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Editorial

Prognosis for Patients With Heart Failure With Preserved Ejection Fraction. Is It the Same As Low Ejection Fraction?

Pronóstico de los pacientes con insuficiencia cardiaca y fracción de eyección preservada. ¿Es el mismo que con fracción de eyección baja?

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Heart failure (HF) is a significant and increasing global public health problem. In the United States, hospital admissions for a principal diagnosis of HF increased from 399 000 in 1979 to 1 093 000 in 2003.[1] The diagnosis of HF continues to be associated with poor quality of life, high morbidity, and high mortality despite contemporary HF management.[2,3] Once admitted to hospital, patients experience high rates of subsequent HF hospitalization and mortality.[2]

HF has been traditionally viewed as a failure of contractile function and left ventricular ejection fraction (LVEF) has been widely used to define systolic function, assess prognosis, and select patients for therapeutic interventions. The combination of evidence-based pharmacotherapy (mainly neurohormonal antagonists) and device-based therapies has now resulted in significant improvements in prognosis for patients with HF with low ejection fraction (HF-lowEF), with annualized mortality rates as low as 6% in recent randomized, controlled trials with optimal therapy.[4] However, the population of patients enrolled in these trials does not reflect those patients seen in clinical practice who typically are older with more comorbidities and for whom annual mortality rates remain high (30% or more in many series).[3,5,6]

HF can also occur in the presence of normal or near-normal EF: so-called "heart failure with preserved EF (HF-PEF)" which accounts for 30%-50% of clinical cases of HF.[5,7–9] Patients with HF-PEF have been identified by a process of exclusion through measurement of EF and inclusion of those LVEF above a certain cut-off value. Variable cut-off values of EF have been used, including 40%, 45%, or 50%.[8,9] However, this process of exclusion rather than inclusion is likely to result in a very heterogeneous group of patients, including those who have breathlessness or peripheral edema but who may not have HF. Consequently, various criteria have been proposed to define patients with "diastolic HF". Some of these criteria have comprised complex algorithms often including invasive hemodynamic measurements. This has resulted in low clinical uptake of such criteria.[10] Despite these difficulties with definition, patients with HF-PEF represent a significant and increasing proportion of the clinical HF population. In 2007 new guidelines were published for the diagnosis of HF-PEF[11]; these include the following criteria: signs or symptoms of HF, normal or mildly abnormal LV systolic function (LVEF>50% and LV end-diastolic volume index<97 ml/m^2), and evidence of LV diastolic dysfunction (LV end-diastolic pressure>16 mmHg, or echo-Doppler E/E'>15, or elevated NT-proBNP>220pg/ml with abnormal echo-Doppler parameters). While these new criteria are theoretically sound and certainly more practical in the clinical setting than previous guidelines, the detailed characteristics and outcomes of patients identified by these criteria remain uncertain.

There are many differences between patients with HF-lowEF and those with HF-PEF. The latter are older and more often women, less likely to have coronary artery disease, and more likely to have underlying hypertension.[5,7] In addition, patients with HF-PEF do not obtain similar clinical benefits from angiotensin-converting enzyme inhibition or angiotensin receptor blockade compared with patients with HF-lowEF.[12–14] While there are now a number of studies that have reported outcomes for patients with HF-PEF compared with those with HF-lowEF the results have been conflicting. Recent high-profile studies have reported on the prevalence and clinical outcome for patients with HF-PEF compared with HF-lowEF. A study from the United States reported that 47% of patients hospitalized with HF in Olmsted County (United States) had HF-PEF, that the proportion of patients with HF-PEF increased over time (1988 to 2001), and that survival was only slightly better among patients with HF-PEF than for those with HF-lowEF (adjusted hazard ratio 0.96, $P = .01$).[5] In this study, survival among patients with HF-lowEF improved over time, but did not change for patients with HF-PEF. In a study of patients hospitalized for HF in Ontario, Canada (1999-2001), 31% had HF-PEF and among these patients mortality and readmission rates were similar to those with HF-lowEF.[7] The OPTIMIZE-HF registry, involving 41 267 patients, reported that 51% of patients had HF-PEF. The 90-day outcome was available from a pre-specified subset of 10% of these patients and demonstrated that survival rates were similar between patients with HF-PEF and HE-lowEF.[9]

However, despite involving large numbers of patients these and other studies may be subject to important bias. Studies of outcome in patients in this setting ideally should include consecutive patients and require accurate assessment of EF in all patients, as it

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is this criterion that is used to define the low and preserved EF groups of patients. Unfortunately, many studies are limited by either not recruiting consecutive patients or not having documented LVEF in all patients. For example, in the studies quoted above EF was not available in 15%,[9] 24%,[5] and 70%[7] of eligible patients, who were then excluded from the analyses. This would not be of major consequence if the number of patients with missing measurements was small and randomly occurred in both groups of patients, but this is not likely to be the case, creating the potential for systematic selection bias. The measurement of EF is performed less frequently in older subjects with HF,[15] and patients in whom EF was missing may have a different outcome than those in whom it was measured.[16] Furthermore, HF-PEF patients are often older and more likely to be female, further supporting the likelihood of systematic bias when comparing patients with HF-PEF with HF-lowEF if patients are excluded on the basis of missing EF measurements. Excluding such patients impacts upon our understanding of the true prevalence and outcome of this condition.

In order to address this issue further we recently undertook a literature-based meta-analysis which demonstrated that patients with HF-PEF may have lower mortality than those with HF-lowEF.[17] However, lack of patient-level data precluded careful adjustment for differences between these patient groups in potentially important prognostic variables such as age, sex, comorbidity and etiology of HF. As a result we have recently undertaken a large scale meta-analysis using individual patient data to examine the differences in outcome for these groups of patients with HF. The MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) meta-analysis, involving a broad collaborative network of HF investigators, aggregated data from 54 416 patients from 31 studies of patients with HF where an EF inclusion criterion was not used and for whom outcome data were reported. The results demonstrated that patients with HF-PEF had lower risk of death from any cause than patients with HF-lowEF (hazard ratio 0.68, 95% confidence interval 0.64, 0.71) [presentation at Clinical Trials Update European Society of Cardiology, 2009]. These results clearly demonstrate that the group of patients with HF-PEF have lower risk of death than patients with HF-lowEF.

The extensive literature regarding patients with HF-lowEF has reinforced the importance of considering the cause of death among patients with HF. Sudden death and death from progressive HF are common causes of death among patients with HF-lowEF and appropriate evidence-based therapies reduce these major causes of death among this group of patients. With the differences in clinical characteristics and all-cause mortality among patients with HF-PEF and HF-lowEF, it is also relevant to consider cause-specific mortality among those with HF-PEF. Cardiovascular deaths are a common cause of death among patients with HF-PEF, although the proportion differs according to study design (60% of all deaths in the randomized, controlled trials[18–20] and 49% of deaths in community-based observational studies[21,22]), which may reflect that observational studies often involve older patients with a wider range of comorbidities than patients in randomized, controlled trials. Sudden death and death due to progressive HF appear to be less common among patients with HF-PEF compared with those with HF-lowEF. Further understanding of the cause of death in patients with HF-PEF will assist with the development of appropriate strategies to improve outcome for these patients.

Patients with HF-PEF represent an important group of patients presenting in clinical practice with HF. Overall, it appears that patients with HF-PEF are at lower risk of death than patients with HF-lowEF, although mortality remains high. Application of the same therapeutic hypotheses that have been so successfully utilized among patients with HF-lowEF has not been demonstrated to result in improved survival. Thus at present no clear evidence-based recommendations can be made for suitable therapeutic interventions for this group of patients. Further detailed characterization of this group of patients is urgently required to understand the mechanisms underlying the HF syndrome and to reveal suitable therapeutic targets that may ultimately improve the outcome for this group of patients.

CONFLICTS OF INTEREST

None declared.

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