# What is Heart Failure with Mid-range Ejection Fraction? A New Subgroup of Patients with Heart Failure

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## Abstract

Since the publication of European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure (HF) in 2016, a new class of HF has been defined, namely HF with mildly reduced ejection fraction (HFmrEF). Although the name was new, there had long been awareness of the existence of a grey area between the two established classes of HF: HF with reduced ejection fraction and HF with preserved ejection fraction. Patients between these two classes were previously either excluded from HF studies or were included in the other groups. With the definition of this new group of patients, a door has opened for researchers to further explore their characteristics, treatment and outcomes. In this article we aim to clarify the existing literature on the clinical characteristics and pathophysiology of this newly-defined group of patients.

## Keywords

Acute and chronic heart failure, left ventricular ejection fraction, heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction, heart failure with preserved ejection fraction

**Disclosure:** The authors have no conflicts of interest to declare.
**Received:** 30 January 2018 **Accepted:** 24 March 2018. **Citation:** *Cardiac Failure Review* 2018;**4**(1):6–8. DOI: https://doi.org/10.15420/cfr.2018:7:2
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The latest guidelines on the diagnosis and management of heart failure (HF) published by the European Society of Cardiology (ESC) introduced a new class of HF: HF with mid-range ejection fraction (HFmrEF).[1] This was in addition to the previously-defined classes: HF with reduced ejection fraction (HFrEF), in which the left ventricular ejection fraction (LVEF) is below 40 %, and HF with preserved ejection fraction (HFpEF), in which the LVEF exceeds 50 %. Although the terminology is new, it should be remembered that even the previous ESC guidelines on the management of HF, published in 2012, acknowledged the existence of this 'grey area' between the two previously-defined groups.[2] Therefore, what these new guidelines have done is merely legitimised this grey area as a distinct entity by giving it a name. It is estimated that the proportion of HF patients falling within this intermediate group is 13–24 %.[3–5]

The guideline authors state that the main reason for the introduction of this new group was to give it importance in its own right, as this group of patients are usually not included in either HFpEF or HFrEF trials. However, this new entity is still confusing for many physicians due to overlapping clinical presentation, management and outcomes. As desired by the guideline authors, subsequent to the publication of these guidelines, there have been many papers on this group of patients, which were mainly new analyses of previous studies, or a re-examination of new data. These studies have shown that patients with HFmrEF exhibit significant differences compared to those with HFrEF and HFpEF.[6–8] It is also known that patients with HFrEF and HFpEF have different responses to conventional HF therapies, with the latter generally being less responsive.[9–11]

So where do HFmrEF patients fit in? The results have been mixed. Chioncel et al. recently published their findings on the analysis of the ESC HF Long-Term Registry.[8] They found that the long-term mortality rate in this group was in between those in patients with HFpEF and HRrEF. On the other hand, Pascual-Figa et al. recently showed that patients in the intermediate category of HFmrEF match a phenotype closer to the clinical profile of HFrEF, associated with a higher risk of sudden cardiac death and cardiovascular death than patients with HFpEF.[6] Still other registries showed that the prognosis of HFmrEF patients is similar to those with HFpEF.[7,12]

## Aetiology and Pathophysiology

HF has many underlying pathologies, including both cardiovascular and systemic conditions. Evaluating the specific cause has profound significance in the diagnosis and treatment of different types of HF. Patients with HFpEF or HFrEF have different epidemiological and aetiological profiles. Typically, those with HFpEF are older, female and with a history of hypertension and AF,[13] whilst those with HFrEF are comparatively younger and have a higher rate of ischaemic heart disease or cardiomyopathy, diabetes and other cardiovascular risk factors.[14]

The underlying pathophysiology of HFmrEF is not clear, although it appears that it may be associated with both mild systolic and diastolic dysfunction. It has been recognised that a subset of patients with HFrEF previously had HFpEF.[15] Thus, this intermediate category could be a group of patients in the HFpEF population who have progressive LV dysfunction.[15,16] It could also comprise a subset of patients with HFrEF that has improved with treatment; such patients may be clinically distinct from those with persistently preserved or reduced EF and would have a better prognosis.[17]

It has been hypothesised that HFmrEF is actually a subset of HFpEF in which patients acquire coronary artery disease and are progressing to HFrEF.[16] Data from the Organized Program to Initiate Lifesaving

Treatment in Hospitalized Patients with HF (OPTIMIZE-HF) and the Acute Decompensated HF Registry (ADHERE) studies have shown the distinct characteristics, management and outcomes of patients with mildly reduced LVEF, distinguishing them from patients with HFrEF and HFpEF.[18,19]

Patients with HFmrEF have also been shown to have multiple comorbidities. Kapoor et al. have described a higher incidence of diabetes, AF, chronic obstructive pulmonary disease (COPD), anaemia and renal insufficiency in these patients compared with the other HF groups.3 However, patients with HFmrEF have a similar incidence of coronary artery disease to the HFrEF population, are more likely to have hypertension than patients with HFrEF and are more likely to have ischaemic heart disease and diabetes than patients with HFpEF.[16]

## Clinical Profile

There is no clear demarcation between HFmrEF and the other two HF entities in terms of clinical presentation. They all have the clinical features of HF as described in the guidelines. HFmrEF has no other specific characteristics on presentation to distinguish it from the other forms. However, patients with HFmrEF have demographic and clinical characteristics that are more similar to those of patients with HFpEF than HFrEF. Cheng and colleagues have shown that, of all the patients hospitalised with HF in the Get With The Guidelines–HF (GWTG-HF) registry, 14 % belonged to the HFmrEF category, and their clinical presentation and demographic characteristics were overlapping with both HFrEF and HFpEF groups, but clearly closer to HFpEF cohort.[20]

Diagnosis based on clinical signs and symptoms is quite difficult in patients with HFmrEF because of the comorbidities involved, especially if the patient is elderly and has other concomitant issues like COPD.[21]

## Diagnosis and Management

All types of HF present with a similar clinical picture, and the distinction between HFrEF, HFpEF and HFmrEF ultimately requires an echocardiogram. In the 2016 ESC guidelines, the diagnostic criteria for HFmrEF include signs and symptoms of HF, an LVEF of 40–49 %, elevated levels of natriuretic peptides and presence of either structural or functional cardiac abnormalities.[1] In case of uncertainty, a stress test or invasively measured elevated LV filling pressure may be needed to confirm the diagnosis.

The ESC guidelines do not give specific recommendations for management of HFmrEF, but they suggest that, since patients with HFmrEF have mostly been included in trials of HFpEF, rather than HFrEF, they should be treated with the same management principle as patients with the former, until new evidence is available.[1]

There is a lack of clinical trials specifically in patients with HFmrEF, and therefore there is a lack of data showing efficacy of specific agents in this patient group. However, recently there have been post hoc analyses of older trials specifically looking at this group. Lund et al. analysed the data from the Candesartan in HF – Assessment of Mortality and Morbidity (CHARM) programme.[22] They found that candesartan improved outcomes in HFmrEF to a similar degree as in HFrEF. Solomon et al., in their analysis of the Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) study, showed that spironolactone was effective at the lower levels of LVEF.[23] Cleland et al. recently published an individual patient meta-analysis of 11 clinical trials of beta-blockers for HF.[24] They found that the use of beta-blockers improved LVEF and prognosis on follow-up in this patient group. These post hoc analyses will help guide our treatments and should form the basis of future prospective trials.

In current clinical practice, compared with HFrEF patients, fewer patients with HFpEF and HFmrEF appear to receive diuretics, beta-blockers, mineralocorticoid receptor antagonists, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[1,11] The American Heart Association recommends to consider aldosterone antagonists in a selected population of patients with HF and LVEF ≥45 %, to decrease hospitalisations, whilst diuretic therapy is recommended to improve symptoms of congestion.[25] However, it is recommended that patients be screened for cardiovascular and non-cardiovascular comorbidities, and management of these comorbidities is an integral part of the management of HFmrEF, as it is for HFpEF.[26]

## Prognosis

Changes in ejection fraction over time are common and seem to be more important than baseline ejection fraction alone, and patients who progress from HFmrEF to HFrEF have a worse prognosis than those who remain stable or transition to HFpEF.[11,14] Mortality rates have been found to be higher among patients with HFrEF, but similar between those with HFmrEF and HFpEF.[14] In the OPTIMIZE-HF trial, the mortality rates were 3.9 % for patients with HFrEF, 3.0 % for HFmrEF and 2.9 % for HFpEF.[27] A meta-analysis of over 40,000 patients with HF found that the adjusted risk of mortality steadily increased with every 5–10 % decrease in LVEF below 40 % but were not significantly different in the groups with LVEF >40 %.[14] On the other hand, the Swedish Heart Failure registry showed that chronic kidney disease was more strongly predictive of mortality in patients with HFmrEF and HFrEF than in patients with HFpEF.[28]

## Conclusions

The newly-defined entity HFmrEF has rapidly gained acceptance among physicians and researchers as, although the nomenclature is new, the existence of a different group or grey area between the two established forms of HF was previously known. Despite some similarities with pre-existing HF categories, this intermediate group seems to be a distinct but heterogeneous group. Although there has been research conducted in this group of patients, albeit as part of HFpEF or HFrEF studies, more work needs to be done to understand this form of HF better. We hope, as the ESC guideline authors did, that defining this group of patients and legitimising them with a separate name will spur more research and help us to understand this previously neglected group of patients. ■


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