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REVIEW ARTICLE

Prognosis in heart failure with preserved ejection fraction

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Abstract

Heart Failure with preserved Ejection Fraction (HFpEF), like other heart failure syndromes, is heterogeneous in etiology and pathophysiology, rather than a single disease. HFpEF may account for about half of all patients with heart failure. Patients have symptoms and signs of HF with normal or near normal left ventricular EF (LV EF>50 %). The classical risk factors for developing HFpEF include advanced age and co-morbidities, notably hypertension, atrial fibrillation, and the metabolic syndrome. When complicated by increasing congestion requiring hospital admission, the prognosis is poor; 30% or more of such patients will die within 1 year (nearly two-thirds die from cardiovascular causes). Patients with chronic stable symptoms have a better prognosis. Patients with HFpEF represent an important group of patients presenting in clinical practice with HF. Overall, it appears that patients with HFpEF are at lower risk of death than patients with HFrEF, although mortality remains high in both groups. Application of the same therapeutic hypotheses that have been successfully utilized among patients with HFrEF have not been demonstrated to result in improved survival.

The syndrome of HFpEF has shown, on virtually every front, consensus-based diagnostic criteria resulting in a heterogeneous population challenging for clinical studies and trials. Moreover, the prevalence, morbidity, mortality, and healthcare costs of HFpEF is rising, in a similar way as HF with reduced EF (HFrEF).

The aging population and increased life expectancy have led to the rising prevalence of heart failure (HF) and despite the improvements in medical therapy, the mortality rate of this condition has remained unacceptably high. [2]

The diagnosis is generally made by history, physical examination and echocardiography (with the possible addition of tests such as plasma natriuretic peptide level or cardiopulmonary exercise testing). The management of HFrEF has improved significantly over the last two decades by contrast, little or no progress has been made in identifying evidence-based, effective treatments for HFpEF. Large phase III international clinical trials investigating interventions to improve outcomes in HFpEF have yielded disappointing results.[3]

Irrespective of specific diagnostic criteria and cut-offs, HFpEF is a syndrome where multiple cardiac and vascular abnormalities, cardiovascular risk factors, and overlapping extra-cardiac comorbidities may be present in various combinations as shown in (Table 1).

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Pathophysiological abnormalities.	Clinical syndromes
Ventricular Dysfunction: **-impaired relaxation** **- impaired filling** **-Systolic dysfunction**	COPD
Atrial Dysfunction	Iron Deficiency Anemia
Autonomic Dysfunction **Chronotropic incompetence**	Renal dysfunction with fluid volume overload
Vascular Dysfunction **Vascular stiffening** **Ventriculo-arterial coupling**	Aging and deconditioning
Elevated Blood **-inadquate BP response and Pulmonary hypertension**	Obesity and Sarcopenia
Dynamic mitral valve regurgitation	Psychiatric disorders (depression)
	Hypertension, Diabetes, ROS production

Table (1) Heterogeneity of the heart failure with preserved ejection fraction syndrome. BP = blood pressure; COPD = chronic obstructive pulmonary disease.

Matching treatment strategies to a specific patient's phenotype in HFpEF is a promising approach that warrants testing in clinical trials and may increase the likelihood of demonstrating clinical benefit (Table 2). Targeting specific phenotypes instead of following the 'one-size-fits-all' approach becomes increasingly important in the light of several failed, non-targeted, large-scale HFpEF trials. [4]

In a recent review of 25 RCTs comprising data for 18101 patients. All-cause mortality was reduced with beta-blocker therapy compared with placebo (RR: 0.78, 95%CI 0.65 to 0.94, p=0.008). There was no effect seen with ACE inhibitors, aldosterone receptor blockers, mineralocorticoid receptor antagonists and other drug classes, compared with placebo. Similar results were observed for cardiovascular mortality. No single drug class reduced heart failure hospitalization compared with placebo.[5]

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HF symptoms with preserved LVEF + Primary comorbidities

COMORBIDITIES	DRUG USED
HYPERTENSION	-ARB/ACEI -MRA -ARNI -Autonomic modulation
Fluid retention/Elevated filling pressure	-ARNI
Diabetes, obesity, metabolic syndrome, conditions associated with oxidative stress	-Glycemic control -Metformin(pleiotropic effects) -Weight loss, bariatric surgery, diet -PKG stimulation
Pulmonary hypertension or right heart involvement	-PDES inhibitor -Orally active soluble guanylate cyclase stimulator
Cardiac fibrosis	-MRA
Ischemia	-Na channel blockers -Nitrates -BB

Table 2: Potential approach for matching key heart failure with preserved ejection fraction phenotypes to select therapeutic interventions. ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; MRA, mineralocorticoid receptor antagonist; ARNI, angiotensin receptor and neprilysin inhibitor; HF, heart failure; HTN, hypertension; PKG, protein kinase G; AGE, advanced glycation end products; PDE, phosphodiesterase; MRA, mineralocorticoid receptor antagonist.[6]

A Mayo Clinic study examined all consecutive patients hospitalized with decompensated HF from 1987 through 2001.The proportion of patients with the diagnosis of HFpEF increased over time and was significantly higher among community patients than among referral patients (55 versus 45 percent). Over the next decade (2000 through 2010), the proportion of HF patients with HFpEF continued to increase while the incidence of HFpEF and HFrEF declined. Diastolic function worsens as part of aging even in individuals without other forms of cardiovascular disease, asymptomatic diastolic dysfunction is a predictor of future cardiovascular morbidity, but prognosis differs from that in patients with symptoms of HFpEF. [7]

Asymptomatic diastolic dysfunction — Diastolic dysfunction with normal systolic function without HF (also known as pre-clinical diastolic dysfunction) is a common finding in older adults and a predictor of mortality, as illustrated by the following studies:

In the Mayo Clinic cross-sectional community survey of 2042 adults ≥45 years of age, 21 percent had mild diastolic dysfunction, 7 percent had moderate

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diastolic dysfunction, and 1 percent had severe diastolic dysfunction. At a median follow-up of 3.5 years, 48 subjects died. After controlling for age, sex, and left ventricular EF (LVEF), all-cause mortality was increased in patients with mild diastolic dysfunction (96 percent without a diagnosis of HF; hazard ratio 8.3) and in those with moderate to severe diastolic dysfunction (90 percent without a diagnosis of HF; hazard ratio 10.2). [8]

In another report, 3008 Native Americans 45 to 74 years of age were followed for three years following Doppler echocardiography. Sixteen percent of patients had an E/A ratio <0.6 (impaired diastolic relaxation) and 3 percent had an E/A ratio >1.5 (restrictive pattern due to reduced compliance). After adjustment for covariates, an E/A ratio >1.5, but not an E/A ratio <0.6, was independently associated with all-cause and cardiac mortality (relative risks 1.7 and 2.8, respectively).[9]

A Cleveland Clinic study followed 36,261 adults (mean age 58) with LVEF ≥55 percent for a mean of 6.2 years. Sixty percent had mild diastolic dysfunction, 4.8 percent had moderate diastolic dysfunction, and 0.4 percent had severe diastolic dysfunction. During the follow-up period, 5789 deaths occurred. Moderate and severe (but not mild) diastolic dysfunction were independent risk factors for mortality after adjustment for cardiovascular risk factors and comorbidities (hazard ratio 1.58; 95% CI 1.20-1.28 and hazard ratio 1.84; 95% CI 1.29-2.62).[10]

In the meta-analysis of Global Group in Chronic Heart Failure (MAGGIC), They compared survival in patients with HFpEF with that in patients with HFrEF in a meta-analysis using individual patient data. Preserved EF was defined as an EF ≥ 50%. The 31 studies included 41 972 patients: 10 347 with HFPEF and 31 625 with HFrEF. Compared with patients with HFrEF, those with HFrEF were older (mean age 71 vs. 66 years), were more often women (50 vs. 28%), and have a history of hypertension (51 vs. 41%). Ischemic etiology was less common (43 vs. 59%) in patients with HFpEF. There were 121 [95% confidence interval (CI): 117, 126] deaths per 1000 patient-years in those with HFpEF and 141 (95% CI: 138, 144) deaths per 1000 patient-years in those with HFrEF. Patients with HFpEF had lower mortality than those with HFrEF (adjusted for age, gender, etiology, and history of hypertension, diabetes, and atrial fibrillation); hazard ratio 0.68 (95% CI: 0.64, 0.71). The risk of death did not increase notably until EF fell below 40%. [11]

Thirty one of the 56 identified studies contributed data on 54 416 patients (Figure 3). One thousand one hundred and seventy-nine patients were excluded due to irresolvable dates or death during an index hospital admission and 2246 excluded as heart failure was secondary to severe valvular heart disease or hypertrophic cardiomyopathy. Ejection fraction data were not available for 9019 patients, and thus the main analysis was based on 41 972 patients for whom EF data were available. Ejection fraction was assessed using echocardiography in 33 717 (80.4%), scintigraphy in 6899 (16.4%), and angiography in 1356 (3.2%). Quantitative EF data were available for 38 484 (92%) patients and the remainder (3488, 8%) had semi-quantitative EF assessment: 10 347 (24.7%) patients had HFpEF and 31 625 (75.3%) had HFrEF. When compared with the HFrEF patients, those with HFpEF were older (mean age 71 years SD 12 vs. 66 years SD 12), were more often women (50 vs. 28%), more often had a history of hypertension (51 vs. 41%) and atrial fibrillation (27 vs. 18%), and less often ischemic etiology (43 vs. 59%). Patients with HFrEF were more commonly receiving

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treatment with an ACE-inhibitor (75 vs. 44%), β-blocker (39 vs. 33%), and spironolactone (24 vs. 16%) compared with those with HFpEF. For the 25 studies for which patient data were not available, the weighted mean from published data showed that these patients were slightly older (mean age 71 years), fewer were women (34%), and the proportion of patients with missing EF was higher (33%) than the included studies.

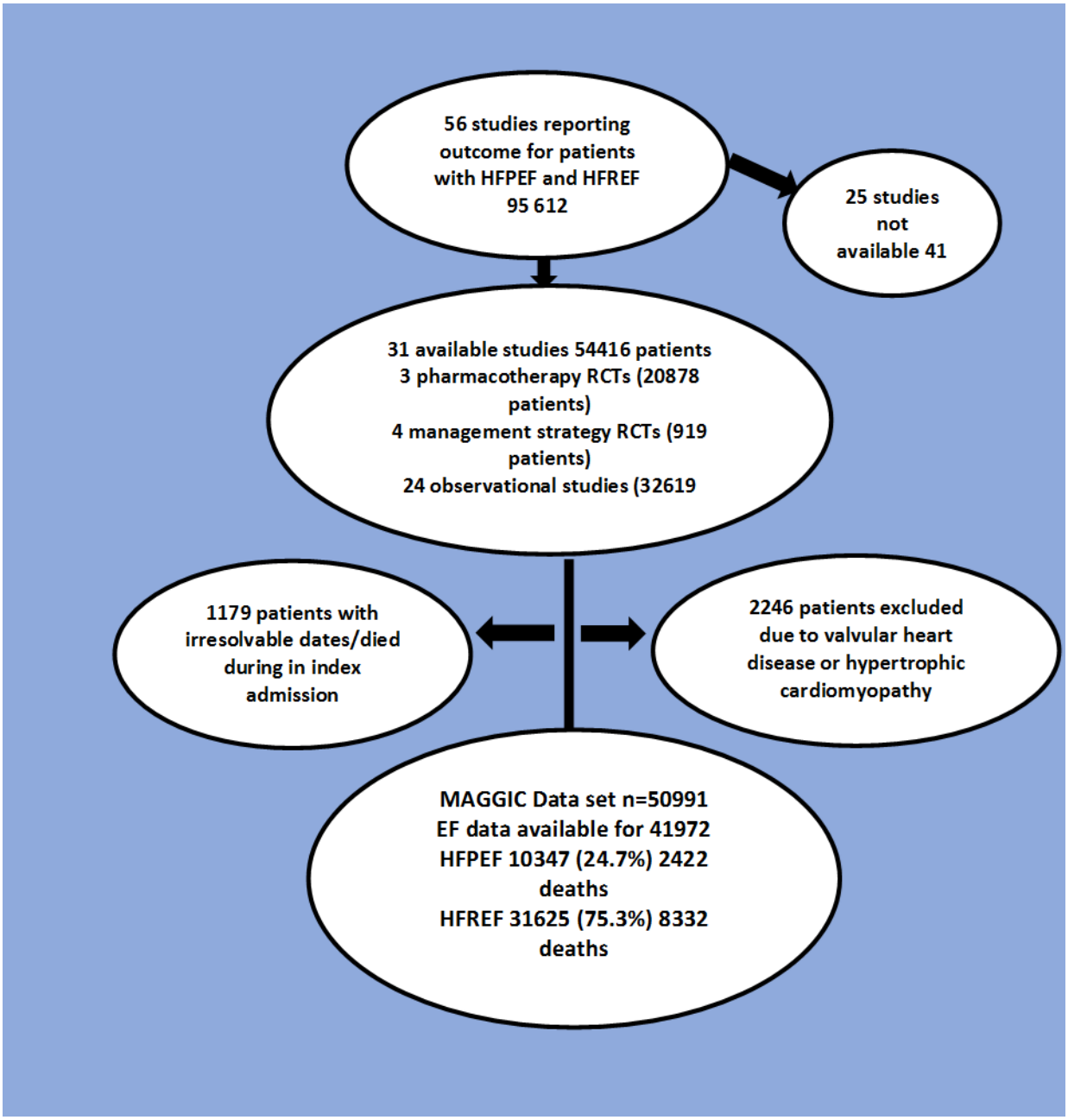

Figure 3: Flow Chart; The meta-analysis of the MAGGIC studies

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The conclusion of this meta-analysis showed that patients with HFpEF have a lower risk of death than patients with HFrEF, and this difference is seen regardless of age, gender, and aetiology of HF. However, absolute mortality is still high in patients with HFpEF highlighting the need for a treatment to improve prognosis.

Symptomatic patients with HFpEF)

The prognosis of patients with HFpEF (ie, symptomatic HF) is less well defined than that of patients with HFrEF. Population-based data from hospitalized patients have shown similar outcomes in patients with HFpEF and HFrEF. However, a large meta-analysis, including community-based studies and trials, observed lower mortality in HFpEF compared with HFrEF, though survival was still much worse than in people without HF. Among patients hospitalized for HF, the mortality rates are higher but the data are again conflicting as to whether or not the prognosis is different in HFpEF and HFrEF:[12]

Among 6076 patients discharged from a Mayo Clinic Hospital in Olmsted County, Minnesota with a diagnosis of decompensated HF over a 15-year period (1987 to 2001), 53 percent had a reduced LVEF and 47 percent had a preserved LVEF. One-year mortality was relatively high in both groups but slightly lower in patients with a preserved LVEF (29 versus 32 percent in patients with reduced LVEF, adjusted hazard ratio 0.96, 95% CI 0.92-1.00). Survival improved over time for those with reduced LVEF but not for those with preserved LVEF.[13]

In a cohort of 2802 patients discharged from 103 hospitals in Ontario with a diagnosis of decompensated HF, one-year mortality was 22 percent in patients with a preserved LVEF versus 26 percent in patients with a reduced LVEF. This difference was not statistically significant.[14]

HFpEF in patients with acute myocardial infarction.

In a study of 1,474 patients with acute myocardial infarction, One-third of patients admitted with heart failure had preserved left ventricular ejection fraction. Although this subgroup exhibited more favorable outcomes than those with systolic dysfunction, this condition presented a three-fold higher risk of death than the group without heart failure. Patients with acute myocardial infarction and heart failure with preserved left ventricular ejection fraction encounter elevated short-term risk and require special attention and monitoring during hospitalization.[15]

Independent predictors of mortality in patients with HFpEF in different studies include older age, male gender, New York Heart Association (NYHA) class, lower LVEF, the extent of coronary artery disease, peripheral artery disease, diabetes, impaired renal function, the degree of diastolic dysfunction as assessed by Doppler echocardiography, and increased red cell distribution width

Morbidity outcomes in HFrEF and HFpEF are similar. These include the rate and frequency of hospitalization for HF, symptomatic status as measured by abnormalities in myocardial oxygen consumption, six-minute walk distance, Minnesota Living with Heart Failure questionnaire scores, and other quality-of-life indicators. Therefore, patients with HFpEF have a morbidity burden equivalent to that in patients with HFrEF.

Diastolic HF is associated with high mortality comparable with that of HF with depressed ejection fraction with a five year survival rate after a first episode of 43% and a higher excess mortality compared with the general population.

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In patients with diastolic HF older age, male gender, non-Caucasian ethnicity, history of coronary artery disease and atrial fibrillation are associated with poor prognosis. Anemia and B-type natriuretic peptide are significant laboratory variable that predict mortality. Two dimensional echocardiography and tissue Doppler imaging measurements including left ventricular ejection fraction, E/Ea ratio ≥ 15, restrictive transmiral filling (deceleration time £ 140 ms) and Em < 3.5 cm/s(early diastolic mitral annulus velocity) are predictors of adverse outcomes in diastolic HF patients.

However, In a retrospective study of 289 patients (Age group 79 ± 7) which investigated 5-year-mortality and its prognostic factors in old patients with HFpEF compared with those with HFrEF

it was found that HFpEF has a better long-term prognosis than HFrEF and a distinct prognostic risk profile. Morbidity outcomes in HFrEF and HFpEF are similar .These include the rate and frequency of hospitalization for HF, symptomatic status as measured by abnormalities in myocardial oxygen consumption, six-minute walk distance, Minnesota Living with Heart Failure questionnaire scores, and other quality-of-life indicators. Therefore, patients with HFpEF have a morbidity burden equivalent to that in patients with HFrEF [16]. Among patients hospitalized with HF, patients with HFpEF with borderline EF had lower mortality and higher all-cause readmission risk than patients with HFrEF, although the mortality differences did not persist after risk adjustment. Irrespective of EF [17].

Conclusion

Although there has been considerable progress in the management of systolic heart failure (SHF), the management of HFpEF remains mostly empirical because of lack of knowledge of the molecular and biochemical mechanisms which produce myocardial structural and functional changes in this syndrome. There is a lack of consensus on the basic pathophysiology, definition, and therapeutic targets for therapy for this syndrome. The syndrome of heart failure with preserved ejection fraction (HFpEF) remains poorly understood and portrays a significant burden in terms of prevalence, morbidity, mortality, and health care costs. The proportions of cardiovascular and non-cardiovascular deaths among patients with HFpEF have varied among trials and epidemiologic studies, with higher proportions of non-cardiovascular deaths in population-based studies. Morbidity in HFpEF is similar to that in HFrEF.

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