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STATE-OF-THE-ART PAPER

What Have We Learned About Patients With Heart Failure and Preserved Ejection Fraction From DIG-PEF, CHARM-Preserved, and I-PRESERVE?

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Examination of patients with reduced and preserved ejection fraction in the DIG (Digitalis Investigation Group) trials and the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) trials provides comparisons of outcomes in each of these types of heart failure. Comparison of the patients in these trials, along with the I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function Trial), with patients of similar age, sex distribution, and comorbidity in trials of hypertension, diabetes mellitus, angina pectoris, and atrial fibrillation provides even more interesting insights into the relation between phenotype and rates of death and heart failure hospitalization. The poor clinical outcomes in patients with heart failure and preserved ejection fraction do not seem easily explained on the basis of age, sex, comorbidity, blood pressure, or left ventricular structural remodeling but do seem to be explained by the presence of the syndrome of heart failure.
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Because heart failure with preserved ejection fraction (HF-PEF) is, in essence, a diagnosis of exclusion and because the symptoms and signs of heart failure (of any type) are nonspecific, there has been some doubt about the nature of patients enrolled in clinical trials of HF-PEF (1,2). Compared with those with heart failure and a reduced ejection fraction (HF-REF), patients with HF-PEF are older, more often female, and have a lower prevalence of coronary artery disease (and higher prevalence of hypertension) (3–10). The higher frequency of obesity (3) and chronic lung disease (4,8) among patients with HF-PEF has even led to the suggestion that these patients may be little more than elderly, overweight women with swollen ankles who do not have heart failure at all (11–14). Although patients with HF-PEF were thought to have a similar prognosis to patients with HF-REF (3,4), more recent studies have suggested that they have a considerably better outcome (15,16), further raising doubts about what the HF-PEF syndrome really is or even whether it exists at all. Is this skepticism justified? What can we learn from what happened to the patients enrolled in DIG (Digitalis Investigation Group)-REF and DIG-PEF (17,18), CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)-REF and CHARM-Preserved (19–21), and I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) trial (22,23) (Tables 1, 2, and 3)? These programs include the 3 largest HF-PEF trials to date, and all reported all-cause mortality and heart failure hospitalization (HFH) rates per 1,000 patient-years of follow-up, allowing comparison between these studies (and with other trials).

HF-PEF Versus HF-REF

DIG and CHARM provide a unique opportunity to compare and contrast patients with HF-REF and HF-PEF because in both of these trials, centers enrolled patients with each type of heart failure simultaneously. Comparison of the baseline characteristics of patients with HF-PEF and HF-REF in these trials confirms the differences noted in epidemiological studies (e.g., patients with HF-PEF were more often female, older, and more likely to have a history of hypertension) (3,4). Another striking difference was in the distribution of body mass index (and higher prevalence of obesity) in patients with HF-PEF. The similar prevalence of diabetes but slightly higher prevalence of atrial fibrillation is also consistent with results of epidemiological studies (4,9,10). These patient differences were much more prominent in the I-PRESERVE trial than in DIG-PEF or CHARM-Preserved, probably because of differences in study

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

EF = ejection fraction

HF-PEF = heart failure–preserved ejection fraction

HF-REF = heart failure–reduced ejection fraction

HFH = heart failure hospitalization

design and inclusion/exclusion criteria, including entry ejection fraction (EF) threshold.

CHARM-Preserved and DIG-PEF Versus I-PRESERVE

The definition of preserved EF differed between studies, with DIG-PEF having an EF inclusion of >45% (with a median of 53% among randomized patients) (17) and CHARM-Preserved having an EF >40% (with a median of 52% among randomized patients) (19). I-PRESERVE recruited only patients with HF-PEF and had the most stringent entry criteria (Table 1) (23). Although the inclusion EF threshold in I-PRESERVE (≥45%) was similar to DIG-PEF, the median EF of 59% in I-PRESERVE was considerably higher than in the other 2 studies. The baseline characteristics also differed between the HF-PEF trials; most notably, the prevalence of coronary heart disease (Table 2). The low prevalence of coronary heart disease in I-PRESERVE may reflect the restriction on use of angiotensin-converting enzyme (ACE) inhibitors (because ACE inhibition is indicated in patients with coronary disease), although it is also consistent with the epidemiological studies. Indeed, I-PRESERVE seems most representative, overall, of patients with HF-PEF in the community (3–10), and CHARM-Preserved and DIG-PEF probably included a fraction of patients with left ventricular systolic dysfunction.

Outcomes in HF-PEF and HF-REF

DIG and CHARM provide a unique opportunity to compare outcomes in patients with HF-REF and HF-PEF, and the rate of the same events (mortality and HFH), expressed in the same manner (per 1,000 patient-years of follow-up), is also available from I-PRESERVE.

The overall mortality rate was consistently higher in the placebo arms of CHARM-Alternative (20) (115 per 1,000 patient-years), CHARM-Added (21) (111 per 1,000 patient-years), and DIG-REF (18) (120 per 1,000 patient-years) compared with CHARM-Preserved (19) (54 per

Table 1 Inclusion Criteria and Key Baseline Characteristics in HF-PEF and Other Cardiovascular Trials

Trial (Ref. #)	Key Inclusion Criteria	Key Exclusion Criteria
DIG-PEF (17)	HF-PEF Age ≥21 years LVEF >45% Current/past symptoms/signs of HF or radiologic pulmonary congestion	AF or atrial flutter Cor Pulmonale
CHARM-Preserved (19)	HF-PEF Age ≥18 years LVEF >40% NYHA class II–IV	Persistent systolic or diastolic hypertension
I-PRESERVE (23)	HF-PEF Age ≥60 years LVEF ≥ 45% NYHA class II–IV and HF hospitalization ≤6 months or NYHA class III/IV and abnormal CXR, ECG, or echocardiogram	AF with resting heart rate >120 beats/min Cor Pulmonale Clinically significant pulmonary disease BP >160/95 mm Hg despite therapy
ACTION (24)	Stable angina pectoris Age ≥35 years Proven CHD	LVEF <40% HF
ACCORD (25)	Type II diabetes mellitus; HbA_{1c} ≥7.5% Age 40–79 years CV disease/risk factors	LVEF <25% Current symptomatic HF NYHA class III/IV Congestive HF at any time
ALLHAT (26)	Hypertension Age ≥55 years ≥1 CHD risk factor	LVEF <35% HF hospitalization or treated symptomatic HF
ANBP-2 (27)	Hypertension Age 65–84 years	No HF/LVEF exclusion reported
LIFE (28)	Hypertension Age 55–80 years LVH (on ECG)	LVEF ≤40% HF
VALUE (31)	Hypertension Age ≥50 years CV disease/risk factors	Congestive HF requiring ACE inhibitor therapy
HYVET (32)	Hypertension Age ≥80 years	HF requiring treatment with antihypertensive medication

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACTION = A Coronary disease Trial Investigating Outcome with Nifedipine; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP-2 = second Australian National Blood Pressure trial; BP = blood pressure; CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CHD = coronary heart disease; CV = cardiovascular; CXR = chest x-ray; DIG= Digitalis Investigation Group; ECG = electrocardiogram; HbA_{1c} = glycosylated hemoglobin; HF = heart failure; HF-PEF = heart failure–preserved ejection fraction; HYVET = Hypertension in the Very Elderly Trial; I-PRESERVE = Irbesartan in Heart Failure with Preserved Systolic Function Trial; LIFE= Losartan Intervention for Endpoint reduction in hypertension; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; VALUE = Valsartan Antihypertensive Long-term Use Evaluation.

Table 2 Baseline Characteristics of I-PRESERVE, DIG, CHARM-Preserved, and CHARM-REF

Characteristic	DIG-REF (18) (n = 6,800)	DIG-PEF (17) (n = 988)	CHARM-REF (20,21) (n = 4,576)	CHARM-Preserved (19) (n = 3,023)	I-PRESERVE (23) (n = 4,133)
Mean age (yrs)	64	67	65	67	72
Age ≥75 yrs (%)	15	23	20	27	34
Women (%)	23	41	26	40	60
Mean LVEF (%)	29	55	29	54	59
HF etiology (%)					
Ischemic	71	56	65	57	25
Hypertensive	8.6	23	6.5	23	64
BMI (kg/m^2)	27	29	29	28	30
BMI categories (%)					
Underweight	2	2	—	—	0.5
Normal	34	26	32	23	16
Overweight	40	38	41	39	42
Obese	24	34	27	38	41
SBP (mm Hg)	126	138	127	136	136
Comorbidity (%)					
Hypertension	45	60	49	64	88
Angina (current)	27	30	51 (21)	53 (28)	40
Myocardial Infarction	65	50	58	44	24
PCI/CABG	—	—	15/25	19/22	13
Atrial fibrillation	NA	NA	26	29	29
Diabetes	28	29	29	28	27
Stroke	—	—	9	9	10

Body mass index (BMI) categories: underweight <18.5 kg/m^2; normal 18.5 to 24.9 kg/m^2; overweight 25.0 to 29.9 kg/m^2; and obese ≥30 kg/m^2.
CABG = coronary artery bypass graft; NA = not available; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; other abbreviations as in Table 1.

1,000 patient-years) and DIG-PEF (17) (76 per 1,000 patient years) (Fig. 1). Mortality rates were somewhat higher in both types of patients in DIG compared with CHARM, perhaps reflecting improvements in the treatment of cardiovascular risk factors and disease over the period between DIG and CHARM. Despite the differences in design, baseline characteristics, and median EF, the mortality rate in I-PRESERVE (23) (53 per 1,000 patient-years) was similar to that in CHARM-Preserved (54 per 1,000 patient-years); however, these rates were not adjusted for age, sex, or difference in other prognostic variables between trials. This lower mortality rate in patients with HF-PEF is consistent with a recent individual-patient meta-analysis of 41,972 participants in 31 cohort studies and clinical trials (16). In that analysis, the mortality difference persisted after adjustment for patient differences.

HFH rates showed a similar pattern, with much higher rates in CHARM and DIG in those with HF-REF (18,20,21) compared with patients in the same trials with HF-PEF (17,19,23) (Fig. 2). Interestingly, I-PRESERVE had an even lower rate of HFH than in CHARM-Preserved and DIG-PEF.

Outcomes in Patients With HF-PEF Versus Those in Other Cardiovascular Trials

Although the patients with HF-PEF in DIG and CHARM clearly had better outcomes than those with HF-REF (as did patients in I-PRESERVE), how do they fare compared with women and men more generally? To look at this, we compared the outcomes of patients with HF-PEF and those enrolled in trials of other types of cardiovascular disease, in which patients had similar age and sex profiles and similar comorbidities. The most obvious comparator is trials of older patients with hypertension, given that elevated blood pressure is thought to be the major underlying etiology of HF-PEF. Trials in patients with type 2 diabetes mellitus and coronary heart disease also provide interesting comparisons. We identified such trials that reported heart failure as an outcome and provided event rates per 1,000 patient-years of follow-up (Tables 1 and 3) (24–32). All of the trials used for comparison were large, randomized, and placebo controlled. Several are notable. For example, 3 hypertension trials enrolled a majority of women. The ANBP-2 (Second Australian National Blood Pressure) trial (27) randomized 6,083 patients with a mean age of 72 years, 51% of whom were female; the HYVET (Hypertension in the Very Elderly Trial) (32) enrolled 3,845 patients with a mean age of 84 years, 60% of whom were women. The Losartan Intervention for Endpoint reduction in hypertension (LIFE) (28) trial randomized 9,193 patients with a mean age of 67 years; 54% were women. The mean ages of patients in DIG-PEF, CHARM-Preserved, and I-PRESERVE were 67, 67, and 72 years, respectively, and the proportions of women were 41%, 40%, and 60%. Systolic blood pressure was higher in the hypertension studies than in the HF-PEF trials, yet in all 3 of the hypertension trials, the mortality and

Table 3 Baseline Characteristics in Other Cardiovascular Trials (Compared With HF-PEF Trials)

Characteristic	ACTION (24) (n = 7,665)	ACCORD (25) (n = 10,251)	ALLHAT (26) (n = 33,357)	ANBP2 (27) (n = 6,083)	LIFE (28–30) (n = 9,193)	VALUE (31) (n = 15,245)	HYVET (32) (n = 3,845)	DIG-PEF (17) (n = 988)	CHARM-Preserved (19) (n = 3,023)	I-PRESERVE (23) (n = 4,133)
Age (yrs)	63	62	67	72	67	67	84	67	67	72
Age ≥75 yrs (%)	—	—	—	30	17	—	100	23	27	34
Women (%)	20	39	47	51	54	43	61	41	40	60
LVEF	57	—	—	—	61*	—	—	55	54	59
BMI (kg/m^2)	—	32.2	29.8	27	28	28.7	24.7	29	28	29.6
Obese (%)	23	—	—	—	—	—	—	34	38	41
Heart rate (beats/min)	64	—	—	—	74	72	75	76	71	79
SBP (mm Hg)	137	136	146	168	174	155	173	138	136	136
DBP (mm Hg)	80	75	84	91	98	88	91	77	78	79
Creatinine (μmolL)	—	80	78	—	86	101	89	111	99	88
Comorbidity (%)										
Hypertension	52†	—	100†	100	100	92	90	60	64	88
Angina pectoris	100	—	26‡	8‡	10	46‡	—	30	53	40
Myocardial Infarction	51	—	—	—	6	—	3	50	44	24
Atrial fibrillation	—	—	—	—	4	—	—	—	29	29
Diabetes	15	100	36	7	13	32	7	29	28	27
Stroke	—	—	—	5§	8	20‖	7	—	9	10‖
Treatment (%)										
Diuretic	11	27¶	46¶	50	—	—	50	76	75	83
Spironolactone	—	—	—	—	—	—	—	8#	12	15
ACE inhibitor	20	53	27	50	—	—	—	86	19	25
ARB	2	—	—	—	50	50	—	—	50	50
Beta-blocker	80	29	—	—	50	—	—	—	56	59
CCB	50	—	27	—	—	50	—	—	31	40
Oral anticoagulant	4	—	—	—	1	—	—	—	25	19
Aspirin	86	55	36	—	21	—	—	—	59	55
Lipid-lowering agent	68	62**	—	13	7	—	—	—	42	31

Values are mean unless otherwise stated. BMI categories: underweight <18.5 kg/m^2; normal 18.5 to 24.9 kg/m^2; overweight 25.0 kg/m^2; and obese ≥30 kg/m^2. *Echocardiography substudy. †BP ≥140/90 mm Hg. ‡Coronary heart disease. §Cerebrovascular disease. ‖Stroke or transient ischemic attack. ¶Thiazide diuretic. #Potassium-sparing diuretic. **Statin.

ARB = angiotensin receptor blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; HR = heart rate; other abbreviations as in Tables 1 and 2.

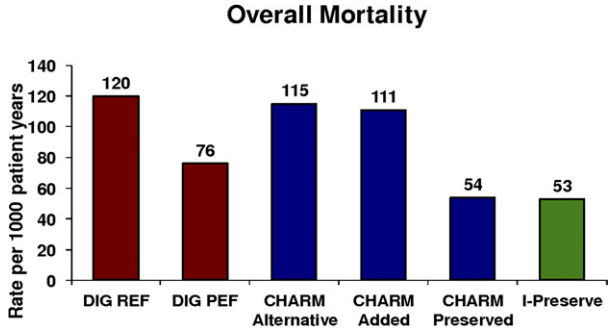

Figure 1 **Overall Mortality in DIG, CHARM, and I-PRESERVE**

Comparison of overall mortality rates between the heart failure–reduced ejection fraction trials (Digitalis Investigation Group [DIG]-REF, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity [CHARM]-Added, and CHARM-Alternative) and heart failure–preserved ejection fraction trials (DIG-PEF, CHARM-Preserved, and Irbesartan in Heart Failure with Preserved Systolic Function Trial [I-PRESERVE]).

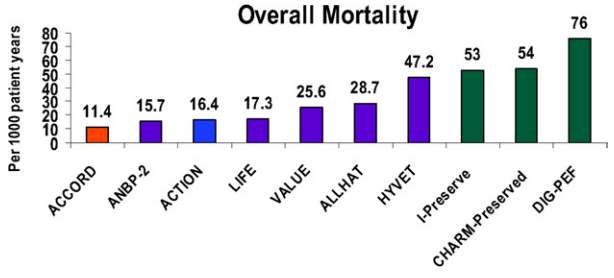

Figure 3 **Overall Mortality in Cardiovascular and HF-PEF Trials**

Comparison of overall mortality rates between cardiovascular trials (ACCORD [Action to Control Cardiovascular Risk in Diabetes], second Australian National Blood Pressure trial [ANBP-2], ACTION [A Coronary disease Trial Investigating Outcome with Nifedipine], Losartan Intervention for Endpoint reduction in hypertension [LIFE], VALUE [Valsartan Antihypertensive Long-term Use Evaluation], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT], and Hypertension in the Very Elderly Trial [HYVET]) and heart failure–preserved ejection fraction (HF-PEF) trials (DIG-PEF, CHARM-Preserved, and I-PRESERVE). Abbreviations as in Figure 1.

especially the HFH rates were lower than in the HF-PEF trials (Figs. 3 and 4). Only in the very elderly patients in HYVET did mortality approach that of CHARM-Preserved or I-PRESERVE, yet the rate of HFH was between 8 and 13 times higher in the HF-PEF trials than in HYVET. Inspection of the mortality and HFH rates from the other trials provides a consistent message: patients enrolled in the HF-PEF trials were at higher risk of death and at strikingly higher risk of HFH than similar patients with hypertension (and diabetes and angina pectoris, as discussed in the following text).

The second Swedish Trial in Old Patients with Hypertension (STOP-2) (33), which enrolled men and women ages 70 to 84 years with systolic blood pressure ≥180 mm Hg, diastolic blood pressure ≥105 mm Hg, or both, is also of interest. The average age of the 6,614 randomized subjects was 76 years; 67% were female. The STOP-2 investigators recorded the development of heart failure, whether requiring hospitalization or not, during a mean follow-up of 5 years. The rate was 16.4 per 1,000 patient-years in the conventional therapy (diuretic and beta-blocker) group, and the rate of death from any cause was 33 per 1,000 patient-years. The incidence of heart failure thus still remained much less than in the HF-PEF trials, even using this much broader definition.

Finally, the Cardiovascular Health Study (CHS) offers some perspective in relation to the mortality rates reported in these trials. This population-based longitudinal study of coronary heart disease and stroke recruited 5,888 persons who were at least 65 years of age from the community in 4 U.S. states (34). The average age of the 4,684 subjects with normal left ventricular systolic function and no heart failure was 73 years, and 60% were women. Their rate of death per 1,000 patient-years of follow-up was 25; it was 87 in those with HF-PEF (mean age 75 years; 56% female) and 154 in patients with HF-REF (mean age 74 years; 37% female).

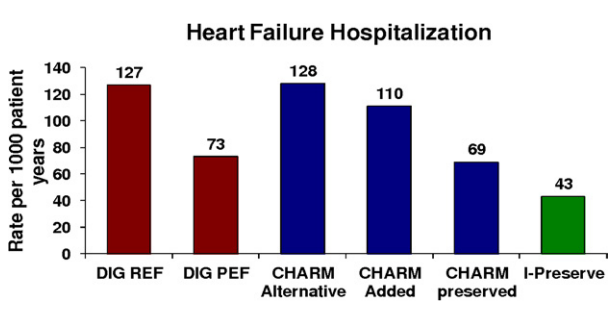

Figure 2 **Heart Failure Hospitalization in DIG, CHARM, and I-PRESERVE**

Comparison of heart failure hospitalization rates between heart failure–reduced ejection fraction trials (DIG-REF, CHARM-Added, and CHARM-Alternative) and heart failure–preserved ejection fraction trials (DIG-PEF, CHARM-Preserved, and I-PRESERVE). Abbreviations as in Figure 1.

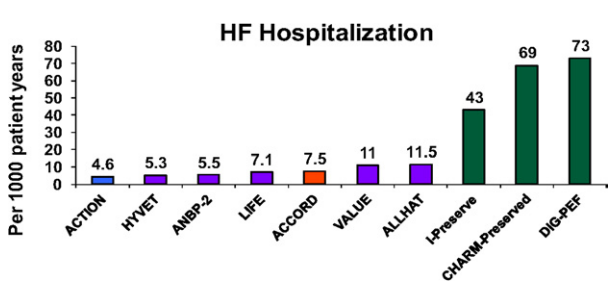

Figure 4 **Heart Failure Hospitalization in Cardiovascular and HF-PEF Trials**

Comparison of heart failure hospitalization rates between cardiovascular trials (ACCORD, ANBP-2, ACTION, LIFE, VALUE, ALLHAT, and HYVET) and HF-PEF trials (DIG-PEF, CHARM-Preserved, and I-PRESERVE). Abbreviations as in Figures 1 and 3.

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Table 4 Cause of Death: Number of Patients (% of Total Mortality)

Factor	ALLHAT (26) (n = 33,357)	ANBP2* (27) (n = 6,083)	HYVET (32) (n = 3,845)	STOP2 (33) (n = 6,614)	DIG-PEF (17,36) (n = 988)	CHARM Preserved (37) (n = 3,023)	I-PRESERVE (38) (n = 4,133)
Total mortality	4727	405	431	1111	231	481	881
CV mortality (%)	2193 (46.4)	166 (41.0)	220 (51.0)	659 (59.3)	162 (70.1)	340 (70.7)	532 (60.4)
Sudden death (%)	—	—	40 (9.2)†	164 (14.8)	36 (15.6)	134 (27.9)	231 (26.2)
Heart failure (%)	263 (5.6)	10 (2.5)	18 (4.1)	—	64 (27.7)	102 (21.2)	125 (14.2)
MI (%)	623 (13.2)	20 (4.9)	40 (9.2)†	162 (14.6)	—	21 (4.4)	45 (5.1)
Stroke (%)	370 (7.8)	44 (10.7)	69 (16.0)	147 (13.2)	7 (3.0)	33 (6.9)	76 (8.6)
Other CV death (%)	937 (19.8)	122 (30.1)	93 (21.6)	186 (16.7)	75 (32.5)	50 (10.4)	55 (6.2)
Non-CV (%)	2223 (47.0)	239 (59.0)	211 (49.0)‡	452 (40.7)	55 (23.8)	141 (29.3)	268 (30.4)
Unknown (%)	311 (6.6)	—	—	—	14 (6.1)	—§	81 (9.2)

*92 coronary events in ANBP-2 (including MI, sudden death, other coronary deaths, and deaths associated with coronary procedures). †MI and sudden death. ‡Noncardiovascular and unknown deaths. §Unknown deaths assumed to be cardiovascular in CHARM-Preserved.

CV = cardiovascular; MI= myocardial infarction; other abbreviations as in Table 1.

These findings suggest that, as expected, the clinical trials discussed earlier selected a relatively healthy and slightly younger cohort, although, even taking this into account, the patients in I-PRESERVE had a considerably higher mortality than would be expected for subjects who were approximately age and sex matched in the general population. Unfortunately, the CHS has not reported HFH rates in subjects with HF-PEF (35).

Cause of Death in Patients With HF-PEF Versus Those in Other Cardiovascular Trials

Relatively few of the other cardiovascular trials give a detailed breakdown of adjudicated cause of death (Table 4) (36–38). Compared with trials in patients with hypertension, a considerably higher proportion of all deaths in patients with HF-PEF was attributed to cardiovascular causes (60% to 70% vs. 40% to 60%), particularly heart failure and sudden death. A greater proportion of deaths in patients with hypertension was attributed to stroke compared with patients with HF-PEF.

Role of Other Comorbidities, Particularly Atrial Fibrillation

Although the hypertension trials allow some indirect control for age, sex, and blood pressure when compared with HF-PEF data, many had a low prevalence of diabetes mellitus. This was not true, however, of either the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (26) or the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial (31); in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (25), in which all enrolled patients had diabetes (Tables 1 and 3), the rates of both mortality and HFH were much lower than in I-PRESERVE (Figs. 3 and 4). Most of the hypertension trials also had a low prevalence of coronary heart disease, although the prevalence was similar in VALUE and I-PRESERVE. Both VALUE (31) and ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine) (24) (in which all patients enrolled had coronary heart disease) reported a much lower mortality and HFH rates than in I-PRESERVE (Figs. 3 and 4). The only comorbidity that is hard to account for in the comparator trials is atrial fibrillation, which is a strong risk factor for HFH. It is therefore useful to compare I-PRESERVE with the ACTIVE-I (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) (39) trial, which enrolled 9,016 patients with atrial fibrillation and other cardiovascular risk factors (including heart failure in 32% and hypertension in 88%). The average age of randomized patients was 70 years, and 39% were female. During a mean follow-up of 4.1 years, the rate of heart failure events ("HFH or other heart failure episodes") was 32 per 1,000 patient-years in the placebo group, and the rate of death was 50 per 1,000 patient-years. Again, even using a broad definition of heart failure in a particularly high-risk population, the rate of heart failure events was one-half that in DIG-PEF and CHARM-Preserved and lower than in I-PRESERVE.

Cardiac Remodeling, Diastolic Function, and Natriuretic Peptides

Whether cardiac remodeling, diastolic dysfunction, or both explain the difference in outcome between patients with HF-PEF and similar patients without HF-PEF is a key question. Unfortunately, this question is presently unanswerable, as matched patients of each type have not undergone cardiac investigation using the same techniques. Nevertheless, 1 non–HF-PEF trial, LIFE, is of interest as electrocardiographic left ventricular hypertrophy was an inclusion criterion in that trial. Probably as a result of this requirement, patients in LIFE had a greater average left ventricular mass than those in I-PRESERVE (as reported in the echocardiographic substudies from these 2 trials) in which left ventricular hypertrophy was not required at entry. Despite this, patients in I-PRESERVE had much worse outcomes (40,41).

No useful comparison of diastolic dysfunction can be made, although the degree of diastolic dysfunction is a predictor of outcome in patients with HF-PEF. It is conceivable that patients with HF-PEF may have more diastolic dysfunction than similar patients without HF-PEF (41,42). This may also be relevant to the finding that median N-terminal pro–B-type natriuretic peptide concentration was much higher in I-PRESERVE (341 pg/ml; interquartile range 135 to 974 pg/ml) than in LIFE (170 pg/ml; interquartile range 88 to 348 pg/ml), despite the greater left ventricular mass in LIFE (43,44). Similarly, while left ventricular mass in CHARM-Preserved was similar to that in LIFE, median N-terminal pro-B-type natriuretic peptide (344 pg/ml, interquartile range: 120 to 846 pg/ml) was twice that of LIFE (42). A better understanding of why N-terminal pro–B-type natriuretic peptide is elevated to a greater extent in patients with HF-PEF than in similar patients without is clearly important, given the prognostic importance of this peptide in HF-PEF (45).

Study limitations. We only considered patients with HF-PEF included in clinical trials (i.e., selected subjects), who tend to be healthier than HF-PEF patients in the community. However, this is also true of the patients enrolled in the other comparator trials and, in that sense, we compared "like with like." We could only compare across trials and did not have individual patient data. However, there was clearly substantial overlap between the HF-PEF trials and the others in key patient characteristics. The non–HF-PEF trials largely excluded patients with symptomatic heart failure, a low EF, or both. Like-with-like comparison of structural remodeling and diastolic function is not possible, and more subtle differences in systolic function have not been examined (46).

Discussion

Although the entry criteria for DIG-PEF (17) and CHARM-Preserved (19) have been criticized for being too lax and although these trials have also been criticized for selecting a healthy cohort as the result of their exclusion criteria (1,2,14), it is clear that the patients enrolled had a distinct clinical syndrome, HF-PEF, associated with a poor prognosis. Although not as bad as patients with HF-REF, the prognosis of patients with HF-PEF is substantially worse than that of patients with hypertension and other conditions that increase cardiovascular risk. What we have learned from DIG, CHARM, and I-PRESERVE is that HF-PEF is not just about old age, female sex, and high blood pressure. Based on a comparison of 2 key trials, LIFE and I-PRESERVE, the poor outcomes in patients with HF-PEF may not be explained by left ventricular hypertrophy either. From the available data, the 2 things that most clearly differentiate patients with HF-PEF from those with hypertension is having the clinical syndrome of heart failure (and often previous hospital admission with heart failure) and elevated natriuretic peptide levels (47). We need to learn more about the extent of diastolic dysfunction in patients with HF-PEF compared with otherwise similar patients without heart failure. Whatever the exact pathophysiological basis of this syndrome, the diagnosis of heart failure without a major reduction in EF clearly identifies a patient at greatly elevated risk of HFH and premature death.

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Key Words: heart failure ■ preserved ejection fraction ■ outcomes ■ reduced ejection fraction.