INPLASY

Reduced- compared with standard-dose direct oral anticoagulant in extended venous thromboembolism treatment: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - Population Health Research Institute, McMaster University, Hamilton, ON, Canada.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - Stephanie Carlin has received honoraria and/or advisory board fees from Pfizer and Servier. Raymond Siu Ming Wong has received grants and/or honoraria from Appellis, Astellas, Astra Zeneca, Bayer, BI, BMS, Daiichi-Sankyo, Gilead, GSK, Janssen, Novartis, Pfizer, Regeneron and Roche. John Eikelboom has received grants and/or honoraria from Anthos, Bayer, BI, BMS, Daiichi-Sankyo, Ionis, Janssen, Merck, Pfizer, and USV.
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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 May 2025 and was last updated on 21 May 2025.

INTRODUCTION

Review question / Objective To determine in patients with a history of VTE the efficacy and safety of reduced-dose compared to standard-dose direct oral anticoagulants for extended treatment, overall and in key subgroups.

Rationale Patients with a first episode of unprovoked VTE face a recurrence risk of up to 10% in the first year after anticoagulation cessation, increasing to 36% over 10 years. While anticoagulation therapy effectively reduces the risk of thrombosis recurrence, this benefit diminishes or is lost upon treatment discontinuation. Extended-duration anticoagulation provides substantial protection, with previous studies demonstrating an 80% reduction in VTE recurrence rate. However, the bleeding risk associated with prolonged anticoagulation presents a major therapeutic challenge, as the threat of major or fatal bleeding persists throughout treatment and may increase with time as patients accrue additional risk factors. Recent clinical trials have investigated the extended use of reduced-dose direct oral anticoagulant (DOAC) regimes in patients with unprovoked VTE to mitigate bleeding risk while maintaining an acceptable therapeutic efficacy, subsequently expanding this paradigm to higher-risk patients, such as those with multiple episodes of VTE, or active cancer.

Condition being studied Recurrent venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a frequent condition associated with morbidity and mortality.

METHODS

Search strategy Outline: ("deep vein thrombosis" OR "pulmonary embolism" OR "venous thromboembolism") AND ("direct oral anticoagulant" OR "non vitamin K oral anticoagulant" OR "DOAC" OR "NOAC" OR "apixaban" OR "dabigatran" OR "edoxaban" OR "rivaroxaban").

Participant or population Patients with VTE requiring extended anticoagulation who have completed at least 3-6 months of standard-dose anticoagulant therapy.

Intervention Reduced-dose direct oral anticoagulants.

Comparator Standard-dose direct oral anticoagulants.

Study designs to be included Randomized controlled trials.

Eligibility criteria
– Randomized controlled trials that investigate reduced-dose versus standard-dose DOAC
– Patients with VTE requiring extended anticoagulation who have completed at least 3-6 months of standard-dose anticoagulant therapy
– Age ≥ 18 years old
– Exclusion: conference abstracts, letters to the editor, reviews.

Information sources MEDLINE, EMBASE, CENTRAL.

Main outcome(s) Recurrent venous thromboembolism, major bleeding, clinically relevant non-major bleeding, mortality.

Quality assessment / Risk of bias analysis Risk of bias will be assessed by two reviewers independently using the RoB 2 Tool. In meta-analyses with at least 10 studies, we will perform funnel plots (visual inspection and Egger's test).

Strategy of data synthesis A meta-analysis will be conducted if at least two eligible studies are identified for the outcomes of interest. Outcome data will be assessed as pooled risk ratios using random-effects model and the Mantel-Haenszel method and the corresponding 95% confidence interval. Heterogeneity will be assessed using the Cochran's Q statistic and quantified by the I^2 statistic, and visual inspection of the forest plot. All analyses will be performed using RevMan 5.4 (Cochrane Collaboration), R Studio, and Comprehensive Meta-analysis Software.

Subgroup analysis Subgroups analysis will be performed on published data where available.
Prespecified subgroups include: sex (male vs. female), age (<75 years vs. ≥ 75 years), initial presentation of VTE event (PE with or without DVT vs. DVT alone), history of recurrent VTE (yes vs. no), body mass index (BMI) (<30kg/m2 vs. ≥30kg/m2), known thrombophilia (yes vs. no), creatinine clearance (<50ml/min vs. 50-<80ml/min vs. ≥80ml/min), and malignancy (yes vs. no).

Sensitivity analysis A sensitivity analysis will be undertaken with the fixed effects model in lieu of the random effects model.

Country(ies) involved Canada (McMaster University, Population Health Research Institute).

Keywords venous thromboembolism; bleeding; direct oral anticoagulant; extended treatment; secondary prevention.

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