

EBEM Commentator
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Antiplatelet Agents for Acute Ischemic Stroke

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Gubitz G, Sandercock P, Counsell C. Antiplatelet therapy for acute ischaemic stroke (Cochrane Review). In: The Cochrane Library, Issue 1. Oxford, United Kingdom: Update Software; 2003.

The *Annals'* EBEM editors helped prepare the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To determine the effect of antiplatelet therapy in presumed acute ischemic stroke.

DATA SOURCES

The Cochrane Stroke Group Trials Register was searched up to May 1999. The Antiplatelet Trialists' collaboration was searched up to June 1998. Medstrategy was searched up to 1995. Additionally, pharmaceutical companies were contacted in an effort to identify unpublished and ongoing trials. This review was updated in February 2002 from the previous one published in May 1999.

STUDY SELECTION

Studies were included if they were randomized, unconfounded, blinded, controlled clinical trials. Patients had to receive antiplatelet therapy or placebo within 2 weeks of their presumed acute ischemic stroke. The antiplatelet agents included in this review are aspirin, ticlopidine, aspirin plus dipyridamole, and OKY 046 (a thromboxane synthase inhibitor). Two of the 8 trials (the Chinese Acute Stroke Trial and the International Stroke Trial) comprised the majority of the evidence in this review (ie, 98% of the data). These studies used acetylsalicylic acid as the antiplatelet agent (160 mg and 300 mg, respectively). Given the weight of their contribution to the data, the term acetylsalicylic acid, rather than antiplatelet agent,

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will be used in the remainder of this review. By presumed ischemic stroke, the authors meant that the researchers made some sort of effort to exclude hemorrhagic stroke, although only 3 of the 8 trials included actually used computed tomography (CT) to make the distinction.

DATA EXTRACTION

Two authors independently selected trials, extracted data, and assessed the quality of the trials. Odds of death, functional outcome, and adverse effects were assessed with 95% confidence intervals (CIs).

MAIN RESULTS

A total of 8 trials involving 41,325 patients were included. The [Table](#) provides a summary of the evidence provided in the review using numbers needed to treat.

Of note, 771 patients with intracerebral hemorrhage were included in the randomization, which occurred before brain CT scan. Even in this group, however, the trend toward a better outcome in the acetylsalicylic acid therapy group persisted, although this was no longer statistically significant.

Table.

Summary of effects of aspirin on acute stroke.

Outcome Measures	Effect of ASA
Dead or dependent at final follow-up	13 more patients per 1,000 alive and independent
Death from any cause during treatment period	5 fewer patients per 1,000
Death from any cause after follow-up period	8 fewer patients per 1,000
Imaging proven DVT during treatment period	Nonsignificant result
Symptomatic PE while alive or any PE at autopsy	1 fewer patient per 1,000
Recurrent stroke during treatment period	7 fewer patients per 1,000
Complete recovery from stroke (post hoc analysis)	10 more patients per 1,000
Symptomatic intracranial hemorrhage	2 more patients per 1,000
Major extracranial hemorrhage (fatal, or requiring transfusion or surgery)	4 more patients per 1,000

ASA, Acetylsalicylic acid; DVT, deep venous thrombosis; PE, pulmonary embolism.

CONCLUSION

Acetylsalicylic acid reduces the risk of death, dependence, recurrent ischemic stroke, and pulmonary embolism after acute ischemic stroke. It also improves the odds of complete recovery. These benefits outweigh the potential adverse effects of intracranial and extracranial hemorrhage.

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COMMENTARY: CLINICAL IMPLICATION

Stroke is a common emergency department (ED) presentation with high morbidity and mortality. Although new therapies, such as thrombolysis, have been proposed, currently most patients are not eligible for any intervention, and treatment options for emergency physicians remain conservative.

Adequate oxygenation, hydration, and nutrition and control of hyperglycemia, fever, and hypertension

remain the cornerstones of conservative approaches to this disease. This review examined the evidence from 8 trials involving more than 40,000 patients, and concluded that acetylsalicylic acid therapy reduced deaths and recurrent strokes after ischemic stroke. Despite these encouraging results, the results are tempered by the fact that acetylsalicylic acid therapy increased rates of intracranial hemorrhage and major bleeding compared with placebo.

Furthermore, the authors re-analyzed the outcome of death, dependence, and recurrent ischemic stroke to determine what the size of a null trial would have to be in order to render the stated results invalid.

They calculated 193,000 and 50,000 additional patients in randomized controlled trials would be required to change the results for recurrent ischemic stroke and death, respectively. One concludes it is unlikely that a trial of such a size would be unpublished, missed in the comprehensive searches described, nor completed in the future. Conversely, smaller trials, although perhaps unpublished, would lack sufficient power to alter the stated results.

The role of acetylsalicylic acid therapy is well established in the care of acute myocardial infarction, and guidelines for its routine ED administration are widely accepted. Emergency physicians have been slower to implement its routine use in acute ischemic stroke, despite the wealth of supporting evidence provided in this systematic review. Much of this is likely due to the fact that recognition of stroke as a medical emergency is still lacking.¹ Suggested approaches include incorporating acetylsalicylic acid therapy into care as soon as CT scan has confirmed a nonhemorrhagic stroke. Emergency physicians must continue to make every effort to ensure

the best possible stroke care for patients by following recommendations of evidence-based guidelines.²

TAKE HOME MESSAGE

Acetylsalicylic acid therapy improves status of acute events and prevents future cerebrovascular ischemic events in patients with nonischemic strokes. For this reason, it has become the standard of care to administer 160 to 320 mg of acetylsalicylic acid to all patients experiencing acute brain ischemia within 48 hours of presentation, provided no major contraindications (eg, hemorrhagic stroke documented by CT, allergy to acetylsalicylic acid, history of major gastrointestinal bleed) exist. This is in keeping with the most recent American Stroke Association Guidelines.² For patients who cannot tolerate acetylsalicylic acid, it is reasonable to consider an alternative antiplatelet agent, although this particular review lacks evidence on which one to support.

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EBEM TEACHING POINT

Number needed to harm. The number needed to harm is the number of patients given the intervention of interest required to detect one adverse outcome. It is calculated in a manner very similar to the number needed to treat. The formula for the number needed to harm is:

Number needed to harm =

$$[\text{CER}(\text{OR}-1)] + 1 / [\text{CER}(\text{OR}-1)(1-\text{CER})]$$
 where CER is the control event rate and OR is the odds ratio, or the pro-

portion of patients with the target event divided by the proportion of patients without the target event.

REFERENCES

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