Novel insights into heart failure with preserved ejection fraction
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Chapter 2

Epidemiology of heart failure with preserved ejection fraction

2.1. Epidemiology and clinical course of heart failure with preserved ejection fraction.


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ABSTRACT
Heart Failure with Preserved Ejection Fraction (HFPEF) is increasingly recognized as a major public health problem worldwide. Significant advances have been made in our understanding of the epidemiology of HFPEF over the last two decades, with the publication of numerous population-based epidemiologic studies, large heart failure registries and randomized clinical trials. These recent studies have provided detailed characterization of larger numbers of patients with HFPEF than ever before. This review summarizes the state of current knowledge with regards to the disease burden, patient characteristics, clinical course and outcomes of HFPEF. Despite the wealth of available data, substantive gaps in knowledge were identified. These gaps represent opportunities for further research in HFPEF, a syndrome that is clearly a rising societal burden and that is associated with substantial morbidity and mortality.

INTRODUCTION
Heart failure (HF) affects about 2% of the western population, with the prevalence increasing sharply from 1% in 40-year-old individuals to 10% above the age of 75 years. It is the most common cause of hospitalization in patients over 65 years of age.(1-3) HF is defined as a syndrome characterized by an impaired ability of the heart to fill with and/or to eject blood commensurate with the metabolic needs of the body, resulting in a classical constellation of signs or symptoms of pulmonary and systemic venous congestion.(1)

While traditionally associated with the concept of “pump failure” or reduced left ventricular (LV) ejection fraction, it has become widely recognized that HF can occur even when ejection fraction is preserved, constituting the syndrome of HF with preserved ejection fraction (HFPEF). Several criteria have been proposed to define the syndrome of HFPEF,(2, 4, 5) the most comprehensive of which are the guidelines by the Echocardiography and Heart Failure Associations of the European Society of Cardiology.(2) In general these diagnostic criteria share three features in common: 1. Clinical signs or symptoms of HF; 2. Evidence of normal LV systolic function; and 3. Evidence of abnormal LV diastolic dysfunction.
Prevalence

The reported prevalence of preserved LVEF among patients with HF varied widely from 13% to 74% in early studies,\(^6\) depending partly on sample inclusion criteria (including the choice of a ‘normal’ EF cut-point) and clinical settings. These selection biases were addressed in recent population-based echocardiographic investigations performed in large community-based samples in the United States (Olmsted County Study,\(^7\) Cardiovascular Health Study,\(^8\) Strong Heart Study,\(^9\)), Portugal (EPICA Study,\(^10\)), the Netherlands (Rotterdam Study,\(^11\)) United Kingdom,\(^12\) Sweden (Vasteras Study,\(^13\) Finland (the Helsinki Aging Study),\(^14\)) and Spain (Asturias Study,\(^15\)). Together, these recent studies provided a more refined estimate of the prevalence of HFPEF among patients with HF, which averaged 54%, with a range from 40% to 71%.\(^16\) Inherent difficulties in making an accurate diagnosis of HFPEF, the lack of standardization of diagnostic criteria and the potential for misdiagnosis in these often elderly, overweight or deconditioned patients limit the precision of these estimates.\(^17\)

Nonetheless, the “true” overall prevalence of HFPEF in the community has been estimated at 1.1% to 5.5% of the general population.\(^16\)

Of note, the prevalence of HFPEF in the community increased with advancing age, and was higher in women; the reported age- and sex- specific prevalence rose from 0 (men) -1% (women) in the age group 25-49 years to about 4-6% in men and 8-10% in women for individuals eighty years and older.\(^10\) Further, the relative prevalence of HFPEF among all HF patients increased over time in a large hospital-based study in Olmsted County, Minnesota, rising from 38% to 54% (of all HF cases) between 1987 and 2001.\(^18\) This temporal trend for increasing HFPEF occurred in association with increases in the prevalence of hypertension, diabetes and atrial fibrillation, but without a corresponding increase in the relative prevalence of HF with reduced ejection fraction (HFREF). In the same time frame, survival was noted to improve in patients with HFREF, but not in those with HFPEF. These secular trends underscore the importance of HFPEF as a major and growing public health problem.
Incidence
Few population-based studies have examined the temporal trends in the incidence of all HF in the community, regardless of ejection fraction, etiology or clinical setting. In the Framingham Heart Study,(19) the incidence of HF remained unchanged in men but declined in women between 1950 and 1999. In Olmsted County, MN,(20) the incidence of HF did not change between 1979 and 2000 among either men or women. In both samples, the survival after onset of HF improved over time in both men and women. With the aging of the population and improved survival after HF onset, we can expect a dramatic increase in cases of HF (prevalence) in spite of the stable incidence rates (Figure 1).

In fact, recent statistical data from the American Heart Association(21) indicate that the annual actual caseload of HF may have exceeded this projected “epidemic”. To date, no study has looked specifically at trends in incidence of HFPEF in the community. However, extrapolating from the observations in all HF patients, and assuming that half the caseload of HF consists of HFPEF, one can project an equal, if not greater, increase in HFPEF burden in the future.

Demographic features and risk factors
Recent large epidemiologic studies characterizing more than 57,000 HF patients have helped to confirm observations from previous smaller studies of selected patients(6), and more clearly define the demographic features of patients with HFPEF (Table 1). In general, these patients are older women with a history of hypertension. The prevalence of other cardiovascular risk factors varies depending on the study setting and the diagnostic criteria for the condition. Although not uniformly reported, cardiovascular risk factors are highly prevalent in HFPEF in population-based studies and registries, and include obesity in 41-46%, coronary artery disease in 20-76%, diabetes mellitus in 13-70%, atrial fibrillation (AF) in 15-41% and hyperlipidemia in 16-77%.

In studies that included both HFPEF and HFREF,(18, 22-27) patients with HFPEF were consistently found to be older, more often female, more predominantly hypertensive and have a higher prevalence of atrial fibrillation but a lower prevalence of coronary artery disease compared to those with HFREF. Notably, non-cardiovascular co-
morbidities also appear to be highly prevalent in HFPEF, consistent with an elderly population, and include renal impairment, chronic lung diseases, anemia, cancer, liver disease, peptic ulcer disease and hypothyroidism. The Charlson index,(28) a weighted prognostic score of co-morbidity, was reported in 2 studies indicating high co-existing disease burden (mean score=2.8(29) and score ≥3 in 70% of HFPEF patients(23)). Controlled clinical trials have, to date, included more than 10,000 HFPEF patients; the demographic characteristics and risk factor profiles of these individuals more closely resemble that of population-based studies in the more recently completed trials (I-PRESERVE, SENIORS, HK DHF, PEP-CHF) (Table 1).

Echocardiographic and hemodynamic features
In the most recent set of diagnostic criteria proposed by the European Society of Cardiology,(2) echocardiographic and hemodynamic features are key components for the diagnosis of HFPEF. After first establishing the presence of signs or symptoms of HF, the presence of an EF >50% and a LV end-diastolic volume index <97 mL/m² is the second essential criterion for the diagnosis.(2) The third criterion is the presence of LV diastolic dysfunction, which can be demonstrated by Doppler
### Table 1: Demographic characteristics and risk factors in patients with HFpEF from recent studies

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Setting</th>
<th>N with HF-PEF</th>
<th>Age</th>
<th>%Women</th>
<th>%Obesity (or mean BMI/weight)</th>
<th>%Hypertension</th>
<th>%Coronary artery disease</th>
<th>%Diabetes mellitus</th>
<th>%Atrial fibrillation</th>
<th>%Renal impairment* (or mean creatinine)</th>
<th>%Hyperlipidemia* (or mean cholesterol)</th>
<th>Non-cardiovascular comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POPULATION-BASED STUDIES</strong></td>
<td></td>
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<tr>
<td>Lee DS, et al.(22)</td>
<td>Framingham Heart Study, Framingham MA, United States</td>
<td>220</td>
<td>80</td>
<td>65</td>
<td>59 (BMI=27 kg/m²)</td>
<td>37</td>
<td>22</td>
<td>29</td>
<td>-</td>
<td>(TC=218 mg/dl)</td>
<td></td>
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</tr>
<tr>
<td>Bursi F, et al.(23)</td>
<td>Rochester Epidemiology Project, Olmsted County MN, United States</td>
<td>308</td>
<td>77</td>
<td>57</td>
<td>86 (BMI=29.6 kg/m²)</td>
<td>36</td>
<td>36</td>
<td>31</td>
<td>59</td>
<td>37% COPD; 53% anemia; 70% Charlson index=3</td>
<td></td>
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</tr>
<tr>
<td>Owan TE, et al.(18)</td>
<td>Olmsted County MN, United States EFFECT Study, Ontario, Canada</td>
<td>2167</td>
<td>74</td>
<td>56</td>
<td>63 (BMI=29.7 kg/m²)</td>
<td>53</td>
<td>33</td>
<td>41</td>
<td>-</td>
<td>Mean Hb=11.8 g/dl</td>
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<tr>
<td>Bhatia RS, et al.(24)</td>
<td>EIGHT Study, Ontario, Canada</td>
<td>880</td>
<td>75</td>
<td>66</td>
<td>55 (BMI=29.7 kg/m²)</td>
<td>36</td>
<td>32</td>
<td>32</td>
<td>22% with Creatinine&gt;150 mmol/l, 1% on dialysis</td>
<td>16% COPD; 8% peptic ulcer disease; 2% hepatitis/ cirrhosis</td>
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<tr>
<td>Gottdiener JS, et al.(55)</td>
<td>Cardiovascular Health Study, Multicenter, United States</td>
<td>170</td>
<td>75</td>
<td>56</td>
<td>59</td>
<td>58</td>
<td>27</td>
<td>15</td>
<td>(Creatinine=1.2 mg/dl)</td>
<td></td>
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<tr>
<td>Devereux RB et al.(9)</td>
<td>Strong Heart Study, American Indian reservations, United States</td>
<td>50</td>
<td>64</td>
<td>84</td>
<td>76</td>
<td>20</td>
<td>70</td>
<td>-</td>
<td>(Creatinine=2.3 mg/dl)</td>
<td>12% cancer; 18% COPD; 8%</td>
<td></td>
<td></td>
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<tr>
<td>Yip GW, et al.(73)</td>
<td>Hong Kong, SAR, China</td>
<td>132</td>
<td>73</td>
<td>55</td>
<td>57</td>
<td>39</td>
<td>35</td>
<td>-</td>
<td>9% end-stage renal failure</td>
<td>21% anemia; 24% hyponatremia</td>
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<td><strong>HF REGISTRIES</strong></td>
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<tr>
<td>OPTIMIZE-HF</td>
<td>Acute HF from 259 hospitals across the United States</td>
<td>21149</td>
<td>75</td>
<td>62</td>
<td>76</td>
<td>38</td>
<td>38</td>
<td>33</td>
<td>(Creatinine=1.3 mg/dl)</td>
<td>32% COPD or asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fonarow GC et al.(25)</td>
<td>AdeHerS Acute HF from &gt;247 hospitals across the United States</td>
<td>26322</td>
<td>74</td>
<td>62</td>
<td>77</td>
<td>50</td>
<td>45</td>
<td>21</td>
<td>26</td>
<td></td>
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<tr>
<td>EuroHeart Failure Survey</td>
<td>Heart failure from 17 centres in metropolitan New York</td>
<td>163</td>
<td>63</td>
<td>28</td>
<td>6</td>
<td>76</td>
<td>-</td>
<td>-</td>
<td>4.5% dialysis (GFR=50.8 ml/min)</td>
<td>25% COPD or asthma; 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klapholz M, et al.(41)</td>
<td>Heart failure from 4 centres in the United Kingdom</td>
<td>619</td>
<td>72</td>
<td>73</td>
<td>78</td>
<td>43</td>
<td>46</td>
<td>23</td>
<td>5</td>
<td></td>
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<tr>
<td>New York HF Registry</td>
<td>Heart failure from 4 hospitals in the United Kingdom</td>
<td>163</td>
<td>63</td>
<td>28</td>
<td>6</td>
<td>76</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>UK-HEART</td>
<td>Hospital-based multicentre trial screening registry, Denmark</td>
<td>2218</td>
<td>73</td>
<td>49</td>
<td>25</td>
<td>49</td>
<td>13</td>
<td>26</td>
<td>2%, 24%, and 34% with creatinine clearance&lt;20, 21-40 and 41-60 ml/min respectively</td>
<td>26% COPD</td>
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<tr>
<td>MacCarthy PA, et al.(74)</td>
<td>DIAMOND-CHF Heart failure from 4 centres in the United Kingdom</td>
<td>163</td>
<td>63</td>
<td>28</td>
<td>6</td>
<td>76</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Gustafsson F, et al.(75)</td>
<td>Hospital-based multicentre trial screening registry, Denmark</td>
<td>2218</td>
<td>73</td>
<td>49</td>
<td>25</td>
<td>49</td>
<td>13</td>
<td>26</td>
<td>2%, 24%, and 34% with creatinine clearance&lt;20, 21-40 and 41-60 ml/min respectively</td>
<td>26% COPD</td>
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<tr>
<td>MISCHF</td>
<td>Acute HF from 10 community hospitals in upstate New York, United States</td>
<td>312</td>
<td>75</td>
<td>70</td>
<td>49</td>
<td>23</td>
<td>33</td>
<td>29</td>
<td>(Creatinine=1.5 mg/dl; creatinine clearance=57 ml/min)</td>
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</tr>
<tr>
<td>Philbin EF, et al.(29)</td>
<td>Seniors Heart failure from 10 hospitals in upstate New York, United States</td>
<td>752</td>
<td>76</td>
<td>50</td>
<td>78</td>
<td>77</td>
<td>24</td>
<td>36</td>
<td>Excluded significant renal dysfunction</td>
<td>47%</td>
<td></td>
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<tr>
<td>SENIORS</td>
<td>11 countries in Europe</td>
<td>752</td>
<td>76</td>
<td>50</td>
<td>78</td>
<td>77</td>
<td>24</td>
<td>36</td>
<td>-</td>
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echocardiography, cardiac catheterization or blood natriuretic peptide measurements. Using Doppler echocardiography, a ratio of mitral early diastolic inflow velocity to mitral early annular lengthening velocity (E/e') exceeding 15 provides evidence for raised LV filling pressures. If the E/e' ratio is ≤ 8, then LV filling pressures are probably ‘normal’. If the E/e' ratio is intermediate (>8-<15), it may be necessary to consider a multi-parametric approach using “second line” indices: the left atrial volume (> 40 ml/m²), LV mass index (>122 g/m² in women and >149 g/m² in men), mitral inflow Doppler (ratio of early to late mitral inflow velocity <0.5 and deceleration time >280 ms), pulmonary venous flow velocity patterns (duration of pulmonary venous A-wave reversal >30 ms longer than duration of mitral A-wave), or the presence of AF.

The utility of these “second line” indices was evaluated in a retrospective study of patients referred to a tertiary echocardiography laboratory,(30) where left atrial enlargement was shown to distinguish patients with E/e'>15 from those with E/e'<8 with better diagnostic accuracy than LV mass index or Doppler measurements. However, prospective evaluation is still needed in patients with confirmed clinical HF and E/e’ in the intermediate range of 8-15.(31) Recognizing that advanced age and hypertension may be associated with changes in echocardiographic diastolic indices even in the absence of HF,
patients with HFpEF (HF by Framingham criteria and EF>50%) were compared to elderly hypertensive and healthy controls without HF from the general community in Olmsted County, MN.(32) While the extent of LV hypertrophy was similar in HFpEF and hypertensive controls, there was greater left atrial enlargement and higher estimated LV filling pressures (based on E/e’ ratio) in HFpEF compared to both control groups, adjusting for age and sex. The E/e’ ratio distinguished HFpEF from hypertensive controls without HF with better accuracy than left atrial volume index,(33) but the best diagnostic utility was observed with Doppler-estimated pulmonary artery systolic pressure in the Olmsted County cohort. Further, increasing pulmonary artery systolic pressure was associated with increasing mortality in HFpEF.(33) Similarly recognizing that age, sex, co-morbidities and LV structural remodeling can all affect circulating natriuretic peptide levels, plasma B-type natriuretic peptide (BNP) concentrations were compared between HFpEF and controls without HF in the former Olmsted County population-based study, adjusting for these covariates.(32) Plasma BNP concentrations were found to be elevated in HFpEF, consistent with findings in the large patient sample of the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial, in which plasma N-terminal(NT)-proBNP levels were also found to be raised in HFpEF.(34) The analysis from I-PRESERVE further showed that the elevation of circulating NT-proBNP was related to severity of symptoms/ functional status as well as to the baseline characteristics indicative of poorer outcomes in HFpEF.(34)

Invasive measurements of LV filling pressures remain the gold standard for diagnosis of HFpEF and should be considered in cases of diagnostic uncertainty. Cardiac catheterization is also useful for the assessment of pulmonary hypertension, which is common in HFpEF patients and may be related to both post-capillary pulmonary venous hypertension(35, 36) as well as a reactive pre-capillary component of pulmonary arterial hypertension.(33) An emerging area of interest is a reduction in the longitudinal component of LV systolic function (relatively easy to measure by echocardiography, Figure 2)(37) The reduction in longitudinal component of LV systolic function is compensated by a preserved/robust radial, circumferential and twist components that
are necessary to maintain a normal LVEF. Whether this can aid the diagnosis of HFPEF warrants validation in larger prospective studies of patients with suspected HFPEF. The potential contribution of mechanical asynchrony to the pathophysiology of HFPEF is also currently being evaluated.

In summary, noninvasive hemodynamic assessment by comprehensive echocardiographic evaluation is recommended in patients with suspected HFPEF. Plasma biomarker measurement (natriuretic peptides) may aid the diagnosis but in equivocal cases, invasive assessment should be considered.
Clinical course
Large prospective national registries have consistently demonstrated that 46-51% of hospitalized acute heart failure patients have a preserved LV ejection fraction. These patients are also just as likely to be re-admitted following discharge as patients with HFREF, with a re-hospitalization rate of 29% within 60-90 days, and a median time to re-hospitalization of 29 days.

The clinical factors precipitating acute decompensation versus the chronic syndrome of HFPEF have been systematically examined in a few studies. Of the clinical risk factors highly prevalent in HFPEF (discussed under “Demographic features and risk factors” above), a few have been consistently identified in these studies to be associated with episodes of acute decompensation: Uncontrolled hypertension is a frequent presenting feature of acute HFPEF. The role of hypertension is underscored by recent large registries of acutely decompensated HFPEF showing raised admission blood pressure (mean systolic blood pressure 149 mmHg and 153 mmHg) and high proportions of patients with uncontrolled systolic hypertension at presentation (12% with uncontrolled hypertension, 61% with systolic blood pressure >140 mmHg). Interestingly, whereas systolic blood pressures were higher, mean diastolic blood pressures in both registries were lower in patients with acute HFPEF compared to patients with HFREF, suggesting the presence of widened pulse pressures and possible arterial stiffening in these patients. Another important potentially reversible precipitating factor for HFPEF is AF. This arrhythmia was found on the initial presenting ECG in 21% of acutely decompensated HFPEF patients in the ADHERE registry. Indeed, these findings lend support to treatment guidelines advocating judicious blood pressure and rhythm control in HFPEF. Further, the potential contribution of non-cardiovascular factors (such as lung disease, renal impairment or sepsis) to acute HFPEF decompensation deserves mention, an observation consistent with the high prevalence of co-morbid conditions in these elderly patients.
Overall mortality rates in HFPEF
Several studies have evaluated the short- and long-term mortality of HFPEF, compared these mortality patterns with that of HFREF, and assessed the prognostic factors that determine mortality risk in patients with HFPEF. In general, mortality rates have varied substantially across studies of HFPEF in part because of the heterogeneity in the diagnosis of the condition (variability in EF cut points used, the requirement for demonstrating presence of diastolic dysfunction or meeting recent criteria for HFPEF advocated by the European Society of Cardiology), differing sampling strategies and study designs (observational cohort versus clinical trial versus hospital-based registries), biases introduced by exclusion of HF patients with missing EF, and possible temporal trends in mortality patterns. Nonetheless, most studies have consistently demonstrated higher mortality rates in HFPEF patients compared to age- and sex-matched controls without HF in the community.

HFPEF is associated with high in-hospital, short-term and long-term mortality rates. In studies that have evaluated mortality during the peri-hospitalization period, the in-hospital mortality rates have ranged from 3-6.5% during the index hospitalization. Short-term (30-90-day) mortality also is high, ranging typically between 5-9.5%. The long-term mortality rates seem more variable in the reported literature. Thus, annualized mortality rates ranged from about 3.5%-6% in 3 of the large randomized clinical trials to about 15% in the observational community-based Framingham Study. The lower mortality of HFPEF patients in clinical trials likely reflects a selection bias favoring relatively younger, more compliant individuals with a lesser co-morbidity burden. A recent meta-analysis of 7688 patients with HFPEF followed for about 4 years noted an overall mortality of 32% mortality, averaging to about an 8% annual mortality rate. The longer-term (5-year) mortality rates across observational studies and registries evaluating prevalence cohorts of HFPEF are consistently high, although absolute rates have varied considerably from about 55% to 74%.
Comparison of mortality rates with HFREF

Numerous investigations have compared long-term mortality rates in patients with HFPEF and HFREF. Several of the observational epidemiological cohort studies have consistently reported similar mortality rates in HFPEF and HFREF. On the other hand, clinical trials that included both kinds of HF patients have typically reported lower mortality in HFPEF compared to HFREF. More recently, Somartane and colleagues published the largest systematic meta-analytic comparison of death rates in the two kinds of HF; the investigators compared mortality in 7688 HFPEF patients with 16,831 HFREF patients from 17 studies, and noted a 50% lower hazard for mortality in HFPEF compared to HFREF. The strengths of this meta-analysis was that it included only studies where all HF patients had an EF measured; as noted above, missing EF is an important source of bias when one compares mortality rates in HFPEF versus HFREF. It is worth noting that notwithstanding the reported higher mortality of HFREF, given the aging of the population and the preponderance of HFPEF in the elderly, the overall absolute number of deaths in the community attributable to HFPEF is likely higher than the number of deaths attributable to HFREF.

Table 2. Proportions of deaths due to cardiovascular versus non-cardiovascular mortality in HFPEF patients according to study design.

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Design</th>
<th>% Non-cardiovascular deaths</th>
<th>% Cardiovascular deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tribouilloy C, et al.(52)</td>
<td>Population based, hospitalized patients single tertiary care hospital</td>
<td>41</td>
<td>59</td>
</tr>
<tr>
<td>Grigorian-Shamagian L, et al.(57)</td>
<td>Clinical trial</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Yusuf S, et al.(51)</td>
<td>Clinical trial</td>
<td>28</td>
<td>72</td>
</tr>
<tr>
<td>Ahmed A, et al.(56)</td>
<td>Clinical trial</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Massie BM, et al.(50)</td>
<td>Clinical trial</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Zile MR, et al. (58)</td>
<td>Clinical trial</td>
<td>30</td>
<td>60*</td>
</tr>
</tbody>
</table>

*Cardiovascular deaths including 26% sudden death, 14% heart failure, 5% myocardial infarction, and 9% stroke; unknown mode of death in 10% in this trial
Patterns of mortality in HFPEF: cardiovascular versus non-cardiovascular mortality
As noted above, there is a general consensus that patients with HFPEF have high co-morbidity burden due to their elderly nature. The proportion of deaths attributed to cardiovascular versus non-cardiovascular causes in HFPEF varies with study design, mode of death ascertainment, and time period of the studies (Table 2).(46, 50-52, 56, 57) Thus, a recent report from the Mayo Clinic(46) (that was community-based, and in which the cause of death was adjudicated by a coroner) underscored that nearly half of HFPEF patients succumbed to non-cardiovascular diseases, and there has been a temporal trend for higher non-cardiovascular mortality in HFPEF in the most recent decade (late 1990s-early 2000). Overall, community-based studies(46, 52, 57) demonstrate a higher proportion of non-cardiovascular deaths, and clinical trials(50, 51, 56, 58) report a higher % of cardiovascular deaths (Table 2). This pattern may reflect the enrollment of healthier patients with fewer co-morbidities in controlled clinical trials. Cardiovascular causes of death in HFPEF patients include sudden death, refractory HF (pump failure), myocardial infarction and other cardiovascular disease (stroke or coronary disease).(46, 50-52, 56-58) When cause-specific mortality patterns are compared between HFPEF and HFREF, the latter has a higher burden of cardiovascular-related death compared to the former.(46)

HFPEF prognostic factors for mortality risk
Several studies have examined the factors influencing mortality risk in HFPEF. Thus, in one of the larger series from Canada(24) that systematically investigated the impact of prognostic factors, the following factors increased mortality risk: older age, associated co-morbidities (presence of peripheral vascular disease, dementia or cancer each doubled mortality risk), worse clinical profile at presentation as reflected by anemia (Hb<10 g/dl), higher serum creatinine (>150 μmol/L), hyponatremia (<136 mmol/l), each of which increased mortality risk by 50%, and a lower systolic BP. Some other studies have emphasized a worse prognosis in men with HFPEF (compared to women),(59) those with diabetes,(60) chronic obstructive lung disease,(61) atrial
fibrillation, a restrictive filling pattern. The presence of diabetes increases the likelihood of cardiovascular-related death in HFPEF.

Some recent investigations have evaluated if the paradigm of reverse epidemiology observed in HFREF is also evident in HFPEF. These studies have reported that lower BMI, lower SBP, and lower total cholesterol are all markers of increased mortality risk in HFPEF, thereby extending the reverse epidemiology concept beyond HFREF. The impact of etiology of HFPEF on mortality risk is less clear, with conflicting reports in the literature; a recent report noted similar mortality risk in HFPEF due to valve disease, hypertension or ischemic heart disease, whereas another study highlighted a worse prognosis in those with coronary disease as the basis of HFPEF.

In summary, HFPEF has a high mortality risk, on an average lower than HFREF, a higher likelihood of non-cardiovascular death, and a range of prognostic factors that are generally similar to those noted for HFREF.

**Future Directions**
As discussed above, several gaps exist in our knowledge of the epidemiology of HFPEF and represent potential areas for future study

Table 3. Unresolved issues in HFPEF epidemiology: Future directions for research

<table>
<thead>
<tr>
<th>1. <strong>Definition and diagnosis</strong></th>
</tr>
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<tbody>
<tr>
<td>- Define optimal cut-point for normal left ventricular ejection fraction</td>
</tr>
<tr>
<td>Characterize epidemiology based on stricter adherence to diagnostic guidelines</td>
</tr>
<tr>
<td>Better characterize varying subsets of disease with different underlying pathophysiology</td>
</tr>
<tr>
<td>Better identify cut-points for natriuretic peptides to diagnose HF in patients with equivocal diagnostic criteria</td>
</tr>
<tr>
<td>Better define role of newer imaging metrics like long axis function, strain rate</td>
</tr>
<tr>
<td>Identify role of exercise testing in unmasking symptoms, signs and imaging features in patients with suspected HFPEF with equivocal rest studies</td>
</tr>
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<table>
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<tr>
<th>2. <strong>Demographic and other clinical features/risk factors</strong></th>
</tr>
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<tbody>
<tr>
<td>- Better data on incidence, prevalence, trends in the same, across regions and by ethnicity</td>
</tr>
<tr>
<td>- Clarify pathophysiologic basis for preponderance in women and elderly, including contributions of multiple non-cardiac organ systems dysfunction, family history, metabolic risk factors (including the metabolic syndrome)</td>
</tr>
<tr>
<td>- Delineate the role of risk factors such as atrial fibrillation, hypertensive crises in the natural progression of HFPEF</td>
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<tr>
<th>3. <strong>Mortality patterns</strong></th>
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<tbody>
<tr>
<td>- Define mortality patterns in studies without selection bias and without missing echocardiograms on patients</td>
</tr>
<tr>
<td>- Delineate the contribution of cardiovascular versus non-cardiovascular deaths in patients with HFPEF</td>
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</table>
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(Table 3). The diagnostic cut points that define a normal LVEF differ across the various studies of HFPEF, with ESC guidelines advocating a threshold of 50%.(2) However, this threshold remains arbitrary, and individuals with a LVEF in the range 50-54% may also potentially have systolic dysfunction.(66) Use of a higher cut-point for defining normal LVEF (55%) would lower the prevalence of HFPEF. Additional investigations describing the natural history of individuals with borderline LVEF (50-54%) may help to resolve this controversy. On a parallel note, the ESC guidelines advocate cut-points for circulating BNP and pro-BNP of 200 and 220 pg/ml respectively for substantiating a diagnosis of HF in patients with suspected HFPEF who have a normal LVEF but an equivocal E/e’.(2) However, given that women and elderly have higher BNP/proBNP levels, these cut-points likely have a greater negative than positive predictive value.(67) Further studies are warranted to identify optimal cut-points for natriuretic peptides to aid the diagnosis of HFPEF in equivocal cases.

Traditionally, HFPEF has been diagnosed based on a normal LVEF, but recent studies have noted the potential importance of abnormalities of the long axis LV function, LV strain and strain rate, torsion and asynchrony in addition to left atrial systolic and diastolic function. (38) Of note, measurement of global strain rate during the isovolumic relaxation period of the cardiac cycle has been advocated as a key diagnostic parameter in individuals with suspected HFPEF but non-diagnostic E/e’ ratios.(38) Future prospective studies are needed to validate these newer measures against invasive gold standards and determine their impact on outcomes in HFPEF.(40, 68)

It is also noteworthy that well-compensated HFPEF patients may be asymptomatic at rest but may be prone to exercise-induced exacerbations of HF symptoms and elevations of LV filling pressures. The role of exercise testing for provocation of symptoms and /or diastolic (and systolic) dysfunction in suspected HFPEF patients needs to be better defined.(69) On a separate note, several investigators have questioned the need for demonstration of abnormal LV diastolic function itself for a diagnosis of HFPEF. Several non-diastolic mechanisms for HFPEF have been reviewed(70) and that include volume expansion, venoconstriction (altered venous capacitance), increased vascular
and ventricular stiffness indices, and chronotropic incompetence. This raises the notion that there are likely several distinct pathophysiological entities encompassed by the syndrome of HFpEF. Thus, describing the principal underlying substrates (diastolic dysfunction versus non-diastolic cardiac mechanisms; or systemic [non-cardiac] mechanisms; or combinatorial factors) may be an important component of the diagnostic strategy. Indeed, Paulus and van Ballegoji have recently opined that strict adherence to ESC diagnostic criteria for HFpEF may facilitate the characterization of specific homogeneous subgroups such as those with HF, concentric hypertrophy and arterial hypertension.(44)

Other gaps in knowledge pertain to the world-wide prevalence of HFpEF (beyond US and Europe) and variation in the burden of HFpEF according to ethnicity. Recent data indicate a potential greater burden of diastolic dysfunction in Africans of Caribbean descent,(71) highlighting the need for future studies of multi-ethnic samples. Given some suggestion of a rising incidence of HFpEF, longitudinal studies are needed to prospectively monitor incidence and prevalence of HFpEF, including assessment of temporal trends.

Several key clinical factors related to HFpEF merit further study. Thus, while a female preponderance for the condition is well known, additional investigations are necessary to identify factors that increase risk for HFpEF in women, including the relative contributions of their greater longevity, the lower burden of coronary disease, sex-related differences in LV remodeling in response to pressure-overload, hormonal factors, and sex-related differences in vascular function, venous capacitance, and susceptibility to volume overload. A family history of heart failure increases risk of the condition in offspring.(72) However, it is unclear if HFpEF aggregates within families, or if parental HFpEF elevates risk of the condition in the offspring, a premise that should be investigated further.(72) Given the high prevalence of obesity, dyslipidemia and diabetes mellitus in patients with HFpEF, investigations to elucidate the contribution of metabolic disturbances (including the metabolic syndrome) to the rising burden of HFpEF are warranted.

From a prevention perspective, further investigation of key precipitating factors for HFpEF in well-compensated individuals with
LV diastolic dysfunction is critical. For instance, the relations of AF and HF in HFPEF are likely complex; it is unclear in what proportion of individuals AF presages HFPEF, and vice versa. Likewise, given the frequent presence of elevated BP at presentation, studies to evaluate the contribution of exacerbations of pulsatile load on the heart to overt decompensation and to identify potential triggers for these BP escalations are warranted.

The sections above also have underscored the current challenges related to describing the mortality patterns in HFPEF. Additional studies without selection bias or missing LVEF data are necessary to fully characterize mortality patterns in HFPEF (overall rates and cardiovascular versus non-cardiovascular mortality), including comparisons with HFREF, and clarifying the impact of etiology of HFPEF on mortality risk. Well-designed studies are needed to ascertain the exact mode of death in these patients, and to better elucidate the contribution of the HF state itself to non-cardiovascular deaths in HFPEF patients. It is not clear if diastolic dysfunction or the HF state is a key contributor to likelihood of death due to non-cardiovascular causes.

In conclusion, major advances have been made in our understanding of the epidemiology of HFPEF over the last two decades, but substantive gaps still exist in our knowledge. These gaps present a window of opportunity for additional research delineating these less-studied aspects of HFPEF, a disorder characterized by substantial morbidity and mortality and a rising societal burden.

Acknowledgments.
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Chapter 2

Epidemiology of heart failure with preserved ejection fraction

2.2. How do patients with heart failure with preserved ejection fraction die?


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ABSTRACT
Understanding how patients with heart failure with preserved ejection fraction (HFPEF) die provides insight into the natural history and pathophysiology of this complex syndrome, thereby allowing better prediction of response to therapy in designing clinical trials. This review summarizes the current state of knowledge surrounding mortality rates, modes of death and prognostic factors in HFPEF. Despite lack of uniform reporting, the following conclusions may be drawn from prior studies: The mortality burden of HFPEF is substantial, ranging from 10-30% annually, and higher in epidemiologic studies than clinical trials. Mortality rates compared to heart failure with reduced ejection fraction (HFREF) appear strongly influenced by the type of study, but are clearly elevated compared to age- and comorbidity-matched controls without heart failure. The majority of deaths in HFPEF are cardiovascular deaths, comprising 51-60% of deaths in epidemiologic studies, and ~70% in clinical trials. Among cardiovascular deaths, sudden death and heart failure death are the leading cardiac modes of death in HFPEF clinical trials. Compared to HFREF, the proportions of cardiovascular deaths, sudden death and heart failure deaths are lower in HFPEF. Conversely, non-cardiovascular deaths constitute a higher proportion of deaths in HFPEF than HFREF, particularly in epidemiologic studies, where this difference may be related to fewer coronary heart deaths in HFPEF. Key mortality risk factors, including age, gender, body mass index, burden of comorbidities and coronary artery disease, offer some explanation for the differences in mortality rates observed across studies.

INTRODUCTION
The importance of understanding how patients with heart failure with preserved ejection fraction (HFPEF) die goes far beyond morbid fascination. Epidemiologic trends show that the prevalence of HFPEF relative to heart failure with reduced ejection fraction (HFREF) is increasing over time; yet at the same time survival in HFPEF has remained dismal whereas prognosis has improved in HFREF.1, 2 In fact, all outcome trials in HFPEF to date have failed to demonstrate survival benefit, despite robust evidence of prognostic benefit using the same
agents in HFREF. The continued absence of guideline-recommended proven therapies for HFPEF may directly impact outcomes in patients with HFPEF, but also importantly points to large gaps in knowledge of therapeutic targets and raises the issue of whether we are measuring the right outcomes in HFPEF trials. Do we really understand how patients with HFPEF die? What is their risk of death in absolute terms, as well as relative to age- and comorbidity-matched adults or patients with HFREF? Do these elderly patients die of the disease itself (i.e. heart failure), related cardiovascular causes (e.g. myocardial infarction) or age-associated non-cardiovascular causes (e.g. cancer)? In other words, do they die with or of HFPEF (analogous to the case with prostate cancer in elderly men, who often die with, but not of, prostate cancer)? What are the factors that contribute to death in HFPEF? Can we expect targeted therapies to influence all-cause mortality, and if not, what cause-specific outcomes are most appropriately studied? We aim to explore these issues in this review, using available data to date.

**WHAT IS THE RISK OF DEATH IN HFPEF?**
Several studies have examined mortality in HFPEF, usually in comparison with HFREF (Table 1).

**Effect of type of study**
Depending on the study design (randomized controlled trials [RCT] versus population-based studies) and selection criteria (left ventricular ejection fraction [LVEF] criteria, hospitalized versus outpatients, number of comorbidities), different HFPEF populations have been sampled, potentially explaining some of the discrepancies amongst reported outcomes. In epidemiologic community-based studies, the 1-year mortality rate of HFPEF was almost 30%. In RCTs, mortality rates 2-3 times lower have been reported (1-year mortality ~10%), a difference that may be partially attributed to selection bias (younger population, better compliance to therapy and lower burden of comorbidities in RCTs). In terms of absolute mortality rates, a recent meta-analysis of 31 studies (both observational studies and RCTs) showed that the pooled death rate in HFPEF was 121 (95% confidence interval [CI]: 117, 126) deaths per 1000 patient-years in all the studies;
Table 1. Characteristics and mortality rates of recent studies reporting outcomes in HFPEF. Dx - diagnosis; ECHO - echocardiography; HF Hosp - heart failure hospitalization; LVEF - left ventricular ejection fraction; NT-proBNP - N-terminal pro B-type natriuretic peptide; NYHA - New York Heart Association Classification; UL – upper limit.

<table>
<thead>
<tr>
<th>Study (Study period)</th>
<th>Setting</th>
<th>HFPEF No.</th>
<th>LVEF criteria</th>
<th>Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
<th>Follow-up duration (years)</th>
<th>Ave. Annual Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population-based Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adabag et al. (1996-2000)</td>
<td>22 hospitals. USA.</td>
<td>787</td>
<td>≥ 45%</td>
<td>Index HF hosp.</td>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Owan et al. (2017-2001)</td>
<td>Mayo Clinic Hospital USA.</td>
<td>2167</td>
<td>≥ 50%</td>
<td>Index HF hosp. + ECHO in ≤30 days</td>
<td></td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Bhatia et al. (1999-2001)</td>
<td>103 hospitals. Canada.</td>
<td>880</td>
<td>&gt; 50%</td>
<td>Index HF hosp.</td>
<td></td>
<td>1</td>
<td>22.2</td>
</tr>
<tr>
<td><strong>Randomized Clinical Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-PRESERVE (2002-2005)</td>
<td>25 Countries. Europe, USA, South Africa &amp; Australia</td>
<td>4128</td>
<td>≥ 45%</td>
<td>≥ 60 yrs NYHA ≥ II HF hosp. ≤ 6 mths</td>
<td>SBP &lt;100 or &gt;160mmHg. DBP &gt;95mmHg. Hb&lt;11g/dL.</td>
<td>4</td>
<td>5.20</td>
</tr>
<tr>
<td>DIG-PEF (1991-1993)</td>
<td>USA (186 centers) Canada (116 centers)</td>
<td>988</td>
<td>&gt; 45%</td>
<td>LVEF &gt;45% Sinus Rhythm at baseline</td>
<td>Cor pulmonale</td>
<td>3</td>
<td>7.6</td>
</tr>
<tr>
<td>CHARM-Preserved (1999-2000)</td>
<td>618 centers in 26 countries.</td>
<td>3022</td>
<td>&gt; 40%</td>
<td>≥18 years NYHA II-IV ≥6wks Previous hosp for cardiac reason ≥70 yrs 3 of 9 clinical symptoms + 2 of 4 ECHO parameters ≥ 60 yrs NYHA ≥II</td>
<td>Persistent systolic or diastolic hypertension</td>
<td>3</td>
<td>5.00</td>
</tr>
<tr>
<td>PEP-CHF (2000-2003)</td>
<td>53 centers in 8 countries.</td>
<td>846</td>
<td>&gt; 40%</td>
<td></td>
<td>Significant valve disease Stroke history.</td>
<td>2.2</td>
<td>5.90</td>
</tr>
<tr>
<td>TIME-CHF (2004)</td>
<td>15 hospitals. Switzerland &amp; Germany.</td>
<td>123</td>
<td>&gt; 45%</td>
<td>Hx HF hosp. ≤1 yr NT-proBNP level ≥2UL of norm.</td>
<td></td>
<td>1.5</td>
<td>14</td>
</tr>
<tr>
<td><strong>National Heart Failure Registries</strong></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Heart Failure Survey in Israel (HFSIS) (2003)</td>
<td>25 hospitals. Israel.</td>
<td>1364</td>
<td>≥ 40%</td>
<td>Clinical dx of HF Confirmed by ECHO &amp; radiography.</td>
<td></td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) (2009)</td>
<td>164 hospitals. Japan.</td>
<td>429</td>
<td>≥ 50%</td>
<td>HF as primary cause of hosp.</td>
<td></td>
<td>2.4</td>
<td>11.60</td>
</tr>
</tbody>
</table>

New York Heart Association Classification; UL – upper limit.
146 (95% CI: 138, 154) deaths per 1000 patient-years in non-RCTs alone; and 101 (95% CI: 96, 107) deaths per 1000 patient-years in the RCTs alone. In aggregate, it is clear that the mortality burden of HFPEF is substantial regardless of setting, but has been reported to be higher in ‘real world’ compared to clinical trial settings.

**Effect of hospitalization**

Studies have also examined short- and long-term mortality rates following hospitalization for HFPEF. In-hospital mortality rates have ranged from 2.5-6.5% with similar or lower risks compared to HFREF. Short-term mortality ranged from 30-day rates of 5.3%, 60- to 90-day rates of 9.5% and 6-month rates of 14.2-16%. Published long-term 5-year mortality rates varied from 22-65%.

The over-riding message from these studies is that the mortality rate in hospitalized HFPEF is high. There appears to be similar mortality rates between HFPEF versus HFREF up to 6 months following hospitalization, after which HFPEF patients may display a better survival probability.

**Comparison to HFREF**

Reported mortality rates in comparison with HFREF are strongly influenced by the type of study from which mortality data are derived. Epidemiologic community-based studies demonstrated similar prognosis between both patient groups, whereas a meta-analysis inclusive of RCTs showed ~32% higher survival in HFPEF than HFREF (pooled hazards ratio 0.68; 95% CI: 0.64, 0.71). Of note, there was a highly significant interaction between type of HF (HFPEF versus HFREF) and the type of study (RCT versus non-RCT) on risk of death, where survival was ~39% higher in HFPEF than HFREF in the RCTs, but only ~24% higher in HFPEF than HFREF in the non-RCTs. Interestingly, the mortality gap between HFPEF and HFREF appeared to be diminished among the very elderly.

**Comparison to age- and comorbidity- matched patients**

The lower mortality of HFPEF compared to “conventional” heart failure (i.e. HFREF) in controlled trials, presence of multiple age-
related comorbidities, and non-specificity of symptoms of HFPEF, have given rise to two controversies: Firstly, do patients enrolled in HFPEF trials truly have the syndrome of HFPEF, or are they misdiagnosed cases (of, for example, lung disease, obesity or myocardial ischemia)? Secondly, is HFPEF a distinct disease entity, or does it merely represent a collection of comorbidities in an elderly breathless patient? The potential for misdiagnosis of HFPEF is clinically relevant and an important consideration particularly in earlier trials such as CHARM-Preserved, where patients were enrolled solely on the basis of symptoms and signs of HF (and normal EF), with or without a history of recent HF hospitalization, and in the absence of additional echocardiographic or biomarker criteria. In fact, Caruana et al. showed that alternative non-HF diagnoses were available that could explain patients’ symptoms and signs in the majority of cases in their cohort of suspected HFPEF from general practice.

A misdiagnosis of HFPEF would be expected to contribute to a lower proportion of cardiovascular deaths. However, when Campbell et al. compared mortality in patients from RCTs of HFPEF (including CHARM-Preserved, DIG-PEF and I-PRESERVE) to patients with similar age, gender and comorbidity distribution in other cardiovascular trials of hypertension (ALLHAT, LIFE, ANBP-2, VALUE and HYVET), coronary heart disease (ACTION) and diabetes mellitus (ACCORD), patients with HFPEF were found to have a significantly higher proportion of cardiovascular deaths compared to non-HFPEF patients. Furthermore, overall mortality rates were found to be strikingly higher in HFPEF trial patients (53-76 per 1000 patient-years) compared to non-HFPEF trial patients (11-47 per 1000 patient-years), despite a lower comorbidity burden in HFPEF than non-HFPEF trial patients. Thus, even acknowledging the potential for misdiagnosis, the substantially worse prognosis of patients with HFPEF compared to patients with hypertension and other cardiovascular risk factors but without HF, suggests that HFPEF is not merely about old age and comorbidities; instead, HFPEF is an entity in itself that identifies patients at an elevated risk of death.

In the community-based setting, Mohammed et al. compared survival, as well as cardiovascular parameters adjusted for comorbidities
and scaled for body size and age, in patients with HFPEF, age-/gender-matched healthy controls and hypertensive controls without heart failure. While each comorbidity was associated with a unique ventricular-vascular profile and impacted survival in HFPEF, the presence of HFPEF itself was associated with further cardiovascular changes that could not be accounted for by comorbidities alone. These findings thus supported the conclusion that HFPEF was a distinct disease rather than an amalgamation of comorbidities, and provided a basis to understand the worse survival in patients with HFPEF compared to age- and comorbidity-matched patients without heart failure.

HOW DO PATIENTS WITH HFPEF DIE?

Importance of defining how patients with HFPEF die

Although several studies have examined outcomes in HFPEF, few have reported specific causes or modes of death. Why is it important to drill down to specifics? As discussed above, multiple age-related comorbidities may co-exist in patients with HFPEF, and each comorbidity may impart a mortality risk. Knowledge of all-cause mortality alone will not allow discernment of risk related to the comorbidity versus risk associated with HFPEF itself. Knowledge of cause-specific mortality, on the other hand, will aid our understanding of the pathophysiology and natural history of HFPEF as a distinct syndrome, and allow better discernment of risk that may be prevented or treated, versus that which cannot. This knowledge then forms the basis for planning and predicting the impact of interventional strategies. Take for instance a patient with HFPEF who suffers an acute myocardial infarction (cause of death [COD]) leading to sudden death (mode of death [MOD]), versus one with severe infective exacerbation of concomitant chronic lung disease (COD) leading to respiratory collapse (MOD). An intervention such as an implantable cardiac defibrillator would be expected to prevent death in the former, but not the latter, and knowledge of the relative proportions of deaths from each cause/mode in HFPEF would guide decisions on whether defibrillators should be considered or tested as a therapeutic strategy in this patient population.
Challenges in the classification of death in HFPEF
Comprehensive clinical data are needed for the accurate classification of death in HFPEF. A previously published ACME system for death in heart failure is a useful guideline for the extent of information required to draw meaningful inferences: 25A for activity and place of death (outpatient or in-hospital), C for COD (e.g. myocardial infarction, ventricular dysfunction or pneumonia), M for MOD (e.g. sudden death or circulatory failure) and E for events associated with death (e.g. recent hospitalizations or de-compensations). Without a priori planning, such detailed information is rarely available to allow accurate classification of death.

CODs are more commonly reported in epidemiologic studies, where data are extracted from death certificates, medical records and autopsy findings. Reliability of the data is increased when death ascertainment is carried out by autopsy findings or a chief medical examiner; however this is available on a large scale in only few communities. MODs are more readily available in RCTs, where there is regular surveillance and formal adjudication of deaths by appointed outcome review committees using pre-specified criteria.

There is a lack of uniformity in definitions used to classify deaths in HFPEF in previous publications. To illustrate, mortal events have been grouped under subheadings of sudden death (MOD) and acute myocardial infarction (COD) within the same table, without distinguishing MOD versus COD. Some other studies have also reported events according to the underlying versus immediate causes of death, rather than COD and MOD.

Cardiovascular versus non-cardiovascular deaths in HFPEF
Notwithstanding the variability of definitions used in different studies, the following conclusions can be derived from published outcomes studies in HFPEF (Figure 1): Firstly, the majority of deaths in HFPEF across all studies are cardiovascular deaths. Secondly, the proportion of cardiovascular deaths varies with the type of study, ranging from 51-60% in epidemiologic studies, to ~70% in RCTs. The only exception was the study by Adabag et al.29 of HF hospitalizations in Minneapolis-St Paul, where 5-year post discharge mortality in HFPEF was classified
based on death certificates as non-cardiovascular deaths in 61% of cases. Lack of autopsy data and selection bias due to large numbers of missing EF data, may have influenced these results. Nonetheless, the higher proportion of non-cardiovascular deaths in this observational study is consistent with the trend for more non-cardiovascular deaths in epidemiologic studies, compared to RCTs in HFPEF.

**MOD in HFPEF**

Specific MODs in HFPEF have been examined in the CHARM-Preserved and I-PRESERVE clinical trials (Figure 2).27, 30 Despite some differences in the populations studied, remarkable consistency was observed in MODs reported: Among the ~70% majority of cardiovascular deaths, sudden death was the commonest cardiac MOD (26-28% of all deaths), followed by heart failure deaths (14-21% of all deaths).

**COD in HFPEF**

In epidemiologic studies, CODs are described, albeit inconsistently. Data from the large Olmsted County cohort, where COD was ascertained from death certificates, >75% of which were completed by coroner or Mayo staff, showed that the predominant single COD in this study was non-cardiovascular death. However, cardiovascular CODs as a group were more common than non-cardiovascular death, and the
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**Figure 2. Distribution of modes of death in HFPEF clinical trials** Numbers represent % of total deaths (left pie charts) and % of total cardiovascular deaths (right pie charts). The pie charts display the modes of death for patients from the I-PRESERVE trial30 (Top) and CHARM-Preserved trial27 (Bottom). Pie charts on the left display the proportion of cardiovascular (CV), non-cardiovascular (non-CV) and unknown deaths with respective % of total death. Further breakdown of cardiovascular deaths into sudden cardiac death, heart failure deaths, stroke, myocardial infarction and other cardiovascular deaths are shown in a separate pie chart on the right with respective % of cardiovascular death displayed.

The most prominent cardiovascular COD was coronary heart disease (29% of all deaths).26

**COD versus MOD in HFPEF**

Both COD and MOD were specifically reported and directly compared in the recent TIME-CHF study, where outcomes were classified according to the ACME criteria after an 18-month follow-up.19 Analysis of COD versus MOD in TIME-CHF showed differences in the proportions of cardiovascular-related events when classified by COD (≈40%) versus MOD (≈66%) (Figure 3). Careful inspection of the data revealed that this difference was primarily attributed to a larger proportion of “unknown” assignments for COD, with less “unknown” and more frequent
assignment of “cardiovascular” for MOD, and otherwise comparable classification of non-cardiovascular events by COD or MOD. These results highlight the challenges in classification of death, the limitations of comparisons across studies using different methods, and provide a possible source of discordance between observational studies (mainly reporting COD) and clinical outcome trials (mainly reporting MOD).

Classification of death in HFPEF versus HFREF

Cardiovascular deaths constitute the majority of deaths in both HFPEF and HFREF (Figure 4). However, the proportion of total deaths that are cardiovascular-related is higher in HFREF than HFPEF, whether considering data from RCTs (~80% versus ~70%),27,30 or community-based studies (~60% versus ~50%).26, 29, 31 Conversely, non-cardiovascular deaths constitute a larger proportion of deaths in HFPEF than HFREF (~30% versus ~15% from RCTs; ~50% versus ~30% in community-based studies).

Specific MODs differ in their distribution between HFPEF and HFREF (Table 2). Sudden death and heart failure deaths constitute a larger proportion of deaths in HFREF compared to HFPEF. In fact, the leading single MOD in HFREF RCTs was sudden death (~42%),
whereas that in HFPEF was non-cardiovascular death (~30%) followed closely by sudden death (26-28%). In epidemiologic studies from Olmsted County, the proportion of deaths attributed to coronary heart deaths was larger in HFREF (43%) than HFPEF (29%). Of note, the lower proportion of coronary heart deaths in HFPEF appeared to account for the lower proportion of cardiovascular deaths, or the higher proportion of non-cardiovascular deaths, in HFPEF compared to HFREF. The Olmsted County study also showed that the proportion of cardiovascular deaths decreased from 69% in 1979–1984 to 40% in 1997–2002 (P=0.007) in HFPEF, in contrast to a modest trend in HFREF (77% to 64%, P=0.08). These observations raise the intriguing notion that HFPEF patients may be increasingly spared of coronary deaths, only to eventually succumb to non-cardiovascular deaths. The role of coronary artery disease as a risk factor for death is discussed in further detail later.

In summary, cardiovascular-related deaths comprise the majority of mortality events in HFPEF patients, with greater predominance seen in RCTs compared to epidemiologic studies. Among cardiovascular deaths, sudden death and heart failure death are the leading cardiac MODs in HFPEF clinical trials. Compared to HFREF, the proportions
of cardiovascular deaths, sudden death and heart failure deaths are lower in HFPEF. Conversely, non-cardiovascular deaths constitute a higher proportion of deaths in HFPEF than HFREF, particularly in epidemiologic studies, where this difference appears to be primarily related to fewer coronary heart deaths in HFPEF.

**WHAT ARE THE RISK FACTORS FOR DEATH IN HFPEF?**

Multiple variables are associated with survival in HFPEF. Key risk factors include age, gender, body mass index, burden of comorbidities and coronary artery disease.

**Age**

Increasing age is associated with higher mortality in HFPEF, in a variety of clinical settings. Increasing age is also associated with higher burden of cardiovascular comorbidities in HFPEF (ischemic heart disease, hypertension, diabetes and atrial fibrillation), at least up to the seventh decade. While age-associated comorbidities confound the risk of death in HFPEF, age alone remains independently predictive of...
mortality. The TIME-CHF study, which included the oldest cohort of HFPEF to date (mean age 80 years), showed that the increase in mortality with age applies even to those ≥75 years compared to those 60-74 years of age. This study further showed that MODs were similar in the 2 age groups, which goes against the perception that greater age-associated non-cardiac comorbidity burden may lead to more non-cardiac deaths in the very elderly.

**Sex**

Women have consistently been shown to have better survival than men with HFPEF. This advantage is observed in both epidemiologic studies and RCTs, all of which analysed long-term follow-up data for at least 2 years. Interestingly, short-term survival odds appear to be non-discriminatory between the sexes, as demonstrated in the Get With The Guidelines-Heart Failure multi-centered registry. This study found similar risks of in-hospital mortality in both sexes, and extends previous findings of similar risks in short-term outcomes for both groups up till 6 months, after which women displayed better survival probabilities. Although it has been postulated that the premise for better survival in women is due to a lower proportion of heart failure with ischemic origins or a higher LVEF in this group, a recent study comprising of a larger HFPEF population has shown no interaction between LVEF or heart failure etiology with outcomes. In the large I-PRESERVE HFPEF trial (60% women), the lower risk of death in women was shown to apply not only to all-cause deaths, but also to both cardiovascular and non-cardiovascular deaths. The latter runs contrary to the hypothesis that women with HFPEF, being older than men with HFPEF, may have more non-cardiac comorbidities contributing to more non-cardiovascular deaths. Most notably, the I-PRESERVE study showed that the association between sex and mortality risk was significantly modified by 4 risk factors (atrial fibrillation, renal dysfunction, angina, New York Heart Association [NYHA] status), such that the sex difference was ameliorated in the presence of atrial fibrillation or renal dysfunction, or in the absence of angina or NYHA class ≥3 symptoms.
Obesity
The obesity paradox refers to a U-shape relationship of body mass index (BMI) with mortality, with highest hazards in groups with the lowest and highest BMI. Although earlier studies of BMI in undifferentiated heart failure showed increased risk only with lower BMI, the U-shape relationship was observed in recent studies of chronic heart failure patients and specifically, the HFPEF population. In I-PRESERVE, BMI at extreme quintiles of <23.5kg/m² and ≥35kg/m² were associated with increased risk of the primary composite outcome (death or cardiovascular hospitalization), as well as all-cause deaths alone. Mortality risk was highest in the lowest BMI quintile. The association between BMI and mortality risk varied with the MOD: heart failure deaths demonstrated the U-shape relationship with BMI, whereas the rates of both sudden death and non-cardiovascular death declined linearly with increasing BMI. Heart failure-related inflammation, stress hormone activation and excessive catabolism leading to muscle wasting may explain the excess heart failure mortality in the lowest BMI group. Greater metabolic reserve and lipoprotein pools to neutralize circulating lipopolysaccharide endotoxins may explain the lower sudden death and non-cardiovascular death in more obese patients, but does not explain the higher heart failure mortality in the severely obese.

![Figure 5. Inverse relationship between prevalence of coronary artery disease and % non-cardiovascular deaths](image-url)

Comparison of baseline burden of coronary artery disease and % of non-cardiovascular related deaths (% total deaths) from similar HF populations (Olmsted and TIME-CHF) shows an inverse relationship regardless of LVEF.
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Non-cardiac comorbidities
Since HFPEF is a disease syndrome of the elderly, age-associated non-cardiac comorbidities are highly prevalent in these patients. A greater comorbidity burden, indexed by the Charlson score, is known to be associated with reduced short- and long-term survival in heart failure regardless of LVEF. 19, 46 Specifically in HFPEF, non-cardiac comorbidities have been shown to be related to increased incidence of future HFPEF, 47 reduced functional status, 48 and increased risk of hospitalizations. 4 In fact, compared to HFREF, non-cardiac comorbidities were found to impact functional status to a greater extent in HFPEF, 48 and to potentially account for more non-heart failure hospitalizations in HFPEF than HFREF. 49 A greater non-cardiac comorbidity burden in HFPEF, particularly in community-based HFPEF, offers a potentially simple explanation for the mortality differences between epidemiologic studies and RCTs, or between HFPEF and HFREF. However, the extent to which non-cardiac comorbidities predict death in HFPEF remains unclear, and non-cardiac comorbidities alone do not explain mortality differences between different heart failure cohorts. For example, in Olmsted County, the burden of non-cardiac comorbidities was similar between HFPEF and HFREF groups, yet % non-cardiovascular deaths was higher in the former. 26 Nonetheless, recent mortality risk scores in HFPEF have attempted to quantify the risk associated with non-cardiac factors in HFPEF. 32, 50 While more research is needed to fully define this risk, it is clear that attention must be paid to non-cardiac comorbidities in the optimal management of HFPEF.

Coronary artery disease
Coronary artery disease plays an important role in the pathophysiology of HFPEF, 51 and coronary heart deaths constitute the chief cardiovascular COD in HFPEF from epidemiologic studies. 26 Whereas differences in prevalence of non-cardiac comorbidities do not fully account for the contrasting burden of non-cardiovascular deaths between cohorts, the extent of coronary artery disease appears to be inversely related to the the burden of non-cardiovascular deaths in different heart failure cohorts. Using the Olmsted County community-based cohort and the RCT population from TIME-CHF as representative studies investigating
COD in both HFPEF and HFREF, a lower baseline proportion of coronary artery disease was related to a higher proportion of non-cardiovascular deaths, in both study designs and HF groups (Figure 5). A potential explanation for these observations is that patients with HFPEF “escape” coronary heart deaths, only to subsequently die from their non-cardiac comorbidities. Alternatively, patients with coronary artery disease may have been more likely to “transition” to HFREF following their myocardial infarctions, thus enriching the HFREF population eventually with more coronary heart deaths. Indeed, a recent study of longitudinal changes in LVEF over time in patients with heart failure showed that coronary artery disease was a major determinant of change in LVEF: over 5 years, ~39% of HFPEF patients transitioned to HFREF (LVEF<50%), whereas a similar % of HFREF transitioned to HFPEF (LVEF≥50%). The presence of coronary artery disease was associated with greater reduction of LVEF in HFPEF, and conversely, the absence of coronary artery disease was associated with a greater improvement of LVEF in HFREF.

CONCLUSION
Our review of how patients with HFPEF die provides the following insights: The mortality burden of HFPEF is substantial, ranging from 10-30% annually, and higher in epidemiologic studies than clinical trials. Mortality rates compared to HFREF appear strongly influenced by the type of study, but are clearly elevated compared to age- and comorbidity-matched controls without heart failure. The majority of deaths in HFPEF are cardiovascular deaths, comprising 51-60% of deaths in epidemiologic studies, and ~70% in clinical trials. Among cardiovascular deaths, sudden death and heart failure death are the leading cardiac modes of death in HFPEF clinical trials. Compared to HFREF, the proportions of cardiovascular deaths, sudden death and heart failure deaths are lower in HFPEF. Conversely, non-cardiovascular deaths constitute a higher proportion of deaths in HFPEF than HFREF, particularly in epidemiologic studies, where this difference may be related to fewer coronary heart deaths in HFPEF. Other key mortality risk factors include age, gender, body mass index, and burden of comorbidities. These prior studies provide some guidance for better
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prediction of response to therapy in designing clinical trials, but also highlight the urgent need for more consistent reporting of COD/MOD in future studies.

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