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Heart Failure with Preserved Ejection Fraction: Emerging Drug Strategies

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Abstract

Approximately half of heart failure patients have a normal ejection fraction, a condition designated as heart failure with preserved ejection fraction (HFpEF). This heart failure subtype disproportionately affects women and the elderly and is commonly associated with other cardiovascular comorbidities, such as hypertension and diabetes. HFpEF is increasing at a steady rate and is predicted to become the leading cause of heart failure within a decade. HFpEF is characterized by impaired diastolic function, thought to be due to concentric remodeling of the heart along with increased stiffness of both the extracellular matrix and myofilaments. In addition, oxidative stress and inflammation are thought to have a role in HFpEF progression, along with endothelial dysfunction and impaired nitric oxide-cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) signaling. Surprisingly a number of clinical studies have failed to demonstrate any benefit of drugs effective in heart failure with systolic dysfunction in HFpEF patients. Thus, HFpEF is one of the largest unmet needs in cardiovascular medicine and there is a substantial need for new therapeutic approaches and strategies that target mechanisms specific for HFpEF. This conclusion is underscored by the recently reported disappointing results of the RELAX trial, which assessed the use of phosphodiesterase-5 inhibitor sildenafil for treating HFpEF. In animal models, endothelial nitric oxide synthase (eNOS) activators and I_f current inhibitors have shown benefit in improving diastolic function and there is a rationale for assessing matrix metalloproteinase-9 (MMP-9) inhibitors and nitroxyl donors. LCZ696, a combination drug of angiotensin II receptor blocker and neprilysin inhibitor, and the aldosterone receptor antagonist spironolactone are currently in clinical trial for treating HFpEF. Here we present an overview of the etiology and diagnosis of HFpEF that segues into a discussion of new therapeutic approaches emerging from basic research, as well as

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drugs currently in clinical trial, that primarily target diastolic dysfunction or imbalanced ventricular-arterial coupling.

Introduction

Although controversial a decade ago, it is now generally accepted that heart failure (HF) occurs in two major subtypes.^{1–3} HF has historically been attributed to systolic dysfunction, as evidenced by a LV ejection fraction of <45%. This HF phenotype is now referred to as HF with reduced ejection fraction (HFrEF) and is characterized by a progressive ventricular dilation. A leading cause of HFrEF is ischemic heart disease resulting in myocardial infarction. HF, defined by dyspnea, fluid retention, and exercise intolerance, however, also occurs in cases of normal ejection fraction (>50%). This form of HF is referred to as HF with preserved ejection fraction (HFpEF) and is generally characterized by concentric remodeling/hypertrophy of the left ventricle (LV) along with increased interstitial fibrosis.¹ In contrast to HFrEF, individuals with HFpEF generally are older, more likely to be female, and have a lower incidence of coronary artery disease but greater occurrence of atrial fibrillation.³ A leading cause of HFpEF is hypertension, and the *sine qua non* of HFpEF is diastolic dysfunction or impaired relaxation of the LV. Although both forms of HF occur at similar prevalences, HFpEF is increasing at a steady rate and is anticipated to become the most common type of HF in the next 10 years.³ Individuals with HFpEF exhibit a higher number of noncardiac comorbidities, including diabetes, obesity, peptic ulcer disease, cancer, chronic obstructive pulmonary disease, psychiatric disorders, and anemia.³ The pattern of concentric cardiac remodeling seen in HFpEF, coupled with prolonged relaxation times, is commonly observed in the elderly irrespective of the presence of HF.³ For more on the pathognomonic and clinical aspects of HFpEF, the reader is referred to several recent articles.^{1–7}

HFpEF was once referred to as diastolic HF, until it became known that a variety of abnormalities in systolic function also occur in this condition.^{1,5} Diastolic dysfunction, evidenced by increased LV stiffness, prolonged isovolumetric LV relaxation, slow LV filling, and elevated LV end diastolic pressures, is the distinguishing feature of HFpEF. Other components that are potential targets for pharmacotherapeutic intervention are thought to contribute to disease symptoms, including chronotropic incompetence, pulmonary arterial hypertension, impaired exercise- and flow-mediated vasodilation, and metabolic abnormalities.¹ Overall, HFpEF is better described as a very complex clinical syndrome rather than a disease, which may make the diagnosis of HFpEF challenging. There is more to HFpEF than LV diastolic dysfunction. In fact, exertional symptoms in HFpEF patients may be attributable to increased large artery stiffness and reduced chronotropic reserve, rather than only diastolic dysfunction.⁸

Patients with HFpEF have better outcomes (decreased mortality and HF hospitalization days) than those with HFrEF, but a substantially poorer prognosis than patients with hypertension or other conditions associated with increased cardiovascular risk (Fig. 1).⁷ While plasma brain natriuretic peptide (BNP) levels (an index of LV wall stress) are in general lower in HFpEF than in HFrEF, for a given BNP level the prognosis for HFpEF is as poor as for HFrEF.⁹ Given the distinctive characteristics of HFpEF, perhaps it is not unexpected that results of a number of recent clinical trials have shown that drugs effective in treating HFrEF have proven much less effective or ineffective in patients with HFpEF.^{1,10}

Diagnosis and Biomarkers

Guidelines for the diagnosis of HFpEF include the presence of signs or symptoms of HF with apparently normal systolic LV function, a LV end-diastolic volume index of <97 mL/m², and evidence for LV diastolic dysfunction (e.g., elevated LV filling pressures or abnormal LV

relaxation) and/or structural abnormalities, such as LV hypertrophy, left atrium enlargement, and atrial fibrillation along with high plasma levels of BNP or the N-terminal fragment of the prohormone of BNP (NT-proBNP).^{1,4} Generally an ejection fraction ≥ 50 is considered normal; however others have noted that ejection fraction increases with a reduction in LV size as seen with the elderly and in that population an ejection fraction < 60 might be evidence for systolic dysfunction.⁵

Serum levels of the propeptide of procollagen type 1, which reflect collagen type I synthesis, are an established early measure of fibrosis in the heart in hypertensive heart disease and correlate with the extent of collagen deposition in the cardiac interstitium.^{11,12} MMP-9 may also be a useful biomarker for HFpEF, particularly when coupled with a panel of other markers. The McDonald laboratory showed that plasma levels of MMP-9 can identify asymptomatic hypertensive patients who are at risk for diastolic dysfunction and HFpEF, indicating that matrix metalloproteinase 9 (MMP-9) induction is an early event in the hypertension-induced HFpEF development.¹³ Using a cross-sectional observational study design, these investigators evaluated 275 stable hypertensive patients divided into asymptomatic hypertension or HFpEF groups. HFpEF associated with biomarkers for inflammation (interleukin 6 (IL-6), IL-8, and monocyte chemoattractant protein 1 (MCP1)), fibrosis (collagen I and III metabolic markers), and extracellular matrix (ECM) turnover (MMP-2, MMP-9, and tissue inhibitor of metalloproteinase-1 (TIMP-1)).¹³ MMP-9 was a significant indicator of greater degrees of asymptomatic LV diastolic dysfunction. Elevated MMP-9 levels would contribute to the cardiac fibrosis common in HFpEF and thought to contribute to LV stiffness by activating TGF- β 1 and allowing for cardiac myofibroblast migration.^{14,15} The McDonald study suggests that inflammatory and fibrosis pathway profiles may vary with the different stages of diastolic dysfunction and HFpEF; therefore, evaluating MMP-9 and TIMP-1 may allow the earlier detection of those patients at risk for HFpEF.

In 116 patients with coronary artery disease and preserved ejection fraction, MMP-9 levels positively associated with the degree of diastolic dysfunction.¹⁶ In 85 Caucasian treated hypertensive patients, the operating characteristic curve analysis for MMP-9 showed significant predictive value for HFpEF but not diastolic dysfunction.¹⁷ However, when patients with HFpEF were compared to patients with HFrEF both groups showed similar MMP-9 levels, indicating that MMP-9 is a marker of HF but may not be useful for distinguishing subtype.¹⁸ A recent study suggests that HFrEF positively associates with higher levels of biomarkers for myocardial injury (e.g., hsTnT) and with increased wall stress (e.g., NT-proBNP), while HFrEF is associated with biomarkers of systemic inflammation (e.g., growth differentiation factor 15 (GDF15)).¹⁹

Cellular and Molecular Causes

HFpEF patients may have less sympathetic overdrive, but significant activation of the renin angiotensin aldosterone system (RAAS), compared to patients with HFrEF.²⁰ As is the case in HFrEF, inflammation and endothelial dysfunction are comorbidities in HFpEF.²¹ Impaired cardiac energetics have also been reported for HFpEF that may impair relaxation especially during exercise.^{22,23} Studies in animal models have shown that both cardiac hypertrophy and fibrosis contribute to the increased LV stiffness that occurs due to hypertension, although the contribution of fibrosis is likely more significant.^{24,25} In addition to the accumulation of total collagen levels with hypertension, there is a shift in the ratio of collagen I to III in favor of the stiffer collagen I isoform. Enhanced collagen cross-linking is seen as well. In many HFpEF patients, the accumulation of cardiac collagen is found in endomyocardial biopsy samples, along with a decrease in MMP-1, the major collagenase in the human heart.²⁶ Collagen turnover is regulated by MMP enzymes and their tissue inhibitors (TIMPs). A decrease in collagenase MMPs and increase in TIMPs may explain collagen accumulation in HFpEF. Increased plasma

TIMP-1 levels are predictive of HF, and higher levels are seen in HFpEF patients compared to asymptomatic patients.^{1,24,26,27} In a substudy of HFpEF patients in the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) trial, increased basal plasma levels of collagen markers were found to be independently associated with adverse outcome on univariable analysis, suggesting that increased cardiac fibrosis contributes to adverse prognosis.²⁸

Intrinsic cardiac myocyte stiffness can contribute to diastolic dysfunction in HFpEF.^{1,29–31} In fact, in one study, 30% of HFpEF patients did not show any increase in collagen in LV endomyocardial biopsies.²⁹ Enhanced cardiac myocyte stiffness has been attributed to changes in the giant cytoskeletal protein titin, which functions as a molecular spring in the sarcomere. There are two isoforms expressed in the heart: a shorter, stiffer N2B and longer, more compliant N2BA.³² Hearts of HFpEF patients were reported to exhibit a lower N2BA/N2B ratio than HFrEF hearts consistent with greater LV stiffness in concentric versus eccentric cardiac remodeling.²⁹ Stiffness of titin is controlled also by posttranslational modification.³² Both isoforms are phosphorylated by protein kinase A (PKA) and protein kinase G (PKG) on a specific serine residue within the N2B element, resulting in a decrease in passive tension.^{32,33} Cysteine residues within the N2B element are targets of oxidative stress also, which increases passive tension.³² Thus, the increased oxidative stress seen in HFpEF could increase titin stiffness directly by targeting cysteine residues or indirectly by interfering with nitric oxide (NO) signaling via a number of ways: depletion of NO through its conversion to peroxynitrite, uncoupling of nitric oxide synthase (NOS) activity from NO formation (with consequently more ROS formation) via peroxynitrite-depletion of its cofactor tetrahydrobiopterin (BH4), oxidation of guanylyl cyclase, and interference of S-nitrosylation posttranslational control of proteins.^{31,34} Besides enhancing titin compliance via PKG-mediated phosphorylation, NO increases cardiac muscle relaxation by stimulating PKG-mediate phosphorylation of troponin I and possibly enhancing Ca^{2+} uptake by the sarcoplasmic reticulum by stimulating the sarco/endoplasmic reticulum Ca^{2+} -ATPase.^{35,36} NO signaling also has anti-fibrotic, anti-hypertrophic, and anti-adrenergic actions that oppose adverse cardiac remodeling^{31,34,37,38} and thus has been the focus of several therapeutic strategies for HFpEF. Of note, PKG activity and cGMP levels were found to be lower in myocardial biopsies of HFpEF patients compared to HFrEF patients.³⁹

Current Treatments and Recent Clinical Trials

Medications prescribed for treating HFpEF are the same as those for treating HFrEF, although analysis of prescription data from sites participating in the NHLBI-sponsored Cardiovascular Research Network indicates physicians may be more aggressive with drugs in treating HFrEF than HFpEF after the index HF event.⁴⁰ Findings from a large observational Swedish HF registry support the benefit of renin-angiotensin system antagonists in treating HFpEF;⁴¹ however, large randomized clinical trials in patients with HFpEF are lacking. A number of studies have failed to observe a distinct benefit of drugs effective for HFrEF in long term outcome (mortality) and/or quality of life (exercise capacity and/or hospitalization) in patients with HFpEF. These include an aldosterone antagonist (eplerenone),⁴² ACE inhibitor (perindopril),⁴³ beta blockers (nebivolol, carvedilol),^{44,45} and angiotensin II receptor antagonists (candesartan, irbesartan).^{46,47} A recent large scale observational study indicated that statin therapy offered no particular benefit in mortality or cardiovascular morbidity to patients with HFpEF.⁴⁸ These studies have been criticized on various grounds, such as small sample size, patient selection, or the concurrent use of similarly acting drugs.^{4,5} In any case, there is no specific evidence-based therapy for treating HFpEF, highlighting the need for a better understanding of its molecular and cellular underpinnings. A large randomized controlled trial of spironolactone versus placebo for HFpEF, Treatment of Preserved Cardiac

Function with an Aldosterone Antagonist (TOPCAT), is currently underway (NCT00094302).⁴⁹

Drugs in the Pipeline

There are several drugs that are under evaluation for effects on HFpEF, in both animal models and humans (Fig. 2).

I. Preclinical

Ivabradine—In a mouse model of heart failure due to chronic angiotensin II infusion, the I_f current inhibitor ivabradine improved LV systolic and diastolic function.⁵⁰ Ivabradine reduced cardiac hypertrophy, fibrosis, inflammation, and apoptosis. In contrast, metoprolol (a selective β_1 receptor blocker) was only effective in reducing inflammation, even though ivabradine and metoprolol reduced heart rate to the same extent. The authors of the study note that ivabradine has a greater impact on diastolic parameters than metoprolol, which may have contributed to the greater effectiveness of ivabradine in this study. In a diabetic mouse model of HFpEF, ivabradine reduced aortic stiffness and fibrosis and improved LV contractility and diastolic function.⁵¹ The later occurred in the absence of any cardiac fibrosis and was associated with a reversal of increased N2B expression and reduced phospholambin phosphorylation.

BH4 and eNOS activators—Evidence was recently reported from a deoxycorticosterone acetate DOCA-salt mouse model that oxidative stress may mediate diastolic dysfunction by inducing S-glutathionylation of cardiac myosin binding protein-C (MyBP-C), thereby enhancing myofilament sensitivity to calcium.⁵² Ranolazine improved diastolic function not as a late sodium current inhibitor, but by directly affecting myofilament cross-bridge kinetics and Ca^{2+} sensitivity by an undefined mechanism. The DOCA-salt mouse model is associated with BH4 depletion and uncoupled NOS activity, and in a subsequent study, BH4 administration reduced DOCA-salt-associated MyBP-C glutathionylation and diastolic dysfunction.⁵³ However, strategies to address the substantial oxidation of BH4 *in vivo* upon oral consumption will need to be devised to make BH4-replenishment approaches therapeutically practical.⁵⁴ A possible way around the issue of BH4 bioavailability is offered by eNOS activators, 4-fluoro-N-indan-2-yl-benzamide (AVE9488) and 2,2-difluoro-benzo [1,3]dioxole-5-carboxylic acid indan-2-ylamide (AVE3085). These are small molecular weight enhancers of eNOS transcription that also (at least for AVE9488) increase BH4 levels *in vivo* and improve NOS coupling.^{55,56} In the DAHL salt sensitive rat model of HFpEF, AVE3085 increased eNOS expression and protein levels, while decreasing expression of NAD (P)H oxidase subunits p22phox and gp91phox.⁵⁷ Diastolic dysfunction was reduced, as were both cardiac hypertrophy and fibrosis.

Nitroxyl donors—Nitroxyl (HNO) is the one-electron reduction product of NO with distinctive actions due to its “thiophylic” nature, which results in interaction with redox-sensitive protein cysteines with high specificity.⁵⁸ HNO donors, such as the newly formulated compound 1-nitrosocyclohexyl acetate (NCA), may have therapeutic benefit in HF due to a direct action of HNO on myofilaments, SERCA2a, and the ryanodine receptor 2 that overall convey positive inotropic and lusitropic effects on the heart.^{59–62} These actions are independent of β -adrenergic signaling and, unlike NO donors (organic nitrates), tolerance is not an issue. Whether HNO donors are beneficial in treating HFpEF will need to be assessed.

MMP-9 inhibitors—In mice, aging is associated with increased MMP-9 levels that precede the development of diastolic dysfunction.⁶³ Furthermore, MMP-9 deletion attenuates this effect, in part by regulating the ECM response. Based on results in humans and mice, there is strong rationale for evaluating MMP-9 selective inhibition in animal models of HFpEF. The

development of such agents, however, has been slow. First generation MMP inhibitors were highly non-specific and non-selective, and achieving MMP-9 selectivity has proven difficult. The Fields laboratory has constructed a triple-helical peptide that incorporates a fibronectin II insert-binding sequence, and this peptide has been shown to selectively inhibit MMP-9 cleavage of collagen V.⁶⁴ This report indicates that MMP-9 selective inhibition may be possible by using exosite-binding triple-helical peptides.

S31–201—The transcription factor STAT3 has been implicated in cardiac protection and remodeling. The small-molecular inhibitor S31–201 blocks canonical STAT3 signaling by preventing phosphorylation of a key tyrosine residue. Recently, S31–201 was found to reduce cardiac fibrosis, hypertrophy, and expression of hypertrophy marker genes, and improve cardiac function in a renal artery ligation model of hypertension.⁶⁵ S31–201 also inhibited IL-6-induced collagen synthesis by cardiac fibroblasts.

II. Clinical Trials (Table 1)

Phosphodiesterase 5 inhibitors (PDE5i)—PDE5 is highly expressed in pulmonary arterial vascular smooth muscle cells and involved in cGMP breakdown and opposing vasodilatation. Sildenafil, a PDE5 inhibitor is currently approved for treatment of pulmonary arterial hypertension (PAH). A Phase III ongoing trial (NCT01726049) is studying the effect of Sildenafil on patients with HFpEF and PAH. This study is supported by positive results from a small trial that observed improvements in pulmonary pressure, RV function, LV relaxation, and lung interstitial water metabolism with Sildenafil in HFpEF.⁶⁶ Sildenafil significantly improved LV structural and diastolic function as well as overall clinical status in a 1-year randomized double-blind placebo controlled study in patients with stable HF but reduced LV ejection fraction.⁶⁷ However, contradictory results emerged from the RELAX trial with HFpEF patients, which reported no significant improvement in exercise capacity, diastolic function, quality of life or clinical status.⁶⁸ Arguably, the population recruited in this trial had more pronounced comorbidities such as diabetes and chronic kidney disease that could negatively affect outcomes. A phase III-12 week ongoing clinical trial is testing the effect of a new long-acting PDE5 inhibitor, Udenafil, on HFpEF in a population with limited comorbidities (NCT01599117).

Alagebrium (ALT-711)—Advanced glycation end-products (AGEs) are formed when glucose interacts nonenzymatically with proteins.⁶⁹ Formation of AGEs or their accumulation (as they are very stable) occurs in hypertension, diabetes and the normal aging process.^{69,70} Plasma levels of two AGEs N(e)-(carboxymethyl)lysine (CML) and pentosidine in HFREF and HFpEF patients were reported to predict HF-related hospitalization and/or mortality with CML being associated with a higher risk of mortality.⁷¹ AGEs can cause increased stiffness of the ECM directly by crosslinking collagen or elastin and indirectly by stimulating the production of collagen and depleting NO thereby increasing oxidative stress.⁷⁰ Cardiac AGE deposition has been observed in diabetic patients with HFREF, but whether it occurs to any great extent in HFpEF is unclear. In any event, the likely involvement of AGE-related crosslinking contributing to diastolic dysfunction in HFpEF patients, prompted studies in this group with the crosslink breaker Alagebrium. An initial small size study showed promise that Alagebrium improves LV diastolic filling and quality of life in HFpEF patients.⁷² A subsequent, larger, randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the effects of Alagebrium on exercise in subjects with HFpEF was recently terminated for unknown reasons (NCT00662116). However, another ongoing study is evaluating the effect of Alagebrium on age-related cardiac stiffness and diastolic function in sedentary or exercising elderly healthy volunteers (NCT01014572). This study will exclude the complication of variable comorbidities and should give better insight on the efficacy of the drug to target diastolic dysfunction.

LCZ696—Although studies conducted with ARBs or ACEi alone did not show improvements in HFpEF patients, numerous lines of evidence support the rationale for targeting the renin angiotensin system (RAS) in these patients.^{4,6} LCZ696 is a new combination drug of the angiotensin II type 1 receptor (AT₁) blocker (ARB) valsartan and the neprilysin inhibitor prodrug AHU377 that has been developed by Novartis. This dual combination exerts a powerful vasodilatory and natriuresis effect by blocking angiotensin II activity on the one hand, while augmenting plasma levels of natriuretic peptides, such as BNP, on the other. Additionally, natriuretic peptides signal through transmembrane receptor guanylyl cyclase, which by increasing PKG activity has been associated with antifibrotic, antihypertrophic, and lusitropic effects on the heart.³⁸ LCZ696 recently completed a phase II double-blind randomized controlled trial on a HFpEF population for 36 weeks compared to valsartan alone and the results were promising.⁷³ NT-proBNP, which is associated with adverse outcomes in HF patients, was significantly reduced, along with reversed left atrial remodeling and good drug tolerance. Clinical and cardiovascular endpoints were not the focus of this trial and warrant further investigation.

Nifedipine and isosorbide dinitrate/hydralazine (HISDN)—Two antihypertensive medications, nifedipine and HISDN, are currently being tested for their potential benefit to HFpEF patients (NCT01157481 and NCT01516346, respectively). The L-type calcium channel blocker Nifedipine is approved for the treatment of hypertension and angina pectoris; HISDN, which combines an antihypertensive (hydralazine) with a vasodilator (isosorbide dinitrate), is the first race-targeted drug that is recommended for African Americans with advanced systolic heart failure.⁷⁴ Pre-clinical data already support the potential therapeutic effect of HISDN in HFpEF.⁷⁵ A possible complication to use of HISDN is that HFpEF patients are reported to exhibit a blunted increase in preload with exercise and greater preload reduction with vasodilators.^{1,76}

Anakinra—High levels of the soluble isoform of ST2 (interleukin 1 receptor-like 1), the receptor for IL-33, may serve as a novel biomarker for detecting HFpEF in the hypertensive patient.⁷⁷ Upregulation of the IL-33/ST2 pathway is a protective response of the heart to chronic stress, such as heart failure, that has anti-fibrotic and anti-hypertrophic actions.⁷⁸ IL-33 is a member of the IL-1 family of cytokines.⁷⁹ IL-1 α and IL-1 β are potent pro-inflammatory cytokines implicated in adverse ventricular-vascular remodeling, including pressure overload-induced cardiac hypertrophy.⁸⁰ Anakinra, an IL-1 receptor antagonist used to treat rheumatoid arthritis, is currently in clinical trial for HFpEF (NCT01542502).

Several potential therapies for HFpEF may also have the benefit of treating comorbidities. For instance, mineralocorticoid receptor antagonists decrease insulin resistance, and may prevent atrial fibrillation (in the absence of heart failure and impaired kidney function);^{81,82} ranolazine has antiarrhythmic effects and improves glycemic control in diabetic patients;⁸³ AVE3085 restores diabetes-impaired endothelial function;⁸⁴ and S31-201 ameliorates angiotensin-induced hypertension, oxidative stress, and endothelial dysfunction.⁸⁵

Conclusions and Perspectives

HFpEF is multifactorial and involves several interconnected physiological systems. For instance, increases in aortic/arterial stiffness, as seen with hypertension and aging, can impair diastole.⁸⁶ Thus, drugs that enhance ventricular-vascular coupling by targeting both ventricular and vascular stiffness are predicted to be of added benefit in treating HFpEF, especially when combined with actions or other drugs that target cardiomyocyte stiffness at the level of the myofilaments or energetics. Since HFpEF is a disease characterized by comorbidities, many of which impact negatively on cardiovascular-renal function, a multi-drug approach will likely prove essential, but the exact combination will need to be defined. To date, there is no empirical

evidence for the effectiveness of particular drugs in treating HFpEF, emphasizing the need for additional large clinical trials. The failure of trials thus far to demonstrate any benefit of drugs that have proven so effective in treating HFrEF supports a need for novel drug approaches to HFpEF. New drugs that target underlying inflammation, oxidative stress, and ageing-related dysfunctions may prove to be particularly effective for HFpEF. Underpowered clinical trials should be avoided and study designs need a focus on selecting more consistent patient populations to control for the impact of comorbidities. Recent findings of the Framingham Heart Study have identified for the first time distinct clusters of antecedent risk factors (BMI, smoking, and atrial fibrillation) that predict new onset HFpEF rather than HFrEF years before symptomatic HF develops. Such information will be valuable in the design of clinical trials on the prevention and treatment of HFpEF.⁸⁷ Additional end points that include quality of life assessment and a consideration of the timing for effective therapeutic intervention need also to be incorporated into the study design. This will allow for the effective evaluation of known and novel strategies to prevent the progressive deterioration in patients with HFpEF.

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TEXT BOX 1

Heart failure with preserved ejection fraction -

- Characterized by concentric remodeling, increased interstitial fibrosis, and impaired relaxation of left ventricle.
- Complicated by chronotropic incompetence, pulmonary arterial hypertension, impaired exercise- and flow-mediated vasodilation, impaired ventricular-arterial coupling, and metabolic abnormalities.

Compared to systolic heart failure -

- Patients are older, more likely female, with lower incidence of coronary artery disease, but atrial fibrillation more likely.
- Higher number of noncardiac comorbidities, such as diabetes and obesity.

TEXT BOX 2

Increased ventricular stiffness due to extracellular matrix remodeling in HFpEF -

- Accumulation of collagen
- Relatively more of the stiffer collagen I vs. collagen III
- Enhanced collagen crosslinking
- Decrease in collagenase MMPs and increase in TIMPs

TEXT BOX 3

Intrinsic cardiac myocyte stiffness in HFpEF -

- Mechanism not established
- Possible shift in titin isoforms, reduced titin phosphorylation, or oxidation of titin cysteine residues

TEXT BOX 4

- In clinical trials, drugs effective for HFrEF have been less effective or ineffective in patients with HFpEF.
- There are no evidence-based therapies for HFpEF.

Figure 1.

Cardiac remodeling in aging and the two types of heart failure. Comorbidities of hypertension, diabetes, obesity, or aging cause changes in the structure of the cardiac muscle and extracellular matrix of the heart that are initially adaptive and reduce wall stress, such as a reduced left ventricle (LV) volume. In some individuals in a high risk population (HRP) due to life style or genetics, the progressive remodeling (PR) leads to increased LV wall thickness and marked concentric remodeling (decreased LV volume) or concentric hypertrophy (increase in overall heart size). Ventricular-arterial stiffness (VAS) is a contributing factor to PR that develops into heart failure with preserved ejection fraction (HFpEF). When cardiac muscle is injured or destroyed due to coronary artery disease (CAD) and myocardial infarction (MI), the heart undergoes eccentric remodeling characterized by LV wall thinning and increased heart size. In this case, heart failure with reduced ejection fraction develops (HFrEF). Though not definitive, evidence indicates that survival rates for HFpEF patients are intermediate between non-heart failure and HFrEF patients; although with equal LV wall stress as indexed by BNP levels, prognosis for HFpEF and HFrEF is equal. Consequently, the disease development gap (DDG) or life expectancy after diagnosis is likely shorter with HFrEF than HFpEF.

Figure 2.

Novel drugs targeting heart failure with preserved ejection fraction. A number of new approaches are under investigation that target contributing factors in the development or progression of HFpEF, such as diastolic dysfunction, increased ventricular-arterial stiffening, and imbalanced ventricular-arterial coupling, as well as pulmonary hypertension that may aggravate the increased pulmonary pressure and congestion associated with HFpEF. See Text for additional details.

Table 1

Current clinical trials for heart failure with preserved ejection fraction

Drug	MOA	Projected Effect	Trial Identifier	Status	Sponsor
Albiglium	AGE crosslink breaker	Reduced myocardial and vascular stiffness	NCT00662116/ NCT01014572	PII terminated/ PII active	Synviva Therapeutics/ UT Southwestern
Anakinra	IL-1 receptor antagonist	Anti-inflammatory, anti-remodeling	NCT01542502	Pilot/active	Virginia Commonwealth University
HISDN	Two vasodilators	Balanced vasodilation, improved VVC	NCT01516346	PII active	Philadelphia Veterans Affairs Medical Center
LCZ696	Valsartan (AT ₁ blocker) + AHU377 (neprilysin inhibitor)	Vasodilation, anti-hypertrophy, anti- remodeling, enhanced lusitropy	NCT00887588	PII completed	Novartis Pharmaceuticals
Nifedipine	L-type CCB in VSMC of systemic and coronary arteries	Systemic and coronary vasodilation, improved VVC	NCT01157481	PIII active	Demand Investigators
Sildenafil (Pulmonary hypertension)	PDE5 inhibitor	Vasodilation, anti-hypertrophy, anti- remodeling, enhanced lusitropy	NCT01726049	PIII active	University Medical Centre Groningen
Spirolactone	Aldosterone receptor antagonist	Diuresis, anti-fibrosis, anti-hypertrophy	NCT00094302	PIII active	New England Research Institutes
Udenafil	PDE5 inhibitor	Vasodilation, anti-hypertrophy, anti- remodeling, enhanced lusitropy	NCT01599117	PIII active	Seoul National University Hospital

Abbreviations: AGE, advanced glycation end-products; AT₁, angiotensin type 1 receptor; CCB, calcium channel blocker; HISDN, isosorbide dinitrate/hydralazine; IL-1, interleukin 1; MOA, mechanism of action; PDE5, phosphodiesterase type 5; PII, phase two; PIII, phase three; VVC, ventricular-vascular coupling.