Adverse cardiovascular effects of concomitant use of proton pump inhibitors and clopidogrel in patients with coronary artery disease: a systematic review and meta-analysis

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CRD summary
This review found that the use of proton-pump inhibitors with clopidogrel, for patients with coronary artery disease, was associated with increased risks of major adverse cardiac events and acute coronary syndrome. In general, the review was well conducted and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess whether proton-pump inhibitors with clopidogrel increased the risks of major cardiovascular events.

Searching
EMBASE and PubMed were searched to June 2011, and CBM was searched to August 2011, for relevant studies in either English or Chinese; search terms were reported. The reference lists of included studies and retrieved reviews were searched for additional studies. The reviewers contacted experts to identify more studies.

Study selection
Controlled trials, cohort studies, or case-control studies that assessed cardiovascular outcomes for patients treated with clopidogrel alone, compared with patients treated with clopidogrel and proton-pump inhibitors, were eligible for inclusion. Studies of platelet data only and non-clinical investigations were excluded from the review. The outcomes of interest included major adverse cardiac events, acute coronary syndrome, all-cause mortality, cardiovascular deaths, stent thromboses, and strokes.

The patients in the included trials had a range of cardiovascular conditions or treatments, including myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, and stent implantation or placement. The proton-pump inhibitors were esomeprazole, omeprazole, pantoprazole, rabeprazole, and lansoprazole.

Two reviewers independently selected studies; any uncertainties or discrepancies were resolved by consensus or by discussion with a third reviewer.

Assessment of study quality
The methodological quality of the randomised controlled trials was assessed using the Cochrane risk of bias tool, for sequence generation, allocation concealment, blinding, complete outcome data, selective reporting, and other sources of bias.

The Newcastle-Ottawa Scale was used to assess the quality of the cohort and case-control studies. Cohort studies were assessed for patient selection, comparability of groups, and outcome measurements. Case-control studies were assessed for adequacy of case definition, representativeness of the cases, selection and definition of controls, comparability of cases and controls, ascertainment of exposure, and non-response rates.

Two reviewers assessed quality; any discrepancies were resolved by discussion or consultation with a third reviewer.

Data extraction
Two reviewers independently extracted the data to calculate hazard ratios, odds ratios, and 95% confidence intervals, for the outcomes. Any discrepancies were resolved by consensus.

Methods of synthesis
Pooled hazard ratios, odds ratios, and 95% confidence intervals, for the summary estimates, were calculated using a Mantel-Haenszel fixed-effect model. Statistical heterogeneity was assessed using \( \chi^2 \) and \( I^2 \) and, where it was significant (p<0.1), a DerSimonian and Laird random-effects model was used.

Sensitivity analyses were performed to evaluate the effect of removing the maximum and minimum effect sizes, to
determine the stability of the results. Meta-regression was conducted to explore potential sources of heterogeneity. The authors examined the potential for publication bias by visual inspection of funnel plots and using the Egger test.

**Results of the review**

Thirty-two studies (159,998 participants) were included in the review; 23 were cohort studies, four were case-control studies, one was a post-hoc analysis of a randomised controlled trial, and four were randomised controlled trials. Five studies were published as abstracts. The randomised controlled trials were of moderate quality; two reported sequence generation, two reported blinding, and one reported allocation concealment. All of the cohort studies received a score of 8 points, except one, which received 7 points. All the case-control studies adequately described the outcomes, follow-up and drop-outs; all but one controlled additional factors in the analyses. Follow-up periods ranged from 30 days to six years.

Pooled data, from three randomised controlled trials, showed no significant differences between patients receiving clopidogrel plus proton-pump inhibitors, and patients receiving clopidogrel alone, in the risk of major cardiovascular events.

Analyses of cohort or nested case-control studies showed that, compared with clopidogrel alone, clopidogrel plus proton-pump inhibitors was associated with statistically significant increases in the risk of major adverse cardiac events (HR 1.40, 95% CI 1.19 to 1.64; I²=87.6%; 13 studies; and OR 1.27, 95% CI 1.13 to 1.42; I²=8.5%; four studies), acute coronary syndrome (HR 1.42, 95% CI 1.14 to 1.77; I²=58.4%; five studies; and OR 1.42, 95% CI 1.08 to 1.87; I²=73.7%; four studies), and stroke (HR 1.39, 95% CI 1.01 to 1.92: I²=68.2%; three studies).

Elimination of the study with the largest effect found that proton-pump inhibitors were no longer associated with an increased risk of stroke. There were no differences between patients receiving proton-pump inhibitors and controls, in all-cause mortality, cardiovascular deaths, and stent thromboses. Meta-regression showed significant interactions between major adverse cardiac events, race, and whether patients had undergone percutaneous coronary intervention or not.

The analysis of individual proton-pump inhibitors showed that pantoprazole was associated with a statistically significant increase in major adverse events (HR 1.52, 95% CI 1.18 to 1.94; I²=83.9%; four studies). Publication bias was possible, with some asymmetry in the funnel plot, and a probability of zero, for the Egger test (10 cohort studies).

**Authors' conclusions**

The use of proton-pump inhibitors with clopidogrel, for patients with coronary artery disease, was associated with increased risks of major adverse cardiac events and acute coronary syndrome. There was insufficient evidence on the interactions between each proton-pump inhibitor and clopidogrel.

**CRD commentary**

The review addressed a clearly defined question and the criteria for the inclusion of studies in the review were specified. Appropriate databases were searched for relevant studies, and attempts were made to identify unpublished studies. The restriction to studies in English or Chinese introduced a risk of language bias. Steps were taken to minimise errors and bias at each stage of the review process.

Methodological quality was assessed and was judged to be moderate to good for most studies. The reviewers summarised the results of the studies grouped by their design, which was justified as non-randomised studies are vulnerable to bias that might overestimate their effect. Little information was provided on the doses of the medications used in each study.

In general, the review was well conducted and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that patients at a high risk of gastrointestinal bleeding should be offered selective proton-pump inhibitors, but those at a low risk should not be routinely offered this preventive treatment.

**Research:** The authors stated that further studies of different proton-pump inhibitors were required to determine the clinical significance of each one, because, in this review, the sample sizes in the subgroups were insufficient.
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