Proton Pump Inhibitors Use and Risks of Cardiovascular Disease and Mortality in Patients with Type 2 Diabetes: A Prospective Study in the UK Biobank

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Abstract

Background: Proton pump inhibitors (PPIs) are widely used drugs for gastric-acid-related diseases, which may have an impact on the gut microbiome. We aimed to evaluate the associations of PPIs use with risks of cardiovascular disease (CVD) and all-cause mortality in patients with type 2 diabetes (T2D).

Methods: We analysed the associations of PPIs use with risks of coronary artery disease (CAD), myocardial infarction (MI), heart failure (HF), stroke, and all-cause mortality in 19,229 adults with T2D using data from the UK Biobank study.

Results: During a median follow-up of 10.9-11.2 years, we documented a total of 2,971 CAD, 1,827 MI, 1,192 HF, and 738 stroke cases, along with 2,297 total deaths. PPIs use was significantly 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 significant association was observed between PPIs use and stroke (HR, 1.11; 95% CI, 0.90-1.36). The results were consistent in the subgroup analyses stratified by factors including indications of PPIs, anti-diabetic medication use, and antiplatelet drug use. Analyses in a 1:1 propensity score-matched cohort of PPIs users versus non-users yielded consistent results.

Conclusion: Our data suggested that PPIs use was associated with higher risks of CVD events and mortality among patients with T2D. Prescription of PPIs among patients with T2D should be cautious, and monitoring of adverse cardiovascular events during PPIs therapy should be enhanced.

Background

Proton pump inhibitors (PPIs) are widely used drugs, either as prescription or over-the counter, for the full spectrum of gastric-acid-related diseases, such as gastro-oesophageal reflux disease (GERD), dyspepsia, and peptic ulcer disease [1, 2]. Along with the widespread use, a series of adverse health outcomes were reported following the use of PPIs, including fracture [3, 4], kidney outcomes (acute kidney injury and chronic kidney disease) [5–8], enteric infections (most notably Clostridium difficile) [9], type 2 diabetes (T2D) [10], and mortality [11].

In the past decade, a number of observational studies showed that PPIs use was associated with an increased risk of re-hospitalized cardiovascular disease (CVD) events and mortality among patients with a prior of CVD due to the drug-drug interactions between PPIs and clopidogrel via the competition for the same pathway (cytochrome P450) [12–17]. However, several studies suggested that the unfavourable effect of PPIs on cardiovascular health was independent of antiplatelet agents [13, 17]. Thereafter, evidence has linked PPIs with risk of adverse CVD outcomes in general populations [18–21]. One of the possible explanations underlying the link between PPIs and CVD risk might be the gut microbiota dysbiosis. Increasing evidence has suggested that PPIs use could influence gut microbiome composition and function [22–24], which may in turn, promote adverse cardiovascular phenotypes [25, 26]. In fact, the gut microbial alterations were even more prominent in PPIs users than antibiotic users [22].

Patients with T2D are at more than three times higher prevalence of using PPIs [27], and two- to fourfold higher risk of developing cardiovascular complications and premature death than general populations [28]; however, the evidence regarding the influence of PPIs use on subsequent risks of CVD and mortality among patients with T2D is scarce. To our best knowledge, only one prospective study from Australia showed PPI initiation was associated with a higher risk of 5-year CVD risk among patients with T2D [29]. However, the previous study had a sample size of 1732, a mean follow-up period of 2.1 years, and only a composite CVD outcome; further studies with larger sample size, longer follow-up period, and a closer investigation of CVD subtypes are needed.

To address the research gaps, we examined the association of PPIs use with risks of coronary artery disease (CAD), myocadiac infarction (MI), heart failure (HF), stroke and mortality among patients with T2D who participated in the UK Biobank study.

Methods

Study population

The UK Biobank is a large population-based prospective cohort study, which incorporated data from more than 500,000 participants (aged 37–73 years) across the U.K. between March 2006 and October 2010. The design of the UK Biobank study has been presented elsewhere [30, 31]. Data on socio-demographics, lifestyle, environmental factors, and medical history were collected via touch-screen questionnaires during interview at baseline visit. Standardized physical measurements (e.g. blood pressure and anthropometrics) and biological sample (blood, urine, and saliva) were taken among all the participants after interview.

A total of 19,229 participants with pre-existing T2D (mean age 59.5 ± 7.0, 59.5% men) were included in the current analysis after excluding patients who had pre-existing CAD, MI, HF, and stroke (ischemic and haemorrhagic). The flowchart for the selection of the study population is presented in **Supplementary Fig. 1**. The prevalent cases of T2D were identified through using the algorithms method [32] or via electronic health records using the ICD-10 codes (E11).

This study was conducted under the UK Biobank Application Number 68307. The UK Biobank study was approved by the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland and the North West Multicentre Research Ethics Committee. All participants gave written informed consent.

Assessment of PPIs use

Information on PPIs use was assessed by asking “Do you regularly take any of the following? (You can select more than one answer)” with the answers including “omeprazole” and “ranitidine”. Regular use is defined as most days of the week for the last four weeks. In addition, participants were asked to provide the medications they were taking later in the visit. Medications that contain lansoprazole, omeprazole,

pantoprazole, esomeprazole, and rabeprazole sodium were counted as PPIs and that contain cimetidine, famotidine, nizatidine, and ranitidine were counted as H2 receptor antagonists.

Assessment of the outcomes

The primary outcomes of the study were the occurrence of CAD, MI, HF and stroke. The secondary outcomes were all-cause mortality. The electronic health records were available up to 30th Sep 2020, 31st Aug 2020, and 28th Feb 2018 for centres in England, Wales and Scotland, respectively. Mortality data were available up to March 31st 2020 for all participants. Patients were censored at occurrence of first endpoint, death, loss to follow-up, or end of follow-up, whichever occurred first.

Assessment of the covariates

Data on age, sex, ethnicity, education levels, smoking history and sleep hours per day were collected through interview at baseline. Townsend deprivation index (TDI) is a composite measure of socio-economic deprivation [33]. Body mass index (BMI, kg/m^2) was calculated by body weight in kilogram divided by square of height in meter using data that were examined during a nurse-led interview. Information on habitual diet and alcohol intake was captured by a touchscreen food frequency questionnaire. We generated a healthy diet score to reflect the overall diet based on five components including vegetables, fruits, whole grains, low-fat dairy, and red/processed meat intake. Participants in the highest quintiles of favourable foods (vegetables, fruits, whole grains, and low-fat dairy) intake received 5 points and those in the lowest quintile of red/processed meat were given 5 points. The overall diet score then was categorized into quintiles. Physical activity was assessed using a short form international physical activity questionnaire, and physically active was defined as ≥ 150 min/week moderate or ≥ 75 min/week vigorous or 150 min/week moderate/vigorous activities [34].

Prevalent hypertension cases were defined by self-report, use of anti-hypertensive medications, essential hypertension cases via linking the electronic health records, or a seated blood pressure ≥ 140/90 mm Hg. Pre-existing cancer was self-report. Comorbidities including GERD, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrointestinal ulcer were identified through self-report and electronic health records. Medication history (e.g. aspirin, clopidogrel, vitamin supplements, and anti-hypertensive, cholesterol-lowering, and anti-diabetic drugs) was self-report. Participants were also asked to provide the medicines in the following visits, if they were not certain about the types of the medications taken. Serum concentrations of glycated hemoglobinA1c (HbA1c) were measured by HPLC analysis on a Bio-Rad VARIANT II Turbo.

Statistical analysis

The differences in baseline characteristics by PPIs users and non-users were examined using Student's t-test for continuous variables and chi-squared test for categorical variables. Missing values for covariates were imputed using sex-specific mean values for continuous variables and missing indicator approach for categorical variables. We used multivariable-adjusted Cox proportional hazards regression models to

compute the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of PPIs use with risks of outcomes of interest.

Three models were fitted. In Model 1, we adjusted for age at recruitment (years) and sex (men, women). In Model 2, we further adjusted for education (college or university degree, other professional qualifications, A/AS levels or equivalent or O levels/General Certificate of Secondary Education [GCSE] or equivalent, none of the above), socio-economic status (TDI, continuous), ethnicity (White, others), BMI (kg/m^2, continuous), alcohol intake (never or special occasions, monthly to weekly, daily), smoking status (never, past, current), healthy diet score (in quintiles), sleep duration (≤ 6, 7–8, ≥ 9 hours/day), physical activity status (yes, no), family history of CVD (yes, no), prevalent hypertension (yes, no), prevalent cancer (yes, no), duration of diabetes (years continuous), HbA1c (mmol/mol, continuous), anti-diabetic medications (none, oral drugs, insulin and others), anti-hypertensive medications (yes, no), cholesterol-lowering medications (yes, no), aspirins use (yes, no), and clopidogrel use (yes, no). In Model 3, indications for PPIs use (GERD, gastric ulcer, duodenal ulcer, peptic ulcer, or gastrointestinal ulcer) were additionally adjusted.

We also stratified the analyses by age (≤ 65, > 65 years), sex (men, women), duration of diabetes (≤ 5, > 5 years), smoking status (never, ever), family history of CVD (yes, no), medications for diabetes (none, oral drugs, insulin and others), antiplatelet drugs (aspirins/clopidogrel; yes, no), and indications of PPIs (yes, no). The multiplicative interactions between PPIs use and the stratified factors on the risk of outcomes were tested using the likelihood ratio test by including an interaction term in Model 3. In addition, we assessed the associations between different type of PPIs (omeprazole, lansoprazole, esomeprazole, and other PPIs) and risks of outcomes to clarify whether the observed associations were agent-specific or class-specific.

To explore the robustness of our primary findings, we performed a number of sensitivity analyses. First, to minimize the residual confounding, we assessed the associations in a propensity score-matched cohort of PPIs users (n = 3275) and non-users (n = 3275). Propensity scores were calculated using a logistic regression model including age, sex, TDI, education, ethnicity, BMI, smoking, drinking, physical activity, sleep duration, healthy diet score, family history of CVD, history of hypertension, history of cancer, HbA1c, duration of T2D, aspirins use, clopidogrel use, medications for hypertension, cholesterol and diabetes as covariates. The PPI users and non-users were 1:1 matched using nearest neighbour method without replacement (caliper = 0.1). Second, we performed a two-year lag year analysis to minimize the possibility of reverse causality on the observed associations. Third, we repeated the main analyses using multiple imputation method for covariates by chained equations with 5 imputations. Fourth, to further account for the potential confounding effect of indications of PPIs, we additionally adjusted for use of H2 receptor antagonists in Model 3. Fifth, we investigated the associations of PPIs use with risks of ischemic and haemorrhagic stroke. Further, to increase the statistical power, we combined stroke and transient ischemic attack (TIA) as a composite outcome, and tested the association between PPIs use and risk of stroke/TIA.

All analyses were performed using Stata statistical software, release 15.1 (StataCorp LP, College Station, Texas), and a two-sided $p < 0.05$ was set as the threshold for statistical significance.

Results

Baseline characteristics

Distributions of the baseline characteristics in PPIs users and non-PPIs users among T2D patients are shown in Table 1. Compared with the non-PPIs users, PPIs users were older, and more likely to be women, White, lower educated, non-current smokers, non-daily drinkers, physically inactive, use clopidogrel, anti-hypertensive medications, cholesterol-lowering medications and insulin. They also tended to have a higher level of BMI, longer duration of T2D, extreme sleep durations (≤ 6 or ≥ 9 hours/day), higher prevalence of family history of CVD, hypertension, cancer, indications for PPIs use.

Table 1
Baseline characteristics by PPIs use among patients with T2D in the UK Biobank study

Characteristics	Non-PPIs users	PPIs users	*P* value
	15,954	3,275	
Age, years	59.3 (7.1)	60.3 (6.8)	< 0.001
Men	9764 (61.2)	1671 (51.0)	< 0.001
White	13,555 (85.0)	2,922 (89.2)	< 0.001
College or higher education	1655 (10.4)	266 (8.1)	< 0.001
BMI, kg/m^2	31.3 (5.9)	32.3 (5.9)	< 0.001
TDI	-0.53 (3.38)	-0.17 (3.44)	< 0.001
Duration of T2D, years	7.1 (8.6)	7.5 (8.5)	0.03
HbA1c, mmol/mol	52.1 (13.2)	52.0 (13.0)	0.75
Physically active	7177 (45.0)	1259 (38.4)	< 0.001
Daily drinkers	2329 (14.6)	418 (12.8)	< 0.001
Current smokers	1702 (10.7)	339 (10.4)	< 0.001
Healthy diet score (Quintile 5)	2422 (15.2)	462 (14.1)	0.007
Sleep 7–8 hours/day	9596 (60.2)	1741 (53.2)	< 0.001
Hypertension	13,727 (86.0)	2950 (90.1)	< 0.001
Cancer	1290 (8.1)	399 (12.2)	< 0.001
Indications of PPIs*	866 (5.4)	1466 (44.8)	< 0.001
Family history of CVD	9310 (58.4)	2076 (63.4)	< 0.001
Medications for hypertension	10,941 (68.6)	2485 (75.9)	< 0.001
Medications for cholesterol-lowing	11,783 (73.9)	2594 (79.2)	< 0.001
Aspirin use	7143 (44.8)	1407 (43.0)	0.06
Clopidogrel use	82 (0.5)	63 (1.9)	< 0.001
Medications for diabetes			< 0.001
Non-users	5005 (31.4)	1001 (30.6)	

Data are presented as mean (SD) or N (%).

* Indications for PPIs use included gastro-oesophageal reflux disease, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrojejunal ulcer

Characteristics	Non-PPIs users	PPIs users	*P* value
Oral drugs	8478 (53.1)	1654 (50.5)	
Insulin users	2471 (15.5)	620 (18.9)	
Data are presented as mean (SD) or N (%).			
* Indications for PPIs use included gastro-oesophageal reflux disease, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrojejunal ulcer			

Associations of PPIs use with cardiovascular outcomes

The median (interquartile rage [IQR]) follow-up time for CAD, MI, HF, stroke and mortality was 11.1 (IQR: 10.2–12.0), 11.1 (IQR: 10.3–12.0), 11.2 (IQR: 10.4–12.1), 11.2 (10.4–12.1), and 10.9 (IQR: 10.1–11.7) years, respectively. During the follow-up period, we documented a total of 2971 CAD, 1827 MI, 1192 HF, and 738 stroke cases, along with 2297 total deaths. Crude incidence rates of CAD, MI, HF, and stroke were 14.1, 8.3, 5.2, and 3.5 per 1,000 person-years in non-PPIs users and 20.5, 12.8, 8.4, and 4.0 per 1,000 person-years in PPIs users, respectively. PPIs use was significantly associated with higher risks of CAD, MI and HF in Model 1 that adjusted for age and sex. After additional adjustment for lifestyle and medical history in Model 2, and indications of PPIs in Model 3, the risk estimates were gradually attenuated but remained significant. In the fully adjusted Model 3, compared with non-PPIs users, the HRs (95% CIs) of CAD, MI and HF for PPIs users were 1.27 (1.15–1.40), 1.34 (1.18–1.52), and 1.35 (1.16–1.57), respectively (Table 2). However, there was no significant difference in stroke risk (HR, 1.11; 95% CI 0.90–1.36) between PPIs users and non-PPIs users.

Table 2
Associations of PPIs use with risks of coronary artery disease, myocardial infarction, heart failure, stroke, and all-cause mortality among patients with type 2 diabetes

	Incidence rate /1000 person-year		HR (95% CI)		
		Cases/person-year	Model 1	Model 2	Model 3
Coronary artery disease					
Non-PPIs users	14.1 (13.5–14.7)	2314/164,379	1	1	1
PPIs users	20.5 (19.0-22.2)	657/32,012	1.48 (1.35–1.61)	1.34 (1.23–1.46)	1.27 (1.15–1.40)
Myocardial infarction					
Non-PPIs users	8.3 (7.9–8.8)	1402/168,478	1	1	1
PPIs users	12.8 (11.6–14.1)	425/33,182	1.57 (1.40–1.75)	1.43 (1.28–1.59)	1.34 (1.18–1.52)
Heart failure					
Non-PPIs users	5.2 (4.9–5.6)	902/172,132	1	1	1
PPIs users	8.4 (7.5–9.4)	290/34,444	1.58 (1.38–1.81)	1.38 (1.20–1.58)	1.35 (1.16–1.57)
Stroke					
Non-PPIs users	3.5 (3.2–3.7)	598/172,876	1	1	1
PPIs users	4.0 (3.4–4.8)	140/34,679	1.15 (0.95–1.38)	1.05 (0.87–1.27)	1.11 (0.90–1.36)
All-cause mortality					
Non-PPIs users	10.5 (10.1–11.0)	1787/169,657	1	1	1
PPIs users	14.9 (13.7–16.3)	510/34,181	1.41 (1.28–1.56)	1.24 (1.12–1.37)	1.30 (1.16–1.45)

Association of PPIs use with all-cause mortality

Crude mortality rates were 10.5 and 14.9 per 1000 person-years in non PPIs users and PPIs users, respectively. Significant association was observed between PPIs use and risk of all-cause mortality. Compared with non-PPIs users, the HR (95% CIs) of all-cause mortality for PPIs users was 1.30 (1.16–1.45) in Model 3 (Table 2).

Secondary analyses and sensitivity analyses

We did not find significant heterogeneity in the risk estimates of the stratified factors including age, sex, smoking, family history of CVD, duration of diabetes, medications for diabetes, aspirins/clopidogrel use, and indications of PPIs with PPIs use on the risk of outcomes considering multiple comparisons (Fig. 1 **& Supplementary Fig. 2**). When analyzing different PPI agents, we found consistent associations of different agents and risks of CAD, MI, HF and all-cause mortality, despite that some insignificant associations, which were possible due to relatively smaller numbers of cases (Fig. 2).

Our results were robust in a number of sensitivity analyses. The propensity-score matched analysis identified 3275 PPIs users and 3275 non-users, with the standardized differences for matching variables all < 0.1 (**Supplementary Table 1**). In this analysis, compared with the non-use group, the HRs (95% CIs) of CAD, MI, HF, stroke, and mortality for PPIs users were 1.23 (1.08–1.40), 1.30 (1.10–1.53), 1.38 (1.13–1.69), 1.08 (0.82–1.41), and 1.43 (1.24–1.66), respectively (**Supplementary Table 2**). Further, the results were consistent when we excluded participants with less than two years of follow-up (**Supplementary Table 3**), used the multiple imputation method to impute the missing values of the covariates (**Supplementary Table 4**), or further adjusted for use of H2 receptor antagonists (**Supplementary Table 5**). Additionally, PPIs use was not significantly associated with risks of ischemic or haemorrhagic stroke, or the composite outcome of stroke/TIA (**Supplementary Table 6**).

Discussion

In this large prospective cohort study of patients with T2D, we found that PPIs use was associated with higher risks of CAD, MI, HF, and all-cause mortality. The associations persisted after adjustment for severity of diabetes, anti-diabetic medications use, antiplatelet agents use, and indications for PPIs use. In addition, our results were robust across multiple sensitivity analyses, including the propensity-score matched analysis, and further adjustment for H2 receptor antagonists use.

Concerns about the PPIs use related adverse CVD outcomes and pre-mature death among patients treated with antiplatelet agents for secondary preventions have been raised in the past decade due to the drug-drug interaction [12–17]. Some studies found that the observed associations between PPIs use and risk of CVD was independent of antiplatelet agents use [13, 17]. Since then, the association between PPIs use and higher risk of CVD were also demonstrated in general populations [18–21]. Retrospective nationwide studies using data from the Taiwan National Health Insurance showed that PPIs use was associated with a higher risk of ischemic stroke and MI in general populations [18, 21]. A Danish national cohort study using pharmacy records also observed PPIs use was associated with a higher risk of ischemic stroke and MI, and the observed association was more prominent with high-dose PPIs use [20].

However, the findings from the randomized controlled trials (RCTs) were highly disparate [35–37]; more studies were required in this field.

In addition, the relationship between PPIs use and risk of cardiovascular events among patient with T2D has been under-investigated. In the abovementioned Taiwan National Health Insurance studies, the stratified analysis by pre-existing diabetes observed a null association between PPIs use and risk of ischemic stroke and MI in patients with pre-existing diabetes [18, 21], whereas the Nurses' Health Study and the Health Professionals Follow-up Study showed that PPIs use was associated with a higher risk of ischemic stroke in patients with diabetes (HR, 1.57; 95% CI, 1.07–2.29), despite a null association observed in the whole cohort [38]. Nevertheless, those studies did not take into account the severity of diabetes, such as HbA1c, duration of diabetes, and oral drugs/insulin use. To our best knowledge, there is only one prospective study that investigated the association of PPIs use and CVD risk among 1732 patients with T2D with an average of 2.1 years of follow-up [29]. In line with the previous study, our study also showed PPIs use was associated with higher risk of CVD, as well as all-cause mortality. However, our study had larger sample size, and longer follow-up and took a closer investigation of associations of PPIs class and different agents with a wide range of CVD subtypes and mortality.

In addition, potential confounding by indications of PPIs use and clinical conditions has been the biggest concern on the observed association between PPIs use and adverse outcomes. In the current analysis, our results were robust with additional adjustments for indications of PPIs use (GERD, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrointestinal ulcer), and severity of diabetes. In addition, our results were robust in the propensity-score matched analysis, which also minimized the differences between users and non-users. Furthermore, the sensitivity analysis with additional adjustment for the use of H2 receptor antagonists, which had similar indications as PPIs use but with mild symptoms, may further account for the indications issue.

There are several potential mechanisms underpinning the observed associations. First, increasing evidence has linked PPIs with alterations of gut microbiota composition, characterized as an increase in oral bacteria and a decrease in microbial diversity in PPIs users via the increased gastric pH [22, 23, 39]. The gut microflora dysbiosis and changes of the gut microbiota derived metabolites after PPIs use could thereby increase the CVD risk through promoting inflammation, regulating the sizes and composition of lipoprotein subclasses, and changing the metabolism of macro and micronutrients [26, 40]. Further, evidence showed similar effects of different agents of PPIs on the gut microbiome [41], which was consistent with our secondary analysis that different agents of PPIs were generally associated with higher risks of CVD events and all-cause mortality among patients with T2D. In addition, PPIs may increase the CVD events through the interactions of PPIs and antiplatelet agents. PPIs and clopidogrel shared the metabolic pathway, namely cytochrome P450 (*CYP2C19*); therefore, the antiplatelet effect might be influenced by PPIs use [42, 43]. Nevertheless, more studies are warranted to clarify the underlying mechanism.

Strengths and limitations

To our best knowledge, this is among the first studies to investigate the associations of PPIs use with risk of subsequent CVD events and mortality among patients with T2D. Importantly, to address the potential confounding issue with the indications of PPIs use and clinical conditions, we leveraged a well-characterized cohort via rigorously accounting for an extensive set of potential confounders including socio-demographics, lifestyle factors, medical history, medications history, severity of diabetes and indications of PPIs. Additional strengths included its prospective study design, large sample size, carefully defined phenotypes, and relatively longer follow-up. Moreover, results from a series of sensitivity analyses were consistent with the primary analyses.

However, the results of this study need to be interpreted in the context of some potential limitations. First, information on PPIs use was assessed once at baseline, and subsequent changes in PPIs use during follow-up were not captured. Second, we were unable to assess the associations of the duration and dosage of PPIs use with adverse outcomes due to lack of the information. Third, as relatively moderate numbers of stroke cases were identified in our study, future studies with larger sample size and more cases are needed to validate the nonsignificant association between PPIs use and stroke risk. Finally, due to the observational nature of the study, residual confounding cannot be completely ruled out although we have carefully adjusted for potential confounders.

Conclusions

Our data suggested that PPIs use were associated with a higher risk of cardiovascular events and all-cause mortality among patients with T2D. Enhanced monitoring of potential cardiovascular events should be implemented among patients with T2D during the PPIs therapy period. Further studies are needed to clarify the safety of PPIs use regarding on duration and dosage among patients with T2D to prevent CVD events and premature death.

Declarations

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Author Contributions

TG designed the research; TG and JC analysed the data; TG, GL and AP interpreted the results; TG wrote the paper with critical input from all authors. All authors approved the manuscript. GL and AP has primary responsibility for final content.

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Availability of data and materials

The UK Biobank data are available on application to the UK Biobank (www.ukbiobank.ac.uk/).

Ethnics approval and consent to participants

The UK Biobank study was approved by the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland and the North West Multicentre Research Ethics Committee. All participants gave written informed consent. This study was conducted under the UK Biobank Application Number 68307.

Consent for publication

Not applicable.

Competing interests

All authors declare no support from companies for the submitted work; no relationships with companies that might have an interest in the submitted work in the previous 3 years; no spouses, partners, or children that have financial relationships that may be relevant to the submitted work; and nonnon-financial interests that may be relevant to the submitted work.

References

1. Targownik LE, Metge C, Roos L, Leung S: **The prevalence of and the clinical and demographic characteristics associated with high-intensity proton pump inhibitor use**. Am J Gastroenterol 2007, **102**(5):942–950.
2. Strand DS, Kim D, Peura DA: **25 Years of Proton Pump Inhibitors: A Comprehensive Review**. Gut Liver 2017, **11**(1):27–37.
3. Yang YX, Lewis JD, Epstein S, Metz DC: **Long-term proton pump inhibitor therapy and risk of hip fracture**. Jama 2006, **296**(24):2947–2953.
4. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K: **Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies**. Am J Gastroenterol 2011, **106**(7):1209–1218; quiz 1219.

5. Blank ML, Parkin L, Paul C, Herbison P: **A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use**. Kidney Int 2014, **86**(4):837–844.
6. Klatte DCF, Gasparini A, Xu H, de Deco P, Trevisan M, Johansson ALV, Wettermark B, Ärnlöv J, Janmaat CJ, Lindholm B *et al*: **Association Between Proton Pump Inhibitor Use and Risk of Progression of Chronic Kidney Disease**. Gastroenterology 2017, **153**(3):702–710.
7. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, Grams ME: **Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease**. JAMA Intern Med 2016, **176**(2):238–246.
8. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z: **Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD**. J Am Soc Nephrol 2016, **27**(10):3153–3163.
9. Aseeri M, Schroeder T, Kramer J, Zackula R: **Gastric acid suppression by proton pump inhibitors as a risk factor for clostridium difficile-associated diarrhea in hospitalized patients**. Am J Gastroenterol 2008, **103**(9):2308–2313.
10. Yuan J, He Q, Nguyen LH, Wong MCS, Huang J, Yu Y, Xia B, Tang Y, He Y, Zhang C: **Regular use of proton pump inhibitors and risk of type 2 diabetes: results from three prospective cohort studies**. Gut 2021, **70**(6):1070–1077.
11. Xie Y, Bowe B, Yan Y, Xian H, Li T, Al-Aly Z: **Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study**. Bmj 2019, **365**:l1580.
12. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS: **Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome**. JAMA 2009, **301**(9):937–944.
13. Charlot M, Ahlehoff O, Norgaard ML, Jørgensen CH, Sørensen R, Abildstrøm SZ, Hansen PR, Madsen JK, Køber L, Torp-Pedersen C *et al*: **Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study**. Ann Intern Med 2010, **153**(6):378–386.
14. Maggio M, Corsonello A, Ceda GP, Cattabiani C, Lauretani F, Buttò V, Ferrucci L, Bandinelli S, Abbatecola AM, Spazzafumo L *et al*: **Proton pump inhibitors and risk of 1-year mortality and rehospitalization in older patients discharged from acute care hospitals**. JAMA Intern Med 2013, **173**(7):518–523.
15. van Boxel OS, van Oijen MG, Hagenaars MP, Smout AJ, Siersema PD: **Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a large Dutch cohort study**. Am J Gastroenterol 2010, **105**(11):2430–2436; quiz 2437.
16. Kreutz RP, Stanek EJ, Aubert R, Yao J, Breall JA, Desta Z, Skaar TC, Teagarden JR, Frueh FW, Epstein RS *et al*: **Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel Medco outcomes study**. Pharmacotherapy 2010, **30**(8):787–796.
17. Valkhoff VE, t Jong GW, Van Soest EM, Kuipers EJ, Sturkenboom MC: **Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors**. Aliment Pharmacol

Ther 2011, **33**(1):77–88.

18. Wang YF, Chen YT, Luo JC, Chen TJ, Wu JC, Wang SJ: **Proton-Pump Inhibitor Use and the Risk of First-Time Ischemic Stroke in the General Population: A Nationwide Population-Based Study**. Am J Gastroenterol 2017, **112**(7):1084–1093.
19. Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, Nead KT, Cooke JP, Leeper NJ: **Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population**. PLoS One 2015, **10**(6):e0124653.
20. Sehested TSG, Gerds TA, Fosbøl EL, Hansen PW, Charlot MG, Carlson N, Hlatky MA, Torp-Pedersen C, Gislason GH: **Long-term use of proton pump inhibitors, dose-response relationship and associated risk of ischemic stroke and myocardial infarction**. J Intern Med 2018, **283**(3):268–281.
21. Shih CJ, Chen YT, Ou SM, Li SY, Chen TJ, Wang SJ: **Proton pump inhibitor use represents an independent risk factor for myocardial infarction**. Int J Cardiol 2014, **177**(1):292–297.
22. Imhann F, Bonder MJ, Vich Vila A, Fu J, Mujagic Z, Vork L, Tigchelaar EF, Jankipersadsing SA, Cenit MC, Harmsen HJ *et al*: **Proton pump inhibitors affect the gut microbiome**. Gut 2016, **65**(5):740–748.
23. Jackson MA, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC, Sutter JL, Welter D, Ley RE, Bell JT *et al*: **Proton pump inhibitors alter the composition of the gut microbiota**. Gut 2016, **65**(5):749–756.
24. Freedberg DE, Toussaint NC, Chen SP, Ratner AJ, Whittier S, Wang TC, Wang HH, Abrams JA: **Proton Pump Inhibitors Alter Specific Taxa in the Human Gastrointestinal Microbiome: A Crossover Trial**. Gastroenterology 2015, **149**(4):883–885.e889.
25. Kazemian N, Mahmoudi M, Halperin F, Wu JC, Pakpour S: **Gut microbiota and cardiovascular disease: opportunities and challenges**. Microbiome 2020, **8**(1):36.
26. Kurilshikov A, van den Munckhof ICL, Chen L, Bonder MJ, Schraa K, Rutten JHW, Riksen NP, de Graaf J, Oosting M, Sanna S *et al*: **Gut Microbial Associations to Plasma Metabolites Linked to Cardiovascular Phenotypes and Risk**. Circ Res 2019, **124**(12):1808–1820.
27. Westergaard N, Tarnow L, Vermehren C: **Use of Clopidogrel and Proton Pump Inhibitors Alone or in Combinations in Persons with Diabetes in Denmark; Potential for CYP2C19 Genotype-Guided Drug Therapy**. Metabolites 2021, **11**(2).
28. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW: **Global trends in diabetes complications: a review of current evidence**. Diabetologia 2019, **62**(1):3–16.
29. Davis TME, Drinkwater J, Davis WA: **Proton Pump Inhibitors, Nephropathy, and Cardiovascular Disease in Type 2 Diabetes: The Fremantle Diabetes Study**. J Clin Endocrinol Metab 2017, **102**(8):2985–2993.
30. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M *et al*: **UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age**. PLoS Med 2015, **12**(3):e1001779.
31. Caleyachetty R, Littlejohns T, Lacey B, Bešević J, Conroy M, Collins R, Allen N: **United Kingdom Biobank (UK Biobank): JACC Focus Seminar 6/8**. J Am Coll Cardiol 2021, **78**(1):56–65.

32. Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, de Lusignan S, Allen N, Chaturvedi N: **Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank**. PLoS One 2016, **11**(9):e0162388.
33. Townsend P PP, Beattie A,. **Health and deprivation**: **inequality and the North**. **Croom Helm**; 1988.
34. Said MA, Verweij N, van der Harst P: **Associations of Combined Genetic and Lifestyle Risks With Incident Cardiovascular Disease and Diabetes in the UK Biobank Study**. JAMA Cardiol 2018, **3**(8):693–702.
35. Sun S, Cui Z, Zhou M, Li R, Li H, Zhang S, Ba Y, Cheng G: **Proton pump inhibitor monotherapy and the risk of cardiovascular events in patients with gastro-esophageal reflux disease: a meta-analysis**. Neurogastroenterol Motil 2017, **29**(2).
36. Farhat N, Fortin Y, Haddad N, Birkett N, Mattison DR, Momoli F, Wu Wen S, Krewski D: **Systematic review and meta-analysis of adverse cardiovascular events associated with proton pump inhibitors used alone or in combination with antiplatelet agents**. Crit Rev Toxicol 2019, **49**(3):215–261.
37. Moayyedi P, Eikelboom JW, Bosch J, Connolly SJ, Dyal L, Shestakovska O, Leong D, Anand SS, Störk S, Branch KRH *et al*: **Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin**. Gastroenterology 2019, **157**(3):682–691.e682.
38. Nguyen LH, Lochhead P, Joshi AD, Cao Y, Ma W, Khalili H, Rimm EB, Rexrode KM, Chan AT: **No Significant Association Between Proton Pump Inhibitor Use and Risk of Stroke After Adjustment for Lifestyle Factors and Indication**. Gastroenterology 2018, **154**(5):1290–1297.e1291.
39. Macke L, Schulz C, Koletzko L, Malfertheiner P: **Systematic review: the effects of proton pump inhibitors on the microbiome of the digestive tract-evidence from next-generation sequencing studies**. Aliment Pharmacol Ther 2020, **51**(5):505–526.
40. Fu J, Bonder MJ, Cenit MC, Tigchelaar EF, Maatman A, Dekens JA, Brandsma E, Marczynska J, Imhann F, Weersma RK *et al*: **The Gut Microbiome Contributes to a Substantial Proportion of the Variation in Blood Lipids**. Circ Res 2015, **117**(9):817–824.
41. Vich Vila A, Collij V, Sanna S, Sinha T, Imhann F, Bourgonje AR, Mujagic Z, Jonkers D, Masclee AAM, Fu J *et al*: **Impact of commonly used drugs on the composition and metabolic function of the gut microbiota**. Nat Commun 2020, **11**(1):362.
42. Malfertheiner P, Kandulski A, Venerito M: **Proton-pump inhibitors: understanding the complications and risks**. Nat Rev Gastroenterol Hepatol 2017, **14**(12):697–710.
43. Gilard M, Arnaud B, Le Gal G, Abgrall JF, Boschat J: **Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin**. J Thromb Haemost 2006, **4**(11):2508–2509.

Figures

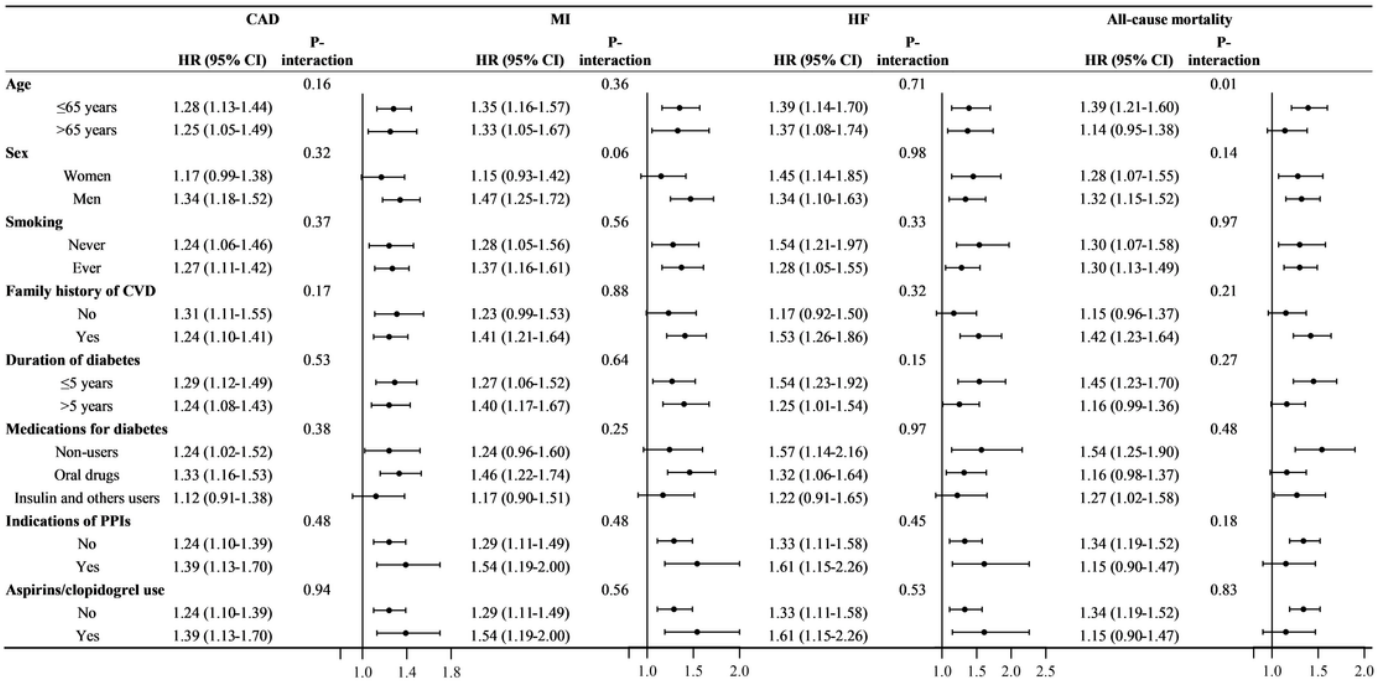

Figure 1

Subgroup analyses of PPIs use in relation to the risks of coronary artery disease (CAD), myocardial infarction (MI), heart failure (HF), and all-cause mortality among patients with type 2 diabetes

HRs were adjusted for age, sex, TDI, education, ethnicity, BMI, smoking, drinking, physical activity, sleep duration, healthy diet score, family history of CVD, history of hypertension, history of cancer, HbA1c, duration of T2D, aspirin use, clopidogrel use, medications for hypertension, cholesterol and diabetes, and indications of PPIs (gastro-oesophageal reflux disease, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrojejunal ulcer).

Figure 2

Associations of different types of PPIs with risks of coronary artery disease (CAD), myocardial infarction (MI), heart failure (HF), stroke, and all-cause mortality among patients with type 2 diabetes

HRs were adjusted for age, sex, TDI, education, ethnicity, BMI, smoking, drinking, physical activity, sleep duration, healthy diet score, family history of CVD, history of hypertension, history of cancer, HbA1c, duration of T2D, aspirin use, clopidogrel use, medications for hypertension, cholesterol and diabetes,

indications of PPIs (gastro-oesophageal reflux disease, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrojejunal ulcer), and also mutually adjusted for different types of PPIs.

A total of 246 participants were multiple types of PPIs users that were excluded from the analysis.

Supplementary Files

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