Angiotensin II Antagonists

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GUIDELINES

a. Angiotensin II receptor antagonists offer specific renoprotection in diabetic nephropathy, beyond their antihypertensive benefit. (Level I evidence for Type 2 diabetics with microalbuminuria or overt nephropathy)

Background

The beneficial effects of angiotensin-converting enzyme inhibitors (ACEIs) in preventing progression of diabetic nephropathy have been broadly assumed to transfer to Angiotensin II receptor antagonists. Recent excellent studies have confirmed benefit in Type 2 diabetes, and are reviewed here.

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, AII receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.
Date of search: 16 December 2003.

What is the evidence?

Recent studies have confirmed that AII receptor antagonists protect against progression of diabetic nephropathy. The number of studies remain small compared with those assesssing ACE inhibitors, and have been largely confined to Type 2 diabetics. However, these studies are well designed and adequately powered.

Type I diabetes

One randomised controlled trial (RCT) [crossover design] of 16 Type 1 diabetics over 10 months (Andersen et al 2000) documented similar effects of losartan 100 mg and enalapril 20 mg on 24-hour mean arterial pressure (MAP) and albuminuria, without change in GFR.

Type 2 diabetes
Microalbuminuric and proteinuric patients

Three major RCTs have recently been published, all showing an advantage of AII receptor antagonists:

The Irbesartan in Patients with Type 2 Diabetes and MicroAlbuminuria (IRMA) Study - Parving et al (2001):

This multicentre RCT randomised 590 hypertensive Type 2 diabetics with microalbuminuria to irbesartan 150 or 300 mg/day, or placebo Target BP was < 135/85 mmHg, achieved with agents other than ACEIs, angiotensin receptor blockers (ARBs) or calcium channel blockers (CCBs).

	Irbesartan 150	Irbesartan 300	Placebo
BP during study	143/83 mmHg	141/83 mmHg	144/83 mmHg
% patients reaching primary end-point	9.7%	5.2%	14.9%
Hazard ratio (CI)	0.61 (.34–1.08)	0.3 (0.14–0.61)	
Regression to normal AER	12/100 Pts/yr	17/100 Pts/yr	10.5/100 Pts/yr

Follow-up was for 2 years, with the primary endpoint of transition to overt proteinuria. being decreased by 70% with irbesartan therapy. Serious adverse events were less frequent among the patients treated with irbesartan (P = 0.02).

The Irbesartan Collaborative Study of Lewis et al (IDNT 2001) randomised 1715 hypertensive Type 2 diabetics with overt nephropathy in 210 centres, to irbesartan 300 mg/day, amlodipine 10 mg/day, or placebo. Antihypertensive agents other than ACEIs, ARBs, and CCBs were used as needed. Target blood pressure was 135/85 mm Hg or less in all groups. Mean follow-up was 2.6 years, with the primary endpoint being the composite of time to a doubling of the baseline serum creatinine level, the onset of ESRD, or death from any cause.

The secondary endpoint was a composite of time to death from cardiovascular event(s).

Treatment with irbesartan resulted in the following outcomes:

- 20% risk reduction for the primary endpoint (P = 0.02) compared with placebo and 23% risk reduction compared with amlodipine (P = 0.006),
- 33% risk reduction for doubling the serum creatinine level (P = 0.003) compared with placebo and 37% risk reduction compared with amlodipine (P = 0.001),
- 23% risk reduction for development of ESRD (P = 0.07) compared with placebo and amlodipine, and
- 24% slower rise in serum creatinine level compared with placebo (P = 0.008) and 21% slower rise compared with amlodipine (P = 0.02)

These differences were not explained by differences in blood pressure that were achieved, and there were no significant differences in the rates of death from any cause or in the cardiovascular composite endpoint. Proteinuria predicted poor renal outcome, and irbesartan decreased proteinuria more than amlodipine or placebo (Atkins et al 2002).

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) Study – Brenner et al (2001):

This multinational (250 centres in 28 countries), double-blind, randomized, placebo controlled study evaluated the effects of losartan in 1513 patients with type 2 diabetes mellitus and overt nephropathy (proteinuria > 500 mg/day and serum creatinine levels of 1.3–3.0 mg/dL) for a mean of 3.4 years. Randomization was to losartan 50–100 mg/day (71% received 100 mg) vs placebo. Conventional antihypertensive therapy was used in both groups. The primary end point was the time to doubling of serum creatinine, ESKD, or death. Secondary endpoints were prespecified and included a composite of cardiovascular morbidity and mortality, changes in level of proteinuria, and the rate of progression of renal disease. Patients treated with losartan had better outcome, with the primary endpoint reached in 43.5% of losartan-treated patients vs 47.1% of placebo patients. Treatment with losartan resulted in:

- 16% risk reduction for the primary endpoint (P = 0.02),
- 25% risk reduction for doubling the serum creatinine level (P = 0.006),
- 28% risk reduction for development of ESKD (P = 0.002),
- 20% risk reduction for ESKD death (P = 0.01),
- 32% risk reduction for rate of first hospitalization for heart failure (P = 0.005), and
- 35% decline in level of proteinuria (P < 0.001).

There was no significant difference between the groups for the composite endpoint of cardiovascular morbidity and mortality. It was estimated that losartan was associated with an average delay of 2 years in the need for dialysis or renal transplantation.

Are angiotensin II antagonists equivalent in renoprotective efficacy to ACEI?

Barnett et al (DETAIL study 2004) randomised 250 hypertensive Type 2 diabetics with AER 11–999 mcg/min to either telmisartan 80 mg or enalapril 20 mg, and performed serial iohexol GFR measurements over 5 years. Double-dummy placebos were used. Rate of GFR decrease was equivalent in both groups (–15 and –18 mL/min/1.73 m_2 in enalapril and telmisartan groups respectively), and there were no significant differences in AER, BP, ESKD or cardiovascular events, although the study was underpowered for the latter. This study had a 1/3 dropout rate, and these patients were not followed beyond 28 days.

Lacourciere et al (2000) compared losartan (50-20 mg, mean 86.3 $\pm$ 22.5 mg) and enalapril (5-20 mg, mean 16.0 $\pm$ 6.2 mg) on kidney function in hypertensive Type 2 diabetics with early nephropathy.

Summary of the evidence

There is a convincing body of Level I evidence that AII receptor antagonists offer renoprotection in diabetic nephropathy, beyond their antihypertensive benefit. Studies have mainly been done in Type 2 diabetic patients with either microalbuminuria or overt nephropathy.

What do the other guidelines say?

American Diabetes Association (2001): ARBs reduce the rate of progression from micro- to macroalbuminuria as well as ESRD in patients with type 2 diabetes. (A) ARBs may induce a smaller rise in potassium than ACE inhibitors in people with nephropathy.

In the treatment of both micro- and macroalbuminuria, either ACE inhibitors or ARBs should be used. (A)
There are no adequate head-to-head comparisons of ACE inhibitors and ARBs. If one class is not tolerated, the other should be substituted. (E) If ACE inhibitors, ARBs, or diuretics are used, monitor serum potassium levels for the development of hyperkalemia. (B)

American Diabetes Association (2004): In hypertensive Type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)
In patients with Type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency, ARBs have been shown to delay the progression of nephropathy. (A)
If ACE inhibitors or ARBs are used, monitor serum potassium levels for the development of hyperkalemia. (B)

Canadian Diabetes Association (2003): In people with Type 2 diabetes, albuminuria, and Ccr > 60 mL/min, an ACE inhibitor (Grade A, Level 1A) or an ARB (Grade A, Level 1A) should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1A).
In people with Type 2 diabetes, albuminuria, and Ccr < 60 mL/min, an ARB (Grade A, Level 1A) should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1A).

Patients placed on an ACE inhibitor or an ARB should have their se Sr and K levels checked within 2 weeks of initiation of therapy and periodically thereafter (Grade D, consensus).

Kidney Disease Outcomes Quality Initiative (2004): Patients with diabetic kidney disease, with or without hypertension, should be treated with an ACE inhibitor or an ARB. Evidence for benefit of ARBs in slowing renal progression is strongest for Type 2 diabetics with macroalbuminuria. There is moderately strong evidence that diuretics may potentiate the beneficial effects of ACE inhibitors and ARBs in diabetic kidney disease.

Implementation and audit

No recommendation.

Suggestions for future research

1. There is room for further head-to-head comparisons of ACE inhibitors and ARBs.

2. Maximum ACEI or ARB therapy have been inadequately compared with combination therapy in long term studies with hard endpoints.

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**
Andersen et al. 2000	16	Randomised crossover clinical trial	Single diabetes centre	16 Type 1 diabetes patients	Losartan 50 mg, losartan 100 mg, enalapril 20 mg	Placebo	2 mo	
Barnett et al. 2004	250	Randomised controlled clinical trial	39 centres in Northern Europe	250 patients with Type 2 diabetes and early nephropathy	Telmisartan	Enalapril	5	
Brenner et al. 2001	1513	Randomised controlled clinical trial	250 centres from 28 countries	1513 patients with Type 2 diabetes and nephropathy	Losartan 50–100 mg once daily	Placebo	3.4	
Lacourciere et al. 2000	92	Randomised controlled clinical trial	8 clinical centres in Canada	92 hypertensive Type 2 diabetics with early nephropathy	Losartan	Enalapril	1	
Parving et al. 2001	590	Randomised controlled clinical trial	96 centres, worldwide	590 hypertensive patients with Type 2 diabetes and microalbuminuria	Irbesartan 150 mg	Placebo	1	Third arm intervention – 300 mg irbesartan

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)**		
Andersen et al. 2000	Not specified	Yes	Yes	Unclear	Unclear	0.0
Barnett et al. 2004	Central	Yes	Yes	Yes	No	0.8
Brenner et al. 2001	Central	Yes	Yes	Yes	Yes	0.2
Lacourciere et al. 2000	Within each centre	Yes	Yes	Unclear	Yes	Unclear
Parving et al. 2001	Not specified	Yes	Yes	Yes	Yes	0.5

Table 3 Results for dichotomous outcomes

Study ID (author, year)	**Outcomes**	**Intervention group (mean [SD])**	**Control group (mean [SD])**	**Difference in means [95% CI]**
Andersen et al. 2000	Losartan 50 mg			
	Mean arterial BP (24 hr mmHg)	95 (8)	104 (8)	-9.00 (95%CI: -14.54, -3.46)
	SBP (24 hr mmHg)	137 (16)	147 (12)	-10.00 (95%CI: -19.80, -0.20)
	DBP (24 hr mmHg)	75 (4)	82 (8)	-73.00 (95%CI: -11.38, -2.62)
	GFR (mL/min/1.73m^2)	91 (24)	90 (24)	1.00 (95%CI: -15.63, 17.63)
	Losartan 100 mg			
	Mean arterial BP (24 hr mmHg)	96 (8)	104 (8)	-8.00 (95%CI: -13.54, -2.46)
	SBP (24 hr mmHg)	135 (12)	147 (12)	-12.00 (95%CI: -20.32, -3.68)
	DBP (24 hr mmHg)	75 (4)	82 (8)	-6.00 (95%CI: -11.54, -0.46)
	GFR (mL/min/1.73m^2)	91 (24)	90 (24)	-1.00 (95%CI: -17.63, 15.63)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Anderson et al. 2000	L 50 mg			
	MABP (24 hr mmHg)	95 (8)	104 (8)	-9.00 (95%CI: -14.54, -3.46)
	SBP* (24 hr mmHg)	137 (16)	147 (12)	-10.00 (95%CI:-19.80, -0.20)
	DBP† (24 hr mmHg)	75 (4)	82 (8)	-73.00 (95%CI:-11.38, -2.62)
	GFR✝ (mL/min/1.73m^2)	91 (24)	90 (24)	1.00 (95%CI:-15.63, 17.63)
	L 100 mg			
	MABP (24 hr mmHg)	96 (8)	104 (8)	-8.00 (95%CI: -13.54, -2.46)
	SBP (24 hr mmHg)	135 (12)	147 (12)	-12.00 (95%CI:-20.32, -3.68)
	DBP (24 hr mmHg)	75 (4)	82 (8)	-6.00 (95%CI:-11.54, -0.46)
	GFR (ml/min/1.73m^2)	91 (24)	90 (24)	-1.00 (95%CI:-17.63, 15.63)
	E 10 mg			
	MABP (24 hr mmHg)	98 (12)	104 (8)	-6.00 (95%CI:-13.07, 1.07)
	SBP (24 hr mmHg)	141 (16)	147 (12)	-6.00 (95%CI:-15.80, 3.80)
	DBP (24 hr mmHg)	77 (8)	82 (8)	-5.00 (95%CI:-10.54, 0.54)
	GFR (ml/min/1.73m^2)	89 (24)	90 (24)	-1.00 (95%CI:-17.63, 15.63)
	E 20 mg			
	MABP (24 hr mmHg)	93 (12)	104 (8)	-11.00 (95%CI:-18.07, -3.93)
	SBP (24 hr mmHg)	135 (16)	147 (12)	-12.00 (95%CI:-21.80, -2.20)
	DBP (24 hr mmHg)	73 (8)	82 (8)	-9.00 (95%CI:-14.54, -3.46)
	GFR (mL/min/1.73m^2)	89 (24)	90 (24)	-1.00 (95%CI:-17.63, 15.63)
Laciouciere et al. 2000	SBP (mmHg)	148.3 (17.1)	145.5 (18.2)	2.80 (95%CI:-4.19, 9.79)
	DBP (mmHg)	86.8 (9.6)	94.4 (8.4)	2.40 (95%CI:-1.17, 5.97)

* SBP = systolic blood pressure; † = diastolic blood pressure; ✝ = glomerular filtration rate.