



CADTH Therapeutic Review Recommendations

New Oral Anticoagulants for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation

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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
GI	gastrointestinal
ICH	intracranial hemorrhage
INR	international normalized ratio
MI	myocardial infarction
MTC	mixed treatment comparison
NMA	network meta-analysis
NOAC	new oral anticoagulant
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SE	systemic embolism
TIA	transient ischemic attack
TTR	time in therapeutic range

BACKGROUND

Atrial fibrillation (AF), the most common cardiac rhythm abnormality, is associated with substantial morbidity. AF-related mortality is mainly attributable to complications of stroke. Stroke risk can be quantified using a validated tool such as the CHADS₂ score.¹ Warfarin, a vitamin K antagonist, is the standard of care for patients with AF and has demonstrated efficacy in the prevention of stroke.² Warfarin has a narrow therapeutic window, produces varied responses among patients, and interacts with some types of food and other drugs, all of which necessitates routine laboratory monitoring.^{3,4}

Improved understanding of the blood clotting cascade has led to the development of several new oral anticoagulants (NOACs) that offer a more targeted mechanism of anticoagulation. These NOACs include the direct thrombin inhibitor, dabigatran, and the direct factor Xa inhibitors, rivaroxaban and apixaban, which have either been approved (dabigatran and rivaroxaban) for use or are currently under regulatory review (apixaban) for the prevention of stroke and systemic embolism (SE) in patients with AF.

Although NOACs have demonstrated efficacy within clinical trials in preventing stroke and SE in patients with AF, the relative effectiveness and cost-effectiveness in clinical practice of these agents is not clear. In addition, the relative effectiveness and cost-effectiveness of the NOACs and warfarin within specific subpopulations of AF patients is not clear.

Evidence-informed recommendations were developed by the Canadian Drug Expert Committee (CDEC) to address the following policy questions:

1. Are there sub-populations of AF patients that would benefit more from using NOACs compared to warfarin?
2. Are there sub-populations of AF patients that would benefit more from one of the NOACs versus another?

At the time of this report, apixaban was not approved by Health Canada for the prevention of stroke and SE in patients with non-valvular AF. Therefore, while the science reports included apixaban in addition to rivaroxaban and dabigatran, the recommendations presented in this report apply at present only to the two NOACs that are approved for this indication in Canada, namely dabigatran and rivaroxaban.

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

- Canadian Collaborative for Network Meta-Analysis for Drug Safety and Effectiveness Project Team (DSEN-NMA Project Team). Safety, effectiveness, and cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2012 Apr. [cited 2012 Apr 9]. Available from: <http://www.cadth.ca/en/products/therapeutic-reviews/anticoagulants/reports>
- Canadian Agency for Drugs and Technologies in Health. Anticoagulation monitoring and reversal strategies for dabigatran, rivaroxaban, and apixaban: A review of clinical effectiveness and cost [Internet]. Ottawa: The Agency; 2012 Apr. [cited 2012 Apr 9]. Available from: <http://www.cadth.ca/en/products/therapeutic-reviews/anticoagulants/reports>

The analysis in the abovementioned reports was limited by the small number of randomized controlled trials (RCTs), and the heterogeneity of patient populations, trial design, 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 compared with warfarin 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.

SUMMARY OF RECOMMENDATIONS

Recommendation 1:

CDEC recommends that new oral anticoagulant agents should be considered for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in whom warfarin is indicated, and who meet all of the following criteria:

- Are unable to achieve adequate anticoagulation with warfarin, and
- Have a CHADS₂ score \geq 2.

Recommendation 2:

- CDEC recommends that the selection of a new oral anticoagulant agent should be made based on individual clinical factors.

NOTE: At the time of this report, apixaban was not approved by Health Canada for the prevention of stroke and SE in patients with non-valvular AF. Therefore, this recommendation should be restricted at present to dabigatran and rivaroxaban.

RECOMMENDATIONS

Recommendation 1:

CDEC recommends that new oral anticoagulants should be considered for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, in whom warfarin is indicated, and who meet all of the following criteria:

- Are unable to achieve adequate anticoagulation with warfarin, and
- Have a CHADS₂ score ≥ 2 .

Of Note

Patients with a CHADS₂ score of 1 may be considered for treatment with warfarin or an appropriate dose of dabigatran,ⁱ based on individual clinical factors.

The Committee noted that the determination of an inability to achieve adequate anticoagulation with warfarin is sensitive both to individual patient characteristics and to locally available resources and, as such, should be determined on a jurisdictional basis.ⁱⁱ Jurisdictions may consider the following factors in making such a determination:

- Access to international normalized ratio (INR) monitoring
- Time to achieve a stable therapeutic INR, as well as time in the therapeutic range
- Ability to maintain a stable therapeutic INR without frequent testing and dose adjustment
- Serious hypersensitivity reaction to warfarin
- Access to management of bleeding
- Ability to provide sufficient patient education and awareness.

Reasons for Recommendation 1

- Despite the small, absolute risk reductions of the NOACs versus warfarin, the daily cost of the NOACs exceeds that of warfarin, even when international normalized ratio (INR) monitoring costs are included.
- For the unstratified patient populations, the NOACs produced a small absolute risk reduction, compared with warfarin, of two to six per 1,000 patients treated annually and one more to eight fewer events per 1,000 patients treated annually for the outcomes of stroke and SE and major bleeding, respectively. These results were the same for patients with a CHADS₂ score of ≥ 2 . A clear benefit was not demonstrated for lower-risk patients.

ⁱ At the time of this report, apixaban was not approved by Health Canada for the prevention of stroke and SE in patients with non-valvular AF. Therefore, this recommendation should be restricted at present to dabigatran and rivaroxaban.

ⁱⁱ For more information related to the optimal use of warfarin, please see the CADTH report, *Optimal Warfarin Management for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation* (<http://www.cadth.ca/en/products/optimal-use/warfarin-management/reports>).

- Most of the patients enrolled in the RCTs reviewed had a CHADS₂ score of ≥ 2 , and patients with a CHADS₂ score of < 2 were not enrolled in all of the RCTs considered in the systematic review and subsequent mixed treatment comparison (MTC) by network meta-analysis (NMA); specifically, patients with a CHADS₂ score of < 2 were not included in the ROCKET-AF trial (for rivaroxaban). Therefore, the most reliable evidence for comparison of the NOACs with warfarin is for patients with a CHADS₂ score of ≥ 2 , which represents patients for whom oral anticoagulation therapy is recommended over other therapies such as acetylsalicylic acid (ASA).^{5,6}

Recommendation 2:

- CDEC recommends that the selection of a new oral anticoagulant should be made based on individual clinical factors.

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.
- Patient subgroups were not defined in the same way in all the relevant RCTs, making comparisons among different NOACs 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 it unreliable to compare the cost-effectiveness of the new agents.

SUMMARY OF THE EVIDENCE

Clinical Evidence

The results of the NMA suggested that dabigatran 150 mg and apixaban, but not rivaroxaban or dabigatran 110 mg, significantly reduced all-cause stroke/systemic embolism compared with adjusted dose warfarin. While this reduction was statistically significant, the committee considered the change to the actual numbers of patients who would avoid stroke or systemic embolism, and felt that the benefit was small overall: Absolute difference in all-cause stroke/systemic embolism for the NOACs versus warfarin translates to a reduction of just two to six fewer patients, with a stroke or systemic embolism per 1,000 patients treated each year. Except for apixaban (one fewer death per 1,000 patients), none of the NOACs significantly reduced all-cause mortality. None of the NOACs statistically significantly reduced the risk of myocardial infarction (MI) relative to adjusted dose warfarin.

Apixaban and dabigatran 110 mg 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 eight 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. By contrast, none of the NOACs significantly reduced the risk of major gastrointestinal (GI) bleeding relative to adjusted dose warfarin, and dabigatran 150 mg and rivaroxaban were associated with a significant increase in the risk of a major GI bleed versus warfarin. The absolute difference in GI bleeding for all the NOACs versus warfarin ranged from one fewer to eight more events per 1,000 patients treated each year.

Subgroup analyses were performed for age, time in therapeutic range (TTR), and stroke risk based on CHADS₂ score. However, data for subgroups were only available for stroke/systemic embolism and all-cause mortality, and not all subgroup data were available for all of the treatments. Therefore, the results of the indirect comparison of treatments within subgroups were associated with substantial uncertainty and were therefore considered to be hypothesis-generating only.

The Committee considered the results of a systematic review conducted to assess the clinical effectiveness and safety of the NOACs compared with warfarin. Five RCTs⁷⁻¹¹ were included in the systematic review that evaluated the non-inferiority of dabigatran, rivaroxaban, and apixaban compared with adjusted dose warfarin. Trials were selected for inclusion in the systematic review and subsequent analyses if they were carried out in AF patients, included treatment with one or more NOAC and warfarin, and included the following outcomes: all-cause stroke/SE, major bleeding, intracranial bleeding, major GI bleeding, all-cause mortality, and MI.

Three of the RCTs included in the systematic review (RE-LY,⁸ ROCKET-AF,⁷ ARISTOTLE¹⁰) were suitable for inclusion in an NMA for indirect comparison of the NOACs and warfarin because, in the other studies, no events were reported in both arms for many outcomes, and trials with zero cells in both arms do not contribute information. The AVERROES trial was excluded because ASA was not a comparator selected for the current review.

The RE-LY study⁸ compared dabigatran 110 mg, dabigatran 150 mg, and warfarin in a partially open-label RCT in which only the dose of dabigatran was blinded. The study enrolled 18,113 patients with a CHADS₂ score of ≥ 1 , and patients were followed for a median time of two years. The ROCKET-AF study⁷ was a double-blind RCT that compared rivaroxaban 20 mg to warfarin in patients with a CHADS₂ score of ≥ 2 . The study enrolled 14,264 patients who were followed for a median time of 1.9 years. The ARISTOTLE study¹⁰ was also a double-blind RCT that compared apixaban 5 mg with warfarin in patients with a CHADS₂ score of ≥ 1 . The study enrolled 18,201 patients who were followed for a median of 1.8 years.

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. A random effects general linear mixed model was also used to conduct the NMA.

Economic Evidence

The Committee recognized that NOACs were higher in cost than warfarin, and it considered the relative cost-effectiveness of the products. The Committee recognized that consideration of relative cost-effectiveness does not take into account the overall budget impact, and noted that the responsibility for considering budget impact rests with the jurisdictions.

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-year) time horizon. The primary objective of the economic review was to determine the cost-effectiveness of the new oral anticoagulants compared to warfarin in patients with non-valvular AF. Secondary objectives included examining the cost-effectiveness of NOACs compared with warfarin when patients are stratified according to: age, CHADS₂ (or CHA₂SDS₂-VASc) scores, and TTR.

The analysis was in the form of a Markov model in which a cohort of patients with non-valvular AF receiving pharmacotherapy to prevent stroke was followed from initiation of pharmacotherapy to death whilst simulating the incidence of death-related events associated with the patient population. The model included the following events: transient ischemic attack (TIA), stroke (fatal, major or minor), bleeding (fatal, intracranial hemorrhage (ICH), major non-ICH, and minor non-ICH), MI, pulmonary embolism (fatal or non-fatal) and death without a preceding clinical event. The probability that such events occur is influenced by a number of factors including treatment and patient characteristics. Patients who experience a stroke, major bleed, or ICH on treatment were assumed to continue with aspirin treatment alone, although a sensitivity analysis was conducted, which assumed patients would remain on therapy. The model assumes no difference in the outcomes of events by treatment. Utility values were derived from published literature for the modelled events and assumed to decline with age.

The costs and recommended doses of oral anticoagulants included in the analysis are provided in the following table.

Drug	Dosing for Atrial Fibrillation	Daily Cost (\$)	Annual Cost (\$)*
Dabigatran	110 mg or 150 mg twice daily	3.20	1,289.44 [†]
Rivaroxaban	15 mg or 20 mg daily	2.84	1,147.53 [‡]
Apixaban	5 mg twice daily	3.20	1,289.44 [§]
Warfarin	5 mg daily	0.07	54.61 [¶]
International Normalized Ratio monitoring for warfarin	Not applicable	Not applicable	240.69 ^{**}

* Drug costs include a \$7 prescription fee (every three months) and an 8% pharmacist's markup.

[†] Published study: Sorensen et al. 2011¹²

[‡] Kory McDonald Ibarra, Director, Federal Government and External Affairs, Ottawa, Bayer, Inc.(personal communication, 2012 Feb.).

[§] Author assumption.

[¶] Ontario Ministry of Health and Long-Term Care, 2011¹³

** Published study: Medical Advisory Secretariat, 2009.¹⁴ Adjusted to 2011 Canadian dollars.

In the base case analysis, dabigatran 150 mg twice daily was associated with an incremental cost per QALY of \$17,525 compared with warfarin. Dabigatran 110 mg twice daily, rivaroxaban, and apixaban were dominated by dabigatran 150 mg twice daily — associated with fewer QALYs and higher costs.

Sensitivity analyses were conducted to examine the impact of parameters on the incremental cost-utility ratio. For most sensitivity analyses, the results did not change, with the exception of:

- Variation in the duration of treatment benefits (treatment effects for apixaban and dabigatran must be assumed to last more than five years for the cost per QALY to fall below \$50,000 compared with warfarin)
- Inclusion of vascular deaths (rivaroxaban preferred over dabigatran)
- Patients with previous stroke (cost per QALY for dabigatran 150 mg twice daily \$133,200 compared with warfarin)
- Daily cost of apixaban reduced by 20% per day (apixaban preferred over dabigatran 150 mg twice daily).

The results of the analysis of specific patient subgroup analyses were very sensitive to the patient population under consideration. Dabigatran 150 mg twice daily was the most cost-effective treatment option irrespective of risk of stroke (CHADS₂ score). Apixaban was most cost-effective in patients 80 years old, while dabigatran 150 mg twice daily was the most cost-effective treatment option in younger patients (assumed to be age 60 or 70 years old). In centres where the TTR was < 66%, dabigatran 150 mg twice daily was the most cost-effective treatment option, while apixaban was the most cost-effective treatment option where the TTR was ≥ 66%. None of NOACs could be considered cost-effective for patients with a previous major stroke.

The results of the cost-effectiveness analysis suggested that either dabigatran 150 mg or apixaban would be the most cost-effective anticoagulant treatment option overall. The results of the cost-effectiveness analysis were highly sensitive to the patient population under consideration, reinforcing the need for tailoring treatment of individual patients according to individual characteristics that affect treatment outcomes, including the degree of control of warfarin therapy (assessed using TTR), age, risk of stroke, and history of thromboembolic events. The results of the analysis of cost-effectiveness of the NOACs and warfarin were limited by the uncertainty regarding the pricing of the NOACs (apixaban is not currently marketed for AF, and therefore the price was assumed to be the same as that of dabigatran), as well as the heterogeneity of the clinical data regarding the patient populations enrolled in each of the three RCTs included in the analysis.

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. The limited follow-up (median of two years) from the three RCTs and the sensitivity of the pharmacoeconomic results to the duration of treatment effect leads to uncertainty around the long term cost-effectiveness of the NOACs.

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, but particularly 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 for comparison of the

different treatments, particularly to comparison among the individual NOACs. Consequently, the results of the cost-effectiveness analyses were noted to be uncertain.

- Despite the above-mentioned limitations, the Committee agreed that the individual RCTs were well-designed, methodologically sound studies that did provide useful clinical information about the efficacy and harms of the individual NOACs in comparison to warfarin.
- The Committee noted that direct comparisons of the NOACs are needed through head-to-head trials to allow effective comparison among the NOACs.
- The Committee noted that any recommendations based on comparison of the NOACs as a class were made more difficult by the fact that the individual NOACs and warfarin have different mechanisms of action.
- The Committee recognized that the results of the cost-effectiveness analysis suggested that rivaroxaban was most likely the least cost-effective treatment. However, the Committee noted that this was possibly due to the fact that the population in the ROCKET-AF was at a higher risk of stroke than the populations in the other RCTs.
- In addition, 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 which treatments were most likely to be cost-effective depended heavily on the assumed duration of benefit, which is not known in the absence of long-term clinical data. Therefore, the Committee noted that it was not certain whether apixaban or dabigatran 150 would be cost-effective in the medium or long term.
- The Committee also noted the fact that there were relatively few patients with CHADS₂ scores of less than 2 in the RCTs, and that one trial (ROCKET-AF) excluded such patients altogether, which made it difficult to recommend the use of the NOACs as a class in preference to warfarin in patients with a low or moderate risk of stroke.
- The Committee noted that the evidence available supported a recommendation to use warfarin in preference to the NOACs based on cost-effectiveness in patients with a higher risk of stroke, as represented by a CHADS₂ score of 2 or more.

Safety

- The Committee noted that there were differences among the trials in the management strategies used to transition patients from study medication to other anticoagulants, and that this illustrated the serious problem of how best to manage patients who are being switched from one anticoagulant to another.
- The Committee discussed the lack of long-term safety data for the NOACs, and contrasted this with the wealth of data available over several decades for warfarin.
- The safety of the NOACs was discussed also with reference to recent safety advisories¹⁵ from regulators regarding the requirement to monitor renal function in certain patients, including the elderly. The Committee noted that this reflected the lack of knowledge regarding the safety of the NOACs, particularly compared to warfarin.
- The Committee noted that the results of the CADTH report¹⁶ emphasized the lack of adequate strategies to manage bleeding in patients treated with the NOACs.
- 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.

Patient Considerations

- There was discussion regarding the recommendation that NOACs be considered only in patients with a CHADS₂ score ≥ 2 . The Committee discussed the most recent guidelines for the treatment of AF^{5,6} from the Canadian Cardiovascular Society (CCS) and American College of Chest Physicians (ACCP) and recognized that either an anticoagulant or ASA can be used when the CHADS₂ score is 1.
- The Committee recognized that a CHADS₂ score of 1 reflects moderate risk, while CHADS₂ scores of 2 or more represent a more serious risk of stroke. Both the CCS and ACCP guidelines recommend

using oral anticoagulant agents in patients with a CHADS₂ score ≥ 2 .^{5,6} Both guidelines also recommend using a NOACⁱⁱⁱ in preference to warfarin; however, the Committee noted that this failed to take into account the cost or cost-effectiveness of these treatments versus warfarin, and therefore noted that warfarin therapy could be the anticoagulant of choice in such patients. In fact, the ACCP guidelines provide several reasons that justify warfarin as a preferable alternative to the NOACs, including when “the cost of medication is an important concern”.⁶

- 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.
- The Committee recognized that a major issue for patients who require anticoagulant therapy is fear of the consequences of acute bleeding due to traumatic injury, but particularly due to falling. Although this issue applies equally to any anticoagulant therapy, including the NOACs and warfarin, the Committee echoed the concern of patients in that the best practices to manage acute bleeding in patients treated with the NOACs are uncertain.
- 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 time within the therapeutic range for warfarin varied widely among individual patients.

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 are a significant concern.
- The Committee noted that the use of the NOACs in some patients with AF in the real world would likely be more complicated (and therefore potentially associated with 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.
- In addition to not being approved for treatment of as many indications as warfarin, the NOACs appear to have different efficacy in different indications; this makes it more difficult to recommend selection of one NOAC over another for AF, when in reality AF patients (particularly high-risk patients) will have multiple related comorbidities.
- In addition to raising safety concerns and complicating patient management, the aforementioned issue led the Committee to question how the cost-effectiveness could be reliably estimated for populations where switching among different anticoagulants occurs due to the development of comorbidities (e.g. in a patient who develops AF while being treated with an anticoagulant for deep vein thrombosis prevention).
- The Committee discussed the need for materials to aid health care professionals and patients in selecting appropriate anticoagulant therapy. In particular, the Committee supported the idea of developing decision aids for the NOACs for health care professionals, as well as patient education aids.
- The Committee discussed adherence. They noted that adherence with anticoagulant therapy to prevent stroke was generally poor, but that this could be applied to the NOACs, as well as warfarin. By contrast, the requirement for INR monitoring in warfarin-treated patients might facilitate the detection of non-adherence.¹⁷ For these reasons, the Committee could not accept an assumption that real-world effectiveness of the NOACs is greater than real-world effectiveness of warfarin.

ⁱⁱⁱ The ACCP guidelines go further and specify a preference for 150 mg dabigatran over apixaban or rivaroxaban.⁶

RESEARCH GAPS

The Committee proposed that the following issues be addressed through research as a high priority in future to facilitate comparisons of the NOACs and warfarin.

Safety

- Identification of optimal evidence-based management strategies to facilitate switching patients among different anticoagulants
- 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
- Comparison of the risk of bleeding or stroke/systemic embolism of the NOACs versus warfarin when first initiating treatment
- Elucidation of additional factors beyond those captured in CHADS₂ regarding risk for stroke or systemic embolism, the significance of their impact on risk, and whether use of a NOAC mitigates risk.

Efficacy

- Direct comparisons between the NOACs
- Evidence for rivaroxaban in AF patients with CHADS₂ 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 are needed 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. Lindsay Nicolle (Vice-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. 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:

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 recommendation document.

CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (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.

The Final CDEC Therapeutic Review Recommendations or Advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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The Therapeutic Review Framework describes the Therapeutic Review process in detail.¹⁸

REFERENCES

1. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001 Jun 13;285(22):2864-70.
2. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J*. 2009 May;157(5):805-10, 810.e1-2.
3. Bendel SD, Bona R, Baker WL. Dabigatran: an oral direct thrombin inhibitor for use in atrial fibrillation. *Adv Ther*. 2011 Jun;28(6):460-72.
4. Eerenberg ES, van Es J, Sijpkens MK, Buller HR, Kamphuisen PW. New anticoagulants: moving on from scientific results to clinical implementation. *Ann Med*. 2011 Dec;43(8):606-16.
5. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol* [Internet]. 2012 Mar [cited 2012 Mar 28];28(2):125-36. Available from: [http://www.onlinecjc.ca/article/S0828-282X\(12\)00046-3/fulltext](http://www.onlinecjc.ca/article/S0828-282X(12)00046-3/fulltext)
6. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012 Feb;141(2 Suppl):e531S-e575S.
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011 Sep 8;365(10):883-91.
8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* [Internet]. 2009 Sep 17 [cited 2012 Mar 28];361(12):1139-51. Available from: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa0905561>
9. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol*. 2007 Nov 1;100(9):1419-26.
10. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011 Sep 15;365(11):981-92.
11. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study-. *Circ J*. 2011;75(8):1852-9.
12. Sorensen SV, Kansal AR, Connolly S. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost*. 2011;105(5):908-19.
13. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: The Ministry; 2011. [cited 2012 Jan 10]. Available from: <https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp>
14. Medical Advisory Secretariat. Point-of-care international normalized ratio (INR) monitoring devices for patients on long-term oral anticoagulation therapy: an evidence-based analysis. Ontario Health Technol Assess Series [Internet]. 2009 [cited 2012 Mar 14];9(12). Available from: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_poc_20090928.pdf

15. Health Canada. Pradax (dabigatran etexilate) - updated labelling regarding kidney function assessment and use in patients with certain types of heart valve disease or artificial heart valves - for health professionals [Internet]. Ottawa: Health Canada; 2012 Mar 16. [cited 2012 Mar 28]. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2012/pradax_hpc-cps-eng.php
16. Canadian Agency for Drugs and Technologies in Health. Anticoagulation monitoring and reversal strategies for dabigatran, rivaroxaban, and apixaban: a review of clinical effectiveness and cost [Internet]. Ottawa: The Agency; 2012 Apr. [cited 2012 Apr 9]. Available from: http://www.cadth.ca/media/pdf/TR0002_New_Oral_Anticoagulants.pdf
17. Kimmel SE, Chen Z, Price M, Parker CS, Metlay JP, Christie JD, et al. The influence of patient adherence on anticoagulation control with warfarin: results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study. *Arch Intern Med*. 2007 Feb 12;167(3):229-35.
18. Canadian Agency for Drugs and Technologies in Health. Therapeutic review framework [Internet]. Ottawa: The Agency; 2012 Jan. [cited 2012 Jun 7]. Available from: http://www.cadth.ca/media/pdf/TR_Framework.pdf