Recent Advance in ADPKD Treatment

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To date 1500 different pathogenic mutations have been recorded in PKD1 AND PKD2 genes

PKD1 encodes PC1
PKD2 encodes PC2

Germline PKD1/ PKD2 mutation + Second hit insult

Aberrant PC1/PC2 expression

Mislocalisation of PC1/PC2

Reduction in PC1/PC2 activity

Dysregulated ciliary signalling and tubular cyst formation

Fluid secretion

Cell proliferation

Inflammation

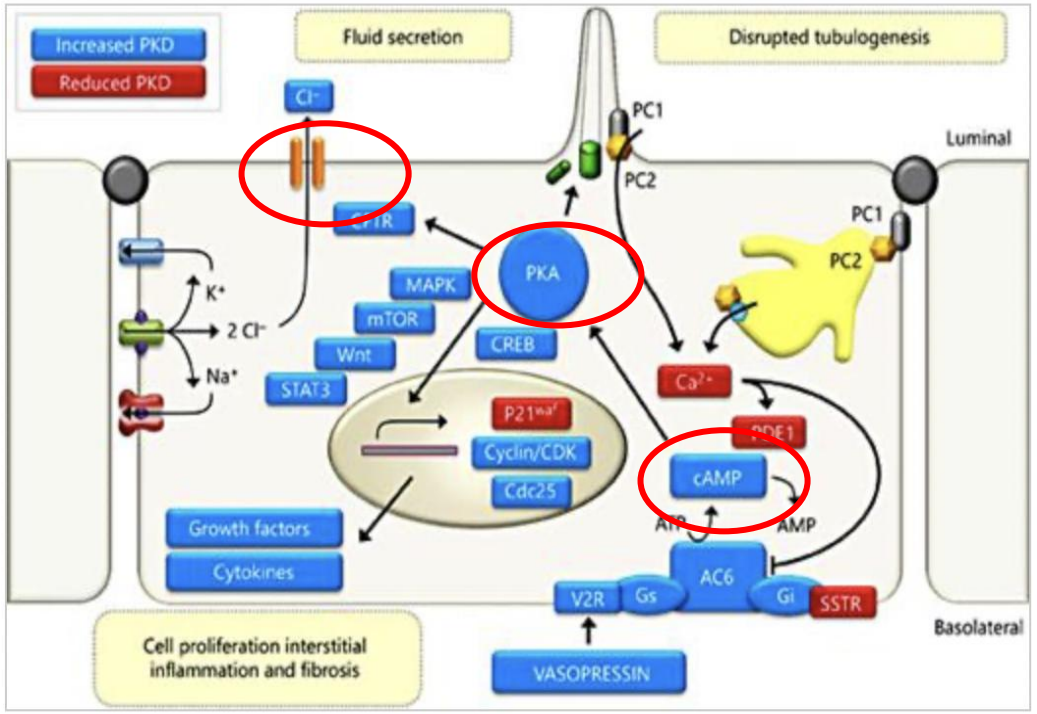
Fibrosis

Cyst growth, loss of nephrons, intraglomerular hypertension, further nephron loss

Graphic adapted from Ron Gansevoort, with permisson

Annu. Rev. Med. 2009 60, 321–337. doi:10.1146/annurev.med.60.101707.125712
Proc. Natl. Acad. Sci. U. S. A. 2011 108 (6), 2462–2467. doi:10.1073/pnas.1011498108

Celullar Level



Abnormal increase vasopressin, vasopressin-mediated intracellular (epithelial cells) cyclic adenosine monophosphate levels and simultaneous dysregulation of intracellular calcium in cyst epithelium

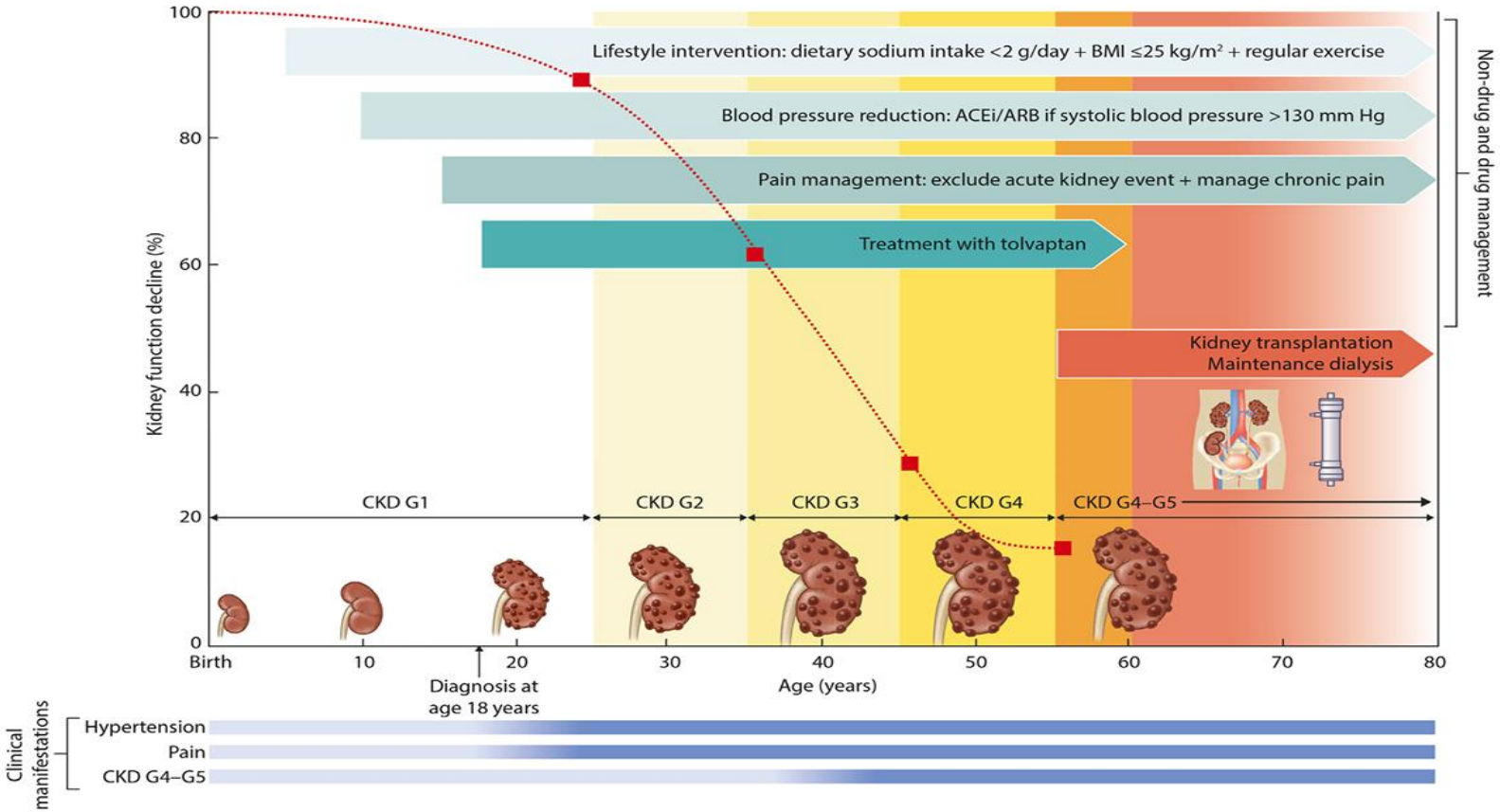
Dysregulating ciliary signaling and tubular cyst formation
Promote cell proliferation, dedifferentiation,inflammation, fibrosis and fluid secretion

Results in growth of these cells into cysts, loss of nephrons,intraglomerular HT, further nephron loss

Any drug that block the pathway that leads to epithelial proliferation would decrease the progression to ESRD

TREATMENT

General Approach
Specific Approach-Disease Modifying Treatment (STOP PROGRESSION)
Management of ADPKD complications



Identifying patients at risk for rapidly progressive disease is necessary to select patients who will benefit the most from treatment, and to protect patients who do not require treatment against **treatment-related costs and side effects.**

KDIGO STATEMENT Kidney International (2025) 107, (Suppl 2S), S1–S239

Identifying the Cases of Rapid Progression

1- eGFR

Slope is a key indicator

However, kidney cysts grow throughout life, eGFR might be preserved for several decades

LATE BIOMARKER BUT USEFUL WHEN IT STARTS TO DECREASE

ERA GROUP-> >40 years and yearly decrease

3 mL/min/1.73 m^2

2- Total Kidney Volume (TKV) and Mayo Imaging Classification (MIC)

- Early prognostic marker and also increased risk of HT, pain, hematuria, hospitalization and poor QOL
- Preferred to measure by MRI or CT (noncontrast)
- Normalized to height and age
- (https://www.mayo.edu/research/documents/pkd-center adpkd-classification/doc-20094754)
- Numerous studies have shown that it is one of the strongest predictors of future kidney function decline and kidney failure
- MIC is not helpful for atypical morphology (unilateral cysts and atrophy)

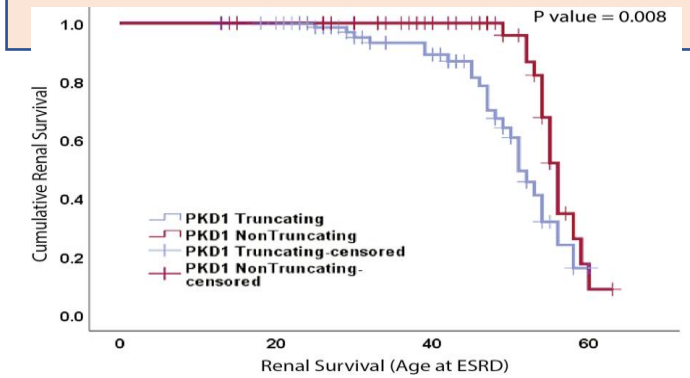
Class	Estimated kidney growth rate: yearly percentage increase	Risk for eGFR decline
1E	>6.0%	High risk
1D	4.5 – 6.0%	High risk
1C	3.0 – 4.5%	High risk
1B	1.5 - 3.0%	Intermediate risk
1A	<1.5%	Low risk

3-Genetic variants

PKD1>PKD2 (almost 20 years earlier)

PKD 1 mutation (truncating>nontruncating)

Non PKD genes or no detectable variants have milder disease



4- Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD)

generated from Genkyst cohort-1341 participants-evaluates teh influence of clinical and genetic factors on kidney survival

- Gender (Male>Female)
- Early ADPKD complications (HT, urologic events <35 years)
- PKD variant

low-risk (0–3 points)

intermediate-risk (4–6 points)

high-risk (7–9 points)

Limitations

- Need genetic analysis
- Cannot be applied for <35 years old

PROPKD Score

Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) Scoring system predicts the likely hood of kidney failure before 60 years old.

Multivariate survival analysis identified four variables that were significantly associated with age at ESKD onset, and a scoring system from 0 to 9 was developed as follows:[1]

PROPKD Calculator

Variable	Points
being male	1
hypertension before 35 years of age	2
first urologic event* before 35 years of age	2
mutation	
PKD2 mutation	0
nontruncating *PKD1* mutation	2
†truncating *PKD1* mutation	4
PROPKD Score =	SUM

Sample PROPKD Score Calculation

ADPKD patient info: 29 year old male with hypertension and a truncating *PKD1* mutation

1 point for being male
2 points for hypertension before 35 years of age
4 points for a truncating *PKD1* mutation

7 points **PROPKD Score**

HIGH Risk of Progression to ESKD

5- others

An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) study-> <55 years ve eGFR<65 ml/min/m^2-> poor prognosis

CRISP investigators-><50 years ve mean kidney size> 16.5 cm (USG, MRI, BT)

GENERAL APPROACH

Lifestyle Modification

Recommendation 4.2.1.1: We suggest adapting water intake, spread throughout the day, to achieve at least 2–3 liters of water intake per day in people with ADPKD and an eGFR ≥30 ml/min per 1.73 m^2 without contraindications to excreting a solute load (2D).

LIBERAL WATER INTAKE

Vasopressin stimulates cystogenesis. Increasing water intake throughout the day suppresses pituitary vasopressin release

reasonable to advise **liberal water** intake to achieve a morning urine osmolality of ≤250-300 mOsm/kg or urine output volume of ≥2 L/d.
PREVENT-ADPKD trial (n=18) Libitum water&increased free water
3 years
No difference for TKV growth
(note: 1/2 of the high water group failed to reach the target urine osmolality)
TEMPO 3:4 posthoc analysis ->3000 cc per day water intake decrease vasopressin and cyst growth

SALT RESTRICTION

High salt intake is associated with a higher increase in kidney volume and a faster drop in kidney function

Dietary sodium restriction <2 g/day
Blood pressure control
Slow TKV and eGFR decrease
Decrease severity of polyuria
HALT PKD trail (the association would be vasopression expression)
CRISP study: ever 18 mEq Na excretion in 24-hour urine is associated with 0.07 ml/min/1.73 m2 eGFR decrease

MAINTAIN HEALTHY WEIGHT

Overweight and obesity are linked to a rapid decline in kidney function and a higher increase in kidney volume

Observational data showed obesity linked to TKV growth
%50 higher risk for eGFR reduction
İncreased back pain
Better CV health

SMOKING CESSATION

Smoking is associated with an increase in cardiovascular risk, worsening proteinuria, and intracranial aneurysm development and rupture

CVD↑
↑cyst growth
↑risk of intracranial aneurysm rupture

EXERCISE

Contact sport should be avoided

Aerobic exercise recommended
avoid contact to abdomen

NO CAFFEINE RESTRICTION

Caffeine intake does not affect kidney volume or kidney function (human data)

Invitro studies showed caffeine increased the cyst size by increasing cyclic adenosine monophosphate
Human data showed no relation

Kidney Int. 2017;91(2):493 *Kidney 360 2023;4(12):1702*
Kidney Int. 2020;98(4):989. Epub 2020 Jun 10

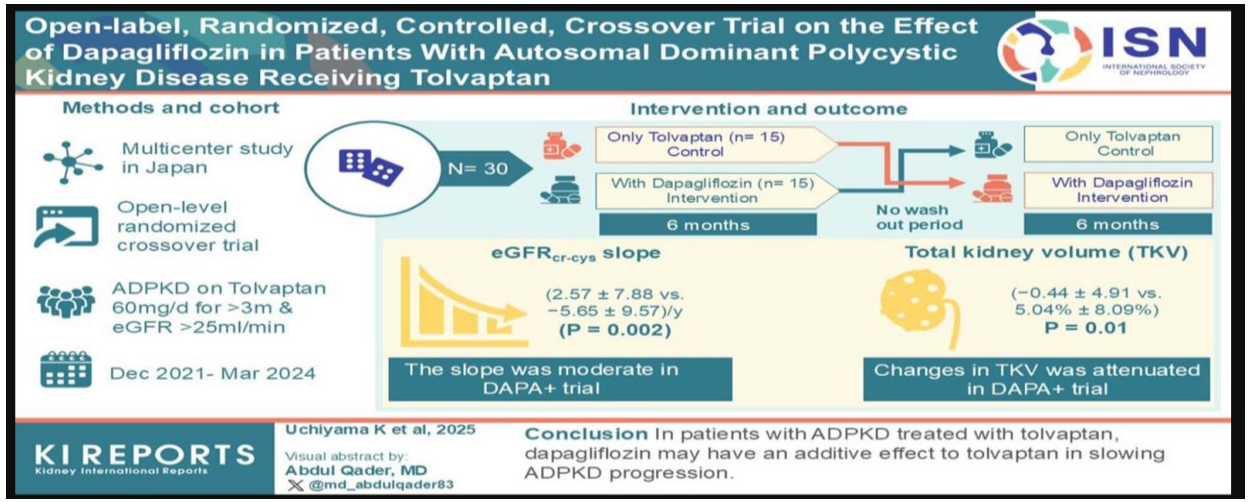
Control Hypertension

- Renal ischemia due to cyst growth-> activation of RAS
- First line treatment-> ACE inh, ARBs
- Target blood pressure <110/75 mmHg(< 50 years, eGFR>60 ml/min/1.73 m^2)
- There is no ADPKD-specific evidence-based blood pressure goal for those older than 50 years of age or with an < 60 eGFR
- SPRINT Trial-> target SBP<120 mmHg is a reasonable approach (indirect evidence since SPRINT excluded the ADPKD patients)
- HALT-PKD trial -> <110/75 mmHg-> slows TKV growth, no benefit for eGFR slope for 8 years of follow-up
- Blood pressure control
  - protection for intracranial aneurism rupture
  - Reduce left ventrikular mass index
  - decrease albuminuria

NEJM 2014;371 (24):2255-66
Clin J Am Soc Nephrol. 2010;5(1):102 HALT-PKD
Kidney International (2025) 107, 234–254

Control Diabetes

- eGFR>30 ml/dk/1.73 m^2-> Metformin
- eGFR <30 ml/dk/1.73 m^2-> GLP1 RA
- No sufficient information regarding SGLT-2 inh



Recruiting

Study of Empagliflozin in Patients with Autosomal Dominant Polycystic Kidney Disease (EMPA-PKD)
(EMPA-PKD)

ClinicalTrials.gov ID NCT06391450

Sponsor Hannover Medical School

Information provided by Hannover Medical School (Responsible Party)

Last Update Posted 2024-10-03

Phase 4 Trial, expected to be closed by 2027
44 participants will be randomly allocated (1:1) to receive a daily dose of either empagliflozin (10 mg/day) or placebo for 18 months. Patients will be stratified according to concomitant tolvaptan use.

Specific Approach-Disease Modifying Treatment

Clinical studies for ADPKD

1820
First PCKD case in the literature

1957
Dalgaard' study

1996
PKD2 geninin konumsal klonlanmacloni ngsı

2006
CRISP results

2009
mTOR inh study

2013
ALADIN study (ADPKD-somatostatin analog)

2017
REPRISE study

1995
PKD1 cloning

2003
CRISP study
First look

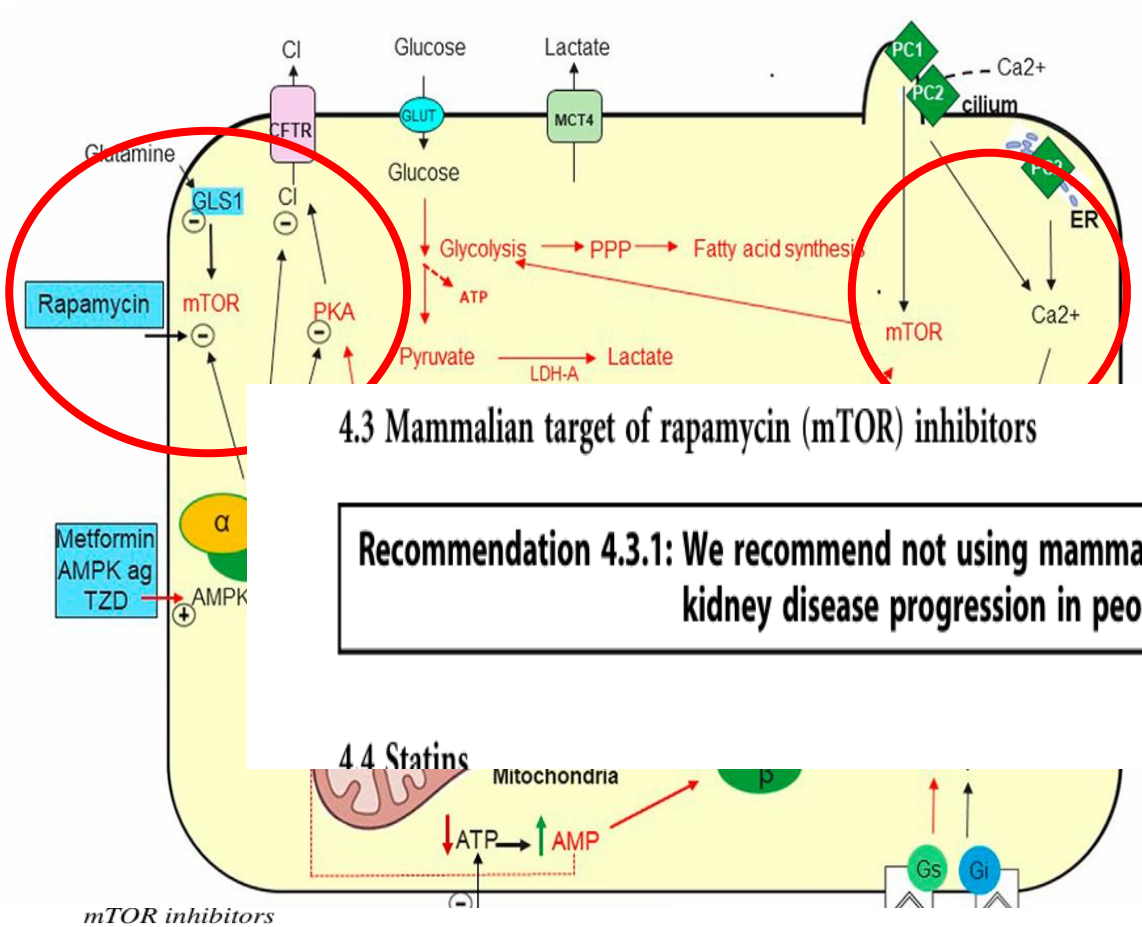
2008
PCKD first study
With tolvaptan

2012
Tolvaptan **TEMPO 3:4 published**

2014
HALT-PKD (RAS blockage in HT)

The clinical trials aimed to treatment effect of the molecule, the required number of patients depends on the treatment effect on the decline of eGFR (set data reduction in 30%)
Although TKV can be used as a surrogate outcome, a trial with eGFR decline as the primary endpoint should always be performed since renoprotection is the ultimate goal for ADPKD treatment.

Target-> mTOR PATHWAY



Alterations of metabolic pathways (metabolic reprogramming) in ADPKD have shown the abdormal cyst growth

Elevated MTOR activity-> CAMP/PKA/ERK/AKT are upstream regulators

OR pathway
s cyst growth
on

n in early and
D

4.3 Mammalian target of rapamycin (mTOR) inhibitors

Recommendation 4.3.1: We recommend not using mammalian target of rapamycin (mTOR) inhibitors to slow kidney disease progression in people with ADPKD (*1C*).

4.4 Statins

mTOR inhibitors

Everolimus	Phase 3, double-blind, placebo-controlled [29]	eGFR > 30 mL/min/1.73m^2 and TKV > 1000 mL	433	24 months	Published	Mucositis, diarrhea, acne, increased proteinuria and reduced hematopoiesis. Angioedema when combined with ACE-inhibitors	Reduction of TKV growth after 1 year (102 mL vs 157 for everolimus and placebo, respectively). Trend towards reduction of TKV growth after 2 years (230 mL for everolimus vs 301 for placebo, p=0.06). No significant differences in eGFR decline between groups
Sirolimus	Phase 3, open label [28]	Age 18–40 years, eGFR ≥ 70 mL/min/1.73m^2	100	18 months	Published	Mucositis, diarrhea, acne and peripheral edema	No significant effects on TKV growth (7.8% per year for sirolimus vs 6.8 for placebo). No differences in eGFR decline between groups. Higher urinary excretion rates in the sirolimus group compared to placebo

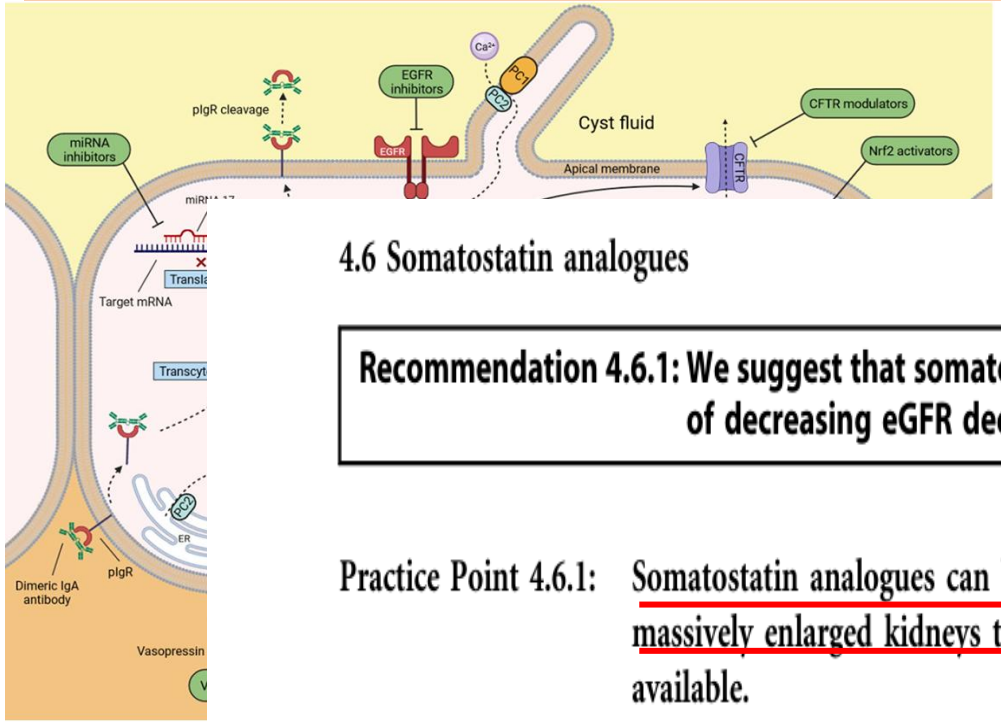
Late stage

Early stage

N Engl J Med. 2010;363:1. N Engl J Med. 830

Front. Mol. Biosci.2023; 10:1126055. doi: 10.3389/fmolb.2023.1126055

Somatostatin analogues



ALADIN trial
Lancet. 2013;382:1485–95

Octreotide long-acting release (LAR)
79 ADPKD (eGFR ≥ 40 mL/ min/1.73 m2)
Octreotide LAR significantly reduced TKV growth after 1 year but not at 3 years. The decline in measured GFR from baseline to year 3 was not significantly dif ferent in the octreotide LAR group compared to placebo, but it was significant when measured from year 1 to 3.
evere disease making it
aw conclusion

4.6 Somatostatin analogues

Recommendation 4.6.1: We suggest that somatostatin analogues should not be prescribed for the sole purpose of decreasing eGFR decline in people with ADPKD (*2B*).

Practice Point 4.6.1: Somatostatin analogues can be considered in people with ADPKD with severe symptoms due to massively enlarged kidneys to lower the growth rate of kidney cysts when no better options are available.

lease (LAR)&placebo
0 mL/ min/1.73 m2)
uced TKV growth at 1 and 3
.
on measured GFR decline
e from baseline to year 3, nor
spite the lack of effect on
treated with octreotide LAR
a composite endpoint of
doubling of serum creatinine or ESKD com pared to placebo (17.6% vs. 42.9%, respectively).

LIPS study
Lanreotid 120 mg sc every 4 weeks & saline 0.5 cc every 4 weeks
159 ADPKD eGFR 30 -89 ml/mn/1.73m2
Completed 2019

DIPAK 1
JAMA. 2018;320:2010–9

Lanreotide &placebo
309 ADPKD
found no significant effect of lanreotide on the primary outcome rate of eGFR decline compared to placebo (− 3.53 mL/ min/1.73 m2 per year vs. -3.46 mL/min/1.73 m2, respec tively), nor on worsening of kidney function (defined as a 30% eGFR decrease or start of dialysis)
this study also demonstrated that the rate of TKV growth was significantly reduced by a somatostatin analogue.

Biguanid Analogues (Metformin)

Rationale: Abnormal polycystin signaling in renal tubular PKD cells is accompanied with a metabolic shift to glycolysis (similar to the Warburg effect in cancer cells) and excessive ATP production
AMPK serves as a cellular energy-sensing molecule that inhibits mTOR signaling and CFTR activity during energy depletion
The enhanced metabolic rate in PKD cells inhibits AMP-activated protein kinase (AMPK), thus leading to increased mTOR signaling and CFTR activity, which respectively stimulate the proliferative and secretory aspects of cyst formation
Metformin activates AMPK and could reduce ADPKD disease
oned mechanisms

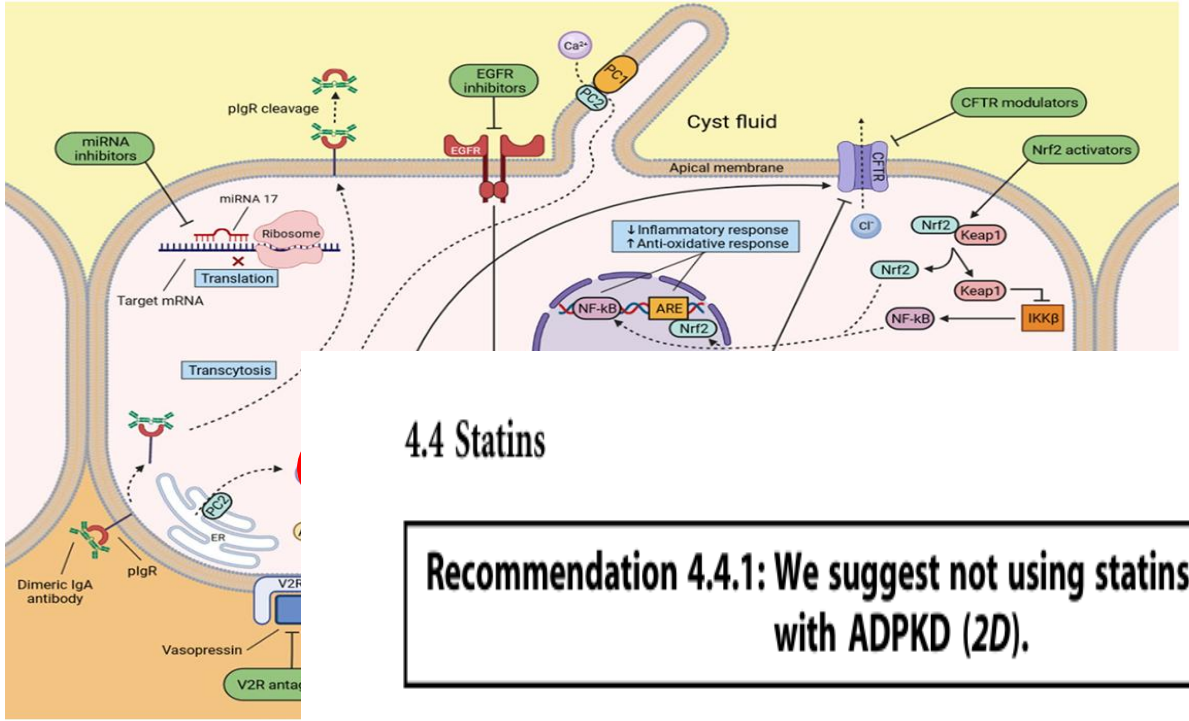
4.5 Metformin

Recommendation 4.5.1: We recommend not using metformin specifically to slow the rate of disease progression in people with ADPKD who do not have diabetes (*1B*).

ed Phase 2 trials
ic ADPKD
ved no effects on height
n or renal function decline
Dis. 2021
;100:684–96.

Recent Phase 3 trial (IMPEDE-PKD) (metfromin dose 1000-2000 mg/day)
Australia, New Zealand, UK,
1174 ADPKD (ckd stage2-3A, eGFR 45–90 mL/min/1.73 m^2), 24 months
Prmary endpoint: change in EGFR
Stuyd start november 2022 , primary completion is expected by december 2026
STILL RECRUITING
Definitive answer should come from IMPEDE PKD

Statins



Possible rationale: Activation of AMPK and cAMP lowering effect
(antiinflammatory and antioxidative protperties)

Baliga conducted targeted metabolomics in plasma samples from a phase III trial designed to test the efficacy of pravastatin on ADPKD progression in children and young

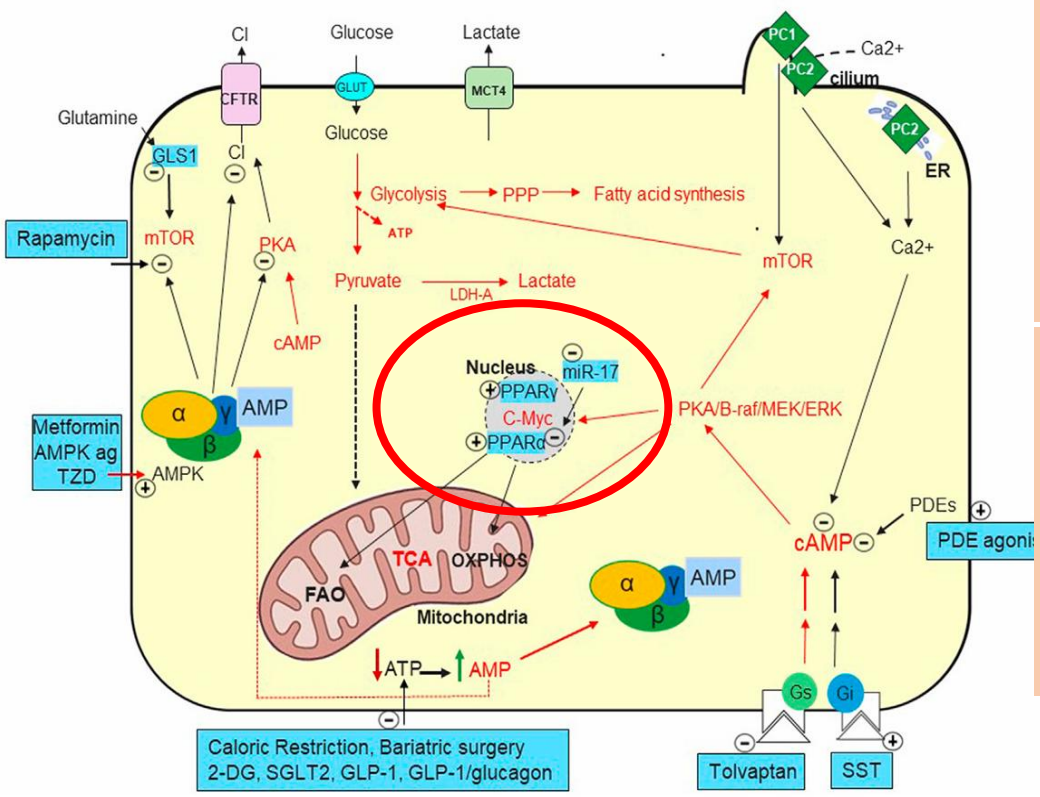
progression
1-84609-8

4.4 Statins

Recommendation 4.4.1: We suggest not using statins specifically to slow kidney disease progression in people with ADPKD (2D).

(NCT03273413) (USA) (patient recruitment completed by 2025/9)
Pravastatin 40 mg &placebo (2 years) (Phase 4)
150 ADPKD (25-60 years) TKV >500 mL egfr ≥60 mL/min/1.73m^2
Primary outcome: Total kidney volume as assessed by renal MRI, at baseline and after 2 years of treatment
Secondary outcome: change in eGFR, plasma levels of cytokines, oxidative stress markers, change in urinary epithelial cells
RESULTS HAVE NOT BEEN PUBLISHED

(PPAR-γ) agonist



Rationale: thiazolidinediones act as a peroxisome proliferator-activated receptor-γ agonist. This nuclear receptor forms a heterodimer with retinoic acid receptor A to control the transcription of multiple target genes. In addition to its insulin-sensitizing effects, pioglitazone may inhibit cystogenesis in animal models through several mechanisms, including the inhibition of CFTR expression and downregulation of proliferative pathways.

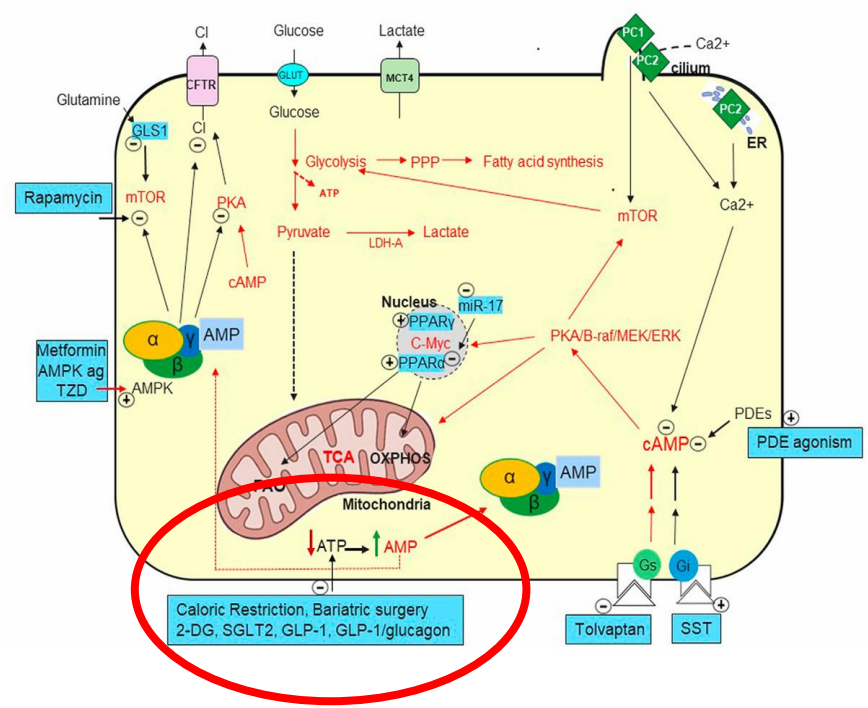
PIOPKD study Phase 1B
18 NON-DM ADPKD Low dose pioglitazone (15 mg/day) &placebo
1 year
No effects of pioglitazone on TKV or renal function were seen compared to placebo treatment

Clin Kidney J. 2021;14:1738–46.

Concerns: Fluid retention, bone loss, weight gain

No mention in KDIGO 2025 GUIDELINE

Ketogenic interventions



4.8 Ketogenic interventions

Practice Point 4.8.1: Ketogenic interventions should not be implemented in people with ADPKD without further evidence from controlled clinical trials.

From a mechanism of action perspective-> it is possible that Ketone bodies may promote metabolic reprogramming by decreasing glucose availability and increasing fatty acids

Retrospective study: 6 months ketogenic diet -> weight loss + improvement in ADPKD symptoms and blood pressure
Clin. Kidney J. 2021;15 (6), 1079–1092.
Ongoing study KETO-ADPKD (NCT04680780)

Bariatric surgery-> promising for weight loss however risk for AKI, nephrolitiasis and oxalate nephropathy

Glucagon-like peptide 1 receptor agonists(GLP-1) -> approved for DM+obesity

Importantly, GLP-1 exerts its effects by binding to GLP-1R and activating adenylate cyclase, which leads to the generation of cAMP, so it will be important to assess the expression of GLP-1R on the cystic epithelium and the potential impact of GLP-1 agonism on cAMP
Dual agonism at the GLP-1 and glucagon receptors has shown superior weight lowering effect to selective GLP-1 agonism. Because glucagon lowers mTORC1 and stimulates AMPK and ketogenesis ,the simultaneous agonism of GLP-1R and glucagon receptors constitute a potential approach for ADPKD.
WE NEED STUDY !!

Front. Mol. Biosci.2023 10:1126055.

SGLT-2 inhibitors

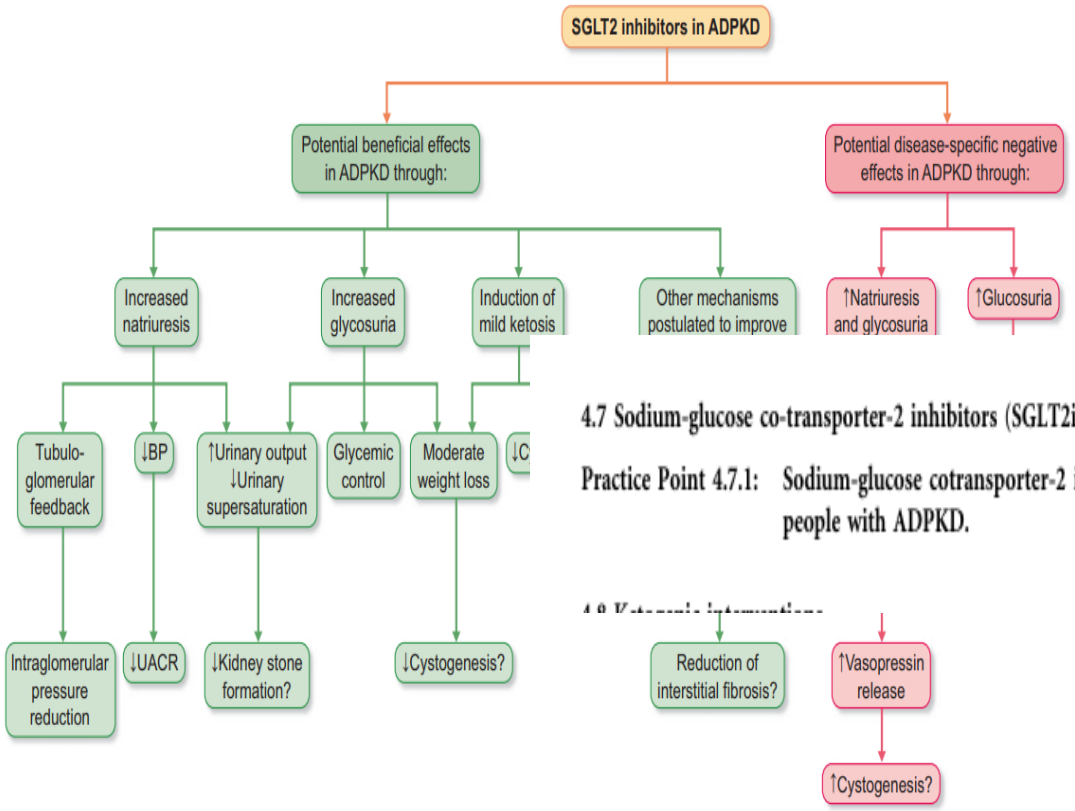


Table 1: Overview of Preclinical Evidence on SGLT2 Inhibitors in Polycystic Kidney Disease (PKD) Animal Models

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.

Currently, there is no evidence from clinical trials on the use of SGLT2i in ADPKD
ı-diabetic CKD trials listing ADPKD as an exclusion

4.7 Sodium-glucose co-transporter-2 inhibitors (SGLT2i)

Practice Point 4.7.1: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) should not be used to slow eGFR decline in people with ADPKD.

				Key inclusion criteria	Primary outcome	Key secondary outcomes	Status
				≥20 y, only individuals already treated by Tolvaptan	Slope of eGFR decline	Change in TKV, BP, metabolic parameters, urine volume, UACR	Completed
				18–55 y; eGFR 30–90 ml/min/1.73 m²; 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 m², 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 m²	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 m² if age <60 or 25–45 ml/min/1.73 m² 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 m², MIC 1D-1E, or 1C with either a *PKD1* truncating variant, or eGFR loss >3 ml/min/1.73 m²/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.

SGLT2i switch metabolism to a ketotic state and increase plasma glucagon potentially regulating PKAand mTOR pathways

Nephrol Dial Transplant, 2025, 40, 2231–2238

Pharmacologic interventions targeting the action of the antidiuretic hormone AVP are presently the cornerstone of treatment in people with ADPKD who are at risk of rapid disease progression

1- Pharmacologic blockade of vasopressin-2 (V2) receptors using tolvaptan (note that other V2 receptor antagonists are available, but only the efficacy of tolvaptan has been evaluated in ADPKD)

2-Increased water intake

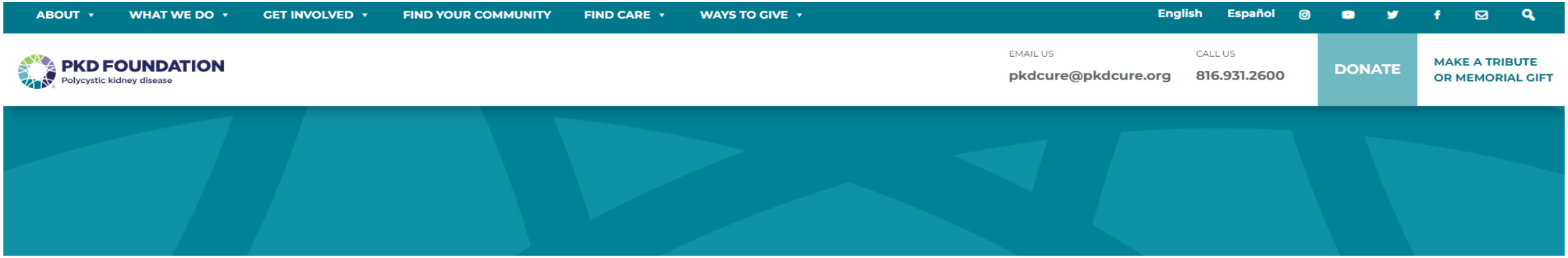
Table 8 | Approaches to reduce AVP activity in ADPKD

Factors	Increased water intake	V_2 receptor antagonist (tolvaptan)
Mechanism	Suppression of AVP release by lowering plasma osmolality	Selective blockade of AVP binding on V_2 receptors
Administration	Drinking water during waking hours	Split-dose tablet (1 tablet upon waking, and 1 tablet 8 h later)
Effect on water intake	Voluntary increase (≥2 l/d)	Involuntary increase due to thirst and aquaresis (>3–7 l/d)
Effect on circulating level of AVP	Reduced level	Increased level
Indication for use in ADPKD	All people with eGFR >30 ml/min per 1.73 m^2	Selected high-risk groups due to cost and side effects
Efficacy to ↓ urine osmolality to 300 mOsmol/kg	~50% of participants in 3-yr (PREVENT-ADPKD trial)[257]	~70% of ADPKD participants, >3 yr treatment in the TEMPO 3:4 trial
Efficacy to ↓ TKV in ADPKD	No (PREVENT-ADPKD trial)[257]	Yes (TEMPO 3:4)
Efficacy to ↓ long-term eGFR decline	No	Yes (~1 ml/min per 1.73 m^2) (TEMPO 3:4 and REPRISE trials)[28,29]
	No data on risk reduction for CKD G5 (PREVENT-ADPKD trial)[257]	No data on risk reduction for CKD G5
Adherence to treatment	~50% over 3 yr (PREVENT-ADPKD trial)[257]	Real-world adherence declines over time and ~75% after 3 yr[377,378]
Disadvantages	Long-term adherence is poor; pollakiuria, polyuria	Thirst/dehydration
	Reversible mild hyponatremia	Pollakiuria, nocturia, polyuria with potential impact on day-to-day living (occupation, habits)
	Environmental issues (bottled water)	Blood tests (every 1–3 mo)
		Hypernatremia; hyperuricemia
		Risk of hepatotoxicity
		Accessibility
Advantages	Access and low cost (tap water)	Standard dose
	More physiological suppression of AVP than V_2 receptor antagonist	Better 24-h inhibition

ADPKD, autosomal dominant polycystic kidney disease; AVP, arginine vasopressin; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PREVENT-ADPKD, Prevent Kidney Failure Due to Autosomal Dominant Polycystic Kidney Disease; REPRISE, Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD; TEMPO 3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV, total kidney volume; V_2, vasopressin-2.

KDIGO STATEMENTKidney International (2025) 107, (Suppl 2S), S1–S239

AN OLDIE BUT A GOODIE



Tolvaptan treatment for ADPKD

Early in the disease, there are generally no symptoms at all. In fact, many people are never diagnosed with PKD because they have few or no symptoms. Often the first sign of PKD is high blood pressure, blood in the urine or a feeling of heaviness or pain in the back or abdomen. Sometimes the first sign may be a urinary tract infection or kidney stones.

On **April 24, 2018, the U.S. Food and Drug Administration (FDA) granted approval of tolvaptan to be the first treatment in the United States** for adult patients with autosomal dominant polycystic kidney disease (ADPKD), the most common form of polycystic kidney disease (PKD).

ACTALERT
ACCELERATING CLINICAL TRIALS

Receive notifications when there are clinical studies in your area.

SIGN UP

4.1.1 Indications for tolvaptan in ADPKD

Recommendation 4.1.1.1: We recommend initiating tolvaptan treatment in adults with ADPKD with an estimated glomerular filtration rate (eGFR) ≥25 ml/min per 1.73 m^2 who are at risk for rapidly progressive disease (Figure 25) (*1B*).

Still only drug that FDA and EMA approved for progression of rapidly progressive ADPKD

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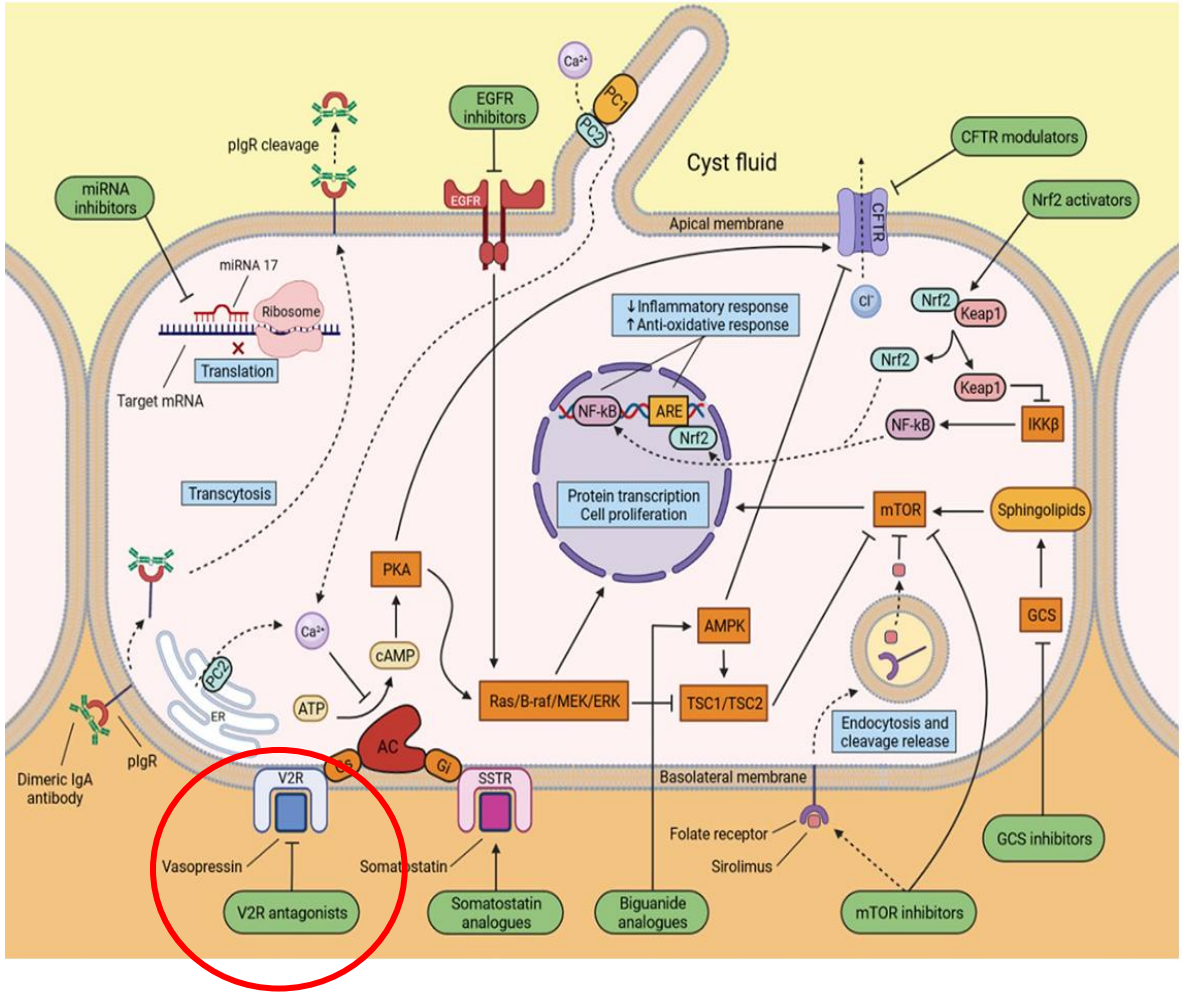
TOLVAPTAN- V2-receptor antagonist



Vasopressin:

- Activates V2r
- Increases cell proliferation by cAMP pathway
- Fluid secretion
- Cystogenesis

Proposed mechanism of action

vasopressin 2 receptor (V2R), located on the basolateral membrane of collecting duct cells, tolvaptan oral nonpeptid vasopressin receptor antagonist that specifically inhibits binding of AVP at the V2 receptor of the collecting duct, causing the selective diuresis of electrolyte-free water (also known as aquaresis)

slow cyst growth by suppressing abnormally increased intracellular cyclic adenosine monophosphate levels in cyst epithelial cells.

Landmark Clinical Trials

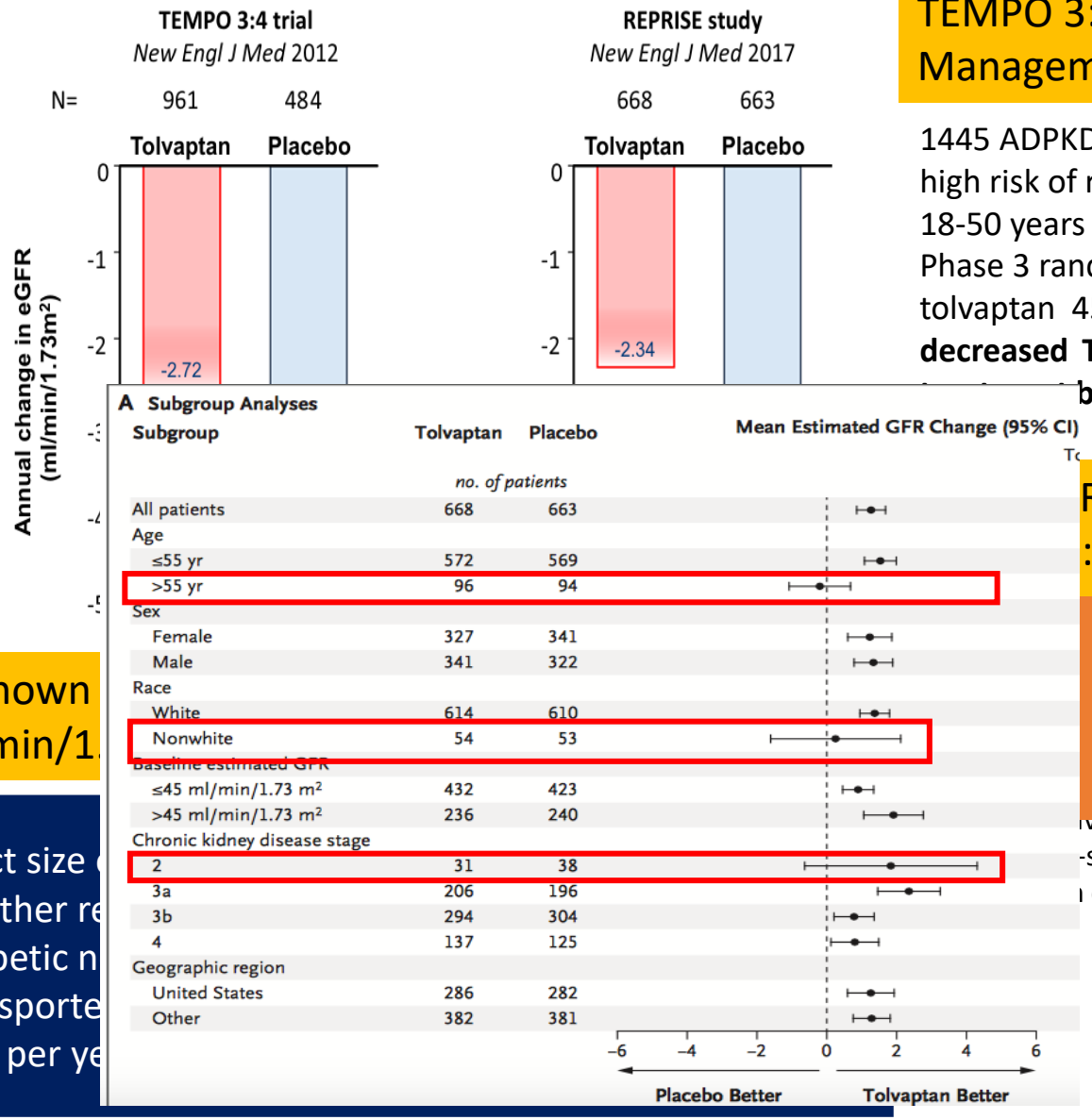
TEMPO 3: 4

TEMPO 4: 4

REPRISE

TOLVAPTAN- V2-receptor antagonist

Fig. 2 Treatment effect of tolvaptan on annual rate of estimated glomerular filtration rate (eGFR) decline in the TEMPO 3:4 and REPRISE trials [25, 26]. Tolvaptan reduced the annual eGFR decline by 26% and 35% in the TEMPO 3:4 and REPRISE studies, respectively



TEMPO 3: 4 (Tolvaptan Efficacy and Safety in the Management of ADPKD and its Outcomes)

1445 ADPKD early stage disease (Egfr> 60 mL/min/1.73 m2) high risk of rapid disease progression (TKV > 750 mL).
18-50 years old
Phase 3 randomized 2:1 3 years of follow-up
tolvaptan 45+15 mg->60+30 mg->90+30 mg (weekly increase)
decreased TKV growth by 49% and the rate of eGFR decline on by 26%

Replicating Evidence of Preserved Renal : An Investigation of Tolvaptan Safety and

- Seems like tolvaptan is not working for >55 years older
- However this group sample size is very limited.

Tolvaptan has been shown approximately 1 mL/min/1

My conclusion: the effect size favorably to that of other re receptor blockade in diabetic n sodium/glucose cotransporte (1.5 mL/min/1.73 m2 per ye

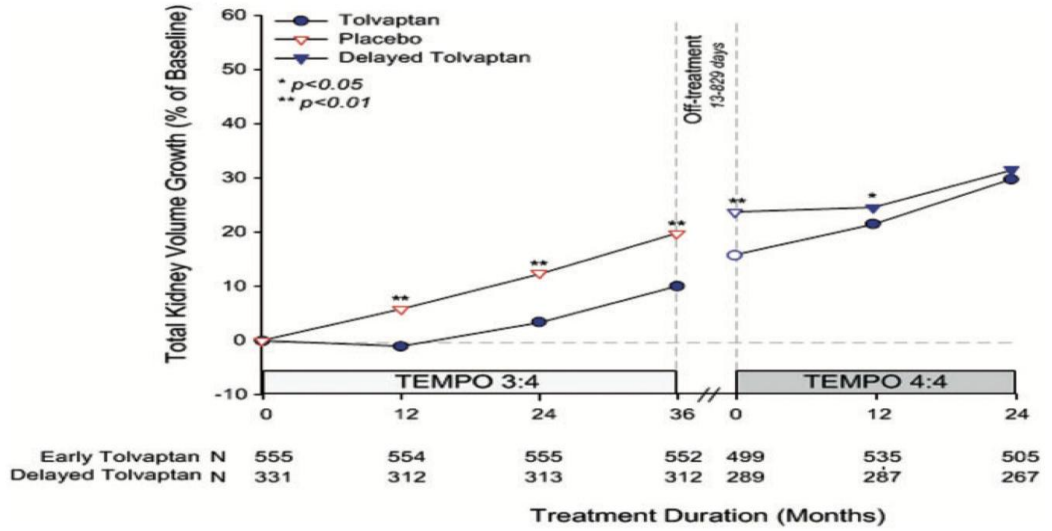
Naptan on eGFR was sustained
-stage disease (REPRISE trial) and in a real-world setting, tolvaptan was effective, with a 38% decrease in the rate of eGFR decline.

N Engl J Med. 2012;367:2407–18
N Engl J Med. 2017;377:1930–42.
Clin J Am Soc Nephrol. 2018;13:1153–61

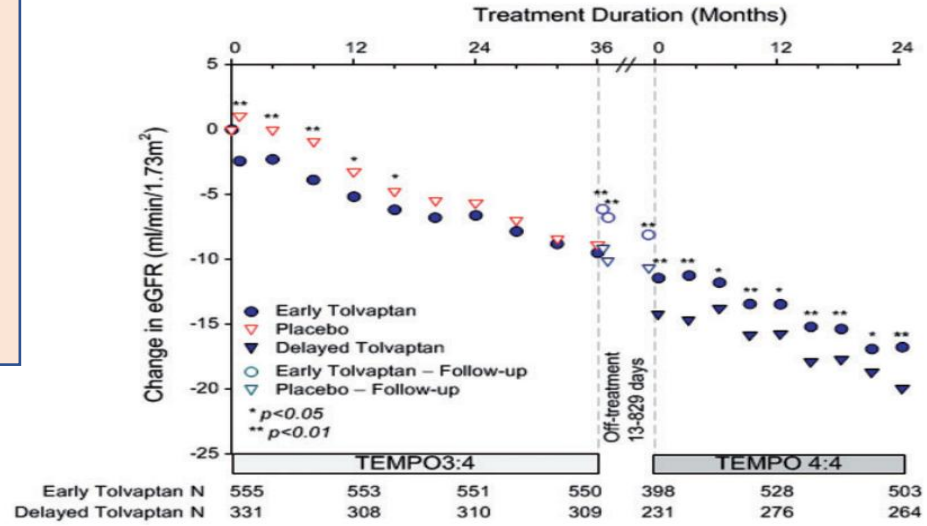
TOLVAPTAN- V2-receptor antagonist

Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease the TEMPO 4:4 Trial

Additional 2 years for TEMPO 3:4
571Under tolvaptan treatment
314 placebo group started tolvaptan
Target: long term effect of tolvaptan



TKV increase rate is lower in the early treated group (%1.7 &%4.15)
The eGFR decrease rate is not different early versus late group
(**-3.26 versus -3.14 mL/min/1.73 m2 per year**; treatment difference -0.11, 95% CI, -0.75, 0.52, P ¼ 0.73)



Nephrol Dial Transplant 2017; 32: 1262

TOLVAPTAN- V2-receptor antagonist

- It is uncertain if the renoprotective effect of tolvaptan is sustained, but, if it is, the cumulative benefit would be anticipated to delay renal replacement therapy by many years.
- Tolvaptan also reduced the incidence of kidney pain and urinary tract infections.

The Effect of Tolvaptan on Blood Pressure in Polycystic Kidney Disease: A Post-hoc Analysis of the TEMPO 3:4 Trial

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Methods

ADPKD patients
- age 18 – 50 yrs
- total kidney volume >750 mL
- creatinine clearance ≥60 mL/min

Treated with either placebo (n=484) or tolvaptan (n=961) for 3 years

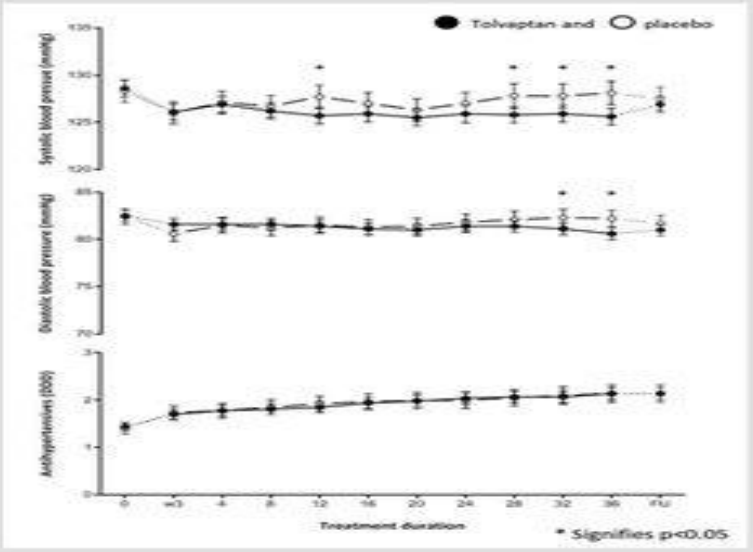
Effect on blood pressure (BP) over time?

Results

At baseline, BP did not differ

After 3 weeks, BP remained similar

At end of study, BP was significantly lower in tolvaptan arm, despite similar use of antihypertensives

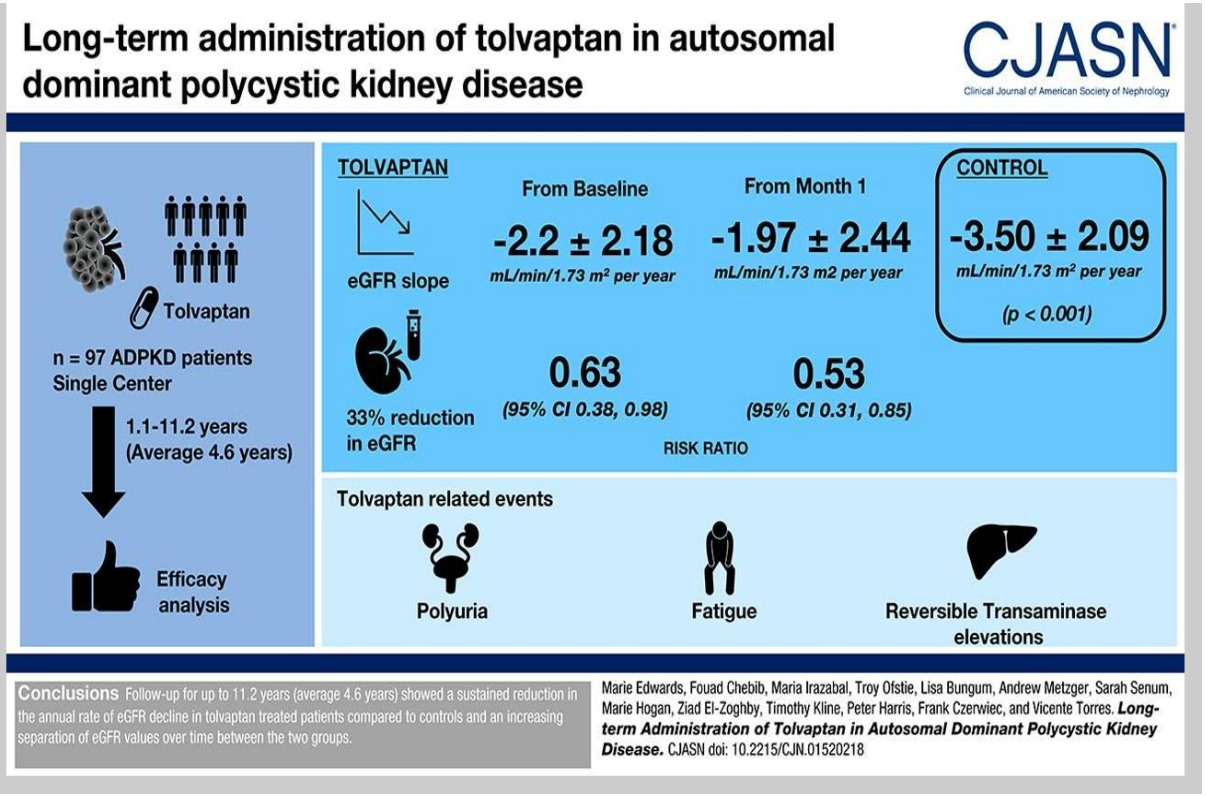


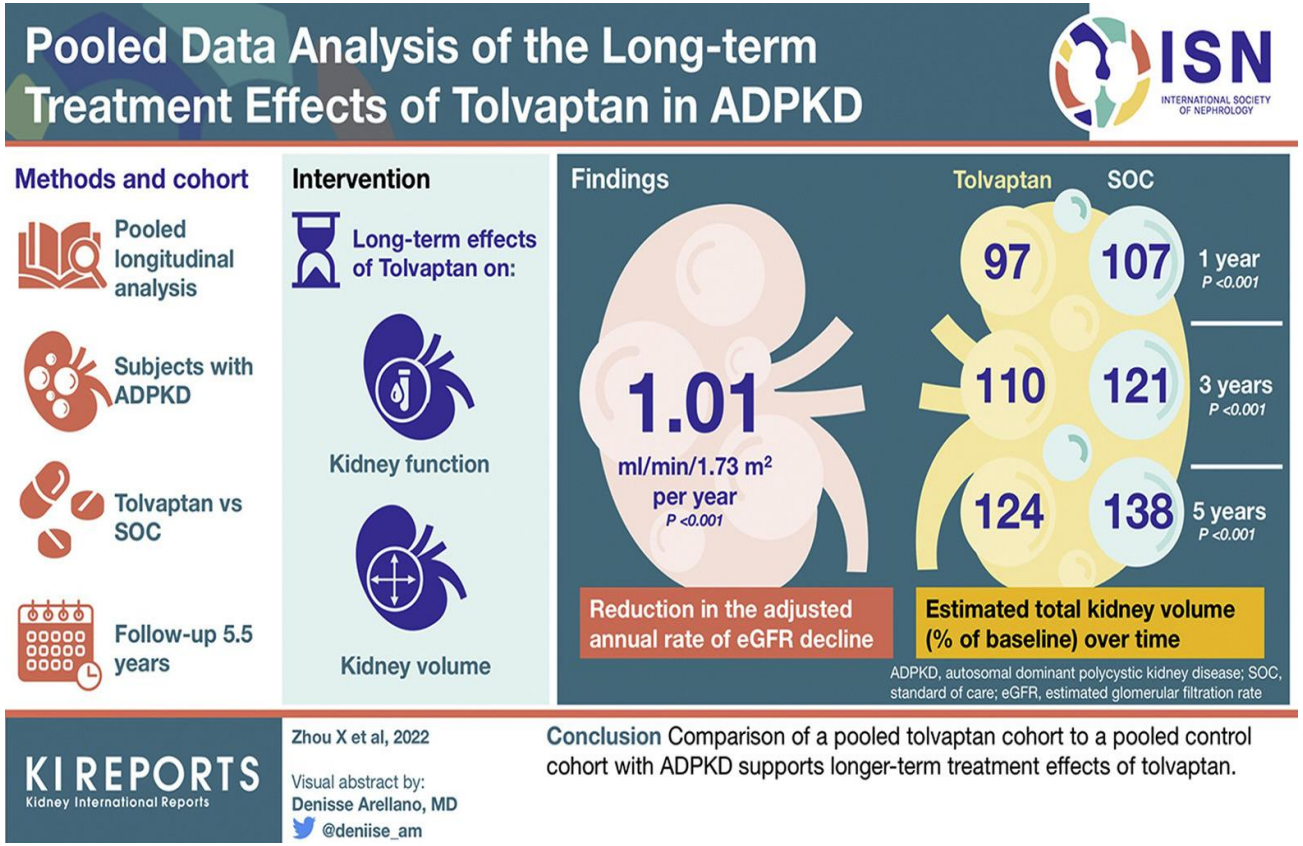
Conclusion

Long-term treatment with tolvaptan gradually lowered BP compared with placebo, which probably can be attributed to a beneficial effect on disease progression, a natriuretic effect, or both.

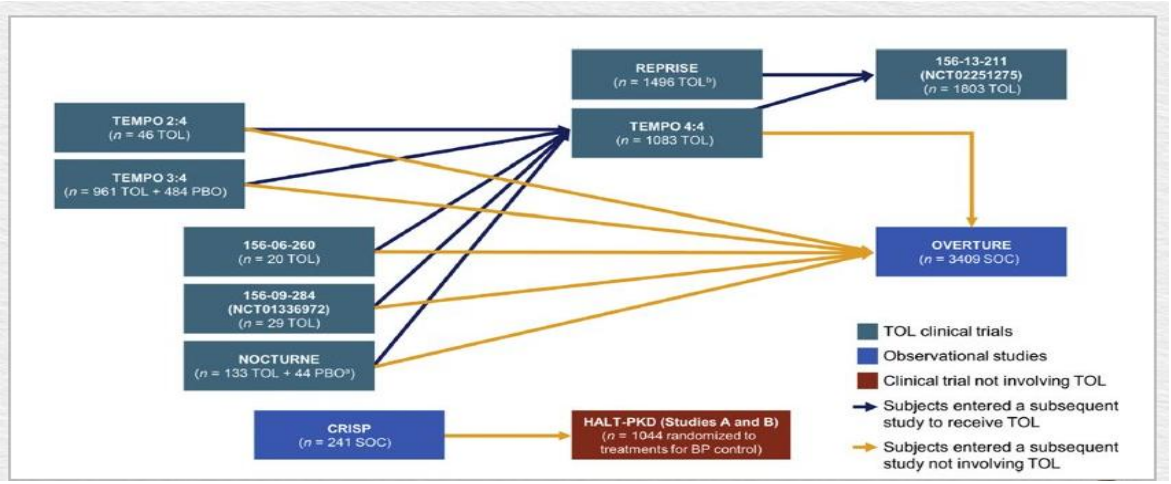
doi: 10.1681/ASN.2020101512

TEMPO3:4 (3 YIL), TEMPO 4:4 (3+2 YIL, REPRISE (1 YIL)





This study includes all patients who participated at the Mayo Clinic in clinical trials of tolvaptan for ADPKD: 156–04–250 (TEMPO 2:4, NCT00413777), 156–04–251 (TEMPO 3:4, NCT00428948), 156–06–260, 156–08–271 (TEMPO 4:4, NCT01214421), 156–09–285 (NCT01210560), 156–09–290 (NOCTURNE, NCT01451827), 156–13–210 (REPRISE, NCT02160145), 156–13–211 (NCT02251275).

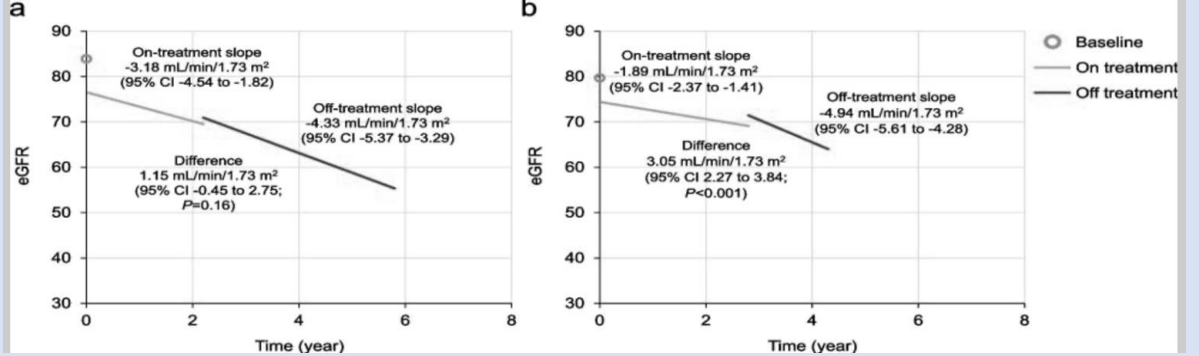


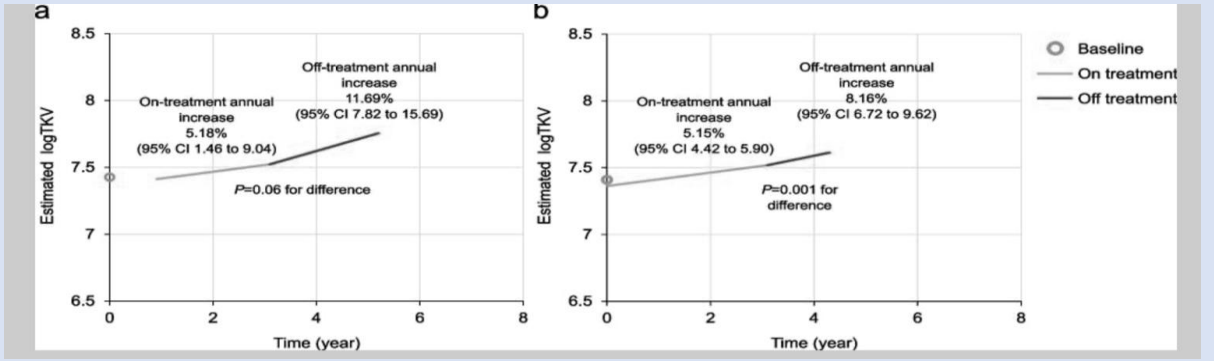
Retrospective Analysis of 10 years

Clin J Am Soc Nephrol. 2018 Aug 7; 13(8): 1153–1161.

PATIENTS WHO ARE UNDER TOLVAPTAN BUT STOPPED FOR ANY REASON

- Posthoc analysis of pooled data TEMPO 2:4, 3:4, 4:4 OVERTURE
- 2 COHORTS
- 1: >2 eGFR results and TKV measurement
- 2: >1 eGFR results and TKV measurement





Lioudis et al. BMC Nephrology (2023) 24:182
https://doi.org/10.1186/s12882-023-03247-6

BMC Nephrology

RESEARCH Open Access

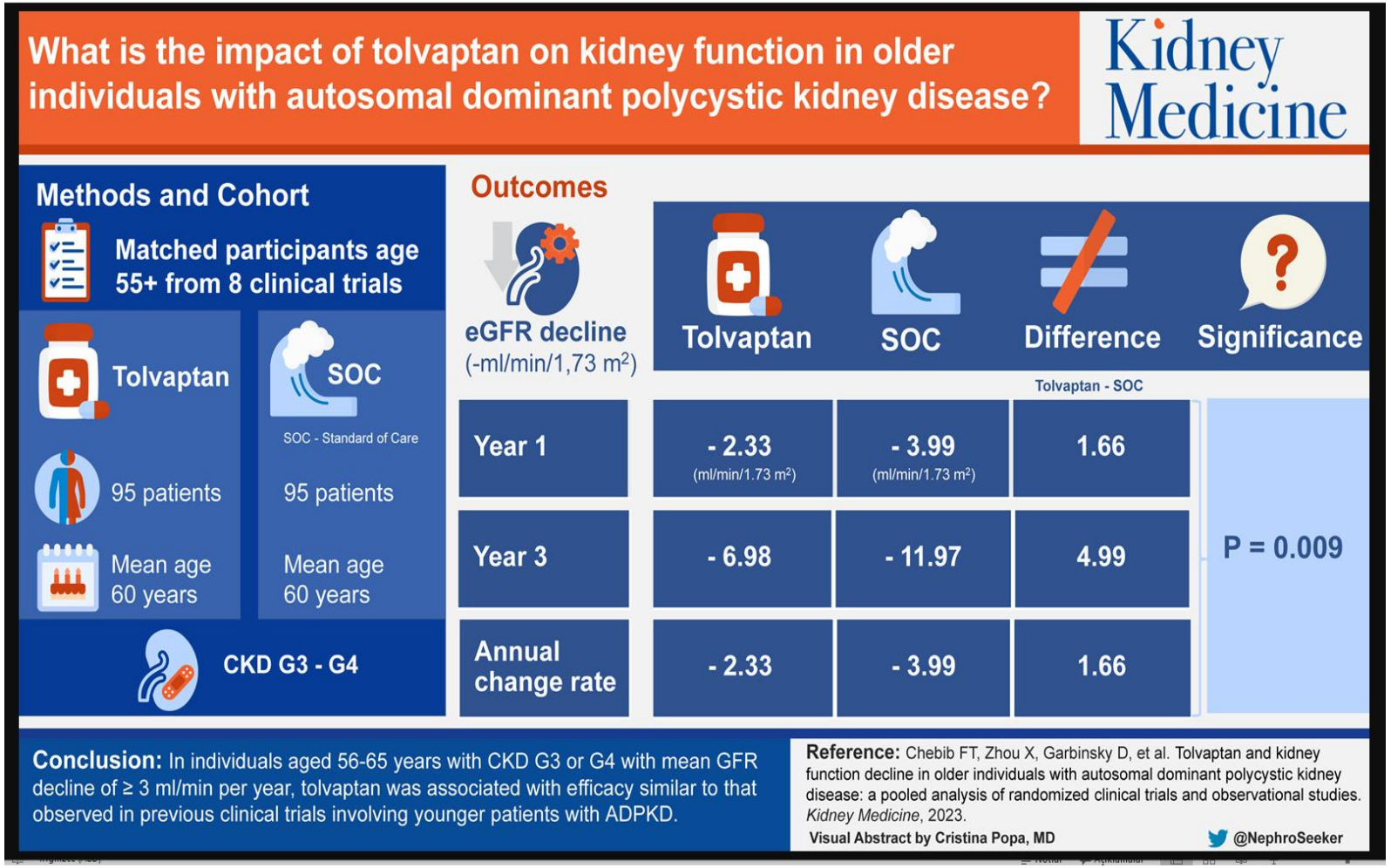
Effects of tolvaptan discontinuation in patients with autosomal dominant polycystic kidney disease: a post hoc pooled analysis

Michael Lioudis[1], Xiaolei Zhou[2], Eric Davenport[2], Sasikiran Nunna[3*], Holly B. Krasa[4], Dorothee Oberdhan[3] and Ancilla W. Fernandes[3]

Characteristic	Statistic or Category	Cohort 1 ≥ 2 on treatment, ≥ 2 post-treatment assessments		Cohort 2 ≥ 1 on treatment, ≥ 1 post-treatment assessments	
		eGFR Analysis (n = 20)	TKV Analysis (n = 11)	eGFR Analysis (n = 82)	TKV Analysis (n = 88)
Age, years	Mean (SD)	39.9 (8.5)	40.9 (8.1)	40.3 (7.4)	40.7 (7.2)
	Median	41.2	41.3	41.1	41.5
	Min, Max	23.6, 50.2	23.6, 50.2	23.6, 52.1	23.6, 51.9
Sex	Male	6 (30%)	3 (27%)	40 (49%)	43 (49%)
	Female	14 (70%)	8 (73%)	42 (51%)	45 (51%)
Race	White	19 (95%)	11 (100%)	76 (93%)	80 (91%)
	Black	1 (5%)	0	3 (4%)	4 (5%)
	Hispanic	0	0	3 (4%)	4 (5%)
	Other	0	0	0	0
Height, m	Mean (SD)	1.72 (0.11)	1.72 (0.11)	1.73 (0.11)	1.74 (0.11)
Weight, kg	Mean (SD)	77.1 (16.6)	77.7 (18.3)	78.3 (16.9)	79.5 (17.3)
Body mass index, kg/m²	Mean (SD)	25.8 (3.5)	25.9 (3.3)	26.0 (4.3)	26.2 (4.6)
Age at ADPKD diagnosis, years	Mean (SD)	27.7 (9.6)	25.5 (8.2)	27.3 (9.3)	27.6 (9.1)
Chronic kidney disease stage, mL/min/1.73 m²	≥ 90 (stage G1)	10 (50%)	5 (50%)	29 (35%)	22 (25%)
	60 to < 90 (stage G2)	5 (25%)	1 (10%)	32 (39%)	37 (43%)
	30 to < 60 (stage G3)	5 (25%)	4 (40%)	21 (26%)	28 (32%)
	< 30 (stage G4)	0	0	0	0
Baseline eGFR, mL/min/1.73 m²	Mean (SD)	84 (26)	82 (27)	80 (22)	75 (22)
	Min, Max	44, 122	45, 116	36, 126	34, 126
Systolic blood pressure, mmHg	Mean (SD)	127.0 (13.1)	125.0 (11.6)	125.4 (11.6)	124.7 (11.7)
Diastolic blood pressure, mmHg	Mean (SD)	80.3 (9.6)	81.2 (11.2)	79.6 (7.9)	79.8 (8.7)
TKV, mL	Mean (SD)	2109 (1467)	1828 (792)	1876 (1120)	1897 (1074)
	Min, Max	836, 6958	873, 3436	572, 6958	416, 6958
ADPKD risk classification	Class 1A	0	0	0	1 (1%)
	Class 1B	2 (10%)	1 (9%)	10 (12%)	8 (9%)
	Class 1C	5 (25%)	3 (27%)	25 (31%)	32 (36%)
	Class 1D	8 (40%)	4 (36%)	31 (38%)	31 (35%)
	Class 1E	5 (25%)	3 (27%)	16 (20%)	16 (18%)

Ait Bilgi

HOW ABOUT PATIENTS >55 YEARS OLD



Post hoc observational analysis of the REPRISE trial (OVERTURE study)

In the pooled studies,
230 tolvaptan-treated & 907 standar of care
aged>55 years (56-65 years)
95 patients matched, all in CKD G3 or G4.
The eGFR annual decline rate was significantly reduced by 1.66mL/min/1.73m² (95% CI, 0.43-2.90; *P*=0.009) in the tolvaptan group compared with SOC (–2.33 versus–3.99mL/min/1.73m²) over 3 years.

Kidney Med. 5(6):100639. Published online April 14, 2023.

Bennett et al. BMC Nephrology (2019) 20:136
https://doi.org/10.1186/s12882-019-1259-5

BMC Nep

RESEARCH ARTICLE Op

Modelling the long-term benefits of tolvaptan therapy on renal function decline in autosomal dominant polycystic kidney disease: an exploratory analysis using the ADPKD outcomes model

Hayley Bennett[1], Phil McEwan[1,2], Karina Hamilton[1] and Karl O'Reilly[2*]

Abstract

Background: The short-term efficacy of tolvaptan in patients with autosomal dominant polycystic kidney disease (ADPKD) has been demonstrated across several phase 3 trials, while the ADPKD Outcomes Model (ADPKD-OM) represents a validated approach to predict natural disease progression over a lifetime horizon. This study describes the implementation of a tolvaptan treatment effect within the ADPKD-OM and explores the potential long-term benefits of tolvaptan therapy in ADPKD.

Methods: The effect of tolvaptan on ADPKD progression was modelled by applying a constant treatment effect to the rate of renal function decline, consistent with that observed in the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes trial (TEMPO 3:4; ClinicalTrials.gov identifier NCT00428948). Predictions generated by the ADPKD-OM were compared against aggregated data from a subsequent extension trial (TEMPO 4:4; ClinicalTrials.gov identifier NCT01214421) and the Replicating Evidence of Preserved Renal Function an Investigation of Tolvaptan Safety Efficacy in ADPKD trial (REPRISE; ClinicalTrials.gov identifier NCT02160145). Following validation, an application of the ADPKD-OM sought to estimate the benefit of tolvaptan therapy on time to end-stage renal disease (ESRD), in a range of ADPKD populations.

Results: Model validation against TEMPO 4:4 and REPRISE demonstrated the accuracy and generalisability of the tolvaptan treatment effect applied within the ADPKD-OM. In simulated patients matched to the overall TEMPO 3:4 trial population at baseline, tolvaptan therapy was predicted to delay the mean age of ESRD onset by five years, compared to natural disease progression (57 years versus 52 years, respectively). In subgroup and sensitivity analyses, the estimated delay to ESRD was greatest among patients with CKD stage 1 at baseline (6.6 years), compared to CKD 2 and 3 subgroups (4.7 and 2.7 years, respectively); and ADPKD patients in Mayo subclasses 1C–1E.

Conclusions: This study demonstrated the potential for tolvaptan therapy to delay time to ESRD, particularly among patients with early-stage CKD and evidence of rapidly progressing disease. Data arising from this study highlight the value to be gained by early intervention and long-term treatment with tolvaptan, which may alleviate the economic and societal costs of providing care to patients who progress to ESRD.

Keywords: Autosomal dominant polycystic kidney disease, Disease modelling, Tolvaptan, End-stage renal disease, Renal function decline

__Mader G__ et al. BMC Nephrol. 2022 Oct 18;23(1):334.

No other pharmacologic agents have been proven to prevent or slow disease progression. However, the benefits have to be balanced against the side effects of polyuria, dehydration, and thirst, and the potential risk of serious drug-induced liver injury

Patient selection for treatment should be based on criteria that indicate they have rapidly progressive kidney disease (MIC subclass 1C–1E, or an historical decline in eGFR), an absence of contraindications, and are tolerant of and adherent to monitoring.

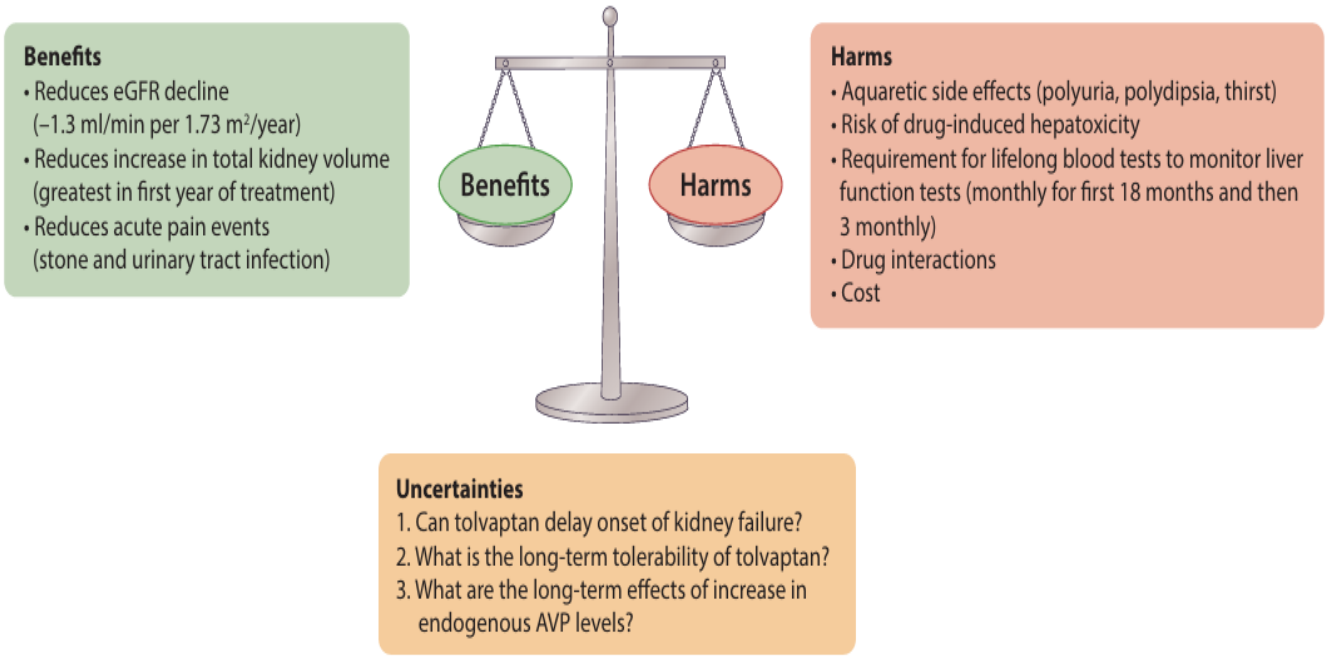


Figure 27 | Schematic diagram summarizing the harms, benefits, and uncertainties regarding long-term treatment with tolvaptan in people with rapidly progressing autosomal dominant polycystic kidney disease. AVP, arginine vasopressin; eGFR, estimated glomerular filtration rate. Adapted with permission from Chebib *et al.*[402]

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CLINICAL PRACTICE

CONCERN

ELEVATED LIVER ENZYMES

- When start check monthly for first 18 months, every 3 months after 18 months

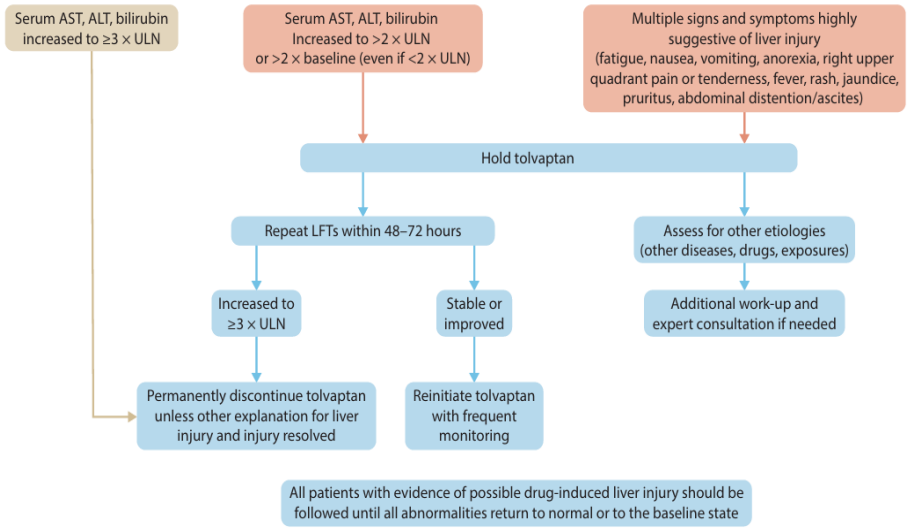


Figure 30 | Algorithm summarizing recommendations for evaluation and management of potential tolvaptan-induced liver injury. ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; ULN, upper limit of normal. Reproduced from Chebib *et al.*[402]

An analysis of the U.S. postmarketing REMS database found that serious or potentially fatal liver events occurred in 0.06% of treated participants, with no deaths or liver trans plants recorded

CONCERN

AQUARETIC SIDE EFFECTS

- Water intake should be advised to achive 3000 ml/day (eGFR>30 ml/min/1.73 m^2).
- Patients should be educated for polyuria is prominent especially first 3 weeks
- Patients <30 ml/min/1.73 m^2 should drink to thirst.
- There is insufficient evidence for thiazide diuretics for reducing aquaresis

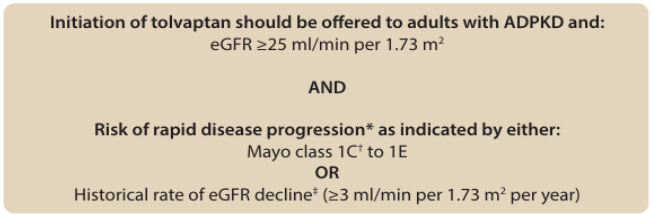
KDIGO STATEMENTKidney International (2025) 107, (Suppl 2S), S1–S239

CLINICAL PRACTICE

4.1 Tolvaptan

4.1.1 Indications for tolvaptan in ADPKD

Recommendation 4.1.1.1: We recommend initiating tolvaptan treatment in adults with ADPKD with an estimated glomerular filtration rate (eGFR) ≥25 ml/min per 1.73 m^2 who are at risk for rapidly progressive disease (Figure 25) (*1B*).



Practice Point 4.1.3.2: Tolvaptan should be initiated with a daily dose of 45 mg upon waking and 15 mg 8 hours later (Figure 28).

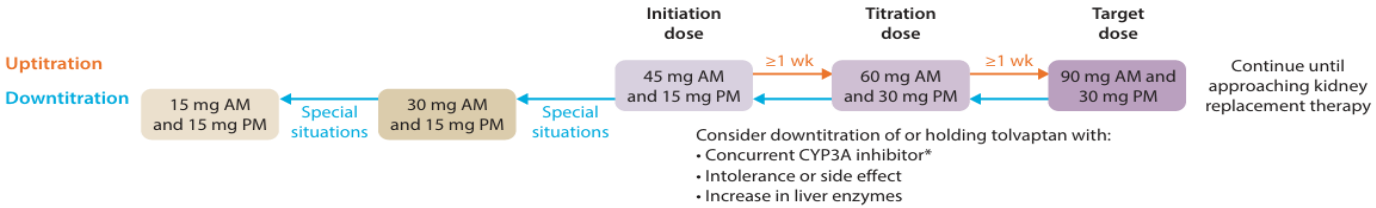


Figure 28 | Commencement of and titration approach to tolvaptan use in autosomal dominant polycystic kidney disease. *Examples of strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors (reduce clearance by >80%) are as follows: antifungals (itraconazole, ketoconazole); antibiotics (clarithromycin); and protease inhibitors (saquinavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir). Examples of moderate CYP3A inhibitors (reduce clearance by 50%–80%) are as follows: antiarrhythmics (amiodarone); antifungals (fluconazole); antibiotics (erythromycin); calcium-channel blockers (diltiazem, verapamil); protease inhibitors (amprenavir, fosamprenavir); and complementary and/or dietary agents: grapefruit juice (240 ml coadministration).

Practice Point 4.1.3.3: Uptitrating to a target daily dose of 90 mg upon waking and 30 mg 8 hours later should generally be the goal of therapy in all people with ADPKD unless this becomes intolerable or is contra-indicated by drug interactions (Figure 28).

Practice Point 4.1.3.4: Tolvaptan use should be discontinued prior to pregnancy, during lactation, and prior to the commencement of KRT.

Practice Point 4.1.3.5: In people who have already commenced tolvaptan, treatment can be continued when they reach an age >55 years or if their eGFR falls below 25 ml/min per 1.73 m^2.

Remember the sick days!
Skip the doses in the situations of volume depletion or AKI

A post hoc analysis retrospectively comparing the rate of eGFR decline in the REPRISE trial and in its open-label extension trial in people with eGFR 15–29 ml/ min per 1.73 m2 suggested that tolvaptan use has a beneficial effect in this population

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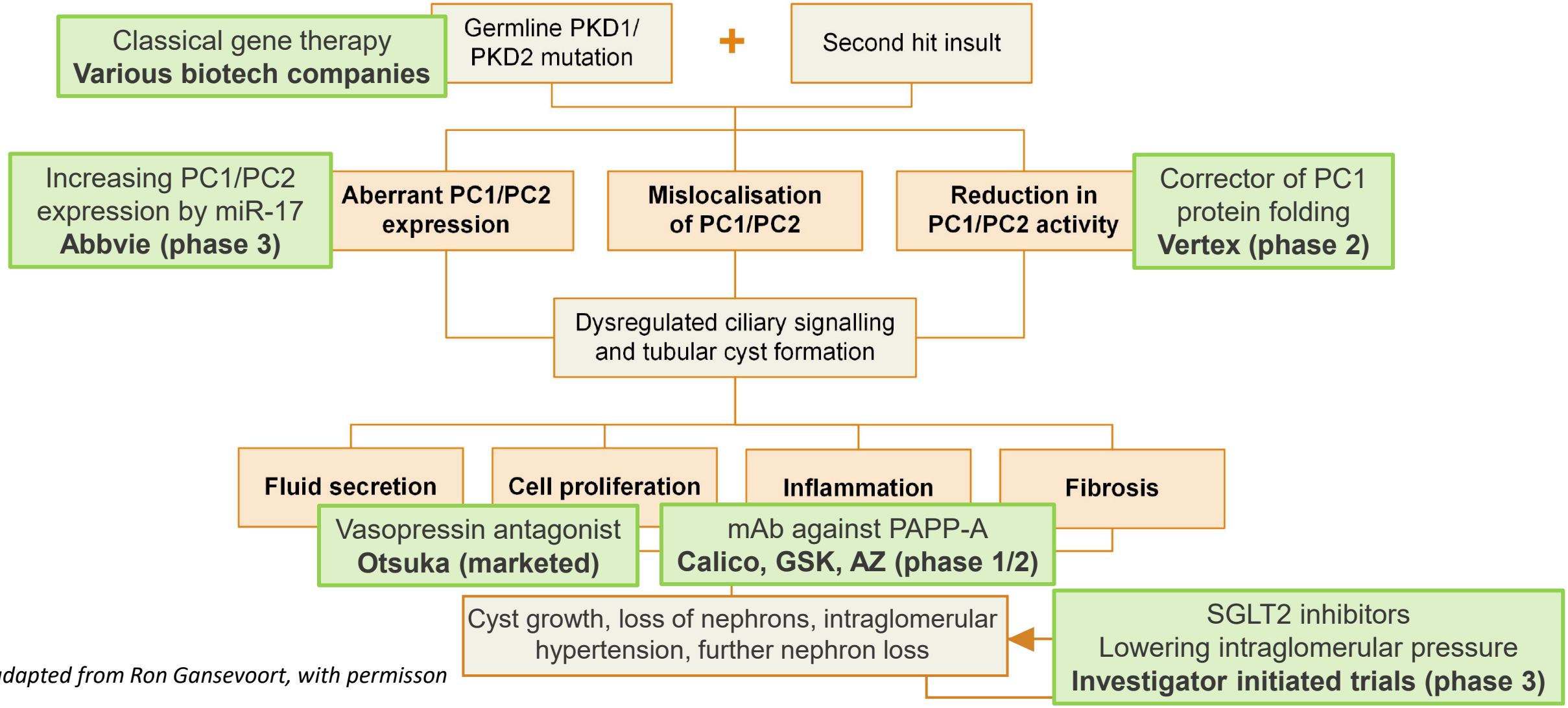
Novel treatments for ADPKD?

What is in the pipeline?



Slide adapted from Ron Gansevoort, with permisson

I WOULD LIKE TO EXPRESS MY SINCERE GRATITUDE TO OUR FOUNDER
ATATURK

DEU NEPHROLOGY TEAM