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The role of SGLT-2 inhibitors in the treatment of acute decompensation of chronic heart failure: a meta-analysis of large clinical trials

Omarov O.M.[1,2], Arabidze G.G.[2]

[1] Moscow State Clinical Hospital named after V.V. Veresaev, Moscow, Russia.
[2] Russian Medical Academy of Continuous Professional Education, Moscow, Russia.

Authors

Omar M. Omarov, cardiologist, Moscow State Clinical Hospital named after V.V. Veresaev, Moscow, Russia; applicant at the Department of Internal Medicine and Adolescent Medicine, Russian Medical Academy of Continuing Professional Education, Moscow, Russia ORCID: 0000-0002-8262-6685

Grigory G. Arabidze*, MD, PhD, head of the Department of Internal Medicine and Adolescent Medicine, Therapeutic Faculty, Russian Medical Academy of Continuing Professional Education, Moscow, Russia, ORCID: 0000-0003-3370-3506

We present a systematic review and meta-analysis of the literature data from the studies conducted to determine the effect of early (up to 24 hours) administration of SGLT-2 inhibitors in patients with acute decompensated chronic heart failure on immediate outcomes and the effect of the therapy on reducing levels of inpatient heart failure markers.

Keywords: sodium-glucose transport protein 2 inhibitors, acute decompensation of chronic heart failure.

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* Corresponding author. Tel. +7 (910) 403-59-64. E-mail: arabidze@mail.ru

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Introduction

Chronic heart failure (CHF) associated with an unfavourable prognosis of patients regardless of its origin. Until recently, three groups of drugs known as "triple neurohumoral blockade" were used to improve prognosis in terms of reduced mortality. This included therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEi/ARBs), beta-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs). It was first adjusted following positive results from studies in which therapy with angiotensin/neprilysin receptor antagonists (ARNIs) demonstrated high efficacy in reducing mortality and risk of rehospitalization. Importantly, the identified benefits were realised in a selective group of patients with CHF with reduced ejection fraction (HFrEF).

A breakthrough in the medical management of CHF was the addition of sodium-glucose cotransporter type 2 inhibitors (SGLT2i) to the standard therapy — dapagliflozin and empagliflozin. They were found to reduce the rehospitalization rate in patients with CHF regardless of EF and the presence of diabetes mellitus, and to improve prognosis in patients with HFrEF [1]. Following the results of the EMPEROR trial, empagliflozin was the first drug to demonstrate efficacy in the treatment of CHF with preserved EF (HFpEF) [2]. The updated optimal medical therapy (OMT) has been termed "quadrotherapy". An analysis of comparative trials of early versus updated OMT at a median of 18–27 months (depending on the trial) showed a 50 % reduction in cardiovascular mortality and a 68 % reduction in the risk of rehospitalization for CHF decompensation in the HFrEF group [3].

The episode of acute decompensation of chronic heart failure (ADHF) is one of the main criteria for the effectiveness of CHF treatment, reflecting its crucial role in the prognosis of these patients. In patients hospitalized with ADHF, the risk of death within one year is 18.5 % if compensation is achieved at the hospital stage. If CHF cannot be fully compensated (subcompensation) and congestion persists at the time of discharge, the mortality rate within one year reaches 28 % [4]. In their study, Chioncel O. et al. identified independent predictors of CHF subcompensation. These include: diabetes mellitus, anemia and tricuspid regurgitation. Predictors suggestive of compensation included CHF de novo, beta-blocker use at the time of hospitalization and any cardiovascular intervention during hospitalization [4].

The successful use of SGLT2i in CHF was the trigger for evaluating the effect of this class of drugs on the prognosis of patients with ADHF. The additional possibility of achieving compensation at the hospital stage when adding SGLT2i to therapy is explained by the the pharmacological action of the drug. Boorsma E.V. et al. showed that the increase in diuresis with the use of SGLT2i in ADHF is achieved through an increase in glucose excretion, but not sodium excretion. The authors also noted a significant decrease in glomerular filtration rate (GFR) during the first 24–72 hours of therapy, with subsequent recovery of renal function at 96 hours and up to 30 days [5]. The beneficial effects of SGLT2i in ADHF have been confirmed in two large clinical trials. The SOLOIST-WHF study was the first to demonstrate the high efficacy and safety of SGLT2i administration in patients with ADHF and type 2 DM immediately after the stabilisation of the condition [6]. Sotagliflozin therapy reduced the incidence of the combined endpoint (mortality and hospitalizations due to ADHF) by 33 % at a median follow-up of 9 months. Another large study (EMPULSE) investigated the role of empagliflozin under similar conditions — administration of the drug after the stabilisation in patients with ADHF, regardless of the type 2 DM presence, was associated with a reduction in mortality and rehospitalization within 90 days [7]. In the EMPULSE study, empagliflozin therapy was administered 1–5 days after hospitalization. Earlier administration of SGLT2i may reduce the time required to achieve HF compensation and may also be associated with an improved prognosis in these patients as soon as possible after an episode of ADHF. However, current studies investigating the role of early (up to 24 hours) initiation of SGLT2i are characterised by small sample sizes and a lack of conclusive results on the efficacy and safety of ADHF treatment.

The aim of this meta-analysis is therefore to review the results of the trials and determine the impact of early (up to 24 hours) administration of SGLT2i in patients with ADHF on immediate prognosis, as well as the effect of therapy on reducing levels of HF markers at the hospital stage.

The information retrieval algorithm was developed according to the PRISMA guidelines for systematic reviews and meta-analyzes [8]. Publications were searched in the English language Pubmed and Google Scholar databases using search queries, keywords (including MeSH) and logical operators. The follow-

ing query was used in the Pubmed database: (acute decompensated heart failure) AND (reduced ejection fraction) AND (Sodium-glucose co-transporter 2) OR (Empagliflozin) OR (Dapagliflozin) OR (Sotagliflozin) NOT (Preserved). Additionally, a query in MeSH — "Sodium-Glucose Transporter 2 Inhibitors/therapeutic use" was performed [MAJR]. In both cases, the filter "randomized clinical trials" was used. To search the Google Scholar database, an advanced search was used with the following queries: "sodium glucose co-transporter 2 inhibition in heart failure" in the string "with all of the words", "acute decompensated heart failure" in the string "with the exact phrase". In order to search for additional sources of information, the reference list of the found publications was used, as well as recommendations from the Pubmed database in the section "similar articles". The search was carried out in the period from 01.01.2020 to 31.10.2022.

The systematic review included randomized clinical trials that investigated the effect of early (up to 24 hours) administration of SGLT2i on the prognosis in patients hospitalized for ADHF with at least 30 days of follow-up. In addition, studies that researched the effect of SGLT2i therapy on NT-proBNP levels in patients hospitalized for ADHF with at least 7 days of follow-up were included. Non-randomized trials, clinical cases or case series, abstracts and reviews were excluded. We assessed the dynamics of NT-proBNP levels on therapy and/or 30-day mortality after discharge as endpoints.

The initial screening using the above search algorithms yielded 322 and 200 publications in the Pubmed keyword and MeSH databases, respectively, and 1140 publications in the Google Scholar database. After removing duplicates and analysing titles and their abstracts, 1655 publications were removed. From the remaining 7 publications, 5 articles (0.03 %) were selected based on the full-text version analysis. The obtained publications were processed using statistical analysis. The results of the selection are shown in Figure 1.

The risk of systematic bias. Systematic error (SB) was assessed using an adapted scale developed by Cochrane University experts [9], which takes into account 6 sources of SB (domains). (1) Randomization method; (2) concealment of the randomization sequence; (3) blinding of patients and nursing staff during treatment; (4) blinding of physicians when assessing the effect of the intervention, (5) patient drop-

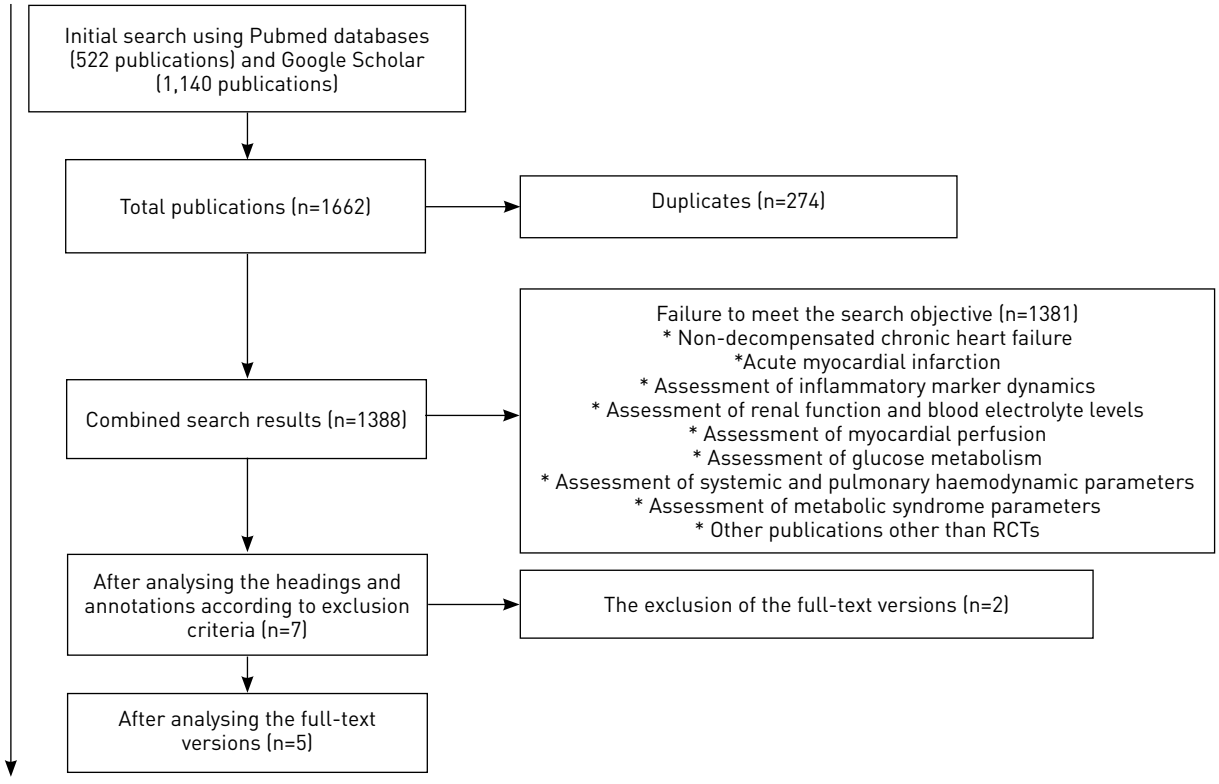

Fig. 1. Publication selection algorithm

out from the study; and (6) presentation of results in a publication. In addition, SB was assessed for the following domains: conflict of interest, complex study design, deviations from the study protocol, insufficient duration of the follow-up and small sample size. For each domain, the risk of SB was classified into three categories: low (0), uncertain (1) and high (2). If there were two or more domains of uncertain probability and one or more of high probability, the overall risk of SB was considered low. If two or more domains of uncertain probability were present, the overall risk of SB was considered uncertain. When one or more high probability domains were present, the overall risk of SB was regarded as uncertain. Thus, three publications out of five were categorised as high risk for the conflict of interest part, one of them with a notable small sample size. Publications were not excluded from the meta-analysis.

The meta-analysis of the differences between the mean values of the parameters in the study and control groups was performed on the mean SB standard deviation data, taking into account the number of subjects in the compared groups. Quantitative parameters in the meta-analysis are presented as mean and standard deviation. Quantitative data given as median in the original publications were converted to mean SB standard deviation using the formula of Luo et al. 2018 and Wan et al. 2014 [8, 9]. The effect was considered statistically significant at $p<0.05$.

Five trials (318 patients) that met the inclusion and exclusion criteria were included in the systematic review and meta-analysis (Table 1). The majority of patients were men (47 % to 62 %), with a mean age of 72 to 82 years. In general, the proportion of patients with the de novo development of CHF was about half (47 % to 80 %) of the total number of patients studied in all publications. The median follow-up varied from 7 to 90 days.

Four out of five studies analyzed the dynamics of the HF marker — brain natriuretic peptide precursor (NT-proBNP) — in the background of SGLT2i treatment compared to placebo. The first analysis for blood NT-proBNP was performed at the stage of randomization (on admission), the second analysis was performed on days 4 to 7 after the start of therapy. All patients received standard treatment plus a drug from the SGLT2i group or placebo. The mean baseline NT-proBNP levels differed between the studies, ranging from 3060 to 4775 pg/mL in the SGLT2i group and from 3996 to 6641 pg/mL in the placebo group. Positive dynamics in terms of a decrease in NT-proBNP levels were observed in all studies (Table 2).

Based on the results of the data obtained, we calculated the difference in mean NT-proBNP levels using statistical analysis methods to assess the benefit of SGLT2i therapy in reducing levels of cardiac markers. To do this, we performed a meta-analysis of the difference in mean NT-proBNP levels between the two groups (Fig. 2).

Figure 2 shows the mean dynamics of NT-proBNP levels in two groups. The values of the HF marker with SGLT2i treatment compared to placebo did not differ in any of the studies. According to the results of the meta-analysis, statistically significant differences were not achieved ($p=0.920$). The heterogeneity of the trials was considered to be low. SGLT2i therapy

Table 1. **Synopsis of the studies that were included in the systematic review**

Author	Sample size, n	Chosen drug and the treatment start	Follow-up period	Endpoints	
				NT-proBNP dynamics	Posthospital mortality
Dammam K., 2020 [10]	79	Emp and 24 h	60 days	Yes	Yes (60 days)
Tamaki S., 2021 [11]	59	Emp and 96 h	7 days	Yes	No
Thiele K., 2022 [12]	19	Emp and 72 h	7 days	Yes	No
Schulze C., 2022 [13]	59	Emp and 12 h	30 days	Yes	Yes
Charaya K., 2022 [14]	102	Dap and 24 h	30 days	No	Yes

Table 2. **NT-proBNP levels in different groups before and after treatment**

Author	NTproBNP (pg/ml) with SGLT2i		NTproBNP (pg/ml) with placebo	
	Before treatment	After treatment	Before treatment	After treatment
Dammam K., 2020 [10]	4775±3157	2196±2147	6641±5625	3852±3881
Tamaki S., 2021 [11]	3060±2374	1618±506	5081±5020	2200±624
Thiele K., 2022 [12]	3562±2527	2050±3243	3996±6293	2202±5807
Schulze C., 2022 [13]	4276±4516	2415±4516	4823±4995	4096±4995

Study or subgroup	SGLTi			Placebo				Std. Mean Difference	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total	Weight (%)	95 % CI	95 % CI
Dammam K.	2.579	7.634	40	2.789	13.665	39	36.5	−0.02 [−0.46.0.42]	
Thiele K.	1.512	8.221	10	1.794	17.124	9	8.8	−0.02 [−0.92.0.88]	
Schulze C.	1.861	4.516	30	727	4.995	30	27.5	0.24[−0.27.0.74]	
Tamaki S.	1.442	7.634	30	2.881	10.476	29	27.2	−0.16 [−0.67.0.36]	
Total (95 % CI)			110			107	100	0.01[-0.25.0.28]	
Heterogenity: Tau²=0.00; Chi²=1.18, df=3(P=0.76), I²=0 %									
Test for overall effect Z=0.10 (P=0.92)									Better in the SGLT2i group / Better in the placebo group

Fig. 2. Blobogram. Results of the meta-analysis of the mean values of NT-proBNP level difference in SGLT2i and placebo groups
Note. ▢ — weighted effect size for each individual study (size of green squares corresponds to study weight), ◆ — 95 % CI, reflects weighted average of mean NT-proBNP values

in patients with ADHF did not have an advantage over placebo in reducing NT-proBNP levels.

Three of the five trials studied post-hospital mortality. These studies included 240 people, 120 in each group. Post-hospital mortality was 9.2 % in the SGLT2i group and 14.2 % in the placebo group. The results of the three trials were combined in a meta-analysis (Fig. 3).

All trials showed a reduction in post-hospital mortality in the SGLT2i group. The results of the meta-analysis demonstrated a 38 % reduction in the probability of death in the immediate post-discharge period. However, there were no statistically significant differences (p=0.772). It is important to note that the first study [10], which showed the best results (69 % reduction in mortality), used 60-day mortality as the endpoint, whereas the other two studies used 30-day mortality. The heterogeneity of the trials was considered to be low. The results suggest that there is an association between early initiation of SGLT2i therapy and the risk of post-hospital mortality. Further large studies are needed to clarify the effect of SGLT2i therapy on the immediate prognosis of patients hospitalized with ADHF.

Studies	Std. Mean Difference (95 % CI)	Death/Total in SGLT2i group	Death/Tota in placebo group	Relative risk of death
Dammam K.,2020	0,308 (0,031; 3,094)	1/40	1/39	
Charaya K.,2022	0,732 (0,278; 1,926)	9/50	12/52	
Schulze C,2022	0,466 (0,040; 5,433)	1/30	2/29	
Overall I^2=0 %(P=0,772)	0,619 (0,268; 1,432)	11/120	17/120	
				Odds ratio (log scale)

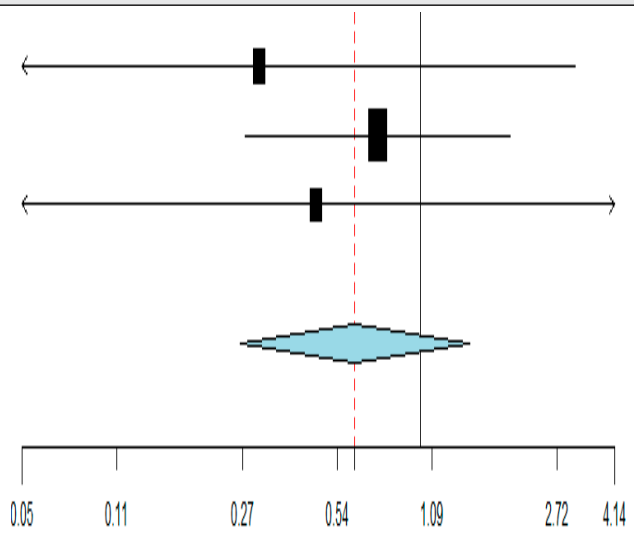

Fig. 3. Blobogram. Results from the meta-analysis of the relative risk of post-hospitalization death in the SGLT2i and placebo groups
Note. ▮— weighted effect size for each case study (the size of the black squares corresponds to the weight of the study), ◇ — 95 % CI, reflects the weighted mean of the mean NT-proBNP values.

Discussion

The results of SGLT2i treatment in ADHF were first analyzed in the EMPA-RESPONSE-AHF pilot study (79 patients). The study did not show an improvement in hospital outcomes. However, the finding of a high safety profile of SGLT2i in ADHF, demonstrated for the first time by the authors, should be considered important. An improvement in clinical outcomes was observed when assessing the combined endpoint (HF worsening at pre-hospital stage, rehospitalization for CHF and all-cause mortality at 60 days) [10]. The EMPULSE study was a logical continuation of this work with a larger number of patients (n=530). For the first time, a statistically significant improvement in clinical status was seen with empagliflozin in patients hospitalized for ADHF (53.9 % vs. 39.7 %, p=0.005). All-cause mortality within 90 days of hospitalization was 2-fold lower in the SGLT2i group compared with the placebo group (4.2 % vs 8.3 %) [7]. We did not include this trial in our meta-analysis because SGLT2i therapy was started within 1–5 days (median 3 days). Another large study, SOLOIST-WHF [6], was excluded from the meta-analysis for the same reasons. In our opinion, the long randomization window may have inadvertently excluded the most severe cohort of ADHF patients; the use of SGLT2i in this group of patients is likely to be of greatest clinical interest.

The main result of our meta-analysis was the demonstration of a 1.7-fold reduction in post-hospital mortality in the immediate postoperative period. At the same time, mortality at 30 to 60 days was higher than in the EMPULSE trials (90 days). In the SGLT2i group, the mortality rate was 9.2 % vs. 4.2 %, while in the placebo group it was 14.2 % vs. 8.3 %. We believe that this difference may be explained by the more comorbid cohort of patients included in the trials analyzed on the first day of hospitalization. Overall, we believe that the results of the meta-analysis show encouraging prospects for improving the prognosis of patients hospitalized with ADHF.

Another finding of the meta-analysis was the lack of change in NT-proBNP levels with SGLT2i therapy. NT-proBNP is one of the most important prognosis predictors in patients with CHF. According to our hypothesis, the benefits of SGLT2i in terms of improvement in clinical status should have been reflected in the reduction of NT-proBNP levels. However, the results obtained show almost similar dynamics of the HF marker.

According to the studies, SGLT2i therapy in ADHF is associated with rapid volume reduction and improvement in LV end-diastolic pressure and diastolic function [12, 15]. However, it remains unclear whether this is a consequence of the diuretic effect of SGLT2i. Packer M. et al. analyzed the EMPEROR study and showed that the efficacy of empagliflozin therapy was comparable in CHF groups with and without congestion [16]. In addition, the authors showed that there was no correlation between NT-proBNP levels and weight loss, regardless of the therapy. The obtained results allowed to conclude that the diuretic effect is not the dominant one in SGLT2i therapy in patients with CHF. It is likely that a similar mechanism of action can be used in the group of patients with ADHF. The search for other, more important properties of the SGLT2i group of drugs may be the subject of future studies.

SGLT2i therapy in ADHF is of great scientific and clinical interest, as reflected in the domestic and international literature [15, 17]. The results from large trials (DICTATE AHF, DAPA-MI, EMPACT-MI, DAPA ACT HF-TIMI 68) are expected in the next few years [18-21]. The EMPACT-MI trial will evaluate whether empagliflozin can reduce the risk of HF and death compared to placebo in patients with acute MI and first-ever LV systolic dysfunction or signs and symptoms of pulmonary congestion [20]. The DAPA-MI study (NCT04564742) will provide information on the efficacy of dapagliflozin compared to placebo in preventing hospitalization for HF or cardiovascular death in patients with acute MI and the evidence of reduced LV systolic function. An important aspect of these two trials is that the DAPA-MI trial will only randomize patients without a known diagnosis or evidence of type 2 DM, whereas the EMPACT-MI trial will include both diabetic and non-diabetic patients. Taking into account the results of the meta-analysis, as well as the results of other studies on the efficacy and safety of SGLT2i in ADHF, we expect that emergency cardiologists will have an additional option to improve the clinical status and prognosis of patients.

This meta-analysis has several limitations. The first one is the small number of studies, the high risk of the systematic bias in most of the included studies, and the small sample size in the study by Thiele K [12]. However, it is important to note that the number of trials investigating SGLT2i in ADHF is limited to date. Other limitations include the differences in the

endpoint of post-hospital mortality described above, as well as the calculated formulas for quantifying NT-proBNP parameters. However, it is important to note that the heterogeneity in both analyzes was low, which should be considered an advantage of the study.

Conclusion

According to a meta-analysis, SGLT2i therapy given early (up to 24 hours) to patients hospitalized for ADHF may reduce the risk of all-cause mortality in the immediate post-discharge period (30–60 days). Larger studies are needed to investigate the effect of SGLT2i on prognosis in this group of patients.

Study limitations. The presented meta-analysis has a number of limitations. These include the small number of studies, the high risk of systematic error in most of the included studies, and the small sample size in the article of Thiele K. It is important to note, that the number of studies investigating SGLT2i in ADHF is limited. Other limitations include the differences in the endpoint of posthospital mortality described above, as well as the calculation formulae for quantifying NT-proBNP levels.

Conflict of interest: none declared.

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