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Dapagliflozin — a breakthrough in the treatment of chronic kidney disease from the perspective of the DAPA-CKD study

ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors (gliflozins) are a new group of oral antidiabetic drugs which inhibit the sodium-glucose co-transporter within the proximal tubules in the kidneys, resulting in increased excretion of glucose and sodium in the urine. This class of drugs had been initially designed to treat type 2 diabetes, but large clinical studies showed that, in addition to the antidiabetic effect, they may provide strong organ protection including potent inhibition of the progression of cardiovascular and kidney diseases. The favorable safety profile of gliflozins was also confirmed in these studies. These initial observations led to the initiation of clinical studies focused on nephroprotection as the primary endpoint. Recently, the seminal DAPA-CKD study was published which showed that dapagliflozin maintained a potent nephroprotective effect not only in patients with diabetic but also with non-diabetic kidney disease. As a result, SGLT2 inhibitors have become a new essential add-on to kidney protection therapy previously based on the inhibition of the renin-angiotensin-aldosterone system. Dapagliflozin has become the first SGLT2 inhibitor that received an extended registration indication to include not only diabetic but also non-diabetic patients with nephropathies and patients with advanced chronic renal disease. However, the awareness of the nephroprotective properties of gliflozins needs to be increased among nephrologists so that the drugs are more often recommended in patients with kidney disease regardless of the concomitance of diabetes, especially in the presence of increased albuminuria and already impaired excretory function of the kidneys.

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Key words: SGLT2 inhibitors, chronic kidney disease, diabetic nephropathy, nephroprotection, kidney glomerular diseases

INTRODUCTION

In addition to atherosclerotic cardiovascular diseases, endemic diseases of modern civilization include hypertension, chronic kidney disease, and type 2 diabetes. The prevalence of these diseases has increased over recent decades in most regions of the world while stabilizing only in some developed countries. Chronic kidney disease (CKD) is the second most common civilization-related disease after arterial hypertension. Type 2 diabetes is the most common cause of CKD and is responsible for approximately one-half of CKD cases. Chronic kidney disease develops in 11 to 15% of adults, and its incidence rates increase rapidly with age [1].

In many patients, civilization diseases develop in a comorbid fashion, having an additive adverse effect on overall health, the incidence of major cardiovascular events, and life expectancy. However, the most important feature of civilization-related diseases consists in their dependence on lifestyle changes, in particular the use of stimulants, obesity, and poor (unhealthy) nutrition. This information clearly shows that prevention and treatment of civilization-related diseases aimed at stopping or slowing down disease progression must be a multi-directional approach that goes beyond mere pharmacotherapy. However, the latter becomes necessary in a vast majority of people with a diagnosed disease.

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Pharmacological management of civilization diseases has evolved considerably in recent decades, the progress being particularly rapid in the treatment of type 2 diabetes [2]. New groups of medications have been introduced whose long-term efficacy and safety have been demonstrated in clinical trials. New groups of antidiabetic drugs that have already made their way to conventional pharmacotherapy of diabetes include incretin drugs, i.e. the inhibitors of dipeptidyl peptidase 4 (DPP4), agonists of glucagon-like peptide 1 (GLP-1), and the most recent (gli)flozins, aka sodium-glucose co-transporter 2 (SGLT2) inhibitors [2]. A significant share of these drugs (including all DPP4 inhibitors) and SGLT2 inhibitors are administered orally, thus increasing the patient's comfort. While incretin-based medications exert their efficacy via the long-known "incretin effect", the rationale for the use of SGLT2 inhibitors is based on the complex mechanisms of glucose transport within the renal tubules as discovered in more recent studies. SGLT2 inhibitors exert their efficacy within the proximal renal tubules by preventing glucose from becoming reabsorbed from the filtrate and facilitating its urinary excretion. As glucose is excreted, its plasma concentration is reduced leading to an improvement in all glycemic parameters. SGLT2 inhibitors increase glucose secretion while simultaneously blocking sodium transport; the excretion of the sodium cation is also increased, probably leading to some additional benefits of using these drugs (reduced arterial blood pressure and reduced systemic retention of sodium). Yet another effect of increased glucose excretion consists in the loss of a larger quantity of calories which facilitates weight loss and is thus beneficial to a large percentage of type 2 diabetes patients who suffer from obesity. SGLT2 inhibitors are also characterized by very favorable safety profiles. The initial concerns suggesting that flozins would significantly increase the risk of urinary tract infections by facilitating bacterial growth due to increased urinary glucose levels proved to be largely unfounded. However, this risk should be taken into account in patients with a history of frequent urinary tract infection incidents, for example, patients with a background of anatomical urinary tract malformations or severe obesity.

The most significant clinical benefit of the use of flozins, as demonstrated in large registrational clinical trials, consisted in effective organ protection, particularly with regard to the cardiovascular system (cardioprotection) and kidneys (nephroprotection) [3]. Following further studies, this led to the indications for the use of this group of drugs being extended to include cardiac disorders and failure and kidney disorders (chronic kidney disease) even in patients without diabetes [4, 5].

FLOZINS — CHARACTERISTICS OF THE GROUP OF THERAPEUTIC AGENTS

As already mentioned, flozins work mainly by inhibiting SGLT2 which is expressed in the kidneys, particularly within the original segments of proximal convoluted tubules [6]. The remaining 11 types of sodium-glucose co-transporters are expressed outside the kidneys and are responsible for several vital functions, including osmoregulation and energy metabolism [7]. In addition to SGLT2, SGLT1 is also worth mentioning as being expressed within the small intestinal mucosa and involved in the regulation of glucose and galactose absorption. Several SGLT2 inhibitor medications have already been registered for the treatment of diabetes following the required clinical trials. All of these drugs, except for sotagliflozin which is a dual SGLT inhibitor blocking both SGLT2 and SGT1, had been originally registered for the treatment of type 2 diabetes. In contrast to other flozins, sotagliflozin has been registered in Europe only for use in obese type 1 diabetes patients [8].

Table 1 presents the primary characteristics of flozins available in the European Union. Several other drugs within this class are also

Table 1. Pharmacological properties of the registered members of the SGLT2 inhibitor class (summarized by the author on the basis of characteristics of medicinal products available at pharmacytimes.com and drugs.com, access date: 24.10.2021)

Medication	Time of action (T½) (hours)	Bioavailability (%)	Dose [mg/day]	Average reduction in glycated Hb levels (%)
Canagliflozin	10.6–13.2 (dose dependent)	65	100–300	0.76–0.86
Dapagliflozin	12.9	78	5–10	0.56–0.66
Empagliflozin	13.2–13.3 (dose dependent)	90–97	10–25	0.60–0.66
Ertugliflozin	11–17	70–90	5–15	0.60–0.80

Table 2. Comparison of the DAPA-CKD (dapagliflozin), EMPA-KIDNEY (empagliflozin), and CREDENCE (canagliflozin) studies (summarized by the author on the basis of data available at clinicaltrials.gov, access date: 25.10.2021)

Study	CREDENCE	DAPA-CKD	EMPA-KIDNEY
Study status	Completed before time* (2018)	Completed before time* (2020)	Ongoing (until June 2022)
Therapeutic intervention	Canagliflozin or placebo	Dapagliflozin or placebo	Empagliflozin or placebo
Patient population	Type 2 diabetes mellitus, eGFR 30–90 mL/min, albumin 300–5000 mg/g	Type 2 diabetes mellitus (2/3 patients) or diabetes-free (1/3 patients), eGFR 25–75 mL/min, albumin 200–5000 mg/g	Type 2 diabetes mellitus or no diabetes, eGFR 20–90 mL/min, albumin > 200 mg/g
Baseline nephroprotection at the time of study qualification	ACE inhibitor or sartan at maximum tolerated dose for at least 4 weeks	ACE inhibitor or sartan at maximum tolerated dose for at least 4 weeks	ACE inhibitor or sartan at maximum tolerated dose
Primary composite endpoint	Doubling of serum creatinine, initiation of renal replacement therapy, death for renal or cardiovascular reasons	Permanent reduction of eGFR by ≥ 50%, initiation of renal replacement therapy, death for renal or cardiovascular reasons	CKD progression, cardiovascular death

* Completed before time due to benefits of active treatment being demonstrated against placebo in the interim analysis
CKD — chronic kidney disease; eGFR — glomerular filtration rate

available outside of Europe (ipragliflozin, luseogliflozin, remogliflozin, tofogliflozin), and several more are examined in phase II and III clinical trials.

In addition to preparations containing flozins as single agent drugs, combinations of flozins and metformin are available, and further fixed combinations of flozins and other drugs have been filed for registration.

NEPHROPROTECTIVE EFFECT OF FLOZINS AS DEMONSTRATED IN CLINICAL TRIALS

Large, multi-center phase-III clinical trials of SGLT2 inhibitors in type 2 diabetes started in the years 2010–2012. These included the CANVAS study of canagliflozin in 10,142 patients [9], the EMPA-REG Outcome study of empagliflozin in 7,020 patients [10], and the largest of all studies conducted to date, namely the DECLARE-TIMI 58 study of dapagliflozin including a total of 17,160 patients [11]. However, the population of these studies consisted of diabetic patients with increased cardiovascular risk typical for family medicine, cardiology, and diabetological clinics. Few patients within the eligible population presented with advanced kidney disease. For example, in the EMPA-REG study, only less than 30% of patients presented with a glomerular filtration rate of < 60 mL/min. The respective percentages in the CANVAS study and the DECLARE study were 20% and 10% [9,10]. As the result, the average eGFR in the qualified for these studies was 85 mL/min in the DECLARE study, about 73 mL/min in the EMPA-REG study [10], and about 76 mL/min in the CANVAS study. Likewise, a small percentage of patients (< 10%) in these studies presented with significant albuminuria (> 300 mg/g creatinine). It was only in 2014 when the CREDENCE study on canagliflozin (4401 patients) was launched, being the first flozin study including a primary composite endpoint consisting of CKD progression including end-stage renal failure [12]. Included in the study were a group of patients with type 2 diabetes and impaired renal excretion (mean eGFR of 56 mL/min). As a result of one of the basic eligibility criteria, almost 90% of CREDENCE study patients had albumin levels of > 300 mg/g while 60% of patients presented with eGFR of < 60 mL/min.

As a result of these changes in the eligibility criteria and with the study population increasingly becoming a nephrological population, breakthrough studies involving also non-diabetic CKD patients were launched in 2017 and 2019, namely the DAPA-CKD (4,304 patients including about 1/3 of non-diabetic patients) and EMPA-KIDNEY (about 6000 patients) studies. Table 2 presents a comparison of the eligibility criteria for these two studies of crucial nephrological importance along with the CREDENCE study.

Such a clear evolution of flozin study indications towards renal patients was only possible after the first findings of the first flozin studies

had demonstrated the exceptionally positive effect of these agents on the renal endpoints, including CKD progression and albuminuria, as part of the secondary endpoint analysis. The first of these studies was the EMPA-REG study, completed in 2016 [13]. The study showed a 39% reduction in the risk of CKD and its progression, as well as a 46% reduction in the risk of doubling the serum creatinine levels, need for renal replacement therapy, or death due to renal disease. Moreover, the analysis of various subgroups of patients in this study revealed that the beneficial effect was similar in patients with eGFR > 60 mL/min, as well as in those with more impaired kidney function (even < 45 mL/min). This effect was also beneficial in subgroups defined based on patients' age, sex, degree of diabetes control, duration of diabetes, and body mass index. Another important finding of the EMPA-REG study consisted in the reduction of the risk of acute renal injury. This was somewhat surprising as increased risk of this complication was expected of hypovolemic agents which increase sodium excretion. Similarly, the risk of hyperkalemia was also reduced. In a similar pattern, beneficial results were obtained from other large flozin studies, such as DECLARE and CANVAS, but the greatest clinical benefits were demonstrated in these, as well as in other earlier studies (e.g. EMPA-REG), in relation to the reduced risk of hospitalization for heart failure and CKD progression. For example, the DECLARE study of dapagliflozin revealed that the reduction of the secondary renal endpoint (consisting of a GFR reduction of ≥ 40% to < 60 mL/min, end-stage renal failure or death due to renal causes) was as high as 47%, while the reduction in the risk of cardiovascular death, heart failure, or emergency medical intervention due to heart failure was as high as 26% [14].

However, the largest body of crucial data on the benefits of flozins in both type 2 diabetes and non-diabetic patients, was provided by the DAPA-CKD study [15], which was terminated before due time in 2020 due to the significant better effect of the drug as compared to placebo, identified in the interim analysis. A more detailed discussion of this study is worthwhile because the DAPA-CKD study population was a typical population of patients presenting at nephrological departments and outpatient clinics, with some of them being non-diabetic CKD patients. As shown in Table 2, participants eligible for the study were only individuals with reduced renal excretion and increased albuminuria, receiving maximum available pharmacological nephroprotection consisting of angiotensin convertase inhibitor or angiotensin receptor 2 antagonists, administered over at least 4 weeks in a stable, tolerated, maximum recommended dose regimen. Among other subjects, type I diabetes patients, patients with polycystic kidney disease, and immunosuppressed patients were not eligible for the study. The average follow-up period until study completion was 2.4 years. DAPA-CKD was a global study and was also conducted in Poland, where 103 patients (out of the 4,304 total participants) had been randomized. The average eGFR, albuminuria, and systolic blood pressure values within the qualified population were 43 mL/min, 965 mg/g, and 137 mmHg, respectively. As per the classification protocol, two-thirds of patients qualified for the study had been previously diagnosed with diabetes. The remaining population, a total of 1,398 patients, had had no history of diabetes. Patients with no history of diabetes had mostly presented with CKD originating from chronic renal glomerular disorders (43%), particularly IgA nephropathy (16.6%), and focal segmental glomerulosclerosis (6.7%). In nearly 35% of patients, nephropathy had had an ischemic or hypertensive background.

However, the most important, from the nephrological point of view, were the results of the analysis of the composite endpoint, which showed a highly significant 39% reduction in the risk of permanent eGFR reduction, end-stage renal failure, and renal or cardiovascular death. When the components of the composite endpoint were limited to renal complications alone (without cardiovascular death), the risk reduction was even higher and amounted to 44%. Overall mortality was reduced by 33% for dapagliflozin as compared to placebo. It is also worth adding that when analyzing the reduction of the composite primary endpoint in different subgroups, no differences were observed (that is the benefits from the use of dapagliflozin as compared to placebo were similar) between the diabetic and non-diabetic patients, patients below or above 65 years of age, and patients of different ethnic and racial backgrounds, sexes, and regions of residence. However, more favorable results were shown for dapagliflozin in patients with better initial control of arterial pressure (systolic blood pressure below 130 mmHg). It

is also worth adding that dapagliflozin was well tolerated. The incidence of severe side effects did not differ from that in placebo patients and no cases of diabetic ketoacidosis were observed in the study group in contrast to the increased incidence of acidosis observed during the treatment with other flozins.

Since the DAPA-CKD study population included a high number of patients with non-diabetic nephropathies, particularly nephropathies derived from glomerular disorders, results of pre-specified analyses within this study group were much anticipated by nephrologists. Such an additional analysis was carried out particularly in the largest group of patients with IgA nephropathy [16]. The DAPA-CKD study population included a group of 270 patients with the diagnosis of IgA nephropathy, in most cases confirmed by renal biopsy. That number was larger than the previously reported largest number of patients participating in studies limited to IgA nephropathy, such as the TESTING study (262 patients) and the STOP-IgA study (162 patients). The risk of the composite endpoint in the DAPA-CKD study, as described above, was reduced by as much as 71%. A publication of another analysis about patients with focal segmental glomerulosclerosis is also pending.

Other pre-specified analyzes carried out as part of the DAPA-CKD study showed, among other things, that the benefits of dapagliflozin versus placebo are independent of the initial level of diabetes control (glycemic status) [17]. This analysis has shown a clear trend toward even greater benefits of dapagliflozin at higher baseline glycated hemoglobin values (i.e. in less effectively controlled diabetes).

The analysis of the study results limited to patients with the highest grade of renal impairment, i.e. those with stage 4 CKD, is also worth mentioning [18]. Within the study group, there were as many as 624 patients with baseline eGFR in the range of 25 to 29 mL/min, corresponding to 14% of the total study population. The analysis of this subpopulation revealed that, despite the cumulative incidence of the primary composite endpoint, the composite renal endpoint, the rate of hospitalization for heart failure or cardiovascular death, and the all-cause mortality were numerically lower for dapagliflozin as compared to placebo. However, the difference was not statistically significant as it concerned the entire study population. Therefore, the benefit from using flozins seems to be reduced at very advanced renal failure (stage 4 CKD), although the medications appear to retain some of their beneficial effects.

An additional (but also pre-specified) analysis of the DAPA-CKD study data was also published, assessing the risk of acute renal impairment for dapagliflozin vs placebo [19]. The risk was shown to have significantly decreased by 31%.

The results of the DAPA-CKD study have raised the nephrologists' hopes for increased efficacy of the management of diabetic renal diseases — inhibition/delay of disease progression using an additional medication complementing the standard nephroprotective therapy based on the suppression of the renin-angiotensin-aldosterone system. However, the highest hopes associated with the results of this study are associated with the potential of using dapagliflozin also in patients with non-diabetic nephropathies, particularly glomerulopathies (including the most common IgA nephropathy). Indeed, following the results of the DAPA-CKD study published in August 2021, indications for using dapagliflozin in CKD patients have been expanded [20]. Currently, the drug is indicated in all adult CKD patients, including non-diabetic patients, with treatment initiation not being recommended in patients with GFR of < 25 mL/min due to limited clinical experience.

Most likely, recommendations of the Kidney Disease: Improving Global Outcomes (KDIGO) group regarding the management of CKD and glomerular renal diseases will also be revised soon following the publication of the DAPA-CKD study results. Flozins have already been included as nephroprotective agents in the 2020 KDIGO recommendations for the management of diabetic renal diseases and are recommended as first-line treatment in combination with metformin (the latter is administered following the principles of dose adjustment in renal failure) in patients with diabetes mellitus and CKD with eGFR > 30 mL/min [21].

MECHANISMS OF NEPHROPROTECTIVE ACTION

As unequivocally shown by the presented study results, flozins present with significant nephroprotective properties, which certainly reach beyond nephroprotection, that could be expected from the relatively small drop in arterial pressure and body weight observed after their administration [22]. The dominant

hypothesis behind the nephroprotective action of flozins consists in their ability to restore tubuloglomerular feedback previously disturbed in the course of CKD. This physiological mechanism combines the extent of glomerular filtration with the load of sodium ions at the macula densa within the juxtaglomerular apparatus. This effect is mediated by adenosine, which affects the tension of the muscular wall of the arteriole supplying blood to the glomerulus. Dysregulation of tubuloglomerular feedback occurs due to hyperfiltration which accompanies the early stages of all nephropathies (both diabetic and non-diabetic). It is caused by the reduction of the inflow of sodium ions to the macula densa due to the increased activity of the mechanisms of reabsorption of sodium from the tubular filtrate within the renal ducts. The administration of flozins inhibits reabsorption of sodium and glucose (by inhibiting the sodium-glucose co-transporter 2 within proximal tubules), restoring the disturbed inflow of sodium ions to the macula densa and consequently increasing the tension of the muscular walls of the blood-supplying arterioles, reducing glomerular hyperfiltration and stopping the progressive deterioration of the glomerular structure.

However, it seems that the mechanism of restoration of tubuloglomerular feedback only partially explains the nephroprotective effect of flozins. Other proposed mechanisms, most of them demonstrated to date only in experimental studies, are set out in Table 3.

Table 3. Nephroprotective mechanisms of action of SGLT2 inhibitors as demonstrated in clinical and pre-clinical studies (summarized by the author based on [23])

Proposed mechanisms of nephroprotective action	
Reported in human studies	• Loss of body weight • Increased natriuresis • Drop in arterial blood pressure • Drop in uricemia • Drop in albuminuria • Increase in HDL cholesterol levels • Drop in triglyceride levels • Improvement in fatty liver disease progression • Increase in hematocrit and erythropoietin production
Proposed mechanisms of nephroprotective action	
Reported in experimental studies	• Increase in ketone production (metabolic pathways switched to achieve better energy efficiency) • Reduced oxidative stress • Anti-inflammatory effect • Improvement in vessel flexibility • Improvement in endothelial dysfunction • Inhibition of Na^+/K^+ pump • Reduced myocardial fibrosis • Reduced epicardial adipose tissue mass

CONCLUSIONS

SGLT2 inhibitors (flozins) have raised hopes for a more effective treatment protecting the kidneys from nephropathies and their possible progression toward end-stage renal failure. Significant efficacy has been shown for these agents in clinical studies in both diabetic and non-diabetic nephropathies, particularly in IgA nephropathy as the most common primary glomerulopathy. Flozins complement and expand the pharmacological armamentarium for the treatment of CKD, which has so far been based on renin-angiotensin-aldosterone system blockers. Dapagliflozin, the first flozin with an expanded range of licensed indications, can already (since August 2021) be used even in advanced renal failure, both in diabetic and non-diabetic patients. However, the knowledge of the nephroprotective properties of flozins needs to be expanded among nephrologists and other professionals so that the benefits of these drugs in achieving more effective diabetes control and organ protection, particularly with respect to the kidneys and the cardiovascular system, can be exploited in full by more frequent prescriptions.

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