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HEART FAILURE

Novel strategies in diastolic heart failure

Walter J Paulus

The diagnosis of diastolic heart failure (DHF) is based on the presence of a triad consisting of signs or symptoms of congestive heart failure, a normal left ventricular (LV) systolic function, and evidence of diastolic LV dysfunction. As diastolic LV dysfunction is not unique to DHF but also occurs in patients with heart failure and reduced LV systolic function (ie, systolic heart failure), DHF is often referred to as heart failure with normal LV ejection fraction (EF) (HFNEF) or heart failure with preserved LVEF (HFpEF). DHF currently accounts for more than 50% of all heart failure cases in western societies. Although prognosis of patients with DHF was initially perceived as superior to patients with systolic heart failure (SHF), recent evidence shows prognosis to be equally poor in both conditions. Furthermore, whereas the prognosis of patients with SHF has improved over the last two decades as a result of modern heart failure treatment, the prognosis of patients with DHF has not improved notably over the same time period. This review will focus on current diagnostic and therapeutic strategies for DHF.

DIAGNOSTIC STRATEGY

In contrast to SHF, which is easily diagnosed by signs or symptoms of fluid overload in the presence of a reduced LVEF (ie, LVEF <40%), the diagnosis of DHF is frequently challenging. Obvious signs of fluid overload such as lung crepitations, distended neck veins or pedal oedema are evident if the DHF patient presents in an emergency room with acute decompensated heart failure; however, the same physical signs are notoriously absent if the patient presents in an outpatient clinic with dyspnoea on exertion. Therefore, if the diagnosis of DHF is simply based on the presence of symptoms and a normal LVEF, physical deconditioning can erroneously be diagnosed as DHF. This high risk for a false positive diagnosis of DHF was convincingly illustrated by the CHARM-Preserved Trial, which recruited patients suffering from dyspnoea (New York Heart Association (NYHA) classes II–IV), a history of hospitalisation for a cardiac reason, and an LVEF >40%. An echocardiographic sub-study of this trial (CHARM-ESES) revealed only half of the recruited patients to have diastolic LV dysfunction. These patients also had a significantly poorer outcome than the patients without diastolic LV dysfunction. Objective measures of diastolic LV dysfunction, LV hypertrophy, left atrial (LA) enlargement or plasma concentrations of natriuretic peptides are therefore considered necessary for the diagnosis of DHF, apart from signs or symptoms of fluid overload and a normal LV systolic function.

Recently, the Heart Failure and Echocardiography Associations of the European Society of Cardiology jointly published an updated set of criteria for the diagnosis of DHF, which makes use of LVEF, LV end-diastolic volume (LVEDV), LV diastolic function indices, LV hypertrophy, LA size, and natriuretic peptides. This update of a previous European consensus document on the diagnosis of DHF had become necessary because of the widespread clinical use of tissue Doppler and natriuretic peptides. In accordance with this updated set of criteria, three conditions need to be satisfied for the diagnosis of DHF (figure 1): (1) signs or symptoms of congestive heart failure; (2) normal LV systolic function, and (3) diastolic LV dysfunction.

Signs or symptoms of congestive heart failure

Since many patients with DHF present with dyspnoea and no detectable signs of fluid overload, symptoms are considered sufficient clinical evidence to suggest the presence of congestive heart failure. Objective evidence of reduced exercise performance is optional and can be provided by exercise testing with measurements of peak exercise oxygen consumption (pronounced limitation: VO2max <14 ml/kg/min), or by the 6 min walking test (pronounced limitation: <300 m).

Normal LV systolic function

An LVEF >50% and an LVEDV index <97 ml/m² are proposed as cut-off values for normal LV systolic function and absence of LV dilatation. LVEDV measurements are frequently overlooked when applying these criteria in clinical practice. LVEF and LVEDV should be measured in accordance with the recommendations of the American Society of Echocardiography and the European Association of Echocardiography. When assessing LVEF, it is also important to realise that in patients with DHF, LVEF and LV chamber dimensions are identical at the time of acute decompensation and a couple of days later following recompensation. Establishing the diagnosis of DHF therefore does not require LVEF to be measured within 72 h of an acute decompensation episode.

Evidence of diastolic LV dysfunction

Invasive diagnostic evidence of diastolic LV dysfunction can be obtained by measuring pulmonary capillary wedge pressure (mPCW >12 mm Hg),
LV end-diastolic pressure (LVEDP > 16 mm Hg), the time constant of LV relaxation (τ > 48 ms), or the LV stiffness modulus (b > 0.27). Non-invasive diagnostic evidence of diastolic LV dysfunction is preferably derived from myocardial tissue Doppler (E/E’ > 15) (E = early mitral valve flow velocity; E’ = tissue Doppler early diastolic lengthening velocity). If myocardial tissue Doppler yields values suggestive but non-diagnostic for diastolic LV dysfunction (15 > E/E’ > 8), tissue Doppler needs to be implemented with other non-invasive investigations to provide diagnostic evidence of diastolic LV dysfunction. These non-invasive investigations can consist of: (1) a blood flow Doppler of mitral valve flow velocity (E/A ratio < 0.5 and deceleration time (DT) > 280 ms for patients over 50 years old) (A = atrial mitral valve flow velocity) or of pulmonary vein flow velocity (Ard-Ad > 30 ms) (Ard: duration of atrial reverse pulmonary vein flow velocity; Ad: duration of atrial mitral valve flow velocity); (2) an echocardiographic measure of LA volume index (LAVI > 40 ml/m²) or of LV mass index (LVMI: female > 122 g/m²; male > 149 g/m²); (3) an ECG with evidence of atrial fibrillation; or (4) a determination of plasma brain natriuretic peptide (BNP) or N-terminal-proBNP (NT-proBNP). If plasma BNP is > 200 pg/ml or NT-proBNP is > 220 pg/ml, diagnostic evidence of diastolic LV dysfunction also requires additional non-invasive investigations, which can consist of: (1) tissue Doppler (E/E ratio); (2) mitral or pulmonary vein blood flow Doppler (E/A ratio and DT; Ard-Ad index); (3) echo measures of LVMI or LAVI; or (4) electrocardiographic evidence of atrial fibrillation. The proposed use of different echocardiographic techniques allows for a comprehensive non-invasive assessment of LV relaxation, LV diastolic stiffness, and LV filling pressures.6

The updated diagnostic strategy provided by the Heart Failure and Echocardiography Associations of the European Society of Cardiology1 uses a dichotomous approach for the diagnosis of DHF, which is either present or absent. A more refined approach consists of scoring systems which yield distinct levels of evidence for DHF labelled as definite, probable, and possible, or which list major and minor criteria, of whom at least two major criteria need to be satisfied and eventually implemented with minor criteria such as LV hypertrophy, LA enlargement or evidence of diastolic LV dysfunction. Unfortunately, these scoring systems antedate the widespread clinical use of tissue Doppler, which is now recognised as the most accurate non-invasive way to assess diastolic LV filling pressures in DHF patients.7–9

As mentioned before, DHF is frequently a challenging differential diagnosis in a work-up for breathlessness in the absence of detectable signs of fluid overload. The Heart Failure and
Echocardiography Associations of the European Society of Cardiology therefore also proposed a set of criteria for the exclusion of DHF (figure 2). If a patient with breathlessness and no signs of fluid overload has a BNP <100 pg/ml or a NT-proBNP <120 pg/ml, any form of heart failure is virtually ruled out because of the high negative predictive value of plasma natriuretic peptides, and pulmonary disease becomes the most likely cause of breathlessness. If an echocardiogram confirms the absence of valvular or pericardial disease, LVEF and LV volumes should be measured. If LVEF exceeds 50%, if LVEDVI is <76 ml/m², and if the patient has no atrial fibrillation, atrial dilatation (LAVI <29 ml/m²), LV hypertrophy (LVMI: female <96 g/m², male <116 g/m²), low tissue Doppler shortening velocity (>6.5 cm/s) or high tissue Doppler E/E' (E/E' <8), the diagnosis of DHF is ruled out.

TREATMENT STRATEGY

The prognosis of patients with SHF has improved considerably over the last two decades as a result of modern heart failure treatment, but the prognosis of patients with DHF has failed to improve over the same time period, despite frequent use of similar pharmacological agents. Contrasting efficacy of comparable pharmacological agents in SHF and DHF was illustrated by the positive outcome of the CHARM-Alternative trial, which assigned SHF patients to the ARB candesartan or placebo, and the neutral outcome of the recent I-PRESERVE trial, which assigned DHF patients to the angiotensin II receptor blocker (ARB) irbesartan or placebo. Discordant outcome of similar pharmacotherapy in both conditions is consistent with different signal transduction cascades driving myocardial remodeling in SHF and DHF. LV structure and myocardial ultrastructure indeed argue in favour of unequal myocardial signal transduction cascades in SHF and DHF. Patients with SHF have eccentric LV remodeling with low LV mass/volume ratio, whereas patients with DHF have eccentric LV remodeling with high LV mass/volume ratio. Myocardial ultrastructure follows a similar trend with loss of myofilaments in SHF and cardiomyocyte hypertrophy in DHF. Because of these divergences of myocardial structure and ultrastructure in SHF and DHF, dissimilar outcome of similar pharmacotherapy in SHF and DHF is no surprise.

Table 1 shows all major trials with angiotensin converting enzyme inhibitors (ACEIs) performed in post-myocardial infarction patients with normal LVEF and in DHF patients. The PREAMI trial

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**Figure 2**  Flow chart for the exclusion of diastolic heart failure (DHF) in a patient presenting with breathlessness and no signs of fluid overload. S, TD shortening velocity; see caption to figure 1 for explanation of other abbreviations. Reproduced with permission from Paulus et al.1
Table 1 Overview of trials using an angiotensin converting enzyme inhibitor (ACEI) in post-myocardial infarction patients with normal left ventricular ejection fraction (LVEF) or in patients with diastolic heart failure (DHF)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Compound</th>
<th>Duration</th>
<th>Ref</th>
<th>Patient population</th>
<th>Systolic LV function</th>
<th>Diastolic LV dysfunction</th>
<th>Positive outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREAMI</td>
<td>Perindopril</td>
<td>1 year</td>
<td>w10</td>
<td>Post MI</td>
<td>LVEF &gt;40%</td>
<td>LVEDV</td>
<td></td>
</tr>
<tr>
<td>Aronow</td>
<td>Enalapril</td>
<td>3 months</td>
<td>w14</td>
<td>Post MI</td>
<td>LVEF &gt;50%</td>
<td>E/A, symptoms</td>
<td></td>
</tr>
<tr>
<td>V-HeFTII</td>
<td>Enalapril</td>
<td>2 years</td>
<td>w15</td>
<td>HF, V0₂ ↓</td>
<td>LVEF &gt;35%</td>
<td>Mortality – 40%</td>
<td></td>
</tr>
<tr>
<td>PEP-CHF</td>
<td>Perindopril</td>
<td>2.1 years</td>
<td>14</td>
<td>HF 3/9 criteria including prior MI</td>
<td>LVEF &gt;40%</td>
<td>WT &gt;13 mm</td>
<td>Hospital. 1 year FU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WMI &gt;1.4</td>
<td>IVRT &gt;105 ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E/A &lt;0.5, DT &gt;280 ms</td>
<td>LA diameter &gt;25 mm/m²</td>
<td></td>
</tr>
<tr>
<td>OPT-HF</td>
<td>ACEIs</td>
<td>3 months</td>
<td>w12</td>
<td>HF</td>
<td>LVEF &gt;50%</td>
<td></td>
<td>S, E, NTproBNP</td>
</tr>
<tr>
<td>Tribouiloy</td>
<td>ACEIs</td>
<td>5 years</td>
<td>w16</td>
<td>HF</td>
<td>LVEF &gt;50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HKDHF</td>
<td>Ramipril + HCTZ</td>
<td>1 year</td>
<td>w17</td>
<td>HF</td>
<td>LVEF &gt;45%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CTR, cardiothoracic ratio; DT, deceleration time; E/A, ratio of early (E) to late (A) mitral valve flow velocity; FU, follow-up; HCTZ, hydrochlorothiazide; HF, heart failure; hospitalisations; IVRT, isovolumetric relaxation time; LA, left atrium; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEDD, left ventricular end-diastolic dimension index; NTproBNP, N-terminal pro-brain natriuretic peptide; MI, myocardial infarction; S, tissue Doppler shortening velocity; V0₂, maximal oxygen consumption during exercise; WMI, wall motion index; WT, wall thickness.

studied NYHA class I–II patients with an LVEF >40% following prior myocardial infarction and observed less eccentric LV remodelling (0.7 vs 4 ml ΔLVEDV/year) when patients were treated with 8 mg perindopril. This trial revealed eccentric LV remodelling to occur even after small myocardial infarctions without compromised baseline LV function. This response is, however, of questionable relevance to the typical DHF patient, who experiences progressive concentric LV remodelling because of comorbidities other than prior myocardial infarction such as arterial hypertension (80% of patients), diabetes (50% of patients), and excess body weight (80% of patients). A result similar to the PREAMI trial was observed 13 years earlier by Aronow et al, who reported symptomatic benefit of enalapril in post-myocardial infarction patients with preserved LVEF (>50%). A study of patients with LVEF >35% of the V-HeFTII trial, which compared enalapril to the combination of hydralazine and isosorbide dinitrate, also reported a beneficial effect on mortality. The enrolment criteria of this study, however, favoured eccentric LV remodelling as patients were obliged to have evidence of LV dilatation (a cardiothoracic ratio >0.55 or an echocardiographic LV end-diastolic dimension index >2.7 cm/m²); therefore this study had again little relevance to DHF, which requires LV dilatation to be excluded.

The PEP-CHF study was the first major randomised controlled trial on the use of an ACEI in DHF patients. It compared perindopril 4 mg daily to placebo in elderly patients (>70 years old) with a diagnosis of heart failure, an LVEF >40%, minimal impairment of segmental LV wall motion, echocardiographic evidence of LA dilatation or LV hypertrophy, and abnormal LV filling kinetics on mitral flow velocity Doppler. The study showed no difference in mortality and heart failure hospitalisations. Premature withdrawal of many patients after 1 year could have contributed to the neutral outcome because an interim analysis at 1 year of follow-up showed a significant reduction (p=0.035) in heart failure hospitalisations. In contrast to PEP-CHF, a 5 year registry of DHF patients surviving a first hospitalisation revealed a 30% decrease in 5 year mortality risk. The patient population of this registry, however, had some unusual features for DHF such as a relatively low prevalence of arterial hypertension (50%) and overrepresentation of male patients (50%). In fact, in the OPTIMISE-HF registry, whose DHF cohort included more hypertensives (76%) and women (62%), discharge use of ACEIs no longer exerted an effect on 60–90 days mortality or hospitalisation rates of DHF patients.

In contrast to all previous trials, which randomised DHF patients between ACEIs and placebo, the Hong Kong diastolic heart failure study randomised DHF patients between diuretics alone, diuretics plus ramipril, and diuretics plus irbesartan. Hospitalisations and exercise tolerance changed similarly in all three groups and addition of ramipril or irbesartan only resulted in lower NT-proBNP values and higher systolic (S) and early diastolic (E) mitral annular velocities. A comparison with diuretics was recently also reported by the ALLHAT collaborative research group. In the ALLHAT trial, chlorthalidone reduced the incidence of new onset DHF compared to lisinopril. In contrast, chlorthalidone and lisinopril had similar effects on the incidence of new onset SHF. The discrepant effect of ACEIs on new onset DHF and SHF supports the idea that already in the presymptomatic stage, myocardial remodelling is driven by distinct gene programmes in both diseases.

Table 2 summarises all major trials with ARBs performed in hypertensives with normal LVEF and diastolic LV dysfunction and in DHF patients. In patients with mitral flow velocity Doppler evidence of diastolic LV dysfunction and with an hypertensive response to exercise, losartan improved exercise tolerance and quality of life both when compared to placebo or to hydrochlorothiazide. In contrast, in a similar patient population with arterial hypertension and TDI evidence of diastolic LV dysfunction, valsartan was not superior to regular antihypertensive agents for improving TDI early diastolic mitral annular lengthening velocity (E’). The first major trial investigating cardiovascular
mortality and heart failure hospitalisations in DHF patients. The CHARM-preserved trial, which randomised 3023 patients between candesartan and placebo, observed no significant difference in cardiovascular death. However, other trials conducted after hospital discharge found a lower mortality in patients treated with ACEIs.

### Table 2: Overview of trials using an angiotensin II receptor blocker (ARB) in hypertensive patients with diastolic left ventricular (LV) dysfunction or in patients with diastolic heart failure (DHF)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Compound</th>
<th>Duration</th>
<th>Ref</th>
<th>Patient population</th>
<th>Systolic LV function</th>
<th>Diastolic LV dysfunction</th>
<th>Positive outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little</td>
<td>Losartan vs HCTZ</td>
<td>6 months</td>
<td>w18</td>
<td>Exert. HT</td>
<td>LVEF &gt;50%</td>
<td>E/A &lt;1</td>
<td>Symptoms</td>
</tr>
<tr>
<td>VALIAD</td>
<td>Valsartan +RR vs RR</td>
<td>38 weeks</td>
<td>w20</td>
<td>HT</td>
<td>LVEF &gt;50%</td>
<td>E &lt;0</td>
<td>Hospital.</td>
</tr>
<tr>
<td>CHARMP</td>
<td>Candesartan</td>
<td>3 years</td>
<td>w3</td>
<td>HF</td>
<td>LVEF &gt;40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HKDFH</td>
<td>Ramipril + HCTZ vs HCTZ</td>
<td>1 year</td>
<td>w17</td>
<td>HF</td>
<td>LVEF &gt;45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-Preserve</td>
<td>Irbesartan</td>
<td>49.5 months</td>
<td>11</td>
<td>HF</td>
<td>LVEF &lt;45%</td>
<td>LAE, LVEH</td>
<td></td>
</tr>
</tbody>
</table>

**Characteristics of the ARB trials:**
- **Overview:** All trials used an angiotensin II receptor blocker (ARB) in hypertensive patients with diastolic LV dysfunction, with the exception of the I-PRESERVE trial, which used irbesartan.
- **DHF population:** Most patients had a history of myocardial infarction, with a high prevalence of arterial hypertension and LV hypertrophy.
- **Positive outcomes:** All trials reported a reduction in heart failure hospitalisations, with the I-PRESERVE trial showing the largest reduction in reported events.

### Table 3: Overview of trials using a β-blocker in post-myocardial infarction patients with normal left ventricular ejection fraction (LVEF) or in patients with diastolic heart failure (DHF)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Compound</th>
<th>Duration</th>
<th>Ref</th>
<th>Patient population</th>
<th>Systolic LV function</th>
<th>Diastolic LV dysfunction</th>
<th>Positive outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow</td>
<td>Propranolol</td>
<td>32 months</td>
<td>w21</td>
<td>HF</td>
<td>LVEF &gt;40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobre</td>
<td>β-blockers</td>
<td>25 months</td>
<td>w22</td>
<td>HF</td>
<td>LVEF &gt;40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COHERE</td>
<td>Carvedilol</td>
<td>1 year</td>
<td>w23</td>
<td>HF</td>
<td>LVEF &gt;40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWEDIC</td>
<td>Carvedilol</td>
<td>6 months</td>
<td>w24</td>
<td>HF</td>
<td>LVEF &gt;45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENIORS</td>
<td>Nebivolol</td>
<td>12 months</td>
<td>16</td>
<td>HF</td>
<td>LVEF &gt;35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NODARI</td>
<td>Nebivolol or atenolol</td>
<td>6 months</td>
<td>w26</td>
<td>HF, VO2max</td>
<td>LVEF &gt;50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Characteristics of the β-blocker trials:**
- **Overview:** All trials used β-blockers in post-myocardial infarction patients with normal LVEF or in patients with diastolic heart failure.
- **Positive outcomes:** All trials reported a reduction in heart failure hospitalisations, with the SENIORS trial showing the largest reduction in reported events.

**Note:** The use of β-blockers and ARBs in DHF patients is a matter of ongoing debate, with some studies suggesting a beneficial effect, while others do not.

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*Ard, duration of reverse pulmonary vein atrial systole flow; Ad, duration of mitral valve atrial wave flow; E/A, ratio of early (E) to late (A) mitral valve flow velocity; Exert. HT, exertional hypertension; HCTZ, hydrochlorothiazide; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; RR ↓, regular blood pressure lowering therapy; S, tissue Doppler shortening velocity.*
Contrasting outcomes of trials using similar compounds in diastolic heart failure (DHF) and systolic heart failure (SHF). For both angiotensin II receptor blocker (ARB) and angiotensin converting enzyme inhibitor (ACEI), a neutral outcome is observed in DHF but a positive outcome in SHF. Conversely, for statins, a positive outcome is observed in SHF but a neutral outcome in DHF.

**Figure 3**

Novel strategies in diastolic heart failure: key points

- Diastolic heart failure (DHF) currently accounts for more than 50% of all heart failure cases.
- The diagnosis of DHF requires three conditions to be simultaneously satisfied: (1) signs or symptoms of congestive heart failure; (2) normal left ventricular (LV) systolic function; and (3) evidence of diastolic LV dysfunction.
- The prognosis of DHF is as poor as the prognosis of heart failure with reduced systolic function. In contrast to heart failure with reduced systolic function, the prognosis of DHF has not improved over the last two decades with modern heart failure treatment.
- Most of the major large trials and registries for DHF showed a neutral outcome of treatment with ACE inhibitors, angiotensin receptor blockers, and β-blockers.
- Discordant outcome of similar pharmacotherapy in DHF and in heart failure with reduced systolic function is consistent with different signal transduction cascades driving myocardial remodelling in both conditions.

The COHERE registry, the group of patients with LVEF >40% again differed from the usual DHF population: 46% were women, 24% of patients had their heart failure attributed to hypertension and 51% to coronary artery disease.

The SWEDIC trial was careful to recruit typical DHF patients by using a wall motion score to exclude dyskinetic segments of previous myocardial infarctions and evidence of age adjusted diastolic LV dysfunction on mitral or pulmonary venous flow velocity Doppler. Six months of carvedilol treatment had no effect on symptomatic status or on an integrated score of all diastolic function indices, which was the primary end point of the study. It only improved the E/A ratio in patients with high baseline heart rate. The SENIORS study used the β-blocker nebivolol in elderly heart failure patients over 70 years of age and observed a 14% reduction in primary outcome (all cause mortality and cardiovascular hospital admission). The effect of nebivolol on primary outcome did not differ between patients with LVEF <35% and those with LVEF >35%.

Beneficial effects of nebivolol in patients with DHF were also demonstrated in a smaller study comparing nebivolol to atenolol. This study performed a rigorous DHF patient recruitment by requiring both an LVEF >50% and an LV end-diastolic dimension <60 mm to establish normal systolic LV function and by obtaining invasive evidence of elevated pulmonary capillary wedge pressure (PCWP). Six months of treatment resulted in improvement of the E/A ratio and reduction in LV mass with both compounds, but only nebivolol lowered rest and exercise PCWP and raised maximal oxygen consumption during exercise.

Various other compounds have also been evaluated for treatment of DHF. As aldosterone is implicated in myocardial fibrosis, the effects of aldosterone antagonism were investigated in hypertensive patients with DHF (NYHA II) using quantitative echocardiographic techniques. In the spironolactone (25 mg) treated group, this study reported improved LV long axis function evident from higher strain, strain rate and integrated backscatter. The treated group also had smaller posterior wall thickness and LA area, but unchanged treadmill exercise time. Large randomised clinical trials exploring the use of spironolactone in DHF are underway (ALDO-DHF; TOPCAT). The Digitalis Investigation Group (DIG) studied outcome of treatment with digoxin both in patients with reduced LVEF (main trial) and in patients with preserved LVEF ( ancillary trial). In both trials, digoxin had no effect on mortality of patients in normal sinus rhythm but reduced their need for heart failure hospitalisations. In the aftermath of studies reporting beneficial effects on diastolic LV function of calcium channel blockers in patients with hypertrophic cardiomyopathy, positive results were reported with verapamil in heart failure patients with normal LV systolic performance and abnormal diastolic LV filling.

Finally, a preliminary report suggested statin treatment to be beneficial in DHF. Statins could improve diastolic LV dysfunction through numerous actions such as regression of LV hypertrophy and
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prevention of myocardial fibrosis. Patients receiving statins had significantly lower mortality rates than those not receiving statins. Conversely, in the same study population, treatment with ACEIs, ARBs, β-blockers and calcium channel blockers had no discernible effect on survival. The positive outcome of statin treatment in DHF patients contrasts with the recently reported neutral outcome of statin therapy in SHF patients of the CORONA trial10–13 (figure 3). A neutral outcome in DHF compared to a positive outcome in SHF, as occurred with ACEIs, ARBs and β-blockers, can be compatible with flawed DHF trial design; however, a positive outcome in DHF compared to a neutral outcome in SHF, as occurred with statins, can no longer be attributed to trial conception but supports distinct pathophysiological mechanisms in both conditions, and justifies a search for a specific DHF pharmacotherapy. Such a specific DHF pharmacotherapy should address the structural and functional myocardial abnormalities13 characteristically observed in DHF such as cardiomyocyte hypertrophy, cardiomyocyte stiffness and a shift in myocardial metabolism from glucose to free fatty acids because of frequent comorbidities such as type 2 diabetes and metabolic syndrome.

Competing interests In compliance with EBAC/EACCME guidelines, all authors participating in Education in Heart have disclosed potential conflicts of interest that might cause a bias in the article. The author has no competing interests.

Provenance and peer review Commissioned; not externally peer reviewed.

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► Consensus document providing a strategy for echocardiographic evaluation of diastolic LV dysfunction in heart failure with normal and reduced LVEF.

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► Pro side of ‘controversies in cardiovascular medicine‘ evaluating echocardiographic evaluation of diastolic LV function.


► Con side of ‘controversies in cardiovascular medicine‘ evaluating echocardiographic evaluation of diastolic LV function.


► Largest DHF trial reported so far showing a neutral outcome of ibiscus.


► First major randomised controlled trial on the use of ACEIs in DHF patients


► In-depth overview of current and future DHF treatment.