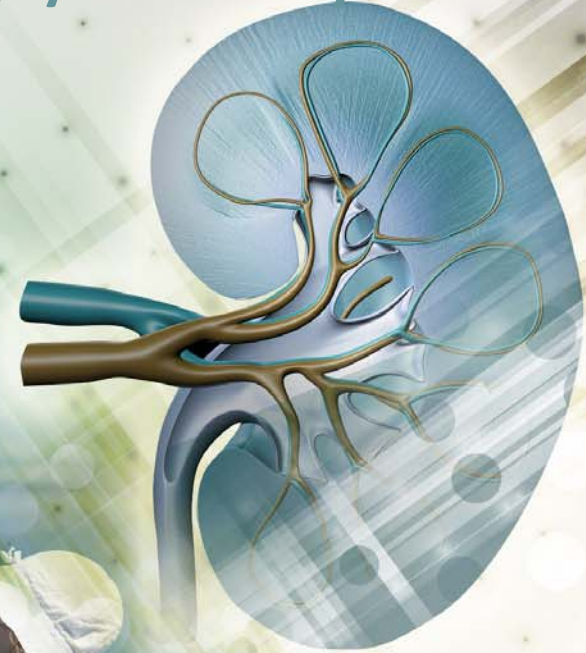


EDUCATIONAL PROGRAM

PKD: SPEAKING VOLUMES

Management of Autosomal Dominant Polycystic Kidney Disease (ADPKD)



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Learning Objectives

At the end of the program, participants will be able to:

- List management options for common complications associated with ADPKD
- Identify the mechanisms of action of medications for ADPKD disease modification
- Cite clinical trial efficacy and safety evidence for ADPKD-specific treatments
- Provide practical tips for the use of tolvaptan for the treatment of ADPKD



INTRODUCTION

The current environment in ADPKD



What is ADPKD?

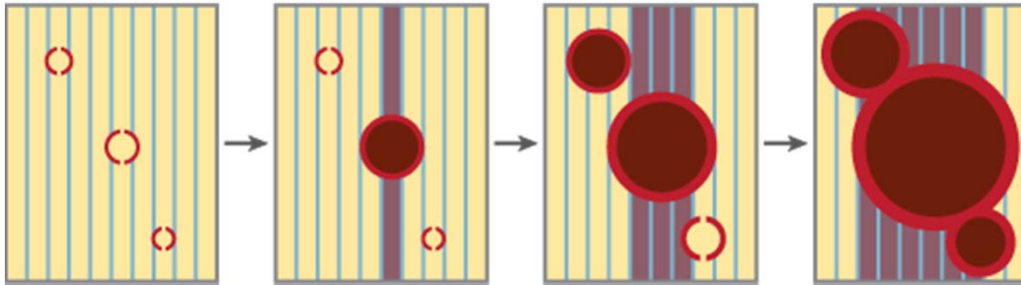
ADPKD...

- Is a dominantly inherited, systemic disease characterized by multiple kidney cysts
- Is a form of tubular obstructive nephropathy
- Results in slow, gradual, and massive bilateral kidney enlargement
- Results in kidney failure in the majority of individuals by the fifth or sixth decade

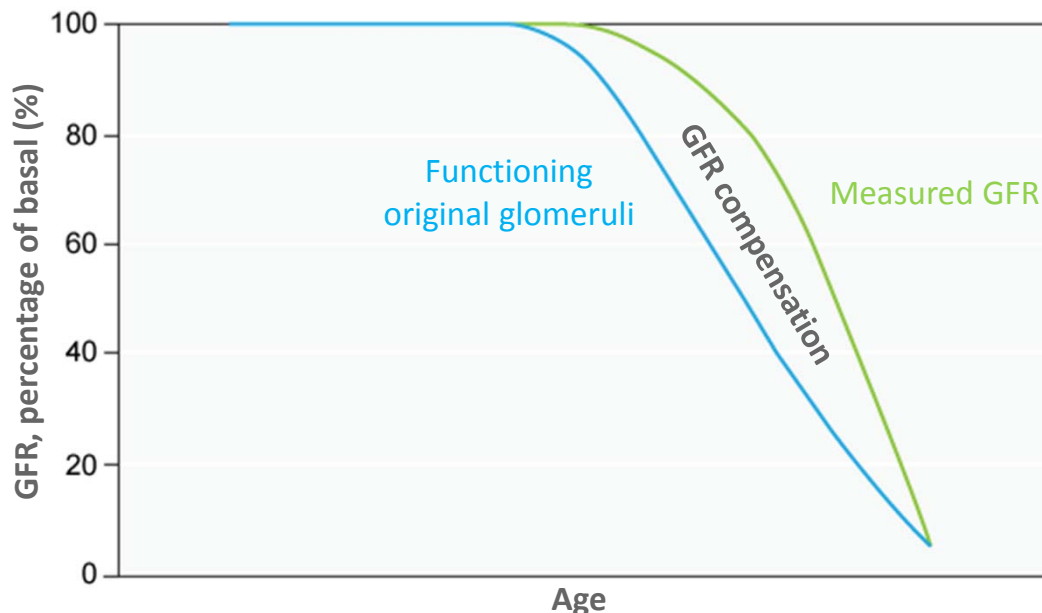


Physiology of Progressive Renal Failure in ADPKD

Expanding cysts negate functional contributions from afferent and distal segments



Compensation temporarily makes up for decreasing number of functional glomeruli



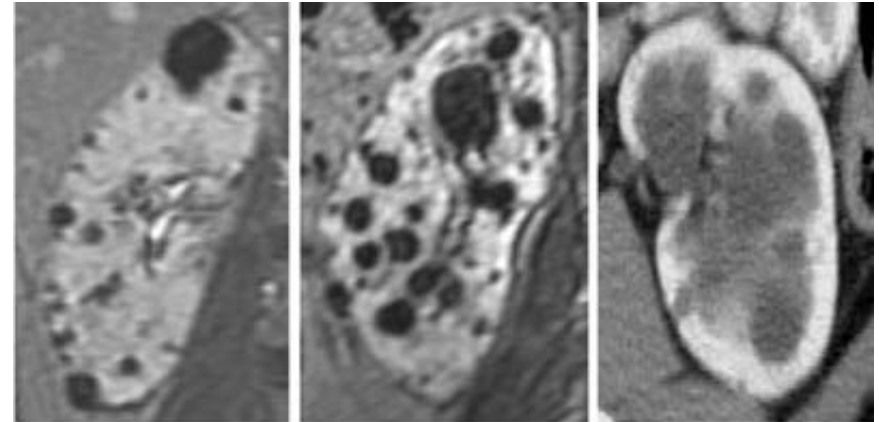
Adapted from Grantham JJ, et al. *Nat Rev Nephrol* 2011; :561-3.,

Cysts can present in different patterns

Superficial

Generalized

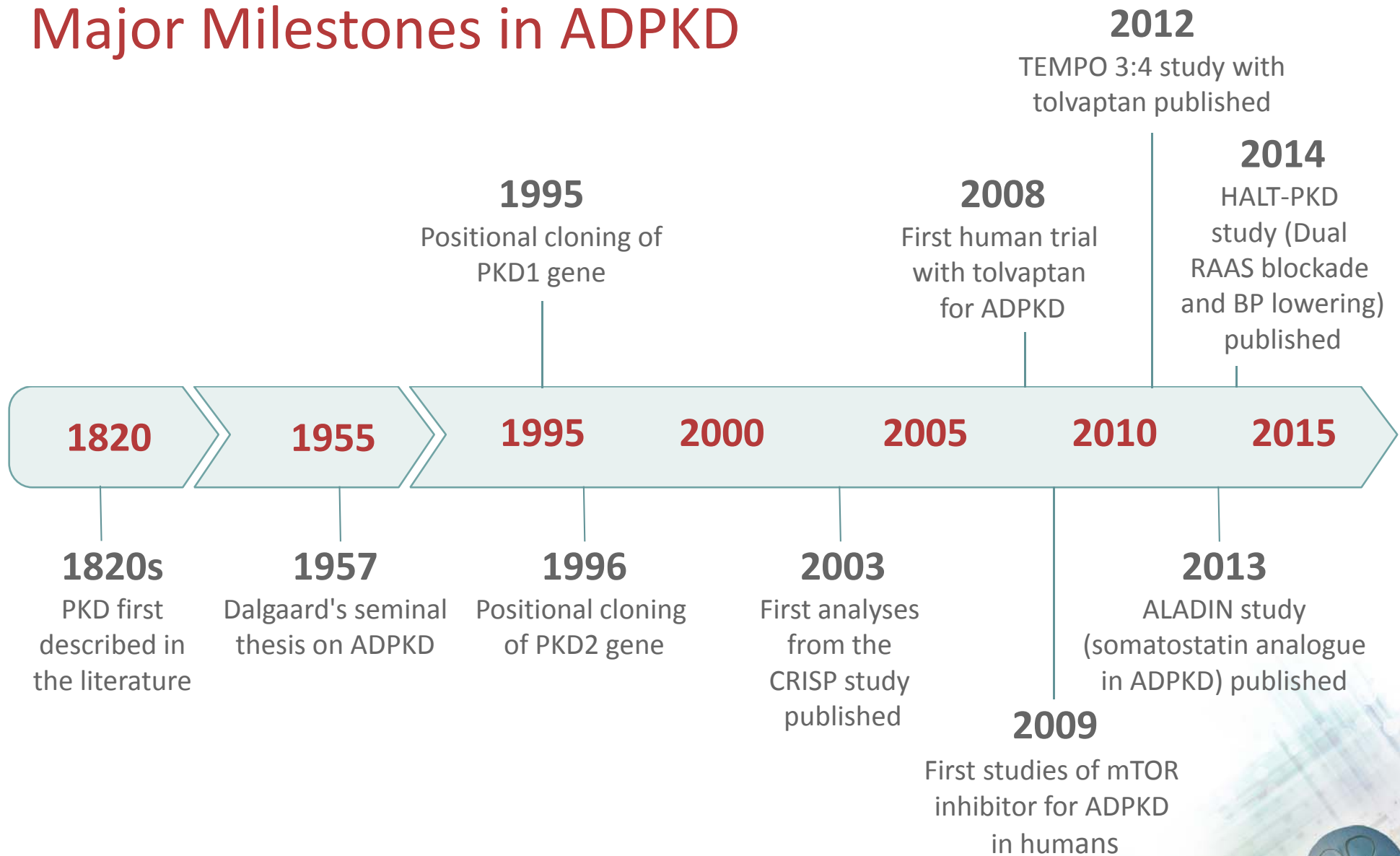
Medullary



- Location of the cysts is important
- Each papillary collecting duct drains ~2,800 upstream tubule segments
- Cysts inhibiting a single papillary collecting duct have greater potential functional impact than cysts forming higher in the collecting duct system



Major Milestones in ADPKD



Management of Patients with ADPKD: Where are we now?

- Until recently, no pharmacotherapies had been proven to have a beneficial impact on ADPKD's natural history
- Management consists of periodic follow-up and treatment of complications, *e.g.*:
 - Hypertension
 - Other cardiovascular complications
 - Chronic pain due to organ enlargement
 - Nephrolithiasis
 - Hepatic cysts



Pathways Under Investigation to Slow Progression of ADPKD: Where are we going?

Target	Agent(s)	Status	
PC2-mediated calcium release	Triptolide	Phase 3 trial currently enrolling	
cAMP	c-Src	Bosutinib	Phase 2 trial completed Sept. 2014
	SSTR	Somatostatin	Phase 3 trial published (ALADIN, 2013)
	MEK	PD98059	Preclinical evidence only (2003)
	Vasopressin V2 receptor	Tolvaptan	Phase 3 trial completed (TEMPO 3:4, 2012); TEMPO 4:4 ongoing, REPRISE study ongoing
EGFR	EGFR	EKI-785	Preclinical evidence only (2000)
	c-Src	Bosutinib	Phase 2 trial completed Sept. 2014 (not published)
mTOR	Sirolimus	Phase 3 trial completed (Serra <i>et al</i> , 2010)	
	Everolimus	Phase 3 trial completed (Walz <i>et al</i> , 2010)	
CDK	Roscovitin	Preclinical evidence only (2012)	
TNF- α	Etanercept	Preclinical evidence only (2013)	
Renin-angiotensin-aldosterone system	ACE inhibitors, ARBs	Phase 3 trial complete (HALT-ADPKD, 2014)	
HMG-CoA reductase	Inhibitors (e.g., statins)	Phase 3 trial completed in children (Cadnapaphornchai <i>et al</i> , 2014)	

Topics Discussed in This Program

- Common manifestations of ADPKD and their management
- Pharmacotherapies under investigation to slow ADPKD progression
- Nonpharmacologic approaches



REVIEW OF SUPPORTIVE MEASURES

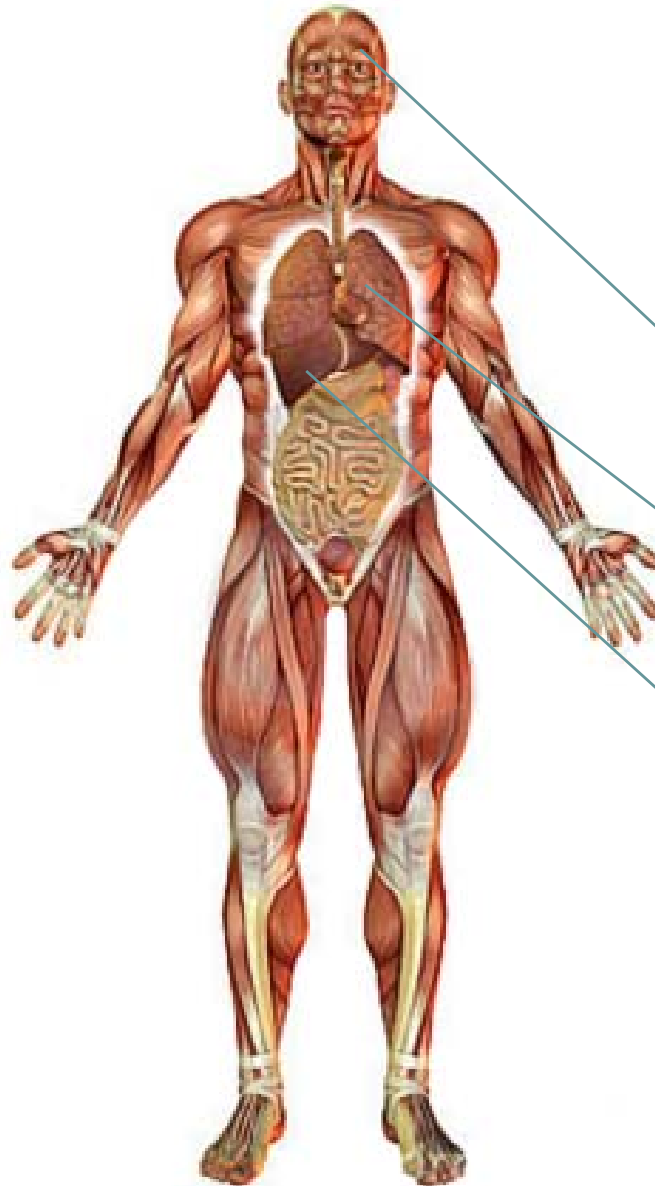
Management of common complications associated with ADPKD



Important Manifestations of ADPKD

Renal manifestations:

- Pain and discomfort
- Kidney stones
- Bleeding into cysts
- Infected cysts
- Declining renal function / kidney failure
- Hypertension



Common extrarenal manifestations:

Intracranial aneurysm

Cardiovascular
(e.g., heart valve abnormalities)

Hepatic cysts

Adapted from:

Braun WE. *Cleve Clin J Med* 2009;76(2):97-104.

Torres VE, et al. *Lancet* 2007;369(9569):1287-301.

Pirson Y. *Adv Chronic Kidney Dis* 2010;17(2):173-80.

Bennett WM, et al. *uptodate.com*; last updated Nov. 11, 2013.



Cardiovascular Complications of PKD: Hypertension and Left-ventricular Hypertrophy

- Hypertension
 - Nearly ubiquitous
 - All patients with PKD should be screened for hypertension
 - Average age of onset is 30, although a substantial minority of children with ADPKD have hypertension as well)¹
 - Early treatment is important
 - RAAS agents are preferred¹
 - Dual RAAS blockade is not indicated^{2,3}
- Left-ventricular hypertrophy:
 - Consequence of hypertension, associated with poor renal and overall outcomes⁴

Adapted from:

1. Chapman AB, et al. *Adv Chronic Kidney Dis* 2010;17(2):153-63.
2. Torres VE, et al. *N Engl J Med* 2014 Nov 15. [Epub ahead of print].
3. Schrier RW, et al. *N Engl J Med* 2014 Nov 15. [Epub ahead of print].
4. Ecker T, et al. *Nat Rev Nephrol* 2009;5(4):221-8.



Impact of Different BP Targets in Early ADPKD: Design of the HALT-PKD Study A

- Double-blind, placebo-controlled trial
- 558 hypertensive participants with ADPKD
 - 15 to 49 years old
 - Baseline eGFR >60 mL/min/1.73 m²
- 2 randomizations:
 - BP target: standard (120/70 to 130/80 mmHg) or low (95/60 to 110/75 mmHg) target range
 - RAAS blockade: ACE inhibitor (lisinopril) + placebo or an ARB (telmisartan)
- Followed for 5 years
- Primary efficacy outcome: Annual % change in total kidney volume

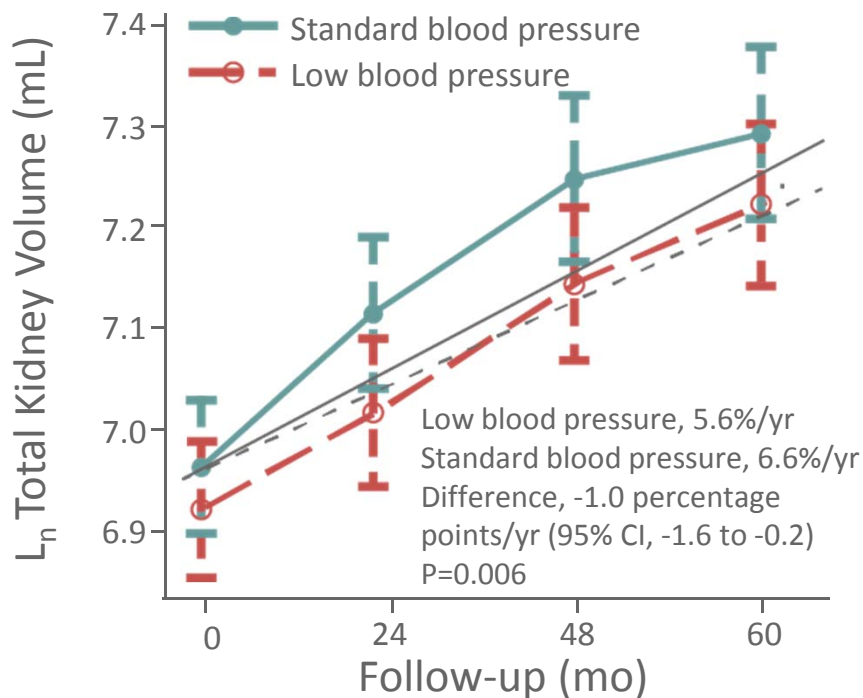


Possible imbalance in randomization: mutations

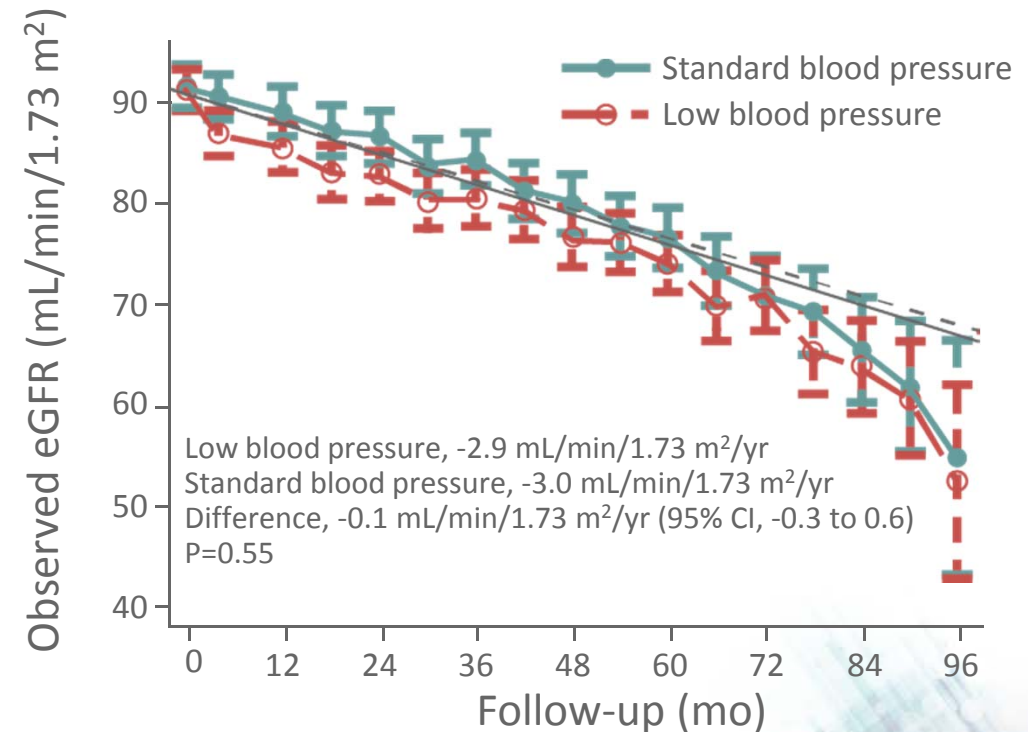
BP Group	PKD1	PKD2
Standard	78.5%	13.1%
Low	70.6%	19.8%

Different BP Targets in Early ADPKD: Changes in Total Kidney Volume and eGFR (HALT-PKD Study A)

Changes in TKV



Changes in eGFR

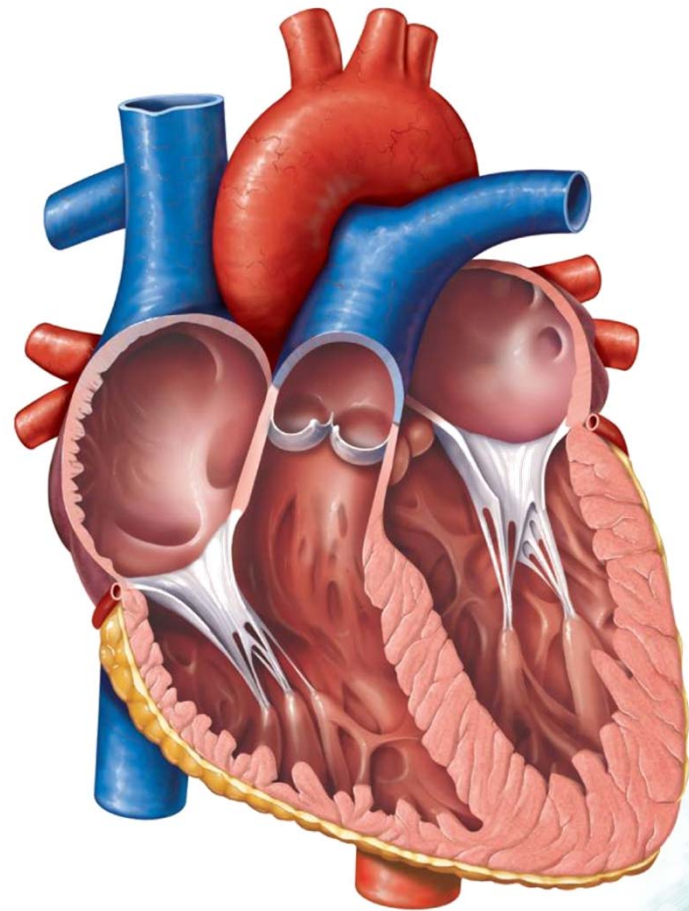


Conclusion of the BP analysis: As compared with standard BP control, rigorous BP control was associated with a slower increase in TKV, no overall change in the eGFR, a greater decline in the LMVI, and greater reduction in UAE.



Cardiovascular Complications of PKD: Valvular Disease

- Defects of the aortic root, annulus, and valve and the mitral valve are the predominant abnormalities
- Mitral valve most common (20-30%)
- No recommendations exist for screening of asymptomatic patients for valvular disease



Cardiovascular Complications of PKD: Intracranial Aneurysms

- Higher prevalence in ADPKD (9-12%) than in the general population (2-3%)¹⁻⁶
- In ADPKD prevalence is ~20-27% among those with a family history and ~6% in those lacking a family history^{1-5,7}
- Account for 4-7 % of all deaths in ADPKD⁸
- Screening:
 - A family history of ruptured aneurysms or sudden death is a strong indication for MRI-based screening¹
 - Repeating negative screens in patient with positive family history can be done in 5-10 years, but there are no data to guide rescreening
 - If positive – refer to neuro/vascular surgery for treatment or follow up
 - Screening in those without a family history is controversial – can be based on physician and patient preferences

1. Ruggieri P, et al. *Radiology* 1994; 91:33-9.

2. Irazabal MV, et al. *Clin J Am Soc Nephrol* 2011;6:1274-85.

3. Huston J, et al. *J Am Soc Nephrol* 1993;3:1871-7.

4. Xu HW, et al. *Stroke* 2011;42:204-6.

5. Graf S, et al. *Nephrol Dial Transplant* 2002;17:819-23.

6. Vlak MH, et al. *Lancet Neurol* 2011;10:626-36.

7. Chapman AB, et al. *N Eng J Med* 1992;327:916-20.

8. Ecker T, et al. *Nat Rev Nephrol* 2009;5(4):221-8.



Additional Factors to Consider When Deciding Whether or Not to Screen For and Treat Intracranial Aneurysms¹⁻³

- Expected survival (*e.g.*, age, health of patient)
- Patient's willingness to undergo intervention
- Potential benefit vs. potential safety concerns of the intervention (vascular clipping or endovascular coil)^{2,3}
 - In a retrospective analysis of 3738 patients with aneurysm clipping and 3498 with endovascular coiling, several key complications occurred more frequently in the clipped population:²

Complication	Clip (%)	Coil (%)	OR (95% CI)	<i>p</i>
Hospital mortality	1.61	0.57	2.83 (1.7 – 4.71)	<0.0001
Intracerebral hemorrhage	2.38	1.37	1.75 (1.23 – 4.49)	0.002
Post-operative stroke	6.71	2.92	2.39 (1.89 – 3.03)	<0.0001)

1. Rozenfeld MN, et al. *AJNR Am J Neuroradiol* 2014;35:3-9.
2. Alsheklee A, et al. *Stroke* 2010; 41:1471-6.
3. Brinjikji W, et al. *AJNR Am J Neuroradiol* 2011;32:1071-5.



Kidney Pain

- Can be caused by ischemia, inflammation, torsion of gut nerve fibres
- Acute pain
 - Causes: stones, hemorrhage, cyst rupture
 - Supportive management — occasional ER
 - Chronic
 - Lower back / abdominal pain reported by >70 % of patients
 - Causes: stretching of capsule by renal enlargement; can be worsened by hepatic cysts



Treatment Options for Kidney Pain

- Noninvasive, nonpharmacologic therapies, *e.g.*:
 - Psychological behavioural modification, ice, heat, massage, whirlpool
- Systemic, non-narcotic options, *e.g.*:
 - Acetaminophen, lidocaine patch, gabapentin, pregabalin, tramadol, clonidine
- Opioids:
 - Start with low dose, added to the above
 - Titrate to higher dose if necessary
- Other options should the above fail:
 - Neuromodulation, neuroaxial opioids, local anesthetics, acupuncture, surgery (both kidney and liver)



Nephrolithiasis

- Occurs in 20-35 % in PKD^{1,2}
 - 2/3 are asymptomatic
- In ADPKD >50% uric-acid based^{1,2}
 - In non-ADPKD population, majority are calcium-oxalate-based^{1,2}
 - Reasons for the difference are not clear
- Two major factors promote uric acid precipitation:³
 - High urine uric acid concentration
 - Acid urine pH (uric acid solubility in the urine falls with lower urine pH)
- Increased TKV is associated with stone development⁴
- Diagnosis of obstruction can be difficult in large PKD kidneys
 - CT is probably the best modality⁴

Adapted from:

1. Torres VE, *et al. Am J Kidney Dis* 1993;22(4):513-9.

2. Gambaro G, *et al. Urol Res* 2006;34(2):102-107.

3. Curhan GC, *et al. uptodate.com*; last updated Oct. 16, 2013.

4. Nishiura JL, *et al. Clin J Am Soc Nephrol* 2009;4(4):838.



Treatment Options for Nephrolithiasis

- Management is not different from non-ADPKD patients
- Recommend at least 2 L of water daily
- Obtain 24-hour urine collection to assess metabolic risk factors
 - If acidified urine – consider alkalinizing with using potassium citrate to a urine pH of 6-7
 - If hyperuricosuria – Consider allopurinol or other uric-acid reducing drugs
 - For calcium oxalate stones – low oxalate, low sodium diet (especially if hypercalciuric)
 - For high calcium excretors (unless due to hypercalcemia): thiazide or thiazide-like diuretics



Hepatic Cysts

- Overall prevalence in ADPKD (assessed by MRI in the CRISP study): 83%¹
 - 4% in the general population by age 70
- More common and more severe in women;^{1,2} in one study:¹
 - Prevalence of hepatic cysts: 85% in women, 79% in men
 - Mean hepatic cyst volume: 5.27 mL in women, 1.94 mL in men
- May be associated with estrogen exposure^{2,3}
 - Estrogen avoidance is recommended (including oral contraceptives)^{4,5}
- Arise from intrahepatic biliary microhamartomas²
- Complications are largely mechanical and rarely affect synthetic liver function²
- Cholestatic enzymes can rise 2 – 5X normal values²

Adapted from:

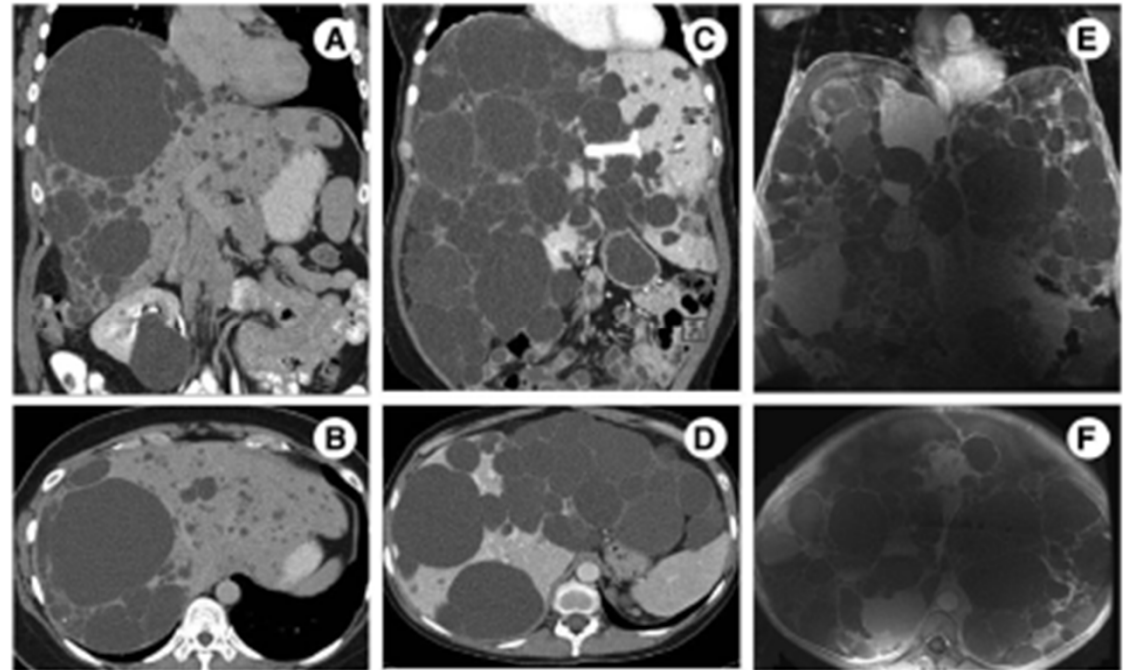
1. Bae KT, et al. Clin J Am Soc Nephrol 2006; (1):64-9.
2. Chauveau D, et al. J Am Soc Nephrol 2000;11(9):1767-75.
3. Drenth JP, et al. Hepatology 2010; 52(6):2223-30.
4. Shertsha R, et al. Hepatology 1997; 6:1282-6.
5. Srivastava A, et al. Am Fam Physician 2014; 90(5):303-7.



Treatment Options for Severe Hepatic Cysts

- Very few patients develop severe PLD (liver 5-10 X normal size)¹
- In these cases, liver resection / transplantation is last resort¹
- Imaging assessment can help determine best option (Figure)¹
- PET/CT can be used to confirm and locate cyst infection²

Presentations of Polycystic Liver Disease and Suggested Surgical Interventions



Cyst Aspiration
or Sclerosis

Right Hepatectomy,
Cyst Fenestration

Liver Transplant

Medical treatment (e.g., long-acting somatostatin) should be considered in patients with severe disease who are not surgical candidates³

Adapted from:

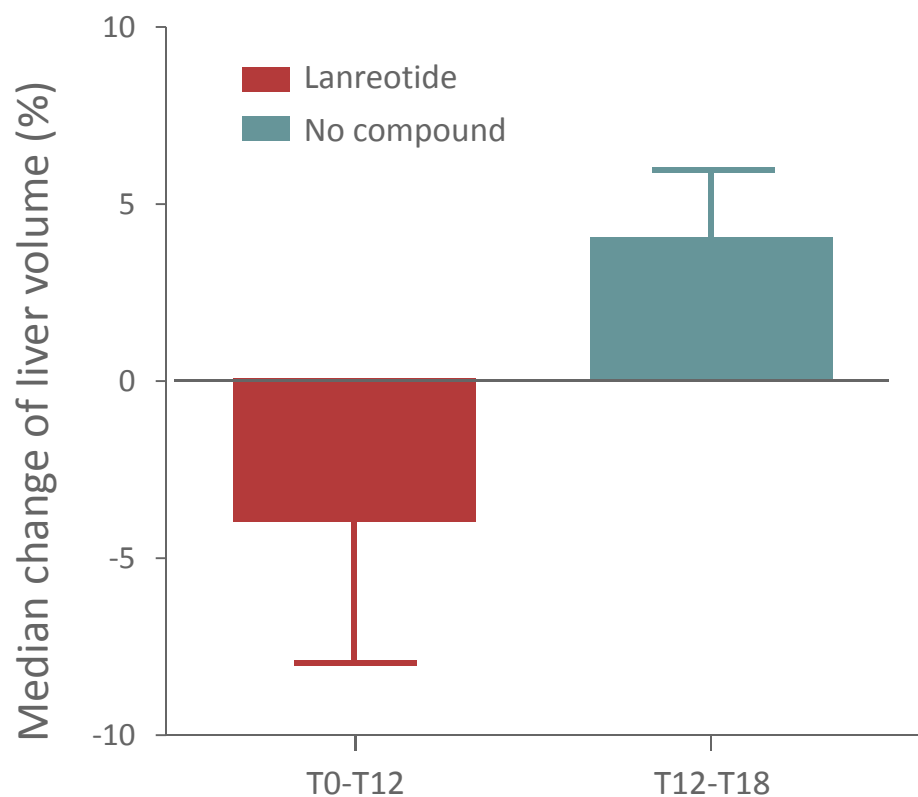
1. Drenth JP, et al. *Hepatology* 2010; 52(6):2223-30.4.

2. Jouret F, et al. *Clin J Am Soc Nephrol* 2011; 6(7):1644-50.

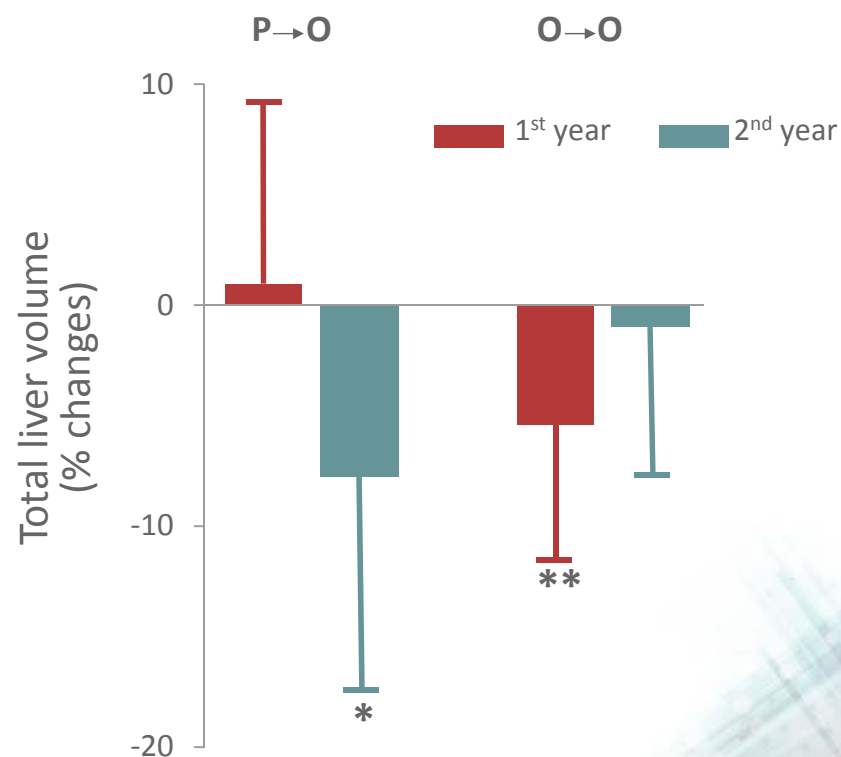
3. Hogan MC, et al. *Nephrol Dial Transplant* 2012; 27(9):3532-9.

Somatostatin Analogues: Effectiveness in Polycystic Liver Disease

Lanreotide vs. Placebo (1 yr)¹



Octreotide vs. Placebo (2 yrs)²



Adapted from:

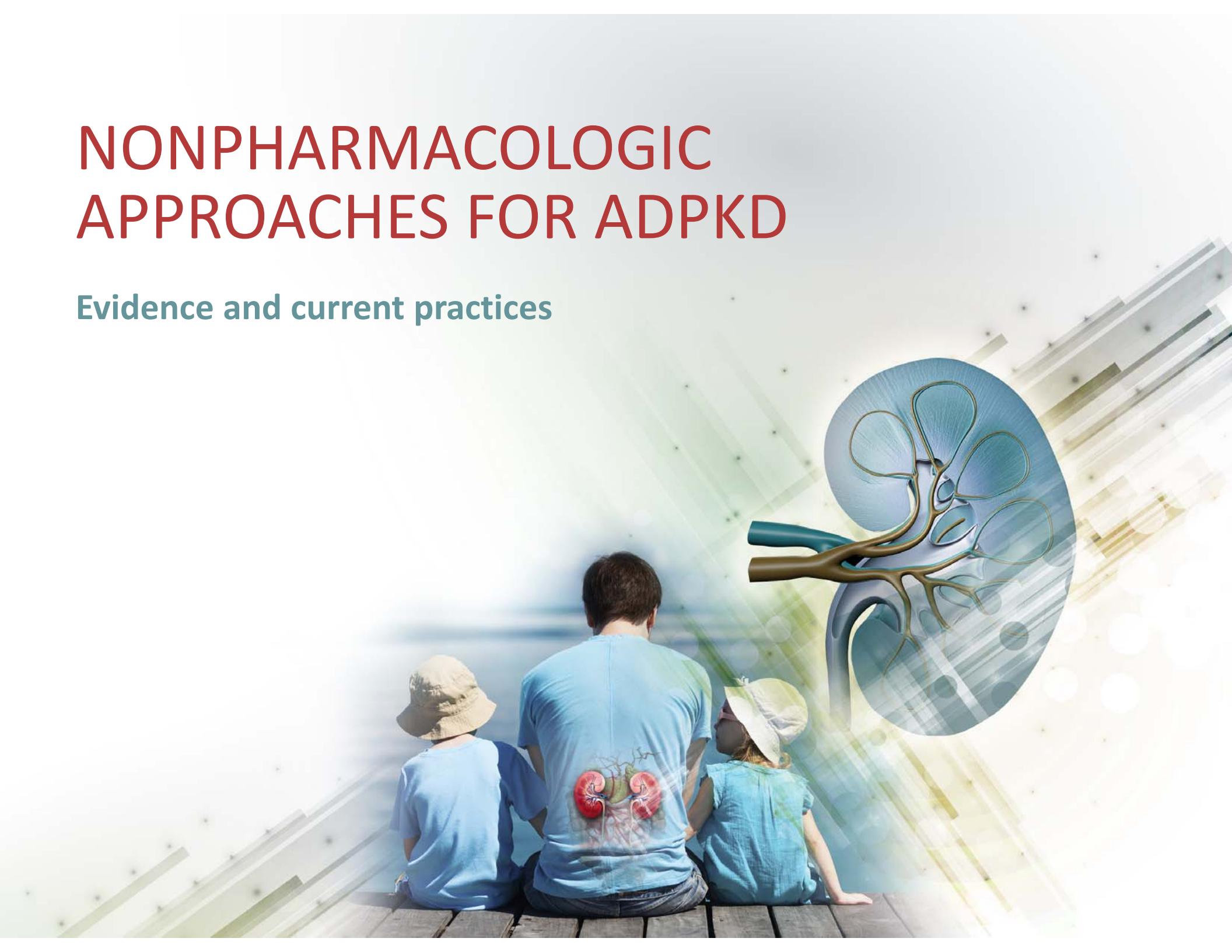
1. Chrispijn M, et al. *Aliment Pharmacol Ther* 2012;35(2):266-74.

2. Hogan MC, et al. *Nephrol Dial Transplant* 2012;27(9):3532-9.



NONPHARMACOLOGIC APPROACHES FOR ADPKD

Evidence and current practices

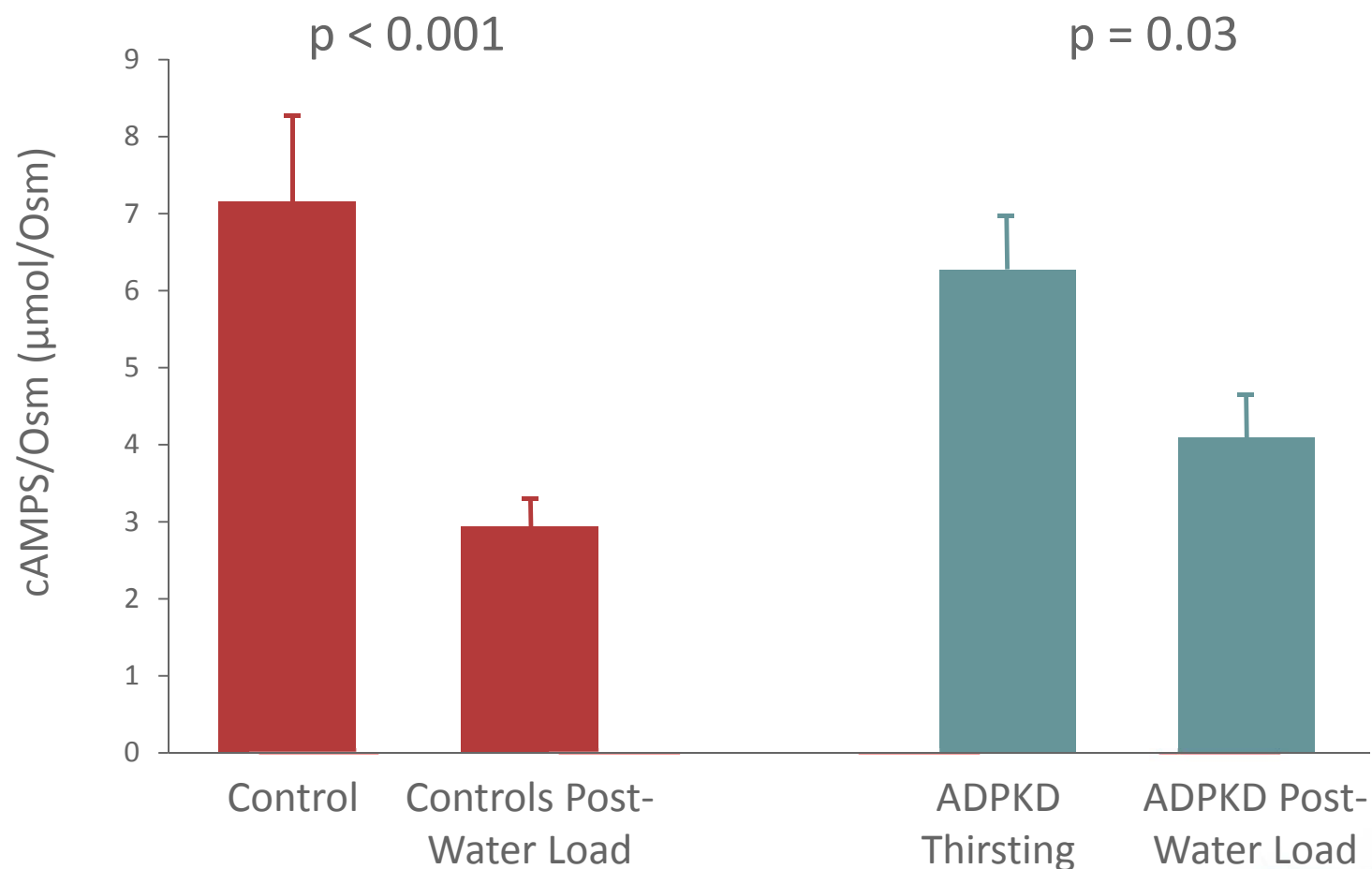


Rationale for Water Therapy in ADPKD

- cAMP is one of the key drivers of cyst enlargement
- In animal models, ingestion of large amounts of water promotes diuresis by suppressing plasma levels of arginine vasopressin (AVP) and renal levels of cAMP, slowing cyst progression



Evidence for Water Therapy in ADPKD: Changes in Urine cAMP Linked to Osmolality

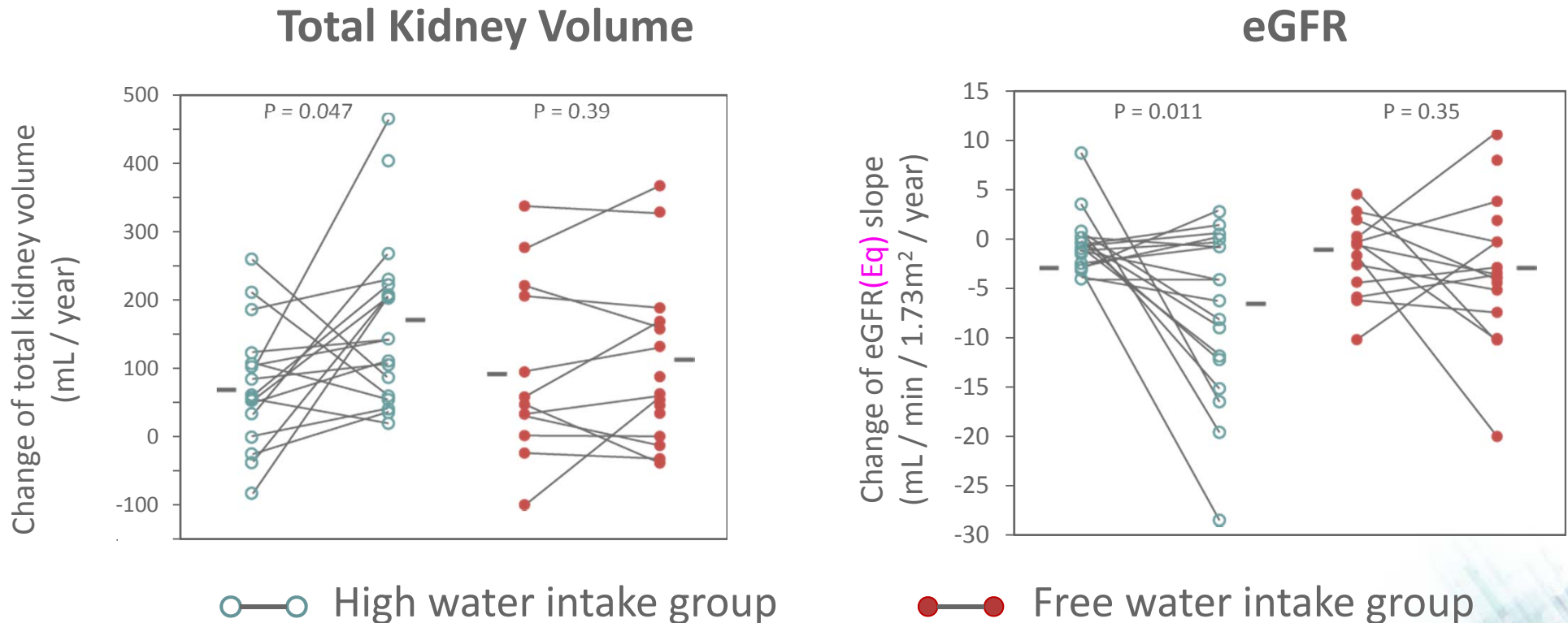


n=8

Adapted from: Wang CJ, et al. *Clin J Am Soc Nephrol* 2011;6(1):192-7.



Observational Study: No Benefit from Water Therapy in ADPKD



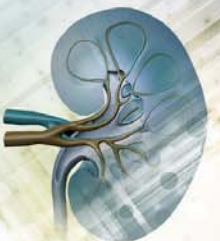
Key limitations of the study

- Small sample size
- One-year duration
- Underpowered, inconclusive



Summary: Current Understanding of Water Therapy for ADPKD

- There is no consensus as to whether increased water can alter the natural course of disease
- The size and quality of the limited available evidence makes definitive conclusions impossible at this point
- There is no consensus or evidence on the appropriate volume of water to recommend
 - 3-4 L daily may be appropriate
 - It is unknown if goals can be achieved over the longer term
- Increased water consumption does have known benefits for prevention of nephrolithiasis¹
- Adherence to water therapy is difficult for many patients



PHARMACOLOGIC THERAPY FOR ADPKD

Rationale, evidence & practical tips



Overview of Most Promising Potentially Disease-modifying Pharmacotherapies for ADPKD

Interventions Targeting cAMP-related Pathways

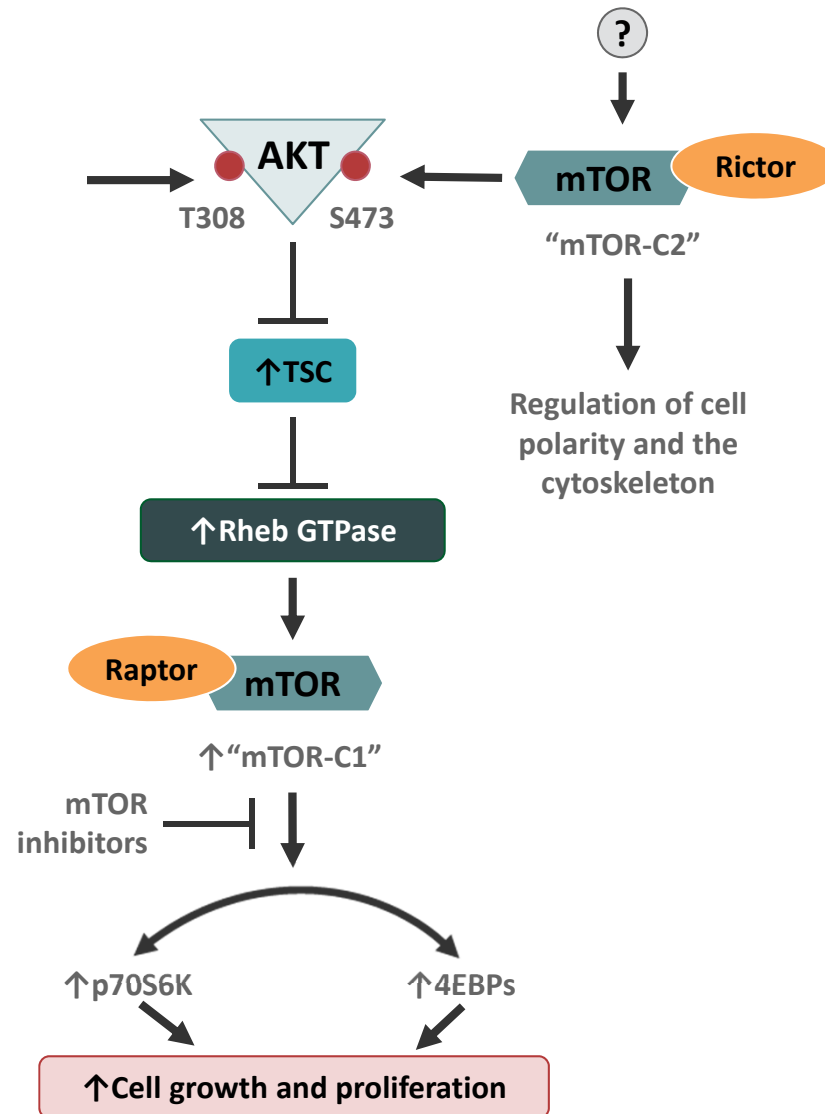
- mTOR inhibitors
(*i.e.*, sirolimus, everolimus)
- Somatostatin analogue
(*i.e.*, octreotide long-acting release)
- Vasopressin-2-receptor antagonist (*i.e.*, tolvaptan)

Interventions Targeting Other Pathways

- Statins (*i.e.*, pravastatin)
- RAAS inhibition
(*e.g.*, ACE inhibitor \pm ARB)



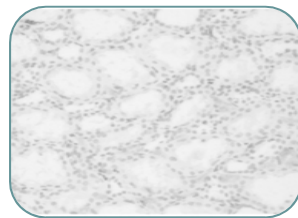
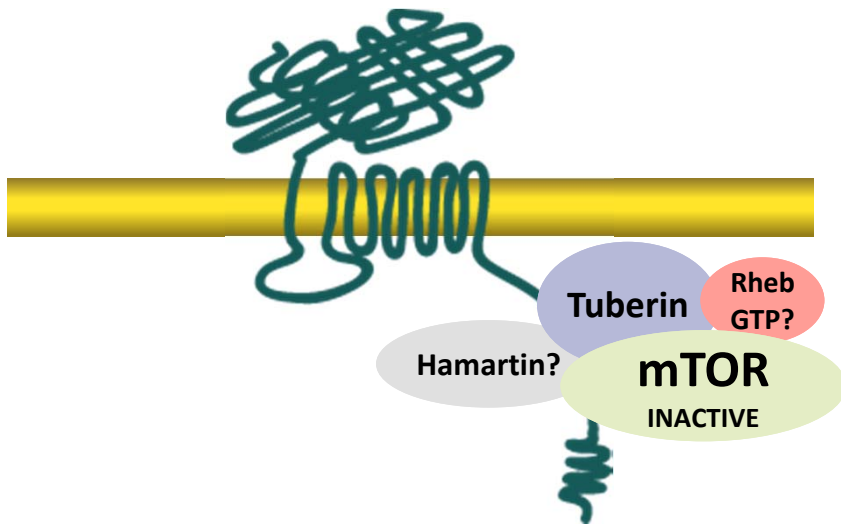
mTOR Inhibitors: Intracellular Signalling Pathways



mTOR Inhibition: Rationale for Use in ADPKD

Normal Kidney

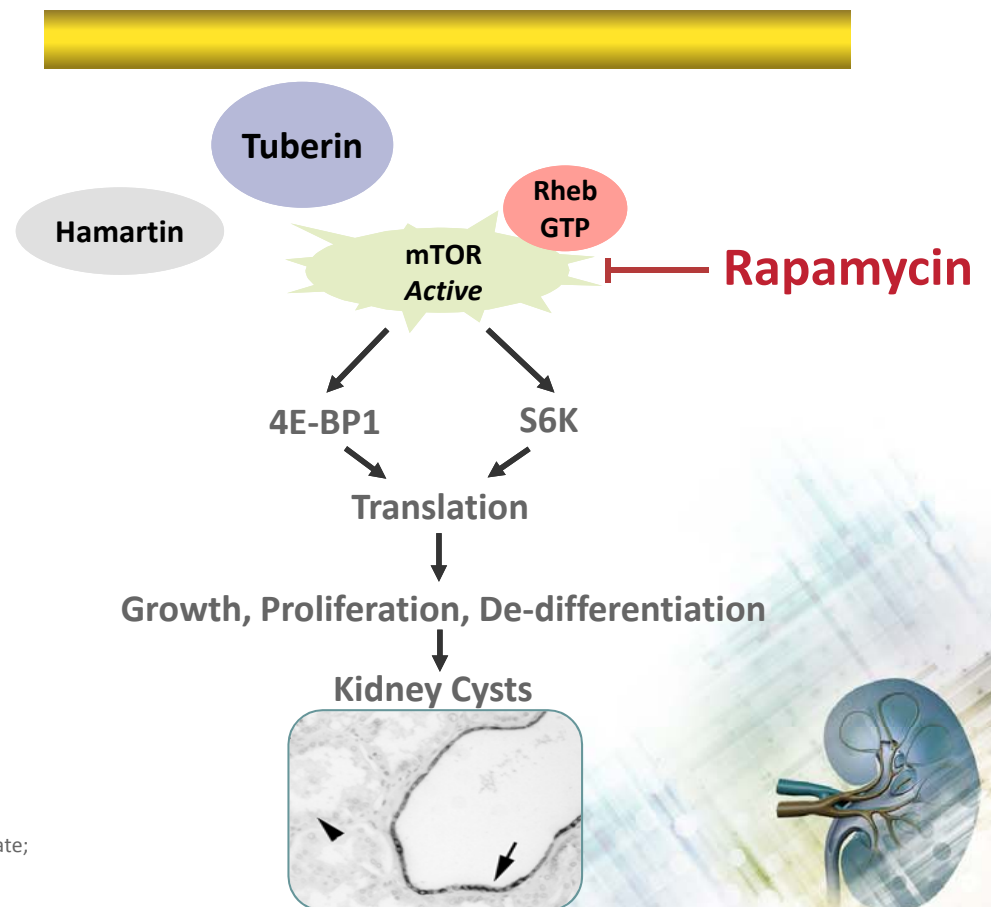
Ploycystin-1



Normal kidney

Polycystic Kidney

~~Ploycystin-1~~

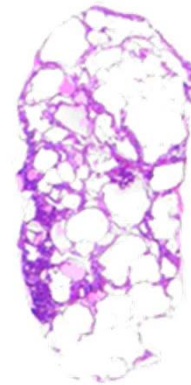


Animal Model: mTOR Inhibition Results in Cystic Disease Regression in *Pkd1* Conditional KO Mice

H&E
Low mag.



Pkd1^{cond/cond},
No treatment

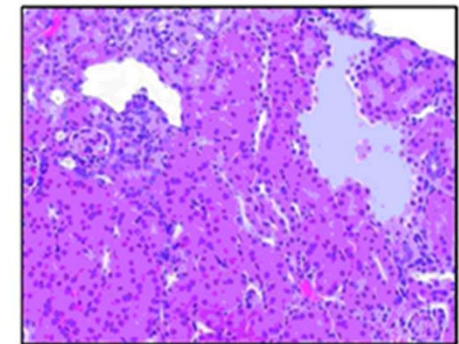
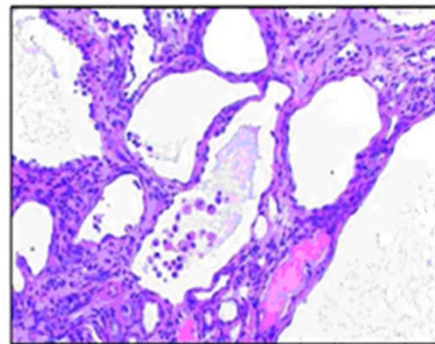
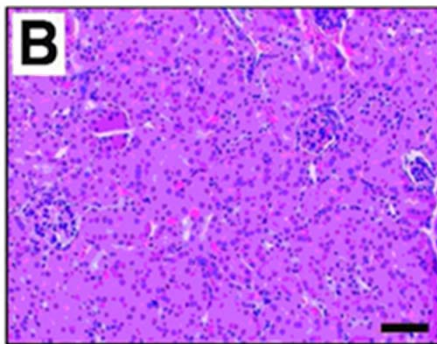


Pkd1^{cond/cond}; Nestin^{cre},
No treatment



Pkd1^{cond/cond}; Nestin^{cre},
Rapamycin

H&E
High mag.



Clinical Study of mTOR Inhibition in ADPKD: Sirolimus

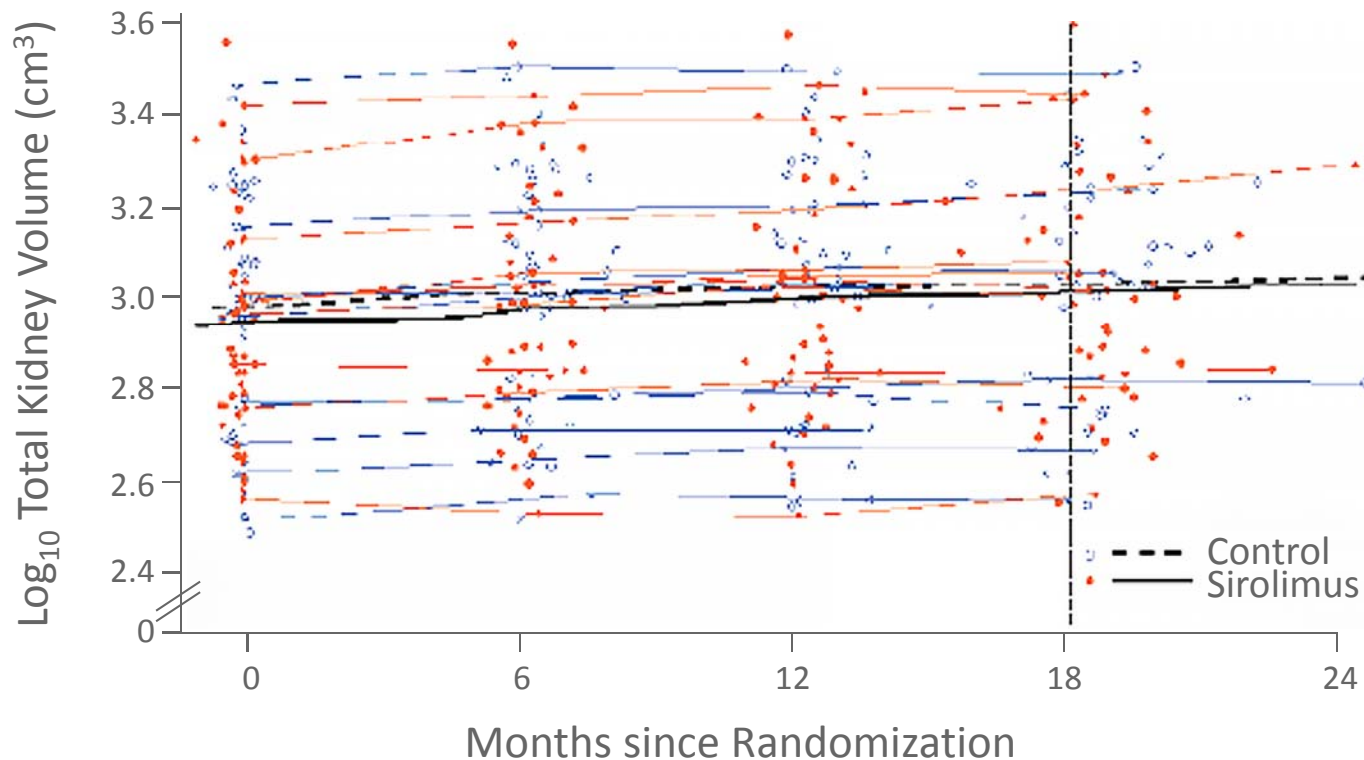
- 18-month, open-label, RCT (n=100)
- **Interventions:** Sirolimus 2 mg daily vs. standard care
- **Baseline TKV:** 875 mL in sirolimus group, 987 mL in control group
- **Baseline eGFR:** 92 mL/min
- **Primary endpoint:** total kidney volume at 18 months

Key limitations of the study

- Small numbers
- Short duration
- Non-maximal dosing of the drug?
- Strictly an early PKD cohort



Changes in Total Kidney Volume: Sirolimus (mTOR inhibitor) vs. Control



Median changes in TKV:
Control: +97 mL
Sirolimus: +99 mL
 $p=0.26$

Key results:

- No significant difference between sirolimus & standard care for TKV over 18 months (primary endpoint).
- No significant difference in eGFR.



mTOR Inhibition in ADPKD: Everolimus

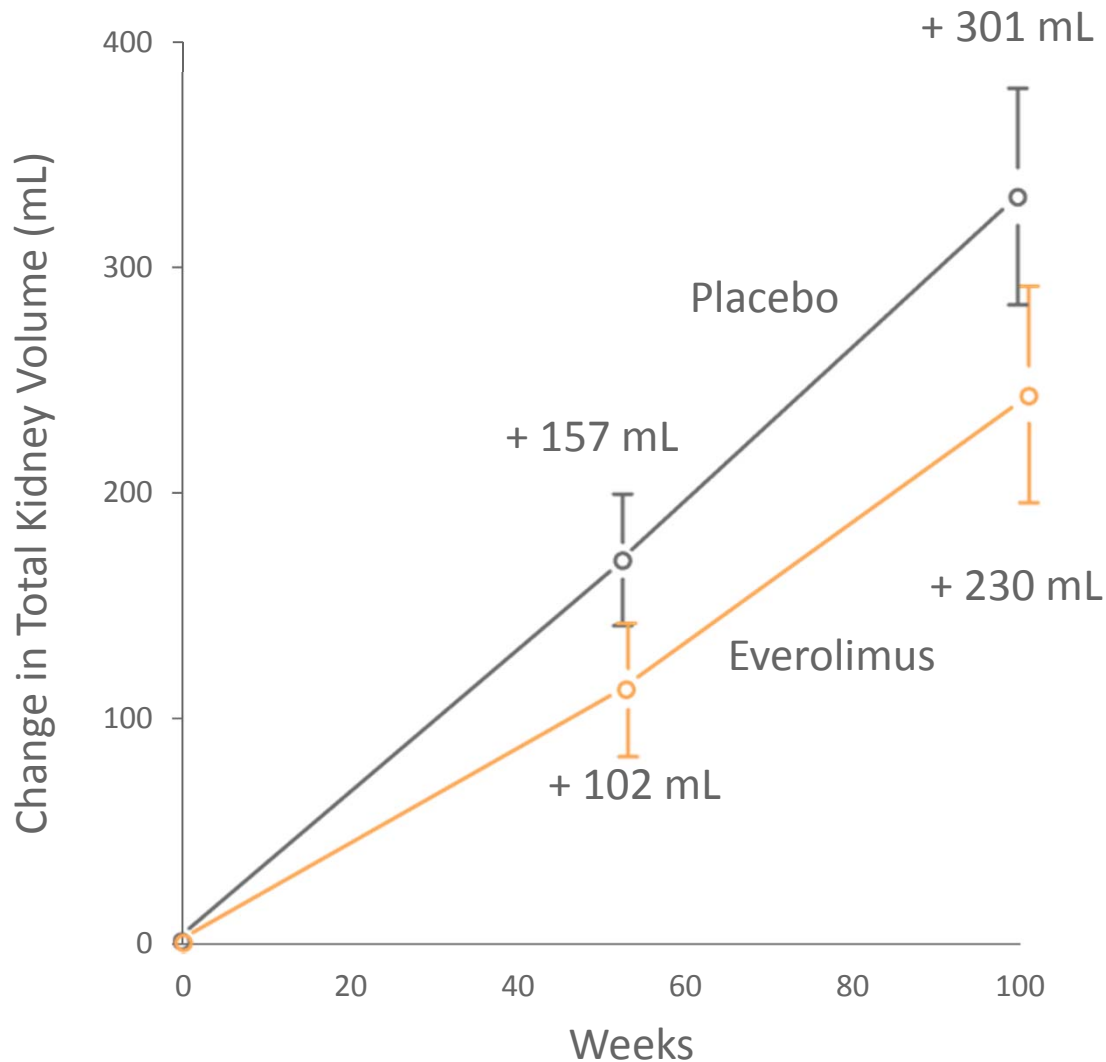
- 2-year, double-blind trial (n=433)
- **Interventions:** Everolimus 2.5 mg b.i.d. vs. placebo
- **Baseline TKV:** 2028 mL in everolimus group; 1911 mL in placebo group
- **Baseline eGFR:** 53 mL/min in everolimus; 56 mL/min in placebo
- **Primary outcome:** Change in TKV

Key limitations of the study

- 32.7% of the treated patients dropped out: no MRIs were available
- Investigators estimated the missing data by imputation (*i.e.*, analysis was not ITT)



Changes in Total Kidney Volume: Everolimus (mTOR inhibitor) vs. Control



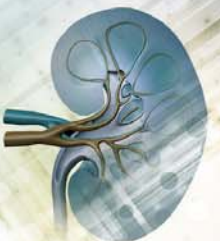
Key results:

- Borderline significant difference between everolimus & placebo for TKV over 2 years (primary endpoint).
- Mean change in eGFR at 2 years (mL/min/1.73 m²):
 - Placebo: 7.7
 - Everolimus: 8.9 (p=0.15)

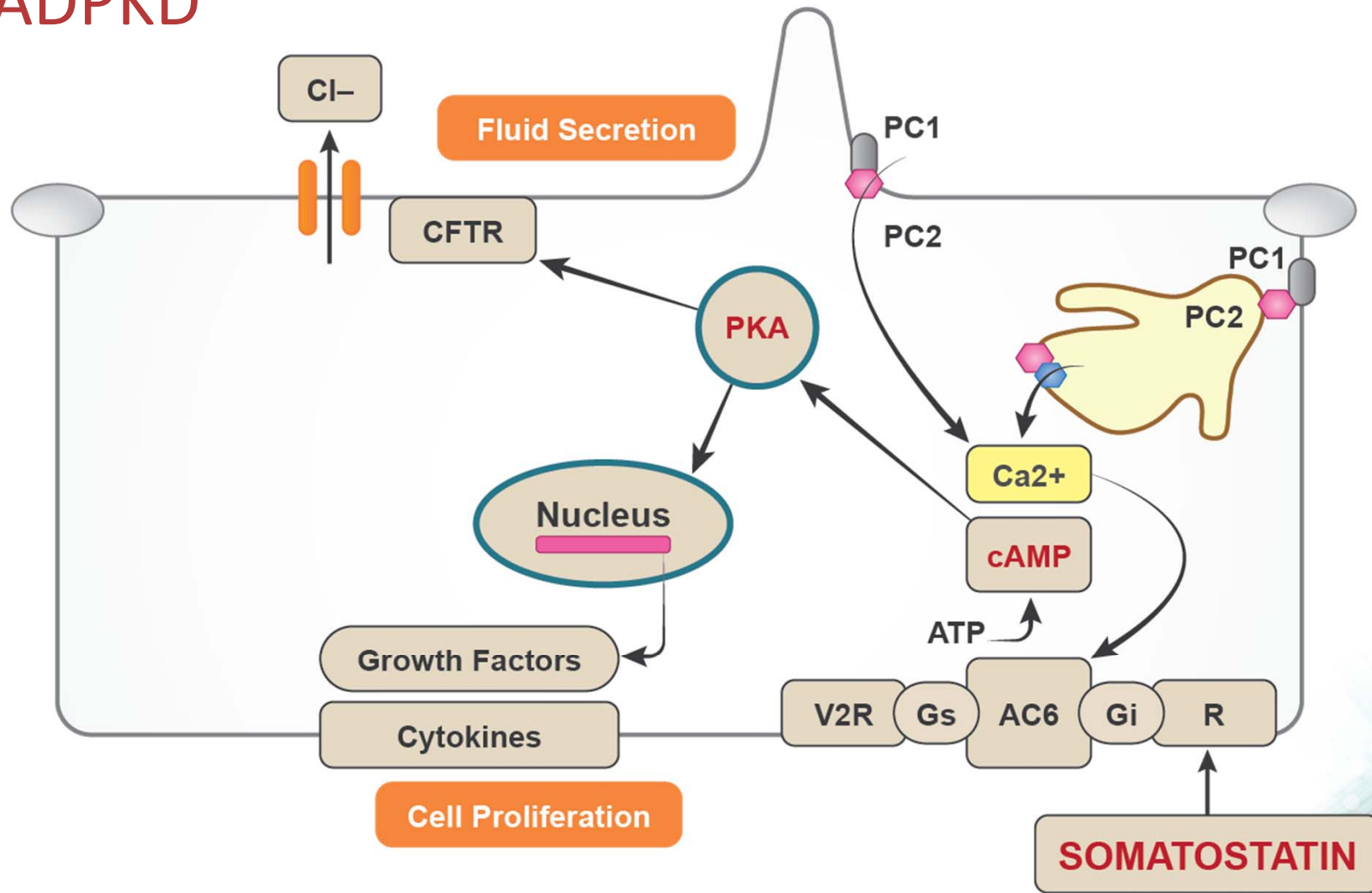


mTOR Inhibition for ADPKD: Summary of Current Knowledge

- Conclusion of recent meta-analysis of sirolimus studies (4 RCTs):¹
 - In ADPKD patients, treatment with sirolimus is safe and can effectively slow kidney growth, but it seems not to slow down the decrease of GFR
- However, data are not currently strong enough to recommend the use of these therapies in ADPKD
- It appears from the study by Walz *et al* that mTOR inhibitors are poorly tolerated at higher doses
- Further study is required



Mechanism of Action of Somatostatin Analogues in ADPKD



AC6: adenylyl cyclase 6; Ca²⁺: calcium; Cl⁻: Chloride; CFTR: cystic fibrosis transmembrane conductance regulator; Gi & Gs: G proteins; mTOR: mammalian target of rapamycin; PC1: polycystin-1; PC2: polycystin-2; PKA: protein kinase A; R: somatostatin receptor; V2R: vasopressin 2 receptor. Adapted from Alam A, et al. *Am J Kidney Dis* 2015; in press.

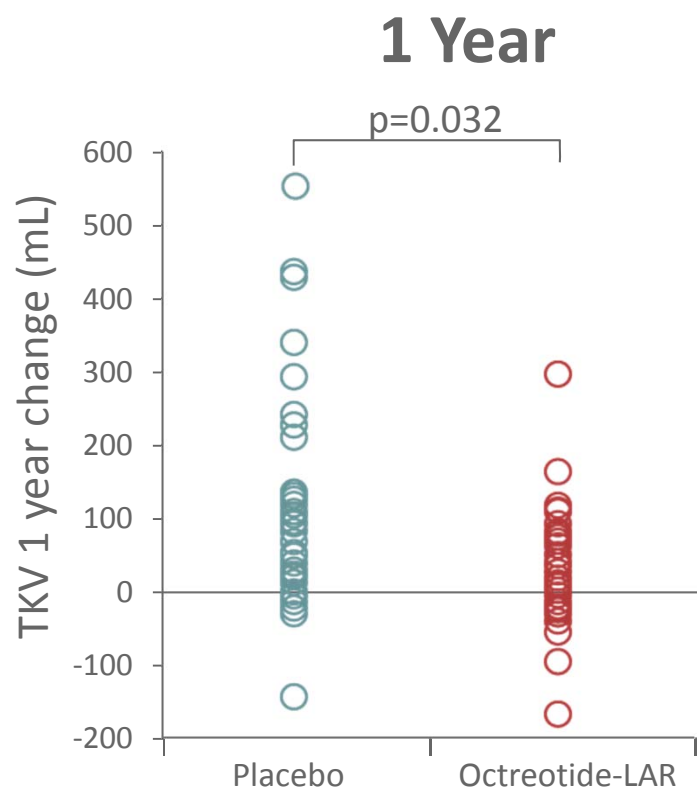


Somatostatin Analogue in ADPKD: The ALADIN Trial

- 3-year, placebo-controlled trial (n=79)
- **Interventions:** Two 20 mg i.m. injections of octreotide-LAR or 0.9% sodium chloride solution q 28 days
- **Baseline TKV:** 1527 mL in octreotide group; 2161 mL in placebo group
- **Baseline eGFR:** 90 mL/min in octreotide group, 76 mL/min in placebo group
- **Primary outcome:** Change in TKV
- **Limitations:**
 - Small sample size
 - Equal randomization is not assured: patients did not have genotype specified – even small differences in numbers of *PKD1*/*PKD2* distribution could skew the results significantly

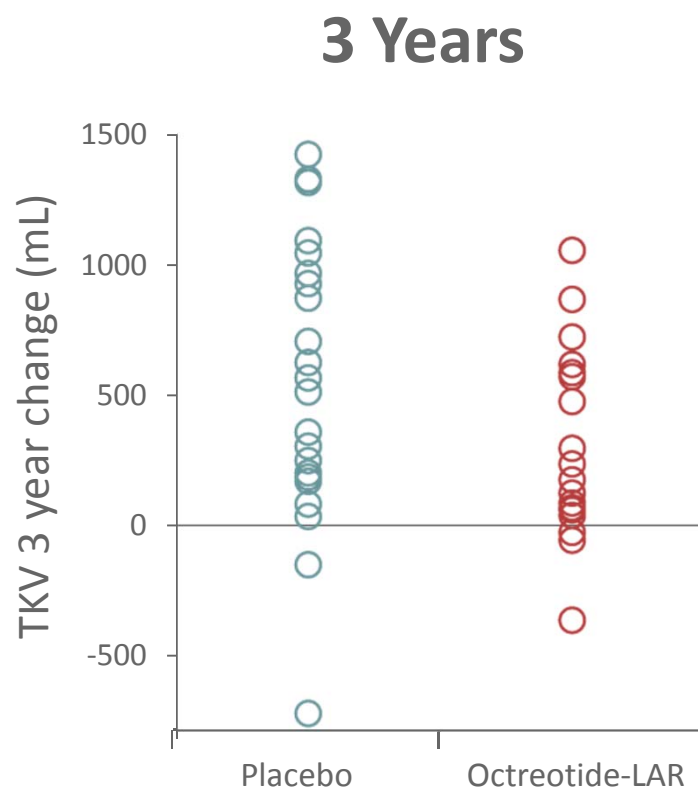


Octreotide LAR vs. Placebo: Change in TKV at 1 Year and 3 Years



n=75 analyzed

Mean TKV changes (mL)	Placebo	Octreotide-LAR
	143.7	46.2
	$p=0.032$	



n=70 analyzed

Mean TKV changes (mL)	Placebo	Octreotide-LAR
	454.3	220.1
	$p=0.25$	

Key results:

- Difference in TKV change significant at 1, but not 3 years
- Mean eGFR changes at 3 years (mL/min/1.73 m²):
 - PBO: -13.13
 - OCT: -12.35 $p=0.13$

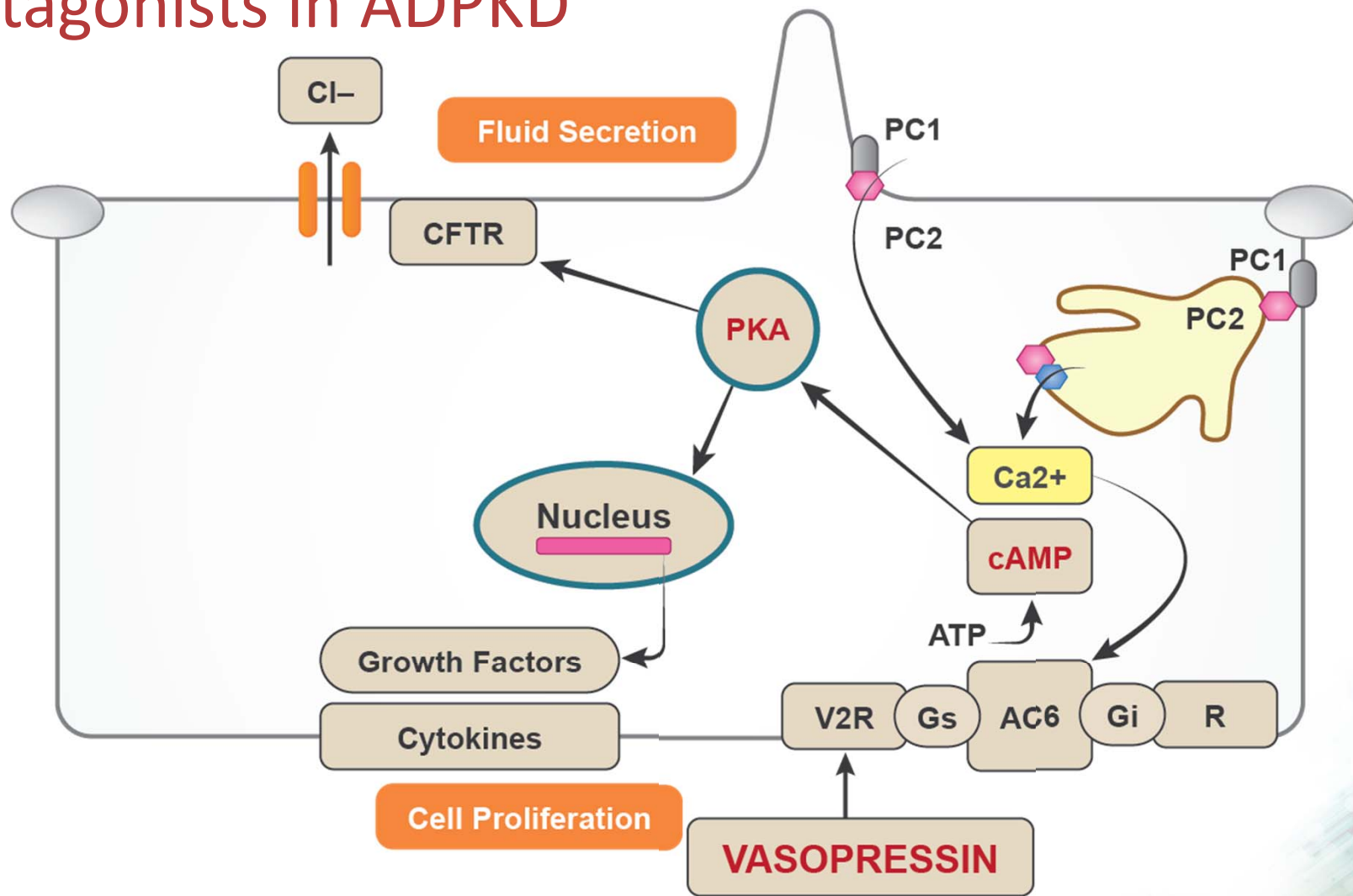


Somatostatin Analogues for ADPKD: Summary of Current Knowledge

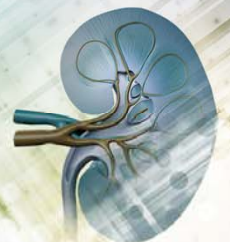
- These agents appear to be efficacious for slowing growth of both liver and perhaps kidney volume
- Trials to date have been small – further research is needed before they can be considered clinical options



Mechanism of Action of Vasopressin-2-receptor Antagonists in ADPKD



AC6: adenylate cyclase 6; Ca²⁺: calcium; Cl⁻: Chloride; CFTR: cystic fibrosis transmembrane conductance regulator; Gi & Gs: G proteins; mTOR: mammalian target of rapamycin; PC1: polycystin-1; PC2: polycystin-2; PKA: protein kinase A; R: somatostatin receptor; V2R: vasopressin 2 receptor. Adapted from Alam A, et al. *Am J Kidney Dis* 2015; in press.



Tolvaptan (Vasopressin-2-receptor Antagonist) in ADPKD: TEMPO 3:4

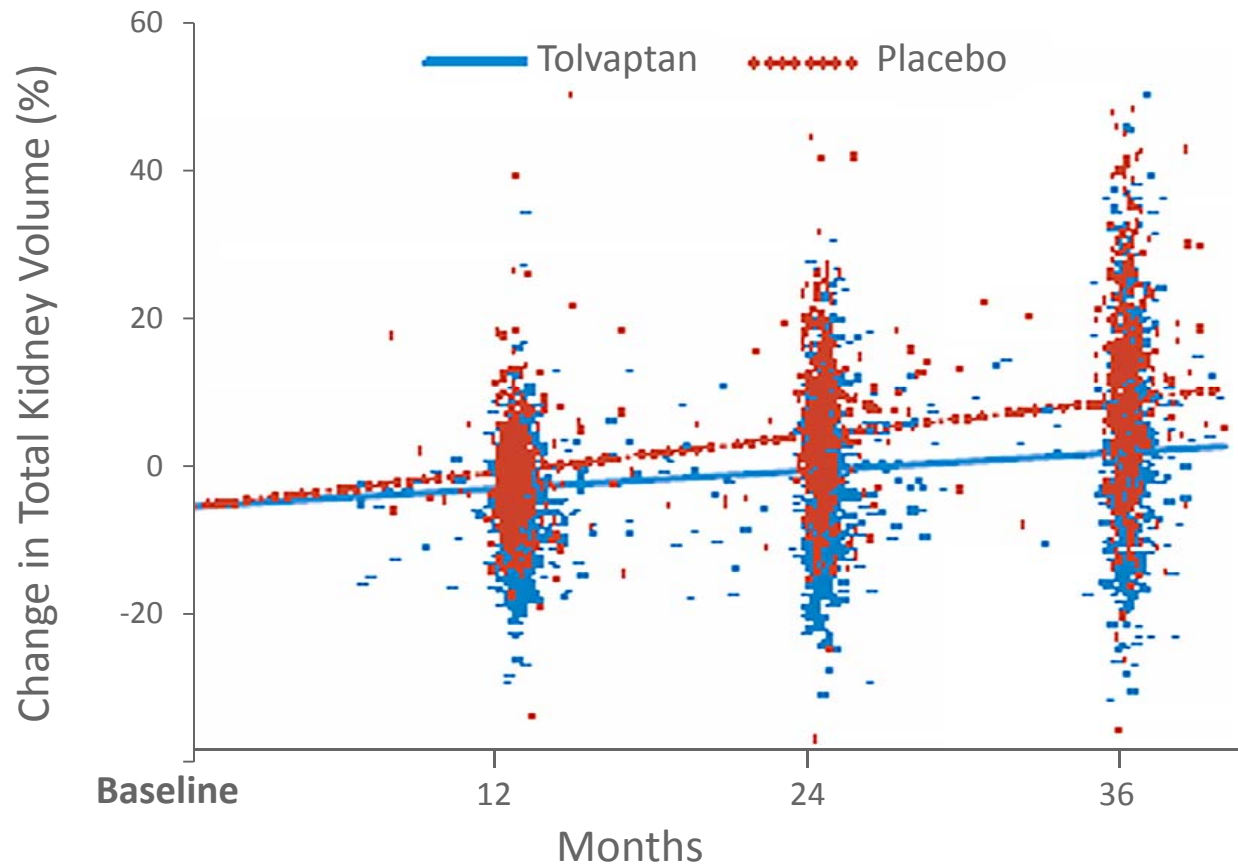
- 3-year, placebo-controlled trial (n=1,445)
- **Interventions:** Tolvaptan twice daily or placebo
- **Baseline TKV:** 1705 mL in tolvaptan group; 1668 mL in placebo group
- **Baseline reciprocal of serum creatinine:** 102 mg/mL in tolvaptan group; 104.3 mg/mL in placebo group
- **Primary outcome:** Annual rate of change in TKV

Key limitation of the study

- All patients in both groups were asked to maintain good hydration and avoid thirst.
 - Suppression of vasopressin release in the placebo group may have led to an underestimation of the beneficial effect of tolvaptan



Tolvaptan in ADPKD: Impact on TKV (TEMPO 3:4 Primary Outcome)

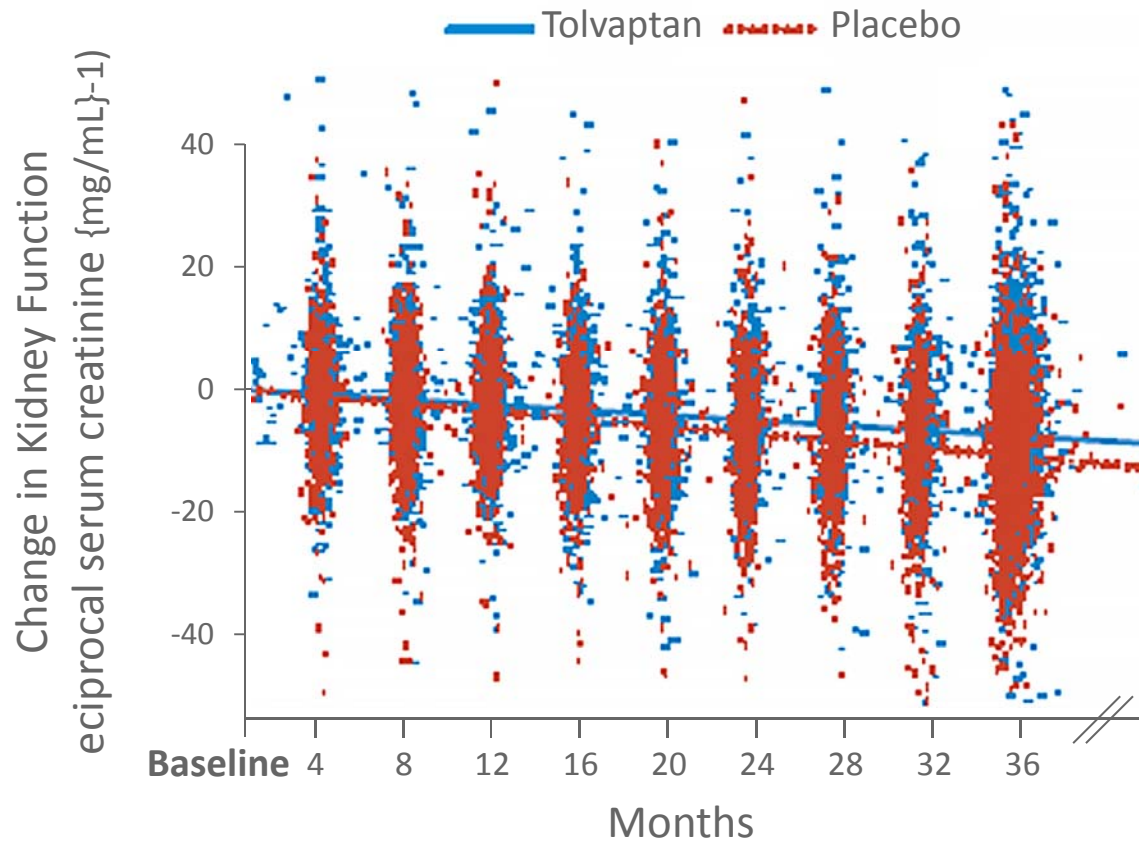


Placebo growth: 5.5%/yr
Tolvaptan growth: 2.8%/yr
 $p < 0.0001$

Dropouts:
Tolvaptan: 23.0%
Placebo: 13.8%



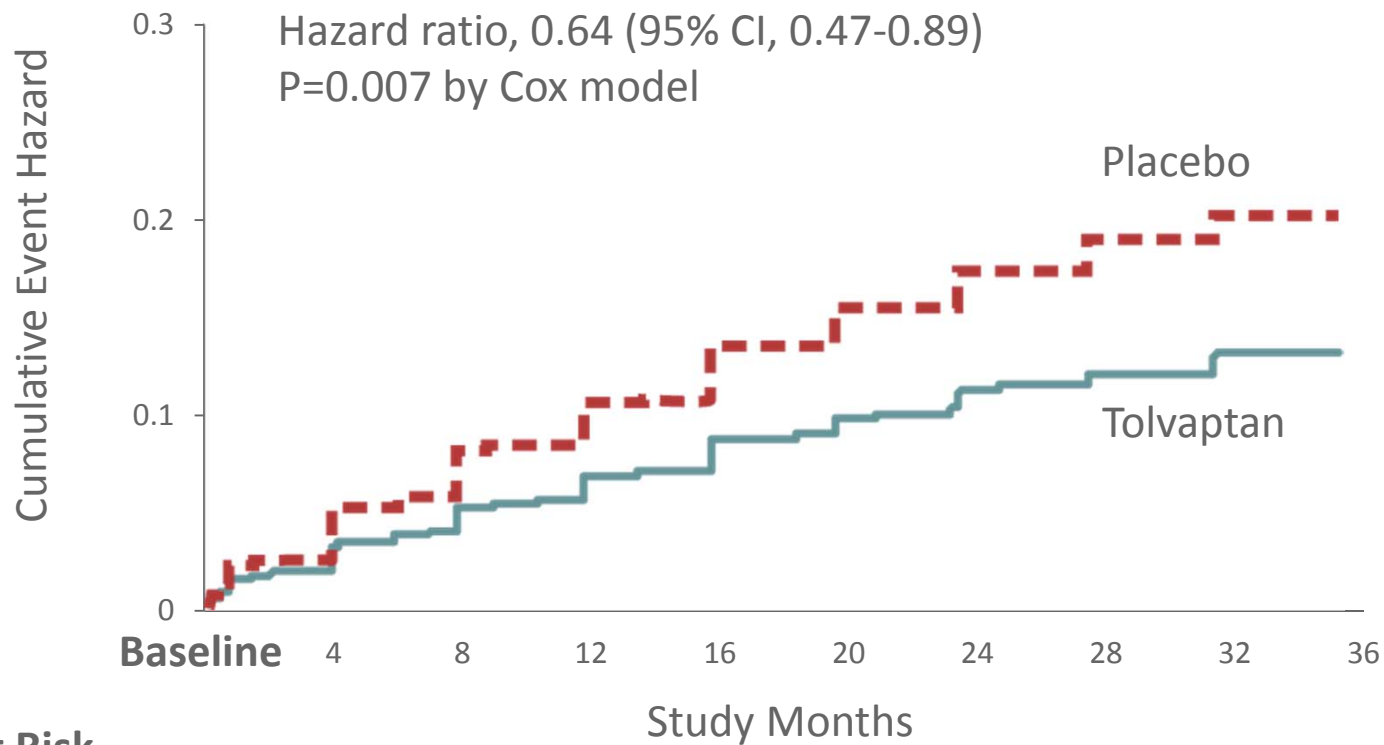
Tolvaptan in ADPKD: Impact on Kidney Function (TEMPO 3:4 Secondary Outcome)



Change in reciprocal of the sCr level:
Tolvaptan: $-2.61 \text{ mg/mL}^{-1}/\text{yr}$
Placebo: $-3.81 \text{ mg/mL}^{-1}/\text{yr}$
 $p < 0.001$



Tolvaptan in ADPKD: Impact on Kidney Pain (TEMPO 3:4 Secondary Outcome)



No. At Risk

Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359



Liver Abnormalities with Tolvaptan in the TEMPO 3:4 Study

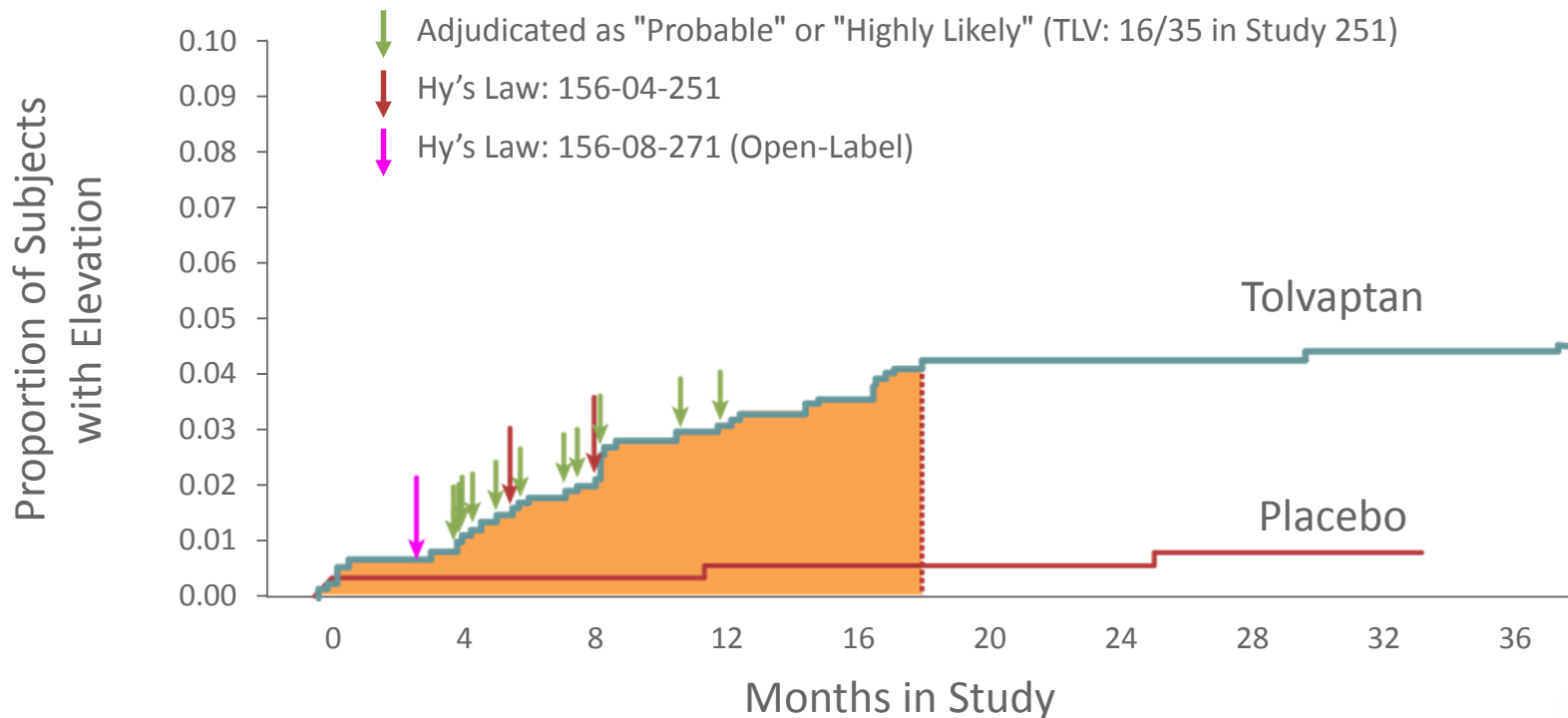
Abnomality	Tolvaptan			Placebo		
	Subjects	Subjects Meeting Criteria	%	Subjects	Subjects Meeting Criteria	%
ALT >3x ULN	961	42	4.4	483	5	1.0
Hy's Law Criteria*	961	2 [‡]	0.2	483	0	0
Death or Liver Failure	961	0	0	483	0	0

*Hy's Law Criteria: ALT >3x ULN with bilirubin >2x, but ALP <2x ULN

[‡]1 additional Hy's Law case in the Open-Label Trial (156-08-271)



Time to First Elevation in ALT (>3x ULN) With Tolvaptan: 18-Month “Window of Susceptibility”



Days in Study	0	100	200	300	400	500	600	700	800	900	1000	1100
Tolvaptan N=	961	884	836	812	769	774	765	751	740	734	726	268
Placebo N=	483	476	468	459	452	445	442	433	425	422	415	147



Tolvaptan for the Treatment of ADPKD: Conclusions

- In the pivotal clinical study, tolvaptan showed efficacy in:
 - Slowing progression of increase in kidney volume
 - Slowing deterioration of kidney function
 - Improving symptoms (*e.g.*, pain)
- Signal of liver toxicity in the pivotal trial led to the recommendations for monitoring at baseline and throughout treatment



HMG-CoA Reductase Inhibitors (Statins) for ADPKD: Mechanism of Action

- Mechanism of action in ADPKD is currently unknown, but presumed to be independent of cholesterol lowering
- Potential mechanisms (from animal studies):^{1,2}
 - Enhanced renal blood flow
 - Attenuate of vascular inflammation through vascular and glomerular nitric oxide production
 - Inhibition of G proteins with resultant decreased cell proliferation

Adapted from

1. Cadnapaphornchai MA, et al. *Clin J Am Soc Nephrol* 2014;9(5):889-96.

2. Zafar I, et al. *Am J Physiol Renal Physiol* 2007; 293:F854–F859.



Pravastatin for the Treatment of ADPKD in Children

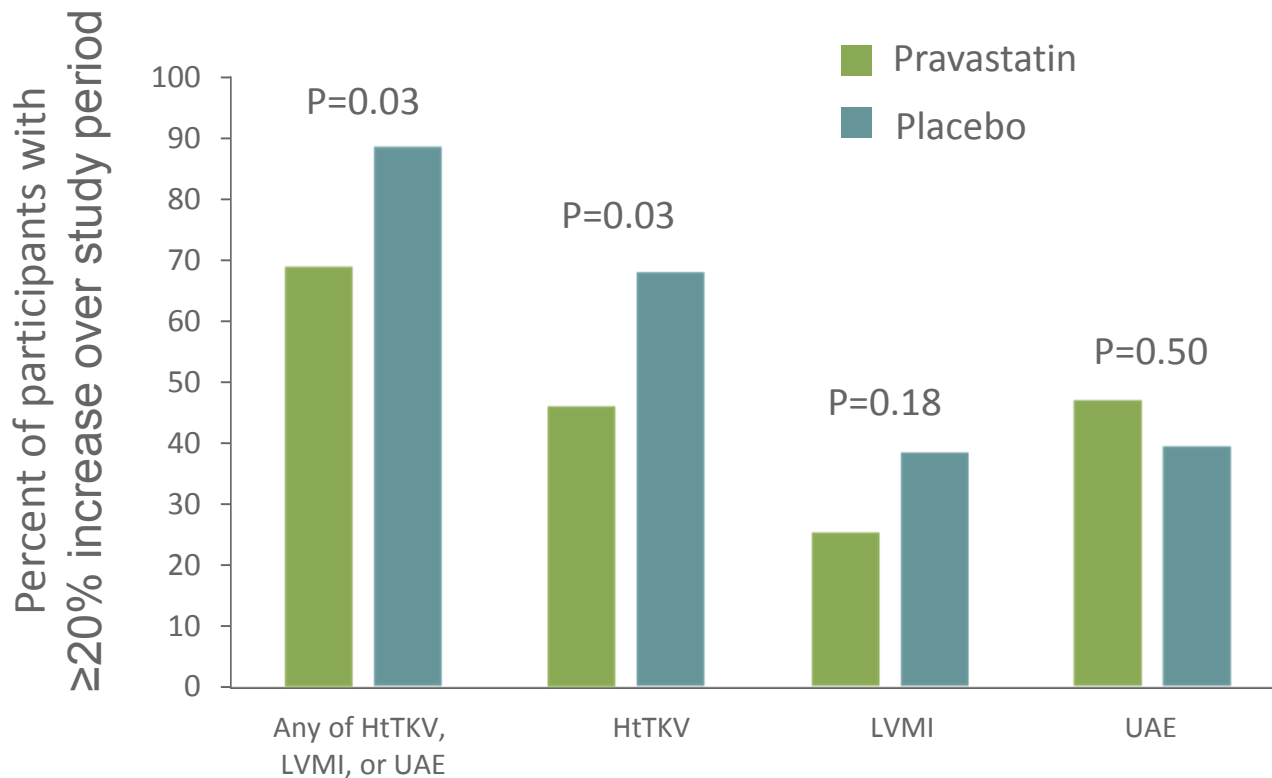
- 3-year, placebo-controlled trial (n=110) in children and adolescents
- **Interventions:** Pravastatin 20-40 mg daily or placebo
- **Baseline TKV:** 571 mL in pravastatin group; 522 mL in placebo group
- **Primary outcomes:** Proportion with $\geq 20\%$ change in height-adjusted TKV, LVMI, or UAE over 3 years (composite)

Key limitations of the study

- Small sample size
- Strictly early disease in children and adolescents
- The patients were not genotyped – randomization of *PKD1*/*PKD2* may not be balanced which may impact interpretation of outcomes



Pravastatin for the Treatment of ADPKD in Children: Primary Composite Endpoint and Components



Key results:

- Fewer participants receiving pravastatin reached the primary endpoint compared with placebo (69% vs. 88%)
- Increase in HtTKV was significantly lower with pravastatin vs. placebo (23% vs. 31%)

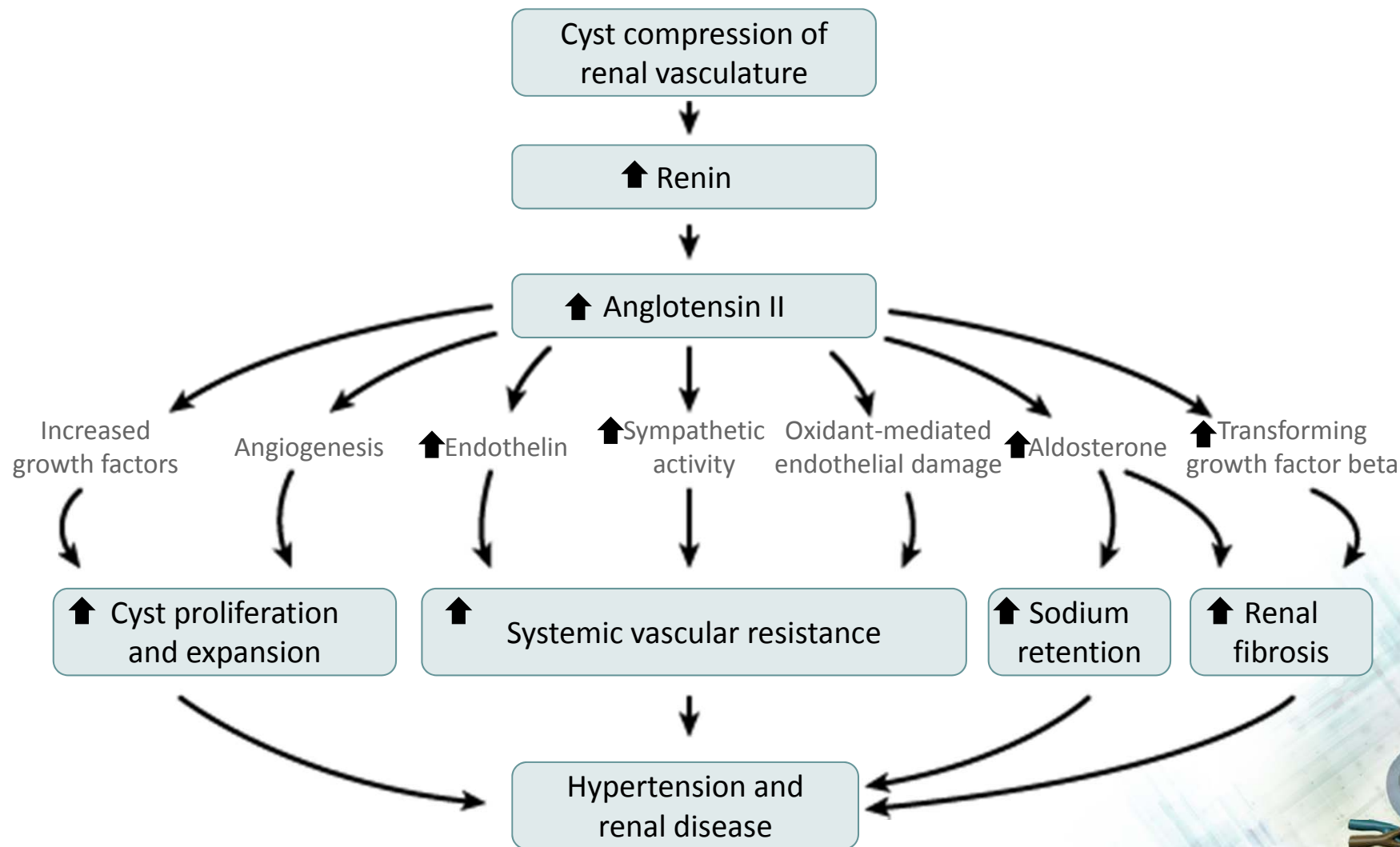


Statin Therapy in ADPKD: Conclusion

- The results of the study with pravastatin in children with ADPKD are suggestive
- While disease modification has not yet been proven based on this single trial it should be the subject of further research
- Mechanism of action has not been established
- Many patients with CKD would have indications for statin therapy independent of the cause of their disease (for cardiovascular protection)

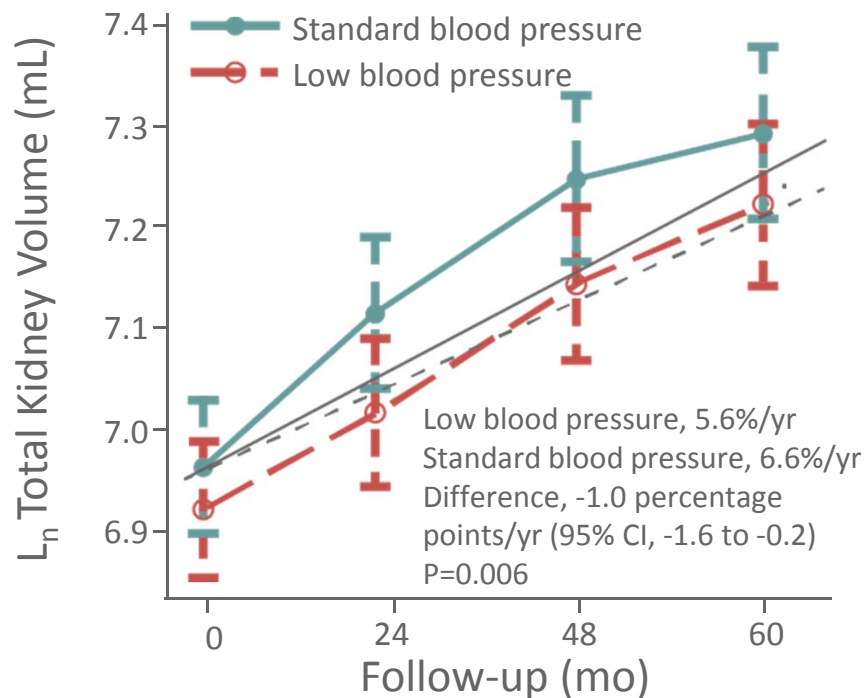


RAS Inhibition for the Treatment of ADPKD: Mechanism of Action

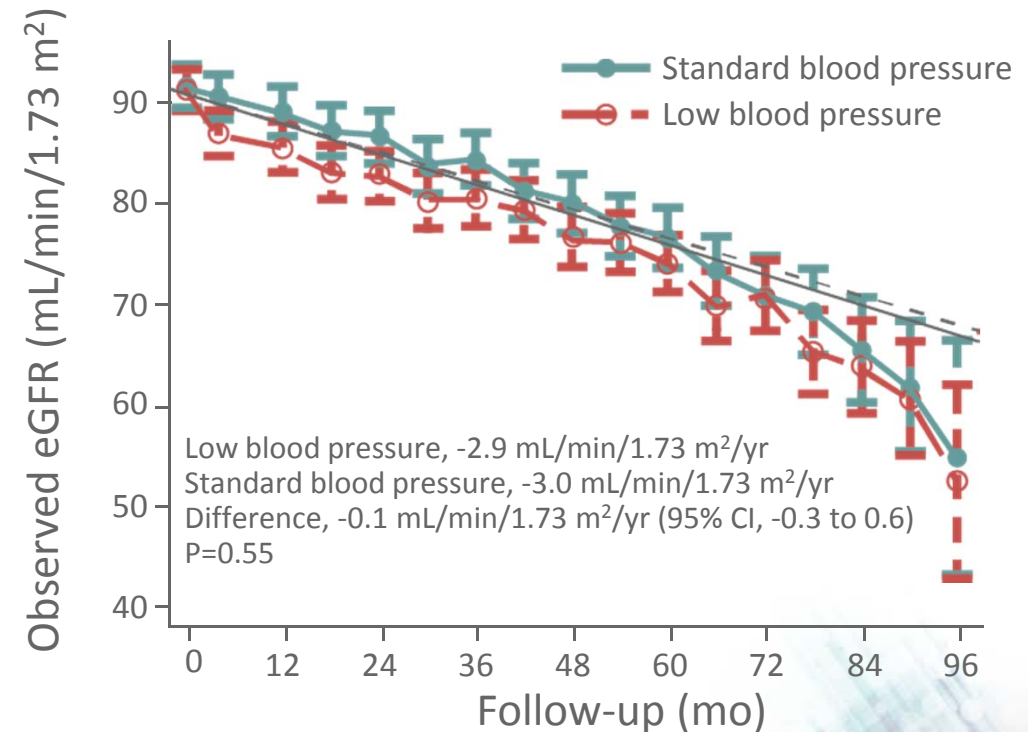


Different BP Targets in Early ADPKD: Changes in Total Kidney Volume and eGFR (HALT-PKD Study A)

Changes in TKV



Changes in eGFR



Conclusion of the BP analysis: As compared with standard BP control, rigorous BP control was associated with a slower increase in TKV, no overall change in the eGFR, a greater decline in the LMVI, and greater reduction in UAE.

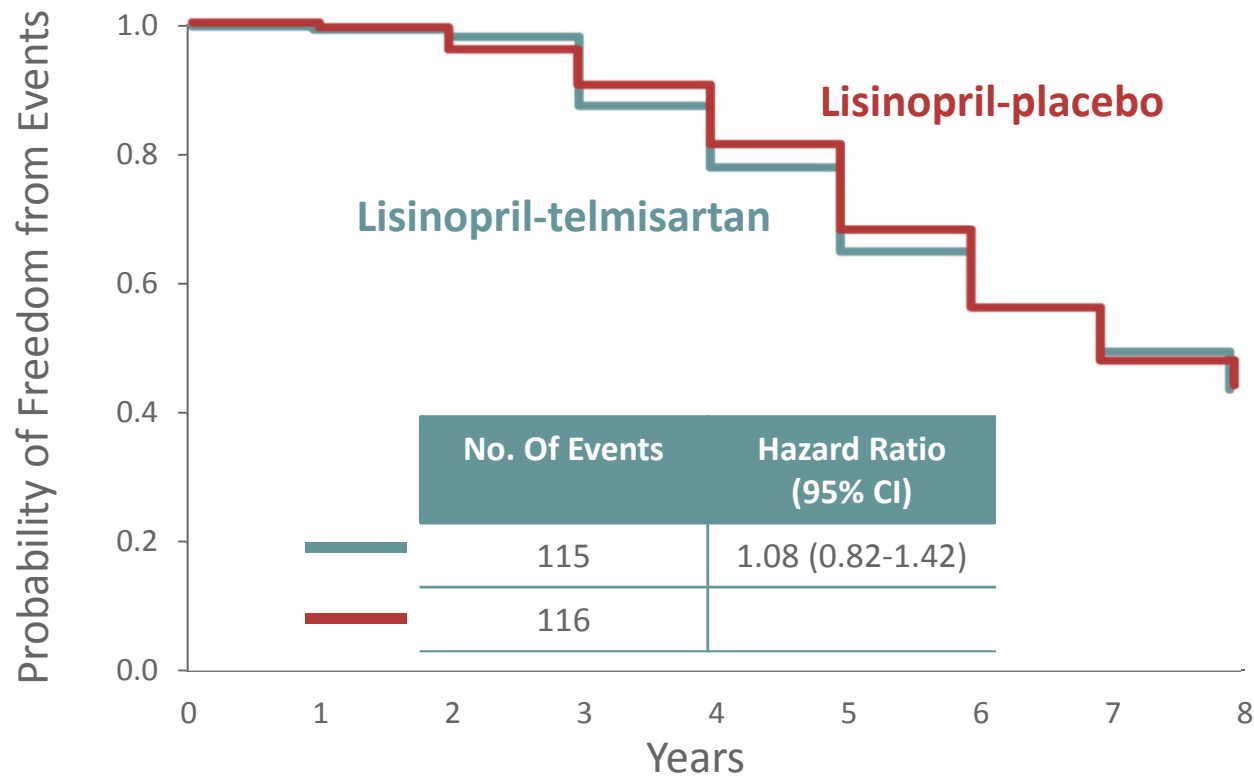


Impact of Single or Dual RAAS Inhibition in Late ADPKD: Design of the HALT-PKD Study B

- Double-blind, placebo-controlled trial
- 486 patients with ADPKD
 - 18 to 64 years old
 - Baseline eGFR 25-60 mL/min/1.73 m²
- Randomized to:
 - RAAS blockade: ACE inhibitor (lisinopril) + placebo or an ARB (telmisartan)
- Followed for 5-8 years
- Primary composite outcome: Time to death, end-stage renal disease, or a 50% reduction from the baseline estimated GFR



Impact of Single or Dual RAAS Inhibition in Late ADPKD: Primary Composite Outcome*



Lisinopril-Telmisartan	243	236	231	224	193	167	104	55	12
Lisinopril-placebo	242	231	224	213	196	172	115	54	20

*time to death, end-stage renal disease, or a 50% reduction from the baseline estimated GFR.
Adapted from Torres VE, et al. *N Engl J Med* 2014 Nov 15. [Epub ahead of print].



RAAS Inhibition in ADPKD: Conclusions From HALT-PKD Studies A and B

- Blood pressure can be controlled with ACE inhibitors
- Rigorous blood pressure control, early in the disease process, may slow cyst growth and reduce the left-ventricular-mass index
 - This approach is, however, complicated by increased dizziness
- The studies dissociate kidney-volume growth from a decline in renal function
- Despite these limitations, the studies indicate that with careful medical care, including meticulous attention to blood pressure, the prognosis for patients with ADPKD remains good



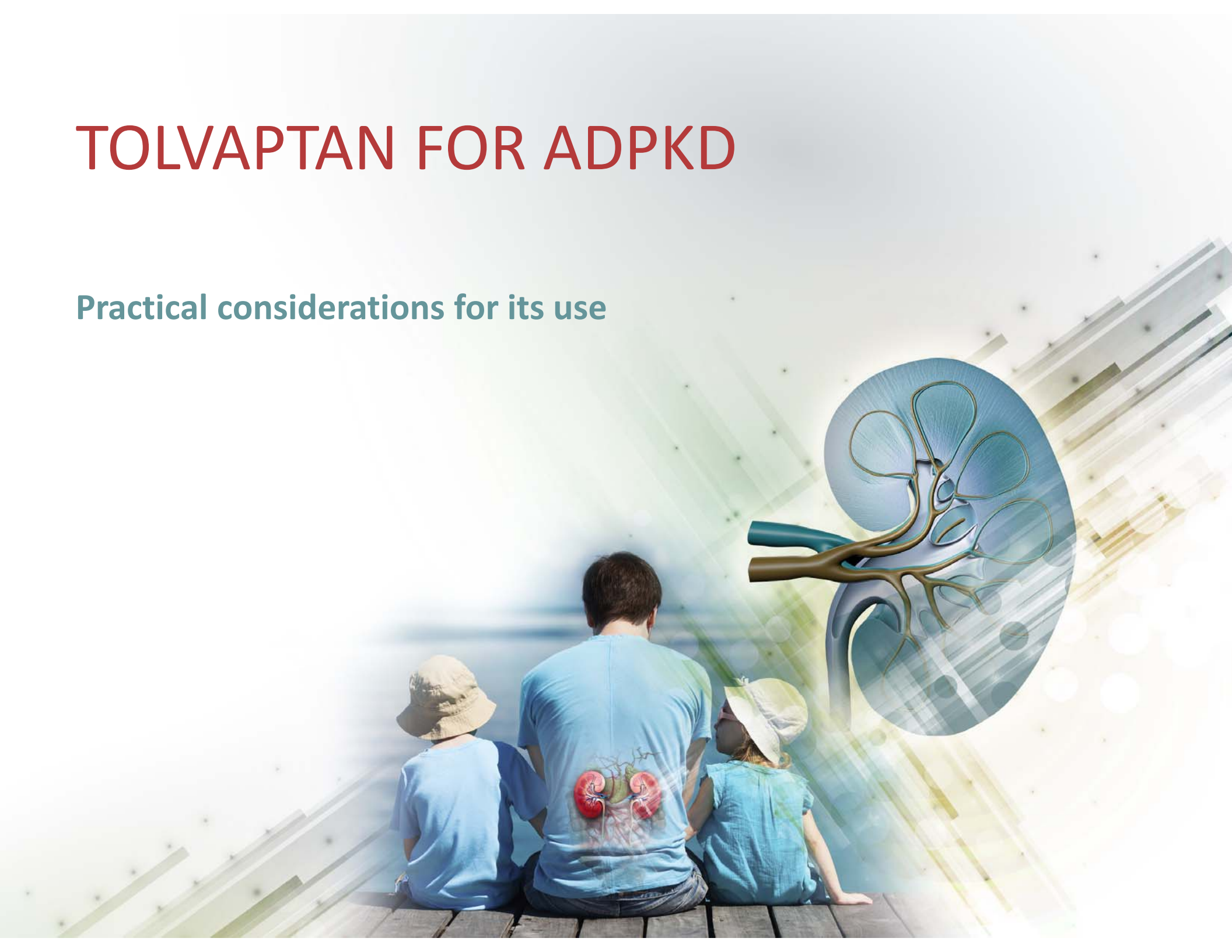
Pharmacotherapy for ADPKD: Conclusions

- There are several therapeutic targets that have been investigated in clinical studies for the treatment of ADPKD, including:
 - Vasopressin-2-receptor antagonists (V2RA)
 - mTOR inhibitors
 - Somatostatin analogues
 - RAAS inhibitors
 - Statins
- There are limitations to the evidence base for each of these interventions
- Tolvaptan (V2RA) is the only pharmacotherapy approved for slowing the progression of kidney enlargement



TOLVAPTAN FOR ADPKD

Practical considerations for its use



Indication and Contraindications for Tolvaptan in ADPKD

Official Canadian indication:*

- Tolvaptan is indicated to slow the progression of kidney enlargement in patients with ADPKD
- In ADPKD, kidney enlargement reflects renal cyst burden

Contraindications

- Hypovolemia
- Anuric patients
- Patients who cannot perceive or respond to thirst
- Patients with clinically relevant impairment of hepatic function
- Patients who are hypersensitive to the drug or to any ingredient in the formulation
- Hypernatremia
- Pregnancy, nursing mothers

*For the full text of the indication section in the product monograph, see the lecture notes.
Otsuka Canada Pharmaceuticals Inc. PrJINARC™ Product monograph. Date of Preparation: February 11, 2015.



Patient Selection Considerations for Tolvaptan in ADPKD—From Health Canada Official Labeling

- The key clinical trial of tolvaptan evaluated ADPKD patients with*:
 - Total kidney volume (TKV) \geq 750 mL
 - Relatively preserved renal function: e.g., CKD-EPI eGFR \geq 30 mL/min/1.73m²
- Patients most likely to benefit from tolvaptan appear to be:
 - Those with rapidly progressive ADPKD, or at a stage of incipient rapid progression, but before widespread destruction of renal architecture
 - Factors associated with rapid progression of ADPKD include:
 - Large total renal cyst mass for a given age, as measured by TKV
 - CKD Stage 2-3
 - Rapid deterioration of renal function
 - Presence of systemic hypertension or albuminuria



Important Risk Factors for ADPKD Progression Not Listed in Tolvaptan Official Labeling

- Type of Genetic Mutation

- *PKD1* mutations cause more severe disease than *PKD2* mutations¹
- Truncating *PKD1* mutations cause more severe disease than non-truncating *PKD1* mutations^{1,2}
- The median age at ESRD for truncating *PKD1*, non-truncating *PKD1*, and *PKD2* mutations are 55.6, 67.9, and 79.7 years, respectively¹

- Family history of early-onset ESRD

- Indicative of a genetic mutation associated with increased risk of progression³
 - *e.g.*, If a family member developed ESRD <55, it is highly predictive of the severe form of *PKD1*

Adapted from:

1. Corneec-Le Gall E, et al. J Am Soc Nephrol 2013; 24(6):1006-13.
2. Pei Y, et al. Kidney Int 2012;81(4):412-7.
3. Barua M, et al. J Am Soc Nephrol 2009;20(8):1833-8.



Recommended Dosing of Tolvaptan for ADPKD

Dosing	
Regimen overview	2 doses daily: one (larger dose) upon waking and one (smaller dose) 8 hours later
Available dosages	45+15 mg, 60+30 mg, 90+30 mg
Usual initial dosage	45+15 mg
Target dose	Highest tolerated dose, up to 90+30 mg
Titration	At least weekly intervals between titrations

Adequacy of vasopressin suppression at a given dose of tolvaptan can be monitored through measurement of urine osmolality and may be used to optimize the clinical benefit of tolvaptan in ADPKD patients.



Warning on Hepatic Toxicity with Tolvaptan

WARNING: IDIOSYNCRATIC HEPATIC TOXICITY

Tolvaptan use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT & AST), rarely associated with concomitant elevations of total bilirubin. To help mitigate the risk of liver injury, blood testing for hepatic transaminases is required prior to initiation of tolvaptan, then continuing monthly for 18 months, every 3 months for the next 12 months, and then every 3-6 months thereafter during treatment with tolvaptan

- In clinical trials, 3 individuals experienced ALT >3x ULN with bilirubin >2x ULN
 - Includes 2 of 957 patients in the TEMPO study and 1 in an open-label study
 - All 3 returned to normal liver function after stopping tolvaptan



Key Elements of the Tolvaptan Hepatic Safety Monitoring and Distribution (HSMD) Programme

1. Restriction of prescription to physicians experienced in the diagnosis and treatment of PKD
2. Deliver tolvaptan and HSMD education to healthcare professionals
3. Patient education
4. Patient-prescriber agreement form (PPAF) prior to initiation of treatment
5. Controlled distribution of tolvaptan supply to pharmacies
6. Tracking liver enzymes and function tests



What to Do if Hepatic Toxicity Occurs with Tolvaptan

- At the onset of symptoms or signs consistent with hepatic injury, or if abnormal ALT or AST increases are detected:
 - Tolvaptan administration must be interrupted
 - Repeat liver tests, *i.e.*, ALT, AST, total bilirubin, alkaline phosphatase, should be obtained as soon as possible, ideally within 48-72 hours
 - Testing should continue at an increased frequency until symptoms/signs/laboratory abnormalities stabilize or resolve, at which point cautious re-initiation of tolvaptan may be considered
- Permanent discontinuation is recommended for:
 - ALT or AST >8x ULN
 - ALT or AST >5x ULN for more than 2 weeks
 - ALT or AST >3x times ULN **and** total bilirubin > 2xULN or INR > 1.5
 - ALT or AST >3x times ULN, with persistent symptoms of hepatic injury



Reporting LFT Result Status and Clinically Significant Elevations with Tolvaptan

- Personnel from the tolvaptan HSMD Programme will send a monthly fax to each prescriber of tolvaptan
 - List of all patients in the practice taking tolvaptan for ADPKD
 - Physician (or proxy) will need to tick off checkboxes indicating whether or not their tolvaptan patients:
 - Have done their blood work according to schedule
 - Have had normal results from the liver function testing
 - Completed form is to be returned by fax

For more information on the tolvaptan hepatic safety monitoring and distribution programme, [click here](#)



The Patient-Prescriber Agreement Form (PPAF) for Tolvaptan in ADPKD

- When the patient and provider decide to undertake treatment with tolvaptan, a signed, duly-documented, product-specific patient-prescriber agreement (PPAF) is required
- The PPAF outlines:
 - Relevant patient selection criteria
 - Expected benefits and risks of treatment
 - Need for mandatory hepatic function monitoring
 - That tolvaptan is a long-term therapy and avoiding interruptions/discontinuations is recommended



Potential Drug Interactions with Tolvaptan

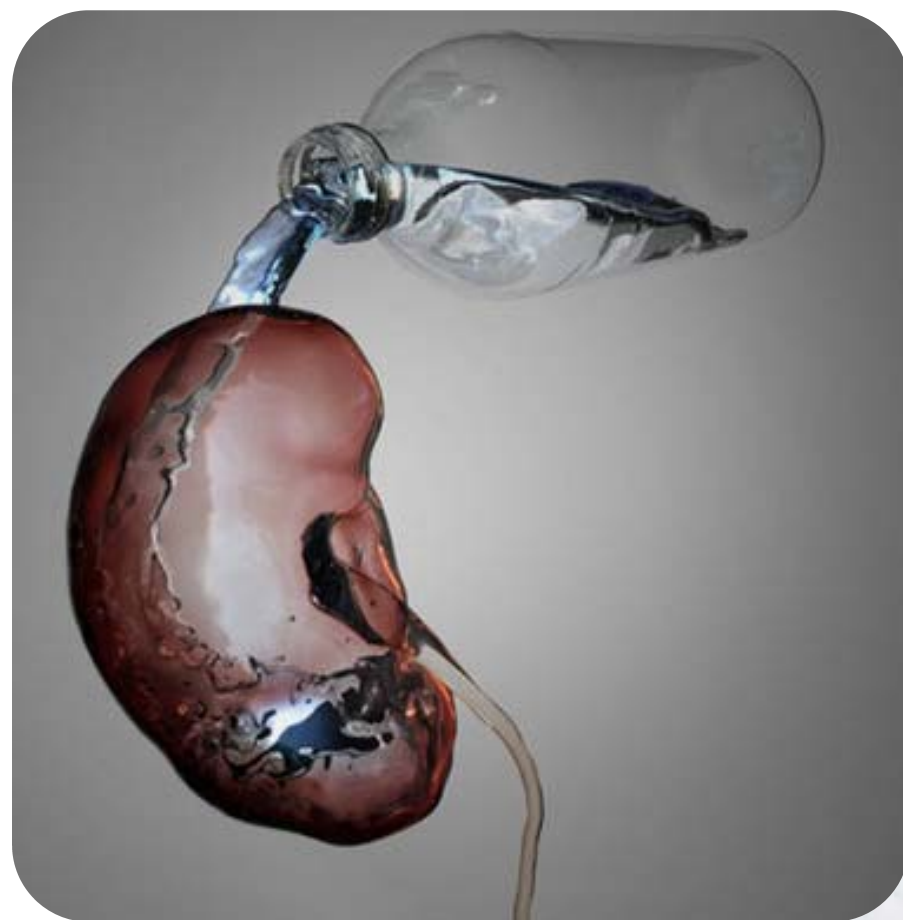
Tolvaptan is a substrate of CYP3A

Recommendation(s)	Examples
Substantial dose reduction of tolvaptan is required for patients prescribed strong CYP 3A inhibitors, especially for those also having P-gp inhibitory properties	Ketoconazole, clarithromycin, ritonavir, saquinavir
Concomitant use with moderate CYP 3A inhibitors, also requires lowered dosing of tolvaptan	Verapamil, fluconazole, erythromycin
Tolvaptan should not be taken with grapefruit juice	
Concomitant use of tolvaptan with strong CYP 3A inducers should be avoided	Rifampin, phenytoin, carbamazepine, St. John's wort
Reduction in the dose of tolvaptan may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors	Cyclosporine, quinidine



Advice on Water Intake with Tolvaptan

- Patients should be generally encouraged to drink water while taking tolvaptan to avoid development of dehydration or hypernatremia, and to improve tolerability of tolvaptan
- Patients should be instructed to drink water or other aqueous fluids at the first sign of thirst in order to avoid excessive thirst or dehydration



Canadian Tolvaptan Patient Outcomes Registry

In order to enhance the continuous evaluation of the long-term effects of tolvaptan in ADPKD, all patients to be initiated on tolvaptan should be offered participation in the Canadian tolvaptan patient outcomes registry

Key data to be captured:

- Total mortality
- Mortality attributable to renal and hepatic causes
- Time to renal replacement therapy (dialysis and transplantation)

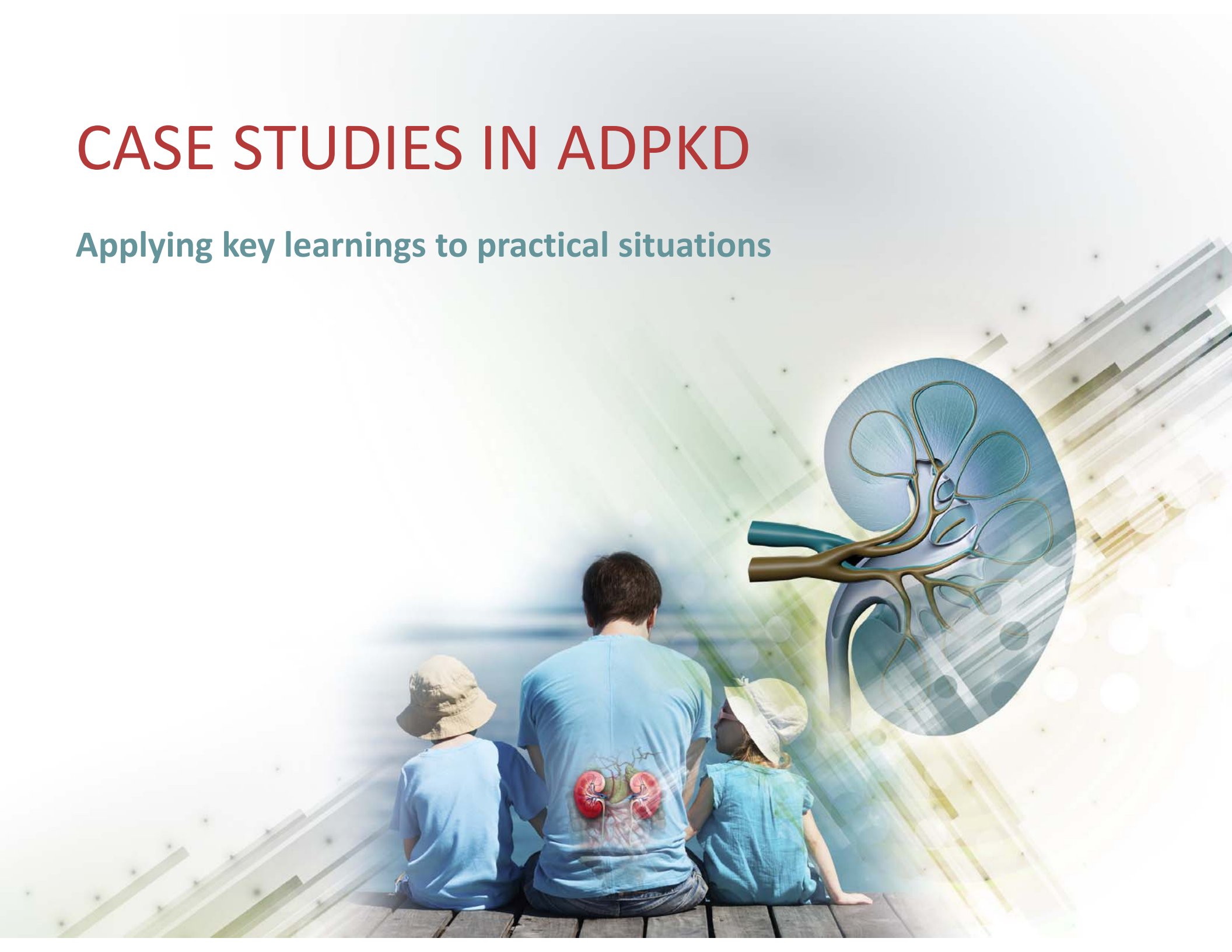
Other variables:

- Patient characteristics
- Disease history and baseline disease status
- Physical examination
- Clinical variables (*e.g.*, markers of renal and liver function)
- Healthcare utilization
- **Patient-reported outcomes**



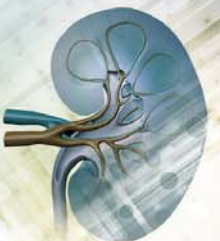
CASE STUDIES IN ADPKD

Applying key learnings to practical situations



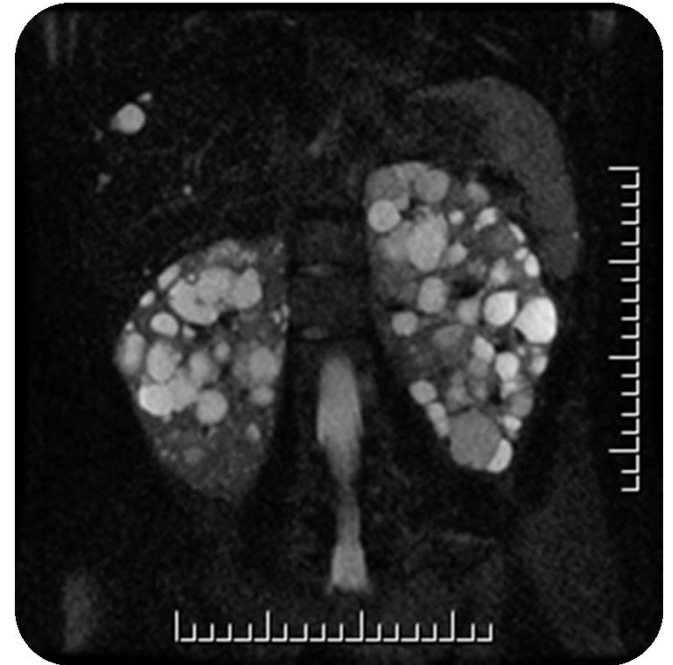
Case 1: Presentation and Overview

- 30-year-old man presenting for nephrology care
- Known to have PKD for more than 10 years, diagnosed by cysts on ultrasound
- Father had PKD, died in a car accident at age 45. Had not reached ESRD. Two unaffected siblings
- Two prior episodes of kidney stones, last about one year ago



Case 1: Physical Examination & Investigations

- Physical exam
 - Palpable kidneys
 - BP 144/92 mmHg average of 5 readings using an unattended automated device
 - Otherwise unremarkable
- Labs
 - Creatinine 92 $\mu\text{mol/L}$, normal electrolytes
 - Remainder of labs are unremarkable
- Imaging
 - MRI shows typical ADPKD distribution
 - Estimated TKV is 1L, height-adjusted TKV: 561.8 mL/m



Case 1: Continued

- Patient is anxious to do "whatever is necessary" to protect his kidneys
- No medications other than amLodipine
- Not following any special diet



Case 1: Discussion questions

- Would you track TKV? If so, how often and by which modality?
- What are some therapeutic options?
 - What pros and cons of the treatments you have recommended would you discuss?
 - How would you monitor the efficacy and safety of your recommended treatments?
- He wants to know how much longer his kidneys will last.
What do you tell him?
- What is your recommended blood pressure target? How would you manage his blood pressure?
- Should he be screened for intracranial aneurysms?
- What will be your follow-up schedule?
- He is recently married and is debating about whether to have children.
What advice or information would you give?



Case 2: Presentation and Overview

- 30-year-old woman presenting for nephrology care
- Grandmother died on dialysis (started on dialysis at age 72)
- Father is 54 and has PKD. He told her his "kidneys are still good" recently
- Asymptomatic and otherwise healthy
- No adverse events related to PKD to date



Case 2: Physical Examination and Investigations

- Physical examination
 - Cannot palpate kidneys
 - BP 129/77 average of 5 readings using an unattended automated device
 - Otherwise unremarkable
- Labs
 - Creatinine 56, normal electrolytes
 - Remainder of labs are unremarkable
- Imaging
 - TKV by MRI recently estimated at 350 mL; htTKV: 218.8 mL/m



Case 2: Continued

- She is very anxious
- She put off getting screened for PKD until recently
- She doesn't like the idea of having to take medications.
- Currently on no medications
- Vegetarian, not following any medically prescribed diet



Case 2: Discussion Questions

- Would you provide treatment for this patient? Why or why not?
- What are some therapeutic options?
 - What pros and cons of the treatments you have recommended would you discuss?
 - How would you monitor the efficacy and safety of your recommended treatments?
- She wants to know how much longer her kidneys will last. What do you tell her?
- Would you do genetic testing to determine the exact mutation that she carries?



Case 3: Presentation and Overview

- 26-year-old female presenting for nephrology care
 - No children
- Referred with suspected ADPKD following ultrasound ordered by family doctor to investigate lower back pain
- No known family history of PKD
- History of borderline hypertension x 8 years, no current pharmacotherapy
- Otherwise healthy



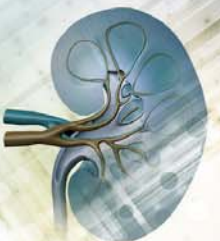
Case 3: Physical Examination and Investigations

- Physical exam
 - Cannot palpate kidneys
 - BP 150/96 mmHg (average of multiple automated office readings)
 - Otherwise unremarkable
- Labs
 - Microalbuminuria: 150 $\mu\text{mol/L}$
 - Serum creatinine: 100 $\mu\text{mol/L}$
 - Remainder of labs are unremarkable
- Imaging: MRI is obtained
 - TKV calculated to be 710 mL: htTKV: 458.1 mL/m



Case 3: Continued

- Patient is concerned not only about her own health, but that of her sibling (21-year-old brother) and parents
- No current medications



Case 3: Discussion Questions

- Does this patient have ADPKD? What else could it be?
 - What type of confirmatory testing might you order?
 - What other potential diagnoses would you consider?
- If the patient was planning to become pregnant, what types of discussions would you need to have, what adjustments would you make to medications, what impact on her health?
- She wants to know how much longer her kidneys will last. What do you tell her?



Case 3: Discussion Questions, Cont'd

- What are the therapeutic options for this patient?
 - What pros and cons of the treatments you have recommended would you discuss?
 - How would you monitor the efficacy and safety of your recommended treatments?
- What will be your follow-up schedule?
- If you chose not to prescribe tolvaptan for this patient, what might be your criteria for recommending it later on for this patient?



APPENDIX

Possible tool for estimating risk of progression /
selection of patients for clinical trials



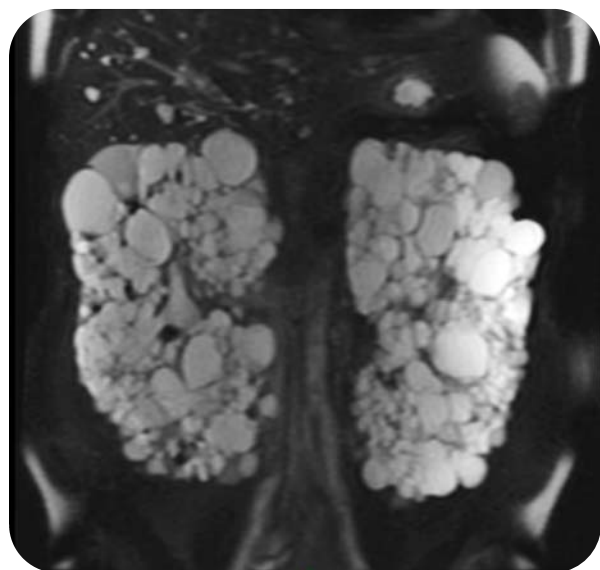
Identifying Individuals at Risk for Progression

- **Objective:** To validate a practical classification of ADPKD as a rapid and reliable tool to select patients who are appropriate for clinical trials or likely to benefit from an effective therapy
- **Subjects:**
 - 590 patients with ADPKD from the Mayo Clinic Translational PKD Center
 - 177 patients from the CRISP study cohort
 - All had computed tomography (CT) or magnetic resonance images (MRI) and three or more eGFR measurements over ≥ 6 months



Classification of ADPKD Based on Imaging Characteristics

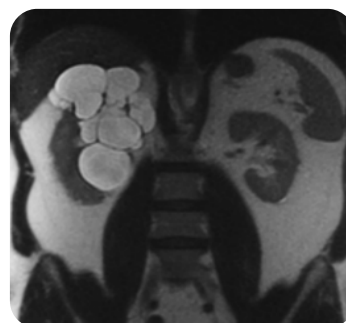
Examples of Atypical presentations



Typical: bilateral,
diffuse distribution



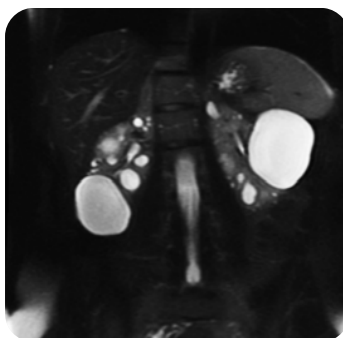
Unilateral



Segmental



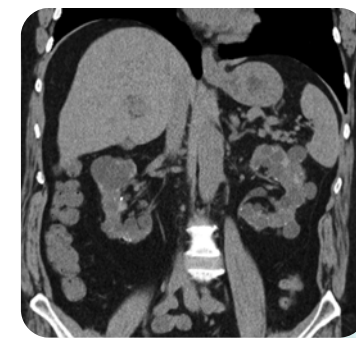
Asymmetric



Lopsided



Bilateral with
unilateral atrophy

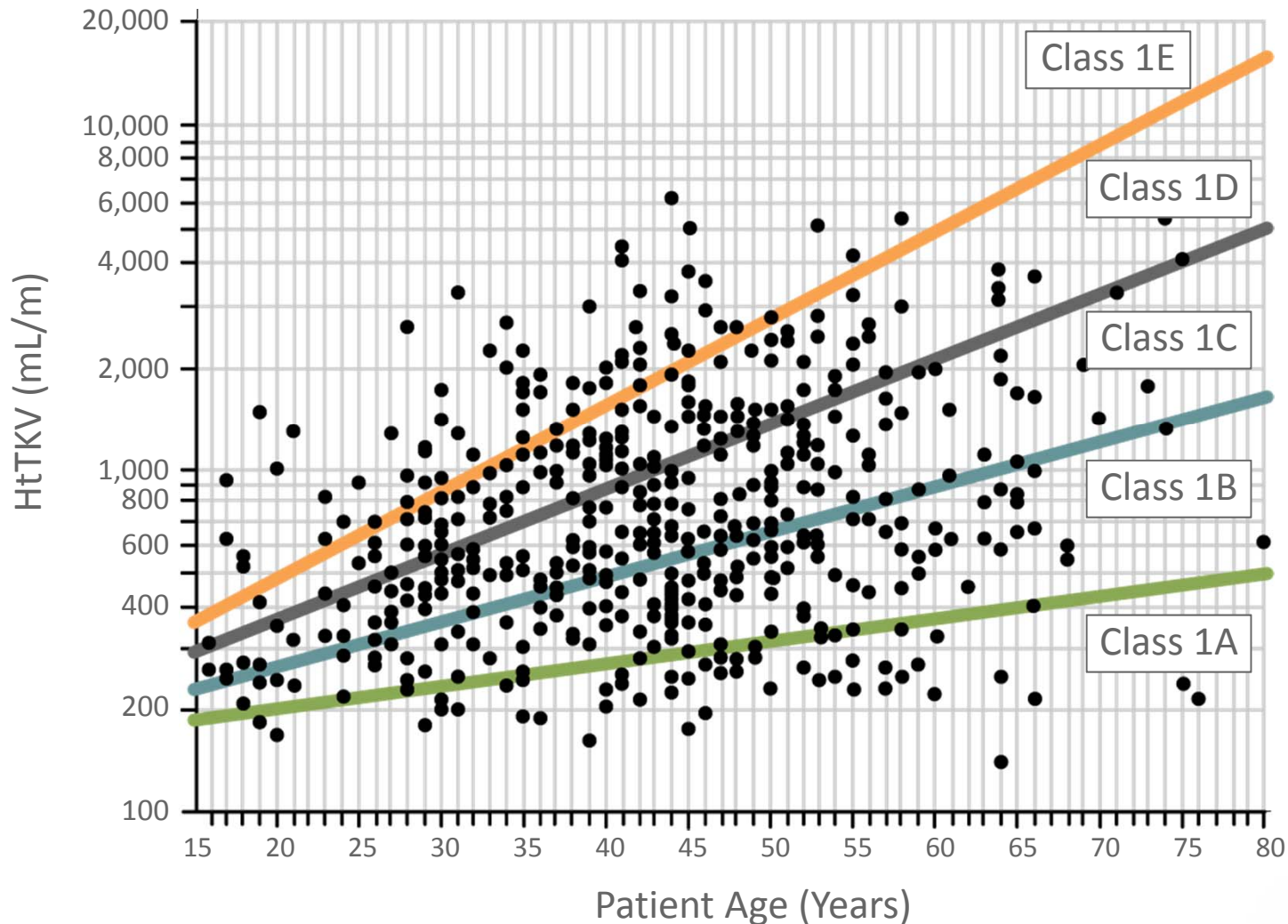


Bilateral with
bilateral atrophy

Risk classification by TKV is only applicable to typical ADPKD



Imaging-based System for Typical ADPKD: Subclassification by Height-adjusted TKV and Age



1 Kidney Volume Calculator based on Ellipsoid equation ($\pi/6 \times L \times W \times D$) from MRI or CT image					
Required Data Entry					
Right Kidney			Left Kidney		
Sagittal Length (mm)	<input type="text"/>	Sagittal Length (mm)	<input type="text"/>		
Coronal Length (mm)	<input type="text"/>	Coronal Length (mm)	<input type="text"/>		
Width (mm)	<input type="text"/>	Width (mm)	<input type="text"/>		
Depth (mm)	<input type="text"/>	Depth (mm)	<input type="text"/>		
Calculated Results					
Right Kidney Volume (mL)	<input type="text"/>	Left Kidney Volume (mL)	<input type="text"/>		
		Total Kidney Volume (mL)	<input type="text"/>		

2 ADPKD Classification using Kidney Volume Calculator			
Required Data Entry		Calculated Results	
Patient Height (m)	<input type="text"/>	Height Adjusted TKV (mL/m)	<input type="text"/>
Patient Age (years)	<input type="text"/>	ADPKD Classification	<input type="text"/>

3 ADPKD Classification if Kidney Volume previously calculated by Stereology			
Required Data Entry		Calculated Results	
Kidney Volume (mL)	<input type="text"/>	Height Adjusted TKV (mL/m)	<input type="text"/>
Patient Height (m)	<input type="text"/>	ADPKD Classification	<input type="text"/>
Patient Age (years)	<input type="text"/>		

Automated Calculator to Classify ADPKD Risk

- Kidney volume is predicted based on 4 measurements from CT or MRI (for typical ADPKD)
 - Or can be entered if previously calculated by stereology
- Other variables:
 - Height
 - Age
- Classified as stage A to E, with increasing risk of progression

[Click here to link to web-based calculator](#)



Disease Progression Based on Imaging-based Classification in Typical ADPKD (Class 1)

