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Antithrombotic Therapy for Patients with Atrial Fibrillation — Project Protocol

Supporting Informed Decisions

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1 CONTEXT AND POLICY ISSUES

Atrial fibrillation (AF) is a common cardiac arrhythmia, associated with increased morbidity and mortality.[1-3] Patients with AF may suffer from a reduction in cardiac output, as well as thrombus formation,[1] which poses a significant risk of arterial thromboembolism and stroke.[2] Embolization of atrial thrombi, most frequently ischemic stroke,[4] can have a substantial debilitating impact, as well as a high risk of recurrence.[2] As a result, preventing strokes and other thrombotic events with antithrombotic strategies is an important part of treating patients with atrial fibrillation.[5] However, antithrombotic therapy is also associated with an increased risk of major bleeding, which may also lead to serious consequences; therefore, the benefits of therapy should always be weighted against a patient's risk of hemorrhage.[6]

The objective of the systematic review is to compare the clinical and cost-effectiveness of oral antithrombotic agents (i.e., anticoagulant and antiplatelet agents) for the prevention of stroke and other thromboembolic events in patients with atrial fibrillation.

2 RESEARCH QUESTIONS

1. How do the clinical safety and efficacy of new oral anticoagulant agents (apixaban, dabigatran, and rivaroxaban) compare with warfarin, ASA, clopidogrel, or ASA plus clopidogrel in preventing morbidity and mortality in patients with non-valvular atrial fibrillation? Are there any differences in clinical safety and efficacy depending on the dose of ASA?
2. In patients with non-valvular atrial fibrillation, what impact do the following have in respect to the clinical safety and efficacy of new oral anticoagulant agents: $CHADS_2$ score, time spent in the therapeutic range[*], age, weight, renal function, history of gastrointestinal bleed, concurrent use of antiplatelet agents (when on oral anticoagulant agents), or NSAIDs?
3. What is the cost-effectiveness[†] of new oral anticoagulant agents compared with warfarin, ASA, clopidogrel, or ASA plus clopidogrel in preventing morbidity and mortality in patients with non-valvular atrial fibrillation?
4. What is the cost-effectiveness[†] of new oral anticoagulant agents compared with warfarin, ASA, clopidogrel, or ASA plus clopidogrel in preventing morbidity and mortality in patients with non-valvular atrial fibrillation based on the $CHADS_2$ score?

3 METHODS

3.1 Literature Search Strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy. Published literature will be identified by searching the following bibliographic databases: MEDLINE (from 1946) with in-process records and daily updates through Ovid; Embase (from 1974) through Ovid; Cochrane Central Register of Controlled Trials through Ovid; and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be dabigatran, apixaban, rivaroxaban, clopidogrel, acetylsalicylic acid, warfarin, acenocoumarol, and atrial fibrillation. Methodological filters will be applied to limit

[*] Applicable only to warfarin

[†] Public payer's perspective

retrieval to randomized controlled trials and controlled clinical trials. Retrieval will be limited to English language articles and studies published after 1988. Conference abstracts will be excluded from search results.

Grey literature (literature that is not commercially published) will be identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, Canadian and major international health technology assessment agencies, and clinical practice guidelines, as well as The Cochrane Library (2012, Issue 6) and the University of York Centre for Reviews and Dissemination (CRD) databases. Google will be used to search for additional web-based materials.

3.2 Article Selection

Two reviewers will independently screen the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria, will order the full text of any articles that appear to meet those criteria. The reviewers will then independently review the full text of the selected articles, apply the selection criteria to them, and compare the independently chosen included and excluded studies. Disagreements will be resolved through discussion until consensus is reached.

Selection criteria are outlined in Table 1.

Table 1: Inclusion and Exclusion Criteria for Primary Studies	
Inclusion Criteria	
Clinical Trial Design	Published RCTs
Patient Population	Individuals with non-valvular AF requiring anticoagulation (including all risk levels and regardless of any comorbidities) Subgroups: $CHADS_2$ score, TTR, age, weight, renal function, history of GI bleed, concurrent use of antiplatelet agents (when on oral anticoagulant agent) or NSAID, prior VKA use, type of AF.
Interventions	Anticoagulant agents: apixaban, dabigatran, rivaroxaban, and dose-adjusted VKA* Antiplatelet agents: ASA† and clopidogrel, placebo
Outcomes	• All-cause stroke or systemic embolism • Major bleeding (ISTH definition) • All-cause mortality • Intracranial bleeding (including intracerebral hemorrhage) • Cardiovascular mortality • Ischemic stroke/uncertain stroke or systemic embolism (including MI) • Life-threatening bleeds • Extracranial hemorrhage • Minor bleeds • Pulmonary embolism • Transient ischemic attacks • Non-cardiovascular mortality
Exclusion Criteria	
Studies in languages other than English Non-randomized studies	

AF = atrial fibrillation; ASA = acetylsalicylic acid; GI = gastrointestinal; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; NSAID = non-steroidal antiinflammatory drug; RCT = randomized controlled trial; TTR = time spent in therapeutic range; VKA = vitamin K antagonist.
* Warfarin and acenocoumarol. VKA trials will only be considered for inclusion if the dosage is adjusted to a standard international normalized ratio target.
†Any dose of ASA will be considered for inclusion; however, these will later be stratified in the analysis according to low or high dose.

3.3 Data Extraction and Critical Appraisal

Two reviewers will proceed with data extraction using a standardized template. Data that are to be extracted include the following:

- baseline characteristics of trial participants
- intervention(s) evaluated; including dose, duration, and relevant co-medication
- efficacy and safety results of the interventions for each of the pre-specified outcomes included in the protocol.

All extracted data will be checked for accuracy by two independent reviewers. Disagreements will be resolved through discussion until consensus is reached.

Findings will be interpreted in light of the heterogeneity of the individual studies (differences in design, study populations, interventions or exposures, and outcome measures) and the validity assessment. Further critical appraisal will be performed based on clinical input from experts.

3.4 Data Analysis Methods

Evidence tables describing the characteristics of the relevant studies will be developed. The results of clinical efficacy and harms will be described using a quantitative approach, as the clinical and economic assessments will be performed by indirect/mixed treatment comparisons, with the use of a network meta-analysis.

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