

What Every Patient Should Know About Polycystic Kidney Disease

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Autosomal Dominant Polycystic Kidney Disease (ADPKD)

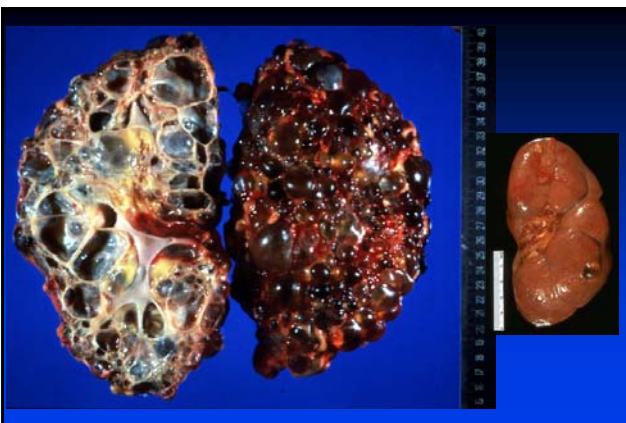
- Hereditary systemic disorder
- Bilateral kidney cysts
- Progressive loss of function leading to kidney failure (need for dialysis or transplant) in ~50% of patients by 50s-60s
- Effects on other organs
 - Cysts
 - Connective tissue abnormalities

Epidemiology of ADPKD

- Frequency: 1/500 to 1/1000
- Affects ~600,000 in USA
- Most common genetic kidney disease
- Accounts for 8 to 10% of patients on dialysis
- Direct medical costs exceed \$1.5 billion/year

O.Z. Dalgaard, *Acta Med Scand*, 1957

- The disease of polycystic kidneys in adults is homochronous, that is, the malformation first shows signs or symptoms after the age of 30-40, and progresses mercilessly with greater or lesser rapidity. The genetically determined disease process is latent for many years, and then becomes manifest in a kidney tissue which has apparently developed and functioned normally.



The Kidneys in ADPKD

- Cysts throughout both kidneys
- Painful, enlarged kidneys
- Progressive loss of kidney function
- High blood pressure (increased activity of kidney hormones renin-angiotensin)
- Blood in the urine (hematuria)
- Cyst infection; pyelonephritis
- Kidney stones
- Impaired concentrating ability

ADPKD is a Slowly Progressive Kidney Disease

- Filtration (GFR) stable for many years; more rapid decline after 50% of function is lost
Males 5 - 6 ml/min/year; Females 4 - 5 ml/min/year
- Polycystic kidneys grow continuously
- 50% of patients require dialysis/transplant by age 60

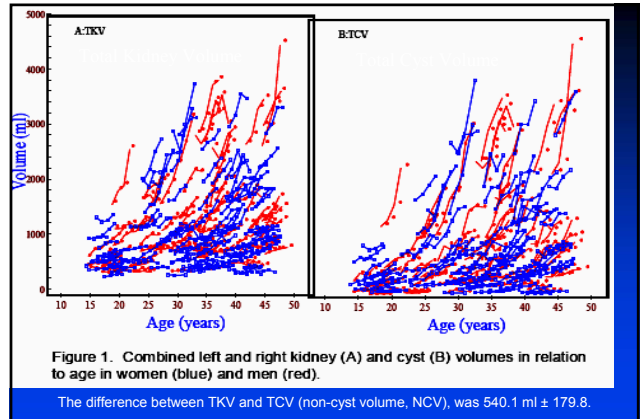
Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)

- Observational trial to determine how to assess changes in polycystic kidneys over a relatively short period of time (3 years)
- 232 subjects with 'normal' kidney function (GFR>70)
- Emory; U. of Alabama; Kansas University; Mayo
Kidney International, 64: 1035-1045, 2003
Kidney International, 64: 2214-2221, 2003

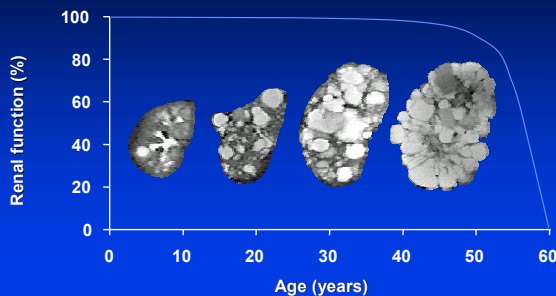
CRISP Results

- Total Kidney Volume (TKV) increased over the three-year interval +204 ml ± 246 (n= 214, P< .001) and Total Cyst Volume (TCV) increased +218 ml ± 263 (n= 210, P < .001).
- There was a direct correlation (r=0.95, P < .001) between the rate of change in TKV and the rate of change in TCV.
- the rates of volume increase, determined from the annual measurements of TKV, were not different between left (5.1%/year ± 4.5) and right (5.4 %/year ± 4.4) kidneys.
- Glomerular filtration rate (GFR) declined by 4.33 ± 8.07 ml/min/year, only in those with the largest kidneys (>1500 milliliters).

New England J. of Medicine 354(20):2122-30



This concept of progression of ADPKD has been validated! We now have a research tool to determine the progression of cystic kidney disease over a relatively short time period



High Blood Pressure in ADPKD

- Associated with activation of the kidney hormones renin and angiotensin
- Correlated with the degree of structural damage
- 66% of males, 41% of females pre-ESRD
- Most patients with ESRD
- Associated with enlargement of the heart muscle (left ventricular hypertrophy)

Hematuria in ADPKD

- **Bloody urine:** microscopic or gross (visible)
- **Affects up to 40% of patients**
- **Symptoms**
 - painless
 - pain in abdomen, back or flank
- **Cause**
 - kidney stone, infection, cyst wall rupture, tumor
- **Treatment**
 - hydration, pain control, diagnosis
 - blood transfusion; transcatheter embolization
- **Gross hematuria before age 30 associated with increased risk of progression**

Kidney Cyst Infection in ADPKD

- **Associated with fever, pain in kidney (back or abdomen)**
- **Distinguish from bladder infection**
- **Fat soluble antibiotics such as ciprofloxacin, norfloxacin, trimethoprim, chloramphenicol for long course of treatment**
- **Percutaneous (needle placed through the skin) or surgical drainage is optional; only for refractory infection**
- **Nephrectomy (removing kidney) is a last resort in life-threatening infection**

Kidney Stones in ADPKD

- **Occur in ~20% of patients**
- **Uric acid and/or calcium oxalate**
- **Diagnosis:** more difficult due to distorted anatomy
 - Intravenous pyelogram (IVP)
 - CT scan most sensitive for small stones
- **Prevention and Treatment:** same as nonADPKD
 - Increased hydration
 - Correction of metabolic factors
 - Stone removal or lithotripsy
 - Retained stone fragments more likely

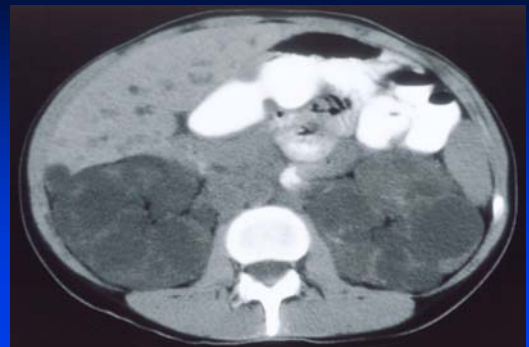
Diagnosis of ADPKD

- **Family history of cystic renal disease (found in 60% of patients; up to 90-95% after ultrasound screening of relatives)**
- **Multiple bilateral renal cysts by ultrasound, CT, or MRI**
- **DNA-based diagnosis: direct DNA sequencing**

Kidney Ultrasound in ADPKD



CT Scan in ADPKD



Ultrasound Diagnosis of ADPKD

- Multiple bilateral renal cysts
- Age and genotype dependent
 - 11 to 24% of gene carriers of ADPKD1 do not have detectable cysts until after age 30
 - Cysts appear even later in ADPKD2

Ultrasound Criteria for Diagnosis of ADPKD1 in a PKD Family

- Age < 30: at least 2 cysts (unilateral or bilateral)
- Age 30-59: at least 2 cysts/kidney
- Age > 60: at least 4 cysts/kidney

Ravine et al, Lancet 343:824, 1994

DNA Analysis

- Direct DNA sequencing
- Not useful for patients with established diagnosis of ADPKD: no impact on treatment
- Most useful for young (<30) potential transplant donor in PKD family where imaging is negative
- May be falsely negative in those with disease
- May detect normal variations in DNA not associated with disease (false positive)
- Research lab test or commercially available from Athena Diagnostics (PKDx)
<http://www.pkdx.com/site/content/index.asp>

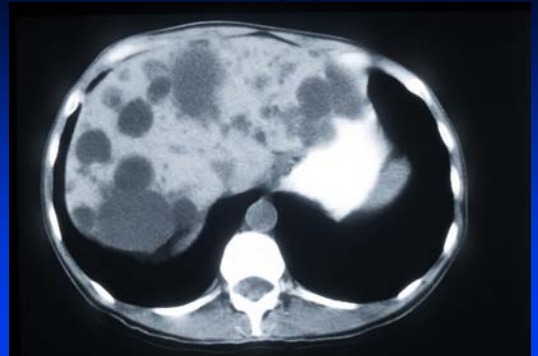
Other Affected Organs

Liver and pancreatic cysts
Congenital liver fibrosis (rare)
Colonic diverticula
Cardiac valvular abnormalities
Intracranial (brain) aneurysms (weakened arteries)
Testicular and seminal vesicle cysts
Cysts of the arachnoid membrane (covers brain)
Abnormally stretched/enlarged brain arteries

Liver Cysts in ADPKD

- Occur in ~50% of patients with ADPKD; increase with age and severity of renal cystic disease
- Liver function is maintained
- Responsible for morbidity and some mortality in ADPKD ESRD patients
- Gender differences in cystic disease
 - Women have increased # and larger cysts than men
 - Pregnancy and female hormones associated with worse disease
 - Massive liver enlargement with disabling pain almost exclusively a disease of women

CT Scan of Polycystic Liver



Complications of Polycystic Liver in ADPKD

- Hemorrhage: unusual
- Rupture: rare
- Infection: 7/229 patients on HD
- Bile duct blockage
- Cholangiocarcinoma: cancer of bile ducts (rare)

Massive Polycystic Liver Disease in ADPKD

- Rare manifestation of PLD
- Occurs primarily in women
- Severe symptoms related to bulk of massively enlarged liver
- With severe symptoms, treated by surgery to reduce liver mass, fenestration of cysts
- Benefit of surgery is sustained for at least several years

Massive Polycystic Liver Disease



Management of Liver Cyst Complications of ADPKD

- Single or few cysts: percutaneous drainage followed by sclerosis with alcohol or minocycline
- Multiple cysts: laparoscopic drainage; surgical fenestration
- Partial hepatectomy or venous shunt by experienced surgeon in referral center
- Liver or liver/kidney transplant

Treatment of Liver Cyst Infection

- Fat soluble antibiotics such as ciprofloxacin, norfloxacin, trimethoprim; consider antibiotics secreted in the bile

In contrast to kidney cysts:

- Chloramphenicol is not thought to penetrate liver cysts
- Limited research suggests that percutaneous (via needle) or surgical drainage is essential

Effect of Estrogen Therapy in ADPKD

- Estrogen therapy (HRT) for 1 year increased total liver volume by 7% (N=11) vs -2% (N=8) in controls
- Symptoms of abdominal pain in 60% and shortness of breath in 40% unaffected by HRT
- No change in kidney volume
- ? use HRT: base on risk of osteoporosis and postmenopausal symptoms

Colonic Diverticular Disease in ADPKD

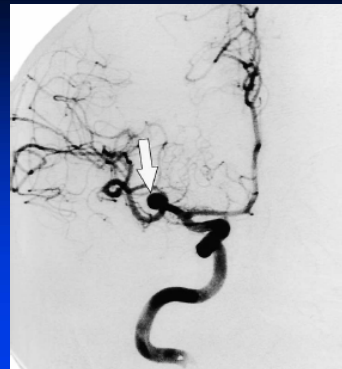
- Early studies suggested high frequency (83%) of diverticulosis in 12 ESRD patients with ADPKD
- Study from Denver group suggests no increase in ADPKD vs control (non-ESRD)
- Complications of diverticulosis overrepresented in ADPKD transplant population

Cardiovascular Disease in ADPKD

- Valvular disease: usually trivial or mild
 - Mitral or tricuspid prolapse (floppy valve)
 - Mitral, tricuspid, or aortic regurgitation (leak)
 - Potential risk of infection of valve (endocarditis)
- Thickened heart muscle (Left Ventricular Hypertrophy (as high as 46%))
- Increased risk of atherosclerotic heart disease (coronary insufficiency, heart attack), as kidney function declines

Intracranial Aneurysm in ADPKD

- ICA: intracranial (within the skull) aneurysm (thinned and weakened portion of an artery)
- SAH: subarachnoid hemorrhage: bleeding into the space around the brain normally occupied by the cerebrospinal fluid



Belz, MM et al
Kidney International,
63: 1824–1830, 2003

U. Of Colorado

Intracranial Aneurysm in ADPKD

- Rupture is a dreaded complication with substantial morbidity (paralysis, dementia) and mortality
- Tend to cluster within families
- Screening of asymptomatic individual with magnetic resonance arteriography (MRA):
 - ICA found in 11-12% overall
 - 22 - 26% in those with family history
 - 5% in those without family history

Who Should Be Screened for ICA?

- + family history of intracranial aneurysm (ICA) or subarachnoid hemorrhage (SAH)
- prior SAH or known ICA
- younger age (<45), not yet on dialysis
- high risk occupation
- prior to major surgical intervention
- need for reassurance of negative study

ICA After Negative Screening

- Asymptomatic, high risk individual (+family history, prior SAH) with negative screening MRA at age <30 should be restudied within 5-10 years
- Asymptomatic, low risk individual (no family history or SAH) with negative screening MRA after age 30 probably doesn't need additional study

Management of Asymptomatic ICA in ADPKD

- consider size and location
- evaluate risk of rupture versus risk of surgery
- consider endovascular technique
- symptoms dictate intervention

Natural History of Asymptomatic ICA in ADPKD

- very limited data
- 15 asymptomatic, small (<7 mm) ICA followed for a mean of 33 months: no ruptures, no changes in size or appearance, no new ICA

ICA After Positive Screening or Rupture

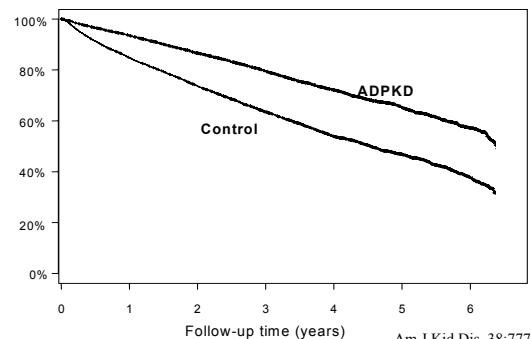
- No recurrence of ICA at less than 10 years
- No predictive factors for recurrent ICA identified
- *Those with ADPKD and ICA are at risk of new ICA and increase in size of known ICA*
- *Rescreen at 5-10 year interval*

MM Belz Kidney Int. 2003 63:1824-30

Pregnancy and Complications of ADPKD

- Hypertensive complications increased in ADPKD pregnancy (poor BP control, edema, preeclampsia, eclampsia, "toxemia")
- Greater likelihood of lower level of kidney function in women with 4 or more pregnancies
- No extrarenal complications reported in 605 pregnancies of 235 women with ADPKD
- 7 ectopic pregnancies in ADPKD group versus 1 in control

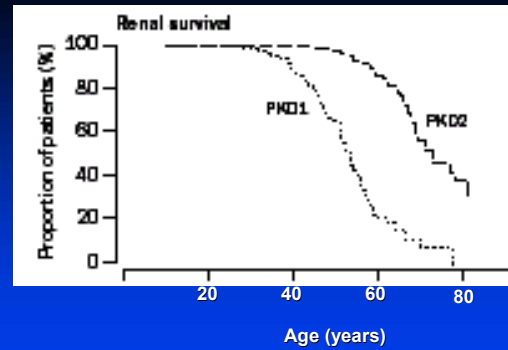
Survival After ESRD: ADPKD vs. Nondiabetic control



Am J Kid Dis. 38:777, 2001

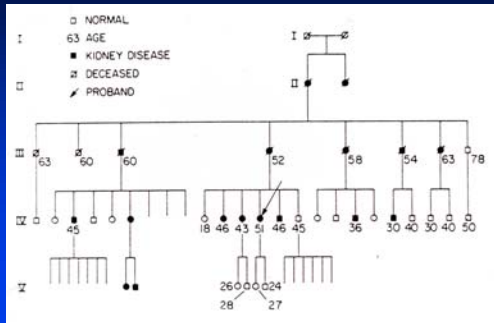
Genetics of ADPKD

- Autosomal dominant: inherit from one affected parent
- Doesn't skip generations
- 2 different genes; both resulting in similar phenotype except loss of kidney function seems to be slower in ADPKD2
 - 85% ADPKD1 (chromosome 16)
 - 10 to 15% ADPKD2 (chromosome 4)



Hateboer N; Lancet 353:103, 1999

ADPKD Pedigree



Treatment of ADPKD (1)

- There is no specific therapy
 - Avoid NSAIDs, IV contrast, Chinese herbs
- Pain
 - Diagnosis: bleed, stone, infection, obstruction, tumor
 - Analgesics
 - Percutaneous drainage; laparoscopic or surgical unroofing of individual cysts
- Infection: fat soluble antibiotics
- High blood pressure
 - ACE inhibitors thought to be beneficial

Treatment of ADPKD (2)

- Progressive renal insufficiency
 - Lack of proven benefit of low protein diets or ACE-I
 - Cyst decompression does not alter progression
 - Renal replacement therapy
- Extrarenal manifestations
 - Intervene as needed for symptoms
 - Screen for cerebral aneurysms; antibiotic prophylaxis for valvular regurgitation
 - Avoid unnecessary estrogen/progesterone in women; consider estrogen patch

K-DOQI WWW.kidney.org

Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	GFR (mL/min/1.73 m ²)	Action
	At increased risk	>=90 (with CKD risk factors)	Screening, CKD risk reduction
1	Kidney damage with normal or ↑ GFR	>=90	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60-89	Estimating progression
3	Moderate ↓ GFR	30-59	Evaluating and treating complications
4	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

J Am Soc Nephrol 2/2002

Children in ADPKD Family

- Each child has 50/50 chance of inheriting disease
- Presymptomatic diagnosis not usually recommended
- Pediatrician should be aware of family history
- Closely follow blood pressure
- Abdominal exam looking for kidney enlargement
 - Protect enlarged kidneys from trauma
- Diagnostic evaluation for symptoms: infection, hematuria, high blood pressure, etc.

Diet in ADPKD

- Definitely should do
 - Low salt
 - Low cholesterol, low fat
 - High fiber
 - Avoid protein excess (0.8 – 1.0 gm/kg body weight)
 - Limit intake of caffeine
 - Drink lots of water
- Insufficient evidence in human studies
 - Replace animal protein with soy protein

Other Health Measures

- Stop smoking
- Loose weight
- Exercise
- General recommendations for CKD
 - Estimate GFR
 - Anemia
 - Bone (calcium and phosphorous)
 - Nutrition
 - Education and planning as needed for ESRD
 - Living donor transplantation

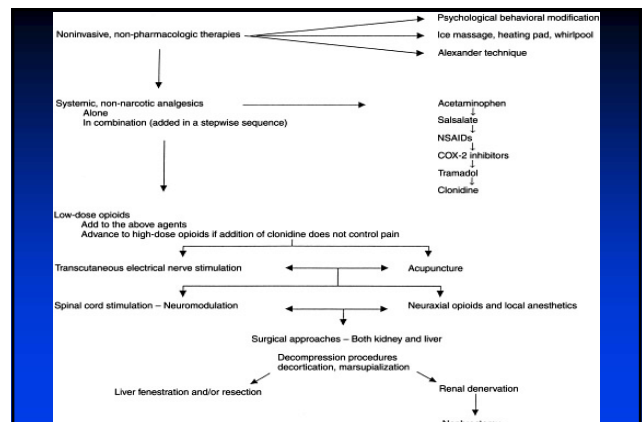
Presymptomatic Diagnosis of ADPKD

- Pretest counseling
- Selection of transplant donor within an ADPKD family
- Prenatal diagnosis
- Benefits
 - Earlier clinical intervention, i.e., for hypertension
- Potential adverse impact on insurability and employment
 - At this time, there is no specific therapy for ADPKD

Pain Management in ADPKD

- Sequential approach to pain management in ADPKD delineated by Bajwa, Steinman and others
- “Since chronic pain cannot be ‘cured,’ an approach must include techniques that allow the patient to adapt to chronic pain so as to limit interference with their life style.”

Kidney Int, 60:1631, 2001



Cyst Fenestration

- Open surgical or laparoscopic fenestration (removing caps) of individual cysts accessible on surface of kidney (or liver)
- Pain relief in 50-80% of patients that lasts for 1-3 years
- No effect on kidney function
- Kidney denervation (limited experience)
- Laparoscopic removal of kidney also possible

HALT-PKD (Halt Progression of Autosomal Dominant Polycystic Kidney Disease)

Objective: Two simultaneous, randomized, double-blinded controlled trials to assess the effects of multi-level blockade of the renin-angiotensin-aldosterone system (RAAS) and aggressive blood pressure control on progression of early (NKF Stage 1-2) and late (NKF Stage 3) ADPKD over a 5-year period

Hypotheses:

- 1) Blockade of RAAS will significantly reduce renal progression as compared to other antihypertensive therapy
- 2) Lower blood pressure will significantly reduce renal progression as compared to standard BP targets

Risks/Benefits of RAAS Interruption in ADPKD

Hypothesized benefits of RAAS Blockade in ADPKD

- Reduction of blood pressure
- Reduce pressure in kidney filters (glomerulus)
- Reduce excretion of protein in the urine
- Reduce production of molecules that cause scarring and inflammation of the kidneys



Risks of RAAS Blockade in ADPKD

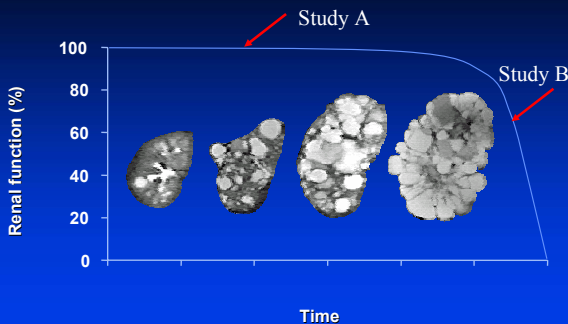
- Ischemia – further reduction of blood flow already compromised by compression from expanding cysts
- Elevated potassium
- Acute renal failure: elevated creatinine



Summary of Interventions and Outcomes of Study A and B

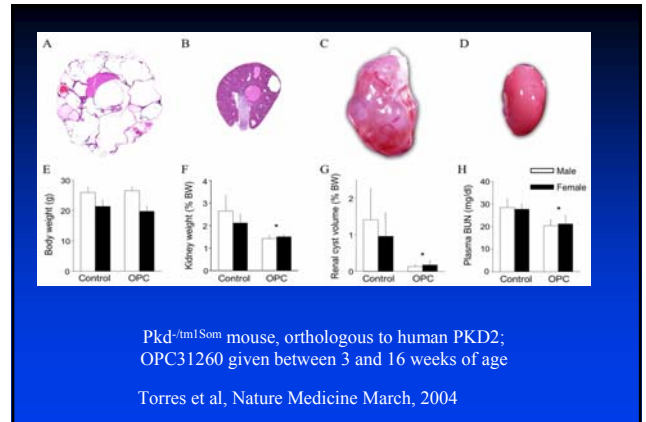
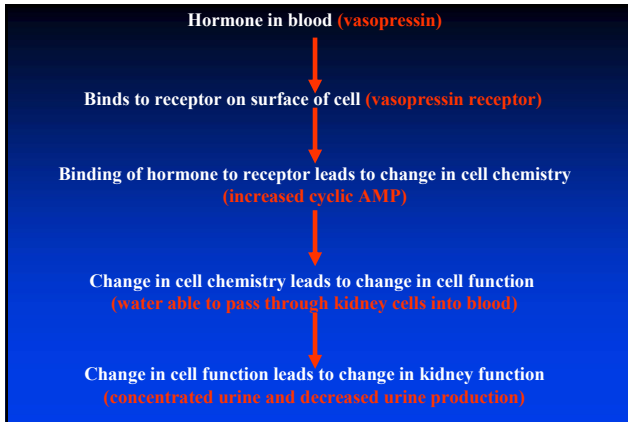
	Baseline GFR ml/min/1.73 m ²	Primary Outcome	Intervention	BP Target (mm Hg)
Study A	>60	% Change in Total Kidney Volume by MRI	1. ACE + ARB	≤130/ 80
			2. ACE	≤130/ 80
			3. ACE + ARB	≤110/ 70
			4. ACE	≤110/ 70
Study B	30-60	50% decrease in eGFR/ ESRD/ Death	1. ACE + ARB 2. ACE	≤130/ 80

When to Treat and What to Measure?



Patient Follow-up

- Year one: 4 visits; screening, baseline, 4 and 12 months
- Year two onwards: study visits every 6 months
- Home BP measurement every month
- Study A only: Magnetic Resonance Imaging of total kidney volume/ Magnetic Resonance Angiogram of kidneys at baseline, 24, and 48 months



Side Effects of Tolvaptan

- Increased urine output: 4-5 quarts/day!!
- Thirst: must drink fluids to keep up!!
- Already well studied and found to be safe and effective in disorders of water retention:
 - congestive heart failure
 - cirrhosis of the liver

Tolvaptan in Human ADPKD

- Phase II studies (safety, dosing, side effects) completed
- Pharmacokinetic profile similar to healthy control population
- Well tolerated with few side effects
- Effective blockade of the AVP V_2 receptor defined as $U_{osm} < 300$ mOsm/kg

- Personal communication: Dr. Vicente Torres

Tolvaptan Open Label Phase 2

- Open label extension *only* for those subjects already participating (48 participants)
- Objective:
 - long-term safety
 - maximal tolerated split dose
 - pilot efficacy
- Planned for 3 years

Tolvaptan Phase 3 Clinical Trial

- Multicenter trial (phase III) TEMPO
 - selection of centers in progress
 - recruitment to begin 2007
- Placebo-controlled (1/3 placebo, 2/3 active drug)
- Split-dose to maximize tolerability
- Assessment of change in kidney size over time as assessed by MRI
- Safety and side effects; tolerability; dose
- 3 years treatment, 5 years total

Tolvaptan Phase 3 Clinical Trial

- 100 centers, global
- 1200-1500 subjects
- Inclusion criteria
 - GFR > 60
 - age 18-50
 - kidney volume >750 ml
- 1-866-712-5837 for information (Otsuka Maryland Research Institute)

