Relation of Left Ventricular Ejection Fraction and Clinical Features or Co-morbidities to Outcomes Among Patients Hospitalized for Acute Heart Failure Syndromes

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The aim of this study was to evaluate the heterogeneity of the association of a preserved or reduced ejection fraction (EF) with the increased risk of outcomes among patients with acute heart failure syndromes. Of the 4,842 patients enrolled in the Acute Decompensated Heart Failure Syndromes (ATTEND) registry in Japan, 4,720 patients were evaluated to investigate the association of EF and clinical features or co-morbidities with all-cause mortality after admission. The median follow-up period after admission was 519 (388 to 781) days. The all-cause mortality rate did not differ between the reduced EF and preserved EF groups (24.9% and 24.5%, respectively). To evaluate the heterogeneity of the influence of a preserved or reduced EF on all-cause mortality, subgroup analyses were performed. As a result, there were significant interactions in the association of a preserved or reduced EF with all-cause mortality when the patients were stratified by an ischemic cause, a hypertensive cause, previous hospitalization for heart failure, diabetes mellitus, and anemia. The influence of a nonischemic cause, a hypertensive cause, or new-onset heart failure on the risk of all-cause mortality was significantly greater in patients with preserved EF than in those with reduced EF. In contrast, the influence of diabetes mellitus or anemia on the risk of all-cause mortality was significantly greater in patients with reduced EF than in those with preserved EF. In conclusion, the present analysis demonstrated that the association of a preserved or reduced EF with the clinical outcome differs markedly in relation to the clinical features or co-morbidities of these patients. **(Am J Cardiol 2015;115:334−340)**

Several epidemiologic studies have recently shown that about half of all patients hospitalized for acute heart failure syndromes (AHFS) have a preserved left ventricular ejection fraction (EF).[1,2] Patients with heart failure (HF) with a preserved EF have been reported to display pathophysiologic characteristics similar to those of patients with HF with a reduced EF.[3−5] Furthermore, most of the large-scale contemporary studies have suggested that differences in survival between the 2 types of HF are generally minimal.[1,5] However, it remains unknown whether there are subgroups of patients with AHFS with a preserved or reduced EF that is associated with a higher risk of morbidity or mortality.[5,6] Additionally, it has been reported that very few hospitalized HF registries have collected data on both in-hospital and postdischarge outcomes.[7] Accordingly, we evaluated the heterogeneity of the association of a preserved or reduced EF with the increased risk of clinical outcomes among patients hospitalized for AHFS who were evaluated in inpatient and outpatient settings.

Methods

As a nationwide hospital-based prospective cohort study, the Acute Decompensated Heart Failure Syndromes (ATTEND) registry, which is a prospective multicenter observational cohort study of AHFS, accumulates data on patients with AHFS admitted to 53 hospitals throughout Japan. Patients are enrolled at their first admission and then followed, with data collection being patient based and not event based. The study design and methods, as well as patient characteristics, have been described previously.[8] In brief, the ATTEND registry study is being performed to clarify the profile of patients with AHFS in Japan, including demographic and clinical characteristics, current treatment, in-hospital mortality, and postdischarge morbidity or mortality. Treatment of AHFS is not specified and is selected by each attending physician. This study was conducted according to the principles of the Declaration of Helsinki. Institutional review board approval was obtained at each participating hospital before commencing the study, and all patients gave written informed consent.

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See page 339 for disclosure information.

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Table 1
Baseline characteristics of all subjects and the groups with a reduced or preserved ejection fraction at baseline

Variables	Overall (n = 4720)	Reduced EF (n = 2585)	Preserved EF (n = 2135)	P-value
Age (years)	72.9±13.8	69.7±14.4	76.8±12.0	<0.001
Men	57.9%	67.9%	45.7%	<0.001
Prior hospitalization for heart failure	36.3%	39.1%	32.9%	<0.001
Hypertension	69.4%	65.2%	74.5%	<0.001
Dyslipidemia	36.8%	38.8%	34.5%	0.002
Diabetes mellitus	33.8%	35.1%	32.1%	0.030
Chronic obstructive pulmonary disease	12.3%	10.8%	14.1%	<0.001
Stroke	14.1%	13.3%	15.0%	0.097
Etiology				
Ischemic	31.3%	39.5%	21.4%	<0.001
Hypertensive	17.8%	12.8%	23.8%	<0.001
Valvular	19.2%	11.0%	29.1%	<0.001
Atrial fibrillation at admission	36.0%	31.2%	41.8%	<0.001
Clinical profile on admission				
Paroxysmal nocturnal dyspnea	53.4%	56.6%	49.6%	<0.001
Orthopnea	63.6%	66.7%	59.8%	<0.001
Jugular venous distension	53.2%	54.5%	51.5%	0.172
Peripheral edema	66.9%	63.6%	70.9%	<0.001
NYHA functional class				
III	37.8%	36.4%	39.6%	0.022
IV	43.9%	48.2%	38.8%	<0.001
Body mass index (kg/m^2)	23.2±4.6	23.2±4.5	23.2±4.6	0.769
Systolic blood pressure (mmHg)	145.3±36.6	143.1±37.4	147.9±35.5	<0.001
Diastolic blood pressure (mmHg)	82.5±22.6	84.5±23.5	80.0±21.2	<0.001
Heart rate (beats/min)	98.5±29.2	103.7±28.3	92.1±29.1	<0.001
Blood urea nitrogen (mg/dl)	27.8±26.1	28.4±29.6	27.0±21.2	0.064
Serum creatinine (mg/dl)	1.43±1.57	1.49±1.71	1.36±1.38	0.004
Estimated GFR (ml/min/1.73m^2)	49.6±26.8	49.9±27.7	49.4±25.6	0.527
Serum sodium (mEq/l)	139.3±4.4	139.2±4.3	139.4±4.5	0.309
Hemoglobin (g/dl)	12.0±2.6	12.6±2.6	11.4±2.4	<0.001
Anemia*	58.0%	50.1%	67.5%	<0.001
B-type natriuretic peptide (pg/ml)	708 (363-1287)	924 (510-1582)	508 (270-927)	<0.001
Intravenous therapy during hospitalization				
Diuretics	76.3%	77.7%	74.7%	0.014
Any vasodilator	78.6%	81.2%	75.4%	<0.001
Any inotrope	18.5%	24.1%	11.8%	<0.001
Oral medications at admission				
Loop diuretic	46.3%	46.4%	46.1%	0.865
Spironolactone or eplerenone	19.8%	20.9%	18.4%	0.160
Angiotensin converting enzyme inhibitor	14.6%	16.2%	12.7%	<0.001
Angiotensin receptor blockers	35.0%	30.9%	39.9%	<0.001
Beta-blockers	33.8%	35.1%	32.2%	0.033
Calcium-channel blockers	29.0%	19.5%	40.4%	<0.001
Digoxin	12.8%	11.4%	14.5%	0.002
Aspirin	32.4%	33.8%	30.7%	0.021
Warfarin	24.5%	23.1%	26.3%	0.010
Statin	23.6%	23.9%	23.3%	0.640

Values are the mean ± SD, proportion (%), or median (interquartile range).
GFR = glomerular filtration rate; NYHA = New York Heart Association.
* Anemia was defined as a hemoglobin <13.0 g/dl for men and <12.0 g/dl for women.

Patients with AHFS who fit the modified Framingham criteria, which only include variables assessed at admission, are eligible for entry into the ATTEND registry.[9] However, patients aged <20 year old, those with acute coronary syndrome, and others considered unsuitable for the study by their physicians are excluded. The present study focused on patients enrolled in the ATTEND registry from April 2007 to December 2011 for whom left ventricular EF data (or qualitative assessment of left ventricular systolic function) at admission, in-hospital data, and follow-up data after discharge were available. A preserved EF was defined as left ventricular EF >40% or qualitative assessment of normal or mildly impaired systolic function (if left ventricular EF was not measured) at admission, whereas a reduced EF was defined as left ventricular EF ≤40% or moderate and/or severe systolic dysfunction on qualitative assessment at admission. Anemia on admission was defined as hemoglobin <13.0 g/dl for men and <12.0 g/dl for women according to