INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Comparative efficacy and safety of reduced dose of DOACs in patients with atrial fibrillation

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Review question / Objective: **To compare the risk of stroke/systemic embolism (S/SE), mortality and bleeding in AF patients with reduced-dose DOACs.**
Rationale: **Although each DOAC has its dose reduction criteria, many physicians still prefer to prescribe the reduced-dose DOACs, regardless of label adherence. However, inappropriate administration of DOACs is an important clinical problem because patients may not benefit from the recommended DOAC dose to prevent stroke and systemic embolism. Therefore, this study aims to investigate the risk of stroke/systemic embolism (S/SE) and mortality in AF patients with reduced-dose DOACs.**
Condition being studied: **Adult patients with AF taking DOACs or Warfarin.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 August 2022 and was last updated on 18 August 2022 (registration number INPLASY202280073).

INTRODUCTION

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METHODS

Search strategy: P: Atrial fibrillation (AF) or non-valvular atrial fibrillation I: Apixaban OR Dabigatran OR Rivaroxaban OR Edoxaban C: Warfarin O: stroke OR cerebral infarction OR TIA OR ischemic heart disease OR myocardial infarction OR acute coronary syndrome OR thrombo-embolism event OR mortality.

Participant or population: Patients with AF.

Intervention: Apixaban, Edoxaban, Dabigatran, Rivaroxaban.

Comparator: Warfarin & each other.

Study designs to be included: No restriction of study designs. Meta-analysis including only original articles.

Eligibility criteria: No restrictions on the starting point of the publication date, or the type of literature.

Information sources: We will search the database for Pubmed, Embase, and Cochrane central until Aug, 2022.

Main outcome(s): Systemic embolism and Stroke; Mortality: cardiovascular mortality, all-cause mortality.

Additional outcome(s): Major bleeding.

Data management: The selection of studies will be performed in two phases: reading of title and abstracts, and reading of full-texts. Two independent researchers will screen and find the relevant studies. Studies will be excluded if there is inaccessibility of full-text. In the case of disagreement between two researchers, a third researcher will be involved to meet the consensus. Literature selection and coding will be carried out using Endnote and Excel. The extracted data will be arranged in a spreadsheet in Excel software.

Quality assessment / Risk of bias analysis: RCT: Risk of bias (RoB); Cohort: Risk of bias by non-randomized studies (RoBANS), NOS.

Strategy of data synthesis: The systematic review and meta-analysis will be performed according the PRISMA 2020 guidelines. The effect sizes will be analyzed and expressed as Hazard ratio (HR) with 95% CI for each study. The comparative study of each DOAC dose with warfarin will be performed through a direct pairwise meta-analysis. The heterogeneity between the included studies will be analyzed with Higgin's I2 statistics and Q statistics using Review Manager 5.4. Additionally, bayesian network model based on the Markov chain Monte Carlo operation will be used for analyzing the therapeutic effects of drugs in multiple groups. Network meta-analysis will be performed using the GeMTC package (1.0-1 version) and Rjags package (4-10 version) of R software (4.1.0 version).

Subgroup analysis: As needed, we will try to perform subgroup analyses in the following subgroups. - Study design - each drug - age.

Sensitivity analysis: We will perform sensitivity analyses for the main outcomes by excluding randomized trials that are judged to be at an overall high risk of bias and non-randomized studies that are judged to be at an overall serious risk of bias.

Language restriction: Only English.

Country(ies) involved: South Korea.

Keywords: DOACs; Warfarin; reduced dose; embolism; stroke; mortality.

Contributions of each author:

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