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The ability of modern therapy to improve the prognosis of patients with HF: role of angiotensin neprilysin inhibitors and sodium-glucose cotransporter inhibitors

	Major principles for treatment of chronic heart failure with reduced left ventricular ejection fraction <40% (HFrEF) include a "triple neurohormonal blockade" as a main approach. However, in recent 6 years, two new classes of drugs for the treatment of HFrEF have appeared, which beneficially influence the prognosis. These drugs are angiotensin receptor neprilysin inhibitors (ARNI) and type 2 sodium-glucose cotransporter 2 (SGLT2) inhibitors.
Aim	To compare the net effect of simultaneous treatment with ARNI and SGLT2 inhibitors with the triple neurohormonal blockade in stable or decompensated patients with CHF based on Russian data.
Material and methods	We analyzed the risk of death per 100 patient-years in patients with HFrEF. Stable patients were followed up at the A.L. Myasnikov Institute of Cardiology (presently, A.L. Myasnikov Research Institute of Clinical Cardiology of the National Medical Research Center of Cardiology) from 2006 through 2007; data from the EPOCH-Decompensation-CHF study were used for decompensated patients (12.2% and 36.8%, respectively).
Results	When patients with stable HFrEF were successively switched from renin-angiotensin-aldosterone system (RAAS) inhibitors to ARNI (–16%) and subsequently supplemented with SGLT2 (–13%) the risk of death per 100 patient-years decreased from 12.2% to 8.9% (total risk decreased by 27%; to save one patient the ARNI+ SGLT2 combination has to be prescribed to 30 patients). The estimated risk of death upon discharge from the hospital for the patients with decompensated CHF switched from RAAS inhibitors to ARNI (–16%) and subsequently supplemented with SGLT2 (–13%) was 26.9 deaths per 100 patient-years, whereas the number of patients to be treated for saving one life was only 10. Based on available data that demonstrate a greater effect of ARNI+ SGLT2 in patients immediately after CHF aggravation, the risk of death was recalculated. According to this analysis, the death rate per 1000 patient-years decreased from 36.8 to 19.9% (relative risk decrease, 46%), and to save one life only 6 patients had to be treated after they have achieved compensation of HFrEF.
Conclusions	This analysis shows the importance of early initiation of the ARNI+ SGLT2 therapy in patients with both decompensated and with stable HFrEF.

Keywords	CHF, ARNI, SGLT2
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Triple neurohormonal blockade, which represents a basic treatment approach to chronic heart failure (CHF) with low left ventricular ejection fraction (LVEF) <40%, was developed by the second decade of the twenty-first century [1, 2]. Renin-angiotensin-aldosterone system (RAAS) inhibitors, primarily angiotensin-converting enzyme (ACE) inhibitors plus beta-blockers (BBs) and mineralocorticoid receptor antagonists (MCRAs), have been repeatedly shown, including in Russian trials, to decrease mortality and prolong life in patients with heart failure having reduced ejection fraction (HFrEF) [3]. It was subsequently determined that the risk of death per 100 patient-years is about 12% in such patients after achieving compensation and during the plateau phase of the disease [4]. Very similar values of the

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risk of death per 100 patient-years (about 10–11%) were obtained in the large randomized clinical trials (RCTs) [5] carried out with participating Russian areas of investigation. Thus, the mortality rate per 100 patient-years ranges from 10 to 12% against the best possible treatment of stable patients with HFrEF using three neurohormonal modulators (Figure 1). According to the EPOCH-CHF epidemiological trial [6], the risk of death per 100 patient-years was 13.7% among all patients with CHF.

However, the continuing failure on the part of physicians to order three-component neurohormonal blockade for patients with CHF [6, 7] results in impaired prognosis. According to the meta-analysis by Zaman et al., a failure to administer MCRAs, BBs, and RAAS inhibitors reduces the chances of saving a patient by 3%, 4.8%, and 4.4%, respectively, while the absence of all three components in the treatment fo HFrEF more than doubles the chances that a given patient will die [8].

When the exacerbation of CHF requires hospitalization, the patient prognosis is significantly worsened, although hospitalization is not always equivalent to actual aggravation of CHF [9, 10]. As shown in Figure 1, patients with confirmed decompensated HFrEF [7] are at 36.8% risk of death per 100 patient years, which is much higher than those in a stable condition.

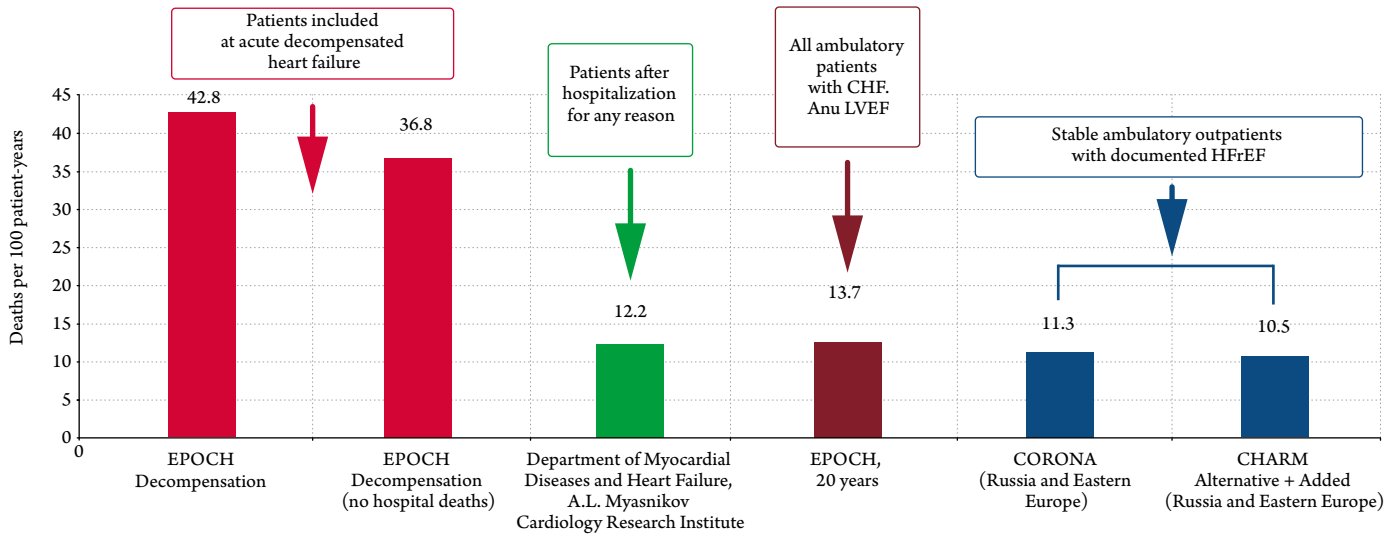
In the past six years, two new classes of drugs for the treatment of HFrEF appeared (angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium-glucose co-transporter 2 (SGLT2)), comprising inhibitors that positively affect the prognosis.

Unlike pure RAAS inhibitors, the ARNI combination valsartan+sakubitril can further reduce the activity of neprilysin, which eliminates their protective vasodilation and diuretic effects by destroying the natriuretic peptides (Figure 2). Such combinations also restore the normal balance of various neurohormones seriously impaired in CHF. In PARADIGM-HF RCT, valsartan+sakubitril significantly reduced by 16% the risk of death in patients having stable HFrEF [11]. When transferred from ACE inhibitors to ARNIs [12], the mean survival time of patients with HFrEF increased by 2.1 years, as well as experiencing statistically significant improvements to their quality of life [13].

The mechanism of sodium-glucose co-transporter-2 (SGLT2) inhibitors is based on allowing the reabsorption of glucose and sodium in the proximal renal tubules [14]. As a result, plasma glucose levels moderately decrease without developing hypoglycemic reactions against drug-induced glycosuria accompanied by the loss of calories and reduction of body weight [15], which initially allowed these drugs to be used in patients with type 2 diabetes mellitus [16, 17]. However, an important role is played by the natriuretic and diuretic effects of SGLT2 inhibitors, which are not correlated with glucose levels maintained in patients without type 2 diabetes mellitus including in HFrEF and in combination with loop diuretics [18].

In the DAPA-HF RCT, the SGLT2 inhibitor dapagliflozin statistically significantly reduced primary endpoint risk (total cardiovascular deaths and heart failure exacerbation) by 26% [19]. At the same time, the mortality rate decreased statistically significantly by 17% accompanied by improvement in quality-of-life metrics. In the EMPEROR-Reduced RCT, although another SGLT2 inhibitor empagliflozin reduced the risk of composite endpoint by 25%, there was no statistically significant reduction in the risk of death. Both protocols were united by the fact that the SGLT2 inhibitors were administered to patients who were receiving the best possible therapy using neurohormonal modulators, including ARNIs (11.6% in DAPA-HF and 19% in EMPEROR-Reduced), i.e., the

Figure 1. Risk of death per 100 patient-years in various subgroups of HFrEF patients



effect was additive. The meta-analysis of these two trials demonstrated a statistically significant reduction in the risk of death in patients with HFrEF against the therapy with SGLT2 inhibitors by 13% compared to the control [20].

Thus, there are now two new classes of drugs that can improve prognosis for patients with HFrEF, having entirely different mechanisms of action and an additive effect on survival. The desire to calculate the cumulative effect of the simultaneous administration of ARNIs and SGLT2 inhibitors compared to the triple neurohormonal blockade therefore seems natural.

In the present study, we took the results of the trial by Solomon et al. of Brigham and Women's Hospital in Boston (USA) as an example. In this analysis, Vaduganathan et al. [21] compared the use of three drugs (MCRA, ARNI, and SGLT2 inhibitors) with dual combination therapy, including RAAS inhibitors and BBs. On average, the new treatment also reduces the risk of death in HFrEF by 47% and gives 55-year-old patients an additional 6.3 years of life; this effect persists for up to 80 years of age when the new therapy is still able to prolong life by another 1.4 years.

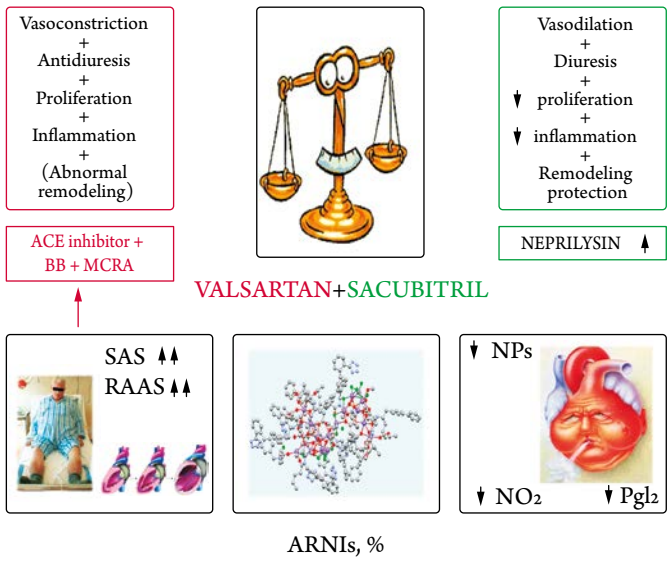
However, this analysis compared the use of three groups of drugs with the combination of two drugs (RAAS inhibitors and BBs), while patients with HFrEF should receive (and many patients already do nowadays) triple therapy (RAAS inhibitors, BBs, MCRAs). Therefore, we decided to perform an analysis of the Russian data (Figure 4).

Material and methods

Our analysis in stable patients with CHF was based on the risks of death of HFrEF patients followed up at the A.L. Myasnikov Institute of Clinical Cardiology (Scientific Research Institute of Clinical Cardiology n.a. A.L. Myasnikov, National Medical Research Center for Cardiology) from 2006 to 2007 [4] (Figure 1), as well as the effects of ARNIs and SGLT2 inhibitors from the results of the PARADIGM-HF RCT [11] (decrease in the risk of death by 16%) and the meta-analysis [20] of DAPA-HF and EMPEROR-Reduced (decrease in the risk of death by 13%), respectively. The conservative calculation based on the findings by Burnett et al. showed that the transfer from ACE inhibitors to ARNIs reduces the risk of death by 7% [22].

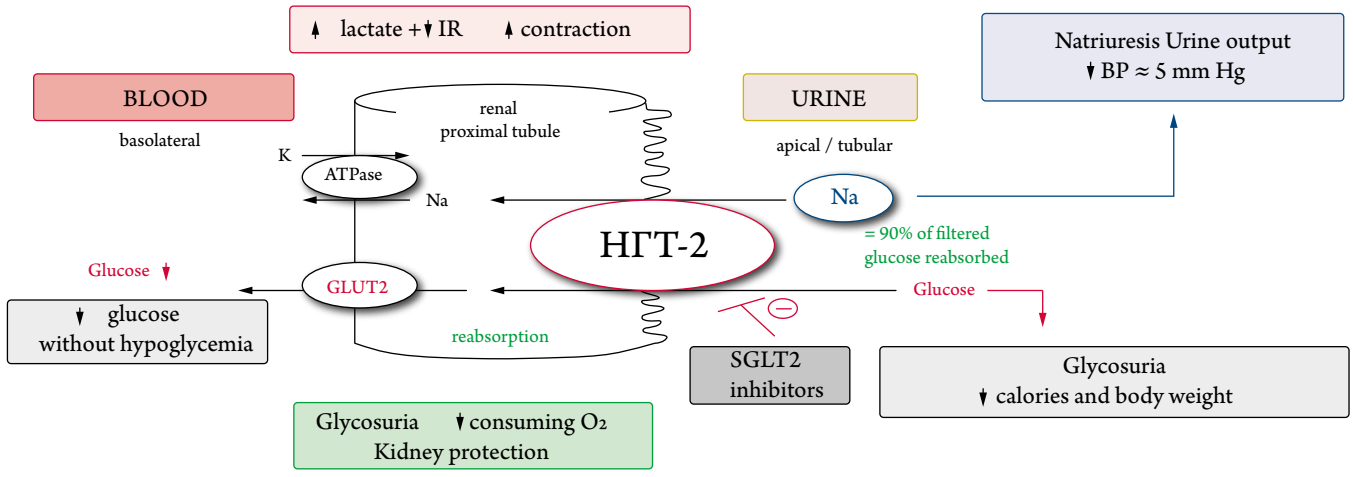
The analysis of patients in the vulnerable phase is based on the mortality data of HFrEF patients in the EPOCH-Decompensation-CHF. In this group, two calculations were made: a conservative calculation using a decrease in the risk of death according to the PARADIGM-HF RCT [11]

Figure 2. Rebalancing of neurohormonal systems in CHF against ARNI therapy



ACE – angiotensin-converting enzyme; BB – beta-blocker; MCRA – mineralocorticoid receptor antagonist; SAS – sympathoadrenal system; RAAS – renin-angiotensin-aldosterone system; ARNI – angiotensin receptor-neprilysin inhibitor; NO_2 – nitric oxide; NP – natriuretic peptide; PGI_2 – prostacyclin.

Figure 3. Mechanism of action of sodium-glucose co-transporter 2 inhibitor



SGLT2 – sodium-glucose co-transporter 2; O_2 – oxygen; BP – blood pressure; BW – body weight; IR – insulin resistance.

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and meta-analysis [20] of the usage of SGLT2 inhibitors in patients with CHF, and an optimistic calculation using data from the PIONEER -HF [23] and SOLOIST-WHF [24] trials performed in patients immediately following compensation, where SGLT2 inhibitors and ARNIs were administered, respectively, prior to discharge from the hospital.

The risk of death was expressed in «deaths per 100 patient-years», which allows the comparison of trials having different durations. If a publication lacked data on this indicator, a letter requesting such information was sent to the authors.

Results

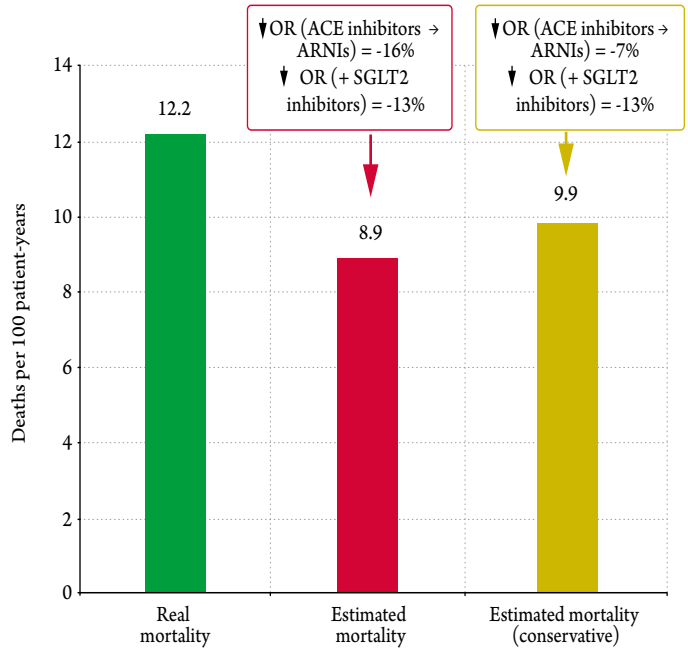
The sequential transfer of patients with stable HFrEF from RAAS inhibitors to ARNIs (– 16%) and later addition of SGLT2 inhibitors (– 13%) reduce the annual mortality rate from 12.2% to 8.9% (a total reduction of the risk 27%), while the combination of ARNI and SGLT2 inhibitors saves 1 in 30 patients. In the conservative calculation, the annual mortality rate decreased from 12.2% to 9.9% (total risk reduction – 19%), while the combination of ARNI and SGLT2 inhibitors saves 1 in 44 patients with stable HFrEF.

The next task involved an evaluation of the use of new classes of drugs in the vulnerable phase of CHF immediately following hospitalization for decompensated CHF. According to the EPOCH-Decompensation-CHF, mortality in these patients was more than 36% even without taking into account hospital deaths (Figure 1). The simplest analysis included calculating changes in the mortality rates using the same data on the treatment with ARNIs and SGLT2 inhibitors, which were obtained in stable patients with HFrEF (Figure 5).

The estimated risk of death in case of the replacement of RAAS inhibitors with ARNIs (-16%) and addition of SGLT2 inhibitors (-13%) following hospitalization will be 26.9 deaths per 100 patient-years at the discharge from the hospital; in such cases, every tenth patient with HFrEF may be expected to survive. Of course, this is only a calculated rate based on a decrease in the risk of death in trials that included more stable patients having a better prognosis.

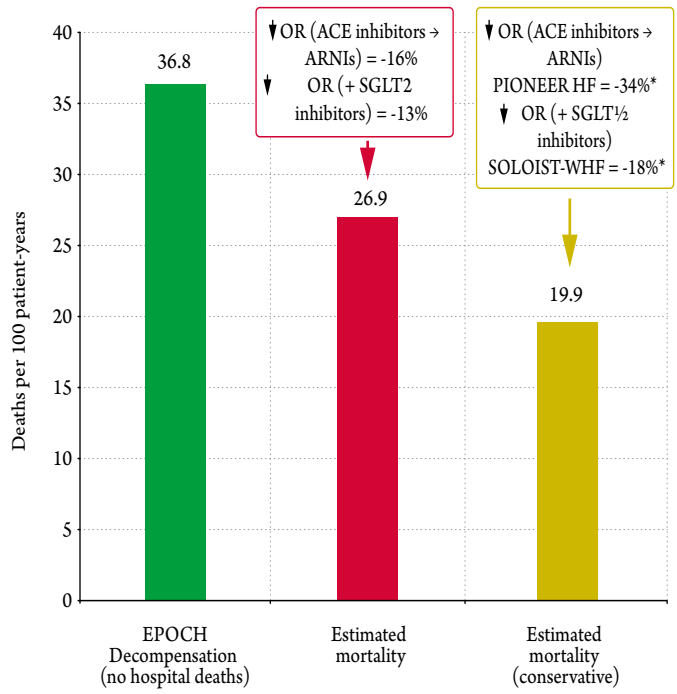
Let us try to better understand the situation with vulnerable patients. With respect to ARNI, we have data of the PIONEER-HF RCT on the use of sacubitril/valsartan versus the ACE inhibitor enalapril directly following the stabilization of hospitalized patients with decompensated CHF. Early administration of ARNI reduces by 46% the risk of composite endpoint, including death, hospitalization for repeat decompensated CHF, the need to refer for transplantation, or mechanical circulatory support within eight weeks of observation [23]. To prevent a single event, it is sufficient to administer valsartan + sacubitril instead

Figure 4. Actual risk of death during the use of RAAS inhibitors, BBs, and MCRAs in Russia; estimated risk of death when replacing RAAS inhibitors by ARNIs and adding SGLT2 inhibitors in stable HFrEF



Calculations are based on: Kardiologiia 2008: 47(2): 6-16;
N Engl J Med 2014; 371: 993-1004 и Lancet 2020; doi: 10.1016/S0140-6736(20) 31824-9;
Circ Heart Fail. 2017; 10:e003529. DOI: 10.1161/CIRCHEARTFAILURE. 116.003529.
OR, decrease in odds ratio.

Figure 5. Actual risk of death during the use of RAAS inhibitors, BBs, and MCRAs in Russia; estimated risk of death when replacing RAAS inhibitors by ARNIs and adding SGLT2 and SGLT½ inhibitors following hospitalization for decompensated HFrEF (in the vulnerable phase)



OR, decrease in odds ratio; SGLT½, INGT ½, sodium-glucose co-transporter ½.
*Decrease in mortality was statistically insignificant.

ACE inhibitors in 13 vulnerable patients with HFrEF. In the PIONEER-HF trial, although the risk of all-cause death decreased by 34% in patients admitted to hospital with pulmonary edema when ARNIs were used instead of ACE inhibitors in the vulnerable phase of the disease, the changes were not statistically significant.

At the same time, the high efficacy of SGLT inhibitors was shown in hospitalized patients with decompensated CHF (LVEF <50%, 79% of patients) immediately following compensation in the SOLOIST-WHF trial [24]. In this trial, the non-selective SGLT 1 and 2 inhibitor sotagliflozin (not registered in Russia) was used. A 33% decrease in the risk of primary endpoint «Cardiovascular death, all hospital admissions and all emergency visits to the hospital due to CHF» was shown in this paper. To prevent one event, the drug was administered to four patients. The decrease in all-cause mortality (deaths per 100 patient-years) was 18% in the sotagliflozin group, although the changes were not statistically significant.

We used the available data on the use of ARNIs and SGLT inhibitors immediately following decompensation of CHF in the vulnerable phase of the disease to estimate the benefits of modern treatments of CHF. In this case, earlier administration of ARNIs (initiation of the treatment instead of ACE inhibitors) reduces the risk of death by 34%, while adding SGLT inhibitors reduces the risk by an additional 18% (Figure 5). As a result, the mortality decreased from 36.8% to 19.9% (relative risk reduction 46%), with every sixth patient surviving following compensation of HFrEF.

Discussion

As shown by the trial results, the inclusion of two new classes of drugs recommended to treat patients with CHF in the complex therapy allows the improvement of treatment outcomes and prolongation of the lives of patients having stable forms of disease. The previous analysis [21], which included the use of three additional classes of drugs, was not entirely in line with changes in the CHF treatment guidelines; for this reason, we tried to simulate the events independently. The results showed that it is possible to prevent one death per 100 patient-years in 30–44 patients depending on the type of simulation.

The second important aspect is the time-to-treatment effect. The analysis of the DAPA-HF trial findings showed that the administration of dapagliflozin is associated with a statistically significant reduction in the risk of cardiovascular death and CHF decompensation by 49% by day 28 of the treatment [25], making it necessary to administer the modern drugs for HFrEF as early as possible. Therefore, overcoming therapeutic inertia will allow treatment results to be improved within a short time.

When exacerbation of CHF requires hospitalization, patient prognosis is significantly deteriorated, although hospitalization is not always equivalent to actual aggravation of CHF [9, 10]. According to the EPOCH-Decompensation-CHF [7], patients with confirmed decompensated HFrEF are at 36.8% risk of death per 100 patient-years, which is almost three times higher than those in a stable condition. Effects on hospitalizations on worsening of prognosis for HFrEF patients and more than two-fold increase in the risk of death were investigated in detail [26]. Moreover, repeated hospitalizations are a major predictor of poor prognosis [27]. Thus, the new term «vulnerable phase» of the HFrEF course was introduced; this occurs when the risk of death is still very high immediately following compensation but prior to the plateau phase [28]. Although we developed this idea further, we still failed to find ways to reduce the risk of death in the early period following hospitalization [29].

The additional analysis of the DAPA-HF trial showed that patients with HFrEF, who had been hospitalized within the year prior to being included in the study, were at 33.8% risk of cardiovascular death or CHF decompensation, while patients treated in hospital more than one year previously were at 25.3% risk, and those who had no history of hospitalizations were only at 21.1% risk [25]. However, the efficacy of dapagliflozin increased in more severe patients. The absolute risk of cardiovascular death and CHF decompensation in stable HFrEF patients without history of hospitalizations was reduced by 2.1% (one event prevented in 48 treated patients), while the reduction of absolute risk increased by 9.9% in the vulnerable phase with history of hospitalizations in the past 12 months (one event prevented in 10 treated patients). In other words, the overall treatment efficacy increased by more than four times.

Therefore, we used both conservative calculation and the findings for ARNIs and SGLT inhibitors in patients with CHF directly following compensation in the simulation of outcomes in patients after hospitalization (in the vulnerable phase of the disease) [23, 24]. Using any calculations, the efficacy of two new classes of drugs recommended for CHF was much higher than when used in stable patients. Subject to the observance of treatment guidelines in the subgroup of CHF patients after compensation, one death per 100 person-years is avoided in 6–10 of treated patients. The more severe the course of CHF, the sooner it is necessary to apply all the current guidelines for the treatment of this syndrome.

Of course, any simulation has disadvantages, especially for patients in the vulnerable phase of CHF immediately following hospitalization for decompensated CHF. On the other hand, it would be naive to assume endless RCTs for studying every aspect and period of the disease course. Nevertheless, the use of dapagliflozin and empagliflozin is currently studied in patients following CHF decompensation.

Therefore, it is possible to maintain a clear focus on the issue: practitioners should implement the achievements of clinical trials in real-world practice as soon as possible. We hope that

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these data will help in the administering of two new life-saving treatments for HFrEF, ARNIs and SGLT inhibitors in a timely manner (in hospitals following CHF compensation).

Conclusion

The presented analysis demonstrates the importance of early initiation of ARNIs and SGLT2 inhibitors in patients with both decompensated and stable HFrEF.

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