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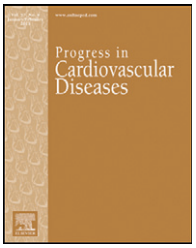

Risk of Myocardial Infarction in Patients with Long-Term Non-Vitamin K Antagonist Oral Anticoagulant Treatment

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ABSTRACT

The relative cardiovascular (CV) safety of oral anticoagulants continues to be debated, and in particular concerns for risk of myocardial infarction (MI) have been raised. We analyzed the risk of MI in patients treated long term with oral anticoagulants (vitamin K antagonists [VKA], direct thrombin inhibitors or activated X factor antagonist) for atrial fibrillation, deep vein thrombosis or pulmonary embolism using a network meta-analysis (NMA).

Methods: Randomized, phase 3 trials comparing novel anticoagulants to VKA were searched. Information on study design and clinical outcomes was extracted. The primary end-point of the analysis was the occurrence of MI or acute coronary syndrome. A Bayesian multiple treatment analysis was performed using fixed-effect and random-effects modeling.

Results: Twelve trials including 100,524 randomized patients were analyzed. The odds for MI in NMA were worse with dabigatran when compared to VKA, rivaroxaban, apixaban, and edoxaban (OR: 0.66 CI: 0.49–0.87; OR: 0.56 CI: 0.38–0.82, OR: 0.59 CI 0.40–0.88, and OR: 0.71 CI: 0.50–1.0, respectively).The posterior probability of being the first best choice of treatment was 53.5% for rivaroxaban, 33.8% for apixaban, 9.5% for ximelagatran, 2.0% for edoxaban, 1.2% for VKA, and 0.007% for dabigatran.

Conclusions: There is a considerable heterogeneity regarding CV safety among oral anticoagulants. Differences in risk of MI may influence the choice of treatment. Multiple treatment NMA found 29%–44% higher odds of MI with dabigatran supporting the concerns regarding its CV safety.

Although inhibition of platelet activation forms the mainstay of our treatment and prevention of acute coronary syndromes (ACS), it is trivial that the coagulation cascade plays an important role in the evolution of these events.[1] An earlier meta-analysis demonstrated that supplementation of the therapy with warfarin in patients after ACS significantly reduced the rate of recurrent events, although with different levels of evidence for aspirin and clopidogrel.[2] However,

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Abbreviations and Acronyms

ACS = acute coronary syndromes

ADP = adenosine diphosphate

AF = atrial fibrillation

Anti Xa = activated factor X antagonist

CHD = coronary heart disease

CrI = credible interval

CV = cardiovascular

DTI = direct thrombin inhibitor

DVT = deep vein thrombosis

INR = international normalized ratio

MI = myocardial infarction

NMA = network meta-analysis

NOAC = non-vitamin K dependent oral anticoagulant

NVAF = non-valvular AF

OR = odds ratio

PE = pulmonary embolism

RCT = randomized clinical trial

VKA = vitamin K antagonist

based on the high frequency of bleeding complications and the multiple drawbacks of vitamin K antagonist (VKA) treatment, this strategy never became part of the routine therapy.

In recent years, more specifically-acting oral anticoagulants were developed providing reliable anticoagulation without the need for laboratory monitoring. Some of these novel, non-vitamin K dependent oral anticoagulants (NOACs) demonstrated similar or higher efficacy in several indications like the treatment of pulmonary embolism (PE), deep vein thrombosis (DVT) and in prevention of systemic embolization and stroke in patients with atrial fibrillation (AF), specifically non-valvular AF (NVAF) and in prevention of DVT after major orthopedic surgery. These drugs caused less frequently life-threatening and intracranial bleeding, however, with higher rates of gastrointestinal bleeding in some instances.[3] These results set the base for the shift in the anticoagulation routine and VKAs are progressively replaced by the NOACs leading to high numbers of patients treated with these drugs for long term.

Importantly, these agents showed dissimilar results regarding their cardiovascular (CV) safety. Notably, patients with NVAF treated with the direct thrombin inhibitor (DTI), dabigatran, had higher rates of myocardial infarction (MI), while those treated with rivaroxaban or apixaban (active factor X inhibitors) had lower frequency of MI.[4–6] Moreover, pairwise meta-analyses of randomized trials in different clinical scenarios and control treatment arms found a significantly higher risk of MI among the dabigatran treated patients, while in similarly structured analyses the risk of MI with rivaroxaban was significantly lower and in the case of apixaban no statistically significant difference was found.[7–9]

Direct head to head comparison of these agents is not available so far. Therefore, we aimed to perform a comprehensive systematic review and Bayesian network meta-analysis (NMA) to gain more insight on the relations in CV safety of oral DTIs and activated factor X antagonists (anti-Xa) as compared to VKAs in patients with need for long term anticoagulation.

Methods

Literature search strategy

Searches were performed in electronic databases (PubMed, www.clinicaltrials.gov and Scopus) for relevant studies published between 01 January, 2000 and 31 December, 2014. We also performed manual searches through the reference lists of studies and reviews, editorials and letters. No language restriction was used. The search key words included the following terms: 'deep vein thrombosis', 'atrial fibrillation', 'pulmonary embolism', 'anticoagulation', 'myocardial infarction', 'apixaban OR edoxaban OR darexaban OR rivaroxaban OR otamixaban OR YM466 OR dabigatran OR argatroban OR ximelagatran'. (For detailed search history refer to the Appendix).

In the analysis we included trials that fulfilled the following criteria:

(A) Prospective, randomized clinical trials (RCTs) that assessed the clinical efficacy and/or safety of an anticoagulant protocol comprising an oral DTI or anti-Xa agents. (B) Controlled treatment with international normalized ratio (INR) adjusted dosage of warfarin or acenocumarol. (C) Reporting the frequency of MI or the rate of ACS during the follow-up compliant with intention to treat analysis. (D) Inclusion of patients in a sufficient number, i.e. at least 1000 cases per treatment arms to assess the frequency of CV events.

Studies that evaluated the clinical impact of short term treatment i.e. less than three months, uncontrolled or cohort studies, trials of parenteral anticoagulants as well as trials merely assessing biological efficacy but not clinical endpoints were excluded.

Data extraction and analysis

Manuscript selection and data abstraction were done independently by two reviewers (AK and AT). Disagreements were resolved by consensus with a third party (DK).The following details were recorded for each study: study name, first author, year of publication, period of study, the applied doses of oral anticoagulant and VKA, design of the trial, number of patient, length of follow-up, inclusion and exclusion criteria, primary outcome, protocol definitions of myocardial infarction as well as patient and procedural characteristics including mean age, sex, the following risk factors: obesity, diabetes, hypercholesterolemia, hypertension, smoking, duration of hospitalization and lost to follow up.

The data from intention to treat analyses were extracted. The main efficacy endpoints were the frequency of MI according to each study definition.

Meta-analysis statistical techniques

The risk of MI was analyzed in a hierarchical Bayesian mixed-treatment comparison meta-analysis. We applied a "non-informative" vague prior distribution [dnorm(0,10000)]; RCT data were then added via the Bayes rule to produce posterior distributions. Treatment effects were obtained from the posterior distributions of the Bayesian analysis and were