Treatment of heart failure with preserved systolic function


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Summary
Heart failure is a major public health problem. Heart failure with preserved systolic function (HF-PSF) is a common form, which is difficult to diagnose. Results of recent studies show that HF-PSF has a poor prognosis, with an annual survival rate similar to that of heart failure with left ventricular systolic dysfunction. Despite these findings, the therapeutic management of HF-PSF is not clearly defined. We will discuss in this review of the literature the current
Heart failure with preserved systolic function (HF-PSF) is a common, complex and severe disease. Its diagnosis is not straightforward as it often affects elderly patients suffering from multiple diseases. In order to better understand HF-PSF, a French working group (the TACTIC group), proposed a diagnostic algorithm based on the patient’s clinical data and on the results of further investigations (Fig. 1) [1]. A working group of the European Society of Cardiology published a similar process leading to the same conclusions [2].

In the present article, the TACTIC group has tried to review from the literature the current therapeutic management of HF-PSF. For this purpose, our conclusions were based on articles published from 1985 to date and selected from medical databases using the following keywords: heart failure, diastolic heart failure, diastolic dysfunction, preserved systolic function, treatment.

In the absence of significant results from randomized trials, the current treatment of HF-PSF is still based on our pathophysiological knowledge. The major factor in this disease is the increase in left ventricular end-diastolic pressure. Aim of the treatment is to reduce the end-diastolic pressure and to avoid its sudden rise in certain circumstances. Kitzman et al. showed that ventricular filling pressures increase significantly with exercise in patients with isolated diastolic dysfunction [3].

Together with the specific treatment of HF-PSF, precipitating factors or concomitant (or causative) diseases involved in HF-PSF must be corrected. These are hypertension, myocardial ischaemia and supraventricular arrhythmias. Isolated left ventricular hypertrophy (LVH) or LVH complicating hypertension predispose to the clinical expression of HF-PSF. Finally, HF-PSF generally occurs in the elderly patient, who often has several comorbidities such as renal failure, which contribute to the symptoms and the deterioration of the disease.
Management of precipitating or causative factors

Role of hypertension and left ventricular hypertrophy

Pathophysiological review

Factors predisposing to LVH in the hypertensive patient

The prevalence of electrical LVH depends on several parameters:
- blood pressure level, particularly systolic [4,5];
- duration of hypertension and its control by antihypertensive treatment [6];
- age and obesity.

A sodium rich diet [7] and alcohol consumption [8] also predispose to the development of LVH in hypertensive patients. LVH occurs more commonly in hypertensive men; however, the direct influence of sex disappears when the severity of hypertension and lifestyle are taken into account [9,10]. Finally, genetic and ethnic factors are also involved [11,12].

Pathophysiological mechanisms of LVH in the hypertensive patient

Several factors contribute to myocyte hypertrophy and fibroblast proliferation.

Mechanical factors. Concentric LVH generally reflects a process of myocyte adaptation to elevated blood pressure (Laplace’s law), which becomes inappropriate and contributes to the deterioration in left ventricular function. In experimental models, genetically modified mice unable to develop LVH when ventricular wall stress is increased by applying an aortic ring, exhibit less degree of heart failure than control animals, which develop hypertrophy [13]. The role of arterial compliance and of central blood pressure in the genesis of hypertensive LVH has also been clearly shown by some authors as an important aetiopathogenic factor of HF-PSF and the main pathophysiological factor for episodes of decompensation [14].

Hormonal factors. The renin-angiotensin-aldosterone system plays a central role in the development of LVH [15]. Many experimental studies have demonstrated the antitrophic role of angiotensin converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARBs) [16—18]. Other hormonal factors are involved: catecholamines, insulin and growth hormone [19]. The antihypertensive effect of some drugs in the spontaneously hypertensive rat is associated with a reduction in heart weight only if the haemodynamic effect is combined with a reduction in catecholergic activity (which was not true with direct acting vasodilators) [20].

Results of clinical trials

Impact of antihypertensive agents on LVH

Results of the first studies on regression of LVH in hypertension were difficult to interpret because of some methodological limitations [21,22]. The results of recent comparative trials with good methodological quality [23] partly contradict those of meta-analyses, which mostly concluded that ACE and ARBs were superior to other drugs [24]. The Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) trial showed no difference between enalapril and nifedipine [25]. The Left Ventricular hypertrophy regression Indapamide versus Enalapril (LIVE) trial [26], which used a rigorous methodology, with a sufficiently large number of patients (200 patients per group), showed indapamide to be more effective than enalapril on reducing left ventricular mass at one year, with a comparable antihypertensive effect. The largest LVH regression trial is the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial [27], which showed that, for a similar blood pressure control, losartan (together with a diuretic in 90% of cases) produced a greater LVH regression than atenolol (combined with a diuretic in the same proportion of patients).

Consequences of LVH regression on prognosis

The incidence of cardiovascular complications appears to be lower in patients whose LVH had regressed on treatment than in those in whom LVH persists [28—31], but these trials included small numbers of patients and do not establish whether there was a parallel reduction in left ventricular mass and in cardiovascular risk. The lower incidence of stroke with losartan in the LIFE trial was associated with a
greater LVH regression [32,33], although this difference may be largely explained by a lower decrease in central blood pressure by atenolol, as clearly shown in the Conduit Artery Function Evaluation study (CAFE) trial [34].

Role of bilateral renal artery stenosis

Secondary hyperaldosteronism and volume overload, related to a decrease of natriuresis, in case of significant bilateral renal artery stenosis could explain the clinical presentation of HF-PSF and particularly the recurrent "flash" acute pulmonary oedema. Revascularization in this situation can prevent the recurrence of heart failure decompensation [35,36]. This justifies to perform a renal artery Doppler study, particularly if predisposing factors for renal stenosis are present: severe systolic—diastolic hypertension resistant to antihypertensive treatments, age greater than 70 years old, multiple vascular lesions, renal insufficiency, significant increase in plasma creatinine after ACE or ARBs introduction. At the opposite, the role of a unilateral renal stenosis in HF-PSF decompensation is still discussed and angioplasty has not been shown to be beneficial in this situation.

Role of myocardial ischaemia

Physiological relationship between ischaemia and HF-PSF

In order to examine the relationship between left ventricular diastolic dysfunction and myocardial ischaemia, two questions need to be answered:

- Is repeated or chronic myocardial ischaemia a factor which initiates or predisposes to diastolic dysfunction?
- Can an acute ischaemic episode be a factor that initiates or predisposes to heart failure in a patient with diastolic dysfunction?

In answer to the first question, we have to keep in mind that left ventricular relaxation requires the active transport of calcium into the sarcoplasmic reticulum, enabling the dissociation of actin—myosin bridges. As a result of hypoxia, which inhibits this dissociation process, ischaemia can impaired active relaxation [37,38]. In addition, by predisposing to cell necrosis and the development of interstitial fibrosis, ischaemia contributes to the deterioration in left ventricular structure and diastolic function. Ischaemia can therefore reduce passive left ventricular compliance. Myocardial ischemia could also be related to microcirculatory abnormalities, as found in hypertension and in diabetes mellitus [39].

In order to answer the second question, many years ago, acute myocardial ischaemia was shown to be involved in the development of heart failure [40,41], and this is still a current issue [42,43]. In 1987, a study demonstrated in 32 patients that all the echocardiographic diastolic parameters were impaired in the first 15 s after coronary artery occlusion [41]. In 2004, in a small study including 18 patients hospitalized for heart failure with left ventricular ejection fraction (LVEF) greater or equal to 50%, a significant coronary artery disease was found by coronary angiography in 39% of patients and in 25% of cases, heart failure was associated with an episode of myocardial ischaemia [43]. Finally, the extend of coronary disease is associated with an increase in mortality in patients with HF-PSF: findings from the coronary artery surgery study (CASS) showed that in patients with HF-PSF, the six-year mortality rate was 8% in the absence of coronary artery disease, compared to 17% in the presence of a significant single or double vessel disease and 32% in case of triple vessel disease [44].

There are therefore arguments indicating that myocardial ischaemia can contribute to diastolic dysfunction and may be the cause of heart failure in a patient with diastolic dysfunction.

Treatment of ischaemia and prevention of HF-PSF and episodes of heart failure

Two questions must be answered to examine the relationship between anti-ischaemic treatment and prognosis of HF-PSF:

- Does anti-ischaemic treatment (pharmacological or revascularization) in a patient without cardiac dysfunction reduces the risk of HF-PSF?
- Does anti-ischaemic treatment (pharmacological or by revascularization) prevent heart failure decompensation in a patient with HF-PSF?

To the best of our knowledge, no clinical trials have answered to these two questions. We just have sub-studies of different clinical trials and/or meta-analyses without any information about the type of heart failure assessed. While the treatment of coronary risk factors, particularly the treatment of hypertension, reduces the risk of heart failure, anti-ischaemic treatment does not appear to reduce the incidence of heart failure [45,46]. In the meta-analysis of the Blood Pressure Lowering Treatment Trialists’ collaboration (BPLTT) [46], beta-blockers were not superior to ACE in preventing heart failure. However, calcium channel blockers appeared to be less effective than ACE, but also less effective than diuretics and beta-blockers in preventing the development of heart failure.

In the Occluded Artery Trial (OAT), desocclusion of a coronary artery by angioplasty did not reduce the risk of heart failure [47]. Furthermore, angioplasty of an occluded artery had no effect on prognosis, whether or not the patients had previous heart failure and whether or not they had LVEF less than 50%.

A study published in 2000 examined the findings from 46 patients hospitalized for rapidly resolving acute pulmonary oedema ("flash" oedema) [45]. Twenty-seven of these patients (58%) had LVEF greater than 40%, 38 (82%) underwent coronary angiography and among these, 33 (86%) had a significant coronary artery disease. Nineteen of these 33 patients underwent bypass surgery and eight a coronary angioplasty. During the three-year of the follow-up period, pulmonary oedema recurred in half of the patients, and in nine patients (47%) of the 19 who were revascularized. Despite its major limitations (small number of patients and lack of randomization), this study suggests that coronary revascularization has no preventive effect on the development of pulmonary oedema in patients with preserved systolic function and a past history of pulmonary oedema.

Finally, the ACC/AHA 2001 guidelines for the management of HF-PSF state that "coronary revascularization is recommended in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischaemia..."
is judged to have an adverse effect on diastolic function" although with a level of evidence of C [48]. This proposal is based on pathophysiological reasoning but not on clinical evidence. In 2005, the European and American guidelines for the management of heart failure both stated that there was a strong evidence to perform coronary revascularization only to patients with angina and not to patients with asymptomatic coronary disease [49,50]. They did not recommend coronary revascularization in order to improve ventricular function or to reduce symptoms of heart failure [51].

Role of supraventricular arrhythmias

Supraventricular arrhythmias are considered to have an adverse effect in HF-PSF. Tachycardia, which reduces the duration of diastole, and the loss of atrial systole considerably decrease cardiac output. LVH increases these abnormalities. In experimental studies in dogs, sinus tachycardia in the presence of LVH rapidly increases left atrial pressure [52]. The theoretical treatment of choice to control heart rate is beta-blockers, which also reduce myocardial ischaemia and blood pressure. Non-dihydropyridine calcium blockers and/or digoxin, particularly in case of atrial fibrillation, are an alternative to beta-blockers. The ideal situation is to obtain a heart rate close to 70 per minute and in any case lower than 90 per minute. Atrial ventricular node ablation with pacemaker implantation is rarely required. Atrial fibrillation ablation may be useful in case of recurrent heart failure decompensations. Finally, the role of ivabradine in controlling heart rate in patients with sinus rhythm is unknown in HF-PSF.

Other triggering factors

Heart failure decompensation may be promoted by extracardiac factors such as non compliance to the low sodium diet or to medical treatment, intake of non-recommended drugs (particularly non-steroidal anti-inflammatory drugs, rich sodium drugs, etc.), pulmonary infection or any other infection and anemia. These extracardiac factors are not specific to HF-PSF but also affect heart failure with systolic dysfunction.

Data from registers and controlled trials on the pharmacological management of HF-PSF

Specific features of HF-PSF

As described in the introduction, the treatment of HF-PSF is currently based on our pathophysiological knowledge. The main goal of the treatment is to reduce the left ventricular end-diastolic pressure.

By avoiding salt and water retention, diuretics are the treatment of choice for this disease. However, as in heart failure with systolic dysfunction, no study has assessed their benefit in HF-PSF. With nitrates, diuretics are effective in the management of acute episodes. In chronic stable patients, the minimal doses of diuretics will be prescribed, particularly in the elderly, in order to control symptoms and to reduce the risk of dehydration. In HP-PSF, the adaptive possibility of the heart is decreased, related to a steeper diastolic pressure—volume curve. Minor changes in volume are associated with large changes in pressure (a moderate increase in volume increases the risk of decompensation, and in contrast, a small reduction in ventricular volume predisposes to hypotension).

Heart rate plays an important role in the increase of diastolic pressures. Alongside diuretics, nitrates and beta-blockers, calcium channel blockers slowing heart rate can be used. Finally, theoretically, renin-angiotensin system inhibitors are useful in the management of these patients: they control blood pressure, reduce left ventricular mass and may improve diastolic function [53].

Epidemiological studies

Several observational epidemiological studies have examined the numbers of prescriptions of different classes of drugs. In some of these studies, the authors examine the impact of various drugs on morbidity and mortality. These studies are not randomized trials and all of these analyses were conducted retrospectively. Nevertheless, they provide useful information on the therapeutic management of HF-PSF.

An important initial finding from these registries is the relatively limited use of LVEF measurement in patients hospitalized for acute heart failure. In American studies [54—57], LVEF measurement was performed in approximately 50—60% of the patients, at the exception of one study, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) trial [58] where LVEF was measured in 85% of the patients. In Europe, LVEF is measured in almost 80% of patients [59,60].

Prescription rates for the different classes of drugs

Prescription rates of the different classes of drugs from some epidemiological studies are summarized in Table 1. Most of these studies involved patients admitted in hospitals for heart failure decompensation. Shamagian et al. divided their Spanish population into three groups depending on the year of hospitalization [60]. The study, from the Cardiovascular Health Study, examined the general population over 65 years old with ambulatory HF-PSF. In the Berry study, diuretic and ACE prescription rates should be interpreted with caution as these drugs were one of the inclusion criteria [59].

In some studies, the authors compared the type of management according to the severity of LV dysfunction. In the Management to Improve Survival in Congestive Heart Failure (MISCHF) register, the 1291 patients were divided into three subgroups depending on LVEF function: less or equal to 39%, 40 to 50%, and greater than 50% [55]. In the majority of cases, ACE were being prescribed more commonly in patients with systolic dysfunction, both on admission and at discharge from hospital. The doses of ACE were also higher in systolic dysfunction [55]. Similar results were found in the EuroHeart Failure survey [62,63]. The same finding also applies to beta-blockers in the most recent analyses [57,63].
Table 1  Prescription rates of different classes of drugs in epidemiological studies.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Date</th>
<th>LVEF (%)</th>
<th>Diur (%)</th>
<th>ACE (%)</th>
<th>ARBs (%)</th>
<th>BB (%)</th>
<th>Spir (%)</th>
<th>Ca-B (%)</th>
<th>Digo (%)</th>
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<tbody>
<tr>
<td>CHS</td>
<td>170</td>
<td>1989—1993</td>
<td>≥ 55</td>
<td>59</td>
<td>25</td>
<td>17</td>
<td>31</td>
<td>41</td>
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<td>REP 91</td>
<td>59</td>
<td>1991</td>
<td>≥ 50</td>
<td>78</td>
<td>31</td>
<td>19</td>
<td>24</td>
<td>27</td>
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<tr>
<td>Alabama</td>
<td>238</td>
<td>1994</td>
<td>≥ 40</td>
<td>30</td>
<td>31</td>
<td></td>
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<tr>
<td>MISCHF</td>
<td>312</td>
<td>1995—1997</td>
<td>≥ 50</td>
<td>76</td>
<td>45</td>
<td>23</td>
<td>39</td>
<td>30</td>
<td></td>
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<tr>
<td>Smith et al.</td>
<td>200</td>
<td>1996—1998</td>
<td>≥ 40</td>
<td>79</td>
<td>34</td>
<td>19</td>
<td>50</td>
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<tr>
<td>Berry</td>
<td>130</td>
<td>2000</td>
<td>≥ 40</td>
<td>95</td>
<td>65</td>
<td>38</td>
<td>12</td>
<td>24</td>
<td>23</td>
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<tr>
<td>Spanish</td>
<td>147</td>
<td>1991—1996</td>
<td>≥ 50</td>
<td>64</td>
<td>42</td>
<td>0</td>
<td>12</td>
<td>10</td>
<td>18</td>
<td>39</td>
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<tr>
<td>Study</td>
<td>109</td>
<td>1997—1999</td>
<td>≥ 50</td>
<td>69</td>
<td>55</td>
<td>5</td>
<td>12</td>
<td>5</td>
<td>30</td>
<td>22</td>
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<tr>
<td></td>
<td>186</td>
<td>2000—2001</td>
<td></td>
<td>64</td>
<td>49</td>
<td>6</td>
<td>28</td>
<td>12</td>
<td>36</td>
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<tr>
<td>EuroHeart Failure</td>
<td>3,148</td>
<td>2000—2001</td>
<td>≥ 40</td>
<td>85</td>
<td>58</td>
<td>4</td>
<td>39</td>
<td>17</td>
<td>28</td>
<td>31</td>
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<tr>
<td>Dobre</td>
<td>443</td>
<td>2000—2005</td>
<td>≥ 40</td>
<td>88</td>
<td>66</td>
<td>12</td>
<td>51</td>
<td>41</td>
<td>15</td>
<td>22</td>
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<tr>
<td>FOCALE</td>
<td>245</td>
<td>?</td>
<td>≥ 45</td>
<td>67</td>
<td>53</td>
<td>16</td>
<td>34</td>
<td>16</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>REP 03</td>
<td>306</td>
<td>2003—2005</td>
<td>≥ 50</td>
<td>24</td>
<td>17</td>
<td></td>
<td>21</td>
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<td>51</td>
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<tr>
<td>ADHERE</td>
<td>26,322</td>
<td>2004</td>
<td>≥ 40</td>
<td>65</td>
<td>36</td>
<td>13</td>
<td>46</td>
<td>5</td>
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<td></td>
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LVEF: left ventricular ejection fraction; Diur: diuretics; ACE: angiotensin II converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BB: beta-blockers; Spir: spironolactone; CaB: calcium channel blockers; Digo: digoxin.

For the trials by Smith et al., Berry et al., Dobre et al. and the Spanish trial, treatment was at discharge from hospital. The second line in the MISCHG, REP 03 and ADHERE studies is treatment at discharge from hospital. The FOCALE trial randomized ambulatory patients over 65 years old with an ECG and echocardiogram at inclusion.

CHS, [61]; REP91, [54]; Alabama, [65]; MISCH, [55]; Smith et al., [82]; Berry et al., [59]; Spanish trial, [60]; EuroHeart Failure Survey, [63]; Dobre et al., [66]; FOCALE, [81]; REP 03, [64]; ADHERE, [57].
In other studies, prescription rates of different drugs before hospitalization and at discharge have been examined [55,57,64]. Diuretics were the most widely prescribed drugs in these studies, followed by the ACE, with an increase in their prescription rates during the hospitalization. However, we do not know whether this approach was guided by blood pressure level. The prescribing rate of beta-blockers also appears to increase in the studies conducted after 2000 whereas digoxin prescription decreased, from 40% in the 1990s to 20% after 2000. Prescription rate of calcium channel blockers remains relatively stable with no information available about the type of calcium blocker (vasodilators or bradycardiac agents).

Relationship between treatments and morbidity—mortality rates

Because of some contradictory results of different retrospective studies from registries, it is difficult to draw any conclusions.

An analysis of a population from the American MEDICARE system including 1091 patients over 65 years old, hospitalized in 1994 for heart failure did not show any relationship between the prescription of ACE and four-year survival in the 238 patients with LVEF greater and equal to 40% [65].

In the MISHC register, ACE prescription was associated with a shorter length of hospitalization and a 60% reduction in the six months mortality rate in patients with LVEF between 40 and 49%. Conversely, prescription of ACE in the subgroup of patients with LVEF greater or equal to 50% was associated with a 30% non-significant decrease in morbidity and mortality [55]. The power of this analysis is limited by the small number of patients per subgroups (less than 200).

In the Spanish study, authors compared mortality of their patients admitted for heart failure decompensation with a separate analysis over three different inclusion periods [60]. Annual mortality was similar during the three periods, between 9 to 12%. By multivariate analysis, the prescription of ACE or of an ARBs was associated with a greater survival rate (36% mortality reduction). On the other hand, digoxin was associated with a 40% significant increase in mortality.

In the Dutch study [66], prescription of beta-blockers was associated with a significant reduction in mortality, with an adjusted relative risk of 0.57 [0.37–0.88, p=0.01], with a dose effect. It is interesting to note that in this study, digoxin prescription was also associated with an excess mortality (adjusted RR = 1.58 [1.006–2.47, p=0.05]).

The ACE and beta-blockers were also found to have a beneficial effect in the EuroHeart Failure Study [63]. After 12-week of follow-up, prescription of ACE and of beta-blockers were associated with a 45% (RR = 0.55 [0.43–0.71]) and with a 39% (RR = 0.61 [0.48–0.77]) reduction in total mortality, respectively.

Clinical trials

Small studies and retrospective analyses

A few small studies (with less than 400 patients) have assessed the effect of different classes of treatment in HF-PSF.

The open study by Aronow et al. assessed the effect of a beta-blocker, propanol (90 mg/d), on prognosis in 158 patients, aged 81 ± 8 years old, in class II-III NYHA with LVEF greater or equal to 40% and a history of myocardial infarction [67]. All the patients were receiving diuretics and ACE for at least two months. Total mortality after 32-months of follow-up was reduced by 35% with propanol (44 deaths compared to 60, p=0.007) and total mortality and non-fatal myocardial infarction were reduced by 37% (p = 0.002).

The Survival of Myocardial Infarction Long-Term Evaluation study (SMILE-ISCHEMIA study) examined zofenopril in 303 patients admitted with myocardial infarction and LVEF greater than 40% [68]. The primary objective of the study was to examine the effect of zofenopril on the extent of myocardial ischemic burden (studied by a 24 h Holter monitoring and by an exercise test) after six months of treatment. The study demonstrated a significant reduction of the primary objective with zofenopril. There were only two deaths during the follow-up period and heart failure developed or worsened in 12 patients: all except for one of these were on placebo.

A retrospective analysis of the European Trial on Reduction of Cardiac Events with perindopril in stable coronary artery disease study (EUROP A) was conducted in patients with LVEF greater than 40% [69]. The EUROP A study was a double-blind, randomized, placebo controlled trial of an ACE, perindopril (8 mg/d), in 12,218 patients with coronary artery disease but without clinical evidence of heart failure. LVEF was measured in 58% of the population, of whom 6,878 patients (56%) had LVEF greater than 40%. Perindopril significantly reduced the incidence of the primary end point (cardiovascular mortality, non-fatal myocardial infarction and resuscitated sudden death) from 9.8 to 8.3% (RR = 0.84 [0.77–0.98]).

Large-scale trials

Four randomized, placebo-controlled, multicenter trials have examined the effects of different pharmacological treatments in HF-PSF: the DiG, CHARM-preserved, PEP-CHF and SENIORS trials.

The major therapeutic characteristics of these trials are summarized in Table 2. Diuretics were still the most commonly prescribed class of drugs, followed by beta-blockers in the two most recent studies. ACE were widely prescribed in the DiG trial and digoxin prescription was variable, between 12 and 40%, in the three other trials.

Digoxis Intervention Group (DIG trial)

The DIG trial can be considered to be the first randomized multicenter trial in HF-PSF. A subgroup of 988 North American patients with a LVEF greater than 45% was randomized to receive digoxin (492 patients) or placebo (496 patients). Digoxin had no impact on total or cardiovascular mortality, mortality from heart failure or on the majority of the combined end-points. Hospitalizations for heart failure were significantly reduced with digoxin but only after two-year of follow-up and this difference was not significant at the end of the trial. There was a trend towards more hospitalization for unstable angina in patients on digoxin [70].
Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity-Preserved study (CHARM-preserved study)

This is to date the largest trial in terms of number of patients, which examines the effects of an ARBs, the candesartan in HF-PSF [71]. CHARM-preserved trial included 3023 patients older than 18 years, with NYHA class II-IV clinical heart failure who had been hospitalized at least once for a cardiac cause and had an LVEF greater than 40%. Patients were randomized double-blind against placebo. The primary objective was to examine the effect of candesartan on cardiovascular mortality and hospitalizations for heart failure. After 36.6-months of follow-up, candesartan had not reduced the incidence of the primary end point (22% versus 24% with a 11% non-significant reduction on candesartan). Candesartan had no impact on the different secondary end points (hospitalization for heart failure, myocardial infarction, stroke or coronary revascularization). The average dose of candesartan at six months was 25 mg/d. There were significantly more adverse effects on candesartan than on placebo: more hypotension (2.4% versus 1.1%), more hyperkalaemia (1.5% versus 0.6%) and a greater rise in serum creatinine (4.8% versus 2.4%).

Despite this statistically negative result, the CHARM trial shows that a large scale randomized trial can be conducted in this complex disease. This study opened the way for new trials in HF-PSF.

Study of the Effect of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure trial (SENIORS trial)

The SENIORS trial cannot be considered to be a specific trial of HF-PSF because HF-PSF patients only represented a subgroup of the total population and because the LVEF cut-off value defining HF-PSF was unusually low (LVEF greater than 35%) [72]. The aim of the trial was to examine the effect of a beta-blocker, nebivolol, in 2135 patients over 70 years, who had either been hospitalized within the previous year for heart failure or in whom an LVEF of less or equal to 35% had been found within the previous six months. The major end-point was total mortality and hospitalizations for a cardiovascular cause. After a follow-up period of 21 months, nebivolol produced a significant 14% reduction in the incidence of the primary end-point (31.1% versus 35.3%, p = 0.04). Median LVEF was 34%, although only 20% of the population had an LVEF greater than 40%. The effect of Nebivolol on the primary end-point was similar whether the LVEF was over or under 35%.

Perindopril in Elderly People — Congestive Heart Failure trial (PEP-CHF)

The PEP-CHF trial examined the effect of an ACE, perindopril 4 mg/d, on morbidity and mortality in elderly patients followed up for HF-PSF [73]. The inclusion criteria were age greater or equal to 70 years, heart failure treated with diuretics, with a LVEF greater than 40%. In addition, three out of nine clinical criteria for heart failure and two out of four echocardiographic criteria for diastolic dysfunction were required. The average age was 75 years and 55% of the patients were women, 79% were hypertensive and 26% had a past history of myocardial infarction. The primary end-point was total mortality and hospitalizations for heart failure at one year. The trial showed a non-significant impact of perindopril on the primary end point. The annual event rate was 12.2% in the perindopril subgroup and 13.2% in the placebo subgroup. At the end of the trial, event rates were 23.6 and 25.1%, respectively. Similar results were found with all the secondary end points: total or cardiovascular mortality, hospitalizations for heart failure, duration of hospitalizations, increase in treatment.

These results are difficult to interpret because of numerous problems. The inclusion period, as well as the follow-up period, were extended in order to obtain a sufficient number of events. The drop-out rate was relatively high, 40% in the perindopril group and 36% in the placebo group. Open label ACE was prescribed in 35% of the patients in the perindopril arm and in 37% in the placebo arm.

In summary, these trials did not show any significant effect of different classes of drugs studies, digoxin, ACE or ARBs, except for a beta-blocker (nebivolol) in a non-specific HF-PSF study.

Two other randomized trials are ongoing: one, the Irbesartan in Heart Failure With Preserved Systolic Function trial (I-PRESERVE) [74] is assessing irbesartan and the other, the trial of aldosterone antagonist therapy in adults with preserved ejection fraction congestive heart failure (TOPOCAT trial) is assessing an aldosterone receptor blocker, spironolactone. The results of these two trials will perhaps enable us to improve the management of patients suffering from HF-PSF.

Special features of elderly patients over 80 years old

The prevalence of HF-PSF increases with age. The diagnosis in octogenarians is often difficult because of atypical
symptoms [75]. In addition, some non-specific "geriatric" signs (asthenia, confusion, behavioral disorders, fall, loss of independence) can also be the only clinical feature of heart failure, which is responsible for a delay in diagnosis and treatment. The clinical presentation is even more atypical and the prognosis even poorer if the heart failure occurs in frail patients with several comorbidities. Epidemiological data from a register of 86,094 institutionalized 85-year-old patients with heart failure [76] indicate that one third of the patients had at least six comorbidities in addition to heart failure, with a higher prevalence of cognitive disorders (57% of cases). In the Euro Heart Failure Survey I [77], infection was present in 42% of patients over 80 years old, confusion in 23%, anemia in 23% and severe renal failure (creatinine clearance less than 30 ml/min) in 15%. The presence of these comorbidities implies geriatric management in order to identify markers of "fragility" in the elderly (cognitive problems, walking disorders, depression, malnutrition, social isolation, loss of independence etc.) [78].

Cardiovascular disease is more serious in the elderly. In the Euro Heart Failure Survey I registry, total mortality at 12 weeks in patients with HF-PSF was significantly higher in octogenarians (average age 85 years old) compared to younger patients (average age 69 years old) (17% versus 7%, p < 0.0001) [77]. The excess mortality was due to both cardiovascular and non-cardiovascular causes. Because of this, it may be useful to consider the best end-points to be used in this population in future clinical trials: mortality, cardiovascular events, rehospitalisation, quality of life? In practice, the therapeutic management for each patient must be based not on actual age but on an individual assessment taking into account the "geriatric evaluation" of the elderly (life expectancy, quality of life, comorbidities, frailty, iatrogenic risk, etc.) [78].

**Educational program**

Few studies have assessed the effect of multidisciplinary management in patients with HF-PSF. Interpretation of the results of these studies are therefore difficult but the effect of multidisciplinary management appears to be less effective than in patients with systolic dysfunction.

It is possible that studies demonstrating a benefit of multidisciplinary management in terms of morbidity and mortality have included patients with HP-FSP, although no analysis by type of dysfunction was available until the publication by Galbreath et al. [79]. These authors randomized 1069 patients with heart failure and compared multidisciplinary follow-up with telephone calls and education to conventional follow up for 18 months. Seventy per cent of patients had systolic dysfunction and 30% had HF-PSF. This study demonstrated a significant reduction in mortality and cardiovascular events in the group of patients with systolic dysfunction whereas no significant effect was found in the subgroup of patients with HF-PSF. Multidisciplinary management in this study had little impact on blood pressure and this subgroup of patients appeared to be at lower risk.

In terms of effect on quality of life, this may be more significant although again there are insufficient studies available. One study conducted in 32 women with NYHA class II or III and LVEF greater than 45%, randomized to 12 weeks of mild to moderate regular physical exercise associated with therapeutic education compared to therapeutic education alone showed significant improvement in walking tolerance, quality of life and depression indices in the intervention group [80].

Therapeutic education and multidisciplinary management in patients with HF-PSF is probably more useful in controlling etiological and precipitating factors than in terms of preventing decompensation and reducing mortality. Therefore, the influence of therapeutic education is undoubtedly involved in the beginning of the disease. Deterioration in diastolic function often precedes the development of the initial symptoms by several years and early diagnosis and treatment of these abnormalities are essential in order to prevent irreversible damages. Primary prevention of HF-PSF requires smoking cessation and drastic control of blood pressure, hypercholesterolaemia and all other risk factors for coronary artery disease.

As for systolic dysfunction, changes in lifestyle are essential and must be combined with an appropriate diet with low sodium and alcohol intake and physical activity must be maintained. Weight monitoring and control of congestive signs are important but often difficult as exacerbations of left heart failure are usually sudden and more rarely preceded by warning signs (reduced walking tolerance, arrhythmia, increase of blood pressure, infection etc.). Knowledge of these warning signs however remains essential and patients must be educated about them.

**Conclusions**

The therapeutic management of patients with HF-PSF is difficult. The lack of clear results from the few randomized trials in this disease does not help us in its management. This management is based on our pathophysiology knowledge of HF-PSF which is multifactorial, involving hypertension, myocardial ischaemia, intrinsic myocardial damage and concomitant diseases (diabetes, renal failure). In the absence of significant results of large therapeutic trials, treatment of HF-PSF is therefore based on patient education and control of salt and water retention, blood pressure, heart rate and episodes of myocardial ischaemia.

**References**


