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Risk of major bleeding in different indications for new oral anticoagulants: Insights from a meta-analysis of approved dosages from 50 randomized trials

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ABSTRACT

Background: A meta-analysis was performed to evaluate the risk of major bleeding with the use of New Oral Anticoagulants (NOACs).
Methods: Randomized controlled trials (RCTs) comparing NOACs (rivaroxaban, dabigatran, apixaban, edoxaban and darexaban) with comparators were selected.
Results: Fifty trials included 155,537 patients. Pooled analysis of all NOACs for all indications together demonstrated no significant difference between NOACs and comparators for risk of major bleeding (odds ratio [OR] 0.93, 95% CI 0.79–1.09). Pooled analysis also showed that NOACs caused significantly less major bleeding compared to vitamin K antagonists (VKA) (0.77, 0.64–0.91). The analysis for individual NOACs showed risk of major bleeding were not different with rivaroxaban, apixaban or dabigatran compared to pharmacologically active comparators or VKA. Indication specific analysis showed that NOACs were associated with significantly higher major bleeding after hip surgery (1.43, 1.02–1.99), in patients with acute coronary syndrome (ACS), (compared against placebo) (2.89, 2.01–4.14), and for medically ill patients (2.79, 1.69–4.60). For the treatment of acute venous thromboembolism (VTE) or pulmonary embolism (PE), NOACs were associated with significantly less bleeding (0.63, 0.44–0.90). No significant difference was found between NOACs and comparators in treatment of atrial fibrillation and for extended treatment of VTE.
Conclusions: Risk of major bleeding with new oral anticoagulants varies with their indication for use. New agents may be associated with comparatively less major bleeding compared to VKA. NOAC may increase the risk of major bleeding after hip surgery, ACS and acute medically ill patients; but may be associated with less bleeding in treatment of acute VTE/PE.

1. Introduction

New oral anticoagulant agents (NOACs) have been developed in recent years for use in different indications. The newer agents have specific advantages over conventional anticoagulants, including rapid onset of action, predictable therapeutic effect, and limited interactions with other drugs [1]. The two groups of NOACs include the factor Xa (FXa) inhibitors (eg. rivaroxaban, apixaban, edoxaban and darexaban) and direct thrombin inhibitors (DTIs, eg. dabigatran and ximelagatran) [1].

Rivaroxaban is approved in the United States and Europe for thromboprophylaxis after orthopedic surgery, treatment of venous thromboembolism (VTE), and for stroke prevention in patients with atrial fibrillation (AF); in Europe rivaroxaban has been recently approved for acute coronary syndrome (ACS) [1–4]. Apixaban is approved in Europe for patients with atrial fibrillation and for thromboprophylaxis after orthopedic surgery and in the United States apixaban recently received approval for patients with atrial fibrillation only [5,6]. Ximelagatran is no longer available because of reports of liver toxicity [1]. Dabigatran is approved in the United States for stroke prevention in non-valvular AF, and in Europe this drug received additional approval for thromboprophylaxis after orthopedic surgery [1,7,8]. Other new drugs, edoxaban and darexaban have been evaluated in phase II trials [1,9].

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However, the major disadvantage of the NOACs is the lack of specific antidotes that would reverse their action in a patient with major bleeding [1,10,11]. Also, no reliable laboratory tests are available to monitor the effects of these agents [10,11]. Thus, there is some concern regarding the risk of major bleeding with these new agents, which on occasion can even be life threatening [1,10,11]. No major study or systematic review focusing only on comparative bleeding risk with these drugs has been published. At the same time there is no previous or ongoing, head-to-head trial among these new agents, although indirect comparisons provide some insights into some differences in safety endpoints [12].

We performed a systematic review and meta-analysis of published randomized clinical trials to evaluate the risk of major bleeding with new oral anticoagulants.

2. Methods

We systematically searched the published literature for trials comparing any of the new oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban and darexaban) with conventionally used medications/anticoagulants among various indications for anticoagulation.

2.1. Data sources and searches

We electronically searched PubMed, Cochrane CENTRAL, EMBASE, EBSCO, Web of Science and CINAHL databases for English language, peer-reviewed publications of NOACs from January 2001 through October 31, 2013. Further details of the search strategy are mentioned in the Online-only Data Supplement Appendix A.

2.2. Study selection

The included studies were randomized clinical trials; the trials evaluated any new oral anticoagulants including dabigatran, rivaroxaban, apixaban, edoxaban or darexaban; the comparator was any active pharmacologic agents or placebo and major bleeding outcome was reported. We included studies with commonly evaluated indications for newer anticoagulants' use in randomized clinical trials: thromboprophylaxis after hip surgery, thromboprophylaxis after knee surgery, treatment of acute VTE or pulmonary embolism (PE), extended treatment of venous thromboembolism, prevention of embolism/stroke in atrial fibrillation (AF), acute coronary syndrome (ACS) and thromboprophylaxis in medically ill patients. The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs [13] was used as a reference method for this study.

2.3. Data extraction and quality assessment

Two authors (PS, SC) reviewed the trials, ensured that they met inclusion criteria and abstracted the data; disagreements were resolved by discussion with other authors. Risk for bias was assessed by the procedures suggested by the Cochrane Handbook of Systematic Reviews [14].

2.4. Data synthesis and analysis

The outcome of interest was major bleeding events in the study group and the comparator group. For trials that evaluated 2 or more doses of NOACs, we used the outcome related to the approved total daily dose/closely related dose of the experimental drug for our analysis. For phase II trials we used the dose, which was subsequently tested in phase III trials, and when only phase II data was available, we chose the most frequently used dose of those drugs (for specific indications) in all trials with acceptable efficacy profile. (Details in Online-only Data Supplement Appendix A).

2.5. Statistical analysis

We performed pooled comparisons between dabigatran, rivaroxaban, apixaban, edoxaban and darexaban versus comparators on safety analysis population. In this analysis, Review Manager Version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2008, Copenhagen) was used. We calculated odds ratio (OR) estimates and associated 95% confidence intervals (CIs) for each of the oral anticoagulants and for each indication of use. We assessed the heterogeneity using the Cochran Q test and the Higgins I^2 statistic. We calculated the total event rates calculated by summing up all events across all trials and dividing by the total number of patients across all trials. For our main analysis random effects models described by Der-Simonian and Laird was used. For studies using dissimilar agents in the control group, the random-effects model was applied. For sensitivity analysis, we used fixed effects model described by Mantel and Haenszel. Indirect comparisons between these drugs (with indication specific conventional drugs as a common comparator) were also done. We used Stata 11.2 (StataCorp LP, College Station, Texas) software for indirect comparisons [Bucher's method] [15]. Small study effects (publication bias) was assessed graphically by evaluating the standard error and the effect size in the funnel plots.

3. Results

A total of 5742 reports were identified by our electronic database search (Fig. 1). Finally, 50 trials involving a total 155,537 patients in safety analysis groups met our inclusion criteria and were selected for the present analysis (Online-only Data Supplement Appendix A).

3.1. Characteristics of included studies

The included trials were conducted for different indications for anticoagulation therapy; thromboprophylaxis after hip surgery (12 studies), thromboprophylaxis after knee surgery (9 studies), treatment of acute VTE/PE (8 studies), treatment of patients with ACS (6 studies), prevention of stroke/embolic events in patients with AF (10 studies), extended treatment of VTE (4 studies), and thromboprophylaxis in medically ill patients (2 studies). The BISTRO II trial included both hip and knee surgery patients, we used the published data for separate analysis [16]. The numbers of included trials appraising rivaroxaban, apixaban, dabigatran, edoxaban and darexaban were eighteen, twelve, twelve, five and three respectively.

Most of the studies used the International Society on Thrombosis and Hemostasis (ISTH) criteria in documenting major bleeding, though there were inter trial variation/modification in the definition (Online-only Data Supplement Appendix A). In the ACS trials, Thrombolysis In Myocardial Infarction (TIMI) major bleeding events were included in the analysis. In acute VTE studies patients received treatment for 3 or 12 months, and in "extended VTE treatment" studies patients received additional 6 to 12 months of treatment. For the studies with acutely ill medical patients, NOAC was given for 30–35 days versus LMWH for 6–14 days followed by placebo for the rest of the period.

Inter-rater reliability between the reviewers in the assessment of risk of bias was good with a kappa statistic of 0.85. A total of 33 studies showed low risk of bias, and among them 25 studies evaluated NOACs against active comparators.

3.2. The pooled effect estimate according to study drug/comparator drug (NOACs versus comparators)

Pooled analysis of all NOACs together for all indications of anticoagulation showed, there was no significant difference between NOACs and pharmacologically active comparators for the risk of major bleeding [Odds ratio (OR) 0.93, 95% Confidence Interval (CI) 0.79–1.09, $I^2 = 56\%$], 2.4% with NOACs versus 2.7% with pharmacologically active comparators (Fig. 2). Sensitivity analysis including trials with only low risk of bias also showed similar result (Online Supplement). Newer agents caused statistically significant less major bleeding compared to vitamin K antagonists (OR 0.77, 95% CI 0.64–0.91, $I^2 = 61\%$, $p = 0.003$), 3.3% versus 3.9%. A similar result was found for pooled analysis with three available/approved NOACs (rivaroxaban, dabigatran, apixaban) (OR 0.76, 95% CI 0.63–0.92, $I^2 = 67\%$, $p = 0.005$), 3.6% versus 4.2% (Fig. 3).

Direct comparison analysis for individual NOACs showed, when considering each NOAC separately, there was on average no evidence of an effect of any of these relative to pharmacologically active agents; for rivaroxaban (OR 1.10, 95% CI 0.77–1.58, $I^2 = 57\%$; 2.4% with rivaroxaban versus 2.3% with active agents), apixaban (OR 0.81, 95% CI 0.56–1.119, $I^2 = 67\%$; 1.9% versus 2.5%) or dabigatran (OR 0.96, 95% CI 0.76–1.20, $I^2 = 20\%$; 3.8% versus 4.0%) (Table 1). Similar findings with these three newer agents were also observed for separate analysis against vitamin K antagonists and low molecular weight heparin (LMWH) (Table 1).

Indirect comparisons between individual NOACs did not show any major differences between rivaroxaban, dabigatran, apixaban,