

# **Key considerations for the clinical management of rapidly progressing ADPKD**

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**Practice aid for ADPKD education**

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## What is ADPKD?

- Estimated prevalence of 4:10,000; most common hereditary kidney disease and **one of the most common causes of ESRD**<sup>1</sup>
- Characterized by **progressive cyst formation**, leading to **kidney enlargement** and **progressive loss of function**<sup>1</sup>
- **Mutated PKD1 or PKD2**, encoding PC1 and PC2, respectively, is the **most common genetic cause**<sup>1,2</sup>

## Symptoms of ADPKD<sup>2,3</sup>

**Heterogenous disease** with phenotypic variability.<sup>4</sup> Some patients remain asymptomatic, while others have some of the following symptoms<sup>2,3</sup>:

- **Early onset hypertension**



- **Abdominal fullness/ pain**



- **Haematuria**



- **Cyst infection**



- **Kidney stones**



- **UTI**



- **Renal insufficiency**



## Rapidly progressing ADPKD<sup>4</sup>









**No international consensus on the definition of rapid progression.**<sup>1,4</sup> **Varying definitions include:**

- ESRD before 75% of ADPKD population who would eventually reach ESRD (~62 years)
- Stage 3 CKD at <40 years
- Hypertension at <18 years
- TKV greater than expected for given age
- Multiple complications




**Risk factors associated with rapid progression:**<sup>4</sup>





- Overweight/obese (BMI  $\geq 25$  kg/m<sup>2</sup>)<sup>5</sup>
- Family history of ESRD  $\leq 55$  years in multiple members with typical ADPKD
- Truncating *PKD1* mutation
- Recurrent bleeding/infection of renal cysts  $\leq 35$  years
- Hypertension  $\leq 35$  years





## Predicting rapid progression in ADPKD<sup>4</sup>

Tools and prognostic biomarkers	Description	Indicator of rapid progression	Region used
<b>Mayo imaging classification</b>	Calculates age-adjusted htTKV in patients with typical bilateral diffuse cystic kidney disease (class 1)	Class 1C–1E	 
<b>PROPKD score</b>	Predicts likelihood of kidney failure by 60 years	Score >6	
<b>Genetic testing</b>	Identifies patients with mutations associated with more severe disease	Truncating <i>PKD1</i> mutation plus early symptoms	
<b>Ultrasound</b>	Used to measure kidney length	>16.5 cm in patients by 45 years of age	
<b>TKV growth rate/year</b>	Measurements by planimetry or stereology at ≥3 time points at least 6 months apart	>5% per year	
<b>htTKV</b>	Baseline measurement predicts GFR decrease	>600 mL/m predicts stage 3 CKD in 8 years	
<b>eGFR slope mL/min/1.73 m<sup>2</sup> per year</b>	Measures progression instead of predicting risk	<ul style="list-style-type: none"> <li>&gt;5 mL/min in 1 year</li> <li>&gt;2.5 mL/min per year over 5 years</li> </ul>	

## Treatments for ADPKD

Approved disease-modifying drug <sup>6-8</sup>	Administration <sup>6-8</sup>	US FDA indication <sup>9</sup> 	European indication <sup>10</sup> 
<b>Tolvaptan</b> (V2RA)	Oral, Q2D 	<ul style="list-style-type: none"> <li>Adults at risk of rapidly progressing ADPKD</li> <li>18–55 years: GFR <math>\geq</math>25 mL/min<sup>4</sup></li> <li>&gt;55 years and evidence of rapid progression<sup>4</sup></li> <li><b>Only available through a REMS programme</b></li> </ul>	<ul style="list-style-type: none"> <li>Adults with stage 1 to 4 CKD with evidence of rapidly progressing ADPKD</li> <li>18–30 years: GFR &gt;45 mL/min<sup>4</sup></li> <li>30–40 years: GFR 45–90 mL/min<sup>4</sup></li> <li>40–50 years: GFR 45–60 mL/min<sup>4</sup></li> <li>50–55 years: GFR 30–45 mL/min<sup>4</sup></li> <li><b>Must be initiated/monitored under supervision of physicians with ADPKD expertise</b></li> </ul>

Emerging disease-modifying drug <sup>1,11</sup>	Administration <sup>11</sup>	Phase <sup>11</sup>
<b>Bardoxolone methyl</b> (NRF2 activator)	Oral, QD 	III
<b>GLPG2737</b> (CFTR modulator)	Oral, QD 	II
<b>Lanreotide</b> (Somatostatin analogue)	SC, Q4W 	III
<b>Metformin XR</b> (Biguanide analogue)	Oral, daily 	III

Emerging disease-modifying drug <sup>1,11</sup>	Administration <sup>11</sup>	Phase <sup>11</sup>
<b>Octreotide-LAR</b> (Somatostatin analogue)	IM*, Q4W 	III
<b>Octreotide-LAR + tolvaptan</b> (Somatostatin analogue + V2RA)	Tolvaptan: Oral, Q2D  Octreotide-LAR: IM, 1 dose <sup>†</sup> 	II
<b>RGLS8429</b> (miR-17 inhibitor)	SC, Q2W (x7 doses) 	Ib

**Supportive measures:** Manage hypertension first-line with ACE inhibitors or ARB<sup>2</sup>

\*Two intragluteal injections; <sup>†</sup>dose consists of two injections.

## Aquaresis: Monitoring and management

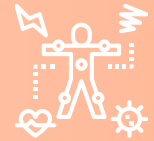
### Symptoms<sup>9,10,12</sup>

- Nocturia
- Thirst
- Polyuria
- Increased urinary frequency



### Potential consequences<sup>9,10</sup>

- Hypernatraemia
- Hypovolaemia
- Dehydration



### Monitor for<sup>9,10,12</sup>

Weight loss (daily)



Tachycardia



Electrolyte imbalance  
(Q3M for LT treatment)



Hypotension



Fluids




### Prevention<sup>12</sup>

- Start tolvaptan on **non-working day** to help adjustment
- **Increase fluid intake** throughout day and night<sup>9,10</sup>
- **Low sodium and protein diet**  
(optimal serum sodium: 135–143 mEq/L)
- Maintain **optimal blood pressure**<sup>3</sup>

### Hold tolvaptan if:<sup>9,10,12</sup>



- Signs of **sodium imbalance/dehydration** (e.g. dizziness, fainting, weight loss, palpitations, confusion, weakness, gait instability)
- **Restricted access to water** or increased **water loss** (e.g. in hot weather)
- FDA: Undergoing **elective surgery** (hold treatment 24–48 hours before; restart once adequate hydration is maintained)<sup>9</sup> 

For contraindications to the use of tolvaptan, please consult the tolvaptan [PI](#) or [SmPC](#)

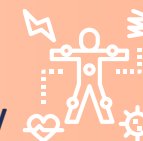
# Hepatotoxicity: Monitoring and management

## Symptoms<sup>9,10</sup>

- Abnormal liver enzymes
- Anorexia
- Dark urine
- Fatigue
- Fever
- Jaundice
- Nausea
- Pruritus
- Rash
- Right upper abdominal discomfort
- Vomiting

## Potential consequences<sup>9,10</sup>


- Acute liver failure
- Serious hepatocellular injury



## Monitoring<sup>9,10</sup>

### LFT (ALT, AST and bilirubin levels):



- Prior to treatment
- FDA: At 2 weeks and 4 weeks after initiation 
- 1–18 months: Monthly
- >18 months: Every 3 months

For liver injury symptoms (as above)

### Hold tolvaptan if:<sup>9,10</sup>



- Symptoms of **hepatic injury**
- Clinically significant **increases in ALT/AST levels** (FDA: >2 x ULN )

### Monitoring LFTs:

- Repeat **within 48–72 hours**
- Test more **frequently**
- **Reinitiate tolvaptan** with increased frequency of monitoring **once symptoms/LFTs stabilize or resolve**
  - (FDA: LFTs <3 x ULN )

### Permanently discontinue tolvaptan if ALT/AST levels:<sup>9,10</sup>



- >8 x ULN
- >5 x ULN for >2 weeks
- >3 x ULN with persistent hepatic injury symptoms
- >3 x ULN and bilirubin >2 x ULN or INR >1.5
- FDA: >3 x ULN 

For contraindications to the use of tolvaptan, please consult the tolvaptan [PI](#) or [SmPC](#)

# Abbreviations and references

## Abbreviations

ACE, angiotensin-converting-enzyme; ADPKD, autosomal dominant PKD; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; CTFR, cystic fibrosis transmembrane conductance regulator; eGFR, estimated GFR; ESRD, end-stage renal disease; FDA, Food and Drug Administration; GFR, glomerular filtration rate; htTKV, height-adjusted TKV; IM, intramuscular; INR, international normalized ratio; LAR, long-acting release; LFT, liver function test; LT, long-term; NFR2, nuclear factor erythroid-2-related factor 2; PC, polycystin; PI, prescribing information; PKD, polycystic kidney disease; PROPKD, predicting renal outcome in PKD; Q2D, twice daily; Q2W, every 2 weeks; Q3M, every 3 months; Q4W, every 4 weeks; QD, once daily; REMS, risk evaluation and mitigation strategies; SC, subcutaneous; SmPC, summary of product characteristics; TKV, total kidney volume; ULN, upper limit of normal; UTI, urinary tract infection; V2RA, vasopressin V2 receptor antagonist; XR, extended release.

## References

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## Clinical trial numbers for emerging disease modifying drugs

Bardoxolone methyl	NCT03918447	Metformin XR	NCT04939935	Octreotide-LAR + tolvaptan	NCT03541447
GLPG2737	NCT04578548	Octreotide-LAR	NCT01377246 NCT00309283	RGLS8429	NCT05521191
Lanreotide	NCT01616927 NCT02127437				

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