INPLASY

Non-vitamin K oral anticoagulants versus warfarin in patients with triple positive antiphospholipid syndrome – protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2023100054

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 October 2023 and was last updated on 16 October 2023.

Dr. Mislav Radić, dr. Hana Đogaš and dr. Tina Bečić contributed equally to this study.

INTRODUCTION

Review question / Objective The aim of this systematic review is to summerize current evidence comparing effects and clinical outcomes in patients with triple positive antiphospholipid syndrome who take direct oral anticoagulants versus warfarin. To this end, the proposed systematic review will give information about clinical outcomes of patients with triple positive antiphospholipid syndrome who take direct oral anticoagulants versus warfarin and also an answer on question do the thrombotic adverse events depend on the dose of DOACs.

Rationale Patients with triple positivity antiphospholipid syndrome appear to have a worse prognosis due to their high risk for recurrent thrombosis and pregnancy complications. Vitamin K antagonists (VKAs) have been recommended as the gold standard agents for the treatment and prevention of recurrent TE events in APS. Direct oral anticoagulants (DOACs) emerged over the last decade as a practicable alternative to VKAs and have been widely used to treat and prevent several TE conditions. Several clinical studies have previously evaluated the use of DOACs, predominantly rivaroxaban, in patients with APS, but the data on their safety and efficacy are conflicting. The results revealed an increased number of recurrent thrombotic events in the DOACs arm compared to warfarin.
Research of clinical outcomes and optimal dosing of DOACs on triple positive patients who develop adverse events are often contradictory and lacking. Determing doses of DOACs to prevent adverse outcomes will be of highest value in clinical approach and treatment of these patients.

Condition being studied Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by at least one thromboembolic (TE) event (venous, arterial, or small vessel) and/or pregnancy morbidity (one or more unexplained fetal deaths, one or more premature births, and three or more unexplained consecutive spontaneous abortions) in the presence of at least one persistent (12 weeks) antiphospholipid antibody (aPL): lupus anticoagulant (LA), IgG or IgM anticardiolipin antibodies (aCL), IgG or IgM anti-β2-glycoprotein antibodies (anti- β2GPI). Patients with triple positivity antiphospholipid syndrome appear to have a worse prognosis due to their high risk for recurrent thrombosis and pregnancy complications. The estimated incidence of APS is approximately five per 100,000 persons per year, with a prevalence of around 40-50 cases per 100,000 persons, and is seen more commonly in women (1:3.5, male-female ratio) between 15-50 years of age. Catastrophic APS, the most severe form of APS, which accounts for approximately 1% of all APS cases, is associated with an overall mortality rate of 37%. Using direct oral anticoagulants in antiphospholipid syndrome, especially DOACs in triple positive patients, remains controversial and could affect on patient qualty of life and survival.

METHODS

Search strategy PubMed: ("antiphospholipid syndrome" OR "antiphospholipid antibody" OR "antiphospholipid positivity" OR APS) AND (NOAC OR dabigatran OR apixaban OR rivaroxaban OR edoxaban OR "non-vitamin K oral anticoagulants") AND (warfarin); no filter used; Web of Science: ("antiphospholipid syndrome" OR "antiphospholipid antibody" OR "antiphospholipid positivity" OR APS) AND (NOAC OR dabigatran OR apixaban OR rivaroxaban OR edoxaban OR "non-vitamin K oral anticoagulants") AND (warfarin); Review Article, Case Report, Abstract, Meeting, Letter, Editorial Material, Reference Material, Biography, Book and Dissertation Thesis filters were used to exclude additional results; Scopus: ("antiphospholipid syndrome" OR "antiphospholipid antibody" OR "antiphospholipid positivity" OR APS) AND (NOAC OR dabigatran OR apixaban OR rivaroxaban OR edoxaban OR "non-vitamin K oral anticoagulants") AND (warfarin); Review, Letter, Note, Editorial, Conference paper, Short survey and Book chapter filters were used to exclude additional results: Cochrane library: ("antiphospholipid syndrome" OR "antiphospholipid antibody" OR "antiphospholipid positivity" OR APS) AND (NOAC OR dabigatran OR apixaban OR rivaroxaban OR edoxaban OR "non-vitamin K oral anticoagulants") AND (warfarin); no filters were used.

Participant or population Patients older than 18 years (men and women) with triple positive antiphospholipid syndrome treated with anticoagulant therapy (NOACs and warfarin) will be included in this review, with no exclusions based on ethnicity or race.

Intervention Comparison Non-vitamin K oral anticoagulants versus warfarin.

Comparator Comparison Non-vitamin K oral anticoagulants versus warfarin in patients with triple positive antiphospholipid syndrome.

Study designs to be included Clinical trials and randomized controlled trials are included in the study.

Eligibility criteria Studies including patients (men and women) older than 18 years with triple positive antiphospholipid syndrome who take NOACs compared with warfarin and their adverse throbmoembolic outcomes, studies available in English and studies with available data needed for analysis.

Information sources Electronic database (MEDLINE, EMBASE, Citation Indeks, Current Contents,SciELO Citation Indeks, Web of Science Core collection, , Connect, Derwnt Innovations Indeks Science Citation Indeks, Emerging Sources Citation Indeks, BIOSIS) and hand search of reference lists of highly relevant articles in this topic.

Main outcome(s) Comparison of adverse outcomes between patients on NOAC and warfarin.

Additional outcome(s) Comparison of adverse outcomes between patients on dabigatran, edoxaban, rivaroxaban and apixaban.

Data management The authors (T.B. and H.Đ.) conducted an independent literature search based on the PICO components. The reviewers T.B. and H.Đ. performed the assessment of studies in searched databases indenpendently and, to reach the final number of included patients and studies, differences were resolved by discussion and consensus among all researches.

Quality assessment / Risk of bias analysis In the assessing the risk of bias and the quality of

included studies the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) is used.
It is the recommended tool to assess the risk of bias in randomized trials included in Cochrane Reviews. RoB 2 is structured into a fixed set of domains of bias, focussing on different aspects of trial design, conduct, and reporting. Within each domain, a series of questions ('signalling questions') aim to elicit information about features of the trial that are relevant to risk of bias. A proposed judgement about the risk of bias arising from each domain is generated by an algorithm, based on answers to the signalling questions. Judgement can be 'Low' or 'High' risk of bias or can express 'Some concerns'. The reviewers H.Đ. and T.B. conducted the assessment independently and to reach the final assessment difference were resolved by discussion and consensus among all researchers.

Strategy of data synthesis To evaluate clinical outcomes in patients with triple positive antiphospholipid syndrome who take DOACs a random – effects meta analysis model is applied with inverse variance weighting and mean difference with a 95% confidence interval is obtained. Mean differences are considered significant if the P – value < 0.05 in the test for overall effect. Heterogeneity between studies is evaluated using the I2 index and significant heterogeneity between the studies is considered if the test for heterogeneity was significant (P value < 0.05).

Subgroup analysis Comparison of adverse outcomes between patients with triple positive antiphospholipid syndrome on dabigatran, edoxaban, rivaroxaban and apixaban regardless of their part of the group with single or double positivity.

Sensitivity analysis The studies are not excluded regarding the quality assessment. Sensitivity analysis will not be conducted due to applicability.

Language restriction Only clinical trials or randomized controlled trials published in English will be considered for inclusion.

Country(ies) involved This study is being carried out in University Hospital of Split, Split, Croatia.

Other relevant information Dr. Mislav Radić, dr. Hana Đogaš and dr. Tina Bečić contributed equally to this study.

Keywords Antiphospholipid syndrome; antiphospholipid antibody; antiphospholipid positivity; APS; dabigatran; apixaban; rivaroxaban; edoxaban; non-vitamin K oral anticoagulants; warfarin.

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