ORIGINAL RESEARCH

Associations of Acid Suppressive Therapy With Cardiac Mortality in Heart Failure Patients

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***Background*—**It has been recently reported that histamine H_2 receptor antagonists (H2RAs) are associated with impairment of ventricular remodeling and incident heart failure. In addition, favorable pleiotropic effects and adverse effects of proton pump inhibitors (PPIs) on cardiovascular disease have also been reported. We examined the associations of acid suppressive therapy using H2RAs or PPIs with cardiac mortality in patients with heart failure.

***Methods and Results*—**In total, 1191 consecutive heart failure patients were divided into 3 groups: a non–acid suppressive therapy group (n=363), an H2RA group (n=164), and a PPI group (n=664). In the follow-up period (mean 995 days), 169 cardiac deaths occurred. In the Kaplan–Meier analysis, cardiac mortality was significantly lower in the PPI group than in the H2RA and non–acid suppressive therapy groups (11.0% versus 21.3% and 16.8%, respectively; log-rank *P*=0.004). In the multivariable Cox proportional hazards analysis, use of PPIs, but not H2RAs, was found to be an independent predictor of cardiac mortality (PPIs: hazard ratio 0.488, *P*=0.002; H2RAs: hazard ratio 0.855, *P*=0.579). The propensity-matched 1:1 cohort was assessed based on propensity score (H2RAs, n=164; PPIs, n=164). Cardiac mortality was significantly lower in the PPI group than in the H2RA group in the postmatched cohort (log-rank *P*=0.025). In the Cox proportional hazards analysis, the use of PPIs was a predictor of cardiac mortality in the postmatched cohort (hazard ratio 0.528, *P*=0.028).

***Conclusions*—**PPIs may be associated with better outcome in patients with heart failure. **(*J Am Heart Assoc*. 2017;6:e005110. DOI: 10.1161/JAHA.116.005110.)**

Key Words: acid suppressive therapy • heart failure • histamine H_2 receptor antagonists • prognosis • proton pump inhibitors

Heart failure (HF) is a systemic disease with a devastating prognosis. HF affects not only the cardiovascular system but other organ systems. Alterations of gastrointestinal function occur in HF patients as a result of low cardiac output, increased central venous pressure, and increased sympathetic vasoconstriction.[1–3] In addition, reduced intestinal perfusion may lead to an increase in transmucosal carbon dioxide pressure, and intramucosal acidosis occurs in nearly 50% of patients with circulatory failure, suggesting the presence of inadequate oxygen supply and intestinal ischemia.[1,4,5] Furthermore, gastrointestinal bleeding in patients with acute coronary syndrome is associated with higher mortality.[6] Protecting gastrointestinal bleeding and intestinal barrier function and altering gut microbiota may be the targets of HF therapy.[2]

Acid suppressive therapies using histamine H_2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) have been widely prescribed for the treatment of upper gastrointestinal disease and/or prevention of gastrointestinal bleeding among patients taking antiplatelet agents and/or anticoagulants.[7–10]

It was reported recently that H2RAs are associated with the blockade of right and left ventricular remodeling and reduce the incidence of HF in persons without cardiovascular disease.[11,12] Myocardial histamine H_2 receptor activation may promote cardiac fibrosis and apoptosis in preclinical models, and the use of H2RAs may improve symptoms in HF patients.[11,12] In addition, favorable pleiotropic effects of PPIs for cardiovascular diseases have been reported.[13–18] Adversely, an observational study previously reported that long-term use of PPIs is associated with adverse effects.[19]

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These studies, however, were not randomized or intended for HF patients and did not consider the presence of gastrointestinal tract disease or the use of antiplatelet agents and anticoagulants. Moreover, the effects of the addition of PPIs to antiplatelet agents (eg, clopidogrel) on platelet formation function and cardiovascular function remain unclear.[20]

Taken together, the previous literature indicates that the association between acid suppressive therapies using H2RAs or PPIs and cardiac mortality in HF patients is still unclear and controversial. Consequently, we examined the impact of acid suppressive therapy on cardiac mortality in HF patients based on an observational study using propensity score (PS) analyses to reduce selection bias and taking into consideration the patients' clinical backgrounds, including the presence of upper gastrointestinal tract disease and the use of antiplatelet agents and anticoagulants.

Methods

Participants and Study Protocol

This observational study was analyzed using PS methods in which consecutive symptomatic HF patients, hospitalized with decompensated HF and discharged from Fukushima Medical University Hospital between 2009 and 2014, were enrolled. The diagnosis of decompensated HF was defined based on the Framingham criteria.[21] From the originally enrolled HF patients (n=1269), those who died in hospital (n=51), received dialysis (n=12), had acute coronary syndrome (n=9), or had advanced cancer (n=6) were excluded, leading to a total of 1191 patients who were finally enrolled. Blood samples were obtained at hospital discharge. Diabetes mellitus was defined as the recent use of antidiabetic drugs, a fasting blood glucose value ≥126 mg/dL, and/or a hemoglobin A_1c value of ≥6.5%. Patients were divided into 3 groups based on the use of H2RAs and PPIs at hospital discharge: a non–acid suppressive therapy group (Non, n=363), an H2RA group (n=164), and a PPI group (n=664). We compared the clinical features and laboratory data collected at discharge. Hypertension was defined as the recent use of antihypertensive drugs, a systolic blood pressure ≥140 mm Hg, and/or a diastolic blood pressure ≥90 mm Hg. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value ≥150 mg/dL, a low-density lipoprotein cholesterol value ≥140 mg/dL, and/or a high-density lipoprotein cholesterol value <40 mg/dL. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 cm^2.[22] Anemia was defined as hemoglobin levels of <12.0 g/dL in women and <13.0 g/dL in men.[23] Atrial fibrillation was identified by an ECG performed during hospitalization and/or from medical records including past history. Endoscopy was recommended by hospital physicians as often as necessary during hospitalization. Peptic ulcer, esophagitis, gastroesophageal reflux disease, and gastritis were identified by endoscopy, which was performed within 1 year prior to admission until discharge. In Japan's health insurance system, PPI and H2RA were prescribed for the treatment of upper gastrointestinal disease and/or prevention of gastrointestinal bleeding among patients taking antiplatelet agents and/or anticoagulants. Left ventricular ejection fraction was calculated using the Simpson method, and recordings were performed on ultrasound systems (ACUSON Sequoia; Siemens Medical Solutions USA, Inc). Reduced left ventricular ejection fraction was defined as a value ≤50%. All patients were followed up until 2016 for cardiac death, which was the primary outcome of the present study. Cardiac death was adjudicated by independent experienced cardiologists and included death caused by worsened HF in accordance with the Framingham criteria,[21] due to ventricular fibrillation documented by ECG or other implantable devices, and acute coronary syndrome. Survival time was calculated from the date of discharge until the date of death or last follow-up. Status and dates of death were obtained from patients' medical records. If these data were unavailable, status was ascertained by a telephone call to the patient's referring hospital physician. The survey was performed blindly to the analyses of this study, and written informed consent was obtained from all study participants. The study protocol was approved by the ethical committee of Fukushima Medical University. The investigation conforms with the principles outlined in the Declaration of Helsinki, and reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.[24]

Statistical Analysis

Normally distributed data are presented as mean±SD, and nonnormally distributed data are presented as median (interquartile range) or log transformed. Categorical variables are expressed as numbers and percentages, and the chi-square test was used for comparisons. Data among the 3 groups were compared using analysis of variance followed by the Tukey post hoc test. In addition, the Student *t* test and the Mann–Whitney test were used to compare the 2 groups for normally and nonnormally distributed data, respectively. The Kaplan–Meier method was used for presenting cardiac mortality, and a log-rank test was used for initial comparisons.

To eliminate imbalances in the measurement of baseline characteristics because of selection bias associated with use of PPIs or H2RAs, we used multiple approaches, including multiple Cox regression analysis in the prematched cohort (n=1191) and PS matching in the postmatched cohort

Table 1. Comparisons of Clinical Features (n=1191)

	Non (n=363)	H2RA (n=164)	PPI (n=664)	*P* Value
Age, y	64.1±16.8	68.9±13.0*	69.3±13.6†	<0.001
Male sex, n (%)	232 (63.9)	97 (59.1)	406 (61.1)	0.524
Body mass index, kg/m^2	23.2±4.1	23.1±4.3	22.7±4.0	0.436
Systolic BP, mm Hg	128.1±31.1	132.3±35.5	127.6±34.1	0.262
Diastolic BP, mm Hg	73.6±21.4	75.7±23.0	72.2±21.1	0.147
Heart rate, bpm	83.2±43.2	85.1±24.7	82.9±25.9	0.726
NYHA class III/IV	6 (1.7)	11 (6.7)	22 (3.3)	0.010
Reduced LVEF, n (%)	191 (52.6)	90 (54.9)	366 (55.1)	0.735
Ischemic etiology, n (%)	57 (15.7)	45 (27.4)	214 (32.2)	<0.001
Comorbidity				
Hypertension, n (%)	266 (73.3)	135 (82.3)	522 (78.6)	0.041
Diabetes mellitus, n (%)	131 (36.1)	69 (42.1)	277 (41.7)	0.181
Dyslipidemia, n (%)	256 (70.5)	127 (77.4)	526 (79.2)	0.007
CKD, n (%)	193 (53.2)	94 (57.3)	417 (62.8)	0.010
Anemia, n (%)	167 (46.0)	89 (54.3)	425 (64.0)	<0.001
Atrial fibrillation, n (%)	136 (37.5)	60 (36.6)	266 (40.1)	0.590
Peptic ulcer, n (%)	24 (6.6)	13 (7.9)	98 (14.8)	<0.001
Esophagitis/GERD, n (%)	8 (2.2)	10 (6.1)	49 (7.4)	<0.001
Gastritis, n (%)	56 (15.4)	35 (21.3)	193 (29.1)	<0.001
Medications				
RAS inhibitors, n (%)	262 (72.2)	132 (80.5)	498 (75.0)	0.125
β-blockers, n (%)	270 (74.4)	112 (68.3)	534 (80.4)	0.002
Diuretics, n (%)	222 (61.2)	105 (64.0)	472 (71.1)	0.004
Inotropic agents, n (%)	45 (12.4)	20 (12.2)	74 (11.1)	0.816
Antiplatelet agents, n (%)	100 (27.5)	81 (49.4)	411 (61.9)	<0.001
Anticoagulants, n (%)	181 (49.9)	89 (54.3)	418 (63.0)	<0.001
Laboratory data				
Log BNP	2.4±0.6	2.5±0.6	2.5±0.3	0.195
Hemoglobin, g/dL	12.8±2.3	12.6±2.4	12.4±2.3†	0.012
Iron, μg/dL	90.5±45.8	74.1±38.1*	72.9±39.3†	<0.001
Ferritin, ng/mL‡	111.0 (57.5–212.0)	105.0 (68.0–173.0)	103.0 (44.8–214.3)	0.152
UIBC, μg/dL	229.2±72.7	218.7±67.0	225.4±70.7	0.562
Transferrin, mg/dL	244.9±50.4	225.0±47.6	231.9±57.5*	0.019
Vitamin B_{12}, pg/mL‡	404.0 (305.0–565.5)	498.0 (321.0–740.0)	457.5 (314.8–641.5)	0.208
Total protein, g/dL	6.9±0.8	6.8±0.8	6.9±0.7	0.442
Sodium, mEq/L	139.5±3.0	138.7±4.0	138.3±4.4†	<0.001
Corrected calcium, mg/dL	9.1±0.6	9.0±0.6	9.0±0.7	0.457
Intact PTH, pg/mL‡	52.0 (32.0–79.0)	52.0 (36.3–83.5)	52.0 (38.0–79.0)	0.791
1,25-dihydroxy vitamin D, pg/mL	53.8±23.4	48.1±29.1	52.1±23.9	0.671
Magnesium, mEq/L	1.81±0.41	1.79±0.23	1.80±0.28	0.766
C-reactive protein, mg/dL‡	0.15 (0.06–0.46)	0.22 (0.07–1.10)	0.28 (0.08–1.28)	0.249
TNF-α, pg/mL‡	1.62 (1.10–2.44)	2.02 (1.25–3.27)	1.86 (1.32–2.93)	0.244

BNP indicates B-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease; H2RA, histamine H_2 receptor antagonist; LVEF, left ventricular ejection fraction; Non, non–acid suppressive therapy; NYHA, New York Heart Association; PPI, proton pump inhibitor; PTH, parathyroid hormone; RAS, renin–angiotensin–aldosterone system; TNF-α, tumor necrosis factor α; UIBC, unsaturated iron binding capacity.

*P<0.05 and †P<0.01 vs Non group.

‡Data are presented as median (interquartile range).

(n=328). In patients who had undergone acid suppressive therapy (H2RAs, n=164; PPIs, n=664), the PS for treatment with PPIs was estimated for each patient by logistic regression with the following clinically relevant variables associated with the introduction of PPIs: presence of CKD, anemia, peptic ulcer, esophagitis/gastroesophageal reflux disease, or gastritis and usage of antiplatelet agents and anticoagulants. The PS is the propensity from 0 to 1 to receive treatment, given a set of known variables, and is used to adjust for potential selection bias, confounding, and differences between treatment groups in observational studies.[25] The PS was used to match patients who were administered and those who were not administered PPIs, using a 1:1 nearest neighbor matching algorithm with a caliper width of 0.2 of the pooled standard deviation of the logit of the PS (caliper=0.03), as described previously.[26] The PS-matched data sets were compared using pairwise analysis,[27] and the postmatched cohort (n=328) was defined.

To prepare for potential confounding in the Cox regression analyses, in addition to the above factors to calculate PS, we considered the following clinical factors, which are known to affect the risk of cardiac mortality in HF patients: age, sex, New York Heart Association functional class III or IV, B-type natriuretic peptide, presence of ischemic etiology, reduced left ventricular ejection fraction, hypertension, diabetes mellitus, dyslipidemia, CKD, anemia, atrial fibrillation, hyponatremia (sodium <135 mEq/L), and use of renin–angiotensin–aldosterone system inhibitors, β-blockers, diuretics, and inotropic agents. These factors, which independently predicted mortality with a value of $P<0.05$, were selected in the final adjusted model as predictors of cardiac mortality. The proportional hazards assumption for the model was checked by examining log minus-log transformed data. In addition, the scaled Schoenfeld residuals from the proportional hazards regression model were investigated to assess the proportional hazards assumption.

To assess potential heterogeneity of the effect of PPI treatment on cardiac mortality, we conducted subgroup analyses in the postmatched cohort (n=328). We tested for first-order interactions using multivariable Cox proportional hazards models by entering interaction terms between PPI use and the subgroup variables. Missing values were handled by estimating 1 logistic regression model for each pattern of missing values. A P value <0.05 was considered significant for all comparisons. Analyses were performed using the statistical software package SPSS version 23.0 (IBM Corp).

Results

Among the HF patients in the present study who were discharged (n=1191), 929 (78.0%) were taking antiplatelets and/or anticoagulants at the time of discharge, 367 (30.8%) had upper gastrointestinal tract disease, and 828 (69.5%) had undertaken acid suppressive therapy. The clinical features of the study participants are summarized in Table 1. The PPI group had a higher prevalence of ischemic etiology, dyslipidemia, CKD, anemia, peptic ulcer, esophagitis/gastroesophageal reflux disease, and gastritis and higher usage of β-blockers, diuretics, antiplatelet agents, and anticoagulants. Thus, patients in the PPI group had a variety of reasons for taking PPIs, such as a history of upper gastric intestinal disease or receiving antiplatelet agents and/or anticoagulants. Although sodium was lower in the PPI group, B-type natriuretic peptide, total protein, calcium, vitamin B12, magnesium, C-reactive protein, and tumor necrosis factor α did not differ significantly among groups (Table 1).

In the follow-up period (mean 995 days), 169 cardiac deaths (worsened HF, n=120; ventricular fibrillation, n=35; acute coronary syndrome, n=14) occurred. As shown in Figure 1, cardiac mortality was significantly lower in the PPI group than in the non–acid suppressive therapy and H2RA groups in the prematched cohort (P=0.004) (Figure 1). The Cox proportional hazards model was used to examine the prognostic value of PPIs in the prematched cohort, as shown in Table 2. After adjusting for potential confounding factors, usage of PPIs was an independent predictor of cardiac mortality in the prematched cohort (hazard ratio 0.488, 95% CI 0.310–0.768, P=0.002) (Table 2).

In addition, in the postmatched cohort, cardiac mortality was significantly lower in the PPI group than in the H2RA group (P=0.025) (Figure 2). Interactions between the PPI group and clinically relevant variables were modeled with Cox

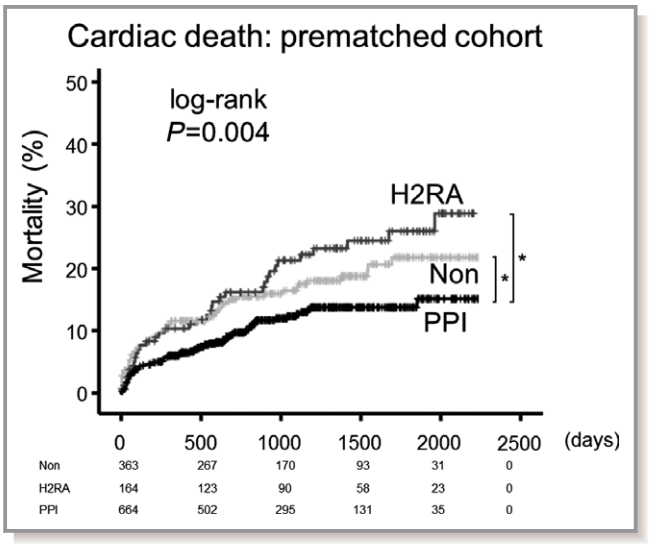

Figure 1. Kaplan–Meier analyses for cardiac death among groups (Non group, n=363; H2RA group, n=164; PPI group, n=664) in the prematched cohort (n=1191). *P<0.05. H2RA indicates histamine H_2 receptor antagonist; Non, non–acid suppressive therapy; PPI, proton pump inhibitor.

Table 2. Cox Proportional Hazards Model of Cardiac Mortality (169 Events, n=1191)

	Univariable			Multivariable		
Risk Factor	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Acid suppressive agents						
H2RA vs Non	1.205	0.795–1.827	0.380	0.855	0.491–1.488	0.579
PPI vs Non	0.653	0.465–0.918	0.014	0.488	0.310–0.768	0.002
Age	1.022	1.010–1.034	<0.001	1.013	0.999–1.028	0.078
Male sex	1.383	0.999–1.914	0.050	…	…	…
NYHA class III or IV	4.839	2.961–7.910	<0.001	4.667	2.504–8.697	<0.001
Ischemic etiology	1.223	0.878–1.704	0.234	…	…	…
Reduced LVEF	2.812	1.984–3.987	<0.001	3.778	2.289–6.238	<0.001
Log BNP	1.685	1.452–1.956	<0.001	1.774	1.233–2.552	0.002
Hyponatremia	1.661	1.086–2.541	0.019	1.198	0.742–1.935	0.459
Hypertension	0.693	0.494–0.973	0.034	0.845	0.563–1.267	0.414
Diabetes mellitus	1.192	0.880–1.614	0.258	…	…	…
Dyslipidemia	0.983	0.687–1.406	0.925	…	…	…
CKD	2.756	1.914–3.97.	<0.001	1.650	1.020–2.645	0.038
Anemia	2.351	1.667–3.315	<0.001	2.111	1.353–3.293	0.001
Atrial fibrillation	1.194	0.881–1.620	0.253	…	…	…
Peptic ulcer	1.049	0.658–1.673	0.841	…	…	…
Esophagitis/GERD	0.763	0.375–1.553	0.456	…	…	…
Gastritis	1.063	0.752–1.502	0.731	…	…	…
RAS inhibitors	0.472	0.345–0.645	<0.001	0.440	0.296–0.654	<0.001
β-blockers	0.650	0.466–0.906	0.014	0.428	0.266–0.689	<0.001
Diuretics	1.370	0.972–1.932	0.066	…	…	…
Inotropic agents	2.978	2.122–4.179	<0.001	2.307	1.470–3.620	<0.001
Antiplatelet agents	0.775	0.572–1.050	0.100	0.863	0.583–1.277	0.460
Anticoagulants	0.649	0.480–0.878	0.005	0.618	0.421–0.908	0.014

BNP indicates B-type natriuretic peptide; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease; H2RA, histamine H_2 receptor antagonist; HR, hazard ratio; LVEF, left ventricular ejection fraction; Non, non–acid suppressive therapy; NYHA, New York Heart Association; PPI, proton pump inhibitor; RAS, renin–angiotensin–aldosterone system.

regression analysis, as shown in Table 3, for cardiac mortality in the postmatched cohort (n=328). In the Cox proportional hazards analysis (Table 3), usage of PPIs was a predictor of cardiac mortality in the postmatched cohort (hazard ratio 0.528, 95% CI 0.298–0.933, *P*=0.028). There was no interaction between PPI use and other important variables (eg, CKD, anemia) that affected cardiac mortality in all subgroups.

After adjusting for PS, the association between PPI usage and cardiac mortality were consistent in both the pre- and postmatched cohorts.

Discussion

To the best of our knowledge, the present study is the first to show the association between PPIs and lower cardiac mortality in hospitalized HF patients based on multiple Cox regression and PS analyses, considering the presence of upper gastrointestinal tract disease and the use of antiplatelet agents and anticoagulants.

Alterations of gastrointestinal function occur in HF patients.[1–3] In congestive HF, there is a low-flow state in the splanchnic microcirculation because of low perfusion, increased venous stasis, and sympathetically mediated arteriolar vasoconstriction, which stimulates O_2 exchange between arterioles and venules, exaggerating the gradient between the villus base and tip.[2] This causes nonocclusive ischemia, resulting in dysfunctional epithelial cells and loss of intestinal barrier function,[2] as well as collagen accumulation and a dysfunctional mucosal barrier in the small intestine.[28] Translocation of bacterial endotoxin has been suggested to play an important role in triggering proinflammatory cytokine

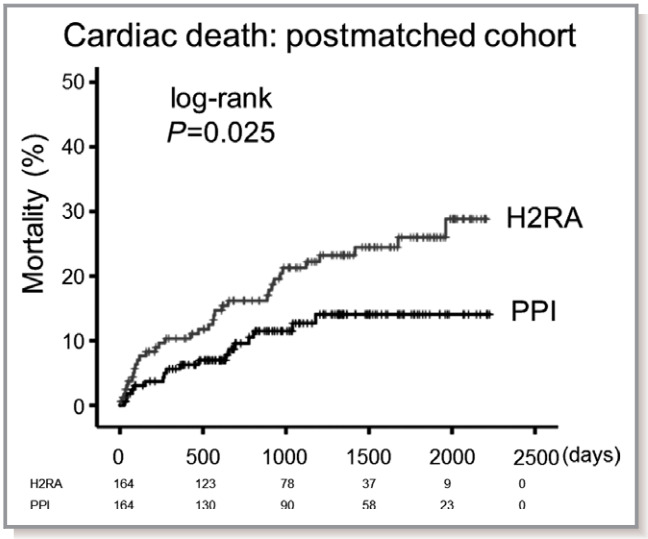

Figure 2. Kaplan–Meier analyses for cardiac death between groups (H2RA group, n=164; PPI group, n=164) in the postmatched cohort (n=328). H2RA indicates histamine H_2 receptor antagonist; PPI, proton pump inhibitor.

activation in HF.[28,29] Furthermore, intramucosal acidosis has been very common in patients who undergo cardiac surgery[30] or in patients in intensive care units,[4] and is associated with inflammation[31] and high mortality.[4] In addition, gastrointestinal bleeding in patients with acute coronary syndrome is associated with higher mortality.[6]

Acid suppressive therapy improves intramucosal acidosis; protects against bacteremia, gastrointestinal bleeding, and anemia; and might be associated with better outcome. Acid suppression and peptic ulcer protection resulting from PPI use are greater than those resulting from H2RA use, and PPIs are recommended over H2RAs for patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants.[7,9] In contrast, despite anxiety about the addition of PPIs to clopidogrel regarding platelet function and cardiovascular outcome, adverse effects of PPI use on clinical outcome in patients on clopidogrel cannot be substantiated.[20,32]

PPIs not only treat upper gastrointestinal tract disease but also cause relaxation of the arteries,[17] reduce atrial fibrillation,[18] and have positive inotropic and negative chronotropic effects.[16] PPIs also have been reported by several in vitro and in vivo studies to have favorable pleiotropic effects, including anti-inflammatory,[13,14,18] antioxidant,[18] antiapoptotic, antiproliferative, and antifibrotic effects.[15] An observational study[33] and a randomized clinical trial[34] both reported minimal to no adverse effects as a result of PPI use in patients with coronary artery disease. In addition, our results are partly consistent with a previous report that showed PPI users had more comorbidities and that the use of PPIs in HF patients is associated with a relative reduction in mortality rates compared with ambulatory patients in whom PPIs are not used (odds ratio 0.87, 95% CI 0.81–0.93).[35] That report,[35] however, did not include data regarding severity of HF or left ventricular ejection fraction, laboratory data including B-type natriuretic peptide, endoscopic findings, and information about the specific cause of death, unlike the results of the current study.

It has recently been reported that long-term use of PPIs is associated with adverse effects,[19] including endothelial senescence,[36] CKD,[37,38] and malabsorption of magnesium, calcium, iron, and vitamin B12, resulting in hypomagnesemia,[39] anemia, fractures,[40] dementia,[41] and enteric infection.[42] These side effects will vary according to patient background (eg, age, comorbidity) and the observation period of study participants. In addition, although use of either PPI or H2RA is associated with short-term risk of adverse cardiac events in patients aged ≥66 years who are hospitalized for acute myocardial infarction within 12 weeks following initiation of PPI,[43] appropriate use of PPI is not denied in patients with coronary artery disease.[43] Among the present study's participants, although the PPI group had a higher prevalence of CKD and anemia, the levels of ferritin, unsaturated iron binding capacity, vitamin B12, corrected calcium, intact parathyroid hormone, 1,25-dihydroxy vitamin D, magnesium, C-reactive protein, and tumor necrosis factor α did not differ significantly among the groups. PPI side effects were not evident in our study participants.

Limitations and Study Strengths

Our study has several strengths and differs from previous studies[11,12,19] in many ways. The present study is the first to show the association of PPIs with lower cardiac mortality in HF patients, considering the presence of upper gastrointestinal tract disease and the use of antiplatelet agents and anticoagulants, with a relatively long follow-up period (≈3 years). In addition, Japan's health insurance system requires objective testing such as endoscopy and/or purpose for prevention of upper gastrointestinal tract disease by antiplatelet agents and anticoagulants for prescribing acid suppressive therapy and may require more adequate indication than those reported in studies in Western countries based on over-the-counter systems.

The present study has some potential limitations. First, our study is a nonrandomized and observational study at a single institution, so the sample size was relatively small and potential biases and confounders may be responsible for our findings. Although PS analyses are powerful, they are inherently limited by the number and accuracy of the variables evaluated. Importantly, we cannot rule out residual confounding from unknown or unmeasured variables. Second, we have assessed this study using variables during hospitalization only, without consideration of changes in medical parameters or

Table 3. Subgroup Analysis for Cardiac Mortality: PPI Versus H2RA Use in Postmatched Cohort

Factor	Subgroup	n	HR	95% CI	*P* Value	Interaction *P* Value
Total		328	0.528	0.298–0.933	0.028	…
Age, y	≥70	183	0.593	0.290–1.216	0.154	0.549
	<70	145	0.384	0.142–1.041	0.060	
Sex	Male	166	0.486	0.205–1.153	0.102	0.897
	Female	162	0.535	0.245–1.165	0.115	
LVEF	Reduced	175	0.588	0.308–1.125	0.109	0.737
	Preserved	153	0.459	0.138–1.531	0.205	
Ischemic etiology	+	84	0.490	0.172–1.394	0.181	0.881
	–	244	0.563	0.284–1.115	0.099	
CKD	+	236	0.437	0.228–0.839	0.013	0.390
	–	92	0.806	0.227–2.865	0.738	
Anemia	+	173	0.549	0.272–1.106	0.093	0.921
	–	155	0.483	0.181–1.288	0.146	
Peptic ulcer	+	23	0.432	0.044–4.200	0.469	0.895
	–	305	0.534	0.296–0.963	0.037	
Esophagitis/GERD	+	26	0.769	0.068–8.687	0.831	0.635
	–	302	0.508	0.280–0.923	0.026	
Gastritis	+	77	0.403	0.121–1.339	0.138	0.643
	–	251	0.570	0.298–1.090	0.089	
RAS inhibitors	+	250	0.340	0.161–0.718	0.005	0.124
	–	78	0.937	0.413–2.701	0.504	
β-blockers	+	250	0.422	0.216–0.823	0.011	0.135
	–	78	0.923	0.375–2.560	0.436	
Diuretics	+	225	0.567	0.305–1.055	0.073	0.477
	–	103	0.302	0.064–1.424	0.130	
Antiplatelet agents	+	175	0.579	0.260–1.291	0.182	0.745
	–	153	0.492	0.216–1.118	0.090	
Anticoagulants	+	204	0.867	0.388–1.938	0.728	0.216
	–	124	0.395	0.160–0.975	0.044	

CKD indicates chronic kidney disease; GERD, gastroesophageal reflux disease; H2RA, histamine H_2 receptor blocker; HR, hazard ratio; LVEF, left ventricular ejection fraction; PPI, proton pump inhibitor; RAS, renin–angiotensin–aldosterone system.

postdischarge treatment. Changes in acid suppressive therapy were not considered, and there might be a little crossover among the groups. Third, the causal relationship and mechanism of our results could not be explained because this study was only observational. Fourth, because there are differences in drug metabolism of PPIs caused by genotype (eg, CYP2C19),[44] our results may not be fully generalized. Fifth, we cannot completely deny the possibility that extended use of PPIs causes adverse effects (eg, endothelial senescence, renal dysfunction, dementia, and fractures). For these reasons, the results of our study should be viewed as preliminary. Further clinical trials for HF using acid suppressive agents are required with a larger population and/or randomization.

Conclusions

The risk–benefit calculus for the appropriate use of PPI is important. Our findings suggest that the use of PPIs may be associated with lower cardiac mortality than without acid suppressive therapy or H2RAs in HF patients. Although we do not recommend the routine use of PPIs in HF patients without considering each patient's clinical background (eg, presence

of upper gastrointestinal tract disease and usage of other medication), PPI use is beneficial for a considerable number of patients.

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Disclosures

None.

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