A metaregression analysis of the dose-response effect of aspirin on stroke
Johnson E S, Lanes S F, Wentworth C E, Satterfield M H, Abede B L, Dicker L W

Authors' objectives
To assess the effect of aspirin dose on the risk of stroke.

Searching
The authors searched the MEDLINE electronic database (dates and search terms not stated). The authors also searched reference lists of retrieved articles for additional relevant studies. The search was limited to studies published prior to April 30, 1996.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) which were placebo-controlled and included an aspirin-only treatment arm. Included studies also had to report the occurrence of stroke alone. Follow-up ranged from 24 to 48 months (average 32 months).

Specific interventions included in the review
Aspirin (50 to 1500 mg/day) and placebo.

Participants included in the review
Patients with a previous transient ischemic attack or stroke. The mean age of participants was 63 years (range 59 to 73 years) and were 63.3% male.

Outcomes assessed in the review
Stroke-risk reduction. Stroke was diagnosed at least partly on the basis of symptoms, with most of the studies requiring symptoms of at least 24 hours duration.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The data were extracted by two of the authors using standardised forms. For quality control, a third author reabstracted data on outcomes, inclusion and exclusion criteria, and health status.

Data were abstracted for the categories of: demographics, inclusion and exclusion criteria, treatment regimen, duration of follow-up, and stroke.

Data were abstracted for published data only.

The authors first computed risk ratios (RRs) and 95% confidence intervals (CIs) for each individual study.

Methods of synthesis
How were the studies combined?
Pooled effects estimates, adjusted for study, were calculated using the Mantel-Haenszel method with 95% confidence intervals (CIs).

The authors then used weighted least-squares 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 meta-regression was done on an intention-to-treat basis.

The authors 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, the authors fit a cubic spline regression model.

How were differences between studies investigated?
The authors examined study-specific data graphically for apparent heterogeneity across studies and also tested heterogeneity formally with a direct pooling method (see Rothman, in Other Publications of Related Interest no.1).

Results of the review
Eleven RCTs were included in the review with 9,629 participants (5,228 randomised to aspirin only and 4,401 randomised to placebo only).

The linear regression model confirmed that there is no linear dose-response trend ($P = 0.49$) or a quadratic dose-response trend ($P = 0.85$) of aspirin therapy on stroke risk-reduction.

The stratified Mantel-Haenszel test for heterogeneity confirmed that the RRs were similar across studies (directly pooled test, $P = 0.23$).

The pooled RR across studies for any aspirin dose gave a risk reduction of 15% (95% CI: 6%, 23%).

Adjusting the RR for study and for length of follow-up did not affect the results substantially.

Authors' conclusions
The authors state that across a broad range of aspirin doses, from 50 to 1500 mg/day, the RR for stroke, based on the regression analysis and the stratified analysis, is essentially uniform. Further, 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. The lowest effective aspirin dose has not yet been identified, but could be lower than 50 mg/day.

CRD commentary
The authors have stated their research question and some inclusion and exclusion criteria. The literature search was limited and may have missed additional studies because only published data were included in the review, only one database was searched. It is also not clear whether there were any language limitations on the search. The authors do not report who, or how many of the authors, performed the selection of studies. The authors do report on the process of data extraction but there is no assessment of validity for the included studies.

The studies were compared using regression analysis. There were calculations to determine the effects of the heterogeneity on the review conclusions. The authors state several methodological limitations in the included studies such as:

1. A possible lack of adherence to treatment by participants.

2. The indirect evaluation of the dose-response effect through the use of metaregression analysis.

The authors conclusions appear to follow from the results but these should be viewed with caution because of the methodological limitations in the process of the review.

Implications of the review for practice and research
Practice: The authors state that the absence of a dose-response relationship supports the use of a low-dose aspirin, because low- dose aspirin may minimise the risk of milder gastrointestinal tract toxic effects.

Research: The authors do not state any implications for research.
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Other publications of related interest

These additional published commentaries may also be of interest.

Hart R. Review: aspirin reduces the risk for stroke in patients with previous TIA or stroke but does not have a dose-response effect. ACP J Club 2000. Available at:
http://pmmp.cnki.net/Resources/CDDPdf/evd%5Cbase%5CACP%20Journal%20Club%5C%E7%B3%BB%E7%BB%9F%E8%AF%84%E4%BB%B7%5CACPJC-2000-132-1-009.pdf [accessed July 2014]

Hart R. review: aspirin reduces the risk for stroke in patients with previous transient ischaemic attack or stroke but does not have a dose-response effect. Evid Based Med 2000;5:9.

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Aspirin /administration & dosage; Cerebrovascular Disorders /prevention & control; Dose-Response Relationship, Drug; Female; Fibrinolytic Agents /administration & dosage; Humans; Linear Models; Male; Middle Aged; Odds Ratio; Platelet Aggregation Inhibitors /administration & dosage; Randomized Controlled Trials as Topic; Risk

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.