Outcomes of patients receiving clopidogrel prior to cardiac surgery
Vorobcsuk A, Aradi D, Farkasfalvi K, Horvath IG, Komocsi A

CRD summary
This review found that concomitant treatment of clopidogrel prior to surgery in patients who underwent cardiac surgery was associated with higher mortality and significantly increased risk of bleeding-related complications. Uncertainty about the completeness of the search and flaws in the presentation of the results mean that the results and conclusions should be interpreted with some caution.

Authors' objectives
To assess the effect of treatment with clopidogrel on clinical outcomes in patients having cardiac surgery.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 2001 to May 2010. Search terms were reported. There were no language restrictions. Reference lists of retrieved articles and review editorials and letters were checked for additional references.

Study selection
Studies of patients in which clinical outcomes were reported after preoperative administration of clopidogrel from same day to seven days prior to cardiac surgery were eligible for inclusion. The primary outcomes were mortality, red blood cell transfusion, major bleeding, reoperation and myocardial infarction.

The mean age of the patients was 64.27 years. Where stated, 11.37% to 40% of patients were female. The studies included patients who required coronary artery bypass graft surgery on an elective and urgent basis. Use of off-pump coronary artery bypass graft surgery was reported in some trials (mean rate of 33.1%). Clopidogrel exposure prior to surgery ranged from two to seven days pre-surgery. Concurrent medications were glycoprotein IIIb/IIIa inhibitors, aprotinin and Factor VII supplementation and aspirin. Follow-up ranged from the in-hospital period to one year after surgery.

Two independent reviewers performed the study selection; any disagreements were resolved by consensus and a third reviewer.

Assessment of study quality
Methodological quality was assessed using the Newcastle-Ottawa 10-point quality scoring system for non-randomised studies for study group selection, group comparability, exposure for case-control studies and outcomes of interest for cohort studies.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted by two independent reviewers to calculate odds ratios (OR) and 95% confidence intervals for the outcomes. Any disagreements between the reviewers were resolved by consensus and a third reviewer.

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using a random-effects model. Statistical heterogeneity was evaluated with $X^2$ and $I^2$. Subgroup analyses were conducted to explore potential causes of heterogeneity.

Results of the review
Twenty studies (23,668 participants) were included in the review: one randomised study (136 participants), 11 prospective studies and eight retrospective studies. Newcastle-Ottawa scores ranged from 7 to 10 points.

Treatment with clopidogrel prior to cardiac surgery was associated with significant increases in mortality (OR 1.24, 95% CI 1.03 to 1.49; 15 studies; $I^2$=0%), red blood cell transfusions (OR 1.82, 95% CI 1.40 to 2.37; 14 studies);
I²=84%) and re-operations triggered by major bleeding (OR 2.15, 95% CI 1.38 to 3.34; 16 studies; I²=54%).

Results of the subgroup analyses indicated that discontinuation of clopidogrel less than three days prior to cardiac surgery was associated with a higher incidence of red blood cell transfusions (OR 7.56, 95% CI 2.38 to 23.99), major bleeding (OR 6.62, 95% CI 1.69 to 25.95) and re-operation (OR 3.40, 95% CI 1.51 to 7.65). Re-operation rates were significantly higher in clopidogrel-treated groups in studies published prior to 2006 (OR 4.73, 95% CI 3.01 to 7.65; seven studies; I²=0%).

There were no differences between the clopidogrel treated groups and control groups in postoperative myocardial infarction; significant statistical heterogeneity was observed across the nine studies for this outcome (I²=56%).

Authors’ conclusions
Concomitant treatment of clopidogrel prior to surgery in patients who underwent cardiac surgery was associated with higher mortality and significantly increased risk of bleeding-related complications.

CRD commentary
Inclusion criteria were defined and reproducible. The specific databases that were searched were not well defined and this made it difficult to assess potential for missed studies. No language restrictions were applied to the search. Steps were taken to minimise reviewer error and bias during study selection and data extraction; no such steps were reported for the assessment of methodological quality. Study quality was formally assessed but the results for specific quality factors were not reported. The review included differing study designs; results of non-randomised studies are associated with a number of biases and confounding factors and it may not have been appropriate to combine the results in a meta-analysis. Significant statistical heterogeneity was observed for some outcomes. The authors used subgroup analyses to explore potential sources of heterogeneity. The limitations of the review for inclusion of observational studies and potentially differing criteria for red blood cell transfusion and re-operation across the included studies were acknowledged by the authors.

Uncertainty about the completeness of the search and flaws in the presentation of the results mean that the results and conclusions should be interpreted with some caution. The reliability of the results is unclear.

Implications of the review for practice and research
Practice: The authors stated that the findings of the review supported recommendations that clopidogrel therapy be discontinued more than five days prior to cardiac surgery to reduce mortality and lessen the risk of bleeding-related adverse events.

Research: The authors did not state any implications for research.

Funding
Hungarian Academy of Sciences; University of Pecs, Hungary.

Bibliographic details

PubMedID
21112646

DOI
10.1016/j.ijcard.2010.10.034

Original Paper URL

Indexing Status
Subject indexing assigned by NLM
Record Status
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