INPLASY PROTOCOL

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None declared.

An updated systematic review and meta-analysis of off-label under- and over-dosed direct oral anticoagulants in patients with atrial fibrillation

Shen, NN[1]; Gu, ZC[2]; Amidei, CB[3].

Review question / Objective: **To investigate the prevalence, effectiveness, safety, and cost of off-label dosing of direct oral anticoagulants (DOACs) for atrial fibrillation patients in real-world setting. This study will answer the following questions: 1) the prevalent rate of off-label dosing of DOACs in real world pratice ; 2) the effectiveness and safety of DOACs off-label dose versus DOACs on-label dose or versus warfarin; 3) cost-effectiveness of DOACs offlabel dose versus DOACs on-label dose or versus warfarin.**
Condition being studied: **Millions of patients worldwide are treated with direct oral anticoagulants (DOACs: dabigatran, rivaroxaban, apixaban, and edoxaban et al.) primarily for the prevention of stroke in atrial fibrillation (AF). Currently, offlabel dosing of DOAC is common in real-world practice, but its prevalence, effectiveness, safety, as well as cost performance remain unclear.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 September 2022 and was last updated on 16 September 2022 (registration number INPLASY202290073).

INTRODUCTION

Review question / Objective: **To investigate the prevalence, effectiveness, safety, and cost of off-label dosing of direct oral anticoagulants (DOACs) for atrial fibrillation patients in real-world setting. This study will answer the following questions: 1) the prevalent rate of off-label dosing of DOACs in real world pratice ; 2) the effectiveness and safety of DOACs off-label dose versus DOACs on-label dose or versus warfarin; 3) cost-effectiveness of DOACs offlabel dose versus DOACs on-label dose or versus warfarin.**

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METHODS

Participant or population: Atrial fibrillation patients receving direct oral anticoagulants (DOACs: dabigatran, rivaroxaban, apixaban, andedoxaban et al.) or warfarin.

Intervention: Atrial fibrillation patients receving off-label dosage of direct oral anticoagulants (underdose or overdose).

Comparator: Atrial fibrillation patients receving on-label dosage of direct oral anticoagulants or warfarin.

Study designs to be included: Inclusion: Real-world studies will be included if they meet the following criterion: 1) included patients withatrial fibrillation and reported prevalent rate of off-label dosing of DOACs: or 2) included atrial fibrillationpatients that compared DOACs off-label dose with DOACs on-label dose or warfarin, and reported benefitand harm outcomes. For the highest quality real-world studies, only nationwide or health insurance databasestudies or multi-center studies or large sample studies (1000 subjects).

Eligibility criteria: The conference abstract and letter will be excluded.

Information sources: MEDLINE, Embase, and Cochrane Library databases were systematically searched to identify potential studies.

Main outcome(s): The effective outcomes is stroke or systemic embolism (SE), and the safety outcomes are major bleeding, intracranial haemorrhage (ICH), gastrointestinal bleeding (GIB), myocardial infarction (MI) and all-cause mortality.

Quality assessment / Risk of bias analysis: The methodological quality of the included real-world studies will be evaluated using the Newcastle–Ottawa Scale (NOS) criteria. The NOS criteria is based on three aspects: 1) subject selection: 0–4 scores; 2) comparability of subject: 0–2 scores; 3) clinical outcome: 0–3 scores. NOS scores range from 0 to 9 with scores ?7 indicating good quality. Potential publication bias will also be evaluated by visually inspecting funnel plots, as well as using Egger's and Begg's tests.

Strategy of data synthesis: A random-effects meta-analysis will be used to calculate the overall pooled prevalence of DOACs off-label dose as well as to synthesize the effectiveness and safety data of real-world studies. Heterogeneity will be evaluated using the I^2 test. A meta-regression analysis will be performed to detect the risk factors associated with DOACs off-label dose. Sensitivity analyses will be carried out to identify the effects of a single trial by the sequential elimination of each trial from the pool. All statistical analyses will be performed using Stata software.

Subgroup analysis: Subgroup analyses on prevalence of DOACs off-label dose and on clinical outcomes will be respectively conducted according to off-label types (underdose or overdose), individual agents (dabigatran, rivaroxaban, apixaban, and edoxaban), countries or regions (USA, UK, China, et al.), and study period. P for the interaction among individual agents will also be determined.

Sensitivity analysis: Analyses were repeated by sequentially removing each study, and the pooled results were consistent with the results of the main analyses.

Country(ies) involved: Department of Pharmacy, Affiliated Hospital of Shaoxing University, Shao Xing, Zhejiang Province, China.

Keywords: atrial fibrillation; direct oral anticoagulants; off-label; stroke; bleeding.

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