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Relation of Beta Blocker Use With Frequency of Hospitalization for Heart Failure in Patients With Left Ventricular Diastolic Dysfunction (From the Heart and Soul Study)

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Abstract

Heart failure (HF) is a common public health problem, and many new cases are now recognized to occur in patients with preserved left ventricular (LV) ejection fraction. Beta blockers improve outcomes in patients with known LV systolic dysfunction, but whether beta blockers provide similar protection in patients with LV diastolic dysfunction is unclear. We studied the association between the use of beta blockers and subsequent hospitalization for HF in patients with diastolic dysfunction and stable coronary heart disease (CHD). We evaluated medication use and performed echocardiography at baseline in a prospective cohort of 911 outpatients with known CHD from the Heart and Soul Study. Hospitalizations for HF were assessed by blinded review of medical records during an average of 5.2 years of follow-up. Of the 911 participants, 118 (13%) had diastolic dysfunction, of which 2 were lost to follow-up. Among the 116 remaining patients, 25% (19/77) of those using beta blockers were hospitalized for HF compared with 41% (16/39) of those not using beta blockers [age-adjusted hazard ratio (HR) 0.51, 95% Confidence Interval 0.26-1.00; $p = 0.05$]. This association remained after further adjustment for sex, smoking, history of myocardial infarction, diabetes, and creatinine (HR 0.46, 0.23-0.93; $p = 0.03$). Results were similar after excluding 31 participants with a history of self-reported HF (HR 0.33, 0.13-0.86; $p = 0.02$) and 24 participants with concurrent systolic dysfunction (HR 0.36, 0.14-0.89; $p = 0.03$). In conclusion, the use of beta blockers is associated with a decreased risk of hospitalization for HF in patients with diastolic dysfunction and stable CHD.

Keywords

Coronary disease; diastole; echocardiography; heart failure; adrenergic beta antagonists

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Introduction

Heart failure (HF) is a common and significant public health problem.¹ Diastolic HF, or HF with preserved left ventricular (LV) ejection fraction (EF), has become a well-recognized subset of heart failure.² Beta blockers are a commonly prescribed class of medications and are known to improve outcomes in patients with LV systolic dysfunction.³⁻⁶ Questions have been raised about the relative benefits of beta blockers in patients with hypertension, and beta blockers remain of uncertain benefit in patients with LV diastolic dysfunction.⁷⁻¹⁰ Furthermore, there is a paucity of data with regards to how beta-blockade affects long-term outcomes in this patient population. The Heart and Soul study represents a large cohort of patients with stable coronary heart disease (CHD) who are commonly prescribed beta blockers. We studied the association between the use of beta blockers and subsequent hospitalization for HF in patients with diastolic dysfunction and stable CHD.

Methods

The Heart and Soul Study is a prospective cohort study designed to determine how psychological factors influence cardiovascular outcomes in patients with CHD. The enrollment process and methods for this study have been previously described.¹¹ Administrative databases were used to identify and enroll outpatients with documented coronary disease from two Department of Veterans Affairs (VA) Medical Centers (San Francisco and Palo Alto, California), one university-based medical center (University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco, California. Criteria for enrollment were: 1) history of myocardial infarction (MI), 2) angiographic evidence of at least 50% stenosis by area in at least one coronary vessel, 3) evidence of exercise-induced ischemia by treadmill electrocardiogram or stress nuclear perfusion imaging, 4) history of coronary revascularization, or 5) prior diagnosis of coronary disease by an internist or cardiologist. Participants were excluded if they had a history of MI in the prior 6 months, deemed themselves unable to walk one block, or were planning to move out of the local area within three years. The study protocol was approved by the institutional review boards at each participating site and all patients provided written informed consent.

Two-dimensional echocardiography was performed on all patients using an Acuson Sequoia ultrasound system with harmonic imaging and a 3.5-MHz transducer (Siemens Medical Solutions, Mountain View, CA). Standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views during quiet respiration or held expiration were obtained. Two highly experienced sonographers made all sonographic measurements, and a single cardiologist reader (N.B.S.), who was blinded to clinical and laboratory information, evaluated, confirmed and, when needed, corrected each measurement. LV end-systolic and end-diastolic volumes were obtained by planimetry using the biplane method of discs as described.¹² The LVEF was calculated as (end-diastolic volume – end-systolic volume)/end-diastolic volume. Using the standard apical 4-chamber view, spectral Doppler signals of mitral inflow and pulmonary vein flow were obtained according to the guidelines of the American society of Echocardiography.¹³ Patterns of LV diastolic dysfunction were based on mitral inflow E/A ratios of peak velocities at early rapid filling (E) and late filling due to atrial contraction (A) and systolic or LV diastolic dominant pulmonary venous flow using velocity time integral. Based on previously published criteria,¹⁴ normal LV diastolic pattern was defined as E/A ratio of 0.75 to 1.5 and systolic dominant pulmonary venous flow. Impaired relaxation pattern (mild LV diastolic dysfunction) was defined as E/A ratio ≤ 0.75 and systolic dominant pulmonary venous flow. Pseudonormal pattern (moderate LV diastolic dysfunction) was defined as E/A ratio of 0.75 to 1.5 and with diastolic dominant pulmonary venous flow. Restrictive filling pattern (severe LV diastolic dysfunction) was defined as an E/A of 1.5 or greater and with diastolic dominant pulmonary venous flow.¹⁵

Our group has previously shown that there is no statistically significant difference between patients with normal LV diastolic pattern and impaired relaxation pattern with regards to all-cause mortality, heart disease death, hospitalization for HF, and hospitalization for MI in our cohort.¹⁵ Thus these two groups were combined to form the comparison group considered to have no clinically significant diastolic dysfunction. Less than 5% of the study population had restrictive filling and thus groups with either a pseudonormal or restrictive filling pattern were combined to form the study group considered to have diastolic dysfunction. Of the 1024 participants enrolled, diastolic function could only be determined in 911 because of either non-sinus rhythm, LV pacing, heart rate > 100 beats/min, severe mitral disease, or technical reasons.

Outcomes evaluated included all-cause mortality and incident hospitalization for HF. A combined outcome of death and hospitalization for HF was included for analysis. We conducted annual follow-up using telephone interviews and questioning participants or their proxies regarding any emergency room visits or hospitalizations. Medical records, death certificates, and coroner's reports were retrieved. Participants were censored at point of HF admission, lost to follow-up, or death. Two blinded adjudicators reviewed each event and, if there was agreement, the outcome classification was binding. If there was disagreement, a third blinded adjudicator reviewed the event and determined the outcome classification.

All-cause mortality was determined using review of death certificates. Hospitalization for HF was defined for a clinical syndrome with a minimum one-night hospital stay and involving at least 2 of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, a third heart sound, cardiomegaly on chest radiography, or pulmonary edema on chest radiography. These clinical signs and symptoms must have represented a clear change from the normal clinical state of the patient and must have been accompanied by either failing cardiac output as determined by peripheral hypoperfusion (in the absence of other causes such as sepsis or dehydration) or peripheral or pulmonary edema treated with intravenous diuretics, inotropes, or vasodilators. Supportive documentation of decreased cardiac index, increased pulmonary capillary wedge pressure, decreasing oxygen saturation, and end-organ hypoperfusion, if available, were included in adjudication.

Each participant completed a detailed questionnaire that included age, gender, race, medical history, level of physical activity, current smoking, and level of alcohol consumption. We measured depressive symptoms in participants using the 9-item Patient Health Questionnaire (PHQ-9). Weekly angina was assessed using the Seattle Angina Questionnaire. Study personnel recorded all current medications and measured height, weight, and blood pressure. Medication use was recorded by having subjects bring medication bottles to the baseline interview and categorize the medications according to Epocrates Rx (San Mateo, CA). Glucose, serum creatinine, log C-reactive protein, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured from fasting serum samples. A symptom-limited graded exercise treadmill test was performed, and we used stress echocardiography to identify inducible ischemia, defined as the presence of cardiac wall motion abnormality at peak exercise that was not present at rest.

Differences in participant characteristics based on beta blocker use were determined using analysis of variance for continuous variables and chi-square tests for dichotomous variables. We used Cox proportional hazard models to evaluate the independent association of beta blocker use with cardiovascular outcomes in patients with and without diastolic dysfunction. To determine the independent effects of beta blocker use on cardiac outcomes, we adjusted these models for the following covariates selected a priori on the basis of inspection of directed acyclic graphs:¹⁶ age, sex, smoking, history of MI, diabetes, serum creatinine. Given the strong association of self-reported history of HF and LV systolic dysfunction (EF < 45%) with both beta blocker use and HF hospitalization, we further adjusted for these variables. For these

analyses, we report hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed using Statistical Analysis Software (version 9, SAS Institute Inc., Cary, North Carolina).

Results

Between September 2000 to December 2002, a total of 1024 participants were enrolled. Of the 909 remaining after diastolic function was measured and excluding two participants lost to follow-up, 534 (59%) were on beta blockers and 375 (41%) were not. Baseline demographics and patient characteristics are reported in Table 1.

Outcomes based on beta blocker use and the presence or absence of LV diastolic dysfunction are reported in Table 2. Mean follow-up was 5.2 years. Of the 909 study participants, a total of 116 patients (13%) had echocardiographic evidence of diastolic dysfunction (pseudonormal or restrictive filling pattern) at baseline. Of these, 77 (66%) patients were on beta blockers and 39 (34%) were not. Of the 116 patients with diastolic dysfunction, 25% (19/77) of those using beta blockers were hospitalized for HF compared with 41% (16/39) of those not using beta blockers ($p = 0.07$). Likewise, there were trends in favor of beta blocker use in patients with diastolic dysfunction for all-cause mortality [31% (24/77) vs. 44% (17/39), $p = 0.19$] and the combined outcome of HF hospitalization or death [40% (31/77) vs. 54% (21/39), $p = 0.16$]. There were no appreciable differences in outcomes for the patients without diastolic dysfunction.

When stratified by the presence or absence of diastolic dysfunction, beta blocker use appeared to significantly decrease the risk for HF hospitalization in those with diastolic dysfunction, but not in patients without diastolic dysfunction (p for interaction = 0.02). Kaplan-Meier Curve showing freedom from HF hospitalization based on beta blocker use and the presence or absence of diastolic dysfunction is presented in Figure. Age-adjusted HRs are presented in Table 2. Beta blocker use was independently associated with a decreased risk for HF hospitalization in the 116 patients with diastolic dysfunction (HR 0.51, 95% CI 0.26-1.00; $p = 0.05$) and the effect remained intact in a multivariable model when adjusted age, sex, smoking, history of MI, diabetes, and creatinine (HR 0.46, CI 0.23-0.93; $p = 0.03$). Results remained strong in subgroup analyses after excluding 31 patients with a history of self-reported HF [(Age-adjusted only, HR 0.40, CI 0.17-0.95; $p = 0.04$) and (Multivariate-adjusted, HR 0.33, CI 0.13-0.86; $p = 0.02$)]. After excluding the 24 patients with LVEF < 45%, the association of beta blocker use with decreased risk for HF hospitalization was similar although not achieving statistical significance (HR 0.51, 0.22-1.17; $p = 0.11$). After multivariable adjustment, the association became significant (HR 0.36, 0.14-0.89; $p = 0.03$).

Discussion

In this prospective cohort study of 909 outpatients with stable coronary heart disease, approximately 60% of the patients were taking beta blockers and approximately 13% had LV diastolic dysfunction. Diastolic dysfunction was common in our study population with about two-thirds of those patients being on beta blockers. We found that use of beta blockers in patients with diastolic dysfunction was associated with a 50% decreased risk for HF hospitalization over a mean 5.2 years of follow-up. Beta blocker use in patients with diastolic dysfunction did not significantly affect the rate of all-cause mortality in our study, but beta blockers appeared to decrease risk of the combined outcome of HF hospitalization or death by 40% and neared statistical significance ($p = 0.06$). Although this result was largely driven by the association of beta blockers with a decreased risk for HF hospitalization, the effect became significantly stronger with multivariable adjustment for potential confounders (HR = 0.48; $p = 0.02$).

We considered the possibility that HF hospitalization in patients with and without LV diastolic dysfunction who were taking beta blockers may be influenced by other factors such as age, sex, smoking, history of myocardial infarction, diabetes, and renal disease. However, after adjusting for these, the association of beta blocker use with less HF in patients with diastolic dysfunction was still present. After excluding patients with a history of self-reported HF and concomitant systolic dysfunction using this modeling, the association remained strong (HR 0.33; $p = 0.02$, and HR 0.36; $p = 0.03$, respectively). Beta blocker use was not associated with a decrease in the risk for HF hospitalization in patients without diastolic dysfunction, even after multivariable modeling.

In this study, we sought to identify whether or not patients with diastolic dysfunction benefited from the use of beta blockers. We used a study population with stable CHD known to be at a particularly high risk for developing heart failure.¹⁷ Our group has previously demonstrated that the presence of diastolic dysfunction is strongly predictive of incident hospitalization for HF in this cohort population (HR 6.3, $p = 0.0003$).¹⁵ Our findings appear to identify a subgroup of patients who might benefit from beta blockers. It has already been demonstrated that beta blockers are associated with better outcomes in patients with systolic HF, or HF with reduced EF.³⁻⁶ Likewise, beta blockers are recommended for patients with acute coronary syndrome (ACS) and even improve mortality over the long-term in those with LV dysfunction on presentation.¹⁸⁻²²

To our knowledge, there has been no previous study, either randomized-controlled clinical trial or cohort study, which has shown beta blockers to markedly decrease incident heart failure hospitalization in patients with HF with preserved EF. In fact, there is currently minimal evidence to support any therapy that significantly improves outcomes that reach statistical significance in these patients suffering from diastolic HF, with the CHARM-Preserved study being the lone trial to reach statistical significance for any outcome in this population.²³ Long-term beta blockade has been shown in randomized-controlled clinical trials to improve the diastolic filling pattern of the left ventricle.^{24, 25} Aronow et al. did not measure HF hospitalization but did show improved mortality, mortality plus non-fatal MI, LVEF, and LV mass with beta blocker therapy in patients with a history of MI and CHF but EF > 40%.²⁶ The Ancillary Digitalis Investigation Group failed to show improved outcomes with digoxin.²⁷ The CHARM-Preserved trial with candesartan therapy in patients, notably with EF > 40%, fell short of reaching statistical significance in its primary outcome of mortality and HF hospitalization but did show a moderate reduction in hospitalization for HF with an adjusted-HR of 0.84 that just reached statistical significance.²³ The I-PRESERVE trial with irbesartan also was unable to demonstrate improved outcomes in patients with HF and preserved EF.²⁸ The registry trial OPTIMIZE-HF confirmed the positive effects of beta blockers in patients with systolic dysfunction but failed to prove beta blockers significantly influence mortality or rehospitalization for HF in patients with diastolic dysfunction and preserved EF (> 40%).²⁹ Most recently, the SENIORS Investigators reported the effect of beta-blockade with nebivolol versus placebo in elderly patients with HF was similar in those with preserved and impaired EF.³⁰ It should be noted that their analyses used an EF cutoff of 35% to define preserved or impaired EF and their hazard ratios for the end point of all-cause mortality or cardiovascular hospitalization for both groups were not statistically significant.

Our study has several limitations. First, our patient population is made up of older, white men, many of whom were recruited from VA medical centers. Thus, our results may not generalize to all populations, including women and men of other races. Second, only 13% (116 patients) of our study population had LV diastolic dysfunction, and it is difficult to draw definitive conclusions from such a small sample size. Third, beta blocker users were more likely than non-users to have diabetes (29 vs. 22%) and a history of myocardial infarction (60 vs. 46%). However, we adjusted for these characteristics in our multivariable analysis. Fourth, we did

not include other pharmacologic agents in this analysis. It is possible that other therapies could play a role in the observed benefit beta blockers had on HF hospitalization in patients with diastolic dysfunction and this needs to be examined in further detail in future studies. Fifth, the principal finding in this study was based on the outcome of HF hospitalization, which may be prone to error despite our rigorous methods for adjudication and depending on clinical assessment, coding, and accuracy of chart review. Finally, our study was limited to outpatients with stable CHD; therefore, we cannot comment of the effect of beta blockers in otherwise healthy patients with diastolic dysfunction and no CHD as well as patients following ACS, for which firm guidelines exist with regards to the use of beta blockers.¹⁸⁻²⁰

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Figure.

Freedom from heart failure hospitalization based on beta blocker use and presence or absence of diastolic dysfunction. Kaplan-Meier Curve with frequency of freedom from heart failure over time (Age-adjusted with P value < 0.0001).

Table 1
Characteristics of participants in users and nonusers of beta blockers

Characteristic	Users (N=534)	Non-users (N=375)	P Value
Age (years)	67±11	67±11	.77
Male	449(84%)	297(79%)	.05
Race or ethnic group			.55
White	317(59%)	227(61%)	
Black	84(16%)	65(17%)	
Hispanic	46(9%)	34(9%)	
Asian	66(12%)	41(11%)	
Other	21(4%)	8(2%)	
Body-mass index (kg/m ²)	29±5	28±5	.12
Current smoking	95(18%)	85(23%)	.08
Regular alcohol	136(26%)	127(34%)	.006
Diabetes	156(29%)	83(22%)	.02
Myocardial infarction	316(60%)	173(46%)	<.0001
Heart failure	106(20%)	44(12%)	.001
Depression (PHQ score ≥10)	106(20%)	67(18%)	.45
Stroke	74(14%)	58(16%)	.49
Weekly angina	109(20%)	60(16%)	.10
Systolic blood pressure (mm Hg)	134±23	131±19	.04
Diastolic blood pressure (mm Hg)	75±11	74±11	.86
Heart rate (bpm)	64±11	73±12	<.0001
Left ventricular ejection fraction	62±9%	62±10%	.44
Fasting plasma glucose (mg/dL)	121±43	118±45	.28
Serum creatinine (mg/dL)	1.2±0.7	1.1±0.5	.01
Log C-reactive protein	0.66±1.29	0.73±1.33	.47
Total cholesterol (mg/dL)	173±38	186±47	<.0001
Triglycerides (mg/dL)	150±130	131±116	.02
High density lipoprotein-cholesterol (mg/dL)	44±13	49±14	<.0001
Low density lipoprotein-cholesterol (mg/dL)	100±31	111±38	<.0001

Data presented as mean ± standard deviation (SD) or number (percent).

PHQ indicates Patient Health Questionnaire.

Table 2
Association of beta blocker use with cardiovascular outcomes among patients with and without diastolic dysfunction (pseudonormal or restrictive filling)

OUTCOME	No Diastolic Dysfunction		Diastolic Dysfunction	
	Users (N=457)	Non-users (N=336)	Users (N = 77)	Non-users (N =39)
			P value	P value
Heart failure hospitalization				
Number (Percent)	48 (11%)	26 (8%)	.20	19 (25%) 16 (41%)
Age-Adjusted HR (95% CI)	1.36 (0.84-2.19)		.21	0.51 (0.26-1.00)
MV-adjusted HR (95% CI)	1.07 (0.66-1.75)		.78	0.46 (0.23-0.93)
All-cause mortality				
Number (Percent)	103 (23%)	67 (20%)	.19	24 (31%) 17 (44%)
Age-Adjusted HR (95% CI)	1.05 (0.77-1.43)		.74	0.68 (0.36-1.28)
MV-adjusted HR (95% CI)	0.93 (0.67-1.28)		.64	0.63 (0.33-1.23)
Heart failure hospitalization or death				
Number (Percent)	122 (27%)	74 (22%)	.16	31 (40%) 21 (54%)
Age-Adjusted HR (95% CI)	1.19 (0.89-1.58)		.25	0.59 (0.34-1.03)
MV-adjusted HR (95% CI)	1.03 (0.76-1.39)		.85	0.48 (0.27-0.88)

Multivariable (MV)-adjusted HR is adjusted for age, sex, smoking, history of myocardial infarction, diabetes, and serum creatinine.
 HRs reported are for beta blocker user (vs. non-use) among patients with and without diastolic dysfunction.