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ORIGINAL RESEARCH

Use of histamine H_2 receptor antagonists and outcomes in patients with heart failure: a nationwide population-based cohort study

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Background: Histamine H_2 receptor activation promotes cardiac fibrosis and apoptosis in mice. However, the potential effectiveness of histamine H_2 receptor antagonists (H2RAs) in humans with heart failure is largely unknown. We examined the association between H2RA initiation and all-cause mortality among patients with heart failure.

Methods: Using Danish medical registries, we conducted a nationwide population-based active-comparator cohort study of new users of H2RAs and proton pump inhibitors (PPIs) after first-time hospitalization for heart failure during the period 1995–2014. Hazard ratios (HRs) for all-cause mortality and hospitalization due to worsening of heart failure, adjusting for age, sex, and time between heart failure diagnosis and initiation of PPI or H2RA therapy, index year, comorbidity, cardiac surgery, comedications, and socioeconomic status were computed based on Cox regression analysis.

Results: Our analysis included 42,902 PPI initiators (median age 78 years, 46% female) and 3,296 H2RA initiators (median age 76 years, 48% female). Mortality risk was lower among H2RA initiators than PPI initiators after 1 year (26% vs 31%) and 5 years (60% vs 66%). In multivariable analyses, the 1-year HR was 0.80 (95% CI, 0.74–0.86) and the 5-year HR was 0.85 (95% CI, 0.80–0.89). These findings were consistent after propensity score matching and for ischemic and nonischemic heart failure, as for sex and age groups. The rate of hospitalization due to worsening of heart failure was lower among H2RA initiators than PPI initiators.

Conclusion: In patients with heart failure, H2RA initiation was associated with 15%–20% lower mortality than PPI initiation.

Keywords: heart failure, epidemiology, histamine H_2 receptor, mortality

Introduction

Despite improvements in treatment and quality of care, heart failure remains a leading cause of morbidity and mortality worldwide.[1,2] Heart failure pathophysiology is characterized by a complex interplay between several neurohormonal pathways, including involvement of adrenergic receptors.[3] Moreover, H_2 receptor activation promotes cardiac fibrosis and apoptosis in mice subjected to transverse aortic constriction,[4] suggesting that histamine H_2 signaling could be involved in the pathophysiology of heart failure. Recently, the Multi-Ethnic Study of Atherosclerosis cohort study demonstrated that histamine H_2 receptor antagonist (H2RA) treatment was associated with 62% reduced risk of new-onset heart failure.[5] In addition, fewer age-related left-heart morphology changes were observed among H2RA-treated than among H2RA-untreated patients.[5]

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These findings have prompted investigation of the potential effectiveness of this antiulcer agent in treating patients with heart failure, but the evidence remains sparse. In a small randomized study among heart failure patients, H2RA treatment was associated with improved New York Heart Association (NYHA) functional class and reverse ventricular remodeling, compared to an antiulcer drug without a histamine H_2 blockade.[6] The impact of H2RA use on heart failure mortality is poorly understood and warrants further investigation. We therefore examined the association between H2RA initiation and mortality in a Danish cohort of heart failure patients.

Methods

Design and setting

We used Danish nationwide population-based health care databases to conduct a cohort study of new users[7] of H2RAs and proton pump inhibitors (PPIs) following hospitalization for heart failure. An active-comparator design was employed to account for potential confounding by the underlying disease for which H2RAs/PPIs were prescribed.[7] Denmark has a tax-supported health care system that guarantees unfettered access to medical care for all residents, as well as partial reimbursement to patients for prescribed drugs, including H2RAs and PPIs. All Danish residents are assigned a unique, permanent civil registration number that allows accurate linkage of individual-level data among national registries.[8]

Heart failure patients

We assembled a cohort of all patients hospitalized with first-time heart failure. The cohort included patients with primary and secondary diagnoses registered in the Danish National Patient Registry during 1 July 1995 through 1 February 2014. The Danish National Patient Registry has maintained records on hospital admissions and discharges since 1977, including dates and diagnoses coded according to the "International Classification of Diseases, Eighth Revision" (ICD-8) through 1993 and "Tenth Revision" (ICD-10) thereafter. Outpatient clinic visits have been recorded since 1995. Heart failure patients treated in the outpatient setting were included in the cohort at the time of their first inpatient hospitalization for heart failure.[9] The positive predictive value of the heart failure diagnosis in the Danish National Patient Registry, using information in the medical record as reference, is around 80%.[9,10]

For validation purposes, we repeated our analyses in a subset of heart failure patients enrolled in the Danish Heart Failure Registry.[11] Patients with ICD-10 codes for heart failure are enrolled in the Danish Heart Failure Registry only if they fulfill the European Society of Cardiology's definition of heart failure.[11] Registrations are supervised by a local senior cardiologist. Regular structured audits of Registry data are conducted to ensure high data quality.[11] The Danish Heart Failure Registry, launched in February 2003, is a nationwide registry aimed at monitoring and improving the quality of care for patients with heart failure.

H2RA and PPI initiators

We used the Danish National Prescription Registry to identify patients who initiated H2RA or PPI treatment following their first hospitalization for heart failure.[12] H2RA or PPI initiation could occur at any time after the hospitalization for heart failure. The Prescription Registry has recorded all redeemed prescriptions according to the "Anatomical Therapeutical Chemical" (ATC) classification system since 1995. We included only the first prescription per individual. The date of prescription redemption was considered the index date. To minimize any influence of previous PPI or H2RA use on heart failure severity as of the index date, we excluded patients who had received a prescription for a PPI or H2RA within 2 years before their first-time hospitalization for heart failure. Patients who initiated a H2RA and a PPI on the same day were also excluded.

We did not use a time-dependent exposure design because the duration of a potential carry-over effect of H2RAs in preventing heart failure progression and mortality is unknown. Thus, all patients were assigned to an exposure group based on the drug they first initiated (H2RA or PPI).

Outcomes

Our primary outcome was all-cause mortality. To ascertain mortality, we used the Danish Civil Registration System, which has recorded dates of death and emigration with daily electronic updates since 1968.[8] To estimate cardiovascular and noncardiovascular mortality, we also examined immediate and underlying causes of death based on data from the Danish Registry of Causes of Death (data available until 31 December 2012).[13] The secondary outcome was hospitalization due to worsening of heart failure, which was defined as the first primary heart failure inpatient admission after the index date.

Covariables

We assessed several covariables, including age group (<60 years, 60–69 years, 70–79 years, and 80+ years), index year (1995−1999, 2000−2004, 2005−2009, and 2010−2014), sex, and time from heart failure hospital admission date until

first prescription of a H2RA or PPI (<3 months, ≥3 to <6 months, ≥6 to <12 months, ≥12 to <18 months, ≥18 to <24 months, ≥24 to <30 months, and ≥30 months). In addition, we retrieved information on the following heart failure risk factors and comorbidities diagnosed from 1977 until the index date: coronary artery disease (defined as angina pectoris or myocardial infarction), valvular heart disease, hypertension, atrial fibrillation or atrial flutter, venous thromboembolism, stroke, intermittent claudication, diabetes mellitus (defined as a diabetes diagnosis or a redeemed prescription of antidiabetic drug), obesity, cancer within 1 year, chronic pulmonary disease, chronic kidney disease, dementia, depression (defined as a depression diagnosis or a redeemed prescription of antidepressants), illicit drug abuse/alcohol abuse/smoking, anemia, peptic ulcer disease, gastroesophageal reflux disease, liver disease, alcoholism-related disorders, musculoskeletal disorders, and inflammatory bowel disease. We also collected information on coronary artery bypass graft surgery and percutaneous coronary intervention within the preceding 90 days. Data on comorbidity and surgery were obtained from the Danish National Patient Registry.[9] As well, we obtained information from the Danish National Prescription Registry on redeemed prescriptions for the following comedications within 90 days prior to the index date: beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor II blockers (ACEIs/ARBs), diuretics, statins, nonsteroidal anti-inflammatory drugs, antithrombotics, benzodiazepines, and opioids.[12] Data on socioeconomic variables, including gross income and employment, were obtained from the Integrated Database for Labour Market Research for the index year or for previous years, depending on data availability.[14] For the subset of patients enrolled in the Danish Heart Failure Registry, we retrieved information on left ventricular ejection fraction group, NYHA functional class, alcohol intake, and smoking habits. All ATC and ICD codes used in the study are provided in Table S1.

Statistical analyses

All patients were followed from their index date until date of death, date of emigration, or 1 September 2014, whichever came first. Patient characteristics were tabulated for PPI and H2RA initiators, and for patients shifting treatment between H2RAs and PPIs during follow-up. We obtained information on H2RA exposure, including total number of prescriptions, the cumulative duration of H2RA treatment (calculated as the number of pills per prescription assuming a daily dose of 300 mg), and the proportion of patients changing exposure group during the first year of follow-up.

We computed all-cause mortality risks and used the Kaplan–Meier method to display survival curves for H2RA and PPI initiators. Unadjusted and adjusted hazard ratios (HRs) were computed based on Cox proportional hazard models. In the multivariable analysis, we adjusted for the potential confounders listed in Table 1 (using knowledge-based variable selection). In analyses of causes of death and of hospitalization due to worsening of heart failure, competing causes

Table 1 Baseline characteristics of the two study cohorts (values are numbers (%) unless stated otherwise)

Baseline characteristics	Histamine H_2 receptor antagonist initiators	Proton pump inhibitor initiators
Total study population	3,296 (100)	42,902 (100)
Median age, years (25th–75th percentile)	76 (68–83)	78 (69–85)
Age groups		
<60 years	395 (12)	4,423 (10)
60–69 years	559 (17)	7,253 (17)
70–79 years	1,179 (36)	13,057 (30)
80+ years	1,163 (35)	18,169 (42)
Index-year groups		
1995–1999	1,558 (47)	4,039 (9)
2000–2004	1,307 (40)	11,921 (28)
2005–2009	388 (12)	15,055 (35)
2010–2014	43 (1)	11,887 (28)
Female	1,593 (48)	19,721 (46)
Time from heart failure diagnosis to first prescription		
Median, days (25th–75th percentile)	297 (71–801)	447 (62–1346)
<3 months	933 (28)	12,319 (29)
≥3 to <6 months	352 (11)	3,255 (8)
≥6 to <12 months	522 (16)	4,355 (10)
≥12 to <18 months	328 (10)	3,146 (7)
≥18 to <24 months	259 (8)	2,620 (6)
≥24 to <30 months	195 (6)	2,309 (5)
≥30 months	707 (21)	14,898 (35)
Heart failure risk factors and comorbidity		
Coronary artery disease	1,659 (50)	23,090 (54)
Valvular heart disease	387 (12)	6,499 (15)
Hypertension	854 (26)	17,489 (41)
Atrial fibrillation or atrial flutter	930 (28)	15,966 (37)
Venous thromboembolism	129 (4)	1,783 (4)
Stroke	359 (11)	6,461 (15)
Intermittent claudication	74 (2)	2,089 (5)
Diabetes mellitus	581 (18)	9,761 (23)
Obesity	228 (7)	3,588 (8)
Cancer within 1 year	197 (6)	3,592 (8)
Chronic pulmonary disease	822 (25)	11,040 (26)

(*Continued*)

Table 1 (*Continued*)

Baseline characteristics	Histamine H_2 receptor antagonist initiators	Proton pump inhibitor initiators
Chronic kidney disease	148 (5)	4,132 (10)
Dementia	82 (3)	1,652 (4)
Depression	834 (25)	14,525 (34)
Illicit drug abuse/alcohol abuse/smoking	131 (4)	2,611 (6)
Peptic ulcer disease	247 (7)	5,274 (12)
Gastroesophageal reflux disease	95 (3)	1,367 (3)
Anemia	311 (9)	7,392 (17)
Liver disease	68 (2)	1,091 (3)
Alcoholism-related disorders	91 (3)	1,399 (3)
Musculosketal disorders	1,168 (35)	19,552 (46)
Inflammatory bowel disease	25 (1)	545 (1)
Cardiac surgery within past 90 days		
Coronary artery bypass grafting	177 (5)	947 (2)
Percutaneous coronary intervention	46 (1)	1,377 (3)
Comedication within past 90 days		
Beta blockers	838 (25)	15,684 (37)
ACEI/ARBs	1,341 (41)	19,213 (45)
Diuretics	2,379 (72)	27,511 (64)
Statins	428 (13)	10,324 (24)
NSAIDs	602 (18)	7,504 (17)
Antithrombotics	1,564 (47)	23,889 (56)
Benzodiazepines	531 (16)	4,522 (11)
Opioids	632 (19)	9,952 (23)
Income		
Low	1,591 (48)	9,946 (23)
Intermediate	687 (21)	10,851 (25)
High	504 (15)	11,031 (26)
Very high	508 (15)	11,032 (26)
Unknown	6 (0.18)	42 (0.10)
Employment		
Employed	343 (10)	4,468 (10)
Early retirement, receiving sickness/incapacity/early retirement	41 (1)	554 (1)
Unemployed	440 (13)	4,852 (10)
State pensioner	2,468 (75)	32,952 (77)
Unknown	4 (0.12)	76 (0.18)

Note: All the abovementioned covariables were included in the regression models.
Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor II blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

of death and death, respectively, were treated as censored and we estimated incidence rates per 1,000 person-years. We also computed each patient' propensity score using a multivariable logistic regression including the covariables presented in Table 1, and we matched each patient initiating H2RA to a patient initiating PPI in a 1:1 ratio using nearest neighbor random-order caliper pair-matching without replacement using caliper 0.2 times the standard deviation of logit(ps) and matching on logit(ps). Covariables were balanced after propensity score matching as evidenced by an absolute standardized difference below 0.1 for each covariate. Using the propensity score-matched cohorts, we estimated unadjusted HRs using stratified Cox regression analysis and generated a Kaplan–Meier curve.

We assessed proportionality of hazards using log–log plots and found no evidence that the assumption was violated within the analyzed follow-up periods. Because the effectiveness of pharmacological treatments may vary by subgroup, we stratified our main analyses by presence/absence of ischemic heart failure (defined as a history of coronary heart disease or myocardial infarction), receipt/nonreceipt of ACEIs/ARBs or beta blockers, sex, age group, and the remaining covariables described earlier.

In sensitivity analyses, we further evaluated the robustness of our estimates for the primary outcome. First, to reduce potential residual confounding by alcohol abuse and smoking, which are underreported in the Danish National Patient Registry,[15] we repeated our analysis, adjusting for these covariables using more complete data from the Danish Heart Failure Registry cohort. Second, we extended the Cox regression model, adjusting for gastroscopy within 6 months (yes or no), which to some extent may reflect gastric ulcer severity (data available from 1997 onward). Third, to reduce the amount of crossover between PPI and H2RA use, we assigned all patients to one of three exposure groups based on PPI, H2RA, or both PPI and H2RA initiation within the first year after the heart failure hospital admission date. For this analysis, patients were required to survive for 1 year, and the follow-up period began 1 year after the heart failure admission date to avoid immortal time bias. Fourth, to ensure that we examined only patients receiving longer-term treatment, we excluded those with only one prescription of H2RA or PPI in the cohort of 1-year survivors. Fifth, we also restricted our main analysis to patients whose second prescription for the same drug was dispensed within 3 months after the index prescription and then started follow-up at the time of the second prescription. Sixth, in the cohort of 1-year survivors, we examined the impact on mortality in the second year after the heart failure admission date, comparing patients with no H2RA prescriptions to those with 1, 2, 3, and ≥4 H2RA prescriptions during the first year. Finally, potential cohort effects and differences in heart failure stages were evaluated in analyses stratified by time period (1995–1999, 2000–2004,

2005–2009, and 2010–2014) and time since heart failure admission date.

All analyses were performed using STATA version 14.1. The study was approved by the Danish Data Protection Agency (record number: 1-16-02-268-14). Approval from an ethical committee or informed consent from patients is not required for registry-based studies in Denmark.

Results

We identified a total of 205,719 heart failure patients. Of these, 159,521 patients were not included in the study: 55,250 who were prevalent users of PPIs or H2RAs; 104,116 who never initiated a PPI or an H2RA; 11 who initiated a PPI and an H2RA on the same day; 135 with negative follow-up time; and 9 lacking data on age. This left 3296 H2RA initiators and 42,902 PPI initiators for inclusion in our analyses (Figure S1). H2RA initiators were slightly younger (76 years vs 78 years) and more likely to have an early index period (Table 1). H2RA users also had a shorter interval between their heart failure admission date and index date. Compared with PPI initiators at the time of the index date, H2RA initiators had fewer heart failure risk factors and comorbid conditions, received ACEIs/ARBs or beta blockers less often and had lower income. Median follow-up time was 3.3 years (25th–75th percentile: 1.8 years) for H2RA initiators and 2.1 years (25th–75th percentile: 0.6–4.7 years) for PPI initiators. In the Danish Heart Failure Registry cohort, the PPI (n=7,243) and H2RA (n=200) cohorts were comparable in terms of left ventricular ejection fraction and NYHA class on the hospital admission date for heart failure (Table S2).

Exposure data

Of the 3,296 patients initiating H2RAs, 1,664 (50%) redeemed one prescription, and 1,632 (50%) patients redeemed two or more prescriptions (Table S3). Cumulative duration of treatment was <30 days for 964 (29%) patients, 30–49 days for 640 (19%) patients, 50–149 days for 837 (25%) patients, and ≥150 days for 855 (26%) patients (Table S3). Among H2RA initiators, 746 (23%) patients also had a subsequent prescription for a PPI within the first year of follow-up. Median time from H2RA initiation to PPI initiation was 439 days (25th–75th percentile: 84–1,322 days). Among PPI initiators, 525 (1%) had a subsequent prescription for an H2RA during the first year of follow-up, and median time from PPI initiation until H2RA initiation was 302 days (25th–75th percentile: 89–742 days) (Table S4). H2RA users who shifted to PPI use during follow-up were slightly younger, but otherwise had fairly similar patient characteristics as members of the H2RA cohort who did not change their treatment regime (Table S5).

Outcomes

All-cause mortality risk was lower among H2RA initiators than among PPI initiators during the first-year following treatment onset (26% vs 31%), and also during the first 5 years (60% vs 66%) (Figures 1 and S2, Table 2). In multivariable analyses, the HR for all-cause mortality was 0.80 (95% CI, 0.74–0.86) within 1 year, 0.85 (95% CI, 0.80–0.89) within 3 years, and 0.84 (95% CI, 0.80–0.88) within 5 years (Table 2). Cause-specific mortality analyses (immediate death causes) yielded similar estimates for noncardiovascular mortality (1-year adjusted HR, 0.75; 95% CI, 0.67–0.84) and cardiovascular mortality (1-year adjusted HR, 0.76; 95% CI, 0.67–0.87) (Table 3). Results were similar in analyses of underlying death causes (data not shown).

Results for all-cause mortality were consistent across subgroups of patients with nonischemic heart failure and ischemic heart failure, and patients receiving/not receiving ACEIs/ARBs and beta blockers, for both sexes, in all age groups (Figure 2) and in prespecified subgroups (Table S6). The associations were unchanged when the analyses were repeated for the heart failure patients enrolled in the Danish Heart Failure Registry (n=7,443, 1-year adjusted HR, 0.84; 95% CI, 0.55–1.31) (Table S7). The associations remained broadly consistent in all sensitivity analyses (Tables S7–S9), although there was low precision for some of the estimates.

The rate of hospitalization due to worsening of heart failure was lower in H2RA initiators than among PPI initiators (Table 4).

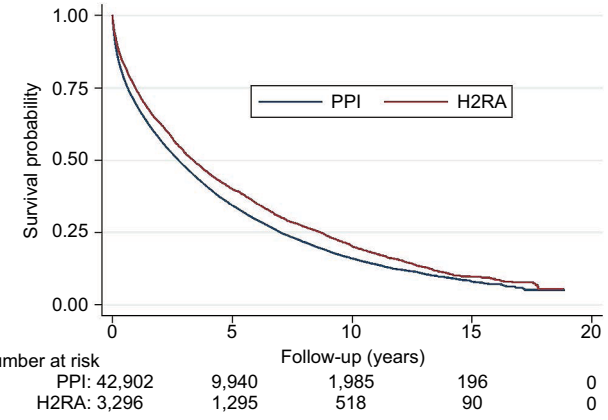

Figure 1 Kaplan–Meier survival curve for initiators of proton pump inhibitors and histamine H_2 receptor antagonists.
Abbreviations: H2RA, histamine H_2 receptor antagonist; PPI, proton pump inhibitor.

Table 2 Association between histamine H_2 receptor antagonists and all-cause mortality by follow-up interval

Follow-up interval	No. of events	Mortality risk, % (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	HR after propensity score matching (95% CI)
1 year					
PPI	13,190	30.8 (30.4–31.3)	Reference	Reference	Reference
H2RA	843	25.6 (24.1–27.1)	0.80 (0.74–0.85)	0.80 (0.74–0.86)	0.78 (0.71–0.86)
3 years					
PPI	21,403	51.9 (51.4–52.4)	Reference	Reference	Reference
H2RA	1,552	47.2 (45.5–48.9)	0.86 (0.81–0.90)	0.85 (0.80–0.89)	0.85 (0.79–0.92)
5 years					
PPI	25,835	65.6 (65.1–66.1)	Reference	Reference	Reference
H2RA	1,964	59.8 (58.1–61.5)	0.85 (0.81–0.89)	0.84 (0.80–0.88)	0.86 (0.79–0.92)

Notes: *Adjusted by age group, sex, index-year categories, time from heart failure diagnosis until first prescription for PPI or H2RA, coronary artery disease, valvular heart disease, hypertension, atrial fibrillation or atrial flutter, venous thromboembolism, stroke, intermittent claudication, diabetes mellitus, obesity, cancer within 1 year, chronic pulmonary disease, chronic kidney disease, dementia, depression, illicit drug abuse/alcohol abuse/smoking, peptic ulcer disease, gastroesophageal reflux disease, anemia, chronic liver disease, alcoholism-related disorders, musculoskeletal disorders, inflammatory bowel disease, cardiac surgery within past 90 days (coronary artery bypass graft surgery and percutaneous coronary intervention), comedication within past 90 days (beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor II blockers, diuretics, statins, NSAIDs, antithrombotics, benzodiazepines, and opioids), income, and employment.

Abbreviations: CI, confidence interval; HR, hazard ratio; H2RAs, histamine H_2 receptor antagonists; PPIs, proton pump inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 3 Association between histamine H_2 receptor antagonists and cause-specific mortality by follow-up interval

Follow-up interval	Cardiovascular mortality			HR after propensity score matching (95% CI)	Noncardiovascular mortality			HR after propensity score matching (95% CI)
	Rate per 1,000 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*		Rate per 1,000 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	
1 year								
PPI	125 (121–129)	Reference	Reference	Reference	232 (227–238)	Reference	Reference	Reference
H2RA	99 (88–112)	0.81 (0.72–0.92)	0.76 (0.67–0.87)	0.80 (0.68–0.96)	142 (129–157)	0.63 (0.57–0.69)	0.75 (0.67–0.84)	0.70 (0.61–0.82)
3 years								
PPI	88 (86–90)	Reference	Reference	Reference	165 (162–168)	Reference	Reference	Reference
H2RA	73 (67–79)	0.86 (0.79–0.95)	0.83 (0.75–0.91)	0.82 (0.71–0.95)	109 (101–117)	0.69 (0.64–0.74)	0.81 (0.75–0.87)	0.78 (0.69–0.88)
5 years								
PPI	80 (78–81)	Reference	Reference	Reference	151 (148–153)	Reference	Reference	Reference
H2RA	65 (60–70)	0.87 (0.80–0.94)	0.82 (0.75–0.89)	0.81 (0.71–0.93)	99 (93–106)	0.70 (0.65–0.74)	0.80 (0.75–0.86)	0.79 (0.71–0.0.89)

Notes: *Adjusted by age group, sex, index-year categories, time from heart failure diagnosis until first prescription for PPI or H2RA, coronary artery disease, valvular heart disease, hypertension, atrial fibrillation or atrial flutter, venous thromboembolism, stroke, intermittent claudication, diabetes mellitus, obesity, cancer within 1 year, chronic pulmonary disease, chronic kidney disease, dementia, depression, illicit drug abuse/alcohol abuse/smoking, peptic ulcer disease, gastroesophageal reflux disease, anemia, chronic liver disease, alcoholism-related disorders, musculoskeletal disorders, inflammatory bowel disease, cardiac surgery within past 90 days (coronary artery bypass graft surgery and percutaneous coronary intervention), comedication within past 90 days (beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor II blockers, diuretics, statins, NSAIDs, antithrombotics, benzodiazepines, and opioids), income, and employment.

Abbreviations: CI, confidence interval; HR, hazard ratio; H2RAs, histamine H_2 receptor antagonists; PPIs, proton pump inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

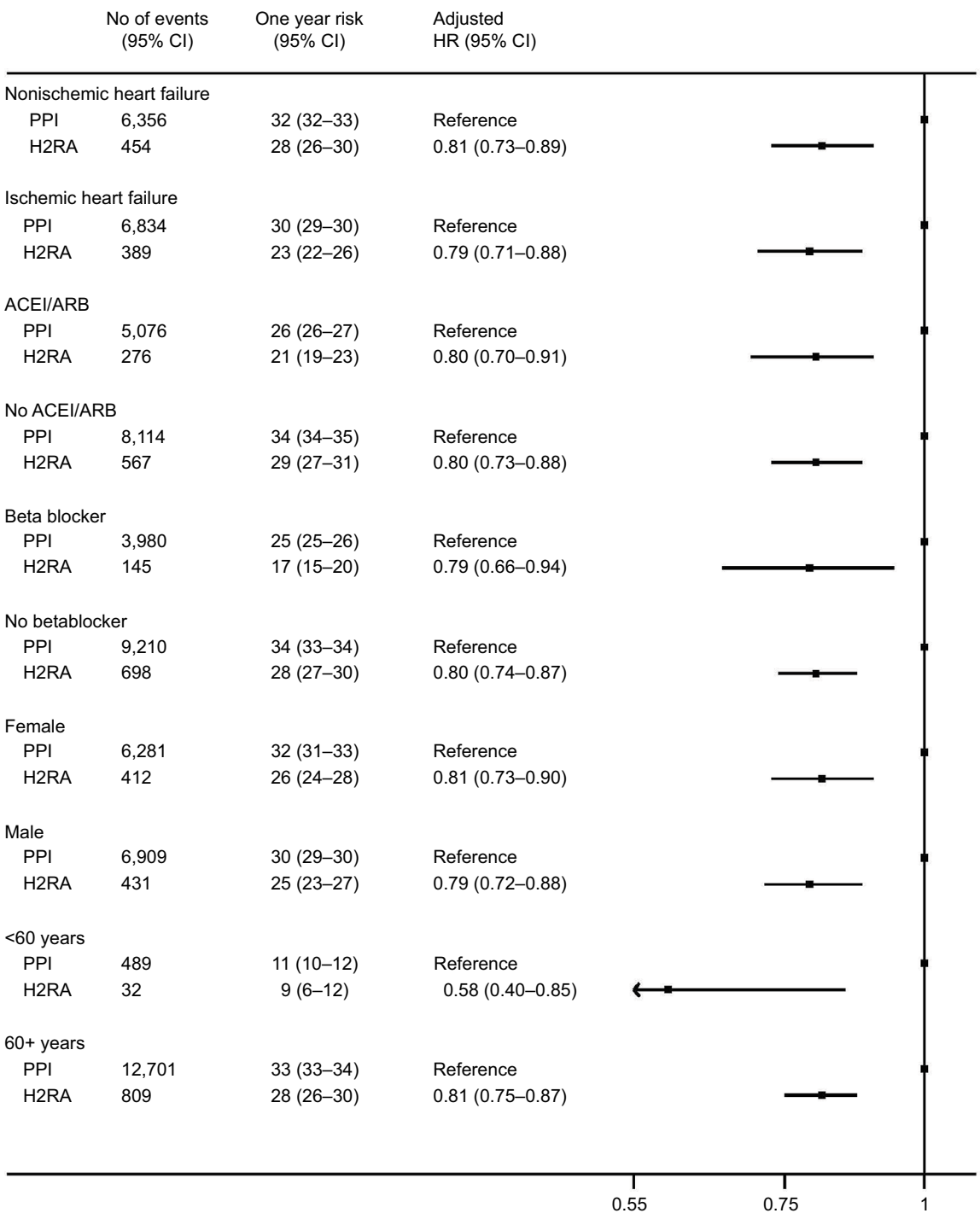

Figure 2 One-year all-cause mortality in subgroups of heart failure patients, comparing new users of H2RA and new users of PPIs.

Notes: Adjusted by age group, sex, index-year categories, time from heart failure diagnosis until first prescription for PPI or H2RA, coronary artery disease, valvular heart disease, hypertension, atrial fibrillation or atrial flutter, venous thromboembolism, stroke, intermittent claudication, diabetes mellitus, obesity, cancer within 1 year, chronic pulmonary disease, chronic kidney disease, dementia, depression, illicit drug abuse/alcohol abuse/smoking, peptic ulcer disease, gastroesophageal reflux disease, anemia, chronic liver disease, alcoholism-related disorders, musculoskeletal disorders, inflammatory bowel disease, cardiac surgery within past 90 days (coronary artery bypass graft surgery and percutaneous coronary intervention), comedication within past 90 days (beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor II blockers, diuretics, statins, NSAIDs, antithrombotics, benzodiazepines, and opioids), income, and employment (except the stratifying variable).

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor II blocker; H2RA, histamine H_2 receptor antagonist; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 4 Association between H2RA and hospitalization due to worsening of heart failure by follow-up interval

Follow-up interval	No. of events	Rate per 1,000 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	HR after propensity score matching (95% CI)
1 year					
PPI	1775	144 (140–148)	Reference	Reference	Reference
H2RA	138	139 (126–154)	0.98 (0.88–1.10)	0.86 (0.76–0.96)	0.85 (0.73–1.00)
3 years					
PPI	4171	94 (92–96)	Reference	Reference	Reference
H2RA	296	88 (80–95)	0.97 (0.89–1.06)	0.85 (0.77–0.93)	0.86 (0.75–0.98)
5 years					
PPI	5821	82 (80–84)	Reference	Reference	Reference
H2RA	422	74 (69–80)	0.97 (0.89–1.05)	0.85 (0.78–0.93)	0.84 (0.74–0.96)

Note: *Adjusted by age group, sex, index-year categories, time from heart failure diagnosis until first prescription for PPI or H2RA, coronary artery disease, valvular heart disease, hypertension, atrial fibrillation or atrial flutter, venous thromboembolism, stroke, intermittent claudication, diabetes mellitus, obesity, cancer within 1 year, chronic pulmonary disease, chronic kidney disease, dementia, depression, illicit drug abuse/alcohol abuse/smoking, peptic ulcer disease, gastroesophageal reflux disease, anemia, chronic liver disease, alcoholism-related disorders, musculoskeletal disorders, inflammatory bowel disease, cardiac surgery within past 90 days (coronary artery bypass graft surgery and percutaneous coronary intervention), comedication within past 90 days (beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor II blockers, diuretics, statins, NSAIDs, antithrombotics, benzodiazepines, and opioids), income, and employment.

Abbreviations: CI, confidence interval; HR, hazard ratio; H2RAs, histamine H_2 receptor antagonists; PPIs, proton pump inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

Propensity score matching yielded results comparable to that of the main analysis (Tables 2–4, Figure S2).

Discussion

In our population-based cohort of heart failure patients, during 5 years of follow-up, H2RA initiators had 15%–20% lower mortality and hospitalization due to worsening of heart failure than PPI initiators. This was consistent across subgroups and in sensitivity analyses.

Our study builds on prior research, by providing population-based data on a large cohort of heart failure patients. Our findings extend those of a small Japanese combined cross-sectional and randomized study of chronic heart failure patients in NYHA functional classes II–III enrolled during 2002−2004.[6] In the cross-sectional study, 159 prevalent famotidine (H2RA) users were age-, gender-, and indication-matched to 159 controls treated with antiulcer drugs other than H2RAs. Plasma B-type natriuretic peptide (BNP) levels were lower, left ventricular dimensions were smaller, and NYHA functional class was more favorable in the famotidine group than in the control group, but the cross-sectional design did not permit any firm conclusions. In the randomized part of the study, 50 patients were assigned to treatment with famotidine or teprenone (antiulcer drug different from PPIs and H2RAs) for 24 weeks. Compared with patients assigned to receive teprenone, those assigned to receive famotidine had improved NYHA functional class ($p<0.05$) and plasma BNP levels (183 pg/mL vs 285 pg/mL, $p<0.05$); lower left ventricular end-diastolic lengths (57 mm vs 64 mm, $p<0.05$) and end-systolic lengths (47 mm vs 55 mm, $p<0.05$); and a lower frequency of readmission due to worsening of heart failure (4% vs 24%, $p<0.05$). More recently, a Japanese cohort study of 1,191 heart failure patients indicated that both use of H2RA and PPI may be associated with a lower rate of cardiac mortality compared with nonuse, although with relatively imprecise estimates (adjusted HR, 0.86; 95% CI, 0.49−1.49 for H2RA and adjusted HR, 0.49; 95% CI, 0.31–0.77 for PPI).[16] In light of these and our findings, additional data bearing on the unintended effects of use of H2RAs clearly are required.

Several mechanisms may underlie the potential beneficial effects of histamine blockade in heart failure patients. Mast cells are present in cardiomyocytes that release renin and histamine.[17] A pig study showed that mast cell-derived renin promotes angiotensin formation and norepinephrine release, and also induces arrhythmias. Mast cell-stabilizing agents attenuated this process,[18] indicating a potentially reversible pathophysiological pathway. Similar to norepinephrine and beta-adrenergic receptors, histamine H_2 receptors are coupled to G-proteins, facilitating the production of cAMP, which enhances myocardial contractility and oxygen consumption.[19] Hence, patients treated with renin–angiotensin–aldosterone system and beta-adrenergic blocking drugs might benefit less from H2RAs. However, this was not apparent in our analysis. Besides local activation of the renin–angiotensin system, mast cell-derived histamine concentrations are high in the human heart.[20,21] Histamine is a vasoconstrictor of atherosclerotic coronary arteries, which may provoke coronary spasm and thus induce myocardial infarction. However, we observed comparable associations between H2RA and mortality in patients with ischemic and nonischemic heart failure. In a study of mice subjected to aortic banding, those

with disrupted H_2 receptors had improved cardiac function and developed less fibrosis than mice with normal H_2 receptors. In another study of dogs with pacemaker-induced heart failure, H2RA preserved cardiac systolic function, even in the presence of carvedilol.[22] These studies suggest a benefit of H2RA treatment in preventing progression of heart failure, in line with our findings.[4]

Our study has several strengths. We used an active-comparator design[7] to reduce confounding by indication. The large study sample allowed us to adjust our analyses for a range of potential confounders and to perform relevant stratified analyses. Use of nationwide, population-based registries with complete follow-up reduced the risk of selection bias.

Several potential weaknesses also must be considered. Our findings lack specificity, in that an association of similar size was seen between use of H2RAs and mortality from both cardiovascular and noncardiovascular causes. It is important to note that information on cause of death is registered according to a physician's subjective assessment. Although misclassification of cause of death in national registries may result, this is likely to be independent of H2RA or PPI initiation. Still, such misclassification would be expected to blur a true difference based on cause of death.

Another concern is that some degree of contamination of the H2RA cohort by subsequent initiation of PPIs was observed, but this would be expected to have biased our results toward the null, and thus cannot explain the observed association. Also, the results remained consistent after assigning patients to exposure groups without crossover in the initial year. Similarly, results of analyses restricted to patients who received a second prescription of a PPI or an H2RA – patients more likely actually to have taken the medication – and exclusion of patients with one prescription only produced results consistent with those in the main analysis.

It is also important to consider that we had a short prescription history for patients from the early post-1995 period; because almost 50% of the H2RA cohort had an index date during 1995−1999, we might have included more prevalent H2RA users than PPI users. However, since the association between H2RA initiation and mortality also was present among patients whose index date was in 2005−2014, this is unlikely to explain our findings. Because data on echocardiogram measures were unavailable at PPI or H2RA initiation, we could not stratify our analyses based on heart failure severity on the index date, and so could not rule out confounding from underlying differences in severity between new users of PPIs and H2RAs. We lacked data on gastric ulcer disease severity. However, we adjusted our analyses for anemia and gastroscopy. Traditionally, pharmacological treatment for peptic ulcer disease and gastrointestinal reflux disease have included both H2RA and PPI. However, PPIs are currently recommended as first-line treatment, as they are more effective than H2RAs in preventing persistent or recurrent bleeding from peptic ulcer.[23]As such, we cannot exclude confounding by indication, including differences in underlying peptic ulcer disease severity.

Conclusion

In a population-based cohort of heart failure patients, we observed lower mortality and hospitalization due to worsening of heart failure among new users of H2RAs than among new users of PPIs. This suggests a potential benefit of treatment with H2RAs in heart failure patients.

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Disclosure

The authors report no conflicts of interest in this work

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