Concomitant use of clopidogrel and proton pump inhibitors: impact on platelet function and clinical outcome- a systematic review

Jeroen Jaspers Focks,[1] Marc A Brouwer,[1] Martijn G H van Oijen,[2,3] Angel Lanas,[4] Deepak L Bhatt,[5] Freek W A Verheugt[1]

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[1]Department of Cardiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
[2]Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands
[3]Department of Gastroenterology and Hepatology, University of California Los Angeles Medical School, Los Angeles, California, USA
[4]Department of Gastroenterology, Hospital Clínico, Universidad de Zaragoza, CIBERehd, Zaragoza, Spain
[5]Department of Cardiology, VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to
Jeroen Jaspers Focks, Radboud University Nijmegen Medical Center, Department of Cardiology 670, PO Box 9101, 6500 HB Nijmegen, The Netherlands; j.jaspersfocks@gmail.com

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ABSTRACT

Background Clopidogrel as an adjunct to aspirin has improved outcomes after acute coronary syndromes, but laboratory studies suggest a reduced antiplatelet effect when proton pump inhibitors (PPIs) are co-administered. Despite corroborating data from retrospective studies, new clinical data fuel the controversy on this issue.

Purpose Systematic review of the impact of the addition of PPIs to clopidogrel on platelet function and cardiovascular outcome.

Data sources PubMed, Web-of-Science, Cochrane Database and reference lists of related articles.

Study selection Published articles on controlled studies addressing the addition of PPIs to clopidogrel. Platelet function studies describe patients as well as healthy volunteers. Clinical studies concern patients using clopidogrel for acute coronary syndromes or because of stent implantation for stable coronary disease.

Data extraction Two investigators independently reviewed the identified articles for eligibility, and one author extracted the data.

Data synthesis In 70% (7/10) of the laboratory studies examining healthy volunteers on clopidogrel, addition of PPIs resulted in a significant reduction in platelet inhibition. For patients, this was observed in 11/18 (61%) studies. The 33 clinical studies showed significant heterogeneity in observed outcomes, with risk ratios for major adverse cardiovascular events varying from 0.64 to 4.58 in the case of PPI use, which was randomly allocated in only two studies. Consequently, imbalances between prognosticators at baseline and PPI prescription bias markedly contributed to the variability in results.

Conclusions Despite indications of reduced antiplatelet activity ex vivo in the case of PPI administration in clopidogrel users, data on the clinical consequences are controversial. With the accumulating evidence from better designed, prospective clinical studies, an adverse effect of PPI use on clinical outcome in patients on clopidogrel cannot be substantiated. This review challenges the validity of conclusions based on quantitative analyses of predominantly non-randomised data.

INTRODUCTION

Optimal antithrombotic therapy has proved to be essential in secondary prevention after an acute coronary syndrome (ACS).[1] Aspirin is associated with a relative reduction of 25% in recurrent events.[1] Addition of clopidogrel has resulted in a further 20% reduction, and the combination is therefore widely implemented.[2] In patients who use antiplatelet agents, gastrointestinal complications are well-known side effects, which are reduced by proton pump inhibitors (PPIs).[3] Therefore the current guideline is to prescribe a PPI in high-risk patients.[4]

However, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) have published warnings about co-therapy of clopidogrel with PPIs, which initially were primarily based on laboratory and retrospective cohort studies.[5–7] The former reported reduced ex vivo inhibition of platelet aggregation, indicative of a pharmacological interaction between (certain) PPIs and clopidogrel.[8–10] Retrospective studies that reported adverse clinical outcomes in the case of co-therapy seemed to corroborate the laboratory findings.[11 12]

From a pharmacological point of view, interference with clopidogrel metabolism seems plausible and could affect clinical efficacy. Transformation of clopidogrel into its active metabolite requires the liver enzyme, cytochrome P450 2C19 (CYP2C19).[13] PPIs also act through this enzyme, thereby reducing the enzyme's bioavailability.[14]

With regard to clopidogrel metabolism in healthy individuals, carriers of a reduced-function allele of CYP2C19 had 30% lower levels of the active clopidogrel metabolite and a 25% relative reduction in platelet inhibition ex vivo.[15] This suggests that CYP2C19 may affect the pharmacodynamics of clopidogrel in patients as well.

A clinical effect of CYP2C19 polymorphisms has been shown among patients using clopidogrel: carriers with a loss-of-function CYP2C19 allele had a 53% increased risk of myocardial infarction (MI), stroke or cardiovascular death compared with non-carriers.[15] Notably, these results were not adjusted for the patient's baseline cardiovascular risk profile and demographic characteristics. In view of the above, addition of a PPI may have an adverse effect on clinical outcome in patients using clopidogrel.[16]

In follow-up of the first retrospective clinical studies, several new prospective studies have been published that questioned the potentially reduced clinical efficacy of clopidogrel in the case of PPI co-administration.[17 18]

Clopidogrel is most commonly prescribed in the case of coronary heart disease—that is, in the clinical setting of an ACS or after a percutaneous coronary intervention for stable angina. For these indications, this review describes the presently available laboratory and clinical data on this controversial issue.

METHODS

The methodology and report of the present review is based on the recommendations described in the PRISMA statement.[19]

Study selection

Eligible studies were identified by searching the following electronic databases: PubMed, Web-of-Science, Cochrane Database. In these databases, we combined the search terms 'clopidogrel' and 'proton pump inhibitors'. The last search was performed on 12 June 2012. In addition, we scrutinised the reference lists of the eligible articles and the reviews, letters or editorials on this subject.

After removing duplicates, we excluded scientific meeting abstracts. Second, articles reporting no original study data (eg, reviews) were excluded. We only included studies written in European languages. There were no restrictions with respect to publication date or the type of PPI studied. Third, studies were excluded if there was no control group that consisted of clopidogrel users without adjunctive use of a PPI. Fourth, studies without data on platelet function test results and/or cardiovascular clinical outcomes were excluded.

Platelet function studies

Patients as well as healthy volunteers were considered. Crossover trials were accepted only for studies investigating healthy volunteers and only when a wash-out period of at least 10 days was used. In patient studies, we only included studies in which clopidogrel was administered in the setting of ACS (with or without coronary intervention) or after stent implantation for stable coronary disease. A crossover design was not accepted given the effect of time on platelet function after ACS and/or stent implantation. We excluded studies that only reported relative reductions between groups. In the case of reported relative reductions, an absolute measure of platelet function should be reported in at least one of the groups. No selection with regard to type of platelet function test used was made.

Clinical outcome studies

Patients using clopidogrel in the setting of ACS (with or without coronary intervention) or after stent implantation for stable coronary disease were considered; studies with other indications for clopidogrel were excluded. We also excluded studies that only reported relative reductions between groups. In the case of reported relative reductions, absolute numbers/proportions should be available in at least one of the groups.

End points

For the laboratory studies, we reviewed the results of reported platelet function tests. The end points for the clinical studies were all-cause mortality, MI and major adverse cardiac events (MACE) as defined by the authors of the original articles, which are outlined in the online appendices. We reported the outcome measures (i.e, RR, OR, HR) as reported by the author.

Quality assessment and data collection

We assessed the methodological validity of each included study using criteria for minimisation of bias. In detail, we determined the investigated populations, the possibility of exclusion bias, measurement of exposure, definition and measurement of outcome, blinding, length of follow-up, loss to follow-up, and control for confounders. In addition, for case–control studies, we assessed matching and the definition of cases and controls. No scales that numerically summarised the components were used.

Two investigators (JJF and MGHvO) independently performed the study selection. One investigator (JJF) then extracted study characteristics and data from the included studies using a prespecified data collection form and assessed the study quality. These data were validated by a second author (MGHvO). In the case of discrepancies, a third independent adjudicator (G E Cramer) was used. Reviewers were not blinded to the author, institution or journal.

Statistical analysis

Given the wide variety of laboratory parameters used as end points, outcome parameters cannot be pooled in comparisons of laboratory studies. Therefore we decided to review and describe the changes in platelet inhibition observed and not perform summarised quantitative comparisons.

For the clinical trials, we assessed the risk of publication bias across studies by visually evaluating a funnel plot. Notably, there were only two randomised trials among the clinical studies, and outcome data showed marked between-study heterogeneity: all-cause death, I^2 83%, $p<0.001$; MI, I^2 96%, $p<0.001$; MACE, I^2 83%, $p<0.001$ (RevMan version 5.0, Copenhagen, 2008). As the terms and conditions for a sound meta-analysis were not met, a systematic review approach was adopted. Finally, we performed separate analyses for certain individual PPIs for the end point MACE.

RESULTS

We identified 838 hits with the search terms 'clopidogrel' and 'proton pump inhibitors'.

After adjustment for duplicates, 577 unique records remained. After application of the exclusion criteria, 59 records remained (figure 1). Of these records, one reported data on both

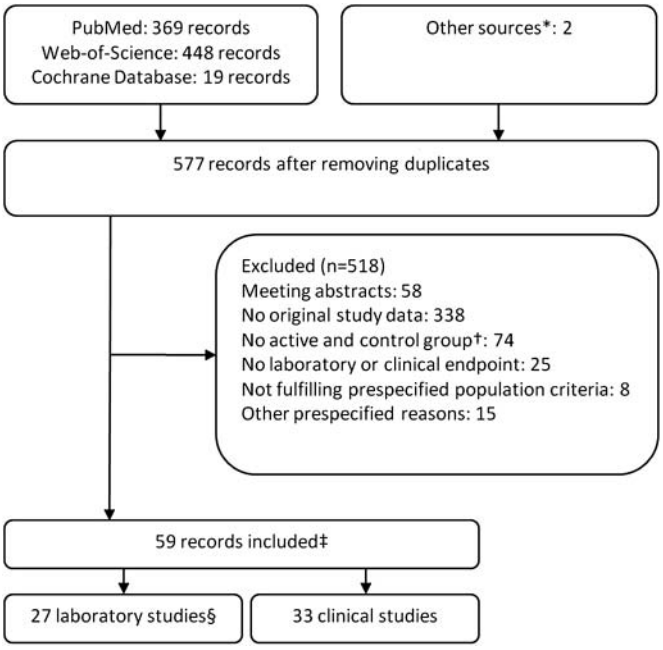

Figure 1 Flowchart of the study selection process. *Records derived by scrutinising the reference lists of the eligible articles and the reviews, letters or editorials on this subject. †Active group is defined as clopidogrel with PPI, and control group is defined as clopidogrel without PPI. ‡One record reported both laboratory and clinical end points. §One laboratory study reported data on both healthy volunteers and patients.

laboratory and clinical end points,[20] and one record addressed data for both healthy volunteers and patients.[21]

Laboratory studies

The study characteristics are outlined in online appendix table 1 for healthy volunteers and online appendix table 2 for patients. Of the studies investigating healthy volunteers, 90% (9/10) were randomised studies.[10 21–28] With regard to the 18 studies investigating patients, 61% (11/18) were of observational design.[8 29–38] Only 28% (5/18) used random allocation of a PPI.[9 21 39–41]

Clinical studies

The study characteristics are outlined in online appendix table 3. In only two of the 33 clinical studies was the use of a PPI randomised.[42 43] Seven studies were prospective registries.[44–50] There were three post hoc analyses of clinical data prospectively collected in the setting of a trial that randomised for stent treatment or for antithrombotic therapy.[20 51 52] Nineteen were retrospective cohort studies,[12 53–70] and two were case–control studies.[11 71]

Outcomes

Laboratory studies

With regard to the studies investigating healthy volunteers, the main results are summarised in table 1 (more detailed description in online appendix table 4). In 70% (7/10) of the studies, addition of PPIs to clopidogrel resulted in significantly reduced platelet inhibition in at least one platelet function test.[10 21 22 24 25 27 72]

The results of the 18 patient studies show that 11 (61%) reported significantly reduced inhibition of platelet aggregation in at least one platelet function test when PPIs were co-administered.[8 9 20 30–32 34 36 37 40 73] Of the five studies with random allocation of a PPI, only two reported a significant difference (table 1 and more detailed description in online appendix table 5).[9 40]

Clinical studies

With regard to the baseline characteristics, there was a higher incidence of established prognosticators for adverse short- and long-term outcome among patients using PPIs, most prominent in the retrospective studies (online appendix table 6).

The main results of the clinical studies are presented in table 2 (summarised description in online appendix table 7). Mortality was reported in 23 studies. In total, 17 (74%) articles reported no risk difference for patients on PPIs.[11 12 42 43 45–51 53 54 58 62 63 68] In the other six studies, the effect ranged from a reduced risk in one study (adjusted HR 0.68, 95% CI 0.47 to 0.96)[20] to an increased risk in five studies, with a RR of up to 2.63 (95% CI 1.17 to 5.94).[44 52 57 61 70] The end point MI was reported in 25 studies, of which 11 (44%) reported a significantly increased RR for PPI users from 1.19 up to 4.58.[11 12 51 55 58–61 63 67 71] The other 14 reported no difference in outcome.[20 42 45 46 48 50 52 54 57 65 66 68–70] Of the 25 studies reporting MACE, 12 (48%) showed a significantly increased risk when PPIs were combined with clopidogrel,[12 44 51–53 58 59 61 63 65 67 70] with an effect that ranged from HRs of 1.20–4.58. The other 13 studies showed no effect on outcome.[20 42 45–50 54 56 62 64 68]

When esomeprazole/omeprazole were examined as specific PPIs of interest, the reported effect between studies showed marked heterogeneity for the end point, MACE, as well: (es) omeprazole, I^2 70%, $p<0.01$. Regarding (es)omeprazole, an increased risk was found in two of seven (29%) studies.[44 65] The other five studies reported no significant risk difference.[42 45 47–49] Of the four studies reporting data for pantoprazole (no significant heterogeneity; I^2 0%, $p=0.69$), one study (25%) reported an increased risk,[59] while the other three studies reported no significant difference.[44 47 49]

Table 1 Summary of the results of the laboratory studies

Population	Design	Number of studies	Total subjects (analysed)	Adverse effect of PPIs on at least one platelet function test
Healthy volunteers	Randomised controlled trial	9	473 (441)	6/9 (67%)
	Prospective study	1	21 (21)	1/1 (100%)
	Total	10	494 (462)	7/10 (70%)
Patients	Randomised controlled trial	5	505 (489)	2/5 (40%)
	Post hoc analyses	2	131 (131)	2/2 (100%)
	Observational	11	4815 (4815)	7/11 (64%)
	Total	18	5451 (5435)	11/18 (61%)

PPI, proton pump inhibitor.

DISCUSSION

The findings of this review are that the majority of laboratory studies suggest that the addition of certain PPIs reduces platelet inhibition ex vivo in clopidogrel users. The studies on clinical outcome are often not well designed, with signs of prescription bias and apparent imbalances in baseline characteristics, which mainly account for the large variability in the observed outcomes. It is only by acknowledgement of these aspects that reports suggesting harm from PPIs with RR increases up to 50–150% can be understood. Considering the firmly and thoroughly established relative benefit of about 20% from the addition of clopidogrel to aspirin,[2] we feel that the reported magnitudes of increased risk cannot (solely) be attributed to the use of PPIs in many of these studies. Notably, nearly all prospective registries and, most importantly, the only two trials with random allocation of a PPI reported no detrimental clinical effect of PPIs in clopidogrel users.

Indisputably, in the (predominantly) randomised trials on healthy individuals using clopidogrel monotherapy, addition of certain PPIs has proven to reduce the inhibition of platelet aggregation as measured by multiple platelet function tests. This supports a pharmacological interaction ex vivo under physiological conditions.

In contrast, acute coronary disease differs from physiological conditions, and patients use both aspirin and clopidogrel. Patients with stable coronary disease who underwent revascularisation and stenting use dual therapy as well. Although about 60% (11/18) of laboratory studies suggest reduced platelet inhibition in the case of co-therapy with a PPI, these results should be interpreted with caution. Importantly, only five of the 18 studies on patients had random allocation of PPIs, two of which demonstrated impaired platelet inhibition. Notably, it has been suggested that PPIs may also adversely affect the platelet response to aspirin. This may be an additional reason for the observed reduced inhibition of platelet aggregation.[74] Finally, some methodological issues characteristic of laboratory studies remain.

First, it is uncertain to what extent reproducibility contributes to the observed results, despite observed relative differences in laboratory outcome parameters of about 10–30%. A difference

Table 2 Study outcome of clinical studies

Design	Author	Number of patients (analysed)	PPIs used	Results for MI*	Results for all-cause mortality*	Results for MACE*
RCT	Bhatt, 2010[42]	3873 (3761)	O	HR 0.92 (95% CI 0.44 to 1.90)	RR 1.00 (95% CI 0.29 to 3.47)	HR 0.99 (95% CI 0.68 to 1.44)
	Wu, 2011[43]	665	P	n.r.	RR 1.03 (95% CI 0.66 to 1.60)	n.r.
Prospective data collection	Gaglia, 2010[44]	820	P, O, L, R, E	n.r.	RR 2.63 (95% CI 1.17 to 5.94)	aHR 1.8 (95% CI 1.1 to 2.7)
	Zairis, 2010[45]	588	O	HR 1.0 (95% CI 0.5 to 1.9)	HR 1.1 (95% CI 0.4 to 2.7)†	HR 1.1 (95% CI 0.6 to 1.8)
	Tentzeris, 2010[46]	1210	P, O, L, R, E	PSaHR 1.27 (95% CI 0.29 to 5.70)‡	PSaHR 0.78 (95% CI 0.34 to 1.76)	PSaHR 1.08 (95% CI 0.53 to 2.22)
	Rossini, 2011[47]	1346	P, O, L	n.r.	aOR 0.97 (95% CI 0.28 to 3.31)	aOR 1.54 (95% CI 0.60 to 4.02)
	Harjai, 2011[48]	2653	O, E, others not specified	PSaHR 1.04 (95% CI 0.64 to 1.69)	PSaHR 0.95 (95% CI 0.56 to 1.63)	PSaHR 0.89 (95% CI 0.63 to 1.27)
	Simon, 2011[49]	3670	P, O, L, R, E	n.r.	aHR 0.97 (95% CI 0.88 to 1.05)	aHR 0.99 (95% CI 0.92 to 1.07)
	Chitose, 2012[50]	630	n.r.	RR 0.79 (95% CI 0.083 to 7.54)	RR 1.90 (95% CI 0.51 to 6.98)†	aHR 1.10 (95% CI 0.45 to 2.68)
Post hoc analysis of prospective study	O'Donoghue, 2009[20]	6795	P, O, L, R, E	aHR 0.98 (95% CI 0.82 to 1.17)	aHR 0.68 (95% CI 0.47 to 0.96)	aHR 0.94 (95% CI 0.80 to 1.11)
	Burkard, 2012[51]	826 (801)	P, O, L, E	aHR 1.88 (1.05 to 3.37)	RR 1.24 (95% CI 0.65 to 2.38)†	RR 1.45 (95% CI 1.06 to 2.00)
	Goodman, 2012[52]	18 601	P, O, L, R, E	PSaHR 1.12 (95% CI 0.90 to 1.40)	PSaHR 1.50 (95% CI 1.22 to 1.83)	PSaHR 1.20 (95% CI 1.04 to 1.38)
Retrospective studies	Ho, 2009[12]	8205	P, O, L, R	aOR 1.86 (95% CI 1.57 to 2.20)§	aOR 0.91 (95% CI 0.80 to 1.05)	aOR 1.25 (95% CI 1.11 to 1.41)
	Gupta, 2010[53]	315	O, L, R	n.r.	aOR 1.20 (95% CI 0.53 to 2.70)	aOR 1.95 (95% CI 1.09 to 3.49)
	Rassen, 2009[54]	18 565	P, O, L, R, E	PSaRR 1.22 (95% CI 0.95 to 1.57)	PSaRR 1.20 (95% CI 0.84 to 1.70)	PSaRR 1.22 (95% CI 0.99 to 1.51)
	Wang, 2009[55]	1751	n.r.	OR 1.62 (95% CI 1.01 to 2.59)	n.r.	n.r.
	Ray, 2010[56]	20 596	P, O, L, R, E	n.r.	n.r.	HR 0.99 (95% CI 0.82 to 1.19)
	Sarafoff, 2010[57]	3338	P, O, L, R, E	aHR 1.3 (95% CI 0.8 to 2.3)	aHR 2.2 (95% CI 1.1 to 4.3)	n.r.
	Kreutz, 2010[58]	16 690	P, O, L, R, E	aHR 1.63 (95% CI 1.40 to 1.90)	aHR 1.10 (95% CI 0.51 to 2.40)†	aHR 1.51 (95% CI 1.39 to 1.64)
	Stockl, 2010[59]	2066	P, O, L, R, E	aHR 1.93 (95% CI 1.05 to 3.54)	n.r.	aHR 1.64 (95% CI 1.16 to 2.32)
	Evanchan, 2010[60]	5794	P, O, L, E	aOR 1.78 (95% CI 1.55 to 2.07)	n.r.	n.r.
	Charlot, 2010[61]	24 702	P, O, L, R, E	aHR 1.19 (95% CI 1.05 to 1.35)	aHR 1.75 (95% CI 1.53 to 1.99)	aHR 1.29 (95% CI 1.17 to 1.42)
	Gaspar, 2010[62]	876	O, L, R	n.r.	aOR 1.04 (95% CI 0.49 to 2.18)	aOR 1.1 (95% CI 0.64 to 1.9)
	Ortolani, 2011[63]	3896	P, O, L, R, E	aHR 3.99 (95% CI 2.29 to 6.93)§	aHR 0.69 (95% CI 0.40 to 1.16)	aHR 1.83 (95% CI 1.39 to 2.45)
	Yasu, 2010[64]	302	R	n.r.	n.r.	HR 1.28 (95% CI 0.54 to 3.00)
	Hudzik, 2010[65]	38	O	OR 6.67 (95% CI 0.89 to 50.2)	No deaths occurred	OR 2.78 (95% CI 1.05 to 7.32)
	Hsiao, 2011[66]	9753	P, O, L, R, E	aHR 1.12 (0.72 to 1.73)§	n.r.	n.r.
	Ulhaq, 2011[67]	188 (184)	n.r.	RR 4.58 (95% CI 1.03 to 20.3)	No deaths occurred	RR 4.58 (95% CI 1.03 to 20.3)
	Aihara, 2012[68]	1887	O, L, R	aHR 0.30 (95% CI 0.08 to 1.11)	aHR 0.74 (95% CI 0.39 to 1.42)	aHR 0.64 (95% CI 0.36 to 1.14)
	Lin, 2012[69]	37 099	P, O, L, R, E	PSaHR 1.02 (95% CI 0.95 to 1.08)§	n.r.	n.r.
	Ching, 2012[70]	3287	P, O, L, R, E	RR 1.77 (95% CI 0.81 to 3.86)	PSaHR 1.79 (95% CI 1.03 to 3.12)	PSaHR 1.70 (95% CI 1.20 to 2.41)
Case–control studies	Juurlink, 2009[11]	2791	P, O, L, R	aOR 1.27 (95% CI 1.03 to 1.57)	aOR 0.82 (95% CI 0.57 to 1.18)	n.r.
	Valkhoff, 2011[71]	23 655	P, O, L, R, E	OR 1.62 (95% CI 1.15 to 2.27)	n.r.	n.r.

*Outcomes represent the risk ratio for combined use of clopidogrel and proton pump inhibitors.
†Study reported cardiovascular death.
‡Study reported acute coronary syndrome.
§Study reported rehospitalisation for acute coronary syndrome.
a, adjusted; E, esomeprazole; L, lansoprazole; MACE, major adverse cardiac events; MI, myocardial infarction; n.r., not reported; O, omeprazole; P, pantoprazole; PPI, proton pump inhibitor; PS, propensity score; R, rabeprazole; RCT, randomised controlled trial.

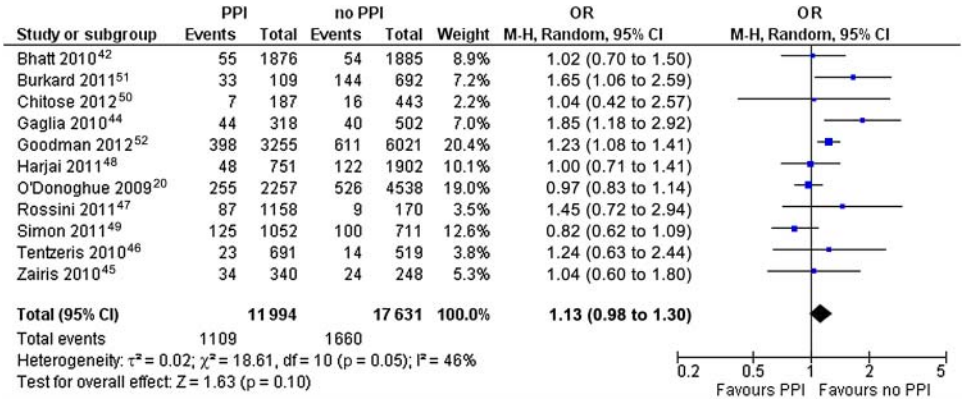

Figure 2 Forest plot of ORs of the prospective clinical studies of the end point, major adverse cardiac events (MACE), for patients using proton pump inhibitors (PPIs) versus those without concomitant PPI therapy. The squares represent risk ratios for the individual studies, and the lines represent the 95% CIs. The pooled 95% CI is visualised by a black diamond.

in laboratory results may be numerically statistically significant, but it depends on the coefficient of variation of the respective test whether there is a true difference between values. Second, issues with regard to the pharmacology of antiplatelet therapy have not been accounted for. It should be appreciated that the timing of the laboratory assessment in relation to the use of the antiplatelet therapy is often not systematically reported.

Although it is tempting to assume that a pharmacological interaction under physiological conditions will also be present in the setting of an ACS, the laboratory findings in patients are less uniform, which also holds true for the quality of the studies. The warnings issued for the combined use of certain PPIs and clopidogrel by the FDA were predominantly based on laboratory studies that showed reduced platelet inhibition and the hypothesis that this surrogate end point might result in adverse outcome. Although data from retrospective studies seemed to support these recommendations, emerging evidence from prospective controlled studies fuelled the controversy on this issue.

It should be appreciated that there is uncertainty with regard to the question whether, and, if so, to what extent, adverse laboratory findings translate into clinical outcome. Even if the platelet function test results for patients on PPIs correlated with prognosis, these laboratory parameters may merely be a marker of poor outcome and not indicate causality. In analogy, the GRAVITAS trial studied the impact of a more intense antithrombotic treatment when platelet function tests indicated inadequate reduction of platelet activity, a strategy that did not result in better clinical outcomes.[75] To date, it is uncertain which, if any, test is (most) reliable in the prediction of incident events, and how large the laboratory effect should be to result in a meaningful clinical difference.

With regard to clinical outcomes, accumulating data from recently published clinical studies fuelled the controversy on the potential adverse effect of PPIs in clopidogrel users. Cardiovascular outcomes of the different studies show marked heterogeneity (statistically significant), in our opinion precluding a reliable meta-analysis. Moreover, in only two of the 33 controlled studies the PPI randomly allocated. Consequently, in most studies, imbalances were present with regard to well-established baseline predictors of adverse outcome, which were more common in PPI users. For example, in the study by Ho *et al*, the OR for all-cause mortality was 1.24 (95% CI 1.10 to 1.40), but after adjustment it changed to 0.91 (95% CI 0.80 to 1.05), indicating the importance of confounders in the observed results.[12]

Another explanation for the observed differences in outcome is indication/prescription bias. According to the latest guidelines, patients on dual antiplatelet therapy (i.e, aspirin and clopidogrel) are—by definition—at increased gastrointestinal risk and should consequently receive gastroprotective therapy in the form of PPIs.[4] Interestingly, only 30–40% of patients were using PPIs. This low incidence of PPI prescription may be due to a delay in guidelines being applied in practice.[76] It is plausible that physicians are more likely to withhold PPIs from the relatively healthy patients and preferentially prescribe them for patients with more comorbidity. Post hoc analyses of the PLATO trial corroborated this hypothesis and stated that PPI use should be interpreted more as a marker than a cause of higher cardiovascular event rates.[52]

To minimise the impact of the abovementioned factors, randomised PPI allocation is of the utmost importance. In the case of controlled studies without random allocation, other aspects of the study design are important. During our process of testing the criteria to perform meta-analysis, exploratory analyses showed that the heterogeneity was primarily caused by the retrospective studies (data not shown). Figure 2 provides insight into the distribution of point estimates of the prospective studies; there is no significant heterogeneity. If pooled estimates for the RR of PPIs were to be calculated, the prospective studies would result in an OR of 1.13 (95% CI 0.98 to 1.30), mutually exclusive from the 95% CI of the retrospective studies (OR 1.63, 95% CI 1.45 to 1.83).

The largest of the two studies with random allocation of a PPI, the COGENT trial, included 3873 patients, with a median follow-up of 106 days, and reported no significant difference in cardiovascular outcome for adjunctive use of omeprazole in clopidogrel users.[42] This result is especially interesting since omeprazole has most often been implicated with regard to warnings based on laboratory findings and observational data on clinical outcome. Notably, if pooled estimates for (es)omeprazole and pantoprazole were to be calculated (online appendix figure 1A, B, respectively), an adverse effect of PPIs on outcome would have been present only for pantoprazole (OR 1.54, 95% CI 1.13 to 2.09). This is one more indication that other factors are of more importance to the observed adverse clinical outcome than the observed pharmacological effect of the individual PPIs in the laboratory.

In summary, 40–50% of the studied records suggested adverse outcome in the case of co-administration of PPIs for the end points, MI and MACE, whereas for mortality this percentage was 22%. In view of the above mentioned methodological aspects, we feel that the many reports suggesting risk increases that are 'out of proportion'—that is, more than the relative benefit of 20% that can be achieved with clopidogrel treatment [2 77 78]—should be interpreted with caution.

In view of the above, only well-designed, randomised trials powered to assess the effect on cardiac events can address the potential adverse effect of adjunctive PPI use in patients on clopidogrel. Until then, methodological flaws in laboratory studies, the fact that there is no one-to-one translation of impaired ex vivo platelet inhibition into adverse clinical outcome, and the marked heterogeneity observed in the clinical studies preclude a definite conclusion. Emerging evidence from recent prospective studies do not support the statement that the addition of PPIs in patients who use clopidogrel should be considered harmful. The suggestion that the potential adverse effect may not hold true for pantoprazole and should especially be considered if omeprazole is prescribed is based on pharmacological assumptions and laboratory measurements, but is contradicted by the available clinical evidence.

Study limitations

As clopidogrel is predominantly prescribed in the setting of ACS or after coronary stent implantation for stable coronary disease, we defined our population accordingly. As a consequence, clopidogrel administration for other indications such as stroke prevention were not included in our analyses. Notably, for these less common indications, the lack of well-designed studies on the effect of PPIs also holds true. With regard to the selection process of the reviewed studies, data presented in the form of an abstract only were not considered. However, the funnel plot did not indicate publication bias. It can be considered a limitation that we do not provide a summarised quantitative effect of the reported studies. As outlined above, we feel there are several arguments not supporting the strategy of meta-analysis. In view of this, we addressed the question whether there are potential differences in effect between the various PPIs (pantoprazole vs (es)omeprazole) only in the form of data review.

Conclusions and implications

In summary, there is clear ex vivo evidence of a pharmacological interaction between clopidogrel and PPIs in healthy individuals. In contrast, data for patients—who use both clopidogrel and aspirin—are less uniform.

To date, the available clinical evidence does not support the statement that PPI co-administration will adversely affect clinical outcome in patients treated with clopidogrel. These findings once again fuel the discussion with regard to the use of ex vivo data as a surrogate end point for clinical outcome. Moreover, it should be realised that summarised quantitative overviews on this subject are mainly driven by non-randomised, retrospective studies, with apparent differences in baseline characteristics and prescription bias.

These observations fuel the debate on this controversial issue and call for recommendations based on well-designed clinical trials.

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REFERENCES

1 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
2 Yusuf S, Zhao F, Mehta SR, *et al*. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. 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.
3 Scheiman JM, Devereaux PJ, Herlitz J, *et al*. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). *Heart* 2011;97:797–802.
4 Bhatt DL, Scheiman J, Abraham NS, *et al*. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2008;52:1502–17.
5 FDA. *Early Communication About an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix)*. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079520.htm
6 FDA. *Follow-Up to the January 26, 2009, Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC)*. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190784.htm
7 EMEA. *Public Statement on Possible Interaction Between Clopidogrel and Proton Pump Inhibitors*. http://www.emea.europa.eu/humandocs/PDFs/EPAR/Plavix/32895609en.pdf
8 Gilard M, Arnaud B, Le GG, *et al*. Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin. *J Thromb Haemost* 2006;4:2508–9.
9 Gilard M, Arnaud B, Cornily JC, *et al*. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008;51:256–60.
10 Small DS, Farid NA, Payne CD, *et al*. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. *J Clin Pharmacol* 2008;48:475–84.
11 Juurlink DN, Gomes T, Ko DT, *et al*. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180:713–18.
12 Ho PM, Maddox TM, Wang L, *et al*. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301:937–44.
13 Kurihara A, Hagihara K, Kazui M, *et al*. In vitro metabolism of antiplatelet agent clopidogrel: cytochrome P450 isoforms responsible for two oxidation steps involved in the active metabolite formation. *Drug Metab Rev* 2005;37(Suppl 2):99.
14 Li XQ, Andersson TB, Ahlstrom M, *et al*. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos* 2004;32:821–7.
15 Mega JL, Close SL, Wiviott SD, *et al*. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360:354–62.
16 Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors–emphasis on rabeprazole. *Aliment Pharmacol Ther* 1999;13(Suppl 3):27–36.
17 Abraham NS, Hlatky MA, Antman EM, *et al*. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *J Am Coll Cardiol* 2010;56:2051–66.
18 Hulot JS, Collet JP, Silvain J, *et al*. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. *J Am Coll Cardiol* 2010;56:134–43.
19 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W65–94.

20 O'Donoghue ML, Braunwald E, Antman EM, *et al*. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;374:989–97.
21 Zhang R, Ran HH, Zhu HL, *et al*. Differential effects of esomeprazole on the antiplatelet activity of clopidogrel in healthy individuals and patients after coronary stent implantation. *J Int Med Res* 2010;38:1617–25.
22 Yun KH, Rhee SJ, Park HY, *et al*. Effects of omeprazole on the antiplatelet activity of clopidogrel. *Int Heart J* 2010;51:13–16.
23 Furuta T, Iwaki T, Umemura K. Influences of different proton pump inhibitors on the anti-platelet function of clopidogrel in relation to CYP2C19 genotypes. *Br J Clin Pharmacol* 2010;70:383–92.
24 Angiolillo DJ, Gibson CM, Cheng S, *et al*. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther* 2011;89:65–74.
25 Ferreiro JL, Ueno M, Capodanno D, *et al*. Pharmacodynamic effects of concomitant versus staggered clopidogrel and omeprazole intake: results of a prospective randomized crossover study. *Circ Cardiovasc Interv* 2010;3:436–41.
26 Ferreiro JL, Ueno M, Tomasello SD, *et al*. Pharmacodynamic evaluation of pantoprazole therapy on clopidogrel effects: results of a prospective, randomized, crossover study. *Circ Cardiovasc Interv* 2011;4:273–9.
27 Frelinger AL III, Lee RD, Mulford DJ, *et al*. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. *J Am Coll Cardiol* 2012;59:1304–11.
28 Uotani T, Sugimoto M, Nishino M, *et al*. Ability of Rabeprazole to Prevent Gastric Mucosal Damage From Clopidogrel and Low Doses of Aspirin Depends on CYP2C19 Genotype. *Clin Gastroenterol Hepatol*. Published Online First: 25 April 2012. doi:10.1016/j.cgh.2012.04.016
29 Siller-Matula JM, Spiel AO, Lang IM, *et al*. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J* 2009;157:148–5.
30 Sibbing D, Morath T, Stegherr J, *et al*. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost* 2009;101:714–19.
31 Zuern CS, Geisler T, Lutilsky N, *et al*. Effect of comedication with proton pump inhibitors (PPIs) on post-interventional residual platelet aggregation in patients undergoing coronary stenting treated by dual antiplatelet therapy. *Thromb Res* 2010;125:e51–4.
32 Price MJ, Nayak KR, Barker CM, *et al*. Predictors of heightened platelet reactivity despite dual-antiplatelet therapy in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2009;103:1339–43.
33 Neubauer H, Engelhardt A, Kruger JC, *et al*. Pantoprazole does not influence the antiplatelet effect of clopidogrel-a whole blood aggregometry study after coronary stenting. *J Cardiovasc Pharmacol* 2010;56:91–7.
34 Amoah V, Worrall AP, Smallwood A, *et al*. Clopidogrel and proton pump inhibitors: can near patient testing help in the tailoring of dual antiplatelet prescription? *J Thromb Haemost* 2010;8:1422–4.
35 Gremmel T, Steiner S, Seidinger D, *et al*. The influence of proton pump inhibitors on the antiplatelet potency of clopidogrel evaluated by 5 different platelet function tests. *J Cardiovasc Pharmacol* 2010;56:532–9.
36 Harmsze AM, van Werkum JW, Taubert D, *et al*. Esomeprazole but not pantoprazole is associated with lower plasma concentrations of clopidogrel's active metabolite. *Ann Pharmacother* 2011;45:542–3.
37 Harmsze AM, van Werkum JW, Souverein PC, *et al*. Combined influence of proton-pump inhibitors, calcium-channel blockers and CYP2C19*2 on on-treatment platelet reactivity and on the occurrence of atherothrombotic events after percutaneous coronary intervention. *J Thromb Haemost* 2011;9:1892–901.
38 Mizia-Stec K, Haberka M, Mizia M, *et al*. Effects of pantoprazole on dual antiplatelet therapy in stable angina pectoris patients after percutaneous coronary intervention. *Pharmacol Rep* 2012;64:360–8.
39 Ren YH, Zhao M, Chen YD, *et al*. Omeprazole affects clopidogrel efficacy but not ischemic events in patients with acute coronary syndrome undergoing elective percutaneous coronary intervention. *Chin Med J (Engl)* 2011;124:856–61.
40 Fernando H, Bassler N, Habersberger J, *et al*. Randomized double-blind placebo-controlled crossover study to determine the effects of esomeprazole on inhibition of platelet function by clopidogrel. *J Thromb Haemost* 2011;9:1582–9.
41 Tunggal P, Ng FH, Lam KF, *et al*. Effect of esomeprazole versus famotidine on platelet inhibition by clopidogrel: a double-blind, randomized trial. *Am Heart J* 2011;162:870–4.
42 Bhatt DL, Cryer BL, Contant CF, *et al*. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010;363:1909–17.
43 Wu H, Jing Q, Wang J, *et al*. Pantoprazole for the prevention of gastrointestinal bleeding in high-risk patients with acute coronary syndromes. *J Crit Care* 2011;26:434–6.
44 Gaglia MA Jr, Torguson R, Hanna N, *et al*. Relation of proton pump inhibitor use after percutaneous coronary intervention with drug-eluting stents to outcomes. *Am J Cardiol* 2010;105:833–8.
45 Zairis MN, Tsiaousis GZ, Patsourakos NG, *et al*. The impact of treatment with omeprazole on the effectiveness of clopidogrel drug therapy during the first year after successful coronary stenting. *Can J Cardiol* 2010;26:e54–7.
46 Tentzeris I, Jarai R, Farhan S, *et al*. Impact of concomitant treatment with proton pump inhibitors and clopidogrel on clinical outcome in patients after coronary stent implantation. *Thromb Haemost* 2010;104:1211–18.
47 Rossini R, Capodanno D, Musumeci G, *et al*. Safety of clopidogrel and proton pump inhibitors in patients undergoing drug-eluting stent implantation. *Coron Artery Dis* 2011;22:199–205.
48 Harjai KJ, Shenoy C, Orshaw P, *et al*. Clinical outcomes in patients with the concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention: an analysis from the Guthrie Health Off-Label Stent (GHOST) investigators. *Circ Cardiovasc Interv* 2011;4:162–70.
49 Simon T, Steg PG, Gilard M, *et al*. Clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction: results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) registry. *Circulation* 2011;123:474–82.
50 Chitose T, Hokimoto S, Oshima S, *et al*. Clinical outcomes following coronary stenting in Japanese patients treated with and without proton pump inhibitor. *Circ J* 2012;76:71–8.
51 Burkard T, Kaiser CA, Brunner-La RH, *et al*. Combined clopidogrel and proton pump inhibitor therapy is associated with higher cardiovascular event rates after percutaneous coronary intervention: a report from the BASKET trial. *J Intern Med* 2012;271:257–63.
52 Goodman SG, Clare R, Pieper KS, *et al*. Association of Proton Pump Inhibitor Use on Cardiovascular Outcomes With Clopidogrel and Ticagrelor: Insights From the Platelet Inhibition and Patient Outcomes Trial. *Circulation* 2012;125:978–86.
53 Gupta E, Bansal D, Sotos J, *et al*. Risk of adverse clinical outcomes with concomitant use of clopidogrel and proton pump inhibitors following percutaneous coronary intervention. *Dig Dis Sci* 2010;55:1964–8.
54 Rassen JA, Choudhry NK, Avorn J, *et al*. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 2009;120:2322–9.
55 Sheng-Wen WS, Tsai SS, Hsu PC, *et al*. Concomitant use of clopidogrel and proton pump inhibitors or cimetidine after acute myocardial infarction would increase the risk of re-infarction. *Am J Gastroenterol* 2009;104:3116–17.
56 Ray WA, Murray KT, Griffin MR, *et al*. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 2010;152:337–45.
57 Sarafoff N, Sibbing D, Sonntag U, *et al*. Risk of drug-eluting stent thrombosis in patients receiving proton pump inhibitors. *Thromb Haemost* 2010;104:626–32.
58 Kreutz RP, Stanek EJ, Aubert R, *et al*. Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel medco outcomes study. *Pharmacotherapy* 2010;30:787–96.
59 Stockl KM, Le L, Zakharyan A, *et al*. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med* 2010;170:704–10.
60 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.
61 Charlot M, Ahlehoff O, Norgaard ML, *et al*. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med* 2010;153:378–86.
62 Gaspar A, Ribeiro S, Nabais S, *et al*. Proton pump inhibitors in patients treated with aspirin and clopidogrel after acute coronary syndrome. *Rev Port Cardiol* 2010;29:1511–20.
63 Ortolani P, Marino M, Marzocchi A, *et al*. One-year clinical outcome in patients with acute coronary syndrome treated with concomitant use of clopidogrel and proton pump inhibitors: results from a regional cohort study. *J Cardiovasc Med (Hagerstown)*. Published Online First: 19 January 2011. doi:10.2459/JCM.0b013e3283416b6b
64 Yasu T, Ikee R, Miyasaka Y, *et al*. [Efficacy and safety of concomitant use of rabeprazole during dual-antiplatelet therapy with clopidogrel and aspirin after drug-eluting stent implantation: a retrospective cohort study] (In Japanese). *Yakugaku Zasshi* 2010;130:1743–50.
65 Hudzik B, Szkodzinski J, Danikiewicz A, *et al*. Effect 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.
66 Hsiao FY, Mullins CD, Wen YW, *et al*. Relationship between cardiovascular outcomes and proton pump inhibitor use in patients receiving dual antiplatelet therapy after acute coronary syndrome. *Pharmacoepidemiol Drug Saf* 2011;20:1043–9.
67 Ulhaq I, Sood R, Hegade V, *et al*. Response to clopidogrel with proton pump inhibitors: safe or not? *Clin Cardiol* 2011;34:721.
68 Aihara H, Sato A, Takeyasu N, *et al*. Effect of individual proton pump inhibitors on cardiovascular events in patients treated with clopidogrel following coronary

stenting:: Results From the Ibaraki Cardiac Assessment Study Registry. *Catheter Cardiovasc Interv*. Published Online First: 10 January 2012. doi:10.1002/ccd.23327
69 Lin CF, Shen LJ, Wu FL, *et al*. Cardiovascular Outcomes Associated with Concomitant Use of Clopidogrel and Proton Pump Inhibitors in Patients of Acute Coronary Syndrome in Taiwan. *Br J Clin Pharmacol*. Published Online First: 24 February 2012. doi:10.1111/j.1365-2125.2012.04250.x
70 Ching GG, Li D, Baker WL, *et al*. Major adverse cardiac events among postpercutaneous coronary intervention patients on clopidogrel and proton pump inhibitors. *Conn Med* 2012;76:205–11.
71 Valkhoff VE, 't Jong GW, Van Soest EM, *et al*. Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors. *Aliment Pharmacol Ther* 2011;33:77–88.
72 Hulot JS, Wuerzner G, Bachelot-Loza C, *et al*. Effect of an increased clopidogrel maintenance dose or lansoprazole co-administration on the antiplatelet response to clopidogrel in CYP2C19-genotyped healthy subjects. *J Thromb Haemost* 2010;8:610–13.
73 Storey RF, Angiolillo DJ, Patil SB, *et al*. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATelet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol* 2010;56:1456–62.
74 Wurtz M, Grove EL, Kristensen SD, *et al*. The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease. *Heart* 2010;96:368–71.
75 Price MJ, Berger PB, Teirstein PS, *et al*. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;305:1097–105.
76 Mehta RH, Montoye CK, Gallogly M, *et al*. Improving quality of care for acute myocardial infarction: the Guidelines Applied in Practice (GAP) Initiative. *JAMA* 2002;287:1269–76.
77 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329–39.
78 Chen ZM, Jiang LX, Chen YP, *et al*. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607–21.

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Concomitant use of clopidogrel and proton pump inhibitors: impact on platelet function and clinical outcome- a systematic review

Jeroen Jaspers Focks, Marc A Brouwer, Martijn G H van Oijen, Angel Lanas, Deepak L Bhatt and Freek W A Verheugt

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