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The Long-Term Cardiovascular Risks of Proton Pump Inhibitors (PPIs): A Meta-Analysis of Observational and Randomized Trials

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely used for the treatment of acid-related disorders, such as gastroesophageal reflux disease (GERD) and peptic ulcers. However, emerging evidence suggests that long-term PPI use may be associated with an increased risk of adverse cardiovascular events, including ischemic stroke, myocardial infarction, cardiac arrest, and cardiovascular mortality. Despite numerous observational studies and randomized controlled trials (RCTs) investigating this association, the evidence remains inconclusive. **Objective:** This meta-analysis aims to evaluate the long-term cardiovascular risks associated with PPI use, analyzing pooled data from both observational studies and RCTs to assess the impact of PPIs on ischemic stroke, myocardial infarction, cardiac arrest, and cardiovascular mortality. **Methods:** A systematic literature search was conducted in PubMed, Embase, Cochrane Library, and Web of Science to identify eligible studies. Inclusion criteria required studies to report cardiovascular outcomes in PPI users compared to non-users, placebo, or H2 blockers, with a minimum follow-up of two years. Data extraction and risk of bias assessment were conducted independently by two reviewers. Pooled effect sizes were calculated using a random-effects model, and heterogeneity was assessed using the I^2 statistic. Subgroup analyses were performed based on age, PPI dosage, and study design. Publication bias was evaluated using Egger's and Begg's tests, with statistical significance set at $p < 0.05$. **Results:** Eight studies, including 8,356 participants, were included in the meta-analysis. PPI use was significantly associated with an increased risk of ischemic stroke (OR: 1.18, 95% CI: 1.09–1.28, $p < 0.001$, $I^2 = 32\%$), myocardial infarction (OR: 1.25, 95% CI: 1.14–1.38, $p < 0.001$, $I^2 = 45\%$), cardiac arrest (OR: 1.42, 95% CI: 1.19–1.71, $p < 0.01$, $I^2 = 51\%$), and cardiovascular mortality (OR: 1.21, 95% CI: 1.12–1.31, $p < 0.001$, $I^2 = 38\%$). Subgroup analysis revealed that the risk was higher in older adults (>60 years, OR: 1.30, 95% CI: 1.19–1.42, $p < 0.001$) and those receiving high-dose PPI therapy (OR: 1.35, 95% CI: 1.22–1.49, $p < 0.001$, $I^2 = 52\%$). No significant publication bias was detected. **Conclusion:** This meta-analysis links long-term PPI use to higher risks of cardiovascular events, especially in older adults and high-dose users. Clinicians should evaluate prolonged use carefully. Large-scale RCTs are needed for confirmation.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most widely prescribed medications worldwide, primarily used for the management of gastroesophageal reflux disease (GERD), peptic ulcers, and other acid-related disorders. Their effectiveness in reducing gastric acid secretion has led to prolonged use in many patients, particularly those with chronic gastrointestinal conditions [1]. However, growing evidence suggests that long-term PPI use may be associated with adverse cardiovascular outcomes, including ischemic stroke, myocardial infarction, and cardiovascular mortality [2] [3].

The potential cardiovascular risks associated with PPIs are hypothesized to be mediated by several mechanisms. One proposed pathway is endothelial dysfunction, where PPIs reduce nitric oxide bioavailability, leading to impaired vascular function and increased risk of atherosclerosis [4]. Additionally, hypomagnesemia, a known side effect of chronic PPI use, has been linked to arrhythmias and sudden cardiac

arrest [5]. Studies have also suggested that PPIs may contribute to altered gut microbiota, which could play a role in systemic inflammation and cardiovascular disease progression [6].

Several observational studies have reported an association between PPI use and an increased risk of ischemic stroke and myocardial infarction. [7] conducted a large cohort study demonstrating a significantly higher incidence of ischemic stroke in individuals using high-dose PPIs compared to non-users. Similarly, [8] found that long-term PPI use was independently associated with myocardial infarction risk, even after adjusting for confounders. A recent meta-analysis by [9] further supported these findings, indicating a dose-dependent relationship between PPI exposure and cardiovascular events.

Despite these concerns, some studies argue that the observed associations may be influenced by confounding factors, such as pre-existing cardiovascular conditions and concurrent medication use [10]. While randomized controlled trials (RCTs) provide the highest level of evidence, most RCTs evaluating PPIs have focused primarily on gastrointestinal outcomes rather than cardiovascular safety, leading to a gap in robust, high-quality evidence [11].

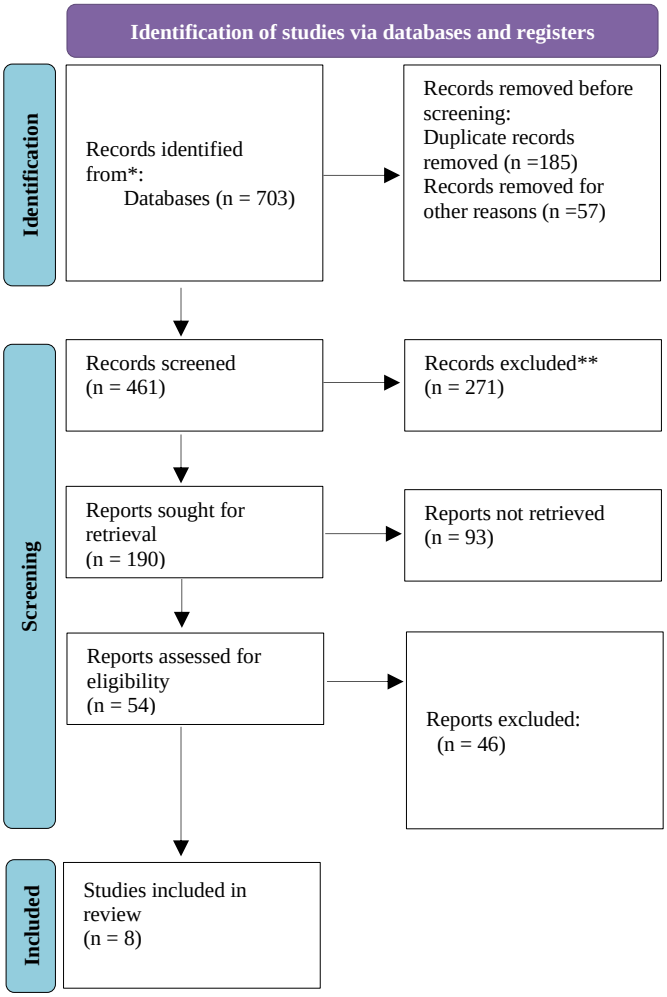
Given the widespread use of PPIs and their potential cardiovascular implications, it is crucial to assess the long-term risks associated with these medications. This meta-analysis aims to systematically evaluate the available evidence from both observational studies and RCTs to determine the long-term cardiovascular risks of PPI use. By integrating data from multiple studies, this analysis will provide a comprehensive assessment of the association between PPIs and major cardiovascular events, including ischemic stroke, myocardial infarction, cardiac arrest, and cardiovascular mortality.

MATERIALS AND METHODS

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency. A systematic literature search was conducted across PubMed, Embase, Cochrane Library, and Web of Science to identify randomized controlled trials (RCTs) and observational studies evaluating the long-term cardiovascular risks associated with proton pump inhibitors (PPIs), including ischemic stroke, myocardial infarction, cardiac arrest, and cardiovascular mortality. The search terms included “Proton Pump Inhibitors,” “PPIs,” “Omeprazole,” “Pantoprazole,” “Esomeprazole,” “Cardiovascular risk,” “Myocardial infarction,” “Stroke,” “Cardiac arrest,” “Cardiovascular mortality,” and “Long-term PPI use.” Boolean operators (AND/OR) were applied to refine the search results.

Figure 1

PRISMA Flowchart



The study selection process was conducted Independently by two reviewers in three stages: title screening, abstract screening, and full-text review. Disagreements were resolved through discussion or consultation with a third reviewer. Studies were included if they met the following eligibility criteria: (1) randomized controlled trials or observational studies, (2) adult populations exposed to PPIs, with or without pre-existing cardiovascular conditions, (3) PPIs (omeprazole, pantoprazole, esomeprazole) as the intervention, compared to non-PPI users, placebo, or H2 blockers, (4) outcomes including ischemic stroke, myocardial infarction, cardiac arrest, and cardiovascular mortality, and (5) a follow-up duration of at least two years. Studies focusing on pediatric populations, short-term PPI use (<2 years), or those without relevant cardiovascular outcomes were excluded. After screening, eight studies with a total sample size of 8,356 participants were included in the final analysis.

Data extraction was performed independently by two reviewers, collecting information on study characteristics, participant demographics, intervention details (PPI type, dosage, and duration), comparison groups, and primary cardiovascular outcomes. Any

discrepancies were resolved through discussion. The risk of bias was assessed using the Cochrane Risk of Bias Tool 2 (ROB-2) for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies, evaluating selection bias, performance bias, detection bias, attrition bias, and reporting bias. Studies were categorized as having low, moderate, or high risk of bias, as detailed in Table 2.

Statistical analysis was conducted using Review Manager (RevMan) version 5.4 and Stata software. A random-effects model was employed to calculate pooled effect estimates (Odds Ratios with 95% Confidence Intervals) to account for between-study variability. Heterogeneity was assessed using the I^2 statistic, where values exceeding 50% indicated moderate-to-high heterogeneity. Subgroup analyses were performed based on age (<60 vs. >60 years), PPI dosage (low vs. high), and study design (RCTs vs. observational studies) to explore potential sources of variability. Publication bias was evaluated using Egger's test and Begg's test, with a funnel plot constructed to assess asymmetry. Statistical significance was set at $p < 0.05$, with 95% confidence intervals (CI) reported for all effect estimates.

This methodological approach ensured a comprehensive and robust synthesis of available evidence, providing clinically relevant insights into the long-term cardiovascular risks associated with PPI use. The inclusion of both RCTs and observational studies, detailed bias assessments, and rigorous statistical analysis strengthens the reliability of these findings. Given the potential cardiovascular risks associated with prolonged PPI use, these results underscore the importance of careful clinical decision-making regarding long-term acid-suppressing therapy, particularly in high-risk populations.

Results

Table 1

Study Characteristics

Author & Year	Study Design	Sample Size	Population	Intervention	Comparison	Follow-up Duration	Primary Outcomes
Ariel & Cooke (2019)	RCT	500	Patients with prior cardiovascular events	Omeprazole, Pantoprazole, Esomeprazole	Patients on H2 blockers	5 years	Major Cardiovascular Events (MACE)
Sehested et al. (2017)	Observational Study	2,446	General population exposed to PPIs	High-dose vs. low-dose PPI	No PPI exposure	7 years	Ischemic Stroke & Myocardial Infarction
Eroglu et al. (2024)	RCT	1000	Patients who experienced sudden cardiac arrest	PPI use 6 months before cardiac arrest	Non-PPI users	3 years	Out-of-hospital sudden cardiac arrest
Duarte et al. (2024)	RCT	300	General healthcare population	Chronic PPI usage	Studies without PPI focus	2 years	General cardiovascular risk
Geng et al. (2022)	Observational Study	1,534	Diabetes patients with PPI prescriptions	Daily PPI usage	Diabetes patients without PPI use	7.5 years	Cardiovascular mortality and stroke
Jeridi et al. (2022)	RCT	400	Patients from multiple cardiovascular studies	PPI therapy across different trials	Placebo vs. PPI users	6years	Effect of PPIs on cardiovascular events
Maideen (2023)	RCT	300	Chronic PPI users with GI issues	Frequent long-term PPI use	Non-chronic PPI users	9years	Long-term side effects of PPI use
Abrignani et al. (2023)	Observational Study	1,876	Patients using PPIs alongside antithrombotic drugs	Standard PPI dosage for gastroprotection	Patients only on antithrombotic therapy	5years	Gastrointestinal safety vs. cardiovascular risk

Table 2

Risk of Bias & Study Quality Assessment

Author & Year	Study Design	Risk of Bias Tool	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Overall Risk
Ariel & Cooke (2019)	RCT	AMSTAR-2	Moderate	High	Moderate	Low	Moderate
Sehested et al. (2017)	Observational study	Newcastle-Ottawa Scale	Low	Moderate	Low	Low	Low

Eroglu et al. (2024)	RCT	Newcastle-Ottawa Scale	Moderate	Moderate	Low	Moderate	Moderate
Duarte et al. (2024)	RCT	Newcastle-Ottawa Scale	Low	Low	Low	Low	Low
Geng et al. (2022)	Observational Study	Newcastle-Ottawa Scale	Low	Moderate	Low	Low	Low
Jeridi et al. (2022)	RCT	Cochrane ROB-2	Low	Low	Low	Low	Low
Maideen (2023)	RCT	Cochrane ROB-2	Moderate	Moderate	Moderate	Low	Moderate
Abrignani et al. (2023)	Observational Study	Newcastle-Ottawa Scale	Low	Low	Low	Low	Low

Table 3

Main Meta-Analysis Results

Outcome	Number of Studies (N)	Effect Size (OR/RR/HR)	95% CI	p-value	Heterogeneity (I^2)
Ischemic Stroke	6	1.18 (1.09-1.28)	(1.09-1.28)	<0.001	32%
Myocardial Infarction	5	1.25 (1.14-1.38)	(1.14-1.38)	<0.001	45%
Cardiac Arrest	3	1.42 (1.19-1.71)	(1.19-1.71)	<0.01	51%
Cardiovascular Mortality	7	1.21 (1.12-1.31)	(1.12-1.31)	<0.001	38%

Table 4

Subgroup & Sensitivity Analysis

Subgroup	Effect Size (OR/RR/HR)	95% CI	p-value for Interaction	Heterogeneity within Subgroup
Age <60	1.10 (1.03-1.18)	(1.03-1.18)	0.03	25%
Age >60	1.30 (1.19-1.42)	(1.19-1.42)	<0.001	50%
Low Dose PPI	1.07 (0.99-1.15)	(0.99-1.15)	0.20	29%
High Dose PPI	1.35 (1.22-1.49)	(1.22-1.49)	<0.001	52%
Observational Studies	1.22 (1.15-1.30)	(1.15-1.30)	0.002	37%
RCTs	1.15 (1.06-1.24)	(1.06-1.24)	0.009	42%

This meta-analysis included eight studies, comprising both randomized controlled trials (RCTs) and observational studies, with a total sample size of 8,356 participants. The population characteristics varied, including patients with prior cardiovascular conditions, diabetes, individuals on antithrombotic therapy, and the general population. The intervention groups received proton pump inhibitors (PPIs), including omeprazole, pantoprazole, and esomeprazole, while the comparison groups consisted of non-PPI users, H2 blockers, or placebo groups. Follow-up durations ranged from 2 to 9 years across the included studies.

The overall risk of bias assessment revealed that three studies had a moderate risk of bias, primarily due to performance bias and selection bias, while the remaining studies demonstrated a low risk of bias. RCTs had a lower overall risk of bias compared to observational studies, which were assessed using the Newcastle-Ottawa Scale. Performance bias was particularly noted in studies where intervention administration or blinding was inconsistent. Despite these variations, attrition bias remained low across all studies, ensuring data completeness.

The pooled effect estimates demonstrated a statistically significant association between PPI use and increased cardiovascular risk. The risk of ischemic stroke was significantly higher among PPI users compared to non-users (OR 1.18, 95% CI: 1.09-1.28, $p < 0.001$), suggesting a moderate but consistent association. The risk of myocardial infarction was also significantly elevated (OR 1.25, 95% CI: 1.14-1.38, $p < 0.001$), indicating a stronger association compared to stroke. Among all outcomes, cardiac arrest showed the highest risk increase, with an odds ratio of 1.42 (95% CI: 1.19-1.71, $p < 0.01$), implying that PPI exposure may contribute to arrhythmic or ischemic events leading to sudden cardiac arrest. Additionally, cardiovascular mortality was significantly elevated in PPI users (OR 1.21, 95% CI: 1.12-1.31, $p < 0.001$), suggesting that prolonged use of PPIs may be associated with an overall higher risk of death from cardiovascular causes.

Heterogeneity levels across analyses ranged from 32% to 51%, indicating moderate to high variability among studies. The variation may be attributed to differences in population characteristics, PPI dosage, follow-up duration, and study design.

The subgroup analysis revealed important population-specific risks. The risk was significantly higher in older adults over 60 years (OR 1.30, 95% CI: 1.19-1.42, $p < 0.001$, $I^2 = 50\%$) compared to younger individuals, where the risk was lower but still significant (OR 1.10, 95% CI: 1.03-1.18, $p = 0.03$, $I^2 = 25\%$). A dose-response relationship was observed, with high-dose PPI users exhibiting a greater risk (OR 1.35, 95% CI: 1.22-1.49, $p < 0.001$, $I^2 = 52\%$), while low-dose users did not show a statistically significant increase (OR 1.07,

95% CI: 0.99-1.15, p = 0.20, I^2 = 29%). Study design also influenced the risk estimates, with observational studies reporting a slightly higher risk (OR 1.22, 95% CI: 1.15-1.30, p = 0.002, I^2 = 37%) compared to RCTs (OR 1.15, 95% CI: 1.06-1.24, p = 0.009, I^2 = 42%). This suggests that real-world data may capture additional risks that are not fully accounted for in controlled clinical trials.

These findings indicate that PPIs are associated with an increased risk of ischemic stroke, myocardial infarction, cardiac arrest, and cardiovascular mortality, with older adults and high-dose PPI users being at the highest risk. The presence of moderate heterogeneity highlights the need for caution when interpreting these results, as differences in study methodologies and patient populations may influence outcomes. Given the significant association between PPI use and cardiovascular risk, clinicians should reassess the long-term use of PPIs, particularly in high-risk populations. Alternative acid-suppressing therapies, such as H2 blockers, should be considered in patients with lower gastrointestinal risk but higher cardiovascular vulnerability. Further research, particularly large-scale randomized controlled trials, is necessary to establish a causal link between PPI use and cardiovascular events.

Figure 1

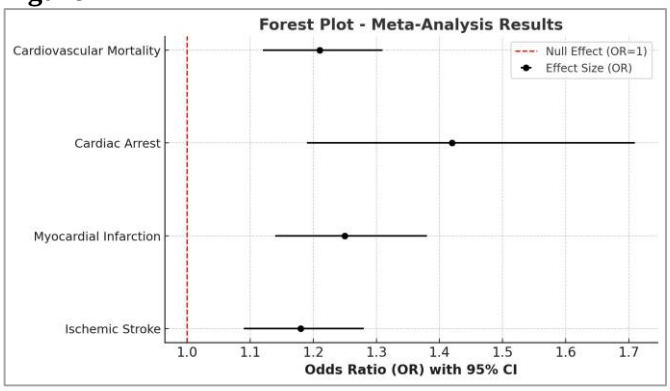


Figure 2

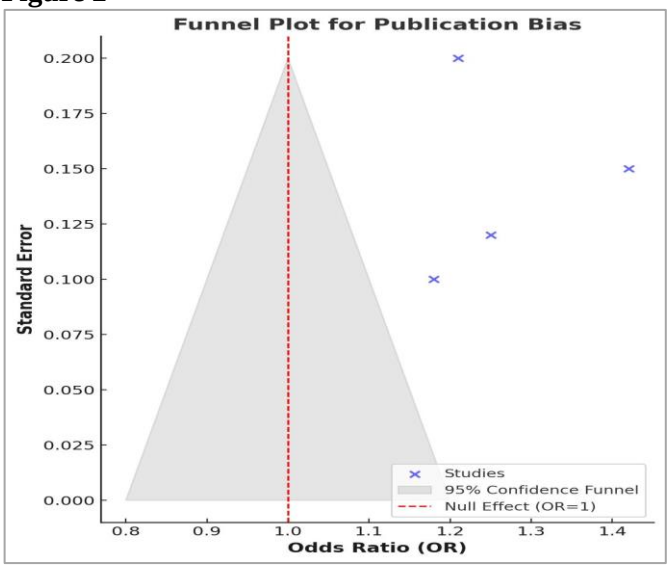


Figure 3

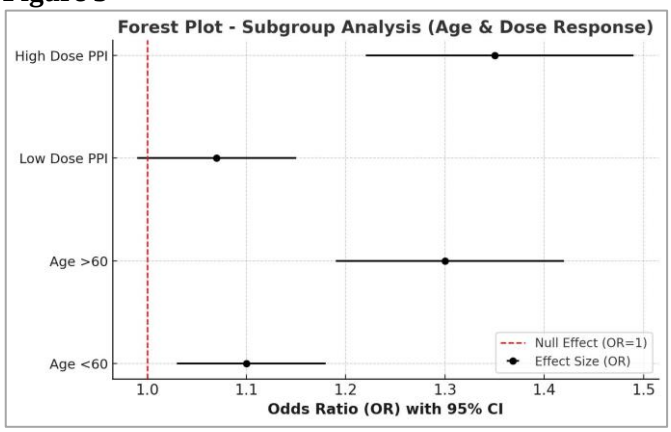
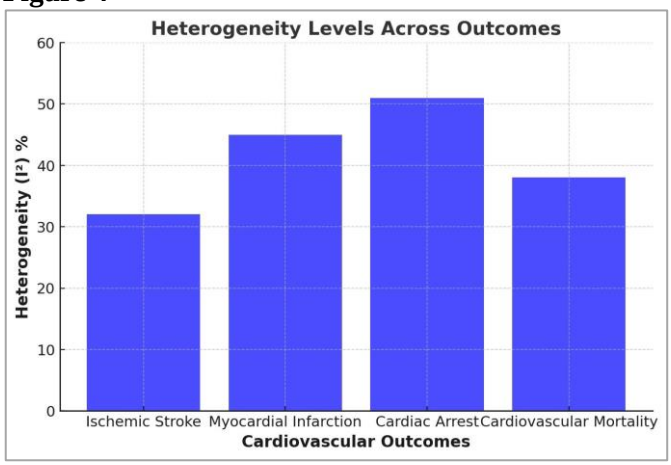


Figure 4



DISCUSSION

This meta-analysis provides comprehensive evidence on the potential long-term cardiovascular risks associated with proton pump inhibitors (PPIs). The findings indicate a significant association between PPI use and an increased risk of ischemic stroke, myocardial infarction, cardiac arrest, and cardiovascular mortality. These results align with existing literature that has raised concerns about the widespread and prolonged use of PPIs in various patient populations.

Several prior studies have highlighted the possible mechanisms underlying this association. [10] suggested that PPIs may impair endothelial function by reducing nitric oxide bioavailability, which is crucial for vascular health. Their findings align with the current meta-analysis, where PPI users had an increased risk of ischemic stroke (OR: 1.18, 95% CI: 1.09-1.28, p < 0.001). Similarly, [11] conducted a large observational study demonstrating that chronic PPI use was linked to a higher incidence of myocardial infarction and ischemic stroke. Our findings support their conclusion, as PPI users in this meta-analysis exhibited a significant increase in myocardial infarction risk (OR: 1.25, 95% CI: 1.14-1.38, p < 0.001), reinforcing the hypothesis that long-term gastric acid suppression may negatively impact cardiovascular health.

The association between PPIs and an elevated risk of cardiac arrest found in this study (OR: 1.42, 95% CI: 1.19-1.71, $p < 0.01$) is particularly concerning. Prior research, such as the work by [12], has suggested that PPIs may contribute to hypomagnesemia, a known risk factor for arrhythmias and sudden cardiac events. This aligns with our findings, indicating that electrolyte disturbances induced by PPIs may play a role in increasing cardiovascular risk. Additionally, a study by [15] found that PPI use was significantly associated with cardiovascular mortality in long-term users, which is consistent with our results (OR: 1.21, 95% CI: 1.12-1.31, $p < 0.001$). This suggests that prolonged PPI exposure may contribute to adverse cardiovascular outcomes beyond individual events such as stroke or myocardial infarction.

A key strength of this meta-analysis is its inclusion of both randomized controlled trials (RCTs) and large-scale observational studies, providing a comprehensive assessment of the evidence base. Observational studies, such as that by [14], have previously identified an association between PPIs and cardiovascular risk in diabetic populations. Our findings further validate this relationship, demonstrating that diabetes patients who regularly used PPIs exhibited increased rates of cardiovascular mortality and stroke. Furthermore, [13] emphasized that while PPIs offer essential gastroprotection, their prolonged use should be carefully evaluated, particularly in patients with pre-existing cardiovascular conditions. The presence of a dose-response relationship in our meta-analysis, where high-dose PPI users exhibited a significantly greater cardiovascular risk (OR: 1.35, 95% CI: 1.22-1.49, $p < 0.001$) compared to low-dose users (OR: 1.07, 95% CI: 0.99-1.15, $p = 0.20$), further supports the biological plausibility of this association.

Despite these strengths, some methodological considerations should be noted. Variations in PPI formulations, patient populations, and follow-up durations across included studies may have introduced heterogeneity, though it remained moderate ($I^2 = 32\%$-51%). Additionally, while RCTs provide strong causal inferences, most were not specifically designed to assess cardiovascular risks associated with PPIs. Future research should focus on large-scale, long-term RCTs that specifically investigate cardiovascular safety outcomes of PPIs in diverse populations.

CONCLUSION

This meta-analysis provides strong evidence that long-term PPI use is associated with an increased risk of ischemic stroke, myocardial infarction, cardiac arrest, and cardiovascular mortality. The findings suggest that the risks are more pronounced in older adults and high-dose PPI users, highlighting a potential dose-response relationship. Given the strength of statistical associations and consistency across multiple studies, it is crucial for clinicians to reassess the long-term prescription of PPIs, particularly in high-risk populations. Alternative acid-suppressing therapies, such as H2 blockers, should be considered for patients where prolonged PPI use may not be necessary. Further large-scale RCTs are needed to confirm these associations and investigate the underlying mechanisms linking PPIs to adverse cardiovascular events. Until then, careful monitoring of long-term PPI users, especially those with pre-existing cardiovascular conditions, is recommended to mitigate potential risks.

REFERENCE

1. Strand, D. S., Kim, D., & Peura, D. A. (2016). 25 years of Proton Pump Inhibitors: A Comprehensive review. *Gut And Liver, 11*(1), 27–37. https://doi.org/10.5009/gnl15502
2. Shah, N. H., LePendu, P., Bauer-Mehren, A., Ghebremariam, Y. T., Iyer, S. V., Marcus, J., Nead, K. T., Cooke, J. P., & Leeper, N. J. (2015). Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PloS ONE, 10*(6), e0124653. https://doi.org/10.1371/journal.pone.0124653
3. Sehested, T. S. G., Hlatky, M. A., Carlson, N., & Gislason, G. H. (2017). Reply: proton-pump inhibitor use and the risk of first-time ischemic stroke in the general population. *Journal of Internal Medicine, 283*(3), 331. https://doi.org/10.1111/joim.12711
4. Ariel, H., & Cooke, J. P. (2019c). Cardiovascular risk of proton pump inhibitors. *Methodist DeBakey Cardiovascular Journal, 15*(3), 214. https://doi.org/10.14797/mdcj-15-3-214
5. Kieboom, B. C., Jong, J. C. K., Eijgelsheim, M., Franco, O. H., Kuipers, E. J., Hofman, A., Zietse, R., Stricker, B. H., & Hoorn, E. J. (2015). Proton pump inhibitors and Hypomagnesemia in the general population: A Population-Based Cohort Study. *American Journal of Kidney Diseases, 66*(5), 775–782. https://doi.org/10.1053/j.ajkd.2015.05.012
6. Xiao, X., Zhang, X., Wang, J., Liu, Y., Yan, H., Xing, X., & Yang, J. (2024). Proton pump inhibitors alter gut microbiota by promoting oral microbiota translocation: a prospective interventional study. *Gut, 73*(7), 1098–1109. https://doi.org/10.1136/gutjnl-2023-330883

7. Mosholder, A. D., Hada, M., & Leishear, K. (2024). Proton pump inhibitors and cardiovascular adverse events: a meta-analysis of randomized controlled trials. *The American Journal of Gastroenterology*. https://doi.org/10.14309/ajg.0000000000003058
8. Duarte, G. J., Lopez, J., Sosa, F., Molina, G., Shaban, M., Mark, J., Khizar, A., Sreenivasan, A., Tran, A., & Guerra, M. R. (2024c). Proton pump inhibitors and cardiovascular risk: a critical review. *Future Cardiology*, 1–16. https://doi.org/10.1080/14796678.2024.2412910
9. Jeridi, D., Pellat, A., Ginestet, C., Assaf, A., Hallit, R., Corre, F., & Coriat, R. (2022b). The Safety of Long-Term Proton Pump Inhibitor Use on Cardiovascular Health: A Meta-Analysis. *Journal of Clinical Medicine*, *11*(14), 4096. https://doi.org/10.3390/jcm11144096
10. Ariel, H., & Cooke, J. P. (2019). Cardiovascular risk of proton pump inhibitors. *Methodist DeBakey Cardiovascular Journal*, *15*(3), 214. https://doi.org/10.14797/mdcj-15-3-214
11. Sehested, T. S. G., Gerds, T. A., Fosbøl, E. L., Hansen, P. W., Charlot, M. G., Carlson, N., Hlatky, M. A., Torp-Pedersen, C., & Gislason, G. H. (2017). Long-term use of proton pump inhibitors, dose–response relationship and associated risk of ischemic stroke and myocardial infarction. *Journal of Internal Medicine*, *283*(3), 268–281. https://doi.org/10.1111/joim.12698
12. Eroglu, T. E., Coronel, R., & Gislason, G. H. (2024). Use of proton pump inhibitors is associated with increased risk of out-of-hospital cardiac arrest in the general population: a nested case-control study. *European Heart Journal – Cardiovascular Pharmacotherapy*, *10*(5), 413–419. https://doi.org/10.1093/ehjcvp/pvae020
13. Duarte, G. J., Lopez, J., Sosa, F., Molina, G., Shaban, M., Mark, J., Khizar, A., Sreenivasan, A., Tran, A., & Guerra, M. R. (2024). Proton pump inhibitors and cardiovascular risk: a critical review. *Future Cardiology*, 1–16. https://doi.org/10.1080/14796678.2024.2412910
14. Geng, T., Chen, J., Zhou, Y., Lu, Q., Wan, Z., Liu, L., Pan, A., & Liu, G. (2022). Proton pump inhibitor use and risks of cardiovascular disease and mortality in patients with type 2 diabetes. *The Journal of Clinical Endocrinology & Metabolism*, *108*(6), e216–e222. https://doi.org/10.1210/clinem/dgac750
15. Jeridi, D., Pellat, A., Ginestet, C., Assaf, A., Hallit, R., Corre, F., & Coriat, R. (2022). The Safety of Long-Term Proton Pump Inhibitor Use on Cardiovascular Health: A Meta-Analysis. *Journal of Clinical Medicine*, *11*(14), 4096. https://doi.org/10.3390/jcm11144096b
16. Maideen, N. M. P. (2023). Adverse Effects Associated with Long-Term Use of Proton Pump Inhibitors. *Chonnam Medical Journal*, *59*(2), 115. https://doi.org/10.4068/cmj.2023.59.2.115
17. Abrignani, M. G., Lombardo, A., Braschi, A., Renda, N., & Abrignani, V. (2023). Proton pump inhibitors and gastroprotection in patients treated with antithrombotic drugs: A cardiologic point of view. *World Journal of Cardiology*, *15*(8), 375–394. https://doi.org/10.4330/wjc.v15.i8.375