (mean age 61 ± 14) who were discharged from hospital on long-term warfarin therapy for indications such as AF, stroke, and other thromboembolism. Four risk factors (age ≥65 years, history of gastrointestinal bleeding, history of stroke, and severe comorbid conditions such as recent MI, renal insufficiency, severe anaemia) were identified by their relative risks as calculated in univariate and multivariate analyses. This OBRI scheme was then further tested on 264 outpatients who were commenced on warfarin after hospital discharge, and who were followed for a period of up to 7 years. The major bleeding incidence reportedly ranged from 3% in the low-risk group to 53% in the high-risk group, yielding modest predictive value for the tool.

Kuijer and colleagues (1999)

A literature review (comprising 15 papers) was conducted to identify risk factors for bleeding in a range of patients using anticoagulant therapy [Kuijer *et al.* 1999]. The risk stratification scheme (Table 2) was constructed according to the odd ratios of the various risk factors, and then initially evaluated in a subset of over 240 patients, followed by more extensive testing in an independent cohort of 780 patients (all from the database of the Columbus Investigators Study [The Columbus Investigators, 1997]); in the Columbus Investigators study over 1020 patients with venous thromboembolism (VTE) were allocated to receive heparin-based therapy plus an oral anticoagulant (OAC). In the initial subgroup of 240 patients, this tool was shown to have modest predictive value for all bleeding complications and major bleeding complications. Then, in the subsequent patient cohort, the tool was able to categorise one-fifth of the patients as high risk, where the absolute risk of bleeding was found to be significantly higher than the low-risk group (10% *versus* 1%).

$HEMORR_2HAGES$ (2006)

The $HEMORR_2HAGES$ (2006) [Gage *et al.* 2006] tool was derived from three previous risk schemes (the OBRI (1998) [Beyth *et al.* 1998],

Table 2. Bleeding risk schema.

Bleeding Risk Schema (year)	Risk factors recruited in score calculation	Low risk	Intermediate risk	High risk	C-statistic*
OBRI [Beyth *et al.* 1998] modification of bleeding index developed by Landefeld and Goldman [Landefeld and Goldman, 1989)]	Age ≥65 years, GI bleeding in last 2 weeks, previous stroke, comorbidities (≥1 of the following: recent MI, hematocrit <30%, diabetes mellitus or creatinine >1.5 mg/dl), 1 point for each above risk factor	0	1–2	3–4	0.78
Kuijer and colleagues (1999) [Kuijer *et al.* 1999]	Age≥60 years old (1.6 point), female sex (1.3 point), malignancy (2.2 point)	0	>0 and <3	≥ 3	0.72
HEMORR$_2$HAGES (2006) [Gage *et al.* 2006]	Hepatic and/or renal disease, ethanol abuse, malignancy, older (age >75 years), low platelet count or function, rebleeding risk, uncontrolled hypertension, anaemia, genetic factor(s) (e.g., CYP2C9 single-nucleotide polymorphisms), excessive fall risk and stroke (1 point for each risk factor, 2 points for previous bleeding)	0–1	2–3	≥ 4	0.67
Shiremand and colleagues (2006) [Shireman *et al.* 2006]	Risk score = [0.49 × aged (>70 years)] + [0.32 × female] + [0.58 × remote bleed] + [0.62 × recent bleed] + [0.71 × alcohol/drug abuse] + [0.27 × diabetes] + [0.86 × anaemia] + [0.32 × antiplatelet drug use], 1 point for each existing condition, 0 if absent	≤ 1.07	> 1.07 and < 2.19	≥ 2.19	0.63
RIETE risk scheme [Ruiz-Giménez *et al.* 2008]	Recent major bleeding (<15 days prior to thrombotic event) (2 points), creatinine > 1.2 mg/dL (1.5 points), anaemia (1.5 points), malignancy (1 point), clinically overt pulmonary embolism (1 point), age > 75 years (1 point)	0	1–4	> 4	N/A
HAS-BLED (2010) [Risters *et al.* 2010]	Hypertension (systolic blood pressure > 160 mmHg), abnormal renal (presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/l), abnormal liver function (chronic hepatic disease (cirrhosis) or bilirubin >2× upper limit of normal, AST/ALT/ALP >3× upper limit of normal), stroke, previous bleeding history or bleeding diathesis or anaemia, labile INRs (high INRs and poor time in therapeutic range), elderly (e.g., age >65 years), drugs (concomitant use of antiplatelet agents or NSAID), alcohol, 1 point each risk factor	0	1–2	≥3	0.72
ATRIA (2011) [Fang *et al.* 2011]	Anaemia (3 points), severe renal disease (e.g., glomerular filtration rate < 30 ml/min or dialysis dependent, 3 points), age ≥ 75 years (2 points), prior bleeding (1 point), and hypertension (1 point)	0–3	4	5–10	0.74

ALP, alkaline phosphatase; ALT, alkaline aminotransferase; AST, aspartate aminotransferase; CYP, cytochrome P; GI, gastrointestinal; INR, international normalized ratio; M.I.: Myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; OBRI, Outpatient Bleeding Risk Index.
*C-statistic: major bleeding (slightly different definition in each scheme, refer to each scheme for exact definition) in validation or testing groups.

the scheme of Kuijer and colleagues [Kuijer *et al.* 1999], and the scheme of Kearon and coworkers [Kearon *et al.* 2003]), a systematic review [Beyth *et al.* 2002], and results from a literature (i.e. Pubmed) search. Overall, 11 risk factors (Table 2) were selected, with prior bleeding assigned 2 points (a higher weighting) and all other risk factors assigned 1 point, according to expert consensus. The scheme was then tested and compared with the other 3 schemes using data from over 3790 Medicare beneficiaries (mean age 80.2 years) listed in the NRAF database (the same database used for validation of the $CHADS_2$). The bleeding risk ranged from 1.9 for a score of 0 up to 12.3 per 100 patient-years for a score over 4. Among patients prescribed warfarin, $HEMORR_2HAGES$ was shown to predict major bleeding better than the schemes by Kearon and colleagues (2003), Kuijer and coworkers (1999), or OBRI (1998).

Shireman and colleagues (2006)

The tool from Shireman and colleagues (2006) [Shireman *et al.* 2006] was developed and validated via a retrospective analysis of data from a cohort of over 26,300 AF patients who were aged over 65 years (identified in a national registry), and followed up for 90 days (NB/ the same database that was used for validation of $CHADS_2$). A total of 18 variables (such as age, gender, and stroke) (Table 2) were initially explored in multivariate modelling, and 8 were finally selected into the risk scheme. The major bleeding rate ranged from 0.9% in the low-risk group up to 5.4% in the high-risk group. Overall, this tool was shown to have better predictive value than the OBRI and Kuijer and colleagues (1999) schemes.

RIETE risk scheme (2008)

The RIETE risk scheme (2008) [Ruíz-Giménez *et al.* 2008] tool was based on the RIETE Registry of patients (mean age 66 ± 17 years) with acute VTE, who were receiving anticoagulant therapy and followed up for 3 months. Over 13,000 patients were used as the derivation sample and over 6500 patients were used as the validation sample. Risk factors such as recent major bleeding, anaemia, malignancy, clinically overt pulmonary embolism, and age were identified based on their odds ratio in multivariate analysis (Table 2). During validation, the scheme was able to identify significant differences in the risk of major bleeding, ranging from 0.1% in low-risk patients to 6.2% in high-risk patients. Since this tool was developed using data from patients with VTE, its application to patients with AF or at risk of stroke is uncertain.

HAS-BLED (2010) [Pisters et al. 2010]

The HAS-BLED (2010) [Pisters *et al.* 2010] scheme was developed by using data from a real-world cohort of 3450 AF patients (mean age 66.8 ± 12.8 years) receiving antithrombotic therapy: OAC, antiplatelet only, OAC plus antiplatelet combined, or no therapy at all. The patient data came from the prospective Euro Heart Survey [Nieuwlaat *et al.* 2008] on AF, where patients were followed up for up to 1 year. The risk factors (such as age, female, hypertension, renal failure, prior major bleeding episode; see Table 2) were identified from univariate and multivariate analysis, with the resultant tool shown to have better predictive value than $HEMORR_2HAGES$. The yearly major bleeding rate varied from 1.13% for a score of 0 up to 12.5% for a score of 5.

ATRIA (2011) [Fang et al. 2011]

ATRIA (2011) [Fang *et al.* 2011] was developed by obtaining the clinical data from over 13,559 nonvalvular AF patients taking warfarin therapy (mean age 71 years), and enrolled and followed up for up to 3.5 years in the ATRIA study [Go *et al.* 1999, 2003]. This cohort was separated into 'derivation' and 'validation' groups. Risk factors were initially selected from six previous published risk stratification schemes [Beyth *et al.* 1998; Gage *et al.* 2006; Kearon *et al.* 2003; Kuijer *et al.* 1999; Ruíz-Giménez *et al.* 2008; Shireman *et al.* 2006], evaluated by univariate and multivariate analyses of data from the derivation group of patients. Five risk factors (Table 2) were finally selected and assigned scores based on their regression coefficients. The scheme was then tested in the validation group of patients from the ATRIA study and compared with other risk stratification schemes. The risk of major bleeding ranged from 0.4% (0 points) to 17.3% (10 points). The predictive value for major bleeding of this tool was shown to be higher than OBRI, Kuijer and colleagues (1999), Kearon and colleagues (2003), $HEMORR_2HAGES$ (2006), Shireman and colleagues (2006), and RIETE risk schemes (2008).

Summary of features of bleeding risk assessment tools

In reviewing these tools, it is important to note their origins and therefore their relevance in the context of AF management. Three of these bleeding risk assessment tools were derived via refinement of previous risk assessment schemes [Beyth

et al. 1998; Gage *et al.* 2006] or literature review [Kuijer *et al.* 1999]. One was derived from retrospective data extraction from clinical databases [Shireman *et al.* 2006]. Only HAS-BLED, the RIETE risk scheme, and ATRIA were derived from prospective studies of selected patient cohorts and all of them excluded patients who were not able to be followed up (selection bias). Although most of the data from which the tools were derived included a follow-up period of approximately 1 year, the schemes by Shireman and colleagues (2006) and RIETE (2008) had relatively minimal follow up (only 90 days) and did not include review of the INR during follow up. Furthermore, among these tools, only HAS-BLED, ATRIA, and Shireman and colleagues (2006) were specifically derived from AF patients, whilst HAS-BLED, ATRIA, $HEMORR_2HAGES$, and Shireman and colleagues have all been validated in AF patients. The schemes by Kuijer and colleagues (1999) and RIETE (2008) are limited in their application by the fact that they were based on VTE patients, whilst ORBI was based on a broad range of patients discharged from hospital using antithrombotics. Indeed, these non-AF specific tools have been shown to be inferior in their application to the target patient population compared to those tools which were validated in AF patients [Fang *et al.* 2011; Gage *et al.* 2006]. In some recent reports, HAS-BLED has been shown to perform better in predicting bleeding risk than the ATRIA, $HEMORR_2HAGES$, Shireman and colleagues (2006), Kuijer and colleagues (1999), and OBRI tools in AF patients [Apostolakis *et al.* 2012, 2013; Lip *et al.* 2012; Roldan *et al.* 2013].

Overall, in considering the inputs in these tools, advancing age has been the most frequently cited risk factor for bleeding, followed by a history of bleeding/prior bleeding, anaemia/thrombocytopenia, and renal dysfunction. The impact of age in the risk assessment process is highlighted again, and highlights the need to carefully assess the medication safety aspects of the decision-making process.

Assessment of medication safety in elderly patients

When exploring the utilization of anticoagulant therapy for stroke prevention in AF, issues impacting on medication safety must necessarily be explored. Age *per se* has often been cited as a key consideration in decision-making and a major barrier to the use of warfarin, reflecting the challenges of using high-risk anticoagulant therapies in the at-risk elderly population. However, a patient's age *per se* is not a contraindication to therapy, but rather it represents an over-arching marker of other age-related factors that impact on their ability to manage complex regimens or which may increase their risk of adverse clinical outcomes. These factors include: impaired cognitive function (e.g. dementia), frailty (e.g. falls risk), comorbidities, decreased renal function, polypharmacy, and poor medication adherence [Alberts *et al.* 2013; Bajorek, 2011; Bajorek *et al.* 2007; Bereznicki *et al.* 2006; De Breucker *et al.* 2010; Hylek, 2008; Tulner *et al.* 2010]. Therefore, it is important to consider medication safety assessments alongside stroke and bleeding risk.

In reviewing the spectrum of risk assessment tools developed to date, only one has been identified that purposefully considers medication safety. The CARAT (Computerised Antithrombotic Risk Assessment Tool) is a web-based tool, which comprises both stroke and bleeding risk assessments (the $CHADS_2$ and $HEMMORR_2HAGES$ schemes, respectively) alongside medication safety issues. The tool evolved from an earlier risk assessment process that was paper-based [Bajorek *et al.* 2012], and which had been shown to be effective, as part of a collaborative and multidisciplinary review process, in optimizing the use of antithrombotic therapy in older persons with AF [Bajorek *et al.* 2005, 2012]. The utility of the tool lies in integrating the risk: benefit assessment and systematically reviewing key medication safety issues such as the individual's function, cognition, drug interactions, medication adherence, medication management capabilities, and relevant social factors. In applying this tool, the clinician can calculate the estimated risk of stroke, risk of bleeding, and identifies any key contraindications to the use of treatment options, before providing a treatment recommendation for an individual patient [Bajorek *et al.* 2005, 2012].

Whereas previous risk assessment tools for stroke and bleeding have been principally evaluated for their ability to predict risk, the evaluation of the CARAT has focused on canvassing clinicians' application of this tool in the decision-making process. In an initial scenario-based survey, four cases (patient profiles describing different levels of risk) were used to test the agreement between clinicians' independent treatment recommendations and those generated by CARAT. The

majority of clinicians (71%, $n = 77$) 'agreed' with CARAT's treatment recommendations (four questions; $n = 108$ responses), and importantly 'agreed' with its estimation of bleeding risk (three questions on bleeding risk; $n = 81$ responses). Regarding the overall usefulness and applicability of CARAT to clinical practice, out of 189 responses, 51% were agree or somewhat agree and 25% were neutral or undecided with CARAT. In their feedback, clinicians provided commentary on the CARAT to identify its potential role in the decision-making process:

> *'Rapid calculation of risks is very useful' (Cardiologist)*
> *'Bleeding risk assessment section is very useful' (Cardiologist)*
> *'Warfarin is not a lifelong decision; people can fail a trial of anticoagulation but embolic stroke is irreversible [this tool helps re-focus away from bleeding risk, highlighting stroke risk]' (Neurologist)*
> *'This tool should ideally be applied in ED and result should go to Local Medical officer' (Cardiologist)*

Discussion

What this review highlights is that there are indeed a number of tools to assess either stroke risk or bleeding risk in patients with AF. However, the tools are not uniform and their differences (including their limitations) need to be considered prior to application in decision-making. It is important to consider the development of these tools, and how their inputs were derived, acknowledging that not all risk factors can be treated equally since they present different relative risks. Indeed, each of the tools presented in this review does weight their input factors differently, and this is particularly reflective in the evolution of the $CHADS_2$ to the CHA_2DS_2-VASc, where different age groups are assigned different points (i.e. the older age group is assigned more points).

In relation to the inclusion of 'age' as an important risk factor in both stroke and bleeding risk assessment needs examination. The age 'cut-off' to define an 'older' person differs across tools, ranging from 60 years up to 75 years, often below the average age (approximately 75 years old) of most AF patients. Whilst a few tools use cohort data to derive the age groupings in tools, some have been determined by expert consensus only. The inclusion of 'age' as a risk factor is not unexpected, given what is known about the increasing prevalence of AF and risk of stroke with advancing age. However, care must be taken about selecting arbitrary age 'cut-offs', noting that age *per se* is often an over-arching marker of other risk factors such as key comorbidities that are more prevalent with age (e.g. cardiovascular disease, diabetes, hypertension) and/or measures of frailty (e.g. falls risk), medication management ability (e.g. adherence), as well as cognition and function (e.g. dementia), although being elderly does not necessarily imply that these risks are present.

Overall, this review shows that most effort to date has focused on the development of tools to predict the risk of stroke, and less so on predicting the risk of bleeding. For stroke risk assessment, current guidelines recommend either that CHA_2DS_2-VASc be used for stroke risk assessment (e.g. European Society of Cardiology (ESC) [Camm *et al.* 2012]), or $CHADS_2$ (e.g. American College of Chest Physicians (ACCP) [You *et al.* 2012], Canadian Cardiovascular Society (CCS) [Skanes *et al.* 2012]). The use of CHA_2DS_2-VASc may increase over time, since it is reported to better predict stroke risk than AFI (1994, 1998), SPAF (1995), $CHADS_2$ modified, $CHADS_2$, Framingham (2003), and NICE (2006) tools in AF patients [Lip *et al.* 2010a; Van Staa *et al.* 2011].

The availability of bleeding risk tools has certainly assisted clinicians in decision-making, enabling a balanced risk *versus* benefit assessment. Tools such as the HAS-BLED have now been incorporated in some guidelines (e.g., ESC guideline), where a score of 3 or more is considered to be an indicator of a high bleeding risk. However, it is important to note that the use of these bleeding risk tools is not to identify patients in whom treatment should be excluded; rather, these tools should be used to identify the potential for bleeding in an individual and identify appropriate risk reduction measures, i.e. treating modifiable risk factors (e.g. anaemia, drug use, alcohol use, uncontrolled hypertension, labile INRs, reduced platelet count), and providing support services to ensure close monitoring and regular review. In other words, a high bleeding risk score indicates the need to correct reversible risk factors and provide additional follow-up services, rather than providing a reason to prescribe anticoagulants [Alberts *et al.* 2013; Camm *et al.* 2012].

In reviewing the available risk tools collectively, it can been seen that there is a certain level of overlap between bleeding risk factors and stroke risk factors, specifically age, hypertension, previous

Table 3. Contraindications of antithrombotic therapy (adapted from Bajorek and colleagues [Bajorek et al. 2005b].

	Absolute contraindications	Relative contraindications
Medical	• Bleeding disorder • Complicated liver disease • Active gastrointestinal ulceration or bleeding in past 3 months • Previous intracranial haemorrhage/surgery • Previous intracerebral aneurysm/tumour • Ophthalmic surgery in past 3 months • Diabetic proliferative retinopathy	• Uncomplicated liver disease • Previous gastrointestinal bleeding or ulceration
Functional	• Fall in past 6 months associated with major bleeding	• High risk of falls • No medication supervision and either visual or colour blindness, deaf, or language barrier
Cognitive	• Uncontrolled psychosis; dementia	• No medication supervision and mild cognitive impairment (Mini Mental State Examination score 15–24/30)
Social	• Current alcoholism (male > 60 g alcohol / day, female >40 g alcohol / day)	• Nursing home resident, socially isolated
Iatrogenic	• No medication supervision and poor • compliance likely • Unable to self-medicate • High-risk drug interactions • Previous adverse drug reaction to warfarin	• Frequent use of nonsteroidal anti-inflammatory drugs

stroke, and diabetes. Indeed, some studies using the $CHADS_2$ and CHA_2DS_2-VASc tools have reported that patients with high bleeding risk have also been shown to have high stroke risk. Over 90% and over 99% of patients with high bleeding risk (HAS-BLED 3 or more) were categorized as high stroke risk by $CHADS_2$ and CHA_2DS_2-VASc, respectively [Lip *et al.* 2011, 2012]. Whether it is sufficient to use tools such as $CHADS_2$ and CHA_2DS_2-VASc to predict both stroke risk and bleeding risk needs further exploration, but would certainly help to simplify the risk assessment.

Integrating bleeding and stroke risks

The simplification of decision-making through the use of such tools is an important goal in this context, recognizing that for the initiation of antithrombotic therapy is always complex for clinicians, since it involves weighing the risk (e.g. bleeding) *versus* benefit (prevention of stroke) of therapy, as well as other clinical characteristics of the patients, and these may vary widely among patients [Bajorek, 2011; Bajorek *et al.* 2007]. This review highlights that a number of tools are available to assess stroke risk or bleeding risk separately, and thus provide some information for antithrombotic therapy decision-making. In this regard, they are all helpful in identifying reversible risk factors (e.g. anaemia, uncontrolled hypertension) that can be modified through targeted intervention. However, the two assessments need to be brought together to complete the decision-making process for the selection of appropriate treatment, and ideally should estimate the relative risk *versus* benefit of available treatment options in an individual AF patient. Furthermore, the decision-making in AF is not solely based on stroke risk *versus* bleeding risk. Previous studies have highlighted that key barriers to the use of anticoagulants often relate to other patient factors that potentially increase the risk of medication misadventure [Bajorek *et al.* 2007, 2009]. Assuring medication safety is especially important for anticoagulants (e.g. warfarin) because they maintain a higher potential for adverse events due to their inherent risk of haemorrhage and/or complex pharmacology. Few of the available tools have provided this functionality (except CARAT), yet it is important to the whole process (Table 3) [Bajorek *et al.* 2005].

Integration of risk schemes and consideration of additional factors does provide a more comprehensive assessment of an individual's suitability for specific antithrombotic therapies. However, this potentially increases the complexity of the risk assessment process; in considering the

usability of any of these tools, the critical issue relates to simplicity and practicality, so that it can be readily applied in everyday clinical practice. Compounding this is the need for regular review of risk, as these can change over time (e.g. increasing age). Although electronic and digital resources are increasingly available (including smart phones, portable computers, iPads) in the health setting, the ability to calculate a score easily and simply in the midst of a busy practice is paramount. The need for a meaningful, individualized risk assessment must be balanced against the need for usability by clinicians. This aspect has been specifically explored for one of the tools described in this review, where clinicians' opinions have been gauged regarding the overall usefulness and applicability of the CARAT to clinical practice. Whilst the CARAT is web-based, it integrates a number of separate assessments (i.e. stroke risk, bleeding risk, medication safety considerations), and therefore requires more input from the clinicians at the time of decision-making. This may potentially affect its usability in some settings, and for this reason such tools might be best incorporated into clinical services that specifically review a person's pharmacotherapy (e.g. accredited Medication Review services, pharmacy-based medicines checks, such as the MedsCheck program in Australia). There is a need to explore the role of support services provided by suitably trained and accredited health professionals (e.g. nurse practitioners, practice nurses, accredited pharmacists, consultant pharmacists) in using these tools within dedicated services, to help support clinicians in decision-making.

Therefore, more effort is needed to synthesize these separate risk assessments and integrate key medication safety issues, particularly in view of the introduction of new anticoagulants into practice. The introduction of these new drugs (e.g. rivaroxaban, dabigatran, apixaban) has been based on data from clinical trials which have included limited numbers of patients and which have applied strict exclusion criteria (e.g. a severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, creatinine clearance of less than 30 ml/min, active liver disease) [Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011]. To date, there are no assessment tools available to predict and/or stratify the risk of bleeding in regard to new anticoagulants. Although there is a perception that these new drugs are significantly safer than traditional antithrombotic options, they are not without risk, and risk *versus* benefit assessments remains critically important.

Summary

Although, separate tools are available to assess stroke risk and bleeding risk independently, they do not estimate the relative risk *versus* benefit of available treatment options in an individual patient, and seldom consider key medication safety aspects of prescribing treatment. More effort is needed to synthesize these separate risk assessments, integrate key medication safety issues, and incorporate them into daily clinical practice, particularly in view of the introduction of new anticoagulants into practice. Among the many factors contributing to risk, age is an important risk factor, but its definition and categorisation need further clarification and validation.

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Original Research

Old age, high risk medication, polypharmacy: a 'trilogy' of risks in older patients with atrial fibrillation

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ABSTRACT*

Background: The safety of pharmacotherapy in atrial fibrillation (AF) is compounded by a trilogy of risks old age, high-risk medications (e.g., antithrombotics, antiarrhythmics), polypharmacy due to multiple patient comorbidities. However, to date, scarce study has investigated the use of polypharmacy (including potentially inappropriate medication (PIM)) in AF patients, and how this may contribute to their overall risk of medication misadventure.

Objectives: To review the extent of polypharmacy and PIM use in older patients (65 years or older) with AF.

Methods: Information was extracted from a database characterising a cohort of older AF patients treated in general practice in New South Wales, Australia. Patient characteristics, number and types of drugs, the degree of PIM use were recorded. The predictors for the use of polypharmacy in older AF patients were identified.

Results: Overall, 367 patients (mean age 77.8 years) were reviewed, among which 94.8% used 5 medications or more and over half used 10 medications or more. Cardiovascular agents were most commonly used (98.9%), followed by antithrombotics (90.7%). Among agents deemed PIMs, digoxin (30.2%) was the most frequently used, followed by benzodiazepines (19.6%), and sotalol (9.8%). AF patients using polypharmacy were more likely to have low bleeding risk (OR=10.97), representing those patients in whom high-risk antithrombotics are mostly indicated. Patients with major-polypharmacy (5-9 medications) are more likely to have obstructive pulmonary diseases (OR=2.32), upper gastrointestinal diseases (OR=2.02) and poor physical function (OR=1.04), but less likely to have cognitive impairment (OR=0.27).

Conclusion: Polypharmacy affects oldest AF patients, comprising medications that are indicated for AF, yet regarded as PIMs. Patients with lower risk of bleeding, obstructive pulmonary diseases, upper gastrointestinal diseases and poor physical function are also at higher risk of using higher number of medications. This may lead to an increased risk for medication misadventure due to the concomitant use of polypharmacy and medications for AF.

Keywords: Polypharmacy; Atrial Fibrillation; Drug-Related Side Effects and Adverse Reactions; Aged; Inappropriate Prescribing; Australia

INTRODUCTION

Atrial fibrillation (AF) is a leading cause of morbidity and mortality. It is associated with a significantly increased risk of stroke, heart failure and dementia.[1] In regard to its management, the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend the use of both antiarrhythmics and antithrombotics.[1,2] Similar recommendations are presented within Australian guidelines.[3] However, despite guidelines, patients with AF present a quandary for health care professionals. First, their age (i.e., being older persons) presents specific challenges in the selection of medicines and associated management, due to age-related physiological changes as well as functional and cognitive impairments.[4] Second, the need to use high-risk medications (e.g., antithrombotics and antiarrhythmics), as indicated by clinical guidelines, increases their risk for medication misadventure (e.g., bleeding, bradyarrhythmias).[1]

However, the risks do not stop here. In fact, patients with AF are exposed to a trilogy of risks, inherent to their overall disease presentation and management. Aside from their advancing age and the use of high-risk medicines, there is an additional risk factor: polypharmacy. A multitude of agents may be prescribed to AF patients for stroke prevention, management of the arrhythmia, treatment of accompanying cardiovascular and stroke risk factors, as well as therapies for other comorbidities. Collectively, these complicate medication management and increase the risk of medication misadventure, manifesting as non-adherence, adverse drug reactions (ADRs), and drug interactions, all of which can lead to poor clinical outcomes.[5] In turn, this complicates health professionals' decision-making, particularly in relation to prescribing anticoagulation for stroke prevention.[6]

International studies have shown that polypharmacy is common in patients with AF[7,8] and in patients using anticoagulants.[3] However, in Australia, little attention has been paid to the degree of polypharmacy in elderly AF patients and how this may contribute to their overall risk of medication misadventure. Therefore, the aim of this study was to characterise AF patients in the Australian primary care setting in terms of this 'trilogy' of risks, and to specifically: 1) describe the extent of use of polypharmacy in older AF patients; 2) determine the degree to which these medications may be potentially inappropriate; 3) identify factors

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associated with the use of polypharmacy; and 4) identify factors associated with major polypharmacy versus minor polypharmacy in older AF patients.

METHODS

Ethical approval

Ethics approval was obtained from the participating institutions.[9] Patient data were coded and de-identified prior to analysis.

Design

In this cross-sectional study, information was extracted from a database pertaining to a cohort of AF patients (65 years or older) recruited for a previous study conducted in general practices within metropolitan and regional areas of New South Wales, Australia (detailed description of the study recruitment/data collection methods is reported elsewhere).[9] Patients with a confirmed diagnosis of AF were recruited by their general practitioners (GPs) during routine care.

Data Collection

Purpose-designed data collection instruments were used to extract and record data from medical notes, patient interviews, and a brief patient survey (e.g., medical history, medication use). All collected data were verified by the patients' GPs.

Definitions and Measures

Polypharmacy is most commonly defined as the use of five or more regular medications.[10] For the purposes of this study, polypharmacy was categorised as follows[11]:

- Non-Polypharmacy: four or less medications
- Minor-Polypharmacy: use of five to nine medications
- Major-Polypharmacy: concomitant use of ten or more medications

Diagnoses were coded using the World Health Organization (WHO) International Statistical Classification of Diseases, 10th Revision (ICD-10).[12] CHADS2[13] and CHA2DS2VASc[14] scores 0, 1, 2 or over were classified as low, intermediate and high stroke risk, respectively. HAS-BLED[15] scores 0, 1-2, 3 or over were classified as low, intermediate and high bleeding risk, respectively. HEMORR2HAGES[16] scores 0-1, 2-3, 4 or over were classified as low, intermediate and high bleeding risk, respectively. In this study, CHA2DS2VASc and HAS-BLED were used as they are commonly recommended by international guidelines.[14,15] Although CHA2DS2VASc and HAS-BLED are advocated in more recent European Society of Cardiology guidelines, CHADS2 was additionally used in this study because it is included in Australian local guidelines (e.g., National Prescribing Service guideline (2013)[17], Therapeutic Guidelines (2012)[18]), while HEMORR2HAGES was used because it is recommended by National Clinical Guideline Centre (UK) and American College of Cardiology/American Heart Association guidelines.[16,19] Moreover, since these scoring tools have different sensitivities and specificities, the use of four scores assisted in reducing any false positives and false negatives in the risk assessment. SF-36, a survey, which provides psychometrically-based physical and mental health summary measures and a preference-based health utility index, was also used.[20]

Recorded medications included both over-the-counter and prescription medicines used by patients (as documented in their medication histories), regardless of short-term or long-term use. All medications were classified according to Anatomical Therapeutic Chemical (ATC) classification system.[21] The medications used by patients were then assessed to whether they were 'potentially inappropriate medicines' (PIMs) for older patients, according to two explicit criteria, i.e. Beers criteria 2012[22] and PRISCUS criteria.[23] Both Beers criteria and PRISCUS criteria were selected because of slight variations in defining certain medications as potentially inappropriate based on the dosage (e.g., digoxin).

Statistical Analysis

Computerised data analysis employed SPSS (Statistical Package for the Social Sciences Version.[19] To explore relationships involving continuous variables, ANOVA (parametric distribution) and Kruskal-Wallis (non-parametric distribution) were used. The Chi-square test examined differences in independent proportions. Multivariate logistic regression (Forward Wald) analysis was used to assess the influence of the predictors on polypharmacy. $p<0.1$ was used in multivariate logistic regression. $p<0.05$ was considered statistically significant for all other analysis.

RESULTS

Patient characteristics

The mean age of patients (N=367) was 77.8 years; two-thirds were less than 75 years old. The age categories were based on those used by clinical guidelines for anticoagulant treatment, as well as the apparent distribution of polypharmacy by age in the cohort (Table 1). In terms of their AF history, most (87.5%) patients had AF for at least 1 year, with over half (57.5%) diagnosed as having persistent AF. Most patients were categorised as being at least at intermediate risk of stroke (92.1% by CHADS2 and 100% by CHA2DS2VASc). Over half of the patients (53.4%) were identified to have 'intermediate' or 'high' bleeding risk as per HEMORR2HAGS and 93.9% patients were identified to have 'intermediate' or 'high' as per HAS-BLED scores.

Extent of polypharmacy

Overall, 348 (94.9%) patients were using some degree of polypharmacy, whilst just over half (55.9%; n=205) of the patients were using major-polypharmacy (Table 1). Compared to patients in the non-polypharmacy group (5.1% of patients), those with minor-polypharmacy and major-polypharmacy had more comorbidities ($p<0.01$)

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Table 1. Patient characteristics

Characteristics N (%) of patients 367 (100)	Non-polypharmacy (0-4 drugs) (% of total) 19 (5.2)	Minor-polypharmacy (5-9 drugs) (% of total) 143 (39.0)	Major-polypharmacy (≥10 drugs) (% of total) 205 (55.9)	p-value*
Gender				0.07
male	13 (3.5)	87 (23.7)	103 (28.1)	
female	6 (1.6)	56 (15.3)	102 (27.8)	
Age μ (SD)	75.5 (6.8)	77.5 (6.9)	78.2 (7.1)	0.17
Age group				0.38
≥75 years	9 (2.4)	91 (24.8)	129 (24.6)	
<75 years	10 (2.7)	52 (14.2)	76 (20.7)	
Type of AF				0.56†
Paroxysmal	5 (1.4)	49 (13.3)	73 (19.9)	
Persistent	12 (3.3)	86 (23.4)	113 (30.8)	
New Onset	1 (0.3)	6 (1.6)	14 (3.8)	
Unknown	1 (0.3)	2 (0.6)	5 (1.4)	
History of AF				0.78
<1 year	3 (0.8)	16 (4.4)	27 (7.4)	
≥ 1 year	16 (4.4)	127 (34.6)	178 (48.5)	
Current Cardiac Rhythm				0.22‡
Normal Sinus Rhythm	2 (0.8)	11 (3.0)	26 (7.6)	
Controlled AF	17 (4.6)	131 (8.4)	177 (48.2)	
Uncontrolled AF	0 (0.0)	1 (0.3)	0 (0.0)	
$CHADS_2$ score§				0.004
Low	4 (1.2)	11 (3.0)	14 (3.8)	
Intermediate	7 (1.9)	53 (14.4)	48 (13.1)	
High	8 (2.4)	77 (20.9)	143 (38.9)	
CHA_2DS_2-VASc score§				0.24
Intermediate	2 (0.6)	6 (1.6)	6 (1.6)	
High	17 (4.6)	137 (37.3)	199 (54.2)	
$HEMORR_2HAGS$ score¶				0.04
Low	14 (3.8)	75 (20.4)	81 (22.1)	
Intermediate	3 (0.8)	65 (17.7)	116 (31.6)	
High	2 (0.6)	3 (0.8)	8 (2.4)	
HAS-BLED score#				0.51
Low	1 (0.3)	2 (0.6)	2 (0.6)	
Intermediate	15 (4.1)	124 (33.8)	177 (48.2)	
High	3 (0.8)	17 (4.6)	26 (7.1)	

* Difference among non-polypharmacy, minor-polypharmacy and major-polypharmacy
† P value: persistent compared with all other
‡ P value: sinus rhythm compared with all other
§ $CHADS_2$ (13) and CHA_2DS_2VASc (14) scores of 0, 1, ≥ 2 were classified as low, intermediate and high stroke risk, respectively.
¶ $HEMORR_2HAGES$ (16) scores of 0-1, 2-3, ≥ 4 were classified as low, intermediate and high bleeding risk, respectively.
# HAS-BLED (15) scores of 0, 1-2, ≥ 3 were classified as low, intermediate and high bleeding risk, respectively.

(Table 2). In terms of major diseases (excluding AF), patients in the major-polypharmacy group had a higher incidence of diabetes (p<0.01), upper gastrointestinal (GI) discomfort (p<0.01), and asthma or chronic obstructive pulmonary disease (p<0.01). Patients in the major-polypharmacy group had a significantly lower SF-36 physical score than those with minor-polypharmacy or non-polypharmacy (p=0.01).

Polypharmacy in AF patients according to 'risk category'

When comparing the use of polypharmacy by stroke risk (per CHADS2), a higher proportion of patients used polypharmacy among those at high risk of stroke, compared to those at low risk of stroke (98.4% vs. 84.6%, p=0.002). When compared by bleeding risk (per HEMORR2HAGS), a higher proportion of patients used polypharmacy among those at intermediate risk of bleeding, compared to those at high risk of bleeding (96.5% vs. 86.2%, p=0.013) (Table 1). When comparing the use of polypharmacy across various risk categories per CHA2DS2VASc and HAS-BLED scores, no significant difference was found.

A number of patients were identified as having specific medication safety issues that might affect a patient's medication management ability and/or put them at a risk of medication misadventure. Among those patients with documented cognitive impairment (n=18), 83.3% had major-polypharmacy and the remainder had minor-polypharmacy. Among all of the patients who reportedly needed assistance with medication management, 46.3% had major-polypharmacy and the remainder had minor-polypharmacy. All patients with poor medication adherence (self-reported) had some degree of polypharmacy; almost three quarters (72.7%) of these patients had major-polypharmacy (Table 2).

Number and types of drugs

Patients with major-polypharmacy used almost two and half times the mean number of medications (mean=2.5, SD=1.0) per diagnosed disease, compared to non-polypharmacy patients (mean=1.1, SD=0.5, P<0.01). Unsurprisingly, drugs

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Table 2. Medication safety considerations

Characteristics N (%) of patients 367 (100)	Non-polypharmacy (0-4 drugs) (% of total) 19 (5.2)	Minor-polypharmacy (5-9 drugs) (% of total) 143 (39.0)	Major-polypharmacy (≥10 drugs) (% of total) 205 (55.9)	p-value*
Comorbidities, μ (SD)	4.7 (3.3)	5.0 (2.4)	6.3 (2.4)	<0.01
Number of drugs (both prescription and non-prescription), μ (SD)	3.9 (0.6)	7.4 (1.4)	13.9 (3.4)	<0.01
Prescription drugs, μ (SD)	3.47 (0.6)	6.3 (1.5)	12.0 (3.3)	<0.01
Non-prescription drugs (e.g., OTC, supplements), μ (SD)	0.21 (0.4)	1.08 (1.0)	1.9 (1.4)	<0.01
Cognitive impairment	0 (0.0)	3 (0.8)	15 (4.1)	0.07
Visual impairment	0 (0.0)	8 (2.2)	14 (3.8)	0.70
Hearing impairment	2 (0.6)	9 (7.9)	20 (6.2)	0.48
Language barrier	0 (0.0)	1 (0.3)	3 (0.8)	0.71
Mobility impairment	1 (0.3)	4 (1.1)	12 (3.3)	0.34
Residential care facility	0 (0.0)	1 (0.3)	3 (0.8)	0.71
Difficulty access medical care	0 (0.0)	2 (0.6)	1 (0.3)	0.63
Need assistance with medication	4 (1.1)	51 (13.9)	95 (25.9)	0.03
Poor adherence (self-reported)	0 (0.0)	6 (1.6)	16 (4.4)	0.27
Other major diseases				
Chronic heart failure	3 (0.8)	38 (10.3)	51 (13.9)	0.65
Hypertension	12 (3.7)	97 (26.4)	140 (38.1)	0.88
Diabetes	1 (0.3)	37 (10.1)	35 (9.5)	0.03
Prior stroke or TIA	5 (7.5)	27 (7.3)	35 (9.5)	0.52
Coronary heart disease	3 (0.8)	43 (11.7)	64 (16.9)	0.40
Asthma or COPD	4 (1.1)	12 (3.7)	43 (11.7)	<0.01
Arthritis (OA, RA, Psoriasis Arthritis)	3 (0.8)	32 (8.7)	62 (16.9)	0.16
Upper GI discomfort †	3 (0.8)	33 (8.9)	88 (24.0)	<0.01
Renal disease	0 (0.0)	7 (1.9)	9 (2.3)	0.92
Previous fall	0 (0.0)	4 (1.2)	7 (1.2)	1.00
Self-reported Health SF-36‡				
Physical, μ (SD)	46.5 (5.9)	45.1 (8.2)	42.4 (7.4)	<0.01
Mental, μ (SD)	58.2 (3.8)	55.4 (7.1)	54.8 (7.4)	0.10

TIA –transient ischaemic attack, COPD –chronic obstructive pulmonary disease, OA –osteoarthritis, RA– rheumatoid arthritis, GI– gastrointestinal, SF-36 –The Short Form (36) Health Survey is a patient-reported survey of patient health.

* Difference between non-polypharmacy, minor-polypharmacy and major-polypharmacy

† Upper GI diseases include gastric ulcer, gastritis, esophagitis/ulcer, duodenal ulcer or gastroesophageal reflux disease

‡ SF-36, a survey, which provides psychometrically-based physical and mental health summary measures and a preference-based health utility index (54). A high score of SF-36 means better health. Physical includes: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning. Mental includes: Role-Emotional, Mental Health

acting on the cardiovascular system, as well as blood and blood forming agents, were the most commonly used medications (Table 3 and 4). Since all patients had at least an intermediate stroke risk (as per CHA2DS2VASc), most were taking warfarin±aspirin (79.8%) and around one in ten were on dabigatran (11.7%). Around one in twenty patients were using aspirin or clopidogrel (6.8%) (Table 5). Among all patients, nearly two-thirds were using beta blockers (59.4%), while around one in ten patients were using sotalol (9.8%) or nondihydropyridine calcium channel blockers (10.3%). Surprisingly, 30.2% patients were using digitalis glycosides (digoxin), despite it not being indicated as a first-line therapy by clinical guidelines (24) and noting that it is identified as a PIM. Among "non-cardiovascular" medications, analgesics (N02) and drugs for acid-related disorders were most commonly used (taken by over half of the patients). Among these, 55.3% of patients were using analgesics in combination with antithrombotics, comprising 137 (37.3%) patients using warfarin concurrently with paracetamol, 32 (8.7%) patients using warfarin concurrently with opioids, and 9 (2.5%) patients using warfarin concurrently with nonsteroidal anti-inflammatory drugs (NSAIDs).

Factors associated with polypharmacy versus non-polypharmacy

Univariate analysis was used to identify the factors associated with polypharmacy (5 medications or more) versus non-polypharmacy. Univariate analysis identified that patients using polypharmacy were more likely to have a higher stroke risk, per CHADS2 (OR=4.40, 95%CI 1.23-15.66, p=0.03 compared with low stroke risk) and a lower bleeding risk, per HEMORR2HAGS (OR=10.97, 95%CI 1.66-72.60, p=0.01 compared with high bleeding risk). In multivariate analysis, only a lower bleeding risk (HEMORR2HAGS) remained a significant predictor of polypharmacy (OR=10.97, 95%CI 1.66-72.60, p=0.01) (Model: Cox&Snell R^2=0.03, Nagelkerke R^2=0.09, 94.8% correctly predicted). CHA2DS2VASc and HAS-BLED were not found to be significantly associated with polypharmacy.

Univariate analysis was used to identify the factors associated with major-polypharmacy versus minor-polypharmacy. Univariate analysis identified that patients using major-polypharmacy were more likely to have higher number of comorbidities (OR=1.28, 95%CI 1.15-1.42, p<0.001), upper gastrointestinal disease (includes gastric ulcer, gastritis, oesophagitis/ulcer, duodenal ulcer or

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Table 3. Pharmacotherapy use and potentially inappropriate medicines (PIM): Cardiovascular agents.

Main therapeutic classes and most common subclasses† N (%) of patients 367 (100)	Overall (% of total) N (%) 367 (100)	Non-polypharmacy (0-4 drugs) (% of total) N (%) 19 (5.2)	Minor-polypharmacy (5-9 drugs) (% of total) 143 (39.0)	Major-polypharmacy (≥10 drugs) (% of total) 205 (55.9)	p-value*
Blood and blood forming agents (B)	361 (98.4)	19 (5.2)	140 (38.1)	202 (55.0)	<0.01
Antithrombotic agents (B01)	361 (98.4)	19 (5.24)	140 (38.1)	202 (55.0)	<0.01
Vitamin K antagonists (B01AA)	293 (79.8)	14 (3.8)	122 (33.3)	157 (42.8)	<0.01
Direct thrombin inhibitors (dabigatran) (B01AE)	43 (11.7)	3 (0.8)	12 (3.3)	28 (7.6)	<0.01
Platelet aggregation inhibitors (B01AC)	38 (10.4)	2 (0.6)	7 (1.7)	29 (7.9)	<0.01
Cardiovascular system (C)	363 (98.9)	17 (4.6)	142 (38.7)	204 (55.6)	0.01
Lipid modifying agents (C10)	228 (62.1)	10 (2.7)	85 (23.2)	133 (36.2)	0.42
HMG CoA reductase inhibitors (C10AA)	220 (59.9)	9 (2.5)	84 (22.9)	127 (34.1)	0.42
Antihypertensive agents (C02)					
Prazosin‡ (C02CA01)	19 (5.2)	1 (0.3)	9 (2.5)	9 (2.5)	0.73
Methyldopa ‡ (C02AB)	6 (1.6)	0 (0.0)	1 (0.3)	5 (1.4)	0.31
Agents acting on the renin-angiotensin system (C09)	241 (65.7)	10 (2.7)	92 (25.1)	139 (37.9)	0.36
ACE inhibitors, plain (C09AA)	144 (39.2)	1 (0.3)	53 (14.4)	90 (24.5)	<0.01
Angiotensin II antagonists (C09CA)	119 (32.4)	4 (1.1)	47 (12.8)	68 (18.5)	0.56
Calcium channel blockers (C08)	95 (25.9)	5 (1.4)	30 (8.2)	60 (16.3)	0.03
Dihydropyridine derivatives (C08CA)	67 (18.3)	2 (0.6)	17 (4.6)	48 (13.1)	0.02
Benzothiazepine derivatives (diltiazem) (C08DB)	17 (4.6)	0 (0.0)	7 (1.9)	10 (2.7)	1.00
Phenylalkylamine derivatives (verapamil) (C08DA)	21 (5.7)	3 (0.8)	6 (1.6)	12 (3.7)	0.12
Diuretics (C03)	162 (44.1)	3 (0.8)	53 (14.4)	106 (28.8)	<0.01
Sulfonamides (C03CA)	140 (38.1)	3 (0.8)	43 (11.7)	94 (25.6)	<0.01
Aldosterone antagonists (spironolactone) (C03DA)	34 (9.3)	0 (0.0)	11 (3.0)	23 (33.5)	0.22
Beta Blocker agents (C07)	218 (59.4)	8 (2.2)	87 (23.7)	123 (3.5)	0.28
Beta blocking agents, non-selective (C07AA)	55 (14.9)	2 (0.6)	26 (7.1)	27 (7.3)	0.40
Sotalol (C07AA07)	30 (9.8)	1 (0.3)	19 (5.2)	16 (4.4)	0.18
Beta blocking agents, selective (C07AB)	154 (41.9)	10 (2.7)	51 (13.9)	93 (25.4)	0.12
Cardiac therapy (C01)	175 (47.7)	10 (2.7)	71 (19.3)	94 (25.6)	0.74
Antiarrhythmics, class III (C01BD) (amiodarone)¶	29 (7.1)	1 (0.3)	11 (3.0)	17 (4.6)	0.90
Digitalis glycosides (digoxin) § (C01AA)	111 (30.2)	8 (2.2)	30 (8.2)	73 (19.9)	<.0.01
Flecainide ‡ (C01BC04)	8 (2.2)	1 (0.3)	3 (0.8)	4 (1.1)	0.67
Organic nitrates (C01DA)	71 (19.3)	1 (0.3)	17 (4.6)	53 (14.4)	<0.01

NSAID: nonsteroidal anti-inflammatory drugs; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors
* Difference between non-polypharmacy, minor-polypharmacy and major-polypharmacy.
†All medications were classified according to Anatomical Therapeutic Chemical (ATC) classification system.
‡ Potentially inappropriate medicines (PIMs) according to both Beers criteria and PRISCUS criteria
§ Within these 111 patients, 22 patients met Beers criteria for potentially inappropriate use of digoxin (i.e. digoxin >0.125mg/d).
¶ Only included in Beers criteria.

gastroesophageal reflux disease, OR=2.51, 95%CI 1.56-4.04, p<0.001), obstructive pulmonary disease (asthma or chronic obstructive pulmonary disease (COPD), OR=2.89, 95%CI 1.47-5.72, p=0.002), and poor physical function (as measured by SF-36 physical score, OR=1.05, 95%CI 1.02-1.08, p=0.003), but less likely to have cognitive impairment (OR=0.27, 95%CI 0.07-0.96, p=0.04). In multivariate analysis, obstructive pulmonary disease (adjusted OR=2.32, 95%CI 1.14-4.71, p=0.02), upper gastrointestinal disease (adjusted OR=2.02, 95%CI 1.23-3.34, p=0.006), cognitive impairment (adjusted OR=0.27, 95%CI 0.07-0.97, p=0.04), and poor physical function (as measured by SF-36 physical score, adjusted OR=1.04, 95%CI 1.00-1.07, p=0.01) remained significant predictors of major-polypharmacy (Model: Cox&Snell R^2=0.10, Nagelkerke R^2=0.13, 63.5% correctly predicted).

Inappropriate use of medications

Overall, 250 (68%) patients (mean age 77.9 years) were using at least 1 PIM (Table 3 and 4). Among the most frequently identified PIMs (Table 4), four agents were for rhythm and/or rate control: digoxin (30.2%), sotalol (9.8%), amiodarone (7.9%), and flecainide (2.2%). Among those on digoxin, only 24 (21.6%) patients had a documented diagnosis of chronic heart failure, as required by guidelines (24).

The most commonly used "non-AF" PIMs were benzodiazepines (long, short and intermediate acting) (19.1%), followed by spironolactone (9.3%) and tricyclic antidepressants (TCA) (amitriptyline, imipramine) (7.6%).

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Table 4. Pharmacotherapy use and potentially inappropriate medicines (PIM): Non-cardiovascular agents & overall use.

Main therapeutic classes and most common subclasses† N (%) of patients 367 (100)	Overall (% of total) N (%) 367 (100)	Non-polypharmacy (0-4 drugs) (% of total) N (%) 19 (5.2)	Minor-polypharmacy (5-9 drugs) (% of total) 143 (39.0)	Major-polypharmacy (≥10 drugs) (% of total) 205 (55.9)	p-value*
Drugs for acid related disorders (A02)	198 (53.9)	6 (1.6)	55 (14.9)	137 (37.3)	<0.01
Proton pump inhibitor (A02BC)	156 (42.5)	6 (1.6)	43 (11.7)	107 (29.2)	<0.01
Drugs for functional gastrointestinal disorders (A03)					
Metoclopramide¶ (A03FA01)	8 (2.2)	0 (0.0)	2 (0.6)	6 (1.6)	<0.01
Psycholeptics (N05)	73 (19.9)	1 (0.3)	17 (4.6)	55 (14.9)	0.01
Benzodiazepine derivatives (N05CD)	70 (19.1)	1 (0.3)	17 (4.6)	52 (14.2)	0.002
Short and intermediate acting ‡	54 (14.7)	1 (0.3)	14 (3.8)	39 (10.6)	0.02
Long acting ‡	18 (4.9)	0 (0.0)	3 (0.8)	15 (4.1)	0.27
Psychoanaleptics (N06)	70 (19.1)	1 (0.3)	13 (3.5)	56 (15.2)	<0.01
Antidepressant (N06A)	68 (18.5)	1 (0.3)	12 (3.3)	55 (14.9)	<0.01
TCA (N06AA) (amitriptyline, imipramine)	28 (7.6)	1 (0.3)	4 (1.1)	23 (6.2)	<0.01
SSRI (N06AB) (fluoxetine) ‡	24 (6.5)	0 (0.0)	5 (1.6)	19 (5.2)	0.03
Analgesics(N02)	207 (56.4)	5 (1.4)	59 (16.2)	143 (39.0)	<0.01
Anilides (paracetamol) (N02BE)	196 (53.4)	5 (1.4)	56 (16.1)	135 (36.8)	<0.01
Opioids (N02A)	42 (11.4)	0 (0.0)	5 (1.4)	37 (10.1)	<0.01
Corticosteroids, dermatological preparations (D07)	93 (25.3)	5 (1.4)	26 (28.0)	62 (16.9)	0.04
Corticosteroid for systemic use (H02)	27 (7.4)	0 (0.0)	5 (1.4)	22 (6.0)	0.02
Drugs for obstructive airway diseases (R03)	89 (24.3)	5 (1.4)	20 (5.4)	64 (17.4)	<0.01
Selective beta-2-adrenoreceptor agonists (R03AC)	51 (13.9)	4 (1.1)	8 (2.2)	39 (10.6)	<0.01
Corticosteroids inhaler (R03BA)	61 (16.6)	4 (1.1)	14 (3.8)	43 (11.8)	0.02
Drugs used in Diabetes (A10)	62 (16.9)	4 (1.1)	14 (3.8)	44 (12.0)	0.02
Insulin and analogues (A10A)	14 (3.8)	0 (0.0)	3 (0.8)	11 (3.0)	0.19
Blood glucose lowering drugs excl. insulin (A10B)	56 (15.3)	4 (1.1)	13 (3.5)	39 (10.6)	0.03
Anti-inflammatory and anti-rheumatic products (M01)					
Non-selective NSAID (M01AB) (diclofenac¶, ibuprofen¶, naproxen¶, indomethacin‡, piroxicam‡)	16 (4.3)	0 (0.0)	5 (1.4)	11 (3.0)	0.29
Sex hormones and modulators of the genital system (G03)					
Estrogen with or without progestin¶ (G03CA)	23 (6.3)	1 (0.3)	4 (1.1)	18 (4.9)	0.59
Urologicals (G04)					
Urological spasmolytic agents (G04BD) (oxybutynine, tolterodine, solifenacin) ‡	9 (2.5)	1 (0.3)	1 (0.3)	7 (1.9)	0.16
Use of potentially inappropriate medications (PIMs)					
Overall use of PIMs	250 (68.2)	12 (3.3)	79 (21.5)	159 (43.3)	<0.001
One PIM (mean age =77.9 years)	144 (40.3)	9 (2.5)	56 (15.3)	84 (22.9)	-
Two PIMs(mean age =76.4 years)	68 (18.5)	2 (0.5)	15 (4.1)	51 (13.9)	-
Three PIMs (mean age =77.0 years)	38 (7.6)	1 (0.3)	7 (1.9)	20 (5.4)	-
Four PIMs (mean age =75.8 years).	5 (1.4)	0 (0.0)	1 (0.3)	4 (1.1)	-

NSAID: nonsteroidal anti-inflammatory drugs; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors
* Difference between non-polypharmacy, minor-polypharmacy and major-polypharmacy.
†All medications were classified according to Anatomical Therapeutic Chemical (ATC) classification system.
‡ Potentially inappropriate medicines (PIMs) according to both Beers criteria and PRISCUS criteria
§ Within these 111 patients, 22 patients met Beers criteria for potentially inappropriate use of digoxin (i.e. digoxin >0.125mg/d).
¶ Only included in Beers criteria.

DISCUSSION

Our study presents some initial findings on the use of high-risk medications and polypharmacy, including PIMs, among older AF patients in a primary care setting. The study has identified a high prevalence of polypharmacy in older patients with AF (94.8%). This rate of polypharmacy is higher than reported in a study of older patients (aged 70 or older years, including AF and non-AF patients), treated in the general practice setting in Germany[25] and higher than in an Australian study of older patients (aged 70 years or older) admitted to general medical units in acute care hospitals.[10] Not unexpectedly, the most frequently prescribed medications included cardiovascular agents, consistent with other studies[26], followed by antithrombotics. The significance of this is that these commonly used medications not only contribute to the burden of polypharmacy in AF patients, but they are also regarded to be high risk medicines and, in some cases, PIMs. Since these are guideline-indicated therapies for AF patients[1], this polypharmacy comprising PIMs creates a particularly high-risk situation for patients, further increasing the likelihood of adverse drug reactions and medication misadventure.[27] Regarding the use of aspirin as a monotherapy, evidence-based clinical practice guidelines suggest that aspirin

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Table 5. Antithrombotic therapy use stratified according to stroke risk

Stroke risk N (% of total)	Warfarin 279 (76.0)	Warfarin+aspirin 14 (3.8)	Dabigatran 43 (11.7)	Clopidogrel 3 (0.8)	Aspirin 22 (6.0)	Nil therapy 6 (1.6)
$CHADS_2$ score§						
Low	25 (6.8)	1 (0.3)	2 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Intermediate	87 (23.7)	1 (0.3)	14 (3.8)	0 (0.0)	7 (1.9)	1 (0.3)
High	167 (45.5)	12 (3.3)	27 (7.4)	3 (0.8)	14 (3.8)	5 (1.4)
CHA_2DS_2-VASc score§						
Intermediate	11 (3.0)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.00
High	268 (73.0)	21 (5.7)	42 (11.4)	3 (0.8)	21 (5.7)	6 (1.6)

§ CHADS2[13] and CHA2DS2VASc[14] scores of 0, 1, 2 or more were classified as low, intermediate and high stroke risk, respectively.

alone is insufficient to reduce stroke risk. In our study, since the stroke risk in this patient sample was at least intermediate (as per CHA2DS2VASc), the observed use of aspirin monotherapy was potentially not aligned with evidence-based guidelines.[14]

It is important to note that among the most commonly used AF therapies in this study, several (i.e., antiarrhythmics) were identified as PIMs according to Beers criteria or the PRISCUS list. In particular, the use of digoxin was surprisingly high in this study population and consistent with other studies.[28,29] Given that digoxin is no longer recommended as a mainstay therapy, being reserved for those AF patients who have congestive heart failure unresponsive to first-line therapies, this possible overuse in patients with AF raises concerns about the safety and necessity of its use.[28]

Medication safety in AF patients is further compounded when patients require pharmacotherapy for other non-AF conditions. As also reported in earlier studies, a surprisingly high number of patients used analgesics, suggesting that in older patients with AF there is a high prevalence of pain conditions (e.g., arthritis).[30] The concurrent use of analgesics with AF pharmacotherapy may lead to drug interactions and/or GI (gastrointestinal) adverse drug reactions which may increase the risk of bleeding, especially GI bleeding. Noting that the prevalence of NSAIDs use in our study was only 4.3%, much lower than other studies of AF patients[33] and the use of NSAIDs in combination with warfarin only 2.5%, the rate of such interactions might be relatively low. Nevertheless, the episodic nature of pain can complicate AF management, because pain is symptomatic and therefore patients may prioritise analgesic use over AF therapy.[34] However, this study found that the use of paracetamol in combination with warfarin is relatively common. As reported by other studies, the interaction between warfarin and paracetamol is often underestimated, but is important because it can potentiate the anticoagulant effect of warfarin and increase the rate of fatal bleeding 2.7 times (compared to warfarin use alone).[19,20] The mechanism of this interaction is not fully understood but some studies support the hypothesis that paracetamol (or its metabolites) interact with certain enzymes responsible for the synthesis of vitamin K dependent coagulation factors (vitamin K-dependent γ-carboxylase and vitamin K epoxide reductase).[19]

Although proton pump inhibitors (PPIs) are commonly used medications, this study shows that the use of PPIs is higher than that in other studies of general older patients in nursing homes[35] and those admitted to hospitals.[36] The frequent use of PPIs for GI conditions in our study raises concerns that many AF patients may potentially suffer from drug-induced GI adverse drug reactions, since a number of AF pharmacotherapies (e.g., antiarrhythmics, antithrombotics) are reported to cause GI symptoms, including upper GI bleeding. Separate to GI adverse drug reactions, according to the approved product information, acid-minimising/suppressing agents (e.g., omeprazole)[37] may also interact with prescribed AF medications (e.g., warfarin, digoxin), increasing the potential for side effects (e.g. bleeding, arrhythmia) leading to suboptimal clinical outcomes.[38]

In relation to the over-use of therapies, a surprisingly high proportion of patients were found to be taking benzodiazepines in this study, which are recognised as a major cause of adverse drug reactions in the older patients.[39] A previous study pertaining to general older patients (aged >65 years) in the Australian general practice setting reported that 45% of patients using benzodiazepines experienced two to six adverse drug reactions, whilst 15% of patients had seven or more reactions during the study period.[39] Benzodiazepines, as well as other psycholeptics, psychoanaleptics, diuretics, antihypertensive agents, anti-inflammatory and anti-rheumatic products (e.g., NSAIDs) are regarded as PIMs in older persons; many of these may lead to a high risk of falls, and/or increased risk of intracranial bleeding, whilst others can cause GI bleeding, exacerbating the background risks already posed by specific AF therapies.[40]

Regarding the different classifications of bleeding risk assessment, two tools were used: HAS-BLED, which is widely incorporated into international treatment guidelines[1,2], and HEMORR2HAGES, as recommended by National Clinical Guideline Centre (UK) and American College of Cardiology/American Heart Association guidelines.[1,19] Compared with HAS-BLED, HEMORR2HAGES uniquely includes a wider range of risk factors namely: malignancy, anemia, genetic factors, reduced platelet count or function, excessive falls risk, in addition to the common bleeding risk factors (e.g., hypertension, abnormal renal/liver function, stroke, bleeding predisposition, age, alcohol use). HAS-BLED has better sensitivity than HEMORR2HAGES in identifying any clinically relevant bleeding in anticoagulated patients with AF.[41] However, HEMORR2HAGES has a higher diagnostic accuracy due to its higher specificity.[41] The

association between a lower HEMORR2HAGES (but not HAS-BLED) score and polypharmacy may be explained by the wider range of risk factors included in it, although none of the individual risk factors were found to be significantly associated with polypharmacy in this study. In this regard, decision support tools (such as CARAT[42]) can help assess these risk factors when recommending antithrombotic therapy, and therefore maybe useful in identifying the potential for polypharmacy (and therefore any medication safety issues).

This study has identified that patients using polypharmacy are also more likely to have a low risk of bleeding. Given that the decision-making around the use of antithrombotics in AF focuses on weighing the risk of stroke versus the risk of bleeding, in this equation these "low risk" patients (low bleeding risk) are generally deemed to be more eligible for anticoagulants (e.g., warfarin) than patients at a higher bleeding risk. However, these same low-risk patients are also more likely to have polypharmacy (as identified here), thereby increasing the risk of drug-drug interactions, adverse drug reactions and treatment non-adherence. Therefore, in prescribing antithrombotics for AF patients, clinicians must consider both the stroke versus bleeding risks alongside the relevant medication safety considerations (i.e., the implications of polypharmacy), to ensure that in optimising antithrombotic therapy they are not inadvertently putting "low risk" patients at high risk of medication misadventure. Whilst this should not stop the use of antithrombotics, it does reinforce the need for comprehensive patient assessment with regular review and follow-up to monitor for medication misadventure in all patients including those apparently at "low risk".

In this study, patients with major-polypharmacy were more likely to have obstructive pulmonary disease (asthma or COPD), upper gastrointestinal disease and poor physical function (as per SF-36), but less likely to have cognitive impairment. This is consistent with other studies showing that asthma or COPD and gastrointestinal disease[43,44] are associated with excessive polypharmacy (≥10 drugs).[45] Possible reasons include that obstructive pulmonary disease can cause a range of different comorbidities, including heart disease (e.g., heart failure, arrhythmias), chronic kidney disease, cancer, metabolic disease (e.g., osteoporosis, diabetes) and pulmonary embolism.[46] Since patients with upper gastrointestinal disease have a higher risk of gastrointestinal bleeding[38], the association of upper gastrointestinal diseases with major-polypharmacy in patients with AF needs some vigilance; the concomitant use of oral antithrombotics (e.g., dabigatran, aspirin) and NSAIDs in the presence of polypharmacy and gastrointestinal disease may predispose patients to an increased risk of GI haemorrhage and associated morbidity and mortality. Similarly, poor physical function (measured by SF-36), as reported by previous studies was found to be associated with the use of an increased number of medications.[47] Since patients with polypharmacy are at higher risk of adverse reactions[5], it is important to balance the need for multiple medications with patients' desired quality of life. In contrast, cognitive impairment has been shown to be associated with a reduced use of medications.[43,44] This may be due to prescribers' concerns about using multiple medications in those patients, as studies have shown that cognitive impairment may cause lower adherence and communication difficulties, including a decreased ability to report adverse effects.[48,49]

The 'trilogy' of risks in older AF patients warrants specific attention when managing their medication regimens. Services such as Home Medicines Review (HMR)[50] can help to assess the medication regimens of such patients, and have been shown to reduce the use of PIMs.[51] Other services such as MedsCheck (medicines use review) and Diabetes MedsCheck (diabetes medication management) are structured pharmacy services, involving face-to-face consultations between the pharmacist and consumer.[52] These services are designed to enhance the quality use of medicines through patient education, self-management and medication adherence strategies, and may help to reduce the medication misadventure experienced by patients.[53] Some available risk assessment tools, such as CHA2DS2VASc[14] and HAS-BLED[15], can assist in quantifying the stroke or bleeding risk for an individual patient. However, medication management in AF patients requires a more careful balance of risks and benefits to ensure optimal therapy that not only minimises the stroke and bleeding risks, but also reduces the risk for medication misadventure from any cause.

Targeted decision support tools, which systematically assess a patient's medical history, stroke and bleeding risk and which consider pertinent medication safety issues (e.g. polypharmacy, drug-drug interactions), may assist here[42]; these tools can support prescribing as well as facilitate the regular review of medication regimens. Regular medication review services using risk assessment tools may help reduce the risk and optimise medication use. However, there are still some gaps in implementing these tools and services in the medication management of AF patients. Designed for specific contexts (e.g., stroke, bleeding) or certain types of medication (e.g., antithrombotics), these tools (CHA2DS2VASc[14], HAS-BLED[15] and CARAT[42]) alone may not be completely useful in the comprehensive review and management of AF patients' overall medication regimen (as opposed to just their antithrombotic therapy). Also, these tools and services have not yet been evaluated in large-scale studies involving older AF patients. Therefore, given that the use of pharmacotherapy in this specific context (older persons with AF) is complex, further research needs to more comprehensively investigate the risk factors and explore the impact of targeted interventions on managing the 'trilogy' of risks.

In considering the findings of this study, some limitations need to be acknowledged. The retrospective nature of the study, and the limited

number of AF patients in the cohort reviewed, result in relatively wide confidence intervals, requiring that the findings to be interpreted with caution. The logistic regression analysis for the outcome "major-polypharmacy versus minor polypharmacy" has limited prediction value, which means that there may be other risk factors associated with major-polypharmacy which need to be explored in future studies. However, the selection of these patients is representative of older patients with AF encountered in the Australian general practice setting, providing an important insight into the specific challenges of using pharmacotherapy in this patient cohort. Furthermore, although there is uncertainty around the reliability of GPs' medication records as the primary source of medication histories, the medication lists recorded in this study were verified by the GPs. Due to the cross-sectional design of this study, only explicit criteria were used to identify PIMs. Though many of the results of this study confirm the previous findings in the literature, this study is first to demonstrate the relationship between low-bleeding risk and polypharmacy.

CONCLUSIONS

Polypharmacy affects most older AF patients, comprising medications that are indicated for AF, yet regarded as PIMs. Patients with a lower risk of bleeding, obstructive pulmonary disease, upper gastrointestinal disease and poor physical function are significantly more likely to use multiple medications. This may lead to an increased risk of medication misadventure due to the concomitant use of polypharmacy and high-risk medications indicated for AF.

CONFLICT OF INTEREST

None to declare.

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