EFFECTS OF ACID SUPPRESSING DRUG TREATMENT IN PATIENTS WITH ACUTE PANCREATITIS AND WITH CONCOMITANT CLOPIDOGREL THERAPY

Ph.D. Thesis

Alexandra Demcsák M.D.

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TABLE OF CONTENTS

I. PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

I.) Demcsák A, Soós A, Kincses L, Capunge I, Minkov G, Kovacheva-Slavova M, Nakov R, Wu D, Huang W, Xia Q, Deng L, Hollenbach M, Schneider A, Hirth M, Ioannidis O, Vincze Á, Bajor J, Sarlós P, Czakó L, Illés D, Izbéki F, Gajdán L, Papp M, Hamvas J, Varga M, Kanizsai P, Bóna E, Mikó A, Váncsa S, Juhász MF, Ocskay K, Darvasi E, Miklós E, Erőss B, Szentesi A, Párniczky A, Casadei R, Ricci C, Ingaldi C, Mastrangelo L, Jovine E, Cennamo V, Marino MV, Barauskas G, Ignatavicius P, Pelaez-Luna M, Soriano Rios A, Turcan S, Tcaciuc E, Małecka-Panas E, Zatorski H, Nunes V, Gomes A, Cúrdia Gonçalves T, Freitas M, Constantino J, Ramos Moreira e Sá MR, Pereira J, Mateescu B, Constantinescu G, Sandru V, Negoi I, Ciubotaru C, Negoita V, Bunduc S, Gheorghe C, Barbu S, Tantau A, Tantau M, Dumitru E, Suceveanu AI, Tocia C, Gherbon A, Litvin A, Shirinskaya N, Rabotyagova Y, Bezmarevic M, Hegyi PJ, Han J, Rodriguez-Oballe JA, Miguel Salas I, Pijoan Comas E, Iglesia Garcia D, Jardi Cuadrado A, Quiroga Castiñeira A, Chang YT, Chang MC, Kchaou A, Tlili A, Kacar S, Gökbulut V, Duman D, Kani HT, Altintas E, Chooklin S, Chuklin S, Gougol A, Papachristou G, Hegyi P. Acid Suppression Therapy, Gastrointestinal Bleeding and Infection in Acute Pancreatitis – An International Cohort Study. *Pancreatology* (2020) 20:1323-1331. doi: 10.1016/j.pan.2020.08.009

IF: 3.629 (2019)**, Q1**

II.) Demcsák A, Lantos T, Bálint ER, Hartmann P, Vincze Á, Bajor J, Czopf L, Alizadeh H, Gyöngyi Z, Márta K, Mikó A, Szakács Z, Pécsi D, Hegyi P, Szabó IL. PPIs Are not Responsible for Elevating Cardiovascular Risk in Patients on Clopidogrel – A Systematic Review and Meta-analysis. *Front Physiol* (2018) 9:1550. doi: 10.3389/fphys.2018.01550

IF: 3.201, Q2

II. INTRODUCTION

Acid suppressing drugs (ASDs), such as histamine-2-receptor antagonists (H2-RAs) and proton pump inhibitors (PPIs), are the cornerstones in the therapy of diseases in which gastric acid has a causative primary or contributory role to prevent the damage or to propagate the healing of gastric mucosa. Nowadays, PPIs are among the most commonly prescribed drugs with constantly increasing usage, while several studies raise concerns regarding their overprescription without further re-evaluation or termination of these treatments, which could lead to prolonged administration with short and long term side effects. Possible reasons for continuous increase in ASD intake can be the empirical treatment of various gastrointestinal (GI) symptoms and prescriptions for inappropriate conditions (1-3).

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas. Its global incidence is 30-100 cases per 100,000 general population per year, and it is one of the most frequent GI causes of hospital admission (4). Unfortunately, research activity in the field is more underrepresented than it should be (5). Not surprisingly, there is no specific therapy available for AP, symptomatic and curative treatments are established based on guidelines and the prior experience of the medical staff. Despite the fact that ASDs are routinely administered in clinical practice in the majority of AP cases, strikingly, current national and international guidelines do not include any information on their administration in AP (6-9), and there are no well established randomized controlled trials (RCTs) or detailed cohort analyses which would analyze their safety and efficacy. Conventionally, the management of AP patients included nothing by mouth from the time of hospital admission. It was believed that by doing so the inflamed pancreas can rest, because fluid intake or solid nutrients would stimulate exocrine pancreatic functions and promote the release of proteolytic enzymes. However, prior studies failed to support this idea and showed no benefit from fasting or nasogastric suction (10-11). In experimentally induced pancreatitis, results showed that pantoprazole treatment reduced tissue infiltration of inflammatory cells and acinar cell necrosis in severe AP. They concluded that pantoprazole possesses anti-inflammatory *in vivo* properties and attenuates the course of AP (12). During fasting, ASD administration could be a potentially good therapeutic option in patients with AP for the protection of the upper GI mucosa and to rest the inflamed pancreas. Patients with severe AP, especially those who require intensive care treatment or mechanical ventilation are carrying a higher risk for stress-related acute gastric mucosal lesions (13), which can lead to ulceration and GI hemorrhage. There are contradictory results in the literature on the beneficial and harmful effects of ASD

administration in patients with AP (13-17). Such therapy might be beneficial if it decreases severity or mortality; however, acid suppression can be harmful as it might increase the risk for GI infections. Although many international cohort studies were published in AP (18-20), few data are available on the use of ASDs, GI bleeding and infection.

To protect the GI mucosa, PPIs are administered not only in GI disorders, but to implement secondary prevention in patients with prior cardiovascular (CV) diseases and long term antithrombotic therapy. A combination of antiplatelet drugs is used for the treatment of acute coronary syndrome (i.e., aspirin and thienopyridines) and for the secondary prevention of further CV events (21). Dual antiplatelet therapy is followed by possible side-effects, such as higher risk for GI bleeding, increasing both mortality and ischaemic complications (22-23). To reduce the risk of GI bleeding in patients with risk factors, PPIs are strongly recommended by the American College of Cardiology Foundation, the American College of Gastroenterology and the American Heart Association (23-25) for these patients. Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation and is commonly used for prevention against CV events. However, the literature consists of contradictory findings on the concomitant use of clopidogrel and PPIs. *In vitro* findings suggested that PPIs reduce the antiplatelet effect of clopidogrel (26), followed by several clinical studies with contradictory outcomes (27-42). A reason for a possible interaction between the drugs is that they are metabolized by similar cytochrome P450 enzymes in the liver. Due to competitive inhibition, PPIs could prevent the formation of the active metabolite of clopidogrel, therefore causing reduced anticoagulant effect and further CV complications. Even though international guidelines are recommending their concomitant administration, there are still contradictory data on them in the literature. A higher risk for CV outcomes was found in several studies, systematic reviews and meta-analyses in patients with clopidogrel on PPI therapy. Generally, whenever observational studies were included, a positive association was described, a higher risk for CV outcomes was found in patients with clopidogrel and PPI therapy. On the other hand, whenever propensity-matched groups were compared the difference between the groups disappeared (32, 41, 43-45).

III. AIMS

Therefore, our first aim was to understand the current national and global practice of ASD administration in patients with AP, to investigate their effect on the disease outcome (severity and mortality), and to analyze the efficacy and safety of these drugs in this patient population by evaluating the risk of GI bleeding and GI infection with a retrospective cohort analysis.

Furthermore, our aim was to carry out a precise investigation on the potential CV risks in co-administration of clopidogrel and PPIs with a systematic review of the current literature and a meta-analysis of available data.

IV. MATERIALS AND METHODS

IV.1) Cohort analysis

IV.1.1.) Patients and data collection

To assess the worldwide trend of ASD administration in AP patients, an invitation letter was sent out to the members of the International Association of Pancreatology in January 2019 to participate in the present study. The time period of data collection was from January 2013 to December 2018. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council in Hungary (TUKEB-22254-1/2012/EKU).

Centers had to provide data on the gender and age of the patient, severity of pancreatitis and mortality. In addition to the general demographic data, they had to indicate whether the patients received ASDs (PPI or H2-RA) upon admission, during hospitalization and at discharge irrespectively to its indication, timing, dosing and form of administration. Centers had to include data on the signs and cause of GI bleeding. It had to be recorded if a stool culture test (SCT) was performed along with its result. In the case of positive testing, the name of the pathogen had to be included.

Based on the data above, patients were assigned to two groups depending on their ASD administration status during hospitalization, one which received ASD treatment (group ‘ASD’) and the other which did not (group ‘NoASD’). In the case of GI bleeding and GI infection, the ASD treatment in the hospital was the indicator to assign a patient to ‘ASD’ or ‘NoASD’ groups.

IV.1.2.) Data quality

Data were complete on age, gender, severity of AP and mortality, in hospital ASD administration, registering the signs of GI bleeding, and whether SCT was performed or not and its result. ASD administration was unknown on admission in 1,046 of the cases, and in 10 patients at discharge. The cause of GI bleeding was unknown in 5 patients.

IV.1.3.) Diagnostic criteria

The diagnosis of AP was based on the IAP/APA evidence-based guidelines for the management of AP A1 recommendation (6). At least two from the following three criteria should be confirmed in patients: clinical (upper abdominal pain), laboratory (serum amylase or lipase >3x upper limit of normal) and/or imaging (CT, MRI, ultrasonography). Severity of pancreatitis was determined based on the revised Atlanta classification (46). This

classification defines three degrees of severity: mild, moderately severe (moderate) and severe AP.

Signs of GI bleeding were provided by each center. These included positive rectal digital examination, macroscopically observed bleeding in the stool, vomit or gastric juice, positive stool blood test, and bleeding verified by an imaging technique. Bleeding cases that occurred in association with endoscopic retrograde cholangio-pancreatography (ERCP) were excluded since administration of ASDs does not have an effect on this type of bleeding. If the cause of the GI bleeding could not be determined, patients were not included in the analyses regarding GI bleeding.

The presence of pathogens in the stool verified by laboratory testing was considered GI infections. Non-specific signs such as fever, diarrhea and vomiting without testing were not accepted. The pathogens were identified for each patient.

IV.1.4.) Statistical analysis

To identify differences between categorical variables the Chi-square with Fisher's exact test was used. The significance level was set at 0.05. Binary logistic regression with stepwise forward elimination was used to observe independent prognostic factors (age, gender, severity, ASD treatment, GI bleeding and infection) for the main outcomes (ASD administration, GI bleeding and infection). All statistical analyses were performed by using IBM SPSS Statistics for Windows software, Version 25.0 (IBM Corp., Amonk, NY, USA).

IV.2.) Systematic review and meta-analysis

IV.2.1.) Literature search

A systematic review of studies was performed accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement (47). After developing our clinical question and translating it into a well-defined systematic review question based on the PICO format (Patients, Interventions, Comparators and Outcomes), a manual search of medical databases, including PubMed (MEDLINE), Embase and the Cochrane Central Register of Controlled Trials, was performed for human observations using the following PICO format: P: patients on clopidogrel; I: patients treated with PPI; C: patients without PPI treatment; O: cardiovascular risk. Two independent investigators separately screened the titles and abstracts for eligible studies published from inception to 30 December 2016. The flowchart for this process is shown in Figure 5. After searching the international prospective register for systematic reviews (PROSPERO) for ongoing or completed meta-

analyses on the examined effects of PPIs, the present meta-analysis was registered on PROSPERO under No. CRD42017054316.

IV.2.2.) Study selection

Inclusion criteria: (1) randomized or observational studies (cohort and case-control studies) carried out either in a retro- or prospective manner; (2) only adult patients (over 18 years); (3) patients receiving clopidogrel treatment; (4) should compare PPI takers (omeprazole, pantoprazole, esomeprazole, lansoprazole and/or rabeprazole; all doses) and non-PPI takers; (5) we only involved studies that stated exact patient number in the preferred groups (total number of patients, patients who received clopidogrel and PPI, outcome number); (6) human studies; (7) studies should show data for either one or more of the following outcomes: (1) major adverse cardiac event (MACE): composite of cardiac and non-cardiac death, non-fatal myocardial infarction, target vessel failure; (2) myocardial infarction (MI): myocardial infarction or new, definitive major coronarographic defect; (3) CV death: only CV death. Studies published in English were selected. Duplicates were eliminated from the analysis manually. Disagreements were resolved by consulting a small committee of three researchers.

IV.2.3.) Data extraction

Numeric and texted data were extracted from the eligible articles as follows: author, publication year, study type, study endpoints, number of patients in the study, in PPI and in non-PPI treatment groups, and number of patients who received clopidogrel. We also collected the specified generic name of the PPI and patient number if indicated. For study characteristics we collected numeric and texted data as follows: country/region, mean follow up, number of male patients, mean age and mean body mass index, other medications (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin), cardio- and cerebrovascular history (MI, percutaneous coronary intervention, stroke) and CV risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking) in the non-PPI and PPI groups.

IV.2.4.) Risk of bias

The Newcastle–Ottawa quality assessment scale (48) has been edited to our study design, and was used to assess the quality of observational studies and post-hoc analyses of RCTs (Figure 9). We used the Cochrane risk of bias tool (49) for quality assessment of RCTs (Figure 10).

IV.2.5.) Statistical analysis

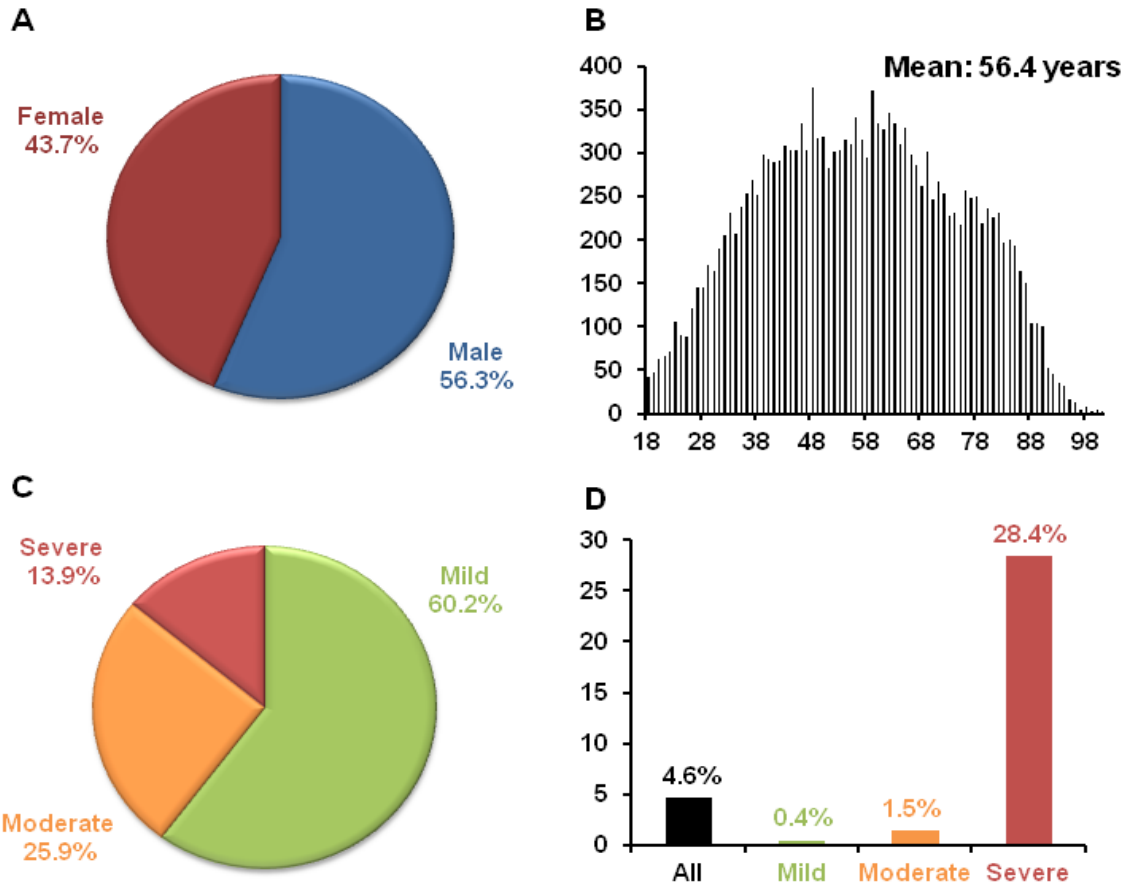
We calculated risk ratio/relative risk (RR) and 95% confidence interval (CI) for CV events (MACE, MI and CV death). As secondary analyses, pooled hazard ratios (HRs) and 95% CI were calculated for the adjusted events for all three major outcomes, which were available from observational studies. Between-study heterogeneity was tested with the I^2 statistic, where I^2 is the proportion of total variation attributable to between-study variability. I^2 heterogeneity was interpreted according to the Cochrane Handbook for Systematic Reviews and Interventions recommendation: 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity (50). Fixed or random effects models were used for comparison between the two groups (clopidogrel alone or clopidogrel plus PPI), based on the degree of heterogeneity, or based on methodological factors such as difference between study designs or applied PPIs, not homogeneous patient population etc. We estimated the effect of follow up and age on the risk of the three major outcomes by performing random effects meta-regression expressed as standard error and 95% CI. P values of less than 0.05 for relative risks and standard errors, and p values of less than 0.10 for heterogeneity were considered as indicators of significance. Publication bias was estimated through a visual inspection of funnel plots (Figure 11A–C). All analyses were performed with the Review Manager (RevMan) software, Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

V. RESULTS

V.1.) Cohort analysis

V.1.1.) Characteristics of the Cohort

Data of 17,422 adult patients with AP were collected retrospectively from 59 centers. 9,803 of patients were male (56.3%) and 7,619 were female (43.7%) (Figure 1A), the average age was 56.4 years (Figure 1B) in the cohort. In the studied population 10,490 (60.2%) of patients had mild, 4,508 (25.9%) had moderate and 2,424 (13.9%) had severe AP (Figure 1C). In total 4.6% (800 patients) of patients died; the mortality rate was 0.4% (n=44/10,490) in mild, 1.5% (n=68/4,508) in moderate and 28.4% (n=688/2,424) in severe AP (Figure 1D). Upon admission, 23.3% of patients (n=3,817/16,376) took some kind of ASD (Figure 1E). From these patients, 88.3% (n=3,369/3,817) was admitted with a PPI, 11.3% (n=432/3,817) with a H2-RA, and 0.4% (n=16/3,817) received both kind of ASD. During hospitalization, 86.6% of patients (n=15,096/17,422) received ASD treatment (Figure 1E), 81.8% (n=12,354/15,096) of these patients had only PPIs, 15.4% (n=2,331/15,096) had solely H2-RAs and 2.7% (n=411/15,096) had both PPIs and H2-RAs. At the time of discharge from the hospital, 57.6% of patients (n=10,034/17,412) were prescribed an ASD (Figure 1E), 92.6% (n=9,293/10,034) of them received prescription for PPIs, 7.3% (n=734/10,034) for H2-RAs and 0.1% (n=7/10,034) for both ASDs. For the following parameters in the result section, only data during hospitalization were analyzed.



E

	ON ADMISSION		IN HOSPITAL		AT DISCHARGE	
GROUPS	n	%	n	%	n	%
NO ASD	12,559	76.7	2,326	13.4	7,378	42.4
ASD	3,817	23.3	15,096	86.6	10,034	57.6
	16,376	100	17,422	100	17,412	100

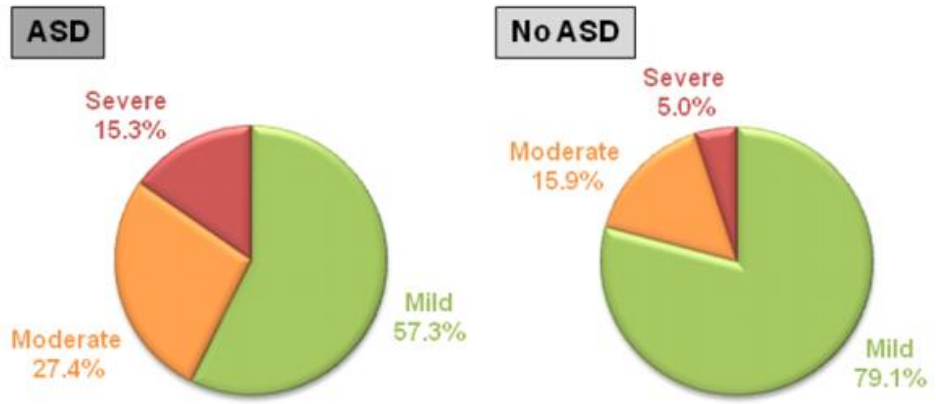
Figure 1. Cohort characteristics. A) Gender distribution of acute pancreatitis (AP) patients. **B)** Age distribution of AP patients. **C)** Disease severity in the included AP patients. **D)** Mortality rate in all AP patients and in the different severity groups. **E)** Number (n) and percentage of patients with or without acid suppressing drug (ASD) treatment on admission, in the hospital and at discharge.

V.1.2.) Acid suppression therapy is associated with more severe AP and higher mortality

Patients were assigned to 'ASD' or 'NoASD' groups based on their ASD administration status in the hospital. Among 'ASD' patients mild AP (n=8,649/15,096, 57.3%) was significantly less frequent compared to those in the 'NoASD' group (n=1,841/2,326, 79.1%, p<0.001). However, in case of moderate and severe pancreatitis, there were significantly more patients in the 'ASD' group (moderate: n=4,139/15,096, 27.4%; severe: n=2,308/15,096, 15.3%) than in the 'NoASD' group (moderate: n=369/2,326, 15.9%, p<0.001; severe: n=116/2,326, 5.0%, p<0.001) (Figure 2A). Mortality was significantly

higher in patients with acid suppressing therapy (n=744/15,096, 4.9%) compared to those without acid suppression (n=56/2,326, 2.4%, p<0.001) (Figure 2B). Based on the results of logistic regression, the patients' gender did not influence the administration of ASD treatment (OR=1.015, 95% CI=0.927-1.110, p=0.748); however, older age (OR=1.006, 95% CI=1.003-1.008, p<0.001) and worse than mild AP severity (OR=2.202, 95% CI=2.031-2.387, p<0.001) increased the patients' chance for receiving ASDs during hospitalization.

A



B

			MILD		MODERATE		SEVERE		MORTALITY	
GROUPS	n	%	n	%	n	%	n	%	n	%
ASD	15,096	86.6	8,649	82.4	4,139	91.8	2,308	95.2	744	4.9
No ASD	2,326	13.4	1,841	17.6	369	8.2	116	4.8	56	2.4
	17,422		10,490	100.0	4,508	100.0	2,424	100	800	

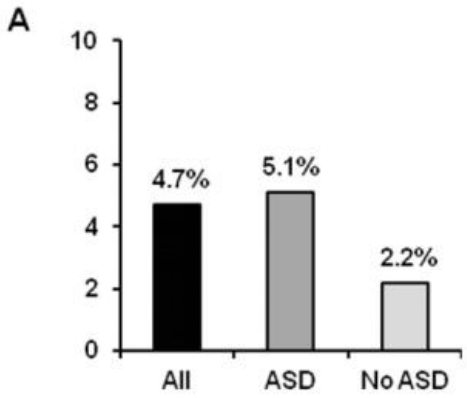
Figure 2. Disease severity and mortality rate in patients with or without acid suppressing drug (ASD) treatment. A) Disease severity in patients with (ASD) or without ASD (No ASD) therapy. **B**) Number (n) and percentage of patients who received ASDs in the different severity groups, and mortality rates in ASD and No ASD groups.

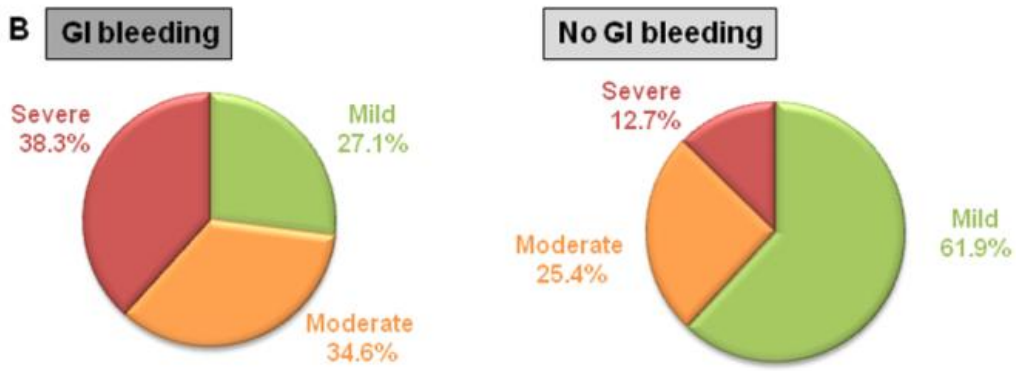
V.1.3.) Acid suppressing drug therapy is associated with higher risk for GI bleeding in AP

Data for 17,282 patients were evaluated after excluding ERCP-associated bleedings and bleedings of unknown origin. From these patients, 817 (4.7%) had GI bleeding (Figure 3A). The number of patients having mild pancreatitis without GI bleeding was significantly higher compared to those with GI bleeding (n=10,193/16,465, 61.9% vs. n=221/817, 27.1%, p<0.001, respectively). However, among patients with GI bleeding there were significantly more moderate (No bleeding: 4,181/16,465, 25.4% vs. Bleeding: n=283/817, 34.6%, p<0.001) and severe AP (No bleeding: 2,091/16,465, 12.7% vs. Bleeding: n=313/817, 38.3%, p<0.001) cases (Figure 3B). In case of GI bleeding, the rate of mortality was significantly higher compared to patients without bleeding (No bleeding: n=650/16,465, 3.9% vs. Bleeding: n=138/817, 16.9%, p<0.001) (Figure 3B). There were significantly more patients suffering

from GI bleeding while receiving acid suppressing treatment compared to those who did not ('ASD': n=766/14,975, 5.1% vs. 'NoASD': n=51/2,307, 2.2%, p<0.001, respectively) (Figure 3A).

The age (OR=0.998, 95% CI=0.992-1.005, p=0.585) and the gender (OR=0.915, 95% CI=0.732-1.143, p=0.432) of patients did not influence the chance of GI bleeding; however, worse AP severity carried an almost 3 times higher probability of GI bleeding (OR=2.994, 95% CI=2.623-3.418, p<0.001). Furthermore, ASD treatment during hospitalization increased the chance of GI bleeding by 1.5-fold (OR=1.543, 95% CI=1.040-2.291, p=0.031), and in case of verified GI infection the chance of GI bleeding was almost 2.8 times higher (OR=2.789, 95% CI=1.997-3.894, p<0.001).





C

	MILD		MODERATE		SEVERE		MORTALITY	
	n	%	n	%	n	%	n	%
GI bleeding	221	2.1	283	6.3	313	13.0	138	16.9
No GI bleeding	10,193	97.9	4,181	93.7	2,091	87.0	650	3.9

Figure 3. Disease severity and mortality rate in patients with or without gastrointestinal (GI) bleeding. A) Percentage of patients with GI bleeding in the entire cohort, in patients with or without acid suppressing drug (ASD) treatment. **B)** Disease severity in patient with and without GI bleeding. **C)** Number (n) and percentage of patients who had GI bleeding or did not have GI bleeding in the different severity groups and mortality rates.

V.1.4.) Characterization of patients undergone SCT

From the 17,422 patients, an SCT was performed in 1,102 cases (6.3%) (Figure 4A). There were significantly more patients with mild AP who did not undergo stool culture testing (NoSCT: n=9,961/16,320, 61% vs. SCT: n=529/1,102, 48%, p<0.001). In case of moderate and severe AP, the number of patients that underwent testing during hospitalization was significantly higher (NoSCT: n=4,214/16,320, 25.8% vs. SCT: n=294/1,102, 26.7%, p<0.001 and NoSCT: n=2,145/16,320, 13.2% vs. SCT: n=279/1,102, 25.3%, p<0.001, respectively) (Figure 4B). Mortality was significantly higher in patients with stool culture testing (NoSCT: n=698/16,320, 4.3% vs. SCT: n=102/1,102, 9.3%, p<0.001) (Figure 4C). The frequency of SCT orders increased with the severity of AP, mild: 5.0% (n=529/10,490), moderate 6.5% (n=294/4,508), severe: 11.5% (n=279/2,424). From the 1,102 patients who underwent stool culture testing, 313 of them (28.4% of tested patients) had positive results. The most common pathogens causing GI infections were *Clostridium difficile* (n=210/347, 60.5%) and the *Klebsiella* species (n=35/347, 10.1%) (Table 1), and there was only a single pathogen verified in 91.4% of the cases (n=286/313) (Table 1).

V.1.5.) Acid suppressing treatment is not associated with higher risk for GI infection

Among patients with GI infections, there was a significantly lower number of patients in the mild AP group (n=95/313, 30.4%) compared to the number of mild cases in patients without an infection (n=434/789, 55%, p<0.001) (Figure 4D). We found significantly more moderate (Positive: n=103/313, 32.9% vs. Negative: n=191/789, 24.2%, p<0.001) and severe (Positive: n=115/313, 36.7% vs. Negative: n=164/789, 20.8%, p<0.001) cases in patients with positive SCT (Figure 4D). In patients with GI infection, the mortality rate was significantly higher compared to the rate in the group tested negative for GI infections (Positive: n=42/313, 13.4% vs. Negative: n=60/789, 7.6%, p=0.003) (Figure 4E). GI bleeding was significantly more frequent in patients with verified GI infection (GI bleeding and GI infection: n=54/302, 17.9% vs. GI bleeding without GI infection: n=81/770, 10.5%, p=0.001) (Table 2). There was no significant difference in the occurrence of GI infection between patients with or without ASD treatment (‘ASD’: n=285/986, 28.9% vs. ‘NoASD’: n=28/116, 24.1%, p=0.276) (Table 3).

Investigating the different factors that could have an effect on the above results we found that the age (OR=0.999, 95% CI=0.992-1.006, p=0.781) and the gender (OR=1.073, 95% CI=0.847-1.359, p=0.559) of patients, and whether they received ASDs or not (OR=1.447, 95% CI=0.969-2.161, p=0.071) did not have an impact on the chance of having

GI infection; however, patients with worse than mild AP severity had a 2.5 times higher odds for GI infections (OR=2.5, 95% CI=2.178-2.870, p<0.001).

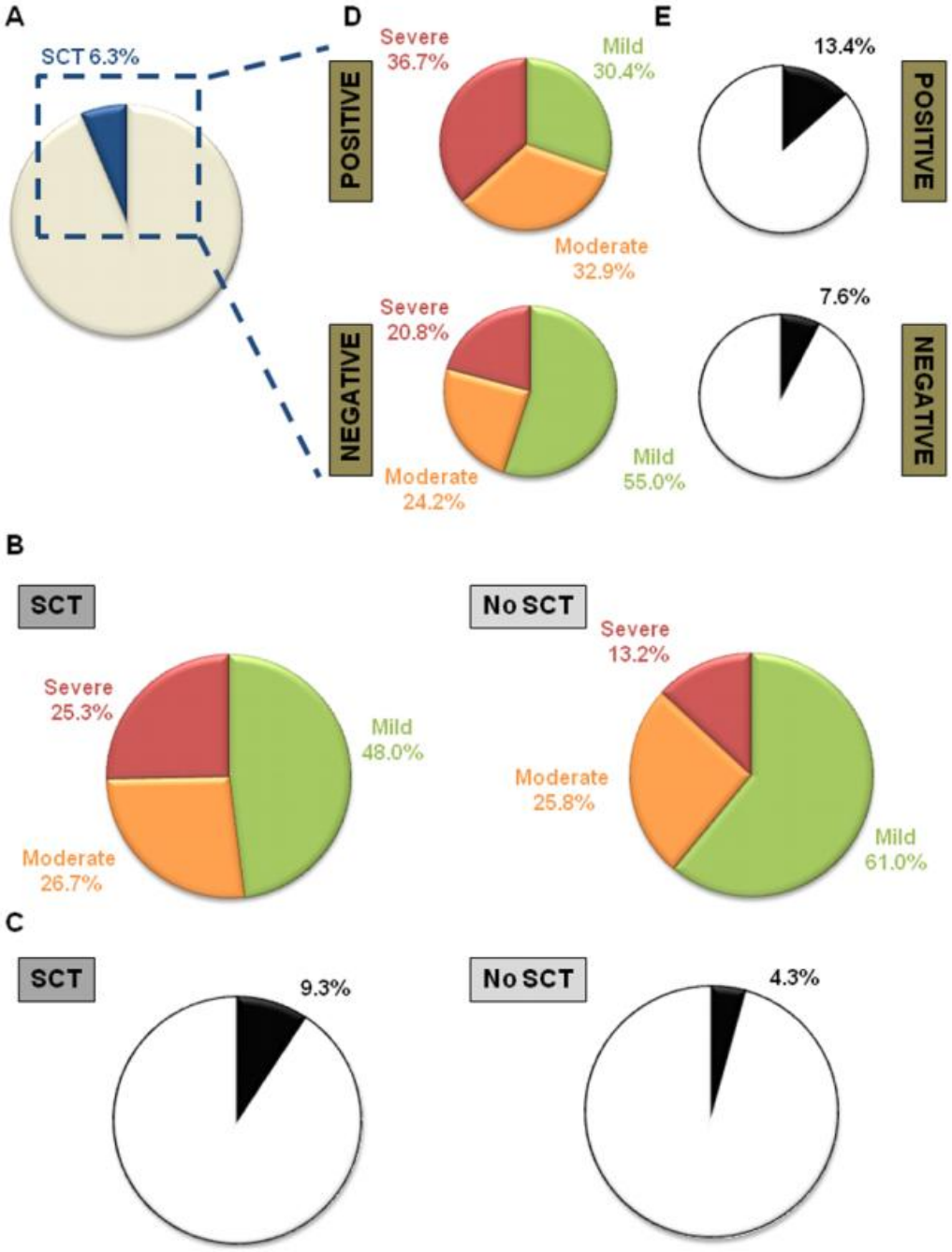


Figure 4. Disease severity and mortality rate in patients undergone stool culture testing (SCT). A) Percentage of patients who had SCT. **B-C)** Severity of acute pancreatitis and mortality rate in tested and not tested patients. **D-E)** Severity and mortality in patients with or without gastrointestinal infection.

A

			SEVERITY			GI BLEEDING	MORTALITY
Name of pathogen	Number	%	MILD	MODERATE	SEVERE	Yes	Yes
Clostridium difficile	210	60.5	60 (28.6%)	72 (34.3%)	78 (37.1%)	38 (18.1%)	25 (11.9%)
Klebsiella spp	35	10.1	13 (37.1%)	7 (20.0%)	15 (42.9%)	4 (11.4%)	5 (14.3%)
Pseudomonas aeruginosa	24	6.9	4 (16.7%)	9 (37.5%)	11 (45.8%)	6 (25.0%)	7 (29.2%)
Candida spp	18	5.2	8 (44.4%)	6 (33.3%)	4 (22.2%)	3 (16.7%)	0 (0.0%)
Escherichia coli	14	4.0	2 (14.3%)	6 (42.9%)	6 (42.9%)	3 (21.4%)	4 (28.6%)
Enterococcus faecium	10	2.9	2 (20.0%)	3 (30.0%)	5 (50.0%)	2 (20.0%)	1 (10.0%)
Enterobacter spp	5	1.4	0 (0.0%)	0 (0.0%)	5 (100.0%)	0 (0.0%)	1 (20.0%)
Helminthiasis	5	1.4	2 (40.0%)	3 (60.0%)	0 (0.0%)	1 (20.0%)	2 (40.0%)
Proteus spp	4	1.2	2 (50.0%)	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)
Acinetobacter spp	3	0.9	0 (0.0%)	0 (0.0%)	3 (100.0%)	0 (0.0%)	1 (33.3%)
Campylobacter spp	3	0.9	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)
Helicobacter pylori	3	0.9	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Salmonella spp	3	0.9	1 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Citrobacter freundi	2	0.6	0 (0.0%)	0 (0.0%)	2 (100.0%)	1 (50.0%)	1 (50.0%)
Morganella morganii	2	0.6	0 (0.0%)	0 (0.0%)	2 (100.0%)	1 (50.0%)	2 (100.0%)
Staphylococcus aureus	2	0.6	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	2 (100.0%)
Amoebiasis	1	0.3	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serratia marcenses	1	0.3	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Shigella	1	0.3	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Stenotrophomonas maltophilia	1	0.3	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)	0 (0.0%)
	347	100					

B

			SEVERITY			MORTALITY
Number of pathogens	Number	%	MILD	MODERATE	SEVERE	Yes
1	286	91.4	93 (32.5%)	95 (33.2%)	98 (34.3%)	35 (12.3%)
2	21	6.7	1 (4.8%)	7 (33.3%)	13 (61.9%)	5 (22.7%)
3	5	1.6	1 (20.0%)	1 (20.0%)	3 (60.0%)	1 (20.0%)
4	1	0.3	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
	313	100				42

Table 1. Detailed stool culture test results. A) Table of the different pathogens with patient number and percentage, severity, gastrointestinal (GI) bleeding and mortality. **B)** Patient number and percentage, severity and mortality in case of one or more GI pathogens.

	No bleeding		GI bleeding	
	n	%	n	%
NEGATIVE SCT	689	89.5	81	10.5
POSITIVE SCT	248	82.1	54	17.9

Table 2. Gastrointestinal (GI) infection in patients with or without GI bleeding. Results of stool culture testing (SCT) in patients with or without GI bleeding with patient number (n) and percentage.

	No ASD		ASD	
	n	%	n	%
NEGATIVE SCT	88	75.9	701	71.1
POSITIVE SCT	28	**24.1**	285	**28.9**

Table 3. Gastrointestinal infection in patients with or without acid suppressing drug (ASD) treatment. Result of stool culture testing (SCT) in patients with or without ASD therapy with patient number (n) and percentage.

V.2.) Systematic review and meta-analysis

V.2.1.) Study selection

236 articles were identified in the preliminary search. 192 studies were excluded (Figure 5). 76 publications (25 full texts, 10 abstracts and 41 articles from previous meta-analyses) were assessed for eligibility and qualitative synthesis. 47 of them were excluded due to insufficient data on study groups and another two for statistical reasons (the event rate was zero). A total of 27 studies (32-40, 51-68) were selected for quantitative analyses. The researchers and committee involved in the selection were in total agreement on all the inclusions and exclusions.

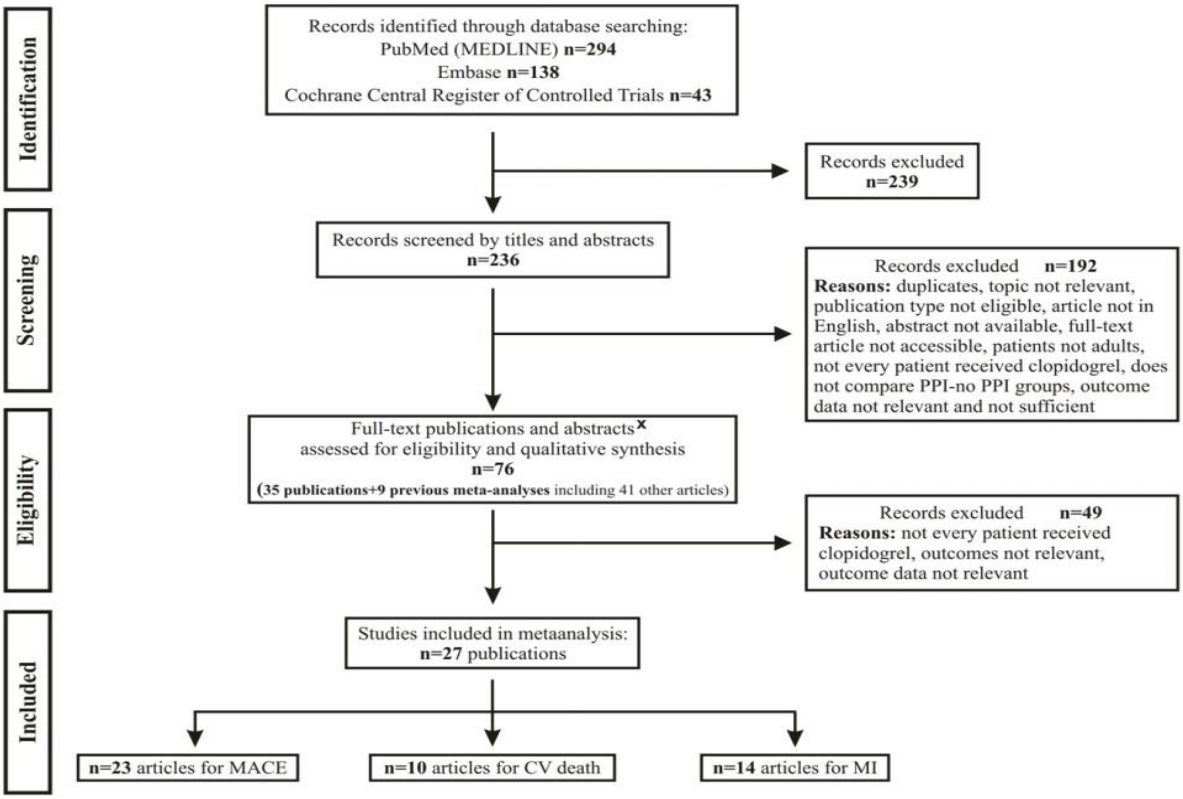


Figure 5. Flowchart for study selection and inclusion.
(CV: cardiovascular; MACE: major adverse cardiac event; MI: myocardial infarction; PPI: proton pump inhibitor; x: full articles were not available by any suitable sources)

V.2.2.) Study characteristics

Altogether, we found data for MACE in 23 publications (31, 33-38, 40, 51, 53, 55-63, 65-68), for CV death in 10 (32-33, 35, 40, 58-60, 63, 65-66, 68), and for MI in 14 (32-33, 36, 38, 40, 52, 54, 58-60, 64-66, 68).

Seventeen of them were observational studies, 16 were cohorts (32, 34-35, 37-38, 52-54, 57-59, 63-67), and one was a case-control study (36). Data from ten RCTs (31, 33, 40, 51, 55-56, 60-62, 68) were also collected. As post-hoc analyses of RCTs, in four studies (31, 40,

60, 68) the populations and outcome of our interest (clopidogrel plus PPI versus clopidogrel plus non-PPI treatment) were not randomized, therefore, their data were included in the statistical analyses of observational studies. The method and the study selection are shown in Figure 5. All the studies included were published between 2009 and 2016. The characteristics of the studies involved in the meta-analysis are summarized in Table 4A–E.

The number of patients involved was 156,823. A total of 63,756 received PPI plus clopidogrel treatment (ranging from 18 to 6,843), and 99,910 (ranging from 20 to 17,949) were in the clopidogrel alone group. Risk of MACE was determined from data from 127,695 patients, MI risk was assessed on the basis of data from 82,330 patients, and risk of CV death was evaluated based on data from 53,905 patients. The PPIs used in the studies were esomeprazole, omeprazole, pantoprazole, rabeprazole and lansoprazole, but in this meta-analysis as a subgroup analysis we only drew conclusions on the results for omeprazole, esomeprazole and pantoprazole due to the low number of studies separating data for different PPIs.

Reference, year	Study type	Number of patients	PPI (generic name)	PPI (number of patients)	Event number: MACE (PPI group)	Event number: CV death (PPI group)	Event number: MI (PPI group)
Ng et al, 2012	RCT	311	Esomeprazole	163	7		
Yano et al, 2012	RCT	130	Omeprazole	65	8		
Hsu et al, 2011	RCT	42	Esomeprazole	21	4		
Ren et al, 2011	RCT	172	Omeprazole	86	22		
Bhatt et al, 2010	RCT	3761	Omeprazole	1876	55	5	14
Cai et al, 2010	RCT	60	Omeprazole Pantoprazole	40	10		
Gargiulo et al, 2016	RCT (post-hoc analysis)	1970	Pantoprazole Lansoprazole Omeprazole, esomeprazole, rabeprazole	738 56 671 11	85	29	41
Burkard et al, 2012	RCT (post-hoc analysis)	801	Esomeprazole Pantoprazole Omeprazole	109 55 27 19	33	10	25
Goodman et al, 2012	RCT (post-hoc analysis)	9276	Omeprazole Pantoprazole Esomeprazole Lansoprazole Rabeprazole	3255 1592 973 387 251 51	398	180	245
O'Donoghue et al, 2009	RCT (post-hoc analysis)	13608	Omeprazole Pantoprazole Lansoprazole Esomeprazole	4529 1675 1844 441 613	255		
Ayub et al, 2016	Observational cohort	740	Omeprazole Esomeprazole Pantoprazole	332 40 81	30 6 10		
Weisz et al, 2015	Observational cohort	8581	NS	2162	238	58	100
Hokimoto et al, 2014	Observational cohort	174	Rabeprazole	50	5		
Shih et al, 2014	Observational cohort	2703	NS	1351			12

Reference, year	Study type	Number of patients	PPI (generic name)	PPI (number of patients)	Event number: MACE (PPI group)	Event number: CV death (PPI group)	Event number: MI (PPI group)
Zou et al, 2014	Observational cohort	7653	 Omeprazole Pantoprazole Esomeprazole	6188 5587 407 194	860	223	132
Chitose et al, 2012	Observational cohort	630	NS	187	7	4	1
Rossini et al, 2011	Observational cohort	1328	 Lansoprazole Pantoprazole Omeprazole	1158 853 178 125	87		
Simon et al, 2011	Observational cohort	2353	 Omeprazole Esomeprazole Pantoprazole Lansoprazole	1453 993 311 99 46	 43 20 12 1	94	24
Charlot et al, 2010	Observational cohort	24702	NS	6753	1058		
Evanchan et al, 2010	Observational cohort	5794	 Esomeprazole Lansoprazole Omeprazole Pantoprazole	1369 749 36 163 693			356
Gupta et al, 2010	Observational cohort	315	 Rabeprazole, omeprazole, lansoprazole	72	40	14	
Hudzik et al, 2010	Observational case-control	38	Omeprazole	18	10		6
Kreutz et al, 2010	Observational cohort	16690	 Omeprazole Pantoprazole Lansoprazole Esomeprazole	6828 2307 1653 785 3257	1710		
Ray et al, 2010	Observational cohort	16221	 Omeprazole Pantoprazole Lansoprazole, rabeprazole, esomeprazole	7226 683 4708	461		
Stockl et al, 2010	Observational cohort	2066	 Pantoprazole Rabeprazole Omeprazole Lansoprazole Esomeprazole	1033 659 159 86 83 46			133
Van Boxel et al, 2010	Observational cohort	18139	 Omeprazole Pantoprazole Esomeprazole Rabeprazole Lansoprazole	5734 1826 2618 1092 133	754		84
Rassen et al, 2009	Observational cohort	18565	 Omeprazole, rabeprazole, esomeprazole, lansoprazole, pantoprazole	3996		61	238

Table 4A. Study characteristics

(CV: cardiovascular; MACE: major adverse cardiac event; MI: myocardial infarction; NS: not shown/not specified; PPI: proton pump inhibitor; RCT: randomized controlled trial.)

Study	Country/region	Mean follow-up	Non PPI Male (n)	PPI Male (n)	Non PPI Mean age (years)	PPI Mean age (years)	Non PPI Mean BMI (kg/m^2)	PPI Mean BMI (kg/m^2)
Ayub et al, 2016	South Asia	24 months	216	331	56,2	57,8	26,5	26,3
Gargiulo et al, 2016	Italy	24 months	976	535	68,1	71,2	26,9	26,2
Weisz et al, 2015	USA, Germany	24 months	4834	1522	63,3	64,6	29,5	29,4
Hokimoto et al, 2014	Japan	18 months	89	28	68,8	69,7	24,3	23,3
Shih et al, 2014	Taiwan	4 months	64675	64675	49,3	49,3		
Zou et al, 2014	China	12 months	1083	4548	65,7	66,2	25,2	25,1
Burkard et al, 2012	Switzerland	36 months	75	553	63,3	66,5		
Chitose et al, 2012	Japan	18 months	326	139	69,6	69,7	24	24,2
Goodman et al, 2012	Europe, Middle East, Africa, Asia, Australia, North America, Central America, South America	12 months	8585	4734	62	63		
Ng et al, 2012	Hong Kong	4 months	107	126	63,1	64,3		
Yano et al, 2012	Japan	12 months	52	50	66	67		
Hsu et al, 2011	Taiwan	6 months	59	65	73,3	70,6		
Ren et al, 2011	China	1 month						
Rossini et al, 2011	NS	12 months						
Simon et al, 2011	France	12 months	644	1058	65	64	27,5	27,1
Bhatt et al, 2010	15 countries (NS)	3.5 months	1308	1255	68,7	68,5	28,3	28,4
Cai et al, 2010	NS	1 month						
Charlot et al, 2010	Denmark	At least 30 days	12801	1775	64,1	67,5		
Evanchan et al, 2010	NS	12 months			62,9	63,5		
Gupta et al, 2010	USA	50 months			62	61,7		
Hudzik et al, 2010	Poland	12 months	13	15	60,5	62,8	27,5	27,1
Kreutz et al, 2010	USA	NS						
Ray et al, 2010	USA	At least 12 months	4776	3295	60,4	60,8		
Stockl et al, 2010	USA	12 months	573	588	68,9	69,2		
Van Boxel et al, 2010	Netherlands	At least 12 months	8296	3356	66,1	68,6		
O'Donoghue et al, 2009	NS	NS	58	19	64,1	63,1	29	30,6
Rassen et al, 2009	USA	6 months	7523	1208	76,8	77,6		

Table 4B. Baseline characteristics: population

(BMI: body mass index; n: number of patients; NS: not specified; PPI: proton pump inhibitor)

Study	Non PPI ACE-I/ARB (n)	PPI ACE-I/ARB (n)	Non PPI Statin (n)	PPI Statin (n)
Gargiulo et al, 2016			1093	671
Hokimoto et al, 2014	100	36	118	47
Shih et al, 2014	15412	15413	7241	7242
Zou et al, 2014	627	2364	1373	5724
Chitose et al, 2012	148	318	317	124
Simon et al, 2011	156	184	220	281
Bhatt et al, 2010			1254	1274
Charlot et al, 2010	9129	3708	16002	5684
Evanchan et al, 2010	2884	960	3322	1060
Gupta et al, 2010	110	39	159	49
Hudzik et al, 2010	15	17	18	16
Van Boxel et al, 2010	7686	3798	10578	4886
O'Donoghue et al, 2009			65	24
Rassen et al, 2009	5807	1686	6275	1639

Table 4C. Baseline characteristics: other medications
(ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; n: number of patients; PPI: proton pump inhibitor)

Study	Non PPI PCI (n)	PPI PCI (n)	Non PPI MI (n)	PPI MI (n)	Non PPI Stroke (n)	PPI Stroke (n)
Gargiulo et al, 2016	229	119	321	199		
Weisz et al, 2015	2651	1025	1547	618		
Hokimoto et al, 2014			35	9	22	5
Shih et al, 2014					15610	15609
Zou et al, 2014			290	1071		
Burkard et al, 2012	115	15	24	193		
Chitose et al, 2012			100	55	45	29
Yano et al, 2012	1,3	5	0	4		
Hsu et al, 2011			54	59	27	33
Simon et al, 2011	93	96	125	141	35	41
Bhatt et al, 2010	1334	1331	566	531	136	151
Hudzik et al, 2010			14	13		
Ray et al, 2010					1700	1503
Stockl et al, 2010	827	825	546	554	8	4
Van Boxel et al, 2010			4163	2001	370	203
O'Donoghue et al, 2009			17	11		
Rassen et al, 2009			954	223		

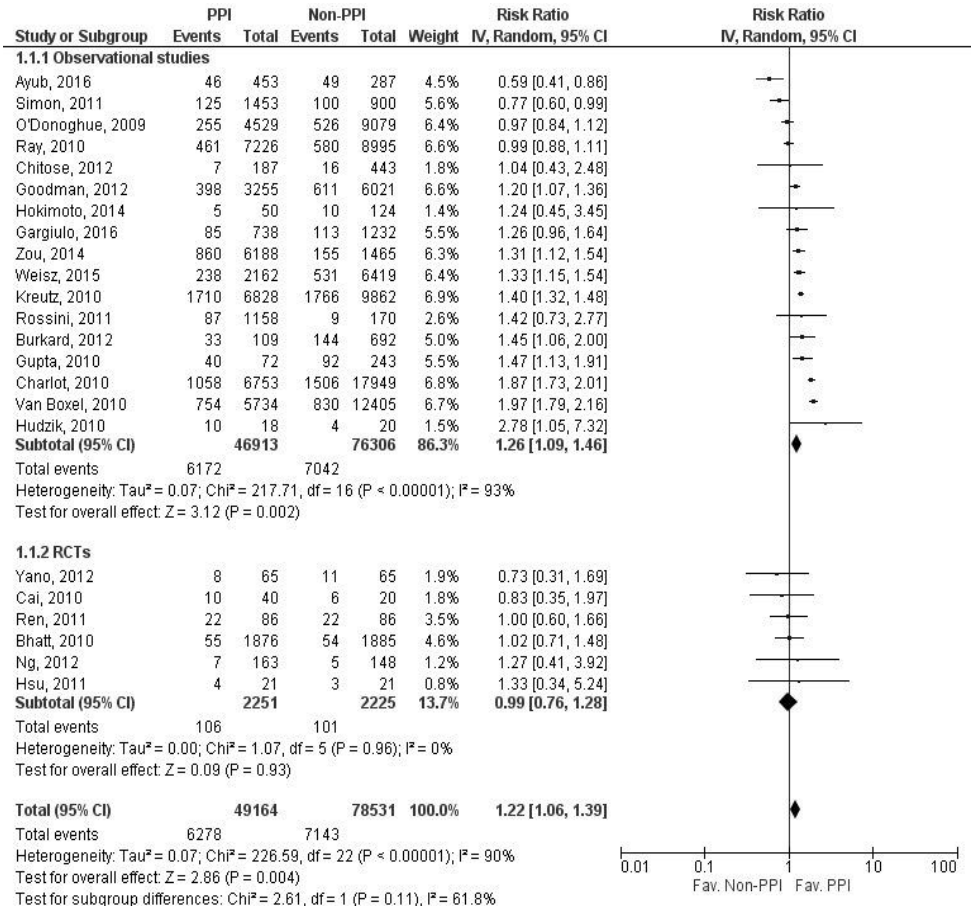
Table 4D. Baseline characteristics: cardio- and cerebrovascular history
(MI: myocardial infarction; PCI: percutaneous coronary intervention; n: number of patients; PPI: proton pump inhibitor)

	Non PPI	PPI	Non PPI	PPI	Non PPI	PPI	Non PPI	PPI
Study	**Hypertension (n)**	**Hypertension (n)**	**DM (n)**	**DM (n)**	**Dyslipidaemia (n)**	**Dyslipidaemia (n)**	**Smoking (n)**	**Smoking (n)**
Ayub et al, 2016	162	294	106	177	131	176		
Gargiulo et al, 2016	879	535	305	172	681	397	301	167
Weisz et al, 2015	5039	1790	2080	703	4731	1645	1464	480
Hokimoto et al, 2014	97	36	57	18	85	32	20	9
Shih et al, 2014	43420	43420	27229	27230	38105	38105		
Zou et al, 2014	1031	4412	346	1597	913	1597	454	1993
Burkard et al, 2012	450	79	119	32	80	525	206	27
Chitose et al, 2012	349	144	151	64	257	110	113	48
Ng et al, 2012							28	32
Yano et al, 2012	44	44	10	19	40	39	37	40
Hsu et al, 2011	57	56	23	35			5	10
Simon et al, 2011	481	749	314	433	431	614	301	512
Bhatt et al, 2010	1497	1526	593	536	1478	1446	234	265
Evanchan et al, 2010	2835	837	1601	630	2734	850		
Gupta et al, 2010	166	55	73	26	146	48	81	18
Hudzik et al, 2010	14	13	6	8	15	13		
Stockl et al, 2010	5	10	3	6				
O'Donoghue et al, 2009	55	22	18	11	61	25	7	9
Rassen et al, 2009	9577	2894	4619	1389				

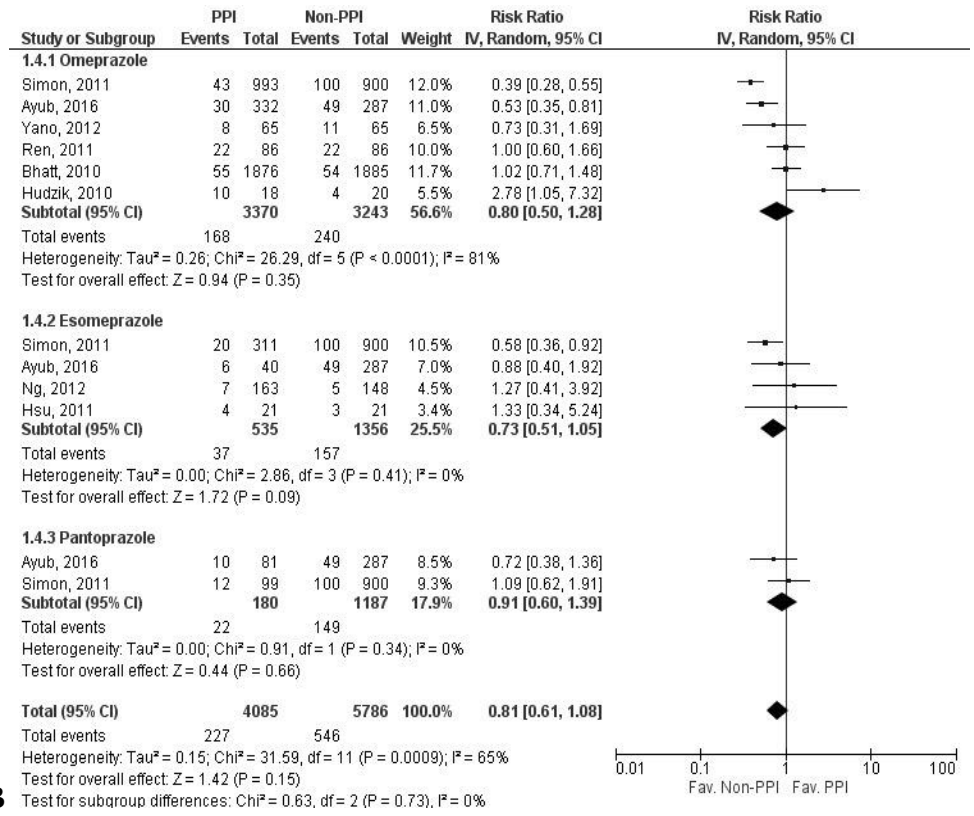
Table 4E. Baseline characteristics: cardiovascular risk factors
(DM: diabetes mellitus; n: number of patients; PPI: proton pump inhibitor)

V.2.3.) Major adverse cardiac event

Twenty-three studies (31, 33-38, 40, 51, 53, 55-63, 65-68) reported the incidence of MACE. Our results showed that the risk of MACE is significantly higher in the PPI group (RR=1.22, 95% CI=1.06–1.39, p=0.004), with considerable heterogeneity across the studies included (I^2=90%, p<0.001). However, separating the data for the RCT studies from that of the non-RCT studies revealed that a significant association of adverse outcomes (MACE) can only be seen in non-randomized studies (observational studies: RR=1.26, 95% CI=1.09–1.46, p=0.002, I^2=93%, p<0.001; RCTs: RR=0.99, 95% CI=0.76–1.28; I^2=0%, p=0.93), although the heterogeneity remained considerable in the observational group, which might not be relevant in the RCT group (Figure 6A). As the result of meta-regression analyses, MACE was not depending on the length of follow up (SE=0.007, 95% CI=-0.014–0.014, p=0.97), based on the results of 18 studies (33-38, 40, 55, 58-63, 65-68), and the age of the patients did not influence the occurrence of the outcome either (SE=0.023, 95% CI=-0.011-0.081, p=0.14), based on the data found in 19 studies (31, 33-38, 40, 55, 58-63, 65-68).



A



B

Figure 6. Forrest plots representing the estimated risk of overall major adverse cardiac events (A) and in case of taking specific proton pump inhibitors (B).

(CI: confidence interval; PPI: proton pump inhibitor; RCT: randomized controlled trials)

In case of patients on omeprazole among the 6 publications included (33, 36, 56, 58, 62, 67), there was no significant difference between the clopidogrel plus PPI and clopidogrel alone groups (RR=0.80, 95% CI=0.50–1.28, p=0.35), but since there was evidence of considerable heterogeneity (I^2=81%, p<0.001), the random effect model was used for comparison (Figure 6B). In the case of esomeprazole (4 publications (55, 58, 61, 67)), results showed no significant difference in the occurrence of MACE between the groups (RR=0.73, 95% CI=0.51–1.05, p=0.09) (Figure 6B). The heterogeneity might not be important (I^2=0%, p=0.41); the fixed effects model was used for comparison. In the pantoprazole group, we only found two eligible publications (58, 67) for MACE, and there was no difference between the two groups (RR=0.91, 95% CI=0.60–1.39, p=0.66) (Figure 6B). The heterogeneity might not be important (I^2=0%, p=0.34); the fixed effects model was used in analyzing of this specific PPI.

Six studies reported adjusted HRs for overall MACE outcome (37-38, 60, 65-66, 68). The results showed that the risk of MACE was significantly higher in the clopidogrel plus PPI group (HR=1.25, 95% CI=1.03–1.51, p=0.02). We have found considerable heterogeneity across the included studies (I^2=88%, p<0.001); the random effects model was used. In the case of specific PPIs, four studies (31, 34, 37, 53) presented data on adjusted HRs for omeprazole, esomeprazole and pantoprazole. The results showed that there is no difference between the clopidogrel alone and clopidogrel plus PPI groups in case of esomeprazole (HR=1.17, 95% CI=0.90–1.53, p=0.25), omeprazole (HR=1.12, 95% CI=0.86–1.45, p=0.41), and pantoprazole (HR=1.25, 95% CI=0.99–1.57, p=0.06). In the specified PPI groups, we also found considerable heterogeneity (esomeprazole: 84%, p<0.001; omeprazole: 82%, p=0.001; pantoprazole: 85%, p<0.001), the random effects model was used for the analysis.

V.2.4.) Cardiovascular death

Data on CV death was reported in ten studies (32-33, 35, 40, 58-60, 63, 65-66, 68), including 53,905 patients; only one study's data was evaluated as RCT (33). There was no significant effect of concomitant clopidogrel and PPI treatment on CV death (RR=1.21, 95% CI=0.97–1.50, p=0.09). The result from the statistical analysis may represent substantial heterogeneity across the studies (I^2=67%, p=0.001). The length of follow up and the age of the patients did not affect the risk for CV death based on results of the included ten studies (follow up: SE=0.009, 95% CI=-0.016–0.021, p=0.81; age: SE=0.022; 95% CI=-0.009–0.079, p=0.12). Unfortunately, the low amount of data prevented us from evaluating the risk of CV death in specific PPIs (Figure 7).

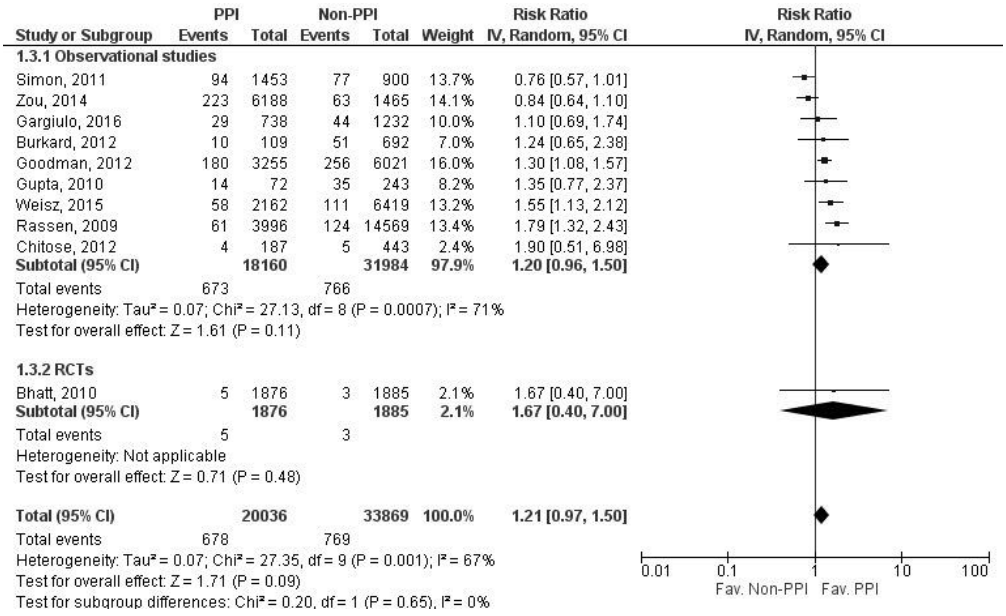


Figure 7. Forrest plot representing the estimated risk of cardiovascular death.
(CI: confidence interval; PPI: proton pump inhibitor; RCT: randomized controlled trials)

Two studies contained eligible data for adjusted analyses on CV death (60, 68), and according to their results, there was no significant effect of concomitant clopidogrel and PPI treatment on CV death (HR=1.16, 95% CI=0.72–1.87, p=0.53). The heterogeneity may represent substantial heterogeneity (70%, p=0.07); therefore, the random effects model was used.

V.2.5.) Myocardial infarction

Fourteen of the twenty-seven studies contained eligible data on MI, with data for 82,330 patients for evaluation (32-33, 36, 38, 40, 52, 54, 58-60, 64-66, 68); one study's data was evaluated as RCT (33). The risk of MI was significantly higher in the PPI group (RR=1.43, 95% CI=1.24–1.66, p<0.001). The results from the statistical analysis may represent substantial heterogeneity across the studies (I^2=66%, p<0.001) (Figure 8A). Similarly to MACE and CV death, MI was not depending on the length of follow up or on the patients' age based on the included fourteen studies (follow up: SE=0.005, 95% CI=-0.005–0.013, p=0.41; age: SE=0.013, 95% CI=-0.045–0.007, p=0.15). We only found two eligible articles (Bhatt 2010, Hudzik 2010) for MI in the case of omeprazole, where there was no difference in risk between the observed groups (RR=1.98, 95% CI=0.31–12.76, p=0.47). There may be substantial heterogeneity across the studies (I^2=69%, p=0.07); the random effects model was used (Figure 8B).

Data on adjusted HRs was reported in six studies in case of MI (38, 54, 60, 64-65, 68), and the risk for MI was significantly higher in the PPI plus clopidgorel group (HR=1.46, 95%

CI=1.08–1.96, p=0.01). The heterogeneity may represent moderate heterogeneity (60%, p=0.03), the random effects model was used.

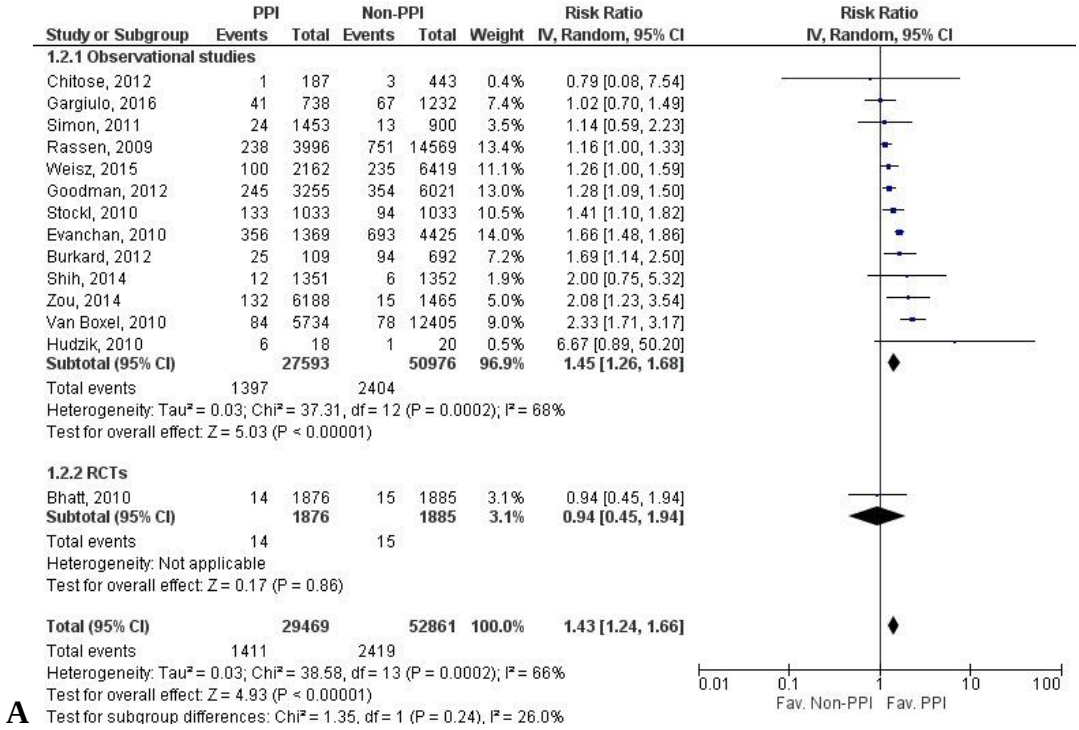


Figure 8. Forrest plots representing the estimated risk of overall myocardial infarction (A) and in case of applying omeprazole as proton pump inhibitor (B).
(CI: confidence interval; PPI: proton pump inhibitor; RCT: randomized controlled trials.)

V.2.6.) Risk of bias within studies

Risk of bias was assessed in seventeen non-RCT studies (32, 34-38, 52-54, 57-59, 63-67), four post-hoc analyses of RCTs (31, 40, 60, 68), and in six RCTs (33, 51, 55-56, 61-62). The risk of bias within the twenty-seven studies included in this meta-analysis is summarized in Figures 9–10.

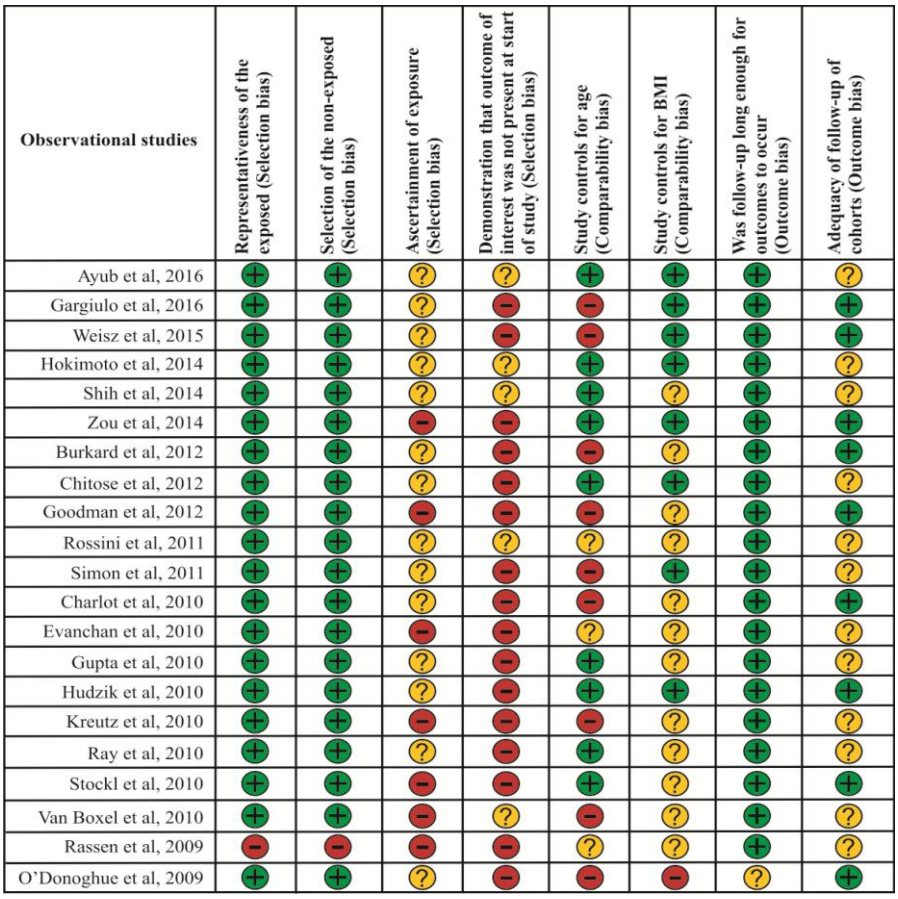


Figure 9. Modified Newcastle–Ottawa scale for risk of bias assessment of observational studies.
(Green: low risk of bias; yellow: uncertain risk of bias; red: high risk of bias; BMI: body mass index)

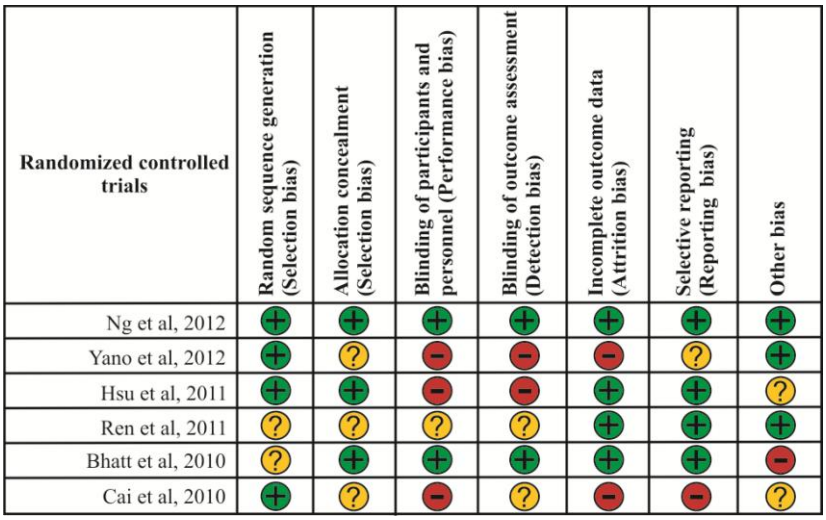


Figure 10. Quality assessment of randomized controlled trials.
(Green: low risk of bias; yellow: uncertain risk of bias; red: high risk of bias; BMI: body mass index)

V.2.7.) Publication bias

Funnel plots were constructed for each outcome and showed symmetry on visual inspection, suggesting that publication bias was not large and was unlikely to alter conclusions (Figure 11A–C).

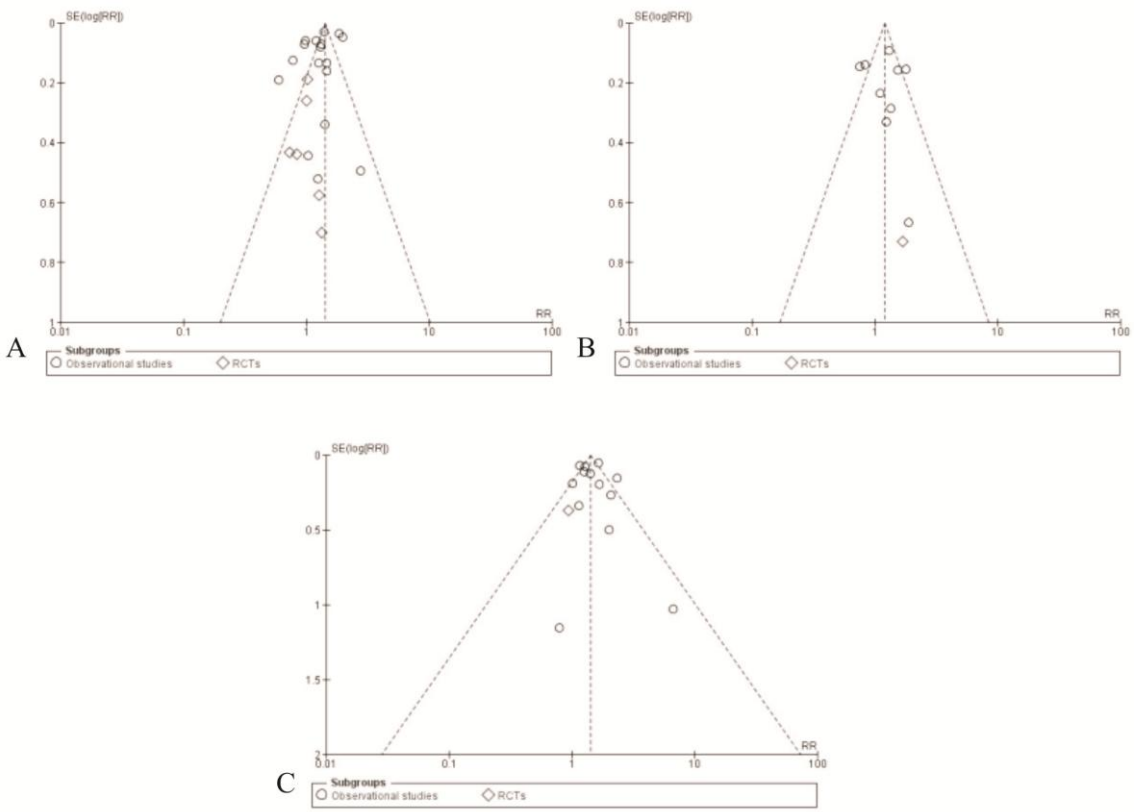


Figure 11. Funnel plots for studies in major adverse cardiac event (A), in cardiovascular death (B) and in myocardial infarction (C) groups.

VI. DISCUSSION

VI.1.) Effects of acid suppressing drugs in acute pancreatitis therapy

The ASDs are widely used in the clinical practice, not solely for the diseases of the gastrointestinal tract, but in other conditions, such as cardiovascular diseases. Especially PPIs are among the most frequently prescribed drugs with increasing use every year. Even though there are well established indications for a wide array of diseases when and how to conduct treatment with ASDs, several studies were published regarding their overprescription, and difficulties to discontinue their application. Data from the cohort analysis supports the worldwide overuse of ASDs, specifically in patients with AP. The number of patients on ASD treatment has increased by 3.7-fold during hospitalization with almost all of the patients receiving some kind of ASD, and more than 50% remained on an ASD after discharge, a more than 2-fold increase relative to the number at admission. These numbers are in accordance with literature data whereas patients after receiving ASDs during hospitalization get usually discharged with them (69). Moreover, ASD treatment in AP was associated with more severe pancreatitis and higher mortality rate in the cohort.

There are contradictory results in the literature about the safety of ASD use in AP. In a Korean RCT, the investigators separated AP patients into two groups, one receiving pantoprazole intravenously during fasting and later orally, and another without PPI treatment. In this study, treatment with pantoprazole did not influence the clinical course of AP (14). In another RCT from China, severe AP patients receiving conventional therapy were compared to patients on conventional therapy with esomeprazole treatment, and PPI therapy did not show benefit on alleviating systemic inflammatory response and improving clinical scores in severe AP patients, and did not prevent the development of peptic ulcer and GI hemorrhage (15). Data from 10,400 severe AP patients were analyzed in a Japanese retrospective study, and even though the rates of upper GI bleeding and organ failure were significantly higher in patients with PPI therapy, after propensity analysis, data showed that PPIs did not have an effect on mortality (16). On the contrary, in a Swedish population-based case-control study, they observed association between current use of H2-RAs or PPIs and increased risk of AP, besides previous literature data where they reported ASDs to cause AP (17).

Systemic inflammatory response syndrome is often a complication of severe AP, which leads to high level of inflammatory markers (70) and organ dysfunctions. Patients with severe AP, especially those who require intensive care treatment or mechanical ventilation are prone to develop stress-related acute gastric mucosal lesions (13). Acute GI mucosal lesions

can range from simple gastritis and erosions to ulceration and bleeding (71), more than half of patients with AP may develop upper GI ulcers, and the occurrence shows positive correlation with the severity of pancreatitis (11, 72). Hypersecretion of gastric acid seems to play a major role at the pathogenesis of stress-related acute gastric mucosal lesions. Therefore, in these cases it can be indicated to use prophylaxis for peptic ulcer disease (11, 73). Based on our results, not only in case of severe, but also in moderate pancreatitis cases there were significantly more patients receiving ASD treatment which supports our previous data about their frequent usage.

Protection of upper GI mucosa could be a possible indication for ASD administration in AP patients, which could decrease the rate of GI bleeding. Since ERCP- and surgery-related vascular complications cannot be prevented with ASD treatment, these types of GI bleedings were not included in the analyses. In the studied population, 4.7% of patients suffered from GI bleeding. The occurrence of GI bleeding was associated with higher morbidity and mortality, which increases the length and cost of hospitalization. Investigating its association between ASD treatment, we found that bleeding occurred more frequently in patients on ASD therapy which correlates with literature data (15-16). Based on the study of Chen et al. (11) in which all the included patients received PPIs when a GI lesion was detected with endoscopy, 22% of severe pancreatitis patients had GI bleeding (11). Data on the time of bleeding and the start of ASD therapy was not collected. A possible explanation could be that when GI bleeding was recognized then ASD therapy was started, although, that still does not give an explanation why more than 80% of patients had to receive ASDs. Especially that more than 60% of patients had mild AP, and in that group only 2.1% of patients were suffering from GI bleeding. Therefore, these results suggest GI bleeding recognition is not the indication of starting ASD treatment in AP patients, and it also does not explain why more than 50% of patients had to receive ASDs upon discharge from the hospital.

ASDs are considered well tolerated and effective, and only rare and mild side effects have been reported in short-term use. However, nonessential long-term ASD treatment can lead to various side effects in spite of their reported good safety profile (2). Such as elevated prevalence of small intestinal bacterial overgrowth which results in malabsorption (74), increased risk for respiratory infections (75-76) and several GI cancers (gastric, colorectal, liver or pancreatic cancers) (3, 77-81). Other long-term side effects can be micronutrient deficiencies, kidney disease, osteoporosis and dementia. Long-term administration without proper re-evaluation and guidelines will lead to polypharmacy and potential drug-drug

interactions (77). Although several studies have shown association between adverse events and complications of long-term ASD use, they have led to contradictory results (1). Side effects are also including elevated risk for GI infections by repressing the gastric acid barrier and altering the microbiome. Notably, *Clostridium difficile* infection has shown strong association with ASD therapy (2, 75-77, 82-83). From the wide array of possible long-term complications, the relationship between acid suppressing therapy and occurrence of GI infections in AP patients was investigated. According to our results, ASD administration did not elevate the risk for GI infections. However, ordering of SCTs has been associated with more severe AP and higher mortality rate. Even though, there was relatively low number of testing among the included patients, almost 30% of them had GI infections. The most common pathogen was *Clostridium difficile* (60%) in accordance with literature data in other diseases. An important factor that has to be taken into consideration is the frequent usage of unnecessary antibiotic drugs in AP patients. and that the most frequently used antibiotics can be effective for the most common GI infections (84). In the studied patient population, GI infections have been associated with more severe AP, higher rate of GI bleeding and worse mortality. Therefore, length of hospitalization and the cost of treatment could be worse in patients with GI infections.

Based on the epidemiologic characteristics of our cohort and the numerous international centers who contributed data, our patient population substantiates a general representation of patients with AP (85-86). The cohort analysis has its limitations, since it is a retrospective data analysis; we cannot draw causative conclusions from the findings above, only associations can be determined between the investigated parameters.

VI.2.) Cardiovascular effects of PPI therapy in patients with clopidogrel

A possible interaction between clopidogrel and PPIs came to the fore after an observational study had been performed in 2006, which found clopidogrel activity on platelets was diminished in patients receiving PPI treatment (87). Later, this potential interaction was tested in the randomized controlled OCLA (Omeprazole CLopidogrel Aspirin) study, where omeprazole significantly decreased the effect of clopidogrel on *in vitro* platelet activation (26).

Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation through irreversible inhibition of the ADP/P2Y12 receptor on the surface of platelets, and, being a prodrug, it requires a two-step oxidative biotransformation intrahepatically, mediated mainly by cytochrome P450 isoenzymes. First, the cytochrome P450 isoenzymes CYP1A2, CYP2B6

and CYP2C19 form 2-oxo-clopidogrel, which is then oxidized by CYP2B6, CYP2C19, CYP2C9 and CYP3A4 to the active metabolite of clopidogrel, with CYP2C19 being the most important isoenzyme. The active metabolite then binds irreversibly to platelet adenosine diphosphate receptor P2Y12 (23, 88-89), therefore preventing platelet aggregation. This is associated with the dephosphorylation of the intraplatelet vasodilator-stimulated phosphoprotein. Vasodilator-stimulated phosphoprotein phosphorylation provides an index to evaluate platelet reactivity to clopidogrel (90). The findings on mechanisms underlying clopidogrel resistance are contradictory; these mechanisms may relate to heterogeneity in clopidogrel metabolism. CYP2C19 activity can have a profound effect on the conversion of clopidogrel to its active metabolite (88).

All PPIs are extensively metabolized to inactive metabolites mainly via CYP2C19 and CYP3A4 in the liver. Rabeprazole uses these enzymes the least being mostly converted to its thioether analogue non-enzymatically. The potency and specificity of five individual PPIs (omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole) with regard to their inhibitory effects on the activities of four major human CYP enzymes (CYP2C9, CYP2C19, CYP2D6 and CYP3A4) have been studied by Li et al (91). Lansoprazole was the most potent inhibitor of CYP2C19 enzyme in vitro, followed by omeprazole and esomeprazole. Pantoprazole showed the lowest potential to CYP2C19, however it was at least twice as potent an inhibitor as other PPIs towards CYP2C9 and CYP3A4. As the metabolite of rabeprazole, rabeprazole thioether was a strong and competitive inhibitor of CYP2C9, CYP2C19 and CYP2D6. It has been suggested that rabeprazole has significantly less drug-drug interactions than other PPIs, and the main reason is claimed to be its non-enzyme catalyzed degradation, but the results of Li et al suggest that omeprazole and rabeprazole have similar affinity to CYP3A4 (91-92). The potential interaction mechanism lies in the fact that both clopidogrel and PPIs, in varying degrees, are metabolized by the same cytochrome P450 enzyme (CYP2C19). PPIs have the potential to competitively inhibit the metabolism of clopidogrel to its active metabolite, which leads to reduced circulating concentrations of the active compound (23).

The data on the interactions between clopidogrel and PPIs remain unclear despite the numerous *in vitro* and *in vivo* studies on the subject. The *in vitro* studies have shown that the effectiveness of clopidogrel decreases with simultaneous use of clopidogrel and PPIs (26), and therefore, the risk for CV events will be elevated. Several possible causative factors may lie behind this phenomenon. One of them is the connected bio-transformational route of clopidogrel and PPIs, or the possible differences in genetic polymorphism of these enzymes

(88). There are several studies, mostly observational ones, whose findings are consistent with these *in vitro* results, showing an elevated risk for CV side-effects in patients on combined clopidogrel and PPI treatment (27-30). However, it should be noted that prophylactic PPIs are more likely prescribed to patients with a higher risk for CV events (23).

There is considerable disagreement between the various clinical studies that show no increased risk of CV outcomes (31-33, 37, 39). Furthermore, a few studies found no difference in the possible disadvantageous effect of PPI drugs causing extended inhibition of CYP2C19 (31, 39). In several cases, the authors used multivariable adjustments for covariates to standardize because the effect of possible factors (such as age, co-morbidities and co-medication) could modify the outcomes (32, 44). In a well-designed case-control study, a current PPI plus clopidogrel group result was compared to the results for patients on current clopidogrel plus past PPI therapy. The association between PPI therapy and the recurrence of MI has disappeared suggesting that the appearance of recurrent MI is a result of a residual confounding (44).

Based on the ACCF/ACG/AHA 2010 Expert Consensus Document (25) to reduce the risk of GI bleeding, PPIs are recommended among patients with history of upper GI bleeding or with multiple risk factors (e.g. advanced age, concomitant use of warfarin, steroid or NSAIDs, or *H. pylori* infection) for GI bleeding who require antiplatelet therapy. Patients with acute coronary syndrome and prior upper GI bleeding are at substantial CV risk, so dual antiplatelet therapy with concomitant use of a PPI may provide the optimal balance of risk and benefit. The risk reduction achieved by concomitant PPIs might outweigh any potential reduction in the CV efficacy of antiplatelet treatment because of a drug–drug interaction. Routine use of ASDs is not recommended for patients at lower risk of upper GI bleeding, who have much less potential to benefit from prophylactic therapy. Clinical decisions regarding concomitant use of PPIs and thienopyridines must be based on whether the potential for benefit outweighs the potential for harm, considering both CV and GI complications. Furthermore, according to the European Cardiology Society's 2017 guideline (93) for the management of acute MI in patients presenting with ST-segment elevation a PPI in combination with dual antiplatelet therapy is recommended (I/B recommendation) in patients at high risk of GI bleeding. Based on the recent European Cardiology Society/European Association for Cardio-Thoracic Surgery guidelines (94) on myocardial revascularization every effort should be undertaken such as routine use of PPIs to avoid bleeding in patients after percutaneous coronary intervention requiring oral anticoagulation and dual antiplatelet therapy. These statements have been supported by several studies which showed that the risk

of upper GI bleeding can be reduced in patients with clopigodrel by concomitant PPI treatment. The occurrence of GI bleeding were 0.2%-1.2% (33), 0-2% (59), 0.4-1.8% (41) in the PPI versus non-PPI groups respectively.

In the meta-analysis, our aim was to focus on this discrepancy and to find a possible resolution. Our combined data from all of the studies involved showed that the presence of MACE and MI is significantly higher in the PPI plus clopidogrel patient population, a finding which is consistent with results from previous observational studies (29-30, 34-36, 38). However, in reducing the degree of heterogeneity by creating subgroups based on study design, we also found that this previously experienced risk elevation and heterogeneity will disappear as in other studies (43). This result is similar to those of previous meta-analyses, where a higher CV risk was found among observational studies without any difference between the clopidogrel plus PPI group and the no PPI group in RCTs (45). In previous meta-analyses by Mo et al. (41) and Chen et al. (95), data only collected from RCTs showed no correlation between simultaneous clopidogrel and PPI therapy and elevated CV risk. An examination of the results, heterogeneity and risk of bias of the studies involved in our meta-analysis points to the low quality of observational studies, whose results are opposite to those of RCT studies, all proving an acceptance of results from RCT studies showing no enhancement of CV risks due to PPIs.

Although the meta-analysis has shown that there is no association between CV risk elevation and PPI usage, the analysis might have limitations. One is that in twenty-two of the included studies, the population had previously had CV diseases, had already undergone percutaneous coronary intervention, or had received dual antiplatelet therapy, meaning that the population under examination may have had severe conditions. In the meta-analysis, we did not analyze the effect of these or other co-morbidities nor evaluate their conditions, but it is possible that the harmful effect of PPIs may be different in patients who need primary or secondary CV prevention. Although we performed secondary analyses on adjusted events, the conclusions drawn from these analyses are limited, because of the insufficient availability of these values across all studies, which were all observational ones, and the applied covariates were different among them. The studies published and available in the databases provided poor descriptions of other risk factors (such as co-morbidities, co-medications, smoking, obesity etc.), preventing us from providing a summary or conclusion in that regard. The other limitation of our study is the substantial heterogeneity among the studies, which may stem from several factors, such as differences in study design. In observational studies or in post-analyses of RCTs, the groups were not allocated randomly. It was usually the physicians'

decision, so this most likely led to a distortion of the results. Therefore, risk of bias within studies should be highlighted, as well. Though the open-label design might have a less prominent effect on hard CV outcomes, lack of blinding should be mentioned, even in RCTs. In addition, incomplete follow-up and not carefully applied objective evaluation of ascertainment of drug exposures may impose additional risk of bias. Bias is inherent in observational studies, the subgroup analysis of RCTs and observational studies yielding discrepant results support this statement. And there is a problem with the definition of MACE, which is not standard in the literature, although it is most often used to express the CV risk of PPIs plus clopidogrel.

VII. CONCLUSIONS

Hereby, I represented two studies on the safety and efficiency of ASDs in two different disease entities; both works have studied ASDs as a primary or secondary prevention in the therapy of patients with AP and CV diseases.

One of my aims was to investigate the current place of ASDs in patients with AP and evaluate their safety and efficiency that we could present in a large AP population first in the literature. Data shows a worldwide unnecessary ASD use in AP patients, even though there is no substantial evidence that ASD treatment is beneficial for the therapy of AP. Thus, we presented their association with higher morbidity and mortality. The cohort analysis is among the firsts to report data on the rate of GI bleeding not related to surgery or ERCP in patients with AP. Based on our data, ASD administration during AP did not increase the risk for GI infections. Taking into consideration the advice from the American Gastroenterological Association, the benefits of ASDs outweigh their risks if appropriately prescribed, but when there is no indication, modest risks become important because there is no potential benefit (15). Therefore, the routine administration of ASDs is not recommended in patients with AP if there is no other indication for their administration. Long-term complications could be avoided by re-evaluating the current clinical practices, incorporate recommendations to current guidelines, and by giving detailed plans for patients and their general practitioners how to gradually reduce or leave the ASDs, and when to follow up on them.

My second aim was to investigate the potential risks of co-administration of clopidogrel and PPIs with a systematic review of the current literature and a meta-analysis. Our results have shown that there is no definitive evidence for any significant association between CV risk elevation and PPI in patients on clopidogrel treatment, based on RCTs. Thus, no definitive evidence exists for an effect on mortality. From this point of view, the previous FDA guidance to use favorable or non-favorable drug combinations does not seem to be relevant by now based on both previous trials and our own analyses. However, taking into account the bias, the meta-analysis should be interpreted with caution, and conducting further RCTs would be beneficial. Because PPI induced risk reduction clearly outweighs the possible adverse CV risk in patients with a high risk of GI bleeding, a combination of clopidogrel with PPI should be recommended.

NEW FINDINGS

VII.1.) Effects of acid suppressing drugs in acute pancreatitis therapy

1. We could show the extensive administration of ASD therapy during the course of AP with the majority of patients receiving acid suppressing treatment during hospitalization.
2. ASD administration was associated with more severe AP and higher mortality. Older age and worse than mild pancreatitis increased the chance of starting ASD treatment.
3. Our analysis has shown that low number of patients suffered from GI bleeding while having AP. GI bleeding was associated with more severe AP and higher mortality, and ASD therapy was associated with higher risk for GI bleeding. AP severity carried a 3 times higher probability, and GI infection carried a 2.8 times higher chance for GI bleeding.
4. ASDs during AP did not elevate the risk for GI infection, which was associated with more severe AP and higher mortality. The most common pathogen associated with ASD therapy was *Clostridium difficile*.
5. According to our data, the routine administration of ASDs is not recommended in patients with AP if there is no other indication for their administration.

VII.2.) Cardiovascular effects of PPI therapy in patients with clopidogrel

1. Based on the results of the meta-analysis, there is no definitive evidence for any significant association between CV risk elevation and PPI in patients on clopidogrel treatment.
2. No definitive evidence exists for an effect on mortality.
3. Heterogeneity and risk of bias of the involved studies points to the low quality of observational studies, whose results are opposite to those of RCT studies. All proving an acceptance of results from RCT studies showing no enhancement of CV risks due to PPIs.
4. Because PPI induced risk reduction clearly outweighs the possible adverse CV risk in patients with a high risk of GI bleeding, a combination of clopidogrel with PPI should be recommended for patients at risk.

VIII. ABBREVIATIONS

AP, acute pancreatitis

ASD, acid suppressing drug

CI, confidence interval

CV, cardiovascular

ERCP, endoscopic retrograde cholangio-pancreatography

GI, gastrointestinal

H2-RA, histamine-2-receptor antagonist

MACE, major adverse cardiac event

MI, myocardial infarction

OR, odds ratio

PPI, proton pump inhibitor

RCT, randomized controlled trial

RR, risk ratio/relative risk

SCT, stool culture test

SE, standard error

IX. ACKNOWLEDGEMENT

Hereby, I would like to express my deepest and sincere gratitude to my supervisors, **Dr. Imre László Szabó** and **Prof. Dr. Péter Hegyi** who guided me during my years as a PhD student with their valuable advice, encouragement and experience, without their help my scientific work and this thesis would not have been possible.

I wish to express my appreciation to my mentor in the United States, **Prof. Dr. Miklós Sahin-Tóth** who gave me a great opportunity to join his laboratory and majorly contributed to widen my basic scientific knowledge on pancreatitis. I would like to say thank you to **Dr. Andrea Geisz** who was guiding and teaching me during the recent years. She showed me a great example on how to carry out valuable scientific work as a young scientist, and she constantly supported me as a dear friend.

I could not perform my scientific work without the help of colleagues at the Hungarian Pancreatic Study Group (HPSG), and at the Institution of Translational Medicine (University of Pécs), especially without the guidance of **Dr. Andrea Szentesi** and **Dr. Nelli Farkas**. I am grateful for the help of **Dr. Andrea Párniczky** and **Dr. Dóra Mosztbacher** who guided my work on the clinical trials of pediatric pancreatitis.

I would like to acknowledge the help of **Dr. Csaba Bereczki** (Department of Pediatrics and Pediatric Health Center, University of Szeged), who facilitated my research activities during my years as a pediatric resident.

Finally, I would like to pay tribute to **my parents** and to **my sister** who always encouraged me, and made it possible for me to be where I am today. I am thankful for my close **friends** who supported me unconditionally during this period of my life.

X. FUNDING

X.1.) Cohort analysis

The cohort study was supported by project grants (K131996 to Péter Hegyi and FK131864 to Alexandra Mikó), by the János Bolyai Research Scholarship granted by the Hungarian Academy of Sciences (to Andrea Párniczky), by 'GINOP-2.3.2-15-2016-00048–STAY ALIVE' co-financed by the European Union (European Regional Development Fund) within the framework of the Széchenyi 2020 Programme, and by a Human Resources Development Operational Programme Grant, Grant Number: EFOP 3.6.2-16-2017-00006–LIVE LONGER, co-financed by the European Union (European Regional Development Fund) within the framework of the Széchenyi 2020 Programme.

X.2.) Systematic review and meta-analysis

The systematic review and meta-analysis was supported by an Economic Development and Innovation Operative Programme Grant (GINOP 2.3.2-15-2016-00048 to Péter Hegyi), an Institutional Developments for Enhancing Intelligent Specialization Grant (EFOP-3.6.1-16-2016-00022 to Péter Hegyi) of the National Research, Development and Innovation Office, and the ÚNKP-17-3-I. New National Excellence Program, Ministry of Human Capacities (PTE/46539/2017 to Katalin Márta).

XI. LIST OF PUBLICATIONS AND SCIENTIFIC METRICS

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IF: 3.629 (2019)**, Q1**

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IF: –

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IF: –

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IF: 2.806, Q1

SCIENTIFIC METRICS

Number of publication **related to the subject** of the thesis:	2 (2 first author)
Cumulative impact factor of publications related to the thesis:	6.83
Q1: 1, Q2: 1, Q3: -, Q4: -	
Number of **total accepted/published** articles:	9 (4 first author)
Cumulative impact factor of published articles:	24.267
Q1: 6, Q2: 1, Q3: -, Q4: -	
Number of total citation by **Google Scholar**:	52
Hirsch index:	3
https://scholar.google.com/citations?user=W-lwh2EAAAAJ&hl=en&citsig=AMD79oqbQIqmauGf8IvpJIBqLm2JIxsCZg	
Number of total citation by **MTMT2**:	23
Hirsch index:	1
https://m2.mtmt.hu/gui2/?type=authors&mode=browse&sel=10064580&view=pubTable	

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Pancreatology 20 (2020) 1323–1331

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Acid suppression therapy, gastrointestinal bleeding and infection in acute pancreatitis – An international cohort study

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Abbreviations: AP, acute pancreatitis; ASD, acid suppressing drug; CI, confidence interval; ERCP, endoscopic retrograde cholangio-pancreatography; GI, gastrointestinal; H2-RA, histamine-2-receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor; SCT, stool culture test.

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https://doi.org/10.1016/j.pan.2020.08.009

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ARTICLE INFO

Article history:
Received 12 August 2020
Accepted 13 August 2020
Available online 22 August 2020

Keywords:
Acid suppressing drug
Gastrointestinal bleeding
Gastrointestinal infection
Acute pancreatitis
Proton pump inhibitor

ABSTRACT

Background: Acid suppressing drugs (ASD) are generally used in acute pancreatitis (AP); however, large cohorts are not available to understand their efficiency and safety. Therefore, our aims were to evaluate the association between the administration of ASDs, the outcome of AP, the frequency of gastrointestinal (GI) bleeding and GI infection in patients with AP.
Methods: We initiated an international survey and performed retrospective data analysis on AP patients hospitalized between January 2013 and December 2018.
Results: Data of 17,422 adult patients with AP were collected from 59 centers of 23 countries. We found that 23.3% of patients received ASDs before and 86.6% during the course of AP. ASDs were prescribed to 57.6% of patients at discharge. ASD administration was associated with more severe AP and higher mortality. GI bleeding was reported in 4.7% of patients, and it was associated with pancreatitis severity, mortality and ASD therapy. Stool culture test was performed in 6.3% of the patients with 28.4% positive results. *Clostridium difficile* was the cause of GI infection in 60.5% of cases. Among the patients with GI infections, 28.9% received ASDs, whereas 24.1% were without any acid suppression treatment. GI infection was associated with more severe pancreatitis and higher mortality.
Conclusions: Although ASD therapy is widely used, it is unlikely to have beneficial effects either on the outcome of AP or on the prevention of GI bleeding during AP. Therefore, ASD therapy should be substantially decreased in the therapeutic management of AP.

Introduction

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas that can involve peripancreatic tissue or remote organ systems. The global incidence of AP is 30–100 cases per 100,000 general population per year, and it is one of the most frequent gastrointestinal (GI) causes of hospital admission [1]. Unfortunately, research activity in the field is more underrepresented than it should be [2]. Not surprisingly, there is no specific therapy available for AP, symptomatic and curative treatments are based on guidelines and the prior experience of the medical staff. Strikingly, current AP guidelines do not include any information regarding the administration of acid suppressing drugs (ASDs) such as proton pump inhibitors (PPIs) and histamine-2-receptor antagonists (H2-RAs) in AP [3–6], despite the fact that ASDs are routinely administered in clinical practice in the majority of AP cases.

Conventionally, the management of AP patients included nothing by mouth from the time of hospital admission. It was believed that by doing so the inflamed pancreas can rest, because fluid intake or solid nutrients would stimulate exocrine pancreatic functions and promote the release of proteolytic enzymes. However, prior studies failed to support this idea and showed no benefit from fasting or nasogastric suction [7,8]. In experimentally induced pancreatitis, results showed that pantoprazole treatment reduced tissue infiltration of inflammatory cells and acinar cell necrosis in severe AP. They concluded that pantoprazole possesses anti-inflammatory *in vivo* properties and attenuates the course of AP [9]. During fasting for the protection of the upper GI mucosa and to rest the inflamed pancreas, ASD administration could be a potentially good therapeutic option. Patients with severe AP, especially those who require intensive care treatment or mechanical ventilation are carrying a higher risk for stress-related acute gastric mucosal lesions [10], which can lead to ulceration and GI hemorrhage. Protection of the gastric mucosa is a critical therapeutic goal in a wide spectrum of gastric-acid-related diseases. H2-RAs and PPIs are the cornerstones in the therapy of diseases in which gastric acid has a causative primary or contributory role to prevent the damage or propagate the healing of gastric mucosa. Nowadays, PPIs are among the most commonly prescribed drugs with constantly increasing usage, while several studies raising concerns regarding their overprescription. Possible reasons for the continuous increase in ASD use can be the empirical treatment of various GI symptoms and prescriptions for inappropriate conditions [11–13].

There are contradictory results in the literature on the beneficial and harmful effects of ASD administration in patients with AP [14–17]. Such therapy might be beneficial if it decreases severity or mortality; however, acid suppression can be harmful as it might increase the risk for GI infections. Although many international cohort studies were published in AP [18–20], few data are available on the use of ASDs, GI bleeding, and infection. Therefore, our aims were to understand the current global practice of ASD administration in AP patients and to investigate the safety and efficacy of these drugs in this patient population.

Materials and methods

Patients and data collection

To assess the worldwide trend of ASD administration in AP patients, an invitation letter was sent out to the members of the International Association of Pancreatology in January 2019 to participate in the present study. The time period of data collection was from January 2013 to December 2018. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council in Hungary (TUKEB-22254-1/2012/EKU).

Centers had to provide data on the gender and age of the patient, severity of pancreatitis and mortality. In addition to the general demographic data, they had to indicate whether the patients received ASDs (PPI or H2-RA) upon admission, during hospitalization and at discharge irrespectively to its indication, timing, dosing and form of administration. Centers had to include data on the signs and cause of GI bleeding. It had to be recorded if a stool culture test (SCT) was performed along with its result. In the case of positive testing, the name of the pathogen had to be included.

Based on the data above, patients were assigned to two groups depending on their ASD administration status during hospitalization, one which received ASD treatment (group 'ASD') and the other which did not (group 'NoASD'). In the case of GI bleeding and GI infection, the ASD treatment in the hospital was the indicator to assign a patient to 'ASD' or 'NoASD' groups.

Data quality

Data were complete on age, gender, severity of AP and mortality, in hospital ASD administration, registering the signs of GI bleeding, and whether SCT was performed or not and its result. ASD administration was unknown on admission in 1046 of the cases, and in 10 patients at discharge. The cause of GI bleeding was unknown in 5 patients.

Diagnostic criteria

The diagnosis of AP was based on the IAP/APA evidence-based guidelines for the management of AP A1 recommendation [3]. At least two from the following three criteria should be confirmed in patients: clinical (upper abdominal pain), laboratory (serum amylase or lipase >3x upper limit of normal) and/or imaging (CT, MRI, ultrasonography). Severity of pancreatitis was determined based on the revised Atlanta classification [21]. This classification defines three degrees of severity: mild, moderately severe (moderate) and severe AP.

Signs of GI bleeding were provided by each center. These included positive rectal digital examination, macroscopically observed bleeding in the stool, vomit or gastric juice, positive stool blood test, and bleeding verified by an imaging technique. We excluded the bleeding cases that occurred in association with endoscopic retrograde cholangio-pancreatography (ERCP) since administration of ASDs does not have an effect on this type of bleeding. If the cause of the GI bleeding could not be determined, patients were not included in the analyses regarding GI bleeding.

The presence of pathogens in the stool verified by laboratory testing was considered GI infections. Non-specific signs such as fever, diarrhea and vomiting without testing were not accepted. The pathogens were identified for each patient.

Statistical analysis

To identify differences between categorical variables the Chi-square with Fisher's exact test was used. The significance level was set at 0.05. Binary logistic regression with stepwise forward elimination was used to observe independent prognostic factors (age, gender, severity, ASD treatment, GI bleeding and infection) for the main outcomes (ASD administration, GI bleeding and infection).

Results

Characteristics of the cohort

Data of 17,422 adult patients with AP were collected retrospectively from 59 centers (Fig. 1, Supplementary Table 1). 9803 of patients were male (56.3%) and 7619 were female (43.7%) (Supplementary Figure A), the average age was 56.4 years (Supplementary Figure B) in the cohort. In the studied population 10,490 (60.2%) of patients had mild, 4508 (25.9%) had moderate and 2424 (13.9%) had severe AP (Supplementary Figure C). In total 4.6% (800 patients) of patients died; the mortality rate was 0.4% (n = 44/10,490) in mild, 1.5% (n = 68/4508) in moderate and 28.4% (n = 688/2424) in severe AP (Supplementary Figure D). Upon admission, 23.3% of patients (n = 3817/16,376) took some kind of ASD (Supplementary Figure E). From these patients, 88.3% (n = 3369/3817) was admitted with a PPI, 11.3% (n = 432/3817) with a H2-RA, and 0.4% (n = 16/3817) received both kind of ASD. During hospitalization, 86.6% of patients (n = 15,096/17,422) received ASD treatment (Supplementary Figure E), 81.8% (n = 12,354/15,096) of these patients had only PPIs, 15.4% (n = 2331/15,096) had solely H2-RAs and 2.7% (n = 411/15,096) had both PPIs and H2-RAs. At the time of discharge from the hospital, 57.6% of patients (n = 10,034/17,412) were prescribed an ASD (Supplementary Figure E), 92.6% (n = 9293/10,034) of them received prescription for PPIs, 7.3% (n = 734/10,034) for H2-RAs and 0.1% (n = 7/10,034) for both ASDs. For the following parameters in the result section, only data during hospitalization were analyzed.

Acid suppression therapy is associated with more severe AP and higher mortality

Patients were assigned to 'ASD' or 'NoASD' groups based on their ASD administration status in the hospital. Among 'ASD' patients mild AP (n = 8649/15,096, 57.3%) was significantly less frequent compared to those in the 'NoASD' group (n = 1841/2326, 79.1%, p < 0.001). However, in case of moderate and severe pancreatitis, there were significantly more patients in the 'ASD' group (moderate: n = 4139/15,096, 27.4%; severe: n = 2308/15,096, 15.3%) than in the 'NoASD' group (moderate: n = 369/2326, 15.9%, p < 0.001; severe: n = 116/2326, 5.0%, p < 0.001) (Fig. 2A). Mortality was significantly higher in patients with acid suppressing therapy (n = 744/15,096, 4.9%) compared to those without acid suppression (n = 56/2326, 2.4%, p < 0.001) (Fig. 2B). Based on the results of logistic regression, the patient's gender did not influence the administration of ASD treatment (OR = 1.015, 95% CI = 0.927–1.110, p = 0.748); however, older age (OR = 1.006, 95% CI = 1.003–1.008, p < 0.001) and worse than mild AP severity (OR = 2.202, 95% CI = 2.031–2.387, p < 0.001) increased the patients' chance for receiving ASDs during hospitalization.

Acid suppressing drug therapy is associated with higher risk for GI bleeding in AP

Data for 17,282 patients were evaluated after excluding ERCP-associated bleedings and bleedings of unknown origin. From these patients, 817 (4.7%) had GI bleeding (Fig. 3A). The number of patients having mild pancreatitis without GI bleeding was significantly higher compared to those with GI bleeding (n = 10,193/16,465, 61.9% vs. n = 221/817, 27.1%, p < 0.001, respectively). However, among patients with GI bleeding there were significantly more moderate (No bleeding: 4181/16,465, 25.4% vs. Bleeding: n = 283/817, 34.6%, p < 0.001) and severe AP (No bleeding: 2091/16,465, 12.7% vs. Bleeding: n = 313/817, 38.3%, p < 0.001) cases (Fig. 3B). In case of GI bleeding, the rate of mortality was significantly higher compared to patients without bleeding (No bleeding: n = 650/16,465, 3.9% vs. Bleeding: n = 138/817, 16.9%, p < 0.001) (Fig. 3B). There were significantly more patients suffering from GI bleeding while receiving acid suppressing treatment compared to those who did not ('ASD': n = 766/14,975, 5.1% vs. 'NoASD': n = 51/2307, 2.2%, p < 0.001, respectively) (Fig. 3A).

The age (OR = 0.998, 95% CI = 0.992–1.005, p = 0.585) and the gender (OR = 0.915, 95% CI = 0.732–1.143, p = 0.432) of patients did not influence the chance of GI bleeding; however, worse AP severity carried an almost 3 times higher probability of GI bleeding (OR = 2.994, 95% CI = 2.623–3.418, p < 0.001). Furthermore, ASD treatment during hospitalization increased the chance of GI bleeding by 1.5-fold (OR = 1.543, 95% CI = 1.040–2.291, p = 0.031), and in case of verified GI infection the chance of GI bleeding was almost 2.8 times higher (OR = 2.789, 95% CI = 1.997–3.894, p <

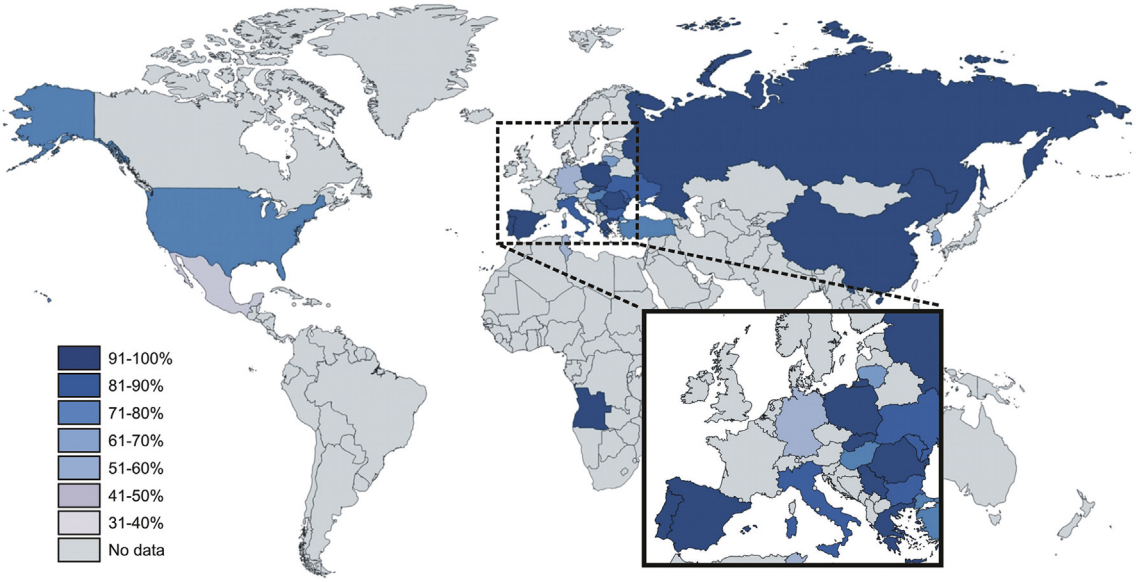
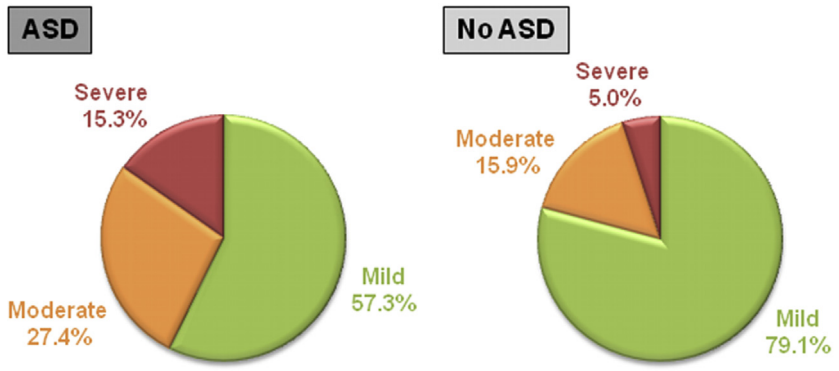


Fig. 1. Map of worldwide acid suppressing drug usage. Map shows the use of acid suppressing drugs in patients with acute pancreatitis during hospitalization.

A



B

			MILD		MODERATE		SEVERE		MORTALITY	
GROUPS	n	%	n	%	n	%	n	%	n	%
ASD	15,096	86.6	8,649	82.4	4,139	91.8	2,308	95.2	744	4.9
No ASD	2,326	13.4	1,841	17.6	369	8.2	116	4.8	56	2.4
	17,422		10,490	100.0	4,508	100.0	2,424	100	800	

Fig. 2. Disease severity and mortality rate in patients with or without acid suppressing drug (ASD) treatment. A) Disease severity in patients with (ASD) or without ASD (No ASD) therapy. **B)** Number (n) and percentage of patients who received ASDs in the different severity groups, and mortality rates in ASD and No ASD groups.

0.001).

Characterization of patients undergone SCT

From the 17,422 patients, an SCT was performed in 1102 cases (6.3%) (Fig. 4A). There were significantly more patients with mild AP who did not undergo stool culture testing (NoSCT: n = 9961/16,320, 61% vs. SCT: n = 529/1102, 48%, p < 0.001). In case of moderate and severe AP, the number of patients that underwent testing during hospitalization was significantly higher (NoSCT: n = 4214/16,320, 25.8% vs. SCT: n = 294/1102, 26.7%, p < 0.001 and NoSCT: n = 2145/16,320, 13.2% vs. SCT: n = 279/1102, 25.3%, p < 0.001, respectively) (Fig. 4B). Mortality was significantly higher in patients with stool culture testing (NoSCT: n = 698/16,320, 4.3% vs. SCT: n = 102/1102, 9.3%, p < 0.001) (Fig. 4C). The frequency of SCT orders increased with the severity of AP, mild: 5.0% (n = 529/10,490), moderate 6.5% (n = 294/4508), severe: 11.5% (n = 279/2424). From the 1102 patients who underwent stool culture testing, 313 of them (28.4% of tested patients) had positive results. The most common pathogens causing GI infections were *Clostridium difficile* (n = 210/347, 60.5%) and the *Klebsiella* species (n = 35/347, 10.1%) (Supplementary Table 2A), and there was only a single pathogen verified in 91.4% of the cases (n = 286/313) (Supplementary Table 2B).

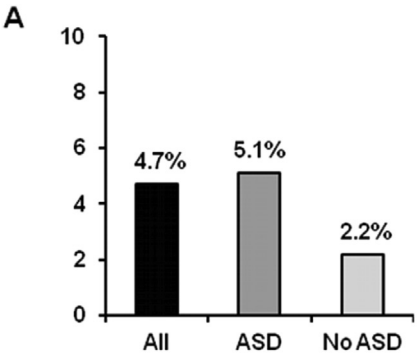
Acid suppressing treatment is not associated with higher risk for GI infection

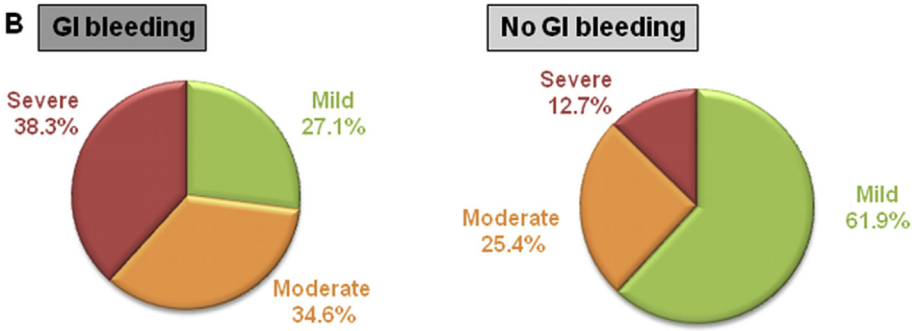
Among patients with GI infections, there was a significantly lower number of patients in the mild AP group (n = 95/313, 30.4%) compared to the number of mild cases in patients without an infection (n = 434/789, 55%, p < 0.001) (Fig. 4D). We found significantly more moderate (Positive: n = 103/313, 32.9% vs. Negative: n = 191/789, 24.2%, p < 0.001) and severe (Positive: n = 115/313, 36.7% vs. Negative: n = 164/789, 20.8%, p < 0.001) cases in patients with positive SCT (Fig. 4D). In patients with GI infection, the mortality rate was significantly higher compared to the rate in the group tested negative for GI infections (Positive: n = 42/313, 13.4% vs. Negative: n = 60/789, 7.6%, p = 0.003) (Fig. 4E). GI bleeding was significantly more frequent in patients with verified GI infection (GI bleeding and GI infection: n = 54/302, 17.9% vs. GI bleeding without GI infection: n = 81/770, 10.5%, p = 0.001) (Table 1). There was no significant difference in the occurrence of GI infection between patients with or without ASD treatment ('ASD': n = 285/986, 28.9% vs. 'NoASD': n = 28/116, 24.1%, p = 0.276) (Table 2).

Investigating the different factors that could have an effect on the above results we found that the age (OR = 0.999, 95% CI = 0.992–1.006, p = 0.781) and the gender (OR = 1.073, 95% CI = 0.847–1.359, p = 0.559) of patients, and whether they received ASDs or not (OR = 1.447, 95% CI = 0.969–2.161, p = 0.071) did not have an impact on the chance of having GI infection; however, patients with worse than mild AP severity had a 2.5 times higher odds for GI infections (OR = 2.5, 95% CI = 2.178–2.870, p < 0.001).

Discussion

ASDs, especially PPIs are among the most frequently prescribed drugs with increasing use every year. Even though there are well established indications for a wide array of diseases when and how to conduct treatment with ASDs, several studies were published regarding their overprescription, and difficulties to discontinue their application. Some suggests that possible reasons could be prescription based on empirical decision or for conditions without any indication [12,13,22,23]. Data from our cohort supports the worldwide overuse of ASDs, specifically in patients with AP. 23.3% of patients received ASD treatment before being admitted to the hospital, and their number has increased by 3.7-fold during hospitalization with almost all of the patients receiving some kind of ASD. More than 50% of patients had remained on an ASD after discharge, a more than 2-fold increase relative to the number at admission. These numbers are in accordance with literature data





C

	MILD		MODERATE		SEVERE		MORTALITY	
	n	%	n	%	n	%	n	%
GI bleeding	221	2.1	283	6.3	313	13.0	138	16.9
No GI bleeding	10,193	97.9	4,181	93.7	2,091	87.0	650	3.9

Fig. 3. Disease severity and mortality rate in patients with or without gastrointestinal (GI) bleeding. A) Percentage of patients with GI bleeding in the entire cohort, in patients with or without acid suppressing drug (ASD) treatment. **B)** Disease severity in patients with and without GI bleeding. **C)** Number (n) and percentage of patients who had GI bleeding or did not have GI bleeding in the different severity groups, and mortality rates.

whereas patients after receiving ASDs during hospitalization get usually discharged with them [23]. Unfortunately, this is another example which shows that big difference can occur between guidelines and their application [24]. Moreover, ASD treatment in AP was associated with more severe pancreatitis and higher mortality rate in our cohort.

There are contradictory results in the literature about the safety of ASD use in AP. In a Korean randomized clinical trial, the investigators separated AP patients into two groups, one receiving pantoprazole intravenously during fasting and later orally, and another without PPI treatment. In this study, treatment with pantoprazole did not influence the clinical course of AP [14]. In another randomized clinical trial from China, severe AP patients receiving conventional therapy were compared to patients on conventional therapy with esomeprazole treatment, and PPI therapy did not show benefit on alleviating systemic inflammatory response and improving clinical scores in severe AP patients, and did not prevent the development of peptic ulcer and GI hemorrhage [15]. Data from 10,400 severe AP patients were analyzed in a Japanese retrospective study, and even though the rates of upper GI bleeding and organ failure were significantly higher in patients with PPI therapy, after propensity analysis, data showed that PPIs did not have an effect on mortality [16]. On the contrary, in a Swedish population-based case-control study, they observed association between current use of H2-RAs or PPIs and increased risk of AP, besides previous literature data where they reported ASDs to cause AP [17].

Systemic inflammatory response syndrome is often a complication of severe AP, which leads to high level of inflammatory markers [26] and organ dysfunctions. Patients with severe AP, especially those who require intensive care treatment or mechanical ventilation are prone to develop stress-related acute gastric mucosal lesions [10]. Acute GI mucosal lesions can range from simple gastritis and erosions to ulceration and bleeding [25], more than half of patients with AP may develop upper GI ulcers, and the occurrence shows positive correlation with the severity of pancreatitis [8,27]. Hypersecretion of gastric acid seems to play a major role at the pathogenesis of stress-related acute gastric mucosal lesions. Therefore, in these cases it can be indicated to use prophylaxis for peptic ulcer disease [8,28]. Based on our results, not only in case of severe, but also in moderate pancreatitis cases there were significantly more patients receiving ASD treatment which supports our previous data about their frequent usage.

Protection of upper GI mucosa could be a possible indication for ASD administration in AP patients, which could decrease the rate of GI bleeding. Since ERCP- and surgery-related vascular complications cannot be prevented with ASD treatment, we did not include these types of GI bleedings in our analyses. In the studied population, 4.7% of patients suffered from GI bleeding. Although we did

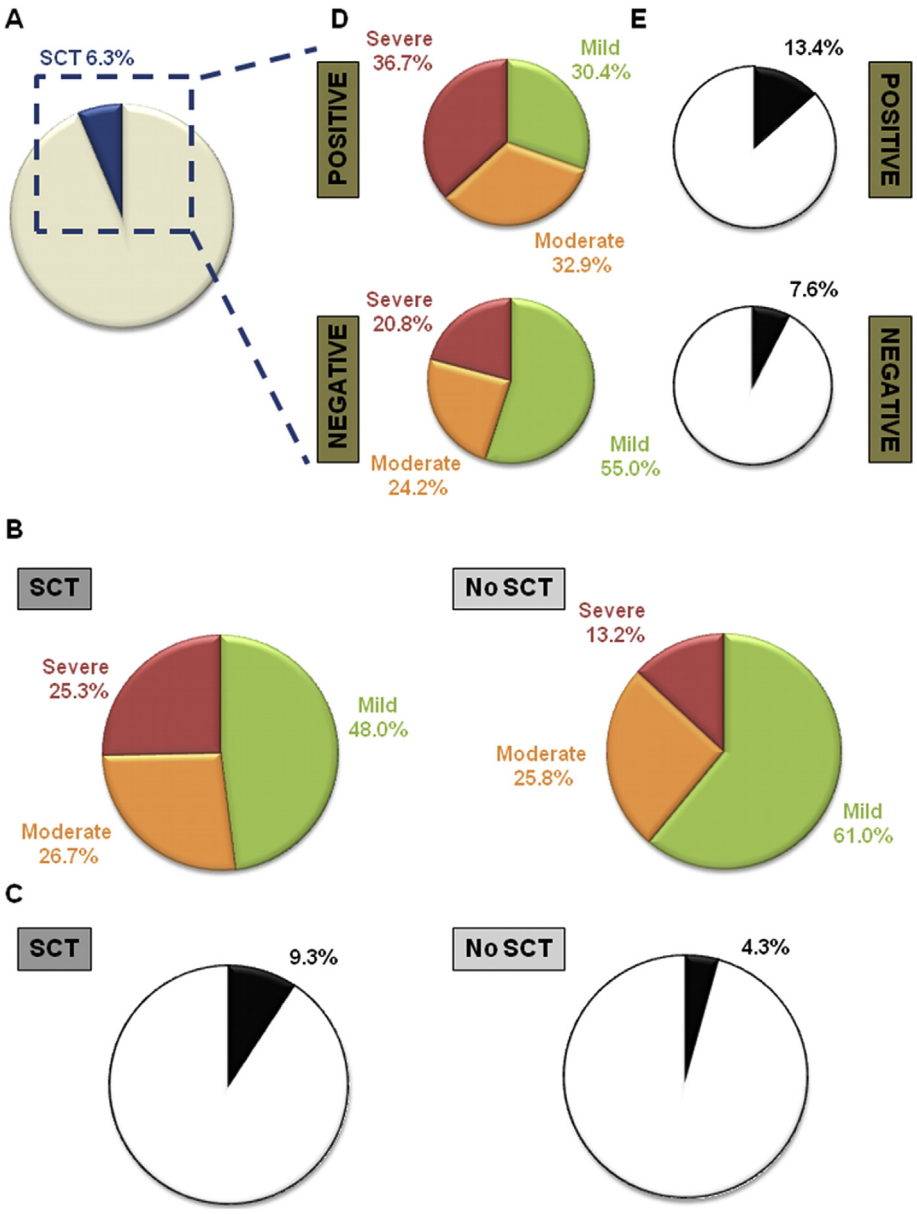


Fig. 4. Disease severity and mortality rate in patients undergone stool culture testing (SCT). A) Percentage of patients who had SCT. **B–C)** Severity of acute pancreatitis and mortality rate in tested and not tested patients. **D-E)** Severity and mortality in patients with or without gastrointestinal infection.

Table 1
Gastrointestinal (GI) infection in patients with or without GI bleeding. Results of stool culture testing (SCT) in patients with or without GI bleeding with patient number (n) and percentage.

	No bleeding		GI bleeding		
	n	%	n	%	
NEGATIVE SCT	689	89.5	81	10.5	770
POSITIVE SCT	248	82.1	54	17.9	302

Table 2
Gastrointestinal infection in patients with or without acid suppressing drug (ASD) treatment. Result of stool culture testing (SCT) in patients with or without ASD therapy with patient number (n) and percentage.

	No ASD		ASD	
	n	%	n	%
NEGATIVE SCT	88	75.9	701	71.1
POSITIVE SCT	28	24.1	285	28.9
	116		986	

not collect data on the cause of death, GI bleeding was associated with higher morbidity and mortality, which increases the length and cost of hospitalization. Investigating the association between ASD treatment and GI bleeding, we found that bleeding occurred more frequently in patients on ASD therapy which correlates with literature data [15,16]. Based on the study of Chen et al. [8] in which all the included patients received PPIs when a GI lesion was detected with endoscopy, 22% of severe pancreatitis patients had GI bleeding [8]. We did not collect data on the time of bleeding and the start of ASD therapy. A possible explanation could be that when GI bleeding was recognized then ASD therapy was started, although, that still does not give an explanation why more than 80% of patients had to receive ASDs. Especially that more than 60% of patients had mild AP, and in that group only 2.1% of patients were

suffering from GI bleeding. Therefore, these results suggest GI bleeding recognition is not the indication of starting ASD treatment in AP patients, and it also does not explain why more than 50% of patients have to receive ASDs upon discharge from the hospital.

ASDs are considered well tolerated and effective, and only rare and mild side effects have been reported in short-term use. However, nonessential long-term ASD treatment can lead to various side effects in spite of their reported good safety profile [12]. Such as elevated prevalence of small intestinal bacterial overgrowth which results in malabsorption [29], increased risk for respiratory infections [30,31] and several GI cancers (gastric, colorectal, liver or pancreatic cancers) [13,31–35]. Other long-term side effects can be micronutrient deficiencies, kidney disease, osteoporosis and dementia. Long-term administration without proper re-evaluation and guidelines will lead to polypharmacy and potential drug-drug interactions [31]. Although several studies have shown association between adverse events and complications of long-term ASD use, they have led to contradictory results [11]. Side effects are also including elevated risk for GI infections by repressing the gastric acid barrier and altering the microbiome. Notably, *Clostridium difficile* infection has shown strong association with ASD therapy [12,22,30,31,36,37]. From the wide array of possible long-term complications, we investigated the relationship between acid suppressing therapy and occurrence of GI infections in AP patients. According to our results, ASD administration did not elevate the risk for GI infections. However, ordering of SCTs has been associated with more severe AP and higher mortality rate. Even though, there was relatively low number of testing among the included patients, almost 30% of them had GI infections. In our cohort, the most common pathogen was *Clostridium difficile* (60%) in accordance with literature data in other diseases. An important factor that has to be taken into consideration is the frequent usage of unnecessary antibiotic drugs in AP patients. The most frequently used antibiotics can be effective for the most common GI infections [38]. In the studied patient population, GI infections have been associated with more severe AP, higher rate of GI bleeding and worse mortality. Therefore, length of hospitalization and the cost of treatment could be worse in patients with GI infections.

Our cohort analysis has its limitations, since it is a retrospective data analysis, we cannot draw causative conclusions from the findings above, only associations can be determined between the investigated parameters.

Our aim was to investigate the current place of ASDs in patients with AP and evaluate their safety and effectiveness that we could present in a large AP population. Based on the epidemiologic characteristics of our cohort and the numerous international centers who contributed data, our patient population substantiates a general representation of patients with AP [39,40]. Our data shows a worldwide unnecessary ASD use in AP patients, even though there is no substantial evidence that ASD treatment is beneficial for the therapy of AP. Hereby, we present their association with higher morbidity and mortality. Our cohort analysis is among the first to report data on the rate of GI bleeding not related to surgery or ERCP in patients with AP. Based on our data, ASD administration during AP did not increase the risk for GI infections. Taking into consideration the advice from the American Gastroenterological Association, the benefits of ASDs outweigh their risks if appropriately prescribed, but when there is no indication, modest risks become important because there is no potential benefit [15]. Therefore, according to our results, the routine administration of ASDs is not recommended in patients with AP if there is no other indication for their administration. Long-term complications could be avoided by re-evaluating the current clinical practices, incorporate recommendations to current guidelines, and by giving detailed plans for patients and their general practitioners how to gradually reduce or leave the ASDs, and when to follow up on them.

Author contributions

AD and PH contributed to study conception and design; AD and LK contributed to data acquisition; IC, GM, MKS, RN, DW, WH, QX, LD, MHo, ASc, MHi, OI, ÁV, JB, PS, LC, DI, FI, LG, MP, JHam, MV, PK, EB, AM, BE, RC, CR, CI, LM, EJ, VC, MVM, GB, PI, MPL, ASR, ST, ET, EMP, HZ, VNu, AGom, TCG, MF, JC, MRRMS, JP, BM, GC, VS, IN, CC, VNe, SBu, CG, SBa, ATa, MT, EDu, AIS, CT, AGh, AL, NS, YR, MB, PJH, JHan, JARO, IMS, EPC, DIG, AJC, AQC, YTC, MCC, AK, ATi, SK, VG, DD, HTK, EA, SCho, SChu, AGou and GP provided substantial patient data; SV, MFJ, KO, EDa and EM managed patient related data; ASz and AP coordinated data collection and controlled data quality; AD, PH and ASo performed data analyses; ASo performed statistical analyses; AD drafted the manuscript and prepared the figures; PH contributed critical revisions and all authors approved the final manuscript.

Funding

This study was supported by Project Grants of the National Research Development and Innovation Office (K131996 to PH and FK131864 to AM), by the János Bolyai Research Scholarship granted by the Hungarian Academy of Sciences (to AP), by 'GINOP-2.3.2-15-2016-00048–STAY ALIVE' co-financed by the European Union (European Regional Development Fund) within the framework of the Széchenyi 2020 Programme, and by a Human Resources Development Operational Programme Grant, Grant Number: EFOP 3.6.2-16-2017-00006–LIVE LONGER, co-financed by the European Union (European Regional Development Fund) within the framework of the Széchenyi 2020 Programme.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgement

We are thankful to the members of the HPSG, who actively recruited patients, and we acknowledge all the patients who were willing to give their consent to be involved in the cohorts. We would like to acknowledge János Novák (Pándy Kálmán Hospital of Békés County, Gyula, Hungary), János Sümegi (Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital, Miskolc, Hungary), István Hritz (Bács-Kiskun County Hospital, Kecskemét, Hungary), Barnabás Bod (Dr. Bugyi István Hospital, Szentes, Hungary), Csaba Góg (Healthcare Center of County Csongrád, Makó, Hungary), Zsolt Szentkereszty (Institute of Surgery, University of Debrecen, Debrecen, Hungary), Árpád Patai (Markusovszky University Teaching Hospital, Szombathely, Hungary), Gyula Farkas Jr (Department of Surgery, University of Szeged, Szeged, Hungary), András Gelley (Polyclinic of the Hospitaller Brothers of St. John of God, Budapest, Hungary), Laura Alberici (Department of Surgery, University of Bologna, Bologna, Italy) and David Aparicio (HPB Surgery, Department of Surgery, Hospital Prof. Dr. Fernando Fonseca, Amadora, Portugal) for their participation in patient recruitment. AD thankfully acknowledges Miklós Sahin-Tóth for his valuable comments and support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2020.08.009.

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II.

frontiers in Physiology

SYSTEMATIC REVIEW
published: 19 November 2018
doi: 10.3389/fphys.2018.01550

PPIs Are Not Responsible for Elevating Cardiovascular Risk in Patients on Clopidogrel—A Systematic Review and Meta-Analysis

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Specialty section:
This article was submitted to Gastrointestinal Sciences, a section of the journal Frontiers in Physiology

Received: 31 July 2018
Accepted: 16 October 2018
Published: 19 November 2018

Citation:
Demcsák A, Lantos T, Bálint ER, Hartmann P, Vincze Á, Bajor J, Czopf L, Alizadeh H, Gyöngyi Z, Márta K, Mikó A, Szakács Z, Pécsi D, Hegyi P and Szabó IL (2018) PPIs Are Not Responsible for Elevating Cardiovascular Risk in Patients on Clopidogrel—A Systematic Review and Meta-Analysis. Front. Physiol. 9:1550. doi: 10.3389/fphys.2018.01550

Background: Clopidogrel and proton pump inhibitors (PPIs) are metabolized by cytochrome P450 enzymes. Contradictory results have been reported on possible complications of simultaneous PPI and clopidogrel use. Our aim was to investigate the clinical relevance of this debate with a systematic review and meta-analysis.

Methods: The PubMed, Embase, and Cochrane Central Register of Controlled Trials electronic databases were searched for human studies [randomized controlled trials (RCTs) and observational studies] using the PICO format (P: patients on clopidogrel; I: patients treated with PPI; C: patients without PPI treatment; O: cardiovascular risk). We screened eligible studies from 2009 to 2016. After study exclusions, we extracted data from 27 articles for three outcomes: major adverse cardiac event (MACE), myocardial infarction (MI) and cardiovascular (CV) death. The meta-analysis was registered on PROSPERO (CRD42017054316).

Results: Data were extracted on 156,823 patients from the 27 trials included (MACE: 23, CV death: 10, MI: 14). The risks of MACE (RR = 1.22, 95% CI = 1.06–1.396, $p = 0.004$) and MI (RR = 1.43, 95% CI = 1.24–1.66, $p < 0.001$) were significantly higher in the PPI plus clopidogrel group. However, subgroup analysis demonstrated that this significance disappeared in RCTs (RR = 0.99, 95% CI = 0.76–1.28, $p = 0.93$) in the MACE outcome group. There was no effect of combined PPI and clopidogrel therapy on CV death outcome (RR = 1.21, 95% CI = 0.97–1.50, $p = 0.09$).

Conclusion: Concomitant use of PPIs and clopidogrel has been proved not to be associated with elevated cardiovascular risks according to RCTs. Based on our results, no restrictions should be applied whenever PPIs and clopidogrel are administered simultaneously.

Keywords: proton pump inhibitors, clopidogrel, cardiovascular risk, drug interaction, cytochrome P450, meta-analysis

INTRODUCTION

The literature consists of contradictory findings on the concomitant usage of clopidogrel and proton pump inhibitors (PPIs). A combination of antiplatelet drugs is used for the treatment of acute coronary syndrome (i.e., aspirin and thienopyridines) and for the secondary prevention of further cardiovascular (CV) events (Yusuf et al., 2001). It is well-documented that dual antiplatelet therapy is followed by possible side-effects, such as higher risk for gastrointestinal (GI) bleeding increasing both mortality and ischaemic complications (Nikolsky et al., 2009; Disney et al., 2011). To reduce the risk of GI bleeding in patients with risk factors, PPIs are strongly recommended by the American College of Cardiology, the American College of Gastroenterology, and the American Heart Association (Bhatt et al., 2008; Abraham et al., 2010; Disney et al., 2011). *In vitro* findings suggested that PPIs reduce the antiplatelet effect of clopidogrel (Gilard et al., 2008), followed by several clinical studies with contradictory outcomes (Pezalla et al., 2008; Ho et al., 2009; Juurlink et al., 2009; O'Donoghue et al., 2009; Rassen et al., 2009; Bhatt et al., 2010; Charlot et al., 2010; Gupta et al., 2010; Hudzik et al., 2010; Kreutz et al., 2010; Ray et al., 2010; van Boxel et al., 2010; Zairis et al., 2010; Burkard et al., 2012; Mo et al., 2015; Sherwood et al., 2015). A higher risk for CV outcomes was found in several studies, systematic reviews and meta-analyses in patients with clopidogrel on PPI therapy. Generally, whenever observational studies were included, a positive association was described. On the other hand, whenever propensity-matched groups were compared the difference between the groups disappeared (Rassen et al., 2009; Kwok and Loke, 2010; Valkhoff et al., 2011; Chen et al., 2012; Mo et al., 2015). Therefore, it is clear that a precise investigation is crucial to understanding the potential CV risk of co-administration of clopidogrel and PPIs.

MATERIALS AND METHODS

Literature Search

A systematic review of studies was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement (Moher et al., 2015). After developing our clinical question and translating it into a well-defined systematic review question based on the PICO format (Patients, Interventions, Comparators and Outcomes), a manual search of medical databases, including PubMed (MEDLINE), Embase, and the Cochrane Central Register of Controlled Trials, was performed for human observations using the following PICO format: P: patients on clopidogrel; I: patients treated with PPI; C: patients without PPI treatment; O: cardiovascular risk. Two independent investigators (AD and ERB) separately screened the titles and abstracts for eligible studies published from inception to 30 December 2016. The flowchart for this process is shown in **Figure 1**. After searching the international prospective register for systematic reviews (PROSPERO) for ongoing or completed meta-analyses on the examined effects of PPIs, we registered our present meta-analysis on PROSPERO under No. CRD42017054316.

Study Selection

Inclusion criteria: (1) randomized or observational studies (cohort and case-control studies) carried out either in a retro- or prospective manner; (2) only adult patients (over 18 years); (3) patients receiving clopidogrel treatment; (4) should compare PPI takers (omeprazole, pantoprazole, esomeprazole, lansoprazole and/or rabeprazole; all doses) and non-PPI takers; (5) we only involved studies that stated exact patient number in the preferred groups (total number of patients, patients who received clopidogrel and PPI, outcome number); (6) human studies; (7) studies should show data for either one or more of the following outcomes: (1) major adverse cardiac event (MACE): composite of cardiac and non-cardiac death, non-fatal myocardial infarction, target vessel failure; (2) myocardial infarction (MI): myocardial infarction or new, definitive major coronarographic defect; (3) CV death: only CV death. Studies published in English were selected. Duplicates were eliminated from the analysis manually. Disagreements were resolved by consulting a small committee of three researchers (PeH, JB, and ÁV).

Data Extraction

Numeric and texted data were extracted from the eligible articles as follows: author, publication year, study type, study endpoints, number of patients in the study, in PPI and in non-PPI treatment groups, and number of patients who received clopidogrel. We also collected the specified generic name of the PPI and patient number if indicated. For study characteristics we collected numeric and texted data as follows: country/region, mean follow up, number of male patients, mean age and mean body mass index, other medications (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin), cardio- and cerebrovascular history (MI, percutaneous coronary intervention, stroke)

Abbreviations: CV, cardiovascular; GI, gastrointestinal; MACE, major adverse cardiac event; MI, myocardial infarction; PPI, proton pump inhibitor; RCT, randomized controlled trial; RR, risk ratio/relative risk

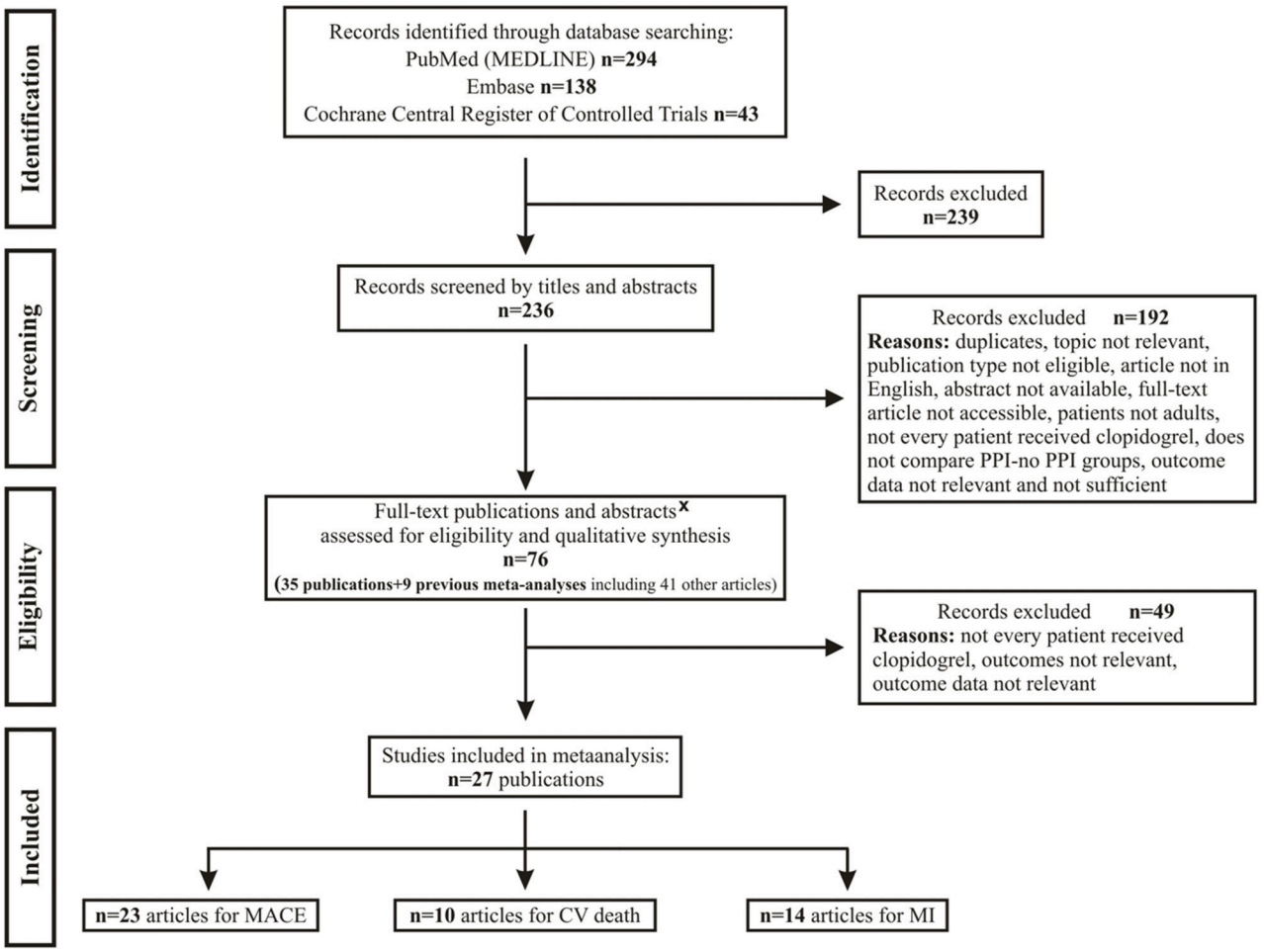

FIGURE 1 | Flowchart for study selection and inclusion. CV, cardiovascular; MACE, major adverse cardiac event; MI, myocardial infarction; PPI, proton pump inhibitor; x, full articles were not available by any suitable sources.

and CV risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking) in the non-PPI and PPI groups (**Supplementary Tables 1A–D**).

Risk of Bias

The Newcastle–Ottawa quality assessment scale (Wells et al., 2013) has been edited to our study design, and was used to assess the quality of observational studies and *post-hoc* analyses of randomized controlled trials (RCTs) (For further details see Supplementary Material, **Supplementary Figure 7B**). We used the Cochrane risk of bias tool (Higgins et al., 2011) for quality assessment of RCTs (**Supplementary Figure 7A**).

Statistical Analysis

We calculated risk ratio/relative risk (RR) and 95% confidence interval (CI) for CV events (MACE, MI and CV death). As secondary analyses, we calculated pooled hazard ratios and 95% CI for the adjusted events for all three major outcomes (**Supplementary Figures 4–6**). Between-study heterogeneity was tested with the I^2 statistic, where I^2 is the proportion of total variation attributable to between-study variability. I^2 heterogeneity was interpreted according to the Cochrane Handbook for Systematic Reviews and Interventions recommendation: 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity (Higgins and Green, 2011). Fixed or random effects models were used for comparison between the two groups (clopidogrel alone or clopidogrel plus PPI), based on the degree of heterogeneity, or based on methodological factors such as difference between study designs or applied PPIs, not homogeneous patient population etc. We estimated the effect of follow up and age on the risk of the three major outcomes by performing random effects meta-regression expressed as standard error and 95% CI. P-values of <0.05 for relative risks and standard errors, and p-values of <0.10 for heterogeneity were considered as indicators of significance. We estimated publication bias through a visual inspection of funnel plots (**Figures 5A–C**). The statistical analysis was performed by a trained biostatistician (TL). All analyses were performed with the Review Manager (RevMan)

software, Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Study Selection

Two hundred and thirty-six articles were identified in the preliminary search. One hundred and ninety-three studies were excluded (**Figure 1**). Seventy-six publications (25 full texts, 10 abstracts, and 41 articles from previous meta-analyses) were assessed for eligibility and qualitative synthesis. Forty-seven of them were excluded due to insufficient data on study groups and another two for statistical reasons (the event rate was zero). A total of 27 studies (Rassen et al., 2009; Bhatt et al., 2010; Cai et al., 2010; Charlot et al., 2010; Evanchan et al., 2010; Gupta et al., 2010; Hudzik et al., 2010; Kreutz et al., 2010; Ray et al., 2010; Stockl et al., 2010; van Boxel et al., 2010; Hsu et al., 2011; Ren et al., 2011; Rossini et al., 2011; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Ng et al., 2012; Yano et al., 2012; Hokimoto et al., 2014; Shih et al., 2014; Zou et al., 2014; Weisz et al., 2015; Ayub et al., 2016; Gargiulo et al., 2016) were selected for quantitative analyses. The researchers and committee involved in the selection (5 investigators) were in total agreement on all the inclusions and exclusions.

Study Characteristics

Altogether, we found data for MACE in 23 publications (O'Donoghue et al., 2009; Bhatt et al., 2010; Cai et al., 2010; Charlot et al., 2010; Gupta et al., 2010; Hudzik et al., 2010; Kreutz et al., 2010; Ray et al., 2010; van Boxel et al., 2010; Hsu et al., 2011; Ren et al., 2011; Rossini et al., 2011; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Ng et al., 2012; Yano et al., 2012; Hokimoto et al., 2014; Zou et al., 2014; Weisz et al., 2015; Ayub et al., 2016; Gargiulo et al., 2016), for CV death in 10 (Rassen et al., 2009; Bhatt et al., 2010; Gupta et al., 2010; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Hokimoto et al., 2014; Zou et al., 2014; Weisz et al., 2015; Gargiulo et al., 2016) and for MI in 14 (Rassen et al., 2009; Bhatt et al., 2010; Evanchan et al., 2010; Hudzik et al., 2010; Stockl et al., 2010; van Boxel et al., 2010; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Shih et al., 2014; Zou et al., 2014; Weisz et al., 2015; Gargiulo et al., 2016). Seventeen of them were observational studies, 16 were cohorts (Rassen et al., 2009; Charlot et al., 2010; Evanchan et al., 2010; Gupta et al., 2010; Kreutz et al., 2010; Ray et al., 2010; Stockl et al., 2010; van Boxel et al., 2010; Rossini et al., 2011; Simon et al., 2011; Chitose et al., 2012; Hokimoto et al., 2014; Shih et al., 2014; Zou et al., 2014; Weisz et al., 2015; Ayub et al., 2016), and one was a case-control study (Hudzik et al., 2010). Data from 10 RCTs (O'Donoghue et al., 2009; Bhatt et al., 2010; Cai et al., 2010; Hsu et al., 2011; Ren et al., 2011; Burkard et al., 2012; Goodman et al., 2012; Ng et al., 2012; Yano et al., 2012; Gargiulo et al., 2016) were also collected. As *post-hoc* analyses of RCTs, in four studies (O'Donoghue et al., 2009; Burkard et al., 2012; Goodman et al., 2012; Gargiulo et al., 2016) the populations and outcome of our interest (clopidogrel plus PPI vs. clopidogrel plus non-PPI treatment) were not randomized, therefore, their data were included in the statistical analyses of observational studies. The method and the study selection are shown in **Figure 1**. All the studies included were published between 2009 and 2016. The characteristics of the studies involved in the meta-analysis are summarized in **Table 1** according to the major outcome groups, and in **Supplementary Tables 1A–D**.

The number of patients involved was 156,823. A total of 63,756 received PPI plus clopidogrel treatment (ranging from 18 to 6,843), and 99,910 (ranging from 20 to 17,949) were in the clopidogrel alone group. Risk of MACE was determined from data from 127,695 patients, MI risk was assessed on the basis of data from 82,330 patients, and risk of CV death was evaluated based on data from 53,905 patients. The PPIs used in the studies were esomeprazole, omeprazole, pantoprazole, rabeprazole, and lansoprazole, but in this meta-analysis as a subgroup analysis we only drew conclusions on the results for omeprazole, esomeprazole, and pantoprazole due to the low number of studies separating data for different PPIs.

Major Adverse Cardiac Event

Twenty-three studies (O'Donoghue et al., 2009; Bhatt et al., 2010; Cai et al., 2010; Charlot et al., 2010; Gupta et al., 2010; Hudzik et al., 2010; Kreutz et al., 2010; Ray et al., 2010; van Boxel et al., 2010; Hsu et al., 2011; Ren et al., 2011; Rossini et al., 2011; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Ng et al., 2012; Yano et al., 2012; Hokimoto et al., 2014; Zou et al., 2014; Weisz et al., 2015; Ayub et al., 2016; Gargiulo et al., 2016) reported the incidence of MACE. Our results showed that the risk of MACE is significantly higher in the PPI group (RR = 1.22, 95% CI = 1.06–1.39, p=0.004), with considerable heterogeneity across the studies included ($I^2 = 90\%$, $p < 0.001$). However, separating the data for the RCT studies from that of the non-RCT studies revealed that a significant association of adverse outcomes (MACE) can only be seen in non-randomized studies (observational studies: RR = 1.26, 95% CI = 1.09–1.46, $p = 0.002$, $I^2 = 93\%$, $p < 0.001$; RCTs: RR = 0.99, 95% CI = 0.76–1.28; $I^2 = 0\%$, $p = 0.93$), although the heterogeneity remained considerable in the observational group, which might not be relevant in the RCT group (**Figure 2A**, **Supplementary Figure 1A**). As the result of meta-regression analyses, MACE was not depending on the length of follow up (SE = 0.007, 95% CI = −0.014 to 0.014, $p = 0.97$), based on the results of 18 studies (Bhatt et al., 2010; Charlot et al., 2010; Gupta et al., 2010; Hudzik et al., 2010; Ray et al., 2010; van Boxel et al., 2010; Hsu et al., 2011; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Ng et al., 2012; Yano et al., 2012; Hokimoto et al., 2014; Zou et al., 2014; Weisz et al., 2015; Ayub et al., 2016; Gargiulo et al., 2016), and the age of the patients did not influence the occurrence of the outcome either (SE = 0.023, 95% CI = −0.011 to 0.081, $p = 0.14$), based on the data found in 19 studies (O'Donoghue et al., 2009; Bhatt et al., 2010; Charlot et al., 2010; Gupta et al., 2010; Hudzik et al., 2010; Ray et al., 2010; van Boxel et al., 2010; Hsu et al., 2011; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Ng et al., 2012; Yano et al., 2012; Hokimoto et al., 2014; Zou et al., 2014; Weisz et al., 2015; Ayub et al., 2016; Gargiulo et al., 2016).

TABLE 1 | Study characteristics.

References, year	Study type	Number of patients	PPI (generic name)	PPI (number of patients)	Event number: MACE (PPI group)	Event number: CV death (PPI group)	Event number: MI (PPI group)
Ng et al., 2012	RCT	311	Esomeprazole	163	7		
Yano et al., 2012	RCT	130	Omeprazole	65	8		
Hsu et al., 2011	RCT	42	Esomeprazole	21	4		
Ren et al., 2011	RCT	172	Omeprazole	86	22		
Bhatt et al., 2010	RCT	3,761	Omeprazole	1,876	55	5	14
Cai et al., 2010	RCT	60		40	10		
			Omeprazole				
			Pantoprazole				
Gargiulo et al., 2016	RCT (*post-hoc* analysis)	1,970		738	85	29	41
			Pantoprazole	56			
			Lansoprazole	671			
			Omeprazole, esomeprazole, rabeprazole	11			
Burkard et al., 2012	RCT (*post-hoc* analysis)	801		109	33	10	25
			Esomeprazole	55			
			Pantoprazole	27			
			Omeprazole	19			
Goodman et al., 2012	RCT (*post-hoc* analysis)	9,276		3,255	398	180	245
			Omeprazole	1,592			
			Pantoprazole	973			
			Esomeprazole	387			
			Lansoprazole	251			
			Rabeprazole	51			
O'Donoghue et al., 2009	RCT (*post-hoc* analysis)	13,608		4,529	255		
			Omeprazole	1,675			
			Pantoprazole	1,844			
			Lansoprazole	441			
			Esomeprazole	613			
Ayub et al., 2016	Observational cohort	740	Omeprazole	332	30		
			Esomeprazole	40	6		
			Pantoprazole	81	10		
Weisz et al., 2015	Observational cohort	8,581	NS	2,162	238	58	100
Hokimoto et al., 2014	Observational cohort	174	Rabeprazole	50	5		
Shih et al., 2014	Observational cohort	2,703	NS	1,351			12
Zou et al., 2014	Observational cohort	7,653		6,188	860	223	132
			Omeprazole	5,587			
			Pantoprazole	407			
			Esomeprazole	194			
Chitose et al., 2012	Observational cohort	630	NS	187	7	4	1
Rossini et al., 2011	Observational cohort	1,328		1,158	87		
			Lansoprazole	853			
			Pantoprazole	178			
			Omeprazole	125			
Simon et al., 2011	Observational cohort	2,353		1,453		94	24
			Omeprazole	993	43		
			Esomeprazole	311	20		
			Pantoprazole	99	12		
			Lansoprazole	46	1		
Charlot et al., 2010	Observational cohort	24,702	NS	6,753	1058		
Evanchan et al., 2010	Observational cohort	5,794		1,369			356
			Esomeprazole	749			
			Lansoprazole	36			
			Omeprazole	163			
			Pantoprazole	693			

(Continued)

TABLE 1 | Continued

References, year	Study type	Number of patients	PPI (generic name)	PPI (number of patients)	Event number: MACE (PPI group)	Event number: CV death (PPI group)	Event number: MI (PPI group)
Gupta et al., 2010	Observational cohort	315	Rabeprazole, omeprazole, lansoprazole	72	40	14	
Hudzik et al., 2010	Observational case-control	38	Omeprazole	18	10		6
Kreutz et al., 2010	Observational cohort	16,690	Omeprazole Pantoprazole Lansoprazole Esomeprazole	6,828 2,307 1,653 785 3257	1710		
Ray et al., 2010	Observational cohort	16,221	Omeprazole Pantoprazole Lansoprazole, rabeprazole, esomeprazole	7,226 683 4,708	461		
Stockl et al., 2010	Observational cohort	2,066	Pantoprazole Rabeprazole Omeprazole Lansoprazole Esomeprazole	1,033 659 159 86 83 46			133
van Boxel et al., 2010	Observational cohort	18,139	Omeprazole Pantoprazole Esomeprazole Rabeprazole Lansoprazole	5,734 1,826 2,618 1,092 133	754		84
Rassen et al., 2009	Observational cohort	18,565	Omeprazole, rabeprazole, esomeprazole, lansoprazole, pantoprazole	3,996		61	238

CV, cardiovascular; MACE, major adverse cardiac event; MI, myocardial infarction; NS, not shown/not specified; PPI, proton pump inhibitor; RCT, randomized controlled trial.

In case of patients on omeprazole among the 6 publications included (Bhatt et al., 2010; Hudzik et al., 2010; Ren et al., 2011; Simon et al., 2011; Yano et al., 2012; Ayub et al., 2016), there was no significant difference between the clopidogrel plus PPI and clopidogrel alone groups (RR = 0.80, 95% CI = 0.50–1.28, $p = 0.35$), but since there was evidence of considerable heterogeneity ($I^2 = 81\%$, $p < 0.001$), the random effect model was used for comparison (**Figure 2B**, **Supplementary Figure 1B**). In the case of esomeprazole (4 publications, Hsu et al., 2011; Simon et al., 2011; Ng et al., 2012; Ayub et al., 2016), results showed no significant difference in the occurrence of MACE between the groups (RR = 0.73, 95% CI = 0.51–1.05, $p = 0.09$) (**Figure 2B**, **Supplementary Figure 1B**). The heterogeneity might not be important ($I^2 = 0\%$, $p = 0.41$); the fixed effects model was used for comparison. In the pantoprazole group, we only found two eligible publications (Simon et al., 2011; Ayub et al., 2016) for MACE, and there was no difference between the two groups (RR = 0.91, 95% CI = 0.60–1.39, $p = 0.66$) (**Figure 2B**, **Supplementary Figure 1B**). The heterogeneity might not be important ($I^2 = 0\%$, $p = 0.34$); the fixed effects model was used in analyzing of this specific PPI. The results of analyzing the adjusted events for the overall outcome and for different PPIs are presented as **Supplementary Material**.

Cardiovascular Death

Data on CV death was reported in 10 studies (Rassen et al., 2009; Bhatt et al., 2010; Gupta et al., 2010; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Zou et al., 2014; Weisz et al., 2015; Gargiulo et al., 2016), including 53,905 patients; only one study's data was evaluated as RCT (Bhatt et al., 2010). There was no significant effect of concomitant clopidogrel and PPI treatment on CV death (RR = 1.21, 95% CI = 0.97–1.50, $p = 0.09$). The result from the statistical analysis may represent substantial heterogeneity across the studies ($I^2 = 67\%$, $p = 0.001$). The length of follow up and the age of the patients did not affect the risk for CV death based on results of the included 10 studies (follow up: SE = 0.009, 95% CI = −0.016 to 0.021, $p = 0.81$; age:

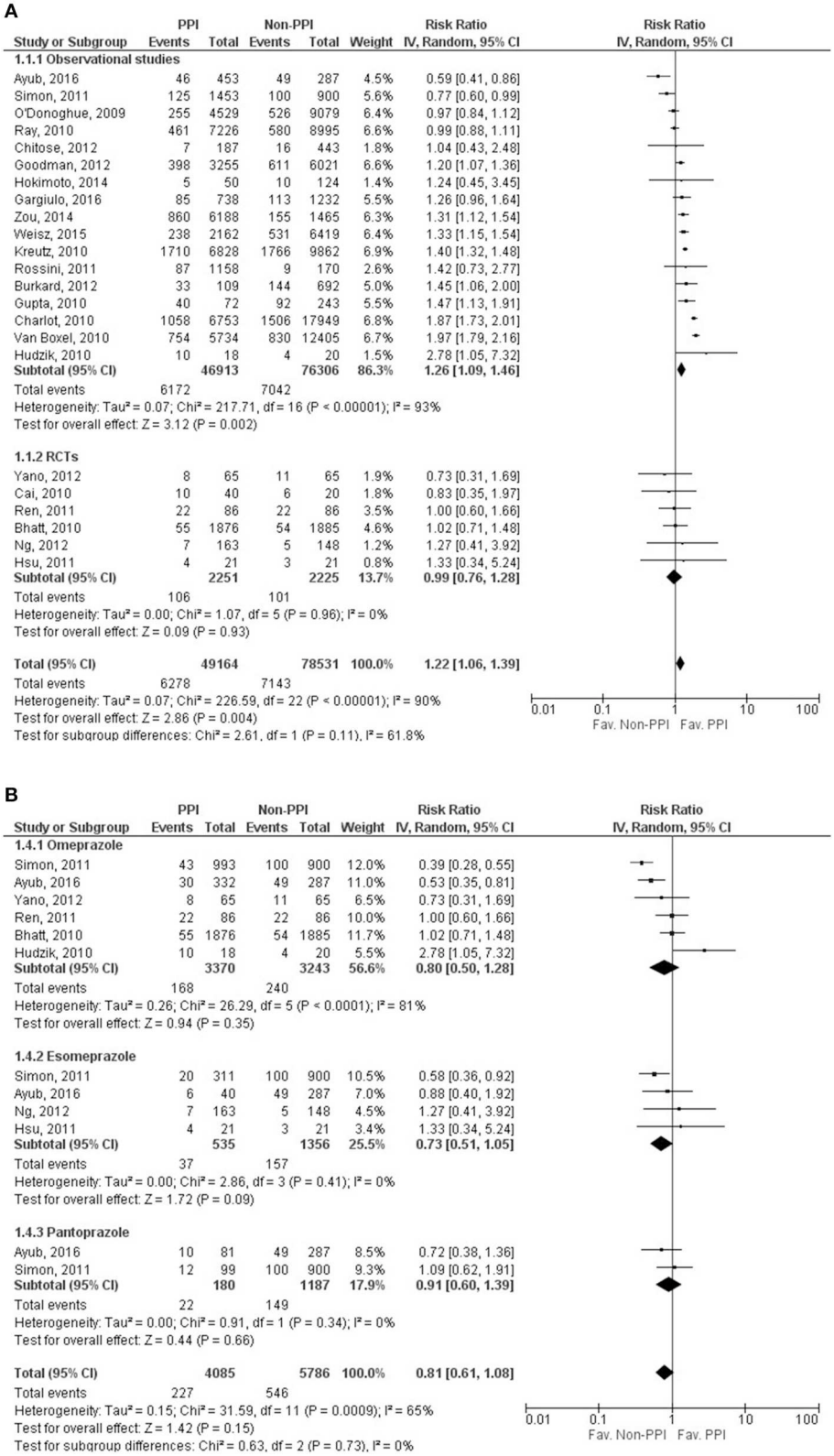

FIGURE 2 | Forrest plots representing the estimated risk of overall major adverse cardiac events **(A)** and in case of taking specific proton pump inhibitors **(B)** CI, confidence interval; PPI, proton pump inhibitor; RCT, randomized controlled trials.

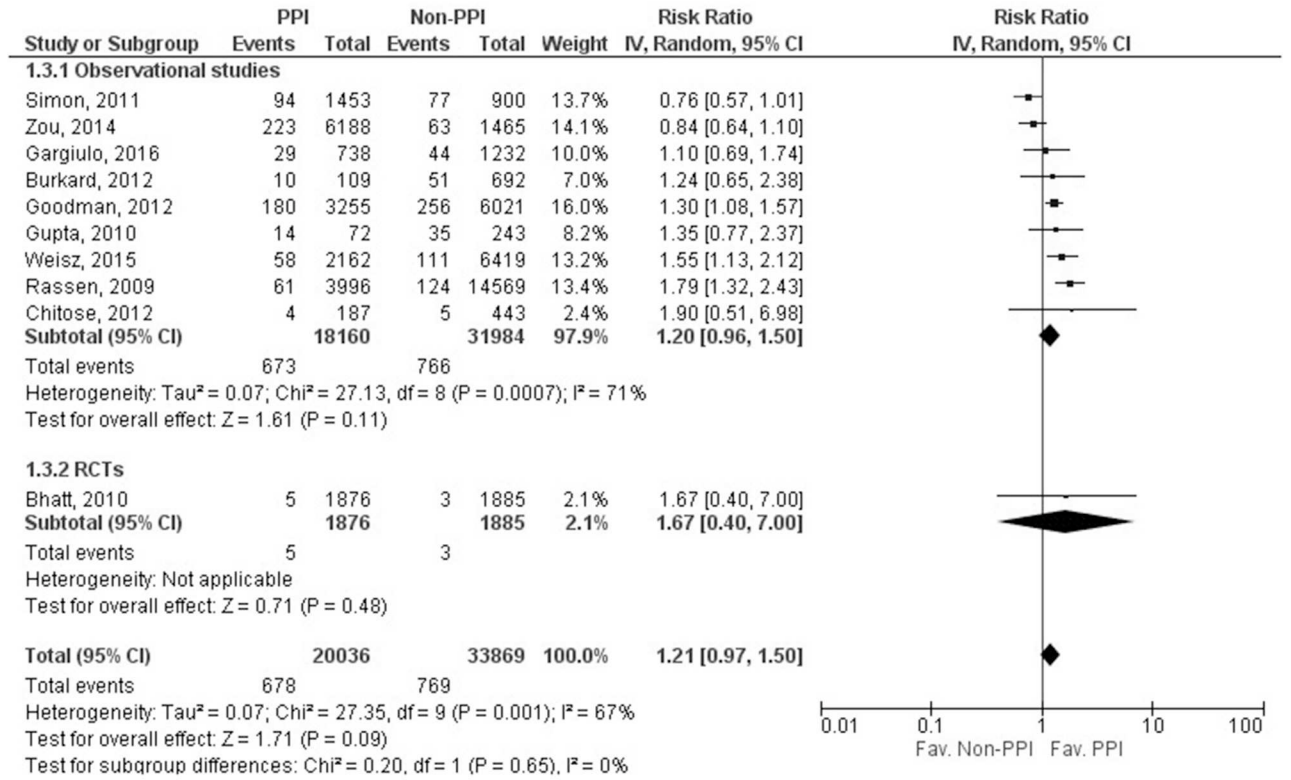

FIGURE 3 | Forrest plot representing the estimated risk of cardiovascular death. CI, confidence interval; PPI, proton pump inhibitor; RCT, randomized controlled trials.

SE = 0.022; 95% CI = −0.009 to 0.079, $p = 0.12$). Unfortunately, the low amount of data prevented us from evaluating the risk of CV death in specific PPIs (**Figure 3**, **Supplementary Figure 2**). Analysis of the adjusted events for CV death can be found in the **Supplementary Material**.

Myocardial Infarction

Fourteen of the twenty-seven studies contained eligible data on MI, with data for 82,330 patients for evaluation (Rassen et al., 2009; Bhatt et al., 2010; Evanchan et al., 2010; Hudzik et al., 2010; Stockl et al., 2010; van Boxel et al., 2010; Simon et al., 2011; Burkard et al., 2012; Chitose et al., 2012; Goodman et al., 2012; Shih et al., 2014; Zou et al., 2014; Weisz et al., 2015; Gargiulo et al., 2016); one study's data was evaluated as RCT (Bhatt et al., 2010). The risk of MI was significantly higher in the PPI group (RR = 1.43, 95% CI = 1.24–1.66, $p < 0.001$). The results from the statistical analysis may represent substantial heterogeneity across the studies ($I^2 = 66\%$, $p < 0.001$) (**Figure 4A**, **Supplementary Figure 3A**). Similarly to MACE and CV death, MI was not depending on the length of follow up or on the patients' age based on the included fourteen studies (follow up: SE = 0.005, 95% CI = −0.005 to 0.013, $p = 0.41$; age: SE = 0.013, 95% CI = −0.045 to 0.007, $p = 0.15$). We only found two eligible articles (Bhatt et al., 2010; Hudzik et al., 2010) for MI in the case of omeprazole, where there was no difference in risk between the observed groups (RR = 1.98, 95% CI = 0.31–12.76, $p = 0.47$). There may be substantial heterogeneity across the studies ($I^2 = 69\%$, $p = 0.07$); the random effects model was used (**Figure 4B**, **Supplementary Figure 3B**). We present the result for the analysis of adjusted MI events in the **Supplementary Material**.

Risk of Bias Within Studies

Risk of bias was assessed in 17 non-RCT studies (Rassen et al., 2009; Charlot et al., 2010; Evanchan et al., 2010; Gupta et al., 2010; Hudzik et al., 2010; Kreutz et al., 2010; Ray et al., 2010; Stockl et al., 2010; van Boxel et al., 2010; Rossini et al., 2011; Simon et al., 2011; Chitose et al., 2012; Hokimoto et al., 2014; Shih et al., 2014; Zou et al., 2014; Weisz et al., 2015; Ayub et al., 2016), four *post-hoc* analyses of RCTs (O'Donoghue et al., 2009; Burkard et al., 2012; Goodman et al., 2012; Gargiulo et al., 2016), and in six RCTs (Bhatt et al., 2010; Cai et al., 2010; Hsu et al., 2011; Ren et al., 2011; Ng et al., 2012; Yano et al., 2012). The risk of bias within the 27 studies included in this meta-analysis is summarized in the **Supplementary Figures 7A,B**.

Publication Bias

Funnel plots were constructed for each outcome and showed symmetry on visual inspection, suggesting that publication bias was not large and was unlikely to alter conclusions (**Figures 5A–C**).

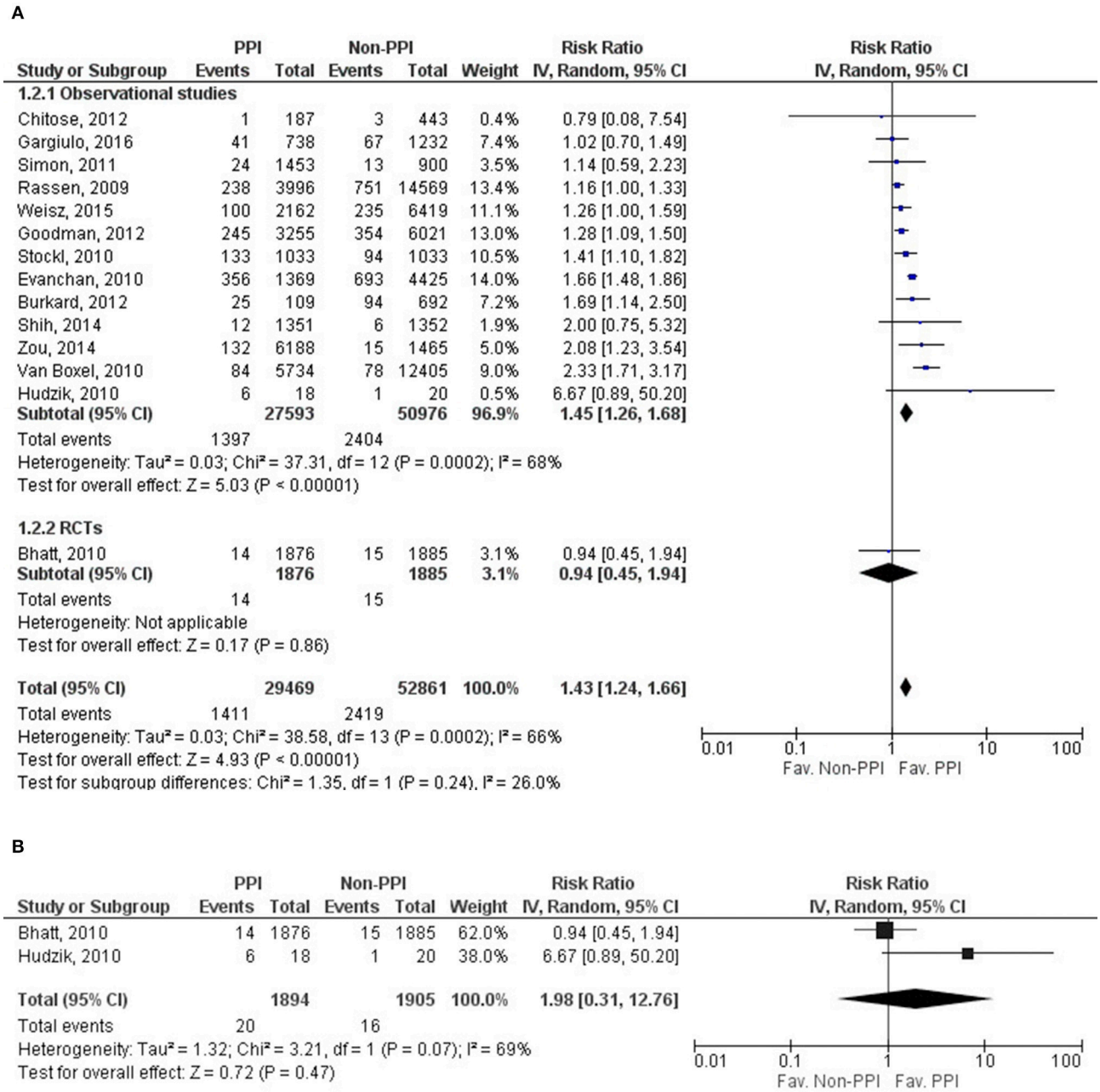

FIGURE 4 | Forrest plots representing the estimated risk of overall myocardial infarction **(A)** and in case of applying omeprazole as proton pump inhibitor **(B)** CI, confidence interval; PPI, proton pump inhibitor; RCT, randomized controlled trials.

DISCUSSION

A possible interaction between clopidogrel and PPIs came to the fore after an observational study had been performed in 2006, which found clopidogrel activity on platelets was diminished in patients receiving PPI treatment (Gilard et al., 2006). Later, this potential interaction was tested in the randomized controlled OCLA (Omeprazole CLopidogrel Aspirin) study, where omeprazole significantly decreased the effect of clopidogrel on *in vitro* platelet activation (Gilard et al., 2008).

Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation through irreversible inhibition of the ADP/P2Y12 receptor on the surface of platelets, and, being a prodrug, it requires a two-step oxidative biotransformation intrahepatically, mediated mainly by cytochrome P450 isoenzymes. First, the cytochrome P450 isoenzymes CYP1A2, CYP2B6, and CYP2C19 form 2-oxo-clopidogrel, which is then oxidized by CYP2B6,

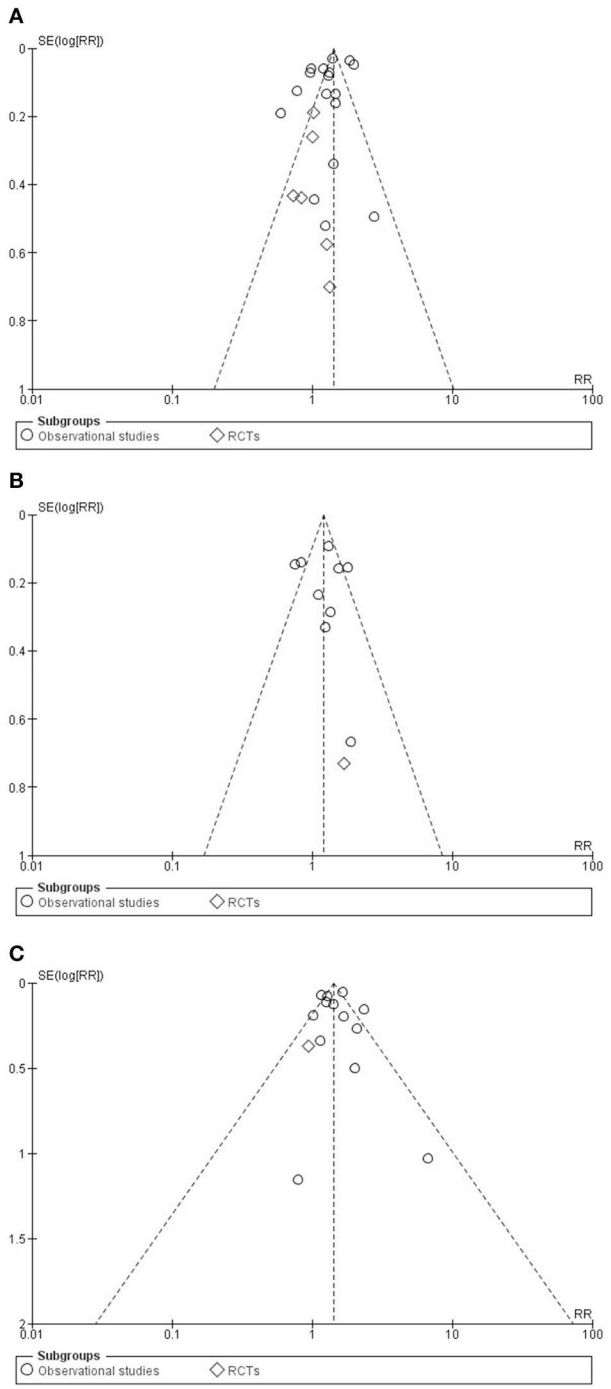

FIGURE 5 | Funnel plots for studies in major adverse cardiac event **(A)**, in cardiovascular death **(B)** and in myocardial infarction **(C)** groups.

CYP2C19, CYP2C9, and CYP3A4 to the active metabolite of clopidogrel, with CYP2C19 being the most important isoenzyme. The active metabolite then binds irreversibly to platelet adenosine diphosphate receptor P2Y12 (Hulot et al., 2006; Disney et al., 2011; Tantry et al., 2011), therefore preventing platelet aggregation. This is associated with the dephosphorylation of the intraplatelet vasodilator-stimulated phosphoprotein. Vasodilator-stimulated phosphoprotein phosphorylation provides an index to evaluate platelet reactivity to clopidogrel (Ward and Kearns, 2013). The findings on mechanisms underlying clopidogrel resistance are contradictory; these mechanisms may relate to heterogeneity in clopidogrel metabolism. CYP2C19 activity can have a profound effect on the conversion of clopidogrel to its active metabolite (Hulot et al., 2006).

All PPIs are extensively metabolized to inactive metabolites mainly via CYP2C19 and CYP3A4 in the liver. Rabeprazole uses these enzymes the least, being mostly converted to its thioether analog non-enzymatically. The potency and specificity of five individual PPIs (omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole) with regard to their inhibitory effects on the activities of four major human CYP enzymes (CYP2C9, CYP2C19, CYP2D6, and CYP3A4) have been studied by Li et al (Li et al., 2004). Lansoprazole was the most potent inhibitor of CYP2C19 enzyme *in vitro*, followed by omeprazole and esomeprazole. Pantoprazole showed the lowest potential to CYP2C19, however it was at least twice as potent an inhibitor as other PPIs toward CYP2C9 and CYP3A4. As the metabolite of rabeprazole, rabeprazole thioether was a strong and competitive inhibitor of CYP2C9, CYP2C19, and CYP2D6. It has been suggested that rabeprazole has significantly less drug-drug interactions than other PPIs, and the main reason is claimed to be its non-enzyme catalyzed degradation, but the results of Li et al suggest that omeprazole and rabeprazole have similar affinity to CYP3A4 (Li et al., 2004; Ogawa and Echizen, 2010). The potential interaction mechanism lies in the fact that both clopidogrel and PPIs, in varying degrees, are metabolized by the same cytochrome P450 enzyme (CYP2C19). PPIs have the potential to competitively inhibit the metabolism of clopidogrel to its active metabolite, which leads to reduced circulating concentrations of the active compound (Disney et al., 2011).

The data on the interactions between clopidogrel and PPIs remain unclear despite the numerous *in vitro* and *in vivo* studies on the subject. The *in vitro* studies have shown that the effectiveness of clopidogrel decreases with simultaneous use of clopidogrel and PPIs (Gilard et al., 2008), and, therefore, the risk for CV events will be elevated. Several possible causative factors may lie behind this phenomenon. One of them is the connected bio-transformational route of clopidogrel and PPIs, or the possible differences in genetic polymorphism of these enzymes (Hulot et al., 2006). There are several studies, mostly observational ones, whose findings are consistent with these *in vitro* results, showing an elevated risk for CV side-effects in patients on combined clopidogrel and PPI treatment (Pezalla et al., 2008; Ho et al., 2009; Juurlink et al., 2009; Kreutz et al., 2010). However, it should be noted that prophylactic PPIs are more likely prescribed to patients with a higher risk for CV events (Disney et al., 2011).

There is considerable disagreement between the various clinical studies that show no increased risk of CV outcomes (O'Donoghue et al., 2009; Rassen et al., 2009; Bhatt et al., 2010; Ray et al., 2010; Zairis et al., 2010). Furthermore, a few studies found no difference in the possible disadvantageous effect of PPI

drugs causing extended inhibition of CYP2C19 (O'Donoghue et al., 2009; Zairis et al., 2010). In several cases, the authors used multivariable adjustments for covariates to standardize because the effect of possible factors (such as age, co-morbidities, and co-medication) could modify the outcomes (Rassen et al., 2009; Valkhoff et al., 2011). In a well-designed case-control study, a current PPI plus clopidogrel group result was compared to the results for patients on current clopidogrel plus past PPI therapy. The association between PPI therapy and the recurrence of MI has disappeared suggesting that the appearance of recurrent MI is a result of a residual confounding (Valkhoff et al., 2011).

Based on the ACCF/ACG/AHA 2010 Expert Consensus Document (Abraham et al., 2010) to reduce the risk of GI bleeding, PPIs are recommended among patients with history of upper GI bleeding or with multiple risk factors (e.g., advanced age, concomitant use of warfarin, steroid or NSAIDs, or *H. pylori* infection) for GI bleeding who require antiplatelet therapy. Patients with acute coronary syndrome and prior upper GI bleeding are at substantial CV risk, so dual antiplatelet therapy with concomitant use of a PPI may provide the optimal balance of risk and benefit. The risk reduction achieved by concomitant PPIs might outweigh any potential reduction in the CV efficacy of antiplatelet treatment because of a drug–drug interaction. Routine use of acid suppressant drugs is not recommended for patients at lower risk of upper GI bleeding, who have much less potential to benefit from prophylactic therapy. Clinical decisions regarding concomitant use of PPIs and thienopyridines must be based on whether the potential for benefit outweighs the potential for harm, considering both CV and GI complications. Furthermore, according to the European Cardiology Society's 2017 guideline (Ibanez et al., 2018) for the management of acute myocardial infarction in patients presenting with ST-segment elevation a PPI in combination with dual antiplatelet therapy is recommended (I/B recommendation) in patients at high risk of GI bleeding. Based on the recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines (Neumann et al., 2018) on myocardial revascularization every effort should be undertaken such as routine use of PPIs to avoid bleeding in patients after percutaneous coronary intervention requiring oral anticoagulation and dual antiplatelet therapy. These statements have been supported by several studies which showed that the risk of upper GI bleeding can be reduced in patients with clopigodrel by concomitant PPI treatment. The occurrence of GI bleeding were 0.2–1.2% (Bhatt et al., 2010), 0–2% (Chitose et al., 2012), 0.4–1.8% (Mo et al., 2015) in the PPI vs. non-PPI groups, respectively.

In this meta-analysis, our aim was to focus on this discrepancy and to find a possible resolution. Our combined data from all of the studies involved showed that the presence of MACE and MI is significantly higher in the PPI plus clopidogrel patient population, a finding which is consistent with results from previous observational studies (Ho et al., 2009; Juurlink et al., 2009; Charlot et al., 2010; Gupta et al., 2010; Hudzik et al., 2010; van Boxel et al., 2010). However, in reducing the degree of heterogeneity by creating subgroups based on study design, we also found that this previously experienced risk elevation and heterogeneity will disappear as in other studies (Kwok and Loke, 2010). This result is similar to those of previous meta-analyses, where a higher CV risk was found among observational studies without any difference between the clopidogrel plus PPI group and the no PPI group in RCTs (Chen et al., 2012). In previous meta-analyses by Mo et al. (2015) and Chen et al. (2013), data only collected from RCTs showed no correlation between simultaneous clopidogrel and PPI therapy and elevated CV risk. An examination of the results, heterogeneity and risk of bias of the studies involved in our meta-analysis points to the low quality of observational studies, whose results are opposite to those of RCT studies, all proving an acceptance of results from RCT studies showing no enhancement of CV risks due to PPIs.

Although our meta-analysis has shown that there is no association between CV risk elevation and PPI usage, our analysis might have limitations. One is that in the 22 studies included, the population had previously had CV diseases, had already undergone percutaneous coronary intervention, or had received dual antiplatelet therapy, meaning that the population under examination may have had severe conditions. In this meta-analysis, we did not analyze the effect of these or other co-morbidities nor evaluate their conditions, but it is possible that the harmful effect of PPIs may be different in patients who need primary or secondary CV prevention. Although we performed secondary analyses on adjusted events, the conclusions drawn from these analyses are limited, because of the insufficient availability of these values across all studies, which were all observational ones, and the applied covariates were different among them. The studies published and available in the databases provided poor descriptions of other risk factors (such as co-morbidities, co-medications, smoking, obesity etc.), preventing us from providing a summary or conclusion in that regard. The other limitation of our study is the substantial heterogeneity among the studies, which may stem from several factors, such as differences in study design. In observational studies or in *post-hoc* analyses of RCTs, the groups were not allocated randomly. It was usually the physicians' decision, so this most likely led to a distortion of the results. Therefore, risk of bias within studies should be highlighted, as well. Though the open-label design might have a less prominent effect on hard CV outcomes, lack of blinding should be mentioned, even in RCTs. In addition, incomplete follow-up and not carefully applied objective evaluation of ascertainment of drug exposures may impose additional risk of bias. Bias is inherent in observational studies, the subgroup analysis of RCTs and observational studies yielding discrepant results support this statement. And there is a problem with the definition of MACE, which is not standard in the literature, although it is most often used to express the CV risk of PPIs plus clopidogrel.

Our aim was to draw conclusion from data for a large patient population; we therefore included as many observational studies as the inclusion criteria permitted despite their limitations. Patients were selected from various ethnic groups; they thus represent the world population. With a few years having passed since previous meta-analyses were published on the subject (the last study in these meta-analyses having been published in 2014) (Mo et al., 2015; Sherwood et al., 2015; Serbin et al., 2016), and

with new studies having been carried out since then, we were prompted to perform this systematic search and meta-analysis to re-evaluate the risks.

CONCLUSION

Our meta-analysis has shown that there is no definitive evidence for any significant association between CV risk elevation and PPI in patients on clopidogrel treatment, based on RCTs. Thus, no definitive evidence exists for an effect on mortality. From this point of view, the previous FDA guidance to use favorable or non-favorable drug combinations does not seem to be relevant by now based on both previous trials (e.g., COGENT, TRITON-TIMI) and our own analyses. However, taking into account the bias, this meta-analysis should be interpreted with caution, and conducting further RCTs would be beneficial. Because PPI induced risk reduction clearly outweighs the possible adverse CV risk in patients with a high risk of GI bleeding, a combination of clopidogrel with PPI should be recommended.

AUTHOR CONTRIBUTIONS

All the authors were involved in the study design and edited, read, and approved the final manuscript. During the study, AD and EB performed the literature search and extracted data from the studies involved. KM, AM, ZS, and DP rechecked the studies involved for inclusion and exclusion criteria. PeH, JB, and ÁV formed a committee to decide on points of contention. AD, LC, HA, and ZG assessed the risks of bias in the studies involved. AD and PéH created the risk-related figures. TL performed the statistical analysis and created the forest and funnel plot figures. AD, IS, and PéH drafted the manuscript. All the authors approved the final draft. PéH and IS contributed equally to this article.

FUNDING

This study was supported by an Economic Development and Innovation Operative Programme Grant (GINOP 2.3.2-15-2016-00048 to PéH), an Institutional Developments for Enhancing Intelligent Specialization Grant (EFOP-3.6.1-16-2016-00022 to PéH) of the National Research, Development and Innovation Office, and the ÚNKP-17-3-I. New National Excellence Program, Ministry of Human Capacities (PTE/46539/2017 to KM).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2018.01550/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.