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Gender, Age, and Heart Failure With Preserved Left Ventricular Systolic Function

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OBJECTIVES This study was designed to determine if women are more likely than men to have heart failure (HF) with preserved systolic function after adjustment for potential confounders, including age.

BACKGROUND Although prior evidence suggests an independent association between female gender and preserved left ventricular systolic function (LVSF) in patients with HF, existing studies are limited by referral biases, small sample sizes, or the inability to adjust for a wide range of potential confounding variables.

METHODS This is a cross-sectional study using data from retrospective medical chart abstraction of a national sample of Medicare beneficiaries hospitalized with the principal discharge diagnosis of HF in acute-care nongovernmental hospitals in the U.S. between April 1998 and March 1999. Patients were eligible for this analysis if they were age 65 years or older, had documentation of LVSF, and corroboration of the diagnosis of HF. We used multivariable logistic regression to identify the correlates of preserved LVSF, which was defined as qualitatively normal function or quantitatively reported ejection fraction ≥0.50. Stratified regressions by gender were performed to identify significant interactions.

RESULTS Of the 19,710 patients in the analysis, preserved LVSF was present in 6,700 (35%), 79% of whom were women. In contrast, among the 12,956 patients with impaired LVSF, only 49% were women. Patients with preserved LVSF were 1.5 years older than those with impaired LVSF. After adjustment for age and other patient factors, female gender remained strongly associated with preserved LVSF (calculated risk ratio = 1.71; 95% confidence interval 1.63 to 1.78). The association was consistent in all age groups, and was similar in patients with or without coronary artery disease, hypertension, pulmonary disease, renal insufficiency, or atrial fibrillation.

CONCLUSIONS In elderly patients hospitalized with HF, preserved systolic function is primarily a condition of women, independent of important demographic and clinical characteristics. (J Am Coll Cardiol 2003;41:217–23) © 2003 by the American College of Cardiology Foundation

Prior studies have demonstrated that as many as half of all patients with heart failure (HF) have preserved left ventricular systolic function (LVSF), and that both advancing age and female gender are correlates of this syndrome (1–3). Evidence demonstrating differences in left ventricular (LV) adaptation with age (4,5) and between women and men (6,7) supports the possibility of a biologic basis for both

See page 224

associations. Patient selection methods, small sample sizes, or the lack of adjustment for important confounders have limited the capacity of existing studies to investigate thoroughly the independent association between gender and HF with preserved LVSF. Ideally, this question would be addressed in a large and unselected cohort of patients with HF, adjusting for a wide range of available clinical data.

We undertook this study to determine the independent association of patient gender with preserved LVSF in a community-based cohort of older persons hospitalized with HF across the U.S. in 1998 and 1999. We sought to determine the relative contributions of gender, age, and comorbidity to the prevalence of preserved LVSF, and to identify patient subgroups in which women were particularly likely to have preserved LVSF.

METHODS

Study sample. The patient cohort in this study is derived from the National Heart Failure (NHF) Project sample. The NHF Project is an effort sponsored by the Centers for Medicare and Medicaid Services (the former Health Care Financing Administration) to improve the quality of care provided to Medicare beneficiaries hospitalized with HF. As part of the project, a database was constructed containing detailed demographic and clinical data on 37,500 fee-for-service Medicare beneficiaries hospitalized with the principal discharge diagnosis of HF (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 428.x, 402.01, 402.11, 402.91, 404.01, 404.11, and 404.9) between April 1998 and March 1999, inclusive. Records were excluded if the patient was transferred to another acute care facility, left against medical

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Abbreviations and Acronyms
HF = heart failure
LV = left ventricular
LVEF = left ventricular ejection fraction
LVSF = left ventricular systolic function
NHF = National Heart Failure Project

advice, or had chronic renal failure requiring hemodialysis. After these selection criteria were applied, up to 800 records per state, territory, and Washington, DC, were selected. In states with fewer than 800 HF discharges during the sampling period, a census of discharges was obtained. In cases where more than one discharge was selected for a particular subject, one of the discharges was randomly included.

We restricted the study population to patients age 65 years and older, as younger Medicare beneficiaries are not representative of the younger population hospitalized with HF. Only subjects with documentation of LVSF measured either during the index hospitalization or previously, as noted in the medical record, were candidates for the analysis. The diagnosis of HF was corroborated by one or both of the following criteria: 1) a prior history of HF documented in the medical record or 2) radiographic evidence of HF on the admission chest radiograph.

Normal LVSF was defined as a quantitative ejection fraction ≥50% or qualitatively normal LVSF. Abnormal LVSF was defined as mild, moderate, or severe LV dysfunction (either a qualitative assessment consistent with LV systolic dysfunction or LV ejection fraction [LVEF] <50). In some cases, patients may have had more than one documented LVSF evaluation. In these circumstances, an evaluation during the index hospitalization took precedence over a prior evaluation. In cases where multiple evaluations occurred during the hospitalization, quantitative results took precedence over qualitative results. Finally, the last evaluation before discharge was used if this prioritization scheme did not result in a single value.

Data source. Trained medical records reviewers abstracted the information from the medical record of the hospitalization and entered the data into an electronic database. The data included demographic variables, past cardiac and noncardiac history, patient characteristics on hospital admission, and in-hospital events. This abstraction process, similar to that used for the Cooperative Cardiovascular Project, is considered highly reliable (8).

Statistical analysis. We performed bivariate comparisons with the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. Continuous variables are reported as a mean ± SD.

We constructed multivariable logistic models to identify variables independently associated with preserved LVSF. The initial model examined the association with demographic variables. Then, in order to identify the effects of coexisting medical conditions on these demographic factors, variables reflecting the medical history and clinical presentation were introduced into a second model.

To identify whether the inclusion of patients with prior evaluations of LVSF biased the analyses, we performed separate regressions including only patients with an evaluation during the index admission. Additionally, because the definition of preserved LVSF has varied among studies, and often includes patients with mild systolic dysfunction, analyses were repeated including patients with normal or near-normal LVSF (LVEF 40% to 49% or mild LV systolic dysfunction). Finally, separate analyses including all patients with documentation of LVSF regardless of other confirmatory evidence of HF were also performed to identify the effects of the case-confirmation criteria.

In the models, univariate logistic regression was used to identify baseline patient characteristics individually associated with preserved LVSF. Those associated in the bivariate analysis with a p value of <0.10 or identified as clinically important from prior studies were candidates for the multivariable logistic models. Models were constructed using forward selection with backward elimination. Variable selection was stopped when the likelihood ratio test was no longer significant ($p < 0.05$).

All two-way interactions of clinical interest were tested for significance. Additionally, stratified analyses were performed, and adjusted odds ratios for gender were calculated, stratified by age and by the presence or absence of the following characteristics: coronary artery disease, hypertension, atrial fibrillation, chronic obstructive lung disease, hypertension, diabetes mellitus, and renal insufficiency (defined as serum creatinine ≥1.4 mg/dl). Finally, we tested variables of clinical but not statistical significance for residual confounding by introducing these variables individually into the full model. Because of the high prevalence of preserved LVSF in the study group, odds ratios in the final models were converted to risk ratios to provide more accurate assessments of association (9). We evaluated the discrimination of the models by calculating the area under the receiver-operating characteristic (c-statistic) (10). We performed all analyses with the SAS v. 8.0 statistical software package (SAS Institute, Cary, North Carolina).

RESULTS

The patient population. Of the 37,500 patients in the NHF cohort, 34,587 were at least 65 years old (Fig. 1). Among these older subjects, 19,710 (57%) had an assessment of LVSF and corroborative evidence of the diagnosis of HF in the hospital record. Of the patients with documentation of LV function, 12,956 (66%) had impaired LVSF and 6,754 (34%) had normal LVSF or a quantitative LVEF ≥0.50. Of the patients with documentation of LVSF, 43% of women (4,795 of 12,022) and 23% of men (1,959 of 8,566) had normal function.

When compared with subjects having documentation of LVSF, those without documentation (n = 14,104) were

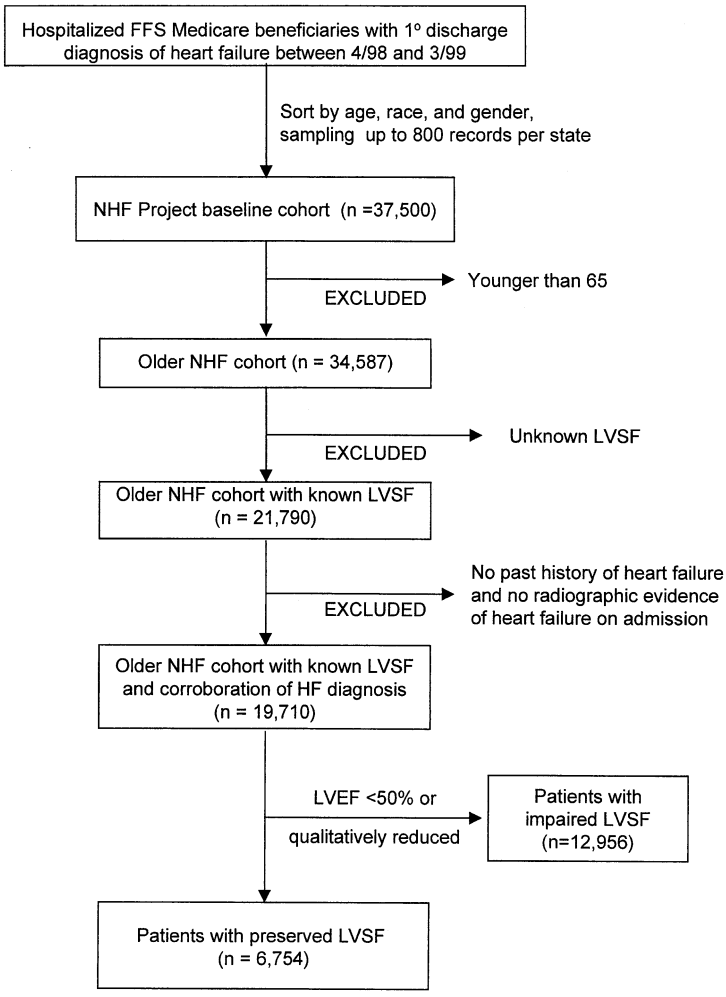

Figure 1. Selection of the study sample. FFS = fee-for-service; LVEF = left ventricular ejection fraction; LVSF = left ventricular systolic function; NHF = National Heart Failure Project.

older, more often women, had a lower prevalence of cardiovascular conditions, and had a higher prevalence of noncardiovascular comorbidities (Table 1).

Most bivariate comparisons between patients with preserved and impaired LVSF were statistically significant because of large sample sizes (Table 1). The mean age of the population with preserved LVSF was nearly one and one-half years greater than the population with impaired LVSF. Patients with preserved LVSF were more likely women, more often had hypertension, and had higher admission blood pressures. These patients also had lower rates of coronary artery disease and its sequelae (such as myocardial infarction or revascularization). Atrial fibrillation and chronic lung disease, although more frequent among patients with preserved LVSF, were common in both groups.

Factors associated with preserved LVSF. In the univariate analyses, female gender and advancing age were both associated with preserved LVSF (Table 2). After adjustment for demographic characteristics, the strong association between female gender and preserved LVSF persisted.

The association between female gender and preserved LVSF remained after further adjustment for medical history and admission characteristics, with an adjusted risk ratio for female gender at 1.71 (95% confidence interval 1.63 to 1.78) (Table 2). After adjustment, the association between increasing age and preserved LVSF was attenuated, especially in ages below 85 years. The Wald chi-squared statistic, reflecting the strength of the association, was more than an order of magnitude higher for gender (461) than for age (for age as a class or continuous variable = 39).

Medical history and admission characteristics were also significantly correlated with preserved LVSF in the multivariable analysis (Table 3). Hypertension, chronic obstructive lung disease, atrial fibrillation, aortic stenosis, and an elevated systolic blood pressure were positively associated with preserved LVSF, whereas coronary artery disease—particularly with a history of myocardial infarction or revascularization—and renal insufficiency were associated with impaired LVSF.

Secondary models, including only patients with an assessment of LVSF during the index hospitalization, only those with quantitative results of LVSF assessments, those not

Table 1. Characteristics of the Study Population

Category/Variable	LVSF Not Documented	LVSF Documented	p	LVSF Preserved	LVSF Impaired	p
n	14,104	19,710		6,754	12,956	
Demographics						
Age (yrs, mean)	80.6 ± 8.0	78.7 ± 7.5	< 0.001	79.7 ± 7.6	78.2 ± 7.4	< 0.001
Age categories						
65–70	12%	16%		14%	17%	
71–75	16%	20%		18%	21%	
76–80	20%	23%	< 0.001	23%	23%	0.001
81–85	22%	21%		21%	21%	
86–90	18%	14%		16%	12%	
91+	12%	6%		8%	5%	
Female gender	61%	57%	< 0.001	71%	49%	< 0.001
Race						
Caucasian	87%	85%		86%	86%	
African American	9%	10%	0.001	9%	10%	0.08
Other non-Caucasian	4%	5%		5%	4%	
Cardiovascular history						
Coronary artery disease	52%	59%	< 0.001	46%	65%	< 0.001
Myocardial infarction	24%	32%	< 0.001	21%	38%	< 0.001
Prior PTCA	7%	10%	< 0.001	7%	11%	< 0.001
Prior CABG	19%	23%	< 0.001	14%	28%	< 0.001
Any prior revascularization	23%	29%	< 0.001	19%	34%	< 0.001
Hypertension (history)	56%	64%	< 0.001	69%	61%	< 0.001
Aortic stenosis	—	9%	—	11%	8%	< 0.001
Atrial fibrillation	31%	32%	0.05	36%	30%	< 0.001
Stroke	19%	18%	0.003	17%	18%	0.3
Other conditions						
Dementia	12%	8%	< 0.001	8%	8%	0.2
Diabetes mellitus	38%	39%	0.01	37%	40%	< 0.001
Chronic obstructive lung disease	35%	32%	< 0.001	34%	31%	< 0.001
Admission data						
Systolic BP ≥160 mm Hg	28%	29%	0.003	37%	25%	< 0.001
Heart rate ≥100 beats/min	30%	33%	< 0.001	29%	36%	< 0.001
Serum creatinine ≥1.4 mg/dl	45%	43%	< 0.001	36%	47%	< 0.001
Left bundle branch block	14%	18%	< 0.001	8%	24%	< 0.001

BP = blood pressure; CABG = coronary artery bypass surgery; LVSF = left ventricular systolic function; PTCA = percutaneous transluminal coronary angioplasty.

requiring corroboration of HF, and those using normal or near-normal LVSF as the dependent variable, did not differ appreciably from the primary models.

Gender as a prediction of preserved LVSF in subgroups. Female gender was a consistent predictor of preserved LVSF in subgroups stratified by age and comorbidity (Fig. 2). The

Table 2. Unadjusted ORs, Adjusted ORs, and Adjusted RRs (95% Confidence Intervals) for Demographic Variables as Correlates of Preserved LVSF

	Unadjusted OR	OR Model 1	OR Model 2	RR Model 2
Female gender	2.49 (2.34–2.65)	2.42 (2.27–2.57)	2.07 (1.93–2.34)	1.71 (1.63–1.78)
Age				
65–69	1.00	1.00	1.00	1.00
70–74	1.12 (1.01–1.24)	1.11 (1.00–1.23)	1.13 (1.01–1.26)	1.09 (1.01–1.17)
75–79	1.24 (1.13–1.37)	1.19 (1.08–1.31)	1.20 (1.08–1.33)	1.13 (1.06–1.21)
80–84	1.32 (1.20–1.46)	1.20 (1.08–1.33)	1.13 (1.02–1.26)	1.09 (1.01–1.17)
85–89	1.70 (1.53–1.90)	1.47 (1.32–1.64)	1.38 (1.22–1.55)	1.24 (1.15–1.34)
90+	1.98 (1.73–2.26)	1.59 (1.38–1.82)	1.42 (1.22–1.64)	1.27 (1.15–1.39)
Race				
Caucasian	1.00	1.00	1.00	1.00
African-American	0.90 (0.82–0.99)	0.87 (0.79–0.96)	0.72 (0.64–0.80)	0.79 (0.73–0.86)
Other non-Caucasian	0.92 (0.80–1.06)	0.93 (0.81–1.08)	0.84 (0.72–0.98)	0.89 (0.79–0.99)

Model 1: adjusted for age, gender, and race. Model 2: adjusted for age, gender, race, medical history, and admission characteristics.

LVSF = left ventricular systolic function; OR = odds ratio; RR = risk ratio.

Table 3. ORs and RRs (95% Confidence Intervals) for Other Correlates of Preserved Left Ventricular Systolic Function in Order of Entry Into the Full Logistic Model

Variable	OR	RR
LBBB on electrocardiogram	0.27 (0.24–0.30)	0.38 (0.34–0.41)
Coronary artery disease		
None	1.00	1.00
Present, without prior MI or revascularization	0.69 (0.63–0.77)	0.80 (0.76–0.86)
Present with prior MI or revascularization	0.42 (0.40–0.46)	0.57 (0.55–0.60)
Systolic blood pressure ≥160 mm Hg	1.66 (1.55–1.78)	1.38 (1.33–1.44)
Heart rate ≥100 beats/min	0.60 (0.56–0.60)	0.70 (0.67–0.75)
Atrial fibrillation	1.39 (1.29–1.49)	1.23 (1.18–1.29)
Chronic obstructive lung disease	1.30 (1.21–1.39)	1.18 (1.13–1.23)
Serum creatinine ≥1.4 mg/dl	0.75 (0.71–0.81)	0.83 (0.80–0.87)
History of hypertension	1.31 (1.23–1.41)	1.20 (1.15–1.26)
Aortic stenosis	1.28 (1.14–1.43)	1.17 (1.09–1.25)

c-index, full model: 0.74

LBBB = left bundle branch block; MI = myocardial infarction; OR = odds ratio; RR = risk ratio.

confidence intervals of the risk ratios for female gender overlapped across all subgroups and all exceeded 1.0. None of the two-way interactions tested were statistically significant.

DISCUSSION

In this national study of older Medicare beneficiaries hospitalized with HF, preserved LVSF was present almost twice as frequently in women as in men. This correlation was consistent across a wide range of patient characteristics, including age and cardiovascular comorbidity, and persisted after adjustment for multiple covariates. In contrast, the correlations with age were relatively modest, and were markedly attenuated by adjustment for other variables.

Biologic changes associated with age may be an important factor underlying the association between increasing age and the prevalence of preserved LVSF in HF. Normal aging is associated with interstitial fibrosis (5) and myocardial hypertrophy (4), which can result in abnormal LV relaxation and compliance. Aging has also been associated with changes in intracardiac blood flow patterns, reflecting alterations in diastolic function (11).

Biologic factors may also underlie the observed relationship between female gender and preserved LVSF. Prior research has identified differences between men and women in changes in LV geometry and wall thickness as a response to chronic pressure overload. Among patients with severe aortic stenosis, Carroll et al. found differences in LV adaptation to chronic pressure overload between men and women. Among patients with similar degrees of LV outflow obstruction and symptoms, women had higher indices of LV function and lower degrees of wall stress than men (7).

Gender differences in the ventricular response to chronic systemic hypertension have also been identified (6,12,13). In a study of patients with isolated systolic hypertension in the Framingham cohort, Krumholz and others found that hypertension conferred a higher risk of echocardiographic LV hypertrophy in women than in men (6). Moreover, the response to isolated systolic hypertension in women was associated with increased LV wall thickness without dilation, whereas in men it was associated with chamber dilation without marked changes in wall thickness. In a clinical trial population with systemic hypertension and electrocardiographic LV hypertrophy, Gerdts et al. (12) found that although women and men had similar absolute LV mass, women had higher indices of LVSF and higher relative wall thickness.

The findings of our study suggest that the differences between women and men in LV adaptation extend beyond the response to pressure overload seen in aortic stenosis or systemic hypertension. Among this older population hospitalized with HF, the correlation between female gender and preserved LVSF was seen in patients with or without hypertension, arrhythmia, valvular disease, or renal insufficiency. Even among patients with prior myocardial infarction, women were more likely to have preserved LVSF, which raises the possibility of gender differences in ventricular remodeling postinfarction. The consistency of the association between gender and preserved LVSF across numerous subgroups of patients implies that gender itself is likely an important determinant of LV adaptation regardless of the underlying pathologic processes associated with the development of HF.

This study corroborates the findings of prior investigations that identify both advancing age and female gender as correlates of preserved LVSF in populations of patients with HF (1–3,14–16). Recent reviews of this topic emphasize, however, that this syndrome is a phenomenon of advanced age and focus less upon the gender association (17,18). Because of the complex interrelationship among age, gender, and coexisting medical conditions, however, it is possible that the gender association either reflects differences in demographics and comorbidity between men and women with HF or an underlying biologic difference between genders.

Although prior studies have identified the gender association, these studies have been methodologically limited. Early studies enrolled consecutive patients, usually among those referred for imaging studies in tertiary centers, and are thus hampered by referral biases, small sample sizes, and homogeneous populations (14–16). Population-based studies have also suggested a female preponderance among incident cases of HF with preserved LVSF (1–3). Investigators from Framingham, Massachusetts, found that among 73 incident cases of HF, 24 of 33 women (73%) and 13 of 40 men (33%) had an ejection fraction of at least 0.50 (2). In Olmsted County, Minnesota, investigators identified 137 incident cases of HF with LVSF assessments, of whom 59 (43%) had normal LVSF (1). Of these, 70% were women, in contrast to the 41% women of 78 patients with reduced LVSF. Similarly, in the Cardiovascular Health Study, a female preponderance was noted among the 149 partici-

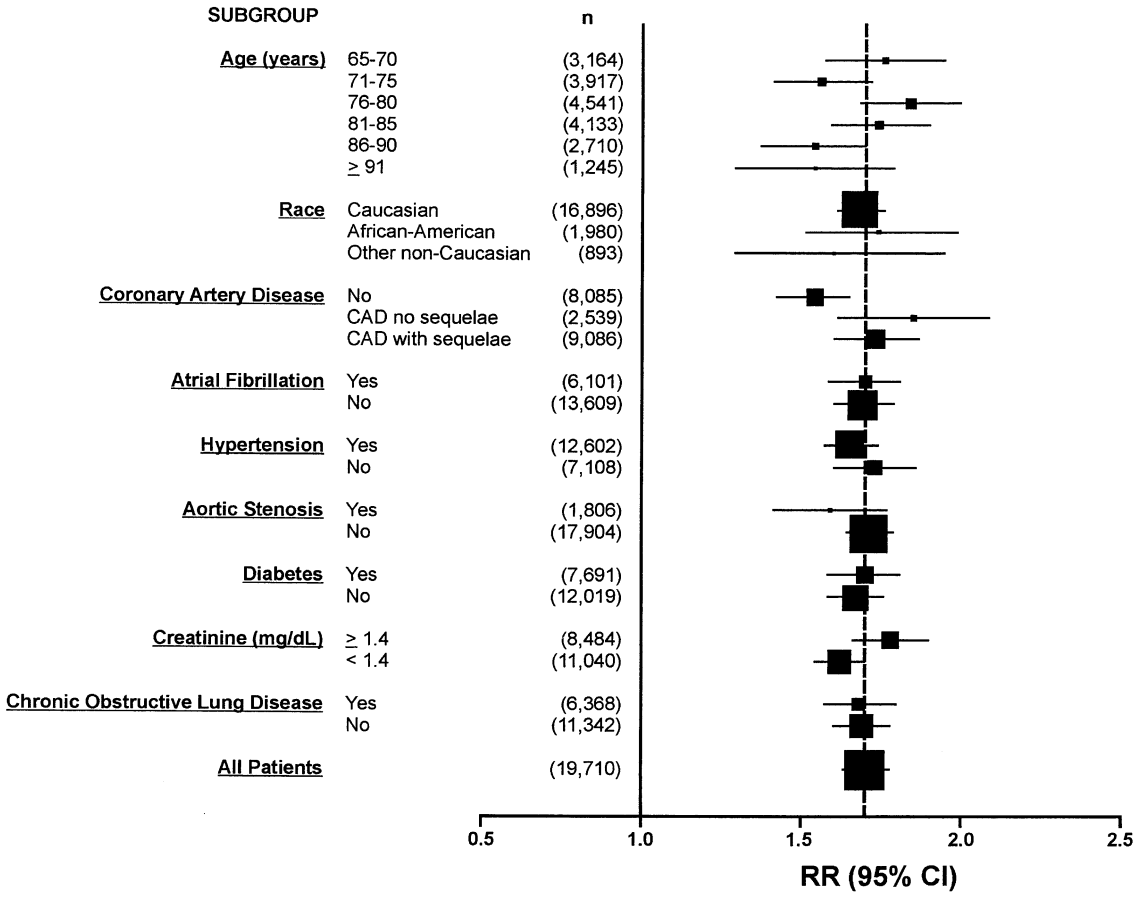

Figure 2. Risk ratios (RR) with 95% confidence intervals (CI) for the association between female gender and preserved left ventricular systolic function in the total study population and in population subgroups. The vertical dashed line represents the point estimate for the fully adjusted risk ratio for female gender in the total study population.

pants with HF and preserved LVSF (3). These studies, although not subject to the referral bias of prior cohort studies and case series, were limited by sample sizes and, in the cases of Framingham and Olmsted County, sociodemographically homogeneous populations.

The scientific and clinical implications of the findings of this study in an unselected community-based sample are significant. Currently, most research in HF has focused upon patients with systolic dysfunction; all major randomized trials demonstrating a reduction in mortality in HF have included only those with impaired LVSF. The absence of randomized trials in patients with preserved LVSF, therefore, likely disproportionately limits the enrollment of women in trials of drug therapy for HF. Our findings provide a compelling explanation for the observation that women are consistently underrepresented in the major clinical trials in HF (19).

Furthermore, on a clinical level, these data should inform the approach to the diagnosis and treatment of women with HF. Care providers should recognize that female patients presenting with the HF syndrome, regardless of the underlying etiology, have a higher likelihood than men of having preserved LVSF.

A few issues merit consideration in the interpretation of these results. The sample for this study included only those NHF subjects with documentation of LVSF. It is conceivable that men hospitalized with a syndrome consistent with HF who have preserved LVSF are more likely than women to be assigned an alternative diagnosis (such as chronic obstructive lung disease or coronary artery disease). However, the proportion of men and women presenting with evidence of HF by radiograph in the NHF cohort is similar (77% and 79%, respectively), implying that the diagnosis of HF was applied uniformly between genders.

Furthermore, the patients without an assessment of LVSF, who were thus excluded from our analyses, were more often women. This could introduce bias in the results. However, given the strength and consistency of the association between gender and preserved LVSF found in this study, one would need to invoke marked and systematic nationwide trends toward the underassessment of LVSF confined to women with LVSD or men with preserved LVSF to invalidate these results.

Because of the lack of reliability of certain data elements obtained by retrospective chart abstraction, case definition using a standardized definition such as the Framingham criteria (20) was not possible. In prior studies, however, the primary discharge diagnosis of HF has been specific for the

diagnosis in hospitalized populations (21). Additionally, the use of corroborating evidence for the diagnosis likely further increases the specificity of the diagnosis.

This study population includes only older fee-for-service Medicare beneficiaries hospitalized primarily for HF. Thus, our sample is not representative of all groups with HF, including the young or older ambulatory patients with the condition. Although it may not be appropriate to generalize the findings of this study to the entire elderly population with HF, our study does examine a large and important subset of this population that suffers a remarkable burden of disease. For example, in 1999 alone HF was the primary diagnosis of more than 750,000 hospital discharges in the U.S. among persons age 65 years and older (22).

Conclusions. In this study of a large national cohort of older persons hospitalized with HF, normal LVSF was common and occurred more frequently in women. Even after adjustment for differences in age and a wide range of coexisting conditions, female gender remained highly correlated with preserved LVSF. This condition, often considered a phenomenon of advancing age, should be considered a condition of women. Future efforts to expand the knowledge base of HF pathophysiology and treatment in HF with preserved LVSF will be important in clarifying the approach to this segment of the population with HF.

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