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REVIEW

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Risk of stroke associated with proton pump inhibitor use among individuals with and without pre-existing cardiovascular diseases: a systematic review and meta-analysis

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Abstract

Background Proton pump inhibitors (PPIs) are commonly used for managing gastroesophageal disorders but concerns about their potential association with increased stroke risk have emerged, especially among patients with pre-existing cardiovascular conditions such as acute coronary syndrome (ACS). This systematic review and meta-analysis aim to assess the risk of stroke associated with PPI use, stratified by the presence or absence of pre-existing CVD.

Methods This review was conducted following the PRISMA guidelines and included studies up to March 2024 from PubMed, Embase, and Web of Science. Eligible studies were longitudinal, including prospective cohorts, nested case-controls, and post-hoc analyses of RCTs that reported stroke outcomes in relation to PPI use. Data were synthesized using random-effects meta-analysis models in R software version 4.3.

Results Our search yielded 41 studies encompassing over 800,000 participants globally. Meta-analysis of 14 observational studies revealed a slight but non-significant increased stroke risk among patients with prior CVD (pooled HR = 1.222, 95% CI: 0.963 to 1.481, $I^2 = 78\%$). In contrast, analysis of 15 studies without prior CVD showed a modestly increased risk (pooled HR = 1.15, 95% CI: 1.023 to 1.288, $I^2 = 98\%$). Five RCTs involving patients with CVD reported a pooled RR of 1.158 (95% CI: 0.914 to 1.466), indicating no significant risk increase.

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Conclusion The association between PPI use and stroke risk appears modest and is influenced by the presence of cardiovascular conditions. Clinical decision-making should consider individual patient risk profiles, and further high-quality studies are needed to guide safer PPI prescribing practices.

Keywords Proton pump inhibitor, Meta-analysis, Systematic review, Stroke, Good health and well being

Introduction

Proton pump inhibitors (PPIs) rank as some of the most frequently prescribed medications globally, mainly for managing conditions like gastroesophageal reflux disease (GERD), peptic ulcers, and other disorders linked to high gastric acid levels [1, 2]. These medications reduce stomach acid by blocking the hydrogen-potassium adenosine triphosphatase (H+/K + ATPase) enzyme complex located in the stomach's parietal cells, which helps alleviate discomfort and facilitates the healing of ulcers [3].

While PPIs are generally well-tolerated and considered safe for short-term use, concerns have emerged regarding their potential adverse effects, particularly with long-term or inappropriate use [4]. Over the past decade, several observational studies have reported associations between PPI use and an elevated risk of cardiovascular events, including stroke, myocardial infarction (MI), and cardiovascular mortality [5–7]. The proposed mechanisms underlying the potential cardiovascular risks associated with PPI use are not fully understood. Still, they may involve nutritional deficiencies, alterations in gut microbiome composition, platelet dysfunction, vascular calcification, and renal complications [8]. However, the available evidence remains conflicting, with some studies reporting no significant link between PPI use and cardiovascular outcomes.

One area of particular interest and debate is the relationship between PPI use and the risk of stroke, a leading cause of mortality and disability globally. Several studies have suggested that PPI use may increase the risk of ischemic and hemorrhagic stroke, potentially through mechanisms such as impaired antiplatelet effects, altered endothelial function, or vitamin and mineral deficiencies that can contribute to vascular dysfunction and thrombosis [9, 10]. However, the risk of stroke associated with PPI use may be further influenced by the presence of pre-existing cardiovascular conditions, such as acute coronary syndrome (ACS) [9]. Individuals with ACS, which includes myocardial infarction and unstable angina, often receive concomitant PPI therapy to prevent gastrointestinal bleeding, a common complication associated with dual antiplatelet therapy. A previous meta-analysis has assessed the risk of stroke with PPI use from randomized controlled trials (RCTs) [11]. Many recent observational studies have reported mixed results on the risk of stroke with PPI use in different populations. It is debated whether PPIs increase the risk of stroke among people without pre-existing coronary diseases.

Given the widespread use of PPIs and the substantial global burden of stroke [12], it is crucial to comprehensively evaluate the available evidence on the stroke risk associated with PPI use, particularly in the context of pre-existing ACS. This systematic review and meta-analysis aimed to synthesize data from longitudinal studies to assess the risk of stroke among PPI users, stratified by the presence or absence of pre-existing ACS.

Methods

The systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1) [13]. The protocol for this review has been registered with PROSPERO. A semi-automated web software (Nested-Knowledge, MN, USA) was used for this review.

Search Strategy

A systematic literature search was conducted in PubMed, Embase, and Web of Science, from inception to March 15, 2024. The search strategy utilized a combination of relevant Medical Subject Headings (MeSH) and text words related to "proton pump inhibitors," "stroke," "cerebrovascular," and the names of individual PPIs. No language restrictions were applied. Table S2 presents the complete search strategy.

Eligibility criteria

Eligibility criteria for the studies included in this analysis were defined as follows: Studies needed a longitudinal design such as prospective cohort studies, nested case-control studies, or post-hoc analyses of RCTs. The exposure of interest specified was the use of proton pump inhibitors. Furthermore, these studies had to report data specifically on stroke and provide risk estimates such as hazard ratios, odds ratios, or relative risks, complete with 95% confidence intervals (CI), or offer sufficient data from which these could be calculated. Cross-sectional studies, case reports, or did not report relevant stroke outcomes were excluded from consideration.

Study selection

Two reviewers independently assessed the titles and abstracts of the identified studies to determine their suitability for inclusion. Full texts of potentially relevant studies were then retrieved and assessed against the predefined inclusion and exclusion criteria. Any

discrepancies were addressed through discussions or by consulting a third reviewer. We used Nested-Knowledge software for de-duplication and screening.

Data extraction

A data extraction template was employed to gather pertinent details from the included studies, such as study characteristics (authors, publication year, study design, location, follow-up duration), participant characteristics (age, sex, comorbidities), risk estimates with 95% confidence intervals, and adjustment for potential confounders. Two reviewers independently extracted the data, and all differences were settled through discussions or by consulting a third reviewer.

Quality Assessment

The methodological quality of the studies was evaluated using relevant assessment tools tailored to their design. Observational studies were appraised with the Newcastle-Ottawa Scale (NOS), and post-hoc analyses of RCTs were assessed using the Cochrane Risk of Bias Tool (RoB 2). Two independent reviewers conducted these evaluations, and any discrepancies were addressed by discussing with a third reviewer or through consultation.

Data synthesis and analysis

The collected data were synthesized using random-effects meta-analysis models, which were utilized to estimate the pooled Hazard Ratios (HRs) and 95% CI for stroke associated with PPI use compared to non-use or placebo. Subgroup analyses were performed based on the presence or absence of pre-existing CVD. Statistical heterogeneity across studies was assessed using the I^2 statistic. An I^2 value exceeding 50% was interpreted as significant heterogeneity [14, 15]. Publication bias was evaluated using the Doi plot and LFKm index. All statistical analyses were conducted using R software version 4.3 [16].

Results

Literature search

The literature search retrieved a total of 4,975 records retrieved from inception to March 15, 2024. Before the screening, 2,706 duplicate records were removed. Subsequently, the screening process was applied to 2,269 records. This led to the retrieval of 165 full-text reports for eligibility assessment. No reports were retrieved at this stage. Upon further examination, 124 full-text articles were excluded because the outcome of interest was not reported in 78 articles, and the exposure was not of interest in 46 articles. A total of 41 studies were incorporated into the systematic review and meta-analysis [5–7, 11, 17–53] (Fig. 1).

Characteristics of included studies

The included studies offer diverse research designs, geographical locations, and participant demographics, highlighting an extensive investigative effort into the link between PPI use and stroke risk (Table 1). Both prospective and retrospective cohort studies dominate the dataset, complemented by nested case-control studies, retrospective studies, post hoc analyses of RCTs, propensity score-matched studies, and prospective observational studies. These studies span a global spectrum, with research conducted in numerous countries such as Taiwan, Denmark, the USA, China, Korea, Sweden, multiple international locations for RCTs, Thailand, the United Kingdom, Italy, Germany, Israel, Japan, Spain, the Netherlands, Canada, and France. The mean age of participants in these studies is varied, with some studies specifying the average age of participants ranging from the early 50s to the late 70s. The sample sizes of the studies are remarkably heterogeneous, from small groups of a few hundred individuals to large-scale datasets involving hundreds of thousands of participants. Such variation underscores the breadth of research contexts, from focused group analyses to extensive population-based studies. These are often evaluated alongside a range of other medications, including statins, anticoagulants, NSAIDs, and beta-blockers, among others. Populations studied are quite diverse, encompassing patients with ACS, those recovering from myocardial infarction (MI), individuals diagnosed with CHD, percutaneous coronary intervention (PCI) patients, healthcare professionals, and more general populations characterized by specific health conditions or associated risks. Regarding control comparisons, most studies utilized non-PPI users, PPI non-prescription groups, H2 receptor antagonist users, or placebo groups, offering a varied approach to establishing comparative baselines. PPIs usage is also detailed, with common PPIs such as omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole being mentioned across different studies. However, not all studies specify the PPIs used, which may be due to the focus of the study being on the outcome rather than the specific treatments. The follow-up periods for these studies vary widely, some extending up to 16 years, allowing for long-term outcome assessments and others providing short-term data. However, a significant number of studies do not report on the follow-up duration, which suggests that either a cross-sectional approach or a varied follow-up not central to the publication's main findings.

Risk of stroke with PPI use in patients with prior CVD

We performed a meta-analysis of 14 observational studies that reported HR and CI for the association of stroke and PPI use among patients with any type of CVD. The forest plot depicts the individual and pooled HRs for the

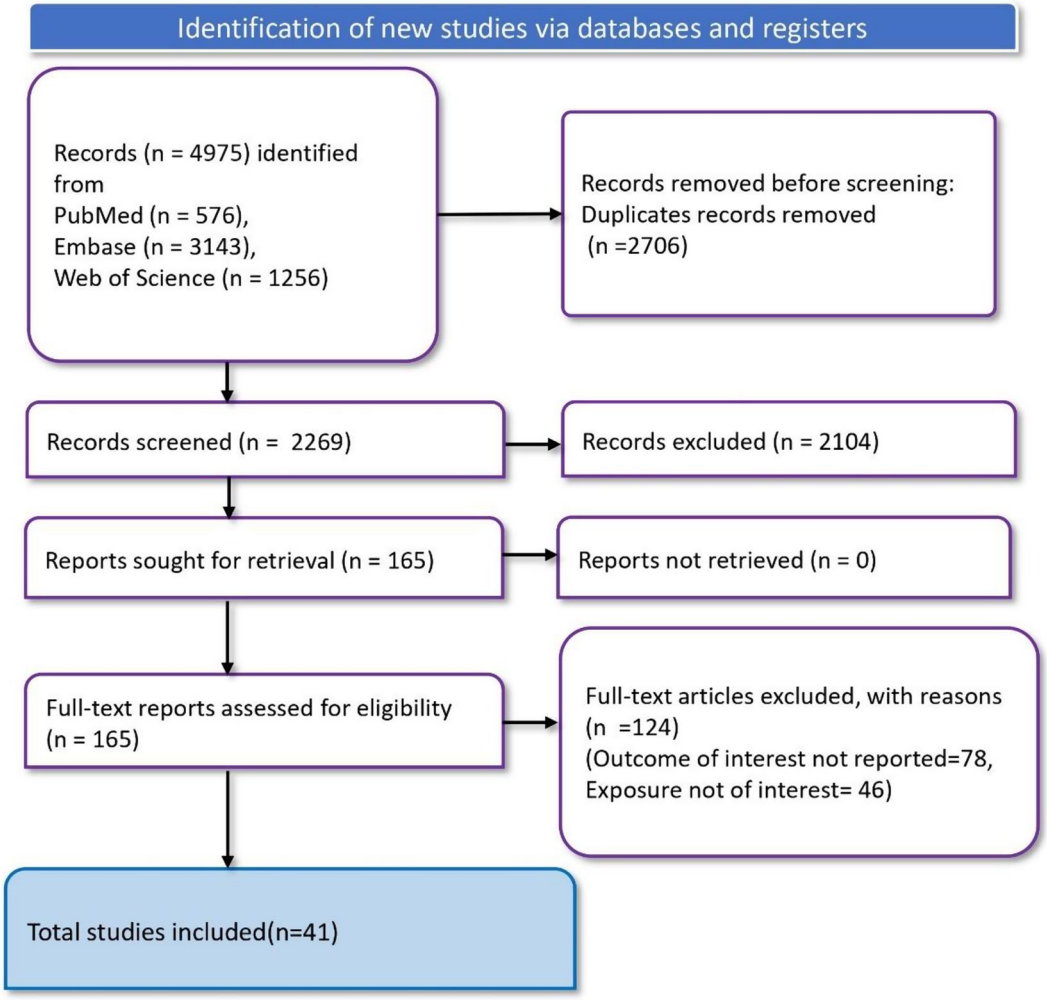

Fig. 1 PRISMA flow diagram depicting article selection and screening

risk of stroke associated with PPI use in patients with prior CVD (Fig. 2). The pooled HR for stroke was found to be 1.222 (95% CI: 0.963 to 1.481), implying a slight overall increased risk of stroke with PPI use in patients with prior CVD. However, the confidence interval spans the null value of 1, suggesting the possibility of no effect. The analysis revealed a substantial heterogeneity among the studies (I^2 = 78%).

Five RCTs reported the stroke outcome with PPI use in patients with CVD. The collective sample size for the PPI group is 11,500 individuals, while the control group comprises 11,528 individuals across all included studies. In terms of stroke events, 189 events were reported in the PPI group and 164 events in the control group. The pooled relative risk (RR) from the meta-analysis is 1.158 (95% CI: 0.914 to 1.466), indicating no statistically significant increase in the risk of stroke for PPI users compared to non-users in the context of CVD (p = 0.15) (Fig. 3). The studies were homogenious (I^2 = 0%).

Risk of stroke with PPI use in patients with no prior CVD

We performed a meta-analysis of 15 observational studies that reported HR and CI for the association of stroke and PPI use among the general population or persons without CVD. The forest plot depicts the individual and pooled HRs for the risk of stroke associated with PPI use in patients with prior CVD (Fig. 4). The pooled HR for stroke was found to be 1.15 (95% CI: 1.023 to 1.288), implying a slight overall increased risk of stroke with PPI use in patients without CVD. The analysis revealed a substantial heterogeneity among the studies (I^2 = 98%).

Publication bias

We evaluated publication bias using the Doi plot and the corresponding LFK index. For the analysis of participants with prior CVD, the LFK index is 2.89, while the meta-analysis of non-CVD participants stands at 3.83 (Fig. 5). An LFK index above 1 indicates potential bias and values exceeding 2 suggest significant asymmetry. This asymmetry suggests that smaller or non-significant studies may

Table 1 Characteics of included studies

Author	Year	Study design	Country	Mean age	Male %	Sample size	Medications	Type of Population	Type of control	HR/OR for Stroke (95% CI)	PPI used	Follow up
Aihara [17]	2012	Retrospective Cohort study	Japan	69	72.6	1887	Ethyl icosapentate, Warfarin, Statins, ACE inhibitors, Angiotensin receptor blocker, β-blockers, Nitrate, Diuretics	Patients treated with clopidogrel following coronary stenting were enrolled in the Ibaraki Cardiac Assessment Study (ICAS) registry	Non PPI users	HR = 1.21 (0.48–3.19)	Lansoprazole, omeprazole, rabeprazole	1 year
Bell [5]	2021	Cohort study	USA	42	75		Antihypertensive medications, lipid medications, and aspirin	General population aged 45 to 64 years	Non PPI users	HR = 1.78; 95% CI, 0.92–3.44	NA	NA
Bhatt [18]	2010	RCT	Multiple countries (15)	68.5	66.9	3761	Asprin, statin, clopidogrel	Patient recieving dual antipletelet therapy	Placebo	HR- 0.6667 (0.1229–3.6263).	Omeprazole	0.5 years
Chang [19]	2024	Cohort study	Taiwan	NA	65.6	1451	Clopidogrel	Patients diagnosed with ACS	Clopidogrel without PPI	HR = 1.65 (1.12–2.86)	Pantoprazole, omeprazole	7 years
Charlot [20]	2010	Cohort study	Denmark	73.3	53.3	56,406	Clopidogrel	Patients older than 30 years who were hospitalized with acute myocardial infarction	Non PPI users	HR = 1.78 (1.47–2.16)	Pantoprazole, lansoprazole, omeprazole, esomeprazole, rabeprazole	1 year
Charlot [7]	2011	Retrospective propensity score-matched study	Denmark	72.7	53.8	19,925	Aspirin	Aspirin treated patients surviving 30 days after a first MI	Non-PPI users	HR = 1.20 (0.99–1.46)	Pantoprazole, lansoprazole, omeprazole, esmoprazole, rabeprazole	
Dunn [21]	2013	Clinical trials (CREDO)	USA	61.8	70.3	2116	NA	CREDO trial patient	Non PPI users	HR = 1.67 (1.06 to 2.64)	Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole	1 year
Farhat [22]	2020	Nested case-control study	USA	67.8	59.3	52,006	Clopidogrel	Patient hospitalized for a first MI	Non PPI users	HR = 0.96 (0.85–1.08)	Omeprazole, lansoprazole	1 year
Foresta [23]	2024	Cohort study	Italy	65	NA	284,068	NA	0lder people with diabetes mellitus	Non PPI users	HR 1.14, 95% CI 95% 1.08–1.20		6.7 years
Geng [24]	2022	Cohort study	UK	NA	NA	19,229	NA	Adults with Type II Diabetes	PPI Non users	HR- 1.30 (1.16–1.45)	NA	10.9 to 11.2 years
Goodman [25]	2012	RCT	USA	63	72.4	18,624	Ticagrelor, Clopidogrel	Patients hospitalized for an ACS	Non PPI users	HR = 1.20 (1.04–1.38) Clopidogrel, HR = 1.24 (1.07–1.45) Ticagrelor	Omeprazole, pantoprazole, esomeprazole, lansoprazole, and rabeprazole	6 months

Table 1 (continued)

Author	Year	Study design	Country	Mean age	Male %	Sample size	Medications	Type of Population	Type of control	HR/OR for Stroke (95% CI)	PPI used	Follow up
He [26]	2021	Retrospective study	China	66.9	61.2	638	Clopidogrel	Patient with CHD	Non-PPI users	HR = 1.88 (0.676–5.258)	Pantoprazole, Rabeprazole, Lansoprazole, Omeprazole, Esomeprazole	1.5 years
Hoedemaker [27]	2018	Prospective cohort study	Netherlands	67.1	69.7	4595	Asprin, OAC, P2Y12 inhibitor, Digoxin, diuretics	ACS patients	Non PPI users	HR 0.33, 95% CI 0.14–0.81	NA	30 days
Hsu [28]	2011	RCT	Taiwan	70.6	78.3	165	NA	Patients with history of gastroduodenal ulcer and CVD	Non PPI users	NA	Esomeprazole	6 Months
Jang [29]	2024	Nested case-control study	Korea	NA	53.9	1,37,715	NA	General population	Non-PPI users	HR = 1.62 (1.57–1.68)	NA	16 years
Juurlink [30]	2010	Nested case-control study	Canada	77	42.4	2765	ACE Inhibitor, ARB, Asprin, Beta blockers, Ca channel blockers, statin, thiazide diuretics, hypertensives	Ischemic stroke or TIA patient on Clopidogrel therapy	Non PPI users	OR: 1.05 (0.60–1.82)	Omeprazole, rabeprazole, pantoprazole, and lansoprazole	6 Months
Kim [31]	2022	Retrospective cohort study	KOREA	NA	NA	8007	NA	PPIs and H2 receptor antagonist (H2RA) users Without history of ischemic stroke	Non PPI users	OR = 1.02, 95% CI 0.71–1.48; I2 = 53%	NA	NA
Kim [32]	2024	Retrospective, cohort study	Korea	69.1	39.2	4128	NA	Patients with CKD	H2RA users	HR- 1.06 (0.75–1.50)	NA	2.8 Years
Kosedo [33]	2019	Cohort study	Japan	66.2	60.6	376	PPI, NSAID, Asprin, Warfarin, ACE inhibitors, AngiotensinII receptor blockers, Calcium channel blockers, statin	Patients undergoing Maintenance hemodialysis	PPI Non users	HR -4.26 (0.94–19.22)	omeprazole, rabeprazole, lansoprazole, esomeprazole	1 year
Kreutz [34]	2010	Retrospective cohort study	USA	65.2	74.9	16,690	NA	Patients who had undergone PCI with stent placement and who were highly adherent to clopidogrel therapy alone or to clopidogrel with a PPI		HR- 1.48 (1.08–2.01)	Omeprazole, esomeprazole, pantoprazole, and lansoprazole	1 year
Lee [35]	2023	Retrospective cohort Study	Korea	67.3	54.2	76,155	Clopidogrel	Patients with stroke or MI	PPI non-prescription group	HR = 1.34 (1.01–1.76)	Pantoprazole, rabeprazole, esomeprazole, lansoprazole	NA
Li [6]	2023	Prospective cohort study	UK	56.2	NA	459,207	NA	General population	PPI Non users	HR- 1.21 (1.09–1.33)	NA	NA

Table 1 (continued)

Author	Year	Study design	Country	Mean age	Male %	Sample size	Medications	Type of Population	Type of control	HR/OR for Stroke (95% CI)	PPI used	Follow up
Ma [36]	2022	Prospective cohort study	UK	68.1	41.6	316,730	NA	Participants without CVD or anti-hypertensive treatment at baseline (2006–2010) in the UK Biobank	H2RA users	HR: 1.16, 95% CI: 1.09–1.23, omeprazole (HR: 1.19, 95% CI: 1.11–1.28), lansoprazole (HR: 1.11, 95% CI: 1.02–1.22), and pantoprazole (HR: 1.40, 95% CI: 1.00–1.97)	Omeprazole, lansoprazole, and pantoprazole	12.5 Years
Maret-Ouda [37]	2022	Retrospective cohort study	Sweden	69	70.8	99,836	Clopidogrel	PCI patients	Clopidogrel without PPI	HR = 1.21 (1.05–1.40)	Omeprazole, pantoprazole, esomeprazole	1 year
Moayedi [38]	2019	RCT	Nordic countries	67.6	78	17,598	NSAID, Diuretics, Beta blockers, ACE Blockers, Angiotensin II, SSRI, lipid-lowering agents	Stable CVD and PAD patients	Placebo	HR = 1.16 (0.94–1.44)	Pantoprazole	3.01 years
Nguyen [39]	2018	Prospective cohort study	USA	69	29	97,503	NA	Health care professionals	Non-PPI users	HR = 1.09 (0.89–1.34)	NA	NA
Nolde [40]	2021	Cohort study	Germany	51.1	44	1,180,181	Antidabetic medicine, Antipletelet, anticoagulants, NSAIDS, Statins, Asprin, Clopidogrel, serotonin, reuptake inhibitors	Individuals with no prior history of MI or stroke, who had an elective upper gastrointestinal endoscopy	H2RA users	HR: 0.98 (0.89–1.08)	NA	8 Years
Ono [41]	2022	Post hoc analysis of RCT	Multiple countries	64.9	24.7	15,839	Aspirin, clopidogrel/ticagrelor	PCI patients	Anticoagulant therapy without PPI	HR = 2.18(1.23–3.86)	NA	2 years
Pannoi [42]	2024	Retrospective cohort study	Thailand	NA	36.26	59,322	NA	Patients administered with PPI and H2RA	H2RA users	HR = 3.53 (2.21–5.64)	Omeprazole	7 years
Rooney [43]	2021	Longitudinal cohort study	USA	75.2	47	4,436	NA	General population aged 45 to 64 years	Participants without PPI	HR = 0.91 (0.58–1.42)	NA	5.6 years
Sehested [53]	2018	Cohort study	Denmark	55	43.3	214,998	Aspirin. Anticoagulant treatment, statin or NSAIDs	Individuals who underwent an elective upper endoscopy	Non PPI users	HR = 1.13 (1.08–1.19)	Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole, Esomeprazole	5.8 year
Shi [44]	2020	Propensity score analysis	China	62.65	74.4	23,380	Clopidogrel	AMI patients	Non PPI users	OR = 1.635 (1.341–2.517)	NA	NA

Table 1 (continued)

Author	Year	Study design	Country	Mean age	Male %	Sample size	Medications	Type of Population	Type of control	HR/OR for Stroke (95% CI)	PPI used	Follow up
Shi [45]	2021	Prospective observational study	China	58.37	78.2	17,247	Cliopidogrel, Heparin, Beta blockers (70–75%)	AMI patients with low risk of gastrointestinal bleeding	Non PPI users	HR = 2.072 (1.388–3.091)	NA	2 Years
Simon [46]	2011	Cohort study	France	65	71	2744	Aspirin, β-blockers, ACE inhibitors, Statin	Patient with MI	Non PPI users	OR = 0.33(0.12–0.92) with clopidogrel, a OR = 3.21 (0.24–42.5) without clopidogrel	Omeprazole, Esomeprazole, Lanzoprazole, Pantoprazole	1 year
Stupnicki [47]	2003	RCT	Multicountry	64	25	515	NSAIDS	Rheumatic patients who were likely to take NSAIDs continuously for at least 6 months	Patient taking Misoprostol	NA	Pantoprazole	NA
Torrero [48]	2020	Cohort study	Spain	67.3	73.6	5170	Diuretics, Beta blockers, ACE Blockers, Angiotensin II antagonist, Clopedogril, Anticoagulants, Statins, Insulin	Patients with symptomatic artery disease with at least, one recent (less than 3 months before enrollment) episode of CAD, CVD or PAD	PPI Non users	HR: 0.93; 95%CI: 0.64–1.35	NA	3 years
Wang [49]	2017	Nested case control study	Taiwan	51.7	53.6	198,148	Asprin, clopedogril, Warfarin, antidepressants, steroids, Antidepressant, ACE inhibitor, Beta blocker, Calcium-channel blocker, Dipyridamole Diuretic, Insulin, Non-steroidal anti-infl ammatory drug, Oral anti-hyperglycemic drug, Statin	Patient aged 20 years and above not been diagnosed as having atrial fi brillation, AIDS, HIV infection, cerebrovascular disease, or cancer before, not used any PPI within 30 days before current prescription, not hospitalized for prior 30 days	Non PPI users	HR 1.36 (95% confi dence interval (CI) 1.14–1.620	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	120 days
Weiss [50]	2020	Cohort study	Israel	82.2	38	29,639	NA	all community-dwelling individuals aged 65–95 years from 2002 through 2016	PPI Non users	HR 0.73, 95% C.I. 0.69–0.77	Omeprazole	10.58 years
Yang [11]	2021	Cohort study	UK	57	55.4	492,479	Asprin, non asprin NSAID, Paracetamol, Antihypertensive drugs, Metformin, Statins, H2RA, Anticoagulants/ antipletelets, Multivitamin, Mineral supplements	Participants enrolled in UK Biobank aged 37–73 year free of stroke (2006–2010)	Non PPI users	HR- 1.16 (1.06,1.27)	omeprazole, lansoprazole, esomeprazole, rabeprazole, pantoprazole.	8.0 years

Table 1 (continued)

Author	Year	Study design	Country	Mean age	Male %	Sample size	Medications	Type of Population	Type of control	HR/OR for Stroke (95% CI)	PPI used	Follow up
Yeoman [51]	2008	RCT	Multicountry	69.5	56.8	992	Asprin	Patients aged ≥ 60 year, without baseline gastroduodenal ulcer at endoscopy, who were receiving aspirin 75–325 mg once daily	Placebo	NA	Esomeprazole	6 months
Zhu [52]	2017	Propensity score analysis	China	60.2	75.4	7868	Aspirin and clopidogrel	Patient who underwent PCI	Non PPI users	HR = 0.730 (0.409–1.302)	NA	1 year

Abbreviations: ACS - Acute Coronary Syndrome; AMI - Acute Myocardial Infarction; ACE - Angiotensin-Converting Enzyme; ARB - Angiotensin Receptor Blocker; CAD - Coronary Artery Disease; CHD - Coronary Heart Disease; CKD - Chronic Kidney Disease; CVD - Cardiovascular Disease; HR - Hazard Ratio; ICAS - Ibaraki Cardiac Assessment Study; MI - Myocardial Infarction; NSAID - Non-Steroidal Anti-Inflammatory Drug; OAC - Oral Anticoagulant; OR - Odds Ratio; PAD - Peripheral Artery Disease; PCI - Percutaneous Coronary Intervention; PPI - Proton Pump Inhibitor; RCT - Randomized Controlled Trial; SSRI - Selective Serotonin Reuptake Inhibitor; TIA - Transient Ischemic Attack

be underrepresented. Therefore, the results of our meta-analysis should be approached with caution, acknowledging the potential overestimation of the effect size.

Discussion

This systematic meta-analysis has brought to light the nuanced relationship between PPI use and the risk of stroke, both in populations with and without pre-existing CVDs. We analyzed 14 observational studies and found a slightly elevated pooled hazard ratio of 1.222 in patients with prior CVD. However, the 95% confidence interval touched the null value, suggesting this could be due to chance. This subtle association remained when looking at RCTs with non-significant pooled RR. Similarly, our analysis of observational studies among individuals without pre-existing CVD yielded a pooled hazard ratio of 1.15, albeit amidst a backdrop of substantial heterogeneity.

Our findings align with the literature that reports mixed outcomes regarding PPI use and cardiovascular events. The mechanisms by which PPIs may contribute to increased stroke risk, although speculative, are multifactorial. Impairment of antiplatelet effects, particularly in individuals on concomitant clopidogrel therapy, has been hypothesized, given the PPIs' potential to inhibit the enzyme CYP2C19 which activates clopidogrel. Furthermore, PPI-induced changes in gut microbiota and subsequent production of trimethylamine N-oxide (TMAO), a pro-atherogenic compound, may offer another plausible pathway. Nutrient deficiencies, such as magnesium and B12, exacerbated by long-term PPI use, could also predispose individuals to vascular dysfunction and subsequent stroke.

A previous meta-analysis assessed the risk of stroke with PPI use from RCTs [54]. They found An RR of 1.22 for stroke. They concluded that consistent use of proton pump inhibitors has been linked to a heightened risk of experiencing a stroke, and this risk tends to be more pronounced in those who already have a greater inherent risk of stroke. However, our results from RCTs and observational studies of patients who already had CVD did not reveal a statistical relationship between stroke and PPI use. In our analysis of the general population without CVD and people with other diseases like diabetes and CKD, we found a significant relationship between stroke and PPI use. This needs further exploration.

The clinical implications of this systematic review and meta-analysis are significant and warrant careful consideration in clinical practice. Despite the widespread use of PPIs for managing gastrointestinal disorders and their generally favorable safety profile for short-term use, our analysis indicates a potential increase in stroke risk, particularly among individuals without pre-existing CVD. In patients with a history of CVD, our analysis did not show a statistically significant relationship between PPI use and

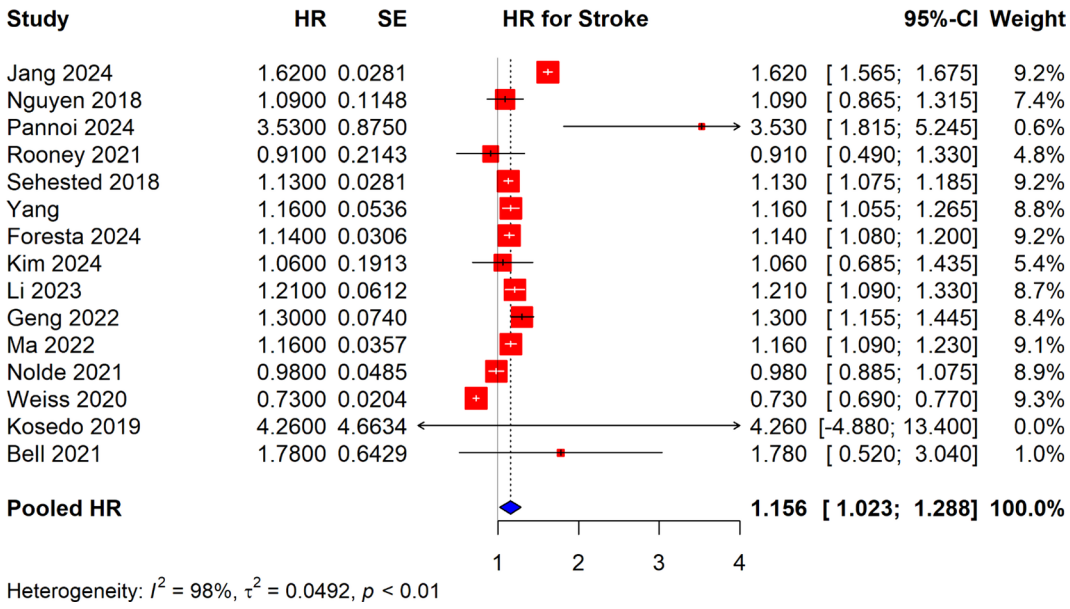

Fig. 2 Forest plot depicting the association of PPI use and stroke risk among patients with prior CVD from observational studies

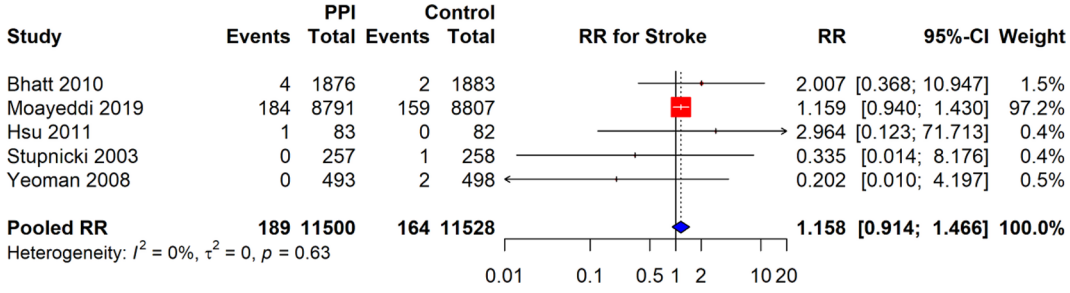

Fig. 3 Forest plot depicting the association of PPI use and stroke risk among patients with prior CVD from RCT

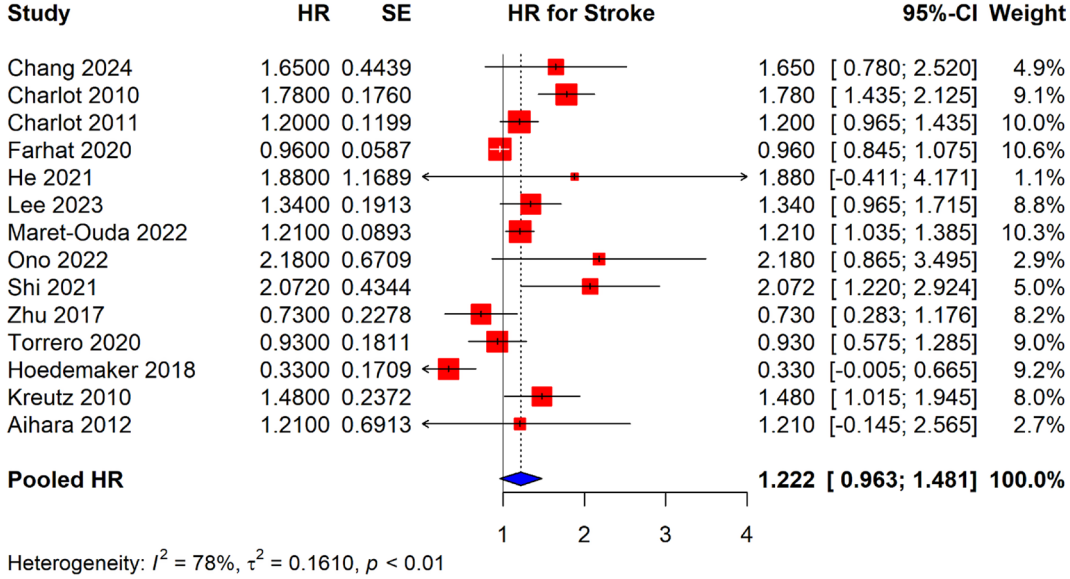

Fig. 4 Forest plot depicting the association of PPI use and stroke risk among patients without prior CVD from observational studies

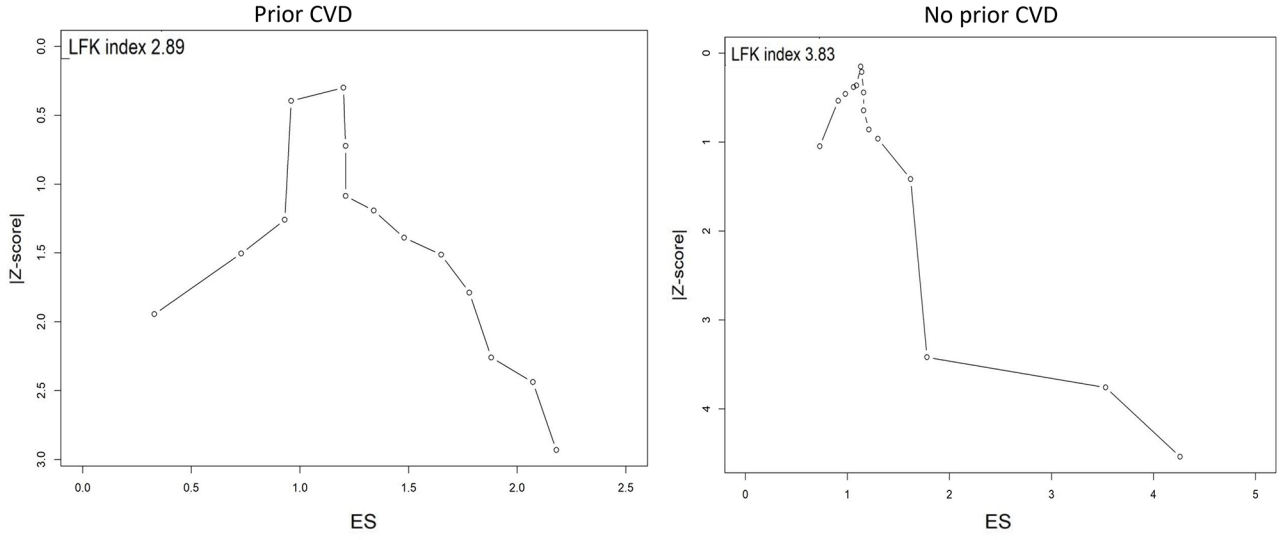

Fig. 5 Publication bias assessment

stroke risk. This suggests that for these patients, the benefits of PPIs in managing gastrointestinal risks associated with antiplatelet therapy may outweigh the potential but uncertain risk of stroke. However, given our study's heterogeneity and potential publication bias, each patient's risk profile must be individually assessed. Clinicians are advised to remain vigilant about the duration and necessity of PPI therapy, opting for the lowest effective dose and considering alternative treatments where possible. The decision to initiate or continue PPI therapy should be based on a thorough evaluation of individual patient risks and benefits, and patients should be adequately informed about the potential risks associated with long-term PPI use. In light of these findings, it is clear that more research is needed to understand the exact mechanisms by which PPIs may influence stroke risk and to identify which patient populations may be most at risk. Until then, the prescribing of PPIs, especially for individuals with risk factors for stroke, should be approached with a judicious and evidence-based perspective.

To refine our understanding of PPI use and its potential association with stroke risk, large-scale, prospective RCTs specifically designed to investigate cardiovascular outcomes are needed. These studies should aim to stratify participants according to their baseline risk for stroke, pre-existing cardiovascular conditions, and other risk factors like diabetes and CKD. There is also a need for mechanistic studies to elucidate the biological pathways through which PPIs may influence stroke risk, which could lead to targeted interventions or the development of safer therapeutic alternatives. Additionally, research into patient subgroups based on genetic predispositions, such as variants in the CYP2C19 gene, which may modify the effect of PPIs, could provide valuable insights for personalized medicine approaches. Finally, long-term observational studies with rigorous methodologies and adjustments for confounders are essential to understanding the real-world implications of chronic PPI use. Another potential consideration for future research could involve the design of a RCT PPIs with Gaviscon for managing conditions like gastroesophageal reflux disease (GERD). Such a study could provide clarity on the relative efficacy and safety profiles of these two widely used treatments, especially in light of increasing concerns around long-term PPI use, including risks of nutrient deficiencies, renal impairment, and altered microbiomes. However, given the extensive and routine clinical use of PPIs, an RCT may present ethical challenges. Patients assigned to a Gaviscon-only group could potentially be deprived of a more established treatment standard, raising concerns about withholding a proven therapeutic option. Careful ethical considerations, along with the establishment of robust monitoring and criteria for therapeutic crossover, would be essential in designing a trial that respects patient welfare while addressing this important question.

Our study is subject to several limitations that merit consideration. The substantial heterogeneity identified, particularly in the non-CVD cohort, reflects the diverse methodologies and populations represented in the included studies. This diversity complicates the task of drawing definitive conclusions. Secondly, the predominance of observational studies in our analysis introduces the inherent limitation of potential confounding factors, precluding the establishment of causality. Studies didn't account for CHADSVasc scores, which could provide additional insights into the stroke risk associated with the patient's pre-existing cardiovascular conditions. Additionally, our review was constrained to studies published in English, which may introduce language bias and overlook relevant research published in other languages. PPI

types varied across studies could influence the associated risk profiles and contribute to the observed heterogeneity. Differences in follow-up durations and patients' comorbid conditions further compound this heterogeneity. These factors were not uniformly addressed in the analysis, which may affect the generalizability and applicability of our findings. Future studies will need to adopt more standardized approaches to minimize such variability and allow for more robust comparative analyses.

Conclusion

Our analysis of PPI use and stroke risk reveals no significant increased risk among individuals with pre-existing cardiovascular conditions but a modest increase in the general population. Significant heterogeneity and potential publication bias among the studies necessitate a cautious interpretation of these findings. Given the widespread use of PPIs, clinicians should judiciously assess the risk-benefit ratio of PPI therapy, especially in patients at risk for stroke. Further high-quality research is needed to clarify the mechanisms underlying PPI-associated stroke risks and to guide more informed clinical decision-making.

Supplementary Information

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Supplementary Material 1

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Author contributions
Muhammed Shabil, Bijaya K Padhi, Edward Mawejje: Conceptualization (lead); writing – original draft (lead), review and editing (equal); Quazi Syed Zahiruddin, Mahalaqua Nazli Khatib: formal analysis (lead); writing – review and editing (equal). Sarvesh Rustagi, Divya Sharma, Mithhil Arora: Software (lead); writing – review and editing (equal). Rakesh Kumar Sharma, Edward Mawejje, Sanjit Sah, Soumya V Menon, Mandeep Kaur, Mukesh Kumari, Puneet Sudan, K. Satyam Naidu, Prakasini Satapathy: Methodology (lead); writing – review and editing (equal).

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Data availability
All data are presented within the manuscript and are available by contacting the corresponding author.

Declarations

Ethic approval
Ethics approval was not required for the study as it is a secondary analysis of existing data that previously published.

Consent for publication
All authors gave consent for publication.

Competing interests
The authors declare no competing interests.

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