Treatment of Heart Failure with Preserved Ejection Fraction

Megan M. Barnes, Pharm.D., Michael P. Dorsch, Pharm.D., M.S., Scott L. Hummel, M.D., M.S., Todd M. Koelling, M.D., and Barry E. Bleske, Pharm.D., FCCP

Heart failure contributes to more than 1 million hospitalizations annually and is one of the most common causes of repeat hospitalizations in the elderly. Previously, it was thought that mortality from heart failure with preserved ejection fraction (PEF) was lower than that from heart failure with reduced ejection fraction (REF), but more recent data infer similar mortality. Although the mortality rate in patients with heart failure with REF is decreasing, the mortality rate in patients with heart failure with PEF remains unchanged—possibly due to the lack of evidence-based treatment regimens or greater recognition of the disease. Without sufficient trials in patients with heart failure with PEF, clinicians are forced to extrapolate treatment from data proven to benefit patients with heart failure with REF. There is no question that clinical trials including only patients with heart failure with PEF are limited. In addition, the definition and clinical diagnosis of this syndrome are not clearly defined, and the guidelines available for treatment lack specificity in recommendations. To describe the current literature for the treatment of heart failure with PEF, we conducted a MEDLINE search of the English-language literature (1950–2009) to identify studies that pertain to the treatment of patients with heart failure with PEF. Ongoing clinical trials continue, but until data become available, clinicians must base their treatment strategies for heart failure with PEF on sparse information.

Key Words: diastolic heart failure, preserved ejection fraction, normal ejection fraction, heart failure.

(Pharmacotherapy 2011;31(3):312–331)

OUTLINE

From the Department of Pharmacy Services, University of Michigan Health System (Drs. Barnes, Dorsch, and Bleske), and the College of Pharmacy (Drs. Barnes, Dorsch, and Bleske), and the Division of Cardiovascular Medicine, Department of Internal Medicine (Drs. Hummel and Koelling), University of Michigan, Ann Arbor, Michigan.

For reprints, visit http://www.atypon-link.com/PPI/loi/phco. For questions or comments, contact Megan M. Barnes, Pharm.D., Department of Pharmacy Services, University of Michigan Health System, 1500 East Medical Center Drive, Ann Arbor, MI 48109.

Diastolic dysfunction is defined as increased resistance to the filling of one or both ventricles due to decreased ventricular relaxation and/or increased ventricular stiffness. Diastolic dysfunction may or may not result in the clinical syndrome of diastolic heart failure, which occurs with maintenance of normal left ventricular ejection fraction (LVEF).[1, 2] Diastolic heart failure is also termed heart failure with preserved ejection fraction (PEF), heart failure with normal ejection fraction, and heart failure with preserved systolic function. For the remainder of this

Table 1. Mortality in Patients with Heart Failure: PEF versus REF

	Patients with PEF Heart Failure		Patients with REF Heart Failure	
Patient Population	LVEF (%)	Mortality (%)	LVEF (%)	Mortality (%)
Community[7]	≥ 50	8.7	< 50	18.9
Hospitalized[8]	> 55	23.5	< 55	16–51.7
Hospitalized[9]	> 48	19	< 36	> 25
Community[10]	≥ 50	16	< 50	16
Hospitalized[11]	≥ 40	21	< 40	13
Hospitalized[6]	≥ 50	65	< 50	68
Hospitalized[12]	> 50	22	< 40	26
Hospitalized[13]	> 55	3[a]	< 55	3.2–4.7[a]

PEF = preserved ejection fraction; REF = reduced ejection fraction; LVEF = left ventricular ejection fraction.
[a]In-hospital mortality reported.

review, systolic heart failure or heart failure with reduced ejection fraction will be referred to as heart failure with REF, and diastolic heart failure will be referred to as heart failure with PEF.

In this review, our aim was to identify and summarize key trials and strategies for the treatment of patients with heart failure with PEF. Therefore, we conducted a MEDLINE search of the English-language literature (1950–2009) to identify studies that pertain to the treatment of patients with heart failure with PEF; additional citations were obtained from the articles retrieved from the literature search.

Epidemiology and Outcomes

The 2010 estimated direct and indirect cost of heart failure in the United States was $39.2 billion.[3] Heart failure contributes to more than 1 million hospitalizations annually and is one of the most common causes of repeat hospitalizations in the elderly.[4] The prevalence of heart failure with PEF in the community is estimated to be 43–71% of patients with heart failure.[5] In a 15-year study of 4596 patients with acutely decompensated heart failure who were discharged with echocardiographic assessment, 53% had reduced LVEF (< 50%) and 47% had preserved LVEF (≥ 50%).[6] Over three consecutive 5-year increments, the proportion of admissions for heart failure with PEF increased from 38% to 47% to 54%.

Patients with heart failure with PEF have a substantial risk of death, although the reported rates varied due to patient selection criteria and the population studied (Table 1).[6–13] A cumulative review of heart failure–related mortality published in 2009 concluded that all-cause mortality was equivalent in patients who had heart failure with PEF and those who had heart failure with REF, both in the community setting and in those hospitalized with acutely decompensated heart failure.[5] Over time, the mortality rate in patients with heart failure with REF have decreased, whereas the mortality rate in those with heart failure with PEF has remained unchanged. Compared with patients with heart failure with REF, more deaths in patients with heart failure with PEF are noncardiac, a distinction that may have important implications for clinical trial design.[14]

Clinical Presentation and Diagnosis

The manifestation of heart failure with PEF is similar to that of heart failure with REF, and typically patients report fluid retention, dyspnea, fatigue, and exercise intolerance. The heterogeneity of the heart failure with PEF patient population makes defining diagnostic criteria and understanding pathophysiology a difficult task. Controversy exists as to whether or not heart failure with PEF can be diagnosed simply in the presence of preserved LVEF and symptoms of heart failure, or whether objective measurements of ventricular diastolic function are needed to confirm the diagnosis.[15] Transthoracic echocardiography is widely available and noninvasive, and is the most commonly used modality to assess diastolic function. Classic parameters include assessment of mitral inflow velocities (i.e., the ratio between early [E] velocity from ventricular filling to late velocity from atrial contraction [A], the E:A ratio), pulmonary vein velocities, and isovolumic ventricular relaxation time. More recent variables include tissue Doppler velocity measurements at the mitral annulus, color M-mode propagation velocity, and diastolic ventricular strain rates (rate or speed of myocardial shortening or thickening used to assess diastolic stiffness). All of these measures have limitations

related to acquisition of data, dependence on loading conditions, and/or reproducibility; the guidelines for echocardiographic assessment of diastolic function are frequently changing.[16]

The Heart Failure and Echocardiography Association of the European Society of Cardiology defines the following three criteria for the diagnosis of heart failure with PEF: signs or symptoms of heart failure; normal or mildly abnormal systolic left ventricular function, defined as an LVEF greater than 50% without severe dilation of the left ventricle; and evidence of diastolic left ventricular dysfunction, defined invasively by elevated filling pressures at left-sided heart catheterization or noninvasively by echocardiography.[17] The Heart Failure Society of America (HFSA) states that the diagnosis of heart failure with PEF can be made by the combination of clinical symptoms and preserved or relatively preserved LVEF.[18] In the American College of Cardiology–American Heart Association (ACC-AHA) 2005 heart failure guidelines, definitive diagnosis is based on symptomatic presentation and evidence of normal LVEF without valvular abnormalities at echocardiography.[19] The 2009 ACC-AHA heart failure guidelines make no new mention of using cardiac catheterization as a preferred method of diagnosis,[20] as is suggested by others.[21] Overall, symptomatic presentation and preserved LVEF will continue to be used as the guideline-based diagnostic criteria for heart failure with PEF, but catheterization may be helpful in cases where the diagnosis is unclear.[22]

Increased natriuretic peptides (B-type [brain] natriuretic peptide [BNP] and N-terminal proBNP [NT-proBNP]) may also have a role in detecting patients with diastolic dysfunction and/or heart failure with PEF. A subset of patients from the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial with preserved LVEF (181 patients) was classified as having mild, moderate, or severe diastolic dysfunction.[23] A BNP level greater than 100 pg/ml or an NT-proBNP level greater than 600 pg/ml was the strongest predictor of moderate or severe diastolic dysfunction. In addition, an elevated BNP level was the most accurate predictor of severe diastolic dysfunction in a direct comparison of 294 patients with either normal or abnormal diastolic function.[24] The European Society of Cardiology guidelines take these findings into account, as a BNP level greater than 200 pg/ml or NT-proBNP level greater than 220 pg/ml may be used to diagnose heart failure with PEF in the setting of indeterminate diastolic function by echocardiography.[17] However, low natriuretic peptide levels cannot be used to rule out a diagnosis of heart failure with PEF,[25] and high levels do not necessarily mean that an individual patient has heart failure with PEF, a clinical diagnosis based on signs and symptoms.

Pathophysiology

Because of increased ventricular stiffness and impaired ventricular relaxation, many patients with heart failure with PEF have an inability to increase left ventricular end-diastolic volumes and use the Frank-Starling mechanism to increase cardiac output.[26] Cellular mechanisms of diastolic dysfunction include abnormalities of calcium homeostasis changes in cardiomyocytes, cytoskeletal proteins and their phosphorylation status, and the regulatory processes of collagen formation and degradation. However, the initial focus on intrinsic ventricular diastolic dysfunction[26, 27] as the primary cause of heart failure with PEF has broadened to include other extrinsic contributing factors including arterial stiffening,[28] endothelial dysfunction,[29, 30] chronically increased plasma volume,[31] impaired atrial transport function,[32] chronotropic incompetence (inadequate heart rate response to exercise),[29] pulmonary hypertension,[33] and even subtle ventricular systolic dysfunction.[34]

The renin-angiotensin-aldosterone system (RAAS) is associated with many of the contributing causes of heart failure with PEF and is therefore thought to be associated with disease progression (Table 2).[35, 36] Chronically overactive sympathetic nervous system activity may contribute to both types of heart failure (PEF and REF), as norepinephrine levels are markedly higher in both patients with PEF and those with REF than norepinephrine levels in control subjects.[37] Patients with heart failure with PEF have reduced responsiveness to β-adrenergic stimulation due to reduced numbers of adrenergic receptors and reduced signaling, which may contribute to chronotropic incompetence compared with healthy and hypertensive control subjects.[38] Results of a recent analysis of the Health, Aging, and Body Composition (Health ABC) study, a large cohort of community-dwelling and previously healthy elderly subjects, suggest that chronic inflammation may play a key role in the genesis and progression of heart failure with PEF.[39]

Risk Factors and Prevention

Risk factors for heart failure with PEF include increasing age, hypertension, and coronary artery disease,[40] although coronary artery disease is less prevalent than in heart failure with REF.[13, 41] Patients with heart failure with PEF are predominantly female,[12, 13, 41–48] with a sex association remaining after adjustment for other predictors.[49] Greater frequencies of hypertension, atrial fibrillation, valvular heart disease, and chronic obstructive pulmonary disease have also been seen with heart failure with PEF versus heart failure with REF.[12, 48] Diabetes mellitus is an independent predictor of mortality[50, 51] in patients with heart failure with PEF and is associated with a significantly greater risk of death or heart failure hospitalization.[51] Factors that precipitate heart failure exacerbation and fluid retention in patients with heart failure with PEF are similar to those of heart failure with REF and include increasing age, uncontrolled hypertension, atrial fibrillation, drug therapy noncompliance, ischemia, anemia, renal insufficiency, and dietary noncompliance.[15]

Table 2. Pathophysiologic Characteristics of Patients with Heart Failure: PEF versus REF

Parameter	PEF	REF
LVEF	Normal	Decreased
LVEDP	Increased	Increased
PCWP	Increased	Increased
Cardiac output	Normal or decreased[a]	Decreased
Stroke volume	Normal or decreased[a]	Decreased
Diastolic function	Impaired	Normal or impaired
BNP	Normal or increased	Increased
Neurohormonal activation	Increased	Increased
Left ventricular wall thickness	Increased	Decreased

PEF = preserved ejection fraction; REF = reduced ejection fraction; LVEF = left ventricular ejection fraction; LVEDP = left ventricular end-diastolic pressure; PCWP = pulmonary capillary wedge pressure; BNP = B-type (brain) natriuretic peptide.
[a]Cardiac output and stroke volume may be normal at rest and abnormal with exercise.

Treatment

The ACC-AHA, European Society of Cardiology, and HFSA treatment guidelines for heart failure with PEF focus on the control of physiologic factors known to adversely affect ventricular diastolic function, including blood pressure, heart rate, blood volume, and myocardial ischemia. However, most of the recommendations are based on expert consensus, and the ACC-AHA guidelines highlight the need for more controlled clinical trials in patients with heart failure with PEF. For the purposes of this review, only published treatment studies that specifically enrolled patients with heart failure with PEF are discussed.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

The benefits of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in patients with heart failure with REF are well described, but there are several specific reasons why these agents could be advantageous in those with heart failure with PEF as well. Angiotensin II promotes interstitial collagen deposition and fibrosis, causing myocardial thickening and decreased ventricular compliance[21]; it may impair ventricular relaxation. Moreover, angiotensin II increases systemic vascular resistance and vascular stiffness, which contribute to hypertension and increased ventricular afterload.

An early study compared the effects of enalapril versus placebo in 22 patients with heart failure, normal LVEF (> 50%), and ability to complete a maximal exercise test.[52] Diagnostic criteria for heart failure included presence of rales heard by two cardiologists and pulmonary vascular congestion on chest radiograph. All patients received more than 2 weeks of furosemide before the study and continued on a stable dose throughout the study. Digoxin and other cardiac drugs were prohibited. Patients in the enalapril arm began therapy by taking 2.5 mg/day, which was increased over 5 weeks to a maximum of 10 mg twice/day. After 3 months, the enalapril group showed a benefit in New York Heart Association (NYHA) functional class, reduction in cardiothoracic ratio, increase in treadmill exercise duration, improvement in left ventricular systolic and diastolic function, and reduction in left ventricular mass, all of which were statistically significantly different from those changes in the placebo group. Although echocardiographic parameters were blinded, a major limitation of this study was the nonblinded assessment of both functional capacity and treadmill exercise duration.

A randomized, double-blind, placebo-controlled crossover study of losartan versus placebo tested

the hypothesis that angiotensin II blockade would improve exercise tolerance in patients with diastolic dysfunction.[42] Patients included were asymptomatic at rest, but had dyspnea with exertion and were undergoing exercise testing for evaluation of coronary artery disease. Patients previously taking ARBs and with concurrent exercise-limiting disease were excluded. All patients' baseline drug therapies were continued throughout the study (35% were taking β-blockers, 30% diuretics, 25% calcium channel blockers, and 30% ACE inhibitors). The mean baseline systolic blood pressure at rest and during exercise was 143 ± 8 and 226 ± 24 mm Hg, respectively, and the mean baseline exercise time was 11.3 ± 2.5 minutes. Patients completed a baseline Minnesota Living with Heart Failure Questionnaire, treadmill exercise tests using the modified Bruce Protocol with blood pressure measurements, and Doppler echocardiography after exercise; all of which were repeated at the end of each phase. Patients assigned to the losartan treatment showed significantly decreased peak systolic blood pressure during exercise, increased exercise tolerance, and improved quality of life (all compared with baseline values) in this 2-week crossover study. Resting blood pressure and echocardiographic measures of diastolic function were not significantly different from baseline. Limitations to this study included the presence of other baseline drugs that reduced the ability to see the effects of losartan alone, as well as the short treatment time. The authors suggested that since ACE inhibitors do not prevent increased angiotensin II during exercise, they also may not be able to produce the same reduction in exercise-mediated increased systolic blood pressure as demonstrated with losartan.

A double-blind, placebo-controlled study compared the effects of quinapril versus placebo in 74 symptomatic patients with heart failure with PEF.[53] Quinapril was started at 5 mg/day and increased to 40 mg/day within 6 weeks. Treatment with diuretics (> 90% of patients), nitrates, digoxin (> 25%), calcium channel blockers (> 15%), and β-blockers (> 7%) was continued, but ACE inhibitors were withdrawn 2 weeks before the run-in period. Mean 6-minute walk distances increased at 6 months and quality-of-life scores increased from baseline, but not significantly for either end point. Compared with the placebo group, patients receiving quinapril tended to be less likely to experience worsened heart failure (15.8% vs 11.1%, p=0.737) or hospital admission due to heart failure (13.1% vs 5.6%, p=0.431).

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial randomly assigned 850 patients in a double-blind fashion to receive perindopril or placebo.[44] All patients were older than 70 years, treated with diuretics, had a clinical diagnosis of heart failure (meeting at least two of four echocardiographic criteria), were able to walk without assistance of another person, and had to have a heart failure hospitalization within the past 6 months. Excluded patients had a wall motion abnormality equivalent to LVEF less than 40%, hemodynamically significant valvular disease, stroke within the previous month, systolic arterial pressure less than 100 mm Hg, serum creatinine level greater than 2.3 mg/dl, potassium level greater than 5.4 mEq/L, history of ACE inhibitor intolerance, use of ACE inhibitor or ARB within the previous week, or use of potassium or potassium-sparing diuretics (other than low-dose spironolactone). The primary end point was a composite of all-cause mortality and unplanned heart failure–related hospitalization, and the mean follow-up was 26.2 months. Many patients were also receiving β-blockers (~55%), loop diuretics (~45%), and calcium channel blockers (~33%), and approximately 50% were receiving nitrates and digoxin. Patients assigned to receive perindopril began by taking 2 mg/day with titration to 4 mg/day (~90% titrated).

Unfortunately, with lower than anticipated enrollment, a lower than expected event rate, and increased use of open-label ACE inhibitor, recruitment was stopped early, and only 107 and 100 patients receiving perindopril and placebo, respectively, reached the primary end point (p=0.545). Looking at only the first year of data, 65 patients (15.3%) in the placebo group and 46 patients (10.8%) in the perindopril group reached the primary outcome (p=0.055), but this study was underpowered for its primary end point with only a calculated 35% power to show statistical significance. During the first year, 12.4% of the placebo group and 8.0% of the perindopril group had an unplanned hospitalization for heart failure (p=0.033), but this was not significant over the entire study period. Of hospitalized patients, those in the perindopril group spent a median of 3 fewer days admitted for cardiovascular reasons (p=0.056) and 5 fewer days for any reason (p=0.229). Of note, perindopril treatment produced significant improvement in NYHA classification and 6-minute walk distance. A major limitation of this

study was its lack of power for primary outcomes. In addition, authors noted that the clinical diagnosis of heart failure was only partially corroborated by patient characteristics. One important observation in this trial was the 3-fold increase in primary end point in patients with NT-proBNP levels above the median value; the authors suggested this may be a key selection criterion for future clinical trials. One of the strengths of this study was its exclusion of patients taking ACE inhibitors or ARBs.

The CHARM-Preserved study compared candesartan versus placebo in patients with heart failure with PEF; the primary outcome was cardiovascular death or hospital admission for worsening heart failure.[54] Patients were permitted concomitant use of other drugs: β-blockers (~55% of patients), diuretics (~75%), calcium channel blockers (~31%), ACE inhibitors (~19%), digoxin (~28%), and spironolactone (~12%). Patients were randomly assigned in a double-blind fashion to placebo or candesartan with initial doses of 4 or 8 mg/day, with dose doubling every 2 weeks to a target dose of 32 mg. Of note, patients in the candesartan group had higher prevalence of several baseline characteristics associated with poorer prognosis, including previous myocardial infarction, stroke, current smoking, hypertension, diabetes, and cancer. After a median of 36.6 months' follow-up, significantly fewer patients in the candesartan group had at least one hospitalization for heart failure (230 vs 279 patients, p=0.017). Candesartan did not reduce the frequency of the primary end point (22% for candesartan vs 24% for placebo, p=0.118), although when adjusted for other predictors the difference approached statistical significance (p=0.051). Approximately 19% of patients were concurrently receiving ACE inhibitors, which may have limited the ability to target candesartan's benefit on RAAS blockade.

The Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial included 4128 patients aged 60 years or older with heart failure symptoms and LVEF greater than 45% who were either hospitalized in the last 6 months for heart failure with current NYHA classes II–IV symptoms or persistent NYHA classes III–IV symptoms.[43] Patients with ACE inhibitor intolerance, probable alternative cause of symptoms, previous LVEF less than 40%, history of acute coronary syndrome, coronary revascularization or stroke within 3 months, valvular abnormalities, hypertrophic or restrictive cardiomyopathy, pericardial disease, cor pulmonale or other right-sided heart failure, systolic blood pressure less than 100 or greater than 160 mm Hg or diastolic blood pressure greater than 95 mm Hg despite antihypertensive therapy, life expectancy less than 3 years (due to other systemic disease), hemoglobin level less than 11 g/dl, serum creatinine concentration greater than 2.5 mg/dl, liver function abnormalities, or characteristics that would inhibit compliance were excluded. The primary outcome was a composite of death from any cause or hospitalization for a cardiovascular cause. Secondary outcomes included a breakdown of components from the primary outcome, as well as proBNP levels and the Minnesota Living with Heart Failure Scale. Baseline drug therapy included diuretics (83% of patients), β-blockers (59%), calcium channel blockers (40%), spironolactone (15%), and ACE inhibitors (25%). Patients successfully completing a 1–2 week run-in phase were randomly assigned to receive irbesartan or placebo stratified by baseline ACE inhibitor use. In patients assigned to receive irbesartan, the dosage began with 75 mg once/day and increased to 300 mg/day (target dose) as tolerated.

Patients in I-PRESERVE were more similar to patients participating in epidemiologic heart failure with PEF studies than those in previous trials, including the breakdown by sex, with more female than male patients. Although ACE inhibitor use was intended to be capped at 33% of the population and only permitted if essential for an indication other than hypertension, the proportion of patients receiving an ACE inhibitor was 39% and 40% in the irbesartan and placebo groups, respectively. No significant benefit was seen in primary or secondary outcomes. Patients in the irbesartan and placebo groups had a respective 36% and 37% rate of composite death from any cause or hospitalization for a cardiovascular cause (p=0.35). The authors noted several possibilities that could have led to the negative trial results, including a high rate of study drug discontinuation (~34% total; discontinuation due to an adverse event 16% for irbesartan vs 14% for placebo, p=0.07); frequent use of other drugs affecting the RAAS system, including approximately 40% ACE inhibitors, 73% β-blockers, and 30% spironolactone; and a potentially suboptimal irbesartan dose.

Despite the largely disappointing results of heart failure with PEF treatment trials, many believe that ACE inhibitors and ARBs have the potential to prevent development of heart failure

with PEF. However, few studies focusing on prevention have been published, and results have not clearly shown benefit. As part of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), lisinopril was compared with chlorthalidone in patients with hypertension.[41] Chlorthalidone was found to decrease the frequency of new-onset heart failure significantly more than lisinopril (see Diuretic section for details). In the Valsartan in Diastolic Dysfunction (VALIDD) study, authors hypothesized that ARBs would improve ventricular diastolic function in patients with hypertension before the development of heart failure with PEF.[55] Patients were randomly assigned to receive valsartan 160 mg once/day titrated to a goal of 320 mg/day or a non–RAAS-blockade regimen with instructions to control systolic blood pressure to less than 135 mm Hg in both groups. Although valsartan treatment did indeed improve ventricular diastolic function, equal blood pressure control with a non-ARB regimen improved diastolic function to a similar degree.

To summarize, several small studies with ACE inhibitors and ARBs showed symptomatic improvement, increased exercise capacity, increased quality of life, and reduced left ventricular mass (Table 3).[41–47, 52–54, 56–64] The CHARM-Preserved trial suggested a benefit in reducing hospital admissions for heart failure,[54] but this result was not confirmed in the more contemporary I-PRESERVE trial.[43] These inconsistent results between two of the largest available trials in heart failure with PEF may be related to concurrent ACE inhibitor use, which made up approximately 20% compared with 40% of enrolled patients in the CHARM-Preserved and I-PRESERVE trials, respectively. Other important differences between these trial populations include age (67 vs 72 yrs), sex (~40% vs 60% female), and LVEF (mean ~54% vs 60%).

The 2008 European Heart Failure guidelines suggest that ACE inhibitors and ARBs be first-line therapy for hypertension control in patients with heart failure with PEF.[65] The HFSA recommends that blood pressure be controlled (target < 130/80 mm Hg) and consideration given to treatment with an ACE inhibitor or ARB. These guidelines also recommend the consideration of an ACE inhibitor in all patients with atherosclerotic heart disease or diabetes with one additional risk factor (ARBs should be considered if intolerant to ACE inhibitors).[18] With hypertension as a common cause of heart failure with PEF, it is reasonable to use an ACE inhibitor or ARB for blood pressure reduction, atherosclerotic heart disease, or diabetes, but there is a lack of information to support use of these agents in a patient with controlled hypertension without another indication.

Aldosterone Antagonists

Aldosterone can promote interstitial collagen deposition and fibrosis, leading to increased ventricular stiffness. A prospective, randomized, double-blind, placebo-controlled trial hypothesized that spironolactone could prevent cardiac fibrosis of aging and therefore prevent or delay age-related worsening of diastolic dysfunction in the elderly.[46] Patients 60–85 years of age with mild diastolic dysfunction (measured by echocardiography) were given spironolactone or placebo. Mitral E:A ratio and deceleration time (load-dependent echocardiographic measures of diastolic function), plasma levels of carboxy-terminal of procollagen type I (PCIP) and BNP were measured at baseline and after 4 months of treatment. After 28 patients completed the 4-month study, the spironolactone group showed significantly improved E:A ratio and deceleration time from baseline values versus no significant changes from baseline in these values in the placebo group. Although a significant difference from baseline was noted in the spironolactone group in both E:A ratio and deceleration time, a significant difference was not seen with spironolactone versus placebo at 4 months. No significant difference in PCIP or BNP levels was found between groups despite previously reported decreases in BNP levels with spironolactone treatment in rats with heart failure with REF.[66]

Another study randomly assigned 30 carefully selected patients with hypertensive heart failure with PEF and confirmed ventricular diastolic dysfunction to receive spironolactone or placebo.[56] Primary end points included changes in long-axis strain and backscatter parameters (sensitive echocardiographic measures of ventricular systolic function) with intervention. Secondary end points included changes in left ventricular wall thickness, left ventricular mass, indexes of diastolic function, and arterial compliance. Patients included in the study were those with exertional dyspnea, without ischemia (no history of angina or myocardial infarction). Patients were excluded if they were receiving ACE inhibitor, ARB, or spironolactone therapy, or had

Table 3. Published Trials in Patients with Heart Failure with Preserved Ejection Fraction

Study Treatment and Duration of Follow-up	Study Population	Study Objective	Significant Results
ACE inhibitors and ARBs			
Enalapril 2.5–20 mg/day vs placebo x 3 mo[52]	Mean age ~80 yrs, 82% men, LVEF > 50%, NYHA class III, MI > 6 mo prior, mean E:A ratio 0.6 (n=22)	To compare the effects of enalapril on elderly patients with previous MI and normal LVEF treated with diuretics	Enalapril vs placebo: ↓ NYHA class: 2.4 ± 0.5 vs 3 ± 0, p=0.005 ↓ cardiothoracic ratio: 0.52 ± 0.01 vs 0.54 ± 0.02, p<0.001 ↑ treadmill exercise duration: 270 ± 44 vs 24 ± 27 sec, p<0.001 ↑ LVEF: 68 ± 9% vs 64 ± 9%, p<0.05 ↑ peak E:A ratio: 0.7 ± 0.1 vs 0.6 ± 0.1, p<0.001 ↓ left ventricular mass: 280 ± 46 vs 313 ± 43 g, p<0.001
Losartan 50 mg/day vs placebo x 2 wks[42]	Mean age 64 yrs, 80% women, LVEF > 50%, E:A ratio < 1.0, SBP at rest < 150 mm Hg, SBP with exercise > 200 mm Hg (n=20)	To test the hypothesis that ARBs would improve exercise tolerance in patients with diastolic dysfunction and increase SBP during exercise	Losartan vs placebo: ↓ peak SBP during exercise: 193 ± 27 vs 217 ± 26 mm Hg, p<0.05 ↑ exercise duration: 12.3 ± 2.6 vs 11.0 ± 2.0 min, p<0.05 ↑ quality of life: MLHFQ score 18 ± 22 vs 22 ± 26, p>0.05 ↑ time to SBP > 190 mm Hg during exercise: 10.6 ± 3.3 vs 8.7 ± 3.5 min, p<0.05
Quinapril 5–40 mg/day vs placebo x 6 mo[53]	Mean age ~78 yrs, > 30% male, LVEF > 40% (mean ~59%) (n=74)	To evaluate the effect of quinapril on functional status of elderly patients with heart failure with PEF and the feasibility of such studies in elderly patients	No significant results reported
Candesartan 4–32 mg/day vs placebo x 4 wks[54]	Mean age 67 yrs, 60% men, 64% had hypertension, LVEF > 40% (mean LVEF 54%) NYHA class II–IV x 4 wks (> 60% NYHA class II), history of hospital admission (n=3023)	To assess the effects of candesartan on composite outcome of cardiovascular mortality or admission to hospital for worsening heart failure	Candesartan vs placebo: ≥ 1 hospital admission for heart failure at 36.6 mo of follow-up: 230 vs 279 patients, p=0.017 Total heart failure admissions: 402 vs 566 admissions, p=0.014
Perindopril 2–4 mg/day vs placebo x 1 yr[44]	Mean age 75 yrs, > 60% NYHA class II, mean E:A ratio 0.7, LVEF ≥ 40% (mean LVEF 64%) (n=850)	To determine if perindopril could improve outcomes in older patients treated for heart failure with evidence of diastolic dysfunction	Perindopril vs placebo: Patients with NYHA class II: 63.7% vs 70.5%, p=0.03 ↑ 6-min walk distance: 328 vs 309 meters, p=0.011
Irbesartan 75–300 mg/day vs placebo x 2 yrs[43]	Mean age 72 yrs, 60% women, > 70% NYHA class II, LVEF > 45%, 88% had hypertension, mean irbesartan dose 275 mg (n=4128)	To evaluate the effect of irbesartan on mortality and cardiovascular morbidity in patients with heart failure with PEF	No significant results reported
Aldosterone antagonists			
Spironolactone 25 mg/day vs placebo x 4 mo[46]	Mean age ~72 yrs, 78% female, LVEF > 45%, E:A ratio < 1.0, > 45% of patients taking ACE inhibitor or ARB (n=28)	To test the hypothesis that spironolactone can prevent progressive cardiac fibrosis and prevent or delay age-related decline in diastolic function in the elderly	↑ E:A ratio from baseline: 0.71 ± 0.08 vs 0.84 ± 0.19, p=0.025 ↓ deceleration time from baseline: 285.5 ± 73.1 vs 230.0 ± 54.7 msec, p=0.035

Table 3. Published Trials in Patients with Heart Failure with Preserved Ejection Fraction (continued)

Study Treatment and Duration of Follow-up	Study Population	Study Objective	Significant Results
Aldosterone antagonists (continued)			
Spironolactone 25 mg/day vs placebo x 6 mo[56]	Mean age > 60 yrs, > 60% female, LVEF > 50% (mean ~68%), E:A ratio < 1.0 (n=30)	To determine the effects of spironolactone on myocardial function by using sensitive quantitative echocardiographic techniques	Spironolactone at baseline vs 6 mo: ↑ strain rate: –1.57 ± 0.46 vs –1.91 ± 0.36 sec^{-1}, p<0.01 ↑ peak systolic strain: –20.3 ± 5.0% vs –26.9 ± 4.3%, p<0.001 ↓ left ventricular posterior wall thickness: 0.95 ± 15 vs 84 ± 0.14 cm, p=0.04
Eplerenone 25–50 mg/day vs placebo x 12 mo[57]	Mean age 80 yrs, 64% female, LVEF > 40%, 91% had hypertension, 64% were taking ACE inhibitor, 34% ARB, and 68% β-blocker (n=44)	To evaluate the impact of eplerenone on collagen turnover in patients with heart failure with PEF	Eplerenone vs placebo: ↓ PIINP from baseline: –0.50 ± 2.01 vs 2.13 ± 2.78 g/L, p=0.006 ↓ deceleration time from baseline: –82 ± 51 vs –7 ± 73 msec, p= 0.032
β-Blockers			
Propranolol 90 mg/day vs placebo x 32 mo[45]	Mean age 81 yrs, > 70% women, LVEF ≥ 40% (mean ~56%) (n=158)	To evaluate the effect of propranolol on total mortality and nonfatal MI	Propranolol vs placebo: ↑ LVEF: mean 6% vs 2%, p<0.0001 ↓ left ventricular mass: 34- vs 20-g reduction, p=0.0001 ↓ total mortality at 32 mo: 56% vs 76%, p=0.007 ↓ total mortality and nonfatal MI at 32 mo: 59% vs 82%, p=0.002
Atenolol 50–100 mg/day vs nebivolol 2.5–5 mg/day x 6 mo[58]	Mean age > 60 yrs, 68% male, LVEF ≥ 50%, E:A ratio < 1.0 (n=26)	To compare effects of atenolol and nebivolol on exercise hemodynamic parameters and maximal exercise capacity	Atenolol vs nebivolol: At rest: change from baseline to 6 mo: Cardiac index: –0.64 vs –0.26 $L/min/m^2$, p=0.01 Systemic vascular index: 118 vs 32 $dyn•sec/cm^5$, p=0.05 mPAP: –1 vs –4 mm Hg, p=0.03 PWP: –1 vs –3 mm Hg, p=0.03 ↑ E:A ratio: 0.05 vs 0.12, p=0.004 At peak exercise: change from baseline to 6 mo: Cardiac index: –0.54 vs –0.05 $L/min/m^2$, p=0.005) mPAP: –2 vs –7 mm Hg, p=0.03 PWP: –1 vs –5 mm Hg, p=0.03
Carvedilol 25–50 mg twice/day vs placebo x 12 mo[59]	Mean age ~66 yrs, LVEF > 45%, > 60% had hypertension, > 50% NYHA class II, >10% had diabetes (n=97)	To investigate the effects of carvedilol in patients with heart failure with PEF	Carvedilol vs placebo: Change from baseline to 6 mo: ↑ age-adjusted E:A ratio: 0.11 vs 0.05, p=0.046
Carvediolol 1.25–20 mg/day vs conventional treatment x 12 mo[60]	Mean age 71 yrs, 48% women, LVEF ≥ 45% (mean 57%) mean E:A ratio 0.74, NYHA class II–III, 83% taking ACE inhibitors, 10% digitalis (n=40)	To evaluate the effect of carvedilol vs conventional therapy on NYHA class, BNP, and exercise capacity	Carvedilol vs conventional therapy: ↓ BNP: 106 vs 174 pg/ml, p<0.02 ↓ NYHA class: –0.77 vs –0.25, p=0.02 ↑ exercise capacity: 5.68 vs 4.72 metabolic equivalents, p<0.02

Table 3. Published Trials in Patients with Heart Failure with Preserved Ejection Fraction (continued)

Study Treatment and Duration of Follow-up	Study Population	Study Objective	Significant Results
β-Blockers (continued)			
Nebivolol 1.25–10 mg/day vs placebo x 21 mo[61]	Age ≥ 70 yrs, LVEF > 35% (mean 49%) (n=752; heart failure with PEF)	To examine the effects of LVEF on outcomes of nebivolol	↓ heart rate (net effect vs placebo): –6.9 beats/min, p<0.001 Nebivolol vs placebo: ↑ LVEF: 48.7 ± 9.9 at baseline to 50.3 ± 11.3 at 12 mo vs 49.1 ± 9.4 at baseline to 48.4 ± 11.8 at 12 mo, p=0.027
Calcium channel blockers			
Verapamil 80 mg twice/day to 120 mg 3 times/day vs placebo x 5 wks[62]	Mean age 68 yrs, 100% men, LVEF > 45% (n=20)	To evaluate the effects of verapamil in men with heart failure with PEF	Verapamil vs placebo: Median improvement in heart failure score: 3 vs 1, p<0.01 ↑ peak filling rate: 2.29 ± 0.54 vs 1.85 ± 0.45 EDV/sec, p<0.05 ↑ exercise capacity from baseline: 13.9 ± 4.3 vs 10.7 ± 3.4 min, p<0.05
Verapamil 120 mg/day vs placebo x 3 mo[63]	Age ≥ 60 yrs, 40% female, LVEF > 50%, E:A ratio < 1.0, NYHA class II–III (n=15)	To evaluate if verapamil is effective in elderly patients with left ventricular diastolic dysfunction as a cause of heart failure	Verapamil at baseline vs verapamil at 3 mo vs placebo at 3 mo: Improved heart failure score: 5.6 ± 0.5 vs 3.5 ± 0.5 vs 5.5 ± 0.5, p<0.05 ↑ exercise time: 7.4 ± 1.2 vs 8.3 ± 1.2 vs 7.4 ± 1.3 min, p<0.05 ↑ Mva:Pva ratio: 0.89 ± 0.08 vs 1.11 ± 0.08 vs 0.91 ± 0.07, p<0.05 ↓ isovolumic relaxation time: 84 ± 12 vs 73 ± 9 vs 86 ± 13 msec, p<0.05
Digoxin			
Digoxin 0.125–0.5 mg/day vs placebo x 2 yrs[64]	Heart failure with REF (mean LVEF ~32%) vs PEF (mean LVEF 55%) mean age ~67 yrs, > 30% women, > 50% NHYA class II > 25% had diabetes > 18% had hypertension > 85% taking ACE inhibitors, > 75% diuretics, > 65% mean digoxin dose 0.25 mg (n=1832)	To examine the effect of digoxin on outcomes separately in propensity-matched patients with heart failure with REF and those with heart failure with PEF in equal samples	↓ 2-yr heart failure hospitalization: PEF: HR 0.64, 95% CI 0.45–0.90, p=0.010 REF: HR 0.73, 95% CI 0.54–0.97, p=0.033 ↓ 2-yr heart failure hospitalization or mortality: PEF: HR 0.69, 95% CI 0.5–0.95, p=0.025 REF: HR 0.72, 95% CI 0.55–0.95, p=0.0022
Diuretics			
Diuretics vs diuretics + ramipril 2.5–10 mg/day vs diuretics + irbesartan 18.75–75 mg/day x 1 yr[47]	Mean age ~74 yrs, > 30% female, LVEF > 45%, > 80% had hypertension, 70% NYHA class II, 20% had diabetes (n=150)	To assess the blockade effect of the renin-angiotensin system with an ARB or ACE inhibitor using symptoms, quality of life, and global left ventricular function	↑ quality-of-life score at baseline vs 1 yr: Diuretics: 20 vs 10.9, p<0.001 Diuretics + ramipril: 23 vs 11.4, p<0.001 Diuretics + irbesartan: 19 vs 9.4, p<0.001 ↓ NT-proBNP: baseline vs 1 yr: Diuretics + ramipril: 488 ± 701 vs 314 ± 422 pg/ml, p<0.001 Diuretics + irbesartan: 568 ± 757 vs 443 ± 603 pg/ml, p<0.001 Blood pressure: baseline vs 24 wks: Diuretics: 145/80 vs 138/80 mm Hg, p<0.001 Diuretics + ramipril: 143/82 vs 137/76 mm Hg, p<0.001 Diuretics + irbesartan: 144/82 vs 136/76 mm Hg, p<0.001

renal impairment, hyperkalemia, or signifi-cant valvular disease. The spironolactone group showed a significant reduction in posterior wall thickness from baseline and a trend toward reduced left atrial area (p=0.09) and, in addition, saw a significant increased long-axis strain rate,

Table 3. Published Trials in Patients with Heart Failure with Preserved Ejection Fraction (continued)

Study Treatment and Duration of Follow-up	Study Population	Study Objective	Significant Results
Diuretics (continued)			
Chorthalidone vs lisinopril, chlorthalidone vs amlodipine, and chlorthalidone vs doxazosin[41]	mean age ~69 yrs, > 30% women (n= 910)	To compare treatments with regard to hospitalization for PEF vs REF heart failure	Death after first heart failure hospitalization: 29.2% PEF vs 41.9% REF, p<0.001 ↓ new-onset heart failure with PEF: Chlorthalidone vs lisinopril: HR 0.74, 95% CI 0.56–0.97, p=0.032 Chlorthalidone vs amlodipine: HR 0.69, 95% CI 0.53–0.91, p=0.009 Chlorthalidone vs doxazosin: HR 0.53, 95% CI 0.38–0.73, p<0.001

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; MI = myocardial infarction; E:A ratio = ratio between early velocity from ventricular filling to late velocity from atrial contraction; SBP = systolic blood pressure; MLHFQ = Minnesota Living with Heart Failure Questionnaire; PEF = preserved ejection fraction; PIINP = procollagen II N-terminal peptide; mPAP = mean pulmonary artery pressure; PWP = pulmonary wedge pressure; BNP = B-type (brain) natriuretic peptide; EDV = end-diastolic velocity; Mva:Pva ratio = ratio of mitral A wave duration to pulmonary venous atrial systolic reversal duration; REF = reduced ejection fraction; HR = hazard ratio; CI = confidence interval; NT-proBNP = N-terminal proBNP.

peak systolic strain, and cyclic variation of integrated backscatter (i.e., had improved ventricular systolic function). Of interest, this effect was independent of blood pressure reduction, and there were minimal effects on ventricular diastolic function.

A pilot study randomly assigned 44 patients with heart failure with PEF to receive eplerenone started at 25 mg/day and titrated to 50 mg/day or placebo.[57] Diagnosis of heart failure with PEF was defined as NYHA class IV symptoms on previous hospital admission or symptoms consistent with heart failure, BNP levels greater than 100 pg/ml, LVEF greater than 40%, and echocardiographic evidence of diastolic dysfunction. Nearly all patients were taking an ACE inhibitor (64%) or ARB (34%) at baseline, and most (68%) were also taking β-blockers. Serum markers of collagen turnover and inflammation including procollagen types I and III amino-terminal peptides, matrix metallo-proteinase type 2, interleukin-6 and -8, and tumor necrosis factor-α, were analyzed at baseline and at 6 and 12 months. Doppler echocardiographic assessment of diastolic filling indexes and tissue Doppler analyses, in addition to NYHA functional class and quality-of-life score, were also obtained. Eplerenone signifi-cantly attenuated the increase in procollagen type III amino-terminal peptides from baseline to 12 months and produced a significant reduction in deceleration time compared with placebo during the study, but no other changes in diastolic functional markers were seen. Of importance, the benefit of eplerenone in this study was seen despite the use of other drugs that directly or indirectly affect RAAS activity.

Current data suggest that aldosterone antagonism may be beneficial in decreasing myocardial stiffness and improving myocardial relaxation independent of blood pressure reduction. Studies have shown that aldosterone antagonists may also be able to improve ventricular systolic function, decrease myocardial wall thickness, and reduce collagen formation in patients with heart failure with PEF. As noted with ACE inhibitors and ARBs, aldosterone antagonists may also be important agents in hypertension management, a common cause of heart failure with PEF. Other ongoing studies, such as the Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function (TOPCAT) trial, may provide future information on aldosterone antagonists (Table 4).

β-Blockers

Increased heart rate causes an increase in myocardial oxygen demand and decreases coronary perfusion time, which may be important in patients with heart failure with PEF and coronary artery disease. Controlling heart rate may be important in patients with heart failure with PEF for other reasons, as incomplete ventricular relaxation between beats may cause an increase in diastolic pressure relative to diastolic volume.[68, 69] However, at least some patients with heart failure with PEF have chronotropic incompetence,[38] and the optimal

Table 4. Ongoing Clinical Trials in Patients with Heart Failure with Preserved Ejection Fraction

Treatment	ClinicalTrials.gov Identifier	Study Objective
Angiotensin II receptor blocker		
Valsartan vs placebo	00241098	To evaluate the response of hypertension and early-stage heart failure
Valsartan vs placebo	00171106	To study the effects of valsartan on exercise tolerance
Aldosterone antagonists		
Spironolactone vs placebo (TOPCAT)	00094302	To evaluate the effectiveness of spironolactone in reducing all-cause mortality in patients with heart failure with PEF. The study began in August 2006 and is expected to be completed in July 2013.
Eplerenone vs placebo (PREDICT)	00293150	To determine the efficacy of eplerenone in patients with heart failure with PEF to reverse cardiac remodeling and improve diastolic function
Spironolactone vs placebo (ARCTIC-D)	00523757	To assess the change in markers of collagen turnover and correlate this with specific measures of left ventricular mass by magnetic resonance imaging, collagen markers, other biomarkers, clinical outcomes, quality of life, and exercise testing
Eplerenone vs placebo	00108251	To determine whether eplerenone has a benefit on exercise ability in patients with heart failure with PEF
Spironolactone	00206232	To observe spironolactone's safety and effectiveness in women
Renin inhibitor		
Aliskerin + spironolactone vs lisinopril + spironolactone (ARID-HF)	00773084	To compare effects of two different combinations of heart failure drugs on certain blood markers that cause or worsen heart failure
Statins		
Statin vs no statin	Not applicable	Statins are thought to have a protective effect on left ventricular remodeling and fibrosis. This study's preliminary report showed that receipt of statin therapy significantly improved survival rate and remained beneficial after adjusting for differences in baseline characteristics (relative risk 0.20, 95% confidence interval 0.06–0.62, p=0.005).[67]
Atorvastatin vs placebo	00585611	To compare the change in carotid-femoral pulse wave velocity and change in flow-mediated dilation between groups
Phosphodiesterase-5 inhibitor		
Sildenafil vs placebo (RELAX)	00763867	To evaluate the effectiveness of sildenafil in reversing cardiac hypertrophy and interstitial fibrosis, inhibiting catecholamine-stimulated hypertrophy, decreasing pulmonary vascular resistance and pressure, stimulating myocardial relaxation, and promoting antiproliferative effects
Ranolazine		
Ranolazine	00574756	To evaluate the effect of ranolazine on echocardiographic indexes of diastolic dysfunction
Endothelian receptor antagonists		
Bosentan vs placebo	00820352	To evaluate the safety and efficacy of bosentan in patients with heart failure with PEF and secondary pulmonary hypertension
Ambrisentan vs placebo	00840463	To evaluate the safety and efficacy of ambrisentan to treat pulmonary hypertension associated with heart failure with PEF
Sitaxsentan vs placebo (phase II study)	00303498	To explore if sitaxsentan is effective in the treatment of heart failure with PEF
Recombinant human BNP		
Nesiritide	00309868	To study the acute hemodynamic and myocardial effects of nesiritide in patients with heart failure with PEF
Xanthine oxidase inhibitor		
Allopurinol	00477789	To assess whether a reduction of uric acid levels will favorably affect diastolic function in patients with chronic heart failure

TOPCAT = Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function; PEF = preserved heart failure; PREDICT = Eplerenone in Reversing Endothelial and Diastolic Dysfunction and Improving Collagen Turnover in Diastolic Heart Failure; ARCTIC-D = Aldosterone Blockade in Heart Failure; ARID-HF = Aliskerin and Renin Inhibition in Diastolic Heart Failure; RELAX = Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People with Diastolic Heart Failure; BNP = B-type (brain) natriuretic peptide.

heart rate may not be the same for all patients. In heart failure with REF, chronic stimulation of the sympathetic nervous system promotes ventricular remodeling that can be prevented with the use of β-blockers; whether similar effects with β-blockers will occur in heart failure with PEF is unknown. Despite the lack of large trials supporting the use of β-blockers in patients with heart failure, data from the Acute Decompensated Heart Failure Registry (ADHERE), which contains information on over 100,000 heart failure–related hospitalizations, showed that more than 60% of 17,045 patients with LVEF greater than 40% received β-blockers.[13]

A 1997 study sought to prove a mortality benefit for β-blockade in patients with heart failure with PEF who previously had experienced a myocardial infarction.[45] The study population of 158 patients had NYHA class II or III symptoms, previous Q-wave myocardial infarction, and an LVEF of 40% or greater after 2 months of treatment with an ACE inhibitor and diuretics. Patients were randomly assigned to receive propranolol starting at 10 mg/day with dosage titration to a target of 30 mg 3 times/day or placebo, and followed for a mean of nearly 3 years. All patients were receiving a diuretic and an ACE inhibitor, 33% were receiving digoxin, and more than 60% had a history of hypertension. One year after randomization, propranolol-treated patients had a significant increase in LVEF and reduction in left ventricular mass. Multivariable Cox regression analysis modeling showed significant benefits of propranolol treatment at a mean follow-up of 32 months, with an odds ratio of 0.65 (95% confidence interval [CI] 0.44–0.96, p=0.03) and 0.63 (95% CI 0.43–0.92, p=0.02) for total mortality and total mortality plus nonfatal myocardial infarction, respectively.

A more contemporary prospective trial randomly assigned 26 patients to receive atenolol or nebivolol and compared exercise hemodynamic parameters and maximal exercise capacity.[58] Entry criteria included NYHA class II or III symptoms for at least 6 months, peak volume of oxygen consumption of 25 ml/kg/minute, evidence of normal systolic function (defined by an LVEF ≥ 50% and end-diastolic diameter < 32 mm/m^2), and diastolic dysfunction (defined by E:A ratio < 1.0 and/or pulmonary capillary wedge pressure > 12 mm Hg at rest and/or > 20 mm Hg at peak exercise). Exclusion criteria were active myocardial ischemia, valvular or congenital heart disease, resting systolic blood pressure greater than 200 mm Hg or diastolic blood pressure greater than 100 mm Hg, atrial fibrillation, or contraindications to β-blockers. All patients underwent cardiopulmonary exercise testing and echocardiography with Doppler measurements at baseline and after 6 months of treatment. Furosemide was given to all but one patient, and an ACE inhibitor or ARB was given to all but one patient in each treatment arm. Of the 13 patients in each treatment arm, 7 of those receiving atenolol and 8 of those receiving nebivolol were also receiving amlodipine. Atenolol and nebivolol doses were titrated from 50 to 100 mg/day and from 2.5 to 5 mg/day, respectively. Nebivolol, but not atenolol, significantly increased the volume of oxygen consumption from baseline, although there was no significant difference in the magnitude of change between groups. No significant change from baseline was noted in end-diastolic diameter or LVEF in either group. Both groups showed similar decreases in left ventricular end-diastolic septal wall thickness. Significantly less reduction in cardiac index, less increase in systemic vascular resistance, greater decrease in mean pulmonary artery pressure, greater increase in the E:A ratio, and greater decrease in pulmonary wedge pressure favored nebivolol over atenolol, both at rest and during peak exercise. Systemic vascular resistance changes were only significant at rest and not during peak exercise.

The Swedish Doppler Echocardiographic (SWEDIC) study was a prospective, randomized, double-blind, placebo-controlled trial that compared the effects of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function versus placebo.[59] Included patients had a wall motion index of 1.2 or less (corresponding to LVEF > 45%) and evidence of abnormal diastolic function. The primary end point was improvement in a diastolic dysfunction score measured by changes in four echocardiographic diastolic variables. In all patients, carvedilol dose was titrated to the maximum tolerated (target of 25 or 50 mg twice/day), with 82% of patients achieving the target dose. Ninety-seven of 113 patients completed the entire study with sufficient data. There was no statistically significant difference in the primary end point between groups, but there was a significant increase in age-adjusted E:A ratio in the carvedilol group. The authors noted that when the data were analyzed by subgroups based on resting heart rate, patients with heart rates of 71 beats/minute or higher had a higher

E:A ratio (i.e., improved early diastolic filling), whereas those with heart rates lower than 71 beats/minute did not. One of the limitations of this study was its small study size; a larger study would need to be conducted before confirming the benefits of carvedilol on ventricular diastolic function.

Another small study compared carvedilol in 19 patients with conventional therapy in 21 patients who had been referred to an outpatient heart failure clinic in Japan.[60] Patients had been treated with conventional therapy—ACE inhibitors, diuretics, and/or digitalis—for 3 or more months. Carvedilol was started at 1.25 mg/day, with doubling every week until a dose of more than 5 mg/day. Greater increases were made by the attending cardiologists to a maximum carvedilol dose of 20 mg/day (mean dose of 10.6 mg/day), generally considered the maximum dose for Japanese patients. Conventional therapy was continued. All patients in both groups were provided guidelines for lifestyle modification. If patients came to the clinic with a heart failure exacerbation, the carvedilol group had their dosage of diuretic up-titrated, but no changes could be made to other cardiovascular drugs; patients in the conventional group could also have their diuretic dosage increased but could also have an ARB administered if they had experienced no diuretic effect. Treatment failure was defined as death from any cause, hospitalization, use of inotropic agents to treat exacerbation, exercise intolerance with NYHA class IV symptoms after treatment adjustment, or carvedilol intolerance. After 12 months of treatment, carvedilol was found to significantly reduce BNP levels, improve NYHA functional class symptoms, and increase exercise capacity. Although this was a small trial, it can be hypothesis generating for a larger trial.

A subanalysis of the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial examined the effects of an LVEF of 35% or less in 1359 patients (REF group) and an LVEF greater than 35% in 752 patients (PEF group) during treatment with nebivolol.[61] The primary outcome was time to first event of a composite end point of all-cause mortality or cardiovascular hospitalization. Eligible patients were aged 70 years or older and had a clinical history of heart failure, with either documented hospital admission within 12 months with a discharge diagnosis of chronic heart failure or an LVEF less than 35% within the previous 6 months. Concomitant drugs in the PEF group included a diuretic (83% of patients), ACE inhibitor (82%), ARB (5.6%), aldosterone antagonist (5.6%), cardiac glycoside (40.4%), antiarrhythmic agent (17.7%), lipid-lowering agent (13.3%), and calcium channel blocker (18.9%). Aldosterone antagonists and ARBs were used less frequently in the PEF group versus the REF group: 5.6% versus 32.1%, and 5.6% versus 9.9%, respectively. The nebivolol dose was titrated from 1.25 mg/day to a target dose of 10 mg/day over 16 weeks.

Both groups showed a significant reduction in heart rate with nebivolol versus placebo. Overall, nebivolol produced a significantly decreased left ventricular end-diastolic volume, increased LVEF, and increased echocardiographic fractional shortening (a measure of systolic function) within both groups combined, but within the PEF population, only a significant increase in LVEF was noted. The occurrence of primary outcomes was not significantly different between patients with heart failure with PEF (31.2%) and those with heart failure with REF (34.2%). The hazard ratio (HR) of β-blockade versus placebo between the subgroups was similar for the primary outcome (HR 0.86, 95% CI 0.72–1.04 vs HR 0.81, 95% CI 0.63–1.04, p=0.720). To ensure primary and secondary outcome results were not related to choice in LVEF cutoff, investigators looked at the effects of nebivolol versus placebo in 643 patients with LVEF of 40% or greater and found results similar to those with LVEF of 35% or greater. A limitation of this study is that it was not powered to show an effect of nebivolol between subgroups of LVEF, but these post hoc analyses suggest potential benefit in patients with heart failure with PEF. With nebivolol's effect on nitric oxide, there is a question of whether these data can be extrapolated to other β-blockers.

The HFSA recommends that blood pressure be controlled to a target of lower than 130/80 mm Hg, and treatment with a β-blocker could be considered in addition to other agents. The HFSA also recommends β-blockers in patients with heart failure with PEF and atrial fibrillation, or previous myocardial infarction.[18] β-Blockers appear to decrease mortality in patients with heart failure with PEF after previous Q-wave myocardial infarction and may have a role in increasing LVEF, improving hemodynamic parameters, and increasing exercise capacity. In addition, data from the large SENIORS trial suggest similarity in clinical outcomes between β-blockers in heart failure with PEF and heart

failure with REF.[61] In addition to the use in patients with atrial fibrillation or previous myocardial infarction as recognized in the guidelines, β-blockers can be considered for treatment of heart failure with PEF for patients without contraindications. It is important to note that some patients with heart failure with PEF have chronotropic incompetence, which may limit the use of β-blockers in this population.

Calcium Channel Blockers

The use of nondihydropyridine calcium channel blockers in patients with hypertrophic cardiomyopathy results in improved diastolic filling. With this concept in mind, calcium channel blockers could be beneficial in patients with heart failure with PEF. Nondihydropyridine agents are more selective for the myocardium with less vasodilatory effects, whereas dihydropyridine agents are highly vascular selective. More specifically, calcium channel blockers bind to L-type calcium channels blocking entry of calcium and promoting relaxation. Most data about heart failure with PEF and calcium channel blockers are with nondihydropyridine agents.

A placebo-controlled, crossover trial assessed the effects of verapamil in patients with heart failure with PEF over 5 weeks.[62] Twenty men with heart failure symptoms for more than 3 months, an LVEF greater than 45%, and abnormal peak diastolic filling rate were assigned to receive verapamil or placebo. Patients were graded through a scoring system with points assigned for increasing grades of dyspnea, pulmonary congestion, jugular venous distension, third heart sound, and peripheral edema, with the highest score of 13 signifying the most severe heart failure. Patients taking digoxin discontinued therapy 7 days before study start, but diuretics could be continued. When beginning verapamil therapy, patients were given verapamil 80 mg 3 times/day with up-titration to 120 mg 3 times/day or down-titration to 80 mg twice/day based on tolerance (mean daily dose = 256 mg). Statistically significant improvement in heart failure score was noted in the verapamil group compared with the placebo group. Although only 12 (60%) of 20 patients were capable of exercise, verapamil significantly improved exercise capacity by 33% compared with baseline values. In addition, peak filling rate increased significantly by 30% with verapamil compared with baseline ($p<0.05$). Mean LVEF and systolic blood pressure were unchanged from baseline. The authors suggested that potential mechanisms of verapamil could be alteration of left ventricular filling, reversal of subclinical ischemia, and alteration of cellular calcium metabolism. The study is limited by its small sample size and the entirely male study population, which is noteworthy due to the increased prevalence of heart failure with PEF in women.

Fifteen elderly patients with normal LVEF were randomly assigned to receive verapamil or placebo in a 3-month, placebo-controlled, crossover trial.[63] Heart failure scores were used for group comparisons and reflected clinical assessment parameters (dyspnea, pulmonary congestion, neck vein distension, peripheral edema, pulmonary edema on independently read chest radiographs, a Bruce modified exercise test, and echocardiograms), with higher scores representing a worsened clinical picture. Patients had significantly improved heart failure scores and exercise time during verapamil treatment. No significant changes were noted in LVEF, left ventricular mass, heart rate, or cardiac output, and effects on diastolic function were mixed with reduced isovolumic relaxation time, increased peak velocity of mitral A wave to peak flow velocity and duration of the flow reversal during atrial systole (Mva:Pva) ratio, but no change in E:A ratio and E-wave deceleration time.

Data on dihydropyridine calcium channel blockers in patients with heart failure with PEF are limited. In the ALLHAT trial, which was a large comparison of several pharmacologic hypertension treatment strategies, chlorthalidone decreased the occurrence of new-onset heart failure with PEF significantly more than amlodipine.[41] The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) compared blood pressure control in patients with hypertension randomly assigned to an amlodipine-perindopril or an atenolol-thiazide regimen. Of interest, a recent subanalysis of ASCOT suggested that patients receiving the amlodipine-based regimen had better diastolic function.[70] Whether this effect was due more in part to amlodipine or perindopril cannot be determined from this analysis.

The 2008 European Heart Failure guidelines suggest that calcium channel blockers may be useful to improve symptoms and exercise capacity.[65] The HFSA recommends that blood pressure be controlled to a target of less than 130/80 mm Hg, and treatment with a calcium-

channel blocker in addition to other agents could be considered. Published trials with calcium channel blockers are mostly limited to non-dihydropyridine agents, more specifically verapamil. These pilot studies suggest benefit in reducing heart failure scores, increasing exercise capacity, and altering left ventricular diastolic parameters, but their results need to be confirmed in larger populations. Again, the possibility of chronotropic incompetence may limit the use of nondihydropyridine calcium channel blockers in some patients.

Digoxin

It has been suggested that digoxin may produce an increase in systolic energy demands, add to a relative calcium overload in diastole, and contribute to diastolic dysfunction. The exact mechanism of how digoxin may benefit patients with heart failure with PEF is not clearly understood.[68] Nonetheless, as an ancillary part of the Digitalis Intervention Group (DIG) trial, the effect of digoxin (492 patients) versus placebo (496 patients) was evaluated in patients with an LVEF greater than 45% by assessing the occurrence of death or hospitalization due to worsening heart failure as a combined primary outcome.[64] In the main study, all patients (REF and PEF) randomly assigned to the digoxin group received one of four algorithm-derived doses.[71] Most patients were receiving diuretics and ACE inhibitors. Patients with an LVEF of 45% or less (6800 patients) had a significantly reduced rate of hospitalizations for heart failure compared with the placebo group (26.8% vs 34.7%, p<0.001). In the main study, no significant difference in event rates was noted in patients with heart failure with PEF.

However, a more recent analysis was conducted with 916 pairs of patients (1832 total patients) with PEF and REF, with baseline characteristics balanced by propensity matching.[64] With use of the same primary outcome of heart failure hospitalization or mortality as in the original DIG trial, a statistically significant benefit was seen with digoxin in both heart failure with REF and heart failure with PEF at the end of 2 years. Digoxin also significantly decreased heart failure–related hospitalization alone in both groups. At the end of the analysis period (median 3.2 yrs), no significant difference was seen between digoxin or placebo in either the REF group (HR 0.85, 95% CI 0.67–1.08, p=0.188) or PEF group (HR 0.79, 95% CI 0.60–1.03, p=0.085), possibly due to the crossover design and higher digoxin doses. There was also no significant difference seen in heart failure–related hospitalizations alone between the REF group (HR 0.80, 95% CI 0.62–1.03, p=0.079) and PEF groups (HR 0.77, 95% CI 0.57–1.03, p=0.074). Of interest, digoxin (an inotropic agent) was not found to be detrimental in patients with heart failure with PEF and may prove to be beneficial.

Although the 2010 HFSA guidelines do not address the use of digoxin in the management of heart failure with PEF, the data above suggest digoxin can be considered for use to decrease hospitalizations in patients with heart failure with PEF. Any additional role, beyond reduction of hospitalizations, will need to be investigated in future studies.

Diuretics

In patients with heart failure with PEF, the stiffened ventricles rely on higher than normal filling pressures to provide adequate cardiac output,[21] making these patients sensitive to the preload reduction induced by diuresis. However, diuretics are clinically useful to reduce pulmonary congestion and peripheral edema, creating a narrow therapeutic window for the use of diuretics in patients with heart failure with PEF.

In one study, 150 patients were randomly assigned to receive diuretics alone, diuretics plus ramipril, or diuretics plus irbesartan.[47] The hypothesis was that the addition of irbesartan or ramipril to diuretics would be superior to diuretics alone with respect to quality of life and ventricular function. Study inclusion criteria were as follows: age older than 18 years, clinical history of heart failure within the past 2 months with pulmonary congestion, NYHA classes II–IV, LVEF greater than 45%, and therapy with a stable dosage of diuretics more than 14 days before recruitment. The primary end points were symptoms (exercise capacity as measured by the 6-minute walk test), quality of life (the Minnesota Heart Failure Symptom Questionnaire), and ventricular function (echocardiographic measurement), assessed at baseline and at 12, 24, and 52 weeks. The initial dose of irbesartan was 18.75 mg/day with titration to 75 mg/day. Ramipril was initially started at 2.5 mg/day and titrated to 10 mg/day. At baseline, 68–80% of patients were receiving furosemide, 6–10% hydrochlorothiazide, ~5% indapamide, and 1–12% hydrochlorothiazide-triamterene.

Echocardiographic results did not show improvement in left ventricular dimensions or LVEF with ramipril and irbesartan added to diuretic therapy. The 6-minute walk test improved slightly, but without clinical or statistical significance. Blood pressure was significantly reduced from baseline in all groups, but was not significantly different between groups. The NT-proBNP levels were significantly improved from baseline with irbesartan and ramipril, but again was not significantly different between treatment groups. Quality of life was significantly improved across all study groups, with no additional benefit seen with the addition of ramipril or irbesartan. If targeting symptomatic relief and increased quality of life in elderly patients, diuretic therapy alone may provide similar improvement to additional ACE inhibitor and ARB therapy.

Of the 42,418 ALLHAT study participants, 1367 had heart failure events (validated by the Heart Failure Evaluation Study); 910 of those patients had an LVEF assessment; 44.4% had heart failure with PEF (LVEF ≥ 50%), and 56% had heart failure with REF (LVEF < 50%).[41] Patients aged 55 years or older with hypertension and one additional risk factor for coronary heart disease were included. Patients with a history of symptomatic heart failure, history of hospitalization for heart failure, or known LVEF less than 35% were excluded. Patients were randomly assigned to receive chlorthalidone, amlodipine, lisinopril, or doxazosin. Chlorthalidone treatment was compared with each of the other treatment arms. Chlorthalidone reduced the risk of new-onset heart failure with PEF compared with amlodipine (HR 0.69, 95% CI 0.53–0.91, p=0.009), lisinopril (HR 0.74, 95% CI 0.56–0.97, p=0.032), and doxazosin (HR 0.53, 95% CI 0.38–0.73, p<0.001). Critics suggest that peripheral edema may have been misclassified as heart failure with PEF, although all incident cases were diagnosed at the time of hospitalization for heart failure, and events were independently adjudicated.

The 2008 European guidelines recommend that diuretics be used to control sodium and water retention, relieve shortness of breath, and reduce edema.[65] The HFSA recommends diuretics in all volume-overloaded patients with heart failure with PEF, with treatment beginning with a thiazide diuretic and transitioning to a loop diuretic if poor response to the thiazide occurs. The HFSA also recommends that blood pressure be controlled to a target less than 130/80 mm Hg, and treatment with a diuretic should be considered.[18] In addition to reducing pulmonary congestion and peripheral edema, diuretics may prevent the development of new-onset heart failure, improve quality of life, and decrease BNP levels in patients with heart failure with PEF.

Clinical Implications

How should clinicians manage a patient who presents with symptoms of heart failure and normal LVEF? Although symptomatic manifestation of heart failure with PEF may be very similar to that of heart failure with REF, treatment for both types of heart failure may not be identical. A vast amount of literature and detailed guidelines exist for the short- and long-term management of patients with heart failure with REF, but the same is not true for those with heart failure with PEF. Clinicians should focus on controlling and treating underlying causes of the disease state and known risk factors, in particular, hypertension.

In patients with hypertension who have multiple risk factors for development of heart failure with PEF, thiazide diuretics may prevent the development of new-onset heart failure.[41] If blood pressure cannot be controlled with diuretics alone, the appropriate agents to add have not been fully defined. Blockade of the RAAS system through the use of ACE inhibitors or ARBs may provide symptomatic improvement, improve quality of life, increase exercise duration, and decrease left ventricular mass, but the effects of these agents on other clinical outcomes including mortality are not yet clear. It is reasonable to use an ACE inhibitor or ARB for blood pressure reduction in the setting of atherosclerotic heart disease or diabetes, but there is a lack of information to support use of these agents in a patient with controlled hyper-tension without another indication. Aldosterone antagonists may reduce inflammation and fibrosis, while also providing hypertensive control and improvements in diastolic function. Nondihydropyridine calcium channel blockers and β-blockers improved exercise capacity in small studies but had mixed effects on ventricular diastolic function and may exacerbate symptoms in patients with chronotropic incompetence. β-Blockers do appear to benefit patients with heart failure with PEF and a previous myocardial infarction and should be considered for patients without contraindications. The use of digoxin in patients with heart failure with PEF without atrial fibrillation

remains controversial, but the drug can be used to reduce the frequency of hospitalization, as it does in patients with heart failure with REF. Diuretics reduce and prevent fluid accumulation and improve quality of life. In addition to pharmacologic management, nonpharmacologic treatments including the following therapeutic lifestyle modifications should be considered for all patients[18]:

- Low-fat diet in patients with obesity, diabetes, hyperlipidemia, or vascular disease
- Low-sodium diet (2–3 g for mild heart failure and < 2 g for moderate-to-severe heart failure)
- Regular exercise
- Weight loss
- Restriction of fluid intake in severely affected patients
- Daily weight monitoring
- Smoking cessation
- Limited alcohol consumption
- Limited caffeine intake

Conclusion

Overall, the results of pharmacologic treatment trials in patients with heart failure with PEF have been disappointing. In large part, this reflects incomplete understanding of what is now recognized as a physiologically heterogenous disease. Future trials must take this heterogeneity into account when defining inclusion criteria. Efforts to standardize diagnostic guidelines should aid in more careful heart failure with PEF phenotyping. In addition, because of a lower cardiac mortality rate in patients with heart failure with PEF than those with heart failure with REF, clinical trials should focus more on quality-of-life and hospitalization end points. Although specific treatment for heart failure with PEF still remains to be clearly defined, treatment regimens within and beyond the typical therapeutic classes are being investigated. Until the results of these studies are available, treatment options for this major public health threat will be based on the limited data that currently exist.

References

1. **Zile MR, Brutsaert DL**. New concepts in diastolic dysfunction and diastolic heart failure. I. Diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105:1387–93.
2. **Wu EB, Yu CM**. Management of diastolic heart failure: a practical review of pathophysiology and treatment trial data. Int J Clin Pract 2005;59:1239–46.
3. **Lloyd-Jones D, Adams RJ, Brown TM, et al**. Heart disease and stroke statistics: 2010 update—a report from the American Heart Association. Circulation 2010;121:e46–215.
4. **Thohan V, Patel S**. The challenges associated with current clinical trials for diastolic heart failure. Curr Opin Cardiol 2009;24:230–8.
5. **Fitzgibbons TP, Meyer TE, Aurigemma GP**. Mortality in diastolic heart failure: an update. Cardiol Rev 2009;17:51–5.
6. **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.
7. **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.
8. **Curtis JP, Sokol SI, Wang Y, et al**. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol 2003;42:736–42.
9. **Gustafsson F, Torp-Pedersen C, Brendorp B, et al**. Long-term survival in patients hospitalized with congestive heart failure: relation to preserved and reduced left ventricular systolic function. Eur Heart J 2003;24:863–70.
10. **Bursi F, Weston SA, Redfield MM, et al**. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.
11. **Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM**. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. J Am Coll Cardiol 2003;41:1510–18.
12. **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.
13. **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 (≥ 55%) versus those with mildly reduced (40–55%) and moderately to severely reduced (< 40%) fractions. Am J Cardiol 2008;101:1151–6.
14. **Lim HS, Beadle R, Frenneaux M**. Death and dying in heart failure with normal ejection fraction. Am J Cardiol 2009;104:1311–14.
15. **Aurigemma GP, Gaasch WH**. Clinical practice: diastolic heart failure. N Engl J Med 2004;351:1097–105.
16. **Nagueh SF, Appleton CP, Gillebert TC, et al**. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.
17. **Paulus WJ, Tschope C, Sanderson JE, et al**. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.
18. **Heart Failure Society of America**. Executive summary: HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010;16:475–539.
19. **Hunt SA, Abraham WT, Chin MH, et al**. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112:e154–235.
20. **Jessup M, Abraham WT, Casey DE, et al**. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119:1977–2016.

21. **Satpathy C, Mishra TK, Satpathy R, Satpathy HK, Barone E**. Diagnosis and management of diastolic dysfunction and heart failure. Am Fam Physician 2006;73:841–6.
22. **Penicka M, Bartunek J, Trakalova H, et al**. Heart failure with preserved ejection fraction in outpatients with unexplained dyspnea: a pressure-volume loop analysis. J Am Coll Cardiol 2010;55:1701–10.
23. **Grewal J, McKelvie R, Lonn E, et al**. BNP and NT-proBNP predict echocardiographic severity of diastolic dysfunction. Eur J Heart Failure 2008;10:252–9.
24. **Lubien E, DeMaria A, Krishnaswamy P, et al**. Utility of B-natriuretic peptide echocardiographic severity of diastolic dysfunction: comparison with Doppler velocity recordings. Circulation 2002;105:595–601.
25. **Dahlstrom U**. Can natriuretic peptides be used for the diagnosis of diastolic heart failure? Eur J Heart Fail 2004;6:281–7.
26. **Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ**. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991;17: 1065–72.
27. **Zile MR, Baicu CF, Gaasch WH**. Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953–9.
28. **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.
29. **Borlaug BA, Melenovsky V, Russell SD, et al**. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006;114:2138–47.
30. **Colombo PC, Onat D, Sabbah HN**. Acute heart failure as "acute endothelitis": interaction of fluid overload and endothelial dysfunction. Eur J Heart Fail 2008;10:170–5.
31. **Maurer MS, King DL, El-Khoury Rumbarger L, Packer M, Burkhoff D**. Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. J Card Fail 2005;11:177–87.
32. **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.
33. **Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM**. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119–26.
34. **Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW**. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195–201.
35. **Hogg K, McMurray J**. Neurohumoral pathways in heart failure with preserved systolic function. Prog Cardiovasc Dis 2005;47:357–66.
36. **Wright JW, Mizutani S, Harding JW**. Pathways involved in the transition from hypertension to hypertrophy to heart failure: treatment strategies. Heart Fail Rev 2008;13:367–75.
37. **Kitzman DW, Little WC, Brubaker PH, et al**. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144–50.
38. **Phan TT, Nallur Shivu G, Abozguia K, et al**. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:29–34.
39. **Kalogeropoulos A, Georgiopoulou V, Psaty BM, et al**. Inflammatory markers and incident heart failure risk in older adults: the health ABC (health, aging, and body composition) study. J Am Coll Cardiol 2010;55:2129–37.
40. **Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ**. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.
41. **Davis BR, Kostis JB, Simpson LM, et al**. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation 2008;118:2259–67.
42. **Warner JG Jr, Metzger DC, Kitzman DW, Wesley DJ, Little WC**. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. J Am Coll Cardiol 1999;33:1567–72.
43. **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.
44. **Cleland JG, Tendera M, Adamus J, et al**. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338–45.
45. **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 ≥ 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol 1997;80:207–9.
46. **Roongsritong C, Sutthiwan P, Bradley J, Simoni J, Power S, Meyerrose GE**. Spironolactone improves diastolic function in the elderly. Clin Cardiol 2005;28:484–7.
47. **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.
48. **Lee DS, Gona P, Vasan RS, et al**. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham heart study of the National Heart, Lung, and Blood Institute. Circulation 2009;119:3070–7.
49. **Masoudi FA, Havranek EP, Smith G, et al**. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol 2003;41:217–23.
50. **Tribouilloy C, Rusinaru D, Mahjoub H, et al**. Prognostic impact of diabetes mellitus in patients with heart failure and preserved ejection fraction: a prospective five-year study. Heart 2008;94:1450–5.
51. **MacDonald MR, Petrie MC, Varyani F, et al**. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the candesartan in heart failure—assessment of reduction in mortality and morbidity (CHARM) programme. Eur Heart J 2008;29:1377–85.
52. **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.
53. **Zi M, Carmichael N, Lye M**. The effect of quinapril on functional status of elderly patients with diastolic heart failure. Cardiovasc Drugs Ther 2003;17:133–9.
54. **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.
55. **Solomon SD, Janardhanan R, Verma A, et al**. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. Lancet 2007;369:2079–87.
56. **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.
57. **Mak GJ, Ledwidge MT, Watson CJ, et al**. Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. J Am Coll Cardiol 2009;54:1674–82.
58. **Nodari S, Metra M, Dei Cas L**. β-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.

59. **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.
60. **Takeda Y, Fukutomi T, Suzuki S, et al**. Effects of carvedilol on plasma B-type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction. Am J Cardiol 2004;94:448–53.
61. **van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al**. β-Blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (study of effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure). J Am Coll Cardiol 2009;53:2150–8.
62. **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.
63. **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.
64. **Meyer P, White M, Mujib M, et al**. Digoxin and reduction of heart failure hospitalization in chronic systolic and diastolic heart failure. Am J Cardiol 2008;102:1681–6.
65. **Dickstein K, Cohen-Solal A, Filippatos G, et al, for the Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology**. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Developed in collaboration with the Heart Failure Association of the ESC and endorsed by the European Society of Intensive Care Medicine. Eur Heart J 2008;29: 2388–442.
66. **Lacolley P, Safar ME, Lucet B, Ledudal K, Labat C, Benetos A**. Prevention of aortic and cardiac fibrosis by spironolactone in old normotensive rats. J Am Coll Cardiol 2001;37:662–7.
67. **Fukuta H, Sane DC, Brucks S, Little WC**. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. Circulation 2005;112:357–63.
68. **Zile MR, Brutsaert DL**. New concepts in diastolic dysfunction and diastolic heart failure. II. Causal mechanisms and treatment. Circulation 2002;105:1503–8.
69. **Westermann D, Kasner M, Steendijk P, et al**. Role of left ventricular stiffness in heart failure with normal ejection fraction Circulation 2008;117:2051–60.
70. **Tapp RJ, Sharp A, Stanton AV, et al**. Differential effects of antihypertensive treatment on left ventricular diastolic function: an ASCOT (Anglo-Scandinavian cardiac outcomes trial) substudy. J Am Coll Cardiol 2010;55:1875–81.
71. **Garg R, Gorlin R, Smith T, Yusuf S, for the Digitalis Investigation Group**. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.