Should patients prescribed long-term low-dose aspirin receive proton pump inhibitors?

A systematic review and meta-analysis

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SUMMARY

Background: Several clinical guidelines recommend the use of proton pump inhibitors (PPIs) in patients taking low-dose aspirin but report no or limited supporting data. We conducted a systematic review and meta-analysis to examine the effects of co-administration of PPIs in patients taking low-dose aspirin on the risks of adverse gastrointestinal (GI) and cardiovascular (CV) events, and on patient adherence to aspirin. **Methods:** We searched PUBMED, EMBASE and Cochrane Central Register of Controlled Trials databases for relevant articles published through November 2013. We included randomised controlled trials (RCTs) and observational studies in patients taking low-dose aspirin with and without PPIs. Risk of bias was assessed using the Cochrane Collaboration's tool (for RCTs) and the Newcastle-Ottawa Scale (for observational studies). Pooled risk ratios (RRs) were computed using a random-effects model. **Results:** We included 13 studies, of which 12 (2 RCTs and 10 observational studies) reported on GI events, and one (cohort study) on both GI bleeding and CV events. No study reported on adherence to aspirin. Co-administration of PPIs in patients receiving low-dose aspirin was associated with risk reductions of 73% (RR 0.27, 95% CI 0.17–0.42) and 50% (RR 0.50, 95% CI 0.32–0.80) in the occurrence of peptic ulcer and GI bleeding respectively. There was evidence of bias in publications reporting on the GI events. **Conclusions:** The practice of co-prescribing PPIs in patients taking low-dose aspirin is supported by some data, but the evidence is rather weak. It currently remains unclear whether the benefits of co-administration of PPIs in users of low-dose aspirin outweigh their potential harms.

Review criteria

- Randomised controlled trials (RCTs) and observational studies in patients receiving low-dose aspirin.
- Studies reporting on adverse gastrointestinal or cardiovascular events, or adherence to aspirin.
- RCTs comparing proton pump inhibitors (PPIs) with placebo, and observational studies assessing the association of concomitant use of aspirin and any PPIs, against the use of aspirin alone, with the outcomes of interest.

Message for the clinic

- Currently there is a lack of evidence and guidelines to support co-administration of PPIs in different patient groups receiving long-term low-dose aspirin, especially in those with low risk of upper gastrointestinal bleeding.
- The benefit-risk ratio of co-administration of PPIs in chronic aspirin users currently remains unclear.

Introduction

Proton pump inhibitors (PPIs) are widely used for prevention and treatment of peptic ulcer disease. Recently, concerns have been expressed about the worldwide overprescription of PPIs in both primary and secondary care (1,2), suggesting a lack of evidence that the benefits outweigh the harms of PPIs.

Patients receiving low-dose aspirin (30–325 mg/day) constitute by far the largest proportion of the population taking antiplatelet drugs to prevent adverse cardiovascular (CV) events. These patients are at risk of peptic ulcer and ulcer complications (3–7), and for that reason are frequently prescribed PPIs. Although several guidelines recommend PPI use in patients receiving low-dose aspirin (8–12), no or limited supporting data are reported (Table 1).

These guidelines generally recommend PPIs in patients at a very high risk of gastrointestinal (GI) bleeding (e.g. a history of peptic ulcer), but are less clear regarding patients at lower risk. On the other hand, no recommendation regarding the use of PPIs in chronic aspirin users is made in other influential guidelines for prevention and management of CV diseases, such as the American Heart Association (AHA) (20–23), European Society of Cardiology (24), Joint British Societies (25) and World Health Organisation guidelines (26).

The argument for prescribing PPIs to prevent GI injury relates to the suppressive effect of these drugs on gastric acid secretion. However, acid does not seem to be an obligatory factor leading to GI injury since aspirin-induced ulcers can develop in an achlorhydric environment (27). Aspirin can accumulate

Table 1 Summary of guidelines recommending co-administration of proton pump inhibitors (PPIs) in aspirin users

Institution	Year	Aim of the guideline	Population considered for a PPI therapy	Risk factors in patients eligible for PPIs	Cited studies supporting co-administration of PPIs in aspirin user
American College of Cardiology Foundation (ACCF) Task Force, American College of Gastroenterology (ACG), and American Heart Association (AHA) (8)	2008	To inform practitioners, payers and other interested parties of the expert consensus on reducing the GI risks of antiplatelet agents and NSAIDs	Patients receiving antiplatelet agents or NSAIDs	History of peptic ulcer or ulcer complications, or Age $\geq$ 60 years, or Use of corticosteroid, or Dyspepsia or GERD symptoms	Two case-control studies (13,14), one cohort study (15) and one RCT (16); In Chin et al. (14), effect of PPIs on UGIB was not separated for patient groups on different antiplatelet (e.g. aspirin) and anticoagulant drugs; In Lanas et al. (15), and Lai et al. (16) only patients with a history of ulcer complications were included; In Lanas et al. (15), there was no direct comparison between patient groups with and without a PPI therapy Not reported
European Society of Cardiology (ESC) (9)	2011	To assist physicians in management of acute coronary syndromes in patients presenting without persistent ST-segment elevation	Patients receiving antiplatelet agents	History of peptic ulcer or GI bleeding, or Multiple other risk factors such as <i>H. pylori</i> infection, age $\geq$ 60 years and concurrent use of anticoagulants or steroids	Not reported
National Institute for Health and Clinical Excellence (NICE) (10)	2007	To assist healthcare professionals, patients and other stakeholders in management of postmyocardial infarction	Patients after an myocardial infarction	History of dyspepsia, or History of aspirin-induced ulcer bleeding	Not reported
International Consensus Conference organised by the Canadian Association of Gastroenterology (11)	2008	To provide an international consensus recommendations for the management of patients with non-variceal UGIB	Patients receiving antiplatelet agents or NSAIDs	History of GI bleeding	Two RCTs (17,18); In both studies, only patients with a history of ulcer complications were included
Dutch College of General Practitioners (12)	2013	To guide diagnosis and management of adults with dyspepsia in general practice	Patients receiving aspirin as an antiplatelet agent	Age $\geq$ 60 years and a history of peptic ulcer or ulcer complications, or Age $\geq$ 70 years and simultaneous use of another (non-aspirin) drug, which increases the risk of ulcer complications such as an oral anticoagulant, an P2Y12 inhibitor (e.g. clopidogrel), an NSAID or an oral corticosteroid, SSRI, venlafaxine, duloxetine or spironolactone, or Age $\geq$ 80 years	Two RCTs (16,19); In Lai et al. (16), only patients with a history of ulcer complications were included; In Yeoman et al. (19), only patients aged 60 years or higher were included

CV, cardiovascular; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; RCT, randomised controlled trial; SSRI, selective serotonin reuptake inhibitor; UGIB, upper gastrointestinal bleeding.

within epithelial cells of the stomach and duodenum and subsequently cause lysis (28). Also, aspirin impairs GI defence mechanisms, making epithelial cells more susceptible to topical attack by endogenous factors like acid and pepsin (29,30). Suppressing acid secretion is, therefore, unlikely to completely prevent adverse GI events in patients receiving aspirin. This raises the question to what extent PPIs reduces the risk of adverse GI events. In addition, co-administration of PPIs may affect the CV preventive effects of low-dose aspirin in several ways; on the one hand, increased adherence to low-dose aspirin because of improved tolerability may enhance CV risk reduction; on the other hand, a PPI-induced reduction in the bioavailability of aspirin (31–33) may diminish the CV preventive effect of aspirin. So far, the overall risk-benefit ratio of co-administration of PPIs in patients receiving low-dose aspirin has not been established.

We performed a systematic review to determine whether, in patients on long-term low-dose aspirin and without a history of peptic ulcer or ulcer complications, co-administration of PPIs (i) reduces the risk of adverse GI events, (ii) modifies the risk of adverse CV events and (iii) increases adherence to aspirin prescriptions.

Methods

Data sources and search strategy

We searched PUBMED, EMBASE and Cochrane Central Register of Controlled Trials in November 2013 to identify all English-language studies on co-therapy with PPIs in patients receiving long-term aspirin for prevention of CV events. We used the search terms ‘acetylsalicylic acid’, ‘aspirin’, ‘proton pump inhibitor’, ‘omeprazole’, ‘esomeprazole’, ‘pantoprazole’, ‘lansoprazole’, ‘dexlansoprazole’, ‘rabeprazole’, ‘gastric’, ‘duodenal’, ‘peptic’, ‘gastroduodenal’, ‘gastro-intestinal’, ‘ulcer’, ‘injury’, ‘damage’, ‘bleeding’, ‘h(a) emorrhage’, ‘obstruction’, ‘perforation’, ‘toxicity’, ‘symptom’, ‘complication’, ‘cardiac’, ‘cardiovascular’, ‘coronary’, ‘carotid’, ‘artery’, ‘atherosclerotic’, ‘diabetes’, ‘event’, ‘risk’, ‘diseases’, ‘heart attack’, ‘myocardial infarction’, ‘stroke’, ‘death’, ‘mortality’, ‘survival’, ‘compliance’ and ‘adherence’. Detailed search queries are provided in Appendix A. We also manually scanned the bibliographies of relevant articles for additional studies.

Eligibility criteria

We included randomised controlled trials (RCTs) and observational studies (i.e. cohort or case-control studies) published through November 2013 that met the following criteria: (i) participants were receiving

low-dose aspirin, defined as 75–325 mg daily, for CV prevention, and (ii) studies reported on any of the following outcomes: peptic ulcer, GI bleeding, gastric-outlet obstruction, gastric perforation, myocardial infarction, ischaemic stroke or CV death and adherence to aspirin.

For RCTs, we included studies that compared PPIs with placebo. For the observational studies, we included studies that assessed the association of concomitant use of aspirin and any PPIs, against the use of aspirin alone, with any of the above-mentioned outcomes. We excluded studies in which participants (i) were concomitantly receiving clopidogrel or any non-steroidal anti-inflammatory drug other than aspirin and (ii) had a history of peptic ulcer or ulcer complications.

Study selection and data extraction

The studies were reviewed in two stages by two independent reviewers (ATD and FHV). In the first stage, the titles and abstracts of all retrieved articles were screened to assess whether the studies met the inclusion criteria and did not meet the exclusion criteria. Where there was any uncertainty about the inclusion of a study, this issue was discussed between the two reviewers. Disagreements were referred to a third reviewer (CDAS or AWH) to achieve a resolution. In the second stage, full text of the potentially relevant studies were retrieved and reviewed using the same methods for selection and disagreement resolution as in the first stage. The following information was independently extracted from the included studies and jointly verified for accuracy: first author’s surname, year of publication, country of study, study design, number of participants, duration of drug exposure, relevant outcomes, outcome definitions and characteristics of participants. We contacted authors when there was unclear information.

We assessed the methodological quality of the observational studies using the Newcastle-Ottawa Scale (NOS; ranging 0–9) (34) as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (35). On this scale, a study is judged by giving points (stars in the NOS terminology) to items belonging to three categories: selection of the study groups, the comparability of the groups and the ascertainment of the exposure (for case-control studies) or outcome of interest (for cohort studies) (see Appendix B for details). To assess the risk of bias in RCTs, we used the Cochrane Collaboration’s tool, which addresses the following domains: sequence generation, concealment of allocation sequence, blinding, incomplete outcome data, selective outcome reporting and any other problems that could put the studies at risk of bias.

Data synthesis and analysis

Risk or rate ratios (RRs) with a 95% confidence interval (CI) were calculated to quantify treatment effects. In case-control studies, odds ratios (ORs) were assumed to provide valid estimates of RRs (36). In cohort studies, we used the reported RRs adjusted for potential confounders whenever available. If RRs were not reported, we computed them by using raw data (if available) or by converting the reported ORs to RRs according to the Cochrane Handbook for Systematic Reviews of Interventions: $RR = OR / [1 - ACR \times (1 - OR)]$, where ACR is assumed control risk (the rate of the event in the control group) (35). Hazard ratios were accepted as RRs. Pooled RRs were computed using a random-effects model.

The heterogeneity across studies was tested by the Q-statistic and quantified by the total inconsistency in the study results (I^2) and the between-study variance (τ^2) (37,38). Subgroup analysis was also performed to assess the potential impact of quality of observational studies ($NOS \geq 5$ vs. $NOS < 5$), duration of PPI exposure (≥ 2 months and > 7 days) and study design (RCTs vs. observational studies) on the effect estimates. In a sensitivity analysis, the influence of individual studies on the summary statistics was examined by omitting one study at a time from the meta-analysis. Publication bias was assessed using funnel plots and Egger's regression test of funnel plot asymmetry (39).

All statistical analyses were performed using the R package metaphor (40). A p-value < 0.05 was considered statistically significant.

Results

Figure 1 shows the flow chart of the selection of studies. The search identified 347 studies. After screening the titles, abstracts and full text, 13 studies were considered eligible for complete data extraction. Of these, four cohort studies (41–44) reported on the effect on peptic ulcer, five studies [two cohort (45,46) and three case-control studies (13,47,48)] on GI bleeding, three studies [two RCTs (19,49) and one cohort study (50)] on both GI bleeding and peptic ulcer, and one cohort study (51) on both GI bleeding and CV events. Among nine studies that reported on GI bleeding, six studies indicated the outcomes as upper GI bleeding (UGIB) while the others did not specify the location of the bleeding. We found no studies investigating the effect of PPIs on adherence to aspirin. Table 2 shows the main characteristics of the included studies and Table 3 shows outcomes, characteristics of the drug treatments and study quality (for detailed

quality assessment of the observational studies, see Appendix B).

Impact of PPIs on peptic ulcer

Pooled effect

Two RCTs and five cohort studies reported on the effect on peptic ulcer. Only two (43,44) of the five cohort studies adjusted the effect estimates for potential confounding. A total number of 5407 patients (2608 patients on PPIs) were included in the analysis. The directions of the estimated RRs and their 95% CIs were consistently in favour of PPI use in all studies. When all the estimates were pooled, concomitant use of PPIs was associated with a 73% risk reduction compared with no PPI therapy (pooled $RR = 0.27$; 95% CI = 0.17–0.42; $p < 0.001$; Figure 2A). Significant heterogeneity was present across studies ($p = 0.0013$; $I^2 = 63.8\%$; $\tau^2 = 0.20$).

Subgroup analysis

The pooled RR (95% CI) of the estimates from the two RCTs was 0.21 (0.13–0.34); no significant heterogeneity between these RCTs was detected ($p = 0.26$; $I^2 = 21.3\%$; $\tau^2 = 0.03$). In contrast, significant heterogeneity was present across the five cohort studies ($p = 0.03$; $I^2 = 58.6\%$; $\tau^2 = 0.26$), of which the pooled RR (95% CI) was 0.29 (0.16–0.53).

Among the cohort studies, the pooled RR (95% CI) of the estimates from those with higher quality ($NOS > 5$; three studies) was 0.37 (0.20–0.72), against 0.17 (0.07–0.40) from those with lower quality ($NOS \leq 5$; two studies). Within each group, no significant heterogeneity was observed ($p > 0.1$).

The pooled RR (95% CI) of the estimates from the three studies with PPI exposure longer than 2 months was 0.28 (0.17–0.49), against 0.25 (0.13–0.50) from the four studies with PPI exposure longer than 7 days. Significant heterogeneity was absent in the former group ($p = 0.41$), but present in the latter ($p < 0.001$).

Sensitivity analysis

The sensitivity analysis showed that the direction of the effect of the use of PPIs on peptic ulcer was not influenced by any single study. Exclusion of any single study, except for the study by Yamamoto et al. (50), did not change the significance of the heterogeneity across the studies. When the study by Yamamoto et al. (50) was excluded, the estimated total inconsistency (I^2) and the between-study variance (τ^2) of the remaining studies were zero (the p-value of the Q-statistic was 0.55). This indicates that the study by Yamamoto et al. (50) was the single cause of statistical heterogeneity among the studies reporting on peptic ulcer.

Figure 1 Flow chart of study selection

Publication bias

Egger's regression test showed a tendency of publication bias ($p = 0.07$). The funnel plot (Figure 3A)

showed one study lying outside the triangle and an absence of small-size studies reporting smaller beneficial effects of PPI co-therapy on the risk of peptic ulcer.

Table 2 Characteristics of included studies

Author	Year	Study design; analysis type; country	Period of recruitment	No. patients receiving aspirin	No. patients receiving PPI	Mean age (SD or range)	% Male	Patient inclusion criteria	Patient exclusion criteria
de Berardis et al. (45)	2012	Cohort; retrospective; Italy	January 2003–December 2008	186 425	84 516	68.99 (11.83)	48.0	Patients aged between 30 and 95 years admitted to private and public hospitals with any primary diagnosis	Patients with prescription of aspirin in the past year, last prescription of aspirin > 75 days before a major bleeding event, and with diabetes without antidiabetic prescription
Charlot et al. (51)	2011	Cohort; retrospective; Denmark	1997–2006	19 925	4306	Patients treated with PPIs: 72.5 (12.1); Patients not treated with PPIs: 72.7 (12.6)	Patient treated with PPI: 53.9; Patient not treated with PPI: 53.2	Patients aged > 30 years admitted to hospital with a first MI and filled a prescription for aspirin within 30 days after discharge	Patients died before or within 30 days of discharge; patients on clopidogrel
Ibanez et al. (47)	2006	Case-control; retrospective; Spain and Italy.	September 1998–December 2001 and November 1999–December 2001	1109	44	Not reported.	Not reported	CASE: Patients aged > 18 years admitted to hospital with a primary diagnosis of acute UGIB from a duodenal or gastric ulcer, acute lesions of the gastric mucosa, erosive duodenitis or mixed lesions; CONTROL: For each case, up to three hospital controls were selected, matched according to center, date of admission (within 2 months), age ($\pm$ 5 years) and gender. Controls included patients admitted to hospital with non-alcohol related trauma, elective surgery for non-painful disorders and acute clinical conditions thought to be	For both CASE and CONTROL: Patients with endoscopic diagnoses other than bleeding from a duodenal or gastric ulcer, acute lesions of the gastric mucosa, erosive duodenitis or mixed lesions; patients on anticoagulant drugs

Table 2 Continued

Author	Year	Study design; analysis type; country	Period of recruitment	No. patients receiving aspirin	No. patients receiving PPI	Mean age (SD or range)	% Male	Patient inclusion criteria	Patient exclusion criteria
Lanas et al. (48)	2000	Case-control; prospective; Spain.	November 1995– February 1998	326	Not reported	CASE: 65.1 (16.6); CONTROL: 65.2 (16.7)	CASE: 69.3; CONTROL: 69.2	unrelated to the intake of the drugs of interest CASE: Patients admitted to hospital because of acute UGIB; CONTROL: For each case, two controls were selected to match age ($\pm$ 5 years) and gender. Controls included patients admitted to hospital and outpatients seen by family practitioners in the same geographical area as the hospital with any primary diagnosis that was neither an indication for nor a known complication of treatment with NSAIDs	CONTROL: Patients with the main reason for admission being painful skeletal-muscle disease, acute MI, acute PU, or UGIB or perforation
Lanas et al. (13)	2007	Case-control; retrospective; Spain	2001–2004	753	133	CASE: 66.1 (14.8); CONTROL: 67.3 (12.9)	CASE: 66.5; CONTROL: 45.9	CASE: Patients aged between 20 and 85 years admitted to hospital because of UGIB; CONTROL: For each case, two controls were selected to match age ($\pm$ 5 years), hospital, and the month of admission. Controls included patients admitted to hospital or were attending an outpatient visit for reasons considered to be unrelated to NSAIDs, either as an indication or contraindication	CASE: Patients with liver disease, coagulation disorders, or malignancies in the previous 5 years; CONTROL: Patients admitted to hospital for any upper GI disorder, lower GI bleeding, osteoarticular condition or CV disorder
Okada et al. (46)	2009	Cohort; prospective; Japan	January 2003– November 2007	453	40	72.5 (43–95)	65.8	Patients prescribed low-dose aspirin from hospital	Patients taking low-dose aspirin for < 7 days, diagnosed with or treated for aspirin-associated gastrointestinal mucosal injury in the past, diagnosed with gastric or duodenal cancer, undergone gastric or

Table 2 Continued

Author	Year	Study design; analysis type; country	Period of recruitment	No. patients receiving aspirin	No. patients receiving PPI	Mean age (SD or range)	% Male	Patient inclusion criteria	Patient exclusion criteria
Pilotta et al. (41)	2004	Cohort; prospective; Italy	January 1998–December 2001	245	49	79.7 (7.5)	45.7	Patients aged 65 years or more with gastrointestinal symptoms undergoing upper gastrointestinal endoscopy	oesophageal surgery, and with any current active cancer. Patients taking NSAID, with concomitant or recent antibiotic use, with gastric cancer or other neoplasms, with previous major uppergastrointestinal surgery and with contraindication to gastric biopsies (bleeding lesions, coagulation diseases and/or anticoagulant therapy)
Scheiman et al. (49)	2011	Randomised controlled trial; 20 countries	February 2007–August 2008	2426	1621	67.6 (21–89)		<p>Patients treated with 20 mg esomeprazole: 53.4; Patients treated with 40 mg esomeprazole: 53.5; Patients treated with placebo: 50.1</p> <p>Patients prescribed or recommended for daily use of low-dose aspirin and <i>H. pylori</i> negative at screening who fulfilled one or more following criteria: (i) aged ≥ 18 years with documented history of uncomplicated peptic ulcer; (ii) aged ≥ 60 years with ≥ 1 risk factor (stable coronary artery disease, complaints of upper gastrointestinal symptoms that, as judged by the investigators, required an endoscopy resulting in a finding of five or more gastric and/or duodenal erosions, or low-dose aspirin naïve) and (iii) aged ≥ 65 year</p>	<p>Patients with unstable hypertension, recent ACS, PCI, CABG, clinically relevant valvular disease, serious cardiac failure or stroke;</p> <p>Grade C-D erosive (reflux) oesophagitis, patient reported severe oesophagitis within 1 year, PU at baseline, history of PU complications (e.g. bleeding, perforation), and previous gastric or duodenal surgery;</p> <p>Patients with unstable DM, continuous treatment with an NSAID within 2 months, with on-going anticoagulant treatment, on drugs that interact with esomeprazole, on a PPI or prostaglandin analogue within 14 days of baseline endoscopy, and with a need for continuous treatment with</p>

Table 2 Continued

Author	Year	Study design; analysis type; country	Period of recruitment	No. patients receiving aspirin	No. patients receiving PPI	Mean age (SD or range)	% Male	Patient inclusion criteria	Patient exclusion criteria
Shiotani et al. (42)	2009	Cohort; prospective; Japan	January 2007– March 2008	305	95	71 (47–90)	65.9	Outpatients taking low-dose aspirin and recommended to undergo upper GI endoscopy for screening purposes	prostaglandin analogues or sucralfate Patients with recent (not defined) start or change in acid suppressing therapy, on other NSAIDs, and with history of gastrectomy, gastric cancer and/or other malignant lesions in the upper GI tract
Tamura et al. (43)	2010	Cohort; retrospective; Japan.	December 2005– November 2006 and January 2007– December 2007	400	80	71 (24–92)	62.5	Outpatients with cardiovascular or cerebrovascular disease, who had been receiving low-dose aspirin regularly for more than 1 month and undergone upper GI endoscopy	Patients with unstable ischaemic heart disease or with ischaemic heart disease after stenting treatment or open-heart surgery (i.e. coronary artery bypass graft) within the last 6 months, with unstable cerebrovascular disease or within 3 months after an episode, and with malignancy within 5 years after the diagnosis of malignancy; Patients after upper gastrointestinal tract, biliary tract or pancreatic disease surgery, within 1 month after any surgery, and with serious injury to the liver, kidney or lung
Tamura et al. (44)	2011	Cohort; prospective; Japan	January 2008– December 2008	150	53	71.6 (10.0)	68.0	Patients aged ≥ 20 years hospitalised to cardiology department or attending outpatient clinics and receiving low-dose aspirin and gastroprotective agents for at least 3 months	Patients with upper GI symptoms, changes of gastroprotective agents within the preceding 3 months; history of operations for the oesophagus, stomach and duodenum, ACS or stroke within the preceding 3 months, severe chronic heart failure and no malignant diseases
Yamamoto et al. (50)	2010		January 2005– December 2006	530	216	69.5 (11.3)	55.7	Patients undergoing upper GI endoscopy who had been	Patients with malignant diseases, haemorrhage

Table 2 Continued

Author	Year	Study design; analysis type; country	Period of recruitment	No. patients receiving aspirin	No. patients receiving PPI	Mean age (SD or range)	% Male	Patient inclusion criteria	Patient exclusion criteria
Yeomans et al. (19)	2008	Cohort; retrospective; Japan Randomised controlled trial; 10 countries	May 2004–October 2005	991	493	69.3 (6.6)	57.1	taking low-dose aspirin for 1 month or more Patients aged ≥ 60 years with a clinical diagnosis that required continuous oral treatment with aspirin 75–325 mg/day that was expected to continue for 26 weeks, (2) were negative <i>H. pylori</i> test, and (3) had no evidence of gastric or duodenal ulcer at baseline endoscopy	from variceal lesions and Mallory–Weiss syndrome Patients with recent positive <i>H. pylori</i> test and incomplete of eradication treatment, unstable angina, MI, stroke, transient ischaemic attack (within 3 months), erosive oesophagitis, Barrett's oesophagus any dysplastic changes in the oesophagus, any suspicion of endoscopic evidence of other gastroduodenal pathology, upper GI symptoms requiring treatment; Patients on NSAIDs, anticoagulants, oral corticosteroids > 10 mg/day prednisolone equivalent, phenytoin, ketoconazole, itraconazole, anticholinergics approved for gastrointestinal disorders, prostaglandin analogues, gastrin receptor blockers, sucralfate, or bisphosphonates; Patients taking PPI, prostaglandin analogue, or H2-receptor antagonist during 14 days before the baseline endoscopy

ACS, acute coronary syndromes; ARF, acute renal failure; CA, cardiac arrhythmias; CABG, coronary artery bypass grafting; CRF, chronic renal failure; CVD, cerebral vascular disease; DM, diabetes mellitus; GI, gastrointestinal; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; PU, peptic ulcer; UA, unstable angina; UGIB, upper gastrointestinal bleeding.

Table 3 Outcomes, characteristics of drug treatments and study quality

Author	Year	Outcome	Outcome definition	Symptom*	Aspirin use	Proton pump inhibitor use	Study quality
de Berardis et al. (45)	2012	Major GI bleeding	Based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)	Not reported	Dose: ≤ 300 mg/day; Exposure time: ≥ 60 days	Type: not reported	NOS = 7
Charlot et al. (51)	2011	All cause death, CV death, readmission to hospital for MI or stroke; GI bleeding	Based on International Classification of Diseases (ICD-9-CM)	Not reported	Dose: 75–150 mg/day; Exposure time: > 3 months	Type: Omeprazole (29.4%), esomeprazole (26.5%), pantoprazole (26.2%), lansoprazole (17.2%), rabeprazole (0.01%); Dose: Not reported; Exposure time: Not reported	NOS = 9
Ibanez et al. (47)	2006	UGIB	Acute UGIB leading to hospital admission, confirmed by endoscopy	Not reported	Median dose: 160 and 150 mg/day for cases and controls respectively; Exposure time: Not reported	Type: omeprazole (over 80%); other types not reported; Dose: Not reported; Exposure time: > 7 days	NOS = 5; No adjustment for baseline difference
Lanas et al. (48)	2000	UGIB	Haematemesis and/or melena that was confirmed by hospital records, accompanied by evidence that peptic lesions (including ulcers, erosions and acute mucosal lesions) of the upper GI tract were the cause of the bleeding episode, as documented by endoscopy performed within the first 24 h after hospital admission	Haematemesis and/or melena	Dose: ≤ 300 mg/day; Exposure time: 91.6% of cases and controls > 3 months	Type and dose: Omeprazole 20 mg (92%); other types not reported; Exposure time: > 7 days	NOS = 6; Odds ratio adjusted using univariate logistic regression for age, sex, UGIB history, peptic ulcer history, CV disease, cerebrovascular disease, NSAID use, nitrovasodilator use, antacid use, H2RA use and hospital
Lanas et al. (13)	2007	UGIB	Haematemesis and/or melena that was confirmed by endoscopically diagnosed peptic ulcers or acute mucosal lesions of the gastroduodenal tract	Haematemesis and/or melena	Dose: 100–300 mg/day; Exposure time: > 7 days	Type: Any types available on the market, including omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole; Dose: Any doses (figures not reported); Exposure time: > 7 days	NOS = 6; Relative risk adjusted using logistic regression for age, sex, ulcer history and use of nitrate, gastroprotective drugs and NSAIDs

Table 3 Continued

Author	Year	Outcome	Outcome definition	Symptom*	Aspirin use	Proton pump inhibitor use	Study quality
Okada et al. (46)	2009	UGIB	Occurrence of melena and/or haematemesis confirmed by hospital staff and bleeding erosions or bleeding ulcers confirmed by endoscopy; subnormal haemoglobin or decrease in the haemoglobin level by at least 2.0 g/dl within a period of 4 weeks in the presence of potential bleeding sites in the stomach or duodenum identified by endoscopy	Not reported	Dose: 81–100 mg/day; Exposure time: > 7 days	Type and dose: lansoprazole 15–30 mg (71%), rabeprazole 10–20 mg (19%), omeprazole 20 mg (10%). Exposure time: not reported.	NOS = 4; Odds ratio adjusted using univariate logistic regression for age, sex, peptic ulcer history, diabetes mellitus, insulin therapy, anticoagulant use, alcohol drinking and smoking.
Pilotto et al. (41)	2004	Peptic ulcer detected by endoscopy	Not reported	Not reported	Dose: 75–300 mg/day; Exposure time: ≥ 3 months	Type and dose: omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg daily. Exposure time: > 7 days	NOS = 5; No adjustment for baseline difference
Scheiman et al. (49)	2011	Peptic ulcer detected by endoscopy; Upper GI complications	Peptic ulcer: A mucosal defect ≥ 3 mm with a base (smooth or regular punched-out defect) and margin (discrete, sharply demarcated and usually raised in relation to base). Upper GI complications: not reported	Upper GI complications; haematemesis and melena	Dose: 75–325 mg. Exposure time: 26 weeks, ≥ 5 days per week	Type and dose: Esomeprazole 20 and 40 mg/day; Exposure time: 26 weeks	Adequate sequence generation; adequate allocation concealment; blinding of participants and study personnel; incomplete outcome data were adequately addressed; outcome reporting was not selective; potential confounders were not taken into account in study design and analysis
Shiotani et al. (42)	2009	Peptic ulcer detected by endoscopy	A mucosal defect > 5 mm	Not reported	Dose: 100 mg/day; Exposure time: > 1 year; > 3 years in 75% of patient†	Type and dose: Omeprazole 10 mg/day, lansoprazole 15 mg/day; Exposure time: > 2 months†	NOS = 3; No adjustment for baseline difference

Table 3 Continued

Author	Year	Outcome	Outcome definition	Symptom*	Aspirin use	Proton pump inhibitor use	Study quality
Tamura et al. (43)	2010	Peptic ulcer detected by endoscopy	Ulcer: a mucosal defect of > 3 mm	47% of patients had abdominal symptoms (reflux, abdominal pain, indigestion, obvious bleeding signs and occult bleeding signs)	Dose: 75–325 mg/day; Exposure time: > 1 month	Type and dose: Not reported. Exposure time: > 7 days	NOS = 7; Odds ratio adjusted using multivariate logistic regression for age, sex, H2RA use, anticoagulant use, antiplatelet use, NSAID use, corticosteroid use and presence of abdominal symptoms; Dependent variables simultaneously analysed were gastric ulcer, duodenal ulcer and gastroduodenal ulcer
Tamura et al. (44)	2011	Peptic ulcer detected by endoscopy	Ulcer: mucosal defect $\geq$ 3 mm	Patients had no upper GI symptoms	Dose: 100 mg/day (95.5%); 81 mg/day (3.3%); and 200 mg/day (1.3%); Exposure time: $\geq$ 3 months	Type and dose: omeprazole 10 mg or 20 mg, lansoprazole 15 mg or 30 mg, rabeprazole 10 mg or 20 mg/day; Exposure time: > 3 months	NOS = 6; Odds ratio adjusted using multivariate logistic regression for age, sex, peptic ulcer history, <i>H. pylori</i> eradication history, hypertension, diabetes mellitus, positive urinary <i>H. pylori</i> antibody, H2RA use, mucoprotective agent use, warfarin use, NSAID use, calcium antagonist use, nitrate use, alcohol drinking and smoking; Dependent variables simultaneously analysed were gastroduodenal ulcer and erosion
Yamamoto et al. (50)	2010	Gastroduodenal bleeding; Gastroduodenal mucosal injury detected by endoscopy	Bleeding: endoscopic evidence of current or recent haemorrhage with drop of haemoglobin 2 g/dl or more judged to require hospitalisation; Ulcer: mucosal defects including both erosion (< 5 mm) and ulcer (> 5 mm)	Not reported	Dose: described as 'low' (exact dose not reported); Exposure time: $\geq$ 1 month	Type and dose: Not reported; Exposure time: $\geq$ 1 month†	NOS = 6; No adjustment for baseline difference

Impact of PPIs on gastrointestinal bleeding

Pooled effect

Two RCTs and seven observational (four cohort, three case-control) studies reported on the effect on GI bleeding. Four (13,46,48,51) of the observational studies adjusted the effect estimates for potential confounding. A total number of 399 360 patients (> 175 886 patients on PPIs; one article (48) did not report the number of PPI users) were included in the analysis. Except for the study by Charlot et al. (RR = 1.02) (51), the directions of the estimated RRs were consistently in favour of PPI use in all studies. However, the 95% CIs of the RRs in five studies (three and two reported on GI bleeding and UGIB respectively) contained 1.0. When all the estimates were pooled, concomitant use of PPIs was associated with a 50% risk reduction compared with no PPI therapy (pooled RR = 0.50; 95% CI = 0.32–0.80; $p < 0.01$; Figure 2B). The studies were clearly heterogeneous ($p < 0.001$; $I^2 = 81.0\%$; $\tau^2 = 0.30$).

Subgroup analysis

The pooled RR (95% CI) of the estimates from the two RCTs was 0.41 (0.12–1.40). No significant heterogeneity between these trials was detected ($p = 0.75$; $I^2 = 0.0\%$; $\tau^2 = 0$). In contrast, there was heterogeneity across the seven observational studies ($p < 0.001$; $I^2 = 86.6\%$; $\tau^2 = 0.35$), of which the pooled RR (95% CI) was 0.51 (0.30–0.85).

Among the observational studies, the pooled RR (95% CI) of the outcomes from five studies with higher quality (NOS > 5) was 0.52 (0.28–0.96), against 0.33 (0.05–2.22) in the two studies with lower quality (NOS ≤ 5). Significant heterogeneity was present across the high as well as low quality studies ($p < 0.05$; $I^2 > 70\%$).

Because exact PPI exposure time was reported in only two studies, we could not perform subgroup analysis based on this criterion.

Sensitivity analysis

The sensitivity analysis showed that the direction of the effect of the use of PPIs on GI bleeding, and the presence of heterogeneity were not influenced by any single study. When the studies that did not specify the location of GI bleeding were excluded, the pooled RR (95% CI) of the estimates from the remaining studies (reporting on UGIB) was 0.36 (0.22–0.57), indicating an effect markedly larger than that observed in all studies combined (RR = 0.50).

Publication bias

Egger's regression test showed significant publication bias ($p = 0.04$). This is in agreement with the funnel

Table 3 Continued

Author	Year	Outcome	Outcome definition	Symptom*	Aspirin use	Proton pump inhibitor use	Study quality
Yeomans et al. (19)	2008	Peptic ulcer detected by endoscopy; GI bleeding	Ulcer: mucosal defect ≥ 3 mm Bleeding: not reported.	Not reported	Mean dose: 124 mg/day (range 75–325 mg/day); Exposure time: 26 weeks	Type and dose: Esomeprazole 20 mg/day; Exposure time: 26 weeks	Unclear sequence generation; adequate allocation concealment; blinding of participants and physicians; incomplete outcome data were adequately addressed; outcome reporting was not selective; potential confounders were not taken into account in study design and analysis

*Subjective evidence of patient's conditions before detection of outcomes. [†]Extra information supplied by the corresponding authors. NOS values were assessed based on a scale from 0 (poorest quality) to 9 (highest quality) using the following criteria: selection of the study groups, comparability of the groups and ascertainment of outcome or exposure of interest for cohort or case-control studies respectively. See Wells et al.27 for scoring methods and Appendix B for detailed assessment of the included studies. CV, cardiovascular; GI, gastrointestinal; H2RA, H2-receptor antagonist; NOS, Newcastle-Ottawa Scale; NSAID, non-steroidal anti-inflammatory drug; UGIB, upper gastrointestinal bleeding.

(A) Outcome: Peptic ulcer **(B)** Outcome: Gastrointestinal (GI) bleeding

Figure 2 Forest plots of relative risk of (A) peptic ulcer and (B) gastrointestinal (GI) bleeding in patients receiving low-dose aspirin and proton pump inhibitors compared with patients receiving only low-dose aspirin. RCT, randomised controlled trial

plot (Figure 3B), which showed an absence of small-size studies reporting smaller or no beneficial effect of PPI co-therapy on the risk of UGIB.

Impact of PPIs on cardiovascular events

Only the cohort study by Charlot et al. (51) reported on CV events and therefore no meta-analysis of the effect of PPIs on CV risk could be performed. In this study, adjusted hazard ratios were computed using a propensity score matched Cox proportional hazards model. The estimated RRs (95% CIs) of myocardial infarction, stroke and CV death were 1.33 (1.13–1.56), 1.20 (0.99–1.46) and 2.19 (1.92–2.49) respectively.

Discussion

Impact of PPIs on peptic ulcer

The current meta-analysis showed that concomitant PPI use in patients receiving low-dose aspirin confers a 73% reduced risk of peptic ulcer. However, the

clinical significance of this effect is questionable. Peptic ulcer in all seven included studies were detected by endoscopy, but the associated symptoms were not reported in five of these studies. One study was conducted in asymptomatic patients (44) and another reported that only 47% of patients had abdominal symptoms (43).

The pooled effect of PPIs on peptic ulcer should be interpreted with caution. The presence of significant heterogeneity indicates that this estimate may be biased. There was methodological diversity as we included both RCTs and cohort studies. Quality assessment of the studies revealed clinical heterogeneity in the treatments and baseline characteristics of the included patients. For example, the inclusion criterion on the minimal exposure time of the patients to aspirin and PPIs differed considerably between the observational studies, ranging from 7 days to 1 year for aspirin use and from 7 days to 3 months for PPI use. Types and doses of PPIs also differed between

Figure 3 Funnel plots for detection of possible bias of publication on the effect of co-administration of proton pump inhibitors on (A) peptic ulcer and (B) gastrointestinal (GI) bleeding in patients receiving long-term low-dose aspirin for prevention of cardiovascular events. In each funnel plot, the standard errors of the estimated risk ratios (RRs) were put on a reversed scale, and the triangle was centered on the pooled RR and extending to 1.96 times the standard errors on either side. These plots show a tendency of publication bias because in the absence of bias otherwise, the scatter of the data points would be subject to sampling variation alone and the plots should resemble symmetrical inverted funnels, which is not the case

studies. One study (41) selected only patients older than 65 years while the others included patients with different age ranges (min age, 18; max age, 92) and averages (67.4–79.7). The patient profiles of CV risk factors also varied across studies, partly because three studies (41,42,50) did not exclude patients at very high CV risk while the others did. Age and the presence of CV risk factors may be confounders as they are likely to be associated with increased risks of GI events as well as with PPI use (52–56). Other potential confounders include a history of peptic ulcer disease (43,46,48,57) and lower socioeconomic status; the latter is associated with *Helicobacter pylori* infection and the risk of peptic ulcer disease (58–60), and also with less access to healthcare resources and thus PPIs. Importantly, among five cohort studies, only two adjusted estimates for baseline differences and therefore potential confounders, including age and peptic ulcer history (43,44). Cardiovascular risk factors and socioeconomic status were not considered as potential confounders in any study.

Among the cohort studies, the pooled RR of the estimates from those with higher quality was considerably higher than that from those with lower quality (0.37 vs. 0.17). This implies that low-quality studies tended to publish results representing large beneficial effect of PPIs. In line with this, the funnel plot indicated an absence of small-size studies reporting small beneficial effect of PPIs. Despite the presence of heterogeneity and low number of studies, the direction of the effects in all studies and of the pooled effects in all subgroups is consistent (< 0.55), with all the upper bounds of the 95% CIs smaller than 1.0. These observations suggest a plausibly beneficial effect of co-therapy with PPIs on the risk of peptic ulcer in patients receiving long-term low-dose aspirin.

These findings on the impact of PPIs on peptic ulcer argue in favour of, but may be insufficient to justify the co-administration of PPIs. First, the clinical relevance of peptic ulcer prevention is unclear because peptic ulcer is a poor predictor of ulcer complications (61,62) and can remain asymptomatic (44,63). In addition, only seven studies, of which five were observational, were included in the meta-analysis. In observational studies, it is difficult to fully prevent or account for confounding, and, unfortunately, most studies included in our analysis failed to appropriately adjust for confounders.

Impact of PPIs on gastrointestinal bleeding

The current meta-analysis showed that concomitant use of PPIs in patients receiving low-dose aspirin corresponds to a 50% and 64% reduced risk of GI bleeding and UGIB respectively. Again, this finding should be interpreted with caution. There was methodological diversity in study design, and clinical heterogeneity in the treatments and baseline characteristics of the included patients. RCTs, case-control and cohort studies were all included in the meta-analysis. The inclusion criterion on the minimal exposure time of aspirin and PPIs differed between studies, ranging from 7 days to 6 months. The specific type of PPIs was not reported in more than half of the included studies, and differed between studies that report these data. Except for the study by Scheiman et al. (49), which included only patients with a negative *H. pylori* test, none of the studies took the status of *H. pylori* infection into account. *Helicobacter pylori* infection may be a confounder, because it is associated with both the risk of UGIB and the use of PPIs in eradication therapy (64). Because the duration of PPI exposure was not reported in two observational studies (46,47), it is not clear whether PPI use in these studies was because of *H. pylori* eradication (short-term) or treatment of peptic ulcer disease (long-term). Among five-observational studies that reported on UGIB, only three studies adjusted the estimates for

potential confounders, including age and peptic ulcer history (13,46,48). Importantly, no studies adjusted the estimates for other major potential confounders, such as *H. pylori* infection, CV risk factors and socioeconomic status.

As in the case of peptic ulcer, these findings on the impact of PPIs on the risk of GI events may not be sufficient to justify the use of PPIs in patients on long-term aspirin therapy. Only six studies reporting on UGIB, of which five were observational, were included in the meta-analysis. Although the findings overall indicate a beneficial effect of adding PPIs to aspirin on the risk of GI bleedings, the directions of the 95% CIs of the estimated RRs were not consistent across all studies. This observation, together with the evidence of publication bias, indicates that the magnitude of the beneficial effect of PPIs on GI bleeding remains uncertain.

Impact of PPIs on cardiovascular events

Because only one study on the effect of PPIs on CV risk was found (51), we could not perform a meta-analysis of this effect. Hypothetically, PPIs might affect aspirin bioavailability by raising gastric pH and therefore attenuate the antiplatelet effect of aspirin. Only a few studies tested the latter hypothesis and showed contradictory results (32,65–67). The clinical significance of these hypotheses has recently also been seriously challenged (33). We found only one study that investigated this clinical significance. In this large retrospective cohort study (51), propensity scores were used to reduce bias in the estimated effect because of confounding factors (68). While residual confounding was considered unlikely, the authors acknowledged that it could not be excluded that the effect of PPIs might be confounded by a number of uncontrolled factors such as lipid levels, body mass index and smoking, on which there was no information (51). In addition, comorbidities that were not considered but might act as confounders in this study included severe reflux and Barrett's oesophagus; patients with these diseases are often prescribed PPIs and are at a high risk of CV death (69). Currently, the clinical impact of PPIs on the effect of aspirin on CV risk therefore remains uncertain.

Study limitations and the need for further research

Our study has some limitations. Because of the low number of the included studies, we pooled data from both RCTs and observational studies. Three case-control studies (reporting on UGIB) (13,47,48) were not nested case-control studies (70) and therefore we considered the odds ratio as RRs (71) assuming that UGIB is a rare event (5). In four observational stud-

ies (42,45,47,50), neither relevant RRs nor relevant odds ratios were provided and we calculated the RRs using the reported number of events in the groups with and without a PPI therapy; in this way, it was not possible to adjust the RRs for differences in the patient baseline characteristics in these two groups.

In this study, we used the random-effects models to estimate the mean true effects in a hypothetical population of studies from which, the studies we found were assumed to be a random sample (72). Because the number of the included studies was relatively small, the estimates of the between-study variances (τ^2), and hence of the pooled effects and their confidence intervals, may not be precise when using the random-effects models (35,72). Additional meta-analyses using fixed-effects models showed that the pooled RRs obtained from the fixed-effects models (0.37 for peptic ulcer and 0.77 for GI bleeding) were slightly larger than those obtained from the random-effects models. The 95% CIs of the pooled RRs from the fixed-effects models [(0.30–0.45) for peptic ulcer and (0.68–0.89) for GI bleeding] were narrower, but both the lower and upper bounds were larger than those from the random-effects models. Thus, the random- and fixed-effects models produced similar results.

Despite the claim that inclusion of unpublished studies may help to avoid publication bias, we did not include unpublished studies because this inclusion can itself introduce bias for several reasons. First, the studies that can be retrieved may not be representative of all unpublished studies. Second, the quality of unpublished studies, given a lack of peer review, may be lower than that of published studies. Finally, data provided by the study investigators may not be complete and this may depend on whether or not the results are favourable (35). Besides the arguments above, there is also a practical reason to not include unpublished research. To ensure that the inclusion of unpublished studies does not cause bias, an exhaustive, manual search should be made to retrieve all relevant studies. In addition, a detailed and critical appraisal of the unpublished studies should be performed. There are numerous national and international registers and therefore a lot of time would be needed to search these sources, retrieve the documents and critically appraise the studies.

The current literature review showed that published studies on the impact of PPIs on the GI and CV outcomes in aspirin users were limited in both quantity and quality. Given the large number of patients concomitantly prescribed aspirin and PPIs, there is an urgent need for further studies on this topic. The clinical significance of peptic ulcer prevention in asymptomatic patients should be rigorously

clarified. Also, more studies on the impact of PPIs on CV events and new studies on the effect of PPIs on aspirin adherence should be conducted. In addition, any possible long-term side effects of PPI co-therapy in patients receiving low-dose aspirin should be carefully reviewed and/or further investigated. A recent large study in 210 155 patients showed that the use of PPIs for two or more years was significantly associated with vitamin B₁₂ deficiency (73). Long-term therapy with PPI might also be associated with increased risks of fracture (74), pneumonia (75), enteric infection (76) and hypomagnesaemia (77), but more evidence is needed to confirm (or refute) these associations.

Since the risks of adverse GI events differ in various patient groups (78), studies should also focus on the benefit-risk ratios of co-administration of PPIs in particular patient groups with different risk factors. Given that long-term use of PPIs is costly, co-therapy with PPIs should be viewed also from a health economic perspective. For this, a pharmacoeconomic study is needed to provide comprehensive information on the clinical, quality of life and cost-consequences of co-prescribing PPIs for decision makers.

Conclusions

Our study shows that the practice of co-prescribing PPIs in patients taking low-dose aspirin is supported

by some data in the literature, but the evidence remains weak. It is currently unclear whether the benefits of co-administration of PPIs in users of low-dose aspirin outweigh the potential harms. Stronger evidence is needed to advise patients and inform decision makers.

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Author contributions

CDAS, AWH and ATD: study concept; ATD, AWH, CDAS and MAJ: study design; ATD and FHV: acquisition and analysis of data; All authors: interpretation of results; ATD: drafting of the manuscript; All authors: Critically revision and approval of the final version of the manuscript for publication.

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Appendix A. Search strategies

Table A1 Search queries for PUBMED

Component	Number	Query
Patients (P)	#1	((cardiovascular[All Fields] OR coronary[All Fields]) AND risk[All Fields]) OR Cardiovascular Diseases[MeSH Terms] OR ((cardiovascular[All Fields] OR heart[All Fields] OR atherosclerotic[All Fields] OR coronary[All Fields] OR cerebrovascular[All Fields]) AND (disease[All Fields] OR diseases[All Fields])) OR Carotid Artery Diseases[MeSH Terms] OR coronary artery[All Fields] OR Diabetes Mellitus[MeSH Terms] OR diabetes[All Fields] OR diabetic[All Fields] OR diabetics[All Fields]
Interventions (I) and comparators (C)	#2	(aspirin[All Fields] OR acetylsalicylic acid[All Fields]) AND (proton pump inhibitor*[All Fields] OR omeprazole[All Fields] OR esomeprazole[All Fields] OR pantoprazole[All Fields] OR lansoprazole[All Fields] OR dexlansoprazole[All Fields] OR rabeprazole[All Fields])
Outcomes (O)	#3	((gastric[All Fields] OR gastrointestinal[All Fields] OR gastroduodenal[All Fields] OR duodenal[All Fields]) AND (symptom* OR complication*)) OR Peptic Ulcer[MeSH Terms] OR ulcer* OR bleeding[All Fields] OR hemorrhage[All Fields] OR haemorrhage[All Fields] OR obstruction[All Fields] OR perforation[All Fields] OR toxicity[All Fields] OR injury[All Fields] OR damage[All Fields]
	#4	((cardiac[All Fields] OR cardiovascular[All Fields] OR atherosclerotic[All Fields]) AND (event[All Fields] OR events[All Fields])) OR heart attack[All Fields] OR Myocardial Infarction[MeSH Terms] OR Myocardial Infarction[All Fields] OR Stroke[MeSH Terms] OR stroke[All Fields] OR death[All Fields] OR Mortality[MeSH Terms] OR mortality[All Fields] OR Survival Rate[MeSH Terms] OR survival rate[All Fields]
	#5	(aspirin[All Fields] OR acetylsalicylic acid[All Fields]) AND (Patient Compliance[MeSH Terms] OR adherence[All Fields] OR compliance[All Fields])
	#6	#3 OR #4 OR #5
PICO	#7	#1 AND #2 AND #6
Limits		Limit #7 to Human and English language

Table A2 Search queries for EMBASE (Ovid)

Component	Number	Query
Patients (P)		((cardiovascular or coronary) and risk) or ((cardiovascular or heart or atherosclerotic or coronary or cerebrovascular) and disease*) or coronary artery or diabet*). ti,ot,sh,ab,kw,tw.
Interventions (I) and comparators (C)	2	((aspirin or acetylsalicylic acid) and (proton pump inhibitor* or omeprazole or esomeprazole or pantoprazole or lansoprazole or dexlansoprazole or rabeprazole)). ti,ot,sh,ab,kw,tw.
Outcomes (O)	3	((gastric or gastrointestinal or gastroduodenal or duodenal) and (symptom* or complication*)) or ulcer* or bleeding or hemorrhage or haemorrhage or obstruction or perforation or toxicity or injury or damage). ti,ot,sh,ab,kw,tw.
	4	((cardiac or cardiovascular or atherosclerotic) and event*) or heart attack or myocardial infarction or stroke or death or mortality or survival rate). ti,ot,sh,ab,kw,tw.
	5	((aspirin or acetylsalicylic acid) and (adherence or compliance)). ti,ot,sh,ab,kw,tw.
	6	3 or 4 or 5
	7	1 and 2 and 6
PICO	7	
Limits	8	limit 7 to Human and English language

ti, title; **ot**, original title; **sh**, subject headings; **ab**, abstract; **kw**, keyword; **tw**, text word.

Table A3 Search queries for Cochrane Central Register of Controlled Trials

Component	Number	Query
Patients (P)	#1	((cardiac or cardiovascular or coronary) and risk) or ((cardiovascular or heart or atherosclerotic or coronary or cerebrovascular) and disease*) or coronary artery or diabet*
Interventions (I) and comparators (C)	#2	(aspirin or acetylsalicylic acid) and (proton pump inhibitor* or omeprazole or esomeprazole or pantoprazole or lansoprazole or dexlansoprazole or rabeprazole)
Outcomes (O)	#3	((gastric or gastrointestinal or gastro duodenal or duodenal) and (symptom* or complication*)) or ulcer* or bleeding or hemorrhage or haemorrhage or obstruction or perforation or toxicity or injury or damage
	#4	((cardiac or cardiovascular or atherosclerotic) and event*) or heart attack or myocardial infarction or stroke or death or mortality or survival rate
	#5	(aspirin or acetylsalicylic acid) and (adherence or compliance)
	#6	#3 or #4 or #5
	#7	#1 and #2 and #6
PICO	#7	

Appendix B. Quality assessment of the observational studies using the Newcastle-Ottawa Scale (NOS)

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Table B1 Assessment of the cohort studies								
Criteria	de Berardis et al. 2012	Charlot et al. 2009	Okada et al. 2009	Pilotto et al. 2004	Shiotani et al. 2009	Tamura et al. 2010	Tamura et al. 2011	Yamamoto et al. 2010
Selection								
1. Representativeness of the exposed cohort								
a. Truly representative of the average age and sex in the community*	1	1						
b. Somewhat representative of the average age and sex in the community*			1	1	1	1	1	1
c. Selected group of users e.g. nurses, volunteers								
d. No description of the derivation of the cohorts								
2. Selection of the non-exposed cohort								
a. Drawn from the same community as the exposed cohort*	1	1	1	1	1	1	1	1
b. Drawn from a different source								
c. No description of the derivation of the non-exposed cohort								
3. Ascertainment of exposure								
a. Secure record (e.g. surgical records)*	1	1		1		1		1
b. Structured interview *								
c. Written self report							x	
d. No description			x		x			
4. Demonstration that outcome of interest was not present at start of study								
a. Yes*		1						
b. No	x		x	x	x	x	x	x
Comparability								
1. Comparability of cohorts on the basis of the design or analysis								
a. Study controls for <i>Helicobacter pylori</i> or socioeconomic status*		1		1			1	
b. Study controls for any additional factor (age and/or CV risk)*	1	1				1	1	1

Table B1 Continued

Criteria	de Berardis et al. 2012	Charlot et al. 2009	Okada et al. 2009	Pilotto et al. 2004	Shiotani et al. 2009	Tamura et al. 2010	Tamura et al. 2011	Yamamoto et al. 2010
Outcome								
1. Assessment of outcome								
a. Independent blind assessment*						1	1	1
b. Record linkage *	1	1	1					
c. Self report				x	x			
d. No description								
2. Was follow-up long enough for outcomes to occur								
a. Yes (> 1 month)*	1	1	1	1	1	1	1	1
b. No								x
3. Adequacy of follow up of cohorts								
a. Complete follow up – all subjects accounted for*	1					1		
b. Subjects lost to follow-up unlikely to introduce bias - small number lost*		1						
c. Follow-up rate < 50% and no description of those lost								
d. No statement			x	x	x		x	x
Total score	7	9	4	5	3	7	6	6

*If the criterion followed by an asterisk is met, the study is awarded one point. A maximum of one point can be given for each numbered item within the Selection and Outcome categories, and a maximum of two points can be given for Comparability.

Table B2 Assessment of the case-control studies

	Ibanez et al. 2006	Lanas et al. 2000	Lanas 2007
Selection			
1. Is the case definition adequate?			
a. Yes, with independent validation*	1	1	1
b. Yes, e.g. record linkage or based on self reports			
c. No description			
2. Representativeness of the cases			
a. Consecutive or obviously representative series of cases*	1	1	1
b. potential for selection biases or not stated			
3. Selection of controls			
a. Community controls*		1	1
b. Hospital controls	x		
c. No description			
4. Definition of Controls			
a. No history of disease (end-point)*	1	1	1
b. No description of source			
Comparability			
1. Comparability of cases and controls on the basis of the design or analysis			
a. Study controls for <i>Helicobacter pylori</i> or socioeconomic status*			
b. Study controls for any additional factors (age and/or CV risk)*	1	1	1
Exposure			
1. Ascertainment of exposure			
a. Secure record (e.g. surgical records)*			
b. Structured interview where blind to case/control status*			
c. Interview not blinded to case/control status	x	x	
d. Written self report or medical record only			x
e. No description			
2. Same method of ascertainment for cases and controls			
a. Yes	1	1	1
b. No			
3. Non-response rate			
a. Same rate for both groups*			
b. Non respondents described			
c. Rate different and no designation	x	x	x
Total score	5	6	6

*If the criterion followed by an asterisk is met, the study is awarded one point. A maximum of one point can be given for each numbered item within the Selection and Exposure categories, and a maximum of two points can be given for Comparability.

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Author/s:

Tran-Duy, A;Vanmolkot, FH;Joore, MA;Hoes, AW;Stehouwer, CDA

Title:

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