ADULT POLYCYSTIC KIDNEY DISEASE

GERALD SCHULMAN, MD, FASN

VANDERBILT UNIVERSITY SCHOOL OF MEDICINE

APCKD

- GENETICS
- SCREENING AND DIAGNOSIS
- MECHANISM OF CYST GROWTH
- RENAL MANIFESTATIONS
- EXTRARENAL MANIFESTATIONS
- COURSE AND TREATMENT
- FUTURE

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AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (APCKD)

- INHERITANCE AS AUTOSOMAL DOMINANT TRAIT
  - AT LEAST 2 LOCI IDENTIFIED
    - 85% WITH CHROMSOME 16 (PKD1 LOCUS); MOST OTHERS WITH CHROMOSOME 4 (PKD2 LOCUS)
  - GENE PRODUCTS IDENTIFIED:
    - POLYCYSTIN 1 - PKD1: 46 EXONS CODING FOR 4000 AA PROTEIN
    - POLYCYSTIN 2 - PKD2: 15 EXONS CODING FOR 1000 AA PROTEIN
- 1 IN 400-1000 LIVE BIRTHS
- PHENOTYPIC EXPRESSION: KIDNEYS WITH EXTENSIVE CYST FORMATION AND OFTEN EXTRARENAL MANIFESTATIONS
  - 50% DETECTION RATE DURING LIFETIME

CHARACTERISTICS OF POLYCYSTIN-1

- LOCATED IN RENAL TUBULAR EPITHEIAL CILIA AND PLASMA MEMBRANE
  - ALSO LOCATED IN HEPATIC AND PANCREATIC DUCTS
- LOCALIZED TO THE LATERAL CELL MEMBRANE – ALLOWING CELL-CELL AND CELL MATRIX INTERACTION AFFECTING GROWTH AND SURVIVAL OF CELLS
- IN MOUSE MODEL, EARLY PKD-1 INACTIVATION (WITHIN 13 POSTNATAL DAYS) RESULTS IN SEVERE CYST FORMATION
- PART OF THE STRUCTURE OF CILIA: SENSING FLOW IN TUBULAR LUMEN AND IN THE CENTROSOME

CHARACTERISTICS OF POLYCYSTIN-2

- MAY SERVE A ROLE IN CALCIUM SIGNALING
- FOUND IN PLASMA MEMBRANE, ENDOPLASMIC RETICULUM AND PRIMARY CILIUM
- INTERACTS WITH POLYCYSTIN-1

SECOND HIT HYPOTHESIS

- ONLY SEVERAL HUNDRED TO A THOUSAND NEPHRONS HAVE TO DEVELOP CYSTS TO RESULT IN RENAL FAILURE
- CYSTIC DILATATION IS FOCAL
- CYSTS MAY FORM ONLY WHEN THERE IS LOSS OF THE NORMAL HAPLOTYPE ***IN ADDITION TO*** THE INHERITED ABNORMAL GENE

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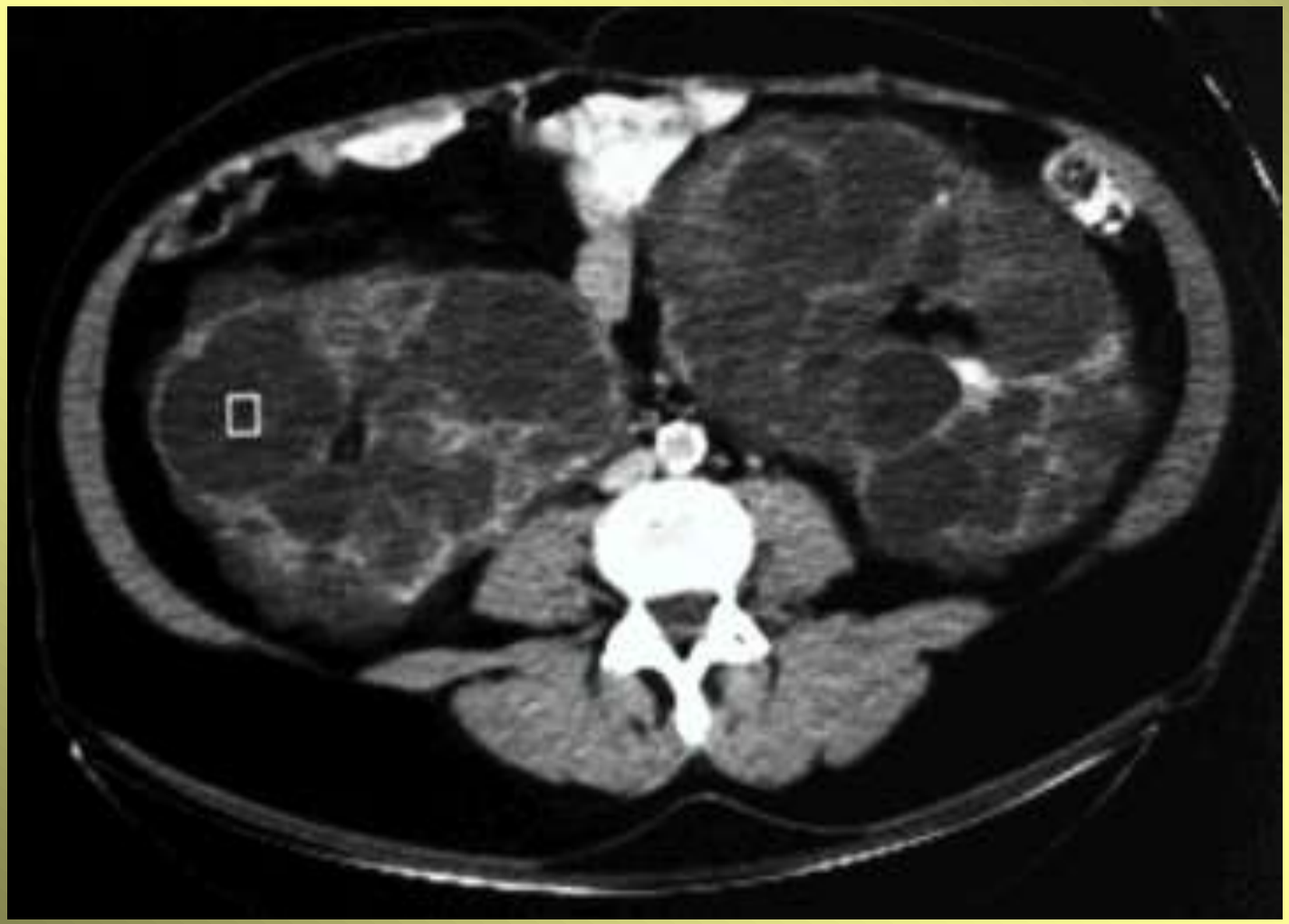
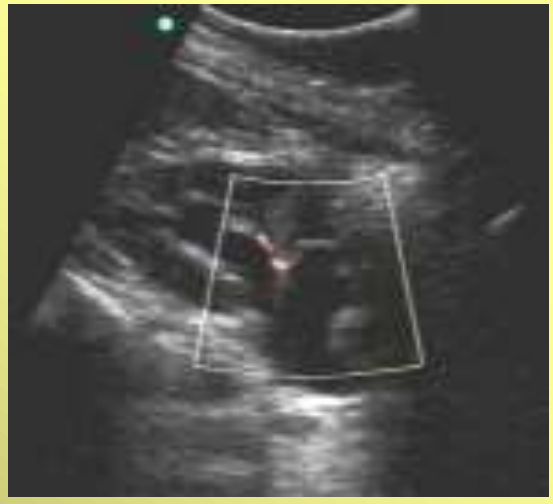
SCREENING

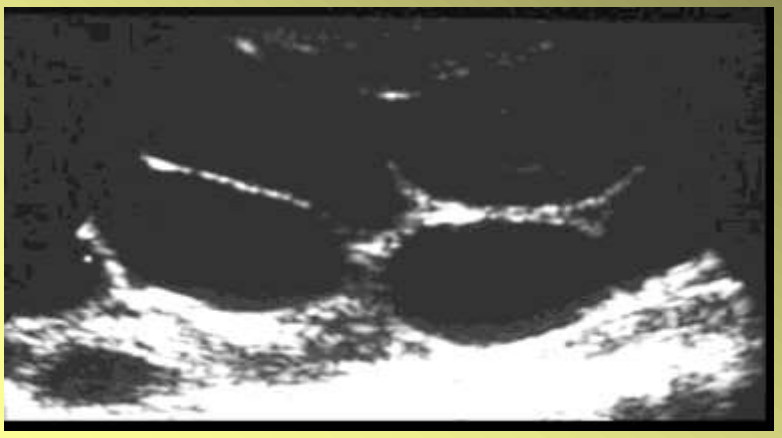
- RENAL ULTRASOUND IS USUAL INITIAL MODALITY; CT AND MRI MAY BE MORE SENSITIVE
- PATIENT AT RISK/UNKNOWN GENOTYPE + FAMILY HX
  - 15-39 YEARS: $\geq$ 3 UNILATERAL OR BILATERAL CYSTS; SENS 82-96%/SPEC 100%
  - 40-59 YEARS: 2 CYSTS IN EACH KIDNEY; SENS 100%/SPEC 98%
  - 60 + YEARS: 4 CYSTS IN EACH KIDNEY; SENS 100%/SPEC 100%
  - NO CYSTS AT AGE 30 RULES OUT APCKD-1
  - DETECTION OF HEPATIC OR PANCREATIC CYSTS
- PATIENT WITH NEGATIVE FAMILY HISTORY
  - 10 OR MORE CYSTS IN EACH KIDNEY
- GENETIC TESTING
  - LINKAGE ANALYSIS- REQUIRES 4 RELATIVES
  - HPLC- 65% DETECTION OF MUTATIONS
  - DIRECT SEQUENCING

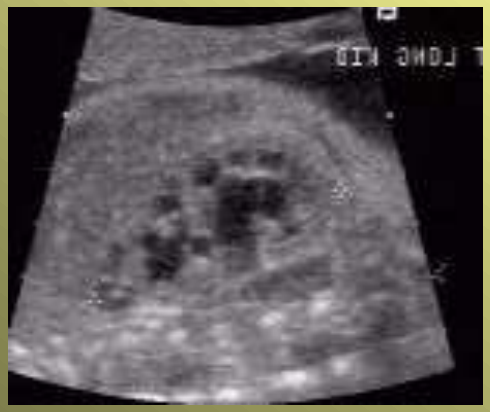
APCKD: COMPUTERIZED TOMOGRAPHY

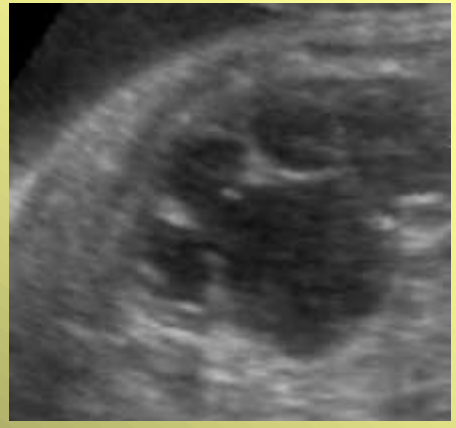


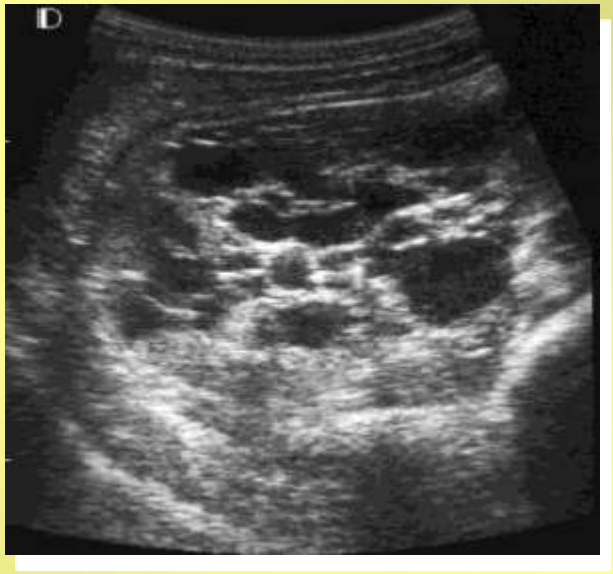
ULTRASOUND PITFALLS











Hogan MC et al J Am Soc Nephrol. 2015 Jul;26(7):1661-70.

Identification of Biomarkers for PKD1 Using Urinary Exosomes

Preliminary study measuring the ratio of exosome-like vesicles (ELV) containing PKD 1 to Transmembrane Protein 2 (similar to fibrocycstin) secreted into the urine.

There is an inverse relationship between this ratio and kidney size in patients with PKD 1.

Eventually it may be useful measure to diagnose and to monitor therapy in PKD 1.

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REQUIREMENTS FOR CYST FORMATION AND GROWTH

- EPITHELIAL PROLIFERATION
- FLUID SECRETION
- MATRIX REMODELING
- FIBROSIS

INTERACTIONS BETWEEN THE POLYCYSTINS

- BOTH LOCALIZE TO CILIA
- BOTH ARE FOUND IN THE CELL MEMBRANE AND IN INTRACELLULAR LOCATIONS
- BOTH INTERACT WITH THE JAK-STAT SIGNALING PATHWAY (CYTOKINE MEDIATED)
- BOTH REGULATE G PROTEIN SIGNALING
- BOTH PROTIENS INTERACT AT THE CELL MEMBRANE
- BOTH PROTEINS CREATE A NON-SELECTIVE CALCIUM PERMEABLE CATION CHANNEL
- MECHANICAL STIMULI LEADS TO POLYCSTIN-2 MEDIATED TRANSLOCATION OF A POLYCYSTIN-1 FRAGMENT TO THE NUCLEI LEADING TO AK-1 TRANSCRIPTION PROMOTING CELL CYCLE ARREST

POSSIBLE DERANGEMENTS LEADING TO CYST FORMATION

- ABNORMALITIES IN CALCIUM CHANNELS
- CYCLIC AMP
  - FLUID SECRETION INTO CYSTS
  - EPITHELIAL PROLIFERATION
- POLYCYTINS LOCATED IN THE CELL MEMBRANE AND/OR IN THE CYTOPLASM INTERACT WITH ONCOGENES AND MITOGENS
- INABLITY OF ABNORMAL CILIA TO DETECT LUMIAL FLOW
  - DECREASE IN CALCIUM TRANSPORT
  - ABNORMAL CACLIUM FLUX LEADS TO EPITHELIAL PROLIFERATION DUE TO CYCLIC AMP SIGNALING

CILIOPATHIC SYPMTOMS

Clinical symptoms and ciliac roles

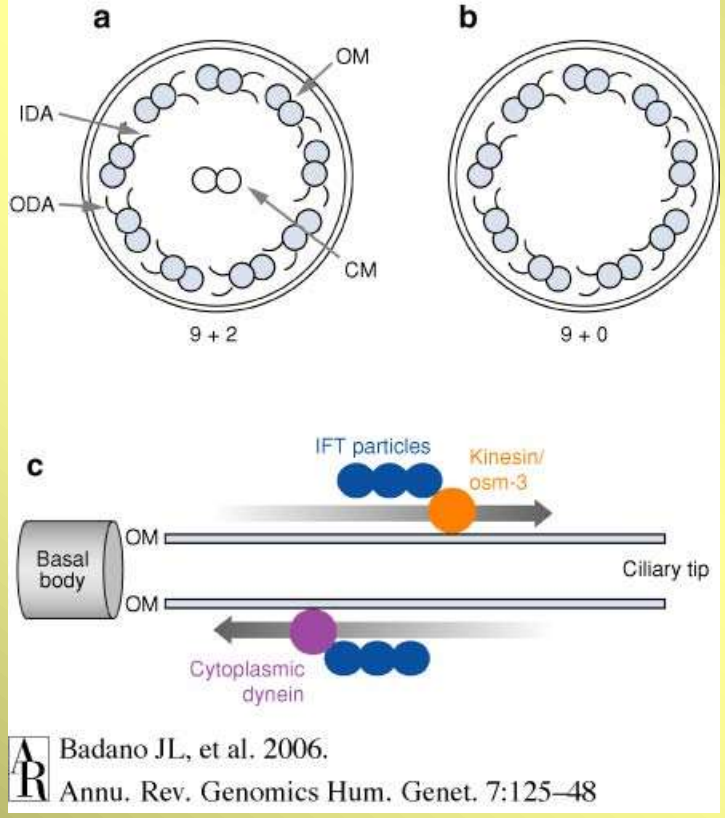
A wide variety of symptoms are potential clinical features of ciliopathy.

Chemosensation abnormalities[6]

Defective thermosensation or mechanosensation[7].

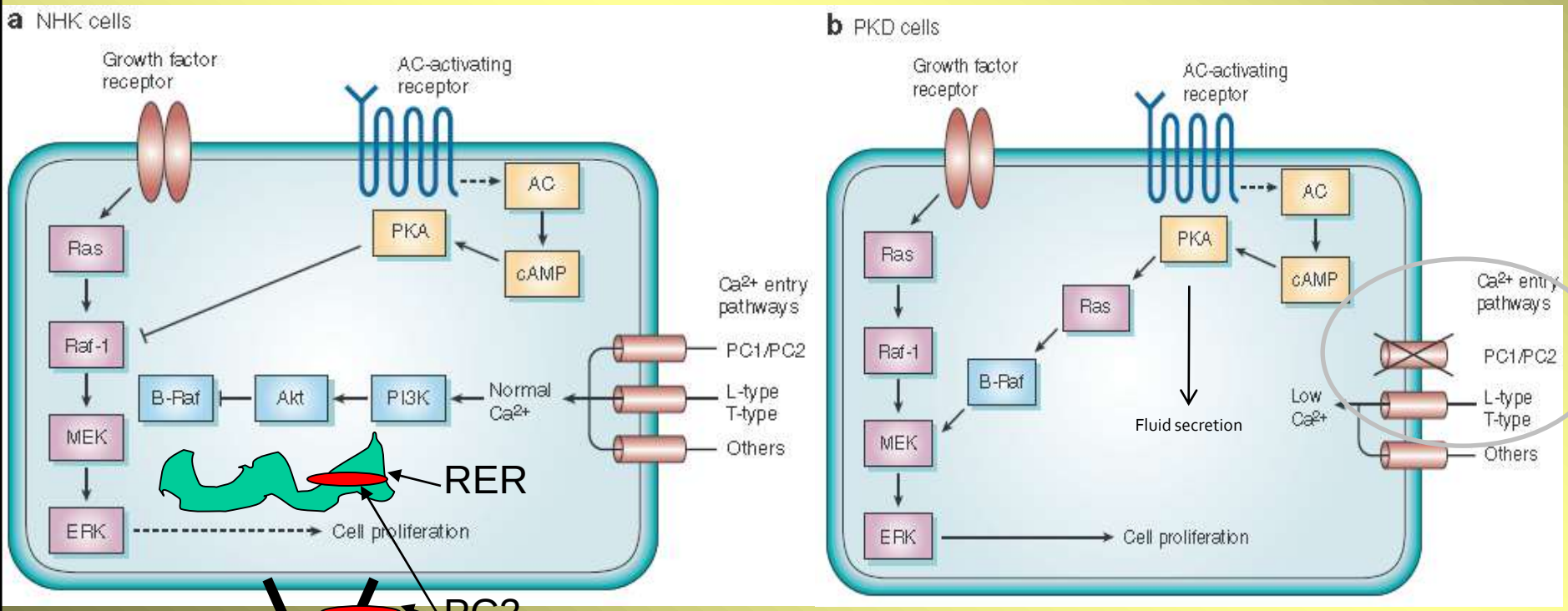
Celluar motility dysfunction[6]

STRUCTURE OF CILUM



Annual Reviews

MAP KINASE CASCADE IN NORMAL AND PCKD CELLS



RER

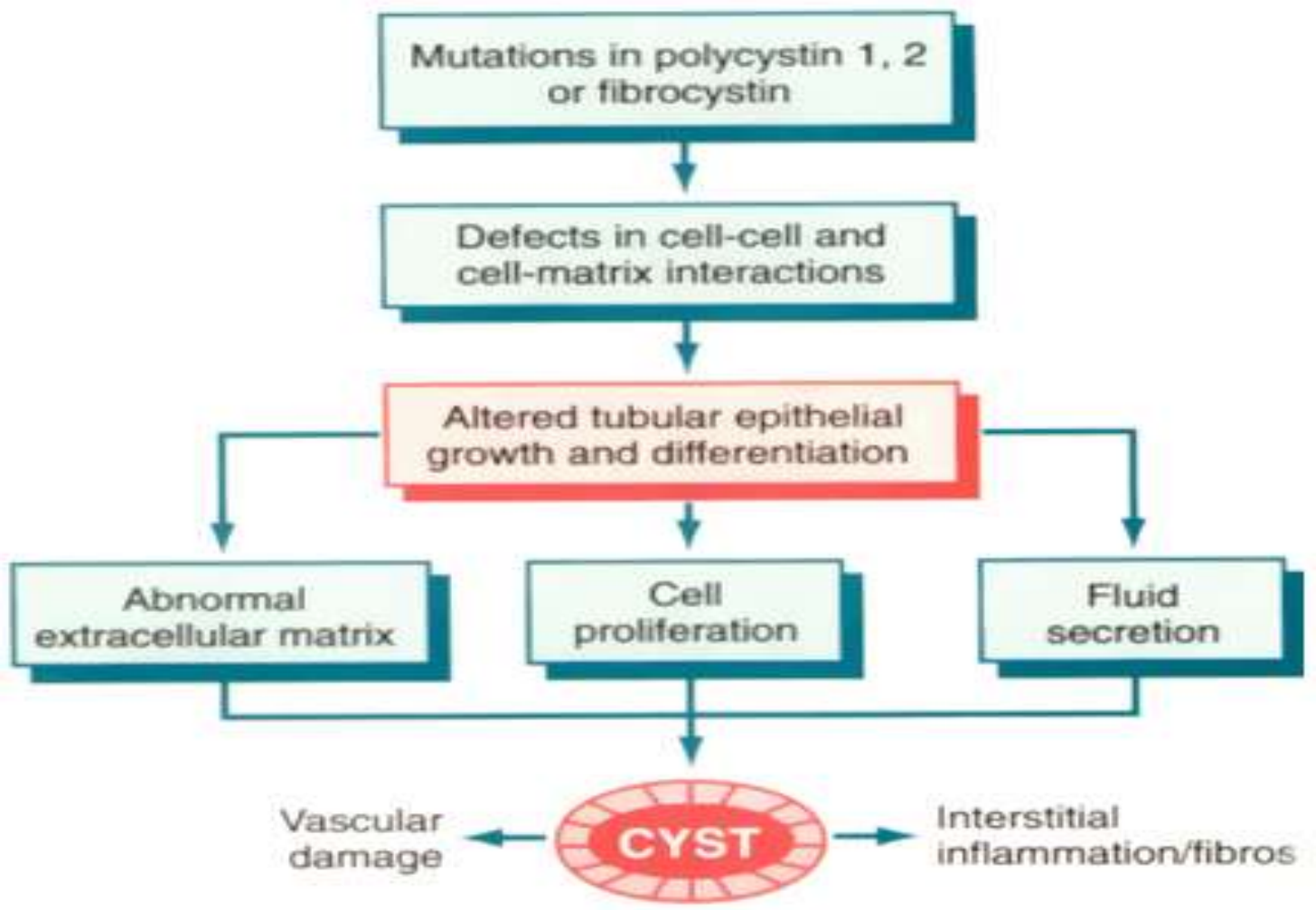
PC2

CILIUM

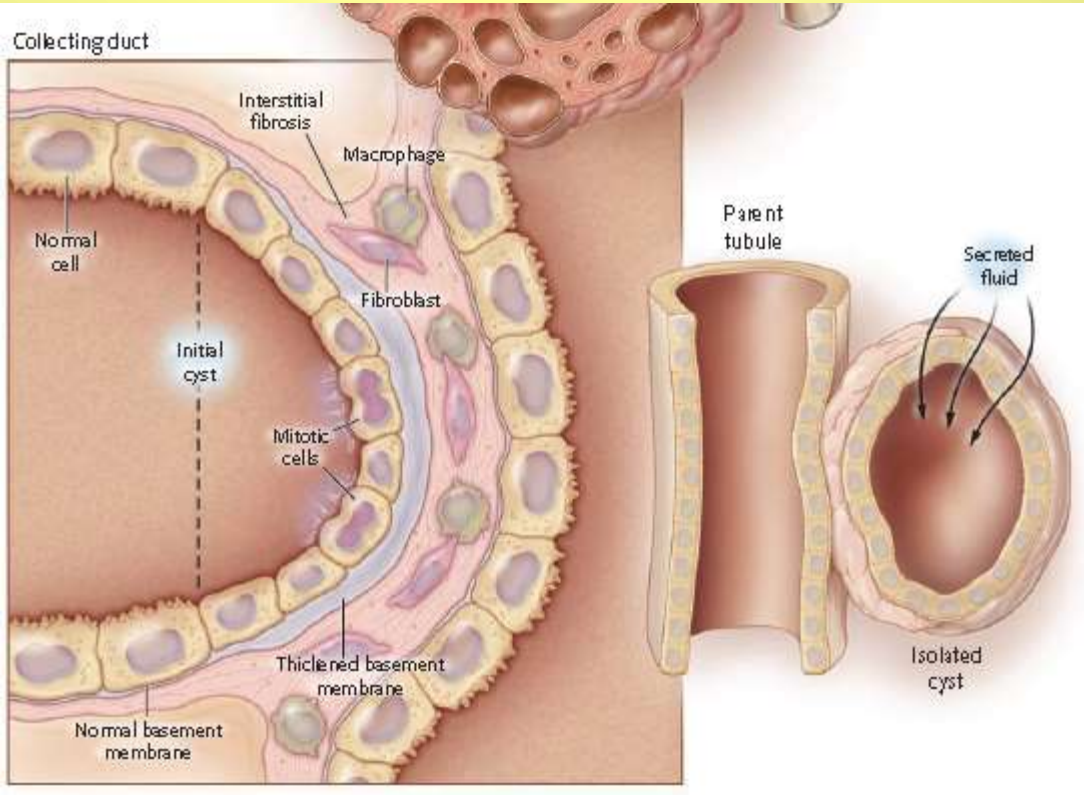
PC1

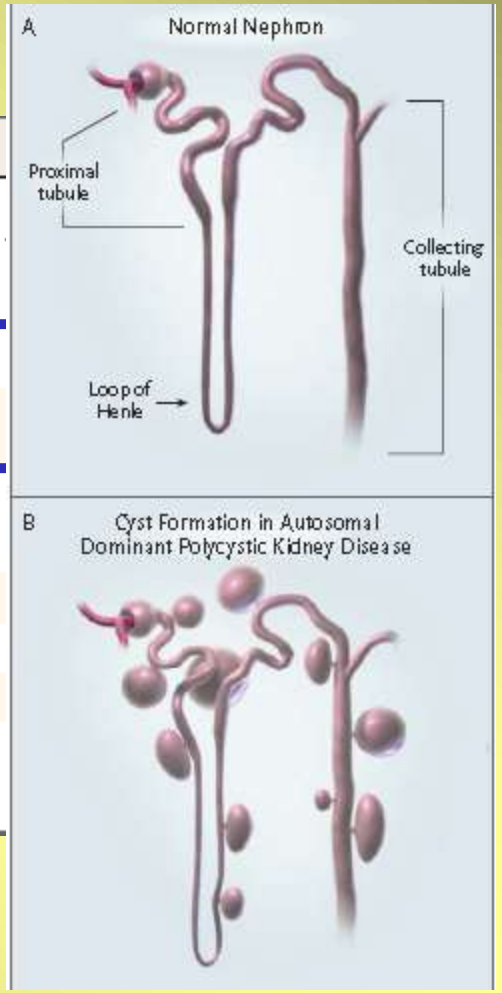
Kidney International (2008) 73, 251–253

POSSIBLE MECHANISMS OF CYST FORMATION IN POLYCYSTIC KIDNEY DISEASE



CYST DEVELOPMENT





N ENGL J MED 350;14 www.NEJM.ORG OCTOBER 2, 2008

N ENGL J MED 350;2 WWW.NEJM.ORG JANUARY 8, 2004

CYST GROWTH

- INITIALLY EXPANDED BY GFR
- FIBROSIS OCCURS LEADING TO LOSS OF CONNECTION TO FUNCTIONING NEPHRONS
- CYST FLUID CONTAINS GROWTH FACTORS AND STIMULATES SECRETION
  - Na-K ATPase FOUND IN APICAL MEMBRANE OF APCKD CELLS
  - CFTR: CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR A C-AMP-DEPENDENT CHLORIDE CHANNEL,IS IN THE APICAL MEMBRANE OF APCKD CELLS
  - CYST FLUID CAUSES RENAL EPITEILIUM IN CULTURE TO FORM CYSTS
- CYTIC FLUID ACCUMULATION ESTIMATED AT 26-475 mL/year
- SODIUM CONTENT OF CYSTS IS VARIABLE

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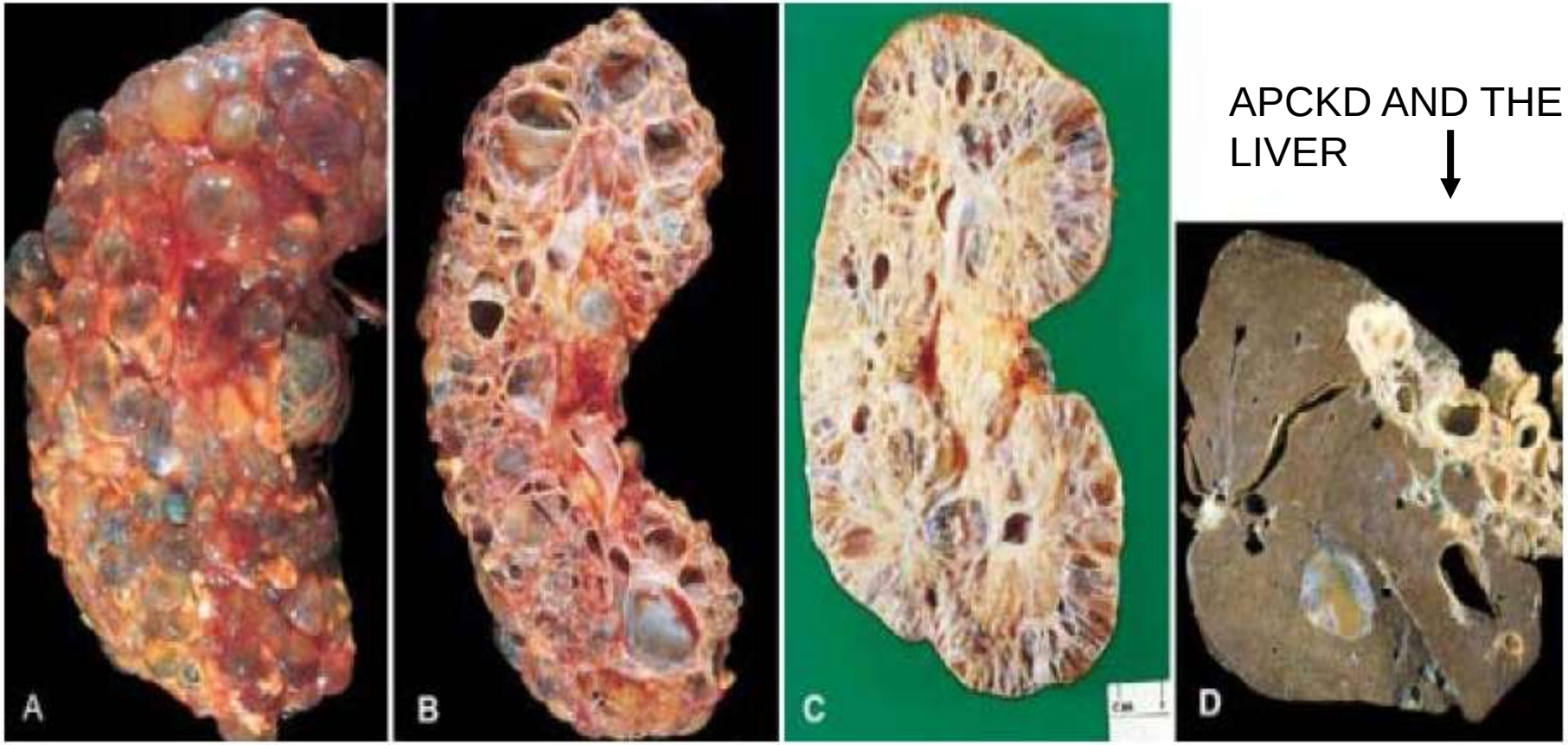
RENAL EFFECTS OF APCKD

- CYST GROWTH AND RENAL FAILURE
- HYPERTENSION
- HEMATURIA
  - CYST RUPTURE
- PROTEINURIA
  - 300MG – 1 GRAM /24 HOURS
- RENAL CALCULI
  - MOST OFTEN URIC ACID
- LOSS OF CONCENTRATNG ABILITY
- INFECTION: NEED TO CHOOSE ANTIBIOTICS THAT CAN ENTER THE CYSTS
- PAIN SYNDROMES
- POLYCYTHEMIA

CYCTIC KIDNEY DISEASE



APCKD AND THE LIVER

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EXTRARENAL EFECTS OF APCKD

- CEREBRAL ANEURYSMS
- HEPATIC CYSTS
- CARDIAC VALVE DISEASE
- COLONIC DIVERTICULI
- HERNIAS
- EARLY SATIETY

ANEURYSMS

- INTRACEREBRAL HEMORRHAGE/SAH
  - 4%-10% INCIDENCE
  - 22% IF A RELATIVE SUFFERED A BLEED
  - 50% DEATH OR DISABILITY
- SCREENING
  - PATIENTS WITH BLEED, POSITIVE FAMILY HISTORY, WARNING SYMPTOMS, HIGH-RISK OCCUPATION, HYPERTENSION, NEED FOR ANTICOAGULATION
- RE-SCREENING
  - HIGH-RISK PATIENTS
    - IF INITIAL STUDY IS NEGATIVE THE IS A 2.6% INCIDENCE OF AN ANEURSM AFTER 10 YEARS OF FOLLOW-UP
    - RE-SCREEN EVERY FIVE YEARS IF INITIAL STUDY IS NEGATIVE; EVERY 2-3 YEARS IF ANEURYSM IS SMALL ~ 7-10M
  - LOW-RISK PATIENTS (- FAMILY HISTORY) ?

OTHER ORGANS

- HEPATIC CYSTS
  - UP TO 80% OF PATIENTS WILL HAVE CYSTS
  - EQUAL MALE/FEMALE INCIDENCE BUT MORE SEVERE IN FEMALES (ASSOCIATED WITH BIRTH CONTROL PILLS)
  - RARELY TRANSPLANTATION IS REQUIRED; RAPAMYCIN REDUCES HEPATIC CYSTS
- CARDIAC
  - MITRAL VALVE PROLAPSE AND AI
  - INCIDENCE 20%
- COLONIC DISEASE
  - DIVERTICULI

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FACTORS AFFECTING PROGRESSION

- YOUNGER AGE
- MALE GENDER
  - PKD 1
- PKD 1 vs PKD2
  - ESRD AT 54 YEARS vs 74 YEARS
- EPISODES OF GROSS HEMATURIA
- PROTEINURIA
- HYPERTENSION
- RAPID RENAL GROWTH
- 25% ESRD AT AGE 50; 40% ESRD AT AGE 60; 70% ESRD AT AGE 70

FAMILIAL FACTORS

- CONTROVERSY REGARDING INTRAFAMILIAL HOMOGENEITY
- CONFOUNDERS
  - DIAGNOSTIC TECHNIQUES
  - NATURE OF THE GENETIC ABNORMALITY
  - GENETIC ANTICIPATION IN OFFSPRING
  - OTHER GENETIC MODIFIERS
  - ENVIRONMENT

GENETIC ANTICIPATION

Anticipation of age at renal death in autosomal dominant polycystic kidney disease (ADPKD)? 1605

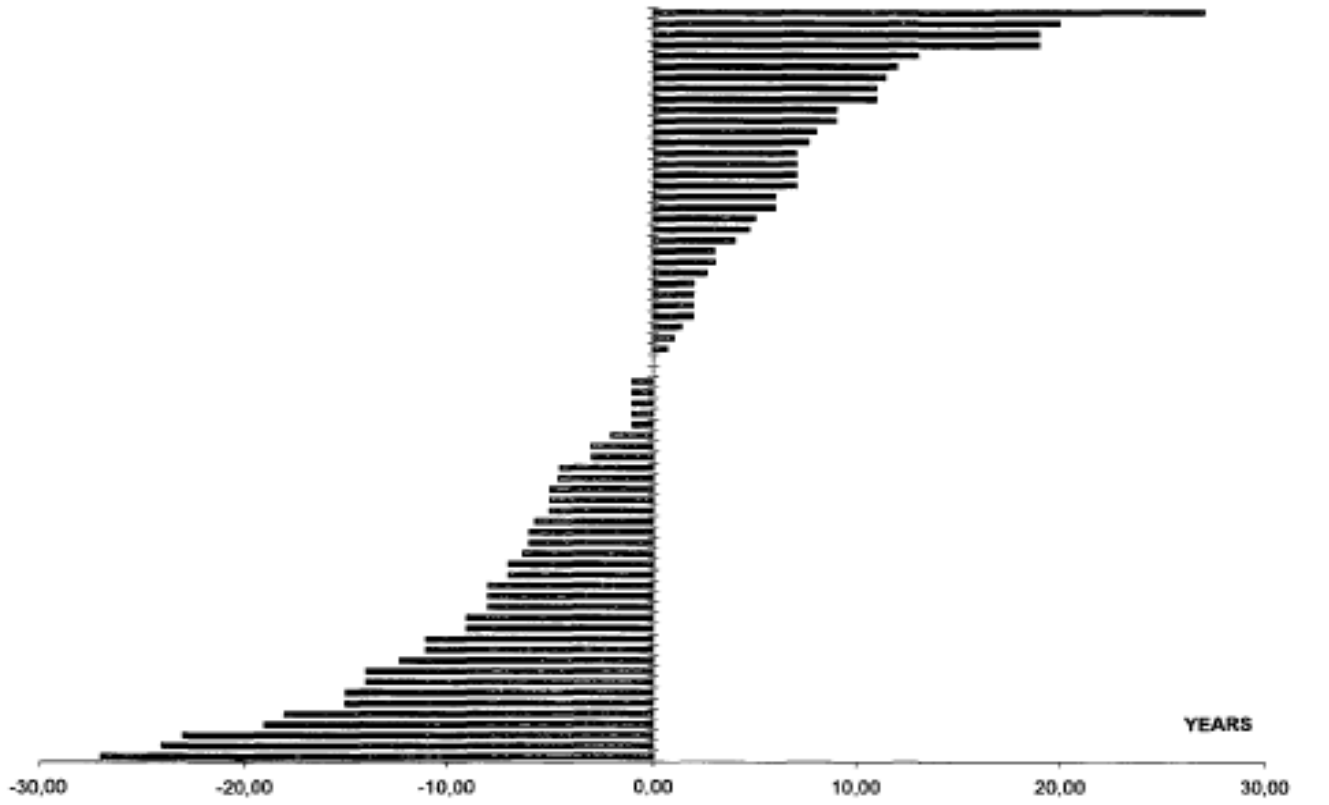

Fig. 1. Difference of age at renal death, (ranked according to the magnitude of the difference [in years] of offspring minus parent) of 70 families with one parent/offspring pair each.

TREATMENT STRATEGIES

- PREVENTION OF CYST GROWTH
  - INIBITION OF TRANSPORT
    - VASOPRESSIN ANTAGONISTS
    - REDUCED CAFFEINE INTAKE
    - SOMATOSTATIN
  - INHIBITION OF CELL PROLIFERATION
    - VASOPRESSIN, STEROIDS, RAPAMYCIN
  - INHIBITION OF FIBROSIS
    - RAAS BLOCKADE, PROTEIN RESTRICTION
  - CYST REDUCTION
  - CONTROL OF HYPERTENSION

APCKD AND ESRD

- CHALENGES IN APCKD
  - LARGE KIDNEYS
    - LOWER PERITONEAL SURFACE
    - DIFFICULTY IN PLACING TRANSPLANT
  - CYST INFECTION/UTI
    - RISK IN TRANSPLANT PATIENTS
    - PERITONITIS IF INFECTED CYSTS RUPTURES
  - DIVERTICULAR DISEASE
    - RISK IN TRANSPLANT PATIENTS
    - RISK IN PD PATIENTS
  - POLYCYTHEMIA, HEMATURIA, CHRONIC PAIN

ESRD MANAGEMENT

- OVERALL ESRD SURVIVAL IS ABOVE AVERAGE IN APCKD
  - APCKD RR DEATH 0.6 vs OTHER HD PATIENTS
- PD
  - DESPITE CHALLENGES APCKD PD SURVIVAL MAY BE SUPERIOR TO APCKD HD SURVIVAL (HR 1.4) COMPARED TO PATIENTS WITHOT APCKD
- TRANSPLANT
  - INDICATIONS FOR NEPHRECTOMY
    - FREQUENT UTI, SIZE, PAIN, CHRONIC HEMATURIA
  - COLECTOMY MAY BE REQUIRED

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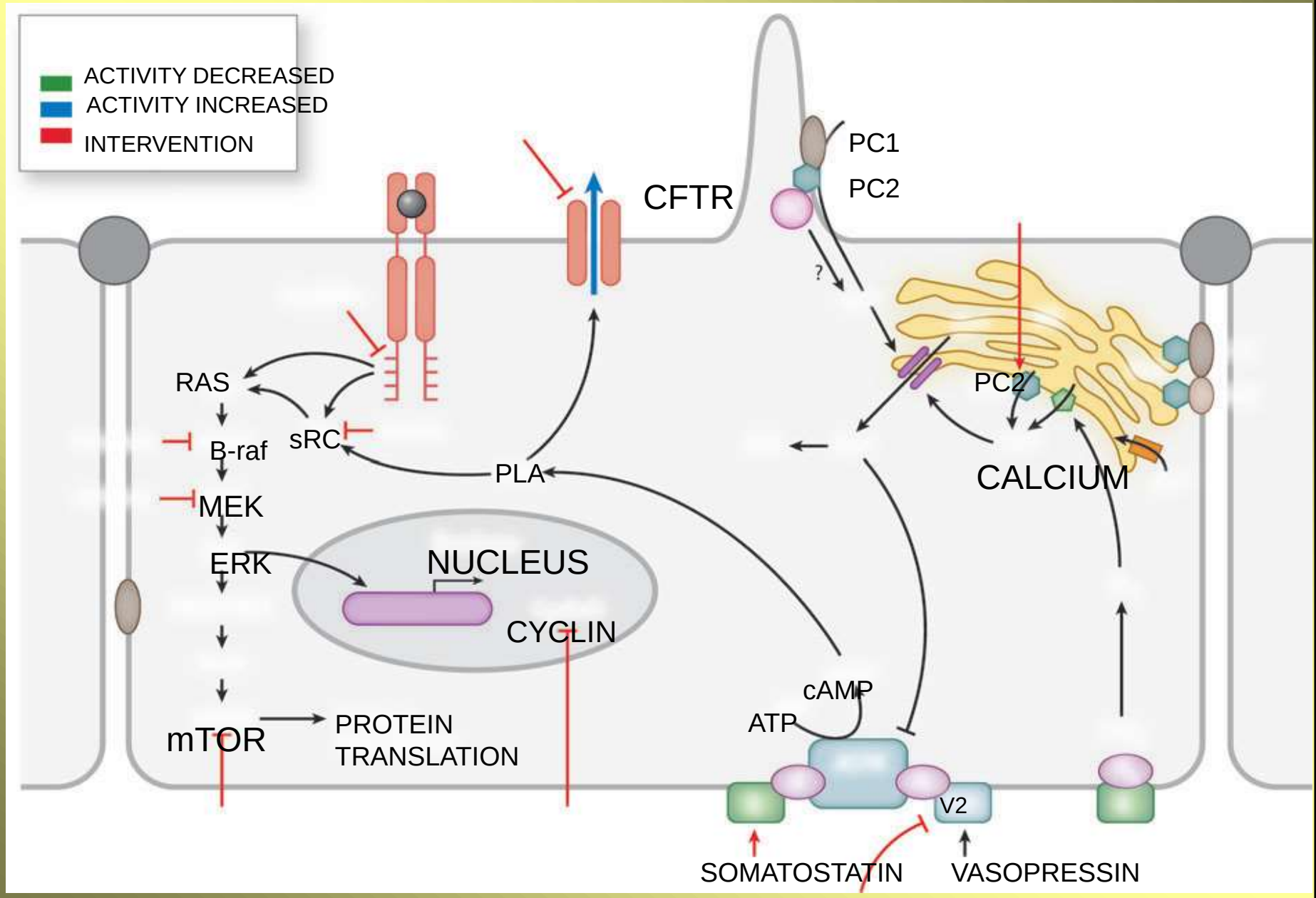
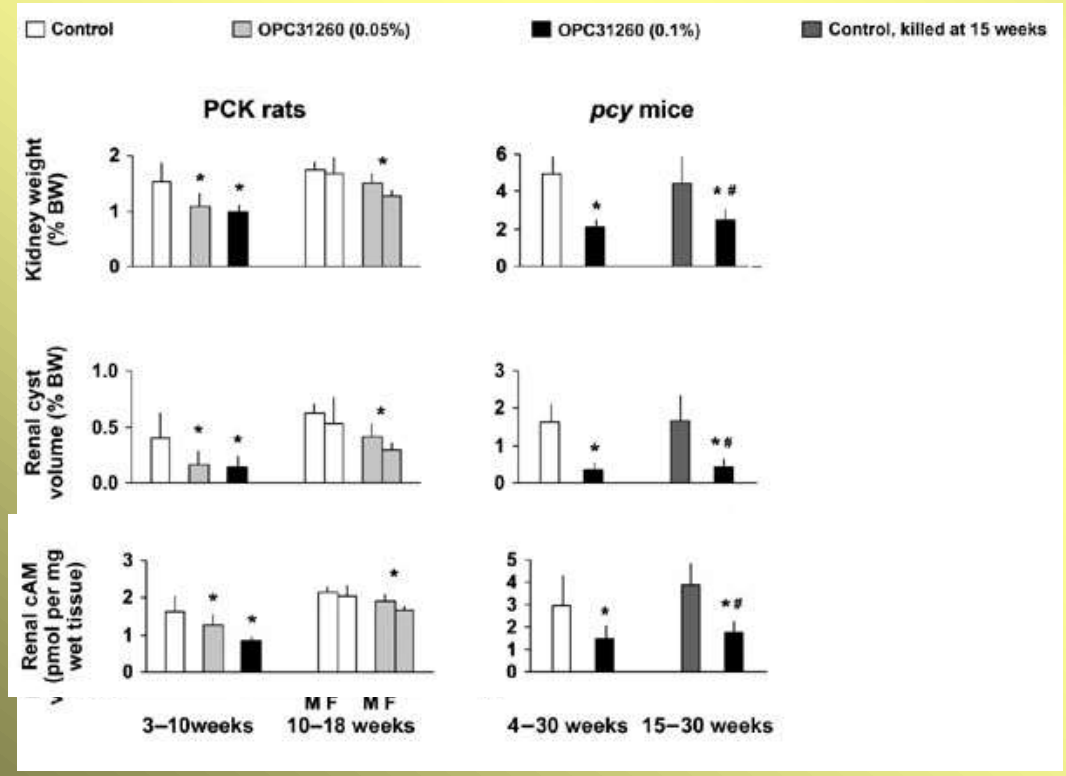
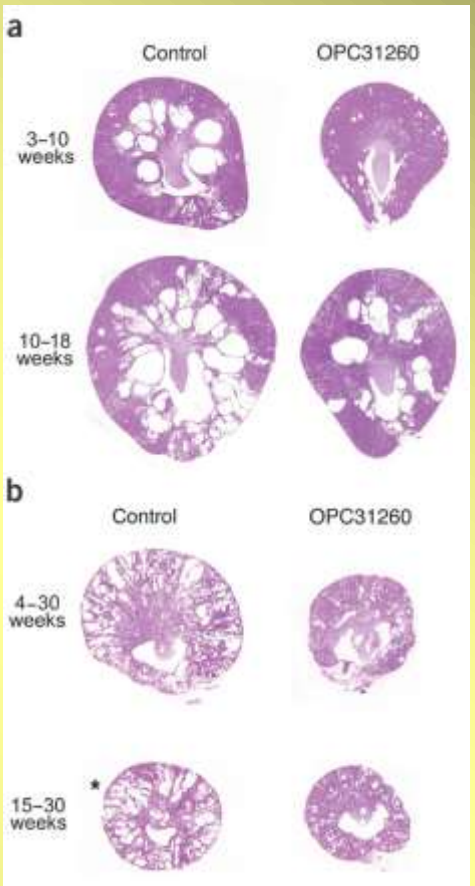
- NEW AND FUTURE DEVELOPMENTS


ACTIVITY DECREASED
ACTIVITY INCREASED
INTERVENTION
CFTR
PC1
PC2
?
PC2
CALCIUM
RAS
B-raf
sRC
MEK
ERK
PLA
NUCLEUS
CYCLIN
mTOR
PROTEIN
TRANSLATION
cAMP
ATP
V2
SOMATOSTATIN
VASOPRESSIN

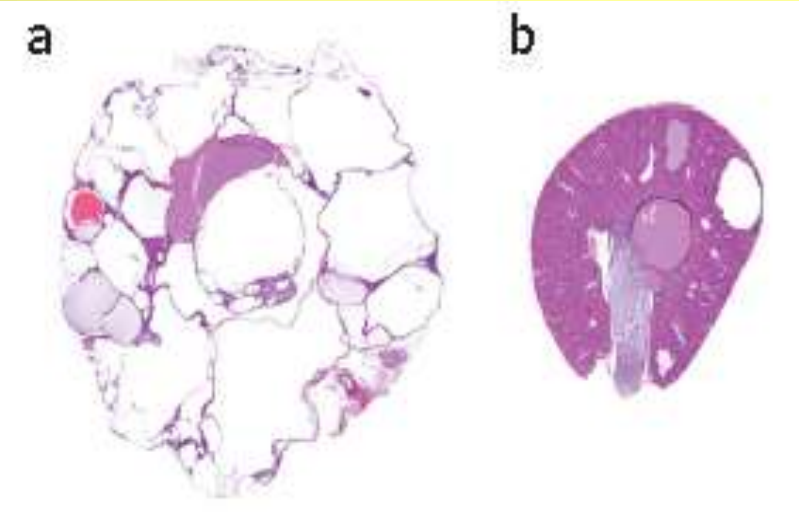
V_2 RECEPTOR ANTAGONISM

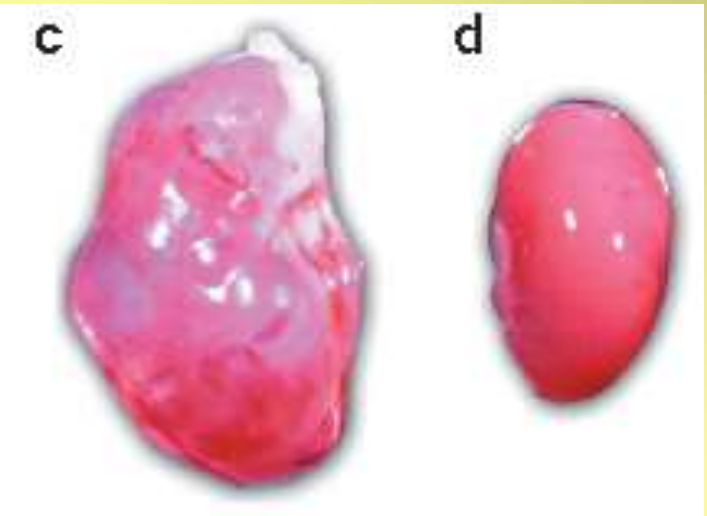




Nature Medicine **9,** 1323 - 1326 (2003)

V_2 RECEPTOR ANTAGONISM





RATIONALE OF EXAMINING INHIBITION OF AVP

- ENDOTHELIAL CELL PROLIFERATION AND FLUID SECRETION NECESSARY FOR RENAL CYST FORMATION IN HERITABLE CYSTIC KIDNEY DISEASE RESULTS FROM ALTERED CALCIUM HOMEOSTASIS AND INCREASED CAMP SIGNALING
- V2 RECEPTOR ANTAGONISTS DECREASE INTRACELLULAR CAMP
- V2 RECEPTOR ANTAGONISTS ARE ATTRACTIVE AS THERAPY BECAUSE OF THEIR RENAL SELECTIVITY
- V2 RECEPTOR ANTAGONISTS CAN BE SAFELY ADMINISTERED BASED ON PRECLINICAL AND CLINCAL DATA IN OTHER DISEASES (CHF, CIRRHOSIS)

INTERVENTIONS

RESULTS OF CURRENT RCTs

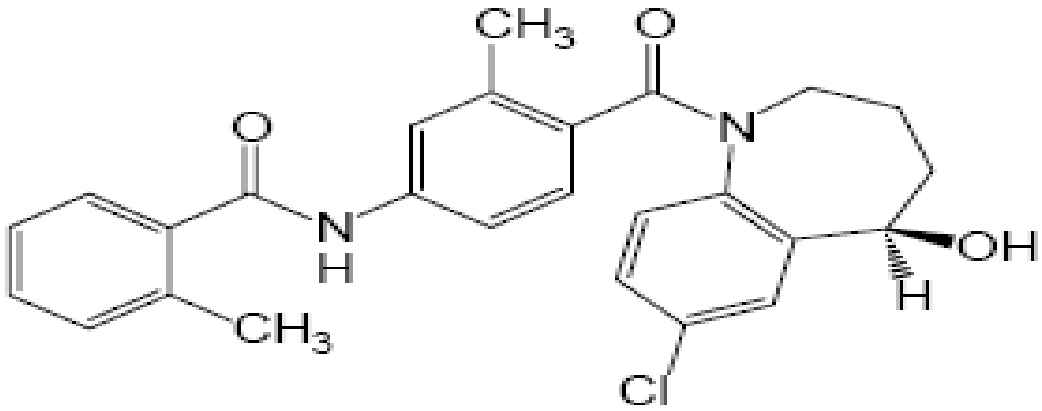
INCREASED WATER INTAKE

If vasopressin stimulates C-amp and cell growth, will reducing stimulus to vasopressin release by increased water intake improve function?

ANSWER: NO

TOLVAPTAN

Chemical structure:



Other name:	OPC-156
INN, USAN:	Tolvaptan
Molecular formula:	$C_{26}H_{25}ClN_2O_3$
Molecular weight:	448.94
Appearance:	OPC-41061 is a white crystalline powder.

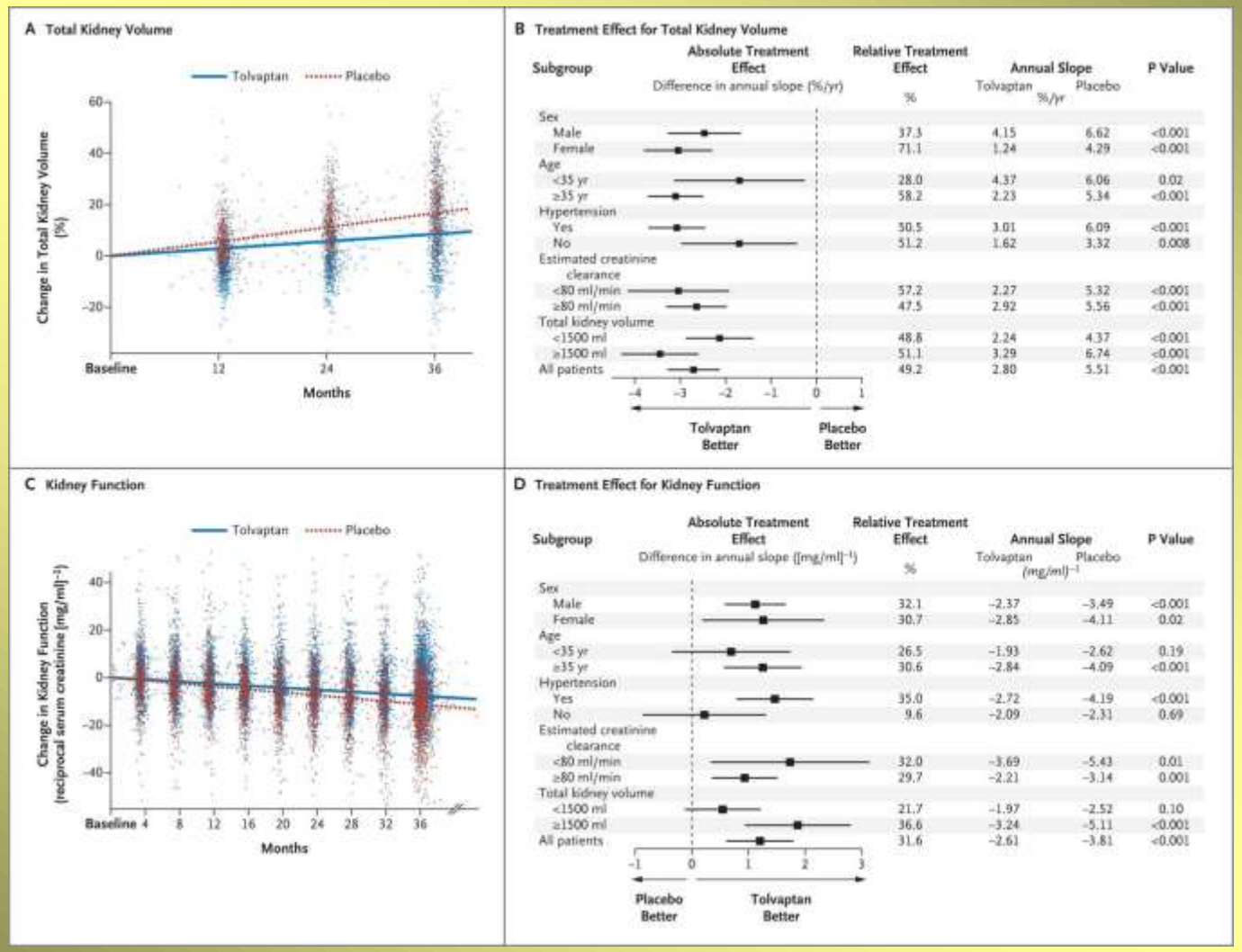
TOLVAPTAN INTERACTION WTH V_1 & V_2 RECEPTORS

- ANTAGONISM TO AVP BINDING:
  - UP TO 300-FOLD INCREASE CONCENTRATION FOR V_1 RECEPTORS
- PLATELET AGGREGATION (MEDIATED BY V_{1a})
  - INHIBITS AVP-INDUCED AGGREGATION BUT NOT ADP-INDUCED AGGREGATION
  - TOLVAPTAN DOES NOT INDUCE AGGREGATION
- DOSE DEPENDENT INCREASE IN URINE VOLUME AND DECREASE IN URINE OSM
  - NO TOLERANCE
  - PARTIAL AGONISTIC WAS NOT DEMONSTATED
- CORRECTS HYPONATREMIA IN MODELS OF CIRRHOSIS, CHF, HYPONATREMIA

TOLVAPTAN STUDY

- PHASE 3 TRIAL
- PROSPECTIVE, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-ARM TRIAL IN PATIENTS WITH APCKD
- 1200-1500 SUBJECTS STUDIED FOR UP TO 36 MONTHS
- SUBJECTS STRATIFIED FOR GFR, RENAL SIZE AND HYPERTENSION

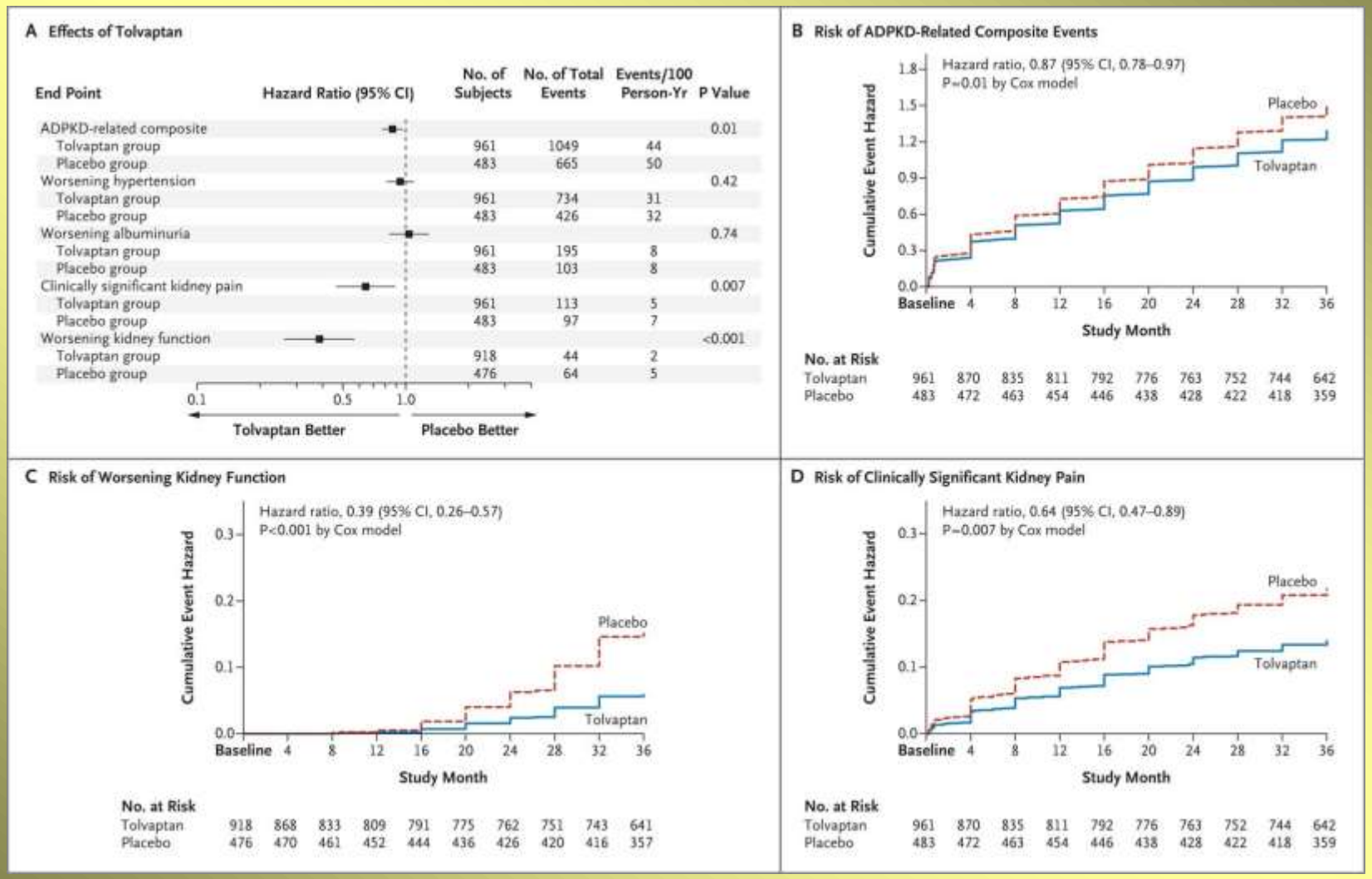
Effect of Tolvaptan on the Annual Slopes of Total Kidney Volume and Kidney Function.



Torres VE et al. N Engl J Med 2012;367:2407-2418

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Tolvaptan on the Time to Multiple Events Associated with Autosomal Dominant Polycystic Kidney Disease (ADPKD).



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Most Common Adverse Events and Serious Adverse Events.

Table 2. Most Common Adverse Events and Serious Adverse Events.*

Event	Tolvaptan (N = 961)	Placebo (N = 483)
	no. of patients with event (%)	
Adverse events more common in tolvaptan group		
Thirst	531 (55.3)†	99 (20.5)
Polyuria	368 (38.3)†	83 (17.2)
Nocturia	280 (29.1)†	63 (13.0)
Headache	240 (25.0)	120 (24.8)
Pollakiuria‡	223 (23.2)†	26 (5.4)
Dry mouth	154 (16.0)	59 (12.2)
Diarrhea	128 (13.3)	53 (11.0)
Fatigue	131 (13.6)	47 (9.7)
Dizziness	109 (11.3)	42 (8.7)
Polydipsia	100 (10.4)†	17 (3.5)
Adverse events more common in placebo group		
Hypertension	309 (32.2)	174 (36.0)
Renal pain	259 (27.0)§	169 (35.0)
Nasopharyngitis	210 (21.9)	111 (23.0)
Back pain	132 (13.7)	88 (18.2)
Increased creatinine level	135 (14.0)	71 (14.7)
Hematuria	75 (7.8)†	68 (14.1)
Urinary tract infection	80 (8.3)§	61 (12.6)
Nausea	98 (10.2)	57 (11.8)
Serious adverse events more common in tolvaptan group		
Alanine aminotransferase elevation	9 (0.9)	2 (0.4)
Aspartate aminotransferase elevation	9 (0.9)	2 (0.4)
Chest pain	8 (0.8)	2 (0.4)
Headache	5 (0.5)	0
Serious adverse events more common in placebo group		
Pyelonephritis	5 (0.5)	5 (1.0)
Renal-cyst infection	6 (0.6)	4 (0.8)
Renal-cyst hemorrhage	3 (0.3)	4 (0.8)
Renal pain	1 (0.1)	4 (0.8)
Appendicitis	1 (0.1)	4 (0.8)
Nephrolithiasis	2 (0.2)	3 (0.6)
Urinary tract infection	1 (0.1)	3 (0.6)
Hypertension	1 (0.1)	3 (0.6)

* Adverse events were categorized according to the *Medical Dictionary for Regulatory Activities* (MedDRA).
† P<0.001 by Fisher's exact test, as compared with the placebo group.
‡ Pollakiuria is more commonly called urinary frequency.
§ P<0.05 by Fisher's exact test, as compared with the placebo group.

Torres VE et al. N Engl J Med 2012;367:2407-2418

The NEW ENGLAND JOURNAL of MEDICINE

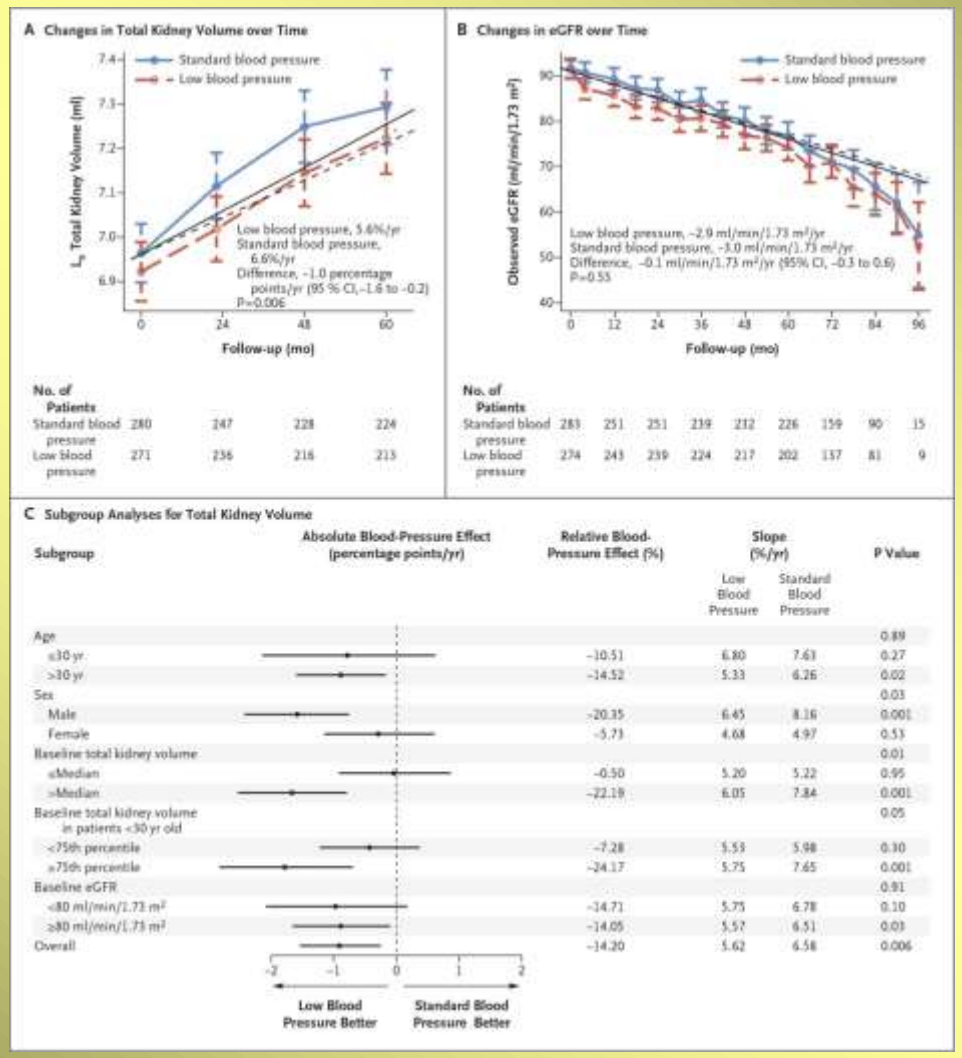
RAAS AND APCKD

- RAAS MAY PROMOTE MITOGEN-INDUCED RENAL CELL GROWTH
- RAAS INHIBITION MAY ATTENUATE RENAL FIBROSIS IN APCKD.

HALT/PKD STUDY

- TO EXAMINE THE EFFECT OF INTENSIVE RAAS BLOCKADE AND BLOOD PRESSURE CONTROL ON PROGRESSION OF APCKD
- 2 PARALLEL STUDIES:
  - A. CKD I-II DESIGN- 2X2 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-MASKED STUDY COMPARING ACE-I MONOTHERAPY vs ACEI + ARB AND STANDARD BP CONTROL vs LOW BLOOD PRESSURE. PRIMARY OUTCOME IS CHANGE IN KIDNY SIZE OVER 5 YEARS
  - B. CKD III DESIGN- 2X1 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE MASKED STUDY COMPARING ACE-I MONOTHERAPY vs ACEI + ARB AND STANDARD BP CONTROL. PRIMARY OUTCOME IS RATE OF PROGRESSION OF RENAL FAILURE (50% REDUCTION IN MDRD eGRF, DDT) OVER 5 YEARS
- STUDY A: n = 550; STUDY B: n = 470

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



Schrier RW et al. N Engl J Med 2014;371:2255-2266

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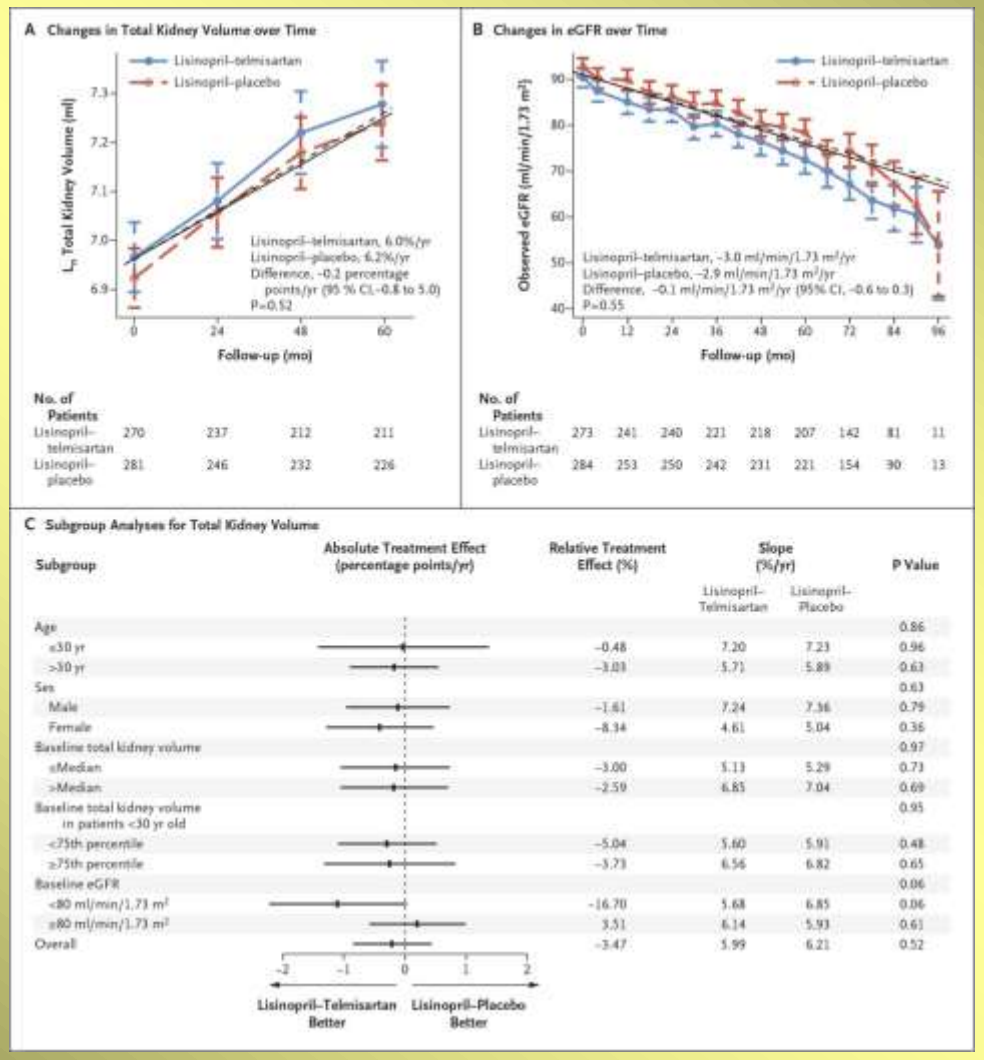
Changes in Total Kidney Volume and eGFR during Follow-up, and Subgroup Analyses, According to Treatment Group.



Schrier RW et al. N Engl J Med 2014;371:2255-2266

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Adverse Events in the 2-by-2 Factorial-Design Trial.

Table 2. Adverse Events in the 2-by-2 Factorial-Design Trial.*

Event	Lisinopril–Telmisartan (N=273)	Lisinopril–Placebo (N=285)	Standard Blood Pressure (N=284)	Low Blood Pressure (N=274)
Mean follow-up — yr	5.6	5.7	5.7	5.6
Acute kidney injury				
No. of events	15	19	17	17
No. of participants — %	13 (4.8)	16 (5.6)	13 (4.6)	16 (5.8)
Hyperkalemia				
No. of events	13	6	11	8
No. of participants — %	11 (4.0)	5 (1.8)	9 (3.2)	7 (2.6)
Hospitalization				
No. of events	85	128	120	93
Incidence — no. of events/100 person-yr	5.53	7.92	7.43	6.07
Cardiac-related hospitalization				
No. of events	13	9	13	9
Incidence — no. of events/100 person-yr	0.85	0.56	0.80	0.59
Cancer				
No. of events	4	4	2	6
No. of participants — %	4 (1.5)	4 (1.4)	2 (0.7)	6 (2.2)
Serious adverse event				
Death — no. of participants (%)†	1 (0.4)	1 (0.4)	2 (0.7)	0
Cardiac disorder				
No. of events	9	6	12	3
No. of participants — %	6 (2.2)	5 (1.8)	8 (2.8)	3 (1.1)
Gastrointestinal disorder				
No. of events	11	17	21	7
No. of participants — %	8 (2.9)	12 (4.2)	16 (5.6)‡	4 (1.5)
Abdominal pain				
No. of events	3	9	7	5
No. of participants — %	3 (1.1)	6 (2.1)	6 (2.1)	3 (1.1)
Nervous system disorder				
No. of events	10	12	14	8
No. of participants — %	8 (2.9)	10 (3.5)	11 (3.9)	7 (2.6)
Renal or urinary system disorder				
No. of events	14	15	16	13
No. of participants — %	12 (4.4)	14 (4.9)	14 (4.9)	12 (4.4)
Nephrolithiasis or renal colic				
No. of events	3	4	7	0
No. of participants — %	3 (1.1)	4 (1.4)	7 (2.5)‡	0

* All serious adverse events were classified with the use of the Common Terminology Criteria for Adverse Events, version 4.0.
† The causes of death were cardiac arrest (in one patient in the lisinopril–placebo group) and a neurologic event (in one patient in the lisinopril–telmisartan group).
‡ P<0.05 for the comparison with the low-blood-pressure group.

Schrier RW et al. N Engl J Med 2014;371:2255-2266

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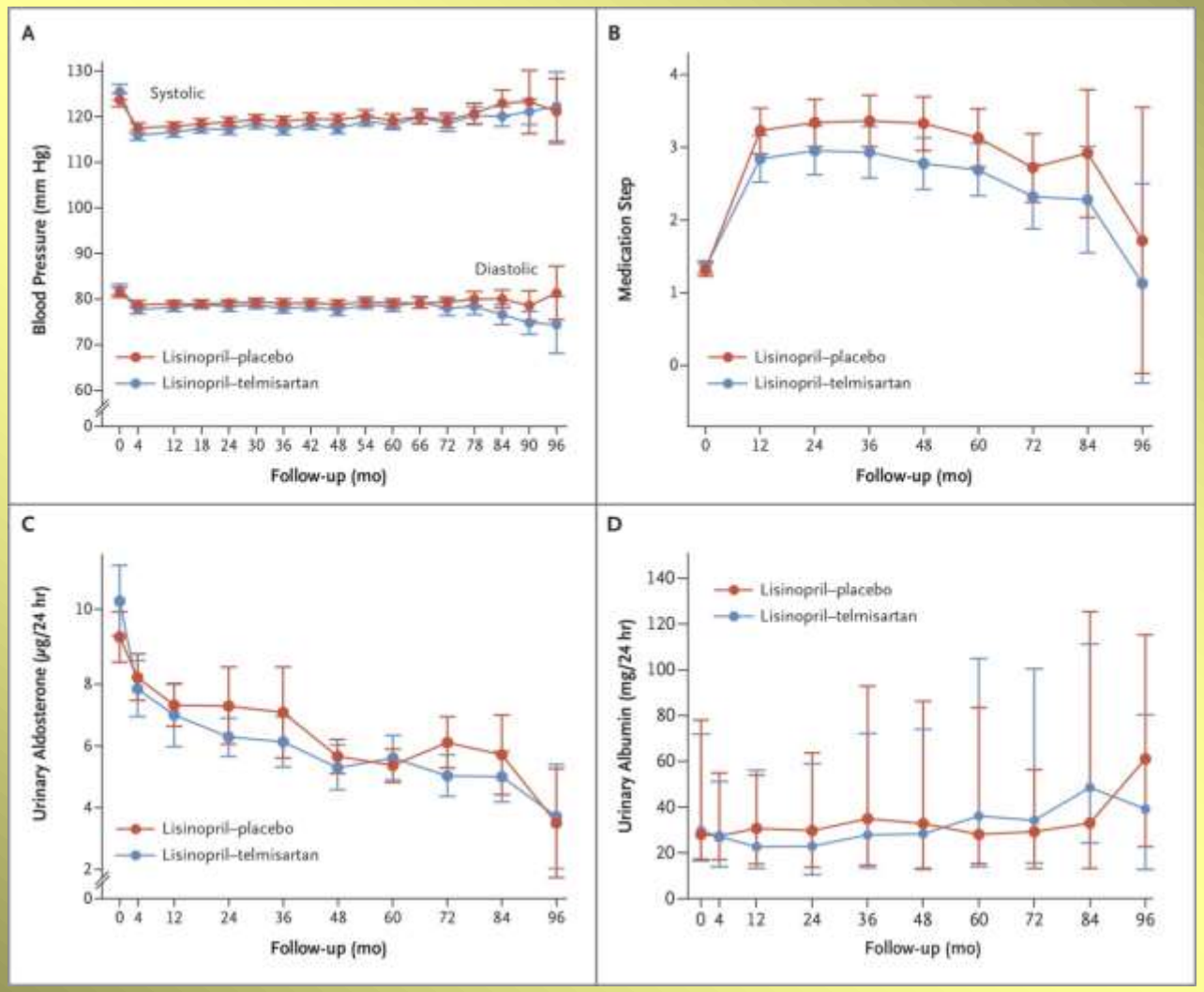
Conclusions

- In early ADPKD, the combination of lisinopril and telmisartan did not significantly alter the rate of increase in total kidney volume.
- As compared with standard blood-pressure control, rigorous blood-pressure control was associated with a slower increase in total kidney volume, no overall change in the estimated GFR, a greater decline in the left-ventricular-mass index, and greater reduction in urinary albumin excretion.

Blood-Pressure Levels, Medication Steps, and Urinary Aldosterone and Albumin Excretion.



Torres VE et al. N Engl J Med 2014;371:2267-2276

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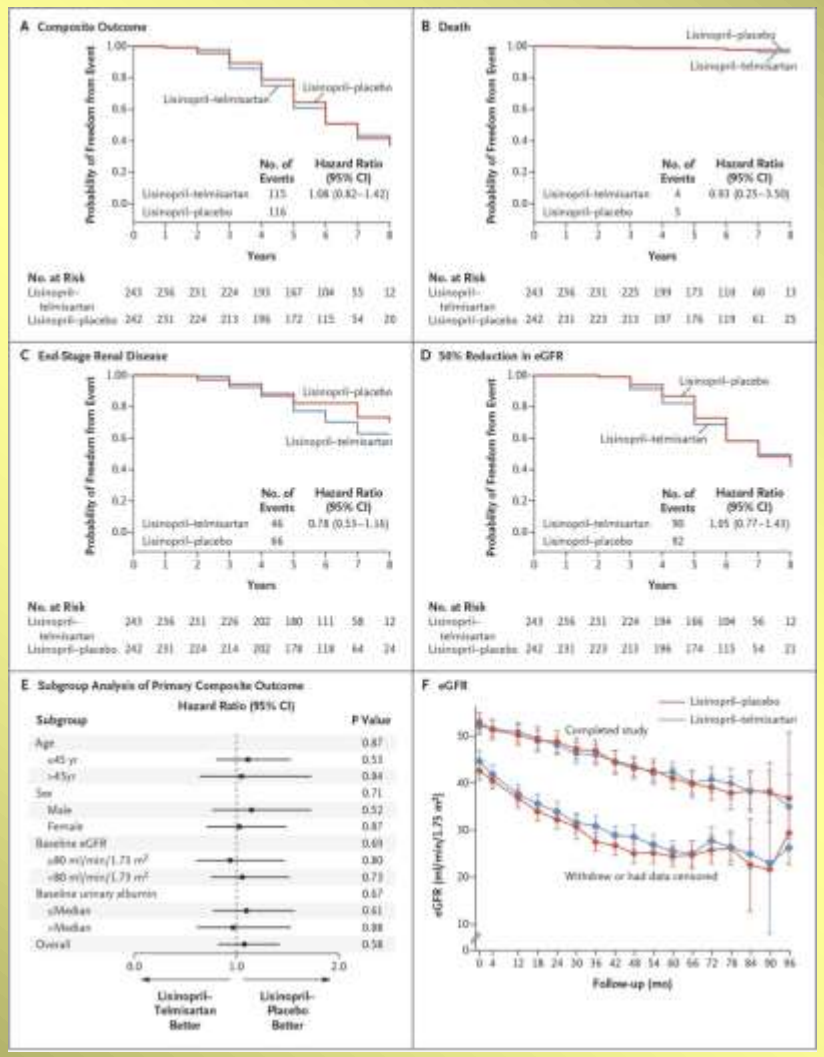
Effect of Lisinopril–Telmisartan, as Compared with Lisinopril–Placebo, on the Time to Primary-Outcome Events and on the Estimated Glomerular Filtration Rate (eGFR).



Torres VE et al. N Engl J Med 2014;371:2267-2276

Serious Adverse Events.

Table 2. Serious Adverse Events.*

Event	Lisinopril–Telmisartan (N=244)	Lisinopril–Placebo (N=242)
Mean duration of follow-up — yr	5.2	5.2
Death — no. of participants (%)†	4 (1.6)	5 (2.1)
Cardiac disorder		
No. of events	12	18
No. of participants (%)	11 (4.5)	13 (5.4)
Coronary artery disease		
No. of events	3	9
No. of participants (%)	3 (1.2)	9 (3.7)
Arrhythmia		
No. of events	5	6
No. of participants (%)	4 (1.6)	3 (1.2)
Other		
No. of events	4	3
No. of participants (%)	4 (1.6)	3 (1.2)
Gastrointestinal disorder		
No. of events	18	33
No. of participants (%)	15 (6.1)	25 (10.3)
Nervous system disorder		
No. of events	9	10
No. of participants (%)	8 (3.3)	9 (3.7)
Cerebrovascular event		
No. of events	4	3
No. of participants (%)	4 (1.6)	3 (1.2)
Headache		
No. of events	2	2
No. of participants (%)	2 (0.8)	2 (0.8)
Other		
No. of events	3	5
No. of participants (%)	3 (1.2)	4 (1.7)
Renal or urinary system disorder		
No. of events	14	34
No. of participants (%)	14 (5.7)	19 (7.9)
Renal hemorrhage or hematuria		
No. of events	5	2
No. of participants (%)	5 (2.0)	2 (0.8)
Nephrolithiasis or renal colic		
No. of events	1	12
No. of participants (%)	1 (0.4)	4 (1.7)
Acute kidney injury		
No. of events	3	5
No. of participants (%)	3 (1.2)	5 (2.1)
Other		
No. of events	5	15
No. of participants (%)	5 (2.0)	12 (5.0)

* All serious adverse events were classified with the use of the Common Terminology Criteria for Adverse Events, version 4.0. Patients may have had more than one event in an overall category but were counted only once in the overall-category total.
† Causes of death in the lisinopril–telmisartan group were glioblastoma multiforme, sudden death, respiratory failure, and renal failure (in one patient each). Causes of death in the lisinopril–placebo group were metastatic melanoma, cerebral hemorrhage, ruptured aneurysm, pulmonary embolism, and renal failure (in one patient each).

Torres VE et al. N Engl J Med 2014;371:2267-2276

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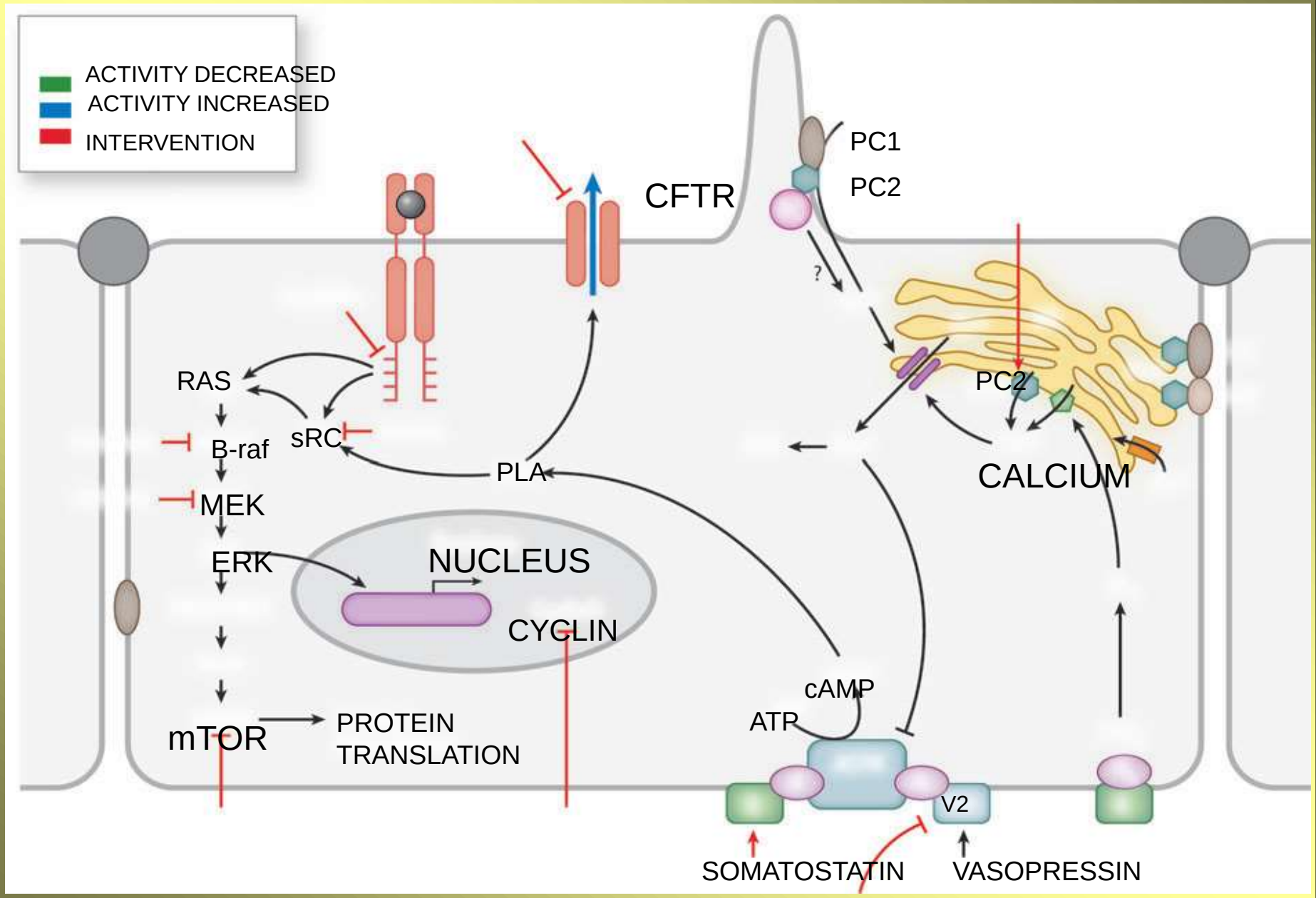
Conclusions

- Monotherapy with an ACE inhibitor was associated with blood-pressure control in most patients with ADPKD and stage 3 chronic kidney disease.
- The addition of an ARB did not alter the decline in the estimated GFR.

TRANSLATING MOLECULAR MECHANISMS INTO OTHER THERAPIES

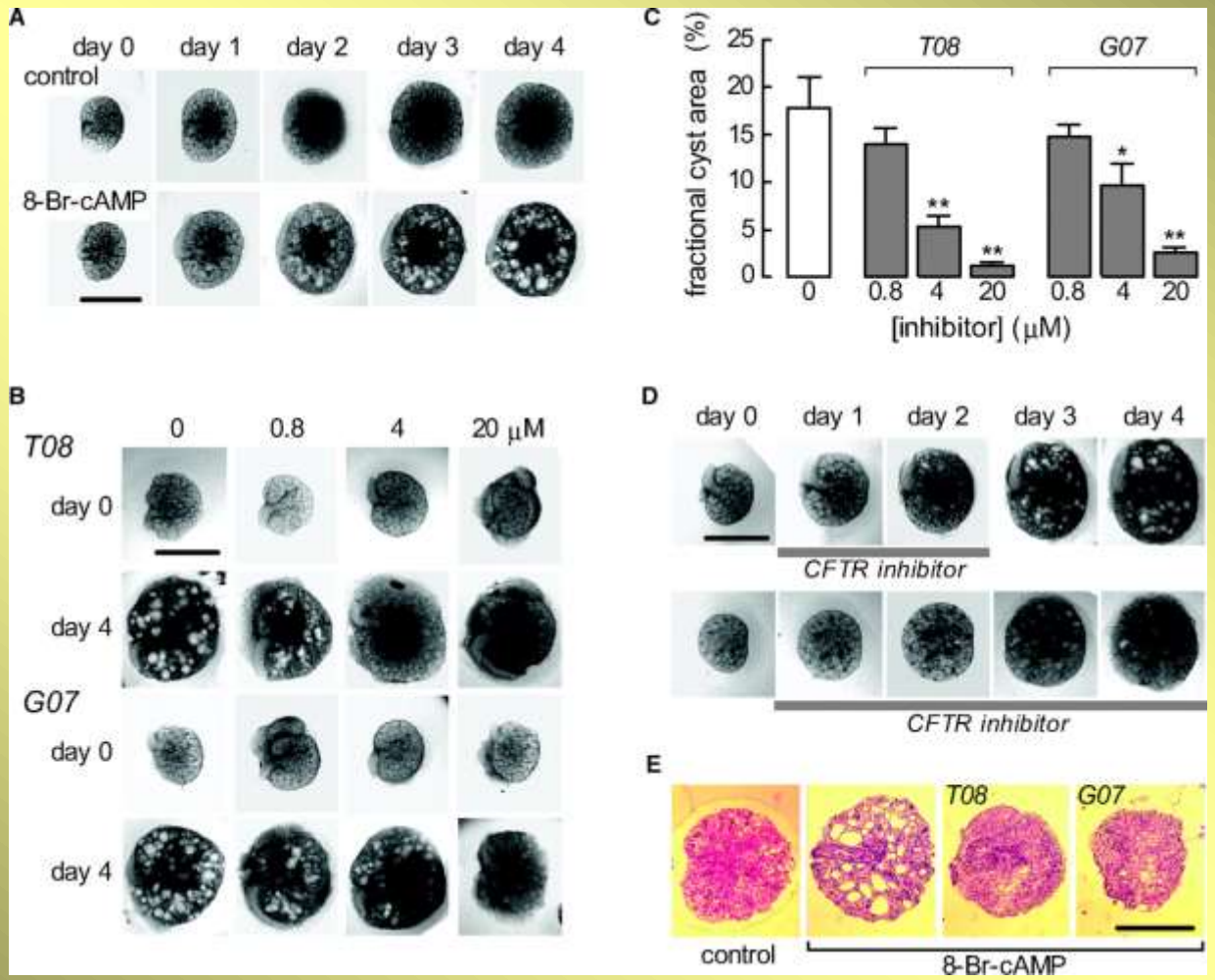
- mTOR (TARGET OF RAPAMYCIN)
- SOMATOSTATIN
- CFTR INHIBITORS (CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE RECEPTOR PROTEIN)
- B-raf
- Src
- CYCLIN
- STATINS


ACTIVITY DECREASED
ACTIVITY INCREASED
INTERVENTION
CFTR
PC1
PC2
?
RAS
B-raf
sRC
MEK
ERK
PLA
NUCLEUS
CYCLIN
mTOR
PROTEIN
TRANSLATION
PC2
CALCIUM
cAMP
ATP
V2
SOMATOSTATIN
VASOPRESSIN

mTOR INHIBITION

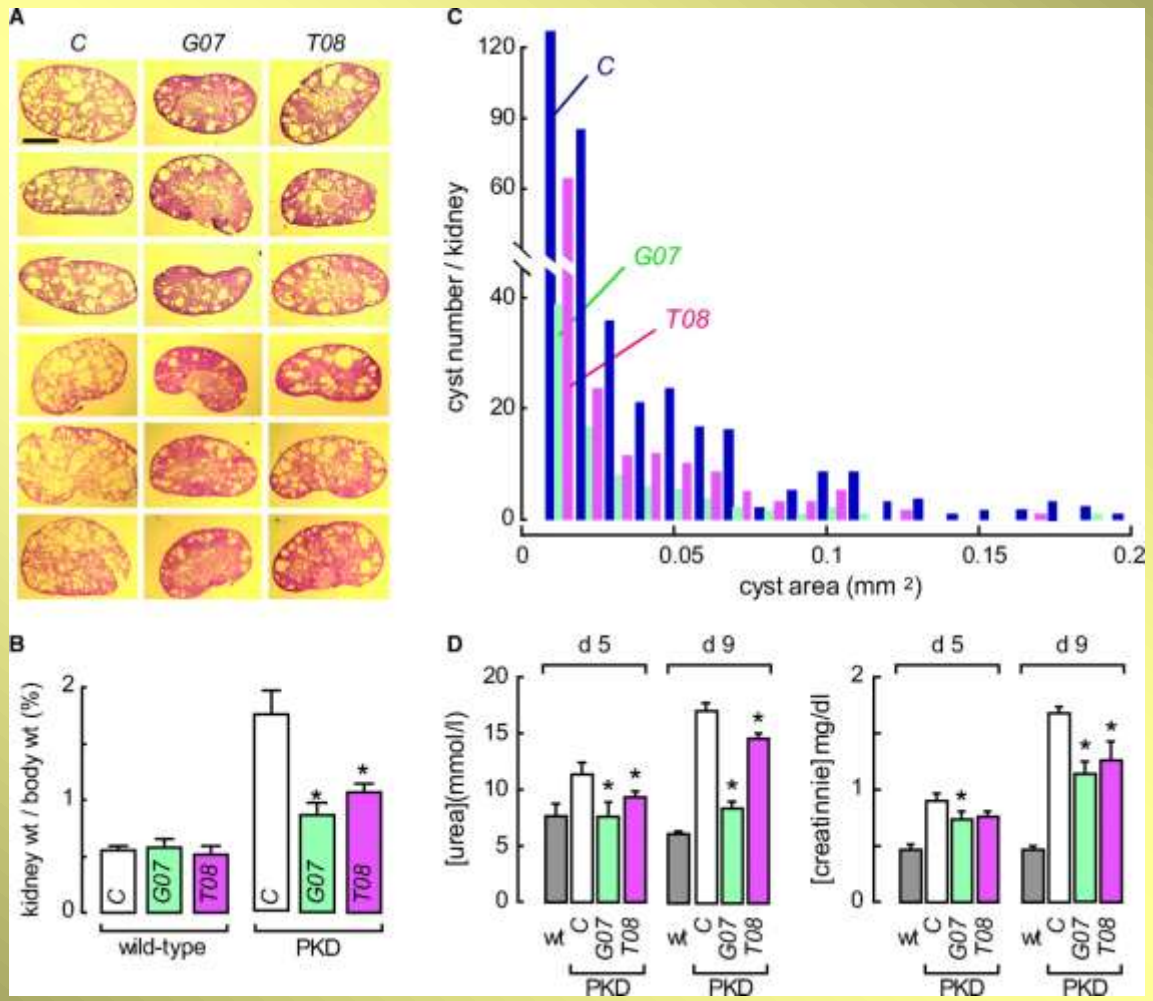
- mTOR successful in mouse model of PKD
- 2 Studies: Sirolimus and Everolimus NEJM 2012; 363
- No effect on GFR
- Everolimus did slow the increase in kidney-growth
- mTOR inhibitor concentration in human epitheial cells my have been inadequate.
- Future trials: “folated” mTOR may have increased uptake of th drug.

Figure 5. CFTR inhibitors slow cyst growth in embryonic kidney organ cultures



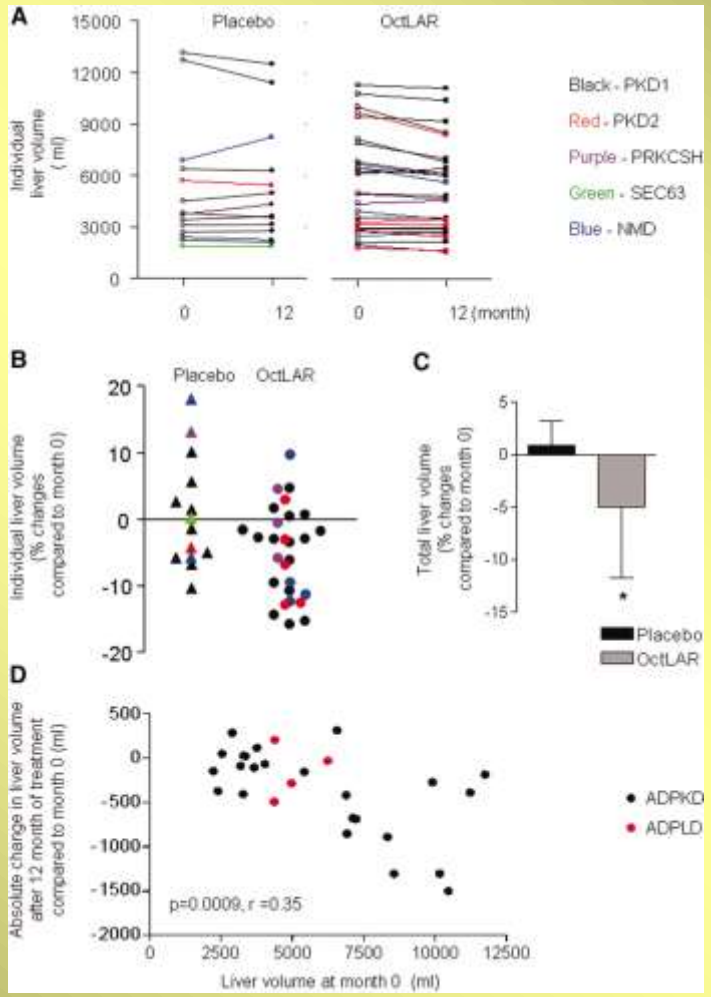
Yang, B. et al. J Am Soc Nephrol 2008;19:1300-1310

Figure 7. CFTR inhibitors slow cyst growth in a Pkd1flox/-;Ksp-Cre mouse model of PKD



Yang, B. et al. J Am Soc Nephrol 2008;19:1300-1310

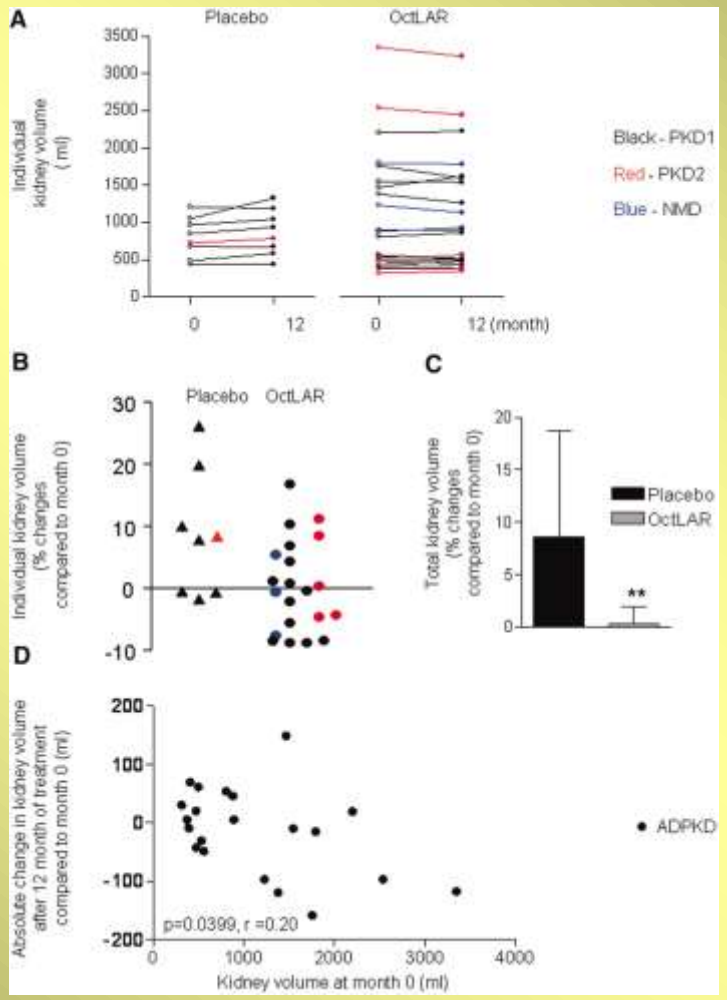
Figure 3. Octreotide therapy (Oct-LAR) decreased total liver volumes



Hogan, M. C. et al. J Am Soc Nephrol 2010;21:1052-1061

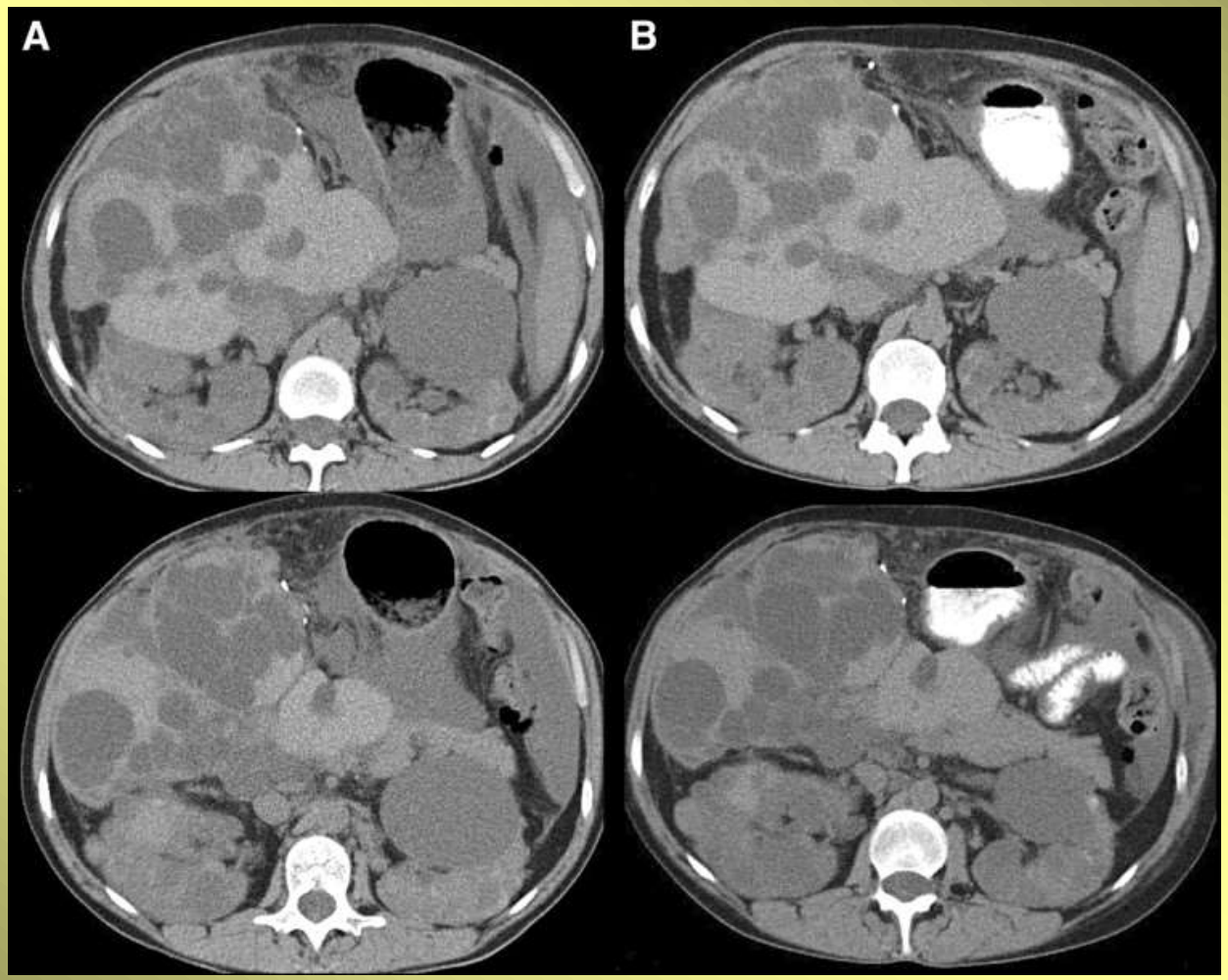
JASN

Figure 4. Octreotide therapy (OctLAR) stalled kidney growth in treated individuals

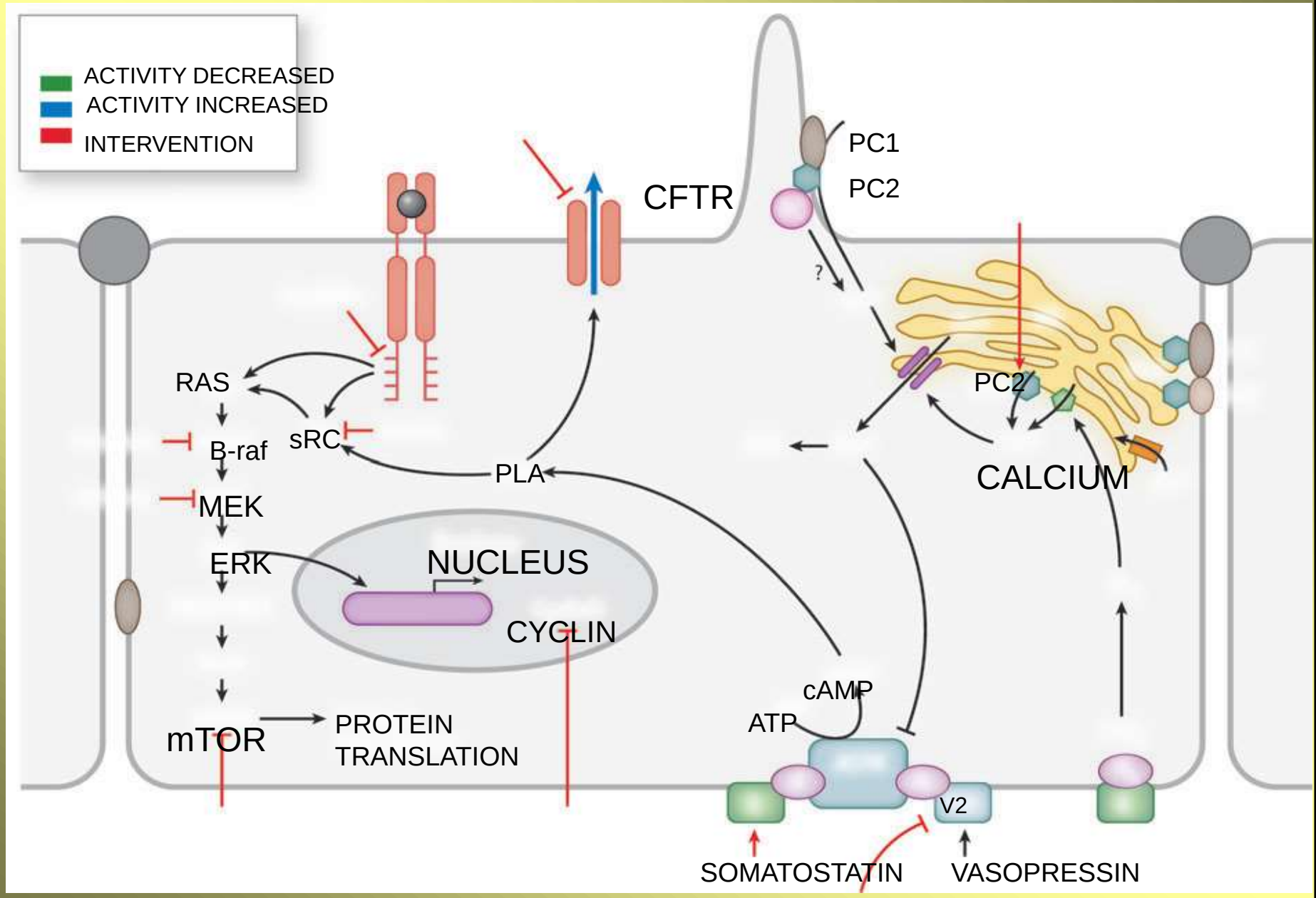


Hogan, M. C. et al. J Am Soc Nephrol 2010;21:1052-1061

Figure 1. Administration of octreotide LAR to a patient with severe PLD resulted in decreased liver and kidney volumes



Hogan, M. C. et al. J Am Soc Nephrol 2010;21:1052-1061


ACTIVITY DECREASED
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PC1
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sRC
MEK
ERK
PLA
NUCLEUS
CYCLIN
mTOR
PROTEIN
TRANSLATION
cAMP
ATP
V2
SOMATOSTATIN
VASOPRESSIN

THANKS FOR YOUR ATTENTION