

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

Adapted from Canadian Agency for Drugs and Technologies in Health. [Antithrombotic agents for the prevention of stroke and systemic embolism in patients with atrial fibrillation \(Therapeutic Review\)](#). Ottawa: Canadian Agency for Drugs and Technologies in Health; 2013.

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Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with increased morbidity and mortality.^{1,2} Patients with AF are at increased 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 of stroke and systemic thromboembolism and are recommended for most patients with AF who are at risk of having a 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 risk assessment tool, such as the CHADS₂ score.^{9,10}

The CHADS₂ scoring system assigns points for each of the individual risk factors referred to in its name — one point each for congestive heart failure, hypertension, age older than 75, and diabetes mellitus; and two points for secondary prevention (prior stroke or transient ischemic attack). A CHADS₂ score of zero corresponds to

a low risk of stroke, a CHADS₂ score of one corresponds to an intermediate risk of stroke, and a CHADS₂ score of two or more corresponds to a high risk of stroke.

Each oral antithrombotic drug used for stroke prevention in patients with AF has advantages and disadvantages. There are decades of experience with the use of the anticoagulant warfarin, a vitamin K antagonist (VKA), as well as compelling evidence of its efficacy with regard to stroke prevention.^{7,11,12} However, warfarin requires individualized dose adjustments and laboratory monitoring,¹³⁻¹⁵ and it remains the most common cause of drug-related emergency hospitalization in the elderly.¹⁶

New oral anticoagulants (NOACs) feature more predictable pharmacokinetics and dosing, but there is less clinical experience outside of randomized controlled trials (RCTs) with these drugs versus warfarin. 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. Although considered less effective at stroke prevention than anticoagulant therapy in most risk categories,¹⁷ the antiplatelet agents, acetylsalicylic acid (ASA) and clopidogrel, may still be the best choice for selected patients.^{3-5,7,10}

A committee of experts convened by the Canadian Agency for Drugs and Technologies in Health (CADTH) developed recommendations on the use of antithrombotic agents for the prevention of SSE in patients with AF based on a systematic review and NMA of the clinical evidence of these drugs and an economic analysis of their cost-effectiveness.

Objective

The objective of the report was to:

1. Conduct a systematic review and mixed treatment comparison (MTC) of the clinical evidence pertaining to antithrombotic agents for the prevention of morbidity and mortality in patients with non-valvular AF.
2. Assess the impact of age, CHADS₂ score, and time spent in the therapeutic range (TTR; relevant to warfarin only) on the clinical safety and efficacy of antithrombotic agents.
3. Conduct a cost-effectiveness analysis of antithrombotic agents based on the results of the systematic review and MTC.

Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy. Conference abstracts were excluded from the search results. The initial search was completed on June 7, 2012. Regular alerts were established to update the search until publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (<http://www.cadth.ca/resources/grey-matters>). Google was used to search for additional web-based materials.

Active and placebo-controlled RCTs of antithrombotic agents for the prevention of stroke and other thromboembolic events in patients with AF were identified through electronic databases, grey literature, and stakeholder consultation. Two reviewers independently screened the titles and abstracts, and independently evaluated the full-text publications for final article selection. RCTs were considered for inclusion if they compared at least two of the antithrombotic strategies

under review, in patients who were eligible for anticoagulant therapy, and reported outcomes related to patient safety or clinical efficacy, as pre-specified in the review protocol.

Pairwise and Bayesian MTC NMAs were conducted to pool trial results, when appropriate. The results of the MTC were used to evaluate the cost-effectiveness of each intervention following standard procedures.

CADTH's committee of experts used clinical, economic, and ethical evaluations, as well as stakeholder feedback, to develop the recommendation.

Results

The systematic review included 12 individual RCTs (28 publications)¹⁸⁻⁴⁵ in which the efficacy and safety of antithrombotic interventions were evaluated in patients with AF. Interventions included the NOACs (dabigatran, rivaroxaban, and apixaban), warfarin, or ASA with or without clopidogrel.

Clinical Evidence

The results of the NMA showed 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 of experts 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 of experts 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 myocardial infarction relative to adjusted-dose warfarin.

Apixaban and dabigatran 110 mg, but not dabigatran 150 mg or rivaroxaban, were associated with a significantly reduced risk of major bleeding relative to adjusted-dose warfarin. The absolute difference in major bleeding for all the NOACs versus warfarin ranged from 1 more to 10 fewer events per 1,000 patients treated each year. All of the NOACs were associated with a significantly reduced risk of intracranial bleeding relative to adjusted-dose warfarin, and the absolute difference versus warfarin ranged from 3 to 5 fewer events per 1,000 patients treated each year.

Subgroup analyses were performed for age, TTR, and stroke risk based on CHADS₂ 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 (CHADS₂ score < 2 or ≥ 2). In addition, a more detailed stratification by CHADS₂ score (0, 1, ≥ 2 no previous stroke, ≥ 2 previous mild stroke, ≥ 2 previous major stroke) was conducted, and a further stratified analysis was conducted for different age subgroups

(≥ 60, < 65, ≥ 65 = 70 and ≥ 70, < 75, ≥ 75 = 80) and based on centre-specific average TTR (< 66%, ≥ 66%). A variety of deterministic and probabilistic sensitivity analyses was carried out.

The committee of experts considered the results of a cost-utility analysis with treatments compared in terms of the incremental cost per quality-adjusted life-year gained over a lifetime 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 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 bleeding), myocardial infarction, 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 antiplatelet treatments were all dominated by one or more of the anticoagulants, irrespective of stroke risk (CHADS₂ score), age, or degree of INR (international normalized ratio) 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 CHADS₂ score of 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 (CHADS₂ score > 0).

Relative cost-effectiveness was influenced by the following:

- Willingness-to-pay threshold: The probability that dabigatran 150 mg is the most cost-effective NOAC in CHADS₂ < 2 increases as the willingness-to-pay threshold increases. Similarly, the probability that apixaban is optimal in patients with a CHADS₂ score ≥ 2 increases as the willingness-to-pay threshold increases.
- Age: Dabigatran 150 mg was the optimal NOAC 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 the optimal NOAC, 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

This review is limited by the heterogeneity among the included trials, both for patient population and trial methodology, as well as by the variability in definitions (e.g., bleeding) and in methodological rigour. In fact, most trials evaluating ASA were substantially smaller, older, and of lower quality than the

anticoagulant trials. Because of the relatively small number of trials available for each individual therapy in the published literature, the limited ability to adjust for such heterogeneity reduces the degree of certainty associated with the results of the analyses.

Because there are no direct comparisons of the NOACs available, indirect comparisons were used to compare the different treatments. This method has inherent limitations, but in the absence of head-to-head trial data, this is the only way to compare different antithrombotic therapies.

Data were not available for all outcomes for all treatments in all subpopulations of interest. In particular, for all interventions, there were very few patients at low risk of stroke (CHADS₂ score = 0). Therefore, the findings cannot be generalized to patients who have a low risk of stroke.

Limitations that affect confidence in the results of the comparison of clinical efficacy and safety would also apply to the results of the pharmacoeconomic analyses.

Conclusions

The results of this review revealed that there were statistically significant differences in clinical outcomes in patients with AF between the NOACs and warfarin, although it is unclear whether the absolute risk difference associated with these differences translates into clinically meaningful benefits in practice.

The review demonstrated that anticoagulant therapy is superior to ASA, both regarding clinical benefit and cost-effectiveness, irrespective of whether ASA is co-administered with clopidogrel. Anticoagulant therapy would appear to be a superior treatment option for preventing SSE in patients with non-valvular AF who have a moderate or high risk of stroke (CHADS₂ score ≥ 1). The superiority of the anticoagulant drugs versus the antiplatelet

drugs was consistent irrespective of age and the degree of INR control (TTR).

These results must be considered in the light of the limitations already noted, particularly the reliance on indirect comparison methodology to compare the different treatments. Based on these results in the context of the limitations, CADTH's committee of experts recommended that:

- NOACs should be considered for the prevention of stroke for patients with non-valvular AF and those:
 - who have a CHADS₂ score ≥ 1 , and who are unable to readily achieve adequate anticoagulation with warfarin.
- if a decision is made to use an NOAC, selection should be based on individual clinical factors.

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Cite as: Canadian Agency for Drugs and Technologies in Health. *CADTH Technology Overviews*, 2013; 3(2).

ISSN: 1481-4501 (online)