Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis

Rhanderson N Cardoso, Alexandre M Benjo, James J DiNicolantonio, Daniel C Garcia, Francisco Y B Macedo, Georges El-Hayek, Girish N Nadkarni, Sebastiano Gili, Mario Iannaccone, Ioannis Konstantinidis, John P Reilly

ABSTRACT

Background: Dual antiplatelet therapy is the standard of care after coronary stent placement but increases the bleeding risk. The effects of proton pump inhibitors (PPIs) on clopidogrel metabolism have been described, but the clinical significance is not yet definitive. We aimed to do an updated meta-analysis comparing outcomes in patients receiving clopidogrel with and without PPIs.

Methods: We systematically searched PubMed, Scopus and the Cochrane Central Register of Controlled Trials for randomised controlled trials (RCTs) and controlled observational studies in patients taking clopidogrel stratified by concomitant PPI use. Heterogeneity was examined with the Cochran Q test and I² statistics; p values inferior to 0.10 and I² >25% were considered significant for heterogeneity.

Results: We included 39 studies with a total of 214 851 patients, of whom 73 731 (34.3%) received the combination of clopidogrel and a PPI. In pooled analysis, all-cause mortality, myocardial infarction, stent thrombosis and cerebrovascular accidents were more common in patients receiving both drugs. However, among 23 552 patients from eight RCTs and propensity-matched studies, there were no significant differences in mortality or ischaemic events between groups. The use of PPIs in patients taking clopidogrel was associated with a significant reduction in the risk of gastrointestinal bleeding.

Conclusions: The results of our meta-analysis suggest that PPIs are a marker of increased cardiovascular risk in patients taking clopidogrel, rather than a direct cause of worse outcomes. The pharmacodynamic interaction between PPIs and clopidogrel most likely has no clinical significance. Furthermore, PPIs have the potential to decrease gastrointestinal bleeding in clopidogrel users.

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is recommended following acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI), as it...
has been shown to decrease the risk of adverse cardiovascular (CV) events.1–5 PPIs significantly decrease the risk of upper gastrointestinal (GI) haemorrhage in patients receiving antiplatelet therapy.6–8

Clopidogrel activation is dependent on the hepatic cytochrome P450, which can be competitively inhibited by PPIs.9–12 The potential interaction between clopidogrel and PPIs has been extensively demonstrated in pharmacokinetic platelet aggregation studies.13 Subsequently, these findings led to label warnings from the Food and Drug Administration regarding the concomitant use of clopidogrel with omeprazole or esomeprazole.17 Furthermore, these concerns have resulted in more restricted guideline indications for PPIs in patients taking antiplatelet therapy.18

Nevertheless, the majority of data on the clinical significance of the PPI-clopidogrel interaction derive from observational studies and the results have been conflicting.19–23 Two randomised controlled trials (RCTs) have failed to show an increased incidence of ischaemic CV outcomes in patients on concomitant use of clopidogrel and a PPI.24 Multiple meta-analyses have been performed, but the most recent one included data only until June 2012.24–29 A substantial number of studies have been published since then, including over 50,000 patients.30–36 We aimed to perform an updated meta-analysis comparing the incidence of adverse CV and GI events in patients receiving clopidogrel with and without PPIs. Furthermore, we sought to identify possible factors in the clopidogrel-PPI interaction, such as ACS, DAPT and specific PPIs.

MATERIAL AND METHODS
Eligibility criteria and data extraction
We restricted our analysis to studies that met all the following inclusion criteria: (1) RCTs, case–control or cohort (retrospective or prospective) studies; (2) patients on clopidogrel stratified into two groups: concomitant PPI-clopidogrel use versus clopidogrel use alone; (3) available data on any of the outcomes of interest in a direct comparison between PPI and non-PPI users; and (4) at least 6 months of follow-up. Exclusion criteria were non-controlled studies (absence of comparison group on clopidogrel without concomitant PPI use), ongoing studies and duplicate reports. In studies with outcomes reported in person-years rather than in absolute values, we attempted contact with the authors to obtain patient-level data.

Each of the four authors (RNC, DCG, FYBM, GEH) independently extracted data following the defined search criteria and quality assessment. Disagreements between these four authors were resolved by consensus. In addition to outcomes of interest, the authors also extracted further information for subgroup analyses, including population characteristics, specific PPI used, concomitant use of aspirin and study design.

Search strategy
We systematically searched PubMed, Scopus and the Cochrane Central Register of Controlled Trials for RCTs and controlled observational studies in patients taking clopidogrel stratified by concomitant PPI use. The search was conducted without date restrictions in February 2014 for studies published in English only. The following medical subject heading terms were included: (clopidogrel OR Plavix) AND (PPI OR proton pump inhibitor OR omeprazole OR esomeprazole OR rabeprazole OR pantoprazole OR lansoprazole OR ilaprazole OR dexlansoprazole). In addition to searching databases, investigators also reviewed abstracts from the main cardiology and GI conferences from 2010 to 2014. Reference lists of all included studies, meta-analysis and reviews were manually searched. There was no patient population size restriction for the search.

End points and subgroup analyses
Outcomes of interest included all-cause mortality, CV mortality, myocardial infarction (MI), ACS, stent thrombosis, revascularisation, cerebrovascular accidents (CVA) and GI bleeding. Given the large number of studies and availability of individual outcomes, combined end points were not used. For the outcome of stent thrombosis, thought to be the most prone to variability in definitions, a subanalysis was performed including only definite cases according to Academic Research Consortium criteria.37 Owing to an anticipated variability in the definitions of GI bleeding, we restricted our analysis to gastric or duodenal bleeding confirmed by endoscopy.

In the search for potential factors associated with a clopidogrel-PPI interaction, prespecified subgroup analyses were performed. These included (1) concomitant treatment with aspirin (DAPT); (2) patients with PCI; (3) patients with ACS; and (4) stratification by risk of clopidogrel interaction according to degree of CYP450 2C19 inhibition. The high-risk PPI group included omeprazole, esomeprazole and lansoprazole, which are considered the most prone to CYP450 2C19 inhibition.38 11 16 17 20 Pantoprazole and rabeprazole were analysed separately in the low-risk PPI group.16 17 20 27 39 Finally, a subanalysis was also performed that was restricted to RCTs and propensity score matched (PSM) studies to evaluate for the possibility of selection bias in observational studies.

Quality assessment
The quality of case–control and cohort studies was evaluated by the Newcastle-Ottawa Scale (NOS).39 This tool for quality assessment of non-randomised studies attributes none to nine stars according to the methodological quality of three parameters: selection of participants; comparability of groups; and assessment of either exposure in case–controls or outcomes in cohort studies. Previous meta-analyses have considered studies with 6 or more stars as high quality.40 41 Post hoc analyses of RCTs were assessed as cohort studies by the
NOS, given that the exposure of interest was not a randomised factor. With the exception of the two conference abstracts, all case-control and cohort studies included received a score of 7 or higher on the Newcastle-Ottawa scale and therefore were considered studies of high methodological quality. Quality assessment of RCTs was performed with the Jadad score, which evaluates randomisation, blinding and follow-up. Publication bias was evaluated by using funnel-plot graphs and checking for symmetrical distribution of trials with similar weights.

### Statistical analysis

Meta-analysis was performed according to recommendations of the Cochrane Collaboration and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Pooled treatment effects were estimated using OR with 95% CIs for binary end points. We used the random-effects DerSimonian and Laird model because of the anticipated wide variability between studies, particularly among observational data. Nevertheless, results were confirmed with the Mantel-Haenszel fixed-effect model to avoid small studies being overly weighted. Heterogeneity was examined with the Cochran Q test and $I^2$ statistics; p values inferior to 0.10 and $I^2 >25\%$ were considered significant for heterogeneity. For statistical analysis, we used Review Manager 5.1 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

### RESULTS

#### Study selection and characteristics

As illustrated in figure 1, overall 2125 studies were identified. After removal of duplicate reports, animal studies and non-relevant studies by title or abstract review, 93 articles remained. These were fully reviewed for satisfaction of inclusion criteria. The main reasons for withdrawal were absence of control group, outcomes of interest not reported or a short follow-up interval.

Thirty-seven manuscripts met all criteria and were included. An additional two studies were included from a review of conference abstracts. A total of 39 studies and 214,851 patients were included, of whom 73,731 (34.3\%) received the combination of clopidogrel and a PPI. The vast majority were observational studies and only three RCTs were identified. Study characteristics are presented in table 1. Baseline characteristics in individual studies were not commonly not comparable between groups; therefore, a subanalysis of RCTs/pro-pensity score matched (PSM) populations was carried out to evaluate the impact of selection bias in study results.

#### Pooled analysis of all studies

All-cause mortality (OR 1.39; 95% CI 1.19 to 1.61; p<0.001) and MI (OR 1.41; 95% CI 1.20 to 1.65; p<0.001) were significantly increased in the group of patients receiving PPIs, as illustrated in figure 2. Stent thrombosis (OR 1.30; 95% CI 1.05 to 1.63; p=0.02), definite stent thrombosis (OR 1.65; 95% CI 1.10 to 2.48; p=0.02; figure 3A), ACS (OR 1.92; 95% CI 1.23 to 3.0; p=0.004; figure 3B) and CVA (OR 1.66; 95% CI 1.40 to 1.97; p<0.001; figure 3C) were also more common in patients receiving both drugs. There was also a strong trend towards increased revascularisation (OR 1.26; 95% CI 1.0 to 1.59; p=0.05; figure 3D) in the PPI-clopidogrel group. Conversely, the concomitant use of PPIs had a protective effect over the risk of GI bleeding (OR 0.40;
### Table 1: Characteristics of studies included in meta-analysis

| Study Design       | Study     | Patients (n) | Location                  | Time frame | Follow-up | PPIs | Patient population | Outcomes available | DAT    |
|--------------------|-----------|--------------|---------------------------|------------|-----------|------|-------------------|-------------------|--------|
| Case–control       | Juurlink et al [6] | PPI: 170 No PPI: 407 | Ontario, Canada            | 4/2002–9/2008 | 6 months | L, O, P, R   | CVA               | All-cause mortality, CVA | <9%   |
| Case–control       | Valkhoff et al [17] | PPI: 4793 No PPI: 1123 | Netherlands              | 1/1999–12/2008 | 42.6 months | E, L, O, P, R | MI               | MI                | NA    |
| Case–control       | Ching et al [8] | PPI: 1128 No PPI: 2159 | Connecticut, USA          | 1/2004–11/2008 | 9 months | E, L, O, P, R | PCI with stent    | All-cause mortality, MI, revascularisation (TVR) | Yes   |
| Case–control       | Jiang et al [7] | PPI: 1570 No PPI: 1110 | Nanjing, China            | 1/2008–1/2011 | 1 year   | E, L, O, P, R | PCI               | GI bleed          | Yes   |
| Case–control       | Garcia Rodriguez et al [20] | PPI: 92 No PPI: 1177 | UK                        | 1/2000–12/2007 | >3.5 years | E, L, O, R | ACS               | GI bleed          | NA    |
| Retrospective cohort | Ho et al [19] | PPI: 5244 No PPI: 2961 | VA hospitals, USA        | 12/2003–1/2006 | 521 days | L, O, P, R   | ACS               | All-cause mortality, ACS, revascularisation | ~90%  |
| Retrospective cohort | Evanchan et al [20] | PPI: 1369 No PPI: 4425 | Ohio, USA                | 1/2003–1/2008 | 1 year   | E, L, O, P  | Stent after MI   | MI                | NA    |
| Retrospective cohort | Gaspar et al [20] | PPI: 318 No PPI: 502 | Washington DC, USA       | 4/2003–4/2007 | 1 year   | E, L, O, P, R | PCI with DES     | All-cause mortality, MI, revascularisation (TVR), ST | Yes   |
| Retrospective cohort | Gupta et al [13] | PPI: 72 No PPI: 528 | Braga, Portugal           | 1/2004–3/2008 | 6 months | L, O, R      | ACS               | All-cause mortality, ACS | Yes   |
| Retrospective cohort | Kreutz et al [4] | PPI: 243 No PPI: 6828 | Medco Health Database, USA| 10/2005–9/2006 | 1 year   | E, L, O, P, R | PCI with stent | CV death, MI, ACS, revascularisation, CVA | NA    |
| Retrospective cohort | Tentzeris et al [5] | PPI: 691 No PPI: 519 | Vienna, Austria          | 1/2003–12/2006 | 7.8 months | E, L, O, P, R | PCI with stent   | All-cause mortality, CV mortality, ACS, ST | Yes   |
| Retrospective cohort | van Boxel et al [3] | PPI: 5734 No PPI: 12405 | The Netherlands           | 1/2006–12/2007 | 1–2 years | E, L, O, R  | NA                | All-cause mortality, MI, ACS, CVA | ~78%  |
| Retrospective cohort | Wu et al [6] | PPI: 311 No PPI: 5511 | Taiwan                   | 7/2002–6/2005 | 1 year    | E, L, O, P  | ACS               | ACS, revascularisation | NA    |
| Retrospective cohort | Yasu et al [7] | PPI: 103 No PPI: 188 | Kamakura, Japan          | 6/2006–3/2009 | 395 days  | R            | PCI with DES     | CV mortality, ACS, revascularisation, ST, GI bleed | Yes   |
| Retrospective cohort | Munoz-Torero et al [8] | PPI: 519 No PPI: 703 | Spain                    | 3/2003–3/2009 | 15 months | L, O, P      | Atherosclerotic disease | All-cause mortality, MI, CVA | ~65%  |
| Retrospective cohort | Hauptle et al [9] | PPI: 87 No PPI: 631 | Switzerland              | 1/2005–12/2006 | 1 year    | E, L, O, P, R | PCI for ACS      | GI bleed          | Yes   |
| Retrospective cohort | Ortolani et al [9] | PPI: 3519 No PPI: 377 | Emilia-Romagna, Italy    | 1/2008–8/2008 | 1 year    | E, L, O, P, R | ACS               | All-cause mortality, ACS, revascularisation | >91%  |
| Retrospective cohort | Nakayama et al [10] | PPI: 280 No PPI: 284 | Tokyo, Japan             | 1/2005–12/2009 | 880 days  | L, O, R      | PCI               | Revascularisation (TLR) | Yes   |
| Retrospective cohort | Zou et al [8] | PPI: 6188 No PPI: 1465 | Nanjing, China          | 10/2005–9/2010 | 1 year    | E, O, P     | ACS with DES    | CV death, MI, revascularisation (TVR), ST | Yes   |
| Cohort             | Zairis et al [10] | PPI: 340 No PPI: 248 | Piraeus, Greece         | 4/2003–1/2005 | 1 year    | O            | PCI with stent   | CV mortality, MI, revascularisation, ST | >97%  |
| Cohort             | Hokimoto and Ogawa et al [11] | PPI: 34 No PPI: 37 | Japan                    | 1/2005–9/2010 | 1 year    | R            | DAT              | CV mortality, ACS, revascularisation, CVA, GI bleed | Yes   |
| Cohort             | Hudzik et al [12] | PPI: 18 No PPI: 20 | Poland                   | 1/2006–1/2008 | 1 year    | O            | PCI with stent   | MI, ACS, CVA      | Yes   |
| Cohort             | Banerjee et al [13] | PPI: 867 No PPI: 3678 | Veteran Affairs Database, USA | 1/2003–12/2008 | 1 year    | E, L, O, P, R | PCI with stent   | All-cause mortality, MI, revascularisation | NA    |
| Study Design | Study | Patients (n) | Location | Time frame | Follow-up | PPIs | Patient population | Outcomes available | DAT |
|--------------|-------|--------------|----------|------------|----------|------|-------------------|-------------------|-----|
| Cohort       | Rossini et al | 64 PPI: 1158 No PPI: 170 | Northern Italy | NA | 1 year | L, O, P | PCI with DES | All-cause mortality, ST | Yes |
| Cohort       | Simon et al  | 22 PPI: 1052 No PPI: 711 | France | NA | 1 year | E, L, O, P | MI | All-cause mortality | NA |
| Cohort       | Chitose et al | 187 PPI: 443 No PPI: 187 | Multicenter, Japan | 6/2008–3/2009 | 18 months | L, O, R | PCI with stent | CV mortality, MI, CVA | Yes |
| Cohort       | Douglas et al  | 12439 PPI: 16900 No PPI: 1690 | UK | 1/2003–7/2009 | 303 days | E, L, O | UK national database | All-cause mortality, CV mortality, MI | Yes |
| Post hoc analysis of RCT | O'Donoghue et al | 2257 PPI: 2257 No PPI: 4538 | Multinational | <9/2007 | 15 months | E, L, O, P, R | PCI for ACS, >94% stent | All-cause mortality, CV mortality, MI, ST | >96% |
| Post hoc analysis of RCT | Burkard et al  | 109 PPI: 109 No PPI: 692 | Basel, Switzerland | 5/2003–5/2004 | 36 months | E, L, O, P | PCI with stent | All-cause mortality, CV mortality, MI, revascularisation (TVR), ST | >91% |
| Post hoc analysis of RCT | Goodman et al  | 6021 PPI: 3255 No PPI: 685 | Multinational | 10/2006–7/2008 | 1 year | E, L, O, R | ACS | All-cause mortality, CV mortality, ST | >97% |
| RCT | Harjai et al  | 685 PPI: 685 No PPI: 685 | Sayre, PA, USA | 7/2001–12/2007 | 6 months | E, O | PCI | All-cause mortality, MI, revascularisation (TVR), ST | >98% |
| RCT | Hsiao et al  | 622 PPI: 622 No PPI: 9131 | Taiwan | 2000–2007 | >6 months | E, L, O, P, R | ACS | ACS | Yes |
| RCT | Alhara et al  | 1068 PPI: 819 No PPI: 819 | Ibaraki, Japan | 2/2006–8/2009 | 1 year | L, O, R | PCI with stent | All-cause mortality, MI, revascularisation, ST, CVA, GI bleed | Yes |
| RCT | Bhurke et al  | 2968 PPI: 2968 No PPI: 7143 | USA | 1/2001–12/2008 | 268 days | E, L, O, P, R | ACS | ACS, revascularisation | NA |
| RCT | Lin et al  | 5173 PPI: 5173 No PPI: 31926 | Taiwan | 1/2006–12/2007 | 580 days | E, L, O, P, R | ACS | ACS, revascularisation | NA |
| RCT | Bhatt et al  | 1876 PPI: 1876 No PPI: 1885 | Multinational | 1/2008–12/2008 | 180 days | O | ACS or stent | All-cause mortality, CV mortality, MI, revascularisation, CVA, GI bleed | Yes |
| RCT | Hsu et al  | 83 PPI: 83 No PPI: 82 | Taiwan | 8/2008–1/2010 | 6 months | E | History of GI ulcer | MI, ACS, CVA | NA |
| RCT | Hsu  | 157 PPI: 157 No PPI: 161 | Taiwan | 1/2008–11/2010 | 6 months | E | History of GI ulcer | GI bleed | NA |

ACCS: acute coronary syndrome; CV: cardiovascular; CVA: cerebrovascular accident; DAT: dual antiplatelet therapy; DES: drug-eluting stent; E: esomeprazole; GI: gastrointestinal; L: lansoprazole; MI: myocardial infarction; NA: not available or not applicable; O: omeprazole; P: pantoprazole; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; PSM: propensity score matched; R: rabeprazole; RCT: randomised controlled trial; ST: stent thrombosis; TLR: target lesion revascularisation; TVR: target vessel revascularisation.
95% CI 0.22 to 0.74; p=0.003; figure 4). A separate analysis restricted to cohort studies revealed similar results to the overall analysis.

Figure 2 Forest plot of studies examining outcomes between patients taking proton pump inhibitor (PPIs) with clopidogrel and those taking only clopidogrel: (A) overall mortality; (B) myocardial infarction.

RCTs and propensity score matched studies
Given the overwhelming majority of non-randomised observational studies in our meta-analysis and the subsequent risk of baseline heterogeneity between groups, a subanalysis was performed including only RCTs and PSM populations. A total of 23,552 patients were entered in the analysis, of whom 11,770 (49.9%) received the combination of clopidogrel and a PPI. Results are illustrated in figure 5 and show that all-cause mortality (OR 0.91; 95% CI 0.58 to 1.40; p=0.66), ACS (OR 0.96; 95% CI 0.88 to 1.05; p=0.35), MI (OR 1.05; 95% CI 0.86 to 1.28; p=0.65) and CVA (OR 1.47; 95% CI 0.66 to 3.25; p=0.34) were not significantly different between treatment groups. Revascularisation (OR 0.88;
95% CI 0.80 to 0.97; p=0.01) was also not increased in patients who received concomitant PPI with clopidogrel. Furthermore, occurrence of GI bleed was significantly decreased in the group of patients who received a PPI (OR 0.24; 95% CI 0.09 to 0.62; p=0.003).

Subgroup analyses

Table 2 illustrates results of comparisons in studies with restricted populations. In studies limited to patients with ACS, only MI (OR 1.41; p=0.01) was significantly increased in patients taking clopidogrel with a concomitant PPI. In patients receiving DAPT, adding a PPI decreased the risk of an upper GI bleed (OR 0.31; p=0.002), but was associated with increased risk of all-cause mortality (OR 1.32; p=0.003), ACS (OR 2.37; p=0.002), MI (OR 1.25; p=0.005), stent thrombosis (OR 1.36; p=0.005) and revascularisation (OR 1.30; p=0.006). Stratification by degree of CYP450 2C19 inhibition revealed that both high-risk (omeprazole, esomeprazole and lansoprazole) and low-risk PPIs (pantoprazole and rabeprazole) were associated with an increased risk of MI and mortality. In patients receiving high-risk PPIs, GI bleed was also decreased by concomitant PPI use (OR 0.17; p<0.001).

Quality assessment

One of the RCTs included was stopped prematurely due to a loss of funding.7 Nevertheless, it was considered a high quality study according to the Jadad criteria. The other two RCTs were considered to be of moderate quality because blinding was not described.24 On funnel plot analysis, studies occupied a symmetrical distribution according to weight and converged towards the pooled effect as the weight increased (see online supplementary figure S1). Egger’s regression test (see online supplementary figure S2) was also performed and showed no
evidence of significant publication bias (p=0.48 and 0.76 for overall mortality and MI, respectively).

DISCUSSION
The pooled analysis of all included studies included 214,851 patients and found that patients who took a PPI in addition to clopidogrel had the worst outcomes, including higher overall mortality, MI, ACS, CVA, stent thrombosis and the need for revascularisation procedures. These results are consistent with previous studies and meta-analyses.26 48 51 67 However, these data emerge mostly from nonrandomised observational studies, which are prone to selection bias and non-comparability between groups at baseline. Therefore, we conducted a separate analysis including data only from RCTs and PSM patients. In a population of 23,552 patients from eight studies, we found that all ischaemic end points evaluated were not increased in the clopidogrel-PPI group (figure 5). This analysis of RCTs and PSM patients highly suggests that PPIs are a marker of increased risk, rather than a direct cause of worse outcomes.

The contrast in outcomes between unadjusted and adjusted/randomised studies is supported by findings of increased CV risk among patients taking PPI regardless of simultaneous clopidogrel use. In a population of 31,704 patients who were not receiving clopidogrel, Charlot et al.73 found that, compared with non-PPI users, patients on PPI had an increased risk of all-cause mortality (HR 1.58; p<0.01), CV mortality (HR 1.49; p<0.01), MI (HR 1.13; p=0.02) and CVA (HR 1.32; p<0.01). Furthermore, the magnitude of increased CV risk in the PPI group was similar between clopidogrel users and patients not receiving clopidogrel. An increased risk of ischaemic outcomes among patients taking a PPI has also been reported in concomitant use of placebo and ticagrelor.68 74

The mechanism of increased CV risk in patients receiving a PPI is most likely related to the difference in baseline characteristics between users and non-users of clopidogrel. In the study by Charlot et al.73 patients who received a PPI were on average 3 years older than the comparison group and also had a higher prevalence of diabetes with complications, chronic kidney injury and cerebrovascular disease at baseline. In Bhurke et al.,30 patients taking clopidogrel had a higher Charlson comorbidity index at baseline, as well as a higher prevalence of heart failure. Similarly, the majority of unadjusted studies that reported an increased risk of CV events in PPI users had an unbalanced distribution of baseline characteristics, with sicker patients in the PPI group.31 52 63 67

Our study found a decreased incidence of GI bleeding among patients taking PPIs, a result that was confirmed in patients with similar baseline characteristics (RCT/PSM populations; figure 5F). Two different mechanisms may contribute as follows to the decreased incidence of GI bleeding with PPI use. The first is by direct inhibition
| Subgroup analysis | ACS | DAPT | E/O/L | P/R |
|-------------------|-----|------|-------|-----|
| Number of patients| PPI: 37 015  No PPI: 77 060 | PPI: 38 244  No PPI: 40 604 | PPI: 23 437  No PPI: 33 000 | PPI: 3008  No PPI: 28 772 |
| Studies included | Bhurke et al., Evanchan et al., Gaspar et al., Goodman et al., Ho et al., Hsiao et al., Lin et al., O’Donoghue et al., Ortolani et al., Simon et al., Valkhoff et al., Wu et al., Zou et al. | Aihara et al., Bhatt et al., Burkard et al., Ching et al., Chitose et al., Douglas et al., Galiga et al., Gaspar et al., Goodman et al., Gupta et al., Harjai et al., Haupl et al., Hokimoto and Ogawa, Hsiao et al., Hudzink et al., Jiang et al., Nakayama et al., O’Donoghue et al., Ortolani et al., Rossini et al., Tentzeris et al., Yau et al., Zairis et al., Zou et al. | Hsiao et al., Ho et al., Lin et al., O’Donoghue et al., Rossini et al., Valkhoff et al., Zairis et al. | Bhatt et al., Douglas et al., Galiga et al., Harjai et al., Hsu et al., Hsu et al., Hudzink et al., Jiang et al., Rossini et al., Valkhoff et al., Zairis et al. |
| All-cause mortality | OR 1.14; CI 0.94 to 1.39; p=0.19 | OR 1.32; CI 1.10 to 1.58; p=0.003 | OR 1.23; CI 0.72 to 2.10; p=0.46 | OR 2.01; CI 1.20 to 3.35; p=0.008 |
| CV mortality | OR 0.99; CI 0.70 to 1.39; p=0.95 | OR 1.16; CI 0.95 to 1.42; p=0.14 | OR 1.28; CI 1.14 to 1.43; p=0.001 | OR 1.96; CI 0.68 to 5.64; p=0.21 |
| ACS | OR 1.91; CI 0.89 to 4.06; p=0.09 | OR 2.37; CI 1.36 to 4.13; p=0.002 | NA | NA |
| MI | OR 1.41; CI 1.08 to 1.85; p=0.01 | OR 1.25; CI 1.07 to 1.45; p=0.005 | OR 1.25; CI 1.09 to 1.44; p=0.002 | OR 2.13; CI 1.60 to 2.85; p=0.001 |
| ST (possible/probable/definite) | NA | OR 1.36; CI 1.10 to 1.68; p=0.005 | OR 1.08; CI 0.67 to 1.73; p=0.76 | OR 2.28; CI 0.66 to 7.89; p=0.20 |
| Revascularisation | OR 1.38; CI 0.82 to 2.30; p=0.22 | OR 1.30; CI 1.08 to 1.58; p=0.006 | OR 1.06; CI 0.73 to 1.54; p=0.74 | NA |
| CVA | NA | OR 1.75; CI 0.98 to 3.16; p=0.06 | OR 2.24; CI 0.62 to 8.11; p=0.22 | NA |
| GI bleed | NA | OR 0.31; CI 0.15 to 0.65; p=0.002 | OR 0.17; CI 0.08 to 0.36; p=0.001 | NA |

References are shown in Table 1.

ACS: acute coronary syndrome; CV: cardiovascular; CVA: cerebrovascular accident; DAPT: dual antiplatelet therapy; E: esomeprazole; GI: gastrointestinal; L: lansoprazole; MI: myocardial infarction; NA: not available or not applicable; O: omeprazole; P: pantoprazole; PPI: proton pump inhibitor; R: rabeprazole; ST: stent thrombosis.
of proton pumps with subsequent suppression of acid production, which has been shown to (1) prevent stress-ulcer related bleeding in critically ill patients;75 (2) decrease rebleeding in patients with a history of ulcer-related bleeding;6 and (3) decrease GI bleeding among patients on anticoagulants and dual anti-platelet therapy.76 Alternatively, the benefit in GI bleeding may be related to a PPI-mediated reduction in the antiplatelet effect of clopidogrel. Several pharmacokinetic studies have demonstrated a lower inhibition of platelet aggregation among patients taking a PPI in addition to clopidogrel, as compared to non-PPI clopidogrel users.14 15 66 Although our findings suggest that this mechanism is not clinically relevant in terms of adverse CV outcomes, platelet aggregation plays an important role in angiogenesis and the healing of peptic ulcers;77 therefore, a lesser degree of platelet inhibition certainly has the potential to decrease GI bleeding.

As illustrated in table 2, among patient with ACS, there was no increased risk of ischaemic CV end points with PPI use. Patients with ACS most likely have more comorbidities and a worse prognosis at baseline compared with elective patients, which can mitigate the differences in outcomes between PPI and non-PPI users. Inhibition of the CYP450 2C19 enzyme is heterogeneous within the class of PPIs. Omeprazole, esomeprazole and lansoprazole have been shown to be the strongest inhibitors,11 16 17 20 whereas some studies have suggested that pantoprazole and rabeprazole have no effect on the CYP450 2C19 enzyme.16 20 38 Our meta-analysis has demonstrated that the association between adverse outcomes and concomitant PPI-clopidogrel use persists in patients taking the low-risk PPIs rabeprazole or pantoprazole. Given that these medications are not expected to have a significant interaction with clopidogrel, this finding further supports the hypothesis that use of a PPI is not the cause of increased adverse outcomes, but rather a marker of increased baseline risk.

This study has limitations. Definitions of outcomes were not reported in a substantial part of the studies, which raises the concern for reporting bias. In addition, 36 of the 39 included studies were non-randomised and are inherently more susceptible to bias. The correction of possible baseline differences between groups led to a subanalysis of randomised and PSM studies; however, this analysis included only eight studies, which did not report on all the studied outcomes. Moreover, the absence of patient-level data, common in meta-analysis designs, prevented more detailed subgroup analyses, such as interaction between different generations of drug-eluting stents and the exact role of baseline characteristics on the clopidogrel-PPI interaction. Also, this systematic review was not registered prospectively, which would have allowed feedback about the protocol, further limiting the possibility of bias. Nevertheless, we believe we have conducted a transparent and reproducible protocol. Finally, given the high number of studies included and the differences in methods and outcome definitions among them, a substantial amount of heterogeneity was encountered. This has already been observed in previous meta-analyses, and therefore only a random-effects model was used. A prespecified definition of GI bleeding and stent thrombosis was also applied to minimise bias resulting from different outcome definitions.

CONCLUSION

In summary, the results of our meta-analyses suggest that the highly controversial interaction between PPIs and clopidogrel observed in platelet aggregation studies has no clinical significance. Rather, patients who are prescribed PPIs have a higher burden of comorbidities and thus most likely have an increased risk for adverse CV events. Importantly, PPIs have the potential to significantly reduce GI bleeding among patients taking clopidogrel.

REFERENCES

1. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:e574–651.

2. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362–425.
3. Writing Committee Members, Jneid H, Anderson JL, Wright RS, et al., American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2012;126:875–910.

4. Yusuf S, Zhao F, Mehta SR, et al. Clopidogrel in unstable angina to prevent recurrent events trial I: effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

5. Steinshlub RB, Berger PB, Marin JT III, et al., CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Observation CItrofRED: early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.

6. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med 2002;346:2033–8.

7. Bhatt DL, Creyer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2003;349:1889–99.

8. Siller-Matula JM, Jilma B, Schror K, et al. Effect of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. Aliment Pharmacol Ther 2010;31:810–23.

9. Gerson LB, McMahon D, Olin K, et al. Lack of significant interactions between clopidogrel and proton pump inhibitors: meta-analysis of existing literature. Dig Dis Sci 2012;57:1304–13.

10. Kwok CS, Jeevanantham V, Dawn B, et al. No consistent evidence of different cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: meta-analysis. Int J Cardiol 2013;167:964–7.

11. Huang B, Huang Y, Li Y, et al. Adverse cardiovascular effects of concomitant use of proton pump inhibitors and clopidogrel in patients with coronary artery disease: a systematic review and meta-analysis. Arch Med Res 2012;43:212–24.

12. Focks J, Brouwer MA, van Oijen MG, et al. Concomitant use of clopidogrel and proton pump inhibitors: impact on platelet function and clinical outcome— a systematic review. Heart 2013;99:520–7.

13. Bibi CE, Martin BC, Clift D, et al. Effect of the clopidogrel–proton pump inhibitor drug interaction on adverse cardiovascular events in patients with acute coronary syndrome. Pharmacotherapy 2012;32:809–18.

14. Douglas IJ, Evans SJ, Hingorani AD, et al. Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. BMJ 2012;345:e4388.

15. Garcia Rodriguez LA, Johansson S, Cea Soriano L. Use of clopidogrel and proton pump inhibitors after a serious acute coronary event: risk of coronary events and peptic ulcer bleeding. Thromb Haemost 2013;110:14–24.

16. Haptele R, Weilenmann D, Schneider T, et al. Individualised PPI prescription in patients on combination antplatelet therapy and upper gastrointestinal events after percutaneous coronary intervention: a cohort study. Wien Med Wochenschr 2012;162:67–73.

17. Jiang Z, Wu H, Duan Z, et al. Proton-pump inhibitors can decrease gastrointestinal bleeding after percutaneous coronary intervention. Clin Res Hepatol Gastroenterol 2013;37:636–41.

18. Nakayama A, Morita H, Ando J, et al. Adverse cardiovascular outcomes associated with concomitant use of proton pump inhibitors and proton-pump inhibitors in patients undergoing percutaneous coronary intervention. Heart Vessels 2013;28:292–300.

19. Zou JJ, Chen SL, Tan J, et al. Increased risk for developing major adverse cardiovascular events in stented Chinese patients treated with dual antiplatelet therapy after concomitant use of the proton pump inhibitor. PLoS ONE 2014;9:e84985.

20. Mauri L, Hsieh WH, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.

21. Hokimoto S, Mizobe M, Akasaka T, et al. Impact of CYP2C19 polymorphism and proton pump inhibitors on platelet reactivity to clopidogrel and clinical outcomes following stent implantation. Thromb Res 2014;133:599–605.

22. eWells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://wwwĥr.ca/programs-clinical-epidemiology/oxford.asp. (accessed 13 Mar 2014).

23. Shabanzadeh DM, Sorensen LT. Laparoscopic surgery compared with open surgery decreases surgical site infection in obese patients: a systematic meta-analysis. Ann Surg 2012;256:934–45.

24. Banaszak DE, Sorensen LT. Laparoscopic surgery compared with open surgery decreases surgical site infection in obese patients: a systematic meta-analysis. Arch Surg 2011;146:382–9.

25. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.

26. Duval S, Tweedie R. Trim and fill. Biometrics 2000;56:455–63.
Is it safe to use a proton pump inhibitor with patients treated with aspirin and clopidogrel after acute coronary intervention.

Ching GG, Li D, Baker WL, Valkhoff VE, t Jong GW, Van Soest EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomized trials. Lancet 2010;374:989–97.

Hokimoto S, Ogawa H. Risk of recurrent acute coronary syndrome with the concomitant use of clopidogrel and proton pump inhibitors. JAMA 2010;303:1964–6.

Evanchan J, Donnally MR, Binkley P, et al. Recurrence of acute myocardial infarction in patients discharged on clopidogrel and a proton pump inhibitor after stent placement for acute myocardial infarction. Clin Cardiol 2010;33:168–71.

Gaglia MA Jr, Torguson R, Hanna N, et al. Histamine2-receptor antagonists are an alternative to proton pump inhibitor in patients receiving clopidogrel. Gastroenterology 2010;139:1165–71.

Hudzik B, Szkodzinski J, Danikiewicz A, et al. Impact of omeprazole on the concentration of interleukin-6 and transforming growth factor-beta1 in patients receiving dual antiplatelet therapy after percutaneous coronary intervention. Eur Cytokine Netw 2010;21:257–63.

Banerjee S, Weideman RA, Weideman MW, et al. Risk of concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention. Am J Cardiol 2011;107:871–8.

Hokimoto S, Ogawa H. Risk of recurrent acute coronary syndrome with the concomitant use of clopidogrel and proton pump inhibitors. JAMA 2010;303:1964–6.

Evanchan J, Donnally MR, Binkley P, et al. Recurrence of acute myocardial infarction in patients discharged on clopidogrel and a proton pump inhibitor after stent placement for acute myocardial infarction. Clin Cardiol 2010;33:168–71.