Supplement

Methods

The data presented in Table 1 were obtained from the literature by manual curation, the National Center for Biotechnology Information (NCBI) Database of Single Nucleotide Polymorphisms (dbSNP) website build 138 (1), and from self-identified race categories in a pharmacogenetics substudy of the β-Blocker Evaluation of Survival Trial (BEST) (2,3). Data from the NCBI dbSNP website come primarily from the HapMap project, from Sub-Saharan African (YRI) or African-American (ASW) populations compared with European populations (CEU) supplemented by African-American or European populations from other studies. Data from BEST are based on self-identified race case report forms, identifying patients as either "White, not Hispanic" or "Black, not Hispanic." Only European ancestry (EA) is considered as the alternative to African ancestry (AA), and other non-AA races, such as Asian, would need a separate analysis. The data in Table 1 are listed as either from populations without heart failure ("NF") or from populations with heart failure and reduced left ventricular ejection fraction ("HF"), by self-identified race. In Table 1 and throughout, genes are designated by italics, while mRNA or protein gene products are in Roman.

"Natural history" in this study encompasses both the risk of developing HF and the clinical course (HF or disease progression) from the time of diagnosis or enrollment in a clinical trial. Effects on HF progression were assessed in placebo-treated patients in the BEST DNA bank adrenergic receptor polymorphism substudy ("Pharmacogenomics of Beta-adrenergic Receptor Polymorphisms and Response to Beta Blockers in Heart Failure") (2,3) that measured clinical events from the time of randomization, using contemporaneously completed case report forms (4,5). Similar data were presented from the Metoprolol CR/XL Randomized Intervention

Trial in Congestive Heart Failure (MERIT-HF) DNA substudy (6). Data are also presented from published information from the Cincinnati/Pennsylvania observational study (7), where the primary endpoint of transplant-free survival was measured from the time of HF diagnosis. In terms of this analysis, "disease progression" means HF clinical outcomes in patients treated with the renin-angiotensin-aldosterone system (RAAS) inhibitor background therapy used in these studies.

For adrenergic receptor polymorphism data from the BEST trial presented in Tables 1 and 3, genomic DNA samples were obtained from from the BEST DNA Bank (2,3), and receptor polymorphisms were measured by RFLP-PCR as previously described (2,3,8).

Allele frequency differences between races were assessed by chi-square analysis on the number of major/minor alleles, or by the Fisher exact test when 2 or more table cells had an expected frequency <5. Time to event endpoints were analyzed with a log-rank statistic for p-value generation and the Cox proportional hazards model for calculation of an estimated hazard ratio with a 95% confidence interval and significance testing of interaction of model parameters. For published studies, clinical endpoint data received precedence, and remodeling or biomarker studies are only included if clinical endpoint data were unavailable. Effect size and between-patient subgroups relative effect size (RES) was calculated as previously described (2). Because of multiple polymorphisms being assessed, in the BEST substudy the critical value for statistical significance between genotype groups was set at $p=0.01$ (2). A $p<0.10$ was considered of interest in interaction tests (9), with a $p<0.050$ statistically significant.

Baseline Characteristics of the BEST Adrenergic Receptor Polymorphism Substudy

The baseline characteristics of the BEST trial's adrenergic receptor polymorphism substudy are given in Table S1.

Table S1. Baseline patient characteristics by race

Characteristic	**AA (n=207)**	**EA (n=762)**	**AA + EA (n=969)**
Age (yr)	56.3 ± 13.0	61.9 ± 11.4	60.7 ± 12.0
Male	154 (74%)	612 (80%)	766 (79%)
HF duration (mo)	46.0 ± 45.4	45.4 ± 47.7	45.5 ± 47.2
NYHA class III/IV (%)	94/6	92/8	92/8
Systolic blood pressure (mmHg)	121.4 ± 18.9	117.5 ± 17.4	118.3 ± 17.8
Ischemic etiology	87 (42%)	482 (63%)	596 (59%)
LVEF (%)	23.6 ± 7.3	23.7 ± 7.0	23.7 ± 7.0
Diabetes	80 (39%)	254 (33%)	334 (34%)
Hypertension	172 (83%)	377 (49%)	549 (57%)
ACEI usage	195 (94%)	700 (92%)	895 (92%)
Diuretic usage	201 (97%)	706 (93%)	907 (94%)
Digoxin usage	184 (89%)	687 (90%)	871 (90%)

Data presented as mean ± SD or n (%).
AA = African ancestry; ACEI = angiotensin-converting enzyme inhibitor; EA = European ancestry; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

Supplement References

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