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VIEWPOINT

Treatment of Heart Failure With Normal Ejection Fraction

An Inconvenient Truth!

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Despite use of similar drugs, outcomes of recent heart failure (HF) trials were frequently neutral in heart failure with normal left ventricular ejection fraction (HFNEF) and positive in heart failure with reduced left ventricular ejection fraction (HFREF). The neutral outcomes of HFNEF trials were often attributed to deficient HFNEF patient recruitment with inclusion of many HFREF or noncardiac patients. Patient recruitment criteria of 21 HFNEF trials were therefore reviewed in reference to diagnostic guidelines for HFNEF. In the 4 published sets of guidelines, a definite diagnosis of HFNEF required the simultaneous and obligatory presence of signs and/or symptoms of HF and evidence of normal systolic left ventricular (LV) function and of diastolic LV dysfunction. In 3 of 4 sets of guidelines, normal systolic LV function comprised both a left ventricular ejection fraction (LVEF) >50% and an absence of LV dilation. Among the 21 HFNEF trials, LVEF cutoff values ranged from 35% to 50%, with only 8 trials adhering to an LVEF >50%. Furthermore, only 1 trial specified a normal LV end-diastolic dimension as an enrollment criterion and only 7 trials required evidence of diastolic LV dysfunction. Nonadherence to diagnostic guidelines induced excessive enrollment into HFNEF trials of HF patients with eccentric LV remodeling and ischemic heart disease compared with HF patients with concentric LV remodeling and arterial hypertension. Nonadherence to guidelines also led to underpowered HFNEF trials with a low incidence of outcome events such as death or HF hospitalizations. Future HFNEF trials should therefore adhere to diagnostic guidelines for HFNEF. (J Am Coll Cardiol 2010; 55:526–37) © 2010 by the American College of Cardiology Foundation

As a result of modern evidence-based heart failure (HF) therapy, the prognosis of patients with heart failure with reduced left ventricular ejection fraction (HFREF) improved progressively over the past 3 decades. Conversely, despite frequent use of similar pharmacological agents, the prognosis of patients with heart failure with normal left ventricular ejection fraction (HFNEF) remained unaltered over the same time period (1). Contrasting efficacy of comparable pharmacological agents in HFREF and HFNEF was convincingly demonstrated by the neutral outcome of the recent I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) trial (2), which assigned HFNEF patients to the angiotensin II receptor blocker (ARB) irbesartan or placebo, and by the positive outcome of the earlier CHARM (Candesartan in Heart Failure–Assessment of Mortality and Morbidity)-Alternative trial (3), which assigned HFREF patients to the ARB candesartan or placebo. Contrasting efficacy has also been reported for the prevention of HFNEF or HFREF. In hypertensive patients of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study (4), lisinopril was inferior to chlorthalidone for preventing new-onset HFNEF but not for new-onset HFREF.

The discordant outcomes of similar pharmacological therapy in HFNEF and HFREF could suggest that the signal transduction cascades driving myocardial remodeling differ in HFNEF and HFREF (5). The left ventricular (LV) structure and myocardial ultrastructure indeed argue in favor of unequal myocardial signal transduction cascades in both HFNEF and HFREF. Patients with HFNEF have concentric LV remodeling with high LV mass/volume ratio in contrast to patients with HFREF, who have eccentric LV remodeling with low LV mass/volume ratio (6–9). Myocardial ultrastructure follows a similar trend, with cardiomyocyte hypertrophy in HFNEF and loss of myofilaments in HFREF (9). Because of these divergences of myocardial structure and ultrastructure in HFNEF and HFREF, an unequal clinical response to similar pharmacological agents is not surprising.

Nevertheless, many concerns persist that mainly methodological issues involving identification and recruitment of HFNEF patients account for the neutral outcomes of HFNEF trials. In the presence of a normal left ventricular ejection fraction (LVEF), the diagnosis of HF is less evident. Inclusion of patients whose complaints of low exercise tolerance and dyspnea are caused by noncardiac causes is therefore more likely in HFNEF than in HFREF trials. The present review of major HFNEF trials addresses these concerns and focuses on

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patient recruitment in reference to published guidelines for the diagnosis of HFNEF. In HFNEF trials, criteria used for patient recruitment were highly variable, disregarded diagnostic guidelines, and were therefore frequently unsatisfactory. This "inconvenient truth" unfortunately leads to a persistent uncertainty of whether the neutral outcomes of these trials resulted from methodological flaws or from specific pathophysiological features characterizing HFNEF.

Diagnostic Guidelines for HFNEF

Originally HFNEF was described as diastolic HF (10). When awareness grew that diastolic LV dysfunction was not unique to diastolic HF but also was present in HF with systolic LV dysfunction, the term diastolic HF was largely abandoned and was replaced by the terms HF with preserved LVEF (11) or HFNEF (12). Both terms, however, also have their shortcomings. The notion of a preserved LVEF implies knowledge of a pre-existing LVEF, which is usually absent, and the exact range of a normal LVEF is hard to define (13,14). The present review, which relates recruitment criteria of trials to diagnostic guidelines, prefers the use of the term HFNEF because formal diagnostic guidelines were only published for diastolic HF (10,15,16) and HFNEF (5).

Four sets of guidelines have so far been published for the diagnosis of HFNEF. They all require the simultaneous and obligatory presence of signs and/or symptoms of HF, evidence of normal systolic LV function, and evidence of diastolic LV dysfunction (Table 1). The first set of guidelines was provided by the Working Group on Myocardial Function of the European Society of Cardiology (10). The criteria used were signs or symptoms of HF, an LVEF >45%, a left ventricular end-diastolic volume index (LVEDVI) <102 ml/m^2, and evidence of diastolic LV dysfunction provided by cardiac catheterization (pulmonary capillary wedge pressure [PCWP] >12 mm Hg or left ventricular end-diastolic pressures [LVEDP] >16 mm Hg) or by mitral or pulmonary venous Doppler flow velocity recordings. A second set of guidelines was provided by the National Heart, Lung, and Blood Institute Framingham Heart Study and combined signs and symptoms of HF, normal LVEF (>50%), and invasive evidence of diastolic LV dysfunction to provide 3 different levels of evidence for HFNEF (15). Definite HFNEF required the 3 conditions to be satisfied and the LVEF data to be procured within 72 h of the congestive HF episode. Probable and possible HFNEF required the first 2 conditions to be satisfied and the LVEF data to be procured within 72 h for probable HFNEF and later than 72 h for possible HFNEF. The emphasis placed on timely acquisition of the LVEF data was subsequently shown to be unwarranted because patients with hypertensive pulmonary edema had normal and comparable LVEF at hospital admission and 3 days later at recompensation (17). A third set of guidelines was proposed by Yturralde and Gaasch from the Lahey Clinic (16). For the definite diagnosis of HFNEF, they also require the same 3 conditions to be satisfied as in the 2 previous sets of guidelines. They implement their assessment with a scoring system of major criteria and confirmatory evidence and use LV hypertrophy and left atrial (LA) enlargement as substitutes for catheterization or Doppler evidence of diastolic LV dysfunction. Finally, the last set of guidelines was recently published by the Heart Failure and Echocardiography Associations of the European Society of Cardiology (5). This set of guidelines was the first to consider the use in HFNEF of tissue Doppler imaging (TDI) and natriuretic peptides (NP). The diagnosis of HFNEF required signs or symptoms of HF, an LVEF >50%, an LVEDVI <97 ml/m^2, and evidence of diastolic LV dysfunction. Only cardiac catheterization and TDI could provide standalone evidence of diastolic LV dysfunction, whereas NP needed to be implemented with TDI, mitral flow velocity Doppler, or measures of LA size or LV mass. When comparing these 4 sets of diagnostic guidelines, it becomes evident that the mere presence of signs or symptoms of HF and a normal LVEF never sufficed to firmly establish the diagnosis of HFNEF, which always required additional evidence of diastolic LV dysfunction, LA size, or LV mass.

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
AGE = advanced glycation end product
ARB = angiotensin II receptor blocker
cGMP = guanosine 3′,5′-cyclic monophosphate
HF = heart failure
HFNEF = heart failure with normal left ventricular ejection fraction
HFREF = heart failure with reduced left ventricular ejection fraction
LA = left atrial
LBBB = left bundle branch block
LV = left ventricle/ventricular
LVEDP = left ventricular end-diastolic pressure
LVEDVI = left ventricular end-diastolic volume index
LVEF = left ventricular ejection fraction
MMP = matrix metalloproteinase
NP = natriuretic peptide
PCWP = pulmonary capillary wedge pressure
PDE5 = phosphodiesterase-5
PFR = peak filling rate
PKG = protein kinase G
TDI = tissue Doppler imaging
TIMP = tissue inhibitors of matrix metalloproteinase

The emphasis on diastolic LV dysfunction in the published sets of diagnostic guidelines does not imply diastolic LV dysfunction to be the sole mechanism underlying HFNEF. Numerous other mechanisms have recently been identified and could be equally important (18). These mechanisms include reduced mitral annular shortening velocity (19), depressed LV longitudinal and radial deformation (20,21), ventriculovascular coupling (22), chronotropic incompetence (23), LA dilation (24), volume overload (25), and pulmonary arterial hypertension (26). In the normal heart, systolic motion of the mitral annulus toward the apex and systolic LV twist help to suck in blood during early diastole through the sudden release of stored energy. In HFNEF patients, this interplay between systolic and diastolic LV function is dis-

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Table 1 Overview of Diagnostic Guidelines for HFNEF

	HFNEF Guidelines Year Published (Ref. #)			
	ESC 1998 (10)	NHLBI 2000 (15)	LAHEY 2005 (16)	ESC 2007 (5)
HF signs and symptoms (other criteria)	Present	Present	Present	Present
Normal LV systolic function	LVEF >45% LVEDVI <102 ml/m^2	LVEF >50% within 72h HF episode	LVEF >50% LVEDVI <97 ml/m^2	LVEF >50% LVEDVI <97 ml/m^2
LV diastolic dysfunction	LVEDP >16 mm Hg PCW >12 mm Hg E/A <0.5 DT >280 ms IVRT >105 ms PVV >0.35 m/s Ard-Ad >20 ms	LVEDP >16 mm Hg PCW >12 mm Hg	LVEDP >16 mm Hg PCW >12 mm Hg E/A <0.5 DT >280 ms IVRT >105 ms LAE LVH	LVEDP >16 mm Hg PCW >12 mm Hg E/E′ >15 E/E′ >8 + NT-proBNP >220 pg/ml

All 4 sets of guidelines require the simultaneous presence of HF signs and/or symptoms and normal LV systolic function and diastolic LV dysfunction. Criteria for normal LV systolic function are comparable, but criteria for diastolic LV dysfunction are variable.

A = atrial wave mitral flow velocity; Ad = duration of atrial wave mitral flow velocity; Ard = duration of reverse pulmonary vein atrial systole flow velocity; DT = deceleration time; E = early mitral flow velocity; E′ = early tissue Doppler lengthening velocity; HF = heart failure; HFNEF = heart failure with normal left ventricular ejection fraction; IVRT = isovolumic relaxation time; LAE = left atrial enlargement; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PCW = pulmonary capillary wedge; PVV = pulmonary vein atrial maximal velocity.

rupted with concomitant elevation of LV filling pressures, especially during exercise (12). Effective arterial elastance, a global measure of arterial stiffness, and end-systolic LV elastance are typically elevated in HFNEF patients. Because of these elevated arterial and ventricular elastances, limited changes in LV end-diastolic volume induce exaggerated swings in systolic blood pressure. Intermittent high arterial systolic blood pressure because of these swings greatly increases cardiac oxygen consumption (22). At similar exercise workloads, HFNEF patients have less increase in heart rate and less systemic vasodilation than matched control subjects (23). Restoring chronotropic competence in HFNEF patients with rate-adaptive pacing is currently being assessed in the RESET (Restoration of Chronotropic Competence in Heart Failure Patients with Normal Ejection Fraction) study. Finally, LA dilation and dysfunction (24); volume overload because of renal insufficiency, anemia, or obesity (25); and pulmonary hypertension with a pre-capillary component (26) can all contribute to HF in HFNEF patients. Future refinements to diagnostic guidelines for HFNEF will probably incorporate criteria based on these nondiastolic mechanisms.

Overview of HFNEF Trials

Table 2 shows all major large outcome trials that have been performed so far in HFNEF patients. An outcome trial is defined as a large-scale, long-duration clinical trial with hard end points, including morbidity and mortality. The V-HeFT II (Vasodilator in Heart Failure Trial II), which compared enalapril with the combination of hydralazine and

Table 2 Enrollment Criteria of Large HFNEF Outcome Trials

	Trial Compound Duration (Ref. #)					
	V-HeFTII Enalapril 2 years (27)	DIG Digoxin 37 months (31)	CHARM-P Candesartan 3 years (33)	SENIORS Nebivolol 12 months (37)	PEP-CHF Perindopril 2.1 years (38)	I-PRESERVE Irbesartan 49.5 months (2)
HF signs and symptoms (other criteria)	Present (VO_2 ↓)	Present	Present	Present	Present (3/9 criteria including prior MI)	Present
Normal LV systolic function	LVEF >35% CTR >0.55 LVEDDI >2.7 cm/m^2	LVEF >45%	LVEF >40%	LVEF >35%	LVEF >40% WMI >1.4	LVEF >45%
LV diastolic dysfunction	—	—	—	—	WT >13 mm IVRT >105 ms E/A <0.5 DT >280 ms LA diameter >25 mm/m^2	LAE LVH
Positive outcomes	Mortality −40%	Hospitalizations	Hospitalizations	Mortality+hospitalizations −14%	Hospitalizations and symptoms at 1 yr follow-up	—

CTR = cardiothoracic ratio; DT = deceleration time; LVEDDI = left ventricular end-diastolic dimension index; MI = myocardial infarction; Vo_2 = maximal oxygen consumption during exercise; WMI = wall motion index; WT = wall thickness; other abbreviations as in Table 1.

isosorbide dinitrate, performed a subanalysis of patients with LVEF >35% and reported a beneficial effect on mortality and incidence of ventricular tachycardia (27). This favorable response to enalapril probably related to reduced eccentric LV remodeling because the enrollment criteria of V-HeFT II explicitly required evidence of LV dilation. Reduced eccentric LV remodeling is, however, of questionable relevance to most HFNEF patients, who are more likely to present with progressive concentric LV remodeling (6–9). Based on data from large HFNEF registries, concentric LV remodeling in HFNEF relates to comorbidities other than prior myocardial infarction, such as arterial hypertension (80% of patients), diabetes (30% of patients), and excess body weight (80% of patients) (28–30). These HFNEF registries, however, also enrolled their patients without requiring evidence of diastolic LV dysfunction. The Digitalis Investigation Group studied outcomes of treatment with digoxin both in patients with reduced LVEF (main trial) (31) and in patients with preserved LVEF (ancillary trial) (32). In both trials, digoxin had no effect on the mortality of chronic HF patients in normal sinus rhythm but reduced their need for worsening HF hospitalizations. Specific clinical characteristics of the patients recruited for the ancillary trial have been reported (32), and again suggested a high prevalence of eccentric LV remodeling because 49% of patients had suffered a prior myocardial infarction. The CHARM-Preserved trial randomized 3,023 patients between candesartan and placebo (33). The CHARM-Preserved trial failed to demonstrate a significant effect on cardiovascular death, but fewer HF hospitalizations in the candesartan-treated patients were observed. Again, HF was mainly of ischemic origin (56% of patients), with a history of prior myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting present in 45%, 17%, and 21% of patients, respectively. Predominant eccentric LV remodeling in the CHARM-Preserved trial was demonstrated by the CHARMES (Candesartan in Heart Failure Reduction in Mortality Echocardiographic Substudy) trial (34), which revealed an LV mass index in the candesartan-treated group of 111 ± 35 g/m^2. This value was within the normal reference range for men (49 to 115 g/m^2) (35), who composed 66% of the CHARMES substudy population. The SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) used the beta-blocker nebivolol in elderly HF patients over 70 years of age and observed a 14% reduction in primary outcomes (all-cause mortality and cardiovascular hospital admission) (36). The beneficial effect on primary outcome did not differ between patients with LVEF <35% and those with LVEF >35%, but favorable effects on LV end-systolic volume and LVEF were limited to nebivolol-treated patients with LVEF <35% (37). The PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) study was the first major randomized controlled trial on the use of angiotensin-converting enzyme inhibitors (ACEI) in HFNEF patients (38). It compared perindopril 4 mg daily with placebo in elderly patients (≥70 years old) with a diagnosis of HF, an LVEF >40%, minimal impairment of segmental LV wall motion, echocardiographic evidence of LA dilation or LV hypertrophy, and abnormal LV filling kinetics on mitral flow velocity Doppler. The study showed no difference in mortality and HF hospitalizations. Premature withdrawal of many patients after 1 year could have contributed to the neutral outcome because an interim analysis at 1 year of follow-up showed a significant reduction ($p = 0.033$) in HF hospitalizations. Criteria for patient enrollment into the PEP-CHF study, however, also had shortcomings. The diagnosis of symptomatic HF was linked to 9 criteria, of which 3 needed to be satisfied. These criteria comprised, among others, prior myocardial infarction and a cardiothoracic ratio >0.55. As a result, 39% of enrolled patients had coronary artery disease, and eccentric LV remodeling again became an important confounder. The I-PRESERVE trial is so far the largest reported trial for HFNEF. It enrolled 4,128 patients and randomly assigned them to irbesartan or placebo (2). Mortality or rates of hospitalizations for cardiovascular causes were not improved by irbesartan. Almost half of the patients were recruited because of HF hospitalization within the previous 6 months. The other half was recruited because they were symptomatic and satisfied at least 1 of the following criteria: pulmonary vascular congestion on chest X-ray film, echocardiographic evidence of LV hypertrophy or of LA enlargement, and electrocardiographic evidence of LV hypertrophy or of left bundle branch block (LBBB). Inclusion of LBBB is worrisome because LBBB is more prevalent in patients with HFREF than with HFNEF. Nevertheless, the clinical characteristics of the I-PRESERVE study population suggest less eccentric LV remodeling than in the previous trials, as there was a lower prevalence of prior myocardial infarction (24%) and a higher prevalence of arterial hypertension (88%) and of electrocardiographic evidence of LV hypertrophy (30%). Echocardiographic measures of LV mass, LVEDVI, and LV mass/volume ratio have not yet been reported and could further substantiate predominant concentric LV remodeling in the I-PRESERVE study population.

In HFNEF registries, the effect of pharmacological treatment on mortality was variable, as evident from Table 3. In a cohort of HFNEF patients prospectively followed up for 25 months after hospital discharge, prescription of a beta-blocker resulted in a 43% mortality reduction (39). In a similar 5-year registry of HFNEF patients surviving a first HF hospitalization, the 5-year mortality risk also decreased by 30% with ACEI treatment (40). In a community-based registry of HF patients (the COHERE [Carvedilol Heart Failure Registry] study), the benefit of carvedilol therapy was less, with a 6% mortality reduction for patients with an LVEF >40% (41). In this registry, the mortality reduction did not differ across the range of LVEF, but functional status and need for hospitalizations showed less improve-

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Table 3 Enrollment Criteria of HFNEF Registries

	Trial Compound Duration (Ref. #)			
	Dobre et al. Beta-Blockers 25 months (39)	COHERE Carvedilol 1 year (41)	OPT-HF ACEI, ARB, Beta-Blockers 60–90 days* (29)	Tribouilloy ACEIs 5 years (40)
HF signs and symptoms (other criteria)	Present	Present	Present	Present
Normal LV systolic function	LVEF >40%	LVEF >40%	LVEF >50%	LVEF >50%
LV diastolic dysfunction	—	—	—	—
Positive outcomes	Mortality −43%	Mortality −6%; hospitalizations	—	Mortality −30%

*Use of beta-blockers also had no effect on 1-year mortality or hospitalization rates (42).
Abbreviations as in Table 1.

ment when LVEF exceeded 40%. Finally, in the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry, discharge use of ACEIs, ARBs, or beta-blockers had no effect on 60- to 90-day mortality or hospitalization rates of HFNEF patients (29,42).

As outlined in Table 4, numerous small mechanistic trials also reported on clinical and hemodynamic effects of pharmacological treatment in HFNEF patients. In the aftermath of studies reporting beneficial effects on diastolic LV function of calcium-channel blockers in patients with hypertrophic cardiomyopathy, positive results were reported with verapamil in HF patients with normal LV systolic performance (LVEF >45%) and abnormal diastolic LV filling (LV peak filling rate [PFR] <2.5 LVEDV/s) (43). Positive results consisted of improvement of a clinical HF score, treadmill exercise capacity, and LV PFR. Although only 22 patients participated in this trial, patient recruitment was performed with great care and derived from a screening procedure of 182 HF patients with an LVEF >45%. This screening procedure drew on earlier experience with HFNEF patients (44), whereby an LV PFR <2.5 LVEDV/s was observed in only 38% of patients with HF and a normal LVEF. The hemodynamic features of the trial population corresponded with concentric LV remodeling as symmetric LV hypertrophy, defined by a wall thickness >1.2 cm, was present in 65% of patients. In line with concentric LV remodeling, HF was attributed to hypertension in 75% of patients and to coronary artery disease in only 25% of patients. In contrast to this initial study, 2 subsequent studies on pharmacological treatment of HFNEF patients focused on patients with limited prior myocardial infarctions (45,46). In this patient group, Aronow et al. (45,46) reported beneficial effects on symptoms with enalapril and on prognosis with propranolol. In the propranolol-treated group, mortality decreased by 30%. Post-myocardial infarction patients are at risk for unfavorable eccentric LV remodeling, and the positive outcomes observed in these studies therefore have limited relevance to HFNEF patients, who usually suffer from concentric LV remodeling. Beneficial effects of beta-blocker therapy also were observed in a small study comparing nebivolol with atenolol (47). This study rigorously adhered to diagnostic HFNEF guidelines by requiring both an LVEF >50% and an LV end-diastolic dimension <60 mm to establish normal systolic LV function and by obtaining invasive evidence of elevated PCWP. Six months of treatment resulted in improvement of the E/A ratio and reduction in LV mass with both compounds. Only nebivolol, however, succeeded to lower rest and exercise PCWP and to raise maximal oxygen consumption during exercise. Another small study, the SWEDIC (Swedish Doppler-Echocardiographic Study), also used stringent entry criteria as it determined a wall motion score index to exclude dyskinetic segments of previous myocardial infarctions and as it required evidence of age-adjusted diastolic LV dysfunction on mitral or pulmonary venous flow velocity Doppler (48). Six months of carvedilol therapy had no effect on symptomatic status; failed to alter an integrated score of all diastolic function indexes, which was the primary end point of the study; but improved the E/A ratio, especially in patients with a higher baseline heart rate. Because aldosterone had been implicated in myocardial fibrosis and hypertrophy, the effects of aldosterone antagonism on myocardial function were investigated in hypertensive patients with diastolic HF (New York Heart Association functional class II) using quantitative echocardiographic techniques (49). In the spironolactone-treated (25 mg) group, LV long-axis function improved with higher strain, strain rate, and integrated backscatter. The treated group also had smaller posterior wall thickness and LA area but unchanged treadmill exercise time. Inspired by these positive results, large outcome trials are currently being carried out to further explore the use of spironolactone in HFNEF. Their results are expected by 2010 for the ALDO-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trial and by 2011 for the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial. In experimental hypertensive HF, statins exert a variety of actions that may directly impact diastolic LV dysfunction, such as regression of LV hypertrophy and prevention of myocardial fibrosis (50). These actions have not yet been confirmed in clinical hypertensive heart disease or HFNEF. Nevertheless, usefulness of statins in HFNEF was suggested in a preliminary report that showed statins to lower mortality with a relative risk reduction of 22% (51).

Table 4 Enrollment Criteria of Small Mechanistic HFNEF Trials

Authors/Trial Compound Duration (Ref. #)	Setaro et al. Verapamil 5 weeks (43)	Aronow et al. Enalapril 3 months (45)	Aronow et al. Propranolol 32 months (46)	Nodari et al. Nebivolol or Atenolol 6 months (47)	SWEDIC Carvedilol 6 months (48)	Mottram et al. Spironolactone 6 months (49)	Fukuta et al. Statins 21 months (51)	HKDHF Irb/Rami+HCTZ Versus HCTZ 1 year (52)
HF signs and symptoms (other criteria)	Present	Present (prior MI)	Present (prior MI)	Present (VO_2 ↓)	Present	Present	Present	Present
Normal LV systolic function	LVEF >45%	LVEF >50%	LVEF >40%	LVEF >50% LVEDD <60 mm	LVEF >45% Wall motion score	LVEF >50%	LVEF >50%	LVEF >45%
LV diastolic dysfunction	PFR <2.5 LVEDV/s	—	—	PCW-R >12 PCW-Ex >20 E/A <1.0	E/A <1.0 IVRT >85 ms S/D <1.0 PWV >0.45 m/s Ard-Ad >20 ms	E/A <1.0 DT >250 ms	—	—
Positive outcomes	Exercise capacity PFR	E/A Symptoms	Mortality −30% LVEF LV mass	LV mass E/A Only nebivolol: VO_2, PCW	E/A	Strain rate Strain LAV LV mass	Mortality −20%	S, E′, NT-proBNP

HCTZ = hydrochlorothiazide; Irb/Rami = irbesartan or ramipril; LAV = left atrial volume; LVEDD = left ventricular end-diastolic dimension; PCW-Ex = pulmonary capillary wedge pressure during exercise; PCW-R = pulmonary capillary wedge pressure at rest; PFR = peak filling rate; S = tissue Doppler mitral annular shortening velocity; S/D = ratio of systolic/diastolic pulmonary venous flow velocity; other abbreviations as in Table 1.

Clinical and hemodynamic features of the HFNEF patient population recruited in this study suggested predominant concentric LV remodeling as most patients were hypertensive (80%) and as LV mass was elevated (204 g). In this study, other compounds, such as ACEIs, ARBs, beta-blockers, or calcium-channel blockers, had no discernible effect on survival. In contrast to most other outcome or mechanistic trials, which randomized patients between medication and placebo, the Hong Kong Diastolic Heart Failure Study randomized HFNEF patients among diuretics alone, diuretics plus ramipril, and diuretics plus irbesartan (52). In elderly HFNEF patients, emphasis on symptomatic improvement instead of survival seems justified, and as such a comparison with diuretics instead of placebo seems defendable. Hospitalizations and exercise tolerance changed similarly in all 3 groups, and addition of ramipril or irbesartan only resulted in lower NT-proBNP levels and higher systolic (S) and early diastolic (E′) mitral annular velocities.

Finally, a series of smaller studies also investigated clinical and hemodynamic effects of pharmacological treatment in patients with prior myocardial infarction or with arterial hypertension who had normal LVEF and no HF. These studies are summarized in Table 5. Their results are of relevance to HFNEF patients as they provide important mechanistic insight. The PREAMI (Randomized Perindopril and Remodelling in Elderly With Acute Myocardial Infarction) trial studied New York Heart Association functional class I to II patients with an LVEF >40% after prior myocardial infarction and observed less eccentric LV remodeling (0.7 ml vs. 4 ml ΔLVEDV/year) when patients were treated with 8 mg perindopril (53). This trial is of interest as it revealed eccentric LV remodeling to occur even after small myocardial infarctions that do not compromise baseline LV function. It also implies that inclusion of patients with prior myocardial infarction can have a confounding effect in an HFNEF trial because these patients will respond favorably through reduced eccentric LV remodeling. A low prevalence of prior myocardial infarction (<30% of patients) has therefore been suggested as a good indicator for a correct HFNEF patient recruitment (30). In patients with mitral flow velocity Doppler evidence of diastolic LV dysfunction and with a hypertensive response to exercise, losartan improved exercise tolerance and quality of life when compared with both placebo (54) and hydrochlorothiazide (55). In contrast, in a similar patient population with arterial hypertension and TDI evidence of diastolic LV dysfunction, valsartan was not superior to regular antihypertensive agents for improving TDI early diastolic mitral annular lengthening velocity (E′) (56). Both studies are of interest because they suggested that in HFNEF trial populations with a high prevalence of arterial hypertension, superiority needs to be established not just over placebo but also over regular blood-pressure-lowering therapy.

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Table 5 Enrollment Criteria of Small Trials With Prior MI or HT

	Trial/Authors Compound Duration (Ref. #)		
	PREAMI Perindopril 1 year (53)	Little et al. Losartan vs. HCTZ 6 months (55)	VALIDD Valsartan + RR ↓ vs. RR ↓ 38 weeks (56)
HF signs and symptoms (other criteria)	Absent (prior MI)	Absent (exertional HTN)	Absent (HTN)
Normal LV systolic function	LVEF >40%	LVEF >50%	LVEF >50%
LV diastolic dysfunction	—	E/A <1.0	E′ <8
Positive outcomes	LVEDV	Symptoms	—

Enrollment criteria of small mechanistic trials in patients with prior myocardial infarction (MI) or with arterial hypertension (HTN), who had normal LVEF and no HF.

RR ↓ = regular blood pressure lowering therapy; other abbreviations as in Table 1.

The Mismatch Between Guidelines and Trials

Evidence of normal systolic LV function was defined in the first set of guidelines (10) as an LVEF >45% and in the 3 most recent sets of guidelines (5,15,16) as an LVEF >50%. The HFNEF trials or registries, however, recruited patients whose LVEF varied from 35% to 50%, with 8 of the 21 trials or registries presented in this review using a cutoff value of 40% or less. Because LVEF of HF patients presents as a unimodal distribution (57), the choice of a specific cutoff value might seem arbitrary. However, data from the CHARM program on the predictive value of LVEF for cardiovascular outcome revealed LVEF to contribute to cardiovascular death only when it fell below 45% (58). Hence, an LVEF >45% seems to be a logical cutoff value for establishing a level of systolic LV function that separates HFREF from HFNEF. Furthermore, raising the LVEF criterion above 45% increases inclusion of women into the trial or registry because the distribution of LVEF in female HF patients peaks at 60%, whereas in male HF patients it peaks at 35% (57).

The LV anatomy characteristically differs between HFNEF and HFREF, with eccentric (low mass/volume ratio) LV remodeling in HFREF and concentric (high mass/volume ratio) LV remodeling in HFNEF (6–9). To account for these anatomical differences, 3 of 4 sets of guidelines (5,15,16) added an LVEDVI criterion to the requirements for establishing normal systolic LV function in HFNEF. Of the 21 HFNEF trials presented in this review, only 1 specified an LV end-diastolic dimension <60 mm as an enrollment criterion (47). In fact, several trials ended up in the reverse situation as they promoted recruitment of patients with eccentric LV remodeling by specifying a cardiothoracic ratio >0.55 as an enrollment criterion (27,38). This seems understandable for V-HeFT (27), which identified HFNEF patients by retrospective analysis of the V-HeFT population, but is less evident for recent trials such as PEP-CHF (38), which specifically recruited HFNEF patients. Another patient characteristic favoring recruitment of patients with eccentric LV remodeling is the presence of LBBB, which was used in the I-PRESERVE trial as an enrollment criterion (2). By not rigorously excluding LV dilation and eccentric remodeling, many HFNEF trials ended up with a patient population in which HF was mainly of ischemic etiology. This was especially true in the CHARM-Preserved trial (33) and the Digitalis Investigation Group studies (31,32), in which HF was of ischemic etiology in respectively 56% and 70% of patients, and in the COHERE registry (41), which reported a 51% prevalence of coronary artery disease. To exclude patients with coronary artery disease and dyskinetic LV segments, an echocardiographic wall motion score has been used as an enrollment criterion in the PEP-CHF (38) and SWEDIC (48) trials. Such a score indeed seems a valuable adjunct to the LVEF and LVEDVI criteria currently proposed to establish normal systolic LV function in patients with HFNEF.

In the 21 HFNEF trials presented in this review, the most frequently overlooked condition for the diagnosis of HFNEF was evidence of diastolic LV dysfunction. In fact, only 7 trials (38,43,47–49,55,56) required this condition to be satisfied. The reasons for overlooking diastolic LV dysfunction in the diagnosis of HFNEF were both conceptual and methodological. Initial studies on diastolic HF (44) already emphasized the heterogeneity of its clinical presentation, with only one-third of the patients who present with HF and a normal systolic LV function also having significant diastolic LV dysfunction evident from a depressed LV PFR on radionuclide LV angiograms. More than 2 decades later, the echocardiographic CHARMES substudy again confirmed these findings (34). Only one-half of the CHARM-Preserved trial patients, whose recruitment was solely based on signs and symptoms of HF and an LVEF >40%, also had diastolic LV dysfunction evident from a pseudonormal or restrictive LV filling pattern on mitral flow velocity Doppler. Furthermore, evidence of diastolic LV dysfunction on mitral flow velocity Doppler appeared to be widespread and aspecific as it also occurred in the elderly patients (59) and in patients with HFREF (60). Because of this lack of sensitivity and specificity of diastolic LV dysfunction, diastolic HF was referred to as HF with

preserved LVEF (11) or as HFNEF (12). Trial design followed this conceptual evolution and largely discarded diastolic LV dysfunction as an inclusion criterion in HFNEF trials. Recently, however, this trend again reversed because of the appearance of superior, less load-sensitive, TDI-derived indexes of diastolic LV dysfunction (5) and because of growing awareness that many HFNEF patients, defined solely by signs and symptoms of HF and normal LVEF, might be suffering from noncardiac illnesses. This reversal was evident from the more recent trials such as the VALIDD (Valsartan In Diastolic Dysfunction) (56) and Hong Kong diastolic HF trials (52), which used TDI-derived mitral annular early diastolic lengthening velocity (E′) as an inclusion criterion or as an outcome measure, respectively. The importance of diastolic LV dysfunction for HFNEF was also reappraised by recent invasive studies in HFNEF patients, which showed uniform presence at rest of slow LV relaxation and elevated diastolic LV stiffness (61) and which demonstrated elevated diastolic LV stiffness to limit cardiac performance during atrial pacing and exercise (62).

A final compelling argument for using evidence of diastolic LV dysfunction as an obligatory inclusion criterion in HFNEF trials was provided by the CHARMES echocardiographic substudy of the CHARM-Preserved trial (34). The CHARMES trial revealed less than one-half of the CHARM-Preserved patients to have moderate or severe diastolic LV dysfunction. Moderate or severe diastolic LV dysfunction was, however, an important predictor of adverse outcomes, in both univariate and multivariate analysis with respective hazard ratios of 3.7 and 5.7. The low event rate observed in the CHARM-Preserved trial was therefore attributed to the inclusion of numerous patients who failed to have significant diastolic LV dysfunction. Similar to the CHARMES trial, an earlier study (44) also compared clinical characteristics of HFNEF patients with or without diastolic LV dysfunction. In the absence of diastolic LV dysfunction, patients mainly suffered from acute myocardial ischemia or from LV volume overload because of chronic renal failure, hemodialysis, or unappreciated mitral regurgitation, whereas in the presence of diastolic LV dysfunction, the HF etiology was arterial hypertension in 60% of patients and coronary artery disease in only 27% of patients. Hence, although inclusion of LVEDVI and diastolic LV dysfunction criteria would make patient enrollment into a large outcome HFNEF trial more cumbersome and limited to a distinct subset of patients, this drawback would largely be compensated by a study population with a higher prevalence of concentric LV remodeling and a higher outcome event rate.

Roadmap for a Specific HFNEF Therapy

Although the neutral outcomes of many HFNEF trials could have resulted from deficient patient enrollment criteria, differences in myocardial structure and function could also account for the unequal outcomes of trials in HFNEF and HFREF (9). Future HFNEF trials should therefore focus on compounds that specifically interfere with structural and functional myocardial abnormalities characteristically observed in HFNEF patients. These abnormalities include: 1) prominent cardiomyocyte hypertrophy; 2) breakdown and turnover of the myocardial extracellular matrix, which leads to concentric instead of eccentric LV remodeling; 3) elevated cardiomyocyte resting tension with higher myocardial expression and less phosphorylation of the stiff N2B titin isoform; and 4) a shift in myocardial metabolism from glucose to free fatty acids use because of frequent comorbidities such as type 2 diabetes, metabolic syndrome, and obesity.

The LV myocardial ultrastructure in HFNEF is characterized by prominent cardiomyocyte hypertrophy (9), with a cardiomyocyte diameter 50% larger than in HFREF. This cardiomyocyte hypertrophy parallels the LV hypertrophy observed in many studies or registries of HFNEF patients (6–9). Regression of myocardial hypertrophy is therefore a meaningful therapeutic goal in HFNEF. Three HFNEF trials thus far reported on regression of myocardial hypertrophy. The subanalysis of patients with LVEF >35% included in the V-HeFT reported a significant reduction in LV mass with enalapril (27). Similarly, lower LV mass was observed in patients treated with candesartan in the echocardiographic substudy of the CHARM-Preserved trial (34). Finally, in a small trial comparing atenolol with nebivolol, both compounds significantly reduced LV mass (47). To specifically target regression of myocardial hypertrophy in HFNEF, statins and phosphodiesterase-5 (PDE5) inhibitors both have been proposed recently.

By suppressing activity of the guanosine triphosphate–binding proteins Ras, Rho, and Rac, statins can decrease cardiomyocyte hypertrophy (63) and reduce collagen synthesis (64). In a rat model of hypertensive HF, statin treatment thereby effectively reduced LV mass both at the stage of compensatory hypertrophy and at the stage of HF (65). The reduction of LV mass was accompanied by reduced fibrosis and lower expression of genes involved in cardiomyocyte hypertrophy, endothelin-1 signaling, or collagen synthesis. In clinical HF, hemodynamic effects of chronic statin therapy have only been reported in HFREF patients. In one study, LV end-diastolic dimension decreased over a 12-month period in the atorvastatin-treated group but increased over the same time period in the placebo group. The LV mass index, however, failed to change in both groups (66). These findings suggest beneficial clinical effects of chronic statin therapy on eccentric LV remodeling, but not on LV hypertrophy regression, which would have been a more relevant finding to HFNEF. Furthermore, in another study on HFREF patients, no significant LV remodeling effects of short-term (14-week) simvastatin treatment were observed (67).

Regression of LV hypertrophy is also the target for using PDE5 inhibitors in HFNEF. In a mouse transverse aortic

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constriction model, the PDE5 inhibitor sildenafil reversed pre-established LV hypertrophy induced by pressure overload and restored LV chamber function to normal (68). In these pressure-overloaded hearts, guanosine 3′,5′-cyclic monophosphate (cGMP) catabolism by PDE5 was increased. Administration of sildenafil restored cGMP levels, reactivated protein kinase G (PKG) activity, and deactivated multiple hypertrophy signaling pathways such as calcineurin/nuclear factor of activated T-cells, phosphoinositide-3 kinase/Akt, and ERK1/2. Overexpression of PDE5 was recently also observed in the right ventricular myocardium of patients with right ventricular hypertrophy and pulmonary hypertension (69) and in the LV myocardium of patients with end-stage HFREF (70). Regression of LV hypertrophy through restored PKG activity supports the use of PDE5 inhibitors in HFNEF, and this hypothesis is currently being tested in the RELAX (PhosphodiesteRasE-5 Inhibition to Improve Quality of Life And EXercise Capacity in Diastolic Heart Failure) trial.

Restored myocardial PKG activity also could directly improve myocardial distensibility through phosphorylation of the giant cytoskeletal protein titin, which is responsible for cardiomyocyte stiffness (71–73). This was confirmed in recent experiments using isolated cardiomyocytes of HFNEF patients in which PKG administration resulted in a prompt decrease of cardiomyocyte resting tension (74,75). Correction of cardiomyocyte stiffness, unrelated to regression of cardiomyocyte hypertrophy, could be especially relevant to early stages of hypertensive heart disease as suggested by the VALIDD (Valsartan In Diastolic Dysfunction) trial, which only observed LV hypertrophy in 3% of asymptomatic hypertensive patients with diastolic LV dysfunction (56).

In both HFNEF and HFREF, there is increased myocardial collagen deposition but the underlying expression patterns of matrix metalloproteinases (MMPs) and of tissue inhibitors of matrix metalloproteinases (TIMPs), which are responsible for breakdown and turnover of the extracellular matrix, are different as they are driving concentric LV remodeling in HFNEF but eccentric LV remodeling in HFREF. In hypertensive patients with HFNEF (76) and in patients with aortic stenosis (77), there is decreased matrix degradation because of down-regulation of MMPs and up-regulation of TIMPs, whereas in patients with dilated cardiomyopathy there is increased matrix degradation because of up-regulation of MMPs (78). In patients with aortic stenosis who develop a depressed LVEF, this balance between proteolysis and antiproteolysis shifts (79). These distinct expression patterns of MMPs and TIMPs in HFNEF and HFREF result in unequal myocardial collagen deposition with mainly interstitial fibrosis in HFNEF and both replacement and interstitial fibrosis in HFREF (9). Moreover, the extent of LV interstitial fibrosis also differs between HFNEF and HFREF. Collagen volume fraction was lower in HFNEF than in HFREF (80), and one-third of the patients presenting with HFNEF had a normal collagen volume fraction (81). Their LVEDP and LV stiffness modulus were, however, comparable to those of patients with an increased collagen volume fraction. This finding suggested that in addition to collagen deposition, other factors also importantly contributed to the high in vivo LV stiffness observed in HFNEF patients (81). Intrinsic cardiomyocyte stiffness is one of these factors. Intrinsic cardiomyocyte stiffness is elevated in patients with HFNEF (9,81), and this mainly relates to transcriptional or post-translational modifications of the cytoskeletal protein titin (73). Hence, an antiproteolytic expression pattern of MMPs and TIMPs, absence of replacement fibrosis, and less interstitial fibrosis could all explain why ACEIs and ARBs, which exert their beneficial action on LV remodeling partly through reduction of collagen deposition, have been less successful in HFNEF.

Increased diastolic LV stiffness is recognized as the earliest manifestation of LV dysfunction induced by diabetes mellitus (82–84) and frequently becomes the main functional deficit as many diabetic patients have HFNEF (28). Excessive diastolic LV stiffness of the diabetic heart has been related to myocardial deposition of advanced glycation end products (AGEs). The AGE deposition results from long-standing hyperglycemia and affects diastolic LV stiffness by direct and indirect mechanisms (85). The AGE cross linking of collagen increases its tensile strength, and this altered biophysical property of collagen increases diastolic LV stiffness. The AGE deposition can also indirectly augment diastolic LV stiffness through reduced nitric oxide (NO) bioavailability. The AGEs quench endothelially produced NO, and low myocardial NO bioavailability raises diastolic LV stiffness (86). The importance of the latter mechanism is supported by the preferential localization of AGEs in small intramyocardial vessels as recently demonstrated in endomyocardial biopsies of both diabetic HF patients (80) and elderly hypertensive dogs (87). Based on these observations, the use of AGE cross-link breakers such as alagebrium chloride seems promising. A small pilot study in HFNEF patients showed alagebrium chloride to reduce LV mass, to improve LV filling, and to ameliorate quality of life (88). A similar study in hypertensive subjects also showed alagebrium chloride to restore endothelial function (89).

Apart from myocardial AGE deposition, diabetes-related diastolic LV dysfunction has been linked to deranged myocardial metabolism with low myocardial phosphocreatine to adenosine-triphosphate ratio and high myocardial triglyceride content. The former could be explained by reduced glucose utilization because of less-insulin-sensitive glucose (GLUT4) transporters and the latter by increased nonesterified fatty acid fluxes (83,90). Myocardial triglyceride accumulation in turn leads to formation of toxic intermediates, mitochondrial dysfunction, and free radical production, which has also been linked to diabetes-related diastolic LV dysfunction (91). Thiazolidinediones restore glucose utilization and have recently been shown to favorably modify diastolic LV dysfunction as evident from improved TDI mitral annular lengthening velocity (E′) (91)

and rightward displacement of the LV diastolic pressure–volume relation (92). Such a rightward shift of the LV diastolic pressure–volume relation could be beneficial in diabetic HFNEF patients with concentric LV remodeling, but deleterious in diabetic HFREF patients, in whom it would exacerbate eccentric LV remodeling (93).

Conclusions

In contrast to HFREF, the prognosis of HFNEF failed to improve over the last 3 decades, despite similar use of ACEIs, ARBs, and beta-blockers in both conditions. An urgent need has therefore arisen for development and evaluation of novel HFNEF treatment strategies. Novel strategies should try to interfere with HFNEF-specific myocardial signal transduction pathways, which account for prominent cardiomyocyte hypertrophy, down-regulation of MMPs, up-regulation of TIMPs, hypophosphorylation of stiff titin isoforms, and substrate shifts from glucose to free fatty acids. To secure correct identification of HFNEF patients and to avoid recruitment of HFREF or noncardiac patients, future HFNEF trials should adhere to the proposed diagnostic guidelines for HFNEF. This implies patient enrollment criteria to include not only a lower limit of LVEF but also an upper limit of LVEDVI and significant evidence of diastolic LV dysfunction. Use of expanded patient enrollment criteria is more likely to result in an HFNEF trial population with concentric LV remodeling and with HF caused by hypertension or diabetes and not by ischemic heart disease.

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