# Key considerations for the clinical management of rapidly progressing ADPKD

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# Expert panel

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# Agenda

**How can we best predict progression and prognosis in ADPKD?**

**What is best practice for the management of rapid progression in ADPKD?**

**How can we manage the side effects of V2RAs in daily practice?**

ADPKD, autosomal dominant polycystic kidney disease; V2RA, vasopressin V2 receptor antagonist.

# How can we best predict progression and prognosis in ADPKD?

**Prof. Bradley Erickson**
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ADPKD, autosomal dominant polycystic kidney disease.

# Aetiology, pathophysiology and symptoms of ADPKD

## Aetiology

- Mutations in *PKD1* or *PKD2*, encoding PC1 and PC2, respectively, are most common[1,2]
- *PKD1* mutations result in a more severe phenotype than *PKD2* and occur in ~80% of cases[2,3]

## Pathophysiology

- PC1 and PC2 regulate calcium signalling in renal tubular epithelia[1,3,4]
- Dysregulated calcium signalling activates PKA and increases cAMP levels, which, in turn, affects other signalling pathways[1,3,4]
- Impaired tubulogenesis, cell proliferation, increased fluid secretion and interstitial inflammation[3]
- Fluid-filled cyst formation[1,3]

## Symptoms[2,5]

- Early onset hypertension
- Abdominal fullness/pain
- Haematuria
- Cyst infection
- Kidney stones
- UTI
- Renal insufficiency

ADPKD, autosomal dominant polycystic kidney disease; cAMP, cyclic adenosine monophosphate; PC, polycystin; PKA, protein kinase A; UTI, urinary tract infection.

1. Bais T, et al. *Drugs.* 2022;82:1095–115; 2. Bergmann C, et al. *Nat Rev Dis Primers*. 2019;4:50; 3. Nobkht N, et al. *Kidney Med*. 2020;2:196–208;
4. Vasileva V, et al. *Front Physiol*. 2021;12:693130; 5. Cornec-Le Gall E, et al. *Lancet.* 2019;393:919–35.

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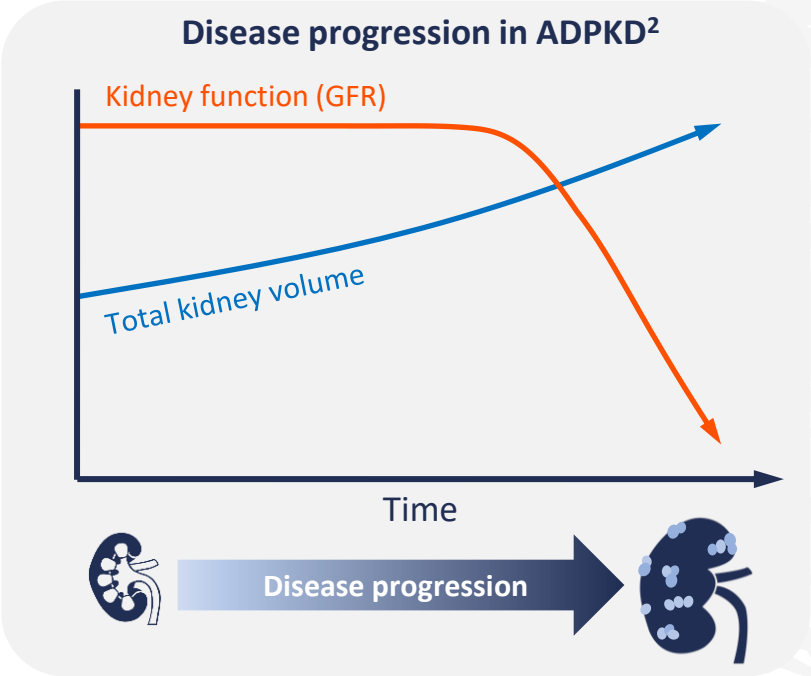
# Mechanism of progression in ADPKD

- Cysts trigger an immune response causing kidney inflammation and fibrosis, leading to new cyst formation, kidney growth and, ultimately, a decrease in GFR[1–3]
- Rate of disease progression is highly variable, but can result in ESRD[4]
- No global consensus on the definition of rapidly progressive ADPKD[3,5]
- Prognostic biomarkers include: eGFR, htTKV[3]

Ascertaining the rate of disease progression in ADPKD impacts the assessment of prognosis and treatment options[3]




ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated GFR; ESRD, end-stage renal disease; GFR, glomerular filtration rate; htTKV, height-adjusted total kidney volume.

1. Capuano I, et al. *J Nephrol*. 2022;35:397–415; 2. Grantham JJ, et al. *Nat Rev Nephrol.* 2011;7:556–66; 3. Chebib FT, Torres VE. *Am J Kidney Dis*. 2021;78:282–92; 4. Bais T, et al. *Drugs.* 2022;82:1095–115; 5. Chebib FT, et al. *J Am Soc Nephrol.* 2018;29:2458–70.

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# What is best practice for the management of rapid progression in ADPKD?

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ADPKD, autosomal dominant polycystic kidney disease.

# Pharmacologic treatments for rapidly progressing ADPKD

## Disease modifying

**V2RA: Tolvaptan**

*Available through a REMS programme*[1]

*Under supervision of physicians with expertise in managing ADPKD*[2]

### Investigational agents

**Biguanide analogue:** Metformin XR (IMPEDE-PKD: NCT04939935, phase III)[3,4]

**CFTR modulator:** GLPG2737 (NCT04578548, phase II)[3,4]

**Combinations:** Octreotide-LAR + tolvaptan[4] (TOOL: NCT03541447, phase II)[3]

**miR-17 inhibitor:** RGLS8429 (NCT05521191, phase Ib)[3,4]

**Somatostatin analogues:**[3]

- Octreotide-LAR (ALADIN: NCT00309283, phase III; ALADIN2: NCT01377246, phase III)
- Lanreotide (DIPAK1: NCT01616927, phase III; LIPS: NCT02127437, phase III)

**NRF2 activator:** Bardoxolone methyl[4] (FALCON: NCT03918447, phase III)[3]

## Management of hypertension[5]

**First line:**

- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers

ADPKD, autosomal dominant polycystic kidney disease; CFTR, cystic fibrosis transmembrane conductance regulator; LAR, long-acting release; NRF2, nuclear factor erythroid-2-related factor 2; REMS, risk evaluation and mitigation strategies; V2RA, vasopressin V2 receptor antagonist; XR, extended release.

1. FDA. Tolvaptan PI. Available at: https://bit.ly/403HhXs (accessed 1 March 2023); 2. EMA. Tolvaptan SmPC. Available at: https://bit.ly/3j4URtb (accessed 1 March 2023);
3. ClinicalTrials.gov. Available at: https://bit.ly/3TAbB8C according to specific trial number (accessed 1 March 2023); 4. Bais T, et al. *Drugs.* 2022;82:1095–115;
5. Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4:50.

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# Tolvaptan: Phase III efficacy data

## TEMPO 3:4 (NCT00428948)[1]

N=1,445

Patients 18–50 years
- TKV ≥750 mL
- Estimated creatinine clearance ≥60 mL/min

Randomized 2:1 to tolvaptan or PBO for 3 years

| TKV increase | Reciprocal of serum creatinine |
|---|---|
| 2.8% vs 5.5% per year (p<0.001) | -2.61 vs -3.81 $(mg/mL)^{-1}$/year (p<0.001) |

Tolvaptan vs PBO

**Tolvaptan slowed the increase in TKV and the decline in kidney function vs PBO**

## TEMPO 4:4 (NCT01214421)[2]

N=871

Single-arm, 2-year extension
- Patients enrolled within 6 months of successfully completing TEMPO 3:4
- eGFR ≥30 mL/min/1.73 $m^2$ within 45 days prior to baseline visit

| TKV increase | Change in eGFR |
|---|---|
| 29.9% vs 31.6% (p=0.38) | -3.15 mL/min/1.73 $m^2$ (p<0.001) |

Early vs delayed tolvaptan treatment*

**Tolvaptan had a sustained disease-modifying effect on eGFR, but not on TKV**

## REPRISE (NCT02160145)[3]

N=1,370

Patients 18–65 years, later-stage ADPKD
- 18–55 years: eGFR 25–65 mL/min/1.73 $m^2$
- 56–65 years: eGFR 25–44 mL/min/1.73 $m^2$

Randomized 1:1 to tolvaptan or PBO for 1 year

| Change in eGFR | Slope of change in eGFR |
|---|---|
| -2.34 vs -3.61 mL/min/1.73 $m^2$ (p<0.001) | -3.16 vs -4.17 mL/min/1.73 $m^2$ (p<0.001) |

Tolvaptan vs PBO

**Tolvaptan slowed the decline in eGFR vs PBO**

*Prior tolvaptan vs prior PBO, from baseline in TEMPO 3:4 to month 24 in TEMPO 4:4.

ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; PBO, placebo; TKV, total kidney volume.

1. Torres VE, et al. *N Engl J Med*. 2012;367:2407–18; 2. Torres VE, et al. *Nephrol Dial Transplant*. 2018;33:477–89; 3. Torres VE, et al. *N Engl J Med*. 2017;377:1930–42.

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# Emerging treatments: Phase II/III efficacy data

## Lanreotide[1]

**DIPAK-1**: Patients 18–60 years with later-stage ADPKD (phase III)[2]
- eGFR 30–60 mL/min/1.73 m$^2$

N=309

Sub-analysis*,[3]

| Slope of change in eGFR | htTKV rate of change | htLV change |
|---|---|---|
| -3.53 vs -3.46 mL/min/1.73 m$^2$ per yr (p=0.81) | 4.15% vs 5.56% (p=0.02) | -1.99% vs +3.92% (p<0.001) |

Lanreotide + SoC vs SoC

**Lanreotide did not slow the decline in kidney function vs SoC**

## Octreotide-LAR[2,4,5]

Patients 18–75 years in Italy (phase III)[2]
- **ALADIN:**[4] eGFR ≥40 mL/min/1.73 m$^2$
- **ALADIN-2:**[5] eGFR 15–40 mL/min/1.73 m$^2$

N=75[1]
N=100[2]

| ALADIN[4] | ALADIN-2[5] |
|---|---|
| Mean TKV increase | Median TKV increase |
| 1 yr: 46.2 vs 143.7 mL (p=0.032)<br>3 yrs: 220.1 vs 454.3 mL (p=0.25) | 1 yr: 135.5 vs 257.7 mL (p=0.027)<br>3 yrs: 604.2 vs 939.1 mL (p=0.002) |

Octreotide-LAR vs PBO

**Octreotide-LAR slowed kidney growth vs PBO**

## Tolvaptan + octreotide-LAR[6]

**TOOL:** Patients >18 years in Italy (phase II)[2]
- GFR ≥80 mL/min/1.73 m$^2$

N=19

| 4-week Median GFR decrease | 1-week Median GFR decrease |
|---|---|
| 7 (p=0.03) vs 3 (p=0.01) mL/min/1.73 m$^2$ (ns difference) | 10 (p<0.001) vs 3 (p=0.006) mL/min/1.73 m$^2$ (difference p=0.01) |

Tolvaptan + octreotide-LAR vs tolvaptan + PBO

**Tolvaptan + octreotide-LAR reduced GFR and TKV more than tolvaptan + PBO**

*n=175 patients with hepatic cysts. ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated GFR; GFR, glomerular filtration rate; ht, height adjusted; LAR, long-acting release; LV, liver volume; ns, not significant; PBO, placebo; SoC, standard of care; TKV, total kidney volume; yr, year.

1. Meijer E, et al. *JAMA*. 2018;320:2010–19; 2. ClinicalTrials.gov. Available at: https://bit.ly/3TAbB8C according to specific trial number (accessed 1 March 2023); 3. van Aerts RMM, et al. *Gastroenterology*. 2019;157:481–91; 4. Caroli A, et al. *Lancet*. 2013;382:1485–95; 5. Perico N, et al. *PLoS Med*. 2019;16:e10027777; 6. Trillini M, et al. *Clin J Am Soc Nephrol*. 2023;18:223–33.

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# How can we manage the side effects of V2RAs in daily practice?

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V2RA, vasopressin V2 receptor antagonist.

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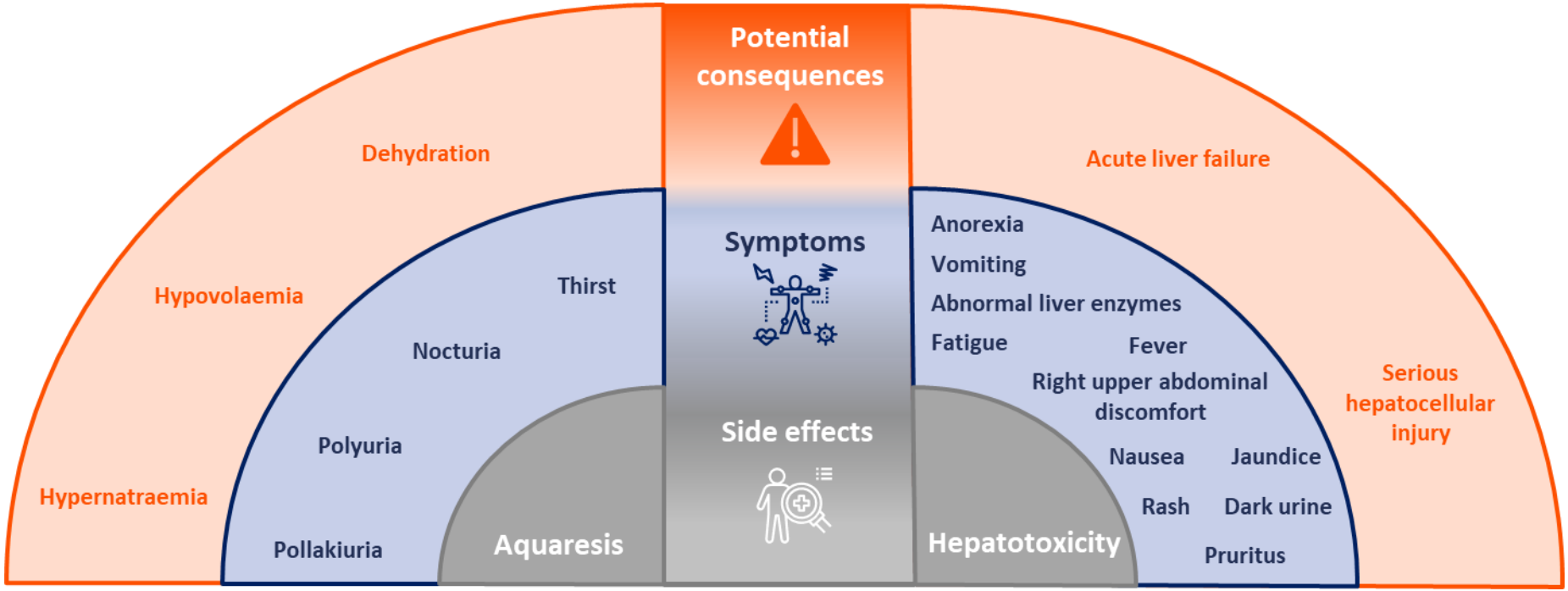
# Potential serious side effects of V2RAs[1–3]




V2RA, vasopressin V2 receptor antagonist.

1. Chebib FT, et al. *J Am Soc Nephrol*. 2018;29:2458–70; 2. FDA. Tolvaptan PI. Available at https://bit.ly/403HhXs (accessed 1 March 2023);
3. EMA. Tolvaptan SmPC. Available at https://bit.ly/3j4URtb (accessed 1 March 2023).

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# Tolvaptan: Phase III safety data

| TEMPO 3:4 (N=1,445)[1] | TEMPO 4:4 (N=871)[2] | REPRISE (N=1,370)[3] |
|---|---|---|
| **AEs:** 98% vs 97% of pts (tolvaptan vs PBO) | **AEs:** 93% vs 97% of pts (early vs delayed tolvaptan) | **AEs:** 85% vs 82% of pts (tolvaptan vs PBO) |
| **AEs more common in tolvaptan vs PBO (p<0.001):** Thirst, polyuria, nocturia, pollakiuria, polydipsia, ALT >2.5x ULN (ns) | **AEs more common in early vs delayed tolvaptan:** Hypertension | **AEs more common in tolvaptan vs PBO:** Polyuria, nocturia, thirst, polydipsia, dry mouth, diarrhoea, fatigue, ALT >3x ULN, hepatic AEs, serious hepatic AEs |
| **AEs more common in PBO vs tolvaptan:** Haematuria (p<0.001), renal pain and UTI (p<0.05) | **AEs more common in delayed vs early tolvaptan:** Renal pain, thirst, polyurea, nasopharyngitis, polydipsia, nocturia, fatigue, dry mouth, dizziness, headache, ALT or AST >3x ULN | **AEs more common in PBO vs tolvaptan:** Peripheral oedema, kidney pain, UTI |
| **Treatment discontinuation due to AEs:** 15.4% vs 5.0% for tolvaptan vs PBO | **Treatment discontinuation due to AEs:** 5.4% vs 15.0% (prior tolvaptan vs prior PBO) | **Treatment discontinuation due to AEs:** 9.5% vs 2.2% (tolvaptan vs PBO) |
| | **Deaths:** n=4 in prior tolvaptan group after tolvaptan discontinuation | **Deaths:** n=2 unrelated to treatment |
| **Fewer ADPKD-related AEs in tolvaptan vs PBO group, but more hepatic AEs and AEs related to aquaresis** | **Safety profile for TEMPO 4:4 similar to tolvaptan arm of TEMPO 3:4** | **Fewer ADPKD-related AEs in tolvaptan vs PBO group, but more hepatic AEs and AEs related to aquaresis** |

ADPKD, autosomal dominant polycystic kidney disease; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ns, not significant; PBO, placebo; pts, patients; ULN, upper limit of normal; UTI, urinary tract infection.

1. Torres VE, et al. *N Engl J Med*. 2012;367:2407–18; 2. Torres VE, et al. *Nephrol Dial Transplant*. 2018;33:477–89; 3. Torres VE, et al. *N Engl J Med*. 2017;377:1930–42.

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