

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

C. S. KWOK & Y. K. LOKE

School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, Norfolk, UK

Correspondence to:

Dr Y. K. Loke, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, Norfolk NR4 7TJ, UK.

E-mail: y.loke@uea.ac.uk

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SUMMARY

Background

Recent studies have suggested an adverse interaction between proton pump inhibitors (PPI) and clopidogrel.

Aim

To perform a meta-analysis of cardiovascular outcomes and mortality in patients taking clopidogrel, with and without concomitant PPI.

Methods

We searched MEDLINE, EMBASE, Cochrane Controlled Trials Register in October 2009, and checked conference abstracts for randomized and nonrandomized studies that reported the risk of cardiovascular events and mortality with PPI exposure in patients taking clopidogrel. We performed random effects meta-analysis, stratified by study design and assessed heterogeneity using the I^2 statistic.

Results

Our review included 23 studies covering 93 278 patients. There was substantial heterogeneity in the meta-analyses of major cardiovascular events (19 studies, $I^2 = 79\%$) or myocardial infarction (12 studies, $I^2 = 77\%$). Analysis of propensity-matched or randomized trial participants showed no associated cardiovascular risk with PPIs, whereas other observational studies generally showed a significant association. Meta-analysis of 13 studies showed no significant association between PPI use and overall mortality (RR 1.09, 95% CI: 0.94–1.26, $P = 0.23$, $I^2 = 60\%$).

Conclusion

As there are conflicting and inconsistent data regarding the adverse clopidogrel–PPI interaction, clinicians should focus on potential harm from ulcers/haemorrhage before deciding to omit PPIs in patients taking clopidogrel.

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INTRODUCTION

There is currently significant controversy regarding cardiovascular (CV) adverse events arising from a potential drug interaction with concomitant use of clopidogrel and proton pump inhibitors (PPI).¹⁻³ On one hand, a number of recent commentaries from experts in the field have argued that there is no evidence that this potential drug interaction carries any major clinical impact.^{4, 5} In contrast, the US Food and Drug Administration (FDA) recently issued an updated statement cautioning against concomitant clopidogrel and PPI use⁶ and this stance appears to be shared by some other researchers who believe that there is a genuine clinical problem.⁷

Given that there has now been a rapid profusion of diverse study designs reporting widely varying results, it seems likely that different opinions may be formed depending on the selection of studies that one has access to. In this complex situation, an up-to-date systematic review of all currently available data may help clarify things. Moreover, when data from many different types of studies are available, the Cochrane Adverse Methods Group recommends that such an analysis can be usefully stratified according to type of study design.⁸ This is particularly important when the risk or level of bias varies with the methods and design used in particular studies.

As such, the aim of our meta-analysis was to determine the effect of concomitant PPIs and clopidogrel use on CV outcomes and mortality, stratified by study design.

METHODS

Eligibility criteria

We selected randomized-controlled trials (RCTs) and controlled observational studies that reported on CV adverse events and death in patients receiving clopidogrel, with and without concomitant PPI exposure.

The specific inclusion criteria for RCTs were (i) parallel group randomized trial of any PPI for at least 30 days; (ii) placebo control arm; (iii) participants were all receiving clopidogrel; and (iv) clear reporting of CV outcomes and mortality.

For the observational studies, we selected case-control or controlled cohort (prospective or retrospective) studies that evaluated the association of CV

outcomes/mortality with concomitant clopidogrel and any PPI exposure, as opposed to clopidogrel alone.

The clinical outcomes of interest were myocardial infarction/acute coronary syndrome, all cause-mortality and a composite measure of major adverse cardiovascular event (MACE) consisting of adverse events such as death or myocardial infarction or revascularization.

Search strategy

We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials with no date limitations in October 2009 using the broad search terms [(proton-pump-inhibitor and clopidogrel)] without any language restriction. Additionally, we signed up with PubMed to receive automated electronic notification for any new articles containing the above search terms. To identify unpublished studies, we checked conference abstracts from the European Society of Cardiology and the American Heart Association in August and November 2009 respectively). We also checked the bibliographies of included trials and recent review articles for relevant studies.

Study selection and data extraction

Two reviewers (CSK and YKL) scanned all titles and abstracts for studies that met the inclusion criteria, and excluded any articles that clearly did not fulfil the selection criteria. Full reports (where available) of potentially relevant trials and studies were retrieved and independently checked by two reviewers. We then independently collected information on study design, drug exposure, study location, characteristics of participants and relevant outcomes onto a spreadsheet. Where there was any uncertainty or discrepancies, the article was discussed between the two reviewers to determine if the studies should be included. We also contacted authors if there were any areas that required clarification.

Assessment of risk of bias

In accordance with the recommendations of the Cochrane Adverse Effects Methods Group, we looked at participant selection, follow-up, ascertainment of exposure, and definition and monitoring of adverse outcomes.⁸

We aimed to reduce the possibility of publication bias through searches of conference abstracts and contacting authors for any additional unreported data.

Data analysis

We used RevMan 5.022 (Nordic Cochrane Centre, København, Denmark) to estimate pooled risk ratio (RRs) based on random effects model meta-analysis (inverse variance method). We assumed similarity between the RR and odds ratio (OR) because CV events and deaths were uncommon events.⁹

Where possible, we chose to pool adjusted RRs from the primary studies; otherwise, we used raw outcome data to yield unadjusted RRs (which may be particularly susceptible to confounding).

In view of the potential diversity of study designs, we chose to stratify the analysis on the basis of three groupings:

(i) Nonrandomized studies where we could only evaluate the unadjusted RRs for the relevant outcomes, with no correction for baseline differences or confounding.

(ii) Nonrandomized studies that presented RRs adjusted for potential confounders.

(iii) Studies that involved participants who had been part of a randomized trial, or studies where a propensity scoring system had been used to match patient groups. The use of a propensity score has been shown to yield estimates that are closer to the true marginal

effect, which would have been found if a randomized study was possible.¹⁰

Statistical heterogeneity

Statistical heterogeneity was assessed using I^2 statistic, with I^2 values of 30–60% representing a moderate level of heterogeneity.¹¹

RESULTS

The search results yielded 23 relevant studies with 93 278 patients and the process of selection is shown in Figure 1. These comprised of 20 retrospective studies, two *post hoc* analyses of randomized trial participants and one prospective RCT.^{12–34} Main characteristics of the included studies are described in Table 1. The outcomes, interventions and quality assessments of the included studies are shown in Table 2.

As many of the included studies were presented in abstract form, we found it difficult to assess methodological quality fully. A majority of studies were based on registries of patients undergoing PCI, or were part of a health insurance database/reimbursement scheme. Database studies relied on prescription claims to ascertain exposure, while outcomes were commonly assessed based on ICD-9 codes. Misclassification or inconsistent recording of exposures and outcomes is a possibility within such databases. In contrast, the few studies that relied on data from trial participants

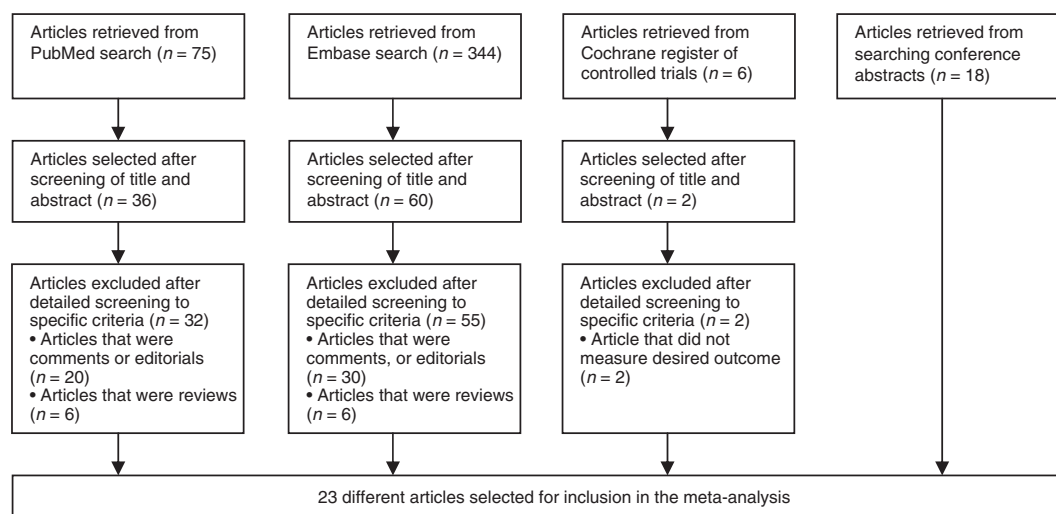


Figure 1. Flow diagram of the process of article selection for meta-analysis.

Table 1. Study design and characteristics

Study	Design; country and setting	No. patients	Mean age	% Male	Selection criteria	Outcome and follow-up
Banjerjee <i>et al.</i> ¹²	Retrospective cohort study in the US	197	NS	96.7	Patients on clopidogrel following insertion of drug eluting stent	MACE at 582 days
Bhatt <i>et al.</i> ¹³	Prospective, double-blind placebo- controlled multicentre RCT	3627	67.2	70.7	Age >21 years with ACS or coronary stent requiring clopidogrel and aspirin for next 12 months Excluded those with significant GI or bleeding history, current use of gastroprotective drugs or anticoagulants	MACE, MI for median of 133 days
Ching <i>et al.</i> ¹⁴	Retrospective cohort study in the US	1192	N.S.	N.S.	Patients with PCI	MACE, mortality at 9 months
Dunn <i>et al.</i> ¹⁵	<i>Post hoc</i> analysis of patients randomized to 12 months of clopidogrel & aspirin in US RCT	1053	61.5	71	Patients undergoing PCI. Excluded those with contraindications to antiplatelets and anticoagulants	MACE at 1 year
Gaspar <i>et al.</i> ¹⁶	Retrospective cohort study in Portugal	922	N.S.	N.S.	Patients admitted with ACS discharged with aspirin and clopidogrel	MACE at 6 months
Gupta <i>et al.</i> ¹⁷	Retrospective study at a single hospital in the US	315	62	N.S.	All PCI patients who were discharged on clopidogrel	MACE and mortality in 4 years
Hall <i>et al.</i> ¹⁸	Retrospective cohort study using healthcare database in the US	10 703	60	62.5	Patients who had received coronary stents and registered in cardiac catheterization database, Intermountain Healthcare	MACE, MI, mortality at 1 year
Ho <i>et al.</i> ¹⁹	Retrospective cohort and nested case control study in 127 hospitals in the US	8205	67	98.5	All patient with acute MI or unstable angina discharged with clopidogrel	MACE and mortality between Oct 2003 and Jan 2006
Jarai <i>et al.</i> ²⁰	Retrospective cohort study in Austria	1082 (propensity matched arm)	N.S.	N.S.	Patients on clopidogrel following PCI. Propensity score analysis was used in matching PPI users and non-users	MACE and death at 723 days
Juurink <i>et al.</i> ²¹	Nested-case control study in Ontario, Canada	2791	77 median	54	Patients age >65 who filled prescription of clopidogrel after hospital discharge for MI. Excluded patients who received clopidogrel, ticlopidine or dipyridamole before admission and those in long-term care facilities	MI and mortality up to 3 months

Table 1. (Continued)

Study	Design; country and setting	No. patients	Mean age	% Male	Selection criteria	Outcome and follow-up
O'Donoghue <i>et al.</i> ²²	Double-blind RCT in hospitals in the US, Europe and other parts of world	6795	60.5	73.9	Patients undergoing PCI who were randomized to the clopidogrel arm or the trial. Excluded those with risk of bleeding, anaemia, thrombocytopenia, pathological intracranial finding or thienopyridine within 5 days before randomization	MACE, MI and mortality
Pezalla <i>et al.</i> ²³	Retrospective cohort study in the US	1010	57.7	67.3	Patients <65 who were adherent to clopidogrel therapy; underlying diagnoses were not stated	MI only at 1 year
Ramirez <i>et al.</i> ²⁴	Retrospective cohort study based on registry data of hospital patients in Pittsburgh, US	535	N.S.	N.S.	Patients on clopidogrel following PCI	Death, MI, MACE (MI/death) at 1 year
Rassen <i>et al.</i> ²⁵	Retrospective cohort study based on 3 insurance databases in the US and Canada, covering patients hospitalized for ACS	18 565	76.1	48.2	Patient on clopidogrel following PCI for ACS, propensity-matched	MI, MACE (MI/death), death at 6 months
Sarafoff <i>et al.</i> ²⁶	Retrospective cohort study in Germany	2025	66.8	N.S.	Patients on clopidogrel randomly selected from database of those who had undergone PCI	Death, MI, MACE (MI/death) at 1 year
Simon <i>et al.</i> ²⁷ and Simon <i>et al.</i> ²⁸	Cohort study based on French Registry of patients post-MI	2208, with Simon <i>et al.</i> ²⁸ = 2178	66.2	70.6	Patients age >18 with serum markers of AMI or ECG pathological Q waves, ST elevation, ST depression	MACE at 1 year ²⁷ ; Death at 1 year ²⁸
Stanek <i>et al.</i> ²⁹	Retrospective cohort study in the US based on medical and pharmacy claims database	16 690	66	68.9	Patient with clopidogrel treatments following coronary stenting	MACE at 1 year
Stockl <i>et al.</i> ³⁰	Retrospective cohort study of patients enrolled in health insurance plan in the US	2066	N.S.	N.S.	Patients discharged from hospital with clopidogrel after MI or coronary stent placement, matched 1:1 for CV risk with propensity scoring method between patients with and without PPI	MI up to 360 days
Sweeny <i>et al.</i> ³¹	Retrospective cohort study based on NY state interventional database	8311	N.S.	N.S.	Patients undergoing PCI with drug eluting stents during study period	Mortality at over 2 years
Torgusen <i>et al.</i> ³²	Retrospective cohort study in the US	1896	N.S.	N.S.	Patients undergoing PCI with drug-eluting stents discharged with aspirin and clopidogrel	MACE at 12 months

Table 1. (Continued)

Study	Design; country and setting	No. patients	Mean age	% Male	Selection criteria	Outcome and follow-up
Yasuda <i>et al.</i> ³³	Retrospective cohort study in Japan	243	68	75.3	Consecutive patients who had undergone PCI. Excluded if cardiogenic death within 1 week, malignancy, chronic haemodialysis and patients on warfarin or single platelet therapy, transferred to other hospitals	MI, unclear follow-up period
Zairis <i>et al.</i> ³⁴	<i>Post hoc</i> analysis of prospective cohort study in Greece	612	N.S.	N.S.	Patients with coronary stenting for stable or unstable coronary disease	MI and mortality at 1 year

MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; CV, cardiovascular; MI, myocardial infarction; ACS, acute coronary syndrome; PPI, proton pump inhibitor.

generally had more rigorous follow-up and predefined ascertainment of CV events that included adjudication by an independent committee.^{13, 15, 22} Four studies used a propensity scoring method to try to match the participants and reduce potential confounding.^{20, 22, 25, 30}

Twelve studies reported either myocardial infarction or acute coronary syndrome events as an outcome (Figure 2). There was a high degree of heterogeneity ($I^2 = 77\%$) in the overall analysis. Unadjusted data from observational studies gave the highest RR of 1.82 (95% CI: 0.90–3.70) that fell to an RR of 1.54 (95% CI: 1.23–1.92) with data adjusted for confounders and an RR of 1.15 (95% CI: 0.89–1.48) based on propensity-matched or trial participants.

Thirteen studies were included in the analysis of all-cause mortality (Figure 3). The overall pooled result was nonsignificant (RR 1.09, 95% CI: 0.94–1.26) with some degree of heterogeneity of $I^2 = 60\%$. Similar to the analysis of MI above, the pooled RR was highest with the unadjusted observational data and lowest (RR 1.00, 95% CI: 0.94–1.26) with the propensity-matched or trial participants.

Nineteen studies were included in the analysis of MACE (Figure 4). Definitions of the composite endpoints within MACE varied considerably between studies and this may have accounted for the substantial heterogeneity in the overall analysis, as illustrated by the diverse pattern in the Forest plots ($I^2 = 79\%$). Again, data from propensity matched or trial participants gave the lowest pooled RR of 1.07 (95% CI: 0.90–1.28), whereas the adjusted observational data yielded a pooled RR of 1.44 (95% CI: 1.24–1.67).

DISCUSSION

While the overall pooled estimates suggest that concomitant clopidogrel and PPI use may be associated with adverse CV events and myocardial infarction, the available evidence shows no effect on mortality. Indeed, even when considering adverse CV outcomes alone, the presence of significant heterogeneity indicates that the evidence is at best, inconsistent, and at worst, potentially biased or confounded, as illustrated by the relative absence of any harm in the studies that were either randomized or based on propensity score-matched participants. For mortality and myocardial infarction, the pooled effect size (for harm) steadily diminished as we moved from RRs from crude raw data to observational studies that adjusted for

Table 2. Study outcomes, interventions and quality

Study	PPI exposure and ascertainment	Lost to follow-up	Definition of outcome and ascertainment	Risk of bias
Banjerjee <i>et al.</i> ¹²	Any PPI, no other details	Not specified	MACE defined as death, MI, revascularization and stroke. Monitoring not stated	Abstract only, no further details
Bhatt <i>et al.</i> ¹³	Omeprazole	Not specified	MACE was prespecified composite of CV death, nonfatal MI, CABG or PCI, or ischaemic stroke, adjudicated by independent committee	Abstract only, low risk of confounding as there were no baseline differences
Ching <i>et al.</i> ¹⁴	Esomeprazole, lansoprazole, omeprazole, pantoprazole	None	MACE defined as recurrent MI, revascularization and death. Monitoring not stated	Abstract only, analysis was adjusted for age, gender, glycoprotein IIb/IIIa inhibitors and stent size; no further details
Dunn <i>et al.</i> ¹⁵	Any PPI, no other details	38 (3.6%) losses	MACE was prespecified as death, MI or stroke and adjudicated by blinded independent committee	Despite adjustment for confounding, PPI exposure alone without clopidogrel still showed significantly increased risk above that of patients taking neither PPI nor clopidogrel
Gaspar <i>et al.</i> ¹⁶	Omeprazole, rabeprazole and lansoprazole were considered (pantoprazole excluded as investigators judged it to be metabolized by another route). Prescription and clinical records used to define exposure	None	Not specified	Abstract only, baseline differences were present, multivariate analysis was performed to assess effect of PPI exposure. Authors concede that compliance was not assessed and prescription records may be incomplete
Gupta <i>et al.</i> ¹⁷	Rabeprazole, omeprazole and lansoprazole for unclear duration, data obtained from discharge summary	None. Mean follow-up of 50 months	Reviewed medical records. MACE defined as composite of death, nonfatal MI and target vessel failure	Risk of confounding as baseline differences were present; adjusted risk ratios were presented. Duration of exposure and treatment compliance unclear
Hall <i>et al.</i> ¹⁸	Omeprazole, lansoprazole, pantoprazole	Not specified	MACE defined as death/MI, monitoring not stated	Abstract only; adjusted for confounders such as comorbid conditions and concomitant medications. Despite adjustment, PPI exposure alone without clopidogrel still showed significantly increased risk above that of patients taking neither PPI nor clopidogrel, thus suggesting possibility of residual confounding
Ho <i>et al.</i> ¹⁹	Omeprazole, rabeprazole, lansoprazole and pantoprazole for unclear duration based on pharmacy dispensing records	Vital status available for all between October 2003 and September 2006, with median follow-up of 521 days	A vital status file and chart review (including ICD-9 codes) using Veterans Administration database for mortality and MACE (death or rehospitalization for ACS)	Risk of confounding as baseline differences were present; this was adjusted for using multivariate logistic regression

Table 2. (Continued)

Study	PPI exposure and ascertainment	Lost to follow-up	Definition of outcome and ascertainment	Risk of bias
Jarai <i>et al.</i> ²⁰	Any PPI, no other details	Not specified	MACE consisted of death or target vessel revascularization. Monitoring not stated	Abstract only, no information on exposure and outcome ascertainment, propensity score was used in patient matching
Juurlink <i>et al.</i> ²¹	Pantoprazole and any other PPI, on Ontario drug prescriptions computerized record	None	Outcomes checked on Health Insurance (using ICD codes) and Health Registered Person databases	Data were adjusted for demographic differences, concomitant medication and comorbidity. Authors state limitations that include possible miscoding of outcome, and inability to verify compliance with exposure
O'Donoghue <i>et al.</i> ²²	Omeprazole, pantoprazole, esomeprazole, lansoprazole at time of randomization, and at various intervals of follow-up	None	MACE defined as CV death, nonfatal MI, or nonfatal stroke. Independent committee adjudicated events	Propensity score was used to adjust for covariates. Variations in PPI exposure with time were checked in sensitivity analysis – no material effect on results was detected
Pezalla <i>et al.</i> ²³	Any PPI use ascertained through pharmacy claims database	None	Health insurance and pharmacy database, using ICD codes for MI	Potential confounding as baseline differences were present, and authors attempted to correct for only a few comorbid factors
Ramirez <i>et al.</i> ²⁴	Any PPI, no other details	None	Not specified	Abstract only, no information on intervention and outcome ascertainment, risk of confounding as potential baseline differences were present
Rassen <i>et al.</i> ²⁵	Omeprazole, esomeprazole, lansoprazole, pantoprazole, or rabeprazole, recorded on pharmacy database	82% were eligible for matched propensity analysis, median follow-up was 29–30 days, with 2% completing maximum follow-up of 180 days	Study endpoints were ascertained up to 180 days of follow-up. MI recorded via discharge coding in health insurance database; death through vital statistics and government agencies	Propensity score was used to match patients
Sarafoff <i>et al.</i> ²⁶	Any PPI, no other details	None	Not specified	High; abstract only, no information on intervention and outcome ascertainment, risk of confounding as baseline differences were present
Simon <i>et al.</i> ²⁷ and Simon <i>et al.</i> ²⁸	Omeprazole and PPI for unspecified duration	222 were not included	Investigators contacted patients' physicians, the patients or their family and registry offices at places of birth. Blinded independent committee adjudicated events, endpoints ascertained at 1 year	Uncertain about ascertainment of PPI exposure; but there was blinding of outcome ascertainment

Table 2. (Continued)

Study	PPI exposure and ascertainment	Lost to follow-up	Definition of outcome and ascertainment	Risk of bias
Stanek <i>et al.</i> ²⁹	Omeprazole, esomeprazole, pantoprazole and lansoprazole based on prescription claims	Not specified	Outcomes recorded via ICD-9 codes on claims database	Abstract only, no information on compliance. Risk of confounding was addressed in multivariate analysis
Stockl <i>et al.</i> ³⁰	Any PPI, no other details	None	Not specified	Abstract only, patients were propensity score-matched based on CV risk; no further details
Sweeny <i>et al.</i> ³¹	Esomeprazole, lansoprazole, omeprazole and pantoprazole	37 excluded from analysis, mean follow-up of 2 years	New York State Interventional database and Social Security Death Index	Abstract only, outcome ascertainment was done, no information on checking of drug exposure, but multivariate adjustment was done for confounders
Torgusen <i>et al.</i> ³²	Any PPI, no other details	None	MACE defined as death, MI or revascularization. Monitoring not stated	Abstract only, author stated that PPI-exposed patients were more complex and sicker than unexposed, and used multivariate regression to adjust
Yasuda <i>et al.</i> ³³	Lansoprazole, omeprazole, rabeprazole for unspecified duration; review of hospital records	None	Review of hospital records and coronary angiography at 6–16 months after stent placement	Intervention exposure and outcomes were not ascertained, risk of confounding as baseline differences were present
Zairis <i>et al.</i> ³⁴	Any PPI, no other details	None	Not specified	High, abstract only, no information on intervention and outcome ascertainment, low risk of confounding because of baseline difference

MACE, major adverse cardiac events; ICD, International Classification of Diseases; CV, cardiovascular; MI, myocardial infarction; ACS, acute coronary syndrome; PPI, proton pump inhibitor.

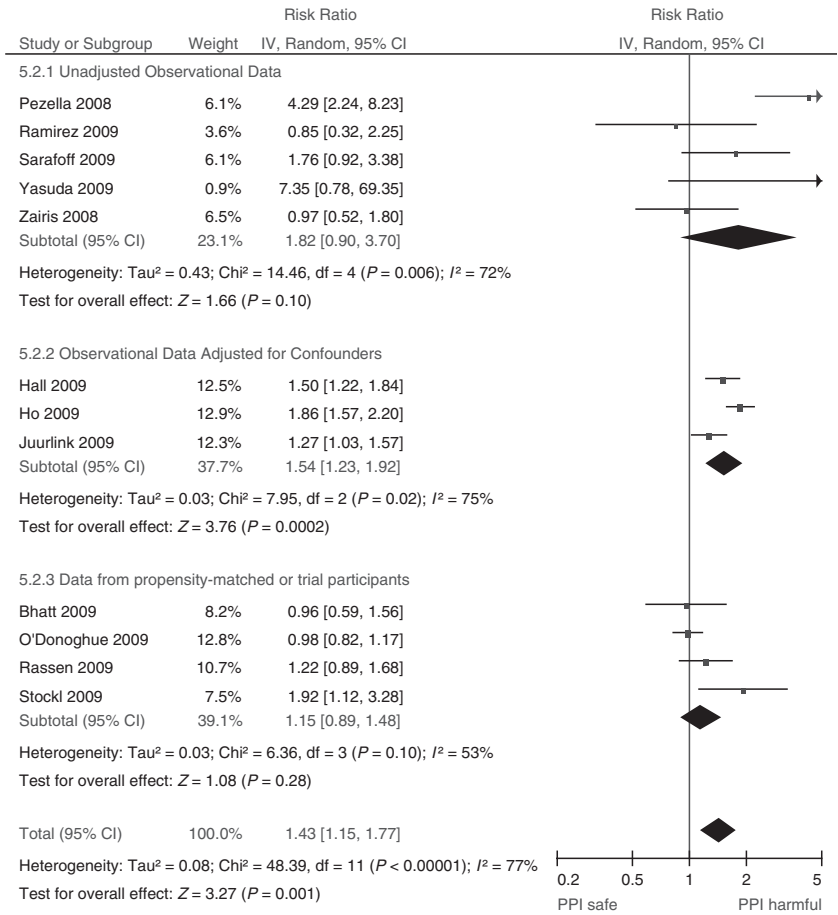


Figure 2. Meta-analysis of myocardial infarction or acute coronary syndrome with clopidogrel and proton pump inhibitor use.

confounders and then to participants from randomized trials or propensity-matched studies.

There are a number of potential explanations for our findings. One possibility is that the studies with the greater risk of bias or confounding tend to yield larger effect sizes for harm, whereas potentially higher quality studies (such as those with prespecified blinded outcome ascertainment, or more uniform participant selection/matching) have shown lesser evidence of harm. The gradations in magnitude of risk, which may depend on risk of bias, are apparent in the subcategories of study design within the Forest plots (Figures 2–4). Alternatively, the heterogeneity may arise from the populations studied, perhaps with varying distribution of CYP2C19 genotypes that confer different susceptibilities to the interaction. Given the considerable variations in type of PPI exposure among the studies, there is also the possibility that the extent of interaction may vary between individual PPIs and genotype of participants in particular populations, thus leading to heterogeneous results. Studies that used propensity matching,

or recruited participants somewhat more uniformly based on tight inclusion criteria from RCTs may have been less susceptible to such confounding.³⁵

The results of the meta-analysis may reflect differences in patient selection amongst the studies. Patients after percutaneous coronary intervention are a specific high-risk group compared with those identified in population-based studies using dispensing databases, where patients may be on long-term clopidogrel therapy for other reasons or have different CV risk factors. While the only prospective randomized trial did not show any evidence of a harmful interaction,¹³ this does not exclude the possibility that certain patients in real-life clinical practice could be susceptible to such harm, as detected by some database studies.

Equally, statistical adjustment for confounding can only account for known confounders. We noted clear baseline differences in the studies between patients exposed to PPIs as compared with those not receiving PPIs and there may be other unknown confounders for which adjustment cannot be made. We are aware of

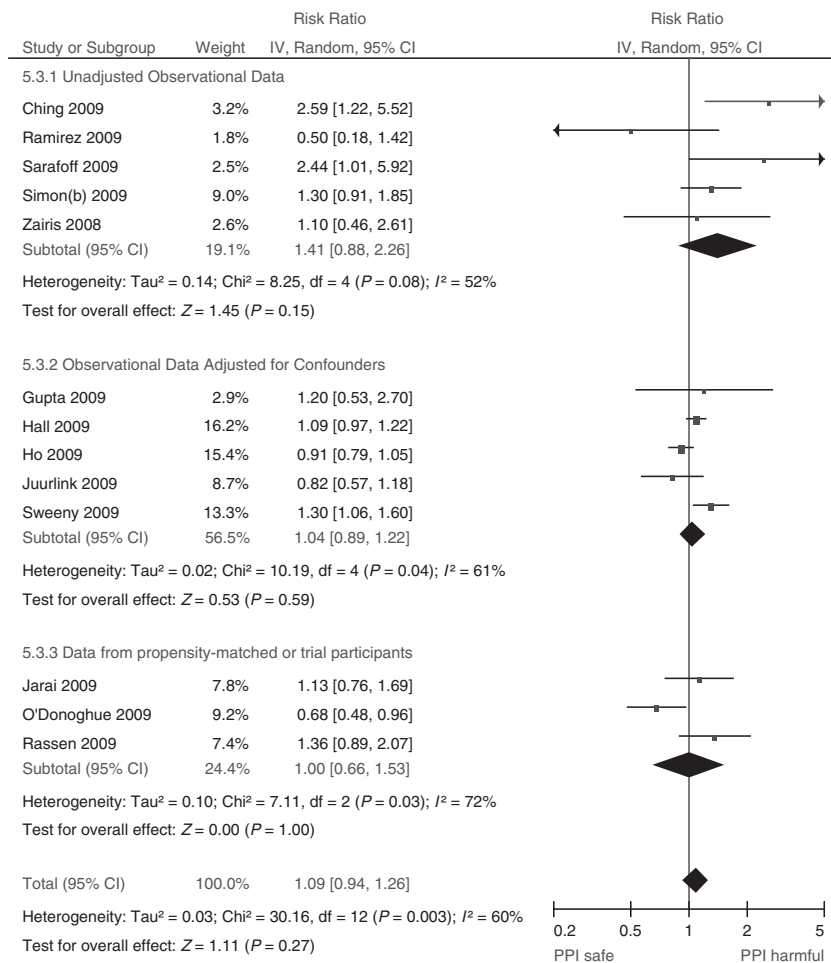


Figure 3. Meta-analysis of overall mortality with clopidogrel and proton pump inhibitor use.

two studies that carried out separate analysis of PPI exposure in patients not taking clopidogrel^{15, 18} and this showed significantly elevated risk with PPI (adjusted RRs of 1.55 and 1.38) compared with no PPI, even in the absence of clopidogrel therapy. This suggests either that there is residual confounding despite adjustment for known covariates or that PPIs have a deleterious effect irrespective of clopidogrel exposure.

However, outcome ascertainment in certain study settings may be more reliable, particularly regarding patients enrolled in, or selected *post hoc* from randomized trials who were followed up according to prespecified protocols, with adjudication of adverse events by independent safety monitoring boards. One large observational registry that used rigorous outcome ascertainment (contacting patients and their physicians, checking with registry offices), as well as blinded independent assessment of outcomes, also failed to show any significant clopidogrel–PPI interaction on death or

major adverse events.^{27, 28} The wide variety of other observational database or registry studies may have relied on different methods of ascertaining CV events that may have been coded differently and we do not have sufficient information to judge the validity of such outcome data.

There are several limitations in this review. The quality of the studies is generally poor as many of the studies had some risk of bias, and we were only able to identify one prospective randomized trial. There was also significant heterogeneity of the pooled studies and this was particularly apparent when comparing results from different designs. In view of this heterogeneity, we have chosen not to focus on the pooled RR from the meta-analysis. As many of the studies were available only in abstract form, we did not have as much detail on the methods, actual drug exposure and results, as compared with a fully peer-reviewed journal publication. Moreover, definitions of MACE were sometimes vague and varied considerably

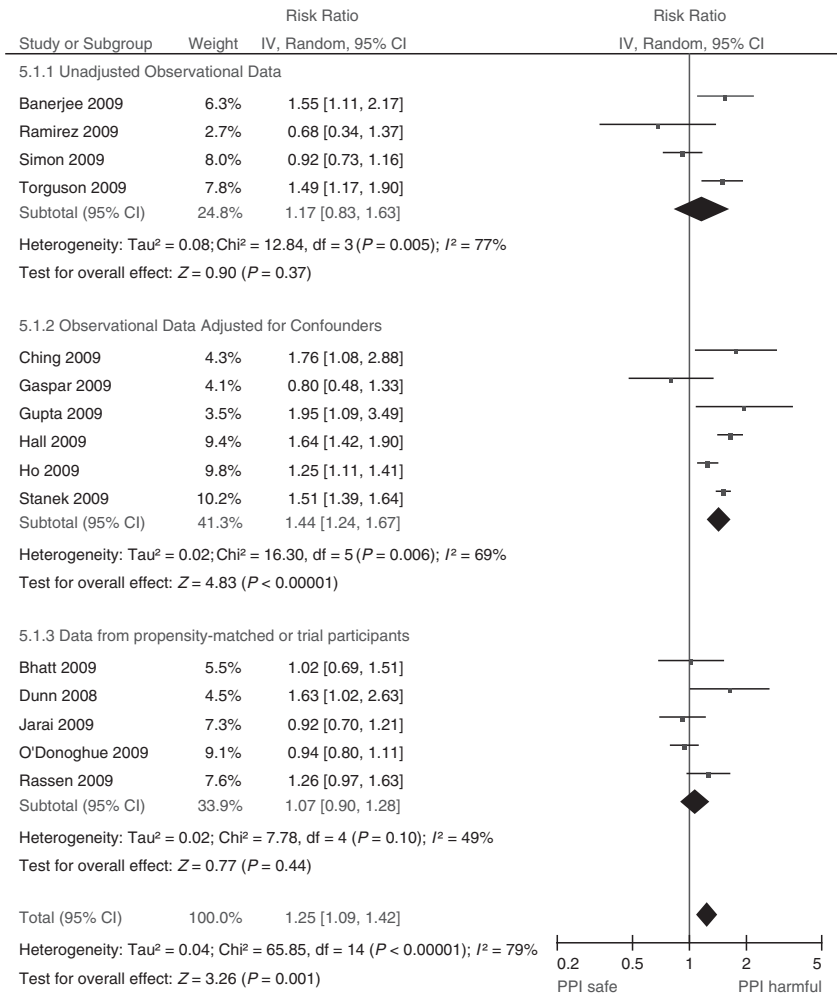


Figure 4. Meta-analysis of major adverse cardiac events with clopidogrel and proton pump inhibitor use.

between studies, thus contributing to weaknesses in assessing this outcome in contrast to the more robust measure of overall mortality. When sufficient details on PPI exposure and exact CV outcomes become available in future, it may then be helpful to evaluate the risk with individual PPIs and correlate this with data on bioavailability and platelet aggregation. Publication bias was not formally assessed with a funnel plot as asymmetry testing should only be carried out when there is no significant heterogeneity.³⁶ While we took other steps to minimize publication bias by searching through conference abstracts and trial registers for unpublished studies, we recognize that statistically significant findings are presented or published earlier, whereas findings of no effect gradually emerge later,³⁷ which is why we chose to evaluate abstracts at the most recent cardiology conferences about 12 months after the initial significant results had been presented.

We believe that the ideal trial would randomize patients on clopidogrel to different PPI, placebo or H2RA and evaluate the risk of MI, death and other prespecified adverse events such as gastrointestinal bleeding. While awaiting further reports from the COGENT trial¹³ and any further new trials, we believe that robust pharmacokinetic and pharmacodynamic studies should be carried out on CYP2C10 genotyped patients to check the biological basis of the interaction with different PPIs and different intervals of drug administration.

CONCLUSIONS

In conclusion, the findings of this meta-analysis suggest that there is conflicting and inconsistent evidence on the impact of the clopidogrel PPI interaction on CV outcomes and certainly no evidence of any effect on overall mortality. Clinicians should carefully weigh up

the real dangers of an increase in gastrointestinal haemorrhage events¹³ before routinely avoiding the use of PPIs in patients taking clopidogrel.

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CONTRIBUTORS

YKL and CSK conceptualized the review, developed the protocol, abstracted and analysed data, and wrote the manuscript. YKL will act as the guarantor for the paper.

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