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Autosomal-dominant polycystic kidney disease

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GUIDELINES

a. Aggressive blood pressure (BP) reduction in patients with polycystic kidney disease (PKD) had not been shown to slow the rate of progression of renal disease (Level II – conflicting), although the beneficial effects of BP control on left ventricular hypertrophy and cardiovascular disease in patients with chronic kidney disease are established.

b. A low protein diet has not been shown to slow the rate of decline of progressive renal disease in patients with PKD (Level II – the Modification of Diet in Renal Disease study).

c. Blockade of the renin angiotensin system (RAS) may be preferable to calcium channel blockade control to slow the rate of decline of progressive renal disease in patients with PKD (Level II – conflicting).

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Clinical trials of other interventions in patients with chronic kidney disease have included a variable number of individuals with PKD. In general, individuals with PKD have not responded to these interventions or its activity has been harmful.[1] Although the role of BP control in the prevention of renal progression in patients with PKD has not been established by clinical trials, this does not diminish its value in preventing or reversing left ventricular hypertrophy (LVH) or preventing cardiovascular morbidity associated with renal disease.[2] Consequently, BP control should remain a component of managing patients with PKD.

While cyst infection may produce transient renal impairment, there is no evidence that persistent or recurrent bacterial infections contribute to the progression of PKD *per se*. Routine monitoring with ultrasound or magnetic resonance imaging may be useful non-invasive methods to monitor progression of cystic masses, but there is currently no evidence that it results in improved clinical outcomes.

Although renal trauma should be avoided to prevent painful cyst haemorrhage, there are no studies to suggest a bleeding into a cyst or parenchyma contributes to renal progression.[3]

There are anecdotal reports of transient improvements in severe or refractory pain or hypertension by aspiration or sclerotherapy of massive cysts.[4–7] However, there is no evidence that these measures improve renal function or delay the rate of disease (Level IV anecdotal reports).

Techniques to retard cystogenesis remain experimental at this time (Level IV, anecdotal reports). However, vasopressin (V2) receptor antagonists will soon enter clinical trials.

BACKGROUND

Polycystic kidney disease is the fourth leading cause of end-stage kidney disease (ESKD) in Australia and New Zealand (ANZDATA).[8] However, progression to ESKD is variable. The type of genetic mutation (i.e. *PKD1* or *PKD2*) may determine the variability in disease phenotype and rate of progression.[9] Some patients maintain a normal renal function and develop only a modest number of renal cysts during their lifetime. Others develop a massive number of renal cysts and may reach renal failure at an early age. Recent evidence indicates that, besides the documented cyst enlargement and interstitial fibrosis, apoptotic loss of non-cystic nephrons is a significant component of the pathology of PKD and may contribute to the progressive loss of renal function. The objective of this guideline was to evaluate the available clinical evidence pertaining to the impact of interventions to prevent or attenuate renal functional decline in PKD. This guideline does not address the known associations between PKD, left ventricular hypertrophy and cardiovascular disease that may be positively influenced by BP control and other clinical interventions.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for PKD were combined with MeSH terms and text words for BP and hypertension. The search was carried out in Medline (1966 to September Week 2, 2004).
Medline (1966 to September week 2, 2003). MeSH term for PKD were combined with MeSH terms and text words for BP and hypertension.
Date of searches: 17 September 2004.

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WHAT IS THE EVIDENCE?

There is evidence from large prospective studies that hypertension is a risk factor for progressive renal impairment and ESKD in patients with PKD.[10] However, results from randomized controlled trials of BP control have been inconsistent in demonstrating any direct effect in preserving renal function and/or reducing renal injury in adult PKD with established renal injury.

- The Modification of Diet in Renal Disease study examined the progression of renal disease in patients with established renal impairment, with a baseline glomerular filtration rate (GFR) between 25 and 55 mL/min. Two hundred patients (24%) in this study had PKD.[11] Assignment to aggressive BP reduction to low BP targets did not slow the rate of progression of kidney disease during the initial study.[10] However, long-term follow up (7 years) of this cohort demonstrated that a low-targeted blood pressure improved clinical outcomes, delayed the onset of ESKD and a composite outcome of kidney failure and all-cause mortality.[12]
- In the *Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study,* benazepril was not effective in 64 patients with PKD and renal impairment (GFR < 60 mL/min per 1.73 m^2), although it proved effective in individuals with renal disease of other causes.[13]
- In a double-blind, placebo-controlled trial of 61 normotensive and 28 hypertensive patients with PKD, angiotensin converting enzyme (ACE) inhibition with enalapril had no significant effect on the progression of renal failure in PKD patients. This was independent to whether patients were normotensive or hypertensive.[14]
- In contrast, in a randomized, open-label study of patients with PKD and progressive renal impairment, fosinipril was able to slow the rate of decline in renal function over and above that seen with nifedipine.[15] However, control of systolic BP was significantly better in those treated with ACE inhibition.
- Kanno *et al.*[16] studied the effects of calcium channel blockers and ACE inhibitors on the progression of renal dysfunction in 26 hypertensive patients with PKD. Creatinine clearance declined in both groups, and despite no difference in BP control, the average decline was smaller in patients receiving amlodipine. This difference was largely influenced by two patients who experienced a rapid decline in renal function on an ACE inhibitor.
- More recently, Nutahara *et al.*[17] randomly assigned 49 patients with PKD and hypertension to a calcium channel blocker (amlodipine, 2.5–10 mg/day, $n = 25$) or angiotensin receptor blocker (candesartan, 2–8 mg/day, $n = 24$) and followed them for 36 months. Six out of 25 patients (24.0%) receiving amlodipine and one out of 24 (4.2%) receiving candesartan experienced a twofold increase in serum creatinine and/or decrease in creatinine clearance to half of the baseline. Overall, the decline in creatinine clearance was larger in the amlodipine-treated individuals than in those receiving candesartan (Change in GFR: -20.9 ± 13.1 *vs* -4.8 ± 13.8 mL/min, $P < 0.01$).

There is no evidence that a low protein diet contributes to slowing of progressive renal disease in patients with PKD and established renal impairment.[10]

SUMMARY OF THE EVIDENCE

There is currently no conclusive clinical evidence for any disease-specific therapy for slowing progressive renal disease in PKD, with some studies demonstrating a positive effect and other showing no activity. However, some smaller randomized controlled trials have suggested that blockade of the RAS may be preferable to other forms of BP control. In addition, interventions that are made in individuals with PKD and only mild renal impairment appear to have been more effective that those limited to individuals with established severe renal impairment.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.

INTERNATIONAL GUIDELINES

No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Genetic diagnosis of PKD is now possible. The utility of early intervention in patients before the onset of massive cystic changes and/or nephrosclerosis remains to be established, but offers an important opportunity for intervention in order to prevent progressive renal injury in PKD.

CONFLICT OF INTEREST

Merlin Thomas has a Level II b conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Characteristics of included studies

Study ID (author, year)	*N*	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow-up	Comments
Klahr *et al*, 1995[11]	840	Randomized controlled clinical trial	15 clinical centres, US	200 participants with PKD	Low MAP (92 mmHg)	Usual MAP (107 mmHg)	2.2 years	Study A compared usual *vs* low protein, Study B compared low *vs* very low protein
Marin *et al*, 2001[15]	241	Randomized controlled clinical trial	17 departments of nephrology in Spain	241 hypertensive patients	Fosinopril, ACEI 10–30 mg once daily	Nifedipine GITS, 30–60 mg once daily	36 months	
Maschio *et al*, 1996[13]	583	Randomized controlled clinical trial	49 European hospitals	583 patients with renal insufficiency caused by various disorders; 64 with PKD	Benazepril	Placebo	3 years	Benazepril was not effective in patients with polycystic disease
Nutahara *et al*, 2005[17]	49	Randomized controlled clinical trial	Multicentre, Japan	49 patients with PKD, 20–70 year with previously treated or untreated hypertension	CCB amlodipine-based (2.5–10 mg/day)	ARB candesartan-based (2–8 mg/day)	36 months	
van Dijk *et al*, 2003[14]	89	Randomized controlled clinical trial	Multicentre, the Netherlands	61 normotensive and 28 hypertensive PKD patients	Enalapril/Atenolol	Placebo	36 months	Enalapril or Atenolol given to hypertensive group

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; GITS, gastrointestinal therapeutic system; MAP, mean arterial blood pressure; PKD, polycystic kidney disease.

Table 2 Quality of randomized trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow-up
		Participants	Investigators	Outcome assessors		
Klahr *et al.*, 1995[11]	Not specified	No	No	No	Yes	Not specified
Marin *et al.*, 2001[15]	Not specified	No	No	No	Yes	38.6%
Maschio *et al.*, 1996[13]	Not specified	Yes	Yes	Yes	No (data were censored after the last visit)	22.1%
Nutahara *et al.*, 2005[17]	Dynamic balancing method	unclear	unclear	unclear	yes	14.3%
van Dijk *et al.*, 2003[14]	Third party (pharmacy)	Yes (normotensive) No (hypertensive)	Yes (normotensive) No (hypertensive)	Yes (normotensive) No (hypertensive)	Yes	12.0% normotensive 20.0% hypertensive total 14.4%

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group mean (SD)	Control group mean (SD)	Difference in means (95% CI)
Klahr *et al*, 1995[11]	STUDY A	5.7 (4.12) usual MAP	6.0 (4.27) low MAP	–0.30 (–1.69, 1.09)
	Mean GFR decline from baseline to end (L/min per year)	5.9 (3.44) usual protein	5.8 (4.09) low protein	0.10 (–1.15, 1.35)
	STUDY A	3.9 (1.53) usual MAP	4.9 (1.72) low MAP	–1.00 (–1.83, –0.17)
	Mean GFR decline from baseline to end (L/min per year)	4.9 (2.15) low protein	4.0 (1.64) very low protein	0.90 (–0.08, 1.88)
Nutahara *et al*, 2005[17]	Serum creatinine at 36 months (mg/dL)	1.71 (0.89)	1.26 (0.46)	0.45 (0.00, 0.90)
	Creatinine clearance (mL/min)	58.5 (14.2)	64.8 (27.8)	–6.30 (–21.09, 8.49)
	Urinary protein excretion (mg/day)	458 (419)	154 (176)	304.00 (29.46, 578.54)
	Urinary albumin excretion (mg/day)	287 (238)	49 (37)	238.00 (81.39, 394.61)
van Dijk *et al*, 2003[14]	Normotensive	100 (11.31)	105 (16.16)	–5.00 (–12.07, 2.07)
	MAP at 3 years (mmHg)			
	Normotensive	97 (28.28)	105 (26.93)	–8.00 (–21.86, 5.86)
	GFR at 3 years (mL/min)			
	Normotensive	393 (124.45)	406 (118.47)	–13.00 (–10.07, 4.07)
	Effective renal plasma flow (mL/min)			
	Hypertensive	102 (10.82)	105 (7.75)	–3.00 (–10.07, 4.07)
	MAP at 3 years (mmHg)			
	Hypertensive	64 (32.45)	83 (30.98)	–19.00 (–42.60, 4.60)
	GFR at 3 years (mL/min)			
	Hypertensive	249 (457.91)	311 (557.71)	–62.00 (–438.32, 314.32)
	Effective renal plasma flow (mL/min)			

CI, confidence interval; GFR, glomerular filtration rate; MAP, mean arterial blood pressure; SD, standard deviation.

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/ number of patients not exposed)	Relative risk (95% CI)	Risk difference (95% CI)
Marin *et al*, 2001[15]	Reached primary endpoint (double serum creatinine or dialysis)	27/129	40/112	0.59 (0.39, 0.89)	–0.15 (–0.26, –0.03)
	Mortality	4/129	6/112	0.58 (0.17, 0.03)	–0.02 (–0.07, 0.03)
	Oedema	1/129	10/112	0.09 (0.01, 0.67)	–0.08 (–0.14, –0.03)
	Hyperkalemia	6/129	0/112	11.30 (0.64, 198.38)	0.05 (0.01, 0.09)
Maschio *et al*, 1996[13]	All cause mortality	8/300	1/283	7.55 (0.95, 59.96)	0.02 (0.00, 0.04)
	Reached primary endpoint (doubling of baseline serum creatinine)	31/300	57/283	0.51 (0.34, 0.77)	–0.10 (–0.16, –0.04)
	Reached primary endpoint (PKD only)	8/30	9/34	1.01 (0.45, 2.28)	0.00 (–0.21, 0.22)
Nutahara *et al*, 2005[17]	Double serum creatinine or decrease in Ccr to $^1/_2$ of baseline value	6/25	1/24	5.76 (0.75, 44.37)	0.20 (0.01, 0.38)

CI, confidence interval; PKD, polycystic kidney disease.