

Antihypertensive therapy in diabetic nephropathy

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GUIDELINES

- a. Adequate control of blood pressure (BP) slows progression in diabetic nephropathy. (Level I evidence)
- b. Goal blood pressures in diabetic nephropathy should be < 130/85 mmHg in patients over 50 years of age and < 120/70–75 mmHg for those under 50 years.* (Level I evidence) Multiple antihypertensives are usually required to achieve target BP.
- c. Protection against both nephropathy progression and cardiovascular events is provided by good BP.

**The recommendation of target BP to vary with age is based on clinical caution in a population at risk of cerebrovascular disease, rather than any evidence for a J-curve effect in the diabetic population.*

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- Effective BP control is the single most important factor in limiting rate of progression of diabetic nephropathy.
- Most hypertensive diabetic patients will require treatment with two or more antihypertensives to achieve optimal BP control.
- The recommendation of target BP to vary with age is based on clinical caution in a population at risk of cerebrovascular disease, rather than any evidence for a J-curve effect in the diabetic population.
- Elderly patients with Type 2 diabetes commonly have high systolic blood pressure (SBP) and pulse pressure, but normal diastolic pressure. Therapy in this group needs to target SBP.

Background

Hypertension is the major accelerant of progressive kidney failure in diabetic nephropathy. This section reviews the large body of evidence demonstrating that BP control slows progression, and discusses target BP goals.

Search strategy

Databases searched:

The Cochrane Renal Group Specialised Register was searched for randomised controlled trials (RCT's) 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, A2 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?

Adequate control of blood pressure slows progression in diabetic nephropathy

Multiple studies have been done over the past 25 years, but many were underpowered and short-term. Included here are major RCTs, meta-analyses, and long-term landmark cohort studies.

Type 1 diabetes mellitus

Kasiske et al (1993) - this meta-analysis of 100 studies providing data on BP, renal function, and/ or proteinuria before and after treatment with an antihypertensive agent, included 12 RCTs. Total patient number was 2494. Most studies were short-term, the study duration exceeded 6 months for only 27% of experimental groups, and exceeded 12 months in only 13%.

Studies included both Type 1 and Type 2 diabetics - 49% of groups were comprised solely of Type 1 patients, 32% solely of Type 2, 11% of groups were mixed, and in 9% type of diabetes was unspecified. While there are excellent reasons for separating Type 1 from Type 2 patients in studies, many studies done before 1995 failed to do so, but can no longer be ethically repeated. Both Type 1 and Type 2 patients benefit from BP control.

Thirty-five per cent of groups had clinical nephropathy, 17% had microalbuminuria, but stage of nephropathy was not clearly indicated for 39% of groups. Patients in 78% of groups were hypertensive. An angiotensin-converting enzyme inhibitor (ACEI) was investigated in 46% of experimental groups.

Also reported was a separate meta-analysis of the 11 included RCTs involving treatment with ACEI.

Blood pressure reduction in itself resulted in benefit in GFR preservation of 3.7 ± 0.92 mL/min/year for each 10 mmHg reduction in mean arterial pressure (MAP).

Specific ACEI effect was additional to this (see CARI 'ACE inhibitor treatment in diabetic nephropathy' guideline).

Deferrari et al (2004) performed a meta-analysis of 9 studies of proteinuric patients with overt nephropathy, and demonstrated a fourfold reduction in the decline of GFR when MAP < 100 mmHg.

Parving et al (1983). This was a prospective, self-controlled, 6-year cohort study of 29 Type 1 diabetics with proteinuria. Patients were followed before (for mean of 29 months, range 23–38 months) and after (for mean of 39 months, range 28–48 months) instigation of antihypertensive treatment with metoprolol, hydralazine and diuretic. BP fell from 144/97 mmHg to 128/84 mmHg. The rate of GFR decline decreased from 0.91 mL/min/month pre-treatment to 0.39 mL/min/month during treatment, and albumin excretion rate (AER) also fell. Crepaldi et al (1998) randomised 92 normotensive Type 1 diabetics with microalbuminuria to lisinopril, nifedipine or placebo. Both antihypertensives effectively prevented progression to macroalbuminuria over 3 years. Ten patients discontinued the study before completion.

Patient Group	n	Number progressing to AER > 200 mcg/min
Placebo	34	7
Lisinopril*	32	2
Nifedipine*	26	2

*p < 0.02

However, this study was not controlled for BP, which was significantly lower in the lisinopril group; AER increase was also less in the lisinopril group.

Type 2 diabetes mellitus

In the meta-analysis of Kasiske et al (1993) discussed above, there was no difference in benefit of antihypertensive treatment between Type 1 and Type 2 diabetes*.

Studies of antihypertensive therapy in Type 2 diabetes show effective protection against the endpoints of proteinuria and/or loss of GFR. The most significant reductions in albuminuria occurred in studies with the largest BP reductions. (Bjorck 1997; Ferder et al 1992) (see CARI 'Angiotensin II antagonists' guideline).

Bjorck (1997) used an endpoint of loss of 40% of initial GFR to examine the effect of diastolic blood pressure (DBP) in 158 patients: those with DBP less than 86 mmHg had a 5-year incidence of nephropathy development of 20%, compared with 60% incidence if DBP was above 85 mmHg.

Biesenbach et al (1994) documented more rapid decline in GFR in hypertensive Type 2 diabetes (SBP > 160 mmHg). This study followed a cohort of 16 Type 1 and 16 Type 2 diabetics with overt nephropathy, from near-normal renal function to end-stage kidney disease (ESKD), over 77 months (44–133 months). The mean rate of creatinine clearance decrease was 1.38 ± 0.40 mL/min/month in patients with SBP > 160 mmHg, and 0.78 ± 0.15 mL/min/month in patients with SBP < 160 mmHg.

The meta-analyses of Weidmann et al (1993, 1995), see CARI 'ACE inhibitor treatment in diabetic nephropathy' guideline) further support the importance of adequate antihypertensive management for both Type 1 and Type 2 diabetics.

The United Kingdom Prospective Diabetes Study (UKPDS) provided strong evidence that control of BP can reduce the development of nephropathy.

Goal BP in antihypertensive treatment in diabetes

Evidence that lower BP provides better protection against cardiovascular endpoints aligns very well with protection against diabetic nephropathy. Actual BP targets are better defined for cardiovascular than for renal endpoints.

Summary of the evidence

Bjorck (1997) documented significantly fewer renal endpoints when DBP was < 85 mmHg.

The meta-analyses of Kasiske et al (1993) and Weidmann et al (1993) also support renal functional benefit from lower BP.

Lewis et al (1999) in the extension of the captopril study of Type 1 diabetics, randomised participants to either intensive (MAP \leq 92 mmHg) or standard (MAP 102–107 mmHg) antihypertensive treatment with ramipril and showed a better outcome (endpoints were proteinuria and GFR) in the intensively-treated group.

Schmitz et al (1994) followed a cohort of 278 Type 2 diabetics for 6 years. Initially, 74% had normal AER, 19% had microalbuminuria and 7% had overt proteinuria. A total of 80 patients died over the time of follow-up; older age and higher albuminuria levels were risk factors for mortality. Multiple regression analysis identified SBP as a risk factor for increase in albuminuria. In a previous report of a subgroup of 24 normoalbuminuric and 13 microalbuminuric patients (Nielsen et al 1993), initial SBP was identified as a significant correlate of GFR fall rate over 3.4 years.

The Appropriate Blood Pressure Control in Diabetes (ABCD) study (Estacio et al 2000) randomised 470 hypertensive Type 2 diabetics to intensive (goal DBP < 75 mmHg, achieved BP 132/78) vs. standard BP control (goal DBP 80–89 mmHg, achieved BP 138/86), with second randomisation to either enalapril or nifedipine. They followed incidence and progression of diabetic complications over 5.3 years. In both groups, patients with normo- or micro-albuminuria stabilized their renal function, but those with overt nephropathy showed steady decline in GFR. The most important finding in this study was that mortality was significantly less in the intensively-treated group (5.5% vs 10.7%, $P = 0.037$).

The data dovetails with evidence that cardiovascular endpoints in diabetic patients are reduced when diastolic BP is lower (e.g. the diabetic subgroup in the HOT Study had fewer CV events when DBP was reduced from 85–81 mmHg).

Bakris et al (2003) performed multivariate analysis on data from the RENAAL Study (Brenner et al 2001) to document in Type 2 diabetics with nephropathy, that baseline SBP is a stronger predictor of renal outcomes than is DBP. Goal BP in this study was < 140/90 mmHg pre-dose. Patients with highest baseline pulse pressure had both the highest risk of progression and the greatest risk reduction when SBP was lowered below 140 mmHg. Losartan patients with baseline pulse pressure > 90 mmHg had a 54% risk reduction of ESKD compared with placebo patients, over the 3.4 year mean follow-up.

In older non-diabetic patients with hypertension, a J-curve effect has been detected i.e. excessive lowering of DBP increases risk of coronary events, presumably by decreasing coronary perfusion pressure (JNC-VI 1997). To date, clinical trials in hypertensive diabetics have not detected a J-curve effect for BP reduction.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: Target BP in diabetic kidney disease should be < 130/80 mmHg. Preferred agents are ACE inhibitors or ARBs.

Canadian Diabetes Association (2003):
<130/80 mmHg.

UK Renal Association: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

JNC VI (1997)

Target blood pressure for diabetics with hypertension (and for any patient with renal impairment and hypertension) is 130/85 mmHg. In hypertensives with proteinuria > 1g/day, recommend goal BP 125/75 mmHg.

JNC VII (2003): In patients with hypertension and diabetes or renal disease, BP goal is < 130/80 mm Hg. Most patients will require 2 or more antihypertensive drugs to achieve goal BP. Lifestyle modifications recommended for all patients.

National Heart Lung & Blood Institute Working Party on Hypertension in Diabetes (1998): Goal BP 130/85 mmHg.

WHO-ISH (1999)

Hypertensive diabetics – aim for < 130/85 mmHg.

American Diabetes Association (2004)

Hypertensive adult diabetics – aim for SBP < 130 and DBP < 80 (B). Drug therapy in addition to lifestyle/behavioral modification is required if BP is 140/90 or above (A). Two or more drugs are usually required to achieve targets (B). Initial drug should be a drug class demonstrated to reduce CVD events in diabetes (ACEI, ARBs, β -blockers, diuretics, CCBs (A). If albuminuria is present, ACEI for Type 1 and either ACEI or ARB for Type 2 are supported by evidence (A), acknowledging that there are no adequate head-to-head comparisons of ACEIs and ARBs.

Children – aim at or below age-adjusted 90th percentile levels.

In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications. (E)

NHF (1999)

Hypertensive diabetics – aim < 130/85 mmHg.

Australian Diabetes Society Position Statement 1996 – aim <130/85 mmHg.

Australian Diabetes Association (2001)

Hypertensive diabetics with urinary protein above 1 g/day should aim for BP < 125/75 mmHg. Uncomplicated diabetics – aim < 130/85 mmHg.

Scottish Intercollegiate Guideline Network (2001)

Target BP in all diabetics < 140/80 mmHg.

ACE (2000)

< 130/85 mmHg.

APEG (2005)

Target BP < 95th centile for age, gender and height normative data.

Implementation and audit

No recommendation.

Suggestions for future research

Optimal BP targets need to be refined for subgroups of patients, especially the elderly with isolated systolic hypertension and diabetes.

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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 (months)	Comments
Bakris et al. 2003	1513	Randomised controlled clinical trial	Multicentre	1531 patients with NIDDM*	Losartan potassium	Placebo	3.4 yrs	
Crepaldi et al. 1998	137	Randomised controlled clinical trial	14 hospital based and diabetes outpatient centres	92 normotensive IDDM [†] -patients	Lisinopril	Placebo	3 yrs	With third arm intervention of slow release nifedipine
Estacio et al. 2000	470	Randomised controlled clinical trial	Identified from health care systems in Denver US	470 hypertensive patients	Intensive blood pressure control (75 mmHg)	Moderate blood pressure control (80–90 mmHg)	5.3 yrs	
Ferder et al. 1992	30	Randomised controlled clinical trial	Hospital	30 Type 2 diabetic patients with proteinuria	Enalapril	Nifedipine	12 mo	
Lewis et al. 1999	129	Randomised controlled clinical trial	17 centres of the Collaborative Study Group	129 Type 1 diabetes mellitus patients	≤ 94 mmHg	100–107 mmHg	2 yrs	

*NIDDM = non-insulin dependent diabetes mellitus; [†]IDDM = insulin dependent diabetes mellitus

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)		
Bakris et al. 2003	Not specified	Yes	Yes	Unclear	Yes	Unclear
Crepaldi et al. 1998	Balanced blocks	Yes	Yes	Unclear	No	10.9
Estacio et al. 2000	Not specified	No	No	Yes	Unclear	39.4
Ferder et al. 1992	Not specified	Yes	Yes	Unclear	Unclear	0.0
Lewis et al. 1999	Standard urn design	No	No	Unclear	Yes	28.7

Table 3 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]
Crepaldi et al. 1998	Albuminuria (lisinopril)	2/32	7/34	0.30 (95%CI: 0.07, 1.35)	-0.14 (95%CI: -0.30, 0.02)
	Albuminuria (nifedipine)	2/26	7/34	0.37 (95%CI: 0.08, 1.65)	-0.13 (95%CI: -0.30, 0.04)
Estacio et al. 2000	Retinopathy ≥ 3 steps	45/151	45/134	0.89 (95%CI: 0.63, 1.25)	-0.04 (95%CI: -0.15, 0.07)
	Neuropathy	60/151	42/134	1.27 (95%CI: 0.92, 1.74)	0.08 (95%CI: -0.03, 0.19)
Lewis et al 1999	Remission of proteinuria	12/43	5/46	2.57 (95%CI: 0.99, 6.68)	0.17 (95%CI: 0.01, 0.33)
	Postural hypotension	11/63	4/66	2.88 (95%CI: 0.97, 8.58)	0.11 (95%CI: 0.00, 0.22)
	Oedema	4/63	10/66	0.42 (95%CI: 0.14, 1.27)	-0.09 (95%CI: -0.19, 0.02)
	Bronchitis	2/63	7/66	0.30 (95%CI: 0.06, 1.39)	-0.07 (95%CI: -0.16, 0.01)
	Sinusitis	3/63	3/66	1.05 (95%CI: 0.22, 5.00)	0.00 (95%CI: -0.07, 0.07)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Crepaldi et al. 1998	Lisinopril treatment group:			
	Serum creatinine at end of study (µmol/L)	77 (16)	95 (19)	-18.00 (95%CI: -26.46, -9.54)
	Creatinine clearances (m/mL/1.73m ²)	109 (19)	105 (15)	4.00 (95%CI: -4.29, 12.29)
	Serum potassium (mmol/L)	4.5 (0.4)	4.4 (0.4)	0.10 (95%CI: -0.09, 0.29)
	Albumin (g/dL)	4.3 (0.3)	4.4 (0.3)	-39.70 (95%CI: -39.84, -39.56)
	SBP (mmHg)	117 (11)	126 (12)	-9.00 (95%CI: -14.55, -3.45)
	DBP (mmHg)	73 (7)	76 (7)	-3.00 (95%CI: -6.38, 0.38)
	Nifedipine treatment group:			
	Serum creatinine at end of study (µmol/L)	86 (10)	95 (19)	-9.00 (95%CI: -15.97, -2.03)
	Creatinine clearances (m/mL/1.73m ²)	101 (15)	105 (15)	-4.00 (95%CI: -10.56, 2.56)
Ferder et al. 1992	Serum potassium (mmol/L)	4.4 (0.3)	4.4 (0.4)	0.00 (95%CI: -0.16, 0.16)
	Albumin (g/dL)	4.2 (0.4)	4.4 (0.3)	-0.20 (95%CI: -0.35, -0.05)
	SBP (mmHg)	129 (15)	126 (12)	3.00 (95%CI: -2.82, 8.82)
	DBP (mmHg)	79 (7)	76 (7)	3.00 (95%CI: -0.06, 6.06)
	24hr proteinuria (g/d)	0.56 (0.78)	2.66 (0.89)	-2.10 (95%CI: -2.72, -1.48)
	Creatinine clearance (mL/min)	66.6 (13.8)	51.4 (7.9)	15.20 (95%CI: 7.41, 22.99)
	BP (mmHg)	82 (8.3)	86 (7)	-4.00 (95%CI: -9.51, 1.51)
	Serum potassium	5.0 (0.4)	3.8 (1.3)	1.20 (95%CI: 0.44, 1.96)