Blood Pressure Control – Targets

Date written: May 2005
Final submission: October 2005
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GUIDELINES

a.   **Lower systolic blood pressure (SBP) minimizes the risk of progression to end-stage kidney disease (ESKD), especially with proteinuria. (Level II evidence)**

b.   **A target blood pressure (BP) of < 125/75 mmHg (or mean BP < 92 mmHg) if proteinuria > 1gm/24 hours, may be beneficial. (Level II evidence)**

c.   **A target BP of < 130/80 mmHg (or mean BP < 97 mmHg) if proteinuria is 0.25 – 1g/24 h, may be beneficial. (Level II evidence)**

d.   **Target BP should be < 130/85 mmHg (or mean BP < 100 mmHg) if proteinuria < 0.25 g/24 hours. (Level II evidence) However, there may be other potential benefits of achieving lower BP than a mean of 100 mmHg with respect to reduced cardiovascular risk.**

There is no evidence concerning Target BP for paediatric patients with progressive kidney disease.

SUGGESTIONS FOR CLINICAL CARE
(Suggestions based on level III and IV evidence)

- **There is evidence for a lower BP target with greater degrees of proteinuria (> 1 g/day). A precise goal below 130/80 mmHg is not clear. These patients should be carefully monitored.**

Background

Most forms of chronic kidney disease (CKD) are associated with hypertension. Uncontrolled hypertension not only increases the risk of serious cardiovascular morbidity or mortality but is also associated with a more rapid progression of CKD. Studies have suggested that a lower BP target is more beneficial for progression of CKD than to reduce cardiovascular disease risk. The objective of this set of guidelines is to evaluate the evidence of differing BP targets for differing severity/cause of CKD in preventing progression.

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?

REIN-2 Study (Ruggenenti et al): This was a multicentre randomised controlled trial (RCT) assessing blood-pressure control for renoprotection in 338 patients with non-diabetic CKD. Participants were randomly allocated to conventional (diastolic < 90 mmHg) or intensified (130/80 mmHg) blood pressure control. Patients with a BP target of 130/80 mmHg by addition of felosipine had the same rate of kidney failure progression as patients with higher BP target on ramipril. A total of 38 of 167 patients in the intensified BP control group and 34 of 168 patients allocated to the control group progressed to ESKD. However, follow up was only 36 months.

MDRD Study (1996): A total of 840 patients enrolled in 2 studies. Study 1 (n = 585): GFR 25-55 mL/min/1.73 m^2 BSA, Study 2 (n = 255): GFR 13-24 mL/min/1.73 m^2 BSA, with 2 interventions (a) usual protein diet or low protein diet (1.3 or 0.58 g/kg/d) and (b) usual or low BP group (MAP 107 or 92 mmHg). At baseline: serum creatinine 106-619 µmol/L for females or 124-619 µmol/L for men, age 18-70 yrs, excluded if < 80% or > 160% of standard body weight, diabetic on insulin, > 10 g/d proteinuria or renal transplant. Primary outcome was rate of change of GFR ([125]Iothalamate clearance). The mean follow up was 2.2 yrs. 60% men, 85% white, average age 52 yrs, 25% glomerular disease, 24% ADPKD, 3% NIDDM. Results showed no significant overall benefit of low protein diet or low blood pressure interventions over the full course of the study. However, secondary analyses showed benefit of lower blood pressure after a more rapid phase of decline in GFR in the first 4 months with both studies. The average rate of decline in GFR was 3.3mL/min/year in all groups combined. It was a mean 29% lower in the low BP group than the usual BP group. GFR declined more rapidly in patients with a higher degree of proteinuria, in those with ADPKD and in blacks. The benefit of low blood pressure was greatest with > 3 g/day proteinuria, of moderate benefit with 1-3 g/day and there was no benefit if proteinuria was < 1 g/day. This study was not designed to show which antihypertensive agent effected renal function decline. A mean BP of 92 mmHg or less was safe and well tolerated up to the 3 years duration of the study. (Leve II evidence)

Observational studies and clinical trials of dietary protein restriction (Marcantoni et al 2000, Brazy et al 1989, 86 patients with mean diastolic BP < 90 mmHg had a slower rate of decline in 1/serum creatinine. Oldrizzi et al (1990) enrolled 423 patients in a long-term low-protein diet study. Survival at 10 years 96% with mean BP < 100 mmHg, 74% with mean BP <100-110 mmHg and 48% with mean BP >110 mmHg.

Northern Italian Cooperative Study, showed 456 patients low protein diet, worst renal survival with mean BP >107 mmHg. (Level III evidence)

He and Whelton (1999) performed a meta-analysis which showed systolic BP greater risk for ESKD than was diastolic BP. (Level II evidence)

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 (3x2 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 an open label study. Outcomes were GFR slope alone or GFR slope combined with reduction in GFR by 50% or more, ESRD or death. The lower blood pressure group achieved a mean BP of 128/78 mmHg, which was 12/8 mmHg lower than the other BP group (mean achieved BP 141/85 mmHg). There was no significant outcome difference between groups. The ramipril group manifested risk reductions in the clinical composite outcome of 22% (95% CI: 1-38%, p=0.04) compared with the metoprolol group and 38% (95%CI: 14–56%, p=0.004) compared with the amlodipine group. (Level II evidence)

There was no evidence from AASK to support a target BP that is lower than current treatment guidelines for cardiovascular disease. This may be peculiar to African-Americans or to the underlying disease of hypertensive nephro-sclerosis and not be true for other kidney diseases.

Summary of the evidence

A meta-analysis has shown that lowering SBP is associated with slowing progression to ESKD. Results from an RCT suggest a target BP of < 125/75 mmHg if proteinuria < 1 g/24 h and a target BP of < 130/80 mmHg if proteinuria is 0.25–1 g/24 h.

What do the other guidelines say?

JNC VI: Recommends mean BP 100 mmHg (130/85 mmHg) in patients with chronic renal disease. If < 0.25g/d of proteinuria, no benefit of a lower BP than above. JNC VII recommends less than 130/80 in patients with CKD and proteinuria (> 300 mg/d).

Hypertension Management for Doctors (2004). NHF of Australia: Goal is < 130/85 mmHg with chronic renal disease or < 125/75 mmHg if >1 g/day of proteinuria.

Kidney Disease Outcomes Quality Initiative: Target BP in non-diabetic kidney disease should be < 130/80 mmHg.

Table 111. Hypertension and Antihypertensive Agents in Nondiabetic Kidney Disease

Clinical Assessment	Target Blood Pressure		Preferred Agents for CKD		Additional Agents to Reduce CVD Risk and Reach Target Blood Pressure	
Blood pressure ≥130/80 mm Hg and spot urine total protein-to-creatinine ratio ≥200 mg/g	<130/80 mm Hg	A	ACE inhibitor or ARB	A	Diuretic preferred, then beta-blocker or calcium-channel blocker	A
Blood pressure ≥130/80 mm Hg and spot urine total protein-to-creatinine ratio <200 mg/g	<130/80 mm Hg	B	None preferred		Diuretic preferred, then ACE inhibitor, ARB, beta-blocker or calcium-channel blocker	A
Blood pressure <130/80 mm Hg and spot urine total protein-to-creatinine ratio ≥200 mg/g			ACE inhibitor or ARB	C	Diuretic preferred, then beta-blocker or calcium-channel blocker	A
Blood pressure <130/80 mm Hg and spot urine total protein-to-creatinine ratio <200 mg/g			None preferred			

Letters in shaded areas represent strength of recommendations.

Scource: NKF K/DOQI Guidelines, 2002.

UK Renal Association: The previous edition of this document suggested a higher standard, 160/90 mmHg, for patients over 60 years of age than for younger patients (140/90 mmHg). In the general population, systolic hypertension is more common in the elderly, probably due to decreased large vessel compliance. Recent studies have shown that increased pulse pressure, a result of decreased conduit artery compliance, is a much more powerful risk factor for death in the general population than systolic or diastolic blood pressure. It has been shown recently that the absolute benefits of blood pressure reduction are greater in the elderly than in younger patients, due to the former having higher baseline risk, and that isolated systolic hypertension or combined systolic and diastolic hypertension in patients up to the age of 80 can be safely treated with good results. However, many of the elderly patients in these trials had marked systolic hypertension, and the question of whether there is benefit from reducing systolic blood pressure from 160 mmHg to, say, 130 mmHg, has not been specifically examined in this patient group, or even in the general population. Setting a more liberal standard for blood pressure in the elderly risks giving the message that control of hypertension is less important in these patients, when the reverse is probably the case. For these reasons, the targets set here are independent of age.

Canadian Society of Nephrology: No recommendations

European Best Practice Guidelines: No recommendations

INTERNATIONAL GUIDELINES:

VA Primary Care Guidelines: In patients with chronic kidney disease….. Vigorous control of hypertension reduces the glomerular capillary pressure and slows the progression of glomerulosclerosis. The goal blood pressure should be < 125/75 or mean arterial pressure less then 92 for patients with proteinuria and 130/85 in patients without proteinuria. ACEI or ARB is the preferred antihypertensive agents (Pitt B 1997)."

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

Out of date

References

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APENDICES

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
MDRD Study, 1996	840	Two randomised two-by-two factorial clinical controlled trials	Multicentre	840 patients with various chronic renal diseases	Restriction of dietary protein and phosphorus; reducing blood pressure to below usual recommended level (MAP* 92 mmHg)	Blood pressure (MAP 107 mmHg)	2.2	Study A compared usual vs low-protein. Study B compared low protein vs very low protein. Both compared usual vs low MAP.
Ruggenenti et al, 2005	338	Randomised controlled clinical trial	Multicentre	228 non-diabetic patients with proteinuric nephropathy	Intensified blood pressure control (<130/80 mmHg)	Conventional blood pressure control (diastolic < 90 mmHg)	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)

*MAP = mean arterial pressure

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)		
MDRD Study, 1996	Not specified	No	No	No	Yes	1.7
Ruggenenti et al, 2005	Central	No	No	No	Yes	1.8
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]
MDRD Study, 1996	Rate of change in GFR at 4 mo in study A (mL/min/month)	-0.32 (0.3)	-0.23 (0.3)	0.09 (95%CI: 0.04, 0.14)
Ruggenenti et al, 2005	Mean SBP (mmHg)	129.6 (10.9)	133.7 (12.6)	-4.10 (95%CI: -6.62, -1.58)
	Mean DBP (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/1.73 m^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]
Ruggenenti et al, 2005	Death	2/169	3/169	0.67 (95%CI: 0.11, 3.96)	-0.01 (95%CI: -0.03, 0.02)
	ESKD	34/169	38/169	0.90 (95%CI: 0.60, 1.36)	-0.02 (95%CI: -0.11, 0.07)