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ORIGINAL RESEARCH ARTICLE

Heart failure with mid-range ejection fraction: characterization of patients from the PINNACLE Registry®

Nasrien E. Ibrahim[1], Yang Song[2], Christopher P. Cannon[3], Gheorghe Doros[2,4], Patricia Russo[5], Angelo Ponirakis[6], Claire Alexanian[6] and James L. Januzzi Jr[1,2*]

[1]*Cardiology Division, Massachusetts General Hospital, 32 Fruit Street, Yawkey 5984, Boston, MA 02114, USA;* [2]*Baim Institute for Clinical Research, Boston, MA, USA;* [3]*Cardiology Division, Brigham and Women's Hospital, Boston, MA, USA;* [4]*Boston University, Boston, MA, USA;* [5]*Novartis Pharmaceuticals, Hanover, NJ, USA;* [6]*American College of Cardiology, Washington, DC, USA*

Abstract

Aims Guidelines for management of patients with heart failure with mid-range ejection fraction [HFmrEF; left ventricular EF (LVEF) 41–49%] do not exist. Disagreement exists whether HFmrEF should be considered a distinct group. The aim of this study is to examine characteristics of patients with HFmrEF with HF with reduced EF (HFrEF; LVEF $\leq$ 40%) or preserved EF (HFpEF; LVEF $\geq$ 50%).

Methods and results We examined data collected in the American College of Cardiology's National Cardiovascular Data Registry (NCDR) Practice Innovation and Clinical Excellence (PINNACLE) Registry® for first HF patient visits between 1 May 2008 and 30 June 2016. Analysis was performed using ANOVA *F*-tests (or Kruskal–Wallis tests for non-normally distributed variables) for continuous parameters and χ^2 tests for nominal covariates at the first diagnosed HF visit. Given the NCDR PINNACLE Registry® is a US-based registry, we opted to define HFmrEF as per the US guidelines, which define HFmrEF as LVEF 41–49% in contrast to European guidelines, which define HFmrEF as LVEF 40–49%. Among 1 103 386 patients with available data, 36.1% (*N* = 398 228) had HFrEF, 7.5% (*N* = 82 292) had HFmrEF, and 56.5% (*N* = 622 866) had HFpEF. Compared with patients with HFrEF or HFpEF, patients with HFmrEF had more prevalent coronary and peripheral artery disease and more history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery (all $P < 0.001$). Patients with HFmrEF were also more likely to have atrial fibrillation/flutter, diabetes, and chronic kidney disease and to have a history of tobacco use (both $P < 0.001$). Among those with EF assessment prior to this analysis, only 4.8% (*N* = 1032) previously had HFrEF that improved to HFmrEF; 32.9% (*N* = 7072) had HFpEF previously and progressed to HFmrEF. Those patients who transitioned from HFpEF to HFmrEF had considerably more complex profiles and were less aggressively managed compared with those who remained with HFmrEF (all $P < 0.001$).

Conclusions In this large descriptive analysis, patients with HFmrEF had an atherothrombotic phenotype distinct from other forms of HF. Interventions aimed at treating coronary ischaemia and addressing prevalent risk factors may play a particularly important role in the management of patients with HFmrEF.

Keywords Heart failure; Mid-range ejection fraction; Co-morbidities

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**Correspondence to: James L. Januzzi Jr, Cardiology Division, Massachusetts General Hospital, 32 Fruit Street, Yawkey 5984, Boston, MA 02114, USA. Tel: +1 617 726 3443; Fax: +1 617 643 1620. Email: jjanuzzi@partners.org*

Introduction

Patients with heart failure (HF) are traditionally grouped based on their left ventricular ejection fraction (LVEF). Several successful HF trials have focused on development of therapies for those with HF with reduced EF (HFrEF; LVEF-40%); such patients have the most clinical evidence with regard to pharmacological and device therapies,[1] and clinical

practice guidelines articulate strategies for management of patients with HFrEF.[2,3] Over recent years, there has been increasing attention paid to patients with HF with preserved EF (HFpEF; LVEF $\geq$ 50%), formerly known as diastolic HF, including focus on characterization of such patients.[4] Patients with HFpEF have a phenotype distinct from those with HFrEF: they are older, more likely to be women, more likely to have hypertension, chronic obstructive pulmonary disease and diabetes, and more likely to have ischaemic heart disease.[5,6] HFpEF patients also have more left ventricular (LV) hypertrophy and left atrial enlargement compared with HFrEF.[7] The impact of these phenotypic differences between HFrEF and HFpEF is most evident in clinical trials of HF therapies, where treatments with benefit in HFrEF have had no consistent impact on mortality in HFpEF. This has led researchers to suggest new approaches to clinical trials in HFpEF, individualizing treatment approaches for those with HFpEF based on phenotypic clusters, somewhat distinct from those of HFrEF.[8,9]

In comparison with HFrEF and HFpEF, little attention has been given to those patients with mid-range EF, that is, HFmrEF, defined as those with HF and an LVEF between 41 and 49%.[10] Although estimates suggest such patients account for up to 10–20% of all patients with HF,[1] substantial knowledge deficits exist regarding patients with HFmrEF, and clinical practice guidelines are largely silent with respect to their management; this is in part due to lack of robust clinical trial data to inform their care[11] because no trials have focused on patients with HFmrEF. In analogy to failed trials for HFpEF, it is not sound to assume that therapies for HFrEF will necessarily be effective in this population. That said, some have argued against this intermediate HF category, arguing such patients merely represent a transitional phenotype between HFrEF and HFpEF. Better understanding of HFmrEF is clearly needed.

In this context, we characterized patients suffering from HF within the American College of Cardiology's (ACC) National Cardiovascular Data Registry (NCDR) Practice Innovation and Clinical Excellence (PINNACLE) Registry®. Among those patients with available LVEF data, we compared those with HFrEF, HFmrEF, and HFpEF to improve our understanding of the diagnosis of HFmrEF. We hypothesized that patients with HFmrEF would represent a population of HF patients clinically different from HFrEF or HFpEF and such differences might inform future approaches to optimize care for HFmrEF patients.

Methods

Data source

The NCDR PINNACLE Registry® was created in 2008 by the ACC as the first national, prospective, office-based cardiac quality improvement registry in the USA. It is the largest ambulatory registry of its kind, with over 32 million patient visits from over 6080 providers, across 1954 unique office locations. The registry was designed to capture the data necessary to report on performance measures across chronic disease areas including coronary artery disease (CAD), hypertension, HF, and atrial fibrillation.

Participating academic and private practices collect longitudinal point-of-care data using a standardized collection tool to comprehensively obtain and transmit uniform data.[12] The NCDR data quality is maintained through standardized data collection and transmission protocols, rigorous data definitions, and periodic data quality audits.[13,14]

The PINNACLE Registry collects data from a broad range of electronic health records systems. To do this, the Registry data mapping team works with practice administrators to ensure proper data mapping as practices are on-boarded with the Registry. Data are checked against specific valid ranges in the Registry specifications and checked against clinical target values for expected usual ranges for clinical data.

Study population

For the purposes of the present analysis, we included those patients in the NCDR PINNACLE Registry® with a clinical diagnosis of HF and with available LVEF information. HFrEF was defined as patients having LVEF $\leq$ 40%, HFpEF as LVEF $\geq$ 50%, and HFmrEF as LVEF 41–49%. LVEF was visually estimated and/or calculated locally and recorded in the NCDR PINNACLE Registry®. Given the NCDR PINNACLE Registry® is a US-based registry, we opted to define HFmrEF as per the ACC/American Heart Association/Heart Failure Society of America guidelines, which define HFmrEF as LVEF 41–49% in contrast to European guidelines, which define HFmrEF as LVEF 40–49%.[10]

Statistical analysis

Data from the index visit include medical history in the 12 months prior to this index visit. Continuous variables are expressed as means ± standard deviation, and categorical variables are expressed as proportions. Statistical analysis was performed using ANOVA *F*-tests (or Kruskal–Wallis tests for non-normally distributed variables) for continuous parameters at the first diagnosed HF visit. χ^2 tests were performed for nominal covariates at the first diagnosed HF visit, that is, the index visit.

Results

There were 1 824 964 patients with a diagnosis of HF in the NCDR PINNACLE Registry®; 721 578 were excluded because of missing LVEF, <18 years of age, or missing gender. Of the 1 103 386 remaining patients, 36.1% (*N* = 398 228) had

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HFrEF, 7.5% (*N* = 82 292) had HFmrEF, and 56.5% (*N* = 622 866) had HFpEF (*Figure 1*). HF was most prevalent in the South (48.8%) followed by the Midwest (22.1%), and among Southern patients, and HFrEF was more common than HFmrEF or HFpEF (*Table 1* and *Figure 2*).

A distribution of the LVEF of the patients in this analysis is detailed in *Figure 3*. At the index visit, patients with HFrEF had a mean LVEF of 29.6 ± 8.4%, those with HFmrEF 45.0 ± 1.9%, and those with HFpEF 60.2 ± 6.7% ($P < 0.001$). To understand the trajectory of LVEF, we examined patients with available LVEF prior to the index visit and considered this the initial LVEF (we used the earliest LVEF measurement available); LVEF at the index visit is considered the final LVEF. Of the 82 292 HFmrEF patients, 26.1% (*N* = 21 512) had LVEF data available prior to the index visit. Using the very first LVEF measurement available, 62.3% (*N* = 13 408) had HFmrEF at both time points, 32.9% (*N* = 7072) had HFpEF previously and progressed to HFmrEF at the time of the present analysis, and only 4.8% (*N* = 1032) previously had HFrEF that improved to HFmrEF during the time of this analysis.

Table 1 details characteristics of patients as a function of their index date HF category. The median New York Heart Association symptom severity in all three groups was Class II at the index visit. Patients with HFrEF were younger and more likely to be men (both $P < 0.001$). Additionally, patients with HFrEF had a higher heart rate and lower systolic blood pressure at index visit compared with those with HFmrEF or HFpEF (*Table 1*). Patients with HFpEF were more likely to be White and had a higher body mass index compared with those with HFrEF or HFmrEF (30.2 ± 6.6 vs. 29.4 ± 6.3 and 30.0 ± 6.4 kg/m^2, respectively, $P < 0.001$). Additionally, patients with HFpEF were more likely to be women (51.5%) ($P < 0.001$) (*Table 1*).

In contrast to those with HFrEF or HFpEF, patients with HFmrEF were more likely to have higher prevalence of CAD and peripheral artery disease and were more likely to have prior myocardial infarction and more often had undergone coronary revascularization procedures. Patients with HFmrEF were also more likely to have atrial fibrillation/flutter, chronic kidney disease, and diabetes mellitus and to have a history of tobacco use (all $P < 0.001$; *Table 1* and *Figure 4*).

Not surprisingly, patients with HFrEF were more likely to be on guideline-directed medical therapy (GDMT) for their diagnosis, including angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/angiotensin receptor neprilysin inhibitor and beta-blocker (*Table 2*). Interestingly, patients with HFmrEF were treated similarly to those with HFrEF, with comparable amounts of GDMT such as ACEi/ARB and beta-blockers when compared with those with HFpEF. Consistent with this, patients with HFmrEF were more likely to be receiving loop or thiazide diuretics (*Table 2*).

Discussion

In this observational analysis of 1 103 386 patients with HF from the PINNACLE Registry®, 36.1% of patients had HFrEF, 7.5% had HFmrEF, and 56.5% had HFpEF. We found important descriptive differences between patients with HFmrEF and other categories of HF: those with an LVEF 41–49% had a distinct atherothrombotic profile, with more prevalent

Figure 1 Distribution of heart failure (HF) patients in the NCDR PINNACLE Registry®. LVEF, left ventricular ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

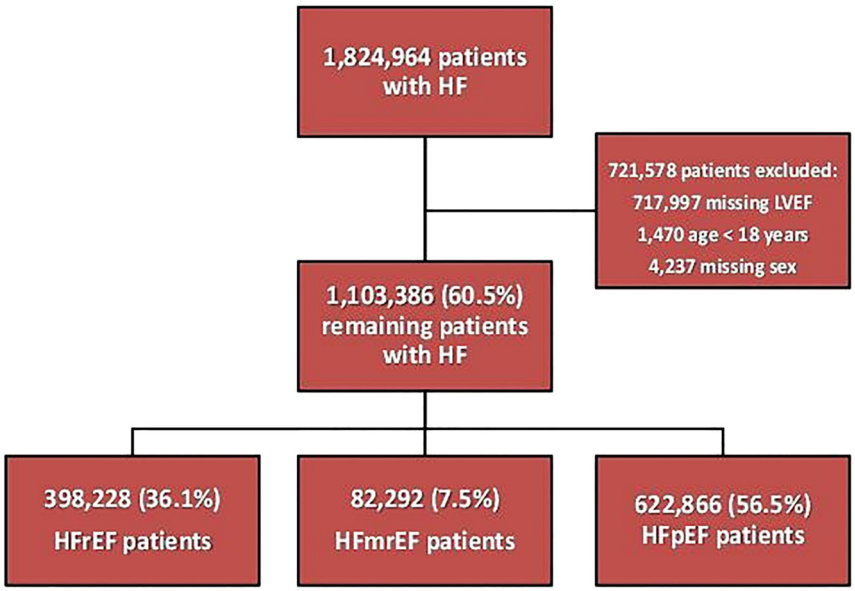


Table 1 Baseline characteristics of heart failure patients in this analysis from the NCDR PINNACLE Registry®

Patient characteristics	All HF patients (*N* = 697 542)	HFrEF patients (EF ≤ 40%) (*N* = 316 628)	HFmrEF patients (EF 41–49%) (*N* = 56 527)	HFpEF patients (EF ≥ 50%) (*N* = 324 387)	*P*
Demographics					
Age (years), mean ± SD	69.1 ± 13.5	67.8 ± 13.5	70.1 ± 12.8	69.7 ± 13.6	<0.001
Sex—male (%)	56.6	66.9	66.9	48.5	<0.001
Race—White (%)	65.0	61.4	64.8	67.4	<0.001
Region (%)					
Midwest	22.1	22.3	23.5	21.8	<0.001
Northeast	13.1	11.0	12.8	14.6	<0.001
South	48.8	49.6	46.6	48.5	<0.001
West	16.0	17.0	17.1	15.2	<0.001
Medical history					
LVEF, mean ± SD	48.5 ± 16.0	29.6 ± 8.4	45.0 ± 1.9	60.2 ± 6.7	<0.001
Coronary artery disease (%)	59.5	63.5	70.1	55.5	<0.001
Atrial fibrillation/flutter (%)	34.4	33.0	40.3	34.4	<0.001
Diabetes (Type I or II) (%)	26.1	25.9	30.0	25.7	<0.001
Hypertension (%)	75.6	69.3	79.1	79.1	<0.001
Peripheral arterial disease (%)	12.9	11.8	15.4	13.2	<0.001
Chronic kidney disease (%)	7.0	6.9	9.0	6.8	<0.001
Myocardial infarction (%)	18.1	22.2	25.2	14.5	<0.001
PCI/PTCA (%)	23.2	23.9	29.2	21.9	<0.001
Stroke (%)	9.7	9.9	10.1	9.5	<0.001
CABG (%)	13.5	14.9	19.0	11.8	<0.001
Physical exam					
BMI (kg/m^2), mean ± SD	29.9 ± 6.5	29.4 ± 6.3	30.0 ± 6.4	30.2 ± 6.6	<0.001
Heart rate (b.p.m.), mean ± SD	73.1 ± 13.6	74.3 ± 14.0	72.9 ± 13.3	72.2 ± 13.2	<0.001
Systolic blood pressure (mmHg), mean ± SD	128.1 ± 18.8	125.3 ± 19.0	127.8 ± 18.9	129.9 ± 18.4	<0.001
Crackles (%)	6.2	6.2	7.0	6.1	<0.001
Peripheral oedema (%)	34.5	31.7	35.9	36.1	<0.001
S3 gallop (%)	5.2	6.6	5.6	4.3	<0.001
Jugular venous distention (%)	5.1	5.7	5.8	4.6	<0.001
Social history (%)					
Tobacco use—never	43.0	39.0	38.9	46.0	<0.001

BMI, body mass index; b.p.m., beats per minute; CABG, coronary artery bypass graft; EF, ejection fraction; 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; LVEF, left ventricular ejection fraction; PCI, percutaneous intervention; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation.

atrial fibrillation/flutter, diabetes, chronic kidney disease, and tobacco use, and of the three categories of HF, those with HFmrEF were more likely to have a history of CAD or peripheral artery disease. Additionally, of the three HF categories, those with LVEF between 41 and 49% were also most likely to have had prior myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery. Taken together, these findings imply a unique profile of patient in this category, emphasizing differences between HFrEF and HFpEF. These results are important given lack of guidance for care of patients with HFmrEF; given failure of clinical trials for HFpEF, assumptions cannot be made about whether treatment for HFrEF would necessarily be successful in those with mid-range LVEF.

The category of HFmrEF, the so-called middle child of HF,[1] has been given recent attention in part due to the paucity of data for this group of patients and lack of concrete guideline recommendations for their management (Supporting Information, *Table S1*). On the other hand, some argue against the creation of a third HF category. To date, it remains unclear whether patients with HFmrEF represent a distinct phenotype of HF patients or if patients with HFmrEF are part of a continuum of patients who progress to overt HFrEF. Our findings are in line with those from Lam and Solomon, albeit in a much larger group of patients, suggesting patients with HFmrEF have heavy representation of risk factors for—or established—vascular disease.[1]

Our results should be taken in context of other reports. In a 2007 analysis of 41 267 registry patients, characteristics of patients with LVEF between 40 and 50% were closer to those of patients with HFpEF.[15] More recently, in a 2014 analysis of 40 239 patients with HFmrEF in the Get With The Guidelines—Heart Failure registry, patients with HFmrEF had clinical characteristics that were more similar to those of patients with HFpEF. However, the characteristic in which the HFmrEF population was more similar to the HFrEF population was in the prevalence of CAD.[16] This was consistent with findings in a recent study, which showed the prevalence of CAD to be the highest in patients with HFmrEF compared with HFpEF and HFrEF.[17,18]

Heart failure with preserved EF may also have unique characteristic physiological responses to exercise as well, and recently, a study by Pugliese and colleagues examined patients with HFrEF, HFmrEF, and HFpEF and demonstrated

Figure 2 Regional map of the USA representing the prevalence of heart failure (HF) phenotypes. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

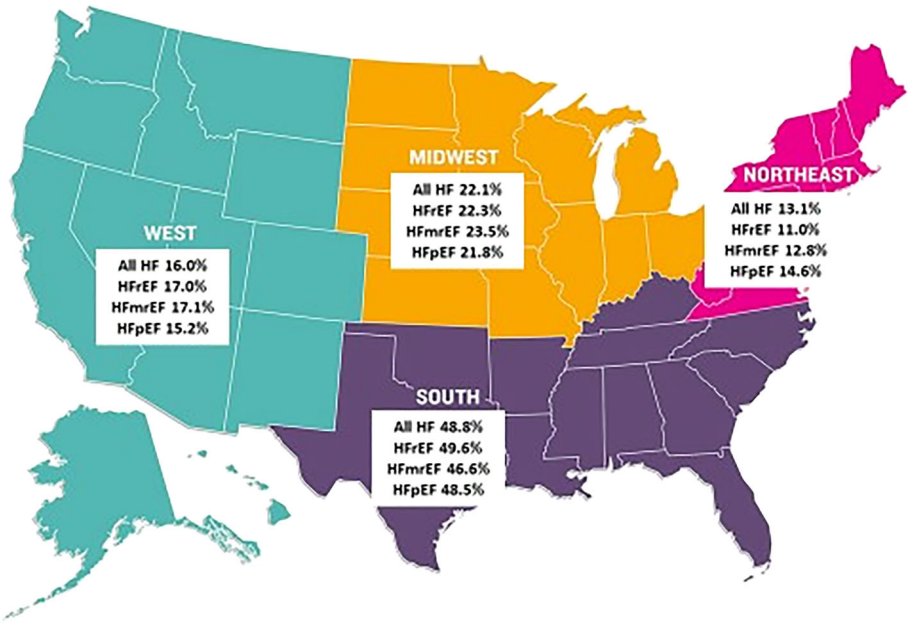
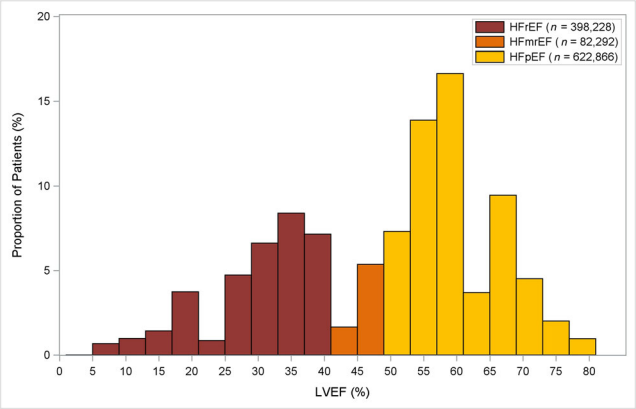


Figure 3 Distribution of the left ventricular ejection fraction (LVEF) of the patients in this analysis. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



that in HFpEF and HFmrEF, exercise effort intolerance is predominantly due to peripheral factors; whereas in HFrEF, peak oxygen consumption is restricted by low increases in stroke volume (74.3 ± 21.8 vs. 88.0 ± 17.4 and 96.5 ± 25.1 mL, HFpEF and HFmrEF, respectively; $P < 0.01$).[19] In another study of patients with HFrEF and HFpEF, exercise intolerance was found to be predominantly due to chronotropic incompetence and peripheral factors.[20] Such physiological differences may have potential for clinical management of HF patients.

Prior studies would suggest HFmrEF is not without risk, making clarity about treatment of these patients important. One study suggested that mortality rates for HFrEF, HFmrEF, and HFpEF were 33.0, 27.8, and 28.0%, respectively. After propensity score matching, however, patients with HFmrEF were at a higher risk of cardiovascular death [subdistribution hazard ratio (SHR) 1.71, 95% confidence interval (CI) 1.13–2.57, 0.01] and sudden cardiac death (SHR 2.73, 95% CI 1.07–6.98, 0.04) than patients with HFpEF.[21] In the Cardiovascular Health Study, the mortality rate of patients with HFmrEF was intermediate between that of HFrEF and HFpEF.[22] Whether HFmrEF represents a distinct clinical entity with unique risk factors and an outcome profile or an entity on the continuum between HFrEF and HFpEF, it is apparent that compared with patients with HFrEF and HFpEF, unique opportunities exist for the mitigation of risk associated with this category of HF.

In keeping with heterogeneity of outcomes in clinical trials of HFpEF vs. HFrEF, it may be that the therapeutic approach in HFmrEF might differ from those with lower LVEF or represent a hybrid of HFrEF GDMT plus strategies to manage the burden of CAD and peripheral artery disease in HFmrEF. Indeed, while lipid-lowering or anti-thrombotic therapy with rivaroxaban has not been shown to be of consistent benefit in those with HFrEF,[23,24] our data would argue intensive therapy with hydroxymethylglutaryl co-A reductase inhibitors or rivaroxaban might be expected to be of substantial benefit in those with HFmrEF, given prevalent CAD and peripheral artery disease. Further, given prevalent type 1 or type 2 diabetes mellitus in those with HFmrEF, referral to diabetes specialists and counselling regarding optimal control of diabetes (including consideration for use of newer diabetes medications that

Figure 4 Distribution of co-morbidities among patients with heart failure with reduced ejection fraction (HFrEF), heart failure with reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF). AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

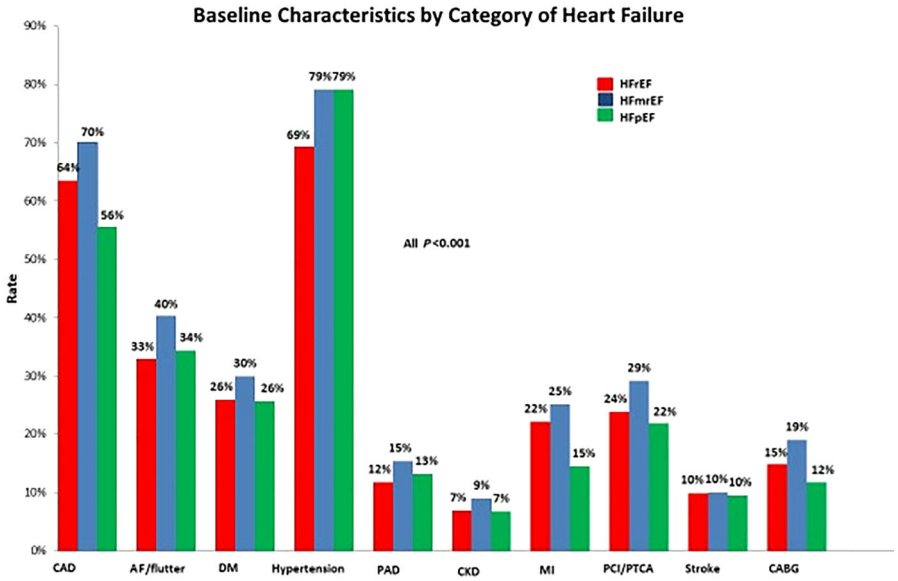


Table 2 Guideline-directed medical therapy in HF patients in this analysis from the NCDR PINNACLE Registry®

Guideline-directed medical therapy	All HF patients (N = 697 542)	HFrEF patients (EF ≤ 40%) (N = 316 628)	HFmrEF patients (EF 41–49%) (N = 56 527)	HFpEF patients (EF ≥ 50%) (N = 324 387)	P
ACEi/ARB (%)	57.3	66.0	61.2	51.1	<0.001
Sacubitril/valsartan[a] (%)	1.1	2.7	0.9	0.2	<0.001
Beta-blocker (%)	68.9	78.1	74.7	61.9	<0.001
Loop and/or thiazide diuretic (%)	48.8	56.1	52.4	43.4	<0.001
Digoxin (%)	3.5	4.9	3.7	2.5	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; 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.
[a]Not approved for treatment of HFrEF until July of 2015.

may reduce cardiovascular risk)[25,26] may further mitigate the risk associated with this class of HF. As will attention to the management of atrial fibrillation/flutter, which appears to be more prevalent in this patient population. While anti-platelet therapy[27] or revascularization of CAD has had mixed results for the management of HFrEF,[28] in those with HFmrEF, an ischaemia-driven management strategy (including revascularization if appropriate) might also be worth consideration in this patient population. Lastly, as with other forms of HF, smoking cessation counselling and referral to programmes to help smokers may play a role in mitigation of development of not only the CAD and peripheral artery disease but also the development of HFmrEF. It is tempting to speculate that all these interventions might be helpful to prevent progression to HFrEF and/or reduce complications such as arrhythmia or death.

We found that patients with HFmrEF in our study were treated with GDMT more similar to those with HFrEF. Clinical practice guidelines are silent regarding the treatment approach for HFmrEF; this may reflect clinician inclination to treat such patients as HFrEF, and it may reflect response to prevalent medical conditions where use of ACEi/ARB (such as in diabetic patients with hypertension) or beta-blockers (such as in patients with CAD) might be indicated. Finally, it is possible that those with HFmrEF represent those with partial recovery of their LVEF from the HFrEF category. However, among those with LVEF assessment prior to this analysis [26.1% (N = 21 512)], 62.3% (N = 13 408) had HFmrEF at both time points, and only 4.8% (N = 1032) previously had HFrEF that improved to HFmrEF during the time of this analysis. Additionally, 32.9% (N = 7072) had HFpEF previously and

progressed to HFmrEF. It appeared that more patients to transition from HFpEF to HFmrEF, suggesting a downward trend in LVEF. Those patients who transitioned from HFpEF to HFmrEF had considerably more complex profiles and were less aggressively managed compared with those who remained with HFmrEF (all $P < 0.001$). On the other hand, an analysis of 3480 patients with HF by Tsuji and colleagues revealed that HFmrEF and HFrEF dynamically transitioned to other categories, especially within 1 year, while HFpEF did not; HFmrEF at baseline transitioned to HFpEF and HFrEF by 44 and 16% at 1 year and 45 and 21% at 3 years, respectively.[29] Treatment strategies to prevent reduction in LVEF are therefore more likely to be of value in this patient population.

While the quality improvement NCDR PINNACLE Registry® afforded us ability to review data from 1 103 386 patients with a diagnosis of HF, our study has limitations. This is, as many large registry studies are, a purely observational analysis. The LVEF data were based on site-reported results, which may suffer from inter-individual variability. The use of more precise means of LVEF measurement would have been desirable but is not feasible with the design of PINNACLE. Additionally, there are several definitions of HFmrEF, and given the NCDR PINNACLE Registry® is a US-based registry, we opted to define HFmrEF as per the ACC/American Heart Association/Heart Failure Society of America guidelines, which define HFmrEF as LVEF 41–49% as opposed to European guidelines, which define HFmrEF as LVEF 40–49%. We concede this may be considered a limitation to our analysis but feel it is highly unlikely this would make a substantial difference in the overall analysis, but our results are nevertheless reflective of a US population rather than a European one. A more global definition of HFmrEF is needed at this time. As well, the missingness rate of medication doses in the NCDR PINNACLE Registry® for this particular analysis was high. This registry also does not have any outcome data, and the rate of missingness of laboratory results and cardiac rehab referrals/enrolment rates that may further help characterize patients with HFmrEF is high. Nonetheless, this is the largest descriptive analysis of patients with HFmrEF to date, providing robust demographic and clinical information, allowing us to more deeply characterize patients with HFmrEF. Most importantly, we identified four potential target areas for intervention including management of atrial fibrillation/flutter, management of CAD and peripheral artery disease, management of diabetes, and smoking cessation to mitigate the risk associated with HFmrEF.

Conclusions

Patients with HFmrEF in the NCDR PINNACLE Registry® have a unique profile characterized by high prevalence of vascular disease and atherothrombotic risk factors when compared with those with HFrEF or HFpEF. Care strategies for patients with HFmrEF may thus differ from other forms of HF. More studies are needed to better understand how to individualize therapy for patients with HFmrEF.

Conflict of interest

N.E.I. has received speaker fees from Novartis. C.P.C. has received grant support from Amgen, Arisaph, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck, and Takeda and consulting income from Alnylam, Amgen, Arisaph, Astra Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Kowa, Lipimedix*, Merck, Pfizer, Regeneron*, Sanofi*, and Takeda. P.R. is an employee of Novartis Pharmaceuticals. J.L.J.J. has received grant support from Siemens, Singulex, and Prevencio and consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Philips, and Novartis and participates in clinical endpoint committees/data safety monitoring boards for Novartis, Amgen, Janssen, and Boehringer Ingelheim. The other authors have nothing to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Evidence-based and uncertain therapies for the management of patients with heart failure with reduced, mid-range, and preserved ejection fraction.

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