Benefits and risks of using clopidogrel before coronary artery bypass surgery: systematic review and meta-analysis of randomized trials and observational studies

Biancari F, Airaksinen KE, Lip GY

CRD summary

The authors concluded that, contrary to analyses of randomised controlled trial data, observational studies showed that clopidogrel before coronary artery bypass grafting increased the risks of death after surgery, reoperation for bleeding, blood loss and needing a blood transfusion. The limitations of the evidence available, and the differences between studies, make the reliability of the authors' conclusions unclear.

Authors' objectives

To assess the impact of clopidogrel, before coronary artery bypass surgery, on cardiovascular complications.

Searching

PubMed, The Cochrane Library, Scopus and ClinicalTrials.govwere searched to July, 2010. Search terms were reported.

Study selection

Randomised and observational studies evaluating clopidogrel plus aspirin, compared with aspirin alone, during initial hospitalisation for patients undergoing coronary artery bypass grafting, were eligible for inclusion. The outcomes were defined as those reported by the original study authors. Studies where most of the control group received clopidogrel (even if it was more than seven days before surgery) or where more than 10% of the control group received aprotinin, were excluded. Studies of patients undergoing procedures other than coronary artery bypass surgery alone were excluded.

The included studies were post-hoc analyses of larger randomised controlled trials (RCTs) or prospective or retrospective observational studies. The randomised trials were of participants with ST-elevation myocardial infarction, non-ST-elevation myocardial infarction or due to undergo percutaneous coronary intervention. In the post-hoc analyses participants were randomised to clopidogrel plus aspirin in varying doses, or placebo plus aspirin in varying doses. The RCTs were conducted in multiple centres in North America or multiple countries. In the observational studies, the time period from discontinuation of clopidogrel to surgery ranged from seven days or less to one day or less. Most participants (87%) discontinued clopidogrel five days or less before surgery. The outcomes were cardiovascular death, myocardial infarction, stroke or a combination of these; major bleeding as defined by thrombosis in myocardial infarction criteria; the need for reoperation due to bleeding; postoperative blood loss; the need for a packed red blood cell transfusion; the units of packed red blood cells used; and fresh-frozen plasma and platelets transfused.

The reviewers did not state how many authors selected studies.

Assessment of study quality

Randomised trials were assessed according to the Cochrane Collaboration criteria for assessing risk of bias. This assessed randomisation, allocation concealment, blinding, completeness of outcome data, absence of selective reporting, and absence of other biases. Each item was rated as yes, no or unclear. Observational studies were assessed using the Newcastle-Ottawa Scale, which has nine items covering selection, comparability of groups and ascertainment of outcomes.

The quality of randomised studies was assessed independently by two authors and reviewed by a third author. Disagreements were resolved by consensus.

Data extraction

For dichotomous outcomes, the number of events in each group was extracted and used to calculate the relative risk, with 95% confidence interval. For continuous outcomes, the mean difference between the intervention and control groups was extracted, with 95% confidence interval. For trials, the composite endpoint of death, myocardial infarction,

or stroke, within 30 days or at 30 days after the median time to coronary artery bypass grafting, was extracted. Where this was not available, data were extracted from the hazard rate curve. The authors were contacted for information, if necessary. Two reviewers extracted the data.

Methods of synthesis

For dichotomous data, the pooled relative risk, with 95% confidence interval, was calculated. For continuous data, the weighted mean difference, with 95% confidence interval, was calculated. Statistical heterogeneity was assessed using I^2 and, where this was greater than 40%, a random-effects model was used for the meta-analysis. Separate analyses were conducted for randomised and observational studies, and a pooled analysis was performed. A subgroup analysis was carried out for patients who stopped taking clopidogrel four days or less before surgery.

Results of the review

Twenty studies were included (n=15,248 patients). Three were post-hoc analyses of multicentre RCTs (n=1,234); nine were prospective non-randomised studies (n=7,214); and eight were retrospective studies (n=6,800). None of the RCTs reported allocation concealment or freedom from other biases; all reported blinding; two were free from selective reporting; and one addressed incomplete outcome data. All of the observational studies met the criteria for ascertainment of exposure, outcome assessment, outcome not present at start of study, and follow-up. Ten were representative; 16 had good selection; and two had comparable groups at baseline.

RCTs: Clopidogrel did not significantly reduce the risk of the composite cardiovascular endpoint of death, myocardial infarction or stroke, compared with aspirin alone (RR 0.77, 95% CI 0.58 to 1.04; three trials; n=1,234). Two trials (n=219) found no significant differences in the immediate postoperative mortality (RR 0.81, 95% CI 0.20 to 3.37), risk of myocardial infarction (RR 0.58, 95% CI 0.25 to 1.33), and risk of major bleeding (RR 1.48, 95% CI 0.72 to 3.04). There was no evidence of statistical heterogeneity for any of these outcomes (I^2=0). One trial found no difference in the rate of reoperation for bleeding, for all participants (p=0.43) and for those who stopped clopidogrel five days or less before surgery (p=1.00).

Observational studies: Participants who received clopidogrel had an increased risk of death (RR 1.30, 95% CI 1.02 to 1.67; 13 studies; n=12,129), reoperation for bleeding (RR 1.88, 95% CI 1.37 to 2.58; 14 studies; n=10,944), blood loss (MD 157.8mL, 95% CI 61.9 to 253.6; 10 studies; n=3,186), need for packed red blood cell transfusion (RR 1.23, 95% CI 1.10 to 1.37; nine studies; n=10,026) and fresh frozen plasma (MD 0.35 units, 95% CI 0.22 to 0.49; number of studies unclear), compared with participants receiving aspirin only. Statistical heterogeneity was low for death and reoperation for bleeding (I^2=1%), but high for blood loss (I^2=90%) and packed red blood cell transfusion (I^2=76%).

Participants receiving clopidogrel had a significantly lower risk of postoperative myocardial infarction (RR 0.63, 95% CI 0.48 to 0.82; nine studies, n=4,084), but a similar risk of stroke compared with participants receiving aspirin only (RR 1.26, 95% CI 0.78 to 2.02). There was no evidence of statistical heterogeneity for risk of myocardial infarction (I^2=0).

The authors reported that clopidogrel increased the amount of packed red blood cells and platelets needed, but the confidence intervals for these analyses crossed zero. The results from subgroup analyses of studies with emergency patients and studies where clopidogrel was withheld for four days or less before surgery were reported. As were the results of the analyses of randomised and non-randomised studies together.

Authors' conclusions

Data from RCTs showed a trend towards reduced complications, but observational studies showed that clopidogrel increased the risks of death after surgery, reoperation for bleeding, blood loss, and needing a blood transfusion.

CRD commentary

The review addressed a clear question with well-defined inclusion criteria for study design, participants and intervention. The inclusion criteria for outcomes were not defined. Three relevant databases were searched, but it was unclear whether unpublished data were sought and whether language restrictions were imposed; language and publication bias cannot be ruled out. Suitable steps were taken in quality assessment and data extraction to minimise the risk of reviewer error and bias. It was unclear whether similar steps were taken during study selection. The quality of the included studies was assessed, using appropriate criteria, and most of the included studies had weak designs.

Post-hoc analyses were conducted for the RCTs, introducing a risk of bias as allocation to the revascularisation subgroups was not randomised. The authors acknowledged that differences could have existed between studies in the definition of coronary artery bypass grafting, and these could have affected the reliability of the findings. The number of participants analysed from the RCTs was small, weakening the evidence. Appropriate methods were used to combine the study data, but statistical heterogeneity was high for some outcomes, weakening these findings. Limited details were reported for the observational studies, making it difficult to draw conclusions on the generalisability of the findings.

As the authors acknowledged, the reliability of the evidence was uncertain and there were differences between studies. The reliability of the authors' conclusions is unclear.

Implications of the review for practice and research

Practise: The authors did not state any implications for practice.

Research: The authors stated that further high-quality research was needed to investigate the benefits and risks of clopidogrel and other anti-platelet medications for patients undergoing coronary artery bypass grafting.

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