OPTIMISING THE USE OF THROMBOPROPHYLAXIS IN ATRIAL FIBRILLATION (AF):

EXPLORING FACTORS AFFECTING DECISION-MAKING

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I, Ekta Pandya declare that this thesis, is submitted in fulfilment of the requirements for the award of Master of Pharmacy, in the School of Pharmacy at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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I. Abstract

The risk of stroke is five-folds higher among patients with atrial fibrillation (AF) in comparison to those without AF. In fact, thromboembolic strokes occurring in AF patients are more disabling and fatal than in patients without AF. This increase in morbidity and mortality due to stroke in patients with atrial fibrillation has become a major global healthcare burden, and for this reason stroke prevention (using antithrombotic agents as the mainstay therapy) has been a critical feature of AF management. Although warfarin (an oral vitamin K antagonist) has been traditionally used for preventing stroke in AF patients, its complex pharmacology (i.e., narrow therapeutic index requiring regular therapeutic monitoring, its interactions with food, alcohol, and other medications), and prescribers' concerns regarding patients' nonadherence to the therapy make the decision-making around the initiation of therapy quite complicated. Consequently, anticoagulants are underutilised in many 'at-risk' patients, exposing them to an increased risk of a preventable stroke. Our research in a hospital-based study that used decision-making support tool i.e., a computerised antithrombotic risk assessment tool (CARAT- a tool developed based on local and international guidelines assists in therapy selection based on patients' individualised risk versus benefit assessment) observed a marginal increase in anticoagulation prescription among eligible patients (57.8% vs 64.7%, P=0.35) in comparison to the baseline prescription. However, many at-risk patients were still not prescribed anticoagulants as recommended by CARAT, and the clinicians' agreement with CARAT recommendation was low. This might have been due to clinicians' perceived fears of risk such as falls,

bleeding, and patients' nonadherence to the therapy. To increase clinicians' acceptance for CARAT tool, studies should further explore its validity in predicting clinical outcomes.

Recently, the direct oral anticoagulants (DOACs) have become available for thromboprophylaxis in patients with AF. These agents have safety and efficacy (in stroke prevention) profiles comparable to warfarin therapy. They also offer some practical advantages over warfarin in terms of not requiring regular therapeutic drug monitoring, plus their interactions with food, alcohol and other medications is limited. However, the DOACs are not completely devoid of risks or challenges to their use. These challenges include: a) the lack of specific drug monitoring tests; b) complicated management of renally-impaired patients; c) limited access to and/or unavailability of antidotes for the management of DOAC-related acute bleeding; d) high 'out-of-pocket' costs for patients in some countries; and e) the potential for patient nonadherence (due to the more frequent dosing required with dabigatran and apixaban). Such conditions present specific challenges for clinicians when prescribing these medications for long-term stroke prophylaxis in patients with AF. In 2014 following the listing of DOACs on the pharmaceutical benefits scheme (PBS) (which subsidises DOACs for stroke prevention in AF), it was important to report their utilisation of anticoagulant prescription in local Australian settings. It was also necessary to updated CARAT 2.0 in assessing whether the prescriptions were based on these revised guidelines. Our study (in a hospital setting in Sydney) found that 52.0% of the people were prescribed anticoagulants. Warfarin was the first-choice anticoagulant prescribed for two-thirds of patients, while the remaining one-third were on DOCAs. However, most of the patients eligible for anticoagulants were not prescribed it but were either prescribed antiplatelets or kept on nil therapy.

In this thesis a structured literature review explored factors influencing patients' preference and adherence for warfarin versus DOACs. This is because research suggests that patients have an important role in the decision-making process for antithrombotic therapy selection in AF. This review discussed patients' perspectives on medications. Here the findings were synthesised to present a framework depicting the five interacting dimensions of adherence: 1) therapy-related factors; 2) patient-related factors; 3) condition-related factors; 4) social–economic factors; and 5) health system factors. From this study, it was clear that patients' views about treatment must be incorporated into the decision-making process to facilitate a) treatment; b) adherence; and c) achieve good clinical outcomes. In line with this study, another study then evaluated the information within web-based resources designed to educate patients on thromboprophylaxis in AF. The content and thematic analysis were conducted on these resources. It was found that the information provided in these resources were varied. It was found that implied bias of some resources towards specific anticoagulant therapies and their imbalanced information on the importance of anticoagulation in AF might misinform or confuse patients. Therefore, patients' engagement in shared decision-making and adherence to medicines might be undermined by the suboptimal quality of information provided in these resources.

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I am grateful to the Graduate School of Health at the University of Technology Sydney for offering me a position in this prestigious institute.

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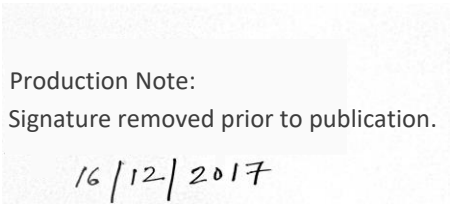
Lastly and most importantly, I would thank Lord Krishna for being so merciful, and giving me the strength and ability to understand, self-reflect and learn from this early research experience.

III. Declaration

This is to 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 research presented in this thesis is genuine, and the outcome of my efforts. Any help that I have received for this research has been acknowledged. In addition, I certify that all information sources and literature used to undertake this research have been acknowledged properly in this thesis.

In accordance with the university-endorsed national guidelines, copy-editing and proofreading services were provided by Dr Leigh Findlay (TrueNature Writing & Editing) and Rosemary Osborne (The Writing Shed).



Signature of Student Date

Ekta Pandya

IV. Abbreviations

ACC	American College of Cardiology
AF	Atrial Fibrillation
AHA	American Heart Association
CARAT	Computerised Antithrombotic Risk Assessment Tool
CCF	Congestive Cardiac Failure
CI	Confidence Interval/s
DOACs	Direct Oral Anticoagulants
DST	Decision Support Tool/s
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HRS	Heart Rhythm Society
Hx	History
NICE	National Institute for Health and Care Excellence
NOACs	Novel/ New Oral Anticoagulants **OR** Non-Vitamin K Antagonist Oral Anticoagulants *Word NOACs was used only in journal articles*
DOACs	Direct Oral Anticoagulants

	Word DOACs is used throughout the thesis expected in some articles
NSAIDs	Non-steroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation
NSW	New South Wales
QoL	Quality of Life
OR	Odds Ratio
PBS	Pharmaceutical Benefits Scheme
SDM	Shared Decision-Making
SPSS	Statistical Software for Social Sciences
TAG	Therapeutic Advisory Group
TIA	Transient Ischemic Attack
TM	Trademark
Tx	Therapy/ Treatment
WATAG	Western Australian Therapeutic Advisory Group

V. List of published articles

CHAPTER 2:

Title: Impact of a Computerized Antithrombotic Risk Assessment Tool (CARAT) on the prescription of thromboprophylaxis in atrial fibrillation: hospital setting.

Authors: Ekta Pandya, Noman Masood, Yishen Wang, Ines Krass, Beata Bajorek

Publication status: Published Online in Clinical and Applied Thrombosis/ Hemostasis

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CHAPTER 3:

Title: Contemporary utilisation of antithrombotic therapy for stroke prevention in atrial fibrillation: an audit in an Australian hospital setting

Authors: Ekta Pandya, Elizabeth Anderson, Clara Chow, Yishen Wang, Beata Bajorek

Publication status: Published Online in Therapeutic Advances in Drug Safety

DOI: 10.1177/2042098617744926

CHAPTER 4:

Title: Factors affecting patients' perception on, and adherence to, anticoagulant therapy: anticipating the role of direct oral anticoagulants (DOACs)

Authors: Ekta Pandya, Beata Bajorek

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Volume: 10

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DOI: 10.1007/s40271-016-0180-1

CHAPTER 5:

Title: Assessment of web-based education resources informing patients about stroke prevention in atrial fibrillation (AF).

Authors: Ekta Pandya, Beata Bajorek

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Volume: 41

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VI. Table of contents

VII. Table of figures

1 Background and Thesis Overview

1.1 Background

It is estimated that the prevalence of AF among patients aged 55 years and above will have almost doubled by the year 2034 (6.39%) compared to that reported in 2014 (3.29%) (1). This is significant because the risk of having a stroke is five-fold higher in patients with AF than in patients without AF (2, 3), and because thromboembolic strokes in AF patients are more disabling and more likely to be fatal than in patients without AF (4). This increase in the morbidity and mortality due to stroke in patients with AF presents a major global healthcare burden (5), and for this reason stroke prevention (using antithrombotic agents as the mainstay therapy) has become a critical feature of AF management. Traditionally warfarin (an oral vitamin K antagonist) has been used for preventing stroke in AF patients (6). Recently, the direct oral anticoagulants (DOACs) have also become available for thromboprophylaxis in patients with AF. These agents have safety and efficacy (in stroke prevention) profiles which are comparable to warfarin (7) Meta-analyses have shown the higher efficacy of anticoagulant therapies in stroke prevention in nonvalvular AF when compared to aspirin (8, 9), reporting that patients treated with aspirin (compared to those treated with warfarin) have a higher relative risk ratio for all-cause stroke (RR=1.8, 95%CI = 1.21 – 2.7). In regard to the DOACs, patients on apixaban have a 56% (RR=0.44, 95%CI=0.28–0.69), dabigatran 49% (RR=0.51, 95%CI=0.33-0.8), and rivaroxaban 53% (RR=0.47, 95%CI=0.3-0.74) reduced risk of all-cause stroke in comparison to those on aspirin (10). Patients taking placebo have a 1.3 times higher relative risk of all-cause stroke when compared to those on warfarin (RR=1.3, 95%CI=0.47–3.38) (10). The pooled analysis of 7 randomised control trials and 4 cohort studies have shown that the relative risk for major bleeding is comparable between patients treated on warfarin, clopidogrel or aspirin (RR=1.01; 95% CI=0.69-1.48; moderate-quality evidence) (11). A mixed retrospective and prospective study reported that the adjusted net clinical benefit of anticoagulation per year was higher among patients aged ≥85 years (2.34%, 95% CI = 1.29% to 3.30%) than younger patients (12). It was

also higher for patients with a previous history of ischemic stroke (2.48%, 95% CI = 0.75% to 4.22%) compared to patients with no previous history of stroke, and in patients with higher $CHADS_2$ scores (2.22%, 95% CI = 0.58% to 3.75%) compared to patients with lower $CHADS_2$ scores (12). This latter study defined net clinical benefit as the yearly rate of thromboembolic events (TE rate) prevented by the anticoagulation minus the annual rate of intracranial haemorrhages (ICH rate) multiplied by a weighting factor (i.e., relative impact of receiving warfarin on mortality and morbidity) (12). Other evidence-based guidelines also recommend long-term therapy, especially anticoagulant therapy, for stroke prevention in patients with AF (13-16). Despite the abundance of evidence supporting the efficacy of anticoagulation in thromboprophylaxis among patients with AF, studies have shown that warfarin is sub-optimally prescribed, particularly among at-risk patients with AF (17, 18). A retrospective audit in a hospital setting in Sydney reported that only 55% of the patients eligible for anticoagulation were prescribed anticoagulants (17).

In trying to explain this utilisation, studies have reported that the complex pharmacology of warfarin (i.e., the narrow therapeutic index requiring regular therapeutic monitoring, and interactions with food, alcohol and other medications) (19, 20) and prescribers' concerns regarding patients' nonadherence to the therapy complicate the decision-making around the initiation of therapy (19, 21, 22). From the clinician's perspective, the impediments to optimum use of warfarin therapy can be divided into four domains:

a. patient clinical characteristics (e.g., risk of bleeding or adverse drug events)
b. healthcare system/clinician factors (e.g., lack of continuity of care, delays in obtaining international normalised ratio (INR) test reports, lack of training in warfarin management)
c. patients lack capability (e.g., self-management of, and adherence to, warfarin therapy)
d. and patients' preferences for therapy (23).

The pharmacological characteristics of the recently available DOACs have to some extent addressed the issues with self-management of, and adherence to, warfarin therapy for example., DOACs obviate the need for the regular INR monitoring and/or dose adjustments to a certain extent, which were routine with warfarin therapy (24). However, DOACs do require some testing, albeit not as often as warfarin. Apart from the ad-hoc monitoring required for DOACs in certain situations such as emergency surgery or other invasive procedures; haemorrhagic events; suspected overdose; acute thrombosis in renal, liver or heart failure; potential drug-drug interactions; trauma; acute disease; and malignancy (25) the regular measurement of non-coagulation parameters (e.g., renal function) may be required according to the specific DOAC used (26). Although ad-hoc monitoring might not affect all patients, the need for regular measurement of renal function might affect elderly patients' preferences for such antithrombotic therapy. Thus, it is safe to say that DOACs are not completely devoid of risks or challenges. Specific challenges for clinicians when prescribing these medications for long-term stroke prophylaxis in patients with AF may include – a) a lack of specific therapeutic drug-monitoring tests; b) the complicated management of patients with renal impairment; c) limited access to and/or unavailability of antidotes for management of DOAC-related acute bleeding; d) high 'out-of-pocket' costs for patients in some countries; and e) the potential for patient nonadherence (due to the more frequent dosing required with dabigatran and apixaban) (27, 28).

Whilst the availability of and access to DOACs has expanded the array of thromboprophylaxis options in AF, it also renders the decision-making process more complex. Several studies have suggested the use of decision-making support tools that are based on patients' individualised risk versus benefit assessment to facilitate the selection of antithrombotic therapy (22, 29). One such decision support tool – the Computerised Antithrombotic Risk Assessment Tool (CARAT 1.0) – was developed using evidence-based studies and international and Australian guidelines for the management of AF (30). The original version of CARAT was based on the patient's stroke risk and bleeding risk scores and generated treatment recommendations within the range of available options at the time, i.e., warfarin, antiplatelet therapy or nil therapy. It

used $CHADS_2$ (*congestive cardiac failure, hypertension, age ≥75 years, diabetes mellitus, prior history of stroke/transient ischemic attack/thromboembolism*) (31) for stroke risk assessment and $HEMORR_2HAGES$ *(Hepatic or renal disease, Ethanol abuse, Malignancy, Older, Reduced platelet count or function, Re-bleeding risk, Hypertension, Anaemia, Genetic factors, Excessive fall risk, Stroke)* (32) for bleeding risk assessment. CARAT also included medication management and safety issues, such as already known potential drug–drug interactions and allergies that may have influenced the risk versus benefit of anticoagulant therapy (33, 34). Following a number of changes impacting on clinical practice, including the listing of DOACs on the Australian Pharmaceutical Benefits Scheme (PBS, the list of medicines that are cost-subsidised by the Australian Government), increasing evidence on the efficacy of DOACs from clinical trials (35), and the revision of AF management guidelines (35-40), the original version of CARAT was upgraded to CARAT 2.0 (41). In addition to $CHADS_2$ and $HEMORR_2HAGES$, the CARAT 2.0 tool included the CHA_2DS_2-VASc score *(congestive cardiac failure, hypertension, age ≥75 years, diabetes mellitus, prior history of stroke/transient ischemic attack/thromboembolism, vascular diseases, age 65–74 years, female)* (42) and HAS-BLED score *(Hypertension, Abnormal renal-liver function, Stroke, Bleeding history, Labile INR, Elderly, Drugs/alcohol)* (43) for stroke and bleeding risk assessments respectively. Furthermore, CARAT 2.0 now considers the three DOACs (dabigatran, apixaban and rivaroxaban), alongside warfarin therapy and nil therapy, among the available treatment options. Antiplatelet medications (i.e., aspirin, clopidogrel) have not been included in CARAT 2.0 as current guidelines no longer recommend these medications for long-term stroke prevention in patients with AF.

For effective shared decision-making (SDM) and to facilitate selection of antithrombotic therapy for long-term conditions, it is necessary to explore patients' views and perspectives on the available treatment options for stroke prevention (44-46). Previous studies have highlighted differences between patients' and prescribers' perceptions of risk and benefit regarding anticoagulant therapy (47, 48). However, little is known regarding the factors influencing the decisions of patients with AF, especially regarding the choice between the recently available DOACs and traditional warfarin therapy. The

recommendation for a shared decision-making approach requires us to study the availability of resources to effectively educate and engage patients within this process.

In view of the changing scenarios around antithrombotic prescription following the availability of DOACs in Australia, and the need to explore factors influencing patients' perceptions and preferences for the available treatment options, the research presented in this thesis focused on the use of DOACs and warfarin in a local Australian practice setting. Furthermore, it explored the literature to uncover the various factors considered by patients in their decision-making around antithrombotic therapy options. The objectives of this research project were to investigate:

a) the impact of the first version of CARAT on antithrombotic therapy prescribing (especially, anticoagulant therapy) by facilitating comprehensive risk-benefit assessment on individual patients
b) the utilisation of antithrombotic post-PBS listing of DOACs in a local Australian hospital setting
c) whether anticoagulants are prescribed according to the current guidelines, which consider three DOACs and warfarin therapy among the treatment options, using CARAT 2.0 tool as a guide
d) the predictors of warfarin and DOACs prescription
e) the factors influencing patients' perspectives on, and adherence to, the currently available anticoagulant therapies (i.e., warfarin, DOACs)
f) the content and quality of the information provided in web-based resources specifically designed for educating patients with AF.

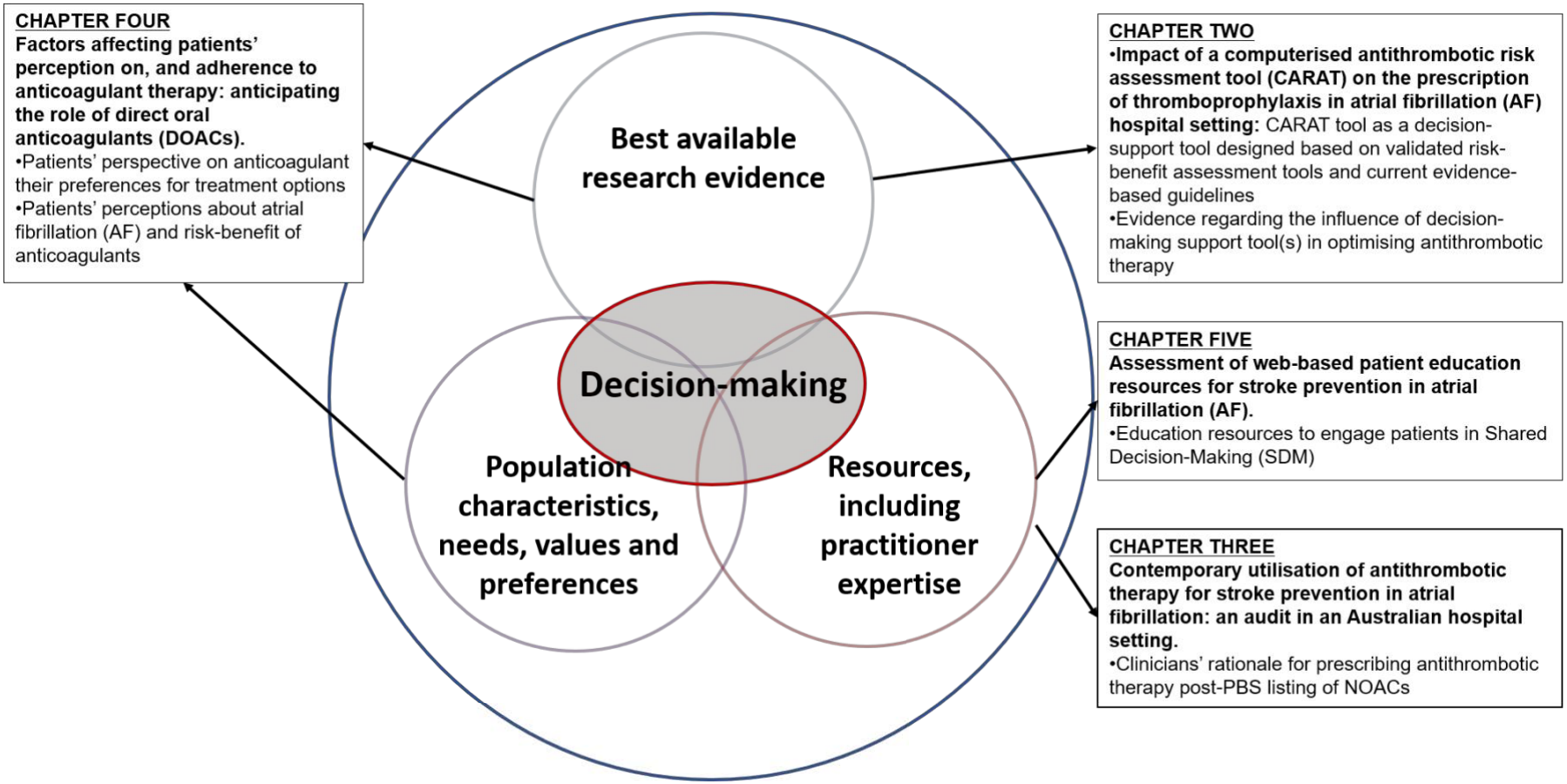

Figure 1-1. Thesis chapters mapped against the three domains of evidence-based decision-making (41).

1.2 Thesis Overview

The content of this thesis is organised and recounted in six separate chapters**.**

Chapter 1 provides a synopsis of this thesis, including the background and context for conducting this research in the local setting, and outlines the specific phases of this research. ***Chapter 1*** sets the scene for the exploration of factors affecting the optimum utilisation of anticoagulants for stroke prevention in AF from the perspective of prescribers (***Chapter 2 and 3***), and then from the perspective of patients (***Chapter 4 and 5***).

Chapter 2 is a pilot study of a customised decision-support tool designed to assist prescribers in the selection of optimal antithrombotic therapy for individual patients with AF. The computerised antithrombotic risk assessment tool (CARAT) is populated with relevant patient information (i.e., medical history including stroke and bleeding risk factors; medication history including antithrombotic therapy use; functional and/or cognitive impairments; medication management issues; social situation) to generate an individualised antithrombotic therapy recommendation. The utilisation of antithrombotic therapy pre- and post- application of the CARAT tool in the local Australian hospital setting is reported in this chapter, including the factors identified as influencing clinicians' decision to prescribe warfarin. This study demonstrates how a decision-support tool facilitates a comprehensive risk-benefit of the patients, to optimise the use of antithrombotics (especially 'warfarin') in 'at-risk' patients.

Given that the CARAT-based intervention ***(Chapter 2)*** was conducted before the PBS-listing of all three DOACs (dabigatran, rivaroxaban, apixaban) for stroke prevention in AF, a subsequent study (***Chapter 3)*** reported the contemporary utilisation of antithrombotics in the local Australian setting (New South Wales, Sydney). This audit study explored whether utilisation of these agents was in accordance with current clinical

guidelines, and identified factors predicting the use of DOACs in preference to warfarin therapy. Overall, the audit shows that target 'at-risk' patients are under-prescribed anticoagulant therapy, despite the availability of DOACs as alternatives to warfarin therapy.

Chapter 4 comprises a purposeful review of the literature targeting patients' perspectives on, and adherence to, anticoagulant therapy for stroke prevention in AF. The review canvasses: patients' viewpoints on warfarin therapy and its management; factors affecting their adherence to warfarin therapy; and, the extent to which the DOACs address the issues with underpinning patients' adherence to warfarin. This review highlights the importance of adopting shared decision-making (SDM) around the use of thromboprophylaxis in AF, i.e., engaging patients in the decision-making for antithrombotic therapy selection, and empowering them to become active partners in managing their treatment and health.

Given the importance of information provision in facilitating SDM, and the increasing role of the internet as a source of health information, ***Chapter 5*** reports a qualitative assessment of the information provided in a range of online resources currently available to help inform patients about stroke prevention in AF, and which might be used to empower patients in decision-making for their therapy selection. The specific study objectives were to identify what aspects of thromboprophylaxis (antithrombotic treatment options) were most commonly described in these resources, in terms of content, i.e., information provided (quantitative), as well as how this information was presented in terms of the themes underpinning this content. This study reveals that the information provided in some of these resources were seemingly biased towards either warfarin or the DOACs and unbalanced in terms of explaining about risk (haemorrhage) and benefits (stroke prevention) associated with antithrombotics use, and this might potentially misinform and confuse patients leading to decrease in patients' acceptance for, and adherence to, anticoagulants.

Finally, ***Chapter 6*** provides an overarching discussion and conclusion on the collective findings of this thesis research.

2 Anticoagulant Therapy Utilisation Pre-NOACs Approval

Title: Impact of a Computerised Risk Assessment Tool (CARAT) on the prescription of thromboprophylaxis in atrial fibrillation: hospital setting.

Author/s: Ekta Pandya, Noman Masood, Yishen Wang, Ines Krass, Beata V. Bajorek

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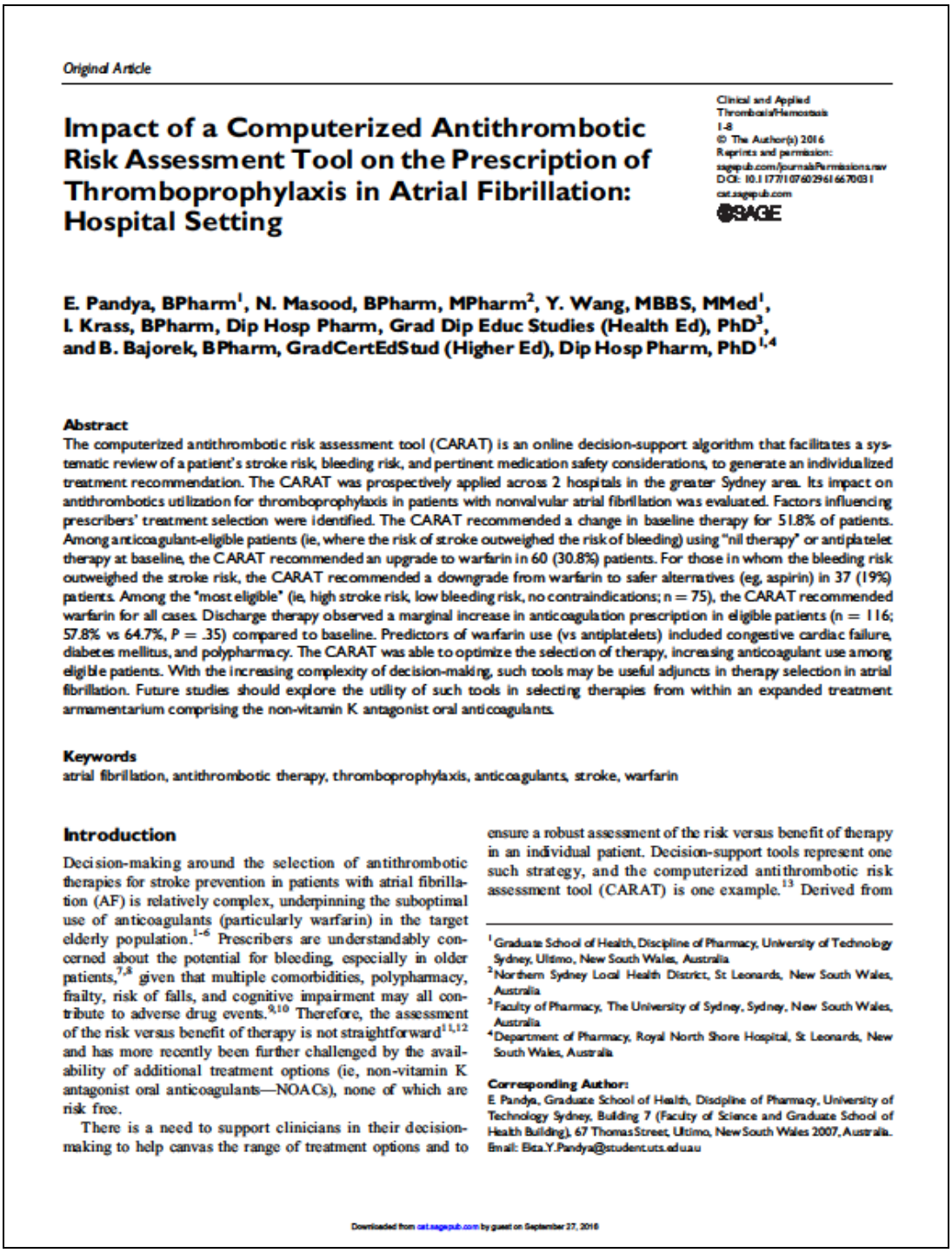
Approval



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 eligible patients. With the increasing complexity of decision-making, such tools may be useful adjuncts in therapy selection in atrial fibrillation. 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.

Keywords

atrial fibrillation, antithrombotic therapy, thromboprophylaxis, anticoagulants, stroke, warfarin

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 (ie, 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 computerized antithrombotic risk assessment tool (CARAT) is one example.[13] Derived from

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2.1 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 anticoagulant 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.(49-54) Prescribers are understandably concerned about the potential for bleeding, especially in older patients, (55, 56) given that multiple comorbidities, polypharmacy, frailty, risk of falls, and cognitive impairment, may all contribute to adverse drug events. (19, 57) Therefore, the assessment of the risk versus benefit of therapy is not straightforward, (58, 59) 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. (30) Derived from hospital-based risk assessment algorithms, (60) 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. (30, 34) 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 (61). 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.

2.2 Patients and Methods

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 (62). 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.

2.2.1 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.

2.2.2 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 2-1). 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 bedside. 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.

2.2.3 Application of CARAT (intervention phase)

The CARAT is a custom-designed online decision-support tool (30, 60) which recommends antithrombotic therapy based on patients' estimated risk (bleeding) versus benefit (stroke prevention) assessment, potential contraindications (medication safety issues), and evidence-based guidelines (32, 42, 43, 63). At the first level, the stroke risk assessment is based on the validated $CHADS_2$ score (63) and CHA_2DS_2-VASc score (42), and the bleeding risk estimated using the $HEMORR_2HAGES$ score (32) and HAS-BLED score (43); 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 (63)
- CHA_2DS_2-VASc stroke risk: 0 points = low risk, 1 point = intermediate risk, and ≥ 2 points= high risk (64)
- HAS-BLED bleeding risk: 0= low risk, 1= intermediate risk, ≥ 2= high risk (43)
- $HEMORR_2HAGES$ bleeding risk: 0-1= low risk, 2-3= intermediate risk, and ≥ 4= high risk (65)

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 (60). 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).

2.2.4 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.

2.2.5 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.

2.3 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 2-1).

2.3.1 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 2-2 and Table 2-3). 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 2-3).

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 2-3).

2.3.2 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 2-3). 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 2-3).

2.3.3 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 2-4). 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 2-3). 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 2-3). 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).

2.3.4 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 2-3). 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 2-3).

2.3.5 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).

2.3.6 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 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).

2.3.7 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.

2.4 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 (66, 67). 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 (68, 69). 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 (68). Prescribers sometimes disagreed with CARAT due to isolated risk factors, such as perceived risk of falls, history of bleeding (70), 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 (71). This study also identified clinicians' perceptions about patients' nonadherence as a deterrent to warfarin use (20). However, in regard to NOACs, the absence of therapeutic monitoring to identify medication nonadherence is also of concern for clinicians (28). This study, akin to other studies (60, 69), 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, (32, 42, 43, 63) 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.

Funding:

Nil

Acknowledgements

We sincerely thank Kate Moffatt and Eunice Chan for their assistance in the conduct of this study

Table 2-1. Patient characteristics and clinical history

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	
Allergic to warfarin AND aspirin	7 (3.6%)
Allergic to aspirin	1 (0.5%)
Allergic to aspirin and clopidogrel	8 (4.1%)
	1 (.5%)
Estimated Stroke Risk* (N = 195)	
High	146 (74.9%)
Intermediate	41 (21.0%)
Low	8 (4.1%)
Estimated Bleeding Risk* (N = 195)	
High	13 (6.6%)
Intermediate	64 (32.8%)
Low	118 (60.5%)

these data were used to populate the CARAT tool
* 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 (72)

Table 2-2. 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 2-3. 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: Distribution of 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 (21.0%)
	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%)
PART B: Distribution of 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%)
PART C: Distribution of 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%)

* 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 2-4. Patients requiring antithrombotic therapy changes pre and post-intervention (N = 195).

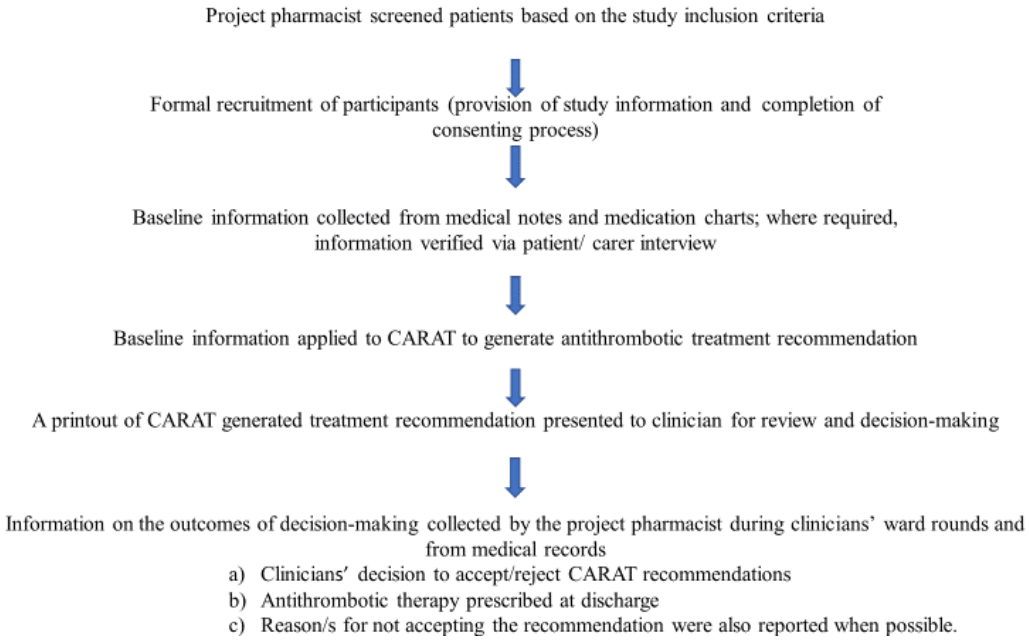
Change in therapy (number of patients, % within group)	**Baseline (N = 101)**	**Discharge (N = 82)**	**P-value**
Upgrade in therapy			
Nil therapy to warfarin	13 (6.6%)	7 (3.5%)	0.02*
Aspirin/clopidogrel to warfarin	36 (18.4%)	34 (17.4%)	
Nil to aspirin/clopidogrel	11 (5.6%)	5 (2.5%)	
Total	**60 (30.8%)**	**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)

2.5 Supplementary: Flow chart depicting the process of data collection



2.6 Contribution of authors

1. Ekta Y Pandya:

a. Conducting the literature search
b. Analysing the studies and designing the structure of the manuscript
c. Writing the drafts
d. Submitting the manuscript to the Journal
e. Revising the manuscript as per reviewers' comments and resubmitting the manuscript.

2. Noman Masood:

a. Responsible for conducting the study in the hospital
b. Recruiting and enrolling the patients for the study
c. Collecting data in the data collection form

3 Yishen Wang

a. Data analysis

4. Ines Krass

a. Designing the evaluation process for the CARAT tool

5. Beata V Bajorek:

a. Conceiving and designing the study
b. Designing the CARAT 2.0 tool
c. Ethics approval for the study
d. Assistance in conducting literature search, and analysing the studies
e. Supervision in designing the structure of the manuscript
f. Ensuring the intellectual content in the manuscript
g. Writing, editing and proof-reading the manuscript
h. Assistance in addressing reviewers' and editor's comments

2.7 Supplementary material

The process of undertaking the logistic regression modelling is iterative. It inherently involves testing for collinearity as well as confounding and therefore, was not reported in the methods / results unless specifically identified. In this study, the variance inflation factor (VIF) value was low at 1.0 and tolerance was 0.97 (testing for multicollinearity), indicating that there was no correlation between the independent variables included in the model (as would be expected with the variables under exploration).

3 Anticoagulant Therapy Utilisation Post-PBS Listing of NOACs

Title: Contemporary utilisation of antithrombotic therapy for stroke prevention in patients with atrial fibrillation: an audit in an Australian hospital setting

Author/s: Ekta Pandya, Elizabeth Anderson, Clara Chow, Yishen Wang, Beata Bajorek

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Contemporary utilization of antithrombotic therapy for stroke prevention in patients with atrial fibrillation: an audit in an Australian hospital setting

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Abstract

Background: To document antithrombotic utilization in patients with nonvalvular atrial fibrillation (NVAF), particularly, recently approved NOACs (nonvitamin K antagonist oral anticoagulants) and warfarin; and identify factors predicting the use of NOACs *versus* warfarin.

Methods: A retrospective audit was conducted in an Australian hospital. Data pertaining to inpatients diagnosed with atrial fibrillation (AF) admitted between January and December 2014 were extracted. This included patient demographics, risk factors (stroke, bleeding), social history, medical conditions, medication history, medication safety issues, medication adherence, and antithrombotic prescribed at admission and discharge.

Results: Among 199 patients reviewed, 84.0% were discharged on antithrombotics. Anticoagulants (± antiplatelets) were most frequently (52.0%) prescribed (two-thirds were prescribed warfarin, the remainder NOACs), followed by antiplatelets (33.0%). Among 41 patients receiving NOACs, 59.0% were prescribed rivaroxaban, 24.0% dabigatran, and 17.0% apixaban. Among patients aged 75 years and over, antiplatelets were most frequently used (37.0%), followed by warfarin (33.0%), then NOACs (14.0%). Compared with their younger counterparts, patients aged 75 years and over were significantly less likely to receive NOACs (14.0% *versus* 28.0%, $p = 0.01$). Among the 'most eligible' patients (Congestive Cardiac Failure, Hypertension (, Age ⩾ 75 years, Age= 65-74 years, Diabetes Mellitus, Stroke/ Transient Ischaemic Attack/ Thromboembolism, Vascular disease, Sex female[CHA_2DS_2-VASc] score ⩾2 and no bleeding risk factors), 46.0% were not anticoagulated on discharge. Patients with anaemia (68.0% *versus* 86.0%, $p = 0.04$) or a history of bleeding (65.0% *versus* 87.0%, $p = 0.01$) were less likely to receive antithrombotics compared with those without these risk factors. Warfarin therapy was less frequently prescribed among patients with cognitive impairment compared with patients with no cognitive issues (12.0% *versus* 23.0%, $p = 0.01$). Multivariate logistic regression modelling identified that patients with renal impairment were 3.6 times more likely to receive warfarin compared with NOACs (odds ratio = 3.6, 95% confidence interval = 0.08–0.90, $p = 0.03$, 60.0% correctly predicted; Cox and Snell $R^2 = 0.51$, Nagelkerke $R^2 = 0.69$).

Conclusion: Despite the availability of NOACs, warfarin remains a preferred treatment option, particularly among patients with renal impairment. The high proportion of eligible patients

3.1 Abstract

Objectives

To document antithrombotic utilisation in patients with non-valvular atrial fibrillation (NVAF), particularly, recently approved NOACs (Non-vitamin K antagonist oral anticoagulants) and warfarin; and identify factors predicting the use of NOACs versus warfarin.

Method

A retrospective audit was conducted in an Australian hospital. Data pertaining to AF diagnosed inpatients admitted between January - December 2014 were extracted. This included patient demographics, risk factors (stroke, bleeding), social history, medical conditions, medication history, medication safety issues, medication adherence, and antithrombotic prescribed at admission and discharge.

Results

Among 199 patients reviewed, 84.0% were discharged on antithrombotics. Anticoagulants (± antiplatelets) were most frequently (52.0%) prescribed (two-thirds of this being warfarin, remainder NOACs), followed by antiplatelets (33.0%). Among 41 patients receiving NOACs, 59.0% were prescribed rivaroxaban, 24.0% dabigatran, and 17.0% apixaban. Among patients aged ≥ 75 years, antiplatelets were most

frequently used (37.0%), followed by warfarin (33.0%), then NOACs (14.0%). When compared to their younger counterparts, patients aged ≥75 years were significantly less likely to receive NOACs (14.0% versus 28.0%, P=0.01). Among the 'most eligible' patients (CHA_2DS_2-VASc score ≥ 2 and no bleeding risk factors), 46.0% were not anticoagulated on discharge. Patients with anaemia (68.0% versus 86.0%, P=0.04) or a history of bleeding (65.0% versus 87.0%, P=0.01) were less likely to receive antithrombotics compared to those without these risk factors. Warfarin therapy was less frequently prescribed among patients with cognitive impairment compared to patients with no cognitive issues (12.0% versus 23.0%, P = 0.01). Multivariate logistic regression modelling identified that patients with renal impairment were 3.6 times more likely to receive warfarin compared NOACs (OR = 3.6, 95%CI=0.08–0.90, P=0.03, 60.0% correctly predicted; Cox and Snell R_2=0.51, Nagelkerke R_2=0.69)."

Conclusion

Despite the availability of NOACs, warfarin remains a preferred treatment option, particularly among patients with renal impairment. The high proportion of eligible patients still being prescribed antiplatelet therapy or 'no therapy' needs to be addressed.

Key words

Antithrombotics, Stroke, Anticoagulants, Warfarin, Nonvitamin K antagonist oral anticoagulants, Novel oral anticoagulants, NOACs

3.2 Background

Stroke prevention is critical to atrial fibrillation (AF) management, given that the risk of embolic stroke is significantly higher in patients with AF compared to persons without the arrhythmia (3). Numerous studies have confirmed the efficacy of warfarin therapy for long-term stroke prevention (73-75). However, the inherent risk of bleeding, and the complex pharmacology of warfarin, renders decision-making complex, such that it requires comprehensive risk-benefit assessment and careful patient management. This ultimately results in its apparent suboptimal use in 'at-risk' patients (75-78).

The non-vitamin K antagonist oral anticoagulants (NOACs) have been recently made available for thromboprophylaxis in AF (16, 79-81). Aside from maintaining an efficacy and safety profile that is non-inferior to warfarin, NOACs have a broader therapeutic index and no dietary vitamin K restrictions, unlike warfarin. Additionally, a key advantage of the NOACs is that they do not require regular monitoring of anticoagulation parameters, unlike the need for regular INR testing with warfarin. However, some studies report conflicting views in regard to the value of regular monitoring in NOAC therapy (82-85). Limited access to, or unavailability of, specific antidotes for each of the NOACs, and their relatively higher drug costs, have raised additional considerations about their use among clinicians, patients, and wider health care systems (28, 86-90).

The availability of NOACs has expanded the treatment armamentarium for stroke prevention in AF. Although other studies have reported on the utilisation of antithrombotic therapies, our study considers prescribing in a particularly unique context, where the availability of NOACs has been delayed, restricted, and somewhat tainted by their initial introduction to practice. Unlike other countries (i.e., USA and UK) there was a considerable delay in the approval of the first NOACs (dabigatran) in Australia and GPs had their qualms about the safety and efficacy of these medications even after the Product Familiarisation Program. The dearth in information regarding the antithrombotic utilisation pattern immediately after the inclusion of NOACs in the PBS lead to conducting this study. This clinical audit might be important in future to study the changing pattern of NOACs prescription over a period in Australian setting. Toward the end of 2013, three NOACs (dabigatran, rivaroxaban, apixaban) were listed on the Pharmaceutical Benefits Scheme (PBS) for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF, i.e., excluding patients with AF having valvular anomalies or those who have undergone valve replacement surgery) (91-93), increasing their accessibility to prescribers and affordability for patients. Currently, there is limited information about the utilisation of NOACs in the local Australian setting, following their approval for use by the Therapeutic Goods Administration (TGA) (94-96).

The aim of this study was to explore the utilisation of antithrombotic therapy (i.e., antiplatelets and anticoagulants) in patients with AF in the local Australian setting following the PBS-listing of NOACs. Specifically, the objectives of this study were to: 1) document the use of

antithrombotics in hospitalised patients with AF; 2) report the proportion of patients prescribed NOACs compared to warfarin; and 3) identify the factors predicting the use of NOACs versus warfarin.

3.3 Methods

Study setting

A retrospective cohort study was undertaken in a tertiary hospital setting within metropolitan Sydney (New South Wales, Australia); the data were collected during the period 1st - 12th October 2015**.** Approval for this study was obtained from Western Sydney Local Health District Human Research and Ethics committee (Reference numbers: LNR/15/WMEAD/156, LNRSSA/15/WMEAD/240), and ratified by the University of Technology Sydney (Protocol number: AU/6/D34E110).

3.3.1 Study design

Data were extracted from the medical records of previously hospitalised patients who:

- were admitted to any ward between January - December 2014
- had NVAF as a primary or secondary diagnosis (diagnosed at any time from pre-admission to discharge), defined per ICD10 codes I48.0, I48.1, I48.2, I48.91 pertaining to paroxysmal, persistent, chronic, and unspecified AF, respectively (valvular AF was excluded)

A target sample size of 196 was calculated based on the estimated (highest) proportion of patients likely to be prescribed NOACs in the local setting (15% based on previous studies) (97), with 95% confidence and a 5% level of precision around the point estimate. To achieve this sample size and allowing for an overage to account for missing and/or miscoded records, all admissions with AF (N=2160; 563 as primary and 1597 as secondary diagnosis) were selected for initial review against the inclusion criteria. Patients were selected using simple randomized sampling (online random number generation).

3.3.2 Data collection

The research pharmacist liaised with hospital's Health Information Services department to retrieve patients' medical records from the archive. The research pharmacist reviewed these records (specifically, admission form, patients' daily progress notes, social history assessment form, discharge medication chart, laboratory reports) to extract the relevant information using a purpose-designed data collection form. The data collection form was based on a tool developed for customised stroke and bleeding risk assessment of patients diagnosed with AF (30), as well as evidence-based guidelines (58, 95). The information extracted included: patient demographics (age, gender, hospital length of stay), medical conditions (comorbidities, contraindications), medication management issues (cognitive impairment, visual or hearing impairment),

social history (residence, family support), medication safety issue (allergies to antithrombotics, adverse drug events, polypharmacy), medication adherence (history of non-adherence), and antithrombotic medication (at admission and discharge) for AF as the primary indication, noting whether any patients were recommended recommencement of antithrombotics following admission for surgical procedures.

The extracted data were utilised to calculate the patients stroke risk scores (per $CHADS_2$ and CHA_2DS_2–VASc) (98, 99) and bleeding risk scores (per HAS-BLED and $HEMORR_2HAGES$) (32, 43), as all of these scores may be used by clinicians in real-world practice. However, for the purposes of this study, only CHA_2DS_2–VASc and HAS-BLED were employed for the individualised risk-benefit stratification of patients (as 'eligible patients' and 'special AF populations') owing to the better risk predicting abilities of these scores over other scores (100-103). Patients with high stroke risk scores (CHA_2DS_2-VASc $\geq$ 2) and low-intermediate risk of bleeding (HAS-BLED $\leq$2) were categorised as 'eligible candidates' for anticoagulation. Patients with high stroke risk (CHA_2DS_2-VASc $\geq$ 2) and high bleeding risk (HAS-BLED $\geq$ 3) were considered to be 'special AF populations' requiring specialist guidance (104). Furthermore, patients with a high stroke-risk and no risk factors for bleeding (i.e., CHA_2DS_2-VASc $\geq$ 2, and HAS-BLED and $HEMORR_2HAGES$ = 0) were deemed to be the 'most eligible' candidates for anticoagulant therapy.

Prior to undertaking the main study, the data collection form was pre-tested on a small sample of medical records.

3.3.3 Data analysis

The extracted data were entered into SPSS™ (Statistical Package for the Social Sciences Version 21) using descriptive and inferential statistical analysis. Categorical variables were represented as frequencies and percentages. Continuous variables were summarised using means and standard deviations (SD) for normally distributed data, or medians and interquartile ranges for non-parametric data. The Pearson Chi-square test and Fisher's exact test were used to determine the relationship between categorical variables. The univariate analysis explored the relationship between the outcome variable (use of warfarin versus NOACs) and independent variables such as individual stroke risk factors, bleeding risk factors, or medication safety and medication management issues. Further, the variables observed to have a significant association were then included in multivariate logistic regression (Forward Wald) modelling to identify factors predicting the use of therapy. A p-value of < 0.05 was considered statistically significant in all analyses.

3.4 Results

Among the 215 patients selected for review, 16 were excluded from the study (due to, missing information, miscoding of valvular atrial fibrillation patients as nonvalvular atrial fibrillation patients, records not being accessible for review at time of data collection). Finally, 199 patient medical records were included the study.

3.4.1 Patient characteristics

The mean age of patients was 73.8 (± 15.4) years. The primary diagnosis (reason for admission) for 22.1% of patients was acute AF, followed by falls (5.5% of patients), stroke or transient ischaemic attack (TIA) (4.5%), bleeding (3%), and other illnesses or surgery in the remainder.

Among all the 199 patients, most were assessed as having a high risk of stroke; 123 (61.8%) per $CHADS_2$ score and 168 (84.4%) per CHA_2DS_2-VASC score (

Table 3-1, ***Figure 3-1*** and ***Figure 3-2***). Less than one-tenth of all patients were assessed to have a high risk of bleeding; 18 (9.0%) per HAS-BLED score and 12 (6.0%) per HEMORR2HAGES score (

Table 3-1, ***Figure 3-3*** and ***Figure 3-4***). Hypertension was the most common risk factor for stroke, whilst falls risk was the most frequently documented risk factor for bleeding (

Table 3-1). Regarding other medication safety considerations, one patient was reportedly allergic to warfarin, whilst two patients were reported to be allergic to aspirin.

3.4.2 Antithrombotic therapy on admission

From the total 199 patients, 131 (65.8%) patients were using some form of antithrombotic therapy on admission to hospital, leaving one-third 68 (34.2%) on 'no therapy' (Figure 3-5). Overall, anticoagulants were most the frequently prescribed therapy (35.7%), followed by antiplatelets (30.2%). Among 71 patients prescribed an anticoagulant, 42 (59.2%) were on warfarin (± antiplatelet) comprising 39 (54.9%) using warfarin alone and 3 (4.2%) using warfarin + aspirin). The remaining 29 (40.8%) patients were using NOACs (± antiplatelet) comprising 27 (38.0%) on a NOAC alone and 2 (2.8%) on NOACs + aspirin).

3.4.3 Antithrombotic therapy utilisation at discharge

Among the 199 patients discharged from hospital, 168 (84.4%) were prescribed some form of antithrombotic therapy (

Table 3-1, ***Figure 3-5***). Patients were most frequently discharged on anticoagulants 103 (51.8%), followed by antiplatelets 65 (32.7%). Among 103 patients prescribed anticoagulants, 62 (60.2%) were prescribed warfarin (± antiplatelet) comprising 55 (53.4%) on warfarin alone and 7 (6.8%) on warfarin + antiplatelets. The remaining 41 (39.8%) patients were discharged on NOACs (± antiplatelet) comprising 37 (35.9%) on a NOAC alone and 4 (3.9%) on NOACs + antiplatelets. Among 41 patients prescribed NOACs, rivaroxaban 24 (58.5%) was the most frequently prescribed agent, followed by dabigatran 10 (24.4%), then apixaban 7 (17.1%).

3.4.4 Changes in antithrombotic therapy use from hospital admission to discharge

Overall, the utilisation of antithrombotic therapy increased at discharge compared to that observed at admission (84.4% versus 65.8%, P<0.01). Specifically, the proportion of patients prescribed warfarin (± antiplatelet therapy) significantly increased at discharge from that observed at admission (31.2% versus 21.1%, P<0.01) (Figure 3-5). Among 68 patients using 'no therapy' on admission, 40 (58.8%) were prescribed an antithrombotic prior to discharge; 18 (26.5%) received aspirin (± other antiplatelet), 9 (13.2%) received warfarin (± antiplatelet), 5 (7.4%) received (rivaroxaban), 3 (4.4%) received apixaban, 3 (4.4%) received clopidogrel, and 2 (2.9%) received dabigatran (Figure 3-5). Among 57 patients on aspirin during admission, 16 (28.1%) were switched to an anticoagulant prior to discharge; 11 (19.3%) changed to warfarin (± antiplatelet), and 5 (8.8%) to rivaroxaban (± antiplatelet).

Among the 16 patients switched to NOACs at discharge; 10 (62.5%) patients were originally on 'no therapy', 5 (31.3%) were on aspirin (± other antiplatelet), and 1(6.3%) was on warfarin. Conversely, from the 5 patients switched from NOACs to other therapies at discharge; 1 (20.0%) was changed from rivaroxaban to aspirin (due to haematuria and gastrointestinal bleeding), 1 was changed (20.0%) from apixaban

to warfarin (due to declining in renal function - estimated glomerular filtration rate (eGFR) = 12mL/min/ 1.73m2), and the reasons for three changes were not documented (2 (40.0%) patients changed from rivaroxaban to aspirin, one (20.0%) patient changed from rivaroxaban to 'no therapy').

3.4.5 Age and antithrombotic therapy utilisation at discharge

Among 104 patients aged ≥ 75 years (

Table 3-1), most patients 46.2% were discharged on anticoagulants (comprising 34 (32.7%) on warfarin and 14 (13.5%) on NOACs) and the remainder on antiplatelets 38 (36.5%) and 'no therapy' 18 (17.3%). There was no significant difference in the proportion of patients aged ≥ 75 years receiving anticoagulants (46.2%) compared to their younger counterparts (57.9%; P=0.10). When compared to their younger counterparts, a significantly lower proportion of patients aged ≥ 75 years received NOACs (13.5% versus 28.4%, P=0.01).

3.4.6 Discharge antithrombotic therapy according to stroke risk

Among patients with a high stroke risk (n=168, CHA_2DS_2–VASc ≥2), most patients 53.0% were discharged on anticoagulants (comprising 57 (33.9%) on warfarin and 32 (19.1%) on NOACs) and the remainder 56 (33.3%) patients were on antiplatelets, and 31 (18.5%) on 'no therapy' (Table 3-2 and Figure 3-2). Among 16 patients with an intermediate stroke risk, most (56.3%) were anticoagulated, comprising 6 (37.5%) on NOACs and 3 (18.8%) on warfarin. Within the low stroke risk group (n=15), two-thirds (66.7%) were either on antiplatelet therapy or 'no-therapy', whilst 5 (33.3%) were on anticoagulants (Table 3-2).

A higher (albeit not statistically significant) proportion of patients with a high stroke risk, received warfarin therapy (33.9%) compared to low-intermediate stroke risk patients (16.1%, P=0.06). Although not significant, a higher proportion of low-intermediate stroke risk patients were discharged on 'no therapy (25.8%), compared to high stroke risk patients (13.7%, P=0.09). A lower proportion of high stroke risk patients received NOACs (19.0%) compared to low-intermediate stroke risk patients (29.0%, P=0.21).

Taking into account specific stroke risk factors, a higher proportion of patients with congestive cardiac failure (CCF) received antithrombotic therapy (97.1%) compared to patients without CCF (81.7%, P=0.02). Similarly, a significantly higher proportion of patients with vascular disease received antithrombotic therapy (90.6%) compared to those without vascular disease (79.8%, P=0.03).

3.4.7 Bleeding risk and antithrombotic utilisation

The mean HEMORR2HAGES and HAS-BLED scores of the patients were 1.3 (±1.2) and 1.2 (± 0.9) respectively, representing an intermediate bleeding risk for the overall sample. Among 18 patients with a high risk of bleeding (per HAS-BLED ≥ 3), most (44.4%) were prescribed anticoagulants (comprising 7 (38.9%) on warfarin and 1 (5.6%) on a NOAC) and the remainder were discharged on antiplatelets (n=6, 33.3%), and 'no therapy' (n=4, 22.2%).

Taking into account specific bleeding risk factors, patients with anaemia were less frequently prescribed antithrombotic therapy (64.8%) compared to those without anaemia (86.1%, P=0.04). Patients with history of bleeding were less frequently prescribed antithrombotic therapy (65.0%) compared to those without a history of bleeding (86.6%, P=0.01). Patients with renal impairment were less frequently prescribed NOACs (8.9%) compared to those without renal impairment (24.0% P=0.02). Patients with cognitive impairment were less frequently discharged on warfarin (11.8%) compared to those without cognitive impairment (23.0%, P = 0.01).

3.4.8 Antithrombotic therapy based on stroke risk versus bleeding risk

Overall, 168 (84.4%) patients had a high stroke risk (per CHA_2DS_2-VASc), and were subsequently categorised as: eligible, most eligible and special AF population, based on their corresponding bleeding risk

Table 3-1 and ***Table 3-2***). Among 'eligible' patients (n=153), most (53.5%) were discharged on anticoagulants, comprising 51 (33.3%) on warfarin and 31 (20.3%) on NOACs. The remaining 71 (46.4%) patients in the 'eligible' group were not anticoagulated, consisting of 51 (33.3%) on antiplatelets and 20 (13.1%) prescribed 'no therapy'.

Among the 'most eligible' patients (n=21,

Table 3-1), 9 (42.9%) were not anticoagulated. The remaining 12 (57.1%) 'most eligible' patients were discharged on anticoagulants, comprising of 6 (28.6%) patients on warfarin and 6 (28.6%) on NOACs. Within the 'special AF' group (n=15,

Table 3-1), 8 (53.3%) patients were discharged on 'no therapy' and the remaining 7 (46.7%) were prescribed anticoagulants, consisting 6 (40.0%) patients on warfarin and 1 (6.7%) on a NOAC. No patients were categorised as having a low risk of stroke and a high risk of bleeding (Table ***3-2***).

3.4.9 Factors influencing NOACs utilisation at discharge

All the stroke risk factors, bleeding risk factors and individual patients' scores for both bleeding (HEMORR2HAGES and HAS-BLED) and stroke (CHA_2DS_2-VASc and $CHADS_2$) were included in the univariate analysis. Patients *aged ≥ 75 years* were 2.4 times less likely (OR=0.41, 95%CI=0.181 – 0.935, P=0.03) and patients with *renal impairment* were 3.6 times less likely (OR=0.28, 95%CI=0.08-0.90, P=0.03) to be prescribed NOACs (i.e., they were more likely to receive warfarin). Subsequently, both these factors were included in multivariate logistic regression (Forward-Wald) modelling. Finally, renal impairment was retained as the only predictor of NOAC use over warfarin; patients with renal impairment were 3.6 times less likely to receive NOACs; i.e., they were more likely to receive warfarin (OR=0.28, 95%CI=0.08–0.90, P=0.03, 59.8% correctly predicted; Cox and Snell R_2=0.51, Nagelkerke R_2=0.69).

3.4.10 Reasons for not prescribing anticoagulant therapy

The reasons for clinicians' treatment choices when an anticoagulant was not prescribed in high stroke risk patients were documented for 12 (6.0%, N=199) patients. In 5 cases, the patient and/or their family preferred to continue using their pre-admission aspirin and/or 'no therapy'. In 4 cases, falls risk was cited by the clinician as the reason for not prescribing an anticoagulant. In 2 cases, medication non-adherence by the patient was cited as the reason for not prescribing anticoagulants (although it was not stated whether there was an actual history of non-adherence or simply concern about the potential for non-adherence). One patient was not anticoagulated due to a history of epistaxis and haematuria (related to previous warfarin use)

3.5 What is new and conclusion

Overall in this study, 84.4% of AF patients were discharged on some type of antithrombotic therapy for stroke prevention. This is slightly less than 85% antithrombotic utilisation rate among AF patients reported in previous Australian study, prior to the PBS-listing of NOACs (17). The GLORIA AF registry reported that for the years 2008 – 2014, the utilisation of NOACs in North and South America, Asia, and Europe (23 countries) ranged from as low as 25.5% to a high of 52.4% (105) while for other studies conducted in USA, Canada, and Europe (7 countries) between 2011 - 2013 it ranged from 6.6% - 13% (97, 106, 107). Our study observed that 20.6% of patients were prescribed NOACs in a local Australian hospital setting.

This research observed that anticoagulants were the most frequently used therapy among eligible patients, prescribed in 50.3% patients. Warfarin was preferred over NOACs in at risk patients. This might be due to the recommendation in the then contemporary local clinical guideline that patients should be prescribed NOACs only if they cannot be managed well on warfarin (95). But, the current local guideline now considers NOACs as the first line of therapy (108) and this might improve in NOACs prescription in future. A systematic review on studies conducted prior to NOACs approval demonstrated that the sub-optimal use of anticoagulants in eligible patients ranges from 39% to 70% (77). Our study showed that considerable proportion, i.e., 46.4% of eligible patients were not anticoagulated despite the availability of the NOACs. These high-risk patients were either prescribed antiplatelets or ‘no therapy’. A recent randomised controlled trial, BAFTA (the Birmingham Atrial Fibrillation Treatment of the Aged Group) found that antiplatelet therapy does not offer thromboprophylactic benefit and carries a high risk of bleeding when compared to warfarin (109). Additionally, evidences show that risk benefit ratios of NOACs are far superior than antiplatelets, especially in at risk patients (110, 111). Hence current guidelines no longer recommend aspirin for stroke prevention in high risk AF population (15, 40, 112-114). Moreover, this study also observed that some of the patients were prescribed anticoagulants in combination with antiplatelet therapy, and this may be for co-existing ischaemic heart disease and related interventions (e.g., previous myocardial infarction, coronary artery disease, percutaneous coronary intervention (115, 116). However, a recent meta-analysis has reported that combination therapy does not provide

any additional stroke prevention benefit compared to anticoagulant therapy alone and increases the risk of bleeding. Hence, it is recommended that patients with AF on an anticoagulant therapy should be cautiously assessed for the indications for antiplatelet therapy (117). Previous studies (97, 118) have demonstrated that older patients with AF are less likely to be prescribed NOACs. This audit reported that renal impairment was observed as a predictor negatively influencing clinicians' choice for NOACs over warfarin therapy, and this factor might be a surrogate to old age. This is in keeping with a similar study conducted to report antithrombotic utilisation when NOACs were newly approved in the USA (119). This might be due to limited or no information regarding safety and efficacy of NOACs versus warfarin in patients with declining renal function in the "real-world" clinical practice. Two sub-group analysis of ROCKET AF and ARISTOTLE observed that both rivaroxaban and apixaban have non-inferior safety and efficacy profile when compared to warfarin in patients with mild - moderate renal impairment (120, 121). It is suggested that any anticoagulants, especially, the NOACs offer benefits in patients with high stroke and bleeding risk when compared to aspirin or 'no therapy'. Nonetheless, more information is required regarding the use of anticoagulants in patients with prior intracranial bleeding, severe renal or hepatic impairment and active malignancy (104). It is likely that NOACs prescription might improve over time with the availability of more evidence regarding their risk-benefits in patients with impaired renal function and the procedures to manage acute bleeding episodes in such patients.

Although the inclusion of NOACs has expanded the scope for prescribing prophylactic therapy in patients with AF, the complexity of decision-making for selecting among available treatment options persists. Studies have demonstrated that decision-support tools may help facilitate comprehensive and individualised risk-benefit assessment for selecting antithrombotic therapy in persons with AF, to optimise the prescription of anticoagulants in those at-risk (60, 68, 122). However, other studies have reported differences in physicians' and patients' perspectives regarding stroke risk and bleeding risk and their individual preferences for therapy (44, 123), which might not be readily addressed in such tools. Indeed, this study reports that some patients were unwilling to use warfarin, reinforcing recommendations that patients' perspectives must also be incorporated into

decision-making to obtain maximum adherence and benefit from the selected therapy (16, 58, 124)

In interpreting the findings from this study, some potential limitations need to be acknowledged. First, the data represent practice in an Australian hospital and may not be generalisable to any other settings. Second, given the retrospective nature of data collection in this study, it is possible that reasons for the treatment decisions made for these patients were not fully documented in the medical records, and therefore appropriate avoidance of certain therapies was not ascertained. Our approach may underestimate the number of people eligible for anticoagulation because the risk categories across the scores may not always be directly equivalent. For example, CHA_2DS_2-VASc=4 and HAS-BLED=4 is associated with ~5% stroke risk without anticoagulation, and ~10% major bleeding risk with anticoagulation. In this regard, our approach potentially emphasis safety (as opposed to benefit) in the decision-making equation. Furthermore, this study reflects prescribing habits in 2014, and these habits may change as prescribers become more familiar with the newer anticoagulants; for this reason, this audit should be repeated over time to identify any temporal changes in prescribing and to reflect a more contemporary utilisation of the NOACs. Finally, it was not possible to determine the level of patient engagement in the decision-making process for stroke prevention treatment selection.

Although most patients with AF are using antithrombotic therapy for stroke prevention, only half are being anticoagulated. Despite the availability of NOACs as alternatives to warfarin not all eligible patients are receiving an anticoagulant, leading to the potential underutilisation of guideline-recommended therapy. Further work is needed to map the

temporal trends in the utilisation of antithrombotics in AF and identify the factors underpinning treatment selection in this context.

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3.6 Contribution of authors

1. Ekta Y Pandya:

a. Conducting the literature search
b. Analysing the studies, and designing the structure of the manuscript
c. Writing the drafts
d. Submitting the manuscript, and coordinating with the Journal
e. Revising the manuscript as per reviewers' comments and resubmitting the manuscript.
f. Responsible for the conduct of the study in the hospital
g. Recruit and enrol patients for the study

2. Elizabeth Andersson

a. Support in the design of the study, ethics application, contribution to the intellectual content of the manuscript

3. Clara Chow

a. Support in the design of the study, ethics application, contribution to the intellectual content of the manuscript

4. Yishen Wang

a. Development of the CARAT 2.0 tool used in the study

b. Data analysis

5. Beata Bajorek

a. Conceiving and designing the study

b. Designing the CARAT 2.0 tool

c. Ethics approval for the study

d. Assistance in conducting literature search, and analysing the studies

e. Supervision in designing the structure of the manuscript

f. Ensuring the intellectual content in the manuscript

g. Writing, editing and proof-reading the manuscript

h. Assistance in addressing reviewers' and editor's comments

3.7 Supplementary material

The process of undertaking the logistic regression modelling is iterative. It inherently involves testing for collinearity as well as confounding and therefore, was not reported in the methods / results unless specifically identified. In this study, the variance inflation factor (VIF) value was low at 1.5 and tolerance was 0.8 (testing for multicollinearity), indicating that there was no correlation between the independent variables included in the model (as would be expected with the variables under exploration).

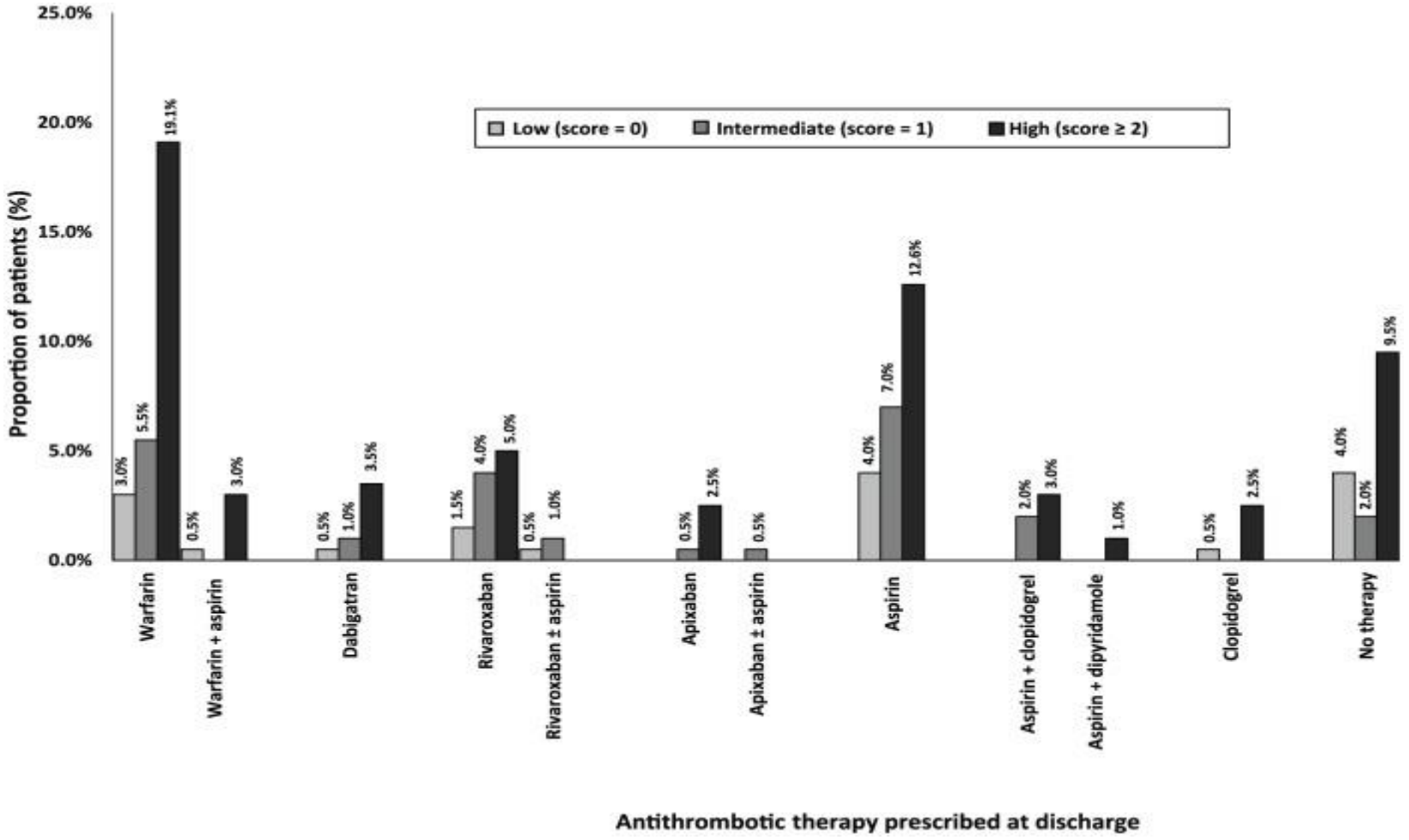

Figure 3-1. Discharge antithrombotic therapy distribution based on CHADS2 scores (N= 199)

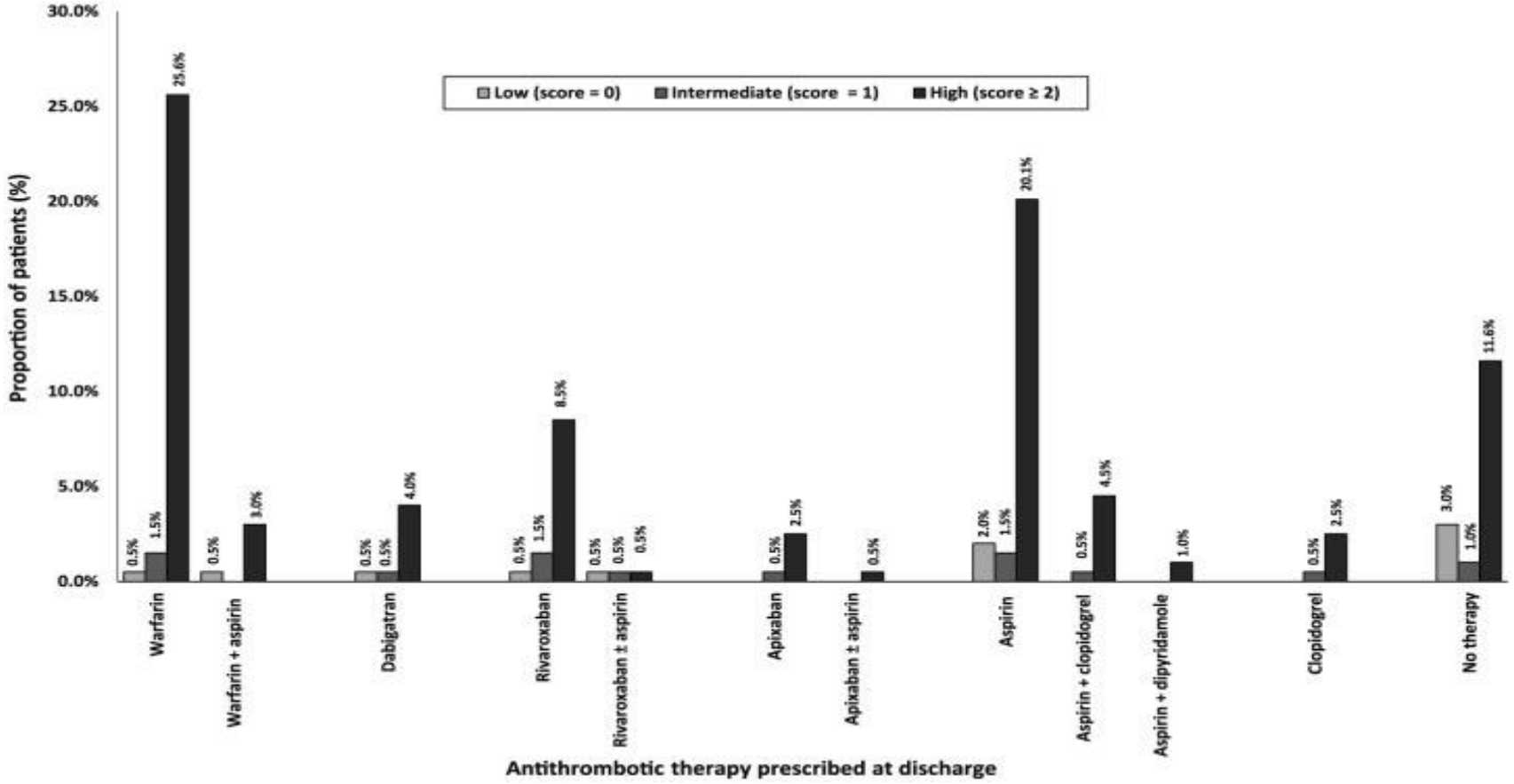

Figure 3-2: Antithrombotics utilisation at discharge according to CHA_2DS_2-VASc (N = 199).

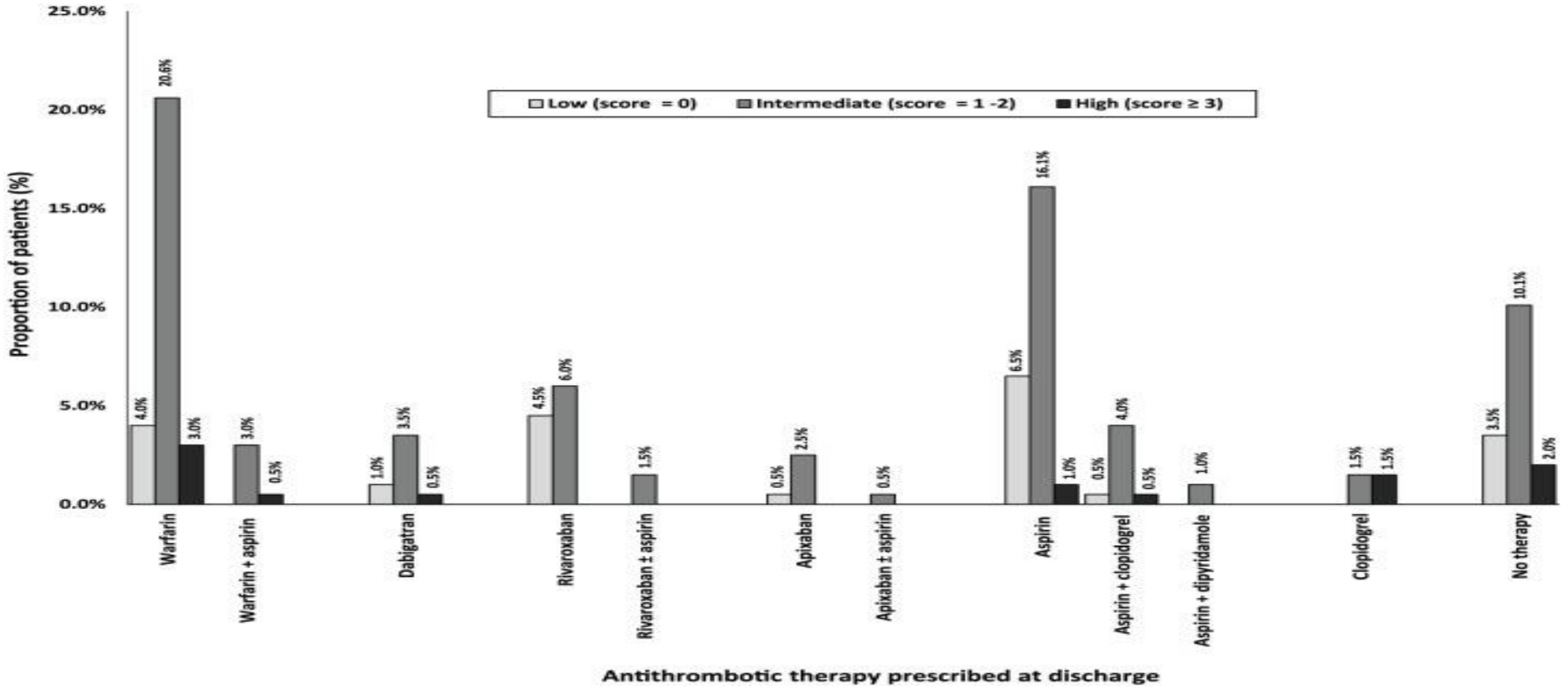

Figure 3-3. Discharge antithrombotic utilisation based on HAS-BLED scores (N = 199).

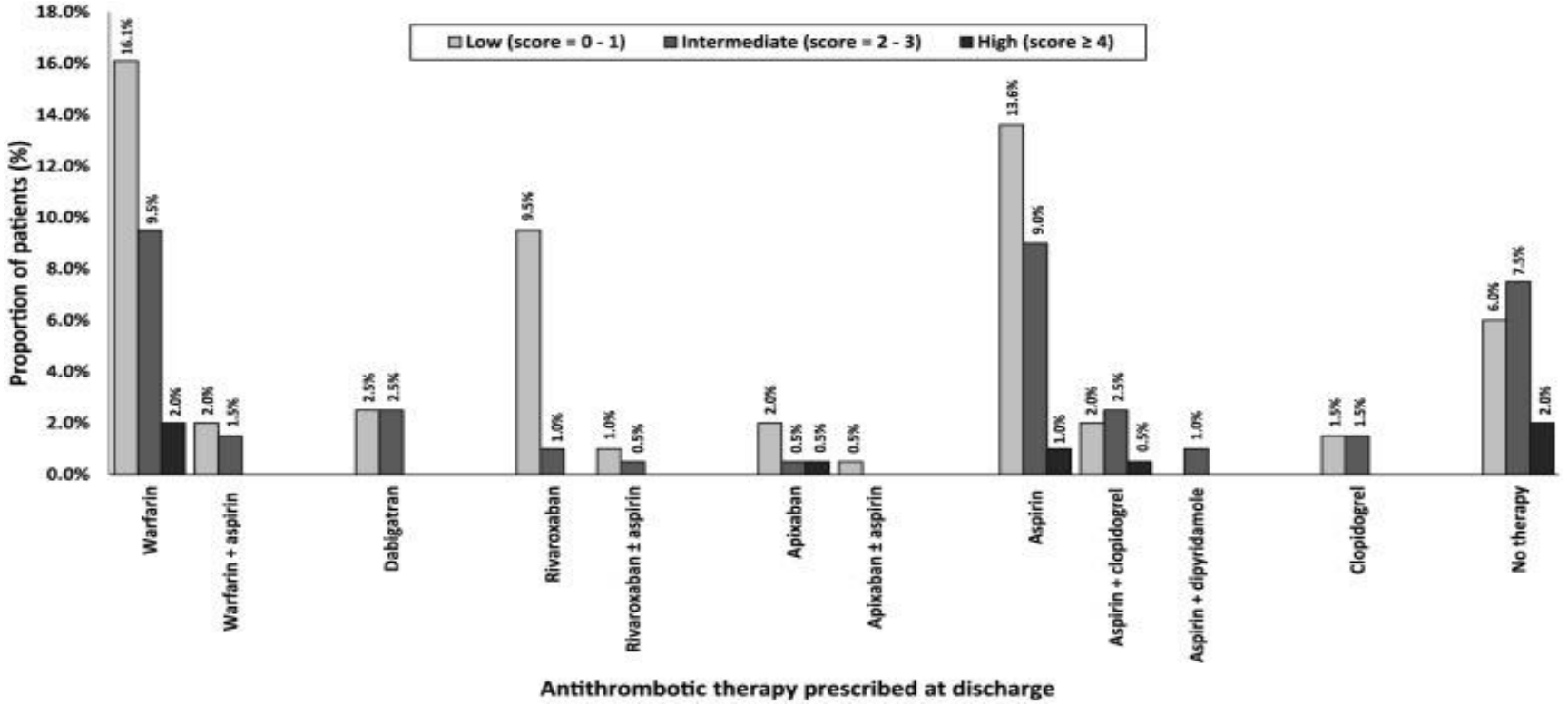

Figure 3-4. Utilisation of antithrombotic therapy based on HEMORR2HAGES scores.

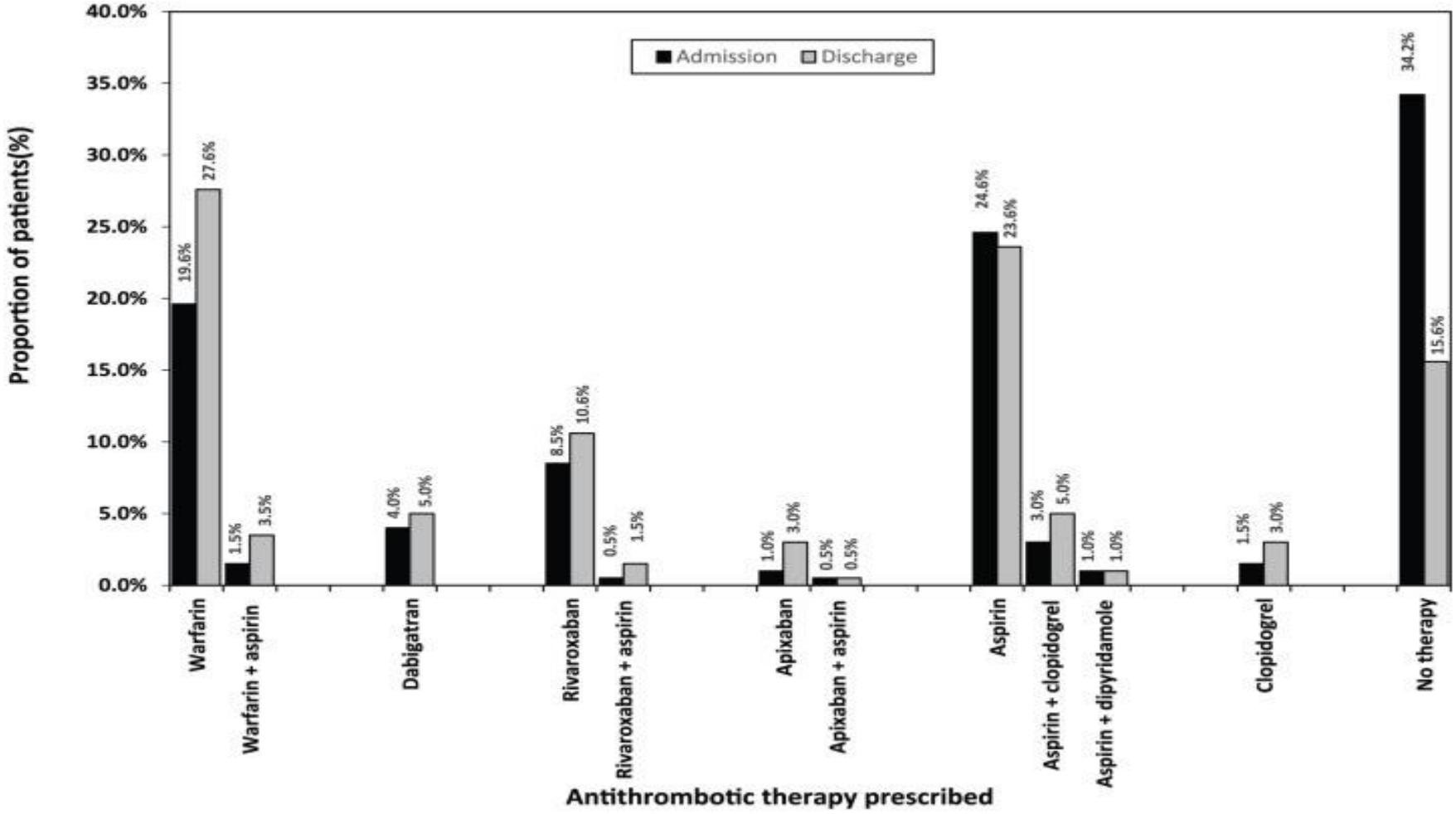

Figure 3-5. Distribution of antithrombotic therapy: Admission versus Discharge (N = 199)

Table 3-1. Distribution of antithrombotic therapy at hospital discharge according to patient characteristics

Patient Characteristics (% of total, N=199)	**Warfarin ± Antiplatelets**	**NOACs ± Antiplatelets**	**Antiplatelet ± Other Antiplatelet**	**No therapy**	**Total (N = 199)**
Total n (%)	62 (31.2%)	41 (20.6%)	65 (32.7%)	31 (15.6%)	199 (100%)
Age group					
<65years	12 (6.0%)	14 (7.0%)	13 (6.5%)	10 (5.0%)	49 (24.6%)
65-74 years	16 (8.0%)	13 (6.5%)	15 (7.5%)	3 (1.5%)	46 (23.1%)
≥ 75 years	34 (17.1%)	14 (7.0%)	38 (19.1%)	18 (9.0%)	104 (52.2%)
Gender					
Male	33 (16.6%)	26 (13.1%)	34 (17.1%)	15 (7.5%)	108 (54.3%)
Female	29 (14.6%)	15 (7.5%)	31 (15.6%)	16 (8.0%)	91 (45.7%)
Congestive Cardiac Failure	15 (7.5%)	4 (2.0%)	15 (7.5%)	1 (0.5%)	35 (17.6%)
Hypertension	41 (20.6%)	29 (14.6%)	41 (20.6%)	20 (10.1%)	
Diabetes Mellitus	22 (11.05%)	11 (5.5%)	15 (7.5%)		

History of stroke/TIA	13 (6.5%)	6 (3.0%)	15 (7.5%)	6 (3.0%)	131 (65.8%)
Thromboembolic diseases	7 (3.5%)	2 (1.0%)	5 (2.5%)	6 (3.0%)	54 (27.1%)
Vascular diseases	29 (14.57%)	14 (7.0%)	34 (17.08%)	6 (3.0%)	37 (18.6%)
				8 (3.0%)	20 (10.1%)
					85 (42.7%)
<u>$CHADS_2$</u>					
High (Score ≥ 2)	44 (22.1%)	22 (11.1%)	38 (19.1%)	19 (9.5%)	123 (61.8%)
Intermediate (Score = 1)	11(5.5%)	14 (7.0%)	18 (9.0%)	4 (2.0%)	47 (23.5%)
Low (Score = 0)	7 (3.5%)	5 (2.5%)	9 (4.5%)	8 (4.0%)	29 (14.5%)
<u>CHA_2DS_2-VASc</u>					
High (Score ≥ 2)	57 (28.6%)	32 (16.1%)	56 (28.1%)	23 (11.5%)	168 (84.3%)
Intermediate (Score = 1)	3 (1.5%)	6 (3.0%)	5 (2.5%)	2 (1.0%)	16 (8.0%)
Low (Score = 0)	2 (1.0%)	3 (1.5%)	4 (2.0%)	6 (3.0%)	

					15 (7.5%)
Cognitive impairment	4 (2.0%)	3 (1.5%)	18 (9.0%)	9 (4.5%)	34
Uncontrolled hypertension	1 (0.5%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	(17.0%)
Low platelet	2 (1.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	5 (2.5%)
Anaemia	4 (2.0%)	1 (0.5%)	8 (4.0%)	6 (3.0%)	4 (2.0%)
Ethanol abuse	2 (0.5%)	2 (1.0%)	3 (1.5%)	2 (1.0%)	19 (9.5%)
Re-bleeding risk	5 (2.5%)	2 (1.0%)	6 (3.0%)	7 (3.5%)	9 (4.5%)
Excessive falls risk	10 (5.0%)	5 (2.5%)	15 (7.5%)	8 (4.0%)	20
Hepatic impairment	2 (1.0%)	1 (0.5%)	1 (0.5%)	4 (2.0%)	(10.0%)
Renal impairment	17 (8.5%)	4 (2.0%)	15 (7.5%)	9 (4.5%)	38
Malignancy	5 (2.5%)	1 (0.5%)	3 (1.5%)	3 (1.5%)	(19.0%)
Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs)	10 (5.0%)	4 (2.0%)	14 (7.0%)	0 (0.0%)	8 (4.0%)
					45
					(22.5%)
					12 (6.0%)
					28
					(14.0%)

HAS-BLED					
Low (Score = 0)	8 (4.0%)	12 (6.0%)	14 (7.0%)	7 (3.5%)	41 (20.5%)
Intermediate (Score 1 – 2)	47 (23.6%)	28 (14.1%)	45 (22.6%)	20 (10.1%)	140 (70.4%)
High (Score ≥ 3)	7 (3.5%)	1 (0.5%)	6 (3.0%)	4 (2.0%)	18 (9.0%)
HEMORR2HAGES					
Low (Score = 0 - 1)	36 (18.1%)	31 (15.5%)	34 (17.1%)	12 (6.0%)	113 (56.7%)
Intermediate (Score = 2 – 3)	22 (11.1%)	9 (4.5%)	28 (14.1%)	15 (7.5%)	74 (37.2%)
High (Score ≥ 4)	4 (2.0%)	1 (0.5%)	3 (1.5%)	4 (2.0%)	12 (6.0%)
Eligible Patients (i.e. CHA_2DS_2 – VASc = High and HAS-BLED = Low – Intermediate)	51 (25.6%)	31 (15.6%)	51 (25.6%)	20 (10.0%)	153 (76.8%)
Most-eligible patients (i.e. CHA_2DS_2 – VASc ≥ 2, HAS-BLED and $HEMORR_2HAGES$ = 0)	6 (3.0%)	6 (3.0%)	7 (3.5%)	2 (1.0%)	21 (10.6%)
Special AF population	6 (3.0%)	1 (0.5%)	5 (2.5%)	3 (1.5%)	15 (7.5%)

(i.e. CHA_2DS_2 – VASc = High and HAS-BLED = High)					

TIA= transient ischaemic attack; NSAIDs= nonsteroidal anti-inflammatory drugs

Uncontrolled hypertension defined as “systolic blood pressure (SBP) >160 mm Hg”.

Renal impairment defined as “the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200µmol/L”.

Hepatic Impairment defined as “chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 times ULN, in association with AST/ALT/Alkaline phosphatase > 3 times ULM.”

Table 3-2. Antithrombotic utilisation according to patient stroke risk (CHA_2DS_2-VASc) versus bleeding risk (HAS-BLED)

CHA_2DS_2-VASc	**HAS-BLED**	**No therapy**	**Warfarin ± Antiplatelets**	**NOACs ± Antiplatelets**	**Antiplatelets ± Other antiplatelets**	**Total (N = 199)**
Low	Low	4 (2.0%)	1 (0.5%)	2 (1.0%)	4 (2.0%)	11 (5.5%)
	Intermediate	2 (1.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	4 (2.0%)
Total	High	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	15 (7.5%)					
Intermediate	Low	1 (0.5%)	1 (0.5%)	4 (2.0%)	3 (1.5%)	9 (4.5%)
	Intermediate	0 (0.0%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	4 (2.0%)
Total	High	1 (0.5%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	3 (1.5%)
	16 (8.0%)					
High	Low	2 (1.0%)	6 (3.0%)	6 (3.0%)	7 (3.5%)	21 (10.6%)
	Intermediate	18 (9.0%)	45 (22.6%)	25 (12.6%)	44 (22.1%)	132 (6.6%)
Total	High	3 (1.5%)	6 (3.0%)	1 (0.5%)	5 (2.5%)	15 (7.5%)
	168 (84.4%)					
Total		31 (15.6%)	62 (31.2%)	41 (20.6%)	65 (32.7%)	199 (100%)

NOACs: Non-vitamin K antagonist oral anticoagulants

HAS-BLED: Low (Score = 0); Intermediate (Score = 1 – 2); High (Score ≥ 3)

CHA_2DS_2-VASc: Low (Score = 0); Intermediate (Score = 1); High (Score ≥ 2)

4 Patients' Perspective On Anticoagulant Therapy

Title: Factors affecting patients' perspectives on and adherence to anticoagulant therapy: anticipating the role of direct oral anticoagulants (DOACs)

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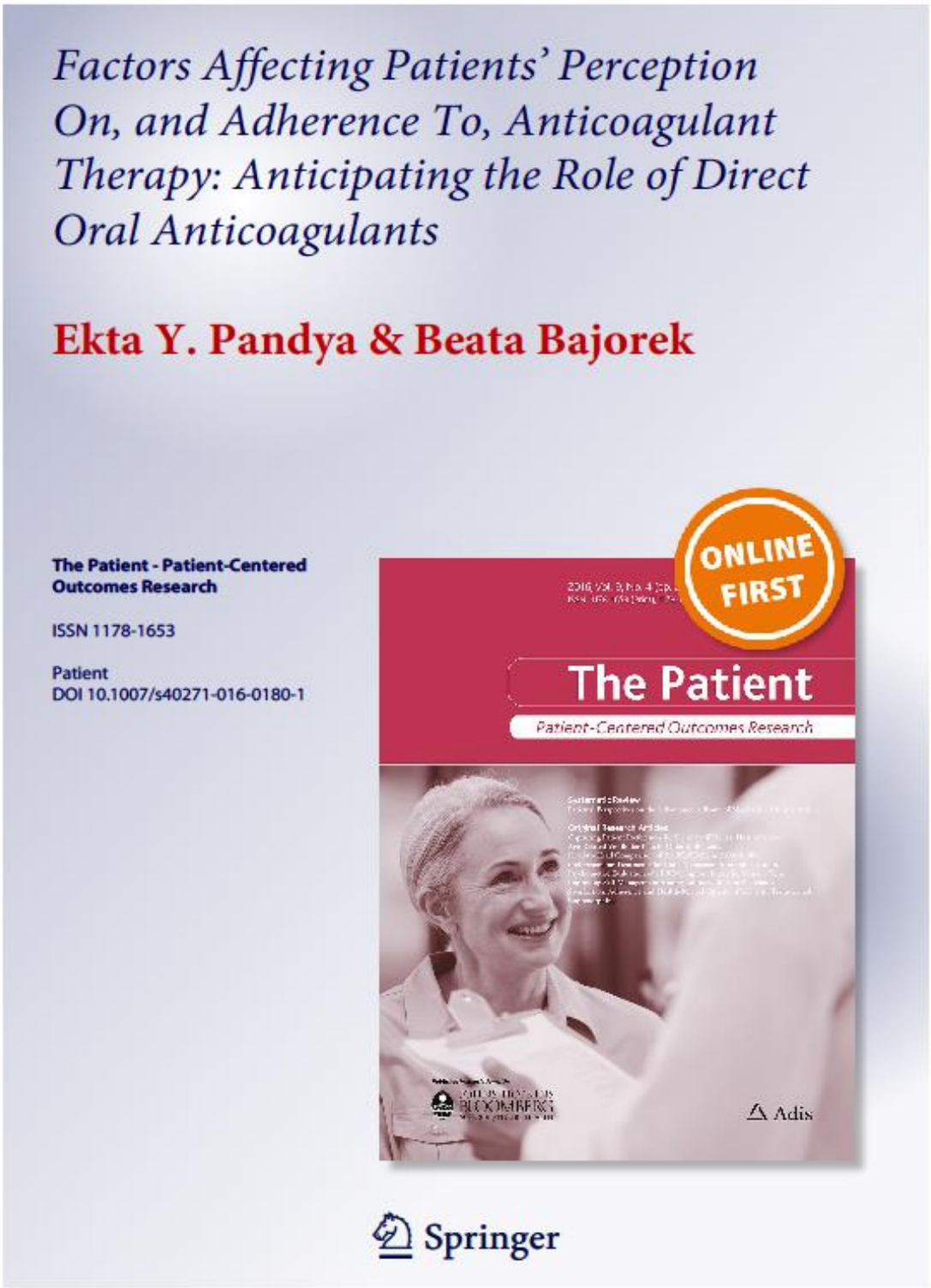

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4.1 Abstract

The role of the direct oral anticoagulants (DOACs) in practice has been given extensive consideration recently, albeit largely from the clinician's perspective. However, the effectiveness and safety of using anticoagulants is highly dependent on the patient's ability to manage and take these complex, high-risk medicines. This structured narrative review explores the published literature to identify the factors underpinning patients' nonadherence to anticoagulants in atrial fibrillation (AF), and subsequently contemplates to what extent the DOACs might overcome the known challenges with traditional warfarin therapy. This review comprised a two-tier search of various databases and search platforms (CINAHL, Cochrane, Current Contents Connect, EMBASE, Medline-Ovid, EBSCO, PubMed, Google, Google Scholar) to yield 48 articles reporting 'patients' perspectives' on, and 'patients' adherence' to, anticoagulant therapy. The findings from the literature were synthesised under five interacting dimensions of adherence: Therapy-related factors, Patient-related factors, Condition-related factors, Social-economic factors and Health-system factors. Factors negatively affecting patients' day-to-day lives (especially regular therapeutic drug monitoring, dose adjustments, dietary considerations) predominantly underpin a patient's reluctance to take warfarin therapy, leading to nonadherence. Other patient-related factors underpinning nonadherence include their: perceptions and knowledge about the purpose of anticoagulation; understanding - of the risks: benefits of therapy; socioeconomic status; and expectations of care from health professionals. In considering these findings, it is apparent that the DOACs may overcome some of the barriers to traditional warfarin therapy at least to an extent, particularly the need for regular monitoring, frequent dose adjustment, and dietary considerations. However, their high cost, twice daily dosing, and gastrointestinal side effects may present additional challenges for patients and health-systems. The review highlights the need to explicitly incorporate patients' perspectives

in decision-making processes for anticoagulant selection, to obtain optimum adherence and treatment outcomes. Further studies should explore resources that can better engage patients in decision-making around the selection of anticoagulant therapy.

Key points for decision-makers

- From the patients' perspective preference for, and adherence to, anticoagulant therapy is primarily based on the extent to which the treatment options affect their day-to-day activities
- For traditional warfarin therapy, the need for regular monitoring, frequent dosage changes and dietary considerations are key challenges for patients, but these can be overcome (to at least some extent) by the use of the newer DOACs
- As is the case for warfarin, factors such as forgetfulness, perceptions of stroke and bleeding risk, condition-related factors, social and economic situation, and health-system constrains, may negatively influence patients' adherence to DOACs
- DOACs may not be the preferred therapies in all patients; major deterrents to the use of these newer agents include the absence of specific antidotes, high out-of-pocket cost, frequency of dosing and specific side-effects

4.2 Introduction

For decades, warfarin has been the mainstay of stroke prevention therapy in patients with atrial fibrillation (AF) (6). Unfortunately, the efficacy of this anticoagulant is somewhat overshadowed by its narrow therapeutic index and variable dose-response relationship, necessitating regular International Normalized Ratio (INR) monitoring and making its management relatively complex. Not surprisingly, many studies have reported patients' nonadherence to warfarin (125-127), thereby compromising its risk (bleeding) versus benefit (prevention of stroke) ratio (128).

The search for alternatives to warfarin has recently yielded a new class of agents, the direct oral anticoagulants (DOACs), which offer comparable risk and benefit profiles to traditional warfarin therapy (79-81). These agents do possess some key pharmacological and practical differences to warfarin, offering particular advantages from the clinician's point of view (28, 129). However, evidence-based guidelines recommend that patients' perspectives and preferences are incorporated in the decision-making around long-term anticoagulation (16, 130), in order to facilitate treatment adherence (71, 131). Therefore, the aim of this review was to explore the factors underpinning patients' acceptance of, and decision to use, anticoagulant therapy. Specifically, the objectives were to: 1) review patients' perspectives and attitudes toward warfarin therapy, and their impact on medication adherence; and 2) to determine the scope of using DOACs in practice, in terms of the extent to which these agents address the challenges and difficulties experienced by patients taking conventional warfarin therapy in AF including those factors affecting medication adherence and acceptance of treatment. The findings were synthesised and presented using a framework depicting the five interacting dimensions of adherence: 1) Therapy-related factors, 2) Patient-related factors, 3) Condition-related factors, 4) Social-economic factors and 5) Health-system factors (132) (Table 4-1).

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4.3 Method

A structured search was conducted to retrieve articles (e.g. original research papers, reviews, reports, grey literature) relevant to the stated objectives. The reference lists of articles were reviewed to identify additional literature. Only articles in the English language were included.

4.3.1 Data sources used

Online databases (i.e., CINAHL, Cochrane, Current Contents Connect, EMBASE, Medline Ovid, EBSCO and PubMed), and the search platforms (Google and Google Scholar) were used to source relevant literature.

4.3.2 Search strategy

A two-phase literature search (Part 1 & 2) was conducted relating to objectives 1 and 2, respectively (Supplementary material). In Part 1, literature broadly pertaining to patients' perspectives on anticoagulation in AF was sourced. The search employed the MeSH (medical subject heading) terms – atrial fibrillation (AF), anticoagulation, antithrombotic, warfarin, stroke - combined with specific terms: patients',' perspective, preferences, satisfaction, perception, quality of life, attitude, views, feedback, barriers, challenges, choices, adherence, and compliance. In Part 2, literature focusing on the DOACs was identified using the search terms - dabigatran, rivaroxaban, apixaban, new and novel oral anticoagulants, NOACs - combined with patients' perspective, preference, satisfaction, perception, attitude, views, feedback, barriers, challenges, choices, adherence and compliance. Additionally, the reference lists of the collected articles were reviewed to retrieve other important and relevant studies.

For the purposes of this review, the terms 'adherence' and 'compliance' were considered as being interchangeable. In the selected studies various methods were used to report patients' adherence to therapy, including blood tests (i.e. INR readings) (126, 133, 134), medication event monitoring systems (MEMS) (125, 135, 136), the Morisky Medication Adherence Scale - 4 (MMAS-4) (134) and prescription refill data (137, 138). Some studies also used the patient's ability to follow medication instructions and attend follow-up appointments as a measure of adherence (126, 133, 139). In the absence of a standard measure of medication adherence, all studies describing patients' adherence to anticoagulants, regardless of methods used, were considered (140, 141).

4.3.3 Data analysis

This narrative review focused on providing decision-makers with objective (142), important up-to-date information (143, 144), and a broader perspective (145) on patients' outlook regarding anticoagulation in AF. The interpretive synthesis method was adopted to conceptualize issues pertinent to patients' adherence to anticoagulant therapy (146). To assist the extraction and organization of the date, and increase the transparency of data synthesized, tables were prepared (Table 4-2, Table 4-3, and Table 4-4), categorizing information (142) according to factors impacting underpinning patient's perception and adherence to anticoagulant therapy, e.g., patients' lifestyle, socio-economic status, functional ability, knowledge about AF and relationship to stroke, risk and benefits of being on anticoagulation, the experience of having a stroke or bleeding event, and healthcare support (147).

4.4 Results

A total of 48 articles were included in the review and among these ten studies specifically compared patients' preference for, and adherence to, warfarin versus DOACs (Figure 4-1).

4.4.1 Therapy-related factors

Among the five dimensions of adherence, therapy-related factors appear to have the greatest influence on patients' perspectives on, and adherence to, warfarin. Specifically, the complexities of warfarin therapy (i.e. aspects of its practical day-to-day management) appear to negatively influence patients' lifestyles and overall quality of life. Up to two-thirds of patients (11% to 67%) experience restrictions to their daily life activities due to being on warfarin therapy (148-154). A cross-sectional study was conducted in an outpatient anticoagulation clinic in Brazil to assess the quality of life of patients on chronic anticoagulant treatment (72.2% of patients were on warfarin). Using the Duke Anticoagulation Satisfaction Scale (DASS) and SF36 analysis, the inconvenience associated with day-to-day management of warfarin therapy, and compromises to social life, had the most negative impact on patients' quality of life, compared to other factors (i.e., performance of physical activities, physical appearance, pain, overall health status, vitality, emotional and mental status) (155). Collectively, the literature highlights that among the various aspects of therapy management, the three major challenges in using warfarin are the need for regular INR monitoring, followed by frequent dose-adjustments and dietary vitamin K consideration. To a lesser extent, drug-drug interactions are also observed as an issue for patients using warfarin.

4.4.1.1 Therapeutic drug monitoring and accompanying dose-adjustment

More than three quarters of studies have cited regular INR monitoring as the key difficulty for patients taking warfarin (71, 128, 148-151, 153, 154, 156-159). In particular, the frequency of blood testing is negatively perceived by patients and serves as a major deterrent to warfarin use. In a survey of 60 patients (aged 26-88 years) attending anticoagulation clinics in the UK, USA and Spain, 95% of those who required a blood test at least once per month felt more inconvenienced than those patients visiting the clinic less frequently (149). Least keen on regular INR testing are patients who are socially and professionally active, and those who travel frequently, ultimately translating to younger patients being more challenged by the need to regularly attend monitoring appointments compared to older patients (148-150). Indeed, a retrospective longitudinal matched cohort study in the USA reported that younger patients were more likely to be nonadherent to monitoring requirements compared to their older counterparts (128).

Aside from its role in therapeutic monitoring, INR testing also serves as a tool to ascertain patients' adherence to therapy. However, patients can be nonadherent to the monitoring requirements in the same way that they can be nonadherent to the therapy (medication-taking) itself. A cross-sectional survey of 204 patients attending an outpatient clinic in Seoul identified that patients who were nonadherent to their medication were also generally more likely to miss their monitoring appointments (7.3% versus 14.4%). Additionally, 84.1% of patients studied had poor knowledge regarding their target INR range (133).

Regular INR testing does polarise patients' perspectives, changing according to whether they are relatively new warfarin users or long-term users. Those using warfarin therapy over the long-

term tend to become accustomed to the need for monitoring, feeling more reassured about the treatment and their overall health management through the testing (149). Also, it is important to note that tests such as dilute thrombin time and ecarin-based assays to effectively quantify the levels of dabigatran, and anti-activated factor X (anti-Xa) assay test is for rivaroxaban and apixaban levels are not easily accessible. In the European Patient Survey in Atrial Fibrillation (EUPS-AF), 13% of patients wanted to know their anticoagulation status and were uncomfortable about the prospect of reduced or no monitoring with the use of alternative therapies (i.e. DOACs) (149). A survey of 290 patients (age = 25 – 94 years), conducted in both metropolitan and rural settings in Australia, reported that the absence of regular monitoring was a major deterrent to switching from warfarin to DOACs in 28% of patients (159).

Hand-in-hand with the need for regular monitoring is the need for dosage adjustment in warfarin therapy. The proportion of patients adversely affected by this specific aspect of management ranges from as low as 9% to as high as 55% (126, 127, 133, 148, 150, 151, 154, 156, 160, 161). Besides the confusion surrounding the dose-adjustments, miscommunication of instructions about dosage adjustment between patients and healthcare professionals has also been cited as a key problem for patients. In a survey of 500 AF patients (mean age = 57.93 years) in the USA, among the one-third of patients expressing difficulties in managing warfarin, 57% reported problems with dose adjustments (154). A study conducted at a family practice clinic in Canada highlighted that older patients (aged ≥ 65 years) with multiple co-morbidities (accompanied by polypharmacy) particularly struggled to manage warfarin dosage adjustments (71).

Difficulties in receiving dosage instructions over the telephone are associated with patients' nonadherence to prescribed doses, as reported in a cross-sectional study of elderly patients (age ≥ 80 years) attending an outpatient anticoagulation clinic in Ireland (151). An inability to

manage dosage adjustments is linked to treatment nonadherence, and subsequently reflected in INR test results (133). Following from this, a study conducted at an outpatient anticoagulation monitoring centre in the USA showed that nonadherence contributed to 36% of out-of-range INRs, of which 9% stemmed from patients' misunderstanding about dosage instructions obtained over the telephone (126).

The complex pharmacological properties of warfarin mandate the need for routine therapeutic drug monitoring and associated dosage adjustments to ensure a favourable risk/ benefit ratio. When comparing warfarin to the DOACs, it is clear that the DOACs' more predictable pharmacokinetic and pharmacodynamic properties may offer some practical advantages, such that they neither require regular monitoring nor frequent dose adjustment (28, 162). NOACs also require testing but not as frequently as warfarin. Measurement of coagulation parameters is necessary in certain situations, such as emergency surgery or other invasive procedures, haemorrhagic events, suspected overdose, acute thrombosis in renal, liver or heart failure, potential drug-drug interactions, trauma, acute medical disease and malignancy (25). Additional monitoring is required in the form of renal function tests (every 6 to 12 months) for those patients above 75 years of age, or those who have mild and moderate renal failure, and doses selected accordingly (163, 164).

Dosage adjustments are recognised as a necessary part of warfarin management (156). The DOACs do relieve patients from the burden of frequent drug monitoring and dose adjustments required with warfarin, swaying patients' preferences toward this treatment (90, 156). A survey involving 1,507 patients (mean age = 70.1 years) from France, Germany, Italy, Spain, and UK reported that among the 1,138 patients receiving anticoagulation for AF, 626 (55%) patients were positive about the fixed daily dose of DOACs, which would render the therapy

management more convenient and less complicated. However, another 161 (14.1%) patients were concerned about the absence of dose-adjustments with the DOACs. Overall, although patients perceived the fixed daily dosing to be more convenient, some felt that this compromised the safety or effectiveness of the therapy (due to lack of dose tailoring) (156). The dosing options are fewer for the DOACs. For example, the dose approved for stroke prevention in AF is 150 mg twice daily and 110 mg twice daily (Europe and elsewhere), or 150 mg twice daily and 75 mg twice daily (USA) (40, 112).

4.4.1.2 Dietary consideration

Among the aspects of daily living that are impacted by the use of anticoagulants, dietary considerations and perceived food restrictions rank highly, with the proportion of patients affected by it as high as 73% across studies (126, 133, 148-150, 154, 156). A number of issues are intertwined here, such as what constitutes the patient's normal diet (particularly in certain ethno-cultural group), the practicalities of maintaining a diet that is balanced in terms of vitamin K intake, as well as patients' poor knowledge about the relationship between warfarin use and diet (126, 133, 148-150, 154, 165). In a study involving 204 patients attending an outpatient clinic in Korea, nonadherent patients were unable to manage their daily dietary intake of vitamin K due to poor knowledge regarding warfarin-food interactions (133). This is reinforced by the findings of an audit conducted at an anticoagulation service in the USA (N= 374 patients) which found that 18% of out-of-range INR results were due to inconsistencies in daily dietary vitamin K consumption (126).

The DOACs appear to have no specific interactions with food, such that there are no implications on a patient's daily diet (16). Indeed, an observational prospective study in a pharmacist-

managed outpatient anticoagulation clinic in the USA (N= 260) reported that perceived dietary freedom was the major reason behind the willingness of over half (52.1%) of the patients to switch from warfarin to dabigatran (DOAC), noting that the daily dietary items reportedly consumed by most of these patients were rich in vitamin K (90, 166). The only extent to which food/ diet impacts on the use of DOACs relates to 1) dose absorption properties (e.g. rivaroxaban 15mg and 20mg doses should be taken with food to improve its absorption and overall bioavailability) (16, 167), and 2) minimization of gastrointestinal side effects (e.g. dabigatran should be taken with food to avoid dyspepsia) (94). In this regard, there is potential for some degree of nonadherence in those patients who are unable to coordinate their meals with the timing of doses, leading to suboptimal anticoagulation and or side-effects that may lead to nonadherence (168-171). Overall, the DOACs appear to present a key advantage over warfarin in this regard, overcoming major obstacles in activities of daily living.

4.4.1.3 Drug-drug interactions

The proportion of patients challenged by warfarin-drug interactions ranges from 8% - 50%, reportedly highest in patients on medications that interact with warfarin (prescription medication or over-the-counter medication) (126, 149-151, 165, 172). A cross-sectional survey conducted at a university affiliated out-patient clinic in Korea (N = 204, mean age = 51.94 ± 11.64 years) reported among patients deemed to be nonadherent, a lower proportion of patients (5.5%) were able to take the dose at the fixed time, when compared to adherent patients (14.4%) (133). In fact, a qualitative study conducted in the UK, USA and Spain identified that 50% of patients were unhappy about the lack of freedom to self-medicate with over-the-counter medications, and were anxious about the possibility of bleeding that might result from warfarin's interaction with over-the-counter medications (149). Similarly, a cross-sectional study assessing patients' quality of life using DASS and SF36 tools, found that patients on concomitant medication that increased anticoagulation effects (increasing the risk of a bleeding event) had a lower quality of life than those taking medication that decreased the anticoagulation effect (i.e. lower the risk of bleeding) (155). Suboptimal patient counselling regarding warfarin-drug interactions by

healthcare professionals has also contributed toward patients' discontent and anxiety about being on warfarin (regardless of whether patients' have experienced drug-drug interactions or not) (172).

The DOACs, especially dabigatran, have relatively low potential for drug-drug interactions compared to warfarin, given that dabigatran is not metabolized by CYP enzymes (163). Nevertheless, there are notable drug-drug interactions observed with DOACs, including with drugs that are commonly used in the treatment of AF (e.g., verapamil, quinidine, digoxin) (16, 163), and complementary medicines such as St. John's Wort (173, 174). At present, the number of drugs identified as interacting with DOACs is relatively short compared to warfarin. In this regard, the DOACs may be more advantageous for patients using extensive polypharmacy and/ or frequently changing medication regimens. Drug interactions remain a potential risk with the use of DOACs, anxieties around this may be heightened by the unavailability of efficient and/or reliable techniques for therapeutic monitoring of drug levels and/ or effects on coagulation. It should be noted, however, that a potential antidote for dabigatran (i.e., a reversal agent) has only recently been approved by the US FDA and EU regulatory bodies. As antidotes for rivaroxaban and apixaban are still under trial (160, 175, 176). The heightened concerns about the unavailability of antidotes may reduce over time as reversal agents become progressively available.

4.4.1.4 Drug-alcohol interactions

To a lesser extent, alcohol intake is a concern for some patients and is linked to dietary and social aspects of living. In part, this is due to a lack of patients' understanding about the relationship between alcohol intake and warfarin, which in turn influences their willingness to limit their alcohol intake. Across four studies, the proportion of patients' restricting their alcohol intake due to warfarin use ranged from 5% to 40% (71, 149, 151, 177). A semi-qualitative study conducted in an outpatient clinic in the UK (N=81, median age= 81 years) reported that 11% of patients declined warfarin as they could not commit to the required daily alcohol intake restriction (177). Although statistically insignificant, a cross-sectional study involving 204 patients (mean ± standard deviation age 59.14 ± 11.64 years) conducted in a Korean a university-

affiliated hospital, non-adherent patients were less able to limit their alcohol intake than adherent patients (36.3 vs. 18.2%; P = 0.14) (133).

Similarly, in the case of DOACs, a retrospective cohort study conducted at the Veterans Health Administration in the USA (N = 5,376) found that nonadherent patients were more likely to indulge in unregulated alcohol consumption compared to adherent patients (11.8% versus 15.5%, P < 0.001) (178). Although DOACs are affected by alcohol to a lesser extent than warfarin, the issue of alcohol intake broadly affects all anticoagulants. Binge drinking is to be avoided even with DOACs due to the risk of hepatic impairment and subsequent impact on the drug metabolism (179-181). Regulating daily alcohol intake is an integral part of anticoagulation management, whether the patient is on warfarin or a DOAC.

3.1.5 *Restricted physical activity*

The inherent risk of bleeding with warfarin may restrict patients in terms of engaging in physical activities, such as sports or gardening, where there is an increased risk of injury and accident. Studies have found that patients feel that being on warfarin deprives them of recreational activities (149, 152, 153, 165). A case-control study conducted at the Massachusetts General Hospital in USA found that restriction of physical activities was a key perceived barrier, moreso among nonadherent patients compared to adherent patients (30% versus 15%, P = 0.03). However, it is important to note that most of the nonadherent patients were relatively younger (age < 53 years) than most warfarin users (153). Just as for warfarin, patients on DOACs are advised to be cautious while undertaking any physical activities that involve a high risk for injury due to the potential for bleeding (57, 182-184).

4.4.1.5 Pill-burden

The reason that pill-burden has not been reported in the literature as an issue by warfarinsed patients might be attributed to its once daily dosing, unlike the case for dabigatran and apixaban (twice daily dosing). A study conducted in Canada involving non-AF patients (mimicking newly diagnosed AF) reported that the vast majority (82.9%) of patients preferred warfarin over dabigatran. Among those preferring warfarin, 74.3% of patients stated that its once daily dosing was more convenient than the twice daily dosing of dabigatran (185). Similarly, a majority (80.7%) of patients who participated in the European Patient Survey in Atrial Fibrillation (EUPS-AF) also preferred an antithrombotic with a once daily dose (156). Hence, the issue of pill-burden may be more challenging for some patients on DOACs (dabigatran and apixaban) compared to patients on warfarin.

4.4.2 Patient-related factors

Various patient-related factors influence adherence to warfarin therapy and predominantly relate to the patients' cognition. This includes aspects of cognitive functioning (e.g., memory), as well as understanding and perceptions about the treatment.

4.4.2.1 Memory capacity

Approximately one-fifth of the studies have reported that patients more often miss taking their daily dose of warfarin, and in some cases take extra doses of warfarin (126, 133, 134, 148, 160, 186). Three studies have reported that forgetfulness is the most common reason for missed warfarin doses, reported in 9.7% to 51% of cases (133, 148, 186). A survey conducted in two anticoagulation clinics in Italy found that 50% of patients were worried about their tendency to miss daily warfarin doses (148). Although statistically insignificant, a cross-sectional survey of

204 patients visiting an outpatient clinic in Korea reported that more patients who were nonadherent were less able to take the recommended daily dose of warfarin at fixed times than adherent patients (14.4 vs. 5.5%; P = 0.082) (133).

Patients using either warfarin or DOACs are equally likely to forget to take their daily dose. However, the risk of suffering a stroke (due to missed doses) is potentially higher with dabigatran and apixaban compared to warfarin due to their relative shorter half-lives (28). This was highlighted in a retrospective cohort study conducted at the Veterans Health Administration in the USA (5376 patients, mean age = 71.3 ± 9.7 years), which reported that a decrease in dabigatran adherence by 10% (measured as proportion of days covered (PDC): number of non-hospitalized out-patient days in which dabigatran was supplied divided by the observation time interval) increased the hazard of both stroke and all-cause mortality by 13% (*HR 1.13, 95% CI 1.08 – 1.19 per 10% decrease in PDC*) (178). Additionally, the need for dabigatran to be stored in its original packing (due to stability issues) might be a concern for those patients who are accustomed to managing their daily doses via weekly pill-boxes or blister packs, to reduce the likelihood of forgetting their doses (166, 187).

4.4.2.2 Attitude towards risk-benefit of therapy

Under half (42%) of the reviewed studies have reported patients' viewpoint on the risk (bleeding) - benefit (stroke prevention) ratio of being on warfarin therapy, and how these views impact on their acceptance for warfarin, their quality of life, and adherence. The literature demonstrates that patients' adherence to warfarin therapy is partly dependent on their perception about the risk of bleeding, especially because the benefit of stroke prevention is not as tangible as the experience of bleeding (188). This perception is underpinned by their knowledge and

understanding about the relationship between stroke and atrial fibrillation, and the role of warfarin in stroke prevention. A survey conducted in the UK identified that a staggering 81% of patients were not able to state that warfarin is used for stroke prevention in AF (189), and similar findings have been reported elsewhere (71, 149, 165, 190). A qualitative study conducted in a metropolitan hospital in Sydney identified that some patients consider warfarin therapy as an alternative to cardioversion; only those patients with a previous history of stroke fully understood the role of warfarin in their care (165).

Studies have observed that patients' perception about the risk of bleeding and its impact on quality of life and adherence is highly patient specific (128, 132, 137, 153). A cross-sectional study (N= 905, mean age = 67.9 years) conducted in Argentina observed that patients' negative perception regarding quality of life was associated with their increased concerns regarding bleeding complications (OR 11.2, 95% CI = 3.08 – 45.47, P = 0.0002), irrespective of their absolute risk of bleeding, and whether they had previous bleeding experience or not (132). While, changes in patients' perceptions' following bleeding experience was reported by Lancaster and colleagues, it was observed that even minor bleeding episodes elevated both patients' health concern scores by an average of 13.4 points ($P < 0.02$), and health distress scores by 15.3 points ($P < 0.05$) (152). Similarly, another study reported that nonadherent patients were more concerned about bleeding risks than were adherent patients (OR = 2.2, 95% CI=1.0, 4.6) (153)

Patients' adherence to warfarin therapy was based on patients' beliefs about the effectiveness and benefits of being on anticoagulation, regardless of whether they were using it for primary stroke prevention or secondary stroke prevention (153, 186). A case-control study carried out in a hospital setting in the USA demonstrated that patients with a history of stroke or TIA have an 80% reduction in the likelihood of being nonadherent (OR = 0.2, 95% CI 0.1- 0.7, P = 0.006),

compared to those who had no previous experience of stroke. The adherent patients in this study understood and acknowledged the long-term protection provided by warfarin therapy (153). While, a Swedish cross-sectional study involving (N = 578), reported that patients with previous history of stroke were more likely to be nonadherent; the nonadherent patients were mostly cognitively impaired, were dependent on others for managing their medications, and scored higher on negative beliefs (concern, harm and overuse) about being on warfarin therapy (186).

In regards to the DOACs, a cross-sectional study conducted in primary care clinics in the USA (N = 137) reported that, regardless of their bleeding risk, 36% of patients exposed and 37% of patients not exposed to anticoagulant therapy preferred using a medication with an antidote (46). In contrast, a discrete choice experiment conducted in Australia involving the general public with no experience of being on anticoagulant therapy (with or without AF), found that patients' choice for an option with an antidote depended on their bleeding risk. Patients' preference for an anticoagulant with antidote (warfarin) decreased as their bleeding risk also decreased (191).

All antithrombotic therapies, including DOACs and warfarin, carry a risk of bleeding (81, 192-194). Studies have reported that dabigatran and rivaroxaban have higher risk of gastrointestinal bleeding than warfarin, while warfarin has a higher risk of intracranial haemorrhage compared to the DOACs (79-81, 195). Moreover, all antithrombotics only reduce the risk of having a stroke and do not guarantee 100% protection against it (71). Hence, patients' perceptions about stroke risk, their perception about gastrointestinal bleeding and intracranial bleeding risk, and access to bleeding management strategies, might collectively influence their willingness to use anticoagulant therapy.

4.4.3 Condition-related factors

AF *per se* as a diagnosis has not been shown to influence medication adherence. However, in some cases, patients might underestimate the risk of stroke associated with AF owing to its asymptomatic nature, as is observed with other cardiovascular diseases, and this may negatively affect patients' adherence to therapy (196). A recent cross-sectional study conducted in 11 countries (N= 825) reported that only one-third of patients considered that the consequences of AF could be serious (197), similar to other studies (189, 190, 198). Additionally, AF is often found in older patients, who concomitantly may suffer from other comorbidities and impairments (dementia, risk of falls, malnutrition, decreased muscle strength, dexterity issues) (199, 200), contributing to overall poorer quality of life and lower adherence (155). AF and cognitive impairment are both strongly associated with advancing age. A longitudinal study (N= 5150, aged ≥ 65 years) reported that cognitive impairment is observed earlier in patients with AF compared to patients without AF, even in the absence of previous stroke (201). In some cases, the aftermath of stroke can leave patients physically and cognitively impaired, which in turn decreases patients' ability to manage medication and reduces overall adherence to therapy (202). A prospective cohort study conducted in two specialized anticoagulation clinics in USA (N= 111) found that lower scores in both mental health (lower Short Form- 36 mental component score, OR 1.4 (1.1–1.6) for each 10 point decrease) and cognitive functioning (≤ 19) (Cognitive Capacity Screening Examination (CCSE), OR 2.9 (1.7–4.8) were independent factors increasing the likelihood for medication nonadherence (135).

Thus, misinformed patients and their misperceptions about AF, as well as patients with functional decline (physical or cognitive), may become nonadherent to treatment, irrespective of whether warfarin or DOACs are being used.

4.4.4 Social-economic factors

Overall, one-fifth of the reviewed studies have explored the impact of patients' social and economic background on their perception of, and adherence to, warfarin therapy (71, 135, 137, 139, 203). The financial burden posed to patients by warfarin and NOAC therapies is dependent on health-care service costs to individuals, and the extent to which these medicines are subsidized by the governments or insurance companies in those countries where they are available. In regard to warfarin, only two studies reported that a small number of patients were financially burdened by additional expenses (INR testing, cost involved in travelling to clinic) associated with managing the therapy. In face-to-face interviews (N = 21, mean age = 74 years) conducted in a family practice clinic in Canada, only some patients felt that the transportation costs associated with travelling to the clinic for INR monitoring were a barrier to using warfarin (71). Similarly, an online survey involving 364 patients (204 on warfarin) in the USA found that the high cost of warfarin management was a key reason for only a few patients (7%) to switch from warfarin to dabigatran (203).

For the DOACs, more than one-half of the studies have reported that high 'out-of-pocket' costs are a key barrier for patients' acceptance of the therapy (46, 159, 191, 203, 204). This has been highlighted in a survey conducted at a pharmacist-managed clinic (N=260) in the USA which reported that the high 'out-of-pocket' costs of DOACs were a major concern for patients who were switched from warfarin to NOAC therapy (90). Additionally, a cross-sectional internet-based survey involving 364 patients (204 on warfarin, 160 on dabigatran), showed that high medication costs (62.5%) and insufficient health insurance coverage (16.8%) were the two main reasons for patients switching from dabigatran to warfarin (203). Similarly, a retrospective cohort analysis of insurance claims in the USA found that the high cost price of rivaroxaban was significantly associated with the increased likelihood of rivaroxaban discontinuation (205).

However, in Australia, currently all the three available DOACs are listed in the Pharmaceutical Benefits Scheme (PBS) for subsidy, costing approximately $37.70 per month for patients with no concession card/s or $6.10/ month for patients with concession card/s (206, 207). Hence, it is anticipated that the high costs of DOACs will not be a barrier to use for Australian patients, but rather an issue for the health-system to manage (39). This is supported by a discrete choice experiment conducted in Australia, (N= 76 patients, aged ≥ 40 years) reporting that patients' preference for DOACs increased from 25% to 70% as the costs decreased from AUD$120 to AUD$30 per month (191). Although the cost of warfarin is lower compared to DOACs, the overhead expenses (cost of regular check-ups, monitoring, transportation) might make it financially burdensome for some patients who cannot maintain INR levels within target ranges, necessitating frequent testing

Social factors, such as family support, living conditions, and busy work schedules tend to influence patients' adherence to warfarin. A qualitative study conducted in a family practice clinic in Canada (N = 21) reported that patients who were actively supported by their spouses in their day-to-day management of warfarin were mostly satisfied with the therapy (71). A descriptive study conducted in the USA found that a lack of social support (e.g., being single) was an independent predictor of nonadherence to warfarin prescription refills (137). In regard to the impact of work commitments on warfarin adherence, a prospective cohort study carried out in two specialized anticoagulation clinics in the USA found that employed patients had poorer adherence to warfarin compared to unemployed patients (OR = 0.6, CI = 0.3 – 1.2) (135).

4.4.5 Health-system related factors

One-third of studies exploring patients' perspective on, and adherence to warfarin therapy, have explored patients' expectations of healthcare systems in regard to warfarin management, and the influence of these expectations on patients' treatment satisfaction, quality of life, and adherence (71, 132, 139, 148, 149, 153, 154, 161, 208). Four studies have identified that in 17% to 60% of cases, prescribers fail to recognize patients' expectations of health care services regarding warfarin management, whether it be information provision or emotional support (153, 154, 172, 197). A cross-sectional survey conducted at a referral centre for anticoagulation in Argentina (N = 905) reported that patients who were in regular telephone contact with their doctors had mostly positive perspectives about warfarin (132). In regard to the impact of emotional support from healthcare professionals, a case-control study conducted at an anticoagulant therapy unit in the USA (N = 132) showed that compared to adherent patients, nonadherent patients frequently felt that their prescribers were not really concerned about them (OR = 3.1, 95% CI = 1.2 - 7.8) (153). Although not statistically significant, a descriptive cross-sectional study conducted in four health care centres in Finland (N= 139 patients, mean age = 70 years) also found that patients who were satisfied with their healthcare support had better adherence, compared to those who received healthcare support below their expectation (55% versus 39%, P = 0.09) (139).

In regard to the DOACs, an online analysis of a discussion forum has found that patients are still not clear about the management, efficacy and safety of DOACs. This analysis highlights that patients on DOACs also need ongoing healthcare support (166). Hence, in this context, the reduced opportunity for patients to be in regular contact with their healthcare provider (in the absence of regular monitoring) may concern some patients (28). Thus, similar to warfarin, healthcare system related factors might also influence patients' ability to adhere to DOACs.

4.5 Discussion

This review reveals that the practical aspects of managing warfarin therapy, particularly the way in which they affect day-to-day lives, are foremost in the minds of patients, serving as a key barrier to therapy adherence. The DOACs seem promising in addressing the issues of regular INR monitoring and dose-adjustment, and consistent dietary vitamin K intake, at least to some extent. However, other factors, such as forgetfulness, attitudes toward stroke and bleeding risk, condition related factors, social and economic factors, and healthcare system related factors, will likely influence patients' adherence to DOACs in a manner similar to warfarin. Although, specific factors such as the absence of regular monitoring, limited access to antidotes, high costs of the medications, twice daily dosing (dabigatran and apixaban), and timing of doses with respect to meals (dabigatran and rivaroxaban), are all additional factors that might make it difficult for some patients to accept, manage and adhere to the DOACs. Overall, the DOACs are viable treatment alternatives, overcoming (at least to some extent) some of the key challenges in warfarin use, notably the day-to-day management of warfarin therapy. However, their use is accompanied by other considerations, such that it is unlikely that warfarin will even be entirely superseded by the advent of DOACs. Ultimately, the DOACs have expanded the treatment armamentarium, enabling the selection of therapy based on individual patient's needs and preferences.

Aside from the features of the therapies themselves, this review also highlights patients' lack of understanding regarding AF and stroke, and the importance of anticoagulant therapy (in any form) in stroke prevention. This understanding is integral to facilitating adherence, as well as for engaging patients in decision-making. Studies have reported that shared decision-making significantly improves patients' knowledge about AF (209), and those involved in shared decision-making have a more practical understanding of the risks and benefits of being on

antithrombotic therapy (210). Clinicians' selection of anticoagulant therapy might be based on evidence-based guidelines in most cases, however, the significant difference observed between patients' preference for anticoagulants and that recommended by the evidence-based guidelines cannot be overlooked (123, 211). This review has helped to identify key points that may guide patient-clinician discussion regarding anticoagulant use, including the choice of agent. Dedicated time should be made available during consultations to discuss key issues in the decision to prescribe an anticoagulant. The key issues must include the information about the following, in order of apparent importance to patients: the role of routine therapeutic monitoring (if warfarin is being considered), dietary considerations, alcohol use, dosing regimens of the DOACs compared to warfarin (and issues relating to non-adherence), and, finally, the rationale for using anticoagulant therapy. These discussions should take place prior to commencing therapy, clarifying patient expectations and ascertaining any concerns that may underpin adherence. To assist clinicians in this, well-designed educational resource designed are available; for example, a resource designed by the National Institute of Clinical Excellence (NICE) covers the above key aspects for the full range of treatment options in an objective manner, and also discusses various factors contributing to stroke risk and bleeding risk. Such resources allow clinicians and patients to navigate through the advantages and disadvantages of the available therapies and assist in the selection of an appropriate therapeutic option (212). Overall, this review reinforces that a patient centered approach to treatment selection. More attention must be paid to developing appropriate decision-making support tools and resources to engage patients in shared decision-making for selecting anticoagulant therapy (213, 214).

4.6 Conclusion

For patients, regular INR monitoring and associated dose adjustments, and dietary vitamin K consideration, are the key barriers to warfarin use, leading to treatment nonadherence. The DOACs overcome these barriers to an extent, although they present their own challenges. Patients' perspectives about the risk versus benefit of therapy, and their understandings about the importance of stroke prevention in AF, underpin their acceptance of anticoagulation in general. Thus, patients' views about treatment must be incorporated into the decision-making process to facilitate treatment adherence and achieve good clinical outcomes. Further work is needed to develop resources that more actively support patient engagement in decision-making in context of stroke prevention.

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EP and BB have no conflicts of interest to declare

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a) Conducting the literature search

b) Analysing the studies, and designing the structure of the manuscript

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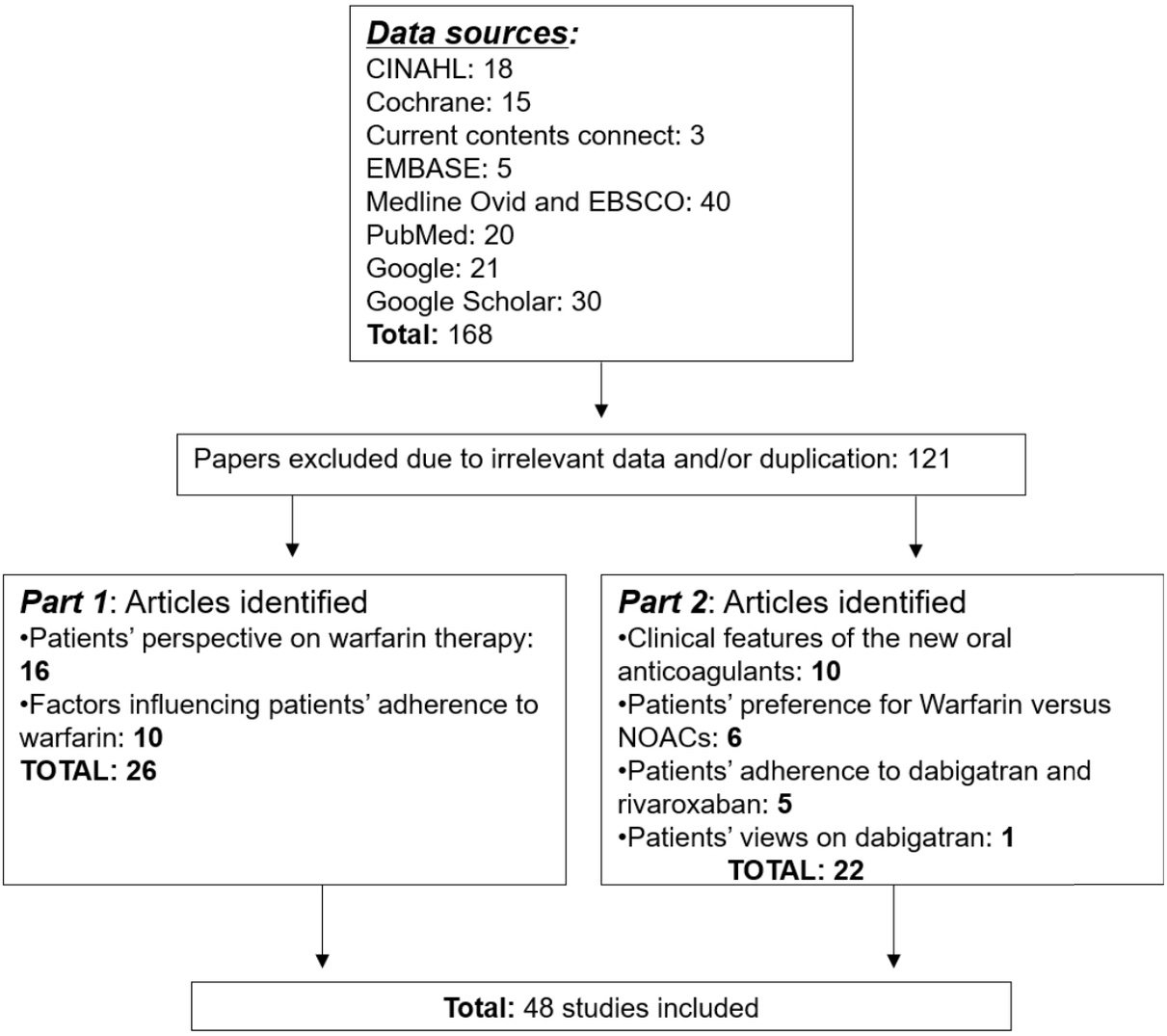

Figure 4-1. Search strategy and results

Table 4-1. Factors affecting patients' adherence to warfarin therapy: Warfarin versus DOACs

Barriers to anticoagulation adherence	**Warfarin**	**DOACs**
1) Therapy related factors		
Regular INR monitoring & Dose adjustment	Issue	Issue addressed to an extent: No INR monitoring required, but elderly patients and patients with renal impairment require regular kidney function tests and dose is adjusted accordingly
Dietary requirements a) Dietary vitamin K restriction b) After meal ingestion of medication to facilitate drug absorption and bioavailability; or ameliorate gastrointestinal side-effects	Issue	Not an issue
Drug-drug interaction	Not an issue	Might be an issue with both rivaroxaban and dabigatran
Drug-alcohol interaction		
Restricted physical activities	Issue	Dabigatran has relatively low potential interaction with concomitant medications. But issue not completely resolved

Pill burden (More than once daily dosing) **Absence of antidote**	 Issue Issue Not an issue Not an issue	Issue not addressed Issue not addressed Issue with dabigatran and apixaban Issue with rivaroxaban and apixaban
2) Patient related factors		
Memory capacity Attitude towards risk-benefit of therapy	Issue Issue	Issue not addressed Issue not addressed
3) Condition related factors	Issue	Issue not addressed
4) Social-economic factors		
Medication cost Costs involved in clinical appointments and laboratory tests	Not an issue Dependent on the distance to clinics,	Dependent on drug subsidizing policies in different countries Not on issue

	frequency of appointments and laboratory test	
5) Health-system related factors	Issue	Issue not addressed

Table 4-2. Studies exploring patients' perspectives on warfarin

Study Title	**Reference (Year)**	**Type of study/ Setting**	**Patients age (Years)**	**Duration spent on warfarin therapy (Years)**	**Number of Total patients**	**Objective(s)**	**Key finding(s)**
The impact of long-term warfarin therapy on quality of life.	Lancaster et al (1991)	Evidence from a Randomised trial Anticoagulant therapy unit.	Mean age = 67.9		177 patients on warfarin	• To determine the effect of long-term warfarin therapy on quality of life	• Patients' quality of quality of life was not significantly affected when warfarin was well managed and tolerated • History of bleeding was the major factor that led to the decrement in the patients' current health perception
Determinants of compliance with anti-	Arnsten et al (1997)	Case-control study	< 53 - > 78		43 cases 89 control	• To identify determinants of nonadherence with anticoagulant therapy	• Patients aged < 53 years more nonadherent (0R = 14.1) than patients aged 53-60 years, old age was a strong predictor of better adherence

coagulation: A case-control study.		Anticoagulant therapy unit					• Nonadherent patients could not see any benefit of being on warfarin therapy, and it also negatively influenced their lifestyle due to restricted physical activities and regular blood test problem.
The management of oral anticoagulant therapy: The patient's point of view.	Barcellona et al (2000)	Two different anticoagulation clinics	Mean age = 55 ± 19		264	• To explore patients' views on anticoagulation management, quality of life, and relationship with their healthcare providers	• Overall, warfarin was well accepted by the patients despite the need for regular monitoring • 89% patients felt that doctors were cooperative in answering their questions and clearing their doubts
Study Title	**Reference (Year)**	**Type of study/ Setting**	**Patients age (Years)**	**Duration spent on warfarin**	**Number of Total patients**	**Objective(s)**	**Key finding(s)**

				therapy (Years)			
Anticoagulation therapy for atrial fibrillation: explaining patients' choices.	Howitt et al (2000)	Interview Primary care setting	NA		56	• To assess the clinical need for antithrombotic therapy based on individualized risk-benefit • To identify the practical impediments to addressing that need	• Most of them unaware about their condition and imminent risk of stroke • Patients perception about the risk of stroke, attitude towards death, and their ability to accept the change associated with anticoagulation management strongly influenced their decision to take warfarin
Ethnic differences in patient perceptions of atrial fibrillation and anticoagulation therapy: the west	Lip et al (2002)	Cross-sectional survey Hospital	Mean age = 69 ± 9	Minimum = 0.5 Range = 1-10	119	• To investigate the ethnic differences in patients' knowledge and preconception about AF and antithrombotic therapy use	• 63% patients unaware about their condition, and 61% felt AF was not serious • Indo-Asians and Afro-Caribbean were less aware about AF than white patients

Birmingham atrial fibrillation project.							
Patients' perspectives on taking warfarin: qualitative study in family practice.	Dantas et al (2004)	Face-face semi structured interview. Family practice clinic situated in a large, tertiary care teaching hospital	Mean age = 74	Minimum = 0.5 Mean = 4.6 Range = 1 - 6 on warfarin	21 (12 males and 9 females)	• To investigate individuals' experience and perspective of taking warfarin.	• Patients had minimal involvement and input in decision-making for therapy selection • 25% of the patients had no issues in adhering to warfarin regimen; they had their own management strategies and support from clinical staff • Warfarin dose-adjustment was a problem for patients on multiple medications
Avoidance hierarchies and preferences for	Fuller et al (2004)	Elderly medicine outpatient clinic	66 – 97		81	• To examine patients' preferences for warfarin when faced with cumulative probability of	• More than 50% of patients declined to be warfarin therapy after individualized information about the benefits (stroke prevention) of warfarin

anticoagulation-semi-qualitative analysis of older patients' views about stroke prevention and the use of warfarin.						treatment risk and benefits.	and the associated intracranial haemorrhage risk was provided to them. • Patients' personal health beliefs and experience about stroke, cerebral haemorrhage, regular blood test, and alcohol restrictions played a major role in their decision-making for warfarin therapy.
Patients' perception regarding oral anticoagulation therapy and its effects on the quality of life.	Casais et al. (2005)	Cross-sectional study Anticoagulation clinic	9 – 90	Range = 0 - > 10	905 125: (13.8% with AF)	• The impact of anticoagulant therapy on patients' quality of life	• Patients who were anxious to be on oral anticoagulant therapy were the ones mostly worried about bleeding complications (OR: 11.72 95% CI: 3.08-45.47, P = 0.0002). • Patients who referred improvement in health status were also the ones that felt protected and were satisfied with

							medical attention and been on OAT for more than 5 years.
Study Title	**Reference (Year)**	**Type of study/ Setting**	**Patients age (Years)**	**Duration spent on warfarin therapy (Years)**	**Number of Total patients**	**Objective(s)**	**Key finding(s)**
Oral anticoagulation in atrial fibrillation: A pan European patient survey.	Lip et al (2006)	General practice	20 – 93	Minimum = 1	711	• To gain a broader view of patient perceptions and understanding of VKA: European countries	• Patients had poor knowledge about the purpose of warfarin therapy in AF, and the deleterious consequences of not being on stroke prevention therapy • Younger counterparts were more bothered with warfarin management (75% of them aged < 65 years) due to compromise with

							socialising, career, diet, and travelling
Management of warfarin in atrial fibrillation patients: views of health professionals, older patients and their carers.	Bajorek et al (2007)	Group interviews Aged care centres, hostels and retirement facilities	≥ 65		14	• To identify the views of health professionals, patients, and their carers on strategies to improve warfarin management	• Patients were dissatisfied with the amount and quality of information on drug-drug and drug-diet interactions, and demanded for more tailored information • There is an immense scope of improvement in the communication involved in decision-making, and information provision
Study Title	**Reference (Year)**	**Type of study/ Setting**	**Patients age (Years)**	**Duration spent on warfarin therapy (Years)**	**Number of Total patients**	**Objective(s)**	**Key finding(s)**

Balancing the risk versus benefit the elderly patient's perspective on warfarin therapy	Bajorek et al (2009)	Semi-structured group interviews	≥ 65	Minimum = 0.5	17	• To explore perspectives of elderly patients and/ or their carers on warfarin therapy	• Overall, patients are mostly accepting of warfarin therapy in spite of the involved management • Patients are concerned about lack of information provided on dietary Vitamin K restrictions, and interpretation of INR test results • Decision to take warfarin is more strongly driven by the fear of stroke risk than barriers
Patient perspective on taking Vitamin K antagonist: a qualitative study in the UK, USA and Spain.	Wild et al (2009)	Interview	Mean age = 65 (36 - 88)	Minimum = 0.5 Range = 0.5 - 19	60 (28 with AF)	• To explore patients' perspective on VKA therapy in UK, USA and Spain.	• Approximately half of the patients found VKA therapy difficult to manage • Regular monitoring was a major issue mostly for working patients • Patients' knowledge about dietary vitamin K and alcohol management varied by county

							• Patients were worried about drug-drug interactions and risk of bleeding
Study Title	**Reference (Year)**	**Type of study/ Setting**	**Patients age (Years)**	**Duration spent on warfarin therapy (Years)**	**Number of Total patients**	**Objective(s)**	**Key finding(s)**
Survey of atrial fibrillation patients demonstrates gaps in awareness of stroke risk and perceived barriers associated	Ansell et al (2010)	Internet survey	20 – 39 = 4% 40 – 69 = 82% 70 - ≥ 80 = 14% Mean age = 57.93		500 259 warfarin users	• To explore AF patient awareness on blood clot and stroke risk	• 60% of AF patients were not provided with additional information about blood-clots/ stroke • Aspirin was prescribed most frequently followed by warfarin • 32% of patients found warfarin therapy to be moderately/ very difficult to use

with anticoagulation therapy.							
Patient preferences for chronic treatment for stroke prevention: results from the European Patient survey in atrial fibrillation (EUPS-AF).	Zamorano et al (2012)	Structured telephone interviews	< 50 = 6.8% 50 – 65 = 21.4% ≥ 65 = 71.9% Mean age = 70.1		1507	• To assess the burden of VKA therapy from patients' perspective • To explore patient preference for antithrombotic therapy in France, Germany, Italy, Spain and UK.	• 77.9% and 55% of respondents (largely from Italy) were mostly positive about the reduced monitoring and dose-adjustments required with NOACs, but patients from France and Germany were least positive about the same
Difficulties encountered by very elderly with atrial fibrillation on	Tan et.al. (2012)	Survey Out-patient Anticoagulation	≥ 80	> 0.5	166	• To define the characteristics of AF patients attending an outpatient anticoagulation monitoring service (AMS)	• 65% patients were reported to have problems with anticoagulant therapy: bleeding, bruising, falls, difficulties in commuting to clinics, medication interactions, and erratic INR reading

warfarin attending outpatients anti-coagulant clinic.		monitoring service					
Study Title	**Reference (Year)**	**Type of study/ Setting**	**Patients age (Years)**	**Duration spent on warfarin therapy (Years)**	**Number of Total patients**	**Objective(s)**	**Key finding(s)**
Patient preferences and willingness to pay for different options of anticoagulant therapy.	Moia et al (2013)	Discrete choice experiment (DCE). Anticoagulation clinic	23 - 91	Both beginners and already on warfarin.	101 stables 176 starters	• To evaluate patients' preferences on relevant characteristics of a hypothetical new anticoagulants • To assess patients' willingness to pay for each characteristic	• Younger and working patients showed higher preference for less frequent monitoring than older and retired patients • Drug and food interaction not of major concern for newly initiated patients but was a matter of concern for the patients on

					89 (34.9% with AF)		warfarin therapy from a long time

AF= atrial fibrillation, AMS= anticoagulation monitoring service, DOACs= direct oral anticoagulants, INR= international normalised ratio, OAT= oral anticoagulation therapy, OR= odds ratio, QOL= quality of life, VKA= vitamin K antagonist, NA= not available

Table 4-3. Studies discussing patients' views on the Novel Oral Anticoagulants (NOACs)

Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and b) Time spent on warfarin**	**Total patients**	**Objective/s**	**Key finding/s**
Patients' perspectives regarding long-term warfarin therapy and the potential transition to new oral anticoagulant therapy.	Hughes et al. (2012)	General Practice Clinics, Survey	a) Mean age = 74.9 ± 12.1 years (25 – 94 years) b) 6.1 ± 5.7 years	290	• To explore patients perspective on long-term warfarin therapy and potential transition to NOACs • To determine the influence of age, sex or residence on their opinions	• 79.5% were 'satisfied' or 'very satisfied' with warfarin therapy • Frequency of medical appointments (20.2%) and dose-adjustments (18.5%) was reported as the most frequently cited barriers followed by INR monitoring, drug-drug interactions, and drug-food interaction • No requirement for INR monitoring (20.4%) ranked first among the benefits of NOACs, followed by fewer dose-alterations, and few drug-drug and drug-food interactions • No availability of antidote (40%) reported as a major deterrent in NOACs use followed by side-effects, absence of drug monitoring method, and anxiousness around new medication • However, the average score of deterrents for NOACs was lower than the benefits score (10.9 ± 4.5 versus 7.6 ± 4.2, P < 0.001)

						• Increased age, and rural residence had positive significant influence on patients' satisfaction with warfarin, while time spend on warfarin had negative significant effect
Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and b) Time spent on warfarin**	**Total patients**	**Objective/s**	**Key finding/s**
Survey of the use of warfarin and the newer anticoagulant dabigatran in patients with atrial fibrillation.	Choi et al (2012)	Cross-sectional survey (internet)	a) Dabigatran mean age: 60.9 years Warfarin mean age: 68.4 years	204-warfarin users 160-dabigatran users	• To describe and compare the characteristics (demographics, treatment characteristics, satisfaction, and medication adherence) of AF patients on dabigatran with that on warfarin therapy	• Patients on dabigatran were younger, more educated and actively participated in the decision-making process when compared to warfarin patients • Change in the routine was most commonly cited as the reason for nonadherence with dabigatran compared to warfarin (34.9% versus 6.1%, P<0.05); while risk of bleeding was more commonly cited reason for nonadherence in warfarin users compared to dabigatran (0% versus 9%, P<0.05) • 2% of nonadherence cases with dabigatran were due to gastrointestinal associated side-effects • Dabigatran users less likely to consider switching compared to warfarin patients (10.7% versus 31.9%, P<0.05)

						• Most common reason for switching from dabigatran was cost and inadequate insurance coverage
Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and b) time spent on warfarin**	**Total patients**	**Objective/s**	**Key finding/s**
Study of warfarin patients investigating attitudes toward therapy change (switch survey)	Attaya et al (2012)	Survey in an Anticoagulation clinic	a) 20 - 90 years b) 2 months	147	• To explore patients' willingness to switch from warfarin to NOACs	• 80% patients satisfied with warfarin treatment • 58% patients in total were ready to switch from warfarin to the NOACs if the alternative was safe and effective • Regular visits to the clinic cited as the most common reason for switching from warfarin • Cost was the major barrier for switching from warfarin
Dabigatran for anticoagulation in atrial fibrillation- Early clinical experience in a hospital population and comparison to trial data-New Zealand	Michel et al (2013)	Observational, open label, prospective study	a) Mean age: 71.9 years (62.7 – 79.0 years)	70 patients on dabigatran	• To investigate the adverse effects, medication adherence, and medication satisfaction in patients initiated on dabigatran	• 10% of the patients stopped dabigatran due to adverse events and bleeding • 8% stopped dabigatran due to planned discontinuation, negative media coverage, and medication adherence issues • 73% of the total patients had no difficulty adhering to the twice daily dose

Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and b) Time spent on warfarin**	**Total patients**	**Objective/s**	**Key finding/s**
Patients' satisfaction with warfarin and willingness to switch to dabigatran: a patient survey.	Elewa et al (2014)	Observational prospective study paper-based survey Anticoagulation clinic	a) < 30 - > 70 years b) < 2years - > 10 years	130	• To assess patients' satisfaction with warfarin therapy, and their willingness to switch from warfarin • To determine the strongest predictors in determining patients' therapy of choice for stroke prevention	• 77.9% of participants were satisfied with warfarin treatment • 52.1% were willing to switch from warfarin to dabigatran due to no interaction with food or beverages, and 40.5% of patients due to less frequent follow-up (once every couple of months)
Patient perspectives of dabigatran: analysis of online discussion forums.	Sarrazine et al (2014)	Analysis of an online discussion forums	-	-	• To examine patients' and carers' perception and experiences with dabigatran	• Many favoured dabigatran over warfarin due to no requirement for regular blood tests and no food restrictions • However, many patients were simultaneously perplexed and scared to take dabigatran due to absence of specific antidote, and also enquired about skipping drug doses, and drug-drug and drug-food interactions with dabigatran
Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and**	**Total patients**	**Objective/s**	**Key finding/s**

			b) Time spent on warfarin			
Medication persistence and discontinuation of rivaroxaban versus warfarin among patients with non-valvular atrial fibrillation.	Nelson et al (2014)	Analysis of Truven Health Marketscan research databases.	-	7259-rivaroxaban 25,627-warfarin	• To compare real-world persistence and discontinuation among AF patients on rivaroxaban and warfarin in the US	• Rivaroxaban showed higher medication persistence compared to warfarin • Older age, higher CHADS2 score, chronic kidney disease, more medications-reduced risk of non-persistence and discontinuation of the therapy • Higher ATRIA score (bleeding risk score), psychiatric disease, and higher out-of-pocket cost increased the risk of non-persistence and discontinuation of the therapy
Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and b) Time spent on warfarin**	**Total patients**	**Objective/s**	**Key finding/s**

Patient perspectives of dabigatran: analysis of online discussion forums	Vaughan et al. (2014)	Analysis of online discussion forums	-	468 posts	• To determine consumers' experience and perception regarding dabigatran on online discussion forums, and thematically analyze it	• Dabigatran was considered as a favourable option than warfarin owing to no requirement for monitoring and dietary restriction in many comments • Comparative efficacy and safety of dabigatran compared to conventional antithrombotic therapies were reported as primary concerns for patients • Questions regarding dabigatran's dosing frequency, storage, drug interactions, and potential side-effects were also reported

AF= Atrial Fibrillation; ATRIA= Anticoagulants and Risk Factors in Atrial Fibrillation; $CHADS_2$= Congestive Cardiac Failure, Hypertension, Age ≥ 75 years, Diabetes Mellitus, Stroke; DOACs= Direct Oral Anticoagulants; INR= International Normalised Ratio

Table 4-4. Studies exploring patients' adherence to Warfarin and/or NOACs

Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and b) Duration spent on warfarin**	**Total patients**	**Objective/s**	**Key finding/s**
Effect of warfarin non-adherence on control of the INR.	Waterman et al (2004)	Telephone interview Anticoagulation service	a) 72.7 ± 10.2 years	347	• The frequency and causes of aberrant International normalized ratios (INRs) and the percentage explainable by warfarin nonadherence	• 18% of poor INR control was due to: inconsistent amounts of vitamin K intake, misunderstanding warfarin dosage instructions and missing warfarin dosing • Mostly patients aged > 80 years, and < 65 years were non adherent
Impact of adherence, knowledge and quality of life on anticoagulation control.	Davis et al (2005)	Cross-sectional survey Anticoagulation clinic	a) 20 – 78 years b) > 2 months	52 17%: AF and 12% past stroke	• To determine association between warfarin adherence, patients' demographics, knowledge about therapy and perceived impact on quality of life with anticoagulation control	• Adherence was significantly associated with good anticoagulation control, older age, and higher income
Predictors of noncompliance with warfarin therapy in an	Orensky et al	Descriptive study (chart and pharmacy	a) (32-82 years)	75	• To assess the impact of patients' perception about risk-benefit, demographics, and quality of health services on	• Nonadherence was directly related to perceived barriers to warfarin therapy, and inversely proportional to perceived benefits of warfarin therapy

outpatient anticoagulation clinic	(2005)	database review, and patient questionnaires) Outpatient anticoagulation clinic	b) > 6months (of data)		their adherence to warfarin therapy	• Patients in unstable living conditions were more likely to be nonadherent • Being divorced or single associated with increased barrier sub-score, and also had poor refill adherence
Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and b) Duration spent on warfarin**	**Total patients**	**Objective/s**	**Key finding/s**
Adherence to warfarin assessed by electronic pill caps, clinician assessment, and patient reports: results from the INR-RANGE study	Parker et al (2007)	Prospective cohort study 3 Pennsylvania-based anticoagulation clinics	a) 68.4 (± 14.6) years b) < 2 months of initiation of therapy	145	• To quantify warfarin adherence over time • To compare both clinician and self-report assessment of patients adherence with Medication event monitoring system (MEMS)	• Overall, 38.6% of the patients had > 20% incorrect bottle opening (erroneous daily dose intake) • Patients were 6 times more likely to miss pill than take extra pills • Clinicians and participants over-estimated their adherence • The adherence in the initial 6 months was poor, and then improved over next six months

The influence of patient adherence on anticoagulation control with warfarin	Kimmel et al (2007)	Prospective cohort study in 3 anticoagulation clinics	a) 58.5 (48.5-70.0) years	136	• To determine the effect of adherence on anticoagulation control	• 40.4% of the INRs were out of range (25.8% below and 14.6% above the target range) • Undercoagulation was significantly associated with low INR
Risk factors for nonadherence to warfarin results from the in range study	Platta et al (2008)	Prospective cohort study Specialised anti-coagulation clinic	a) 55 years (23 – 83 years) b) Within two months of the initiation of therapy.	111	• To determine the demographic, clinical, psychological, health utilization and pill-taking practices related to warfarin nonadherence.	• Higher education level, current employment, low scores on mental health and cognitive functioning were associated with poor adherence to warfarin • Disabled subjects aged > 55 years had worse adherence than younger disabled subjects
Factors affecting medication adherence and anti-coagulation control in Korean patients taking warfarin.	Kim et al (2011)	Cross-sectional survey Outpatient clinic	a) 59.14 ± 11.64 years	204	• To examine medication adherence and factors influencing it: Korean patients • To examine the impact of nonadherence on anticoagulation control	• Nonadherent patients had low efficacy in self-management of the therapy: daily intake of dietary Vitamin K, taking medicine at regular time interval, and drug-drug interactions • Adherent patients had more knowledge than nonadherent cases

Study Title	**Author/s**	**Type of study/ Setting**	**a) Patients age and b) Duration spent on warfarin**	**Total patients**	**Objective/s**	**Key finding/s**
Adherence with health regimens of patients on warfarin therapy.	Kaariainen et al (2013)	Descriptive cross sectional study Health care centres for INR testing	a) ≤ 65 - > 75 years b) > 2 years	139	• To explore the patients adherence to health regimen and warfarin therapy	• 74% of the patients had good adherence with warfarin therapy; women and patients aged 27-65 years had better adherence than others • Respondents on therapy for 1 - 4 years had better adherence than those on therapy for > 4 years • Adherent patients had good collaboration with health care professionals • Patients with will power and energy to take care of themselves had good adherence, while who had no will power and energy had poor adherence

Non-adherence with INR monitoring and anticoagulant complications.	Will et al (2013)	Cross-sectional survey	-	Adherent: 4995 Nonadherent: 2544	• To assess relationship between adherence to INR monitoring and risk of bleeding and thromboembolism • To describe patients' characteristics associated with INR monitoring nonadherence	• Adherent group more likely to take warfarin for AF, more likely to have comorbid condition (cancer, hypertension, liver diseases and prior history of gastrointestinal bleeding and have been hospitalized) • Nonadherent patients were younger to adherent patients, and more likely to be males
Adherence and outcomes of patients prescribed dabigatran (Pradaxa) in routine clinical practice	Thorne et al. (2014)	Telephone survey, Primary Healthcare Organizations	a) Mean age = 73 years	92	• To study the real-world patients' experience with dabigatran in New Zealand	• 70% patients continued to take dabigatran • Gastrointestinal side-effects, no antidote, declining renal function and myocardial infarction were first three major reasons for dabigatran discontinuation

AF= Atrial Fibrillation; INR= International Normalised Ratio

5 Assessment of Web-based Educational Resources on Atrial Fibrillation

Title: Assessment of Web-based education resources informing patients about stroke prevention in atrial fibrillation

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Assessment of Web-based education resources informing patients about stroke prevention in atrial fibrillation

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SUMMARY

What is known and objective: The importance of 'shared decision-making' is much emphasized in recent clinical guidelines regarding stroke management in atrial fibrillation (AF), more so following the inclusion of non-vitamin K oral anticoagulants (NOACs) among the treatment options. It is important that patients are navigated through balanced and unbiased information about the available treatment options, so as to understand the risk and benefits associated with the therapies, and to enable them to accordingly communicate their concerns and views with their clinicians prior to therapy selection. Given the increasing popularity of the Internet as a source of health information, the specific objectives of this study were to identify what aspects of thromboprophylaxis (antithrombotic treatment options) were most commonly described in these resources, both in terms of content, that is to report the information provided (quantitative) and the underlying themes underpinning this content, and in terms of how this information might guide patient preferences (qualitative).

Method: Resources for patients were identified via online search engines (Google, Yahoo, Ask, Bing), using the terms 'atrial fibrillation' and 'stroke' combined with patient/consumer information, patient/consumer resources and patient/consumer education. The researchers employed pragmatic (mix-method) approach to analyse the information presented within the resources using manual inductive coding, at two levels of analysis: manifest (reported surface theme or codes that are obvious and are countable) and latent (thematic, interpretative presentation of the content in the data set).

Results and discussion: In total, 33 resources were reviewed. The 'manifest-level' analysis found that warfarin was the most frequently mentioned thromboprophylactic option among the anticoagulants, being cited in all resources, followed by the NOACs – dabigatran (82·3% of resources), rivaroxaban (73·5%) and apixaban (67·6%). Only one-third of resources discussed the role of stroke risk and/or bleeding risk within the decision-making. At the 'latent-level' analysis, three overarching themes emerged: (i) The practical ease of managing NOACs over warfarin; (ii) Unbalanced explanation about stroke risk versus bleeding risk; and (iii) Individualized antithrombotic therapy selection. In general, the benefit of stroke prevention with anticoagulant use was emphasized less compared to the risk of bleeding. Overall, one in four resources had an implied preference for either warfarin or the NOACs.

What is new and conclusion: The implied inclination of some resources towards particular anticoagulant therapies and imbalanced information about the importance of anticoagulation in AF might misinform and confuse patients. Patients' engagement in shared decision-making and adherence to medicines may be undermined by the suboptimal quality of information provided in the resources. Health professionals have an important role to play in referring patients to appropriate resources to enable patient engagement in shared decision-making when selecting treatment.

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WHAT IS KNOWN AND OBJECTIVE

Long-term stroke prophylaxis using anticoagulants is key to managing atrial fibrillation (AF),[1–3] and warfarin has been the recommended treatment for decades.[4] Recently, the effective and safe non-vitamin K oral anticoagulants (NOACs) have been added to the line-up of treatments.[5–7] The inclusion of NOACs alongside conventional warfarin has expanded the thromboprophylaxis armamentarium; however, the overall superiority of one medication over another is uncertain, given that each has its own advantages and disadvantages.[8] Moreover, previous studies have highlighted that patients have their own specific views, beliefs, perceptions and preferences about treatments for various medical conditions, affecting their understanding of the relative risk versus benefit of treatments, and this in turn underpins their medication adherence and clinical outcomes.[9–14] Current clinical guidelines advocate a more patient-centric, 'preference sensitive' approach to treatment selection for stroke prevention in AF, which can be facilitated via 'shared decision-making' (SDM).[15,16,2]

Shared decision-making is much more than seeking informed consent from a patient.[17] It provides clinicians an opportunity to:

- explore patients' perspectives on their illness and treatment options
- discuss the pros and cons of the available options
- exchange information and verify patients' understanding of this
- negotiate a treatment plan based on the individual patient's values, preferences and needs.[18–20]

Shared decision-making empowers patients, supporting their right to appropriate information and enabling their role in managing their own health.[21] However, this requires the patient to have information about all treatment options and understand

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5.1 Abstract

What is known and objective: The importance of 'shared decision-making' is much emphasised in recent clinical guidelines regarding stroke management in atrial fibrillation (AF), moreso following the inclusion of non-vitamin K antagonist oral anticoagulants (NOACs) among the treatment options. It is important that patients are navigated through balanced and unbiased information about the available treatment options, to understand the risk and benefits associated with the therapies, and to enable them to accordingly communicate their concerns and views with their clinicians prior to therapy selection. Given the increasing popularity of the internet as a source of health information, the specific objectives of this study were to identify what aspects of thromboprophylaxis (antithrombotic treatment options) were most commonly described in these resources, both in terms of content, i.e., to report the information provided (quantitative) and the underlying themes underpinning this content, in terms of how this information might guide patient preferences (qualitative).

Method: Resources for patients were identified via online search engines (Google, Yahoo, Ask, Bing), using the terms 'atrial fibrillation' and 'stroke' combined with patient/ consumer information, patient/ consumer resources, and patient/ consumer education. The researchers employed pragmatic (mix-method) approach to analyse the information presented within the resources using manual inductive coding, at two levels of analysis: manifest (reported surface theme or codes that are obvious, and are countable) and latent (thematic, interpretative presentation of the content in the dataset).

Results and discussion: In total, 33 resources were reviewed. The 'manifest level' analysis found that warfarin was the most frequently mentioned thromboprophylactic option among the anticoagulants, being cited in all resources, followed by the NOACs - dabigatran (82.3% of resources), rivaroxaban (73.5%), apixaban (67.6%). Only one-third of resources discussed the role of stroke risk and/or bleeding risk within the decision-making. At the 'latent level' analysis, three overarching themes emerged: 1) The practical ease of managing NOACs over warfarin; 2) Unbalanced explanation about stroke risk versus bleeding risk; 3) Individualised antithrombotic therapy selection. In general, the benefit of stroke prevention with anticoagulant use was emphasised less compared to the risk of bleeding. Overall, one in for resources had an implied preference for either warfarin or the NOACs.

What is new and conclusion: The implied inclination of some resources toward anticoagulant therapies, and imbalanced information about the importance of anticoagulation in AF might misinform and confuse patients. Patients' engagement in shared decision-making, and adherence to medicines may be undermined by the suboptimal quality of information provided in the resources. Health professionals have an important role to play in referring patients to appropriate resources to enable patient engagement in shared decision-making when selecting treatment.

5.2 What is known and objective

Long-term stroke prophylaxis using anticoagulants is key to managing atrial fibrillation (AF) (14, 16, 215), and warfarin has been the recommended treatment for decades (6). Recently, the effective and safe non-Vitamin K antagonist oral anticoagulants (NOACs) have been added to the line-up of treatments (79-81). The inclusion of NOACs alongside conventional warfarin has expanded the thromboprophylaxis armamentarium; however, the overall superiority of one medication over another is uncertain, given that each has its own advantages and disadvantages (7, 216). Moreover, previous studies have highlighted that patients have their own specific views, beliefs, perceptions and preferences about treatments for various medical conditions, affecting their understanding of the relative risk versus benefit of treatments, and this in turn underpins their medication adherence and clinical outcomes (128, 186, 196, 217-219). Current clinical guidelines advocate a more patient-centric, 'preference sensitive' approach to treatment selection for stroke prevention in AF, which can be facilitated via 'shared decision-making' (SDM) (15, 40, 220).

SDM is much more than seeking informed consent from a patient (221). It provides clinicians an opportunity to:

- explore patients' perspectives on their illness and treatment options
- discuss the pros and cons of the available options
- exchange information and verify patients' understanding of this
- negotiate a treatment plan based on the individual patient's values, preferences and needs (222-224).

SDM empowers patients, supporting their right to appropriate information and enabling their role in managing their own health (225). However, this requires the patient to have information

about all treatment options and understand the associated risks and benefits of each, prior to selecting a treatment preference (213).

Although patients consider health professionals to be their main source of information, discrepancies have been observed between patients' need for information on AF management and what is actually provided by health professionals (172). For this reason, patients with AF tend to refer to other sources of information and decision aids to learn about the condition and stroke prevention; these alternative sources include online portals which provide access to brochures, patient support groups, and discussion forums (226-228). However, the credibility of health information provided via some online resources is questionable. In a study evaluating web-based videos designed to help educate patients about hypertension, one-third (33%) of the resources were reported to either: contain potentially misleading information about the treatments; promote commercial products; and/or include videos that were not uploaded by medical professionals (229). As per the International Patient Decision Aid Standards (IPDAS) Collaboration, patient decision aids and resources are expected to provide information about the illness, treatment options, and risk-benefits of therapy. These resources should provide balanced information and never be biased toward, nor specifically recommend, any particular therapy (230).

Given the increasing use of web-based tools and resources as decision-making aids (231-233), the aim of this study was to qualitatively review the information provided in a range of online resources currently available to help inform patients about stroke prevention in AF, and which might be used to empower patients in decision-making for their therapy selection. The specific study objectives were to identify what aspects of thromboprophylaxis (antithrombotic treatment

options) were most commonly described in these resources, in terms of content, i.e., information provided (quantitative), as well as how this information was presented in terms of the themes underpinning this content (qualitative).

5.3 Method

A structured online search was conducted to obtain all freely accessible online educational resources and tools designed for patients, as at March - April 2015.

5.3.1 Data search and selection

An online search was conducted using the search engines Google, Yahoo, Ask and Bing, and terms such as atrial fibrillation and stroke combined with patient/ consumer information, patient/ consumer resources, and patient/ consumer education. The search was limited to a time-span of five years (2011 to 2015), representing the immediate period following the inclusion of the first marketed NOAC (dabigatran) as a treatment option for stroke prevention in AF within clinical guidelines (234). Only the first ten pages of each search engine were reviewed.

The websites were screened to identify resources that:

- contained information designed for patients
- described antithrombotic treatment options for AF
- were available in the English language
- did not have access/ subscription charges
- were last updated or reviewed date after August 2011
- were not solely sponsored by pharmaceutical companies (had no obvious conflict of interest)."

5.3.2 Data analysis

A pragmatic approach (mixed method) (235) was adopted for the qualitative analysis of the information provided in these online resources, comprising both content and thematic analysis (i.e., framework analysis) (236). The pragmatic approach provides the researcher the methodological flexibility and adaptability to address the research questions (237-239). The analysis sought to appraise the resources in terms of whether they: provided current and neutral (unbiased) information regarding the available antithrombotic treatment options for AF and their respective management; objectively discussed the risk of bleeding and risk of stroke; and whether these resources provided information about the need for individualised therapy selection. This process involved independent manual inductive coding of the data (i.e., information transcribed from the information resources) by each author. Subsequently, both authors compared their assigned labels and codes to ensure that consensus was attained in the analysis. An analytical framework was prepared by grouping codes into categories, which was then used to index the data extracted from the resources (236).

The identified codes were analysed at two levels: manifest (reports surface theme or codes that are obvious, and are countable, i.e., quantitative data) and latent (interpretative presentation of the content in the dataset, i.e., qualitative data) (240, 241). The manifest level of analysis identified and quantitatively summarised the various facets of stroke prevention therapy in AF addressed in the online content, including how many resources provided an explicit explanation of the relationship between AF and stroke, how frequently the various treatment options and aspects of their management were described, and what information regarding stroke risk and

bleeding risk was provided across the resources. The latent level of analysis identified the underlying themes across these resources (240, 242).

5.4 Results

The initial search yielded 50 resources, after which 17 were excluded as they failed to meet the inclusion criteria e.g., the review date was not published on the website, the website referred/ linked to materials on external sites. Finally, 33 sites were included in the analysis (Table 5-1 and Table 5-2).

5.4.1 Manifest level analysis:

The manifest level analysis revealed that the information within these resources covered four core aspects: Pharmacotherapies available for stroke prevention in atrial fibrillation; antithrombotic management; Anticoagulant therapy management; Risk-benefit assessment (Table 5-3 and Table 5-4). The volume of information presented in these resources ranged from one paragraph up to 36 online pages. One-quarter of the resources (8 out of 33) presented minimal information, such as simply listing the various antithrombotic medications used in AF.

3.1 Pharmacotherapies available for stroke prevention in atrial fibrillation

Most (75.7%) of the resources explained that patients living with AF are at high risk of stroke. Antithrombotic therapy was mentioned as a distinct part of AF management, separate to rhythm and rate control therapy, in all resources; however, only 21.2% of resources clearly stated that the duration of therapy was long-term. Warfarin was the most frequently mentioned thromboprophylactic option among the anticoagulants, being cited in all resources, followed by

dabigatran (82.3% of resources), rivaroxaban (73.5% of resources) and apixaban (67.6% of resources). Aspirin (47%) was the most commonly discussed antiplatelet therapy followed by clopidogrel (23.5%). Other anticoagulants (edoxaban, fluindione, phenindione, phenocoumarone, acenocoumaral), antiplatelet therapy (dipyramidole, ticlopidine), and combination therapy (dipyramidole plus aspirin, aspirin plus clopidogrel, and trifusal plus moderate intensity anticoagulant) were listed in at least two resources each.

The scope for using aspirin for thromboprophylaxis in AF was discussed in over one-third (37%) of resources. Most resources acknowledged the reduced effectiveness of antiplatelet therapy in stroke prevention, compared to anticoagulant therapy, although some suggested that aspirin could be used in certain scenarios (e.g., patient resistance for warfarin, low stroke risk patients, high bleeding risk, and where warfarin is contraindicated), as recommended by USA (40), Canada (243), and Australia (61, 215) based clinical guidelines. Only 11.5% of resources stated that the role of aspirin in thromboprophylaxis in AF was now obsolete, in-line with current UK-based NICE guideline (113), and consensus European guideline (114).

5.4.2 Anticoagulant therapy management

Different aspects of the day-to-day management of the treatment options were described within the resources (Table 5-4: Supplementary attachment). The need for regular blood tests was the most commonly (72.7%) discussed facet of therapy. Patients were also frequently cautioned regarding drug-drug interactions (with over the counter medications, herbal medicines, prescription medicines, supplements) followed by drug-food interactions, then drug-alcohol interactions. Less than one-half of the resources instructed patients to be consistent with their

daily intake of dietary vitamin K whilst taking warfarin. Almost 18.2% of resources cautioned patients regarding the use of anticoagulant during surgery and/ or dental procedures, and 9.1% during pregnancy and/ or breastfeeding. Overall, only half of the resources clearly advised patients to consult doctors before making any changes in how they used or managed their anticoagulants.

5.4.3 Risk-benefit assessment

Approximately one-third of resources explained the role of stroke and/ or bleeding risk assessment in treatment selection; only 21% of resources discussed both stroke and bleeding risk factors (Table 5-3).

Latent level analysis

From the latent analysis of data, three key themes emerged:

Theme 1: The practical ease of managing NOACs over warfarin
Theme 2: Unbalanced explanation about stroke risk versus bleeding risk
Theme 3: Individualised antithrombotic therapy selection

Theme 1: The practical ease of managing NOACs over warfarin

The day-to-day management of warfarin and NOACs was discussed in more than three quarters of resources. Among these, almost two-thirds discussed aspects of regular therapeutic drug monitoring; some resources were suggestive of the relative convenience of using NOACs compared to warfarin.

All of these (NOACs) are simpler to use and less risky than warfarin (bleeding risk is lower) ***(USA-4;Non-Profit)***

This means that they work differently to vitamin K antagonists (for example warfarin and acenocouramol) and there are no restrictions on food if you are taking one of the new blood-thinning medicines. In addition, the way the body responds to these new medications is much more stable than with warfarin, so you do not need regular blood tests to measure the effectiveness of these new blood-thinning medicines, as you do with vitamin K antagonists such as warfarin and acenocoumarol. ***(UK-1;Non-Profit)***

Dabigatran, apixaban and rivaroxaban do not need regular blood tests. ***(UK-2;Non-profit)***

However, some (9%) of the resources criticised warfarin's complex management relating to regular INR monitoring, directly favouring the NOACs due to their comparatively easier management.

While Coumadin™(warfarin) has been around longer, periodic blood tests to check on Coumadin (warfarin) levels may be less desirable. Pradaxa™(dabigatran) (twice a day) and Xarelto™(rivaroxaban) (once a day) may be more convenient ***(USA-17;Commercial)***

The newer agents that are as effective as warfarin in preventing strokes in patients with atrial fibrillation that do not require such intense monitoring or dietary restrictions. ***(USA resource-16;Commercial organization)***

Dabigatran controls your clotting levels, but you do not need the same rigorous INR monitoring as you need with warfarin ***(UK-3;Non-Profit)***

In contrast, only some (9%) resources presented a more accommodating portrayal of warfarin therapy management.

While the instructions for warfarin seem daunting at first, many people are able to take warfarin without experiencing problems ***(Australian-3;Non-Profit)***

This all can sound a bit daunting but the vast majority of people who take warfarin can do so without any problems ***(UK-6; Non-Profit)***

Theme 2: Unbalanced explanation about stroke risk versus bleeding risk

Although many of the resources did discuss the bleeding risks associated with anticoagulation, only a selected few also mentioned the dangerous consequences of having a stroke. Overall, the benefit of anticoagulation was overshadowed by the focus on bleeding risk. More than three-quarters of the resources mentioned only that all antithrombotic therapies carry an inherent risk of bleeding, pertaining to various sites of the body such as brain, nose, gastrointestinal tract, and urinary tract, without emphasising the consequences of experiencing a stroke.

> *Warfarin is a powerful medication that may cause dangerous bleeding* ***(USA-8; Non-profit)***
>
> *The greatest risk with blood thinners is the chance of bleeding* ***(USA-1; Commercial)***
>
> *More serious type of bleeding (for example: into the brain or the digestive system) needs immediate medical care* ***(Canada-1; Non-profit)***

Only 9% of resources also explained the deleterious effects of having a stroke.

> *Strokes can cause brain damage. This may affect the ability to talk, move and think. Strokes can be life-threatening* ***(International organisation-1; Non-profit)***
>
> *Sometimes stroke is so severe that it can kill the person straight away* ***(UK-6; Non-profit)***
>
> *Such clots can travel from the heart to the brain where they can block blood flow-resulting in a stroke that can be debilitating and deadly* ***(USA-11; Non-profit)***

Relatively few resources conveyed views on the risk versus benefit of antithrombotic therapy, emphasising the benefit of antithrombotic therapy in stroke prevention, and clarifying that the risk of bleeding was overestimated in most cases.

When used as directed, however, anticoagulants have proven very effective for AF patients. Although the potential risks seem severe, the life-saving effects give these drugs a bright upside ***(USA-4; Non-Profit)***

The most serious type of bleeding is bleeding into the brain. However, the benefit of preventing stroke is greater than the small risk of bleeding in most of the cases ***(USA-16; Commercial)***

Although the risk of bleeding related to warfarin does exist, it is often exaggerated. Fears of bleeding unnecessarily put off many people from taking this very important drug ***(UK-1; Non-Profit)***

There is an increased risk of bleeding in people who take warfarin, but this small risk is usually outweighed by the benefits of preventing stroke ***(UK-4; Non-Profit)***.

Theme 3: Individualised antithrombotic therapy selection

Almost half of the resources stated that the choice of therapy was highly patient specific, requiring patient engagement in the decision-making process. This was explained in terms of the health professional selecting the anticoagulant therapy best suited to patients' needs, based on their individual risk-benefit assessment, and after the consideration of pros and cons of the available options. More than one-fifth of the resources also provided a detailed explanation on stroke risk assessment (CHA_2DS_2-VASc) (42) and bleeding risk assessment (HAS-BLED) (43).

Each treatment also has other advantages and disadvantages that different people feel differently about. This decision aid is intended to give you information about these advantages and disadvantages to help you and your health professional make the best choice for you. Your healthcare professional should use risk scores to estimate your risk of stroke (called the CHA_2DS_2-VASc) and risk of bleeding (called the HAS-BLED) ***(UK-1;Non-Profit)***

Your healthcare professionals will help you weigh the pros and cons of taking an anticoagulant and decide which one to take. Make the decision together ***(USA-12; Non-Profit)***

The medicine that is most suitable for you depends on your risk of having a stroke, other medical conditions and risk factors you might have. This will differ from person to person according to individual circumstances. After discussing your individual risks and the benefits of treatment, you and your doctor can decide which medicine is most suitable for you ***(Australia-3; Non-Profit)***

In contrast to the individualised risk-benefit approach presented in some resources, a few (almost 6%; mostly from USA) seemed to have an implied preference for NOACs over warfarin therapy and inferred that the newer agents may be superior choices.

Talk to your doctor about taking one of these newer anticoagulants as an alternative to warfarin if you're concerned about your risk of stroke ***(USA-8; Non-profit)***

Several newer drugs are also available: dabigatran, rivaroxaban and apixaban. These drugs are increasingly used instead of warfarin ***(USA-13; Commercial)***

In other resources (12.5%) warfarin was still presented as the first choice for thromboprophylaxis in AF, unless specific problems arose, thereby moderating the need to switch to the newer agents.

If you are already taking warfarin, and your INR is stable, there is little or no benefit in switching to another anticoagulant ***(Australian-3; Non-Profit)***

If you find it difficult to remember to take your regular dose, then the newer anticoagulants may not be suitable for you because the protective effect wears off quickly ***(UK-5; Non-Profit)***

When INR control is very good, it (warfarin) may be a better treatment overall. If warfarin control is poor, despite taking it properly the newer anticoagulants may offer a better treatment ***(UK-5; Non-Profit)***

The choice of these drugs which are used to reduce chance of clot formation in patients with chronic Afib (Atrial Fibrillation) is often determined by the patient's problems with

Coumadin™ (warfarin) and the preference or experience of the cardiologist with these drugs ***(USA-6; Commercial)***

5.5 Discussion

To our knowledge, this is the first study that has qualitatively assessed the content presented within web-based resources that have been designed to inform patients regarding stroke prevention therapies. This study has found that some of the resources did not provide information regarding the availability of NOACs as treatment options for stroke prevention in AF. Additionally, the described scope for using aspirin as a treatment option was highly variable across these resources, which may reflect the lack of consensus among clinical guidelines in terms of its use (40, 61, 113, 114, 215, 243). Nevertheless, the citation of aspirin as a thromboprophylactic option in AF is of major concern, given that recent studies have highlighted that aspirin offers poor protection from thromboembolism compared to anticoagulant therapy, with an equivalent risk of bleeding (244), and that current clinical guidelines explicitly recommend that aspirin should not be considered for stroke management in AF (113, 114).

This study shows that, while most of the websites have provided a neutral perspective on the treatment options (and their associated risks and benefits), some resources potentially present relatively unbalanced information, as reported in similar studies informing patients about other health conditions (245-247). It was also noted that some patient resources were inclined toward either using NOACs or warfarin. For instance, some of the resources did inform patients about the ease of managing NOACs in comparison to warfarin therapy given the absence of regular therapeutic monitoring. Although this statement may be factually correct, it does not provide the full picture in terms of using these medications, given that NOACs are not completely devoid

of the requirement for therapeutic drug monitoring. First, in certain situations, such as emergency surgery or other invasive procedures, haemorrhagic events, suspected overdose, acute thrombosis in renal, liver or heart failure, potential drug-drug interactions, trauma, acute medical disease and malignancy, it is important to monitor coagulation parameters (25). Second, studies have also reported that some patients are not concerned by regular therapeutic drug monitoring as it gives them a sense of protection and safety (149, 159). Third, these resources also need to inform patients that point-of-care devices are now available to assist with self-testing, removing some of the burden of coagulation monitoring (248). In this context, it is also important to know that neither warfarin nor the NOACs are equally appropriate choices in all patients; the treatment selection is highly patient-specific (40, 191, 203), and decision-making may become complicated and time-consuming if patients with AF (especially newly diagnosed) have pre-existing negative perceptions about any specific therapy before discussing the options with their doctors. Studies have stated that patients do not always possess the required skills and expertise to differentiate among the information provided from one resource to the next, leading to confusion and misinformation (249, 250).

This study observed that most of the resources provided seemingly unbalanced information about the risks versus benefits of using anticoagulants, such that bleeding risk was discussed relatively more compared to stroke risk. This is important because most patients already possess an exaggerated fear of bleeding (132), which may be exacerbated by an unbalanced discussion about the risks of the therapy. This in turn may negatively impact on patients' quality of life during anticoagulant therapy, and/or undermine their medication adherence (137, 153, 158, 159). Moreover, although the information about risks may be factually-correct, the phrasing used in

these resources must also be considered, such that, instead of using descriptive terms like ‘high risk’ or ‘low risk’, resources may use expressions such as ‘likelihood of having stroke/bleeding.

This study highlights that few resources provide a detailed explanation of the role of risk-benefit assessment in the selection of antithrombotic therapy. Specific tools are available to help assess a person’s risk of stroke and risk of bleeding; the tools currently advocated by many clinical guidelines are CHA_2DS_2-VASc and $CHADS_2$ (the latter two for stroke risk), and $HEMORR_2HAGES$ and HAS-BLED (the latter two for bleeding risk). The assessment of stroke and bleeding risks are essential to determining the probable risk versus benefit of treatment in an individual. Giving patients’ access to these tools may help them better understand their specific risks, as well as help engage them in the decision-making process. However, such tools alone are insufficient to inform patients about their treatment options, and therefore they must be presented within well-designed, balanced information. Furthermore, these tools possess their own limitations as prediction aids, such that they may not be accurate, given their low-to-moderate prediction abilities (as reflected in their reported c-indices) (251, 252). Therefore, such tools should be aids to decision-making, not replacements for SDM comprising discussion between health professionals and patients, and which should be supported by well-designed information resources.

The information presented in resources that support shared decision-making must be balanced, objective, and unbiased, so as to allow patients to make informed decisions whilst accounting for their individual preferences (253, 254). To an extent, patients and caregivers can themselves appraise the quality hallmarks of online content by using tools such as HONcode (which assesses: authority; complementarity; privacy; attribution; justifiability; transparency; financial

disclosure; advertising policy) and DISCERN tool (which comprises 16 questions for assessing online resources) (255, 256). However, the usefulness of the information contained in such resources requires more than these types of assessment. Studies conducted in other health contexts, where individualised risk versus benefit assessments are important to therapy selection (e.g., hormone replacement therapy for menopause), have reported that many patients find it difficult to understand the description of risks and benefits (e.g., difference between relative risk and absolute risk reduction) presented in online information resources (257). These concepts are at the core of decision-making for stroke prevention in AF, and for this reason it is important for health professionals to engage patients in discussion of these issues, particularly in terms of how they relate to an individual person.

Unlike other studies that have focused on assessing the readability and suitability of patient education resources (258), this study has holistically appraised the nature of the content (information) presented within these resources. Overall, the findings suggest that resources must better align with patients' needs, factor patients' perceptions which might influence their decision, and should contain information that supports patient engagement in decision-making (259, 260). Shared decision-making empowers patients (or their carers) to be actively involved in the decision-making around therapy selection, engages them in setting treatment goals, and enables them to optimally use the available educational resources and tools (261). The effectiveness of such approaches is highlighted in studies of other health conditions; for example, in a randomised controlled trial, patients with diabetes who participated in an empowerment programme (providing targeted education on self-management of diabetes in their day-to-day life) were better able to set treatment goals, obtain appropriate social support, engage in decision-making, and improve their blood glucose control, compared those not in the

programme (262). SDM thereby gives rise to the 'Informed Patient', focusing on achieving optimum health benefits by involving patients in their own healthcare via knowledge empowerment. This demands the provision of evidence-based, high quality, accessible resources information taking into account patients' cultural, functional (physical, cognitive), psychological, and social status, thereby addressing individuals' needs for knowledge and support (224, 263, 264). In regard to antithrombotic therapy, studies have demonstrated that suboptimal education leads to patient dissatisfaction with the healthcare services, inability to self-manage, and poor adherence to treatment plans, leading to adverse outcomes (172, 265).

5.5.1 Study Limitation

In interpreting the study findings, it is important to consider some potential methodological limitations. First, restricting the search to resources available in the English language means that the findings of this study may not be representative of resources or websites written in other languages. Given that most of the reviewed websites are English-language sites originating from western countries (UK, USA, Canada, Australia), the findings of this study might not apply to websites designed in developing countries. In general, the literature suggests that most of the research undertaken around patient education and online information is based in so-called developed western countries where there is relatively high health literacy among the population and good access to online resources. In developing countries it is likely that there are fewer online resources, less access to these resources for those patients who need it, and lower health literacy (266). Culturally, there may also be differences in patient expectations around decision-making (190, 267), which need to be further explored.

Second, newsletters and periodic articles published on AF were not included in study. Third, given that this online search was conducted via an Australian online domain, it may not have identified all potentially relevant resources hosted on international domains. Lastly, given the focus on assessing resources targeting patients, resources designed for clinicians were not reviewed, although these may also be accessed by patients on some websites.

5.6 What is new and conclusion

Although online resources are highly accessible, there needs to be consideration of the quality and nature of information provided in them. This information needs to support patients in informed decision-making, leading to enhanced adherence to treatment, and improved clinical outcomes. It is important that healthcare professionals recommend reliable resources to their patients and educate patients on how to evaluate the quality of online resources.

Table 5-1. Representation of AF patients' educational resources from various sources included in the study

Country	Sources (Last visited)	Type of Resource
United States of America (USA)	➢ National Blood Clot Alliance (5/03/2015) http://www.stoptheclot.org/learn_more/blood_clot_treatment.htm	Non-profit
	➢ North American Thrombosis Forums (3/03/2015) http://www.natfonline.org/afib-action/resources-for-patients-and-clinicians/patient-resources/ http://www.natfonline.org/media/57782/living_well_with_atrial_fibrillation_and_reducing_your_risk_of_stroke.compressed.pdf	Non-profit
	➢ American College of Cardiology (04/01/2015) https://www.cardiosmart.org/healthwise/hw16/0870/hw160870#hw160870-HealthTools	
	➢ American College of Chest Physicians (31/03/3015) http://www.chestnet.org/Search#q/q=ATRIAL%20FIBRILLATION	
	➢ National Stroke Association (30/03/2015) http://www.stroke.org/sites/default/files/resources/NSA_FactSheet_Afib_2014.pdf	Non-profit
	➢ American Heart Association/ American Stroke Association (31/03/2015) http://www.strokeassociation.org/STROKEORG/LifeAfterStroke/HealthyLivingAfterStroke/ManagingMedicines/Anti-Clotting-Agents-Explained_UCM_310452_Article.jsp	
	➢ University of Utah (30/03/2015) http://healthcare.utah.edu/cardiovascular/conditions/understanding_atrial_fibrillation.pdf	Non-profit
	➢ National Institute of Neurological Disorder and stroke (30/03/2015) http://www.ninds.nih.gov/disorders/atrial_fibrillation_and_stroke/atrial_fibrillation_and_stroke.htm#Is_there_any_treatment	

➢ University of Maryland Medical Centre (1/03/2015) http://umm.edu/health/medical/ency/articles/atrial-fibrillation-or-flutter	Non-profit
➢ The Internet Stroke Centre (1/03/2015) http://www.strokecenter.org/patients/stroke-treatment/stroke-medications/anticoagulants/	
➢ Mayo Clinic (1/03/2015) http://www.mayoclinic.org/diseases-conditions/atrial-fibrillation/basics/treatment/con-20027014	Non-profit
➢ Alliance for Ageing Research (31/03/2015) http://www.agingresearch.org/Publications/view/116#.VWaPZeN3jxR	Academic
➢ UpToDate (28/03/2015) http://www.uptodate.com/contents/ischemic-stroke-treatment-beyond-the-basics	
➢ Healthline (28/03/2015) http://www.healthline.com/health/living-with-atrial-fibrillation/medication- guide#BloodThinners4	Non-profit
➢ Drugs.com (25/03/2015) http://www.drugs.com/health-guide/atrial-fibrillation.html	
➢ Patient Education Centre (25/03/2015) http://www.patienteducationcenter.org/articles/atrial-fibrillation/	Academic
➢ Emedicine (25/03/2015) http://www.emedicinehealth.com/atrial_fibrillation/page8_em.htm#atrial_fibrillation_afib_medical_treatment	
➢ MedicineNet.com (25/03/2015) http://www.medicinenet.com/atrial_fibrillation/page6.htm#anticoagulation_drugs_to_prevent_blood_clots_and_strokes	Non-profit
➢ WedMD (25/03/2015) http://www.webmd.com/heart-disease/atrial-fibrillation/ http://www.webmd.com/stroke/understanding-stroke-treatment?page=2	Non-profit

	Non-profit
	Commercial
	Commercial
	Commercial
	Non-profit
	Commercial
	Commercial

		Commercial Commercial
Europe/ United Kingdom (UK)	➢ British Heart Foundation (1/03/2015) https://www.bhf.org.uk/~/media/files/publications/large-print/his24lp_atrial-fibrillation_0312.pdf ➢ Atrial Fibrillation Association(AFA)- UK (2/04/2015) http://www.atrialfibrillation.org.uk/files/file/140917-cjw-%20Fin%20-%20Anticoagulation%20and%20AF%20PS.pdf ➢ National Health Services(NHS) (31/03/2015) http://www.nhs.uk/Conditions/atrial-fibrillation/Pages/Introduction.aspx ➢ National Health Services(NHS) York Hospital (31/03/2015) https://www.google.com.au/#q=NHS+York+hospital+Atrial+fIBRILLATION ➢ National Institute of Health and Care Excellence (NICE) (2/4/2015) http://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-update-patient-decision-aid-243734797 ➢ AFIBMATTERS (01/03/2015) http://www.afibmatters.org/ ➢ Patient.co.uk (30/03/2015) http://www.patient.co.uk/health/preventing-stroke-when-you-have-atrial-fibrillation	Non-profit Non-profit Non-profit Non-profit

		Non-profit Non-profit Non-profit
Australia	➢ NPS Medicine Wise (05/03/2015) http://www.nps.org.au/search-result?collection=nps&morph_query=query&morph_target_query=ATRIAL+FIBRILLATION ➢ Anticoagulation.com.au (31/03/2015) http://www.anticoagulation.com.au/Home/Welcome/tabid/125/Default.aspx ➢ Better Health Channel (05/03/2015) http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Stroke_-_risk_factors_and_prevention http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/heart_conditions_atrial_fibrillation	Non-profit Non-profit Non-profit

Canada	➢ Heart and Stroke Foundation (04/04/2015) http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484137/k.2CCE/Heart_disease__Anticoagulants.htm http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.8767207/k.2C2C/Your_Complete_Guide_to_Atrial_Fibrillation_AF_htm	Non-profit
International	➢ American Academy of Neurology (World Stroke Organisation) (31/03/2015) http://www.world-stroke.org/images/atrial_fibrillation_PS_web.pdf	Non-profit
	➢ National Heart, Lung and, Blood Institute (31/03/2014) http://www.nhlbi.nih.gov/health/health-topics/topics/af/treatment	
	➢ Heart Rhythm Society (01/03/2015) http://resources.hrsonline.org/pdf/patient/HRS_AF-Patient-Broch_FINAL2014.pdf	Non-profit
Total Resources	**33**	Non-profit

Table 5-2. List of educational resources excluded from the study

Resources	**Reason for exclusion**
Anticoagulation Europe	Broken Link
Bupa Aged Care	Directed to another site for information which is included in this study for analysis
Cleveland Clinic	No information about last review/ update date
European Society of Cardiology	Directed to another site for information which is included in this study for analysis
Get Smart	No information about last review/ update date
Medscape	Site for health professionals and not for patients
Stroke Alliance for Europe	No information provided on pharmacotherapy for stroke prevention in AF
Merck Manuals	Site specifically for health professionals and not for patients
Stroke Foundation	Directed to another site for information which is included in this study for analysis
Stroke Recover Association-NSW	No information provided on pharmacotherapy for stroke prevention in AF

Team-A	Resource designed by the drug company- Bristol Mayer Squibb and Pfizer
Thrombosis Advisor	Resource designed by the drug company- Bayer
Health Care Victoria	No information about last review/ update date
Drugs.com	No information about last review date, and directed to other sites which are included in this study for analysis
StopAfib.org	Directed to another site for information which is included in this study for analysis
Heart Foundation	Outdated
Clot Connect	No information regarding clot prevention treatment in connection with AF
Total	**17**

Table 5-3. Information about stroke and bleeding risk assessment scores presented within various web-based information resources

Resource	**Factor/s for selecting best medication**	**Stated purpose of risk assessment scores**
United States of America		
University of Maryland	Age and other medical problems	
American College of Cardiology	Stroke risk calculator	
North American Thrombosis Forum	Mentions $CHADS_2$ score	
United Kingdom		
Atrial Fibrillation Association	AF related stroke risk- CHA_2DS_2-VASc	Whether to be on anticoagulation or not

	Medical procedures Comorbidities: kidney impairment or heart valve disease	
NHS	Age, history of stroke, heart valve problems, heart failure, high blood pressure, diabetes, heart disease	-
AFibMatters	Calculator (MD+CALC): ATRIA bleeding risk scores, ATRIA stroke risk score, CHA_2DS_2, CHA_2DS_2-VASc, HASBLED, and $HEMORR_2HAGES$	Stroke risk: whether patients should be on anticoagulation or not Bleeding risk: Whether patients should be on anticoagulants or other alternatives
NICE Guideline	CHA_2DS_2-VASc score and HASBLED score	How risk of bleeding and stroke varies depending on the risk scores if patient takes anticoagulant or if patient doesn't take anticoagulant

British Heart Foundation	CHA_2DS_2-VASc score	-
Australia		
NPS MedicineWise	$CHADS_2$ and CHA_2DS_2-VASc HAS-BLED	-
Emergency Care Institute New South Wales	Calculator (MD+CALC): ATRIA bleeding risk scores, ATRIA stroke risk score, $CHADS_2$, CHA_2DS_2-VASc, HASBLED, and $HEMORR_2HAGES$	Stroke risk: whether patients should be on anticoagulation or not Bleeding risk: Whether patients should be on anticoagulant or other alternatives
Canada		
Heart and Stroke Foundation	$CHADS_2$ and HAS-BLED	-

Table 5-4. Various aspects of anticoagulant therapy management discussed within the web-based information resources.

No.	Resource	Regular monitoring-INR (dose adjustments)		Drug-food interactions		Drug-alcohol interactions		Drug-drug interactions		Bleeding risk		Periodic kidney function test with NOACs	Antidote for NOACs	Short half-lives of NOACs		Alert card advised	Dose adjustments required when undergoing Surgery or dental procedures	Caution in pregnancy/ breast-feeding (consult doctor)	NOACs are expensive
		W	NOACs	W	NOACs	W	NOACs	W	NOACs	W	NOACs			Bleeding management	Missed dose (↑ stroke risk)				
1	**Atrial Fibrillation Association (AFA-UK)**	✓	N	*	×	✓	×	×	×	×	×	✓	N	✓	✓ (Rivaroxaban and Dabigatran)	×	×	×	×
2	**British Heart Foundation**	✓	N	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
3	**NHS York**	✓	N	*	N	✓	N	✓	↓		↑ : Noseble ed and	✓	N	×	✓	✓	✓	×	×

											Hematuria **(Rivaroxaban and Apixaban)** ↓: Intracranial **(Dabigatran and Apixaban)** ↑: Gastrointestinal								
4	**NHS**	✓	×	*	×	✓	N	✓	×	×	×	×	×	×	×	×	✓	✓	×
5	**Nice**	✓	N	*	N	✓	N	✓	✓	×	×	✓	N	✓			✓	×	×
6	**Patient.co.uk**	✓	N	✓	↓	✓	↓	✓	↓	×	×	×	N	✓	×	×	×	×	×

7	**NPS MedicineWise (National Stroke Foundation)**	✓	N	*	N	✓	✓	✓	✓	×	×	✓	N	×	×	×	×	×	×
8	**Heart foundation**	✓	×	✓	×	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
9	**anticoagultion. com.au**	✓	N	*	↓	✓	✓	✓	↓	×	×	×	N	×	×	✓	×	✓	×
10	**American heart association/ American Stroke association**	×	×	*	×	✓	×	✓	×	×	×	×	×	×	×	✓	✓	✓	×
11	**Mayo clinic**	✓	N	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
12	**American College of Cardiology**	✓	N	×	×	×	×	✓	√	×	×	×	×	×	×	×	×	×	×
13	**National Blood Clot Alliance**	✓	N	*	✓	✓	×	✓	↓	×	×	×	N	×	×	×	×	×	✓
14	**Clot connect**	✓	N	*	×	×	×	✓	↓	×	×	×	N	×	×	×	×	×	✓
15	**National Stroke Association**	✓	N	×	×	×	×	×	×	×	×	×	N	×	×	×	×	×	×

16	**Heart Rhythm Society**	✓	N	*	×	×	×	×	↓	×	×	×	N	×	✓ **(Apixaban)**	×	×	×	✓
18	**UpToDate**	✓	N	*	×	✓	×	×	×	×	×	×	×	×	×	✓	✓	×	×
19	**Healthline**	✓	×	×	×	×	×	✓	✓	×	×	×	×	×	×	×	×	×	×
20	**Patient education centre**	✓	N	×	×	×	×	×	×		↓	×	×	×	×	×	×	×	✓
21	**WebMD**	✓	N	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	✓
22	**Heart and Stroke foundation**	×	×	✓	×	✓	✓	×	×	×	×	×	×	×	×	×	✓	×	×
23	**American Academy of Neurology (World Stroke Organisation)**	✓	N	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
24	**Afibmatters**	✓	N	*	N	✓	×	✓	✓		↓: Intracranial	✓	×	×	✓	×	×	×	×
25	**American Academy of Neurology**	✓	×	×	×	×	×	×	×		↓	×	×	×	×	×	×	×	×

	(World Stroke Organisation)																		
24	**Health Care Victoria**	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
25	**Aetna**	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
26	**Emergency care institute (New South Wales)**	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
27	**North American Thrombosis forums**	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
28	**National Institute of Neurological Disorder and stroke**	×	N	✓	×	×	×	✓	×		↓	×	×	×	×	×	×	×	×

W = Warfarin; NOACs= Novel Oral Anticoagulants; *= Dietary restriction with respect to daily vitamin K intake; N= No interaction OR No regular monitoring required OR No Antidote available; ×= Information not available in the resource; ✓= requires regular monitoring OR has drug interactions OR information provided in the resource; ↑= one has potentially more risk than other; ↓= one has potentially less risk than other

5.7 Supplementary material

Secondary-analysis: Evaluating web-based resources on treatment options for stroke prevention in atrial fibrillation using HONCODE 1.5 criteria.

"The HONCODE certification is an ethical standard for providing quality health information. It demonstrates whether a website publishes transparent information. The health websites for HONCODE certification are evaluated according to 8 criteria" (268):

Principle 1	**Authority** Give qualifications of authors
Principle 2	**Complementarity** Information to support, not replace
Principle 3	**Confidentiality** Respect the privacy of site users
Principle 4	**Attribution** Cite the sources and dates of medical information
Principle 5	**Justifiability** Justification of claims / balanced and objective claims
Principle 6	**Transparency** Accessibility, provide valid contact details
Principle 7	**Financial disclosure** Provide details about funding
Principle 8	**Advertising** Clearly distinguish advertising from editorial content

5.8 Supplementary material - HONECODE 1.5 Assessment of the web-based resources for stroke prevention in atrial fibrillation

HONCODE Checklist	Total resources providing information n (%)

	N=33
1. Authoritative Indicate the qualifications of the authors	29 (87.9)
2. Complementarity Information should support, not replace, the doctor-patient relationship	29 (87.9)
3. Privacy Respect the privacy and confidentiality of personal data submitted to the site by the visitor	30 (90.9)
4. Attribution a) Cite the source(s) of published information, b) Date medical and health pages	 1 (3.0) 27 (81.8)
5. Justifiability Site must back up claims relating to benefits and performance	2 (6.1) - provided justification about the benefit of being on anticoagulants but without any references
6. Transparency Accessible presentation, accurate email contact	32 (97.0)
7. Financial disclosure Identify funding sources	15 (45.5)
8. Advertising policy Clearly distinguish advertising from editorial content	22 (66.7)

5.9 Contribution of authors

1.Ekta Pandya

a. Conducting the literature search
b. Analysing the studies, and designing the structure of the manuscript
c. Writing the drafts
d. Submitting the manuscript, and coordinating with the Journal
e. Revising the manuscript as per reviewers' comments and resubmitting the manuscript.
f. Responsible for the conduct of the study in the hospital
g. Recruit and enrol patients for the study

2. Beata Bajorek

a. Conceiving and designing the study

b. Assistance in conducting literature search, and analysing the studies

c. Supervision in designing the structure of the manuscript

d. Ensuring the intellectual content in the manuscript

e. Writing, editing and proof-reading the manuscript

f. Assistance in addressing reviewers' and editor's comments

6 Discussion and Conclusion

6.1 Discussion

The broader context for the research presented in this thesis is that anticoagulant therapy is recommended as the first-line treatment for stroke prevention in AF (38, 130). However, such studies have reported that suboptimal anticoagulant prescribing in eligible patients is a major public health issue and contributes to the burden of preventable stroke (17, 18, 269). The availability of DOACs among the range of treatment options has expanded the scope thromboprophylaxis in AF. Nevertheless, as with the warfarin therapy, the risk of bleeding versus benefit of stroke prevention assessment is equally important with using of DOACs, and this adds to the complexities in decision-making around individualised therapy selection. Thus, it is important to explore the factors influencing decision-making for antithrombotic therapy selection in AF, from both prescribers' and patients' point of view.

This research primarily studied the impact of a decision-making support tool (CARAT) on the utilisation of antithrombotic therapy (especially warfarin), and reported the predictors of warfarin therapy prescription, on the background of a retrospective clinical audit that explored the use of anticoagulants for stroke prevention in AF post-PBS listing of the DOACs in Australia, and subsequently identified the factors affecting the prescription of DOACs. The rapid changes taking place in this clinical context must be acknowledged as the evidence around treatment options grows and as new treatment options continue to emerge. Thus, even within the timeframe of this thesis, some of the findings from the earlier stages should be considered in light of these rapid changes. For example, the original CARAT used $CHADS_2$ and $HEMORR_2HAGES$ risk scoring algorithms, but more recent research focuses on variations of these scoring tools (i.e., CHA_2DS_2-VASc and HAS-BLED), which have already been incorporated in certain guidelines (39, 40, 270). This does not invalidate the work in this thesis, as the findings demonstrate the value of such tools in facilitating a comprehensive risk–benefit assessment. However, it does highlight the need to ensure that such tools are updated to reflect current evidence, and that much is still unknown regarding the quantification of risk in this clinical context. Indeed, in the decision-making process within the CARAT tool, significant emphasis is placed on the safety of treatment selection (i.e., on the 'risk' in the assessment of

risk versus benefit). The research in this thesis reflects the recommendations made at the time of the study, which have evolved as the evidence-base has changed. A salient feature of the CARAT is that it has always strived to practically address any known risks in order to facilitate the appropriate use of antithrombotic therapy for the individual patient. This goal is reflected in the study's finding of improved use of treatment following application of the tool.

6.1.1 Prescription of anticoagulants in an Australian setting

Within a local hospital setting in Sydney, our study confirmed that despite the availability of comparatively easy-to-manage DOACs, a considerable proportion (42.8%) of the 'most eligible' patients (i.e., patients with high risk of stroke and no contraindications for antithrombotic therapy) were still not treated with anticoagulation therapy in 2014. However, recent studies conducted at hospitals in Tasmania, Australia, one study found an increase in anticoagulant use 54.4% in 2013 to 68.1% in 2015 (P <0.001) (271) and the other found increase from 52.5% versus 60.7% (P <0.001) (272), which can be attributed to the recent listing of DOACs on the PBS. However, the Tasmanian study also highlighted that DOACs were more commonly prescribed in preference to warfarin therapy mostly among younger patients with a relatively lower stroke and bleeding risk scores (271). In support of this finding, our research also observed that DOACs were prescribed in preference to warfarin therapy mostly among younger patients with lower bleeding risk and stroke risk scores (although not statistically significant). This suggests that anticoagulants remain sub-optimally prescribed in at-risk older patients. In general, the under-treatment of eligible patients appears to be underpinned by a number of issues, as highlighted in our research and other similar studies. The reasons for the suboptimal prescription of anticoagulants include prescribers' propensity to underestimate the risk of stroke in patients with paroxysmal AF, and their lack of experience in managing complex anticoagulant therapies (273).

This thesis research observed that DOACs were less likely to be used than warfarin therapy among patients with renal impairment. This may be explained by the complexity surrounding the decision-making for therapy selection, being attributed to the specific factors listed below:

- The specific pharmacological differences between warfarin (i.e., hepatically cleared) versus DOACs (i.e., more commonly renally cleared) (163, 274)

- the need for caution when managing patients with renal impairment who have also been prescribed DOACs (28), in particular dabigatran (the most renally cleared of the currently available DOACs)
- the dearth of data on the safety and efficacy of DOACs in the 'real-world' settings, specifically within Australia (275)
- the limited access or unavailability of antidotes to manage episodes of acute bleeding were associated with DOACs (28)

6.1.2 Using decision-support tools in therapy optimisation

The CARAT intervention study observed that, during hospital admission (pre-CARAT application), the prescription of antithrombotic therapy in more than half of the patients was not based on their individualised risk-benefit assessment. A lack of knowledge about thromboprophylaxis, difficult risk–benefit assessment of patients, and restricted consultation time reduced prescribers' ability to initiate and manage anticoagulant therapy (172, 197, 276). Various interventions have been implemented to assist clinicians in complex decision-making including: a) educating clinicians on current guidelines; b) use of validated stroke risk assessment scores ($CHADS_2$/ CHA_2DS_2-VASc) (31, 42, 64); c) use of bleeding risk assessment scores ($HEMORR_2HAGES$/ HAS-BLED) (32, 43); and d) providing clinicians with comprehensive decision-support tool(s) such as the Computerised Antithrombotic Risk Assessment Tool (CARAT) (30). However, it is important to be able to correctly identify cases of new-onset atrial fibrillation at baseline when reviewing treatment use and determining the impact of decision-making tools, such as CARAT 2.0. In the study described in Chapter 2 of this thesis, a total of 24 (12.3%) patients had new-onset of AF surprisingly,17 of these were receiving anticoagulant therapy (either warfarin or warfarin in combination with antiplatelets) at baseline, while the remaining 6 patients were receiving 'nil therapy' at baseline. It is possible that the baseline (pre-CARAT intervention) antithrombotic use is underestimated among these 6 patients, because those with new-onset of AF were mistakenly categorised as upgrades during the data analysis. This in turn would have led to a very slight overestimation of CARAT's role in optimising antithrombotic therapy. Nevertheless, this should not discount the potential of CARAT

2.0 as a tool for individualised selection of treatment based on a comprehensive assessment of stroke risk - bleeding risk and medication safety issues. This can be supported by findings from a previous hospital based study in Sydney, which also reported that CARAT particularly optimised anticoagulant prescribing in patients aged ≥ 65 years (60) who are otherwise under-treated and who were at high risk of stroke (17).

Decision-support tools, such as CARAT, have the potential to improve evidence-based antithrombotic therapy prescribing in practice thereby preventing strokes, adverse drug events, and improving overall clinical outcomes (22). In fact, a recent study highlighted that most health professionals involved in antithrombotic therapy management acknowledge the usefulness of using CARAT as an adjuvant to their daily practice resources to optimise therapy selection (33), as also evidenced in our research and other similar studies (60, 277). However, this research reported that, in some cases, clinicians still refrain from prescribing anticoagulants due to fear of patients' nonadherence and patients' refusal to take anticoagulants. Thus, some health practitioners have suggested that prior to prescribing antithrombotics, clinicians could use the CARAT to help patients navigate through their stroke risk and bleeding risk whilst also assessing their perceptions about, and expectations of, the therapy (33).

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6.1.3 Influencers of patients' acceptance for, and adherence to, anticoagulant therapy (warfarin/ DOACs)

The literature review in this thesis demonstrated that a range of factors underpin patients' preference for, and adherence to, anticoagulant therapies: i) therapy-related factors; ii) patient-related factors; iii) condition-related factors; iv) social–economic factors; and v) health-system factors. This research highlighted the impact of the treatment on patients' lifestyles, which played a key role in their acceptance for, and adherence to, the prescribed therapy. More than three-quarter of the studies in the review reported that patients had issues with the regular INR monitoring required with warfarin therapy. However, these attitudes may have been affected by the mode of testing, with studies showing that the use of home-based self-testing devices could improve patients' time in therapeutic range (278, 279), their satisfaction with these self-testing devices (278), and their quality of life in comparison to those patients who undergo INR testing in clinics (278). Furthermore, these self-testing devices are cost-effective when used properly by patients (280). The other concerns were the requirement for dose adjustment with warfarin and consideration of dietary vitamin K intake, alongside its interactions with various drugs. Additionally, specific factors, such as the necessity to take some medications (rivaroxaban and dabigatran) after meals, the limited availability of antidotes, frequent dosing (twice daily dosing as observed in dabigatran and apixaban) have negatively influenced their acceptance among some patients. On the other hand, rivaroxaban 20 mg (once daily) has a prolonged pharmacological effect (i.e., prolonged inhibition of factor Xa activity and endogenous thrombin potential for up to 24 hours) and does not require frequent dosing. Moreover, a 20 mg once daily dose of rivaroxaban also provides optimum safety and efficacy in long-term conditions, such as, AF and deep vein thrombosis (DVT) (281). Therefore, rivaroxaban and warfarin might be preferred by patients who are on polypharmacy to reduce the total pill-burden.

This study also observed that patients in generally had a poor understanding of the relationship between AF and the associated risk of stroke. Such perceptions lead

patients to downplay the importance of long-term anticoagulation in their overall care, and resulting in their decreased acceptance of, and adherence to anticoagulant therapy (71, 165, 189). Patients who tend to adhere to anticoagulants often strongly believe that the benefits of anticoagulation outweigh the associated risks (186, 218). In some cases, adherence was also influenced by the support offered by health professionals. Patients that were provided with current information regarding treatment options and their day-to-day management were motivated to self-manage their treatment plan and health (172, 282). Shared decision-making (SDM) enabled the prescribers to understand patients' perceptions about AF, their need for information, need care, and their preferences for therapy. This enabled prescribers to provide patients with tailored information, counselling, and treatment options (283).

6.1.4 Inclusion of patients' perspectives in decision-making

Our studies conducted in the local settings reported that prescribers' perceived fears regarding patients' inability to self-manage and adhere to anticoagulant therapy, resulted in undertreatment of eligible patients with anticoagulants. Similarly, another study has observed that out of 41 barriers identified for anticoagulation prescription, 17 were patient related, such as, patients incapability to adhere to the therapy and their reluctance to take the therapy negatively influence anticoagulant prescribing (23). However, patients are often not involved as active partners in the decision-making around stroke prevention therapy selection (46, 284), further resulting in discordance between prescribers' and patients' choice of treatment (47, 285, 286). Studies of shared decision-making in AF have demonstrated reduced conflicts between prescribers and patients regarding their knowledge and perceptions about risk-benefits associated with the treatment options, and their preference for anticoagulant therapy (44).

6.1.5 Lack of emphasis of the quality of content within educational resources

This research highlighted has some of the online AF resources lack objective explanation about the use of warfarin therapy or DOACs, and also present unbalanced information about the risk versus benefit of thromboprophylaxis in AF. The suboptimal quality of the information in the these freely available web-based resources is worrying given the increasing popularity and dependence of AF patients on such resources (227, 287, 288). The unbalanced presentation of information in these resources might potentially misguide and confuse patients, in turn rendering the decision-making more complicated and time-consuming for both prescribers and patients (249, 250).

Among the web-based AF resources assessed in our study, the consequences of suffering a stroke were not discussed as frequently as the risk of suffering major bleeding. This finding is important given that patients often have exaggerated fears about the risk of bleeding (132, 158), and this can be because the benefits of anticoagulant therapy in stroke prevention are not as tangible as the experience of bleeding (188). Ultimately, this perception tends to overshadow patients' ability to understand the protection offered by anticoagulation (158). Thus, information emphasising the risk of bleeding over the benefit of stroke prevention might exacerbate patients' fear and anxiety about the risk of haemorrhage, in turn reducing their acceptance for, and adherence to, anticoagulant therapy (132, 152, 177).

The information provided within these educational resources might be seemingly biased towards warfarin and may be artefact of limited research available on the DOACs, especially at the time when some of these web-based resources were initially created. The inclination towards DOAC use in some newer resources might be influenced by the increasing evidence available on the risk–benefit of DOACs over time. In addition, some resources may have been authored by 'commercial organisations' biased toward their own products and therefore, their own commercial interests. Although organisations providing online patient resources should ideally review and update them regularly, this does not always occur. Therefore, 'older' resources (dating back to 2012 and 2013) may have been less positive about the DOACs

due to the relative lack of clinical experience and confidence in prescribing these newer agents and/ or may reflect the guidelines that were current at the time of the last update or review. Whatever the reasons, patients generally lack the required skills and discrimination to accurately assess the authenticity and currency of the content in these resources, which might lead to misinterpreting the information (249, 250).

Our research highlighted how some educational resources for patients do not provide updated, evidence-based, and reliable information. The availability of potentially misleading information might be an issue for both patients and clinicians, especially if they cannot assess the quality of the information provided within such resources. For instance, the inappropriate prescription of aspirin for stroke prevention in AF, as observed in our research (Chapter 3) may partially be explained by whether the clinicians are actively updated on the recent evidence-base around the treatment options. In turn this raises the question about the most effective way of communicating guideline updates to clinicians. Guideline recommendations can be disseminated to clinicians via different modalities, including via professional medical associations, by governments, by medical colleagues, by lobbyists, or by pharmaceutical companies. They may also be presented as manuscripts, textbooks, factsheets, or interactive learning modules. However, passive and non-interactive educational materials: monographs, publications, and mass mailing of guidelines are demonstrated to have been shown to have a weak influence on prescribing practices (289). In addition, pharmaceutical companies engage in marketing strategies to influence prescribers' decision-making, employing strategies such as face-to-face detailing about their products, offering free samples of their products, conducting regular medical education and product launches at medical conferences and offering other forms of gifts (290). However, the success of such

marketing is dependent on physician-pharmaceutical company dynamics (290). In some cases, the clinicians' decision is also influenced by patient pressure (290). Managing misinformed patients can be more challenging (291) as educating them, and trust building can take time (292). Collectively, a range of factors might adversely influence the rational objective decision-making process (290). Interactive tools, such as online continuing medical education and decision-support tools, and the voice of key opinion leaders appear to more strongly influence evidence-base decision-making (289). Hence, tools such as, CARAT 2.0 may offer interactive and engaging way to operationalise guidelines in real-world practice, allowing clinicians to apply the recommendations in a practical way while also engaging patients in the decision-making process.

Overall, our research has suggested that educational resources or aids must be updated regularly based on the current guidelines and align with the needs of both clinicians and patients. These resources should also consider how patients' perceptions influence their decisions and their level of understanding, as well as empower them to confidently engage in decision-making for therapy selection (259, 260). In future studies, patients from diverse socio-economical, educational, and cultural backgrounds should be engaged to assess these AF education resources and aids.

6.1.6 Further scope of using CARAT in practice

Decision-support tools, such as CARAT should continue to update their underpinning algorithms to encompass any new evidence pertaining to the long-term safety and efficacy of DOACs. Noting this, CARAT 2.0 might also incorporate newly developed stroke risk assessment ABC scores (Age, biomarkers- NT-proBNP, cTn-hs, and clinical history- prior stroke/transient ischaemic attack). The ABC-stroke score has had higher c-indices than the CHA_2DS_2-VASc score in both the derivation cohort (0.68 vs.

0.62, $P < 0.001$) and the external validation cohort (0.66 vs. 0.58, $P < 0.001$), i.e., it is better at predicting stroke risk among patients with AF than the CHA_2DS_2 -VASc score (293). Furthermore, to confirm the full benefit of CARAT in optimising antithrombotic therapy utilisation, it should be further tested for its validity in predicting clinical outcomes (i.e., stroke and bleeding events) in various health care settings with an emphasis on engaging both prescribers and patients in the decision-making process.

Our study provides a snapshot of the use of antithrombotic therapies in the local setting in the year 2014, the period immediately following the listing of all the three DOACs on the Pharmaceutical Benefits Scheme (for subsidisation of costs to patients) and when there was limited information available about their use in the "real-world" setting. A more recent study conducted in a similar Australian setting reported that the prescription of anticoagulant therapy (both warfarin and DOACs) had increased across the time period from 2011 to 2015 (272). Aside from reviewing the overall utilisation of anticoagulant therapy, our research found that DOACs were used preferentially (over warfarin), especially among younger patients, and this may be due clinicians' increasing trust in the DOACs over time. However, our study also highlighted that anticoagulants were still used sub-optimally among high stroke risk patients (272). Additionally, the ongoing widespread use of antiplatelet agents (i.e., aspirin) observed in our and other studies (294, 295) is concerning given the high risk of bleeding alongside the insignificant stroke prevention offered by these agents. To optimise anticoagulant prescribing and reduce aspirin use, GRASP-AF tool is developed in the United Kingdom and is integrated with the clinical medical records. The GRASP-AF tool identifies the AF patients based on the information provided in the medical records and calculates their risk of stroke based on CHA_2DS_2 -VASc and $CHADS_2$ scores and flag patients not treated with anticoagulant therapy (296). Thus, guideline-based tools, such as CARAT, can be developed further and merged with electronic medical records and statistical software to serve as audit tools in hospitals and clinics to provide real-time information about the prevalence of AF and utilisation patterns of thromboprophylactic therapies.

However, supporting clinicians with such tools may address only a part of the decision-making conundrum, especially when there is a gap between clinicians' and patients' perceptions and views regarding atrial fibrillation and stroke prevention therapies. This is supported by increasing evidence that patients wish to actively participate in the decision-making process for anticoagulant therapy selection, thereby prompting the need to review whether the information available to support decision-making is based on patients' needs and levels of understanding (46). Hence, decision-support tools, such as CARAT 2.0, might incorporate additional factors that influence decision-making, including patients' preferences for therapy (Chapter IV). Taking into account patients' and clinicians' different and collective requirements, individualised decision-support tools, such as CARAT 2.0, can be applied in the real-world setting to facilitate shared-decision making, factoring in the local and cultural contexts within which the tool is applied (297).

Other researchers have proposed different models for facilitating shared decision-making around stroke prevention in AF (297-300). These shared-decision making models can be divided into several discrete phases: a) educating patients on AF and anticoagulation (298, 301); b) conducting individualised stroke versus bleeding risk assessment ; c) verifying whether patients have understood the information as intended and to confirm their satisfaction with the information provided (298); d) scoring patients' preferences for various characteristics of each available anticoagulant option (canvassed in Chapter 4 of this thesis) ; e) quantifying the degree of matching between patient preferences and therapy characteristics i.e., assigning a percentage to the therapy that provides the best match and/ or discussing the available options based on individual patients' risk-benefit and preference profile (301); f) therapy selection (298); and documenting via a summary report the therapy selection process (301). Shared-decision making can also be supported in various other ways for example, through the use of videos and graphics that can portray stroke and bleeding risks, structured discussion to explain available treatment options during clinical visits, or the use of smart phone or other device applications (Apps) (302-304). Therefore, future research should also explore the possibility of designing a CARAT 2.0 application that would be intuitive and/ or compatible with smart-phones and other electronic devices.

Despite the availability of shared decision-making tools, studies have cited specific hurdles that clinicians face when applying these in their routine practice. These hurdles primarily relate to a lack of time or motivation, lack of experience in using such tools, and sparse knowledge about the benefits of these tools on the clinical outcomes (305). Noting the hurdles faced by clinicians, alternative models of care have been explored. Within these, several studies have demonstrated the positive influence of pharmacists in exploring patients' preferences and attitudes toward anticoagulants during therapy selection, reviewing patients' medical history, managing patients' therapy to ensure dosing to the target INR range, and addressing potential medication safety issues (306-308). Pharmacists are well-placed to support the decision-making around anticoagulant therapy by assessing patients for their stroke and bleeding risk. Moreover, pharmacists can educate and engage patients in decisions about anticoagulation management, help manage patients dosing regimens, ensure a safe transition from one anticoagulant therapy to another – where required, prepare individualised treatment plans, and facilitate regular patient follow-up . An intervention at a UK-based anticoagulant review clinic demonstrated the key role of clinical pharmacists in effectively following the standard NICE protocol for managing at-risk patients who are unable to maintain their target INR (309). A similar study in Canada observed that patients attending pharmacist-managed anticoagulation clinics spent more time in the therapeutic INR range than those receiving standard care (66.5% versus 48.8%, P <0.0001). During the 10.7 months of follow-up it was observed that in comparison to the pharmacist-managed anticoagulation clinics (3.6 events/100 patient years) more patients receiving normal care (49.2 events/100 patient years) were admitted to the emergency department, because of thrombotic events and these same patients also spent more time in hospital (relative time spent in hospital 17.6; 95% CI 6.0–51.9; $p < 0.0001$) (310). Several authors have argued the important role of allied health professionals, particularly clinical pharmacists, in overcoming the barriers to shared decision-making for long-term therapies and that this should be further explored (305, 308, 311). Future research can also explore how pharmacists and anticoagulant clinic nurses can assist and engage patients in decision-making around antithrombotic therapy selection using CARAT 2.0 tool.

6.2 Conclusions

This thesis demonstrates the role and impact of specific decision-support tool that has evolved from a paper-based algorithm applied in the hospital context (focusing on warfarin and aspirin as treatment options) into the electronic CARAT2.0 tool. This evolution reflects changes to practice in terms of decision-making and has been in direct response to the improved accessibility of various health technologies (electronic and online decision-support platforms), the development of new treatment options (DOACs), and a changing evidence base regarding the effectiveness of traditional treatment options (e.g., aspirin). The research in this thesis contributes to that evolution, providing evidence on the original CARAT tool (as a resource to support decision-making) and creating new data to help guide its ongoing refinement. The collective findings of this thesis research conclude the following:

- In current practice, most patients are not prescribed anticoagulant therapy based on their individual risk-benefit assessment, nor their preferences and values, and this practice is not in accordance with that recommended in evidence-based guidelines

- In general, both prescribers and patients fail to acknowledge and realise the importance of anticoagulant therapy for stroke prevention; often underestimating the risk of stroke and overestimating the risk of bleeding

- Tools such as CARAT can support prescribers in the shared decision-making process within the 'real-world' setting, helping to ensure individualised therapy selection, as well as engaging patients in this process in turn optimising medication utilisation and adherence

- Prescribers should consider the ability of individual patients to understand, perceive, and interpret information about the risk-benefit of various treatment

options, which in turn influences patients' acceptance for, and adherence to anticoagulant therapy.

- Patients should refer to online AF education resources only under the guidance and supervision of health professionals noting the need for stricter quality assurance checks for such patient decision aids.

Thus, to bridge the gap between physicians' and patients' perceptions regarding thromboprophylaxis in AF, future research should explore the facilitators and barriers to implementation of shared decision-making in 'real-world' practice from both health professional and patient perspectives, as well as the role of tools such as CARAT 2.0 in shared decision-making.

7 Appendices

7.1 Patient Follow up Questionnaire – CARAT Tool Intervention

If interviewing the patient:

"Hello, my name is Noman Masood. I am the project pharmacist for CARAT project from Royal North Shore/ Wyong/Gosford Hospital"

I

"Hello, my name is Noman Masood. I am the project pharmacist for CARAT project from Royal North Shore/ Wyong/Gosford Hospital" "I /my team member met you 3 months ago when you were caring for Mr/Ms/Mrs/ Miss _____who was admitted into the hospital and during that stay you kindly agreed to participate in this project" You might remember that during your stay you admitting physician reviewed your requirement and suitability for Anti-clotting medications for the purpose of stroke

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'To start, I'll ask you a few questions about whether there have been any changes to the "blood thinning" medications since discharge from the hospital".

At discharge the therapy selected was: _____

1. Is this still the current therapy?
   a. Yes *(go to part 2)*
   b. No *(go to part 1)*

Part 1: CHANGES TO THERAPY POST-DISCHARGE FROM HOSPITAL

1. When was the medication changed?

_____
_

2. Who changed the medication? *(please tick)*

- ❑ Local doctor
- ❑ Carer
- ❑ Nurse
- ❑ Pharmacist
- ❑ Patient
- ❑ Specialist
- ❑ Other *(please specify)* ……..

3. What was the main reason for this change?

- ❑ Side effects
- ❑ Therapy too complicated
- ❑ Did not want to be on it anymore
- ❑ Therapy considered unnecessary
- ❑ Therapy not working
- ❑ Difficult to achieve required INR
- ❑ Other.

Give details

_____
_____
_____

4. Have you had any side effects occur?
- ❑ Yes
- ❑ No

5. Can you please tell me what side effects occurred?

- ❑ Vomiting, coughing or spitting of blood.
- ❑ Blood in the stools / urine.
- ❑ Severe bruising
- ❑ Uncontrolled superficial bleeding
- ❑ GI upset/nausea or vomiting.
- ❑ bleeding in the brain
- ❑ Any other type of bleeding. *(please specify)* ……..
- ❑ Any other side effects *(please specify)* ……..

Give details

_____
_____
_____

6. Was hospital based treatment necessary for these side effects?

- ❑ Yes
- ❑ No

Give details

_____
_____
_____

7. What other problem(s) have you experienced with this therapy?

- ❑ None
- ❑ Therapy too complicated
- ❑ Wasn't aware so much work was involved.
- ❑ Having trouble accessing regular health care.
- ❑ Others *(please specify)* ……..

Give details

_____
_____
_____

8. Has your problem resolved because of changes in therapy?

- ❑ Yes
- ❑ No

9. Have you had any hospitalisation since?

- ❑ Consenting to join the study.
- ❑ Changes in therapy.

Give details

_____
_____
_____

Part 2: FOR PATIENTS CONTINUING THE SAME THERAPY.

1. Have you had any side effects from the current therapy?

- ❑ Yes
- ❑ No

2. Can you please tell me what side effects occurred?

- ❑ Vomiting, coughing or spitting of blood.
- ❑ Blood in the stools / urine.
- ❑ Severe bruising
- ❑ Uncontrolled superficial bleeding
- ❑ GI upset/nausea or vomiting.
- ❑ Bleeding in the brain.
- ❑ Any other type of bleeding. *(please specify)* ……..
- ❑ Any other side effects *(please specify)* ……..

Give details

_____

_____

_____

3. Was hospital based treatment necessary for these side effects?

- ❑ Yes
- ❑ No

Give details

_____

_____

_____

4. What other problem(s) have you experienced with this therapy?

- ❑ None
- ❑ Therapy too complicated
- ❑ Wasn't aware so much work was involved.
- ❑ Having trouble accessing regular health care.
- ❑ Others *(please specify)* ……..

Give details

_____

_____

_____

Part 3: EFFICACY OF THERAPY

1. Have you experienced any of the following in the last three months?	Yes	No
a. Stroke / CVA	❑	❑
b. Mini-stroke or TIA.	❑	❑
c. Blood clot in the lungs. (Pulmonary emboli)	❑	❑
d. Blood clots in any other part of the body	❑	❑

Give details

_____

_____

_____

Additionally, for patients on Warfarin:

1. How often is your INR being tested?

❑ Weekly
❑ Fortnightly
❑ Monthly
❑ Other *(Please specify)* ……..

2. How often has the INR been out of range?

❑ Never.
❑ Few times.
❑ Half of the time.
❑ A lot of times.
❑ Almost always.

3. Approximately how many times has the dose changed?

❑ Never changed
❑ Sometimes (50% of dose reviews)

- ❑ Many times (Almost after each INR tests)

4. What other comments would you like to make about the therapy or study?

_____
_____
_____
_____

That's the end of the interview. All of this information will be kept confidential. I will contact you again in THREE months' time to see how you are going. If you need to contact me for any reason, please do so. Thank you very much for your patience.

7.2 Ethics Approval Letter – CARAT Tool Intervention

6 September 2007

«Name1»

«Addressa»

«Addressb»

«Addressc»

Dear «Name2»,

Re: Protocol «ProtNumb»«ProtType1» **«Investigators»**

«ProtName»

Thank you for providing additional information as requested at the meeting on the 20 June 2007 by the **HAWKESBURY** Human Research Ethics Committee (HREC) of Northern Sydney Central Coast Health (NSCCH). Please be advised that your study have now been approved. The documentation included in the approval is as follows:

- Updated Unit 1 Core Application, dated 03 September 2007
- Participant Information Sheet and Consent Form, version 2 dated 27th August 2007
- Physician Information Sheet version 1 dated 27th April 2007
- Physician Consent Form, version 1 dated 27/3/2007

- Patient Follow-up Questionnaire
- CARAT Project Flow Chart
- CARAT Tool

It is noted that the approval covers the following NSCCH site/s:

- Royal North Shore and Wyong/Gosford Hospital

**If you wish to add an additional site to the project within the area you will be required to complete a 'Site Specific Assessment Form', downloadable from the Research Office Web Page.*

The HREC recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purpose of conducting this clinical trial.

In order to comply with the *Guidelines for Good Clinical Research Practice (GCRP) in Australia,* and in line with NSH HREC policy, may I remind you that it is the chief investigator's responsibility to ensure that:

1. You notify the HREC at the completion of the study at this site and submit a final report (including final results) when available.
2. The HREC is notified as soon as possible of any changes to the protocol. All changes must be approved by the HREC before continuation of the research project. This includes notifying the HREC of any changes to the staff involved with the protocol.

3. All serious and unexpected adverse events are reported to the HREC within 15 working days.
4. The HREC is notified of the outcome of all submissions of this protocol to other Ethics Committees.

As at 18th May 2004, HREC approval is now valid for four (4) years from the date of the approval letter. **Your approval will therefore expire on the 6 September 2011.** Investigators are requested to submit a progress report annually on 31st October. **Your first progress report is due on the 31 October 2007.** The forms for progress/final reports can be downloaded from the Research Office web page.

Yours sincerely

Professor Stewart Dunn

Chairperson

HAWKESBURY HREC

NORTHERN SYDNEY

CENTRAL COAST HEAL

7.3 Data Collection Form Hospital Audit

Appendix 1

UNIVERSITY OF TECHNOLOGY SYDNEY

University of Technology Sydney, Graduate School of Health	Westmead Hospital
A/ Prof. Beata Bajorek Telephone: +61 2 9514 8301 Facsimile: +61 2 9514 8300 Email: Beata.Bajorek@uts.edu.au Department: Pharmacy	**A/ Prof. Clara Chow (Consultant Cardiologist)** Telephone: +61 2 9993 4525 Email: clara.chow@sydney.edu.au Department: Cardiology
Ekta Pandya Telephone: +61 2 9514 9225 Email: [redacted]@student.uts.edu.au Department: Pharmacy	
Yishen Wang Telephone: +61 2 9514 9226 Email: [redacted]@student.uts.edu.au Department: Pharmacy	

DATA COLLECTION FORM

Title: Contemporary utilisation of antithrombotic therapy for stroke prevention in atrial fibrillation: an audit in an Australian hospital setting

References:
The format and content of this form is adopted from:

1. Bajorek B, Magin P, Hilmer S, Krass I. A cluster-randomized controlled trial of a computerized antithrombotic risk-assessment tool (CARAT) to optimize stroke prevention in general practice: a study protocol, BMC Health Service RES. 2014: 14(1):55.

Version 2 dated: 11/08/2015

Contemporary utilisation of antithrombotic therapy for stroke prevention in atrial fibrillation: an audit in an Australian hospital setting

Appendix 1

Data collection form (*Please tick ☑ in the box for the correct option)*

1. Patient code: 2. Age: 3.Gender: 1) M: ☐ 2) F: ☐

4. Date of admission: 5.Ethinicity: 6. Weight/Height (BMI):

6. Indication for anticoagulation

1. Non-valvular Atrial fibrillation (NVAF): ☐
New onset: ☐Paroxysmal AF (≤ 48 hours): ☐. Persistent (> 7 days or requires Cardioversion): ☐ Long-standing persistent (>1 year): ☐ Permanent: ☐
2. VTE prophylaxis for hip replacement surgery:☐
3. VTE prophylaxis knee replacement surgery: ☐
3. Treatment of DVT: ☐
Symptomatic:☐ Asymptomatic:☐
4. Treatment of PE: ☐
5. Secondary prevention of DVT: ☐
6. Secondary prevention of PE: ☐
7. Secondary prevention of stroke: ☐
Stroke/TIA/CVA (Ischemic/haemorrhagic): ☐
9. Mitral stenosis: ☐
10. Mechanical Valves: a) Bileaflet: ☐ b) monoleaflet: ☐ c) caged ball: ☐
11. Bioprosthetic Valves: a) Stented: ☐ b) Stentless: ☐ c) percutaneous
12. PCI (after 12months): ☐
13. Stable CAD (ACS after 12months): ☐
14. ACS without stent (within 12months): ☐
15. PCI (bare-metal stent over 1 month and less than 12 months): ☐
16. PCI (drug-eluting stent over 6 months and less than 12 months): ☐
17. PCI (bare-metal stent in 1 month): ☐
18. PCI (drug-eluting stent within 6months): ☐

7. Reason for admission

8. Prescriber

1) GP : ☐
2) Cardiologist : ☐
3) Geriatrician : ☐
4) Neurology : ☐
5) Other:

9. Current sinus rhythm (at discharge) 1. Normal: ☐ 2. Controlled AF: ☐ 3. Uncontrolled AF: ☐

10. Other co-morbidities

Cardiovascular disease	
1. Congestive cardiac failure/ Left ventricular dysfunction	1.☐
2. Vascular diseases (prior myocardial infarction, peripheral artery disease, or aortic plaque/aneurysm)	2.☐
3. Prosthetic heart valve	3.☐
4. Hyperlipidemia	4.☐
5. Ischemic heart diseases (MI/Angina)	5.☐
6. Rheumatic heart diseases	6.☐
7. Cardiomyopathy	7.☐
8. Hypertension (defined as SBP > 160 mm Hg): Systolic/ Diastolic: mmHg	8.☐
9. Dissecting aorta	9.☐
10. Intracranial aneurysm	10.☐
11. Intracranial haemorrhage	11.☐
12. Other:	12.☐
Neurological	
13. Parkinson's disease	13.☐
14. Alzheimer's/ dementia	14.☐
15. Other:	15.☐
Hepatic	
16. Encephalopathy	16.☐
17. Other:	17.☐
Liver function assessment	
1) Total serum bilirubin: mg/dl 2) Serum albumin: mg/dl 3) INR: 4) Ascites: 5) Encephalopathy: 6) SGOT 7) SGPT:	
CHILD-PUGH scores:	18.☐
Renal	19.☐
18. Chronic renal failure (CRF)	20. ☐
19. Acute renal failure (ARF)	
20. Other:	
Renal function assessment	
a) CrCl: ml/min b) eGFR: ml/min/1.73m² c) Sr. Creatinine: (µmol/L)	
Visual	21. ☐
21. Macular degeneration	22. ☐
22. Glaucoma	
Endocrine	23. ☐
23. Thyroid:	24. ☐
24. Diabetes:	
Haematological	25. ☐
25. Anaemia:	26. ☐
26. Thrombocytopenia:	27. ☐
27. Thrombophilia	

Contemporary utilisation of antithrombotic therapy for stroke prevention in atrial fibrillation: an audit in an Australian hospital setting

Appendix 1

28. Haemophilia: 28. ☐
29. Other: 29. ☐
History of Bleeding: ☐ History of Falls: ☐
Coagulation profile test 1) APTT: 2) PT/ INR: 3) Platelet count: 4) TT: 5) RBC: 30. ☐
30. Malignancy
Gastrointestinal disease 31. ☐
31. Gastro-esophageal reflux syndrome (GORD) 32.
32. Peptic ulcer disease 33. ☐
33. Other:

11. Prescription drugs and doses

1. Beta-blockers	1.☐
2. Calcium channel blockers	2.☐
3. Alpha blockers	3.☐
4. Nitrates	4.☐
5. Other antihypertensive	5.☐
6. Sedatives	6.☐
7. Opioid	7.☐
8. Antihyperlipidemic	8.☐
9. PPI/H_2 antagonists	9.☐
10. Anti-asthmatics	10☐
11. Diuretics	11.☐
12. Tricyclic antidepressants	12.☐
13. SSRIs	13.☐
14. Typical antipsychotic	15.☐
15. Atypical antipsychotic	16.☐
16. Antiparkinsons	17.☐
17. Hypoglycaemic	18.☐
18. Corticosteroids	19.☐
19. Hormone replacement therapy	20.☐
20. Biphosphonate	21.☐
21. Others:	

12. OTC medications

13. Medication Management Issue

1. Cognitively impaired MMSE: *1.Y☐ 2.N☐*

2. Lives in Nursing home? *1. Y☐ 2.N☐* — 1. Dependent: ☐ 2. Independent: ☐ — **1. Alone: ☐** **2. Carer: ☐**

3. Patients have difficulty in accessing medical care? *1. Y☐ 2.N☐*

4. Patient has visual or colour blindness? *1. Y☐ 2.N☐*

5. Patient is deaf? *1. Y☐ 2.N☐*

6. Patient have language barrier? *1. Y☐ 2.N☐*

7. Working status of the patient *1. Employed: ☐ 2. Unemployed: ☐ 3. Retired: ☐*

8. Education level of the patient *1. Illiterate: ☐ 2. High school: ☐ 3. University: ☐*

9. Patients have difficulty in reading or understanding the instructions: *1 Y☐ 2. N☐*

10. Does patient have impaired dexterity: *1. Y☐ 2. N☐*

11. Patient physically active: *1. Mobile: ☐ 2. Immobile: ☐*

12. Alcohol abuse: *1. Y☐ 2. N☐*

13. Problem with regular monitoring: *1. Y☐ 2. N☐*

14. Frequency of monitoring: *1. Y☐ 2. N☐*

15. ***Problem in managing dose-adjustments:*** *1. Y☐ 2. N☐*

16. Frequency of dose-adjustment:

17. Difficulty in managing daily Vitamin K intake (for Warfarin users only): *1. Y☐ 2. N☐*

14. Medication safety issues

1. Patient allergic to aspirin/warfarin/ NOACs	1. Y☐ 2. N☐
2. Patient educated on antithrombotics	1. Y☐ 2. N☐
3. Patient/ family member/s refused Warfarin	1. Y☐ 2. N☐
4. Patient/ family member/s refused NOACs	1. Y☐ 2. N☐
5. Medication adherence issue	1. Y☐ 2. N☐
6. Medications interacting with warfarin	1. Y☐ 2. N☐
7. Medications interacting with NOACs	1. Y☐ 2. N☐
8. Previous experience of adverse events	1. Y☐ 2. N☐
9. Patient is on ≥ 4 medications	1. Y☐ 2. N☐

Comments

15. Medication adherence
1) Forget/ miss medicine dose: ☐
2) Take extra doses of medication: ☐
3) Difficulty in understanding the risk-benefit of the therapy: ☐
4) Poor understanding about the medication and its management: ☐
5) Poor knowledge about their condition: ☐
6) Other (***please mention***):

Appendix 1

16. Baseline (Admission) antithrombotic *Date: Dose:*	**Discharge antithrombotic therapy** *Date: Dose:*	**Post discharge antithrombotic therapy** *Date: Dose:*
1. Warfarin: □ 2. Dabigatran: □ 3. Rivaroxaban: □ 4. Apixaban: □ 5. Nil: □ 6. Antiplatelet: a) Aspirin: □ b) Dipyridamole: □ c) Clopidogrel: □ d) Prasugrel: □ e) Ticagrelor: □ Total: 7. Low Molecular Weight Heparin: 8. Unfractionated Heparin (UFH): □ 9. Fondaparinux: □ 10. Other:	1. Warfarin: □ 2. Dabigatran: □ 3. Rivaroxaban: □ 4. Apixaban: □ 5. Nil: □ 6. Antiplatelet: a) Aspirin: □ b) Dipyridamole: □ c) Clopidogrel: □ d) Prasugrel: □ e) Ticagrelor: □ Total: 7. Low Molecular Weight Heparin: 8. Unfractionated Heparin (UFH): □ 9. Fondaparinux: □ 10. Other:	1. Warfarin: □ 2. Dabigatran: □ 3. Rivaroxaban: □ 4. Apixaban: □ 5. Nil: □ 6. Antiplatelet: a) Aspirin: □ b) Dipyridamole: □ c) Clopidogrel: □ d) Prasugrel: □ e) Ticagrelor: □ Total: 7. Low Molecular Weight Heparin: 8. Unfractionated Heparin (UFH): □ 9. Fondaparinux: □ 10. Other:

17. Duration of stay in hospital		**18. Duration of therapy**	

19. Reason for therapy change at discharge/ post-discharge ***(if applicable)***

Appendix 1

FOR INTERNAL USE ONLY

32. Stroke risk assessment scores:		**33. Bleeding risk assessment scores:**	
a. $CHADS_2$ b: CHA_2DS_2-VASc	☐ ☐	a. HAS-BLED b.$HEMMOR_2HAGES$	☐ ☐
➢ Hypertension (treated/untreated) ➢ Diabetes mellitus ➢ Prior stroke/ TIA/ systemic emboli ➢ Vascular disease (prior MI, PAD, aortic plaque) ➢ Congestive Cardiac Failure/ LV dysfunction ➢ Sex female ➢ a) Age 65-74 years, b) ≥ 75 years	☐ ☐ ☐ ☐ ☐ ☐ a) ☐ b) ☐	➢ Hepatic Disease ➢ Renal Disease ➢ Malignancy ➢ Reduced platelet count or function ➢ Ethanol Abuse ➢ History of bleeding (GI/IC) ➢ Anaemia ➢ Previous falls ➢ Labile INR (TTR <60%) ➢ Uncontrolled hypertension (BP : mmHg) ➢ Genetic factor (CYP 2C9 nucleotide polymorphism) ➢ Low platelet count/ platelet dysfunction	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

7.4 Coded Identifier List – Hospital Audit

Patient initials	Medical record number	Patient study code

7.5 Ethics Approval Letter – Hospital Audit

Health
NSW GOVERNMENT Western Sydney Local Health District

WSLHD Research Governance Officer
Room 2050 Research & Education Network Building
Westmead Hospital
Cnr Hawkesbury and Darcy Roads
Westmead NSW 2145

Telephone: (02) 9845 9634
Facsimile: (02) 9845 9636
Email: margaret.piper@health.nsw.gov.au

3 September 2015

A/Prof Clara Chow
Cardiology Department
Westmead Hospital

Dear A/Prof Chow

HREC reference number: LNR/15/WMEAD/156
SSA reference number: LNRSSA/15/WMEAD/240
Project title: Contemporary utilisation of antithrombotic therapy for stroke prevention in atrial fibrillation: an audit in an Australian hospital setting
Protocol number: version 2, dated 11 August 2015

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following sites:

- Westmead Hospital

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Insurance certificate must be current for governance clearance to remain valid. The insurance certificate submitted expires 1 November 2015. Please submit updated certificate when issued.

2. 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;

3. 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.

Yours faithfully

Maggie Piper
WSLHD Research Governance Officer

CC: Ekta Pandya, University of Technology Sydney,
[redacted]@student.uts.edu.au

WESTERN SYDNEY LOCAL HEALTH DISTRICT
ABN 48 702 394 764
WSLHD Executive Office Level 1, Education Block
Westmead Hospital
PO Box 574, Wentworthville NSW 2145
Telephone 02 9845 5555

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