Original Research

Evaluation of Antiplatelet Agents for Secondary Prevention of Stroke Using Mixed Treatment Comparison Meta-analysis

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ABSTRACT

Background: The current guidelines recommend various antiplatelet agents used alone or in combination for secondary prevention of noncardioembolic stroke.

Objective: The purpose of this study was to conduct a mixed treatment comparison meta-analysis to determine which antiplatelet or combination of antiplatelet agents is most efficacious and tolerable in patients with prior stroke.

Methods: A comprehensive literature search was conducted in MEDLINE (1945 through March 2012), EMBASE (1974 through March 2012), and the Cochrane Controlled Trials Registry (1975 through April 2012) to identify randomized trials evaluating the role of various antiplatelet agents and combinations for the secondary prevention of stroke. Key articles were cross-referenced for additional studies. Data were screened and evaluated to generate direct and indirect comparisons for recurrent stroke and overall hemorrhagic events. Data were reported as rate ratios (RRs) and 95% CIs.

Results: A total of 24 articles were included in the analysis. Eleven antiplatelet regimens were compared in >88,000 patients. The combination of acetylsalicylic acid (ASA) plus dipyridamole (DP) was more protective against recurrent stroke than ASA alone (RR = 0.78; 95% CI, 0.64–0.93), and no differences were found in all other direct and indirect comparisons with active treatment. ASA plus DP was associated with more overall hemorrhagic events than DP (RR = 1.83; 95% CI, 1.17–2.81), cilostazol (RR = 2.12; 95% CI, 1.21–3.48), and triflusal (RR = 1.67; 95% CI, 1.05–2.78) but fewer events than the combination of ASA plus clopidogrel (RR = 0.38; 95% CI, 0.25–0.56). The combination of ASA plus clopidogrel was associated with an excess of overall hemorrhagic events compared with clopidogrel (RR = 2.81; 95% CI, 1.96–4.10), cilostazol (RR = 5.56; 95% CI, 3.03–9.66), DP (RR = 4.78; 95% CI, 2.80–8.21), sarpogrelate (RR = 3.59; 95% CI, 1.96–6.45), terutroban (RR = 2.13; 95% CI, 1.21–3.61), ticlopidine (RR = 2.80; 95% CI, 1.69–5.00), and triflusal (RR = 4.36; 95% CI, 2.62–7.81).

Conclusion: We found that ASA plus DP was more protective than ASA alone for preventing recurrent stroke; however, no difference was found between most direct and indirect comparisons of antiplatelet agents and combinations. More overall hemorrhagic events seemed to occur with the combination of ASA and clopidogrel than with other treatments. Selection of antiplatelet therapy for the secondary prevention of stroke must be individualized according to patient comorbidities, including risk of stroke recurrence and bleeding. (*Clin Ther*. 2013;35:1490–1500)

Key words: antiplatelet, stroke prevention, bleeding, mixed treatment comparison, aspirin, dipyridamole.

INTRODUCTION

Stroke is a leading cause of morbidity and mortality worldwide and remains a major health care problem with an increasing economic burden.[1,2] Current projections suggest that death caused by stroke will increase exponentially in the next 30 years due to the aging population and inadequate management of risk factors.[3] Furthermore, it is estimated that 25% of strokes that occur each year are recurrent events in which risk is highest during the initial hours to days after a transient ischemic attack (TIA) or ischemic

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stroke. Thus, a focus on secondary prevention is important in this patient population, and the choice between antiplatelet or anticoagulant therapy often depends on the cause of the stroke and patient-specific risks of recurrence and bleeding.[4–7]

Acetylsalicylic acid (ASA) has been an essential drug for secondary prevention of stroke, in conjunction with risk factor modification, such as blood pressure control, management of dyslipidemia, diabetic control, and smoking cessation. In recent years, several antiplatelets and combinations of these antiplatelet agents have become available. The current guidelines on the prevention of thrombotic events in patients with a history of noncardioembolic ischemic stroke or TIA give strong recommendations with high quality of evidence to any one of the following agents: ASA, clopidogrel, cilostazol, or the combination of ASA plus dipyridamole (DP) over no therapy, the combination of ASA plus clopidogrel, or triflusal.[8] However, in a weaker recommendation supported by moderate or low quality of evidence, the preferred agents are clopidogrel or the combination of ASA plus DP over ASA or cilostazol. The weaker recommendation is potentially due to the lack of direct comparisons among all antiplatelet agents.

Given the mixed evidence and various antiplatelet options, it becomes challenging for clinicians to select an optimal agent. Therefore, we conducted a mixed treatment comparison (MTC) meta-analysis to evaluate how well antiplatelet therapy protected against recurrent vascular events while minimizing hemorrhagic events in patients with noncardioembolic ischemic stroke in a network of direct and indirect comparisons.

METHODS

This analysis evaluated the efficacy and tolerability of 11 antiplatelet regimens used in patients with prior noncardioembolic stroke: ASA, cilostazol, clopidogrel, DP, ticlopidine, triflusal, sarpogrelate, and the combination of ASA with cilostazol, clopidogrel, DP, or triflusal. Efficacy end points included recurrent stroke, the composite of vascular events, death from any cause, death from vascular causes, and myocardial infarction (**Table I**). Tolerability end points included any hemorrhagic and major hemorrhagic events and intracranial hemorrhage (**Table I**).

A systematic search was conducted in MEDLINE (1945 through March 2012), EMBASE (1974 through March 2012), and the Cochrane Controlled Trials Registry (1975 through April 2012) for human, English-language, and randomized controlled trials evaluating the role of various antiplatelets used separately or in combination for the secondary prevention of stroke. The following terms were used in the search: *aspirin, dipyridamole, Aggrenox, clopidogrel, ticlopidine, triflusal, cilostazol, stroke, transient ischemic attack, secondary stroke prevention,* and *stroke prevention*. Key articles were cross-referenced for additional studies. Studies were included in the analysis if patients had a prior cerebral ischemic event (defined as ischemic stroke, TIA, reversible ischemic neurologic deficit, or any combination thereof) and were using antiplatelet therapy as the primary method for secondary stroke prevention (**Table II**). Studies were excluded if they (1) did not meet the prespecified population, (2) did not assess efficacy of the intervention, (3) were not an original study, and/or (4) were not a randomized controlled trial. All authors reviewed studies to evaluate methods; to identify patient characteristics; to ascertain randomization, blinding, and allocation concealment; and to assign quality scores. Any identified discrepancies were resolved with additional review and discussion.[9]

We used an MTC meta-analysis to create a bayesian evidence network and evaluate direct and indirect treatment effects.[10–12] The Aggregate Data Drug Information System (ADDIS), version 1.16.3, software package was used to build a Markov Chain Monte Carlo analysis using antiplatelet trials in patients with a history of stroke[13] (see the **Supplemental Appendix I** in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.09.004). An evidence network was constructed to make direct (A vs B or B vs C) and indirect (A vs C) treatment comparisons along with the number of trials in each node.[14,15] Treatment networks were evaluated to identify heterogeneity and consistency within closed loop evidence structures.[13,16–18] The MTC methods preserved the benefit of within-trial randomization and allowed combinations of direct and indirect evidence because studies had comparable patient characteristics without notable heterogeneity[11,18] (see the **Supplemental Appendix II** in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.09.004). Data were reported as odds ratios (RRs) and 95% CIs because rates allow for comparisons when multiple events occur in the same individuals.

RESULTS

Study Demographic Characteristics

A total of 661 potentially relevant articles were identified and reviewed, 637 of which were excluded