

EDITORIAL COMMENT

Understanding Heart Failure With Mid-Range Ejection Fraction*



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Heat failure (HF) with borderline or mid-range ejection fraction (HFmEF; $40\% \leq EF < 50\%$), the previously neglected “middle child of HF” (1), is increasingly receiving attention along with its famous older sibling, HF with reduced EF (HFrEF; $EF < 40\%$), and the favored baby of the HF family, HF with preserved EF (HFpEF; $EF \geq 50\%$). Prior knowledge on HFmEF was limited to a handful of studies (2-4), which collectively estimated the prevalence of HFmEF at 10% to 20% of the HF population and showed that the clinical, echocardiographic, hemodynamic, and circulating biomarker characteristics of HFmEF were intermediate between HFrEF and HFpEF. However, although addressing HFmEF, the prior studies also highlighted the large knowledge gap in the understanding of distinguishing features, triggers, prognosis, and response to therapy in HFmEF.

The Get With The Guidelines-HF (GWTG-HF) registry of hospitalized HF has helped to fill this gap by providing the largest cohort to date characterizing HFmEF (5,6). In this issue of *JACC: Heart Failure*, Kapoor et al. (6) describe 99,825 patients hospitalized for HF from 305 hospitals across all

census regions of the United States between 2005 and 2013, of whom 48,950 (49%) had HFrEF, 12,819 (13%) had HFmEF, and 38,056 (38%) had HFpEF. Beyond

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baseline characteristics, the study uniquely investigated precipitating factors for hospitalization among the 3 HF groups, and how these precipitants influenced in-hospital outcomes. Overall, the most common precipitants for HF hospitalization (regardless of EF group) were pneumonia/respiratory process (28%), arrhythmia (22%), medication noncompliance (16%), worsening renal failure (15%), and uncontrolled hypertension (15%). Furthermore, in all HF groups, pneumonia was independently associated with longer hospital stays and higher in-hospital mortality, increasing the adjusted odds for in-hospital death by 48% to 61%. The high frequency and potent prognostic impact of precipitating factors, observed in the unselected real world setting of GWTG-HF, provide support for guideline recommendations to identify and treat these factors in patients hospitalized for HF. In particular, the results underscore the importance of targeting pneumonia. Extending from this, Medicare data have demonstrated the major public health burden of rehospitalizations following both HF and pneumonia (7). Although the study did not provide long-term follow-up or interventional outcomes, others have shown that influenza is a trigger for HF exacerbations and contributes to long-term cardiovascular risk, and that this risk may be reduced via influenza vaccination (8). Prospective, adequately powered outcomes trials of influenza or pneumococcal vaccination in HF are warranted.

The Kapoor et al. (6) study provided unprecedented power to characterize HFmEF, compared with HFrEF and HFpEF. Patients with HFmEF were older (median age, 77 years) and more likely female (49%)

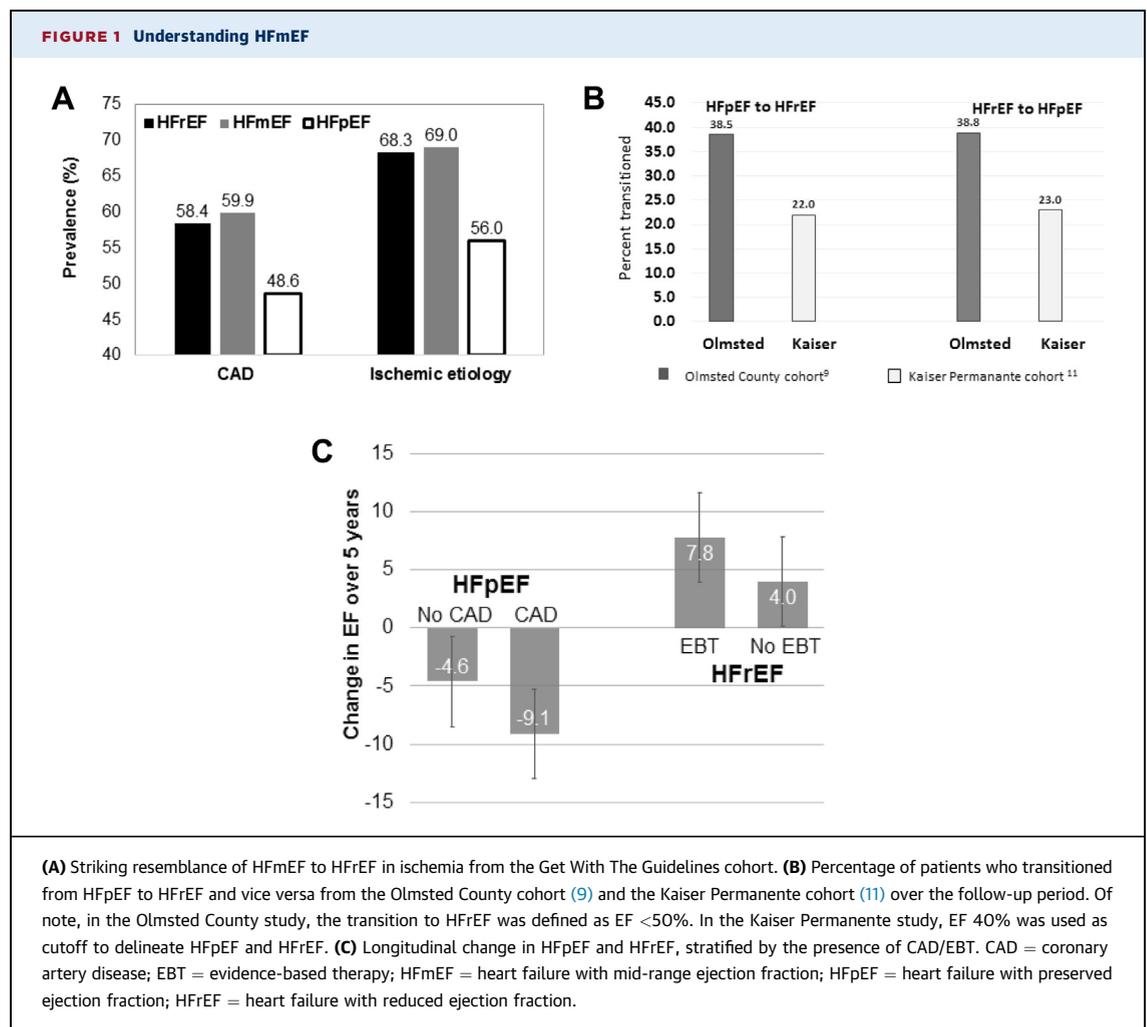
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compared with HFrEF (median age, 72 years; 37% women), thus resembling HFpEF (median age, 78 years; 65% women). Furthermore, there was a high comorbidity burden in HFmEF (diabetes in 50%, atrial fibrillation in 42%, chronic obstructive pulmonary disease in 36%, anemia in 27%, and renal insufficiency in 26%), which was higher than in HFrEF and similar to HFpEF. Yet, in sharp contrast to HFpEF, there was a strikingly high prevalence of ischemic history/etiology in greater than two-thirds of HFmEF, similar to HFrEF. Consistently, the precipitants for HFmEF hospitalization resembled those of HFpEF except for ischemia, which was almost twice as common in HFmEF (10%) and HFrEF (11%) compared with HFpEF (6%) (**Figure 1**).

In essence HFmEF seems to resemble HFpEF with the key exceptional characteristic of ischemia, in which it resembles HFrEF (**Figure 1A**). This brings up the question of whether some patients with HFmEF were those with coronary disease “caught in

transition” between HFrEF and HFpEF (i.e., representing either recovering EF following anti-ischemic therapy, or deteriorating EF following an ischemic event. Longitudinal data on EF changes over time were not available in GWTG-HF, but studied in Olmsted County, Minnesota, where EF decreased by ~6% over 5 years in HFpEF, with greater declines in older individuals and those with coronary disease; conversely, EF increased by ~7% over 5 years in HFrEF, with greater increases among women and those treated with evidence-based medications (**Figures 1B and 1C**) (9). Furthermore, among patients with HFpEF undergoing coronary angiography, it was only in patients with coronary disease that there was deterioration in EF (10). Similarly, longitudinal data from Kaiser Permanente Colorado showed that transition from HFpEF to HFrEF over time was more likely in patients with a prior myocardial infarction, whereas transition from HFrEF to HFpEF was more likely in women and those adherent to β -blockers (11).



The significance of recognizing that some or most patients with HFmEF are indeed those “in transition” with coronary disease lies in the fact that they may be expected to respond to evidence-based anti-ischemic therapies. Although not tested in the current study, data are emerging to suggest this may be the case: a subanalysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial showed that EF modified the spironolactone treatment effect, with patients at the lower end of the EF spectrum (EF 44% to 50% [i.e., those with HFmEF]) showing greater potential benefit of spironolactone with respect to the primary outcome and HF hospitalization, compared with those with higher EF (12). In fact, the hazard ratios for the primary outcome, cardiovascular death, and HF hospitalization in the HFmEF subgroup of TOPCAT were similar to that observed in the post-myocardial infarction HFrEF trials with mineralocorticoid antagonists (13). Similarly, subanalyses from CHARM (Candesartan in Heart Failure Reduction in Mortality)-preserved also revealed that patients with HFmEF had greater benefit from candesartan than those with HFpEF (14).

Importantly, previously mentioned considerations do not exclude a role of coronary disease or ischemia in HFpEF. In the prior study from Olmsted County, the presence of angiographically proven epicardial coronary disease was associated with worse survival in HFpEF; and complete revascularization attenuated both the decline in EF and prognostic impact of coronary disease (10). In the current study from GWTG-HF, ischemia at presentation was associated with >70% higher adjusted odds of in-hospital mortality in HFpEF. We are unable to determine if the prognostic impact of ischemia differed among EF groups because formal statistical tests for interaction by EF were not performed. Although some differences in determinants of length of stay and

in-hospital mortality were found in analyses stratified by EF group, the absolute differences were small (median, 25th, and 75th percentile for length of stay was 4, 3, and 7 days in all 3 EF groups; in-hospital mortality rate varied from 2.62% to 3.06% among groups), and their clinical significance remains uncertain (despite strong statistical significance caused by large sample sizes). The contribution of under-detection of ischemic heart disease in HFpEF is unknown, especially because microvascular ischemia (as opposed to macrovascular epicardial coronary disease) is increasingly recognized to play a key role in HFpEF, arising from comorbidity-induced inflammatory endothelial activation and microvascular rarefaction (15-17).

The understanding of each of the HF family members, and particularly the middle child HFmEF, has been deepened by the work of Kapoor et al. (6) in GWTG-HF. Although generalizability to the entire universe of HF across other geographic and nonacute settings may not be possible, these are the largest most comprehensive real-world data to date. A call for larger prospective randomized clinical trials in HFmEF is easier said than done; prior attempts at a targeted approach in HFmEF failed because of difficulties in recruiting adequate numbers of patients (1). It is therefore wise to take heed from the current registry observations and subgroup analyses from prior large clinical trials that included HF across the spectrum of EF groups (12,14) and recognize that HFmEF may look like HFpEF except for strong features of ischemia, although potentially behaving like ischemic HFrEF in response to standard anti-ischemic therapy.

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