



Approach to the Treatment of Heart Failure With Preserved Ejection Fraction and Mid-Range Ejection Fraction

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Abstract

In this article we discuss the treatment of heart failure (HF) with preserved ejection fraction (HFpEF) and of HF with mid-range ejection fraction (HFmrEF) as has received considerable interest since the publication of the 2016 European Society of Cardiology (ESC) heart failure guidelines. Since clinical trials on HFpEF have included also patients with HFmrEF, due to the lack of an agreed definition, the ESC recommendations here described apply to both phenotypes. As a consequence of the recent characterisation of this HF syndrome, it is expected that upcoming research will provide data specifically regarding HFmrEF and tailored recommendations will be developed in the future.

Keywords: Heart Failure; Guidelines; HFpEF; HFmrEF

Citation: Jankowska EA, Coats AJS, Anker SD. Approach to the Treatment of Heart Failure with Preserved Ejection Fraction and Mid-Range Ejection Fraction. International Cardiovascular Forum Journal. 2017;10:34-36 10.17987/icfj.v10i0.431

Introduction

In this chapter, treatment of heart failure (HF) with preserved ejection fraction (HFpEF) and of HF with mid-range ejection fraction (HFmrEF) according to the recent European Society of Cardiology (ESC) guidelines[1] will be described. Since clinical trials on HFpEF have included also patients with HFmrEF, due to the lack of a consensual definition (see article on diagnosis), ESC recommendations here described apply to both phenotypes. As a consequence of the recent characterisation of this HF syndrome, it is expected that upcoming research will provide data specifically regarding HFmrEF and tailored recommendations will be developed.

Symptomatic treatment of HFpEF/HFmrEF

Patients with HFpEF and HFmrEF are often treated with diuretics, beta-blockers, MRAs and ACEIs or ARBs in clinical trials,[2] similarly to patients with HFrEF. This may be possibly due to an anecdotal clinical assumption that these drugs may be beneficial in HFpEF/HFmrEF patients. Other reasons may be the lack of adherence to the guidelines and the treatment of comorbidities. [1] However, so far, the efficacy of these agents on mortality or

morbidity in patients with HFpEF/HFmrEF has not been clearly demonstrated. Thus, the ESC guidelines indicate as the goal

of therapy in HFpEF/HFmrEF the relief of symptomatology and the consequential improvement in quality of life.[3] In fact, patients in these categories are often elderly and present worse symptomatology, more comorbidities and poorer prognosis than HFrEF patients.[4,1]

In order to alleviate symptoms/signs, the ESC guidelines recommend the use of diuretics to improve congestion in HFpEF/HFmrEF patients. Congestion improvement has been obtained in HF patients regardless of the degree of left ventricular ejection fraction impairment.[5] Conversely, there is the need to investigate whether relief of symptoms/signs may be obtained with beta-blockers and MRAs in HFpEF/HFmrEF. There are inconsistencies about the efficacy of ARBs in HFpEF.[6-7] As for ACEIs, the Perindopril in elderly people with chronic heart failure (PEP-CHF) trial[8] has found that perindopril improved symptoms and exercise capacity with also fewer HF hospitalisations. Further studies are awaited to draw firm conclusions.

For hospitalisation reduction, the following agents have been found to be efficacious in HFpEF patients: nebivolol [9–11], digoxin [12], spironolactone [13] and candesartan. [6] It must be remembered that these findings are secondary analyses and therefore not as firm as primary end-point analyses of major RCTs. Notably, nebivolol has been shown its efficacy on a combined endpoint of death or cardiovascular hospitalization [9,11] in older patients with HFrEF, HFpEF and HFmrEF. These conclusions apply for patients in sinus rhythm. In HFpEF patients with atrial fibrillation, there is no evidence on digoxin, inconsistent results for ARBs or ACEIs and data so far collected suggest beta-blockers to be inefficacious. [1]

Finally, exercise capacity is compromised in HFpEF/HFmrEF and is often associated with an increased blood pressure response to exercise and chronotropic inability. Exercise training has been shown to improve exercise tolerance and to be safe [14,4] and is therefore indicated by the ESC guidelines.

Treatment of comorbidities in HFpEF/HFmrEF

In the clinical management of HFpEF/HFmrEF patients, assessment and treatment of comorbidities are pivotal. The guidelines recommend screening in these patients for both cardiovascular and non-cardiovascular comorbidities. In case the patient presents comorbidities, these should be treated with safe and effective interventions. This should facilitate improved symptoms, quality of life and/or prognosis. Patients with HFpEF/HFmrEF and atrial fibrillation should receive an anticoagulant to reduce the risk of thromboembolic events, according to the ESC guidelines. It should be noted that antiplatelet agents are not effective and NOACs are not indicated in the case of renal dysfunction due to the haemorrhagic risk. [1] The guidelines also indicate to consider rate control in these patients with caution. To date, due to the paucity of studies, it is unknown which agent should be chosen for rate-control and whether ablation strategies should be applied.

Another comorbidity that often affects HFpEF/HFmrEF patients is myocardial ischaemia, which also impacts symptomatology and prognosis. Further studies are needed to clarify whether revascularization has efficacy on symptoms, morbidity or mortality in HFpEF/HFmrEF. According to the ESC guidelines, HFpEF/HFmrEF patients with angina should be treated following the same protocol as HFrEF patients. [15] Also, HFpEF/HFmrEF patients may benefit from the treatment of hypertension, especially systolic hypertension. [16,17] Whereas beta-blockers are not effective in reducing systolic blood pressure, diuretics, ACEIs, ARBs and MRAs may be efficacious. [1] Circumstantial evidence [18] suggests that HFpEF/HFmrEF patients with hypertension should not be treated with an ARB in combination with ACEIs and beta-blockers.

Hyperglycaemia may be treated with metformin, the preferred oral agent in HFpEF patients according to the ESC Guidelines on diabetes. [19] Empagliflozin has been found [20] to decrease blood pressure and body weight, possibly acting on glycosuria and osmotic diuresis and this may in part explain the significant reduction in HF related hospitalisations it produced. However, an aggressive treatment of dysglycaemia should be avoided as it may be unsafe. [21,22]

What treatments can be indicated for the new concept of HFmrEF?

Treatment of HFmrEF remains largely empirical as no acknowledged standards currently exist. However, clinical trials on HFpEF published so far may give some indications to the clinician treating a patient with HFmrEF, although upcoming studies specifically including patients with this diagnosis are strongly needed. Clinical trials with upper left ventricular ejection fraction boundaries above 40% have yielded conclusions that may be clinically useful for the symptomatic treatment of HFmrEF patients. The Study of the Effects of Nebivolol Intervention on Outcomes and Hospitalisation in Seniors with Heart Failure (SENIORS) [9,10] suggests that nebivolol is well tolerated and effective in patients with HF, even when left ventricular systolic function is not markedly depressed. In this trial, nebivolol reduced the composite outcome of all-cause mortality or cardiovascular hospital admissions in older patients with HF [10] and nebivolol treatment was associated with a one-third reduction in the risk of ischaemic events, independently of ejection fraction. [23]

Similarly, regardless of ejection fraction, digoxin reduced mortality and hospitalisations in a wide spectrum of ambulatory chronic HF patients in the Digitalis Investigation Group: Preserved Ejection Fraction (DIG-PEF) trial. [12] Digoxin may be considered to alleviate HF symptoms before considering aggressive therapy (i.e. with high-dose non-potassium-sparing diuretics) [12] that may increase mortality and hospitalisations [24] in HFmrEF patients.

Results from clinical trials with RAAS antagonists need to be interpreted with caution, for both HFpEF and HFmrEF. The Treatment of preserved cardiac function heart failure with an Aldosterone antagonist (TOPCAT) [13] failed to show improvement in mortality with the use of spironolactone in HFpEF. However, as aforementioned, there is some evidence on RAAS efficacy on morbidity in HFpEF. Perindopril showed improvement in exercise capacity, and candesartan decreased hospitalisations for HF; however, irbesartan showed no benefit in either improving quality of life or decreasing hospitalisations for HF. [25] Thus, data collected so far suggest therapy with RAAS antagonists for HFpEF/HFmrEF only in presence of comorbidities such as hypertension, diabetes mellitus, or coronary artery disease. [25,26]

Declaration of Interest

The author declares no conflicts of interest.

Acknowledgements

The authors have abided by requirements for ethical publishing in biomedical journals [27].

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