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Therapeutic Decision-making around Stroke Prevention in Atrial Fibrillation

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Certificate of Original Authorship

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

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

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Signature of Student: Date

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Yishen Wang

Table 1: Abbreviations

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

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

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

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

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This thesis comprises the following peer-reviewed publications

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Yishen Wang, Beata V. Bajorek. New oral anticoagulants in practice: pharmacological and practical considerations. American Journal of Cardiovascular Drugs. 2014;14(3):175 – 89 (Chapter 2)

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Other related peer-reviewed publications

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Research presentations

Yishen Wang, Beata V. Bajorek. Review of antithrombotic risk assessment tools for stroke prevention in atrial fibrillation patients. ASCEPT-APSA Conference, 2-5 December 2012, Sydney, Australia

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Yishen Wang, Beata V. Bajorek. Selecting antithrombotic therapy for stroke prevention in atrial fibrillation: health professionals' feedback on a decision support tool. New Horizons Conference, 17–19 November 2014, Sydney, Australia.

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Thesis Abstract

Background

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

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

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

Aim

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

Methods

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

Results

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

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

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

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

Conclusion

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