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Exploring the Role of SGLT2 Inhibitors in Autosomal Dominant Polycystic Kidney Disease: A Systematic Review of Clinical and Preclinical Evidence

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Background

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Most common inherited kidney disorder (Affects 1 in 400–1,000 individuals worldwide)
- Genetic basis: mutations in PKD1 and PKD2 genes
- 5-8% of ESRD cases

Characterized by:

- Progressive kidney cyst formation
- Increased total kidney volume (TKV)
- Declining kidney function → eventual kidney failure

Causes significant morbidity, mortality, and healthcare costs

1. Lanktree et al. (2021). J Am Soc Nephrol
2. Cornec-Le Gall et al. (2017). Lancet
3. Chapman et al. (2015). Kidney Int.
4. Torres et al. (2007). Lancet
5. Torres & Harris (2014). J Am Soc Nephrol

Background

Current Therapy:
TOLVAPTAN

- Slows TKV growth and preserves renal function
- **Limitations:** polyuria, liver toxicity, strict eligibility criteria

?

Emerging Therapy:
SGLT2 Inhibitors

- Reduce hyperfiltration, inflammation, and fibrosis in CKD
- **Role in ADPKD remains unclear**

Aim of Review

Summarize clinical and preclinical evidence of SGLT2 inhibitors in ADPKD

1. KDIGO (2025). Kidney Int.
2. Spiazzi et al. (2025). Clin J Am Soc Nephrol
3. Heerspink et al. (2016). Kidney Int.
4. Dharia et al. (2023). Annu Rev Med

Methods

Literature Search:


ScienceDirect PubMed Cochrane Library Google Scholar

- Literature search spanned until June 2025
- Key Search Terms*:
  - **Intervention terms:** "SGLT2 inhibitor*," "sodium-glucose cotransporter 2 inhibitor*," "dapagliflozin," "empagliflozin," "canagliflozin," "ertugliflozin," "sotagliflozin," "ipragliflozin," "tofogliflozin," "gliflozin*"
  - **Disease terms:** "autosomal dominant polycystic kidney disease," "ADPKD," "polycystic kidney disease," "PKD," "kidney cystic disease"
  - **Study design terms:** "randomized controlled trial," "clinical trial," "cohort study," "observational study," "case report," "pilot study," "preclinical," "animal study"

  Boolean operators (AND/OR) and wildcards used
- English-language
- Reference lists screened for additional studies

Study Selection:

Inclusion Criteria

- Studies on SGLT2 inhibitors in ADPKD (human or animal)
- Outcomes: kidney function, TKV, cyst progression, safety
- Original research: RCTs, cohort studies, case series, preclinical studies

Exclusion Criteria

- Reviews, commentaries, abstracts without full data
- Studies without accessible full texts
- Ongoing trials without published results
- Studies not focused on ADPKD or SGLT2 inhibitors

Methods

Data Extraction:

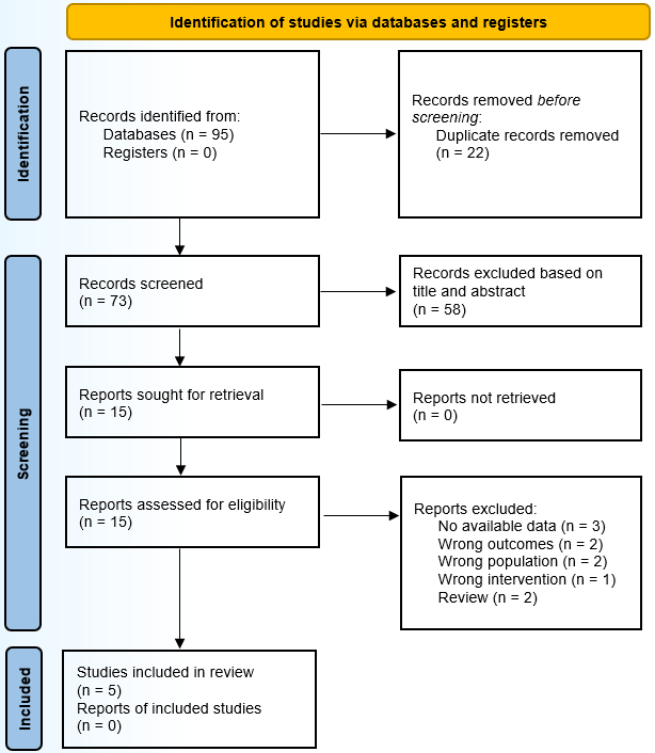
- **Study details:** authors, year, country, design, sample size, follow-up
- **Population:** demographics, diagnostic criteria, baseline eGFR
- **Intervention:** SGLT2 type, dosage, duration, concomitant meds
- **Comparator:** placebo, standard care, baseline
- **Outcomes:** eGFR, TKV, cyst growth, adverse events, biomarkers
- **Measurement:** MRI, CT, US, assays, histology
- **Key findings and conclusions**

Quality Assessment:

Risk categorized as low, moderate, or high

- RCTs: Cochrane Risk of Bias Tool 2.0
- Observational studies: Newcastle-Ottawa Scale (NOS)
- Animal studies: SYRCLE's Risk of Bias Tool

Results



Summary of Included Studies

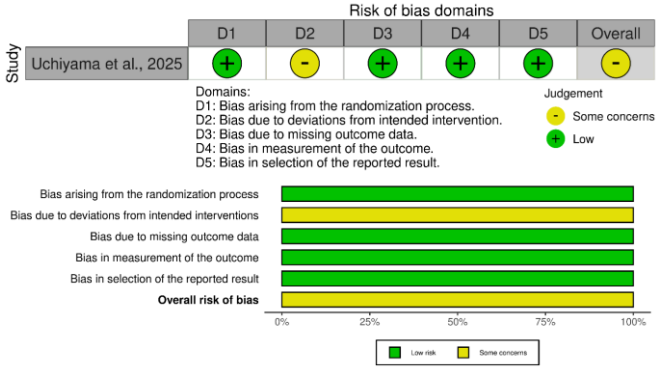
Author(s), year	Study Type	Population / Follow Up Time	SGLT2i agent / Comparison	Measurement
Uchiyama et al., 2025	Open-label RCT, crossover	27 ADPKD patients on stable tolvaptan 6 months per phase	Dapagliflozin 10 mg daily + Tolvaptan Tolvaptan only	eGFR (serum creatinine, CKD-EPI), MRI for TKV (Sheffield TKV Tool)
Yoshimoto et al., 2024	Retrospective observational	7 ADPKD patients with CKD Median 20 months	Dapagliflozin 10 mg daily Baseline (pre-treatment)	eGFR (serum creatinine), MRI or ultrasound for htTKV
Morioka et al., 2023	Retrospective single-arm case series	20 ADPKD patients Short-term (~3 months)	Dapagliflozin 10 mg daily Baseline	eGFR, MRI or CT for htTKV measurement
Yu et al., 2024	Retrospective cohort (target trial emulation)	31,070 patients with PKD and type 2 diabetes (2,640 matched SGLT2i vs. non-users) Not specified	SGLT2 inhibitors (various) Non-users, antidiabetics (DPP-4i, GLP-1RA)	eGFR from electronic health records, ICD-10 codes, CPT codes, propensity score matching
Kapoor et al., 2015	Preclinical animal study	PCK rat model of PKD 6 weeks	Dapagliflozin 10 mg/kg/day Vehicle control	Histology, kidney weight, urine albumin, biochemical assays

Results

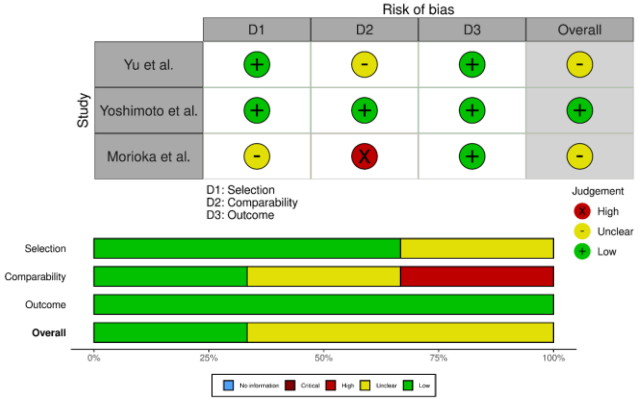
Quality Assessment of Included Studies

Study (Year)	Design	Quality Tool	Score / Risk Level	Key Strengths	Key Limitations
Uchiyama et al. (2025)	RCT, open-label crossover	Cochrane RoB 2.0	Moderate to low risk	Randomized, crossover design	Open-label, short follow-up
Yoshimoto et al. (2024)	Observational cohort	Newcastle-Ottawa Scale	High quality (8/9)	Large sample, confounder control	Observational design
Morioka et al. (2023)	Short-term observational	Newcastle-Ottawa Scale	Moderate quality (6/9)	Objective imaging	Small sample, no control group
Yu et al. (2024)	Retrospective observational	Newcastle-Ottawa Scale	Moderate-high quality (8/9)	Large dataset, adjusted analysis	Retrospective, info bias risk
Kapoor et al. (2015)	Preclinical animal study	SYRCLE's RoB	Moderate-high risk	Mechanistic insights	Lack of blinding, limited translatability

RCT



Observational Studies



Results

Kidney Function and Kidney Volume Outcomes in Included Studies

Study (Year)	Design / Sample Size	Intervention	Follow-up Duration	Kidney Function Outcome (eGFR)	Kidney Volume Outcome (TKV / htTKV)	Statistical Significance
Uchiyama et al. (2025)	Open-label RCT crossover, 27 ADPKD patients on tolvaptan	Dapagliflozin 10 mg + Tolvaptan	6 months per phase	eGFR_cr-cys slope improved from -5.65 ± 9.57 to 2.57 ± 7.88 mL/min/1.73 m²/year (P = 0.002)	TKV % change: -0.44 ± 4.91% (dapagliflozin + tolvaptan) vs 5.04 ± 8.09% (tolvaptan alone) (P = 0.01)	**Significant improvement in both eGFR and TKV growth** (P < 0.05)
Yoshimoto et al. (2024)	Retrospective observational, 7 ADPKD patients	Dapagliflozin (likely 10 mg daily)	Median 20 months	eGFR slope improved from approx. -2.7 to -1.9 mL/min/1.73 m²/year (no formal p-value)	htTKV increased ~4.5% per year; consistent increase across all patients (p-value not reported)	**Kidney volume increase** consistent; **eGFR improvement** observed
Morioka et al. (2023)	Retrospective single-arm, 20 ADPKD patients	Dapagliflozin 10 mg daily	~3 months	Transient eGFR decrease from 47.9 to 40.8 mL/min/1.73 m² (P < 0.001)	htTKV increased from 599 to 617 mL/m (P = 0.002)	**Significant transient eGFR dip** and **kidney volume increase**
Yu et al. (2024)	Retrospective cohort, 31,070 PKD + T2DM patients (2,640 SGLT2i users)	SGLT2 inhibitors (various)	Not specified (real-world)	Lower risk of dialysis initiation (HR 0.657; 95% CI 0.497–0.868), AKI (HR 0.896; 95% CI 0.823–0.975)	Not reported	**Significant reduction in adverse kidney events** (P < 0.05)
Kapoor et al. (2015)	Preclinical PCK rat model	Dapagliflozin	6 weeks	Increased albuminuria (P < 0.05); no eGFR data	Kidney weight increased ~15% (P < 0.05); cyst volume increased	**Significant adverse effects** on kidney pathology

Results

Safety and Adverse Events in Included Studies

Study (Year)	Sample Size/ Population	Intervention	Follow-up Duration	Common Adverse Events (AEs)	Serious AEs / Discontinuations	Statistical Notes
Uchiyama et al. (2025)	27 ADPKD patients on tolvaptan	Dapagliflozin 10 mg + Tolvaptan	6 months per phase	Transient eGFR dip; urinary tract infections in 2 patients (7.4%)	None	**No significant difference vs. control** ($P > 0.05$)
Yoshimoto et al. (2024)	7 ADPKD patients	Dapagliflozin (likely 10 mg)	Median 20 months	Mild genital infection in 1 patient (14.3%)	None	**No formal statistical testing** due to small sample size
Morioka et al. (2023)	20 ADPKD patients	Dapagliflozin 10 mg	~3 months	Transient polyuria and thirst in 3 patients (15%)	None	**No serious AEs reported**
Yu et al. (2024)	2,640 SGLT2i users with PKD + T2DM	SGLT2 inhibitors (various)	Not specified	No increased diabetic ketoacidosis or severe hypoglycemia	None reported	**Lower AKI incidence** (HR 0.896; $P = 0.01$); **mortality reduced** (HR 0.840; $P = 0.002$)
Kapoor et al. (2015)	PCK rat model	Dapagliflozin	6 weeks	Increased albuminuria	N/A (animal study)	**Significant adverse renal effects** ($P < 0.05$)

Discussion

Principal Findings

Kidney Function Outcomes

- **SGLT2 inhibitors (esp. dapagliflozin) show renoprotection in ADPKD** → Slower eGFR decline in RCTs and observational studies
- **Transient eGFR dip after initiation** = hemodynamic, not harmful

Consistent with broader CKD data → **kidney and CV protection beyond glycemic control**[1,2]

- **Mechanisms:** hemodynamic + anti-inflammatory, mitochondrial, autophagy support [2,3]
- **Clinical implication:** slowing eGFR decline delays ESRD & dialysis/transplant [3]
- Preserved function improves BP control → ↓ CV risk [4,5]
- **Prevents complications:** anemia, electrolyte imbalance, bone-mineral disorders [3]

Kidney Volume Outcomes

Functional benefit ≠ consistent effect on kidney volume

- Dapagliflozin + tolvaptan: attenuated TKV growth
- Other studies: ↑ htTKV despite stable/ improved function

Short-term volume rise may reflect natural course (predictor of progression), **not drug effect**
Function preserved via nephron protection despite cyst growth [6,7,8]

Variability due to:

- Different designs and follow-up period
- Imaging (MRI gold standard vs ultrasound)

1. Spiazzi et al. (2025). *Clin J Am Soc Nephrol.*
2. Dharia et al. (2023). *Annu Rev Med*
3. Chebib & Torres (2016). *Am J Kidney Dis.*
4. Chapman et al. (2015). *Kidney Int.*
5. Torres et al. (2007). *Lancet*
6. Heerspink et al. (2016). *Kidney Int.*
7. Müller et al. (2025). *Nephrol Dial Transplant*
8. Morioka et al. (2023). *Kidney Int Rep.*

Discussion

Principal Findings

Mechanistics Insights

- **ADPKD pathophysiology:** impaired signaling, autophagy, mitochondrial dysfunction, inflammation [1,2]
- **SGLT2i mechanisms:** ↓ intraglomerular pressure, improve BP, glucose, weight [3,4]
- Preclinical data mixed:
  - SGLT2i alone may ↑ cyst growth [5]
  - **Dual SGLT1/2 inhibition may ↓ cyst growth** [2]

Safety Profile

Generally well tolerated, but there are ADPKD-specific risks:

- Genitourinary & cyst infections (due to glucosuria) [1, 6-10]
- Volume depletion & AKI risk, esp. with tolvaptan [1, 11, 12]
- Electrolyte changes (↑ Mg, K, phosphate; hypernatremia risk) [9, 13]

Evidence gap: ADPKD is excluded from major SGLT2i CKD trials

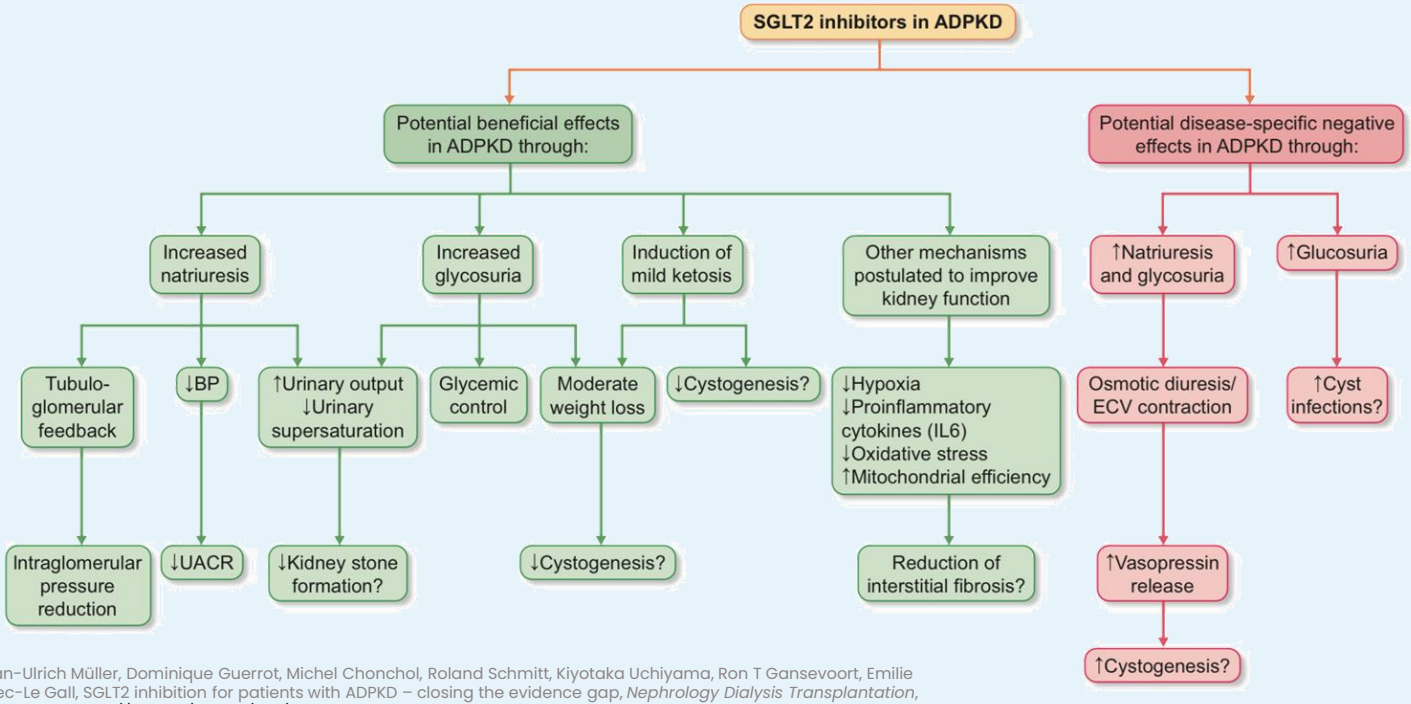
Dedicated ADPKD RCTs are still ongoing

Awaiting stronger safety data from ongoing RCTs

1. Chebib & Torres (2016). Am J Kidney Dis.
2. Geng et al. (2003). Kidney Int.
3. Heerspink et al. (2016). Kidney Int.
4. Neuen et al. (2019). Lancet Diabetes Endocrinol.
5. Kapoor et al. (2015). PLoS One
6. Yoshimoto et al. (2024). Clin Kidney J.
7. Morioka et al. (2023). Kidney Int Rep.
8. Dave et al. (2024). J Am Coll Cardiol.
9. Arshad et al. (2024). Drug Res (Stuttg).
10. Lavalle-González et al. (2013). Diabetes Obes Metab.
11. Uchiyama et al. (2025). Kidney Int Rep.
12. Yu et al. (2024). ScienceDirect
13. KDIGO (2025). Kidney Int.

Discussion

SGLT2 inhibitors in ADPKD



Roman-Ulrich Müller, Dominique Guerrot, Michel Chonchol, Roland Schmitt, Kiyotaka Uchiyama, Ron T Gansevoort, Emilie Cornec-Le Gall, SGLT2 inhibition for patients with ADPKD – closing the evidence gap, *Nephrology Dialysis Transplantation*, 2025;, gfaf061, https://doi.org/10.1093/ndt/gfaf061

Discussion

Clinical Recommendations

- Individualize use; prefered in trial settings or with strong indications [1]
- Monitor eGFR + kidney volume (standardized imaging)[1,2]
- Monitor for infections & volume status early in treatment [3,4]
- Hydration & electrolyte monitoring essential (esp. with tolvaptan) [5]
- Consider added benefits: BP, weight, metabolic effects [6]

Research Priorities

- Long-term, large RCTs on kidney function and cyst growth [1,4]
- Mechanistic studies: vasopressin signaling, cyst metabolism, hemodynamics [1,7]
- Safety of combination therapy with tolvaptan [2]
- Biomarker development for integrated monitoring [8]

1. Müller et al. (2025). Nephrol Dial Transplant
2. Uchiyama et al. (2025). Kidney Int Rep.
3. Yoshimoto et al. (2024). Clin Kidney J.
4. Morioka et al. (2023). Kidney Int Rep.
5. Yu et al. (2024). ScienceDirect
6. Cornec-Le Gall et al. (2017). Lancet
7. Kapoor et al. (2015). PLoS One
8. Torres & Harris (2014). J Am Soc Nephrol

Discussion

Strength and Limitation

Strength:

- Focused specifically on ADPKD
- Integrated mechanistic + clinical insights
- Includes emerging evidence & ongoing trials (EMPA-PKD, DAPA-PKD, STOP-PKD)
- Balanced discussion of conflicting findings
- Practical clinical and research implications

Limitation:

- Limited evidence base (ADPKD excluded from major trials)
- Heterogeneous study designs & short follow-ups
- Publication bias possible
- Limited data on combo with tolvaptan
- Different imaging & biomarkers reduce comparability

Conclusion

SGLT2 inhibitors → promising for kidney function preservation in ADPKD

Impact on Cyst Growth → Uncertain/Conflicting

Safety → generally tolerable, but ADPKD-specific risks exist

Use cautiously, preferably in trials or selected patients

Further RCTs critical for definitive guidance

Supplementary

Ongoing Research on SGLT2 Inhibitors in ADPKD

- **DAPA-ADPKD Trial (NCT04680780)**
  A randomized controlled trial assessing dapagliflozin's impact on eGFR and kidney volume over 2 years.
- **EMPA-KIDNEY Substudy in ADPKD (NCT03594110)**
  A substudy evaluating empagliflozin's effects on kidney function and cyst progression in ADPKD.
- **Preclinical Studies**
  Animal research exploring how SGLT2 inhibitors affect cyst metabolism, vasopressin signaling, and kidney hemodynamics.
- **Combination Therapy Trials**
  Early-phase studies investigating safety and efficacy of SGLT2 inhibitors combined with tolvaptan or RAS inhibitors.
- **Metabolic Intervention Studies**
  Trials comparing SGLT2 inhibitors with dietary approaches like ketogenic or time-restricted diets targeting ADPKD metabolism.