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CME

Developing Therapies for Heart Failure With Preserved Ejection Fraction

Current State and Future Directions

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JACC: HEART FAILURE CME

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CME Objective for This Article: After reading this article, the reader should be able to discuss the following: 1) the prevalence of HFpEF (heart failure with preserved ejection fraction) is increasing, these patients face a high risk for adverse outcomes, and the associated economic consequences are rising; 2) there are no approved therapies for these patients; and 3) to identify new therapies, a deeper understanding of the sub-populations that fit under the HFpEF umbrella, more specific molecular targets for engagement, and improvements in clinical trial design, are needed.

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Developing Therapies for Heart Failure With Preserved Ejection Fraction

Current State and Future Directions

The burden of heart failure with preserved ejection fraction (HFpEF) is considerable and is projected to worsen. To date, there are no approved therapies available for reducing mortality or hospitalizations for these patients. The pathophysiology of HFpEF is complex and includes alterations in cardiac structure and function, systemic and pulmonary vascular abnormalities, end-organ involvement, and comorbidities. There remain major gaps in our understanding of HFpEF pathophysiology. To facilitate a discussion of how to proceed effectively in future with development of therapies for HFpEF, a meeting was facilitated by the Food and Drug Administration and included representatives from academia, industry, and regulatory agencies. This document summarizes the proceedings from this meeting. (J Am Coll Cardiol HF 2014;2:97–112) © 2014 by the American College of Cardiology Foundation

Epidemiologic studies suggest that the prevalence and hospitalizations related to heart failure with preserved ejection fraction (HFpEF) is rising (1), and the growing elderly population guarantees further worsening of these trends. To date, there are no approved therapies to reduce hospitalization or mortality for HFpEF. There remains a lack of consensus on the basic pathophysiology and definition, classification, therapeutic targets, and goals for therapy for this syndrome. To facilitate consensus for the next steps in developing therapies for HFpEF, the Food and Drug Administration hosted a meeting on February 6, 2013, that was attended by representatives from academia, industry, and the regulatory agencies from the United States and Europe. This meeting was not industry sponsored. This document represents the proceedings from this meeting.

Importance

Considering its prevalence and outcomes, future projections, and lack of effective therapies, HFpEF represents the single largest unmet need in cardiovascular medicine.

Epidemiology. Table 1 summarizes the epidemiology of HFpEF and the difference in prevalence and outcomes based on the definitions used and the population studied (1–7). Hospitalizations for HFpEF have increased over time, whereas those for heart failure with reduced ejection fraction (HFrEF) have declined. These patients have longer length of stay and are more likely to require skilled nursing care (1). Mortality in outpatient cohorts appears to be lower for HFpEF than HFrEF (8), but data are inconsistent for in-hospital mortality (5,6). Observational studies show a higher mortality for HFpEF than clinical trials (9). The combined mortality and readmission rates at 60 to 90 days post-discharge are comparable for HFrEF (36.1%) and HFpEF (35.3%) (7). In the I-PRESERVE (Irbesartan in Heart Failure With Preserved Systolic Function) and the CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity) trials, 70% of mortality in HFpEF was cardiovascular (8,10), whereas in HFrEF, cardiovascular causes accounted for 83% of deaths (8). Exercise capacity and quality of life are similarly reduced in HFpEF and HFrEF (11,12).

Summary of clinical trials in HFpEF. No specific treatment for HFpEF is established, and management is limited to diuretics and treatment of comorbidities. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were not effective in reducing mortality (13–19) (see also Table 2 [13–30]). Digoxin had no effect on mortality in either HFrEF or HFpEF, but had similar benefits on the composite of hospitalizations or death due to worsening HF regardless of EF (25). β-blockers have not shown benefits in HFpEF (14,22,23,29,30). Therapy with spironolactone (27) showed improvement in diastolic function and hypertrophy but not in clinical outcomes, which may be related to inclusion of relatively stable patients. Sildenafil (28) showed no improvement in exercise capacity, quality of life, or clinical status in HFpEF. The PARAMOUNT (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blockers on Management of HFpEF) trial (31) showed favorable effects of angiotensin receptor neprilysin inhibitor on natriuretic peptides and left atrial (LA) volumes, and a phase III trial with this agent is ongoing. Exercise training in HFpEF has been shown to improve symptoms and quality of life (32–37).

Clinical Variants

Although there are common comorbidity profiles among patients with HFpEF, specific underlying etiologies are only seen in a small proportion of patients. The vast majority of patients do not have any known *specific* genetic, pericardial, myocardial, or valvular etiology. The most urgent need is to develop therapies targeting this majority of HFpEF patients; however, future trials will benefit from enhanced phenotypic characterization and categorization that may allow improved targeting of experimental therapies.

There are several specific etiologies of HFpEF (e.g., hypertrophic cardiomyopathy) but the vast majority does not have a specific underlying primary cardiac cause. Better understanding of the pathophysiologic pathways may allow identification of better therapeutic targets. Studies suggest

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Abbreviations and Acronyms

EF = ejection fraction

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LV = left ventricular

LA = left atrial

NP = natriuretic peptide

that HFpEF is a heterogeneous entity, and careful phenotyping is needed to target the right population for understanding the pathophysiology and response to treatments (38–40). Most patients have 1 or more comorbidities that may worsen HFpEF. Nevertheless, many of these patients do not have any yet identified specific primary cardiac pathology. Understanding the basic disease process and targeting novel therapies to this vast majority of typical HFpEF patients is urgently needed.

Pathophysiology

The pathophysiology of HFpEF is incompletely understood. There are no animal models ideally suitable for drug testing. Changes leading to hospitalization and the differences between hospitalized versus outpatients are incompletely understood. Future research should focus on understanding the basic and clinical mechanisms of HFpEF.

The pathophysiology of HFpEF is complex, incompletely understood, and related to cardiac structural and functional alterations, and systemic and pulmonary vascular abnormalities, which, coupled with extra-cardiac causes of volume overload (e.g., kidney disease), can lead to the signs and symptoms of HF.

Left ventricle. Left ventricular (LV) abnormalities in HFpEF are varied and compounded by abnormal ventricular-arterial coupling, poor vasodilator reserve, chronotropic incompetence, coronary disease, microvascular dysfunction, and right ventricular dysfunction with or without coexisting pulmonary vascular disease.

STRUCTURAL CHANGES. LV size is normal or near normal in most patients with HFpEF. Most patients have increased LV mass or relative wall thickness, and may have concentric remodeling or hypertrophy. In 1 study, mean LV mass index was 102 ± 29 g/m^2; 27% of patients had concentric LV remodeling, 26% had concentric LV hypertrophy, and 16% had eccentric LV hypertrophy in HFpEF (41). Changes in myocyte structure (42) with increased diameter in HFpEF than HFrEF have been reported.

DIASTOLIC FUNCTION. Diastolic dysfunction in HFpEF can result from increased LV stiffness from hypertrophy and interstitial fibrosis, as well as from abnormal LV relaxation due to abnormal calcium cycling. Titin functions as a bidirectional spring responsible for early diastolic recoil and late diastolic distensibility, regulates diastolic function. Alterations in titin phosphorylation cause diastolic dysfunction, suggesting that titin may be a therapeutic target (43,44). Abnormal myocardial energetics in HFpEF can impact relaxation and filling. Ischemia and microvascular dysfunction are associated with changes in intracellular calcium and are related to HFpEF. Diastolic dysfunction results in ineffective LA emptying and LV filling, and reduced ability to augment cardiac output with exercise, increases in pulmonary

Table 1 Epidemiology of HF With Preserved EF

First Author (Ref. #) (Trial)	Population	Prevalence and EF	Mortality	Readmission
Cohort studies				
Vasan et al. (3) (FHS)	73 outpatients	51%, EF ≥50%	Annual during median 6.2 yrs: 8.7%	
Owan et al. (5) (Olmsted County)	4,596 HHF patients	47%, EF ≥50%	1 yr: 29% 5 yrs: 65%	
Bhatia et al. (6) (Ontario)	2,802 HHF patients	31%, EF ≥50% 13%, 40% ≤ EF <50%	30 days: 5.3 1 yr: 22.2%	30 days: 4.5, EF ≥50% 1 yr: 13.5%, EF ≥50%
Steinberg et al. (1) (GWGL-HF)	110,621 HHF patients	36%, EF ≥50% 14%, 40% ≤ EF <50%	In-hospital: 2.5%, EF ≥50% 2.3%, 40% ≤ EF <50%	
Registries				
Philbin et al. (2) (MISCHF)	1,291 HHF patients	24%, EF ≥50% 18%, 40% ≤ EF <50%	In-hospital: 3.0%, EF >50% 5.0%, 40% ≤ EF <50%; 6 months: 14.0%, EF >50% 15.0%, 40% ≤ EF <50%	
Fonarow et al. (7) (OPTIMIZE-HF)	41,267 HHF patients	51.2%, EF ≥40% 34.6%, 40% ≤ EF <50% 47.6%, EF >50%	In-hospital: 2.9%, EF ≥40% 3.0%, 40% ≤ EF <50% 2.9%, EF >50% 60–90 days: 9.5%, EF ≥40% 9.2%, 40% ≤ EF <50% 9.3%, EF >50%	60–90 days: 29.2%, EF ≥40% 29.0%, 40% ≤ EF <50% 30.9%, EF >50%
Yancy et al. (4) ADHERE	52,187 HHF patients	50.4%, EF ≥40%	In-hospital: 2.8%, EF ≥40%	

ADHERE = Acute Decompensated Heart Failure National Registry; EF = ejection fraction; FHS = Framingham Heart Study; GWGL-HF = Get With the Guidelines – Heart Failure; HF = heart failure; HHF = hospitalized heart failure; MISCHF = Management to Improve Survival in Congestive Heart Failure; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

pressure, and resulting in symptoms and fluid retention. HFpEF patients have increased LV stiffness (41) with increased passive elastance. Echocardiography can describe impaired relaxation using longitudinal mitral annular early diastolic tissue velocity (e'), and increased LV filling pressures via the ratio of early mitral inflow (E) to e' (i.e., E/e' ratio). Measurement of chamber compliance requires analysis of the end-diastolic pressure volume relationship, which is shifted upward and leftward in HFpEF. Assessment of diastolic function and filling pressures during exercise has emerged as a useful tool (45). Left bundle branch block deteriorates diastolic dysfunction with increased E/e', LA diameter, and reduced deceleration and isovolumic relaxation time (46).

SYSTOLIC FUNCTION. Although LVEF is preserved and some patients may even have normal-appearing LV size and geometry, systolic function may be abnormal in HFpEF, including an increase in end-systolic elastance (47). However, when normalized for remodeling, the end-systolic elastance/volume to mass ratio is normal. The increases in end-systolic elastance and effective arterial elastance may contribute to decreased exercise capacity due to limited ability to increase both above baseline. In HFpEF, longitudinal strain is typically reduced whereas radial strain is preserved, resulting in preservation of LVEF despite longitudinal systolic dysfunction (48). Systolic reserve during exercise is also impaired in HFpEF (38).

INTERSTITIAL MATRIX. Diffuse myocardial fibrosis maybe a mediator or a modifier of HFpEF. Myocytes embedded in fibrotic tissue are prone to energy starvation as fibrosis affects capillary blood supply by interposing collagen and by perivascular collagen limiting vasomotor reserve. Diffuse fibrosis is linked with diastolic dysfunction, vasomotor dysfunction, arrhythmias, and mortality (49). Experimental models have produced HF by creating diffuse fibrosis from cardiac fibroblast activation (50), suggesting a primary role for fibroblast activity.

Left atrium. HFpEF patients may have ineffective LA emptying, increased size, and abnormal function. In the CHARM-Preserved study (Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity), LA volume index was >32 ml/m^2 in 71% of the patients (51), and in the I-PRESERVE echocardiographic substudy, 66% of patients had LA enlargement (52). The LA size is a predictor of outcomes (52). Recruitment of LA contractility during stress is impaired in HFpEF and may contribute to the transition from asymptomatic state to overt HFpEF (53).

Endothelial function and arterial stiffness. Endothelial function and nitric oxide influences arterial stiffness in HFpEF and arterial stiffness increases with hypertension. Arterial distending pressure leads to recruitment of inelastic collagen fibers (54). Age and cardio-metabolic abnormalities are related to arterial stiffness, which in turn is associated with HFpEF. Increases in LV end-systolic and arterial elastance occur with aging, particularly in women, and may result in ventricular-vascular stiffening leading to HFpEF (55). Pulse wave velocity is higher (56) and venous capacitance lower in HFpEF than in HFrEF, explaining why these patients are more sensitive to vasodilators and diuretics (47). Worsening vascular failure is proposed as a precipitant for hospitalization in HFpEF, but few data are available. HFpEF patients have limited vasodilatory response to exercise. Endothelial dysfunction in HFpEF is associated with adverse outcomes (57) and it also affects microvasculature that in turn may modulate diastolic function via paracrine effects (58).

Pulmonary hypertension. Increased LV stiffness augments end-diastolic pressure (59), leading to increased pulmonary venous pressure and a passive increase in pulmonary artery pressure. Chronically elevated pressures induce a reactive component (60), and the transpulmonary gradient increases out of proportion to the wedge pressure, leading to a higher mean pressures than expected. Pulmonary vasculopathy similar to HFrEF can be postulated in HFpEF, but has not yet been shown.

Right ventricle. The right ventricle better tolerates volume than pressure (61), leading to high prevalence of dysfunction when pulmonary hypertension develops. Right ventricular dysfunction worsens prognosis and is related to the transmission of elevated LV filling pressures to the pulmonary bed. The chronic elevated pulmonary pressure leads to right ventricular hypertrophy and later, to contractile dysfunction, tricuspid regurgitation, and diminished cardiac output. Subendocardial right ventricular dysfunction in HFpEF has been shown (62).

Animal models. A few animal models of HFpEF have been described, but they mimic some but not all of the characteristics described in humans with HFpEF, significantly limiting their usefulness for testing novel therapies. Development of better animal models, especially large animal models that mimic human disease more closely, may be useful in drug testing in future. However, until that time, the lack of animal models should not prevent human testing of promising therapies.

Comorbidities

HFpEF patients usually have multiple comorbid conditions, the treatment of which may improve outcomes.

Comorbidities are highly prevalent in these patients and are related to ventricular-vascular dysfunction and prognosis (63). Hypertension affects the risk of developing HFpEF and treatment substantially lowers this risk. Obesity, anemia, diabetes, and renal dysfunction are associated with unique ventricular-vascular characteristics contributing to HFpEF; however, changes seen in HFpEF cannot be accounted for by these comorbidities alone (64). Subclinical lung disease is related to HFpEF (65). The exact role of sleep apnea in HFpEF needs further study. Atrial fibrillation is prognostically important in HFpEF (66). Comorbidity burden increases hospitalization risk in HFpEF, with more non-HF

Table 2 Clinical Trials in Patients With Heart Failure and Preserved Ejection Fraction

First Author (Ref. #) Drug	Duration (months)	n	Systolic Function	Diastolic Function as Inclusion Criterion	Positive Outcomes	Mortality/ Readmission
Medication Trials						
Setaro et al. (20) Verapamil	1.25	40	LVEF >45%	Peak filling rate <2.5 edv/s	Improved clinical status Increased exercise time and diastolic filling rate	
Aronow and Kronzon (13) Enalapril	3	21	LVEF >50%	Not determined	Improved clinical status Increased exercise time Decreased LV mass/increased E/A ratio	
Aronow et al. (14) Propanolol + ACEI	12	158	LVEF ≥40%	Not determined	Reduced mortality: 30% and combined mortality + nonfatal MI Increased LVEF: reduced LV mass	1 yr: 65.8%
Hung et al. (21) Verapamil	3	30	LVEF >50%	Not determined	Improved clinical status Increased exercise time Increased mitral A wave duration/pulmonary venous atrial systolic reversal duration and isovolumic relaxation	
Nodari et al. (22) Nebivolol versus atenolol	6	26	LVEF ≥50%, LVEDD <60 mm or <32 mm/m^2	E/A <1.0 and PCWP rest >12 mm Hg or exercise >20 mm Hg	Nebivolol: Improved exercise capacity (VO_2peak; VO_2AT; VE/VCO_2). Decreased LVED posterior wall thickness. Decreased mPAP and PCWP at rest and exercise. Both: reduced LV mass. Increased E/A. Decreased LVED septal wall thickness	
Yusuf et al. (15) Candesartan	36.6 (median)	3,023	LVEF >40%	Not determined	Reduction in CV death+HF-hospitalization Fewer recurrent HF-hospitalizations	Median 36.6 months: 11.3%/17.1% (for HF)
Bergström et al. (23) Carvedilol	6	97	LVEF >45%, LVWMI ≤1.2	E/A < ARRV or IVRT > ARRV; E/A normal plus PVS/DV < ARRV or PVARD-MAD >20 ms or PVARV > ARRV	Increased E/A	
Mottram et al. (24) Spironolactone	6	30	LVEF >50%	E/A <1 DT >250 m/s	Increased SR and peak systolic strain Decreased LA area and PVARV	
Ahmed et al. (25) Digoxin	37 (mean)	988	LVEF >45%	Not determined	No long-term effect on mortality or HF-hospitalization	Mean 37 months: 23.4%/20% (for HF)
Cleland et al. (16) Perindopril	25.2	850	LVEF >40%, LVWMI 1.4–1.6	LAD >25 mm/m^2 or >40 mm; LVWT ≥12 mm, IVRT >105 ms, E/A <0.5, DT >280 ms	Reduced mortality + HF-hospitalization trend at 1 yr Reduced HF-hospitalization at 1 yr Improved NYHA functional class at 1 yr and 6MWT at 1 yr	1yr: 13.1% combined mortality + HF admission 10.2% HF admission
Massie et al. (17) Irbesartan	49.5	4,128	LVEF ≥45%	LVH and LAD >46 mm in men and 42 mm in women	None	Mean 49.5 months: 36.5% combined mortality + CV admission
Yip et al. (18) Ramipril versus irbesartan	12	151	LVEF >45%	Not determined	Short term increased Em and Sm Decreased NT-proBNP levels at 1 yr	1 yr: 2.7%/ 11.3% (for HF)

Continued on the next page

Table 2 Continued

First Author (Ref. #) Drug	Duration (months)	n	Systolic Function	Diastolic Function as Inclusion Criterion	Positive Outcomes	Mortality/ Readmission
Kitzman et al. (19) Enalapril	12	71	LVEF ≥50%	Not determined	None	
Deswal et al. (26) Eplerenone	6	44	LVEF ≥50%	Not determined	Reduced collagen turnover circulating biomarkers Decreased E/e'	6 months: 0%/ 6.8% (for HF)
Conraads et al. (29) Nebivolol	6	116	LVEF >45% LVEDD <3.2 cc/m^2 or LVEDVI <102 ml/m^2	E/e' >15 or E/e': 8–15 if: E/A <0.5 DT >280 ms	None	
Solomon et al. (31) Neprilysin	3	301	LVEF ≥45%	Not determined	NT-proBNP reduced	3 months: 1%/ 3.3% (for HF)
Yamamoto et al. (30) Carvedilol	38	245	LVEF >40%	Not determined	None	38 months: 25.7% mortality + HF admission
Edelmann et al. (27) Aldosterone	13	422	LVEF ≥50%	Grade ≥1	E/e' declined at 6 months and maintained at 12 months LVEDD and LVM index decreased	
Redfield et al. (28) Sildenafil	6	216	LVEF ≥50%	Not determined	None	
Other Types of Trials						
Kitzman et al. (32) Aerobic exercise	4	53	LVEF ≥50%	Not determined	Improved exercise capacity (VO_2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Increased HRpeak, HRR, O_2 pulse. Improved physical score of MLHFQ	
Edelmann et al. (33) Aerobic and anaerobic exercise	3	64	LVEF ≥50%	Grade ≥1	Improved exercise capacity (VO_2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). Improved E/e'. Decreased LAVI. Improved SF-36 and MLHFQ scores. Reduced procollagen type 1 blood levels	
Smart et al. (34) Aerobic exercise	4	30	LVEF >45%	Delayed relaxation or pseudonormal filling pattern	Increased exercise capacity (VO_2peak, workload). Increased CO. Improved strain rate, SV, and CO, in patients with >10% increase in VO_2peak	
Haykowsky et al. (35) Aerobic exercise	4	40	LVEF ≥50%	Not determined	Improved exercise capacity (VO_2peak). Increased HRpeak, HRR. Increased estimated peak and reserve A-VO_2 Diff and peak and reserve circulatory power	
Fujimoto et al. (36) Aerobic exercise	12	20	LVEF >50%	Not determined	Improved E/A	
Kitzman et al. (37)	4	63	LVEF ≥50%	Not determined	Improved exercise capacity (VO_2peak, workload, exercise time) and submaximal exercise performance (VAT, 6MWT). increased HRpeak, Improved SF-36 score	

6MWT = 6-min walk test; ACEI = angiotensin-converting enzyme inhibitor; ARRV = age-related reference value; A-VO2 Diff = arterial-venous oxygen difference; CO = cardiac output; DT = deceleration time; edv = end-diastolic volumes; Em = peak early diastolic velocity; HRpeak = peak heart rate; HRR = heart rate reserve; IQR = interquartile range; IVRT = isovolumic relaxation time; LAD = left atrial diameter; LAVI = left ventricular atrial volume; LV = left ventricular; LVED = left ventricular end-diastolic; LVEDD = left ventricular end-diastolic diameter; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVM = left ventricular mass; LVWMI = left ventricular wall motion index; LVWT = left ventricular wall thickness; MAD = mitral atrial duration; MI = myocardial infarction; MLHFQ = Minnesota Living with Heart Failure Questionnaire; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; PVARD = pulmonary vein atrial reversal duration; PVARV = pulmonary vein systolic diastolic velocity; PVS/DV = pulmonary vein systolic/diastolic velocity; SF-36 = 36-Item Short Form Health Survey; Sm = peak systolic velocity; SR = strain rate; VAT = ventilatory anaerobic threshold; VE/VCO_2 = ventilatory equivalent for carbon dioxide; VO_2peak = peak oxygen consumption; VO_2AT = oxygen consumption at anaerobic threshold.

Table 3 Potential Phase II Clinical Trial Targets

Parameters	
Left ventricle	
Systolic function	
Ejection fraction	Systolic time intervals
Regional myocardial velocities, strain, systolic strain rate	Isovolumic contraction time
dP/dt	Noninvasive single-beat end-systolic elastance
End-systolic pressure/volume ratio	End-systolic stress–velocity of circumferential fiber shortening relation
Stroke work	Pre-load recruitable stroke work
Diastolic function	
E wave velocity	E/A ratio
E wave deceleration time	Pulmonary venous flow
Color M-mode velocity of propagation	E'
E/e' ratio	Noninvasive single-beat end-systolic elastance
End-diastolic pressure/end-diastolic volume	End-diastolic pressure/stroke volume
Early diastolic strain rate	
Structure	
Left ventricular end-systolic volume index	Left ventricular end-diastolic volume index
Left ventricular mass index	Extracellular volume fraction
Relative wall thickness	LV mass/volume ratio
Left atrium	
Left atrial volume/index (LAVI)	Left atrial strain
A velocity	a' velocity
Left atrial function/index (LAFI)	
Hemodynamics	
Right heart catheterization	
Pulmonary capillary wedge pressure	Pulmonary artery pressure
Pulmonary vascular resistance	Transpulmonary gradient (mPAP-PCWP)
Pulmonary vascular gradient (PADP-PCWP)	
Echocardiogram-derived	
Pulmonary capillary wedge pressure approximation by E/e'	Mean pulmonary artery pressure by end-diastolic pulmonary regurgitation gradient
Systolic pulmonary artery pressure by tricuspid regurgitation gradient	Pulmonary vascular resistance approximation by TR velocity/TVIRVOT ratio or RVSP-E/e'/RVOT VTI
Vascular and endothelial function	
Central pulse pressure	Pulse wave velocity
Flow mediated dilation	Reactive hyperemia index
Augmentation index	
Exercise capacity	
Walking tests	
6-min walk test	Shuttle walking test
Cardiopulmonary exercise test	
VO_2max	VO_2 at anaerobic threshold
VE/VCO_2	Exercise oscillatory breathing (EOB)
Biomarkers	
Cardiac load and wall stress	
Natriuretic peptides	
Cardiac fibrosis and collagen turnover	
Procollagen type I N-terminal pro-peptides	Procollagen type III N-terminal pro-peptides
Matrix metalloproteinases	Tissue inhibitors of matrix metalloproteinases
β-galactoside-binding protein Galectin-3	
Inflammation	
Growth differentiation factor-15	High-sensitivity C-reactive protein
Interleukins	
Myocardial injury	
High-sensitivity troponin T	

LV = left ventricular; mPAP = mean pulmonary artery pressure; PADP = pulmonary artery diastolic pressure; PCWP = pulmonary capillary wedge pressure; RVOT = right ventricular outflow tract; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation; TVIRVOT = right ventricular outflow tract time-velocity integral; VE/VCO_2 = ventilatory equivalent ratio for carbon dioxide; VO_2 = oxygen consumption; VO_2max = maximum oxygen consumption.

admissions compared with HFrEF (63). In these patients, 30% of mortality is noncardiovascular, underscoring the importance of comorbidities.

Whether HFpEF simply represents a collection of comorbidities has been questioned. Campbell et al. (9) compared mortality in HFpEF patients with similar age, sex, and comorbidity distribution to patients enrolled in other cardiovascular trials. Striking differences were found in mortality between non-HFpEF patients (11 to 47 per 1,000 patient-years) and HFpEF mortality rate (53 to 76 per 1,000 patient-years) patients, suggesting that HFpEF risk goes beyond that explained by age and comorbidities. A recent paper suggested that both the cardiac and vascular abnormalities seen in HFpEF may be related to an underlying milieu of systemic inflammation that is related to the combination of various comorbidities seen commonly in HFpEF patients (67).

Therapeutic Targets and Endpoints

Phase II trials. There are many structural and functional targets that may be amenable to novel interventions. Further research is needed to assess the magnitude and the time frame of change in these targets, and how they relate to clinical outcomes (Table 3, Fig. 1).

LEFT VENTRICLE AND LEFT ATRIUM. Multiple LV and LA parameters predict outcomes (Table 4) (51,52,68–71). Diastolic dysfunction, increased LV mass, mass/volume ratio, LA area, diastolic wall stress, and e' that is relatively pre-load independent predict outcomes. One may target the fundamental cellular and molecular signaling pathways that result in increased LV distensibility and improve relaxation, recoil, and filling, and diastolic function. The best way of measuring LV diastolic function to assess therapy remains to be clarified, but may include assessing relaxation, untwist, suction, stiffness, distensibility, compliance, elastance, and ventriculoarterial coupling. Other potential parameters include volume, mass, wall thickness, LVEF, E/e' ratio, e' velocity, and longitudinal strain. Diffuse fibrosis is

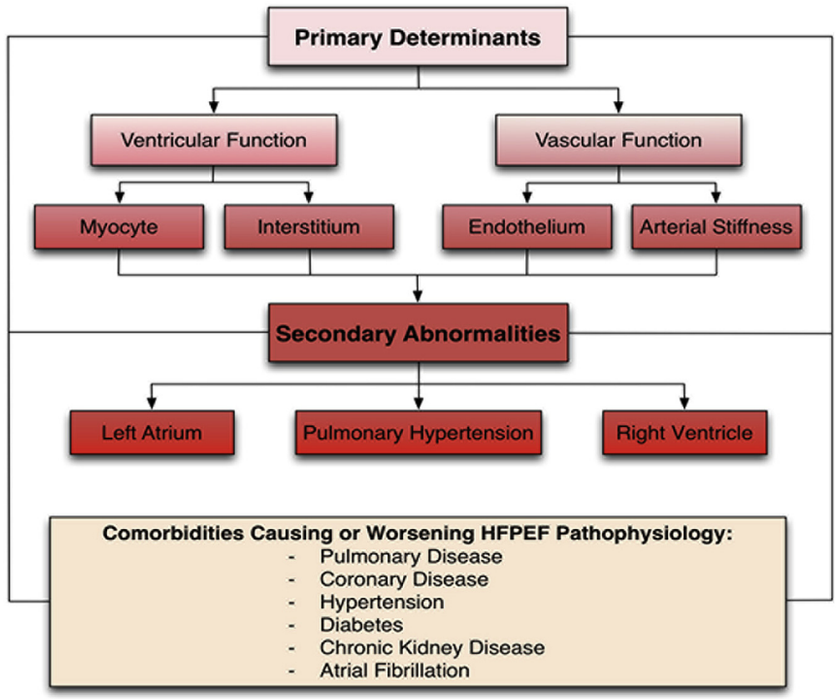

Figure 1 **Potential Therapeutic Targets in HFpEF**

HFpEF = heart failure with preserved ejection fraction.

prognostically important (72,73). Dynamic measures of LV function may be normal at rest but become abnormal during exercise. The role of exercise in improving surrogate markers of LV function in clinical trials needs studying. Changes in LA size may integrate extent and duration of increased diastolic pressure and changes related to diastolic dysfunction, mitral regurgitation, and atrial fibrillation. Magnetic resonance imaging, tissue Doppler techniques including transmitral flow (A velocity) and longitudinal velocity of the mitral annulus attributable to LA systolic function (tissue Doppler a' velocity), and speckle-tracking echocardiography can provide insight through analysis of regional and global LV and LA function. A comprehensive list of variable for patients with HFpEF is presented in Figure 2.

HEMODYNAMICS. HF is characterized by altered hemodynamics. Detailed analysis of contractility, relaxation, and volumes require methods such as conductance catheters, which show impaired adaptation including blunted increase in stroke volume with heart rate in HFpEF (74). Exercise during hemodynamic assessment may unmask HFpEF (45). Data in acute HFpEF are limited. Increases in intracardiac pressures occur days before the onset of clinical signs and symptoms. Information from an implanted pulmonary artery pressure sensor was associated with a 30% reduction in HF hospitalization at 6 months and 38% per year; 23% of participants had HFpEF in this study (75). Continuous hemodynamic monitoring-based management strategy (76) showed a nonsignificant 21% reduction in HF hospitalizations; 25% of participants had HFpEF.

VASCULAR AND ENDOTHELIAL FUNCTION. Higher pulse pressure is seen in HFpEF (77). Increased pulse wave velocity and augmentation index are associated with systolic and diastolic dysfunction. Impaired flow-mediated dilation and changes in peripheral artery tonometry are associated with worse outcomes in HF (78).

BIOMARKERS. Collagen expression is increased in HFpEF and increases in collagen-related biomarkers are associated with hypertrophy and diastolic dysfunction. The association between galectin-3 and the risk of mortality and readmission is stronger in HFpEF than HFrEF (79). In animal models, galectin-3 was causally implicated in the HFpEF pathophysiology, suggesting galectin-3 as a possible target. Inhibition of galectin-3 is associated with attenuation of diastolic dysfunction and LV fibrosis (80). Several other collagen-related biomarkers correlate with higher risk (81). Other biomarkers that reflect different mechanisms and may be useful in HFpEF include growth differentiation factor-15, ST2, and cardiac troponins.

Natriuretic peptides (NPs) are lower in HFpEF, and many patients have B-type NP levels of <100 pg/ml (82). Irbesartan is associated with improved outcomes in patients

Table 4 Echocardiographic Changes, Biomarkers, and Prognosis of Heart Failure With Preserved Ejection Fraction

Marker (Method)	First Author (Ref. #)	Population	Outcome	Predictive Properties HR (95% CI)
E/A (severity of DD) (echocardiography)	Persson et al. (51)	293 HF patients with LVEF >40% participating in CHARMES	Composite CV mortality or HF admission	Moderate or severe DD 3.27 (1.41–7.56)*
e' (echocardiography)	Wang et al. (71)	174 hypertensive individuals with LVH	Cardiac mortality	0.49 (0.32–0.76)†
LV mass‡ (echocardiography) LV mass/volume (echocardiography) Enlarged LA‖ (echocardiography)	Zile et al. (52)	745 HF patients with LVEF ≥45% participating in I-PRESERVE	All-cause mortality or hospitalization for worsening HF, MI, stroke, unstable angina, or ventricular or atrial dysrhythmia	1.019 (1.009–1.029)§ 1.296 (1.074–1.564) § 1.470 (1.029–2.101) §
LAD¶ (echocardiography)	Rossi et al. (69)	183 HF patients with LVEF >45%	All-cause mortality	2.45 (1.12–5.41)#
Diastolic wall stress** (echocardiography)	Ohtani et al. (70)	327 HF patients with LVEF ≥50%	Composite CV mortality or HF admission	1.03 (1.01–1.06)††
Natriuretic peptides (blood sample analysis)	Grewal et al. (68)	181 HF patients with LVEF >40% participating in CHARMES	Composite CV mortality or HF admission or MI or stroke	NT-proBNP >300 pg/ml 5.8 (1.3–26.4) NT-proBNP >600 pg/ml 8.0 (2.6–24.8) BNP >100 pg/ml 3.1 (1.2–8.2)

*After adjustment for age, sex, left ventricular ejection fraction (LVEF), diabetes mellitus, atrial fibrillation, previous heart failure (HF) admission, and treatment arm. †After adjustment for age, and interventricular septal thickness in diastole, LVEF, peak velocity during systole, peak velocity during late diastole, peak E-wave velocity to peak velocity during early diastole ratio (E/Em), and pseudonormal diastolic filling pattern or restrictive diastolic filling pattern. ‡Indexed to height$^{2.7}$. §After adjustment for log N-terminal pro–B-type natriuretic peptide (NT-proBNP), age, diabetes mellitus, hospitalization for worsening HF within 6 months preceding randomization, chronic obstructive pulmonary disease or asthma, neutrophils, and LVEF. ‖Mildly enlarged left atrium (LA) if LA area was 20 to 30 cm^2 and moderately to severely enlarged LA if LA area was >31 cm^2. ¶LA diameter >5 cm used to define LA enlargement. #After adjustment for clinical and echocardiographic parameters. **Diastolic wall stress was defined as the ratio of the posterior wall thickness at end-systole minus the posterior wall thickness at end-diastole to the posterior wall thickness at end-systole. ††After adjustment for age, sex, echocardiographic variables, and log B-type natriuretic peptide (BNP).

CHARMES = CHARM Echocardiographic Substudy; CI = confidence interval; CV = cardiovascular; DD = diastolic dysfunction; HR = hazard ratio; I-PRESERVE = Irbesartan in Heart Failure With Preserved Systolic Function; LVH = left ventricular hypertrophy; MI; myocardial infarction.

with NP levels below but not above the median (83). The role of NP as a marker of potential responders is being investigated. In the PARAMOUNT trial, N-terminal pro–B-type NP was reduced more with LCZ696 than valsartan (31). NP may be normal or near normal in symptomatic HFpEF patients but indicate poor outcome once elevated. Selection of patients on the basis of elevated NP may identify a cohort with higher risk, and lowering NPs may be a target. This needs to be studied, however, because patients with elevated NP levels may have advanced HFpEF with fibrosis and/or atrial fibrillation, which will make the myocardium less responsive to intervention.

EXERCISE CAPACITY. Exercise training studies show that the improved arterial-venous oxygen difference after exercise may be responsible for the improved exercise capacity. The exact underlining mechanisms for this are uncertain, and improved peripheral vascular microvascular function and/or increased oxygen utilization has been proposed. Skeletal muscles can be relatively rapidly rejuvenated and represent a possible target for interventions. Symptom limited exercise tests offer important information about the maximum exercise capacity whereas submaximal tests provide information about the ability to independently complete daily activities. In the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot trial, 3 months of exercise training improved exercise capacity in HFpEF (33).

COMORBIDITIES. Important targets for HFpEF treatment include comorbidities. The benefits of treating hypertension and coronary disease are known. Treatment with continuous positive airway pressure may reverse diastolic dysfunction in sleep apnea (84). Maintaining sinus rhythm, and if not possible then rate control, is important. Catheter ablation of atrial fibrillation improves diastolic function (85). Renal denervation has shown promise in animal models, but specific human HFpEF data are lacking. Treatment of cardiometabolic diseases also represents potential targets.

Phase III trials. Mortality and hospitalization rates remain important targets; however, most patients with HFpEF are elderly and many will die of conditions other than HF. Improving symptoms and maintaining independence and exercise capacity are important for this population. A novel endpoint focusing on the "patient journey" should be developed and tested.

The goals for HFpEF treatment remain only partially understood. These patients are generally older and the competing risk for death is substantial. Targeting HFpEF-related abnormalities may improve physiology and patient status but not mortality. Due to increased HF readmission scrutiny, care is increasingly being shifted to other venues. Also, the determinants of quality of life in general depend on issues larger than any specific disease process, and data in this regard are problematic (e.g., patients using tobacco report better quality of life [86] defibrillators may worsen quality of life but improve survival, and inotropes improve symptoms but worsen mortality). Though all of these remain important endpoints, considering their limitations, there is a need to develop new endpoints. The common HFpEF

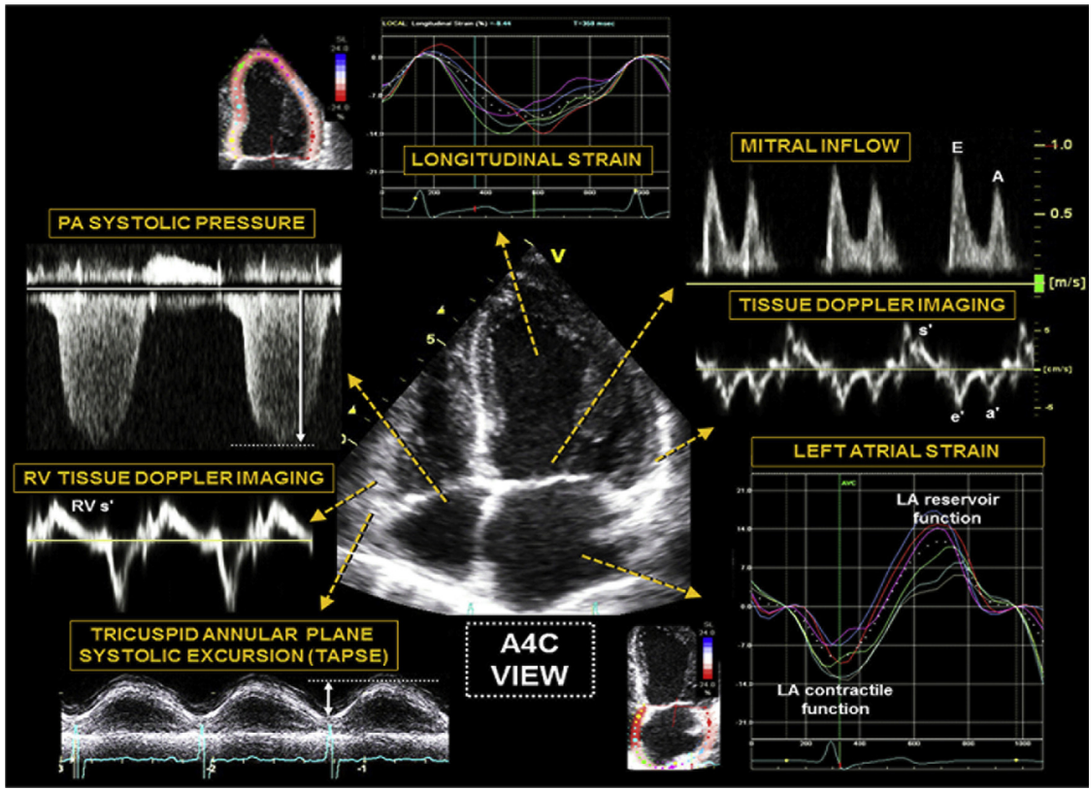

Figure 2 **Comprehensive Echocardiographic Phenotypic Analysis of Heart Failure With Preserved Ejection Fraction**

Comprehensive echocardiography, including 2-dimensional, Doppler, tissue Doppler, and speckle tracking, allows for detailed phenotypic analysis of cardiac structure, function, and mechanics in patients with heart failure with preserved ejection fraction. The figure shows examples of information that can be obtained from the apical 4-chamber (A4C) view. Clockwise from the top: speckle-tracking echocardiography for assessment of left ventricular (LV) regional and global longitudinal strain (early diastolic strain rate can also be obtained in this view). Mitral inflow and tissue Doppler imaging of the septal and lateral mitral annulus provide information on LV diastolic function grade and estimated LV filling pressure (E/e' ratio), along with assessment of longitudinal systolic (s') and atrial (a') function. Speckle-tracking analysis of left atrial (LA) function provides peak LA contractile function (peak negative longitudinal LA strain) and LA reservoir function (peak positive longitudinal LA strain). Tricuspid annular plane systolic function (TAPSE) and basal right ventricular (RV) free wall peak longitudinal tissue Doppler velocity (RV s') provide information on longitudinal RV function, as does speckle tracking echocardiography of the RV (not shown). Finally, analysis of the tricuspid regurgitant jet Doppler profile, when added to the estimated right atrial (RA) pressure, provides an estimate of the PA systolic pressure. Additional data available from the apical 4-chamber view include assessment of LV volumes and ejection fraction, LA volume, and RV size and global systolic function (e.g., RV fractional area change). PA = pulmonary artery. Figure courtesy of Sanjiv J. Shah, MD.

manifestation includes worsening congestion, requirement to frequently alter therapy, declining functionality, and end-organ dysfunction. One may develop an endpoint that is both related to HF and responsive to changes over time, acting not as a surrogate for *hard outcomes* but as an additional *primary* outcome. The pertinent domains of such an endpoint may include cardiac structure and function, congestion and medication status, and functionality. Designing, scoring, and validating such an endpoint needs further research.

Clinical Trial Protocol Development and Conduct

Careful attention should be focused on clinical trial protocol development, patient selection, and the trial execution.

Hospitalized HF. Whether patients with dyspnea who have preserved EF truly have HFpEF in the outpatient setting is often debated. The criteria used to select patients in previous trials have varied (Table 5), and most included a clinical diagnosis and an LVEF above a certain threshold, which in turn also varied and was arbitrary. In contrast, hospitalized patients with obvious fluid overload may provide a more definitive HFpEF population, who are also at a significantly higher risk. There is a tremendous need to identify HFpEF treatment in general, but especially in patients who are hospitalized.

Need for sustained therapies. For the most part, only transient intravenous therapies have been studied in hospitalized patients. Most of these did not improve outcomes, with the exception of serelaxin. In the RELAX-AHF (Relaxin in Acute Heart Failure) trial (87), about 45% of patients had LVEF ≥40%, hence representing 1 potential avenue to treat hospitalized HFpEF patients. However, considering the continued worsening post-discharge outcomes, oral long-term therapies are needed to improve

Table 5 Inclusion Criteria in Randomized Clinical Trials for Patients With Heart Failure With Preserved Ejection Fraction

First Author (Ref. #)	Inclusion Criteria	First Author (Ref. #)	Inclusion Criteria
Setaro et al. (20)	Not determined etiology LVEF >45%* LV peak filling rate >2.5 edv/s	Aronow and Kronzon (13)	Prior MI (>6 months) LVEF >50%
Aronow et al. (14)	Prior MI (>6 months) LVEF ≥40%	Hung et al. (21)	LVEF >50%
Nodari et al. (22)	Mild hypertension VO_2peak ≤25 ml/kg/min LVEF ≥ 50% LVEDD <60 mm or <32 mm/m^2 E/A <1.0 PCWP rest >12 mm Hg or exercise >20 mm Hg	Yusuf et al. (15)	LVEF >40%
Bergström et al. (23)	LVEF >45% LVWMI ≤1.2† At least 1 of the following: • E/A < ARRV • IVRT > ARRV • E/A normal plus PVS/DV < ARRV or PVARD-MAD >20 ms or PVARV > ARRV	Mottram et al. (24)	Hypertension requiring antihypertensive medication and exertional dyspnea No MI or angina LVEF >50% E/A <1 DT >250 m/s
Little et al. (88)	LVEF >50%	Ahmed et al. (25)	In sinus rhythm LVEF >45%
Cleland et al. (16)	At least 2 of the following criteria • LVEF >40% • LVWMI: 1.4–1.6 • LAD >25 mm/m^2 or >40 mm • LVWT ≥12 mm At least 1 of the following criteria • E/A <0.5 • Isovolumic relaxation time >105 ms	Massie et al. (17)	LVEF ≥45% LVH LAD >46 mm in men and >42 mm in women
Zile et al. (89)	LVEF ≥50%	Yip et al. (18)	LVEF >45%
Kitzman et al. (19)	No other conditions (cardiac/pulmonary/other) that could mimic HF LVEF ≥50%	Kitzman et al. (32)	No other conditions (cardiac/pulmonary/other) that could mimic HF LVEF ≥50%
Orozco-Gutierrez et al. (90)	LVEF ≥45% Fractional shortening ≥28% LAD >45 mm LV septal and posterior thickness >12 mm Slow, inverted, pseudonormal, or restrictive pattern of transmitral Doppler flow	Deswal et al. (26)	LVEF ≥50% BNP ≥100 pg/ml
Guazzi et al. (91)	In sinus rhythm LVEF ≥50% SPAP ≥40 mm Hg	Desai et al. (92)	LVEF ≥45% BNP ≥100 pg/ml or NT-proBNP ≥360 pg/ml
Conraads et al. (29)	LVEF >45% LVEDD <3.2 cc/m^2 or LVEDVI <102 ml/m^2 E/e' >15 or E/e': 8–15 if: • E/A <0.5 in patients >50 yrs • DT >280 ms in patients >50 yrs • Ard-Ad >30 ms • LAVI >40 ml/m^2 • LVMI >149 g/m^2 and >122 g/m in women	Solomon et al. (31)	LVEF ≥45% NT-proBNP >400 pg/ml
Smart, 2012 (34)	LVEF >45% Delayed relaxation or pseudonormal filling	Yamamoto et al. (30)	LVEF >40%
Edelmann et al. (27)	LVEF ≥50% Diastolic dysfunction grade ≥1 or atrial fibrillation VO_2peak ≤25 ml/kg/min	Redfield et al. (28)	LVEF ≥50% LA enlargement VO_2peak ≤60%‡ NT-proBNP ≥400 pg/ml or NT-proBNP <400 pg/ml PCWP 20 mm Hg at rest and >25 mm Hg at exercise
Maurer et al., 2013 (93)	LVEF >40%		

*Determined by radionuclide ventriculograms. †Determined as akinesia of ≤ 1 segment or hypokinesia of ≤ 2 segments , using a 16-segment model with at least 10 segments visible. ‡Based on the age- and sex-specific normal value while respiratory exchange ration is ≥1.0. Bulleted items indicate where 1 or more diagnostic findings can be sued to fulfill a criterion.

Ard-Ad = reverse pulmonary vein atrial systole flow–mitral valve atrial wave flow; ARRV = age-related reference value; BNP = B-type natriuretic peptide; DT = deceleration time; edv = end-diastolic volumes; HF = heart failure; IVRT = isovolumic relaxation time; LAD = left atrial diameter; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVWMI = left ventricular wall motion index; LVWT = left ventricular wall thickness; MAD = mitral atrial duration; MI = myocardial infarction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PCWP = pulmonary capillary wedge pressure; PVARD = pulmonary vein atrial reversal duration; PVARV = pulmonary vein systolic diastolic velocity; PVS/DV = pulmonary vein systolic/diastolic velocity; SPAP = pulmonary artery systolic pressure; VO_2peak = peak oxygen consumption.

outcomes. Length of hospital stay, degree of decongestion at discharge, changes in standard treatment, and post-discharge monitoring, all bring additional heterogeneities that need consideration in trial conduct.

Study population. It is important to identify the drivers of adverse events in HFpEF. Determining how the risks can be identified with routine parameter versus specific tests (e.g., exercise pulmonary pressure measurement), needs study. It is unclear whether patients with a specific cause leading to admission (e.g., hypertensive emergency or tachyarrhythmia) should be included in trials. Other markers such as wedge pressure remain ill characterized (e.g., how high does it need to be at rest or exercise to identify a responder population and how does its role differ in hospitalized vs. ambulatory patients). Biomarkers may be helpful, but most have often been mostly validated in HFrEF and their role may differ in HFpEF, necessitating better characterization in this population.

Summary

HFpEF prevalence is increasing, and these patients face impaired health status and an unabated high risk for adverse outcomes. The economic burden of HFpEF is substantial. To date, there is no approved therapy for these patients. To identify new therapies, a deeper understanding of the subpopulations that fit under the HFpEF umbrella, and more specific molecular targets for engagement, are needed. The following are the summary recommendations from the meeting:

1. There is an urgent need to focus on drug and device development for HFpEF and clinical, translational, and basic research should receive a high priority for support from academia, industry, nongovernmental organizations, and federal agencies.
2. The diagnostic certainty and the high post-discharge event rate identify hospitalized HFpEF patients as a particularly important HFpEF population.
3. Currently, there are no animal models that sufficiently approximate the HFpEF syndrome to allow drug and device testing before application to human studies. Research to develop relevant animal models is needed.
4. The lack of animal models should not, however, prevent human testing of promising therapies. To promote fundamental understanding, animal models of HFpEF should be developed alongside attempts to understand better the clinical phenotypes of HFpEF.
5. There is a need to characterize HFpEF further to understand better clinical manifestations, contribution of comorbidities, and mechanisms. This may aid development of objective classification of HFpEF. Developing longitudinal registries focused on collecting clinical, imaging, laboratory, treatment patterns and outcomes data may facilitate this.
6. There are many potential cardiovascular structural and functional targets for phase II trials. However, their responsiveness to change and correlation with phase III outcomes are not known. All phase II HFpEF studies should consider incorporating a set of cardiovascular structural and functional parameters, biomarkers, and functional capacity indicators to improve our understanding of the basic mechanisms of the disease. Currently, there is no consensus in this regard, necessitating the need for a dialogue between academia, industry, and regulators.
7. Though many mechanisms for the development and progression of HFpEF are cited (e.g., endothelial dysfunction), data for them are sparse, underscoring the need for further human mechanistic studies.
8. Further data are needed to understand the differences between hospitalized and stable outpatients with HFpEF, and the triggers for decompensation, to develop new therapies.
9. Novel phase III outcome measures that supplement mortality and hospitalization risk, and incorporate features reflective of the "patient journey" with HFpEF longitudinally, should be developed.
10. Careful patient selection and a focus on safety in drug development are important considerations in HFpEF.

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REFERENCES

1. Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation 2012;126:65–75.
2. Philbin EF, Rocco TA Jr., Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. Am J Med 2000;109:605–13.
3. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.
4. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47:76–84.
5. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

6. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260–9.
7. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768–77.
8. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005;112:3738–44.
9. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol 2012;60:2349–56.
10. Zile MR, Gaasch WH, Anand IS, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. Circulation 2010;121:1393–405.
11. Farr MJ, Lang CC, Lamanca JJ, et al. Cardiopulmonary exercise variables in diastolic versus systolic heart failure. Am J Cardiol 2008;102:203–6.
12. Lewis EF, Lamas GA, O'Meara E, et al. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. Eur J Heart Fail 2007;9:83–91.
13. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. Am J Cardiol 1993;71:602–4.
14. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol 1997;80:207–9.
15. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.
16. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338–45.
17. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–67.
18. Yip GW, Wang M, Wang T, et al. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. Heart 2008;94:573–80.
19. Kitzman DW, Hundley WG, Brubaker PH, et al. A randomized double-blind trial of enalapril in older patients with heart failure and preserved ejection fraction: effects on exercise tolerance and arterial distensibility. Circ Heart Fail 2010;3:477–85.
20. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol 1990;66:981–6.
21. Hung MJ, Cherng WJ, Kuo LT, Wang CH. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. Int J Clin Pract 2002;56:57–62.
22. Nodari S, Metra M, Dei Cas L. Beta-blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized, comparison of the long-term effects of atenolol vs. nebivolol. Eur J Heart Fail 2003;5:621–7.
23. Bergstrom A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail 2004;6:453–61.
24. Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. Circulation 2004;110:558–65.
25. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006;114:397–403.
26. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). J Card Fail 2011;17:634–42.
27. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 2013;309:781–91.
28. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013;309:1268–77.
29. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail 2012;14:219–25.
30. Yamamoto K, Origasa H, Hori M. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail 2013;15:110–8.
31. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387–95.
32. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail 2010;3:659–67.
33. Edelmann F, Gelbrich G, Dungen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011;58:1780–91.
34. Smart NA, Haluska B, Jeffriess L, Leung D. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. Congest Heart Fail 2012;18:295–301.
35. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. J Am Coll Cardiol 2012;60:120–8.
36. Fujimoto N, Prasad A, Hastings JL, et al. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. Am Heart J 2012;164:869–77.
37. Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol 2013;62:584–92.
38. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol 2010;56:845–54.
39. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. J Am Coll Cardiol 2010;56:855–63.
40. Paulus WJ. Culprit mechanism(s) for exercise intolerance in heart failure with normal ejection fraction. J Am Coll Cardiol 2010;56:864–6.
41. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115:1982–90.
42. van Heerebeek L, Borbely A, Niessen HW, et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation 2006;113:1966–73.
43. Kotter S, Gout L, Von Frieling-Salewsky M, et al. Differential changes in titin domain phosphorylation increase myofilament stiffness in failing human hearts. Cardiovasc Res 2013;99:648–56.

44. Chung CS, Hutchinson KR, Methawasin M, et al. Shortening of the elastic tandem immunoglobulin segment of titin leads to diastolic dysfunction. Circulation 2013;128:19–28.
45. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588–95.
46. Bruch C, Stypmann J, Grude M, Gradaus R, Breithardt G, Wichter T. Left bundle branch block in chronic heart failure-impact on diastolic function, filling pressures, and B-type natriuretic peptide levels. J Am Soc Echocardiogr 2006;19:95–101.
47. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. Heart Fail Clin 2008;4:23–36.
48. Shah SJ. Evolving approaches to the management of heart failure with preserved ejection fraction in patients with coronary artery disease. Curr Treat Options Cardiovasc Med 2010;12:58–75.
49. Tamarappoo BK, John BT, Reinier K, et al. Vulnerable myocardial interstitium in patients with isolated left ventricular hypertrophy and sudden cardiac death: a postmortem histological evaluation. J Am Heart Assoc 2012;1:e001511.
50. Thum T, Gross C, Fiedler J, et al. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature 2008;456:980–4.
51. Persson H, Lonn E, Edner M, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic Substudy-CHARMES. J Am Coll Cardiol 2007;49:687–94.
52. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation 2011;124:2491–501.
53. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. J Am Coll Cardiol 2007;49:198–207.
54. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness;definitions and reference values. Am J Hypertens 2002;15:426–44.
55. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation 2005;112:2254–62.
56. Balmain S, Padmanabhan N, Ferrell WR, Morton JJ, McMurray JJ. Differences in arterial compliance, microvascular function and venous capacitance between patients with heart failure and either preserved or reduced left ventricular systolic function. Eur J Heart Fail 2007;9:865–71.
57. Akiyama E, Sugiyama S, Matsuzawa Y, et al. Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol 2012;60:1778–86.
58. Lam CS, Brutsaert DL. Endothelial dysfunction: a pathophysiologic factor in heart failure with preserved ejection fraction. J Am Coll Cardiol 2012;60:1787–9.
59. Borlaug BA, Kass DA. Mechanisms of diastolic dysfunction in heart failure. Trends Cardiovasc Med 2006;16:273–9.
60. Guazzi M, Arena R. Pulmonary hypertension with left-sided heart disease. Nat Rev Cardiol 2010;7:648–59.
61. Abel FL, Waldhausen JA. Effects of alterations in pulmonary vascular resistance on right ventricular function. J Thorac Cardiovasc Surg 1967;54:886–94.
62. Morris DA, Gailani M, Vaz Perez A, et al. Right ventricular myocardial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. J Am Soc Echocardiogr 2011;24:886–97.
63. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59:998–1005.
64. Mohammed SF, Borlaug BA, Roger VL, et al. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. Circ Heart Fail 2012;5:710–9.
65. Lam CS, Lyass A, Kraigher-Krainer E, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation 2011;124:24–30.
66. McManus DD, Hsu G, Sung SH, et al. Atrial fibrillation and outcomes in heart failure with preserved versus reduced left ventricular ejection fraction. J Am Heart Assoc 2013;2:e005694.
67. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263–71.
68. Grewal J, McKelvie RS, Persson H, et al. Usefulness of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide to predict cardiovascular outcomes in patients with heart failure and preserved left ventricular ejection fraction. Am J Cardiol 2008;102:733–7.
69. Rossi A, Cicoira M, Florea VG, et al. Chronic heart failure with preserved left ventricular ejection fraction: diagnostic and prognostic value of left atrial size. Int J Cardiol 2006;110:386–92.
70. Ohtani T, Mohammed SF, Yamamoto K, et al. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction. Eur Heart J 2012;33:1742–9.
71. Wang M, Yip GW, Wang AY, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. J Hypertens 2005;23:183–91.
72. Wong TC, Piehler K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. Circulation 2012;126:1206–16.
73. Wong TC, Piehler KM, Kang IA, et al. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. Eur Heart J 2013; June 11 [E-pub ahead of print].
74. Wachter R, Schmidt-Schweda S, Westermann D, et al. Blunted frequency-dependent upregulation of cardiac output is related to impaired relaxation in diastolic heart failure. Eur Heart J 2009;30:3027–36.
75. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658–66.
76. Bourge RC, Abraham WT, Adamson PB, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol 2008;51:1073–9.
77. Sweitzer NK, Lopatin M, Yancy CW, Mills RM, Stevenson LW. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (> or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. Am J Cardiol 2008;101:1151–6.
78. Katz SD, Hryniewicz K, Hriljac I, et al. Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. Circulation 2005;111:310–4.
79. de Boer RA, Lok DJ, Jaarsma T, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. Ann Med 2011;43:60–8.
80. Yu L, Ruifrok WP, Meissner M, et al. Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. Circ Heart Fail 2013;6:107–17.
81. Krum H, Elsik M, Schneider HG, et al. Relation of peripheral collagen markers to death and hospitalization in patients with heart failure and preserved ejection fraction: results of the I-PRESERVE collagen substudy. Circ Heart Fail 2011;4:561–8.
82. Anjan VY, Loftus TM, Burke MA, et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. Am J Cardiol 2012;110:870–6.
83. Anand IS, Rector TS, Cleland JG, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. Circ Heart Fail 2011;4:569–77.
84. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation 2005;112:375–83.

85. Cha YM, Wokhlu A, Asirvatham SJ, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. Circ Arrhythm Electrophysiol 2011;4:724–32.
86. Allen LA, Gheorghiade M, Reid KJ, et al. Identifying patients hospitalized with heart failure at risk for unfavorable future quality of life. Circ Cardiovasc Qual Outcomes 2011;4:389–98.
87. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet 2013;381:29–39.
88. Little WC, Zile MR, Kitzman DW, Hundley WG, O'Brien TX, Degroof RC. The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure. J Card Fail 2005;11:191–5.
89. Zile MR, Bourge RC, Bennett TD, et al. Application of implantable hemodynamic monitoring in the management of patients with diastolic heart failure: a subgroup analysis of the COMPASS-HF trial. J Card Fail 2008;14:816–23.
90. Orozco-Gutierrez JJ, Castillo-Martinez L, Orea-Tejeda A, et al. Effect of L-arginine or L-citrulline oral supplementation on blood pressure and right ventricular function in heart failure patients with preserved ejection fraction. Cardiol J 2010;17:612–8.
91. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation 2011;124:164–74.
92. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. Am Heart J 2011;162:966–972.e10.
93. Maurer MS, Teruya S, Chakraborty B, Helmke S, Mancini D. Treating anemia in older adults with heart failure with a preserved ejection fraction with epoetin alfa: single-blind randomized clinical trial of safety and efficacy. Circ Heart Fail 2013;6:254–63.

Key Words: epidemiology ■ heart failure ■ preserved ejection fraction ■ prognosis ■ treatment.

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Head-to-Head Comparison of Serial Soluble ST2, Growth Differentiation Factor-15, and Highly-Sensitive Troponin T Measurements in Patients With Chronic Heart Failure

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Objectives This analysis aimed to perform a head-to-head comparison of 3 of the promising biomarkers of cardiovascular (CV) outcomes in heart failure (HF)—soluble ST2 (sST2), growth differentiation factor (GDF)-15, and highly-sensitive troponin T (hsTnT)—and to evaluate the role of serial measurement of these biomarkers in patients with chronic HF.

Background sST2, GDF-15, and hsTnT are strongly associated with CV outcomes in HF.

Methods This post-hoc analysis used data from a study in which 151 patients with chronic HF due to left ventricular systolic dysfunction were followed up over 10 months. At each visit, N-terminal pro–B-type natriuretic peptide (NT-proBNP), sST2, GDF-15, and hsTnT were measured and any major CV events were recorded.

Results Baseline values of all 3 novel biomarkers independently predicted total CV events even after adjusting for clinical and biochemical characteristics, including NT-proBNP, with the best model including all 3 biomarkers ($p < 0.001$). Adding serial measurement to the base model appeared to improve the model's predictive ability (with sST2 showing the most promise), but it is not clear whether this addition is a unique contribution. However, when time-dependent factors were included, only sST2 serial measurement independently added to the risk model (odds ratio: 3.64; 95% confidence interval: 1.37 to 9.67; $p = 0.009$) and predicted reverse myocardial remodeling (odds ratio: 1.22; 95% confidence interval: 1.04 to 1.43; $p = 0.01$).

Conclusions In patients with chronic HF, baseline measurement of novel biomarkers added independent prognostic information to clinical variables and NT-proBNP. Only serial measurement of sST2 appeared to add prognostic information to baseline concentrations and predicted change in left ventricular function. (Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting (PROTECT)]; NCT00351390). (J Am Coll Cardiol HF 2014;2:65–72) © 2014 by the American College of Cardiology Foundation

The introduction of B-type natriuretic peptide and N-terminal pro–B-type natriuretic peptide (NT-proBNP) as biomarkers of heart failure (HF) has dramatically altered the standard of care for HF patients. Inclusion of these biomarkers in determining the diagnosis and prognosis in HF is now a frequent element of standard HF care. Additionally, a decrease in natriuretic peptide levels with proven HF therapy and parallel improvement in prognosis has led to the concept of biomarker-"guided" HF management, with promising results (1).

Fueled by this success of natriuretic peptides, together with an accumulation of data regarding the pathophysiology of HF development and progression, there has been a surge of interest in novel HF biomarkers. Promising novel biomarkers for HF evaluation include soluble ST2 (sST2), growth differentiation factor (GDF)-15, and highly-sensitive troponin T (hsTnT). Each has a growing body of data supporting its use, and sST2 and troponin measurements were both recently included in the American College of Cardiology/American Heart Association guidelines for the evaluation of HF (2).

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Abbreviations and Acronyms

AIC = Akaike information criterion

CV = cardiovascular

GDF = growth differentiation factor

HF = heart failure

hsTnT = highly-sensitive troponin T

LV = left ventricular

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro–B-type natriuretic peptide

NYHA = New York Heart Association

sST2 = soluble ST2

Elevated circulating concentrations of all 3 markers have been closely linked with adverse clinical outcomes, with an ability to predict prognosis often surpassing that of the natriuretic peptides; change in the concentration of each also appears to predict prognosis, suggesting that their serial measurement could potentially be of use for HF evaluation and management (3–5).

Despite the growing number of studies that have explored sST2, GDF-15, and hsTnT in chronic HF, almost nothing is known regarding the value of their measurement at more than 2 time points, and data regarding a direct comparison between all 3 novel biomarkers in a multimarker analysis are lacking. Further, despite biological links to myocardial remodeling, it is unclear whether any of these biomarkers can predict changes in left ventricular (LV) structure and function. Lastly, it is not known whether medications commonly used for HF affect concentrations of the biomarkers. It is in this context that we aimed to characterize serial measurements of sST2, GDF-15, and hsTnT at multiple time points in the cohort from the PROTECT (ProBNP Outpatient Tailored Chronic Heart Failure study (1,6).

Methods

Study design and patient population. The PROTECT study was a prospective, randomized, controlled, single-center trial of 151 patients with New York Heart Association (NYHA) functional class II to IV symptoms and left ventricular ejection fraction (LVEF) ≤40%; the study was designed to evaluate NT-proBNP–guided HF management versus standard HF care over the course of 10 months (1). These patients were recruited in the outpatient clinic if they had a history of recent HF decompensation. The primary endpoint of the PROTECT study and this post-hoc analysis was *total cardiovascular (CV) events*—a composite outcome defined as worsening HF (new or worsening symptoms/signs of HF requiring unplanned intensification of decongestive therapy), hospitalization for acutely decompensated HF, clinically significant ventricular arrhythmia, acute coronary syndromes, cerebral ischemia, and cardiac death. For secondary analysis, *time to first CV event* was used as a secondary outcome. There were a total of 160 endpoints in the PROTECT study, and 15 patients had a single event, 18 patients had 2 events, 9 patients had 3 events, 7 patients had 4 events, 8 patients had 5 events, 1 patient had 6 events, and another patient had 8 events. Total number of events for the PROTECT study (1) was updated to reflect a correction to a coding issue. The Partners Healthcare Institutional Review Board approved all study procedures, and all patients gave informed consent.

Study procedures. Study subjects were seen every 3 months at a minimum and more frequently as needed to achieve an aggressive guideline-compliant medication regimen. At each visit, a detailed medication list and a blood sample for routine laboratory tests and biomarker measurements were obtained. An echocardiogram was performed at study enrollment and at the final follow-up visit when possible; LVEF, LV end-systolic volume index, and LV end-diastolic volume index were measured.

Biomarker measurement. Plasma was sampled at each visit and stored at −80°C with a single freeze-thaw cycle. A total of 145 patients had at least 2 plasma samples. (Online Table 1 reports the number of blood samples available at 0, 3, 6, and 9 months.) Biomarkers measured included NT-proBNP (Elecsys proBNP, Roche Diagnostics, Indianapolis, Indiana), sST2 (Critical Diagnostics, San Diego, California; coefficient of variation ≤1.4%), GDF-15 (Roche Diagnostics, Rotkreuz, Switzerland; coefficient of variation ≤2.3%), and a 5th-generation hsTnT (Roche Diagnostics; coefficient of variation ≤6.2% at the 99th percentile). The lot of hsTnT reagents used for our analysis were affected by calibration issues, as reported (7); to address this, a new standard curve was utilized to recalibrate concentrations.

Prognostic thresholds. For our initial analysis, consistent with results found in the prior literature, concentrations of sST2, GDF-15, and hsTnT were expressed relative to previously defined thresholds for each; the cutoff points were 35 ng/ml for sST2, 2,000 ng/l for GDF-15, and 14 pg/ml for hsTnT. *Patient response* was defined as achievement of a concentration below each cutoff point subsequent to baseline; thus, responders had concentrations below the cutoff, whereas nonresponders had concentrations above.

In a more comprehensive analysis, to evaluate whether there may be other relevant prognostic thresholds, we examined each novel biomarker as a continuous variable as well as a categorical variable. The changes in concentrations over time were also treated as continuous variables (absolute change and percent change from baseline) as well as categorical variables (study-determined optimal cutoff points as determined by receiver-operating characteristic curve analysis and the optimal area under the curve, and change greater than literature-defined biological variability of sST2 >30% increase from baseline, GDF-15 >7% increase from baseline and hsTnT >85% increase from baseline [8–11]).

Because we had the benefit of multiple measurements across an extended period of time for each subject, a *percent time in response* for each biomarker was derived as the proportion of time spent below the prognostic threshold relative to the total time enrolled in the study.

Statistics. Differences in categorical variables between 2 groups (≤ cutoff point and > cutoff point) were assessed using the chi-square test, whereas for continuous variables,

the Student *t* test, Mann-Whitney *U* test, or Kruskal-Wallis test was employed, as appropriate. Continuous variables were expressed as mean ± SD or median (interquartile range), with the latter reported in the context of non-normality. For correlation analysis, biomarker concentrations were natural logarithm transformed, and Pearson correlation analysis was performed. In initial exploratory analysis, all novel biomarkers (sST2, GDF-15, and hsTnT) were examined simultaneously in a single model that included traditional clinical and biochemical characteristics—age, sex, current smoking status, diabetes, prior CV events (i.e., at least 1 myocardial infarction, atrial fibrillation or flutter, hypertension, ventricular tachycardia, or coronary artery disease), NYHA functional class III or IV, and baseline NT-proBNP concentration. Mainly, novel biomarkers were treated as categorical variables relative to previous literature-defined cutoff point for each in determining total CV events in a linear regression model, then in predicting time-to-first CV event in a Cox proportional hazards model. Patients who were lost to follow-up or who did not experience any CV events were censored at the earlier of 1 year or the date last known to be event-free. Additionally, novel biomarkers were treated as categorical variables relative to study-determined optimal cutoff points in predicting total CV events in a linear regression model.

In a more comprehensive analysis, novel biomarkers were treated as continuous variables and the incremental role of each biomarker to a base model adjusting for traditional clinical and biochemical characteristics evaluated using a negative binomial regression model. Similar analyses were performed using Cox proportional hazard methods. Additional analyses adjusting for LVEF and study arm were performed.

For each of the novel biomarkers, the role of serial biomarker measurement was assessed by adding a change in biomarker status from response to nonresponse during the study to a base model containing a baseline biomarker status, and traditional clinical and biochemical characteristics were assessed by performing multivariable linear regression analysis to predict total CV events. Similar analyses were performed with a Cox regression model. Additionally, landmarking approaches with previous literature-determined cutoff values for each biomarker were used to determine the value of additional measurement at specified time points from baseline (3 and 6 months). Comparisons were made using the log-rank test.

Changes in biomarker levels over time were defined in various methods, and their roles in predicting clinical outcomes were assessed. The best definition of a change in biomarker concentrations was then used to examine the role of a change in each biomarker concentration in predicting CV events at 3 and 6 months.

Finally, logistic regression was used to assess the role of time in response in predicting the occurrence of CV events and major remodeling markers (LVEF, LV end-systolic volume index, and LV end-diastolic volume index).

The relationship between changes in specific HF medications and changes in logarithm of each biomarker concentration was evaluated with the use of a generalized estimation equation using a Gaussian family model with an identity canonical link function, without and with adjustment for age, NYHA functional class, and study arm.

In all statistical analyses, a 2-tailed p value <0.05 was considered to indicate statistical significance. All analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) or PASW versions 17 and 18 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

Results

Baseline characteristics. Table 1 details baseline patient characteristics for each of the biomarkers by the primary cutoff-point category.

Change in biomarkers over time. There were significant correlations between biomarkers examined, with stronger correlation between NT-proBNP and GDF-15 or hsTnT, and GDF-15 and hsTnT (Online Table 2). Next, after correlating within-patient paired baseline and final measurements of each biomarker (Fig. 1), there was a strong correlation between paired logarithm baseline and final biomarker concentrations of GDF-15 (Pearson r: 0.87; $p < 0.001$) and hsTnT (Pearson r: 0.86; $p < 0.001$). In contrast, sST2 showed a lesser correlation (Pearson r: 0.67; $p < 0.001$), similar to NT-proBNP (Pearson r: 0.67; $p < 0.001$). Indeed, sST2 showed the greatest change over study procedures, with 40% of the participants changing their response status. This was followed by NT-proBNP (25%), GDF-15 (21%), and hsTnT (15%) (Table 2).

Prognostic value of baseline biomarker measurements. First, when all 3 novel baseline biomarker concentrations (expressed relative to previously-defined cutoff points for each) were included in a single model with traditional clinical and biochemical characteristics, NT-proBNP, sST2, and GDF-15 were independently predictive of total CV events (R^2: 0.216; F[10,138]: 3.80; $p =< 0.001$; sST2 beta: 0.20, $p = 0.02$; GDF-15 beta: 0.31, $p = 0.002$; hsTnT beta: 0.07, $p = 0.45$). All 3 novel biomarkers independently predicted time to first CV event (sST2, $p = 0.01$; GDF-15, $p = 0.01$; hsTnT, $p = 0.01$). When novel biomarkers were expressed relative to study-determined optimal cutoff points (42 ng/ml for sST2, 3,270 ng/l for GDF-15, and 24 pg/ml for hsTnT), all 3 novel biomarkers predicted total CV events (R^2: 0.344; F[10,138]: 7.23; $p < 0.001$; sST2 beta: 0.22, $p = 0.004$; GDF-15 beta: 0.37, $p < 0.001$; hsTnT beta: 0.28, $p < 0.001$).

In a secondary analysis, the novel biomarkers were treated as continuous variables, and the incremental role of each of the novel biomarkers was comprehensively evaluated (Table 3). Adding each of the novel biomarkers to the baseline model containing traditional clinical and biochemical characteristics including NT-proBNP added independent information in predicting total CV events (sST2, beta: 0.23, $p < 0.001$; GDF-15, beta: 0.17, $p = 0.004$; hsTnT,

Table 1 Baseline Characteristics of the Study Cohort as a Function of Baseline Biomarker Status

Characteristic	sST2			GDF-15			hsTnT		
	≤35 ng/ml (n = 69)	>35 ng/ml (n = 82)	p Value (n = 151)	≤2,000 ng/l (n = 53)	>2,000 ng/l (n = 97)	p Value (n = 150)	≤14 pg/ml (n = 38)	>14 pg/ml (n = 112)	p Value (n = 10)
Age (yrs)	64.1 ± 13.1	62.7 ± 14.7	0.53	54.2 ± 9.9	68.1 ± 13.3	<0.001	54.4 ± 12.2	66.1 ± 13.2	<0.001
Male sex	52 (75.4)	75 (91.5)	0.007	43 (81.1)	84 (86.6)	0.37	30 (78.9)	97 (86.6)	0.26
White race	56 (81.2)	75 (91.5)	0.06	44 (83.0)	86 (88.7)	0.33	32 (84.2)	98 (87.5)	0.61
LVEF	27.7 ± 8.3 (n = 55)	26.4 ± 8.9 (n = 61)	0.34	24.7 ± 8.4 (n = 43)	28.3 ± 8.6 (n = 73)	0.02	26.8 ± 8.9 (n = 49)	27.1 ± 8.6 (n = 67)	0.84
NYHA functional class									
II	31 (44.9)	37 (45.1)	0.54	33 (62.3)	35 (36.1)	0.008	27 (71.1)	41 (36.6)	0.001
III	31 (44.9)	32 (39.0)		16 (30.2)	46 (47.4)		9 (23.7)	53 (47.3)	
IV	7 (10.1)	13 (15.9)		4 (7.5)	16 (16.5)		2 (5.3)	18 (16.1)	
NT-proBNP–guided study arm	32 (46.4)	43 (52.4)	0.46	24 (45.3)	50 (51.5)	0.46	22 (7.9)	52 (6.4)	0.30
Medical history									
Ischemic HF	33 (47.8)	43 (52.4)	0.57	17 (32.1)	59 (60.8)	<0.001	9 (23.7)	67 (59.8)	<0.001
Atrial fibrillation	25 (36.2)	36 (43.9)	0.34	16 (30.2)	45 (46.4)	0.05	5/29 (17.2)	17/96 (17.7)	0.95
Hypertension	34 (49.3)	45 (54.9)	0.49	16 (30.2)	62 (63.9)	<0.001	12 (31.6)	66 (58.9)	0.004
Diabetes mellitus	27 (39.1)	36 (43.9)	0.55	14 (26.4)	49 (50.5)	0.004	9 (23.7)	54 (48.2)	0.008
Examination									
BMI (kg/m^2)	29.5 ± 6.3	27.9 ± 6.1	0.11	30.3 ± 6.8	27.7 ± 5.8	0.02	30.7 ± 7.9	27.9 ± 5.4	0.02
HR (beats/min)	72.8 ± 12.4	73.7 ± 12.5	0.65	73.9 ± 14.0	72.8 ± 11.5	0.62	70.7 ± 13.4	74.0 ± 11.9	0.18
Systolic BP (mm Hg)	110.9 ± 14.2	108.1 ± 15.4	0.25	109.2 ± 15.2	109.5 ± 14.9	0.92	109.9 ± 16.6	109.2 ± 14.4	0.80
JVD	20 (29.0)	34 (41.5)	0.11	12 (22.6)	41 (42.3)	0.02	6 (15.8)	47 (42.0)	0.004
Pulmonary rales	9 (13.0)	10 (12.2)	0.88	3 (5.7)	16 (16.5)	0.06	4 (10.5)	15 (13.4)	0.65
Edema	16 (23.2)	31 (37.8)	0.05	10 (18.9)	36 (37.1)	0.02	5 (13.2)	41 (36.6)	0.007
Laboratory results									
eGFR (ml/min/1.73 m^2)	61.4 ± 19.0	60.1 ± 22.3	0.69	69.7 ± 15.7	55.8 ± 21.7	<0.001	69.9 ± 14.7	57.6 ± 21.7	0.001
NT-proBNP (pg/ml)	1,804 (45–18,865)	2,401 (212–36,414)	0.19	1,453 (45–9,368)	2,570 (170–36,414)	<0.001	882 (45–5,212)	2,429 (278–36,414)	<0.001

Values are mean ± SD, n (%), or median (interquartile range).

BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; GDF = growth differentiation factor; HF = heart failure; HR = heart rate; hsTnT = highly-sensitive troponin T; JVD = jugular venous distention; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; sST2 = serial soluble ST2.

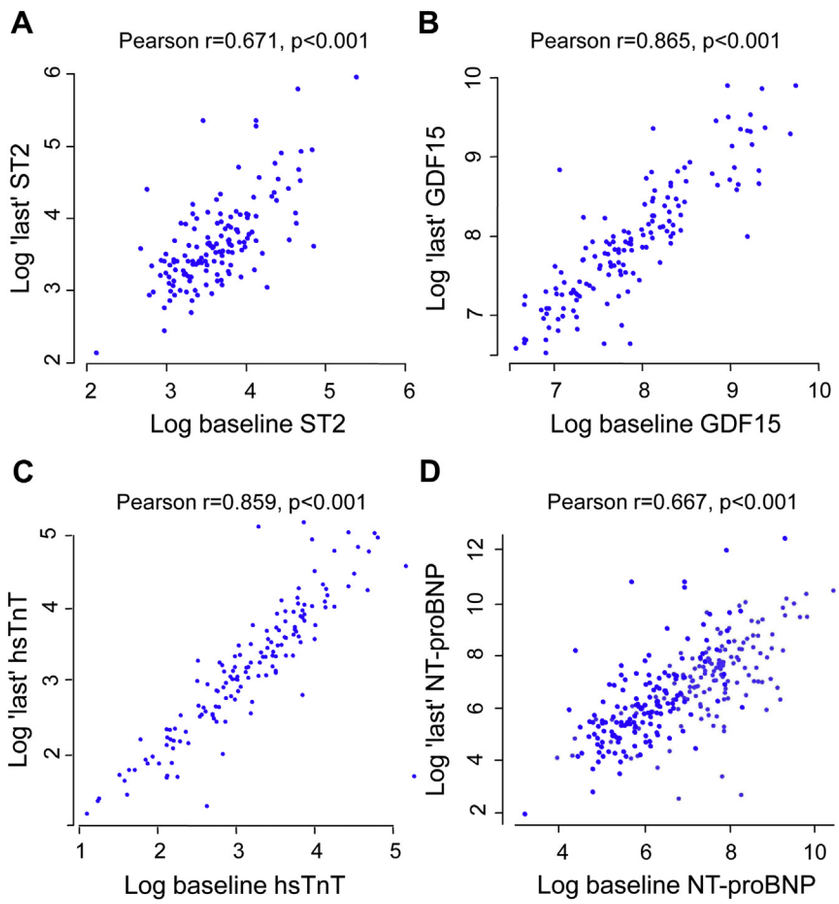

Figure 1 **Logarithm Baseline Versus Final Biomarker Concentrations**

(A) Serial soluble ST2 (sST2); **(B)** growth differentiation factor (GDF)-15; **(C)** highly sensitive troponin T (hsTnT); and **(D)** N-terminal pro–B-type natriuretic peptide (NT-proBNP). The correlations between baseline and final sST2 and NT-proBNP were considerably lower than those for GDF-15 and hsTnT, suggesting a greater degree of change from baseline.

beta: 0.13, p = 0.04). As reflected by decreasing Akaike information criterion (AIC) values, adding any 2 of the 3 novel biomarkers to the baseline model further improved our ability to predict clinical outcomes, but the best model was when all 3 novel biomarkers were added to the base model. Similar results were seen in models predicting time to first CV event (Online Table 3). In a model further adjusting for LVEF and study arm, continuous concentrations of all 3 markers remained independently predictive (sST2, hazard ratio [HR]: 1.12, p = 0.02; GDF-15, HR: 1.17, p = 0.001; hsTnT, HR: 1.09, p = 0.02).

Prognostic value of serial biomarker measurements. In a multiple regression model that adjusted for traditional risk factors including NT-proBNP and baseline sST2 status (according to the previously defined cutoff point of 35 ng/ml), adding a change in sST2 status from ≤35 to

Table 2 **Changes in Biomarker Status**

	sST2 (n = 145)	GDF-15 (n = 146)	hsTnT (n = 146)	NT-proBNP (n = 142)
Cutoff	≤35 ng/ml	≤2,000 ng/l	≤14 pg/ml	≤1,000 pg/ml
Stayed above cutoff	46 (31.7)	80 (54.8)	96 (65.8)	79 (55.6)
Above cutoff to below cutoff	32 (22.1)	14 (9.6)	12 (8.2)	28 (19.7)
Below cutoff to above cutoff	26 (17.9)	17 (11.6)	10 (6.8)	7 (4.9)
Stayed below cutoff	41 (28.3)	35 (24.0)	28 (19.2)	28 (19.7)

Values are n (%) of patients unless otherwise specified.
Abbreviations as in Table 1.

Table 3 Regression Model Predicting Total CV Events With All 3 Baseline Biomarkers Treated as Continuous Variables

Variable	Beta (SE)	p Value	AIC
Traditional clinical and biochemical variables			419.83
Age	−0.0002	0.98	
Male	−0.02	0.96	
Any prior CV events	1.26	0.04	
Diabetes	−0.06	0.86	
Smoker	0.07	0.91	
NYHA functional class 3 or 4	0.70	0.02	
NT-proBNP*	0.08	0.06	
Traditional variables + sST2†	0.23	<0.001	403.87
Traditional variables + GDF-15†	0.17	0.004	411.14
Traditional variables + hsTnT‡	0.13	0.04	415.53
Traditional variables			411.52
+ hsTnT	0.08	0.20	
+ GDF-15	0.15	0.02	
Traditional variables			398.67
+ hsTnT	0.05	0.35	
+ GDF-15	0.11	0.05	
+ sST2†	0.21	<0.001	

*Scaled by 0.01. †Scaled by 0.1. ‡Scaled by 0.001.
AIC = Akaike information criterion; CV = cardiovascular; other abbreviations as in Table 1.

>35 pg/ml (from response to nonresponse) during the study improved the model (R^2 from 0.145 to 0.158), with both models being significant (p = 0.004 and 0.005, respectively). However, sST2 status change did not appear to add any unique contribution to the model (beta: 0.13; p = 0.15). Adding GDF-15 status change to the base model containing traditional risk factors and baseline GDF-15 status improved the model for predicting total CV events (R^2 from 0.130 to 0.177; p < 0.001 and p = 0.001, respectively) but did not appear to be uniquely significant (beta: 0.004; p = 0.96). Adding a change in hsTnT status to the baseline model with baseline hsTnT status did not improve the model (R^2 from 0.110 to 0.111; p = 0.03 and 0.06, respectively), which, again, was not a unique contribution (beta: −0.02; p = 0.80). Of note, when NT-proBNP status change was included in the base model that adjusted for traditional risk factors including NT-proBNP, this model no longer predicted total CV events (R^2: 0.090; p = 0.12).

Next, time-dependent data were incorporated in a Cox regression model. When traditional risk factors as well as baseline sST2 status and a change in the sST2 responder status during the study were included in the model, a baseline sST2 <35 ng/ml was associated with longer time to first CV event (HR: 0.30; 95% confidence interval [CI]: 0.14 to 0.63; p = 0.002), whereas a change in the sST2 responder status from ≤35 ng/ml to >35 ng/ml (from response to nonresponse) during the study was associated with significantly shorter time to first CV event (HR: 3.64; 95% CI: 1.37 to 9.67; p = 0.009). In a similar analysis of GDF-15, only baseline values ≤2,000 pg/l were predictive of longer time to first CV event (HR: 0.32; 95% CI: 0.14 to 0.73; p = 0.007), whereas serial measurements did not add clear value; the results for hsTnT were similar, with baseline values adding overwhelming prognostic information (HR: 0.29; 95% CI: 0.13 to 0.61; p = 0.001) relative to serial measurement.

Next, using landmarking approaches with dichotomous cutoffs, of the 3 novel biomarkers evaluated, sST2 was the only test with information added from measurement at the 3-month (p = 0.03) and 6-month (p = 0.02) landmarked time points beyond baseline (p = 0.005). Only baseline values of GDF-15 (p = 0.001) and hsTnT (p = 0.01) were significant. In regression modeling for time to first event, 3-month sST2 biomarker concentrations added incremental prognostic information to baseline (p = 0.01); such findings were not seen with GDF-15 (p = 0.19) or hsTnT (p = 0.91), not surprisingly.

In a secondary analysis, changes in biomarker levels were defined in various ways: absolute change in concentration from baseline, percent change, and change greater than literature-defined biological variability for each biomarker. Each of these definitions of changes from baseline to 3 months and baseline to 6 months was used in a model to predict CV events. Of these, the best definition appeared to be a change greater than biological variability for each biomarker. This definition of change in biomarker was used in a regression model to assess whether there were any improvements in prediction of CV events. When a change in sST2 from baseline to 3 months, as defined earlier, was added to a base model that adjusted for traditional risk factors including NT-proBNP, the predictive power of the model improved, with AIC decreasing from 403.87 to 318.80, but the contribution of the change in sST2 to the model was not significant (beta: −0.19; p = 0.68). Similar findings were seen with GDF-15 (AIC decreased from 411.14 to 323.88; beta: 0.31; p = 0.38) and hsTnT (AIC decreased from 415.53 to 324.88; beta: 0.50; p = 0.65). Lastly, in a logistic regression analysis harnessing time-integrated prognostic information across all blood draws (Table 4), increasing percent time spent below prognostic thresholds (*time in response,* scaled by a factor of 10%) predicted lower CV events for all of the novel biomarkers. The relationship between categories of percent time spent in response and CV events is shown in Figure 2.

Biomarker concentrations and LV remodeling. More time spent in sST2 response predicted decreasing left ventricular end-diastolic index (odds ratio: 1.22; 95% CI: 1.04 to 1.43; p = 0.01) after adjusting for relevant baseline

Table 4 Logistic Regression Modeling Using Biomarker Percentage in Response to Predict CV Events

	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
sST2	0.87 (0.80–0.94)	<0.001	0.86 (0.79–0.95)	0.002
GDF-15	0.85 (0.78–0.93)	<0.001	0.84 (0.75–0.94)	0.002
hsTnT	0.87 (0.79–0.96)	0.004	0.89 (0.80–1.00)	0.04

Abbreviations as in Tables 1 and 3.

characteristics. Other biomarkers did not show any significant relationship with major remodeling markers evaluated.

Medication effects on biomarker levels. Online Table 4 summarizes significant medication effects on each biomarker in adjusted analyses. The greatest magnitude of interaction was a significant inverse association between β-blocker dose changes and sST2 concentrations.

Discussion

We rigorously examined a combination of emerging risk markers in chronic HF. In doing so, we modeled each marker individually and collectively, and examined their results in various ways, including using continuous concentrations, previously established cutoffs, as well as integrating their results over time in a manner mimicking their use in clinical practice.

Individually, single measurements of sST2, GDF-15, and hsTnT concentrations have been reported to be predictive of adverse HF outcomes, but no study has evaluated them all together in patients with chronic HF, or with extensive serial measurement. In a general-population cohort from the Framingham Heart Study, we found that these 3 markers were additively predictive of risk (12). In the present study in chronic HF patients, the 3 markers examined were relatively loosely correlated, and each revealed prognostic information independent and additive of each other when adjusted for traditional clinical and biochemical characteristics including NT-proBNP. This reflects the intricate pathophysiology of HF; the best approach to determine prognosis (and perhaps select therapies) may thus be a multimarker profile using several complementary biomarkers, a concept first reported by Ky et al. (13). Beyond the baseline measurement, only sST2 appeared to provide incremental prognostic information and reflect changes in myocardial remodeling over time. A novel biomarker's dynamic ability to reflect the underlying HF biology makes it an ideal candidate for potentially monitoring and guiding HF management.

Much in the way that natriuretic peptides are induced when cardiomyocytes are stretched, concentrations of sST2 are thought to represent a cellular response to cellular stress; ST2 biology appears to play a pivotal role in LV remodeling and fibrosis (14). Concentrations of sST2 are increasingly accepted to reflect important prognostic information not already revealed by natriuretic peptides (15). Although data from a pilot study of repeated sST2 testing in chronic HF were promising (5), very little is known about the merits of serial sST2 measurement at multiple time points in chronic HF. In the present analysis, sST2 appeared to add prognostic information above the natriuretic peptides across multiple time points of measurement, and to indicate significant dynamic change of the biomarker in parallel with risk for adverse events and myocardial remodeling.

GDF-15 is a member of the transforming growth factor-β cytokine superfamily. Expression of GDF-15 is strongly induced in cardiomyocytes in response to metabolic stress, and appears to be involved in the regulation of cell differentiation and tissue repair. GDF-15 is thereby closely linked with tissue remodeling and is prognostic of adverse outcomes in HF (3). Anand et al. (3) reported that baseline values of GDF-15 were strongly prognostic in chronic HF but that adding a follow-up value did not inform substantial extra prognostic information; in our analysis of sampling at multiple time points, we now report similar results.

In the past decade, highly-sensitive troponin assays have been developed that provide ability to detect even minute degrees of cardiac injury. Elevation of highly-sensitive troponin above the 99th percentile of a normal population has been shown to be common in chronic HF patients and of prognostic importance (16). Much like with GDF-15, we found a single measurement of hsTnT provided much of the ability to predict adverse events, but serial measurement did not add significant incremental prognostic data. Our results with multiple measurements agree with those reported by Masson et al. (4) using paired measurements.

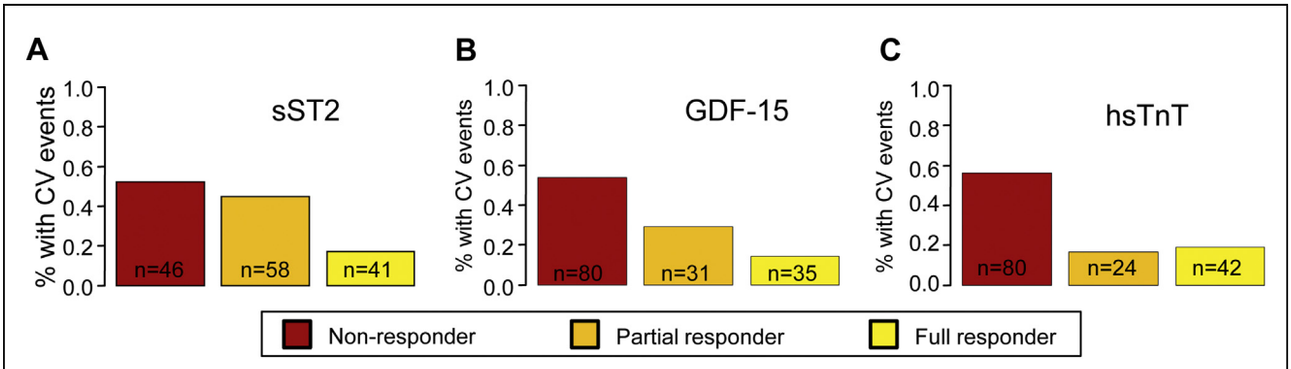

Figure 2 CV Events, by Categories of Biomarker Time in Response

(A) sST2; **(B)** GDF-1; and **(C)** hsTnT. There was a direct relationship between percentage of time spent below prognostic thresholds (*time in response*) and cardiovascular (CV) event rates for sST2 and GDF-15. Abbreviations as in Figure 1.

To date, no specific medication changes have been shown to be associated with change in the concentration of any of the biomarkers studied. In this hypothesis-generating analysis, we found potential associations between therapy changes and biomarker concentrations. Notably, we found a significant relationship between β-blocker changes and sST2. As β-blockers have been shown to reverse myocardial remodeling (17), we are currently examining the potential link between this class of agents and sST2 in more depth. As stated earlier, the link between β-blocker dose changes and sST2 changes may be leveraged in identifying patients who may particularly benefit from aggressive titration of β-blockers.

With the growing number of unique biomarkers that may be available in HF, we have previously argued that a rigorous assessment process is necessary to best understand which markers would be of greatest use and how to best deploy them (18). Our results show value for each marker measured at baseline, but only sST2 appeared to provide incremental prognostic data beyond initial measurement. Further data in this regard are needed.

Study limitations. This was a post-hoc analysis of a small, single-center study. Small numbers of subjects might limit the ability to detect subtle changes in biomarker values over time; however, we had numerous measures from each subject over time, and were able to extensively characterize our cohort, following each medication change, clinical events, and biomarker changes over time. Another issue is that we did not have uniform clinical follow-up time intervals. This resulted in smaller numbers of patients available for repeated-measures analyses. Nonetheless, leveraging the unique strength of the volume of biomarker measures available, our use of time in response is unique, and allows for prognostic comparisons of various markers drawn at the same time points using a time-integrated approach. This time-in-response approach (widely used in studies of response to anticoagulant therapy [19]) is likely to be more widely employed as more studies of HF-biomarker testing across multiple time points become available. Lastly, although the use of discrete cutoffs facilitates analysis of prognostic ramification of changes from "normal" to "elevated," the starting level of the biomarker as well as the degree of change should both be considered when interpreting a change in concentration.

Conclusions

In patients with chronic HF, baseline measurements of novel biomarkers added independent prognostic information to clinical variables and NT-proBNP. Only serial measurement of sST2 appeared to add prognostic information to baseline concentrations and predicted change in LV function.

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REFERENCES

1. Januzzi JL Jr., Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 2011;58:1881–9.
2. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47:76–84.
3. Anand IS, Kempf T, Rector TS, et al. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. Circulation 2010;122:1387–95.
4. Masson S, Anand I, Favero C, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. Circulation 2012;125:280–8.
5. Bayes-Genis A, Pascual-Figal D, Januzzi JL, et al. Soluble ST2 monitoring provides additional risk stratification for outpatients with decompensated heart failure. Rev Esp Cardiol 2010;63:1171–8.
6. Bhardwaj A, Rehman SU, Mohammed A, Baggish AL, Moore SA, Januzzi JL Jr. Design and methods of the Pro-B Type Natriuretic Peptide Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) Study. Am Heart J 2010;159:532–8. e1.
7. Apple FS, Jaffe AS. Clinical implications of a recent adjustment to the high-sensitivity cardiac troponin T assay: user beware. Clin Chem 2012;58:1599–600.
8. Vasile VC, Saenger AK, Kroning JM, Jaffe AS. Biological and analytical variability of a novel high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:1086–90.
9. Frankenstein L, Remppis A, Frankenstein J, et al. Reference change values and determinants of variability of NT-proANP and GDF15 in stable chronic heart failure. Basic Res Cardiol 2009;104:731–8.
10. Dieplinger B, Januzzi JL Jr., Steinmair M, et al. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma—the Presage ST2 assay. Clin Chim Acta 2009;409:33–40.
11. Ordonez-Llanos J, Collinson PO, Christenson RH. Amino-terminal pro-B-type natriuretic peptide: analytic considerations. Am J Cardiol 2008;101:9–15.
12. Wang TJ, Wollert KC, Larson MG, et al. Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. Circulation 2012;126:1596–604.
13. Ky B, French B, Levy WC, et al. Multiple biomarkers for risk prediction in chronic heart failure. Circ Heart Fail 2012;5:183–90.
14. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 2007;117:1538–49.
15. Ky B, French B, McCloskey K, et al. High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. Circ Heart Fail 2011;4:180–7.
16. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116:1242–9.
17. Khattar RS. Effects of ACE-inhibitors and beta-blockers on left ventricular remodeling in chronic heart failure. Minerva cardioangiologica 2003;51:143–54.
18. van Kimmenade RR, Januzzi JL Jr. Emerging biomarkers in heart failure. Clin Chem 2012;58:127–38.
19. Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. Heart 2005;91:472–7.

Key Words: biomarker ■ heart failure ■ prognosis.

APPENDIX

For supplemental tables, please see the online version of this article.

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CLINICAL RESEARCH

Sitagliptin Use in Patients With Diabetes and Heart Failure

A Population-Based Retrospective Cohort Study

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ABSTRACT

OBJECTIVES The study objective was to evaluate the effects of sitagliptin in patients with type 2 diabetes (T2D) and heart failure (HF).

BACKGROUND There is uncertainty in the literature about whether dipeptidyl peptidase (DPP)-4 inhibitors cause harm in patients with HF and T2D.

METHODS We analyzed data from a national commercially insured U.S. claims database. Patients with incident HF were identified from individuals with T2D initially treated with metformin or sulfonylurea and followed over time. Subjects subsequently using sitagliptin were compared with those not using sitagliptin in the 90 days before our primary outcome of all-cause hospital admission or death using a nested case-control analysis after adjustment for demographics and clinical and laboratory data. HF-specific hospital admission or death also was assessed.

RESULTS A total of 7,620 patients with diabetes and incident HF met our inclusion criteria. Mean (SD) age was 54 years (9), and 58% (3,180) were male. Overall, 887 patients (12%) were exposed to sitagliptin therapy (521 patient years of exposure) after incident HF. Our primary composite endpoint occurred in 4,137 patients (54%). After adjustment, sitagliptin users were not at an increased risk for the primary endpoint (7.1% vs. 9.2%, adjusted odds ratio [aOR]: 0.84, 95% confidence interval [CI]: 0.69 to 1.03) or each component (hospital admission 7.5% vs. 9.2%, aOR: 0.93, 95% CI: 0.76 to 1.14; death 6.9% vs. 9.3%, aOR: 1.16, 95% CI: 0.68 to 1.97). However, sitagliptin use was associated with an increased risk of HF hospitalizations (12.5% vs. 9.0%, aOR: 1.84, 95% CI: 1.16 to 2.92).

CONCLUSIONS Sitagliptin use was not associated with an increased risk of all-cause hospitalizations or death, but was associated with an increased risk of HF-related hospitalizations among patients with T2D with pre-existing HF. (J Am Coll Cardiol HF 2014;2:573–82) © 2014 by the American College of Cardiology Foundation.

Heart failure (HF) is a frequent complication of type 2 diabetes (T2D), but how best to control blood glucose in patients with diabetes and HF is a clinically relevant question that has been the source of considerable controversy in both the research and the medical communities (1).

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ABBREVIATIONS AND ACRONYMS

aOR = adjusted odds ratio

CI = confidence interval

DPP = dipeptidyl peptidase

HF = heart failure

ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

T2D = type 2 diabetes

TZD = thiazolidinedione

The antidiabetic agent metformin is currently considered first-line therapy in this population (2,3). Sulfonylureas and insulin are also treatment options; however, undesirable side effects, including fluid retention, weight gain, and hypoglycemia (2,3), often limit their use in patients with HF. Thiazolidinediones (TZDs) are contraindicated in patients with HF because of fluid retention. Thus, there is significant interest in the potential role of incretin therapies for patients with concomitant diabetes and HF.

In addition to the antihyperglycemic effects of dipeptidyl peptidase (DPP)-4 inhibitors, they have been shown to improve cardiorenal function (4). Sitagliptin has also been found to reduce cardiac apoptosis, hypertrophy, and fibrosis (5). In addition, DPP-4 inhibitors are considered weight neutral and have generally been shown to improve other cardiovascular risk factors, including low-density lipoprotein, high-density lipoprotein, and blood pressure (6,7).

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A number of recent safety analyses have suggested improved cardiovascular outcomes in sitagliptin-treated subjects, including a 52% relative risk reduction in major adverse cardiovascular events in pooled analyses (8), whereas others have found a neutral effect of DPP-4 inhibitors on cardiovascular outcomes (9,10). Of note, these studies were of short duration, enrolled highly selected patients, and were not designed with cardiovascular outcomes as the primary endpoints. The recently published SAVOR (Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes) trial suggested that saxagliptin was associated with increased risk of HF compared with placebo (11). Conversely, the EXAMINE (Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes) study with alogliptin found no significant benefit or risk related to HF in patients with T2D and a history of myocardial infarct or angina (12). Because of the recent controversies surrounding the safety of these drugs, the Food and Drug Administration has requested additional data from the SAVOR trial to further investigate the potential link between saxagliptin therapy and HF hospital admission (13).

In light of the current debate surrounding the safety of DPP-4 inhibitors in patients with existing HF, we designed this study to evaluate the effects of sitagliptin, the first marketed and most widely used DPP-4 inhibitor in North America, in patients with T2D and incident HF.

METHODS

We conducted a population-based, retrospective cohort study using a large U.S. claims and integrated laboratory database that included employed, commercially insured individuals from all 50 states (Clinformatics Data Mart, OptumInsight Life Sciences Inc.). Patient-level data included administrative and demographic information (type of insurance plan, sex, age, dates of eligibility, income) and billable medical services claims, including inpatient and outpatient visits and medical procedures (physician and facility identifier, date and place of service, cost of service, admission, and discharge dates, procedures and diagnostic codes), all laboratory tests and results (including fasting lipids, renal function, liver function, blood glucose [glycosylated hemoglobin], and complete blood count), and pharmacy claims data (prescribing physician, drug dispensed on the basis of national drug codes, quantity and date dispensed, drug strength, days supply, cost of service) (14–17). All clinical diagnoses were recorded according to the International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) codes and procedure codes.

COHORT SELECTION. We identified those individuals who had a prescription claim for metformin or sulfonylurea therapy from January 1, 2003, to December 31, 2009, and subsequently developed incident HF (i.e., any claim with ICD-9-CM code of 428.XX with no history of a diagnosis of HF in 1 year before incident HF event). These agents were chosen because they are the most commonly prescribed oral antidiabetic agents in patients with diabetes and would provide a more homogenous study population. Moreover, several studies in diabetes and HF have evaluated the effects of metformin and sulfonylurea (1). Because TZD therapy has been shown to increase the risk of HF and is contraindicated in patients with established HF, all patients were excluded if they received a TZD before HF diagnosis. Moreover, subjects not initially using TZDs but who subsequently initiated TZDs after incident HF were censored on the date they first filled a TZD prescription (**Figure 1**). Patients also had to be at least 20 years of age and had to have at least 1 year of continuous medical insurance before diagnosis of HF (so we could be certain any cases of HF were new diagnoses) to be included in our cohort. Subjects were followed from the date of incident HF until death, termination of medical insurance, or December 31, 2010 (study exit date) (**Figure 2**).

OUTCOMES. We followed our cohort after incident HF to measure their health outcomes. Our primary

outcome of interest was a composite endpoint of "all-cause hospital admission or death" with our secondary endpoints, including HF-related hospital admission or all-cause death. We also evaluated each component of our composite endpoints separately (i.e., all-cause hospital admission, all-cause death, HF-specific hospital admission). It is important to note that the incident HF event used to define our cohort of interest and our subsequent outcome of HF-related hospital admission during follow-up are 2 distinct events. Vital status was determined through linkage to the U.S. national death index files (18), although cause of death was not ascertained. Linkage to this index is highly reliable and valid (>98% specificity) and has been used in previous analyses (19,20).

NESTED CASE-CONTROL POPULATION. To reduce confounding by indication and account for time-varying changes in exposure during follow-up, we used a nested case-control approach to evaluate the effects of sitagliptin treatment in patients with HF with T2D. All subjects with the primary outcome of interest (e.g., all-cause hospital admission or death) were considered cases, with the date of all-cause death or hospital admission being considered the index date. Cases were matched on age (quartiles) and sex with up to 10 controls with no hospital

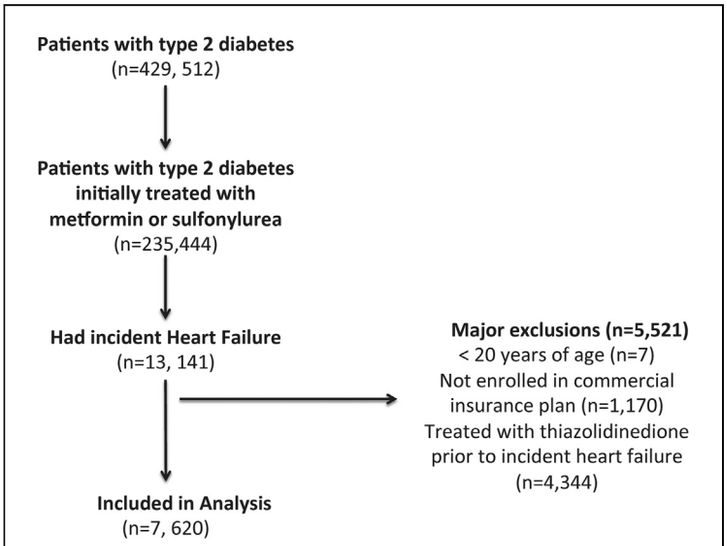

FIGURE 1 Flowchart of Exclusions

Individuals with type 2 diabetes (T2D) initially treated with metformin or sulfonylureas subsequently developing incident heart failure (HF) were included in our analysis after relevant exclusions.

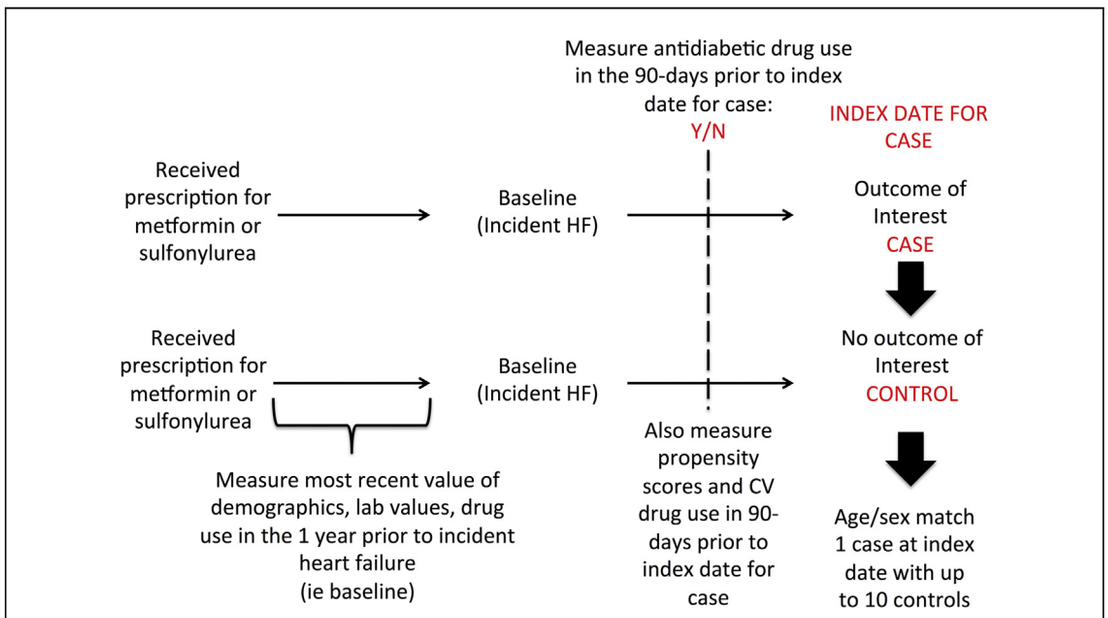

FIGURE 2 Schematic of Cohort Study Design

Patients included in our analysis were age/sex matched with up to 10 controls at the time each case arose. Drug use was measured in the 90 days before the index date for each case, and cohort characteristics were evaluated within the year before incident HF. CV = cardiovascular; HF = heart failure.

TABLE 1 Characteristics of Cases (for Primary Composite Endpoint) and Matched Controls in the 1 Year Before Incident Heart Failure

	Control (n = 41,297)	Case (n = 4,137)	p Value*
Characteristics			
Age (yrs)	54.6 ± 8.7	54.6 ± 8.7	0.97
Male	24,556 (59.5)	2,457 (59.4)	0.93
Income ($)	48,341 ± 6,262	48,316 ± 6,266	
Type of insurance			0.001
Point of service	24,874 (60.2)	2,391 (57.8)	
Exclusive provider	7,192 (17.4)	747 (18.1)	
Preferred provider	3,394 (8.2)	394 (9.5)	
Health Maintenance	4,740 (11.5)	516 (12.5)	
Independent	1,097 (2.7)	89 (2.2)	
Clinical parameters			
Mortality risk score	45.6 ± 12.8	47.8 ± 13.3	<0.001
History of cardiovascular disease			
Ischemic heart disease	17,158 (41.6)	1,703 (41.2)	0.63
Myocardial infarction	2,300 (5.6)	302 (7.3)	<0.001
Dyslipidemia	28,638 (69.4)	2,808 (67.9)	0.51
Hypertension	33,950 (82.2)	3,438 (83.1)	0.15
Arrhythmia	7,128 (17.3)	750 (18.1)	0.16
Valve disease	3,366 (8.2)	379 (9.2)	0.024
History of diabetes complications	16,459 (39.9)	1,612 (39.0)	0.27
Estimated glomerular filtration rate category (ml/min)			<0.001
<30	1,225 (3.0)	222 (5.4)	
30–<60	5,488 (13.3)	646 (15.6)	
≥60	19,983 (48.4)	1,843 (44.6)	
Total cholesterol (mg/dl)	177.1 ± 50.3	181.0 ± 55.2	0.0002
Triglycerides (mg/dl)	191.3 ± 254.7	197.6 ± 315.4	0.25
HDL cholesterol (mg/dl)	44.7 ± 13.7	44.7 ± 14.4	0.89
LDL cholesterol (mg/dl)	96.7 ± 37.1	99.7 ± 39.2	0.0059
HbA1c (%)	7.5 ± 1.7	7.8 ± 1.9	<0.001
Hemoglobin (mg/dl)	13.5 ± 1.8	13.2 ± 1.9	<0.001
Drug use			
ACE inhibitor/ARB	28,961 (70.1)	2,816 (68.1)	0.006
Statin	22,926 (55.5)	2,224 (53.8)	0.03
Beta-blocker	20,920 (50.7)	2,109 (51.0)	0.69
Dihydro calcium channel blocker	9,524 (23.1)	1,038 (25.1)	0.003
Non-dihydro calcium channel blocker	4,153 (10.1)	453 (11.0)	0.069
Nitrates	5,469 (13.2)	597 (14.4)	0.032
Diuretics	7,710 (18.7)	788 (19.1)	0.55
Anticoagulants	4,013 (9.7)	469 (11.3)	0.001
Antiplatelet agents	7,567 (18.3)	801 (19.4)	0.10

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admission and who were alive on the same index date for their given case using conventional risk set sampling (i.e., incident density sampling) (21,22). On the basis of considerations of statistical power, up to 10 controls per case were selected to provide approximately 90% power to the study. Controls were "at risk" for the outcome of interest (i.e., actively followed, alive, and event free) before the matched case index date. By convention, controls were selected one subject at a time with replacement (i.e., a subject can be a control subject for several cases across time points) and given an analogous index date as their matched case (23). This process was repeated for each endpoint assessed.

EXPOSURE TO ANTIDIABETIC DRUGS. Patients were considered exposed to an antidiabetic agent if the duration of the drug prescription, based on the dispensed days supplied, was within 90 days of the index date (i.e., time of event or pseudo date for matching controls) (24). Exposure status was classified into 5 categories that were not mutually exclusive: any sitagliptin use, any metformin use, any sulfonylurea use, other oral antidiabetic drug use (acarbose, meglitinides, pramlintide), and any insulin use as has been done previously (20). We attributed outcome events to the drugs the patient was receiving at the time of the event, and we assumed no legacy or carryover effects from remote exposures beyond 90 days with any of the glucose-lowering drugs for the primary analysis.

STATISTICAL ANALYSIS. We used conditional logistic regression to compare the effect of our drugs of interest on the primary outcome and obtained estimates of the odds ratio and 95% confidence intervals (CIs) from the regression analysis. We included each drug exposure class in the model as a dummy variable with the reference group being no exposure to that particular agent (e.g., sitagliptin use compared with no sitagliptin use in the 90 days before index date, after adjustment for the use of other antidiabetic agents).

In addition to our antidiabetic agents, covariates in our models included demographics (age, sex, and socioeconomic status [type of medical insurance and median household income according to 2010 U.S. census]) (25), most recent clinical laboratory data (glycosylated hemoglobin; low- and high-density lipoprotein cholesterol; triglycerides; estimated glomerular filtration rate stratified into ≥60, 59.9 to 30, and <30 ml/min; albuminuria; and hemoglobin concentrations), history of cardiovascular disease (ischemic heart disease, myocardial infarction, dyslipidemia, hypertension, arrhythmia, and valve disease), and prescription drug use (antiplatelet drugs, anticoagulants, statins, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates). For patients who were missing clinical laboratory information, we used the missing indicator approach (26). To further control for the clinical complexity of patients, we used specific variables and adjusted clinical groups derived from the Johns Hopkins adjusted clinical groups system (27). More specifically, we adjusted for the number of inpatient hospitalizations that patients had in the 1 year before HF diagnosis and the number

of chronic conditions. A frailty flag also was calculated on the basis of patient characteristics, including malnutrition, difficulty walking, dementia, incontinence, and barriers to access of care (27). This measure of frailty has been validated and found to accurately identify elderly populations who have the clinical characteristics of frailty and to predict adverse outcomes (28). To further control for comorbidities, we also calculated a mortality risk score based on the weighted components of the 32 adjusted diagnostic groups from the Johns Hopkins System, which has been shown to perform as well as or better than other comorbidity scores, such as the Charlson or Elixhauser scores (29). Because we did not have information available on HF severity (e.g., New York Heart Association class, brain natriuretic peptide levels, left ventricular ejection fraction), we adjusted for the location of the initial HF diagnosis as a proxy because patients with more symptomatic HF would be more likely to be hospitalized (30). We also evaluated the use of common HF drugs (i.e., agents effecting the angiotensin system, beta-blockers, spironolactone, loop diuretics, hydralazine, digoxin, and amiodarone) in the 90 days before the index date for each individual (both cases and controls).

To help control for confounding by indication, we used a generalized propensity score. Traditionally, propensity scores predict a patient's probability of receiving one treatment versus a single alternative; however, this does not reflect the real-world treatment choices for diabetic patients in whom more than 1 medication may be used. Therefore, we calculated a generalized propensity score with 4 treatment levels (metformin, sulfonylurea, insulin, or sitagliptin) in the 90 days before the index date for each individual (both cases and controls) using multinomial logistic regression (31).

SENSITIVITY ANALYSIS. We conducted several sensitivity analyses to confirm the robustness of our results. First, we evaluated the effects of combination therapy, such as metformin/sitagliptin combination, sitagliptin/sulfonylurea combination, and sitagliptin/other combination treatment all compared with metformin/sulfonylurea combination as the reference. Next, we evaluated the impact of sitagliptin therapy in patients with renal impairment (estimated glomerular filtration rate <60 ml/min). Third, we restricted our cohort to include only those who developed incident HF from 2007 to 2009 considering sitagliptin was not made available in the United States before 2007. Fourth, we excluded patients if they were exposed to insulin therapy before incident HF or during the follow-up period after HF, given that insulin treatment is most often prescribed in those with more advanced diabetes. Fifth, we restricted our analysis to those who were new users of metformin or sulfonylurea therapy before incident HF therapy in an attempt to mitigate any biases introduced to the analysis by prevalent users before the onset of HF. Next, we included those individuals who were treated with TZDs before incident HF in our analysis and did not censor individuals if they initiated TZD therapy over the follow-up. Seventh, we extended our definition of incident HF and analyzed those with no history of diagnosis of HF in the 3 years before the incident HF event. Eighth, we censored individuals if they terminated all antidiabetic drug treatment for at least 90 days after incident HF. Ninth, we considered any legacy effects of antidiabetic drug exposure by considering individuals exposed to a particular antidiabetic therapy for the remainder of the follow-up after their first prescription after incident HF, irrespective of whether the patient stopped therapy. In light of recent safety concerns, we also evaluated the effects of sitagliptin use on the risk of acute pancreatitis, although we fully acknowledge that power is extremely low for this endpoint. We also assessed whether exposure to sitagliptin affected the risk of cardiovascular-related hospital admission excluding HF (ICD-9-CM codes 410, 411, 430-438) and noncardiovascular-related hospital admission. Last, to explore the potential for unrecognized confounding, we evaluated the risk of glaucoma

TABLE 1 Continued

	Control (n = 41,297)	Case (n = 4,137)	p Value*
Health care use			
Inpatient hospital admission in year before incident HF			<0.001
0	29,957 (72.5)	2,629 (63.6)	
1	8,738 (21.2)	1,027 (24.8)	
2+	2,602 (6.3)	481 (11.6)	
Frailty	3,455 (8.4)	448 (10.8)	<0.001
Chronic conditions			<0.001
≥1	3,034 (7.4)	293 (7.08)	
2	3,400 (8.2)	290 (7.0)	
3+	34,868 (84.4)	3,554 (85.9)	
Location of HF diagnosis			
Ambulatory	164 (0.4)	5 (0.1)	0.005
Emergency department	120 (0.3)	16 (0.4)	0.28
Physician's office	19,652 (47.6)	1,167 (28.2)	<0.001
Hospital	9,339 (22.6)	1,921 (46.4)	<0.001
Outpatient facility	7,186 (17.4)	725 (17.5)	0.85
Other	4,836 (11.7)	303 (7.3)	<0.001

Values are mean ± SD or n (%). *p value is for difference in characteristics between cases and controls.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HF = heart failure; LDL = low-density lipoprotein.

TABLE 2 Characteristics in the 1 Year Before Incident Heart Failure According to Antidiabetic Drug Exposure During Follow-Up After Incident Heart Failure Diagnosis

	No Sitagliptin Exposure (n = 6,733)	Exposed to Sitagliptin (n = 887)	Exposed to Metformin (n = 3,799)	Exposed to Sulfonylurea (n = 2,954)	Exposed to Other Antidiabetic Agents† (n = 821)	p Value*
Characteristics						
Age (yrs)	54.4 ± 8.8	54.8 ± 7.6	54.3 ± 8.3	55.3 ± 8.2	53.9 ± 7.7	0.15
Male	3,902 (58.0)	538 (60.7)	1,596 (42.0)	1,850 (62.6)	468 (57.0)	0.13
Income ($)	48,337 ± 6,304	48,486 ± 6,459	48,181 ± 6,224	48,085 ± 6,110	48,196 ± 6,182	0.51
Type of insurance						0.023
Point of service	3,928 (58.3)	563 (63.5)	2,256 (59.4)	1,758 (59.5)	485 (59.1)	
Exclusive provider	1,189 (17.7)	150 (16.9)	688 (18.1)	514 (17.4)	152 (18.5)	
Preferred provider	596 (8.9)	69 (7.8)	314 (8.3)	255 (8.6)	76 (9.3)	
Health Maintenance	880 (13.1)	87 (9.8)	463 (12.2)	359 (12.2)	93 (11.3)	
Independent	140 (2.1)	18 (2.0)	78 (2.1)	68 (2.3)	15 (1.8)	
Clinical parameters						
Mortality risk score	46.3 ± 13.2	45.7 ± 11.9	44.5 ± 12.6	46.1 ± 12.4	44.6 ± 12.2	0.16
History of cardiovascular disease						
Ischemic heart disease	2,726 (40.5)	403 (45.3)	1,522 (40.1)	1,218 (41.2)	343 (41.8)	0.006
Myocardial infarction	435 (6.5)	40 (4.5)	208 (5.5)	172 (5.8)	33 (4.0)	0.02
Dyslipidemia	4,636 (68.9)	641 (72.3)	2,679 (70.5)	1,986 (67.2)	585 (71.3)	0.038
Hypertension	5,574 (82.8)	746 (84.1)	3,118 (82.1)	2,419 (81.9)	672 (81.9)	0.33
Arrhythmia	1,184 (17.6)	160 (18.0)	622 (16.4)	525 (17.8)	145 (17.7)	0.74
Valve disease	585 (8.7)	78 (8.8)	304 (8.0)	256 (8.7)	67 (8.2)	0.92
History of diabetes complications	2,622 (38.9)	429 (48.4)	1,639 (43.1)	1,393 (47.2)	337 (41.1)	0.001
Estimated glomerular filtration rate category (ml/min)						0.006
<30	274 (4.1)	17 (1.9)	12 (0.32)	70 (2.4)	17 (2.1)	
30-<60	995 (14.2)	117 (13.2)	363 (9.6)	416 (14.1)	103 (12.6)	
≥60	3,249 (48.3)	428 (48.3)	2,080 (54.8)	1,417 (48.0)	425 (51.8)	
Total cholesterol (mg/dl)	180.0 ± 53.0	173.9 ± 47.9	177.0 ± 52.5	178.8 ± 52.6	177.3 ± 62.4	0.014
Triglycerides (mg/dl)	193.5 ± 296.4	196.8 ± 198.3	197.5 ± 305.9	198.6 ± 271.3	231.7 ± 590.6	0.8
HDL cholesterol (mg/dl)	45.0 ± 13.9	43.3 ± 13.2	44.0 ± 12.3	43.5 ± 12.7	43.1 ± 11.9	0.006
LDL cholesterol (mg/dl)	99.4 ± 38.8	92.1 ± 33.1	98.0 ± 37.5	98.4 ± 36.2	96.3 ± 38.4	0.0094
HbA1c (%)	7.7 ± 1.9	7.7 ± 1.7	7.5 ± 1.7	7.6 ± 1.7	7.9 ± 1.8	0.47
Hemoglobin (mg/dl)	13.3 ± 1.9	13.6 ± 1.8	13.6 ± 1.7	13.6 ± 1.8	13.6 ± 1.7	0.012
Drug use						
ACE inhibitor/ARB	4,609 (68.5)	645 (72.7)	2,686 (70.7)	2,103 (71.2)	601 (73.2)	0.01
Statin	3,677 (54.6)	517 (58.3)	2,172 (57.2)	1,649 (55.8)	461 (56.2)	0.039
Beta-blocker	3,380 (50.2)	476 (53.7)	1,843 (48.5)	1,529 (51.8)	434 (52.9)	0.052
Dihydro calcium channel blocker	1,604 (23.8)	218 (24.6)	797 (21.0)	733 (24.8)	177 (21.6)	0.62
Non-dihydro calcium channel blocker	700 (10.4)	71 (8.0)	346 (9.1)	298 (10.1)	86 (10.5)	0.026
Nitrates	911 (13.5)	108 (12.2)	512 (13.5)	403 (13.6)	119 (14.5)	0.27
Diuretics	1,244 (18.5)	185 (20.9)	684 (18.0)	558 (18.9)	156 (19.0)	0.088
Anticoagulants	696 (10.3)	92 (10.4)	340 (9.0)	308 (10.4)	94 (11.5)	0.97
Antiplatelet agents	1,226 (18.2)	171 (19.3)	636 (16.7)	544 (18.4)	150 (18.3)	0.44
Health care use						
Inpatient hospital admission in year before incident HF						0.022
0	4,639 (68.9)	664 (74.9)	2,840 (74.8)	2,153 (72.9)	614 (74.8)	
1	1,498 (22.3)	175 (19.3)	744 (19.6)	618 (20.9)	155 (18.9)	
2+	596 (8.85)	48 (5.4)	215 (5.7)	183 (6.2)	52 (6.3)	
Frailty	644 (9.6)	73 (8.2)	324 (8.5)	233 (7.9)	88 (10.7)	0.2
Chronic conditions						0.38
≥1	489 (7.3)	62 (7.0)	286 (7.5)	234 (7.9)	67 (8.2)	
2	518 (7.7)	68 (7.7)	346 (9.1)	264 (8.9)	54 (6.6)	
3+	5,726 (85.0)	757 (85.3)	3,167 (83.4)	2,456 (83.1)	700 (85.3)	

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TABLE 2 Continued

	No Sitagliptin Exposure (n = 6,733)	Exposed to Sitagliptin (n = 887)	Exposed to Metformin (n = 3,799)	Exposed to Sulfonylurea (n = 2,954)	Exposed to Other Antidiabetic Agents† (n = 821)	p Value*
Location of HF diagnosis						
Ambulatory	22 (0.3)	3 (0.3)	13 (0.3)	5 (0.2)	4 (0.5)	0.96
Emergency department	22 (0.3)	2 (0.2)	9 (0.2)	7 (0.2)	3 (0.4)	0.61
Physician's office	2,556 (38.0)	405 (45.7)	1,652 (43.5)	1,230 (41.6)	378 (46.0)	<0.001
Hospital	2,291 (34.0)	230 (25.9)	1,084 (28.5)	919 (31.1)	216 (26.3)	<0.001
Outpatient facility	1,186 (17.6)	159 (17.9)	652 (17.2)	495 (16.8)	129 (15.7)	0.82
Other	656 (9.7)	88 (9.9)	389 (10.2)	298 (10.1)	91 (11.1)	0.87

Values are mean ± SD or n (%). *p value is for difference in characteristics between sitagliptin users and nonusers. Antidiabetic drug exposure was at any point after incident HF (ever use vs. never use). †Other antidiabetic agents can include acarbose, meglitinides, and pramlintide.

Abbreviations as in Table 1.

between sitagliptin users and nonusers (a condition chosen because it should not differ by sitagliptin exposure) (32,33).

RESULTS

Of the 7,620 diabetic patients with incident HF included in our study, the median follow-up was 1.4 years; thus, we analyzed 12,704 person years at risk. Overall, 887 patients (12%) were exposed to sitagliptin therapy (521 total patient years of exposure), 3,799 patients (49.9%) were exposed to metformin (3,383 total patient years of exposure), and 2,954 patients (38.8%) were exposed to sulfonylureas (3,107 total patient years of exposure) at any point after incident HF. The mean age was 54 (SD 8) years, and 4,440 (58%) were male.

As expected, we found that for our primary composite endpoint of all-cause hospitalization or death, cases were more likely to have a higher mortality risk score, prior hospitalizations, and a history of myocardial infarct or renal impairment, and to have been treated with cardiovascular medications before their incident HF event compared with controls (Table 1). Cases also had higher cholesterol and glycosylated hemoglobin levels, and were less likely to have been treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers before HF diagnosis.

Those exposed to sitagliptin during follow-up were similar to those not exposed to sitagliptin with respect to most covariates, including age, sex, and socioeconomic status (Table 2). However, those exposed to sitagliptin were more likely to have a history of diabetes complications (microvascular, macrovascular, and other) or ischemic heart disease before incident HF, slightly lower total cholesterol, and higher use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins, but fewer hospitalizations in the year before HF diagnosis compared with those who were not exposed to sitagliptin. Moreover, sitagliptin users were more likely to be diagnosed with HF in the physicians' office as opposed to the hospital setting.

By the end of follow-up, our primary composite endpoint of all-cause hospital admission or death occurred in 4,137 patients (54.3%); 4,076 patients (53.5%) were admitted to the hospital at least once (824 for HF), and 408 patients (5.4%) died. Our secondary endpoint of HF-related hospital admission or all-cause death occurred in 1,146 patients (15.0%).

Sitagliptin users demonstrated a lower crude risk of all-cause hospital admission or death compared with nonusers (7.1% vs. 9.2%), but the difference was not statistically significant after covariate adjustment (adjusted odds ratio [aOR]: 0.84, 95% CI: 0.69 to 1.03). There were no significant differences noted between sitagliptin users and nonusers for all-cause death alone or all-cause hospitalization alone (Table 3). In addition, we found that after adjustment, those exposed to metformin exhibited a lower risk of all-cause death or hospital admission (aOR: 0.78, 95% CI: 0.71 to 0.85), whereas users of insulin (aOR: 1.16, 95% CI: 1.05 to 1.28) or sulfonylureas (aOR: 1.10, 95% CI: 1.00 to 1.23) exhibited higher risk for our primary composite endpoint. For our secondary endpoint of interest, we found that sitagliptin use was not associated with an increased risk of HF-related hospital admission or death (9.0% vs. 9.1%, aOR: 1.34, 95% CI: 0.93 to 1.92) but was associated with an increased risk of HF-related hospital admission alone (aOR: 1.84, 95% CI: 1.16 to 2.92) (Table 3, Figure 3).

For the results of our sensitivity analyses, we found that compared with metformin and sulfonylurea

TABLE 3 Outcomes According to Antidiabetic Drug Exposure 90 Days Before Index Date for Each Outcome

Outcome	Agent	Exposed Cases/Total Exposed	Unexposed Cases/Total Unexposed	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p Value*
All-cause death or hospital admission	Sitagliptin	113/1,588	4,024/43,846	0.75 (0.62-0.92)	0.84 (0.69-1.03)	0.10
	Metformin	756/10,734	3,381/34,700	0.64 (0.59-0.70)	0.78 (0.71-0.85)	<0.001
	Insulin	800/7,149	3,337/38,285	1.37 (1.25-1.50)	1.16 (1.05-1.28)	0.004
	Sulfonylurea	673/7,710	3,464/37,724	0.94 (0.86-1.03)	1.10 (1.00-1.23)	0.043
	Other	109/1,429	4,028/44,005	0.81 (0.67-1.00)	0.95 (0.77-1.17)	0.64
All-cause death	Sitagliptin	19/274	389/4,193	0.73 (0.45-1.18)	1.16 (0.68-1.97)	0.59
	Metformin	66/1,530	342/2,937	0.33 (0.25-0.44)	0.52 (0.37-0.71)	<0.001
	Insulin	142/1,411	266/3,056	1.18 (0.95-1.47)	1.11 (0.84-1.47)	0.46
	Sulfonylurea	73/1,247	335/3,220	0.53 (0.41-0.69)	0.83 (0.61-1.14)	0.25
	Other	13/214	395/4,253	0.63 (0.36-1.12)	0.87 (0.46-1.63)	0.66
All-cause hospital admission	Sitagliptin	112/1,489	3,964/43,274	0.80 (0.6-0.98)	0.93 (0.76-1.14)	0.46
	Metformin	750/10,556	3,326/34,207	0.65 (0.59-0.71)	0.79 (0.71-0.87)	<0.001
	Insulin	795/7,215	3,281/37,548	1.34 (1.23-1.47)	1.13 (1.03-1.25)	0.014
	Sulfonylurea	669/7,683	3,407/37,080	0.93 (0.85-1.03)	1.08 (0.97-1.19)	0.15
	Other	109/1,277	3,967/43,486	0.93 (0.76-1.13)	1.06 (0.86-1.31)	0.56
HF-related hospital admission or death	Sitagliptin	37/409	1,109/12,172	0.99 (0.70-1.41)	1.34 (0.93-1.92)	0.12
	Metformin	154/2,556	992/10,025	0.53 (0.44-0.64)	0.70 (0.57-0.86)	0.001
	Insulin	217/2,126	929/10,455	1.20 (1.01-1.42)	1.02 (0.84-1.24)	0.81
	Sulfonylurea	156/2,063	990/10,518	0.76 (0.63-0.92)	0.92 (0.75-1.13)	0.41
	Other	21/302	1,125/12,279	0.74 (0.47-1.16)	0.85 (0.53-1.36)	0.50
HF-related hospital admission	Sitagliptin	25/200	799/8,862	1.47 (0.95-2.27)	1.84 (1.16-2.92)	0.01
	Metformin	106/1,378	718/7,684	0.76 (0.60-0.96)	0.87 (0.66-1.12)	0.28
	Insulin	113/1,114	711/7,948	1.19 (0.94-1.50)	0.97 (0.75-1.27)	0.83
	Sulfonylurea	103/1,067	721/7,995	1.09 (0.86-1.39)	1.11 (0.84-1.45)	0.47
	Other	14/147	810/8,905	0.98 (0.56-1.72)	1.08 (0.59-1.96)	0.81

*p value is for adjusted odds ratio.
CI = confidence interval; HF = heart failure.

therapy, sitagliptin and metformin combination therapy was associated with a lower risk of our primary composite endpoint (aOR: 0.56, 95% CI: 0.44 to 0.82), whereas sitagliptin and sulfonylurea combination therapy was not associated with an increased risk for our primary composite endpoint (aOR: 0.90, 95% CI: 0.54 to 1.47), as was sitagliptin in combination with therapy other than metformin or sulfonylurea (i.e., sitagliptin and other combination therapies; aOR: 2.23, 95% CI: 0.74 to 6.67).

Our remaining sensitivity analyses confirmed the results of our primary analysis (results available on request). We also found that there was no increased risk of cardiovascular-related hospital admission (excluding HF) with sitagliptin use compared with nonuse (aOR: 1.12, 95% CI: 0.75 to 1.65) with a trend toward a decreased risk of noncardiovascular-related hospital admission with sitagliptin use (aOR 0.77, 95% CI: 0.58 to 1.03). Last, we found a neutral association between sitagliptin use and risk of glaucoma (aOR:1.09, 95% CI: 0.88 to 1.34, p = 0.44), suggesting there was no unrecognized confounding influencing our results.

DISCUSSION

This is the first population-based study to evaluate the effects of sitagliptin therapy in patients with T2D and HF. Although our study suggests the use of sitagliptin is not associated with significant risk of all-cause death or hospital admission in patients with T2D and HF, sitagliptin use was associated with an apparent increase in HF-related hospital admissions. The increase in HF events is likely clinically relevant (resulting in a number need to harm of 29) and may have implications for choice of add-on therapy for patients with HF and diabetes poorly controlled with other agents.

Although our results are intriguing, it is clear that additional studies are required, specifically in patients with HF, to solidify the risk:benefit picture. Indeed, even results from large-scale randomized controlled trials have not been consistent for the DPP-4 inhibitors as a whole. The recently completed SAVOR trial found saxagliptin to be noninferior for a composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke

compared with placebo (34); however, an unexpected increase in the risk of HF events was observed. Conversely, the EXAMINE trial assessing the effect of alogliptin therapy in patients with acute myocardial infarction or unstable angina compared with placebo found no effect on HF-specific events in post hoc analyses (12). Moreover, no substantial risk has been observed with sitagliptin in large population-based studies on cardiovascular endpoints in the broader diabetic population (20). Thus, the ongoing TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) is key to further assessing the safety of this drug (but is not set to report until 2015). Although all of these trials enrolled patients with established cardiovascular disease or risk factors, none specifically identified individuals with established HF. Therefore, it is unlikely the upcoming results of the TECOS trial will provide evidence for the safety of sitagliptin therapy in those with preexisting HF, unless evaluate as a subgroup. As a result, observational studies, like ours, are currently the sole source of evidence regarding this important area of research.

Our study had several important strengths, including the availability of detailed clinical data (glycosylated hemoglobin, cholesterol, and markers of renal function); the use of advanced statistical techniques, such as time-varying drug exposures and calculation of propensity scores within each risk set; and large sample size, considering the agent and population under study.

STUDY LIMITATIONS. Although this was a rigorous observational study, we must still be cautious in our interpretations and conclusions because causal inferences cannot be made on the basis of observational studies alone. Despite the use of propensity scores, confounding by indication may still introduce bias. Indeed, patients at risk for HF or with asymptomatic left ventricular dysfunction will be potentially less likely to be prescribed other drugs that may make HF worse according to clinical judgment. However, we did find that sitagliptin use was not associated with risk of glaucoma, arguing against any substantial residual confounding. In addition, we were not able to control for body weight or blood pressure. The inability to adjust for these variables in our analysis may have introduced bias given that DPP-4 inhibitors are weight neutral, and thus sitagliptin may have been preferentially prescribed to those in the highest body mass index categories. Because increased body mass index has been paradoxically associated with improved outcomes in patients with HF (35), this may have resulted in lower event rates in sitagliptin-treated subjects compared with those not treated with sitagliptin; therefore, if anything, our results may underestimate the potential risks of sitagliptin. Furthermore, although we included the use of antihypertensive agents, as well as physician-assigned diagnoses of hypertension, this may not fully account for differences in blood pressure among our groups. We also did not have data available for HF severity or ventricular function. Although we attempted to account for this by adjusting for location of HF diagnosis, sitagliptin still may have had differential effects or may have been differentially prescribed in those with more or less severe HF. Finally, because sitagliptin has only recently come onto the market, the number of patients exposed to sitagliptin was relatively small and we had a relatively short duration of follow-up to detect adverse effects or potential benefits, resulting in wide CIs around our risk estimates, particularly for HF-specific events.

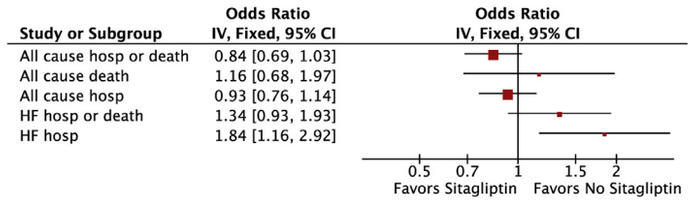

FIGURE 3 Forest Plot of Primary and Secondary Endpoints According to Sitagliptin Use

Primary and secondary endpoints after incident HF were evaluated according to sitagliptin use versus nonuse 90 days before each outcome. CI = confidence interval; HF = heart failure; hosp = hospitalization; IV = interval.

CONCLUSIONS

Current clinical practice guidelines suggest that metformin should be considered first-line therapy in patients with diabetes and HF, with the choice of second-line therapy left to the discretion of the attending physician on the basis of other patient considerations (2,3). Other studies have found that sitagliptin has a similar efficacy for lowering blood glucose compared with other agents, rarely causes hypoglycemia, and is weight neutral, whereas in the current study we found that sitagliptin therapy does not seem to be associated with increased risk of all-cause death or hospital admission. In addition, our ancillary analyses demonstrated that metformin/sitagliptin combination therapy was safer than metformin/sulfonylurea combination for our primary outcome. However, we also found that there may be

a safety signal associated with sitagliptin in terms of an excess of HF-related hospitalizations in those with established HF. Therefore, both the benefits and the potential risks of sitagliptin therapy should be weighed when choosing a second-line therapy in those with diabetes and HF.

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REFERENCES

1. Eurich DT, McAlister FA, Blackburn DF, et al. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. BMJ 2007;335:497.

2. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008;32 Suppl 1:S1–201.

3. Summary of revisions for the 2013 clinical practice recommendations. Diabetes Care 2013; 36 Suppl 1:S3.

4. Gomez N, Touihri K, Matheeussen V, et al. Dipeptidyl peptidase IV inhibition improves cardiorenal function in overpacing-induced heart failure. Eur J Heart Fail 2012;14:14–21.

5. Picatoste B, Ramirez E, Caro-Vadillo A, et al. Sitagliptin reduces cardiac apoptosis, hypertrophy and fibrosis primarily by insulin-dependent mechanisms in experimental type-II diabetes. Potential roles of GLP-1 isoforms. PLoS One 2013; 8:e78330.

6. Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. Diabetes Care 2010;33:428–33.

7. Peters A. Incretin-based therapies: review of current clinical trial data. Am J Med 2010;123: S28–37.

8. Patil HR, Al Badarin FJ, Al Shami HA, et al. Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. Am J Cardiol 2012;110:826–33.

9. Engel SS, Golm GT, Shapiro D, Davies MJ, Kaufman KD, Goldstein BJ. Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: a pooled analysis. Cardiovasc Diabetol 2013;12:3.

10. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomised clinical trials. Diabetes Obes Metab 2014;16:38–47.

11. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013; 369:1317–26.

12. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–35.

13. US Food and Drug Administration. FDA Drug Safety Communication: FDA to review heart failure risk with diabetes drug saxaglipitin (marketed as Onglyza and Kombiglyze XR). Silver Spring, MD: US Food and Drug Administration; 2014.

14. Segal JB, Dy SM, Millman EA, Herbert R, Bass EB, Wu A. Diffusion into use of exenatide for glucose control in diabetes mellitus: a retrospective cohort study of a new therapy. Clin Ther 2007;29:1784–94.

15. Riedel AA, Heien H, Wogen J, Plauschinat CA. Loss of glycemic control in patients with type 2 diabetes mellitus who were receiving initial metformin, sulfonylurea, or thiazolidinedione monotherapy. Pharmacotherapy 2007;27:1102–10.

16. Duh MS, Gosselin A, Luo R, Lohoues H, Lewis BE, Crawley JA. Impact of compliance with proton pump inhibitors on NSAID treatment. Am J Manag Care 2009;15:681–8.

17. Borah BJ, Darkow T, Bouchard J, Aagren M, Forma F, Alemayehu B. A comparison of insulin use, glycemic control, and health care costs with insulin detemir and insulin glargine in insulin-naive patients with type 2 diabetes. Clin Ther 2009;31: 623–31.

18. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. Am J Epidemiol 1994; 140:1016–9.

19. Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. Ann Epidemiol 2002;12: 462–8.

20. Eurich DT, Simpson S, Senthilselvan A, Asche CV, Sandhu-Minhas JK, McAlister FA. Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes: retrospective population based cohort study. BMJ 2013;346: f2267.

21. Lubin JH, Gail MH. Biased selection of controls for case-control analyses of cohort studies. Biometrics 1984;40:63–75.

22. Essebag V, Platt RW, Abrahamowicz M, Pilote L. Comparison of nested case-control and survival analysis methodologies for analysis of time-dependent exposure. BMC Med Res Methodol 2005;5:5.

23. Richardson DB. An incidence density sampling program for nested case-control analyses. Occup Environ Med 2004;61:e59.

24. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA 2007;298:2634–43.

25. Penson DF, Stoddard ML, Pasta DJ, Lubeck DP, Flanders SC, Litwin MS. The association between socioeconomic status, health insurance coverage, and quality of life in men with prostate cancer. J Clin Epidemiol 2001;54:350–8.

26. Huberman M, Langholz B. Application of the missing-indicator method in matched case-control studies with incomplete data. Am J Epidemiol 1999;150:1340–5.

27. Johns Hopkins University. The Johns Hopkins ACG System Reference Guide. Baltimore, MD: John Hopkins University; 2012.

28. Sternberg SA, Bentur N, Abrams C, et al. Identifying frail older people using predictive modeling. Am J Manag Care 2012;18:e392–7.

29. Austin PC, Walraven C. The mortality risk score and the ADG score: two points-based scoring systems for the Johns Hopkins aggregated diagnosis groups to predict mortality in a general adult population cohort in Ontario, Canada. Med Care 2011;49:940–7.

30. Ezekowitz JA, Kaul P, Bakal JA, Quan H, McAlister FA. Trends in heart failure care: has the incident diagnosis of heart failure shifted from the hospital to the emergency department and outpatient clinics? Eur J Heart Fail 2011;13: 142–7.

31. Rassen JA, Shelat AA, Franklin JM, Glynn RJ, Solomon DH, Schneeweiss S. Matching by propensity score in cohort studies with three treatment groups. Epidemiology 2013;24:401–9.

32. Juurlink DN, Gomes T, Shah BR, Mamdani MM. Adverse cardiovascular events during treatment with glyburide (glibenclamide) or gliclazide in a high-risk population. Diabet Med 2012;29: 1524–8.

33. Abdelmoneim AS, Eurich DT, Gamble JM, et al. Risk of acute coronary events associated with glyburide compared with gliclazide use in patients with type 2 diabetes: a nested case-control study. Diabetes Obes Metab 2014;16:22–9.

34. Bristol-Myers Squibb. AstraZeneca and Bristol-Myers Squibb Announce Top Line Results for SAVOR-TIMI-53 Cardiovascular Outcomes Trial of Onglyza® (saxagliptin). New York, NY: Bristol-Myers Squibb; 2013.

35. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008;156:13–22.

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The Diastolic Pulmonary Gradient Does Not Predict Survival in Patients With Pulmonary Hypertension Due to Left Heart Disease

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ABSTRACT

OBJECTIVES This study sought to evaluate if diastolic pulmonary gradient (DPG) can predict survival in patients with pulmonary hypertension due to left heart disease (PH-LHD).

BACKGROUND Patients with combined post- and pre-capillary PH-LHD have worse prognosis than those with passive pulmonary hypertension. The transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR) have commonly been used to identify high-risk patients. However, these parameters have significant shortcomings and do not always correlate with pulmonary vasculature remodeling. Recently, it has been suggested that DPG may be better a marker, yet its prognostic ability in patients with cardiomyopathy has not been fully assessed.

METHODS A retrospective cohort of 1,236 patients evaluated for unexplained cardiomyopathy at Johns Hopkins Hospital was studied. All patients underwent right heart catheterization and were followed until death, cardiac transplantation, or the end of the study period (mean time 4.4 years). The relationships between DPG, TPG, or PVR and survival in subjects with PH-LHD ($n = 469$) were evaluated with Cox proportional hazards regression and Kaplan-Meier analyses.

RESULTS DPG was not significantly associated with mortality (hazard ratio [HR]: 1.02, $p = 0.10$) in PH-LHD whereas elevated TPG and PVR predicted death (HR: 1.02, $p = 0.046$; and HR: 1.11, $p = 0.002$, respectively). Similarly, DPG did not differentiate survivors from non-survivors at any selected cut points including a DPG of 7 mm Hg.

CONCLUSIONS In this retrospective study of patients with cardiomyopathy and PH-LHD, an elevated DPG was not associated with worse survival. (J Am Coll Cardiol HF 2015;3:9–16) © 2015 by the American College of Cardiology Foundation.

Patients with pulmonary hypertension (PH) due to left heart disease (PH-LHD), defined as pulmonary capillary wedge pressure (PCWP) >15 mm Hg and mean pulmonary artery pressure (mPAP) ≥25 mm Hg, have worse prognosis compared to those without PH (1). Among those patients with PH, 2 phenotypes have been described: 1) a group of isolated post-capillary or "passive" PH in which elevated pulmonary pressures are reversible and in proportion to increases in left atrial pressure; and 2) a group with "pre-capillary" component (combined post-capillary and pre-capillary pulmonary hypertension [CpcPH]) whose pulmonary hypertension is worse than can be fully explained by passive elevation secondary to elevated left atrial pressure. This latter group may have comorbid pulmonary vascular

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ABBREVIATIONS AND ACRONYMS

CpcPH = combined post-capillary and pre-capillary pulmonary hypertension

dPAP = diastolic pulmonary artery pressure

DPG = diastolic pulmonary gradient

HR = hazard ratio

mPAP = mean pulmonary artery pressure

PCWP = pulmonary capillary wedge pressure

PH = pulmonary hypertension

PH-LHD = pulmonary hypertension due to left heart disease

PVR = pulmonary vascular resistance

TPG = transpulmonary gradient

remodeling and therefore may demonstrate persistent PH after interventions to lower left-sided filling pressures. The ability to accurately define and separate a high-risk subgroup has major implications in the management and outcomes of heart failure patients as those with CpcPH due to left heart disease have worse prognosis (1,2) and may not be suitable for cardiac transplantation (2).

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In an effort to better characterize the 2 populations, several hemodynamic parameters have been used. A transpulmonary gradient (TPG), mPAP-PCWP, >12 to 15 mm Hg and a pulmonary vascular resistance (PVR), TPG/cardiac output, >2.5 to 3 Wood units have been used to describe patients with "out of proportion": or those with a pre-capillary component to PH (1). TPG however, is flow dependent (3) and influenced by elevation in left atrial pressure (4), making it an unreliable marker of the pulmonary vascular contribution to PH-LHD. Although not without limitations, most favor PVR to identify high-risk patients. Our group and others have shown that elevated PVR predicts outcomes in patients with PH-LHD better than TPG (5–7).

More recently diastolic pulmonary gradient (DPG), diastolic pulmonary artery pressure (dPAP) minus PCWP has been proposed to distinguish CpcPH from isolated post-capillary PH (3,8). Elevated DPG (≥7 mm Hg) may be associated with pulmonary vascular remodeling and predict worse survival in individuals with elevated TPG and PH-LHD (9). We have previously shown, however, that DPG is not associated with death after heart transplant, which may call into question the assertion that DPG is a strong marker of intrinsic pulmonary vascular disease in PH-LHD (10). In this study, we sought to determine whether an elevated DPG predicted survival using a cohort of 1,236 patients previously evaluated for unexplained cardiomyopathy (5).

METHODS

PATIENTS. Study subjects included inpatients and outpatients referred to the Johns Hopkins Hospital Cardiomyopathy Service for further evaluation of heart failure due to undiagnosed cardiomyopathy. All patients received treatment of their heart failure prior to undergoing right heart catheterization and biopsy. A total of 1,236 patients were evaluated between December 1982 and December 1997 as previously described (11). All patients underwent extensive work up, which included endomyocardial biopsy with right heart catheterization by a heart failure cardiologist and coronary angiography when indicated. After the evaluation, all patients were assigned a cause of cardiomyopathy. Age, gender, race, height, and weight were recorded at the time of their initial evaluation. The patients were followed until death, cardiac transplantation, or the end of the study period (January 1, 1998). Vital status was obtained from medical records and through a search of the Nation Death Index (12). The study was approved by the Joint Committee on Clinical Investigation at Johns Hopkins Hospital. All patients provided informed consent to use their data in the study.

RIGHT HEART CATHETERIZATION. Patients underwent right heart catheterization by heart failure specialists at the Johns Hopkins catheterization laboratory with a balloon-tipped, flow-directed catheter placed into the right internal jugular vein. Hemodynamics were measured at the time of presentation before optimizing medical therapy. Cardiac output was determined as the mean of 3 to 5 separate measurements with the thermodilution method. Systemic arterial pressure was measured noninvasively. Mean right atrial pressure, systolic pulmonary artery pressure, dPAP, mPAP, and PCWP were recorded at end expiration. PVR was calculated in Wood units as the difference between mPAP and PCWP divided by cardiac output. TPG was calculated as the difference between mPAP and PCWP. DPG was calculated as the difference between the dPAP and PCWP.

STATISTICAL ANALYSIS. Comparison of groups was performed with a Mann-Whitney rank sum test or, for multiple groups, by 1-way analysis of variance. Categorical variables were compared with chi-square test. Hazard ratios (HRs) of death for DPG, TPG, and PVR were estimated with Cox proportional hazards regression analysis in all patients with PH-LHD (PCWP >15 mm Hg and mPAP ≥25 mm Hg). The primary endpoint was death from all causes. Participants who underwent transplantation (n = 36 of 469) were censored at the time of transplantation. Unadjusted and adjusted models for age, gender, race and body mass index were considered. For our sample size (n = 469) and mortality rate (43%), we had adequate power (80%) to detect a 10% or smaller difference in the hazard of death for all of the evaluated hemodynamic parameters. While we might have been underpowered to detect smaller differences in the hazard of death, such small difference in mortality would argue against the use of these parameters to discriminate survivors. Survival was also estimated

with the nonparametric methods of Kaplan and Meier and compared using the log-rank test. A p value (2-tailed) of <0.05 was considered significant. Medians are presented with interquartile range. Statistical analyses were performed using STATA version 12 (Stata Corp., College Station, Texas) and SigmaPlot version 11.0 (Systat Software Inc., San Jose, California).

RESULTS

STUDY POPULATION. Among 1,236 patients who were evaluated with a right heart catheterization for a new diagnosis of heart failure, 1,174 had a complete set of hemodynamics. Most patients had diagnosis of a dilated cardiomyopathy. Of the 1,174 patients, 558 had an elevated PCWP >15 mm Hg. Of those, 469 had mPAP ≥25 mm Hg consistent with PH-LHD. Also, 650 patients did not have PH (mPAP <25 mm Hg). Of the 1,174 patients, 124 (10.6 %) had a DPG ≥7 mm Hg, and, of those, 92 (74.2%) also had PH and 62 (50.0%) had PH-LHD. Therefore, 32 patients without PH (mPAP <25 mm Hg) had a DPG ≥7 mm Hg. In addition, 355 (30.2%) of all patients evaluated and 169 (36.0%) of the subjects with PH-LHD had a negative DPG value. The clinical characteristics and hemodynamics of those patients with a negative DPG are found in Online Table 1. On average, the negative DPG group had worse hemodynamics, as evidenced by lower right and left ventricular stroke work index and higher PCWP.

ASSOCIATION BETWEEN DPG, TPG, OR PVR AND DEATH IN PH-LHD. DPG was not significantly associated with mortality in unadjusted (HR: 1.02, p = 0.08) analysis or after adjusting for age, gender, race, and body mass index (HR: 1.02, p = 0.10) (**Table 1**). TPG was associated with mortality (unadjusted HR: 1.02, p = 0.03) and was borderline significant after adjustment (HR: 1.02, p = 0.046). PVR predicted mortality in our cohort (unadjusted HR: 1.13, p = 0.002; adjusted HR: 1.11, p = 0.002) (**Table 1**). Because DPG, TPG, and PVR have different units, qualitative comparison of HRs per unit change is difficult. Reparameterization of markers by interquartile range allowed comparison between markers. The hazard of mortality appeared more similar in this context; however, the strength of association with reparameterization is not changed and the association with mortality remained strongly significant for PVR, of borderline significance for TPG, and not significant for DPG.

SURVIVAL IN PATIENTS WITH PH-LHD AND ELEVATED DPG. In keeping with the results of the Cox analysis, there was no statistical difference in mortality between high (defined as ≥1, ≥3, ≥5, ≥7, or ≥9 mm Hg) and low DPG groups (<1, <3, <5, <7, or <9 mm Hg) (**Table 2**). We further examined the cutoff of 7 mm Hg, which has previously been shown to be a surrogate marker for CpcPH (9) and has been proposed for clinical use (8). Demographic, diagnostic and hemodynamic data for those subjects (DPG <7 and DPG ≥7 mm Hg) as well as the 650 patients without PH are presented in **Table 3**. Demographic and heart failure diagnosis were similar between the high and low DPG groups. Compared with the lower DPG group (<7 mm Hg), patients with DPG ≥7 mm Hg had higher systemic and pulmonary artery pressures,

TABLE 1 Hazard of Death in DPG, TPG, or PVR

	Hazard Ratio (95% CI) per Unit Increase	Hazard Ratio (95% CI) per Interquartile Increase	p Value
DPG			
Unadjusted	1.02 (1.00–1.05)	1.15 (0.98–1.34)	0.08
Adjusted	1.02 (1.00–1.05)	1.14 (0.98–1.34)	0.10
TPG			
Unadjusted	1.03 (1.00–1.05)	1.20 (1.02–1.41)	0.03
Adjusted	1.02 (1.00–1.05)	1.19 (1.00–1.40)	0.046
PVR			
Unadjusted	1.13 (1.06–1.20)	1.29 (1.12–1.48)	<0.001
Adjusted	1.11 (1.04–1.19)	1.25 (1.09–1.44)	0.002

Adjusted model accounts for age, gender, race, and body mass index.

CI = confidence interval; DPG = diastolic pulmonary gradient; PVR = pulmonary vascular resistance; TPG = transpulmonary gradient.

TABLE 2 Hazard of Death for Participants Using a Variety of Commonly Used DPG Cutoffs

	Hazard Ratio (95% CI) per Interquartile Range	p Value
DPG: cutoff 1 mm Hg (251 participants with high DPG, 218 with low DPG)		
Unadjusted	1.21 (0.92–1.61)	0.18
Adjusted	1.20 (0.90–1.60)	0.21
DPG: cutoff 3 mm Hg (174 participants with high DPG, 295 with low DPG)		
Unadjusted	1.30 (0.98–1.73)	0.07
Adjusted	1.28 (0.96–1.71)	0.09
DPG: cutoff 5 mm Hg (117 participants with high DPG, 352 with low DPG)		
Unadjusted	1.15 (0.84–1.58)	0.40
Adjusted	1.19 (0.87–1.64)	0.28
DPG: cutoff 7 mm Hg (62 participants with high DPG, 407 with low DPG)		
Unadjusted	0.91 (0.60–1.38)	0.66
Adjusted	0.93 (0.61–1.42)	0.74
DPG: cutoff 9 mm Hg (37 participants with high DPG, 432 with low DPG)		
Unadjusted	0.74 (0.43–1.28)	0.28
Adjusted	0.75 (0.42–1.31)	0.31

Adjusted model accounts for age, gender, race, and body mass index.

Abbreviations as in **Table 1**.

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TABLE 3 Demographic, Diagnostic, and Hemodynamic Data of the Different Patient Cohorts

	DPG ≥7 (n = 62)	DPG <7 (n = 407)	p Value*	No PH (n = 650)	p Value†
Demographics					
Age, yrs	49.3 [39.5 to 58.5]	49.0 [36.7 to 60.9]	0.98	46.7 [35.4 to 57.4]	0.11
Height, m	1.75 [1.65 to 1.80]	1.73 [1.68 to 1.83]	0.08	1.73 [1.35 to 1.98]	0.21
Weight, kg	83.8 [68.7 to 98.0]	79.0 [65.9 to 91.8]	0.15	76.8 [63.6 to 89.0]	0.017
Body mass index, kg/m^2	27.3 [22.9 to 30.7]	26.1 [22.9 to 30.9]	0.47	25.5 [22.4 to 29.1]	0.021
Female	18 (29)	149 (37)	0.31‡	274 (42.1)	0.045‡
Race					
Black	29 (47)	140 (35)		208 (32)	
Caucasian	32 (52)	257 (63)		425 (66)	
Other	1 (2)	8 (2)	0.18‡	12 (2)	0.24‡
Diagnosis					
Idiopathic	27 (44)	205 (50)		326 (50)	
Coronary artery disease	5 (8)	41 (10)		36 (6)	
Myocarditis	4 (6)	28 (7)		76 (12)	
Toxic/metabolic	5 (8)	19 (5)		28 (4)	
Other	21 (34)	114 (28)	0.63‡	184 (28)	0.033‡
Hemodynamics					
Heart rate, beats/min	94 [82 to 107]	93 [80 to 106]	0.69	84 [72 to 95]	<0.001
Systemic blood pressure					
Systolic, mm Hg	128 [105 to 151]	117 [104 to 138]	0.04	120 [107 to 137]	0.09
Diastolic, mm Hg	82 [72.0 to 90.3]	77.5 [68.0 to 86.0]	0.01	73 [67.0 to 81.2]	<0.001
Mean, mm Hg	98.2 [87.2 to 111.3]	90.7 [80.7 to 105.4]	0.01	89.5 [81.0 to 100.0]	0.001
Systemic vascular resistance, WU	22.6 [16.3 to 30.1]	20.6 [16.4 to 27.3]	0.52	19.1 [15.2 to 23.1]	<0.001
Left ventricular stroke work index, mm Hg ml/m^2	1,521 [1,208 to 2,236]	1,342 [1,033 to 1,870]	0.035	2,316 [1,766 to 3,041]	<0.001
Right atrial pressure, mm Hg	13 [8.8 to 17.0]	10.0 [7.0 to 15.0]	0.048	4 [2.0 to 6.0]	<0.001
Pulmonary artery pressures					
Systolic, mm Hg	60.0 [51.5 to 70.0]	52.0 [45.0 to 59.0]	<0.001	28 [23.0 to 33.0]	<0.001
Diastolic, mm Hg	31.5 [28.0 to 36.5]	26.0 [22.0 to 30.0]	<0.001	11.5 [8.0 to 15.0]	<0.001
Mean, mm Hg	40.2 [36.7 to 48.8]	34.0 [29.7 to 40.0]	<0.001	17 [13.7 to 10.7]	<0.001
PCWP, mm Hg	22.0 [18.0 to 27.0]	26.0 [22.0 to 30.0]	<0.001	10 [7.0 to 13.0]	<0.001
Cardiac index, l/min/m^2	1.90 [1.55 to 2.5]	1.93 [1.60 to 2.35]	0.96	2.4 [2.0 to 2.8]	<0.001
Right ventricular stroke work index, mm Hg ml/m^2	604 [456 to 795]	511 [354 to 665]	0.001	369 [322 to 432]	<0.001
PVR, WU	4.7 [3.5 to 6.3]	2.2 [1.4 to 3.3]	<0.001	1.37 [0.95 to 2.0]	<0.001
TG, mm Hg	18.3 [16.3 to 21.8]	8.3 [5.7 to 11.7]	<0.001	6.3 [4.7 to 8.3]	<0.001
DPG, mm Hg	9.0 [8.0 to 11.0]	0 [-3.0 to 3.0]	<0.001	1 [-1.0 to 3.0]	<0.001
RA/PCWP	0.54 [0.42 to 0.69]	0.40 [0.29 to 0.56]	<0.001	0.4 [0.25 to 0.57]	<0.001

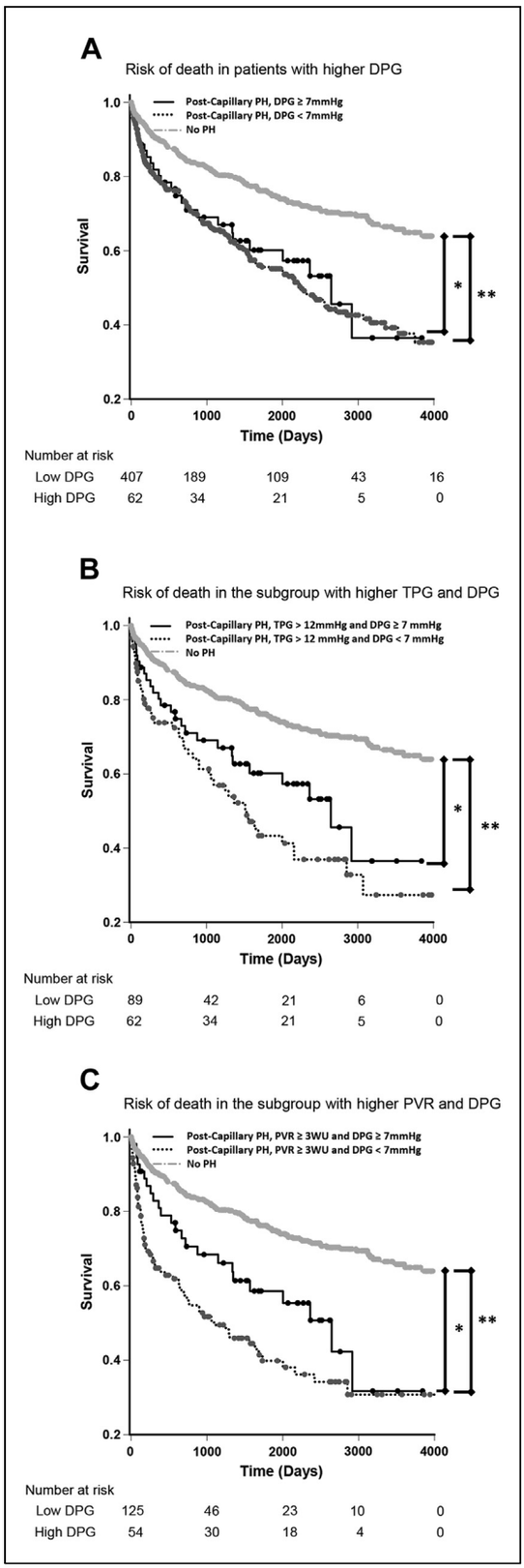
Values are median [interquartile range] or n (%). No variable was missing in more than 3.3% of participants. *DPG ≥7 versus DPG <7; rank sum test unless otherwise indicated. †Comparison of all 3 groups; analysis of variance unless otherwise indicated. ‡Chi-square test.

PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; RA = right atrial; WU = Wood units; other abbreviations as in Table 1.

higher right and left ventricular stroke work index, and higher PVR. Patients with a lower DPG had a higher PCWP (26 vs. 22 mm Hg; p < 0.001). No difference in survival between the 2 groups at a mean follow-up time of 4.4 years was observed (Figure 1A).

SURVIVAL IN PATIENTS WITH PH-LHD AND ELEVATED TPG OR PVR. After exploring various TPG cutoff points (high defined as >6, >9, >12, or 15 mm Hg and low defined as ≤6, ≤9, ≤12, or ≤15 mm Hg), a TPG >9 mm Hg significantly differentiated survivors from nonsurvivors (Table 4). In a subcohort of patients with TPG >12 mm Hg (n = 151), higher DPG (≥7 mm Hg) was not associated with increased mortality (Figure 1B).

All PVR cutpoints explored (low defined as <2, <2.5, <3, or <3.5 and high defined as ≥2, ≥2.5, ≥3, or ≥3.5 Wood units) predicted worse survival in the original cohort (Table 4). In exploratory models, PVR was considered as an effect modifier of the relationship between DPG or TPG and death. PVR did not significantly modify the association between TPG and death (p for interaction = 0.13). PVR did modify the association between DPG and death such that increasing DPG decreased the hazard of death at high levels of PVR (p for interaction = 0.02; interaction term HR: 0.98). Similarly, Figure 1C suggests that in subjects with PVR ≥3 mm Hg (n = 179), those subjects with a low DPG (<7 mm Hg) trended toward worse



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survival compared with high DPG (≥7 mm Hg; p = 0.051). The number of participants at risk in these exploratory subgroup analyses was relatively small and estimates of association may be unstable.

Removing patients with HIV diagnosis (who had an overall worse prognosis during this study period), those with an infiltrative disease (amyloid/sarcoid), and those with a diagnosis of restrictive cardiomyopathy left a cohort of 419 PH-LHD patients. DPG also did not predict survival in this cohort (Online Table 2).

DISCUSSION

In the present study, we used a well-characterized, large cohort of patients previously evaluated by the cardiomyopathy service at Johns Hopkins Hospital with right heart catheterization and cardiac biopsy (5), to assess the ability of DPG to predict mortality. DPG used independently or in combination with elevated TPG or PVR and in either unadjusted or adjusted analyses, failed to predict mortality in patients with PH-LHD. Conversely, PVR was associated with decreased survival in all analyses in subjects with PH-LHD, similar to prior analyses (6,7,13).

In PH-LHD, elevated left heart filling pressures are transmitted to the pulmonary veins and lead to increased dPAP. Persistent pulmonary venous congestion results in endothelial dysfunction with decreased nitric oxide production and increased production of vasoactive factors (e.g., endothelin-1, angiotensin II) favoring vasoconstriction, and may ultimately lead to irreversible remodeling of the pulmonary vasculature (8,14). Elevation in left atrial pressure also leads to increased vascular stiffness (decreased compliance). This results in an increased systolic pulmonary artery pressure, and therefore mPAP, leading to elevation of TPG as well as PVR

FIGURE 1 Kaplan-Meier Survival Curves in All Patients Evaluated for Heart Failure

(A) In patients with pulmonary hypertension due to left heart disease (PH-LHD), mean pulmonary artery pressure ≥25 mm Hg and pulmonary capillary wedge pressure >15 mm Hg, higher diastolic pulmonary gradient (DPG) (≥7 mm Hg) failed to discriminate survivors. Patients without pulmonary hypertension (PH) had better survival. **(B)** In the subgroup of increased transpulmonary gradient (TPG), low DPG did not discriminate survivors. **(C)** In subjects with PH-LHD and pulmonary vascular resistance (PVR) ≥3 Wood units, lower DPG showed a trend toward worse survival (p = 0.051). *p < 0.05, **p < 0.001.

TABLE 4 Hazard of Death for Participants for a Variety of Commonly Used TPG and PVR Cutoffs

	Hazard Ratio (95% CI) per Interquartile Range	p Value
TPG: cutoff 6 mm Hg (362 participants with high TPG, 107 with low TPG)		
Unadjusted	1.26 (0.90–1.78)	0.18
Adjusted	1.29 (0.91–1.84)	0.16
TPG: cutoff 9 mm Hg (236 participants with high TPG, 233 with low TPG)		
Unadjusted	1.34 (1.01–1.77)	0.04
Adjusted	1.34 (1.00–1.79)	0.05
TPG: cutoff 12 mm Hg (152 participants with high TPG, 317 with low TPG)		
Unadjusted	1.24 (0.92–1.66)	0.14
Adjusted	1.19 (0.88–1.60)	0.26
TPG: cutoff 15 mm Hg (89 participants with high TPG, 380 with low TPG)		
Unadjusted	0.91 (0.60–1.38)	0.66
Adjusted	0.93 (0.61–1.42)	0.74
PVR: cutoff 2 WU (298 participants with high PVR, 171 with low PVR)		
Unadjusted	1.60 (1.18–2.18)	0.003
Adjusted	1.48 (1.07–2.03)	0.02
PVR: cutoff 2.5 WU 223 participants with high PVR, 246 with low PVR)		
Unadjusted	1.78 (1.34–2.36)	<0.001
Adjusted	1.59 (1.18–2.13)	0.002
PVR: cutoff 3 WU 184 participants with high PVR, 285 with low PVR)		
Unadjusted	1.79 (1.35–2.36)	<0.001
Adjusted	1.57 (1.18–2.10)	0.002
PVR: cutoff 3.5 WU (132 participants with high PVR, 337 with low PVR)		
Unadjusted	1.60 (1.18–2.18)	0.003
Adjusted	1.48 (1.07–2.03)	0.02

Adjusted model accounts for age, gender, race, and body mass index.
WU = Wood units; other abbreviations as in Table 1.

(4,14). Both of these factors depend on the flow (cardiac output) (3). The dPAP, however, is less sensitive to these effects, and therefore DPG (dPAP minus PCWP) has been recommended as an alternative and more reliable marker of PH-LHD with a pre-capillary component (8).

The prognostic capability of DPG in patients with CpcPH was recently evaluated in a cohort of 1,094 patients with PH-LHD. In this study by Gerges et al. (9), participants with a TPG >12 mm Hg and a DPG ≥7 mm Hg had worse survival compared to those with a TPG ≤12 mm Hg and a DPG <7 mm Hg. In 18 of these participants, lung tissue was evaluated and participants with elevated DPG had advanced remodeling of the pulmonary vasculature (9). This study coupled with sound physiologic reasoning has led to the recent recommendations from the Fifth World Symposium on Pulmonary Hypertension that DPG be the sole discriminator of pre- and post-capillary PH in those with left heart disease (8). Our heart failure cohort was significantly different from the study population of Gerges et al. (9) as it had relatively lower incidence of PH (44% vs. 91%) Our patients were also younger and were less likely to have an ischemic cardiomyopathy. When considering only the PH-LHD patients, the distribution of CpcPH (TPG >12 mm Hg) was relatively similar (32% vs. 45%).

Using the United Network of Organ Sharing database, we recently demonstrated that elevated pre-transplant DPG had no association with post-transplant survival (10). These findings argued against DPG as a marker of clinically significant irreversible pulmonary vascular remodeling, although they did not necessarily exclude the possibility that DPG could predict outcomes in a heart failure population that did not undergo transplant. Unfortunately, the findings of the current study do not support the use of DPG in this regard. DPG was not associated with survival in any analysis and high DPG may have even been a marker of better prognosis in an exploratory subgroup of CpcPH with high PVR. The lack of association or even inverse association with mortality may be related to the important observation in our cohort that low DPG may have identified a sicker group of patients with a higher PCWP and lower systemic blood pressure. This was true in both the entire cohort of 1,174 patients as well as those only with PH-LHD.

Despite its promise, the use of DPG has significant shortcomings and limitations. The DPG may be particularly susceptible to technical errors. Measurement of dPAP, particularly when using fluid filled catheters, is subject to error from catheter motion artifacts. This likely accounts for the negative DPG values observed in our study as well as others. In a study of critically ill patients by Wilson et al. (15), the DPG was negative in 18.5% of the readings. Similar results have been reported after coronary artery bypass surgery (16). Moreover, in a classic investigation by Harvey et al. (17), patients with left heart disease had a mean DPG of -2 mm Hg. Even small errors in the measurement of dPAP or PCWP will have a major impact on the DPG given its relatively low absolute value. As previously highlighted by Ryan et al. (18), the use of computerized mean PCWP pressures averaged throughout the respiratory cycle rather than end-expiratory measurements leads to an underestimation of the true PCWP, particularly in patients with higher intrathoracic pressures. In addition, inaccurate wedging of the pulmonary artery catheter can overestimate PCWP leading to falsely low DPG. Finally, DPG itself accounts for only a small proportion of total right ventricular load in patients

with PH-LHD and therefore may not be necessarily associated with significant right ventricular dysfunction. Right ventricular function is a well-known prognosticator of outcomes in heart failure, and therefore, PVR may be a superior prognosticator because it includes flow assessment (19). However, even in patients with an elevated PVR, an elevated DPG was not associated with worse prognosis.

The use of DPG in PH is not new and it was extensively studied in previous decades (15,17,20). Many factors other than pulmonary vascular remodeling also affect the DPG. DPG is acutely elevated in several different clinical scenarios including hypoxemia in patients with acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD) (17,21,22), after coronary artery bypass surgery (15), and in sepsis due to acidosis, release of endotoxins, or microthrombi (17,23). Tachycardia, which is commonly encountered in individuals with LHD due to decreased cardiac output, tachyarrhythmias, or inotropic support, also increases the DPG (24).

STUDY LIMITATIONS. We acknowledge that our retrospective study has several limitations. First, our cohort included patients evaluated for unexplained cardiomyopathy with a broad representation of different heart failure pathologies, which may not necessarily represent the general heart failure population. Although this cohort consisted of patients with both preserved and reduced function, most patients had a diagnosis of a dilated cardiomyopathy, leaving open the possibility that DPG may have a prognostic ability in heart failure with preserved ejection fraction, or in a more select group of heart failure patients. Because the incidence of PH-LHD was relatively low in our population (44%), this could limit our power to detect a difference in survival between the low and high DPG groups. However, TPG, and in particular PVR, did discriminate survivors from nonsurvivors. The large number of patients with a negative DPG (assuming the negative DPG is the result of measurement error) could bias the results, as the actual DPG may have been elevated in these patients. If this limitation is true then this may speak to a real-world limitation to the use of DPG because these measurements were performed by heart failure cardiologists with significant experience in hemodynamic evaluations. It also remains possible that a very high DPG similar to those seen in idiopathic pulmonary artery hypertension (~20 mm Hg) (25) could predict survival. Nevertheless, those patients are quite rare in PH-LHD (in this analysis only 9 patients had a DPG>15 mm Hg and only 4 had a DPG >20 mm Hg). PVR and TPG might have influenced the decision of who was ultimately transplanted. In accordance with previous investigations on this topic, we censored participants who went on to require transplantation (n = 36) at the time of transplantation. Censoring participants at the time of transplant could lead to an underestimation of mortality. Furthermore, information regarding medical therapies, echocardiography, and other comorbid conditions such as COPD, smoking, sleep apnea, atrial fibrillation, and renal failure was not available and therefore their association with PH-LHD and survival could not be assessed. In addition, our analysis did not correct for multiple comparisons. Finally, hemodynamic data on response to vasodilators to evaluate the reversibility of PH was not routinely tested in this cohort.

CONCLUSIONS

Our study shows that in a large cohort of patients with PH due to left heart disease, including those with out-of-proportion (elevated TPG and PVR) PH, the DPG did not discriminate survivors from nonsurvivors. Considering the technical limitations interfering with the accurate measurement of DPG and other clinical factors that affect the DPG aside from pulmonary vasculature remodeling, this work argues against the use of DPG as a marker of prognosis in patients with PH-LHD. Likewise, the routine use of DPG in diagnostic algorithms of PH-LHD is premature and requires further validation.

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REFERENCES

1. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012;126:975–90.

2. Mehra MR, Jessup M, Gronda E, Costanzo MR. Rationale and process: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant 2006;25:1001–2.

3. Naeije R, Vachiery JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 2013;41:217–23.

4. Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation 2012;125:289–97.

5. Cappola TP, Felker GM, Kao WH, Hare JM, Baughman KL, Kasper EK. Pulmonary hypertension

and risk of death in cardiomyopathy: patients with myocarditis are at higher risk. Circulation 2002; 105:1663–8.

6. Khush KK, Tasissa G, Butler J, McGlothlin D, De MT. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. Am Heart J 2009;157:1026–34.

7. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction. J Am Coll Cardiol HF 2013;1:290–9.

8. Vachiery JL, Adir Y, Barbera JA, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 2013;62:D100–8.

9. Gerges C, Gerges M, Lang MB, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest 2013;143:758–66.

10. Tedford RJ, Beaty CA, Mathai SC, et al. Prognostic value of the pre-transplant diastolic pulmonary artery pressure to pulmonary capillary wedge pressure gradient (DPG) in cardiac transplant recipients with pulmonary hypertension. J Heart Lung Transplant 2014;33:289–97.

11. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;342:1077–84.

12. Boyle CA, Decoufle P. National sources of vital status information: extent of coverage and possible selectivity in reporting. Am J Epidemiol 1990;131:160–8.

13. Aronson D, Eitan A, Dragu R, Burger AJ. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure. Circ Heart Fail 2011;4:644–50.

14. Guazzi M, Arena R. Pulmonary hypertension with left-sided heart disease. Nat Rev Cardiol 2010;7:648–59.

15. Wilson RF, Beckman SB, Tyburski JG, Scholten DJ. Pulmonary artery diastolic and wedge pressure relationships in critically ill and injured patients. Arch Surg 1988;123:933–6.

16. Heinonen J, Salmenpera M, Takkunen O. Increased pulmonary artery diastolic-pulmonary wedge pressure gradient after cardiopulmonary bypass. Can Anaesth Soc J 1985;32:165–70.

17. Harvey RM, Enson Y, Ferrer MI. A reconsideration of the origins of pulmonary hypertension. Chest 1971;59:82–94.

18. Ryan JJ, Rich JD, Thiruvoipati T, Swamy R, Kim GH, Rich S. Current practice for determining pulmonary capillary wedge pressure predisposes to serious errors in the classification of patients with pulmonary hypertension. Am Heart J 2012; 163:589–94.

19. Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37:183–8.

20. Sibbald WJ, Paterson NA, Holliday RL, Anderson RA, Lobb TR, Duff JH. Pulmonary hypertension in sepsis: measurement by the pulmonary arterial diastolic-pulmonary wedge pressure gradient and the influence of passive and active factors. Chest 1978;73:583–91.

21. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 1977;296:476–80.

22. Her C, Mandy S, Bairamian M. Increased pulmonary venous resistance contributes to increased pulmonary artery diastolic-pulmonary wedge pressure gradient in acute respiratory distress syndrome. Anesthesiology 2005;102:574–80.

23. Marland AM, Glauser FL. Significance of the pulmonary artery diastolic-pulmonary wedge pressure gradient in sepsis. Crit Care Med 1982;10:658–61.

24. Enson Y, Wood JA, Mantaras NB, Harvey RM. The influence of heart rate on pulmonary arterial-left ventricular pressure relationships at end-diastole. Circulation 1977;56:533–9.

25. Adir Y, Humbert M, Sitbon O, et al. Out-of-proportion pulmonary hypertension and heart failure with preserved ejection fraction. Respiration 2013;85:471–7.

KEY WORDS diastolic pulmonary gradient, pulmonary hypertension, left heart disease, survival

APPENDIX For supplemental tables, please see the online version of this article.

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The Effect of Coenzyme Q_{10} on Morbidity and Mortality in Chronic Heart Failure

Results From Q-SYMBIO: A Randomized Double-Blind Trial

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ABSTRACT

OBJECTIVES This randomized controlled multicenter trial evaluated coenzyme Q_{10} (CoQ_{10}) as adjunctive treatment in chronic heart failure (HF).

BACKGROUND CoQ_{10} is an essential cofactor for energy production and is also a powerful antioxidant. A low level of myocardial CoQ_{10} is related to the severity of HF. Previous randomized controlled trials of CoQ_{10} in HF were underpowered to address major clinical endpoints.

METHODS Patients with moderate to severe HF were randomly assigned in a 2-year prospective trial to either CoQ_{10} 100 mg 3 times daily or placebo, in addition to standard therapy. The primary short-term endpoints at 16 weeks were changes in New York Heart Association (NYHA) functional classification, 6-min walk test, and levels of N-terminal pro-B type natriuretic peptide. The primary long-term endpoint at 2 years was composite major adverse cardiovascular events as determined by a time to first event analysis.

RESULTS A total of 420 patients were enrolled. There were no significant changes in short-term endpoints. The primary long-term endpoint was reached by 15% of the patients in the CoQ_{10} group versus 26% in the placebo group (hazard ratio: 0.50; 95% confidence interval: 0.32 to 0.80; $p = 0.003$) by intention-to-treat analysis. The following secondary endpoints were significantly lower in the CoQ_{10} group compared with the placebo group: cardiovascular mortality (9% vs. 16%, $p = 0.026$), all-cause mortality (10% vs. 18%, $p = 0.018$), and incidence of hospital stays for HF ($p = 0.033$). In addition, a significant improvement of NYHA class was found in the CoQ_{10} group after 2 years ($p = 0.028$).

CONCLUSIONS Long-term CoQ_{10} treatment of patients with chronic HF is safe, improves symptoms, and reduces major adverse cardiovascular events. (Coenzyme Q10 as adjunctive treatment of chronic heart failure: a randomised, double-blind, multicentre trial with focus on SYMptoms, BIomarker status [Brain-Natriuretic Peptide (BNP)], and long-term Outcome [hospitalisations/mortality]; ISRCTN94506234) (J Am Coll Cardiol HF 2014;2:641–9) © 2014 by the American College of Cardiology Foundation.

Optimal therapy of heart failure (HF) is a considerable challenge. Standard treatments are administered to block rather than to enhance cellular processes (1), and some important requirements of the myocardium may not be covered. There are multiple causes of HF, but dysfunction of bioenergetics leading to energy starvation of the cardiac myocytes may be an important

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CoQ_{10} = coenzyme Q_{10}

EF = ejection fraction

HF = heart failure

HR = hazard ratio

MACE = major adverse cardiovascular event(s)

6MWT = 6-min walk test

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

RCT = randomized controlled trial

VAS = visual analogue scale

contributive mechanism (2,3). Coenzyme Q_{10} (CoQ_{10}) is a powerful lipid-soluble antioxidant (4), as well as a central redox component of the electron transport chain and the synthesis of adenosine triphosphate (5). A reduced myocardial tissue content of CoQ_{10} has been demonstrated in patients with HF, and it correlates with the severity of symptoms and the degree of left ventricular dysfunction (6). Low plasma CoQ_{10} has been shown to be an independent predictor of mortality in HF (7), but this was not replicated in another observational study (8). Published meta-analyses of randomized controlled trials (RCTs) with CoQ_{10} in HF have mostly indicated a positive effect on left ventricular ejection fraction (EF) with or without improvement of New York Heart Association (NYHA) functional class (9–11). The RTCs have been underpowered to address major clinical endpoints. In 2 systematic reviews, there was either a nonsignificant trend toward reduced mortality (12) or no effect on total mortality from CoQ_{10} (13).

SEE PAGE 650

We report the results of Q-SYMBIO, a prospective, randomized, double-blind, placebo-controlled, multicenter trial of CoQ_{10} as adjunctive treatment of chronic HF focusing on changes in *SYM*ptoms, *BI*omarker status, and long-term *O*utcome.

METHODS

Patients were enrolled in 17 European, Asian, and Australian centers from 2003 to 2010. Q-SYMBIO was conducted according to good clinical practice guidelines.

In previous RCTs with CoQ_{10} in HF, the authors aimed for a serum level of CoQ_{10} of at least 2 μg/ml, by using a dosage of 100 to 200 mg/day to obtain a positive clinical effect. A dosage of CoQ_{10} 100 mg twice daily provided a better absorption and a higher serum level compared with 200 mg once daily, probably because of a saturation phenomenon with a delay of uptake in the small intestine (14). In Q-SYMBIO, we selected the CoQ10 dosage in the active treatment group to be 100 mg 3 times daily to ensure a significant increase in the serum level.

The study data from clinical record forms were sent by the investigators to the Data and Safety Monitoring Board, which blindly evaluated all possible adverse events in the 2 treatment arms. Clinical endpoints were adjudicated in a blinded fashion by the Clinical Endpoint Committee. All analyses were performed by the independent statistician after the study was terminated. The study was approved by the institutional review board and the regional ethics committee of each participating institution and by the appropriate national ethics committees and was conformed to the ethical guidelines of the Declaration of Helsinki. All patients provided written informed consent. The study was registered at the International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN94506234).

OBJECTIVES

The study had a 2-phase objective. The aim of the short-term part (16 weeks) was a blinded evaluation of patients' symptoms (NYHA functional class) and functional status with visual analogue scale (VAS) for symptoms (Online Appendix 1), a 6-min walk test (6MWT), and echocardiography (left ventricular EF and cavity dimensions). Serum samples were obtained for determination of CoQ_{10} and N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of HF (15). The aim of the long-term part (106 weeks) of the study was to test, on an intention-to-treat basis, whether CoQ_{10} could reduce cardiovascular morbidity and mortality in HF as a composite endpoint.

The primary short-term endpoints were NYHA functional class, 6MWT, and NT-proBNP. A secondary endpoint was scoring of symptoms on VAS: dyspnea, fatigue, and change of symptoms.

The primary long-term endpoint was composite major adverse cardiovascular events (MACE), consisting of unplanned hospital stay resulting from worsening HF, cardiovascular death, mechanical assist implantation, or urgent cardiac transplantation; a time to first event analysis was used. Secondary long-term endpoints were NYHA functional class, NT-proBNP, echocardiography, and mortality.

PATIENTS. Patients were eligible for enrollment if they had chronic HF in NYHA functional class III or IV. Patients were included with typical symptoms and signs of HF. A specific cut-point with respect to EF was not used. The trial enrollment criteria are listed in the Online Table 1.

STUDY DESIGN AND FOLLOW-UP. Patients meeting the inclusion criteria were further assessed for eligibility in the run-in period of 2 weeks on placebo capsules 3 times daily. The patients were evaluated at the start and end of the run-in period regarding NYHA functional classification, with VAS, 6MWT, and echocardiography. Serum samples were obtained for measurements of CoQ_{10} and NT-proBNP. Patients with stable standard HF therapy were randomized in parallel groups to either CoQ_{10} or identical placebo

capsules (Online Appendix 2). The randomization code was prepared by means of a random number generator software in blocks of 6 and was kept in sealed envelopes. Sequentially numbered coded drug packs were distributed, supervised by a central pharmacist to the local center with the instruction to assign new patients to the next available randomization number.

Clinical parameters were registered again after 16 weeks with VAS, 6MWT, and echocardiography, and serum samples for CoQ_{10} and NT-proBNP were repeated. An overview of the times of effect recordings up to 106 weeks is shown in the Online Table 2. All patients continued to receive the assigned treatment for the intended duration of the study. Patients were censored when they reached their first primary endpoint (MACE), and only the first event was included in this analysis. Patients were offered to continue the study medication blindly after a MACE (i.e., hospital stay for HF) for up to 2 years from randomization.

Patients undergoing implantation of a cardiac resynchronization device were censored at the time of implantation. Devices were not inserted for worsening HF but as a result of logistics in the centers after this therapy was introduced while our study was ongoing (16). Patients listed in status 2 for heart transplantation were censored at the admission for the procedure. This was not an endpoint but an elective procedure because of a matching donor arrival. Hospital stay for worsening of HF was defined as the occurrence of increasing symptoms and the need for intravenous treatment with diuretics. In addition, the necessity for using inotropic support and the use of intra-aortic balloon pumping were recorded.

In Q-SYMBIO, hospital stays within 30 days of randomization in either group were not counted as primary endpoints. In previous observational studies, improvements in HF symptoms were observed after approximately 4 weeks (up to 12 weeks) of supplementation with CoQ_{10} (14). From absorption trials, it was estimated that at least 2 weeks would be needed before the raised serum level could be translated into an increase in the mitochondrial content of CoQ_{10} (17). Based on this estimate, we found a blanking period of 30 days appropriate. Incorporation of an early quarantine has been applied in other RCTs of HF (16). All possible adverse effects were monitored from the start of the study.

The randomization code was unavailable to investigators, participants, or statisticians at any time during the study until all data material had been collected, all blood samples had been analyzed, and statistical analysis had been performed. The Q-SYMBIO study was closed in the fall of 2012 by the Steering Committee before the planned number of 550 patients was reached, as a result of a low recruitment rate. The DSMB was not involved in the decision to stop the trial, and the code was broken after the final statistical analysis was done and the database had been locked.

DETERMINATION OF SERUM COENZYME Q_{10} AND N-TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE. A sample of 25 ml of venous blood was drawn for measurement of serum CoQ_{10} and NT-proBNP while the patients were resting and before they had breakfast and medications. Serum was isolated from blood samples by centrifugation at 3.000 g and thereafter stored at −20° C or at −80° C (for storage >6 months). Samples of serum were investigated for levels of CoQ_{10} by using high-performance liquid chromatography with ultraviolet detection (18) and NT-proBNP using the Elecsys 2010 immunoassay method (Roche Diagnostics, Mannheim, Germany) (19).

STATISTICAL ANALYSIS. The results of the power calculations in the protocol are presented in the Online Table 3. All pre-specified analyses of responses and endpoints were conducted according to the intention-to-treat principle. Descriptive analyses of baseline data were reported as frequencies. Percentages for categorical data and for continuous data were reported as mean ± SD for normally distributed data and median and lower upper quartile for non-normal data. All responses at weeks 16 and 106 recorded from the health status questionnaires and blood samples were analyzed as individual changes from baseline. The significance of treatment on continuous responses was analyzed by a linear model with each investigational center treated as a random intercept effect. The treatment effects were analyzed and adjusted for pre-defined confounders such as age, sex, NYHA functional class, inclusion diagnosis (HF from ischemic heart disease or dilated cardiomyopathy), and center. A chi-square test for independence with exact p values was calculated for the evaluation of the treatment effect on categorical responses. Cumulative incidence curves for the risk of MACE, hospital stay for HF, total cardiovascular mortality, and all-cause mortality were constructed by the Kaplan-Meier method and were analyzed by the Cox proportional hazards regression model stratified according to center. After the intention-to-treat analysis had been carried out, an additional sensitivity analysis was performed with a worst-case scenario for the primary endpoint by assuming MACE events in patients in the intervention group who were censored because they were lost to follow-up, whereas the

corresponding patients taking placebo were assumed to be event free. The hazard ratio (HR) was adjusted in subanalyses on MACE stratified by the presence of a series of risk factors at baseline; tests of treatment-by-factor interactions were performed. The rates for adverse effects were compared between treatment groups by means of a chi-square test for independence reported with exact p values.

For the primary efficacy variables in the short-term phase, the study would achieve its pre-specified objective if the difference between the groups in all 3 endpoints had a p value ≤0.05. For the primary endpoint in the long-term phase, the study would achieve its pre-specified objective if the difference between the groups had a p value <0.05. For secondary endpoints, p values <0.05 were used to assess statistical significance. All data were analyzed with the statistical analysis program Stata/SE 11·2 for Windows (StataCorp LP, College Station, Texas).

TABLE 1 Baseline Characteristics of the Patients

Characteristic	Current HF Therapy + CoQ_{10} (N = 202)	Current HF Therapy + Placebo (N = 218)
Age, yrs	62.3 ± 12	62.3 ± 11
Male/female ratio	154/48	151/67
Weight, kg	77.1 ± 17	77.9 ± 18
BMI, kg/m^2	28 ± 5	28 ± 6
Heart rate, beats/min	80 ± 16	82 ± 14
Systolic blood pressure, mm Hg	125 ± 18	122 ± 16
Diastolic blood pressure, mm Hg	78 ± 11	77 ± 11
Sinus rhythm	148 (73)	161 (74)
Atrial fibrillation	33 (16)	41 (19)
Rhythm, other (pace)	21 (10)	16 (7)
Ischemic heart disease	137 (68)	156 (72)
Dilated cardiomyopathy	54 (27)	59 (27)
Valvular heart disease	11 (5)	3 (1)
Duration of HF, months	38 ± 47	35 ± 36
NYHA functional class II	6 (3)	8 (4)
NYHA functional class III	178 (88)	189 (87)
NYHA functional class IV	18 (9)	21 (10)
Left ventricular EF, %	31 ± 10 (10-65)	31 ± 10 (10-70)
Left ventricular EDD, mm	66 ± 8	64 ± 9
Left ventricular ESD	55 ± 11	54 ± 11
6MWT (m)	287 ± 98 (25-525)	286 ± 92 (90-490)
Serum CoQ_{10}, μg/ml*	1.14 ± 0.08	0.91 ± 0.06
NT-proBNP, pg/ml*†	1,883 ± 271 (50-799)	1,692 ± 229 (50-735)
Use of medications		
ACE inhibitors/ARBs	178 (90)	195 (90)
Beta-blockers	141 (72)	164 (76)
Digoxin	90 (46)	97 (45)
Diuretics	155 (79)	176 (81)
Aldosterone antagonists	66 (34)	74 (34)
Statin derivatives	74 (38)	77 (35)
Anticoagulation	49 (25)	54 (25)
Diabetes treatment	44 (22)	51 (24)
Device therapy,		
Cardiac resynchronization device	2	5
Implanted cardioverter defibrillator	3	4

Values are mean ± SD, n (%), mean ± SD (range), mean ± SD (median), or n. *Values are mean ± SE. †To convert values for NT-proBNP to picomoles per liter, divide by 8.457.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CoQ_{10} = coenzyme Q_{10}; EDD = end-diastolic diameter; ESD = end-systolic diameter; EF = ejection fraction; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; 6MWT = 6-min walk test.

RESULTS

A total of 420 patients were randomly assigned to active treatment with CoQ_{10} (N = 202) or placebo (N = 218), (Online Appendix 2). There were 36 withdrawals (i.e., 22 patients in the CoQ_{10} group and 14 patients in the placebo group) (consort flow diagram, Online Figure 1). An analysis of the reasons for the withdrawals did not show any significant between-group difference (p = 0.118). Withdrawals were not removed from the intention-to-treat analysis. By the end of the study, the survival status of all patients was known, except for 4 patients in each treatment group who were classified as lost to follow-up. A total of 87 patients had reached the primary endpoint (MACE), and 60 patients had died.

BASELINE CHARACTERISTICS OF THE STUDY POPULATION. The 2 groups were similar with respect to a range of baseline characteristics established after the run-in period at week 2 (**Table 1**). Mean duration of HF was around 3 years in both groups, and baseline EF of mean 31% and 6MWT distances were equal between groups. The standard treatments of HF were balanced between the study groups at baseline. Of these patients, 90% received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 75% received beta-blockers with use of evidence-based dosages according to the guidelines. Modifications of dosages were infrequent throughout the study period, and it is unlikely that the minor changes should have affected differences in endpoints.

Two of 4 patients treated for <30 days with CoQ_{10} (protocol deviation, consort flow diagram) (Online Figure 1) had unplanned hospital stays for HF within 30 days after randomization. There were no fatal events in any of the treatment groups in the blanking period.

EFFECT ON THE SPECIFIED ENDPOINTS AT WEEK 16. There were improvements in NYHA functional class, VAS score, and 6MWT in both treatment groups at week 16, and differences between groups were not statistically significant. There were no significant differences in heart rate, blood pressure, and echocardiographic measurements (Online Table 4). The level of serum CoQ_{10} at week 16 increased significantly to about 3 times the baseline value in the CoQ_{10}-treated group. The between-group changes in

serum NT-proBNP from baseline to week 16 were not significantly different. However, there was a trend with a mean reduction of 384 pg/ml (20%) of NT-proBNP in the CoQ_{10} group and a proportional rise of 199 pg/ml (12%) of NT-proBNP in the placebo group (Online Table 5).

EFFECT ON THE SPECIFIED PRIMARY ENDPOINT AT WEEK 106. At week 106, there were significantly fewer MACE in the CoQ_{10} group (N = 30, 15%) than in the placebo group (N = 57, 26%), findings corresponding to a 43% relative reduction (p = 0.005, Fisher-exact test) (Table 2). From a Cox regression analysis stratified by center, the HR for CoQ_{10} versus placebo was 0.50; 95% confidence interval (CI): 0.32 to 0.80; p = 0.003 (Figure 1A).

Four patients were lost to follow-up in each treatment group. A regulatory approach to a sensitivity analysis could be that the 4 patients in the CoQ_{10} arm are counted as deaths, and the 4 patients in the placebo arm are counted as survivors. If the 2 hospital stays <30 days are included in the sensitivity analysis of the primary endpoint and the 4 patients lost to follow-up in the CoQ_{10} group are counted as deaths and the 4 patients in the placebo group are counted as survivors, the result remains in favor of CoQ_{10} treatment (HR [CoQ_{10} vs. placebo]: 0.64; 95% CI: 0.42 to 0.98; p = 0.038).

EFFECT ON THE SPECIFIED SECONDARY ENDPOINTS AT WEEK 106. At week 106, the CoQ_{10} group showed a greater proportion of patients with improved NYHA functional classification (N = 86, 58%) compared with the placebo group (N = 68, 45%), (p = 0.028), comprising an improvement of at least 1 grade in NYHA functional class. There were no significant between-group differences in the echocardiographic measurements. Serum NT-proBNP was reduced by a mean of 1,137 pg/ml (60%) in the CoQ_{10} group and by a mean of 881 pg/ml (52%) in the placebo group compared with baseline, which was not significantly different between groups (Online Tables 5 and 6).

Cardiovascular deaths. The total number of cardiovascular deaths within the study period of 106 weeks was lower in the CoQ_{10} group (N = 18, 9%) compared with the placebo group (N = 34, 16%), corresponding to a 43% relative reduction (p = 0.039, Fisher-exact test). From a Cox regression analysis stratified by center, the HR (CoQ_{10} vs. placebo) was 0.51; 95% CI: 0.28 to 0.92; p = 0.026 (Online Table 7, Online Figure 2A).

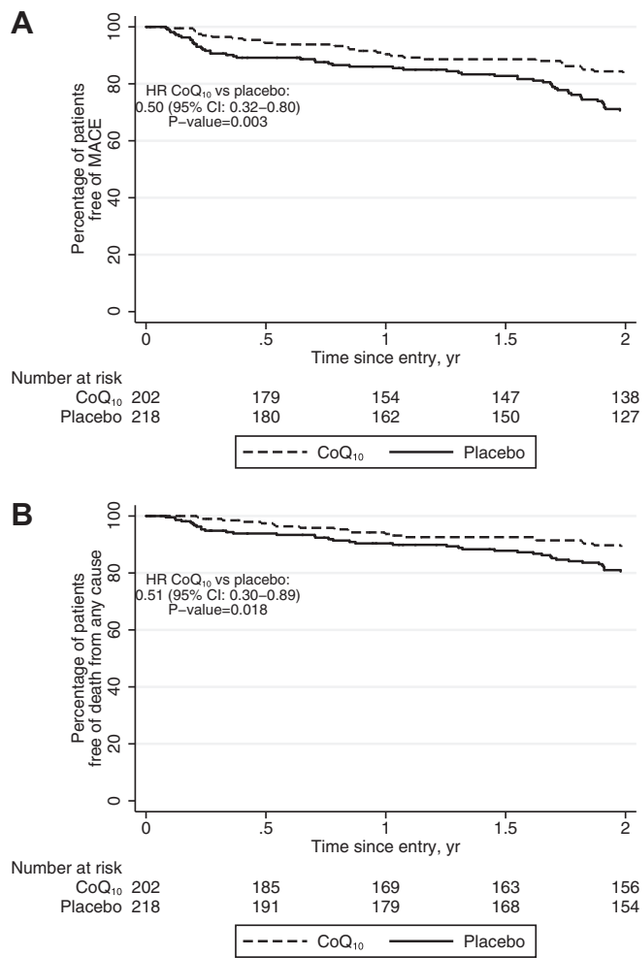

FIGURE 1 Kaplan-Meier Estimates of the Time to Primary and Secondary Endpoints

Kaplan-Meier estimates of the time to the primary endpoint major adverse cardiovascular events (MACE) **(A)** and the secondary outcome death **(B)** in the placebo group **(solid line)** and the coenzyme Q_{10} (CoQ_{10}) group **(dashed line)**. The primary endpoint was composite MACE of hospital stay for worsening heart failure, cardiovascular death, mechanical support, or urgent cardiac transplantation. A specified secondary outcome was death from any cause. CI = confidence interval; HR = hazard ratio.

TABLE 2 Major Adverse Cardiovascular Events

Endpoint	CoQ_{10} (n = 202)	Placebo (n = 218)	Total (N = 420)
Death from MI	2	3	5
Death from HF	1	10	11
Sudden cardiac death	9	13	22
Hospital stay for worsening HF	12	24	36
Hospital stay for acute HF	3	5	8
Hospital stay for acute HF + IABP	2	2	4
LVAD	1	0	1
Total	30* (15%)	57 (26%)	87

Values are n or n (%). *p = 0.005.

IABP = intra-aortic balloon pumping; LVAD = left ventricular assist device; MI = myocardial infarction; other abbreviations as in Table 1.

Hospital stays for heart failure. The number of hospital stays for HF (counted as MACE) was lower in the CoQ_{10} group (N = 17, 8%) versus the placebo group (N = 31, 14%); HR (CoQ_{10} vs. placebo): 0.51; 95% CI: 0.27 to 0.95; p = 0.033 (Online Figure 2B).

Death from any cause. Within the study period of 106 weeks, there were 21 deaths (10%) from all causes in the CoQ_{10} group compared with 39 deaths (18%) in the placebo group, corresponding to a 42% relative reduction (p = 0.036, Fisher-exact test) (Online Table 8). From a Cox regression analysis stratified by center, the HR (CoQ_{10} vs. placebo) was 0.51; 95% CI: 0.30 to 0.89; p = 0.018 (**Figure 1B**). Retrospectively, all-cause mortality was lower in the CoQ_{10} group also at week 16, with HR: 0.18; 95% CI: 0.04 to 0.87; p = 0.032.

Adverse events. The number of adverse events tended to be lower in the CoQ_{10} group compared with the placebo group, 26 (13%) versus 41 (19%), respectively, p = 0.110, (Fisher-exact test) (**Table 3**).

Subgroup analyses. HRs were adjusted in a series of subgroup analyses on MACE (**Figure 2**). No significant subgroup interactions were observed. There were trends with favorable effects of treatment with CoQ_{10} in the following groups: elderly patients, male patients, patients in NYHA functional class III, patients with dilated cardiomyopathy, patients with NT-proBNP ≥300 pg/ml, and patients with left ventricular EF of ≥30% (p = 0.065). In addition, the benefits of CoQ_{10} were in addition to those afforded by beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

TABLE 3 Adverse Events

Event	CoQ_{10} (n = 202)	Placebo (n = 218)	Total (N = 420)
Peripheral arterial vascular events	2	2	4
Deep venous thrombosis	1	0	1
Cerebral stroke	1	6	7
Probable or definitive MI	3	2	5
CABG	1	2	3
PCI	3	3	6
Arrhythmia	3	4	7
Chest pain	0	3	3
Gastrointestinal disturbances	2	8	10
Allergy	1	3	4
Infection	3	2	5
Malignancy	1	1	2
Non-CV or unknown causes of deaths	3	2	5
Other adverse events	2	3	5
Total	26* (13%)	41 (19%)	67

Values are n or n (%). *p = 0.110.

CABG = coronary artery bypass graft; CV = cardiovascular; PCI = percutaneous coronary intervention; other abbreviation as in Tables 1 and 2.

DISCUSSION

Results from RCTs with CoQ_{10} in HF have accumulated since the late 1980s. Although encouraging, the studies have been underpowered to address major clinical endpoints.

Q-SYMBIO is the first RCT with adequate size, dosage of CoQ_{10}, and duration of follow-up to evaluate the efficacy of CoQ_{10} on morbidity and mortality in HF.

Despite considerable improvements in pharmacological HF therapy, the supplementation with CoQ_{10} significantly reduced MACE and cardiovascular death by 43% and all-cause mortality by 42% in our study. Furthermore, CoQ_{10} supplementation improved the patients' symptoms according to the NYHA functional classification after 2 years.

The combination of the selected dosage and formulation of CoQ_{10} in Q-SYMBIO may have given the therapeutic threshold in serum and tissue of CoQ_{10} (17) required for efficacy to achieve the positive result in MACE. In addition to a higher dosage of CoQ_{10}, the CoQ_{10} formulation used has shown good bioavailability in controlled studies (20,21) (Online Appendix 2).

We found an insignificant reduction in NT-proBNP in the CoQ_{10} group at 16 weeks. After 106 weeks, NT-proBNP levels were more than halved in both study groups compared with baseline; this finding may reflect that the most symptomatic patients with the highest NT-proBNP levels have died. Monitoring with NT-proBNP may be an important tool to ensure clinical stability in outpatients with HF (15).

In meta-analyses of RCTs with CoQ_{10}, small, significant improvements were found in left ventricular EF (9–11). Despite improvements of the long-term endpoints in Q-SYMBIO, we found insignificant positive changes in EF in both treatment groups. The absolute figures of improved EF have been small in RCTs with CoQ_{10}, as well as in trials with angiotensin-converting enzyme inhibitors or beta-blockers (22,23). We did not exclude patients from our study with HF and preserved EF, and 7% of the patients had EF ≥45%. In general, patients are selected with decreased EF in HF trials; however, physical signs of HF may provide important prognostic information above and beyond echocardiographic parameters (24).

The changes of other parameters obtained from the RCTs with CoQ_{10} (e.g. improvement in exercise capacity) have been modest, as in the Scandinavian cross-over study with CoQ_{10} 100 mg daily versus placebo (25). Nonetheless, the improvement of exercise capacity during CoQ_{10} therapy has been in the

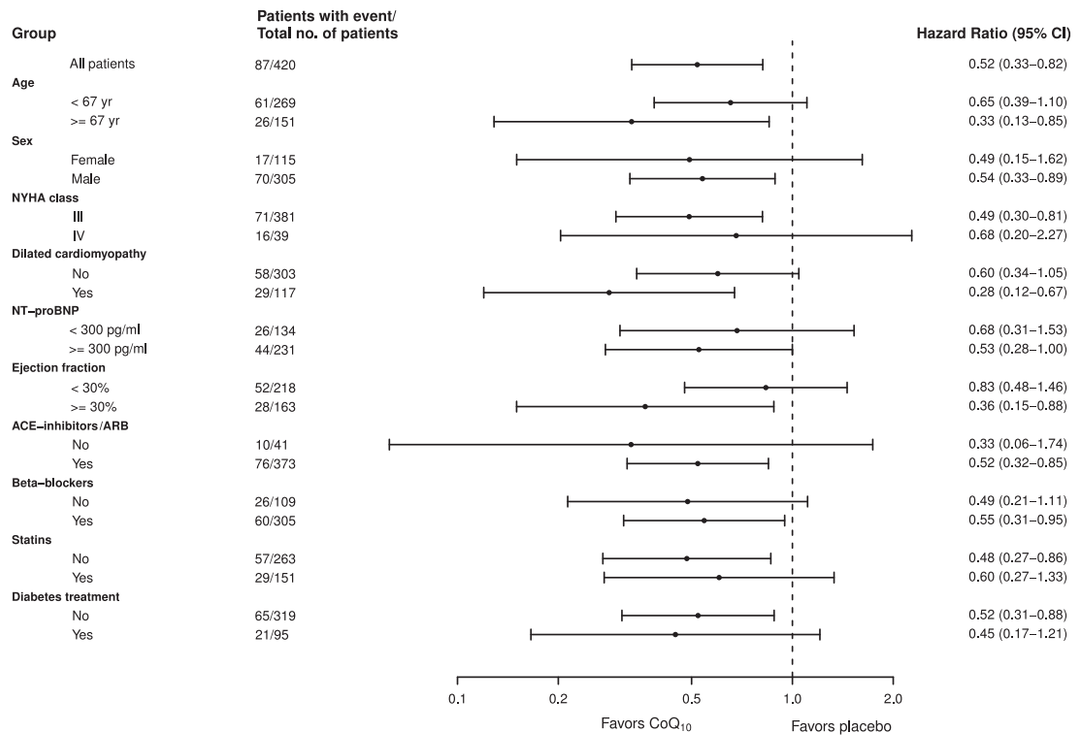

FIGURE 2 Results of Subgroup Analyses

Shown are the adjusted HR for the primary endpoint within specific subgroups. The **dotted line** denotes HR; **horizontal lines** represent 95% CI. HR indicates the relative risk in the coenzyme Q_{10} (CoQ_{10}) group versus the placebo group within each stratum. To convert values for NT-proBNP to picomoles per liter, divide by 8.457. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; other abbreviations as in Figure 1.

same order of magnitude as that found in previous studies with angiotensin-converting enzyme inhibitors (26). In the largest 1-year study from Italy (1993), the dosage of CoQ_{10} was 50 mg 2 to 3 times daily according to weight versus placebo. Significantly fewer patients in this study were readmitted for worsening HF in the CoQ_{10} group, and fewer patients in the CoQ_{10} group died (N = 16) compared with the placebo group (N = 21), but the difference was not statistically significant (27).

The biological mechanisms behind the improvement of symptoms and survival from CoQ_{10} in HF may be multiple (1,28,29). The velocity of the oxidative phosphorylation in the respiratory chain strongly depends on the CoQ_{10} concentration of the inner mitochondrial membrane (5), and small changes of the availability of CoQ_{10} may lead to significant changes in the respiratory rate.

CoQ_{10} treatment may impede the vicious metabolic cycle in HF (30), via a favorable alteration in redox signaling in the mitochondria that leads to increased energy production in the failing heart. In addition, CoQ_{10} therapy may lead to increased stabilization of the mitochondrial permeability transition pore and may shield the myocardium against apoptotic cell loss (28). Furthermore, it has been shown that CoQ_{10} may improve endothelial function (31), and it may protect the myocardium against ischemia (17). The high level of reactive oxygen species resulting from oxidative stress in HF increases the demand of antioxidants (32). This may lead to compromised function of CoQ_{10} in the respiratory chain and may ultimately explain the low levels seen in myocardial tissue from patients with HF (6).

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) block the mevalonate pathway and the synthesis of both cholesterol and CoQ_{10} (33,34). Additional CoQ_{10} depletion via statins in patients with HF and pre-existing CoQ_{10} deficiency may be a critical issue and may at least theoretically have contributed to neutral outcomes of RTCs with statins in HF (6).

The endogenous synthesis of CoQ_{10} in the body declines with age, and there may be a rationale for supplementation in the elderly patients (35). In a 5-year randomized double-blind placebo-controlled study of healthy elderly people, supplementation with a combination of CoQ_{10} and selenium reduced cardiovascular mortality significantly (36).

Many patients with HF are malnourished as a result of defects in substrate utilization and energy supply (37,38). Because the current medications for HF do not substitute for essential micronutrients, the possible deficiencies of these factors remain and contribute to symptoms and reduced survival in HF (29). Several dysfunctions may be present, and more research is required for further elucidation of the molecular causes of HF.

STUDY LIMITATIONS. CoQ_{10} is a nonpatentable substance, and with Q-SYMBIO having a low budget, the competition with other HF trials using licensed pharmaceuticals was difficult. This explains why the study was not completed according to the original enrollment plan and why the predefined estimate of the study population of 550 patients was not reached.

About 20% of the patients in both treatment groups at baseline were stabilized on standard therapy without diuretics. Therefore, we cannot exclude that more patients were in NYHA functional class II than specified in **Table 1**. The possible higher proportion of patients with milder symptoms may explain the death rate after 2 years that was lower than expected.

CONCLUSIONS

Our results demonstrate that treatment with CoQ_{10} in addition to standard therapy for patients with moderate to severe HF is safe, well tolerated, and associated with a reduction in symptoms and MACE.

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REFERENCES

1. Hadj A, Pepe S, Rosenfeldt F. The clinical application of metabolic therapy for cardiovascular disease. Heart Lung Circ 2007;16 Suppl 3: S56–64.

2. Scolletta S, Biagioli B. Energetic myocardial metabolism and oxidative stress: let's make them our friends in the fight against heart failure. Biomed Pharmacother 2010;64:203–7.

3. Sheeran FL, Pepe S. Energy deficiency in the failing heart: linking increased reactive oxygen species and disruption of oxidative phosphorylation rate. Biochim Biophys Acta 2006;1757:543–52.

4. Beyer R, Ernster L. The antioxidant role of coenzyme Q. In: Lenaz G, Barnabei O, Rabbi A BM, editors. Highlights in Ubiquinone Research. London: Taylor and Francis, 1990:191–213.

5. Littarru GP. Location and function of coenzyme Q in the respiratory chain. In: Energy and Defense. Facts and Perspectives on Coenzyme Q10 in Biology and Medicine. Rome: Casa Editrice Scientifica Internazionale, 1994:14–22.

6. Folkers K, Vadhanavikit S, Mortensen S. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. Proc Natl Acad Sci U S A 1985;82: 901–4.

7. Molyneux SL, Florkowski CM, George PM, et al. Coenzyme Q10: an independent predictor of mortality in chronic heart failure. J Am Coll Cardiol 2008;52:1435–41.

8. McMurray JJV, Dunselman P, Wedel H, et al. Coenzyme Q10, rosuvastatin, and clinical outcomes in heart failure: a pre-specified substudy of CORONA (controlled rosuvastatin multinational study in heart failure). J Am Coll Cardiol 2010;56:1196–204.

9. Soja A, Mortensen S. Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. Mol Aspects Med 1997;18 Suppl:s159–68.

10. Sander S, Coleman CI, Patel AA, Kluger J, White CM. The impact of coenzyme Q10 on systolic function in patients with chronic heart failure. J Card Fail 2006;12:464–72.

11. Fotino A, Thompson-Paul A, Bazzano L. Effect of coenzyme Q10 supplementation on heart failure: a meta-analysis. Am J Clin Nutr 2013;97: 268–75.

12. Rosenfeldt F, Hilton D, Pepe S, Krum H. Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. Biofactors 2003;18:91–100.

13. Madmani ME, Solaiman AY, Tamr Agha K, et al. Coenzyme Q10 for heart failure. Cochrane Database Syst Rev 2013;(9):CD008684.

14. Mortensen S. Overview on coenzyme Q10 as adjunctive therapy in chronic heart failure: rationale, design and end-points of "Q-symbio"—a multinational trial. Biofactors 2003;18:79–89.

15. Januzzi JL, Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 2011;58:1881–9.

16. Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.

17. Rosenfeldt F, Marasco S, Lyon W, et al. Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and in vitro contractility of myocardial tissue. J Thorac Cardiovasc Surg 2005; 129:25–32.

18. Littarru G, Mosca F, Fattorini D, Bompadre S, Battino M. Assay of coenzyme Q10 in plasma by a single dilution step. Methods Enzymol 2004;378: 170–6.

19. Karl J, Borgya A, Gallusser A, et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl 1999;230:177–81.

20. Folkers K, Moesgaard S, Morita M. A one year bioavailability study of coenzyme Q10 with 3 months withdrawal period. Mol Aspects Med 1994;15 Suppl:s281–5.

21. Weis M, Mortensen S, Rassing M, Møller-Sonnergaard J, Poulsen G, Rasmussen S. Bioavailability of four oral coenzyme Q10 formulations in healthy volunteers. Mol Aspects Med 1994;15 Suppl:s273–80.

22. No authors listed. A placebo-controlled trial of captopril in refractory chronic congestive heart failure: Captopril Multicenter Research Group. J Am Coll Cardiol 1983;2:755–63.

23. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure: the PRECISE trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation 1996;94: 2793–9.

24. Caldentey G, Khairy P, Roy D, et al. Prognostic value of the physical examination in patients with heart failure and atrial fibrillation: insights from the AF-CHF trial (Atrial Fibrillation and

Chronic Heart Failure). J Am Coll Cardiol HF 2014;2:15–23.

25. Hofman-Bang C, Rehnqvist N, Swedberg K, Wiklund I, Åström H. Coenzyme Q10 as an adjunctive in the treatment of chronic congestive heart failure: the Q10 Study Group. J Card Fail 1995;1:101–7.

26. Townend JN, Littler WA. Angiotensin converting enzyme inhibitors in heart failure: how good are they? Br Heart J 1993;69:373–5.

27. Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. Clin Investig 1993;71 Suppl: 134–6.

28. Haas RH. The evidence basis for coenzyme Q therapy in oxidative phosphorylation disease. Mitochondrion 2007;7 Suppl:S136–45.

29. Folkers K. Heart failure is a dominant deficiency of coenzyme Q10 and challenges for future clinical research on CoQ10. Clin Investig 1993;71 Suppl:s51–4.

30. Opie LH. The metabolic vicious cycle in heart failure. Lancet 2004;364:1733–4.

31. Belardinelli R, Macaj A, Lacalaprice F, et al. Coenzyme Q10 and exercise training in chronic heart failure. Eur Heart J 2006;27:2675–81.

32. Ferrari R, Guardigli G, Mele D, Percoco G, Ceconi C, Curello S. Oxidative stress during myocardial ischaemia and heart failure. Curr Pharm Des 2004;10:1699–711.

33. Ghirlanda G, Oradei A, Manto A, et al. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. J Clin Pharmacol 1993;33:226–9.

34. Mortensen S, Leth A, Agner E, Rohde M. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. Mol Aspects Med 1997;18 Suppl:s137–44.

35. Kalén A, Appelkvist E, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. Lipids 1989;24:579–84.

36. Alehagen U, Johansson P, Björnstedt M, Rosén A, Dahlström U. Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: a 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. Int J Cardiol 2013;167:1860–6.

37. Soukoulis V, Dihu JB, Sole M, et al. Micro-nutrient deficiencies an unmet need in heart failure. J Am Coll Cardiol 2009;54:1660–73.

38. Krim SR, Campbell P, Lavie CJ, Ventura H. Micronutrients in chronic heart failure. Curr Heart Fail Rep 2013;10:46–53.

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