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SGLT2 inhibition for patients with ADPKD – closing the evidence gap

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ABSTRACT

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2i) were originally developed to treat diabetes mellitus but have shown important renoprotective benefits independently from blood glucose levels. SGLT2i have thus become an important addition to the therapeutic armamentarium to treat patients with chronic kidney disease. However, specific patient populations were excluded from the pivotal trials, for instance patients with very low eGFR, patients on dialysis, kidney transplant recipients, and patients with autosomal dominant polycystic kidney disease (ADPKD), the most common genetic kidney disorder. Considering the lack of potent treatment modalities in ADPKD, the use of SGLT2i in this patient population would be of major interest. However, the combination of inconclusive results from preclinical models with the lack of clinical efficacy data and potential disease-specific safety concerns currently exclude patients with ADPKD from this promising therapeutic opportunity. This results in an urgent need for adequately powered clinical trials examining SGLT2i in ADPKD. This review summarizes the current knowledge on SGLT2i in this specific patient population and outlines running and upcoming clinical trial programs in different geographic regions aiming to make SGLT2i accessible to patients with ADPKD.

Keywords: ADPKD, dapagliflozin, empagliflozin, polycystic kidney disease, SGLT2i

SGLT2i—MECHANISM OF ACTION IN CHRONIC KIDNEY DISEASE

Inhibitors of the sodium-glucose cotransporter 2, SGLT2i, have transformed the treatment landscape for chronic kidney disease (CKD), primarily through mechanisms that transcend their glucose-lowering effects. By targeting SGLT2 in the proximal tubule, these agents reduce sodium and glucose reabsorption, increasing sodium delivery to the macula densa [1]. This process reduces intraglomerular pressure via tubuloglomerular feedback and alleviates hyperfiltration, thereby protecting the glomerulus from excessive stress contributing to reduce albuminuria [2]. By promoting glycosuria, osmotic diuresis, and enhancing sodium excretion, SGLT2i also improve glycemic control, reduce body weight and extracellular fluid volume, and afford a slight decrease in blood pressure [3]. These effects are observed across diabetic and non-diabetic kidney disease. Beyond their renal and systemic hemodynamic impact, SGLT2i have other effects on several cellular and metabolic pathways involved in CKD progression [4]. The combined impact of these effects may also explain why SGLT2i improves not only glomerular but also tubular health as exemplified by the reduction of acute kidney injury (AKI) supported by data from several randomized clinical trials (RCT) [5]. By decreasing proximal tubular workload, they lower oxygen demand, mitigating effects of hypoxia in the renal cortex, a critical driver of tubular injury and interstitial fibrosis [6]. In parallel, these agents enhance mitochondrial efficiency and reduce oxidative stress, mechanisms that contribute to their protective effects on renal cells. The induction of mild ketosis by SGLT2i provides an alternative energy source, offering additional metabolic advantages by reducing reliance on glucose metabolism and limiting the generation of reactive oxygen species [7]. SGLT2i also reduce pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, and downregulate pathways involved in fibrosis, particularly those mediated by transforming growth factor-beta [8–11]. These multifaceted effects are currently believed to explain the kidney protection afforded by SGLT2i across a broad spectrum of CKD stages and etiologies.

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SGLT2i AS A NEW TREATMENT OPPORTUNITY IN DIABETIC AND NON-DIABETIC KIDNEY DISEASE

Regarding the effect of SGLT2i in CKD in general, three large RCTs with a primary endpoint focusing on kidney function have been completed to date [12–14]. The CREDENCE trial included only diabetic CKD patients with an estimated glomerular filtration rate (eGFR) between 30 and 90 ml/min/1.73 m^2 and an albumin-creatinine ratio (ACR) of 300–5000 mg/g (n = 4401, median follow-up 2.62 years) and showed a hazard ratio of 0.70 [95% confidence interval (CI), 0.59 to 0.82] for the primary composite endpoint of end-stage kidney disease (ESKD), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. The DAPA-CKD trial examined the effect of dapagliflozin in 4304 (diabetic and non-diabetic) CKD patients with an eGFR of 25–75 ml/min/1.73 m^2 and an ACR of 200–5000 mg/g over a median follow-up of 2.4 years and found a hazard ratio of 0.61 (95% CI, 0.51 to 0.72) for a similar primary endpoint. A meta-analysis of large placebo-controlled trials including CREDENCE and DAPA-CKD found that SGLT2i resulted in 11 and 15 fewer events of kidney disease progression in diabetic and non-diabetic CKD patients, respectively [5]. More recently, the EMPA-KIDNEY trial designed to assess the effects of treatment with empagliflozin in CKD patients with an eGFR of 20–45 or 45–75 ml/min/1.73 m^2 in combination with an ACR >200 mg/g was published [14]. This study, again, found a highly significant benefit of empagliflozin regarding the primary endpoint, a composite of progression of kidney disease or death from cardiovascular causes (hazard ratio 0.72, 95% CI, 0.64 to 0.82). The annual decline in eGFR from 2 months to the time of the final follow-up visit was −2.75 ml/min/1.73 m^2 in the placebo group and −1.73 ml/min/1.73 m^2 in the empagliflozin group with a between-group difference of 1.37 ml/min/1.73 m^2 (95% CI, 1.16 to 1.59) per year. Of note, CREDENCE, DAPA-CKD, and EMPA-KIDNEY all excluded patients with ADPKD. Besides, both DAPA-CKD and EMPA-KIDNEY primarily examined SGLT2i with reduced kidney function. Mean age was 61.8 ± 12.1 years in DAPA-CKD and 63.9 ± 13.9 years in EMPA-KIDNEY, mean eGFR was 43.2 ± 12.3 and 37.4 ± 14.5 ml/min/1.73 m^2, respectively. In summary, most patients in the CKD trials studying SGLT2i had a relatively low eGFR. For a genetically determined disease such as ADPKD, however, starting treatment as early as possible in life, i.e. in a phase with yet (near) normal eGFR, is a crucial aim further limiting the overlap of the target ADPKD patient group with currently available trial data. Nonetheless, it is important to note that the populations in the heart failure trials included patients at a higher eGFR and provide evidence toward benefits on CKD progression and AKI [5]. Besides, the high levels of albuminuria typical for participants in the landmark SGLT2i trials are not typical for ADPKD. Importantly, a *post hoc* analysis of EMPA-KIDNEY revealed maintained nephroprotection at low ACR regarding eGFR slope and no association with baseline eGFR was observed [15]. Nonetheless, based on the currently available evidence the KDIGO CKD guideline recommends the use of SGLT2i in individuals with T2DM and CKD irrespective of UACR level, while for non-diabetic patients with CKD for an eGFR ≥20 ml/min/1.73 m^2 exclusively in the presence of either an ACR >200 mg/g or heart failure (1A evidence level). In adults with an ACR <200 mg/g and an eGFR of ≥20-45 ml/min/1.73 m^2, the guideline only suggests (2B evidence level) using these drugs. ADPKD is typically a disease associated with low albuminuria and many affected subjects have an eGFR >45 ml/min/1.73 m^2 when SGLT2i should be considered as a treatment option [16]. So, even if patients with ADPKD had not been excluded from the pivotal trials, in fact most of them would currently not qualify for treatment. Taken together, despite the highly beneficial effects of SGLT2i regarding non-ADPKD CKD [17] and its excellent safety profile, data to implement the use of this concept in patients with ADPKD are lacking and urgently required.

SAFETY PROFILE OF SGLT2i

The incidences of (serious) adverse events (SAEs) were similar overall in the SGLT2i and placebo groups in both DAPA-CKD and EMPA-KIDNEY. Rates of diabetic ketoacidosis were low but higher than in the placebo group for canagliflozin in CREDENCE while no such signal was detected in the two more recent trials in non-diabetic CKD. Meta-analyses of the large RCTs looking at side effects in an integrated manner further underline the excellent risk–benefit profile of this class of drugs [5, 18]. Importantly, despite increased glycosuria, the overall risk of urinary tract infections (UTI) is only marginally increased in the CKD population, similar as in the overall population (relative risk 1.09 versus 1.08, respectively). Only the incidence of genital fungal infections is elevated in a clinically relevant manner, but again similar in the CKD and the overall population (relative risk 2.98 versus 3.57, respectively). This is of special importance since, currently, many physicians still appear to place undue emphasis on the risk of UTIs when counseling patients about SGLT2i. Besides, the risk of genital infections can well be managed by pointing toward the importance of genital hygiene and early treatment once symptoms occur. Despite the broad evidence on safety of SGLT2i, there are theoretical mechanisms that could create specific risks in ADPKD patients, such as cyst infections or accelerated cystogenesis. These mechanisms warrant further investigations in future trials and will be discussed next.

SGLT2i IN ADPKD—DISEASE-SPECIFIC CONSIDERATIONS AND RISKS?

Considering the effects of SGLT2i on metabolism and renal physiology, use of these therapeutics in ADPKD appears to be promising on several levels [19] (Fig. 1). Importantly, high intraglomerular pressure has been suggested to play a role in ADPKD [20, 21], and is effectively targeted by SGLT2i. Indeed, already at a young adult age, ADPKD patients exhibit marked renal abnormalities, including a decreased effective renal plasma flow, increased filtration fraction, and slightly increased urinary albumin excretion, despite only modestly enlarged total kidney volume (TKV) and near-normal or preserved GFR [21]. SGLT2i ameliorates albuminuria, which is known to be associated with disease progression in ADPKD [22, 23]. Interestingly, the only available targeted treatment of ADPKD, the V2-receptor antagonist tolvaptan, also lowers albuminuria [24]. Besides, the induction of mild ketosis by SGLT2i is of interest in ADPKD. Ketogenic diets have been implicated as a potential treatment for ADPKD [25, 26] and elevated levels of β-hydroxybutyrate (a key ketone body) at baseline have been shown to correlate with milder future eGFR decline [27]. Along these lines, obesity appears to be a key driver of disease progression in ADPKD [28, 29] and SGLT2-inhibition contributes to lowering body weight [30]. A potential reduction of kidney stone formation through SGLT2i [31, 32] would be important in ADPKD considering the impact on disease progression [33, 34]. However, despite these promises of SGLT2-inhibition with potential disease-specific beneficial effects in ADPKD, safety risks cannot be excluded until actual evidence is generated (Fig. 1). Notably, SGLT2

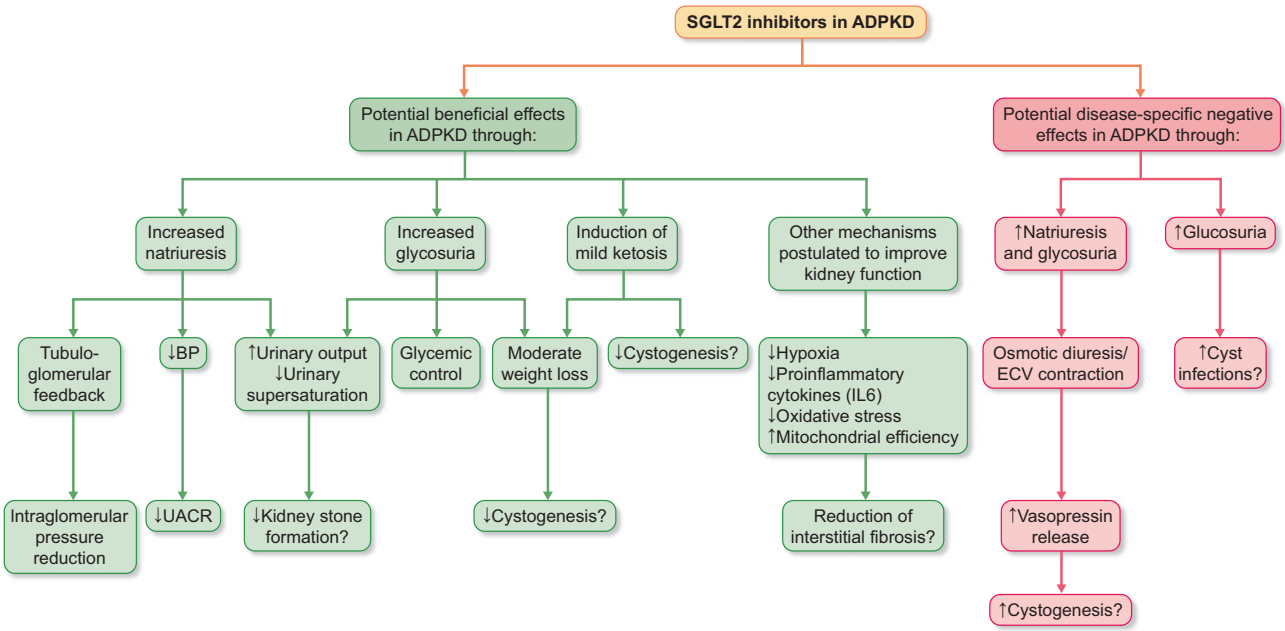

Figure 1: Potential disease-specific effects of SGLT2 inhibitors in ADPKD: benefit or risk? Mechanistically, SGLT2 inhibition could be beneficial in ADPKD on several pathophysiological levels. This includes the effect on natriuresis and its impact on both blood pressure and intraglomerular pressure as well as the observed decrease in kidney stone risk, the impact on body weight, and the induction of mild ketosis. Besides, both improvements in energy homeostasis linked to increased mitochondrial efficiency as well as decreased hypoxic and oxidative stress and reduction of inflammatory tone may reduce interstitial fibrosis. Potential ADPKD-specific safety concerns primarily stem from the observation of a mild increased vasopressin secretion in both humans and model animals treated with SGLT2i. Since infectious events of the urinary tract and specifically cyst infection may drive disease progression in ADPKD an increased risk of UTIs would be a specific concern. However, while not studied in ADPKD to date, the trials in CKD have shown exclusively an increased risk for genital infections and none of these trials found any increase in the incidence of UTIs on exposure to SGLT2i.

inhibition has been observed to increase vasopressin levels: a key hormone driving disease progression in ADPKD and the primary target of tolvaptan, the only targeted therapeutic approach proven effective for this condition [35, 36]. The effect of SGLT2i on vasopressin was first shown in rodents and then recapitulated in young adults with type 1 diabetes mellitus [37, 38]. Furthermore, two mechanistic studies in CKD patients without diabetes, DAPASALT and DIAMOND, further confirmed this result [39, 40]. Besides, glucosuria may increase the abundance of the pro-renin receptor at the plasma membrane of collecting ducts stimulating fibrosis [41] and empagliflozin has been implicated to elevate kidney weight by increasing the size of tubular epithelial and collecting duct-lining cells [42]. Whether the modest treatment-induced increase in vasopressin and glucosuria indeed could drive disease progression in ADPKD is not clear. However, this finding clearly underlines the need for evidence from randomized controlled trials specifically examining SGLT2i in patients with ADPKD including safety data on TKV.

PRECLINICAL DATA ON SGLT2i IN ADPKD

There are four studies on SGLT2i in animal models of polycystic kidney disease (PKD). Phlorizin, a dual SGLT1/2 inhibitor, and dapagliflozin, a selective SGLT2i, were analyzed in two separate studies performed in Cy/+ Han: SPRD rats, a preclinical model of ADPKD [43, 44]. Both treatments induced sustained glucosuria and osmotic diuresis. Phlorizin led to significant reductions in renal cyst growth, improved renal function, and decreased urinary albumin excretion. *In vitro*, on tubular epithelial cells isolated from Cy/+ Han: SPRD rats phlorizin inhibited MAP kinase pathway activation. Dapagliflozin improved renal function and reduced albuminuria, but did not lead to a reduction in cyst growth or tubular epithelial cell proliferation, suggesting a more limited effect in this model compared to that reported with phlorizin. In PCK rats, after 3 weeks treatment with dapagliflozin, creatinine and blood urea nitrogen clearances were increased, but the rats treated developed a 4-fold increase in albuminuria. After 6 weeks, the effect on renal function was no longer significant, whereas kidney cyst volume and kidney weight had increased in the group treated with dapagliflozin [45].

Canagliflozin, another SGLT2i, was tested in the conditional iKsp-*Pkd1*^{del} mouse model of ADPKD. The study found that canagliflozin did not slow cyst growth or improve renal function in this model and showed higher kidney weights in mice treated with a metformin/canagliflozin combination than in the untreated controls [46]. In addition, the role of glucose transport in cystogenesis was studied in a human organoid-on-chip model of ADPKD. The findings showed that glucose absorption drives cyst growth, with phlorizin and dapagliflozin reducing cyst expansion in this model [47]. It is important to note, that the differences in the models used may explain some of the conflicting findings. As an example, cysts in the Cy/+ Han: SPRD rats, in contrast to the PCK rat and the iKsp-Pkd1del mouse model, derive from proximal tubules, limiting the relation to human ADPKD where the cysts originate primarily from the distal nephron. Similarly, the human organoid model does not contain collecting duct elements. Furthermore, the fact that the apical membrane faces outwards in the cysts of this model limits the translatability of the findings. Taken together, the preclinical data available to date remain inconclusive with one out of four studies suggesting a possible harmful effect in ADPKD, one being inconclusive, one indicating a possible beneficial effect, and one

Table 1: Overview of Preclinical Evidence on SGLT2 Inhibitors in Polycystic Kidney Disease (PKD) Animal Models

Study	Model (origin of cysts)	SGLT2i	Kidney function	Kidney weight	Other findings
Wang et al. KI 2013	Han:SPRD rat (proximal tubules)	phlorizin	↑	↓	albuminuria ↓
Rodriguez et al. Kidney Blood Press Res 2015	Han:SPRD rat (proximal tubules)	dapagliflozin	↑	↑	albuminuria ↓
Kapoor et al. PLoSOne 2015	PCK rat (collecting ducts, distal tubules, loop of Henle)	dapagliflozin	?	↑	albuminuria ↑
Leonhard et al. eBioMedicine 2019	*Pkd1*$^{fl/fl}$ inducible (collecting ducts, distal and proximal tubules)	canagliflozin	↔		

Kidney function was assessed by these studies using the following measures: Wang et al. - creatinine clearance; Rodriguez et al. - blood urea nitrogen clearance and creatinine clearance; Kapoor et al. - (blood urea nitrogen clearance + creatinine clearance)/2; Leonhard et al. - blood urea nitrogen.

study reporting opposite results toward kidney function and TKV change (see Table 1).

IS THERE CLINICAL EVIDENCE REGARDING SGLT2i IN ADPKD?

Currently, there is no evidence from clinical trials on the use of SGLT2i in ADPKD due to previous diabetic and non-diabetic CKD trials listing ADPKD as an exclusion criterion. The general notion in available expert statements and reviews on the topic is that the data from preclinical models is inconclusive and that, due to the lack of clinical trial safety data, SGLT2i should currently not be used in ADPKD [19] (see Supplementary Table 1). Current evidence available in Medline is limited to observational data, comprising two case series and two case reports, collectively providing retrospective data on 29 patients with ADPKD treated with SGLT2 inhibitors [48–51]. The largest series analyzed data from 20 patients during a period of 102 ± 20 days and indicates a potential TKV increase associated with SGLT2i [51]. The retrospective study design and the use of the ellipsoid equation to estimate TKV highlight methodological limitations, suggesting that the results should be interpreted with caution. In another case series ($n = 7$, median observation time 20 months), while a significant TKV increase was also noted, eGFR slopes improved, leading the authors to speculate on a potential beneficial effect of combined therapy with RAS and SGLT2 inhibitors [49]. The lack of evidence is underlined by the recently published KDIGO guideline on the diagnosis and treatment of ADPKD, which states that "use of SGLT2i in ADPKD is not presently recommended, because people with ADPKD have been excluded from the clinical trials; thus, its safety has not been evaluated" and that "Management of diabetes in people with ADPKD should be the same as for people with other forms of CKD, with the possible exception that sodium-glucose cotransporter-2 inhibitors (SGLT2i) are not recommended at this time for people with ADPKD" [52]. Consequently, in the opinion of the KDIGO working group, at the moment, the only potential justification for using SGLT2i in people with ADPKD is the presence of heart failure. In accordance, despite the broad CKD indication in both the EMA and FDA approvals for SGLT2 inhibitors, the FDA labeling information of both dapagliflozin and empagliflozin declares that these treatments are not recommended in patients with PKD.

ONGOING STUDIES ON SGLT2i IN ADPKD

In principle, subgroup analyses of patients with ADPKD in CKD trials could contribute to our knowledge in this specific indication. However, as described before, the pivotal trials excluded this patient group and running studies allowing this subgroup are limited. There are worldwide several observational studies investigating SGLT2i in various disease states, such as in symptomatic heart failure and with CKD stage 3b-4. While these studies do not exclude patients with ADPKD, they are unlikely to result in a relevant number of these patients. Consequently, trials specifically designed for patients with ADPKD will be crucial to answer this question. In this regard, four RCT with a phase-2 design are registered in the WHO International Clinical Trials Registry Platform (Table 2). One of these studies will start in Switzerland, but primarily examines the impact of SGLT2i on electrolyte handling in ADPKD using a 2-week intervention (NCT06435858). Besides, a US-based pilot trial is currently enrolling 50 non-diabetic ADPKD patients with an eGFR of 30–90 ml/min/1.73 m^2 at risk of disease progression and not on tolvaptan at two sites (NCT05510115). The primary goal of this 12-month parallel-group, randomized, double-blind, placebo-controlled trial is to determine the safety and tolerability of the SGTL2i empagliflozin. Secondary, exploratory goals include preliminary estimates of the effect on TKV and kidney function decline as well as vascular stiffness as measured by aortic pulse wave velocity (aPWV). The single-center EMPA-PKD trial initiated in Germany has a similar recruitment aim and treatment duration (44 patients, 18 months) and examines the change in TKV as primary outcome and change in eGFR, copeptin levels, albuminuria, and blood pressure as secondary outcomes (NCT06391450). Randomization to 10 mg of empagliflozin or placebo is stratified according to absence or presence of concomitant tolvaptan intake [53]. In addition, a Japanese multicenter trial uses a randomized crossover design in 30 patients to study the effect of 10 mg of dapagliflozin on eGFR slope in a 6-month intervention (JPRN-UMIN000046275) including only patients on tolvaptan. Secondary endpoints include change in TKV, plasma vasopressin level, and 24-hour urine volume. Besides, the Renal Lifecycle Trial (NCT05374291), an RCT assessing the effect of dapagliflozin on renal and cardiovascular outcomes in patients with severe CKD, does not exclude patients with ADPKD and may thus allow for a dedicated *post hoc* subgroup analysis in this regard.

Table 2: Overview of clinical trials investigating SGLT2 inhibitors in ADPKD.

Trial	Registry no.	Design	N, duration	Key inclusion criteria	Primary outcome	Key secondary outcomes	Status
The effect of dapagliflozin in ADPKD patients using tolvaptan	JPRN-UMIN 000046275	Crossover RCT, multicenter (Japan)	30, 6 months	≥20 y, only individuals already treated by Tolvaptan	Slope of eGFR decline	Change in TKV, BP, metabolic parameters, urine volume, UACR	Completed
Feasibility of Study of empagliflozin in Patients with ADPKD	NCT05510115	RCT, parallel assignment, multicenter (USA)	50, 12 months	18–55 y; eGFR 30–90 ml/min/1.73 m^2; MIC 1C-1D-1E, Tolvaptan users excluded	Safety (adverse events, tolerability, adherence)	HtTKV; Kidney function; Aortic stiffness; Plasma copeptin levels and urinary kidney injury molecule-1; ADPKD Impact Scale	Recruitment completed
EMPA-PKD (empagliflozin 10 mg)	NCT06391450	RCT, parallel assignment single center (Germany)	44, 18 months	≥18 y, eGFR 25–90 ml/min/1.73 m^2, MIC 1C-1D-1E; Tolvaptan users eligible if taken ≥3 months	Change in TKV measured by MRI	Change in eGFR, copeptin levels, albuminuria, and blood pressure	Recruiting
SIDIA (empagliflozin 10 mg)	NCT06435858	Crossover RCT, single center (Switzerland)	40, 2 weeks	18–75 y, eGFR >30 ml/min/1.73 m^2	Calcium, phosphate, Magnesium measured by fractional excretions	24-hour urine volume, tubular handling of other electrolytes, kidney function	In Preparation
DAPA-PKD (dapagliflozin 10 mg)	NA	Phase 3 RCT, parallel assignment, multicenter (France)	400, 24 months	18–75 y, eGFR 25–90 ml/min/1.73 m^2 if age <60 or 25–45 ml/min/1.73 m^2 if age >60, MIC 1C-1D-1E or mean kidney length >16.5 cm, Tolvaptan users excluded	Change of TKV measured by MRI	Chronic slope of eGFR decline and alternative kidney function outcomes, composite cardiovascular outcome, health related QoL, kidney stones, urinary infections	In Preparation
STOP-PKD (dapagliflozin 10 mg)	NA	Phase 3 RCT, parallel assignment, multicenter (Germany, Netherlands, Spain, Austria)	420, 36 months	18–60 y, eGFR ≥25 ml/min/1.73 m^2, MIC 1D-1E, or 1C with either a *PKD1* truncating variant, or eGFR loss >3 ml/min/1.73 m^2/y, or a PROPKD score >6; Tolvaptan users excluded	Annual (chronic) slope of eGFR decline	Alternative kidney function outcomes, TKV, albuminuria, kidney stones, urinary infections, patient-reported outcome measures (QoL, pain, ADPKD Impact scale)	In Preparation

HtTKV: height-adjusted TKV; MIC: Mayo Imaging Classification; MRI: magnetic resonance imaging; QoL: quality of life.

All these studies will add very important information on safety of SGLT2i in ADPKD, but, due to their relatively small-scale and their short-term nature, are not expected to answer the question of efficacy with respect to long-term preservation of kidney function. The latter will require data from adequately powered trials with sufficient follow-up.

Upcoming trials with a phase 3 design—the final step toward using SGLT2i in ADPKD

Recently, two initiatives reported successful acquisition of funding for adequately powered trials to prove efficacy of SGLT2i in ADPKD. DAPA-PKD, a trial coordinated from Rouen and Brest (France) will recruit 400 participants in 32 study sites. Participants will be randomized to 10 mg of dapagliflozin or placebo in a 1:1 ratio over a period of 24 months; the primary endpoint will be the evolution of magnetic resonance imaging-measured TKV, while the secondary endpoints will include analyses of eGFR slope and cardiovascular endpoints. TKV was selected as the primary outcome because it is an established surrogate marker for disease progression in ADPKD, sensitive to structural changes over a relatively short follow-up period, and particularly relevant given the conflicting preclinical data suggesting that SGLT2i could potentially influence cyst growth. STOP-PKD, an initiative coordinated from Cologne (Germany) in close interaction with the Dutch DIPAK-consortium will recruit 420 patients at 24 sites in four European countries (Germany, Netherlands, Spain, Austria). As in DAPA-PKD, participants will be randomized to 10 mg of dapagliflozin or placebo in a 1:1 ratio, but for a longer period of 36 months. Importantly, the primary endpoint will be the chronic eGFR slope in STOP-PKD and secondary endpoints will cover additional outcomes relevant to renal disease progression including total eGFR slope, albuminuria, and kidney stones. To account for the vasopressin induction by SGLT2i, an interim safety analysis focusing on TKV changes at 1 year will be conducted on the first 150 participants to rule out major signals toward TKV increase while also considering eGFR data obtained until this point. Besides, a futility analysis focusing on eGFR change at 2 years will be performed on the first 200 participants. DAPA-PKD and STOP-PKD are expected to start recruitment in late 2025/early 2026. Both trials include patients from the age of 18 reflecting the urgent need for early treatment in a genetic disease like ADPKD. STOP-PKD has an upper age limit of 60 years considering that patients older than 60 years with maintained kidney function are unlikely to show rapid disease progression and comorbidities may be the key drivers of kidney function loss at this age. Examining true ADPKD-specific effects on kidney function decline of SGLT2i is central to this trial with eGFR slope as its primary endpoint. By contrast, DAPA-PKD recruits patients up to the age of 75, based on the different primary endpoint (TKV) and the key secondary endpoint (cardiovascular events). These two pivotal trials will be coordinated in close interaction including harmonization of inclusion criteria and outcome parameters to allow for an individual patient level pooled analysis after completion of the trials, the FLOZIN-PKD study, to increase power overall and for relevant subgroup analyses and to definitively settle the question on the value of SGLT2i in ADPKD. Neither DAPA-PKD nor STOP-PKD trials include participants treated with tolvaptan. This decision is driven by multiple considerations: higher urine osmolality could enhance the aquaretic effect, potentially leading to severe polyuria; patients on combined therapy may face a greater risk of discontinuation; interruptions in tolvaptan treatment during the study could complicate eGFR slope analysis; and the small size of the tolvaptan-treated subgroup would limit the potential for meaningful analyses. If SGLT2 inhibitors demonstrate benefit in ADPKD, the safety of co-administration with tolvaptan and potential added effects will need to be evaluated. Preliminary insights into short-term safety and feasibility of such association may emerge from the pilot studies outlined in Table 2.

CURRENT POSITION AND CONCLUSION

The addition of SGLT2i to the currently available treatment strategies in diabetic and non-diabetic kidney disease was an important milestone. Several lines of arguments underline their potential benefit also for patients with ADPKD. However, considering the lack of data on efficacy in this specific patient population and disease-specific safety concerns prevent the use of these therapeutics in patients with ADPKD. Several ongoing initiatives now aim to close this evidence gap including two adequately powered trials with a phase-3 design, which will allow to come to a final conclusion on the risk–benefit ratio for SGLT2i in ADPKD over the coming years.

METHODS

Literature search strategy and search results

To identify studies examining SGLT2i in ADPKD, we searched Medline, the German Clinical Trials Register DRKS, Clinicaltrials.gov, and the Cochrane library using the following combination of search terms (search date 24 November 2024): ((ADPKD) OR (PKD) OR ('polycystic kidney disease')) AND ((SGLT2i) OR (SGLT2) OR (SGLT) OR ('sodium-glucose') OR ('sodium glucose') OR (dapagliflozin) OR (empagliflozin) OR (sotagliflozin) OR (canagliflozin) OR (ertugliflozin) OR (ipragliflozin) OR (luseogliflozin) OR (remogliflozin) OR (tofogliflozin)). Medline (27 results): 12 reviews/expert opinions, four original basic research studies, two retrospective case series, two case reports, and seven publications were not considered, as they do not address SGLT2i in ADPKD in the full text; Clinicaltrials.gov: three clinical trials; ICTRP search portal: four clinical trials (five results, one trial listed twice). The results of the Medline search are summarized in Supplementary Table 1 and the results of the Clinicaltrials.gov search are in Table 2.

SUPPLEMENTARY DATA

Supplementary data are available at *Nephrology Dialysis Transplantation* online.

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AUTHORS' CONTRIBUTIONS

All authors wrote and reviewed the manuscript.

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No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

R.U.M. has received fees for consultancy from Abbvie, AICURIS, Alnylam, GSK, Vertex and Vifor and the Department II of Internal Medicine has received research funding from Alnylam, Otsuka, ThermoFisherScientific, and Vifor. Besides, R.U.M. is a member of the scientific advisory board of Santa Barbara Nutrients and leads the STOP-PKD trial. R.T.G. has received fees for consultancy and/or grants for research during the last 5 years by Abbvie, Astra-Zeneca, Bayer, Calico, Galapagos, GSK, Mironid, Otsuka, Roche, Sanofi-Genzyme, Travere, and Vertex. All money is paid to the employing institution. In addition, R.T.G. co-leads the STOP-PKD trial. D.G. and E.C.L.G. lead the DAPA-PKD trial initiative. Besides, E.C.L.G. has participated to boards or received consultancies fees from Rhythm Pharmaceuticals, Vertex, and GSK. R.S. has received fees for consultancy or study grants during the last 5 years by Astra-Zeneca, FMC, Boehringer-Ingelheim. R.S. is PI of the EMPA-PKD trial. M.C. leads the US-based SGLT2i trial (NCT05510115). K.U. leads the Japanese trial on SGTL2i in ADPKD (JPRN-UMIN 000046275).

REFERENCES

1. Vallon V, Platt KA, Cunard R *et al.* SGLT2 mediates glucose reabsorption in the early proximal tubule. *J Am Soc Nephrol* 2011;**22**:104–12. https://doi.org/10.1681/ASN.2010030246
2. Thomson SC, Rieg T, Miracle C *et al.* Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. *Am J Physiol-Regul Integr Comp Physiol* 2012;**302**:R75–83. https://doi.org/10.1152/ajpregu.00357.2011
3. Cs W. Antihypertensive and renal mechanisms of SGLT2 (sodium-glucose linked transporter 2) inhibitors. *Hypertension* 2020; **75**:894–901. https://doi.org/10.1161/HYPERTENSIONAHA.119.11684
4. Ferrannini E, Muscelli E, Frascerra S *et al.* Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014;**124**:499–508. https://doi.org/10.1172/JCI72227
5. Nuffield Department of Population Health Renal Studies Group, SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022;**400**:1788–801. https://doi.org/10.1016/S0140-6736(22)02074-8
6. Albalawy WN, Youm EB, Shipman KE *et al.* SGLT2-independent effects of canagliflozin on NHE3 and mitochondrial complex I activity inhibit proximal tubule fluid transport and albumin uptake. *Am J Physiol Renal Physiol* 2024;**326**:F1041–53. https://doi.org/10.1152/ajprenal.00005.2024
7. Sasaki T, Sugawara M, Fukuda M. Sodium-glucose cotransporter 2 inhibitor-induced changes in body composition and simultaneous changes in metabolic profile: 52-week prospective LIGHT (Luseogliflozin: The Components of Weight Loss in Japanese Patients with Type 2 Diabetes Mellitus) Study. *J Diabetes Invest* 2019;**10**:108–17. https://doi.org/10.1111/jdi.12851
8. Heerspink HJL, Perco P, Mulder S *et al.* Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. *Diabetologia* 2019;**62**:1154–66. https://doi.org/10.1007/s00125-019-4859-4
9. Zhang Y, Lin X, Chu Y *et al.* Dapagliflozin: a sodium-glucose cotransporter 2 inhibitor, attenuates angiotensin II-induced cardiac fibrotic remodeling by regulating TGFβ1/Smad signaling. *Cardiovasc Diabetol* 2021;**20**:121. https://doi.org/10.1186/s12933-021-01312-8
10. Uthman L, Homayr A, Juni RP *et al.* Empagliflozin and dapagliflozin reduce ROS generation and restore NO bioavailability in tumor necrosis factor α-stimulated human coronary arterial endothelial cells. *Cell Physiol Biochem* 2019;**53**:865–86.
11. Lee SY, Lee TW, Park GT *et al.* Sodium/glucose co-transporter 2 inhibitor, empagliflozin, alleviated transient expression of SGLT2 after myocardial infarction. *Korean Circ J* 2021;**51**:251–62. https://doi.org/10.4070/kcj.2020.0303
12. Perkovic V, Jardine MJ, Neal B *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–306. https://doi.org/10.1056/NEJMoa1811744
13. Heerspink HJL, Stefánsson BV, Correa-Rotter R *et al.* Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–46. https://doi.org/10.1056/NEJMoa2024816
14. The EMPA-KIDNEY Collaborative Group,Herrington WG, Staplin N *et al.* Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023;**388**:117–27.
15. Staplin N, Haynes R, Judge PK *et al.* Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the EMPA-Kidney trial. *Lancet Diabetes Endocrinol* 2024;**12**:39–50.
16. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024;**105**:S117–314. https://doi.org/10.1016/j.kint.2023.10.018
17. van der Aart-van der Beek AB, de Boer RA, Heerspink HJL. Kidney and heart failure outcomes associated with SGLT2 inhibitor use. *Nat Rev Nephrol* 2022;**18**:294–306. https://doi.org/10.1038/s41581-022-00535-6
18. Ge S, Liu R, Mao Y *et al.* Safety of SGLT2 inhibitors in three chronic diseases. *Int Heart J* 2023;**64**:246–51. https://doi.org/10.1536/ihj.22-441
19. Afsar B, Afsar RE, Demiray A *et al.* Sodium–glucose cotransporter inhibition in polycystic kidney disease: fact or fiction. *Clin Kidney J* 2022;**15**:1275–83. https://doi.org/10.1093/ckj/sfac029
20. Ishii R, Kai H, Nakajima K *et al.* Renal hemodynamic and functional changes in patients with ADPKD. *Kidney360* 2024;**5**:724–31. https://doi.org/10.34067/KID.0000000000000412
21. Meijer E, Rook M, Tent H *et al.* Early renal abnormalities in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2010;**5**:1091–8. https://doi.org/10.2215/CJN.00360110
22. Chapman AB, Johnson AM, Gabow PA *et al.* Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1994;**5**:1349–54. https://doi.org/10.1681/ASN.V561349
23. Sharp C, Johnson A, Gabow P. Factors relating to urinary protein excretion in children with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1998;**9**:1908–14. https://doi.org/10.1681/ASN.V9101908
24. Gansevoort RT, Meijer E, Chapman AB *et al.* Albuminuria and tolvaptan in autosomal-dominant polycystic kidney disease: results of the TEMPO 3:4 Trial. *Nephrol Dialysis Transplant* 2016;**31**:1887–94.
25. Cukoski S, Lindemann CH, Arjune S *et al.* Feasibility and impact of ketogenic dietary interventions in polycystic kidney disease: KETO-ADPKD—a randomized controlled trial. *Cell Rep Med* 2023; **4** 101283. https://www.cell.com/cell-reports-medicine/abstract/S2666-3791 (23)00477-9
26. Oehm S, Steinke K, Schmidt J *et al.* RESET-PKD: A pilot trial on short-term ketogenic interventions in autosomal

dominant polycystic kidney disease. *Nephrol Dialysis Transplant* 2023;**38**:1623–35.
27. Knol MGE, Bais T, Geertsema P *et al.* Higher beta-hydroxybutyrate ketone levels associated with a slower kidney function decline in ADPKD. *Nephrol Dialysis Transplant* 2024;**39**:838–47. https://doi.org/10.1093/ndt/gfad239
28. Nowak KL, You Z, Gitomer B *et al.* Overweight and obesity are predictors of progression in early autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2018;**29**:571–8. https://doi.org/10.1681/ASN.2017070819
29. Hopp K, Catenacci VA, Dwivedi N *et al.* Weight loss and cystic disease progression in autosomal dominant polycystic kidney disease. *iScience* 2022;**25**:103697. https://doi.org/10.1016/j.isci.2021.103697
30. Cho YK, Kim Y-J, Jung CH. Effect of Sodium-glucose cotransporter 2 inhibitors on weight reduction in overweight and obese populations without diabetes: a systematic review and a meta-analysis. *J Obes Metabol Synd* 2021;**30**:336.
31. Paik JM, Tesfaye H, Curhan GC *et al.* Sodium-glucose cotransporter 2 inhibitors and nephrolithiasis risk in patients with type 2 diabetes. *JAMA Intern Med.* 2024;**184**:265–74. https://doi.org/10.1001/jamainternmed.2023.7660
32. Schietzel S, Bally L, Cereghetti G *et al.* Impact of the SGLT2 inhibitor empagliflozin on urinary supersaturations in kidney stone formers (SWEETSTONE trial): protocol for a randomised, double-blind, placebo-controlled cross-over trial. *BMJ Open* 2022;**12**:e059073. https://doi.org/10.1136/bmjopen-2021-059073
33. Cornec-Le Gall E, Audrézet M-P, Rousseau A *et al.* The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016;**27**:942–51. https://doi.org/10.1681/ASN.2015010016
34. Torres JA, Rezaei M, Broderick C *et al.* Crystal deposition triggers tubule dilation that accelerates cystogenesis in polycystic kidney disease. *J Clin Invest* 2019;**129**:4506–22.
35. Torres VE, Harris PC. Strategies targeting cAMP signaling in the treatment of polycystic kidney disease. *J Am Soc Nephrol* 2014;**25**:18–32. https://doi.org/10.1681/ASN.2013040398
36. Torres VE, Chapman AB, Devuyst O *et al.* Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012;**367**:2407–18. https://doi.org/10.1056/NEJMoa1205511
37. Masuda T, Muto S, Fukuda K *et al.* Osmotic diuresis by SGLT2 inhibition stimulates vasopressin-induced water reabsorption to maintain body fluid volume. *Physiol Rep* 2020;**8**:e14360. https://doi.org/10.14814/phy2.14360
38. Lytvyn Y, Bjornstad P, Katz A *et al.* SGLT2 inhibition increases serum copeptin in young adults with type 1 diabetes. *Diabetes Metab* 2020;**46**:203–9.
39. Sen T, Scholtes R, Greasley PJ *et al.* Effects of dapagliflozin on volume status and systemic haemodynamics in patients with chronic kidney disease without diabetes: results from DAPASALT and DIAMOND. *Diabetes Obes Metab* 2022;**24**:1578–87.
40. Marton A, Saffari SE, Rauh M *et al.* Water conservation overrides osmotic diuresis during SGLT2 inhibition in patients with heart failure. *J Am Coll Cardiol* 2024;**83**:1386–98. https://doi.org/10.1016/j.jacc.2024.02.020
41. Gogulamudi VR, Arita DY, Bourgeois CRT *et al.* High glucose induces trafficking of prorenin receptor and stimulates profibrotic factors in the collecting duct. *Sci Rep* 2021;**11**:13815. https://doi.org/10.1038/s41598-021-93296-4
42. Sinha F, Federlein A, Biesold A *et al.* Empagliflozin increases kidney weight due to increased cell size in the proximal tubule S3 segment and the collecting duct. *Front Pharmacol* 2023;**14**:1118358. https://doi.org/10.3389/fphar.2023.1118358
43. Wang X, Zhang S, Liu Y *et al.* Targeting of sodium-glucose cotransporters with phlorizin inhibits polycystic kidney disease progression in Han:SPRD rats. *Kidney Int* 2013;**84**:962–8. https://doi.org/10.1038/ki.2013.199
44. Rodriguez D, Kapoor S, Edenhofer I *et al.* Inhibition of sodium-glucose cotransporter 2 with dapagliflozin in Han: SPRD rats with polycystic kidney disease. *Kidney Blood Press Res* 2015;**40**:638–47.
45. Kapoor S, Rodriguez D, Riwanto M *et al.* Effect of sodium-glucose cotransport inhibition on polycystic kidney disease progression in PCK rats. *PLoS ONE* 2015;**10**:e0125603. https://doi.org/10.1371/journal.pone.0125603
46. Leonhard WN, Song X, Kanhai AA *et al.* Salsalate, but not metformin or canagliflozin, slows kidney cyst growth in an adult-onset mouse model of polycystic kidney disease. *EBioMedicine* 2019;**47**:436–45. https://doi.org/10.1016/j.ebiom.2019.08.041
47. Li SR, Gulieva RE, Helms L *et al.* Glucose absorption drives cystogenesis in a human organoid-on-chip model of polycystic kidney disease. *Nat Commun* 2022;**13**:7918. https://doi.org/10.1038/s41467-022-35537-2
48. Minatoguchi S, Hayashi H, Umeda R *et al.* Additional renoprotective effect of the SGLT2 inhibitor dapagliflozin in a patient with ADPKD receiving tolvaptan treatment. *CEN Case Rep* 2024;**13**:419–24. https://doi.org/10.1007/s13730-024-00859-1
49. Yoshimoto M, Sekine A, Suwabe T *et al.* Dapagliflozin treatment in patients with chronic kidney disease associated with autosomal dominant polycystic kidney disease. *Clin Kidney J* 2024;**17**:sfae186. https://doi.org/10.1093/ckj/sfae186
50. Nakatani S, Morioka F, Uedono H *et al.* Dapagliflozin administration for 1 year promoted kidney enlargement in patient with ADPKD. *CEN Case Rep* 2024;**13**:284–9. https://doi.org/10.1007/s13730-023-00840-4
51. Morioka F, Nakatani S, Uedono H *et al.* Short-term dapagliflozin administration in autosomal dominant polycystic kidney disease-a retrospective single-arm case series study. *JCM* 2023;**12**:6341. https://doi.org/10.3390/jcm12196341
52. Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical Practice Guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD). *Kidney Int* 2025;**107**:S1–S239. https://doi.org/10.1016/j.kint.2024.07.009
53. Bahlmann-Kroll E, Häckl S, Kramer S *et al.* Empagliflozin in patients with autosomal dominant polycystic kidney disease (EMPA-PKD): study protocol for a randomised controlled trial. *BMJ Open* 2024;**14**:e088317. https://doi.org/10.1136/bmjopen-2024-088317

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