A meta-analysis of impact of proton pump inhibitors on antiplatelet effect of clopidogrel
Chen M, Wei JF, Xu YN, Liu XJ, Huang DJ

CRD summary
The review noted that there was a discrepancy between the results of randomised controlled trials and observational studies when comparing clopidogrel plus proton pump inhibitor with clopidogrel alone on cardiovascular and stroke outcomes; more research was required to adequately assess effects. Given substantial differences between the included studies and limitations in the evidence base, the authors’ conclusions are appropriate.

Authors' objectives
To compare the effects of the combination of proton pump inhibitors and clopidogrel versus clopidogrel alone for antiplatelet treatment.

Searching
MEDLINE, EMBASE, The Cochrane Library, clinical trials registers, cardiology websites and abstracts or presentations from cardiovascular meetings were searched up to October 2010; no search terms were reported.

Study selection
Studies that compared a combination of clopidogrel and proton pump inhibitors against clopidogrel alone were eligible for inclusion. Published studies and those presented at a major cardiovascular meeting were eligible. The outcomes of interest were clinical endpoints (cardiovascular death, readmission for myocardial infarction or acute coronary syndrome and nonfatal stroke) and platelet function (platelet reactivity index, residual platelet reactivity, platelet aggregation and inhibition of platelet aggregation).

Most patients in the included studies underwent percutaneous coronary interventions; some patients had acute myocardial infarction, unstable angina or had received stent implantation.

Two reviewers independently selected studies for the review. Disagreements were resolved by discussion and consultation with other reviewers.

Assessment of study quality
The authors did not report whether they undertook quality assessment of the included studies.

Data extraction
Data were extracted on the clinical outcomes to enable calculation of risk ratios (RRs), together with 95% confidence intervals (CIs). Data were extracted on effects on platelet function according to how they were analysed in individual trials.

Two reviewers independently extracted data for the review.

Methods of synthesis
For assessment of clinical endpoints, study results were pooled in meta-analyses and summary effect risk ratios, with 95% confidence intervals, were calculated using both fixed-effect and random-effects models. Separate analyses were made for studies with a randomised controlled trial (RCT) design and observational design. Heterogeneity was assessed by the X² test and quantified by the I² value.

Studies of effects on platelet function were summarised in narrative format.

Results of the review
Thirteen studies were included in the review. Nine studies (88,643 participants, range 1,053 to 24,702) assessed effects on clinical endpoints and four studies (1,718 participants, range 140 to 1,000) assessed effects on platelet function. Study designs included randomised controlled trials (five studies), retrospective cohorts (five studies), nested case control (one study) and cross sectional (two studies). Reported follow-up times ranged from 106 days to 521 days for...
assessment of clinical endpoints and seven to 15 days for assessment of platelet function.

In observational studies, there was a significant increase in risk of cardiovascular death, readmission for myocardial infarction, acute coronary syndrome and non-fatal stroke with clopidogrel and proton pump inhibitors when compared with clopidogrel alone with fixed-effect (RR 1.40, 95% CI 1.15 to 1.70; I²=96%; four studies) and random-effects (RR 1.49, 95% CI 1.43 to 1.55; I²=96%; four studies) analyses. Randomised controlled studies showed no evidence of significant differences in clinical endpoints between the two treatment groups in fixed-effect (RR 1.20, 95% CI 0.82 to 1.76; I²=67%; three studies) and random-effects (RR 1.03, 95% CI 0.91 to 1.18; I²=67%; three studies) analyses. One nested case control study reported that use of proton pump inhibitors in patients prescribed with clopidogrel increased the risk of reinfarction compared to clopidogrel alone (RR 1.27, 95% CI 1.03 to 1.57).

Using various methods, co-administration of clopidogrel with proton pump inhibitors was associated with attenuation of the antiplatelet effect of clopidogrel alone (four studies); figures for each study were provided in the paper.

**Authors' conclusions**

In the assessment of cardiovascular and stroke cerebrovascular outcomes, a discrepancy was found between the results of randomised controlled trials and observational studies when comparing clopidogrel plus proton pump inhibitors with clopidogrel alone; more research was required to adequately assess efficacy and safety. Combined treatment weakened the antiplatelet effect of clopidogrel.

**CRD commentary**

The review addressed a clear research question supported by appropriate inclusion criteria. Various relevant sources (including sources of unpublished studies) were searched and this minimised potential for publication bias. The authors did not state whether there were language restrictions in their searches which made it difficult to assess the risk of language bias. Appropriate methods were used for study selection and data extraction which minimised the chance of reviewer error or bias. It appeared that the studies were not assessed for quality and this made it difficult to assess the reliability of the evidence base.

Various study designs met the inclusion criteria and the decision to separately analyse randomised and non randomised studies was appropriate. Synthesis of some of the studies in meta-analyses and assessment of heterogeneity was appropriate; synthesis in narrative text was appropriate for other studies that used varied methods. Substantial heterogeneity in the analyses was identified (particularly for observational studies) and the authors advised caution in interpreting the results. Few study details were reported and this made it difficult to adequately assess applicability of the findings. There was a discrepancy between the numbers of participants reported in the O'Donoghue RCT and actual participants as the authors assessed only two arms of this three-arm trial and it was not clear why one observational study that assessed clinical endpoints was not included in the forest plots. The authors attempted to explain the differences in the summary effect measures for clinical endpoints in subgroups according to study design; they acknowledged that selection bias in the observational studies could not be excluded (patients taking combination treatment were likely to be older and sicker).

Given substantial differences between the included studies and limitations in the evidence base, the authors' conclusions are appropriate.

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

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

**Research:** The authors stated that further large scale RCTs with longer follow-up were needed to assess the interactions of proton pump inhibitors with clopidogrel.

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