STATE-OF-THE-ART PAPER

Heart Failure With Preserved Left Ventricular Systolic Function
Epidemiology, Clinical Characteristics, and Prognosis

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Recent cross-sectional, population-based echocardiographic studies show that about half of all patients with heart failure have preserved left ventricular systolic function (HF-PSF). Cohort studies of hospitalized patients show a smaller proportion of HF-PSF. Compared to those with reduced systolic function, patients with HF-PSF are more often female, older, less likely to have coronary artery disease, and more likely to have hypertension. Patients with HF-PSF are less symptomatic and receive different pharmacologic therapy than patients with reduced systolic function. Morbidity and mortality rates in patients with HF-PSF are high but not quite as high as in patients with reduced systolic function. Though much has recently been learned about the syndrome of HF-PSF, many questions remain to be answered, not least how it should be treated. (J Am Coll Cardiol 2004;43:317–27) © 2004 by the American College of Cardiology Foundation

After years of focus on chronic heart failure (CHF) arising from reduced left ventricular (LV) systolic function, there has been a recent growth in interest in the syndrome of CHF associated with "preserved" LV systolic function (1–5). The pathophysiology of this type of heart failure (HF) has been discussed in depth (6–8). The aim of the present review is to describe, in detail, the epidemiology, clinical characteristics, and prognosis of patients with HF and preserved LV systolic function (PSF).

INCIDENCE OF HF-PSF

There are only two studies of incident cases of CHF differentiating between preserved or reduced systolic function (9,10). In the Olmsted County study, 216 patients with new CHF presenting during the calendar year 1991 were identified (5). Of these, 137 (63%) had a recent echocardiographic assessment of LV ejection fraction (LVEF), 59 (43%) of whom had PSF (LVEF ≥50%). Five had significant valve disease—that is, 54 (39%) had PSF and no valve disease. Patients with PSF were more often female (69% vs. 41%), more likely to have been diagnosed as an out-patient than an in-patient (86% vs. 71%), and older (78 vs. 74 years). Coronary heart disease (CHD) (31% vs. 53%), electrocardiographic (ECG) evidence of myocardial infarction (MI) (15% vs. 42%), radiographic cardiomegaly, and pulmonary edema were all less common in patients with PSF. Atrial fibrillation (AF) was more frequent (29% vs. 24%), whereas renal dysfunction (serum creatinine ≥1.3 mg/dl) was less common (37% vs. 51%) in patients with PSF.

In the Bromley CHF study, all local primary care physicians were asked to refer new cases of CHF to a special clinic; all local patients admitted to hospital with CHF were also identified (10). Of the 332 new cases of CHF detected between February 1996 and April 1997, 310 (93%) had an echocardiogram: 16% of patients were found to have PSF; 68% a "mild to moderate" reduction in LV systolic function; and 16% severe LV systolic dysfunction on qualitative assessment. The PSF and LV systolic dysfunction groups were not compared.

Three factors may explain the discrepancy between these two studies. First, the Bromley study included 54 cases where CHF had developed after acute MI, likely increasing the proportion with reduced systolic function. Second, the "threshold" for differentiating PSF from "reduced" systolic dysfunction, which is critical in determining the proportion with systolic dysfunction (see following text), may have differed between the studies. Third, two biases may have occurred. Only 63% of patients in the Olmsted County study had an echocardiogram, compared to 93% in the Bromley study. In the Bromley study, 208 of the 332 cases (63%) were identified during hospital admission; these cases may be more likely to have reduced LV systolic function. Prevalence studies show better agreement than the incidence studies.

PREVALENCE OF HF-PSF

Cross-sectional population echocardiographic studies.
We identified 10 such studies, 1 confined to Native Americans (Table 1) (11–20). The number of individuals screened and their age range varied widely. The means of identification of "CHF" also varied, from clinical examination by a single investigator to the use of an epidemiological questionnaire (e.g., Framingham score). The definition of

Abbreviations and Acronyms

AF   = atrial fibrillation
CHF = chronic heart failure
CHD = coronary heart disease
DD   = diastolic dysfunction
ECG = electrocardiogram/electrocardiographic
FS   = fractional shortening
IVRT = isovolumic relaxation time
LV   = left ventricle/ventricular
LVEF = left ventricular ejection fraction
PSF = preserved systolic function

PSF ranged from qualitative assessment of LVEF to quantitative measurement of fractional shortening (FS), a wall motion score or LVEF; FS was used most frequently but has certain limitations (see the following text). Table 1 and Figure 1 summarize the findings of the 10 studies.

The prevalence of both types of CHF increased with age. The proportion of patients with PSF ranged from 40% to 71% (with a mean of 56%) and was probably influenced by the method used to assess LV systolic function and the threshold dividing "preserved" from "reduced." For example, FS measures systolic function at the base of the heart and can be normal in patients with apical hypokinesis (whereas LVEF may be reduced). Regarding "threshold," comparison of the Copenhagen (13) and Västeras (14) studies shows that very different proportions of PSF may be calculated depending upon whether a left ventricular wall motion index (LVWMI) of >1.5 or >1.7 is used as the cut-point (see also FS in the Rotterdam (12) and Helsinki (16) studies and EuroHeart Failure survey later) (Table 1). In the Cardiovascular Health Study (CHS), 80% of patients had an LVEF >0.45, but only 55% had an LVEF >0.55 (18). There is no simple binary division between "preserved" and "reduced" systolic function. Instead, there is a "border zone" or "gray area" where there is uncertainty. Some investigators may define these patients as having preserved systolic function and others as having mildly reduced systolic function (Fig. 2).

Only three studies cite separate prevalence figures for men and women. The proportion of women with HF-PSF exceeds that of men in all three studies. A case-control study from Framingham is consistent with this conclusion (3). In that study, 73% of 33 women but only 33% of 40 men with CHF had PSF (also see the EuroHeart Failure survey later).

Though not strictly epidemiological studies, both the Improvement Programme in Evaluation and Management of Heart Failure (IMPROVEMENT-HF) (21) study, undertaken in primary care in 15 member countries of the European Society of Cardiology, and the Italian Network on Congestive Heart Failure (IN-CHF) study (22), conducted in out-patients between 1995 and 1999 in 133 of the 192 Italian cardiology centers, are in close agreement with the findings summarized earlier.

Indices of diastolic function. Though often considered synomonous with CHF owing to diastolic dysfunction (DD), these two syndromes are not identical. There is the obvious minority of patients with significant valvular disease (and these have been poorly defined in most of the studies reviewed). Less obvious may be other causal mechanisms such as intermittent myocardial ischemia and AF (23,24). It is, therefore, of interest to know whether there is evidence of DD in patients with PSF. Four of the population echocardiographic studies have also reported indices of DD. In the CHS, mean atrial flow, early flow, and the ratio of early/atrial flow (E/A ratio) did not differ between patients with HF-PSF and those with CHF and reduced systolic function (18). Patients with HF-PSF had increased systolic wall thickness compared to those with reduced systolic function.

In the Helsinki Ageing Study, there was no difference in E/A ratio, isovolumic relaxation time (IVRT), LV mass, or LV hypertrophy between patients with PSF and those with reduced systolic function, though all of these measures differed between patients with CHF and subjects without (16).

In the study from Asturias, all 10 patients with HF-PSF had Doppler evidence of DD (11). In eight patients this was an IVRT >110 ms, and in the other two an abnormal mitral valve E deceleration time (DT) was the cause. Eight of the 10 patients also had echocardiographic LV hypertrophy.

Two extensive studies of DD in the general population have recently been reported (20,24). In 2,042 randomly selected residents of Olmsted County, Minnesota (20), aged ≥45 years, the prevalence of symptomatic CHF was measured using the Framingham criteria, and systolic and diastolic LV function was assessed by Doppler echocardiography. The prevalence of CHF was 2.2%; 20.8% of the population had mild, 6.6% moderate, and 0.7% severe DD; 6% had an LVEF ≤50%, and 2% an LVEF ≤40%; CHF was more frequent in those with systolic or diastolic dysfunction, although even in subjects with moderate or severe ventricular dysfunction of either type, fewer than half of them had CHF (Fig. 3). There was a considerable overlap between systolic and DD (e.g., the prevalence of moderate or severe DD in subjects with an LVEF ≤50% was 35.2%). Conversely, in subjects with mild, moderate, or severe DD, 10.5%, 19.5%, and 61.5%, respectively, had an LVEF ≤50%. "Isolated DD" was also common; that is, the prevalence of moderate or severe DD in subjects with an LVEF >50% was 5.9%. Interestingly, DD was as prevalent in men as in women.

In the second study (24), the prevalence of DD was measured in 1,274 men and women age 27 to 75 years (mean 51 years) in Augsburg, Germany. The criteria advocated by the European Study Group on Diastolic Heart Failure were used to measure DD (25). Some 2.3% of the population had an LVEF <45%. Of the remainder, 11.1% fulfilled the European criteria for DD. The prevalence of DD increased from 2.8% between ages 25 and 35 years, to 15.8% in those >65 years. The prevalence of DD in healthy

Table 1. Prevalence of Heart Failure With Preserved Left Ventricular Systolic Function: Echocardiographic Cross-Sectional Population Studies

Country (Ref. No.)	No. Pts.	Age Range (yrs)	Mean Age (yrs)	Definition of Preserved LV Systolic Function	Prevalence of CHF (%)			How CHF Was Defined	Proportion of Patients With Preserved LV Function (%)		
					Male	Female	All		Male	Female	All
Spain (Asturias) (11)	391	>40	60	LVEF >50%	6.6	3.3	4.9	Framingham criteria	—	—	59
Netherlands (Rotterdam) (12)	1,698	55–95	65	FS >25%	3.7	4.0	3.9	Physician exam/clinical score	—	—	71
Denmark (Copenhagen) (13)	2,158	≥50	—	LVWMI >1.5 or FS ≥26%	—	—	6.4	Boston criteria	—	—	71
Sweden (Västeras) (14)	433	75	75	LVWMI >1.7 or LVEF ≥43%	4.0	9.5	6.7	Physician exam	—	—	46
U.K. (Poole) (15)	817	70–84	76	Qualitative (normal; mild, moderate, severe dysfunction)	—	—	8.1	Patient self-reported	—	—	68
Finland (Helsinki)* (16)	501	75–86	—	FS ≥25%	5.2	9.3	8.2	Physician exam/clinical score	—	—	72
Portugal (EPICA) (17)	5,434	>25	68	FS ≥28%/no LV regional dyskinesia and dilation	4.3	4.4	4.4	ESC/Boston criteria	20	55	39
U.S. (CHS) (18,44)	a) 4,842	66–103	78	Qualitative†	—	—	8.8	Panel review	42	67	55
	b) 5,888	≥65	74	Qualitative†	–	—	5.1‡	Panel review	—	—	63
U.S. (second SHS) (19)	3,184	47–81	60	LVEF >54%	2.7	3.1	3.0	Hospitalized and Framingham criteria	26	67	53
U.S. (Olmsted) (20)	2,042	≥45	63	LVEF >50%	2.7	1.7	2.2	Chart review/Framingham criteria	—	—	44

*Fifty-one patients with valve disease were excluded. †Normal (LVEF ≥55%); mild (LVEF 45%–54%), moderate (LVEF 30%–44%) or severe (LVEF <30%) dysfunction. ‡A total of 4.9% when value disease is excluded. a) = data from reference 18; b) = data from reference 44.

CHF = chronic heart failure; CHS = Cardiovascular Health Study; EPICA = Epidemiologia da Insuficîencia Cardiaca e Aprendiazagem; ESC = European Society of Cardiology; FS = fractional shortening; LV = left ventricular; LVEF = left ventricular ejection fraction; LVWMI = left ventricular wall motion index; SHS = Strong Heart Study.

PREVALENCE OF HEART FAILURE
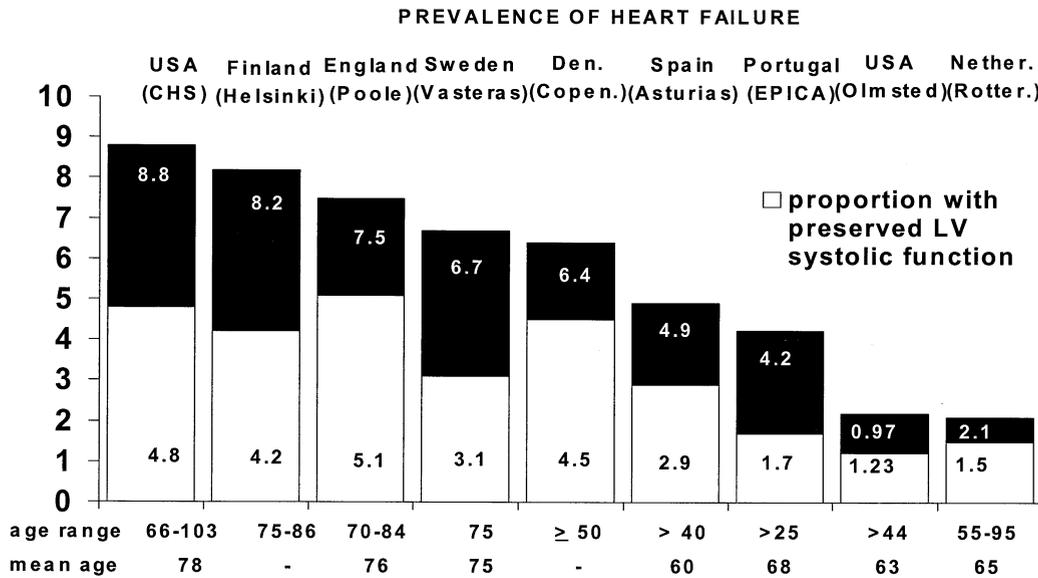
Figure 1. Prevalence of heart failure in cross-sectional, population-based, echocardiographic studies. **Black bars** show percent prevalence; **lower portion of the bars** show the proportion of cases associated with preserved systolic function. LV = left ventricular.

individuals (i.e., those without cardiac disease, hypertension, etc.) was 4.3%. Diastolic dysfunction was more common in men (13.8%) than in women (8.6%, p < 0.01), in keeping with the Olmsted County Study: 3.1% of subjects had more severe DD, defined as DD associated with either left atrial enlargement or diuretic treatment. These new studies tell us that Doppler evidence of DD is common in the general population (even more so than systolic dysfunction), is often asymptomatic, and adversely affects prognosis. Paradoxically, DD is more common in men, despite the predominance of women with HF-PSF.
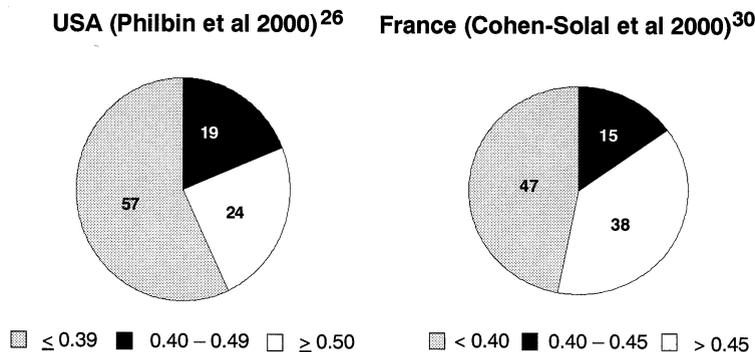
Hospitalization cohorts. We have identified 12 such studies published since January 2000 (Table 2) (26–37). They are heterogeneous, ranging from small single-center studies with a majority of African American patients, through a large sample of Medicare beneficiaries in the United States, to a countrywide epidemiological survey from France. Most have incomplete information on assessment of LV function. The proportion of patients with PSF was less than in population studies, ranging from 24% to 55% (mean 41%), consistent with the evidence that patients with CHF and

PSF have less severe symptoms and are less likely to require in-patient treatment (see subsequent text).

Patients with PSF were less likely to have had a prior history of, or hospitalization for, CHF. As in the population studies, there was a clear preponderance of females, and Masoudi et al. (34) confirmed in a multivariate analysis that female gender was an independent predictor of PSF in patients with CHF. The recent Euro Heart Failure survey of 11,327 hospital discharges from 115 hospitals in 24 European countries supports these findings (Fig. 4) (38). Only 28% of women with CHF had an LVEF of <0.40, compared to 51% of men. Patients with PSF were also older, though the relationship between age and PSF appears to be less strong than that between PSF and female gender (34).

SYMPTOMS, SIGNS, QUALITY OF LIFE, OTHER INDICES OF MORBIDITY, AND HOSPITAL STAY

In two studies, the frequency of characteristic symptoms (dyspnea at rest and on exercise; orthopnea) and signs (elevated jugular venous pressure, pedal edema, and pulmo-

USA (Philbin et al 2000)[26]   **France (Cohen-Solal et al 2000)**[30]

☒ ≤ 0.39   ■ 0.40 – 0.49   ☐ ≥ 0.50   ☒ < 0.40   ■ 0.40 – 0.45   ☐ > 0.45

Figure 2. Distribution of left ventricular ejection fraction in patients hospitalized with heart failure.
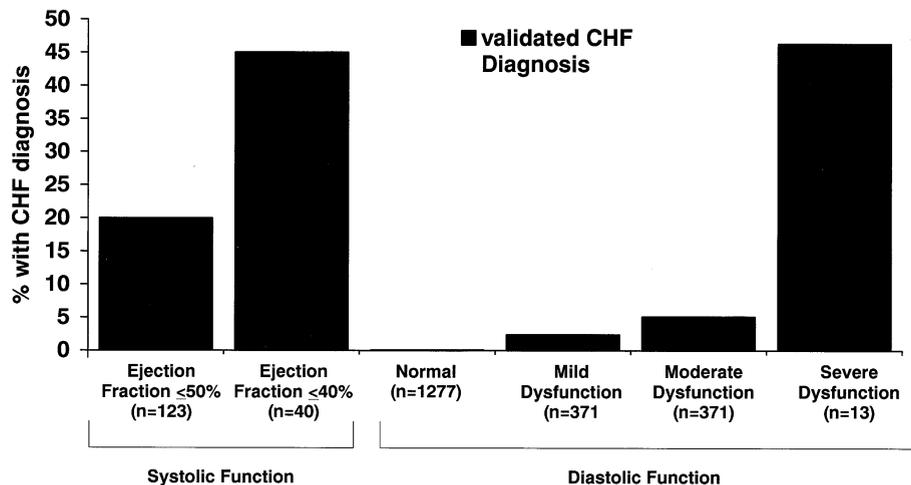
Figure 3. Prevalence of heart failure in subjects in the general population with left ventricular systolic and diastolic dysfunction (Olmsted County Study, Minnesota). CHF = chronic heart failure.

nary crackles) was similar in patients with PSF and reduced systolic function (though both these studies enrolled mainly African Americans (27,33). The exception was a third heart sound that was less frequent in PSF. In four studies, radiographic cardiomegaly was less common in patients with PSF. The (IN-CHF) study supports this finding, showing that patients with PSF have smaller echocardiographic LV dimensions in diastole and systole (22). Philbin et al. (26) and Varela-Roman et al. (31) found that patients with PSF are less likely to be in a higher New York Heart Association (NYHA) class, a finding confirmed in the IN-CHF study (22). Smith et al. (35) recently reported that severe dyspnea was less common in patents with PSF. Philbin et al. (26) also measured quality of life (QoL) using the ladder of life score (maximum score 10 = perfect health). The mean score was 6.5 in patients with reduced systolic function and 6.4 in those with PSF, scores almost identical to those in another study of a clinic cohort, using the same QoL instrument (39). In a more recent study (6), however, both a general QoL instrument (the Short Form 36) and disease-specific one (the Minnesota Living With Heart Failure Questionnaire) showed greater reductions in QoL in patients with reduced LV systolic function than in those with PSF (though both groups of patients had a lower QoL than expected for the general population).

Other insights into the morbidity can be gleaned from the studies summarized in Table 2. The mean Charlson co-morbidity index was 2.8 and 2.9 in the preserved and reduced systolic function groups, respectively, in the study by Philbin et al. (26). Smith et al. (35) found that patients with reduced systolic function had limitation of a greater number of daily living activities.

Ahmed et al. (29) found that 6% of both groups of patients had been admitted from a nursing home, and Philbin et al. (26) reported this proportion to be 13% in the PSF group and 10% in the reduced systolic function group.

In the four studies reporting length of hospital stay, there was little difference between the two types of CHF. For the preserved and reduced systolic function groups, respectively, the durations of stay were 11 versus 11 days (French study), 7.5 versus 7.9 days (Philbin et al.), 6.1 versus 7.0 days (Dauterman et al.), and 5.2 versus 5.9 days (Malki et al.) (26–28,30). In a more detailed analysis, both Philbin et al. and Malki et al. noted that length of stay tended to increase with decreasing LVEF (26,27). Presumably, the powerful effect of age offsets this effect when patients are dichotomized into preserved and reduced LV systolic function groups (the former group being older on average).

CONCOMITANT MEDICAL PROBLEMS

Few of the population-based echocardiographic studies provide details on co-morbidity and medical therapy, but more is provided by the hospitalization cohort studies (Table 3).

Myocardial infarction (or any evidence of CHD) was much *less* common in patients with PSF than in those with reduced systolic function (though more common in patients with HF-PSF than in age- and gender-matched controls) (3). Other evidence of atherosclerotic disease (peripheral arterial/cerebrovascular) was also less common. The IN-CHF registry reported similar findings (22). In a multivariate analysis, Masoudi et al. (34) found that CHD was an independent predictor of a *lower* risk of finding PSF in patients hospitalized with CHF.

Conversely, hypertension (and a suspected hypertensive etiology) was *more* common in patients with PSF (40,41). The IN-CHF study also supports this finding (22). In a multivariate analysis, Masoudi et al. (34) were also able to confirm that a history of hypertension was an independent predictor of PSF in patients hospitalized with CHF.

Both of these co-morbidities showed considerable geographical/ethnic variation. Hypertension was considered the etiology in about a third of Japanese patients but only 16% in the predominantly white U.S. patients studied by Philbin et al. (26). Hypertension appeared to be particularly common in Native Americans with PSF (19). Left ventricular

Table 2. Prevalence of Heart Failure With Preserved Left Ventricular Systolic Function: Hospitalization Cohort Studies

First Author/Country (Ref. No.)	Year Published	No.*	Design	Criteria for Preserved LV Systolic Function	Preserved/Total (%)	Female % (P/R)	Mean Age† (P/R)	AA % (P/R)
Philbin (U.S.-MISCHF Registry) (26)	2000	1,291 (2,906)	MISCHF registry, DRG 127, LV function assessment within 6 months of discharge, numeric LVEF available	Echo/RNVG/other LVEF ≥50%	312/1,291 (24)	70/50	75/74	4/3†
Malki (U.S.-Detroit) (27)	2002	187 (?)	Prospective, clinical, and radiologic pulmonary congestion; echo within 6 months	Echo LVEF ≥50%	57/187 (30)	63/46	69/65	60/79
Dauterman (U.S.-California) (28)	2002	782 (1,720)	Retrospective chart review, Medicare ≥65 yrs, CXR cardiomegaly/pulmonary edema, LV function measurement, no C/I to ACE-I	Echo/RNVG/other LVEF ≥40% or qualitative LV assessment	238/438 (54)	69/49	—	15/14‡
Ahmed (U.S.-Alabama) (29)	2002	438 (1,091)	Medicare ≥65 yrs; clinical score; LV function measurement	LVEF >40% or qualitative LV assessment	430/782 (55)	69/49	—	14/19
Cohen-Solal (France) (30)	2000	739 (1,058)	Prospective, national epidemiological survey; Framingham criteria clinical diagnosis	Echo/RNVG/other LVEF, echo LVEF >40%	200/438 (46)	51/29	76/71	—
Varela-Roman (Spain) (31)	2002	229 (301)	Prospective, Framingham criteria; LV function assessment within 2 weeks	Echo LVEF ≥50%	66/229 (29)	64/33	67/66	—
Tsutsui (Japan) (32)	2001	172 (236)	Retrospective chart review; Framingham criteria; deaths excluded; echo LVEF	Echo LVEF >50%	61/172 (35)	51/33	69/68	—
Thomas (U.S.-Chicago) (33)	2002	225 (282)	Prospective, consecutive admissions over 4 months; Framingham criteria	Qualitative echo LVEF ≥45%	104/225 (46)	56/35	59/54	‖
Masoudi (U.S.-Medicare) (34)	2003	19,710 (33,814)	Medicare (≥65 yrs) sample April 1998 to March 1999	LVEF ≥50% or qualitatively normal LV systolic function, past history of CHF or radiographic evidence	6,700/19,710 (35)	79/49	80/78	9/10
Smith (U.S.-Connecticut) (35)	2003	413	Prospective, consecutive admissions, 1996 to 1998; NHANES criteria	Echo/RNVG/other LVEF ≥40%	200/413 (48)	63/35	73/70	21/25§
Gustafsson (Denmark) (36)	2003	5,491	Randomized controlled trial; admissions with CHF 1993 to 1996	Echo WMI >1.6 (approximates to LVEF >48%)	2,218/5,240 (42)	49/33	73/71	—
Varadarajan (U.S.-California) (37)	2003	2,258	Retrospective chart review, 1990 to 1999; echocardiogram	Echo LVEF ≥55%	963/2,258 (43)	3/97	70/71	11/10

*Number with LVEF measurement (total number in cohort); it is unclear whether entire cohort had an LVEF measurement. †In years. ‡Nonwhite. §Non-Caucasian. ‖75% overall.

AA = African American; ACE-I = angiotensin-converting enzyme inhibitor; CHF = chronic heart failure; C/I = contraindication; CXR = chest X-ray; DRG = diagnosis-related group; Echo = echocardiographic; ESC = European Society of Cardiology; LV = left ventricular; LVEF = left ventricular ejection fraction; MISCHF = Management to Improve Survival in Congestive Heart Failure; P/R = preserved/reduced LV systolic function; RNVG = radionuclide ventriculogram; WMI = wall motion index.
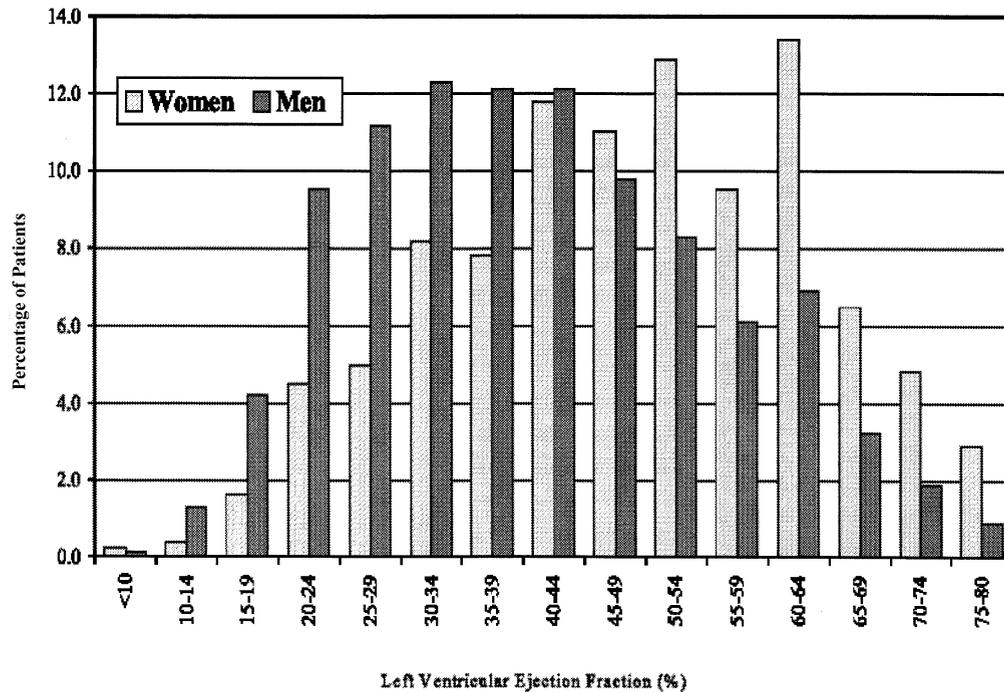
Figure 4. Distribution of left ventricular ejection fraction measured within 12 months of the survey among women (n = 2,048; 41% of total enrolled) and men (n = 3,249; 57% of total enrolled) enrolled in the EuroHeart Failure survey. Where more than one ejection fraction measurement was available, the most recent one was used. Fifty-one percent of men but only 28% of women had a left ventricular ejection fraction <40%.

hypertrophy was also more common in patients with PSF (the exception is the study by Thomas et al. [33]).

The incidence of AF was also more frequent in subjects with PSF and, overall, was remarkably common in this patient subset (occurring in a quarter to a third of patients). In the IN-CHF registry, 16% of low LVEF patients had AF, compared to 25% of patients with an LVEF >45% (22). In a multivariate analysis, Masoudi et al. (34) showed that AF was an independent predictor of a higher risk of PSF in patients hospitalized with CHF. This raises the question of whether AF is the primary cause of CHF in patients with PSF, rather than a secondary problem (23,34).

Diabetes mellitus was also common in both types of CHF. However, apart from the Strong Heart Study (19), this co-morbidity was not more frequent in patients with PSF, despite prior speculation that diabetes may be a risk factor for DD (though Redfield et al. [20] found that diabetes did seem to be associated with an increased prevalence of DD). Moreover, chronic lung disease was more common in patients with PSF, raising the concern of misdiagnosis (42).

There was also no clear difference in the frequency of renal impairment, creatinine concentration, or creatinine clearance between the two patient groups. This may appear odd, given the older average age in the PSF cohort. However, renal blood flow and renal function may be depressed more in patients with reduced systolic function, and use of angiotensin-converting enzyme (ACE) inhibitors is greater in these patients.

MEDICAL TREATMENT

Use of ACE inhibitors and digoxin was employed less frequently in patients with PSF, as might be expected, though the rate of use of both types of medication varied greatly between studies (Table 3). Beta-blocker use was greater in the PSF group, although these studies, generally, predate the recent evidence for this treatment in patients with reduced LV systolic function. The findings of the IMPROVEMENT-HF study (21) and the IN-CHF registry (22) are consistent with the above studies.

Calcium channel blocker use was much greater in patients with PSF, reflecting the view that these agents may be of benefit in this type of CHF (and that they are harmful in reduced systolic function) (43). In the IN-CHF registry, 23% of patients with an LVEF >45% were taking a calcium channel blocker compared to 8% of low-LVEF patients (22).

ECONOMIC CONSIDERATIONS

There are few formal cost studies dealing with the problem of HF-PSF. However, some crude estimate of cost can be inferred from the rate of hospitalization, which accounts for most of the overall cost of CHF to health care systems. This is primarily driven by length of stay. Approximately 40% of patients hospitalized with CHF have PSF, and they have the same length of stay as those with reduced systolic function (see previous text). Consequently, 40% of the overall cost of CHF is probably accounted for by patients with PSF (though some expensive procedures are used less in patients with PSF). Support for this conclusion comes

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Table 3. Co-Morbidity and Medical Therapy in Chronic Heart Failure: Comparison of Patients With Preserved Left Ventricular Systolic Function to Those With Reduced Systolic Function

Co-Morbidity	Thomas P/R (33)	Dauterman P/R (28)	French Hospital P/R (30)	Philbin P/R (26)	Ahmed P/R (29)	Malki P/R (27)	Tsutsui P/R (32)	Varela-Roman P/R (31)	Masoudi P/R (34)	Olmsted Incidence P/R (9)	Framingham‡ P/R (3)	CHS P/R (44)	SHS P/R (19)	Smith P/R (35)	Varadarajan P/R (37)	Gustafsson P/R (36)
Angina	4/11	—	—	—	—	—	—	—	—	—	46/36	—	—	33/43	—	—
Prior MI	—	11/15	—	—	—	26/35	34/36	—	21/38	15/42*	24/69	—	8/39	39/55	—	25/46
Any CHD	22/30	—	31/35	23/35‖	20/24	—	—	53/52	46/65	31/53	57/72	58/78	20/38	24/76	—	25/63
Hypertension	78/74	55/51	54/36	49/43	19/15	88/84	66/44	53/52	69/61	58/50	75/71	59/57	76/8	80/65	27/27	25/23
LVH	22/42*	—	31/31*	—	—	—	51/25	49/36*	—	17/19*	22/14*	—	—	—	—	—
AF	19/10*	—	42/34	29/24	—	—	30/32	45/34*	36/30	29/24*	35/36	15/5*	—	—	20/26	26/23
PAD	—	6/6	—	—	—	7/13	—	—	—	—	—	—	—	—	—	—
Hyperlipidemia	6/6	—	—	—	—	—	—	29/35	—	—	—	—	—	—	—	—
CVD	—	4/6	—	—	—	5/17	—	—	17/18	—	—	—	—	15/15	—	—
Smoking	39/45	—	—	—	—	32/46	28/26	24/34	—	—	14/14	—	18/13	—	—	—
Diabetes mellitus	40/34	23/20	—	33/36	25/26	40/50	30/31	17/24	37/40	—	14/22	27/23	70/6	48/48	4/12	13/19
Obesity	62/48	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Renal disease†	15/9	2/3	—	—	—	26/24	11/14	—	36/47	37/51	—	—	—	50/52	1/1	60/67
COPD	—	33/29	—	—	24/24	—	—	—	34/31	15/14	—	—	—	31/26	4/9	26/19
Alcohol use	20/37	—	—	—	—	—	26/23	—	—	—	—	—	—	—	—	—
Medications									—		—					
Diuretic	93/95	—	86/97	59/64	30/27	—	61/75	76/79	—	78/78	68/67	59/78	—	79/89	—	78/90
ACE-I	62/85	48/72	63/78	29/48	31/39	—	43/68	12/45	—	31/69	19/36	25/42	—	34/70	—	26/70
Beta-blocker	18/10	—	4/10	23/17	—	—	18/26	8/6	—	19/10	32/11	17/7	—	40/34	—	—
Digoxin	27/57	—	33/44	30/44	47/51	30/60	39/52	71/56	—	27/55	42/32§	41/52	—	30/75	—	—
CCB	34/14	—	24/12	39/24	—	39/16	51/30	18/12	—	24/15	14/14	31/30	—	50/17	—	—
Nitrates	—	—	41/50	—	—	—	—	30/31	—	—	46/39	—	—	35/43	—	—

*ECG diagnosis. †Variably defined. ‡Comparison of patients with heart failure and not controls. §Patients without atrial fibrillation. ‖Causes of heart failure.

ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; CCB = calcium channel blocker; CHD = coronary heart disease; CHS = Cardiovascular Health Study; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; MI = myocardial infarction; PAD = peripheral arterial disease; P/R = preserved/reduced left ventricular systolic function; SHS = Strong Heart Study.
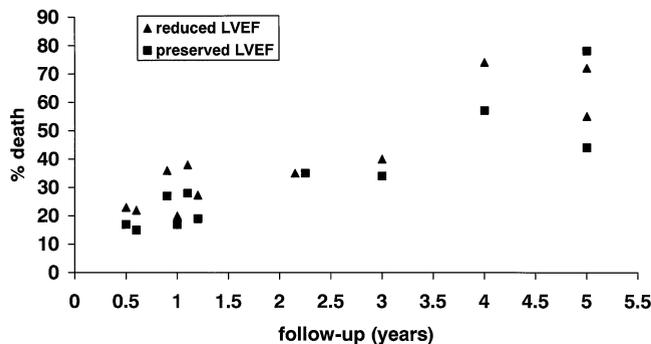
Figure 5. Mortality in recent cohort studies of patients hospitalized with heart failure split according to whether left ventricular ejection fraction (LVEF) is reduced **(black triangles)** or preserved **(black squares)**.

from Philbin et al., where the mean hospital charge for both types of patient was approximately $8,600 (26).

PROGNOSIS: MORTALITY

Population-based epidemiological studies. Two of the population-based *prevalence* studies reported prognosis (the Framingham case-control study also reports outcomes) (3). In the Helsinki Ageing Study, four-year mortality in individuals free of CHF was 30% (16). Of those with CHF, the mortality rate was 43% among subjects with PSF and 54% in those with reduced systolic function (46% in patients with any CHF). In the Cardiovascular Health Study (CHS), the 6.4-year mortality rate in subjects without CHF was 16% compared to 45% in those with CHF (44). The mortality rate in subjects without CHF and with PSF was 25 deaths per 1,000 patient-years. This rate rose to 87 in subjects with CHF and PSF, 115 in those with CHF and borderline systolic function, and 154 per 1,000 patient-years in subjects with CHF and reduced systolic function. These figures compare to an overall five-year mortality rate of 65% in the Olmsted County *incidence* study (9). In that investigation, age- and gender-adjusted mortality rates were higher than in individuals free of CHF, though survival was not significantly different between patients with and without reduced systolic function. Patients with CHF in the Framingham Heart Study with reduced LV systolic function had an annual mortality rate of 18.9% compared to 4.1% in age- and gender-matched controls (over 6.2 years) (3). In patients with PSF, the annual mortality rate was 8.7% compared to 3% in their matched controls. In an adjusted analysis, patients with both types of CHF had four times the risk of death of their age- and gender-matched controls (3). The median survival in patients with reduced systolic function was 4.3 years, and it was 7.1 years in those with HF-PSF.

Notably in the CHS, the population-attributable mortality risk was greater for those with HF-PSF (7.5%) than for CHF with reduced systolic function (5.9%). This is explained by the higher prevalence (combined with moderate risk) of HF-PSF, compared to the lower prevalence of CHF

with reduced systolic function (but at higher risk), in the elderly population studied (44).

Redfield et al. (20) recently described the prognostic importance of DD in the population. Mortality increased as the degree of DD increased, an effect independent of age, gender, and LVEF. In a multivariate analysis, compared to normal diastolic function, mild DD increased the risk of death 8.3-fold ($p < 0.001$) and moderate to severe DD increased this risk 10.2-fold ($p < 0.001$).

Hospital cohort studies. Nine of the 12 hospital cohort studies identified report mortality, with follow-up periods ranging from six months to eight years (the French hospital survey also describes in-patient mortality rates) (26–37). It is not clear whether all these studies calculated mortality in the same way, that is, whether these include only postdischarge deaths or both in-patient (postadmission) and postdischarge deaths. Figure 5 shows the mortality rates from these studies (and two earlier ones), assuming these were calculated from admission. Patients with PSF have a better survival at all time points from admission. Nevertheless, patients with PSF still have a high mortality following admission to hospital, with rates of 40% to 50% after four to five years. The annual death rate in these studies agrees closely with that in the Framingham Heart Study (3). Gustafsson et al. (36) also showed that survival decreases as LV systolic function decreases in a graded way.

The IN-CHF registry has also reported one-year outcome data for *out-patients* with CHF (22). One-year mortality was 18.8% in patients with an LVEF <35% (Group 1), 8.9% in patients with an LVEF >45% (Group 2), and 11.5% in patients with an LVEF between 35% and 45% (Group 3). Though survival was better in these ambulatory patients compared to hospitalized ones, the differential mortality effect was still apparent. Notably, an LVEF <35% (compared to an LVEF >45%) was an *independent* predictor of survival at one year.

PROGNOSIS: HOSPITAL ADMISSSIONS

Population-based studies. The risk of hospitalization was quantified in the Olmsted County incident case study (9). Of patients with reduced LV systolic function, 10% were never hospitalized, 41% were hospitalized once, and 49% were hospitalized >2 times, *for CHF*, over five years. These proportions in patients with PSF were 24%, 51%, and 25%, respectively. Patients with reduced systolic function had significantly more hospitalizations.

The CHS also reported the risk of nonfatal MI and stroke (44). In subjects with no CHF and PSF these rates were 10.9 and 12.5, respectively, per 1,000 patient-years at risk. The rates increased to 23.3 and 27.5 in patients with CHF and PSF, 37.7 and 50.7 in those with CHF and borderline systolic function, but fell again to 19.4 and 45.2, respectively, per 1,000 patient-years, in subjects with CHF and reduced systolic function. Even after adjustment in the Cox proportional hazards survival model, the risk of MI and

Table 4. Hospital Re-Admission Rates in Patients With CHF

Study (Ref. No.)	Follow-Up	CHF Re-Admission (%) P/R	Any Re-Admission (%) P/R
Philbin et al. (26)	6 months	23/23	44/42
Malki et al. (27)	6 months	—	26/33*
Ahmed et al. (29)	6 months	14/23	—
Smith et al. (35)	6 months	16/22	46/46
Dauterman et al. (28)	12 months	33/31	58/58
Tsutsui et al. (32)	2.4 years (mean)	36/48	—

*It is not entirely clear from the original study whether these are readmissions for any reason or just for worsening CHF.
CHF = chronic heart failure; P/R = preserved/reduced left ventricular systolic function.

stroke was less in subjects with CHF and reduced systolic function than in the remainder of individuals with CHF. This finding is unexplained.

Hospital cohort studies. Six of these studies report the risk of hospital readmission six months to 2.4 years following discharge (Table 4) (26,37). Three studies show lower readmission rates for CHF in patients with PSF, whereas two do not (data not reported in one). In the IN-CHF registry, one-year rates of hospitalization for any cause, for a cardiovascular reason, or for worsening CHF were, respectively, 27.1%, 22.6%, and 16.5% in Group 1, 18.4%, 13.2%, and 8.3% in Group 2, and 19.5%, 14.9%, and 9.7% in Group 3 (22). In a multivariate analysis, however, reduced systolic function (compared to PSF) was not an *independent* predictor of hospitalization (whereas it was for death).

It is important to note that readmission rates in patients with PSF are very high—15% to 25% of patients are readmitted within six months and a third within a year with an exacerbation of CHF (and about 45% to 60% at one year for any reason).

It is clear that both types of CHF have a grim prognosis. Philbin et al. (26) showed that the six-month rate of death or readmission was 50% in patients with PSF and 52% in those with reduced systolic function.

REMAINING QUESTIONS

Many questions remain about the syndrome of HF-PSF. The proportion of such patients with valve disease has not been clearly defined in most studies. The higher prevalence of lung disease seen in patients with reduced systolic function raises the possibility of misdiagnosis, especially as HF-PSF is essentially a diagnosis of exclusion (4,42). Reliable non-invasive measures or markers of ventricular dysfunction are badly needed, but it is not clear whether natriuretic peptides will fulfill this need (45). Similarly, the role of AF requires clarification. Is it AF that is the cause of CHF in many of these patients? Or does AF only precipitate CHF because of underlying DD?

The interaction between this type of CHF and AF is further confounded by evidence that DD is itself a predictor of future AF (23). Also, why is HF-PSF more a problem for women than for men? As DD appears to be more common in men it would seem that the female left ventricle is less able to cope with DD. This is surprising given the more favorable remodeling changes seen in the overloaded female LV (46). Indeed, the pathophysiology of this type of CHF remains poorly explained, and it may have as much to do with peripheral mechanisms as with cardiac dysfunction (47). The greatest question of all, of course, is how to treat these patients. Symptom control is important. However, the finding from the CHS that the population-attributable risk for deaths from CHF is greater for PSF than for reduced systolic function emphasizes the public health imperative of developing treatments to reduce mortality (and morbidity) in these patients (48–50).

The CHARM-Preserved trial (using the ARB candesartan) showed that candesartan reduced the risk of hospital admission for worsening heart failure but did not affect mortality. Other outcome studies with an ARB, ACE inhibitor, and beta-blocker are ongoing (48–50). From a pathophysiological basis, it would also be of interest to study an aldosterone antagonist in this syndrome (6–8). Unfortunately, no study to date has provided detailed data on the *causes* of death in patients with HF-PSF, information that should be of value in the development and testing of treatments for this type of CHF.

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