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

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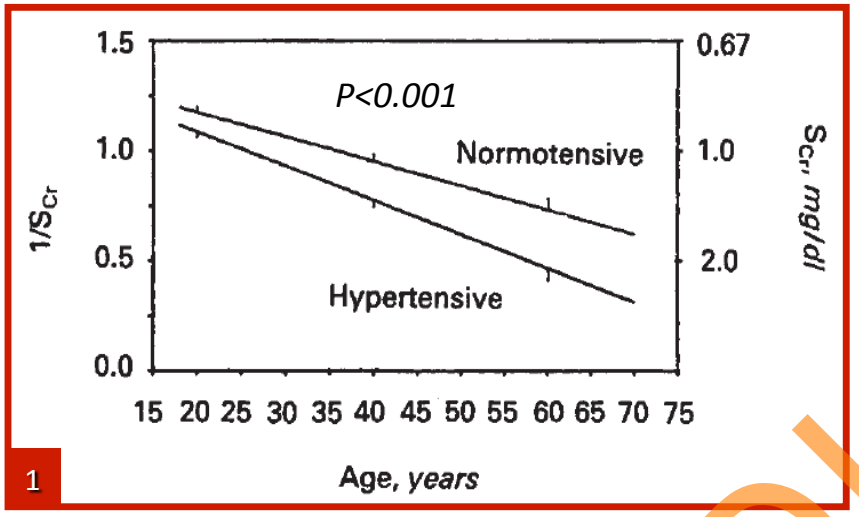
Disclosure of Interests

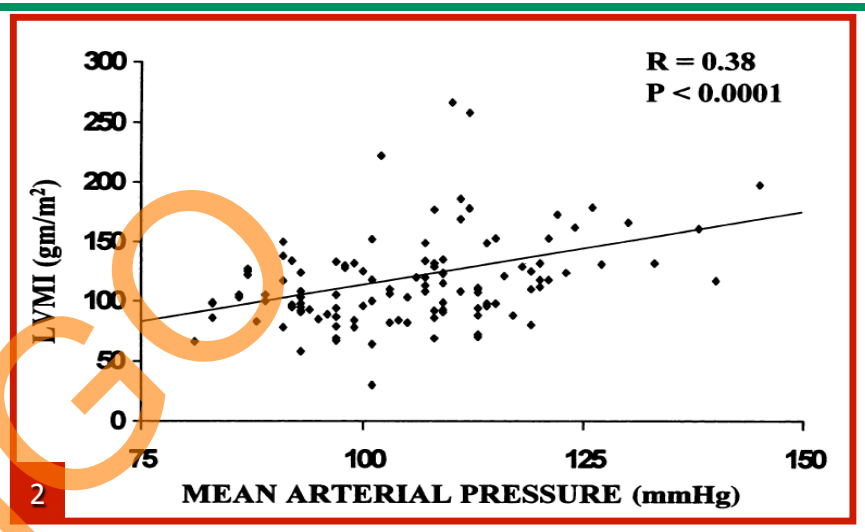
No relevant disclosures

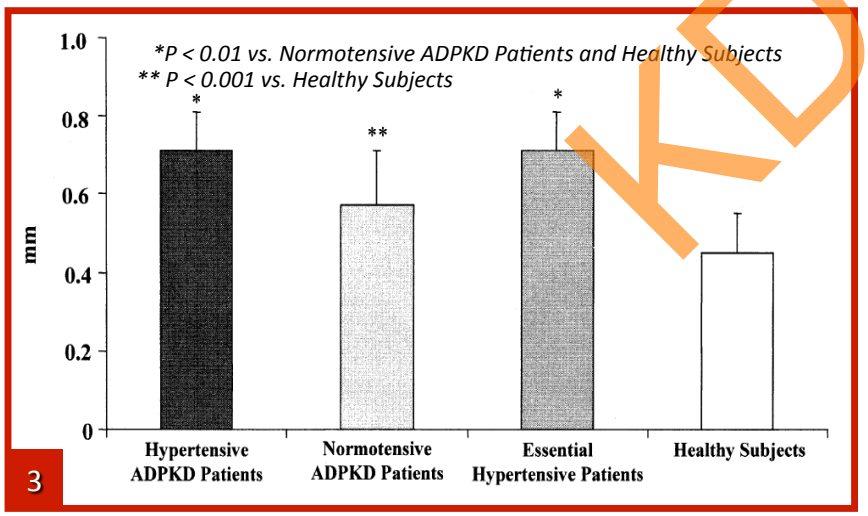
Breakout Session Questions

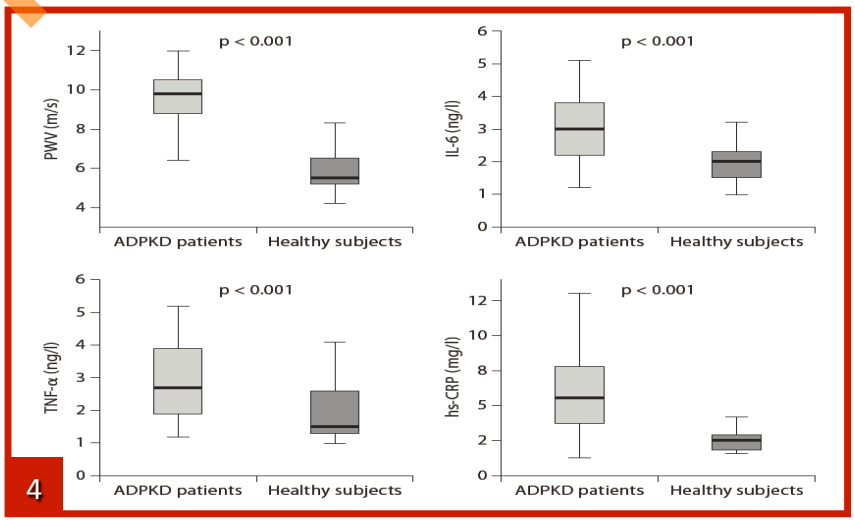
1. Should high BP be detected and treated earlier in ADPKD? How? How should BP be evaluated and managed in children?
2. Should RAAS blockade be the first line treatment? Are ACEIs and ARBs equivalent?
3. Are the guidelines for management of hypertension in CKD valid for ADPKD? When to treat adults? What 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



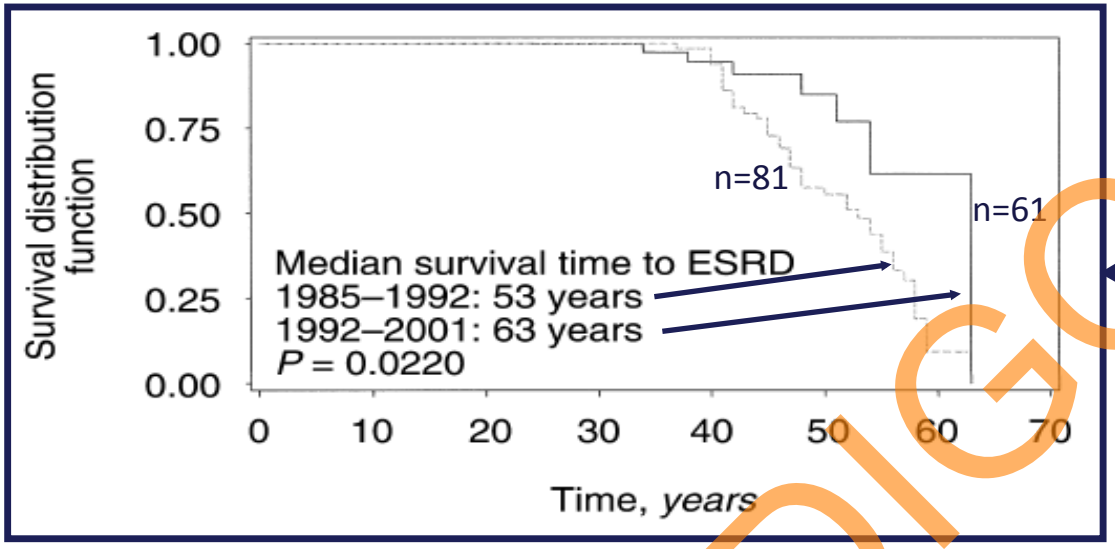






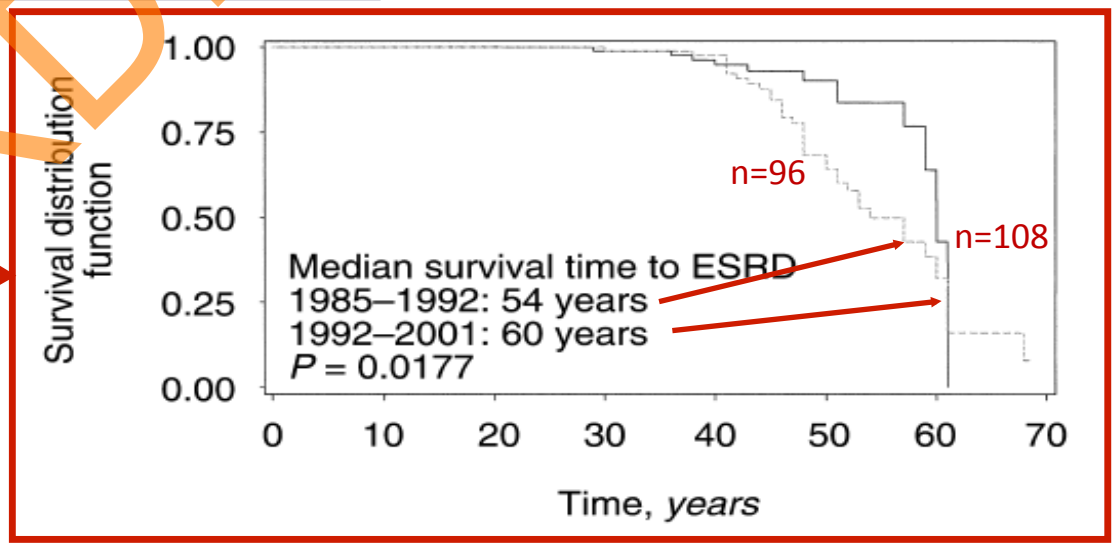
1.Gabow et al: Kidney Int 1992; 2. Chapman et al: J Am Soc Nephrol 1997; 3. Kocaman et al: Am J Kidney Dis 2004; 4. Kocyigit et al : Am J Nephrol 2012

Survival Time to ESRD in ADPKD



Hypertensive Male Patients

Hypertensive Female Patients



Schrier et al: Kidney Int 63: 678-685, 2003

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

Male Patients

	June 1985–May 1992 $N = 81$		June 1992–May 2001 $N = 61$		
	Mean	SD	Mean	SD	*P*
Age *years*	40	9	38	10	NS
BMI *kg/m²*	26.5	4.3	27.5	4.3	NS
SBP *mm Hg*	138	13	135	12	NS
DBP *mm Hg*	94	9	85	9	<0.0001
MAP *mm Hg*	109	10	102	9	<0.0001
Urinary protein excretion *mg/24 h*	474	652	305	612	NS
Renal volume *cm³*	935	587	944	902	NS
Serum creatinine *mg/dL*	2.2	1.4	1.8	1.2	NS
N of antihypertensive medications	1.2	1.1	1.2	0.94	NS
ACEIs %	16.1		54.1		<0.0001
CCBs %	9.9		23.0		0.0331
Diuretics %	42.2		13.1		0.0003
Sympathetic blocking agents (SBAs) %	40.7		23.0		0.0033
α-Blockers %	13.6		8.2		NS
β-Blockers %	34.6		16.4		0.0155
Hematuria %	48.1		27.9		0.0151

Female Patients

	1985–May 1992 $N = 96$		June 1992–May 2001 $N = 108$		
	Mean	SD	Mean	SD	*P*
Age *years*	40	10	42	11	NS
BMI *kg/m²*	24.7	4.8	27.9	7.0	0.0004
SBP *mm Hg*	130	12	131	14	NS
DBP *mm Hg*	87	9	82	9	<0.0001
MAP *mm Hg*	101	9	99	10	0.0384
Urinary protein excretion *mg/24 h*	267	360	276	420	NS
Renal volume *cm³*	703	631	697	419	NS
Serum creatinine *mg/dL*	1.7	1.3	1.6	1.3	NS
N of antihypertensive medications	1.0	0.90	1.2	0.81	NS
ACEIs %	13.5		48.2		<0.0001
CCBs %	6.3		15.7		0.0345
Diuretics %	34.4		24.1		NS
Sympathetic blocking agents (SBAs) %	40.6		24.1		0.0113
α-Blockers %	6.3		5.6		NS
β-Blockers %	34.4		19.4		0.0158
Hematuria %	46.8		41.7		NS

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, FFPH[2]

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.

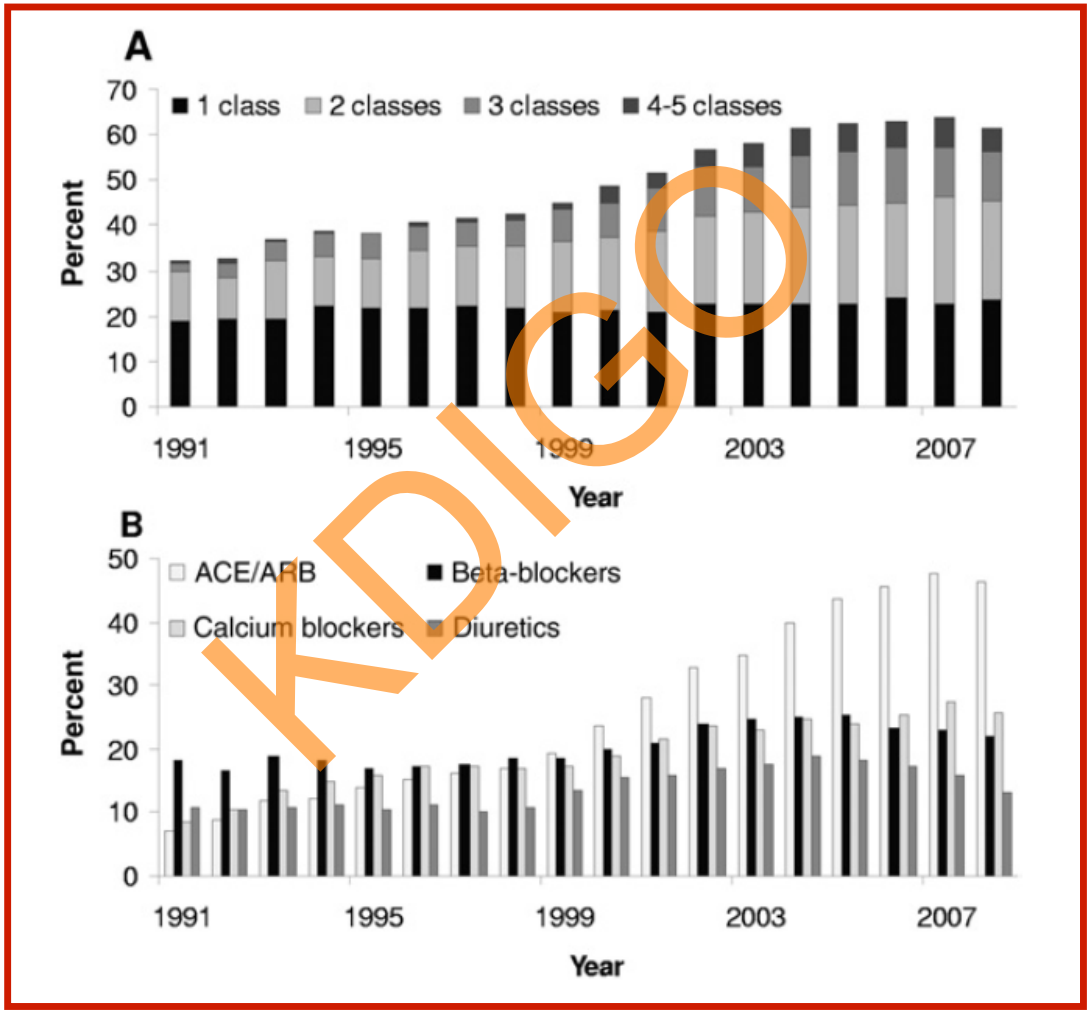
Results: From 1991-2008, there were 2,085 cases of ADPKD, with 1,877 contributing person-time for ages older than 15 years. In 1991, antihypertensive drugs were not prescribed for 68% of participants, which decreased to 38% by 2008. The proportion for which 1 class of antihypertensive drug was prescribed 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.

Am J Kidney Dis. 57(6):856-862.

Change in Use of Antihypertensive Medications



Patch et al: Am J Kidney Dis 57(6):856-862, 2011

Change in Use of Antihypertensive Medications

Table 3. Associations of Antihypertensive Therapy With Outcomes

	Death		Death or RRT	
	IRR (95% CI)	*P*	IRR (95% CI)	*P*
No. of classes of antihypertensive drug				
0	Reference		Reference	
1	0.26 (0.17-0.42)	<0.001	0.91 (0.66-1.23)	0.5
2	0.15 (0.09-0.24)	<0.001	0.80 (0.58-1.10)	0.2
3	0.11 (0.06-0.21)	<0.001	0.79 (0.53-1.16)	0.2
≥4	0.11 (0.05-0.27)	<0.001	0.69 (0.40-1.17)	0.2
Class of antihypertensive drug[a]				
Renin-angiotensin system drugs[b]	0.44 (0.29-0.66)	<0.001	0.75 (0.58-0.96)	0.02
β-Blockers	0.58 (0.37-0.91)	0.02	1.07 (0.83-1.38)	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, α-blockers, and vasodilators.

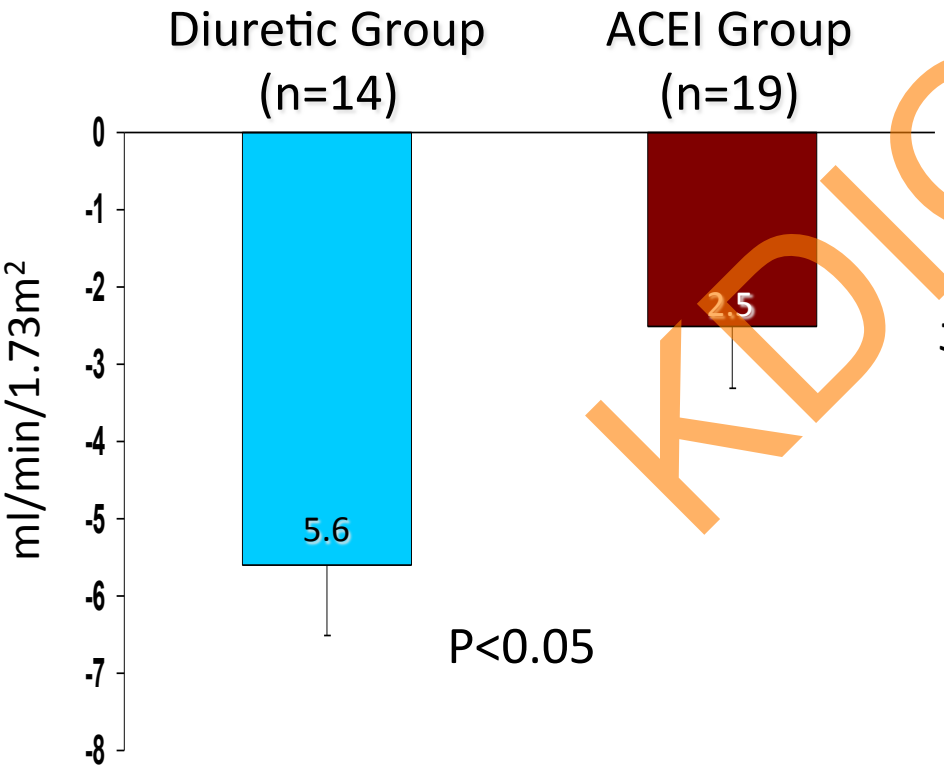
Increasing coverage and intensity of antihypertensive therapy is associated with decreasing mortality in patients with ADPKD.

Patch et al: Am J Kidney Dis 57(6):856-862, 2011

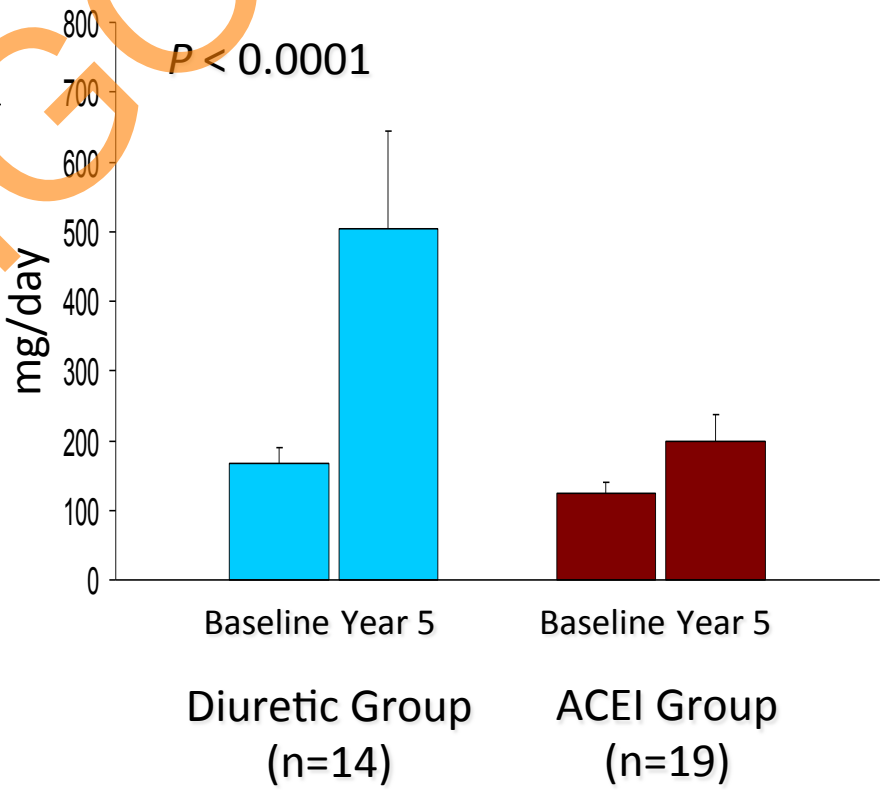
What should be the first line antihypertensive medication?

Diuretics versus ACE Inhibitors in ADPKD

Annual Loss of Creatinine Clearance



Proteinuria



Ecder et al: Am J Nephrol 21:98-103, 2001

Renal and Cardiac Effects of Ramipril versus Metoprolol in ADPKD

Baseline Clinical Characteristics of the Study Population

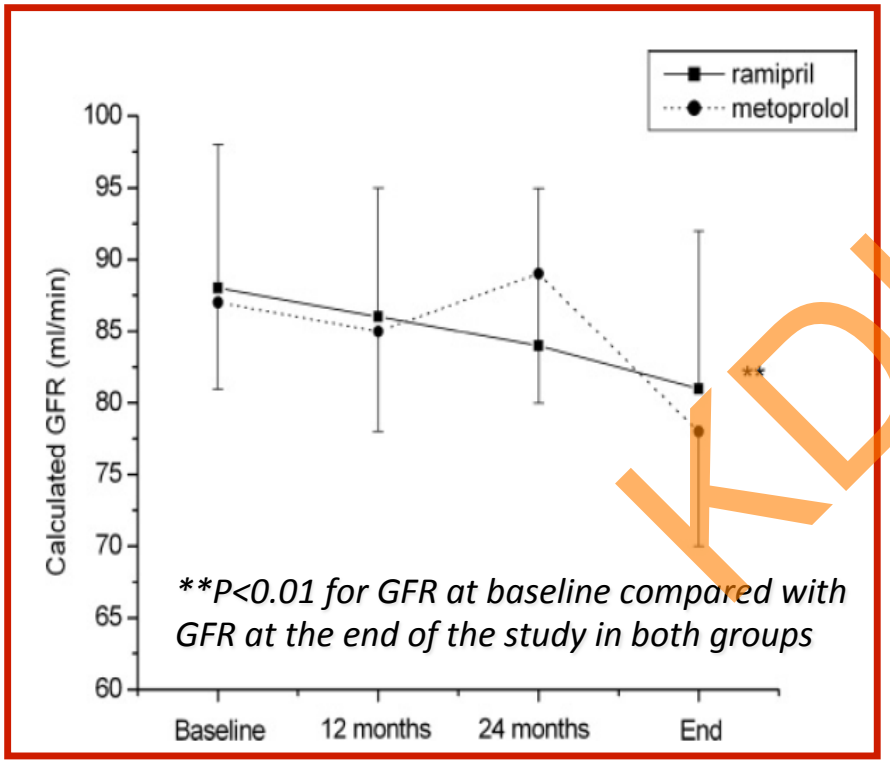
	Ramipril ($n = 17$)	Metoprolol ($n = 20$)	P-value
Age (years)	40.7 ± 2.2	40.0±2.2	NS
Males/Females	10/7	7/13	NS
Weight (kg)	78.5 ± 3.1	74.2 ± 2.1	NS
Body surface area (m^2)	1.96 ± 0.05	1.90 ± 0.04	NS
Body mass index (kg/m^2)	25.5 ± 0.6	24.6 ± 0.4	NS
Duration of hypertension (years)	5.9 ± 1.9	8.1 ± 1.9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

[a]24-h ambulatory BP.

Zeltner et al: Nephrol Dial Transplant 23:573-579, 2008

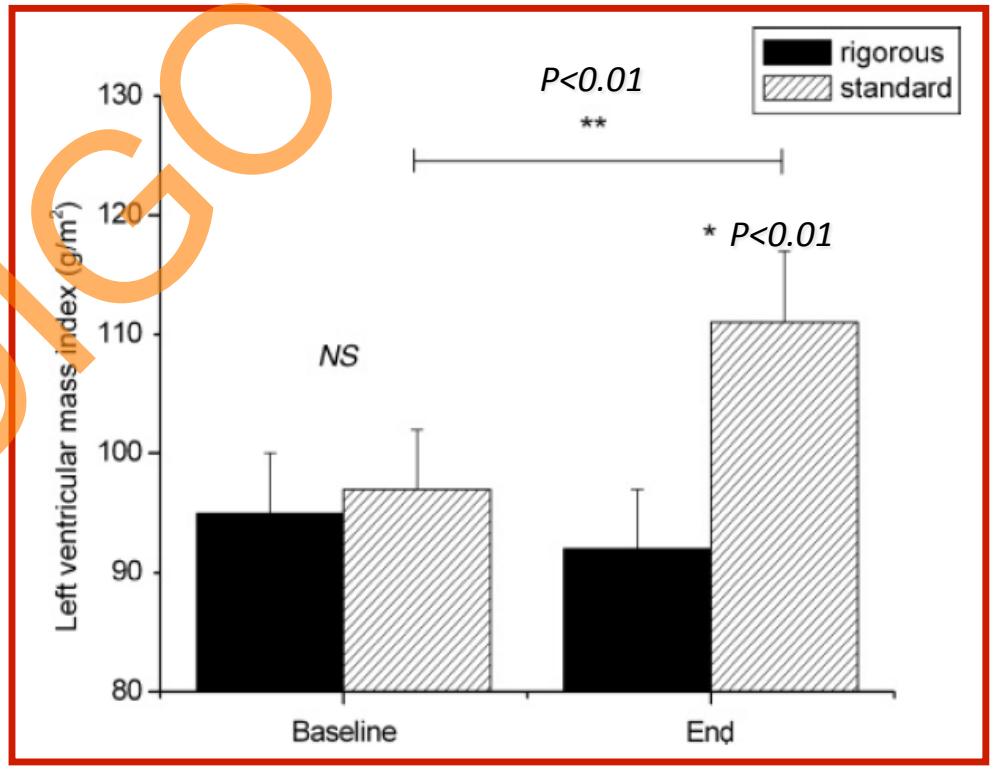
Renal and Cardiac Effects of Ramipril versus Metoprolol in ADPKD

Mean GFR



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

LVMI

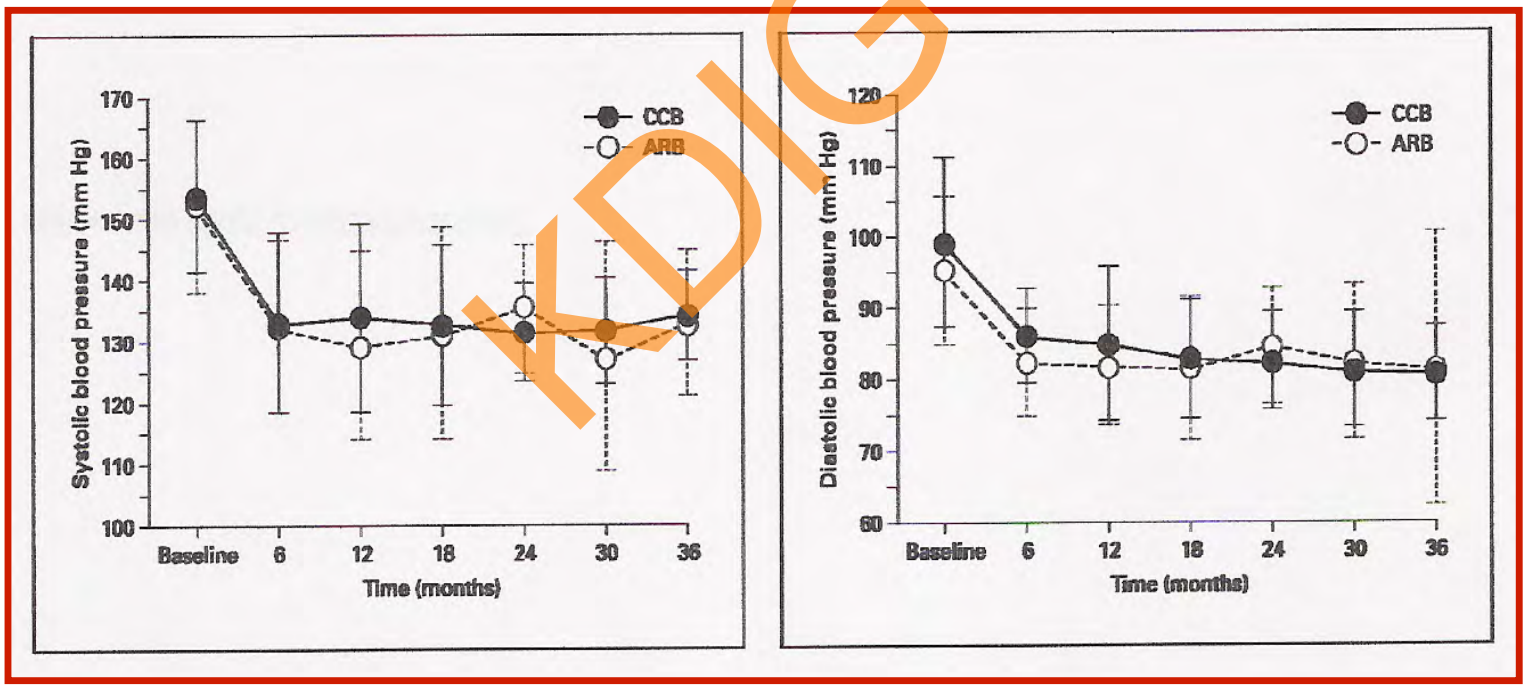


Rigorous BP Control: MAP ≤97 mm Hg
Standard BP Control: MAP >97 mm Hg

Zeltner et al: Nephrol Dial Transplant 23:573-579, 2008

Candesartan versus Amlodipine in ADPKD

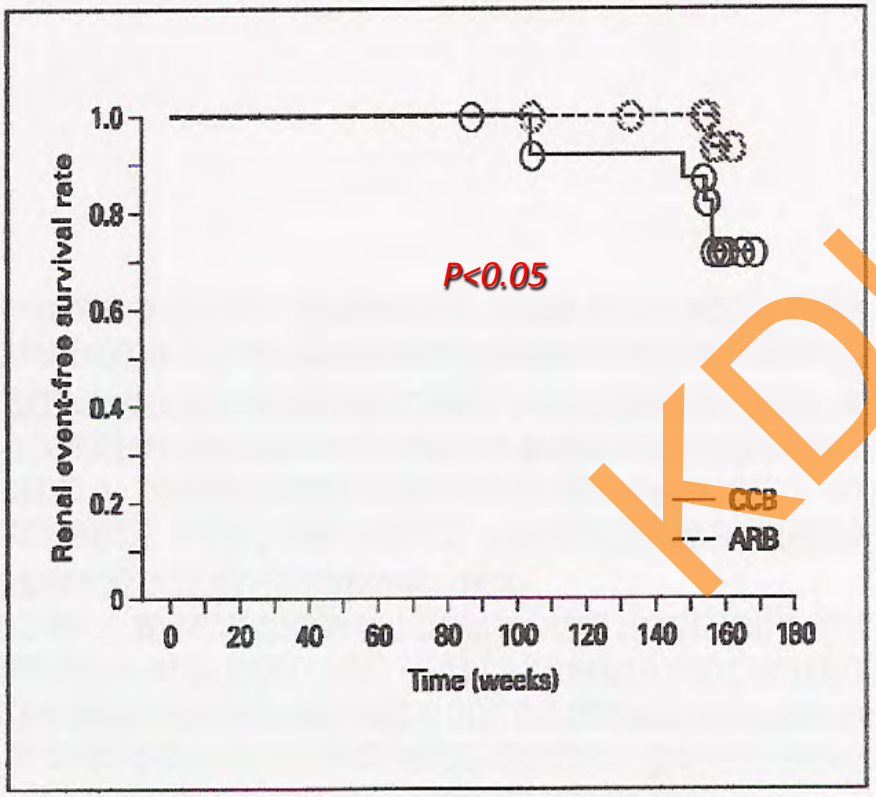
- Multicenter, prospective and randomized clinical trial
- 49 patients with hypertension and ADPKD
- Amlodipine 2.5-10 mg/day vs. candesartan 2-8 mg/day
- Target BP: <130/85 mm Hg; Follow-up: 36 months
- Primary Outcome: A composite endpoint of patient's serum creatinine levels increased twofold over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



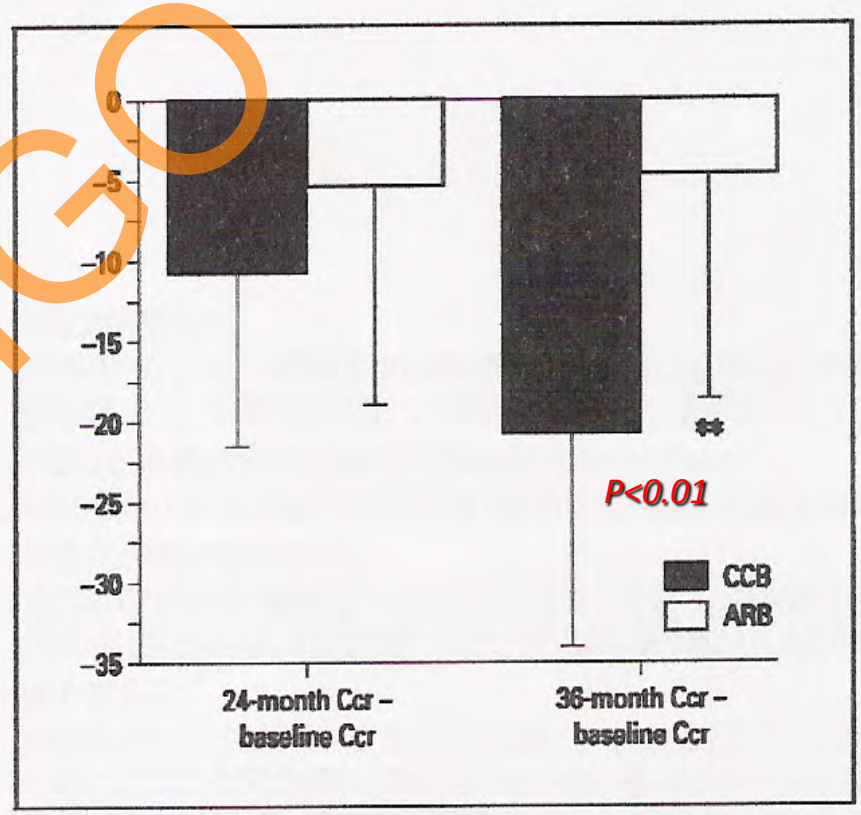
Nutahara et al: Nephron Clin Pract 99: c18-c23, 2005

Candesartan versus Amlodipine in ADPKD

Renal event-free survival rate



Changes in Ccr from baseline



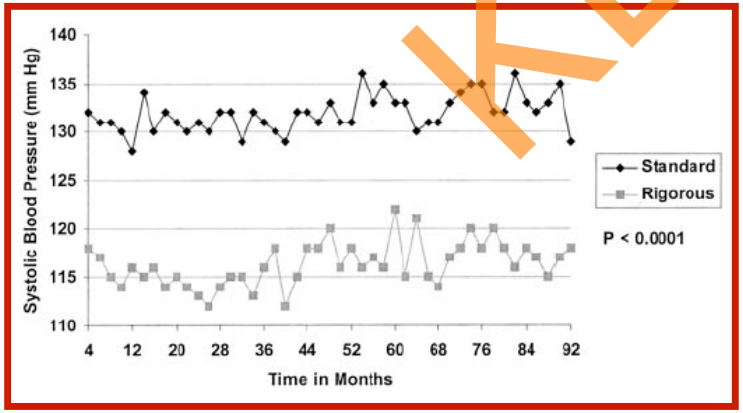
Nutahara et al: Nephron Clin Pract 99: c18-c23, 2005

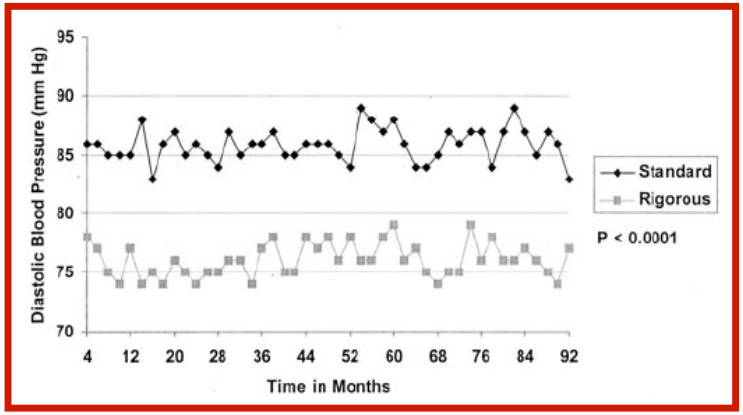
Cardiac and Renal Effects of Standard vs. Rigorous BP Control in ADPKD

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

Parameter	Standard Group			Rigorous Group			*P* Values
	Mean	SD	*n*	Mean	SD	*n*	
Age (yr)	40	8	34	42	8	41	NS
Left ventricular mass index (g/m^2)	156	27	34	161	24	41	NS
Systolic BP (mmHg)[a]	142	17	34	143	15	41	NS
Diastolic BP (mmHg)[a]	96	11	34	95	11	41	NS
Mean arterial pressure (mmHg)[a]	111	12	34	111	12	41	NS
Hematocrit (%)	42.5	4.69	34	42.3	4.30	41	NS
Serum creatinine (mg/dl)[b]	1.4	0.51	34	1.3	0.47	41	NS
Creatinine clearance (ml/min per 1.73 m^2)	82	28	34	84	29	41	NS
Male/Female	19/15		34	22/19		41	NS
Amlodipine/enalapril	15/19			15/26			NS

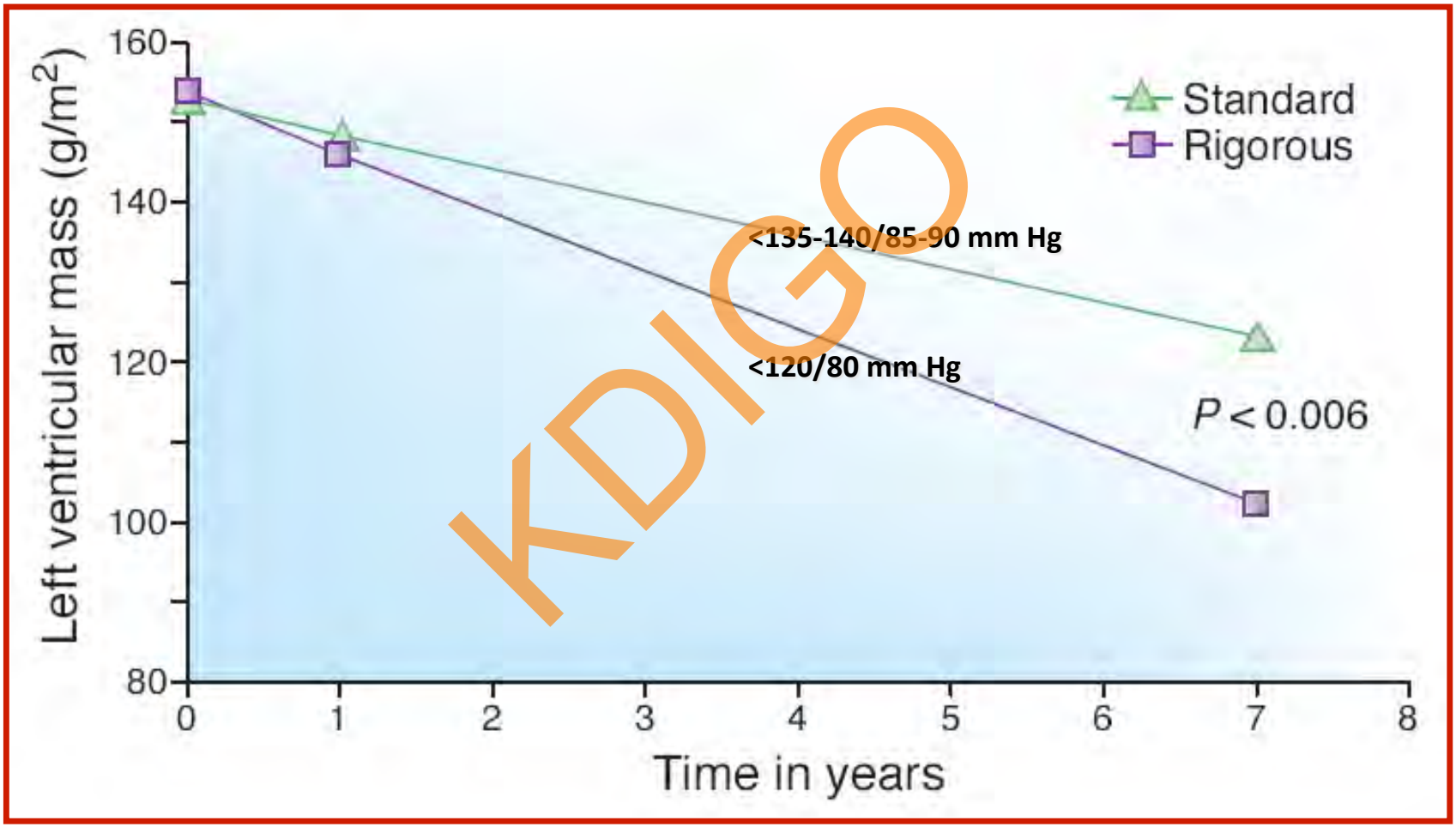
[a] Blood pressures were measured after a 2- to 4-week washout period without hypertensive medications.
[b] To convert serum creatinine values to micromoles per liter, multiply by 88.4.





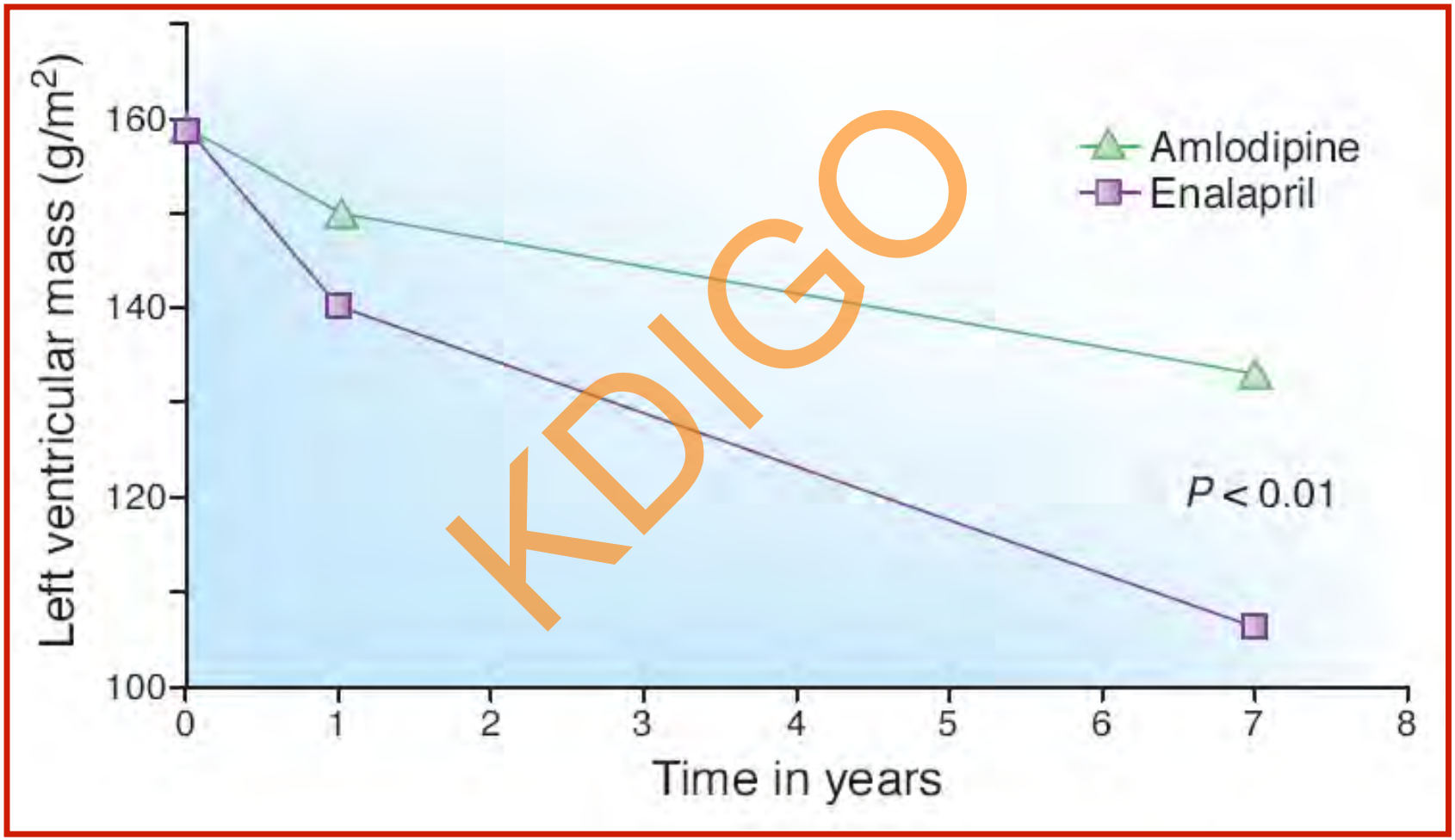
Schrier et al: J Am Soc Nephrol 13: 1733-1739, 2002

Effect of Rigorous vs. Standard BP Control on LVMI in Patients with ADPKD



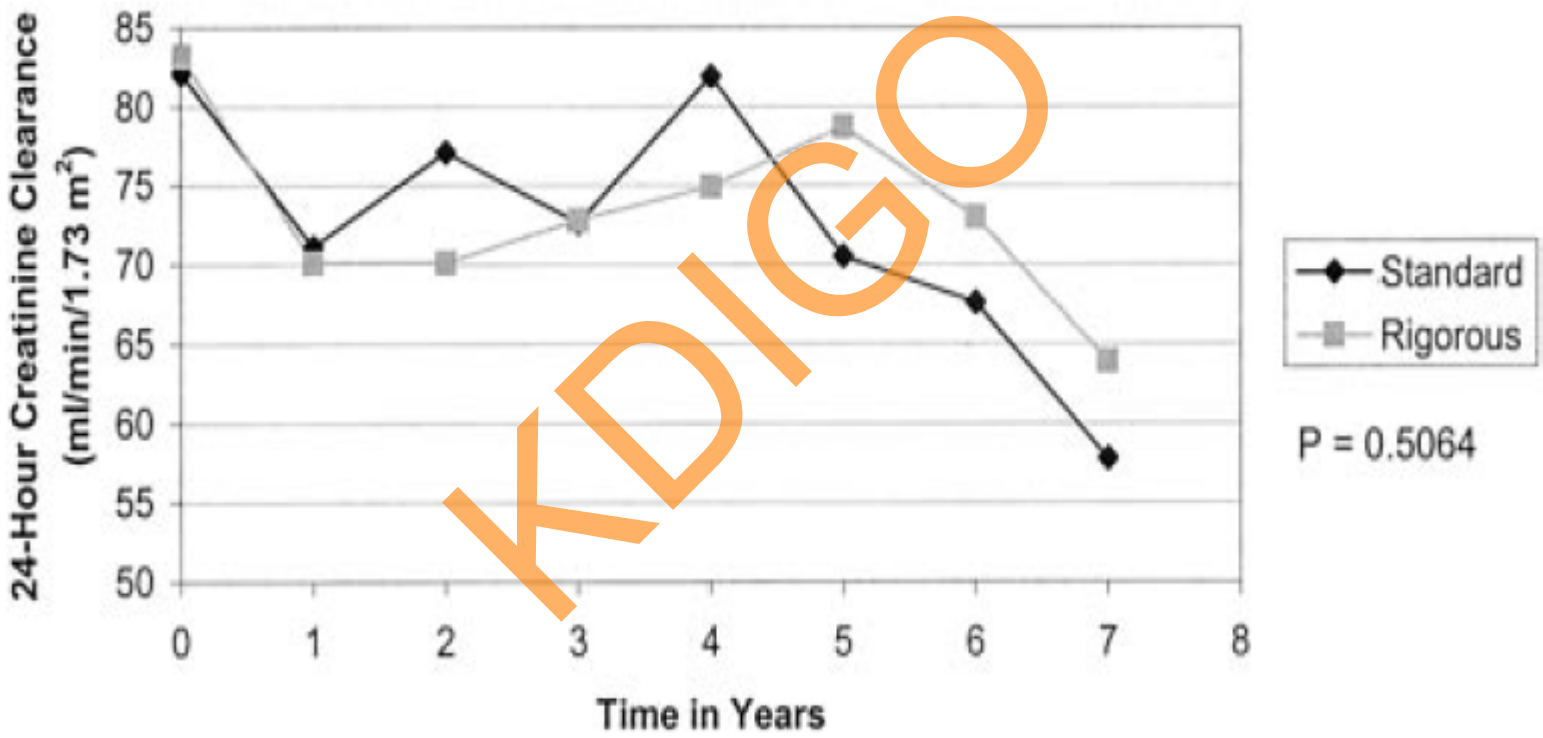
Schrier et al: J Am Soc Nephrol 13: 1733-1739, 2002

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



Schrier et al: J Am Soc Nephrol 13: 1733-1739, 2002

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



Schrier et al: J Am Soc Nephrol 13: 1733-1739, 2002

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.

HALT PKD Trials

The HALT Polycystic Kidney Disease Trials: Design and Implementation

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*Emory University School of Medicine, Atlanta, Georgia; †Mayo College of Medicine, Rochester, Minnesota; ‡Tufts 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

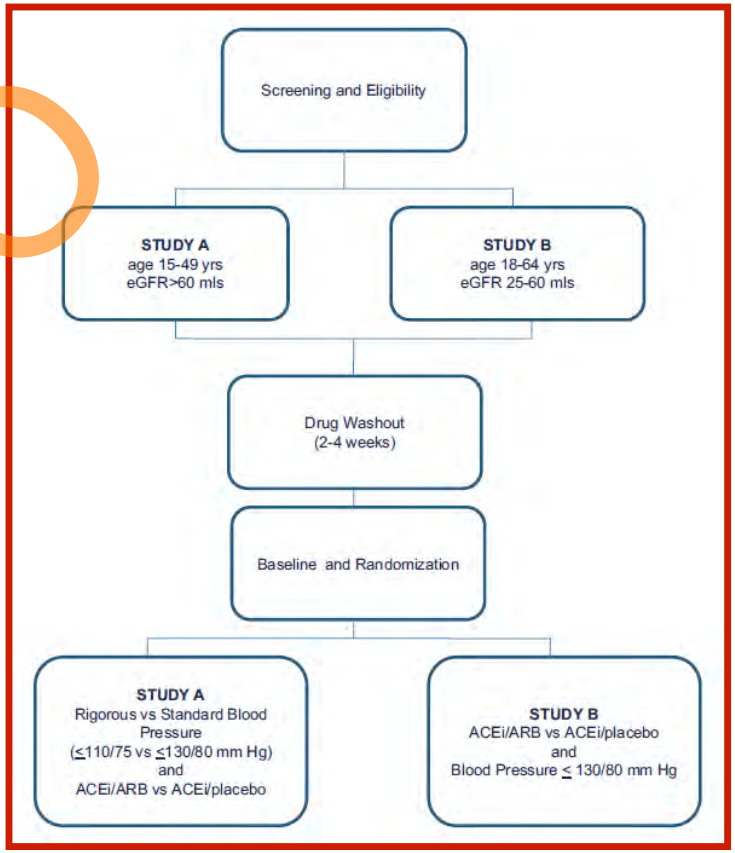
Background and objectives: Two HALT PKD trials will investigate interventions that potentially slow kidney disease progression in hypertensive autosomal dominant polycystic kidney disease (ADPKD) patients. Studies were designed in early and later stages of ADPKD to assess the impact of intensive blockade 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 m^2 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 m^2 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 will evaluate potential benefits of rigorous BP control and inhibition of the renin-angiotensin-aldosterone system on kidney disease progression in ADPKD.

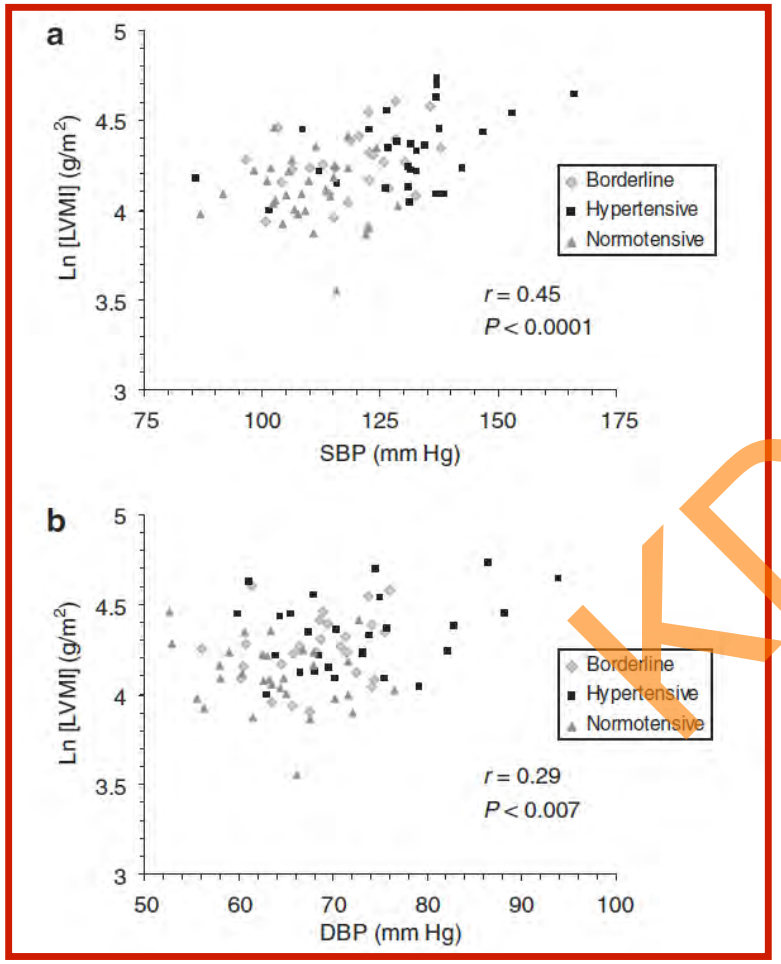
Clin J Am Soc Nephrol 5: 102–109, 2010. doi: 10.2215/CJN.04310709

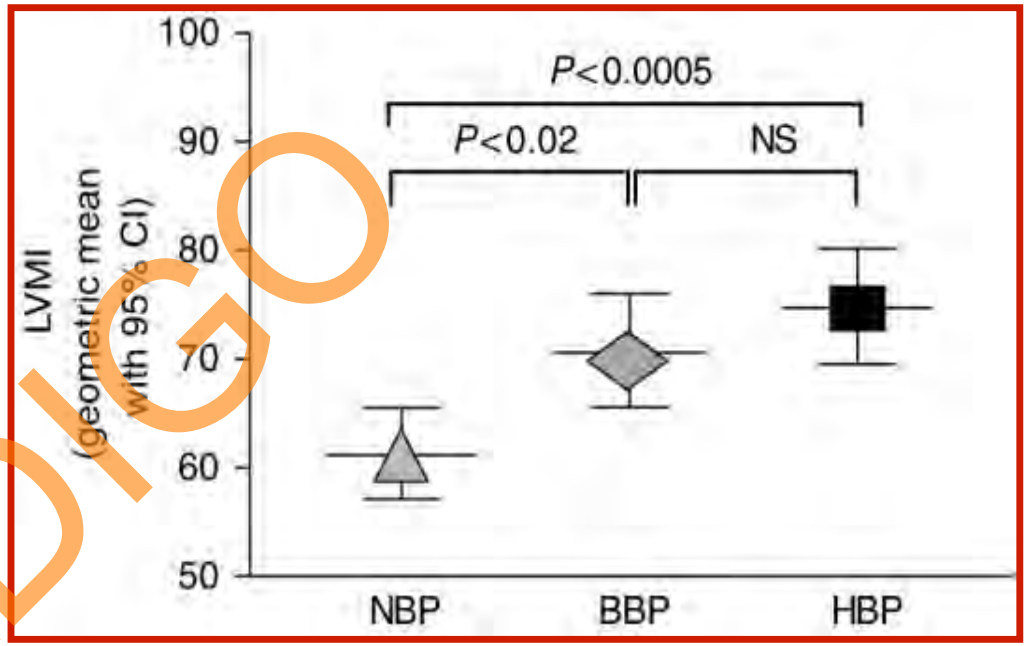


Chapman et al: Clin J Am Soc Nephrol 5: 102-109, 2010

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

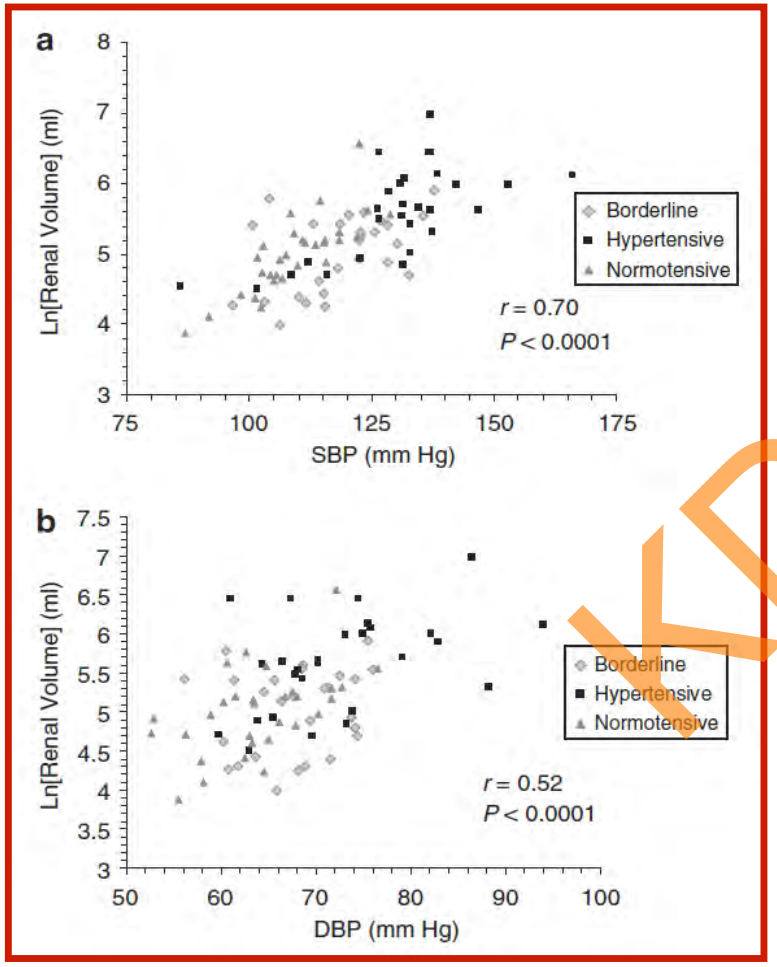


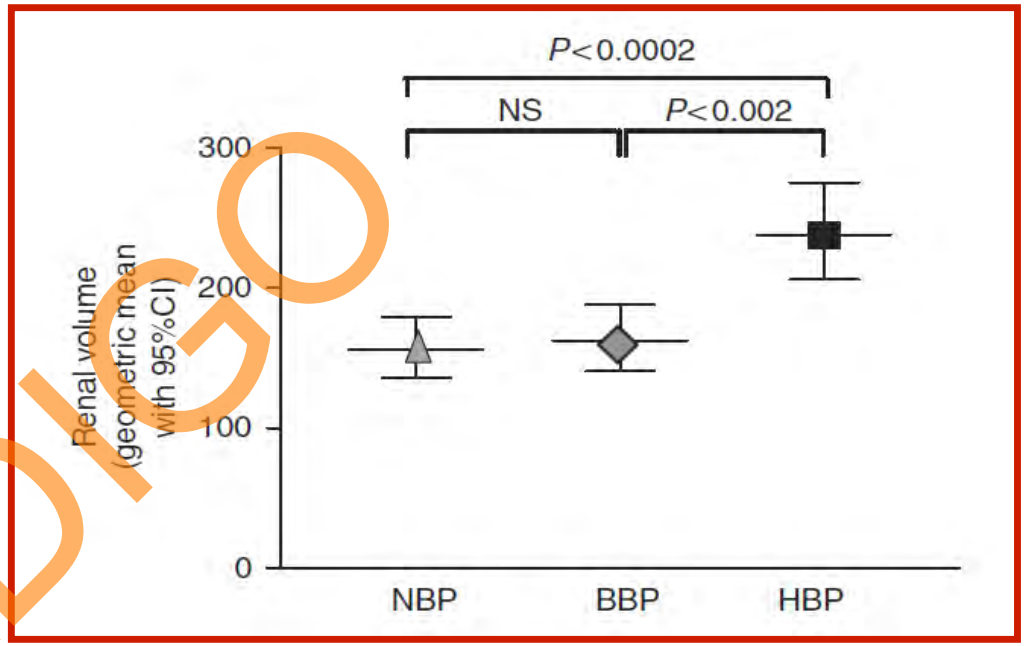


	NBP (Normotensive)	BBP (Borderline Hypertensive)	HBP (Hypertensive)
SBP (mm Hg)	109 ± 2	119 ± 2	130 ± 3
DBP (mm Hg)	64 ± 1	68 ± 1	72 ± 2

Chadnapaphornchai et al.: Kidney Int 74: 1192-1196, 2008

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





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Chadnapaphornchai et al.: Kidney Int 74: 1192-1196, 2008

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

	A		B		C	
	HBP50	HBP90	BBP + ACEI	BBP-ACEI	SPKD + ACEI	SPKD-ACEI
N						
baseline	14	14	15	12	15	15
year 5	10	10	9	8	13	12
Renal volume adjusted for sex and height (ml)						
baseline	246 (174–350)	315 (226–439)	157 (125–196)	168 (132–214)	162 (133–198)	177 (142–220)
year 5	417 (290–600)[e]	516 (366–727)[f]	231 (184–290)[j]	263 (202–342)[l]	260 (214–318)[p]	311 (248–391)[q]
LVMI (g/m^2)						
baseline	76 (68–84)	76 (69–84)	76 (68–84)	66 (59–74)	61 (55–68)	61 (55–68)
year 5	79 (69–90)	80 (71–90)	77 (69–87)	77 (67–88)[l]	75 (67–83)[o]	71 (62–80)[s]
UMA (mcg/day)						
baseline	21 (14–32)	32 (20–50)	17 (9–32)	26 (14–48)	36 (22–60)	19 (11–34)
year 5	29 (18–46)	40 (25–63)	29 (11–35)	23 (12–46)	22 (14–36)[p]	20 (11–36)
SCr (mg/dl)						
baseline	0.70 (0.63–0.78)	0.78 (0.71–0.85)	0.77 (0.69–0.85)	0.67 (0.60–0.74)	0.66 (0.61–0.72)	0.69 (0.63–0.76)
year 5	0.98 (0.88–1.10)[e]	1.03 (0.93–1.15)[g]	0.73 (0.66–0.82)	0.80 (0.70–0.90)[l]	0.73 (0.67–0.80)	0.68 (0.61–0.76)
ClCr (ml/min/1.73 m^2)						
baseline	142 (129–156)	128 (117–140)	122 (111–135)	135 (121–150)	138 (127–150)	137 (125–149)
year 5	101 (90–112)[e]	97 (88–108)[g]	126 (113–140)	114 (100–129)[l]	127 (117–138)	136 (123–151)

Chadnapaphornchai et al.: Clin J Am Soc Nephrol 4: 820-829, 2009

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

Parameter	GH	Without GH	*P*
N	32	148	
Age (years)	11.4 ± 3.6	10.8 ± 3.9	0.27
Male/Female	19/13	63/85	0.08
Median follow-up (years)	4.6 (2.6 to 7.1)	5.7 (1.3 to 7.3)	0.68
BMI (kg/m^2)	20.4 ± 5.2	20.0 ± 5.9	0.40
SBP (mmHg)	120 ± 18	114 ± 14	0.09
DBP (mmHg)	72 ± 12	71 ± 11	0.70
Symptoms and complications of ADPKD			
hypertension	17 (53.13%)	51 (34.46%)	0.10
recurrent flank pain	4 (12.5%)	24 (16.44%)	0.08
history of macrohematuria	8 (25.0%)	18 (12.16%)	0.15
history of cyst infection	5 (15.63%)	38 (25.85%)	0.35
Median serum creatinine (mg/dl)	0.6 (0.4 to 0.7)	0.7 (0.6 to 0.8)	0.005
Median CrCl (ml/min per 1.73 m^2)	153.9 (145.1 to 168.6)	111.7 (93.2 to 124.5)	<0.0001
Total kidney volume (cm^3)	431.9 ± 196.0	400.1 ± 317.1	0.03
Medication			
DIU	0 (0%)	1 (0.68%)	0.82
ACEI	3 (9.38%)	13 (8.9%)	1.00
ARB	0 (0%)	0 (0%)	
NSAID	1 (3.23%)	10 (6.94%)	0.69

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 m^2

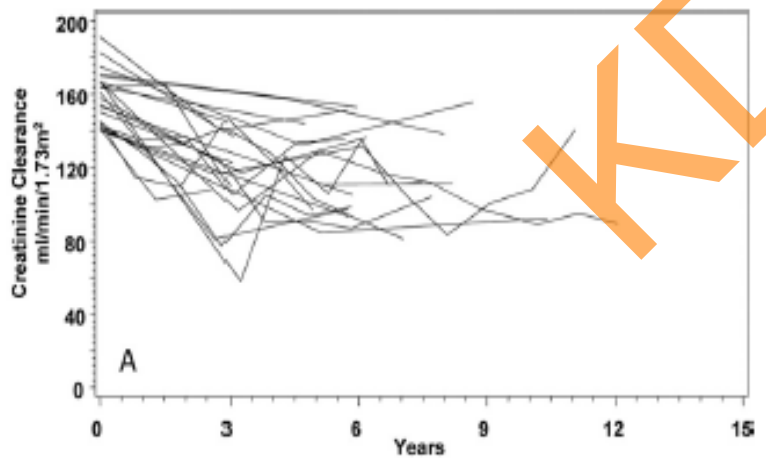
Helal et al.: Clin J Am Soc Nephrol 6: 2439-2443, 2011

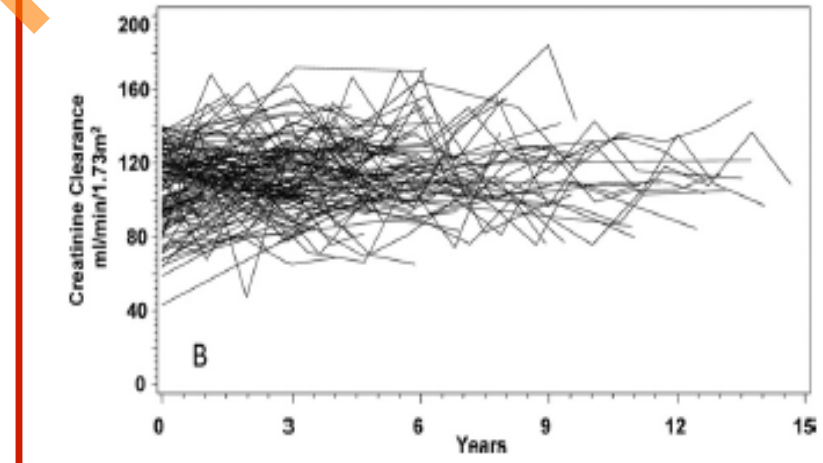
Glomerular Hyperfiltration in ADPKD Children is Associated with a Faster Decline in Renal Function and Higher Rate of Kidney Enlargement

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

Incremental Rate of TKV/ BSA Growth Per Year	GH	Without GH	*P*
Adjusted for age, gender	$+19.3 \pm 10.8\ cm^3$	$-4.3 \pm 7.7\ cm^3$	0.008
Adjusted for age, gender, ACEI/ARB use, hypertension	$+37.2 \pm 7.8\ cm^3$	$+15.3 \pm 4.1\ cm^3$	0.005
% increase in TKV (year)	$9.2 \pm 9.1\%$	$8.8 \pm 10.4\%$	0.45

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





Helal et al.: Clin J Am Soc Nephrol 6: 2439-2443, 2011

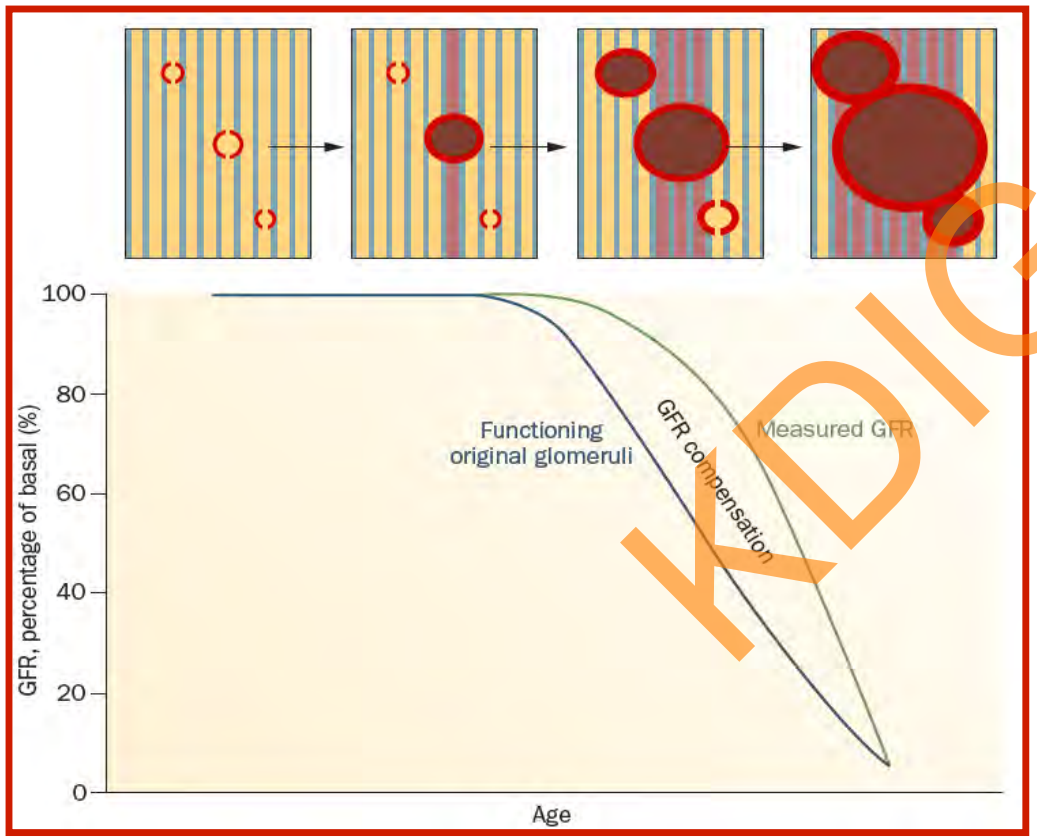
Are the guidelines for management of hypertension in CKD valid for ADPKD?

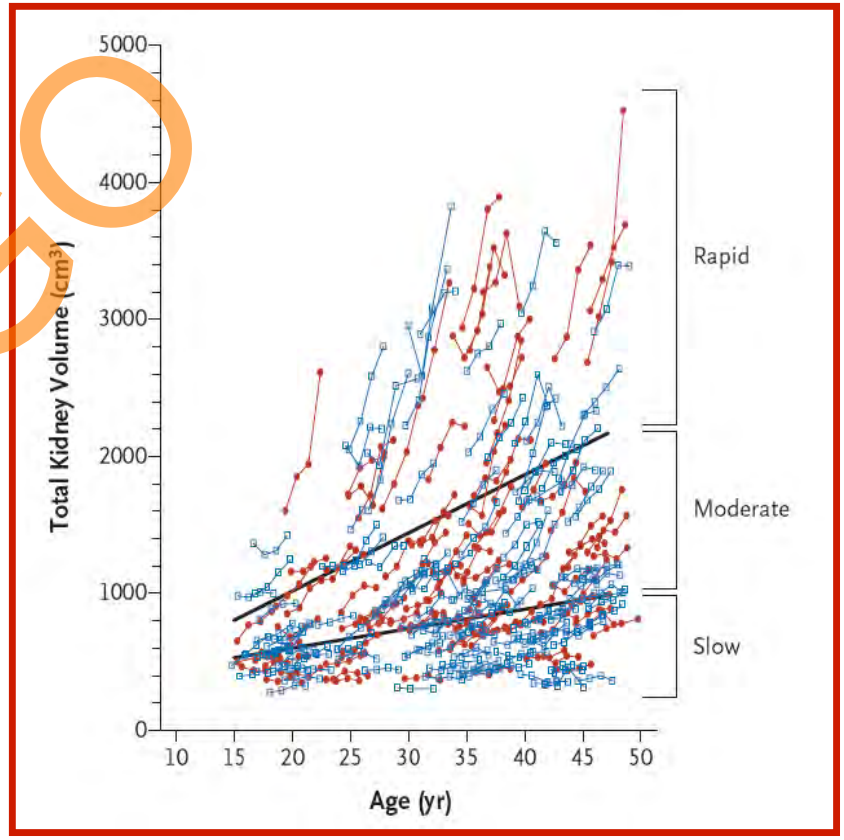
Guideline Comparisons of Goal Blood Pressure and Initial Drug Therapy for Adults with Hypertension

Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB
	General <60 y	<140/90	Black: thiazide-type diuretic or CCB
	Diabetes	<140/90	Thiazide-type diuretic, ACEI, ARB, or CCB
	CKD	<140/90	ACEI or ARB
ESH/ESC 2013[37]	General nonelderly	<140/90	β-Blocker, diuretic, CCB, ACEI, or ARB
	General elderly <80 y	<150/90	
	General ≥80 y	<150/90	
	Diabetes	<140/85	ACEI or ARB
	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	
CHEP 2013[38]	General <80 y	<140/90	Thiazide, β-blocker (age <60y), ACEI (nonblack), or ARB
	General ≥80 y	<150/90	
	Diabetes	<130/80	ACEI or ARB with additional CVD risk ACEI, ARB, thiazide, or DHPCCB without additional CVD risk
	CKD	<140/90	ACEI or ARB
ADA 2013[39]	Diabetes	<140/80	ACEI or ARB
KDIGO 2012[40]	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	
NICE 2011[41]	General <80 y	<140/90	<55 y: ACEI or ARB
	General ≥80 y	<150/90	≥55 y or black: CCB
ISHIB 2010[42]	Black, lower risk	<135/85	Diuretic or CCB
	Target organ damage or CVD risk	<130/80	

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; DHPCCB, 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?





Grantham JJ et al: Nat Rev Nephrol 7: 556-566,2011

Grantham JJ et al.: N Engl J Med 359: 1477-1485, 2008

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 m^2

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

Performance of the 4 equations in ADPKD patients with GFR <60 ml/min/1.73 m^2

Equations	n	Bias	Precision	P_{15}, %	P_{30}, %
CKD-EPI	41	2.5	4.8	49	85
MDRD	41	4.1	4.5	41	85
MDRD with cystatin C	32	–0.5	5.8	59	91
Cockcroft-Gault (BSA)	41	–3.2	6.9	49	78

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

Equations	n	Bias	Precision	P_{15}, %	P_{30}, %
CKD-EPI	101	5.0	10.2	50	90
MDRD	101	10.8	10.5	37	83
MDRD with cystatin C	91	3.8	9.3	65	97
Cockcroft-Gault (BSA)	101	–1.3	12.5	52	90

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.

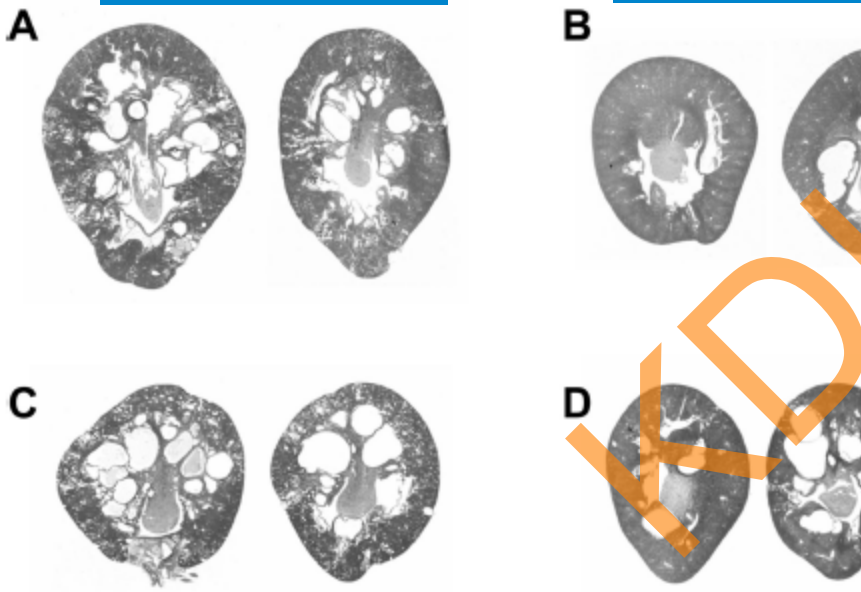
Orskov et al: Am J Nephrol 31: 53-57,2010

What are the appropriate recommendations for water and salt intake?

Increased Water Intake Decreases Progression of Polycystic Kidney Disease in the PCK Rat

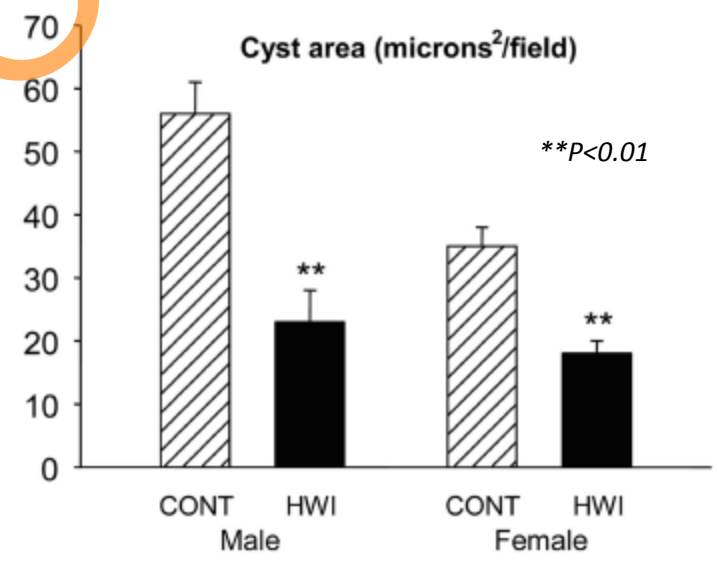
PCK male rat with normal water intake

PCK male rat with high water intake



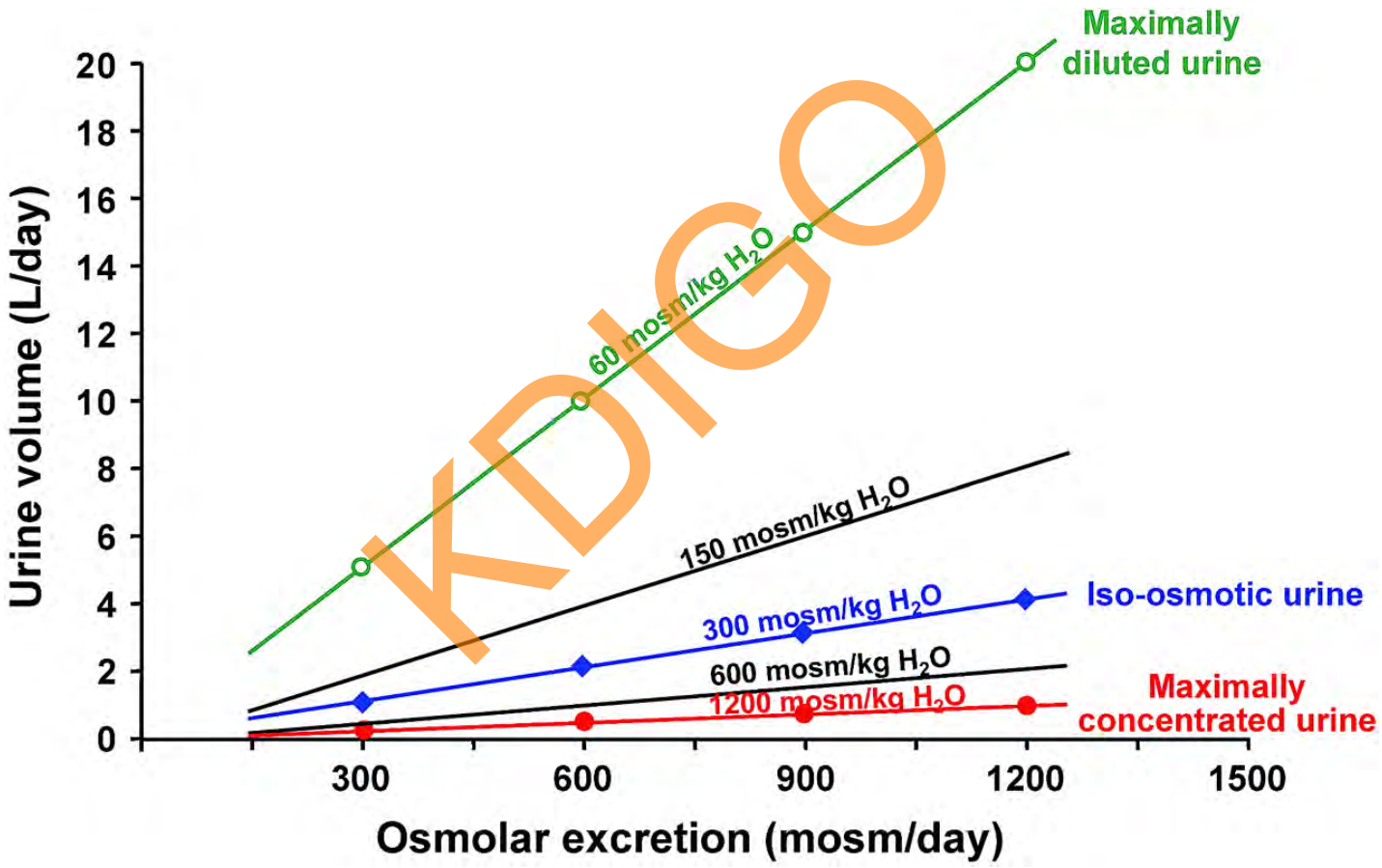
PCK female rat with normal water intake

PCK female rat with high water intake



Nagao S et al: J Am Soc Nephrol 17: 2220-2227,2006

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



Torres, Bankir, Grantham: Clin J Am Soc Nephrol 4: 1140-1150,2009

Recommendations for Water Intake in Patients with ADPKD

	GFR ≥ 60 ml/min/1.73 m^2	60 > GFR > 30 ml/min/1.73 m^2	GFR ≤ 30 ml/min/1.73 m^2
Recommendation	Enough to achieve an average U_{osm} of 250 mosm/kg H_2O, usually 2.5–4 L per day	Enough to achieve an average U_{osm} of 250 mosm/kg H_2O, usually 2.5–4 L per day	Not recommended, follow thirst
Risk	Minimal	Low	NA
Benefit	Likely reduction in the rate of cyst growth by suppressing the secretion of AVP and its effect on tubular cell proliferation and fluid secretion	Likely reduction in the rate of cyst growth by suppressing the secretion of AVP and its effect on tubular cell proliferation and fluid secretion	NA
Follow-Up	Recheck serum sodium within 1–3 wk after increasing water intake, more frequently in patients on drugs which may enhance AVP secretion or effect	Recheck serum sodium within 1–3 wk after increasing water intake and regularly thereafter	NA
Exclusions	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	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	NA

NA, not applicable.

Torres, Bankir, Grantham: Clin J Am Soc Nephrol 4: 1140-1150,2009

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)*

KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int Volume 2, Issue 5, December 2012

Urinary Sodium is Associated with Larger TKV

Potentially Modifiable Factors Affecting the Progression of Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres,* Jared J. Grantham,† Arlene B. Chapman,‡ Michal Mrug,§ Kyongtae T. Bae,‖ Bernard F. King Jr.,* Louis H. Wetzel,† 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

Parameter	Baseline to YR3 (n = 205)		Baseline to YR6 (n = 165)	
	Coefficient	P	Coefficient	P
Year	−0.072	**0.004**	0.011	0.655
Age	0.0002	0.705	0.001	0.466
lnTKV	1.001	**<0.001**	1.014	**<0.001**
Serum HDL	0.00004	0.915	0.001	0.205
Urine sodium	−0.000003	0.960	0.00001	0.930
Year*age	−0.0005	**0.049**	−0.001	**<0.001**
Year*lnTKV	0.022	**<0.001**	0.014	**<0.001**
Year*serum HDL	−0.001	**<0.001**	−0.001	**<0.001**
Year*urine sodium	0.0001	**0.001**	0.0001	**0.008**
Intercept	−0.017	0.776	−0.155	0.118

Bold values indicate $P \leq 0.05$.

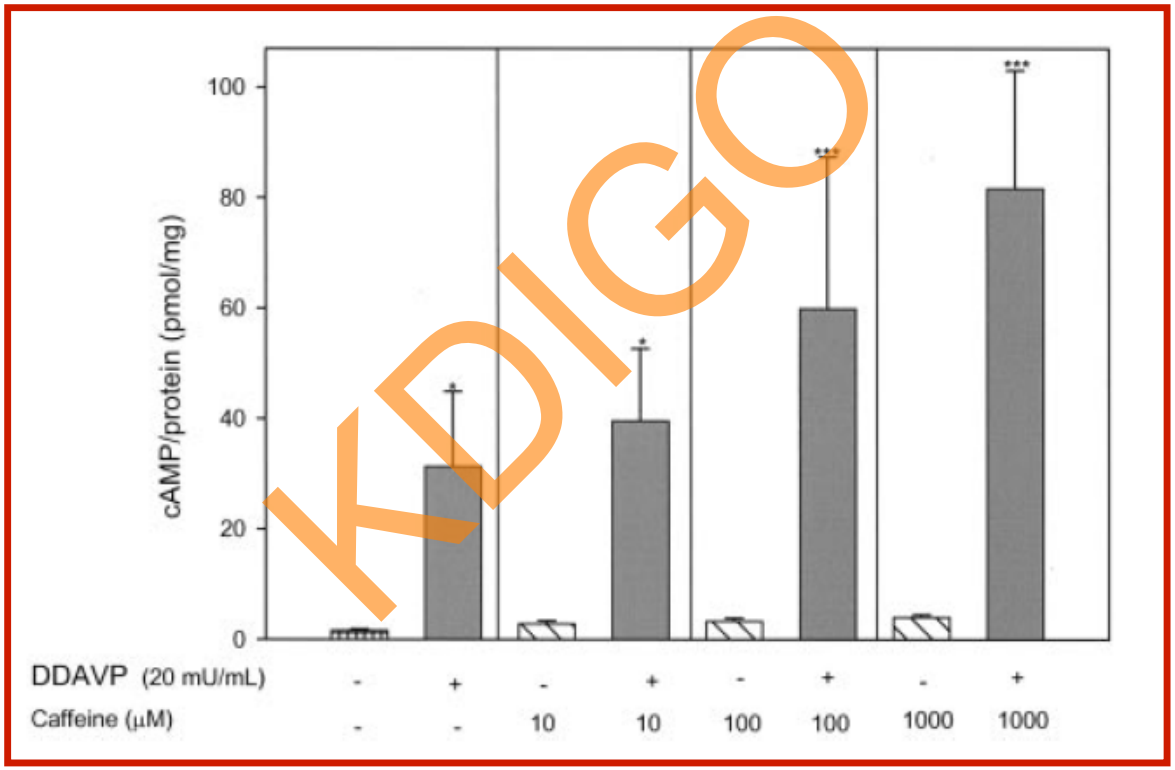
Conclusions Serum HDL-cholesterol, $U_{Na}V$, and 24-hour urine osmolality likely affect ADPKD progression. To what extent their modification may influence the clinical course of ADPKD remains to be determined.

Clin J Am Soc Nephrol 6: 640–647, 2011. doi: 10.2215/CJN.03250410

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

Belibi et al: J Am Soc Nephrol 13: 2723-2729, 2002

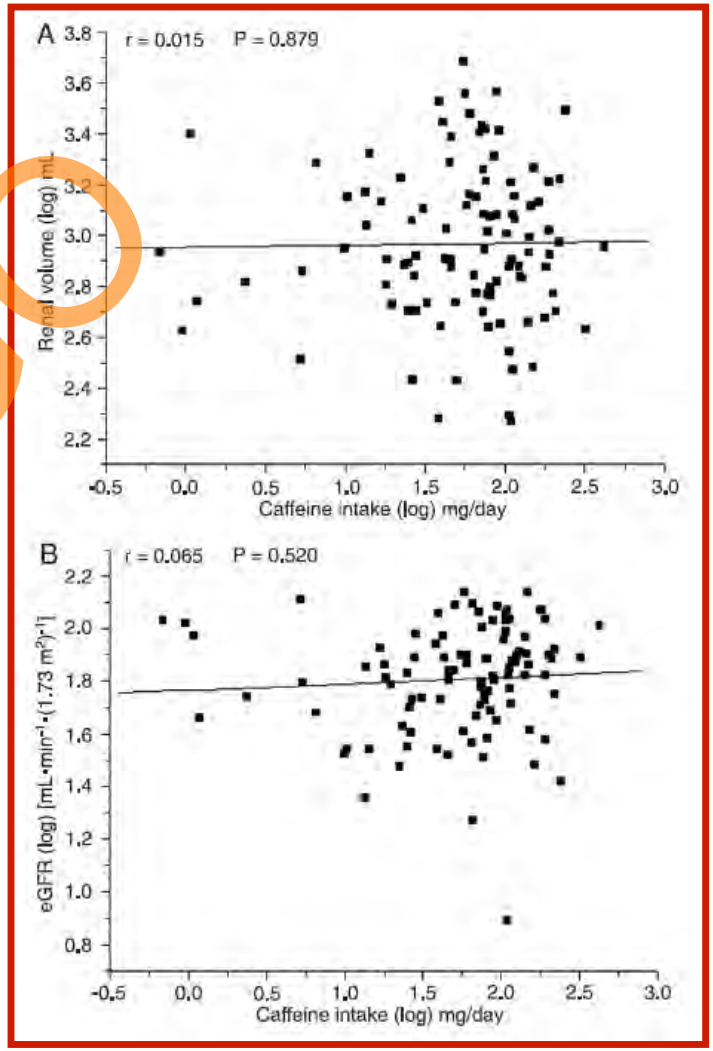
Caffeine Intake by Patients with ADPKD

Parameters	Controls (N = 102)	ADPKD (N = 102)
Gender (F/M)	74/28	68/34
Age (years)	38 ± 14	39 ± 12
BMI (kg/m^2)	24.8 ± 4.8	25.7 ± 4.5
Energy (kcal/day)	1966 ± 601	2018 ± 608
Protein intake (g·kg^{-1}·day^{-1})	1.2 ± 0.3	1.2 ± 0.4
PRAL (mEq/day)	20 ± 14	21 ± 14
Carbohydrate intake (g/day)	246 ± 78	268 ± 82
Lipid intake (g/day)	70 ± 26	68 ± 25
Caffeine intake (mg/day)	134 ± 116	86 ± 77*

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).

Parameters	Caffeine intake		
	0-41.6 mg/day (N = 34)	41.7-98.7 mg/day (N = 34)	98.8-471.4 mg/day (N = 34)
Age (years)	36 ± 12	39 ± 13	43 ± 11
Time since diagnosis (months)	112 ± 103	99 ± 88	101 ± 99
CKD1/2 (N, %)	21 (62)	19 (56)	23 (68)
CKD3 (N, %)	13 (38)	15 (44)	11 (32)
Hypertension (N, %)	16 (47)	26 (76)	22 (65)
Serum creatinine (mg/dL)	1.3 ± 0.73	1.3 ± 0.7	1.4 ± 1.2
eGFR [mL·min^{-1}·(1.73 m^2)$^{-1}$]	74 ± 33	74 ± 35	73 ± 35
Renal volume (mL)	787 (306-3848)	1100 (260-5517)	746 (219-3588)

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 categorical variables).



Vendramini et al: Braz J Med Biol Res 45: 834-840, 2012