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

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To cite: Cardoso RN, Benjo AM, DiNicolantonio JJ, *et al*. Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis. *Open Heart* 2015;**2**:e000248. doi:10.1136/openhrt-2015-000248

► Additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/openhrt-2015-000248).

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Received 7 February 2015
Revised 12 May 2015
Accepted 2 June 2015

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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 I^2 statistics; p values inferior to 0.10 and I^2 >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.

KEY MESSAGES

What is already known about this subject?

- Proton pump inhibitors have the potential to decrease the risk of upper gastrointestinal haemorrhage among patients taking antiplatelet therapy. However, pharmacokinetic data and observational studies have suggested a potential interaction between clopidogrel and proton pump inhibitors, which could have a significant effect in clinical events.

What does this study add?

- We studied potential factors associated with the interaction between clopidogrel and proton pump inhibitors, such as stent placement, presentation as an acute coronary syndrome, use of dual antiplatelet therapy, and stratification by different proton pump inhibitors. Importantly, in a subanalysis of studies with randomised or propensity score matched data, no significant difference was observed in adverse outcomes between patients who received a proton pump inhibitor and those who did not. The reduction in gastrointestinal bleeding among patients taking a proton pump inhibitor was consistent throughout the different subgroups.

How might this impact on clinical practice?

- The results of our study suggest that the previously reported interaction between clopidogrel and proton pump inhibitors may be dependent on selection bias and different patient baseline characteristics, as a clinically significant effect was not observed in a randomised/propensity score matched population. On the basis of these findings, physicians may consider proton pump inhibitors for patients receiving clopidogrel, as there is a benefit in terms of reduced gastrointestinal bleeding.

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is recommended following acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI), as it

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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.[13–16] 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.[7 24] Multiple meta-analyses have been performed, but the most recent one included data only until June 2012.[25–29] 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.[11 16 17 20] Pantoprazole and rabeprazole were analysed separately in the low-risk PPI group.[16 20 27 38] 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

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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.[42] Publication bias was evaluated by using funnel-plot graphs and checking for symmetrical distribution of trials with similar weights.[43]

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.[44] 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.[45] 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 most commonly not comparable between groups; therefore, a subanalysis of RCTs/propensity 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;

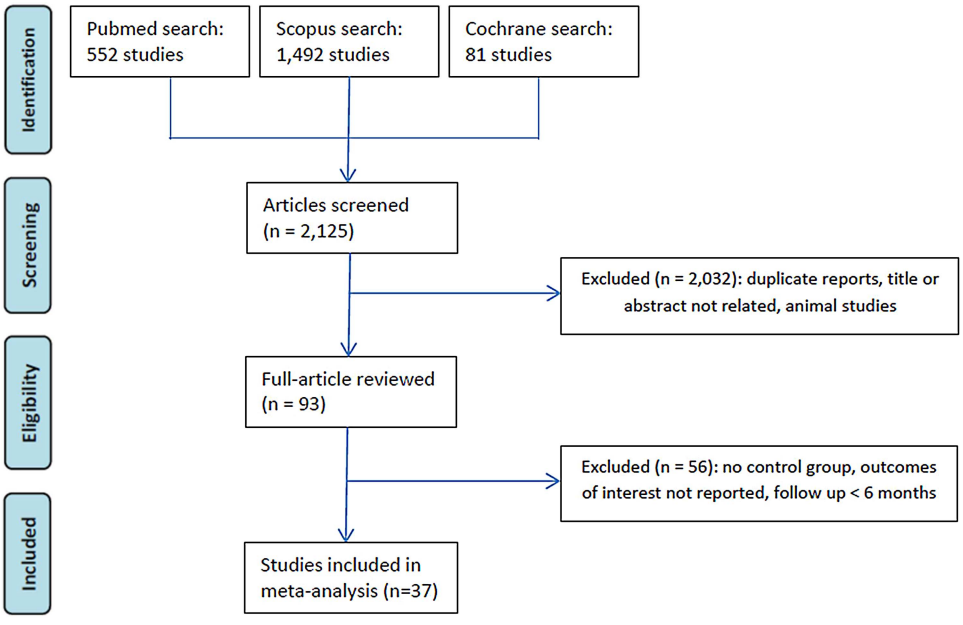

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of study selection.

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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*[46]	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*[47]	PPI: 4793 No PPI:11 237	Netherlands	1/1999–12/2008	42.6 months	E, L, O, P, R	MI	MI	NA
Case–control	Ching *et al*[48]	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*[34]	PPI: 1570 No PPI: 1110	Nanjing, China	1/2008–1/2011	1 year	E, L, O	PCI	GI bleed	Yes
Case–control	Garcia Rodriguez *et al*[32]	PPI: 192 No PPI: 177	UK	1/2000–12/2007	>3.5 years	E, L, O, P, R	ACS	GI bleed	NA
Retrospective cohort	Ho *et al*[49]	PPI: 5244 No PPI: 2961	VA hospitals, USA	8/2003–1/2006	521 days	L, O, P, R	ACS	All-cause mortality, ACS, revascularisation	~90%
Retrospective cohort	Evanchan *et al*[50]	PPI: 1369 No PPI: 4425	Ohio, USA	1/2003–1/2008	1 year	E, L, O, P	Stent after MI	MI	NA
Retrospective cohort	Gaglia *et al*[51]	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	Gaspar *et al*[52]	PPI: 274 No PPI: 528	Braga, Portugal	1/2004–3/2008	6 months	L, O, R	ACS	All-cause mortality, ACS	Yes
Retrospective cohort	Gupta *et al*[53]	PPI: 72 No PPI: 243	Little Rock, AR, USA	1/2003–8/2004	4 years	L, O, R	PCI with stent	All-cause mortality, revascularisation (TLR)	>95%
Retrospective cohort	Kreutz *et al*[54]	PPI: 6828 No PPI: 9862	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*[55]	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*[23]	PPI: 5734 No PPI:12 405	The Netherlands	1/2006–12/2007	1–2 years	E, L, O, P, R	NA	All-cause mortality, MI, ACS, CVA	~78%
Retrospective cohort	Wu *et al*[56]	PPI: 311 No PPI: 5551	Taiwan	7/2002–6/2005	1 year	E, L, O, P, R	ACS	ACS, revascularisation	NA
Retrospective cohort	Yasu *et al*[57]	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-Torrero *et al*[58]	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*[33]	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*[59]	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*[35]	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*[36]	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*[60]	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[61]	PPI: 37 No PPI: 133	Japan	NA	1 year	R	DAT	CV mortality, ACS, revascularisation, CVA, GI bleed	Yes
Cohort	Hudzik *et al*[62]	PPI: 18 No PPI: 20	Poland	1/2006–7/2008	1 year	O	PCI with stent	MI, ACS, CVA	Yes
Cohort	Banerjee *et al*[63]	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

Continued

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Table 1 Continued

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*[65]	PPI: 187 No PPI: 443	Multicenter, Japan	6/2008–3/2009	18 months	L, O, R	PCI with stent	CV mortality, MI, CVA	Yes
Cohort	Douglas *et al*[31]	PPI: 12 439 No PPI:16 900	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*[66]	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*[67]	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*[68]	PPI: 3255 No PPI: 6021	Multinational	10/2006–7/2008	1 year	E, L, O, P, R	ACS	All-cause mortality, CV mortality, ST	>97%
PSM cohort	Harjai *et al*[19]	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%
PSM cohort	Hsiao *et al*[69]	PPI: 622 No PPI: 9131	Taiwan	2000–2007	>6 months	E, L, O, P, R	ACS	ACS	Yes
PSM cohort	Aihara *et al*[70]	PPI: 1068 No PPI: 819	Ibakari, Japan	2/2006–8/2009	1 year	L, O, R	PCI with stent	All-cause mortality, MI, revascularisation, ST, CVA, GI bleed	Yes
PSM cohort	Bhurke *et al*[30]	PPI: 2958 No PPI: 7143	USA	1/2001–12/2008	268 days	E, L, O, P, R	ACS	MI, revascularisation	NA
PSM cohort	Lin *et al*[71]	PPI: 5173 No PPI:31 926	Taiwan	1/2006–12/007	580 days	E, L, O, P, R	ACS	ACS, revascularisation	NA
RCT	Bhatt *et al*[7]	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*[24]	PPI: 83 No PPI: 82	Taiwan	8/2008–1/2010	6 months	E	History of GI ulcer	MI, ACS, CVA	NA
RCT	Hsu[72]	PPI: 157 No PPI: 161	Taiwan	1/2008–11/2010	6 months	E	History of GI ulcer	GI bleed	NA

ACS: 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.

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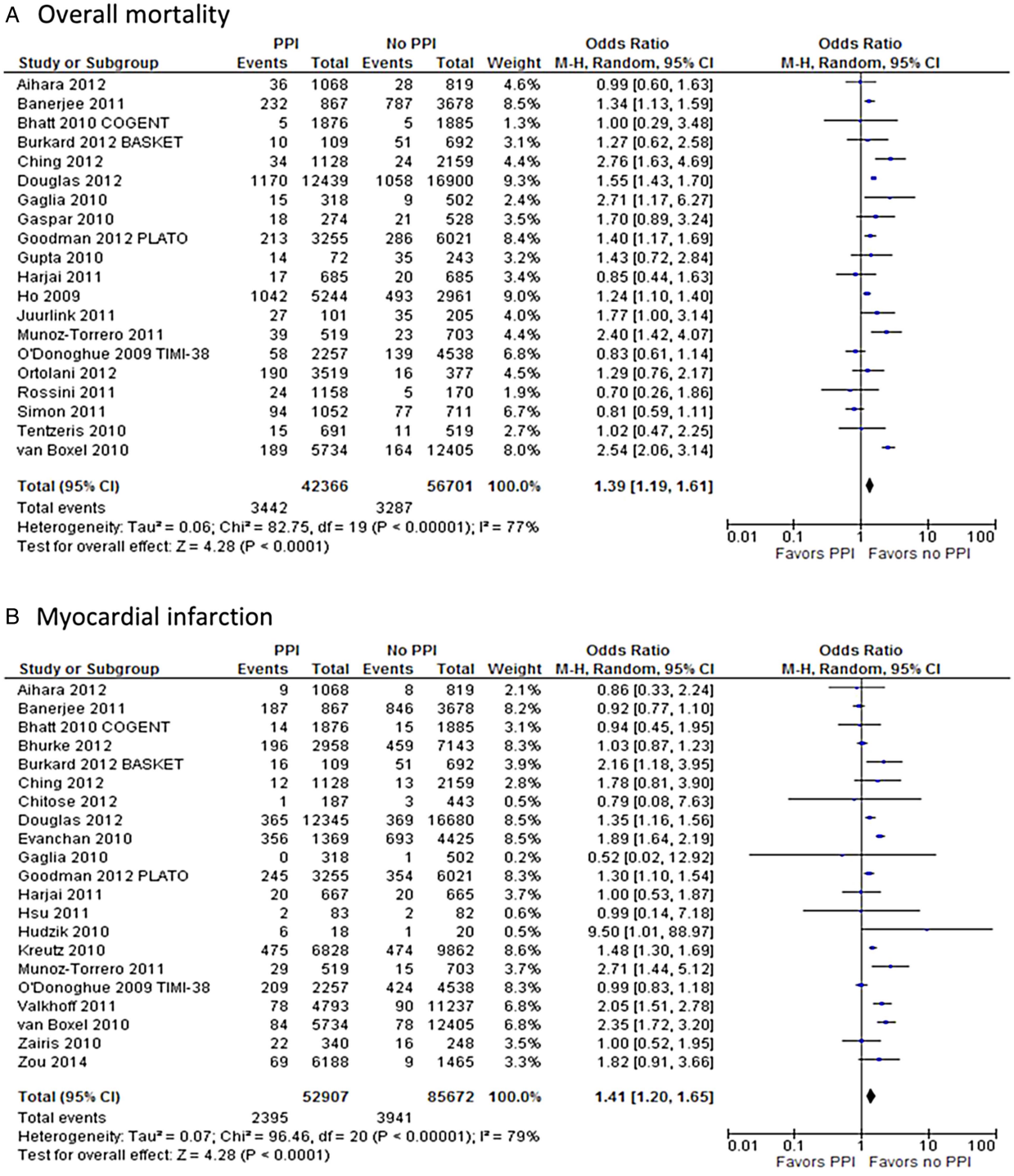

Figure 2 Forest plot of studies examining outcomes between patients taking proton pump inhibitor (PPIs) with clopidogrel and those taking only clopidogrel: (A) overall mortality; (B) myocardial infarction.

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.

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;

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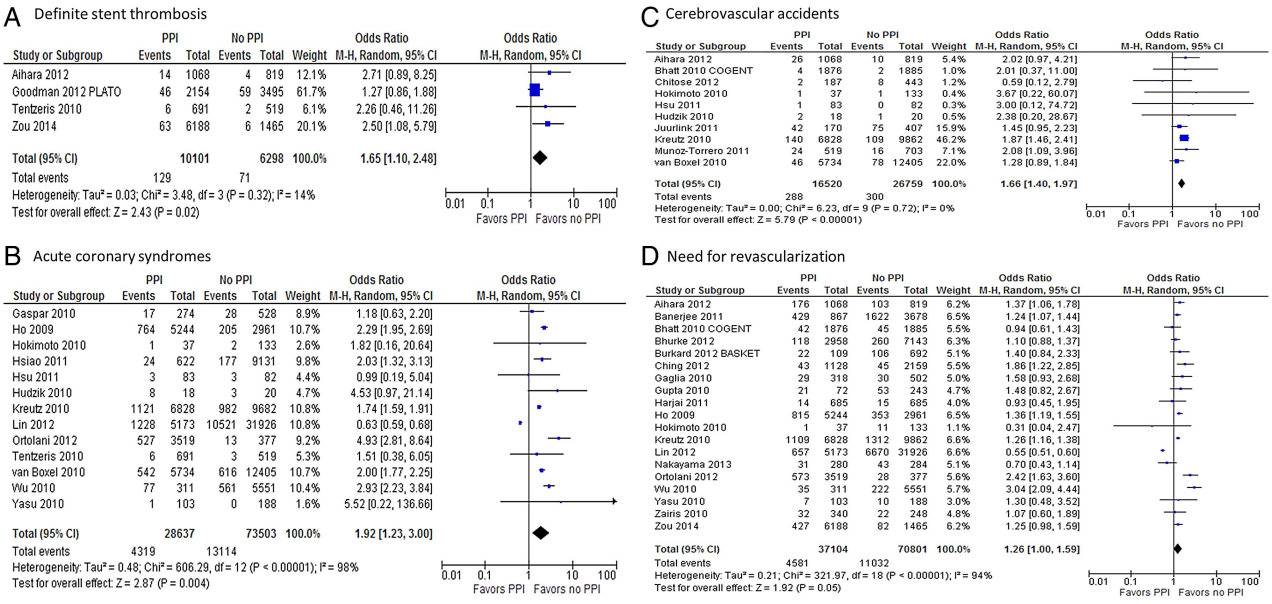

Figure 3 Forest plot of studies examining outcomes between patients taking proton pump inhibitor (PPIs) with clopidogrel and those taking only clopidogrel: (A) definite stent thrombosis; (B) need for revascularisation; (C) cerebrovascular accidents; (D) acute coronary syndromes.

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

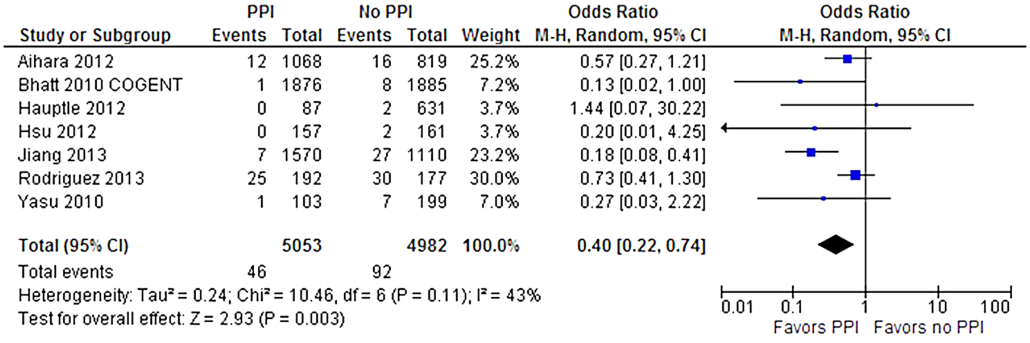

Figure 4 Forest plot of studies examining gastrointestinal bleeding between patients taking proton pump inhibitor (PPI) with clopidogrel and those taking only clopidogrel.

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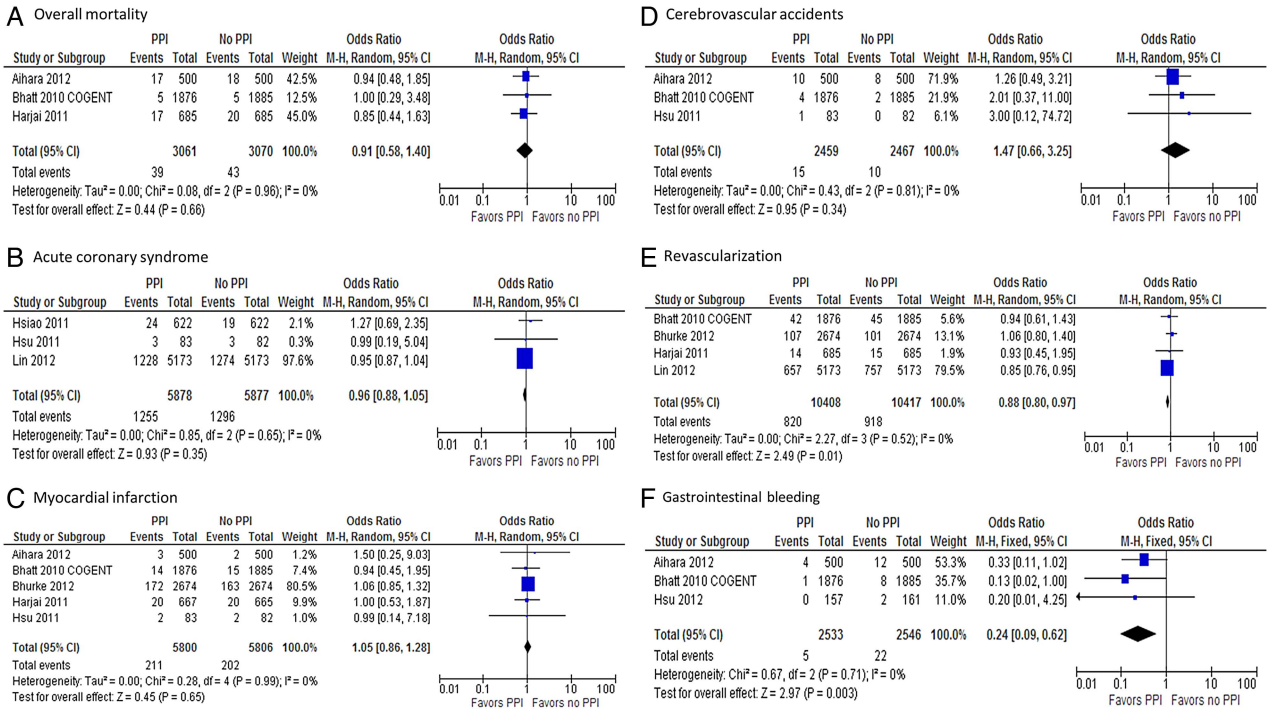

Figure 5 Forest plots of randomised controlled trials and propensity score matched studies examining outcomes between patients taking proton pump inhibitor (PPIs) with clopidogrel and those taking only clopidogrel: (A) overall mortality; (B) acute coronary syndromes; (C) myocardial infarction; (D) need for revascularisation; (E) cerebrovascular accidents; (F) gastrointestinal bleeding.

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

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Table 2 Subgroup analyses

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*,[30] Evanchan *et al*,[50] Gaspar *et al*,[52] Goodman *et al*,[68] Ho *et al*,[49] Hsiao *et al*,[69] Lin *et al*,[71] O'Donoghue *et al*,[66] Ortolani *et al*,[59] Simon *et al*,[22] Valkhoff *et al*,[47] Wu *et al*,[56] Zou *et al*,[36]	Aihara *et al*,[70] Bhatt *et al*,[7] Burkard *et al*,[67] Ching *et al*,[48] Chitose *et al*,[65] Douglas *et al*,[31] Gaglia *et al*,[51] Gaspar *et al*,[52] Goodman *et al*,[68] Gupta *et al*,[53] Harjai *et al*,[19] Hauptle *et al*,[33] Hokimoto and Ogawa,[61] Hsiao *et al*,[69] Hudzik *et al*,[62] Jiang *et al*,[34] Nakayama *et al*,[35] O'Donoghue *et al*,[66] Ortolani *et al*,[59] Rossini *et al*,[64] Tentzeris *et al*,[55] Yasu *et al*,[57] Zairis *et al*,[60] Zou *et al*,[36]	Bhatt *et al*,[7] Douglas *et al*,[31] Gaglia *et al*,[51] Harjai *et al*,[19] Hsu *et al*,[24] Hsu,[72] Hudzik *et al*,[62] Jiang *et al*,[34] Rossini *et al*,[64] Valkhoff *et al*,[47] Zairis *et al*,[60]	Douglas *et al*,[31] Gaglia *et al*,[51] Hokimoto and Ogawa,[61] Rossini *et al*,[64] Valkhoff *et al*,[47] Yasu *et al*,[57]
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.

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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.

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Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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