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Dapagliflozin therapy for patients with CKD according to current guidelines and clinical trials

ABSTRACT

The publication of the DAPA-CKD study in 2020 has revolutionised the strategy of nephroprotective therapy in chronic kidney disease (CKD) worldwide. From 01.07.2022 we have a reimbursement of dapagliflozin registered for nephrological indications in Poland. However, the lack of specific guidelines for SGLT2 inhibitors therapy in CKD patients creates a barrier to their widespread use. Hence, the recommendations of other European countries published so far have been reviewed and an attempt was made to translate them into Polish background. Certain concerns about the new treatment strategy were also highlighted and discussed. In the near future, we should expect the publication of the official position of the Working Group of the Polish Nephrology Society on this item.

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Key words: chronic kidney disease, dapagliflozin, suppression of CKD progression, nephroprotection

INTRODUCTION

Chronic kidney disease (CKD) has an insidious course, and its early stages are completely asymptomatic, hence it should be systemically covered by an early detection program.

CKD is a civilisational problem affecting a population of about 600 million people worldwide. As demonstrated by research conducted in Poland, in 2020 about 4.2 million Poles suffered from CKD, 90% of whom were unaware of the disease [1]. Complete loss of kidney function, which occurs in at least 6,500 people each year (about 170 people per million inhabitants), requires the initiation of renal replacement therapy with dialysis or kidney transplantation, which entails huge healthcare costs [1]. It is currently estimated that we have about 4.7 million patients with CKD in Poland. For comparison, within the last 5 years, the disease affected 13% of the population over 16 years of age in the United Kingdom [2], and one in 10 adult inhabitants in Sweden [3].

Impaired kidney function is closely associated with obesity, cardiovascular disease, diabetes, arterial hypertension and other chronic diseases. Targeted early diagnosis in risk groups offers the opportunity to significantly reduce morbidity and mortality from CKD and related complications.

The results of screening tests can result in treatment modification, for example through adjustment of drug dosage and lifestyle changes. The simple tests recommended by KDIGO (*The Kidney Disease: Improving Global Outcomes*) are neither expensive nor invasive; they include blood creatinine measurement and calculation of the estimated Glomerular Filtration Rate (eGFR) on the basis of its result and, in risk groups, measurement of albuminuria [4]. The severity of CKD is invariably assessed according to the KDIGO classification that includes five grades of kidney damage (dependent on eGFR, G1–G5) and three grades of albuminuria (A1–A3). It is recommended to measure albuminuria by determining the Urinary Albumin/Creatinine Ratio (UACR) (Fig. 1). The benefits of screening tests go beyond the treatment which can slow down or even stop the progression of CKD. It is equally important to reduce cardiovascular risk, as cardiovascular diseases are the leading cause of death in this patient population.

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UACR was developed with an assumption that an average adult with a body surface area of 1.73 m² excretes on average 1 g of creatinine (8.84 mmol/d) in the urine per day.

It should be borne in mind that not every adult has the assumed body surface area and excretes 1 g of creatinine per day.

Urinary excretion of creatinine depends on:

1. The muscle mass — a higher urinary excretion of creatinine is observed in muscular people in comparison with people with a low muscle mass (e.g. cachectic subjects), hence in the first case UACR is underestimated, in the second case it is overstated.
2. With reduced eGFR, urinary creatinine excretion is lower, hence UACR may be overstated.

The concentration of albumin in a single sample depends on:

1. The specific gravity of urine (i.e. the amount of fluids drunk) and the pH of urine (which is influenced by the type of consumed foods, medications taken).
2. Urinary excretion of albumin exhibits fluctuations:
   a. during the day (posture — time of day, physical exercise, ambient temperature),
   b. from day to day (as above),
   c. depending on the presence of other diseases — UTI, exacerbation of heart failure etc.

The correct measurement of UACR should be carried out in a urine sample collected from the first (or second) micturition after a day without intense exercise, sauna, etc., in a state of relatively good physical performance (without febrile diseases etc.), and under stable therapy.

To diagnose or rule out the presence of albuminuria, the UACR measurement should be performed three times at intervals of 3 months — only two positive results confirm the diagnosis (two negative ones rule it out). However, for patients with confirmed CKD and documented overt proteinuria observed for many months, one test result is sufficient to determine eligibility for SGLT2i treatment. The value determinant for the diagnosis is albuminuria ≥ 30 mg/g (3 mg/mmol).

The measurement should be performed in the same laboratory, because the method used for the test influences the repeatability of the result.

Figure 1. Correct determination and interpretation of UACR according to UpToDate 2022 [28]

NEW THERAPEUTIC HORIZON IN CKD

Optimisation of blood glucose, blood pressure, lipidaemia, reduction of albuminuria and the use of medicines that block the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), are of key importance in CKD therapy and help slow down its progression [4]. However, despite this treatment strategy, many patients experience continuous worsening of kidney function, and thus there is an unmet need for new nephroprotective therapies.

Over the past 2 years, evidence emerged of the possibility of using new therapeutic solutions to slow down the progression of CKD in people with and without diabetes, with particular emphasis on mineralocorticoid receptor antagonists (MRA) and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Finerenone, a non-steroidal selective MRA, proved effective in patients with CKD and type 2 diabetes (T2D). As demonstrated by the FIDELIO-DKD study, randomisation to finerenone resulted in a lower risk of CKD progression and cardiovascular events compared to placebo in a group of patients with diabetic kidney disease [5].

Finerenone is currently approved by the European Medicines Agency (EMA) for the treatment of CKD associated with type 2 diabetes (T2D) [6].

Recently, there has been an increasing interest in the potential of using SGLT2 inhibitors in clinical practice. A recently concluded DAPA-CKD study found that an SGLT2 inhibitor (dapagliflozin) added to ACEi/ARB, apart from its documented benefits in patients with CKD with associated heart failure (HF) and type 2 diabetes with albuminuria, also contributes to prevention of CKD progression in the absence of diabetes [7].

On the basis of the results of DAPA-CKD, dapagliflozin has been approved for use in the treatment of CKD by the U.S. Food and Drug Administration (FDA), the European Commission, the Medicines and Healthcare products Regulatory Agency, and in many other countries in the world [6]. At the moment, there is no doubt that an increased use of SGLT2 inhibitors in patients with CKD may have significant clinical benefits. Since 01.07.2022 dapagliflozin has been reimbursed in Poland in nephrological indications; the reimbursement decision was a real breakthrough in the therapeutic approach to this group of patients. Dapagliflozin is currently the only representative of SGLT2 inhibitors approved for the treatment of CKD in adults. The results of the EMPA-KIDNEY study, which ended in July 2022, are expected to be announced in November 2022. That study included patients with eGFR 20–45 mL/min/1.73 m² (not necessarily with albuminuria) and patients with eGFR ≥ 45 to

Table 1. Administration of SGLT2 inhibitors in chronic renal disease, broken down by its stages (table developed by author)

SGLT-2 inhibitor	eGFR, mL/min/1.73 m²					
	> 90	60–90	45–60	30–45	15–30	< 15
Canagliflozin (type 2 DM)	✓ 100–300 mg	✓ 100–300 mg	✓ 100 mg	✓ 100 mg Initiation in the treatment of DKD with uACR > 30 mg/mmol	— 100 mg Continuation if albuminuria is present	— 100 mg Continuation if albuminuria is present
Dapagliflozin (type 2 DM)*	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg	—
Dapagliflozin (CKD)	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ Limited data at eGFR < 25	—
Dapagliflozin (HFrEF)	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ Limited data at eGFR < 30	—
Empagliflozin (type 2 DM)	✓ 10–25 mg	✓ 10–25 mg	— 10 mg	✓ 10 mg	×	×
Empagliflozin (HFrEF)	✓ 10 mg	✓ 10 mg	✓ 10 mg	✓ 10 mg	× When eGFR < 20	×
Ertugliflozin	✓ 5–15 mg	✓ 5–15 mg	— 5–15 mg	×	×	×

DM — diabetes mellitus; HFrEF — heart failure with reduced ejection fraction; SGLT2 — sodium-glucose co-transporter 2

< 90 mL/min/m² and UACR ≥ 20 mg/mmol (200 mg/g). An overview of the SGLT2 inhibitors used worldwide in the treatment of CKD is presented in Table 1.

Since the indication for the use of SGLT2 inhibitors in CKD is new, physicians and payers may not be aware of the potential clinical and economic benefits of this therapeutic approach. In addition, nephrologists may also be hesitant to initiate these drugs due to concerns about the potential adverse events and ambiguities about the algorithms for using the new therapy. Therefore, this article is devoted to reviewing the available guidelines and interpretations of clinical trials published up to July 2022 to provide support to health-care professionals responsible for the treatment of CKD, as regards the role of SGLT2 inhibitors in clinical practice. As so far only one SGLT2 inhibitor — dapagliflozin — has been registered in Poland for CKD therapy, most of the guidelines apply to this particular medicine.

CLINICAL EFFECTIVENESS OF SGLT2 INHIBITORS IN CKD

SGLT2 inhibitors block glucose reabsorption in the proximal tubule and increase glucose excretion in the urine, which consequently leads to a slight decrease in blood glucose levels. In addition to blood glucose-lowering properties, SGLT2 inhibitors also cause a simultaneous increase in sodium excretion, which results in a reduction in blood pressure. It is believed that a decrease in sodium and glucose reabsorption in the proximal tubule leads to the restoration of tubuloglomerular feedback, which leads to narrowing of the afferent arterioles and a decrease in glomerular blood flow. The resulting reduction in intraglomerular pressure and glomerular hyperfiltration are considered to constitute a nephroprotective factor and lead to a slower decline in renal function as measured by the estimated eGFR [8]. Pathogenic mechanisms of the potential beneficial effect of SGLT2 inhibitors are shown in Figure 2.

The nephroprotective mechanism of action of SGLT2 inhibitors has been proven on the basis of the reduced rate of progression to end-stage kidney disease (ESKD) patients with diabetes (EMPA-REG, CANVAS, DECLARE-TIMI 58, CVD-REAL 3) [9–12] and HF (DAPA-HF and EMPEROR-Reduced) [13, 14]. Both DAPA-HF and EMPEROR-Reduced have shown a similar effect of SGLT2 inhibitors on slowing the decline of eGFR. However, the results for the composite renal endpoint were divergent; in DAPA-HF, this result was numerically lower for dapagliflozin in comparison with placebo but not statistically significant, while it was significantly lower for empagliflozin in comparison with placebo in the EMPEROR-Reduced study. This may have been due to a relatively lower number of renal events in DAPA-HF, due to higher baseline eGFR inclusion criteria and a different definition of site endpoint. However, after combining the results of DAPA-HF

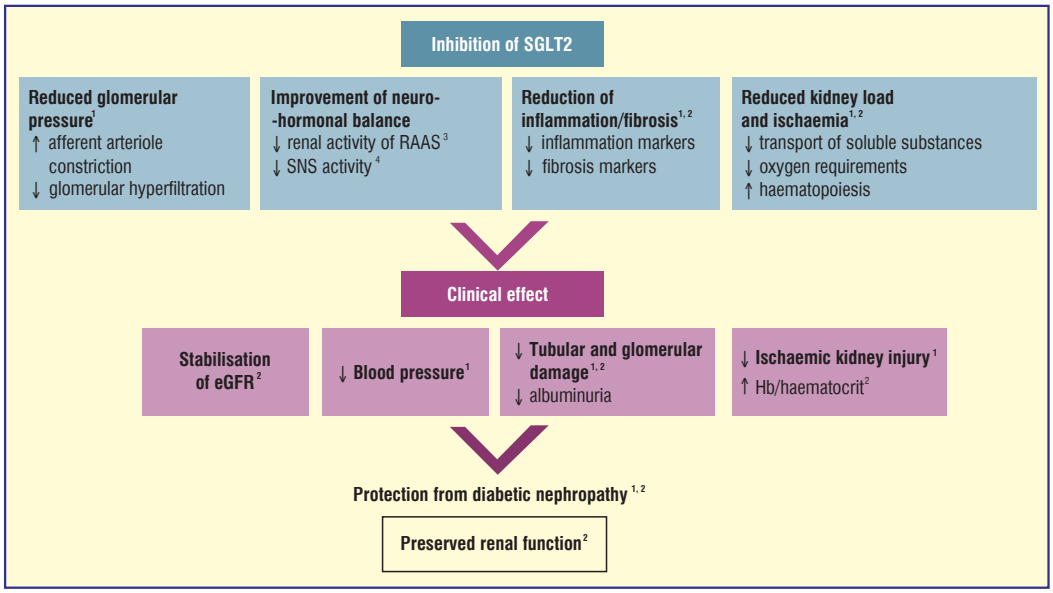

Figure 2. Potential mechanisms of the beneficial effect of SGLT2 inhibitors in renal disease. Adapted from:
[1]Heerspink H.J.L. et al. Kidney Int. 2018; 94 (1): 26–39.
[2]Tamargo J. Eur. Cardiol. 2019; 14 (1): 23–32.
[3]Shin S.J. et al. PLoS One. 2016; 11: e0165703.
[4]Sano M. J. Cardiol. 2018; 71 (5): 471–476.
eGFR — estimated glomerular filtration rate; Hb — haemoglobin; RAAS — renin–angiotensin–aldosterone system; SGLT2 — sodium-glucose co-transporter 2; SNS — sympathetic nervous system

and EMPEROR-Reduced in a meta-analysis, the risk of serious renal complications was reduced by 38% (hazard ratio 0.62; 95% confidence interval 0.43–0.90) when SGLT2 inhibitors were used in comparison with placebo.[15]

The DAPA-CKD study had broader criteria for the inclusion of patients with CKD and included patients both with and without T2D. The study evaluated the effects of dapagliflozin in 4304 subjects (eGFR 25–75 mL/min/1.73 m^2 and UACR 22.6––565 mg/mmol) treated with maximal tolerated doses of ACEi or ARB unless they were contraindicated. After a median follow-up of 2.4 years, there was a 39% relative reduction in the risk of the primary composite endpoint, i.e. a sustained decline in eGFR of at least 50%, ESKD, or death from cardiovascular or renal causes (refusal to receive renal replacement therapy) in the dapagliflozin group, as compared with placebo [7]. It is worth noting that the results were independent of the diabetes status. Randomisation to dapagliflozin also resulted in a significant 44% reduction in the risk of worsening renal function or death from renal failure, a 31% reduction in overall mortality, and a 29% reduction in hospitalisation for HF or cardiovascular death in comparison with placebo [7]. The study confirmed the safety profile of dapagliflozin, with no significant differences in the incidence of adverse events between the actively treated and placebo groups. Fournier gangrene was not reported in any subject who received dapagliflozin, but it occurred in one subject in the placebo group. Ketoacidosis was not reported in any subject with T2D who received dapagliflozin but was observed in two subjects who received placebo. In subjects without T2D, neither ketoacidosis nor severe hypoglycaemia was observed.

OVERVIEW OF THE CURRENT PUBLISHED GUIDELINES FOR THE USE OF SGLT2 INHIBITORS

To date, the basis for treatment to delay the progression of CKD have been ACEis or ARBs recommended in the guidelines of the National Institute for Health and Care Excellence (NICE) [CG 182] "Chronic kidney disease in adults: assessment and management" [16]. However, the 2015 update of those guidelines does not take into account recent clinical trials.

KDIGO Diabetes Work Group, American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), European Society of Cardiology (ESC), Association of British Clinical Diabetologists (ABCD) and UK Kidney Association (UKKA) recom-

mends in its current guidelines the use of an SGLT2 inhibitor in patients with T2D and eGFR ≥ 30 mL/min/1.73 m^2, if the approved reimbursed indications allow it [17–19]. The UK consensus published in December 2021 goes a step further and states that people with eGFR ≥ 15 mL/min/1.73 m^2, regardless of their diabetes and albuminuria status, should be considered for treatment with SGLT2i [6]. In view of the complementary mechanism of action, the combination of SGLT2i with a one-component RAA blockade should be adopted in most patients in clinical practice. An extended version of these guidelines (see below) is currently the most detailed and practical European paper on this subject.

Very similar to the UK guidelines, although less detailed, are the recommend-dations of KDIGO and the International Society of Nephrology (ISN) published in the form of an information brochure about early identification of CKD and nephroprotective measures. According to these recommendations, it is justified to add an SGLT2 inhibitor to ACEi/ARB in patients diagnosed with CKD whose eGFR is < 60 mL/min/1.73 m^2 and UACR is ≥ 30 mg/g [20].

The Guidelines of the Swiss Society of Nephrology (SNN) for CKD screening in the general population recommend the addition of an SGLT2 inhibitor to ACEi/ARB (in the absence of contraindications) in patients with eGRF within a range of 25–60 mL/min/m^2 and with UACR ≥ 30 mg/g. Screening tests assessing kidney function should be performed in a group of patients at an increased risk of developing CKD, i.e., people with hypertension, diabetes, cardiovascular diseases, history of acute kidney damage, family history of kidney disease or systemic diseases (HIV, systemic lupus erythematosus, vasculitis), receiving nephrotoxic drug therapy, with obesity, and the elderly [21].

A deviation from European guidelines are the ministerial guidelines in Hungary, in force since 19.10.2021, which recommend the use of SGLT2 inhibitors for nephroprotection from the G1 to G4, i.e. also in patients at risk but still with a normal eGFR value [22].

The Italian guidelines, published on the basis of the ESC guidelines in April 2022, apply to patients with HF with reduced ejection fraction and varying degrees of kidney damage [23]. The guidelines indicate the need to use (in the absence of contraindications) a full dose of an SGLT2 inhibitor in quadruple therapy (up to eGFR 30 mL/min/m^2) or in triple therapy (up to eGFR 15 mL/min/m^2). The regimens include low doses of a beta-blocker, mineralocorticoid receptor antagonist, ACEi, or neprilysin inhibitor/ARB.

Unfortunately, at present there are no current Polish nephrological guidelines. The first guidelines that position SGLT2 inhibitors in the basic nephroprotective strategy appeared as the position of the Working Group of the Polish Society of Nephrology (PTN) in 2019 [24]. However, they could not have contained any details because the results of the DAPA-CKD study were not published until 2020 [7].

USING AN SGLT2 INHIBITOR IN CLINICAL PRACTICE IN PATIENTS WITH CKD

Since the UK recommendations are the most detailed and recent (published at the beginning of 2022) and have been developed with the due care, it seems reasonable to use them [25]. Their funny and very clear presentation in the form of traffic lights facilitates their understanding and use in medical practice.

The guidelines are addressed not only to nephrologists, but also to cardiologists, diabetologists, endocrinologists and all related specialties, with particular attention to primary care physicians. Selecting the right individuals with CKD for the treatment with SGLT2 inhibitors is critical to maximising the risk-benefit profile associated with this treatment approach. On the basis of the DAPA-CKD data as well as of the latest clinical guidelines, a checklist has been developed that serves as a tool to reduce the risk of adverse drug reactions.

It provides a sense of security for clinicians using these medicines. The checklist follows the traffic light system, which recommends that those in the green section be treated with SGLT2i therapy in addition to the RAAS blockade. That group included patients with CKD with or without T2D, and with eGFR ≥ 15 mL/min/1.73 m^2 (for dapagliflozin) and CKD with T2D and albuminuria and with eGFR ≥ 30 mL/min/ 1.73 m^2 (for canagliflozin). For the purposes of national reimbursed indications, three changes should be adopted regarding the inclusion of dapagliflozin therapy: eGFR ≥ 25 mL/min/1.73 m^2, albuminuria ≥ 200 mg/g (20 mg/mmol) and ACEi/ARB treatment for not less than 4 weeks (or its lack in the case of existing contra-indications) (Fig. 3). The limit laboratory values in the Polish reim-

Consider SGLT2i in patients with CKD*	
green	• eGFR ≥ 25mL/min/1.73m^2 • albuminuria ≥ 200 mg/g • AND on ACEi/ARB therapy for at least 4 weeks or contraindications to ACEi/ARB treatment
Consider SGLT2i with caution in patients with CKD (with or without diabetes) and any of the following	
yellow	• previous amputation, severe peripheral neuropathy, severe peripheral vascular disease, diabetic foot or active soft tissue infection • history of recurrent fungal urinary infections • risk of clinically significant dehydration
Do not consider SGLT2i in patients with CKD (with or without diabetes) if any of the following occurs	
red	• eGFR < 25 mL/min/1.73 m^2 • renal replacement therapy (dialysis) • history of transplantation • ADPKD, systemic lupus erythematosus, ANCA-related vasculitis • cytotoxic therapy, immunosuppression or other immunotherapy in the last 6 month • type 1 diabetes • history of diabetic ketoacidosis • pregnancy, breastfeeding

*on-label indication of dapagliflozin is chronic kidney disease in adult patients
eGFR — estimated glomerular filtration rate; ADPKD, autosomal dominant polycystic kidney disease; ANCA, anti-neutrophil cytoplasmic antibody; SGLT2i, sodium-glucose cotransporter-2 inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Figure 3. Checklist for proper qualification of patients with CKD for dapagliflozin therapy (modified from Evans M. et al. Drugs. 2022, taking into account reimbursement indications in Poland)

bursed indications were directly adopted from the DAPA-CKD study.

PRECAUTIONS (YELLOW AND RED SECTIONS)

Since the relationship between the use of SGLT2 inhibitors and the need for amputation remains unclear, caution should be exercised when initiating this therapy in patients found eligible for this procedure (yellow light) [6]. While canagliflozin was associated with an increased risk of lower limb amputation in the CANVAS study [10], dapagliflozin therapy in the CREDENCE study [26], as in the DAPA-CKD study [7], was not associated with a significantly more frequent need for amputation in comparison with placebo.

There is still a lack of formal evidence for the safety of SGLT2i in organ transplant (tx) patients, and this group was not included in the DAPA-CKD study. In line with the position of UKKA (UK Kidney Association), there is currently insufficient evidence for the safety and efficacy of SGLT2i use in patients with a functioning kidney transplant (Tab. 2, 3) [25].

It is not recommended to start using an SGLT2 inhibitor (red part of the checklist) when the eGFR is less than 25 mL/min/1.73 m^2 (value adjusted to the approved and reimbursed indications in Poland). However, if the patient has been receiving an SGLT2 inhibitor for a long time, and then the eGFR falls below the limit value, therapy can be continued. In addition, treatment with an SGLT2 inhibitor should not be considered in people with autosomal dominant polycystic kidney disease, lupus nephritis or anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis, in patients receiving cytotoxic therapy, immunosuppressants or another form of immunotherapy (within the past 6 months), in dialysis patients, and in pregnant or breast-feeding women. The experience in the above-listed populations is limited [6, 26]. Caution results from the exclusion of these patient groups from the DAPA-CKD study and therefore the lack of evidence for the safety of SGLT2i therapy in these patients.

SGLT2 inhibitors are not currently recommended in the CKD population with concomitant type 1 diabetes. In people with type 1 diabetes, the incidence of diabetic ketoacidosis (DKA) was found to be significantly higher with SGLT2i use. Since SGLT2 inhibitors lower blood glucose levels, this is accompanied by a decrease in insulin secretion, which leads to increased glucagon production. Insulinopenia and elevated glucagon levels increase the risk of developing ketoacidosis (including euglycaemic ketoacidosis), especially in the presence of other contributing factors. Ketoacidosis is rare in people without diabetes, although it can be observed during

Table 2. Recommendations for initiating SGLT2 inhibitor therapy in patients with chronic kidney disease according to the UK Kidney Association [26]

RECOMMENDATIONS FOR IMPLEMENTATION OF SGLT2 INHIBITOR THERAPY		
PATIENTS WITH AND WITHOUT DIABETES (EXCLUDING PEOPLE WITH T1D)		**GRADE**
1.	We recommend using SGLT-2 inhibitors with demonstrated efficacy for their given indications.*	1A
2.	We recommend using clinically appropriate single agent RAS blockade in combination with SGLT-2 inhibition, wherever RAS blockade is indicated and tolerated.	1A
3.	We suggest following NICE guidelines on screening for albuminuria: a single uACR of ≥ 70 mg/mmol or a confirmed measurement between 25-69 mg/mmol fulfil recommendations for use of SGLT-2 inhibitors based on albuminuria.	2C
4.	We suggest using uACR to assess for sufficient proteinuria to guide SGLT-2 inhibitor use: reagent strips and protein: creatinine ratio should generally not be used (NICE NG203). We recognise that more pragmatic approaches to identifying risk of kidney disease progression may be necessary whilst local access to UACR measurement is improved.	2C
5.	We suggest that when used to slow kidney disease progression or heart failure risk, SGLT-2 inhibition can be continued until the need for dialysis or kidney transplantation arises.	2B
6.	We suggest that co-prescription of SGLT-2 inhibition with MRA can be considered, where each are individually indicated.	2B
7.	We suggest the beneficial effects of SGLT-2 inhibition on renal outcomes in people with type 2 DM are likely to be a class effect, but there is insufficient data in people without DM to be conclusive.	2B
8.	We suggest the beneficial effects of SGLT-2 inhibition on heart failure are likely to be a class effect, irrespective of the presence or absence of DM.	2B

*Please follow the current indications for use/uses of medicines in accordance with the SmPC in force in the given area The strength of recommendations determined with the use of *The Grading of Recommendations Assessment, Development and Evaluation* (GRADE) (Neumann I., Santesso N., Akl E.A. et al. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach. J Clin Epidemiol 2016; 72: 45–55).
DM — diabetes mellitus; MRA — mineralocorticoid receptor antagonist; NICE — National Institute for Health and Care Excellence; T2D — type 2 diabetes; SGLT2i — sodium-glucose co-transporter-2 inhibitor; UACR — albumin-to-creatinine ratio in a spot urine sample

pregnancy, after long-term alcohol use, or as a result of starvation. In most clinical trials involving people with diabetes, a slight increase in the number of cases of DKA in the SGLT2 inhibitor group was observed in comparison with placebo, and cases of DKA seem to be more frequent in routine clinical practice: most involve patients with type 1 diabetes, secondary diabetes or T2D with other risk factors for ketoacidosis. Because of the serious consequences of this metabolic disorder, in patients who develop DKA while taking an SGLT2 inhibitor this medicine should be permanently discontinued.

Among the adverse events in clinical trials with SGLT2i, urinary tract infections (UTIs), including fungal genital infection, were mainly reported in groups of patients with T2D. However, the DAPA-CKD study did not confirm these reports. It should be borne in mind that T2D is an independent risk factor for urinary tract infections, which may mistakenly indicate the role of SGLT2 inhibitors in causing them. In any case, before SGLT2i treatment initiation it is mandatory to talk to the patient about hygienic recommendations and measures to prevent UTIs.

In view of their mechanism of action, SGLT2 inhibitors may induce diuresis and natriuresis, raising concerns about the potential effects of this class of drugs on electrolyte (sodium, potassium, magnesium, calcium and phosphates) metabolism and their adverse effects related to fluid volume deficiency. Data from clinical trials in people with and without diabetes showed fewer adverse events and cases of acute kidney injury (AKI) associated with the use of an SGLT2 inhibitor in comparison with placebo [7]. There was also no difference in the effect of dapagliflozin on AKI depending on age, diabetes status, baseline eGFR, degree of albuminuria, diuretic use, or the presence of heart failure. However, in the DAPA-CKD study there was a slight increase in adverse events associated with a reduction in vascular bed volume in relation to the use of an SGLT2 inhibitor [7]. Symptoms of fluid deficiency were observed in 5.9% of the patients in the dapagliflozin group versus 4.2% in the placebo group (p value = 0.01). In routine clinical practice, it has been recommended to assess the patient's hydration status both when starting an SGLT2 inhibitor and when monitoring a patient treated with this agent. Pref-

Table 3. Recommendations for precautions in SGLT2 inhibitor therapy in patients with chronic kidney disease according to the UK Kidney Association [26]

ACUTE KIDNEY INJURY, HYPOVOLAEMIA AND POTASSIUM		GRADE
1.	We recommend that individuals initiated on an SGLT-2 inhibitor do not routinely require an early assessment of renal function or potassium following initiation of treatment.	1C
2.	We suggest that if an individual has a renal function assessment within the first few weeks post initiation of an SGLT-2 inhibitor, a decline in eGFR needs to be interpreted with caution and in the context of an expected drug effect to avoid unwarranted discontinuation of treatment.	2B
3.	We recommend that SGLT-2 inhibitors are temporarily withheld during acute illness.	1C
URINARY TRACT INFECTION		
1.	We recommend temporary discontinuation of SGLT-2 inhibitors when treating pyelonephritis or urosepsis.	1C
KIDNEY TRANSPLANT RECIPIENTS		
1.	There is currently insufficient evidence on safety and efficacy to provide recommendations for use of SGLT-2i in people with a functioning kidney transplant.*	—

*DAPA-CKD provides key clinical evidence and excluded kidney transplant recipients, people with polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis, and people using immunotherapy for kidney disease within 6 months before enrolment. The strength of recommendations was determined with the use of *The Grading of Recommendations Assessment, Development and Evaluation* (GRADE) (Neumann I., Santesso N., Akl E.A. et al. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach. J Clin Epidemiol 2016; 72: 45–55.
SGLT2i — sodium-glucose co-transporter-2 inhibitor

erence should be given to maintaining stable doses of RAAS inhibitors and reducing other antihypertensive drugs if blood pressure oscillates around the lower part of the target range. While dose reduction of other antihypertensive drugs may be appropriate in the context of hypotension concerns, the dosage of diuretics may be reduced to alleviate potential concerns about fluid deficiency.

Previously, there were some concerns about the eGFR decline that may occur after the initiation of SGLT2 inhibitor therapy. It should be borne in mind that a decrease in eGFR observed shortly after the use of an SGLT2i probably reflects its mechanism of action and should not constitute a barrier to treatment continuation. Overall, a long-term benefit of slowing the progression of CKD was observed, despite the initial eGFR decline. Data from clinical trials have shown that the initial eGFR decline associated with the initiation of an SGLT2 inhibitor (first weeks of therapy) is followed by long-term stabilisation of renal function parameters [7]. The UKKA guidelines make it clear that routine monitoring of creatinine and potassium levels is not recommended in patients in the early period after SGLT2i initiation (Tab. 3) [27]. At the same time, it is suggested that if renal function assessment was performed in the patient within the first few weeks after initiation of the above treatment, the eGFR decline should be interpreted in the context of the expected effect of the medicine, in order to avoid unjustified treatment discontinuation. Data suggest that a sudden decrease in eGFR to 30% from the baseline may be tolerated after initiation of treatment [according to 6]. In addition, a systematic review and a meta-analysis have showed that SGLT2 inhibitors reduce the risk of acute kidney injury by 36% [27].

SUMMARY

Since the RAAS inhibitor study published more than 20 years ago, treatment options to slow the progression of CKD have been limited. The recently demonstrated benefits in clinical trials with finerenone and SGLT2 inhibitors, recruiting patients with CKD, confirmed far-reaching hopes for inhibiting/slowing the progression of kidney damage. Currently, one SGLT2 inhibitor (dapagliflozin) has been approved in Poland for the treatment of patients with CKD (both with and without T2D), while other agents from this group are in the queue for approval. In the future, it will probably be possible to use the combination of an RAAS inhibitor with SGLT2i and finerenone at the same time. In the meantime, the addition of an SGLT2 inhibitor to the standard nephroprotective therapy in CKD creates an opportunity to significantly slow down the loss of kidney function.

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