

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

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BMJ 2008;336:195-8
doi:10.1136/bmj.39430.529549.BE

ABSTRACT

Objective To determine if there is a relation between aspirin “resistance” and clinical outcomes in patients with cardiovascular disease.

Design Systematic review and meta-analysis.

Data source Electronic literature search without language restrictions of four databases and hand search of bibliographies for other relevant articles.

Review methods Inclusion criteria included a test for platelet responsiveness and clinical outcomes. Aspirin resistance was assessed, using a variety of platelet function assays.

Results 20 studies totalling 2930 patients with cardiovascular disease were identified. Most studies used aspirin regimens, ranging from 75-325 mg daily, and six studies included adjunct antiplatelet therapy. Compliance was confirmed directly in 14 studies and by telephone or interviews in three. Information was insufficient to assess compliance in three studies. Overall, 810 patients (28%) were classified as aspirin resistant. A cardiovascular related event occurred in 41% of patients (odds ratio 3.85, 95% confidence interval 3.08 to 4.80), death in 5.7% (5.99, 2.28 to 15.72), and an acute coronary syndrome in 39.4% (4.06, 2.96 to 5.56). Aspirin resistant patients did not benefit from other antiplatelet treatment. **Conclusion** Patients who are resistant to aspirin are at a greater risk of clinically important cardiovascular morbidity long term than patients who are sensitive to aspirin.

INTRODUCTION

The major controversy about aspirin therapy is why some patients do not benefit from such therapy and how they might be identified. Such patients have been labelled aspirin “resistant” and those who seem to benefit from aspirin as aspirin “sensitive.”¹⁻⁶ Little consistency exists about which measure should be used to identify patients who seem resistant to aspirin,¹⁻⁶ and few studies have assessed the effect of aspirin resistance on clinically important outcomes. We systematically reviewed studies of aspirin resistance and its effect on adverse cardiovascular outcomes.

METHODS

We searched four databases for studies on antiplatelet therapy from 1966 to the present (see bmj.com).

Of 36 573 identified papers, 210 remained after refining the searches to aspirin resistance and clinical outcome (see bmj.com for exclusions). Overall 20 of 57 papers independently reviewed met the inclusion criteria.^{w2 w3 w10-w13 w14-w20}

We included studies that met several criteria: (a) participants were receiving aspirin as an anti-thrombotic; (b) participants were classified prospectively for aspirin status before determining clinical outcome, or were grouped on the basis of clinical outcome and then classified for aspirin status (we considered patients to be aspirin sensitive if their platelets responded as expected to aspirin, and platelet function, however measured, was inhibited, and we considered patients to be aspirin resistant if their agonist induced platelet response was not inhibited by aspirin as expected); (c) allocation concealment was adequate (investigators were blinded to patients’ aspirin status); (d) a measure of prospective clinical outcome was used in both patient groups; and (e) patients receiving other antiplatelet treatment were included.

The platelet function assays we considered acceptable for inclusion were whole blood platelet function tests, light transmission platelet rich plasma platelet function tests, and bleeding time as a function of platelet haemostasis.

The papers reported on four primary outcomes: any cardiovascular or cerebrovascular event, death, acute coronary syndromes, and failure of vascular interventions.

Statistical analysis

We present the results as odds ratios with 95% confidence intervals. We considered a two tailed P value of less than 0.05 as significant. Calculations were done using the fixed effects model. Heterogeneity was assessed using the Q test. We determined the robustness of our findings by removing the most positive studies one at a time. Planned sensitivity analyses were assessment of the platelet function assays, dose of aspirin, and the inclusion of another platelet inhibitor. Potential publication bias was assessed by a funnel plot, and we used an Egger’s regression test to assess any dose related effect.⁷

This article is an abridged version of a paper that was published on bmj.com on 17 January 2008.

Cite this article as:
BMJ 17 January 2008, doi:
10.1136/bmj.39430.529549.BE

RESULTS

The systematic search identified 20 studies, totalling 2930 patients with cardiovascular disease. The studies included only prospectively collected data on a variety of vascular related diseases (see bmj.com). All but three studies were assessed as of A quality (low risk of bias).^{w10 w14 w20}

Thirteen studies reported on aspirin only as antiplatelet therapy, with daily doses ranging from 75-325 mg; one study used a daily dose of 500 mg three times daily, and six studies included a loading dose of clopidogrel (Plavix) or another antiplatelet inhibitor tirofiban, or both, as adjunct therapy.^{w15-w20}

Several assays were used to assess patients' aspirin status: measuring serum thromboxane A₂ in relation to platelet haemostasis,^{w6} a platelet or collagen adhesion assay,^{w13} platelet rich plasma aggregometry,^{w2 w4 w7 w15 w18 w20} whole blood platelet aggregometry,^{w1 w3 w5 w8 w9 w12 w14} or some combination or modification of these assays.^{w10 w13 w16 w17 w19}

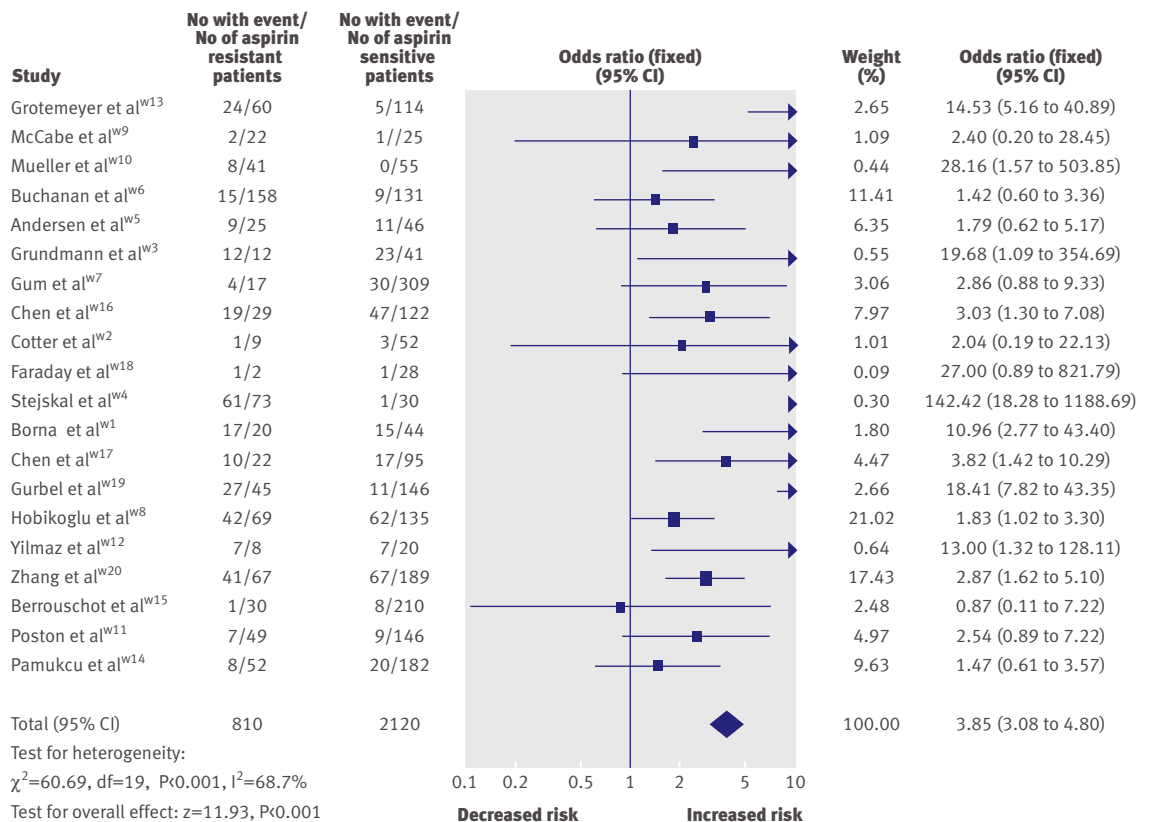
Overall, 2120 of the 2930 patients were classified as aspirin sensitive and the remaining 810 (28%) as aspirin resistant (see bmj.com for patients' characteristics). Aspirin resistance was less prevalent in men and higher in patients with previous renal impairment (P<0.001 and P<0.03).

All aspirin resistant patients, regardless of underlying clinical symptoms, were at a greater risk of death, acute coronary syndrome, failure in vascular intervention, or a new cerebrovascular event (table): 39% of

aspirin resistant patients compared with 16% of aspirin sensitive patients had a cardiovascular event (odds ratio 3.85, 95% confidence interval 3.08 to 4.80; P<0.001, figure). The odds ratios for increased acute coronary syndrome, graft failure, or a new cerebrovascular event were 4.06, 4.35, and 3.78. Moreover, the odds ratio for increased mortality in aspirin resistant patients was 5.99 (2.28 to 15.72; P<0.003).

The overall heterogeneity for cardiovascular outcome was 68.3%. Most of the heterogeneity (50.3%) was contributed to by the eight studies using the whole blood platelet function analyser 100 test; 33% of those patients were aspirin resistant (2.94, 1.88 to 4.55; P=0.00001). In contrast, heterogeneity was 0% in the seven studies that used a platelet rich plasma aggregation assay; 16% of patients were identified as aspirin resistant (3.85, 2.5 to 5.88); P<0.001.

In the planned sensitivity analysis no evidence was found of a dose-response relation between aspirin resistance and any cardiovascular outcome in those patients who received aspirin alone or who received a second antiplatelet (table and bmj.com). Thus the overall odds ratio was 3.28 (95% confidence interval 2.39 to 4.49, P<0.001), but no relation was found between dose and adverse outcome measures (R²=0.0046; see bmj.com). Moreover, concomitant therapy with clopidogrel or tirofiban (the inhibitor of platelet glycoprotein IIb/IIIa), or both, provided no benefit to aspirin resistant patients (aspirin and clopidogrel, 3.06, 1.99 to 4.70; aspirin alone, 2.52,



Risk of any cardiovascular event in aspirin resistant patients

Risks of adverse outcomes and aspirin dose response in patients who are resistant to aspirin

Variable	No of studies (n=20)	No of patients (n=2930)	Odds ratio (95% CI)	Heterogeneity (%)	P value
Outcome:					
All cerebrovascular events*	20	2930	3.85 (3.08 to 4.80)	68.3	<0.001
Death	4	728	5.99 (2.28 to 15.72)	5.5	<0.003
Acute coronary syndrome	9	1275	4.06 (2.96 to 5.56)	58.6	<0.001
Graft failure	3	420	4.35 (2.26 to 8.37)	28.2	<0.001
New cerebral event	4	340	3.78 (1.25 to 11.41)	38.1	<0.02
Dose response:					
75-100 mg/day	3	228	21.17 (8.83 to 50.77)	74.7	<0.003
>100-325 mg/day	9	1,309	2.81 (2.00 to 3.94)	37.9	<0.001
500 mg three times daily	1	174	14.53 (NA)	NA	<0.001
All doses	12	1710	3.28 (2.39 to 4.49)	56.7	<0.001

NA=not applicable.

*Fatal or non-fatal cardiovascular or cerebrovascular events (death, stroke, myocardial infarction), acute coronary syndrome, acute coronary syndrome.

1.79 to 3.56; see bmj.com). Little evidence was found of publication bias using the classic funnel plot (see bmj.com).

DISCUSSION

Meta-analysis showed that patients who are “resistant” to aspirin are at greater risk of clinically important adverse cardiovascular events, regardless of the assay used to measure aspirin resistance. Not only did aspirin resistance have an effect on clinical outcome but this risk was not ameliorated by currently used adjunct antiplatelet therapies.

Patients who were classified as aspirin resistant were at about a fourfold increased risk of non-fatal and fatal cardiovascular, cerebrovascular, or vascular events while taking aspirin than their aspirin sensitive counterparts. This risk can be generalised to a wide variety of patient populations with cardiovascular or cerebrovascular disease.

We thought that the pooling of data from studies using a variety of assays for aspirin resistance was both a limitation and a strength of our study. Specifically, we rationalised that if any or all of the assays were unreliable or inaccurate in identifying patients with aspirin resistance, then any real aspirin resistant effect on clinical outcome would be undetectable. If, however, most or all of the assays did reflect some rationale and some degree of validity and sensitivity, albeit variable, then any real impact of aspirin resistance on clinical outcome should be apparent. This interpretation seemed more logical to us, since we would expect that most, if not all, investigators had considered their particular assay in good faith and with a scientific basis.

The findings of a recent review and meta-analysis of laboratory testing for aspirin resistance and clinical outcome⁹ are consistent with those of our study. These investigators reported on 15 studies, 10 of which overlapped with our findings, and another three that were related to pilot or follow-up studies cited by us.

Currently used adjunct antiplatelet therapies did not ameliorate the risk of clinical outcomes. Platelet inhibitors clopidogrel and tirofiban did not provide

any benefit to aspirin resistant patients. The relative effectiveness of these newer antiplatelet agents compared with aspirin was established when their effectiveness was compared with that of aspirin alone in aspirin treated patients—the Aspirin Trialists’ Collaboration⁹ suggested that when used as an antiplatelet agent aspirin provides an overall 25% risk reduction. These investigators did not, however, consider aspirin resistance and how it might influence overall risk reduction. When their data are reassessed with an aspirin resistance odds ratio factored in, the risk reduction in aspirin sensitive patients is likely to be greater than a 50% risk reduction, whereas in aspirin resistant patients the risk seems to be noticeably increased.¹⁰

Our analyses also indicate that the effect of aspirin resistance on clinical outcome is applicable to the entire community of aspirin treated patients at risk of cardiovascular and cerebrovascular events. Thus the increased risk of these events in aspirin resistant patients occurs in those with stable cardiovascular disease or coronary artery disease, those who have had percutaneous coronary intervention or coronary artery bypass grafting, those undergoing other vascular procedures, and after stroke.

Limitations of study

We assessed 17 of the 20 included studies as of A quality (low risk of bias),^{w1-w9 w11-w13 w15 w17-w20} Three studies^{w10 w14 w20} had insufficient data on compliance with blindness or lacked sufficient information to assess quality objectively. As these studies met the other inclusion criteria and contained 586 patients (20% of the total), we included them in our analysis. These studies may have skewed our analysis, but as their overall outcomes were consistent with the overall analysis of the other 17 studies, we do not think this was the case.

None of the included studies provided any specific information about comorbidities between patients who had an adverse event and those who did not in either aspirin status group. The risk from being aspirin resistant seemed to be lower in men and higher in

patients with previous renal impairment. The sex related difference occurred in about half of the 2930 patients, and this difference may be real.

We were unable to determine which platelet function test best identifies aspirin resistant patients. It might be argued that the platelet aggregation assays are the better assays since those tests label fewer patients as aspirin resistant with less heterogeneity and a higher odds ratio than the whole blood platelet function assays. Moreover, lower heterogeneity was found with the platelet aggregation assays despite the use of a variety of agonists. It also can be argued that the greater heterogeneity seen when using the whole blood platelet function assays better reflects what is happening in vivo, as this type of assay concerns other cell types, such as inflammatory cells, that could contribute to the overall response of circulating platelets in aspirin resistant patients. A systematic review found a higher prevalence of aspirin resistance when using the platelet function analyser 100 assay than when using a platelet rich plasma aggregation assay, similar to our findings.¹¹ These investigators also adjusted the prevalence of aspirin resistance on the basis of dose, study population, and aspirin resistance assay used. We did not do this because we did not find any dose related effect and could not exclude other variables such as comorbidity, which the previous systematic review also did not exclude.¹¹

Data were insufficient to establish whether patients initially identified as aspirin resistant remained aspirin resistant or whether patients identified as aspirin sensitive became aspirin resistant. Either possibility could skew the overall prevalence of being aspirin resistant. Some investigators have suggested that chronic aspirin use is ineffective after about two years.^{3,12} This possible variance is unlikely to alter the overall increased odds ratio of having an adverse event when aspirin resistant, because the clinical outcome measures in these studies were related to the initial assay for aspirin resistance.

Only a few of the studies measured a biochemical marker of compliance (thromboxane A₂ or thromboxane B₂). However, most of the other investigators identified their patients as aspirin resistant or aspirin sensitive in hospital—in a controlled environment after a specific procedure and before and after known aspirin treatment. Thus aspirin status measured at that time could be assured independent of non-compliance. As such it is difficult to imagine that most patients had subsequently become non-compliant, and yet a significant difference in odds ratios would remain between the initially labelled aspirin resistant patients and those who were sensitive to aspirin.

Finally, a classic funnel plot suggested a modest publication bias, since there was an absence of small patient number studies that reported on a negative or no relation between aspirin resistance and adverse clinical outcomes. We found little evidence of any publication bias using a classic funnel plot and Egger's modification,¹³ suggesting that the overall findings of our study were not skewed by publication bias.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Many patients with cardiovascular disease are "resistant" or non-responsive to aspirin

WHAT THIS STUDY ADDS

Aspirin resistance can be measured by a variety of tests, all of which are associated with clinically important adverse events

Recommendation and future directions

We strongly advise that doctors continue to prescribe aspirin for chronic therapy to prevent adverse cardiovascular events as the overall risk reduction is well reported.⁹ However, we also recommend that patients are informed about potential adverse effects of aspirin use as it is possible that the currently perceived overall benefit in all aspirin treated patients (about a 25% decrease in risk) is more likely offset by the fourfold increased risk in the subpopulation of patients identified as aspirin resistant.

We thank M Dang and M Kirchhoff-Dobias for translating the Chinese and Czech papers. This study was supported by discretionary funds of SJB and MRB. The following authors verified our data interpretations: K Andersen (Norway); J Berrouschot, K-H Grotemeyer, and H Topka (Germany); W-H Chen (China); G Hobikoölu and MB Yilmaz (Turkey); and R Poston (United States).

Contributors: See bmj.com.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 6 November 2007