Review: Aspirin reduces the risk for stroke in patients with previous TIA or stroke but does not have a dose–response effect

Johnson ES, Lanes SF, Wentworth CE 3d, et al. **A metaregression analysis of the dose-response effect of aspirin on stroke.** Arch Intern Med. 1999 Jun 14;159:1248-53.

QUESTION

In patients with a previous transient ischemic attack (TIA) or stroke, does a dose–response relation exist for aspirin use and the risk for stroke?

DATA SOURCES

Studies were identified by searching MEDLINE (to April 1996) and by scanning reference lists of relevant articles.

STUDY SELECTION

Studies were selected if they were randomized, placebo-controlled, secondary prevention trials that included a comparison of aspirin alone and reported stroke as an outcome.

DATA EXTRACTION

2 reviewers extracted published data on demographics, inclusion and exclusion criteria, treatment regimen, duration of follow-up, and all strokes (ischemic and hemorrhagic). Another reviewer independently extracted data on outcomes, inclusion and exclusion criteria, and health status at entry.

MAIN RESULTS

11 randomized controlled trials met the selection criteria (9629 patients [5228 allocated to aspirin and 4401 to placebo], mean age 63 y, 63% men, mean follow-up 32 mo). 1391 strokes occurred. Aspirin doses ranged from 50 to 1500 mg/d. The combined results for all doses showed a benefit for aspirin in stroke (relative risk reduction 15%, 95% CI 6% to 23%). Results were similar after adjustment for study and length of follow-up. A linear regression model showed that no linear dose–response relation ($P > 0.2$) or quadratic dose–response relation ($P > 0.2$) existed for aspirin dose and the risk for stroke.

CONCLUSIONS

In patients with a previous transient ischemic attack or stroke, aspirin reduces the risk for stroke. No dose–response relation exists for aspirin doses between 50 and 1500 mg/d and the risk for stroke.

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COMMENTARY

The optimal dose of aspirin for prevention of stroke has been a long-standing controversy. Some neurologists believe that the most effective dose of aspirin to prevent stroke is higher than that for prevention of myocardial infarction. Although debated ad nauseum in recent years, the issue has risen again with the results of the European Stroke Prevention Study II, which showed that high-dose dipyridamole enhanced the protective effect of low-dose aspirin (i.e., 25 mg twice daily) (1). This combination was recently approved by the U.S. Food and Drug Administration (FDA) for secondary prevention of stroke and will be marketed soon by Boehringer Ingelheim (who sponsored this metaregression analysis by Johnson and colleagues). Whether the combination of high-dose dipyridamole and low-dose aspirin is considered superior to aspirin alone depends in large part on whether it is accepted that the dose of aspirin has no important effect on stroke prevention.

Johnson and colleagues report a sophisticated biostatistical analysis based on indirect comparison of the results of 11 randomized clinical trials, including the European Stroke Prevention Study II, and conclude that the protective effect of aspirin on stroke is uniform across aspirin doses from 50 to 1500 mg/d. More convincing to me is the similar conclusion reached from considering the randomized clinical trials that directly compared ranging aspirin doses from 50 to 1200 mg/d and, most recently, the Aspirin and Carotid Endarterectomy trial (81 vs 325 vs 650 vs 1300 mg/d)(2; see next page). Although some have disputed the generalizability of the results of these direct randomized comparisons (3, 4), no persuasive evidence exists that higher doses of aspirin offer additional protection. In 1998, the FDA recommended aspirin doses between 50 and 325 mg/d for secondary prevention of stroke.

For prevention of stroke in patients with TIA and previous ischemic stroke, consensus on aspirin doses ≤ 325 mg/d is emerging. Is aspirin alone the best available antiplatelet prophylaxis? Clopidogrel (congener of ticlopidine without its toxicity) and high-dose dipyridamole have also been shown to be efficacious (see the critical, balanced, recent reviews by Gorelick and colleagues [5] and Wilterdink and Easton [6]). Aspirin remains the mainstay, but the era of combined antiplatelet therapies using aspirin with such agents as clopidogrel or dipyridamole for secondary prevention of stroke is on the near horizon, pending confirmatory evidence from ongoing clinical trials.

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