CJEM Journal Club

Clopidogrel with aspirin versus aspirin alone in prevention of stroke following transient ischemic attack or acute minor stroke

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Clinical question
Following transient ischemic attack or acute minor stroke, does the combination of clopidogrel and aspirin reduce the risk of stroke greater than aspirin alone?
Article chosen
Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;369:11-9.
Objective
The primary outcome measured in this study was ischemic or hemorrhagic stroke at 90 days of follow-up in groups assigned to treatment with a combination of aspirin and clopidogrel or aspirin alone following transient ischemic attack or acute minor stroke. The secondary outcomes were new clinical vascular events, including vascular death.

Keywords: antiplatelet, aspirin, clopidogrel, prevention, stroke

BACKGROUND

Stroke is a disabling condition frequently seen in the emergency department. It has been noted that the period immediately following transient ischemic attack (TIA) or stroke itself is particularly high risk of further strokes,[1,2] and this has been the subject of secondary prevention research. Antiplatelets have been established as the standard of care in prevention of stroke in high-risk patients who do not warrant anticoagulation. Aspirin has long been the only antiplatelet shown to be of benefit in secondary prevention of stroke.[3,4] Therapy with clopidogrel and aspirin has been studied for prevention of ischemic events in other situations, such as acute coronary syndrome. This same combination has been studied in cerebrovascular event prevention after stroke, with no statistically significant difference.[5–7] However, these studies did not target the immediate postevent period following TIA or minor stroke. Smaller trials have suggested the benefit of combination therapy in these patients,[8–10] but no large trials have demonstrated the same.

POPULATION STUDIED

Patients were considered for inclusion in the study if they met the following criteria: 1) age > 40, 2) able to start therapy within 24 hours of symptom onset, and 3) diagnosis of acute minor stroke (defined as a score of 3 or less on the National Institutes of Health Stroke Scale) or TIA with a moderate to high risk of stroke recurrence (defined as focal brain ischemia with resolution of symptoms with 24 hours of onset plus an ABCD score ≥ 4).

Patients were excluded from the study if they met any of the following criteria: intracranial hemorrhage, major nonischemic brain disease, isolated sensory symptoms or visual changes, isolated dizziness or vertigo without changes on head computed tomography (CT) or magnetic resonance imaging (MRI), a modified Rankin score of more than 2 prior to the event, indication for anticoagulation (e.g., presumed cardiac source of embolus), contraindication to aspirin

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or clopidogrel, anticipated need for nonstudy antiplatelet agents or nonsteroidal antiinflammatory drugs (NSAIDs), planned or probable revascularization within 3 months postscreening, life expectancy of less than 3 months, planned surgery or interventional requiring cessation of study drugs, iatrogenic TIA or minor stroke, or potentially pregnant.

STUDY DESIGN

This was a randomized, double blind, placebo-controlled study that took place across 114 centres in China. The study enrolled 5,170 patients diagnosed with acute minor stroke or TIA who were randomized into group receiving either clopidogrel and aspirin or aspirin alone. Both groups received aspirin at 75 to 300 mg daily, as dosed by the treating physician on day 1. The clopidogrel-aspirin group then continued aspirin at 75 mg from days 2 to 22 and switched to placebo aspirin from days 23 to 90. This group also received 300 mg of clopidogrel on day 1 and 75 mg of clopidogrel on days 2 to 90. The aspirin group received 75 mg of aspirin and placebo clopidogrel daily from days 2 to 90.

OUTCOMES MEASURED

The primary end point measured in the study was ischemic or hemorrhagic stroke within 90 days. A number of secondary end points, including efficacy and safety, were also measured. Efficacy-related secondary end points included vascular events, ischemic stroke, hemorrhagic stroke, myocardial infarction, death from cardiovascular causes, all-cause mortality, and TIA. Safety-related end points included various levels of bleeding.

RESULTS

This study screened 41,561 patients with stroke or TIA and randomized 5,170 patients, with 2,586 patients receiving aspirin alone and 2,584 patients receiving both clopidogrel and aspirin. There were no significant differences in the baseline characteristics of the two groups, including type of event, time to randomization, and TIA severity.

There was a significant reduction in the primary end point of stroke at 90 days in the clopidogrel and aspirin group (8.2% v. 11.7% [$p < 0.001$]; number needed to treat [NNT] = 29). The combined group also demonstrated statistically significant decreases compared to the aspirin group in the secondary end points of ischemic stroke (7.9% v. 11.4% [$p < 0.001$]) and vascular events (8.4% v. 11.9% [$p < 0.001$]). All other secondary end points showed no statistically significant differences.

STUDY CONCLUSION

Based on the significant difference in the primary end point, the authors concluded that in patients presenting with acute minor stroke or TIA within 24 hours of symptom onset, therapy with clopidogrel and aspirin together is superior to aspirin alone in preventing stroke.

COMMENTARY

For the primary end point of ischemic or hemorrhagic stroke within 90 days following the initial event, this trial demonstrated the superiority of clopidogrel and aspirin over aspirin alone with an NNT of 29. Secondary end points echoed this finding, showing a significant reduction in vascular events (primarily ischemic stroke).

This study was conducted in China, where death from stroke is 150 to 250 per 100,000 persons per year; in Canada, this rate is approximately 40 per 100,000 persons per year.[11] Because of national differences in ethnicity, risk factor modification, and health care systems, it is possible that the benefits seen in this study may differ in a Canadian population.

There are some concerns regarding this study's design. First, patients were not given a standard loading dose of aspirin. The initial treating physician chose from a range of 75 to 300 mg. Second, there was no indication of the number of patients in each group who received the various loading doses. If more patients in the combined group received a higher loading dose than the aspirin group, this may have affected the results.

The investigators chose to discontinue the aspirin in the combined group after 3 weeks, leaving this group as a clopidogrel-only group after 21 days. There is no explanation of the rationale behind this in the primary publication.

There were 41,561 patients screened for inclusion, but only 5,170 patients were enrolled. Although the

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long list of exclusions was reasonable, they certainly limit the extent to which these results are generalizable. In particular, "probable revascularization" in the next 3 months may be highly variable and difficult to define in practice.

CONCLUSION

This randomized clinical trial was largely well designed and demonstrated a potential benefit of clopidogrel and aspirin over aspirin alone in the prevention of stroke following TIA or minor stroke. Given a lack of information on loading dose and specific timing to treatment initiation, the emergency medicine community will need to wait for further studies to solidify the evidence regarding the immediate management of TIA and minor stroke in the emergency department.

Competing interests: None declared.

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