Disclosure of Interests

- Otsuka: Consulting, Research Grants
- Pfizer Inc: Consulting
- Sanofi/Genzyme: Consulting
- NIDDK: CRISP, HALT and Modifier Research Grants
What Endpoints Should be Used in Clinical Trials for Autosomal Dominant Polycystic Kidney Disease?

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School of Medicine
Division of Renal Diseases
Fact 1: Kidney and Cyst Volume are Determinants of Renal Outcomes in ADPKD

- Renal cysts are the first verifiable primary manifestation of ADPKD
- Cyst formation ALWAYS precedes:
  - flank pain
  - hypertension
  - gross hematuria
  - reduced GFR
  - nephrolithiasis
  - kidney infections
- The inverse correlation between kidney volume and function has been observed for over 30 years in ADPKD

FACT 2: Renal Characteristics of ADPKD Associate with ESRD

- **Genotype:** > 95% PKD1 individuals demonstrate renal cysts by age 30
- **Hypertension:** occurs in 60% with intact renal function by age 30
- **Proteinuria:** is not a common feature of this disease, but has important prognostic implications
- **Gross hematuria:** > 50% will have had an episode by age 40
- **Renal insufficiency:** progression to renal failure in > 80% of all PKD patients

**ALL CHARACTERISTICS HAVE NOW BEEN SHOWN TO MITIGATE THEIR RISK THROUGH TKV**
FACT 3: PKD Patients suffer from Renal Complications Prior to Loss of Kidney Function:

Initially: 284 ADPKD patients longitudinally in the 1950’s

O.Z. Dalgaard 1957. 284 patients longitudinal study; 350 cases clinical data; uremia = BUN > 100 mg/dl
NIH CRISP Natural History Study Participants Demonstrate Frequent Renal Complications

<table>
<thead>
<tr>
<th>Baseline Parameter</th>
<th>N=241</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>33.8 (± 9) years</td>
</tr>
<tr>
<td>Mean Age of Diagnosis</td>
<td>24.5 (± 9) years</td>
</tr>
<tr>
<td>Mean TKV</td>
<td>1076 (± 670) ml</td>
</tr>
<tr>
<td>Mean Serum Creatinine Concentration</td>
<td>1.0 (± 0.2) mg/dl</td>
</tr>
<tr>
<td>Mean Glomerular Filtration Rate</td>
<td>98.2 (± 24.9) ml/min/1.73m²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical History</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>69.3 %</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>40.7 %</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>16.2 %</td>
</tr>
<tr>
<td>Flank/Kidney Pain</td>
<td>80.1 %</td>
</tr>
</tbody>
</table>

Age of onset of renal complications in the CRISP population

By age 30, over 50% have at least one complication

NIH CRISP Studies; Rahbari-Oskoui, ASN
Renal Week, 2013.
## Increased Kidney Volume Associates with Renal Complications in ADPKD

<table>
<thead>
<tr>
<th>Renal Complication</th>
<th>N</th>
<th>Complication Present</th>
<th>Complication Absent</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of GFR</td>
<td>220</td>
<td>598 ± 368</td>
<td>366 ± 168</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>241</td>
<td>628 ± 48</td>
<td>352 ± 33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>191</td>
<td>820 ± 87</td>
<td>588 ± 52</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>49</td>
<td>853 ± 87</td>
<td>535 ± 52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>270</td>
<td>1190 ± 93</td>
<td>578 ± 32</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

FACT 5: Total Kidney Volume can be measured accurately and reliably in ADPKD

Inter-observer variability: 2.1%
Intra-observer variability: 2.4%
Day-to-day variability: 2.4%

CHANGE in TOTAL KIDNEY VOLUME, BL-YR3

Log10 MR K Vol

Year 3

Baseline

5.3 \%
Average
(-5.3 to 17.5\%) yearly increase in renal size

Grantham NEJM 354:2122-2130, 2006
Risk of Clinical Events Increases with Every 100ml Increase in TKV

CRISP Cohort followed for 8 years n=201

Hypertension, Pain, Gross Hematuria, CKD Stage 3

NIH CRISP Studies
Rahban-Oskui, ASN week 2013
Progressive Rise in Total Kidney Volume

Signs and Symptoms of Injury Develop Long Before ADPKD Reaches End

FACT 6: Kidney Volume predicts GFR in an age and time dependent fashion

- Kidney enlargement begins *in utero* and continues at a rate characteristic of each individual.
- TKV associates inversely with kidney function in 7 cross-sectional and 3 longitudinal studies.
- Kidney enlargement precedes renal insufficiency by many years.

TKV predicts onset of renal insufficiency (2012 CRISP (n=241), 2013 PKDOC (n=1066)).
Change in Kidney Volume Precedes Change in Kidney Function

p < 0.05 for htTKV change from baseline; # p < 0.05 for GFR change from baseline; htTKV = Height-adjusted total kidney volume; \(^1\) Percent Change Standardized to a common unit; NIH CRISP Studies; Chapman CJASN 7:479, 2012
Future Decline in Renal Function is Predicted by Baseline Kidney Volume

The relationship improves significantly with longer follow-up time

NIH CRISP Studies; htTKV=height-adjusted total kidney volume; GFR by iothalamate clearance
Chapman CJASN 7:479, 2012
ROC AUC Values predicting CKD Stage 3 within 8 years in CRISP Participants

<table>
<thead>
<tr>
<th>hTCKV</th>
<th>Serum Creatinine</th>
<th>Serum Blood Urea Nitrogen</th>
<th>Urinary MCP1</th>
<th>Urine Albumin Excretion</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity (%)</td>
<td>75</td>
<td>64</td>
<td>51</td>
<td>81</td>
<td>63</td>
</tr>
<tr>
<td>specificity (%)</td>
<td>74</td>
<td>81</td>
<td>79</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>correctly classified (%)</td>
<td>75</td>
<td>76</td>
<td>74</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>ROC</td>
<td>0.850</td>
<td>0.770</td>
<td>0.760</td>
<td>0.760</td>
<td>0.690</td>
</tr>
<tr>
<td>Cut Point</td>
<td>600</td>
<td>1.1</td>
<td>16</td>
<td>410</td>
<td>30</td>
</tr>
</tbody>
</table>

* P<0.05 ROC hTCKV vs. others
Total Kidney Volume, ml

AGE
years

0 10 20 30 40 50 60

0 500 1000 1500 2000 2500 3000 3500 4000

Predicts CKD Stage 3 in 8 Years

5.7%

3.4%

Normal

Effect of Kidney Growth Rate on Development of ESRD

Appropriate Selection of ADPKD Patients to Test New Interventions

Exclude subjects with slow kidney cyst growth

Preferred

Acceptable

J.J. Grantham 2006 NEJM 354:2128
Interventional trials designed based on disease natural history

Trial Population
Mid-Stage ADPKD

Significant cystic burden for age
TKV ≥ 750 ml Age 18-50

Preserved kidney function
CKD 1-3: eCrCl >60 ml/min

Endpoints: Disease Specific Modifiable Outcomes

Cyst Growth by TKV
Kidney Function Decline
Progression related events
GAPS IN KNOWLEDGE:

- Knowledge regarding the characteristics of renal clinical, TKV and GFR events in African Americans
- Knowledge regarding the characteristics of renal clinical, TKV and GFR events in Asians
- Potential contribution of individual cyst conformation to future loss of kidney function
- Features of TKV when kidney function begins to decline
GFR Compensation for Loss of Parenchyma

KDIGO

GFR (mL/min/1.73 m²)

Compensation

Functioning Parenchyma

Observed GFR

Loss of Compensated Nephrons

Age

0 10 20 30 40 50 60 70

Cyst Distribution (Renal Parenchyma), in Atypical Forms of ADPKD, May Add Relevant Clinical Information in Addition to TKV

Antiga, et al, CJASN 2006
Controversy 1: Which is the most appropriate imaging modality to monitor ADPKD patients for TKV

- TKV measurements in clinical trials are done to detect small changes in TKV accurately over a relatively short period of time.
- TKV measurements done clinically are performed to risk stratify individuals for progression to renal failure and to monitor progression over longer periods of time.
Controversy 2: What role if any does TKV have in monitoring patients in later stages of PKD

- At what stage of CKD, is monitoring of kidney function alone adequate to measure disease progression?
- Does TKV provide additive information regarding assessment of disease progression in later stages?
Fact 7: Kidney Function Declines in ADPKD Rapidly in the Late Stages of Disease

Distribution of GFR Slopes

- ADPKD
- Glomerular
- Other

MDRD Study A Usual BP
(n=141)

GFR 22-55 mL/min/1.73m²
5 Year Follow-up

Klahr JASN 5:2037-2047, 1995; MDRD Study
Risk of progressing to ESRD with TKV > or < 1 L and eGFR < or > 50ml/min
Comparison of US vs. CT/MRI estimates of TKV and risk for progression to ESRD

CT/MRI

ULTRASOUND

Relative Risk of Progression to ESRD based on TKV at age 20, 40 or 60 years
Ultrasound and MR Renal Length Predicts Future CKD Stage 3


Area under ROC curve = 0.8718

Adjusted Prediction of CKD stg 3a based on MR Length

AUROC = 0.84
95% CI = (0.79, 0.90)
Sensitivity = 74%
Specificity = 75%
Cut Point = 600 (cc/m)

Area under ROC curve = 0.8867

Adjusted Prediction of CKD stg 3a based on US Length

Area under ROC curve = 0.84

Adjusted Prediction of CKD stg 3a based on US Length

Area under ROC curve = 0.8718
Summary

TKV is needed in RCT in ADPKD, both for subject enrichment AND as a primary endpoint.

TKV alone currently provides predictive information regarding renal disease progression in ADPKD.

While MR remains the imaging modality of choice in RCT, other less expensive and invasive imaging modalities such as ultrasound may be used for risk prediction and management of ADPKD.