Research Square

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Proton Pump Inhibitor Taking Associates with Higher All-Cause Mortality and CV Events in Peritoneal Dialysis Patients

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Abstract

Background: A long period of inappropriate proton pump inhibitors (PPI) treatment have been proved to be associated with adverse prognosis in general population and hemodialysis (HD) patients. This study was conducted to clarify the impact of PPI taking on mortality and adverse cardiovascular (CV) events in peritoneal dialysis (PD) patients.

Methods: This is a retrospective study. We enrolled 904 patients from two PD centers, included 211 patients on PPI treatment and 618 patients not taking PPIs. Kaplan-Meier curves were used to identify the incidence of adverse outcomes. Multivariate Cox regression models and inverse probability of treatment weighting (IPTW) were applied to analyze hazard ratios (HRs) for adverse outcomes.

Results: During follow-up, 162 deaths and 102 CV events were recorded. Kaplan-Meier curve demonstrated all-cause mortality (log-rank test P=0.018) and CV events (log-rank test P=0.024) were significantly higher in PPI usage group. Multivariate COX regression models and IPTW showed that PPI taking was an indicator for all-cause mortality (HR=1.33, 95%CI=1.07-1.65, P=0.010) and CV events (HR=1.81, 95%CI=1.38-2.38, P<0.001).

Conclusions: PPI usage associates with higher all-cause mortality and CV events in PD patients. Clinicians are supposed to be more careful when using PPI and need to master the indications more rigorously in patients receiving PD treatment.

Introduction

Proton pump inhibitors (PPI) are currently one of the most commonly prescribed medications. Recently, emerging evidences suggested that PPI have been over- prescribed. Investigation demonstrated that 25–70% of patients taking PPIs do not have the appropriate indications in the United States[1]. Considerable studies showed that PPI use is associated with adverse events, such as dementia[2], fractures[3], hypomagnesemia[4], vitamin B12 deficiency[5] and cardiovascular (CV) events[6,7]. Besides, PPI use also indicated adverse kidney outcomes, accelerating the progression of chronic kidney diseases[8].

As CV events are the main complications, anti-platelet drugs are widely used to treat CV diseases (CVD) in patients with end stage renal disease (ESRD)[9]. Accordingly, PPIs are also widely used to avoid gastrorrhagia inducing by anti-platelet drugs. Over the past years, more and more reports have linked the long-term use of PPI to various CV and non-CV adverse reactions. In that case, we do necessary to access whether it is appropriate to take PPIs for a long period in ESRD patients. PPI usage closely associated with mortality in general population and hemodialysis (HD) patients recently[10]. Angel L.M et al analyzed 2222 HD patients including 1776 on PPI therapy and 466 patients not on PPI, they found that PPI use was associated with all-cause mortality[11]. Up till now, the relationship between PPI usage and mortality as well as CV events have not been reported in peritoneal dialysis (PD) patients.

Therefore, this study was conducted to clarify the impact of PPI taking on mortality and CV events in PD patients.

Materials And Methods

Subjects

This retrospective multi-center study was conducted to evaluate the effect of PPI use on CV events and mortality in PD patients. We studied 904 PD patients from the Second Affiliated Hospital of Guangzhou Medical University and Zhujiang Hospital Affiliated to Southern Medical University from January 1, 2010 to December 31, 2016. Patients were divided into PPI group (Use of PPIs at baseline) and no-PPI group. Patients using PPI for more than 1 week continuously were included in the PPI group. Patients were exclude for the following reasons: age younger than 18 years or older than 80 years (n=22), PD was maintained for less than 3 months (n=21), missing data (n=33). In all, 829 patients were enrolled in the study, including 211 on PPI therapy and 618 not receiving PPI. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was warranted by the Institutional Review Board of two PD centers. Owing we had collected the existing medical records, written informed consent wasn't required.

Study outcome

All patients were followed up until CV events or death, transferring to HD therapy, transferring to kidney transplantation, transferring of care to other centers, lost to follow up or censoring on December 31, 2017. The primary outcome was all-cause mortality, the second outcome was CV events. CVD are defined as recording any of the following conditions in the patient's medical records: coronary heart disease, coronary atherosclerotic heart disease, acute myocardial infarction, cardiac arrest, cerebrovascular accident, stroke, congestive heart failure.

Clinical data

The baseline demographic data included center, age, gender and comorbid (history of hypertension, diabetes, CVD and gastrointestinal bleeding). Baseline data were collected within 3 month of the initiation of PD. Clinical biochemical indicators included body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), medication history (including calcium channel blockers (CCB), angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB),βblockers, aspirin, statins), hemoglobin, creatinine, urea nitrogen, uric acid, fasting blood glucose (FBG), cholesterol, triglycerides, calcium, potassium, phosphorus, total Kt/v, residual renal function (RRF). Patients who reported current use of insulin or oral hypoglycemic agents and / or who had a clinical diagnosis of type 1 or type 2 diabetes mellitus were considered to have diabetes mellitus. Hypertension was recorded if the patient took antihypertensive drugs or had 2 separate blood pressure measurements ≥ 140/90mmHg.

Laboratory measurements were obtained using standard methods in the clinical laboratory. Total Kt/V were calculated using PD Adequest software 2.0 (Baxter, Deerfield, IL). Medicine use was recorded based on prescriptions. Patients returned to these centers for quarterly evaluation, and trained nurses interviewed the patients by telephone monthly to assess general conditions.

Statistical Analyses

Continuous variables were described as means±standard deviations (SD) or median (25th-75th percentile), and categorical data were given as number (percentages). Comparisons of the variable between groups were performed using the t test for normally distributed variables and Mann-Whitney U test for skewed continuous variables. Differences among the two groups were tested using chi-square test for categorical variables. Mortality and incidence of CV events were calculated using the Kaplan-Meier curve and differences among distributions were assessed by log-rank test. Cox regression models were used to evaluate the relationship among PPI use with mortality and CV events in patients undergoing PD, initially without adjustment and subsequently adjusting for several groups of covariates. Inverse probability of treatment weighting (IPTW) analysis was applied to assess the influence of PPI use. IPTW analysis is obtained by using the propensity scores of all indicators before matching, and statistically adjusting the covariates to reduce the bias, thereby achieving randomization. Variables included in the IPTW analysis were center, age, sex, BMI, diabetes mellitus, hypertension, systolic pressure, history of CVD, history of gastrointestinal bleeding, ACEI / ARB use, βblcoker use, CCB use, aspirin use, statins use, hemoglobin, creatinine, urea nitrogen, cholesterol, triglycerides, uric acid, calcium, potassium, phosphorus and Kt/V, RRF.

In Cox regression models, time at risk was from study entry until CV events, death, transferring to HD therapy, transferring to kidney transplantation, transferring of care to other centers, or the end of study on December 31, 2017. Missing data were filled by miss Forest method. Statistical analysis are completed by SPSS 23.0 and R software(version R-3.6.2, www.r-project.org). All tests were performed bilaterally, and $P < 0.05$ was considered to be statistically significant.

Results

During follow-up, 162 deaths and 102 CV events were recorded, the cause of death included CVD (n = 65), infection (n = 32), gastrointestinal bleeding (n = 5), malignant tumor (n = 8), uremic encephalopathy (n = 25) and others (n = 27). Baseline characteristics of the cohort were shown in Table 1. Median age is 53 (42, 63), of which 463 were male and 366 were female. 212 (25.6%) patients had a history of diabetes, 179 (21.6%) patients had a history of CVD, while 58 (7.0%) patients had a history of gastrointestinal bleeding. Patients in PPI group were older, and more often suffered from diabetes and CVD than no PPI group.

Kaplan-Meier cumulative incidence curve demonstrated all-cause mortality (log-rank test P = 0.018) (Fig. 2A) and the incidence of CV events (log-rank test P = 0.024) (Fig. 2B) were significantly higher in PPI group. Besides, Kaplan-Meier cumulative incidence curve after IPTW also showed a significant

association among all-cause mortality (log-rank test P = 0.01) (Fig. 3A) and the incidence of CV events (log-rank test P < 0.001) (Fig. 3B) in PPI group. Multivariate COX regression models showed that PPI was an independent risk factor for all-cause mortality (HR = 1.47, 95%CI = 1.02–2.13, P = 0.042) and CV events (HR = 1.80, 95%CI = 1.13–2.87, P = 0.014) in PD patients after adjusting for complications, medication, age, sex, center and biochemical examination. IPTW method also confirmed PPI use as a predictor for all-cause mortality (HR = 1.33, 95%CI = 1.07–1.65, P = 0.010) and CV events (HR = 1.81, 95%CI = 1.38–2.38, P < 0.001). (Table 3).

Discussion

In this retrospective multicenter study of 904 PD patients, we found that PPI use was related to all-cause mortality and CV events. PPI is widely used around the world to treat and prevent gastrointestinal bleeding, but its safety and indication have never been clarified. Plenty of studies proposed that PPI usage resulted in increased adverse prognosis in both general population and ESRD patients. Yan Xie et al draw a conclusion that PPI was related to the increased risk of death in the general population[10]. Christopher B Chen et al showed the result of a retrospective study, with the aim of disclosing the effect of concomitant use, suggested that PPI use was associated with death[12]. Angel L.M et al analyzed 2222 HD patients including 1776 on PPI therapy and 466 patients not on PPI, they reported a association between PPI use and all-cause mortality in HD patients[11]. More recently, a prospective multicenter observational study of 367 patients by Ippei Kosedo indicated that the usage of PPI in HD patients increased the risk of mortality and CV event[13]. However, to the best of our knowledge, few studies have reported the relationship between adverse prognosis and PPI use in PD patients.

Our study suggested that PPI was an independent risk factor for all-cause mortality in PD patients. The result was consistent with other studies in general population and HD patients. Several reasons are considered to be related to the results. First of all, experiments in mice have shown that the application of PPI up-regulates mRNA and protein expression and leads to increased heme oxygenase-1 enzyme activity in gastric and renal cells[14]. Heme oxygenase-1 is generally considered beneficial, however, when PPI is applied, it will destroy the acidification and protein stabilization of lysosomes and cause oxidative stress, dysfunction[15] as well as promotes the aging of endothelial cell[16]. Secondly, PPI use have been proved to be related to hypomagnesemia in not only general population but also HD patients[17–20]. There are increasing evidences indicated that hypomagnesemia might accelerate mortality among HD patients[21, 22]. On the one hand, it was reported that magnesium deficiency was associated with insulin resistance and metabolic syndrome[23]. Magnesium is an important cofactor for many enzymes involved in glucose metabolism, while metabolic syndrome have been found to be a predictor of mortality hazard[24]. Magnesium is closely related to the immune system in both non-specific and specific immune responses (also known as innate and acquired immune responses), and involves in a variety of immune responses such as immune globulin synthesis, C3 converting enzymes and immune cell adherence[25]. Unfortunately, serum magnesium concentration is not available in our database, so the above conclusions cannot be determined in our study. Thirdly, The use of PPI had also been correlated to a higher incidence of bone

fracture[3]. PPI is an effective gastric acid secretion blocker, which is believed to be necessary to absorb calcium. PPI can reduce the absorption of alkaline calcium and even lead to a decrease in bone mineral density, further resulting in bone fracture. A previous study by Aliasghar A Kiadaliri et.al reported that fracture was mentioned as a contributory cause of death[26]. Potential comorbidities are likely to affect long-term risk of death. After suffering from bone fracture, a series of complications such as infection and embolism will gradually occur due to the long-term bed rest, which will affect the quality of life, even lead to the increased risk of death.

Our results also indicated PPI taking was an independent risk factor for CV events in PD patients. PPIs are widely used to avoid gastrorrhagia inducing by anti-platelet drugs in patients who suffer from CVD. Accumulating clinical data had uncovered associations between PPI use and adverse CV event in general population[27, 28]. In a large study including 396296 patients confirmed that the risks of first-time ischemic stroke in the general population may be higher in the PPI group compared to non-PPI group[29]. Nitric oxide(NO) has a protective effect on vascular endothelium by reducing the interaction between platelets and endothelium and activating platelets[30]. Studies have shown that PPI inhibit the activity of dimethylarginine dimethylaminohydrolase (DDAH), while DDAH is the catalytic enzyme that predominates the metabolism of asymmetric dimethylarginine (ADMA). The decreasing of DDAH activity reduces the inactivation of ADMA and leads to accumulation of ADMA in the body. ADMA is an inhibitor of endogenous nitric oxide synthase (NOs), which can compete to inhibit the production of nitric oxide (NO), the reduction of NO will increase peripheral vascular resistance, induce oxidative stress, further result in inflammation and thrombosis[31], finally accelerate the development of CVD. A study suggested that after 1 week of PPI treatment, serum ADMA also significantly increased in mice[32]. Yet the exactly mechanism of PPI usage and CVD in PD patients need to be illuminated by more studies.

This research has several limitations. Because of missing sufficient follow-up data, we cannot perform subgroup analysis on the total duration and dose of PPI usage; but after tracking one of the centers, we found that the vast majority of patients used PPI continuously for more than 1 month. In addition, the total number of patients in this study is not large enough, we need to enroll more multicenter data to verify our conclusion in the future. Finally, since this study is a retrospective analysis, the patient's medication data cannot be fully recorded, and a comparative analysis of H2 receptor blockers has not been performed.

Conclusions

In this multicenter retrospective research, we have shown that PPI use was associated with increased risk of all-cause mortality and CV events in PD patients. It means that clinicians are supposed to be more careful when using PPI for treatment, and need to master the indications more rigorously.

Declarations

Acknowledgments

None.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the Second Affiliated Hospital, Guangzhou Medical University.

Consent for publication

A written informed consent was obtained from all patients prior to the initiation of this study.

Competing interests

The authors declare that they have no competing interests.

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Authors'contributions

Yueqiang Wen and Jiao Li designed the research. Yingsi Zeng, Lingling Liu, Liya Zhu wrote the paper. Xiaojiang Zhan, Fenfen Peng, Xiaoran Feng, Yujing Zhang, Zebin Wang, Jianbo Liang collected and provided data. Qian Zhou is responsible for statistical analysis.

All authors read and approved the final manuscript.

Availability of data and materials

All data are available on request.

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Tables

Table1. Patient Demographic and Clinical Characteristics.

	Group1 PPI (n=211)	Group2 No PPI (n=621)	P value
No.of C1/C2	308/310	46/165	<0.001
No.of men/women	361/257	102/109	0.011
Demographics			
Age(y)	52.0(42.0,63.0)	56.0(45.0,65.0)	0.012
BMI(kg/m2)	22.6(20.6,25.0)	22.5(20.7,24.5)	0.573
Comorbid			
Diabetes	145(23.5%)	67(31.8%)	0.017
Hypertension	310(50.2%)	152(72.0%)	<0.001
Systolic BP(mm Hg)	144(136,160)	151(133,171)	0.098
Diastolic BP(mm Hg)	85.2(79,93)	84(77,96)	0.236
Cardiovascular disease	120(19.4%)	59(28.0%)	0.009
Gastrointestinal bleeding	35(5.7%)	23(10.9%)	0.010
Laboratory variables			
Hemoglobin(g/L)	96.0(84.0,110.0)	90.0(82.0,104.0)	0.009
Creatinine(umol/L)	751.5(549.0,977.8)	799.0(568.0,1104.0)	0.054
Urea nitrogen(mmol/L)	18.9(14.6,24.7)	18.9(13.1,24.0)	0.256
Uric acid(mmol/L)	434.0(371.0,491.0)	412.0(359.0,479.0)	0.034
FBG(mmol/L)	4.6(4.1,5.6)	4.5(3.8,5.9)	0.145
Cholesterol(mmol/L)	4.4(3.9,5.0)	4.4(3.8,5.3)	0.437
Triglycerides(mmol/L)	1.4(1.0,2.0)	1.5(1.1,2.3)	0.069
Calcium(mmol/L)	2.1(2.0,2.3)	2.0(1.9,2.2)	<0.001
Potassium(mmol/L)	3.9(3.4,4.4)	3.9(3.4,4.4)	0.941
Phosphorus(mmol/L)	1.5(1.2,1.9)	1.6(1.2,2.0)	0.353
Total Kt/V	2.3(1.9,2.7)	2.2(1.8,2.6)	0.495
RRF(ml/min)	7.0(2.6,26.2)	17.4(4.1,34.3)	<0.001
Treatments			
CCB	519(84.0%)	180(85.3%)	0.647
B blocker	322(52.1%)	111(52.6%)	0.899

ACEI/ARB	348(56.3%)	95(45.0%)	0.005
Aspirin	76(12.3%)	19(9.0%)	0.195
Statins	93(15.0%)	56(26.5%)	<0.001

Note: All continuous variables are skewed distribution-the values for continuous variables are given as median(P25,P75).

Abbreviations: PPI-proton pump inhibitor; C1-center 1; C2-center 2; BMI-body mass index; FBG-fasting blood-glucose; Kt/V- K-dialyzer clearance of urea- t-dialysis time- V-volume of distribution of urea; RRF-residual renal function; CCB-calcium channel blocker; ACEI-angiotensin converting enzyme inhibitors; ARB- angiotensin receptor blocker.

Table 2. Significant Risk Factors for all-cause mortality and CV events

Risk Factors	Univariable logistic regression		Multivariable logistic regression	
	HR（95% CI）	P value	HR（95% CI）	P value
All-cuase mortality				
C2 vs C1	0.43(0.31-0.62)	<0.001	0.86(0.79-0.94)	0.001
Sex(female vs male)	2.10(1.48-2.98)	<0.001	2.15(1.43-3.25)	<0.001
Age(years)	1.09(1.07-1.10)	<0.001	1.06(1.04-1.08)	<0.001
Diabetes(yes vs no)	6.21(4.29-8.98)	<0.001	2.69(1.70-4.25)	<0.001
Hypertension(yes vs no)	5.20(3.35-8.07)	<0.001	2.03(1.20-3.45)	0.009
CVD history(yes vs no)	5.81(3.99-8.45)	<0.001	2.23(1.41-3.54)	0.001
Bblocker(yes vs no)	1.42(1.01-2.02)	0.047	1.78(1.17-2.71)	0.007
Aspirin(yes vs no)	5.85(3.73-9.18)	<0.001		
Diastolic BP(mm Hg)	0.96(0.94-0.97)	<0.001		
Creatinine(umol/L)	0.998(0.998-0.999)	<0.001		
Urea nitrogen(mmol/L)	0.95(0.93-0.97)	<0.001		
FBG(mmol/L)	1.23(1.15-1.31)	<0.001		
Cholesterol(mmol/L)	1.31(1.13-1.51)	<0.001		
Potassium(mmol/L)	0.60(0.46-0.76)	<0.001		
ACEI/ARB(yes vs no)	1.54(1.09-2.19)	0.015		
Calcium(mmol/L)	2.00(1.04-3.97)	0.047		
Uric acid(mmol/L)	0.998(0.996-1.00)	0.028		
Phosphorus(mmol/L)	0.72(0.53-0.97)	0.032		
RRF(ml/min)	0.99(0.98-1.00)	0.047		
CV events				
Age(years)	1.06(1.04-1.08)	<0.001	1.04(1.02-1.06)	<0.001
Hypertension(yes vs no)	5.44(3.09-9.60)	<0.001	3.49(1.89-6.45)	<0.001
Aspirin(yes vs no)	5.46(3.35-8.89)	<0.001	2.20(1.23-3.92)	0.008
Systolic BP(mm Hg)	0.99(0.98-1.00)	0.029	0.99(0.98-1.00)	0.037
FBG(mmol/L)	1.21(1.13-1.30)	<0.001	1.13(1.04-1.22)	0.003
Bblocker(yes vs no)	1.63(1.07-2.50)	0.024	2.02(1.26-3.24)	0.004

Diastolic BP(mm Hg)	0.96(0.94-0.98)	<0.001
C2 vs C1	0.50(0.33-0.76)	0.001
ACEI/ARB(yes vs no)	1.97(1.27-3.06)	0.002
CVD history(yes vs no)	3.33(2.16-5.14)	<0.001
Diabetes(yes vs no)	3.52(2.30-5.38)	<0.001

Abbreviations: PPI-proton pump inhibitor; C1-center 1; C2-center 2; CVD- cardiovascular disease; BP-blood pressure; FBG-fasting blood glucose; ACEI-angiotensin converting enzyme inhibitors; ARB-angiotensin receptor blocker; RRF-residual renal function.

Table 3. Relationship between PPI and the adverse prognosis

	HR(95%CI)	P value
All-cause mortality		
Unadjusted	1.52(1.07-2.15)	0.019
Model 1	1.67(1.15-2.41)	0.006
Model 2	1.46(1.01-2.10)	0.044
Model 3	1.47(1.02-2.13)	0.042
IPTW	1.33(1.07-1.65)	0.010
New-onset CVE		
Unadjusted	1.64(1.06-2.54)	0.026
Model 1	1.89(1.19-3.00)	0.007
Model 2	1.72(1.08-2.74)	0.022
Model 3	1.80(1.13-2.87)	0.014
IPTW	1.81(1.38-2.38)	<0.001

Model 1: sex,age,center.

Model 2:

All-cause mortality: Model 1 plus Comorbid conditions(Diabetes, SBP, History of CVD, History of gastrointestinal bleeding, βblocker) .

New-onset CVE: Model 1 plus Comorbid conditions(Diabetes, SBP, History of gastrointestinal bleeding, βblocker,)

Model 3: Model 2 plus Uric acid, Total cholesterol, Kt/V, RRF.

IPTW：Inverse probability of treatment weighted method.

Abbreviations: PPI, proton pump inhibitor; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; CVE, Cardiovascular event; SBP, Systolic pressure; Kt/V, K-dialyzer clearance of urea, t-dialysis time, V-volume of distribution of urea; RRF, residual renal function.

Note: Reference group is No PPI group.

Figures

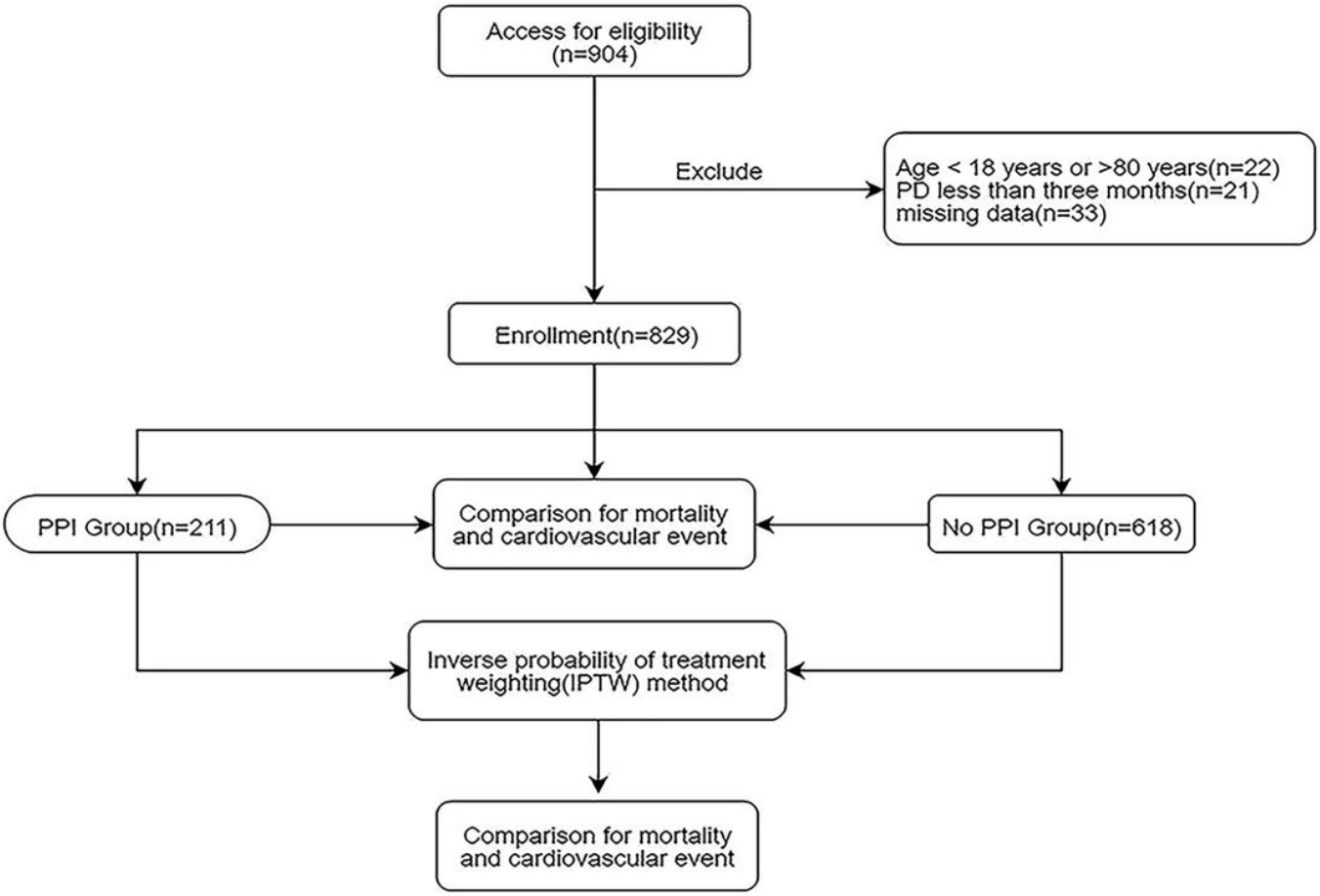

Figure 1

Flow chart-including patent enrollment and outcomes

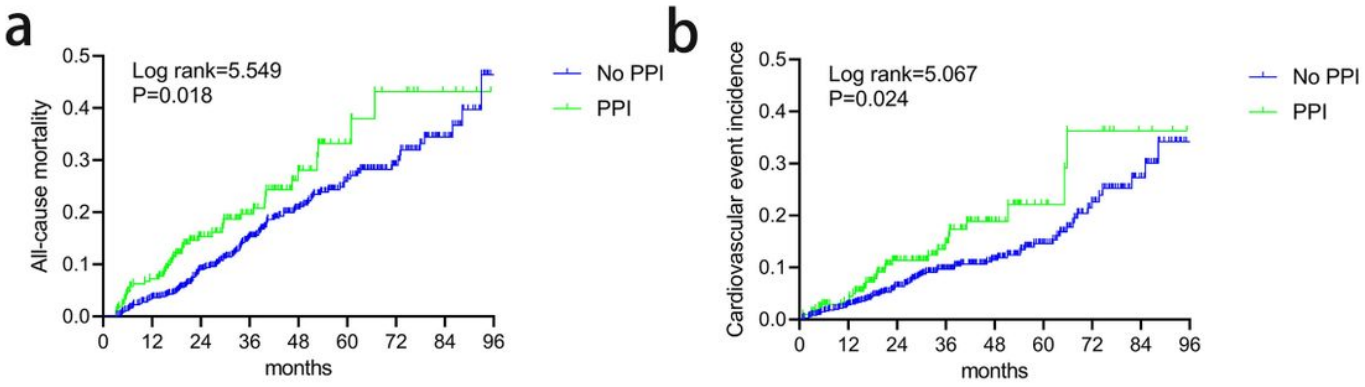

Figure 2

Cumulative incidence curves for mortality and CV events by category of the use of PPI. (a) Cumulative incidence curves for all-cause mortality, (b) Cumulative incidence curves for the incidence of CV events.

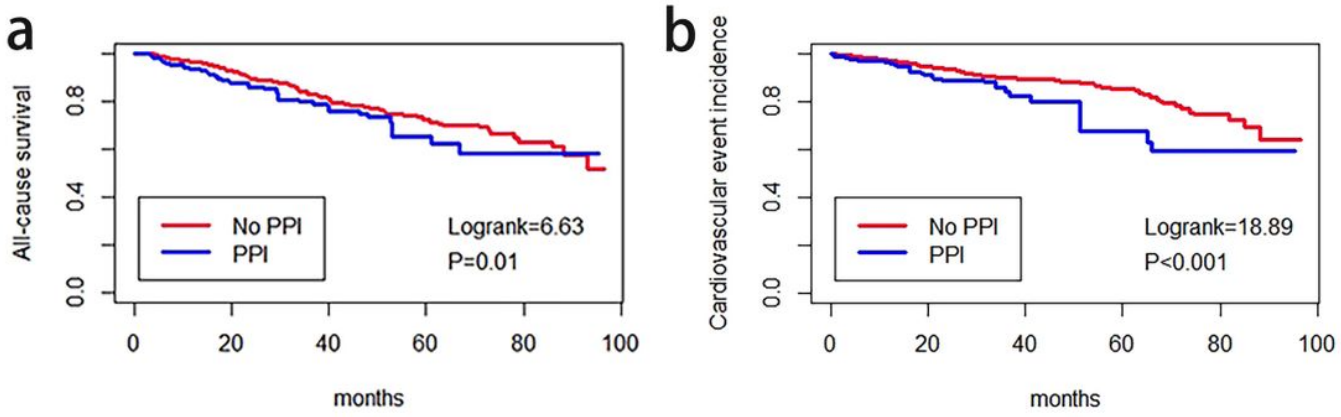

Figure 3

Cumulative incidence curves for mortality and CV events by category of the use of PPI. after IPTW. (a) Cumulative incidence curves for all-cause survival, (b) Cumulative incidence curves for the incidence of CV events.