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RESEARCH

Proton pump inhibitors associated with an increased risk of mortality in elderly: a systematic review and meta-analysis

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Abstract

Purpose The increased use of proton pump inhibitors (PPIs) in the elderly has raised concerns about potential severe adverse effects. Our systematic review investigated the mortality associated with PPI use in elderly populations.

Methods We searched MEDLINE, EMBASE, and the Cochrane Library for relevant publications until August 2022. We included randomized controlled trials (RCTs), quasi-RCTs, and observational studies on the association between proton pump inhibitors and mortality in the elderly. To estimate the pooled relative risk (RR) and 95% confidence interval (CI), the inverse-variance random effect model was used. Heterogeneity was assessed using the I^2 test. Subgroup analyses were performed by follow-up period, population, and study design.

Results A total of 4 RCTs and 36 cohort studies were included in the meta-analysis. Four RCTs showed that there was no significant association between PPIs and the risk of death. From 23 observational studies (26 cohorts), the use of proton pump inhibitors was not significantly associated with increased mortality in the elderly (RR 1.14; 95% CI, 0.90–1.45). However, when controlling for covariates from 33 observational studies (41 cohorts), proton pump inhibitors in older adults aged 50 years or more were significantly associated with a 15% higher risk of mortality compared to nonusers (RR 1.15; 95% CI, 1.10–1.20).

Conclusions Our meta-analysis of RCTs found that PPIs did not show a significant association with increased mortality risk in older adults. However, the meta-analysis of cohort studies and long-term follow-up studies showed a higher increased risk of death with PPI use in older adults. The prescription of PPIs in patients aged 50 years or older should be carefully considered.

Keywords Proton pump inhibitors · Mortality · Elderly · Systematic review · Meta-analysis

Introduction

In recent decades, gastrointestinal diseases have been on the rise in older populations [1]. In this demographic, proton pump inhibitors (PPIs) are commonly used to treat heartburn, gastroesophageal reflux disease, peptic ulcer disease, and *Helicobacter pylori* infections [2, 3]. In an Irish study among adults aged 40 years or older with intellectual disabilities, the largest population of PPI users was aged 50–64 years (53.4%), and 30.2% were aged 65 years or older [4].

Concerns of potentially severe adverse effects of PPIs have increased, particularly in older adults. A recent review demonstrated that the use of PPI in older adults was associated with an increased risk of osteoporotic-related fractures, *Clostridium difficile* infection, community-acquired pneumonia, vitamin B12 deficiency, kidney disease, and dementia [5]. These potential side effects are of particular concern to the elderly because this vulnerable population is already

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Key points
- Little is known about the excess risk of death associated with proton pump inhibitor use in the elderly.
- We conducted a systematic review and meta-analysis of randomized controlled trials and observational studies regarding the association between proton pump inhibitors and the risk of death in adults aged 50 years or older.
- Our meta-analysis found a 15% increased risk of death in elderly people with PPI use compared to nonusers. Longer follow-up and cohort studies revealed an increased risk of death among older patients with cancers, cardiovascular disease, and kidney disease.
- Awareness of the increased mortality with PPI use should be raised, and the need to limit PPI prescriptions to the elderly where the benefits outweigh the potential risks should be emphasized.

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more likely to suffer from an increased risk of these conditions and consequently, severe morbidity. As a result, the guidelines recommend avoiding the use of PPIs for longer than 8 weeks in the elderly except in high-risk patients and discontinuing or reducing PPIs in older adults with more than 8-week usage of PPIs for uncomplicated peptic ulcer disease or erosive peptic esophagitis [5–7].

Additionally, recent studies have reported that PPIs were associated with increased mortality in the general population and/or patients with cancer [8–11]. The association between PPIs and mortality in the elderly population is undefined, but it has been shown that they are potentially affected [10, 11]. Since previous studies have yielded inconsistent results for mortality in older adults who take PPIs and the excess risk of death associated with PPI use has not been systematically investigated, pooled estimates that combined relative risks for mortality from each study are needed. Thus, we performed a systematic review and meta-analysis of the association between PPIs and mortality in older adults.

Methods

Literature search and study selection

We conducted searches on MEDLINE, EMBASE, and the Cochrane Library for articles published up to August 24, 2022. To search for relevant articles, we used MeSH terms and text words related to outcome, such as "mortality," "death," and "fatality," and intervention-related search terms, including the drug, brand, and chemical names of "proton pump inhibitor" (i.e., benatoprazole, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, and tenatoprazole). The search strategy is presented in Supplement Table 1.

All studies that met the following criteria were included: (1) investigated the association between PPIs and the risk of mortality in adults aged 50 years or older; (2) compared PPIs and control such as placebo or active comparator; (3) reported the quantified relative risk of death; (4) conducted randomized controlled trials (RCTs), non-randomized controlled studies, and observational studies; and (5) written in English. If the participants' age was not clearly mentioned in the inclusion criteria for the study, we included studies with participants of both a mean or median ≥ 66 years of age and an interquartile range of ≥ 56 years. Two independent reviewers examined the study selection, and the third reviewer was consulted when there was a disagreement. We registered the study protocol in PROSPERO (CRD42020179631) and followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [12].

Quality assessment

Two independent researchers conducted a quality assessment of the included studies. For RCTs, we used version 2 of the Cochrane Risk of Bias (ROB 2) tool, which is composed of five items (bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result), to assess the quality of studies with three levels (low, some concerns, and high risk of bias) [13]. The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) was used to evaluate the quality of non-RCTs. ROBINS-I consists of five items from three domains: pre-intervention, at-intervention, and post-intervention domains [14]. Pre-intervention domain includes bias due to confounding and bias in selection of participants into the study. At-intervention domain includes biases in classification of intervention, and post-intervention domain includes bias due to deviations from intended interventions, bias due to missing data, bias in measurement of the outcome, and bias in selection of the reported result. Four levels were used to assess the risk of bias in included studies: low, moderate, serious, and critical.

Data extraction

We collected information on the study and demographic characteristics (country, study design, data source, study period, mean age, percentage of male participants), exposure (definition and number of PPI users and controls, follow-up period), and outcomes (number of death of PPIs and comparators, relative risk [RR] of mortality) from the included studies. The confounding variables were extracted in regression analysis when applicable.

The primary outcomes were the unadjusted and adjusted estimates of the risk of mortality associated with PPI use. We used the best-adjusted relative risks with a 95% confidence interval (CI) after controlling the confounding variables from each included study for the meta-analysis.

Statistical analysis

To estimate the pooled RRs with CIs, the inverse-variance random effect model was used. We calculated log RR and standard error (SE) using the 95% CIs or *P*-values reported in the studies. Each study reported a different type of relative risk, such as RR, hazard ratio (HR), or odds ratio (OR). In our meta-analysis, HRs were considered RRs [15, 16], and ORs were converted to RRs using the method described by Zhang and Yu, which uses OR and the incidence of mortality in the control group [17]. The studies that reported OR

Table 1 Study characteristics of included studies

Author, year	Country	Study design	Data source/study period	Definition and number of participants (PPIs/nonusers)	Mean age (SD)/male	Exposure/co-medication	Follow-up	Numbers of death	Adjustments (matching variables in case–control studies)	Mortality (95% CI)
Randomized controlled trials										
Hasselgren et al., 1997 [31]	Sweden, Norway	RCT	29 centers/NR	Patients aged ≥ 60 years with peptic ulcer bleeding 322 (159/163)	Omeprazole 74.5 (8.2), placebo 74.3 (7.4)/58.1%	Omeprazole	21 days	Omeprazole 11/159 (6.9%), placebo 1/163 (0.6%)	NA	Omeprazole vs placebo, $P = 0.012$
Marker et al., 2019 [39]	Denmark, Finland, Norway, Switzerland, Netherlands, UK	RCT	International Stress Ulcer Prophylaxis in the Intensive Care Unit (ISP-ICU) trial 2016–2017	Patients at risk for gastrointestinal bleeding 3261 (1635/1626)	Median 67 (IQR 56–75)/64%	Pantoprazole	1 year	Pantoprazole 610/1635 (37.3%), placebo 601/1626 (37.0%)	Age, type of admission, sepsis-related organ failure assessment score, hematological malignancy	aRR 0.99 (0.90–1.09)
Moayyedi et al., 2019 [40]	580 centers in 33 countries	RCT	Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial/2013–2016	Patients aged ≥ 65 years with stable coronary or peripheral arterial disease 17,598 (8791/8807)	Pantoprazole 67.6 (8.1), placebo 67.7 (8.1)/78.4%	Pantoprazole	3 years	PPI 630/8791 (7.2%), placebo 614/8807 (7.0%)	NR	HR 1.03 (0.92–1.15)
Wu et al., 2011 [56]	China	RCT	Three cardiology centers/2008–2010	Patients with acute coronary syndromes and high risk for GI bleeding 665 (333/332)	NR/73.7%	Pantoprazole	30 days	Pantoprazole 35/333 (10.5%), placebo 34/332 (10.2%)	NA	Pantoprazole vs placebo, $P = 1.00$
Observational studies										
Adelborg et al., 2018 [18]	Denmark	Cohort	Danish medical registries/1995–2014	Patients with heart failure 46,198 (42,902/3296)	PPI median 78 (IQR 69–85)/54% H2RA median 76 (IQR 68–83)/52%	PPIs H2RA	5 years	PPI 25,835/42,902 (76.8%), H2RA 1964/3296 (60.7%)	Age, index year, sex, time from heart failure hospital admission date until first prescription of a H2RA or PPI, CAD, valvar heart disease, hypertension, atrial fibrillation, atrial flutter, VTE, stroke, intermittent claudication, diabetes, obesity, cancer, chronic pulmonary disease, CKD, dementia, depression, illicit drug abuse, alcohol abuse, smoking, anemia, PUD, GERD, liver disease, alcohol disorders, musculoskeletal disorders, inflammatory bowel disease, beta blockers, ACEI/ARB, diuretics, statins, NSAID, antithrombotics, benzodiazepines, opioids, gross income, employment	NR
Ayyagari et al., 2020	USA	Cohort	VA Central Cancer Registry/2002–2016	1. Patients with esophageal adenocarcinoma 6530 (3865/2665) 2. Patients with esophageal squamous cell carcinoma 3227 (1466/1761) 3. Patients with cardia gastric cancer 2361 (1361/1000) 4. Patients with non-cardia gastric cancer 3142 (1818/1324)	1. 67.1 (9.2)/99.5% 2. 67.0 (9.6)/98.7% 3. 68.1 (9.8)/98.6% 4. 69.6 (11.0)/97.5%	PPIs H2RA	NR	NR	Age, sex, race, BMI, alcohol use, smoking status, stage, grade, chemotherapy, radiation, surgery, pre-diagnosis PPI use, post-diagnosis aspirin/NSAID use, post-diagnosis statin use GNCC only: H. pylori infection	1. aHR 0.97 (0.91–1.03) 2. aHR 1.05 (0.98–1.14) 3. aHR 1.13 (1.03–1.24) 4. aHR 1.04 (0.96–1.13)
Baek et al., 2022 [20]	South Korea	Cohort	National Health Insurance Service/2017–2018	Patients treated ICIs for advanced NSCLC 955	NR	PPIs/immune checkpoint inhibitors	NR	NR	Age, sex, respiratory disease, viral hepatitis, antibiotics, corticosteroid	65–74 years: aHR 1.12 (0.91–1.36) ≥ 75 years: aHR 1.82 (1.34–2.47)

Table 1 (continued)

Author, year	Country	Study design	Data source/study period	Definition and number of participants (PPIs/nonusers)	Mean age (SD)/male	Exposure/co-medication	Follow-up	Numbers of death	Adjustments (matching variables in case–control studies)	Mortality (95% CI)
Baik et al., 2022 [21]	USA	Cohort	Medicare Prescription Drug (Part D) enrollees/2007–2017	Elderly Medicare fee-for-service beneficiaries 1,930,728 (336,619/1,522,073)	NR/42.4%	PPIs H2RA	Median 3.8 years	PPI 25,774/336,619 (7.7%), nonuser 45,346/1,462,216 (3.1%)	Age, gender, race, living area, AMI, atrial fibrillation, cataract, CKD, COPD, heart failure, diabetes, glaucoma, hip/pelvic fracture, IHD, depression, Alzheimer's disease, dementia, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack, breast cancer, colorectal cancer, prostate cancer, lung cancer, endometrial cancer, anemia, asthma, hyperlipidemia, hypertension, hyperplasia, hypothyroidism, alcohol use disorders, anxiety disorders, bipolar disorder, drug use disorder, personality disorders, schizophrenia, epilepsy, cystic fibrosis, fibromyalgia, viral hepatitis (general), liver disease cirrhosis, leukemias and lymphomas, migraine, mobility impairments, obesity, opioid use disorder, PVD, tobacco use disorders, pressure ulcers, deafness	aHR 1.10 (1.08–1.11)
Bakhshwin et al., 2022 [22]	Soudi Arabia	Cohort	King Faisal Medical Complex/2020	COVID-19 hospitalization patients aged ≥ 60 years 145	69.2 (8.1)/55.2%	PPIs	NR	PPI 12/102 (11.8%), nonuser 4/43 (9.3%)	-	NR
Bell et al., 2010 [23]	Finland	Cohort	1. Long-term care wards 2. Acute geriatric wards, nursing homes/1999–2000	Institutionalized older people 1. 1004 (231/773) 2. 425 (91/334)	1. 81.3 (10.9)/25.5% 2. 96.1 (7.0)/18.4%	PPIs	12 months	1. PPI 77/231 (33.3%), nonuser 206/773 (26.6%) 2. PPI 33/91 (36.3%), nonuser 73/334 (21.9%)	1. Age, sex, CCI, malnutrition 2. Age, sex, CCI, delirium	1. aHR 1.37 (1.05–1.78) 2. aHR 1.82 (1.20–2.78)
Bradley et al., 2019 [24]	USA	Cohort	University of Massachusetts Memorial Health Care System Theradoc Clinical Surveillance Software System/2012–2014	Elderly patients with *Clostridium difficile* infection (> 65 years of age) 874 (320/554)	Survivors76.5 (8.1), died 78.4 (8.2)/41.6%	PPIs	180 days	PPI 24/320 (7.5%), nonuser 85/554 (15.3%)	Age, Hispanic, African American, Nursing home, CCI, severe infection, hospital acquired, bacterial other, probiotic	aHR 0.45 (0.28–0.72)
Brozek et al., 2017 [25]	Austria	Cohort	13 Austrian social insurance authorities/2008–2011	Hip fracture patients ≥ 50 years without anti-osteoporotic drugs 15,958 (11,390/4568)	NR PPIs 32.1%	PPIs	3 years	NR	Age, gender	aHR 1.37 (1.17–1.60)
Cetin et al., 2020 [26]	Austria	Cohort	13 Austrian statutory sickness funds/2005–2016	1. Patients with dementia 28,428 (12,979/15,449) 2. Patients without dementia 56,856 (21,948/34,908)	1. Median 82.2 (IQR 76.8–86.6)/32.2% 2. Median 82.8 (IQR 77.9–86.5)/30%	PPIs	≥ 4 years	1. 19,267/28,428 (67.8%) 2. 20,484/56,856 (36.0%)	Age, sex, NSAID, the number of distinct drug classes	1. aHR 1.03 (1.01–1.05) 2. aHR 1.15 (1.05–1.26)
Cholin et al., 2021 [27]	USA	Cohort	Chronic kidney disease registry/2007–2017	Patients with chronic kidney disease 25,455 (8646/15,961)	PPI: 72.8 (10.9)/38.4% Nonuser 73.4 (11.1)/44.4%	PPIs	Median 4.14 years	PPIs 1845/8646 (21.3%), nonuser 3521/15,961 (22.1%)	Age, race, sex, eGFR, BMI group, hemoglobin, potassium, CO_2, diabetes, hypertension, CVD, PVD, CAD, CHF, malignancy, ACE/ARB, beta blockers, smoking and insurance	aHR 0.97 (0.91–1.03)

Table 1 (continued)

Author, year	Country	Study design	Data source/study period	Definition and number of participants (PPIs/nonusers)	Mean age (SD)/male	Exposure/co-medication	Follow-up	Numbers of death	Adjustments (matching variables in case–control studies)	Mortality (95% CI)
De Francisco et al., 2017 [28]	Spain	Cohort	Fresenius Medical Care NephroCare dialysis clinics/2014	Hemodialysis patients 2242 (1776/466)	68 (56–76)/62.8%	PPIs	22.8 months	PPIs 433/1776 (24.4%), nonuser 82/466 (15.6%)	Age, sex, dialysis vintage, diabetes mellitus, CCI, hemodialysis clinical parameters, laboratory values, antithrombotic agents	aHR 1.37, 95% CI 1.05–1.78
Farhat et al., 2020 [29]	Canada	Case–control	Cerner Health Facts database/2000–2016	Patients with myocardial infarction and started clopidogrel treatment 16,823 (9301/7522)	Case 70.2 (12.1)/56.3% Control 70.4 (11.7)/56.7%	PPIs	12 months	NR	Demographics, smoking, comorbidities, use of comedications, prior cardiovascular procedures, and hospital characteristics	aOR 1.04 (0.95–1.15)
Hálfdánarson et al., 2020 [30]	Iceland	Cohort	Icelandic Cancer Registry, Icelandic Medicines Registry, Icelandic Population Register, Cause of Death Register, Landspitali/2007–2012	Patients with prostate cancer 1058 (347/711)	PPI median 69 (IQR 63–76) Nonuser median 69 (IQR 62–75)	PPIs	Median 4.6 years	PPI 59/347 (17.0%), nonuser 144/711 (20.3%)	Age, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy	aHR 1.02 (0.73–1.43)
Jun et al., 2021 [32]	USA, Europe, Asia	Cohort	11 tertiary referral centers/2017–2019	HCC patients treated with immunotherapy 314 (85/229)	66 (IQR 59–72)/79%	PPIs	Median 9.2 months	NR	-	HR 1.14 (0.84–1.54)
Juurlink et al., 2011 [33]	Canada	Case–control	Canadian Institute for Health Information Discharge Abstract Database, Ontario Public Drug Program Benefit Program, Ontario Health Insurance Plan database, Registered Persons Database/2002–2008	Older adults ≥ 66 years treated with clopidogrel after stroke 300 (96/205)	Median 78 (IQR 73–83/46.8%	PPIs	Up to 78 months	PPI 22/78 (28.2%), nonuser 35/205 (17.1%)	Age, gender, income quintile, CCI, length of stay in the hospital, hospital type, history of diabetes, stroke, coronary revascularization, ACEI, ARB, aspirin, adrenergic receptor antagonists, CCB, statins, lipid-lowering agents, diuretics, warfarin, cytochrome P-450 2C19 inhibitors/inducers, cytochrome P-450 3A4 inhibitors/inducers (age, gender, stroke, transient ischemic attack)	aOR 1.84 (0.88–3.89)
Liabeuf et al., 2021 [34]	France	Cohort	CKD-REIN/2013–2016	Patients with stage 3 or 4 chronic kidney diseases 3023 (981/2042)	PPI 70 (IQR 64–77), no PPI 68 (IQR 58–76)/65.5%	PPIs	PPI median 3.9 years	PPI 49/981 (5.0%), nonuser 167/2042 (8.2%)	Age, sex, education, diabetes, estimated glomerular filtration rate, BMI, smoking, albuminemia, anemia, systolic blood pressure, history of acute kidney injury, CVD	aHR 2.42 (1.73–3.39)
Lo et al., 2022 [35]	USA	Cohort	Nurses' Health Survey, Health Professionals/2004	Female registered nurse, male registered professionals 71,887 (13,943/57,944)	68.6/30.2%	PPIs	Median 13.8 years	PPI 2033/13,943 (14.6%), nonuser 20,092/57,944 (34.7%)	Race, smoking, BMI, physical activity, Alternate Healthy Eating Index-2010, alcohol, NSAID, H2RA, cancer, MI, stroke, hypertension, diabetes mellitus, hypercholesterolemia, gastroesophageal reflux disease, Barrett's esophagus, PUD, gastrointestinal bleeding, COPD	aHR 1.19 (1.13–1.24)
Maggio et al., 2013 [36]	Italy	Cohort	Acute care medical awards, long-term care, rehabilitation units/2007	Older patients discharged from acute care hospitals 491 (174/317)	80.0 (5.9)/46.0%	Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole	1 year	PPI 32/174 (18.4%)	Age, sex, BMI, hypoalbuminemia, cognitive impairment, depression, dependency in activities of daily living, cumulative illness rating scale, peptic ulcer, diarrhea, infectious disease, fracture, the number of drugs at discharge, antithrombotic use, NSAIDs	aHR 1.51 (1.03–2.77)

Table 1 (continued)

Author, year	Country	Study design	Data source/study period	Definition and number of participants (PPIs/nonusers)	Mean age (SD)/male	Exposure/co-medication	Follow-up	Numbers of death	Adjustments (matching variables in case–control studies)	Mortality (95% CI)
Mahabaleshwarkar et al., 2013 [37]	USA	Case–control	Medicare beneficiaries /2006–2008	Patients aged ≥ 65 years receiving clopidogrel 43,159 (15,415/28,104)	76.8/38.5%	PPIs/clopidogrel	Mean 443.1 days	NR	Sex, race, ESRD, dual eligibility, angina, COPD, CHF, diabetes, dialysis, erosive esophageal reflux disease, GI bleeding, history of AMI, CABG, PCR, stroke, hyperlipidemia, hypertension, PVD, CYP2C19 inhibitors, CYP2A4 inhibitors, ACEI, beta-adrenergic antagonists, calcium channel antagonists, diuretics, statins, sulfonylureas, aspirin, digoxin, spironolactone (age, time to cohort entry)	aOR 1.40 (1.29–1.53)
Maret-Ouda et al., 2022 [38]	Sweden	Cohort	Swedish Prescribed Drugs and Health Cohort/2005–2019	Patients who received clopidogrel after primary percutaneous coronary intervention 99,836 (35,772/64,064)	PPI median 69 (IQR 61–77) Nonuser median 67 (IQR 59–75)/72.2%	PPI/clopidogrel	Up to 12 months	PPI 1434/36,110 (4.0%), nonusers 1074/64,064 (1.7%)	Age, sex, calendar year, obesity-related diseases, tobacco-related diseases, hypertension, CHF, CCI	aHR 1.71 (1.58–1.86)
Muñoz-Torrero et al., 2020 [41]	Spain	Cohort	The Factores de Riesgo y ENfermedad Arterial (FRENA) Registry/2003–2016	Patients with coronary, cerebrovascular, or peripheral artery disease 5170 (2289/2881)	PPI 67.30 (11.69) Nonusers 65.96 (12.04)/73.9%	PPIs	Median 36 months	PPI 135/2289 (5.9%), nonuser 132/2881 (4.6%)	Age, sex, BMI, cancer, chronic lung disease, heart failure, atrial fibrillation, hypertension, diabetes, smoking, creatinine clearance, cholesterol, CCB, diuretics, antiplatelets, insulin, statins, antidiabetics, beta-blockers	aHR 1.37 (1.04–1.79)
Nayan et al., 2018 [42]	Canada	Cohort	Canadian Institute for Health Information Discharge Abstract Database/1997–2013	Patients aged ≥ 65 with newly diagnosed kidney cancer 9124 (4651/4473)	73.8 (6.0)/58.7%	PPIs	60 months	NR	Age, sex, comorbidity score, disease stage, socioeconomic status, rurality, year of diagnosis	aHR 0.95 (0.92–0.98)
Oudit et al., 2011 [43]	Canada	Cohort	linked administrative databases/1999–2005	Patients aged ≥ 65 with newly diagnosed with heart failure 22,107 (6431/15,676)	Median 80 years (IQR 74–86)/48%	PPIs	1 year	PPI 1153/6431 (26%), nonuser 5659/15,676 (32%)	Sex, age, hypertension, diabetes, IHD, CVD, PVD, COPD, renal disease, cancer, anemia, GI bleeding, cardiac medications, ACEI, ARB, beta-blockers, spironolactone, digoxin, statin, CCB, non-cardiac medications, sulfonylurea	aOR 0.87 (0.81–0.93)
Pani et al., 2020 [44]	Italy	Cohort	Internal Medicine Units of the Niguarda Hospital/2015–2018	Patients admitted to internal medicine ward 531 (231/300)	77.3 (13.1)/60.3%	PPIs	NA	PPI 22/231 (9.5%), nonuser 31/300 (10.3%)	-	OR 0.940 (0.527–1.678)
Pegoli et al., 2017 [45]	Australia	Cohort	Older hospital patients discharged to residential aged care facilities/2014–2015	Patients ≥ 75 years and discharged from a tertiary hospital to residential aged care facilities 102 (51/51)	87 (6)/39.2%	PPIs	6 months	PPI 19/51 (37.3%), nonuser 14/51 (27.5%)	Age, gender, initial place of residence, CCI, total number of days spent in hospital within 6 months, number of regular medications taken on discharge	aHR 2.24 (1.01–4.96)

Table 1 (continued)

Author, year	Country	Study design	Data source/study period	Definition and number of participants (PPIs/nonusers)	Mean age (SD)/male	Exposure/co-medication	Follow-up	Numbers of death	Adjustments (matching variables in case–control studies)	Mortality (95% CI)
Rassen et al., 2009 [46]	Canada, USA	Cohort	Health insurance program (British Columbia, Pennsylvania, New Jersey)/2001–2005	Patients aged ≥ 65 years and who underwent percutaneous coronary intervention or were hospitalized for acute coronary 18,565 (3996/14,569)	British Columbia 74 (range 65–100), Pennsylvania 78 (range 65–101), New Jersey 78 (range 65–104)/76.1%	PPIs	Median 29–30 days	PPI 61/3996 (1.5%), nonuser 124/14,569 (0.9%)	Age, sex, race, calendar year, outpatient visit, PCI performed, inpatient, MI, gastrointestinal bleed, angina, hemorrhagic stroke, nonselective NSAID, COX-2 inhibitor, diabetes drug, statin, beta-blocker, ACEI/ARB, warfarin, history of diabetes, hypertension, PVD, CHF, nursing home residence, number of medications, time in hospital, office visits, CCI	aRR 1.20 (CI 0.84–1.70)
Roberts et al., 2021 [47]	Australia	Cohort	Five major public hospitals/2017	Patients aged ≥ 75 years, admitted to general medical wards, discharged to a RACF and receiving ≥ 5 regular medications at admission 170 (95/75)	86.7 (6.9)/44.7%	PPIs/≥ 5 regular medications	NR	NR	Residence, CCI, number of medications	aHR 1.09 (0.63–1.89)
Rooney et al., 2021 [48]	USA	Cohort	Four US communities (Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; Washington County, MD)/2011–2017	Participants who have atherosclerosis Risk without prevalent cardiovascular disease 4436 (1067/3369)	PPI 75.3 (5.1), nonuser 75.2 (5.1)/36.8%	PPIs	Median 5.6 years	PPI 39/1067 (3.7%), nonuser 82/3369 (2.4%)	Age, race-center, sex, education, smoking status, drinking status, physical activity, obesity, diabetes, systolic blood pressure, antihypertension medication use, lipid-lowering medication use, HDL, total cholesterol, eGFR., hypomagnesemia	aHR 1.34 (0.86–2.09)
Sharma et al., 2019 [11]	USA	Cohort	National linked SEER-Medicare databases/2007–2012	Patients aged ≥ 66 years and received tyrosine kinase inhibitors 12,538 (9695/2842)	Median 76 years/48.7%	PPIs/TKIs	1 year	PPI 5745/9695 (59.3%), nonusers 1600/2842 (56.3%)	Age, sex, race, marital status, region, primary cancer type, stage at diagnosis, receipt of radiation, score on Deyo adaptation of the CCI, year of TKI start, polypharmacy, prior PPI use within 90 days before the TKI start date, receipt of prior chemotherapy, NSAID, history of gastric ulcer, duodenal ulcers, time between cancer diagnosis and the TKI start date	aHR 1.10 (1.04–1.17)
Sturm et al., 2021 [49]	Germany	Cohort	University Medical Center Freiburg, Germany/2009–2019	Patients with hepatocellular carcinoma treated by transarterial chemoembolization 358 (167/191)	Median 69 (IQR 60–75)/83.0%	PPIs	Median transplant- free survival 22 months	PPI 15/167 (9.0%), nonusers 15/191 (7.9%)	Age, sex, Child Pugh stadium, Solitary vs multifocal tumor, tumor diameter, portal vein thrombosis, Serum alpha-fetoprotein, PPI dose	aHR 1.53 (1.13–2.06)
Teramura-Grönblad et al., 2012 [50]	Finland	Cohort	1. Assisted living facilities/2007 2. Long-term care hospitals/2003 3. Nursing homes, acute geriatric wards	Institutionalized older people 1. 1389 (367/1022) 2. 1004 (231/773) 3. 425 (91/334)	1. PPIs 83.6 (7.7), nonusers 82.4 (7.8) 2. PPIs 80.6 (11.4), nonusers 81.5 (10.8) 3. PPIs 85.5 (7.4), nonusers 86.3 (6.8)	Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole (ATC code A02BC)	1 year	1. PPIs 74/367 (20.2%), nonusers 208/1022 (20.4%) 2. PPIs 77/231 (33.3%), nonusers 206/773 (26.6%) 3. PPIs 33/91 (36.3%), nonusers 73/334 (21.9%)	1. Age, sex, CCI, immobility, SSRIs 2. Age, sex, CCI, SSRIs, malnutrition 3. Age, sex, CCI, delirium, aspirin, SSRIs	1. aHR 1.06 (0.77–1.46) 2. aHR 1.36 (1.04–1.77) 3. aHR 1.90 (1.23–2.94)

Table 1 (continued)

Author, year	Country	Study design	Data source/study period	Definition and number of participants (PPIs/nonusers)	Mean age (SD)/male	Exposure/co-medication	Follow-up	Numbers of death	Adjustments (matching variables in case–control studies)	Mortality (95% CI)
Tomisaki et al., 2022 [51]	Japan	Cohort	Hospital of the University of Occupational and Environmental Health/2018–2021	Patients with advanced urothelial carcinoma 40 (15/25)	72 (IQR 67–79)/75%	PPIs/pembrolizumab	Median 11.2 months	NR	Age, gender, ECOG-PS, hemoglobin, liver metastasis, time from prior chemotherapy, antibiotics	aHR 4.00 (1.22–13.15)
Tran et al., 2021 [52]	UK	Cohort	United Kingdom Clinical Practice Research Datalink, Hospital Episode Statistics, Office for National Statistics/2003–2017	Patients with idiopathic pulmonary fibrosis 3036 (1852/1852)	PPI 75.4 (9.4), nonusers 75.6 (9.5)/77.7%	PPIs	Median survival 2.8 years	PPI 1221/1852 (66.0%), nonuser 482/1852 (26.0%)	Age, sex, BMI, smoking, excessive alcohol use, ethnicity, prior hospitalizations, comorbidities, asthma, COPD, GERD, Nissen fundoplication, CVD, diabetes, cancer, renal disease, depression, corticosteroids, ACEI, beta-blockers, anticoagulants, diuretics, statins, NSAID, H2-blockers	aHR 1.07 (0.94–1.22)
Tsai et al., 2021 [53]	Taiwan	Cohort	Taiwan's National Health Insurance Research Database/1999–2011	Patients with dialysis 18,230 (9115/9115)	PPI 66.59 (14.82), nonusers 66.58 (14.82)/57.8%	PPIs	3.52 years	PPI 4660/9115 (51.1%), nonusers 4449/9115 (48.8%)	Age, sex, peptic ulcer, duodenal ulcer, gastric ulcer, liver cirrhosis, CKD, acute on chronic kidney disease after index discharge, propensity covariates	aHR 1.03 (0.98–1.08)
Wang et al., 2021 [54]	Sweden	Cohort	Swedish Prescribed Drug Registry, Swedish Causes of Death Registry/2006–2013	Patients with colorectal cancer 32,411 (17,801/14,610)	> 65 years 71%/52%	PPIs	Median 2.74 years	PPI 4746/17,801 (26.7%), nonusers 8439/14,610 (57.8%)	Age, sex, pre-diagnosis PPI use, tumor site, tumor stage, surgery, low-dose aspirin, non-aspirin NSAIDs, CCI	aHR 1.38 (1.32–1.44)
Wilson et al., 2011 [55]	Australia	Cohort	Intermediate-level residential aged care facilities	Institutionalized older people 602 (246/356)	85.7 (6.4)/29.1%	PPIs	1 year	PPIs 27/246 (11.0%), nonusers 35/356 (9.8%)	Age, sex, MCCI	aHR 1.08 (0.63–1.86)
Xie et al., 2022 [57]	China	Cohort	Medical Information Mart for Intensive Care/2011–2019	Patients with acute myocardial infarction and admitted to ED 2001 (426/1575)	69.6 (14.2)/59.2%	PPIs	NR	PPI 18/426 (4.2%), nonusers 86/1575 (5.5%)	Age, sex, ethnicity, troponin T, creatinine kinase, PTCA, dilation of coronary artery, CCI, CHF, cerebrovascular disease, PVD, dementia, chronic pulmonary disease, mild liver disease, renal disease	aHR 1.08 (0.58–1.99)

ACEI angiotensin-converting enzyme inhibitor, *aHR* adjusted hazard ratio, *aOR* adjusted odds ratio, *APRI* Platelet Ratio Index, *ARB* angiotensin receptor blocker, *aRR* adjusted risk ratio, *ATC* anatomical therapeutic chemical classification, *BMI* body mass index, *CAD* coronary artery disease, *CCB* calcium channel blockers, *CCI* Charlson comorbidity index, *CHF* congestive heart failure, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *EAC* esophageal adenocarcinoma, *ECOG* Eastern Cooperative Oncology Group, *eGFR* estimated glomerular filtration rate, *ESCC* esophageal squamous cell carcinoma, *GCC* cardia gastric cancer, *GERD* gastroesophageal reflux disease, *GI* gastrointestinal, *GNCC* non-cardia gastric cancer, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HR* hazard ratio, *ICI* immune checkpoint inhibitor, *IHD* ischemic heart disease, *MCCI* medical-based Charlson comorbidity index, *MELD* Model for End-Stage Liver Disease, *MI* myocardial infarction, *NA* not applicable, *NAFLD* nonalcoholic fatty liver disease, *NOAC* non-vitamin K antagonist oral anticoagulants, *NR* not reported, *NSCLC* nonsmall cell lung cancer, *NSAID* nonsteroidal anti-inflammatory drug, *OAC* oral anticoagulants, *PPI* proton pump inhibitor, *PTCA* percutaneous transluminal coronary angioplasty, *PUD* peptic ulcer disease, *PVD* peripheral vascular disease, *RCT* randomized controlled trial, *SEER* Surveillance, Epidemiology, and End Results, *TACE* transarterial chemoembolization, *TKI* tyrosine kinase inhibitors, *VTE* venous thromboembolism

were included in the meta-analysis when we could calculate RRs from the data on OR and the incidence of mortality in the control group. In addition, we performed subgroup and sensitivity analyses according to follow-up period, population, country, study design, the median age of included studies, and quality of the studies. We conducted a duration analysis of the risk of death among PPI users by follow-up period: ≤ 6 months, > 6 months–≤ 1 year, > 1–≤ 2 years, > 2–≤ 3 years, > 3–≤ 4 years, and > 4 years. To further evaluate disease-specific mortality, we evaluated the association between PPIs and mortality among patients with cancers, cardiovascular disease, and kidney diseases as well as people who were institutionalized and hospitalized. To assess the impact of different health care systems, the subgroup analysis by countries was conducted: USA/Canada, Europe, Australia, and Asia. The association of subgroups was also examined by patient's age to take into account differences in mortality by age groups (≤ 75, 76–85, and > 85 years old) as well as by quality assessment of included studies (low, moderate, and serious/critical risk of bias) to incorporate assessment into the analyses. We also analyzed the association in studies that included and did not include Charlson Comorbidity Index (CCI) as a covariate.

Heterogeneity was assessed using the I^2 test and Q statistic, with the significance of the Q-statistic test being considered at $p < 0.05$. Heterogeneity was considered for I^2 values of more than 50% [13]. The funnel plot was used to estimate possible publication bias owing to the tendency to publish studies with positive results. We used Review Manager 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Literature search

An initial search was performed on 15,202 articles; we identified 13,544 relevant ones after excluding 1658 duplicate articles (Fig. 1). In the screening process, 12,992 articles were removed during the title/abstract review, and 511 articles were excluded during the full-text review due to one of the following reasons: no elderly patients, no PPI therapy, ineligible study design, no comparator group available, no outcomes of interest reported, and non-original studies. Finally, 49 cohorts among 41 studies (four RCTs and 37 observational studies) were included in our systematic review [11, 18–57] since five studies included more than one cohort in their studies [19, 20, 23, 26, 50]. In the meta-analysis, 4 cohorts among 4 RCTs and 44 cohorts among 36 observational studies were included. One study/cohort was not included in the meta-analysis as we could not calculate RR from OR due to a lack of data on the number of deaths [29].

General characteristics of the included studies

We included four RCTs, 34 cohort studies, and three case–control studies (Table 1). In RCTs, PPIs including omeprazole and pantoprazole were included as interventions with comparators of placebo. In observational studies, most studies included all kinds of PPIs as interventions and non-PPI users as controls including H2RA. The studies were conducted in the USA, Canada, Europe, Australia, and Asia. The study participants included the following: patients with cancer ($n = 9$), cardiovascular disease ($n = 11$), kidney disease ($n = 4$), institutionalization ($n = 6$), and hospitalization ($n = 5$). All studies included 2,515,079 participants with a median age ranging from 67 to 96 years and the percentage of males ranging from 18.4 to 99.5%. Study follow-up periods were from 21 days to 13.8 years. When estimating adjusted HRs or ORs, baseline demographics, disease-related clinical factors, comorbidities, and medications were included as confounding variables (Table 1).

Quality assessment

The included RCTs had a low risk of bias from missing outcome data, measurement of the outcome, and selection of the reported result (Supplement Fig. 1). For measurement of the outcome, we determined a low risk because mortality was not affected by any measurement methods. We evaluated some concerns for deviations from intended interventions for half of the included RCTs because PPIs can also be used as over-the-counter (OTC) drugs.

All cohort studies had a low risk of bias from deviations from intended interventions, missing data, measurement of the outcome, and selection of the reported result (Supplement Table 2). Among 37 cohort studies, 10 studies had moderate, serious, or critical risk of bias because appropriate confounding covariates for the adjusted estimates were not included, and 19 had a moderate risk for classification of interventions because OTC use of PPIs could not be captured. The overall risk of bias was assessed as low at 27%, moderate at 57%, and serious or critical risk at 16%.

Proton pump inhibitors and mortality in RCTs

Among 4 RCTs, the death rates were 11.8% in PPI users (1286/10,918) and 11.4% in nonusers (1250/10,928). The PPI use and risk of mortality in unadjusted RR among

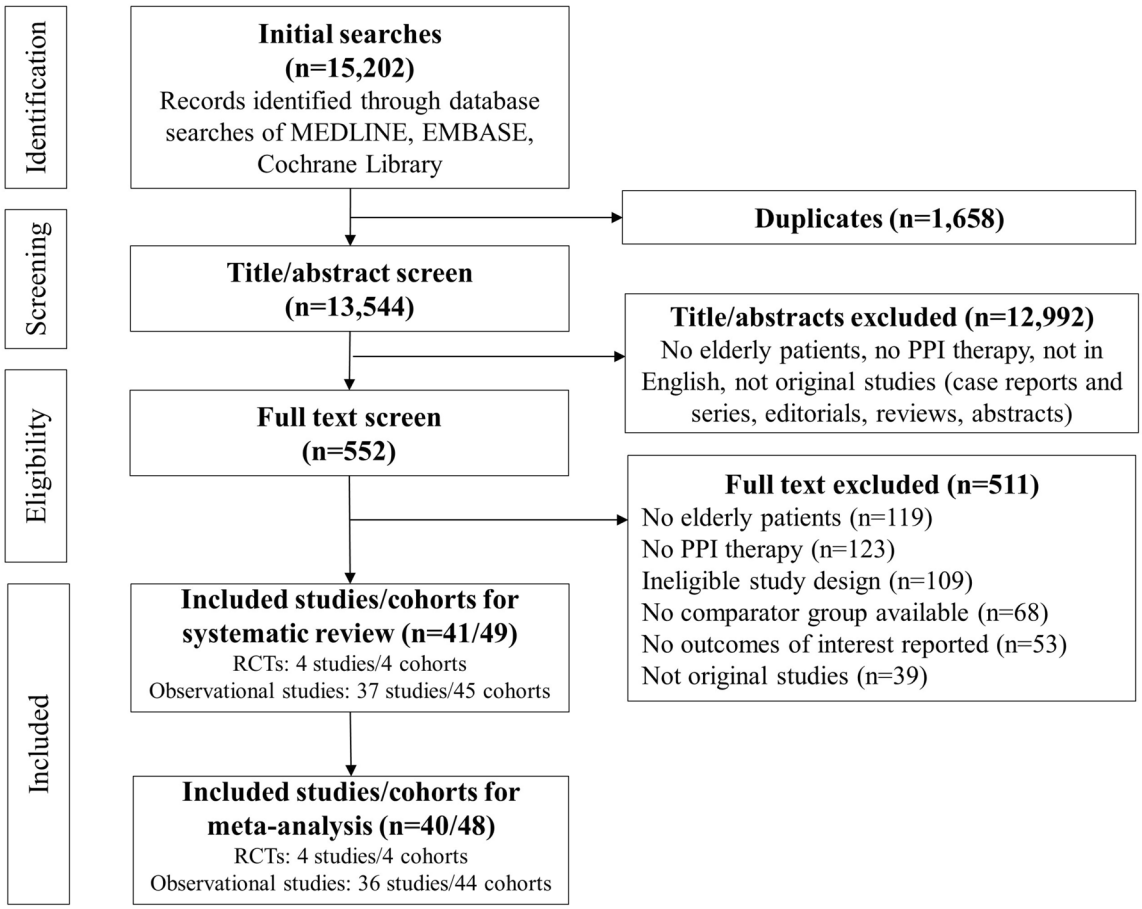

Fig. 1 PRISMA flow diagram of study selections

individuals aged 50 years or older were not significantly associated (RR 1.03; 95% CI, 0.91–1.16), with moderate heterogeneity was moderate ($I^2 = 45\%$, $p = 0.14$ (Fig. 2A). When estimating adjusted risk ratio among 20,859 elderly people from 2 RCTs, the association between PPI users and death was not significantly associated compared to nonusers (aRR, 1.01; 95% CI, 0.94–1.08), with 0% of heterogeneity ($I^2 = 0\%$, $p = 0.60$) (Fig. 2C).

Proton pump inhibitors and mortality in observational studies

In 26 observational studies (29 cohorts), there were 75,675 deaths in 512,263 PPI users (14.8%) and 94,428 deaths in 1,731,521 nonusers (4.9%). We found no significant association between the use of PPI and mortality from unadjusted RR in the elderly (RR 1.14; 95% CI, 0.90 – 1.45) (Fig. 2B). There was significant heterogeneity ($I^2 = 100\%$, $p < 0.001$), and funnel plots showed no evidence of publication bias (Fig. 3A). For adjusted estimates, 41 cohorts from 33 studies of the association between PPIs and death included 2,429,961 individuals aged 50 years or older. The use of PPI was significantly associated with a 15% increased risk of mortality compared to non-use (aRR, 1.15; 95% CI, 1.10–1.20) (Fig. 2D). Significant heterogeneity was detected ($I^2 = 93\%$, $p < 0.001$), and there was no evidence of publication bias based on the funnel plot (Fig. 3B).

Additionally, we conducted subgroup and sensitivity analyses of adjusted risk ratios among observational studies. PPI use among the elderly was significantly associated with an increased risk of mortality (by 17–32%) compared to non-use in the follow-up period between more than 6 months and less than 4 years, while the association was not significant in a shorter follow-up of a less than 6 months (aRR, 1.02; 95% CI, 0.45–2.33) and ˃ 4-year follow-up (aRR, 1.06; 95% CI, 0.99–1.14) (Table 2). The mortality risk of PPI users among patients with cancer, cardiovascular diseases, kidney diseases, and institutionalization showed a similar trend. When investigating the risk of death by country, the association between PPIs

Table 2 Subgroup analysis of the association between proton pump inhibitors and the adjusted risk of mortality of observational studies

Observational studies	Cohort, *n*	PPI, *n*	Control, *n*	Random effects, risk ratio (95% CI)	Effect, *P*-value	I^2	Heterogeneity, *P*-value
Follow-up							
≤ 6 months	3	4367	15,174	1.02 (0.45–2.33)	0.960	87%	< 0.001
> 6 months– ≤ 1 year	12	53,429	86,745	1.19 (1.07–1.33)	0.001	94%	< 0.001
> 1 year– ≤ 2 years	3	17,358	28,761	1.32 (1.24–1.40)	< 0.001	0%	0.690
> 2 years– ≤ 3 years	4	33,332	23,911	1.28 (1.12–1.49)	< 0.001	77%	0.004
> 3 years– ≤ 4 years	3	346,715	1,533,230	1.17 (1.03–1.32)	0.020	93%	< 0.001
> 4 years	8	63,677	133,020	1.06 (0.99–1.14)	0.100	89%	< 0.001
Patients							
Cancers[a]	13	41,271	29,835	1.15 (1.03–1.27)	0.009	94%	< 0.001
Cardiovascular diseases	8	65,492	130,443	1.29 (1.01–1.64)	0.040	97%	< 0.001
Kidney diseases	4	20,518	27,584	1.20 (1.02–1.42)	0.030	88%	< 0.001
Institutionalization	7	1308	3643	1.08 (1.01–1.16)	0.020	64%	0.010
Hospitalization	2	269	392	1.36 (0.99–1.86)	0.060	0%	0.340
Countries							
USA/Canada	15	409,389	1,672,520	1.06 (0.99–1.12)	0.070	93%	< 0.001
Europe	17	109,963	146,758	1.27 (1.18–1.38)	< 0.001	95%	< 0.001
Australia	3	392	482	1.27 (0.85–1.89)	0.250	23%	0.280
Asia[a]	5	9556	10,715	1.28 (0.99–1.66)	0.060	78%	0.001
Study design							
Cohort[a]	39	512,398	1,800,932	1.14 (1.09–1.20)	< 0.001	93%	< 0.001
Case-control	2	15,510	28,309	1.31 (1.23–1.40)	< 0.001	0%	0.490
Median age							
≤ 75 years old[a]	20	89,642	171,648	1.17 (1.08–1.27)	< 0.001	93%	< 0.001
76—85 years old	13	72,129	115,548	1.09 (1.02–1.16)	0.007	88%	< 0.001
> 85 years old	4	328	794	1.38 (0.95–2.00)	0.090	71%	0.020
ROBINS-I							
Low[a]	8	15,845	36,801	1.13 (1.01–1.28)	0.040	82%	< 0.001
Moderate	22	455,643	1,715,161	1.17 (1.10–1.24)	< 0.001	92%	< 0.001
Serious/critical	5	12,043	6260	1.08 (1.02–1.15)	0.010	71%	0.007
CCI							
Include CCI as a covariate	16	71,285	102,594	1.22 (1.09–1.36)	< 0.001	95%	< 0.001
Did not include CCI as a covariate[a]	25	469,836	1,748,500	1.11 (1.06–1.16)	< 0.001	90%	< 0.001

CCI Charlson comorbidity index, *PPI* proton pump inhibitor, *RCT* randomized controlled trial, *ROBINS-I* Risk of Bias Assessment tool for Non-randomized Studies of Interventions, *USA* United States

[a]Baek et al. did not report the number of PPIs and nonusers of patients aged 65 years or older

and increased mortality was significant among studies conducted in Europe (aRR, 1.27; 95% CI, 1.18–1.38), while the association was towards significant among studies conducted in USA/Canada, Asia, and Australia. The significant association between PPI use and mortality appeared consistent among cohort studies (aRR, 1.14; 95% CI, 1.09–1.20) and case–control studies (aRR, 1.31; 95% CI, 1.23–1.40). According to the median age of participants in the included studies, the results of the association between PPI use and mortality remain similar to the base-case analysis results. The lower the risk of bias of the included cohort studies, the larger the RR (aRR, 1.13; 95% CI, 1.01–1.28 in low risk of bias vs aRR, 1.08; 95% CI, 1.02–1.15 in serious/critical risk of bias). The association of risk of death and PPI users among both studies included CCI as a covariate and studies that did not include CCI as a covariate remained significant.

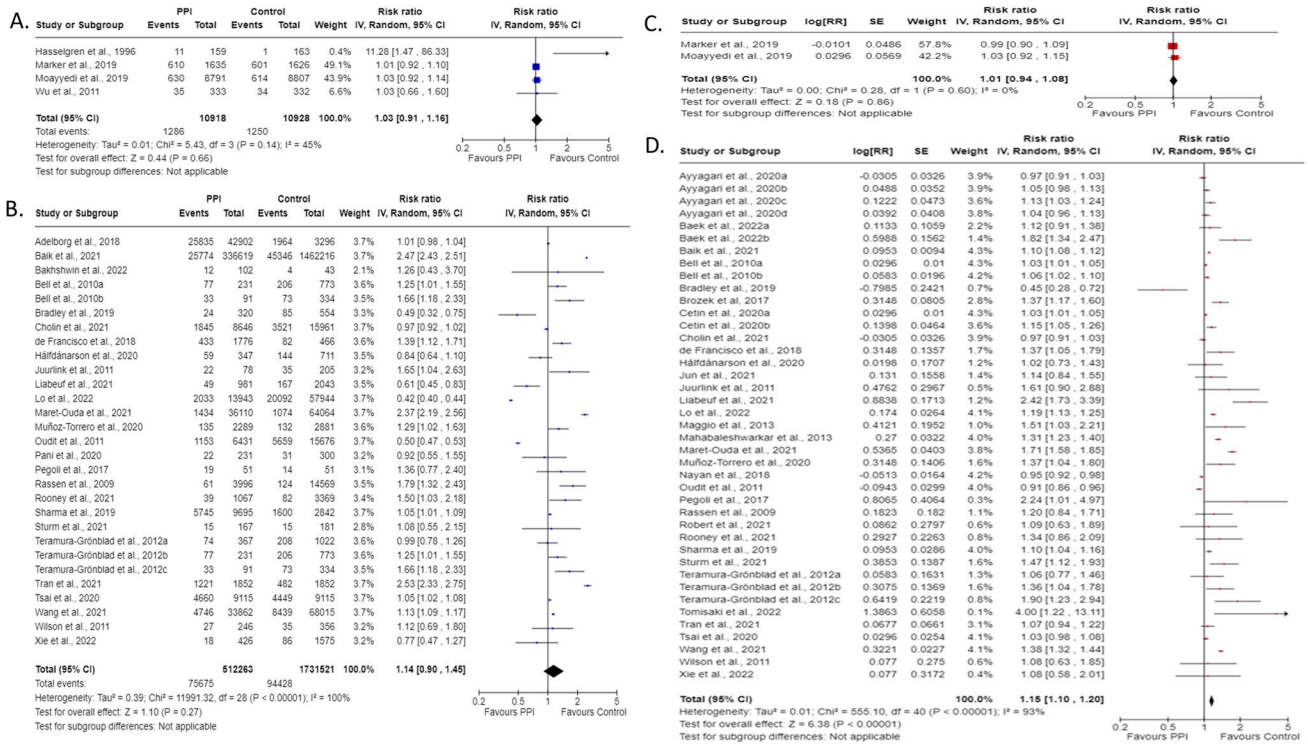

Fig. 2 The association between proton pump inhibitors and mortality. **A** Unadjusted risk ratio in randomized controlled trials. **B** Unadjusted risk ratio in observational studies. **C** Adjusted risk ratio in randomized controlled trials. **D** Adjusted risk ratio in observational studies

Discussion

This systematic review found a 15% increase in the risk of death among elderly people taking PPI compared to those not taking PPI. In particular, the association between PPI use and mortality was significant in studies among senior adults with cancer, cardiovascular diseases, and kidney diseases as well as studies with longer follow-ups and cohort studies.

Our results are aligned with those of previous studies that included not only adults but also elderly [9, 58]. A previous study using administrative data from Veterans Affairs demonstrated an excess risk of death among adults taking PPIs with a mean age of 61 years [9]. A systematic review also showed that all-cause mortality increased in adults treated with PPI, especially older adults treated with long-term PPI, compared to patients not treated with PPI [58]. Although a

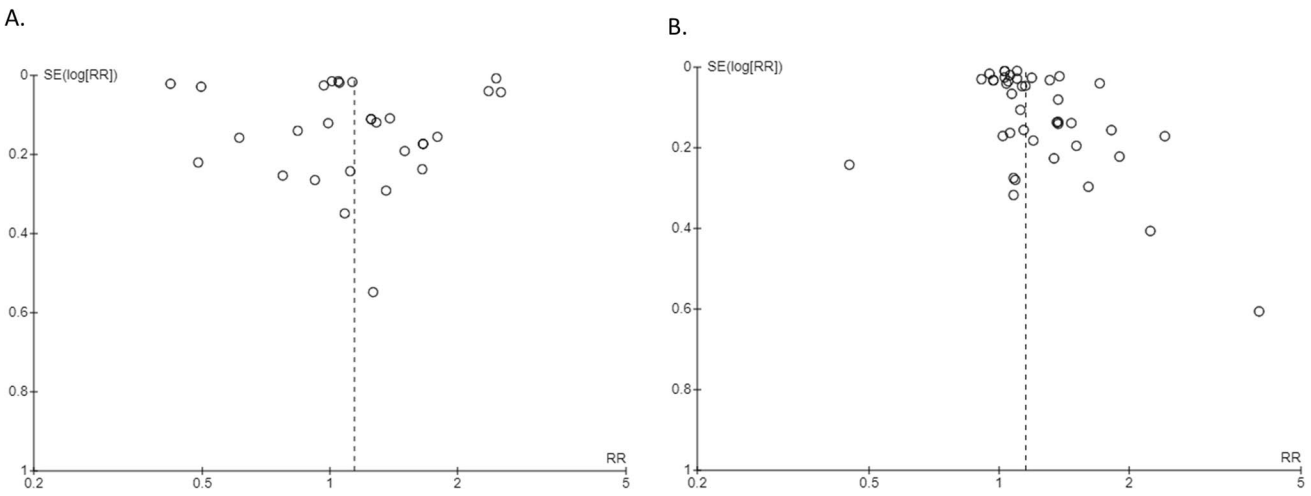

Fig. 3 Funnel plot of observational studies. **A** Unadjusted risk ratio. **B** Adjusted risk ratio

clear mechanism is not known for the association between PPIs and the risk of death, a potential biological mechanism was suggested. Prolonged exposure to PPI impairs endothelial function, increases oxidative stress, slows lysosomal acidification and protein accumulation in endothelial cells, and accelerates human endothelial aging by shortening telomere length [59]. PPIs also upregulate the expression of protein levels and mRNA resulting in increased activity of the heme oxygenase-1 enzyme in gastric and endothelial cells, which reduces beneficial effects, including antiapoptotic, anti-inflammatory, antioxidant, antiproliferative, and immunomodulatory effects in vascular cells [9, 60, 61]. Elderly patients may be more vulnerable to side effects during long-term PPI use on account of their comorbidities, use of multiple drugs, and poor nutrition [36]. PPIs have also been significantly overused in the elderly, contrary to the recommendation to restrict the PPI treatment period to fewer than 12 weeks [58].

Our subgroup and sensitivity analyses demonstrated that PPI use significantly affected the increased death among older patients with cancer, cardiovascular disease, and kidney disease. These results are similar to those of previous studies that were not limited to the elderly, which correlated PPI usage with excess mortality from cardiovascular disease, chronic kidney disease, and upper gastrointestinal and lung cancers [10, 62, 63] and also suggested an association between PPI usage and increased risk of the aforementioned diseases [62, 64]. The authors suggested a mechanism leading to the excess cause-specific mortality related to PPI use is linked to the exacerbation of underlying disease or the development of a new disease that increases the risk of cause-specific death. This mechanism was also suggested as a unifying mechanism [59]. In addition, inappropriate prescription of high-dose PPI during or after hospitalization is frequent as antithrombotic agents are widely used in elderly patients [36].

Notably, in cohort studies and studies with long-term follow-up (more than 1 year to 3 years), 28–32% of increased risk of death was clearly observed. However, this was not observed when the follow-up period was shortened (less than 6 months). A previous review also showed that there was no immediate apparent increase in all-cause mortality in adults taking PPIs in one RCT, while increased mortality with PPI use was observed in the observational studies followed up to 1 year [58]. Although RCTs have a higher hierarchy of an evidence-based approach than observational studies because of randomization, the findings from observational studies can show the results with all confounders, including unidentified confounders in the real-world population [58]. Our systematic review showed that significant results were obtained in terms of real-world evidence rather than in RCT settings, suggesting that real-world evidence should be considered when applied to clinical settings for patient care, such as pharmacovigilance criteria.

Our systematic review has strengths that, to our best knowledge, this is the first meta-analysis study to explore the association between PPI use and mortality in the older adult population with a large sample size. The significance of the pooled estimates was higher in high-quality studies with a low overall risk of bias. Our diverse subgroup results categorized by the follow-up period, disease, study design, country, and risk of bias provide comprehensive and detailed information. Notably, our results clearly showed that PPI use was significantly associated with increased death in older patients with cancer, cardiovascular disease, and kidney disease. In addition, we provide real-world evidence based on results from cohort studies and long-term follow-up studies.

Our study has several limitations. Primarily, we were not able to investigate the impact of mortality by the duration or dosage of PPI use due to a lack of data. However, our best available evidence supports the association the PPIs and mortality in elderly people. Secondly, the level of heterogeneity was low in RCTs, and it may be caused by study design or the small number of included studies. However, the pooled estimates in observational studies have significant heterogeneity although we conducted several subgroup analyses to find the cause. It may be caused by various populations, different levels of controlling covariates, and unknown factors. Despite the diversity of included studies, results were consistent across subgroups. Thirdly, half of the cohort studies in the meta-analysis showed a moderate risk of bias in the classification of intervention due to self-administrated OTC without prescriptions in most countries. However, the significant association between PPI use and mortality remained consistent in studies with low, moderate, and serious/critical risk of bias. Furthermore, the relative estimates can be considered conservative as individuals who may take OTCs may be included as both PPI users and nonusers. Finally, we cannot identify the causal relationship between PPI use and the risk of mortality since most of the included studies investigated the association between PPI use and the risk of mortality. Also, there was no clear association between PPIs and death from the four RCTs in the meta-analysis.

Conclusions

Our meta-analysis showed that the association between PPIs and the risk of mortality of RCTs was inconsistent with the association from observational studies in the elderly. The meta-analysis of RCTs showed that PPI use was not powered to detect an increased risk of death compared to nonusers. However, the increased risk of death was identified in observational studies and studies with long-term follow-ups, and

the association was consistent in the subgroup population, including among patients with cancer, cardiovascular disease, and kidney disease. Our findings highlight the need to increase awareness of increased mortality due to PPI use and to restrict PPI prescriptions to elderly people, wherein the benefits outweigh the potential risks.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-023-03606-0.

Author contribution HJS was involved in study concept and design, literature search, data extraction, data analysis, data interpretation, and manuscript writing. HJS was involved in data interpretation and manuscript writing. XJ was involved in literature search, data extraction, and data interpretation. NJ, YJL, and IHH were involved in literature search and data interpretation. All authors reviewed and approved the final version.

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Data availability The datasets generated during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interest The authors declare no competing interests.

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