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CADTH Therapeutic Review

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Recommendations for Antithrombotic Agents for the Prevention of Stroke and Systemic Embolism in Patients With Atrial Fibrillation

Supporting Informed Decisions

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ABBREVIATIONS

ACCP	American College of Chest Physicians
AF	atrial fibrillation
ASA	acetylsalicylic acid
CADTH	Canadian Agency for Drugs and Technologies in Health
CCS	Canadian Cardiovascular Society
CDEC	Canadian Drug Expert Committee
ESC	European Society of Cardiology
ICH	intracranial hemorrhage
INR	international normalized ratio
MI	myocardial infarction
NMA	network meta-analysis
NOAC	new oral anticoagulant
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SSE	stroke or systemic embolism
TTR	time in therapeutic range
VKA	vitamin K antagonist

BACKGROUND

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with increased morbidity and mortality.[1,2] Patients with AF are at risk of stroke and systemic embolism (SSE), which can cause death, disability, and impaired quality of life.[1] Antithrombotic therapies, such as oral anticoagulant and antiplatelet drugs, can reduce the risk for stroke and systemic thromboembolism and are recommended for most AF patients with risk factors for stroke.[3-7] The risk of stroke varies considerably across patients; therefore, major guidelines[3,4,8] recommend antithrombotic therapy based on risk assessment, quantified using a validated tool such as the $CHADS_2$ score.[9,10]

There are decades of experience with the use of the vitamin K antagonist (VKA) warfarin, as well as compelling evidence of efficacy with regard to stroke prevention.[7,11,12] However, individualized dose adjustments and laboratory monitoring are required,[13-15] and warfarin remains a frequent cause of drug-related emergency hospitalization in the elderly.[16] New oral anticoagulants (NOACs) may feature more predictable pharmacokinetics and dosing, but there is less clinical experience outside of randomized controlled trials (RCTs) with these drugs at the moment. These NOACs include the direct thrombin inhibitor, dabigatran, and the direct factor Xa inhibitors, rivaroxaban and apixaban, which have been approved for use for the prevention of SSE in patients with AF. However, uncertainty remains regarding whether these agents show increased real-world benefits compared with warfarin. Although considered less effective at stroke prevention than anticoagulant therapy,[17] antiplatelet agents may nevertheless be an option for selected patients.[3-5,7,10]

The Canadian Agency for Drugs and Technologies in Health (CADTH) previously reviewed the clinical effectiveness and cost-effectiveness of the NOACs compared with warfarin.[18] At that time, apixaban was not approved for use in Canada, and was therefore not included in the Canadian Drug Expert Committee (CDEC) recommendation; in addition, antiplatelet drugs were not included. The current review was undertaken to allow the development of recommendations that include all the NOACs as well as the antiplatelet agents, acetylsalicylic acid (ASA) and clopidogrel.

Evidence-informed recommendations were developed by CDEC to address the following policy questions:

- In AF patients with a lower risk of stroke ($CHADS_2$ score < 2), which antithrombotic therapy is optimal?
- In AF patients with a higher risk of stroke ($CHADS_2$ score ≥ 2) who are unable to achieve adequate anticoagulation with warfarin, i.e., whose time in therapeutic range (TTR) is < 66%, which new oral anticoagulant (NOAC) is optimal?

The evidence for developing recommendations was derived from the following CADTH report:

- Canadian Agency for Drugs and Technologies in Health. Antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation [internal draft]. Ottawa: The Agency; 2013 Jan.

The analysis in the abovementioned report was limited by the small number of RCTs, and the heterogeneity of patient populations, trial designs, definitions of outcomes, and reporting of results of the included RCTs.

The Committee considered the evidence and its limitations primarily from a population-based perspective. The anticipated absolute benefits, harms, and cost-effectiveness of the NOACs, warfarin, and antiplatelet agents were considered to be fundamental in the development of system-level recommendations. The Committee also recognized that clinical guidelines related to the use of the NOACs have been developed based on clinical judgment and consideration of individual patient characteristics, but these guidelines failed to take into account the cost or cost-effectiveness of these treatments.

SUMMARY OF RECOMMENDATIONS

Recommendation 1:

CDEC recommends that new oral anticoagulants should be considered for the prevention of stroke for patients with non-valvular atrial fibrillation and:

- Who have a $CHADS_2$ score ≥ 1; AND
- Who are unable to readily achieve adequate anticoagulation with warfarin.

Recommendation 2:

CDEC recommends that, if a decision is made to use a new oral anticoagulant, selection should be based on individual clinical factors.

Of Note

The Committee noted that there was insufficient evidence to identify a preferred anticoagulation treatment strategy for patients with AF who have a lower risk of stroke ($CHADS_2$ score < 1). For patients with a $CHADS_2$ score of 0, clinical guidelines may be consulted for treatment options based on individual risk factors such as age, gender, and the presence of vascular disease.

CDEC determined that the high degree of uncertainty associated with the results did not support a recommendation regarding ASA alone or in combination with clopidogrel to prevent SSE. The Committee noted that ASA alone or in combination with clopidogrel failed to prevent SSE to the same extent as anticoagulants and was associated with an increased risk of bleeding compared with anticoagulants. Despite their low cost, antiplatelet agents were dominated in the economic analysis by warfarin and by one or more of the NOACs. There was consensus among the Committee members regarding the view that anticoagulant therapy should be used in preference to ASA alone or ASA in combination with clopidogrel for the prevention of stroke in non-valvular AF for individuals with a $CHADS_2$ score ≥ 1. While the Committee agreed that these conclusions were justified by the results of the analyses, they recognized the high degree of uncertainty associated with these results, and considered limitations such as the quality of trials that evaluated antiplatelet agents, among other limitations.

RECOMMENDATIONS

Recommendation 1:

CDEC recommends that new oral anticoagulants should be considered for the prevention of stroke for patients with non-valvular atrial fibrillation and:

- Who have a $CHADS_2$ score ≥ 1; AND
- Who are unable to readily achieve adequate anticoagulation with warfarin.

Of Note

The Committee noted that because patients with a $CHADS_2$ score < 2 were excluded from the ROCKET-AF trial, in which rivaroxaban was compared with warfarin, there was no evidence from this trial related to the use of rivaroxaban in patients with a $CHADS_2$ score of 1 or less.

The Committee felt that there was insufficient evidence to explicitly define "adequate anticoagulation with warfarin." The Committee felt that failure to achieve adequate anticoagulation with warfarin is sensitive to locally available resources and, as such, should be determined on a jurisdictional basis in collaboration with Clinical Experts. Considerations to be included in such a definition are:

- access to testing
- access to responsive primary care
- time to achievement of a stable international normalized ratio (INR)
- maintenance of a stable INR without frequent testing
- impact of short-term perturbations (e.g., antibiotic usage)
- patient-specific TTR
- serious hypersensitivity reaction to warfarin.

The Committee identified the values of safety, efficacy, and cost-effectiveness as of particular importance in making this recommendation.

Reasons for Recommendation 1

- While there were statistically significant differences between some of the NOACs and warfarin for some outcomes, absolute risk differences for the NOACs versus warfarin were generally fewer than 10 events per 1,000 patients treated each year.

Recommendation 2:

CDEC recommends that, if a decision is made to use a new oral anticoagulant, selection should be based on individual clinical factors.

Of Note

The Committee identified the values of safety, efficacy, and cost-effectiveness as of particular importance in recommending the use of patient-specific clinical factors in selecting a NOAC.

Reasons for Recommendation 2

- The lack of head-to-head trials and the small number of trials available to definitively assess comparative effectiveness indirectly makes evidence-based differentiation of these agents difficult.
- The relative cost-effectiveness of the NOACs is uncertain.
- The lack of long-term data for the NOACs and the assumption of persistent benefit of the NOACs beyond the durations of the individual RCTs available make comparison of the cost-effectiveness of the new agents unreliable.

SUMMARY OF THE EVIDENCE

Clinical Evidence

The Committee considered the results of a systematic review[19] conducted to assess the clinical effectiveness and safety of the new oral anticoagulants compared with warfarin. Twelve RCTs (28 publications)[20-47] were included in the systematic review that evaluated the efficacy and safety of antithrombotic interventions in patients with AF. Interventions included the NOACs apixaban, dabigatran, and rivaroxaban; warfarin; or ASA with or without clopidogrel. Trials were selected for inclusion in the systematic review and subsequent analyses if they included at least one treatment comparison between two of the antithrombotic strategies under review, reported any of the pre-specified outcomes related to patient safety or clinical efficacy (all-cause SSE, major bleeding, intracranial bleeding, all-cause mortality, and myocardial infarction (MI), and involved patients with AF eligible to receive anticoagulant therapy, regardless of the level of stroke risk. Trials that included patients with contraindication to anticoagulant treatment were excluded.

All twelve RCTs included in the systematic review (ACTIVE-W,[20-23] AFASAK,[24] AFASAK-2,[25,26] ARISTOTLE,[27-30] ARISTOTLE-J,[31] BAFTA,[32] CAFA,[33] JAST,[34] PETRO,[35] RE-LY,[36-43] ROCKET-AF[44-46] and WASPO[47]) were suitable for inclusion in a network meta-analysis (NMA) for indirect comparison of the antithrombotic agents. The AVERROES and ACTIVE A trials were excluded because the inclusion criteria for our systematic review required patients to be eligible for anticoagulant therapy, including treatment with a VKA.

Of the 61,050 randomized patients included in this review, four large multicentre trials accounted for 94% of patients: ARISTOTLE,[27-30] RE-LY,[36-43] ROCKET-AF[44-46] and ACTIVE-W.[20-23] Trials recruited patients with AF, most of them with at least one risk factor for stroke; however, patients with recent stroke or transient ischemic attack were usually excluded. In ARISTOTLE, a dose-modification algorithm was used to reduce the dose of apixaban to 2.5 mg twice daily to minimize the potential for higher exposure in patients who may be at an inherently higher bleeding risk and to maintain a balance between efficacy and safety in such populations. Mean $CHADS_2$ score was reported in five trials, encompassing the vast majority of patients included in the systematic review: ARISTOTLE,[27-30] ARISTOTLE-J,[31] RE-LY,[36-43] ROCKET-AF,[44-46] and ACTIVE-W.[20-23] Reported $CHADS_2$ scores in these trials were consistent with a high-risk population ($CHADS_2 \geq 2$). ROCKET-AF excluded patients with $CHADS_2$ scores of less than 2 and its population showed the highest risk for stroke (mean $CHADS_2$ of 3.5).

For the NMA, adjusted dose warfarin was chosen as the reference group. Bayesian mixed treatment comparison meta-analyses were conducted for the pre-specified outcomes using a binomial likelihood model. Both fixed and random-effects network meta-analyses were conducted.

The results of the NMA suggested that apixaban and dabigatran 150 mg, but not dabigatran 110 mg or rivaroxaban, significantly reduced all-cause SSE compared with adjusted dose warfarin. This reduction was statistically significant; however, the Committee considered the change to the actual numbers of patients who would avoid SSE: absolute difference for the NOACs versus warfarin translates into a reduction of one to six fewer patients with SSE per 1,000 patients treated each year. The Committee felt that the benefit was small overall, and questioned whether these absolute risk differences would translate into clinically meaningful benefits in practice. Low-dose ASA and the combination of clopidogrel plus low-dose ASA were statistically significantly less effective at preventing SSE compared with all anticoagulants. Except for apixaban (four fewer deaths per 1,000 patients), none of the other agents significantly reduced all-cause mortality. Except for dabigatran 150 mg (two more events per 1,000 patients), none of the agents significantly increased the risk of MI relative to adjusted dose warfarin.

Apixaban and dabigatran 110 mg, but not dabigatran 150 mg or rivaroxaban, significantly reduced the risk of major bleeding relative to adjusted dose warfarin. The absolute difference in major bleeding for all the NOACs versus warfarin ranged from one more to 10 fewer events per 1,000 patients treated each year. All of the NOACs significantly reduced the risk of intracranial bleeding relative to adjusted dose warfarin, and the absolute difference versus warfarin ranged from three to five fewer events per 1,000 patients treated each year.

Subgroup analyses were performed for age, TTR, and stroke risk based on $CHADS_2$ score. However, data for subgroups were only available for SSE and major bleeding, and not all subgroup data were available for all of the treatments. The results of the indirect comparison of treatments within subgroups were associated with substantial uncertainty and were therefore considered to be hypothesis-generating only.

Economic Evidence

The primary objective of the economic review was to determine the cost-effectiveness of the NOACs (dabigatran, rivaroxaban, and apixaban) and antiplatelet drugs (ASA with or without clopidogrel) compared with warfarin in patients with non-valvular AF, stratified by stroke risk ($CHADS_2$ score < 2 or ≥ 2). In addition, a more detailed stratification by $CHADS_2$ score (0, 1, ≥ 2 no previous stroke, ≥ 2 previous mild stroke, ≥ 2 previous major stroke) was conducted, and further stratified analysis was conducted for different age subgroups (≥ 60 < 65, ≥ 65 = 70 and <75 = 70, ≥ 75 = 80) and based on centre specific average TTR (< 66%, ≥ 66%). A variety of deterministic and probabilistic sensitivity analyses was carried out.

The Committee considered the results of a cost-utility analysis with treatments compared in terms of the incremental cost per quality-adjusted life-year (QALY) gained over a lifetime (40 years) time horizon. The target population for the analysis was Canadians with non-valvular AF requiring anticoagulation, and the economic analysis was conducted from a third party payer perspective, specifically a Canadian Ministry of Health.

The annual costs for all treatments considered are presented in Table 1.

Table 1: Annual Treatment Costs

Drug	Annual Cost* (C$)	Source
ASA — low dose	$20.44	Manufacturer
ASA — medium dose	$40.88	Manufacturer
Clopidogrel plus ASA	$307.67	Manufacturer/ Ontario MoH (2012)
Warfarin 5 mg, q.d.	$54.61	Ontario MoH (2012)
Dabigatran 110 mg b.i.d.	$1,289.44	Ontario MoH (2012)
Dabigatran 150 mg, b.i.d.	$1,289.44	Ontario MoH (2012)
Rivaroxaban 20 mg, q.d.	$1,147.53	Ontario MoH (2012)
Apixaban 5 mg b.i.d.	$1,289.44	Manufacturer
Monitoring INR for warfarin (per annum)	$240.69	Medical Advisory Secretariat (2009)

ASA = acetylsalicylic acid; b.i.d. = twice daily; MoH = Ministry of Health; q.d. = once daily.

*Drug treatment costs include a $7 prescription fee (every three months) and an 8% pharmacist's mark up. Estimates of drug costs were obtained from the Ontario Drug Benefit formulary or from the drug manufacturer.

The economic analysis was in the form of a Markov model in which a cohort of patients with non-valvular AF received pharmacotherapy to prevent stroke. The cohort was followed from initiation of pharmacotherapy to death while simulating the incidence of death and other events associated with the patient population. Specific events modelled were transient ischemic attack, SSE (fatal, major, or minor), bleeding (fatal, intracranial hemorrhage [ICH], major non-ICH, and minor), MI, pulmonary embolism (fatal or non-fatal), and death without an event. Utility values were derived from published literature for the modelled events and assumed to decline with age.

The results of the economic analyses suggested that for patients with $CHADS_2$ <2, dabigatran 150 mg was likely the optimal treatment with an incremental cost per QALY gained versus warfarin of $20,845. For patients with $CHADS_2$ ≥ 2, dabigatran 150 mg and apixaban were the most cost-effective treatments among the NOACs, and the incremental cost per QALY gained for both apixaban and dabigatran 150 mg versus warfarin was $17,795. Apixaban was likely optimal as it dominated dabigatran 150 mg in probabilistic analyses, but the difference between these two treatments is marginal.

The antiplatelet treatments were all dominated by one or more of the anticoagulants, irrespective of stroke risk ($CHADS_2$ score), age, or degree of INR control (TTR). Therefore, compared with anticoagulants, antiplatelet therapy was never optimal in any of the subgroups analyzed. However, the paucity of data for patients with a $CHADS_2$ score = 0 suggests that these findings cannot be generalized to patients with a low risk of stroke, and must be limited to patients with a moderate or high risk of stroke ($CHADS_2$ score > 0).

Relative cost-effectiveness was influenced by the following:

- Willingness-to-pay threshold (λ): The probability that dabigatran 150 mg is the most cost-effective NOAC in $CHADS_2$ < 2 increases as the willingness-to-pay threshold increases. Similarly, the probability that apixaban is optimal in patients with a $CHADS_2$ score ≥ 2 increases as the willingness-to-pay threshold increases.
- Age: Dabigatran 150 mg was optimal in younger patients (60 or 70 years old); whereas, apixaban was optimal in older patients (80 years old). None of the antiplatelet agents was optimal irrespective of age.
- Degree of INR control: In centres with poor INR control (TTR < 66%), dabigatran 150 mg was optimal, while apixaban was optimal in centres with good INR control (TTR ≥ 66%), although there was little difference in cost-effectiveness for both therapies.

The results of the cost-effectiveness analysis were highly sensitive to the patient population under consideration, reinforcing the need for tailoring the treatment of individual patients according to individual characteristics that affect treatment outcomes, including the degree of control of warfarin therapy (assessed using TTR), age, and risk of stroke.

Limitations of the Evidence

Heterogeneity of patient populations, trial design, definitions of outcomes, and reporting of results of the included RCTs are key limitations, and the small number of trials available in the published literature further limited the ability to adjust for this heterogeneity during analysis.

DISCUSSION POINTS

Efficacy and Cost-Effectiveness

- The clinical data available for comparison of the various treatments were recognized as being heterogeneous, due to several factors as specified in the main science report,[19] but mainly due to differences in the patient populations enrolled in each of the RCTs. The Committee recognized that the NMA approach to indirect comparison would be expected to be able to adjust for the observed heterogeneity, but that adjustment in the NMA could still not account for heterogeneity within patient subgroups. The Committee noted that this led to considerable uncertainty in comparing the different treatments, but particularly to comparison among the individual NOACs. The Committee noted that direct comparisons of the NOACs are needed through head-to-head trials to allow effective comparison among the NOACs, and that direct comparisons are unlikely to be available in the near-term. Despite the lack of such rigorous high-quality evidence, the Committee acknowledged that jurisdictions must rely on the evidence available to inform decision-making about the use of antithrombotic agents, and that an indirect comparison is the only option available at present to support this need.
- The Committee acknowledged that some of the NOACs had demonstrated statistical superiority to warfarin for some outcomes in some studies, but determined that there was relatively more uncertainty associated with claims of superiority versus claims of non-inferiority.
- The Committee noted that several assumptions in the NMA and within the economic model resulted in uncertainty associated with the cost-effectiveness analyses. Specifically, the Committee recognized that treatments that were most likely to be cost-effective depended heavily on the assumed duration of benefit of the NOACs. Due to the limited duration of the RCTs (two to three years long), the long-term persistence of the clinical effects of the NOACs is unknown.
- The Committee noted the fact that there were relatively few patients with $CHADS_2$ scores of less than 2 in the RCTs, and that one trial (ROCKET-AF) excluded such patients altogether.
- The Committee noted that the evidence available could support a recommendation to use warfarin in preference to the NOACs, based on cost-effectiveness in patients with a higher risk of stroke.
- The Committee noted that ASA alone or in combination with clopidogrel failed to prevent SSE to the same extent as anticoagulants and was associated with an increased risk of bleeding compared with anticoagulants. Despite their low cost, antiplatelet agents were dominated in the economic analysis by warfarin and by one or more of the NOACs. There was consensus among the Committee members regarding the view that anticoagulant therapy should be used in preference to ASA alone or ASA in combination with clopidogrel for the prevention of stroke in non-valvular AF for individuals with a $CHADS_2$ score > 1. While the Committee agreed that these conclusions were justified by the results of the analyses, they recognized the high degree of uncertainty associated with these results, and considered limitations such as the quality of trials that evaluated antiplatelet agents, among other limitations.
- The Committee discussed the relative benefits in terms of stroke prevention and how this is balanced against the potential for increased harm due to bleeding. The Committee recognized that antiplatelet drugs appear to have a less favourable relative risk and benefits profile than the anticoagulants, and that this was likely a credible result despite the analytical limitations.
- The Committee discussed the difficulty associated with determining the true value of differences among the various anticoagulant treatments, because the statistical significance of differences often translated into an absolute risk reduction of less than 10 fewer events per 1,000 patient years. The Committee noted that such small absolute differences in risk translate into number-needed-to-treat (NNT) values well in excess of 100, and frequently in excess of 500. The Committee recognized that perspective (e.g., patient, payer) influences the relative importance of apparently small absolute differences in clinical benefit among the different treatments.

Safety

- The Committee noted the lack of adequate strategies to manage bleeding in patients treated with the NOACs, whereas strategies are available to reverse VKA anticoagulation to attenuate bleeding in patients treated with warfarin. However, this was not determined to be a major differentiating factor between NOACs and warfarin in managing acute major bleeding events such as ICH, where damage occurs rapidly and typically cannot be reversed even in VKA-treated patients.
- The Committee noted that managing bleeding in patients treated with the NOACs is complicated by the fact that the NOACs act via different mechanisms of action that might require different approaches to manage bleeding.
- The Committee discussed the lack of long-term real-world safety data for the NOACs, and contrasted this with the wealth of data for warfarin available over several decades.
- Among safety issues discussed, the Committee highlighted renal impairment, or changing renal function over time, which may lead to an unrecognized risk as an anticoagulant drug accumulates. The Committee recognized that the risk to patients with renal impairment likely differed among the NOACs, but did not believe that there is sufficient evidence to differentiate among all the antithrombotic therapies beyond the guidance already available through regulatory agencies such as Health Canada.
- The Committee discussed the issue of regional differences in access to products that might be required to manage bleeding in the absence of a specific antidote (e.g., prothrombin complex concentrate). Such regional heterogeneity increases the difficulty of managing bleeding in anticoagulated patients.

Patient Considerations

- There was discussion related to the recommendation that NOACs be considered only in patients with a $CHADS_2 > 0$. The Committee discussed the most recent guidelines for the treatment of AF from the Canadian Cardiovascular Society (CCS),[3] the American College of Chest Physicians (ACCP)[4] and the European Society of Cardiology (ESC),[8] which recommend treatment with ASA or an anticoagulant in patients with a $CHADS_2$ score = 0, when there are additional risk factors for stroke. However, the Committee felt that there was insufficient evidence currently available to definitively identify a preferred strategy for this subgroup of patients.
- The Committee recognized that a $CHADS_2$ score of 1 reflects moderate risk, while $CHADS_2$ scores of 2 or more represent a more serious risk of stroke. The CCS, ACCP and ESC guidelines[3,4,8] recommend using oral anticoagulant agents in patients with a $CHADS_2$ score ≥ 1. These guidelines also recommend using a NOAC in preference to warfarin; however, the Committee noted that this failed to take into account the cost or cost-effectiveness of these treatments, and therefore noted that warfarin should be the anticoagulant of choice when cost is an important concern in patients with a $CHADS_2$ score ≥ 1.
- The Committee discussed the challenges related to the definition of "adequate anticoagulation with warfarin." In earlier CADTH work, attempts have been made to identify when there has been a "warfarin failure," defined as meaning that it is difficult to achieve, and sustain, an INR within the desired therapeutic range. There is no standard definition of "warfarin failure" in the literature but the Committee listed several factors based on expert opinion that can be considered within any definition in Recommendation 1.
- The Committee discussed the concept of adequate anticoagulation in patients treated with warfarin, and the role of INR monitoring in such patients. They noted that the frequency of INR monitoring required to ensure an acceptable TTR for warfarin varied widely among individual patients, as well as among various clinical settings.
- In addition, the period of time required to achieve adequate anticoagulation was discussed. The Committee concluded that there is insufficient evidence available to make a determination of an appropriate length of time within which patients should be expected to be able to reach a stable INR. Moreover, whether such evidence could be made available was doubtful, given the apparently large variations among individual patients and different

treatment settings in the time required to achieve a stable INR. The Committee suggested that given these issues, individual jurisdictions should each determine the length of such a period based on local factors and in consultation with local clinical experts.

- The Committee noted that convenience was not included in the economic analysis, and that there were no data available to determine whether this might have altered the outcomes of the economic analysis.

Other Discussion Points

- The Committee noted strongly that warfarin was an effective and cost-effective treatment for preventing stroke in AF patients, and that the NOACs represent potentially useful additional treatment options in certain patients. However, the paucity of long-term clinical and particularly long-term safety data is a significant concern.
- The Committee noted that the use of the NOACs in some patients with AF in the real-world setting would likely be more complicated (and therefore potentially associated with an increased risk of stroke and bleeding) than managing the same patients with warfarin, because while warfarin can be used across multiple indications and without regard to renal function, this is not true for the NOACs.
- The Committee discussed adherence. They noted that adherence with anticoagulant therapy to prevent stroke was generally poor, and that this could be applied to the NOACs, as well as to warfarin. By contrast, the requirement for INR monitoring in warfarin-treated patients might facilitate the detection of non-adherence.[48] For these reasons, the Committee did not accept an assumption that real-world effectiveness of the NOACs is greater than real-world effectiveness of warfarin.
- In further discussion of adherence, the Committee noted that there is a potential for increased risk of harm to patients who discontinue or interrupt NOAC therapy, based on the fact that the new drugs have relatively short half-lives versus warfarin. The Committee identified that the increase in stroke rates in patients who discontinued anticoagulation therapy in the ROCKET-AF trial might reflect the risk of discontinuing or interrupting NOAC therapy.
- The Committee discussed the exclusion of the AVERROES and ACTIVE A trials. The Committee reiterated the intent of the therapeutic review to include trials that enrolled patients who were eligible to receive treatment with an anticoagulant, and to analyze whether or not the trial designs may have resulted in patients being randomized to other interventions such as antiplatelet agents or placebo. Trials conducted in a population of patients who were ineligible to receive anticoagulant treatment for any reason were excluded. The AVERROES trial evaluated apixaban in comparison with ASA in patients who had failed a VKA (40% of patients) or were deemed unsuitable for VKA therapy (60%) yet were considered to be eligible for anticoagulation therapy by risk factor for stroke as per the $CHADS_2$ criteria. It was also not possible to determine definitively whether patients had been excluded due to risk factors that would prevent them being treated with another NOAC in addition to warfarin. The ACTIVE A trial, likewise, was designed to test the addition of clopidogrel to ASA in a population deemed to be “unsuitable” for a VKA. Both trials were therefore excluded under the terms of the inclusion/exclusion criteria for the therapeutic review.

RESEARCH GAPS

The Committee proposed that the following issues be addressed through research as high priorities in the future to facilitate comparisons of the NOACs, warfarin, and antiplatelet agents.

Safety

- Identification of optimal evidence-based management strategies to facilitate switching patients among different anticoagulants.
- Availability of reversal agents for the NOACs.
- Identification of the longer-term harms and benefits of each of the NOACs.
- Perioperative management of NOAC-treated patients.
- Management of bleeding in NOAC-treated patients.

Efficacy

- Direct comparisons between the NOACs.
- Evidence for rivaroxaban in AF patients with $CHADS_2$ scores < 2.
- Evidence of efficacy and effectiveness of the NOACs in a population that has not been managed successfully (i.e., “failed”) on warfarin.
- More specific trials that are directed at subpopulations within which one or another of the newer agents may have a particular role to play.
- Assessment of real-world adherence to NOAC therapy, and knowledge of how to manage poor adherence in NOAC-treated patients.

Committee Members:

Dr. Robert Peterson (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe,
Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets: Three CDEC members were not available to participate in deliberations and voting.

Conflicts of Interest: None

Three external Clinical Experts attended the meeting and participated in the discussion, but did not vote on the recommendations.

About this document:

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http://www.cadth.ca/media/pdf/TR0003_AntithromboticAgents-AF_RecsReport_e.pdf

The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations is considered in the preparation of this Recommendations document.

The Therapeutic Review Framework describes the Therapeutic Review process in detail.[49]

CDEC is a Committee of the CADTH. It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation and drug therapy and public members.

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