Concomitant use of clopidogrel and proton pump inhibitors: impact on platelet function and clinical outcome – a systematic review

Jaspers Focks J, Brouwer MA, van Oijen MG, Lanas A, Bhatt DL, Verheugt FW

CRD summary
This review concluded that the evidence for the clinical consequences of clopidogrel given with proton-pump inhibitors was controversial. Prospective clinical studies did not support any adverse effects. These conclusions reflect the evidence and seem reliable; the limitations of the evidence should be borne in mind.

Authors' objectives
To evaluate the impact of clopidogrel plus proton-pump inhibitors on platelet function and cardiovascular outcomes for patients with acute coronary syndrome or stents for stable coronary disease.

Searching
PubMed, Web of Science and The Cochrane Library were searched up to June 2012, for studies published in European languages. Search terms were reported. Reference lists of relevant reviews, letters or editorials, and eligible articles were searched.

Study selection
Controlled studies (laboratory or clinical) comparing the impact of clopidogrel with proton pump inhibitors versus clopidogrel alone were eligible. Outcomes could be platelet function or cardiovascular (all-cause mortality, myocardial infarction, or major adverse cardiac events). Clopidogrel had to be administered in an acute coronary syndrome setting (with or without coronary intervention) or after stent implantation for stable coronary disease. Studies that only reported relative reductions between groups were excluded.

In the included laboratory studies, platelet function was assessed using various methods and at various times. In the clinical studies, the mean patient age ranged from 64.4 to 68.7 years, and the percentage of male patients ranged from 57.1 to 72.4. Some patients had prior myocardial infarction (range 12.1% to 28.1%), renal insufficiency (range 3.8% to 9.9%), or diabetes (range 25.6% to 33.9%). In all studies, the proton-pump inhibitors were omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole, and many studies assessed more than one type. Where reported, most studies were funded by government/charitable organisations; some were funded by pharmaceutical companies.

Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
The quality of the included studies was assessed for the investigated populations, exclusion bias, measurement of exposure, definition and measurement of outcomes, blinding, length of follow-up, loss to follow-up, and control for confounders. For case-control studies, matching and definitions of cases and controls were also assessed.

One reviewer assessed study quality; this was checked by a second reviewer and any discrepancies were resolved by a third reviewer.

Data extraction
For platelet function, results from function tests were extracted from laboratory studies. For cardiovascular outcomes, effect estimates and 95% confidence intervals were extracted or calculated using data from clinical studies.

The data were extracted by one reviewer and checked by a second reviewer. Any discrepancies were resolved by a third reviewer.

Methods of synthesis
The findings for platelet function were synthesised in a narrative. For cardiovascular outcomes, effect estimates and 95% confidence intervals were presented for each study. For major adverse cardiac events, the data were pooled using a
random-effects model. Statistical heterogeneity was assessed using $I^2$. Subgroup analyses were performed for individual proton-pump inhibitors. Publication bias, for the clinical studies, was assessed using a funnel plot.

**Results of the review**

Twenty-seven laboratory studies and 33 clinical studies were included; the total number of patients was unclear. Nine laboratory studies recruited healthy volunteers, and are not included in this abstract. Of the remaining 18 studies, 11 were observational, five were randomised, and two were post-hoc analyses of randomised crossover studies. The 33 clinical studies were two randomised controlled trials, 19 retrospective cohort studies, seven prospective cohort studies, three post-hoc analyses of randomised trials, and two nested case-control studies. The follow-up in the clinical studies ranged from 30 days to four years. Method limitations were noted for all studies; often for several domains.

Eleven of the 18 laboratory studies reported significant reductions in the inhibition of platelet aggregation when proton-pump inhibitors were administered with clopidogrel, compared with clopidogrel alone. Of the five studies that randomly allocated proton-pump inhibitors, only two demonstrated a significant difference between groups.

In the clinical studies, mixed results were demonstrated for all-cause mortality (23 studies), myocardial infarction (25 studies), and major adverse cardiac events (25 studies).

Pooling prospective clinical studies, no statistically significant difference was found between groups in the likelihood of major adverse cardiac events (OR 1.13, 95% CI 0.98 to 1.30; $I^2=46%$; 11 studies). Similar results were found in the subgroup analyses of esomeprazole or omeprazole (OR 1.09, 95% CI 0.74 to 1.62; $I^2=70%$; seven studies) and pantoprazole (OR 1.54, 95% CI 1.13 to 2.09; $I^2=0$; four studies). No evidence of publication bias was found.

**Authors’ conclusions**
The evidence for the clinical consequences of clopidogrel with proton-pump inhibitors was controversial. Prospective clinical studies did not support any adverse effects.

**CRD commentary**
The review question and inclusion criteria were clearly defined. Appropriate databases were searched, but the language restriction means that relevant studies may have been missed. Attempts were made to minimise the risk of reviewer error and bias throughout the review. Relevant quality criteria were employed, and all studies were found to have method limitations. Few study details were presented. Given the diversity in the included studies, the primarily narrative synthesis was appropriate.

The authors’ conclusions reflect the evidence presented and seem reliable; the limitations of the evidence should be borne in mind.

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

**Practice:** The authors did not state any implications for clinical practice.

**Research:** The authors stated that randomised proton-pump inhibitor allocation was important to minimise the risk of indication or prescription bias. Well-designed, randomised clinical trials were advised to investigate the likelihood of adverse effects with proton-pump inhibitors in patients on clopidogrel.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
22851683
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.