

RESEARCH PAPER

Gliflozins in Cardiovascular Disease: From Glycemic Control to Cardiorenal-Metabolic Protection

Ajayta Chaudhary¹, Aadhya Agarwal², Renu Chane^{3*}, Thuraya Abdulsalam A.A. Al-Azazi⁴, Pradeep Kumar⁵,
Manoj Kumar Nandkeoliar⁶

^{1,2}2nd-year MBBS Students,

Sharda School of Medical Sciences and Research, Sharda University, Greater Noida, Uttar Pradesh, India

³Associate Professor, Department of Biochemistry,

Sharda School of Medical Sciences and Research, Sharda University, Greater Noida, Uttar Pradesh, India

Email: renu.chane@sharda.ac.in.

⁴Ph.D. Scholar, Department of Biochemistry,

Sharda School of Medical Sciences & Research, Sharda University, Greater Noida, Uttar Pradesh, India

⁵Research Fellow, Department of Biochemistry,

Sharda School of Medical Sciences & Research, Sharda University, Greater Noida, Uttar Pradesh, India

⁶Professor Emeritus, Department of Biochemistry,

Sharda School of Medical Sciences & Research, Sharda University, Greater Noida, Uttar Pradesh, India

ABSTRACT

Sodium-dependent glucose cotransporter-2 (SGLT-2) inhibitors, commonly known as gliflozins, have become crucial in managing cardiovascular diseases (CVDs), particularly in individuals with heart failure and type 2 diabetes mellitus (T2DM). This review summarizes findings from various scientific studies on the cardiovascular benefits, mechanisms of action, safety profiles, and emerging applications of SGLT-2 inhibitors. Evidence from large-scale randomized controlled trials and meta-analyses highlights their effectiveness in reducing cardiovascular mortality, hospitalizations for heart failure, and progression of renal disease. Additionally, the review examines the molecular mechanisms at play, such as modulation of myocardial metabolism, inflammation, and fibrosis, which contribute to the therapeutic effects of SGLT-2 inhibitors in managing broader cardiovascular risks. This includes potential applications in non-diabetic populations and in combination therapies.

Keywords Sodium-Dependent Glucose Cotransporters-2(SGLT-2), Cardiovascular Diseases (CVDs), Type 2 Diabetes Mellitus (T2DM).

How to cite this article: Ajayta Chaudhary, Aadhya Agarwal, Renu Chane, Thuraya Abdulsalam A.A. Al-Azazi, Pradeep Kumar, Manoj Kumar Nandkeoliar, "Gliflozins in Cardiovascular Disease: From Glycemic Control to Cardiorenal-Metabolic Protection" Int. J Drug Deliv Technol. 2026;16(85s): 1297-1301; DOI: 10.25258/ijddt.16.85s.136.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic condition characterised by elevated blood sugar levels due to impaired insulin production, insulin action, or both [1]. Worldwide, cardiovascular diseases remain the leading cause of morbidity and mortality, significantly affecting individuals with type 2 diabetes [2]. According to the International Diabetes Federation (IDF) Diabetes Atlas, 11th Edition [3], approximately 590 million adults aged 20-79 years have diabetes. In India, the estimated burden ranges from 101 million to 212 million people with the condition. The lower estimate, 101 million, comes from the ICMR-INDIAB Study published in 2023, which analysed data up to 2021 [4]. The higher estimate, 212 million, comes from the NCD Risk Factor Collaboration pooled analysis [5]. The variation in estimates is attributable to differing methods and diagnostic criteria.

Between 2012 and 2017, leading agents-canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin-received regulatory approval from the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) to

lower hyperglycaemia in individuals with Type 2 Diabetes Mellitus (T2DM) [6-9]. Traditional therapies primarily aimed at glycemic control, with limited impact on cardiovascular outcomes. Gliflozins are a class of oral medications that treat Type 2 diabetes by promoting the excretion of glucose through the urine. Additionally, they slow the progression of chronic kidney disease. Importantly, SGLT-2 inhibitors exert their effects independently of insulin secretion, opening new avenues for diabetes management and cardiovascular protection [2, 10]. This review assesses the impact of gliflozins on cardiovascular outcomes, their molecular and physiological mechanisms of action, and their safety profile in patients with cardiovascular disease.

2. HISTORICAL EVOLUTION AND MOLECULAR MECHANISMS

The scientific exploration of glycosuria as a therapeutic strategy dates back nearly two centuries to the isolation of phlorizin from the apple tree by Petersen in 1835. It was not until 1886 that Von Mering discovered phlorizin's

glucosuric properties, and subsequently, in the 1980s, researchers learned that the resultant reduction in blood glucose concentrations stemmed from phlorizin's ability to inhibit glucose reabsorption by the renal tubules. The development of orally absorbed, highly specific SGLT-2 inhibitors, also referred to as gliflozins, began in the 1990s with the work of Tsujihara and his team at Tanabe Seiyaku. Initial clinical trials affirmed the efficacy of this class of agents, and achieved an incline of approximately 0.5 to 1.1% in glycated hemoglobin levels (HbA1c) [2, 11].

These mandatory Cardiovascular Outcome Trials (CVOTs), such as the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), revealed potent cardiorenal protective benefits that were independent of glycemic control. Across the class, the most consistent and significant finding was a substantial reduction in hospitalisation for heart failure (HHF), with benefit observed early in therapy and across a broad spectrum of cardiovascular risk [10, 12].

However, the true potential of this drug class was unexpectedly revealed by a 2008 regulatory event. The Food and Drug Administration (FDA) mandated that novel antidiabetic medications undergo CVOTs to demonstrate cardiovascular safety [2, 13].

Over the past decades, six subtypes of sodium-glucose cotransporters (SGLTs) have been identified in the human body, with SGLT-1 and SGLT-2 being the most prominent. The concept of SGLTs was first introduced in the 1960s. SGLT-2, characterised by low affinity and high transport capacity for glucose, is predominantly located in the epithelium of the proximal tubule. Conversely, SGLT-1, which exhibits high affinity and low transport capacity for glucose, is found in the intestine, heart, prostate, trachea, brain, and skeletal muscle [14, 15].

The molecular structure of SGLT-2 inhibitors is derived from phlorizin, a natural glucoside. Modern gliflozins are synthetic β -D-glucosides featuring a hydrophobic diarylmethane moiety and metabolically stable C-aryl glucoside linkages, enabling oral bioavailability and selective SGLT-2 inhibition. The glycoside portion interacts directly with the SGLT-2 receptor binding site, whereas the hydrophobic moiety is key to the drug's activity and selectivity profile. A critical feature enabling these molecules to function as orally administered drugs is the chemical bond between the two portions: the C-aryl glucoside linkage (as seen in agents such as dapagliflozin). This linkage provides metabolic stability because it is resistant to hydrolysis by intestinal β -glycosidases. This stability ensures that the drug is absorbed effectively into the bloodstream rather than being broken down in the gut. While all members of the gliflozin class share this fundamental C-aryl glucoside core, individual agents differ in their substitution patterns around the aromatic rings. These minor chemical variations result in differences in potency, selectivity (e.g., between SGLT-2 and SGLT-1), efficacy, and clinical dosing [2, 15]. A central working hypothesis suggests that the cardiac benefits are associated with inhibition of sodium channels in the plasma membrane, including the sodium-hydrogen exchanger. This action

modulates intracellular sodium homeostasis, providing a unifying explanation for the effects observed on balance, oxidative stress, inflammation, and metabolism—the so-called cardiac sodium interactome [16]. Given their glycemic-independent benefits, the therapeutic spectrum is rapidly expanding, positioning SGLT-2 inhibitors as foundational agents for chronic heart failure with reduced ejection fraction (HFrEF) and chronic kidney disease (CKD), transcending diabetes status [2, 17].

3. MECHANISMS OF CARDIOVASCULAR PROTECTION

The precise mechanisms by which SGLT-2 inhibitors confer the benefits observed in recent research remain incompletely understood. Biomarkers and surrogate endpoints from these studies suggest that SGLT-2 inhibition affects multiple cardiovascular risk factors. These effects extend beyond glucose regulation to include blood pressure, body weight, visceral fat, hyperinsulinaemia, arterial stiffness, albuminuria, circulating uric acid, and oxidative stress. These factors play key roles in pathways linked to cardiorenal health. SGLT-2 inhibitors work by increasing sodium and glucose excretion—natriuresis and glycosuria—which subsequently influence these pathways [18–20]. Natriuresis and diuresis reduce sodium and glucose reabsorption, thereby decreasing plasma volume and interstitial fluid, reducing congestion while maintaining perfusion [18, 19]. Blood pressure and weight reduction occur primarily through fat loss [20]. Natriuresis and diuresis result from blocking renal reabsorption of glucose and sodium. SGLT2i reduce plasma volume and interstitial fluid, alleviating congestion without significantly affecting arterial perfusion. SGLT2i promote a metabolic shift towards ketone and fatty acid use, improving myocardial energy efficiency—a concept known as the "thrifty substrate" hypothesis. They reduce inflammation and oxidative stress by lowering inflammatory markers and uric acid levels, and by suppressing the AGE-RAGE pathway and NLRP3 inflammasome activity [20–23]. They preserve kidney function, reduce albuminuria, and confer cardiorenal benefits even as glycemic control declines [18, 19].

SGLT2i inhibits cardiac Na^+/H^+ exchangers, thereby improving sodium-calcium handling and mitochondrial function, which enhances cardiac structure and function. Animal and imaging studies have shown reduced cardiac fibrosis, improved cardiac function, and reduced ventricular mass and volume. SGLT2i also improves vascular compliance and endothelial health [16, 24].

4. NEGATIVE CONSEQUENCES

Although SGLT2 inhibitors are usually well tolerated, there are a few possible side effects to consider, such as genital mycotic infections (increased risk due to glucosuria) and urinary tract infections (elevated incidence, particularly in female patients). Volume depletion may lead to hypotension, especially in patients on concomitant diuretics. Euglycemic diabetic ketoacidosis is a rare but serious complication [25, 28].

Amputations have been notably associated with

canagliflozin, as observed in the CANVAS program [11]. Bone fractures may also pose a risk for certain patient populations taking canagliflozin. It is crucial to monitor these adverse effects, particularly in high-risk patients [18, 26].

5. UPCOMING APPLICATIONS

Gliflozins are under investigation for other cardiovascular applications. Studies have demonstrated that SGLT-2 inhibitors can reduce the risk of cardiovascular events and end-stage renal disease by delaying the onset of chronic kidney disease [16, 18, 26].

NON-DIABETIC POPULATIONS: Recent data suggest that SGLT-2 inhibitors may confer cardiovascular benefits in individuals without diabetes, thereby broadening their therapeutic applications [16, 18, 22-24].

Ongoing research is examining the synergistic effects of combining gliflozins with other cardiovascular agents, such as GLP-1 receptor agonists, to improve treatment outcomes.

6. DISCUSSION

Large clinical trials have demonstrated significant reductions in cardiovascular events, mortality, and hospitalizations for heart failure, particularly among patients with type 2 diabetes, especially those with pre-existing cardiovascular disease [2, 18, 25].

7. COMPARATIVE CARDIOVASCULAR EFFECTS OF INDIVIDUAL GLIFLOZINS: CLASS EFFECTS VERSUS AGENT-SPECIFIC EVIDENCE

Although SGLT-2 inhibitors share a common mechanism of increasing urinary glucose and sodium excretion, available clinical evidence indicates that their cardiovascular effects should be interpreted in light of both class effects and agent-specific data.

8. CLASS EFFECTS

A substantial body of randomised controlled trial evidence supports cardiovascular and cardiorenal benefits as a class effect of SGLT2 inhibition. In patients with type 2 diabetes at increased cardiovascular risk, several SGLT2 inhibitors have demonstrated reductions in heart failure hospitalisation and/or cardiovascular and renal outcomes. Meta-analyses of randomised trials have further supported a consistent reduction in hospitalisation for heart failure and progression of kidney disease across the class. However, the magnitude and individual components of benefit vary by the population studied and the specific trial [18].

The cardiovascular benefits of SGLT2 inhibitors also extend beyond glucose lowering. Proposed mechanisms include natriuresis and osmotic diuresis, reduced intraglomerular pressure, favourable haemodynamic effects, improved myocardial energy utilisation, attenuation of oxidative stress and inflammation, and potential antifibrotic effects [17, 22]. These mechanisms provide a biological rationale for cardiovascular and renal protection that is partly independent of changes in HbA1c.

9. AGENT-SPECIFIC EVIDENCE

Cardiovascular outcome trials of individual agents provide valuable evidence. However, these findings should be interpreted in the context of the characteristics of the respective study populations.

EMPAGLIFLOZIN: In the EMPA-REG OUTCOME trial, empagliflozin significantly reduced cardiovascular death and hospitalisation for heart failure in patients with type 2 diabetes and established cardiovascular disease. These findings provided some of the earliest evidence that SGLT2 inhibition could substantially improve cardiovascular outcomes beyond glycemic control [25].

CANAGLIFLOZIN: The CANVAS Program demonstrated a reduction in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes at increased cardiovascular risk. A significant reduction in hospitalisation for heart failure was also observed. However, the CANVAS Program identified safety considerations, including an increased risk of lower-limb amputation, which subsequently became an important component of the agent-specific safety discussion.

DAPAGLIFLOZIN: The DECLARE-TIMI 58 trial demonstrated a significant reduction in the composite of cardiovascular death or hospitalization for heart failure, driven predominantly by fewer hospitalizations for heart failure. Subsequently, DAPA-HF showed that dapagliflozin reduced the risk of worsening heart failure or cardiovascular death in patients with heart failure with reduced ejection fraction, including those without diabetes. These findings were pivotal in establishing SGLT2 inhibitors as heart failure therapies rather than exclusively glucose-lowering agents [12, 26].

ERTUGLIFLOZIN: The VERTIS-CV trial demonstrated the cardiovascular safety of ertugliflozin in patients with type 2 diabetes and established cardiovascular disease. Although the trial did not show superiority for the primary major adverse cardiovascular event endpoint, reductions in hospitalisations for heart failure were observed.

SOTAGLIFLOZIN: Sotagliflozin differs pharmacologically from the other agents discussed because it inhibits both SGLT2 and SGLT1. In the SCORED trial, sotagliflozin reduced the composite of total cardiovascular deaths, hospitalizations for heart failure, and urgent heart failure visits in patients with type 2 diabetes, chronic kidney disease, and cardiovascular risk. In the SOLOIST-WHF trial, initiating sotagliflozin around the time of discharge after hospitalization for worsening heart failure reduced the composite of cardiovascular death and heart failure-related hospitalizations and urgent visits. These findings support cardiovascular and heart failure benefits with sotagliflozin, including in patients with diabetes and heart failure [20, 29].

10. EVIDENCE FROM INDIRECT AND NETWORK META-ANALYSES

Comparing individual SGLT2 inhibitors is difficult to interpret because most major cardiovascular outcome trials were placebo-controlled rather than head-to-head comparisons between active SGLT2 inhibitors. Consequently, apparent differences in efficacy among agents often stem from indirect comparisons or network meta-analyses.

A network meta-analysis by Tornyos *et al.* evaluated cardiovascular outcomes across randomised trials of various SGLT2 inhibitors and suggested differences in the magnitude of protection for selected cardiovascular endpoints [20]. However, such analyses compare treatments across trial populations with varying baseline cardiovascular risk profiles, follow-up periods, endpoint definitions, and background therapies. Therefore, these findings should be regarded as hypothesis-generating rather than definitive evidence of clinical superiority of one SGLT2 inhibitor over another.

Accordingly, the finding that Sotagliflozin may rank favourably for selected outcomes in network analyses should not be presented as proof of superiority over dapagliflozin, empagliflozin, canagliflozin, or ertugliflozin. In the absence of adequately powered direct head-to-head randomised trials, differences observed in network meta-analyses should be interpreted cautiously.

11. CLINICAL INTERPRETATION

Taken together, current evidence supports a strong class effect of SGLT2 inhibition for heart failure and renal protection, while evidence for individual cardiovascular endpoints varies across agents and clinical populations. These differences should therefore be interpreted as agent-specific rather than as evidence of universal superiority.

Empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, and sotagliflozin each have distinct cardiovascular outcome-trial evidence, and the choice of agent should consider the patient's clinical phenotype, indication, kidney function, heart failure status, cardiovascular risk, adverse-effect profile, and regulatory indication.

Thus, rather than concluding that sotagliflozin is superior to other SGLT2 inhibitors, the available evidence supports a more nuanced interpretation: sotagliflozin demonstrates significant cardiovascular and heart failure benefits in the populations studied, while network meta-analyses may suggest differences in relative efficacy for selected outcomes. However, these indirect comparisons cannot establish definitive superiority in the absence of direct head-to-head trials.

12. CONCLUSION

SGLT2 inhibitors have ushered in a paradigm shift in the management of cardiovascular diseases, offering significant benefits by slowing the progression of chronic renal disease, reducing heart failure hospitalizations, and lowering cardiovascular mortality. Their mechanisms of action extend beyond glycemic control, encompassing hemodynamic, metabolic, anti-inflammatory and antifibrotic effects. While generally well-tolerated, these agents require careful monitoring for potential adverse

effects. The expanding indications and ongoing research into combination therapies underscore the growing impact of SGLT2 inhibitors on comprehensive cardiovascular risk management. This review is aligned with UN Sustainable Development Goal No.3 (Good Health and Well-being) implementation of Govt. of India.

13. REFERENCES

1. Sinha R, Priya A, Sinha A, Rahman MHU. Prevalence of diabetes distress among type 2 diabetes mellitus patients in India: a systematic review and meta-analysis. *Health Psychol Behav Med.* 2024;12(1). DOI: 10.1080/21642850.2024.2324091.
2. Braunwald E. Gliflozins in the management of cardiovascular disease. *N Engl. J Med.* 2022;386(21):2024-2034.
3. International Diabetes Federation. IDF Diabetes Atlas. 11th ed. Brussels: International Diabetes Federation; 2024.
4. Arokiasamy P, Anjana RM, Unnikrishnan R, Deepa M, Jayawardana R, Mohan V, *et al.* Prevalence and burden of diabetes and prediabetes in India: results from the ICMR-INDIAB national study. *Lancet Diabetes Endocrinol.* 2023;11(7):474-489. DOI: 10.1016/S2213-8587(23)00138-0.
5. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet.* 2024;403(10442):1788-1802. DOI: 10.1016/S0140-6736(24)02317-1.
6. U.S. Food and Drug Administration. Canagliflozin prescribing information. Silver Spring (MD): U.S. Food and Drug Administration; 2013.
7. European Medicines Agency. Dapagliflozin assessment report. Amsterdam: European Medicines Agency; 2012.
8. U.S. Food and Drug Administration. Empagliflozin prescribing information. Silver Spring (MD): U.S. Food and Drug Administration; 2014.
9. U.S. Food and Drug Administration. Ertugliflozin prescribing information. Silver Spring (MD): U.S. Food and Drug Administration; 2017.
10. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128. DOI: 10.1056/NEJMoa1504720.
11. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erond N, *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl. J Med.* 2017;377(7):644-657. DOI: 10.1056/NEJMoa1611925.
12. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, *et al.* Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl. J Med.* 2019;380(4):347-357. DOI: 10.1056/NEJMoa1812389.
13. Suthahar N. Stroke survivors with type 2 diabetes:

- repositioning pioglitazone in an era dominated by gliflozins [editorial]. *Mayo Clin Proc.* 2025;100(2):187-189. DOI: 10.1016/j.mayocp.2024.12.006.
14. Cice G. Preserving renal function: gliflozins, GLP-1 agonists and antialdosterones. *Eur Heart J Suppl.* 2025;27(3)-ii178. DOI: 10.1093/eurheartjsupp/uaaf019.
15. Marques F, Valicelli FH, Tanaka DM, Simões MV. The trajectory of gliflozins: from apple tree bark to reduced overall mortality in heart failure. *Arch Bras Cardiol Heart Fail.* 2025;4(1). DOI: 10.36660/abchf.20240027.
16. Xiang B, Zhao X, Zhou X. Cardiovascular benefits of sodium-glucose cotransporter 2 inhibitors in diabetic and nondiabetic patients. *Cardiovasc Diabetol.* 2021;20(1):78. DOI: 10.1186/s12933-021-01266-x.
17. Chen S, Coronel R, Hollmann MW, Weber NC, Zuurbier CJ. Direct cardiac effects of SGLT2 inhibitors. *Cardiovasc Diabetol.* 2022;21(1):45. DOI: 10.1186/s12933-022-01480-1.
18. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, *et al.* Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol.* 2020;5(11):1257-1269. DOI: 10.1001/jamacardio.2020.2647.
19. Li HL, Lip GYH, Feng Q, Fei Y, Tse YK, Wu MZ, *et al.* Sodium-glucose cotransporter 2 inhibitors and cardiac arrhythmias: a systematic review and meta-analysis. *Cardiovasc Diabetol.* 2021;20(1):100. DOI: 10.1186/s12933-021-01293-8.
20. Tornyos D, Meuer M, Lukács R, El Alaoui Abdallaoui O, Kupo P, Faludi R, *et al.* Cardiovascular outcomes in patients treated with sodium-glucose transport protein 2 inhibitors: a network meta-analysis of randomized trials. *Front Cardiovasc Med.* 2022;9:1041200. DOI: 10.3389/fcvm.2022.1041200.
21. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al.* 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. *Diabetes Care.* 2023;46(1)-S157.
22. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia.* 2018;61(10):2108-2117. DOI: 10.1007/s00125-018-4670-7.
23. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, *et al.* SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res.* 2015;12(2):90-100. DOI: 10.1177/1479164114559852.
24. Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, *et al.* Sodium glucose cotransporter 2 inhibition and cardiorenal protection in diabetes: potential.
25. Gager GM, Gelbenegger G, Jilma B, Von Lewinski D, Sourij H, Eyileten C, *et al.* Cardiovascular outcome in patients treated with SGLT2 inhibitors for heart failure: a meta-analysis. *Front Cardiovasc Med.* 2021;8:691907. DOI: 10.3389/fcvm.2021.691907.
26. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al.* Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl. J Med.* 2019;381(21):1995-2008. DOI: 10.1056/NEJMoa1911303.
27. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al.* Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl. J Med.* 2020;383(15):1413-1424. DOI: 10.1056/NEJMoa2022190.
28. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, *et al.* Empagliflozin in heart failure with a preserved ejection fraction. *N Engl. J Med.* 2021;385(16):1451-1461. DOI: 10.1056/NEJMoa2107038.
29. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, *et al.* Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl. J Med.* 2021;384(2):117-128. DOI: 10.1056/NEJMoa2030183.