A Metaregression Analysis of the Dose-Response Effect of Aspirin on Stroke

Eric S. Johnson, MPH; Stephan F. Lanes, PhD; Charles E. Wentworth III, MS; Margaret H. Satterfield, MSN; Bethlehem L. Abebe, BA; Linda W. Dicker, PhD

Background: We evaluated whether the risk of stroke depends on aspirin dose in patients with a previous transient ischemic attack or stroke.

Methods: We conducted a metaregression analysis of stroke by using published randomized, placebo-controlled trials. We analyzed studies of patients who had recently had a transient ischemic attack or stroke (ie, secondary prevention). We abstracted data on the treatment regimen and stroke. To evaluate the dose-response relationship, we conducted a metaregression analysis of study-specific risk ratios by means of weighted linear regression.

Results: Eleven randomized, placebo-controlled trials contributed a total of 5228 patients randomized to aspirin only and 4401 patients randomized to placebo only. The slope of the dose-response curve was virtually flat across a wide range of aspirin doses from 50 to 1500 mg/d (P = .49 for test of slope ≠ 0). Summarizing across studies, aspirin decreases the risk of stroke by about 15% (risk ratio, 0.85; 95% confidence interval, 0.77-0.94).

Conclusions: Aspirin reduces the risk of stroke by approximately 15%, and this effect is uniform across aspirin doses from 50 to 1500 mg/d. The lowest effective aspirin dose has not yet been identified, but it could be lower than 50 mg/d.

Experts disagree about the optimal aspirin dose in preventing stroke. Patrono and Roth1(p756) claim that “good clinical practice should dictate the use of the lowest dose of aspirin shown effective in the prevention of stroke and death in patients with ischemic cerebrovascular disease, i.e., 75 mg daily.” Barnett et al16(p936) believe otherwise: “We postulate that the evidence is uncertain and available only from indirect comparisons but that it leans toward the moderate- to higher-dose regimens.”

Disagreement is common in the absence of sound scientific data, but it is surprising that controversy about the appropriate aspirin dose persists despite numerous randomized controlled trials. Individual studies may be inconclusive, at least in part, because the studies are small and stroke is rare. Consequently, few studies report statistically significant reductions in stroke. Some studies report statistically significant benefits of aspirin only when stroke is combined with myocardial infarction (MI).3-11 This strategy is not directly informative about stroke, however, because combining stroke with MI could produce a statistically significant reduction in risk of the combined outcome, even if aspirin were reducing only the risk of MI.

Small studies of rare events lend themselves to meta-analyses, and several quantitative reviews have attempted to summarize the available data.12-18 Several of the meta-analyses evaluated combined outcomes (ie, vascular events), instead of stroke alone.12,14,16 Three of the meta-analyses specifically evaluated stroke risk reduction in trials that compared aspirin with placebo, and all of them found a modest protective effect of aspirin therapy (risk reduction ranged from 11% to 17%).15,17,18 Only the meta-analysis by Barnett and colleagues18 evaluated the dose-response relationship between aspirin and stroke: risk reduction was comparable for low-dose aspirin (75-300 mg/d) and high-dose aspirin (900-1300 mg/d) —15% and 11%, respectively, with no evidence of heterogeneity between dose groups. Since Barnett and colleagues published their meta-analysis18 in 1995, another trial has been published: the European Stroke Prevention Study 2,19 which essentially doubles the amount of statistical informa-
Patients participating in randomized controlled trials of secondary stroke prevention had a mean age of 63 years, were 63.3% male, and were followed up for an average of 32 months (Table 1). The 11 studies contributed 9629 patients to the analysis: 5228 randomized to aspirin only and 4401 randomized to placebo only. In these 9629 patients, 63.3% were male, and were followed up for an average secondary stroke prevention had a mean age of 63 years, and were followed up for an average of 32 months (Table 1). The 11 studies contributed 9629 patients to the analysis: 5228 randomized to aspirin only and 4401 randomized to placebo only. Patients with stroke. Stroke was diagnosed at least partly on the basis of symptoms, with most of the studies requiring symptoms of at least 24 hours' duration.

We abstracted data on demographics, inclusion and exclusion criteria, treatment regimen, duration of follow-up, and stroke. We abstracted only published data. A few studies included treatment arms in addition to those of interest for this analysis (eg, aspirin plus other antiplatelet medication), but we abstracted data only from aspirin-only and placebo-only treatment arms.

We sought detailed information on the number of participants with stroke. The number of participants with stroke was reported at least partly on the basis of symptoms, with most of the studies requiring symptoms of at least 24 hours' duration.

We abstracted information from the studies to conduct an intention-to-treat metaregression analysis, the primary analysis in most of the published studies. Accordingly, outcome data represent the number of people experiencing an outcome of interest among all randomized subjects, although one study appeared to report only the number of events. Study protocols varied regarding follow-up of individuals. Most studies attempted to follow up all subjects for the duration of the study regardless of whether they experienced an event of interest or withdrew for another reason; other studies discontinued follow-up after withdrawal or after subjects experienced certain end points. We included events that occurred after study withdrawal or medication discontinuation whenever they were reported.

Of the 11 studies analyzed, 10 included only subjects who had a history of at least 1 recent transient ischemic attack (TIA) or stroke. Subjects in the remaining study were required to have had a previous TIA, stroke, or retinal artery occlusion; 94% of the patients in both the aspirin and placebo arms had had a previous TIA or stroke. Consequently, we considered all 11 studies secondary prevention trials.

We estimated risk ratios (RRs) by reconstructing contingency tables based on the number of patients randomized and the number of patients experiencing events. We first computed RRs and 95% confidence intervals for each study separately. We used the width of the confidence interval to evaluate the precision of the effect estimate. We examined study-specific data graphically for apparent heterogeneity across studies, and we also tested formally with the direct pooling method. Summary effect estimates adjusted for study with the Mantel-Haenszel estimator and 95% confidence intervals were calculated with Stata software (Release 5.0; Stata Corporation, College Station, Tex).

We used weighted least-squares linear regression to evaluate variation between studies, to model the RR as a function of aspirin dose in milligrams, to test for trends, and to graph the predicted dose-response curve. The dependent variable for the regression was the natural log of each study-specific RR for stroke (or, equivalently, the percentage risk reduction [1 — RR]), weighted by the inverse of its variance. The aspirin dose for each study was then treated as a continuous, independent variable. The coefficient of the aspirin term in the regression model estimates the slope of the linear aspirin-stroke dose-response effect. Solving the regression equation estimates the percentage risk reduction in stroke predicted at any given dose of aspirin therapy (in milligrams). We also explored the possibility of a quadratic relation by adding a squared term to the model. To explore the possibility of a dose-response relation more complex than a quadratic relation, we fit a cubic spline regression model. Stata was used for all regression analyses.

The results of the linear regression model (Table 3) confirmed the visual impression of the data (Figure): there is no linear dose-response effect of aspirin therapy on stroke risk reduction. In other words, the RR (or equivalently, the percentage risk reduction) is invariant across the range of aspirin doses used in the trials. The coefficient for the aspirin term in the regression model is the natural logarithm of the change in percentage risk reduction for each 1-mg increase in aspirin dose. For example, an increase in aspirin dose from 50 mg/d to 1200...
mg/d would translate into an 8% smaller risk reduction for stroke (e\(^{-0.000068}\)3\(^{1150} - 1 = 8\%), although the confidence interval for the aspirin coefficient shows that the data are reasonably compatible with a range of nearly flat dose-response curves. We found no evidence of a linear dose-response trend (\(P = .49\)), or a quadratic dose-response trend (\(P = .85\)).

In addition to the metaregression analysis, we conducted a stratified Mantel-Haenszel analysis to evaluate between-study variation. The formal test of homogeneity across the 11 studies confirmed the visual impression of the Figure, ie, that the RRs are similar across studies (directly pooled test, \(P = .23\)). Therefore, we computed a Mantel-Haenszel summary RR across all studies. The overall effect estimate for any aspirin dose is reasonably precise and corresponds to a risk reduction of about 15% (95% confidence interval, 6%-23%). We adjusted the summary RR for study—analogous to adjusting for clinical center in a multicenter trial—although this did not alter the results appreciably. Controlling for duration of follow-up did not affect the results substantially.

Because there is so little information on aspirin doses greater than 300 mg/d and less than 990 mg/d, attempts to smooth these data by means of curves drawn by a cubic spline regression model (with a range of bands) produced biologically implausible wave-shaped curves that suggest overfitting of the available data (cubic spline not shown). That is, the trial at 650 mg/d was the only data point in the range greater than 300 mg/d and less than 990 mg/d, so the cubic spline produced a line that dipped downward to include the RR of 0.21 for the 650-mg/d trial.

We conducted this metaregression analysis of 11 randomized, placebo-controlled trials of aspirin therapy in patients with previous TIA or stroke to evaluate whether the risk of stroke depends on the dose of aspirin. Evaluation of dose response is an established application of metaregression analysis.\(^{30}\) Across a broad range of aspirin doses, from 50 to 1500 mg/d, the RR for stroke, based on the regression analysis and the stratified analysis, is essentially uniform.
least aspirin dose ever compared with placebo in stroke prevention. Inclusion of the 50-mg/d trial adds considerable information regarding effects of low-dose aspirin and increases the precision of the risk reduction estimate as compared with earlier meta-analyses of secondary prevention trials.\textsuperscript{16,18} The results strengthen the evidence of the effectiveness of aspirin in reducing the risk of stroke by approximately 15%, and show an absence of additional risk reduction with higher doses of aspirin.

Opinion in the scientific literature is divided on whether there is a dose-response effect of aspirin on the risk of stroke. In 1993, Barnett and colleagues\textsuperscript{18} stressed the findings of the North American Symptomatic Carotid Endarterectomy Trial in recommending a daily dose of at least 650 mg for secondary stroke prevention. Barnett and colleagues\textsuperscript{'s} other reasons for not recommending a lower dose of aspirin were that aspirin's antiplatelet effects may be incomplete in some patients at lower doses and, further, that complications of aspirin therapy, such as gastrointestinal tract and cerebral hemorrhage, are not related to dose.\textsuperscript{18}

In 1992, Dyken and colleagues\textsuperscript{31} argued that several studies identified a large risk reduction for stroke in patients taking at least 975 mg of aspirin per day, but that there was no evidence from secondary prevention trials that doses as low as 300 mg/d offered a statistically significant benefit. Dyken and colleagues\textsuperscript{31} explained that the initial recommendation for using lower doses was based on the first meta-analysis by the Antiplatelet Trialists' Collaboration,\textsuperscript{32} which was not specific to stroke, aspirin, or secondary prevention, and therefore may not have been applicable to the clinical decision to use aspirin therapy in patients with a high risk of stroke. The pharmacological argument for low-dose aspirin was based on a surrogate marker: doses as low as 40 mg/d had been shown to inhibit platelet aggregation, so low-dose aspirin should also prevent stroke.\textsuperscript{31} Until the publication of the European Stroke Prevention Study 2, however, proponents of low-dose aspirin therapy lacked data on stroke events from a placebo-controlled trial that included such low doses.

Previous meta-analyses did not identify a dose-response relationship between aspirin and stroke.\textsuperscript{12,14,16,18} However, with the exception of the meta-analysis by Barnett and colleagues,\textsuperscript{18} these meta-analyses were not specific to stroke; all vascular events (combined) served as the outcome measure. Barnett and colleagues' meta-analysis showed a very similar reduction of risk of stroke for both high-dose and low-dose aspirin, although they did not interpret these results as evidence against a dose-response effect.\textsuperscript{18} Instead, they stressed the lack of statistical significance of each dose-specific estimate. The other 3 meta-analyses that evaluated the dose-response relationship between aspirin and vascular events found that the risk reduction was comparable across doses of aspirin.\textsuperscript{12,14,16}

The dose-response effect for adverse events is an important consideration in the clinical decision regarding choice of aspirin dose. Those who support moderate- to high-dose aspirin for secondary stroke prevention cite literature suggesting no dose-response effect between aspirin and gastrointestinal tract hemorrhage and cerebral hemorrhage.\textsuperscript{2,18} Those in favor of low-dose aspirin cite literature suggesting an increased risk of milder gastrointestinal tract toxic effects with increasing dose.\textsuperscript{1,33} The United Kingdom Study Group found that patients randomized to 1200 mg/d were more likely to have both gastrointestinal tract symptoms and gastrointestinal tract hemorrhage than were patients randomized to 300 mg/d.\textsuperscript{11} Two meta-analyses have also suggested that high-dose aspirin results in an increased risk of milder gastrointestinal tract toxic effects (ie, gastrointestinal tract symptoms).\textsuperscript{14,34} One of the meta-analyses\textsuperscript{14} did not identify an increased risk of major gastrointestinal tract toxic effects (ie, gastrointestinal tract hemorrhage) with higher aspirin doses; the other meta-analysis\textsuperscript{33} identified a slightly increased risk of major gastrointestinal tract toxic effects with higher aspirin doses, although the estimate was quite imprecise. Overall, there is considerable evidence of a dose-response effect for mild gastrointestinal tract toxic effects (ie, symptoms). While this dose-response effect may apply to more serious gastrointestinal tract toxic effects (eg, bleeding), the current evidence is limited because serious gastrointestinal tract toxic effects are rare.

Given equal efficacy for stroke prevention across doses, the dose-response effect for milder gastrointestinal tract toxic effects, and its implications for adherence to therapy,\textsuperscript{14} the clinical decision would seem to lean toward low-dose aspirin. However, Barnett and colleagues' argued that the existing data are insufficient to
guide clinical decision making because no single trial has tested low-dose (30 to 80 mg) vs high-dose (650 to 1300 mg) aspirin. In the absence of data from a single trial with both low-dose and high-dose aspirin regimens, Barnett and colleagues recommended high-dose aspirin because it may offer a theoretical advantage to some patients whose platelets are not completely inhibited by lower doses. A recommendation for high-dose aspirin was more defensible before the publication of the European Stroke Prevention Study 2, when the clinical benefit of low-dose aspirin for stroke alone had not been demonstrated so clearly. We now see that the stroke risk reduction from high-dose trials is no larger than that from low-dose trials. Apparently, the more complete platelet inhibition associated with higher doses of aspirin does not translate into more impressive stroke risk reduction.

Limitations of individual studies also carry forward to this meta-analysis. Lack of adherence with assigned therapy will mask the true effect of actually taking aspirin (compared with assignment to take aspirin). If patients were less adherent at higher doses, as a result of more frequent gastrointestinal tract symptoms, for instance, then an intent-to-treat analysis would not necessarily show the biological effect of high-dose aspirin; the observed RR would be closer to the null value (ie, RR = 1.0). From a pragmatic standpoint, if patients were less adherent at higher doses, dose would be an important determinant of its effectiveness. If the high-dose aspirin trials conducted to date have been unable to demonstrate large reductions in stroke risk (ie, >15%), then it seems unlikely to expect such benefits in routine clinical practice where adherence to therapy is less carefully monitored.

Another potential limitation of our meta-regression analysis is the “indirect” evaluation of the dose-response effect. Because of the need to maintain each study as a distinct analytical unit, it was not possible for our metaregression analysis to compare directly the effects of different aspirin doses and to simultaneously maintain comparability of treatment groups. Instead, we compared each dose group with its placebo group, and compared RR estimates across studies. Our metaregression analysis might have missed a dose-response relationship (in which high-dose aspirin is more effective) if patients who participated in trials with low-dose aspirin were more responsive to aspirin (because of their baseline characteristics) than patients who participated in high-dose trials. However, we are unaware of any baseline characteristic that differed between patients who participated in low-dose vs high-dose secondary stroke prevention trials. Moreover, the one trial that directly compared high-dose and low-dose aspirin therapy, the United Kingdom Transient Ischemic Attack trial, found an identical risk of stroke in both the 1200-mg/d arm and the 300-mg/d arm (both 12.4%), which lends support for the findings in our metaregression analysis.

The Antiplatelet Trialists’ Collaboration meta-analysis reported a larger effect of aspirin (ie, 25% odds reduction) than did our meta-analysis. One reason that our effect estimate is smaller is that they combined stroke with MI and vascular death in reporting a primary outcome called “vascular events.” In contrast, our outcome was stroke alone. Since aspirin has a greater effect on MI than on stroke, grouping stroke with MI produces an effect estimate (eg, RR) for the combined outcome that is intermediate in value between the effect estimates for each of the individual outcomes. Therefore, effect estimates for combined outcomes that include MI are greater than effect estimates for stroke alone.

Another reason that the effect of aspirin reported herein is smaller than the Antiplatelet Trialists’ Collaboration effect estimate relates to the measure used to assess effects. Their meta-analysis used odds ratios to estimate the effect, whereas we used RRs. In general, odds ratios exaggerate the true effect as the risk of the outcome increases. This bias is negligible when risks are small (ie, <10%). Risks of combined outcomes, however, are not necessarily small, especially in high-risk populations such as patients with previous TIA or stroke, among whom the risk of stroke alone may be greater than 10%. For example, in our meta-analysis, the overall odds ratio (Mantel-Haenszel) for vascular events is 0.82; the RR (Mantel-Haenszel) for the same outcome is 0.86. While both effect estimates have the same qualitative interpretation, namely that aspirin prevents vascular events, the odds ratio suggests a risk reduction of 18%, whereas the RR indicates that the risk reduction is actually 14%.

In conclusion, existing randomized studies provide reasonably precise estimates of the effects of aspirin dose on stroke: the risk reduction of 15% is uniform across a wide range of doses (30-1500 mg/d). The absence of a dose-response relationship supports the use of low-dose aspirin, because low-dose aspirin may minimize the risk of milder gastrointestinal tract toxic effects. The lowest effective aspirin dose has not yet been identified, but could be lower than 50 mg/d.

Accepted for publication October 22, 1998.

This study was funded through a contract with Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Conn.

Reprints: Eric S. Johnson, MPH, Epidemiology Resources Inc, One Newton Executive Park, Newton Lower Falls, MA 02162 (e-mail: epidemiol@aol.com).

REFERENCES