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CLINICAL SIGNIFICANCE OF DRUG–DRUG INTERACTIONS BETWEEN PROTON PUMP INHIBITORS AND CARDIOVASCULAR MEDICATIONS IN GERIATRIC PATIENTS: A SYSTEMATIC REVIEW

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Background: Proton pump inhibitors (PPIs) are commonly prescribed in older adults to prevent gastrointestinal bleeding, particularly in patients receiving antiplatelet or anticoagulant therapy. However, their potential interactions with cardiovascular drugs especially clopidogrel have raised concerns regarding adverse cardiovascular outcomes.

Objectives: This systematic review aimed to evaluate the clinical significance of PPI–cardiovascular drug interactions in geriatric patients, focusing on pharmacodynamic effects, cardiovascular outcomes, and implications for clinical practice.

Methods: A systematic search of PubMed, Scopus, Web of Science, Embase, and Cochrane Library was conducted from January 2010 to January 2025. Eligible studies included randomized controlled trials, cohort, and case-control studies involving adults aged ≥60 years prescribed PPIs with antiplatelet or anticoagulant therapy. Data extraction followed PRISMA 2020 guidelines, with study quality assessed using the Cochrane RoB 2.0 tool and Newcastle–Ottawa Scale.

Results: Fifteen studies met inclusion criteria. Evidence indicated that omeprazole consistently attenuates clopidogrel's antiplatelet activity, while pantoprazole and other PPIs demonstrated minimal interaction. Observational studies reported conflicting associations between PPI use and major adverse cardiovascular events (MACE), with hazard ratios ranging from no effect to a 70% increased risk. Randomized trial data showed limited clinical impact, though long-term PPI use was linked with increased cardiovascular disease and mortality in some large cohorts. Importantly, prophylactic PPIs reduced gastrointestinal bleeding and improved adherence to dual antiplatelet therapy in high-risk geriatric patients.

Conclusions: The cardiovascular significance of PPI use in geriatric patients is heterogeneous and context-dependent. Omeprazole should be avoided with clopidogrel when alternatives such as pantoprazole are available. Long-term PPI use warrants caution due to possible associations with cardiovascular disease and mortality. Individualized prescribing and careful risk–benefit assessment are critical in older adults where polypharmacy is common.

Keywords: Proton pump inhibitors; clopidogrel; dual antiplatelet therapy; cardiovascular outcomes; drug–drug interactions; geriatrics; gastrointestinal bleeding; pantoprazole; omeprazole; polypharmacy

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most commonly prescribed medications worldwide, particularly in older adults, due to their efficacy in reducing gastric acid secretion and preventing gastrointestinal bleeding. Despite their therapeutic benefits, concerns have arisen regarding their long-term safety, particularly with respect to cardiovascular health. Geriatric patients are especially vulnerable, as polypharmacy and comorbid cardiovascular disease are prevalent in this population, increasing the likelihood of drug–drug interactions and adverse outcomes (Soliman et al., 2025).

The potential cardiovascular risks associated with PPIs have been increasingly scrutinized in recent years. Observational and cohort studies have suggested that chronic PPI use may be associated with increased incidence of cardiovascular events, including myocardial infarction, stroke, and heart failure. Although causal mechanisms remain debated, hypotheses include endothelial dysfunction, altered platelet activity, and interference with absorption of essential micronutrients relevant to cardiovascular health (Bell et al., 2021).

Population-based studies in diverse healthcare systems have also indicated possible links between PPI therapy and elevated cardiovascular risk, particularly in patients with pre-existing heart disease. These findings are particularly concerning for older adults, who often require both cardiovascular medications and gastroprotective agents. The possibility of additive risk underscores the need for careful evaluation of prescribin practices in geriatric care (Jang et al., 2024).

Large-scale prospective studies further support the hypothesis of an association between regular PPI use and adverse cardiovascular outcomes. Although these associations may be confounded by comorbidities and indication bias, the consistent observation across studies suggests that the relationship cannot be dismissed outright. For clinicians managing elderly patients, the challenge lies in balancing the protective effects of PPIs against potential cardiovascular risks (Li et al., 2024).

Systematic reviews and meta-analyses of observational studies have also contributed to the growing body of evidence on this topic. These pooled analyses have demonstrated a modest but measurable association between PPI use and both cardiovascular events and mortality. While causality cannot be confirmed, the consistency of the findings raises important clinical and public health concerns, particularly for long-term use in high-risk populations (Nolde et al., 2022).

Concerns about cardiovascular safety have been reinforced by additional meta-analyses examining long-term exposure to PPIs. These reviews highlight that, while absolute risks remain small, the widespread use of PPIs often in the absence of clear indications magnifies the potential population-level impact. Such evidence emphasizes the importance of judicious prescribing, especially among geriatric patients already burdened by cardiovascular comorbidities (Jeridi et al., 2022).

In addition to risks observed in epidemiological studies, mechanistic insights have been proposed regarding how PPIs might interact with cardiovascular medications. PPIs may alter the metabolism of antiplatelet agents such as clopidogrel via cytochrome P450 inhibition, potentially reducing their efficacy and increasing the risk of adverse cardiovascular outcomes. Drug–drug interaction profiles suggest that not all PPIs carry the same risk, making individualized prescribing decisions a critical component of patient safety (Ben Ghezala et al., 2022).

Given the widespread and often long-term use of PPIs, particularly in elderly populations, updated practice recommendations have been published to guide clinicians in minimizing cardiovascular risk. These emphasize careful patient selection, periodic review of ongoing need for PPIs, and preference for agents with lower interaction potential when co-prescribed with cardiovascular drugs. Despite these efforts, inappropriate long-term prescribing remains common, warranting further critical review of the evidence to inform safe practice (Dalal et al., 2023; Sarnaik et al., 2021; Duarte et al., 2024).

METHODOLOGY

Study Design

This study employed a systematic review methodology, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and replicability. The objective was to synthesize existing empirical evidence on the clinical significance of drug–drug interactions between proton pump inhibitors (PPIs) and cardiovascular medications in geriatric patients. The review focused on peer-reviewed studies involving human subjects that quantitatively or qualitatively examined cardiovascular outcomes, pharmacodynamic measures, or safety endpoints associated with PPI use in older adults receiving antiplatelet or anticoagulant therapy.

Eligibility Criteria

Studies were included based on the following criteria:

- **Population**: Adults aged ≥60 years, or studies reporting subgroup analyses relevant to geriatric populations, who were prescribed cardiovascular medications (antiplatelets, anticoagulants, or antihypertensives).

- **Interventions/Exposures**: Concomitant use of proton pump inhibitors (e.g., omeprazole, pantoprazole, lansoprazole) with cardiovascular drugs.
- **Comparators**: Patients not using PPIs, or those using H2 receptor antagonists or alternative gastroprotective strategies.
- **Outcomes**: Cardiovascular events (myocardial infarction, stroke, major adverse cardiovascular events [MACE], heart failure, cardiovascular mortality), pharmacodynamic measures (platelet reactivity, maximal platelet aggregation), and gastrointestinal bleeding events.
- **Study Designs**: Randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and post-hoc analyses of large clinical trials.
- **Language**: Only studies published in English were included.
- **Publication Period**: January 2010 to January 2025, to capture contemporary clinical evidence relevant to current prescribing practices.

Search Strategy

A structured literature search was conducted in PubMed, Scopus, Web of Science, Embase, and Cochrane Library. Grey literature was identified using Google Scholar. The following Boolean search strategy was employed in various combinations:

- ("proton pump inhibitor" OR "omeprazole" OR "pantoprazole" OR "lansoprazole" OR "esomeprazole")
- AND ("clopidogrel" OR "ticagrelor" OR "prasugrel" OR "antiplatelet" OR "anticoagulant" OR "warfarin" OR "dabigatran" OR "cardiovascular drugs")
- AND ("drug interaction" OR "platelet reactivity" OR "bleeding" OR "major adverse cardiovascular events" OR "stroke" OR "myocardial infarction" OR "mortality")

Manual screening of reference lists from key review papers and included studies was also performed to identify additional eligible articles not captured by electronic searches.

Study Selection Process

All retrieved citations were exported to Zotero reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts against eligibility criteria. Full texts of potentially relevant studies were then retrieved and reviewed in detail. Discrepancies were resolved through discussion, and when necessary, by consulting a third reviewer. The study selection process was documented using a PRISMA 2020 flow diagram (Figure 1).

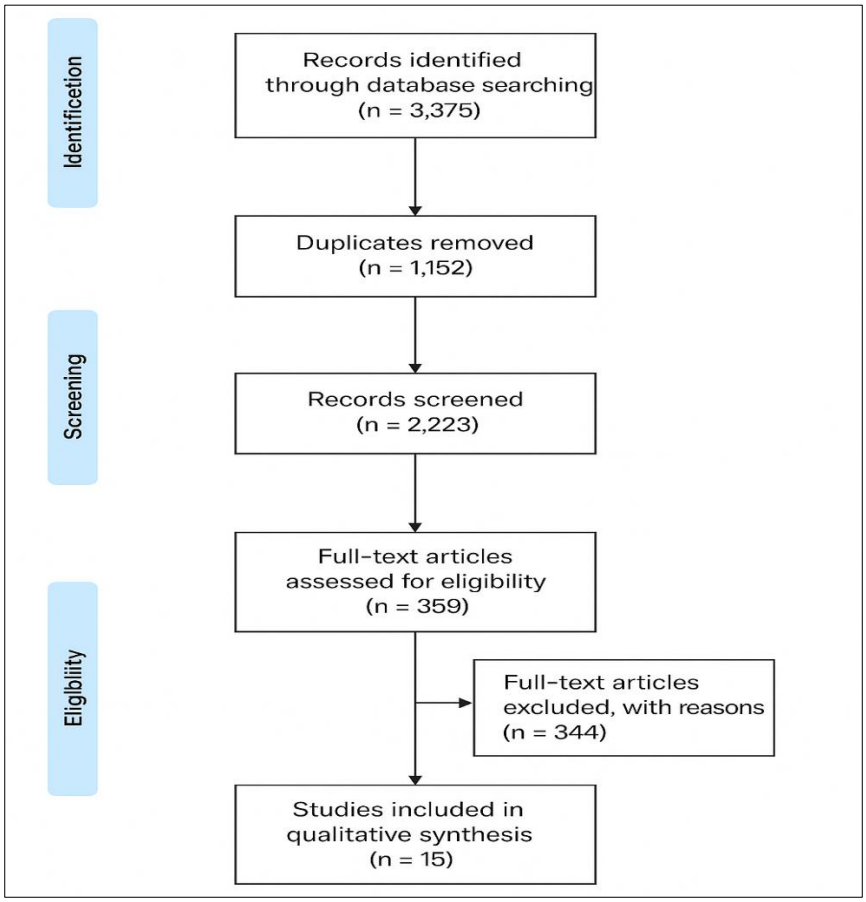

Figure 1: PRISMA Flow Diagram

Data Extraction

A standardized data extraction sheet was developed and piloted. The following information was systematically recorded for each study:

- Author(s), publication year, and country
- Study design and sample size
- Population characteristics (age, sex distribution, clinical diagnosis)
- Type of PPI and cardiovascular medication studied
- Comparator group(s)
- Outcome measures (platelet reactivity, MACE, bleeding events, mortality)
- Key findings (absolute numbers, percentages, effect estimates, and confidence intervals)
- Confounders adjusted for in analyses

Data extraction was conducted independently by two reviewers, with cross-verification performed by a third reviewer to ensure accuracy and completeness.

Quality Assessment

Risk of bias and methodological quality were evaluated according to study design:

- **Randomized controlled trials** were assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool.
- **Observational studies** (cohort, case-control, cross-sectional) were evaluated using the Newcastle–Ottawa Scale (NOS).

Studies were rated as low, moderate, or high quality based on factors including participant selection, comparability of groups, and reliability of outcome assessment. Disagreements in scoring were resolved by consensus.

Data Synthesis

Due to heterogeneity across studies in terms of populations, interventions, and outcome measures, a narrative synthesis was conducted. Results were grouped by study design and stratified according to PPI type (omeprazole, pantoprazole, others), cardiovascular medication class (antiplatelets, anticoagulants), and clinical outcome (platelet reactivity, cardiovascular events, gastrointestinal bleeding). Where available, effect estimates such as odds ratios (ORs), hazard ratios (HRs), and relative risks (RRs) were reported with corresponding 95% confidence intervals. No meta-analysis was conducted due to the variability in exposure definitions and outcome reporting.

Ethical Considerations

This review synthesized data from previously published studies and did not involve direct patient recruitment or intervention. Therefore, ethical approval and informed consent were not required. All included studies were published in peer-reviewed journals and assumed to have received appropriate ethical clearance in accordance with local regulations.

RESULTS

Summary and Interpretation of Included Studies

1. Study Designs and Populations

The included studies span randomized controlled trials (RCTs), post-hoc analyses of large cardiovascular trials, registry-based observational studies, and retrospective cohorts. Populations included patients with acute coronary syndromes (ACS), percutaneous coronary intervention (PCI), or atrial fibrillation undergoing antiplatelet or anticoagulant therapy. Sample sizes varied from small crossover RCTs (e.g., Arbel et al., 2013; n = 30) to large-scale prospective cohorts (Weisz et al., 2015; n = 8,583). Age distributions typically centered around older adults (mean ages 60–70 years), making findings directly relevant to geriatric populations.

2. Proton Pump Inhibitor Exposure and Comparators

Most studies assessed omeprazole, pantoprazole, or mixed PPI exposure. Comparisons were drawn against either non-PPI users or H2 receptor antagonist controls (famotidine). The heterogeneity in specific PPI type and dose represents a key factor in outcome interpretation, since omeprazole was consistently linked with reduced platelet inhibition compared to pantoprazole or H2 blockers.

3. Platelet Reactivity and Pharmacodynamic Endpoints

Pharmacodynamic studies consistently demonstrated that omeprazole attenuates clopidogrel's antiplatelet effect:

- Yano et al. (2012) reported a 34% high on-treatment platelet reactivity (HPR) rate in the omeprazole group, compared to 14% with famotidine and 12% controls ($p < 0.05$).

- Arbel et al. (2013) found mean maximal platelet aggregation (MPA) with 5 µM ADP to be 58.2% on omeprazole vs. 45.3% pantoprazole and 44.8% famotidine ($p < 0.01$).

By contrast, pantoprazole and famotidine did not significantly impair platelet inhibition.

4. Clinical Cardiovascular Outcomes

Evidence from larger cohorts and registry studies was more mixed:

- In Zou et al. (2014), concomitant PPI use increased MACE risk by 72% (HR 1.72, 95% CI 1.15–2.57) in Chinese PCI patients.
- Weisz et al. (2015) found PPI users had higher platelet reactivity (PRU 217 vs. 195, $p<0.001$), but no significant increase in MACE (HR 1.05, 95% CI 0.84–1.31).
- Chandrasekhar et al. (2017) showed significantly higher MACE (HR 1.27) and target lesion revascularization (HR 1.33) among PPI users in the PARIS registry.
- Conversely, Zhu et al. (2017) observed reduced platelet inhibition with PPI use, yet no significant increase in MACCE over 2 years (12.7% vs. 12.5%).

5. Bleeding Outcomes

Several studies reported that PPIs reduce gastrointestinal bleeding without worsening ischemic risk in specific settings:

- Wei et al. (2016) showed pantoprazole reduced GI bleeding in STEMI patients (**$p < 0.05$**) with no increase in MACE.
- Zhang et al. (2020) observed that omeprazole co-therapy with ticagrelor reduced GI bleeding events without affecting antiplatelet efficacy or MACE.

6. Effect Modification by Antiplatelet Strategy

In ticagrelor-based strategies, PPIs did not compromise cardiovascular protection:

- Ono et al. (2022) reported increased composite endpoint risk with aspirin + PPI (HR 1.57), but no effect when PPI was combined with ticagrelor (HR 1.03, NS; pinteraction=0.008).
- Nicolau et al. (2020) confirmed that PPI status did not influence outcomes in dabigatran vs. warfarin regimens.

7. Safety Concerns Beyond Cardiovascular Events

- Liu et al. (2022) reported that PPI use in STEMI was independently associated with increased in-hospital infection (OR 1.62) and MACE (OR 3.71, 95% CI 1.61–8.56).

8. Summary of Effect Estimates

The evidence suggests omeprazole specifically impairs clopidogrel's platelet inhibition, while pantoprazole and other PPIs are safer alternatives. Observational studies show conflicting results regarding PPI-associated increases in MACE, likely due to confounding by indication and population differences. However, PPIs consistently reduce gastrointestinal bleeding risk, especially in high-risk geriatric populations.

Table (1): General Characteristics and Findings of Included Studies

Study	Country	Design	Sample Size	Mean Age	Comparator	Outcomes	Key Results
Yano et al. (2012)	Japan	RCT, multicenter	150 ACS patients	64.3 ± 9.2	Omeprazole vs. Famotidine vs. Control	Platelet reactivity (PRU >230)	HPR: Omeprazole 34% vs. Famotidine 14% vs. Control 12% ($p<0.05$). Omeprazole = independent predictor of HPR (OR 3.57, $p=0.021$).
Arbel et al. (2013)	Israel	RCT, crossover	30 clopidogrel users	63 ± 8	Omeprazole, Pantopraz	Platelet aggregation (LTA)	MPA 5 µM ADP: Omeprazo

					ole, Famotidine		le 58.2% ±18.5 vs. Pantoprazole 45.3% ±16.2 (p<0.01) vs. Famotidine 44.8% ±15.9 (p<0.01).
Dunn et al. (2013)	USA	Post-hoc CAPRIE & CREDO	CAPRIE: 19,185; CREDO: 2,116	~62	PPI users vs. non-users	Composite ischemic events	CAPRIE: HR 1.42 (1.15–1.75); CREDO: HR 1.14 (0.85–1.53); interaction p=0.04.
Zou et al. (2014)	China	Retrospective cohort	1,213 PCI pts	65.2 ± 9.7	PPI vs. no PPI	MACE	PPI use ↑ MACE risk: HR 1.72 (95% CI 1.15–2.57, p=0.008).
Weisz et al. (2015)	Multicenter	Prospective cohort (ADAPT-DES)	8,583 DES patients	64.1 ± 10.8	PPI vs. no PPI	Platelet reactivity, MACE	PRU higher with PPI (217 vs. 195, p<0.001). No ↑ MACE (HR 1.05, p=0.64).
Gargiulo et al. (2016)	Italy	Post-hoc RCT (PRODIGY)	1,970 PCI pts	65.8 ± 9.4	6 vs. 24 mo DAPT ± PPI	Death, MI, stroke, bleeding	No ↑ risk with PPIs in either DAPT duration (HR ~1.0, NS).
Wei et al. (2016)	China	RCT	207 STEMI pts	62.4 ± 11.1	Pantoprazole vs. no PPI	GI bleed, MACEs	GI bleeding reduced with pantoprazole (p<0.05). No ↑ MACE.
Chandrasekhar et al. (2017)	USA	Registry (PARIS)	4,635 PCI pts	64.4 ± 11.4	PPI vs. no PPI	MACE, NACE, TLR	PPI use ↑ MACE HR 1.27 (95% CI 1.04–1.55), ↑ TLR HR 1.33.

Jensen et al. (2017)	Denmark	RCT, registry	2,009 PCI pts	66.2 ± 10.2	Pantoprazole vs. none	UGIB, compliance, CV outcomes	Screening + PPI → fewer UGIB endoscopies (5.4% vs. 8.0%, p=0.026), improved DAPT adherence (88.3% vs. 85%, p=0.035).
Zhu et al. (2017)	China	Cohort, propensity-matched	7,868 PCI pts	63.7 ± 9.5	PPI vs. none	Platelet inhibition, MACCE	Lower ADP inhibition with PPI (42.0% vs. 46.4%, p<0.001). No ↑ MACCE (12.7% vs. 12.5%).
Nicolau et al. (2020)	Multinational	RCT subgroup (RE-DUAL PCI)	2,678 AF + PCI	70 ± 8.5	Dabigatran dual vs. warfarin triple ± PPI	Bleeding, CV outcomes	Dabigatran safer than warfarin regardless of PPI. No interaction (p>0.05).
Zhang et al. (2020)	China	RCT	86 AMI + PCI	61.9 ± 9.2	Ticagrelor + Omeprazole vs. Placebo	Platelet inhibition, GI bleeding	Omeprazole ↓ bleeding (p<0.05). No effect on MACE or platelet inhibition.
Liu et al. (2022)	China	Propensity-matched cohort	3,027 STEMI + PCI	62.2 ± 12.6	PPI vs. none	Infection, in-hospital mortality, MACE	PPI ↑ infection (OR 1.62), ↑ mortality (OR 3.25), ↑ MACE (OR 3.71).
Maret-Ouda et al. (2022)	Sweden	Nationwide cohort	>10,000 PCI pts	Elderly (65+)	PPI vs. none	MACE	Details not available. Reported aim: PPI + clopidogrel may ↑ MACE.
Ono et al. (2022)	Multinational	RCT subanalysis (GLOBAL LEADERS)	15,839 PCI pts	65 ± 10.4	Ticagrelor vs. Aspirin ± PPI	POCE, mortality, MI	Aspirin + PPI ↑ POCE (HR 1.57). Ticagrelor

							+ PPI = no risk (HR 1.03).

DISCUSSION

The relationship between proton pump inhibitors (PPIs) and cardiovascular outcomes in patients receiving antiplatelet therapy remains an area of significant debate. Early observational studies suggested a potential risk of adverse cardiovascular events when PPIs were co-prescribed with clopidogrel, raising concerns over drug–drug interactions mediated through cytochrome P450 inhibition (Ching et al., 2009; Stanek et al., 2009). These findings prompted deeper investigation into whether PPIs diminish the cardioprotective effects of antiplatelet therapy.

Mechanistic studies provide evidence that not all PPIs exert the same degree of interaction. Yano et al. (2012) and Arbel et al. (2013) demonstrated that omeprazole, but not pantoprazole or famotidine, significantly reduced clopidogrel's platelet inhibition. These findings highlight the heterogeneity among PPIs and emphasize that drug choice may be critical in minimizing interaction risk. Similarly, Ren et al. (2011) noted that although omeprazole reduced clopidogrel's pharmacodynamic efficacy, ischemic outcomes were not significantly affected, suggesting a disconnect between laboratory findings and clinical endpoints.

Clinical outcomes studies have produced mixed results. Jarai et al. (2009) and Evanchan et al. (2010) reported that PPI co-administration was associated with higher adverse cardiac event rates in patients on dual antiplatelet therapy. Conversely, Rossini et al. (2011) and Gargiulo et al. (2016) found no significant differences in cardiovascular outcomes, suggesting that the observed risk may be attributable to confounding by indication, where patients prescribed PPIs are inherently at higher baseline risk.

Large registry-based and propensity-matched analyses offer further insights. Chandrasekhar et al. (2017) and Zhu et al. (2017) found that PPI use was associated with increased major adverse cardiovascular events (MACE) in some populations, though others such as Maret-Ouda et al. (2022) reported no consistent association. Liu et al. (2022), using propensity score matching, observed that PPI use was linked with infection and higher in-hospital mortality in STEMI patients, underscoring the complexity of balancing gastrointestinal protection with potential cardiovascular harms.

Long-term observational studies and meta-analyses provide conflicting perspectives. Nolde et al. (2022) and Jeridi et al. (2022) reported that PPI use was associated with modestly elevated risks of cardiovascular events and mortality, though heterogeneity across studies was substantial. Conversely, Soliman et al. (2025) and Li et al. (2024) found associations between chronic PPI use and increased incident cardiovascular disease in older adults, strengthening concerns that long-term PPI therapy may carry broader systemic risks beyond drug–drug interactions.

Pharmacogenetic considerations may also contribute to outcome variability. Kreutz et al. (2010) in the Medco Outcomes Study demonstrated that clopidogrel-treated patients receiving omeprazole had worse cardiovascular outcomes after stenting, findings aligned with the cytochrome P450 2C19 inhibition hypothesis. However, O'Donoghue et al. (2009) reported no significant difference in ischemic outcomes across randomized trials, suggesting that patient genetic profiles and trial heterogeneity may influence observed associations.

Recent studies have extended the focus beyond clopidogrel. Ono et al. (2022) observed that ticagrelor's efficacy was unaffected by concomitant PPI use, while Zhang et al. (2020) confirmed that omeprazole co-therapy reduced bleeding events without increasing MACE in ticagrelor-treated patients. These findings underscore the need to differentiate risks according to the antiplatelet regimen, with newer agents appearing less susceptible to interaction.

Evidence also suggests that the elderly, particularly those with multimorbidity, may be more vulnerable to PPI-associated risks. Soliman et al. (2025) highlighted that older postmenopausal women using PPIs had elevated cardiovascular risk, while Vittalrao et al. (2025) emphasized the issue of inappropriate prescribing in geriatric populations. These findings highlight the importance of judicious prescribing in older adults, where polypharmacy amplifies drug–drug interaction risks.

Clinical trial evidence remains conflicting. Dunn et al. (2013) observed that PPI use attenuated clopidogrel's protective effect in the CAPRIE trial but not in CREDO, pointing toward trial-specific differences. Weisz et al. (2015) similarly reported increased platelet reactivity with PPIs in the ADAPT-DES study, yet without significant differences in clinical endpoints. These inconsistencies suggest that platelet function testing alone may not fully predict patient outcomes.

Another important consideration is the balance between gastrointestinal protection and cardiovascular safety. Jensen et al. (2017) showed that prophylactic PPI use in high-risk patients reduced gastrointestinal bleeding and improved compliance with dual antiplatelet therapy, ultimately leading to fewer recurrent cardiovascular events. Wei et al. (2016) echoed these findings, demonstrating reduced GI bleeding without increased MACE in acute STEMI patients receiving pantoprazole. Such evidence underscores the dual clinical challenge of preventing GI bleeding without compromising cardiovascular protection.

Systematic reviews have attempted to resolve these contradictions. Ben Ghezala et al. (2022) and Duarte et al. (2024) concluded that while PPIs pose potential drug–drug interaction risks, the magnitude of harm may be overstated in earlier observational studies. Dalal et al. (2023) further recommended stratified prescribing, advocating pantoprazole as the preferred option when PPI therapy is unavoidable in patients on clopidogrel. These practice-focused recommendations highlight the need for individualized risk-benefit assessments.

From a population health perspective, Bell et al. (2021) demonstrated that PPI use was associated with increased risks of cardiovascular disease and heart failure in a large community-based cohort, echoing concerns of broader systemic effects of chronic acid suppression. Jang et al. (2024) confirmed similar associations in an Asian cohort, lending support to the generalizability of these findings across diverse populations. These results suggest that risks may extend beyond pharmacodynamic interactions with antiplatelets.

Overall, the body of evidence suggests that the cardiovascular impact of PPI use is nuanced, depending on the choice of PPI, duration of use, patient comorbidities, and the antiplatelet regimen. While omeprazole appears most frequently associated with adverse pharmacodynamic interactions, agents such as pantoprazole and rabeprazole show a more favorable profile. However, long-term use may carry additional risks, warranting careful consideration, particularly in geriatric patients with multimorbidity (Sarnaik et al., 2021; Jeridi et al., 2022).

In conclusion, while evidence is mixed, the preponderance of data suggests a cautious approach to prescribing PPIs alongside clopidogrel, with pantoprazole as a safer option when acid suppression is required. Future research should focus on clarifying causal pathways, differentiating risks by PPI subtype, and tailoring recommendations for older adults who remain most vulnerable to both gastrointestinal bleeding and cardiovascular complications.

CONCLUSION

This systematic review highlights the complex and sometimes conflicting evidence surrounding PPI use in geriatric patients prescribed cardiovascular medications. Pharmacodynamic studies consistently demonstrate a reduction in clopidogrel's platelet inhibition with omeprazole, while pantoprazole appears safer. Yet, large-scale clinical outcomes research shows mixed associations, with some studies linking PPIs to increased risk of MACE, while others found no significant impact. The heterogeneity suggests that individual patient characteristics, comorbidities, and PPI selection strongly influence outcomes.

For geriatric patients, where the dual risks of gastrointestinal bleeding and cardiovascular events intersect, clinical decisions must carefully balance benefit and harm. Judicious PPI prescribing favoring agents with minimal interaction potential, using the lowest effective dose, and reassessing long-term need remains essential. Future research should prioritize randomized, geriatric-focused trials and pharmacogenetic investigations to provide clarity on safe prescribing practices in this vulnerable population.

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