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How to Manage Heart Failure Patients with Not Reduced Ejection Fraction Based on Available Evidence?

EDITORIAL

The main topic of the June 2022 issue of the Archives of the Turkish Society of Cardiology was heart failure with mildly reduced and preserved ejection fraction (HFmEF and HFpEF). The related article of the issue was Türkoğlu et al.'s study showing the relationship between coronary slow flow and the H2FPEF score, which is used for the diagnosis of HFpEF.[1] The study was important in demonstrating the relationship between microvascular dysfunction and the pathophysiology of HFpEF using findings from current clinical practice. Undoubtedly the most important article about the topic was the journal's supplement Heart failure with Non-reduced Ejection Fraction.[2] The main purpose of preparing this supplement was to raise awareness of physicians on the patient group with an ejection fraction >40%, where uncertainties in diagnosis and treatment persist despite numerous studies on the subject, and to try to shed light on the approach to these patients in the light of current information.

The supplement Heart Failure with Non-reduced Ejection Fraction brought various novelties in terminology, treatment and diagnosis. To start with the terminology, the term non-reduced ejection fraction heart failure (HFnEF) was introduced as an umbrella term to cover HFpEF and HFmEF. In the past, the abbreviation HFnEF had been used for heart failure with 'normal' ejection fraction (EF >49%). This term was not very accurate in the context of the "how valuable is ejection fraction alone and what is its normal" debate and had been abandoned. In this article, the same abbreviation was chosen to describe patients without reduced ejection fraction.

In the HFnEF supplement, a large space has been reserved for the diagnostic approach. The main messages, especially in the diagnosis of the HFpEF patient group were to perform a detailed echocardiographic examination and to consider not only the resting values, but also the hemodynamic changes that develop with exercise. A confirmed diagnosis of HFpEF based on changes in heart rate, blood pressure, left ventricular filling pressure, and pulmonary artery pressure during exercise should be the basis of future clinical studies. However, it is also questionable how much detailed evaluation is required in daily practice. In clinical trials such as PARAGON-HF[3] and EMPEROR-Preserved[4]; in a patient with (1) ejection fraction ≥40-45%, (2) functional capacity NYHA class II-IV, and (3) left atrial enlargement or left ventricular hypertrophy on echocardiography, or who had been hospitalized for heart failure within the past year, only (4) measurement of an NT-proBNP value >200-300 pg/mL in patients sinus rhythm and >900 pg/mL in atrial fibrillation was considered sufficient to diagnose HFpEF. None of those studies used the H2FPEF or the HFA-PEFF score. Whether the diagnosis should be made as in clinical trials or with scoring systems is important not only in terms of detecting the undiagnosed patients, but also for determining the number of patients in the population and to make health economics projections.

According to the 2021 data of the Turkish Statistical Institute, the population aged ≥65 years in our country is 8.245.124 people and 55.7% of this population are women.[5] In this age group where comorbidities such as hypertension, obesity and frailty are frequent, determining patient profiles who will benefit more from certain treatments (especially sodium glucose co-transporter 2 inhibitors [SGLT2I], whose positive findings have been increasing in recent years) will be important for public health.

Today, there is increasing evidence that treatment strategies of HFmHF and HFpEF should be different and patients with HFmEF should be treated more like the HFrEF

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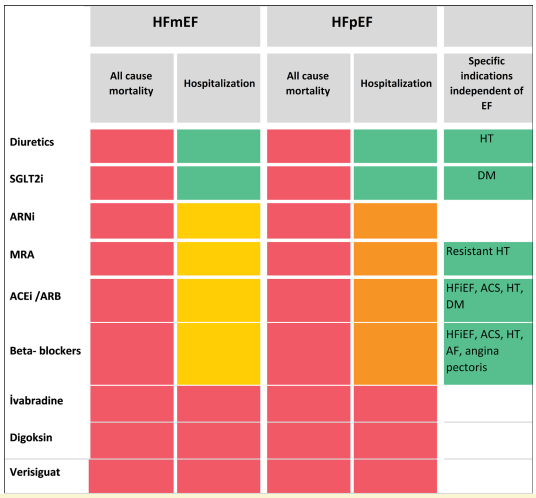

Figure 1
ACEi: angiotensin converting enzyme inhibitor, ACS: acute coronary syndrome, AF: atrial fibrillation, ARB: angiotensin receptor blocker, ARNi angiotensin receptor blocker-neprilysin inhibitor, DM: diabetes, EF: ejection fraction, HFiEF: heart failure with improved ejection fraction, HFmEF: heart failure with mildly reduced ejection fraction, HFpEF: heart with preserved ejection fraction, HT: hypertension, MRA: mineralocorticoid receptor antagonist, SGLT2i sodium glucose co-transporter 2 inhibitor. Green: should be recommended, yellow: should be considered, orange: may be considered, red: not recommended.

group. However, it should be kept in mind that there is no specific treatment study for the HFmEF group, and the available data are always obtained from subgroup analyzes of HFrEF or HFpEF studies. On the other hand, encouraging developments are seen in the treatment of HFpEF, the unlucky group of heart failure. In particular, the positive results of SGLT2i studies in terms of hospitalization and improvement in quality of life affected the current guidelines recommendations and made them recommended at class IIa level in the treatment of patients with HFpEF.

One of the ongoing debates is whether only the primary endpoints must be considered when determining the level of evidence for recommendations. In studies such as TOPCAT,[6] PARAGON-HF and EMPEROR-Preserved, drug efficacy has different statistical significance for different endpoints. Although there was no positive effect on mortality in these studies, the improvement in heart failure hospitalizations and quality of life, and also a relatively protective effect on kidney functions, is important for this patient group, where physicians are relatively helpless. In this context, an approach may be adopted in which treatment recommendations are shaped differently according to different endpoints (Figure 1).

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