Thrombosis Research 135 (2015) 1117–1123

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Safety of the direct-acting anticoagulants in patients with atrial fibrillation: a meta-analysis

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ARTICLE INFO

Article history:
Received 14 October 2014
Received in revised form 1 April 2015
Accepted 6 April 2015
Available online 11 April 2015

Keywords:
DOACs
Warfarin
Safety
Meta-analysis

ABSTRACT

Introduction: Atrial fibrillation (AF) is known as one of the independent risk factors for stroke and might significantly increase its risk. Nowadays, direct-acting oral anticoagulants (DOACs) have been developed and demonstrated a more promising option to warfarin, the conclusion for safety is heterogeneous in different studies. It indicates the importance of comprehensive comparison of safety between DOACs and warfarin.
Material and Methods: Four studies including ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY and ROCKET-AF were included in the meta-analysis to perform separate meta-analyses for high-dose regimen, low-dose regimen and their combination. The events included major bleeding, intracranial haemorrhage, gastrointestinal bleeding, non-major clinically relevant and minor bleeding.
Results: Regardless of high dose or low dose regimen, DOACs were associated with lower risk of intracranial haemorrhage but due to no significant association for gastrointestinal bleeding, the overall effect measured by the major bleeding was also insignificant (High dose: RR = 0.86, 95% CI 0.73 to 1.01; Low dose: RR = 0.63, 95% CI 0.38 to 1.04). However, the combined result of high-dose and low-dose regimens showed DOACs were associated with lower risk of major bleeding events (RR = 0.77, 95% CI 0.63 to 0.95).
Conclusions: Meta-analyses have showed the comparative safety of the direct-acting oral anticoagulants than warfarin in most endpoints and even better in intracranial haemorrhage. Therefore, without the need of INR monitoring, DOACs demonstrated promising alternatives to warfarin in prevention of stroke in patients with AF.

Introduction

Atrial fibrillation (AF) is a common arrhythmia and there are about 8 million patients with AF in China, 2.2 million in US and 4.5 million in Europe Union [1,2]. AF is known as one of the independent risk factors for stroke and might significantly increase its risk. The strokes caused by AF are at higher risk of morbidity and mortality than non-AF strokes [3,4]. Clinicians used to prescribe vitamin K antagonist (most commonly warfarin) for the patients with AF. With the proven efficacy, Warfarin is always a preferred option to prevent stroke or systemic embolism events [5,6]. But its use is limited by some drawbacks including the narrow therapeutic window requiring frequent international normalized ratio (INR) monitoring and a high risk of bleeding [7,8].

In recent decades, through inhibiting either activated factor X (factor Xa) or thrombin, some direct-acting oral anticoagulants (DOACs) have been developed and demonstrated a more promising option [9,10]. There are 4 large phase III randomized controlled trials (RCTs): Dabigatran Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), and Edoxaban once daily to prevent stroke or systemic embolism (ENGAGE AF-TIMI 48) [11]. They have separately examined the long-term effect of DOACs compared with warfarin to prevent stroke and systemic embolism in patients with AF. Although more efficacious than warfarin for the primary efficacy endpoint of stroke and systemic embolism for DOACs, the conclusion for the secondary efficacy endpoints as well as safety endpoints are heterogeneous in different studies [12,13]. It indicates the importance of comprehensive comparison of safety and efficacy between DOACs and warfarin in the patients with AF [14,15].

Abbreviations: AF, atrial fibrillation; INR, international normalized ratio; factor Xa, activated factor X; DOACs, direct-acting oral anticoagulants; RCTs, randomized controlled trials; RE-LY, Dabigatran Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF-TIMI 48, Edoxaban once daily to prevent stroke or systemic embolism; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke doubled; RR, relative risk; CI, confidence interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; GCP, Good Clinical Practice.

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http://dx.doi.org/10.1016/j.thromres.2015.04.004
0049-3848/

Currently, there are some published meta-analyses for DOACs [16, 17], and they included five phase III studies: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48, and J-ROCKET AF [18]. In this paper, different from previous analyses, we performed separate meta-analyses: one is for the high dose groups of RE-LY (150 mg twice daily) and ENGAGE AF-TIMI 48 (60 mg twice daily) combined with the single dose studies ARISTOTLE, and ROCKET AF and the other is for low dose groups of RE-LY (110 mg twice daily) and ENGAGE AF-TIMI 48 (30 mg twice daily) respectively. This will separate the benefit and risk of different doses.

Considering the INR target level of 1.6-2.6 was reduced from the regular therapeutic range 2.0-3.0 in J-ROCKET AF [19], it was not included in our analysis to avoid potential bias.

Materials and Methods

Data Sources and Search Strategy

From the Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest, we systematically searched the publications of RCTs comparing DOACs to warfarin in patients with AF in July 2014. The keywords or medical terms included "new oral anticoagulants", "oral thrombin inhibitors", "oral factor Xa inhibitors", "dabigatran", "rivaroxaban", "apixaban", "edoxaban", "betrixaban", "ym-150", "ly-517717", "warfarin", "ENGAGE AF-TIMI 48", and "RE-LY". The clinical trials were searched from the Embase and MEDLINE. The Science Citation Index Expanded and ProQuest searches were limited to the reports with full-text available. In addition, we manually searched the clinical databases including the website of ClinicalTrials, related review and reports for further any eligible studies. Two team members selected the studies independently and the disagreements were resolved by discussion among all the authors.

Study Selection

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to report systematic reviews and meta-analyses of RCTs for this analysis [20]. The criteria for studies screening were as following: (1) they were randomized controlled trials between DOACs and warfarin; (2) all the patients were randomized to warfarin or DOACs; (3) the target population was the patients with AF. Besides, the open-label studies were also included in the search since the frequent INR monitoring for warfarin was needed; (4) ongoing trials will be also considered.

Data Extraction and Quality Assessment

The data extracted from these studies included patients' age, median follow-up time, mean scores of Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke doubled ($CHADS_2$) [21], gender, mean time in the therapeutic range of warfarin, and some specific medical history. For all the included studies, the principal safety endpoint was major bleeding defined as fatal bleeding or bleeding in a critical site and the secondary endpoint included gastrointestinal and intracranial bleeding. The primary efficacy endpoint was composite of stroke and systemic embolism. The secondary efficacy endpoints included ischemic stroke, hemorrhagic stroke, all-cause mortality, and myocardial infraction. We only considered the studies approved or ongoing so the trials for ximelagatran which had been withdrawn [22], and studies for darexaban which was no longer in development [23] were excluded from our analysis.

We used the Cochrane Collaboration's tool to conduct quality assessment to the risk of bias in a RCT within the following domains: blinding of participants, personal, and outcome assessors; allocation concealment; sequence generation; incomplete outcome data; selective outcome reporting; and other potential threats to validity. In each domain, the risk of bias was classified into high, low or unclear for each RCT [24].

Statistical Analysis

We used the DerSimonian and Laird random-effects model [25] to calculate the pooled relative risk (RR) and their corresponding 95% confidence interval (CI). The presence of between-study variability was assessed by the Cochran's Q statistic ($P < 0.10$ was used as indicator of statistically significant result), and the proportion of heterogeneity by the I^2 index ($I^2 > 25\%$ was used to indicate statistically significant result). All the analyses were conducted in statistical software Stata 11.0 (StataCorp LP, College Station, Texas).

The safety events included major bleeding, intracranial haemorrhage, and gastrointestinal bleeding. These bleeding endpoints analyses were based on safety population. In RE-LY and ENGAGE AF-TIMI 48, there were two DOACs doses regimens compared with warfarin respectively. Instead of combing both doses to one group in the meta-analysis, which might merge the benefit and risk of different doses, the high dose groups of RE-LY (150 mg twice daily) and ENGAGE AF-TIMI 48 (60 mg twice daily) were combined with the single dose studies ARISTOTLE, and ROCKET AF. Another separate meta-analysis was performed for the low dose groups of RE-LY (110 mg twice daily) and ENGAGE AF-TIMI 48 (30 mg twice daily).

Results

Studies Identification and Characteristics

832 publications were identified through database search (Fig. 1). During the study screening process, the 4 studies from 54 publications (ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, and ROCKET-AF) assessing the safety of DOACs compared to warfarin in patients with AF were evaluated for eligibility. The principal safety objective was to demonstrate that DOACs were superior or non-inferior to warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.

There were 42,411 patients receiving direct-acting oral anticoagulants and 29,272 receiving warfarin. Baseline characteristics of the 4 studies included in the meta-analysis were shown in Table 1. The average age was over 70 and the proportions of female were similar between DOACs and the control groups for the 4 studies. However, according to the

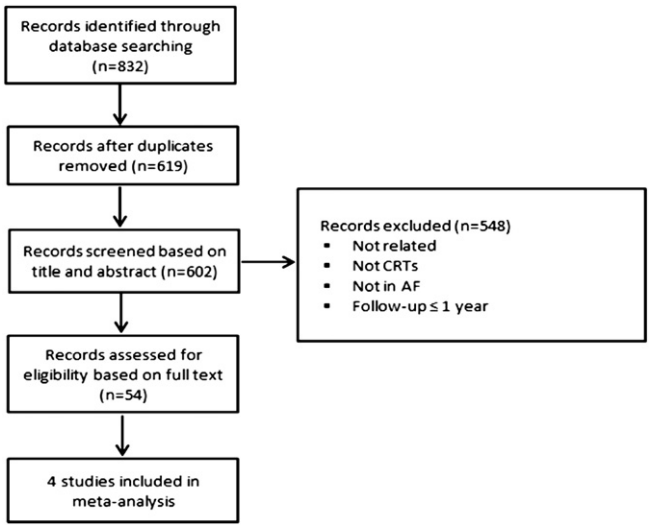

Fig. 1. Flow chart of study selection process.