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

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Abstract

Background: *The decision-making process for stroke prevention in atrial fibrillation (AF) requires a comprehensive assessment of risk vs. benefit and an appropriate selection of antithrombotic agents (e.g., warfarin, non-vitamin K antagonist oral anticoagulants [NOACs]). The aim of this pilot-test was to examine the impact of a customised decision support tool — the Computerised Antithrombotic Risk Assessment Tool (CARATV2.0) using antithrombotic therapy on a cohort of patients with AF.*

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

Results: *At baseline (admission), 30.3% of patients were prescribed warfarin, 26.7% an antiplatelet, 8.4% apixaban, 8.0% rivaroxaban, 3.6% dabigatran. CARATV2.0 recommended a change of therapy for 153 (61.0%) patients. Through recommendations of CARATV2.0, at discharge, 40.2% of patients were prescribed warfarin, 17.7% antiplatelet, 14.3% apixaban, 10.4% rivaroxaban, 5.6% dabigatran. Overall, the proportion of patients receiving an antithrombotic on discharge increased significantly from baseline (admission) (baseline 77.2% vs. 89.2%; $p < 0.001$). Prescribers moderately agreed with CARATV2.0's recommendations (kappa = 0.275, $p < 0.001$). Practical medication safety issues were cited as major reasons for not accepting a desire to continue therapy with CARATV2.0's recommendations. Factors predicting the prescription of antiplatelets rather than anticoagulants included higher bleeding risk and high risk of falls. An inter-speciality difference in therapy selection was detected.*

Conclusions: *This decision support tool can help optimise the use of antithrombotic therapy in patients with AF by considering risk versus benefit profiles and rationalising treatment selection.* (Cardiol J 2017; 24, 2: 176–187)

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

Introduction

The decision-making process in antithrombotic therapy for stroke prevention in atrial fibrillation (AF) is complicated by therapy options and considerations of risk versus benefit assessment. Three non-vitamin K antagonist oral anticoagulants (NOACs) — dabigatran, rivaroxaban and apixaban — have been developed and approved to overcome the limitations of warfarin, but they are not without risk and have different pharmacological profiles [1, 2]. Compared with warfarin, the NOACs do not require routine monitoring of coagulation parameters and have fewer interactions with other

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drugs and foods, which enhances the convenience of therapy management. However, in contrast to warfarin, most NOACs need dosage adjustment in patients with renal impairment and are contraindicated in severe liver impairment. For patients with gastrointestinal disease, some NOACs (such as dabigatran) are not tolerated as well as with warfarin treatment. More frequent dosing is needed for some NOACs (e.g., twice daily for dabigatran and apixaban) compared to warfarin (once daily), which may reduce patients' adherence, especially in older patients who were using polypharmacy [1]. Additionally, they are more expensive, which underpins recent recommendations to prioritise the use of warfarin for those patients with whom it is appropriate [3]. Regarding the risk versus benefit assessment of using antithrombotics, currently both international (the ESC and AHA/ACC/HR guidelines) and Australian guidelines (the Therapeutic and NPS guidelines) recommend consideration of both the risk of bleeding and anticoagulation control (INR, time in therapeutic range) in addition to the risk of stroke [4–7]. Therefore, health professionals could improve care with a more tailored evaluation by having a complete assessment of patients with AF for both initiation of therapy and follow-up [8, 9].

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

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

Methods

Design and setting

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

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

Participant recruitment

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

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

Data collection (trial scenario)

The researcher visited target wards daily and liaised with the ward staff to identify patients with AF. The medical records of each eligible consenting patient were then reviewed to extract relevant data such as medical history. Where key data needed

specific clarification, the relevant health professionals, the patients, or both, were approached directly.

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

Algorithm of CARATV2.0

CARATV2.0 (currently an Excel prototype) is an electronic tool that canvases a range of factors to determine a patient's risk of stroke versus risk of bleeding. Stroke risk was assessed with $CHADS_2$ [17] and CHA_2DS_2VASc [18]; bleeding risk was assessed with HAS-BLED [19] and $HEMORR_2$-HAGES [20]. The two sets of scores verify each assessment, giving weight to the highest score (level of risk). The four scores are each categorized into low, intermediate or high risk. CARATV2.0 additionally considers major medication safety issues that may affect treatment choice (e.g. renal and liver function, drug interactions, fall risk and cognitive function) [10].

When applying CARATV2.0, a patient is considered eligible for oral anticoagulants when the risk of stroke (assessed by $CHADS_2$ [17] or CHA_2DS_2VASc [18]) is equal to or higher than the risk of bleeding (assessed by HAS-BLED [19] or $HEMORR_2HAGES$ [20]). When the bleeding risk of using oral anticoagulants in the patient outweighs the benefit of stroke prevention, CARATV2.0 considers the patient unsuitable for oral anticoagulants; alternative treatment (e.g. an oral antiplatelet) and specialist consultation are recommended instead. Given that CARATV2.0 was developed primarily for an Australian setting, its treatment recommendations followed the Australian Therapeutic Guidelines [4] and were aligned with the Australian Government Review [3]. Whenever the patient was deemed to be eligible for oral anticoagulants, either warfarin or NOACs, and had no contraindications to warfarin or NOACs, CARATV2.0 considered warfarin as the first-line therapy and NOACs as an alternative therapy. However, it should be noted that the Australian guidelines differ slightly from international guidelines (ESC [2012] and the EHRA [2015]) in that the international guidelines advocate the use of NOACs over warfarin [7, 21].

The primary function of CARATV2.0 is to assess the need for antithrombotic therapy in patients who have AF as the primary indication. It does not make specific recommendations about combination therapies in the presence of multiple indications (an anticoagulant plus an antiplatelet), given the lack of evidence about the safety of using multiple agents. The tool does however, screen for other indications, such as ischemic heart disease (with or without stent) and valvular AF, which may also require antithrombotics and which may lead to the need for combination therapy, as identified by the American Chest Physician Guidelines [14]. Thereby, CARATV2.0 brings to the attention of prescribers that their patients may have other indications requiring additional antithrombotic therapy that may need to be carefully managed. CARATV2.0 does not make any recommendations about deprescribing any antithrombotic therapy that a patient may be taking for other indications.

Post hoc analysis

Post hoc analysis of CARATV2.0's recommendations was conducted after data collection was completed. This analysis assumed that CARATV2.0 considered NOACs as the first-line therapy and warfarin as the second-line therapy (i.e. reversal of first- versus second-line therapies, in line with international guidelines [6, 7]). The patient data collected in the pilot study (trial scenario) were applied to CARATV2.0 to generate treatment recommendations. Finally, the therapy recommended by CARATV2.0 (NOACs as first-line) was compared with the therapy received by patients in the trial scenario upon discharge. The purpose of this post hoc analysis was to demonstrate the adaptability of CARATV2.0 to the international guidelines and to review the recommendations when international guidelines were adopted.

Data analysis

Computerized data analysis employed SPSS (Statistical Package for the Social Sciences) Version 19. T-tests, ANOVA, and Mann-Whitney U and Kruskal-Wallis tests were used to explore continuous variables. The χ^2 test examined differences in independent proportions. Kappa analysis assessed the level of agreement between CARATV2.0's recommendations and the antithrombotic therapy actually prescribed at discharge. Logistic regression analysis identified predictors for

the use of antithrombotic therapy. All the relevant patient data (all variables listed in Table 1 and Table 2), including age, gender, admission department, risk of stroke (assessed by $CHADS_2$ [17] or CHA_2DS_2VASc [18]), risk of bleeding (assessed by HAS-BLED [19] or $HEMORR_2HAGES$ [20]), medical conditions (e.g., renal impairment, liver impairment. gastrointestinal bleeding, intracranial bleeding [ICH]), medication safety issues (e.g., adherence, cognition, fall risk), the number of medications were included in the univariate analysis. All variables showing a significant association in the univariate analysis were then considered in the multivariate logistic regression modeling (Forward Wald). Although age and gender were not significant in the univariate analysis, they were also further explored in the multivariate analysis. The significance level for all analyses, univariate and multivariate, was set at $p < 0.05$.

Results

Patient characteristics

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

Baseline therapy at admission (pre-CARATV2.0)

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

CARATV2.0's recommendations

Overall, CARATV2.0 recommended a change of therapy in 146 (58.2%) patients (Table 2). Among the 124 patients who were receiving an oral anticoagulant at admission, only 102 (82.3%) patients were assessed as eligible for therapy by CARATV2.0. Among the 76 patients who were taking warfarin on admission, 8 (9.5%) were specifically recommended an alternative therapy. Among the 50 patients who were taking one of the NOACs on admission, 32 (64.0%) were specifically recommended an alternative therapy by CARATV2.0.

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

Discharge therapy (post-CARATV2.0)

At discharge, the proportion of patients receiving antithrombotics (Table 2) significantly increased to 89.2% (from 77.2% at baseline; $p < 0.001$) (Fig. 1). More than 40% of patients were prescribed warfarin, while more than one-third were prescribed one of the NOACs. Among the 146 (58.2%) patients who were recommended therapy changes by CARATV2.0, 36 (24.7%) were adopted by the prescribers before discharge.

Among the factors affecting the selection of antithrombotics (at discharge), fall risk, bleeding risk, chronic kidney disease and being admitted to the neurology department had the greatest impact. Patients with a high risk of falls or a high risk of bleeding were more likely to receive antiplatelets than anticoagulants. Notably, patients with chronic kidney disease and those admitted to the neurology department were more likely to receive NOACs than warfarin (**Supplemental Table 1 — see journal website**).

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

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

However, at discharge, prescribers did not follow the specific therapy recommendations of CARATV2.0 in 119 cases (**Supplemental Table 2 — see journal website**). Most common reasons given were (a) desire to continue existing therapy, i.e. continue pre-admission therapy, (b) practical management issues (e.g. "NOACs better/easier to manage/no need for monitoring") and (c) perceived is-

Table 1. Utilization of antithrombotic therapy (at discharge).

Characteristics (at discharge) Mean ± SD or N [%] N = 251	Total N = 251 [100]	Nil N = 27 [10.8]	Warfarin (± antiplatelet) N = 101 [40.2]	Aspirin (± antiplatelet) N = 37 [14.7]	Dabigatran N = 14 [5.6]	Rivaroxaban (± antiplatelet) N = 26 [10.4]	Apixaban (± antiplatelet) N = 36 [14.3]	Clopidogrel N = 10 [4.0]
PART 1. SOCIODEMOGRAPHICS AND RISK STRATIFICATION								
Age [years]	82.3 ± 8.2	85.7 ± 8.4	81.7 ± 7.8	84.1 ± 8.6	81.9 ± 8.2	79.3 ± 8.7	82.1 ± 7.1	82.2 ± 9.1
Type of AF								
Paroxysmal	97 [38.6]	11 [11.3]	36 [37.1]	13 [13.4]	3 [3.1]	13 [13.4]	17 [17.5]	4 [4.1]
Persistent	106 [42.2]	9 [8.5]	44 [41.5]	19 [17.9]	7 [6.6]	10 [9.4]	14 [13.2]	3 [2.8]
New onset	9 [3.6]	2 [22.2]	3 [33.3]	2 [22.2]	1 [11.1]	1 [11.1]	0 [0.0]	0 [0.0]
Unknown	39 [15.5]	5 [12.8]	18 [46.2]	3 [7.7]	3 [7.7]	2 [5.1]	5 [12.8]	4 [7.7]
Current cardiac rhythm								
Normal sinus rhythm	108 [43.0]	14 [13.0]	44 [40.7]	11 [10.2]	3 [2.8]	12 [11.1]	18 [16.7]	6 [5.6]
Controlled AF	109 [43.4]	9 [8.3]	45 [41.3]	17 [15.6]	9 [8.3]	13 [11.9]	14 [12.8]	2 [1.8]
Paced	34 [13.5]	4 [11.8]	12 [35.3]	9 [26.5]	2 [5.9]	1 [2.9]	4 [11.8]	2 [5.9]
Gender								
Female	128 [51.0]	14 [10.9]	47 [36.7]	17 [13.3]	6 [4.7]	17 [13.3]	20 [15.6]	7 [5.5]
Principle managers of antithrombotics								
GP	207 [82.5]	21 [12.0]	70 [40.0]	33 [18.9]	7 [4.0]	15 [8.6]	22 [12.6]	7 [4.0]
GP + specialist	32 [12.7]	3 [7.3]	14 [34.1]	4 [9.8]	6 [14.6]	6 [14.6]	8 [19.5]	0 [0.0]
Specialist	41 [16.3]	2 [6.3]	16 [50.0]	0 [0.0]	1 [3.1]	5 [15.6]	5 [15.6]	3 [9.4]
None	3 [1.2]	1 [33.3]	1 [33.3]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]
Department								
General medicine	77 [30.7]	8 [10.4]	33 [42.9]	9 [11.7]	6 [7.8]	6 [7.8]	10 [13.0]	5 [6.5]
Cardiology	85 [33.9]	6 [7.1]	39 [45.9]	12 [14.1]	2 [2.4]	12 [14.1]	12 [14.1]	2 [2.4]
Aged care	51 [20.3]	11 [21.6]	19 [37.3]	12 [23.5]	1 [2.0]	4 [7.8]	3 [5.9]	1 [2.0]
Neurology	38 [15.1]	2 [5.3]	10 [26.3]	4 [10.5]	5 [13.2]	4 [10.5]	11 [28.9]	2 [5.3]
Other indications for antithrombotics								
History of PE/DVT	20 [8.0]	2 [10.0]	10 [50.0]	5 [25.0]	0 [0.0]	3 [15.0]	0 [0.0]	0 [0.]
CHD	92 [35.1]	10 [10.9]	40 [43.5]	12 [13.0]	5 [5.4]	10 [10.9]	13 [14.1]	2 [2.2]
CABG	26 [10.4]	1. [3.8]	16 [61.5]	2 [7.7]	0 [0.0]	5 [19.2]	0 [0.0]	2 [7.7]
Stent	14 [5.6]	1 [7.1]	6 [42.9]	0 [0.0]	0 [0.0]	3 [21.4]	4 [28.6]	0 [0.0]
CABG + stent	4 [1.6]	[0.0]	2 [50.0]	0 [0.0]	1 [25.0]	0 [0.0]	0 [0.0]	1 [25.0]

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Table 1. (cont.) Utilization of antithrombotic therapy (at discharge).

Characteristics (at discharge) Mean ± SD or N [%] N = 251	Total N = 251 [100]	Nil N = 27 [10.8]	Warfarin (± antiplatelet) N = 101 [40.2]	Aspirin (± antiplatelet) N = 37 [14.7]	Dabigatran N = 14 [5.6]	Rivaroxaban (± antiplatelet) N = 26 [10.4]	Apixaban (± antiplatelet) N = 36 [14.3]	Clopidogrel N = 10 [4.0]
$CHADS_2$ score								
Low	10 [4.0]	1 [10.0]	5 [50.0]	1 [10.0]	0 [0.0]	2 [20.0]	0 [0.0]	1 [10.0]
Intermediate	55 [21.9]	8 [14.5]	18 [32.7]	10 [18.2]	3 [5.5]	9 [16.4]	6 [10.9]	1 [1.8]
High	186 [74.1]	18 [9.7]	78 [41.9]	26 [14.0]	11 [5.9]	15 [8.1]	30 [16.1]	8 [4.3]
CHA_2DS_2-VASc score								
Intermediate	2 [0.8]	0 [0.0]	1 [50.0]	0 [0.0]	0 [0.0]	1 [50.0]	0 [0.0]	0 [0.0]
High	249 [99.2]	27 [10.8]	100 [40.2]	37 [14.9]	14 [5.6]	25 [10.0]	36 [14.5]	10 [4.0]
HAS-BLED score								
Low	3 [1.2]	0 [0.0]	2 [66.7]	0 [0.0]	0 [0.0]	1 [33.3]	0 [0.0]	0 [0.0]
Intermediate	199 [79.3]	22 [11.1]	86 [43.2]	25 [12.5]	10 [5.0]	22 [11.1]	29 [14.6]	5 [2.5]
High	49 [19.5]	5 [10.2]	13 [26.5]	12 [24.5]	4 [8.2]	3 [6.1]	7 [14.3]	5 [10.2]
$HEMORR_2HAGES$ score								
Low	86 [34.3]	8 [9.3]	38 [44.2]	9 [10.5]	5 [6.0]	13 [15.1]	12 [14.0]	1 [1.2]
Intermediate	126 [50.2]	12 [9.5]	56 [44.4]	14 [11.1]	7 [5.6]	10 [7.9]	22 [17.5]	5 [4.0]
High	39 [15.5]	7 [17.9]	7 [17.9]	14 [35.9]	2 [5.1]	3 [7.7]	2 [5.1]	4 [10.3]
PART 2. CLINICAL AND MEDICATION SAFETY CONSIDERATIONS								
Disease condition								
Previous cerebrovascular accident (yes)	74 [30.0]	6 [7.9]	26 [34.2]	13 [17.1]	8 [10.5]	3 [3.9]	15 [19.7]	5 [6.6]
Previous intracranial haemorrhage§ (yes)	11 [4.4]	0 [0.0]	3 [27.3]	6 [54.5]	0 [0.0]	0 [0.0]	0 [0.0]	2 [18.2]
Prior gastrointestinal bleeding or ulcer (yes)	16 [6.4]	2 [12.5]	2 [12.5]	3 [18.8]	1 [6.3]	3 [18.8]	4 [25.0]	1 [6.3]
Other gastrointestinal disease* (yes)	11 [4.4]	10 [14.3]	26 [37.1]	8 [11.4]	2 [2.9]	10 [14.3]	12 [17.1]	2 [2.9]
Chronic kidney disease (yes)	44 [17.5]	9 [20.5]	22 [50.2]	3 [6.8]	0 [0.0]	2 [4.5]	4 [9.1]	4 [9.1]
Liver impairment** (yes)	10 [4.0]	2 [20.0]	4 [40.0]	3 [30.0]	0 [0.0]	0 [0.0]	1 [10.0]	0 [0.0]

Table 1. (**cont.**) Utilization of antithrombotic therapy (at discharge).

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Medication safety issue								
Allergy/ADR to warfarin (yes)	14 [5.6]	6 [42.9]	2 [14.3]	1 [7.1]	0 [0.0]	3 [21.4]	1 [7.1]	1 [7.1]
ADR to dabigatran (yes)	6 [2.4]	0 [0.0]	4 [66.7]	0 [0.0]	1 [16.7]	0 [0.0]	1 [16.7]	0 [0.0]
ADR to rivaroxaban (yes)	5 [2.0]	0 [0.0]	1 [20.0]	2 [40.0]	0 [0.0]	1 [20.0]	1 [20.0]	0 [0.0]
Allergy/ADR to apixaban (yes)	3 [1.2]	1 [33.3]	1 [33.3]	0 [0.0]	0 [0.0]	1 [33.3]	0 [0.0]	0 [0.0]
Allergy/ADR to aspirin (yes)	4 [1.6]	1 [20.0]	3 [60.0]	0 [0.0]	0 [0.0]	1 [20.0]	0 [0.0]	0 [0.0]
ADR to clopidogrel (yes)	2 [0.8]	2 [100.0]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]
Cognitive impairment (yes)	32 [12.7]	8 [25.0]	5 [15.6]	10 [31.2]	1 [3.1]	1 [3.1]	7 [21.9]	0 [0.0]
Visual impairment (yes)	63 [25.1]	3 [7.0]	19 [44.2]	9 [20.9]	2 [4.7]	2 [4.7]	5 [11.6]	3 [7.0]
Hearing impairment (yes)	63 [25.1]	7 [11.1]	31 [49.2]	10 [15.9]	2 [3.2]	2 [3.2]	8 [12.7]	3 [4.8]
Mobility disorder (yes)	58 [23.1]	8 [13.8]	22 [37.9]	13 [22.4]	3 [5.2]	2 [3.4]	10 [17.2]	0 [0.0]
Language barrier (yes)	10 [4.0]	1 [10.0]	1 [10.0]	6 [60.0]	0 [0.0]	0 [0.0]	2 [20.0]	0 [0.0]
High fall risk/history of frequent falls (yes)	74 [29.5]	8 [10.8]	26 [35.1]	20 [27.0]	3 [4.1]	5 [6.8]	7 [9.5]	5 [6.8]
Poly pharmacy (≥ 4 kinds of medications) (yes)	239 [95.2]	25 [10.5]	96 [40.2]	36 [15.1]	12 [5.0]	25 [10.5]	35 [14.6]	10 [4.2]
Needs assistance with medication (yes)	120 [47.8]	15 [12.5]	49 [40.8]	17 [14.2]	8 [6.7]	11 [9.2]	15 [12.5]	5 [4.2]
Poor adherence (Morisky score > 2) [31] (yes)	10 [4.0]	1 [12.5]	2 [25.0]	3 [37.5]	1 [12.5]	1 [25.0]	1 [12.5]	1 [0.0]

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Table 1. (cont.) Utilization of antithrombotic therapy (at discharge).

Characteristics (at discharge) Mean ± SD or N [%] N = 251	Total N = 251 [100]	Nil N = 27 [10.8]	Warfarin (± antiplatelet) N = 101 [40.2]	Aspirin (± antiplatelet) N = 37 [14.7]	Dabigatran N = 14 [5.6]	Rivaroxaban (± antiplatelet) N = 26 [10.4]	Apixaban (± antiplatelet) N = 36 [14.3]	Clopidogrel N = 10 [4.0]
Medications that interact with antithrombotics								
Verapamil (yes)	4 [1.6]	0 [0.0]	3 [75.0]	0 [0.0]	0 [0.0]	0 [0.0]	1 [25.0]	0 [0.0]
Diltiazem (yes)	3 [1.2]	0 [0.0]	2 [66.7]	0 [0.0]	0 [0.0]	0 [0.0]	1 [33.3]	0 [0.0]
Amiodarone (yes)	33 [13.1]	4 [12.1]	14 [42.4]	4 [12.1]	2 [6.1]	3 [9.1]	5 [15.2]	1 [3.0]
Flecainide (yes)	12 [4.8]	1 [8.3]	6 [50.0]	0 [0.0]	0 [0.0]	1 [8.3]	2 [16.7]	2 [16.7]
Propranolol (yes)	4 [1.6]	0 [0.0]	3 [75.0]	1 [25.0]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]
Digoxin (yes)	56 [22.3]	6 [10.7]	18 [32.1]	8 [14.3]	6 [10.7]	9 [16.1]	6 [10.7]	3 [5.4]
Beta-blocker (yes)	113 [45.0]	12 [10.6]	48 [42.4]	15 [13.3]	7 [6.2]	12 [10.6]	14 [12.4]	5 [4.4]
Oral corticosteroid (yes)	32 [12.7]	6 [18.8]	8 [25.0]	6 [18.8]	2 [6.3]	3 [9.4]	7 [21.9]	0 [0.0]

Morisky score: the Morisky Medication Adherence Scale-MMAS-4 [31]. Need assistance with medication: patients need carers, home nursing service, dosing aid, blister pack or acute post-acute care service to help with daily medication management; ADR — adverse drug event; AF — atrial fibrillation; CABG — coronary artery bypass grafting; CHD — coronary heart disease; DVT — deep venous thrombosis; GP — general practitioners; PE — pulmonary embolism; SD — standard deviation
§Including prior haemorrhagic stroke, subdural or subarachnoid haemorrhage; *Including gastroesophageal reflux disease, gastritis and other gastrointestinal diseases (except malignancy) without bleeding or ulcer; **Liver impairment is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin 2 to 3 times the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 times the upper limit normal, etc.) (baseline INR ≥ 1.3)

sues of medication safety associated with potential risk of bleeding (fall risk, old age, dementia) (Fig. 2). In contrast, the benefit of treatment (reduction in stroke risk) and specific bleeding events (history of gastrointestinal bleeding) were among the least common reasons for not adhering to CARATV2.0's recommendations.

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

In the post hoc analysis, patients who were identified as unsuitable for any oral anticoagulant in the trial scenario also remained ineligible for any oral anticoagulant. Among those who were eligible for oral anticoagulants, 119 (47.4%) patients were recommended any of the NOACs (dabigatran, rivaroxaban or apixaban); 50 (19.9%) were recommended either rivaroxaban or apixaban; 29 (11.6%) apixaban only; 3 (1.2%) either dabigatran or rivaroxaban; and 1 (0.4%) either dabigatran or apixaban. Only 21 (12.6%) patients were recommended warfarin, 17 due to severe renal impairment (creatinine clearance < 25 min/1.73 m^2) and 4 due to hepatic impairment. When examining the distribution of therapy, CARATV2.0's recommendations in the trial scenario were better aligned with the treatment prescribed to patients at discharge in 132 (52.6%) patients, while CARATV2.0 recommendations in the post hoc analysis (NOACs as first-line therapy) only aligned with treatment prescribed to patients at discharge in 98 39.0% patients ($p = 0.002$).

Discussion

In this study, a novel decision support tool (CARATV2.0), which considers warfarin as first-line therapy and NOACs as alternative treatment options, was pilot-tested in a tertiary hospital. Results showed that CARATV2.0 assisted treatment selection and optimised the use of antithrombotic therapy in this patient population. More importantly, CARATV2.0 significantly increased the use of anticoagulants (warfarin and NOACs) in patients identified as eligible for oral anticoagulant therapy by this decision support tool. Moreover, since the average age of the patient population in this study was older than that of the general population of patients with AF [22], antithrombotic use in the general population may be further increased by the application of CARATV2.0. Because both national and international guidelines indicate the superiority of anticoagulants over antiplatelets for stroke prevention in patients with AF, the ability of

Table 2. Predictors of antithrombotic therapy choice.

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

†Antiplatelets (including aspirin + clopidogrol, aspirin + dipyramidole, aspirin, clopidogrol) anticoagulants include warfarin and non-vitamin K antagonist oral anticoagulants (NOACs)
‡As assessed by HEMORR$_2$HAGES
§Including dabigatran or rivaroxaban or apixaban
$Patients admitted to the department
High risk of fall: previous frequent falls or high risk of fall as documented in clinical notes
Prior intracranial haemorrhage: all type of haemorrhagic stroke and subdural or subarachnoid haemorrhage
Cognitive impairment: all types of dementia and other cognitive impairment as documented in clinical notes
Chronic kidney disease: all types of chronic renal impairment as documented in clinical notes
Prior gastrointestinal bleeding/ulcer: all types of gastrointestinal bleeding and ulcer as documented in clinical notes

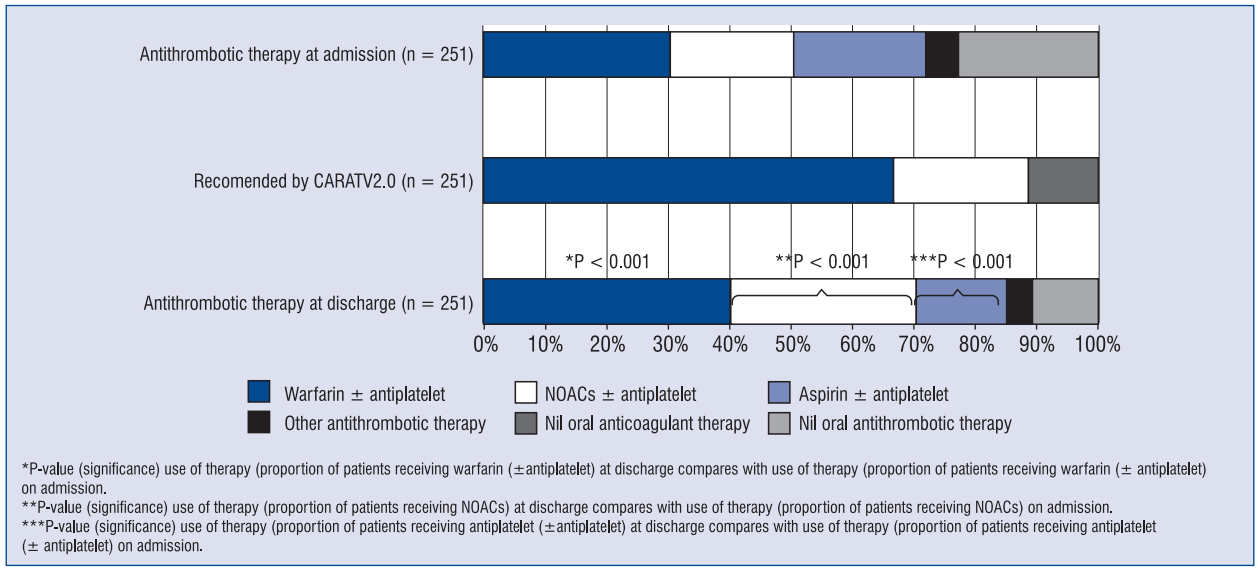

Figure 1. Changes to antithrombotic therapy over the course of the study; NOACs — dabigatran, rivaroxaban or apixaban.

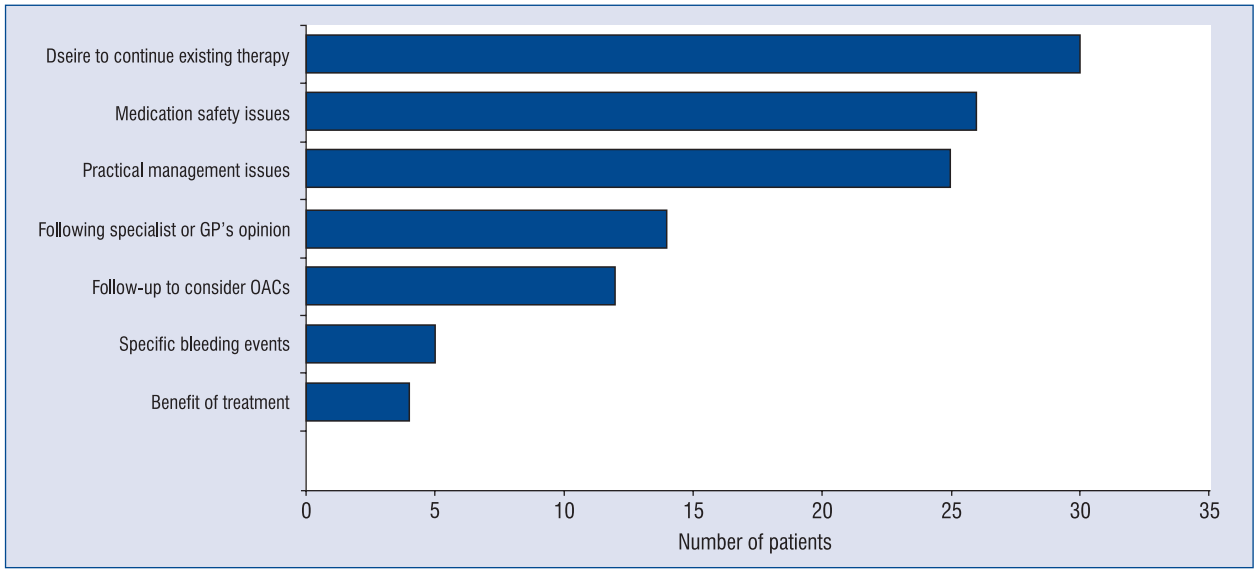

Figure 2. Main reasons for not taking CARATV2.0's recommendations; OAC — oral anticoagulants; GP — general practitioner.

CARATV2.0 to improve the use of anticoagulants has a valuable role in clinical practice.

Among factors affecting the selection of antithrombotics, bleeding risk and fall risk were the major barriers to prescribing anticoagulants [23]. The perceived association between a high risk of falls and ICH may have driven prescribers to avoid prescribing oral anticoagulants in those patients with a high fall risk [24]. However, a patient would need to fall about 300 times per year before their risk of ICH exceeds the benefits of using anticoagulation [25]. Moreover, there is no significant difference in the risk of ICH between therapy with NOACs such as apixaban and therapy with antiplatelets [26]. Therefore, for most patients, fall risk should not be a major barrier to prescribing an anticoagulant.

In contrast, prescribers' preference for prescribing warfarin to patients with chronic kidney disease is understandable, as studies have shown

that NOACs should be used with caution in patients with renal impairment, and are contraindicated in patients with severe renal impairment [1]. Interestingly, compared with admission to the other departments, patients admitted to the neurology department were more likely to be prescribed NOACs than prescribed warfarin. Possibly, neurologists have a different approach to selecting an antithrombotic therapy that is more aligned with international guidelines [27].

The treatment received by patients at discharge better aligned with CARATV2.0 recommendations when warfarin was considered as the first-line therapy, which suggests that most prescribers are still cautious of using NOACs as the first-line therapy. Although the majority of prescribers agreed with CARATV2.0 recommendations to prescribe anticoagulants, some cited reasons for not taking CARATV2.0 recommendations for specific antithrombotic agents. The desire to continue therapy, and issues of practical management and medication safety were cited as the major reasons for not accepting CARATV2.0 recommendations. Among these reasons, the desire to continue pre-admission therapy was commonly cited, which indicates that prescribers are reluctant to change therapy once initiated [28]. Although important issues of medication safety (fall risk, advanced age and dementia) and bleeding risk are considered by CARATV2.0 when making recommendations, some prescribers still cited these reasons for not prescribing anticoagulants. Thus, prescribers apparently perceived some factors as more risky than the evidence suggests. The concerns about issues of practical management and medication safety indicate that hospital prescribers are still worried about the long-term management of antithrombotic therapy by general practitioners and about the risk of adverse events. However, studies have shown that general practitioners are more focused on the benefits of antithrombotic therapy for patients [29].

In the post hoc analysis, it was also shown that CARATV2.0 can be adapted to an international setting, where there may be differences in guideline recommendations (in terms of whether NOACs or warfarin are used first-line). The assessment process of CARATV2.0 may be adjusted in terms of which agent is advocated as the first-line therapy. Therefore, for international users, CARATV2.0 can be customised to align with the local guidelines of each country. The tool's adaptability to other settings may be important, not only in terms of what the local guidelines advocate, but also in terms of cost implications. In Australia, both warfarin and NOACs are cost-subsidised by the Australian government [30], whereas in other countries the high-cost of NOACs may be borne by the patients, and these cost implications may impact treatment preferences.

Limitations of the study

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

Conclusions

In this study, CARATV2.0 successfully increased the use of anticoagulants in patients with AF and, when risk versus benefit profiles were taken into account, it demonstrated potential in the selection of an appropriate antithrombotic therapy. In the decision-making process of antithrombotic therapy, there are inter-speciality differences in therapy selection. In addition, prescribers were reluctant to change therapy once initiated citing perceived factors such as fall risk and age as being more risky than the evidence would suggest.

Conflict of interest: None declared

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