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Original article

Comparative efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation: A network meta-analysis with the adjustment for the possible bias from open label studies

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ABSTRACT

Background: This study was designed to compare efficacy and safety among novel oral anticoagulants (NOACs), which have not been directly compared in randomized control trials to date.
Method: We performed network meta-analyses of randomized control trials in preventing thromboembolic events and major bleeding in patients with atrial fibrillation. PubMed, Embase, and the Cochrane Database of Systematic Reviews for published studies and various registries of clinical trials for unpublished studies were searched for 2002–2013. All phase III randomized controlled trials (RCTs) of NOACs (apixaban, edoxaban, dabigatran, rivaroxaban), idraparinux, and ximelagatran were reviewed.
Results: A systematic literature search identified nine phase III RCTs for primary analyses. The efficacy of each NOAC was similar with respect to our primary composite endpoint following adjustment for open label designs [odds ratios (ORs) versus vitamin K antagonists: apixaban 0.79; dabigatran 150 mg 0.77; edoxaban 60 mg 0.87; rivaroxaban 0.86] except for dabigatran 110 mg and edoxaban 30 mg. Apixaban and edoxaban 30 mg and 60 mg had significantly fewer major bleeding events than dabigatran 150 mg, ricvaroxaban, and vitamin K antagonists. All NOACs were similar in reducing secondary endpoints with the exception of dabigatran 110 mg and 150 mg which were associated with a significantly greater incidence of myocardial infarction compared to apixaban, edoxaban 60 mg, and rivaroxaban.
Conclusions: Our indirect comparison with adjustment for study design suggests that the efficacy of the examined NOACs is similar across drugs, but that some differences in safety and risk of myocardial infarction exist, and that open label study designs appear to overestimate safety and treatment efficacy. Differences in study design should be taken into account in the interpretation of results from RCTs of NOACs.

Introduction

The introduction of novel oral anticoagulants (NOACs) has ushered in a new era in treatment strategies for the prevention of stroke and systemic embolism in patients with atrial fibrillation. However, as all approved NOACs were compared with vitamin K antagonists in their respective phase III trials, possible differences in the efficacy and safety among individual drugs have not yet been formally tested. Moreover, study design has varied widely among clinical trials of NOACs, potentially influencing individual study results as well as confounding cross-study analyses.

An example of the former includes the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation Trial (SPORTIF) III [1] and SPORTIF V [2] studies, which reported divergent results in open design and double-blind comparisons of ximelagatran and warfarin. This potential study design effect is further supported by a pair of systematic reviews. Schulz et al. assessed the methodological quality of 33 meta-analyses, containing 250 controlled trials, to evaluate study differences impacting treatment efficacy and found that trials that were not adequately blinded significantly

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overestimated treatment effects [3]. Jüni et al. conducted a meta-analysis to evaluate the extent of potential bias related to open versus blinded studies and found similar results [4].

In addition to concerns of study design, patient factors may also complicate comparisons of NOAC findings. White et al. reported that clinical outcomes, including risk of death, stroke and systemic embolism, myocardial infraction, and major bleeding, were correlated to international normalized ratio (INR) control in patients with atrial fibrillation taking a vitamin K antagonist (warfarin) [5]. Such a patient condition-mediated outcome variability in response to vitamin K antagonist therapy could pose a potential stumbling block for inter-study analyses.

In order to adjust for potential study design biases and outcome variability due to patient condition and to effectively compare the safety and efficacy of NOACs and vitamin K antagonists using the available data, we conducted an indirect comparison by network meta-analysis of the available literature. The novelty of our analysis is indirect comparison of NOACs based on results adjusted for un-blindness, which might have been relevant in the assessment of efficacy and safety of NOACs compared to warfarin.

Methods

Study design

We conducted a network meta-analysis to compare NOACs in preventing thromboembolic events in patients with atrial fibrillation. In our present study, we defined apixaban, betrixaban, dabigatran, edoxaban, and rivaroxaban as NOACs; ximelagatran as an oral anticoagulant; and warfarin, idraparinux, and aspirin as comparators. Our literature search included all phase III randomized controlled trials (RCTs) of NOACs for the primary analysis. In instances where two doses were examined in one trial, we considered both doses as independent interventions.

Neither the approval of an institutional review board nor informed consent was required due to the nature of our study design.

Patients and endpoints

We included patients with either chronic or paroxysmal atrial fibrillation, irrespective of cause. No criteria were enforced for gender or age.

The primary endpoint was a composite of stroke and systemic embolism. Stroke was defined to include ischemic, hemorrhagic, and uncertain stroke, but not transient ischemic attack; systemic embolism included any embolism other than cerebrovascular or of a cardiac origin. Secondary endpoints included stroke and myocardial infarction. We included major bleeding as a safety endpoint. Other endpoints of interest included: all-cause death, ischemic stroke (including stroke of unknown origin), hemorrhagic stroke, and intracranial hemorrhage.

Literature search

One investigator (KW) conducted the literature search through PubMed, Embase, and the Cochrane Database of Systematic Reviews for published studies meeting inclusion criteria. We also reviewed registries of clinical trials (TrialResults-center, clinicalstudyresults.org, clinicaltrials.gov, the World Health Organization International Clinical Trials Registry Platform), ISI Web of Knowledge, the US Food and Drug Administration, and the European Medicines Agency sites for unpublished studies. References from retrieved articles found were also examined.

Our search included terms for the following interventions: apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban, and ximelagatran. We included all English language studies published between January 1, 2002 and December 31, 2013. The population of interest was patients with atrial fibrillation. Retrieved studies were limited to phase III RCTs. Complete search strategy details are provided in Appendix 1 as Table A1.

Data extraction and synthesis

Two investigators (TM, SU) independently assessed articles identified by the literature search for inclusion, and articles fulfilling inclusion criteria were compiled for data extraction and synthesis.

A network meta-analysis was conducted by a statistician (BC) taking into account study bias and correcting for indirect comparisons. This approach was based on an empirical estimate of bias from meta-epidemiological studies comparing results of open studies with those of double-blind studies addressing the same research question (treatment and disease). The mean empirical bias (and its distribution) was obtained by calculating the ratio of the odds ratios (ORs), that is, dividing the OR from the open studies by the OR of the double-blind studies. A ratio of less than 1 indicates an overestimation of effect by the open studies. This method incorporates not only the magnitude but also the uncertainly of the bias (its distribution). We used the method described by Jüni et al. [4] to estimate the pooled ORs for taking study design into account. Statistical techniques for network analyses have been described elsewhere [6]. In brief, to obtain the OR for two treatments A versus B (OR_{AB}), we divided the OR for A versus C by the OR for B versus C. Confidence intervals were calculated as $EXP(\ln(OR_{AB}) \pm 1.96\sqrt{[SE_{AC}^2 + SE_{BC}^2]})$ where the SE is from the log-odds. Network analyses require the same assumptions as traditional meta-analyses in that studies are assumed to be independent and should be performed under similar conditions. Adjustments for open and blinded studies were made to account for this difference; however, other study differences that could impact outcomes were evaluated and are discussed in the limitations. Microsoft Excel 2010 for Windows was used for statistical analyses and graphical presentation.

We first estimated the pooled ORs of the NOACs compared to vitamin K antagonists with and without an adjustment of study design on the primary and safety endpoints. If a study design effect was observed, we thereafter used the bias adjustment method to estimate the pooled ORs for primary and secondary endpoints. We compared the pooled ORs of each NOAC to those of every other NOAC as well as those of aspirin and vitamin K antagonists. The choice of a fixed or random effect model was based on the goodness of fit of the model to the data. The Cochrane χ^2 (i.e. *Q*-statistic) was used for model fit in assessing whether a fixed or random effects model was used for each endpoint.

As a sensitivity analysis, we added phase II studies to the main analyses (phase III studies) and recalculated treatment effects to assess the robustness of the main analyses.

Results

Literature search

Our literature search identified 139 articles, of which nine were selected for the primary analyses (Fig. 1). One of these nine articles was an unpublished RTC of idraparinux [7], which was identified while conducting a manual search for clinical trials in TrialResults-center. Three articles were excluded from the primary analyses because they were phase II RCTs; however, they were later included for sensitivity analyses. The agreement for inclusion and exclusion between investigators was 100%.