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Diastolic Dysfunction in Heart Failure With Preserved Systolic Function: Need for Objective Evidence

Results From the CHARM Echocardiographic Substudy–CHARMES

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Objectives We tested the hypothesis that diastolic dysfunction (DD) was an important predictor of cardiovascular (CV) death or heart failure (HF) hospitalization in a subset of patients (ejection fraction [EF] >40%) in the CHARM-Preserved study.

Background More than 40% of hospitalized patients with HF have preserved systolic function (HF-PSF), suggesting that DD may be responsible for the clinical manifestations of HF.

Methods Patients underwent Doppler echocardiographic examination that included assessment of pulmonary venous flow or determination of plasma NT-pro-brain natriuretic peptide ≥14 months after randomization to candesartan or placebo. The patients were classified into 1 of 4 diastolic function groups: normal, relaxation abnormality (mild dysfunction), pseudonormal (moderate dysfunction), and restrictive (severe dysfunction).

Results There were 312 patients in the study, mean age was 66 ± 11 years, EF was 50 ± 10%, and 34% were women. The median follow-up was 18.7 months. Diastolic dysfunction was found in 67% of classified patients (n = 293), and moderate and severe DD were identified in 44%. Moderate and severe DD had a poor outcome compared with normal and mild DD (18% vs. 5%, $p < 0.01$). Diastolic dysfunction, age, diabetes, previous HF, and atrial fibrillation were univariate predictors of outcome. In multivariate analysis, moderate (hazard ratio [HR] 3.7, 95% confidence interval [CI] 1.2 to 11.1) and severe DD (HR 5.7, 95% CI 1.4 to 24.0) remained the only independent predictors ($p = 0.003$).

Conclusions Objective evidence of DD was found in two-thirds of HF-PSF patients. Moderate and severe DD, which were found in less than one-half of the patients, were important predictors of adverse outcome. The results demonstrate the prognostic significance and need for objective evidence of DD in HF-PSF patients. (J Am Coll Cardiol 2007;49:687–94) © 2007 by the American College of Cardiology Foundation

Approximately one-half of the patients with clinical heart failure (HF) have preserved left ventricular (LV) systolic function (HF-PSF), suggesting that diastolic dysfunction (DD) may be responsible for their clinical manifestations (1). Recent studies have indicated that patients with HF and ejection fraction (EF) >40% have relatively high mortality and hospitalization rates (2). Prospective data in HF-PSF are limited with respect to the relationship among objective measures of DD, symptoms and signs of HF, outcome, and therapy. A major reason for the paucity of randomized controlled trials in HF-PSF patients is the difficulty in defining and measuring diastolic function. Although hemodynamic data obtained by heart catheterization can be used to measure diastolic function, the invasive nature of this assessment limits its applicability to most patients (3). Therefore, Doppler echocardiography is the method of choice in routine clinical practice to assess for DD (4). However, Doppler assessment of DD is complex and requires expert interpretation. Furthermore, loading conditions affect mitral inflow pulsed-wave Doppler parameters,

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Abbreviations and Acronyms

CI = confidence interval
CV = cardiovascular
DD = diastolic dysfunction
EF = ejection fraction
HF = heart failure
HF-PSF = heart failure and preserved systolic function
HR = hazard ratio
LAVI = left atrial volume index
LV = left ventricular
NT-proBNP = N-terminal pro-brain natriuretic peptide

making the differentiation between normal and pseudonormal diastolic function particularly difficult. Therefore, in addition to mitral inflow parameters, pulmonary venous (PV) flow Doppler and changes in mitral inflow parameters during Valsalva maneuver are commonly used to distinguish pseudonormal from normal diastolic function.

An alternative approach to assess the presence of abnormal hemodynamics and DD is assessment of plasma natriuretic peptides (5–8). This approach may be of greatest benefit in distinguishing normal from pseudonormal diastolic function in HF-PSF patients but may be of limited value in detecting patients with relaxation abnormalities (5).

The CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity)-Preserved study (9) examined the effect of adding candesartan cilexetil or placebo to usual therapy in symptomatic HF-PSF patients (LVEF >40%). Candesartan led to a nonsignificant 11% reduction in the primary composite outcome, but there was a nominally significant 29% reduction in the number of admissions for HF. The trial offered a unique opportunity to describe diastolic function and its impact on prognosis in HF-PSF patients. We conducted a multicenter international echocardiographic substudy evaluating LV diastolic function in a subset of HF-PSF patients participating in the CHARM-Preserved study.

Aim. The primary objective of the CHARM echocardiographic substudy (CHARMES) was to assess whether LV diastolic function was an important predictor of the combined outcome of cardiovascular (CV) mortality or hospitalization for HF, the primary end point in the CHARM-Preserved trial. The secondary objectives were 1) to evaluate the effects of candesartan compared to placebo on LV diastolic function measured at least 14 months after enrollment and 2) to evaluate the effects of candesartan compared to placebo on LV mass and LV systolic function.

Study design. CHARMES was a prospective, randomized, controlled, double-blind cross-sectional study evaluating LV diastolic function using Doppler echocardiography and N-terminal pro-brain natriuretic peptide (NT-proBNP). The study was originally planned to be a serial echocardiographic study with an extensive Doppler echocardiographic protocol and assessments at baseline, after 14 months, and at study end. Because of difficulties recruiting into this complex study, the protocol was changed to perform a simplified classification of diastolic function.

Methods

Patients. Patients participating in the CHARM-Preserved study were asked to participate in CHARMES. The inclusion and exclusion criteria for CHARMES were the same as for the main study (9) and aimed at selecting patients with symptoms of HF and LVEF >40%. We excluded patients with poor-quality echocardiograms, prosthetic mitral valves, or greater than moderate mitral or aortic regurgitation.

Measurement of diastolic function. DOPPLER ECHOCARDIOGRAPHY. The examination was performed while the patient was in a period of quiet respiration. All recordings were performed at a high sweep speed (100 mm/s) and with simultaneous electrocardiographic (ECG) recording and included complete M-mode, 2-dimensional, and Doppler echocardiographic examinations, with emphasis on evaluation of LV diastolic (10–12) and systolic function (13), LV size, and mass (13). Assessment of PV flow and E/A during a Valsalva maneuver were optional, performed only in centers experienced in completing those assessments. A minimum of 10 to 15 beats was recorded for all 2-dimensional, M-mode, and Doppler parameters. Apical 2-, 3-, and 4-chamber views were obtained in all echocardiographic studies. The following measurements were used for the assessment of LV diastolic function: 1) early filling peak velocity (E), 2) atrial filling peak velocity (A), 3) E/A ratio, 4) deceleration time (DT), 5) isovolumic relaxation time (IVRT), 6) a wave duration (MVa) at the AV plane, and 7) E/A ratio during Valsalva manuever. The following measurements were used for the assessment of PV flow: 1) systolic peak velocity (S), 2) diastolic peak velocity (D), 3) S/D ratio, 4) atrial systolic reversal wave velocity (PVa), 5) a wave duration (PVa dur), and 6) difference between PVa and MVa duration. Left atrial volume index (LAVI) was calculated by the biplane area-length method from apical 2- and 4-chamber views indexed to body surface area (13).

NT-proBNP. Blood for NT-proBNP measurement was sampled through a venflon or butterfly needle inserted into an antecubital arm vein. The patients rested for 15 min (seated or lying) before 10 ml of blood being drawn and placed in a standard EDTA tube. The blood was centrifuged within 30 min of sampling at 5°C and 2,000 rpm for 15 min. The plasma (3 to 4 ml) was removed and frozen at −20°C in a plastic tube labeled with the date, patient number, and site numbers. Plasma NT-proBNP was determined using Elecsys proBNP sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). The normal NT-proBNP cutoff values were prospectively chosen according to age and gender (14): for men ≤65 years ≤184 ng/l and >65 years old ≤268 ng/l and for women age ≤65 years ≤269 ng/l and >65 years ≤391 ng/l.

CLASSIFICATION OF DIASTOLIC FUNCTION. The classification of diastolic function was defined prospectively based on age-adjusted values for all echo-Doppler parameters (Table 1) and NT-proBNP measurements using the algorithm out-

Table 1 Normal Values for Mitral and Pulmonary Vein Doppler Flows by Age

	Age (yrs)					
	20–29	30–39	40–49	50–59	60–69	70–85
E/A	1.1–3.0	1.1–2.7	0.9–2.5	0.8–1.9	0.7–1.5	0.6–1.3
IVRT (ms)	50–90	50–90	50–90	55–100	60–110	60–110
DT (ms)	140–200	140–200	140–200	140–220	140–220	140–260
S/D	0.6–1.1	0.7–1.4	0.8–1.8	0.9–2.2	1.0–2.5	1.0–2.5
PVa (cm/s)	12–28	12–28	12–28	15–30	15–30	15–30
PVa − MVa (ms)	<20	<20	<20	<20	<20	<20
E/A − E/A Valsalva	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5

The given ranges for variables are meant to approximate the 95% confidence limits for normal patients (10–12). Mitral values are for sampling at leaflet tips.

DT = deceleration time; E/A = early (E) mitral inflow peak/atrial (A) filling peak ratio; IVRT = isovolumic relaxation time; PVa = pulmonary vein atrial reversal peak flow velocity; PVa − MVa = pulmonary vein atrial duration − mitral inflow atrial duration; S/D = pulmonary vein peak systolic/diastolic ratio.

lined in Figure 1. Classification was as follows: 1) normal, 2) relaxation abnormality (mild dysfunction), 3) pseudonormal (moderate dysfunction), and 4) restrictive abnormality (severe dysfunction). Two investigators (H.P. and E.L.) blinded to the patients' clinical characteristics performed this assessment. Relaxation and restrictive abnormalities were assessed by mitral inflow parameters, and the classification was based on a minimum of 2 abnormal mitral inflow parameters pointing to the same category. To distinguish pseudonormal from normal diastolic function, one of the following measures had to be abnormal: 1) PV flow parameters, 2) E/A during Valsalva maneuver, or 3) plasma NT-proBNP concentration measured at the time of echocardiography. In patients with atrial fibrillation, DT was used to classify patients as abnormal relaxation or restrictive diastolic dysfunction, whereas S/D (15–17) or NT-proBNP (6–7) was used to classify patients as pseudonormal diastolic dysfunction. Left atrial volume index was analyzed as an independent measure and not included in the classification of DD.

Statistical analysis. The baseline characteristics at the time of randomization into the CHARM-Preserved study are presented as standard summary statistics. The prognostic power of the presence of DD to predict the combined end point of cardiovascular mortality or rehospitalization for HF was tested by Cox regression analysis from the date of the echocardiogram to end of follow-up. The univariate analysis included the 11 prospectively chosen variables: age, gender, New York Heart Association functional classification, EF (by study echocardiogram), hypertension, diabetes mellitus, previous admission for HF (before date of echo), previous myocardial infarction (before date of echo), atrial fibrillation (at time of echo), LAVI, and treatment allocation. Any term that was significant at ≤0.1 in the univariate analysis was included as a potential predictor in the first multivariate model. In a second step, the best prognostic model was constructed by testing the remaining significant variable(s) with forced adjustment for age, gender, EF, and treatment allocation. Chi-square tests were used to relate DD to background variables. Analysis of variance was used to assess

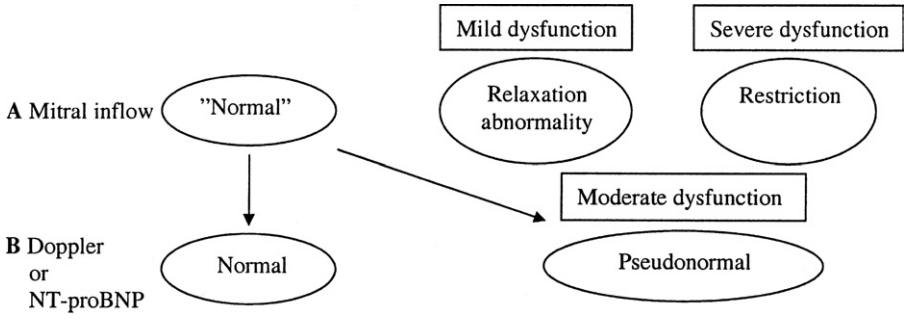

Figure 1 Classification of LV Diastolic Function

Left ventricular (LV) diastolic function categorized into 4 groups. 1) Normal: mitral inflow parameters within normal range and normal pulmonary vein flow or normal N-terminal pro-brain natriuretic peptide (NT-proBNP). 2) Abnormal relaxation: a) early filling peak velocity/atrial filling peak velocity (E/A) ratio lower than age-related value and/or b) isovolumic relaxation time/deceleration time (IVRT/DT) longer than age-related value. 3) Pseudonormal: normal mitral inflow parameters and a) elevated NT-proBNP, b) abnormal pulmonary venous flow, or c) abnormal E/A–E/A during Valsalva. 4) Restrictive: a) E/A ratio higher than age-related value and/or b) IVRT/DT shorter than age-related value. Pulmonary venous flow was considered abnormal if any one of the following criteria were present: 1) pulmonary vein systolic/diastolic velocity less than age-related value, 2) pulmonary vein a-duration longer than mitral a-duration, or 3) pulmonary vein peak a-velocity greater than age-related value. Normal values are in Table 1.

a trend for difference in LAVI within the groups of DD. The study sample size was calculated to allow the detection of a 12% difference in DD, categorized as normal + abnormal relaxation versus pseudonormal + restrictive pattern between the 2 treatment groups (for alpha = 0.05 and 80% power and using the chi-square test). Mitral inflow data, LV mass, EF, and LV end-systolic and -diastolic diameters were compared between treatment groups. For continuous variables, the difference in means, 95% confidence intervals, and the *t* test p value are reported. Survival curves were estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. Statistical Analysis System (SAS), proprietary software release 8.2 (SAS Institute Inc., Cary, North Carolina), was used for the analysis.

Study organization. All investigators participating in the CHARM-Preserved study were invited to participate in the CHARMES substudy. Danderyd University Hospital and Hamilton Health Sciences were the core laboratories, responsible for the protocol, training of sites, and reading study echocardiograms. A training tape and an echocardiographic study manual were sent to the respective sites, and a recorded test echocardiogram was reviewed at one of the core laboratories. Sites were approved if the quality of the test echocardiogram was good. Forty-eight sites participated in the study. Echocardiograms were recorded at the investigator's site and shipped to one of the core laboratories, with a single reader at each site. Inter-reader variability for 10 diastolic function measurements was assessed in 25 patients between the 2 laboratories using intra-class correlation coefficients (median intra-class correlation coefficients 0.784, range 0.667 to 0.954). All NT-proBNP measurements were performed at the Western Infirmary, Glasgow, Scotland.

Ethical considerations. The echocardiographic substudy was approved by the ethical review boards of Karolinska Institutet, Stockholm, Sweden; the Hamilton Health Sciences, Hamilton, Canada; and the ethical committees in the respective centers participating in the substudy. The study was conducted according to the rules outlined in the Helsinki declaration.

Results

Study sample. A total of 312 patients, representing 10% of the patients in the CHARM-Preserved study (9), were included in the CHARMES substudy. The baseline characteristics of the patients in the substudy are shown (Table 2). Compared with the main trial, CHARMES patients were

Table 2 Baseline Characteristics

Variable	Group	Candesartan (n = 166)	Placebo (n = 146)	Total (n = 312)
Age (yrs)	Mean ± SD	66 ± 11	66 ± 11	66 ± 11
Gender	Female	57 (34%)	49 (34%)	106 (34%)
Ethnicity	European	141 (85%)	131 (90%)	272 (87%)
Smoking	Non-smoker	50 (30%)	41 (28%)	91 (29%)
Heart rate (beats/min)	Mean ± SD	68.9 ± 10.9	67.0 ± 12.0	68.0 ± 11.5
Systolic BP (mm Hg)	Mean ± SD	133.7 ± 19.4	135.7 ± 18.7	134.7 ± 19.1
Diastolic BP (mm Hg)	Mean ± SD	76.8 ± 11.4	76.2 ± 10.5	76.5 ± 11.0
BMI (kg/m^2)	Mean ± SD	30.1 ± 6.7	29.0 ± 5.3	29.6 ± 6.1
Ejection fraction (%)	Mean ± SD	50 ± 10	50 ± 10	50 ± 10
New York Heart Association functional class				
II		87 (52%)	89 (61%)	176 (56%)
III		75 (45%)	54 (37%)	129 (41%)
IV		4 (2.4%)	3 (2.1%)	7 (2.2%)
Previous hospitalization for heart failure		103 (62%)	75 (51%)	178 (57%)
Previous myocardial infarction		83 (50%)	72 (49%)	155 (50%)
Angina pectoris		103 (62%)	93 (64%)	196 (63%)
Hypertension		109 (66%)	102 (70%)	211 (68%)
Diabetes mellitus		56 (34%)	45 (31%)	101 (32%)
Atrial fibrillation		53 (32%)	40 (27%)	93 (30%)
ECG: atrial fibrillation/flutter		20 (12%)	15 (10%)	35 (11%)
Digitalis glycoside		51 (31%)	30 (21%)	81 (26%)
Diuretics		123 (74%)	108 (74%)	231 (74%)
Spironolactone		19 (11%)	7 (5%)	26 (8%)
Beta-blocker		99 (60%)	86 (59%)	185 (59%)
Calcium-channel blocker		50 (30%)	53 (33%)	103 (33%)
Oral anticoagulant		37 (22%)	37 (25%)	74 (24%)
Acetylsalicylic acid		106 (64%)	93 (64%)	199 (64%)
ACE inhibitor		38 (23%)	31 (21%)	69 (22%)

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram.

Table 3 Diastolic Function in All Patients and Left Atrial Volume Index by Diastolic Function Class

	Normal	Mild	Moderate	Severe	p Value
n (%)	98 (33)	65 (22)	109 (37)	21 (7)	
LAVI (ml/m^2)	36 ± 11	39 ± 16	46 ± 16	55 ± 23	<0.00001

LAVI = left atrial volume index.

less often women (34% vs. 40%) and had a less frequent (57% vs. 69%) history of admission for HF. The 2 treatment groups in the CHARMES substudy were well balanced regarding age, gender, EF, and other variables.

Systolic function. Echocardiograms were performed 17.7 months (median) after randomization. The LVEF measured at ≥14 months into the study was <35% in 12% (n = 39) of patients, in contrast to the baseline LVEF that was >40% in all patients as defined by CHARM-Preserved study criteria.

Diastolic function. A total of 293 patients (94%) could be classified according to the protocol. In the patients with normal mitral inflow, NT-proBNP was used in 86% of patients (n = 178) to distinguish pseudonormal patients from normal patients, whereas Doppler measurements were used in the remaining 14% (n = 29). Diastolic dysfunction was found in 67% (n = 197) of all patients, similar to the 64% (n = 27) of the 42 patients who were assessed at baseline. Moderate dysfunction was the most common abnormality, whereas severe DD was relatively rare (Table 3). Diastolic dysfunction was related to a number of baseline characteristics, including higher age ($p < 0.01$), worse New York Heart Association functional class ($p < 0.05$), previous admission for HF ($p < 0.01$), and atrial fibrillation by history or ECG ($p < 0.001$); hypertension, EF, and diabetes mellitus were not associated with DD. Left atrial volume index was abnormal (>32 ml/m^2) in 71% of the patients and showed a powerful relation to severity of DD (Table 3).

Prognosis. The median follow-up time was 18.7 months after the echocardiogram. Cardiovascular mortality or rehospitalization for HF during follow-up was 10.3% (n = 32), with a CV mortality of 4.5% (n = 14). The combined end point of CV death or hospitalization for HF was related to the severity of DD ($p = 0.0015$) (Fig. 2), but not to LAVI ($p = 0.13$). Similar hazard ratios as those reported in Figure 2 for the 3 groups of DD versus normal were found in patients without atrial fibrillation (1.6, $p = 0.48$; 3.6, $p = 0.03$; and 8.4, $p = 0.01$) and excluding patients with EF <35% (1.1, $p = 0.94$; 3.2, $p = 0.04$; and 6.5, $p < 0.01$). Patients with normal diastolic function had a low event rate (5%). Patients with a relaxation abnormality had a nonsignificantly higher event rate than normal patients (6%), whereas patients with moderate and severe DD had significantly higher event rates (16% and 29%, respectively). Patients with pseudonormal DD diagnosed by abnormal NT-proBNP or Doppler criteria had similar outcomes (Fig. 3). Higher age, diabetes mellitus, previous HF admission, and atrial fibrillation were all significantly related to worse outcome ($p < 0.05$) (Table 4). In the multivariate analysis,

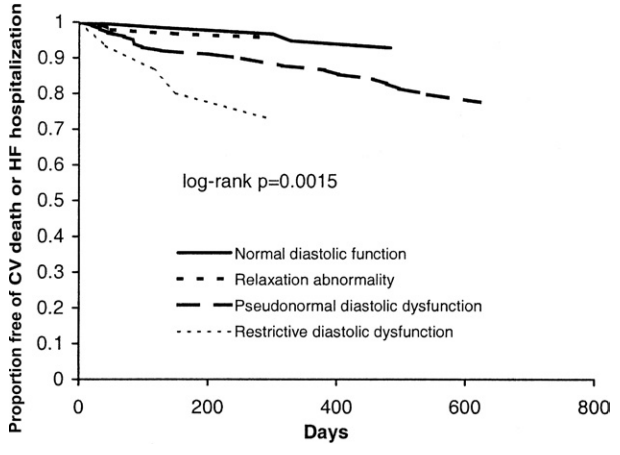

Figure 2 CV Death or HF Hospitalization According to Diastolic Function Class

Univariate hazard ratios (95% confidence intervals) for relaxation abnormality versus normal = 1.4 (0.4 to 5.7); pseudonormal versus normal = 4.5 (1.5 to 13.2); and restrictive versus normal = 7.2 (1.8 to 29.0). CV = cardiovascular; HF = heart failure.

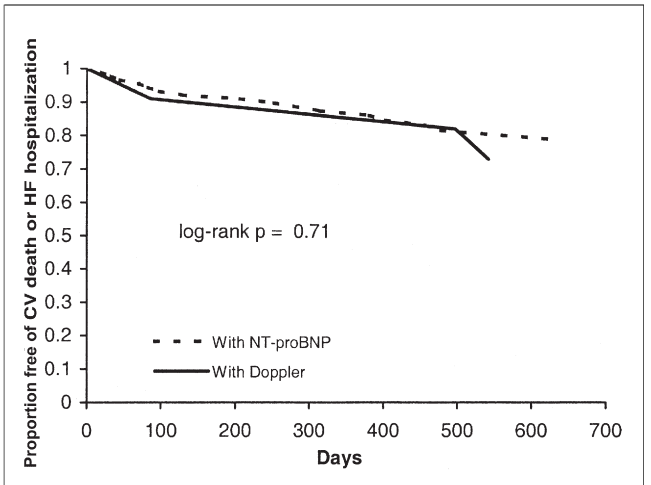

Figure 3 CV Death or HF Hospitalization in Group With Pseudonormal Diastolic Function

Univariate hazard ratio (95% confidence intervals) for outcome in patients with pseudonormal diastolic dysfunction characterized by N-terminal pro-brain natriuretic peptide (NT-proBNP) versus Doppler = 0.8 (0.2 to 2.7). Abbreviations as in Figure 2.

Table 4 Univariate and Multivariate Analyses of Factors Related to CV Death or HF Hospitalization

	Univariate HR (95% CI)	p Value		Multivariate HR (95% CI)	p Value
Diastolic dysfunction (moderate/severe vs. normal/mild)	4.13 (1.85–9.24)	<0.001	Diastolic dysfunction (moderate/severe vs. normal/mild)	3.27 (1.41–7.56)	0.003
Age	1.04 (1.01–1.08)	0.023	Age	1.03 (0.99–1.07)	0.205
Diabetes	2.13 (1.06–4.26)	0.033	Male gender	1.58 (0.69–3.66)	0.261
Previous HF admission	2.24 (1.04–4.90)	0.040	EF	1.02 (0.98–1.06)	0.331
Atrial fibrillation	2.17 (1.03–4.59)	0.042	Treatment allocation	1.40 (0.67–2.92)	0.372
LA volume index	1.02 (0.99–1.04)	0.127			
NYHA III vs. II	1.70 (0.84–3.44)	0.139	Diastolic dysfunction (mild vs. normal)	1.49 (0.37–6.00)	*
EF	1.02 (0.98–1.07)	0.200	Diastolic dysfunction (moderate vs. normal)	3.69 (1.23–11.11)	0.023*
Male gender	1.65 (0.74–3.68)	0.218	Diastolic dysfunction (severe vs. normal)	5.72 (1.36–23.99)	*
Previous MI	1.36 (0.67–2.45)	0.398	Age	1.02 (0.98–1.06)	0.238
NYHA IV vs. II	1.90 (0.25–14.37)	0.535	Male gender	1.62 (0.71–3.71)	0.248
Treatment allocation C vs. placebo	1.19 (0.59–2.39)	0.627	EF	1.02 (0.98–1.06)	0.288
Hypertension	1.05 (0.51–2.18)	0.894	Treatment allocation	1.39 (0.67–2.90)	0.390

*One p value for mild-severe diastolic dysfunction versus normal diastolic function.
C = candesartan; CI = confidence interval; ECG = electrocardiography; EF = ejection fraction; HF = heart failure; HR = hazard ratio; LA = left atrial; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association.

only moderate and severe DD remained significantly related to outcome. This relationship persisted after adjusting for age, gender, EF at time of echo, and treatment allocation.

Differences by treatment group. There were no significant differences in LV diastolic and systolic function or size between the placebo and candesartan groups (Table 5); there was a similar distribution of DD class in both treatment groups ($p = 0.85$). Of note, candesartan treated patients had lower LV mass and LV mass index ($p < 0.05$). Fewer patients on candesartan had LV hypertrophy (45% vs. 59%, $p = 0.04$), defined as 116 g/m^2 for men and 104 g/m^2 for women (18).

Discussion

We have identified DD in 67% of the patients with HF-PSF. Significant DD, classified as moderate to severe, which was found in fewer than one-half of the patients, was an important independent predictor of adverse outcome. This was in contrast to lower EF, which was not related to outcome in patients with HF-PSF. Furthermore, we have found that DD was related to measures of disease severity, atrial fibrillation, LAVI, and higher age. The lower LV mass in candesartan-treated patients suggests a treatment effect by candesartan compared to placebo.

Diastolic dysfunction and prognosis. In population studies, mild, moderate, or severe DD is related to long-term mortality compared with normal patients (4). Our findings of a favorable intermediate-term prognosis in patients with mild DD might seem in conflict with previous studies. Most likely, this discrepancy results from the longer duration of follow-up in the population studies. Our findings support only a weak link between echocardiographically determined relaxation abnormality and HF; however, this does not exclude its role as a predictor of long-term mortality. Moderate and severe DD were the strongest predictors of adverse outcomes in our study, confirming previous population-based studies, which

Table 5 LV Size, Mass, Systolic, and Diastolic Function by Treatment Allocation

	Candesartan	Placebo	Difference of Means	95% Confidence Interval	p Value
E/A	1.15 ± 0.84	1.10 ± 0.60	0.05	−0.13–0.24	0.56
IVRT (ms)	99 ± 23	98 ± 22	0.50	−4.87–5.87	0.85
DT (ms)	215 ± 57	213 ± 63	1.51	−11.9–14.9	0.83
LV mass (g)	225 ± 75	250 ± 109	−25	−49–−1.8	0.04
LVMI (g/m^2)	111 ± 35	124 ± 49	−13	−24–−1.5	0.02
LVEDD (mm)	54 ± 7	55 ± 9	−1.1	−3.1–0.8	0.26
LVESD (mm)	36 ± 7	37 ± 10	−0.8	−3.0–1.4	0.49
EF (%)	48 ± 11	49 ± 10	−1.50	−3.95–0.94	0.23
	50 (20–65)	50 (15–65)			

Mean ± SD are presented for all variables. Mean ± SD and median (range) are presented for ejection fraction (EF).
LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVMI = left ventricular mass index; other abbreviations as in Table 1.

suggest a graded relationship between severity of DD and outcomes, especially HF.

The absence of objective criteria of DD in 33% of study patients at 14 months after randomization may reflect an improvement in diastolic function over the course of the trial. However, given that we found normal diastolic function in a similar proportion (36%) of patients who underwent assessment of DD at baseline, it appears likely that about one-third of patients randomized in the study did not have objective evidence for DD at study entry. These findings highlight the difficulty associated with establishing a diagnosis of DD on the basis of clinical criteria alone and may explain the better than expected prognosis in the CHARM-Preserved study.

Prevalence of diastolic dysfunction. The prevalence and role of DD in patients with HF-PSF is unclear. We report a 6-fold higher prevalence of moderate-to-severe DD (44%) in HF-PSF compared with the 7% prevalence of moderate-to-severe isolated DD in the community-based study of Redfield et al. (4). The event rate was high in these patients. Thus, our prognostic results suggest that moderate and severe DD is an important pathophysiologic mechanism in HF-PSF (3), more important than atrial fibrillation, LVEF, or LAVI. Transient or mild systolic dysfunction has been suggested to be the mechanism for HF in HF-PSF (19), although this has been disputed (3,20). Misdiagnosis of presumed HF is a common explanation for symptoms due to noncardiac disease or ischemia, especially if objective criteria of LV systolic and diastolic dysfunction are not included for diagnosis (21). The CHARM-Preserved study may thus be biased by inclusion of misdiagnosed patients without HF, so careful objective entry criteria need to be sought in future trials of HF-PSF.

Diastolic dysfunction and relation to background factors. Atrial fibrillation and LAVI were the strongest background factors related to DD (4,22). The relationship between atrial fibrillation and more severe DD was strong whether atrial fibrillation was defined by ECG (low prevalence) or by history (high prevalence), suggesting that it is not simply because of the difficulties in measuring DD in patients in atrial fibrillation. In our study, age was an important factor even after using age-adjusted normal values, pointing to a strong link between DD and age. Systolic dysfunction by EF was not related to the degree of DD. Others (4,23) have found a relation between severe DD and severe systolic dysfunction. Our patients were defined by showing no or borderline systolic dysfunction at study entry, thus reducing the chance to confirm this relation. We found no relationship between DD and diabetes mellitus, hypertension, or LV hypertrophy by ECG, which is surprising and contrasts with other reports (24,25).

Methodology for diagnosis of diastolic dysfunction. Our definition of diastolic function reflects diastolic filling rather than intrinsic parameters of diastolic function. Although Doppler echocardiography plays a pivotal role in assessing the diastolic filling dynamics of the LV, this technique is limited by the confounding influences of changes in heart rate and loading conditions. These limitations suggest the need for other objective measures of DD. In this regard, recent studies support the value of BNP determination in the evaluation of LV diastolic function. The release of BNP has been shown to be directly proportional to pressure overload (6,7), and several studies have shown that elevated BNP levels accurately predict the presence of DD seen with both Doppler velocity recordings (8,23,26–28) as well as with tissue Doppler imaging (29). Indeed, these findings suggest that in patients with normal systolic function, either elevated BNP or echocardiographic diastolic filling abnormalities might help to reinforce the diagnosis of DD (8,28,29). The increase of LAVI by severity of DD supports the diagnostic model we have used. Left atrial volume index did not predict outcome, which may be related to low power. However, DD may be the underlying mechanism, and increase of LAVI the consequence. This interpretation is supported by others (22), who found that DD, but not LAVI, was of prognostic importance in multivariate analysis. More novel echo-Doppler approaches, including tissue Doppler and color M-mode, may be more accurate in identifying and classifying DD; however, these techniques were not widely available and standardized at the time the study was done.

Treatment effects of angiotensin-receptor blockers in HF-PSF. We found no difference in LV size or systolic or diastolic function for candesartan compared to placebo. The observed differences in LV mass are interesting and suggest a treatment effect by candesartan, but are of low evidence grade owing to the lack of baseline data. The findings are consistent with other studies using angiotensin-receptor blockers in general and candesartan specifically (18,30).

Study limitations. There are several limitations to our study. The most important ones are 1) the difficulties in measuring diastolic function in an international multicenter setting, 2) the difficulties measuring diastolic and systolic function in atrial fibrillation, 3) the absence of tissue Doppler imaging, 4) the use of NT-proBNP as a tool for assessing DD, and 5) the cross-sectional design of the study.

However, our protocol has a number of strengths, including its prospective nature, use of age-adjusted values, and assessment of left atrial volume and EF. In addition, we were able to obtain good standardization, most studies sent by the centers were of adequate quality for evaluation, and there was good agreement among the core labs. Most importantly, DD as identified in our study was a very potent predictor of outcomes.

The issue of DD in atrial fibrillation is complex, but our results were similar when patients with atrial fibrillation were excluded. The similar outcome for pseudonormal patients diagnosed by Doppler or NT-proBNP argues for the use of NT-proBNP when there are difficulties in performing a more complex echocardiogram.

Implications. Our results show the predictive value of DD in HF-PSF, which demonstrates the need to obtain objec-

tive evidence of abnormal diastolic filling in patients with HF-PSF. We could identify patients at elevated risk who are likely to benefit from HF treatments. Furthermore, in low-risk patients, misdiagnosis and unnecessary treatment can be avoided. Our findings support current guidelines for patients with suspected HF, which emphasize the need to show objective evidence of systolic or diastolic dysfunction.

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APPENDIX

For a list of investigators and staff participating in the CHARMES substudy, please see the online version of this article.