Comparative analysis of SGLT2 inhibitors in the treatment of heart failure

Kuat Sultan¹, Sampiyeva Radmila², Tolenbekova Aruzhan³, Beisebay Symbat⁴, Itinova Aruzhan⁵, Zhanakhmetova Shyrai⁶

¹ Master of the first year of study in the specialty «Molecular Biology and Genetics»; ISTinye University; Republic of Turkey
² School of Medicine, Faculty of General practitioner, the 7th course; NJSC «Astana Medical University»; Republic of Kazakhstan
³ School of Medicine, Faculty of General practitioner, the 6th course; NJSC «Astana Medical University»; Republic of Kazakhstan
⁴ School of Medicine, Faculty of General practitioner, the 6th course; NJSC «Astana Medical University»; Republic of Kazakhstan
⁵ School of Medicine, Faculty of General practitioner, the 6th course; NJSC «Astana Medical University»; Republic of Kazakhstan
⁶ School of Medicine, Faculty of General Medicine, the 4th course; NJSC «Astana Medical University»; Republic of Kazakhstan

Abstract.
Heart failure (HF) remains a significant disease with a high risk of complications and mortality, underscoring the need for effective therapeutic approaches. Sodium-glucose cotransporter 2 inhibitors (SGLT2), such as dapagliflozin, empagliflozin, and canagliflozin, have garnered considerable attention as potential remedies for HF. This review is based on a comparative analysis of these SGLT2 inhibitors and their impact on HF. Preliminary data indicate a positive effect in reducing the risk of HF exacerbation and hospitalizations among patients receiving dapagliflozin and empagliflozin. Interestingly, empagliflozin demonstrates potential in reducing the risk of cardiac death and hospitalizations among patients with preserved ejection fraction. This review underscores the significance of further research to deepen the understanding of the mechanisms of action of each drug and their efficacy in different types of heart failure, potentially contributing to personalized patient treatment.

Keywords:
heart failure
SGLT2
dapagliflozin
empagliflozin
canagliflozin
Introduction

The contemporary epidemiological landscape reflects a growing prevalence of type 2 diabetes mellitus (T2DM). This metabolic pathology, characterized by impaired glucose metabolism and insulin resistance, poses an increasingly significant public health issue, substantially impacting patients' quality of life and substantially escalating healthcare costs. In a scenario where the pharmaceutical industry provides clinicians and patients with an increasing array of tools for effective glucose control, scientists and physicians are focused not only on aspects of glycemic reduction but also on the prevention of complications such as cardiovascular and renal diseases. In this context, sodium-glucose cotransporter 2 inhibitors (SGLT2) acquire particular relevance, offering a unique approach to treating T2DM. This review aims to comprehensively investigate three SGLT2 inhibitors - dapagliflozin, empagliflozin, and canagliflozin - considering their effectiveness in glucose level control, impact on the cardiovascular system, and an assessment of their influence on kidney function. Presently, there exists a necessity for a systematic comparison of these medications, considering their unique characteristics and practical applicability in the context of individualized therapy. The specificity of SGLT2 inhibitors lies in their prevention of glucose reabsorption in the kidneys, promoting its excretion through urine. Such a mechanism not only ensures glucose level control but also exerts a positive influence on the circulatory system and kidney function. In light of recent studies establishing a connection between T2DM, heart failure, and kidney impairment, SGLT2 inhibitors attract attention not only from endocrinologists but also cardiologists, nephrologists, and other specialists.

Throughout this article, we will explore the efficacy of each considered medication, as well as their impact on the cardiovascular system and kidney function, comparing research data and highlighting key elements influencing the selection of a specific drug for individual prescription. A scholarly perspective on this matter will not only broaden our understanding of the metabolic mechanisms underlying T2DM but also provide valuable practical recommendations for
clinicians tasked with effectively managing this complex condition.

**Material and methods**

To perform the literature review and systematise the findings, scientific articles, reviews and meta-analyses were searched in medical databases such as PubMed, Web of Science and other relevant sources. The studies included in the review covered the period from 2018 to 2023 and were limited by language of scientific publication (English). Keywords and phrases such as "heart failure", "SGLT2", "dapagliflozin", "empagliflozin", "canagliflozin" were used to search and select eligible studies.

**Results**

1. SGLT2 Inhibitors: General Overview of Molecular Mechanisms, Indications, and Contraindications

Sodium-glucose cotransporter 2 (SGLT2) inhibitors - Dapagliflozin, Empagliflozin, and Canagliflozin - represent an innovative class of drugs used in the treatment of type 2 diabetes mellitus (T2DM). They exert their effect by influencing the renal mechanism of glucose reabsorption. Molecularly, they inhibit SGLT2 in the proximal tubule of the kidneys, preventing glucose reuptake and promoting its excretion in urine. This mechanism of action leads to reduced blood glucose levels in patients with T2DM, contributing to effective disease management [1-3].

Key indications for the use of SGLT2 inhibitors include not only treating T2DM but also additional benefits for patients with cardiovascular diseases and renal impairments. They may be recommended for patients at high risk of cardiovascular complications and those facing challenges in achieving target glucose levels with other antihyperglycemic agents.

Contraindications encompass conditions such as severe renal impairment, pregnancy and lactation, as well as individual intolerance to the components of the medications. Special attention is warranted when using these inhibitors in elderly patients and in the presence of other concurrent conditions such as urinary tract infections.

It's crucial to consider the potential side effects of SGLT2 inhibitors, including urinary tract infections, hyperkalemia, hypovolemia, and dehydration. Patients should
also monitor their kidney and cardiovascular health during treatment. These side effects require careful monitoring and treatment adjustment if necessary.

These SGLT2 inhibitors, representing a significant advancement in treating T2DM and associated conditions, require a personalized approach by physicians when selecting a medication, taking into account not only molecular mechanisms and effectiveness but also the individual health status of each patient.

2. Dosage of SGLT2 Inhibitor Group Medications

Dapagliflozin, Empagliflozin, and Canagliflozin – SGLT2 inhibitors integrated into modern clinical protocols for effective treatment of type 2 diabetes mellitus (T2DM) and associated cardiovascular diseases. According to recent clinical recommendations, the dosage of these medications is closely linked to the individual characteristics of the patient and their overall condition [4-5].

Typically, the initial dosage of dapagliflozin is 5 mg per day, preferably in the morning, and may be increased to 10 mg based on patient effectiveness and tolerance. Empagliflozin usually begins at 10 mg per day, with a possible increase to 25 mg based on glucose profile dynamics. Regarding canagliflozin, it is recommended to start at 100 mg daily, with a possible increase to 300 mg depending on achieving therapeutic goals.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td></td>
</tr>
<tr>
<td>Doses available</td>
<td>5 mg daily</td>
<td>10 mg daily</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Renal considerations</td>
<td>Studies did not include patients with eGFR &lt;25 ml/min/1.73m²</td>
<td>Studies did not include patients with eGFR &lt;20 ml/min/1.73m²</td>
<td>Studies did not include patients with eGFR &lt;25 ml/min/1.73m²</td>
</tr>
</tbody>
</table>

An important aspect in determining dosages is the thorough evaluation of kidney function for each patient, as medications of this class impact this organ. For patients with impaired
kidney function, dosage adjustments need to be made considering the degree of glomerular filtration deficit. Additionally, concurrent conditions such as heart failure should be considered to achieve an optimal balance between treatment efficacy and patient safety [1-6].

The general principle of modern protocols is an individualized approach to dosage, considering the molecular characteristics of drugs and the specific conditions of each patient. This allows for optimal control of glucose levels, prevention of cardiovascular complications, and minimization of side effects.

3. Regarding Dapagliflozin:

In contemporary medical practice, heart failure remains a serious condition requiring constant attention and effective treatment. Recent studies, notably DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), have provided valuable data on the impact of dapagliflozin on heart failure, signaling new perspectives in treating this condition.

DAPA-HF [14-17], a randomized, placebo-controlled study, involved ambulatory patients with heart failure and an ejection fraction of less than 40%. The results demonstrated that the use of dapagliflozin significantly reduced the risk of heart failure worsening or cardiovascular death, irrespective of ejection fraction. Over a median follow-up of 18.2 months, patients receiving dapagliflozin showed consistent positive changes, confirmed by reduced hospitalizations and mortality rates.

Similar positive outcomes were observed in the DELIVER study [7-13], involving patients with chronic heart failure, preserved ejection fraction, and structural heart changes. Dapagliflozin also reduced the risk of the first cardiovascular event by 17%, emphasizing its effectiveness in treating this category of patients. Assessing the quality of life in heart failure patients is a crucial aspect of treatment effectiveness. Studies have shown that the use of dapagliflozin is accompanied by a significant improvement in quality-of-life indicators, including reduced
hospitalizations and overall well-being. A comparative analysis of dapagliflozin's effectiveness against other medications and placebos underscores its superiority in reducing cardiovascular complications. Patients, including both women and men, equally benefit from dapagliflozin without significant differences in safety profiles.

Thus, the results of the DAPA-HF and DELIVER studies advocate for the widespread use of dapagliflozin in heart failure treatment. This medication is not only effective in reducing the risk of cardiovascular complications but also contributes to improving patients' quality of life, making it an important tool in modern cardiology. The DAPA-HF study [14-17] provided compelling figures on dapagliflozin's impact on heart failure, showing that in patients with systolic heart dysfunction (where ejection fraction is less than or equal to 40%), this drug reduces the risk of heart failure worsening by 26% and cardiovascular mortality risk by 18%. This significant risk reduction from the study holds immense practical value in clinical medicine.

4. About Empagliflozin:

Empagliflozin has shown significant potential in treating patients with chronic heart failure (HF). In the EMPEROR-Preserved study [18-20], aimed at assessing its impact on patients with chronic heart failure and preserved ejection fraction (HFpEF), it was found that the drug reduces the risk of cardiac death or hospitalization due to heart failure. This is a significant finding as HFpEF accounts for a substantial portion of heart failure cases and previously had limited effective medications.

Additionally, EMPEROR-Preserved demonstrated that Empagliflozin significantly improves the health and quality of life of patients with HFpEF. This was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ), revealing improvements in all aspects of patients' quality of life at different time intervals, from 12 to 52 weeks. These results are crucial considering that HFpEF, comprising a substantial portion of heart failure cases, previously lacked a wide spectrum of effective medications. Empagliflozin, by improving quality of life and reducing the risk of cardiac complications, demonstrates potential in enhancing treatment.
outcomes for patients with HFPeF.

Directly associated data concerning the improvement of quality of life in patients with HFPeF at a scale sufficient for comprehensive statistical evaluation were not presented in this review. However, they underscore the importance of further research and analysis of the drug for specific age groups and subtypes of heart failure patients [18–20].

From the analysis of blood proteomics conducted on samples of participants pooled from the EMPEROR-Reduced and EMPEROR-Preserved trials [28], it was revealed that approximately 30 blood proteins significantly changed with the inhibition of SGLT2 using empagliflozin. The concentration of these proteins changed by at least 10%, exhibiting substantial statistical significance, even after multiple testing corrections. Most of these proteins exert favorable effects on the heart and kidneys, aligning with results from animal experiments simulating cardiac and renal injuries.

Interestingly, an increase in the levels of IGFBP1, TfR1, and EPO was observed with the administration of empagliflozin, which are functionally linked to increased hemoglobin, potentially serving as key statistical mediators of empagliflozin's benefit in reducing heart failure and major renal complications. Some of these proteins are also associated with increased sirtuin-1 activity, a nutrient deficiency sensor promoting autophagy [22–27]. Empagliflozin, by influencing these proteins, reduces oxidative stress, stimulates autophagy, and possesses cardioprotective and nephroprotective effects. It is important to note that these manifestations appeared similar in both early and extended treatment periods. However, despite significant conclusions, further research requires deeper analysis and experiments for a precise understanding of empagliflozin's mechanisms of action at the cellular level and the organs/sources responsible for the release of these proteins [25–26].

It should also be considered that these articles have certain limitations, including a small number of participants and a limited quantity of measured proteins. Blood proteomic data only reflect a small portion of intracellular proteins associated with the action of SGLT2 inhibitors. However, the results of proteomic analyses align with the findings of
experimental studies linking the beneficial effects of SGLT2 inhibitors on the heart and kidneys with their effects on autophagy, inflammation, fibrosis, and cellular stress [21-27].

**Conclusion**

SGLT2 inhibitors such as dapagliflozin, empagliflozin, and canagliflozin represent promising pharmacological agents in treating heart failure (HF). In this article, we conducted a comparative analysis of the effectiveness and potential of these drugs in improving treatment outcomes for HF patients.

The research data confirm the positive impact of dapagliflozin and empagliflozin in reducing the risk of HF exacerbation and hospitalizations. Particular attention has been given to empagliflozin's potential in reducing the risk of cardiac death and hospitalizations in patients with preserved ejection fraction. These results present important perspectives for optimizing treatment and improving the prognosis of patients with different forms of HF. However, it is necessary to note that for a complete understanding of the effectiveness and mechanisms of action of each drug, further research is required. An individualized approach to selecting a drug for a specific patient and type of heart failure remains a key aspect in successful treatment. Moreover, expanding studies across different age and gender groups, along with a deeper exploration of drug mechanisms, will help more accurately define their role in improving the quality of life and prognosis of HF patients. Overall, the use of SGLT2 inhibitors holds promise for further improving HF treatment outcomes. It is crucial to continue scientific research to optimize the use of these drugs and integrate them into treatment practice to enhance effectiveness and the quality of life for patients with heart failure.

**References:**


