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Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis

Diana M. Sobieraj [a], Craig I. Coleman [a,*], Vinay Pasupuleti [b], Abhishek Deshpande [c], Roop Kaw [d], Adrian V. Hernandez [e]

[a] University of Connecticut School of Pharmacy, Department of Pharmacy Practice, 69 North Eagleville Rd Unit 3092, Storrs, CT 06269, USA
[b] Case Cardiovascular Research Institute, Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH, USA
[c] Medicine Institute Center for Value Based Care Research, Cleveland Clinic, Cleveland, OH, USA
[d] Department of Hospital Medicine & Outcomes Research, Anesthesiology, Cleveland Clinic, Cleveland, OH, USA
[e] Medical School, Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru, Health Outcomes and Clinical Epidemiology Section, Dept. of Quantitative Health Sciences, Lerner, Research Institute, Cleveland Clinic, Cleveland, OH, USA

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ABSTRACT

Objective: To systematically review the literature and to quantitatively evaluate the efficacy and safety of extended pharmacologic treatment of venous thromboembolism (VTE) through network meta-analysis (NMA).
Methods: A systematic literature search (MEDLINE, Embase, Cochrane CENTRAL, through September 2014) and searching of reference lists of included studies and relevant reviews was conducted to identify randomized controlled trials of patients who completed initial anticoagulant treatment for VTE and then randomized for the extension study; compared extension of anticoagulant treatment to placebo or active control; and reported at least one outcome of interest (VTE or a composite of major bleeding or clinically relevant non-major bleeding). A random-effects Frequentist approach to NMA was used to calculate relative risks with 95% confidence intervals.
Results: Ten trials (n = 11,079) were included. Risk of bias (assessed with the Cochrane tool) was low in most domains assessed across the included trials. Apixaban (2.5 mg and 5 mg), dabigatran, rivaroxaban, idraparinux and vitamin K antagonists (VKA) each significantly reduced the risk of VTE recurrence compared to placebo, ranging from a 73% reduction with idraparinux to 86% with VKAs. With exception of idraparinux, all active therapies significantly reduced VTE recurrence risk versus aspirin, ranging from a 73% reduction with either apixaban 2.5 mg or rivaroxaban to 80% with VKAs. Apixaban and aspirin were the only therapies that did not increase composite bleeding risk significantly compared to placebo. All active therapies except aspirin increased risk of composite bleeding by 2 to 4-fold compared to apixaban 2.5 mg, with no difference found between the two apixaban doses.
Conclusion: Extended treatment of VTE is a reasonable approach to provide continued protection from VTE recurrence although bleeding risk is variable across therapeutic options. Our results indicate that apixaban, dabigatran, rivaroxaban, idraparinux and VKAs all reduced VTE recurrence when compared to placebo. Apixaban appears to have a more favorable safety profile compared to other therapies.

Introduction

Over 1.8 adults per 1000 develop acute venous thromboembolism (VTE) annually [1]. International guidelines recommend initial parenteral anticoagulation plus an oral vitamin-K antagonist (VKA) for ≥3 months [1]. While highly effective in reducing the risk of deep-vein thrombosis (DVT) and pulmonary embolism (PE) recurrence during therapy, there is considerable risk after treatment is stopped. One and five-year VTE recurrence risk is estimated to be 1-5% and 3-15% in patients with provoked VTE and 10% and 30% in those with unprovoked VTE [1,2]. This ongoing risk raises the question as to the appropriate duration of anticoagulant therapy and whether extending treatment beyond the acute period would improve patient outcomes. Extended anticoagulant therapy also comes with risks, primarily that of bleeding that must be weighed against the possible benefits. Several randomized controlled trials (RCTs) have evaluated the practice of extended anticoagulation for the treatment of VTE. We aimed to systematically review the literature and to quantitatively evaluate the efficacy and

* Corresponding author. Tel.: +1 860 972 2096; fax: +1 860 545 2277.
E-mail addresses: Diana.sobieraj@hhchealth.org (D.M. Sobieraj), craig.coleman@hhchealth.org (C.I. Coleman), lepiscean@gmail.com (V. Pasupuleti), abhishekdp@gmail.com (A. Deshpande), kawr@ccf.org (R. Kaw), adrianhernandezdiaz@gmail.com (A.V. Hernandez).

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safety of extended pharmacologic treatment of VTE through network meta-analysis (NMA).

Methods

We conducted a systematic literature search in MEDLINE (via Ovid), Embase and Cochrane Central databases from the earliest possible search date through September 2014. The search strategy for MEDLINE is presented in Appendix A and a similar strategy was used for the other databases. A manual search was also performed using the references of clinical trials and review articles to identify additional relevant articles. Results of identified studies were supplemented when possible by contacting investigators for clarification or additional data. For a study to be included in the analysis, it had to: 1) be an RCT evaluating patients who completed initial anticoagulant treatment for either a DVT, PE or both prior to randomization for the extension study; 2) compare extension of VTE treatment with an anticoagulant or antiplatelet to placebo or active control; and 3) report at least one outcome of interest [e.g., recurrent VTE (DVT and/or PE) or the composite of major bleeding or clinically relevant non-major bleeding (CRNMB)]. We also evaluated the individual components of these composite outcomes separately (DVT, nonfatal PE, fatal PE, major bleeding, CRNMB and all-cause mortality).

Two independent investigators separately reviewed all citations identified by the search for inclusion (title and abstract stage, full text stage) and abstracted data from included trials. Disagreements were resolved through discussion. The following data were 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 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 biases. Each individual domain is assessed as having low, high, or unclear risk of bias using the guidance provided by the tool. The risk of bias was evaluated for each trial by two separate investigators and conflicts were resolved through discussion.

We first ran traditional pairwise meta-analysis on the primary outcomes of interest, when more than one trial comparing the same interventions was available. A random-effects model was used to calculate relative risks (RR) and pool baseline event rates, each with corresponding 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant for all analyses. Statistical heterogeneity was addressed using the I^2 statistic, with values of 25%, 50% and 75% representing cut-off values for low, moderate and high likelihood

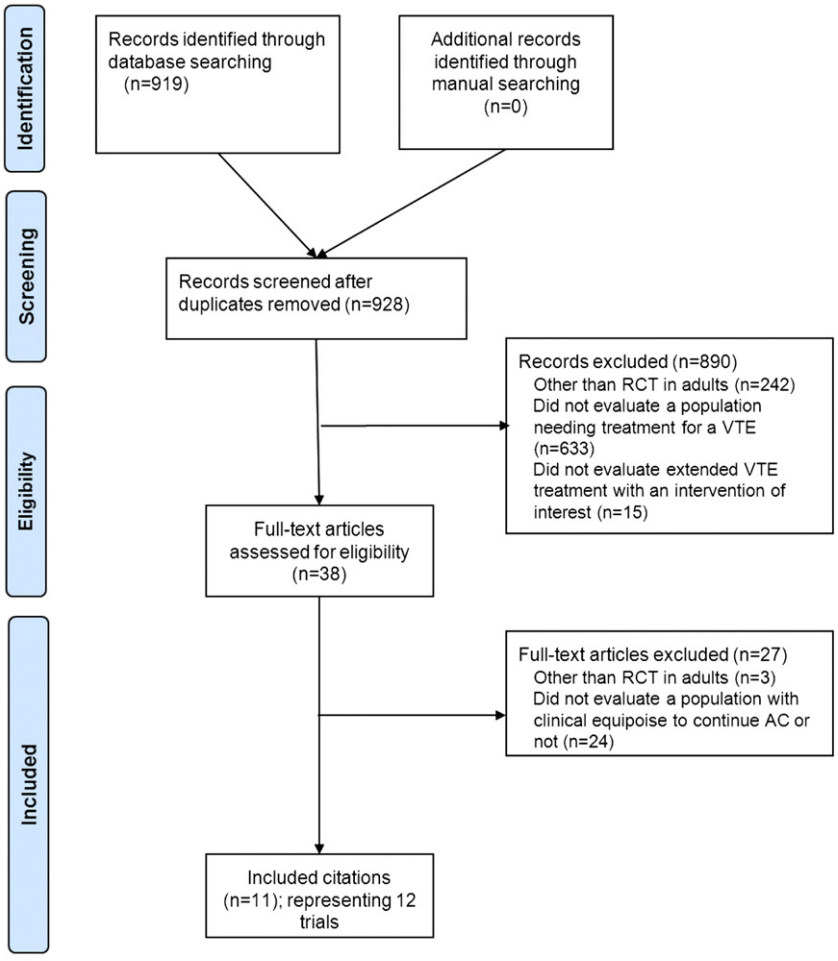

Fig. 1. Flow diagram of selected randomized controlled trials.