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Meta-Analysis of Efficacy and Safety of Proton Pump Inhibitors with Dual Antiplatelet Therapy for Coronary Artery Disease

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Abstract

Background: There is inconsistency in the literature regarding the clinical effects of proton pump inhibitors (PPI) when added to dual antiplatelet therapy (DAPT) in subjects with coronary artery disease (CAD). We performed meta-analysis stratified by study design to explore these differences.

Methods and results: 39 studies [4 randomized controlled trials (RCTs) and 35 observational studies) were selected using MEDLINE, EMBASE and CENTRAL (Inception-January 2018). In 221,204 patients (PPI = 77,731 patients, no PPI = 143,473 patients), RCTs restricted analysis showed that PPI did not increase the risk of all-cause mortality (Risk Ratio (RR): 1.35, 95% Confidence Interval (CI), 0.56–3.23, P = 0.50, $I^2 = 0$), cardiovascular mortality (RR: 0.94, 95% CI, 0.25–3.54, P = 0.92, $I^2 = 56$), myocardial infarction (MI) (RR: 0.97, 95% CI, 0.62–1.51, P = 0.88, $I^2 = 0$) or stroke (RR: 1.11, 95% CI, 0.25–5.04, P = 0.89, $I^2 = 26$). However, PPI significantly reduced the risk of gastrointestinal (GI) bleeding (RR: 0.32, 95% CI, 0.20–0.52, P < 0.001, $I^2 = 0$). Conversely, analysis of observational studies showed that PPI significantly increased the risk of all-cause mortality (RR: 1.25, 95% CI, 1.11–1.41, P < 0.001, $I^2 = 82$), cardiovascular mortality (RR: 1.25,95% CI, 1.03–1.52, P = 0.02, $I^2 = 71$), MI (RR: 1.30, 95% CI, 1.16–1.47, P < 0.001, $I^2 = 82$) and stroke (RR: 1.60, 95% CI, 1.43–1.78, P < 0.001, $I^2 = 0$), without reducing GI bleeding (RR: 0.74, 95% CI, 0.45–1.22, P = 0.24, $I^2 = 79$).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2019.02.002.

Conclusion: Meta-analysis of RCTs endorsed the use of PPI with DAPT for reducing GI bleeding without worsening cardiovascular outcomes. These findings oppose the negative observational data regarding effects of PPI with DAPT.

Keywords

Proton pump inhibitors; Dual antiplatelet therapy; Coronary artery disease; Meta- analysis

1. Introduction

Dual antiplatelet therapy (DAPT) reduces the risk of adverse cardiovascular events in patients with coronary artery disease (CAD) [1,2]. However, the addition of P2Y12 inhibitor to aspirin is associated with increased risk of significant bleeding [3,4]. The European Society of Cardiology (ESC) guidelines endorse PPI prescription (class I, Level: B) with DAPT for all CAD patients [5], whereas, the 2016 American College of Cardiology/ American Heart Association focused update recommend the concomitant use of proton pump inhibitors (PPI) with DAPT in the following patients: (a) prior history of GI bleeding (Class I) and (b) higher risk of GI bleeding (i.e. advanced age, concomitant use of warfarin, steroids or non-steroidal inflammatory drugs (Class II a). The routine use of PPIs is not recommended for patients at low risk of GI bleeding (Class III: No Benefit) [6]. While there is paucity of randomized controlled trials (RCTs) on this subject, various meta-analyses and observational studies showed drug interaction and adverse cardiovascular outcomes with co-administration of PPI and DAPT [7-9]. Furthermore, these studies were also inconsistent regarding the protective effects of PPI on GI bleeding. We performed meta-analysis stratified according to study design to explore these clinical differences among RCTs and observational studies regarding use of PPI with DAPT in CAD.

2. Methods

Current meta-analysis was conducted and reported according to Cochrane Collaboration guidelines [10] and Preferred Reporting Item for Systematic Reviews and Meta-Analyses [11].

2.1. Data sources and searches

Electronic search was carried out by two authors (ANL and HR) using MEDLINE (Ovid SP, PubMed), EMBASE and CENTRAL data bases (Inception-January 2018). Following key search terms were used: “proton pump inhibitor” OR “omeprazole” OR “pantoprazole” OR “lansoprazole” OR “esomeprazole” OR “rabeprazole” OR “PPI” OR “dual antiplatelet therapy” OR “DAPT” OR “clopidogrel” AND “Acute coronary syndrome” OR “ACS” OR “percutaneous coronary intervention”. There was no restriction on article types, language, sample size, publication dates, co-morbidities or follow up duration. We also reviewed references contained in the relevant articles. All the citations were downloaded into End note X7 (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania, USA) and duplicates were removed electronically and manually.

2.2. Study selection

Two authors (ANL and HR) screened the search results in a two steps process. Citations were screened at title and abstract level followed by full text screening based on prespecified inclusion criteria: [1] studies comparing PPI versus no PPI in patients with CAD receiving DAPT, [2] studies reporting at least one event for outcomes of interest in adult population (age ≥ 18 years) and [3] Full text articles. Studies were excluded if interaction of PPI was studied with single antiplatelet agent only or if DAPT was used for any other indication such as peripheral vascular disease or stroke.

2.3. Data extraction

Data abstraction was done by two authors (MSK and ANL) on study design, baseline characteristics of the participants, medical therapy, events, non-events, sample size and follow up duration on Microsoft Excel spreadsheets (Microsoft Corporation, Redmond, WA, USA). When available, data was extracted for intention to treat analysis. When possible, standard adjusted estimates were collected. Quality assessment of RCTs was appraised by Cochrane bias assessment tool [12](Supplement Table 1); while observational studies were evaluated using New-Castle Ottawa Scale [13]. We assessed eight domains in New-Castle Ottawa Scale and score of 6/8 was consistent with good quality data (Supplement Table 2).

2.4 Outcome measures

The primary outcome was all-cause mortality. The secondary outcomes were cardiovascular mortality, myocardial infarction(MI), stroke, and GI bleeding events. We used the definitions as reported in the included studies.

2.5 Statistical analysis

Meta-analysis was stratified according to study design (RCT and observational studies). Estimates were pooled using generic invariance weighted random effects model. Statistical heterogeneity was checked by Q statistics and quantified via I2 with value ≥75% was consistent with high degree of heterogeneity [14]. Outcomes were calculated as risk ratio (RR) and risk difference (RD) with 95% confidence interval (CI). Since both summary measures account for same data, forest plots are generated for RRs only. However, RDs are provided in Supplement Table 3. All analyses were conducted at 5% significance. Publication bias was assessed using Egger's regression test [15]. Comprehensive Meta-analysis software version 3.0 (Biostat, Englewood, NJ) was used for all the analyses.

3. Results

Initial search yielded 38,725 citations, 21,480 were duplicates and 15,830 were excluded at titles and abstract level screening and 1376 articles were removed based on prior inclusion/exclusion criteria. Ultimately, 39 studies (4 RCTs and 35 observational studies) were selected (Fig. 1). 15 studies recruited patients with acute coronary syndrome (ACS) while 24 studies had participants with mixed presentation (stable CAD and ACS). The pooled mean age was 65 ± 3 years, 72% were males, 25% had prior MI, 69% had hypertension and 33% had diabetes mellitus. Except for two studies [16,17], all studies used Clopidogrel as P2Y12

inhibitor. Whereas, different PPIs were used across all the studies. The pooled average follow-up duration was 15 months (Table 1).

A total of 221,204 patients (PPI = 77,731 patients and no PPI = 143,473 patients) participated in meta-analysis. In the RCTs restricted analysis, PPI did not increase all-cause mortality (RR: 1.35, 95% CI, 0.56–3.23, P = 0.50, $I^2 = 0$; Fig. 2), cardiovascular mortality (RR: 0.94, 95% CI, 0.25–3.54, P = 0.92, $I^2 = 56$; Fig. 3), MI (RR: 0.97, 95% CI, 0.62–1.51, P = 0.88, $I^2 = 0$; Fig. 4) or stroke (RR: 1.11, 95% CI, 0.25–5.4, P = 0.89, $I^2 = 26$; Fig. 5). While, PPI significantly reduced the risk of GI bleeding (RR: 0.32, 95% CI, 0.20–0.52, P < 0.001, $I^2 = 0$; Fig. 6). Conversely, analysis of the observational studies showed that PPI was associated with significant increase in risk of all-cause mortality (RR: 1.25, 95% CI, 1.11–1.41, P < 0.001, $I^2 = 82$; Fig. 2), cardiovascular mortality (RR: 1.25, 95% CI, 1.03–1.52, P = 0.02, i2 = 71; Fig. 3), MI (RR: 1.30, 95% CI, 1.16–1.47, P < 0.001, $I^2 = 82$; Fig. 4) and stroke (RR: 1.60,95% CI, 1.43–1.78, P < 0.001, $I^2 = 0$; Fig. 5), without providing meaningful protection against GI bleeding (RR: 0.74, 95% CI, 0.45–1.22, P = 0.24, $I^2 = 79$; Fig. 6). Egger's regression test did not detect publication bias [Intercept: −0.56, 95% CI, −1.89, 0.76, P (2-tailed) =0.39].

4. Discussion

In this review of 39 studies enrolling 221,204 subjects with CAD requiring DAPT, meta-analysis of RCTs suggested that over an average follow up duration of one year, PPI prevented 36 GI bleeding events per 1000 patients compared with no PPI. This benefit was achieved without increasing the risk cardiovascular events or mortality. Conversely, analysis of observational studies suggested that the use of PPI was associated with significant risk of mortality and cardiovascular outcomes without providing protection against GI bleeding.

Several observational studies have shown that PPIs interfere with the efficacy of DAPT and subsequently may cause adverse cardiovascular outcomes [8,16,18,19]. The interaction between omeprazole and clopidogrel is considered vigorous due to the inhibitory effect of PPI on CYP2C19 isoenzyme [20,21]. Clopidogrel is a prodrug and requires conversion to its active metabolite for inhibition of platelet aggregation. While the conversion from prodrug to active metabolite requires CYP2C19 enzymes, there are genetic variations in CYP2C19 enzymes leading to poor metabolism of the drug in certain patients. Subsequently these patients have reduced efficacy of Clopidogrel. Similarly, Omeprazole and Esomeprazole are inhibitors of CYP2C19 and they can significantly reduce the efficacy of Clopidogrel by preventing conversion to its active metabolite. Therefore, FDA precautions against use of Omeprazole and Esomeprazole use in patients taking Clopidogrel [22].

There is observational data suggesting that the blunting effect of PPI could be expanded to ticagrelor and prasugrel. In a post hoc analysis of PRINCIPLE (Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation)-TIMI 44 and TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel)-TIMI 38 trials, there was modest attenuation of the in vitro antiplatelet effects of prasugrel and clopidogrel in the setting of PPI therapy. Another hypothesis for PPI related enhanced cardiovascular risk is that PPI use is a marker for high risk of

cardiovascular complications rather than a cause of cardiovascular complications [16,23]. In post hoc analysis of the PLATO (Platelet Inhibition and Patient Outcomes) trial the use of PPI was independently associated with higher risk of cardiovascular events for both clopidogrel and ticagrelor [16]. Similar observation was made in the post-hoc analysis of CREDO (Clopidogrel for Reduction of Events During Observation) and CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) where PPI use was associated with worse cardiovascular outcomes in both clopidogrel (Estimated hazard ratio (EHR): 1.67, 95% CI 1.06 to 2.64) and placebo arms (HER: 1.56, 95% CI 1.06 to 2.30) [24].

Despite this negative interaction between PPI and antiplatelet therapy shown by observational data, this effect was not translated into any significant clinical impression in RCTs. Gao and colleagues [25] reported that early use of omeprazole in acute MI not only reduced the incidence of GI bleeding compared with control (5.3% versus 14.6%, P = 0.017) but also had protective effect on all-cause mortality (3.5% versus 10.6%, P = 0.035). In another trial by Ng et al. [26], omeprazole was superior to famotidine in reducing the risk of GI bleeding (HR: 0.212, P = 0.008) without increasing the risk of cardiovascular outcomes (P = 0.77). In the largest COGENT study (Clopidogrel and the Optimization of Gastrointestinal Events Trial) [27], the addition of omeprazole to DAPT significantly reduced the risk of major GI bleeding without increasing the risk of cardiovascular events, though with broader confidence interval around HRs and limited statistical power. Our meta-analysis is in consensus with these findings and highlights the importance of potential bias introduced by observational studies which results in conflicting outcomes.

We compare our results with prior meta-analyses. Cardoso et al. [28] (39 studies and 214,851 patients) reported 60% relative risk reduction in GI bleeding with PPI (odds ratio (OR): 0.40, 95% CI, 0.22–0.74) but at the cost of increased risk of cardiovascular events. However, Cardoso's meta-analysis had certain limitations. First, authors combined RCTs and observational studies together in their pooled analysis. This strategy has the potential to generate higher risk of selection and attrition biases. Second, the analysis was primarily focused on interaction of PPI with single clopidogrel therapy and a subgroup analysis on DAPT was limited by various confounders due to mixing of RCTs and propensity matched score studies. Third, post hoc analyses of various RCTs were treated as RCTs which is issue of standardized and comprehensive reporting because post hoc analyses generally do not fill the criteria of a RCT [29]. Another systematic review by Melloni and colleagues (35 studies) was in consensus with our findings [9]. However, authors focused on observational studies only and lacked separate examination of RCTs. Hence, comparison of the effect sizes among RCTs and observational studies could not be performed. Furthermore, key endpoint of GI bleeding was not included. Similar issues related to study design [7,8] or lack of assessment of important endpoints [7] were noticed in other meta-analyses.

That said, the current meta-analysis has certain limitations. First, RCTs data is dominated by the COGENT study population which contributes ~ 84% of RCTs cohort [27]. The COGENT suffered from premature study termination, abbreviated follow up duration and had a high-risk population. Furthermore, due to low event rate and limited follow up duration, COGENT lacked statistical power to detect cardiovascular harm. Second, studies had heterogeneities with regards to clinical presentation, drugs and dosages, procedural

techniques, definition of the endpoints and follow up duration which could not be compensated due to lack of access to individual patient data. Therefore, certain outcomes such as stent thrombosis or coronary revascularization could not be assessed. Finally, this review predominantly generates the evidence regarding clopidogrel based DAPT.

In conclusion, we report that meta-analysis of RCTs endorse the use of PPI with DAPT (predominantly clopidogrel based therapy) in CAD patients for prevention of GI bleeding without worsening cardiovascular outcomes. The findings of RCTs restricted analysis are in line with current professional guidelines [6] and oppose the negative observational data on the use of PPI with DAPT. Our review serves as refined summary of published literature on this issue and would allow the clinicians to compare the effects of PPI with concomitant clopidogrel based DAPT based on quality of evidence. This review also highlights the importance of conducting further well-designed RCTs comparing use of specific PPIs with different DAPT regimens (Ticagrelor and Prasugrel) to generate more durable evidence and compensate for relative scarcity of quality data on this subject.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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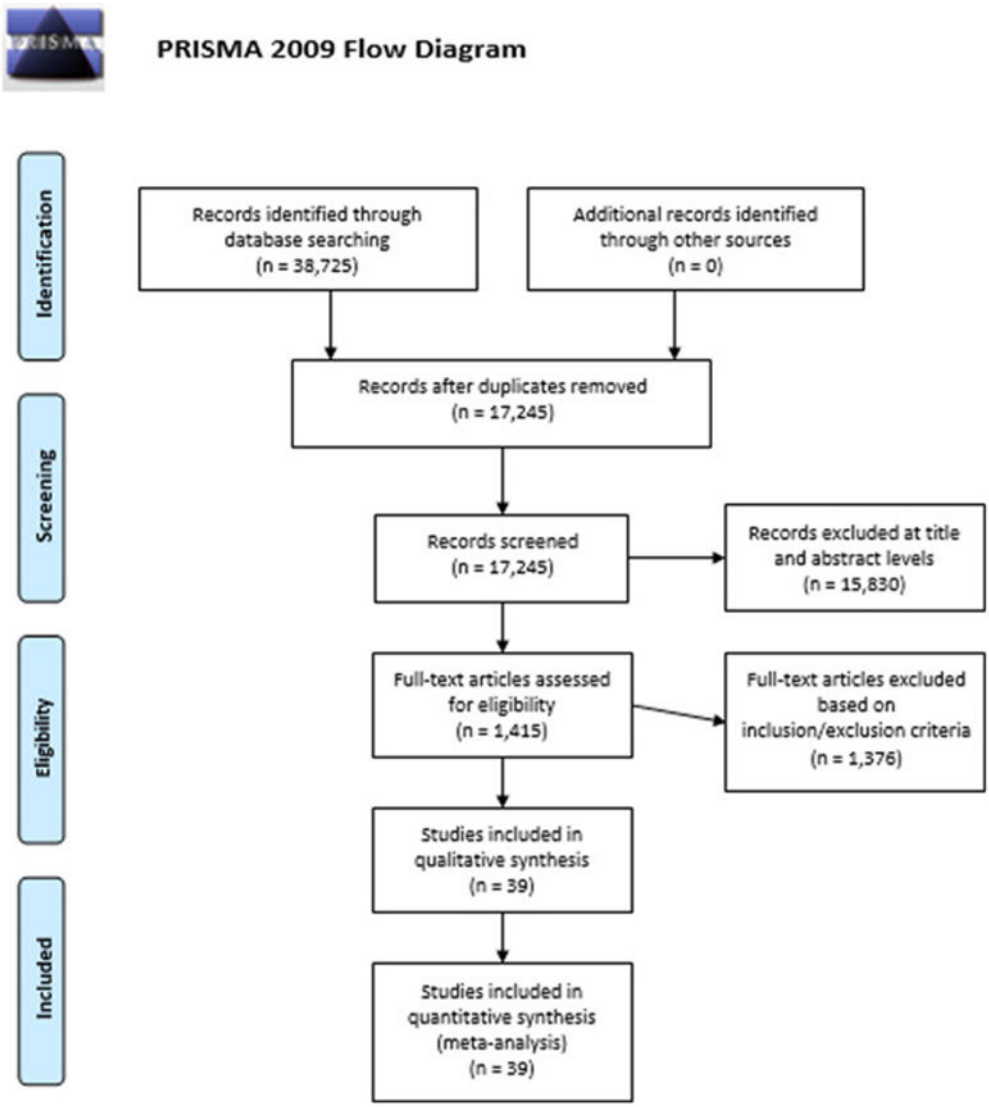

Fig. 1.

Search strategy according to preferred reporting items of systematic reviews and meta-analyses.

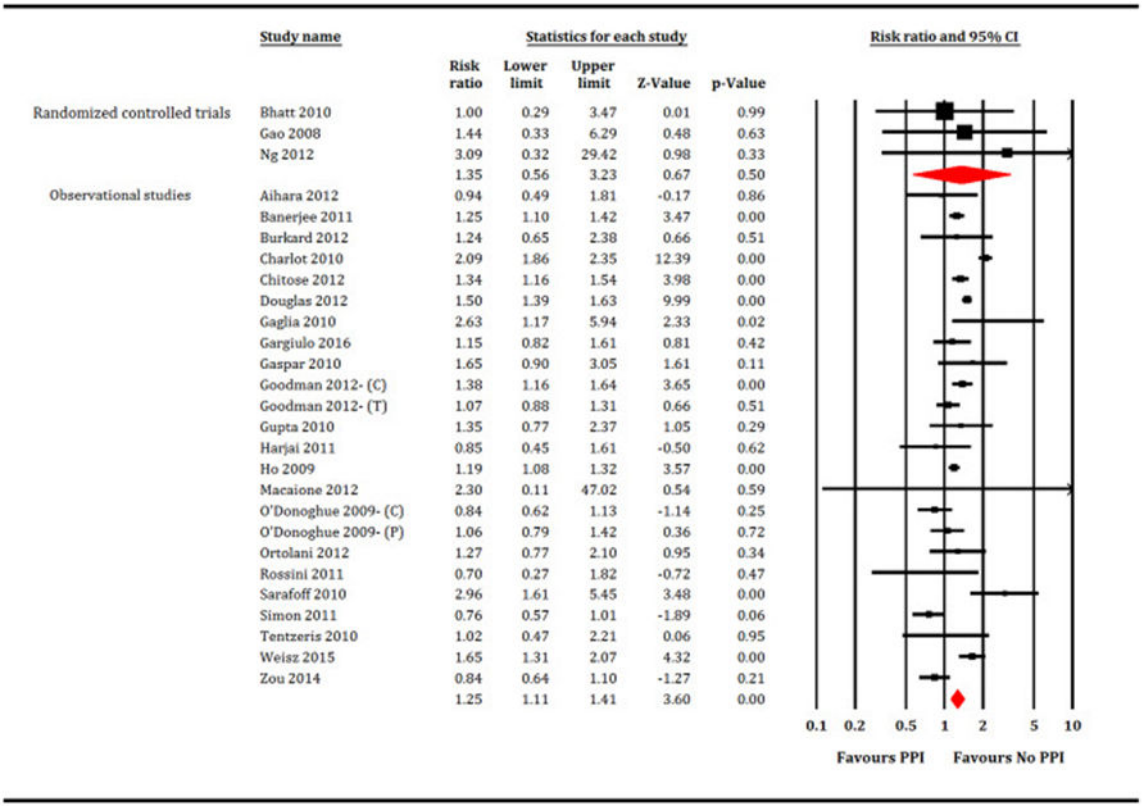

Fig. 2.

Forest plot showing comparison between proton pump inhibitors (PPI) versus no PPI for all-cause mortality. C = Clopidogrel, T = Ticagrelor, P = Prasugrel.

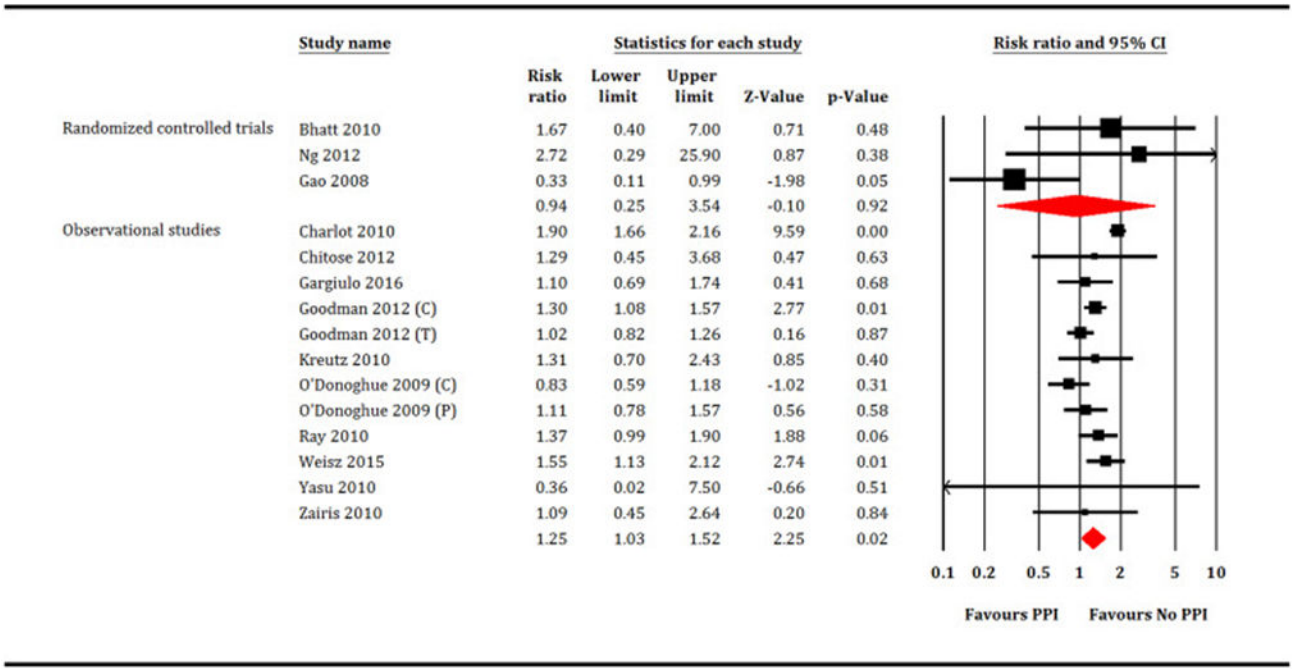

Fig. 3.

Forest plot showing comparison between proton pump inhibitors (PPI) versus no PPI for cardiovascular mortality. C = Clopidogrel, T = Ticagrelor, P = Prasugrel.

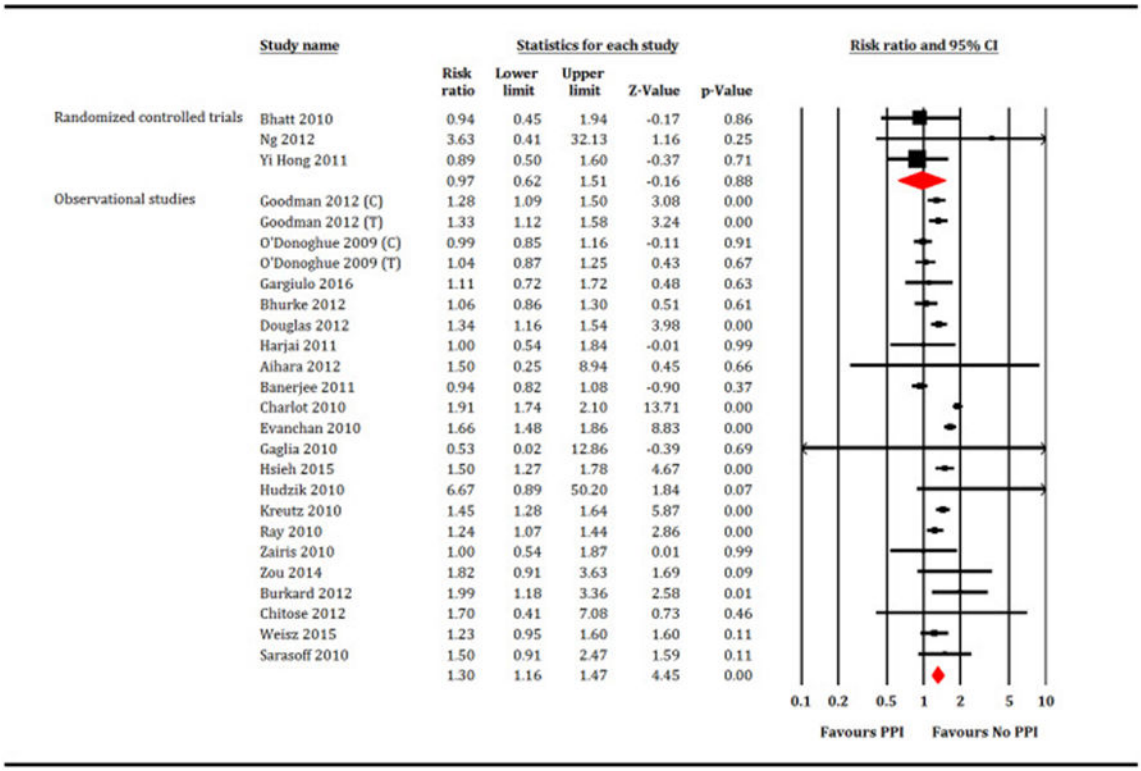

Fig. 4.

Forest plot showing comparison between proton pump inhibitors (PPI) versus no PPI for myocardial infarction. C = Clopidogrel, T = Ticagrelor, P = Prasugrel.

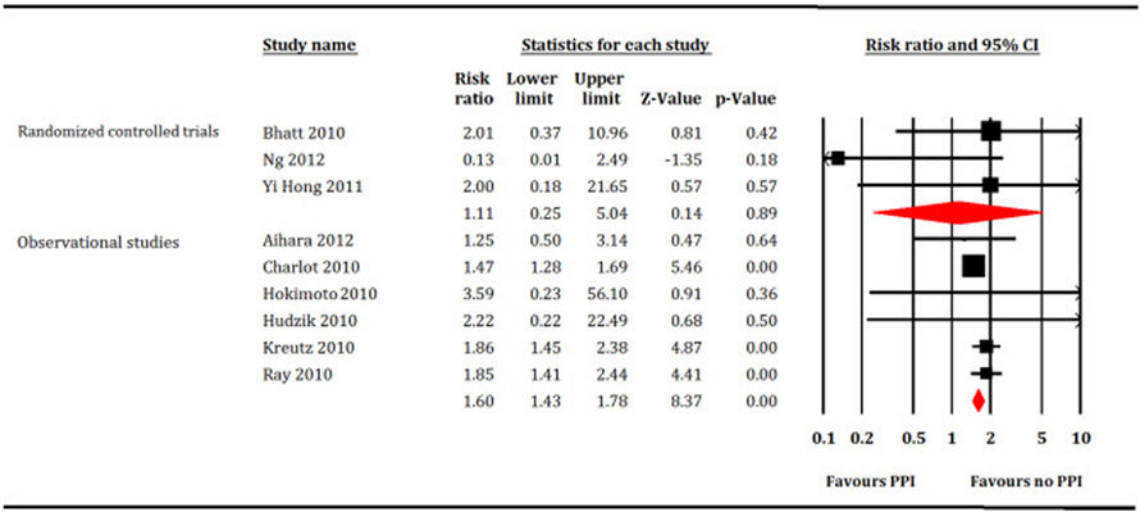

Fig. 5.

Forest plot showing comparison between proton pump inhibitors (PPI) versus no PPI for stroke.

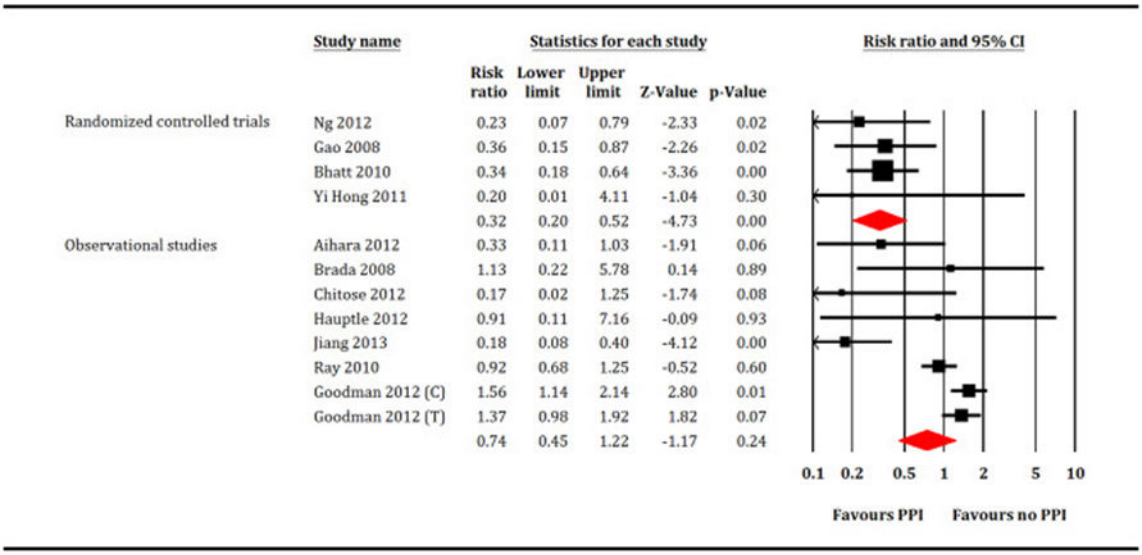

Fig. 6.

Forest plot showing comparison between proton pump inhibitors (PPI) versus no PPI for gastrointestinal bleeding. C = Clopidogrel, T = Ticagrelor.

Table 1

baseline characteristics of the studies and participants.

Studies (year/design)	Setting	Groups	N	Age (years)	Men (%)	Type of P2Y12 inhibitors	Type of PPI	Prior MI (%)	DM (%)	HTN (%)	Smoking (%)	Follow up (months)
Brada [30] (2008/OS)	ACS	PPI	705	64.3 ± 13.0	75	Clopidogrel	NR	59	31	53	58	In-hospital
		No PPI	318	62.6 ± 11.4	79		27	34	61	62		
Gao [25] (2009/RCT)	ACS	PPI	114	58.2 ± 8.7	NR	NR	Omeprazole	NR	NR	NR	NR	0.5
		No PPI	123	57.5 ± 9.2	NR			NR	NR	NR	NR	
Ho [19](2009/OS)	ACS	PPI	5244	67.7 ± 11.4	98.4	Clopidogrel	Omeprazole, Rabeprazole	26.4	45.5	NR	NR	17.3
		No PPI	2961	65.7 ± 11.7			98.9	20.1	38	NR	NR	
O'Donoghue (PRINCIPLE-TIMI 44/ TRITON-TIMI 38) [17] (2009/OS)	Mixed	PPI	28/2257	63.1/62	67.9/70.3	Clopidogrel	Pantoprazole, Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole	39.3/17.2	39.3/24.2	78.6/65.9	32.1/36.7	6
		No PPI	71/4538	64.1/60	71.3/74.7			23.9/18.1	23.9/22.5	77.5/63.5	9.9/38.7	
		PPI	25/2272	61.8/61	72.0/73.0	Prasugrel		52.0/17.6	52.0/23.5	92.0/64.6	24.0/38.5	
		No PPI	77/4541	64.7/60	71.4/76.0			23.4/18.2	23.4/23.0	83.1/63.9	15.6/38.3	
Bhatt [27] (2010/RCT)	Mixed	PPI	1876	68.5	66.9	Clopidogrel	Omeprazole	30.5	31.7	80.1	12.5	3.5
		No PPI	1885	68.7	69.5			28.5	28.6	81.4	14.1	
Charlot [31](2010/OS)	ACS	PPI	6753	67.5 ± 12.5	61.8	Clopidogrel	Pantoprazole, Lansoprazole, Omeprazole, Esomeprazole, Rabeprazole	NR	5.8	NR	NR	12
		No PPI	17,949	64.1 ± 12.5	71.3			NR	3.7	NR	NR	
Evanchan [32] (2010/OS)	ACS	PPI	1369	63.5	NR	Clopidogrel	Esomeprazole, Pantoprazole, Omeprazole, Lansoprazole	-	46	61	NR	12
		No PPI	4425	62.9	NR			-	36	64	NR	
Gaglia [33] (2010/OS)	Mixed	PPI	318	63.8 ± 11.6	61.9	Clopidogrel	Esomeprazole, Omeprazole, Lansoprazole, Rabeprazole	28.1	36.3	78.5	13.8	12
		No PPI	502	63.7 ± 11.6	64.1			23.7	33.1	74.8	18.9	
Gaspar [34] (2010/OS)	ACS	PPI	274	65 ± 13	73.7	Clopidogrel	Lansoprazole Omeprazole, Rabeprazole	20.1	25.5	67.5	34.7	6
		No PPI	528	61 ± 13	76.7			20.1	27.1	61.4	43	
Gupta [18] (2010/OS)	Mixed	PPI	72	61.7 ± 1.2	NR	Clopidogrel	Rabeprazole, Omeprazole, Lansoprazole	NR	36	76	25	50
		No PPI	243	62.0 ± 0.7	NR			NR	30	68	33	
Huzdik [35] (2010/OS)	Mixed	PPI	18	62.8 ± 9.4	83.3	Clopidogrel	Omeprazole	76.5	44.4	72.2	NR	12
		No PPI	20	60.5 ± 11.8	65			70	30	70	NR	

Studies (year/design)	Setting	Groups	N	Age (years)	Men (%)	Type of P2Y12 inhibitors	Type of PPI	Prior MI (%)	DM (%)	HTN (%)	Smoking (%)	Follow up (months)
Kreutz [36] (2010/OS)	Mixed	PPI	6828	67.5 ± 10.4	62	Clopidgrel	Esomeprazole, Omeprazole, Pantoprazole, Lansoprazole	NR	25.9	50.6	NR	12
		No PPI	9862	65.2 ± 10.6	73.9			NR	22.7	46.5	NR	
Ray [37] (2010/OS)	Mixed	PPI	7593	60.8 ± 11.3	45.6	Clopidogrel	Pantoprazole, Lansoprazole Omeprazole, Esomeprazole, Rabeprazole	NR	NR	NR	NR	12
		No PPI	13,003	60.4 ± 11.2	53.1			NR	NR	NR	NR	
Sarasoff [38] (2010/OS)	Mixed	PPI	698	68.7 ± 11.1	62.9	Clopidogrel	Pantoprazole, Lansoprazole Omeprazole, Esomeprazole, Rabeprazole	36.1	28.8	62.9	16.5	1
		No PPI	2640	66.3 ± 10.8	66.1			29.5	25	66.1	17.2	
Tentzeris [39] (2010/OS)	Mixed	PPI	691	64.1 ± 12.4	65.4	Clopidogrel	Pantoprazole, Lansoprazole Omeprazole, Esomeprazole, Rabeprazole	18.7	18.7	73.7	27.9	7.8
		No PPI	519	64.4 ± 11.9	72.6			19.7	26	78.2	23.1	
Yasu [40] (2010/OS)	Mixed	PPI	103	69.0 ± 9.6	67	Clopidogrel	Rabeprazole	32	35	64.1	24.3	13
		No PPI	188	67.4 ± 10.1	72.4			17.6	39.7	64.8	27.1	
Ziaris [41] (2010/OS)	Mixed	PPI	340	62.1 ± 10.5	82.4	Clopidogrel	Omeprazole	17.1	30	50.9	49.7	12
		No PPI	248	61.7 ± 10.8	81.9			17.7	26.2	46.4	50.8	
Banerjee [42] (2011/OS)	ACS	PPI	867	64.5 ± 10.3	98.2	Clopidogrel	NR	24.9	51.4	92.4	40	72
		No PPI	3678	63.8 ± 9.9	98.3			17.6	45.1	88.9	39.5	
Yi-hong [43] (2011/ RCT)	ACS	PPI	86	62.1 ± 10.6	72.1	Clopidogrel	Omeprazole	NR	NR	NR	NR	1
		No PPI	86	61.8 ± 11.2	73.3			NR	NR	NR	NR	
Harjai [44] (2011/OS)	Mixed	PPI	751	66 ± 11	62	Clopidogrel	Omeprazole, Esomeprazole	22	30	73	21	6
		No PPI	1902	64 ± 12	72			21	27	65	26	
Nakayama [45] (2011/OS)	Mixed	PPI	280	68.4 ± 9.9	79	Clopidogrel	Lansoprazole Omeprazole, Rabeprazole	16	37	89	65	30
		No PPI	284	66.9 ± 9.9	75			21	45	89	61	
Rossini [46] (2011/OS)	Mixed	PPI	1158	64 ± 11	75.6	Clopidogrel	Lansoprazole Omeprazole, Pantoprazole	24.9	27.1	63.6	49.3	12
		No PPI	170	63 ± 11	81.2			29	28	65.2	49.7	
Simon [47] (2011/OS)	ACS	PPI	1453	64 ± 13	73	Clopidogrel	Pantoprazole, Lansoprazole Omeprazole, Esomeprazole	10	30	52	35	12
		No PPI	900	65 ± 14	72			14	35	53	33	

Studies (year/design)	Setting	Groups	N	Age (years)	Men (%)	Type of P2Y12 inhibitors	Type of PPI	Prior MI (%)	DM (%)	HTN (%)	Smoking (%)	Follow up (months)
Aihara [48] (2012/OS)	Mixed	PPI	500	68 ± 11	72.6	Clopidogrel	Lansoprazole Omeprazole, Rabeprazole	15.8	40.8	71.2	44.6	12
		No PPI	500	69 ± 10	75.8			16.8	39.4	69	43.2	
Bhurke [49] (2012/OS)	ACS	PPI	2674	61.3 ± 11.7	70	Clopidogrel	Pantoprazole, Lansoprazole, Omeprazole, Esomeprazole, Rabeprazole	NR	29.1	NR	NR	9
		No PPI	2674	61.3 ± 11.7	70.1			NR	28.6	NR	NR	
Burkard [50] (2012/OS)	Mixed	PPI	109	66.5 ± 10.5	68.8	Clopidogrel	Pantoprazole, Lansoprazole Omeprazole, Esomeprazole	22	29.6	72.5	24.8	36
		No PPI	692	63.3 ± 11.3	79.9			27.9	17.2	65	29.8	
Chitose [51] (2012/OS)	Mixed	PPI	331	70.3 ± 11.0	71.6	Clopidogrel, Ticlopidine	NR	25.4	35.3	77.9	23.9	18
		No PPI	939	68.9 ± 10.9	72.2			22.9	33.7	79	26.2	
Douglas [52] (2012/OS)	ACS	PPI	9111	71	58	Clopidogrel	Lansoprazole Omeprazole, Esomeprazole	NR	34	NR	69	10
		No PPI	15,360	68	65			NR	29	NR	69	
Goodman [16] (Clopidogrel/Ticagrelor) (2012/OS)	ACS	PPI	6539	63	72.4	Clopidogrel/ Ticagrelor	Pantoprazole, Lansoprazole, Omeprazole, Esomeprazole, Rabeprazole	20.8	25.8	65.6	36.2	12
		No PPI	12,062	62	71.2			20.5	24.7	65.4	35.7	
Ng [26] (2012/RCT)	ACS	PPI	163	64.3 ± 13.8	77.3	Clopidogrel	Esomeprazole	NR	NR	NR	19.6	6
		No PPI	148	63.1 ± 13.2	72.3			NR	NR	NR	18.9	
Hauptle [53] (2012/OS)	ACS	PPI	87	68 ± 9	70.1	Clopidogrel	NR	NR	12.6	79.3	29.9	12
		No PPI	631	64 ± 11	74.3			NR	15.8	62.1	34.5	
Lin [54] (2012/OS)	ACS	PPI	5173	68.3 ± 11.4	66.2	Clopidogrel	Pantoprazole, Lansoprazole Omeprazole, Esomeprazole, Rabeprazole	NR	35.1	54.1	NR	12
		No PPI	31,926	65.4 ± 12.4	71.6			NR	33	55.7	NR	
Macaione [55] (2012/OS)	ACS	PPI	121	63.7 ± 10.6	80.2	Clopidogrel	Pantoprazole, Lansoprazole Omeprazole, Esomeprazole	16.5	41.3	70.2	37.2	36
		No PPI	55	65.8 ± 8.8	87.3			14.5	49.1	81.8	27.3	
Ortolani [56] (2012/OS)	ACS	PPI	3519	69 ± 12	69	Clopidogrel	Pantoprazole, Lansoprazole Omeprazole, Rabeprazole	20	24	63	NR	12
		No PPI	377	63 ± 12	77			15	20	57	NR	
Jiang [57] (2013/OS)	Mixed	PPI	1570	72.4 ± 12.3	66	Clopidogrel	Lansoprazole Omeprazole, Esomeprazole	NR	NR	NR	19.2	12
		No PPI	1110	69.5 ± 13.8	65			NR	NR	NR	15.6	

Studies (year/design)	Setting	Groups	N	Age (years)	Men (%)	Type of P2Y12 inhibitors	Type of PPI	Prior MI (%)	DM (%)	HTN (%)	Smoking (%)	Follow up (months)
Zou [58] (2014/OS)	ACS	PPI	6188	66.2 ± 10.2	73.5	Clopidogrel	Pantoprazole, Omeprazole, Esomeprazole	17.3	25.8	71.3	32.2	12
		No PPI	1465	65.7 ± 10.6	73.9			19.8	23.6	70.4	31	
Hsieh [59] (2015/OS)	Mixed	PPI	670	68.3 ± 10.7	63.6	Clopidogrel	NR	31.8	100	NR	NR	12
		No PPI	5933	66.5 ± 10.5	66.4			31.3	100	NR	NR	
Weisz [60] (2015/OS)	Mixed	PPI	2697	64.4 ± 10.5	70.1	Clopidogrel	NR	28.6	34.8	83.7	22.7	24
		No PPI	5885	63.2 ± 11.0	75.9			23.7	31.4	77.8	22.6	
Gargiulo [61] (2016/OS)	Mixed	PPI	738	71.2	72.5	Clopidogrel	Pantoprazole, Lansoprazole	27	23.3	72.5	22.6	24
		No PPI	1232	68.1	79.2			26.1	24.8	71.3	24.4	

ACS = Acute Coronary Syndrome, DM = Diabetes Mellitus, HTN = Hypertension, MI = Myocardial Infarction, NR = Not Reported, OS = Observational Studies, PPI = Proton Pump Inhibitors, RCT = Randomized Controlled Trial, Mixed = Both ACS and non-ACS presentations.