Antiplatelet Agents for the Secondary Prevention of Ischemic Stroke or Transient Ischemic Attack: A Network Meta-Analysis

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Stroke can cause high morbidity and mortality, and ischemic stroke (IS) and transient ischemic attack (TIA) patients have a high stroke recurrence rate. Antiplatelet agents are the standard therapy for these patients, but it is often difficult for clinicians to select the best therapy from among the multiple treatment options. We therefore performed a network meta-analysis to estimate the efficacy of antiplatelet agents for secondary prevention of recurrent stroke. We systematically searched 3 databases (PubMed, Embase, and Cochrane) for relevant studies published through August 2015. The primary end points of this meta-analysis were overall stroke, hemorrhagic stroke, and fatal stroke. A total of 30 trials were included in our network meta-analysis and abstracted data. Among the therapies evaluated in the included trials, the estimates for overall stroke and hemorrhagic stroke for cilostazol (Cilo) were significantly better than those for aspirin (odds ratio [OR] = .64, 95% credibility interval [CrI], .45-.91; OR = .23, 95% CrI, .08-.58). The estimate for fatal stroke was highest for Cilo plus aspirin combination therapy, followed by Cilo therapy. The results of our meta-analysis indicate that Cilo significantly improves overall stroke and hemorrhagic stroke in IS or TIA patients and reduces fatal stroke, but with low statistical significance. Our results also show that Cilo was significantly more efficient than other therapies in Asian patients; therefore, future trials should focus on Cilo treatment for secondary prevention of recurrent stroke in non-Asian patients. **Key Words:** Antiplatelet agents—cilostazol—meta-analysis—ischemic stroke—transient ischemic attack.

Introduction

Stroke can cause dysfunctions in the brain that can rapidly lead to high morbidity and mortality.[1] Patients who suffer from an ischemic stroke (IS) or a transient ischemic attack (TIA) have a high stroke recurrence rate of approximately 30%.[2] Thus, secondary prevention in these patients is extremely important.

Antiplatelet agents are the standard therapy for patients with IS or TIA.[3] Among these agents, cilostazol (Cilo), a phosphodiesterase inhibitor, has both vasodilatory and antiatherogenic activities.[4-7] Clinical trials have shown that Cilo is highly effective in preventing stroke recurrence.[8,9]

Recently, several large-scale randomized controlled trials (RCTs) were completed in which different antiplatelet agents were tested as secondary prevention agents following IS and TIA. However, the best therapy for the prevention of overall stroke recurrence (OS), especially

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W.W., L.Z., and W.M.L. performed the literature search. Q.L. and Q.Z. independently performed the data extraction. W.W. wrote the paper and was responsible for the final approval of the version submitted for publication. J.Z.Z. conceived and designed the experiments.

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hemorrhagic stroke recurrence (HS) and fatal stroke recurrence (FS), remains unclear.

Traditional meta-analyses can only compare interventions that utilize the same comparator. In contrast, a Bayesian network meta-analysis can integrate all RCTs into a single analysis, thereby allowing direct and indirect comparisons between different therapeutic strategies to be conducted simultaneously. Moreover, a Bayesian network meta-analysis can increase the precision of a comparison by combining direct evidence with indirect evidence[10] to produce a more accurate ranking of all of the analyzed therapeutic strategies.

It is often difficult for clinicians to select the best therapy for a patient from among multiple treatment options. We therefore performed a Bayesian network meta-analysis to accurately evaluate the efficacy of different antiplatelet agents for secondary prevention of recurrent stroke.

Methods

Search Strategy

Two independent investigators (W.W. and L.Z.) systematically searched the PubMed, Embase, and Cochrane databases for RCTs that were conducted in humans and published through August 2015. No language restriction was applied. The terms used for the search included *ischemic stroke*, *transient ischemic attack*, and *antiplatelet agents*. We also broadened the search criteria by checking the references cited by the identified studies. The primary end points of this meta-analysis were OS, HS, and FS. Any disagreements during the identification of studies and data extraction were resolved through discussion.

Study Eligibility

The inclusion criteria for the retrieved studies were the following: (1) patients with a prior cerebral IS or TIA, mean age older than 50 years; (2) use of antiplatelet therapy as the primary method for secondary stroke prevention; (3) RCT; and (4) specification of or the ability to calculate the incidence of events in the study population.

Data Abstraction and Quality Assessment

All reviewers performed data abstraction using standardized criteria. The reviewers also verified sequence generation, allocation concealment, blinding, incomplete data outcomes, selective outcome reporting, and other causes of bias to evaluate the risk of bias in each study using the Cochrane Collaboration tool. We also assessed the influence of the methodological quality of the trials on the results by evaluating the reported randomization and follow-up procedures in each trial. The defined end points (OS, HS, and FS) were the same across all trials. OS was defined as the recurrence of IS as well as the occurrence of hemorrhagic and unknown stroke, including fatal or nonfatal strokes. HS and FS were defined as the recurrence of hemorrhagic and fatal stroke, respectively. We resolved disagreements and reached consensus through discussion.

Statistical Analysis

We performed a network meta-analysis within a Bayesian framework to evaluate the direct and indirect effects of treatments in each node.[11-13] This approach allowed direct and indirect evidence to be combined; the different types of evidence were combined because the included studies had less heterogeneity.[14]

All data analyses were performed using the Aggregate Data Drug Information System, version 1.16.5 (Drugis, Groningen, The Netherlands) and reported as odds ratios (ORs) and 95% credibility intervals (CrIs). Significant heterogeneity was defined as a P value less than .05. Results were considered statistically significant when the CrI did not include 1.0. For each outcome, the different antiplatelet therapies were ranked according to the estimated size of the effect. Direct and indirect evidence was analyzed using node-splitting assessments, which are used to determine whether the direct evidence and indirect evidence for a specific comparison agree; a large P value indicates no significant inconsistency was found. Forest plots were made in R software (version 3.2.3) with the R2winBUGS package. The characteristics of all trials were recorded, including the mean age of the patients, the presence of hypertension, the follow-up duration, and the relevant outcomes (OS, HS, and FS).

Results

Literature Search

A total of 6111 relevant publications (1205 from PubMed, 2453 from Embase, and 2453 from CENTRAL) were identified and reviewed. These studies were limited to RCTs involving human subjects that were published before August 2015. No additional trials were selected during the systematic review. We excluded 6081 articles because they were duplicate studies or did not meet the inclusion criteria.

Finally, a total of 30 trials[8,9,15-42] were included, and the data from these studies were abstracted for our network meta-analysis (Fig 1).

Study Characteristics

The 30 included trials tested 12 different therapeutic strategies in patients with a history of IS or TIA. Detailed characteristics of these 30 trials were recorded, including the mean age of the patients, the presence of hypertension, the follow-up duration, and the relevant outcomes (OS, HS, and FS) (Table 1). Four trials[8,30,32,37] compared Cilo to aspirin (ASA) therapy, and 2 studies[9,40] compared Cilo plus aspirin (Cilo + ASA) combination therapy to ASA therapy alone. Sixteen studies tested dual