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Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism

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ABSTRACT

Background: Numerous new oral anticoagulants (NOACs) have been compared to a parenteral anticoagulant/oral vitamin K antagonist (VKA) for the treatment of acute venous thromboembolism (VTE). We aimed to conduct a systematic review and adjusted indirect comparison meta-analysis to compare the efficacy and safety of NOACs for this indication.

Methods: We conducted a systematic literature search through November 2013 for randomized trials that evaluated treatment of acute VTE with a NOAC including rivaroxaban, apixaban, dabigatran and edoxaban. Trials had to report at least one of the following outcomes of interest: mortality, recurrent VTE, recurrent pulmonary embolism (PE), recurrent deep vein thrombosis (DVT), or major bleeding. Included trials were evaluated for quality using the Cochrane Risk of Bias tool. We performed an adjusted indirect comparison meta-analysis to evaluate the comparative efficacy and safety of NOACs, reporting relative risks (RRs) and 95% confidence intervals for each outcome.

Results: Six trials (n = 27,069) met inclusion criteria, one each evaluating apixaban and edoxaban and two trials each evaluating rivaroxaban and dabigatran. Risk of bias was low for all trials. NOACS did not differ significantly in the risk of mortality, recurrent VTE, recurrent PE or recurrent DVT. Dabigatran increased major bleeding risk compared to apixaban [RR 2.69 (1.19 to 6.07)] as did edoxaban compared to apixaban [RR 2.74 (1.40 to 5.39)].

Conclusion: Although NOACs do not appear to differ in the efficacy of treating acute VTE, data suggests apixaban to be the safer than some of its competitors.

Introduction

Acute venous thromboembolism (VTE) is a common disorder with an estimated annual incidence of 1.83 adults per 1000, with deep vein thrombosis (DVT) occurring more frequently than pulmonary embolism (PE) [1]. For decades, the standard treatment strategy has been bridging a parenteral heparin product and an oral vitamin-K antagonist (VKA) until a therapeutic international normalized ratio (INR) is achieved, with continuation of the VKA for a minimum of three months [2]. While effective, this treatment regimen has several limitations. Parenteral administration can be unfavorable to patients and requires additional nurse time in the inpatient setting and possibly on an outpatient basis. Routine INR monitoring requires transportation and often leads to dose-adjustments which presents an opportunity for medication errors. Lastly, there is a potential for significant drug and food interactions with VKAs which can become important given their narrow therapeutic window.

In recent years, several new oral anticoagulants (NOACs) have been under development for the treatment of acute VTE. NOACs that are currently approved by the Food and Drug Administration (FDA) or with phase III trial results include the factor Xa inhibitors apixaban, rivaroxaban, and edoxaban and the direct thrombin inhibitor dabigatran. For the acute treatment of VTE, NOAC have been compared to the gold standard regimen of a parenteral heparin product plus an oral VKA, although they have yet to be evaluated in head-to-head trials. In the absence of direct comparative evidence, indirect comparisons may provide information to aid in clinical decision making and therefore we aimed to conduct a systematic review and an adjusted indirect comparison meta-analysis to evaluate the efficacy and safety of NOACs for the treatment of acute VTE.

Methods

We conducted a systematic literature search in MEDLINE and Cochrane Central databases through November 2013 using the search strategy in e-Appendix A. A manual search was also performed using the references of clinical trials and review articles to identify additional

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; FDA, Food and Drug Administration; LMWH, low-molecular weight heparin; NOAC, New oral anticoagulant; PE, pulmonary embolism; RR, relative risk; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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relevant articles. In order for a study to be included in the analysis, it had to be a randomized controlled trial that evaluated patients with acute VTE treated with a NOAC and reported at least one outcome of interest. NOACs included were those with current FDA approval or with published phase III trial results. Only studies evaluating the FDA approved dosing regimen for rivaroxaban were included and only studies using the same dosing regimen evaluated in phase III trials were included for the remaining NOACs. Outcomes of interest included mortality, recurrent VTE, recurrent DVT, recurrent PE and major bleeding.

Two independent investigators separately reviewed all citations identified by the search for inclusion and abstracted data from included trials. Disagreements were resolved through discussion. The following data was collected from each trial: author identification, year of publication, funding source, report of conflicts of interest, study design characteristics, study population (inclusion and exclusion criteria, geographic location, length of study, duration of patient follow-up), patient baseline characteristics, VTE treatment regimen (name, strength, frequency, dose, route of administration, duration of therapy, time in therapeutic range for VKA arms), and outcomes data (number of events, definitions, period of follow-up, and diagnostic tests for confirmation).

To assess the methodological quality of the included trials, the Cochrane Collaboration's risk of bias tool was used [3]. This tool evaluates seven domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and any other identifiable issues. Each domain is assessed as having low, high, or unclear risk of bias and then a summary assessment of each trial across domains is made as low, high or unclear risk of bias.

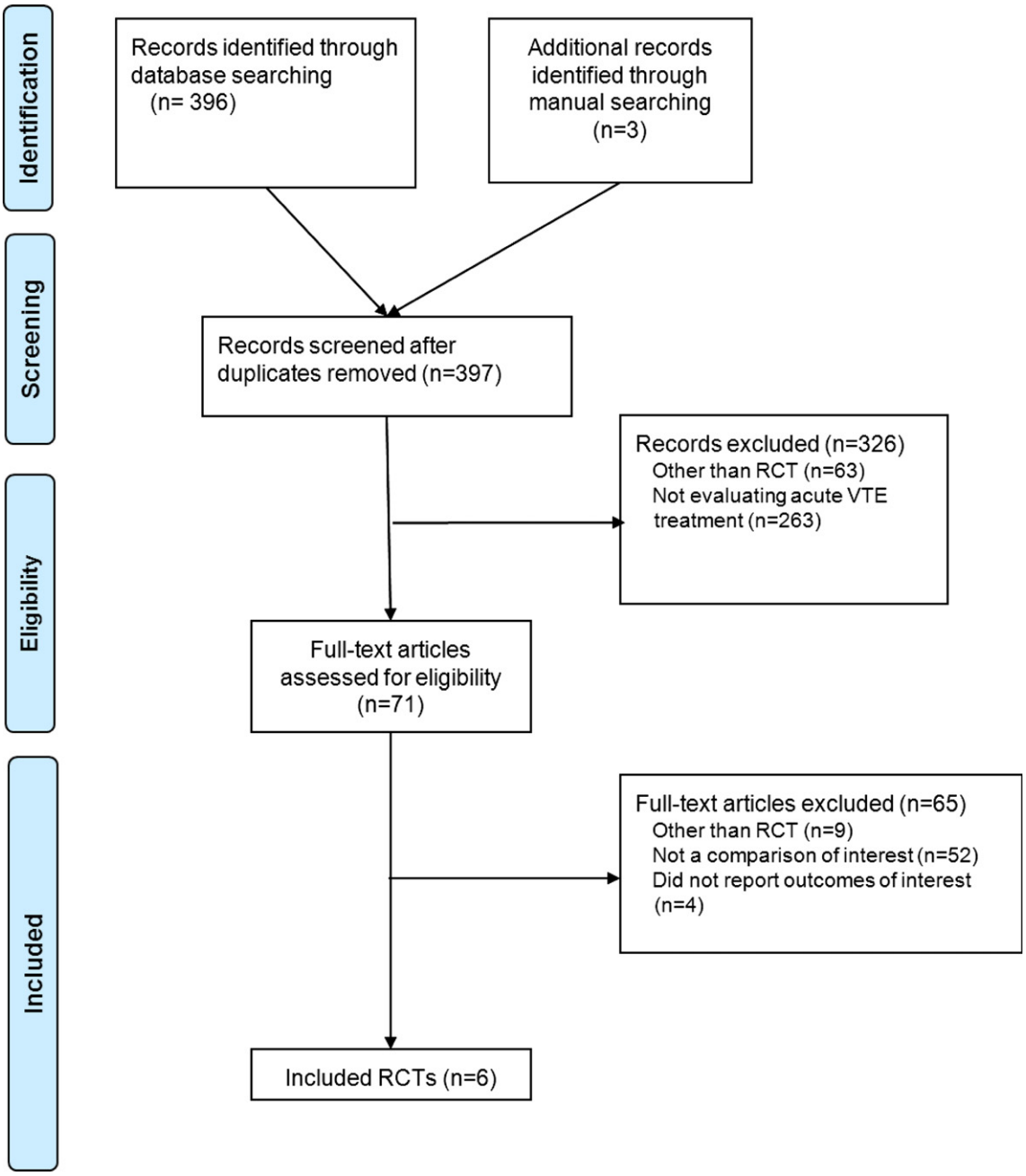

Fig. 1. Inclusion of studies. Abbreviations: RCT = randomized controlled trial; VTE = venous thromboembolism.