A globe made of puzzle pieces with the KDIGO logo in the center, resting on a stethoscope. The logo features a green globe with the text 'KIDNEY DISEASE' at the top, 'KDIGO' in large blue letters in the center, and 'IMPROVING GLOBAL OUTCOMES' at the bottom. The background is a blurred medical setting with a stethoscope and a computer monitor.

# **KDIGO ADPKD Controversy Conference Report**

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# C.O.I

- Honorarium for lecture
  - Otsuka Pharm, Kyowahakko-Kirin Pharm, Chugai Pharm, Dainippon-Sumitomo Pharm, Bayer Japan

# Burden of Illness Associated with ADPKD

12.5 million ADPKD patients world-wide were born with:

- 50% risk for ESRD by age 55 years of age (*PKD1 trunc. mut.*)
- 80% risk of hypertension
- 60% risk for painful kidney complications
- 20% risk for symptomatic PLD (if female)
- 3% risk for ICA rupture
- Variably increased risk for cardiovascular and cerebrovascular disease, gastrointestinal disorders, hernias, neurologic and other disorders

# Scope of KDIGO ADPKD Controversy Conference 2014

- There have been many recent advances in the understanding of its molecular genetics and biology, and in the diagnosis and management of its manifestations.
- Yet, diagnosis, evaluation, prevention, and treatment vary widely and there are no broadly accepted practice guidelines.
- Barriers to translation of basic science breakthroughs to clinical care exist, with considerable heterogeneity across countries.

# #1 Diagnosis

- Presymptomatic screening of ADPKD is not currently recommended for at-risk children.
- For at-risk adults the potential benefits of presymptomatic diagnosis usually outweigh the risks, and it is most commonly performed by ultrasonography (US), which is inexpensive and widely available.

# #1 Diagnosis

- Conventional US is suboptimal for disease exclusion in subjects at-risk for ADPKD who are younger than 40 years, often evaluated as potential living kidney donors. In this setting, the finding of fewer than five renal cysts by magnetic resonance imaging (MRI) is sufficient for disease exclusion.
- A positive family history is absent in 10–15% of patients with ADPKD because of de novo mutations, mosaicism, mild disease from PKD2, and non-truncating PKD1 mutations, or because of unavailability of parental medical records.<sup>1</sup>

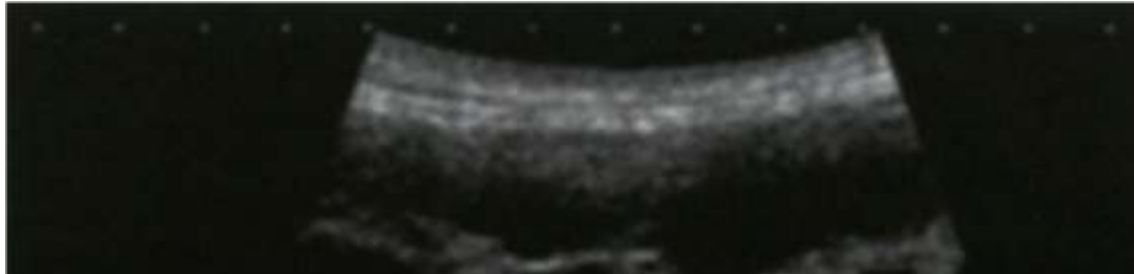


# Differential diagnosis of other renal cystic diseases

| Disorder  | Inheritance | Family history                                    | Clinical features  |
|---|-------------|---|--|
| Autosomal-recessive polycystic kidney disease                       | AR          | Siblings (25%)                                    | ~1 in 20,000. Neonatal deaths in 30%; Potter's phenotype; biliary dysgenesis (congenital hepatic fibrosis, intrahepatic bile duct dilatation), resulting in portal hypertension and cholangitis.   |
| Renal cysts and diabetes syndrome (RCAD/MODY5/HNF-1B <sup>a</sup> ) | AD          | <i>De novo</i> mutations (often deletions) in 50% | Renal cysts or malformation in 90%, diabetes mellitus in 45%, hypomagnesemia in 40%, genital tract abnormalities in 20%, hyperuricemia in 20%, elevated liver enzymes in 15%.  |
| Tuberous sclerosis complex  | AD          | Absent in two thirds of families                  | ~1 in 10,000 live births. Skin lesions (facial angiofibromas, periungual fibroma, hypomelanotic macules, shagreen patch), >90%; cerebral pathology (cortical tuber, subependymal giant cell astrocytoma), 90%; renal (polycystic kidneys, angiomyolipoma), 50–70%; retinal hamartomas, 50%; lymphangioliomyomatosis. |
| PKD1-TSC contiguous gene syndrome                                   | AD          | Spontaneous presentation frequent                 | Presentation of severe ADPKD at an early age, with polycystic kidneys with renal angiomyolipomas frequently present after the first year of age.   |
| von Hippel-Lindau disease   | AD          | <i>De novo</i> mutations in 20%                   | ~1 in 36,000. Cerebellar and spinal hemangioblastoma; retinal angiomas; serous cystadenomas and neuroendocrine tumors of pancreas; pheochromocytoma; renal cell carcinoma.   |
| Medullary cystic kidney disease <sup>b</sup>                        | AD          | Rare  | Slowly progressive kidney disease; medullary cysts (but uncommon in families with type 2 MCKD (now known as ADTKD-UMOD)); hyperuricemia and gout in type 2 MCKD (now known as ADTKD-UMOD); small- to normal-sized kidneys.   |
| Medullary sponge kidney   | Unclear     | Familial clustering reported                      | ~1 in 5000. Medullary nephrocalcinosis; kidney stones; 'brush' or linear striations on intravenous pyelogram.  |
| Simple renal cysts  | Acquired    | None  | Common; increase in number and size with age; normal renal function; normal-sized kidneys.   |
| Acquired cystic kidney disease                                      | Acquired    | None  | Common in patients with chronic renal failure or ESRD; multiple cysts associated with normal- or small-sized kidneys.  |

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# Performance of ultrasound-based unified criteria for diagnosis or exclusion of ADPKD



| Age (years)                    | PKD1   | PKD2                      | Unknown gene type         |
|--------------------------------|--|---------------------------|---------------------------|
| <i>Diagnostic confirmation</i> |  |                           |                           |
| 15–29                          | A total of $\geq 3$ cysts <sup>a</sup> : PPV = 100%; SEN = 94.3% | PPV = 100%; SEN = 69.5%   | PPV = 100%; SEN = 81.7%   |
| 30–39                          | A total of $\geq 3$ cysts <sup>a</sup> : PPV = 100%; SEN = 96.6% | PPV = 100%; SEN = 94.9%   | PPV = 100%; SEN = 95.5%   |
| 40–59                          | $\geq 2$ cysts in each kidney: PPV = 100%; SEN = 92.6%           | PPV = 100%; SEN = 88.8%   | PPV = 100%; SEN = 90%     |
| <i>Disease exclusion</i>       |  |                           |                           |
| 15–29                          | No renal cyst: NPV = 99.1%; SPEC = 97.6%                         | NPV = 83.5%; SPEC = 96.6% | NPV = 90.8%; SPEC = 97.1% |
| 30–39                          | No renal cyst: NPV = 100%; SPEC = 96%                            | NPV = 96.8%; SPEC = 93.8% | NPV = 98.3%; SPEC = 94.8% |
| 40–59                          | No renal cyst: NPV = 100%; SPEC = 93.9%                          | NPV = 100%; SPEC = 93.7%  | NPV = 100%; SPEC = 93.9%  |

Abbreviations: ADPKD, autosomal-dominant polycystic kidney disease; NPV, negative predictive value; PPV, positive predictive value; SEN, sensitivity; SPEC, specificity.

<sup>a</sup>Unilateral or bilateral.

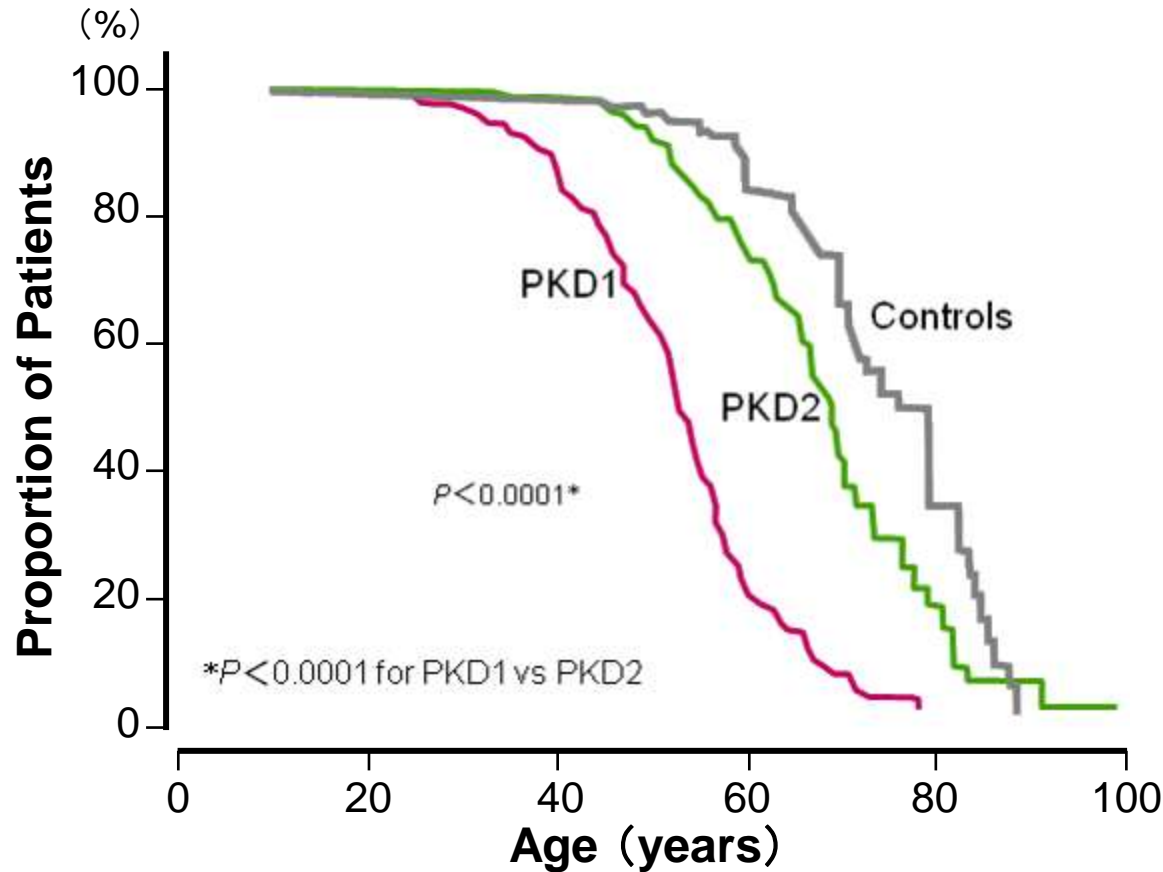


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# Patients in *PKD1* mutation developed ESRD faster than those in *PKD2* mutation

Cumulative probabilities of survival to ESRD or death



Controls were unaffected family members.  
UTI=urinary tract infection.

- Median age of uremic death or ESRD was 53 y/o in *PKD1* and 69 y/o in *PKD2*
- *PKD2* had lower risk of hypertension, UTI or macroscopic hematuria than *PKD1*

# Gene-based diagnostics for ADPKD

- Genetic testing may be helpful when imaging results are equivocal and firm diagnosis required
  - Living related donors
    - Confirming negative diagnosis in young potential donor when imaging results may be unreliable!
    - Clarifying the diagnosis in a potential donor when 1 or 2 cysts detected by imaging !
- Individuals with a negative family history and/or an unusual disease presentation: to clarify the diagnosis
  - Early onset ADPKD
  - Mild PKD
  - Atypical radiological presentation
- Once therapies available: testing of young patients to obtain a firm diagnosis before starting treatment

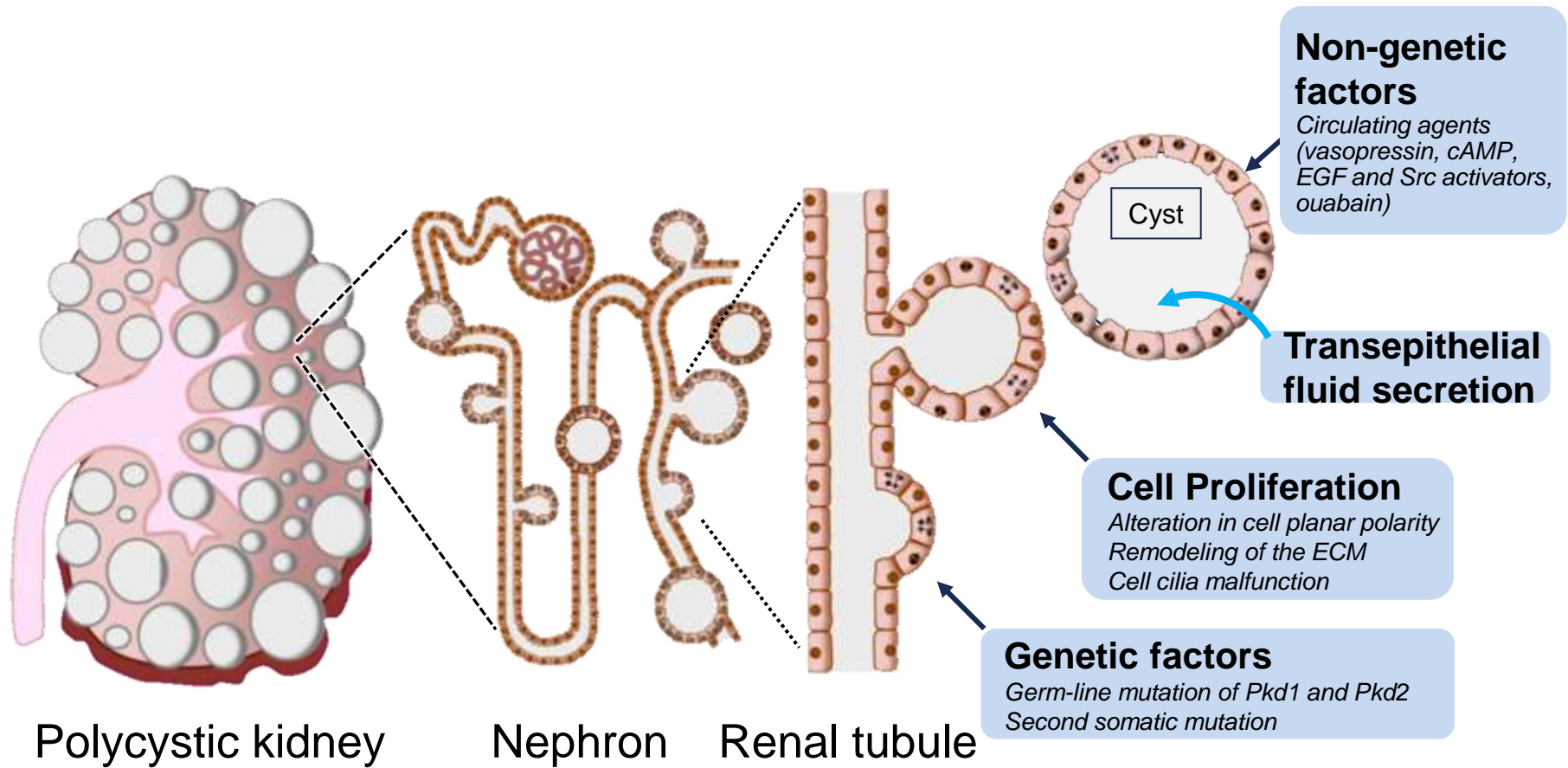
# Gene-based diagnostics for ADPKD

- Linkage-based diagnosis of ADPKD using polymorphic markers flanking the two disease genes, which requires multiple affected family members and can be confounded by de novo mutations, mosaicism, and bilineal disease is now rarely performed.
- Presently, direct mutation screening by Sanger sequencing of the PKD1 and PKD2 genes is the method of choice for molecular diagnosis of ADPKD. However, mutation screening for PKD1 is technically challenging, labor intensive, and costly because of its large size and complexity (i.e., duplication of its first 33 exons in 6 pseudogenes with high DNA sequence identity).
- In sequencing-negative cases, multiplex ligation–dependent probe amplification can be used as a follow-up test to detect large gene rearrangements in <5% of cases.

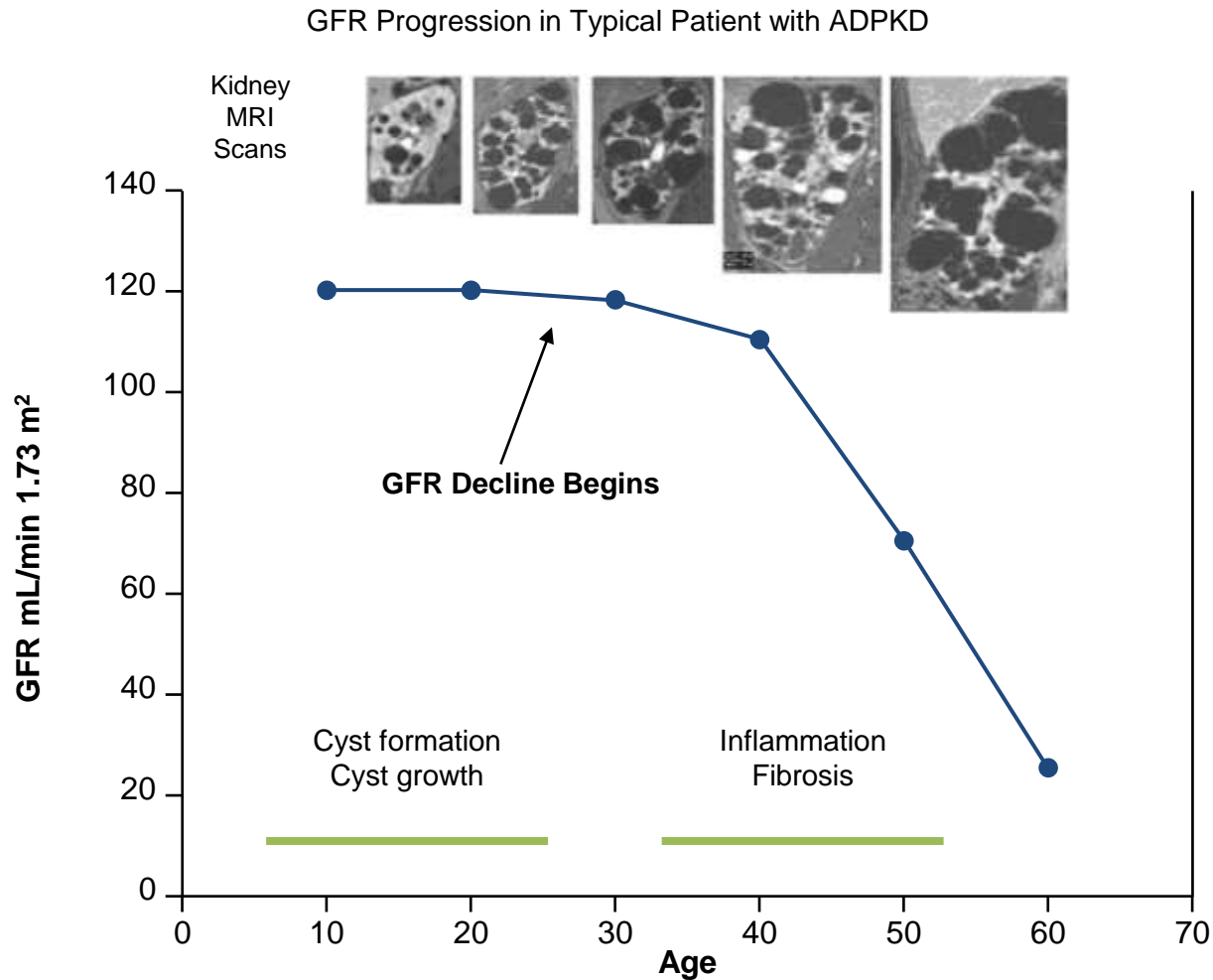
# #2 MONITORING KIDNEY DISEASE PROGRESSION IN ADPKD

- Kidney function may remain normal for several decades and is therefore not informative. By contrast, total kidney volume (TKV) in relation to age can identify patients with progressive disease. TKV is an accurate estimate of kidney cyst burden and associates with pain, hypertension, gross hematuria, proteinuria or albuminuria, and loss of kidney function.
- TKV increases exponentially in virtually every ADPKD patient, with an average of 5–6% per year in adults.
- Elevated TKV, particularly when used together with age and kidney function, identifies individuals who are at-risk for progression to ESRD.

# Evolution of ADPKD cysts from epithelial cells of renal tubules



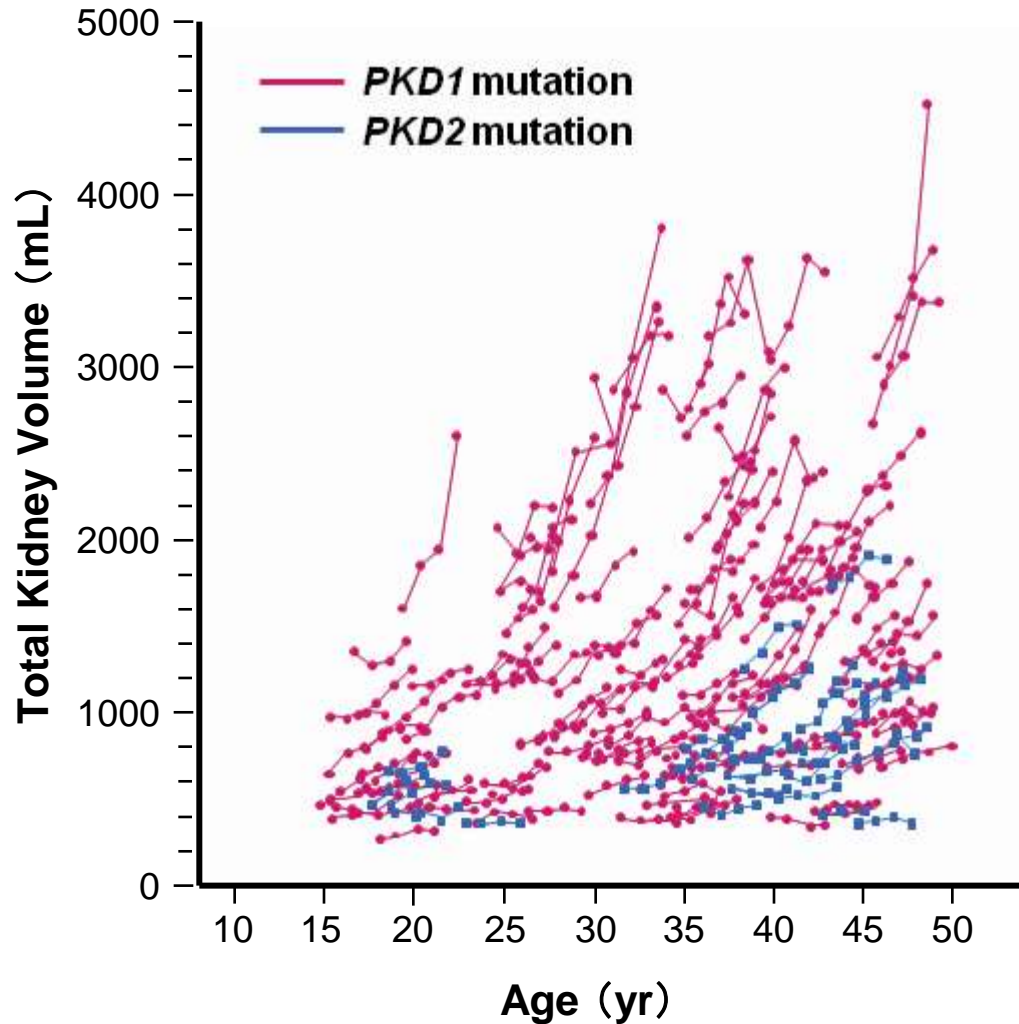
# Decline of glomerular filtration rate (GFR) in autosomal dominant polycystic kidney disease (ADPKD)





# Age dependent increase in TKV

from CRISP Study

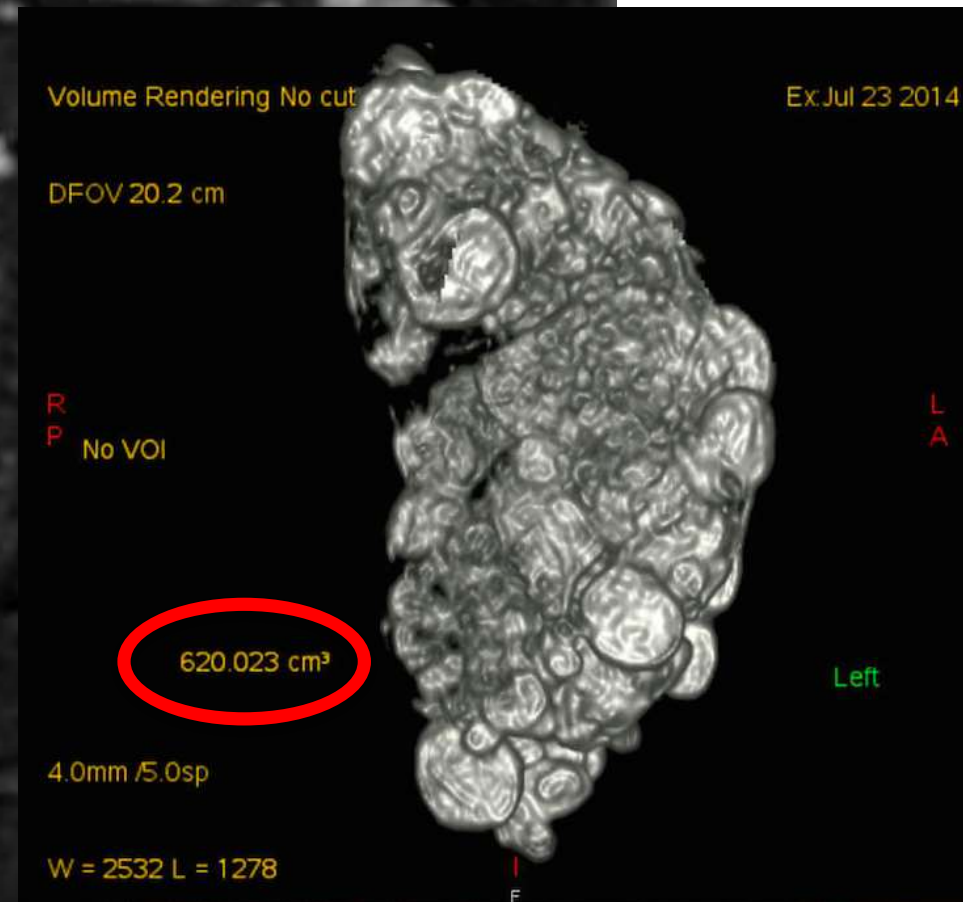
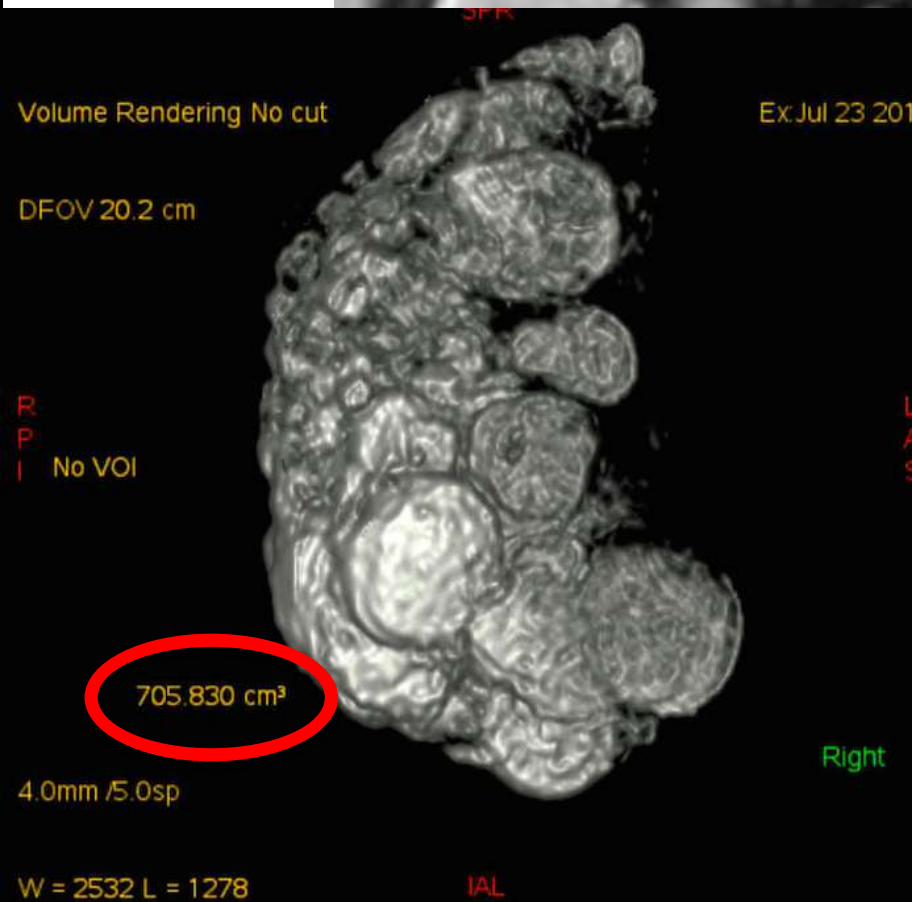


- *Both baseline TKV and kidney expansion speed was larger in PKD1 than PKD2.*

# Importance in measuring TKV

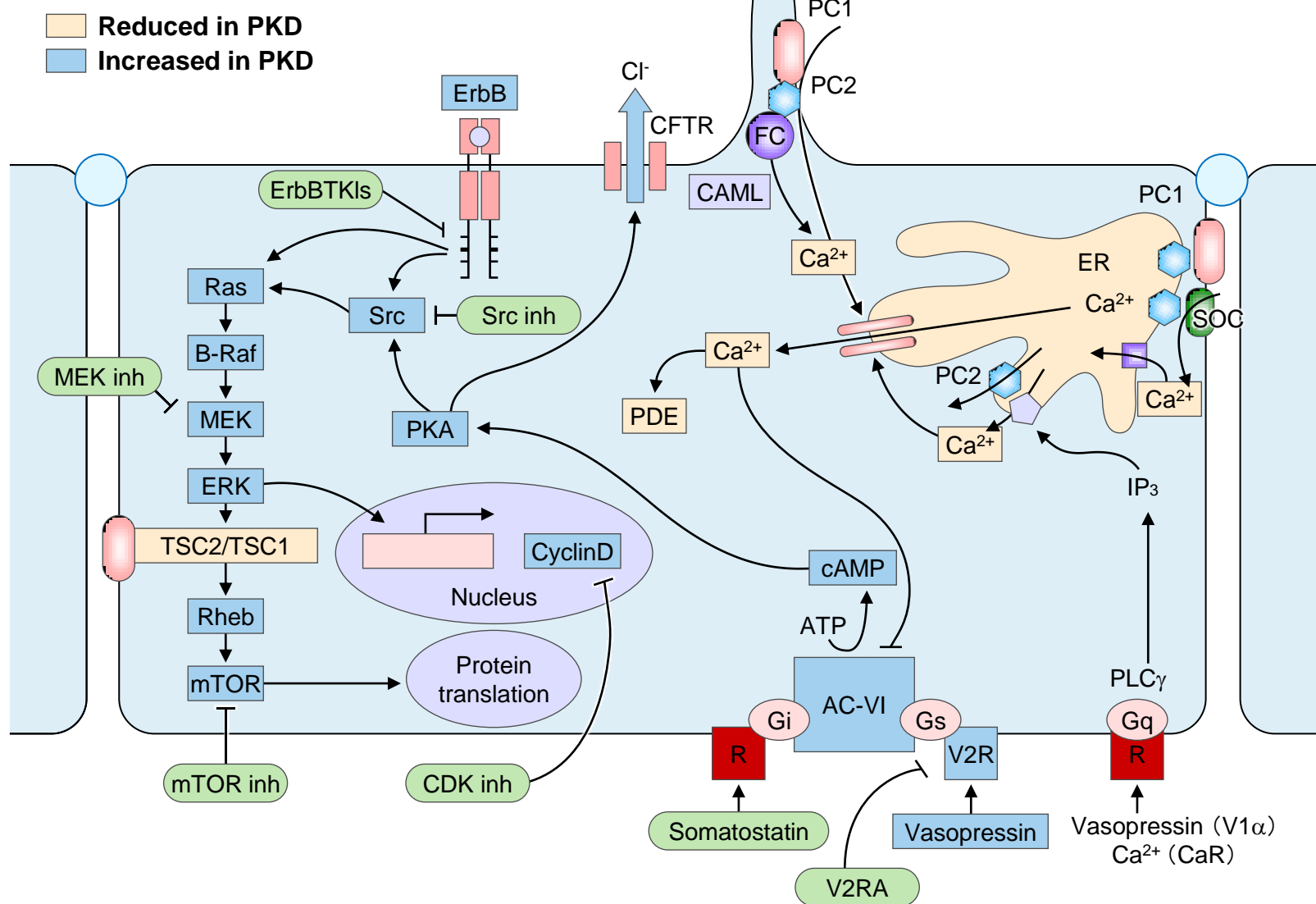
- Imaging of the kidneys (preferably by CT or MRI) should be part of the initial evaluation in ADPKD patients. Radiology reports should be standardized and should include maximum kidney length, width and depth measurements, and an estimate of TKV.
- In investigating the effect of disease-modifying therapies such as Torvaptan and lifestyle modifications, repeated imaging is an important management tool.

# Measuring TKV by MRI



# #3 Therapy targets of ADPKD

-hypothetical pathways in up and down-regulated

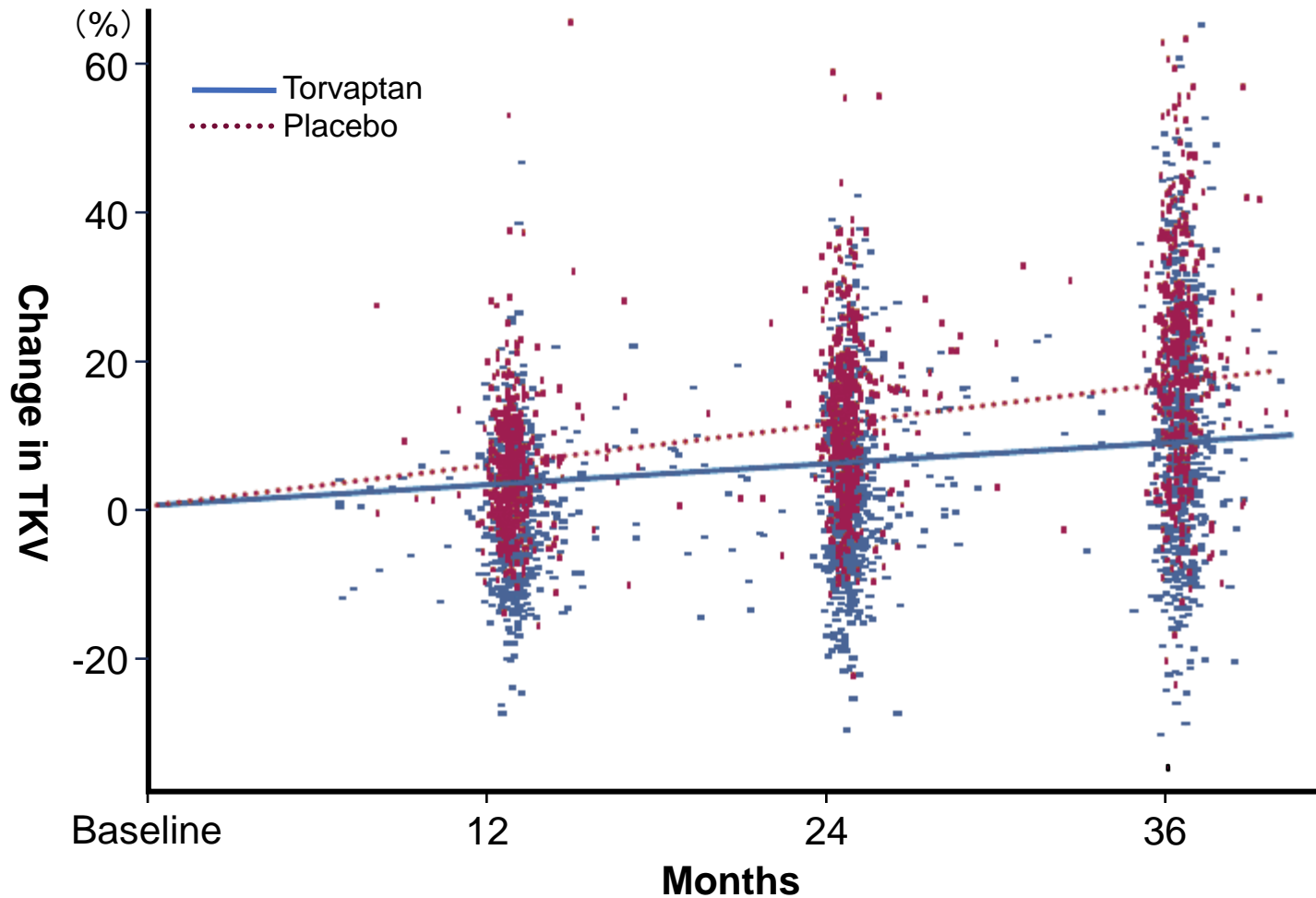


# Main therapeutic trials in PKD, published or in progress

(listed in ClinicalTrials for trials in progress)

| Published Trials                     |  |                             |                                 |                                    |  |   |   |                              |
|--------------------------------------|--|-----------------------------|---------------------------------|------------------------------------|--|---|---|------------------------------|
| Study/<br>molecule<br>name           | Study type   | Study location              | Treatment<br>length<br>(months) | Number of<br>patients <sup>a</sup> | Inclusion criteria   | Outcome<br>measure(s) <sup>b</sup>            | Results   | NCT (clinicaltrials.<br>gov) |
| <b>Sirolimus</b>                     | Single center,<br>randomized,<br>controlled, open<br>label | Switzerland,<br>Zürich,     | 18                              | 100<br>(1 to 1)                    | 18-40 years<br>GFR (CG) >70 mL/min   | Change in TKV<br>Decline in GFR<br>(MDRD)     | TKV and GFR: no<br>difference   | NCT00346918                  |
| <b>Everolimus</b>                    | Multicenter,<br>randomized,<br>controlled,<br>double-blind | Germany,<br>Austria, France | 24                              | 431<br>(1 to 1)                    | > 18 years<br>GFR (MDRD) 30-89<br>mL/min or GFR >90<br>mL/min and single<br>kidney volume estimate<br>>1 L | Change in TKV<br>Decline in GFR               | TKV: less change at one<br>year, but same at two<br>years<br>GFR: same as placebo   | NCT00414440                  |
| <b>Octreotide</b>                    | Single center,<br>randomized                               | United States               | 12                              | 34 (2 to 1)                        | >18 years<br>TKV >4000 mL  | LV and TKV<br>modification<br>Decline in GFR  | LV reduction and TKV<br>stabilization at one<br>year                                | NCT00426153                  |
| <b>ALADIN:<br/>Somatostat<br/>in</b> | Multicenter,<br>randomized,<br>controlled,<br>single-blind | Italy                       | 36                              | 75 (1 to 1)                        | 18-75 years<br>GFR (MDRD)>40<br>mL/min   | Change in TKV<br>GFR measured with<br>Iohexol | TKV: less change at one<br>year, but no significant<br>difference at three<br>years | NCT00309283                  |
| <b>TEMPO 3/4:<br/>Tolvaptan</b>      | Multicenter,<br>randomized,<br>controlled,<br>double-blind | International               | 36                              | 1445<br>(2 to 1)                   | 18-50 years<br>GFR (CG) >60 mL/min<br>TKV >750 mL  | Change in TKV<br>Decline in GFR<br>Pain       | 50% reduction of<br>change in TKV/year<br>GFR: benefit 1<br>mL/min/y                | NCT00428948                  |

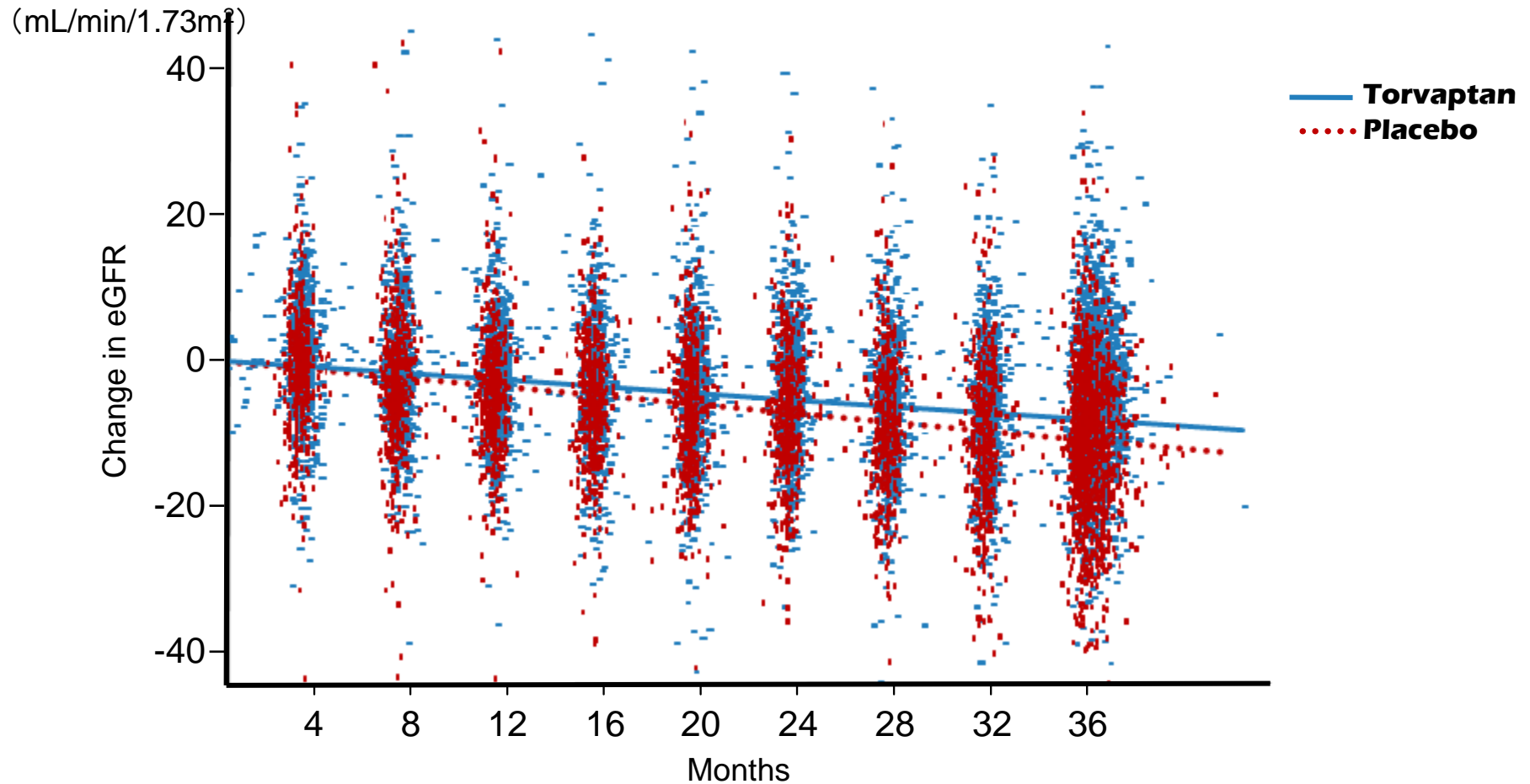
# Effect of Tolvaptan on the Annual Slopes of Total Kidney.



The ratio of the geometric mean was 0.97 (95% CI, 0.97 to 0.98;  
P<0.001)

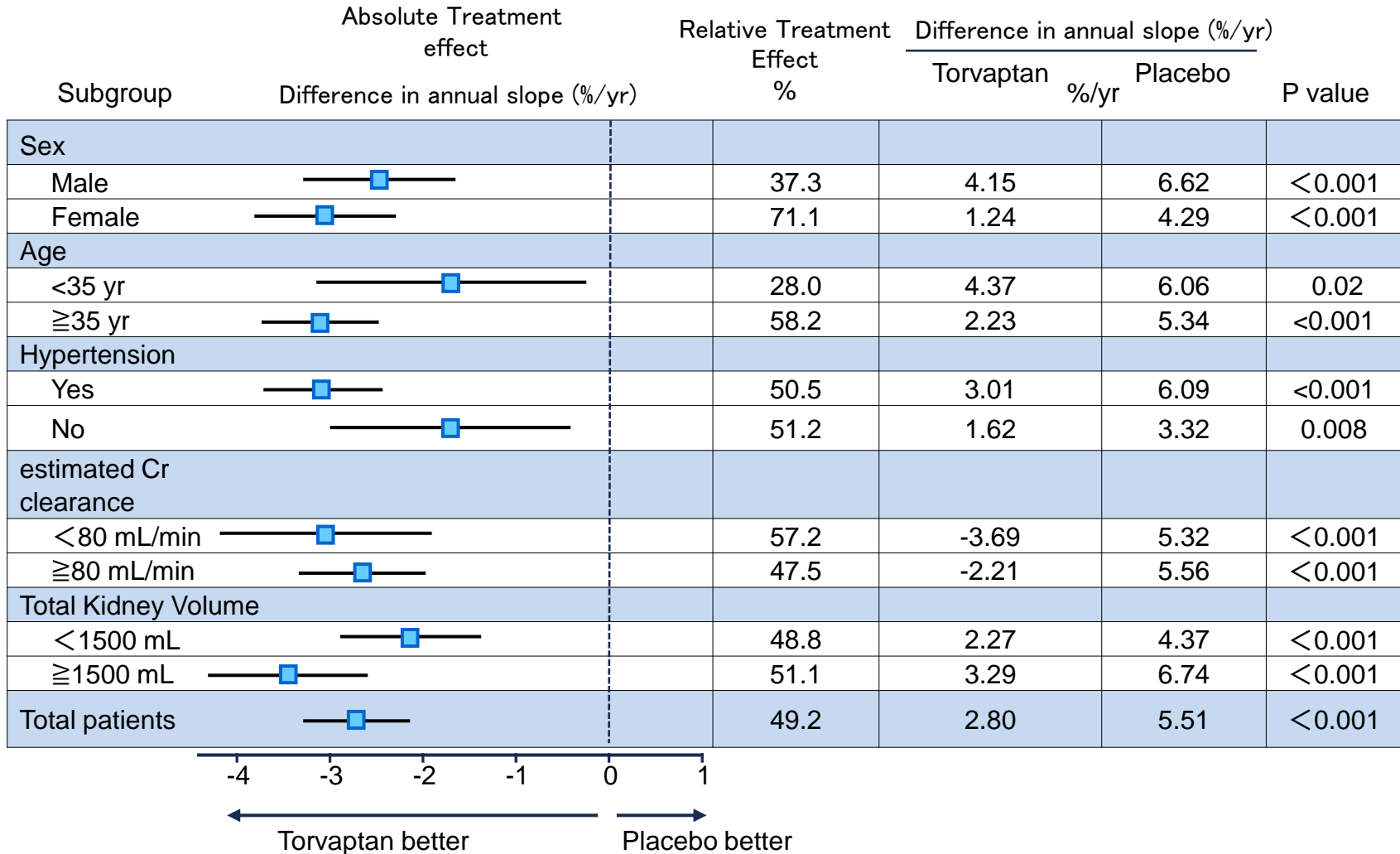


# Effect of Tolvaptan on the Annual Slopes of Total Kidney Function.



The annual difference in slope was 1.202 (mg per milli- liter)<sup>-1</sup> per year (95% CI, 0.62 to 1.78; P<0.001)

# Treatment Effect of Total Kidney Volume

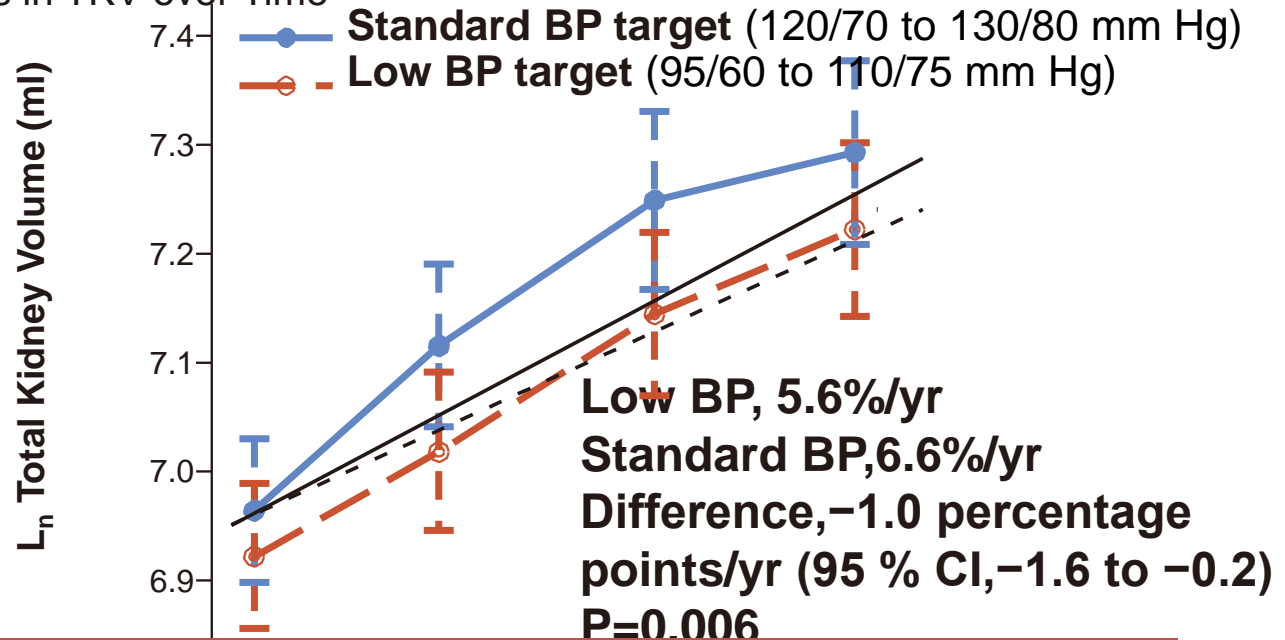


## #4 MANAGEMENT OF HYPERTENSION, RENAL FUNCTION DECLINE, AND RENAL COMPLICATIONS

- Patients with ADPKD are at increased risk for hypertension and cardiovascular events when compared with the general population.
- Data supporting disease-specific blood-pressure (BP) targets are limited. The general advice of the 2012 KDIGO CPG for the Management of BP in CKD can therefore be followed, suggesting a BP target  $\leq 140/90$  mm Hg.
- Agents that interfere with the renin-angiotensin-aldosterone system (RAAS) are first-line BP-lowering agents in combination with a sodium-restricted diet.

# Changes in TKV and eGFR during Follow-up and Subgroup Analyses, According to Blood-Pressure Group.

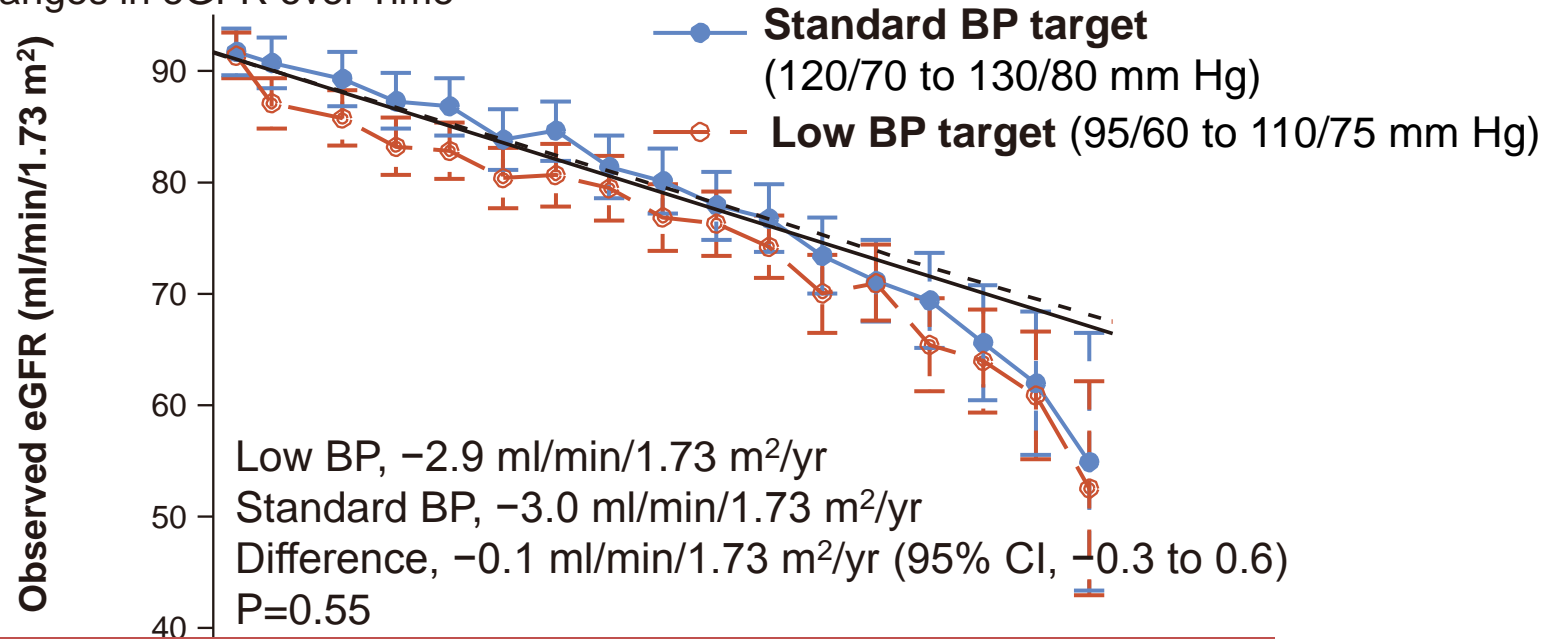
A. Changes in TKV over Time



This study showed that lowering blood pressure to levels below those recommended by current guidelines in young patients with good kidney function reduced the rate of increase in kidney volume by 14%, the increase in renal vascular resistance, urine albumin excretion, left ventricular mass index, and marginally (after the first 4 months of treatment) the rate of decline in eGFR.

# Changes in TKV and eGFR during Follow-up and Subgroup Analyses, According to Blood-Pressure Group.

B. Changes in eGFR over Time



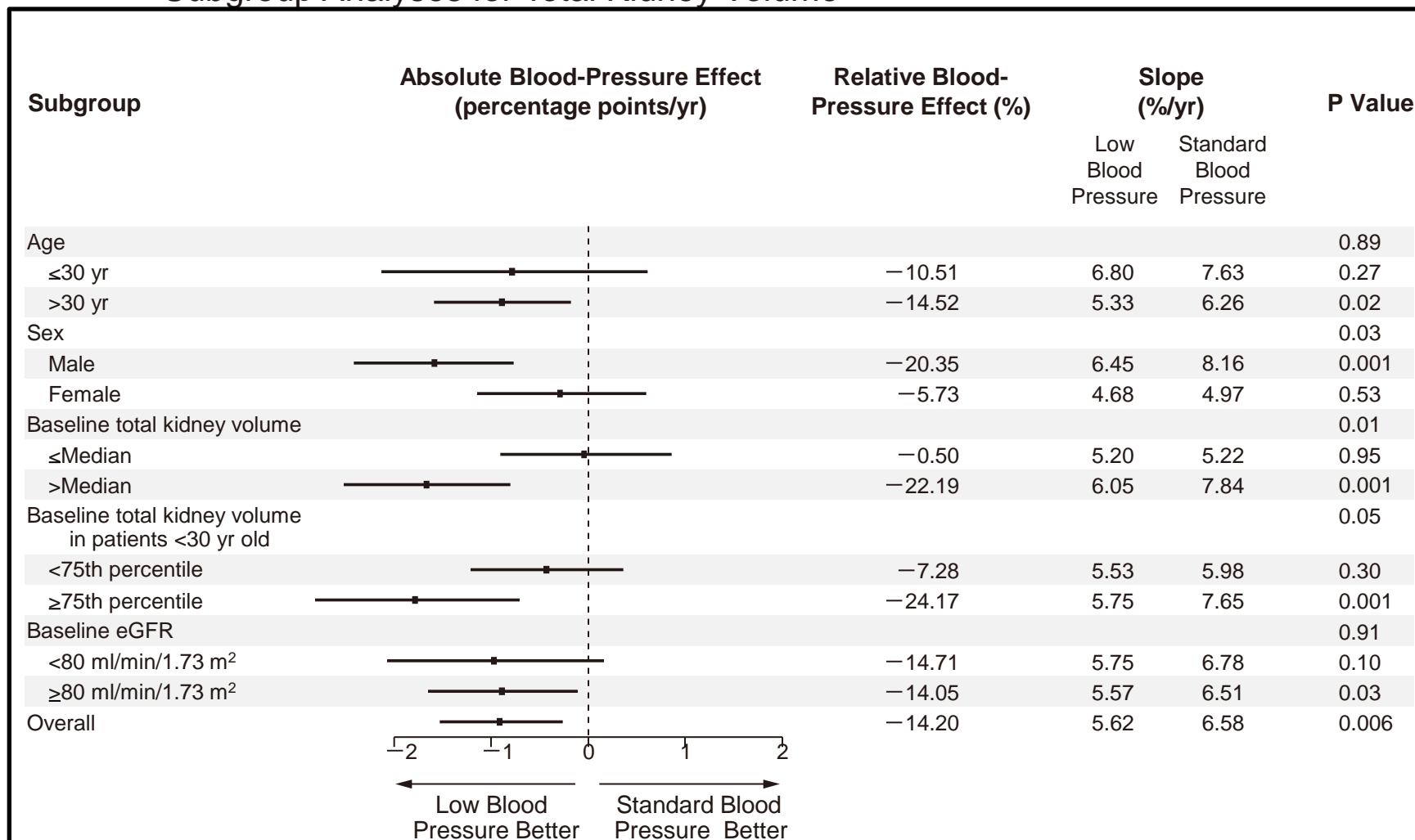
The overall effect of low blood pressure on eGFR, however, was not statistically significant, possibly because the reduction of blood pressure to low levels was associated with an acute reduction in eGFR within the first 4 months of treatment.

No. of  
Patients  
Standard  
blood  
pressure  
Low blood  
pressure

274 243 239 224 217 202 137 81 9

# Changes in Total Kidney Volume and Estimated Glomerular Filtration Rate (eGFR) during Follow-up and Subgroup Analyses, According to Blood-Pressure Group.

## C Subgroup Analyses for Total Kidney Volume





# #5 Other renal manifestations

- Hematuria and cyst hemorrhage
  - Episodes of cyst hemorrhage or gross hematuria are usually self-limited and resolve within 2–7 days. If symptoms persist, a possible neoplasm should be excluded.
  - Temporary discontinuation of RAAS inhibitors and diuretics to avoid acute kidney injury during an episode of acute cyst hemorrhage has been suggested.

# #5 Other renal manifestations

- Nephrolithiasis
  - Nephrolithiasis and cyst wall calcifications are common in ADPKD, favored by urinary stasis and metabolic factors (reduced urine pH, ammonium excretion, and urinary citrate).
  - Potassium citrate is the treatment of choice in the three stone-forming conditions associated with ADPKD: uric acid nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects.
  - Extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy can be used in most patients with ADPKD without increased complications compared with patients without ADPKD.
  - Flexible ureterorenoscopy with laser fragmentation has also been used safely and effectively with less risk for traumatic nephron loss.

# #5 Other renal manifestations

- Management of renal cyst infection
  - The presence of fever, abdominal pain, and high sedimentation rate or level of C-reactive protein should raise the suspicion of a cyst infection, but the differential diagnosis is broad.
  - Blood and urine cultures may be negative.
  - 18 F-fluorodeoxyglucose- positron emission tomography may be helpful in identifying infected cysts.
  - Lipid-permeable anti-microbial agents such as fluoroquinolones and trimethoprim-sulfamethoxazole, depending on sensitivity (if available), remain the standard treatment for cyst infections.
  - There is wide variability in the duration of treatment and indications and timing of percutaneous or surgical draining.

# #5 Other renal manifestations

- Management of chronic pain
  - Kidney pain is the most common renal manifestation in ADPKD.
  - Diagnostic percutaneous cyst aspiration is helpful to determine whether a more permanent intervention such as cyst sclerosis or laparoscopic cyst fenestration is worth pursuing.
  - Celiac plexus blockade, radiofrequency ablation, and spinal cord stimulation have also been used.
  - Thoracoscopic sympathectomy may be helpful in some patients with disabling pain, but it is invasive and has potential complications such as pneumothorax and orthostatic hypotension.
  - Laparoscopic renal denervation has been helpful in a small series of patients. In recent times, percutaneous transluminal catheter-based denervation has also been shown to be effective in case reports and deserves further evaluation.

# #6 Reproductive issues

- All women of reproductive potential should receive counseling on potential aggravation of polycystic liver disease (PLD) with exogenous estrogen or progesterone exposure.
- In general, ADPKD women with normal BP and kidney function have a favorable course during pregnancy. Pregnancy-induced hypertension and preeclampsia occur more frequently.
- Multiple pregnancies (more than three) have been reported to be associated with a greater risk for decline in kidney function in ADPKD.
- Preemptive discontinuation of RAAS inhibitors is necessary because of the potential teratogenicity and increased risk for acute renal failure in the developing fetus.

# #7 Optimal choice of renal replacement therapy

- Transplantation is the optimal choice of renal replacement therapy in appropriate patients with ADPKD.
- Living kidney donation, ideally preemptive, is likely to be associated with best outcomes.
- The limited number of potential donors in affected families raises the question about donation priorities, requiring individual and family counseling.
- Although intra-abdominal space restrictions, increased risk for abdominal wall hernias, and increased prevalence of colonic diverticula may pose challenges, ADPKD is not a contraindication for peritoneal dialysis.

# Preparation for transplantation

- Kidneys should not be routinely removed prior to transplantation, as nephrectomy in ADPKD patients is associated with significant morbidity and mortality.
- Indications for nephrectomy include recurrent and/or severe infection, symptomatic nephrolithiasis, recurrent and/or severe bleeding, intractable pain, suspicion of renal cancer, and space restrictions prior to transplantation, taking into account that kidney size typically declines after transplantation.



# #8 MANAGEMENT OF EXTRARENAL COMPLICATIONS

- ICAs
  - ICAs occur in 9–12% of patients with ADPKD compared with 2–3% in the general population.
  - There are no clear risk factors for ICA rupture in patients with ADPKD, other than family history of rupture.
  - Mean age at rupture is lower than in the general population (41 vs. 51 years). Overall, there appears to be no difference in the rate of rupture between ADPKD and the general population.

# #9 MANAGEMENT OF EXTRARENAL COMPLICATIONS

- Individuals with small, untreated unruptured ICAs should be reevaluated every 6–24 months.
- Smoking cessation and control of cardiovascular risk factors are strongly recommended.
- Patients with a family history of ICA and a negative screening should be rescreened at 5–10-year intervals.

# #10 Polycystic Liver disease

- Liver cysts occur in >80% of adults with ADPKD.
- The cyst burden increases with age and is greater in women, especially in those with multiple pregnancies or those who have taken exogenous estrogens.
- Most patients with PLD are asymptomatic, whereas ~ 20% of them will suffer compressive symptoms including abdominal pain and distension, back pain, early satiety, and gastroesophageal reflux.
- Surgical options encompass aspiration/sclerotherapy, fenestration, partial or segmental hepatectomy, and liver transplantation.
- Somatostatin analogs were shown to reduce or stabilize liver volume in severe PLD though their use is currently restricted to either clinical trials or compassionate use.

# #11 PRACTICAL INTEGRATED PATIENT SUPPORT

- First diagnosis consultation and follow-up
- Family planning
  - Key issues include genetic counseling and preimplantation genetic diagnosis/in vitro fertilization access.
- Screening children
- Lifestyle modifications
- Exercise and sports
- Patient psychological care
  - Anxiety and depression are reported by >60% of those with ADPKD.
- Financial impacts
- Support
- PKD centers of excellence