Proton Pump Inhibitor Use and Risks of Cardiovascular Disease and Mortality in Patients With Type 2 Diabetes

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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 gastroesophageal reflux disease (GERD), dyspepsia, and peptic ulcer disease .
Along with the widespread use, a series of adverse health outcomes were reported following the use of PPIs, including fracture , kidney outcomes (acute kidney injury and chronic kidney disease) , enteric infections (most notably Clostridium difficile) , type 2 diabetes (T2D) , and mortality In the past decade, a number of observational studies showed that PPI use was associated with an increased risk of rehospitalized cardiovascular disease (CVD) events and mortality among patients with prior CVD due to the drug-drug interactions between PPIs and clopidogrel via competition for the same pathway (cytochrome P450)

However, several studies suggested that the unfavorable effect of PPIs on cardiovascular health was independent of antiplatelet agents . Thereafter, evidence has linked PPIs with risk of adverse CVD outcomes in general populations . One of the possible explanations underlying the link between PPIs and CVD risk might be the gut microbiota dysbiosis. Increasing evidence has suggested that PPI use could influence gut microbiome composition and function , which may in turn promote adverse cardiovascular phenotypes. In fact, the gut microbial alterations were even more prominent in PPI users than antibiotic users .

Patients with T2D are at more than 3 times higher prevalence of using PPIs , and a 2- to 4-fold higher risk of developing cardiovascular complications and premature death than general populations .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. 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

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

Materials and Methods

The UK Biobank is a large population-based prospective cohort study that incorporated data from more than 500 000 participants (aged 37-73 years) across the United Kingdom between March 2006 and October 2010. The design of the UK Biobank study has been presented elsewhere. A total of 19 229 participants with preexisting T2D (mean age, 59.5±7.0; 59.5% men) were included in the present analysis after excluding patients who had preexisting CAD, MI, HF, and stroke (ischemic and hemorrhagic). The flowchart for the selection of the study population is presented in
Fig. 1. The prevalent cases of T2D were identified through using the algorithms method or via electronic health records using the International Classification of Diseases 10th Revision (ICD-10) codes (E11).

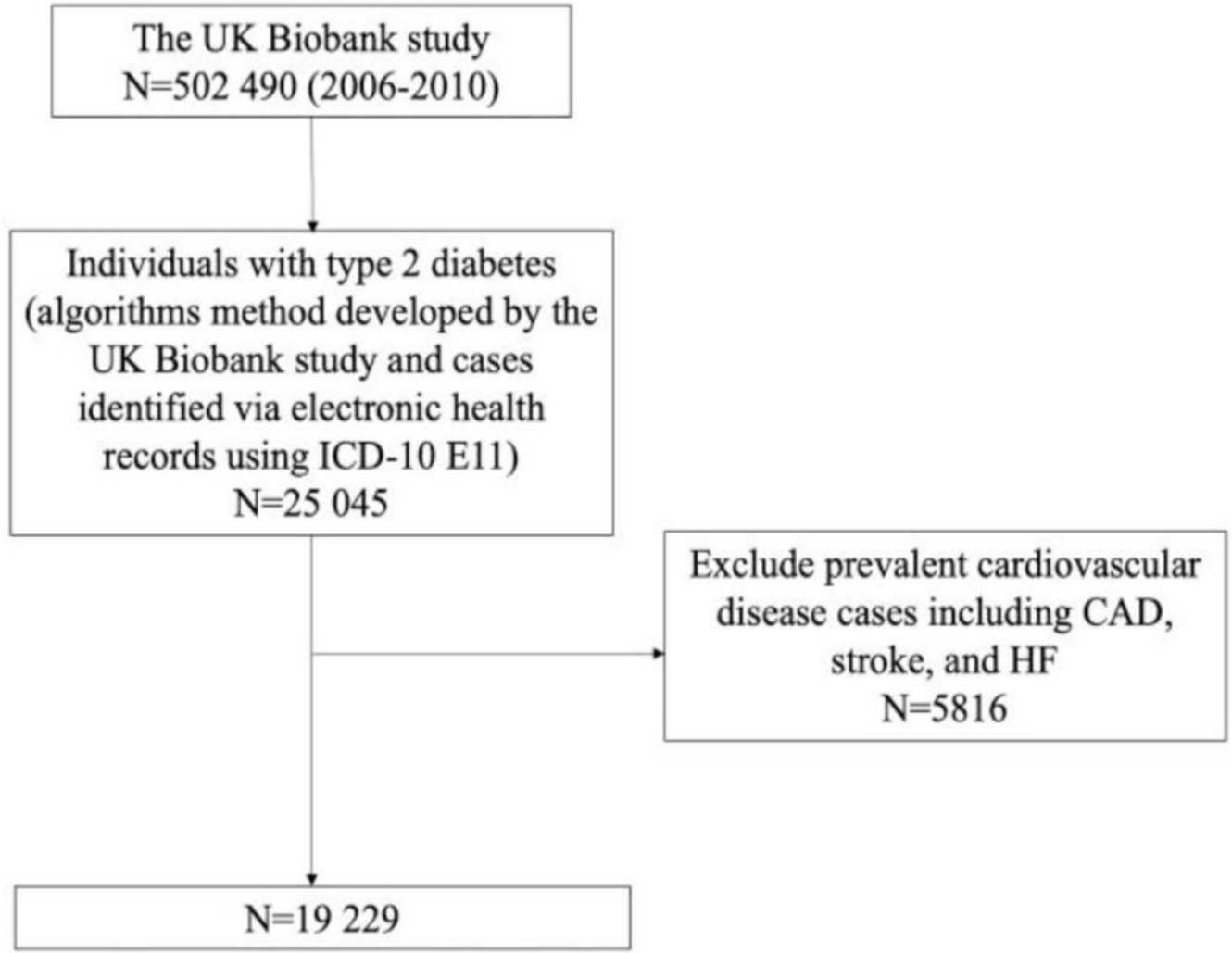

Figure 1. Flowchart for the selection of the study population from the UK Biobank study.

Information on PPI and H2 receptor antagonist 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” for the last 4 weeks . In addition, participants were asked to
provide the medications they were taking later in the visit.
Medications containing lansoprazole, omeprazole, pantoprazole, esomeprazole, and rabeprazole sodium were counted as PPIs and medications containing cimetidine, famotidine, nizatidine, and ranitidine were counted as H2 receptor antagonists.
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Ascertainment of the Outcomes

The primary outcomes of the study were the occurrence of CAD (ICD-10 I21-I25), MI (ICD-10 I20-23), HF (ICD-10 I50), and stroke (ICD-10 I60-I64). The secondary outcome was all-cause mortality. Cases were identified through multiple resources including self-reported data, primary care data, hospital admission records, and death register records. The electronic health records were available up to September 30, 2020; August 31, 2020; and February 28, 2018 for centers in England, Wales, and Scotland, respectively. Mortality data were available up to March 31, 2020 for all participants. Patients were censored at occurrence of the first end point, death, loss to follow-up, or end of follow-up, whichever occurred first .

Statistical Analysis

The differences in baseline characteristics by PPI users and nonusers were compared by standardized differences. We used multivariable-adjusted Cox proportional-hazard regression models to compute the hazard ratios (HRs) and 95% CIs for the associations of PPI use with risks of outcomes of interest. Three models were fitted. In model 1, we adjusted for age at recruitment (years, continuous) 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 or equivalent, none of the above), Townsend deprivation index (continuous), ethnicity (White, others), body mass index (BMI) (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), glycated hemoglobin A1c (HbA1c) (mmol/mol, continuous), antidiabetic medications (none, oral drugs, insulin, and others), antihypertensive medications (yes, no), cholesterol-lowering medications (yes, no), acetylsalicylic acid use (yes, no), and clopidogrel use (yes, no).

In model 3, indications of PPI (GERD, gastric ulcer, duodenal ulcer, peptic ulcer, or gastrointestinal ulcer) were additionally adjusted. We also stratified the analyses by age (≤ 50, 50-60, > 60 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 (acetylsalicylic acid/clopidogrel; yes, no), and indications of PPI (yes, no). The multiplicative interactions between PPI 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 types of PPI (omeprazole, lansoprazole, esomeprazole, and other PPIs) and risks of outcomes to clarify whether the observed associations were agent specific or class specific. we assessed the associations in a propensity score–matched cohort of PPI users (n=3275) and nonusers (n =3275).

Propensity scores were calculated using a logistic regression model including age, sex, Townsend deprivation index, 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, acetylsalicylic acid use, clopidogrel use, medications for hypertension, cholesterol, and diabetes as covariates. The PPI users and nonusers were 1:1 matched using the nearest neighbor method without replacement (caliper=0.1). Second, we performed a 2-year lag year analysis to minimize the possibility of reverse causality on the observed associations. Third, we repeated the main analyses using the multiple imputation method for covariates by chained equations with 5 imputations. Fourth, to further account for the potential confounding effect of indications of PPI, we additionally adjusted for H2 receptor antagonist use in model 3. Fifth, we investigated the associations of PPI use with risks of ischemic and hemorrhagic strokee. Further, to increase the statistical power, we combined stroke and transient ischemic attack as
a composite outcome, and tested the association between PPI use and risk of stroke/transient ischemic attack. Sixth, we investigated the association between PPI use and risk of CVD mortality. Finally, we repeated the analysis with an additional adjustment for lipid profile and preexisting microvascular complications.

Table 1. Baseline characteristics by proton pump inhibitor use among patients with type 2 diabetes in the UK Biobank study

Characteristics	Non-PPI users	PPI users	Standardized difference
	15 954	3275	
Age, y	59.4 (7.1)	60.3 (6.8)	−0.14
Men	9764 (61.2)	1671 (51.0)	0.21
White	13 555 (85.0)	2922 (89.2)	0.13
College or higher education	3985 (25.0)	627 (19.1)	0.18
BMI	31.3 (5.9)	32.3 (5.9)	−0.16
Townsend deprivation index	−0.53 (3.38)	−0.17 (3.44)	−0.10
Duration of diabetes, y	7.1 (8.6)	7.5 (8.5)	−0.04
HbA_{1c}, mmol/mol	52.1 (13.2)	52.0 (13.0)	0.01
Physically active	7177 (45.0)	1259 (38.4)	0.13
Daily drinkers	2329 (14.6)	418 (12.8)	0.14
Current smokers	1702 (10.7)	339 (10.4)	0.12
Healthy diet score (quintile 5)	2422 (15.2)	462 (14.1)	0.08
Sleep, 7-8 h/d	9596 (60.1)	1741 (53.2)	0.14
Hypertension	13 727 (86.0)	2950 (90.1)	0.12
Cancer	1290 (8.1)	399 (12.2)	0.14
Indications of PPI[a]	866 (5.4)	1466 (44.8)	1.02
Family history of CVD	9310 (58.4)	2076 (63.4)	0.10
Medications for hypertension	10 941 (68.6)	2485 (75.9)	0.16
Medications for cholesterol-lowing	11 783 (73.9)	2594 (79.2)	0.13
Acetylsalicylic acid use	7143 (44.8)	1407 (43.0)	0.04
Clopidogrel use	82 (0.5)	63 (1.9)	0.13
Medications for diabetes			0.09
Nonusers	5005 (31.4)	1001 (30.6)	
Oral drugs	8478 (53.1)	1654 (50.5)	
Insulin users	2471 (15.5)	620 (18.9)	
HDL cholesterol, ≥ 50 mg/dL	4279 (26.8)	851 (26.0)	0.02
LDL cholesterol, < 70 mg/dL	1243 (7.8)	231 (7.1)	0.03
Non-HDL cholesterol, < 100 mg/dL	3478 (21.8)	660 (20.2)	0.04
Triglycerides, < 150 mg/dL	6587 (41.3)	1185 (36.2)	0.10

Data are presented as mean (SD) or N (%).
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPI, proton pump inhibitor.
[a]Indications of PPI included gastroesophageal reflux disease, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrojejunal ulcer.

Results

Comparing PPI users with non-PPI users, the ageand sex-adjusted HR was 1.48 (1.35-1.61) for CAD, 1.57 (1.40-1.75) for MI, and 1.58 (1.38-1.81) for HF. The risks estimated were gradually attenuated with the adjustment for the covariates in model 2 and indications of PPI in model 3. In the fully adjusted model 3, compared with non-PPI users, the HRs (95% CIs) of CAD, MI, and HF for PPI 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 statistically significant difference in stroke risk (HR, 1.11; 95% CI, 0.90-1.36) between PPI users and non-PPI users.A statistically significant association was observed between PPI use and risk of all-cause mortality. Compared with non-PPI users, the HR (95% CIs) of all-cause mortality for PPI users was 1.41 (1.28-1.56) in model 1 and 1.30 (1.16-1.45) in model 3 (see Table 2)

Table 2. Associations of proton pump inhibitor 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-y	HR (95% CI)			
		Cases/person-y	Model 1	Model 2	Model 3
Coronary artery disease					
Non-PPI users	14.1 (13.5-14.7)	2314/164 379	Ref.	Ref.	Ref.
PPI 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-PPI users	8.3 (7.9-8.8)	1402/168 478	Ref.	Ref.	Ref.
PPI 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-PPI users	5.2 (4.9-5.6)	902/172 132	Ref.	Ref.	Ref.
PPI 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-PPI users	3.5 (3.2-3.7)	598/172 876	Ref.	Ref.	Ref.
PPI 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-PPI users	10.5 (10.1-11.0)	1787/169 657	Ref.	Ref.	Ref.
PPI 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)

Model 1: age and sex. Model 2: model 1 + Townsend deprivation index, education, ethnicity, BMI, smoking, drinking, physical activity, sleep duration, healthy diet score, family history of CVD, history of hypertension, history of cancer, HbA_{1c}, duration of T2D, acetylsalicylic acid use, clopidogrel use, medications for hypertension, cholesterol and diabetes. Model 3: model 2 + indications of PPI (gastroesophageal reflux disease, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrojejunal ulcer).
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin A_{1c}; HR, hazard ratio; PPI, proton pump inhibitor; Ref., reference; T2D, type 2 diabetes.

Discussion

In this large, prospective cohort study of patients with T2D, we found that PPI use was associated with higher risks of CAD, MI, HF, and all-cause mortality. The associations persisted after adjustment for severity of diabetes, antidiabetic medication use, antiplatelet agent use, and indications for PPI use. Our findings suggest that benefit-risk assessments should be considered by clinicians before prescribing PPIs to patients with T2D. Concerns about PPI use–related adverse CVD outcomes and premature death among patients treated with antiplatelet agents for secondary preventions have been raised in the past decade because of the drug-drug interaction . Some studies found that the observed associations between PPI use and risk of CVD was independent of antiplatelet agent use. Since then, the association between PPI use and higher risk of CVD have also been demonstrated in general populations. . In line with the previous study, our study also showed PPI use was associated with a higher risk of CVD, as well as all-cause mortality. However, our study had a larger sample size, longer follow-up, and undertook a closer investigation of associations of different PPI agents with a wide range of CVD subtypes and mortality.

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 PPI users via the increased gastric pH. The gut microflora dysbiosis and changes of the gut microbiota–derived metabolites after PPI use could thereby increase CVD risk by promoting inflammation, regulating the composition of lipoprotein subclasses, and changing the metabolism of macronutrients and micronutrients. Further, PPIs may increase the risk of macrovascular complications by the direct effect on glycemic control among patients with diabetes. A retrospective observational study showed that PPI users had an increase in HbA1c levels compared with non-PPI users . In addition, PPIs may increase the CVD events through the interactions of PPIs and antiplatelet agents. PPIs and clopidogrel share the metabolic pathway, namely cytochrome P450 (CYP2C19); therefore, the antiplatelet effect might be influenced by PPI use.

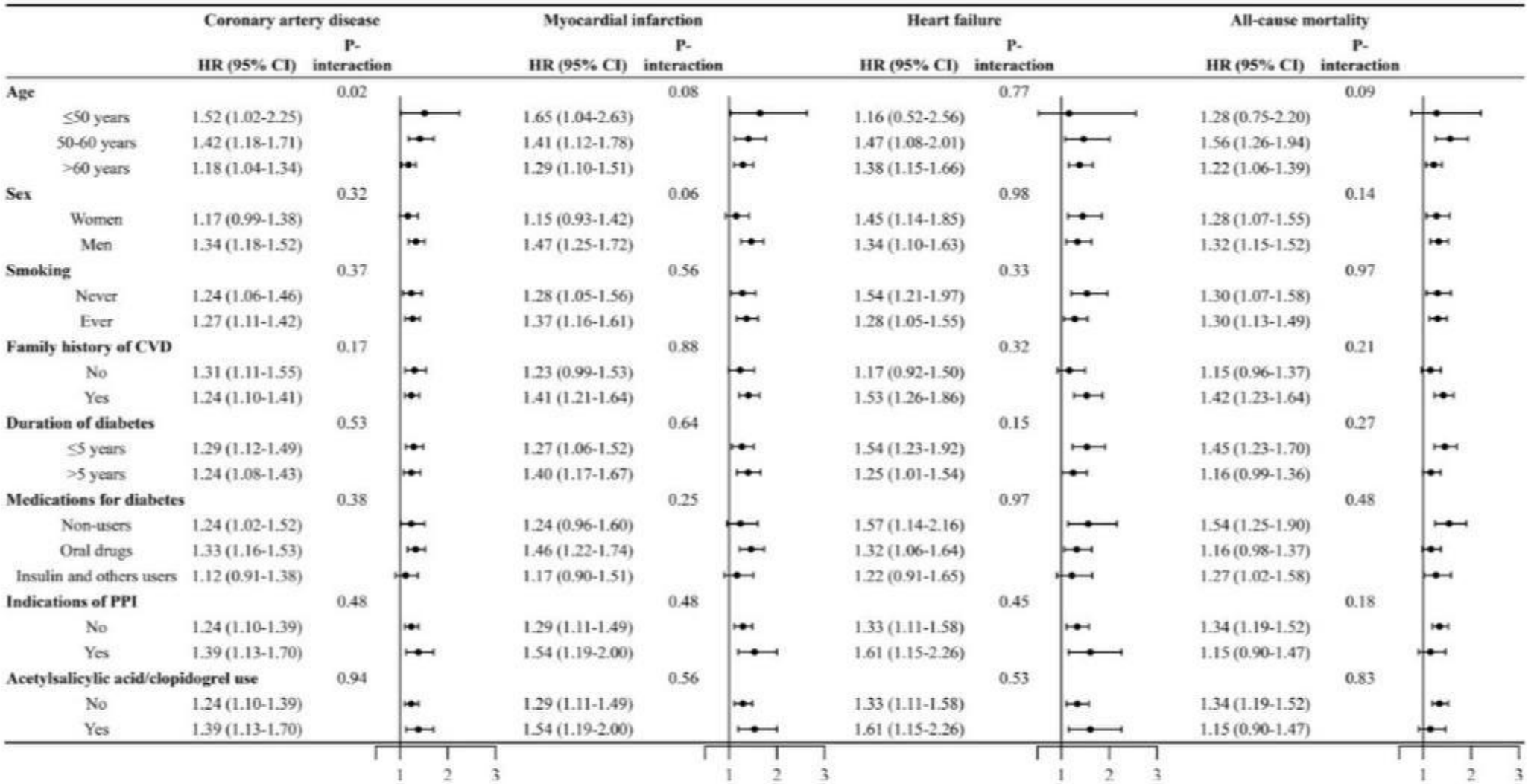

Figure 2. Subgroup analyses of proton pump inhibitor (PPI) use in relation to the risks of coronary artery disease, myocardial infarction, heart failure, and all-cause mortality among patients with type 2 diabetes. Hazard ratios (HRs) were adjusted for age, sex, Townsend deprivation index, education, ethnicity, body mass index, smoking, drinking, physical activity, sleep duration, healthy diet score, family history of cardiovascular disease (CVD), history of hypertension, history of cancer, glycated hemoglobin A_{1c}, duration of type 2 diabetes, acetylsalicylic acid/clopidogrel use, medications for hypertension, cholesterol, and diabetes, and indications of PPI (gastroesophageal reflux disease, gastric ulcer, duodenal ulcer, peptic ulcer, and gastrojejunal ulcer). The strata variable was not included in the model when stratifying by itself.

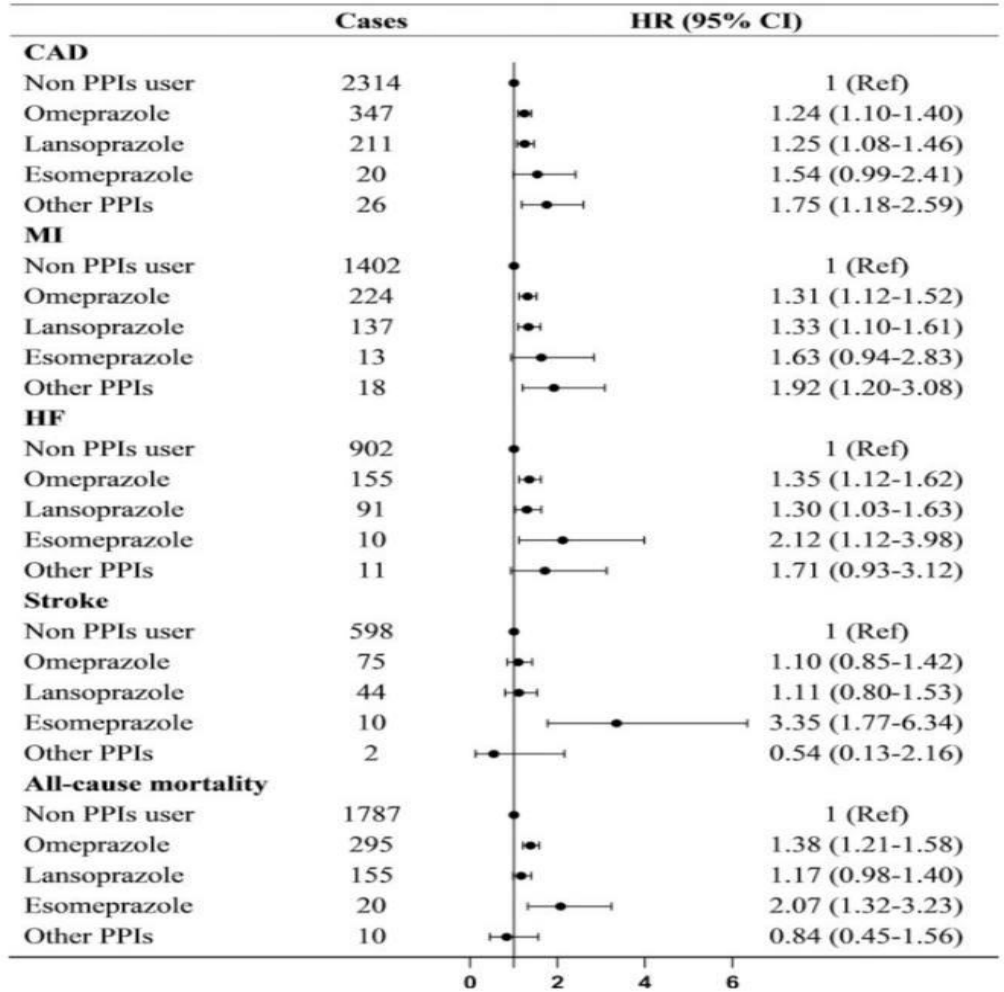

Figure 3. Associations of different types of proton pump inhibitor (PPI) with risks of coronary artery disease (CAD), myocardial infarction (MI), heart failure (HF), stroke, and all-cause mortality among patients with type 2 diabetes. Hazard ratios (HRs) were adjusted for age, sex, Townsend deprivation index, education, ethnicity, body mass index, smoking, drinking, physical activity, sleep duration, healthy diet score, family history of CVD, history of hypertension, history of cancer, glycated hemoglobin A_{1c}, duration of type 2 diabetes, acetylsalicylic acid use, clopidogrel use, medications for hypertension, cholesterol, and diabetes, indications of PPI (gastroesophageal 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 PPI users that were excluded from the analysis.

با تشکر از توجه شما