Real-World Relationship Between Proton Pump Inhibitors and Cerebro-Cardiovascular Outcomes Independent of Clopidogrel
A Meta-Analysis of Observational Studies

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Summary
Previous studies have provided established evidence on adverse outcomes of the coadministration of proton pump inhibitors (PPIs) and clopidogrel, whereas cerebro-cardiovascular outcomes of PPI use in the absence of clopidogrel therapy remain controversial.

In this study, we aimed to assess the association between PPIs and cerebro-cardiovascular outcomes independent of clopidogrel.

Systematic searches were conducted in the Cochrane Library, PubMed, and Embase databases for all relevant studies up to August 2018. Odds ratios (ORs) with its 95% confidence intervals (CIs) were abstracted and pooled using the random-effects model.

A total of 14 observational studies (13 cohort studies and 1 case-control study) were identified. Compared with non-PPI users, PPI users experienced higher risks of stroke (OR: 1.22, 95% CI: 1.08-1.36), myocardial infarction (MI; OR: 1.23, 95% CI: 1.14-1.32), cardiovascular death (OR: 1.83, 95% CI: 1.69-1.98), and major adverse cardiovascular events (MACEs; OR: 1.22, 95% CI: 1.05-1.40) independent of clopidogrel use, but not all-cause death (OR: 1.50, 95% CI: 0.99-2.25). In the subgroup analysis, PPI alone was associated with significant risks of new-onset MI (OR: 1.23, 95% CI: 1.13-1.35) and stroke (OR: 1.17, 95% CI: 1.05-1.30) in patients without previous MI or stroke and recurrent MI (OR: 1.24, 95% CI: 1.02-1.51) and stroke (OR: 1.36, 95% CI: 1.19-1.55) risks in patients with a previous MI.

Based on current publications, PPI use seems to be associated with increased risks of stroke, MI, cardiovascular death, and MACEs independent of clopidogrel. Greater caution should be therefore exercised while considering its clinical benefits and further investigate any causal relationships.

Key words: Stroke, Myocardial infarction, Death, Mechanism

Proton pump inhibitors (PPIs) can effectively suppress gastric acid secretion and have become the most widely used therapeutic agents for several acid peptic disorders.37 PPIs are generally considered safe and well tolerated.38 However, long-term and large-scale administration of these drugs has been recently found to be associated with potential adverse effects on multiple organs and systems.39 Moreover, several meta-analyses have suggested that inappropriate use of PPIs may increase the risks of certain conditions such as kidney disease, dementia, and cardiac events.40 However, in the cardiovascular field, most analyses have focused on the association of PPI comedication with adverse cerebro-cardiovascular events.41 A recent study showed that clopidogrel could increase the risk of bleeding when administered to patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI).42 Because PPIs significantly reduce the risk of gastrointestinal (GI) bleeding associated with antiplatelet therapy, they are often administered in combination with clopidogrel. Both PPIs and clopidogrel are metabolized via the same cytochrome P450 pathway (CYP2C19), leading to hypothesizing the competition between these agents for the same pathway.43,44 Inhibition of CYP2C19 by PPIs may reduce the bioavailability of active metabolites of clopidogrel, thereby attenuating the cardiovascular benefits rendered by clopidogrel. In 2009, the United States Food and Drug Administration (FDA) and European Medicines Agency published a update to avoid the concomitant use of clopidogrel and PPIs (particularly omeprazole).45 Re-
recently, a study indicated significant changes in the prescription pattern for omeprazole after the FDA update by taking off omeprazole from the patient’s prescription or, to a lesser extent, replacing it with ranitidine.43

Consequently, a retrospective cohort study, which included 56,406 participants discharged after first-time MI, demonstrated that PPIs are associated with an increased incidence of cardiovascular death, recurrent MI, or stroke, regardless of clopidogrel use.46 Furthermore, these risks may extend from patients with coronary artery disease to the general population.17,20 However, there are several studies with conflicting results that PPIs do not manifest as an independently increased risk of adverse cardiovascular events.22,23 To help address this association, a meta-analysis of randomized controlled trials (RCTs) demonstrated that PPI monotherapy could be a risk factor for adverse cardiovascular events in patients with gastroesophageal reflux disease (GERD).41 Despite this result, the subject has never been extensively explored in real-world patients. RCTs are typically designed to investigate the efficacy of drugs in ideal conditions and are not adequately powered to detect adverse events. In addition, older patients with complex conditions treated with polypharmacy regimens during long-term treatment with PPIs have been persistently excluded from RCTs. Thus, large observational studies involving real-world patients should be considered as an important informative source about potential risks associated with PPIs. In this meta-analysis of observational studies, we aimed to investigate the association between PPIs and cerebro-cardiovascular outcomes in the absence of clopidogrel.

Methods

Data sources and search strategy: Three reviewers (L-S, L-FW, and C-C) carefully searched the Cochrane Library, PubMed, and Embase databases for relevant studies up to August 2018. Electronic search strings included keywords pertaining to the outcome of cerebro-cardiovascular events (stroke, myocardial infarction [MI], death, and major adverse cardiovascular events [MACEs]) in combination with the intervention of PPIs (omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole). The Boolean operator “and” was used to combine the 2 categories of keywords. Additional studies for inclusion were identified by screening the references lists of the included studies. The authors of potentially relevant abstracts or conference proceedings were contacted via email for additional information. We did not apply language restrictions in this meta-analysis.

Study selection: Studies were included if they met the following criteria: (1) explored the associations between the use of PPIs and cerebro-cardiovascular risks, (2) assessed PPIs as an independent risk factor, (3) reported the adjusted odds ratios (ORs) with its 95% confidence intervals (CIs) as the risk estimates, and (4) had at least 4 month follow-up period. Studies were excluded if they reported or did not adjust for concomitant antiplatelet therapy or involved participants aged less than 18 years. For duplicate publications, the publication with the longest follow-up duration or the most number of participants was excluded. RCTs and studies with insufficient data were also excluded.

Data abstraction and quality assessment: Three investigators (L-S, L-FW, and C-C) independently assessed the eligibility of the literature. A fourth author (H-K) adjudicated any discordance during the assessments. Two investigators independently abstracted the basic characteristics of each included study. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of all the included studies in terms of the selection of cohorts, comparability of cohorts, and assessment of outcomes.29 NOS scores of < 6 and ≥ 6 indicated low- and moderate- to high-quality studies, respectively.

Statistical analysis: Risk of bias was assessed by two investigators (L-S and L-FW), and discrepancies were resolved by consensus with a third author (H-K). All statistical analyses were performed using Review Manager (RevMan) version 5.30 software (the Nordic Cochrane Center, Rigshospitalet, Denmark; http://ims.cochrane.org/revman). The ORs with its 95% CIs were extracted from included studies. A fixed-effects model (I² < 50%) or a random-effects model (I² ≥ 50%) was used depending on the I² value obtained. In this study, a random-effects model was used because it was better able to explain between-study heterogeneity than a fixed-effects model. Sensitivity and publication bias analyses were performed where appropriate. A P value of < 0.05 was considered statistically significant.

Results

Search results: Our systematic searches identified 1,183 unique studies, and 391 studies were excluded because of duplicate data. A total of 739 studies were excluded based on the title and abstract screening. The full texts of the 53 remaining studies were reviewed. Finally, 14 observational studies (13 cohort studies and 1 case-control study)16-20,22,23,26-32 were included in this meta-analysis. Of them, 4 studies reported stroke,16,19,20,23 5 studies reported MI,16,19,26 2 studies reported cardiovascular death,16,18 4 studies reported all-cause death,16,22,27,32 and 6 studies reported MACEs.16,22,28-31 With regard to the outcome of MI, we included 5 studies with 6 risk estimates because Shah, et al. provided 2 databases: the Stanford Translational Research Integrated Database Environment (STRIDE) and Practice Fusion (PF).30 The reasons for study exclusion are documented using the PRISMA flow diagram (Figure 1).

Study quality and publication bias: The Table presents the basic characteristics and the reporting quality of each included study. According to the Cochrane Handbook for Systematic Reviews of Interventions, when fewer than 10 studies are included for one primary outcome, neither funnel plots nor statistical tests (Begg’s test and Egger’s test) can be used to meaningfully test for publication bias.

PPI use and cerebro-cardiovascular outcomes: As shown in Figure 2, for the overall study population, PPI users experienced an independently higher risk of stroke (OR: 1.22, 95% CI: 1.08-1.36, P = 0.0008, I² = 72%) than non-PPI users. Similar results were observed for the risks of MI (OR: 1.23, 95% CI: 1.14-1.32, P < 0.00001,
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Figure 1. Flow diagram of the search process and study selection.

\[ OR: 1.22, 95\% CI: 1.05-1.40, P = 0.007, I^2 = 84\% \] and MACEs (OR: 1.22, 95\% CI: 1.05-1.40, P = 0.007, I^2 = 84\%). A marked heterogeneity existed across the included studies. The associations between PPIs and stroke, MI, and MACEs were respectively stable in the sensitivity analysis in which studies were excluded one by one. An increased risk for cardiovascular death (OR: 1.83, 95\% CI: 1.69-1.98, \( P < 0.00001, I^2 = 0\% \)) was also observed from these studies, but not for all-cause death (OR: 1.50, 95\% CI: 0.99-2.25, \( P = 0.05, I^2 = 99\% \)), probably because of the diversity of definitions or clinical designs.

We also performed subgroup analysis based on the study participants. Among the patients without previous MI or stroke receiving PPIs, the risks of new-onset MI (OR: 1.23, 95\% CI: 1.13-1.35, \( P < 0.00001, I^2 = 70\% \)) and stroke (OR: 1.17, 95\% CI: 1.05-1.30, \( P = 0.005, I^2 = 55\% \)) were increased in PPI users compared with non-PPI users (Figures 3, 4). Similarly, we analyzed these above-mentioned risks in patients with a previous MI. The use of PPI was associated with increased recurrent MI (OR: 1.24, 95\% CI: 1.02-1.51, \( P = 0.03, I^2 = 77\% \)) and stroke (OR: 1.36, 95\% CI: 1.19-1.55, \( P < 0.00001 \)) in the absence of clopidogrel (Figures 3, 4).

Discussion

Our meta-analysis indicated that the use of PPIs was associated with increased risks of stroke, MI, cardiovascular death, and MACEs in real-world patients, independent of clopidogrel therapy.

PPIs are considered relatively safe drugs with few adverse reactions. However, with long-term (\( \geq 2 \) months) and large-scale (standard dose doubling) drug administration, the safety and potency of PPIs have been questioned.\(^{38}\) In the cardiovascular field, these effects were initially attributed to the fact that PPIs may impair the metabolic activation of certain antiplatelet agents, thereby increasing a risk of adverse cerebro-cardiovascular events. For patients receiving clopidogrel therapy, the inhibition of hepatic isoenzyme CYP2C19 by PPIs may reduce the bioavailability of the active metabolites of clopidogrel, leading to an increase in the cardiovascular risks.\(^{33}\) For patients receiving aspirin therapy, PPIs exert their antacid effect by inhibiting the H^+\text/K^+ exchanging ATP-ase of the gastric parietal cells, thus raising intragastric pH and thereby reducing the lipophilicity of aspirin, leading to the absorption of the drug.\(^{34}\) Currently, these risks may extend from patients with coronary artery disease to the general population. The chronic use of PPIs in the general population may also increase the risks of incident ischemic/composite stroke, MI, and death.\(^{19,20,24}\) Of interest, there is some suggestion that PPIs may be involved in cardiac arrhythmias (ventricular tachycardia and torsades de points).\(^{35}\)

Meanwhile, most of the included studies in our meta-analysis did not report or adjusted for concomitant antiplatelet therapy. We also performed a subgroup analysis based on the study participants. Nevertheless, the results were consistent in the general population and in patients with coronary heart disease. Our results indicate that the increased risks of cardiovascular and cerebrovascular events could be explained by mechanisms other than interference with antiplatelet activities. To date, several pathophysiological hypotheses by which PPIs may directly affect the risks of cardiovascular and cerebrovascular events have been proposed. Ghebreabriam, et al. demonstrated that PPIs significantly inhibited human dimethylarginine
### Table: Basic Characteristics and Qualities of the Studies

| Study (author year) | Study design | Region | Patients Mean age (years) | Female (%) | PPI subtypes | Follow-up time | Maximum adjusted covariates | NOS Items (stars) |
|---------------------|--------------|--------|----------------------------|------------|--------------|----------------|--------------------------------|------------------|
| Charlton 2010 (16)  | Retrospective cohort study | Denmark | First MI 73.1 | 46.5 | Esomeprazole, lansoprazole, omeprazole, pantoprazole | 1 years | Age, sex, PCI, income, concomitant medical treatment, and comorbid conditions. | 8 |
| Shih 2014 (17)      | Propensity Score-matched cohort study | Taiwan | No previous history of MI 49.3 | 48.8 | NA | 4 months | Age, sex, comorbidities, and concomitant drugs. | 8 |
| Shah 2015 (18)      | Data mining analysis | United States | GERD, without previous MI 54.9 | 43.31 | Omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, dexlansoprazole | 25 months | STRIDE; PF: age, sex, race, length of observation, number of unique drugs in the record, number of unique disease concepts, clopidogrel use. GenePAD: age, sex, race, total cholesterol, systolic blood pressure, antihypertensive medications, and lifetime pack-years. | 8 |
| Sehested 2017 (19)  | Retrospective cohort study | Denmark | Upper endoscopy without CVD 55 | 56.7 | Omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole | 5.8 years | Sex, age, calendar year, socioeconomic position, relevant comorbidities and concomitant medication. | 8 |
| Wang 2017 (20)      | Retrospective cohort study | Taiwan | No history of CVD 51.7 | 46.4 | Omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole | 4 months | Age, gender, monthly income, urbanization, outpatient visits in the past 1 year, antiplatelets or anticoagulants, concomitant medications, hypertension, coronary artery disease, MI, heart failure, valvular heart disease, dyslipidemia, diabetes mellitus, chronic liver disease, chronic kidney disease, drug abuse, physical limitation, autoimmune disease, cancer. | 8 |
| Simon 2011 (22)     | Prospective cohort study | French | MI 71 | 42 | Omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole | 1 year | Age, gender, BMI, hypertension, diabetes mellitus, hyperlipidemia, current smoking, family history, peripheral artery disease, history of MI, PCI, CABG, heart failure and stroke, prior treatment with aspirin, blockers, statins, ACE inhibitors, STEMI, GRACE score, medication 48 h after admission (aspirin, blockers, statins, ACE inhibitors), in-hospital PCI. | 8 |
| Nguyen 2017 (23)    | Prospective cohort study | United States | No history of stroke 69 | 70.3 | NA | 12 years | Age, years, smoking, exercise, BMI, regular ASA use, regular NSAID usage, past/current PMH, AHEI score, hypertension, hyperlipidemia, coronary heart disease, diabetes mellitus, GERD, prior PUD, prior GI bleed, and past/current HZRA use. | 8 |
| Valkhoff 2011 (26)  | Case-control study | Netherlands | MI 64.7 | 32.8 | Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole | 42.6 months | Age, sex, concomitant medical conditions, length of stay, days of follow-up, PCI, multiple cardiovascular and sugar lowering medications, and total number of prescriptions prior to baseline MI | 8 |
| Xie 2017 (27)       | Prospective cohort study | United States | Patients with acid suppression therapy 61.7 | 6.18 | Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole | 5.71 years | eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. pylori infection, Barrett’s esophagus, achalasia, stricture, and esophageal adenocarcinoma, unless used in analysis inclusion criteria. | 8 |
| Study (author year) | Study design | Region | Patients | Mean age (years) | Female (%) | PPI subtypes | Follow-up time | Maximum adjusted covariates | NOS Items |
|---------------------|--------------|--------|----------|-----------------|------------|--------------|----------------|--------------------------|------------|
| Ho 2009 | Retrospective cohort study | United States | ACS | 67.7 | NA | Omeprazole, lansoprazole, pantoprazole, rabeprazole | 3 years | Age, diabetes, prior myocardial infarction, PCI within past 6 months, CABG, heart failure, cerebrovascular disease, peripheral vascular disease, prior clopidoogrel use, cancer, COPD, renal disease, liver disease, dementia, TIMI risk score, LVEF 40%, ACS presentation (STEMI, NSTEMI), PCI performed, CABG performed, and discharge medications (aspirin, blockers, statins, and ACE inhibitors). | 8 |
| Kreutz 2010 | Retrospective cohort study | New Jersey | PCI with stent placement | NA | NA | Omeprazole, lansoprazole, pantoprazole, esomeprazole, | 1 year | Age, gender, prior cardiovascular event, heart failure, diabetes mellitus, hypertension, dyslipidemia treatment, dyslipidemia diagnosis or treatment, chronic kidney disease, upper gastrointestinal disease, hospitalization for upper gastrointestinal bleeding within preceding 6 months, prior or active PPIs use. | 7 |
| Schmidt 2011 | Prospective cohort study | Denmark | PCI with stent placement | 64 | 27.7 | Omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole | 1 year | Gender, age, diabetes, hypertension, obesity and time-varying use of aspirin, proton pump inhibitors, and statins. | 7 |
| Hall 2009 | Retrospective cohort study | United States | PCI with stent placement | 60 | 37.5 | Omeprazole, lansoprazole, pantoprazole, esomeprazole | 1 year | NA* | 7 |
| Maggio 2013 | Prospective cohort study | Italy | Patients discharged from acute care hospitals ≥65 | 54 | Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole | 1 year | Age, sex, BMI, hypalbuminemia, cognitive impairment, depression, dependency in ADLs, comorbidity score, cardiovascular diseases, GERD, PUD, diarrhea, infectious disease, fracture, no. of drugs prescribed at discharge, anti-thrombotic use, NSAID use. | 8 |

CVD indicates cardiovascular disease; MI, myocardial infarction; STRIDE, the Stanford Translational Research Integrated Database Environment; PF, Practice Fusion; GenoPAD, Genetic Determinants of Peripheral Arterial Disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase; ACE, angiotensin-converting enzyme; PTCA, percutaneous transluminal coronary angioplasty; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; BMI, body mass index; ASA, acetylsalicylic acid; AHEI, Alternative Healthy Eating Index; GERD, gastroesophageal reflux disease; PUD, peptic ulcer disease; GI, gastrointestinal; HIRA, histamine-2 receptor antagonist; ADLs, activities of daily living; GFR, estimated glomerular filtration rate; and NA, not available. * Abstract only, but adjusted for confounders.
**Figure 2.** Forest plot of the risks of cerebro-cardiovascular events in patients receiving a PPI therapy. Gene PAD indicates Genetic Determinants of Peripheral Arterial Disease; STRIDE, the Stanford Translational Research Integrated Database Environment; PF, Practice Fusion; PPIs, proton pump inhibitors; and MI, myocardial infarction.

dimethylaminohydrolase (DDAH) activity. DDAH is primarily responsible for metabolizing 80% of asymmetric dimethylarginine (ADMA), an endogenous and competitive inhibitor of endothelial nitric oxide synthase (eNOS). Increased ADMA levels may lead to a disruption of vascular homeostasis by decreasing NO release. In addition to inhibiting DDAH, PPIs seem to directly affect NOS expression. Both phosphorylated (active) and nonphosphorylated endothelial NOS proteins were downregulated by omeprazole. PPIs may also directly impair NO production. Dietary inorganic nitrite needs gastric acidity to form nitrous acid, which can spontaneously release NO. Furthermore, PPIs may downregulate eNOS expression by reducing vitamin C and B12, which are essential for maintaining endothelium homeostasis and counteracting oxidative stress.

Another mechanism may be related to the acceleration of atherosclerotic risk factors induced by PPIs. Esomeprazole was demonstrated to cause changes in gene expression, including an increase in plasminogen activator inhibitor-1 expression (an inhibitor of fibrinolysis), and induction of telomeric shortening (an indicator of cell senescence). These esomeprazole-induced changes unrelated to NOS were proposed to be due to impaired endothelial function caused by lysosomal alkalinization, secondary to inhibition of lysosomal proton pumps by PPIs. Recently,
omeprazole and lansoprazole were reported to downregulate the antiatherogenic chemokines CXCL11, CXCL12, and CX3CL1 in senescent, but not in nonsenescent, human coronary artery endothelial cells, suggesting another potential mechanism for increased cardiovascular risk.

Finally, PPI-induced hypomagnesemia may also mediate adverse cardiovascular effects. Hypomagnesemia was observed in patients taking PPIs and may cause cardiac arrhythmias. Indeed, magnesium plays a key role in maintaining cardiovascular homeostasis; has vasodilator, anti-inflammatory, and antioxidative properties; reduces platelet activation; and regulates cardiac electric activity by modulating potassium and calcium channels. In addition, hypomagnesemia is involved in many of the processes underlying atherosclerosis by promoting proatherogenic lipid profile, increased vascular calcification, impaired insulin activity, and vascular chronic inflammation.

Current evidence has provided the molecular mechanisms for this association; therefore, careful consideration should be given to the prescription of PPIs. We should emphasize the relationships between the dose and duration of PPI use and cardiovascular and cerebrovascular outcomes. In an investigation using Danish national registry data, Sehested, et al. indicated that the lowest dose of PPIs was not associated with fatal or nonfatal ischemic stroke or MI, but a stepwise dose-dependent increase in associated risk was observed (particularly for MI). In addition, only long-term use of PPIs was significantly associated with an increased rate of the either outcome. Furthermore, the meta-analysis of 16 RCTs demonstrated that PPI monotherapy was associated with increased risk of cardiovascular events in patients with GERD, especially

| Study or Subgroup | log(Odds Ratio) | SE | Weight | Odds Ratio | SE | Weight | Odds Ratio |
|------------------|----------------|----|--------|------------|----|--------|------------|
| **1.2 Patients with a previous MI** |
| Valdivia 2011     | 0.3220835      | 0.0792524 | 12.5%    | 1.30 [1.18, 1.41] | 0.0792524 | 12.5%    | 1.30 [1.18, 1.41] |
| Charlot 2011      | 0.1220835      | 0.05444 | 17.9%    | 1.13 [1.02, 1.26] | 0.05444 | 17.9%    | 1.13 [1.02, 1.26] |
| Subtotal (95% CI) |                |        |         | 1.24 [1.12, 1.37] |        |         | 1.24 [1.12, 1.37] |
| Heterogeneity:    |                |        |         | Tau² = 0.02, df = 1 (P = 0.04), P² = 77% |        |         | Tau² = 0.02, df = 1 (P = 0.04), P² = 77% |
| Test for overall  |                |        |         | effect: Z = 2.14 (P = 0.03) |        |         | effect: Z = 2.14 (P = 0.03) |
| **1.2 Patients without previous MI or stroke** |
| Shah 2014         | 0.4570000      | 0.1802 | 3.7%     | 1.60 [1.11, 2.25] | 0.1802 | 3.7%     | 1.60 [1.11, 2.25] |
| Shah 2015 (PF)    | 0.1740000      | 0.0446 | 20.3%    | 1.19 [1.02, 1.39] | 0.0446 | 20.3%    | 1.19 [1.02, 1.39] |
| Shah 2015 (STRIDE) | 0.1110000    | 0.034 | 21.8%    | 1.14 [1.05, 1.23] | 0.034 | 21.8%    | 1.14 [1.05, 1.23] |
| G-Schulze et al. 2017 | 0.2700000 | 0.0312 | 23.0%    | 1.31 [1.23, 1.39] | 0.0312 | 23.0%    | 1.31 [1.23, 1.39] |
| Subtotal (95% CI) |                |        |         | 1.23 [1.13, 1.33] |        |         | 1.23 [1.13, 1.33] |
| Heterogeneity:    |                |        |         | Tau² = 0.01, df = 3 (P = 0.02), P² = 70% |        |         | Tau² = 0.01, df = 3 (P = 0.02), P² = 70% |
| Test for overall  |                |        |         | effect: Z = 4.59 (P = 0.00001) |        |         | effect: Z = 4.59 (P = 0.00001) |

Figure 3. Forest plot of the risk of (recurrent) MI in patients receiving PPI therapy. STRIDE indicates the Stanford Translational Research Integrated Database Environment; PF, Practice Fusion; PPI, proton pump inhibitor; and MI, myocardial infarction.

| Study or Subgroup | log(Odds Ratio) | SE | Weight | Odds Ratio | SE | Weight | Odds Ratio |
|------------------|----------------|----|--------|------------|----|--------|------------|
| **1.3 Patients with a previous MI** |
| Charlot 2010     | 0.3074847      | 0.0874239 | 24.8%    | 1.36 [1.19, 1.55] | 0.0874239 | 24.8%    | 1.36 [1.19, 1.55] |
| Subtotal (95% CI) |                |        |         | 1.36 [1.19, 1.55] |        |         | 1.36 [1.19, 1.55] |
| Heterogeneity: Not applicable |                |        |         | Test for overall effect: Z = 4.55 (P = 0.00001) |        |         | Test for overall effect: Z = 4.55 (P = 0.00001) |
| **1.3 Patients without previous MI or stroke** |
| G-Schulze et al. 2017 | 0.1222176 | 0.0247420 | 34.7%    | 1.13 [1.08, 1.19] | 0.0247420 | 34.7%    | 1.13 [1.08, 1.19] |
| Nguyen 2017      | 0.07606104    | 0.08593285 | 26.7%    | 1.06 [1.01, 1.12] | 0.08593285 | 26.7%    | 1.06 [1.01, 1.12] |
| Wong 2017        | 0.3074847     | 0.0874239 | 24.8%    | 1.36 [1.14, 1.62] | 0.0874239 | 24.8%    | 1.36 [1.14, 1.62] |
| Subtotal (95% CI) |                |        |         | 1.17 [1.05, 1.30] |        |         | 1.17 [1.05, 1.30] |
| Heterogeneity:    |                |        |         | Tau² = 0.01, df = 2 (P = 0.11), P² = 55% |        |         | Tau² = 0.01, df = 2 (P = 0.11), P² = 55% |
| Test for overall  |                |        |         | effect: Z = 2.80 (P = 0.005) |        |         | effect: Z = 2.80 (P = 0.005) |

Figure 4. Forest plot of the risk of stroke in patients receiving PPI therapy. PPI indicates proton pump inhibitor.
duration of our meta-analysis findings. The studies with a follow-up duration of ≥ 4 months were only included.

In contrast, the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) study did not find omeprazole to increase the risk of cardiovascular events in patients with prior cardiovascular disease. Of note, because the study was prematurely terminated, it may not have the statistical power to reveal such a relationship between PPIs and cardiovascular events. Nguyen, et al. indicated PPI use alone was significantly associated with an increased rate of ischemic stroke after adjusting for known stroke risk factors. However, with additional adjustment for several indications for PPI use, including an earlier history of peptic ulcer disease, GERD, or gastrointestinal (GI) bleeding or previous use of histamine-2 receptor antagonist (H2RA), the association between PPI use and ischemic stroke was substantially attenuated. It seemed that the previously reported association of PPI use with ischemic stroke or other adverse cardiovascular events may be because of residual confounding by factors related to the indication for PPI use. Therefore, further studies are needed to investigate these associations after adjusting for several important potential stroke risk factors associated with PPI use or the likelihood of receiving acid-suppression therapy.

PPIs have been shown to be effective for treating GERD and peptic ulcer disease. Considering the extensive use of PPIs without sufficient evidence, this meta-analysis offers an opportunity to systematically evaluate cerebro-cardiovascular risks from PPI use alone. Our findings should be of value for exploring the potential cerebro-cardiovascular risks of PPI therapy. Of note, the current evidence is insufficient to change the clinical application of PPIs in patients. However, the results could be regarded as supporting information to perform some new studies to test the hypothesis that PPI use increases cerebro-cardiovascular risks. Future studies should adjust for more important potential cerebro-cardiovascular risk factors. It is important to note that the dose and time of use can affect the association between PPI use and the abovementioned risks. In addition, to improve the inclusion criteria for our analysis, the definitions of primary outcomes should be more accurate, which would make the results more credible. Meanwhile, cellular or animal experiments should be used to find more possible mechanisms of action of PPIs.

Several potential limitations of this meta-analysis merit emphasis. First, there was a significant heterogeneity in our analysis. The heterogeneity may have been partly due to the variability in the definitions of some outcomes, study designs, sample sizes, analysis strategies, and participant characteristics across studies. Second, the role of comorbidities and concomitant medications cannot be fully accounted for, despite multivariate adjustments. The increased risks of cerebro-cardiovascular events associated with PPI use may have been influenced by unmeasured confounders, such an earlier history of peptic ulcer disease, GERD, or GI bleeding or previous use of H2RA. Third, we have to point out that the difference of follow-up period of studies included in the present study is enormous. This might affect the results. Finally, it was undeniable that these studies cannot provide a causal link between PPI use alone and cerebro-cardiovascular outcomes due to their observational designs.

Conclusion

In conclusion, current published studies indicate that PPI use is associated with increased risks of stroke, MI, cardiovascular death, and MACEs independent of clopidogrel therapy. However, it is necessary to be cautious when considering the clinical relevance of these results, and the causal relationships remain to be established. Large RCTs to assess the cardiovascular safety during long-term treatment with PPIs are needed, especially in older patients.

Disclosure

Conflicts of interest: None.

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