X. Treatment of Hypertension in Association With Nondiabetic Chronic Kidney Disease

PREVENTION AND TREATMENT

Previous Next

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Recommendations

1. For patients with nondiabetic chronic kidney disease , target BP is <140/90 mmHg (Grade B).
2. For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor (Grade A) or an ARB if there is intolerance to ACE inhibitors (Grade B).
3. Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy (Grade D). For patients with chronic kidney disease and volume overload, loop diuretics are an alternative (Grade D).
4. In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels (Grade D).
5. The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease (Grade B).

Background

1. For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg (Grade B).

Results of three randomized controlled trials (RCTs) primarily underpin the evidence for the treatment of hypertensive patients with nondiabetic CKD. The MDRD trial included patients with a glomerular filtration rate (GFR) between 13 and 55 mL per minute per 1.73m2, who were randomly assigned to either a usual BP target (mean arterial pressure [MAP], 107 mm Hg, equivalent to 140/90 mm Hg) or a low BP target (MAP, 92 mm Hg, equivalent to 125/75 mm Hg) (1–3). In the primary analysis, there was no difference between the usual and low BP groups with respect to slope of decline in the GFR. Secondary outcomes including kidney failure, death, a composite of kidney failure or death, and cardiovascular events were also not significantly different between groups.

A post hoc subgroup analysis showed rate of GFR decline appeared to increase above a MAP of 98 mm Hg in patients with proteinuria between 0.25–3.0 gr/day, while in patients with proteinuria of ≥ 3.0 gr/day, rate of GFR decline increased above a MAP of 92 mm Hg. However, this post hoc analysis was limited by the fact there was no stratification based on pre-specified levels of proteinuria, a priori power calculations were not performed for subgroups, baseline patient characteristics were not presented according to subgroups, and adjustment for multiple testing was not performed. Furthermore, use of angiotensin-converting enzyme (ACE) inhibitors was higher in the low BP target group.

In the AASK trial, African-American individuals with hypertensive CKD and GFR between 20 and 65 mL per minute per 1.73m2 were randomly assigned to a usual BP target (MAP, 102–107 mm Hg) or a low BP target (MAP, 92 mm Hg) (4–6). In addition, patients were randomly assigned to treatment with ramipril, metoprolol, or amlodipine in a 2 x 3 factorial design. There was no significant difference in the chronic slope or the overall rate of decline in GFR per year between groups. Patients in the low BP group experienced a 17% reduction in proteinuria as compared with an increase of 7% in the usual BP group.

There was no difference in risk of other secondary outcomes including kidney failure, composite of kidney failure or death, composite of a GFR event or death, or combined endpoint of GFR event, kidney failure, or death. Additionally, no difference in cardiovascular mortality or nonfatal cardiovascular events was shown. In the original AASK trial there was an interaction between baseline proteinuria and BP target, which was not reported in the original analysis but in a subsequent analysis. Similar to the MDRD trial, this analysis was a post hoc sub-group one, and randomization was not stratified based on pre-specified levels of proteinuria, there were no a priori power calculations for the subgroups, and adjustment for multiple testing was not performed. The suggestion patients with proteinuria of > 300 mg per day at baseline may derive benefit from a lower BP target, and that those patients with less proteinuria may experience worse outcomes, should be interpreted as hypothesis-generating.

The REIN-2 trial randomly assigned patients with nondiabetic CKD and > 1 gr/day of proteinuria to usual BP target (target DBP < 90 mm Hg) or low BP target (target BP < 130/80 mm Hg) (7). All patients were treated with ramipril, and the low BP group received felodipine 5–10 mg/day together with additional agents as needed to achieve targets. The trial was stopped early due to futility after a median follow-up of 19 months; this follow-up was defined a priori. Mean achieved BP was 134/82 mm Hg in the usual BP group compared with 130/80 mm Hg in the low BP group. There was no difference in risk of progression to kidney failure between groups (adjusted HR, 1.0; 95%CI, 0.61–1.64). Significant limitations of this study included use of dihydropyridine CCBs in the low BP group, the small difference in achieved BP (4/2 mm Hg) between groups, limited follow-up, as well as the fact all patients received therapy with a fixed dose of an ACE inhibitor.

Overall, there is no compelling evidence to support a low BP target of < 130/80 mm Hg in **all** patients with hypertension and nondiabetic CKD. Therefore, the general BP target (< 140/90 mm Hg) is recommended for many patients with CKD and hypertension. However, the results of the SPRINT study suggest that high-risk patients with CKD may benefit from intensive BP lowering (see Global Vascular Protection Section). Please refer to this section for further detail.

2. For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 mg per 24 hours or albumin to creatinine ratio (ACR) >30 mg/mmol), initial therapy should be an ACE inhibitor (Grade A) or an ARB if there is intolerance to ACE inhibitors (Grade B).

It is well established that elevated levels of urinary protein are associated with progressive decline in renal function (13). ACE inhibitors are recommended as initial therapy for patients with urinary protein excretion greater than 0.5 g/day (or an ACR > 30 mg/mmol) rather than for all individuals with nondiabetic CKD. This distinction was made based on evidence demonstrating the response to ACE inhibition is modified by baseline urinary protein excretion (BUPE). Jafar et al. (14) evaluated the response to ACE inhibitors according to baseline urinary protein excretion levels in an individual-level meta-analysis of 11 randomized controlled trials involving 1860 nondiabetic patients with CKD. ACE inhibitors conferred progressively greater benefits in reducing risk of developing end stage renal disease (ESRD) with increasing levels of urinary protein excretion beginning at a threshold of approximately 0.5 g/day. Whether benefits of ACE inhibition extend below this threshold is unknown given the paucity of ACE inhibitor studies evaluating patients with lower urinary protein excretion rates, and the imprecision of urinary protein measurements at these lower levels.

The evidence supporting ARBs as an alternative to ACE inhibitors, is derived from patients with baseline urinary protein excretion greater than 0.5 g/day (15). Patients who are initiated on ACE inhibitor or ARB should have their serum creatinine and potassium levels monitored carefully, preferably within the first 2 weeks of therapy (16). These agents may be continued as long as serum creatinine levels do not rise by more than 30% from baseline, because acute increases generally plateau within two months (16).

The ONTARGET study investigators conducted a pre-specified analysis of a composite renal endpoint of dialysis, doubling of serum creatinine or death (17). Approximately 20% of the ONTARGET population had CKD with an estimated GFR (eGFR) of 60 mL/min/1.73 m2 or lower at baseline. However, it is uncertain what proportion of these patients had nondiabetic CKD. Risk of the composite renal endpoint was similar in the telmisartan (13.4%) and ramipril (14.5%) groups (HR, 1.00; 95%CI, 0.92 to 1.09). These results were consistent across subgroups of patients with and without diabetic nephropathy, micro- and macro-albuminuria, and patients with an eGFR of 60 mL/min/1.73 m2 or lower.

For patients with nondiabetic CKD but normal or low urinary protein excretion, physicians should select initial therapy from first-line agents for patients with systolic and/or diastolic hypertension without compelling indications (Additional references 18–25).

3. Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy (Grade D). For patients with chronic kidney disease and volume overload, loop diuretics are an alternative (Grade D).

This is an expert consensus recommendation based on the synergistic action of ACE inhibitor/ARB classes with thiazide/thiazide-like combinations.

4. In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels (Grade D).

This recommendation is based on expert consensus.

5. The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease (Grade B).

Dual renin-angiotensin system (RAS) inhibition has been shown to reduce significantly proteinuria (27), a surrogate endpoint for cardiovascular disease, and renal impairment in patients with CKD. The Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial (28) found a reduced risk of dialysis with combination therapy compared with monotherapy; however, serious inconsistencies among the data since publication have raised concerns about the validity of the results.

The ONTARGET study (17) similarly found greater BP reduction and reduced proteinuria with combination therapy. However, likely through a mechanism independent of proteinuria, full doses of combination therapy were associated with an increased risk of doubling of serum creatinine, dialysis or death compared with ramipril monotherapy. Thus, CHEP recommends this combination should not be used in patients with nonproteinuric CKD.

Care providers should refer to the Canadian Society of Nephrology practice guidelines for managing hypertension in dialysis patients (31). The CHEP RTF is actively working with the Canadian Society of Nephrology to develop future recommendations for these patient populations.

References

1. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood- pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994;330:877-84.
2. Sarnak MJ, Greene T, Wang X, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease study. *Ann Intern Med* 2005;142:342-51.
3. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 1995;123:754-62.
4. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002;288:2421-31.
5. Norris K, Bourgoigne J, Gassman J, et al. Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial. *Am J Kidney Dis* 2006;48:739-51.
6. Appel LJ, Wright JT Jr., Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;363:918-29.
7. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005;365:939-46.
8. Remuzzi G, Ruggenenti P, Benigni A. Understanding the nature of renal disease progression. *Kidney Int* 1997;51:2-15.
9. Brazy PC, Stead WW, Fitzwilliam JF. Progression of renal insufficiency: role of blood pressure. *Kidney Int* 1989;35:670-4.
10. Kes P. Ratkovic-Gusic I. The role of arterial hypertension in progression of renal failure. *Kidney Int* 1996;49 (suppl 55):S72-S74.
11. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 1994;330:877-84.
12. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, et al. Blood pressure control, proteinuria and the progression of renal disease. The modification of diet in renal disease study. *Ann Intern Med* 1995;123:754-62.
13. Remuzzi G, Chiurchiu C, Ruggenenti P. Proteinuria predicting outcome in renal disease: Nondiabetic nephropathies (REIN). *Kidney Int* Suppl 2004;92:S90-6.
14. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 2001;135:73-87. (Erratum in 2002;137:299).
15. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. *Lancet* 2003;361:117-24. (Erratum in 2003;361:1230).
16. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? *Arch Intern Med* 2000;160:685-693.
17. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;372:547-53.
18. Maschio G, Alberti D, Janin G, Locatelli F, Mann JFE, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996;334:939-45.

19. Locatelli F, Carbarns IRI, Machio G, Mann JFE, Ponticelli C, Ritz E, et al. Long-term progression of chronic renal insufficiency in the AIPRI extension study. *Kidney Int* 1997;52(suppl 63):S63-S66.
20. The GISEN Group. Randomized placebo-controlled trial of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997;349:1857-63.
21. Hannedouche T, Landais P, Goldfarb B, El Esper N, Fournier A, Godin M, et al. Randomised controlled trial of enalapril and beta-blockers is non-diabetic chronic renal failure. *BMJ* 1994;309:833-7.
22. Toto RD, Mitchell HC, Smith RD, Le HC, McIntire D, Pettinger WA. “Strict” blood pressure control and the progression of renal disease in hypertensive nephrosclerosis. *Kidney Int* 1995;48:851-9.
23. Burgess E. Conservative treatment to slow deterioration of renal function: evidence-based recommendations. *Kidney Int* 1999;55(suppl 70):S17-S25.
24. Ruggenenti P, Perna A, Gherdi G, Benini R, Remuzzi G, on behalf of the Gruppo Itiliano di Studi Epidemiologici in Nephrologia (GISEN). Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 1998;352:1252-6.
25. Zucchelli P, Zuccala A, Borghi M, Fusaroli M, Sasdelli M, Stallone C, et al. Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int* 1992;42:452-8.
26. Bianchi S, Bigazzi R, Baldari G, Campese VM. Long-term effects of enalapril and nicardipine on urinary albumin excretion in patients with chronic renal insufficiency: a 1-year follow-up. *Am J Nephrol* 1991;11:131-7.
27. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: Effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008;148:30-48.
28. Kunz R, Wolbers M, Glass T, Mann JF. The COOPERATE trial: A letter of concern. *Lancet* 2008;371:1575-6.
29. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. US Renal Data System, USRDS 2000 Annual Data Report. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2000. <http://www.usrds.org/atlas_2000.htm> (Version current at September 12, 2003).
30. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32:S112-S119.
31. Jindal K, Chan CT, Deziel C, et al. Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. *J Am Soc Nephrol* 2006;17:S1-27.