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Proton Pump Inhibitors and Cardiac Safety: Emerging Evidence Linking Cardiovascular Disease, Arrhythmias, and Mechanistic Pathways

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Abstract

Proton pump inhibitors (PPIs) are globally prescribed medications long perceived as pharmacologically safe. However, emerging evidence challenges this, revealing a potential association between chronic PPI exposure and adverse cardiovascular outcomes, including arrhythmogenesis. This review synthesizes findings from large, robust epidemiologic cohorts (ARIC, UK Biobank, Danish registries, Women's Health Initiative (WHI)), consistently demonstrating that long-term PPI use is associated with higher risks of myocardial infarction, stroke, heart failure, and malignant arrhythmias, including out-of-hospital cardiac arrest and atrial fibrillation. These associations exhibit clear duration and dose-response patterns and are not replicated with H2-receptor antagonists, suggesting a PPI-specific pharmacologic effect. Arrhythmic outcomes, while clinically consequential, remain under-investigated. We place particular emphasis on their biological plausibility. Mechanistic evidence provides converging pathways, including TRPM6/7-mediated hypomagnesemia, direct blockade of the hERG potassium channel, oxidative stress-driven remodeling, sympathetic hyperinnervation, and nitric oxide signaling impairment. Collectively, these influence myocardial repolarization and autonomic tone, offering a cohesive framework linking PPIs to both arrhythmic and atherosclerotic risk. Agents such as pantoprazole, omeprazole, and lansoprazole are most consistently implicated. The potential role of confounding by indication is discussed, noting that cardiovascular associations often persist after adjusting for underlying reflux disease. By integrating large-scale data with mechanistic insights, this review underscores the need to reconsider the cardiovascular neutrality of PPIs, particularly with long-term use. Future studies must clarify causality, identify susceptible phenotypes, and determine if therapy modification can mitigate downstream cardiovascular and arrhythmic risk.

Keywords: Proton pump inhibitors; Cardiovascular disease; Arrhythmia; Atrial fibrillation; QT prolongation; hERG potassium channel; Hypomagnesemia; Oxidative stress; Endothelial dysfunction; Sudden cardiac death

Introduction

Proton pump inhibitors (PPIs) represent one of the most widely prescribed classes of medications worldwide [1]. Over the past two decades, their use has expanded significantly, partly due to the availability of generic formulations, over-the-counter accessibility, and the perception of a favorable safety profile [2]. Interestingly, while the prevalence of conditions for which PPIs are

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formally indicated, such as gastroesophageal reflux disease, peptic ulcer disease, and Helicobacter pylori infection, has remained relatively stable, the overall consumption of PPIs has continued to rise. This trend has raised concerns regarding potential misuse, as clinical guidelines generally recommend short-term therapy, often limited to 8 to 12 weeks, yet many patients remain on these agents indefinitely without ongoing indication, especially the elderly [3]. Although PPIs are effective in controlling gastric acid secretion, long-term and widespread use has prompted growing scrutiny of their adverse effects. In addition to established associations with renal dysfunction, bone health, micronutrient deficiencies, Clostridioides difficile infection, enteric colonisation with multidrug-resistant organisms, and gastric cancer, increasing attention has been directed toward possible cardiovascular implications [4]. Emerging data suggest that PPIs may contribute to adverse cardiovascular outcomes, including ischemic events, heart failure progression, and disturbances of cardiac electrophysiology. Among these, the potential for PPIs to predispose patients to arrhythmias through mechanisms such as electrolyte imbalances, impaired ion channel regulation, and interactions with concomitant cardiovascular therapies remains under-explored [4]. The rising incidence of atherosclerotic cardiovascular disease (ASCVD) and arrhythmias represents a growing public health challenge, particularly in the context of an ageing population. While traditional risk factors have long been recognized, emerging evidence suggests that commonly prescribed medications such as PPIs may also contribute to cardiovascular risk [4]. Highlighting this overlooked association is important, as it may inform prevention strategies, guide risk stratification, and support de-prescription initiatives aimed at minimizing unnecessary long-term PPI use [2,3]. Unlike prior reviews that primarily emphasize ischemic or atherosclerotic outcomes, this review focuses specifically on arrhythmic endpoints and integrates electrophysiologic and autonomic mechanisms with population-level data. This arrhythmia-centered synthesis represents a distinct and underexplored dimension of PPI-associated cardiovascular risk. Importantly, the majority of data linking PPI use to cardiovascular and arrhythmic outcomes remains observational, and causality cannot be definitively inferred. While emerging mechanistic studies provide biological plausibility, these findings should be interpreted as hypothesis-generating rather than confirmatory. Accordingly, this review aims to synthesize epidemiologic signals and mechanistic insights while explicitly acknowledging the current limitations of causal inference. Moreover, this review does not constitute a systematic review or meta-analysis but rather a narrative synthesis focusing on arrhythmic outcomes and mechanistic plausibility.

PPIs and Cardiovascular Disease (CVD) - Current Evidence

ARIC Cohort Studies

Among the first studies to suggest potential cardiovascular risk associated with chronic PPI use was the analysis by Shah et al [5], which used electronic health record data from large clinical databases and identified an excess risk of myocardial infarction among PPI users, a signal not observed with H2-receptor antagonists. While exploratory and limited by the nature of retrospective data mining, this study raised the possibility of a cardiovascular safety concern and laid the groundwork for subsequent investigations in large, prospective cohorts discussed below.

Table 1 as seen below, provides an overview of the major cohort studies that have investigated the association between long-term PPI use and cardiovascular outcomes, highlighting differences in study design, populations, exposure definitions, and primary endpoints. In the ARIC population cohort, Rooney et al. showed that PPI use was significantly associated with an elevated risk of cardiovascular disease. Over a median follow-up of 5.6 years, PPI users had a 31% higher risk of incident composite CVD, which remained significant after multivariable adjustment for demographics, lifestyle factors, and traditional cardiovascular risk factors (HR 1.31, 95% CI 1.10-1.57).

Interestingly, H2-receptor blockers, used as a negative control, showed no association with cardiovascular risk, indicating that the observed relationship may not be attributable to acid suppression alone but rather to a PPI-specific association. Also, a mediation analysis tested whether hypomagnesemia explained the association between PPI use and composite cardiovascular outcomes, but the effect was not statistically significant [6]. In a complementary analysis of the same ARIC cohort, Bell et al. evaluated the impact of cumulative PPI exposure and found that individuals with over five years of regular use had nearly double the risk of cardiovascular disease and heart failure compared to non-users, even after comprehensive adjustment for demographic, clinical, and socioeconomic variables. These findings underscore the importance of exposure duration, suggesting that long-term use may carry more pronounced cardiovascular consequences, particularly for heart failure [7].

UK Biobank cohort

A similar study was conducted by Li *et al.* in the UK Biobank cohort, PPI use was also significantly associated with increased cardiovascular risk across multiple outcomes over a median follow-up of 8 years. In fully adjusted models controlling for demographic, lifestyle, and clinical covariates, PPI use was associated with a 44% higher risk of composite cardiovascular disease (HR 1.44, 95% CI 1.39-1.50).

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Table 1: Summary of Key Epidemiological Studies Evaluating the Association Between Proton Pump Inhibitor Use and Cardiovascular Outcomes. AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; ARIC, Atherosclerosis Risk in Communities; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; EMR, electronic medical record; GERD, gastroesophageal reflux disease; H2B, histamine-2 receptor blocker; HF, heart failure; HR, hazard ratio; ICD, International Classification of Diseases; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease; PPI, proton pump inhibitor; RCT, randomized controlled trial; RR, risk ratio; T2D, type 2 diabetes.

Study (Author, Year)	Study Design & Population	Exposure Definition	Comparator	Primary Outcome(s)	Key Findings (Effect Estimates)
Shah et al., 2015 [5]	Data-mining analysis of two large EMR datasets (Stanford STRIDE, n≈70,000 GERD patients ≥18 years; Practice Fusion, n≈227,000 GERD patients) plus a prospective cohort (GenePAD) of patients with PAD.	Any recorded PPI use after GERD diagnosis; class-level and individual drug analyses; exposure defined from text-mined prescription/medication mentions.	GERD patients not exposed to PPIs (propensity-matched up to 5:1 on demographics, comorbidity proxies, and observation time); H2B users evaluated as an active comparator group.	Acute MI in EMR datasets; cardiovascular mortality in the GenePAD cohort.	In STRIDE, PPI use was associated with higher MI risk versus nonusers (adjusted OR 1.16, 95% CI 1.09-1.24); similar association in Practice Fusion (adjusted OR 1.19, 95% CI 1.09-1.30). H2Bs showed no MI signal (adjusted OR 0.93, 95% CI 0.86-1.02). In GenePAD, PPI use was associated with higher cardiovascular mortality (HR 2.22, 95% CI 1.19-4.16).
Rooney et al., 2021 [6]	Prospective community-based cohort (ARIC) including 4,436 participants free of prevalent CVD at visit 5 (2011-2013); mean age 75±5 years; 63% women, 23% Black.	PPI use at visit 5 (pill-bottle inspection); hypomagnesemia defined as serum Mg ≤0.75 mmol/L; PPI use treated as a baseline exposure for cross-sectional hypomagnesemia analyses and for subsequent CVD follow-up (~5 years).	Non-users of PPIs at visit 5.	Cross-sectional prevalence of hypomagnesemia; incident composite CVD (AF, CHD, HF, stroke, and CVD mortality) through 2017.	PPI use was associated with higher prevalence of hypomagnesemia (RR 1.24, 95% CI 1.08-1.44) and higher risk of incident CVD (HR 1.31, 95% CI 1.10-1.57) vs nonusers after multivariable adjustment. Adding hypomagnesemia to the Cox models did not significantly attenuate the PPI-CVD association, arguing against Mg as a major mediator.
Bell et al., 2021 [7]	Prospective cohort analysis within ARIC including 4,346 participants free of total CVD at visit 5 (2011-2013); mean age 75 years; White and African American adults.	Cumulative PPI exposure from visit 1 (1987-1989) through visit 5, quantified as total days of use based on repeated pill-bottle inspections (up to 11 visits); primary exposure category: >5.1 years cumulative PPI use vs nonuse.	Participants with no PPI use across visits (nonusers); intermediate exposure categories analyzed but key contrast is highest exposure vs nonuse.	Incident total CVD (composite of stroke, CHD, and HF) and incident HF alone, from visit 5 through December 31, 2016.	After multivariable adjustment (including Framingham CVD risk factors), >5.1 years of cumulative PPI exposure was associated with higher risk of total CVD (HR 2.02, 95% CI 1.50-2.72) and higher risk of HF (HR 2.21, 95% CI 1.51-3.23) compared with nonusers.
Li et al., 2024 [8]	Prospective cohort using the UK Biobank; 459,207 participants without prevalent CVD at baseline (enrolled 2006-2010), mean age ≈56 years, followed until 2018.	Regular PPI use at baseline in UK Biobank (any PPI reported as regularly used); exposure modeled as users vs nonusers with multivariable adjustment for demographics, lifestyle, comorbidities, and clinical indications for PPIs.	Participants not reporting regular PPI use (nonusers).	Incident composite CVD and individual components: CHD, stroke, AF, HF, and venous thromboembolism.	Regular PPI use was associated with higher risk of incident CVD (HR 1.44, 95% CI 1.39-1.50), CHD (HR 1.65, 95% CI 1.57-1.74), stroke (HR 1.21, 95% CI 1.09-1.33), AF (HR 1.17, 95% CI 1.08-1.28), HF (HR 1.61, 95% CI 1.37-1.89), and venous thromboembolism (HR 1.36, 95% CI 1.24-1.50) compared with nonusers.

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Ma et al., 2022 [9]	Regular PPI use at baseline (any PPI), and regular H2B use; exposure categorized as PPI users, H2B users, or nonusers.	Regular PPI use at baseline (any PPI), and regular H2B use; exposure categorized as PPI users, H2B users, or nonusers.	Nonusers of acid suppressants; H2B users also evaluated as an active comparator for PPIs.	Incident ASCVD (composite) and subtypes: CAD, MI, PAD, and ischemic stroke.	Regular PPI use was associated with increased ASCVD risk (HR 1.16, 95% CI 1.09-1.23) and higher risk of each ASCVD subtype. By individual drugs: omeprazole HR 1.19 (95% CI 1.11-1.28), lansoprazole HR 1.11 (95% CI 1.02-1.22), pantoprazole HR 1.40 (95% CI 1.00-1.97). Associations were stronger among participants without clear indications for PPIs. H2B use was not associated with ASCVD (HR 0.97, 95% CI 0.85-1.11).
Yang et al., 2021 [10]	Population-based prospective cohort plus meta-analysis; 492,479 UK Biobank participants free of stroke at baseline, with linkage to hospital and death registries; followed for 3.9 million person-years. Also a meta-analysis of 9 RCTs comparing PPIs vs control.	Regular PPI use at baseline (self-reported regular use in UK Biobank); exposure modeled as regular users vs nonusers with adjustment for demographics, lifestyle, comorbidities, concomitant medications, and PPI indications.	Nonusers of PPIs in the cohort; in the meta-analysis, RCT control arms (placebo, no treatment, or alternative therapy).	Incident stroke (ischemic and hemorrhagic, ICD-10 I60, I61, I63, I64); secondary: pooled stroke risk in RCTs.	In the cohort, regular PPI use was associated with a 16% higher risk of stroke vs nonuse (HR 1.16, 95% CI 1.06-1.27). In the meta-analysis of 9 RCTs (371 stroke events/26,642 participants), pooled RR for stroke with PPI use was 1.22 (95% CI 1.00-1.50). Absolute 5-year risk difference increased with baseline Framingham Stroke Risk Score.
Geng et al., 2022 [11]	Prospective cohort study within the UK Biobank; 19,229 adults with T2D at baseline, median follow-up ≈11 years.	PPI use at baseline (any PPI) vs no PPI use; exposure assessed at enrollment and analyzed with multivariable adjustment. Additional analyses in a 1:1 propensity score-matched cohort of PPI users and nonusers.	T2D participants not using PPIs; propensity-matched nonusers in secondary analyses.	Incident CAD, MI, HF, stroke, and all-cause mortality among patients with T2D.	PPI use in T2D was associated with higher risks of CAD (HR 1.27, 95% CI 1.15-1.40), MI (HR 1.34, 95% CI 1.18-1.52), HF (HR 1.35, 95% CI 1.16-1.57), and all-cause mortality (HR 1.30, 95% CI 1.16-1.45); no statistically significant association with stroke (HR 1.11, 95% CI 0.90-1.36). Results were consistent across subgroups and in propensity-score-matched analyses.
Sehested et al., 2018 [12]	Nationwide registry-based cohort from Denmark including 214,998 adults with no prior MI or stroke who underwent elective upper GI endoscopy between 1997-2012; median follow-up 5.8 years.	Current PPI use at the time of endoscopy (class-level), with dose categories (high vs low) and long-term use.	Nonusers of PPIs; H2Bs users analyzed as an active comparator group.	First-time ischemic stroke and first-time MI.	Current PPI use was associated with higher risk of ischemic stroke (HR 1.13, 95% CI 1.08-1.19) and MI (HR 1.31, 95% CI 1.23-1.39) after multivariable adjustment. High-dose PPI was associated with further increased risks of stroke (HR 1.31, 95% CI 1.21-1.42) and MI (HR 1.43, 95% CI 1.30-1.57). H2Bs were not significantly associated with stroke (HR 1.02, 95% CI 0.84-1.24) or MI (HR 1.15, 95% CI 0.92-1.43). Long-term PPI users had a 29% (95% CI 5-59%) greater absolute 6-month risk of ischemic stroke and a 36% (95% CI 7-73%) greater absolute 6-month risk of MI compared with nonusers.

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Charlot et al., 2010 [13]	Nationwide cohort study using linked Danish administrative registries; 56,406 patients discharged after first-time MI between 2000-2006; 1-year follow-up.	Post-discharge PPI use identified from prescription data; exposure groups defined by concomitant use of PPIs and clopidogrel vs PPIs without clopidogrel at 7, 14, 21, and 30 days after discharge.	Within strata of clopidogrel use, patients not receiving a PPI served as the reference; main contrasts were PPI amd clopidogrel vs clopidogrel alone, and PPI without clopidogrel vs no PPI and no clopidogrel.	Composite of cardiovascular death, rehospitalization for MI, or stroke within 1 year after index MI.	Among patients assembled 30 days after discharge, concomitant clopidogrel and PPI use was associated with higher risk of the composite outcome vs clopidogrel alone (HR 1.29, 95% CI 1.17-1.42). A similar excess risk was seen for PPI use among patients not treated with clopidogrel (HR 1.29, 95% CI 1.21-1.37). There was no significant interaction between PPI and clopidogrel use (P for interaction = 0.72), indicating that PPIs themselves were associated with increased post-MI cardiovascular risk independent of clopidogrel.
Soliman et al., 2025 [14]	Prospective cohort from the Women's Health Initiative; 85,272 postmenopausal women aged 50-79 years without known CVD at baseline; mean follow-up 11.8 years.	Self-reported regular PPI use at baseline and during follow-up; cumulative exposure categorized as <1 year, 1-3 years, and >3 years; exposure updated in follow-up questionnaires.	Nonusers of PPIs; H2B users also examined as secondary active comparator but not primary reference.	Incident composite CVD (first occurrence of nonfatal MI, CHD death, stroke, transient ischemic attack, or coronary revascularization).	Fully adjusted model: PPI use associated with 21% higher risk of incident CVD (HR 1.21, 95% CI 1.02-1.43). Clear cumulative exposure gradient: <1 year use HR 1.11 (95% CI 0.96-1.28), 1-3 years HR 1.27 (95% CI 1.10-1.48), >3 years HR 1.33 (95% CI 1.14-1.56); p for trend = 0.02. Associations remained significant after adjustment for demographics, comorbidities, lifestyle factors, and indications.

Associations were consistently observed across individual endpoints, including coronary heart disease (HR 1.65, 95% CI 1.57-1.74), stroke (HR 1.21, 95% CI 1.09-1.33), heart failure (HR 1.61, 95% CI 1.37-1.89), and venous thromboembolism (HR 1.36, 95% CI 1.24-1.50). Importantly, the associations persisted even when the analysis was restricted to participants with clear clinical indications for PPI therapy, suggesting that the observed relationships were not solely attributable to indication bias. Subgroup analyses suggested that the adverse associations were more pronounced in participants <60 years of age and in current smokers. Intriguingly, to further address residual confounding, the investigators reported an E-value of 2.17, indicating that only an unmeasured confounder with a very strong association with both PPI use and cardiovascular disease could fully account for the observed relationship, making the findings more robust [8].

Another UK Biobank-based study by Ma *et al.* conducted on participants without prior cardiovascular disease or antihypertensive treatment, regular PPI use was again associated with elevated risk of ASCVD during a median follow-up of 12.5 years. In fully adjusted models accounting for demographics, socioeconomic status, lifestyle behaviors, cardiometabolic risk factors, comorbidities, and gastrointestinal indications, PPI use remained significantly associated with incident ASCVD (HR 1.16, 95% CI 1.09-1.23), including coronary artery disease (HR 1.12, 95% CI 1.04-1.21), myocardial infarction (HR 1.11, 95% CI 1.02-1.20), peripheral artery disease (HR 1.25, 95% CI 1.09-1.43), and ischemic stroke (HR 1.17, 95% CI 1.03-1.35). Consistent with the findings of Rooney *et al.*, H2-receptor antagonists showed no significant associations with ASCVD or its components, further suggesting a result specific to PPIs rather than an effect of acid suppression. Notably, in drug-specific analyses, omeprazole, lansoprazole, and pantoprazole were associated with elevated ASCVD risk, where pantoprazole had the strongest association, whereas esomeprazole and rabeprazole were not. As discussed in the following section, these same agents (omeprazole, lansoprazole, and pantoprazole) have also demonstrated pro-arrhythmic effects in basic science models, including altered ion channel function and impaired myocardial repolarization, raising the possibility of shared electrophysiologic mechanisms contributing to both atherosclerotic and arrhythmogenic risk [9]. Similarly to Li *et al.*'s study, Ma *et al.* also found that younger participants (age <65) carried a greater excess risk with PPI use. However, in contrast to Li's findings, Ma *et*

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al. observed that the association was limited to individuals without a documented indication for acid suppression, whereas Lee *et al.* demonstrated that the risk remained significant even after adjusting for clinical indications [9].

Complementing these findings, Yang et al. conducted a focused analysis of stroke outcomes in nearly 500,000 UK Biobank participants without baseline cerebrovascular disease and similarly found that regular PPI use was associated with a significantly increased risk of incident stroke (HR 1.16, 95% CI 1.06-1.27) [10]. The absolute risk difference was particularly notable among individuals at higher baseline stroke risk, where excess event rates were more than fourfold higher compared to those in the lowest-risk strata. Additionally, Yang et al performed a meta-analysis of nine randomized controlled trials and reported a comparable yet modestly elevated risk (pooled RR 1.22, 95% CI 1.00-1.50), reinforcing the consistency of this association across observational and experimental settings. These findings extend prior work by highlighting stroke as a distinct cardiovascular endpoint that may be influenced by chronic PPI exposure [10]. In contrast to Ma et al.'s focus on ASCVD in a general population sample, Geng et al. examined PPI use in a UK Biobank cohort restricted to individuals with type 2 diabetes and found similar statistically significant elevated risks of coronary artery disease, myocardial infarction, and heart failure. Unlike Ma et al., however, Geng et al. did not observe a significant association with stroke, but did report a 30% higher risk of all-cause mortality, underscoring potential vulnerability in this high-risk subgroup [11].

Danish National Registries

In a nationwide Danish registry cohort of 214,998 individuals undergoing upper gastrointestinal endoscopy and free of prior stroke or MI, Sehested et al. found that current PPI use was associated with increased risk of both ischemic stroke (HR 1.13, 95% CI 1.08-1.19) and myocardial infarction (HR 1.31, 95% CI 1.23-1.39) during a median 5.8-year follow-up. A dose-dependent and cumulative exposure relationship was observed, with increased risks at higher doses, reaching a hazard ratio of 1.31 (95% CI 1.21–1.42) for stroke and 1.43 (95% CI 1.30–1.57) for myocardial infarction. Importantly, only long-term PPI use was significantly associated with increased cardiovascular risk, conferring a 29% increase in absolute risk of ischemic stroke and a 36% increase in risk of myocardial infarction within six months compared with non-users. Importantly, H2-receptor antagonists again showed no significant association with either outcome, further suggesting the effect may be specific to PPIs [12]. In another Danish nationwide cohort, Charlot et al. evaluated over 56,000 patients discharged after myocardial infarction and found that PPI use was independently associated with a significantly elevated risk of cardiovascular death and rehospitalization for MI or stroke, even after adjusting for age, comorbidities, and concurrent clopidogrel use [13]. Notably, the observed excess risk persisted regardless of clopidogrel exposure, challenging the assumption that cardiovascular harm is solely driven by pharmacodynamic interference with antiplatelet therapies and instead pointing toward a broader vascular liability associated with chronic PPI use.

U.S. Women's Health Initiative

In yet another study by Soliman et al. who studied a prospective cohort of 85,000 older post menopausal women, PPI use was associated with a significantly higher risk of incident cardiovascular disease, with the fully adjusted model showing a 21% increased risk (HR 1.21, 95% CI 1.02-1.43). Importantly, a cumulative exposure effect was observed, with progressively higher risks among those using PPIs for <1 year, 1-3 years, and >3 years (HRs 1.11, 1.27, and 1.33, respectively; p for trend = 0.02) [14].. This mirrors the findings of Sehested et al., who also reported elevated risk confined to long-term PPI use [12]. Stratified analyses suggested stronger associations in women aged 60–69 and in NSAID users, though other subgroup effects were less consistent. Taken together, the above studies provide converging evidence from multiple large-scale, prospective cohorts and national registries that long-term PPI use is associated with increased cardiovascular risk. While the magnitude of association varies across populations and endpoints, consistent patterns emerge: risk appears to rise with longer duration of use, is not replicated with H2-receptor antagonists, and persists across diverse settings including general, diabetic, and post-MI populations. Moreover, findings from high-quality studies in Denmark, the UK, Sweden, and the U.S. collectively reinforce the robustness of this association. These insights underscore the need for careful risk-benefit evaluation in prolonged PPI therapy, especially in individuals with elevated baseline cardiovascular risk or without a clear indication for continued acid suppression.

PPI and Arrhythmogenesis

Although epidemiologic studies have reported associations between proton pump inhibitor use and increased arrhythmic risk, direct causal evidence remains limited. Mechanistic studies to date largely consist of preclinical, translational, and pharmacologic investigations that support biological plausibility rather than definitive causation. The following section synthesizes these mechanistic signals to contextualize observed epidemiologic associations.

Experimental and Translational Evidence

Hypomagnesemia

Hypomagnesemia promotes QT prolongation and TdP by disturbing ion channel homeostasis. Magnesium normally stabilizes cardiac repolarization by enhancing potassium outward currents and inhibiting L-type calcium currents.

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Depletion removes these stabilizing effects, prolonging action potential duration [15,16]. Figure 1 summarizes the proposed mechanistic pathways through which chronic proton pump inhibitor use may contribute to arrhythmogenesis, integrating experimental, translational, and epidemiologic evidence.

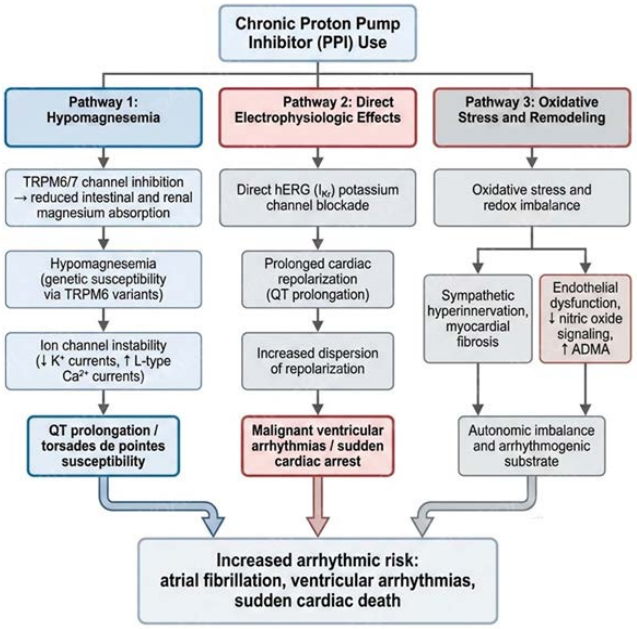

Figure 1: Proposed mechanisms linking chronic proton pump inhibitor use to arrhythmic risk. Chronic proton pump inhibitor (PPI) use may increase arrhythmic risk through three converging pathways: hypomagnesemia-mediated ion channel instability, direct hERG/IKr potassium channel inhibition with delayed repolarization, and oxidative stress–mediated myocardial and endothelial remodeling. These mechanisms may contribute to QT prolongation, torsades de pointes susceptibility, malignant ventricular arrhythmias, atrial fibrillation, and sudden cardiac death. ADMA, asymmetric dimethylarginine; hERG, human ether-à-go-go–related gene; IKr, rapid delayed rectifier potassium current; TRPM, transient receptor potential melastatin.

hERG Potassium Channel Blockade

While electrolyte imbalances play a central role, PPIs may also exert direct electrophysiologic effects on cardiac ion channels. In a Clinical Cardiology study utilizing the MIMIC-III ICU database, Liu et al. demonstrated that ICU patients treated with PPIs had a significantly greater prevalence of QT prolongation, even after controlling for confounding medications and serum electrolytes [17]. Complementary experimental data by Lorberbaum et al [18]. demonstrated that lansoprazole reduced human ether-à-go-go–related gene (hERG) potassium channel, responsible for the rapid delayed rectifier current, by up to 14% alone and by 58% when combined with ceftriaxone, suggesting additive or synergistic channel blockade. This was corroborated by Lazzerini et al., who provided compelling translational data by combining patch-clamp experiments with clinical observations [19]. The authors demonstrated that commonly prescribed PPIs, particularly pantoprazole and lansoprazole, directly inhibited the hERG potassium channel in a concentration-dependent manner, leading to prolonged cardiac repolarization at clinically relevant levels. This electrophysiologic effect translated to a significantly higher incidence of QT prolongation among PPI users in a large veteran population, even after controlling for magnesium levels and other confounders. These findings underscore that PPIs may provoke arrhythmogenesis through direct interference with cardiac ion currents independent of electrolyte status. Collectively, these findings support a potential electrophysiologic mechanism, but are derived primarily from experimental and retrospective clinical data, limiting causal inference.

Oxidative stress

Beyond ion channel blockade and magnesium depletion, PPIs may promote arrhythmias through oxidative stress-induced cardiac remodelling. In a rat myocardial infarction model, Lee et al. found that chronic omeprazole administration exacerbated ventricular arrhythmias by inducing superoxide-mediated nerve growth factor upregulation and sympathetic hyperinnervation in the infarct border zone. These effects were reversible with magnesium supplementation or antioxidant therapy (Tiron), confirming the mechanistic link between magnesium deficiency, reactive oxide generation, and sympathetic sprouting. The resultant autonomic imbalance increases ventricular excitability and arrhythmogenic potential [20]. Similarly, Chen et al. demonstrated nearly parallel findings using a rat myocardial infarction model, where prolonged omeprazole exposure triggered oxidative cardiac remodeling through a distinct but complementary pathway [21]. Specifically, omeprazole reduced gastric vitamin C absorption and impaired nitric oxide signaling by suppressing endothelial nitric oxide synthase (eNOS) activity while increasing levels of asymmetric dimethylarginine, an endogenous eNOS inhibitor. This redox imbalance led to enhanced myocardial fibrosis and structural remodeling, changes known to promote arrhythmogenesis. Notably, these effects were mitigated by either vitamin C supplementation or angiotensin receptor blockade, further supporting the involvement of redox-sensitive mechanisms.

Extending these findings beyond animal models, Yepuri et al. demonstrated that PPIs also induce oxidative and structural dysfunction at the vascular level [22]. In cultured human endothelial cells, esomeprazole was shown to accelerate endothelial aging, characterized by telomere shortening, increased oxidative stress, and disruption of lysosomal pH homeostasis. These alterations were accompanied by blunted nitric oxide signaling. This mirrors the redox-related mechanisms observed in cardiac models. Importantly, these

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effects were not seen with H2-receptor antagonists, further crystallizing the notion of a PPI-specific effect. This indicates that endothelial dysfunction might provide a unifying biological link between the arrhythmogenic and atherogenic potential of PPIs through shared redox-sensitive pathways. Translation of these experimental findings to clinical arrhythmic risk in humans remains incompletely defined.

Observational and Epidemiologic Evidence

Consistent with experimental observations, few large scale cohort studies have demonstrated a significant association between PPI use and increased arrythmic burden. A nationwide Danish registry study by Eroglu et al. identified a significantly increased risk of out-of-hospital cardiac arrest among current PPI users [23]. Among more than 46,000 cases, PPI use was associated with a 32% higher odds of sudden arrhythmic death, independent of cardiovascular comorbidities or other medications (OR 1.32, 95% CI 1.28-1.37). Individual analyses revealed that omeprazole, esomeprazole, lansoprazole, and pantoprazole were each significantly associated with increased odds of out-of-hospital cardiac arrest. Risk was most pronounced with pantoprazole (OR 1.52, 95% CI 1.45-1.60), aligning with in vitro studies showing the strongest hERG inhibition with this agent [19]. These findings provide real-world support for a consistent signal that PPIs may be associated with an increased risk of malignant arrhythmias and sudden death, potentially through both ion channel blockade and additive interactions with other QT-prolonging therapies. Moreover, in the ARIC cohort, Rooney et al. reported that PPI use was independently and significantly associated with a 37% increased risk of incident AF, even after controlling for demographic factors, comorbidities, cardiovascular medications, and serum magnesium levels (HR 1.37, 95% CI 1.07-1.77) [6]. This association was reinforced in the UK Biobank by Li et al., who observed a statistically significant 17% elevated risk of AF among regular PPI users over a median follow-up of 8 years (HR 1.17, 95% CI 1.08-1.28) [8]. Notably, drug-specific analyses from the UK Biobank identified omeprazole, lansoprazole, and pantoprazole as the agents most strongly associated with increased cardiovascular risk, including arrhythmic outcomes, whereas esomeprazole and rabeprazole did not show significant associations [9].

Collectively, mechanistic data from translational models and real-world population studies point in the same direction: proton pump inhibitors may contribute to arrhythmogenesis through multiple interrelated pathways. These include hypomagnesemia-induced repolarization instability, direct blockade of hERG potassium channels, and oxidative stress driven cardiac and vascular remodeling. Among the various agents, pantoprazole, lansoprazole, and omeprazole have emerged as the most consistently implicated compounds, with evidence demonstrating both molecular effects and corresponding clinical risk signals. Importantly, these arrhythmogenic effects appear independent of acid suppression and distinct from H2-receptor antagonists, suggesting a potential class effect.

GERD, AF, and Confounding by Indication

AF represents both a major independent cardiovascular risk factor [24-26] and a potential downstream consequence of GERD [27-30], so it is important to distinguish whether PPI-associated CV risks arise from the drug itself or from the underlying condition for which it is prescribed. Atrial fibrillation itself is an established, independent risk factor for adverse cardiovascular outcomes. Longitudinal studies (e.g., the Framingham Heart Study) have shown that AF confers a markedly elevated risk of stroke (around 5-fold) and doubles all-cause mortality even after adjustment for other risk factors [24,25]. Likewise, a large meta-analysis of 104 cohorts (around 9.7 million participants) confirmed that AF is associated with significantly higher risks of stroke, heart failure, and cardiovascular death [26]. These observations underscore that any intervention or comorbidity influencing AF incidence can substantially impact downstream cardiovascular risk. Emerging evidence suggests that GERD, the primary indication for chronic PPI therapy, may itself predispose patients to AF. Multiple observational studies link GERD to modestly increased AF incidence (HRs around 1.3 in population-based cohorts) [27]., although findings are mixed and not all analyses reach significance [28,29]. Notably, recent Mendelian randomization analyses support a causal relationship, reporting that genetically predetermined predisposition to to GERD increases AF risk by approximately 17-34% [28,30]. This interrelationship creates potential for confounding by indication: the apparent association between PPI use and AF or CVD events may reflect the presence of underlying GERD (and its arrhythmogenic or inflammatory consequences) rather than a direct pharmacologic and class specific effect of PPIs. Accordingly, future studies of PPI-associated cardiovascular or arrhythmic risk should rigorously adjust for GERD diagnosis and severity to delineate drug effects from the risk conferred by the underlying esophageal disease.

Limitations and Interpretation

The current evidence linking PPI exposure to cardiovascular and arrhythmic outcomes is predominantly observational, and therefore susceptible to residual confounding and confounding by indication. Mechanistic studies largely remain preclinical or translational, supporting biological plausibility rather than establishing causality in humans. Furthermore, GERD itself may contribute to arrhythmic risk, complicating attribution of observed associations solely to PPIs. Accordingly, the available data

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are best interpreted as a consistent risk signal that warrants cautious clinical awareness and prospective validation.

Conclusion

Taken together, the totality of evidence from experimental, translational, and population-based studies suggests a consistent association between chronic PPI use, arrhythmic outcomes, and adverse cardiovascular events. Across diverse cohorts, including ARIC, UK Biobank, and Danish national registries, PPI exposure has been reproducibly linked to increased risk of atherosclerotic events, heart failure, and arrhythmias, with signals of duration and dose dependent patterns. Importantly, these associations are not mirrored with H2-receptor antagonists, suggesting an effect that may be specific to PPIs rather than to acid suppression. Mechanistic studies support biological plausibility, demonstrating that PPIs may influence multiple pathways critical to myocardial and vascular stability, including impaired magnesium homeostasis via TRPM6/7 channel inhibition, direct blockade of the hERG potassium current, and oxidative stress-mediated endothelial and myocardial remodeling. However, because most human evidence is observational, causality cannot be definitively inferred, and residual confounding remains possible. The convergence of findings across molecular, electrophysiologic, and epidemiologic domains strengthens concern for a clinically relevant risk signal, but does not establish a causal relationship. At the same time, the interplay between GERD, AF, and cardiovascular risk introduces an additional layer of complexity that warrants careful consideration. GERD, the primary indication for chronic PPI therapy, appears to possibly increase AF risk through inflammatory, autonomic, and possibly mechanical mechanisms. This creates potential for confounding by indication, where part of the cardiovascular signal attributed to PPIs may in fact reflect the arrhythmogenic effect conferred by the underlying reflux disease. Nonetheless, the observation that PPIs most strongly associated with adverse cardiovascular outcomes in cohort studies are the same agents shown to disrupt cardiac repolarization in basic models suggests that a portion of the observed risk may reflect drug-specific electrophysiologic effects in susceptible individuals. Collectively, these patterns support the need for prospective studies and mechanistic human investigations that can delineate drug-related effects from disease-related risk, identify susceptible patient subgroups, and clarify whether modification of PPI therapy, magnesium status, or reflux control can mitigate downstream cardiovascular and arrhythmic events. Until such data are available, long-term PPI therapy should be periodically re-evaluated to ensure an ongoing indication, particularly in patients at elevated arrhythmic risk or exposed to other QT-prolonging therapies.

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