Heart Failure Mid-Range Ejection Fraction
— Heart Failure With Multiple Personalities —

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In 2016, the ESC guidelines categorized heart failure (HF) into 3 classes according to LVEF: HFrEF, HFmrEF and HFpEF (HF with reduced, mid-range and preserved ejection fraction (EF), respectively). However, HFmrEF, a newly provided category of HF, is quite expedient for filling the blank zone or a buffer zone between HFrEF and HFpEF. Nevertheless, the ESC 2016 classification was generally accepted and clinical reports on HFmrEF have been extensively published since then. In the beginning, most reports on HFmrEF were from European countries and North America. More recently, reports from Asian countries, including Cho et al's paper in this issue of the Journal, followed, some of them investigating...
HFmrEF in the setting of acute HF. In the meantime, 2 meta-analyses comparing the mortality of patients in the 3 EF categories were also published.9,10

**Patients’ Characteristics in the Meta-Analyses and Individual Reports**

*Figure 1* shows the patients’ characteristics in the meta-analysis by Lauritsen et al9 and in the studies from Asia.2,5–8 One may notice the wide variety of patients in these reports but also appreciate the distribution of each component of the patients’ characteristics in HFmrEF as just in between HFrEF and HFpEF, excepting ischemic etiology, which occurred in HFmrEF as frequently in HFrEF, and more frequently than in HFpEF. In Cho et al’s report,2 patients were younger and less ischemic than in any of the other studies listed in *Figure 2*. Such difference in the patients’ characteristics may well influence the mortality in each category of HF. The time domain of investigated HF cohort (i.e., acute or chronic HF) may also affect the patients’ outcome. Moreover, treatment patterns, including pharmacotherapy, are an also important determinant of mortality, as discussed later.

**Long-Term Mortality According to LVEF**

In Lauritsen et al,’s total mortality was significantly lower in HFmrEF than in either HFrEF or HFpEF and cardiovascular (CV) mortality in HFmrEF was also the lowest among the 3 categories of HF. Another meta-analysis by Altaie and Khalife,10 also demonstrated that mortality in HFmrEF lower than that with HFrEF, although it was comparable to that of HFpEF. In this meta-analysis, which has stronger statistical power by outnumbering Lauristen et al, CV mortality in HFmrEF was significantly lower than for HFpEF and also tended to be lower than for HFrEF. In Cho et al’s report,2 however, post-discharge long-term mortality did not differ in the 3 EF groups. These differences in mortality between the meta-analysis and Cho et al’s report may well influence the mortality in each category of HF. The time domain of investigated HF cohort (i.e., acute or chronic HF) may also affect the patients’ outcome. Interestingly, in Cho et al’s report, the mortality of ischemic patients was worst in HFrEF, among the 3 categories, while mortality in non-ischemic patients was lowest in HFrEF compared with HFmrEF and HFpEF. Because patients with ischemic heart disease comprised only 28% of all patients, which was much lower than in the meta-analyses, the effect of ischemic etiology on mortality may have been “diluted” in the whole cohort.
In-Hospital Mortality in Acute HF Patients According to LVEF

There are several reports so far that focus on the acute HF phase of patients with HFmrEF; 3 are from the KorAHF registry, 3 are from different Japanese registries. Among these studies on acute HF, Cho et al’s report and Yaku et al’s report are yet to be established. We should not leave this child out. Considering that cardiomyopathy patients with recovered EF may induce malignant arrhythmias, 

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encouraged and if patients are already on -blockers should be continued. Thus in HFmrEF patients, use of inotropes was high and almost double compared with the former. In Cho et al’s report, the in-hospital prescription rate of IV inotropes was high and almost double compared with the Western countries, Miró et al analyzed data from 6,858 Spanish patients from the EAHFE Registry and reported in-hospital mortality rates for HFrEF, HFmrEF and HFP EF, respectively. From 2 other Japanese reports, Yaku et al’s report and 3 are from different Japanese registries.

In Cho et al’s study the prescription rate of IV inotropes was high and almost double compared with the 2 other Japanese reports. Excessive use of inotropes during the acute phase of HF may negatively modify the outcomes of patients not only in hospital but also after discharge.

On the other hand, in Cho et al’s study the prescription rate of -blockers, the most potent cardioprotective drugs for HFrEF, was lowest, although prescription rates of other guideline recommended drugs such as ACEI/ARB and MRA were comparable to the other reports. This low rate of prescribing -blockers may modify the long-term mortality, especially in HFrEF patients, and may also be the case in HFmrEF. Cleland et al reported that -blockers greatly reduced CV mortality in HFmrEF as well as HFrEF patients with sinus rhythm in individual patient data meta-analysis of 11 trials. Tsuji et al also demonstrated that -blockers exerted positive prognostic impact in HFmrEF as well as HFrEF, but not HFP EF. Thus in HFmrEF patients, use of -blockers should be encouraged and if patients are already on -blockers, it may not be a good choice to discontinue them even after LV function improves. Very recently, Halliday et al reported that withdrawal of pharmacological treatment in dilated cardiomyopathy patients with recovered EF may induce recurrence of HF. Therefore, in patients who have recovered from HFmrEF, the guideline-recommend treatment should be maintained.

In conclusion, the concept and treatment of HFmrEF, the “a middle child” born between HFrEF and HFP EF, are yet to be established. We should not leave this child out in the cold but rather bring up this unblessed child with great affection and watch over its growing up.

References


9. Lauritsen J, Gustafsson F, Abdulla J. Characteristics and long-term prognosis of patients with heart failure and mid-range ejection fraction compared with reduced and preserved ejection fraction: A systematic review and meta-analysis. ESC Heart Fail 2018; 5: 685–694.


