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Histamine H₂ Receptor Antagonists, Left Ventricular Morphology, and Heart Failure Risk: MESA

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Abstract

Background—Myocardial H₂ receptor activation may promote cardiac fibrosis and apoptosis in preclinical models and histamine H₂ receptor antagonist (H2RA) use may improve symptoms in participants with heart failure (HF); however, relationships between H2RA use, incident HF, and longitudinal change in left ventricular (LV) morphology are not known.

Objectives—We sought to determine whether H2RA use is associated with incident HF and change in LV morphology over time.

Methods—This study included 6,378 men and women from MESA (Multi-Ethnic Study of Atherosclerosis), a multicenter prospective observational cohort of participants without cardiovascular disease at baseline. Cox proportional hazards were used to estimate the association between H2RA use and incident HF in adjusted models. In participants with cardiac magnetic resonance imaging (CMR), associations between H2RA use, baseline LV morphology (n = 4,691), and longitudinal change in the LV (n = 2,806) were estimated using linear regression.

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Results—H2RAs were used by 313 participants but not by the other 6,065 individuals. During a median follow-up of 11.2 years, 236 participants developed HF. In adjusted models, baseline H2RA use relative to nonuse was associated with 62% lower risk for incident HF ($p = 0.02$). H2RA use was associated with preserved stroke volume, LV end-diastolic volume, and mass/volume ratio as measured by CMR over approximately 10 years (all $p < 0.05$). There were no associations between H2RA use and LV mass or ejection fraction.

Conclusions—H2RA use was associated with reduced risk for incident HF. Changes in left heart morphology over time suggest less age-related change in H2RA users. These associations suggest histamine signaling may be important in the pathogenesis of HF.

Keywords

cardiac magnetic resonance imaging; heart failure; prevention

Histamine H₂ receptor antagonists (H2RAs) are commonly used to treat gastroesophageal reflux disease (1) and have a relatively strong safety profile. Beyond their use for symptomatic control of gastroesophageal reflux, H2RAs also may have a role in cardiac disease. Similar to beta receptors, H₂ receptors activate stimulatory G-proteins in the myocardium (2,3). Blockade of histamine receptors or histamine release can prevent heart failure (HF) in rabbits exposed to doxorubicin and dogs with pacemaker-driven tachycardia (4-6). Relative to mice with an intact H₂ receptor, mice with the H₂ receptor knock-out had improved cardiac function and developed less fibrosis when subjected to aortic banding (7). Additionally, H₂ receptor activation may increase mitochondrial permeability in cardiac myocytes and myocardial susceptibility to stress (8).

In men and women with HF and reduced ejection fraction (HF_rEF), H2RA use is associated with smaller left ventricular (LV) volumes and less severe symptoms; we have previously shown H2RA use is associated with lower right ventricular mass and smaller volumes (9,10). Alongside the observations in animals, these data suggest histamine signaling may be relevant to the pathogenesis of human heart failure.

This study examined associations between H2RA use and incident HF in a multiethnic cohort of adults free of clinical cardiovascular disease (CVD) at baseline. This study further evaluated associations between H2RA use, LV morphology, and change in LV morphology over time. The study investigators hypothesized that H2RA use would be associated with a reduced risk for heart failure.

Methods

MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective cohort study designed to investigate subclinical CVD (11). From 2000 to 2002, MESA recruited participants aged 45 to 84 years old from 6 U.S. communities. Evaluation included 5 MESA examinations over approximately 10 years. Exclusion criteria included clinical CVD (physician-diagnosed myocardial infarction, stroke, transient ischemic attack, HF, angina, current atrial fibrillation, any cardiovascular procedure), weight >136 kg, pregnancy, or impediment to

long-term participation. Institutional review boards of participating institutions approved the MESA protocols. All participants provided informed consent.

Cardiac magnetic resonance imaging (CMR) was obtained at the baseline examination for the majority of MESA participants. In a subset of these participants, CMR was repeated approximately 10 years later (12). The CMR protocol and interpretation of LV parameters in MESA have been previously described and are included in the Online Appendix (13,14).

Medication Use

A validated medication inventory was used to assess medication use (10,15). Participants were asked to bring all medications used during the 2 weeks prior to a MESA examination. Participants were considered H2RA users in primary analyses if they used prescription or over-the-counter H2RAs at the baseline MESA examination. Other baseline medication use considered for confounding included proton pump inhibitors, angiotensin-converting enzyme inhibitors (\pm diuretic), angiotensin II receptor blockers (\pm diuretic), beta-blockers (\pm diuretic), any diuretic alone (including potassium-sparing diuretics), oral steroids, nonsteroidal anti-inflammatory drugs (NSAIDs) (including aspirin, COX-2 inhibitors, and other NSAIDs), digoxin, and leukotriene antagonists.

Ascertainment of Events

Full details of event ascertainment and definition are available in MESA's manual of procedures (MOP) (16). Briefly, clinical outcomes were assessed at MESA study examinations and by telephone interview every 9 to 12 months. Records were obtained for approximately 99% of hospitalizations and 97% of outpatient cardiovascular diagnostic encounters through the end of calendar year 2012. Incident HF required symptoms of heart failure, a physician diagnosis of HF, and another objective feature of heart failure (dilated or poor LV function, pulmonary edema by chest radiograph, treatment, or evidence of diastolic dysfunction). Two physicians from the MESA events committee independently reviewed all medical records for classification and dating of events. If reviewers disagreed, they adjudicated differences. If disagreement persisted, the full events committee made the final classification.

Statistical Analysis

The methods of Kaplan and Meier were used to estimate unadjusted associations and Cox proportional hazards to estimate adjusted associations of H2RA use at the baseline exam with incident HF. Covariates were assessed at the initial MESA exam, described in MESA's MOP, and chosen a priori (16). In limited models, we adjusted for age, sex, race, height, weight, and study site. In adjusted models, we included participants' education and cardiovascular risk factors including intentional exercise, smoking status, pack-years of smoking, hypertension, systolic blood pressure, diabetes mellitus, cholesterol, and fasting glucose. In separate models we further adjusted for comedication use or level of the aminoterminal fragment of pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin T.

Two restricted cohorts were considered in fully-adjusted analyses to further address the possibility of confounding. To account for confounding by indication (in which the underlying disease of gastroesophageal reflux, rather than treatment, could be linked to incident disease or LV morphology), analyses were repeated in a restricted cohort comparing participants who used H2RAs to those who used proton pump inhibitors (8). In a second cohort, to account for confounding related to a participant's likelihood to use H2RAs, propensity scores were used to match H2RA users with nonusers of a similar propensity to use H2RAs. The propensity to use H2RAs was calculated as a logit function including factors hypothesized to predict H2RA use, such as comorbidity, body mass index (BMI), and insurance status (see the Online Appendix for all covariate choices and matching scheme).

Exploratory analyses evaluated associations between H2RA use and heart failure in groups with differing predicted HF risk. These analyses were predicated on the hypothesis that, if a treatment effect exists, it might be most apparent in individuals at the highest risk for heart failure. A HF risk score derived from the ARIC (Atherosclerosis Risk in Communities) study was estimated for each participant with available measures using baseline characteristics (17). The percent of participants with incident HF at any point during follow-up for a given predicted baseline risk (determined by the ARIC risk score) was evaluated using locally-weighted scatterplot smoothing (LOWESS). This allowed a depiction of the observed HF incidence in groups of individuals with different predicted risk at baseline. Kaplan-Meier cumulative event curves, HF incidence, relative risk, and risk difference were also presented in stratified cohorts with high (ARIC risk score >11) and low (ARIC risk score ≤ 11) risk at baseline. Further exploratory models evaluated whether age, sex, BMI category, beta-blocker use, or baseline NT-proBNP level modified associations between H2RA use and heart failure.

In the primary analyses, H2RA exposure was evaluated at the earliest available time point (baseline) since the etiologic window of H2RA use relevant to HF is unknown, but may be protracted given potential biologic mechanisms involving cardiac fibrosis or remodeling. To test the validity of this assumption for H2RA use and explore timing and duration of H2RA use, time-varying exposure models characterized the association between active/current H2RA use with incident HF (Online Figure 1 and Online Appendix).

Linear regression was used to characterize associations between H2RA use at the baseline exam, initial LV parameters, and change in LV parameters over time (e.g., baseline LV mass subtracted from LV mass at the follow-up CMR). Models with limited adjustment, full adjustment, and full adjustment with comedication use were considered in both full and restricted cohorts. We adjusted for the sum of LV parameters (e.g., baseline LV mass added to LV mass at the follow-up CMR) in all models of LV change to address concerns that change in LV parameters was confounded by baseline differences. This allowed inference on LV change independent of differences in the absolute magnitude of LV measures. We used consistency of H2RA use (nonuse, use during any single MESA examination, or use noted during at least 4 MESA examinations) as a plausible surrogate for cumulative dose over time in analyses of LV change and presented these results as marginal predictions from fully-adjusted linear regression models. Analyses were performed using STATA 12.0 (StataCorp, College Station, Texas).

Results

Of 6,814 participants enrolled in MESA, follow-up for incident HF was obtained for 6,783 individuals. Covariates were missing in 405 participants, leaving 6,378 subjects in the cohort evaluated for incident HF (94% of all participants). Of these, 4,691 completed a baseline CMR and were included in the cohort describing cross-sectional associations between H2RA use and the LV. A follow-up CMR was obtained in 2,806 participants (107 H2RA users and 2,699 nonusers) a median of 9.4 years after the first CMR (interquartile range [IQR]: 9.1 to 9.7 years). These participants were included in the cohort describing associations between H2RA use and longitudinal changes in the LV (Figure 1).

The mean age of the study sample was 62.3 years, 52.7% were women, and 37.9% were white. The 313 H2RA users in the cohort evaluated for incident HF tended to be older and heavier, were more likely to be white and to use other non-H2RA medications, and had a higher prevalence of hypertension than 6,065 nonusers (Table 1). Of 313 H2RA users, 170 (54.3%) reported use at only 1 MESA exam and 47 (15.0%) reported H2RA use at 4 or more MESA exams. Median follow-up was 11.2 years (IQR: 10.6 to 11.7 years) and total follow-up was 65,082 person-years. In unadjusted analyses, 6 H2RA users developed HF in 3,082 person-years (1.9 events per 1,000 person-years) and 230 nonusers developed HF in 62,000 person-years (3.7 events per 1,000 person-years) (p value from a log-rank test of the Kaplan-Meier survival function = 0.11) (Central Illustration).

H2RA use at the baseline exam was associated with a 62% lower risk of HF (adjusted hazard ratio [HR]: 0.38; 95% confidence interval [CI]: 0.17 to 0.86; p = 0.02) (Table 2). This association was stronger when accounting for NT-proBNP and troponin T at baseline (adjusted HR: 0.18; 95% CI: 0.05 to 0.62; p = 0.007) (Table 2). Associations were similar with adjustment for comedication use, when the cohort was restricted to propensity-matched participants, and when the cohort was restricted to participants who used either H2RAs or proton pump inhibitors (Table 2).

The largest unadjusted risk difference for heart failure was seen in participants with the highest predicted risk for HF at baseline (Central Illustration). H2RA users with low predicted HF risk (ARIC score ≤ 11) had a relative risk for heart failure of 0.5 and experienced 0.5 fewer episodes of incident HF per 1,000 person-years than nonusers. H2RA users with higher HF risk (ARIC score >11) had a relative risk for heart failure of 0.4 and experienced 5.3 fewer episodes of incident HF per 1,000 person-years (Central Illustration).

Age, sex, BMI and beta-blocker use did not modify associations between H2RA use and HF (p for the interaction: 0.37, 0.13, 0.49, and 0.25 respectively). Similar to results stratified by HF risk score, baseline NT-proBNP was an effect modifier of the association between H2RA use and HF (p < 0.001). Individuals with a higher level of NT-proBNP at baseline had a greater reduction in the hazard of heart failure with H2RA use relative to individuals with a lower level of NT-proBNP at baseline. Use of time-varying exposure models to describe associations between active H2RA use and clinical outcomes suggested a more modest association between concurrent “active” H2RA use and HF development (HR: 0.75; 95% CI: 0.37 to 1.51; p = 0.42). The association was stronger but still not statistically significant

when H2RA use was restricted to participants with at least 1 year of H2RA use (HR: 0.51; 95% CI: 0.21 to 1.23; $p = 0.13$) (Online Tables 1 and 2 for adjusted and unadjusted associations incorporating time varying definitions of H2RA exposure).

H2RA use was associated with differences in baseline CMR. After adjustment for covariates, H2RA use was associated with a smaller LV end-diastolic volume (LVEDV) (-5.7 ml; 95% CI: -8.8 to -2.6 ml, $p < 0.001$), smaller stroke volume (-3.5 ml; 95% CI: -5.6 to -1.4 ml; $p = 0.001$), and a higher mass/volume ratio (0.04 g/ml; 95% CI: 0.02 to 0.07 g/ml; $p < 0.001$). Associations were unchanged with adjustment for comedication use and in the propensity-matched cohort. Restriction to participants who used H2RAs or proton pump inhibitors attenuated associations between H2RA use and baseline CMR metrics (Online Table 3). There was no association between H2RA use and baseline LV ejection fraction or mass.

H2RA use was associated with blunted LV change over time. Among participants who completed both CMRs, LVEDV decreased, LV stroke volume decreased, and mass/volume ratio increased over time. Compared to nonusers, H2RA users had a smaller decline in LVEDV (4.6 ml; 95% CI: 0.4 to 8.8 ml; $p = 0.03$), a smaller decline in LV stroke volume (3.9 ml; 95% CI: 0.7 to 7.1 ml; $p = 0.02$) and a smaller increase in mass/volume ratio (-0.05 g/ml; 95% CI: -0.09 to -0.02 g/ml; $p = 0.005$) over time (Figure 2). Results were not different after further adjustment for comedication use and in the propensity-matched cohort. Restricting analyses to participants with gastroesophageal reflux disease attenuated associations with LV change (Online Table 4). Increasing consistency of H2RA use over time suggested progressively stronger associations with change in LVEDV, LV stroke volume, and mass/volume ratio (Table 3).

Discussion

In the current study, H2RA use was associated with a lower risk for incident heart failure in a multiethnic cohort without CVD at baseline. The strongest association (in absolute terms) was seen in individuals at highest risk for HF. H2RA users had smaller LVEDV and stroke volume at baseline, but over time, H2RA use was associated with a smaller decline in stroke volume, a smaller decline in LVEDV, and a smaller increase in the LV mass/volume ratio.

The association between baseline H2RA use and incident HF persisted regardless of the method used to account for confounding. The cohort matched by propensity to use H2RAs suggested H2RA use, and not characteristics of H2RA users, was responsible for the association. Comparing H2RA users to proton pump inhibitor users again suggested H2RA use, and not the presence of gastroesophageal reflux disease, was responsible for the association. Multivariate models argue that measured differences in cardiovascular risk factors between groups do not explain the reduced HF risk. In fact, there was a particularly large association between H2RA use and HF when adjusting for NT-proBNP (one of the strongest predictors of incident heart failure) and in participants with a high risk of HF as predicted by their ARIC HF risk score (17,18). These findings joined previous observations in animal models to suggest a biologically plausible histamine-related mechanism important to the pathogenesis of heart failure (4,6,7).

This is the first report to suggest H2RA use is associated with decreased HF incidence in humans, but not the first to suggest H2RA use may be important for the heart. Among 318 Japanese participants with HFrEF, use of famotidine (an H2RA) was associated with better New York Heart Association functional class, lower BNP, and a smaller LVEDV (9). In a subsequent prospective randomized trial of 50 participants with HF, Kim et al. compared famotidine to teprenone use over 24 weeks and found improved functional class, decreased BNP, and decreased LV diameter in the famotidine arm (9).

Improved HF symptoms may be related, but are distinct from our description of decreased HF incidence, and our study suggested important differences relative to these previous studies. Among participants with HFrEF, randomized famotidine use was associated with a smaller LV diameter. This agrees with our current cross-sectional observation of a smaller LVEDV among H2RA users, but differs from our finding of a smaller decline in LVEDV over time among H2RA users. This discrepancy may reflect the difference in duration (10 years vs. 24 weeks) and differences in the population being studied. The famotidine trial studied participants with HFrEF where a decrease in the size of a pathologically enlarged LV was a marker of improvement (19). MESA participants were initially free of clinical CVD and without a pathologically enlarged LV at baseline. Some developed HFrEF, some developed HF with preserved ejection fraction (HFpEF), but most did not develop heart failure. Decrease in LV size is not always a marker of improvement. In HFpEF, decreased LV size is associated with disease progression, hospitalization, and death (20). Protection from an age-related decrease in LV size appears better aligned with the current findings and protection from HFpEF might provide a rationale for our observations. Pathophysiology relevant to HFpEF may be further suggested by the less pronounced increase in mass/volume ratio over time in H2RA users, which may imply less concentric remodeling, and the lack of an association between H2RA use and ejection fraction (21,22). Currently there are no beneficial therapies for HFpEF, which is common and serious (23). Although highly speculative based on the current findings, further study of histamine signaling in the pathogenesis of HFpEF may be warranted.

Timing and duration of H2RA use are likely important. Associations with LV morphology were strongest in individuals who reported consistent H2RA use over several MESA exams. Also, while baseline H2RA use was strongly related to HF risk, “active use” was only weakly related to incident HF unless “active use” was restricted to participants who used H2RAs for at least 1 year, possibly suggesting that benefits with early, prolonged, and/or consistent H2RA use exist that are not present with short-term use or use beginning during later stages of HF pathogenesis.

Study Limitations

Associations with cardiac morphology were less consistent than those with heart failure, particularly after restricting to participants with gastroesophageal reflux disease. Furthermore, H2RA users had smaller LVEDV and LV stroke volume at baseline but less decline in these measures over time, which could represent regression to the mean. Regression to the mean would not explain associations with HF and small sample size likely contributed to inconsistency after restriction to participants with gastroesophageal reflux

disease; however, inference on cardiac structure and a paradigm of “protection” from age-related changes in cardiac morphology, which informed our discussion of mechanism, should be more cautious. In addition, HF is a heterogeneous disease. Because of the small number of HF events among H2RA users, this study could not reliably characterize important differences between types of HF relative to H2RA use. Importantly this included an inability to characterize differences in HFpEF relative to HFrEF. Timing and duration of H2RA use may be important, but could not be fully evaluated as MESA did not assess medication use more frequently than every other year and medication use before the baseline exam was not known. Residual confounding, unmeasured confounding, and misclassification in a nonrandomized study are always possible and for this reason inference on pharmaco-epidemiology must be cautious. The relatively small sample size of participants who used H2RAs might lead to less stable estimates of HF incidence than would be seen in a larger population, which further reinforces the need for cautious inference when interpreting the current findings.

Conclusions

H2RA use was associated with a lower risk for incident HF and better preserved stroke volume, LVEDV, and mass/volume ratio over time in community-dwelling adults. Histamine signaling may be important in the pathogenesis of HF and could be an important target for therapy or prevention of heart failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CMR	cardiac magnetic resonance imaging
EDV	end-diastolic volume
H2RA	histamine H ₂ receptor antagonists
HFpEF	heart failure with preserved ejection fraction
HF_rEF	heart failure with reduced ejection fraction
LV	left ventricle
NT-proBNP	N-terminal pro-B-type natriuretic peptide

Perspectives

Competency in Medical Knowledge

Histamine signaling may be important in the pathogenesis of heart failure by inhibiting myocardial fibrosis and apoptosis, and in a cohort observed over 10 years the use of H2 receptor antagonists was associated with a lower the risk of incident heart failure.

Translational Outlook

Randomized trials are needed to verify whether the use of H2 receptor antagonists can influence the development or progression of heart failure and clarify the mechanisms responsible for this effect.

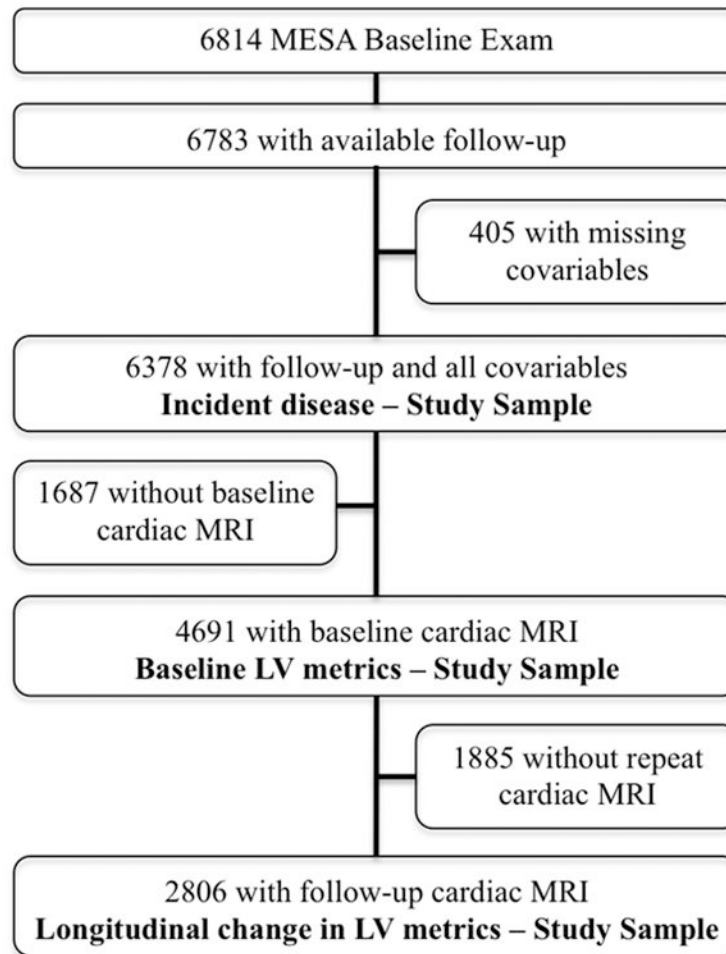


Figure 1. Study Sample

Flow diagram characterizes MESA participants who contributed to each of the analysis cohorts evaluating the relationships between H₂ receptor antagonists (H2RA) and heart failure (HF), baseline cardiac morphology, and change in cardiac morphology over time. MESA = Multi-Ethnic Study of Atherosclerosis.

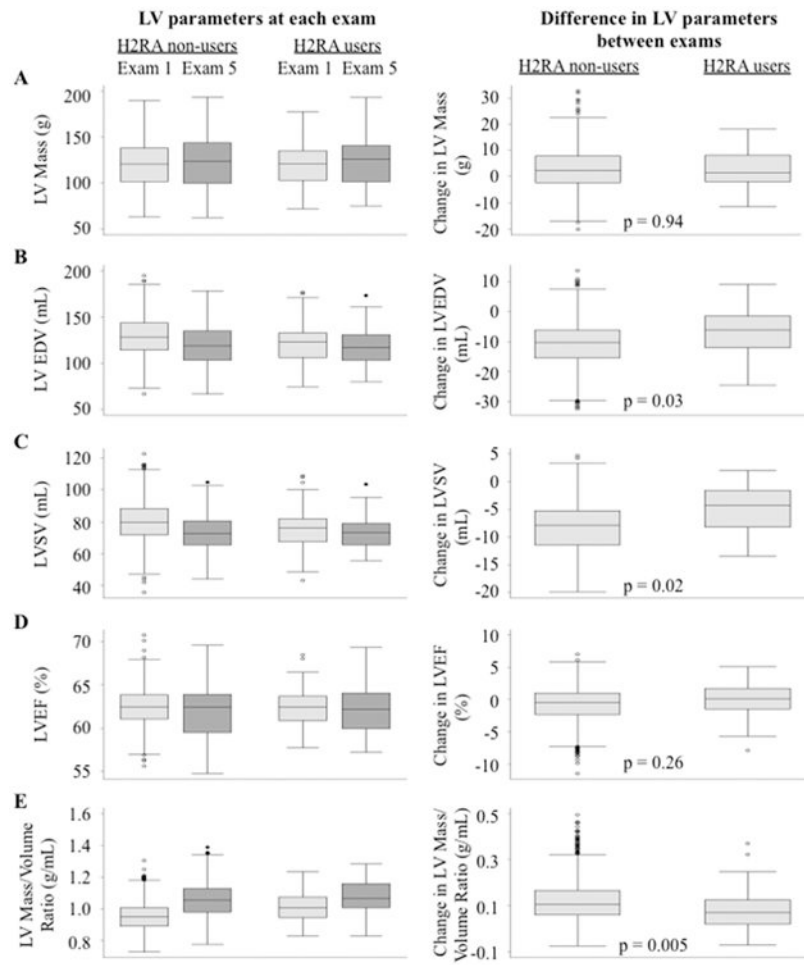
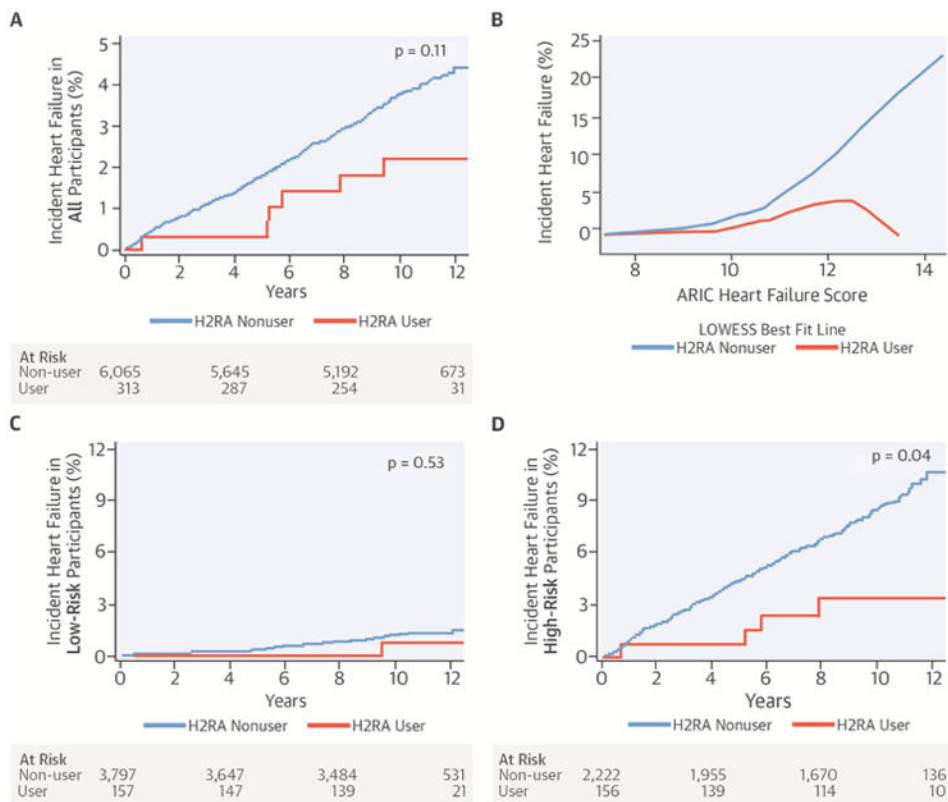


Figure 2. Change in Cardiac Morphology over time in H2RA users relative to non-users
 Change in left ventricular (LV) (A) mass, (B) end-diastolic volume (EDV), (C) stroke volume (SV), (D) ejection fraction (EF), and (E) mass/volume ratio over approximately 10 years can be seen among users and nonusers of H2RAs. Other abbreviations as in Figure 1.



Central Illustration. H2-receptor antagonists and heart failure: Unadjusted associations between H2 receptor antagonists (H2RA) use and heart failure

(A) unadjusted Kaplan-Meier cumulative event curve for incident heart failure in all participants, (B) locally weighted scatterplot smoothing (LOWESS) comparing incident heart failure occurring at any point during follow-up relative to the baseline predicted risk of heart failure (predicted by the ARIC heart failure score), (C) unadjusted Kaplan-Meier cumulative event curve for incident heart failure in participants at LOW risk for heart failure (predicted by an ARIC heart failure score ≤ 11), (D) and unadjusted Kaplan-Meier cumulative event curve for incident heart failure in participants at HIGH risk for heart failure (predicted by an ARIC heart failure score > 11)

ARIC = Atherosclerosis Risk in Communities.

Table 1
Baseline Characteristics

	H2RA Users (n = 313)	H2RA Nonusers (n = 6,065)	p Value
Age, yrs	65.2 ± 9.9	62.1 ± 10.2	<0.001
Female	52.1	52.7	0.84
Race			
White	43.8	37.6	
Chinese	8.0	12.5	0.008
African-American	23.3	28.0	
Hispanic	24.9	21.9	
Height, cm	165.8 ± 9.8	166.3 ± 10.0	0.44
Weight, kg	80.3 ± 16.7	78.5 ± 17.4	0.06
Body mass index, kg/m ²	29.2 ± 5.6	28.3 ± 5.5	0.005
Educational attainment			
No high school degree	18.5	18.2	
High school degree	22.4	17.8	
Some college	17.6	16.2	0.26
Bachelor's degree	17.6	17.5	
Higher than bachelor's degree	13.4	18.2	
Cigarette smoking status			
Never	48.9	51.0	
Former	39.0	36.2	0.62
Current	12.1	12.8	
Pack-years	16.3 ± 26.6	11.0 ± 20.4	<0.001
Hypertension	54.0	44.8	0.002
Systolic blood pressure, mm Hg	129.3 ± 20.4	126.5 ± 21.6	0.03
Diabetes mellitus	14.4	13.6	0.71
Cholesterol, mg/dl	192 (169-214)	192 (170-215)	0.46
Glucose, mg/dl	91 (84-101)	90 (83-99)	0.11
NT-proBNP, pg/ml [*]	66 (30-121)	54 (24-112)	0.02
Medications			
NSAIDs	54.3	40.1	<0.001
Oral steroids	3.8	1.4	0.003
Beta-blockers	12.8	9.4	0.001
ACE inhibitors/ARBs	25.6	18.0	0.001
Any diuretic	19.2	13.3	0.005

Values are mean ± SD, percentage, or median (interquartile range); differences were evaluated with Student *t* test, Fisher exact test, or Wilcoxon rank sum test respectively.

^{*} Available for 5,285 participants.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; H2RA = H₂ receptor antagonist; NSAIDs = nonsteroidal anti-inflammatory drugs; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Table 2
Association of H2RA Use at Baseline and HF

	Adjusted Risk of HF in H2RA Users Relative to Nonusers (N = 6,378)		
	Hazard Ratio	95% CI	p Value
Unadjusted	0.52	0.23 to 1.18	0.12
Limited adjustment [*]	0.40	0.18 to 0.90	0.03
Full adjustment [†]	0.38	0.17 to 0.86	0.02
Full adjustment [†] + comedication use [‡]	0.35	0.16 to 0.80	0.01
Full adjustment [†] + NT-proBNP & troponin T (n = 5,285)	0.18	0.05 to 0.62	0.007
Restricted to H2RA users and PPI users [§] (n = 698)	0.42	0.15 to 1.16	0.09
Restricted to PS matched participants [§] (n = 593)	0.31	0.11 to 0.86	0.03

^{*}Limited adjustment accounts for age, sex, race/ethnicity, height, weight, and study site.

[†]Full adjustment accounts for the limited model and education, cigarette smoking, pack-years, hypertension, systolic blood pressure, diabetes, cholesterol, glucose, and daily exercise.

[‡]Comedication use included NSAIDs (aspirin, Cox-2 inhibitors, and other nonsteroidal inflammatory medications), steroids, beta-blockers (\pm diuretics), ACE inhibitors (\pm diuretics), ARBs (\pm diuretics), any diuretic alone (including potassium-sparing diuretics), leukotriene antagonists, and digoxin.

[§]Participants in the restricted cohorts were considered in models with full adjustment.

CI = confidence interval; PPI = proton pump inhibitor; PS = propensity score; other abbreviations as in Table 1.

Table 3
Consistency of H2RA Use and LV Changes*

Change in LV Parameters Relative to Baseline Exam (n = 2,806)		
	Change	95% CI
<u>Change in LV end-diastolic volume</u>		
No H2RA use	-10.9 ml	-11.7 to -10.0 mL
H2RA use at only 1 study exam	-8.8 ml	-14.4 to -3.2 mL
Consistent H2RA use at 4+ study exams	0.8 ml	-8.1 to 9.6 mL
	Test of trend:	p = 0.02
<u>Change in LV ejection fraction</u>		
No H2RA use	-0.7%	-1.0 to -0.4
H2RA use at only 1ne study exam	-0.1%	-1.9 to 1.8
Consistent H2RA use at 4+ study exams	0.0%	-3.0 to 2.9
	Test of trend:	p = 0.61
<u>Change in LV stroke volume</u>		
No H2RA use	-8.3 ml	-9.0 to -7.7
H2RA use at only 1 study exam	-5.8 ml	-10.1 to -1.5
Consistent H2RA use at 4+ study exams	-0.8 ml	-7.6 to 5.9
	Test of trend:	p = 0.04
<u>Change in LV mass</u>		
No H2RA use	2.9 g	2.2 to 3.6 g
H2RA use at only 1 study exam	0.7 g	-3.8 to 5.2 g
Consistent H2RA use at 4+ study exams	6.3 g	-0.8 to 13.3
	Test of trend:	p = 0.60
<u>Change in LV Mass/Volume Ratio</u>		
No H2RA use	0.12 g/ml	0.11 to 0.13
H2RA use at only one study exam	0.08 g/ml	0.03 to 0.13
Consistent H2RA use at 4+ study exams	0.04 g/ml	-0.03 to 0.12
	Test of trend:	p = 0.02

* Changes between the initial and the follow-up cardiac magnetic resonance imaging (CMR) exam.

All models fully adjusted for age, sex, race/ethnicity, height, weight, study site, the sum of the left ventricular (LV) parameter of interest at CMR 1 and CMR 2, education, cigarette smoking, pack-years, hypertension, systolic blood pressure, diabetes, cholesterol, glucose, and daily exercise.

Other abbreviations as in Tables 1 and 2.