VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2011, Vol. 18, No. 3, pp. 222–232

ISSN 1897–5593

Diastolic heart failure: Predictors of mortality

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Abstract

Diastolic heart failure (HF) as defined by the symptoms and signs of HF, preserved ejection fraction and abnormal diastolic function is estimated to occur in half of all patients presenting with HF. Patients with preserved ejection fraction are older and more often female. The underlying etiology of HF differs, with hypertension being more common in patients with preserved ejection fraction and ischemic heart disease predominant among those with reduced ejection fraction. 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. Despite significant disease burden, clinical and biological prognostic factors in diastolic HF remain poorly understood. There is limited data from well designed studies regarding the effective treatment strategies for this group of patients. The purpose of this review is to summarize the mortality data and predictors of mortality in patients with diastolic HF for better understanding of the prognosis. 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 are predictors of adverse outcomes in diastolic HF patients.
(Cardiol J 2011; 18, 3: 222–232)

Key words: diastolic heart failure, heart failure with preserved ejection fraction and mortality

Introduction

Diastolic heart failure (DHF) is a clinical syndrome defined by the presence of symptoms and signs of heart failure (HF), preserved ejection fraction (EF), and abnormal diastolic function [1]. Diastolic dysfunction refers to an abnormality of diastolic distensibility, filling, or relaxation of the left ventricle [2]. DHF is also known by other terms such as heart failure with preserved ejection fraction (HFPEF) or HF with preserved systolic function, which describe patients with symptoms and signs of HF with normal EF. Objective evidence for diastolic dysfunction is not necessary in using these terms. It is estimated that approximately half of all patients with HF have a preserved EF [3]. Although the prevalence of HFPEF has been increasing, the survival of this group of patients has not improved over the past several decades [4].

The syndrome is associated with significant morbidity. Studies have shown a similar length of hospitalization, decline in functional status, and re-hospitalization in patients with HFPEF compared to patients with HF and reduced EF [5, 6]. The

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mortality in patients with HFPEF is reported to be as high as the mortality in patients with HF and depressed systolic function, although a few reports have suggested better survival in patients with HFPEF. The mortality rate for patients with DHF is reported to be 5–8% annually compared to 10––15% in patients with depressed systolic function, whereas the mortality for age-matched controls approaches 1% [1]. In a nested case control study, the mortality among patients with HF and normal EF was 8.7%, as compared with 3.0% among matched control subjects [7]. In a study of 413 patients hospitalized for HF with EF ≥ 40% from March 1996 through September 1998, a similar number of deaths were observed among patients with preserved EF compared to those with depressed EF at the end of a six month follow-up (13% *vs* 21%, p = 0.02) [6]. There was no difference in the rates of functional decline among those with preserved and depressed EF (30% *vs* 23%, respectively; p = 0.14). No significant difference was seen in the risk of readmission (hazard ratio [HR] 1.01, p = 0.96) or the odds of functional decline or death (odds ratio [OR] 1.01, p = 0.97). The results from this study highlight the significantly high absolute burden from mortality and morbidity associated with HFPEF.

Tribouilloy et al. [8] described the long-term prognosis of HFPEF in patients hospitalized for a first episode of HF. During a five year follow-up, 370 (56%) patients died. Patients with HFPEF had significantly lower five year survival than the age- and sex-matched general population (43% *vs* 72%). Five year survival rates were not significantly different in patients with preserved and reduced EF (43% *vs* 46%, p = 0.95). Both groups had similar relative five year survival rates compared to the general population. The study concluded that HFPEF has a poor prognosis, comparable with that of HF with reduced EF, with a five year survival rate after a first episode of 43% and a high excess mortality compared to the general population.

In a population based study, Bhatia et al. [9] reported an unadjusted mortality rate of 5% in patients with an EF > 50% compared to 7% in patients with EF < 40% at 30 days (p = 0.08) and at one year (22% *vs* 26%, p = 0.07), respectively. Adjusted one-year mortality rates were also not significantly different in the two groups (HR 1.13, p = 0.18). The rates of readmission for HF and of in-hospital complications did not differ between the two groups. The survival of patients with HF with preserved EF was similar to that of patients with reduced EF.

Other reports have suggested a favorable prognosis in patients with HFPEF compared to those with HF with depressed systolic function. The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-Preserve) trial annual mortality was 5.2% in patients with HFPEF [10]. The mortality rates in patients with HFPEF/DHF in epidemiological studies and randomized clinical trials are summarized in Table 1 and Table 2, respectively. The varying mortality rates are driven by numerous factors including study designs, patient age, EF criteria, and outpatient or inpatient study population. Patients with DHF tend to be older, more female, with a higher prevalence of hypertension and less coronary artery disease (CAD) compared to patients with HF and reduced EF [3, 11].

In patients with DHF, cardiovascular (CV) diseases (60%) are the leading cause of death including sudden cardiac death (26%), HF (15%), myocardial infarction (5%) and stroke (9%) followed by non-CV causes (30%) and unknown (10%) [3]. The prognostic factors in patients with HF and depressed systolic function are well understood. However, there remains uncertainty regarding important prognostic factors in patients with HFPEF. Knowledge of these important clinical and biological variables will help identify subgroups of patients at very high risk for adverse outcomes. There is limited data from well designed studies regarding effective treatment strategies for HF patients with diastolic dysfunction. In this review, we describe from the literature the demographic, clinical and laboratory variables that significantly affect the outcomes of patients with DHF.

Hypertension

Hypertension is one of the greatest risk factors for diastolic dysfunction. Through a variety of mechanisms, including increased afterload, left ventricular hypertrophy, myocardial fibrosis and impaired diastolic filling, hypertension may lead to subsequent HF. Diastolic dysfunction is believed to be a 'pathophysiological intermediate' between hypertension and HF. Studies have indicated that echocardiographic evidence of diastolic dysfunction is an independent risk factor for the future development of HF and cardiac death [12].

In a cross-sectional study from Olmsted County, Minnesota, USA, 20.8% of participants had mild, 6.6% had moderate, and 0.7% had severe, diastolic dysfunction, with 5.6% having moderate or severe diastolic dysfunction with normal EF. The presence of mild diastolic dysfunction (HR 8.31, p ≤ 0.001) and moderate to severe diastolic dysfunction (HR 10.17, p ≤ 0.001) was associated with marked increases in

Table 1. Summary of mortality rates from epidemiological studies in patients with heart failure with preserved ejection fraction.

Study	Design	N	Study population	Mortality	Follow-up
Vasan et al. [7]	Nested case control	CHF cases: 73 Age/gender control: 146	LVEF > 50 51% LVEF > 50 Outpatients	Cases normal EF *vs* control: 8.7% *vs* 3.0% Reduced EF *vs* control: 18.9% *vs* 4.1%	6.2 years (median)
Owan et al. [4] 1/87 to 12/01	Retrospective study	N = 4,596 Preserved EF: 2,167 Reduced EF: 2,429	LVEF ≥ 50 Hospitalized	29% *vs* 32%	10.0 ± 4.2 years (mean)
O'Connor et al. [21] 1/84 to 12/96	Prospective study	2,498	LVEF > 40 class II–IV Had cardiac catheterization	28% mortality	Five years
Smith et al. [6] 3/96 to 9/98	Prospective	413	LVEF ≥ 40 Hospitalized	Preserved EF *vs* reduced EF: 13% *vs* 21%	Six months
Bhatia et al. [9] 4/99 to 3/01	Retrospective	2,802	LVEF < 40 LVEF > 50%	22% *vs* 26%	One year
Tribouilloy et al. [8] 1/00 to 12/00	Prospective	799	LVEF ≥ 50% Hospitalized	Preserved EF *vs* reduced EF: 57% *vs* 54%	Five years

CHF — congestive heart failure; EF — ejection fraction; HF — heart failure; LVEF — left ventricular ejection fraction

Table 2. Summary estimates of mortality from randomized clinical trials in patients with heart failure and preserved left ventricular ejection fraction.

Trial	N	Population	Protocol	Primary outcome	Event rate	Hazard ratio (p)	Follow-up
PEP-CHF [17]	850	HF and LVEF ≥ 45%	Perindopril 4 mg *vs* placebo	All-cause mortality and HF hospitalization	Primary outcome Placebo *vs* perindopril: 25.1% *vs* 23.6% All cause mortality: 13.3% *vs* 12.4% Annual mortality: 4.5% *vs* 4%	0.92 (0.5)	25 months
CHARM--Preserve [18]	3,023	HF and LVEF > 40%	Candesartan 32 mg *vs* placebo	CV death and HF hospitalization	Primary outcome Placebo *vs* candesartan: 24% *vs* 22% CV mortality: 11.3% *vs* 11.2% All-cause mortality: 16.1% *vs* 15.7%	0.89 (0.118)	36 months
Digoxin trial [19]	988	HF and LVEF ≥ 45%	Digoxin 0.25 mg *vs* placebo	HF mortality and HF hospitalization	Primary outcome Placebo *vs* digoxin: 24% *vs* 21% All-cause mortality: 23.4% *vs* 23.4%	0.82 (0.136)	37 months
I-Preserve [3]	4,128	HF and LVEF ≥ 45%	Irbesartan 300 mg *vs* placebo	All-cause mortality and CV hospitalization	Primary outcome Placebo *vs* irbesartan: 21.1% *vs* 21.5% CV mortality: 14.6% *vs* 15% Annual mortality: 5.2% 25% sudden deaths	0.95 (0.35)	60 months

HF — heart failure; LVEF — left ventricular ejection fraction; CV — cardiovascular

all-cause mortality [13]. Better blood pressure control leads to significant reduction in the development of new HF. The results from the Systolic Hypertension in the Elderly Program (SHEP) evaluated the role of anti-hypertensive agents to prevent HF in 4,736 patients with a history of isolated systolic hypertension, randomized to chlorthalidone *vs* placebo or atenolol *vs* matching placebo in a step-care plan. This stepped care treatment of hypertension led to a significant reduction in the development of new HF. The relative risk (RR) reduction was approximately 50% (RR 0.51, $p < 0.001$) [14].

Data from the Anti-Hypertensive Lipid Lowering to Prevent Heart Attack Trial (ALLHAT) showed that chlorthalidone significantly reduced the incidence of new onset HFPEF compared to lisinopril. However, the effects of chlorthalidone and lisinopril on reducing the incidence of HF with reduced ejection fraction were similar [15].

Adequate blood pressure lowering improves diastolic dysfunction irrespective of the type of anti-hypertensive medications. The hypothesis that renin–angiotensin–aldosterone system (RAAS) blocking agents improve diastolic dysfunction more significantly than other anti-hypertensive medications was evaluated in a study of patients with hypertension, left ventricular ejection fraction (LVEF) > 50% and evidence of diastolic dysfunction [16]. Patients were randomly assigned to receive either the angiotensin receptor blocker (ARB) valsartan or a matched placebo. Patients in both groups were also treated with other anti-hypertensive agents that did not block RAAS. There was no significant difference in blood pressure reduction in either group. However, diastolic relaxation velocity increased by 0.60 cm/s from baseline in the valsartan group ($p < 0.0001$) and by 0.44 cm/s in the placebo group ($p < 0.0008$) at the end of 38 weeks of treatment. The study concluded that among patients with hypertension and diastolic dysfunction, lowering blood pressure improves diastolic function irrespective of the type of anti-hypertensive.

Clinical trials in HFPEF and DHF

There is limited data from well-designed randomized clinical trials (RCT) regarding the effectiveness of numerous therapeutic agents in patients with DHF. Overall, various agents including angiotensin converting enzyme inhibitor and ARB, which have been shown to improve mortality in patients with HF and reduced EF, did not show similar results in patients with HFPEF. A brief review of the RCTs in patients with DHF is presented in Table 2.

Perindopril in Elderly Patients with Chronic Heart Failure (PEP-CHF) was the first RCT to evaluate the role of adding perindopril to diuretics in patients with HF and preserved LV function. Elderly patients ≥ 70 years with a diagnosis of HF, LVEF of ≥ 45% and echocardiographic features suggesting possible diastolic dysfunction were randomized to receive perindopril at 4 mg/day or a placebo. The study showed no difference in mortality or HF hospitalization [17].

The Candesartan in Heart Failure Assessment of Mortality and Morbidity (CHARM) preserved trial showed that candesartan did not reduce mortality in patients with symptomatic HF and preserved LVEF. However, there was a significant reduction in re-hospitalization for HF in the candesartan group (230 *vs* 279, $p = 0.017$). Three thousand and twenty three patients with a history of congestive heart failure, New York Heart Association (NYHA) class II–IV symptoms and LVEF > 40% were randomly assigned to candesartan *vs* matching placebo in 1999––2000. Patients were on other anti-hypertensive agents as well in both arms. At the end of a 36.6 month median follow-up, there was no difference in CV deaths in both groups (170 *vs* 170) [18].

The ancillary Digitalis Investigation Group (DIG) study evaluated the role of digoxin in patients with HFPEF > 45%. In a mean follow-up of 37 months, digoxin did not reduce the risk of death from any cause, or hospitalization for a CV cause, compared to a placebo. However there was a trend in reducing the risk of hospitalization for worsening HF (HR 0.79, $p = 0.09$) [19].

Most recently, the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-Preserve) trial randomized 4,128 patients, aged 60 and above, NYHA class II–IV HF symptoms, LVEF ≥ 45%, to receive irbesartan 300 mg/d *vs* placebo. Annual mortality was 5.2% in the study. There was no difference in mortality in irbesartan *vs* placebo (HR 0.95, $p = 0.35$). Irbesartan did not reduce the primary endpoints of death and protocol-specified CV hospitalizations, nor did it significantly benefit pre-specified secondary endpoints. For this large group of patients constituting half of all HF patients, there continues to be no specific evidence-based therapy [10].

Predictors of mortality in patients with HFPEF and DHF (Table 3)

Demographics

Age has been recognized as one of the most important determinants of prognosis in patients with DHF. The approximate five-year mortality rate

Table 3. Predictors of mortality in patients with diastolic heart failure.

Clinical parameter	Risk estimates
Age	
For every SD increase in the age^2 [20]	HR 1.28, p = 0.0019
5 year mortality [1]:	
< 50 years	15%
50–70 years	33%
> 70 years	50%
Male gender [20]	HR 1.71
Caucasian race (adjusted risk ratio) [21]	RR 0.75
Coronary artery disease (adjusted risk ratio) [21]	RR 1.1
AF	
Five-year survival sinus rhythm *vs* AF [25]	72% *vs* 56%, p = 0.0001
LVEF ≥ 55%	62% *vs* 78%, p < 0.0001
LVEF 41–54%	57% *vs* 72%, p = 0.02
LVEF ≥ 55% (n = 5130)	HR 1.29, p = 0.0002
Anemia (relative risk of death) [32]	HR 1.57, p = 0.015
BNP	
Adjusted OR to predict mortality [37]	OR 2.23, p < 0.0001
To predict the cardiac mortality and CHF re-hospitalization [39]	Chi-square =17, p < 0.0001
Pre-discharge BNP (for death and re-admission) (after adjusting for clinical variables) derivation study [38]	HR 1.14 (95% CI 1.02–1.28), p = 0.027
Pre-discharge BNP level > 350 ng/L related to death or readmission (validation study) [38]	HR 12.6 (95% CI 5.7–28.1), p = 0.0001
Echocardiographic parameters:	
LVEF	
10% reduction in the EF below 45% [44]	Risk for total mortality increased by up to 39%
E/Ea ratio ≥ 15	
Cardiac mortality and CHF re-hospitalization [39]	Chi-square = 13.6, p = 0.0001
Restrictive transmitral filling	
DT ≤ 140 ms [46]	HR 2 (95% CI 1.1–3.4), p = 0.02
Em < 3.5 cm/s [48]	HR 5.29 (95% CI 2.64–10.60)

HR — hazard ratio; OR — odds ratio; RR — risk ratio; CI — confidence interval; CHF — congestive heart failure; DT — deceleration time; EF — ejection fraction; BNP — brain natriuretic peptide; AF — atrial fibrillation

in patients with DHF who were < 50 years has been reported to be 15%. For those aged 50–70 years it is 33%, and for > 70 years it approaches 50% [1]. Older age and male gender were recognized as important predictors of death in patients with HFPEF enrolled in the Digitalis Investigation Group (DIG) trial. The adjusted hazard ratio for one standard deviation increase of age was 1.28, p = 0.0019 and hazard ratio for male gender was 1.71, p = 0.0005. Other determinants of mortality were impaired renal function and worse functional class [20].

There is evidence that patients of non-Caucasian ethnicity have an increased risk of developing HF with preserved EF and poorer outcomes than Caucasian patients. In a study by O'Connor et al. [21], non-Caucasian ethnicity was a predictor of mortality in patients with HF and EF > 40%. There were 21% non-Caucasian patients in this study. These findings emphasize the importance of better understanding of the disease process in ethnic minorities in order to improve outcomes.

Coronary artery disease

The presence of CAD is known to increase the risk of developing HFPEF and is also associated with increased mortality. Several studies have suggested that the prevalence of CAD in HFPEF is lower than that in HF and reduced EF. Among 52,187 patients hospitalized for acute decompensated HF, the prevalence of CAD in HFPEF was re-

ported as 50%, while in patients with reduced EF it was 59% ($p \leq 0.0001$) [5].

O'Connor et al. [21] described the prognostic significance of CAD in a study of 2,498 consecutive patients with NYHA class II to IV symptoms and EF > 40%. Sixty five per cent of the patients had CAD while 62% had a history of hypertension. The median LVEF was 58% and the overall five-year mortality for the total study population was 28%. In multivariate Cox proportional hazard models, the strongest predictors were age, NYHA class IV symptoms, and CAD index. Other important predictors included diabetes, peripheral vascular disease, and minority ethnic group.

Atrial fibrillation

Atrial fibrillation (AF) is common among patients with diastolic dysfunction. The study from Olmsted County, Minnesota showed 41% prevalence of AF among patients with HF and preserved EF [22]. Age adjusted five-year risk of AF was found to be 12%, 14%, and 21% in patients with abnormal relaxation, pseudonormal and restrictive diastolic filling, respectively [23].

Rusinaru et al. [24] evaluated the relation between AF and long-term survival in patients with HFPEF. Three hundred and sixty eight patients with a first episode of HFPEF were followed for five years. The prevalence of AF was 36% in this study population. Patients with AF were older and more often had hypertensive heart disease. AF was associated with an excess mortality mainly related to advanced age. On univariate analysis, AF was associated with increased five-year mortality (HR 1.36, $p = 0.03$). After adjustment for the co-morbidities, baseline AF was not a predictor of long--term mortality.

A subgroup analysis of the CHARM study evaluated the effect of AF and risk of clinical events in HF patients with and without LV systolic dysfunction [4]. Patients were divided by baseline EF ($\leq 40\%$ or $> 40\%$) into low or preserved EF groups. Patients with AF and preserved EF had a higher risk for adverse CV outcomes (34% with CV death or HF hospitalization) relative to those with preserved EF and sinus rhythm (21%). After covariate adjustment, AF at baseline remained an independent predictor of all-cause mortality regardless of baseline EF. Also, absolute risk of CV death or HF hospitalization increased from 20% to 47% by the new development of AF in the preserved EF group.

Similarly, Pai and Varadarajan [25] investigated the prognostic implications of AF as a function of LVEF in 8,931 consecutive patients undergoing echocardiography. The prevalence of AF was 11% in patients with normal LVEF ($\geq 55\%$, n = 5,130), and 18% each in those with mild reduced LVEF (41–54%, n = 1,209). The effect of AF on five-year survival was most pronounced in those with normal LVEF (62% *vs* 78%, $p < 0.0001$) followed by those with a mild reduction in LVEF (57% *vs* 72%, $p = 0.02$).

The discordant results regarding the prognostic significance of AF in HFPEF might be due to a different patient population in these studies. The impact of loss of atrial kick might be different among the patients with LVEF > 50 compared to those with slightly reduced EF 40–50%. In the study by Rusinaru et al. [24], the patients had LVEF > 50 while the CHARM study included all patients with EF > 40%. Furthermore, the impact of AF might also depend on the etiology of diastolic HF. Raunso et al. [26] found that in patients with HF with a history of CAD, chronic AF was associated with an increased risk of death. There was no increased mortality in patients with HF and chronic AF who did not have ischemic heart disease. This study showed a significant interaction between the etiology of HF and the prognostic importance of chronic AF ($p = 0.003$).

Mamas et al. [27] carried out meta-analysis of the prognostic significance of AF in HF [27]. They looked at 16 studies, of which five studied patients with preserved LVEF. Analysis of the pooled data from three of these studies showed 35.3% mortality in patients with HF and AF compared to 20.3% mortality in patients with HF and normal sinus rhythm ($p < 0.0001$). None of these studies addressed the etiology of mortality however, so whether this excess mortality was due to HF, stroke, CAD or a non-cardiac cause remains unclear.

Anemia

Anemia is a common co-morbidity in patients with HF and is defined by the WHO as a hemoglobin level below 12 g/dL in women and below 13 g/dL in men [28]. A large community study, based on International Classification of Diseases ninth revision (ICD9) codes, estimated that 58% of patients with HF had anemia of chronic disease [29]. In a substudy of the CHARM program, the prevalence of anemia in patients with preserved and systolic EF was similar: 27% and 25%, respectively. In the CHARM sub-study, there were 133 *vs* 69 deaths and 527 *vs* 352 hospitalizations per 1,000 patient-years of follow-up in anemic patients *vs* non-anemic patients ($p < 0.001$) [30].

The exact underlying mechanisms regarding the causes of anemia and increased mortality in

patients with HF are not well understood. Some of the proposed etiologic mechanisms include hemodilution causing a state of 'pseudoanemia', defective iron utilization, renal dysfunction, insufficient erythropoietin production, neurohormonal and proinflammatory cytokine activation causing anemia of chronic disease [28]. The increased mortality observed in HF patients with anemia is also complex, with interplay between many confounding factors. Very high hemoglobin levels (≥ 17 g/dL) or very low levels (< 13 g/dL) are associated with significantly higher risk of death and re-hospitalization for HF regardless of the level of systolic function [31].

Tehrani et al. [32] concluded that the presence of anemia was associated with increased five-year mortality in patients with DHF. They reported the results from a retrospective analysis of 294 patients with HF and preserved LVEF ≥ 50%, of whom 162 had anemia as defined by the WHO definition. In the same study, elderly patients (> 75 years) with diastolic HF and anemia had higher mortality rates and worse outcomes. The presence of anemia did not influence re-hospitalization during a mean follow-up of 3.3 ± 1.8 years in this study.

Kerzner et al. [33] in a study of 359 hospitalized HF patients did not find a correlation between hemoglobin level and mortality in very elderly patients (≥ 75 years). The lower hemoglobin did predict worse survival in patients who were younger than 75 years.

In this study, 43.5% of patients had preserved LVEF (≥ 40%). Hemoglobin was divided into three categories: 41% of patients had hemoglobin < 11.5 g/dL; 38.4% had hemoglobin of 11.5–13.4 g/dL; and 17.5% had hemoglobin ≥ 13.5 g/dL [33].

Despite growing evidence regarding the prognostic significance of anemia in HF patients, there are no practice guidelines regarding the assessment and management of anemia in HF. The use of iron supplements and erythropoietin-stimulating agent to target the hemoglobin 11.0–12.0 g/dL is only considered in patients with concomitant chronic kidney disease as outlined by the National Kidney Foundation KDOQI guidelines [34].

B-type natriuretic peptide

B-type natriuretic peptide (BNP) is a neurohormone synthesized by the ventricular myocardium that plays an important role in volume homeostasis [35]. It is released in response to myocardial wall stretch, either by increased volume or pressure. It helps prevent volume overload by inhibiting the RAAS and initiating natriuresis, diuresis and vasodilatation [36]. Recent studies have evaluated the prognostic value of plasma BNP level alone or in combination with echocardiographic parameters in patients presenting with decompensated DHF.

The role of plasma BNP to predict in-hospital mortality in acute decompensated HF was evaluated in 48,629 patients from the ADHERE (Acute Decompensated Heart Failure National Registry) database. The BNP was measured within 24 hours of the presentation of patients for acute decompensated HF. In-hospital mortality was assessed by BNP quartiles in the entire cohort and in patients with both reduced LVEF < 40% (n = 19,544) as well as preserved LVEF ≥ 40% (n = 18,164) and LVEF > 50% (n = 12,631). It was reported that there was a near-linear relationship between BNP quartiles and in-hospital mortality for the entire cohort: (Q1 [1.9%], Q2 [2.8%], Q3 [3.8%], and Q4 [6.0%], $p < 0.0001$). BNP quartiles independently predicted mortality in patients with both reduced and preserved systolic function, and these findings for BNP and mortality were independent of significant clinical and laboratory variables (adjusted OR 2.23, $p < 0.0001$) [37].

Logeart et al. [38] evaluated the prognostic value of serial BNP assay for the prediction of early death or re-admission for HF in patients hospitalized for HF exacerbation. In this study, 114 patients were included from the derivation study and 109 from the validation study. Plasma BNP measurements were obtained upon hospital admission and subsequently on the day of discharge, or on the day before discharge. All patients also underwent Doppler echocardiograms to assess LVEF, Doppler mitral inflow pattern and systolic pulmonary artery pressure. High pre-discharge BNP level was the most significant predictor of short-term death or re-admission after an acute exacerbation. The study also showed that the prognostic information of pre-discharge BNP assay was greater than most common clinical variables and Doppler echocardiographic findings.

Dokainish et al. [39] reported that pre-discharge BNP levels and tissue Doppler derived transmitral early diastolic velocity/tissue Doppler early diastolic annular velocity E/Ea-ratio in patients who had been admitted for acute exacerbation of HF were strong predictors of cardiac mortality and re-admission for HF.

Echocardiographic parameters

The American Heart Association and the American College of Cardiology recommend initial clinical assessment of patients with HF using two-dimensional echocardiography with Doppler to as-

sess LVEF, LV size, wall thickness, and valve function [40]. Echocardiography not only provides diagnostic information regarding LV function and valvular dysfunction, its parameters can be used for prognostic value as well [41, 42].

Left ventricular ejection fraction

LVEF is a widely used clinical measure to assess LV function and has been shown to predict mortality in HF patients with low EF [43]. The relationship between a wide range of LVEF and both fatal and non-fatal outcomes was assessed in 7,599 patients enrolled in the CHARM study population [44]. The mean LVEF was 38.8 ± 14.9%. The study concluded that LVEF predicts mortality with overall better survival in patients with increasing EF up to 45%. For each 10% reduction in the EF below 45%, the risk for total mortality increased by up to 39%.

Mitral flow velocities and tissue Doppler imaging

Doppler recordings of ventricular filling velocities, and more recently tissue Doppler imaging (TDI) derived parameters, have been studied for prognosis in patients with systolic and diastolic HF [39, 45]. Akkan et al. [46] evaluated the prognostic value of deceleration time (DT) in 972 patients with symptomatic HF. Restrictive transmitral filling, as defined by DT ≤ 140 ms, was an independent predictor of mortality at 51 months of follow-up. For patients with LVEF ≥ 50, hazard ratio for DT ≤ 140 was two (confidence interval: 1.1–3.4, p = 0.02).

Moller et al. [47] studied pseudonormal and restrictive filling patterns in patients with myocardial infarction. Echocardiography was performed in 125 patients with first myocardial infarction within 24 hours. Normal filling was defined as DT 140 to 240 ms and color M-mode flow propagation velocity (Vp) ≥ 45 cm/s. Impaired relaxation was DT ≥ 240 ms; pseudonormal filling was DT 140 to 240 ms and Vp < 45 cm/s; and restrictive filling was DT < 140 ms. During a follow-up of 12 ± 7 months, 33 patients died. No patients with normal filling pattern died. Five patients with impaired relaxation, 11 patients with pseudonormal filling, and 17 patients with restrictive filling died during the follow-up. Pseudonormal filling pattern, a restrictive filling pattern and Killip class ≥ II proved to be independent predictors of cardiac death. LVEF did not provide independent prognostic information after the LV filling pattern was included in the model. These results indicate that assessment of LV filling patterns provide superior prognostic information, compared to systolic variables.

Tissue Doppler imaging measures the velocity of the myocardium during the cardiac cycle. Early diastolic velocity measured at mitral annulus (Ea) or myocardial segments (Em) are relatively preload-insensitive and reflect myocardial relaxation. Wang et al. [48] evaluated the incremental value of TDI for prognosis in addition to standard mitral flow velocity in patients with hypertension and left ventricular hypertrophy. The pseudonormal and restrictive filling patterns were associated with cardiac mortality. Em was the most powerful predictor of cardiac death. Em < 3.5 cm/s provided the prognostic utility incremental to clinical information and standard echocardiographic parameters of left ventricular hypertrophy and diastolic filling pattern.

Incremental predictive power of TDI was evaluated in a small study of 110 patients with HF [39]. This study included patients with LVEF < 35% (54 patients), 36% to 49% (15 patients) and LVEF ≥ 50% (41 patients). Ratio of transmitral flow to early mitral annulus diastolic velocity (E/Ea) and BNP were among the significant predictors of re-hospitalization for HF or cardiac death. BNP ≥ 250 pg/mL and mitral E/Ea ≥ 15 had incremental predictive power, to which conventional predictors, such as LVEF and mitral flow velocity, did not add further prognostic information.

In another study of 239 consecutive patients admitted for acute coronary syndrome who underwent echocardiography, the ratio of early transmitral flow to early mitral annulus velocities was calculated. At two year follow-up, ratio of transmitral flow to early mitral annulus velocity ≥ 15 was an independent predictor of cardiac death [49].

In summary, pseudonormal flow pattern, restrictive flow pattern, Em < 3 cm/s and E/Ea ≥ 15 provide independent prognostic information in patients with both systolic and diastolic HF and patients with a history of myocardial infarction and hypertensive heart disease. These parameters predict cardiac mortality. Further studies are needed to understand the mechanisms underlying these findings, and whether they derive from HF mortality or sudden cardiac death.

Electrocardiograms and Holter parameters

There are differences in electrocardiogram (ECG) parameters in patients with DHF *vs* those with systolic HF [50]. Patients with DHF are reported to have more AF, a slower heart rate, shorter QRS (102 ± 35 ms *vs* 122 ± 41 ms, p < 0.001) and shorter QTc interval than patients with systolic HF. The prevalence of left bundle branch block (LBBB) was reported as 25% in patients with HF.

However, among patients with LVEF ≥ 40%, the prevalence of LBBB was reported as 12.3% [51]. The presence of complete LBBB was associated with a 70% increase in all-cause mortality in patients with HF. The impact of LBBB on mortality in patients with HFPEF remains unknown.

There have been reports of novel Holter parameters regarding their prognostic significance in patients with HFPEF. Cygankiewicz et al. [52] evaluated 112 patients with HF and preserved LV function for heart rate turbulence (HRT). Abnormal HRT was found in 49% of patients. The mean values of turbulence onset and slope in this group of patients were 0.87% and 6.05 ms/RR, respectively. Abnormal HRT reflected the severity of the HF. In another study of 651 patients, 24-hour Holter monitoring was performed to assess the prognostic value of QT/RR slope on mortality in patients with HF [53]. Forty four per cent of patients had LVEF > 35%. Increased QT/RR slopes were independently associated with increased total mortality. Further studies are needed to evaluate the roles of abnormal HRT and QT/RR slope on mortality in patients with HFPEF.

Cardiac resynchronization therapy (CRT) is currently limited to those with LVEF ≤ 35%. There has been growing interest in evaluating the role of CRT in patients with DHF. A recent retrospective analysis from the PROSPECT trial evaluated the predictors of response to CRT in patients with HF and LVEF > 35%. The study showed that patients with LVEF > 35%, NYHA functional class III–IV symptoms, and QRS > 130 ms appeared to derive clinical and structural benefit from CRT [54]. Penicka et al. [55] demonstrated a reduction in dyssynchrony, and an improvement in functional class and exercise capacity, with the use of CRT in patients with DHF. CRT, a valuable option for patients with DHF and LBBB, should be formally tested in a prospective, randomized multi-center trial.

Summary and conclusion

Diastolic heart failure currently accounts for more than 50% of all HF cases. The mortality and morbidity in patients with DHF is comparable with those of patients with reduced EF. Pharmacologic agents that have been shown to benefit patients with HF and reduced EF have failed to show similar results in DHF patients. However, the management of these patients should include the treatment of hypertension, maintenance of normal sinus rhythm, and the prevention of myocardial ischemia and diabetes mellitus [56]. There is a need for exploration of novel treatments and strategies, including medications, ECG, Holter parameters and cardiac implantable devices, in DHF patients. One such possibility is the newer anti-anginal drug ranolazine which blocks inward sodium current and reduces intracellular calcium. Ranolazine could potentially emerge as a treatment for DHF.

Acknowledgements

Dr Sherazi has been supported by an award from the Empire Clinical Research Investigator Program.

The authors do not report any conflict of interest regarding this work.

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