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Commentary

Sodium-Glucose Co-Transporter 2 Inhibitors as a Powerful Cardioprotective and Renoprotective Tool: Overview of Clinical Trials and Mechanisms

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Abstract: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been linked to beneficial effects on cardiovascular risk factors, blood pressure, body weight, and lipid profile, according to a substantial body of literature. Significant cardiac and renal benefits with the use of SGLT2 inhibitors have been shown in patients with type 2 diabetes, as well as in those with heart failure and/or chronic kidney disease (CKD), regardless of diabetes status, in subsequent large cardiovascular outcome trials. Thus, SGLT2 inhibitors have become a mainstay of therapy for type 2 diabetes in patients with established cardiovascular disease and CKD due to their benefits for the heart and kidneys. Based on data from randomized controlled trials and meta-analyses, this article attempts to present a thorough review of the mechanism of action, as well as the benefits of SGLT2 inhibitors for cardiac and renal protection. On the basis of a growing body of literature on diabetes and other conditions, clinical practice guidelines have been updated to suggest the use of SGLT2 inhibitors in specific patient populations. These modifications will also be concisely described, based on evidence-based medicine principles.

Keywords: antidiabetic; antihyperglycemic; cardioprotection; cardiovascular outcome trial; clinical trials; diabetes; pharmacology; renal outcomes; renoprotection; sodium-glucose co-transporter 2 inhibitors

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1. Introduction

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are the latest class of antihyperglycemic drugs for the treatment of type 2 diabetes mellitus. Four SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin) are currently authorized in the European Union and are available on the market as monocomponent drugs or in combination with metformin or dipeptidyl peptidase 4 inhibitors [1,2]. SGLT2 inhibition reduces glucose reabsorption from glomerular filtrate in the proximal renal tubule and at the same time sodium reabsorption, ultimately achieving glycosuria (and consequently, regulation of fasting and postprandial glycemia), natriuresis, and osmotic diuresis. It should be noted that the amount of glucose that the kidney eliminates by this glucose mechanism is dependent on the concentration of glucose in the blood and on the rate of glomerular filtration (GFR). Furthermore, increased delivery of sodium to the distal tubule increases tubuloglomerular feedback and reduces intraglomerular pressure, which in combination with osmotic diuresis consequently leads to a decrease in preload and afterload, and thus, among other things, has beneficial effects on cardiac remodeling and preservation of renal function [2–4].

SGLT2i has shown good efficacy and tolerability in the treatment of people with type 2 diabetes mellitus, regardless of the duration of the disease and the function of

β-cells of Langerhans islets. According to meta-analyses of clinical studies, the use of SGLT2 inhibitors achieves a noticeable effect on the regulation of fasting and postprandial glycemia, with an average decrease in glycated haemoglobin (HbA1c) of about 0.5–1%, without increasing the risk of hypoglycemia. This group of drugs generally has a good safety profile, and the most common side effects (urinary tract infections, vulvovaginal candidiasis, polyuria, polakysuria) are precisely the product of the basic pharmacological glycosuric effect. A rare but serious adverse reaction that may occur during treatment with SGLT2 inhibitors is (euglycemic) ketoacidosis, the mechanism of which has not yet been fully understood, but it is known to occur more frequently in type 1 diabetes mellitus patients (which is why dapagliflozin recently abolished the indication for type 1 diabetes mellitus). According to meta-analytic data, no significant differences in safety profile between different SGLT2 inhibitor agents were shown generally [5]. Other beneficial effects of SGLT2 inhibition, in addition to the basic glycemic effects, are cardioprotection, renoprotection, and antiobesogenic effect (loss of energy/calories and reduction in body weight $\approx$ 2 kg) [6–9].

Based on data from randomized controlled trials and meta-analyses, this article attempts to present a thorough review of the mechanism of action, as well as the benefits of SGLT2 inhibitors for cardiac and renal protection. Clinical practice guidelines have been updated to suggest the use of SGLT2 inhibitors in specific patient populations regardless of diabetes status. Thus, these modifications will also be concisely described, based on evidence-based medicine principles.

2. Cardiovascular and Renal Events in the Setting of Type 2 Diabetes Mellitus Clinical Trials

Encouraged by the adverse cardiovascular effects of rosiglitazone, the Food and Drug Administration (FDA) since 2008 and the European Medicines Agency (EMA) since 2012, in addition to the standard evidence of antihyperglycemic efficacy and safety, require evidence from randomized double-blind placebo-controlled clinical studies on the effect of the antihyperglycemic agent on cardiovascular outcomes (CV Outcome Trial; CVOT). The primary outcome measure of the latter studies is the time until the first occurrence of a major adverse cardiovascular event (MACE, which is a composite of death due to cardiovascular cause, myocardial infarction, or ischemic stroke) [10]. To highlight, valid conclusions can be drawn from studies solely on the basis of primary outcomes (e.g., MACE here), while this should not be done on the basis of secondary outcomes (which are exclusively affirmative) due to insufficient statistical strength. In addition to the primary MACE outcomes, this paragraph will also present isolated secondary renal outcomes and outcomes for heart failure (HF) of some conducted CVOTs purely because they have hinted towards the renoprotective effects of SGLT2i and beneficial effects on chronic heart failure and thus set the need to conduct further targeted trials primarily designed to demonstrate the effectiveness of some representatives in these indications [11–13].

The EMPA-REG OUTCOME study (n = 7020; median follow-up of 3.1 years) demonstrated a 14% relative reduction in MACE in subjects receiving empagliflozin (HR (hazard ratio) 0.86, 95% CI (confidence interval) 0.74–0.99; $p = 0.04$ for superiority). Empagliflozin reduced the risk of heart failure that would require hospitalization compared to placebo (2.7% vs. 4.1%, HR 0.65, 95% CI 0.50–0.85; $p = 0.002$; the secondary outcome). Furthermore, the investigational drug hinted towards possible beneficial effects in terms of slowing down the rate of eGFR reduction, given the results obtained in terms of secondary MARE outcomes (doubling of serum creatinine levels with eGFR $\leq$ 45, initiation of renal function replacement or death due to renal cause)—HR 0.54, 95% CI 0.40–0.75, $p \leq 0.001$ [14]. Canagliflozin demonstrated superiority (HR 0.86, 95% CI 0.75–0.97, $p = 0.02$ for superiority) over placebo in the MACE reduction in the CANVAS study (n = 10,142, median follow-up of 2.4 years). In terms of secondary outcomes, the group of subjects who received canagliflozin had a significantly lower risk of heart failure that would require hospitalization (HR 0.67, 95% CI 0.52–0.87), and some renal benefit was already suggested [15]. The

latter was later confirmed in CREDENCE, a double-blind, randomized, placebo-controlled study, involving patients with an eGFR of 30–90 and albuminuria (albumin/creatinine 300–5000 mg/g) who had concomitant medicamentous blockade of the renin–angiotensin system. The primary outcome was composite, and it consisted of the terminal stage of CKD (dialysis, kidney transplantation, eGFR < 15), doubling the values of serum creatinine, or death due to renal or cardiovascular cause. The study was completed earlier (median follow-up 2.6 years; 4401 subjects randomized), since the planned interim analysis verified a 30% relative reduction in this MARCE composite outcome (HR 0.70, 95% CI 0.59–0.82, $p = 0.00001$) [16]. Furthermore, in the DECLARE-TIMI 58 study (n = 17,160, median follow-up for 4.2 years), a non-inferiority of dapagliflozin to placebo in terms of MACE reduction (HR 0.93, 95% CI 0.84–1.03), as well as superiority in terms of co-primary composite outcome resulting from cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%, HR 0.83, 95% CI 0.73–0.95; $p = 0.005$; primarily at the expense of heart failure outcome HR 0.73, 95% CI 0.61–0.88) were detected. Among the secondary outcomes of this study was MARCE composite outcome (40% reduction in eGFR with its value < 60, progression to the terminal stage of CKD including the need for renal function replacement, or death due to renal or cardiovascular cause), where its 47% relative reduction was achieved along with dapagliflozin (HR 0.53, 95% CI 0.43–0.66, $p < 0.001$) [17]. Finally, ertugliflozin in the VERTIS CV study (n = 8246, median follow-up of 3.5 years) proved to be exclusively non-inferior to placebo in terms of MACE reduction (HR 0.97, 95% CI 0.85–1.11, $p < 0.001$ for non-inferiority). Among secondary outcomes, HR for hospitalization for heart failure was 0.70 (95% CI 0.54–0.90), while for MARE it was 0.81 (95% CI 0.63–1.04) [18].

Given the surprisingly favorable cardiovascular and renal benefits of individual SGLT2i representatives, further targeted clinical trials on the effectiveness of SGLT2 inhibition in chronic heart failure and chronic kidney disease (CKD) were conducted. Thus, in recent years, we are able to prescribe dapagliflozin for the treatment of HF with reduced ejection fraction (HFrEF) and CKD and empagliflozin for the treatment of HFrEF, HF with mildly reduced EF (HFmrEF), and HF with preserved EF (HFpEF), both regardless of the existence of type 2 diabetes mellitus.

3. Cardioprotective Effects and Mechanisms of SGLT2 Inhibitors

Cardioprotective effects of SGLT2 inhibition are associated with (i) reduction in preload (natriuresis, osmotic diuresis) and afterload (reduction in blood pressure, improvement of vascular function), which consequently carries favorable effects on cardiac remodeling, (ii) improvement of cardiac metabolism and bioenergetics, (iii) inhibition of myocardial Na+/H+ exchange, (iv) reduction in cardiac fibrosis and necrosis, and (v) alteration of the production of adipokines, cytokines, and the amount of epicardial adipose tissue. Certainly, in addition to the above, the overall cardioprotection is indirectly (secondarily) contributed by the associated antiobesogenic effect, reduction in blood pressure, reduction in stiffness of the arteries, as well as better regulation of glycemia [19–21].

Dapagliflozin demonstrated efficacy and safety in the treatment of HFrEF ($\leq$40%) in the DAPA-HF clinical study. It was a double-blind randomized placebo-controlled clinical study that involved 4744 patients with HFrEF ($\leq$40%) and NYHA (New York Heart Association) stage II–IV, with or without diabetes. After 1.5 years of follow-up, a 26% relative reduction with dapagliflozin at a dose of 10 mg per os/day was achieved in terms of primary composite outcome (death from cardiovascular cause or worsening of heart failure—hospitalization for heart failure or visit to the emergency tract due to the need for parenteral diuretic therapy)—HF 0.74, 95% CI 0.65–0.85, $p < 0.001$. The latter benefit was demonstrated in both patients with (n = 2139) and without (n = 2605) diabetes mellitus, and the safety profile was congruent with that previously known from clinical studies with dapagliflozin for type 2 diabetes [22]. Furthermore, the EMPEROR-Reduced clinical study proved the efficacy and safety of empagliflozin (10 mg/day per os) in the treatment of HFrEF. There were 3730 randomized subjects (1:1) who were followed for 1.3 years; subjects receiving empagliflozin had a 25% relative reduction in

primary composite outcome (death from cardiovascular cause or hospitalization due to heart failure)—HR 0.75, 95% CI 0.65–0.86, $p < 0.001$. The analysis of the subgroups again proved that this benefit is evident in both subjects with (n = 1856) and without (n = 1874) diabetes mellitus [23]. Consequently, the SGLT-2 inhibitor (empagliflozin or dapaglifozin at a dose of 10 mg per os/day) was included in the recent guidelines of the European Society of Cardiology for the treatment of HFrEF with the aim of reducing the risk of hospitalization and cardiovascular mortality—recommendation Ia [24].

In the double-blind placebo-controlled EMPEROR-Preserved study (n = 5988, median follow-up of 26.2 months), empagliflozin also showed potential in the treatment of HF with ejection fraction >40%. It achieved a 21% relative reduction in terms of primary composite outcome consisting of death from cardiovascular cause or hospitalization for heart failure—HR 0.79, 95% CI 0.69–0.90, $p < 0.001$, and mostly at the expense of reducing the risk of hospitalization due to heart failure (27% relative reduction) [25]. It should be noted that further clinical studies (e.g., DELIVER study) are still being conducted to assess the effectiveness of SGLT2 inhibition in HF with a medium range of ejection fraction (mrEF; 41–49%) and with preserved ejection fraction (pEF; ≥50%), in order to achieve an even stronger body of evidence for SGLT2i prescription in this indication. For instance, in the DELIVER study (n = 6264), dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction by 18%—HR 0.82, 95% CI 0.73–0.92, $p < 0.001$ [26].

Finally, according to recent relevant meta-analytic data, SGLT2i reduced the risk of cardiovascular death and hospitalizations for HF in a broad range of patients with HF, irrespective of ejection fraction or care setting [27].

Last but not least, it would be useful in further randomized clinical studies to separately evaluate the effectiveness of SGLT2 inhibition in patients with medium range and those with preserved ejection fraction, given the different pathophysiological bases and clinical determinants HFmrEF and HFpEF.

4. Renoprotective Effects and Mechanisms of SGLT2 Inhibitors

The mechanism of renoprotection of SGLT2 inhibitors has not yet been fully understood. However, one of the most important renoprotective mechanisms is the restoration of tubuloglomerular feedback by increasing the delivery of sodium to the distal tubule (macula densa), i.e., the consequent constriction of the afferent arteriole and the reduction in glomerular hyperfiltration. The second proposed mechanism is actually related to the latter because it is a decrease in the degree of activity of the renal renin–angiotensin–aldosterone system, which also contributes to the reduction in glomerular hyperfiltration, i.e., intraglomerular pressure. Other possible secondary mechanisms mentioned in the literature are (i) a slightly more pronounced production of ketone bodies (β-hydroxy butyrate), which are then used as an alternative fuel for the production of adenosine triphosphate in mitochondria and thus help the attenuation of inflammation, and (ii) the effect of protection against hypoxia, oxidative stress, and fibrosis (extensively presented elsewhere [28,29]).

In the DAPA-CKD study, 4304 subjects with chronic kidney disease (eGFR 25–75 and albuminuria—albumin/creatinine ratio of 200–5000 mg/g) were randomized to receive dapagliflozin at a dose of 10 mg or placebo, on top of concomitant medicamentous blockade of the renin–angiotensin system. The median follow-up was 2.4 years, and the primary MARCE composite outcome of the study included a sustained reduction in eGFR by ≥50%, end-stage renal disease (chronic dialysis, kidney transplantation, eGFR < 15), or death due to cardiovascular or renal cause. Subjects receiving dapagliflozin achieved a 39% relative reduction in terms of primary MARCE outcome (HR 0.61, 95% CI 0.51–0.72, $p < 0.001$). All four components of the primary unified outcome measure individually contributed to this therapeutic effect, and the benefit was present in patients with and without diabetes [30]. In the randomized, double-blind, placebo-controlled EMPA-KIDNEY trial, patients' responses to empagliflozin were assessed in two groups: those with GFRs of 20 to 45 and any albumin-to-creatinine ratio, and those with GFRs of 45 to 90 and at least

200 ACR. The study randomized 6609 patients to either empagliflozin 10 mg once daily or placebo. When compared to the placebo group, those who were taking empagliflozin had significantly lower rates of CKD development and mortality from CV causes at the 2-year median follow-up (13.1% vs. 16.9%, respectively; HR 0.72 [0.64 to 0.82], $p = 0.001$). These findings persisted across all CKD levels and among patients with and without diabetes [31].

Finally, recent meta-analytic data of randomized controlled trials support their use for modifying risk of kidney disease progression and acute kidney injury, not only in patients with type 2 diabetes at high cardiovascular risk, but also in patients with chronic kidney disease or heart failure irrespective of diabetes status, primary kidney disease, or kidney function [32].

5. Brief Discussion on Existing Challenges and Gaps in the Research and Application of SGLT2 Inhibitors

Despite the undeniable cardiorenal clinical benefit of SGLT2i, a notable percentage of non-diabetic patients with HF or CKD still do not receive these medications. Some physicians still reference them exclusively as antihyperglycemic or "diabetes" drugs. The latter may be due to various barriers and limitations such as clinical inertia, lack of familiarity of physicians with the evidence-based practice and current guidelines, non-promotion of cross-disciplinarity, cost, availability, etc. [33,34]

It would be important to directly identify and investigate the relative importance of each factor in prescribing practices. A collaborative multidisciplinary effort at the local, national, and international levels should be undertaken to address and resolve clinical inertia by doing the following: (i) identifying barriers and practices to change; (ii) improving knowledge of how to weigh risks and benefits on a case-by-case basis (phenotype principle); (iii) advocating for post-CVOT treatment pathways; (iv) advocating for local guidelines and collaborating on local educational initiatives; (v) fostering interdisciplinary collaboration; (vi) educating and updating reimbursement authorities on new clinical data; (vi) helping patients understand the benefits and goals of cardiorenal protection; and (vii) measuring the performance of individual clinicians to provide feedback and incentivize change [35].

It is of interest to understand which patients (phenotype influence) benefit most from the cardiorenal protection provided by SGLT2 inhibitor therapy, independent of diabetes status or glycemic control.

Another issue that future research should address is the question of (non)discontinuation of SGLT2i after the episode of euglycemic diabetic ketoacidosis on a case-by-case basis, taking into account the recent evidence on mortality reduction, cardiac and renal protection, etc. [36]

In addition, continued patient monitoring (both for effectiveness and safety profile) and longer-term real-world clinical data collection on SGLT2 inhibition in different comorbidities, as well as head-to-head comparisons between different SGLT2 inhibitors and with different treatment modalities of proven benefit, are extremely important [37]. This is even more important from the perspective of patient groups that are generally underrepresented in clinical trials (e.g., older adults) and for whom relevant secondary outcomes (e.g., functional status and quality of life) were not included in the study design [38].

To evaluate the effects of SGLT2i drugs on glomerular disorders, reduced eGFR, non-proteinuric CKD, dialysis and transplant populations, HFmrEF and HFpEF, and other diseases, the results of upcoming studies are eagerly awaited.

6. Conclusions

SGLT2 inhibitors, in addition to their already known antihyperglycemic and antiobesogenic effects, have been shown to be beneficial in terms of cardioprotection, renal protection, and thus, more recently, as a valuable form of therapy in chronic heart failure and chronic kidney disease, regardless of the presence of diabetes. Thus, SGLT2 inhibitors are becoming an increasingly valued medical resource in the field of endocrinology, cardiology, and nephrology. For this reason, it is very important to improve the knowledge of physicians of all specialties about this promising group of drugs so that they can be better integrated

into clinical practice in all indications for which they have shown indisputable benefits in randomized clinical trials.

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Abbreviations

CI	confidence interval
CKD	chronic kidney disease
CVOT	cardiovascular outcomes trial
GFR	glomerular filtration
HbA1c	glycated hemoglobin
HF	heart failure
HR	hazard ratio
mrEF	mildly reduced ejection fraction
NYHA	New York Hear Association
pEF	preserved ejection fraction
rEF	reduced ejection fraction
SGLT2i	Sodium-glucose co-transporter 2 inhibitors

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