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The Emerging Epidemic of Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF), which currently represents approximately 50 % of heart failure (HF) cases, is common and associated with high morbidity and mortality. Understanding the epidemiology of HFpEF has been difficult due to the challenges in HFpEF diagnosis and the heterogeneous etiologies and pathophysiologies that underlie HFpEF. Nevertheless, several high-quality epidemiology and observational registry studies of HFpEF demonstrate that an increasing prevalence of HFpEF in both the outpatient and inpatient settings, coupled with a lack of evidence-based effective treatments for HFpEF, is resulting in an emerging epidemic of HFpEF. In this review, we discuss the emerging HFpEF epidemic, focusing on: (1) reasons for the rising prevalence of HFpEF; (2) the abnormalities in cardiac structure and function that dictate the transition from risk factors to HFpEF; (3) novel HFpEF mechanisms that may underlie the increase in HFpEF prevalence; (4) prognosis of HFpEF; and (5) risk prediction in HFpEF. We conclude with 10 unanswered questions on HFpEF epidemiology that will be important areas for future investigation.

Keywords

Diastolic heart failure; Epidemiology; Pathophysiology; Prognosis; Risk estimation

Introduction

Heart failure with preserved ejection fraction (HFpEF), a common clinical syndrome, is a leading cause of morbidity and mortality and currently represents approximately 50 % of heart failure (HF) cases. Understanding the epidemiology of HFpEF has been difficult due to challenges in HFpEF diagnosis and the heterogeneous etiologies and pathophysiologies that underlie HFpEF. Nevertheless, several high-quality epidemiologic studies, such as the Framingham Heart Study and the Rochester Epidemiology Project, among others, have provided important insight into HFpEF on a population level. These studies have shown that

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Compliance with Ethics Guidelines

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patients with HFpEF are predominantly elderly, more likely to be female than male, and have a high prevalence of comorbidities such as hypertension, coronary artery disease (CAD), diabetes mellitus (DM), obesity, anemia, chronic kidney disease (CKD), atrial fibrillation, and chronic obstructive pulmonary disease [1–3, 4•]. These studies have also demonstrated that survival with HFpEF is poor, especially after hospitalization for HFpEF. Arguably, the most important finding from these studies and observational registries is that HFpEF is an emerging epidemic. The prevalence of HFpEF is increasing over time, and a population burden of aging and comorbidities predicts even higher rates of HFpEF in the coming decades.

Here we review the current landscape of HF epidemiology, focusing on: (1) reasons for the rising prevalence of HFpEF; (2) the abnormalities in cardiac structure and function that dictate the transition from risk factors to HFpEF; (3) novel HFpEF mechanisms that may underlie the increase in HFpEF prevalence; (4) prognosis of HFpEF; and (5) risk prediction in HFpEF.

The Changing Landscape of HF Epidemiology

HF is the most common cause of hospitalization among individuals above 65 years of age [5]. It affects about 1 % of 40-year-old individuals and its prevalence sharply increases to 10 % in those over 75 years of age [6, 7]. Overall prevalence of HFpEF has been reported to be 1.1–5.5 % in the general population [8]. However, accurate estimation of the prevalence of HFpEF has been challenging due to lack of standardization in the diagnostic criteria and inherent difficulties in the diagnosis of HFpEF [9, 10•]. Relative prevalence of HFpEF among all HF patients is approximately 50 %, although there is significant variation (40–71 %) among different studies [8], likely due to a combination of differing definitions of HFpEF, study type (epidemiologic study vs. observational registry), practice setting (inpatient vs. outpatient), and geographic location.

An epidemiologic study from Olmstead County, Minnesota found that the prevalence of HFpEF relative to HF with reduced ejection fraction (HFrEF) is increasing at a rate of 1 % per year, indicating that HFpEF is on track to become the most common type of HF in the near future [1]. Among patients with HF who require hospitalization, the proportion of HFpEF has also been rising. Get With The Guidelines–Heart Failure (GWTG-HF), a very large, nationwide study of HF hospitalization in the United States (N>110,000), recently showed that the proportion of patients hospitalized with HF who had HFpEF increased from 33 % in 2005 to 39 % in 2010. Within the same time interval, the proportion of HF hospitalizations due to HFrEF decreased from 52 % to 47 % [11•]. It is also well known that the rate of rehospitalization in HFpEF is equal to that of HFrEF [3, 12]. In HFpEF, the rehospitalization rate was found to be 29 % within 60–90 days of hospital discharge [3].

Taken together, these data show that the epidemiology of HF is changing and that HFpEF is becoming the predominant form of HF. Figure 1 demonstrates that if current trajectory rates continue, by 2020 65 % of patients hospitalized with HF will have EF>40 %. Given the high prevalence of HF overall, the increasing frequency of HFpEF, and the lack of therapeutic options for HFpEF, the need to better understand the emerging epidemic of HFpEF is critical.

Why is HFpEF Increasing in Prevalence?

Several factors are likely contributing to both the increasing overall prevalence of HFpEF and the increasing proportion of HF that is due to HFpEF. These factors include: (1) increased life expectancy and aging of the population; (2) the epidemic of cardiac and non-cardiac comorbidities; and (3) increased clinical recognition of HFpEF.

Increasing Life Expectancy and Aging of the Population—The world's population has been aging rapidly since the 1950s. For example, in the USA, the percentage of people aged 65 years or older has increased from 9 % in 1960s to 13 % in 2010, with a projected increase to 20.2 % by 2050 [13, 14]. In addition, within the past four decades, life expectancy for both sexes has increased significantly in the USA [15]. The increase in the prevalence of HFpEF is closely related to this rapid change in the demographics of the general population.

The relationship between age and prevalence of HFpEF was well demonstrated in the Prevention of Renal and Vascular End-stage Disease (PREVEND) Study, a community-based epidemiological study conducted in Europe [16••]. The age- and sex-specific prevalence of HFpEF was only 1 % in women and 0 % in men between aged 25–49 years but much higher (8–10 % in women and 4–6 % in men) in individuals aged 80 years [16••]. Consistent with these findings, the proportion of HFpEF among patients with HF increases with age, from 46 % in younger patients (age<45 years) to 59 % in older patients (age>85 years) [28]. In addition, a recent report from the Framingham Heart Study demonstrated that increasing age is associated with a higher risk of incident HFpEF compared to incident HFrEF [25].

Importantly, studies such as PREVEND have shown that the trend of increasing HFpEF prevalence with age is associated with an increase in the prevalence of hypertension, diabetes, and atrial fibrillation, a relationship that was not present in HFrEF [16••]. Thus, the increasing prevalence of comorbidities that occurs with aging is likely a key factor underlying the age-associated increases in HFpEF prevalence. Several studies have confirmed that, compared to those with HFrEF, patients with HFpEF are more likely to be older, more often females, and have higher rates of hypertension and atrial fibrillation, but a lower prevalence of CAD [1, 3, 12]. Consistent with the elderly population, non-cardiovascular comorbidities are more common in patients with HFpEF, and include chronic lung disease, CKD, anemia, cancer, and hypothyroidism [10]. Cardiac and non-cardiac comorbidities were found to be associated with higher incidence of future HFpEF, increased risk of hospitalizations, and reduced functional status [17–20]. Non-cardiac comorbidities were also shown to have a greater impact on functional status in HFpEF compared to HFrEF [21].

Cardiac Comorbidities: Coronary Artery Disease and Atrial Fibrillation—

Although several epidemiologic and observational studies have found that CAD is less common in HFpEF compared to HFrEF [11••, 12], CAD is still very common in HFpEF. The prevalence of CAD varies among studies; however, pooled data across studies suggests that the prevalence of CAD in HFpEF is approximately 40–50 % [22]. Mortality from CAD has declined since the 1960s, and survival after the onset of CAD has improved significantly over time [5]. With decreased mortality associated with acute myocardial infarction, and increased salvage of the myocardium with revascularization in the setting of acute coronary syndromes, patients with CAD are more likely to survive and more likely to have a preserved ejection fraction (EF). However, many of these patients have chronic, multi-vessel CAD with ongoing ischemia which results in impaired relaxation, decreased LV compliance, and increased LV filling pressures, all of which can lead to HFpEF. Thus, it is not surprising that CAD has been associated with increased risk of developing HFpEF [29, 30].

Atrial fibrillation is the most common cardiac arrhythmia, and its prevalence has been increasing due to an aging general population and increased longevity. The link between atrial fibrillation and HFpEF is multifactorial. Atrial fibrillation may trigger HFpEF via shortening of diastolic filling time and loss of the atrial contribution to LV filling [23]. In

addition, atrial fibrillation is often associated with left atrial enlargement, which can cause mitral annular dilation and functional mitral regurgitation, which can further lead to HFpEF or exacerbate HFpEF. Atrial fibrillation may also occur in response to HFpEF due to increased left atrial pressure overload, dilation, and fibrosis. Finally, atrial fibrillation and HFpEF are both associated with underlying myocardial fibrosis, and atrial fibrillation was recently shown to be independently associated with LV fibrosis, which plays a key role in the pathogenesis of diastolic dysfunction [24].

Non-Cardiac Comorbidities: The Epidemics of Obesity, Metabolic Syndrome, and Diabetes Mellitus—Obesity is common in the general population (~35 % of men and women in the USA) and the prevalence of obesity has been rising at an alarming rate over the past several years. Obesity has been associated with adverse cardiac remodeling and dysfunction in both experimental models and in humans, and obesity is associated with a high output state. Together, these pathophysiologic abnormalities result in the HF syndrome, often with a preserved EF. Thus, the high prevalence of obesity in the general population (and the increases in rates of obesity over time) contributes to the epidemic of HFpEF. Accordingly, obesity is highly prevalent in HFpEF (32–46 %), and high body mass index (BMI) is known to be a risk factor for HFpEF [10, 16••, 19, 25]. In a recent Framingham Heart Study report, higher BMI was shown to be a predictor of HFpEF but not HFrEF [19].

The worldwide epidemic of obesity has also led to increased prevalence of metabolic syndrome, which is a constellation of biochemical and clinical abnormalities and is recognized as a major risk factor for heart disease. Metabolic syndrome has been associated with diastolic dysfunction and pulmonary venous hypertension. In a small study by Robbins et al., the prevalence of metabolic syndrome was 94 % in patients with pulmonary venous hypertension [26]. In another study, the prevalence of diastolic dysfunction was found to be significantly higher in patients with metabolic syndrome compared to those without metabolic syndrome (35 % vs. 9 %) [27]. Increased myocardial stiffness, left ventricular hypertrophy, impaired energy availability, and increased propensity for CAD are the major abnormalities which lead to HFpEF in patients with metabolic syndrome [28].

Like obesity and the metabolic syndrome, the prevalence of diabetes mellitus has also been increasing over the past several decades. Diabetes is a well-known risk factor for both HFpEF and HFrEF [19, 29]. Diabetes is associated with increased filling pressures and greater arterial stiffness in patients with HFpEF [30]. Diabetes also causes subclinical LV remodeling, especially in females. Data from Framingham Heart Study showed that individuals with diabetes mellitus develop greater age-associated increases in LV wall thickness, and the presence of diabetes is associated with a lesser decrease in LV diastolic dimensions with increasing age, suggesting the possibility of volume overload [31, 32]. Markers of insulin resistance, including serum insulin levels, are associated with greater LV mass and concentric LV remodeling [33, 34]. Diabetes and metabolic syndrome share several underlying mechanisms that result in increased HF risk; these include insulin resistance, metabolic derangements, endothelial dysfunction, oxidative stress, mitochondrial dysfunction, and autonomic neuropathy [28, 32]. Interestingly, a recent study found that the presence of HF was an independent risk factor for the development of incident diabetes [35], indicating that HF itself may be considered an insulin-resistant state [36].

Increased Clinical Recognition of HFpEF—Although difficult to prove, it is quite possible that the increasing prevalence of HFpEF is in part related to the increased recognition of HFpEF as a clinical entity. Until relatively recently, the focus of HF diagnosis and treatment was on HFrEF (i.e., systolic HF). In the 1970s and 1980s, there was increasing recognition of the concepts of diastolic dysfunction and diastolic HF. With advances in cardiac catheterization and echocardiography, the possibility of HF in the

presence of a normal EF was increasingly recognized. Natriuretic peptides and sophisticated measurement of diastolic function by echocardiography in the 1990s and 2000s have undoubtedly increased the recognition of HFpEF even more. Guidelines on the diagnosis of diastolic dysfunction and HFpEF have been published [7, 37], and these have also likely helped with the recognition and diagnosis of HFpEF.

Epidemiology of the Transition from Risk Factors to HFpEF: Abnormalities in Cardiac Structure and Function

Historically, HFpEF was termed diastolic HF or HF due to diastolic dysfunction. However, better understanding of the pathophysiology of “diastolic HF” has led to an evolution in its nomenclature. It is now believed that HFpEF develops as a consequence of the complex interplay between a variety of pathophysiologic mechanisms, including diastolic dysfunction, longitudinal LV systolic dysfunction (despite a normal EF), pulmonary hypertension, abnormal exercise-induced vasodilation, abnormal ventricular-arterial and ventriculoatrial coupling, chronotropic incompetence, and extracardiac volume overload [38–48]. Given the wide variety of pathophysiologic abnormalities in HFpEF, epidemiologic studies of the transition from risk factors (comorbidities) to overt HF have focused on the abnormalities in structure and function that dictate the development of HFpEF.

As described above, HFpEF is well known to be associated with several cardiac and non-cardiac comorbidities. Comorbidities synergistically result in abnormalities in ventricular and vascular structure and function, which ultimately result in HFpEF [16•, 18, 19]. These findings have even led to a debate as to whether HFpEF is a specific entity or simply a combination of age-related comorbidities [25, 49]. In a recent prospective cohort study, comorbidities were shown to be associated with unique clinical, functional, structural, and prognostic profiles among patients with HFpEF. However, it was also shown that abnormalities in cardiovascular structure and function cannot solely be attributed to the influence of comorbidities; fundamental, disease-specific processes underlie the development of HFpEF [25]. For example, a new paradigm on the relationship between comorbidities and the development of HFpEF was proposed by Paulus et al. [50], who hypothesized that the high prevalence of comorbidities induces a systemic proinflammatory state, which causes coronary microvascular and generalized endothelial inflammation, thereby leading to increased diastolic LV stiffness and HF development by reducing nitric oxide bioavailability, cyclic GMP content, and protein kinase G activity in adjacent cardiomyocytes. These changes ultimately trigger LV hypertrophy and raise resting LV tension due to hypophosphorylation of titin.

Current HF management guidelines emphasize the importance of the progressive nature of HF by classifying the presence of asymptomatic cardiac structural or functional abnormalities as a form of HF (i.e., Stage B HF [51]). Although these guidelines were initially focused on HFrEF, the same principles can be applied to HFpEF. In a large, prospective epidemiological study, the presence of asymptomatic LV diastolic dysfunction was found to increase the risk of incident HF by 30 % [18]. Cross-sectional studies have demonstrated that LV diastolic dysfunction is commonly prevalent in asymptomatic individuals who are at risk for development of HF [52].

Advancing age and cardiac and non-cardiac comorbidities can promote ventricular and vascular remodeling and dysfunction, thus providing a link between risk factors, abnormal cardiac structure/function, and HF development [25]. In community-based studies, female gender and advancing age were found to be associated with increases in ventricular and vascular systolic and diastolic stiffness in the absence of cardiovascular diseases [53]. However, the factors that mediate progression from asymptomatic abnormalities in cardiac structure/function to symptomatic HFpEF require further investigation.

Recent studies have shed some light into the relationship between progression of cardiac dysfunction and development and progression of HFpEF. A large epidemiological study comparing hypertensives with and without HFpEF showed that although both groups had similar EF and ventricular-arterial coupling parameters, patients with HFpEF cannot respond to increases in LV end-systolic stiffness with increased contractility as opposed to patients with hypertension only [40]. When compared to hypertensive and normal controls, patients with HFpEF were also found to have global impairment in cardiovascular reserve function, including limitations in chronotropic, contractile, endothelial, and vascular reserve [54]. These findings suggest that the transition from asymptomatic hypertensive diastolic dysfunction to symptomatic HFpEF is promoted by the presence of a sufficient number of individual abnormalities in reserve [55]. A retrospective study on Japanese individuals showed that transition from asymptomatic diastolic dysfunction to HFpEF is associated with progressive LV diastolic dysfunction, which is primarily due to exacerbation of LV distensibility [56]. However, it is also known that progressive contractile dysfunction was found to play a role in the pathophysiology of HFpEF [57].

Finally, community-based studies have shown that pulmonary artery systolic pressure increases with aging, resulting in a high prevalence of pulmonary hypertension in the elderly, most likely due to the high burden of HFpEF in the aging population [45, 58, 59]. The HFpEF syndrome results in elevated pulmonary artery pressures, primarily due to passive pulmonary venous congestion from elevated left ventricular diastolic pressures. Indeed, increased pulmonary artery systolic pressure has been found to be the best echocardiographic marker to differentiate between HFpEF and hypertensive controls [45]. These data highlight the important relationship between pulmonary hypertension and HFpEF on a population level, and suggest that future epidemiologic studies of pulmonary hypertension are necessary to shed light on the epidemiology of HFpEF overall.

The Heterogeneity of HFpEF

HFpEF is a heterogeneous syndrome with multiple underlying etiologies and pathophysiologies. Recent studies have confirmed the heterogeneity in the pathogenesis of HFpEF, and multiple cardiac and non-cardiac mechanisms have been shown to play a role in the development of HFpEF [60]. Adding to the heterogeneity of HFpEF are novel mechanisms that may be playing a role in increasing the burden of HFpEF on a population level. For example, in participants of the Framingham Heart Study, airflow obstruction was shown to be a strong predictor of incident HFpEF [18]. Anemia, kidney dysfunction, hypoalbuminemia, albuminuria, and cystatin C have been shown to predict the development and/or progression of HFpEF, highlighting the importance of CKD in HFpEF [16•, 25, 61]. These novel mechanisms leading to, or associated with, HFpEF are not well understood and require further study using a “mechanistic epidemiology” approach. The following sections highlight two related areas that provide insight into the epidemiology of HFpEF, and should be further explored on a population level.

Extracardiac Volume Overload—HF, including HFpEF, is thought to be a syndrome of normal or low cardiac output associated with high LV filling pressures in most patients. However, it is possible that the changing epidemiology of HF will include progressively higher frequencies of patients with high-output HF who may also have extracardiac causes of volume overload.

Obesity is known to cause increased central and total blood volumes accompanied by decreased systemic arterial resistance. These changes in the vasculature and blood volume, along with increased oxygen consumption result in increased cardiac output in obese patients. Persistence of these hemodynamic changes can lead to subclinical left ventricular

hypertrophy, increased left ventricular diastolic pressures and increased mean pulmonary arterial pressure, thereby leading to HFpEF in obese patients [62, 63].

The findings of a high-output state, extracardiac volume overload, and abnormal cardiac structure/function can occur in other disease states as well. Examples include CKD (including end-stage renal disease with elevated cardiac output due to arteriovenous fistula), chronic liver disease, and anemia (including sickle-cell disease), all of which are prevalent in the general population. Each of these entities may lead to high-output HFpEF, but the epidemiology of these conditions remains underexplored.

Cardio-Abdomino-Renal Syndromes and Renal Venous Congestion—The HF syndrome involves multiple organ systems besides the heart. Thus, manifestation of overt HF may be accelerated if there is even mild functional derangement of non-cardiac organs [18]. Cardiorenal syndrome is characterized by the pathophysiologic disequilibrium between the heart and the kidneys, in which functional impairment in one organ consequently leads to dysfunction of the other [64]. A decline in kidney function may exacerbate volume overload by affecting fluid homeostasis and sodium balance [18]. Presence of renal dysfunction in patients with HF often complicates the treatment due to inadequate response to diuretics and other therapeutic agents.

The pathophysiological link between HF and renal dysfunction has not been well understood. However, growing evidence suggests that “backward” failure plays a significant role in the pathophysiology and disease progression of HF and cardiorenal syndrome [65•]. In HF, increased arteriolar vasoconstriction and “backward” failure lead to a progressive shift of blood from the peripheral circulation to the splanchnic venous system. Normally, splanchnic veins play a crucial role in maintaining optimal cardiac preload by pooling or releasing blood as a response to volume status. Furthermore, it is speculated that such a shift in blood volume in patients with HF can eventually cause impairment in the capacitance function of the splanchnic veins [66]. Progressive volume overload, insufficient splanchnic vein capacitance, and abnormalities in the splanchnic microcirculation lead to increased intraabdominal pressure and may further cause worsening of HF syndromes, including HFpEF.

Renal dysfunction in patients with HF has traditionally been attributed to decreased kidney perfusion and low cardiac output. However, recent studies have emphasized the importance of “backward” HF, rather than “forward” HF in the pathogenesis of renal dysfunction in HF, as stated above [67]. Several studies have showed that renal impairment is associated with elevated right atrial pressure (i.e., central venous pressure) [68, 69] but not LV systolic dysfunction or cardiac index [69–71]. Renal venous congestion due to right-sided HF leads to renal impairment and this effect has been explained by several mechanisms including neural, hormonal, and inflammatory mediators, and decreased renal blood flow due to decreased transglomerular pressure gradient [67]. Like high-output HFpEF and extracardiac causes of volume overload, the impact of cardio-abdominorenal syndrome and renal venous congestion on the epidemiology and prognosis of HFpEF requires further study, and are ripe areas for future epidemiologic investigation.

Prognosis of HFpEF

Patients with HFpEF have poor quality of life similar to patients with end-stage renal disease, and they require frequent hospitalizations [4•, 11••, 72]. Survival of patients with HFpEF is poor, and HFpEF is associated with high in-hospital, short-term, and long-term mortality rates [2, 3, 20, 23]. In a major observational study, 5-year-survival among patients with HFpEF was reported as 35–40 % after hospitalization for HF [1]. While survival in HFrEF has significantly improved over the past decades with the help of HFrEF-specific

treatments [73], prognosis of patients with HFpEF has not shown any significant change within the same time period despite the use of similar pharmacological agents. Lack of evidence-based treatment options may be one of the key reasons underlying the high mortality and morbidity in HFpEF [1].

Mortality rates in HFpEF compared to HFrEF vary among studies and are strongly influenced by study design and selection criteria [20]. A recent patient-level meta-analysis showed that risk of death was lower in HFpEF compared to HFrEF; nevertheless, regardless of the underlying EF, the overall risk of death is high when symptomatic HF is present [74]. Some studies have found that the majority of deaths (51–72 %) among patients with HFpEF are due to cardiovascular causes [75, 76], however, data on specific modes of death in HFpEF is relatively sparse. That being said, clinical trials with adjudicated outcomes have found that the primary causes of death in HFpEF are non-cardiovascular (28–30 %), sudden death (26–28 %), progressive HF (14–28 %), stroke (7–9 %), and myocardial infarction (3–5 %) [77•]. The proportion of non-cardiovascular deaths is almost two-fold higher in HFpEF compared to HFrEF (~30 % vs. ~15 %) [20, 77•].

Risk Prediction in HFpEF

Although the morbidity and mortality associated with HFpEF is similar to HFrEF, there is a less data on risk prediction in HFpEF compared to HFrEF. Whereas several well-validated risk prediction models such as the Seattle Heart Failure Model [78] and the Heart Failure Survival Score [79] exist for HFrEF, risk prediction in HFpEF has been less well studied.

While many individual HFpEF risk factors have been identified in clinical trials, observational studies, and large registries, the ability of any single variable to predict survival in individual HFpEF patients remains limited, lending support for the development of HFpEF-specific risk models to generate a more accurate estimate of prognosis. The ability to determine risk estimates for individual HFpEF patients has several potential applications: risk estimation may (1) serve to motivate patients to adhere to recommended treatments and lifestyle modifications; (2) help clinicians identify those patients who need intensification of treatment regimens and closer follow-up; and (3) help inform the design of future HFpEF clinical trials.

HFpEF risk models are beginning to be published but have been less well-validated compared to HFrEF risk models. One HFpEF risk model emerged from data collected in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) [80], in which 12 independent predictors of all-cause mortality (Table 1) were incorporated into a risk model, successfully stratifying patients into septiles of increasing risk [81•]. However, the widespread application of the I-PRESERVE risk model in HFpEF may be somewhat limited by its derivation from a clinical trial population, the specific exclusion of patients with moderate or worse renal dysfunction and/or anemia (both of which are common comorbid conditions in HFpEF), and its lack of racial/ethnic diversity (93 % of I-PRESERVE participants were white). A more recently published risk model, the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) model [82••], which incorporated individual, patient-level data from 30 studies with a total of 39,372 patients with HF (N=17,930 with EF 40 %) may hold even greater promise in HFpEF. The MAGGIC HFpEF risk model is comprised of 13 commonly collected variables (Table 1). Using a goodness of fit model, the investigators demonstrated that the MAGGIC risk score was able to accurately stratify HFpEF patients into quintiles of risk, and the predicted 3-year mortality from the risk model closely matched the observed mortality over that same time period. One potential limitation of the MAGGIC risk model is the absence of biomarker data from the multivariable analyses. For example, B-type natriuretic peptide (BNP) is a potent

predictor of adverse outcomes in HFpEF, and was incorporated into the I-PRESERVE model.

For any risk model to have clinical utility in HFpEF (and in general), the model should (1) outperform any individual variable in predicting mortality and/or morbidity; (2) contain only routinely collected variables for easy application in the clinical setting; and (3) undergo successful validation by others across HFpEF patient populations of differing racial/ethnic, demographic, and geographic backgrounds. The MAGGIC risk model appears to meet the first two criteria; thus, if this risk model can be validated by others, both with and without the addition of BNP, it has the potential to be applied widely in HFpEF for risk stratification.

Conclusions

Our knowledge of the epidemiology and pathophysiology of HFpEF has broadened significantly within the past decade. However, many unanswered questions still exist (Table 2).

In addition, while guidelines have been published for the diagnosis of HFpEF [7, 83, 84], there is still no consensus on how to best diagnose HFpEF, which will continue to make the study of HFpEF epidemiology challenging. Nevertheless, several large-scale, multi-ethnic, ongoing cardiovascular epidemiologic studies, such as the Coronary Artery Risk Development in Young Adults (CARDIA) Study, the Multi-Ethnic Study of Atherosclerosis (MESA), the Atherosclerosis Risk in Communities (ARIC) study, the Study of Latinos (SOL), and several others in progress worldwide, should provide significant insight into the development of HF syndrome (and the progression of abnormalities in cardiac structure and function) in individuals with a normal or near-normal EF. Understanding the emerging pathophysiologic science of HFpEF, including the relationship between comorbidities and HFpEF development, the non-cardiac risk factors for fluid retention, and the impact of the aging population on HF development will be key to further understanding of the HFpEF epidemic. The study of HFpEF epidemiology remains critical, because prevention (i.e., treatment of Stage A and Stage B HF) is the only way to truly curb the epidemic of HFpEF.

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•• Of major importance

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Fig. 1.

The Changing Landscape of Heart Failure: The Projected Trajectory of HFpEF in Hospitalized Heart Failure Patients. Based on results from Get With the Guidelines-Heart Failure (GWTG-HF) Study (Steinberg et al. [11••]; N=110,621), using actual data on the proportion of hospitalization patients with three types of HF (HFpEF [EF>50 %]; HFrEF [EF<40 %]; and HF borderline-EF [EF 40–50 %]) at each time point between 2005–2010. The trajectories for 2011–2020 were estimated for HFpEF and HFrEF using linear regression analyses, while HF borderline-EF was held at a constant 14 % proportion of hospitalized HF patients. The regression equation for the projected HFpEF trajectory= $-0.86(\text{Year})+1771$ ($P=0.015$ for the trend of decreasing HFrEF over time); the equation for the projected HFrEF trajectory= $1.086(\text{Year})-2144$ ($P=0.008$ for the trend of increasing HFpEF over time).

Table 1

A Comparison of the Variables Included in the MAGGIC and I-PRESERVE Risk Models*

MAGGIC (13 variables)	I-PRESERVE (12 variables)
Age	Age
Ejection fraction	Ejection fraction
Creatinine	Glomerular filtration rate
Diabetes	Diabetes
COPD	COPD or asthma
Systolic blood pressure	Systolic blood pressure
Male gender	Heart failure hospitalization within the last 6 months
Heart failure duration	Ischemic etiology
NYHA class	Myocardial infarction
Current smoker	Heart rate
ACE-inhibitor use	Neutrophil count
Beta-blocker use	NT-proBNP
Body mass index	

* Variables in **bold** are meant to highlight the common variables between the two risk prediction models.

MAGGIC=Meta-Analysis Global Group In Chronic Heart Failure, I-PRESERVE=Irbesartan in Heart Failure with Preserved Ejection Fraction Study, COPD=chronic obstructive pulmonary disease, NYHA=New York Heart Association, ACE=angiotensin converting enzyme, NT-proBNP=N-terminal pro-B-type natriuretic peptide

Table 2**Heart Failure with Preserved Ejection Fraction Epidemiology: Unanswered Questions**

Questions	
1	What is the trajectory of HFpEF prevalence (in general and in comparison to HFrEF) in non-white populations? Is the HFpEF epidemic in non-white and global populations similar to, worse than, or better than in whites?
2	What are the genetic risk factors for abnormalities in cardiac structure and function known to lead to HFpEF? What are the gene–environment interactions that predispose individuals to abnormal cardiac structure/function and HFpEF? How do comorbidities interact with the genetic predisposition and environmental factors to lead to HFpEF?
3	What is the epidemiology of high-output HFpEF? How do risk factors for high-output HFpEF vary from traditional forms of HFpEF?
4	What is the role of non-cardiac causes of HFpEF and volume overload in HFpEF development? For example, do obesity/metabolic syndrome, non-alcoholic fatty liver disease, and elevated cardiac output lead to HFpEF at the population level?
5	What is the population prevalence of right-sided heart failure, pulmonary hypertension, and tricuspid regurgitation in HFpEF? How do these abnormalities lead to adverse outcomes?
6	How can HFpEF be better classified and categorized? Will sophisticated multi-phenotypic analysis (e.g., phenomapping, cluster analysis, principal components analysis) result in improved HFpEF classification?
7	In hospitalized patients with HFpEF, how common is renal venous congestion and other cardio-abdominorenal syndromes? How do these pathophysiologic abnormalities influence outcomes in HFpEF?
8	What is the mode of death in HFpEF? Is the cause of death in HFpEF changing over time? With improved adjudication techniques, will sudden cardiac death still be a leading cause of death in HFpEF? Is sudden death in HFpEF arrhythmic in nature?
9	How does the MAGGIC risk score perform in clinical HFpEF studies? Can the MAGGIC risk score be validated, how does it compare to natriuretic peptides and other biomarkers, and will it be clinically useful as a risk estimation tool?
10	Can HFpEF be prevented using strategies such as decreasing salt intake on a population level or widespread screening using biomarkers/ imaging?

* HFpEF=heart failure with preserved ejection fraction, HFrEF=heart failure with reduced ejection fraction, MAGGIC=Meta-Analysis Global Group in Chronic Heart Failure