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EXPERT OPINION

New statement on chronic heart failure in patients with diabetes mellitus of the Heart Failure Association of the European Society of Cardiology: comments of Russian experts

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In 2018 the European Journal of Heart Failure published the new statement on chronic heart failure (CHF) in patients with diabetes mellitus (DM). It contained the data of major clinical trials on CHF prevalence, CHF clinical features and complications, pathophysiological aspects of myocardial dysfunction, CHF treatment in patients with DM, safety and possibility of use of hypoglycemic agents in patients with CHF and DM. The current article presents the comments of the Russian experts on principal positions of this new statement.

Key words: *chronic heart failure, diabetes mellitus, clinical features, treatment, prevention.*

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In 2018 the European Journal of Heart Failure published the new statement on chronic heart failure (CHF) in patients with diabetes mellitus (DM). The document was prepared by the group of international experts (Petar M. Seferović, Mark C. Petrie, Gerasimos S. Filippatos et al., 35 experts in general, including an expert from Russia — professor U.M. Lopatin) [1].

The statement included data of large investigations on the CHF prevalence in patients with diabetes mellitus, CHF clinical features and complications, pathophysiological aspects of myocardial dysfunction, CHF treatment in patients with DM, safety and possibility of use of hypoglycemic agents in patients with CHF and DM.

The comments of the Russian experts on principal positions of this new statement are presented below.

Chromic heart failure prevalence in patients with diabetes mellitus

DM and CHF are serious chronic diseases, which significantly affect the prognosis and life expectancy of the patients. Death, caused by cardiovascular events, is significantly more common in patients with CHF and DM with normal or decreased ejection fraction, compared with patents only with CHF. At the same time, CHF is an independent predictor of fatal and non-fatal complications in patients with type 2 diabetes mellitus (T2DM). The main causes of heart failure in patients with DM are not only coronary artery disease (CAD) and arterial hypertension (AH), but also diabetic cardiomyopathy, which plays significant role in its development [2].

It is known, that T2DM represents about 90–95% of diabetes mellitus cases. The frequency of T2DM has significantly increased during the past years. Its prevalence raised from 4,7% in 1980 to 8,5% in 2014 among people of working age. Average prevalence is about 11,8% (4,7–13,3%) worldwide nowadays [3].

There are few studies on CHF prevalence in patients with DM. According to different data, its prevalence is about 12% and it increases with age approximately to 19% [4–7]. DM is 2–4 times more prevalent (from 24% and higher) in patients with CHF, depending on their region, compared with patients without CHF. According to registries of hospitalized patients with CHF in North America and Europe, the prevalence of DM is 40–45%. According to Swedish CHF registry (68% patients admitted to hospital and 32% outpatient ones), DM was diagnosed in 30% of cases, whereas in patients without CHF, its prevalence was 19%.

According to Kaiser Permanente study, the incidence of DM was significantly higher in patients with HF than without it (13.6 cases of 1000 patients versus 9.2 cases of 1000 patients) over a 5-year follow-up. CHF is the most common CVD in patients with DM in general, compared with myocardial infarction or stroke [8]. According to perspective UKPDS 35 trial, which included newly diagnosed diabetic patients, HF incidence steeply increased with the severity of hyperglycemia (ranging from 2.3 to 11.9/1000 person-years for patients with glycated hemoglobin (HbA1c) < 6% and HbA1c >10%, respectively [9].

The results of the ARIC study showed, that CHF frequency was higher on the stage of early carbohydrate metabolism disturbances (prediabetes) compared with patients with normoglycemia [10].

Obviously, CHF is one of the most frequent macrovascular complication of diabetes. On the other hand, the frequency of carbohydrate metabolism disturbances, including newly diagnosed diabetes, is also very high in patients with CHF. Age and blood glucose levels are important in the development of morbidity and complications.

Type 2 diabetes mellitus and chronic heart failure: clinical presentation and cardiovascular prognosis

The key point in the management and treatment strategy of CHF patients is the identification of the causes of its development. The estimation of the dia-

stolic/ systolic left ventricular dysfunction severity is clinically and prognostically significant [10]. Patients with decreased (low) left ventricular ejection fraction (HFrEF), usually have severe diseases, associated with atherosclerosis, and coronary artery bypass grafting has the same benefit for cardiovascular mortality reduction in patients with or without DM [11].

The diagnosis and treatment of acute and chronic HF working group of European Society of Cardiology (ESC) in 2016 identified the new group of patients with CHF and LV ejection fraction between 40–49 %, named «HF with preserved EF (HFpEF)». The number of patients is increasing in both groups, mostly due to patients with DM without CAD, who has non-ischemic etiology of cardiovascular system lesion: cardiovascular autonomic neuropathy, specific cardiomyocyte damage due to glucose toxicity and oxidative stress, interstitial fibrosis, reduction of coronary reserve due to microangiopathy [12]. That's why the concept of early preventive strategy is very important in patients with DM.

Interestingly, some clinical studies have shown significantly higher risk of diabetes development in patients with CHF, which seems to be associated with insulin sensitivity disturbances: more pronounced insulin resistance leads to more severe CHF manifestation.

In the massive CHARM program 8 % of patients with CHF developed DM over 3 years of follow-up. However, more severe circulatory insufficiency lead to higher possibility of diabetes development [13].

Patients with DM have more severe manifestation of CHF, despite similar parameters of heart's pumping function, compared with patients without DM. They have more chances of death, caused by cardiovascular events with ischemic and non-ischemic etiology [14]. Carbohydrate metabolism decompensation, estimated by HbA1c, also has negative impact on cardiovascular prognosis in patients with CHF and DM.

Observational studies demonstrate, that about 30 % of patients aged over 60 years, have asymptomatic CHF manifestation (22,9 % and 4,8 % of patients with HFpEF and HFrEF, respectively). On the other hand, undiagnosed cases of DM and prediabetes have the same prevalence in the population with CHF [10, 15].

In the PARADIGM-HF trial, 13 % of patients with CHF had undiagnosed DM and 25 % had pre-diabetes [16]. In the CHARM study undiagnosed DM had the same frequency in patients with preserved and decreased left ventricular ejection fraction [17].

There is no doubt, that combination of DM and CHF is a severe comorbid state, and each of its components is associated with an extremely high cardiovascular risk. These patients require early diagnosis of both carbohydrate metabolism disturbances and preclinical manifestation of CHF.

Pathophysiological aspects of myocardial dysfunction in patients with type 2 diabetes mellitus

The combination of T2DM with CAD and AH can lead to CHF development. It is suggested that pathological processes during DM can directly affect heart structure and function [18]. The main factors that cause myocardium dysfunction in patients with DM are insulin resistance and high level of insulin [19]. Their adverse effects are associated with deposition of glycation end products, lipotoxicity and microvascular rarefication [18]. Insulin resistance increases the amount of free fatty acids [20, 21]. The capture of free fatty acids by cardiomyocytes in the amount exceeding the beta-oxidation potential, leads to triglyceride accumulation in the myocardium, which can be manifested by steatosis, which, in turn, can lead to diastolic dysfunction [22]. Insulin resistance is the factor of left ventricular hypertrophy development [23].

Hyperglycemia also affects cardiovascular system by disrupting cardiomyocytes and mitochondria function and activating protein kinase C [24, 25]. In addition, hyperglycemia leads to reactive oxygen species activation, deposition of glycation end products in both endothelium and smooth muscle cells, which leads to concentric myocardial remodeling and an increase in left ventricular diastolic stiffness [25].

Phenotypes of chronic heart failure in patients with diabetes mellitus

Diastolic dysfunction occurs in 75 % of patients with T2DM, and usually develops on early stages of the disease [26, 27], and the severity of diastolic dysfunction correlates with carbohydrate metabolism dysregulation, CHF prevalence and cardiovascular mortality. About half of the patients with T2DM have HFpEF. The main cause of HFrEF development in patients with T2DM is accompanying CAD, the likelihood of which increases in patients with T2DM. HFpEF usually occurs on the early stages of T2DM, whereas HFrEF occurs during more severe T2DM, which means that the severity of hyperglycemia is important for the development of left ventricular dysfunction.

Diabetic cardiomyopathy

In 1954, Lundbaek was the first to propose the existence of a specific diabetic heart muscle disease without involvement of CAD or AH [28]. Two decades later, Rubler et al. [29] described diabetic-related post-mortem findings in patients with DM and HFrEF with normal epicardial coronary arteries and without AH or/and cardiac valves lesions. It is remarkable, that there is no definition of diabetic cardiomyopathy, which makes studies of epidemiology, pathophysiology and clinical course of the disease challenging. The most commonly accepted definition refers to a myocardial dysfunction which occurs in the absence of all other CV disease.

Treatment of heart failure in patients with type 2 diabetes mellitus

According to the results of subanalyses during controlled randomized studies, standard pharmacological therapy of CHF by angiotensin-converting enzyme inhibitors [30], angiotensin II receptor blockers [31], beta-blockers [32], mineralocorticoid receptor antagonists [33], sacubitril / valsartan [34], nitrates and hydralazine [35], ivabradine [36] were similarly effective whether or not patients had DM. Accurate monitoring of blood potassium level is required during angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists treatment due to frequent renal lesions in patients with Beta-blockers can mask the manifestations of developing hypoglycemia (tachycardia, tremor).

Implantation of cardioverter-defibrillators [37] and cardiac resynchronization therapy [38] were similarly effective whether or not patients had T2DM. The frequency of infectious and other complications, connected with implanted devices, did not depend on the presence of T2DM.

Coronary artery bypass grafting had similar effect on mortality independently on presence of T2DM [39].

The mortality of patients with T2DM after cardiac transplantation was significantly higher due to renal dysfunction, arteries lesions development and infectious complications during immunosuppressive therapy with corticosteroids [40].

Type 2 antidiabetic drugs and the risk of heart failure

The investigations over the past years revealed different effects of several hypoglycemic drugs on the most frequent cardiovascular diseases and its complications, including CHF. The importance of this circumstance was emphasized by the decision of FDA in 2008 on the increase of requirements for hypoglycemic drugs registration, which should not only reduce the level of glycemia, but also have cardiovascular safety profile [41]. However, in modern diabetology, the principles of hypoglycemic drugs use were not clearly formulated, taking into account their impact on the risk of HF development and progression, until recently.

The new position statement of HF Association of the ESC 2018 for patients with CHF and T2DM was a big step forward, which represented the division of the entire arsenal of hypoglycemic drugs, depending on their impact on the risk of CHF development, into four groups for first time.

Drugs that are now known to increase the risk for CHF are hypoglycemic drugs from the group of thiazolidinediones (rosiglitazone, pioglitazone) and a iDPP-4, saxagliptin [43], which increased the rate of CHF hospitalizations in patients with T2DM. Patients at greatest risk were those with a history of CHF, an estimated glomerular filtration rate ⩽60 mL/min, or elevated baseline levels of NT-proBNP, which is a HF marker. On that basis, pioglitazone, rosiglitazone and saxagliptin are contraindicated in patients with T2DM and CHF or at high risk of CHF. At the same time, another drug from iDPP-4 group, sitagliptin, did not have any negative effect on the course of CHF and can be used among this category of patients [44]. Although the increase of the CHF progression risk during alogliptin treatment in patients with T2DM after recent acute coronary syndrome was unreliable [45], iDPP-4 is contraindicated in patients with T2DM and III–IV functional classes of CHF.

Insulin, which causes sodium and water retention and sulphonylurea derivatives as insulin secretagogues are hypoglycemic drugs that might increase the risk of CHF. These drugs can be used only after metformin or other drugs with positive effect on patient's prognosis treatment in patients with CHF.

It has been proposed, that metformin might be safe and efficacious in patients with T2DM and CHF. Previous concerns that metformin may cause metabolic acidosis are no longer justified, and it could be recommended as first-line treatment for patients with T2DM and CHF who have preserved or moderately reduced renal function (i.e. eGFR >30 mL/min) [10]. Glucagon-like peptide 1 receptor agonists, for example liraglutide, exenatide, lixisenatide, semaglutide, are also the drugs with neutral effect on the risk of HF hospitalization [46].

A significant breakthrough in contemporary diabetology was the identification of the hypoglycemic drugs, that lower the risk of CHF progression — sodium–glucose co-transporter type 2 (SGLT2) inhibitors (iSGC2). The use of empagliflozin (EMPA-REG OUTCOME trial, n=7020) [47] and canagliflozin (CANVAS trial, n=10143) [48] was associated with significant lower risk of CHF hospitalizations (35 % and 33 %, respectively).

Considering the numerous mechanisms of the cardiac- and nephroprotective effects of iSGC2, it is assumed, that the drugs of this group may be effective for the treatment of CHF in patients without T2DM. In order to confirm this hypothesis, large randomized placebo-controlled studies of the empagliflozin effect on the CVD associated mortality and CHF hospitalizations in patients with HFrEF were initiated in 2017 (EMPEROR-Reduced, NCT03057977) and with HFpEF (EMPEROR-Preserved, NCT03057951) and of dapagliflozin efficacy in patients with HFrEF (Dapa-HF, NCT03036124).

According to the results of these studies, it can be decided to expand the indications for the use of drugs from iSGC2 group by including the patients without carbohydrate metabolism disturbances.

Conclusion

Consequently, T2DM and CHF are very common. The causes of HF in T2DM are numerous, but CAD and AH are likely the most important contributors to concurrent T2DM and HF, whereas a direct effect of T2DM on the myocardium (diabetic cardiomyopathy) might also play a role. Data from registers and prospective studies indicate that regardless of the etiology and phenotypes, the risk of complications development in patients with T2DM and CHF is high. Some new antidiabetic drugs have a neutral or beneficial effect in reducing CHF hospitalizations in patients with DM.

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