Reducing proteinuria

Date written: May 2005
Final submission: October 2005
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GUIDELINES

a. The beneficial effect of treatment regimens that include angiotensin-converting enzyme inhibitors (ACEIs) in slowing progression of kidney disease, is greater in patients with greater degrees of proteinuria. (Level I evidence)

b. There may be a proteinuria threshold for beneficial effect of ACEIs, of approximately 0.5 g/day. (Level I evidence)

c. Combined therapy with an ACEI and an angiotensin receptor blocker (ARB) does result in significantly greater antiproteinuric effect than with either agent alone and without further hypotensive effect. (Level II evidence)

d. Dihydropyridine calcium channel blocker-based treatment regimens are less effective than beta-blocker and ACEI-based regimens in slowing progression in non-diabetic kidney disease. (Level II evidence)

Background

Proteinuria is an important prognostic feature of chronic kidney disease (CKD). The degree of proteinuria relates to the severity of the kidney disease and with a greater likelihood of progression to end-stages of CKD. Studies primarily using ACEIs to slow progression to CKD indicate that responsiveness differs depending on the baseline (pretreatment) degree of proteinuria and the degree of reduction in proteinuria. Other antihypertensive classes have been evaluated in a similar fashion. Thus, the aim of this set of guidelines is to explore the pharmacological reduction in proteinuria leading to a slowing in the rate of progression of various types of CKD.

Search strategy

Databases searched: MeSH terms and text words for chronic kidney disease were combined with MeSH terms and text words for angiotensin II antagonists, ACE inhibitors and blood pressure. These were then combined with MeSH terms and text words for locating randomised controlled trials. The search was carried out in Medline (1966 – November Week 1, 2004). The Cochrane Renal Group Register of randomised controlled trials was also searched for any additional relevant trials not indexed in Medline.

Date of searches: 12 November 2004.

What is the evidence?

Russo et al (1999) An observational study in 8 selected normotensive patients with biopsy-proven IgA nephropathy and mild proteinuria (1–3 g/d) and normal to mildly impaired renal function (Creatinine clearance 69–119 mL/min). Subjects were given a maximum tolerated dose of a variety of ACEIs for 12 weeks, followed by addition of losartan (LOS) 50 mg/d for 4 weeks, then LOS alone for 12 weeks and then combined therapy again. ACEI and LOS reduced protein excretion by the same extent (-39 ± 2.5% and –27 ± 20.8%). Combined therapy reduced proteinuria by a significantly ($P < 0.05$) greater extent than ACEI alone or LOS alone (-69.8 ± 5.5% - ACEI + Los or -63.0 ± 9.3% – LOS + ACEI). The reduction in urinary protein was independent of the degree of BP decrease. LOS was as effective as ACEIs in reducing proteinuria. Larger trials are needed for definitive information. (Level IV evidence)

Perico et al (1998) ran a randomised placebo-controlled trial in 20 patients with biopsy-proven IgA nephropathy, persistent proteinuria (0.5–4.0 g/day), and mildly reduced renal function (serum Creatinine < 0.22 mmol/L); 12 patients had hypertension. There were 3 phases in the study, with washout of 4 weeks. (Level II evidence)

Both MDRD (1996) and REIN (2004) suggest that proteinuria is a significant independent predictor of CKD progression. Both report a strong association of greater baseline proteinuria with a more rapid decline in GFR. MDRD found that a reduction in proteinuria independent of BP was associated with a further decrease in the rate of decline in GFR, also degree of renoprotection achieved by lowering BP below the usual targets was dependent on the level of proteinuria. Proteinuria is an independent predictor of CV mortality in nondiabetic subjects.

Ramipril Efficacy in Nephropathy (REIN) study (*see above, also*): Patients with baseline proteinuria (< 3 g/d) have a slower ($P = 0.001$) rate of decline in GFR compared with those with baseline proteinuria (> 3 g/d) [0.53 ± 0.08 vs 0.88 ± 0.13 mL/min/month]. The degree of ramipril-induced reduction in proteinuria correlated with GFR decline and not with the degree of renal impairment. In both strata, all variables of benefit (e.g. rate of decline of renal function) could be explained by decline in proteinuria. Antihypertensive effect only explains part of the benefit. Ramipril was safe. The benefit of ramipril was greater with higher levels of proteinuria. (Level II evidence)
MDRD Study: In secondary analyses, reducing proteinuria was associated with lowering the rate of decline in renal function. (Level II evidence)

The beneficial effect of ACEIs on slowing progression of CKD is greater in those with higher baseline proteinuria (includes non-nephrotic and nephrotic syndromes) with questionable effect in those with minimal or no proteinuria (< 0.5 g/d) (Marcantoni et al 2003).

The COOPERATE Trial: enrolled 366 patients with nondiabetic CKD in Japan. A total of 263 patients were treated with losartan (100 mg/day), trandolapril (3 mg/day) or a combination of both drugs at equivalent doses and followed for a median of 2.9 years. Survival analysis of the endpoints of doubling of serum creatinine or end-stage kidney disease showed that combination treatment safely retards progression of non-

diabetic renal disease compared with monotherapy. “The benefit of combination treatment in retardation of renal progression was shown not only for patients with a great rate of (*baseline*) urine protein excretion but also for those with a small amount of proteinuria.” However, the greater the baseline proteinuria excretion, the more significant a reduction in proteinuria excretion after treatment was seen (Nakao et al 2003). (Level II evidence)

The meta-analysis by Jafar et al (2001) showed a stronger beneficial effect of ACEIs in slowing progression when baseline proteinuria was > 0.5 g/day. The benefit was inconclusive below this level. (Level I evidence)

In the AASK study, proteinuria increased by 58% in the amlodipine group and declined by 20% in the Ramipril group, during the first 6 months of the study. This difference persisted throughout the study and was significant ($P < 0.001$). In addition, even though patients with proteinuria > 2.5 g/day were excluded, proteinuria was still a strong predictor of GFR decline. Ramipril did not significantly slow GFR decline in those patients without proteinuria (Agodoa et al 2001). (Level II evidence)

Ruggeneti et al (2005) examined 273 patients randomised to ramipril or conventional therapy. Short term changes in proteinuria and residual levels of proteinuria predicted long term disease progression. Thus any treatment that reduces proteinuria may have a possible long term benefit on progression. The suggested goal was to lower proteinuria to < 0.5 g/day. (Level II to Level III evidence)

Summary of the evidence

Results from MDRD and REIN show that CKD progression is associated with higher baseline proteinuria. In non-diabetic patients, proteinuria is an independent predictor of cardiovascular mortality. Data from meta-analyses of RCTs show that treatment regimes which include ACEIs are effective in slowing the progression of kidney disease, this effect being stronger in patients with more severe proteinuria. A proteinuria threshold of approximately 0.5 g/day was also suggested for the beneficial effect of ACEIs in reducing progression of CKD. A greater antiproteinuric effect was seen with combined therapy of ACEI and ARB compared to either administered alone, however, there are limitations to the COOPERATE study. It is unclear whether ACEI or ARB at maximal doses are the same, or less efficacious than combined therapy. Evidence from RCTs suggests that beta-blockers and ACEI-based regimens in non-diabetic kidney disease are more effective in slowing progression of disease.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: See Guideline 11 of “Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease.” ACEIs and ARBs can be used in combination to lower blood pressure or reduce proteinuria (C).

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International guidelines:

VA Primary Care Guidelines: "ACEI reduces proteinuria, an effect that may—in itself—be renoprotective. These agents reduce proteinuria at any given level of blood pressure reduction more than other antihypertensive drugs. Risks associated with use of these drugs include dangerous hyperkalemia and acute kidney failure when they are used in situations associated with decreased glomerular filtration pressure such as dehydration or kidney artery stenosis (Wynckel 1998). Careful monitoring of potassium levels and serum creatinine is warranted."

Consensus statement ISN 2004: Workshop on Prevention of Progressive Renal Disease. Hong Kong, June 29, 2004. –Suggested use ACEI and/or ARB to reduce proteinuria. The optimal dose was not determined. The role of combined therapy was still uncertain due to insufficient data (INS 2004).

Implementation and audit

No recommendation.

Suggestions for future research

1. More studies on the combination of ARB and ACEI are required to confirm the benefits in slowing progression.

References

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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 (years)	Comments
Agodoa et al, 2001	1094	Randomised controlled clinical trial	Multicentre, US	1094 African-Americans with hypertensive renal disease	Ramipril	Amlodipine	3	3 x 2 factorial trial with third intervention metoprolol, with other agents to achieve 1 of 2 BP goals
Nakao et al, 2003	336	Randomised controlled clinical trial	1 renal department, Japan	336 patients with non-diabetic renal disease	Angiotensin-II receptor blocker, losartan 100 mg/d	Angiotensin-converting-enzyme inhibitor, trandolapril 3 mg/d	3	3-arm trial with a third arm receiving combination of both drugs at equivalent doses
Perico et al, 1998	20	Randomised controlled clinical trial	1 outpatient clinic, Italy	20 patients with IgA glomerulo-nephritis	Enalapril 20 mg/d	Irbesartan 100 mg/d	1 mo	Study also evaluated addition of indomethacin 75 mg 2 x /d
Ruggenenti et al, 2005	338	Randomised controlled clinical trial	Multicentre, Italy	Patients with non-diabetic nephropathy and persistent proteinuria	Intensified blood-pressure control, dihydropyridine calcium-channel blocker, felodipine (5–10 mg/d)	Conventional blood pressure control	3	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Agodoa et al, 2001	Central	Yes	Yes	Yes	Yes	
Nakao et al, 2003	Permuted blocks of 6, independent, computer-generated	Yes	Yes	Yes	Yes	2.1
Perico et al, 1998	Not specified	Yes	Yes	Yes	Yes	0.0
Ruggenenti et al, 2005	Central	No	No	No	Yes	38.2

Table 3 Results of continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Agodoa et al, 2001	Acute phase: mean total decline in GFR to 3 yrs (mL/min/1.73 m^2/yr); UP/Cr ≤ 0.22	-1.02 (5.22) Ramipril	0.20 (2.95) Amlodipine	-1.22 (95%CI: -1.85, -0.59)
	Acute phase: mean total decline in GFR to 3 yrs (mL/min/1.73 m^2/yr); UP/Cr > 0.22	-3.60 (7.10) Ramipril	-5.62 (9.58) Amlodipine	2.02 (95%CI: 0.58, 3.46)
	Chronic phase: mean GFR decline (mL/min per 1.73 m^2/yr); UP/Cr>0.22	3.55 (8.56) Ramipril	5.92 (10.16) Amlodipine	-2.37 (95%CI: -3.94, -0.80)
	Chronic phase: mean GFR decline (mL/min/1.73 m^2/yr); UP/Cr ≤ 0.22	1.22 (5.22) Ramipril	2.02 (5.60) Amlodipine	-0.80 (95%CI: -1.69, 0.09)
Nakao et al, 2003	Decrease in mean systolic pressure from baseline (mmHg)	5.1 (1.6) Losartan	5.2 (1.3)	-0.10 (95%CI: -0.53, 0.33)
	Decrease in mean systolic pressure from baseline (mmHg)	5.3 (1.4) Combination	5.2 (1.3)	0.10 (95%CI: 0.30, 0.50)
	Decrease in mean diastolic pressure (mmHg)	2.9 (0.9) Losartan	2.9 (0.8)	0.00 (95%CI: -0.25, 0.25)
	Decrease in mean diastolic pressure (mmHg)	3.0 (0.7) Combination	2.9 (0.8)	0.10 (95%CI: -0.12, 0.32)
Perico et al, 1998	Systolic BP at end of study, trough value	133 (9)	149 (14)	-16.00 (95%CI: -26.58, -5.42)
	Systolic BP at end of study with indomethacin, trough value	132 (11)	149 (13)	-17.00 (95%CI: -27.70, -6.30)
	Diastolic BP at end of study, trough value	77 (10)	91 (7)	-14.00 (95%CI: -21.47, -6.53)
	Diastolic BP at end of study with indomethacin, trough value	80 (12)	89 (8)	-9.00 (95%CI: -17.81, -0.19)
	Urinary protein excretion rate at end of study (g/24 h)	0.72 (0.39)	1.54 (1.46)	-0.82 (95%CI: -1.80, 0.16)
	Urinary protein excretion rate at end of study (g/24 h) with indomethacin	0.29 (0.13)	0.57 (0.43)	-0.28 (95%CI: -0.57, 0.01)
	GFR (ml/min/1.73 m^2) at end of study	65 (25)	55 (11)	10.00 (95%CI: -6.43, 26.43)

Table 3 Continued

	GFR (ml/min/1.73 m^2) at end of study with indomethacin	67 (25)	54 (11)	13.00 (95%CI: -3.43, 29.43)
Ruggenenti et al, 2005	Mean systolic blood pressure throughout follow up (mmHg)	129.6 (10.9)	133.7 (12.6)	-4.10 (95%CI: -6.62, -1.58)
	Mean diastolic blood pressure throughout follow up (mmHg)	79.5 (5.3)	82.3 (7.1)	-2.80 (95%CI: -4.14, -1.46)

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 (RR) [95% CI]	Risk difference (RD) [95% CI]
Agodoa et al, 2001	Mortality	18/436 (Ramipril)	13/217 (Amlodipine)	0.69 (95%CI: 0.34, 1.38)	-0.02 (95%CI: -0.06, 0.02)
Nakao et al, 2003	Primary endpoint	20/86 (Losartan)	20/85	0.99 (95%CI: 0.57, 1.70)	0.00 (95%CI: -0.13, 0.12)
		10/85 (Combination)	20/85	0.50 (95%CI: 0.25, 1.00)	-0.12 (95%CI: -0.23, 0.00)
	Mortality	1/89 (Losartan)	0/86	2.90 (95%CI: 0.12, 70.23)	0.01 (95%CI: -0.02, 0.04)
		0/88 (Combination)	0/86	Not estimable	0.00 (95%CI: -0.02, 0.02)
	Non-fatal stroke	0/89 (Losartan)	1/86	0.32 (95%CI: 0.01, 7.80)	-0.01 (95%CI: -0.04, 0.02)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: -0.03, 0.03)
	Non-fatal angina	1/89 (Losartan)	1/86	0.97 (95%CI: 0.06, 15.21)	0.00 (95%CI: -0.03, 0.03)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: -0.03, 0.03)
	Myocardial infarction	1/89 (Losartan)	0/86	2.90 (95%CI: -0.02, 0.04)	0.01 (95%CI: -0.02, 0.04)
		0/88 (Combination)	0/86	Not estimable	0.00 (95%CI: -0.02, 0.02)

Table 4 Continued

	Hypotension	0/89 (Losartan)	1/86	0.32 (95%CI: 0.01, 7.80)	-0.01 (95%CI: -0.04, 0.02)
		1/88 (Combination)	1/86	0.98 (95%CI: 0.06, 15.38)	0.00 (95%CI: -0.03, 0.03)
	Total adverse reactions	11/89 (Losartan)	19/86	0.56 (95%CI: 0.28, 1.11)	-0.10 (95%CI: -0.21, 0.01)
		18/88 (Combination)	19/86	0.93 (95%CI: 0.52, 1.64)	-0.02 (95%CI: -0.14, 0.11)
Ruggenenti et al, 2005	Mortality	2/167	3/168	0.67 (95%CI: 0.11, 3.96)	-0.01 (95%CI: -0.03, 0.02)
	Progression to ESRD	38/167	64/168	0.60 (95%CI: 0.43, 0.84)	-0.15 (95%CI: -0.25, -0.06)
	Non-fatal serious adverse events	37/167	25/168	1.49 (95%CI: 0.94, 2.36)	0.07 (95%CI: -0.01, 0.16)