

Histamine H2-receptor antagonists, left ventricular morphology and the risk for heart failure: The Multi-Ethnic Study of Atherosclerosis

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Online Supplement

Supplemental Methods

Cardiac MRI

At baseline examination (2000-2002), endocardial and epicardial borders of the LV were obtained from cMRI short axis fast gradient recalled (FGRE) cine images using a semi-automated method (MASS 4.2, Medic, Leiden, the Netherlands). At exam 5 (2010-2012), endocardial and epicardial borders of the LV were determined from steady state free precession (SSFP) cine images using the CIM software package (version 6.2, Auckland MRI Research Group, University of Auckland, New Zealand). Reflecting changes in clinical cardiac MRI technology that has occurred since the baseline exam, the MRI follow-up protocol used a different pulse sequence (SSFP) than that of the baseline exam (FGRE). SSFP allows faster imaging exams with higher image quality but is known to produce LV mass measurements that are smaller than FGRE. In addition, the follow-up exam used different imaging readers and incorporated advances in analysis software.

To adjust for these differences, two calibration curves were sequentially applied to each participant's baseline LV mass and volume measurements: one curve to correct for potential reader-software differences and one to correct for potential pulse sequence differences. The latter also corrects for scanner equipment differences between baseline and follow-up exams. To provide data for these calibration curves, 498 participants were randomly chosen to form a calibration group that underwent FGRE and SSFP MRI during the follow-up exam. In selecting this group, body surface area quintiles were equally sampled so that subsequent calibration curves would be representative of all body sizes.

Data from the calibration group was used to construct two calibration curves as follows. MESA Exam 5 imaging readers re-analyzed the calibration group's MESA Exam 1 MRI data using MESA Exam 5 software (CIM) and reading protocols. The reader-software calibration curves were constructed by plotting these readings against the MESA Exam 1 baseline measurements. The MESA Exam 5 readers also used CIM to analyze the calibration group's MESA Exam 5 FGRE images. The pulse sequence calibration curves were constructed by plotting these FGRE readings against the main SSFP measurements by the same readers. Calibration curves were found to be linear and fitted with ordinary regression methods.

Papillary muscles and trabeculae were included in LV volumes and excluded from LV mass. LV end-systolic volume and LV end-diastolic volume (LVEDV) were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. The difference between epicardial and endocardial volumes (septum and free wall) multiplied by the specific gravity of the heart (1.04g/mL) was used to estimate LV mass. LV stroke volume

was calculated by subtracting LV end-systolic volume from the LVEDV. LV ejection fraction (LVEF) was calculated by dividing LV stroke volume by LVEDV. The LV Mass/Volume ratio was obtained by dividing LV mass (g) by LVEDV (mL).

Propensity score models

Propensity of a participant to use H2RAs was calculated as a logit function accounting for demographics (age, sex, race/ethnicity, study site), comorbidity (hypertension, diabetes, arthritis, metabolic syndrome, glucose, cholesterol, creatinine), health behaviors (height, weight, body mass index, hip circumference, waist circumference, body surface area, intentional exercise, a fiery temperament, smoking status, pack-years of smoking, co-medication use, total number of medications used), and socio-economic status (education, income, home ownership or rental, insurance status: military, private, medicare, or uninsured). Nearest-neighbor matching was used to create pairs of H2RA users and non-users who had an otherwise similar likelihood of use. Only H2RA users with a propensity score less extreme than non-users were matched (common support). Matched pairs were included only if propensity scores differed by less than 0.05 standard deviations to ensure similarity.

Time-varying exposure

H2RA use was assessed at each MESA examination (Exams 1 – 5). We constructed five discrete time blocks and assigned exposure status based on the corresponding MESA examination. Each time block ranged from the index exam and continued until the subsequent exam (except in the case of the last block where the time block started at Exam 5 and continued until the conclusion of follow-up). The time block was participant and block specific depending on the number of days between each exam. This is depicted in Figure e1 where the H2RA exposure for “time block 1” would be defined at “Exam 1”, for “time block 2” would be defined at “Exam 2”, and so forth. If a participant missed an interval exam their exposure status was carried forward from the previous exam.

Extended Cox proportional hazard models were used to describe the relationship between ‘active’ H2RA use and clinical outcomes. A participant was analyzed separately for each time block in which they contributed follow-up time based on their H2RA exposure status in that time block. Results were clustered on individual participants to account for intra-individual correlation and avoid erroneously suppressing the variance.

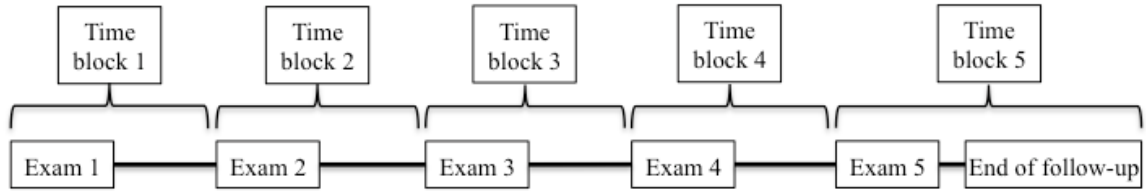
Three time-varying analyses were considered to explore aspects related to the timing of exposure:

- (1) In the first analysis “active” use was compared to non-use such that a participant could contribute risk-time as both an H2RA users and non-users. In this analysis only H2RA use at the exam preceding a heart failure event was used to determine exposure status for that event.
- (2) We hypothesized that previous use might lead to durable changes in heart failure risk; therefore, “active” use was compared to non-use among “never-users.” A participant was considered an H2RA user only during time blocks preceded by an exam documenting H2RA use. Distinct from the first analysis, a participant who used H2RAs at any exam was not considered as a non-user in time blocks where they were not “actively” using H2RAs. The reference group was participants who did not use H2RAs at any MESA exam.
- (3) We hypothesized that relationships between H2RA use and heart failure might take time to

develop; therefore, in a final time-varying analysis, a participant was not considered an H2RA user until they had used H2RAs for at least one year. A participant was considered an H2RA user if (a) they reported use at the first exam (where previous use could not be determined), (b) 365 days or more after a subsequent MESA exam reporting H2RA use, or (c) immediately after an exam documenting use in a participant who reported use at the previous MESA exam. The reference group was participants who did not use H2RAs at any MESA exam.

A model accounting for time-varying differences in diabetes, hypertension, and weight was considered to evaluate whether associations between H2RA use and heart failure were dependent on changes in these cardiac risk factors over time.

Figure E1. Discrete time intervals for the analysis of H2 Receptor Antagonist Use as a time-varying exposure



Online Table 1. Unadjusted relative risk of heart failure among H2RA users and non-users with use defined at either the baseline exam or time-varying over the course of follow-up

	H2RA users			non-H2RA users			RR
	Events (n)	Person-time (years)	Incidence*	Events (n)	Person-time (years)	Incidence*	
H2RA use determined at the baseline exam (Primary analysis)							
Heart Failure	6	3,082	1.9	230	62,000	3.7	0.5
Time-varying H2RA use: “active” use relative to non-use							
Heart Failure	8	2,334	3.4	228	62,748	3.6	0.9
Time-varying H2RA use: “active” use relative to non-use among “never-users”							
Heart Failure	8	2,334	3.4	217	58,573	3.7	0.9
Time-varying H2RA use: “active” use for at least 365 days relative to non-use among “never-users”							
Heart Failure	5	2,080	2.4	217	58,573	3.7	0.6

Definition of abbreviations: H2RA-H2 receptor antagonist; RR- relative risk

**Incidence is in 1,000 person-years*

Online Table 2. Relationship of H2-receptor antagonist use (time-varying exposure*) with heart failure (n=6,378)

Outcome	Risk of heart failure in H2RA users relative to non-users		
	Hazard Ratio	95% CI	p-value
<u>“Active” H2RA use relative to non-use</u>			
Limited adjustment	0.78	0.38 to 1.58	0.49
Full adjustment	0.75	0.37 to 1.51	0.42
Full adjustment + time-varying diabetes, hypertension, & weight	0.76	0.37 to 1.54	0.44
Full adjustment + Co-medication use	0.74	0.36 to 1.51	0.41
Restricted to H2RA users & PPI users (n=697)	0.70	0.23 to 2.10	0.52
Restricted to PS matched participants (n=592)	0.64	0.18 to 2.20	0.47
<u>“Active” H2RA use relative to non-use among “never-users”</u>			
Limited adjustment	0.76	0.38 to 1.54	0.45
Full adjustment	0.72	0.36 to 1.47	0.37
Full adjustment + time-varying diabetes, hypertension, & weight	0.73	0.36 to 1.48	0.39
Full adjustment + Co-medication use	0.69	0.34 to 1.42	0.32
Restricted to H2RA users & PPI users (n=697)	0.42	0.12 to 1.45	0.17
Restricted to PS matched participants (n=592)	0.48	0.14 to 1.68	0.25
<u>“Active” H2RA use for at least 365 days relative to non-use among “never users” (n=6,299)</u>			
Limited adjustment	0.53	0.22 to 1.29	0.16
Full adjustment	0.51	0.21 to 1.23	0.13
Full adjustment + time-varying diabetes, hypertension, & weight	0.51	0.21 to 1.26	0.15
Full adjustment + Co-medication use	0.49	0.20 to 1.20	0.12
Restricted to H2RA users & PPI users (n=685)	0.18	0.05 to 0.68	0.01
Restricted to PS matched participants (n=585)	0.21	0.04 to 1.07	0.07

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

Co-medication use included non-steroidal anti-inflammatory medications (aspirin, cox-2 inhibitors, and other non-steroidal inflammatory medications), steroids, beta-blockers (\pm diuretics), ACE-inhibitors (\pm diuretics), angiotensin receptor blockers (\pm diuretics), any diuretic (including potassium-sparing diuretics), leukotriene antagonists, and digoxin

Participants in the restricted cohorts were considered in models with full adjustment

Online Table 3. A cross-sectional comparison of left ventricular morphology at baseline between participants who used H2-receptor antagonists relative to those participants who did not use H2-receptor antagonists (n=4,691)

	Difference in baseline LV parameter for H2RA users relative to non-users		
	Difference	95% CI	p-value
<u>LV End Diastolic Volume (mL)</u>			
Limited adjustment	-5.9	-9.0 to -2.7	<0.001
Full adjustment	-5.7	-8.8 to -2.6	<0.001
Full adjustment + Co-medication use	-5.7	-8.8 to -2.6	<0.001
Restricted to H2RA users & PPI users (n=475)	-2.5	-6.9 to 1.8	0.25
Restricted to PS matched participants (n=427)	-5.3	-9.8 to -0.8	0.02
<u>LV Ejection Fraction (%)</u>			
Limited adjustment	-0.1	-0.9 to 0.7	0.81
Full adjustment	-0.1	-0.9 to 0.7	0.78
Full adjustment + Co-medication use	-0.1	-0.9 to 0.7	0.86
Restricted to H2RA users & PPI users (n=475)	0.0	-1.1 to 1.1	0.98
Restricted to PS matched participants (n=427)	-0.9	-2.0 to 0.3	0.15
<u>LV Stroke Volume (mL)</u>			
Limited adjustment	-3.5	-5.7 to -1.4	0.001
Full adjustment	-3.5	-5.6 to -1.4	0.001
Full adjustment + Co-medication use	-3.4	-5.6 to -1.3	0.002
Restricted to H2RA users & PPI users (n=475)	-1.5	-4.6 to 1.6	0.35
Restricted to PS matched participants (n=427)	-4.3	-7.5 to -1.0	0.01
<u>LV Mass (g)</u>			
Limited adjustment	-0.8	-3.5 to 1.9	0.58
Full adjustment	-0.6	-3.2 to 1.9	0.63
Full adjustment + Co-medication use	-0.9	-3.4 to 1.7	0.51
Restricted to H2RA users & PPI users (n=475)	-0.5	-4.0 to 2.9	0.77
Restricted to PS matched participants (n=427)	0.9	-2.6 to 4.3	0.61
<u>LV Mass/Volume Ratio (g/mL)</u>			
Limited adjustment	0.04	0.02 to 0.07	<0.001
Full adjustment	0.04	0.02 to 0.07	<0.001
Full adjustment + Co-medication use	0.04	0.02 to 0.06	<0.001
Restricted to H2RA users & PPI users (n=475)	0.02	-0.01 to 0.05	0.26
Restricted to PS matched participants (n=427)	0.05	0.02 to 0.08	0.004

Definition of abbreviations: CI-confidence interval; H2RA-H2 receptor antagonist; LV-left ventricular; PPI-proton pump inhibitor; PS-propensity score

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

Co-medication use included non-steroidal anti-inflammatory medications (aspirin, cox-2 inhibitors, and other non-steroidal inflammatory medications), steroids, beta-blockers (± diuretics), ACE-inhibitors (± diuretics), angiotensin receptor blockers (± diuretics), any diuretic (including potassium-sparing diuretics), leukotriene antagonists, and digoxin

Participants in the restricted cohorts were considered in models with full adjustment

Online Table 4. A comparison of the change in left ventricular morphology between initial and follow-up cardiac MRIs in participants who used H2-receptor antagonists relative to those participants who did not use H2-receptor antagonists (n=2,806)

	Change in LV parameters for H2RA users relative to non-users		
	Change	95% CI	p-value
<u>Change in LV End Diastolic Volume (mL)</u>			
Limited adjustment	4.8	0.6 to 9.0	0.03
Full adjustment	4.6	0.4 to 8.8	0.03
Full adjustment + Co-medication use	4.6	0.4 to 8.9	0.03
Restricted to H2RA users & PPI users (n=262)	2.0	-3.8 to 7.7	0.49
Restricted to PS matched participants (n=230)	4.8	-1.2 to 10.8	0.12
<u>Change in LV Ejection Fraction (%)</u>			
Limited adjustment	0.7	-0.7 to 2.1	0.31
Full adjustment	0.8	-0.6 to 2.2	0.26
Full adjustment + Co-medication use	0.7	-0.7 to 2.1	0.35
Restricted to H2RA users & PPI users (n=262)	0.7	-1.2 to 2.6	0.46
Restricted to PS matched participants (n=230)	1.1	-1.0 to 3.3	0.31
<u>Change in LV Stroke Volume (mL)</u>			
Limited adjustment	3.9	0.7 to 7.1	0.02
Full adjustment	3.9	0.7 to 7.1	0.02
Full adjustment + Co-medication use	3.7	0.5 to 7.0	0.02
Restricted to H2RA users & PPI users (n=262)	1.9	-2.4 to 6.1	0.39
Restricted to PS matched participants (n=230)	4.3	-0.3 to 9.0	0.07
<u>Change in LV Mass (g)</u>			
Limited adjustment	-0.1	-3.5 to 3.3	0.97
Full adjustment	0.0	-3.4 to 3.3	0.99
Full adjustment + Co-medication use	0.2	-3.2 to 3.6	0.89
Restricted to H2RA users & PPI users (n=262)	0.9	-3.5 to 5.3	0.69
Restricted to PS matched participants (n=230)	-1.0	-5.9 to 3.8	0.68
<u>Change in LV Mass/Volume Ratio (g/mL)</u>			
Limited adjustment	-0.06	-0.10 to -0.02	0.005
Full adjustment	-0.05	-0.09 to -0.02	0.005
Full adjustment + Co-medication use	-0.05	-0.09 to -0.01	0.01
Restricted to H2RA users & PPI users (n=262)	-0.01	-0.07 to 0.05	0.78
Restricted to PS matched participants (n=230)	-0.07	-0.12 to -0.01	0.03

Limited adjustment accounts for age, sex, race/ethnicity, height, weight, study site, the sum of the LV parameter of interest at from both MRIs

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

Co-medication use included non-steroidal anti-inflammatory medications (aspirin, cox-2 inhibitors, and other non-steroidal inflammatory medications), steroids, beta-blockers (\pm diuretics), ACE-inhibitors (\pm diuretics), angiotensin receptor blockers (\pm diuretics), any diuretic (including potassium-sparing diuretics), leukotriene antagonists, and digoxin

Participants in the restricted cohorts were considered in models with full adjustment