The Efficacy and Safety of 3 Types of Interventions for Stroke Prevention in Patients With Cardiovascular and Cerebrovascular Diseases: A Network Meta-analysis

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ABSTRACT

Purpose: The goal of this study was to compare the relative efficacy and safety of different types of interventions for stroke prevention in patients with cardiovascular and cerebrovascular diseases.

Methods: This network meta-analysis (NMA) was conducted with a random effects model of Bayesian framework using Stata version 12.0. Odds ratios (ORs) and their credible intervals (CrIs) were applied for the efficacy and safety evaluation of various medical interventions, including aspirin, dipyridamole, ticlopidine, warfarin, and apixaban. In addition, the ranking of probability of every clinical outcome was estimated by comparing the surface under the cumulative ranking curve.

Findings: Compared with dabigatran, both edoxaban and aspirin + warfarin exhibited a higher rate of all-cause stroke (OR, 2.84 [95% CrI, 1.17–6.97]; OR, 3.42 [95% CrI, 1.20–9.84]). With respect to intracranial hemorrhage, aspirin + clopidogrel yielded worse outcomes than 7 treatments, including placebo, apixaban, aspirin, aspirin + dipyridamole, cilostazol, clopidogrel, and dabigatran (OR, 2.21 [95% CrI, 1.45–3.40]; OR, 2.11 [95% CrI, 1.05–4.17]; OR, 1.53 [95% CrI, 1.11–2.15]; OR, 1.78 [95% CrI, 1.01–3.03]; OR, 4.17 [95% CrI, 1.37–14.28]; OR, 1.85 [95% CrI, 1.22–2.86]; and OR, 2.56 [95% CrI, 1.37–4.76]). In terms of ischemic stroke, dabigatran provided better efficacy than placebo, aspirin, and aspirin + dipyridamole (OR, 0.36 [95% CrI, 0.18–0.72]; OR, 0.43 [95% CrI, 0.21–0.84]; and OR, 0.41 [95% CrI, 0.17–0.94]). As for mortality, dabigatran resulted in a lower mortality compared with aspirin, aspirin + clopidogrel, edoxaban, and warfarin (OR, 0.48 [95% CrI, 0.23–0.97]; OR, 0.40 [95% CrI, 0.17–0.92]; OR, 0.27 [95% CrI, 0.10–0.72]; and OR, 0.52 [95% CrI, 0.28–0.92]).

Implications: There are still some limitations to our NMA research. For instance, the lack of direct evidence for some therapies resulted in inconsistencies, particularly for warfarin compared with placebo and clopidogrel under different end points. Moreover, the included randomized controlled trials for patients with cardiovascular and cerebrovascular diseases are relatively broad, involving atrial fibrillation, myocardial infarction, and large-artery atherosclerosis stroke. Although further research is needed, dabigatran is highly recommended based on the present NAM for the treatment of cardiovascular and cerebrovascular diseases due to the drug's efficacy and safety. (*Clin Ther.* 2017;39:1291–1312)

Key words: anticoagulants, antiplatelet, cardiovascular and cerebrovascular disease, intracranial hemorrhage, medical interventions, network meta-analysis, statins, stroke.

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INTRODUCTION

Cardiovascular and cerebrovascular diseases have a high incidence rate, especially among the elderly population. They usually occur with the development of atherosclerosis, which could result in ischemic stroke.[1,2] In general, ischemic stroke can be effectively treated with the use of thrombolytic drugs.[3,4] However, these drugs have some side effects, such as intracranial hemorrhage; the incidence of intracranial hemorrhage can reach 1.7% to 6.4% in patients after being treated with thrombolytic drugs.[2] In addition, thrombolytic therapy is mostly used within the first 3 to 6 hours of ischemic stroke onset[5] or the initial 3 to 4.5 hours according to the Japanese guidelines for the management of stroke,[6] which restricts its use. Therefore, classifying and summarizing the medical interventions applied for the prevention and treatment of cardiovascular and cerebrovascular diseases is necessary.

The numerous studies that focused on the efficacy of various medications used for patients with vascular diseases (mainly nonperipheral vascular disease) can be grouped into 3 categories: statins, antiplatelets, and anticoagulants. Statins can be used before or during the stroke stage to decrease its recurrence and stimulate the repair of tissue.[3] Platelet aggregation could induce arterial thermogenesis, and thus antiplatelet drugs may play an important role in the prevention of vascular disorders.[2] Therefore, antiplatelets and anticoagulants may contribute to reductions in major vascular disorders by decreasing platelet aggregation.[7,8]

Apart from the monotherapies, such as rosuvastatin, simvastatin, aspirin, dipyridamole, ticlopidine, warfarin, apixaban, cilostazol, clopidogrel, coumarin, dabigatran, rivaroxaban, and edoxaban, dual therapies are also considered to be effective (eg, aspirin + clopidogrel, aspirin + dipyridamole, warfarin + aspirin). Previous studies have found that compared with the aforementioned monotherapies, dual antiplatelet therapy could be more efficacious in reducing the recurrence of stroke.[2] The therapeutic effects of antiplatelet therapy were considered to be efficacious. It mainly focused on several functional effects; for example, the treatment of the primary event and the reduction of the incidence for deterioration and recurrence.[9]

Ticagrelor is a direct non-thienopyridine $P2Y_{12}$ inhibitor that has been shown to have rapid onset and a noticeable platelet aggregation inhibition effect.[10] Aspirin has been proved to be an effective intervention for reduction of cardiovascular or cerebrovascular events.[11] The adenosine diphosphate receptor antagonist ticlopidine and the phosphodiesterase inhibitor cilostazol have effects similar to the other antiplatelet agents.[12] In terms of anticoagulant agents, warfarin is effective in reducing the risk of atrial fibrillation but associated with the risk of hemorrhage, and its dose response needs frequent monitoring.[13] Coumarin is a type of anticoagulation drug that has been shown to have effects on reducing the incidence of thromboembolic events.[14] In addition, the anticoagulant dabigatran acts as an inhibitor of thrombin, whereas the anticoagulants apixaban, rivaroxaban, and edoxaban are inhibitors of factor Xa.[15–17] They all play important roles in the prevention of stroke.[18]

Although these interventions seem to be efficacious in treating cardiovascular and cerebrovascular diseases, their relative efficacy and safety in some cases remain controversial. In addition, the existing meta-analysis studies are limited to the direct comparison of 2 or 3 medications.[4,7,8,19] It is difficult for traditional meta-analysis research to include all treatments and extract all the available data. Moreover, they failed to define the clinical end points clearly for medical recommendations. In conclusion, it is still controversial to compare efficacy and reliability between dual therapy and monotherapy.

The goal of the present network meta-analysis (NMA) was to analyze results from currently published, randomized controlled trials (RCTs) to compare and assess their relative efficacy and reliability, directly and indirectly. Two-arm, three-arm, and even four-arm trials were included, and they were evaluated by using different end points, including intracranial hemorrhage, all-cause stroke, ischemic stroke, mortality, and withdrawal. Our aim was to provide optimal interventions in terms of medical recommendations according to the results of this NMA.

MATERIALS AND METHODS

Search Strategy

The PubMed, EMBASE, and China National Knowledge Infrastructure databases were widely searched for eligible articles published before March 10, 2016, without any restriction of date. The following key terms were used for searching: *statins, anticoagulants, antiplatelet drugs, randomized controlled trials (RCTs), cardiovascular diseases*, and *cerebrovascular*