ADULT POLYCYSTIC KIDNEY DISEASE

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APCKD

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

• **GENETICS**
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• FUTURE
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (APCKD)

- INHERITANCE AS AUTOSOMAL DOMINANT TRAIT
  - AT LEAST 2 LOCI IDENTIFIED
    - 85% WITH CHROMOSOME 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
  - ESRD PREVALENCE 7-10%
Polycystic Kidney Disease

- Normal Nephron
  - Proximal tubule
  - Loop of Henle
  - Collecting tubule

- Cyst Formation in Autosomal Dominant Polycystic Kidney Disease
  - Normal basement membrane
  - Thickened basement membrane
  - Normal cell
  - Macrophage
  - Fibroblast
  - Initial cyst
  - Collecting duct
  - Parent tubule
  - Secreted fluid
  - Isolated cyst

References:
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
APCKD: COMPUTERIZED TOMOGRAPHY
CYCTIC KIDNEY DISEASE
CHARACTERISTICS OF POLYCYTIN-1

- Located in renal tubular epithelial 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, PRIMARY CILIUM AND ENDOPLASMIC RETICULUM (MAIN SITE)
• INTERACTS WITH POLYCYSTIN-1
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 PROTEINS INTERACT AT THE CELL MEMBRANE
• BOTH PROTEINS CREATE A NON-SELECTIVE CALCIUM PERMEABLE CATION CHANNEL
• MECHANICAL STIMULI LEADS TO POLYCYSTIN-2 MEDIATED TRANSLOCATION OF A POLYCYSTIN-1 FRAGMENT TO THE NUCLEI LEADING TO AK-1 TRANSCRIPTION
APCKD

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SCREENING

- RENAL ULTRASOUND IS USUAL INITIAL MODALITY; CT AND MRI MAY BE MORE SENSITIVE
- PATIENT AT RISK/UNKNOWN GENOTYPE
  - 15-39 YEARS: ≥ 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
ULTRASOUND PITFALLS
APCKD

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REQUIREMENTS FOR CYST FORMATION AND GROWTH

• EPITHELIAL PROLIFERATION
• FLUID SECRETION
• MATRIX REMODELING
• FIBROSIS
CYST DEVELOPMENT

A: Normal Nephron
- Proximal tubule
- Loop of Henle
- Collecting tubule

B: Cyst Formation in Autosomal Dominant Polycystic Kidney Disease
- Normal basement membrane
- Thickened basement membrane
- Normal cell
- Initial cyst
- Mural cells
- Interstitial fibrosis
- Macroage
- Parent tubule
- Secreted fluid
- Isolated cyst
- Collecting duct
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
• INABILITY OF ABNORMAL CILIA TO DETECT LUMIAL FLOW
  – DECREASE IN CALCIUM TRANSPORT
  – ABNORMAL CALCIUM FLUX LEADS TO EPITHELIAL PROLIFERATION DUE TO CYCLIC AMP SIGNALING
• ABNORMAL CILIA ON CENTROSOMES
STRUCTURE OF CILUM


Annual Reviews
CILIOPATHIC SYMPTOMS

Clinical symptoms and ciliary roles
A wide variety of symptoms are potential clinical features of ciliopathy.
Chemosensation abnormalities
defective thermosensation or mechanosensation.
Cellular motility dysfunction
Issues with displacement of extracellular fluid
Paracrine signal transduction abnormalities
CILIOPATHIES

• BARDET-BIEDL SYNDROME
• JOUBERT SYNDROME
• MECKEL-GRUBER SYNDROME
• NEPHRONOPHTHISIS
• POLYCYSTIC LIVER DISEASE
• DANDY-WALKER SYNDROME
• KARTAGENER SYNDROME
• OROFACIODIGITAL SYNDROME
• RETINITIS PIGMENTOSA
• AGENESIS OF THE CORPUS CALLOSUM
MAP KINASE CASCADE IN NORMAL AND PCKD CELLS

INTACT CILIUM

- NHK cells
- PC2
- PC1
- AC-activating receptor
- Growth factor receptor
- Ras
- Raf-1
- B-Raf
- NEK
- ERK
- PI3K
- PKA
- CAMP
- Normal Ca^{2+}
- Cell proliferation
- RER

DEFECTIVE CILIUM

- PKD cells
- Growth factor receptor
- AC-activating receptor
- Ras
- Raf-1
- B-Raf
- MEK
- ERK
- Fluid secretion
- Cell proliferation
- Ca^{2+} entry pathways
- PC1/PC2
- L-type
- T-type
- Others

Kidney International (2008) 73, 251-253
VASOPRESSIN SIGNALING AND CYCLIC AMP

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 EPITHELium IN CULTURE TO FORM CYSTS
• CYTIC FLUID ACCUMULATION ESTIMATED AT 26-475 mL/year
• SODIUM CONTENT OF CYSTS IS VARIABLE
EGF, EGFR AND TGF AXIS IN Han:SPRD Rat Model

Torres et al Kidney Int 64:1573-9; 2003
EGF, EGFR AND TGF AXIS IN Han:SPRD Rat Model

Torres et al Kidney Int 64:1573-9; 2003
<table>
<thead>
<tr>
<th></th>
<th>+/+ Control (N = 11)</th>
<th></th>
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<th>Cy/+ Control (N = 9)</th>
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<tbody>
<tr>
<td>EKI-785 mg/kg body weight</td>
<td></td>
<td></td>
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<tr>
<td>Body weight g</td>
<td>332.6</td>
<td>22.1</td>
<td></td>
<td>321.7</td>
<td>27.6</td>
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<tr>
<td>Kidney weight % body weight</td>
<td>0.82</td>
<td>0.04</td>
<td></td>
<td>0.85</td>
<td>0.03</td>
<td>0.090</td>
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<tr>
<td>Liver weight % body weight</td>
<td>4.23</td>
<td>0.17</td>
<td></td>
<td>4.42</td>
<td>0.29</td>
<td>0.115</td>
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<tr>
<td>Serum blood urea nitrogen mg/dL</td>
<td>20.3</td>
<td>2.5</td>
<td></td>
<td>22.7</td>
<td>4.1</td>
<td>0.177</td>
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<tr>
<td>Kidney cyst index %</td>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
<td></td>
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<tr>
<td>Kidney fibrosis score %</td>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
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</tr>
<tr>
<td>Serum blood urea nitrogen mg/dL</td>
<td></td>
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</tr>
</tbody>
</table>

P value:
- *: p < 0.05
- **: p < 0.01
- ***: p < 0.001

Cy/++/+ EGFR, EGFR AND TGF AXIS IN Han:SPRD Rat Model
APCKD, EGFR, and TGFβ
APCKD, EGFR AND TFGβ

Fig. 3. Immunostaining of different types of cystic epithelia in the end-stage polycystic kidney. A and B, TGFα and EGFR receptor staining, respectively, in subcapsular type epithelia; C and D, TGFβ and protein kinase A (PKA) receptor staining; E, TGFβ staining in flattened epithelium; F, negative control of A–D. Bar = 0.05 mm; E–F, Bar = 0.01 mm.
POSSIBLE MECHANISMS OF CYST FORMATION IN POLYCYSTIC KIDNEY DISEASE

- Mutations in polycystin 1, 2 or fibrocystin
  - Defects in cell-cell and cell-matrix interactions
    - Altered tubular epithelial growth and differentiation
      - Abnormal extracellular matrix
      - Cell proliferation
      - Fluid secretion
        - Vascular damage
        - Interstitial inflammation/fibrosis
APCKD

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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 CONCENTRATING ABILITY
• INFECTION
• PAIN SYNDROMES
• POLYCYTHEMIA
APCKD: COMPUTERIZED TOMOGRAPHY
APCKD

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EXTRARENAL EFFECTS OF APCKD

- CEREBRAL ANEURYSMS
- HEPATIC CYSTS
- CARDIAC VALVE DISEASE
- COLONIC DIVERTICULI
- HERNIAS
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 ANEURYSM 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) ?
LIKELIHOOD OF RUPTURE OF INTRACRANIAL ANEURYSM

No history of SAH from a different aneurysm

- No history of SAH from a different aneurysm
- History of SAH from a different aneurysm

Probability of hemorrhage

- ≤10 mm
- 10-24 mm
- ≥25 mm

Years after diagnosis
OTHER ORGANS

• HEPATIC CYSTS
  – UP TO 80% OF PATIENTS WILL HAVE CYSTS
  – EQUAL MALE/FEMALE INCIDENCE BUT MORE SEVERE IN FEMALES
  – RARELY TRANSPLANTATION IS REQUIRED; RAPAMYCIN REDUCES HEPATIC CYSTS

• CARDIAC
  – MITRAL VALVE PROLAPSE AND AI
  – INCIDENCE 20%

• COLONIC DISEASE
  – DIVERTICULI
APCKD

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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)?

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
  – INHIBITION 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
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND PROGRESSION

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Decline in urine protein g/day</th>
<th>Doubling of baseline serum creatinine or onset of kidney failure relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.52 (0.36, 0.68)</td>
<td>0.73 (0.41 to 1.29)</td>
</tr>
<tr>
<td>Adjusted for baseline characteristics</td>
<td>0.34 (0.21, 0.47)</td>
<td>0.81 (0.44 to 1.47)</td>
</tr>
<tr>
<td>Adjusted for baseline characteristics and change in systolic blood pressure during follow-up</td>
<td>0.34 (0.21, 0.47)</td>
<td>0.81 (0.44 to 1.47)</td>
</tr>
<tr>
<td>Adjusted for baseline characteristics and change in urine protein excretion during follow-up</td>
<td>N/A</td>
<td>0.88 (0.49 to 1.61)</td>
</tr>
<tr>
<td>Adjusted for baseline characteristics changes in systolic blood pressure and urine protein during follow-up</td>
<td>N/A</td>
<td>0.91 (0.49 to 1.68)</td>
</tr>
</tbody>
</table>

*a* Declines in blood pressure and urine protein excretion were calculated by subtracting the respective values at each follow-up visit from the baseline value.

*b* Kidney failure is defined as the onset of long-term dialysis therapy.
ACE-I, PROTEINURIA & PROGRESSION

- **Graph A:**
  - x-axis: Baseline urine protein, g/d
  - y-axis: Decline in urine protein in g/d, 95% CI
  - Trend: Decrease in urine protein with increasing baseline urine protein
  - Statistical significance: \( P < 0.001 \)

- **Graph B:**
  - x-axis: Baseline urine protein, g/d
  - y-axis: Relative risk (95% CI) of kidney disease progression
  - Trend: Decrease in relative risk with increasing baseline urine protein
  - Statistical significance: \( P = 0.03 \)
APCKD AND ESRD

• CHALLENGES 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 WITHOUT APCKD

• TRANSPLANT
  – INDICATIONS FOR NEPHRECTOMY
    • FREQUENT UTI, SIZE, PAIN, CHRONIC HEMATURIA
  – COLECTOMY MAY BE REQUIRED
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V₂ RECEPTOR ANTAGONISM

V2 RECEPTOR ANTAGONISM
MAP KINASE CASCADE AND V₂-RECEPTOR ANTAGONIST
CONCLUSIONS

- ENDOTHELIAL CELL PROLIFERATION AND FLUID SECRETION NECESSARY FOR RENAL CYST FORMATION IN HERITABLE CYSTIC KIDNEY DISEASE RESULTS FROM ALTERED CA 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 CLINICAL DATA IN OTHER DISEASES (CHF, CIRRHOSIS)
TOLVAPTAN

Chemical structure:

Other name: OPC-156
INN, USAN: Tolvaptan
Molecular formula: C_{26}H_{25}ClN_{2}O_{3}
Molecular weight: 448.94
Appearance: OPC-41061 is a white crystalline powder.
TOLVAPTAN INTERACTION WITH V₁ & V₂ RECEPTORS

• **ANTAGONISM TO AVP BINDING:**
  – UP TO 300-FOLD INCREASE CONCENTRATION FOR V₁ RECEPTORS
• **PLATELET AGGREGATION (MEDIATED BY V₁a):**
  – 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

Primary Objective:

- Evaluate long-term efficacy of tolvaptan in ADPKD through rate of renal volume change (%) for tolvaptan-treated compared to placebo-treated subjects

Secondary Objectives:

- Evaluate long-term efficacy of tolvaptan in ADPKD through a composite of ADPKD progression clinical markers (i.e., hypertension, renal pain, albuminuria and renal function)
- Evaluate long-term efficacy of tolvaptan in ADPKD using single clinical markers of ADPKD progression
- Evaluate long-term safety of tolvaptan through standard clinical measures
- Evaluate pharmacokinetic (PK), pharmacodynamic (PD) and exploratory parameters for tolvaptan in ADPKD
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
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 KIDNEY 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
THANKS FOR YOUR ATTENTION

THE SMILE