

STATE-OF-THE-ART REVIEW

Heart Failure With Mid-Range (Borderline) Ejection Fraction

Clinical Implications and Future Directions

Jeffrey J. Hsu, MD,^a Boback Ziaeeian, MD, PhD,^{a,b} Gregg C. Fonarow, MD^{a,c}

ABSTRACT

Heart failure (HF) with borderline ejection fraction was first defined in 2013 in the American College of Cardiology/American Heart Association guidelines as the presence of the typical symptoms of HF and a left ventricular ejection fraction (LVEF) of 41% to 49%. In 2016, the European Society of Cardiology specified HF with mid-range ejection fraction (HFmrEF) as LVEF of 40% to 49%. This range of LVEF is less well studied compared with HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). Although there are effective, guideline-directed medical therapies for patients with HFrEF, no therapies thus far show measurable benefit in HFpEF. Patients with HFmrEF have a clinical profile and prognosis that are closer to those of patients with HFpEF than those of HFrEF, with certain distinctions. Whether these patients represent a unique and dynamic HF group that may benefit from targeted therapies known to be beneficial in patients with HFrEF, such as neurohormonal blockade, requires further study. This review summarizes what is known about the clinical epidemiology, pathophysiology, and prognosis for patients with HFmrEF and how these features compare with the more well-studied HF groups. Although recommended treatments currently focus on aggressive management of comorbidities, we summarize the studies that identify a potential signal for beneficial therapies. Future studies are needed to not only better characterize the HFmrEF population but to also determine effective management strategies to reduce the high cardiovascular morbidity and mortality burden on this phenotype of patients with HF. (J Am Coll Cardiol HF 2017;■:■-■) © 2017 by the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

The modern management of heart failure (HF) is predominantly guided by objective assessments of left ventricular ejection fraction (LVEF), which has been shown to be predictive of adverse outcomes even in the absence of symptomatic HF (1). Historically, patients with HF have been categorized into 2 groups based on their LVEF: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). This distinction has been important in HF management because of the different demographic characteristics, etiologies, and comorbidities between

the 2 groups (2). More importantly, numerous clinical trials have shown that these groups differ in their response to therapies; although a number of medical and device therapies are proven to reduce morbidity and mortality in patients with HFrEF, there have been no therapies thus far that have been proven to improve these outcomes in patients with HFpEF (3).

As the field has steadily characterized important differences between these categories of HF over the years, there has been substantial variability in the LVEF ranges used to define patients with reduced and preserved EF. Studies using data from the

From the ^aDivision of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, California; ^bDivision of Cardiology, Veteran Affairs Greater Los Angeles Healthcare System, Los Angeles, California; and the ^cAhmanson-UCLA Cardiomyopathy Center, University of California, Los Angeles Medical Center, Los Angeles, California. Dr. Fonarow has received research funds from the National Institutes of Health; and consulting fees from Amgen, Janssen, Medtronic, Novartis, and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ABBREVIATIONS
AND ACRONYMS****ACCF** = American College of Cardiology Foundation**AHA** = American Heart Association**ARB** = angiotensin receptor blocker**BNP** = B-type natriuretic peptide**CAD** = coronary artery disease**COPD** = chronic obstructive pulmonary disease**DM** = diabetes mellitus**ESC** = European Society of Cardiology**GWTG-HF** = Get With The Guidelines-Heart Failure**HF** = heart failure**HFmrEF** = heart failure with mid-range ejection fraction**HFpEF** = heart failure with preserved ejection fraction**HFrEF** = heart failure with reduced ejection fraction**HR** = hazard ratio**LVEF** = left ventricular ejection fraction

OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) and the ADHERE (Acute Decompensated Heart Failure Registry) studies began to explore the characteristics, treatment patterns, and outcomes of patients with mildly reduced LVEF, suggesting these patients may have important distinctions from those patients with HFrEF and HFpEF (2,4). The most recent guidelines from the American Heart Association/American College of Cardiology Foundation (AHA/ACCF) and the European Society of Cardiology (ESC) have defined HFrEF as having symptoms and signs of HF with an LVEF <40%, whereas HFpEF is defined as HF with an LVEF \geq 50% (5,6). These definitions allow for a clearer distinction between the HFrEF and HFpEF groups based on LVEF, but in the process, they create an intermediate range of LVEF that has been less rigorously studied. Although the 2013 ACCF/AHA guidelines first classified this range of LVEF 41% to 49% as borderline HFpEF (5), the 2016 ESC guidelines have identified patients with HF and an LVEF 40% to 49% as having heart failure with mid-range ejection fraction (HFmrEF) (6).

Often considered a “gray” area or the “middle child” in HF (7), HFmrEF is gaining increasing attention in recent studies. Even though patients with HFmrEF have higher readmission rates than patients with HFpEF and mortality rates comparable to HFrEF and HFpEF (8), HFmrEF remains insufficiently characterized compared with the other groups. More importantly, therapies for patients with HFmrEF are unclear, as clinical trials have not directly targeted this sizeable HF population. Although much of the attention has been on HFpEF, with unsuccessful attempts at improving cardiovascular outcomes, HFmrEF may be a group primed to benefit from targeted therapies. The present review describes what is currently known about the HFmrEF population and discusses future directions to better understand and manage this vulnerable group of patients.

EPIDEMIOLOGY OF HFmrEF

PREVALENCE. More than 6.5 million people in the United States carry the diagnosis of HF and, with the aging of the population, this number will continue to rise (9). Based on recent studies, the percentage of the HF population that falls into the HFmrEF category is anywhere between 13% and 24% (10–12),

suggesting that approximately 1.6 million people in the United States have HFmrEF. Analysis of temporal trends in the Get With The Guidelines-Heart Failure (GWTG-HF) registry have found that although the percentage of patients with HFpEF has increased (from 33% to 39%) and the percentage with HFrEF has decreased (from 52% to 47%) from 2005 to 2010, the portion with HFmrEF has remained relatively steady (between 13% and 15%) over this period (13).

CLINICAL CHARACTERISTICS. Determining the true clinical profile of the HFmrEF population has been challenging, as this range of LVEF is only partially included (LVEF >45%) or fully excluded (LVEF >50%) in clinical trials for HFpEF. Nonetheless, insight gained from cohort and registry studies has helped to shed light on the clinical features of this group. In 2007, an analysis of 41,267 patients in OPTIMIZE-HF analyzed patients hospitalized with HF according to LVEF group, finding that the demographic characteristics, symptom profile, comorbidities, laboratory values, and short-term outcomes of patients with LVEF between 40% and 50% were closer to those of patients with HFpEF (2). These findings were consistent with a similar analysis performed on the ADHERE registry in 2008 comparing patients with LVEF 40% to 55% (4). More recently, a specific analysis of the HFmrEF population was performed in >40,000 Medicare patients hospitalized with HF in the GWTG-HF registry, in which 14% of patients with HF fell into the HFmrEF category (8). Comparing these patients versus those in the other HF categories, patients with HFmrEF had clinical characteristics that, although intermediate between those in the HFrEF and HFpEF groups, were more similar to those of the HFpEF cohort (Table 1). These characteristics include older age, female sex, comorbidities (hypertension, chronic obstructive pulmonary disease [COPD], and diabetes mellitus [DM]), laboratory values (creatinine, B-type natriuretic peptide [BNP], and troponin), and medication use (beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [ARBs]). Notably, the characteristic in which the HFmrEF population was more similar to the HFrEF population was the comorbidity of coronary artery disease (CAD) (8). These findings were consistent with the clinical profiles seen in other recent studies (11,14).

PATHOPHYSIOLOGY OF HFmrEF

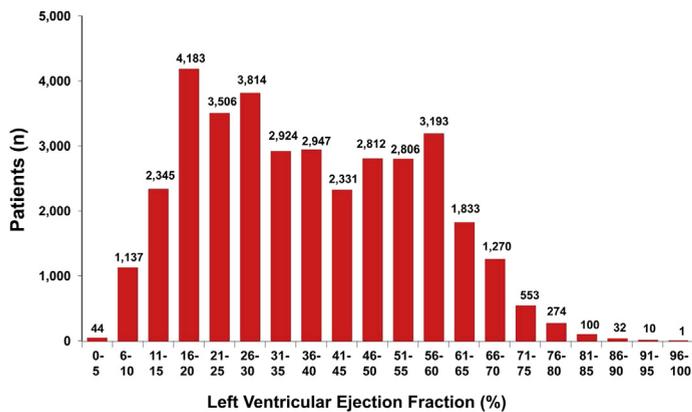
Studies suggest that HFrEF and HFpEF are distinct pathophysiological syndromes (15). HFrEF is generally characterized predominantly by systolic

TABLE 1 Clinical Characteristics of Patients With HFmrEF Compared With Those of Patients With HFrEF and HFpEF

	GWTG-HF (8)			OPTIMIZE-HF (2)			TIME-CHF (14)			CHART-2 (11)		
	HFrEF (n = 15,716)	HFmrEF (n = 5,626)	HFpEF (n = 18,897)	HFrEF (n = 20,118)	HFmrEF (n = 7,321)	HFpEF (n = 10,072)	HFrEF (n = 402)	HFmrEF (n = 108)	HFpEF (n = 112)	HFrEF (n = 730)	HFmrEF (n = 596)	HFpEF (n = 2,154)
Demographic characteristics												
Age, yrs	79.0	81.0	82.0	70.4	74.3	75.6	75.5	79.0	80.2	66.9	69.0	71.7
Male, %	60.0	49.5	32.7	62.0	48.0	32.0	67.4	53.7	28.0	76.7	71.8	60.8
BMI, kg/m ²	25.7	26.5	27.4	-	-	-	-	-	-	22.7	22.8	23.2
Comorbidities, %												
Atrial fibrillation	36.1*	40.2*	40.6*	28.0†	33.0†	32.0†	30.0	39.6	42.9	38.1	43.5	51.8
COPD	26.7‡	29.6‡	31.4‡	-	-	-	20.6	21.3	16.1	-	-	-
DM							33.6	39.8	39.3	38.1	36.1	33.8
Insulin treated	15.9	17.8	17.5	15.0	18.0	16.0	-	-	-	-	-	-
Non-insulin treated	23.4	23.7	23.1	24.0	26.0	25.0	-	-	-	-	-	-
Hypertlipidemia	48.1	48.2	45.3	34.0	35.0	31.0	52.2	48.1	36.6	82.2	80.2	78.8
Hypertension	73.1	77.9	81.3	66.0	74.0	77.0	68.9	82.4	85.7	84.7	89.8	91.2
Peripheral vascular disease	14.5	15.5	13.3	-	-	-	18.9	18.5	25.0	-	-	-
Coronary artery disease	58.0	56.7	44.9	-	-	-	73.9§	79.6§	63.4§	-	-	-
Previous MI	24.9	19.8	12.5	-	-	-	50.2	45.4	31.3	39.3	41.1	26.9
Previous PCI	-	-	-	-	-	-	15.4	15.7	8.0	29.2	34.5	26.0
Previous CABG	17.6	17.1	11.1	-	-	-	13.9	16.7	11.6	10.1	8.6	9.6
Stroke or TIA	15.8	17.1	17.4	-	-	-	14.9	15.7	18.8	18.9	22.1	21.9
Anemia	16.0	21.3	22.4	-	-	-	23.6	38.0	34.8	-	-	-
CKD							54.0	63.9	61.6	-	-	-
No dialysis	18.4	18.1	16.3	-	-	-	-	-	-	-	-	-
Dialysis	2.5	3.0	3.3	-	-	-	-	-	-	-	-	-
Depression	8.8	10.0	11.5	-	-	-	14.2	13.0	7.1	-	-	-
Smoking	11.2	8.7	7.6	-	-	-	63.5	60.2	41.1	-	-	-
Cancer	-	-	-	-	-	-	12.7	16.7	15.2	11.5	13.3	15.8
Laboratory values, mean												
Sodium, mEq/l	138.0	138.0	138.0	137.7	137.9	137.8	-	-	-	-	-	-
BUN, mg/dl	26.0	25.0	25.0	-	-	-	-	-	-	21.9	21.1	20.5
Creatinine, mg/dl	1.4	1.3	1.3	1.4	1.3	1.2	-	-	-	1.2	1.1	1.0
BNP, pg/ml	1,197.0	790.0	561.0	1,170.0	757.0	537.0	-	-	-	216.0	164.5	126.9
Hemoglobin, g/dl	12.2	11.7	11.5	12.5	11.9	11.8	-	-	-	13.4	13.0	12.8
Albumin, g/dl	3.4	3.4	3.4	-	-	-	-	-	-	4.0	3.9	4.0
Troponin, ng/dl	0.06	0.05	0.05	0.1	0.1	0.1	-	-	-	-	-	-
HbA _{1c} , %	6.9	6.8	6.7	-	-	-	-	-	-	-	-	-
Medications, %												
ACE inhibitors	40.3	35.6	31.8	45.0	38.0	34.0	95.5	90.7	86.6	57.7	51.0	42.2
ARB	14.6	16.2	17.4	11.0	12.0	14.0	-	-	-	26.7	29.0	34.1
Beta-blocker	46.9	45.5	45.3	56.0	54.0	50.0	79.4	79.0	78.0	69.6	63.8	46.4
Aldosterone antagonist	11.7	6.8	5.4	10.0	6.0	4.0	42.5	33.3	25.0	43.7	29.3	19.4
Nitrate	19.0	18.8	15.4	22.0	23.0	20.0	27.9	32.4	33.0	-	-	-
Hydralazine	5.3	4.9	5.6	3.0	3.0	3.0	-	-	-	-	-	-
Digoxin	20.9	14.5	12.8	30.0	19.0	15.0	21.1	13.9	12.5	-	-	-
Loop diuretic	61.4	57.8	57.0	63.0	59.0	57.0	93.5	89.8	91.1	76.2¶	63.3¶	52.2¶
Antiarrhythmic	11.4	9.0	7.6	13.0	10.0	8.0	-	-	-	-	-	-
Aspirin	50.4	47.2	43.4	42.0	41.0	36.0	-	-	-	-	-	-
Calcium channel blocker	12.2	20.7	29.2	5.0#	9.0#	11.0#	-	-	-	18.1	27.0	44.2
Statin	48.5	48.1	43.4	40.0	41.0	37.0	-	-	-	38.8	39.6	33.4

Values are n. *Italicized* numbers denote median values. *Atrial fibrillation or flutter. †Atrial arrhythmias. ‡Chronic obstructive pulmonary disease (COPD) or asthma. §Atherosclerosis. ||Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). ¶Any diuretic. #Amlodipine.

BMI = body mass index; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; CHART-2 = Chronic Heart Failure Analysis and Registry in the Tohoku District-2; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; GWTG-HF = Get With The Guidelines-Heart Failure Registry; HbA_{1c} = glycosylated hemoglobin; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; TIME-CHF = Trial of Intensified Versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure.

FIGURE 1 Distribution of LVEF in the OPTIMIZE-HF Study

A modest bimodal distribution of left ventricular ejection fraction (LVEF) was observed among patients hospitalized for heart failure. OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure. Reprinted with permission from Fonarow et al. (2).

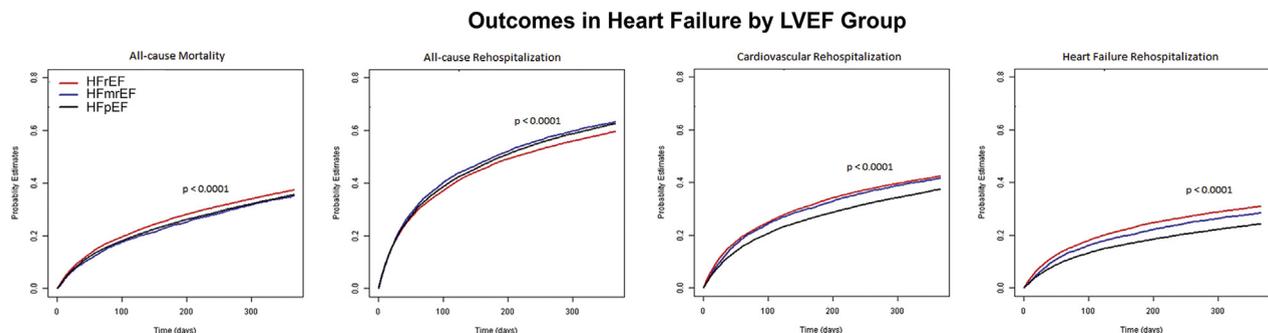
dysfunction and HFpEF by diastolic dysfunction, although varying degrees of overlap are often seen. Indeed, in the OPTIMIZE-HF study (2) as well as in others (16), there was a modest bimodal distribution of LVEF among patients hospitalized for HF (Figure 1), suggesting 2 distinct disease processes. However, as with HFpEF, the underlying pathophysiology of HFmrEF is not entirely clear. The ESC guidelines suggest that patients with HFmrEF likely have mild systolic dysfunction as well as diastolic dysfunction (6). A critical question is whether HFmrEF is in itself a distinct clinical syndrome or whether patients with

HFmrEF are “in transition” between HFrfEF and HFpEF (Online Appendix).

PROGNOSIS IN HFmrEF

MORTALITY RISKS. Mortality rates are modestly higher among patients with HFrfEF but similar between those with HFmrEF and HFpEF. In OPTIMIZE-HF, the mortality rates were 3.9% for patients with HFrfEF, 3.0% for HFmrEF, and 2.9% for HFpEF (2). Among patients in ADHERE, in-hospital mortality was 4.7% in patients with LVEF <25%, 3.4% in patients with LVEF 25% to 40%, 3.2% in those with LVEF 41% to 54%, and 3.0% in those with LVEF ≥55% (4). In a Canadian study of hospitalized patients with HF, patients with HFmrEF had unadjusted mortality rates of 5.1% at 30 days and 21.3% at 1 year (17). These 30-day and 1-year mortality rates were intermediate between those of patients with HFpEF (5.3% and 22.2%, respectively) and HFrfEF (7.1% and 25.5%, respectively), but the differences were not statistically significant. Data from GWTG-HF found that patients with HFmrEF also had 30-day and 1-year mortality rates (8.2% and 35.1%) that were intermediate between those in the HFpEF (8.5% and 35.6%) and HFrfEF (9.5% and 37.5%) groups (Figure 2) (8). In both studies, mortality rates in HFmrEF were more similar to those in the HFpEF group.

A meta-analysis of individual data from almost 40,000 patients with HF found that the adjusted risks of mortality steadily increased with every 5% to 10% decrease in LVEF below 40% but were not significantly different in the groups with LVEF >40% (18). This trend was also seen in the CHARM (Candesartan in Heart Failure: Assessment of Reduction

FIGURE 2 Comparisons of the Outcomes in Patients With HFpEF, HFmrEF, and HFrfEF in the GWTG-HF Registry

Cumulative incidence functions for all-cause mortality, all-cause rehospitalization, cardiovascular (CV) rehospitalization, and heart failure (HF) rehospitalization in the heart failure with preserved ejection fraction (HFpEF) (black lines), heart failure with mid-range ejection fraction (HFmrEF) (blue lines), and heart failure with reduced ejection fraction (HFrfEF) (red lines) groups. GWTG-HF = Get With The Guidelines-HF Registry. Adapted with permission from Cheng et al. (8).

in Mortality and Morbidity) study, in which there was an adjusted hazard ratio (HR) of 1.31 for all-cause mortality per 10% reduction in LVEF <45% (19). When comparing the predictors of mortality between HF patients with LVEF <40% or ≥40%, most characteristics were similarly predictive in the 2 groups (20).

More recent studies of the HFmrEF population analyzed differential characteristics that may predict increased mortality in each HF group. A recent study of the Swedish Heart Failure registry observed that chronic kidney disease was more strongly predictive of mortality in patients with HFmrEF and HFrEF than in patients with HFpEF (21). Meanwhile, in a separate study, age ≥85 years and COPD were associated with a higher risk of mortality within 1 year after hospital discharge in the HFmrEF group compared with the other groups (12).

Several studies have assessed the trends of mortality rates in the different HF groups. In the GWTG-HF registry from 2005 to 2010, although unadjusted in-hospital mortality for patients with HFpEF decreased from 3.32% to 2.35%, it remained relatively stable in patients with HFmrEF (2.69% to 2.88%) and HFrEF (3.03% to 2.83%) (13). In addition, an analysis of patients admitted for acute decompensated HF found that although 1-year mortality has improved slightly for all HF groups over the past approximate 20 years, longer-term mortality (2- and 5-year) has remained high (22). There were differential associations of physiological factors and comorbidities with 1-year mortality in each HF group, with age ≥85 years and comorbid COPD found to be more strongly associated with 1-year mortality in patients with HFmrEF (12).

MORBIDITY IN HFmrEF. Similar to the mortality rate trends, readmission rates in HFmrEF are intermediate to those seen in HFrEF and HFpEF. In the GWTG-HF registry, all-cause readmission rates for patients with HFmrEF were 20.9% at 30 days and 63.2% at 1 year, which were similar to those seen in patients with HFpEF (20.5% and 62.5%) and slightly higher than those seen in patients with HFrEF (19.7% and 59.6%) (Figure 2) (8). However, rates of cardiovascular readmission for patients with HFmrEF (11.3% at 30 days, 41.6% at 1 year) were higher than those seen in HFpEF (9.9% and 37.4%) and closer to those observed in patients with HFrEF (12.9% and 42.4%). HF-specific readmission rates were intermediate in HFmrEF compared to those seen in HFrEF and HFpEF (8). An analysis of factors leading to HF-specific readmissions in each HF group showed that the precipitants in HFmrEF (e.g., respiratory issues,

uncontrolled hypertension) more closely resembled those in HFpEF, with the exception of coronary ischemia, which resembled the contributions seen in HFrEF (10).

MANAGEMENT OF HFmrEF

Contrary to HFrEF, there have been no therapies thus far that have conclusively been shown to improve outcomes in patients with HFmrEF and HFpEF (3). Thus, the recommendations from the AHA/ACCF and the ESC guidelines for the HFmrEF population currently focus on managing comorbidities and risk factors (5,6). In addition, diuretic therapy is recommended to help alleviate symptoms in patients who exhibit signs of congestion. Otherwise, there are currently no specific guideline-directed medical therapies that are Class I or Class IIa recommended to improve outcomes for patients with HFmrEF.

PHARMACOLOGICAL THERAPY. The central feature of pharmacological guideline-directed medical therapy in patients with HFrEF is neurohormonal blockade with beta-adrenergic receptor blockers and inhibitors of the renin-angiotensin-aldosterone system (5,6). Although these agents have not been found to be effective at improving outcomes in patients with HFpEF, they have not been specifically studied in the HFmrEF population. Nonetheless, several studies have partially or wholly included the LVEF 40% to 50% range and may help provide insight into the potential benefit of these therapies in this group.

The most recent trial of note that evaluated the effects of neurohormonal blockade in patients with HF and LVEF ≥45% was the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study (23). In this study of >3,000 patients, there was no effect of spironolactone on the composite primary outcome of cardiovascular death, aborted cardiac arrest, or HF hospitalization; however, there was a reduction in HF hospitalizations in the treatment group (HR: 0.83). Moreover, there was a significant interaction between treatment and LVEF, with stronger benefit seen in patients with LVEF 45% to 50% (24). In light of these findings from TOPCAT, the AHA/ACCF recently released an update to its guidelines, adding the Class IIb recommendation that in a selected population of patients with HF with LVEF ≥45%, aldosterone antagonists may be considered to decrease hospitalizations (25).

Similarly, the CHARM-Preserved trial evaluated the effects of the ARB candesartan in patients with HF with LVEF >40% (26) and found a reduced risk of HF

hospitalization in the treatment group (HR: 0.84). However, in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial, in which the effects of irbesartan were assessed in patients with HF and LVEF $\geq 45\%$, there were no significant benefits seen (27), although the average LVEF was notably higher in I-PRESERVE (mean LVEF, 59%) compared with the CHARM-Preserved trial (mean LVEF, 54%). In addition, one of the major advances to therapy for patients with HFrEF has been the coadministration of the neprilysin inhibitor sacubitril with the ARB valsartan. The ongoing PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction) trial (NCT01920711) will compare treatment with sacubitril/valsartan versus valsartan alone in patients with HF and LVEF $\geq 45\%$, which may help provide some insight into the role of neprilysin inhibition in HFmrEF management.

Given the paucity of randomized clinical trial data, observational studies on the use of angiotensin-converting enzyme inhibitors/ARBs and beta-blockers have been undertaken. In OPTIMIZE-HF, although use of angiotensin-converting enzyme inhibitor/ARB therapy was associated with lower death and rehospitalization at 60 to 90 days in patients with HFrEF, patients with either HFmrEF or HFpEF had no associated benefit (2). Similar findings were observed for beta-blockers. The effects of beta-blockade were examined in the OPTIMIZE-HF registry linked to Medicare data, and those with LVEF $< 40\%$ were compared with those with LVEF $\geq 40\%$ for long-term outcomes (2). Although initiation of beta-blocker therapy was associated with improved outcomes in patients with HFrEF, it was not found to significantly influence outcomes in patients with LVEF $\geq 40\%$ (28). The same findings were observed when the analysis was confined to patients with LVEF 40% to 50%.

In the TIME-CHF (Trial of Intensified Versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure), N-terminal proBNP-guided management was found to be improve HF hospitalization-free survival in patients with HFmrEF and HFrEF but not in patients with HFpEF (14). However, the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment) trial also used N-terminal proBNP-guided therapy in patients with HFrEF, but this study was terminated prematurely due to futility (29). The role of biomarkers in the management of HFmrEF thus remains to be determined.

MANAGEMENT OF COMORBIDITIES. As mentioned previously, the comorbidities seen in patients with

HFmrEF track more closely with those of patients with HFpEF (8). CAD has been associated with greater declines in LVEF among patients with HFpEF (30). Accordingly, screening for and management of CAD is a reasonable approach that may help prevent further progression of left ventricular systolic dysfunction in patients with HFmrEF, as they have been shown to have a higher rate of transitioning to HFrEF compared with patients with HFpEF (11).

Nonetheless, noncardiac comorbidities (i.e., COPD, hypertension, chronic kidney disease, DM) are highly prevalent in the HF population and contribute significantly to the overall morbidity of these patients (31). In patients with HFmrEF, uncontrolled hypertension was more often the precipitating factor for HF hospitalization compared with the other HF groups (10). In light of the modest signals for reduced hospitalizations with ARBs or aldosterone antagonist therapy in patients with HFpEF, these agents may be reasonable to use in efforts to manage hypertension and reduce the risk of progressive decline in LVEF in the HFmrEF population. In addition, with regard to the management of DM in patients with HF, the use of sodium glucose cotransporter 2 inhibitors in patients at high cardiovascular risk has been shown to reduce cardiovascular morbidity and mortality, including a reduction in HF hospitalization (32), and these agents are gaining favor in the management of DM in patients with HF (33).

FUTURE DIRECTIONS

Following the definition of HFmrEF by the AHA/ACC and ESC, a number of studies have helped to elucidate some of the mysteries of this “gray” area of HF, including its prevalence, clinical characteristics, and outcomes (Central Illustration). However, as with HFpEF, there currently are no effective, guideline-directed medical therapies that improve major outcomes in this vulnerable population of patients. With the ongoing struggle of finding effective therapies for patients with HFpEF, a specific focus on and/or inclusion of patients with HFmrEF may lead to more promising results.

As discussed by Lam and Solomon (7), however, specifically targeting the HFmrEF population in clinical trials is challenging, and recent trials studying patients with the middle range of LVEF had to be stopped early due to difficulties with enrollment. In addition, the variability of LVEF measurements based on echocardiography is rather high, and the potential misclassifications of patients with HF into the different HF groups may cloud the true efficacy of therapies being studied. Thus, there are limitations to

CENTRAL ILLUSTRATION Characterization of HFpEF, HFmrEF, and HFrEF

Heart Failure	Characteristics			Outcomes		Guideline-Directed Medical Therapies				
	Older Age	Male Sex	CAD	Morbidity	Mortality	ACEI	ARB	ARNI	BB	MRA
HFpEF (LVEF>50%)	+++	+	++	++	++	X (IIB)	✓ (IIB)	? (IIB)	X (IIB)	✓ (IIB)
HFmrEF (LVEF40-50%)	++	++	+++	++/+++	++	? (IIB)	✓ (IIB)	? (IIB)	? (IIB)	✓ (IIB)
HFrEF (LVEF<40%)	+	+++	+++	+++	+++	✓ (I)	✓ (I)	✓ (I)	✓ (I)	✓ (I)

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General comparisons of the clinical characteristics, outcomes, and guideline-directed medical therapies for each heart failure group. Class of recommendation is denoted in parentheses, if applicable. ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blockers; CAD = coronary artery disease; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

a classification system based on LVEF alone, and further refinement of the particular HF etiologies (i.e., ischemic, familial, hypertensive) and detailed phenotyping may help to maximize the discovery of more effective treatment strategies. Whether this EF classification approach adopted in recent versions of the guidelines increases clarity, facilitates improved care, and helps move the field forward remains to be seen.

In the era of precision medicine, the next advances in the management of HFmrEF may involve identifying features of each patient with HF that can help provide further risk stratification beyond what is predicted by LVEF alone. In addition, advanced imaging modalities may identify high-risk patients within the HFmrEF group. Detection of late gadolinium enhancement on cardiac magnetic resonance imaging was found to be predictive of death or appropriate implantable cardioverter-defibrillator discharge in HF patients with LVEF >30% (34). A recent study has shown that in patients with dilated cardiomyopathy and LVEF \geq 40%, the presence of mid-wall late gadolinium enhancement on cardiac magnetic resonance imaging was strongly predictive of the composite endpoint of sudden cardiac death or aborted sudden cardiac death (HR: 35.9) and in patients with LVEF 40% to 50% had marked predictive value beyond that of LVEF alone (35). Thus, studies

suggest the potential value of incorporating cardiac magnetic resonance imaging assessment in patients with HFmrEF and HFpEF, and further research is needed to determine whether these subgroups of patients with late gadolinium enhancement would benefit from implantable cardioverter-defibrillator placement.

Furthermore, expansion of the tools clinicians use to refine their assessment of a patient's hemodynamic variables may improve outcomes in patients with HFmrEF. The use of an implantable micro-electromechanical systems pressure sensor in the pulmonary artery to guide management of patients with HF was found to reduce hospitalizations for HF, including in those patients with LVEF \geq 40% (36). In addition, the role of biomarkers in guiding the management of patients with HF remains an active area of investigation (37).

CONCLUSIONS

With a clearer definition of HFmrEF established by the professional guidelines, we now have a better understanding of the heterogeneous clinical profile and similarly poor outcomes of these patients compared with the other HF groups. Beyond close clinical monitoring and aggressive management of comorbidities, particularly CAD, there may be

benefit to earlier initiation of neurohormonal blockade if otherwise indicated. Further studies are needed to determine whether therapies that are ineffective in HFpEF are in fact effective in reducing morbidity and mortality in the HFmrEF population.

ADDRESS FOR CORRESPONDENCE: Dr. Gregg C. Fonarow, Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan UCLA Medical Center, 10833 LeConte Avenue, Room A2-237 CHS, Los Angeles, California 90095-1679. E-mail: gfonarow@mednet.ucla.edu.

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APPENDIX For supplemental material, please see the online version of this paper.