Comparison of Predictors of Heart Failure−Related Hospitalization or Death in Patients With Versus Without Preserved Left Ventricular Ejection Fraction

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Heart failure with preserved ejection fraction (HFpEF) is recognized as a major cause of cardiovascular morbidity and mortality. An ability to identify patients with HFpEF who are at increased risk for adverse outcomes can facilitate their more careful management. We studied the patients having heart failure (HF) using data from the Heart Failure Adherence and Retention Trial (HART). HART enrolled 902 patients in the New York Heart Association (NYHA) class II or III who had been recently hospitalized for HF to study the impact of self-management counseling on the primary outcome of death or HF hospitalization. In HART, 208 patients had HFpEF and 692 had HF with reduced ejection fraction (HFrEF) and were followed for a median of 1,080 days. Two final multivariate models were developed. In patients having HFpEF, predictors of primary outcome were male gender (odds ratio [OR] 3.45, p = 0.004), NYHA class III (OR 3.05, p = 0.008), distance covered on a 6-minute walk test (6-MWT) of <620 feet (OR 2.81, p = 0.013), and <80% adherence to prescribed medications (OR 2.61, p = 0.018). In patients having HFrEF, the predictors were being on diuretics (OR 3.06, p = 0.001), having ≥3 co-morbidities (OR 2.11, p = 0.0001), distance covered on a 6-MWT of <620 feet (OR 1.94, p = 0.001), NYHA class III (OR 1.90, p = 0.001), and age >65 years (OR 1.63, p = 0.01). In conclusion, indicators of functional status (6-MWT and NYHA class) were common to both patients with HFpEF and those with HFrEF, whereas gender and adherence to prescribed therapy were unique to patients having HFpEF in predicting death or HF hospitalization. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;112:1907−1912)

Given the increasing recognition of heart failure with preserved ejection fraction (HFpEF) as a growing and difficult-to-treat clinical problem, the identification of predictors of adverse outcomes can help to identify those patients who are at the highest risk and who would benefit from more personalized and aggressive management. To be useful, such predictors should be easy to identify in routine clinical practice, thereby making them potentially valuable in personalizing the approach to patient care, monitoring disease progression, and evaluating therapeutic effectiveness. Comparing these predictors among patients having HFpEF and those having heart failure with reduced ejection fraction (HFrEF) can further our understanding of the differences in the 2 subtypes of heart failure (HF).

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The study was conducted at the principal site: Rush University Medical Center, Chicago, Illinois; and other hospitals: John H. Stroger Hospital of Cook County, University of Illinois College of Medicine at Chicago, Advocate Lutheran General Hospital, Evanston Hospital, Rush North Shore Medical Center, Glenbrook Hospital, Advocate Christ Medical Center, and South Suburban Hospital.

See page 1912 for disclosure information.

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Methods

We analyzed data from the Heart failure Adherence and Retention Trial (HART). HART was a single-center, multiple-hospital, partially blinded, randomized controlled behavioral trial that was based in the Chicago metropolitan area. HART was designed to assess the impact of self-management counseling versus education alone on the composite primary outcome of death or HF hospitalizations in patients with HFrEF or those with HFpEF.[1,2] HART enrolled a total of 902 patients. Of the patients who could be classified, 692 had HFrEF and 208 had HFpEF. Details on patient enrollment, data collection, and follow-up within HART have been reported elsewhere.[1] Briefly, patients having HF were recruited through inpatient and outpatient screening and through referrals from cardiologists and internists. The recruitment continued from October 2001 to October 2004. The follow-up was completed in May 2007. All patients were receiving some form of active HF treatment, including diuretics, for the previous 3 months. HFrEF was defined as an ejection fraction of ≤40% by echocardiography, radiographic ventriculography, or radionuclide ventriculography. HFpEF was defined as an ejection fraction of >40% by 1 of the 3 previously listed methods and ≥1 previous hospitalizations for HF.

Baseline data were collected on demographics, medications, co-morbidities, and adherence to medications. The median follow-up period was 1,080 days. Primary end points were ascertained through blind adjudication by

Table 1
Baseline characteristics of patients in Heart Failure Adherence and Retention Trial

Characteristic	All Patients, n = 900 (%)	HFpEF, n = 208 (%)	HFrEF, n = 692 (%)
Age (yrs), mean ± SD*	63.6 ± 13.5	67.3 ± 13.0	62.4 ± 13.4
Women*	426 (47)	136 (65)	290 (42)
Minority race or ethnicity	361 (40)	79 (38)	282 (41)
Lesser than high school education	393 (44)	82 (39)	311 (45)
Annual family income of <$30,000	426 (52)	106 (56)	320 (50)
Married or living with someone else as if unmarried*	502 (56)	93 (45)	409 (60)
In treatment arm	450 (50)	107 (51)	343 (50)
NYHA class III	284 (32)	64 (31)	220 (32)
6-MWT distance (feet), mean ± SD*	821 ± 465	718 ± 449	852 ± 465
Hypertension**	675 (75)	168 (81)	507 (74)
Diabetes mellitus	361 (40)	89 (43)	272 (39)
Co-morbid conditions, mean ± SD***	3.2 ± 1.7	3.5 ± 1.6	3.1 ± 1.7
Total number of medications, mean ± SD	6.8 ± 3.0	6.7 ± 2.9	6.8 ± 3.0
ACE inhibitor or ARB use*	772 (86)	163 (78)	609 (88)
β-Blocker use*	635 (71)	111 (53)	524 (76)
Major depressive symptoms	264 (29)	66 (32)	198 (29)
Social support-emotional, mean ± SD	75.2 ± 22.2	75.6 ± 22.5	75.0 ± 22.1
Purpose in life, mean ± SD	4.5 ± 0.8	4.4 ± 0.8	4.5 ± 0.8
Quality of life, mean ± SD			
SF-36			
Physical function*	48.2 ± 24.9	43.2 ± 22.7	49.7 ± 25.4
Energy and vitality,	46.5 ± 23.7	44.4 ± 23.8	47.1 ± 23.6
Quality of Life Index—Cardiac			
Satisfaction with health and function	4.3 ± 1.0	4.2 ± 1.1	4.3 ± 1.0
Satisfaction with psychological or spiritual function	4.7 ± 1.1	4.7 ± 1.1	4.8 ± 1.0
Nonadherence to drug therapy	273 (37)	60 (36)	213 (37)
Sodium intake, median (IQR), (mg/day)	3,332 (2,647−4,269)	3,129 (2,615−4,095)	3,416 (2,655−4,290)
Current smoker	85 (9.5)	20 (9.6)	65 (9.4)
Body mass index (kg/m²), mean ± SD*	31.0 ± 7.7	32.9 ± 8.4	30.5 ± 7.4
Self-efficacy at self-management, mean ± SD	7.6 ± 1.7	7.4 ± 1.8	7.7 ± 1.7

Sample sizes in any particular comparison may be slightly different because of missing data.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; SF-36 = Short-form 36.

*p <0.001; **p <0.05; ***p <0.01.

a designated team of cardiologists.[2] All patients, or in the case of death, their family members, were contacted every 3 months by telephone to ascertain occurrence of a death or hospitalization. Reports of death were confirmed by medical record, death certificate, emergency medical services record, or queries from the Social Security Death Index. HF admissions were adjudicated by the presence of shortness of breath, peripheral edema, or chest radiographic evidence of pulmonary edema without evidence of another disease process accounting for symptoms or signs. HF admissions were confirmed if the patient responded to HF therapy or had a documented decrease in left ventricular function.

Medication adherence was tested using electronic pill cap monitoring. The patient was asked to place a month's supply of an angiotensin-converting enzyme inhibitor (angiotensin receptor blocker, β blocker, or diuretics, if the patient was not taking an angiotensin-converting enzyme inhibitor) into a Medication Event Monitoring System electronic pill cap container (MEMS V TrackCap; AARDEX, Zug, Switzerland). They were taught to use it for the ensuing month. Adherence to drug therapy was defined by way of the percentage of pills taken relative to pills prescribed, with a cut-off point of <80% indicating nonadherence. New York Heart Association (NYHA) class was assessed by the

treating physicians at the time of enrollment and during follow-up. Six-minute walk test (6-MWT) was performed by measuring the distance that patients could walk during a period of 6 minutes. For analysis, distance covered on a 6-MWT was dichotomized at the lowest tertile.[2] Glomerular filtration rate was calculated using the Cockroft-Gault equation. Diabetes was self-reported at the time of enrollment and during follow-up. Other co-morbid conditions that were assessed included previous myocardial infarction, hypertension, cancer, stroke, arthritis, lung disease, liver disease, asthma, sleep apnea, and Parkinson's disease. Depression was assessed using Geriatric Depression Scale with a score of >10 having high sensitivity and specificity for diagnosing depression. Other psychosocial factors that were assessed using standardized questionnaires included quality of life, purpose in life, and social support.[1]

Statistical analyses began with a description of the baseline characteristics in overall population of 900 patients and then a comparison of patients with HFpEF and those with HFrEF. To identify predictors of the primary outcome (death or HF hospitalization), univariate unadjusted odds ratios reflecting risk for the primary end point were computed for each of the baseline factors separately in patients with HFpEF and those with HFrEF. Next, and again