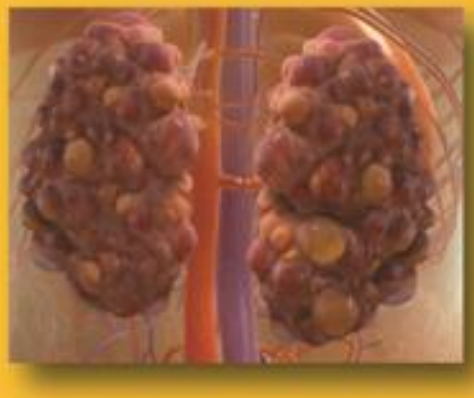
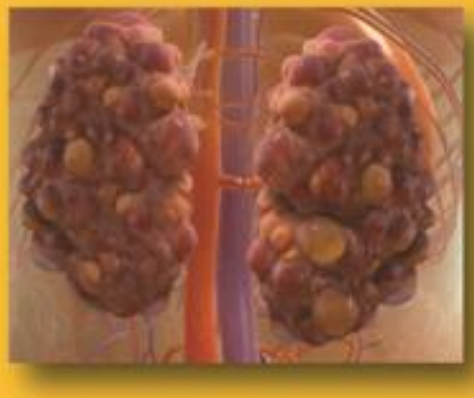


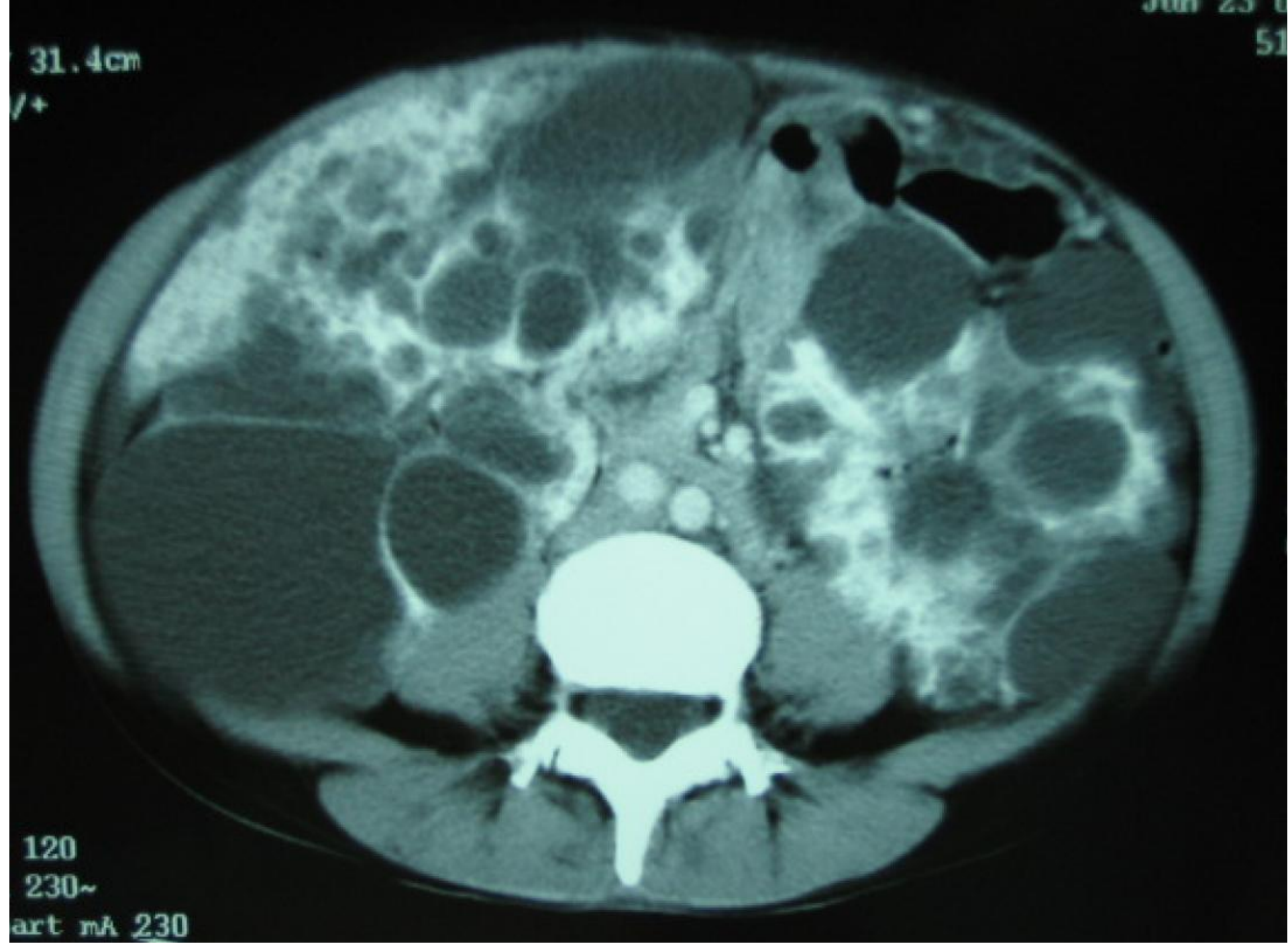
Update of pathophysiology and clinical practice of polycystic disease

Shigeo Horie, M.D.
Juntendo University Graduate School of Medicine



ADPKD

The most prevalent hereditary disease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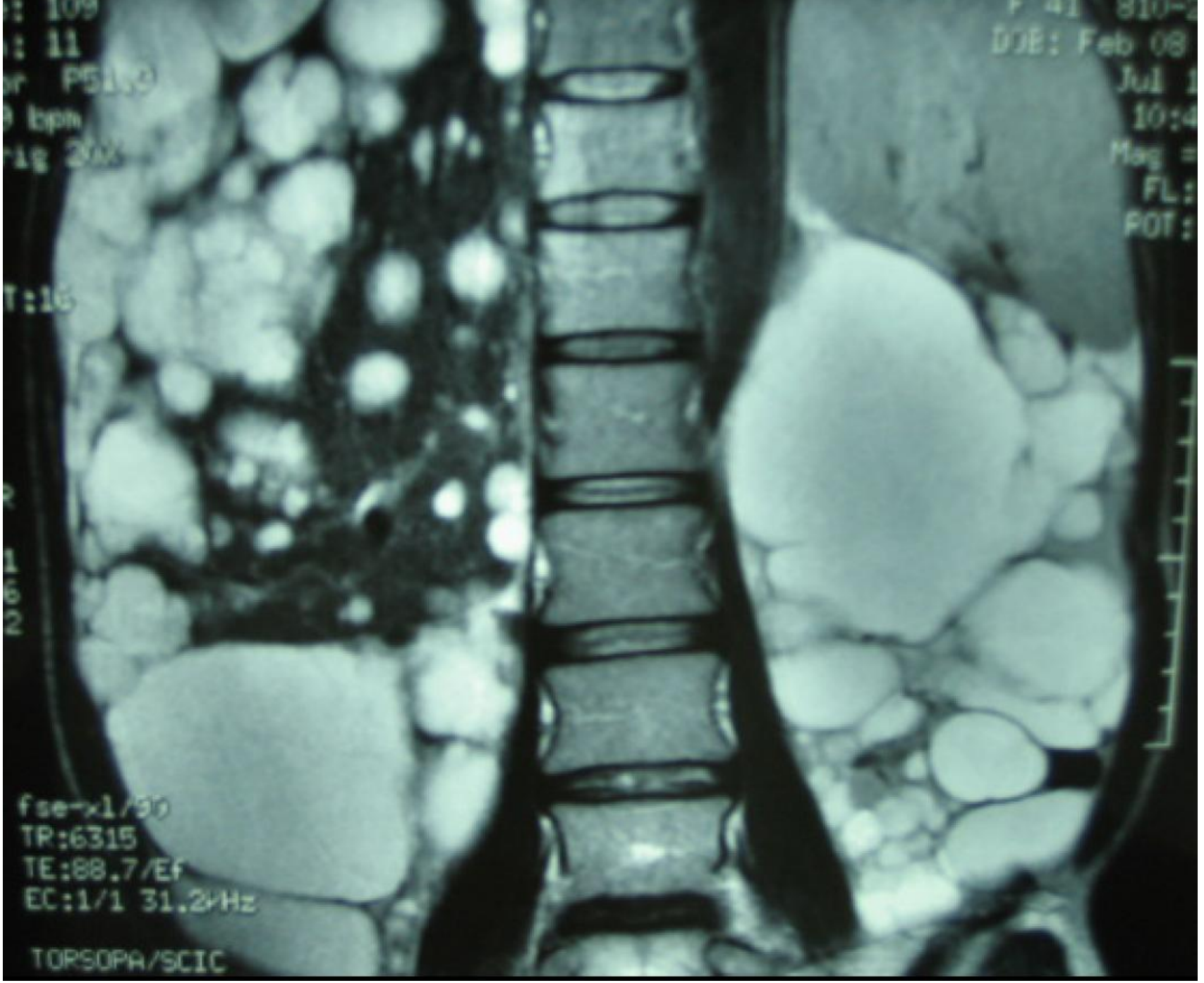
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Polycystic Kidney Disease

- Polycystic kidney disease (PKD) is a group of monogenic disorders characterized by the propensity to develop numerous renal cysts and progressive renal disease[1]
- The 2 main types of PKD[1]
  - Autosomal dominant PKD (ADPKD)
  - Autosomal recessive PKD (ARPKD)
- Approximately 90% of PKD cases are the ADPKD type[2]

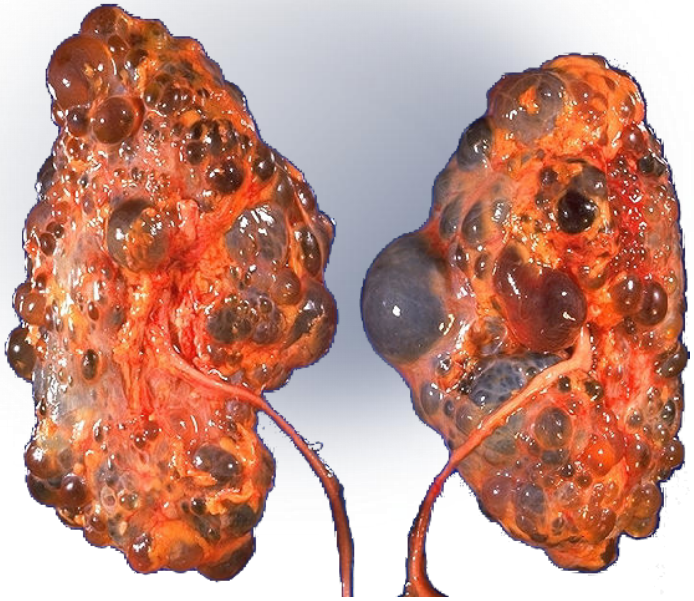
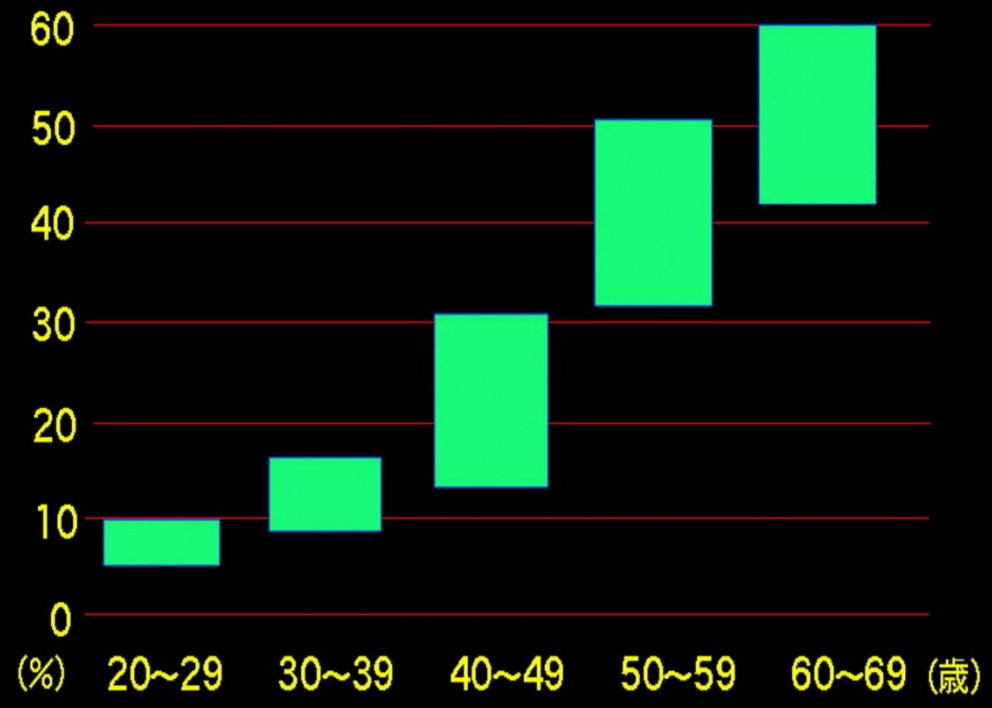


Image courtesy of CDC/Dr Edwin P. Ewing, Jr.

1. Harris PC, Torres VE. *Annu Rev Med*. 2009;60:321-337; 2. National Kidney and Urologic Diseases Information Clearinghouse. Polycystic Kidney Disease. http://kidney.niddk.nih.gov/kudiseases/pubs/polycystic/PKD_508.pdf. Accessed October 22, 2013.

Renal survival of ADPKD



% of patients with CRF on dialysis

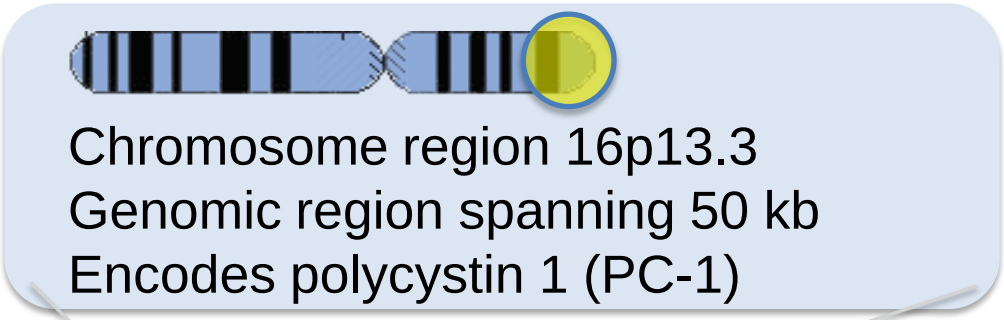
Higashihara 1998

ADPKD: A Common Inherited Monogenic Disease

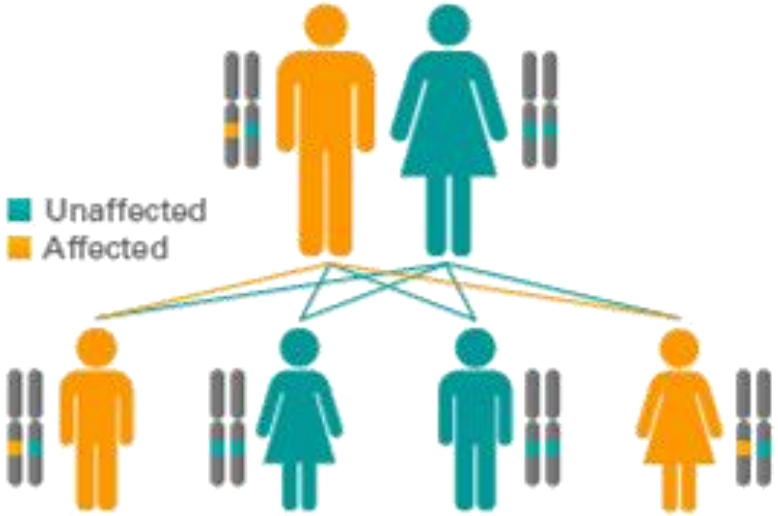
- Prevalence of diagnosed ADPKD in the US is approximately 1:2000[1]
- Including undiagnosed cases, ADPKD is thought to be more prevalent than Huntington's disease, sickle cell disease, cystic fibrosis, myotonic dystrophy, and hemophilia *combined*[2,3]

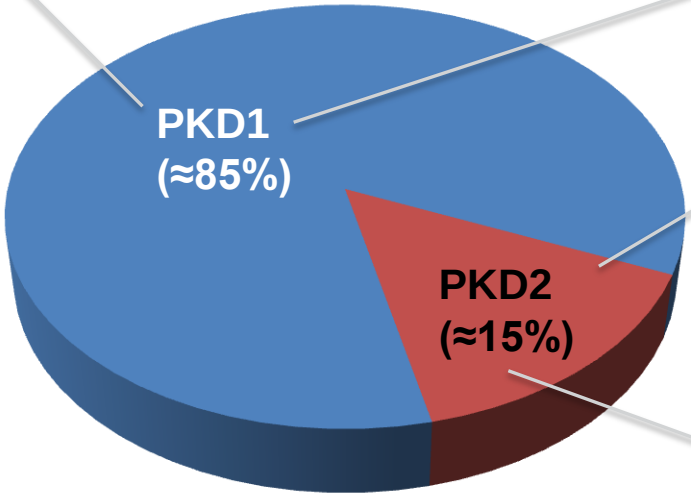
1. Data on file. Otsuka America Pharmaceutical, Inc. 2. Belibi FA, Edelstein CL. *Expert Opin Investig Drugs*. 2010;19(3):315-328; 3. Gabow PA. *N Engl J Med*. 1993;329(5):332-342.

ADPKD Is Inherited as an Autosomal Dominant Trait With Complete Penetrance[1-5]



Chromosome region 16p13.3
Genomic region spanning 50 kb
Encodes polycystin 1 (PC-1)

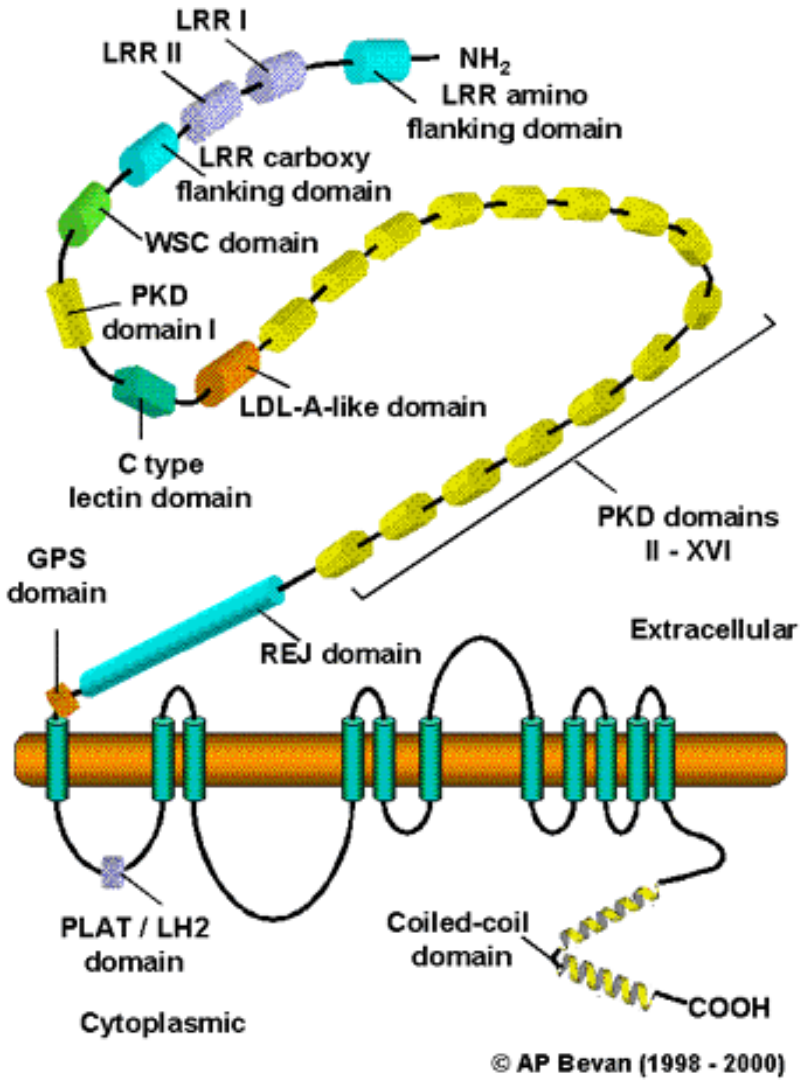




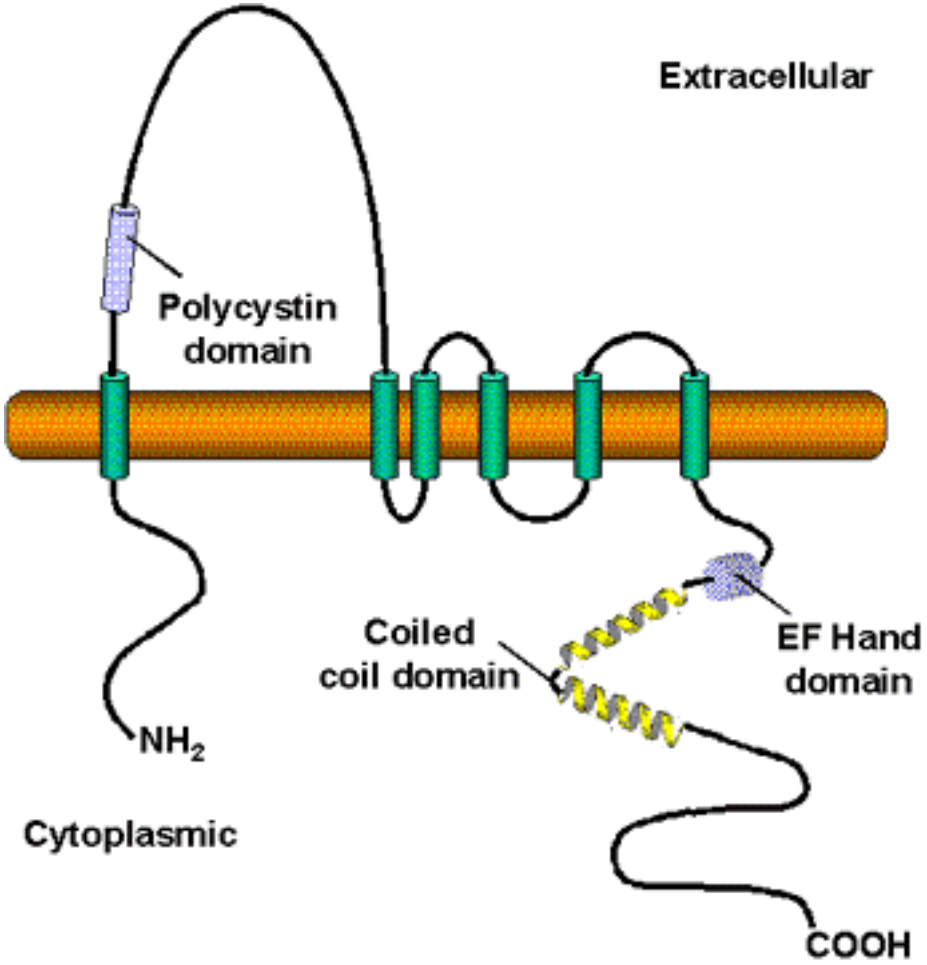
Chromosome region 4q21
Genomic region spanning 68 kb
Encodes polycystin 2 (PC-2)

1. Harris PC, Rossetti S. *Nat Rev Nephrol*. 2010;6(4):197-206; 2. Chapman AB. *J Am Soc Nephrol*. 2007;18(5):1399-1407; 3. Torres VE, Grantham JJ. Cystic diseases of the kidney. In: Taal MW, Chertow GM, Marsden PA, et al, eds. *Brenner and Rector's The Kidney*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2011:chap 45; 4. US National Library of Medicine. PKD1. http://ghr.nlm.nih.gov/gene/PKD1. Reviewed June 2006. Accessed June 5, 2013; 5. US National Library of Medicine. PKD2. http://ghr.nlm.nih.gov/gene/PKD2. Reviewed June 2006. Accessed June 5, 2013.

Polycystin 1



Polycystin 2



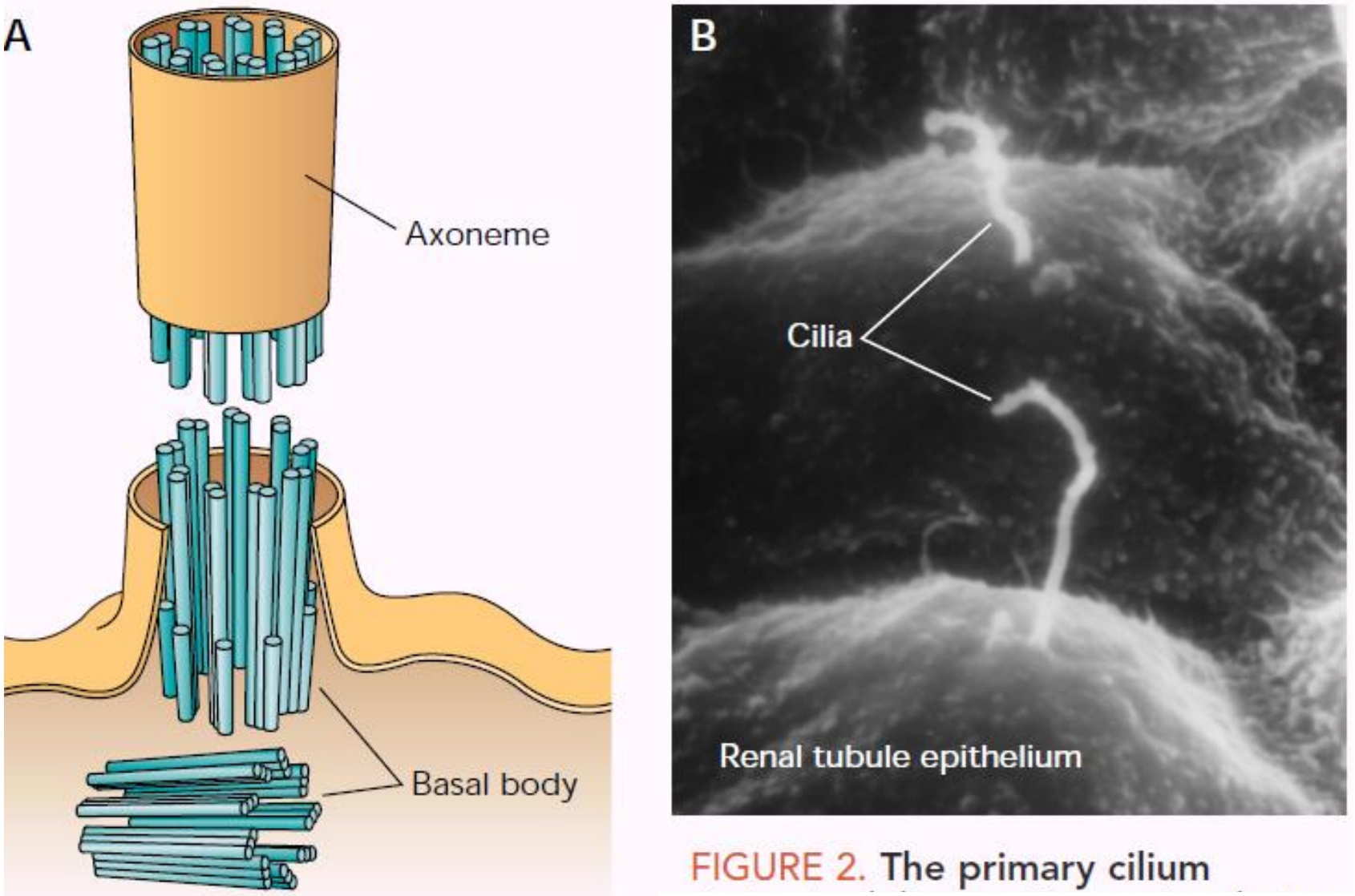


FIGURE 2. The primary cilium

PC-1 and PC-2 on the Primary Cilium of Renal Tubular Epithelial Cells

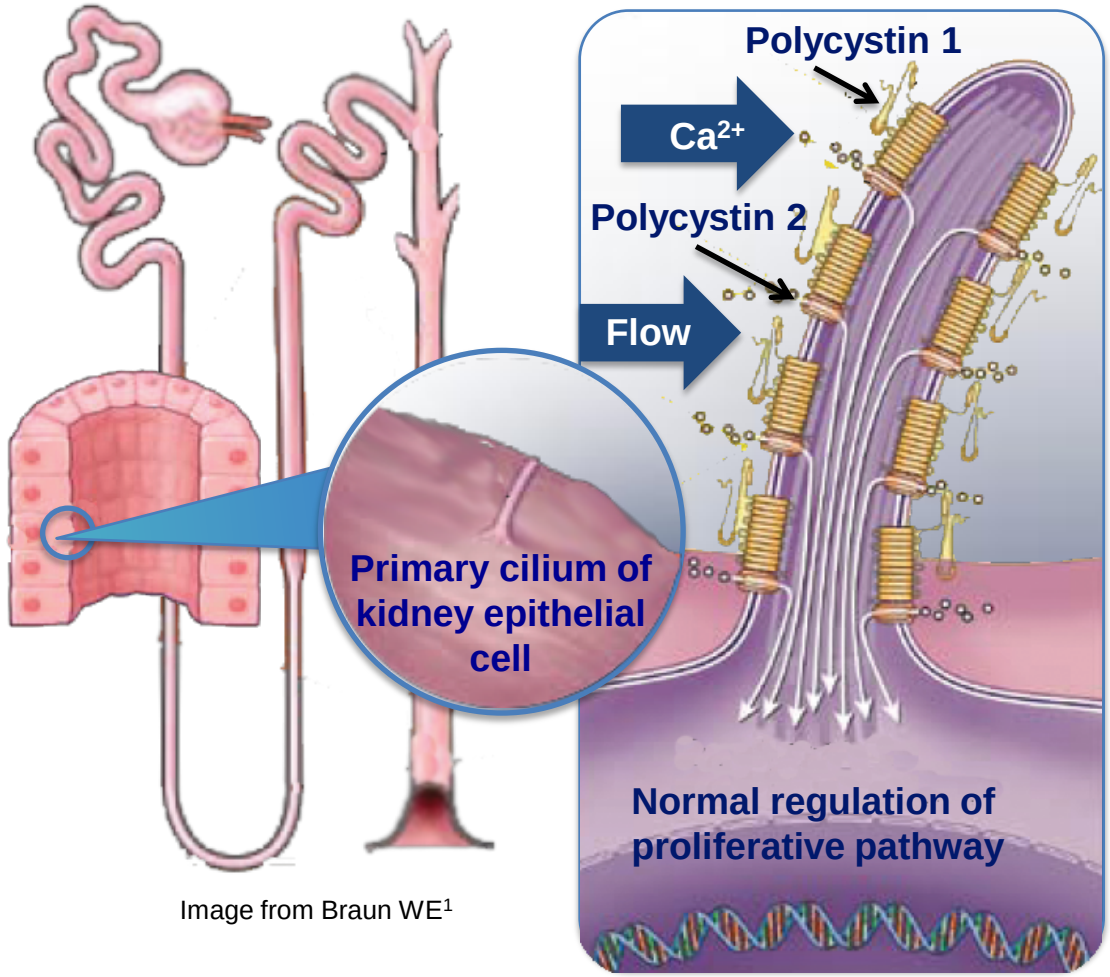


Image from Braun WE[1]

- The primary cilium in kidney tubular epithelial cell may play a chemo- or flow-sensing role in the kidney tubule[1,2]
- PC-1 and PC-2 co-localize on the primary cilium and are thought to interact and regulate the chemo- or flow-dependent influx of Ca^{+} [1,2]
- Ca^{+} flux helps regulate the proliferative state of renal tubular cells[1,2]

1. Braun WE. *Cleve Clin J Med*. 2009;76(2):97-104; 2. Torres VE, Grantham JJ. Cystic diseases of the kidney. In: Taal MW, Chertow GM, Marsden PA, et al, eds. *Brenner and Rector's The Kidney*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2011:chap 45.

Abnormal or Insufficient Polycystins in ADPKD Lead To Cystogenesis

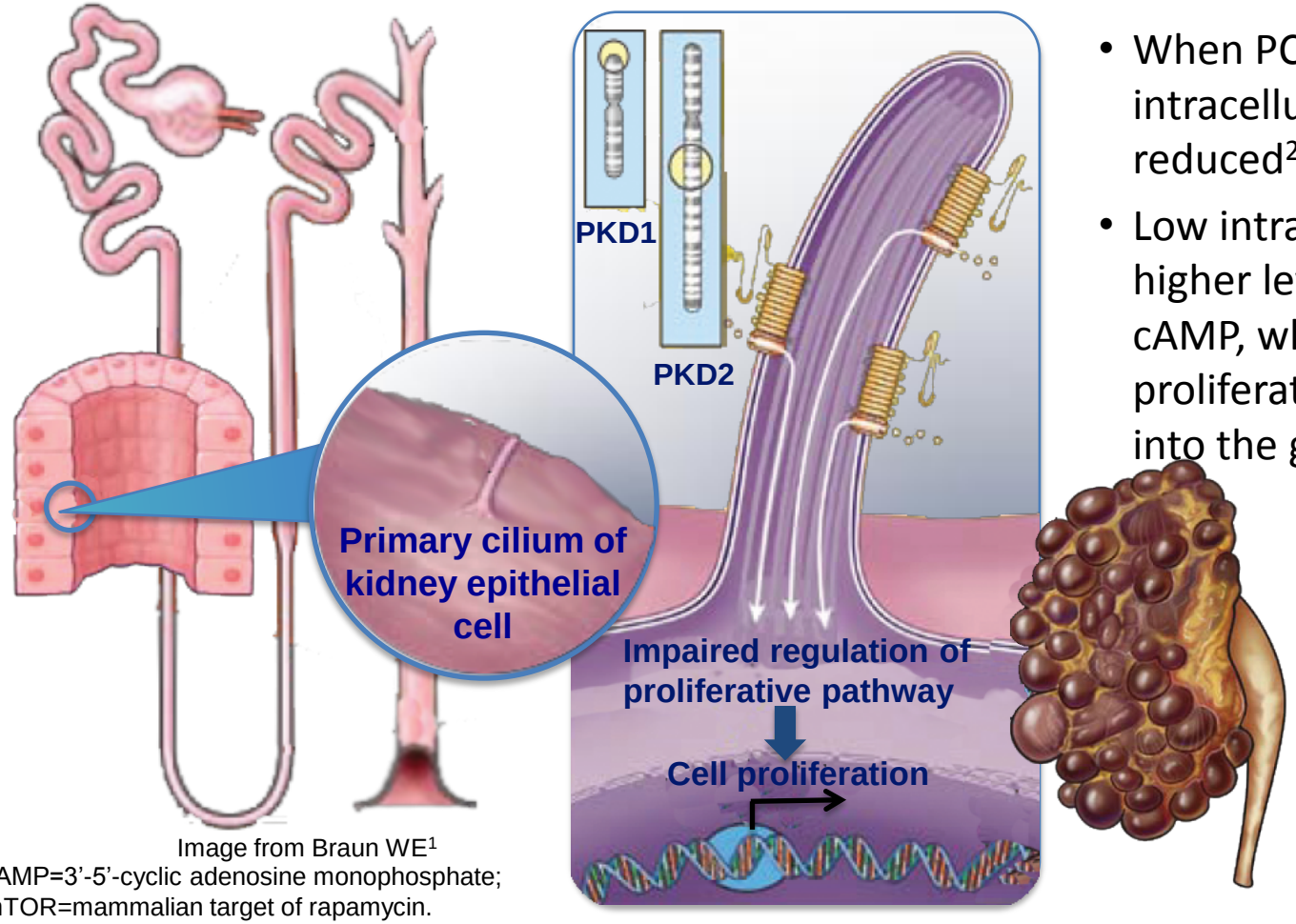
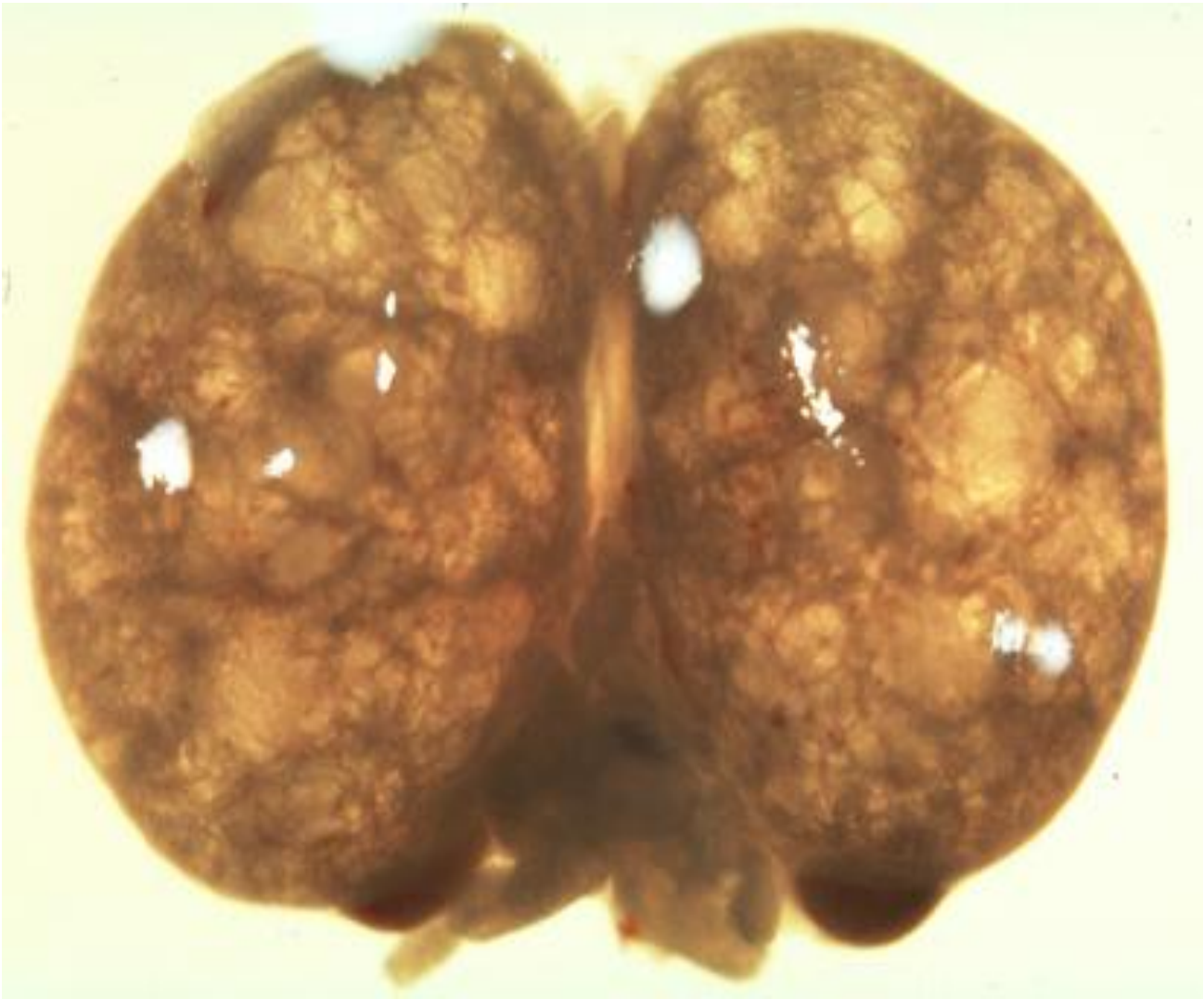


Image from Braun WE[1]
cAMP=3'-5'-cyclic adenosine monophosphate;
mTOR=mammalian target of rapamycin.

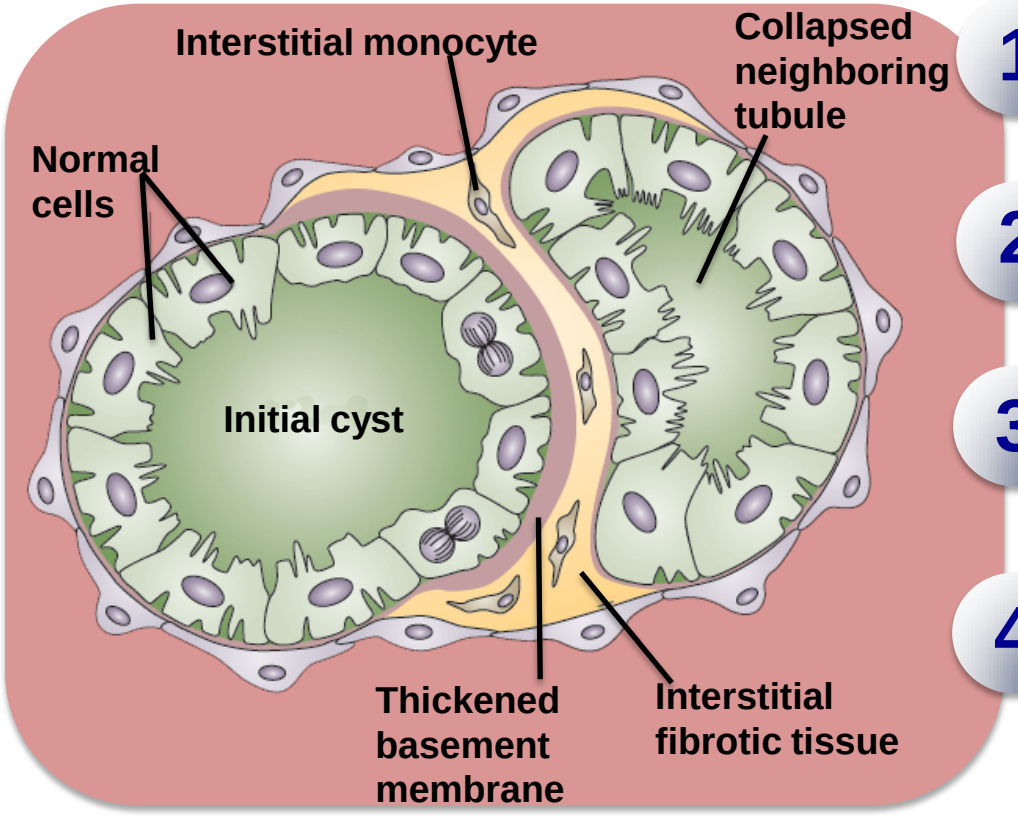
- When PC-1 or PC-2 are mutated, intracellular levels of Ca^{+} are reduced[2]
- Low intracellular Ca^{+} triggers higher levels of intracellular cAMP, which drives cell proliferation and fluid secretion into the growing cysts[1,2]
  - Other pathways are also involved in cystogenesis (cell proliferation and fluid secretion), such as the mTOR pathway and several other growth factors[1,2]

1. Braun WE. *Cleve Clin J Med*. 2009;76(2):97-104; 2. Torres VE, Grantham JJ. Cystic diseases of the kidney. In: Taal MW, Chertow GM, Marsden PA, et al, eds. *Brenner and Rector's The Kidney*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2011:chap 45.

Multiple renal cysts in *Pkd1* $^{-/-}$ embryo (E17.5)



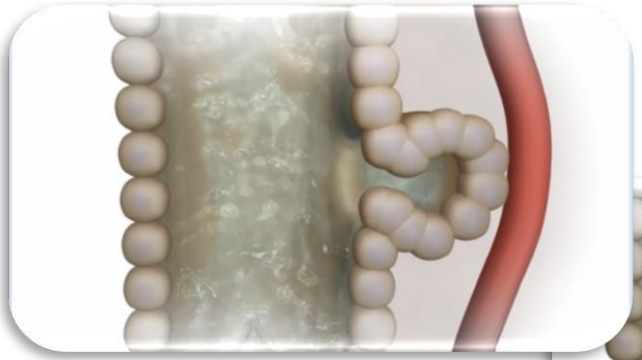
Cystogenesis Is the Hallmark Pathogenetic Factor in ADPKD



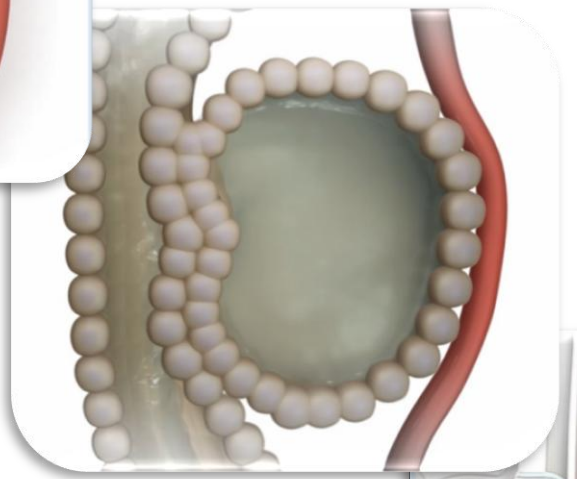
1. Tubule cell divides repeatedly and generates less well differentiated daughter cells
2. Excess tubule basement membrane material is deposited
3. Mononuclear cells and collagen fibrils appear in the interstitium next to the evolving cyst
4. Cyst expansion compresses adjacent tubules and compromises capillaries, lymphatics, arterioles, and venules

Grantham JJ et al. *Nat Rev Nephrol*. 2011;7(10):556-566.

Cyst Enlargement in ADPKD

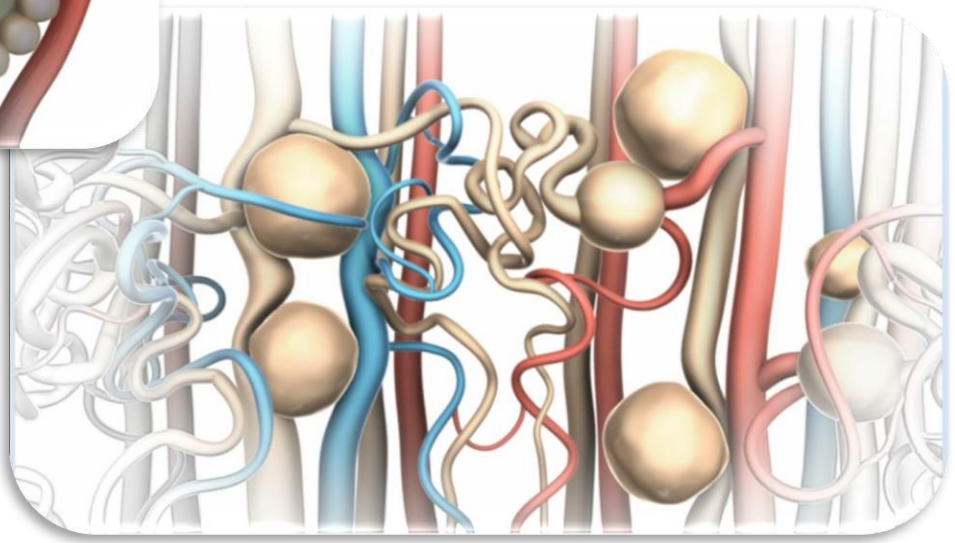


Cysts separate from tubules and…



Compress neighboring structures…

…Resulting in enlarged kidneys



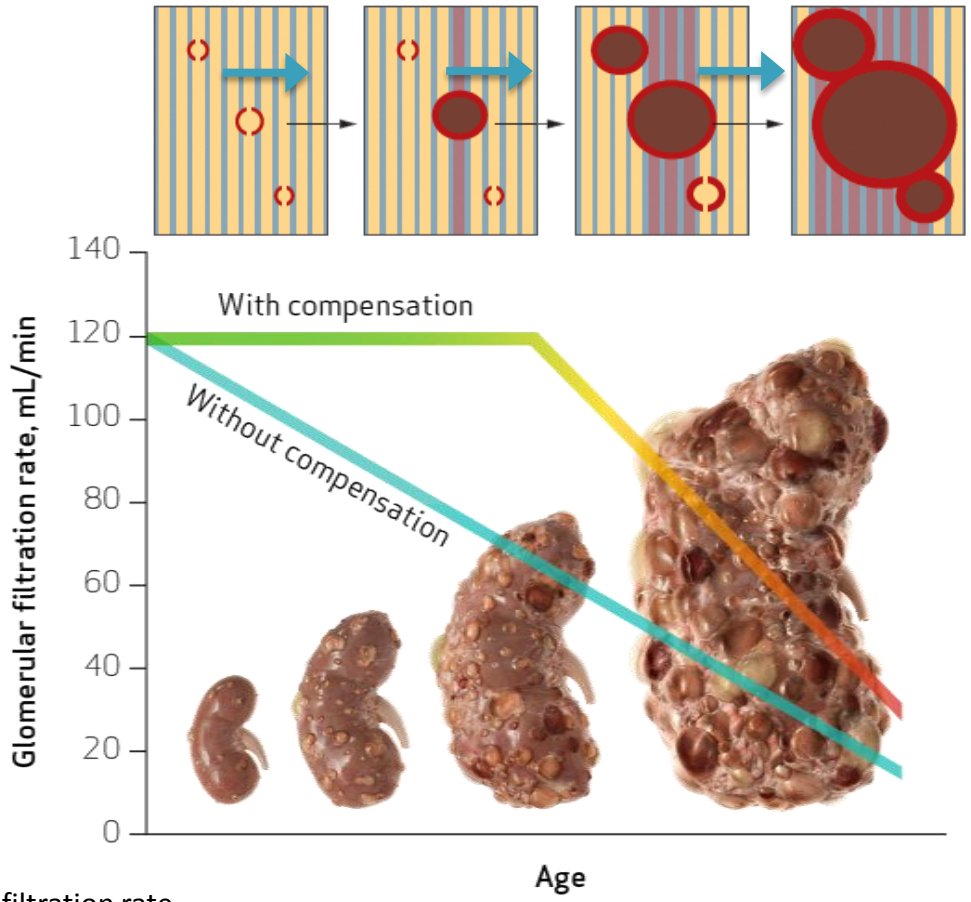
Cyst Development and Growth in ADPKD

Permission granted from Dr. Andrew Evan, Indiana University, School of Medicine.

- ADPKD cysts arise from all segments of the nephron and collecting ducts[1]
  - Detach from renal tubules and grow as blind sacs[2]
  - Growth requires cell proliferation, fluid secretion, and remodeling of extracellular matrix[2]
- Cysts increase in number and size over time[3]
  - Mean increase in total kidney volume of 5.3% per year[4]
  - Kidneys are massively enlarged (up to 20 times their normal size) in late-stage disease[1]

1. Torres VE, Grantham JJ. In: Taal MW, Chertow GM, Marsden PA, et al, eds. *Brenner and Rector's The Kidney*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2011:chap 45; 2. Torres VE, Harris PC. *Nat Rev Nephrol*. 2011;8(2):66-68; 3. Braun WE. *Cleve Clin J Med*. 2009;76(2):97-104; 4. Grantham JJ et al. *N Eng J Med*. 2006;354(20):2122-2130.

Cystogenesis Destroys Renal Tissue and Causes Loss of Renal Function



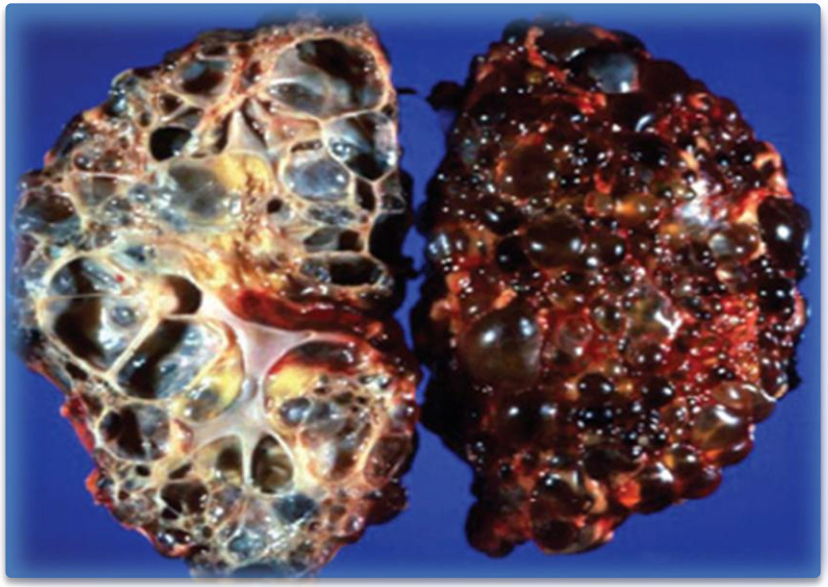
- Renal function remains steady until kidney volumes increase to 4–6 times normal size[1]
- By the time GFR declines, marked irreversible damage has occurred[2]

GFR=glomerular filtration rate.

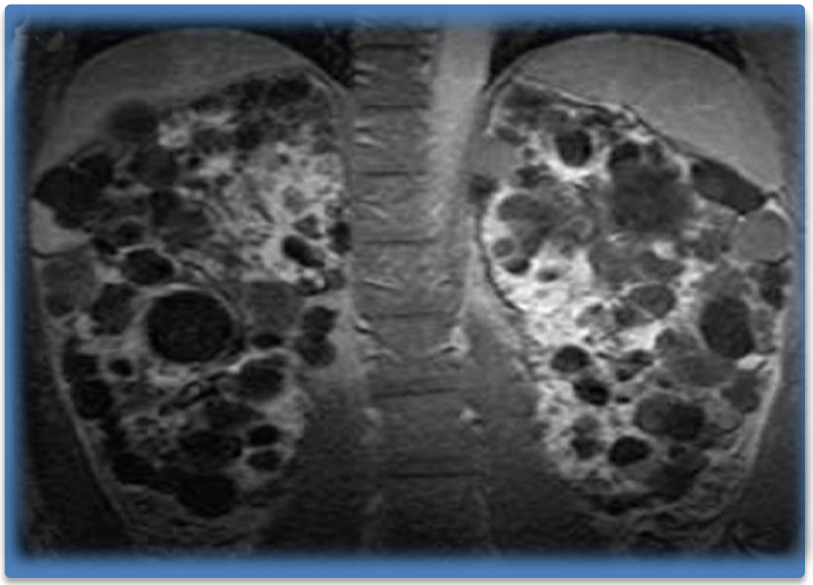
Image adapted from Grantham JJ et al. *Nat Rev Nephrol*. 2011;7(10):556-566 and Grantham JJ et al. *Clin J Am Soc Nephrol.* 2006;1(1):148-157.

1. Braun WE. *Cleve Clin J Med*. 2009;76(2):97-104; 2. Grantham JJ et al. *N Eng J Med*. 2006;354(20):2122-2130.

Cysts in End-Stage Polycystic Kidneys



Cysts are separated by fibrotic bands, leaving no visible parenchyma

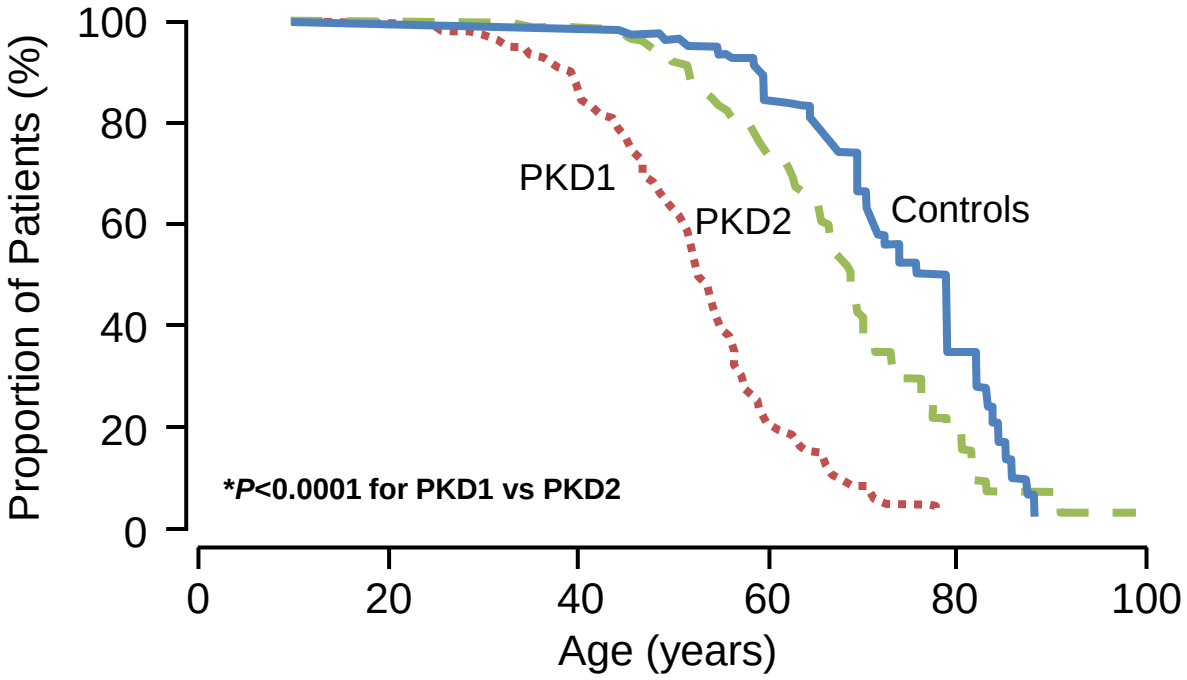


Residual parenchyma (white) stand out among the cysts; focal areas of gadolinium enhancement identify functioning tissue

Grantham JJ et al. *Nat Rev Nephrol*. 2011;7(10):556-566.

PKD1 Mutations Cause More Aggressive Disease Than *PKD2* Mutations

Cumulative Probability of Survival to ESRD or Death Among Patients with ADPKD[1]

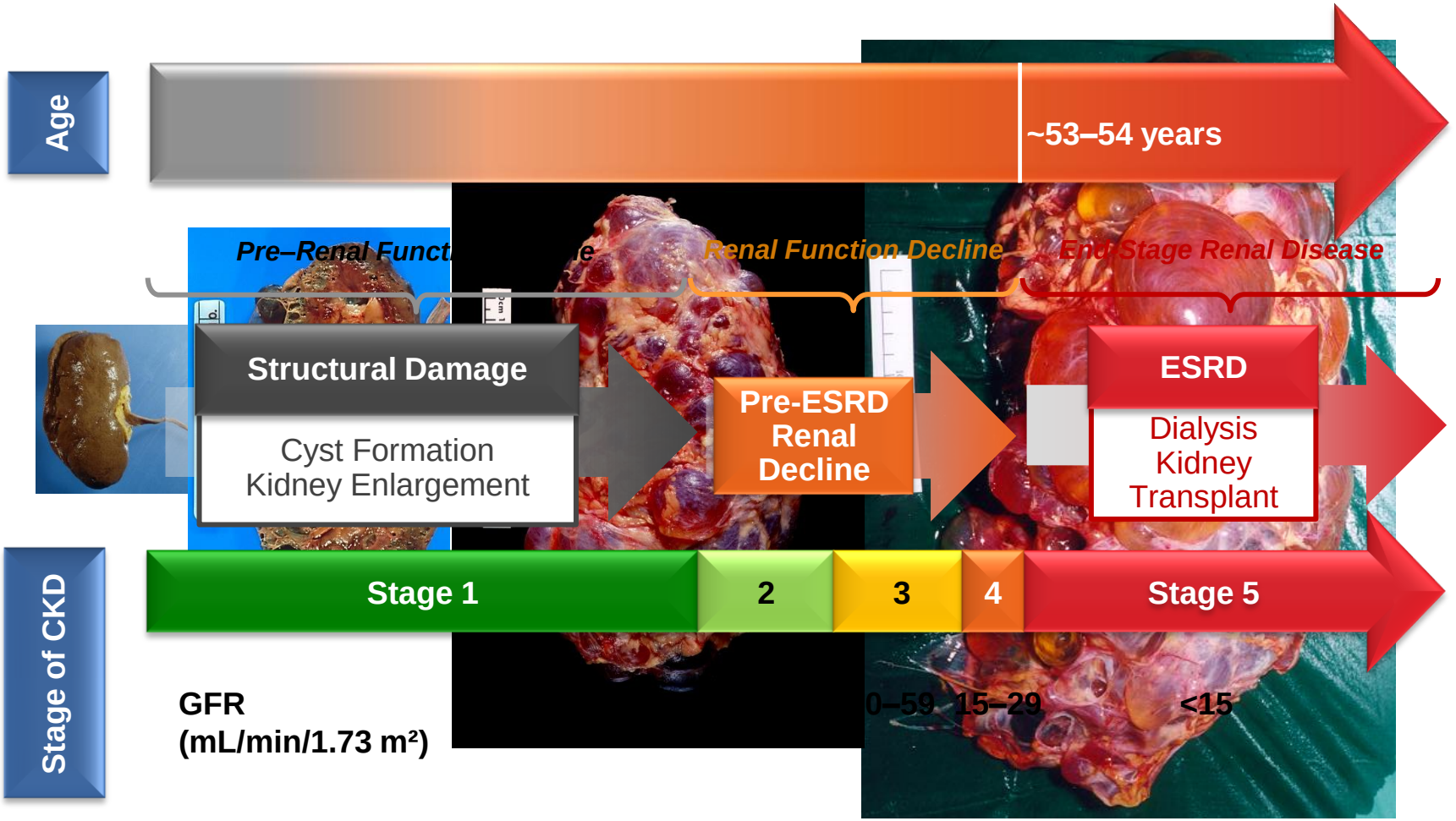


- Median age at death or onset of ESRD was 53 years for PKD1 and 69 years for PKD2
- Median age at onset of ESRD was 54 years for PKD1 and 74 years for PKD2
- Patients with PKD2 were less likely to have hypertension, UTI, or gross hematuria than those with PKD1

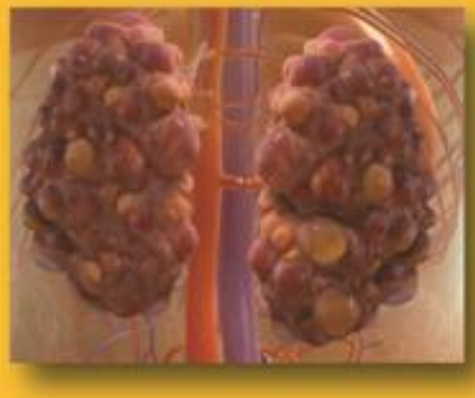
Controls were unaffected family members.
UTI=urinary tract infection.

Hateboer N et al. *Lancet*. 1999;353(9147):103-107.

Typical Course of Disease for Patients With the PKD1 Genotype



1. Hateboer N et al. *Lancet*. 1999;353(9147):103-107; 2. Dicks E et al. *Clin J Am Soc Nephrol*. 2006;1(4):710-717; 3. Grantham JJ et al. *Nat Rev Nephrol*. 2011;7(10):556-566; 4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl*. 2013;3(1):1-150.



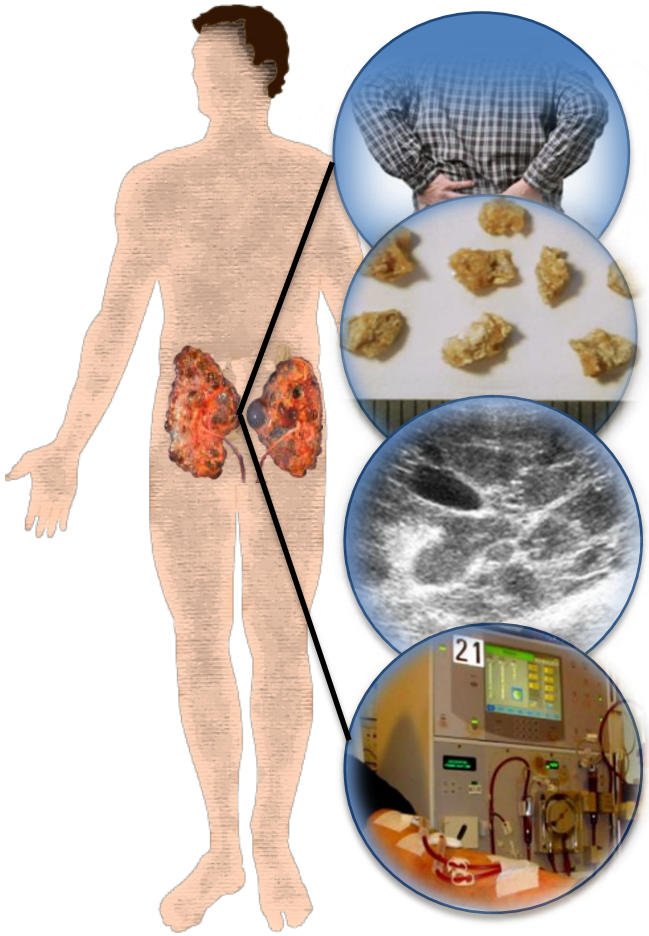
Clinical Presentation and Manifestations

Clinical Presentation of ADPKD

- ADPKD often diagnosed upon[1]:
  - Sudden onset of renal pain or hematuria
  - Discovery of hypertension
  - Finding of nephromegaly or renal cysts on physical or radiologic examinations
- Pain is most common symptom reported by adult patients[2]
- Other signs/symptoms may include loss of appetite, nausea, weight loss, and pyelonephritis[3]
- Initial awareness of renal dysfunction typically delayed beyond patient's fourth decade[1]

1. Grantham JJ et al. *Nat Rev Nephrol*. 2011;7(10):556-566; 2. Torres VE et al. *Lancet*. 2007;369(9569):1287-1301; 3. Taylor M et al. *Am J Kidney Dis*. 2005;46(3):415-423.

Renal Manifestations of ADPKD



Pain and discomfort[1,2]

Cysts put pressure on abdominal wall, flanks, and back; impinge on organs (reported by 60% of patients)

Kidney stones[1,2]

20% of patients

Bleeding into cysts[1]

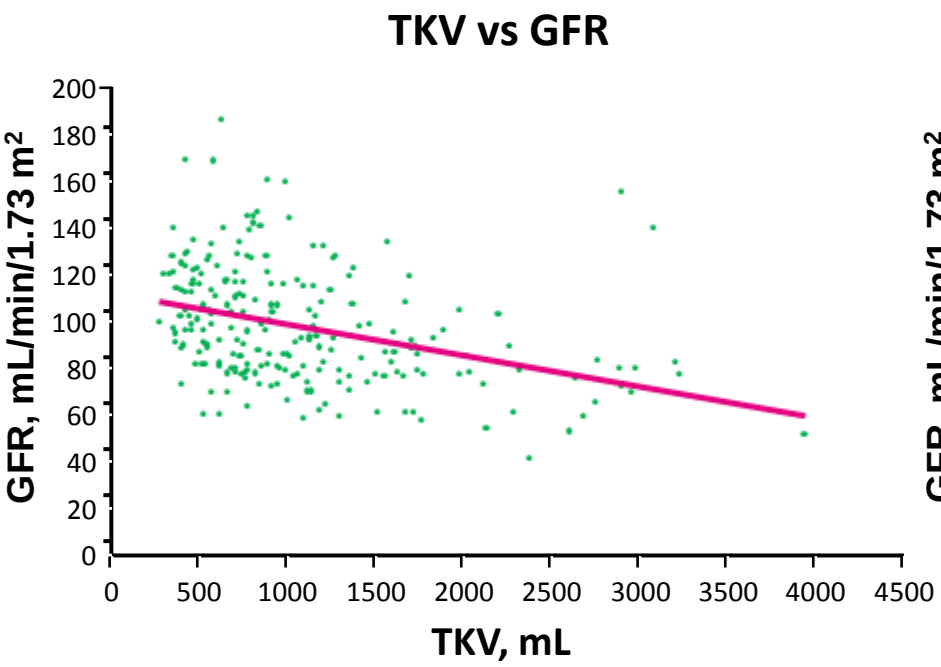
Infected cysts[1]

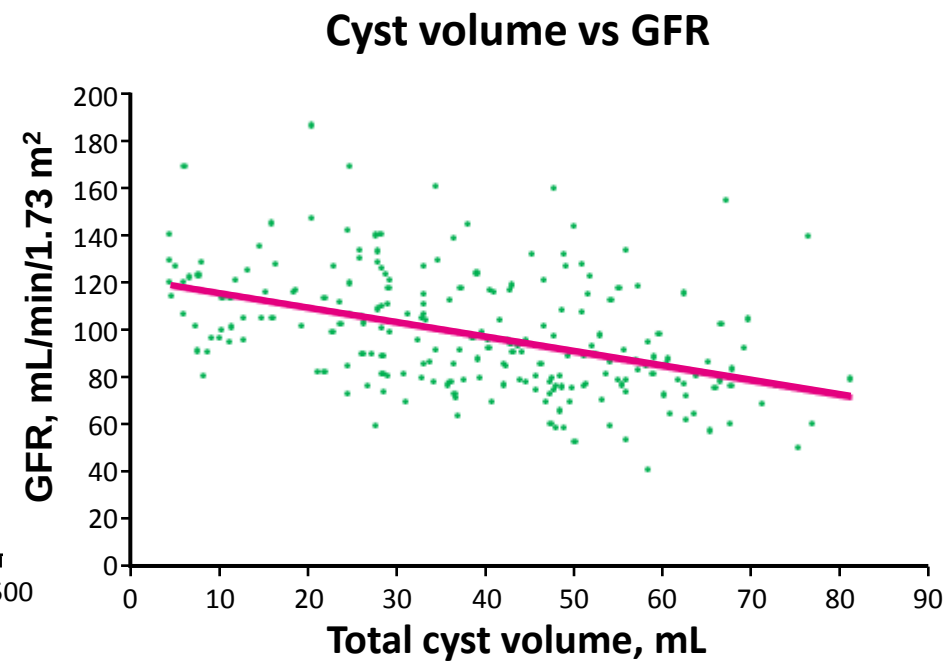
Declining renal function/ESRD[2,3]

1. Braun WE. *Cleve Clin J Med*. 2009;76(2):97-104; 2. Torres VE et al. *Lancet*. 2007;369(9569):1287-1301; 3. Lentine KL et al. *Clin J Am Soc Nephrol*. 2010;5(8):1471-1479.

Total kidney volume (TKV) is associated with GFR

CRISP: Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease

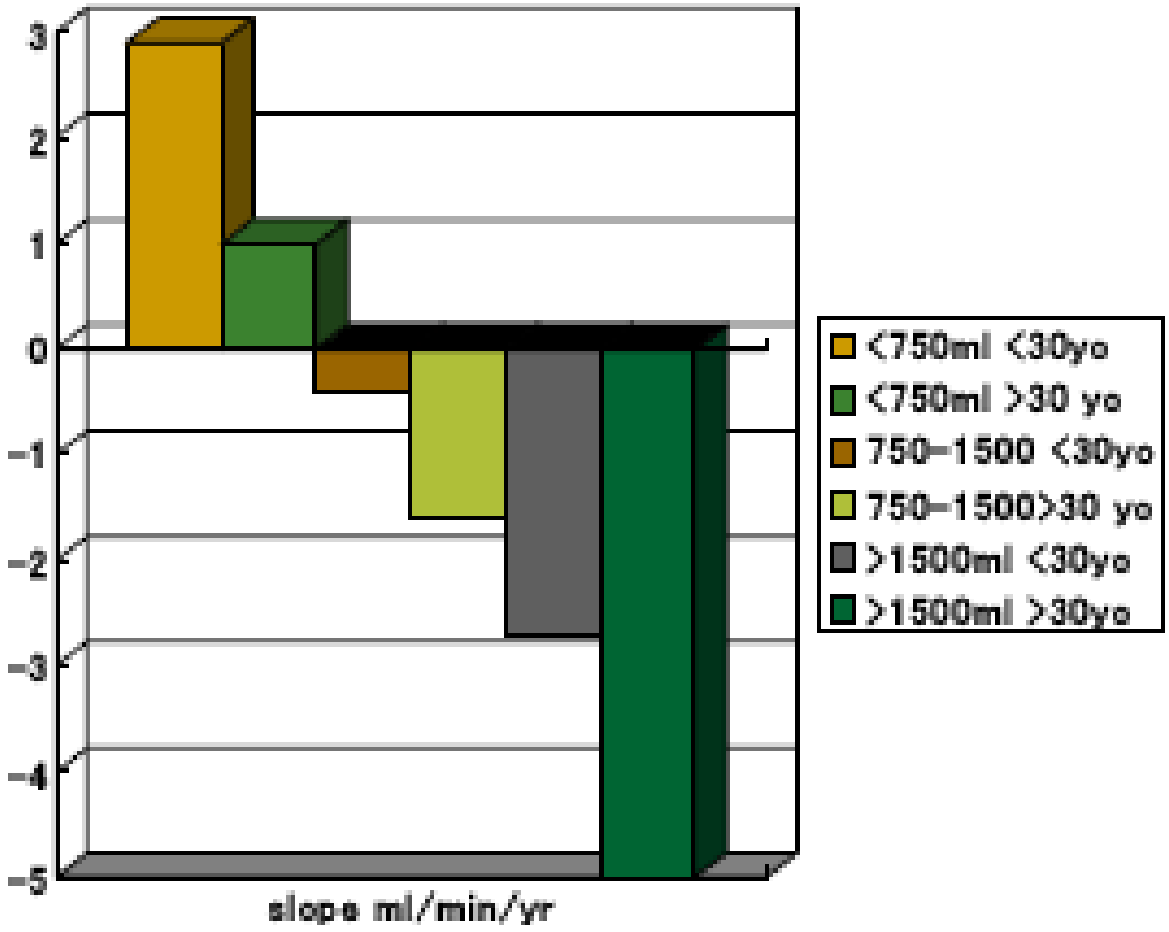




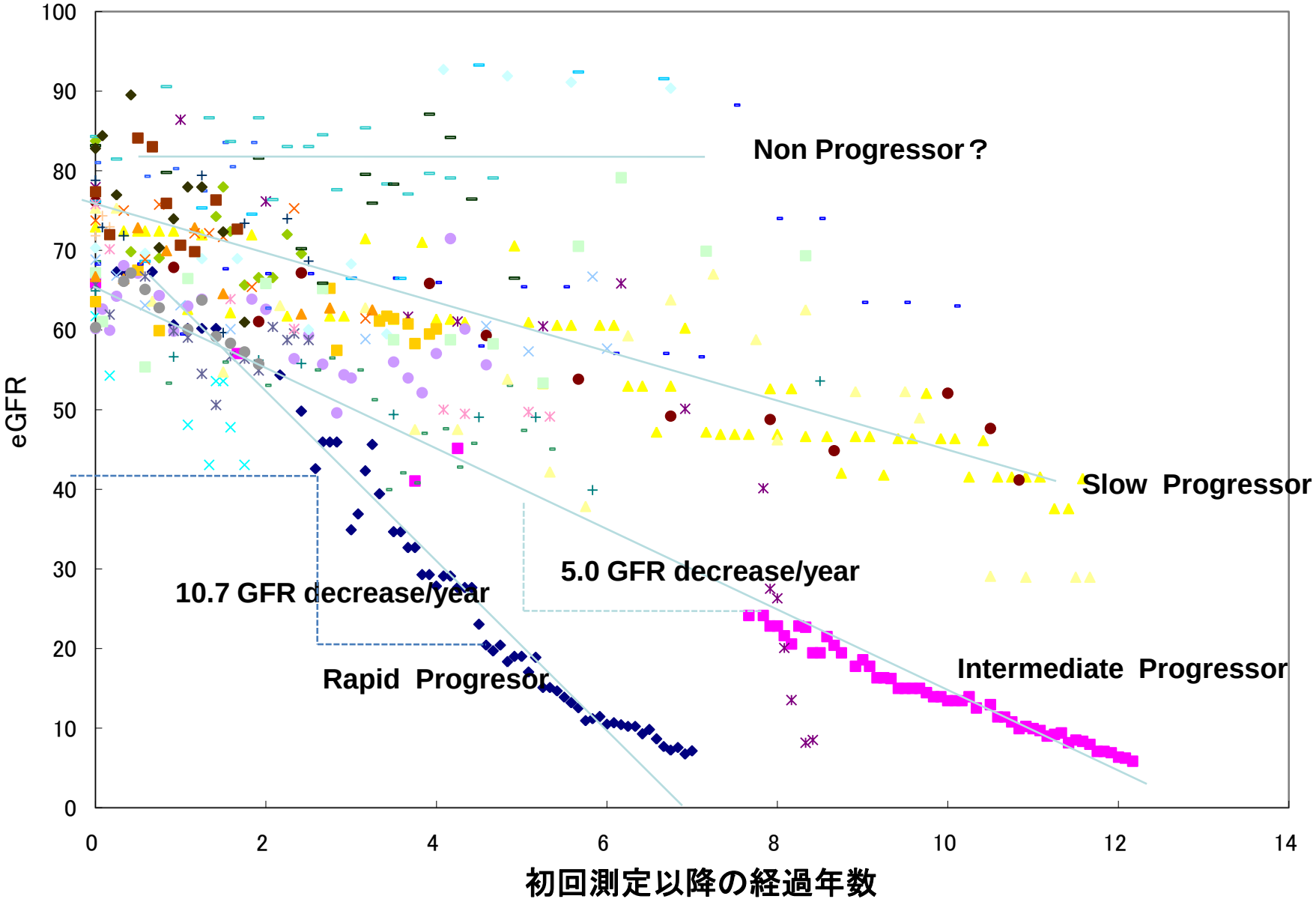
GFRはイオタラム酸クリアランス法で測定
両側腎容積はMRIを用いて測定

CRISP Studies; Chapman, AB. et al.: Kidney Int, **64**, 1035-1045, 2003

TKV>750ml is a turning point for CKD



Decline of renal function in pts with eGFR 90-60

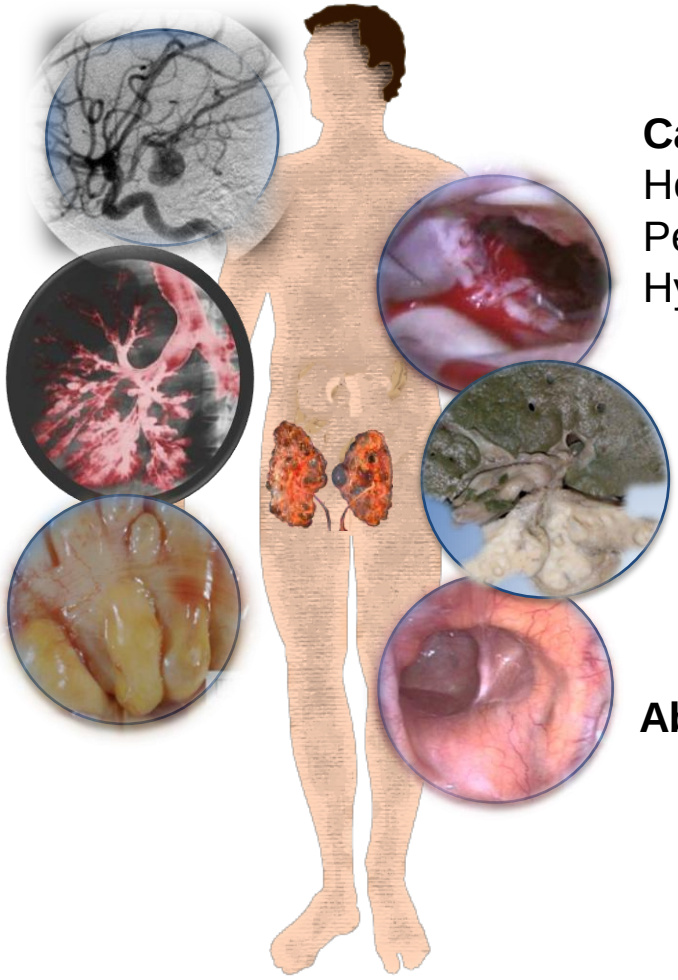


Extrarenal Manifestations of ADPKD

Intracranial aneurysm (8%)[1,2]

Bronchiectasis (37%)[1]

Diverticulosis[1-3]



Cardiac
Heart valve abnormalities (26%)[2]
Pericardial effusion (35%)[1]
Hypertension[2,3]

Cystic involvement
Liver (94% at age >35 years)[1]
Seminal tract (39%–43%)[1]
Pancreas (~10%)[2]
Arachnoid membrane (8%)[1]

Abdominal wall hernia (~10%)[1]

1. Pirson Y. *Adv Chronic Kidney Dis*. 2010;17(2):173-180; 2. Gabow PA. *N Engl J Med*. 1993;329(5):332-342; 3. Torres VE et al. *Lancet*. 2007;369(9569):1287-1301.

Hypertension in ADPKD

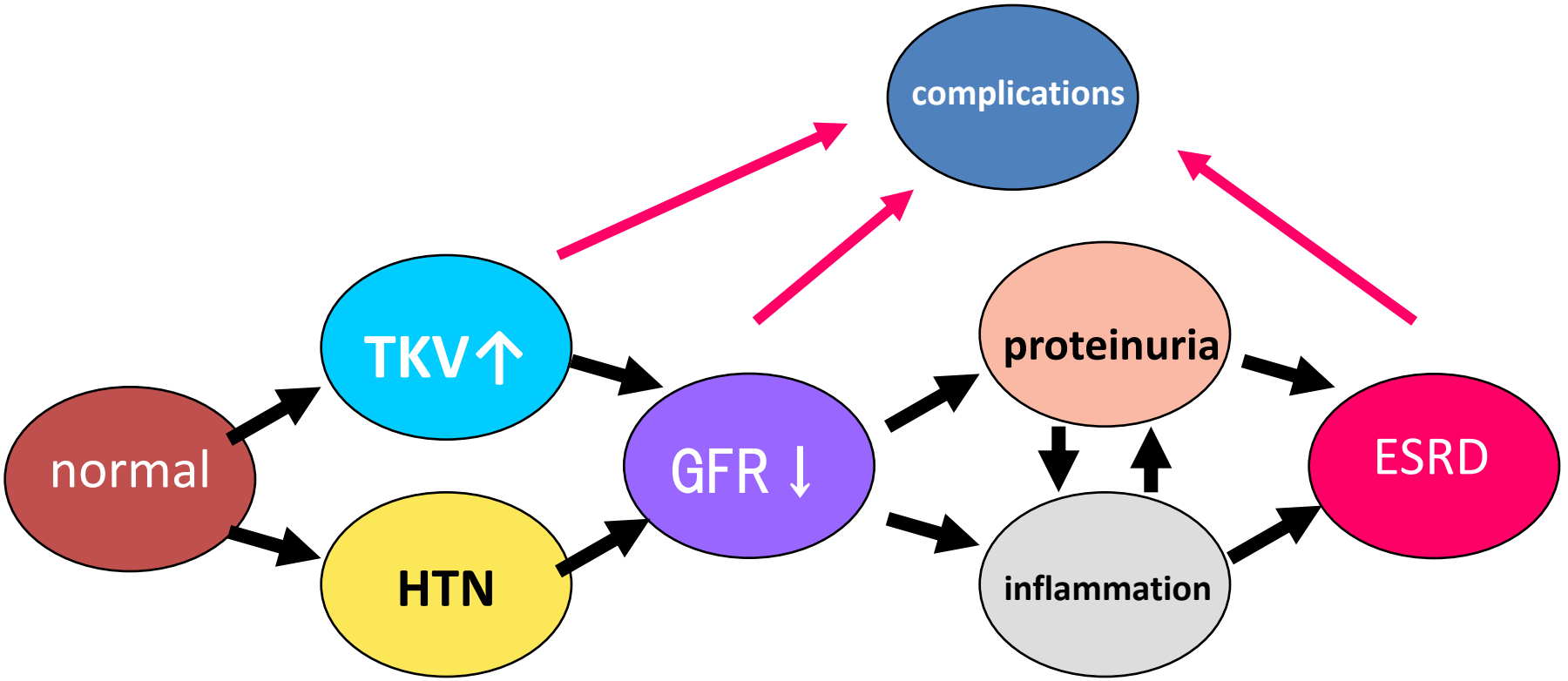
It is believed that the RAAS system, stimulated as a result of cyst expansion, and local renal ischemia play an important role in the development of HTN[1]

- ~70% of individuals with ADPKD have HTN[1-3]
  - ~20%–30% of children[1,2]
- Generally occurs before decrease in GFR[1-3]
- Earlier onset than HTN in the general population[2]
- Associated with left ventricular hypertrophy[1,2]

RAAS=renin-angiotensin-aldosterone system.

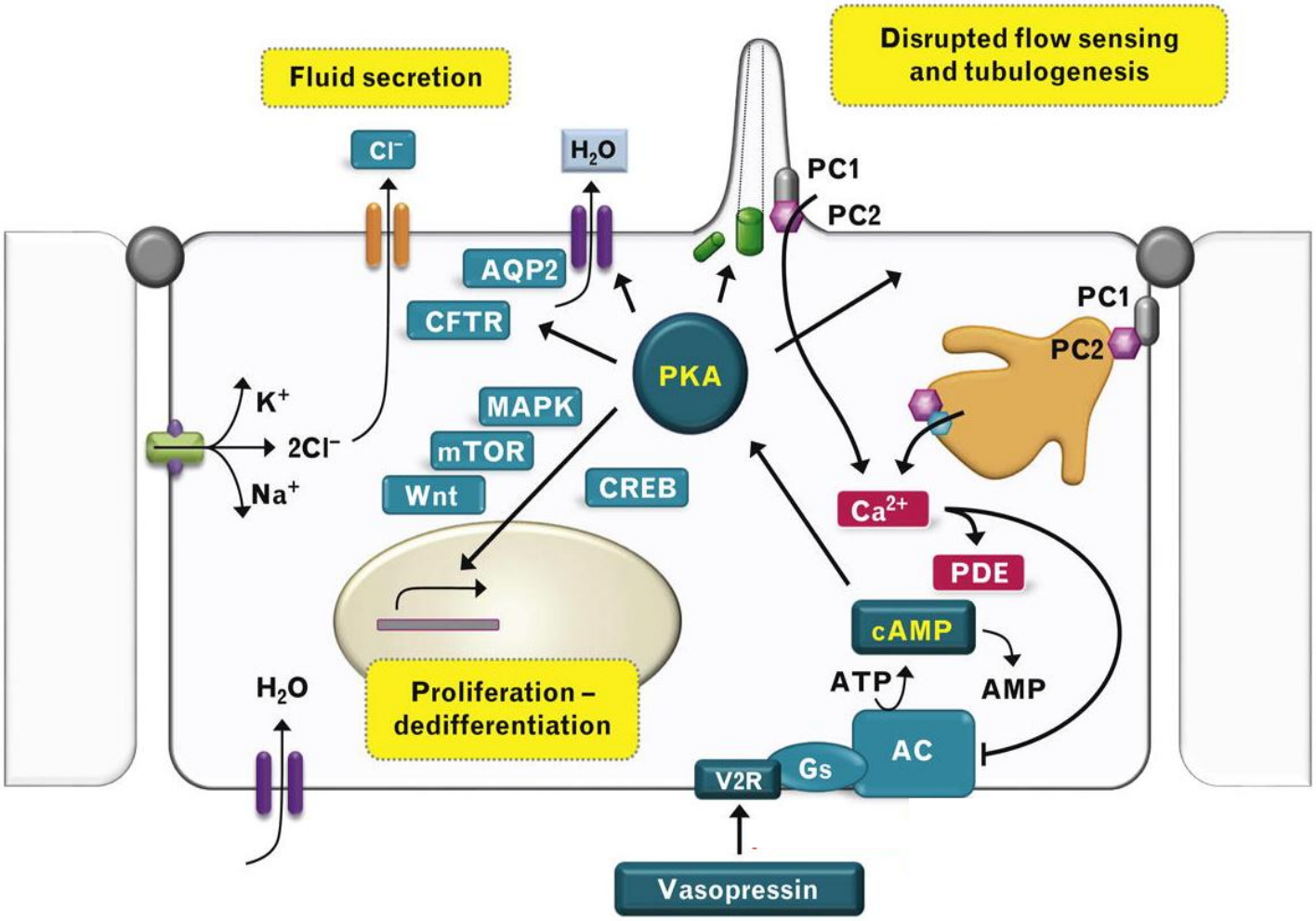
1. Ecder T, Schrier RW. *J Am Soc Nephrol*. 2001;12(1)194-200; 2. Ecder T, Schrier RW. *Nat Rev Nephrol*. 2009;5(4):221-228; 3. Schrier RW. *Am J Kidney Dis*. 2011;57(6):811-813.

ADPKD: progressive CKD



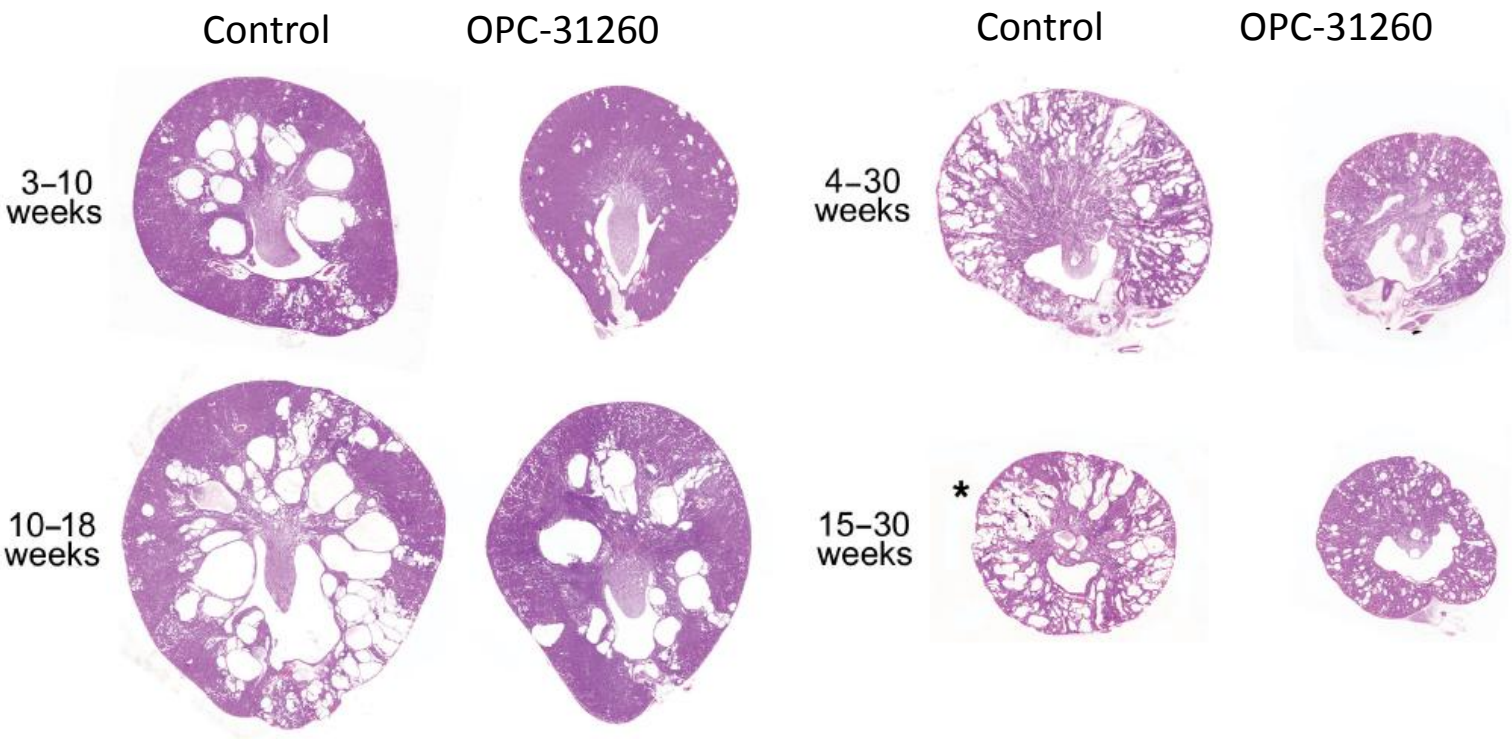
Tolvaptan for ADPKD

Role of cAMP in ADPKD



Devuyst O, Torres VE. *Curr Opin Nephrol Hypertens*. 2013;22(4):459-470.

Effect of V2 receptor antagonist (OPC-31260) for PKD model animals

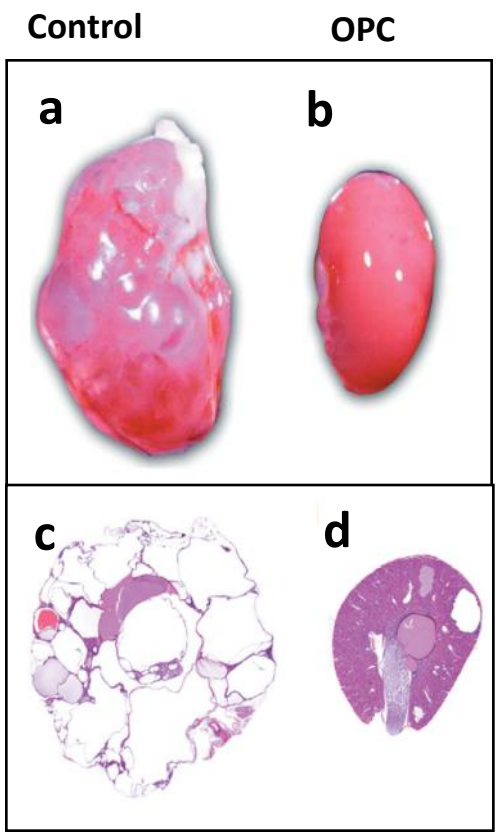


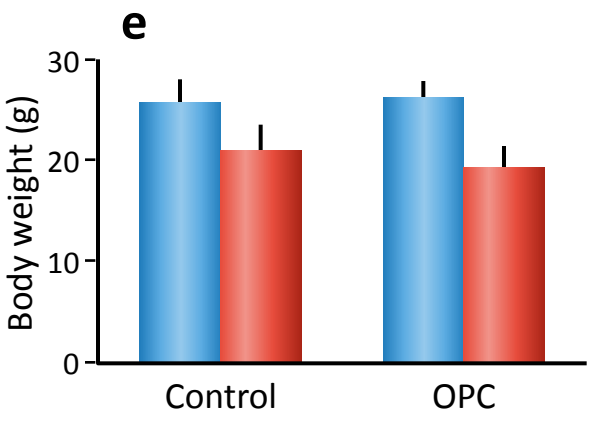
PCK Rats

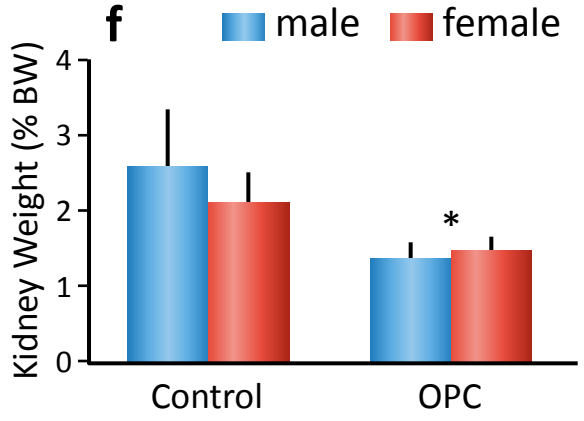
CD 1 / *pcy* mice

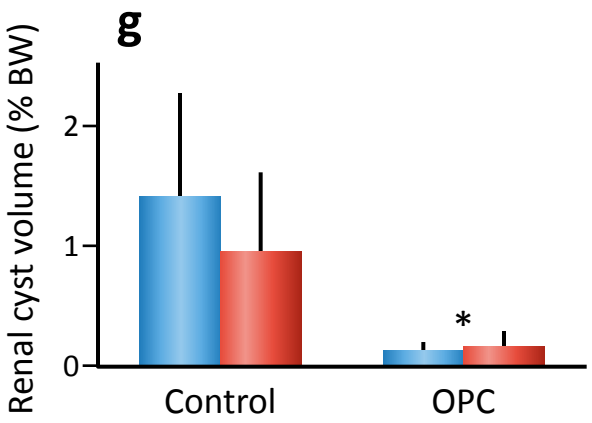
Gattone VH, Wang X, Harris PC, Torres VE, Nature Med, 9 (10), 1323-1326, 2003

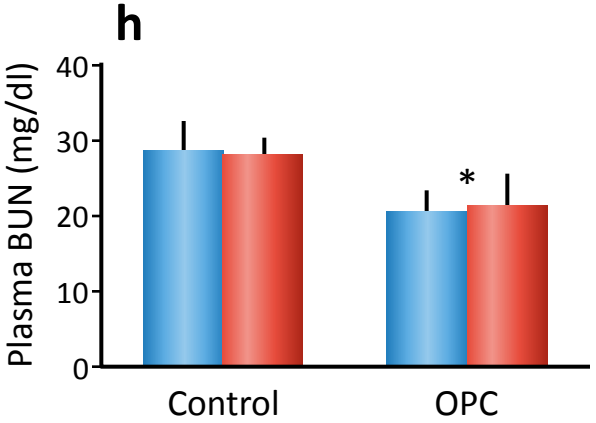
Effect of V2 receptor antagonist (OPC-31260) on development of PKD in *Pkd2* mutant mice







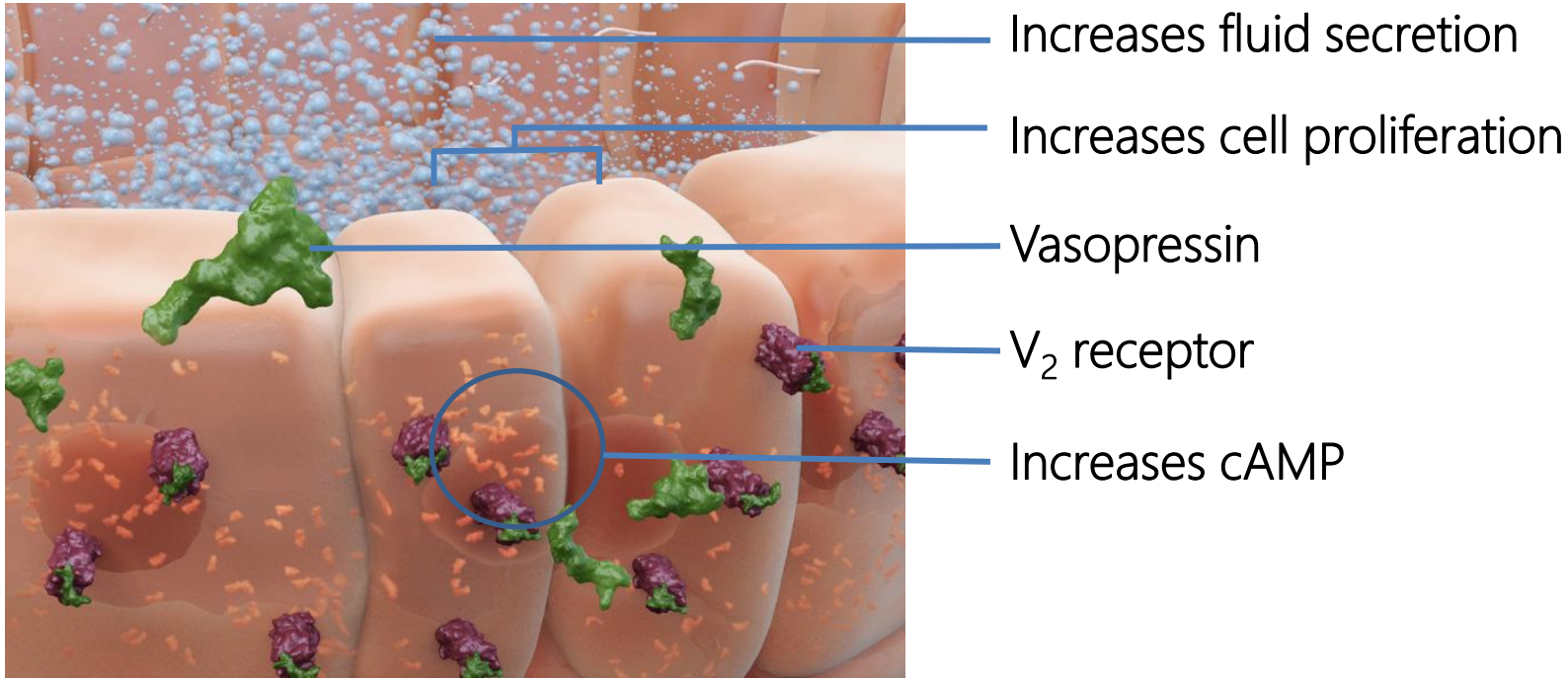




Torres VE et al: Nat Med. 2004;10(4):363-4.

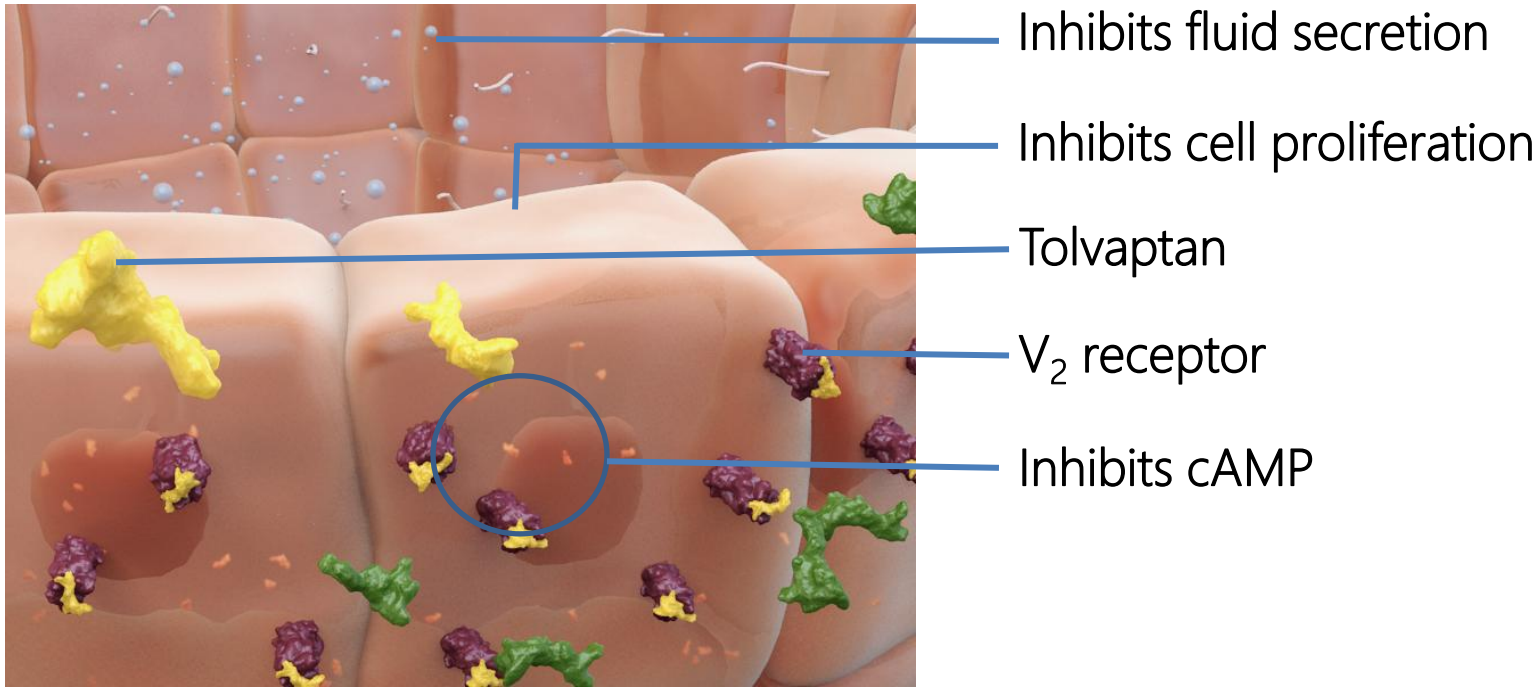
Tolvaptan
Mechanism of Action

Vasopressin binding accelerates cyst growth in ADPKD



Tolvaptan
Mechanism of Action (cont'd)

Tolvaptan blocks vasopressin binding at the V_2 receptor



TEMPO Trial

Tolvaptan Efficacy and Safety in Management of Polycystic Kidney Disease and its Outcomes

Torres, VE. et al.: N Engl J Med. 367(25), 2407-18, 2012

TEMPO Trial


Canada
United States
Belgium
Denmark
France
Germany
Italy
Netherlands
Poland
Romania
United Kingdom
Russia
Japan
Australia
Argentina
129 enrolling sites in 15 countries

Indication and Contraindication

- Tolvaptan is a selective vasopressin V_2-receptor antagonist indicated to slow kidney disease in adults at risk of rapidly progressing ADPKD
- Early-stage predictors for patients who may be at risk of rapidly progressing ADPKD may include:
  - Family history of ESRD at or before age 55
  - Enlarged kidneys by age 35
  - Numerous bilateral cysts by age 35
  - Early onset hypertension before age 35
- Efficacy was established in patients with enlarged kidneys who were in chronic kidney disease (CKD) stages 1-3 at initiation of treatment
- Tolvaptan is contraindicated in patients unable to adequately sense or respond to thirst

1. Barua M et al. *J Am Soc Nephrol*. 2009;20(8):1833-1838; 2. Harris PC et al. *J Am Soc Nephrol*. 2006;17(11):3013-3019; 3. Johnson AM, Gabow PA. *J Am Soc Nephrol*. 1997;8(10):1560-1567.

Eligibility Criteria of the TEMPO Trial

Key Inclusion Criteria

- Adult patients with a diagnosis of ADPKD (18-50 years old)
- Compliance with reproductive precautions
- > eCCr 60 mL/min (Cockcroft-Gault formula)
- Total kidney volume > 750 mL (MRI)

Torres, VE. et al.: Am J Kidney Dis. 57(5), 692-699, 2011.

Primary End Points of the TEMPO Trial

Rate of total kidney volume change

Tolvaptan v.s. placebo

Torres, VE. et al.: Am J Kidney Dis. 57(5), 692-699, 2011.

Secondary End Points of the TEMPO Trial

1. Rate of eGFR change
2. Change of mean arterial pressure
3. Change of kidney pain

Torres, VE. et al.: Am J Kidney Dis. 57(5), 692-699, 2011.

Population Characteristics

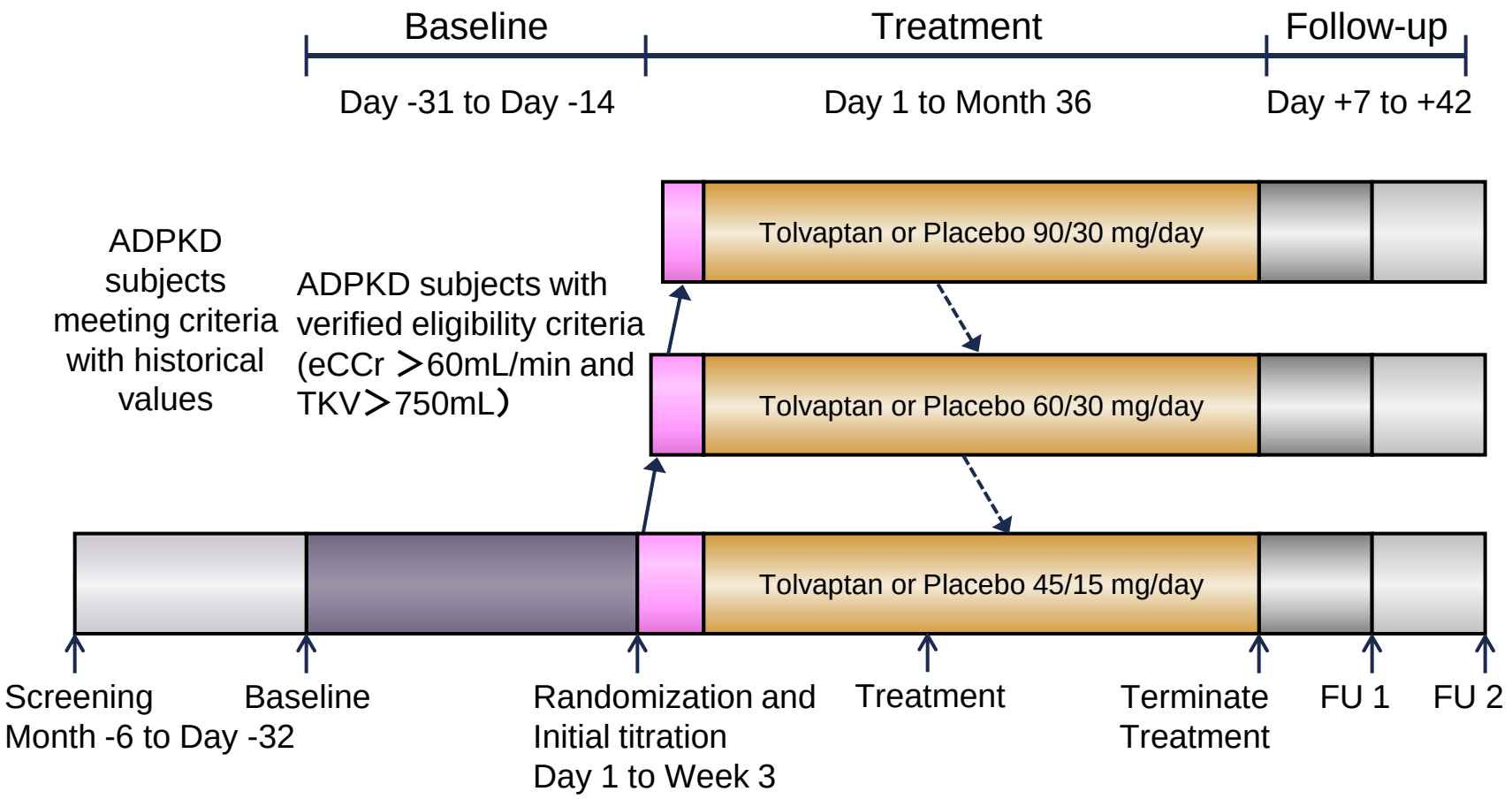
Characteristic	Tolvaptan (N=961)	Placebo (N=484)
Age, years*	39 ± 7	39 ± 7
Male, %	52	52
Caucasian, %	84	84
Hypertension at baseline, %	80	79
ACEIs and/or ARBs, %	71	72
History of kidney pain, %	52	50
History of proteinuria, %	24	24
Total kidney volume, mL*	1705 ± 921	1668 ± 873
eGFR (CKD-EPI), mL/min/1.73 m^2*	81 ± 21	82 ± 23

*Mean ± SD

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration calculator; eGFR=estimated glomerular filtration rate.

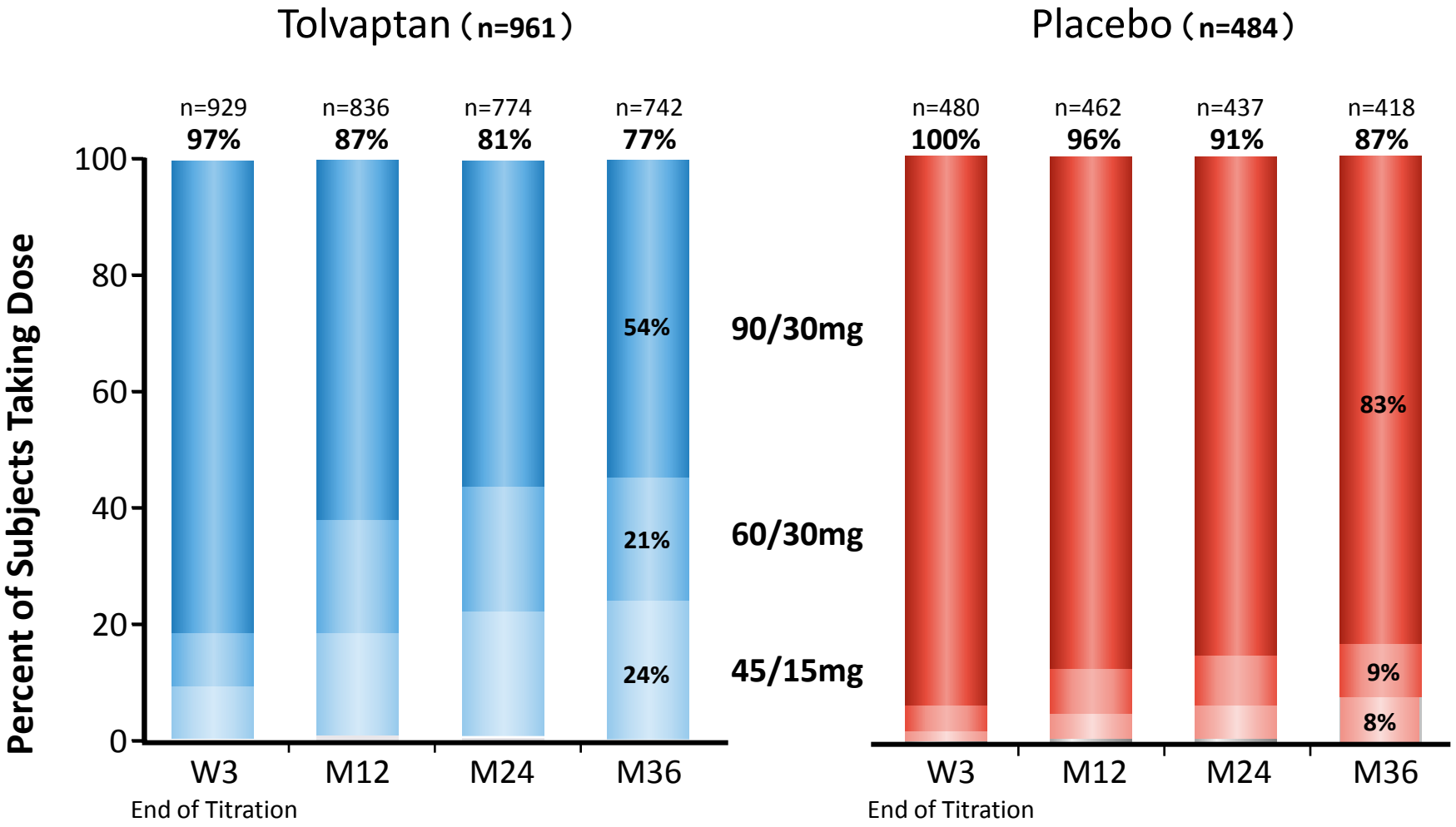
Torres, VE. et al.: N Engl J Med. 367(25), 2407-18, 2012

Schematic trial design of the TEMPO Trial



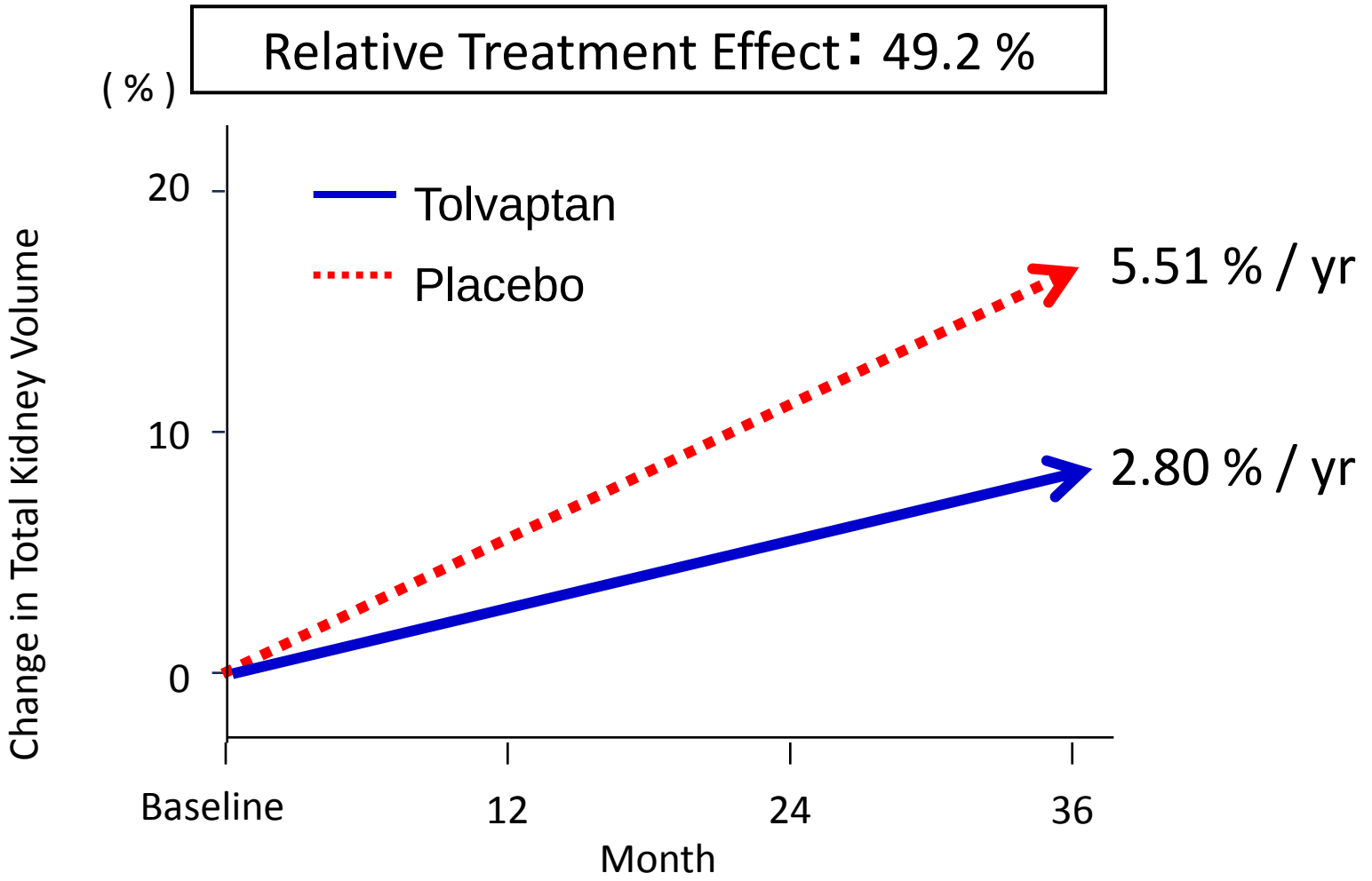
Torres, VE. et al.: Am J Kidney Dis. 57(5), 692-699, 2011.

Majority of Completers Maintained on Highest Dose



FDA Advisory Committees
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm364581.htm

Effect of Tolvaptan on the Annual Slopes of Total Kidney Volume

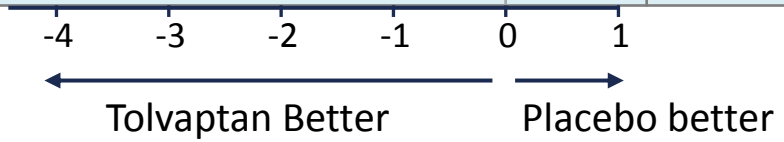


The slopes of the growth in total kidney volume in the intention-to-treat population during the 3-year treatment period are shown, with individual patient data included in the slope calculations. The ratio of the geometric mean was 0.97 (95% CI, 0.97 to 0.98; P<0.001)

Torres, VE. et al.: N Engl J Med. 367(25), 2407-18, 2012

Treatment Effect for Total Kidney Volume

	Relative Treatment Effect (%)	*P* Value
Sex		
Male	37.3	＜0.001
Female	71.1	＜0.001
Age		
＜35yr	28.0	0.02
≧35yr	58.2	＜0.001
Hypertension		
Yes	50.5	＜0.001
No	51.2	0.008
Estimated creatinine clearance		
＜80 mL/min	57.2	＜0.001
≧80 mL/min	47.5	＜0.001
Total kidney volume		
＜1500 mL	48.8	＜0.001
≧1500 mL	51.1	＜0.001
All patients	49.2	＜0.001

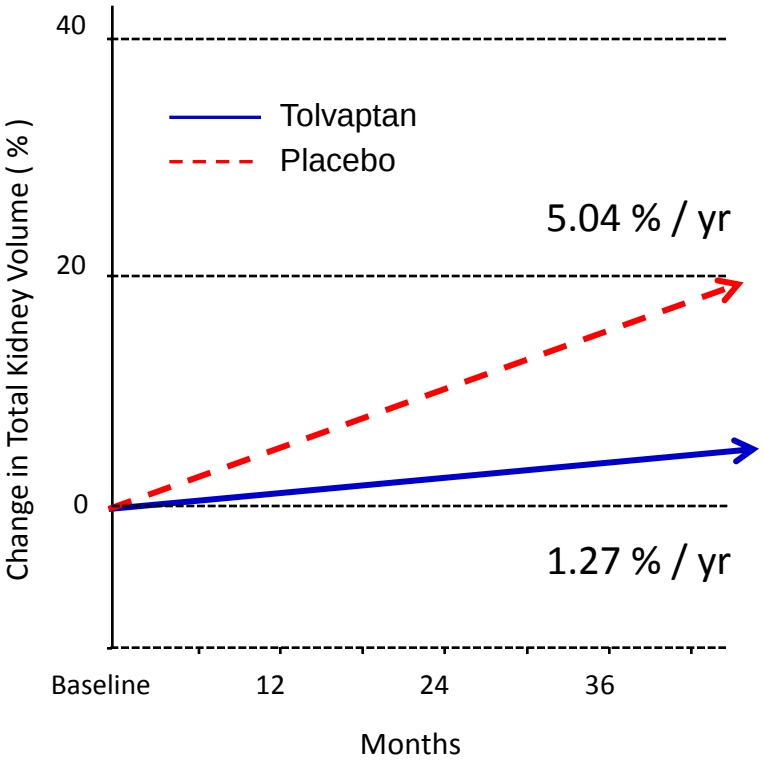


Torres, VE. et al.: N Engl J Med. 367(25), 2407-18, 2012

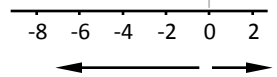
Treatment Effect for Total Kidney Volume

Sub-analysis of Japanese Population (n=177)

Relative Treatment Effect：74.9 %



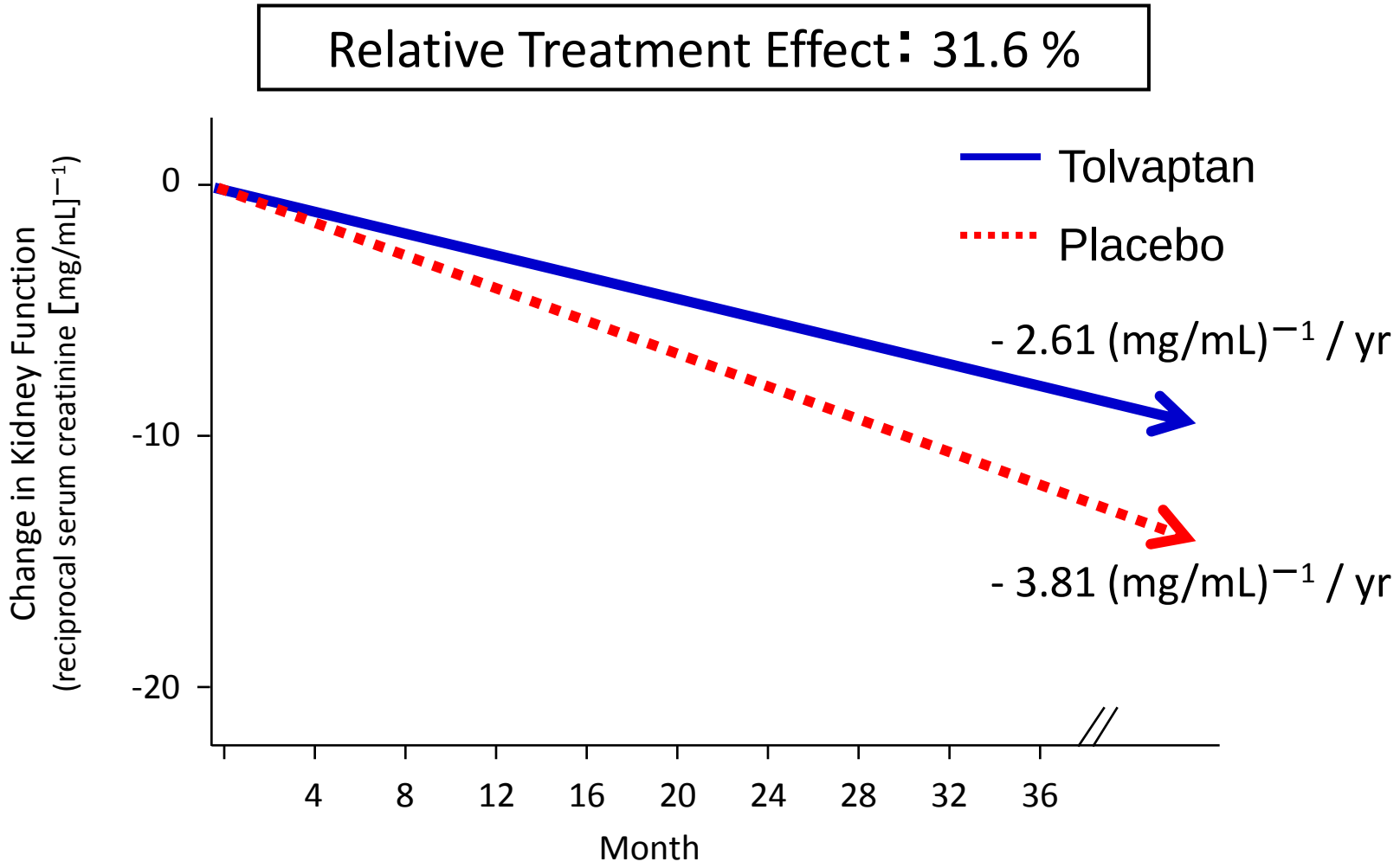
Subgroup	Difference in annual slope (% / yr)	Relative Treatment Effect (%)	*P* Value
All Patients		74.9	< 0.001
Sex			
Male		53.9	0.002
Female		110.3	< 0.001
Age			
< 35 yr		30.7	0.340
≥ 35 yr		85.3	< 0.001
Hypertension			
Yes		68.8	< 0.001
No		95.9	< 0.001
eCCL			
< 80 mL/min		93.0	< 0.001
≥ 80 mL/min		57.8	0.002
Total kidney volume			
< 1500 mL		81.7	< 0.001
≥ 1500 mL		66.3	0.002



Tolvaptan better　Placebo better

Horie S et al, ASN Kidney Week 2013 (Atlanta)

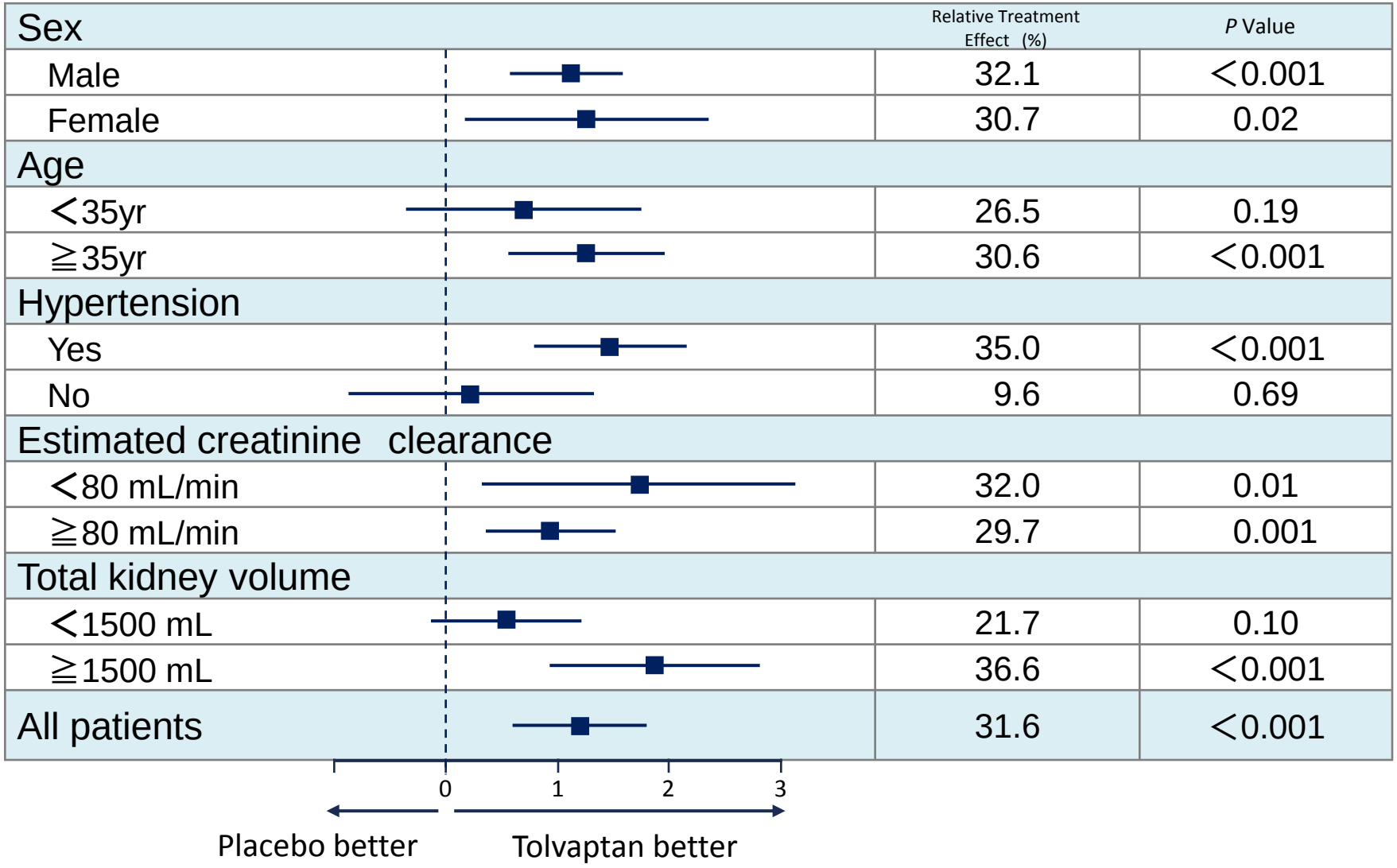
Effect of Tolvaptan on the Annual Slopes of Kidney Function



The annual difference in slope was 1.202 (mg per milliliter)$^{-1}$ per year (95% CI, 0.62 to 1.78; P<0.001)

Torres, VE. et al.: N Engl J Med. 367(25), 2407-18, 2012

Treatment Effect for Kidney Function

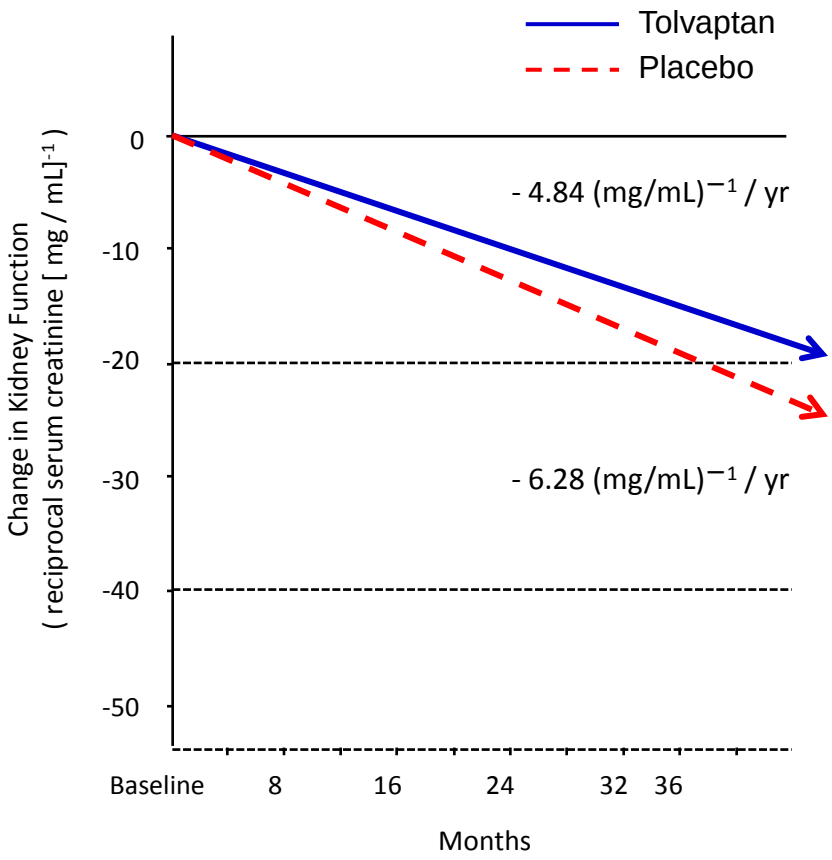


Torres, VE. et al.: N Engl J Med. 367(25), 2407-18, 2012

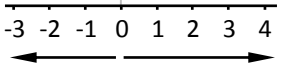
Treatment Effect for Kidney Function

Sub-analysis of Japanese Population (n=177)

Relative Treatment Effect：23.0 %



Subgroup	Difference in annual slope ([mg / mL]$^{-1}$)	Relative Treatment Effect (%)	P Value
All Patients		23.0	0.012
Sex			
Male		32.4	0.005
Female		13.9	0.332
Age			
< 35 yr		-6.3	0.788
≥ 35 yr		26.9	0.006
Hypertension			
Yes		22.7	0.033
No		24.2	0.127
eCCL			
< 80 mL/min		24.8	0.033
≥ 80 mL/min		21.3	0.106
Total kidney volume			
< 1500 mL		10.9	0.435
≥ 1500 mL		29.9	0.008

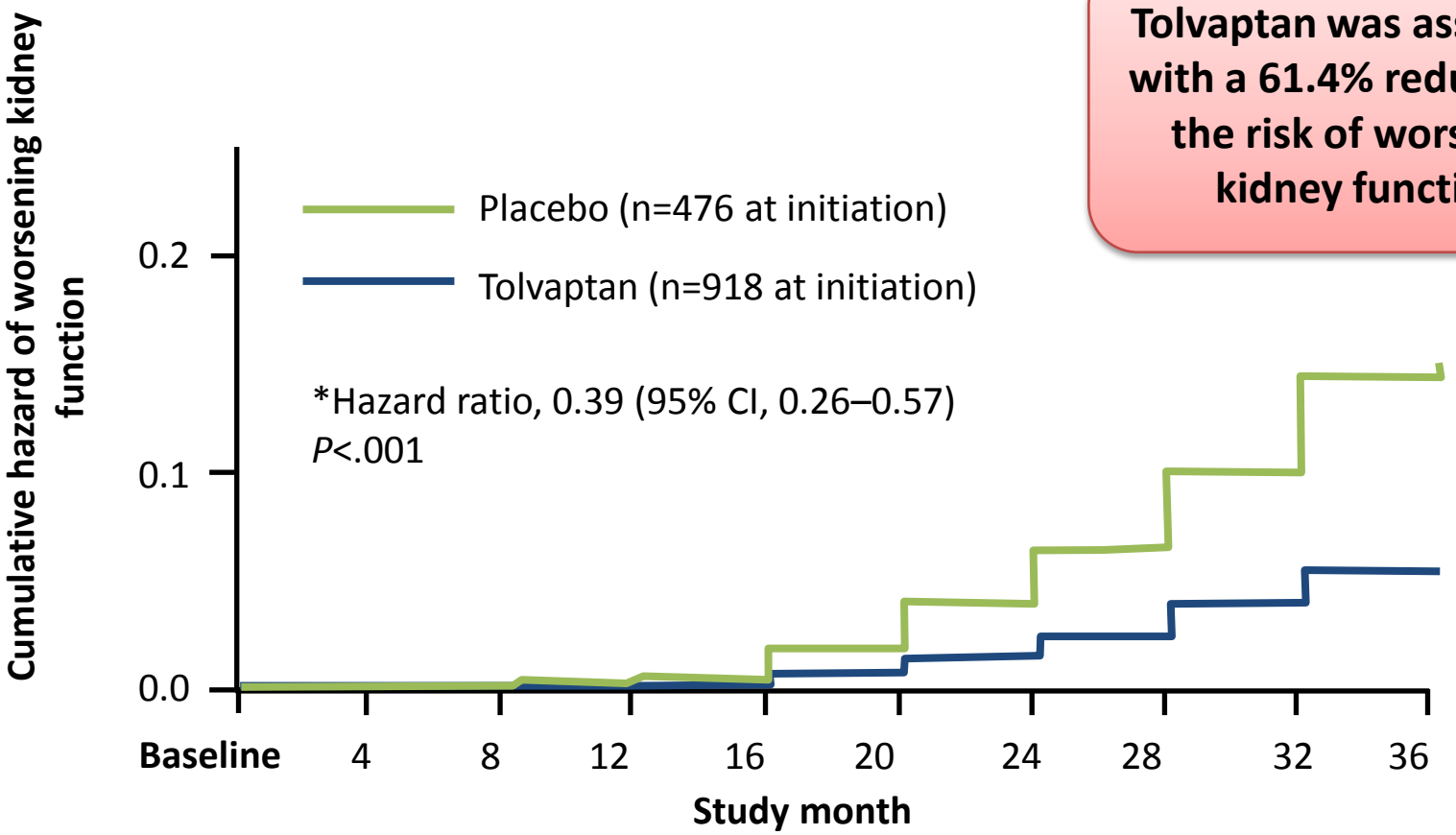


Placebo better　Tolvaptan better

Horie S et al, ASN Kidney Week 2013 (Atlanta)

Tolvaptan on Risk of Worsening Renal Function

Tolvaptan was associated with a 61.4% reduction in the risk of worsening kidney function*

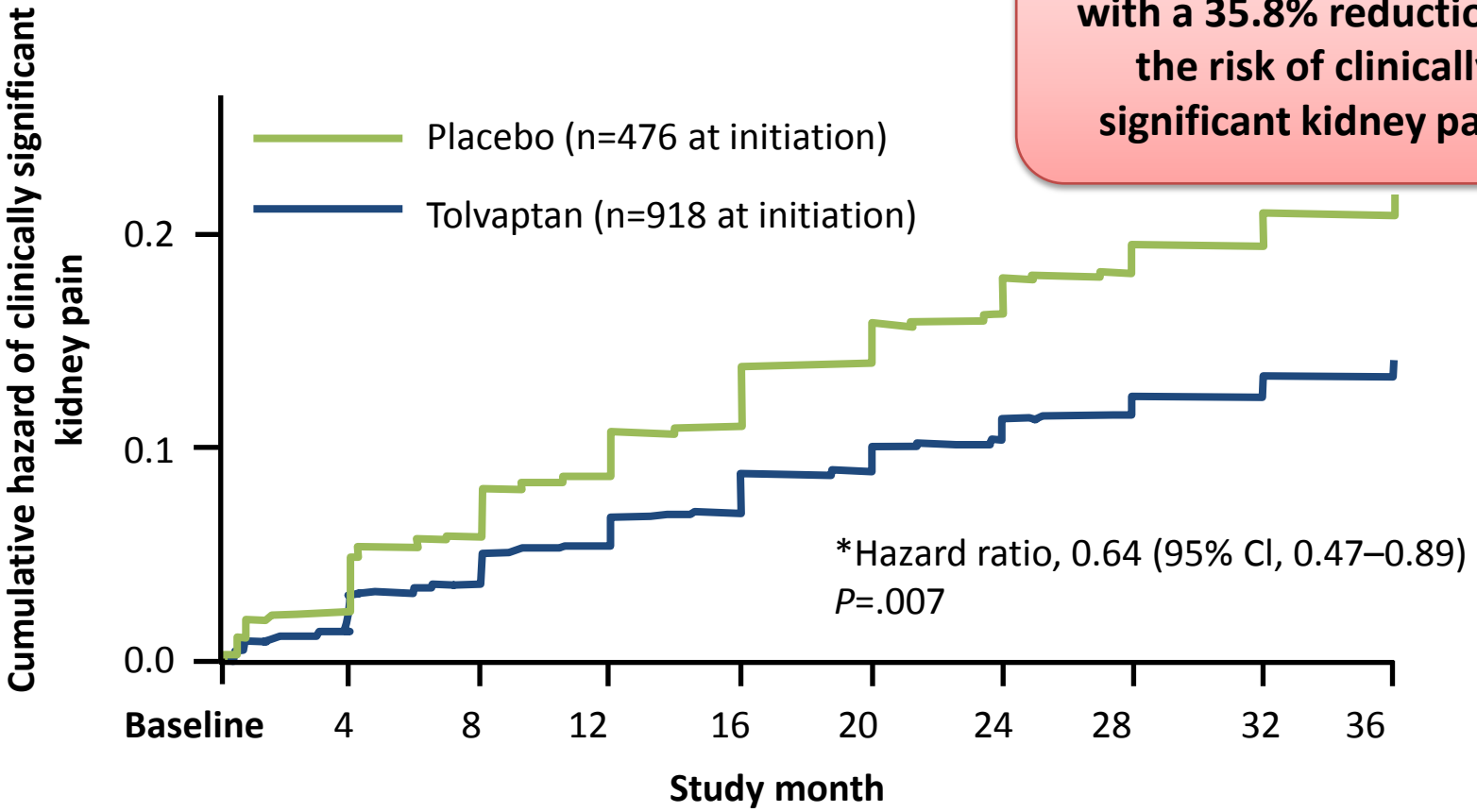


Worsening kidney function was defined as a 25% reduction in reciprocal serum creatinine. The rate of decline of reciprocal serum creatinine value is consistent with the rate of decline of glomerular filtration.

PROJECT J [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Co; 2013.

Tolvaptan on Risk of Clinically Significant Kidney Pain

Tolbaptan was associated with a 35.8% reduction in the risk of clinically significant kidney pain*



Clinically significant kidney pain was defined as requiring prescribed leave, last-resort analgesics, narcotics, or invasive interventions.

PROJECT J [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Co; 2013.

Tolvaptan Slows Kidney Disease in Adults at Risk of Rapidly Progressing ADPKD

- By selectively blocking AVP from binding to V_2 receptors, Tolvaptan results in a decrease in intracellular cAMP and reduces fluid secretion and cell proliferation
- In TEMPO 3:4, a 3-year trial of 1445 patients in CKD stages 1–3, Tolvaptan:
  - Slowed the growth of total kidney volume by 49%
  - Reduced the risk of worsening kidney function by 61%
  - Lowered the risk of clinically significant pain by 36%
  - Decreased the relative rate of ADPKD-related composite events by 13.5%
    - The effect on this endpoint was driven by reduction in the risk of an event of worsening kidney function and/or worsening pain

TEMPO 3:4 Adverse Reactions

(≥3% and Greater Than Placebo)

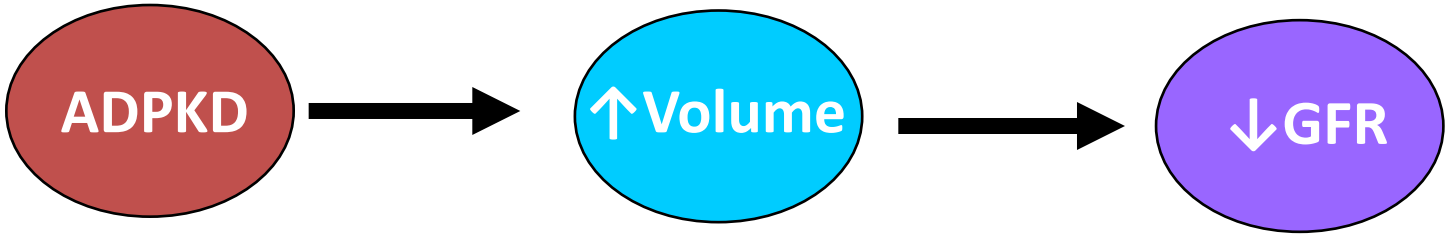
System Organ Class MedDRA Preferred Term	% of Patients	
	Tolvaptan (n=961)	Placebo (n=483)
Cardiac Disorders		
Palpitations	3.5	1.2
Gastrointestinal Disorders		
Abdominal Distension	4.9	3.3
Constipation	8.4	2.5
Diarrhea	13.3	11.0
Dry Mouth	16.0	12.4
Dyspepsia	7.9	3.3
Gastroesophageal Reflux Disease	4.5	3.3
General Disorders and Administration Site Conditions		
Chest Pain	4.4	2.5
Fatigue	13.6	9.7
Thirst	55.3	20.5
Infections and Infestations		
Gastroenteritis	5.6	4.3
Investigations		
Alanine aminotransferase increased	4.1	3.5
Aspartate aminotransferase increased	3.7	3.5
Weight decreased	4.8	3.3

TEMPO 3:4 Adverse Reactions

(≥3% and Greater Than Placebo) (cont'd)

System Organ Class MedDRA Preferred Term (cont'd)	% of Patients	
	Tolvaptan (n=961)	Placebo (n=483)
Metabolism and Nutrition Disorders		
Decreased Appetite	7.2	1.0
Hyperuricemia	3.9	1.9
Polydipsia	10.4	3.5
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	7.2	5.8
Myalgia	5.2	3.3
Nervous System Disorders		
Dizziness	11.3	8.7
Psychiatric Disorders		
Anxiety	3.1	1.7
Insomnia	5.7	4.3
Renal and Urinary Disorders		
Nocturia	29.1	13.0
Pollakiuria	23.2	5.4
Polyuria	38.3	17.2
Skin and Subcutaneous Tissue Disorders		
Dry Skin	4.9	1.7
Rash	4.2	1.9
Pruritus	3.4	2.7

Tolvaptan



INDICATIONS in Japan

1. Volume overload in HEART FAILURE when adequate response is not obtained with other diuretics

2. Body fluid retention in HEPATIC CIRRHOSIS when adequate response is not obtained with other diuretics

3. **Suppression of progression of AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD) in patients with increased kidney volume and a rapid rate of increase**

Limitation:
Total kidney volume: over 750 mL
Kidney volume increase rate: over approximately 5% per year

Approved on March 24, 2014 !!

Tolvaptan will bring dialogues between doctor and patient

Summary (1 of 2)

- ADPKD is the most common inherited monogenic disease and the fourth leading cause of ESRD
- The hallmark of ADPKD, cystogenesis, contributes to many of the renal and systemic manifestations of the disease, often before renal function declines
  - Numerous signaling pathways are involved in cellular proliferation and fluid secretion, including cAMP and mTOR
  - AVP is a modulator of cystogenesis, likely via an effect on cAMP
- Enlarging cysts compress surrounding nephrons and may cause damage, even when kidney function is normal
- Mutations in *PKD1* affect ~85% of people with ADPKD and are associated with a more aggressive type of the disease
- Increased TKV, early family history of ESRD, numerous cysts at baseline, and early hypertension are potential risk factors for rapid disease progression

Summary (2 of 2)

- Tolvaptan is a selective vasopressin V_2-receptor antagonist with demonstrated efficacy to slow kidney disease in adults at risk of rapidly progressing ADPKD
- In a 3-year, phase 3, multicenter, randomized, double-blind, placebo-controlled trial conducted in 1445 patients with ADPKD, PRODUCT J was associated with a:
  - 49% reduction in TKV growth
  - 61% reduction in the risk of worsening kidney function
  - 36% reduction in the risk of clinically significant kidney pain
- Initial dose is a split-dose regimen of 45 mg (upon awakening) and 15 mg (8 hours later) and should be titrated upward as tolerated
- Commonly observed adverse reactions include thirst, polyuria, nocturia, pollakiuria, and polydipsia