
Is there an association between aspirin dosing and cardiac and bleeding events after treatment of acute coronary syndrome? A systematic review of the literature

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CRD summary

This review concluded that the only difference between high-dose and low-dose aspirin in patients being treated for acute coronary syndrome was increased major bleeding with a higher dose in patients receiving medical therapy. The authors indirectly compared populations for whom the baseline risks were uncertain; therefore the reliability and applicability of their conclusions based on these comparisons is uncertain.

Authors' objectives

To assess the clinical outcomes in patients with acute coronary syndrome following coronary stent insertion, coronary artery bypass grafting, or medical treatment.

Searching

PubMed, EMBASE, Current Contents and The Cochrane Library were searched without language restrictions from 1970 to February 2010; search strategies were reported. Reference lists of reviews were scanned.

Study selection

Controlled trials and observational studies that assessed the efficacy and safety of a maintenance dose of aspirin (with or without adenosine diphosphate inhibitors) in patients with acute coronary syndrome who underwent coronary stent insertion, coronary artery bypass grafting or medical treatment, were eligible for inclusion.

Most included patients received an adenosine diphosphate inhibitor, primarily clopidogrel. The age of patients ranged from 52 to 69 years; almost 75% were men (where reported). Both bare-metal and drug-eluting stents were used across the studies. Nearly 60% of patients who underwent stent insertion had hypertension and 25% had diabetes. Comorbidity was less well reported in those who underwent medical therapy, but (where reported) 40% had hypertension and 16% had diabetes.

Two reviewers independently selected studies for the review.

Assessment of study quality

The quality of the randomised controlled trials (RCTs) was evaluated using the Jadad scale.

The authors did not state how many reviewers assessed study quality.

Data extraction

The numbers of patients experiencing a range of cardiovascular outcomes and mortality were extracted by two independent reviewers.

Methods of synthesis

The mean proportion of patients across study arms experiencing each outcome for each aspirin dose was calculated along with 95% confidence intervals (CI) using a random-effects model. Aspirin dose was classified for the analysis as low (75 to 149/159mg), high (150/160 to 325mg) or very high (over 325mg). Where the dose administered fell into more than one category, the category into which most patients fell was used; if this could not be established, it was excluded. The authors stated that heterogeneity was investigated where observed and was assessed using X^2 and I^2 .

Outcomes for patients undergoing stent implantation and medical therapy were presented separately. The authors stated that there was insufficient data to analyse patients who had undergone coronary artery bypass grafting.

Meta-regression was used to adjust for age, publication date, gender and aspirin dose.

Results of the review

Sixty-eight studies using stent insertion and 68 using medical therapy met the inclusion criteria for the review; the proportion of overlap between these studies was unclear. Of the 68 studies using stent insertion, 43 were RCTs; 24 of these scored 3 or more on the Jadad scale. Of the 68 studies using medical therapy, 61 were RCTs; 49 of these scored 3 or more on the Jadad scale. The remaining studies were cohort studies, case-control studies or case series.

Stent insertion (113 treatment arms; 81,807 patients): There were no significant differences between low-dose and high-dose aspirin for major adverse cardiovascular events or for major bleeding at any time point, even when meta-regression was used to adjust for predictive variables.

Medical therapy (111 treatment arms; 207,523 patients): When adjusted for prognostic variables, the incidence of major bleeding was significantly (7 percentage points) higher at one month in those who received a high dose of aspirin. There was no significant difference between low-dose and high-dose aspirin for any other outcome at any time point, even when meta-regression was used to adjust for predictive variables.

Authors' conclusions

There were no differences in clinical outcomes between high-dose and low-dose aspirin after stent implantation or with medical therapy. High-dose aspirin may be associated with a higher rate of major bleeding in patients during medical therapy.

CRD commentary

The review addressed a clear research question supported by broad but reproducible inclusion criteria. Relevant sources were searched without language restrictions. However, there was no attempt to identify unpublished studies, which may have been beneficial given the lack of RCTs randomising on aspirin dose. The review process was conducted in duplicate, reducing the potential for error and bias.

The authors seemed to have derived cohorts from the treatment arms of the RCTs that did not randomise on the aspirin dose. Baseline characteristics were not available for individual studies, which made it difficult to assess the evidence base. The authors acknowledged that there was substantial clinical heterogeneity across the treatment arms. The comparability of the populations who underwent stent insertion or received medical therapy, or between the different aspirin doses within these populations, was uncertain; baseline characteristics seem to be poorly reported and unavailable for a large proportion of the study arms. Therefore, it was unclear whether indirect comparisons between these groups were appropriate. Two of the authors were employees of AstraZeneca (who also funded the review), so there was a potential conflict of interests.

Given these limitations, the reliability and generalisability of the conclusions drawn based on these comparisons is uncertain.

Implications of the review for practice and research

The authors did not state any implications for practice or research.

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