

# Management of diastolic heart failure

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## Abstract

*Diastolic heart failure (HF) is also referred to as HF with preserved left ventricular systolic function. The distinction between systolic and diastolic HFs is a pathophysiological one and isolated forms of left ventricular dysfunction are rarely observed. In diastolic HF left ventricular systolic function is normal or only slightly impaired, and the typical manifestations of HF result from increased filling pressure caused by impaired relaxation and compliance of the left ventricle. The predisposing factors for diastolic dysfunction include elderly age, female sex, obesity, coronary artery disease, hypertension and diabetes mellitus. Treatment of diastolic HF is aimed to stop the progression of the disease, relieve its symptoms, eliminate exacerbations and reduce the mortality. The management should include antihypertensive treatment, maintenance of the sinus rhythm, prevention of tachycardia, venous pressure reduction, prevention of myocardial ischemia and prevention of diabetes mellitus. The European Society of Cardiology specifies the type of therapy in diastolic HF based on: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, non-dihydropyridine calcium channel blockers, diuretics. In order to improve the currently poor prognosis in this group of patients the treatment of diastolic HF must be optimised. (Cardiol J 2010; 17, 6: 558–565)*

**Key words:** diastolic heart failure, impaired relaxation, ejection fraction, left ventricular compliance

## Introduction

Diastolic heart failure (HF) is also referred to heart failure with preserved ejection fraction (HF-PEF). The distinction between systolic and diastolic HFs is a pathophysiological one. Isolated forms of left ventricular (LV) dysfunction are, however, rarely observed. The majority of patients with HF have both systolic and diastolic dysfunction [1, 2]. It is estimated that in 55% of patients with systolic HF diastolic dysfunction is also present [3].

Gaining an understanding of the pathomechanisms underlying this disease entity is required to make any attempts at its treatment. While the clini-

cal manifestations in systolic HF result from impaired contractility of the left ventricle coupled with reduced ejection fraction (EF), LV systolic function in HFPEF is normal or only slightly decreased (EF  $\geq$  40% in echocardiography). In this case the manifestations of HF result from increased filling pressure caused by impaired relaxation and decreased compliance of the left ventricle. Moreover, in the pathomechanism of this form of HF, stiffness is not only observed in LV myocardium but in the arteries, which translates to high systemic resistance.

The differences between the two forms of HF are also observed at the cellular level. Van Heerbeeck et al. [4] showed that the presence of elon-

gated cardiac myocytes with a considerably elevated resting tone is typical of HFPEF. The stiffness of the walls and decreased compliance of the myocardium result from the increased amounts of collagen in the interstitial layer. An abnormal expression of metalloproteinases and their inhibitors results in the predominance of degradation processes over myocardial remodeling [4, 5].

Stroke volume not only depends on EF but also on diastolic volume. In diastolic dysfunction the impaired LV filling leads to the preservation of cardiac output at the expense of elevated left atrial filling pressure. Hypertrophic cardiomyopathy is a classic example of HF symptoms occurring with a preserved very good systolic function. In extreme cases patients manifest overt signs of HF at LVEF values exceeding 70%.

The diagnosis of HFPEF is justified when the patient complains about symptoms typical of HF, the physical examination reveals venous congestion and pulmonary congestion or even pulmonary edema, and an echocardiogram shows a normal or slightly decreased LVEF. A Working Group of the European Society of Cardiology (ESC) believes that the diagnosis of diastolic HF requires three conditions to be simultaneously satisfied [1]:

- presence of signs and/or symptoms of congestive HF (exercise intolerance is the first sign of diastolic failure, as increased heart rate during exercise shortens the duration of the already impaired diastole impairing LV filling and secondarily leading to pressure overload of the pulmonary circulation manifested by dyspnea); it should, however, be borne in mind that identifying the form of HF on the sole basis of the signs is not possible, as the differential diagnosis should include the following disease entities:
  - cardiovascular conditions: ischemic heart disease, valvular disease, hypertrophic and restrictive cardiomyopathies, constrictive pericarditis,
  - non-cardiac conditions: lung diseases, obesity, anemia, hyperventilation, hyperthyroidism, pulmonary hypertension;
- presence of normal or only mildly abnormal LV systolic function — EF > 40–50%; EF is the most important parameter for making the distinction between systolic and diastolic HFs;
- documented impairment of relaxation, filling, diastolic compliance or diastolic stiffness of the left ventricle.

The above parameters are mainly assessed by echocardiography. The echographic signs of diastolic dysfunction are identified analysing abnormal-

ities of the diastolic phase from the mitral inflow (in patients with sinus rhythm), the blood flow profile in the pulmonary veins and the ratio of early mitral filling flow velocity and early diastolic mitral annular velocity (E/E') measured by tissue Doppler echocardiography [6].

The predisposing factors of diastolic dysfunction include elderly age, obesity and such co-morbidities as hypertension and diabetes mellitus. The risk of HFPEF is also increased in patients with coronary artery disease of many years' duration, patients with a history of acute coronary syndromes and patients with a history of myocarditis. A large proportion of HFPEF patients are patients with LV hypertrophy (LVH) of various aetiologies: in hypertrophic cardiomyopathy, aortic stenosis, chronic kidney disease complicated by hypertension.

Population studies show that about 30–50% of patients with congestive HF have normal LVEF values. Elderly patients (> 75 years of age), women, hypertensive patients, often diabetics, and patients with elevated body mass index (BMI) predominate in this group [3].

The prognosis worsens with age. An analysis of multiple studies suggests that over a period of five years the percentage of HFPEF patients who die is 15% among those aged below 50, 33% among those aged 50–70 and 50% among those aged over 70. According to Aurigemma [7], the survival of patients with HFPEF is only slightly longer than that in patients with systolic dysfunction. Qwan et al. [3] point out that the survival of patients with systolic HF is systematically improving, while that of patients with HFPEF does not change significantly. As HFPEF may become the predominant form of HF in the near future, every effort should be made to disseminate the knowledge about its management. On the other hand, it should be emphasised that it is incomparably scantier than the knowledge about the management of systolic HF. In contrast to systolic HF, to which multiple randomised studies have been devoted, treatment of HFPEF is nearly exclusively based on recommendations of expert groups.

Treatment of HFPEF is aimed to stop the progression of the disease, relieve its symptoms, eliminate exacerbations and reduce mortality. Successful treatment of HF is conditional upon establishing the etiology. Echocardiography is the principal diagnostic tool. It is widely available, reproducible and inexpensive, and its results are complemented by the results of electrocardiography and chest X-rays. The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines emphasise that the measurement of brain

natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) is helpful in risk stratification in patients with diastolic and systolic LV dysfunctions, although these should not be used as markers of treatment efficacy (class IIa recommendations). This statement results from the fact that the measurement of BNP for the purposes of treatment monitoring has not been shown to be associated with a reduction in mortality [8].

While such drugs as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, aldosterone antagonists and diuretics are established treatments for systolic HF, the use of these drugs in HFPEF is not supported by multiple studies. According to the AHA/ACC guidelines, the management of HFPEF should involve [1, 8]:

- treatment of hypertension;
- maintenance of sinus rhythm;
- prevention of tachycardia;
- venous pressure reduction;
- prevention of myocardial ischemia.

Causative treatment, when used in the early stages of the disease, preferably in stage A (high risk of development of HF in the absence of symptoms) is most effective. Effective treatment of hypertension, coronary artery disease and diabetes mellitus reduces the risk of late complications.

### Treatment of hypertension

Antihypertensive treatment is an important element of management, as it is estimated that hypertension coexists in about 60% of patients with HFPEF. The close correlation between these two disease entities supports intensive antihypertensive treatment. It should, however, be borne in mind that elderly patients predominate in this group and it is necessary to avoid rapid blood pressure reductions. It is especially important because of the impaired function of the autonomic nervous system and the risk of postural hypotension. Effective treatment of hypertension results in immediate (improved exercise capacity and alleviation of dyspnea) and remote benefits. Normalization of systolic blood pressure allows the left ventricle to work against a lower afterload, which leads to a reduction in LV diastolic volume and left atrial pressure. The indirect beneficial effects of blood pressure normalization are the improvement of oxygen balance in the myocardium with the resulting improvement of myocardial perfusion and a more rapid relaxation. The remote benefits result from the suppression or even reversal of LVH and from the decrease in

the percentage content of collagen in the wall of the left ventricle.

Gandhi et al. [9] examined 38 patients with acute pulmonary edema occurring in the course of hypertension. The mean age of the patients was 67. During the pulmonary edema the mean systolic blood pressure was  $200 \pm 26$  mm Hg, LVEF was  $50 \pm 15\%$  and the wall motion score index (WMSI) was  $1.6 \pm 0.6$ . The subsequent examinations 1–3 days after the resolution of acute LV failure showed identical values of EF and WMSI with the only change being a reduction in systolic blood pressure ( $139 \pm 17$  mm Hg,  $p < 0.01$ ). None of the patients was diagnosed with mitral regurgitation during the pulmonary edema episode.

The selection of the agent to be used in the treatment of pulmonary edema in the course of hypertension should principally be based on the onset of action. The patient management should include oxygen therapy, morphine, intravenous diuretics, and glyceryl trinitrate (GTN). It should, however, be borne in mind that aggressive use of diuretics and GTN in patients with WMSI may lead to dangerous hypotension as a result of a rapid fall in LV filling pressure and the resulting decrease in cardiac output. The selection of the antihypertensive agent for chronic use in patients with HFPEF should take into consideration the role of angiotensin in the process of LVH and structural changes in the LV wall associated with the increased collagen content. Taking this aspect of management into consideration, the drugs of choice should be ACE inhibitors, AT1 receptor blockers and aldosterone antagonists. Already in 1993 Aronow and Kronzon [10] showed that in elderly patients with normal LVEF following myocardial infarction exercise capacity is improved following the use of enalapril. Several years later similar beneficial effects of losartan were shown by Warner et al. [11]. They also pointed out that limited exercise capacity is a consequence of increased blood pressure, hence the fundamental goal of treatment should be prevention of blood pressure increase during exercise.

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study [12], in the group of patients with hypertension and LVH, a higher efficacy of losartan *vs* atenolol was shown in the reduction of the composite primary endpoint (cardiovascular death, myocardial infarction or stroke;  $p = 0.021$ ) and in regression of LVH assessed by echocardiography ( $p < 0.0001$ ).

The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Preserved (CHARM-Preserved) study [13] compared the

effect of candesartan *vs* placebo in a group of NYHA class II, III and IV patients with EF > 40%. Out of the 3023 patients 1514 were randomized to candesartan (target dose 32 mg/day) and 1509 to placebo. The primary endpoint was cardiovascular death or hospitalization for HF. Over a period of 36.6 months the primary endpoint occurred in 333 (22%) patients receiving candesartan and 366 (24%) patients receiving placebo ( $p = 0.051$ ). Cardiovascular deaths occurred in both groups in 170 patients. Hospitalizations for HF were less frequent in the candesartan group *vs* placebo (230 *vs* 279,  $p = 0.017$ ) [13].

Another published study evaluating the efficacy of treatment with ACE inhibitors is the Perindopril In Elderly People With Chronic Heart Failure (PEP-CHF) study [14]. A total of 850 patients aged  $\geq 70$  with signs of HFPEF were randomized to perindopril 4 mg or placebo. The primary composite endpoint included all-cause mortality and unplanned hospitalization for HF. The mean follow-up period was 26.2 months. The primary endpoint occurred in 107 placebo patients and 100 perindopril patients ( $p = 0.545$ ). The effect of perindopril treatment was more beneficial in the first year of the study. In this period the primary endpoint was observed in 65 (15.3%) patients in the placebo group and 46 (10.8%) patients in the perindopril group ( $p = 0.055$ ), and hospitalizations for HF were less frequent in the perindopril group ( $p = 0.033$ ). The mortality rate in both groups was similar. A significant improvement in the NYHA class was observed in patients receiving perindopril ( $p < 0.030$ ). There was also a significant improvement in the six-minute walk distance in the perindopril group ( $p = 0.011$ ). Perindopril treatment did not affect the levels of NT-proBNP [14].

Based on the results of the above studies it may be concluded that pharmacological intervention in the renin-angiotensin-aldosterone system makes it possible to improve exercise capability in HFPEF patients and possibly reduces the risk of hospitalization for HF but does not affect the prognosis. When discussing the results of the PEP-CHF study we suggest that the severity of HF in the study population was mild, as evidenced by the NT-proBNP levels (the mean values in the placebo and perindopril groups were 453 pg/mL and 335 pg/mL, respectively). Also the relative low number of adverse events, much lower than expected, may support the above hypothesis. Achieving a significant mortality risk reduction in such a population would therefore require a much longer follow-up and a considerable increase in the sample size.

The investigators conducting the Valsartan In Diastolic Dysfunction (VALIDD) study [15] of valsartan point to the fact that blood pressure reduction improves diastolic function of the myocardium in hypertensive patients without HF and that this effect is independent of the type of antihypertensive agents used.

The ACA/AHA guidelines placed systolic and diastolic blood pressure control in the highest class of recommendations for the management of HFPEF (class I of recommendations, level of evidence A) [8].

The effects of blood pressure normalization include:

- reduction of LV end-diastolic pressure;
- reduction of left atrial pressure;
- improvement of relaxation leading to improved early filling;
- decrease in myocardial ischemia (by reducing oxygen demand and improving perfusion as a result of reduced end-diastolic pressure);
- reduction of LVH and the resulting reduction of the risk of development or progression of HF.

In the Systolic Hypertension in the Elderly Program (SHEP) study [16] good control of isolated systolic hypertension allowed to significantly reduce the risk of HF and led to the reduction of LV mass index by 13%. Treatment was based on chlorthalidone and atenolol [16, 17].

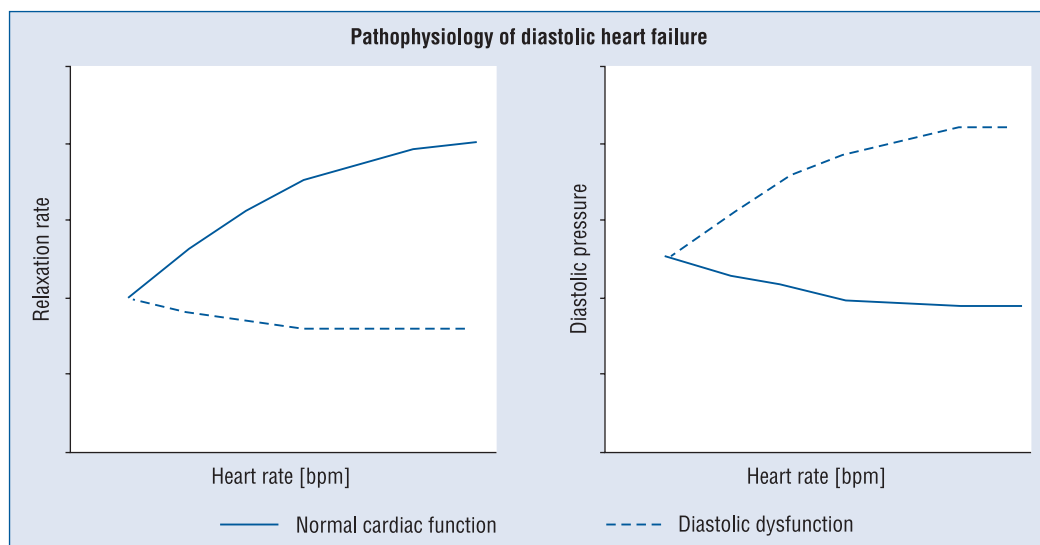
### Maintenance of sinus rhythm and prevention of tachycardia

The ACC/AHA recommendations place ventricular rate control in patients with atrial fibrillation (AF) and reversal to sinus rhythm in patients with AF in class II recommendations with the level of evidence A.

Under physiological conditions heart rate increase improves relaxation and slightly reduces diastolic pressure in the ventricle (Fig. 1). In diastolic HF tachycardia results in delayed relaxation and increased diastolic pressure.

In addition, the percentage contribution of the diastole in relation to the systole decreases with increasing heart rate. The diastole accounts for nearly 70% of the cardiac cycle at a heart rate of 60 bpm, slightly over 50% at 120 bpm, and only 40% at 180 bpm. The LV filling time is therefore considerably shortened. Decreasing heart rate therefore results in reduced pressure in the early period of the diastole by improving relaxation, and increasing the ventricular filling time improves cardiac output. The coronary perfusion time also increases, which — together with the reduced oxygen con-





**Figure 1.** The relationship between relaxation rate and between left ventricular diastolic pressure and heart rate in physiological conditions and in diastolic heart failure.

sumption by the myocardium — improves myocardial blood supply. The ESC experts recommend beta-blockers or calcium channel blockers (CCB) for decreasing heart rate [1].

The Swedish Doppler-echocardiographic (SWEDIC) study [18] evaluated the effect of 6-month carvedilol treatment on the echocardiographic parameters of diastolic function in 97 hypertensive patients. There was a significant improvement *vs* placebo in E/A from 0.72 to 0.83 ( $p = 0.046$ ).

In one of our previous publications we showed a beneficial effect of intravenous verapamil on the LV filling parameters in patients with hypertrophic cardiomyopathy [19].

Taking into account the close relationship between LV filling pressure and the patient's exercise capacity, reduction of heart rate in HFPEF should be treated as a priority. In patients with HFPEF, the heart is unable to take advantage of the Frank-Sterling mechanism during exercise. A stiff ventricle, despite elevated filling pressure, does not increase in volume. As a consequence filling pressure increases but cardiac output does not. This is why, in great simplification, by reducing ventricular rate cardiac output can be improved. These symptoms may be relieved by beta-blockers and CCB. In the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) [20] nebivolol significantly reduced mortality risk and cardiac hospitalization rate both in the group of patients with HF

and reduced EF and in the group of patients with normal EF.

An important difference in the management of both types of HF lies in the approach to using dihydropyridine CCB, which may be beneficial in diastolic dysfunction. This results, first of all, from their documented relaxing effect on the myocardium. In addition, their blood pressure and heart rate reducing properties are also taken advantage of.

The role of digitalis in the treatment of HFPEF is controversial, particularly in the case of maintained sinus rhythm. In the Digitalis Investigation Group (DIG) [21] study 988 patients with HF had EF > 45%, 492 of whom were randomized to digoxin and 496 to placebo. The benefits of digitalis in this group were similar to those in the group of patients with reduced EF. It is, however, widely believed that the use of digitalis in HFPEF should be limited to patients with AF, and the principal goal of using this drug is ventricular rate control. Digitalis should not be used if sinus rhythm is maintained.

It should also be borne in mind that the impaired LV filling in diastolic dysfunction may be further exacerbated by a non-sinus rhythm. For this reason elimination of such arrhythmias as AF or atrial flutter is an important element of treatment. Where sinus rhythm cannot be maintained, a close ventricular rate control is recommended. As a last resort, atrioventricular node ablation with subsequent pacemaker implantation may be considered.

## Venous pressure reduction

An increase of wedge pulmonary artery pressure of 1 mm Hg results in a 23% increase in all-cause mortality risk and a 13% increase in the risk of cardiovascular events. By reducing the wedge pressure exercise capacity and the prognosis are improved. The difficulty in optimizing LV filling pressure in HFPEF lies in the fact that in this group of patients the pressure/volume curve differs from the physiological curve. In HFPEF patients even a small decrease in filling pressure results in a very marked reduction of LV diastolic volume, which may lead to a significant reduction of cardiac output. Increased filling pressure frequently fails to significantly affect cardiac output but may put the patient at risk of pulmonary edema.

Patients with HFPEF show a tendency towards fluid retention, which is why restricted dietary intake of salt and fluids is recommended, while diuretics are the mainstay of symptomatic treatment. In light of the above risks when using diuretics or long-acting nitrates considerable caution should be exercised and, particularly in the early phase of the treatment, these drugs should be used under strict medical supervision. Diuretics do not directly affect the myocardium, while nitrates improve the ability of the left ventricle to increase its volume by releasing nitrogen nitrate.

The effects of venous pressure reduction are listed below:

- reduced LV compression → improved function;
- reduced LV end-diastolic pressure → improved exercise capacity;
- improved oxygen balance in the myocardium → elimination of ischemia.

The above therapy, however, requires considerable caution due to the risk of excessive dehydration leading to the manifestations of low-output syndrome, poorly tolerated hypotension and impaired renal function. The doses of dehydrating agents in this group of patients are much lower than those in patients with systolic dysfunction.

Spironolactone is a drug that combines diuretic action with beneficial effects on the structure of the left ventricle. The results of the ongoing Treatment of Preserved Cardiac Function Heart failure with an Aldosterone Antagonist (TOPCAT) and the Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study studies may provide answers about the justifiability of treatment with an aldosterone antagonist in HFPEF.

## Prevention of ischemia

Myocardial ischemia is one of the most important mechanisms underlying HFPEF. It is therefore justified to use drugs that reduce oxygen consumption by the myocardium (beta-blockers, CCB, nitrates) and revascularization to improve oxygen supply to the myocardium. It should, however, be noted that even successful revascularization does not prevent recurrences of HF in patients with hypertension and coronary artery disease [22].

Improved oxygen balance leads to:

- improved relaxation;
- reduced LV end-diastolic pressure;
- reduced risk of cardiac arrhythmias;
- reduced heart rate.

Zile [23] points out that in patients with diastolic HF ischemia, especially subendocardial ischemia, is possible without significant atheromatous changes in the epicardial arteries. It results, among other things, from LVH, hypertension and a high diastolic pressure which interferes with perfusion.

## Other treatments

Fukuda et al. [24] investigated the effect of statins in patients with HFPEF managed with a beta-blocker or a CCB, an ACE inhibitor or an ARB. Sixty-eight patients received a statin and the remaining 69 did not. The authors showed that only the use of a statin beneficially affected two-year survival in this group of patients resulting in a 20% reduction in mortality in the group receiving statins (mortality risk 0.06 vs 0.62,  $p = 0.005$ ). There was also a trend towards less frequent cardiovascular hospitalizations ( $p = 0.082$ ). The use of any of the other drugs resulted in no benefit. This is the first report to demonstrate the efficacy of statins in HFPEF, which most certainly requires further studies, especially since statins are the first class of drugs used in HFPEF that shows a documented beneficial effect on survival. The beneficial effect of statins in HFPEF may not only result from the stabilization of atheromatous plaques in the coronary arteries in patients in whom coronary artery disease is the aetiological factor, but also from the documented effect of this drug class on the reduction of LV mass and fibrosis. In a small study on rats Chang et al. [25] showed a beneficial effect of rosuvastatin on the LV myocardium in the form of suppressed fibrosis with the resulting reduction in LV wall stiff-

ness. These drugs also show a weak antihypertensive action.

The management of HFPEF should not ignore effective treatment of diabetes mellitus as a factor exacerbating diastolic dysfunction. It is also justified to encourage obese patients to lose weight.

### Summary

The ESC recommendations specify the type of therapy in HFPEF. In order to reduce heart rate and increase the diastole beta-blockers or non-dihydropyridine CCB are recommended. In order to eliminate fluid retention diuretics are used, administered with considerable caution, while ACE inhibitors are used to control blood pressure, suppress (regress) LVH and to improve relaxation. High doses of ARB are recommended to reduce the risk of hospitalization.

When the ACC/AHA 2009 guidelines were being updated data from randomized clinical trials did not contribute much to the current state of knowledge about the pathomechanism and treatment of diastolic dysfunction. It is still emphasised that the key elements of management in this group of patients include: very careful control of hydration, optimization of antihypertensive treatment and, in the case of AF, restoration and maintenance of sinus rhythm or ventricular rate control in patients with persistent arrhythmia. The physician should also remember about revascularization in symptomatic patients or, if it is suspected that diastolic dysfunction could be caused by ischemia, about taking steps to restore sinus rhythm in patients with AF.

In summary it should be emphasised that treatment of HFPEF needs to be optimized in order to improve the prognosis in this considerably numerous group of patients. The commencement of treatment is, however, conditional on the correct diagnosis based on a thorough history supplemented with diagnostic investigations, mainly echocardiography. It seems, however, that optimal outcomes can only be achieved if doctors are vigilant for this particular form of HF with normal systolic function of the left ventricle on the one hand, and randomized studies are conducted which will allow to use a therapy in line with evidence-based medicine. This will result in improved long-term prognosis in this group of patients, which continues to be poor which — according to various researchers — is associated with the annual mortality rate of 5–24%.

Taking into account the current state of knowledge, the management of HFPEF should be based on:

- causative treatment of: hypertension, type 2 diabetes mellitus, arrhythmias (prevention of tachyarrhythmias and, if possible, maintenance of sinus rhythm), ischemic heart disease, weight reduction, restricted salt intake;
- symptomatic treatment with: beta-blockers, non-dihydropyridine CCB, ACE inhibitors, ARB, diuretics, statins and aldosterone antagonists.

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