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Beyond the Average Patient: A Population-Focused Review of Sodium-Glucose Cotransporter 2 Inhibitors in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors slow the loss of kidney function across a wide range of causes of chronic kidney disease (CKD). Still, the trials that established this benefit excluded autosomal dominant polycystic kidney disease (ADPKD) because these drugs raise vasopressin, the main hormonal driver of cyst growth. Since then, observational studies, a small crossover trial, and two meta-analyses with differing conclusions have appeared. This review argues that the question of whether SGLT2 inhibitors work in ADPKD cannot be answered for the disease as a whole, because ADPKD varies widely in genotype, rate of progression, CKD stage, comorbidity, and tolvaptan use. In this structured narrative review, PubMed and ClinicalTrials.gov were searched, and the clinical, trial, and preclinical evidence was mapped to these patient groups. Thirteen clinical studies were identified (two randomised, four comparative cohorts, four single-arm studies and three case reports), most of them small, short, and from Japan. The reassuring data come from two groups: older patients, many with type 2 diabetes or cardiovascular disease, whose kidney decline may owe as much to comorbidity as to cysts; and a few rapidly progressing patients already taking tolvaptan, in whom the only randomised trial reporting kidney outcomes found slower kidney growth and a better estimated glomerular filtration rate (eGFR) slope despite higher vasopressin. The evidence is almost silent on young, rapidly progressive patients not taking tolvaptan, the group in whom the concern about cyst growth is greatest, and the few case-level data in this group show kidney enlargement and falling eGFR. No study reports results by genotype or Mayo imaging class beyond individual case descriptions, and there are few or no data for slow progressors, early CKD, or heart failure. Phase 3 trials will answer the question for rapid progressors off tolvaptan from about 2030, but not for most other groups. Until then, SGLT2 inhibitors seem reasonable when there is a diabetic or heart-failure indication, based on evidence in those conditions rather than in ADPKD. The KDIGO guideline, although the Kidney Disease: Improving Global Outcomes (KDIGO) guideline does not yet recommend them in ADPKD. They should be considered within trials for rapid progressors, and should not be used off tolvaptan solely to slow ADPKD. Future trials should report results by genotype, imaging class, and tolvaptan use.

Categories: Internal Medicine, Nephrology, Endocrinology/Diabetes/Metabolism
Keywords: autosomal dominant polycystic kidney disease (adpkd), ckd (chronic kidney disease), dapagliflozin, empagliflozin, patient selection , sglt2-inhibitors, tolvaptan, total kidney volume, vasopressin

Introduction And Background

Autosomal dominant polycystic kidney disease (ADPKD) is a major inherited cause of kidney failure and the fourth most common cause of kidney replacement therapy worldwide [1]. Its course is far from uniform. Disease caused by truncating variants in PKD1 typically reaches kidney failure in the sixth decade, while non-truncating PKD1 variants follow a more variable course and PKD2 disease progresses more slowly, with kidney failure often arising in the eighth decade [1]. Within each genotype, the Mayo imaging classification assigns patients with typical (class 1) disease to five classes (1A to 1E) according to height-adjusted total kidney volume (htTKV) for age, with each successive class reflecting increasingly rapid loss of kidney function [1]; the trials discussed below use classes 1C to 1E to define rapid progression. Patients also differ in chronic kidney disease (CKD) stage, in comorbidities such as diabetes and heart failure, and in whether they take tolvaptan. Tolvaptan, a vasopressin V2 receptor antagonist, is the only approved disease-modifying drug for ADPKD [2,3]. However, it is recommended only for people at risk of rapid progression, causes an aquaresis that requires patients to drink large volumes, and requires regular liver monitoring [1].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have transformed the treatment of CKD. In DAPA-CKD, EMPA-KIDNEY, and CREDENCE, they slowed estimated glomerular filtration rate (eGFR) decline and reduced the risk of kidney failure in people with and without diabetes (CREDENCE enrolled only people with type 2 diabetes), and some trials also showed cardiovascular benefits [4-6]. ADPKD, however, was an exclusion criterion in these trials [7,8]. The reason was mechanistic: SGLT2 inhibitors cause glycosuria and an osmotic diuresis, and the body responds by raising vasopressin to conserve water. Because vasopressin, acting through cyclic AMP, is the main hormonal driver of cyst growth, an SGLT2 inhibitor could in principle

accelerate the very process that tolvaptan is designed to block [8,9]. Given this uncertainty, the 2025 Kidney Disease: Improving Global Outcomes (KDIGO) guideline for ADPKD does not currently recommend SGLT2 inhibitors for people with ADPKD, including for the management of diabetes, because their safety in ADPKD has not been evaluated. The guideline also suggests not using them to slow eGFR decline until further research is available [1,8].

Since 2023, evidence has accumulated in the form of observational cohorts, case series, one open-label crossover trial, and two meta-analyses published in 2026 [10,11]. Tantush et al. pooled eight studies including 3,180 patients and reported slower eGFR decline with SGLT2 inhibitors, but 2,640 of those patients came from a single US cohort of people with type 2 diabetes [10]. A second meta-analysis, by Kanbay et al., pooled six studies and 451 patients. It found slower eGFR decline than before treatment (mean difference: 0.65 mL/min/1.73 m^2 per year, 95% CI: 0.05 to 1.26) but no significant difference compared with patients not taking SGLT2 inhibitors and no effect on total kidney volume. The authors concluded that the evidence was insufficient to establish benefit [11]. Several other reviews have also appeared [9,12,13]. Bou Antoun et al., in particular, proposed that future studies should stratify patients by genotype, mechanism, albuminuria, and diabetes status [9].

These pooled results need careful reading. The two analyses drew on the same small body of evidence but reached different conclusions. The larger analysis combined studies of very different people, from older American adults with diabetes to relatively younger Japanese patients taking tolvaptan, and it answered a population-average question. If the balance of benefit and harm differs between these groups, as the mechanism suggests it should, a pooled estimate can be reassuring overall while saying little about the patients for whom the decision matters most.

The aim of this review is therefore different from that of the existing syntheses. Instead of estimating an average effect, it divides patients into groups by rate of progression, genotype, comorbidity, CKD stage, and tolvaptan use. For each group, it summarises the clinical, trial, and preclinical evidence, identifies where evidence is lacking, and considers whether ongoing trials are likely to fill these gaps.

Review

Literature search approach

This is a structured narrative review. PubMed was searched on October 7, 2026, and again on October 12, 2026, by combining ADPKD terms (the MeSH heading for autosomal dominant polycystic kidney disease, "polycystic kidney*", ADPKD, PKD1 and PKD2) with SGLT2 terms (the MeSH heading for SGLT2 inhibitors, SGLT2 and its variants, "gliflozin*" and the names of individual agents, including phlorizin). Both runs returned 58 records. For the preclinical section, a separate PubMed search on October 12, 2026, combining polycystic kidney disease terms with SGLT and glucose-transport terms and with animal and organoid terms, returned 12 records. ClinicalTrials.gov was searched on both dates for registered trials of SGLT2 inhibitors in polycystic kidney disease, identifying four ADPKD trials, and the reference lists of included studies and reviews were checked. The full search strings are presented in the Appendix.

Clinical studies of any design, trial registrations, meta-analyses, and preclinical studies of SGLT2 inhibitors in ADPKD were included. Studies in children and adolescents (under 18 years) were excluded. The review focused on PKD1- and PKD2-related disease, but only one included study reported a genetic diagnosis [14], so in practice the evidence describes clinically diagnosed ADPKD, which may include some patients with variants in other cystic kidney disease genes [1]. Risk of bias was assessed with the Cochrane risk-of-bias tool for randomised trials, version 2 (RoB 2) [15] for randomised trials, the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool [16] for non-randomised comparative studies, the Joanna Briggs Institute (JBI) critical appraisal checklists [17] for case series and case reports, and A MeaSurement Tool to Assess systematic Reviews, version 2 (AMSTAR 2) [18] for meta-analyses.

These ratings were used to weigh the evidence for each patient group rather than to pool it. Each group was assigned a confidence rating based on study design, size and consistency. Moderate confidence required at least one randomised trial reporting kidney outcomes at low risk of bias, or more than one randomised trial with some concerns, supported by consistent findings from other studies. Low confidence was assigned when the evidence included one randomised trial with some concerns, or two or more comparative observational studies with consistent findings. Very low confidence was assigned when the evidence was limited to single-arm studies, case series or case reports, or when comparative studies were inconsistent. No usable data were assigned when there were no data or data from only one to three patients. This rating summarises the overall body of evidence for each group, is specific to this review and is shown at the end of each patient group's section.

Because no pooled analysis was performed, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was not applied. A single author carried out study selection, data extraction, and risk-of-bias assessment, and the authors of included studies were not contacted for missing data. One cohort study whose full text was not accessible to the author was assessed from its abstract and from the data reported by Tantush et al. [10], and a second meta-analysis was also only accessible as an abstract, which

was described but not appraised [11].

Mechanistic rationale by patient group

The expected balance of benefit and harm from an SGLT2 inhibitor in ADPKD is not the same for every patient. It depends primarily on whether tolvaptan has already blocked the effect of vasopressin on cysts.

Potential Benefits

SGLT2 inhibitors act on the proximal tubule, whereas most ADPKD cysts arise from the distal nephron and collecting duct [8]. Their established kidney benefits come from restoring tubuloglomerular feedback and lowering glomerular pressure, which should apply in ADPKD as in other forms of CKD [9]. They also raise haemoglobin, lower serum uric acid, lower blood pressure and body weight, and induce mild ketosis [9]. Ketosis is of particular interest because ketogenic diets and β-hydroxybutyrate slowed cyst growth in rodent models of polycystic kidney disease [19]. Several of these effects have been seen in patients with ADPKD: in the only randomised trial reporting kidney outcomes, haemoglobin was higher (14.1 vs 13.4 g/dL) and uric acid lower (5.09 vs 5.84 mg/dL) during the dapagliflozin period [20].

Potential Harms

The osmotic diuresis caused by glycosuria is followed by a compensatory rise in vasopressin. In rats, SGLT2 inhibition increased vasopressin and water reabsorption in the collecting duct [21,22]. In people, copeptin (a stable marker of vasopressin) rose with SGLT2 inhibitors in type 1 diabetes, in non-diabetic CKD (the DAPASALT and DIAMOND studies) and in heart failure [23-25]. In ADPKD, this response would increase cyclic AMP signalling in exactly the nephron segments from which most cysts arise. Blocking proximal sodium and glucose reabsorption also delivers more solute to downstream segments, adding to their workload [8].

Animal Models and Their Limits

Only four studies have tested SGLT inhibitors in animal models of polycystic kidney disease, and their results depend on the model. In the Han:SPRD rat, whose cysts arise mainly in the proximal tubule, the dual SGLT1 and SGLT2 inhibitor phlorizin reduced cyst growth and preserved kidney function [26], whereas dapagliflozin did not affect cyst growth in the same model, although it improved creatinine clearance and albuminuria and significantly increased kidney weight [27]. In the PCK rat, a model of autosomal recessive polycystic kidney disease (ARPKD) caused by a Pkhd1 mutation, with distal and collecting-duct cysts, dapagliflozin increased cyst volume and kidney weight (by 23%), with hyperfiltration and a four-fold rise in albuminuria; renal cyclic AMP was unchanged [28] (Figure *1*). In an orthologous Pkd1 mouse model, canagliflozin had no effect on cyst growth or kidney function [29]. In a human kidney organoid-on-chip model, cyst expansion was driven by glucose absorption through SGLT2 on the cyst-lining epithelium, and both phlorizin and dapagliflozin held cyst growth at baseline, although they did not shrink established cysts; the cysts in this model were polarised inside out, with their apical surface facing outwards, which limits how far the findings apply to human kidneys [30]. None of these models reproduces the slow, decades-long course of human ADPKD, and none tested an SGLT2 inhibitor alongside a vasopressin antagonist. These gaps mean that the group-specific hypotheses set out below cannot yet be tested in animal models.

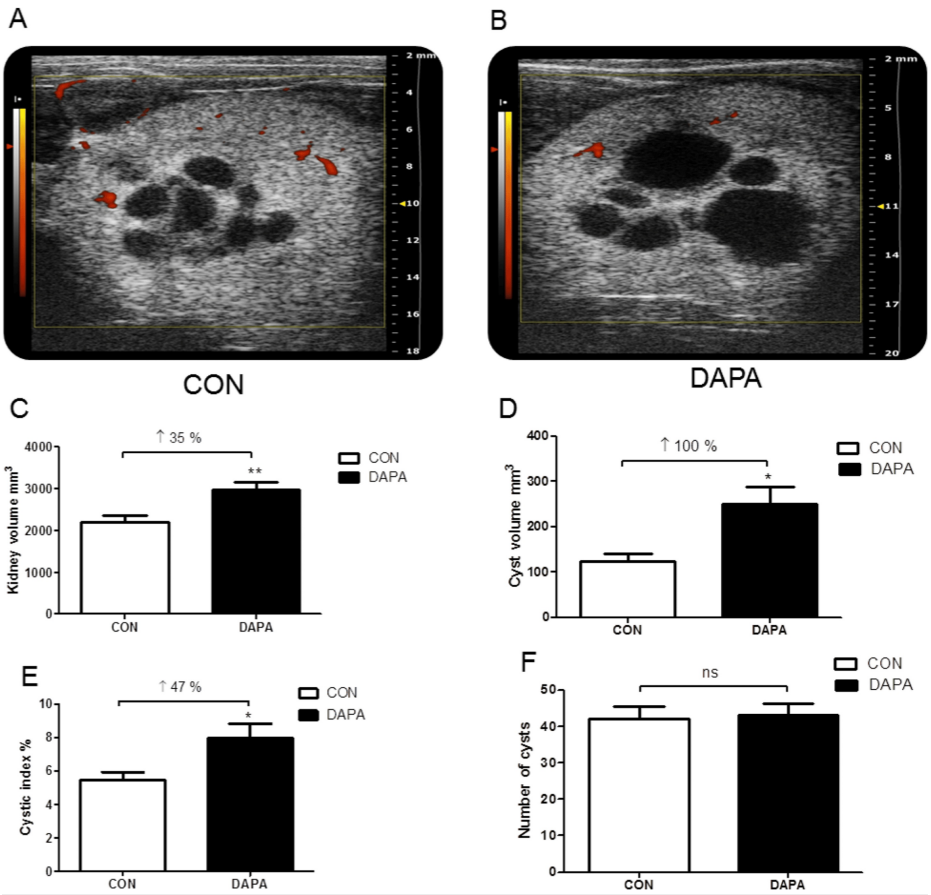


FIGURE 1: Effect of dapagliflozin on kidney volume and cystic index in the PCK rat, a model of autosomal recessive polycystic kidney disease

*P < 0.05. **P < 0.01

(A, B) Typical power Doppler ultrasound images of a kidney from a control (CON) and a dapagliflozin-treated (DAPA) rat. (C-F) Change in kidney volume, cyst volume, cystic index, and number of cysts; n = 6 rats (12 kidneys) per group; columns show mean ± standard error

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ns: not significant

Why Kidney Volume May Mislead on SGLT2 Inhibitors

Total kidney volume (TKV) is the main imaging marker of ADPKD progression. However, SGLT2 inhibition enlarges normal mouse kidneys by about 13% through tubular hypertrophy, without any cysts; the enlarged segments include the S3 proximal tubule and the collecting duct, the segment from which most cysts arise [31]. An early rise in TKV after starting an SGLT2 inhibitor may therefore reflect hypertrophy or fluid shifts rather than cyst growth. This matters for interpreting the case series below, in which TKV rose within weeks to months, and for trials that use TKV as their primary endpoint.

Expected Balance by Group

Putting these strands together suggests a different expected balance for each patient group (Figure *2*). These expectations are qualitative hypotheses drawn from the benefits, harms and animal data described above; they are not the output of a quantitative or computational model, and they are tested against the clinical evidence in the next section. In patients taking tolvaptan, the V2 receptor is already blocked, so the rise in vasopressin may have little effect on cysts and the general kidney benefits should remain; the hypothesised balance is favourable. In rapid progressors not taking tolvaptan, the rise in vasopressin is unopposed in kidneys that are already growing quickly; the hypothesised balance is uncertain at best and possibly unfavourable. In patients with type 2 diabetes or heart failure, there are proven benefits for the comorbidity

itself, and decline is often driven by factors other than cyst growth; the hypothesised balance is favourable. In slow progressors and in early CKD, the expected balance is unknown: cyst-driven harm would matter less in slow progressors, but benefit would take years to show, and early CKD is the window in which disease-modifying treatment has most to gain or lose.

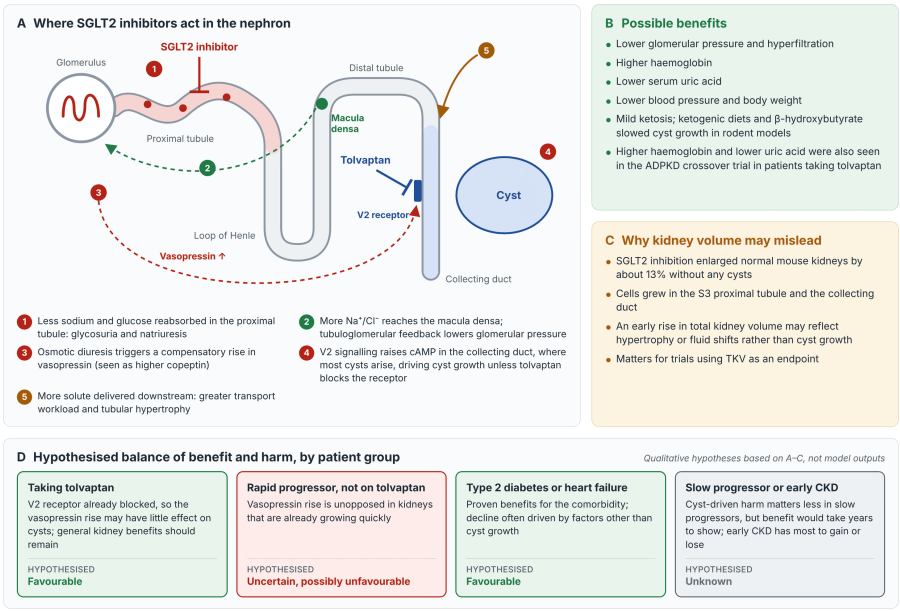


FIGURE 2: Proposed mechanisms by which SGLT2 inhibitors may benefit or harm the kidney in ADPKD

(A) SGLT2 inhibition in the proximal tubule causes glycosuria and natriuresis (1); more sodium chloride reaches the macula densa, restoring tubuloglomerular feedback and lowering glomerular pressure (2); the osmotic diuresis triggers a compensatory rise in vasopressin (3), which acts on V2 receptors in the collecting duct, where most cysts arise, raising cyclic AMP and driving cyst growth (4) unless the receptor is blocked by tolvaptan; and more solute is delivered to downstream segments, increasing their workload (5). (B) Possible benefits. (C) Tubular hypertrophy can increase kidney volume without cyst growth. (D) Hypothesised balance of benefit and harm by patient group, based on (A) to (C); these are qualitative hypotheses, not model outputs

ADPKD: autosomal dominant polycystic kidney disease; cAMP: cyclic adenosine monophosphate; CKD: chronic kidney disease; Na^+/Cl^-: sodium and chloride ions; SGLT2: sodium-glucose cotransporter 2; TKV: total kidney volume; V2: vasopressin type 2

Original figure created by the author with the assistance of Claude (Anthropic, San Francisco, CA), based on [8,9,19-25,31]

What the clinical evidence shows, by patient group

Overview of the Evidence Base

Thirteen clinical studies of SGLT2 inhibitors in ADPKD were identified (Table *1*). Two were randomised: an open-label crossover trial of dapagliflozin in 27 patients taking tolvaptan [20] and a mechanistic crossover study of empagliflozin with two two-week treatment periods in 16 patients (15 completed both periods) whose results have been posted on ClinicalTrials.gov but not yet published [32]. Four were comparative cohort studies [33-36], four were single-arm studies or case series [37-40], and three were case reports [14,41,42]. Seven came from Japan and two from the United States. Apart from three electronic health record studies [34-36], most were small, and follow-up ranged from two weeks to several years, although most studies followed patients for two years or less. No study reported Mayo class in all patients alongside genotype, and some patients may appear in more than one Japanese report from the same centres [33,38,41,42].

Study	Design	Country	Patients on SGLT2i	Comparator	Follow-up	Age (years)	T2D	Tolvaptan	Kidney function findings	Kidney volume and other findings	Risk of bias (tool)
Uchiyama et al., 2025 [20]	Open-label crossover RCT	Japan	27	Own control period	12 months (two 6-month periods)	49.7	0%	100%	eGFRcr-cys slope 2.57 vs −5.65/year (p = 0.002)	TKV −0.44% vs +5.04% over 6 months (p = 0.01)	Some concerns (RoB 2)
SIDIA, 2026 [32]†	Single-blind crossover RCT	Switzerland	16 (15 analysed)	Placebo period	6 weeks (two 2-week periods, 2-week washout)	Median 43	NR	Allowed	Not assessed	Urine volume 4.6 vs 3.8 L/day	Some concerns, provisional (RoB 2)
Nakajima et al., 2025 [33]	Retrospective cohort	Japan	24	24 on tolvaptan alone	Mean 21 months	47	0%	100%	Adjusted chronic slope −1.72 vs −2.30/year (p = 0.60)	–	Serious (ROBINS-I)
Eswarappa et al., 2025 [34]	Cohort with target trial emulation	USA	348 (217 in diabetic subgroup)	198 on DPP-4i (diabetic subgroup)	12 months	68	62%	0.3%	Steeper decline 0–3 months, then 1.29/90 days slower than DPP-4i	–	Serious for pre/post; moderate vs DPP-4i (ROBINS-I)
Yen et al., 2025 [35]‡	Target trial emulation, propensity-matched	USA (TriNetX)	2,640	2,640 matched non-users	Up to 7 years (2015–2022)	64.6	100%	NR	Dialysis HR 0.657 vs non-users and 0.458 vs DPP-4i	AKI HR 0.896; death HR 0.840	Serious, abstract only (ROBINS-I)
Chang et al., 2026 [36]	TriNetX cohort, propensity-matched	Global	187	187 non-users	Median 4 years	About 60	0%	Matched	Dialysis 10.2% vs 23.0% (HR 0.35)	–	Serious (ROBINS-I)
Yoshimoto et al., 2024 [37]	Case series	Japan	7	None	Median 20 months	52	0%	57%	Slope improved in five of six (p = 0.12)	htTKV growth faster in five of five (p = 0.04)	High risk (JBI)
Morioka et al., 2023 [38]	Case series	Japan	20	None	About 3 months	51	5%	55%	eGFR 47.9 to 40.8	htTKV growth −1.4% to +23.9%/year	High risk (JBI)
Nishida et al., 2025 [39]	Case series	Japan	4	Two on tolvaptan alone	About 28 months	39–74	0% at baseline	100%	Slopes improved in all four	htTKV grew in two of four	High risk (JBI)
Cau et al., 2025 [40]	Registry cohort	Canada	17	None	Median 21 months	66	67%	15%	No change in slope (p = 0.48)	AKI in one of 17	Moderate to high risk (JBI)
Nakatani et al., 2024 [41]	Case report	Japan	1	None	11 months	38	No	No	eGFR 67.3 to 51.4	TKV +40%	Anecdotal (JBI)
Minatoguchi et al., 2024 [42]	Case report	Japan	1	None	24 months	NR (diagnosed at 30)	No	Yes	Slope −4.90 to −1.44/year	TKV stable	Anecdotal (JBI)
Uruci et al., 2026 [14]	Case report (PKD2 genotype)	Italy	1	None	18 months	58	No	No	eGFR stable	Proteinuria fell 82–85%	Anecdotal (JBI)

TABLE 1: Characteristics and main findings of clinical studies of SGLT2 inhibitors in ADPKD

†Registry results only; not yet published. ‡Abstract only; full text not available; age from Tantush et al. [10]

A dash indicates that no further findings are summarised

AKI: acute kidney injury; DPP-4i: dipeptidyl peptidase 4 inhibitor; eGFR: estimated glomerular filtration rate (mL/min/1.73 m²); eGFRcr-cys: eGFR calculated from creatinine and cystatin C; HR: hazard ratio; htTKV: height-adjusted total kidney volume; JBI: Joanna Briggs Institute; NR: not reported; PKD2: polycystin 2 gene; RCT: randomised controlled trial; RoB 2: Cochrane risk-of-bias tool for randomised trials, version 2; ROBINS-I: Risk Of Bias In Non-randomised Studies of Interventions; SGLT2i: sodium-glucose cotransporter 2 inhibitor; T2D: type 2 diabetes; TKV: total kidney volume

Rapid Progressors on Tolvaptan

This is the only group with randomised evidence. In the crossover trial by Uchiyama et al., 27 non-diabetic patients on tolvaptan (20 of 27, or 74%, in Mayo class 1C to 1E) received dapagliflozin 10 mg for six months and usual care for six months [20]. The eGFR slope, calculated from cystatin C and creatinine over months one to six of each period (deliberately leaving out the initial dip, because there was no washout), was 2.57 ±

7.88 mL/min/1.73 m² per year with dapagliflozin and −5.65 ± 9.57 without it (p = 0.002); with creatinine alone the difference was smaller and not significant (1.03 vs −3.66, p = 0.06). TKV changed by −0.44% over six months with dapagliflozin and +5.04% without it (p = 0.01). Plasma vasopressin was higher during the dapagliflozin period (4.52 vs 3.58 pg/mL), yet urine volume did not change. In other words, vasopressin rose, but kidney growth slowed, which is what one would expect if tolvaptan blocks the effect of the extra vasopressin. Without a washout, effects of dapagliflozin could have carried over into the usual-care period.

The investigators found no significant carryover or order effects for the eGFR slope (carryover p = 0.17), or TKV change (p = 0.39), but a trial of 27 patients has little power to detect them. Any carryover is more likely to have narrowed the difference between periods than widened it: in patients who took dapagliflozin first, eGFR rose slightly after it was stopped as the initial dip reversed. The trial was open label, had no washout, and lasted only a year, so it is rated as having some concerns for bias. Supporting data come from a two-centre cohort that compared 24 patients on tolvaptan and dapagliflozin with 24 on tolvaptan alone and found a similar adjusted chronic eGFR slope (−1.72 vs −2.30 per year, p = 0.60), with higher haemoglobin and lower uric acid in the dapagliflozin group [33], and from a case series and a case report in which eGFR slopes improved after dapagliflozin was added to tolvaptan [39,42]. In the Mayo class 1E patient described by Minatoguchi et al., the slope improved from −4.90 to −1.44 per year while vasopressin rose from 3.9 to 6.7 pg/mL [42]. Not all data are reassuring: in Nishida's series, htTKV grew by 3.65% per year in a 39-year-old patient despite tolvaptan [39]. Overall confidence for this group: low.

Rapid Progressors Not on Tolvaptan

There are no reassuring data for this group. The clearest case is a 38-year-old woman with Mayo class 1D disease and no diabetes who declined tolvaptan and asked for dapagliflozin [41]. Over 340 days, her TKV rose from 1,641 to 2,297 mL, about 40%, and her eGFR fell from 67.3 to 51.4 mL/min/1.73 m². After the drug was stopped, TKV fell slightly to 2,263 mL, and eGFR recovered to 55.1, which suggests that part of the change may have been haemodynamic or due to hypertrophy rather than cyst growth. In a single-centre series of 20 patients, annual htTKV growth rose from −1.4% per year before dapagliflozin to 23.9% per year after about three months of treatment, and htTKV increased both in the nine patients not taking tolvaptan and in the 11 who were [38]. Eight of the 20 stopped the drug within six months because of falling eGFR or rising kidney volume. This was a single-centre retrospective series with very short follow-up and TKV estimated with a simple ellipsoid formula, and it may overlap with the case above. Overall confidence for this group: very low.

Patients With Type 2 Diabetes or Cardiovascular Disease

Many of the patients studied belong to this group, and they look quite different from the patients in the Japanese series. In a cohort of 348 US veterans (mean age 68, 93% men, 62% with type 2 diabetes, almost none on tolvaptan), eGFR fell more steeply in the first three months after starting an SGLT2 inhibitor, as expected from the initial dip, and then stabilised: the slope was −0.07 mL/min/1.73 m² per 90 days from months three to 12, compared with −0.79 before treatment [34]. In a target trial emulation in the diabetic subgroup, the decline from months three to 12 was 1.29 mL/min/1.73 m² per 90 days slower than with DPP-4 inhibitors [34]. The largest data set, a target trial emulation in the TriNetX US network, matched 2,640 SGLT2 inhibitor users with polycystic kidney disease and type 2 diabetes to non-users and found lower risks of dialysis (hazard ratio 0.657), acute kidney injury (0.896) and death (0.840); against DPP-4 inhibitors, the hazard ratio for dialysis was 0.458 [35]. Only the abstract of this study was available; it did not specify ADPKD, and it lacked imaging and genetic data, so residual confounding is likely.

A province-wide Canadian registry of 17 patients (mean age 66, 67% with diabetes, 20% with heart failure) found one episode of acute kidney injury (AKI) and no change in eGFR slope [40]. These findings agree with each other, but they come from older patients whose kidney decline is likely to be driven as much by diabetes, hypertension, and vascular disease as by cysts. None of these studies reported Mayo class or TKV change, and only the TriNetX cohort reported hard kidney outcomes such as dialysis. Overall confidence for this group: low.

Patients Without Diabetes

Most of the non-diabetic evidence comes from small Japanese studies in which most patients were also taking tolvaptan [20,33,39,42]. Outside that setting, the data are a single-centre case series of seven patients with advanced CKD [37], the short series discussed above [38], and one large cohort study from the TriNetX network (TriNetX, LLC, Cambridge, MA) [36]. In that study, 187 non-diabetic patients with ADPKD who took an SGLT2 inhibitor had a lower rate of chronic dialysis than 187 matched non-users (10.2% vs 23.0%, hazard ratio 0.35) [36]. The effect is very large for an observational study without information on TKV or genotype, and larger than the effect of tolvaptan, the only approved disease-modifying drug, in the same data set (hazard ratio 0.66); this points to residual confounding by indication.

The study also identified patients by diagnosis code (Q61.2) rather than by imaging or genetic confirmation, and a later corrigendum corrects only a figure caption. In the single-arm data pooled by Tantush et al., the post-treatment eGFR slope in patients without diabetes (n = 41) was −1.07 mL/min/1.73 m² per year; the

diabetic subgroup (n = 217) consisted only of the veteran cohort, whose slope (−0.17) was measured per 90 days, so the two subgroups cannot be compared directly [10,34]. Their abstract nonetheless reports a greater eGFR benefit in patients without diabetes, which these single-arm subgroup data do not show; with only 41 non-diabetic patients, neither subgroup estimate is informative. Overall confidence for this group: low.

By CKD Stage

Early CKD (G1 to G2) has barely been studied. Apart from six patients in stage G2 in Nakajima's cohort, all taking tolvaptan [33], the data consist of a single harm case of tolvaptan [41]. Most of the evidence concerns stage G3, where slopes after the initial dip were generally stable or improved, except in the three-month series [38]. In stage G4, small series did not show faster decline: in Yoshimoto's series of seven patients with a median eGFR of 26.9, the eGFR slope improved in five of six assessable patients (p = 0.12), and the only patient whose slope worsened was the only one not on renin-angiotensin system blockade [37]. In the same patients, however, annual htTKV growth increased in all five who could be assessed (p = 0.04). Nakajima's cohort included seven patients in stage G4, although results were not reported separately for them [33]. Overall confidence for this group: very low.

Tolvaptan as a Possible Effect Modifier

The mechanistic case that tolvaptan changes the effect of SGLT2 inhibitors in ADPKD is strong. SGLT2 inhibitors raise vasopressin [20,23,24]; tolvaptan blocks its receptor; the only randomised trial reporting kidney outcomes (in which all patients took tolvaptan) showed slower kidney growth [20], and the clearest harm case occurred off tolvaptan [41]. In the TEMPO 3:4 trial, patients with higher copeptin had a greater response to tolvaptan, which is consistent with vasopressin-driven disease being most open to modification by V2 receptor blockade [43]. The clinical data are not consistent, however. Morioka et al. saw kidney volume increase over about three months whether or not patients took tolvaptan (annual htTKV growth across the series rose from −1.4% to 23.9% per year after dapagliflozin was started, but growth rates were not reported separately by tolvaptan use) [38], Yoshimoto et al. found no difference by tolvaptan use [37], and one patient in Nishida's series grew despite tolvaptan [39]. No study has compared patients on and off tolvaptan within the same population. Tolvaptan is therefore presented as a plausible effect modifier, not as an established one. Only the EMPA-PKD trial, which allows tolvaptan users, can test it directly.

Interpreting the Pooled Estimate

Tantush et al. combined one randomised trial, one target trial emulation and six retrospective studies, giving a pooled difference in post-treatment eGFR slope of 1.34 mL/min/1.73 m² per year (95% CI: 0.84 to 1.85) from four comparative studies [10]. Their analysis pooled before-and-after designs with comparative designs, and older diabetic cohorts with young Japanese patients on tolvaptan; 2,640 of the 3,180 patients came from a single US electronic health record cohort of people with type 2 diabetes. Their comparison with DPP-4 inhibitors rests on a single study, and its forest plot enters the per-90-day slopes reported by Eswarappa et al. (−0.17 vs −1.45 mL/min/1.73 m² per 90 days) as per-year values; the same per-90-day data also contribute to the overall pooled estimate and to two single-arm analyses [10,34]. On AMSTAR 2, the review's overall confidence was rated as critically low. Kanbay et al., pooling six studies, found a smaller improvement against each patient's pre-treatment slope (0.65 mL/min/1.73 m² per year) and no significant difference against non-SGLT2 inhibitor comparators (2.12, 95% CI: −8.13 to 12.38) or in TKV; only the abstract of this analysis was available, so it could not be appraised with AMSTAR 2 [11]. With so few studies, such different populations and such different designs, a new pooled estimate is unlikely to help. The more useful conclusion is that a population-average answer depends heavily on which populations are included, as the differing conclusions of the two meta-analyses illustrate.

Where the evidence is silent

The patient groups with most at stake have the least evidence. Six gaps stand out (Figure *3*).

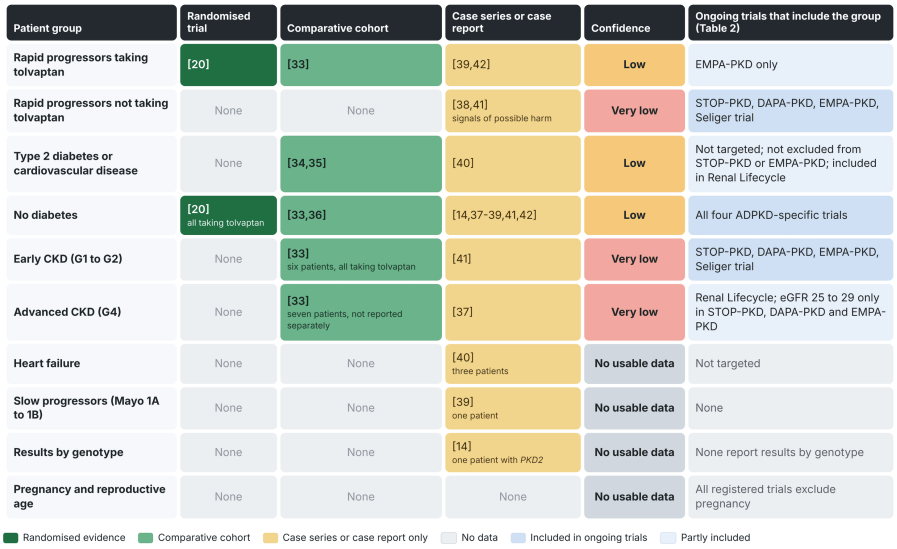


FIGURE 3: Evidence map of SGLT2 inhibitor studies in ADPKD by patient group

Cells list the reference numbers of the studies providing each type of evidence; the confidence column gives this review's overall rating for each group, and the final column shows which ongoing or pending trials include the group (details in the subsequent table)

Original figure created by the author with the assistance of Claude (Anthropic)

ADPKD: autosomal dominant polycystic kidney disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; PKD2: polycystin 2 gene; SGLT2: sodium-glucose cotransporter 2

Young Rapid Progressors Not on Tolvaptan

This is the group in whom the concern about vasopressin-driven cyst growth is greatest, in whom decades of kidney function are at stake, and in whom tolvaptan may be declined or poorly tolerated [2,41]. The only data are three single young patients (two aged 38 and 39, and one diagnosed at 30 who had taken tolvaptan for about five years) [39,41,42], only one of whom was off tolvaptan, and that patient's kidneys grew by about 40% in a year [41].

Slow Progressors (Mayo 1A to 1B)

Patients in class 1B were included in the Japanese studies, including six of 24 in the dapagliflozin arm of Nakajima's cohort [20,33,39], but no study reported results for class 1B separately, apart from one patient in Nishida's series (a 62-year-old woman in stage G3b whose slope improved from −1.02 to −0.66 per year) [39]. The older North American cohorts may have consisted largely of patients with milder disease, as Eswarappa et al. suggested, but none recorded imaging class [34,40].

Genotype

No study reported results by PKD1 or PKD2 genotype. The only genotyped patient in the evidence base had PKD2 disease and probable coexisting IgA nephropathy; with empagliflozin, proteinuria fell from 2.0 to about 0.3 to 0.4 g per day, and eGFR stayed stable at 33 to 35 mL/min/1.73 m^2 over 18 months [14]. This benefit more likely reflects the glomerular disease than ADPKD.

Early CKD (G1 to G2)

This is the window in which slowing ADPKD would preserve the most kidney function, yet apart from six patients in stage G2 who were taking tolvaptan [33], there are almost no data.

Heart Failure

Müller et al. regard heart failure as the only setting in which SGLT2 inhibitor use in ADPKD is currently justified [8], and cardiac disease has been the most common cause of death in ADPKD since dialysis became

widely available [44], yet there are no ADPKD-specific heart failure data beyond three patients in one registry [40].

Reproductive Age and Pregnancy

ADPKD often affects people of reproductive age, and the KDIGO guideline includes recommendations on preconception counselling and care in pregnancy [1]. Because SGLT2 inhibitors are already advised against in pregnancy (see Practical implications), the gap is not whether they can be used in pregnancy but how to counsel people of reproductive age who take them, including on contraception and when to stop the drug. The registered trials enrol people of reproductive age, but all of them exclude pregnancy and breastfeeding, and two also require effective contraception; DAPA-PKD's full eligibility criteria have not been published.

Safety by population

No consistent safety signal was found across the 13 studies, but follow-up was short and adverse events were reported inconsistently, so the absence of a signal is weak reassurance.

The Early eGFR Dip Versus Harm

SGLT2 inhibitors cause an early, reversible fall in eGFR as glomerular pressure falls. In the studies pooled by Tantush et al., the dip averaged about 10% (9.99%, 95% CI: 7.99 to 11.98) [10]; large CKD trials also showed an acute fall in eGFR on starting treatment, followed by slower long-term decline [5]. What matters for long-term outcome is the slope after the dip. In the veteran cohort, eGFR fell steeply for three months and then levelled off [34]. In contrast, the three-month series by Morioka et al. measured eGFR at a single point after the dip and could not tell whether the continuing decline it found was haemodynamic or harmful [38]. Studies shorter than about six months cannot separate the two.

AKI and Volume Depletion, Especially With Tolvaptan

Combining an osmotic diuretic effect with the water diuresis of tolvaptan could, in theory, cause volume depletion and AKI. This has not been seen in the small numbers studied: AKI occurred in one of 17 patients in the Canadian registry [40], and in the large TriNetX cohort of patients with type 2 diabetes, AKI was less common with SGLT2 inhibitors than without them (hazard ratio 0.896) [35]. In the crossover trial, urine volume on tolvaptan did not increase further with dapagliflozin [20], whereas in the SIDIA study (two two-week treatment periods), in which tolvaptan use was allowed but not required, median daily urine volume was 4.6 L with empagliflozin and 3.8 L with placebo [32]. Tolerability on top of tolvaptan may be a practical limit: 19% of patients in Nakajima's cohort stopped dapagliflozin because of frequent urination, nausea, low blood pressure, or abnormal liver tests [33].

Urinary, Genital and Cyst Infections

Glycosuria raises the risk of genital and urinary infections, and cyst infection is a known complication of ADPKD. Urinary tract infection occurred in two of 17 patients in the Canadian registry, neither needing hospital care [40], and pyelonephritis in two of four patients in Nishida's series, both resolving with antibiotics [39]. In the crossover trial, one patient was admitted with a cyst infection during the dapagliflozin period, which the investigators judged unlikely to be related [20]. The veteran cohort did not report infections [34].

Interpreting Kidney Volume Rises

Rises in TKV after starting an SGLT2 inhibitor should be interpreted with care. Tubular hypertrophy enlarges normal kidneys [31], the case of rapid enlargement improved slightly after the drug was stopped [41], and the largest rise in htTKV growth appeared within three months [38]. Some of this rise may represent hypertrophy or fluid rather than cysts. Equally, the absence of a TKV rise in short studies does not exclude a slow effect on cysts. Cyst-specific imaging measures and eGFR slope should be reported alongside TKV. These measures separate cysts from the surrounding kidney tissue on MRI and include total cyst volume, total cyst number, cyst-parenchyma surface area, and cystic index (cyst volume as a percentage of TKV) [45,46]. In the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort, total cyst number and cyst-parenchyma surface area predicted eGFR decline over eight years better than htTKV, although all of the correlations were moderate [47]. These measures still need validation, however, and TKV remains the only imaging biomarker qualified by regulatory agencies [46,47]. Because they separate cysts from the rest of the kidney, they could help to distinguish cyst growth from tubular hypertrophy [31].

Ongoing trials and the questions they will answer

Five ongoing or pending trials will shape practice (Table *2*). Two are phase 3 trials of dapagliflozin 10 mg in rapid progressors. STOP-PKD will randomise 420 patients aged 18 to 60 years in Mayo class 1D or 1E, or class 1C with another marker of rapid progression, to dapagliflozin or placebo for 36 months, with chronic

eGFR slope as the primary endpoint; results are expected around 2030 [48]. DAPA-PKD, a French multicentre trial of 400 patients aged 18 to 75 years in Mayo class 1C to 1E (or with a mean kidney length over 16.5 cm), compares dapagliflozin with placebo over 24 months, with change in magnetic resonance imaging (MRI)-measured TKV as its primary endpoint and eGFR slope and cardiovascular events among its secondary endpoints. The two trials have harmonised their inclusion criteria and outcomes so that they can be combined in an individual-patient analysis (FLOZIN-PKD) [8]. DAPA-PKD is not registered on ClinicalTrials.gov. Both trials exclude patients taking tolvaptan.

Trial	Drug and dose	Phase	Planned (n)	Primary endpoint	Completion	Age (years)	eGFR	Rapid	Slow	Tolvaptan	T2D	Genotype
STOP-PKD (NCT07280585) [48]	Dapagliflozin 10 mg	3	420	Chronic eGFR slope	May 2030 (est.)	18–60	25 to < 90 (25 or more if aged 18–39)	Yes	No	No	Not excluded	No
DAPA-PKD‡ [8]	Dapagliflozin 10 mg	3	400	MRI TKV change	Not reported	18–75	25–90 (25–45 if over 60)	Yes	No	No	Not reported	Not reported
EMPA-PKD (NCT06391450) [49]	Empagliflozin 10 mg	4	44	Annual TKV change	May 2027 (est.)	18 or over	25–90 (25–65 if over 50)	Yes	No	Yes	Not excluded	Not reported
Seliger trial (NCT05510115) [50,51]	Empagliflozin 10–25 mg	2	50	Safety and tolerability	March 2026, results pending	18–55	30–90	Yes	No	No	No	Not reported
Renal Lifecycle (NCT05374291) [52]	Dapagliflozin 10 mg	3	1,750 (all CKD)	Death, kidney failure or HF hospitalisation	July 2027 (est.)	Over 18	25 or less	Not selected	Not selected	No	Yes	No

TABLE 2: Ongoing and pending trials of SGLT2 inhibitors relevant to ADPKD, and the patient groups they include

‡Not registered on ClinicalTrials.gov; details from Müller et al. [8]

The last five columns show whether each group can enrol: Rapid and slow: rapid and slow progressors; Tolvaptan: current tolvaptan users; Genotype: results reported by genotype. Groups not covered by any trial: slow progressors (Mayo 1A–1B), results by genotype, pregnancy (all registered trials exclude pregnancy; DAPA-PKD's full criteria are not published)

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate (mL/min/1.73 m²); est.: estimated; HF: heart failure; MRI: magnetic resonance imaging; n: planned number of participants; T2D: type 2 diabetes; TKV: total kidney volume

Three smaller trials add to this. EMPA-PKD is a single-centre (Hannover), placebo-controlled trial of 18 months of empagliflozin in 44 rapid progressors, with randomisation stratified by tolvaptan use and TKV change as the primary endpoint, and it is the only trial that includes tolvaptan users; it is expected to finish in 2027 [49]. The Seliger trial, a 50-patient phase 2 pilot of empagliflozin in non-diabetic rapid progressors aged 18 to 55 years who are not taking tolvaptan, has a primary endpoint of safety and tolerability; it reached primary completion in March 2026, but no results had been posted on ClinicalTrials.gov by 12 October 2026 [50,51]. The Renal Lifecycle trial of dapagliflozin in 1,750 people with advanced CKD (eGFR 25 or less), on dialysis or with a transplant, excludes only tolvaptan-treated ADPKD, so a post hoc ADPKD subgroup analysis may be possible [52].

Mapped against patient groups, these trials will answer the question well for one group: rapid progressors aged roughly 18 to 60 years who are not taking tolvaptan, with an eGFR between 25 and 90. This is the group in which the evidence is currently thinnest, so the trials are aimed in the right place. Other groups are covered only partly: tolvaptan users (EMPA-PKD, 44 patients), people over 60 (DAPA-PKD and EMPA-PKD), people with type 2 diabetes or heart failure (excluded from the Seliger trial and not targeted by the others), and advanced CKD (Renal Lifecycle, only if ADPKD is analysed separately). No trial includes slow progressors, none of the registered trials includes pregnant participants (all exclude pregnancy and breastfeeding, and STOP-PKD and EMPA-PKD also require effective contraception [48,49]), and none plans to report results by genotype; STOP-PKD uses a truncating PKD1 variant only as an entry criterion for class 1C.

Finally, DAPA-PKD's TKV endpoint, and the week-48 TKV measurement in the first 150 STOP-PKD participants that feeds an interim safety analysis with eGFR and copeptin [48], should be interpreted in the light of the hypertrophy caveat above [31]. A small increase in TKV on dapagliflozin would not necessarily mean faster cyst growth, and a combined reading of TKV, cyst-specific imaging and eGFR slope will be needed. Cardiovascular and patient-reported outcomes, which matter to patients and are included as secondary outcomes in the Seliger trial, deserve more attention across the programme [50,53].

Practical implications and research priorities

A Cautious Framework by Group

Until trial results are available, the following approach is suggested. In patients with ADPKD who have type 2 diabetes or heart failure, the indication for an SGLT2 inhibitor is the comorbidity; the observational data show no harm and the expected benefits for that condition are large; prescribing in line with the guidelines for that condition seems reasonable, with monitoring of eGFR and, where available, kidney volume. This goes further than the 2025 KDIGO guideline, which does not currently recommend SGLT2 inhibitors in ADPKD even for diabetes [1,8], and clinicians should discuss that uncertainty with patients. In heart failure, this rests on trials in the general heart failure population [54], not on ADPKD data, which are limited to three patients in one registry [40].

In rapid progressors already taking tolvaptan, the limited randomised data are encouraging but come from one small, open-label crossover trial without a washout, in which the difference in creatinine-based eGFR slope was not significant [20]; adding an SGLT2 inhibitor could be considered, ideally within a trial such as EMPA-PKD or a structured registry. In rapid progressors not taking tolvaptan, SGLT2 inhibitors should not be used solely to slow ADPKD outside trials, consistent with the KDIGO guideline [1]. In slow progressors and in early CKD, there is no evidence on which to base a recommendation. Pregnancy is different: SGLT2 inhibitors are already advised against in pregnancy and breastfeeding, because animal studies show harm to the developing kidney at stages corresponding to the second and third trimesters [55]. For people of reproductive age, the practical issues are contraception and preconception counselling, in line with the KDIGO guideline [1].

Research Priorities

Trials and observational studies should report results by genotype and Mayo imaging class, so that their findings can be applied to individual patients. Analyses should be stratified by tolvaptan use, to test whether tolvaptan modifies the effect of SGLT2 inhibitors. Preclinical studies should test SGLT2 inhibitors together with V2 receptor antagonists and in models that reflect the patient groups considered here, such as diabetes or advanced CKD, to clarify downstream and off-target effects. Cyst-specific imaging should be used alongside TKV to separate cyst growth from tubular hypertrophy. Follow-up should be long enough to separate the early eGFR dip from the long-term slope. Patient-reported and cardiovascular outcomes should be collected, and slow progressors should be included in at least some studies. Until these data are available, decisions about SGLT2 inhibitors in ADPKD should be made for the patient in front of the clinician, not for the average patient in a pooled analysis.

Limitations

This review has several limitations. It is a structured narrative review rather than a systematic review, and its protocol was not registered. PubMed and ClinicalTrials.gov were searched, but not Embase, the Cochrane Library, or other trial registers, so relevant studies, particularly conference abstracts and reports in languages other than English, may have been missed. A single author carried out study selection, data extraction, and risk-of-bias assessment, assisted by a large language model (Claude, Anthropic). The evidence base itself is small and mostly observational: several Japanese reports come from overlapping centres and may include the same patients; the three electronic health record studies identified ADPKD or polycystic kidney disease by diagnosis codes rather than by imaging or genetic confirmation; one included study has so far reported its results only on a trial registry, and another could be assessed only from its abstract, as could one of the two meta-analyses. Finally, the assignment of studies to patient groups relied on the characteristics each study reported, which were often incomplete, particularly for Mayo class and genotype.

Conclusions

The current evidence for SGLT2 inhibitors in ADPKD comes mostly from older patients, many with diabetes or cardiovascular disease, and from a small group of patients already taking tolvaptan. It says almost nothing about young, rapidly progressive patients who are not taking tolvaptan, the group in which the concern about cyst growth is greatest and on which the phase 3 trials are now focused. For this reason, asking “do SGLT2 inhibitors work in ADPKD?” is the wrong question. The answer is likely to differ between patient groups, and pooled estimates that combine them can mislead. Until trial results are available, prescribing an SGLT2 inhibitor for diabetes or heart failure in a person with ADPKD seems reasonable if kidney function and, where possible, kidney volume are monitored. This approach goes further than current guideline recommendations. In rapid progressors already taking tolvaptan, adding an SGLT2 inhibitor is best done within a trial or registry. In rapid progressors not taking tolvaptan, these drugs should not be used solely to slow ADPKD. Future studies should report results by genotype, imaging class, and tolvaptan use, so that decisions can be made for the patient in front of the clinician rather than for the average patient in a pooled analysis.

Appendices

Search strings

PubMed search (7 October 2026, repeated 12 October 2026; 58 records): ("Polycystic Kidney, Autosomal Dominant"(Mesh) OR "polycystic kidney*"(tiab) OR ADPKD(tiab) OR PKD1(tiab) OR PKD2(tiab)) AND ("Sodium-Glucose Transporter 2 Inhibitors"(Mesh) OR SGLT2(tiab) OR SGLT-2(tiab) OR "sodium-glucose cotransporter 2"(tiab) OR "sodium glucose cotransporter 2"(tiab) OR "sodium-glucose co-transporter 2"(tiab) OR gliflozin*(tiab) OR dapagliflozin(tiab) OR empagliflozin(tiab) OR canagliflozin(tiab) OR ertugliflozin(tiab) OR ipragliflozin(tiab) OR luseogliflozin(tiab) OR tofogliflozin(tiab) OR sotagliflozin(tiab) OR phlorizin(tiab))

Preclinical search (12 October 2026, 12 records): ("polycystic kidney*"(tiab) OR ADPKD(tiab) OR PKD(tiab)) AND (SGLT*(tiab) OR dapagliflozin(tiab) OR empagliflozin(tiab) OR canagliflozin(tiab) OR phlorizin(tiab) OR "glucose transport*"(tiab)) AND (rat(tiab) OR rats(tiab) OR mice(tiab) OR mouse(tiab) OR organoid*(tiab) OR "animal model"(tiab) OR "animal models"(tiab))

ClinicalTrials.gov search (7 October 2026, repeated 12 October 2026): condition "polycystic kidney" combined with SGLT2 inhibitor terms; four ADPKD trials (NCT07280585, NCT06391450, NCT05510115, NCT06435858)

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Aashish Aggarwal

Acquisition, analysis, or interpretation of data: Aashish Aggarwal

Drafting of the manuscript: Aashish Aggarwal

Critical review of the manuscript for important intellectual content: Aashish Aggarwal

Disclosures

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