

Efficacy and safety of Dabigatran vs. Rivaroxaban among Asians with non-valvular atrial fibrillation

Protocol for a systematic review and meta-analysis

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Protocol

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Abstract

Atrial fibrillation(AF) increases the risk of ischemic stroke and systemic embolism in patients. Moreover, Asian patients with AF are more likely to have ischemic stroke than non-Asian patients. Oral anticoagulants could effectively prevent thrombotic events. Dabigatran and Rivaroxaban are two most commonly used novel oral anticoagulants (NOACs) in Asia, but those clinical studies in relation with them are mostly in American and European countries. Therefore, whether there are differences between Dabigatran and Rivaroxaban among Asian patients with AF in terms of efficacy and safety is still unknown. This systematic review and meta-analysis will mainly assess clinical efficacy and safety of Dabigatran versus Rivaroxaban in Asian patients with AF by a pooled analysis. We will follow the PRISMA (preferred reporting items for systematic reviews and meta-analyses) and the reporting MOOSE (Meta-analyses of Observational Studies in Epidemiology) when performing this study. Then Cochrane Library, Web of Science, PubMed and China national knowledge infrastructure will be searched for eligible retrospective investigation that report the efficacy and safety outcomes of AF patients who utilised Dabigatran or Rivaroxaban for stroke prevention in Asian countries. The abovementioned database will be comprehensively searched from inception to September 30, 2019 to locate all potentially eligible studies. Outcome measures will include safety and efficacy indicators. Safety indicators include intracranial hemorrhage, major bleeding and gastrointestinal bleeding. Efficacy indicators include systemic embolism and stroke. New evidence for clinical profile of Dabigatran versus Rivaroxaban in AF patients will be provided for decision-making of Asian patients.

PROSPERO registration number: CRD42020156197

Background

Non-valvular atrial fibrillation (NVAF) is one of the most common arrhythmia in clinical practice, and is associated with elevated risk of ischemic stroke and systemic thromboembolism, and the risk of ischemic stroke is 4–5 times higher than that of non-AF patients^[1]. Therefore, the prevention of thromboembolic events caused by NVAF is an essential part in the treatment strategy. Oral anticoagulants can reduce the risk of thromboembolic events significantly and improve the prognosis of patients as well^[2, 3].

Oral anticoagulants consist of vitamin K antagonist warfarin and novel oral anticoagulants (NOACs) rivaroxaban, apixaban, edoxaban and dabigatran. Warfarin is the most classic one among oral anticoagulants. It has established efficacy in terms of anticoagulant effect, but patients need to monitor international normalized ratio(INR) frequently as warfarin is tend to interact with a variety of drugs and foods, which limits its use in clinical application^[2]. The results of four large-scale randomized controlled trials(RCTs) of NOACs showed that the efficacy of NOACs was not inferior to warfarin in the prevention of thrombosis, while the incidence of intracranial hemorrhage and all-cause mortality of NOACs were lower than that of warfarin in terms of safety^[4–7]. Besides, NOACs are widely accepted in clinical practice because of their stable correlation between dose and anticoagulation, no need to monitor blood

coagulation frequently, and little influence from food and other drugs. Therefore, both American and European AF guidelines recommend that NOACs should be the first choice for AF patients when starting oral anticoagulants if there was no present contraindication^[8, 9].

The prescription of NOACs in patients of AF with the risk of stroke was steadily increased in recent years. Data from GLORIA-AF, a large-scale global registry to study anticoagulation status in patients with AF, suggested that the proportion of NOACs used in patients with newly diagnosed AF with the risk of stroke has exceeded warfarin^[10]. NOACs were also widely prescribed in patients with AF in east Asian countries. In a subgroup study of GLORIA-AF, the proportion of NOACs used in Japanese patients with newly diagnosed AF from 2015 to 2016 was 67.9%, which was 17% far more than the figure of warfarin^[11]. The statistics from National Health Insurance Department of South Korea also showed that, the usage ratio of NOACs in patients with AF in South Korea was more than 50% in 2015^[12].

The research data in Asian countries were limited as the published RCTs directly or indirectly comparing the effect of NOACs mainly focus on western countries so far. Of the 71783 subjects in the four RCTs comparing NOACs with warfarin, only 7650 subjects were from Asian countries^[13]. In two retrospective studies published recently, rivaroxaban and dabigatran were the most frequently used and the longest used in several Asian countries or regions among four NOACs^[12-15].

There is no large-scale RCT to study whether there are differences among NOACs in terms of efficacy and safety. A meta-analysis of fourteen observational studies worldwide comparing the efficacy of NOACs, concluded that rivaroxaban had a significantly higher risk of major bleeding compared with that of dabigatran, and the same is true for all-cause mortality and gastrointestinal bleeding^[16]. However, there is no available evidence to support whether there are similar differences between rivaroxaban and dabigatran in Asian patients with AF, and whether these results consistent with each other in terms of efficacy at present.

Based on the abovementioned evidence, this systematic review and meta-analysis aims to compare the safety and efficacy of two most commonly used NOACs in Asia, rivaroxaban and dabigatran, with the purpose of providing evidence-based recommendations for clinical drug selection.

Methods

This systematic review and meta-analysis has been registered in the International Prospective Register of Systematic Reviews(CRD42020156197), and the protocol was conceived according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (supplemental table 1). If there was any changes generated in relation to this protocol, PROSPERO registration information will be revised consequently.

Data sources and search strategy

We will follow the PRISMA (preferred reporting items for systematic reviews and meta-analyses) and the reporting MOOSE (Meta-analyses of Observational Studies in Epidemiology) when performing this study^[17,18].

Data sources

The following databases will be used to comprehensively search for relevant keywords: PubMed, Web of science, Cochrane Library and China national knowledge infrastructure(CNKI). The search will be performed for studies from inception to September 30, 2019 to locate all potentially eligible studies.

Search strategy

The search strategy will be conducted as follows: “Pradaxa” or “dabigatran”, “xareltro” or “rivaroxaban”. For the theme “atrial fibrillation”, we will use “atrial fibrillation” or “AF”. Study type will include real world studies, observational studies and registry studies. Additionally, the language of the publications will be limited to English and Chinese. As study population will be Asian, the main study site will not out of Asia, for instance mainland of China, Hongkong, Taiwan, Korea, Japan, Singapore and etc.

Study selection

Inclusion criteria:

Studies will be chosen if they met the following criteria: Asian patients with NVAf; treatments with rivaroxaban and dabigatran; real world studies including prospective or respective cohort studies; Case control studies; registry studies.

Exclusion criteria:

Studies that include patients with mitral stenosis or prosthetic cardiac valves, mean or median follow-up duration < 6 months, and study participants < 200. For trials reporting multiple publications, the most relevant data will be extracted.

Data extraction

Two investigators(LJ and MZ) independently extracted the relevant information from each included study regarding the population, interventions, comparisons, the study design, patient characteristics, the number of enrolled patients, follow-up duration, and outcomes of interested. Outcome measures include safety and efficacy indicators. Safety indicators include intracranial hemorrhage, major bleeding and gastrointestinal bleeding. Efficacy indicators include systemic embolism and stroke.

Quality assessment

The Newcastle Ottawa quality assessment scale (NOS) will be utilised to assess the risk of bias for all included studies. NOS is recommended by Cochrane Collaboration to evaluate the quality of literature in

retrospective cohort studies, and it has eight items included in three domain, i.e. selection (representativeness), comparability (due to design or analysis), and outcomes (assessment and follow-up). Two investigators will review the selected articles separately and evaluate them. Disagreements will be settled by discussions between two investigators or consulting with a third expert in this field.

Data analysis

Incidence rate for primary and secondary outcomes will be accessed in this study. Primary outcomes will include stroke, systemic embolism and major bleeding, and secondary outcomes will contain ischemic stroke, gastrointestinal bleeding and intracranial hemorrhages. 95% confidence interval will be used for interval estimation, *P* value will be used to determine whether the combined effect size has statistical significance, and *P* value of < 0.05 represents a statistical significance. The statistical heterogeneity of the literature will be analyzed by I^2 test. I^2 of > 50% will indicate substantial heterogeneity among studies, a random-effects model will be used. Otherwise, we will use a fixed-effects model for evaluation.

Patient and Public Involvement

No patient involved

Publication bias assessment

The publication bias of the included studies will be considered if more than 10 studies will be included in the process of data processing. The possible methods may contain the funnel plot, Egger's intercept and Begg and Mazumdar's test.

Discussion

AF patients in Asia benefit more from NOACs, compared with their counterparts in Europe and America, this may be due to the fact that Asians are more likely to have intracranial hemorrhage and low quality of international normalized ratio (INR) control when they were taking warfarin to prevent thromboembolic events^[18]. When warfarin plays its role in anticoagulant therapy, its efficacy and safety depend mostly on the intensity and stability of the treatment. One clinical study reported that warfarin could prevent stroke events without increasing the risk of bleeding when the INR of anticoagulation treatment is 2.0–3.0^[19]. This index mainly comes from clinical studies of European and American, and there is a lack of large prospective RCTs in Asia to evaluate the efficacy and safety of warfarin in preventing stroke among AF patients. So far only the Japanese AF guidelines recommend that the ideal index of INR is 1.6–2.6 based on the J-RHYTHM registry^[20, 21]. Four large RCT studies, comparing the cases of warfarin in Asian and non-Asian AF patients, showed that time in therapeutic range (TTR) in Asian patients was lower than that of non-Asian patients, and INR of most patients was lower than 2.0, which means that the average anticoagulation intensity of Asian AF patients was lower than that of non-Asian patients, when Asian patients were randomly assigned to warfarin group^[22, 23].

NOACs are able to ensure the anticoagulant effect and significantly reduce the risk of bleeding as they could specifically block one activated coagulation factor^[24]. NOACs has a stable dose-dependent anticoagulant effect, which is less likely affected by food and other drugs, and there is no need for routine monitoring of coagulation function when they are applied in clinical practice, thus bringing convenience for patients with long-term treatment. Based on these advantages for Asian AF patients, NOACs have been prescribed widely in Asia. However, there are some questions following this prevalence. For example, whether there are differences among these four NOACs in terms of efficacy and safety, particularly the distinction between Dabigatran and Rivaroxaban that is widely used in Asia. There is no large-scale RCT on this study, neither the focus population was Asian patients.

The results of several published retrospective studies on Asian population are not consistent with each other in relation to the efficacy and safety between Dabigatran and Rivaroxaban. One study from Korean reported that Dabigatran was superior to rivaroxaban in intracranial hemorrhage and all-cause mortality^[25]. However, a retrospective study in Hong Kong showed that the incidence of dabigatran was lower than that of rivaroxaban in terms of intracranial hemorrhage, and the incidence of stroke showed the same trend for dabigatran and rivaroxaban^[26]. Another study in Israel focused on bleeding showed that dabigatran and rivaroxaban had the same incidence of bleeding if they were imposed on clinical intervention, while dabigatran had a higher incidence than rivaroxaban in terms of fatal bleeding^[27].

In view of these inconsistent results, we plan to do a meta-analysis to compare the efficacy and safety of rivaroxaban and dabigatran among Asians with non-valvular AF with the aim to provide supportive evidence for clinicians in anticoagulation decision-making.

There are several limitations we have to admit for this meta-analysis. First, the trials that met the inclusion criteria might not originally be created to assess the efficacy and safety of Dabigatran and rivaroxaban in Asian patients with AF. The differences in influential factors, such as patient demographics, bleeding risk factors, concomitant drugs, may need to be considered in further analysis. However, meta-regression analysis will be conducted to evaluate potential existing effect in baseline characteristics. Second, the statistical Singer's method using 1.5 weighted index may not be the explanation for all clinical variables. As a result, sensitivity analysis will be performed using weighted factor of 1.0 and 2.0. Lastly, the scarcity of head-to-head comparisons of Dabigatran and Rivaroxaban in Asian patients, and restricted number of included studies, may give rise to a single-faceted explanation, results in this paper may only be applicable to a part of the Asian population.

Conclusion

New evidence for clinical profile of Dabigatran versus Rivaroxaban on SSE, major bleeding, all-cause death, and NCB in AF patients will be provided for decision-making of Asian patients.

Abbreviations

AF = atrial fibrillation, CI = confidence interval, NCB = net clinical benefit, SSE = stroke/systemic embolism.

Declarations

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Conflicts of interest: None.

Contributorship statement: LJ, MZ, LS and LY conceived the initial idea of this study. LJ and MZ developed and revised the search strategy. LJ, MZ and LS completed the study design. LS and LY solved the clinical issues in relation to this study. LJ and MZ drafted the first manuscript. LJ, MZ, LS, and LY revised the draft accordingly. LJ and MZ contributed equally to this article. All of the authors confirmed the final work before the submission.

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