Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel

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CRD summary
This review found conflicting and inconsistent data on the adverse interaction between clopidogrel and proton-pump inhibitors. The authors’ conclusions agreed with the results of their review and appear to be appropriate.

Authors’ objectives
To evaluate cardiovascular outcomes and mortality in patients taking clopidogrel with versus without concomitant proton-pump inhibitors.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched in October 2009, without language restrictions. The search terms were reported and a PubMed alert was set up to identify newly published studies. Abstracts from two relevant conferences were screened to identify unpublished studies and reference lists of included studies and relevant reviews were checked.

Study selection
Randomised controlled trials (RCTs) that compared cardiovascular outcomes and mortality in patients receiving clopidogrel with versus without proton-pump inhibitors (for at least 30 days) were eligible for inclusion. Case-control and cohort studies were eligible if they reported cardiovascular outcomes or mortality in patients taking clopidogrel with versus without proton-pump inhibitors. The outcomes of interest were myocardial infarction or acute coronary syndrome, all-cause mortality, and the composite outcome of major adverse cardiovascular events.

Included studies were conducted in the USA, Europe, Canada, Japan, and other parts of the world. The mean or median age ranged from 57 to 77 years, and the percentage of patients who were male ranged from 48 to 99, where reported. Patients had undergone stenting and/or percutaneous coronary intervention, had acute coronary syndrome, had serum markers of acute myocardial infarction, or were receiving clopidogrel for unreported diagnoses. A variety of proton-pump inhibitors were assessed, the main ones being omeprazole, pantoprazole, esomeprazole, lansoprazole, and rabeprazole.

Two reviewers independently assessed studies for inclusion; disagreements were resolved through consensus.

Assessment of study quality
The risk of bias was assessed for patient selection, follow-up, ascertainment of drug exposure, and definition and monitoring of adverse events. The authors did not state how many reviewers performed this assessment.

Data extraction
Two reviewers independently extracted the data to calculate relative risks and 95% confidence intervals. Where possible, adjusted estimates were extracted, otherwise raw data were extracted to calculate unadjusted estimates. If the studies only reported odds ratios, these were extracted to approximate the relative risks as the outcomes were rare. Where necessary, the authors were contacted for additional information.

Methods of synthesis
Summary relative risks were estimated, using the inverse-variance random-effects model. Pooling was sub grouped by study design: observational studies that presented only unadjusted data; observational studies that reported adjusted estimates; and RCTs and observational studies that used propensity scoring systems to match patients. Statistical heterogeneity was assessed using the I² statistic.

Results of the review
Twenty-two studies were included (n=93,278) and 19 were retrospective studies, two were post hoc analyses of RCTs, and one was a RCT. Many of the studies were available only as abstracts and their quality was difficult to assess. Most of them were based on patient registries or existing databases and misclassification or inconsistent recording of exposures and outcomes was possible. Four studies used a propensity scoring method to match participants to reduce potential confounding.

The analysis of RCTs and studies that used propensity scoring systems to match patients found no significant difference in myocardial infarction or acute coronary syndrome events (four studies), all-cause mortality (three studies) and major adverse cardiovascular events (five studies). Some of the analyses of observational studies found significant differences for some of these outcomes. There was significant heterogeneity for all analyses.

Authors’ conclusions
There were conflicting and inconsistent data on the interaction between clopidogrel and proton-pump inhibitors.

CRD commentary
The review addressed a clear question and the inclusion criteria were fully defined. The literature search included relevant databases and steps were taken to minimise the risk of language and publication bias. Appropriate steps were taken to minimise bias and errors when selecting studies and extracting the data, but it was unclear whether such steps were taken when assessing the risk of bias in the studies. This assessment included relevant criteria and the main results were reported in a table. The data were pooled and analysed by study design, but the substantial statistical, clinical, and methodological heterogeneity mean that it might not have been appropriate to pool the data. There were some discrepancies between the study details reported in the tables and those in the text.

The authors’ conclusions were in accordance with the results of the review and appear to be appropriate.

Implications of the review for practice and research
Practice: The authors stated clinicians should weigh up the real dangers of an increase in gastrointestinal haemorrhage events before routinely avoiding the use of proton-pump inhibitors in patients taking clopidogrel.

Research: The authors stated that robust pharmacokinetic and pharmacodynamic studies should be carried out to assess the biological basis of the interaction between clopidogrel and different proton-pump inhibitors, with different intervals of drug administration.

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