Are Prevention of Decline in Renal Function and Cardiovascular Complications Interconnected in ADPKD?

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Division of Nephrology
Disclosure of Interests

No relevant disclosures
Breakout Session Questions

1. Should high BP be detected and treated earlier in ADPKD? How? How should BP be evaluated and managed in children?
2. Should RAAS blockade be the first line treatment? Are ACEIs and ARBs equivalent?
3. Are the guidelines for management of hypertension in CKD valid for ADPKD? When to treat adults? What should be the target BP?
4. On the basis of the available RCTs, which type of patients should be recruited in large trials? How should GFR be measured in these trials?
5. Dietary recommendations:
   - What are the appropriate recommendations for water and salt intake? Should they be monitored?
   - What is the evidence for limiting or avoiding caffeine? To what extent?
High Blood Pressure is Significantly Associated with End Organ Damage in Patients with ADPKD


**P < 0.01 vs. Normotensive ADPKD Patients and Healthy Subjects**

**P < 0.001 vs. Healthy Subjects**

R = 0.38
P < 0.0001
Survival Time to ESRD in ADPKD

Median survival time to ESRD
1985–1992: 53 years
1992–2001: 63 years
P = 0.0220

Hypertensive Male Patients

Median survival time to ESRD
1985–1992: 54 years
1992–2001: 60 years
P = 0.0177

Hypertensive Female Patients

n=81

n=61

n=96

n=108

## Comparison of Characteristics of Hypertensive ADPKD Patients in Two Cohorts at the Initial Study Visit

### Male Patients

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>40</td>
<td>9</td>
<td>38</td>
<td>10</td>
<td>NS</td>
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<tr>
<td>BMI kg/m²</td>
<td>26.5</td>
<td>4.3</td>
<td>27.5</td>
<td>4.3</td>
<td>NS</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>138</td>
<td>13</td>
<td>135</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>DBP mm Hg</td>
<td>94</td>
<td>9</td>
<td>85</td>
<td>9</td>
<td>&lt;0.0001</td>
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<tr>
<td>MAP mm Hg</td>
<td>109</td>
<td>10</td>
<td>102</td>
<td>9</td>
<td>&lt;0.0001</td>
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<tr>
<td>Urinary protein excretion mg/24 h</td>
<td>474</td>
<td>652</td>
<td>305</td>
<td>612</td>
<td>NS</td>
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<tr>
<td>Renal volume cm³</td>
<td>935</td>
<td>587</td>
<td>944</td>
<td>902</td>
<td>NS</td>
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<tr>
<td>Serum creatinine mg/dL</td>
<td>2.2</td>
<td>1.3</td>
<td>1.8</td>
<td>1.2</td>
<td>NS</td>
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<tr>
<td>N of antihypertensive medications</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
<td>0.94</td>
<td>NS</td>
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<tr>
<td>ACEIs %</td>
<td>16.1</td>
<td></td>
<td>54.1</td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>CCBs %</td>
<td>9.9</td>
<td></td>
<td>23.0</td>
<td></td>
<td>0.0331</td>
</tr>
<tr>
<td>Diuretics %</td>
<td>42.2</td>
<td></td>
<td>13.1</td>
<td></td>
<td>0.0003</td>
</tr>
<tr>
<td>Sympathetic blocking agents (SBAs) %</td>
<td>40.7</td>
<td></td>
<td>23.0</td>
<td></td>
<td>0.0033</td>
</tr>
<tr>
<td>α-Blockers %</td>
<td>13.6</td>
<td></td>
<td>8.2</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>β-Blockers %</td>
<td>34.6</td>
<td></td>
<td>16.4</td>
<td></td>
<td>0.0155</td>
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<tr>
<td>Hematuria %</td>
<td>48.1</td>
<td></td>
<td>27.9</td>
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<td>0.0151</td>
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### Female Patients

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<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>P</td>
</tr>
<tr>
<td>Age years</td>
<td>40</td>
<td>10</td>
<td>42</td>
<td>11</td>
<td>NS</td>
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<tr>
<td>BMI kg/m²</td>
<td>24.7</td>
<td>4.8</td>
<td>27.9</td>
<td>7.0</td>
<td>0.0004</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>130</td>
<td>12</td>
<td>131</td>
<td>14</td>
<td>NS</td>
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<tr>
<td>DBP mm Hg</td>
<td>87</td>
<td>9</td>
<td>82</td>
<td>9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MAP mm Hg</td>
<td>101</td>
<td>9</td>
<td>93</td>
<td>10</td>
<td>0.0384</td>
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<tr>
<td>Urinary protein excretion mg/24 h</td>
<td>267</td>
<td>360</td>
<td>276</td>
<td>420</td>
<td>NS</td>
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<tr>
<td>Renal volume cm³</td>
<td>703</td>
<td>631</td>
<td>697</td>
<td>419</td>
<td>NS</td>
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<tr>
<td>Serum creatinine mg/dL</td>
<td>1.7</td>
<td>1.3</td>
<td>1.6</td>
<td>1.3</td>
<td>NS</td>
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<tr>
<td>N of antihypertensive medications</td>
<td>1.0</td>
<td>0.90</td>
<td>1.2</td>
<td>0.81</td>
<td>NS</td>
</tr>
<tr>
<td>ACEIs %</td>
<td>13.5</td>
<td></td>
<td>48.2</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CCBs %</td>
<td>6.3</td>
<td></td>
<td>15.7</td>
<td></td>
<td>0.0345</td>
</tr>
<tr>
<td>Diuretics %</td>
<td>34.4</td>
<td></td>
<td>24.1</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Sympathetic blocking agents (SBAs) %</td>
<td>40.6</td>
<td></td>
<td>24.1</td>
<td></td>
<td>0.0113</td>
</tr>
<tr>
<td>α-Blockers %</td>
<td>6.3</td>
<td></td>
<td>5.6</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>β-Blockers %</td>
<td>34.4</td>
<td></td>
<td>19.4</td>
<td></td>
<td>0.0158</td>
</tr>
<tr>
<td>Hematuria %</td>
<td>46.8</td>
<td></td>
<td>41.7</td>
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<td>NS</td>
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</tbody>
</table>
Use of Antihypertensive Medications and Mortality of Patients With Autosomal Dominant Polycystic Kidney Disease: A Population-Based Study

Christine Patch, PhD,1 Judith Charlton, MSc,2 Paul J. Roderick, FFPH,3 and Martin C. Gulliford, FFPH2

Background: This study aimed to estimate the association between antihypertensive therapy and mortality in patients with autosomal dominant polycystic kidney disease (ADPKD).

Study Design: Cohort study.

Setting & Participants: Participants with ADPKD from the UK General Practice Research Database older than 15 years between 1991 and 2008.

Predictors: Use of 5 major classes of antihypertensive drug.

Outcomes: Deaths, new renal replacement therapy events.

Measurements: Random-effects Poisson models were adjusted for age, sex, year of entry into the cohort, calendar year, prevalent coronary heart disease, stroke, diabetes, hyperlipidemia, and lipid-lowering therapy.

Results: From 1991-2008, there were 2,085 cases of ADPKD, with 1,877 contributing person-time for ages older than 15 years. In 1991, antihypertensive drugs were not prescribed for 68% of participants, which decreased to 38% by 2008. The proportion for which 1 class of antihypertensive drug was prescribed increased from 19% in 1991 to 24% in 2008; 2 classes, from 11% to 22%; 3 classes, from 2% to 11%; and 4 or 5 classes, from 1% to 5%. In 1991, drugs acting on the renin-angiotensin system were prescribed for only 7% of participants; by 2008, this had increased to 46%. There was evidence of a trend toward decreasing mortality as the number of antihypertensive drug classes prescribed in a year increased. For participants with 3 classes of drugs prescribed, the incident rate ratio was 0.11 (95% CI, 0.05-0.21; P < 0.001). Each annual increment in year of entry into the cohort was associated with a 6% (95% CI, 2%-10%; P = 0.008) decrease in mortality.

Limitations: Reported associations might be accounted for by unmeasured or incompletely measured confounders. These might include changes in other aspects of medical care for patients with ADPKD.

Conclusion: Increasing coverage and intensity of antihypertensive therapy is associated with decreasing mortality in people with ADPKD.

Change in Use of Antihypertensive Medications


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### Change in Use of Antihypertensive Medications

**Table 3. Associations of Antihypertensive Therapy With Outcomes**

<table>
<thead>
<tr>
<th>No. of classes of antihypertensive drug</th>
<th>Death</th>
<th>Death or RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>0</td>
<td>Reference</td>
<td>0.26 (0.17-0.42)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>0.15 (0.09-0.24)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.11 (0.06-0.21)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.11 (0.05-0.27)</td>
</tr>
<tr>
<td>≥4</td>
<td></td>
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</tr>
</tbody>
</table>

**Class of antihypertensive druga**

- Renin-angiotensin system drugs\(^b\) | 0.44 (0.29-0.66) | <0.001 | 0.75 (0.58-0.96) | 0.02 |
- \(\beta\)-Blockers | 0.68 (0.37-0.91) | 0.02 | 1.07 (0.63-1.38) | 0.6 |
- Calcium channel blockers | 0.53 (0.35-0.80) | 0.003 | 1.29 (1.01-1.65) | 0.04 |
- Diuretics\(^c\) | 0.29 (0.17-0.49) | <0.001 | 0.32 (0.22-0.46) | <0.001 |
- Other drugs\(^d\) | 0.75 (0.45-1.23) | 0.3 | 1.38 (1.04-1.82) | 0.02 |

**Note:** IRRs adjusted for age, sex, calendar year, year of entry to cohort, coronary heart disease, stroke, diabetes, hyperlipidemia, and prescription of lipid-lowering drugs.

**Abbreviations:** CI, confidence interval; IRR, incident rate ratio; RRT, renal replacement therapy.

\(^a\)For each class, comparison is with “class not prescribed” as reference.

\(^b\)Including angiotensin-converting enzyme inhibitors and angiotensin receptor blocking drugs.

\(^c\)Including thiazide diuretics and potassium-sparing diuretics.

\(^d\)Including centrally acting drugs, \(\alpha\)-blockers, and vasodilators.

**Increasing coverage and intensity of antihypertensive therapy is associated with decreasing mortality in patients with ADPKD.**

What should be the first line antihypertensive medication?
Diuretics versus ACE Inhibitors in ADPKD

Annual Loss of Creatinine Clearance

Diuretic Group (n=14)

ACEI Group (n=19)

Proteinuria

P < 0.0001

Baseline Year 5

Diuretic Group (n=14)

ACEI Group (n=19)

P < 0.05


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Renal and Cardiac Effects of Ramipril versus Metoprolol in ADPKD

Baseline Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Ramipril (n = 17)</th>
<th>Metoprolol (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.7 ± 2.2</td>
<td>40.0 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Males/Females</td>
<td>10/7</td>
<td>7/13</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.5 ± 3.1</td>
<td>74.2 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.96 ± 0.05</td>
<td>1.90 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5 ± 0.6</td>
<td>24.6 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension (years)</td>
<td>5.9 ± 1.9</td>
<td>8.1 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>143 ± 2</td>
<td>142 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>93 ± 2</td>
<td>90 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial BP (mm Hg)</td>
<td>106 ± 2</td>
<td>104 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.30 ± 0.19</td>
<td>1.16 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Estimated GFR (ml/min)</td>
<td>88.0 ± 9.5</td>
<td>87.3 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin/creatinine ratio (mg/g)</td>
<td>64.0 ± 21.6</td>
<td>75.3 ± 22.8</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>97.6 ± 6.1</td>
<td>95.0 ± 4.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

24-h ambulatory BP.
Renal and Cardiac Effects of Ramipril versus Metoprolol in ADPKD

Mean GFR

**P<0.01 for GFR at baseline compared with GFR at the end of the study in both groups**

LVMI

Rigorous BP Control: MAP ≤97 mm Hg
Standard BP Control: MAP >97 mm Hg

Candesartan versus Amlodipine in ADPKD

- Multicenter, prospective and randomized clinical trial
- 49 patients with hypertension and ADPKD
- Amlodipine 2.5-10 mg/day vs. candesartan 2-8 mg/day
- Target BP: <130/85 mm Hg; Follow-up: 36 months
- Primary Outcome: A composite endpoint of patient’s serum creatinine levels increased twofold over baseline or GFR decreased to half of the baseline.

Candesartan versus Amlodipine in ADPKD

Renal event-free survival rate

Changes in Ccr from baseline

Cardiac and Renal Effects of Standard vs. Rigorous BP Control in ADPKD

Table 1. Baseline characteristics of standard and rigorous BP control groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard Group</th>
<th>Rigorous Group</th>
<th>P Values</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>156</td>
<td>161</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)ᵃ</td>
<td>142</td>
<td>143</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)ᵃ</td>
<td>96</td>
<td>93</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)ᵃ</td>
<td>111</td>
<td>111</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42.5</td>
<td>42.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)ᵇ</td>
<td>1.4</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min per 1.73 m²)</td>
<td>82</td>
<td>84</td>
<td>NS</td>
</tr>
<tr>
<td>Male/Female</td>
<td>19/15</td>
<td>22/19</td>
<td>NS</td>
</tr>
<tr>
<td>Amlodipine/enalapril</td>
<td>15/19</td>
<td>15/26</td>
<td>NS</td>
</tr>
</tbody>
</table>

ᵃ Blood pressures were measured after a 2- to 4-week washout period without hypertensive medications.

ᵇ To convert serum creatinine values to micromoles per liter, multiply by 88.4.
Effect of Rigorous vs. Standard BP Control on LVMI in Patients with ADPKD

Effect of BP Control with Amlodipine vs. Enalapril on LVMI in Patients with ADPKD

Effect of Rigorous vs. Standard BP Control on 24-h Creatinine Clearance in Patients with ADPKD

A BP goal of less than 120/80 mm Hg and the use of an ACEI should be recommended for patients with ADPKD who have hypertension and LVH.
The HALT Polycystic Kidney Disease Trials: Design and Implementation


*Emory University School of Medicine, Atlanta, Georgia; †Mayo College of Medicine, Rochester, Minnesota; ‡Tafts Medical Center, Boston, Massachusetts; §Beth Israel Deaconess Medical Center, Boston, Massachusetts; ¶University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; ‡Washington University, St. Louis, Missouri; **University of Colorado, Aurora, Colorado; ††Kansas University Medical Center, Kansas City, Kansas; ‡‡Cleveland Clinic, Cleveland, Ohio; §§Sanford Research, University of South Dakota, Sioux Falls, South Dakota; and ¶¶National Institutes of Health (NIDDK), Bethesda, Maryland

Background and objectives: Two HALT PKD trials will investigate interventions that potentially slow kidney disease progression in hypertensive autosomal dominant polycystic kidney disease (ADPKD) patients. Studies were designed in early and later stages of ADPKD to assess the impact of intensive blockade of the renin-angiotensin-aldosterone system and level of BP control on progressive renal disease.

Design, settings, participants, and measurements: PKD-HALT trials are multicenter, randomized, double-blind, placebo-controlled trials studying 1018 hypertensive ADPKD patients enrolled over 3 yr with 4 to 8 yr of follow-up. In study A, 548 participants, estimated GFR (eGFR) of >60 ml/min per 1.73 m² were randomized to one of four arms in a 2-by-2 design: combination angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) therapy versus ACEI monotherapy at two levels of BP control. In study B, 470 participants, eGFR of 25 to 60 ml/min per 1.73 m² compared ACEI/ARB therapy versus ACEI monotherapy, with BP control of 120 to 130/70 to 80 mmHg. Primary outcomes of studies A and B are MR-based percent change kidney volume and a composite endpoint of time to 50% reduction of baseline estimated eGFR, ESRD, or death, respectively.

Results: This report describes design issues related to (1) novel endpoints such as kidney volume, (2) home versus office BP measures, and (3) the impact of RAAS inhibition on kidney and patient outcomes, safety, and quality of life.

Conclusions: HALT PKD trials will evaluate potential benefits of rigorous BP control and inhibition of the renin-angiotensin-aldosterone system on kidney disease progression in ADPKD.


doi 10.2215/CJN.04310709
When should antihypertensive agents be started in ADPKD?
Hypertensive and Borderline Hypertensive Children with ADPKD have a Significantly Higher LVMI than Normotensive Children with ADPKD

Hypertensive Children with ADPKD have a Significantly Higher Renal Volume than Normotensive and Borderline Hypertensive Children with ADPKD

### Prospective Change in Renal Volume and Function in Children with ADPKD

5-year randomized trial to assess the effect of BP control with enalapril on disease progression in 85 children and young adults with ADPKD.

**Primary Outcome:** Renal volume by ultrasound;  **Secondary Outcomes:** LVMI, UMA

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>HBP50</td>
<td>HBP90</td>
<td>BBP + ACEI</td>
</tr>
<tr>
<td>baseline</td>
<td>14</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>year 5</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Renal volume adjusted for sex and height (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>76 (68–84)</td>
<td>76 (69–84)</td>
<td>66 (59–74)</td>
</tr>
<tr>
<td>baseline</td>
<td>79 (69–90)</td>
<td>80 (71–90)</td>
<td></td>
</tr>
<tr>
<td>year 5</td>
<td>22 (14–32)</td>
<td>29 (20–50)</td>
<td></td>
</tr>
<tr>
<td>UMA (mcg/day)</td>
<td>21 (14–32)</td>
<td>32 (20–50)</td>
<td>17 (9–32)</td>
</tr>
<tr>
<td>baseline</td>
<td>29 (18–46)</td>
<td>40 (25–63)</td>
<td>29 (11–35)</td>
</tr>
<tr>
<td>year 5</td>
<td></td>
<td></td>
<td>13 (9–32)</td>
</tr>
<tr>
<td>SCr (mg/dl)</td>
<td>0.70 (0.63–0.78)</td>
<td>0.78 (0.71–0.85)</td>
<td>0.77 (0.69–0.85)</td>
</tr>
<tr>
<td>baseline</td>
<td>0.98 (0.88–1.10)</td>
<td>1.03 (0.93–1.15)</td>
<td>0.73 (0.66–0.82)</td>
</tr>
<tr>
<td>year 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CICr (ml/min/1.73 m²)</td>
<td>142 (129–156)</td>
<td>128 (117–140)</td>
<td>122 (111–135)</td>
</tr>
<tr>
<td>baseline</td>
<td>104 (90–112)</td>
<td>97 (88–108)</td>
<td>126 (113–140)</td>
</tr>
<tr>
<td>year 5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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ACEI treatment in borderline hypertensive children with ADPKD may prevent the development of increased LVMI and deterioration in renal function.
Glomerular Hyperfiltration* in ADPKD Children is Associated with a Faster Decline in Renal Function and Higher Rate of Kidney Enlargement

Table 1. Baseline characteristics of ADPKD patients with GH versus without GH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GH</th>
<th>Without GH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>32</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.4 ± 3.6</td>
<td>10.8 ± 3.9</td>
<td>0.27</td>
</tr>
<tr>
<td>Male/Female</td>
<td>19/13</td>
<td>63/85</td>
<td>0.08</td>
</tr>
<tr>
<td>Median follow-up (years)</td>
<td>4.6 (2.6 to 7.1)</td>
<td>5.7 (1.3 to 7.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.4 ± 5.2</td>
<td>20.0 ± 5.9</td>
<td>0.40</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 18</td>
<td>114 ± 14</td>
<td>0.09</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 12</td>
<td>71 ± 11</td>
<td>0.70</td>
</tr>
<tr>
<td>Symptoms and complications of ADPKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (53.13%)</td>
<td>51 (34.46%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Recurrent flank pain</td>
<td>4 (12.5%)</td>
<td>24 (16.44%)</td>
<td>0.08</td>
</tr>
<tr>
<td>History of macrohematuria</td>
<td>8 (25.0%)</td>
<td>18 (12.16%)</td>
<td>0.15</td>
</tr>
<tr>
<td>History of cyst infection</td>
<td>5 (15.63%)</td>
<td>38 (25.85%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Median serum creatinine (mg/dl)</td>
<td>0.6 (0.4 to 0.7)</td>
<td>0.7 (0.6 to 0.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Median CrCl (ml/min per 1.73 m²)</td>
<td>153.9 (145.1 to 168.6)</td>
<td>111.7 (93.2 to 124.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total kidney volume (cm³)</td>
<td>431.9 ± 196.0</td>
<td>400.1 ± 317.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIU</td>
<td>0 (0%)</td>
<td>1 (0.68%)</td>
<td>0.82</td>
</tr>
<tr>
<td>ACEI</td>
<td>3 (9.38%)</td>
<td>13 (8.9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>ARB</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.69</td>
</tr>
<tr>
<td>NSAID</td>
<td>1 (3.23%)</td>
<td>10 (6.94%)</td>
<td></td>
</tr>
</tbody>
</table>

ADPKD, autosomal dominant polycystic kidney disease; GH, glomerular hyperfiltration; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; CrCl, creatinine clearance; DIU, diuretic; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drugs.

Values are numbers of patients (%), mean ± SD, or median (interquartile range).

*Glomerular hyperfiltration is defined as creatinine clearance ≥140 ml/min per 1.73 m²

Glomerular Hyperfiltration in ADPKD Children is Associated with a Faster Decline in Renal Function and Higher Rate of Kidney Enlargement

Table 2. Annual total kidney volume in autosomal dominant polycystic kidney disease patients without and with GH in relation to time

<table>
<thead>
<tr>
<th>Incremental Rate of TKV/BSA Growth Per Year</th>
<th>GH</th>
<th>Without GH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age, gender</td>
<td>+19.3 ± 10.8 cm³</td>
<td>−4.3 ± 7.7 cm³</td>
<td>0.008</td>
</tr>
<tr>
<td>Adjusted for age, gender, ACEI/ARB use, hypertension</td>
<td>+37.2 ± 7.8 cm³</td>
<td>+15.3 ± 4.1 cm³</td>
<td>0.005</td>
</tr>
<tr>
<td>% increase in TKV (year)</td>
<td>9.2 ± 8.1%</td>
<td>8.8 ± 10.4%</td>
<td>0.45</td>
</tr>
</tbody>
</table>

GH, glomerular hyperfiltration; TKV/BSA, total kidney volume/body surface area; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Are the guidelines for management of hypertension in CKD valid for ADPKD?
## Guideline Comparisons of Goal Blood Pressure and Initial Drug Therapy for Adults with Hypertension

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Population</th>
<th>Goal BP, mm Hg</th>
<th>Initial Drug Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 Hypertension guideline</td>
<td>General ≥60 y</td>
<td>&lt;150/90</td>
<td>Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB</td>
</tr>
<tr>
<td></td>
<td>General &lt;60 y</td>
<td>&lt;140/90</td>
<td>Black: thiazide-type diuretic or CCB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;140/90</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>ESH/ESC 2013</td>
<td>General nonelderly</td>
<td>&lt;140/90</td>
<td>β-Blocker, diuretic, CCB, ACEI, or ARB</td>
</tr>
<tr>
<td></td>
<td>General elderly &lt;80 y</td>
<td>&lt;150/90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;140/85</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD no proteinuria</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD + proteinuria</td>
<td>&lt;130/90</td>
<td></td>
</tr>
<tr>
<td>CHEP 2013</td>
<td>General &lt;80 y</td>
<td>&lt;140/90</td>
<td>Thiazide, β-blocker (age &lt;60 y), ACEI (nonblack), or ARB</td>
</tr>
<tr>
<td></td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB with additional CVD risk</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>ADA 2013</td>
<td>Diabetes</td>
<td>&lt;140/80</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>KDIGO 2012</td>
<td>CKD no proteinuria</td>
<td>≤140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD + proteinuria</td>
<td>≤130/80</td>
<td></td>
</tr>
<tr>
<td>NICE 2011</td>
<td>General &lt;80 y</td>
<td>&lt;140/90</td>
<td>&lt;55 y: ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
<td>≥55 y or black: CCB</td>
</tr>
<tr>
<td>ISHIB 2010</td>
<td>Black, lower risk</td>
<td>&lt;135/85</td>
<td>Diuretic or CCB</td>
</tr>
<tr>
<td></td>
<td>Target organ damage or CVD risk</td>
<td>&lt;130/80</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADA, American Diabetes Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; DHPCBB, dihydropyridine calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISHIB, International Society for Hypertension in Blacks; JNC, Joint National Committee; KDIGO, Kidney Disease: Improving Global Outcome; NICE, National Institute for Health and Clinical Excellence.
Who Should be Recruited in Large Trials?

Estimating GFR in Patients with ADPKD

101 ADPKD patients with CKD stages 1 – 5 were recruited. GFR was measured with $^{51}$Cr-EDTA clearance method, and estimated with the MDRD equation with 4 variables, CKD-EPI equation, the Cockcroft-Gault equation adjusted for BSA and the MDRD equation with cystatin C.

Performance of the 4 equations in ADPKD patients with GFR ≥60 ml/min/1.73 m²

<table>
<thead>
<tr>
<th>Equations</th>
<th>n</th>
<th>Bias</th>
<th>Precision</th>
<th>$P_{15}$, %</th>
<th>$P_{30}$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD-EPI</td>
<td>60</td>
<td>6.7</td>
<td>12.4</td>
<td>52</td>
<td>93</td>
</tr>
<tr>
<td>MDRD</td>
<td>60</td>
<td>15.5</td>
<td>10.7</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td>MDRD with cystatin C</td>
<td>59</td>
<td>6.1</td>
<td>10.0</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>Cockcroft-Gault (BSA)</td>
<td>60</td>
<td>0.0</td>
<td>15.0</td>
<td>55</td>
<td>98</td>
</tr>
</tbody>
</table>

Performance of the 4 equations in ADPKD patients with GFR <60 ml/min/1.73 m²

<table>
<thead>
<tr>
<th>Equations</th>
<th>n</th>
<th>Bias</th>
<th>Precision</th>
<th>$P_{15}$, %</th>
<th>$P_{30}$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD-EPI</td>
<td>41</td>
<td>2.5</td>
<td>4.8</td>
<td>49</td>
<td>85</td>
</tr>
<tr>
<td>MDRD</td>
<td>41</td>
<td>4.1</td>
<td>4.5</td>
<td>41</td>
<td>85</td>
</tr>
<tr>
<td>MDRD with cystatin C</td>
<td>32</td>
<td>-0.5</td>
<td>5.8</td>
<td>59</td>
<td>91</td>
</tr>
<tr>
<td>Cockcroft-Gault (BSA)</td>
<td>41</td>
<td>-3.2</td>
<td>6.9</td>
<td>49</td>
<td>78</td>
</tr>
</tbody>
</table>

Performance of the 4 equations in ADPKD patients with CKD stages 1 – 5

<table>
<thead>
<tr>
<th>Equations</th>
<th>n</th>
<th>Bias</th>
<th>Precision</th>
<th>$P_{15}$, %</th>
<th>$P_{30}$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD-EPI</td>
<td>101</td>
<td>5.0</td>
<td>10.2</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>MDRD</td>
<td>101</td>
<td>10.8</td>
<td>10.5</td>
<td>37</td>
<td>83</td>
</tr>
<tr>
<td>MDRD with cystatin C</td>
<td>91</td>
<td>3.8</td>
<td>9.3</td>
<td>65</td>
<td>97</td>
</tr>
<tr>
<td>Cockcroft-Gault (BSA)</td>
<td>101</td>
<td>-1.3</td>
<td>12.5</td>
<td>52</td>
<td>90</td>
</tr>
</tbody>
</table>

Bias is defined as mGFR minus eGFR. Precision is the standard deviation of the bias. 
$P_{15}$ (accuracy) = Percentage of eGFR within 15% of mGFR. 
$P_{30}$ (accuracy) = Percentage of eGFR within 30% of mGFR.

What are the appropriate recommendations for water and salt intake?
Increased Water Intake Decreases Progression of Polycystic Kidney Disease in the PCK Rat

Influence of Daily Osmolar Load on Daily Urine Volume at Different Urine Osmolalities


Controversies Conference on ADPKD | January 17-19, 2014 | Edinburgh, United Kingdom
# Recommendations for Water Intake in Patients with ADPKD

<table>
<thead>
<tr>
<th>GFR = 60 ml/min/1.73 m²</th>
<th>60 &gt; GFR &gt; 30 ml/min/1.73 m²</th>
<th>GFR ≤ 30 ml/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>Enough to achieve an average U₁₀₀₀ of 250 mosm/kg H₂O, usually 2.5–4 L per day</td>
<td>Enough to achieve an average U₁₀₀₀ of 250 mosm/kg H₂O, usually 2.5–4 L per day</td>
</tr>
<tr>
<td>Risk</td>
<td>Minimal</td>
<td>Low</td>
</tr>
<tr>
<td>Benefit</td>
<td>Likely reduction in the rate of cyst growth by suppressing the secretion of AVP and its effect on tubular cell proliferation and fluid secretion</td>
<td>Likely reduction in the rate of cyst growth by suppressing the secretion of AVP and its effect on tubular cell proliferation and fluid secretion</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>Recheck serum sodium within 1–3 wk after increasing water intake, more frequently in patients on drugs which may enhance AVP secretion or effect</td>
<td>Recheck serum sodium within 1–3 wk after increasing water intake and regularly thereafter</td>
</tr>
<tr>
<td>Exclusions</td>
<td>Severe protein or sodium restriction, volume contraction or reduced effective intravascular volume, diuretics or drugs enhancing the release or effect of AVP, abnormal voiding mechanisms</td>
<td>Severe protein or sodium restriction, volume contraction or reduced effective intravascular volume, diuretics or drugs enhancing the release or effect of AVP, abnormal voiding mechanisms</td>
</tr>
</tbody>
</table>

NA, not applicable.

---

Recommendations for Salt Intake in Patients with ADPKD

LIFESTYLE MODIFICATION

2.3: Encourage lifestyle modification in patients with CKD to lower BP and improve long-term cardiovascular and other outcomes:

2.3.1: We recommend achieving or maintaining a healthy weight (BMI 20 to 25). (1D)

2.3.2: We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride), unless contraindicated. (1C)

2.3.3: We recommend undertaking an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 minutes 5 times per week. (1D)

2.3.4: We suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women. (2D)
Potentially Modifiable Factors Affecting the Progression of Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres,* Jared J. Grantham,† Arlene B. Chapman,‡ Michal Mrug,§ Kyonggae T. Bae,∥ Bernard F. King Jr.,* Louis H. Wetzell,† Diego Martin,‡ Mark E. Lockhart,§ William M. Bennett,* Marva Moxey-Mims,** Kaleab Z. Abebe,∥

Table 3. Final regression models predicting structural disease progression measured as lnTKV across time from baseline parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline to YR3 (n = 205)</th>
<th>Baseline to YR6 (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>p</td>
</tr>
<tr>
<td>Year</td>
<td>-0.072</td>
<td>0.004</td>
</tr>
<tr>
<td>Age</td>
<td>0.0002</td>
<td>0.705</td>
</tr>
<tr>
<td>InTKV</td>
<td>1.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum HDL</td>
<td>0.00004</td>
<td>0.915</td>
</tr>
<tr>
<td>Urine sodium</td>
<td>-0.00003</td>
<td>0.960</td>
</tr>
<tr>
<td>Year*age</td>
<td>-0.0005</td>
<td>0.049</td>
</tr>
<tr>
<td>Year*InTKV</td>
<td>0.022</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year*serum HDL</td>
<td>-0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year*urine sodium</td>
<td>0.0001</td>
<td>0.001</td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.017</td>
<td>0.776</td>
</tr>
</tbody>
</table>

Bold values indicate p ≤ 0.05.

Conclusions Serum HDL-cholesterol, U$_{\text{Na}}$V, and 24-hour urine osmolality likely affect ADPKD progression. To what extent their modification may influence the clinical course of ADPKD remains to be determined.

What is the evidence for limiting or avoiding caffeine? To what extent?
The Effect of Caffeine on Renal Epithelial Cells from Patients with ADPKD

Potentiation of Desmopressin (DDAVP)-induced cAMP Accumulation by Caffeine in ADPKD Cells

Values are mean ± SE (n=12) from three different ADPKD patients

*P < 0.05 and ***P < 0.001 compared with the baseline value

Caffeine Intake by Patients with ADPKD

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (N = 102)</th>
<th>ADPKD (N = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>74/28</td>
<td>68/34</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38 ± 14</td>
<td>39 ± 12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 4.8</td>
<td>25.7 ± 4.5</td>
</tr>
<tr>
<td>Energy (kcal/day)</td>
<td>1966 ± 601</td>
<td>2018 ± 608</td>
</tr>
<tr>
<td>Protein intake (g·kg⁻¹·day⁻¹)</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>PRAL (mEq/day)</td>
<td>20 ± 14</td>
<td>21 ± 14</td>
</tr>
<tr>
<td>Carbohydrate intake (g/day)</td>
<td>246 ± 78</td>
<td>268 ± 82</td>
</tr>
<tr>
<td>Lipid intake (g/day)</td>
<td>70 ± 26</td>
<td>68 ± 25</td>
</tr>
<tr>
<td>Caffeine intake (mg/day)</td>
<td>134 ± 116</td>
<td>86 ± 77*</td>
</tr>
</tbody>
</table>

Data are reported as means ± SD. ADPKD = autosomal dominant polycystic kidney disease patients; BMI = body mass index; PRAL = potential renal acid load. *P = 0.001 compared to controls (t-test).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>0-41.8 mg/day (N = 34)</th>
<th>41.8-68.7 mg/day (N = 34)</th>
<th>68.7-98.6 mg/day (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36 ± 12</td>
<td>39 ± 13</td>
<td>43 ± 11</td>
</tr>
<tr>
<td>Time since diagnosis (months)</td>
<td>112 ± 103</td>
<td>99 ± 88</td>
<td>101 ± 99</td>
</tr>
<tr>
<td>CKD1/2 (N, %)</td>
<td>21 (62)</td>
<td>19 (56)</td>
<td>23 (68)</td>
</tr>
<tr>
<td>CKD3 (N, %)</td>
<td>13 (38)</td>
<td>15 (44)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Hypertension (N, %)</td>
<td>16 (47)</td>
<td>26 (76)</td>
<td>22 (65)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.3 ± 0.73</td>
<td>1.3 ± 0.7</td>
<td>1.4 ± 1.2</td>
</tr>
<tr>
<td>eGFR (mL·min⁻¹·(1.73 m²)⁻¹)</td>
<td>74 ± 33</td>
<td>74 ± 35</td>
<td>73 ± 35</td>
</tr>
<tr>
<td>Renal volume (mL)</td>
<td>787 (306-3848)</td>
<td>1100 (280-5517)</td>
<td>748 (219-3588)</td>
</tr>
</tbody>
</table>

Parametric variables are reported as means ± SD. Renal volume (nonparametric variable) is reported as median (25th to 75th percentile). CKD1/2 = chronic kidney disease stages 1/2; CKD3 = chronic kidney disease stage 3; eGFR = estimated glomerular filtration rate. No statistically significant differences were detected among tertiles (ANOVA or chi-square test for categorial variables).
