Blood Pressure Control – role of specific antihypertensives

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Author: Adrian Gillian

GUIDELINES

a. Regimens that include angiotensin-converting enzyme inhibitors (ACEIs) are more effective than regimens that do not include ACEIs in slowing progression of non-diabetic kidney disease. (Level I evidence)

b. Combination therapy of ACEI and angiotensin receptor blocker (ARB) slows progression of non-diabetic kidney disease more effectively than either single agent. (Level II evidence)

c. ACEIs appear to be more effective than beta-blockers and dihydropyridine calcium channel blockers in slowing progressive kidney disease. (Level II evidence)

d. Beta-blockers may be more effective in slowing progression than dihydropyridine calcium channel blockers, especially in the presence of proteinuria. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

- **Use ACEIs cautiously in patients with renal impairment. A safe level of renal impairment has not been clearly defined; therefore one should monitor plasma electrolytes and renal function closely during therapy.**

Background

In general, different classes of antihypertensive agents reduce BP to a similar degree. Some antihypertensive class agents have specific benefits to patients with other comorbidities, e.g. diuretics in oedematous patients due to nephrotic syndrome. ACEIs have been shown to have greater beneficial effects on slowing the rate of diabetic CKD than other antihypertensive agents, when similar BP control is achieved. This set of guidelines evaluates the evidence for the various classes of antihypertensive agent in slowing the rate of progression of non-diabetic 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?

Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: A meta-analysis of randomised trials. Giatras et al (1997) included 10 studies (6 blinded), 1594 patients 44-66 years. ACEIs were found to be more effective than other antihypertensive agents in reducing the development of non-diabetic End-stage Kidney Disease (ESKD); they also do not increase mortality. Pooled relative risk for ESKD was 0.70 (95%CI: 0.51-0.97) indicated a significantly lower risk for developing ESKD in ACEI group. However, risk of death was not improved [pooled relative risk, 1.24 (95%CI:, 0.55 to 2.83)]. No significant association between BP reduction and ACEI benefit. (Level II evidence)

REIN Study: The R/DB/PC trial, 352 patients (18-70yrs) with non-diabetic nephropathy (Creatinine clearance of 20-70 mL/min $\pm$ 30%). Participants were stratified by degree of proteinuria (1: 1-3 g/d, II: > 3 g/d), ramipril or placebo plus conventional antihypertensives to achieve target < 90 mmHg diastolic. The endpoint was rate of decline of GFR (iohexol clearance method). Patients included were normotensive (140/90 mmHg) and hypertensive. Other ACEIs and ARBs prohibited as BP controlling agents.

This study reported a significantly (P = 0.001) slower rate of decline in GFR/month in patients with < 3 g/d proteinuria on ramipril (n = 38) compared with the placebo-treated patients (n = 49) [0.39$\pm$0.10 vs 0.89 $\pm$0.11 mL/min]. Ramipril decreased protein excretion by 55% at 36 months treatment and while it did not change in the placebo group (P = 0.002). Risk reduction was significantly predicted by the percentage reduction from baseline in urinary protein excretion during treatment. Improvement was not related to baseline or follow-up blood pressure. In stratum I, there was no significantly different decline in GFR in either group. (Level II evidence)

AIPRI Trial: This multicentre, randomised, placebo-controlled trial entailed 583 patients with mild to moderate renal insufficiency (Creatine clearance 30 – 60 mL/min) due to a variety of causes, target BP - diastolic < 90 mmHg. Outcome measure – twofold increase in baseline serum creatinine. Results showed a lower rate of decline of renal function with benazepril. There was a small final difference in serum creatinine (0.1 – 0.2 mg/dL). No effect shown on progression to ESKD. There was a higher death rate in the ACEI-treated group (1/94 /year vs 1/657 /year). Target BP was attained in 82% on benazepril and 68% of control group, ACEI attained mean DBP <85 mmHg and controls attained < 90 mmHg DBP. This study did not

conclusively establish the magnitude of the beneficial effect or the safety of the ACEI therapy (Locatelli et al 1997). (Level I evidence)

Early Randomised ACEI studies: Small sample size usually. Results not uniform – some beneficial effect of ACEI while others not beneficial.

Zuchelli et al.(1992) 121 patients were studied to compare captopril vs nifedipine. Conventional antihypertensives for 1 year then randomised for 2 years on treatment. Similar BP reduction in both groups. Urinary protein fell more with ACEI, but GFR decline was similar for both groups. If mean BP < 100 mmHg, it was associated with slower rate of decline in renal function. (Level III evidence)

Himmelmann et al (1995): Cilazapril vs atenolol was studied in 260 patients with presumed diagnosis of hypertensive nephrosclerosis and near-normal renal function (GFR 82 mL/min). During 2 year follow-up, ACEI significantly slowed decline in renal function. (Level III evidence).

The COOPERATE Trial: Enrolled 366 patients with nondiabetic CKD in Japan. 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 ESKD showed that combination treatment safely retards progression of non-diabetic kidney disease compared to monotherapy. Of the combination treatment group, 11% reached the combined primary endpoint compared to 23% (95%CI: 0.18-0.63, P = 0.018) on trandolapril and 23% (95%CI: 0.17-0.69, P = 0.016) on losartan (Nakao et al 2003). (Level II evidence)

The Jafar et al (2001) meta–analysis sourced individual patient data from 11 RCTs that compared efficacy of antihypertensive regimens including ACEIs to the efficacy of regimens without ACEIs in predominantly non-diabetic kidney disease. Data from 1860 patients were analysed and mean follow-up was 2.2 years. All patients were hypertensive. The ACEI group achieved a lower BP (mean 4.5/2.3 mmHg) and had greater proteinuria reduction (mean 0.46 g/day). Regimens that include an ACEI are more effective than regimens without an ACEI in slowing progression of nondiabetic renal disease. It is mediated by factors in addition to decreasing BP and urinary protein excretion and is greater in patients with proteinuria. The data were inconclusive as to whether the benefit extended to those with baseline proteinuria less than 0.5 g/day. (Level I evidence)

The AASK Trial (Wright et al 2002) studied 1094 African-Americans with nondiabetic, hypertensive renal disease. It compared 2 levels of BP control and 2 antihypertensive drug classes on GFR decline (3 x 2 factorial design). The BP goals were MAP of (i) 102-107 mmHg or (ii) $\leq$ 92 mmHg. The drugs were ramipril (2.5-10 mg/day, n= 436), metoprolol (50-200 mg/day, n=441) and amlodipine (5-10 mg/day, n=217). It was open label. Outcomes were GFR slope alone or GFR slope combined with reduction in GFR by 50% or more, ESKD or death. The lower blood pressure group achieved a mean BP of 128/78 mmHg, which was 12/8 lower than the other BP group (mean achieved BP 141/85 mmHg). There was no significant outcome difference between groups. The ramipril group manifest risk reductions in the clinical composite outcome of 22% (95%CI: 1-38%, P = 0.04) compared to the metoprolol group and 38% (95%CI: 14-56%, P = 0.004) compared to the amlodipine group. (Level II evidence)

Summary of the evidence

Results from a meta-analysis of RCTs showed treatments which included ACEIs are more effective than treatment regimens without ACEIs in slowing the progression of kidney disease. The data was inconclusive about the benefit for patients with baseline proteinuria < 0.5 g/day. Evidence from RCTs suggest that combination therapy of ACEI and ARB slows the progression of non-diabetic kidney disease more effectively than other agents and ACEIs are more effective in slowing progressive kidney disease compared with beta-blockers and dihydropyridine calcium channel blockers. However, there are limitations to the COOPERATE study, as it is unclear whether ACEI or ARB at maximal doses are the same, or less efficacious than combined therapy. RCTs have also shown that dihydropyridine calcium channel blockers are less effective in slowing progression of kidney disease compared with beta-blockers, particularly when proteinuria is present.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: See Guideline 11 of Pharmacological therapy: Nondiabetic Kidney Disease – 'Clinical Practice Guidelines on Hypertension and Antihypertensive agents in Chronic Kidney Disease'. ACEIs and ARBs can be used safely in most patients with CKD. They…"should be used at moderate to high doses, as used in clinical trials. (A) " They should be used as alternatives to each other, if the preferred class cannot be used (B).

Also see Guideline 9 – 'Patients with non-diabetic kidney disease and spot urine protein to creatinine ratio > 200 mg/g, with or without hypertension should be treated with an ACE inhibitor or ARB.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

VA Primary Care Guidelines – 'ACEI has beneficial effects in patients with diabetic nephropathy and other kidney diseases. These drugs slow progression independent of their effect on blood pressure. ARBs are a new class of drugs which may be used in patients who are intolerant of ACEI. (Pitt B 1997). Studies on their effect are in progress.'

Consensus statement ISN 2004 – Workshop on Prevention of Progressive Renal Disease. Hong Kong, June 29, 2004. Suggested target BP < 130/80 mmHg. They suggested that BP control was more important than the choice of BP lowering agent.

Implementation and audit

No recommendation.

Suggestions for future research

Evaluate more precise BP targets for differing degrees of protein excretion.

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
Locatelli et al, 1997	583	Randomised controlled clinical trial	49 centres in Italy, France, Germany	Patients with chronic renal insufficiency	Benazepril	Placebo	6.6	Core trial with extended follow up, post hoc data included when treatment was not randomised
Nakao et al, 2003	336	Randomised controlled clinical trial	1 renal department in Japan	336 patients with non-diabetic renal disease	Angiotensin-II receptor blocker, Iosartan 100 mg/d	Angiotension-converting-enzyme inhibitor, trandolapril 3 mg/d	3	3-arm trial with a third arm receiving combination of both drugs at equivalent doses
Ruggenenti et al, 2005	338	Randomised controlled clinical trial	Multicentre in 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	
Wright et al, 2002	1094	Randomised controlled clinical trial	21 clinical centres in the US	1094 African-Americans with hypertensive renal disease, 18–70 yrs	Low MAP < 92 mmHg	Usual MAP 102–107 mmHg	3–6.4	3 x 2 factorial trial (2 levels of MAP, 3 anti-hypertensive drug classes)

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)		
Locatelli et al, 1997	Not specified	Yes	Yes	Yes	Yes	13.6
Nakao et al, 2003	Permuted blocks of 6, independent, computer-generated	Yes	Yes	Yes	Yes	2.1
Ruggenenti et al, 2005	Central	No	No	No	Yes	38.2
Wright et al, 2002	Not specified	No	No	No	Yes	0.8

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
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)
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)
Wright et al, 2002	Mean GFR decline (mL/min/1.73m^2 per year)	2.21 (4.0)	1.95 (4.0)	0.26 (95%CI: -0.21, 0.73)

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]
Locatelli et al, 1997	Mortality	25/300	23/283	1.03 (95%CI: 0.60, 1.76)	0.00 (95%CI: -0.04, 0.05)
	Doubling of baseline serum creatinine at 3 yrs follow up, core study	31/300	57/283	0.51 (95%CI: 0.34, 0.77)	-0.10 (95%CI: -0.16, -0.04)
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)
	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)