Clinical Trials in Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction

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KEYWORDS

• HFpEF • NT-proBNP • Comorbidity • Clinical trials

KEY POINTS

- Neither clinical history nor echocardiography is a reliable diagnostic method in patients with heart failure and preserved left ventricular ejection fraction (HFpEF).
- Natriuretic peptides provide a powerful diagnostic and prognostic tool in patients with HFpEF.
- Diuretics can improve symptoms and congestion.
- There is compelling but not irrefutable evidence that angiotensin-converting enzyme inhibitors improve symptoms, functional capacity, morbidity, and possibly mortality amongst patients with HFpEF.
- There is compelling but not irrefutable evidence that mineralocorticoid receptor antagonists improve outcome in patients with HFpEF and an elevated N-terminal fragment of the prohormone of brain natriuretic peptide.
- There is less evidence that digoxin or β-blockers improve the outcome of HFpEF.

INTRODUCTION

Epidemiologic reports suggest that approximately 50% of patients who have signs or symptoms of heart failure (HF) have preserved left ventricular ejection fraction (LVEF). Compared to patients with HF and a reduced LVEF (HFrEF), patients with HF and preserved LVEF (HFpEF) are older, more likely to be women, and more often have hypertension and atrial fibrillation contributing to the development of HF. Epidemiologic studies suggest that patients with HF have a similar outcome regardless of LVEF; clinical trials do not! (**Fig. 1**).

Most clinical trials, with some notable exceptions,[1] defined HFpEF as a clinical diagnosis in the absence of a reduced LVEF. This weak definition causes problems because it does not exclude patients who have breathlessness or peripheral edema that are not primarily cardiac in origin. Treatments directed at cardiac dysfunction may be ineffective against chronic lung disease, obesity, lack of fitness, or venous insufficiency! Moreover, some of these comorbidities may be important drivers of outcome in HFpEF. The unintended consequence of excluding patients with comorbidities from clinical trials to increase their specificity for HF is a reduction in clinical event rates and loss of statistical power to show differences. The problem is further compounded by the fact that HFpEF is not one entity but many. For patients with HFrEF, using a reduced LVEF as an inclusion criterion ensures that the patient

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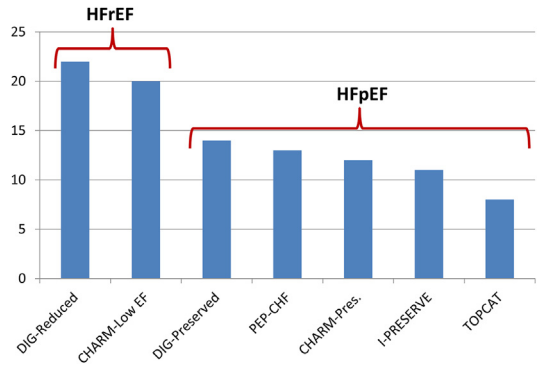

Fig. 1. Two-year mortality in patients with HFrEF and HFpEF. See text for explanation of acronyms and references.

has a cardiac problem, which may account for why clinical trials have been able to show that at least 6 interventions can reduce morbidity or mortality.[2–12] On the other hand, a normal LVEF provides no reassurance that a patient who is breathless or has swollen ankles has HF.

DIAGNOSIS AND CLASSIFICATION OF HFPEF

The diagnosis and classification of HFpEF is dealt with in detail later elsewhere in this issue, but it is appropriate to make some observations pertinent to clinical trials here. Although consensus and guidelines groups have made various recommendations for the diagnosis of HFpEF, they are relatively complex, none is universally accepted, and none has been applied to major clinical trials.[13–15] These recommendations are based on demonstrating an elevated LV filling pressure under resting conditions. However, filling pressures may be unremarkable at rest, especially if the patient is taking diuretics, but increase steeply with volume overload or exercise.[16,17] Normal filling pressures at rest do not exclude HFpEF. Exercise capacity may not be a reliable guide either, because there are so many factors that can limit it. Natriuretic peptides are consistently powerful prognostic markers in patients with either HFrEF or HFpEF, with few exceptions,[18] and therefore provide a valuable perspective on the disease (**Fig. 2**). However, natriuretic peptides also have problems with specificity, being heavily influenced by heart rhythm and renal function, as well as myocardial function.[19,20]

The ACC/AHA guidelines for the management of HF have introduced an important distinction between those patients who have HF and those who have preserved LVEF (>40%), with 3 groups of patients being identified: "possible" HFpEF (LVEF>50%), "borderline" HFpEF (40<LVEF<49), and "improved" HFpEF (LVEF>40%) but previous evidence of HFrEF.[21] Although there is still debate about whether HFpEF and HFrEF are a continuum of the same disease or heterogeneous clusters of separate clinical entities,[22,23] the risk factors for and patient characteristics of these 2 syndromes are different.[24] The ACC/AHA guidelines also emphasize that patients with HF often have a prodromal period with a paucity of symptoms. This prodromal phase, a pathophysiology characterized by cardiomyocyte hypertrophy, an increase in myocardial collagen, and expansion of the extracellular matrix, is probably a lot longer for

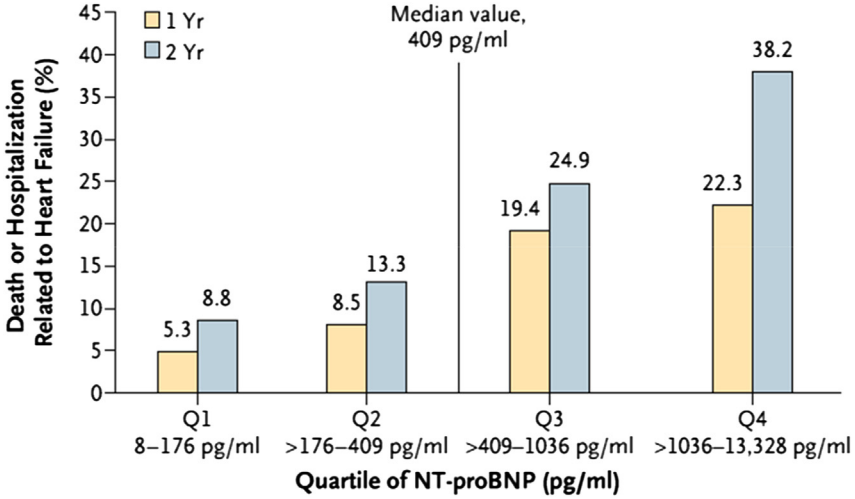

Fig. 2. Outcome according to quartiles of the plasma concentration of NT-proBNP in patients with HFpEF enrolled in the PEP-CHF study. (*From* Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27(19):2338–45; with permission.)

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