Medicine by the Numbers

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Antiplatelet Agents for Preventing Early Recurrence of Ischemic Stroke or TIA

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Details for This Review

Study Population: Five randomized controlled trials including a total of 10,739 patients with atherothrombotic ischemic stroke or transient ischemic attack (TIA)

Efficacy End Points: Stroke recurrence and vascular death; secondary outcomes included myocardial infarction, vascular death, and death from all causes

Harm End Points: Intracranial or extracranial hemorrhage

Narrative: Ischemic strokes range in severity from minor to debilitating. Minor strokes and TIAs may be followed by recurrent strokes, with the highest risk in the first 48 hours.[1] Approximately 30% of strokes are recurrent.[2] Antiplatelet agents may reduce the risk of recurrence and prevent disability, but they may also increase the risk of hemorrhage.[2-4] This Cochrane review updates a previous review examining the effect of adding clopidogrel (Plavix) to aspirin therapy after atherothrombotic acute ischemic stroke or TIA.

This Cochrane review included randomized controlled trials evaluating patients taking any combination of multiple antiplatelet agents vs. a single agent within 72 hours of an atherothrombotic acute ischemic stroke or TIA.[5] The primary outcome was stroke recurrence during at least three months of follow-up. Secondary outcomes included myocardial infarction, intracranial hemorrhage, extracranial hemorrhage, and death. When there was more than one follow-up period, the authors included outcomes at one week, one month, three months, and six months.

The meta-analysis included five randomized controlled trials with 10,739 patients that compared aspirin plus clopidogrel vs. aspirin alone.[3,6-9] All medications were administered orally, and most used a loading dose of clopidogrel, 300 mg. Dosing of aspirin ranged from 75 mg to 300 mg. Follow-up ranged from 30 days to one year.

Dual antiplatelet therapy with aspirin plus clopidogrel was associated with less risk of recurrent stroke compared with aspirin alone (6.5% vs. 9%; absolute risk reduction [ARR] = 2.5%; number needed to treat = 40; risk ratio [RR] = 0.7; 95% CI, 0.6 to 0.8). There was no difference in vascular death (RR = 1.4; 95% CI, 0.6 to 2.9) or myocardial infarction (RR = 1.5; 95 CI, 0.6 to 3.4). Extracranial hemorrhage was more likely with aspirin plus clopidogrel vs. aspirin alone (1.4% vs. 0.3%; absolute risk increase = 1.1%; number needed to harm = 91; RR = 4.8; 95% CI, 2.2 to 10.6), whereas the risk of intracranial hemorrhage was not statistically different (RR = 1.3; 95% CI, 0.6 to 2.9). The risk of hemorrhage in both groups significantly increased after three months of therapy.

CLOPIDOGREL PLUS ASPIRIN VS. ASPIRIN ALONE AFTER ISCHEMIC STROKE OR TIA

Benefits	Harms
1 in 40 had a reduced stroke recurrence	1 in 91 had a major extracranial hemorrhage
2.5% reduction in stroke recurrence	1.1% increase in major extracranial hemorrhage

TIA = transient ischemic attack.

Caveats: The Cochrane review had several limitations. Most data concerning aspirin plus clopidogrel vs. aspirin alone came from a single trial conducted in China (CHANCE [Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events]).[3] However, exclusion of this study did not significantly change the primary or secondary outcomes. Several studies reported data from before 2010, and stroke care has significantly changed since then.[4] Only three studies reported on intracranial hemorrhage, and only two reported on extracranial hemorrhage.[3,6-9] Four trials included patients with TIA or nondisabling stroke (3 points or greater on the National Institutes of Health Stroke Scale), and one trial included strokes regardless of severity.[3,6-9] Other adverse outcomes, such as myocardial infarction, were reported in only a few studies.

The NNT Group Rating System

Green	Benefits greater than harms
Yellow	Unclear benefits
Red	No benefits
Black	Harms greater than benefits

Another significant consideration is that the results apply to atherothrombotic and not cardioembolic strokes. Finally, duration of therapy is an important consideration. Included patients received at least one month of antiplatelet therapy, and follow-up was three months in most studies.

Broadly, the Cochrane review found that a strategy of initiating multiple antiplatelet agents within 72 hours of the event compared with a single agent reduced stroke in the short term but increased the risk of major hemorrhage.[5] This finding is consistent with results from trials that added clopidogrel to aspirin.[3,6-9]

Conclusion: Based on the evidence, we have assigned a recommendation of green (benefit outweighs harm) for the use of aspirin plus clopidogrel vs. aspirin alone after atherothrombotic ischemic stroke or TIA. Although further study is needed, the CHANCE trial suggests that a duration of 21 days to one month is appropriate.[3] Further data are needed to better evaluate adverse events, cardioembolic events, and specific durations of therapy.

This series is coordinated by Christopher W. Bunt, MD, *AFP* assistant medical editor, and Daniel Runde, MD, from the NNT Group.

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