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## «SGLT2 INHIBITORS: RATIONALE FOR THE USE IN HEART FAILURE», RESOLUTION ON THE RESULTS OF THE PANEL OF EXPERTS WITH INTERNATIONAL PARTICIPATION, ALMATY

Patients with heart failure have a high risk of developing cardiovascular complications, and prevention of thereof requires timely medical care and diagnostic assessment. An expert meeting was held with the participation of the NGO “Society of Specialists in Arterial Hypertension and Cardiovascular Prevention”, NGO “Evidence-Based Cardiology”, NGO “Association of Endocrinologists of Kazakhstan”. On April 29, 2022 a panel of experts discussed the rationale for the use of SGLT2 inhibitors in heart failure. The EMPEROR-Reduced and EMPEROR-Preserved trials analyzed cardiovascular and renal outcomes in empagliflozin treatment in patients with and without type 2 diabetes mellitus (T2DM). Several proposals and recommendations have been adopted for further research on the cardiovascular and renal effects of empagliflozin and its use in clinical practice in patients with chronic heart failure, regardless of the presence of type 2 diabetes.

At the experts meeting, issues were considered on the creation of heart failure rooms in outpatient settings and the possibility of studying the concentration of brain natriuretic peptides and performing echocardiography, including the assessment of left ventricular deformity and electrocardiography (ECG).

**Key words:** ECG, diabetes mellitus, CHF.

The Panel of Experts was held with the participation of the NGO “Society of Specialists in Arterial Hypertension and Cardiovascular Prevention”, NGO “Evidence-Based Cardiology”, NGO “Association of Endocrinologists of Kazakhstan”.

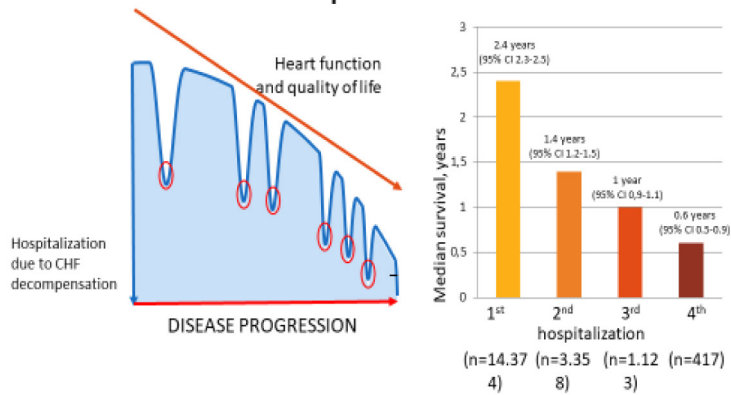
At the meeting of experts held on April 29, 2022 the rationale for the use of SGLT2 inhibitors in heart failure was discussed. The EMPEROR-Reduced and EMPEROR-Preserved trials analyzed cardiovascular and renal outcomes in empagliflozin treatment in patients with and without type 2 diabetes mellitus (T2DM). Several proposals and recommendations have been adopted regarding further study of the cardiovascular and renal effects of empagliflozin and its use in clinical practice in patients with chronic heart failure, regardless of the presence of type 2 diabetes.

Chronic heart failure (CHF), as one of the cardiovascular complications, is among the most com-

mon causes of death in patients and repeated hospitalizations, representing a great burden on the healthcare system. Despite the existence of proven therapies, the prognosis of patients suffering from chronic heart failure (CHF) remains unfavorable [1-4] (Fig. 1).

During a 10-year follow-up period, a patient hospitalized once with a diagnosis of de novo CHF has some limited number of hospitalizations for CHF [3]. The repeated hospitalization frequency graph is a two-phase curve that has 2 peaks: the first peak, the early one, is due to an increase in the number of hospitalizations for decompensation in the first 2-3 months after the diagnosis of CHF (up to 30% of hospitalizations are formed in this time interval) [2]. The second peak of hospitalizations is formed 2-3 months before death, and it accounts for about half of hospitalizations.

## Heart Failure is a constantly degenerative disease with high hospitalization rate



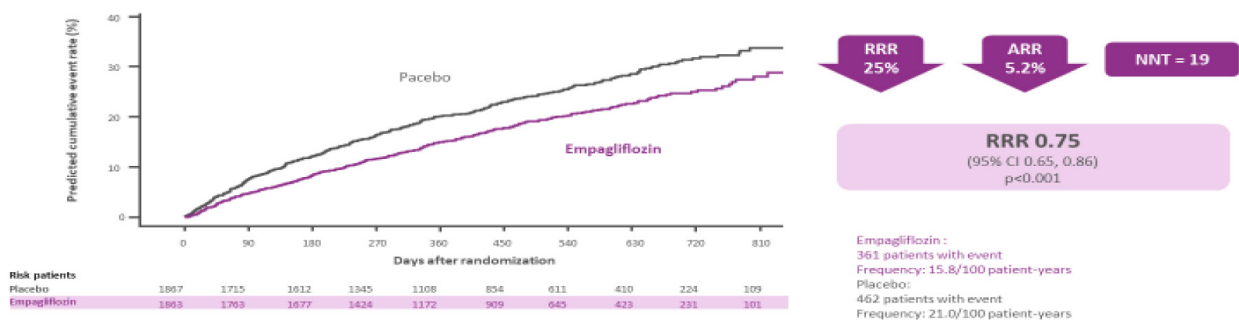
Adapted from Gheorghiade et al. Am J Cardiol 2005;96:11-17; Gheorghiade and Pang. J Am Coll Cardiol 2009;53:557-75; Setoguchi S. et al. Am Heart J. 2007;154:260-6

**Figure 1** – Heart failure is a steadily progressive disease with a high rate of hospitalization [1]

Between them there is a “plateau phase”, which lasts for years, and the frequency of rehospitalizations during this time is 15-20% of the total number of rehospitalizations. Thus, it is obvious that the longer the patient remains in the plateau phase, the longer his life expectancy will be. With

each subsequent hospitalization, the functional reserves of the myocardium are significantly reduced and are not restored to their original values over time. At the same time, the risk of death with each re-hospitalization increases on average by 3.6 times [5].

### Primary end point: cardiovascular death or hospitalization due to cardiovascular disease



Cox's regression model, including covariates of age, initial level of GFR, region, initial status of diabetes, sex, LVEF and treatment. GFR – glomerular filtration rate; LVEF – left ventricular ejection fraction; ARR – absolute risk reduction; RRR – relative risk reduction; NNT – number needed to treat. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. DOI: 10.1056/NEJMoa2022290

Packer M, Anker SD, Butler J. Cardiovascular and renal outcomes with empagliflozin in heart failure [6].

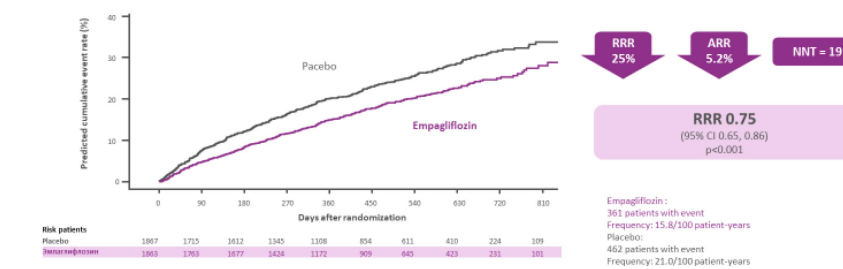
In patients with type 2 diabetes mellitus (DM), sodium glucose linked cotransporter type 2 (iSGLT-2) inhibitors significantly reduce the risk of heart failure (HF) and progression of chronic kidney disease (CKD), showing benefits that no other group of antidiabetic drugs has. In major randomized placebo-controlled trials, the risk of hospitalization for heart failure in patients treated with iSGLT-2 was 30-35% lower than in the placebo group.

This effect was more evident in the group of patients with left ventricular ejection fraction (LVEF) <30% [5,7]. In addition, the risk of CKD progression (including death from renal causes, initiation of dialysis, and kidney transplantation) was 35-50% lower among patients treated with iSGLT-2 in current combination therapy compared with those treated with pla-

cebo. These cardiorenal effects cannot be explained by the glucose-lowering effect of iSGLT-2 alone, as drugs with greater antihyperglycemic efficacy do not show similar tendencies [8]. As a result of this observation, a hypothesis was formed that iSGLT-2 can have a cardioprotective and nephroprotective effect, regardless of the cause of damage to the heart or kidneys, and also regardless of the presence or absence of DM.

One of the latest breakthroughs in the treatment of patients with CHF<sub>r</sub>EF was the EMPEROR-Reduced study, in which empagliflozin significantly affected the primary endpoint (relative risk reduction of cardiovascular death or hospitalization due to heart failure (HF) by 25%, absolute – by 5.2%), and secondary endpoints regarding hospitalizations for HF and renal dysfunction [9-10].

Primary end point: cardiovascular death or hospitalization due to cardiovascular disease (EMPEROR-Reduced study)



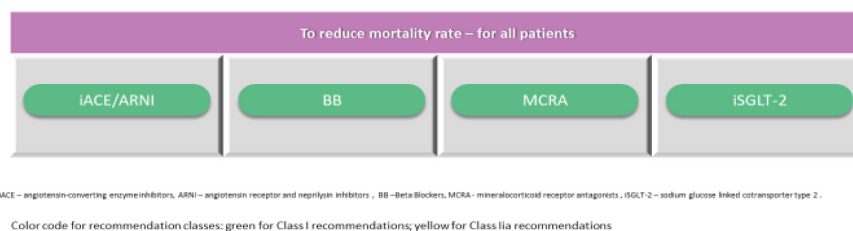
Cox's regression model, including covariates of AGE, initial level of GFR, region, initial status of diabetes, sex, LVEF and treatment  
 RRR – relative risk reduction, ARR – absolute risk reduction, NNT – number needed to treat  
 Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. DOI: 10.1056/NEJMoa2022209

Packer M, Anker SD, Butler J. Cardiovascular and renal outcomes with empagliflozin in heart failure [6].

A modern strategy for the treatment of CHF<sub>r</sub>EF is a quadrupletherapy – the use of 4 main components that affect the prognosis in patients: an angiotensin receptor and neprilysin inhibitors (ARNI),

angiotensin-converting enzyme inhibitors (iACE), angiotensin 2 receptor antagonists (ARA2), (2) sodium glucose cotransporter 2 inhibitors (iSGLT2), beta-blockers (BB), ivabradine and AMP.

ESC 2021: drug therapy for all HFrEF patients



Theresa A McDonagh, et al., 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, *European Heart Journal*, 2021; ehab368, <https://doi.org/10.1093/eurheartj/ehab368>, *dana docmyna* 31.08.2021

Theresa A., Mc Donagh 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [2].

As of today, heart failure with preserved ejection fraction (HFpEF) is one of the largest unmet needs for cardiovascular disease therapy due to its prevalence, poor outcomes and lack of clinically proven effective treatments [11].

The results of the EMPEROR-Preserved study showed that empagliflozin demonstrated a 21% relative risk reduction for the combined primary end point of cardiovascular death or hospitalization for heart failure in adults with heart failure with preserved ejection fraction (HFpEF) compared with placebo [12- 13]. An analysis of the key secondary endpoints of the study showed that empagliflozin also reduced the relative risk of first and readmission for heart failure by 27% and slowed the decline in kidney function. It is being noted that empagliflozin shows these results in patients with any type of heart failure, regardless of ejection fraction or the presence of diabetes mellitus.

The AHA/ACC/HFSA American Cardiology Society has identified the positions of the so-called “quadrotherapy” for patients with CHF with reduced EF: SGLT2 inhibitors, beta-blockers, mineralocorticoid receptor antagonists and drugs that block the RAAS. From the latter group, it is preferable to use sacubitril / valsartan, if this is not possible – ACE inhibitors (in patients with angioedema or cough – ARA2). For CHF patients with slightly reduced ejection fraction (“HF with mildly reduced ejection fraction (HFmrEF)”), SGLT2 inhibitors have class IIa recommendations, all other drugs listed above are IIb [14-17].

During the discussion with active participation of the invited experts and the exchange of views the following issues were discussed: choice of therapy, specialists’ prescriptions, availability of diagnostic methods and updating protocols for the treatment of HF.

The experts noted that according to the EMPEROR-REDUCED and EMPEROR-Preserved studies iSGLT-2, in particular empagliflozin, has certain advantages over the traditional four classes of drugs in

the treatment of CHF (beta-blockers, inhibitors of the renin-angiotensin-aldosterone system, mineralocorticoid receptor antagonists, ARNI). These advantages include a single dose administration of the drug in one recommended dose, which eliminates the need for drugs titration, the absence of a significant effect on hemodynamics, the presence of proven cardioprotective and nephroprotective effects.

The experts expressed the general opinion that iSGLT-2 should be prescribed in accordance with the indications for use and the above recommendations by any of the specialists: a general practitioner, cardiologist or endocrinologist, taking into account known restrictions and as appropriate to the patient.

Patients with heart failure have a high risk of developing cardiovascular complications. To prevent them, timely medical care and timely diagnosis of heart failure is required. In this connection, there were discussed issues of creating heart failure rooms in outpatient environment and available studies regarding concentration of brain natriuretic peptides and performing echocardiography, including the assessment of left ventricular deformity and electrocardiography (ECG)

Further to the discussions during the Scientific meeting and discussions, the need for the following activities was recognized.

- Development of recommendations for cardiologists and general practitioners in the form of “pocket book” for HF patients’ care assisted by a multidisciplinary team
- Arrangement of workshops for cardiologists, primary health care as part of creation of HF rooms
- Update of CHF treatment standards as per international recommendations of AHA/ACC/HFSA (2022)
- Inclusion of iSGLT2 into the list of medications and medical devices for government-funded and medicine assistance scheme at inpatient or outpatient level as part of the state benefit package for HF patients.

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