INPLASY PROTOCOL

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No competing interests.

The association of fracture risk in atrial fibrillation patients and chronic anticoagulant therapy category: A systematic review and meta-analysis

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Review question / Objective: **Our study is aim to evaluate the risk of all fracture and hip fracture in atrial fibrillation (AF) patients taken non-vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin. P: patients with atrial fibrillation; I: oral anticoagulants; C: non-vitamin K antagonist oral anticoagulants (NOACs) vs warfarin; O: all fracture, hip fracture.**
Condition being studied: **Long-term warfarin therapy in atrial fibrillation patients has been reported to increase relatively risk of fracture. Recently, several real-world studies demonstrated that non-vitamin K antagonist oral anticoagulants (NOACs) were associated with lower fracture risk when compared with warfarin in atrial fibrillation patients. The results remained controversial.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 April 2020 and was last updated on 21 April 2020 (registration number INPLASY202040126).

INTRODUCTION

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were associated with lower fracture risk when compared with warfarin in atrial fibrillation patients. The results remained controversial.

METHODS

Search strategy: PubMed:#1: (anticoagulant[MeSH Terms]) OR (direct oral anticoagulant[Title/Abstract]) OR (non-vitamin K antagonist oral anticoagulants[Title/Abstract]) OR (vitamin K antagonist oral anticoagulants[Title/Abstract]) #2:(rivaroxaban[Title/Abstract])OR(apixaban[Title/Abstract])OR(dabigatran[Title/Abstract])OR(edoxaban[Title/Abstract]) OR warfarin[Title/Abstract] #3:(fracture[MeSH Terms]) OR(hip fracture) OR (osteoporosis[MeSH Terms]) OR (rarefaction of bone) OR (osteoporotic fracture) #4: #1 OR #2 #5 #3 AND #4. Embase: #1: 'anticoagulant'/exp OR 'direct oral anticoagulant':ti, ab, kw OR 'non-vitamin k antagonist oral anticoagulants':ti, ab, kw 'vitamin K antagonist oral anticoagulants':ti, ab, kw #2: rivaroxaban:ti, ab, kw OR apixaban:ti, ab, kw OR dabigatran:ti, ab, kw OR edoxaban:ti, ab, kw OR warfarin:ti, ab, kw #3: 'fracture'/exp OR 'hip fracture':ti, ab, kw OR osteoporosis:ti, ab, kw OR 'rarefaction of bone':ti, ab, kw OR 'osteoporotic fracture':ti, ab, kw #4: 'atrial fibrillation'/exp #5:#1 OR #2 / #6: #3 AND #4 AND #5 Cochrane Library: #1: MeSH descriptor: [Anticoagulants] explode all trees #2: (direct oral anticoagulant):ti, ab, kw OR (non-vitamin K antagonist oral anticoagulants):ti, ab, kw OR (vitamin K antagonist oral anticoagulants):ti, ab, kw #3:(rivaroxaban):ti, ab, kw OR (apixaban):ti, ab, kw OR (dabigatran):ti, ab, kw OR (edoxaban):ti, ab, kw OR ("Warfarin"):ti, ab, kw #4: (fractures):ti, ab, kw OR ("osteoporosis"):ti, ab, kw OR (rarefaction of bone):ti, ab, kw OR (osteoporotic fractures):ti, ab, kw #5: #1 OR #2 OR #3 #6: #4 AND #5 ClinicalTrials.gov: Condition or disease: atrial fibrillation Other terms: anticoagulant.

Participant or population: Inclusion criteria: diagnosed atrial fibrillation with the age more than 18 years old and taken oral anticoagulants (non-vitamin K antagonist oral anticoagulants or warfarin) due to atrial fibrillation more than 12 months.

Intervention: Taken oral anticoagulants (non-vitamin K antagonist oral anticoagulants or warfarin) due to atrial fibrillation more than 12 months.

Comparator: Patients with atrial fibrillation received warfarin treatment.

Study designs to be included: All studies identified as potentially relevant on the basis of title or abstract will be selected for full review with no pre-specified restrictions.

Eligibility criteria: Inclusion criteria: diagnosed atrial fibrillation with the age more than 18 years old and taken oral anticoagulants (non-vitamin K antagonist oral anticoagulants or warfarin) due to atrial fibrillation more than 12 months. exclusion criteria: long-term oral anticoagulants therapy for other reasons, age less than 18 years old.

Information sources: We search PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrial.gov for studies using the terms. Search keywords were “atrial fibrillation,” “anticoagulant,” “direct oral anticoagulant,” “non-vitamin K antagonist oral anticoagulants,” “vitamin K antagonist oral anticoagulants,” “ warfarin,” “dabigatran,” “rivaroxaban” “apixaban,” “edoxaban,” “fracture,” “osteoporosis,” “osteoporotic fractures,” “rarefaction of bone,”. A thorough search through the bibliography of each published trial, meta-analysis and review will be also performed, including also studies presented or published in other languages.

Main outcome(s): All fracture, hip fracture or other fracture.

Additional outcome(s): None.

Quality assessment / Risk of bias analysis: Cochrane Collaboration’s tool was used to

assess the risk of bias of randomized controlled trials (RCTs). The assessment included random sequence generation, blinding of patients and study personnel, allocation concealment, blinding of outcome assessment, selective reporting of outcomes, completeness of outcome data, and other threats to validity. The Newcastle–Ottawa quality assessment scale (NOS) are used to evaluate the quality of real-world studies. Score of 7 or more were considered high quality studies.

Strategy of data synthesis: Baseline characteristics of continuous variables and categorical variables were documented by mean (standard deviation [SD]) and percentages. The RR and 95% confidence intervals (CI) were pooled for dichotomous data. Heterogeneity of the meta-analysis was tested with Q statistics and the extent of inconsistency among results with I2 statistics (significant heterogeneity was considered a P values 50%). The effect size conduction of hazard ratio (HR) or risk ratio (RR) were merged by random-effect models.

Subgroup analysis: Subgroup analysis was analyzed each NOACs all fracture and hip fracture risk compared with warfarin.

Sensibility analysis: Sensitivity analysis assessed the impact of each research on the pooled results by sequentially deleting each study.

Country(ies) involved: China.

Keywords: Atrial fibrillation, non-vitamin K antagonist oral anticoagulants, warfarin, fracture, meta -analysis.

Contributions of each author:
Author 1 - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy, collected the data, drafted the manuscript.
Author 2 - The author revised the paper.
Author 3 - The author provided statistical expertise.
Author 4 - The author read, provided feedback and approved the final manuscript.
Author 5 - The author conceived and designed research.
Author 6 - The author collected data and analyzed data.