Factors Associated With Outcome in Heart Failure With Preserved Ejection Fraction: Findings From the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE)

Summary: Recent surveys suggest that up to half of patients with heart failure have a preserved ejection fraction. In this condition, which is associated with poor outcome and in particular a high rate of rehospitalization, identification of factors predicting mortality or morbidity remains largely unexplored, in contrast to patients with heart failure and low ejection fraction. The authors evaluated data from 4128 patients in the I-PRESERVE trial (Irbesartan in Heart Failure with Preserved Ejection Fraction Study). They report an analysis identifying clinical, demographic, and biological factors associated with the primary end point outcome (all-cause mortality or cardiovascular hospitalization), all-cause mortality, and heart failure death or hospitalization. They found that log N-terminal pro-B-type natriuretic peptide, age, diabetes mellitus, previous hospitalization for heart failure, ejection fraction, and other simple clinical or biological variables were associated with a more unfavorable outcome. The models were able to identify subgroups of patients at very high and very low risk. This analysis provides new tools for the prognostic evaluation of heart failure with preserved ejection fraction and the factors that should be taken into consideration when assessing the prognosis of patients with heart failure and preserved ejection fraction.

Conclusions: In a large sample of elderly patients with HF and preserved EF enrolled in I-Preserve, simple clinical, demographic, and biological variables were associated with outcome and identified subgroups at very high and very low risk of events.1

Usefulness of Carvedilol in the Treatment of Chronic Aortic Valve Regurgitation

Summary: The medical treatment of asymptomatic patients with severe aortic valve regurgitation (AR) remains controversial. No pharmacological treatment has been clearly shown to be effective to protect the myocardium against the deleterious effects of chronic volume overload. Despite the recent publication of promising human data, β-blockade in chronic AR remains controversial because of the deleterious effects of bradyarrhythmia. More data are needed to support this potentially new treatment strategy. The authors hypothesized that carvedilol might be a safe treatment option in chronic AR, considering its combined β-blocking and α-blocking effects and proven efficacy in patients with established heart failure. They have designed a study in a rat model of chronic AR testing the efficacy of carvedilol at maintaining cardiac function and slowing the development of eccentric left ventricular hypertrophy over 6 months, starting treatment 2 weeks after surgical AR induction. Carvedilol treatment resulted in less left ventricular dilatation. Ejection fraction was improved and filling pressures were reduced by carvedilol. β1-Adrenoreceptor expression was also improved. Those beneficial effects were noted despite the presence of drug-induced bradycardia. The results of this study revealed that carvedilol exerted protective effects against volume-overload cardiomyopathy in this model of AR with preserved ejection fraction. These results, in addition to those shown previously with metoprolol, suggest a protective class effect of β-blockers.

Conclusions: Carvedilol exerted protective effects against volume-overload cardiomyopathy in this model of aortic valve regurgitation with preserved ejection fraction. These results suggest a protective class effect of β-blockers. Combined with the recent publication of promising human data, these findings support the need to carefully design a prospective study in humans to evaluate the effects of β-blockers in chronic aortic valve regurgitation.2

Clinical Characteristics of Pulmonary Hypertension in Patients With Heart Failure and Preserved Ejection Fraction

Summary: Pulmonary vascular disease associated with left-side heart failure and preserved ejection fraction (PH-HFpEF) is an increasingly common cause of pulmonary hypertension. There is concern that PH-HFpEF may often be misclassified as having WHO category I pulmonary arterial hypertension (PAH) because both these patient groups can have a normal left ventricular ejection fraction and evidence of left ventricular diastolic dysfunction. The distinction between PH-HFpEF and PAH is particularly important because therapies indicated for PAH can be detrimental in HFpEF. Thus, the authors sought to characterize the clinical, echocardiographic, and hemodynamic features of patients with PH-HFpEF and to determine the clinically relevant differences in these parameters in patients with PAH and in patients with HFpEF who do not have pulmonary vascular disease. Compared with PAH patients, PH-HFpEF patients are more symptomatic with a worse exercise capacity, which may be related to increased age, comorbidities, or higher pulmonary capillary wedge pressure. Compared with HFpEF patients without pulmonary vascular disease, patients with PH-HFpEF also had a worse functional class, which probably reflects the influence of RV dysfunction. Patients with HFpEF without pulmonary vascular disease and PH-HFpEF had remarkably similar hemodynamics, with the exception of a higher pulmonary artery pressure, aortic diastolic pressure, and mRAP in
PH-HFpEF. These data suggest that PH-HFpEF is more likely the result of the development of pulmonary vascular disease in patients with HfPpEF, rather than the development of HFpEF in patients with PAH. Because of the increasing frequency in which these patients are becoming diagnosed, a better understanding of their outcome and response to treatments is urgently needed.

Conclusions: These data should help better identify PH-HFpEF, an entity that has become increasingly recognized and difficult to treat.1

Body Mass Index and Adverse Cardiovascular Outcomes in Heart Failure Patients With Preserved Ejection Fraction: Results From the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) Trial

Summary: Obesity is a major risk factor for incident heart failure (HF). Paradoxically, in HF with reduced left ventricular ejection fraction (HFREF) a high body mass index (BMI) appears to be beneficial. However, approximately 50% of HF patients have a preserved left ventricular ejection fraction (HFpEF). Compared with HFREF, patients with HFpEF are usually older and more frequently female. The relationship between BMI and adverse cardiovascular (CV) outcomes was studied in the HFpEF patient cohort (n=4109) from the I-PRESERVE trial (mean age, 72 years, >60% female, mean BMI, approximately 30 kg/m²). Depending on their BMI, the patients were characterized by multiple differences in clinical variables. After adjustment for 21 key variables, patients in the lowest (BMI <23.5 kg/m²) and those in the highest BMI categories (BMI ≥35 kg/m²) had the highest CV event rate and the highest mortality. The lowest event rates were seen in overweight patients, that is, those with a BMI between 26.5 and 30.9 kg/m², indicating a U-shaped relationship. Only HF hospitalization was less frequently seen in normal-weight patients with HFpEF. This is the largest cohort of HFpEF patients studied so far, showing a significant impact of BMI on adverse CV outcomes. Whether weight changes, for example, weight gain in underweight and weight reduction in severe obesity, improve CV outcomes with irbesartan were consistent with the neutral results of the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Trial) who had a baseline measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP). Baseline NT-proBNP level was independently associated with an increased risk of all end points measured. Overall, irbesartan had no effect on any of the outcomes; however, its use was associated with improved outcomes in patients with NT-proBNP levels below, but not above, the median. After adjusting for 20 baseline covariates, irbesartan still had a beneficial effect on the primary outcome (hazard ratio, 0.74; 95% CI, 0.60 to 0.90; P=0.003), all-cause mortality (hazard ratio, 0.75; 95% CI, 0.56 to 0.99; P=0.046), and HF composite outcome (hazard ratio, 0.57; 95% CI, 0.41 to 0.80; P=0.001) in patients with NT-proBNP below the median.

Conclusions: The unexpected benefit of irbesartan in lower-risk patients with HFpEF in this post hoc analysis may indicate effects on early, but not later, high-risk stages of the disease. These findings question the strategy of using elevated plasma concentrations of NP as a patient selection criterion in HFpEF trials. More studies are needed to support or contest this practice.6

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

Summary: Natriuretic peptides are independent predictors of adverse outcomes in patients with heart failure (HF) and reduced ejection fraction, but data to support their role in HF and preserved ejection fraction are limited. Several recent HF trials have excluded patients with low natriuretic peptide levels to increase the likelihood of including patients with more severe HF and to increase the number of outcome events. This approach also assumes that the study intervention will have a greater effect in higher-risk patients, but this presumption is not well established. The authors tested this hypothesis in a post hoc analysis of 3480 patients in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Trial) who had a baseline measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP). Baseline NT-proBNP level was independently associated with an increased risk of all end points measured. Overall, irbesartan had no effect on any of the outcomes; however, its use was associated with improved outcomes in patients with NT-proBNP levels below, but not above, the median. After adjusting for 20 baseline covariates, irbesartan still had a beneficial effect on the primary outcome (hazard ratio, 0.74; 95% CI, 0.60 to 0.90; P=0.003), all-cause mortality (hazard ratio, 0.75; 95% CI, 0.56 to 0.99; P=0.046), and HF composite outcome (hazard ratio, 0.57; 95% CI, 0.41 to 0.80; P=0.001) in patients with NT-proBNP below the median.

Conclusions: The unexpected benefit of irbesartan in lower-risk patients with HFpEF in this post hoc analysis may indicate effects on early, but not later, high-risk stages of the disease. These findings question the strategy of using elevated plasma concentrations of NP as a patient selection criterion in HFpEF trials. More studies are needed to support or contest this practice.6

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

Summary: Heart failure with preserved ejection fraction (HFpEF) still is a poorly understood condition with no proven evidence-based effective therapy despite its large public health impact. Understanding the pathophysiology of this condition, therefore, is critical to develop specifically focused treatment strategies. The findings of the present study indicate that plasma levels of collagen turnover markers are predictive of future events in the HFpEF population (albeit nonsignificantly so when adjusted for other variables) and that 6 months of angiotensin receptor blockade is insufficient to meaningfully reduce levels of these markers. These study findings with irbesartan were consistent with the neutral results of the I-PRESERVE (Irbesartan in Heart Failure With Preserved Systolic Function) study overall. The clinical implication of these findings is that if fibrosis and its sequelae are presumed to be important drivers of the disease process of HFpEF at the cellular level as well as contributory to future major cardiovascular events, then more specifically targeted blockade of fibrosis and its consequences is required. These targeted therapies may be through specific antifibrotic drugs as well as use of existing or novel agents that act at least in part through potent antifibrotic actions. Furthermore, in evaluating the clinical utility of therapies in HfPpEF, assessment of the effect of these agents on fibrotic status of the heart may be mechanistically revealing.

Conclusions: Increased peripheral collagen turnover markers were not independently associated with increased mortality and cardiovascular hospitalization in an HFpEF population on multivariable analysis but were associated on single-variable analysis. These findings provide some support to the hypothesis that pathological fibrosis in the heart, and possibly the peripheral vasculature, may be contributory to adverse clinical outcomes in patients with HFpEF.3

Care and Outcomes of Hispanic Patients Admitted With Heart Failure With Preserved or Reduced Ejection Fraction: Findings From Get With The Guidelines–Heart Failure

Summary: Although Hispanics comprise the largest ethnic group in the United States, data on differences between Hispanic patients with heart failure (HF) with preserved ejection fraction (PEF) and those with reduced EF (REF) are limited. Using the Get With The Guidelines database, the present study aimed to compare clinical characteristics, quality of care, and outcomes between Hispanic
Conclusions: Hispanic HF patients with PEF had better in-hospital survival than non-Hispanic whites with PEF. Inpatient mortality was similar between groups with REF. Quality of care was similar and improved over time irrespective of ethnicity, highlighting the potential benefit of performance improvement programs in promoting equitable care.7

Assessment of Long-Term Effects of Irbesartan on Heart Failure With Preserved Ejection Fraction as Measured by the Minnesota Living With Heart Failure Questionnaire in the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) Trial

Summary: Patients with heart failure often seek medical care for relief of symptoms, functional limitations, and psychological distress that adversely affect their quality of life. The multinational Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial enrolled a large number of patients with symptomatic heart failure with preserved ejection fraction (HF-PEF) to test whether irbesartan can reduce mortality and cardiovascular hospitalizations and secondarily the adverse impact of heart failure on quality of life as measured by the Minnesota Living With Heart Failure Questionnaire. In-depth analyses indicated that the Minnesota Living With Heart Failure Questionnaire scores provided a reliable, valid, and sensitive measure of the adverse effects of heart failure with preserved ejection fraction on patients’ lives. Although the quality of subjects’ lives was adversely affected at baseline, there was no indication that irbesartan reduced the adverse effects during more than 4 years of follow-up.8

Conclusions: The MLHFQ scores are a reliable, valid, and sensitive measure of the adverse impact of HF-PEF on patients’ lives. Irbesartan did not substantially improve MLHFQ scores during a long period of follow-up.8

Renal Dysfunction in Patients With Heart Failure With Preserved Versus Reduced Ejection Fraction: Impact of the New Chronic Kidney Disease-Epidemiology Collaboration Group Formula

Summary: Compared to the radionuclide gold standard for the assessment of renal function, the Chronic Kidney Disease-Epidemiology Collaboration Group equation more accurately calculates estimated glomerular filtration rate than the Modification of Diet in Renal Disease equation. In an analysis of 20754 patients (15 962 with heart failure with reduced ejection fraction and 4792 with heart failure with preserved ejection fraction), the authors found that using the Chronic Kidney Disease-Epidemiology Collaboration Group equation rather than the Modification of Diet in Renal Disease equation results in higher estimates of renal dysfunction (55% versus 51%) and better mortality risk stratification. Regardless of which equation was used, reduced estimated glomerular filtration rate was a stronger predictor of all-cause mortality in patients with heart failure with reduced ejection fraction than those with heart failure with preserved ejection fraction.

Conclusions: Use of the CKD-EPI rather than the MDRD equation to calculate eGFR leads to higher estimates of renal dysfunction in HF and a more-accurate categorization of mortality risk. Renal function is more closely related to outcomes in HF-REF than in HF-PEF.9

Lifetime Analysis of Hospitalizations and Survival of Patients Newly Admitted With Heart Failure

Summary: Hospital readmissions for heart failure (HF) contribute to increased morbidity and resource burden. However, the predictors of hospitalization and patterns of cardiovascular events over the lifetime of patients with HF have not been elucidated. In this study, the authors examined recurrent hospitalizations, cardiovascular events, and survival over extended follow-up among patients with HF who were newly discharged. Among 8543 patients followed for 22 567 person-years, 60.7% had HF of ischemic etiology and HF with reduced ejection fraction (left ventricular ejection fraction ≤45% versus >45% [HF with preserved ejection fraction]) was present in 67.3%. Over the 10-year follow-up period, 98.8% of the cohort died, and 35 966 hospital readmissions occurred. Cardiovascular readmissions occurred frequently and were largely due to episodes of recurrent HF. Within the first year postdischarge, 66.5% of patients were rehospitalized for cardiovascular disease, and 61.3% were readmitted for HF. There was a preponderance of readmissions in the months comprising the initial and final deciles of the lifespan of the cohort. Of all recurrent HF hospitalizations, 26.8% occurred in the first and 39.8% in the last deciles of cohort survival duration. Similarly, 29.7% and 52.3% of all cardiovascular readmissions occurred in the first and last deciles of the cohort survival duration, respectively. The presence of ischemic HF etiology was a ubiquitous predictor of the first cardiovascular readmission, recurrent hospitalizations for cardiovascular, HF, and coronary heart disease on repeated-events analysis. Although presence of HF with reduced ejection fraction was associated with a shorter time to first recurrent HF or coronary heart disease readmission, it was not a predictor of repeat hospitalizations.

Conclusions: Among newly discharged patients with HF, cardiovascular events were clustered at early postdischarge and prefinal time periods, and were increased among those with ischemic etiology.10

Exercise Hemodynamics in Patients With and Without Diastolic Dysfunction and Preserved Ejection Fraction After Myocardial Infarction

Summary: Several studies have demonstrated that normal left ventricular (LV) filling pattern is only seen in one third of patients in the acute phase of myocardial infarction. When LV filling is severely abnormal, survival is poor and the risk of developing heart failure is high. However, most patients do not present with severely abnormal LV filling pattern, and patients with less severe diastolic dysfunction often display only minor evidence of myocardial damage, with preserved LV systolic function. The cause and hemodynamic consequences of abnormal LV filling in these patients are poorly understood, and abnormalities may only be apparent during
increased circulatory demands, such as exercise. The present study demonstrates that in patients with a recent myocardial infarction, with preserved LV ejection fraction and diastolic dysfunction on Doppler echocardiography, filling pressures with exercise increase substantially and significantly more than in comparable myocardial infarction patients without baseline diastolic dysfunction or in healthy controls. Thus, abnormal LV filling on Doppler echocardiography at rest identifies a group of patients who are only able to obtain a sufficient increase in cardiac output during exercise at the expense of elevated filling pressures. Abnormal LV filling is an early morphological expression that may identify patients at increased risk of developing heart failure.

Conclusions: In post-MI patients with preserved ejection fraction and left ventricular DD, cardiac output with exercise is maintained at the expense of substantially increased filling pressure. DD and loss of diastolic reserve may promote progression from stage B to stage C heart failure after MI.11

Sex Differences in Clinical Characteristics and Outcomes in Elderly Patients With Heart Failure and Preserved Ejection Fraction: The Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) Trial

Summary: Epidemiological studies have revealed sex-related differences in clinical presentation, risk factors, and prognosis of heart failure (HF). One of the most notable sex-related differences in HF is that most women have HF with preserved ejection fraction (HFpEF). However, there are few sex-specific outcome data in HFpEF. The authors assessed sex differences in baseline characteristics and outcomes among 4128 patients with HFpEF in the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. There were notable sex-related differences in baseline risk factors. Women were more likely to be obese and have a history of hypertension or renal impairment and were only ≈1 year older than men. Men were more likely to have an ischemic cause for HFpEF, atrial fibrillation, chronic obstructive pulmonary disease, and anemia. Even accounting for these baseline differences, women with HFpEF were 20% less likely than men to experience death or hospitalization for any cause during follow-up. A lower risk was observed in women for both cardiovascular and noncardiovascular events. This lower relative risk for women could not be explained by adjustment for differences in baseline characteristics. However, the sex-related difference in risk of all-cause events was modified by atrial fibrillation, stable angina pectoris, New York Heart Association functional class, and renal function. A better understanding of sex-specific risk factors may help inform strategies aimed at improving outcomes in this important disorder.

Conclusions: In patients with typical heart failure with preserved ejection fraction, there were prominent sex differences in baseline characteristics and outcomes. Women had better overall prognosis, although the presence of 4 common baseline characteristics seemed to moderate this finding.12

Comorbidity and Ventricular and Vascular Structure and Function in Heart Failure With Preserved Ejection Fraction: A Community-Based Study

Summary: Heart failure and preserved ejection fraction (HFpEF) is common in the elderly and is usually associated with comorbidities. However, it is controversial whether HFpEF is a distinct entity, or merely a constellation of comorbidities that interact with and modify age-related ventricular and vascular dysfunction. Using a community-based cohort of HFpEF, age and sex matched to normotensive and hypertensive controls, this study defined cardiac structure and function in HFpEF independent of the cofounding effects of age, sex, body size, and common comorbidities (ane-mia, diabetes mellitus, and renal dysfunction). Among HFpEF patients, obesity, anemia, diabetes mellitus, and renal dysfunction were each associated with unique clinical, structural, functional, and prognostic profiles. However, after accounting for body size and comorbidities, greater concentric left ventricular hypertrophy, atrial enlargement, systolic dysfunction, lower diastolic operating compliance, and more vascular stiffness were observed in subjects with HFpEF compared with normotensive and hypertensive age and sex-matched controls. This study supports the notion that HFpEF is a distinct disease entity, wherein ventricular and vascular dysfunction occur independent of common comorbidities. This study also underscores the influence of each of the comorbidities on characteristics of patients with HFpEF and lends support for search for specific therapies for HFpEF.

Conclusions: Comorbidities influence ventricular-vascular properties and outcomes in HFpEF, yet fundamental disease-specific changes in cardiovascular structure and function underlie this disorder. These data support the search for mechanistically targeted therapies in this disease.13

Longitudinal Changes in Ejection Fraction in Heart Failure Patients With Preserved and Reduced Ejection Fraction

Summary: Heart failure (HF) can occur in patients with preserved (HFpEF) and reduced (HFrEF) ejection fraction (EF). These may represent distinct diseases, as they occur in different patient populations, and respond differently to therapies. Among 1233 community heart failure patients followed longitudinally, the authors found that changes in EF over time also differed in patients with HFpEF versus HFrEF. In those with HFpEF, EF declined with greater reductions noted in older patients and those with significant coronary artery disease. In patients with HFrEF, EF increased with greater improvements in women, younger patients, those without coronary artery disease, and those treated with evidence-based medications. Greater decline or less improvement in EF was associated with worse prognosis in HFpEF and HFrEF patients, respectively. These findings suggest that progressive contractile dysfunction may contribute to the pathophysiology of HFpEF. The clinical implications of these findings are 2-fold. First, when evaluating patients with HFpEF, it is important to recognize that progressive decline in EF can occur, and may be associated with worse prognosis. Second, HFpEF and HFrEF, while sharing similar clinical manifestations, represent distinct pathophysiological entities and require differential approaches to care.

Conclusions: These data suggest that progressive contractile dysfunction may contribute to the pathophysiology of HFpEF. Prospective longitudinal studies are needed to confirm these observations and establish the mechanism and clinical relevance of decline in EF over time in HFpEF.14

Myosin Cross-Bridge Dynamics in Patients With Hypertension and Concentric Left Ventricular Remodeling

Summary: Hypertension is the most common substrate for the syndrome of heart failure with a preserved ejection fraction. Abnormal diastolic function is thought to represent a major pathophysiological feature of heart failure with a preserved ejection fraction, but underlying mechanisms are not fully understood. This study, performed in human left ventricular myocardial tissue obtained
at time of coronary bypass surgery, was designed to determine if abnormal myofilament properties contribute to diastolic dysfunction in patients with concentric left ventricular remodeling due to hypertension. The authors found that compared with controls, patients with hypertension have abnormal myosin cross-bridge dynamics, consisting of a substantial increase in cross-bridge attachment time (ton) and a corresponding reduction in its inverse, cross-bridge detachment rate, at submaximal [Ca\(^{2+}\)]. These parameters are key determinants of the rate of tension decline. Preliminary results implicate reduced phosphorylation of tropinin I as a mechanism of this alteration. The implication of these findings is that abnormal myofilament cross-bridge dynamics contribute to slowed relaxation in patients with hypertension and concentric remodeling and, potentially by extension, in patients with hypertension associated heart failure with a preserved ejection fraction.

**Conclusions:** Compared with controls, patients with HTN and concentric remodeling display prolonged cross-bridge attachment time at submaximal [Ca\(^{2+}\)] without a change in the tension–pCa relation. Prolonged cross-bridge attachment time implicates altered cross-bridge dynamics as a cause of slowed relaxation in these patients. This finding was associated with reduced phosphorylation of troponin I, suggesting decreased phosphorylation of protein kinase A/G sites as a mechanism.\(^{15}\)

**Cardiac Dysfunction and Noncardiac Dysfunction as Precursors of Heart Failure With Reduced and Preserved Ejection Fraction in the Community**

**Summary:** In this prospective study of a large, community-based sample, antecedent subclinical cardiac and noncardiac major organ system dysfunction was associated with risk of future heart failure. The presence of asymptomatic left ventricular systolic and diastolic dysfunction preceded and increased the risk of incident heart failure by >2-fold and >30%, respectively. With adjustment for cardiac dysfunction, the presence of subclinical renal impairment, airflow limitation, or anemia was each associated with 30% increased risk of incident heart failure. Notably, the significant risk factors differed according to the type of incident heart failure (preserved versus reduced ejection fraction). Antecedent left ventricular systolic dysfunction, subclinical renal impairment, and lower hemoglobin concentrations were associated with a higher incidence of heart failure with reduced ejection fraction, whereas antecedent diastolic dysfunction and baseline airflow obstruction were related positively to the risk of future heart failure with preserved ejection fraction. This study provides longitudinal evidence for the progressive nature of heart failure as emphasized in current heart failure guidelines and underscores the potential importance of noncardiac risk factors in predisposing to the manifestation of overt heart failure. The implications for the early identification of individuals at risk of heart failure and potential strategies to prevent progression to overt heart failure deserve further study.

**Conclusions:** Antecedent cardiac dysfunction and noncardiac organ dysfunction are associated with increased incidence of HF, supporting the notion that HF is a progressive syndrome and underscoring the importance of noncardiac factors in its occurrence.\(^{16}\)

**Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Target of Phosphodiesterase-5 Inhibition in a 1-Year Study**

**Summary:** Heart failure with left ventricular diastolic dysfunction and preserved ejection fraction is a considerable public health concern. Its prevalence is increasing rapidly, and the outcome is similar to that of systolic heart failure. Because of development of pulmonary vasoconstriction and hypertension, heart failure with preserved ejection fraction may turn into right ventricular failure, an event highly predictive of poor outcome. Thus, prevention and treatment of the unfavorable backward hemodynamic and vascular effects are relevant clinical challenges. In heart failure, nitric oxide–dependent pulmonary vasodilatation is impaired. Because phosphodiesterase-5 is highly expressed in the lungs and its inhibition potentiates nitric oxide signaling by increasing cGMP concentration, the authors tested whether sildenafil could benefit patients with heart failure with preserved ejection fraction. In this 1-year, placebo-controlled, randomized study, the authors found that at 6 and 12 months, sildenafil, and not placebo, improved life quality; reduced pulmonary artery, wedge, and right atrial pressures and right ventricular end-diastolic pressure and dimension; shifted leftward the right ventricular Frank-Starling relationship; increased cardiac output and contractile function in parallel with decrease of pulmonary artery elastance; and improved alveolar-capillary membrane gas conductance, whose changes inversely correlated with those in mean right atrial pressure. Thus, in heart failure with preserved ejection fraction, sildenafil modulates pulmonary vasoconstriction, improves right ventricular function, and reduces right ventricular dimensions. As a consequence, chronic phosphodiesterase-5 inhibition may facilitate left ventricular filling through ventricular interdependence. Alveolar-capillary membrane gas conductance improvement likely reflects lung interstitial water reabsorption, and its relationship with right atrial pressure suggests that pulmonary lymphatic drainage, a safety mechanism against interstitial edema, is at least partially restored by right atrial pressure reduction. Results may lead to promising prognostic insights.

**Conclusions:** The multifaceted response to phosphodiesterase-5 inhibition in heart failure with preserved ejection fraction includes improvement in pulmonary pressure and vasomotility, RV function and dimension, left ventricular relaxation and distensibility (structural changes and/or ventricular interdependence), and lung interstitial water metabolism (wedge pulmonary pressure decrease improving hydrostatic balance and right atrial pressure reduction facilitating lung lymphatic drainage). These results enhance our understanding of heart failure with preserved ejection fraction and offer new directions for therapy.\(^{17}\)

**Prevalence and Significance of Alterations in Cardiac Structure and Function in Patients With Heart Failure and a Preserved Ejection Fraction**

**Summary:** The purpose of this study was to examine the prevalence and pattern of structural remodeling and alterations in function present in patients with heart failure and a preserved ejection fraction (HFPEF) and to determine whether there was an association among changes in cardiac structure, function, morbidity, and mortality. An echocardiographic substudy of the Irbesartan in Heart Failure With Preserved Ejection Fraction trial (I-PRESERVE) enrolled 745 patients. Structural remodeling and diastolic dysfunction was present in the majority of patients with HFPEF. Structural remodeling and diastolic dysfunction predicted clinical outcomes. Increased left ventricular mass, mass/volume ratio, and left atrial size were independently associated with an increased risk of morbidity and mortality. These findings may be pivotal to the development of improved diagnostic criteria and prognostic assessment of patients with HFPEF. For example, the inclusion of measurements of left ventricular mass, geometry, and diastolic function could be added to the diagnostic criteria for HFPEF and could be used to predict the risk of morbidity and mortality in patients with HFPEF. With these data, studies could be developed to test the hypothesis that...
the reversal of the changes in left ventricular structure and function would result in reduced morbidity and mortality in patients with HFPEF. Taken together, these findings serve to enhance our understanding of the pathophysiology underlying clinical heart failure in these patients with HFPEF.

**Conclusions:** Left ventricular hypertrophy or concentric remodeling, LA enlargement, and diastolic dysfunction were present in the majority of patients with HFPEF. Left ventricular mass and LA size were independently associated with an increased risk of morbidity and mortality. The presence of structural remodeling and diastolic dysfunction may be useful additions to diagnostic criteria and provide important prognostic insights in patients with HFPEF.¹⁸

**Trends in Patients Hospitalized With Heart Failure and Preserved Left Ventricular Ejection Fraction: Prevalence, Therapies, and Outcomes**

**Summary:** Heart failure with preserved ejection fraction (HF–preserved EF) is an increasingly common syndrome, but relatively little is known about recent trends in patient characteristics and early clinical outcomes. The present study evaluated 110 621 heart failure patients from 275 hospitals participating in Get With The Guidelines–Heart Failure from January 2005 to October 2010. Patients were grouped by EF as reduced EF (EF <40% [HF–reduced EF]), borderline EF (40%≤EF<50% [HF–borderline EF]), or preserved EF (EF ≥50% [HF–preserved EF]). Using multivariable models, we examined trends in therapies and outcomes. There were 55% of patients with HF–reduced EF, 14% with HF–borderline EF, and 36% with HF–preserved EF. From 2005 to 2010, the proportion of hospitalizations for HF–preserved EF increased from 33% to 39% (P<0.0001). Although many heart failure quality metrics cannot be applied appropriately to the HF–preserved EF population, there are broadly applicable cardiovascular prevention goals such as blood pressure control and discharge instructions that are particularly important for patients with HF–preserved EF but less likely to be achieved. In-hospital mortality for patients with HF–preserved EF remains comparable to that for patients with HF–reduced EF. In-hospital mortality for HF–preserved EF decreased from 3.32% in 2005 to 2.35% in 2010 but was stable for patients with HF–reduced EF. Among hospitalizations for heart failure, HF–preserved EF represents a growing proportion and may overtake HF–reduced EF as the predominant form of acute heart failure. There remains an important opportunity for identification of evidence-based therapies in patients with HF–preserved EF.

**Conclusions:** Hospitalization for HF–preserved EF is increasing relative to HF–reduced EF. Although in-hospital mortality for patients with HF–preserved EF declined over the study period, an important opportunity remains for identifying evidence-based therapies in patients with HF–preserved EF.¹⁹

**Low Myocardial Protein Kinase G Activity in Heart Failure With Preserved Ejection Fraction**

**Summary:** Large trials testing modern heart failure pharmacotherapy in heart failure with preserved ejection fraction (HFPEF) had a neutral outcome, probably because of failure to address features of myocardial dysfunction specific for heart failure with preserved ejection fraction such as high-diastolic left ventricular stiffness. The latter results not only from myocardial fibrosis, but also from high cardiomyocyte stiffness, which is linked to hypophosphorylation of the cytoskeletal protein titin and corrected by in vitro administration of protein kinase G (PKG). In vivo administration of sildenafill, which raises myocardial PKG activity by inhibiting breakdown of cyclic guanosine monophosphate, similarly improves diastolic left ventricular stiffness in a HFPEF dog model and HFPEF patients with pulmonary hypertension. Because of these findings and the ongoing RELAX trial testing sildenafill in HFPEF, the present study compared PKG activity, its downstream effects, and its upstream controls in left ventricular endomyocardial biopsies of patients with HFPEF, HF with reduced ejection fraction, and aortic stenosis. Patients were free of coronary artery disease, but more HFPEF patients were obese or had diabetes mellitus. The lowest myocardial PKG activity was observed in HFPEF and associated with the highest cardiomyocyte stiffness, the lowest myocardial cyclic guanosine monophosphate concentration, and the highest myocardial nitrosative/oxidative stress. The high prevalence among HFPEF patients of metabolic disorders probably accounted for their high myocardial nitrosative/oxidative stress, which led to high cardiomyocyte stiffness through a cascade of derangements consisting of low cyclic guanosine monophosphate concentration, low PKG activity, and reduced phosphorylation of titin by PKG. Metabolic derangements therefore underlie diastolic left ventricular dysfunction in HFPEF and should be targeted in future HFPEF treatment strategies.

**Conclusions:** Low myocardial PKG activity in HFPEF was associated with raised cardiomyocyte F pass and was related to increased myocardial nitrosative/oxidative stress. The latter was probably induced by the high prevalence in HFPEF of metabolic comorbidities. Correction of myocardial PKG activity could be a target for specific HFPEF treatment.²⁰

**Echocardiographic Indices Do Not Reliably Track Changes in Left-Sided Filling Pressure in Healthy Subjects or Patients With Heart Failure With Preserved Ejection Fraction**

**Summary:** Several modalities of echocardiography including Doppler, tissue Doppler, and color M-mode have shown promise in the estimation of left-sided filling pressures. Two such indices, E/e′ and E/Vp, have received recognition for their utility in the 1-time estimation of left-sided filling pressures in healthy subjects as well as select populations with cardiovascular disease. Some have extrapolated these findings, proposing the serial use of these indices to monitor changes in left-sided filling pressures in healthy research subjects or to titrate medical therapy in patients with heart failure. However, doing so would require demonstration that changes in noninvasive indices accurately track changes in left-sided filling pressures within individuals as filling pressures vary. To test this hypothesis, the authors made multiple, simultaneous measures of E/e′, E/Vp, and pulmonary capillary wedge pressure within healthy subjects and outpatients with heart failure with preserved ejection fraction as preload was manipulated using lower body negative pressure and rapid saline infusion. The key finding was that as left-sided filling pressures were manipulated, the relationships between E/e′ and pulmonary capillary wedge pressure and E/Vp and pulmonary capillary wedge pressure were highly variable, with individual subject linear regression slopes ranging from steeply negative to steeply positive and coefficients of determination ranging from very low to very high. In this study, noninvasive indices did not adequately track changes in left-sided filling pressures because these pressures varied within individual subjects. These findings raise concern about the use of these techniques in research studies with healthy volunteers or to titrate medical therapy in patients with heart failure with preserved ejection fraction.

**Conclusions:** Within individual subjects the noninvasive indices E/e′ and E/Vp do not reliably track changes in left-sided filling pressures as these pressures vary, precluding the use of these techniques in...
research studies with healthy volunteers or the titration of medical therapy in patients with HFpEF.21

Subclinical Left Ventricular Dysfunction in Preeclamptic Women With Preserved Left Ventricular Ejection Fraction: A 2D Speckle-Tracking Imaging Study

Summary: Patients with preeclampsia are at an increased risk of cardiovascular disease, which has been associated with long-term postpartum morbidity and mortality. Ejection fraction remains relatively preserved until late in the course of the disease. Measurement of strain using speckle echocardiography is being increasingly used to detect subclinical myocardial dysfunction. In this study, the authors show that women with preeclampsia have subclinical myocardial dysfunction as demonstrated by a decreased global longitudinal, radial, and circumferential strain in the setting of preserved ejection fraction. These data are a step toward early detection of myocardial dysfunction in preeclampsia.

Conclusions: Myocardial strain imaging using speckle tracking is more sensitive than left ventricular ejection fraction to detect differences in left ventricular systolic function in women with and without preeclampsia.22

Success of Ablation for Atrial Fibrillation in Isolated Left Ventricular Diastolic Dysfunction: A Comparison to Systolic Dysfunction and Normal Ventricular Function

Summary: Although ablation of atrial fibrillation has been followed by an improvement in left ventricular (LV) ejection fraction in selected patients with LV systolic dysfunction, there are concerns that ablation procedures in patients with heart failure have the potential for greater risk, less efficacy, and limited impact on quality of life. For patients with isolated diastolic dysfunction, these issues are also unclear. This investigation compared outcomes after catheter ablation in patients with depressed LV ejection fraction, preserved LV ejection fraction with diastolic dysfunction, and normal systolic and diastolic function. At 1 year, the atrial fibrillation elimination rate of 75% in patients with isolated LV diastolic dysfunction was comparable to that in patients with normal LV function and was better than that in patients with LV systolic dysfunction (62%). All 3 groups experienced improvement in physical and mental quality of life. LV ejection fraction improved to near normal in 31% of the LV dysfunction group. In the diastolic dysfunction group, 30% of patients showed improvement in diastolic dysfunction. Over 5 years, there were more atrial fibrillation recurrences in the LV systolic and diastolic dysfunction groups than in the normal group. Therefore, repeat ablation or supplemental antiarrhythmic therapy may be required more often in the long-term management of atrial fibrillation in populations with LV dysfunction.

Conclusions: Although an ablative approach for AF in patients with systolic or diastolic dysfunction is associated with an increased long-term recurrence risk, there is potential for substantial quality of life improvement and left ventricular functional benefit.23

References


