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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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SGLT2 INHIBITORS: FROM GLYCEMIC CONTROL TO CARDIO-RENAL PROTECTION

Evloev Kharon Kh[1]*, Snitsa Daniil V[2], Pankov Danil S[2], Gasparyan Mariya A[1], Zaycev Matvey V[3], Koifman Natalya A[1], Buglo Elena A[4], Zefirova Margarita S[2], Rachkova Tamara A[2], Gurtiev Dmitrii A[1], Zaseeva Victoria V[1], Tolmasov Jaloliddin M[1].

[1]North-Western State Medical University named after I.I. Mechnikov, Saint-Petersburg, Russia.

[2]Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia.

[3]Pavlov First Saint-Petersburg State Medical University, Saint-Petersburg, Russia.

[4]Institute of Medical Education, Almazov National Research Centre, Saint-Petersburg, Russia.

Abstract.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were originally developed as glucose-lowering agents for patients with type 2 diabetes mellitus (T2DM). However, a growing body of robust clinical evidence has demonstrated their profound cardioprotective and nephroprotective effects that extend beyond glycemic control. This review summarizes the current understanding of the mechanisms underlying these benefits and the clinical implications across a wide range of patient populations. We discuss landmark cardiovascular and renal outcome trials, evaluate the physiological and molecular mechanisms, including hemodynamic modulation, anti-inflammatory and antifibrotic effects, and improvements in myocardial and renal energetics, and assess the role of SGLT2 inhibitors in heart failure with reduced and preserved ejection fraction, as well as in chronic kidney disease with and without diabetes. The translation of these findings into clinical guidelines has reshaped therapeutic strategies in both endocrinology and cardiology, underscoring the importance of SGLT2 inhibitors as a cornerstone in cardiorenal protection.

Key words. SGLT2 inhibitors, type 2 diabetes, heart failure, chronic kidney disease, cardioprotection, nephroprotection, dapagliflozin, empagliflozin, canagliflozin, cardiovascular outcomes.

Introduction.

Type 2 diabetes mellitus (T2DM) has evolved into one of the most prevalent and costly chronic conditions worldwide. According to the International Diabetes Federation, over 537 million adults globally were living with diabetes in 2021, and this number is projected to exceed 783 million by 2045, driven largely by demographic shifts, urbanization, sedentary lifestyles, and nutritional transitions [1]. T2DM contributes significantly to premature mortality and health system burden, not only through direct glycemic effects but primarily through its systemic complications.

Although hyperglycemia has historically been the primary therapeutic target, it is now well-established that normalization of blood glucose alone does not eliminate the elevated risks of cardiovascular (CV) events, heart failure (HF), and chronic kidney disease (CKD) in patients with T2DM [2,3]. Landmark trials such as ACCORD, ADVANCE, and VADT demonstrated that intensive glycemic control modestly reduces the risk of microvascular complications but has little to no effect on macrovascular outcomes and may even increase mortality in certain subgroups [4-6]. These findings underscored the need for pharmacological interventions capable of modifying disease progression at the cardiorenal level, independent of glucose-lowering efficacy.

The introduction of sodium-glucose cotransporter 2 inhibitors (SGLT2i) represented a pivotal shift in the therapeutic landscape. Originally developed as insulin-independent antihyperglycemic agents, SGLT2i act by inhibiting the SGLT2 protein in the renal proximal tubule, thereby promoting glycosuria and natriuresis. This mechanism results in moderate reductions in plasma glucose, body weight, and systolic blood pressure, along with mild diuresis [7]. However, emerging evidence from large-scale cardiovascular outcome trials (CVOTs) rapidly redefined their clinical role.

The EMPA-REG OUTCOME trial (empagliflozin), CANVAS Program (canagliflozin), DECLARE-TIMI 58 (dapagliflozin), and VERTIS-CV (ertugliflozin) collectively established that SGLT2i not only reduce hospitalization for heart failure (HHF) but also significantly lower the risk of cardiovascular death, particularly in patients with pre-existing ASCVD or multiple risk factors [8-11]. Furthermore, studies such as DAPA-HF and EMPEROR-Reduced demonstrated that these benefits extend to patients without diabetes, confirming SGLT2 inhibition as a viable strategy for heart failure management independent of glycemic status [12,13].

The renoprotective properties of SGLT2 inhibitors have also garnered considerable attention. Trials such as CREDENCE (canagliflozin) and DAPA-CKD (dapagliflozin) reported marked reductions in albuminuria, preservation of estimated glomerular filtration rate (eGFR), and delayed progression to end-stage kidney disease (ESKD) among patients with CKD, including those without diabetes [14,15]. The EMPA-KIDNEY trial further reinforced these outcomes, leading to the endorsement of SGLT2i by nephrology societies as cornerstone therapy for CKD [16].

The mechanisms underlying the cardiorenal protection offered by SGLT2 inhibitors are multifactorial and incompletely understood. Hemodynamic effects, including reductions in preload, afterload, and intraglomerular pressure, appear to play a key role, as do metabolic shifts such as increased ketone availability, improved myocardial energetics, and decreased tubular oxygen consumption [17,18]. Additionally, SGLT2i may exert anti-inflammatory and antifibrotic actions by downregulating pro-inflammatory cytokines (e.g., TNF-α, IL-6), reducing oxidative stress, and inhibiting NLRP3 inflammasome activation in cardiac and renal tissues [19,20].

Beyond these mechanisms, emerging data suggest potential benefits on endothelial function, sympathetic nervous system modulation, epicardial adipose tissue reduction, and

hematopoiesis via increased erythropoietin production [21-23]. Notably, these effects occur independently of glycemic control and are observed across diverse populations, reinforcing the concept of SGLT2 inhibitors as organ-protective agents rather than purely metabolic drugs.

The broad spectrum of efficacy and favorable safety profile have prompted updates in international clinical guidelines. The American Diabetes Association (ADA), European Society of Cardiology (ESC), kidney disease: Improving Global Outcomes (KDIGO), and American Heart Association (AHA) now endorse the use of SGLT2i as first-line or early adjunctive therapy in patients with established ASCVD, HF with reduced ejection fraction (HFrEF), or CKD – regardless of the presence of T2DM [24-27].

Given these transformative developments, the present review aims to provide an in-depth synthesis of the current evidence surrounding SGLT2 inhibitors. We critically examine their pharmacokinetic and pharmacodynamic properties, cardiovascular and renal outcome data, mechanisms of action, safety considerations, and positioning in current treatment algorithms. By integrating clinical trial findings with mechanistic insights, this article seeks to clarify the evolving role of SGLT2 inhibitors across the cardio-renal-metabolic continuum and to highlight their implications for real-world practice.

Historical Background and Conceptual Evolution.

The clinical development of sodium-glucose cotransporter 2 (SGLT2) inhibitors stems from decades of investigation into renal glucose handling. In healthy individuals, approximately 180 grams of glucose are filtered daily by the glomeruli, with nearly complete reabsorption occurring in the proximal tubules. SGLT2 accounts for approximately 90% of this reabsorption, while SGLT1 handles the remainder in the more distal nephron segments [17]. This physiologic mechanism provided the rationale for targeting SGLT2 as a means to lower plasma glucose levels via enhanced urinary excretion.

The therapeutic concept was inspired by phlorizin, a natural compound isolated from the bark of apple trees in the 19th century, which was later found to inhibit both SGLT1 and SGLT2. Although phlorizin demonstrated glycosuric properties in animal studies, its clinical application was hindered by poor oral bioavailability and significant gastrointestinal side effects due to SGLT1 inhibition [17,21]. These limitations led to the development of more selective and orally bioavailable SGLT2 inhibitors in the early 2000s, including dapagliflozin, canagliflozin, and empagliflozin [24].

Initial phase 2 and 3 clinical trials of these agents demonstrated moderate reductions in glycated hemoglobin (HbA1c), along with favorable effects on body weight and systolic blood pressure [24]. Their insulin-independent mechanism of action and low risk of hypoglycemia distinguished SGLT2 inhibitors from other antidiabetic agents such as sulfonylureas or insulin [5,24]. However, following concerns about cardiovascular risks raised by the rosiglitazone experience, the U.S. FDA introduced a requirement in 2008 for all new glucose-lowering agents to demonstrate cardiovascular safety in large-scale trials [4].

The EMPA-REG OUTCOME trial, published in 2015, fundamentally altered the perception of SGLT2 inhibitors. In patients with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD), empagliflozin significantly reduced cardiovascular death by 38%, hospitalization for heart failure (HHF) by 35%, and all-cause mortality by 32% [8]. These findings were both unexpected and unprecedented in the field of diabetology, as no previous glucose-lowering therapy had demonstrated such robust cardiovascular benefit.

Subsequent trials, including CANVAS (canagliflozin), DECLARE-TIMI 58 (dapagliflozin), and VERTIS-CV (ertugliflozin), confirmed consistent reductions in HF hospitalizations across broader patient populations, including individuals without prior cardiovascular events but with multiple risk factors [9-11]. Notably, DAPA-HF and EMPEROR-Reduced extended these findings to patients with heart failure with reduced ejection fraction (HFrEF), irrespective of diabetes status, thus demonstrating the benefit of SGLT2 inhibition beyond glycemic control [12,13].

In nephrology, a similar transformation occurred. The CREDENCE trial showed that canagliflozin significantly reduced the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, and renal or cardiovascular death in patients with type 2 diabetes and chronic kidney disease [14]. Shortly after, DAPA-CKD demonstrated that dapagliflozin improved renal and cardiovascular outcomes in patients with CKD, including those without diabetes [15]. These results were further reinforced by the EMPA-KIDNEY trial, which confirmed the renoprotective effect of empagliflozin across diverse populations [16].

Based on these consistent findings, international clinical guidelines rapidly evolved. The American Diabetes Association (ADA) and the European Society of Cardiology (ESC) began recommending SGLT2 inhibitors as foundational therapies in patients with T2DM and comorbid ASCVD, heart failure, or CKD [24,25]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and the American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines further endorsed SGLT2 inhibitors in non-diabetic populations with HF and CKD [26,27].

This repositioning of SGLT2 inhibitors from purely antihyperglycemic agents to cardio-renal protective drugs represents a major paradigm shift in clinical pharmacology. The cardiovascular and renal benefits observed appear to be largely independent of their glucose-lowering effects and are instead attributed to mechanisms such as improved hemodynamics, reductions in intraglomerular pressure, modulation of neurohormonal activation, and attenuation of inflammation and fibrosis [18-20].

Moreover, the success of SGLT2 inhibitors has renewed scientific interest in the renal-cardiac-metabolic axis. This has led to the development of dual SGLT1/2 inhibitors such as sotagliflozin, which showed efficacy in the SOLOIST-WHF and SCORED trials for heart failure and chronic kidney disease in patients with diabetes [7]. These findings support the growing recognition of sodium-glucose co-transport modulation as a promising therapeutic avenue beyond glycemic control.

Understanding the trajectory of SGLT2 inhibitors – from physiologic curiosity and glycosuric agents to multifaceted

organ-protective therapies – is essential for contextualizing their role in contemporary and future clinical practice. The next section will examine the pharmacodynamics and mechanisms of action that underlie this expanded therapeutic potential.

Pharmacodynamics and Mechanisms of Action of SGLT2 Inhibitors.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) represent a novel class of antidiabetic drugs with multifaceted biological effects extending far beyond glycemic control. Their primary pharmacological action occurs in the proximal convoluted tubule, where they inhibit SGLT2 – a high-capacity, low-affinity transporter responsible for reabsorbing ~90% of filtered glucose [17,28]. Inhibition of this transporter induces glycosuria, leading to modest reductions in plasma glucose and glycated haemoglobin (HbA1c), typically in the range of 0.5–1.0% [29].

However, the profound cardiovascular and renal benefits observed in major outcome trials have made it clear that SGLT2 inhibitors exert a wide array of non-glycaemic effects, involving hemodynamic modulation, metabolic remodelling, and anti-inflammatory mechanisms. These pleiotropic actions have redefined their therapeutic role in modern medicine.

Hemodynamic Modulation: One of the earliest and most robust effects of SGLT2i is osmotic diuresis, which arises due to urinary glucose excretion. This promotes a shift in volume from interstitial to intravascular compartments, reducing preload and afterload without triggering sympathetic overactivation [30,31]. Unlike traditional diuretics, SGLT2i primarily reduce interstitial rather than intravascular volume, which may explain their favourable effects on congestion in heart failure [32].

Renal sodium excretion also leads to increased delivery of sodium to the macula densa, restoring tubuloglomerular feedback. This in turn reduces intraglomerular hypertension, one of the key drivers of nephron injury in both diabetic and non-diabetic chronic kidney disease (CKD) [33,34]. This effect underpins the renoprotective outcomes demonstrated in the CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials [14-16].

Metabolic and Energetic Effects: SGLT2 inhibition alters substrate utilization by promoting a mild ketogenic state. By decreasing insulin and increasing glucagon levels, SGLT2i enhance lipolysis and hepatic ketogenesis, resulting in higher circulating levels of ketone bodies – particularly β-hydroxybutyrate [35]. Ketones are more energy-efficient than glucose or fatty acids, improving cardiac mitochondrial energetics, especially in the failing myocardium [36].

Additionally, SGLT2 inhibitors:

1. Reduce body weight through caloric loss (~200–300 kcal/day via glycosuria).
2. Lower uric acid levels via uricosuric effects.
3. Improve hepatic steatosis by enhancing fatty acid oxidation.
4. And reduce visceral adiposity, all of which contribute to improved cardiometabolic profiles [29,37,38].

Anti-inflammatory and Antifibrotic Mechanisms: A growing body of evidence highlights the anti-inflammatory properties of SGLT2 inhibitors. They reduce circulating levels of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and suppress activity of the NLRP3 inflammasome, a key innate immune mediator implicated in cardiac and renal fibrosis [39,40]. Preclinical studies demonstrate reduced macrophage infiltration and fibrotic remodelling in both myocardial and renal tissues following SGLT2 inhibition [41].

These actions may directly contribute to the attenuation of left ventricular hypertrophy, interstitial fibrosis, and glomerulosclerosis, which are central to the progression of heart failure and CKD [42].

Neurohormonal and Hematologic Effects: SGLT2 inhibitors have been shown to modulate neurohormonal activation, particularly by reducing plasma norepinephrine levels, suggesting sympathetic downregulation [43]. This may explain improved heart rate variability and reductions in arrhythmic burden observed in clinical practice [44].

Another intriguing effect is stimulation of erythropoiesis via increased erythropoietin production, leading to modest rises in hematocrit and hemoglobin [21,45]. This may enhance oxygen delivery and tissue perfusion, further supporting cardiac and renal function in patients with HF or anemia of chronic disease.

Additional Mechanistic Pathways.

Further proposed mechanisms include:

1. Improved endothelial function via increased nitric oxide bioavailability and reduced oxidative stress [46].
2. Reduction in epicardial adipose tissue, which serves as a source of local pro-inflammatory mediators affecting cardiac contractility and stiffness [47].
3. And enhanced autophagy and mitochondrial biogenesis, especially under conditions of metabolic stress [48].

These diverse effects underscore the systemic impact of SGLT2 inhibition and its potential applications across a broad spectrum of pathologies.

Thus, while SGLT2 inhibitors were initially developed as glucose-lowering agents, their true therapeutic potential lies in their multi-organ, multi-pathway modulation, which has expanded their indications into cardiology, nephrology, and beyond.

Cardiovascular Outcomes of SGLT2 Inhibitors:

SGLT2 inhibitors have redefined cardiovascular risk management in patients with type 2 diabetes mellitus (T2DM) and, more recently, in those without diabetes. Initially developed as glucose-lowering agents, these drugs demonstrated a surprising and consistent ability to reduce cardiovascular (CV) events, particularly hospitalization for heart failure (HHF), prompting rapid expansion of their indications across cardiometabolic populations.

Landmark Cardiovascular Outcome Trials in Diabetes: The pivotal EMPA-REG OUTCOME trial (empagliflozin) demonstrated a 38% relative risk reduction in CV death, 35% reduction in HHF, and 32% reduction in all-cause mortality in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) [8]. These were the first such results ever reported for a glucose-lowering agent and represented a paradigm shift in diabetes care.

Subsequent trials provided additional evidence:

1. CANVAS Program (canagliflozin): 14% reduction in major adverse cardiovascular events (MACE); notable renal protection; signal for increased amputation risk [9].

2. DECLARE–TIMI 58 (dapagliflozin): non-significant reduction in MACE, but a 27% reduction in HHF, which was consistent across subgroups regardless of ASCVD status [10].

3. VERTIS-CV (ertugliflozin): demonstrated non-inferiority to placebo for MACE but confirmed benefit in reducing HHF [11].

Across these trials, reduction in HHF emerged as a consistent and class-wide effect, regardless of baseline cardiovascular history.

Heart Failure Trials in Non-Diabetic Populations.

The scope of benefit expanded further with trials enrolling patients with heart failure but without diabetes:

1. DAPA-HF (dapagliflozin): among patients with heart failure with reduced ejection fraction (HFrEF), dapagliflozin reduced the composite endpoint of CV death or worsening HF by 26%, with similar benefit in both diabetic and non-diabetic subgroups [12].

2. EMPEROR-Reduced (empagliflozin): demonstrated a 25% reduction in the same composite, along with slower eGFR decline [13].

These results firmly positioned SGLT2 inhibitors alongside ACE inhibitors, beta-blockers, and mineralocorticoid receptor antagonists as foundational therapies in HFrEF.

Even more striking were the findings from:

1. EMPEROR-Preserved (empagliflozin), which showed a 21% relative risk reduction in the composite of CV death or HF hospitalization in patients with heart failure with preserved ejection fraction (HFpEF) [49].

2. DELIVER (dapagliflozin), which confirmed this benefit in a similar population, including those with mildly reduced EF [50].

Together, these trials closed a long-standing therapeutic gap in HFpEF, a condition with historically limited treatment options.

A meta-analysis combining EMPEROR-Preserved and DELIVER showed a 22% reduction in HHF, consistent across age, sex, and ejection fraction subgroups, affirming the class effect in HFpEF [51].

Meta-Analyses and Broader Implications. Multiple comprehensive meta-analyses have solidified these observations:

1. A 2022 JACC meta-analysis of over 90,000 patients confirmed that SGLT2 inhibitors reduce HHF by 28%, CV death by 14%, and all-cause mortality by 13%, across diverse populations [52].

2. The benefit in HFpEF is now considered statistically robust and clinically meaningful, even if effects on CV mortality remain more modest [51,52].

In addition, these findings support the integration of SGLT2 inhibitors into multidisciplinary heart failure care – not merely as adjuncts, but as disease-modifying agents.

Reflecting this, recent guidelines from the AHA/ACC/HFSA (2022), ESC (2023), and ADA (2024) now recommend SGLT2 inhibitors as class I agents in HFrEF, and class IIa in HFpEF, regardless of diabetes status [24-27].

Mechanistic Basis for Cardiovascular Benefits. While the glucose-lowering effects of SGLT2 inhibitors are modest, the cardioprotective benefits appear to derive from pleiotropic mechanisms, including:

1. Hemodynamic modulation: reduction of preload and afterload via osmotic diuresis and natriuresis [30].

2. Myocardial energetic shift: increased ketone body utilization improves myocardial ATP generation and oxygen efficiency [35,36].

3. Anti-fibrotic and anti-inflammatory effects: attenuation of NLRP3 inflammasome activation and macrophage infiltration limits myocardial and vascular fibrosis [39-41,53].

4. Neurohormonal effects: dampening of sympathetic tone and increased erythropoietin-mediated hematopoiesis improve oxygen delivery [21,43,45].

5. Endothelial and mitochondrial protection, through reduction in oxidative stress and improved nitric oxide bioavailability [46,48].

SGLT2 inhibitors have decisively moved from metabolic adjuncts to core cardiovascular therapeutics. Their ability to reduce heart failure hospitalizations, slow renal function decline, and improve survival in both HFrEF and HFpEF, regardless of glycemic status, positions them as one of the most significant pharmacologic advancements in contemporary cardiovascular medicine.

Renal Outcomes of SGLT2 Inhibitors.

Beyond their cardiovascular benefits, SGLT2 inhibitors have demonstrated remarkable nephroprotective effects in both diabetic and non-diabetic populations. These effects, originally observed as secondary outcomes in cardiovascular outcome trials, have since been confirmed in dedicated renal studies and have reshaped the management of chronic kidney disease (CKD).

Early Signals from Cardiovascular Trials: In the EMPA-REG OUTCOME trial, empagliflozin significantly slowed the progression of kidney disease, as evidenced by a 39% relative risk reduction in incident or worsening nephropathy [8]. Similarly, in the CANVAS Program, canagliflozin reduced the risk of sustained albuminuria progression and improved renal composite endpoints [9]. The DECLARE–TIMI 58 trial also reported a 47% reduction in a renal composite outcome with dapagliflozin [10].

These consistent renal findings across CVOTs suggested a class effect and motivated the initiation of trials specifically designed to assess renal outcomes.

Dedicated Renal Outcome Trials: The CREDENCE trial was the first renal outcome trial to prospectively evaluate SGLT2 inhibition in patients with type 2 diabetes and CKD. Canagliflozin reduced the risk of the composite endpoint of end-stage kidney disease (ESKD), doubling of serum creatinine, or renal/cardiovascular death by 30% compared to placebo [14].

Following this, the DAPA-CKD trial extended the benefit to patients with and without diabetes. Dapagliflozin reduced the risk of the primary composite outcome (≥50% eGFR decline, ESKD, or renal/CV death) by 39%, with consistent benefit in both diabetic and non-diabetic subgroups [15].

More recently, the EMPA-KIDNEY trial evaluated empagliflozin in a broader CKD population (including non-diabetics with lower eGFR and albuminuria) and demonstrated a 28% relative risk reduction in the primary outcome [16].

Collectively, these trials confirmed that SGLT2 inhibitors

are nephroprotective regardless of diabetes status, prompting guideline bodies to recommend their use in CKD management.

Pathophysiologic Basis for Renoprotection.

The renal benefits of SGLT2 inhibitors are attributed to several interrelated mechanisms:

1. Reduction of intraglomerular hypertension via restoration of tubuloglomerular feedback through increased sodium delivery to the macula densa [33,34,54].
2. Mitigation of glomerular hyperfiltration, which slows nephron damage over time.
3. Attenuation of renal hypoxia and oxidative stress, reducing inflammation and fibrosis in tubular and interstitial compartments [55,56].
4. Reduction in albuminuria, reflecting improved glomerular barrier function [15,16].
5. Slower decline in eGFR with a characteristic initial "dip" followed by long-term preservation – a pattern now recognized as beneficial [31,54].

Additionally, SGLT2i lower uric acid levels, reduce renal tubular workload, and may preserve mitochondrial function, enhancing cellular resilience [37,55].

Clinical Implications and Guidelines.

On the basis of robust clinical trial evidence, multiple international societies have now endorsed the use of SGLT2 inhibitors in CKD:

• KDIGO 2022 guidelines recommend SGLT2i as first-line therapy in patients with T2DM and CKD with eGFR ≥20 mL/min/1.73m², regardless of glycemic control [26].

• ADA Standards of Care and ESC guidelines also highlight their use for slowing CKD progression and reducing CV risk in patients with albuminuric CKD [24,25].

• Real-world data continue to confirm the safety and effectiveness of SGLT2 inhibitors in routine nephrology practice [57].

Their renal benefits are now considered independent of HbA1c reduction, positioning SGLT2 inhibitors as first-in-class nephroprotective agents rather than merely antidiabetic drugs.

Expanding Indications and Unanswered Questions.

Ongoing trials are exploring the potential of SGLT2 inhibitors in:

1. Glomerulonephritides (e.g., IgA nephropathy).
2. Polycystic kidney disease.
3. And even acute kidney injury prevention in surgical or septic contexts [58].

While the initial eGFR drop remains a source of concern for some clinicians, long-term follow-up has consistently shown sustained benefit and low rates of adverse renal events, including hyperkalemia and acute kidney injury [31,59].

Still, open questions remain regarding:

1. Optimal timing of initiation in early-stage CKD.
2. Use in combination with finerenone and other renin-angiotensin system blockers.
3. And efficacy in non-proteinuric renal phenotypes.

The consistent, substantial, and durable renal benefits of SGLT2 inhibitors mark one of the most important therapeutic advancements in nephrology over the past two decades. Their ability to slow eGFR decline, reduce progression to ESKD, and decrease cardiovascular risk has established SGLT2 inhibitors as essential agents in the care of patients with chronic kidney disease – irrespective of diabetes status.

Safety and Adverse Effects of SGLT2 Inhibitors.

While SGLT2 inhibitors are generally well tolerated and possess an excellent benefit-risk profile, they are associated with several class-specific adverse events. Awareness of these effects is crucial for appropriate patient selection, counselling, and monitoring.

Genitourinary Infections: The most frequently reported adverse effects are genital mycotic infections, particularly in women. The mechanism involves glucosuria-induced alterations in the urogenital microbiome and pH, which favor Candida overgrowth [60].

The incidence of vulvovaginal candidiasis ranges from 4-10% in clinical trials, and may be higher in real-world settings [60,61]. In uncircumcised men, balanitis is more common. These infections are typically mild to moderate, respond to topical or oral antifungals, and rarely require discontinuation.

Urinary tract infections (UTIs) may also occur but were not significantly increased in most meta-analyses [62].

Euglycemic Diabetic Ketoacidosis (euDKA): A rare but serious adverse event is euglycemic diabetic ketoacidosis, particularly in:

1. Patients with insulin deficiency (e.g., T1DM or latent autoimmune diabetes).
2. Prolonged fasting.
3. Surgery or severe illness [63].

Clinical features include nausea, abdominal pain, and high anion gap acidosis with near-normal glucose levels. Diagnosis can be delayed due to the absence of marked hyperglycemia.

1. Incidence is low (<0.1–0.2% in most studies) but higher in off-label use for type 1 diabetes [64].
2. Patient education, temporary discontinuation during acute illness ("sick-day rules"), and avoidance in at-risk populations are critical for prevention.

Volume Depletion and Hypotension: Due to their mild diuretic effect, SGLT2 inhibitors can cause:

1. Orthostatic hypotension,
2. Dizziness,
3. Volume depletion, especially in elderly or those on loop diuretics [29,30,65].

Although generally well tolerated, volume-related adverse events may require:

1. Dose reduction of concomitant antihypertensives,
2. Increased fluid intake in selected patients,
3. Monitoring blood pressure in frail individuals or those with autonomic dysfunction.

Acute Kidney Injury (AKI): Initial concerns about AKI have been largely mitigated by real-world evidence and pooled analyses from major trials:

1. AKI is not more frequent with SGLT2 inhibitors compared to placebo [59,66].
2. In fact, some studies show reduced incidence of AKI, likely due to improved renal hemodynamics and reduced hypoxic stress [66].

The initial dip in eGFR, typically observed within 2-4 weeks, reflects hemodynamic changes and is not indicative of renal damage [54].

Lower Limb Amputation and Bone Fracture Risk: The CANVAS Program raised concern about increased amputation risk (primarily at the toe or midfoot) with canagliflozin [9], leading to an FDA boxed warning (since removed in 2020).

1. No significant increase in amputations has been observed with other agents (dapagliflozin, empagliflozin) or in subsequent trials [67].
2. Risk appears to be agent-specific and patient-dependent, particularly in those with active ulcers, peripheral arterial disease, or previous amputation.

Similarly, increased fracture risk was initially noted with canagliflozin but not replicated in other large trials.

Other Considerations:

• Fournier's gangrene (necrotizing fasciitis of the perineum) has been reported in rare cases, mostly in patients with multiple risk factors. While causality is unclear, patients should be advised to seek immediate medical attention for genital pain or swelling [63].

• Lipid profile: slight increase in LDL-C has been observed but without significant impact on cardiovascular outcomes [29].

• Pregnancy and breastfeeding: SGLT2 inhibitors are contraindicated due to lack of safety data and potential risks during renal development in the fetus [60].

Overall, SGLT2 inhibitors exhibit a favorable safety profile, with most adverse events being mild, preventable, or manageable. When used appropriately and with adequate patient education, the risk-benefit ratio of these agents is overwhelmingly positive, particularly given their ability to reduce mortality and organ failure across multiple systems.

Clinical Use and Recommendations: Who, When, and How?

Based on robust evidence from multiple large-scale trials, SGLT2 inhibitors have earned a place in the standard of care for patients across a spectrum of diseases, including type 2 diabetes (T2DM), heart failure (HF), and chronic kidney disease (CKD). International guidelines now emphasize early initiation of these agents – often regardless of glycemic status.

Patient Populations That Benefit:

1. Patients with T2DM and Atherosclerotic Cardiovascular Disease (ASCVD).

SGLT2 inhibitors are recommended in patients with established ASCVD to reduce cardiovascular events and mortality, independent of baseline HbA1c or metformin use [24,25,68].

2. Patients with Heart Failure (HFrEF and HFpEF).

As supported by DAPA-HF, EMPEROR-Reduced, DELIVER, and EMPEROR-Preserved, SGLT2 inhibitors improve outcomes in:

• HFrEF: Class I indication, with or without diabetes [12,13].

• HFpEF: Class IIa (ESC, AHA/ACC/HFSA) [49,50].

3. Patients with CKD.

Indicated for patients with:

• eGFR ≥20 mL/min/1.73 m², especially if albuminuria ≥30 mg/g.

• Diabetic and non-diabetic CKD [15,16,26,69].

Contraindications and Cautions.

Contraindications include:

1. Type 1 diabetes (except in research settings due to DKA risk).
2. Pregnancy and lactation.
3. Active DKA or serious illness with reduced oral intake [64,70].

Caution is advised in:

1. Frail elderly with orthostatic hypotension.
2. Those on loop diuretics.
3. Patients with recurrent genital infections.

Temporary interruption is recommended during:

1. Acute illness.
2. Surgery.
3. Volume depletion (to prevent AKI or ketoacidosis) [64,70].

Initiation and Monitoring Strategy:

Before Starting	Ongoing Monitoring
Check eGFR (>20–25)	eGFR every 3–6 months
Screen for mycotic infections	Monitor volume status and blood pressure
Educate on "sick day" rules	Watch for DKA symptoms (especially if low-carb)

Doses are fixed per agent (e.g., empagliflozin 10 mg, dapagliflozin 10 mg daily), with no titration needed. Most can be used without dose reduction unless eGFR falls below threshold.

Combining with Other Medications:

1. Metformin: fully compatible; often used together in initial therapy [24].
2. ACEi/ARBs: synergistic for renal protection.
3. GLP-1 RAs: complementary; combination reduces both ASCVD and progression of CKD [71].
4. Diuretics: monitor volume status – may need to reduce loop dose.
5. Mineralocorticoid receptor antagonists (MRAs): combination with finerenone is being studied; early data promising [72].

Algorithmic Implementation in Practice: Multiple guidelines provide stepwise algorithms. In summary:

1. For T2DM + ASCVD / HF / CKD → Initiate SGLT2i as early as possible.
2. For HF (regardless of diabetes) → Part of quadruple therapy (with BB, ACEi/ARNI, MRA) [27].
3. For CKD → Initiate when eGFR ≥20 and albuminuria present; continue until dialysis or transplant considered.

Real-world implementation remains suboptimal, with <50% of eligible patients receiving therapy due to therapeutic inertia, cost, or lack of awareness [73].

SGLT2 inhibitors are no longer just glucose-lowering drugs – they are disease-modifying agents that improve survival, delay organ failure, and reduce hospitalizations. Their timely integration into clinical practice, across disciplines, represents a critical shift toward organ-protective pharmacotherapy in modern medicine.

Future Directions and Conclusions.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have

revolutionized the treatment of cardiovascular and renal diseases, particularly in patients with type 2 diabetes. However, while their benefits are now well-established in heart failure, chronic kidney disease, and diabetes management, several key areas remain for future investigation. Ongoing studies will likely expand the use of SGLT2 inhibitors to broader patient populations and clarify their full range of therapeutic potentials.

Expanding Indications: Beyond Diabetes and Heart Failure.

SGLT2 inhibitors are currently prescribed primarily for patients with type 2 diabetes, heart failure, and chronic kidney disease. However, several other indications are under investigation:

• Type 1 Diabetes (T1DM): Although SGLT2 inhibitors are contraindicated in T1DM due to the risk of euglycemic diabetic ketoacidosis (DKA), there is growing interest in their potential role in T1DM management, particularly as adjuncts to insulin therapy for improving glycemic control and weight loss.

• Non-diabetic Kidney Disease: Early studies suggest that SGLT2 inhibitors may benefit patients with non-diabetic CKD, including those with IgA nephropathy, lupus nephritis, and polycystic kidney disease. Ongoing trials like EMPA-KIDNEY are assessing the benefits of SGLT2 inhibitors in these populations [16].

• Acute Kidney Injury (AKI): Preclinical data suggest that SGLT2 inhibitors may have a protective effect in the setting of acute kidney injury, particularly in surgical or septic settings, by reducing inflammation and preserving renal perfusion.

Understanding the Mechanisms of Action.

Although the hemodynamic effects of SGLT2 inhibitors are well-documented, their full mechanistic profile remains incompletely understood. Future research should aim to:

1. Further elucidate the cardiometabolic effects of SGLT2 inhibition, particularly regarding mitochondrial function, inflammation, and endothelial dysfunction [39,40].

2. Investigate the role of ketone bodies in myocardial energy metabolism, particularly in heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) [36].

3. Examine the long-term impact of SGLT2 inhibitors on fibrosis and myocardial remodeling, as well as their potential in treating heart diseases with extensive fibrosis such as restrictive cardiomyopathies.

Personalized Therapy and Biomarkers.

Given the broad range of effects of SGLT2 inhibitors, further studies are required to:

• Identify biomarkers that predict individual patient responses to therapy. For example, genetic markers or biomarkers of fibrosis, inflammation, or renal function could help identify patients most likely to benefit from SGLT2 inhibitors.

• Explore personalized dosing regimens based on kidney function, comorbidities, and genetic predisposition to side effects such as genital infections and hypotension.

• Investigate the role of SGLT2 inhibitors in combination with other novel therapies (e.g., GLP-1 receptor agonists, finerenone) for more tailored treatment of heart failure and CKD [72,73].

Addressing Safety Concerns.

While the safety profile of SGLT2 inhibitors is favorable, adverse effects such as euglycemic DKA, genital infections, and volume depletion still require vigilance. Future research should focus on:

• Further investigating the long-term safety of SGLT2 inhibitors, especially in patients with multiple comorbidities or those who are frail and elderly.

• Developing strategies for minimizing the risk of DKA, including improving patient education, refining diagnostic criteria, and exploring adjunctive treatments to prevent the condition.

• Evaluating the risk-benefit ratio in more diverse populations, including those with non-proteinuric CKD, severe renal impairment, and diabetic ketoacidosis risk.

Exploring New Mechanisms and Drug Combinations.

As the understanding of SGLT2 inhibitors deepens, their application in combination therapy with other agents (such as SGLT1/2 inhibitors, GLP-1 receptor agonists, or PCKS9 inhibitors) may offer synergistic benefits in treating cardiovascular, renal, and metabolic diseases. Furthermore:

• The use of dual SGLT1/2 inhibitors (e.g., sotagliflozin) could provide enhanced glucose-lowering effects, and early studies suggest they may confer additional benefits for patients with more severe forms of diabetes and heart failure.

• There is also growing interest in the role of SGLT2 inhibitors in autophagy and mitochondrial dysfunction, especially in aging populations and those with neurodegenerative diseases.

Conclusion: A Transformative Therapy with Expanding Potential.

SGLT2 inhibitors have already proven themselves as game-changing therapeutics for diabetes, heart failure, and chronic kidney disease. Their organ-protective effects – beyond glucose control – have established them as a cornerstone of modern medical treatment. As clinical evidence continues to grow, these agents will likely play an increasingly important role in treating a wider range of diseases and improving long-term patient outcomes.

SGLT2 inhibitors offer more than just glucose control – they provide cardioprotective, nephroprotective, and metabolic benefits, positioning them as multi-organ protective agents.

Future research will likely expand their use to other conditions, such as acute kidney injury and non-diabetic CKD, and improve personalized treatment approaches.

Safety concerns (e.g., DKA, genital infections) remain, but careful patient management and education can mitigate most risks.

Combination therapies (SGLT1/2 inhibitors, GLP-1 RAs) may offer even greater benefits in treating complex cardiometabolic diseases.

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