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# Effects of Proton Pump Inhibitors on Adverse Gastrointestinal Events in Patients Receiving Clopidogrel

## Systematic Review and Meta-Analysis

*Chun Shing Kwok, Ramanpreet Singh Nijjar* and *Yoon Kong Loke*

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

## Abstract

**Background:** There has been recent concern regarding a possible adverse interaction between clopidogrel and proton pump inhibitors (PPIs), coupled with uncertainty as to whether PPIs genuinely help in reducing gastrointestinal (GI) harm.

**Objective:** To perform a meta-analysis of GI outcomes in patients taking clopidogrel, with and without concomitant PPI.

**Methods:** We searched MEDLINE, EMBASE and the Cochrane Controlled Trials Register from inception to March 2010, and checked conference abstracts for randomized and non-randomized studies that reported on adverse GI events (haemorrhage, ulcer, perforation or obstruction) with PPI exposure in patients taking clopidogrel. Relevant studies were subcategorized according to the degree of aspirin (acetylsalicylic acid) co-administration and nature of GI events, where available. We performed random effects meta-analysis for risk of adverse GI events with PPI exposure in clopidogrel-treated patients, and assessed heterogeneity using the $I^2$ statistic.

**Results:** Our review evaluated 71 277 participants in nine retrospective studies and one randomized trial. Exposure to PPI for patients receiving dual antiplatelet therapy (aspirin and clopidogrel in seven studies) was associated with a significant reduction in adverse GI events, odds ratio (OR) 0.38 (95% CI 0.21, 0.68; $p = 0.001$; $I^2 = 17\%$). There was significant heterogeneity in the analysis of patients receiving clopidogrel monotherapy (two studies), and no definite benefit was found. Restricting the analysis to studies specifically reporting upper GI bleeds with any clopidogrel exposure yielded an OR of 0.31 (95% CI 0.19, 0.51; $p < 0.001$; $I^2 = 27\%$) with associated PPI exposure.

**Conclusions:** Use of PPIs is associated with a reduction in adverse GI events (particularly haemorrhages) in patients who are receiving dual antiplatelet therapy. Clinicians should carefully weigh up the evidence for potential GI benefits against the uncertainties surrounding any possible adverse cardiovascular impact of concomitant clopidogrel PPI therapy.

## Background

Clopidogrel is an antiplatelet agent used in the secondary prevention of cardiovascular conditions, and is often prescribed concomitantly with aspirin (acetylsalicylic acid) after acute coronary syndrome or percutaneous coronary intervention.[1] Antiplatelet drugs can increase the risk of gastrointestinal (GI) bleeding, and drugs such as proton pump inhibitors (PPIs) are often used to reduce this GI risk; however, there has been recent controversy regarding a negative cardiovascular interaction between clopidogrel and PPIs.[2-5] Nevertheless, a recent meta-analysis suggests that the evidence for this adverse interaction is inconsistent and potentially biased, and that there is no significant impact on mortality.[6]

Recent studies on the clopidogrel PPI interaction have focused mainly on platelet function and cardiovascular events. The role of PPIs in reducing adverse GI events among patients treated with clopidogrel has yet to be systematically evaluated and we aimed to determine the extent of benefit (if any) from combined PPI and clopidogrel therapy.

## Methods

### Eligibility Criteria

We selected randomized controlled trials (RCTs) and observational studies that reported adverse GI events in patients receiving clopidogrel, with and without concomitant PPI exposure. We accepted studies where clopidogrel was used alone, or in combination with aspirin.

The specific inclusion criteria for RCTs were those that had clear reporting of adverse GI events and where patients receiving clopidogrel were randomized to PPI for at least 30 days compared with a control arm with no PPI exposure.

The specific inclusion criteria for observational studies were studies of case-control or cohort (retrospective or prospective) design that evaluated adverse GI events with concomitant clopidogrel and PPI exposure.

The main clinical outcomes of interest were adverse GI events such as ulceration, bleeding, perforation or obstruction.

### Search Strategy

We searched PubMed, EMBASE and the Cochrane Central Register of Controlled Trials from inception to March 2010 using free text and indexing terms ('proton pump inhibitor' and 'clopidogrel') without any language restriction. In addition, we used the PubMed automated electronic notification to retrieve any new articles using the same search terms. Unpublished literature was found by checking conference abstracts (European Society of Cardiology 2009, American Heart Association 2009, American College of Cardiology 2010, Digestive Disease Week 2009 and 2010, and GASTRO 2009) using a broader search term 'clopidogrel' and contacting authors for unpublished data. We searched the bibliographies of included trials for relevant studies.

### Study Selection and Data Extraction

Two reviewers (CSK, and either RSN or YKL), independently and in duplicate, assessed all titles and abstracts for studies that met the inclusion criteria, and excluded any articles that failed to meet the criteria. Full reports (where available) of potentially relevant trials and studies were retrieved and independently checked by all reviewers (CSK, RSN, YKL). Independent data collection on study design, drug exposure, study location, participant characteristics and exact nature of outcomes were collected on a spreadsheet. Where there was uncertainty or discrepancies, the articles were discussed among the reviewers for inclusion. Authors were contacted if there were areas that required clarification.

### Assessment for 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.[7]

To reduce publication bias, we searched conference abstracts and contacted authors for additional unreported data.

### Data Analysis

We used RevMan 5.0.24 (Nordic Cochrane Centre, Copenhagen, Denmark) to conduct random effects meta-analysis using inverse variance method for pooled odds ratios (OR) and their 95% confidence intervals (CIs).

We assumed similarity between the risk ratio and OR because adverse GI events were uncommon events.[8] Where possible, we chose to pool adjusted odds ratios from the primary studies, otherwise we used raw outcome data to calculate unadjusted OR (which may be particularly susceptible to confounding).

The main analysis was the risk of adverse GI events with clopidogrel exposure, with or without concomitant PPI use. Owing to variation in outcomes reporting, and concomitant aspirin usage, we subgrouped studies based on the medication used (clopidogrel alone, or clopidogrel with definite or possible aspirin use) and the nature of adverse GI event (GI bleeding alone, or with ulcer, perforation and obstruction).

### Statistical Heterogeneity

Statistical heterogeneity was assessed using the $I^2$ statistic, with $I^2$ values of 30–60% representing a moderate level of heterogeneity.[9]

## Results

The search results yielded ten relevant studies with 71 277 patients; the process of selection is shown in figure 1. These were comprised of nine retrospective studies and one RCT.[5,10-18] The main characteristics of the studies and participants are described in table I. The outcomes, interventions and quality assessments of the included studies are shown in table II.

In general, most of the included studies had some susceptibility to the risk of bias. There was only one RCT, with well defined intervention, and outcome ascertainment through endoscopic or radiological investigations.[10] This trial was reported as a conference abstract and although we had access to the slide presentation, the full data have yet to be published.

All the other studies were retrospective in design, based mainly on review of health records and prescription databases. The accuracy of such database studies relies heavily on ascertainment of exposure based on prescription claims (rather than actual medication use) and outcomes assessed by International Classification of Diseases (or other diagnostic) codes. Three studies had endoscopic verification of upper GI outcomes.[10,14,18] We judged one retrospective study to have a relatively lower risk of bias because structured medication histories were obtained from patients and their families, as well as endoscopic confirmation of upper GI bleeds.[14] Although two studies used propensity scoring in order to try to match the participants,[5,12] all the retrospective observational studies suffer from potential risk of confounding.

The exact outcome definitions of adverse GI events varied according to study and we were unable to obtain detailed descriptions of the severity and eventual consequences of the adverse event. Table II shows that upper GI bleed was the broad category measured in a number of studies, with one study explicitly stating that haematemesis, melaena or fall in haemoglobin were the upper GI bleed criteria,[18] whereas another study recorded major bleeds leading to death or transfusion or readmission.[15] Other studies used composite outcomes such as GI complications, e.g. bleeding, ulcers or perforation.[10,12]

### Type of Antiplatelet Exposure

The ten included studies yielded eleven separate risk estimates according to category of antiplatelet exposure, with one study reporting on two different exposures.[17] Seven studies provided data on participants receiving dual antiplatelet therapy, two studies looked at clopidogrel without specifically reporting on aspirin intake, and two studies reported on clopidogrel monotherapy (figures 2 and 3) For the seven studies that analysed dual antiplatelet therapy (aspirin and clopidogrel), PPI exposure was associated with a significant reduction in adverse GI events, pooled OR of 0.38 (95% CI 0.21, 0.68; $p = 0.001$; $I^2 = 17\%$). We separately analysed the two studies where we were uncertain about aspirin exposure;

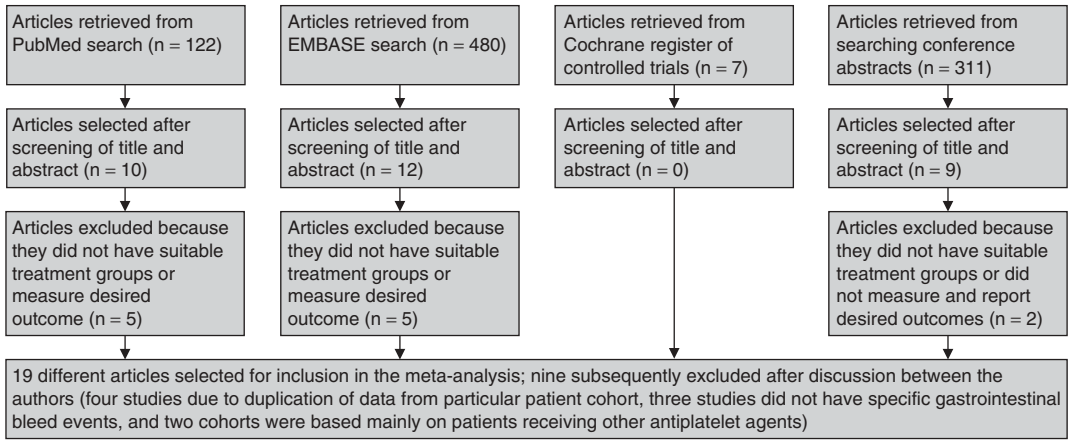


**Fig. 1.** Flow diagram of the process of article selection for meta-analysis.

the pooled OR was 0.34 (95% CI 0.14, 0.87; $p = 0.02$) with substantial heterogeneity ($I^2 = 73\%$). Overall, it is important to note that all nine studies yielded a consistent direction of effect, and pooling the seven dual antiplatelet studies with the two studies of uncertain aspirin exposure led to an OR of 0.40 (95% CI 0.28, 0.58; $p < 0.001$) with some heterogeneity ($I^2 = 27\%$). Here, the number needed to treat per year to prevent one additional hospitalization for GI bleed would be 239 (95% CI 199, 342) and 37 (95% CI 30, 53), respectively, based on the low and high GI risk categories in a large population-based study.[5]

The results for patients receiving antiplatelet monotherapy (i.e. clopidogrel alone) were widely divergent, with one study suggesting potential benefit from PPI exposure while the other found no demonstrable GI effect. The pooled OR here was 0.60 (95% CI 0.14, 2.61; $p = 0.50$; $I^2 = 75\%$) [figure 3].

### Nature of Gastrointestinal Adverse Events

Nine studies specifically evaluated upper GI bleed as the outcome, yielding a pooled RR of 0.31 (95% CI 0.19, 0.51; $p < 0.001$; $I^2 = 27\%$). In contrast, the results for overall adverse GI events (comprising bleeds, ulcers, perforation and obstruction) were widely divergent ($I^2 = 87\%$), with the RCT demonstrating significant benefit from PPI exposure while the retrospective observational study found no demonstrable GI effect (figure 4).[10,12]

### Use of Other Gastroprotective Agents

From the ten included studies, we identified three that reported on the associated risk of upper GI bleeds with histamine $H_2$ receptor antagonists, as well as with PPIs (table III). Owing to the sparse data, we did not proceed to do a comparative meta-analysis of the relative benefits of PPIs versus histamine $H_2$ receptor antagonists, although the risk reductions in table III indicate that PPIs may possibly be more efficacious.

## Discussion

The overall pooled estimates suggest that there is a significant reduction in GI adverse events when PPIs are used by patients on dual aspirin and clopidogrel therapy. However, the potential GI benefits of PPIs in patients receiving clopidogrel monotherapy are much less certain, with sparse data. This would be consistent with the recognized mechanisms of harm stemming from dual antiplatelet therapy whereby aspirin promotes the development of ulcers, which are then more prone to bleed because of exposure to two antiplatelet agents. However, we should also recognize that patients prescribed clopidogrel alone may have different underlying GI and cardio-

**Table I.** Study design and characteristics

| Study (y) | Design, country and setting | No. of participants and lost to follow-up | Mean age (y) | Male (%) | Selection criteria |
|---|---|---|---|---|---|
| Bhatt et al.[10] (2009) | Double-blind, prospective, placebo-controlled, multicentre, international, randomized controlled trial | 3627 participants | 67.2 | 70.7 | Patients >21 years with ACS or coronary stent requiring clopidogrel and aspirin (acetylsalicylic acid) for next 12 mo. Excluded were those with significant GI or bleeding history, current use of gastroprotective drugs or anticoagulants |
| Hokimoto and Ogawa[11] (2010) | Cohort study in Japan from August 2008 to December 2009 | 191 patients followed up for 12 mo | 68.8 | 69 | Patients undergoing coronary intervention who received dual antiplatelet therapy |
| Hsiao et al.[12] (2009) | Retrospective cohort study in Taiwan of National Health Insurance Database from January 2001 to December 2006 | 14 627 participants; 2626 participants were treated with clopidogrel | 71.6 | 59.6 | Patients on antiplatelet therapy between January 2001 and December 2006 with a history of hospitalization for GI complications of peptic ulcer or GI bleed, or perforation detected on surgery. Patients whose records suggest continuous use of antiplatelet therapy were included and those with combinational therapy were excluded |
| Joshi et al.[13] (2009) | Retrospective cross-sectional study of patients in a Canadian hospital | 129 patients had complete data | NS | NS | Patients aged >60 y who received a drug-eluting stent between January 2007 and April 2008, identified via a Department of Cardiology database |
| Lanas et al.[14] (2007) | Case-control study of patients recruited from hospitals in Spain | 8309 participants; 2777 cases matched to 5532 controls | 61.3 | 59.1 | Patients with upper GI bleed who were admitted to hospital, with matched controls who did not have GI, cardiovascular or arthritic conditions |
| Luinstra et al.[15] (2010) | Retrospective cross-sectional study of patients recruited from hospitals in Australia | 385 participants, 1 patient had an unknown result | 62.4 | 70.4 | All patients newly started on clopidogrel between July 2006 and June 2007 |
| Ng et al.[16] (2008) | Retrospective cohort study of hospital patients in Hong Kong | 1364 treated with clopidogrel and aspirin; 377 were excluded for stopping therapy | 66.9 | 75.4 | Patients treated with aspirin and clopidogrel during the study period between January 2001 and September 2006 |
| Ray et al.[5] (2010) | Retrospective cohort study of Tennessee Medicaid patient data in the US | 20 596 total; 7593 receiving clopidogrel and PPI | 60.5 | 50.3 | Patients >30 years enrolled in Medicaid with at least 1 day of clopidogrel use with available study data. The exclusion criteria was those who had events unlikely due to medication, used cocaine or alcohol, had cancer, HIV, renal hepatic or respiratory failure, organ transplantation, liver cirrhosis, esophageal varices and bariatric or other surgery, and nursing home residents |
| Rodriguez and Johansson[17] (2010) | Retrospective case-control study of primary care patients in the UK (Health Information Network database) | 2049 cases matched to 20 000 controls | Range 40–84 | NS | Patients with a diagnosis of upper GI bleed between 1997 and 2007. Diagnostic categories of controls were not stated but were age-, sex- and calendar-matched |
| Yasuda et al.[18] (2009) | Retrospective cohort study of hospital patients in Japan | 243 total participants; 67 receiving PPI, 135 not receiving PPI | 68 | 75.3 | Patients who had undergone PCI with dual antiplatelet therapy between January 2006 and December 2007 |

**ACS** = acute coronary syndrome; **GI** = gastrointestinal; **NS** = not stated; **PCI** = percutaneous coronary intervention; **PPI** = proton pump inhibitor.

**Table II.** Study outcomes, interventions and quality

| Study (y) | Treatment exposure and ascertainment | Outcome and follow-up | Outcome ascertainment | Results | Risk of bias |
|---|---|---|---|---|---|
| Bhatt et al.[10] (2009) | Aspirin (acetylsalicylic acid) and clopidogrel, with or without omeprazole in a randomized, placebo-controlled trial | Adverse upper GI events: bleeds, ulcer, erosions, perforation or obstruction | Endoscopic or radiological confirmation | Rate of adverse GI events: 38/1878 (2.0%) with omeprazole vs 67/1895 (3.5%) without omeprazole | Abstract only; low risk of confounding due to randomized design. Placebo-control, with double blinding. Loss to follow-up not reported |
| Hokimoto and Ogawa[11] (2010) | Aspirin and clopidogrel, with or without rabeprazole (at clinician's discretion) | GI bleeding at 12-mo follow-up | NS | Rate of GI bleed: 0/50 with rabeprazole vs 2/141 (1.4%) without rabeprazole | Abstract only; baseline differences unclear with no adjustment for confounders, no details of loss to follow-up and outcomes ascertainment |
| Hsiao et al.[12] (2009) | Clopidogrel and PPI vs no PPI. Ascertainment of exposure based on prescription data from insurance claims database | Hospitalization for recurrence of major GI complication (bleed, ulcer or perforation) | ICD codes on database | Recurrent major GI complication with PPI 141/590, without PPI 438/2036, adjusted HR 1.08 (95% CI 0.89, 1.33) | Treatment exposure and outcomes were based on computerized records – validation was not reported; propensity score was used, but residual confounding is possible |
| Joshi et al.[13] (2009) | Aspirin plus clopidogrel, with or without PPI, identified from chart review | Upper GI bleed | Chart review | Rate of upper GI bleed was 1/39 (2.6%) in PPI-exposed group vs 4/90 (4.4%) in those without PPI | Abstract only; no attempt to adjust for confounding. Validation of treatment exposure and outcomes unclear |
| Lanas et al.[14] (2007) | Clopidogrel and PPI vs no PPI, structured interview with patient and family, plus review of hospital records | Upper GI bleed | Outcomes confirmed by endoscopy | PPI use in clopidogrel-treated cases was 13/107 (12%) and 23/81 (28%) in clopidogrel-treated controls. PPIs were associated with a reduced risk of GI bleed, adjusted RR 0.19 (95% CI 0.07, 0.49) | Attempted to select matched controls and adjust for several variables to reduce confounding in regression analysis |
| Luinstra et al.[15] (2010) | Aspirin/clopidogrel and PPI use was determined from a retrospective review of medical records and pharmacy database | Major GI bleeds (leading to death/transfusion/readmission) | Review of hospital records | GI bleeds in patients with risk factors: aspirin/clopidogrel + PPI 2/60, no PPI 5/54<br>With no risk factors: aspirin/clopidogrel + PPI 0/53, no PPI 3/170 (Kwok CS, unpublished observations) | Risk of confounding. Outcomes may have been missed if patients sought medical attention elsewhere |
| Ng et al.[16] (2008) | Discharged or treated with aspirin and clopidogrel at hospital, using computerized records | Upper GI bleed during study period | ICD codes and review of clinical records | Adjusted OR of GI bleed with PPI was 0.04 (95% CI 0.002, 0.21) | Validation of treatment exposure and outcomes unclear, risk of confounding despite adjustment |

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**Table II.** Contd

| Study (y) | Treatment exposure and ascertainment | Outcome and follow-up | Outcome ascertainment | Results | Risk of bias |
|---|---|---|---|---|---|
| Ray et al.[5] (2010) | Clopidogrel with PPI vs without PPI, prescriptions filled on pharmacy database | Hospitalization for gastroduodenal bleeding | Validated computerized diagnostic codes with 91% sensitivity | Adjusted incidence for hospitalization for GI bleed: HR 0.50 (95% CI 0.39, 0.65) | Adherence to drug therapy not verified. Propensity scoring system was used to reduce risk of confounding |
| Rodriguez and Johansson[17] (2010) | Clopidogrel alone, or clopidogrel plus aspirin, with and without PPI. Prescribing records from general practice database | Upper GI bleed during study period | NS | Upper GI bleed: PPI and clopidogrel vs no PPI, RR 0.23 (95% CI 0.05, 1.01), PPI plus clopidogrel/aspirin vs no PPI, OR 0.21 (95% CI 0.05, 0.87) | Abstract only; validation of treatment exposure and outcomes uncertain. Unclear risk of confounding |
| Yasuda et al.[18] (2009) | Clopidogrel/ticlopidine and aspirin with or without PPI, ascertained via medical records of patients post-PCI | Upper GI bleed (haematemesis, melaena or fall in haemoglobin) during study period | Peptic ulcers confirmed by endoscopy | Rates of upper GI bleed for clopidogrel + aspirin and PPI 0/67, no PPI 8/135 | Validation of treatment exposure unclear, potential risk of confounding |

**GI** = gastrointestinal; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **NS** = not stated; **OR** = odds ratio; **PCI** = percutaneous coronary intervention; **PPI** = proton pump inhibitor; **RR** = relative risk.

vascular conditions compared with those on dual antiplatelet therapy.

The potential benefits of concomitant PPI appear related to the reduction in upper GI bleeds, but are less clear for overall GI adverse events that include bleeding, ulcer, perforation or obstruction. This partly stems from the heterogeneity in the analysis of major GI adverse events, where no demonstrable effect was seen in the retrospective study of recurrent GI events in patients receiving clopidogrel monotherapy,[12] in contrast to the significant benefit found in a placebo-controlled randomized trial in patients receiving dual antiplatelet therapy.[10] As the clinical trial data are not fully published yet, we do not know if the main benefit here stems from reduction in haemorrhage or in other GI events.

Our findings will help clinicians to weigh up the pros and cons in the recent controversy over the role of concomitant PPIs in patients receiving clopidogrel. A systematic evaluation on the potential benefits of PPIs has so far been missing from the current debate; this meta-analysis aims to address the gap in the evidence. Although there are weaknesses in the quality of the studies, the available data does suggest a possible benefit from PPIs that may perhaps balance out controversial concerns over any adverse cardiovascular interaction with clopidogrel. The postulated interaction could arguably be a double-edged sword where the diminished antiplatelet effect can lead to cardiovascular harm but also beneficially reduces the likelihood of GI haemorrhage. Some researchers have recommended that prescribers carefully weigh up the magnitude of cardiovascular problems against any potential GI harm before omitting PPI therapy in patients taking clopidogrel.[5,6]

Clinicians should also bear in mind that while cardiovascular adverse events can result in serious morbidity and mortality, the same also applies for severe GI adverse events. The risk of death from upper GI bleeds from NSAIDs and aspirin intake appears to be rising, with a mortality rate of 20.9% for studies published after 1997.[19] Given that the risk of adverse cardiovascular outcomes with concomitant use of clopidogrel and PPI is at best inconsistent, there will

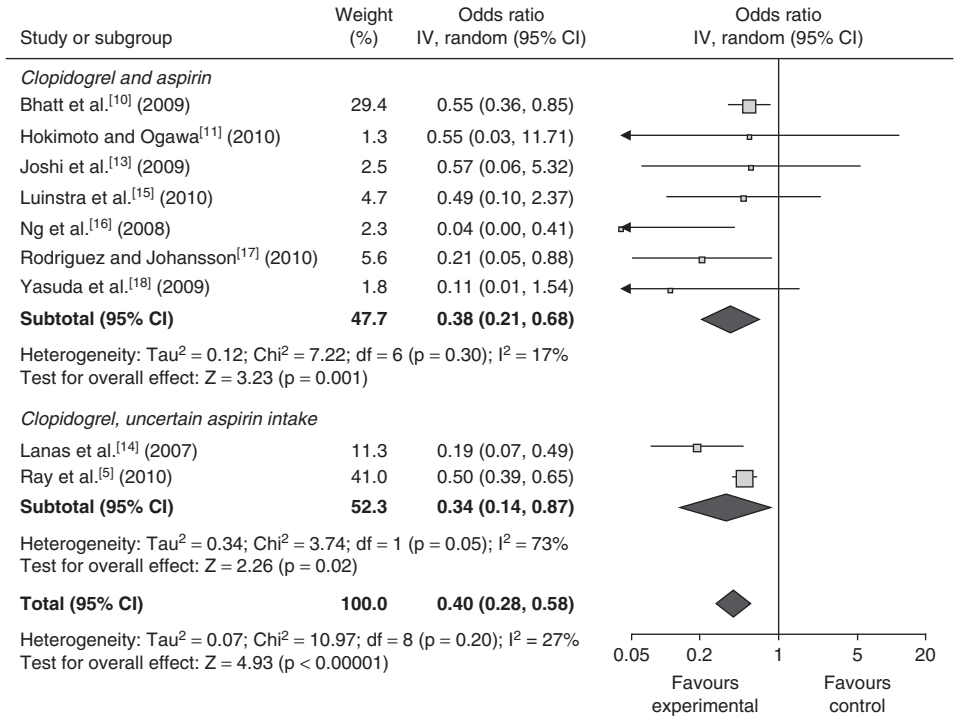


**Fig. 2.** Meta-analysis of adverse gastrointestinal events with proton pump inhibitor (PPI) plus dual antiplatelet therapy (aspirin [acetylsalicylic acid] and clopidogrel), or PPI plus clopidogrel with uncertain level of aspirin intake vs control. **df** = degrees of freedom; **IV** = inverse variance.

be individual patients for whom the GI benefits probably outweigh the unproven cardiac risk. Conversely, there will certainly be patients at high cardiovascular risk who have no GI history in whom routine use of PPIs with clopidogrel is not recommended. There are alternative gastroprotective agents available, but we do not have information on their safety and efficacy when used together with clopidogrel. Some studies have reported the risk of GI adverse events with different gastroprotective agents (PPIs or histamine $H_2$ receptor antagonists), but the data were too sparse for us to perform a more detailed analysis (table III). A future trial where aspirin

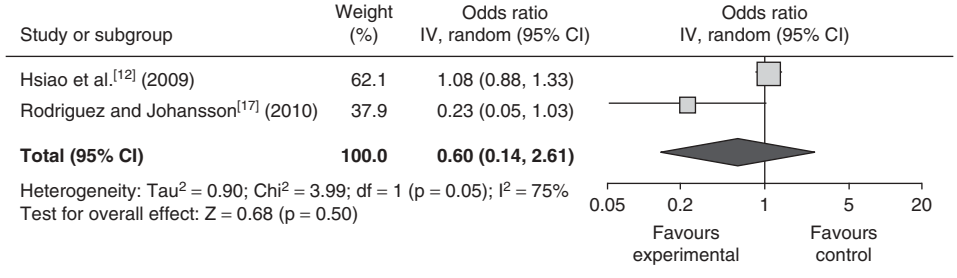


**Fig. 3.** Meta-analysis of adverse gastrointestinal events with proton pump inhibitor plus clopidogrel alone vs control. **df** = degrees of freedom; **IV** = inverse variance.

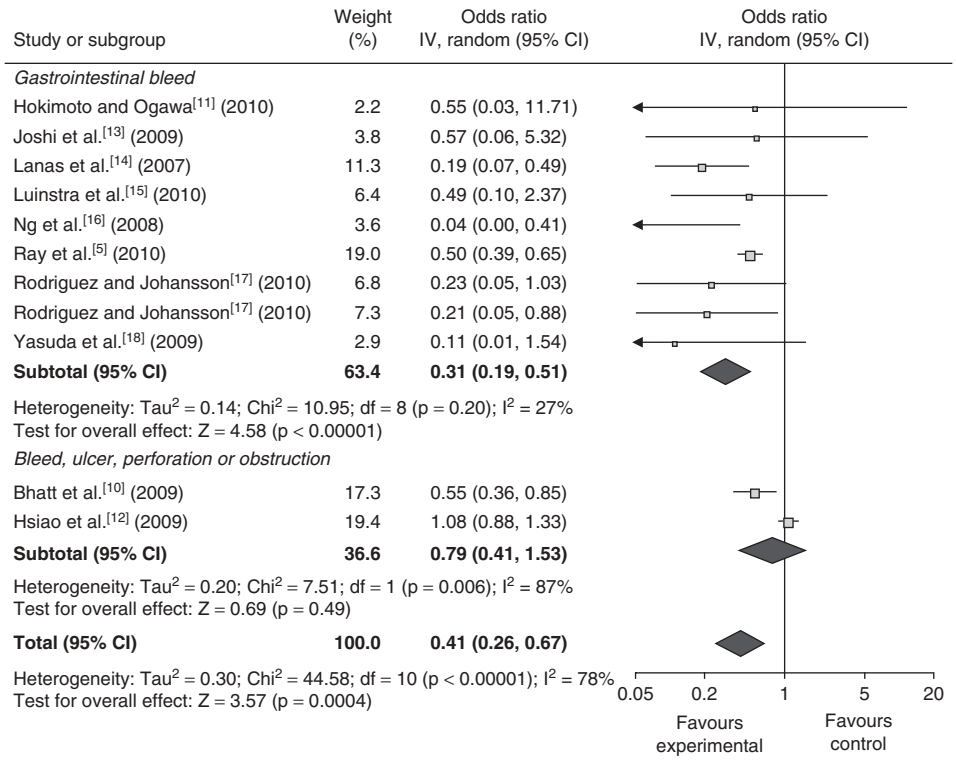


**Fig. 4.** Meta-analysis of subtypes of adverse gastrointestinal events with clopidogrel plus proton pump inhibitor use vs control. **df** = degrees of freedom; **IV** = inverse variance.

and clopidogrel patients are randomized to either PPI or histamine $H_2$ receptor antagonists will help to clarify if patients can derive greater benefit from either agent, in terms of cardiovascular events or GI bleeds.

One major strength of this study is the large number of participants in the analysis. While aspirin-induced adverse GI events are well recognized, severe ulceration and bleeding is uncommon and a large sample size is needed in order to arrive at more precise estimates of risk. Another advantage of this analysis was that we were able to partially stratify the analysis to separately evaluate dual therapy antiplatelet therapy against clopidogrel monotherapy, as well as the risk of upper GI bleed versus other major GI adverse events (ulcer, bleed, perforation or obstruction).

While we were able to synthesize all relevant information on the risk of adverse GI events with PPI and clopidogrel, our analysis has some

**Table III.** Studies that reported on risk of upper gastrointestinal bleed with proton pump inhibitor (PPI) or histamine $H_2$ receptor antagonist exposure in patients receiving clopidogrel

| Study (y) | PPI exposure vs control (95% CI) | $H_2$ receptor antagonist vs control (95% CI) |
|---|---|---|
| Lanas et al.[14] (2007) | RR 0.19 (0.07, 0.49) | RR 0.83 (0.20, 3.51) |
| Ng et al.[16] (2008) | OR 0.04 (0.002, 0.21) | OR 0.43 (0.18, 0.91) |
| Yasuda et al.[18] (2009) | Rate: 0/67 | Rate: 0/41 |

**OR** = odds ratio; **RR** = relative risk.

limitations. Only one of the ten studies was an RCT and the other studies were all retrospective in design, with risk of bias and confounding. Many studies relied on computerized diagnostic codes, pharmacy claims databases and retrospective chart reviews, and threats to validity may arise from limited reliability in ascertainment of drug exposures and GI outcomes. Two studies in particular lacked clarity regarding the degree of aspirin exposure.[5,14] Similarly, there was very little detail about the actual severity and clinical consequences of GI adverse events. Also, there was some degree of heterogeneity in the results and we were unable to reliably assess the risk of publication bias as recent research has suggested that asymmetry tests such as funnel plots should only be done when there are more than ten studies.[20] Finally, the generalizability of the RCT may be limited because it only investigated patients receiving omeprazole, rather than other PPIs.[10]

## Conclusions

In conclusion, this meta-analysis has uncovered evidence that the risk of adverse GI events may be reduced by co-administration of PPI therapy in patients receiving dual antiplatelet therapy with aspirin and clopidogrel. Careful patient selection, based on the evidence presented in this study, may help to justify PPI use in patients receiving dual antiplatelet therapy who have substantial risk factors for upper GI haemorrhage.

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Correspondence: Dr *Yoon K. Loke*, School of Medicine, Health Policy and Practice, University of East Anglia, Earlham Road, Norwich NR4 7TJ, UK.
E-mail: y.loke@uea.ac.uk