Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis

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CRD summary
The authors concluded that aspirin resistance adversely affects clinical outcomes in patients with cardiovascular disease, whether aspirin is used alone or with another antiplatelet agent. These conclusions appear to be supported by the data presented, but poor reporting of review methods, differences between the studies and possible publication bias mean that they should be treated with some caution.

Authors' objectives
To investigate the relationship between aspirin resistance and clinical outcomes in patients with cardiovascular disease.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane CENTRAL Register were searched from inception; the search terms were reported. The reference lists of relevant articles retrieved by the search were also examined. Studies reported in foreign languages were translated.

Study selection
Study designs of evaluations included in the review
Prospective studies in which investigators were blind to the patients' aspirin sensitivity or resistance status were eligible for inclusion.

Specific interventions included in the review
Studies that evaluated antithrombotic aspirin therapy, either alone or in combination with other antiplatelet treatments, were eligible. The included studies reported on aspirin (generally at a dose of 75 to 325 mg/day), either alone or with a loading dose of clopidogrel and/or tirofiban hydrochloride or glycoprotein IIb/IIIa.

Participants included in the review
Eligible studies included patients with cardiovascular disease whose aspirin resistance status had been determined by platelet function assay. Aspirin-sensitive patients were defined as those in whom platelets responded as expected to aspirin therapy and in whom platelet function (however defined) was inhibited. Aspirin-resistant patients were defined as those in whom agonist-induced platelet response was not inhibited by aspirin as expected. Several platelet function assays were considered equally acceptable. However, studies that evaluated only the inhibition of thromboxane A2 (thromboxane B2) levels were excluded. The participants in the included studies had a history of stroke, acute coronary syndrome, coronary arterial bypass grafting, percutaneous coronary intervention, stable cardiovascular disease or peripheral vascular disease. A variety of platelet function assays were used in the included studies.

Outcomes assessed in the review
Studies that reported clinical mortality or morbidity were eligible for inclusion. The included studies reported any fatal or nonfatal cerebrovascular event, death, specific cardiovascular or cerebrovascular events, acute coronary syndrome, and/or failure of vascular intervention. The review also reported the prevalence of aspirin resistance, the characteristics of aspirin-resistant patients, dose and response, and the effect of concomitant antiplatelet therapy.

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

Assessment of study quality
Quality was scored from A (low risk of bias) to D (unable to ascertain risk of bias due to inadequate reporting). The following features were assessed: whether the study was blinded with respect to aspirin resistance status and clinical outcome and whether compliance with blinding was assessed; and whether sufficient information was reported to assess
quality. It is unclear whether other criteria were assessed. The authors did not state how the validity assessment was performed.

**Data extraction**
All authors extracted the data from primary studies. The authors did not state whether they worked independently, or how any discrepancies were resolved. Where possible, attempts were made to contact original authors for verification of the extracted data. Data were extracted as the numbers with each outcome in each group, with odds ratios (ORs) and 95% confidence intervals (CIs) for each study.

**Methods of synthesis**
**How were the studies combined?**
Studies were meta-analysed to obtain a pooled OR with 95% CI using a fixed-effect model (level of significance, \( p<0.05 \)). Potential publication bias was assessed using a funnel plot.

**How were differences between studies investigated?**
Heterogeneity was assessed using the I-squared test, followed by the Q test where I-squared was greater than 50%. Sensitivity analyses were conducted to assess the effect of platelet function assay, aspirin dose and the inclusion of a secondary platelet inhibitor. The dose-response relationship was explored using mixed random-effects and fixed-effect meta-regression analysis and Egger’s regression test.

**Results of the review**
Twenty studies (\( n=2,930 \)) were included. The tables listed one randomised controlled trial (RCT; \( n=71 \)), one case-control study (\( n=28 \)), 17 prospective cohort studies (\( n=2,542 \)), and one prospective descriptive study (\( n=289 \)). However, the text stated that no RCTs were included.

Most of the studies (17 out of 20) were graded A for quality. Three studies reported insufficient information to ascertain the risk of bias. However, the results of these 3 studies were consistent with the overall findings of the other 17 studies. Compliance with treatment was reported in 17 of the 20 studies.

**Prevalence of aspirin resistance and characteristics of aspirin-resistant patients.**
Overall, 28% of patients were classified as aspirin resistant (810 out of 2,930). Resistance was more prevalent in women (\( p<0.01 \)) (n approximately 1,460) and in patients with renal impairment (\( p<0.03 \)) (2 studies, \( n=268 \)).

**Clinical outcomes.**
Aspirin-resistant patients were at a significantly higher risk of any cerebrovascular event (20 studies, \( n=2,930 \); OR 3.85, 95% CI: 3.08, 4.80, \( p<0.001 \)), death (4 studies, \( n=728 \); OR 5.99, 95% CI: 2.28, 15.72, \( p<0.003 \)), acute coronary syndrome (9 studies, \( n=1,275 \); OR 4.06, 95% CI: 2.96, 5.56, \( p<0.001 \)), failure in vascular intervention (3 studies, \( n=420 \); OR 4.35, 95% CI: 2.26, 8.37, \( p<0.001 \)) and new cerebrovascular event (4 studies, \( n=340 \); OR 3.78, 95% CI: 1.25, 11.41, \( p<0.02 \)).

There was significant statistical heterogeneity associated with the outcome ‘any cerebrovascular event’ (I-squared 68.3%, \( p<0.001 \)). Most of the heterogeneity (I-squared 50.3%) derived from the 8 studies that used the whole blood platelet function analyser, which defined 33% of patients as aspirin resistant, in contrast to the 7 studies that used the rich plasma aggregation assay, which defined 16% of patients as aspirin resistant and had relatively higher odds of a cerebrovascular event in this group (OR 3.85, 95% CI: 2.5, 5.88, \( p<0.001 \)). There were insufficient data to assess the degree to which other platelet assays contributed to heterogeneity. Significant heterogeneity was also found for the analysis of acute coronary syndrome (I-squared 58.6%, no \( p \)-value reported).

**Dose response.**
There was no evidence of a dose-response relationship between aspirin resistance and any cardiovascular outcome, with or without secondary antiplatelet treatment.
Concomitant antiplatelet therapy.

Concomitant therapy with clopidogrel or tirofiban provided no benefit to patients identified as aspirin resistant. There was significant statistical heterogeneity associated with this analysis (I-squared 70.6%, p=0.004).

There was modest evidence of publication bias, with an absence of small studies that reported on a negative or no relation between aspirin resistance and adverse clinical outcomes.

Authors' conclusions
Compared with non aspirin-resistant patients, patients with cardiovascular disease who are aspirin resistant have a four-fold increased risk of adverse cardiovascular outcomes while taking aspirin. This risk is not reduced by currently used adjunctive antiplatelet agents.

CRD commentary
The review question was clear, several relevant sources were searched for eligible studies, and attempts were made to contact authors for missing data. However, some of the inclusion criteria were imprecise, the process used to assess validity was not reported clearly, and it was also unclear whether adequate steps were taken to minimise potential error and bias during the study selection and data extraction processes.

The meta-analysis of studies appears appropriate. Heterogeneity associated with the outcome ‘any cardiovascular event’ was assessed and possible reasons for it explored, but statistically significant heterogeneity associated with other outcomes was not discussed. There were some inconsistencies in reporting, for example between the text and table and in the discussion of publication bias. The authors' conclusions appear to be supported by the data presented, but poor reporting of review methods, clinical and statistical heterogeneity between the studies, and possible publication bias mean that these conclusions should be treated with some caution.

Implications of the review for practice and research
Practice: The authors stated that doctors should continue current practice in prescribing aspirin for long-term therapy to prevent adverse cardiovascular events in patients with cardiovascular disease. However, patients should be warned about the possible adverse effects of aspirin, which offset the benefits in the 16 to 30% of patients who are aspirin resistant.

Research: The authors stated that studies are needed to determine the most effective way of identifying patients who are non-responsive to aspirin.

Bibliographic details

PubMedID
18202034

DOI
10.1136/bmj.39430.529549.BE

Original Paper URL
http://www.bmj.com/content/336/7637/195

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Coronary Syndrome /epidemiology; Aspirin /therapeutic use; Cardiovascular Diseases /epidemiology; Death,
AccessionNumber
12008008057

Date bibliographic record published
01/04/2008

Date abstract record published
09/08/2008

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.