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Histamine H_2 Receptor Polymorphisms, Myocardial Transcripts and Heart Failure (From the Multi-Ethnic Study of Atherosclerosis and Beta-blocker Effect on Remodeling and Gene Expression Trial)

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Abstract

Myocardial H_2 receptor activation contributes to heart failure (HF) in preclinical models and H_2 receptor antagonists are associated with decreased HF incidence. This study evaluated whether H_2 histamine receptor (HRH2) single nucleotide polymorphisms (SNPs) are associated with HF incidence or myocardial transcript abundance is associated with recovery. The association of SNPs in HRH2 with incident HF were characterized using Cox proportional hazards regression among participants in the Multi-Ethnic Study of Atherosclerosis (MESA). Differences in myocardial HRH2 transcripts were characterized in participants with dilated cardiomyopathy comparing six "Super-responders" with six Non-responders to beta-blockade in the Beta-blocker Effect on Remodeling and Gene Expression (BORG) Trial. In MESA, no candidate SNP was associated with HF in Black, Hispanic, or White participants. The rs2241562 minor allele was only present in

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Chinese participants and the adjusted HF hazard among those with one or more copies of this allele was 3.7, 95% CI 1.0 to 13.4. In BORG, super-responders to beta-blockade had higher levels of myocardial HRH2 transcript at baseline compared with non-responders (Fragments per kilobase per transcript per million mapped reads: Variant 2, 5.5 ±1.1 compared with 3.2 ±0.8 in non-responders, p=0.002; variant 1+2, 32.1 ±7.4 compared with 23.3 ±4.2 in non-responders, p=0.04). In conclusion, **t**he presence of a minor allele at rs2241562 was associated with increased HF incidence in Chinese participants. Differences in myocardial HRH2 transcript abundance were seen in participants with dilated cardiomyopathy who responded to beta-blockade. These observations support the hypothesis that HRH2 is involved in the pathogenesis of HF.

Keywords

Heart failure; histamine; genetic epidemiology

Introduction

We previously observed that H_2 receptor antagonist use was associated with favorable cardiac morphology and decreased heart failure (HF) incidence in community dwelling adults.[1,2] Although we attempted to account for confounding, residual or unmeasured confounding related to medication use could not be excluded as the basis for the association. Associations between HF and H_2 receptor (HRH2) genetic variants or HRH2 transcript abundance in the myocardium should not be subject to confounding from characteristics that influence medication use. These genetic and transcriptional characteristics of HRH2 might help to understand whether H_2 receptor signaling is important in myocardial dysfunction in human disease. In the current report, we further tested the general hypothesis that H_2 receptor mediated signaling is important in the establishment or progression of HF using data from two prospectively conducted studies. We tested the specific hypotheses that (1) HRH2 gene variants are associated with incident HF in the Multi-Ethnic Study of Atherosclerosis (MESA) and (2) that myocardial HRH2 gene expression is related to the ventricular response to beta-blocker therapy in the Beta-blocker Effect on Remodeling and Gene Expression (BORG) Trial of persons with dilated cardiomyopathy.[3,4]

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study designed to investigate subclinical cardiovascular disease. MESA recruited participants aged 45–84 years old without clinical cardiovascular disease from 6 US communities between 2000 and 2002.[3] Evaluation included 5 examinations over approximately 10 years. Clinical outcomes in MESA participants were assessed at study examinations and by annual telephone interview. Criteria for incident HF consisted of first-time HF symptoms, a physician diagnosis of HF, and an objective feature of HF (dilated left ventricle (LV) 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. Differences were adjudicated or presented to the full events committee for

a final determination. Full details of covariate measurement and event ascertainment are available in MESA's manual of procedures (MOP).[5]

The Beta-blocker Effect on Remodeling and Gene Expression Trial (BORG, NCT01798992) was conducted at the Universities of Colorado and Utah between 2000 and 2008.[4] Participants with idiopathic dilated cardiomyopathy (IDC) and HF with reduced left ventricular ejection fraction (LVEF) (defined as LVEF <40%) were randomized to carvedilol, metoprolol or metoprolol plus doxazosin, regimens that have in common blockade of beta-1 adrenergic receptors. All participants in the current H_2 receptor sub-study were evaluated with radionuclide SPECT ventriculography to estimate LVEF and had an endomyocardial biopsy before and after treatment with beta-blocking agents.[4] Six of 47 participants who completed the BORG Trial were classified as reverse remodeling "Super-responders" and 6 participants were classified as Non-responders. Super-responders were defined as participants whose LVEF increased ≥10 absolute % (EF Units) on follow-up study at either 3 or 12 months after starting beta-blockers. A random sample of gender matched non-responders had an LVEF change of <5 EF units.[4] Institutional Review Boards of participating institutions approved all protocols in both MESA and the BORG trial and all participants provided written informed consent.

For HRH2 genotypes, DNA was extracted from the peripheral leukocytes of MESA participants using a commercially available isolation platform (Puregene; Minneapolis, MN). Genotyping was performed by Illumina Genotyping Services using the GoldenGate Assay. After removal of failed SNPs and samples, the genotyping call rate was 99.93%. HRH2, located on chromosome 5q35.2, covers 28 kilobases and has two introns.[6,7] Sixteen SNPs in HRH2 were measured in MESA. After removal of variants with a minor allele frequency <1% and SNPs in high linkage disequilibrium, 4 SNPs remained for analysis (rs2241562, rs6864183, rs643586, rs647384). Rs2241562 is a non-coding variant in the 3′ untranslated region within a half a kilobase of the 3′ end of the gene. Rs6864183 and rs643586 are intron variants. Rs647384 is an upstream non-coding variant within two kilobases of the 5′ start of the gene.[8]

For transcript analyses, whole transcriptome shotgun RNA sequencing (RNA-Seq) was used to assess characteristics of myocardial HRH2 gene expression in failing compared with reverse remodeled, non-failing human ventricular myocardium.[4] RNA was extracted from RV distal septum endomyocardial biopsies taken from 12 IDC patients before and after treatment with beta-blocking agents for 3 (1 super-responder and 1 non-responder) or 12 (5 super-responders and 5 non-responders) months.[4] RNA-Seq methodology is described in the online supplement. For HRH2, 2 transcripts were identified by RNA-Seq. Variant 1 (ENST00000377291) is a 2561 base pair transcript with 2 retained introns and 3 exons, two of which are translated into a 397 amino acid protein.[8] Variant 2 (ENST00000231683) is a lower abundance, 1080 base pair intronless transcript that codes for a 359 amino acid protein that is homologous to that predicted from the originally cloned human HRH2 cDNA, considered to be the canonical sequence of HRH2.[7–9] Variant 2 is contained within exon 2 of Variant 1.

In the candidate gene analysis, Cox proportional hazards were used to estimate adjusted and unadjusted associations between SNPs and HF incidence. Given the low minor allele frequency for most SNPs, the risk for HF in individuals with one or more minor alleles was compared to those without a minor allele (dominant model). Minor allele frequencies for measured SNPs varied substantially by race/ethnicity and results were stratified by race/ethnicity to minimize potential bias from population stratification. In adjusted models, we included participants' age, gender, and the first three principal components of genetic ancestry. Principal components are a continuous measure of genetic ancestry with the potential to account for differences in race/ethnicity not apparent in self-identified racial/ethnic categories and were included to further minimize the impact of population stratification. A third *a priori* analysis explored associations between SNPs and HF incidence only in participants with a history of hypertension. This analysis intended to explore a 'multi-hit' hypothesis. Pre-clinical models suggest differences in myocardial fibrosis with H_2 intervention are most pronounced following aortic banding, which has some similarity to the myocardial stress imposed by clinical hypertension.[10] In candidate gene analyses, p=0.05 was considered significant for primary inference; however, analyses involved 8 core evaluations of SNPs in racial/ethnic groups with a sufficient minor allele frequencies to permit analysis. A Bonferroni corrected p-value of 0.006 was also considered in the strength of inference on results.

In the myocardial gene expression analysis, HRH2 transcript levels were compared by Wilcoxon rank-sum and signed-rank tests. HRH2 myocardial transcript levels were compared between Super-responders and non-responders before and after beta-blocker treatment. In BORG analyses, p=0.05 was considered significant for primary inference; however, a Bonferroni corrected p-value of 0.004 for twelve comparisons was considered in the ultimate strength of inference on the results. All analyses were performed using STATA 12.0 (StataCorp, College Station, TX, USA) or GraphPad Prism 7.

Results

The MESA study population for the HRH2 candidate gene analysis consisted of 6,270 persons with available SNPs in HRH2 and principal components of genetic ancestry. There were 767 participants with Chinese ancestry, 1,598 Black participants, 1,425 Hispanic participants, and 2,480 White participants (Figure 1). The incidence of HF per 1000 person-years was 2.0 (n=16) among Chinese participants, 4.3 (n=68) among Black participants, 3.8 (n=55) among Hispanics, and 3.8 (n=100) among Whites. Traditional cardiovascular disease risk factors including cigarette smoking, hypertension, diabetes, medication use, cardiac morphology, and NT-pro-BNP differed between racial/ethnic groups at baseline (Table 1). Minor allele frequency of evaluated SNPs by race/ethnicity is presented in Table 2.

The minor allele for rs2241562 was present only in Chinese participants (Table 2). Chinese participants possessing one or more copies of the minor allele were at increased risk of HF in adjusted models compared with persons homozygous for the major allele (p=0.05). Of 764 Chinese participants, 708 were homozygous for the major allele, 55 were heterozygous, and 1 was homozygous for the minor allele. Thirteen Chinese participants homozygous for the major allele at rs2241562 developed HF over 7,395 person-years (1.8 events per 1,000

person years) and three participants who were heterozygous developed HF over 537 person-years (5.6 events per 1,000 person-years). The participant who was homozygous for the minor allele did not develop HF over eight years of follow-up. Restricting the analysis to Chinese participants with a history of hypertension, the hazard for HF with a minor allele at rs2241562 increased (p=0.01). Of 287 Chinese participants *with a history of hypertension* at the baseline MESA exam, 263 were homozygous for the major allele and 24 were heterozygous at rs2241562. No Chinese participant *with a history of hypertension* was homozygous for the minor allele at rs2241562. Nine participants who were homozygous for the major allele *and had a history of hypertension* developed HF over 2,669 person-years (3.4 events per 1,000 person-years) and three participants who were heterozygous *and had a history of hypertension* developed HF over 208 person-years (14.4 events per 1,000 person-years).

The presence of one or more minor alleles in rs643586 or rs647384 was not associated with HF incidence in the ethnic groups in which these genotypes were evaluable (Table 2). Among Chinese participants there was a trend toward increased HF incidence among individuals with one or more copies of rs6864183 (p=0.10), but this trend was not evident in other ethnic groups (Table 2). When considering a conservative Bonferroni correction, no association in MESA was significant.

The study population for HRH2 gene expression in ventricular myocardium consisted of 6 super-responder and 6 non-responder IDC patients treated with beta-blockers (Figure 2). Baseline LVEF was similar between super-responders and non-responders (Table 3). By design, the end-of-study LVEF was higher among super-responders with an LVEF change among super-responders of 31 ± 9 % compared with a non-responder change of 1 ± 6 % (p=0.005). Levels of Variant 1 were not significantly different between super-responders and non-responders at baseline, but Variant 2 and total HRH2 (variant 1 + 2) transcript levels were higher in super-responders (Table 4). Non-responders increased expression of Variant 1 and total HRH2 (Variant 1 + 2) transcripts over the follow-up period, while super-responders did not; however, change over time was not statistically different between the two groups. Super-responders achieved an end of study LVEF of 55 ± 6 %, which is within the normal range. Comparing HRH2 gene expression for biopsies of hearts with normal (follow-up for super-responders) versus abnormal function (baseline for super-responders, baseline for non-responders, and follow-up for non-responders) did not suggest differences in Variant 1 (p = 0.89) or Variant 2 (p = 0.75) (Table 4).

Discussion

Of 4 evaluated SNPs in the H_2 receptor coding region, three were not associated with the occurrence of HF. The presence of a minor allele at rs2241562 in HRH2 was associated with increased risk for HF in participants of Chinese ancestry, particularly among those with hypertension. RNA-Seq confirmed the HRH2 receptor is expressed in human ventricular myocardium and suggested differences in pre-treatment HRH2 expression between participants who ultimately did and did not respond to beta-blockade by normalizing their LV function. These results suggest H_2 receptor signaling may be important in the pathogenesis and progression of HF. These results are unlikely to be confounded by factors

that had the potential to influence our previous work on the pharmacoepidemiology of H_2 receptor antagonist use.

Sequence ontology, rule-based mathematical models based on SNP position, suggests rs2241562 is an intron variant, could be involved in non-sense mediated decay, or may be an enhancer.[11] A nonsense mediated decay variant or enhancer may have functional significance by allowing mRNA coding for dominant negative or deleterious gain-of-function proteins to persist; however, there is no direct evidence that this is true for rs2245162.[12–14] If the association between rs2241562 and HF incidence is true and reproducible, we can suggest, but not conclude the mechanism may involve a gain of function in the H_2 receptor in individuals with the minor allele. The alternative exists that genotypes at rs2241562 may merely be correlated with those at a SNP in a different mechanistically-relevant gene.

Previous candidate gene analyses related to histaminic signaling identified associations between HF and genotypes for the H_3 receptor or histidine decarboxylase.[15,16] Similar to our study, associations with HF were identified, but the relationship between genotype and protein activity was not evaluated. Previous studies found an association with Chinese participants and in our study, the link between HF and HRH2 gene variants was only observed in participants with Chinese ancestry living in the United States.

H_2 signaling is relatively understudied in HF and the association between genetic variation and H_2 receptor function is not known. In pre-clinical models, H_2-receptor knock-out mice had less fibrosis and remodeling in response to increased left heart afterload with aortic banding.[10] In our study, at least among Chinese participants, we observed the largest hazard of HF in individuals with a minor allele at rs2241562 *and* hypertension. Although there are differences between aortic banding and clinical hypertension, the core impact of each is increased load on the left ventricle and an increase in ventricular fibrosis.

We confirmed HRH2 is expressed in human ventricular myocardium and identified two transcripts using RNA-seq. Variant 2 is an intronless variant homologous to the first cloned human HRH2 cDNA and considered to be the canonical sequence. Variant 1 has two retained introns and three exons.[7] Interestingly, participants who responded to beta-blocker therapy had higher baseline levels of the intronless HRH2 transcript (variant 2) and the summary product of both variants. Non-responders subsequently increased expression of the larger transcript (Variant 1) and the summary of both variants after beta-blocker therapy while super-responders experienced little change. Associations between HRH2 transcript levels and protein activity are not known and the associations between myocardial HRH2 transcript, protein levels and/or cardiac remodeling would need confirmation in subsequent investigations.

Cardiac beta-adrenergic and histaminic systems are known to cross-regulate, and it is possible that HRH2 receptor expression could play a role in the remodeling process or in the response to beta-blockers.[17] Furthermore, HRH2 transcript abundance did not differ between failing and non-failing human hearts, which agrees with previous data on H_2-receptor mediated stimulation of adenylate cyclase or muscle contraction in failing and non-failing

hearts.[18,19] Unlike beta-adrenergic signaling in the failing heart, H_2 histamine receptor signaling may remain intact in the failing heart and continue to mediate adverse effects throughout the disease course.[19]

One core limitation is that both cohorts were small. In the MESA cohort, only three participants carrying a minor allele at rs2241562 developed HF. Multiple comparisons further increase the possibility that associations may have occurred by chance, which is underscored by the loss of significance with a Bonferroni corrected α in the MESA population. Thus, the current hypothesis-generating study needs to be repeated in a larger cohort enriched in East Asian ancestry participants. While we showed HRH2 is expressed in human ventricular myocardium and may be altered or predictive of changes in ventricular remodeling, the associations between SNPs and H_2 receptor activity was not evaluated. Also, DNA and RNA was derived from separate studies, the gene expression BORG cohort was too small to detect the low frequency variants identified in MESA, and there were no East Asian ancestry participants in BORG.

At least in part, our results support the hypothesis that the H_2 receptor plays a role in HF pathogenesis. While our observations are not definitive, given the limitations imposed by the sample size, multiple comparisons, and population, the hypothesis is important given the clear potential for existing well-tolerated drugs to target the H_2 receptor. This work joins previous work to suggest randomized study of H_2 receptor antagonism in men and women with or at risk for HF may be justified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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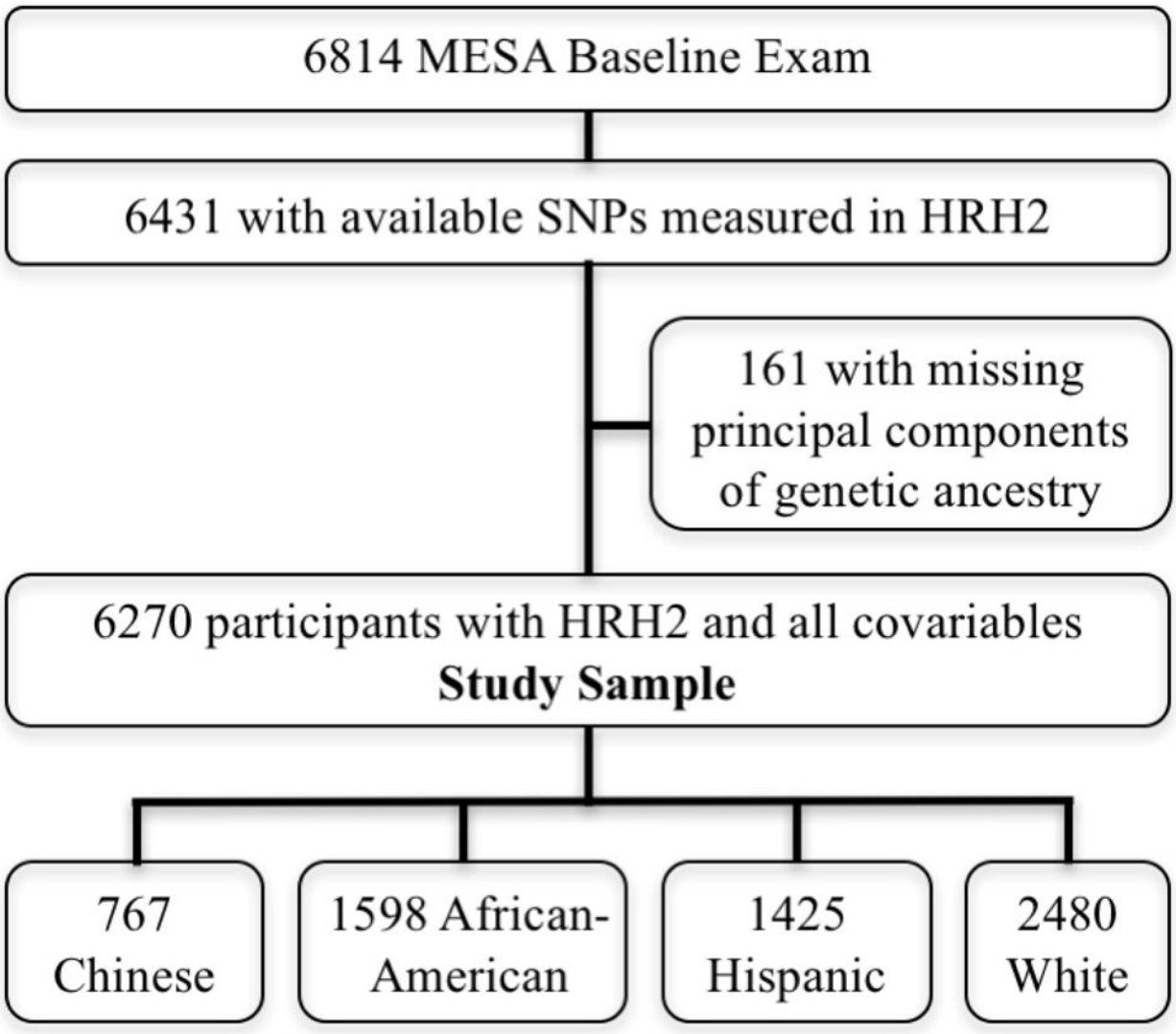

Figure 1.
Study Sample. Flow diagram characterizing MESA participants who contributed the analysis cohorts.

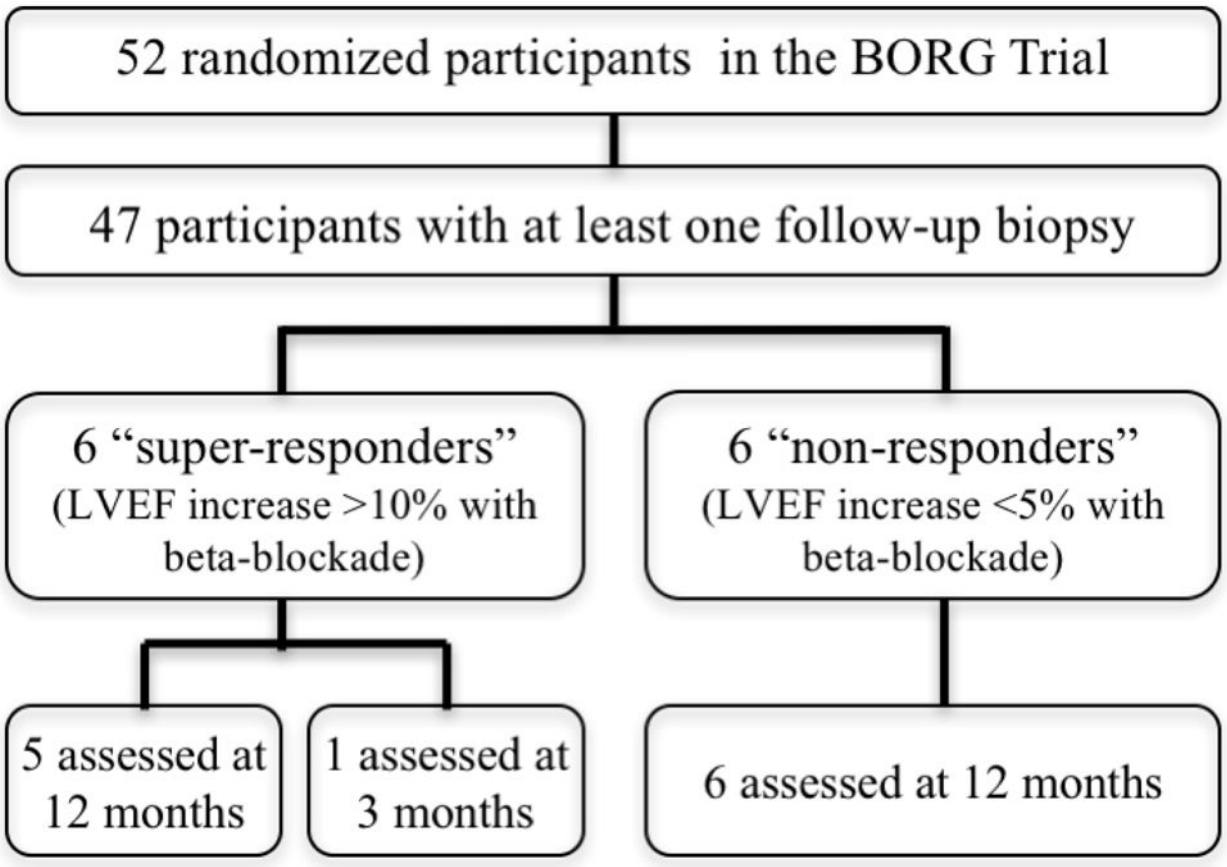

Figure 2.
Study Sample. Flow diagram characterizing BORG participants who contributed the analysis cohort.

Table 1

Baseline characteristics of the MESA study sample

Variable	Chinese n=767	Black n=1,598	Hispanic n=1,425	White n=2,480	p-value
Age (years)	62.3 ± 10.4	62.1 ± 10.1	61.4 ± 10.3	62.7 ± 10.3	0.009
Women	50.6 %	54.4 %	51.7 %	52.3 %	0.06
Body mass index (kilograms/meter^2)	24.0 ± 3.3	30.1 ± 5.9	29.4 ± 5.1	27.8 ± 5.1	<0.001
Cigarette smoking					
Never	74.8 %	45.7 %	53.9 %	44.3 %	
Former	19.5 %	36.1 %	32.6 %	44.2 %	<0.001
Current	5.7 %	18.2 %	13.5 %	11.5 %	
Hypertension	38.7 %	59.6 %	42.2 %	38.5 %	<0.001
Diabetes mellitus	13.6 %	18.7 %	19.3 %	6.8 %	<0.001
Medications					
H_2 Receptor Blocker	3.4 %	3.6 %	5.4 %	5.7 %	0.004
Non-steroidal Anti-inflammatory Medications	22.7 %	41.3 %	35.7 %	55.4 %	<0.001
Oral steroids	0.5 %	1.8 %	1.4 %	1.9 %	0.05
Beta-blockers	10.4 %	10.4 %	8.6 %	9.6 %	0.19
Angiotensin Converting Enzyme					
Inhibitors or Angiotensin II receptor blockers	12.5 %	25.0 %	17.9 %	15.3 %	<0.001
Cardiac Morphology					
Left ventricular mass	123.5 ± 29.7	158.6 ± 41.6	146.6 ± 38.3	144.0 ± 38.2	<0.001
Left ventricular ejection fraction	72.1 ± 6.1	68.1 ± 7.8	68.9 ± 7.3	68.7 ± 7.3	<0.001
Left ventricular end diastolic volume	111.1 ± 22.9	130.9 ± 32.6	127.6 ± 30.3	128.5 ± 32.1	<0.001
NT-pro-BNP (pg/mL)	75.0 ± 110.3	92.3 ± 197.5	113.8 ± 432.0	113.2 ± 154.9	0.007

Results presented as mean ± SD or percentiles as appropriate and compared using analysis of variance

Table 2

The relationship of heart failure occurrence to the presence of minor alleles of SNPs in the H_2 receptor, by race

	Ancestry			
	Chinese HR (95%CI)	**African-American HR (95%CI)**	**Hispanic HR (95%CI)**	**White HR (95%CI)**
rs2241562	MAF (C=3.7%)	MAF (C=0.0%)	MAF (C=0.0%)	MAF (C=0.0%)
Unadjusted	3.1 (0.9–11.0)	–	–	–
Adjusted for age, sex, and PC 1–3	**3.7 (1.0–13.4)** *	–	–	–
Restricted to participants with hypertension †	**6.3 (1.6–25.7)** **	–	–	–
rs6864183	MAF (T=37.5%)	MAF (T=46.6%)	MAF (T=49.3%)	MAF (T=48.6%)
Unadjusted	2.8 (0.8–9.9)	1.1 (0.6–1.8)	1.4 (0.7–2.8)	1.3 (0.8–2.2)
Adjusted for age, sex, and PC 1–3	2.9 (0.8–10.4)	1.1 (0.6–1.9)	1.6 (0.8–3.0)	1.3 (0.8–2.1)
Restricted to participants with hypertension †	3.7 (0.8–17.5)	1.3 (0.7–2.4)	1.2 (0.6–2.6)	1.3 (0.7–2.2)
rs643586	MAF (C=0.1%)	MAF (C=16.4%)	MAF (C=3.0%)	MAF (C=0.0%)
Unadjusted	–	1.3 (0.8–2.0)	0.6 (0.1–2.3)	–
Adjusted for age, sex, and PC 1–3	–	1.3 (0.8–2.1)	0.5 (0.1–2.1)	–
Restricted to participants with hypertension †	–	1.2 (0.7–2.1)	0.8 (0.2–3.7)	–
rs647384	MAF (A=0.0%)	MAF (A=5.4%)	MAF (A=0.9%)	MAF (A=0.0%)
Unadjusted	–	0.6 (0.3–1.6)	–	–
Adjusted for age, sex, and PC 1–3	–	0.7 (0.3–1.8)	–	–
Restricted to participants with hypertension †	–	0.5 (0.2–1.7)	–	–

Abbreviations: HR - hazard ratio associated with each additional minor allele; CI - confidence interval; MAF - minor allele frequency; PC - principal components;

* $p<0.05$,

** $p<0.01$,

† adjusted analyses

Sample Size: Chinese (n=764 or 287 when restricted to those with hypertension); African-American (n=1,598 or 954 when restricted to those with hypertension); Hispanic (n=1,425 or 601 when restricted to those with hypertension); White (n=2,480 or 965 when restricted to those with hypertension)

Table 3

Baseline characteristics of the BORG Trial study sample

Variable	Super-Responders n=6	Non-Responders n=6	p-value
Age (years)	38 ± 20	55 ± 11	0.09
Women	50%	50%	1.00
Race/Ethnicity			
White	67%	67%	
Black	16.5%	0%	0.36
Hispanic	0%	16.5%	
Other	16.5%	16.5%	
Hypertension	33%	0%	0.17
Creatinine clearance (milliliters/minute)	95 ± 17	77 ± 16	0.09
Medications			
Carvedilol	33%	33%	1.00
Metoprolol	33%	33%	1.00
Metoprolol + Doxazosin	33%	33%	1.00
Metoprolol Equivalent Dose (milligrams)	142 ± 67	117 ± 52	0.55
Change in systolic blood pressure (millimeters of mercury)	14 ± 21	−6 ± 12	0.13
Change in diastolic blood pressure (millimeters of mercury)	2 ± 13	0 ± 13	0.81
Left ventricular ejection fraction (baseline)	24 ± 7	31 ± 12	0.34
Left ventricular ejection fraction (follow-up)	55 ± 6	32 ± 12	0.008

Results presented as mean ± SD or percentiles as appropriate. Compared using a 2-sample t-test.

Table 4

RNA transcripts from the HRH2 gene in human ventricular myocardium before and after beta-blocker therapy.

Group and RNA Transcript (Ensembl#)	FPKM			P value	
	Baseline	Follow-up	Fold Change	Within group	Between groups
Non-Responders					
ENST00000377291 (Variant 1)	20.2 ±3.8	26.4 ±8.3	1.3 ±0.3	0.03	–
ENST00000231683 (Variant 2)	3.2 ±0.8	3.5 ±1.4	1.1 ±0.4	0.84	–
Variant 1 + Variant 2	23.3 ±4.2	29.9 ±9.3	1.3 ±0.3	0.03	–
Super-Responders					
ENST00000377291 (Variant 1)	†26.6 ±6.8	24.6 ±7.5	1.0 ±0.5	0.56	0.18
ENST00000231683 (Variant 2)	‡5.5 ±1.1	4.2 ±1.1	0.8 ±0.3	0.18	0.13
Variant 1 + Variant 2	§32.1 ±7.4	28.8 ±8.6	0.9 ±0.4	0.56	0.13
Normal versus abnormal heart function	**Normal**	**Abnormal**			
ENST00000377291 (Variant 1)	24.6 ± 23.0	24.9 ± 25.8			
ENST00000231683 (Variant 2)	4.2 ± 4.0	4.4 ± 4.5			

Normal heart function includes samples from super responders at follow-up and abnormal heart function includes samples from super-responders at baseline and samples from non-responders at both baseline and follow-up. *Within group* comparisons evaluate change in transcript abundance between baseline and follow-up for non-responders or super-responders separately; *Between group* comparisons evaluate whether the change between baseline and follow-up was different in super-responders compared with non-responders. Abbreviations: FPKM - Fragments Per Kilobase of transcript per Million mapped reads;

† p = 0.13 vs. non-responders;

‡ p = 0.002 vs. non-responders;

§ p 0.04 vs. non-responders.