Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis
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CRD summary
This review concluded that concomitant use of proton pump inhibitors and clopidogrel might be associated with an increased risk of cardiovascular events but did not influence the risk of death in patients with established cardiovascular disease. These cautious conclusions appear appropriate, although risk of publication bias and lack of details on study quality should be borne in mind.

Authors' objectives
To assess whether proton pump inhibitors negatively affect clinical outcomes in patients treated with clopidogrel.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science were searched up to April 2010 without language restrictions. Search terms were reported. Six relevant conference proceedings were searched from 2008 to 2010. Reference lists of retrieved publications were screened. Ongoing studies were excluded.

Study selection
Randomised controlled trials (RCTs), post hoc analyses of RCTs and non-randomised studies that reported adjusted effect estimates were eligible for inclusion. Eligible studies compared proton pump inhibitors plus clopidogrel versus clopidogrel alone in patients with acute coronary syndrome and/or underwent percutaneous coronary intervention. The primary outcome was rate of major adverse cardiac events. Secondary outcomes were incidences of death, myocardial infarction, stent thrombosis and gastrointestinal bleeding. Studies had to report on at least one of the primary or secondary outcomes to be included.

Most of the included studies were non-randomised studies. Where reported, included studies used various types of proton pump inhibitors (these included omeprazole, esomeprazole, pantoprazole, lansoprazole and rabeprazole). The percentage of included patients who concomitantly used proton pump inhibitors in combination with clopidogrel was 34%.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
The quality of non-randomised studies was assessed using the Newcastle Ottawa Scale (maximum score of 10). Criteria included representativeness of the sample, selection of patients, ascertainment of exposure, comparability, assessment of outcome and adequacy of follow-up. Studies with a score of at least 7 were classified as high quality. The authors did not state that they assessed the quality of RCTs.

The authors did not state how many reviewers performed validity assessment.

Data extraction
Data were extracted on event rates to enable calculation of risk ratios (RRs) with 95% confidence intervals (CIs). Study authors were contacted for any missing data. Authors of studies that reported unadjusted effect estimates were contacted and asked to calculate adjusted odds ratios (ORs) or hazard ratios (HRs). The reported odds ratios were converted to risk ratios according to a recognised formula. Hazard ratios were accepted as risk ratios.

The authors did not state how many reviewers performed data extraction.
Methods of synthesis
The studies were combined in meta-analyses. Pooled risk ratios with 95% CIs were calculated using a random-effects model. Statistical heterogeneity was assessed using the Q and I² statistics and by examination of forest plots. Publication bias was assessed with a funnel plot. Sensitivity analyses were performed on publication type, study quality, study size, risk of developing an event, length of follow-up and study design. For the outcome of major adverse cardiac events, subgroup analyses were performed on different types of proton pump inhibitors.

Results of the review
Twenty-five studies were included in the review (159,138 participants): one RCT, two post hoc analyses of RCTs, 20 retrospective cohort studies and two case-control studies. Follow-up ranged from one month to four years.

Compared with clopidogrel alone, use of proton pump inhibitors plus clopidogrel was significantly associated with an increased risk of combined major cardiovascular events during a mean follow-up of 13 months (RR 1.29, 95% CI 1.15 to 1.44; 20 studies) and an increased risk of myocardial infarction during a mean follow-up of 14 months (RR 1.31, 95% CI 1.12 to 1.53; 12 studies). However, it was associated with a significant decrease in the risk of developing a gastrointestinal bleed during a mean follow-up of seven months (RR 0.50, 95% CI 0.37 to 0.69; three studies). There was no significant difference in rates of stent thrombosis and mortality between the two groups. Significant heterogeneity was observed only in the outcomes of combined major cardiovascular events (I²=72%) and myocardial infarction (I²=77%).

Sensitivity analysis did not materially alter the results. Funnel plots showed that publication bias could not be ruled out. Results of subgroup analyses were reported.

Authors' conclusions
Concomitant use of proton pump inhibitors and clopidogrel might be associated with an increased risk of cardiovascular events, but does not influence the risk of death in patients with established cardiovascular disease.

CRD commentary
This review's inclusion criteria were clear. Relevant databases were searched. No language restrictions were applied in the search, which minimised the risk of language bias. Attempts were made to locate conference abstracts. Publication bias was further assessed and results indicated that publication bias could not be ruled out. Steps were made to minimise reviewer biases and errors during study selection, but it was unclear whether data extraction and validity assessment were performed in duplicate. The quality of non-randomised studies was assessed using appropriate criteria, but the results of study quality were not reported. RCTs were not assessed for quality. Most of the included studies were observational studies. Statistical heterogeneity was assessed. Appropriate methods were used to pool the results.

The authors' cautious conclusions appear to be appropriate, but the risk of publication bias and lack of details on study quality should be borne in mind.

Implications of the review for practice and research
Practice: The authors did not state any implication for practice.

Research: The authors stated that further RCTs were required in order to examine whether a cause-and-effect relationship between proton pump inhibitor use and adverse outcomes existed and explore whether different proton pump inhibitors worsened clinical outcome in clopidogrel-treated patients.

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Not stated.

Bibliographic details
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.