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ORIGINAL RESEARCH

Histamine H_2 Receptor Antagonists and Heart Failure Risk in Postmenopausal Women: The Women's Health Initiative

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BACKGROUND: Prior studies suggested lower risk of heart failure (HF) in individuals taking H_2 receptor antagonists (H2RA) compared with H2RA nonusers in relatively small studies. We evaluated the association of H2RA use and incident HF in postmenopausal women in the large-scale WHI (Women's Health Initiative) study.

METHODS AND RESULTS: This study included postmenopausal women from the WHI without a history of HF at baseline. HF was defined as first incident hospitalization for HF and physician adjudicated. Multivariable Cox proportional hazards regression models evaluated the association of H2RA use as a time-varying exposure with HF risk, after adjustment for demographic, lifestyle, and medical history variables. Sensitivity analyses examined (1) risk of HF stratified by the ARIC (Atherosclerosis Risk in Communities) score, (2) propensity score matching on H2RA use, (3) use of proton pump inhibitors rather than H2RA nonuse as the referent, and (4) exclusion of those taking diuretics at baseline. The primary analysis included 158 854 women after exclusion criteria, of whom 9757 (6.1%) were H2RA users. During median 8.2 years of follow-up, 376 H2RA users (4.9 events/1000 person-years) and 3206 nonusers (2.7 events/1000 person-years) developed incident HF. After multivariable adjustment, there was no association between H2RA use and HF in the primary analysis (hazard ratio, 1.07; 95% CI, 0.94–1.22; *P*=0.31) or in any of the sensitivity analyses.

CONCLUSIONS: Clinical H2RA use was not associated with incident HF among postmenopausal women. Future studies are needed to evaluate potential effect modification by sex, HF severity, or patterns of use on H2RA exposure and HF risk.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00000611.

Key Words: heart failure ■ postmenopausal women ■ prevention

Based on data from 2013 to 2016, an estimated 6.2 million Americans ≥20 years of age were diagnosed with heart failure (HF), and 3.2 million of those are women.[1] In 2014, an estimated 504 000 new cases of HF were diagnosed in women ≥55 years of age.[1] Recently, there has been increasing attention to sex differences in HF risk factors and clinical phenotypes of HF. Traditional risk factors, including obesity, tobacco use, hypertension, and diabetes, are thought to be more predictive of risk for HF in women.[2]

Histamine H_2 receptor antagonists (H2RA) are commonly used to treat gastroesophageal pathologies, such as gastroesophageal reflux disease (GERD) and peptic ulcer disease.[3] H2RAs may also have a role in cardiac disease as histamine is abundant in the myocardium, and myocardial H_2 receptors activate

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CLINICAL PERSPECTIVE

What Is New?

- In a large cohort of postmenopausal women followed over 8 years, use of histamine H2 receptor antagonists was not associated with incident heart failure (HF).

What Are the Clinical Implications?

- It has previously been suggested that histamine signaling may be important in the pathogenesis of HF and histamine H_2 receptor antagonist use may be cardioprotective; however, based on our results, histamine H_2 receptor antagonist use may not be associated with lower HF risk as previously suggested.
- Randomized trials are needed to determine whether the use of histamine H_2 receptor antagonists are associated with HF risk, and the potential effect modification by sex, HF severity, or patterns of use.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
H2RA	histamine H_2 receptor antagonist
MESA	Multi-Ethnic Study of Atherosclerosis
WHI	Women's Health Initiative

stimulatory G-proteins by a mechanism similar to myocardial β-receptors.[4,5] H2RAs act directly on histamine receptors to reduce vasoconstriction, reduce blood pressure and heart rate, and increase cyclic adenosine monophosphate levels in cardiomyocytes.[6] Prior studies have suggested that H2RAs may be effective at both improving outcomes, including mortality, in patients with established HF[6–9] and in reducing the risk for incident HF in patients without known cardiovascular disease.[10]

In an observational study using the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, the authors found a 62% lower risk of incident HF in patients using H2RAs compared with nonusers.[10] The strongest inverse association between H2RA use and incident HF occurred in individuals at highest risk for HF. However, this study was limited by a small sample size with only 313 H2RA users. Alongside preclinical data, these observations suggest histamine signaling may be relevant to the pathogenesis of human HF and that H2RA use may be cardioprotective against adverse remodeling.

We evaluated the association of H2RA use with incident HF requiring hospital admission among postmenopausal women in the well-characterized WHI (Women's Health Initiative) cohort. The WHI has a robust sample size with long-term follow-up, rigorously ascertained medication inventory, and adjudicated clinical end points, including HF.

METHODS

The data sets generated and analyzed during the current study are not publicly available in accordance with policies developed by the National Heart, Lung, and Blood Institute and the WHI. Data requests must be approved by the Fred Hutchinson Cancer Research Center, which currently serves as the institutional review board of record for the WHI. Data requests may be made by emailing helpdesk@WHI.org.

Study Population

The WHI is a nationwide, prospective cohort study of 161 808 generally healthy US postmenopausal women. Women aged 50 to 79 were enrolled at 40 clinical centers between 1993 and 1998.[11,12] Women were enrolled in either 1 or more of 3 clinical trials or an observational study with follow-up through 2005. For this analysis, participants were excluded if they self-reported a history of HF at baseline (n=2048), reported being on both an H2RA and proton pump inhibitors (PPI) at baseline (n=228), or were missing follow-up time (n=678), resulting in a final analytic cohort of 158 854 women (Figure 1). Informed consent was obtained from participants and all protocols were approved by the institutional review board of the participating institutions.

Exposure

The primary exposure was H2RA use, which was modeled as a time-varying exposure. Medication inventories were collected at baseline and repeated at years 1, 3, 6, and 9 for women in the clinical trials and year 3 for women in the observational study during the study period.[11] Participants were instructed to bring all current medications in their original containers, both prescription and nonprescription, to the baseline and follow-up WHI clinic visits. The medication name and strength were entered into the WHI database and assigned a drug code using Medi-Span software. Duration of medication use was also recorded based on participant recollection.

Outcome

The primary outcome was incident adjudicated HF, defined as the first hospitalization for HF. A hospitalization was deemed to be related to HF after physician review of hospital records that was initiated when a participant self-reported a hospitalization on the annual survey.[13]

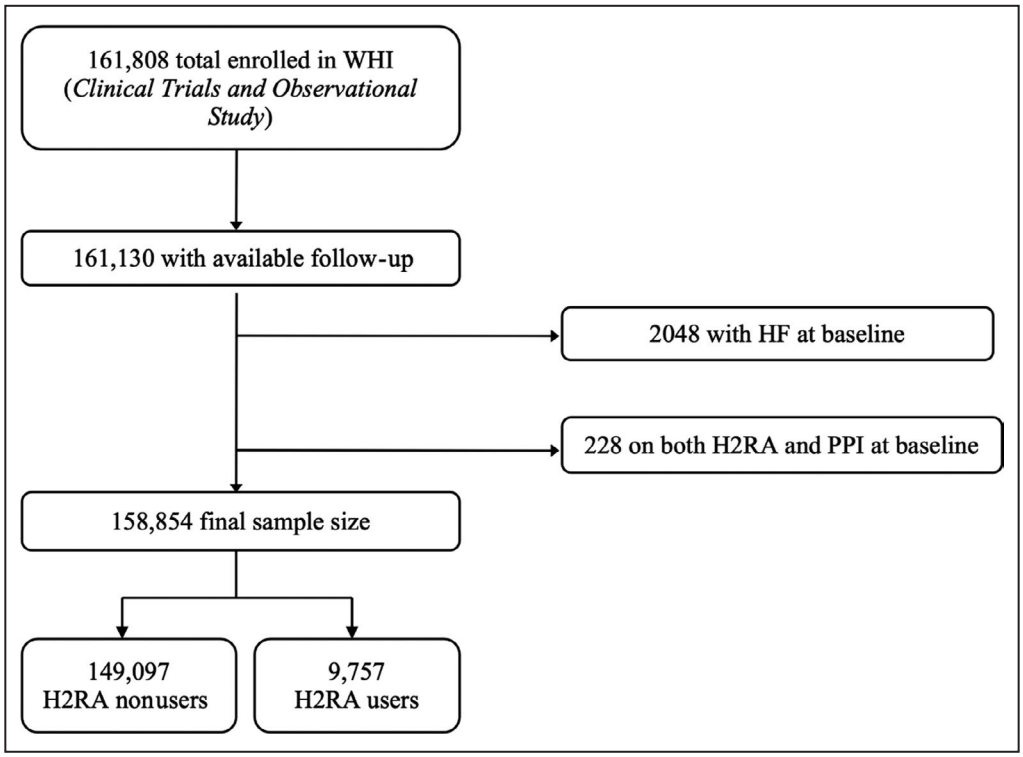

Figure 1. Study sample.
Flow diagram characterizes the WHI participants who contributed to the analysis evaluating the relationship between H2RA use and incident HF requiring hospitalization. H2RA indicates histamine H_2 receptor antagonist; HF, heart failure; PPI, proton pump inhibitor; and WHI, Women's Health Initiative.

Only HF requiring hospital admission was included as an outcome. A hospitalization was determined to be related to HF if there were symptoms and signs consistent with HF, plus an objective feature of HF such as pulmonary edema by chest X-ray, or dilated ventricle or poor ventricular function by imaging studies after physician review of hospital records.[13] Alternatively, a physician diagnosis of congestive HF and consistent medical treatment would be considered an HF admission.[13]

Statistical Analysis

All continuous variables were visually assessed and were normally distributed. Baseline characteristics of the cohort are reported as means and SDs, median and interquartile range, or frequencies and proportions for normally distributed continuous, nonnormally distributed continuous, and categorical variables, respectively. Bivariate statistics using *t* tests, Wilcoxon rank sum tests, chi-square tests for normally distributed continuous, nonnormally distributed continuous, and categorical variables, respectively, were used to compare H2RA users to nonusers at baseline. We assessed patterns of H2RA and PPI use among participants by calculating the proportion of users who are exposed to H2RAs and PPIs at multiple time points and calculating the proportion of participants with multiple medication inventories completed.

Multivariable-adjusted Cox proportional hazards models were used to assess the association of H2RA use and incident HF. Hazard ratios (HRs) and 95% CIs were calculated. The proportional hazards assumption was evaluated using Schoenfeld residuals; there were no violations of this assumption. Multicollinearity between independent variables was assessed by calculating variance inflation factors. All variance inflation factors were below a cutoff of 5 suggesting no issue of multicollinearity. H2RA use was examined as a time-varying exposure, meaning a participant was not classified as exposed to a H2RA until she first reported using it on a medication inventory and classification of exposure was changed if a participant later reported nonuse. To better approximate medication changes that occurred between inventories, medication duration data were used to refine the time of medication initiation during follow-up. Additionally, medication inventories became out of date 3.5 years after the last medication inventory collection. Thus, if a participant was missing a subsequent medication inventory, follow-up time was censored; however, participants were allowed to reenter the model upon completion of a current medication inventory. Follow-up time was defined

as days from WHI enrollment to incident HF. Women were censored at death, loss to follow-up, or the end of the study period (through 2005), whichever came first. All models were adjusted for age at enrollment and WHI study component (observational study versus clinical trial).

Baseline covariates were decided a priori based on clinical relevance and known association with HF from previous literature. Covariates in the adjusted models included education, income, ethnicity, body mass index, smoking use, pack-years, alcohol use, physical activity, PPI use, antihypertensive use, beta blocker use, calcium channel blocker use, diuretic use, lipid-lowering drug use, antiarrhythmic drug use, corticosteroid use, nonteroidal anti-inflammatory drug (NSAID) use, family history of myocardial infarction, history of diabetes, history of hypertension, systolic blood pressure, waist circumference, and history of cardiovascular disease.

A number of sensitivity analyses were conducted. To test whether there was effect modification according to established risk of HF, we tabulated the ARIC (Atherosclerosis Risk in Communities) HF scores at baseline and stratified by ARIC HF risk score.[14] We evaluated the optimal discriminatory threshold of risk for the ARIC score in this cohort using the Youden index to stratify the cohort into low- and high-risk groups. We examined other prespecified subgroups including stratification by race/ethnicity, diuretic use, presence of GERD, and age 65 years. To assess for selection bias, we conducted a propensity score analysis to account for the propensity of a participant to be a H2RA user. For this, the propensity function was calculated as a logit function that incorporated all of the variables from the multivariable adjustment minus beta blocker use, calcium channel blocker use, diuretic use, family history of myocardial infarction, systolic blood pressure, heart rate, and NSAID use. Users were matched 1:1 to nonusers based on their propensity score using nearest neighbor matching without replacement and matched pairs were included if the distance between propensity scores differed by no more than 0.05 SDs. This resulted in a total of 8303 matched pairs. Balance of covariates between H2RA users and nonusers after matching was assessed by standardized mean differences using a threshold of 0.1. To investigate the potential for reverse causality, we excluded those with an adjudicated HF event that occurred during the first 2 years of the study to exclude the possibility that undiagnosed HF at baseline may have influenced the use of H2RAs. We also examined whether duration of H2RA use was associated with HF. For this analysis, H2RA duration was modeled categorically as nonuse (reference), short-term use (those who completed 1 medication inventory), and long-term use (those who completed more than 1 medication inventory). To assess whether an association was observed because of a history of GERD rather than H2RA use, we conducted an analysis with PPI use as the referent category (rather than nonuse of H2RAs). This analysis was restricted to participants who were users of either PPIs or H2RAs and looked at H2RA use at baseline, rather than as a time-varying analysis. We additionally explored whether self-reported GERD symptoms were associated with incident HF. Lastly, we excluded participants on a diuretic at baseline to remove participants who may have had HF that was undetected or potentially misclassified at baseline.

We performed a complete case analysis. A 2-sided *P* value of 0.05 was used to determine statistical significance. All analyses were performed using R Version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among 158 854 women, there were 9757 (6.1%) H2RA users and 149 097 (93.9%) H2RA nonusers at baseline (Figure 1). Baseline characteristics of the study population stratified by H2RA use are shown in Tables 1 and 2. H2RA users were more likely to be obese, more frequently used other non-H2RA prescription medications including diuretics and NSAIDs, and had a higher baseline prevalence of hypertension, diabetes, and history of cardiovascular disease than the 149 097 nonusers. Median follow-up time was 8.2 years (interquartile range: 7.2–9.1). During study follow-up, 3582 (2.3%) participants developed incident HF requiring hospitalization, comprising 376 H2RA users (4.9 events per 1000 person years) and 3206 nonusers (2.7 events per 1000 person years). The proportion of H2RA users remained relatively stable over the study duration ranging from 4.7% to 6.1% whereas the proportion of PPI users increased steadily over the study duration ranging from 1.9% at baseline to 13.3% at year 9 (see Figure S1). A total of 85.8% of participants in the observational study completed both medication inventories and 80.7% of participants in the clinical trial completed either 4 or 5 medication inventories (out of 5 total) (see Table S1).

When examining H2RA use modeled as a time-varying analysis, H2RA use was associated with a higher risk of HF after adjusting for age (HR, 1.44; 95% CI, 1.29–1.62; $P<0.001$), but this association between H2RA use and increased HF risk was no longer significant in the fully adjusted model (HR, 1.07; 95% CI, 0.94–1.22; $P=0.31$) (Table 3).

Sensitivity Analyses

No sensitivity analysis suggested an association of H2RA use with HF by prespecified subgroups or after adjustment for clinical characteristics other than diuretic

Table 1. Baseline Characteristics for the Total Cohort and by H2RA User Status

Baseline characteristic	Total (N=158 854)	H2RA nonusers (N=149 097)	H2RA users (N=9757)
Age*, y (mean [SD])	63.2 (7.2)	63.1 (7.2)	64.2 (7.1)
Race and ethnicity* (%)			
American Indian or Alaskan Native	685 (0.4)	635 (0.4)	50 (0.5)
Asian or Pacific Islander	4134 (2.6)	4031 (2.7)	103 (1.1)
Non-Hispanic Black or African-American	14 096 (8.9)	13 190 (8.8)	906 (9.3)
Hispanic/Latino	6247 (3.9)	5907 (4.0)	340 (3.5)
Non-Hispanic White	131 482 (82.8)	123 253 (82.7)	8229 (84.3)
Other	1804 (1.1)	1704 (1.1)	100 (1.0)
Body mass index*, kg/m^2 (mean [SD])	27.9 (5.9)	27.8 (5.9)	29.5 (6.1)
Height*, cm (mean [SD])	161.8 (6.7)	161.8 (6.7)	161.2 (6.6)
Weight*, kg (mean [SD])	73.4 (16.8)	73.2 (16.8)	77.0 (17.0)
Smoking status* (%)			
Never smoker	80 084 (50.4)	75 430 (50.6)	4654 (47.7)
Past smoker	65 819 (41.4)	61 484 (41.2)	4335 (44.4)
Current smoker	10 903 (6.9)	10 265 (6.9)	638 (6.5)
Pack-years*, median (IQR)	0.0 (0.0, 12.5)	0.0 (0.0, 12.5)	0.1 (0.0, 15.0)
Alcoholic servings/wk*, median (IQR)	0.4 (0.0, 2.7)	0.4 (0.0, 2.7)	0.0 (0.0, 1.3)
Women's Health Initiative clinical trial (%)	67 125 (42.3)	63 029 (42.3)	4096 (42.0)

H2RA indicates histamine H_2 receptor antagonist; and IQR, interquartile range.
*$P \leq 0.05$.

use (Table 4, Figure 2). An ARIC HF score of <10 signified low risk and an ARIC score of ≥10 was high risk based on optimal discrimination from the Youden index (see Figure S2). However, there was no interaction by ARIC score in the association between H2RA use and HF (P=0.86). This was also qualitatively apparent when comparing stratified results. After multivariable adjustment, there was no significant association of H2RA

Table 2. Baseline Clinical Factors for the Total Cohort and by H2RA User Status

Clinical characteristic	Total (N=158 854)	H2RA nonusers (N=149 097)	H2RA users (N=9757)
Systolic blood pressure*, mm Hg (mean [SD])	127.3 (17.7)	127.2 (17.8)	129.4 (17.1)
History of diabetes* (%)	9058 (5.7)	8264 (5.5)	794 (8.1)
History of treated diabetes* (%)	6695 (4.2)	6123 (4.1)	572 (5.9)
History of hypertension* (%)	52 581 (33.1)	48 319 (32.4)	4262 (43.7)
History of treated hypertension* (%)	12 083 (7.6)	11 339 (7.6)	744 (7.6)
History of cardiovascular disease* (%)	25 164 (15.8)	22 973 (15.4)	2191 (22.5)
Family history of myocardial infarction* (%)	78 535 (49.4)	73 196 (49.1)	5339 (54.7)
Beta blocker use* (%)	12 417 (7.8)	11 197 (7.5)	1220 (12.5)
Calcium channel blocker use* (%)	15 226 (9.6)	13 697 (9.2)	1529 (15.7)
Proton pump inhibitor use* (%)	3063 (1.9)	3063 (2.1)	0 (0.0)
Angiotensin-converting enzyme inhibitor use* (%)	11 434 (7.2)	10 449 (7.0)	985 (10.1)
Angiotensin receptor blocker use* (%)	836 (0.5)	756 (0.5)	80 (0.8)
Other antihypertensive use* (%)	5335 (3.4)	4879 (3.3)	456 (4.7)
Diuretic use* (%)	19 597 (12.3)	17 557 (11.8)	2040 (20.9)
Lipid-lowering medication use* (%)	13 620 (8.6)	12 221 (8.2)	1399 (14.3)
Corticosteroid use* (%)	1330 (0.8)	1141 (0.8)	189 (1.9)
Antiarrhythmic use* (%)	553 (0.3)	484 (0.3)	69 (0.7)
Nonsteroidal anti-inflammatory drug use* (%)	30 329 (19.1)	27 255 (18.3)	3074 (31.5)

H2RA indicates histamine H_2 receptor antagonist.
*$P \leq 0.05$.

Table 3. Primary Analyses—Association of H2RA Use With Incident HF Requiring Hospitalization

Cox proportional hazards models	N	Hazard ratio	95% CI	*P* value
Primary analyses				
Incident HF, age adjustment	158 851	1.44	1.29–1.62	<0.001
Incident HF, multivariable adjustment*	128 106	1.07	0.94–1.22	0.31

H2RA indicates histamine H_2 receptor antagonists; and HF, heart failure.

*Multiple variable Cox proportional hazards models adjusted for age, education, income, ethnicity, body mass index, smoking use, pack-years, alcohol, physical activity, proton pump inhibitor use, antihypertensive use, lipid-lowering drugs, antiarrhythmic drugs, beta blockers, calcium channel blockers, diuretics, corticosteroid use, family history of myocardial infarction, diabetes, hypertension, systolic blood pressure, heart rate, waist circumference, nonsteroidal anti-inflammatory drugs, history of cardiovascular disease.

use with HF for women with an ARIC score <10 or ARIC score ≥10 (Figure 2). We repeated this analysis using an ARIC score ≥11 as this was the cutoff used in a prior study with the MESA cohort,[10] but this did not change the directionality or significance of our findings after multivariable adjustment (see Table S2).

In the propensity matched analysis, the standardized mean differences for all covariates were below 0.1 indicating adequate balance was achieved (see Figure S3, Table S3). There was no association between H2RA use and HF (Table 4). When HF events that occurred during the first 2 years of the study were excluded, there was no association between H2RA use and HF after multivariable adjustment (Table 4).

We further found that there was no association with the presence of GERD, duration of H2RA use, or the use of PPIs with HF risk. There was no association of self-reported GERD with risk of HF after multivariable adjustment (Table 4). There was no association with HF for either short-term or long-term H2RA users (short-term user compared with nonuser, HR, 1.01; 95% CI, 0.86–1.12; *P*=0.92, long-term user compared with nonuser, HR, 1.08; 95% CI, 0.75–1.07; *P*=0.39) (see Table S4). With PPI use compared with PPI nonuse, there was no significant association with HF (multivariable HR, 1.14; 95% CI, 0.93–1.40; *P*=0.21). When the analysis was restricted to the cohort of women being treated for GERD with either a PPI or H2RA, there was no difference in HF between PPI and H2RA users seen in either the age-adjusted analysis (HR, 1.02; 95% CI, 0.82–1.26; *P*=0.87) or with the multivariable adjusted analysis (Table 4).

Diuretic use at baseline was nearly 2-fold higher for H2RA users compared with nonusers (Table 2). However, diuretic use was not found to be an effect modifier between H2RA use and HF (*P* for interaction=0.08) (see Table S5). We repeated our analysis excluding all participants on any diuretics at baseline. After excluding participants on diuretics, multivariable analyses did not suggest that H2RA use was associated with HF (Table 4). This null finding was also seen

Table 4. Sensitivity Analyses—Association of H2RA Use With Incident HF Requiring Hospitalization

Risk for incident heart failure				
	N	Hazard ratio	95% CI	*P* value
Model (sensitivity analyses)				
Propensity matched for H2RA use*	16 806	1.07	0.91–1.26	0.42
Multivariable adjustment,† HF within first 2 y excluded	158 538	1.05	0.91–1.22	0.49
Multivariable adjustment,† baseline gastroesophageal reflux disease, participants on diuretics excluded	139 267	0.96	0.89–1.94	0.35
Restricted cohort comparing H2RA users only to PPI users (referent group)†	12 820	0.98	0.78–1.24	0.88
Multivariable adjustment†, participants on diuretics excluded	139 267	0.97	0.82–1.15	0.71

H2RA indicates histamine H_2 receptor antagonists; HF, heart failure; and PPI, proton pump inhibitor.

*Propensity score calculated as logit function that included all of the variables from the multivariable adjustment minus beta blocker use, calcium channel blocker use, diuretic use, family history of myocardial infarction, systolic blood pressure, heart rate and nonsteroidal anti-inflammatory drug use.

†Multiple variable Cox proportional hazards models adjusted for age, education, income, ethnicity, body mass index, smoking use, pack-years, alcohol use, physical activity, PPI use, antihypertensive use, lipid-lowering drug use, antiarrhythmic drug use, beta blocker use, calcium channel blocker use, diuretic use, corticosteroid use, family history of myocardial infarction, diabetes, hypertension, systolic blood pressure, heart rate, waist circumference, nonsteroidal anti-inflammatory druguse, history of cardiovascular disease.

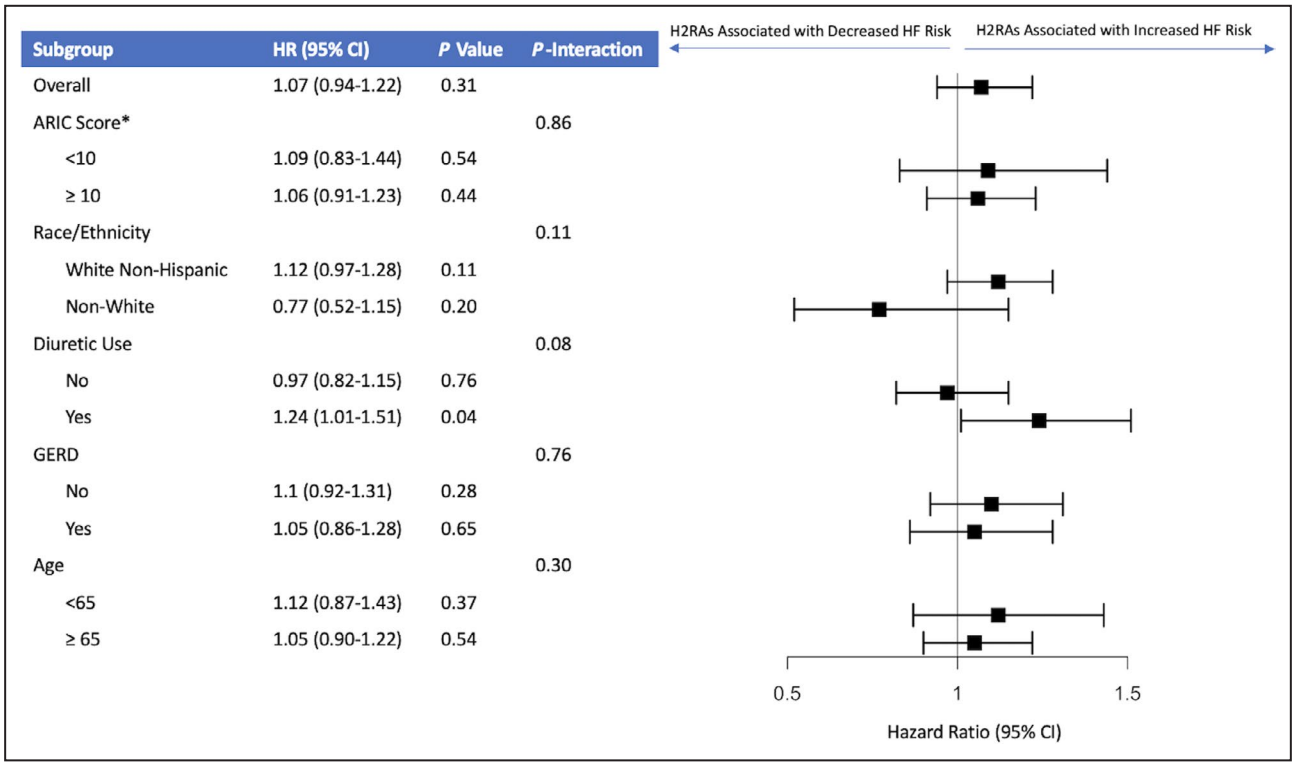

Figure 2. H2RA use and heart failure risk in women: subgroup analyses.
Forest plot of subgroup analyses including hazard ratios for the association between H2RA use and incident HF. ARIC indicates Atherosclerosis Risk in Communities; GERD, gastroesophageal reflux disease; H2RA, histamine H_2 receptor antagonists; HF, heart failure; and HR, hazard ratio. *ARIC score <10 signifies participants at low risk of HF, ARIC score ≥10 signifies participants at high risk of HF.

in the propensity matched analysis in the cohort after excluding participants on diuretics (HR, 1.13; 95% CI, 0.91–1.40; *P*=0.29).

DISCUSSION

In a large cohort of postmenopausal women, H2RA use was not associated with incident HF requiring hospitalization. The lack of an association with H2RA use and HF was supported by multiple, prespecified sensitivity analyses, including stratification based on the ARIC score, a propensity matched cohort for H2RA use, excluding participants with HF within 2 years of study entry and on diuretics at baseline, and using PPI users as the referent category.

Our study has several strengths, including almost 10 000 H2RA users and a comparator cohort of almost 150 000 nonusers. Further, in the WHI, medication inventories were collected sequentially, allowing accurate adjustment for time-varying exposure. Incident HF was physician adjudicated and required hospitalization, reducing the risk for misclassification. Our cohort included only women, who are traditionally underrepresented in clinical trials and observational studies. Lastly, our findings were consistent across extensive, rigorous sensitivity analyses.

Our findings may differ from prior studies including the prior study by Leary and colleagues that found an association with a lower risk of incident HF among H2RA users in the MESA cohort compared with H2RA nonusers.[10] Explanations for these disparate findings could be differences in definition of HF, patterns of H2RA use including timing and duration of use, or differences in the populations studied. In the MESA study, the incidence of any new HF diagnosis (including ambulatory clinic) was used as the outcome rather than incident HF requiring hospitalization, as was used in our study. Although these outcomes are related, they are not the same. Requiring admission for HF represents the more severe end of the spectrum but also ensures a higher specificity for the HF diagnosis. Alternatively, both physiologic or nonphysiologic contributors of the need for admission, such as social determinants of health, in an otherwise similar disease might have obscured the relationship with H2RAs in the current analyses.

Differences in patterns of H2RA use, including timing and duration of use, may also be contributing to the differences seen between the 2 studies. In WHI, the percentage of participants on H2RAs remained relatively stable over the study period ranging from 4.7% to 6.1% (see Figure S1). The MESA cohort reported H2RA

use at each of 5 follow-up exams; for participants who used H2RAs, 54% noted use at only 1 MESA exam, whereas 15% noted use at 4 or more exams.[10] The timing of H2RA use relative to risk for HF is unknown but is likely an important factor. In the MESA cohort, the attenuation of negative cardiac remodeling by magnetic resonance imaging and the association with a decreased risk of incident HF among H2RA users was seen in their primary analysis, which looked at baseline H2RA use. To further explore the association of H2RA use with HF, they also performed a time-varying analysis that did not show a significant association between H2RA use and incident HF (HR, 0.75; 95% CI, 0.37–1.51; *P*=0.42), similar to our findings.[10] These analyses attempt to tackle different mechanisms of action. Whereas a baseline analysis addresses mechanisms not anchored on active presence of H2RA drug in the body (such as fibrosis), a time-varying analysis is based on active use association and is suitable for assessing H2RA use and incident HF. The impact of duration of use is also unknown but likely important. In the MESA cohort, when the time-varying analysis was restricted to participants who used H2RAs for at least 1 year, there was no significant association (HR, 0.51; 95% CI, 0.21–1.23; *P*=0.13).[10] This is consistent with our analysis, which did not find an association with either short-term or long-term H2RA use (see Table S4). Further prospective studies are needed to better evaluate the role of timing and duration of H2RA use on cardiac remodeling and HF risk.

Another possible explanation for our findings is the differences in demographics of our populations and modifying effects of these variables. The WHI cohort was all women, mean age of 63.2 years, and 83% were White. In the MESA cohort 53% were women, with a mean age of 62.3 years and only 38% were White.[10] Hence, our study population had a higher proportion of women and a higher frequency of White race compared with the MESA cohort (see Table S6). Although we did not see an association with H2RA use and HF risk stratified by race, we did see that in non-White women there was a point estimate toward reduced HF risk with H2RA use (Figure 2). There is increasing recognition of sex and racial differences in clinical treatment effects.

Although lifetime risk of HF is comparable between men and women, there are well-recognized sex differences in risk factors for and clinical phenotype of HF.[15,16] In older women, HF typically presents with a higher rate of diabetes and more frequently with preserved ejection fraction.[2] Traditional risk factors, including obesity, tobacco use, hypertension, and diabetes are believed to be more predictive of risk for HF in women than men, and may be driven by endothelial inflammation and microvascular dysfunction. Conversely, men are more likely to present with macrovascular coronary artery disease and associated ischemic cardiomyopathy.[2] Supporting this, recent preclinical models have suggested context dependence with H2RA signaling such that H2RA signaling may be detrimental in ischemic and lipopolysaccharide-induced HF but beneficial in hypoxia and hypertrophic models.[17] In addition, another animal study in rats suggested that males may be more sensitive than females to prostaglandin H_2 receptor antagonism.[18]

Although there have been animal studies suggesting that H2RA use may mitigate cardiotoxicity from anthracyclines,[5,19] from rapid-pacing induced tachycardia-related left ventricle dysfunction,[20] and in a knockout model of the H_2 receptor,[21] these animal studies included limited duration of H2RA exposure and short duration of follow-up. Although the full cardiovascular effects of histamine pathways are not completed defined, it is possible that H2RA may have a differential role in cardioprotection against incident HF between sexes that relate to differences in risk factors or HF phenotype.

Study Limitations

As with any observational study, there is risk for residual confounding or unmeasured confounding. Although we attempted to minimize this with multiple sensitivity analyses, these forms of confounding can be particularly insidious in pharmaco-epidemiology and with studies around disease-specific admissions. Owing to our very large cohort size, almost all of the baseline characteristics were significantly different between the 2 groups. The robustness of our findings was confirmed with both multivariable adjustment and a propensity matched analysis, reducing the risk for residual confounding. Misclassification of exposure or outcome is also possible but less likely in a study where end points were ascertained as part of a clinical trial and a long-term observational cohort. Thus, findings should be interpreted with caution.

NSAID use was found to be significantly higher in the H2RA users (Table 2). NSAIDs clearly interact with H2RA use as they are known to be a cause of gastric ulcers. NSAID use has been associated with increased blood pressure as well as fluid retention and has also been associated with a small increase in risk of new HF in some[22] but not all studies,[23] and this risk is higher in patients with prior HF.[23] It is possible that NSAID use may have confounded our results; however, as our cohort was without known HF, the impact of increased HF risk from NSAID use, if present, was likely minimal and NSAID use was also included in our multivariable adjustment.

CONCLUSIONS

In this large epidemiological study, we found no association of H2RA use with incident HF requiring

hospitalization in postmenopausal women over a median 8.2 year follow-up. Future, randomized studies should be considered to clarify these findings.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S6
Figures S1–S3

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Supplemental Material

Table S1. Proportion of OS and CT participants who completed multiple medication inventories

# of Medication Inventories Completed	OS (N = 91,729)	CT (N = 67,125)
1	13,041 (14.2%)	1,869 (2.8%)
2	78,688 (85.8%)	3,702 (5.5%)
3	Na	7,395 (11.0%)
4	Na	43,072 (64.2%)
5	Na	11,087 (16.5%)

1. OS participants completed inventories at baseline and year 3
2. CT participants completed inventories at baseline, year 1, 3, 6, and 9

Table S2. Cox proportional hazard model for association of time-varying H2RA use and incident HF stratified by ARIC score at baseline

	Multi-variable Adjusted*			
Strata	N	Events	HR (95% CI)	P-value
Total	127,571	2,786		
ARIC < 11	120,034	1,938	1.06 (0.90, 1.25)	0.47
ARIC >=11	7,537	848	1.09 (0.88, 1.34)	0.44
				P-interaction
				0.87

*Adjusted for age, education, income, ethnicity, BMI, smoking use, pack-years, alcohol, physical activity, PPI use, antihypertensive use, beta-blockers, calcium channel blockers, diuretics, lipid-lowering drugs, antiarrhythmic drugs, corticosteroid use, NSAID use, family history of MI, diabetes, hypertension, systolic BP, heart rate, waist circumference, NSAID, hx of CVD

Table S3. Baseline covariate distribution by matched H2RA and non-H2RA users

	Non-H2RA	H2RA	p-value	SMD
n	8303	8303		
Age (years), mean (SD)	64.18 (7.01)	64.19 (7.01)	0.944	0.006
Ethnicity, n (%)			0.99	0.014
American Indian or Alaskan Native	40 (0.5)	44 (0.5)		
Asian or Pacific Islander	94 (1.1)	95 (1.1)		
Black or African American	781 (9.4)	773 (9.3)		
Hispanic/Latino	293 (3.5)	280 (3.4)		
White	7016 (84.5)	7032 (84.7)		
Other	79 (1.0)	79 (1.0)		
Education, n (%)			0.673	0.023
< High School	613 (7.4)	600 (7.2)		
High School or GED	1705 (20.5)	1653 (19.9)		
> High School - Bachelor's Degree	4110 (49.5)	4180 (50.3)		
> Bachelor's Degree	1875 (22.6)	1870 (22.5)		
Income, n (%)			0.858	0.013
Less than $34,999	3798 (45.7)	3783 (45.6)		
$35,000 - $74,999	3150 (37.9)	3169 (38.2)		
$75,000 - $99,999	574 (6.9)	587 (7.1)		
> $100,000	563 (6.8)	534 (6.4)		
Don't Know	218 (2.6)	230 (2.8)		
BMI ($kg/m^{2)}$), mean (SD)	29.50 (6.44)	29.50 (6.04)	0.996	0.011
Waist circumference (cm), mean (SD)	90.49 (14.64)	90.51 (13.73)	0.913	0.013
Alcoholic servings/week, mean (SD)	1.86 (3.94)	1.80 (4.29)	0.316	0.021
Physical activity (MET-hours/week), mean (SD)	9.63 (11.10)	9.80 (11.77)	0.338	0.013
Smoking status, n (%)			0.582	0.018
Never smoker	4027 (48.5)	4091 (49.3)		
Past smoker	3709 (44.7)	3663 (44.1)		
Current smoker	567 (6.8)	549 (6.6)		
Pack-years, mean (SD)	12.29 (21.34)	12.12 (20.91)	0.603	0.006
Diabetes, n (%)	641 (7.7)	672 (8.1)	0.388	0.024
Hypertension, n (%)	3709 (44.7)	3649 (43.9)	0.357	0.003
Cardiovascular disease, n (%)	1891 (22.8)	1966 (23.7)	0.174	0.021
Antihypertensive use, n (%)	391 (4.7)	386 (4.6)	0.883	0.003
Lipid-lowering drug use, n (%)	1167 (14.1)	1212 (14.6)	0.330	0.015
Antiarrhythmic drug use, n (%)	55 (0.7)	56 (0.7)	0.999	0.001

Table S4. Cox proportional hazard model for association of H2RA duration (non-user vs. short-term vs. long-term based on # of inventories) and incident HF during WHI follow-up

	Multi-variable Adjusted *			
	N	Events	HR (95% CI)	P-value
Total	115,669	2,049		
Non-User	103,509	1,741	1.00 (reference)	
Short-term User (1 inventory)	8,109	184	1.01 (0.86, 1.12)	0.92
Long-term User (2 or more inventories)	4,051	128	1.08 (0.75, 1.07)	0.39
				P-trend
				0.44

*Adjusted for age, education, income, ethnicity, BMI, smoking use, pack-years, alcohol, physical activity, PPI use, antihypertensive use, beta-blockers, calcium channel blockers, diuretics, lipid-lowering drugs, antiarrhythmic drugs, corticosteroid use, NSAID use, family history of MI, diabetes, hypertension, systolic BP, heart rate, waist circumference, NSAID, hx of CVD

Table S5. Cox proportional hazard model for the interaction of H2RA use (time-varying) and diuretic use at baseline and incident HF during WHI follow-up

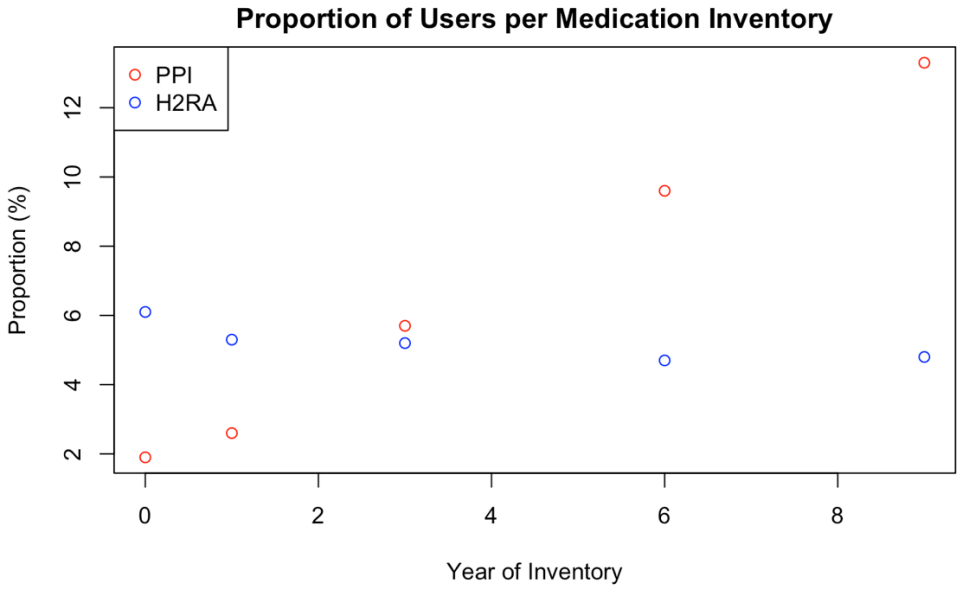
	Multi-variable Adjusted*			
Strata	N	Events	HR (95% CI)	P-value
Total	127,966	2,810		
No diuretic	110,337	2,008	0.97 (0.82, 1.15)	0.76
Diuretic	14,779	802	1.24 (1.01, 1.51)	0.04
				P-interaction
				0.08

*Adjusted for age, education, income, ethnicity, BMI, smoking use, pack-years, alcohol, physical activity, PPI use, antihypertensive use, beta-blockers, calcium channel blockers, diuretics, lipid-lowering drugs, antiarrhythmic drugs, corticosteroid use, NSAID use, family history of MI, diabetes, hypertension, systolic BP, heart rate, waist circumference, NSAID, hx of CVD

Table S6. Comparison of MESA vs. WHI characteristics

	MESA	WHI
% HF	3.7%	2.3%
% H2RA users at baseline	4.9%	6.1%
% HF in baseline H2RA users	1.9%	3.9%
Median follow-up time	11.2 years	8.2 years
% Women	53%	100%
Mean age	62.3	63.2
% White	38%	83%
# of H2RA users with HF	6 (1.9 events per 1,000 person-years)	376 (4.9 events per 1,000 person-years)
# of non-users with HF	230 (3.7 events per 1,000 person-years)	3206 (2.7 events per 1,000 person-years)

Figure S1. Proportion of Medication Users (PPI & H2RA) per Medication Inventory



Note: Medication inventories collected at years 0,1,3,6,9 in the CT and 0,3 in the OS

Proportion of Users per Medication Inventory

Year of Medication Inventory	H2RA	PPI
0	6.1%	1.9%
1	5.3%	2.6%
3	5.2%	5.7%
6	4.7%	9.6%
9	4.8%	13.3%

Figure S2. Youden Index Results

AUC	Sample size	Number positive	Number negative
0.78	152,659	3,371	149,288
Optimal cut point	**Youden**	**Sensitivity**	**Specificity**
10.0	0.43	0.75	0.68

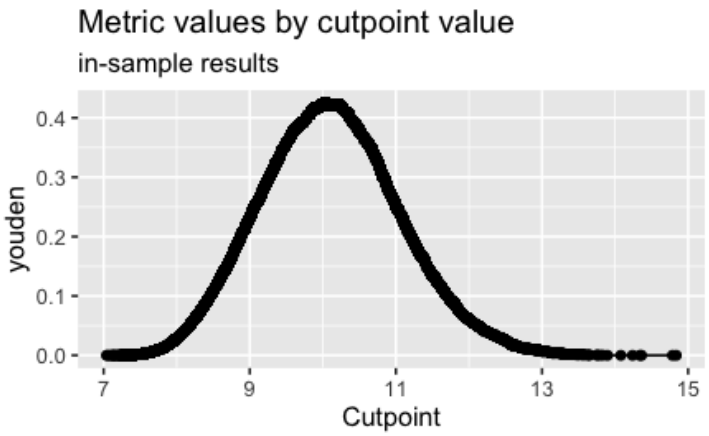


Figure S3. Love plot depicting standardized mean differences before and after propensity matching