

An Editorial Update: What Level of Blood Pressure Control in Chronic Kidney Disease?

Chronic kidney disease affects about 11% of adults in the United States (1). Hypertension causes about 20% of new cases of kidney failure and complicates 60% to 80% of cases of chronic kidney disease caused by other disorders (2). Irrespective of the cause of chronic kidney disease, hypertension increases the risk for important adverse outcomes, such as progressive loss of kidney function and kidney failure, early development and accelerated progression of cardiovascular disease, and premature death. Angiotensin-converting enzyme (ACE) inhibitors are recommended in chronic kidney disease because in addition to lowering blood pressure, they reduce proteinuria, slow the decline of glomerular filtration rate, and delay the onset of kidney failure (3). However, we do not know the optimal level of blood pressure for slowing the progression of kidney disease. In March 2005, we published follow-up data from the Modification of Diet in Renal Disease (MDRD) Study that showed the long-term benefits of 2 years of a lower-than-usual blood pressure in nondiabetic kidney disease (4). At the same time, the Ramipril Efficacy in Nephropathy 2 (REIN-2) Trial suggested no benefit of lower blood pressure in nondiabetic kidney disease (5). The only other randomized, controlled trial of lower blood pressure in nondiabetic kidney disease was the African-American Study of Kidney Disease and Hypertension (AASK), published in 2002, which also showed no benefit (6). Here's our take on the REIN-2 Trial results and how they compare with the other 2 trials.

WHAT DID THIS IMPORTANT TRIAL SHOW?

The REIN-2 Trial, a multicenter, randomized, controlled, nonblinded superiority trial, included patients with nondiabetic kidney disease, proteinuria, and decreased glomerular filtration rate (Table). Participants were randomly assigned to either a lower or usual blood pressure goal and received the ACE inhibitor ramipril (2.5 to 5 mg/d). Those assigned to the lower blood pressure group also received the dihydropyridine calcium-channel blocker felodipine (5 to 10 mg/d). About 60% of patients in both groups received other antihypertensive agents, such as diuretics, sympatholytic drugs, or β -blockers, that were titrated as necessary to achieve and maintain blood pressure goals. The primary outcome was development of kidney failure, defined as initiation of dialysis or transplantation. After 388 patients were enrolled and followed for a median of 1.6 years, an independent adjudicating panel terminated the study for "futility," because interim analyses suggested differences less than 25% between groups in progression to kidney failure. Blood pressure levels during the trial in the lower and usual blood pressure groups were 130/80 mm

Hg and 134/82 mm Hg, respectively. About one fifth of the patients in both groups developed kidney failure (relative hazard, 1.00 [95% CI, 0.61 to 1.64]). Decline in glomerular filtration rate, assessed in approximately one half of patients, and urinary protein excretion were similar in both groups. Approximately 22% and 15% of patients in the lower and usual blood pressure control groups, respectively, had nonfatal serious adverse events.

HOW DOES THE REIN-2 TRIAL COMPARE WITH THE OTHER TWO TRIALS ON THIS TOPIC?

The REIN-2 Trial showed that adding felodipine, an agent that does not directly inhibit the renin-angiotensin system, to ramipril and other antihypertensive agents can reduce blood pressure, but probably does not have a large effect in slowing the progression of kidney disease during short-term follow-up. In the MDRD Study, the lower blood pressure was achieved primarily with an ACE inhibitor, a nondihydropyridine calcium-channel blocker, and a diuretic. During short-term follow-up, lower blood pressure slowed the decline in glomerular filtration rate in the subgroup of patients with higher levels of baseline urine protein (7); during long-term follow-up, lower blood pressure slowed the onset of kidney failure and the combined outcome of kidney failure or death in the entire group (4). In AASK, patients were randomly assigned to antihypertensive agents (an ACE inhibitor, a dihydropyridine calcium-channel blocker, or a β -blocker) as well as blood pressure goals using a 3×2 factorial design (7). The ACE inhibitor, but not the lower blood pressure, slowed the decline in glomerular filtration rate.

The REIN-2 Trial, AASK, and the MDRD Study were designed to evaluate the effect of lower blood pressure on kidney disease, not cardiovascular disease. Reasons for the varied outcomes are not entirely clear, but may involve differences in levels of proteinuria, antihypertensive agents, and duration of follow-up (Table). First, the effect of lower blood pressure may be more important in patients with higher levels of baseline proteinuria. A recent meta-analysis of ACE inhibitor trials showed that a lower systolic blood pressure (110 to 129 mm Hg) was associated with lower risk for kidney disease progression in patients with high levels of proteinuria (>1000 mg/d), but not in those with lower levels (8). This could explain the greater effect observed in the MDRD Study compared with AASK but not with the REIN-2 Trial. Second, in the MDRD Study, ACE inhibitors were used more frequently in the lower blood pressure group (51%) than in the usual blood pressure group (32%). However, this difference is probably too small to account for the beneficial effects of the lower

Table. Comparison of Clinical Trials of Level of Blood Pressure Control in Nondiabetic Kidney Disease*

| Variable | Study (Reference) | | | |
|---|---|------------------------------------|--|--|
| | MDRD Study (7) | MDRD Study Long-Term Follow-up (4) | AASK (6) | REIN-2 Trial (5) |
| Study characteristics | | | | |
| Years | 1988–1993 | 1988–2000 | 1995–2001 | 1999–2003 |
| Patients, <i>n</i> | 840 | 840 | 1094 | 338 |
| Duration, y | 2.2 (mean) | 6.2 (mean) | 3.8 (mean) | 1.6 (median) |
| Baseline patient characteristics | | | | |
| Age, y | 52 | 52 | 55 | 54 |
| Men, % | 61 | 61 | 59 | 75 |
| Black, % | 8 | 8 | 100 | NA |
| Mean GFR, mL/min per 1.73 m ² | 32 | 32 | 46 | 35 |
| Mean (median) urine protein, g/d | 1.09 (0.35) | 1.09 (0.35) | 0.53 (0.081) | 2.85 (NA) |
| Blood pressure intervention | | | | |
| Lower | MAP < 92 mm Hg (blood pressure < 125/75 mm Hg) | NA | MAP < 92 mm Hg (blood pressure < 125/75 mm Hg) | Blood pressure < 130/80 mm Hg + felodipine |
| Usual | MAP < 107 mm Hg (blood pressure < 140/90 mm Hg) | NA | MAP 102–107 mm Hg (blood pressure 135/85–140/90 mm Hg) | Diastolic blood pressure < 90 mm Hg |
| Medications used in both blood pressure groups | | | | |
| | Enalapril†, diltiazem, β-blockers, diuretics | NA | Ramipril‡, amlodipine, metoprolol, furosemide | Ramipril§, β-blockers, diuretics |
| Mean differences in blood pressure between randomly assigned groups, mm Hg | | | | |
| Systolic | 7.6 | NA | 13 | 4.8 |
| Diastolic | 3.8 | NA | 7 | 2.1 |
| MAP | 5.1 | NA | 7 | 3.0 |
| Outcomes | | | | |
| Kidney failure, % | 15 | 66 | 15 | 21 |
| Approximate mean decline in GFR, mL/min per y | 4 | NA | 2 | 3 (assessed in subgroup) |
| Treatment effects | | | | |
| Kidney failure | No difference | Benefit | No difference | No difference |
| GFR decline | Benefit in patients with higher proteinuria | NA | None | No difference (assessed in subgroup) |
| Proteinuria | Benefit | NA | Benefit | No difference |

* AASK = African-American Study of Kidney Disease and Hypertension; GFR = glomerular filtration rate; MAP = mean arterial pressure; MDRD = Modification of Diet in Renal Disease; NA = not available; REIN-2 = Ramipril Efficacy in Nephropathy 2.

† 51% vs. 32%, respectively, in the usual vs. lower blood pressure group.

‡ 40% by assignment in usual and lower blood pressure groups.

§ 100% by assignment in usual and lower blood pressure groups.

blood pressure in that study. Third, the differences in blood pressure levels between groups in the REIN-2 Trial were modest. Fourth, the REIN-2 Trial was too small to precisely estimate the effect of a lower blood pressure goal; the lower bound of the confidence interval for the hazard ratio for kidney failure does not rule out the possibility of a clinically important beneficial effect. Fifth, the duration of observation in AASK and the REIN-2 Trial may have been too brief to observe a beneficial effect. In the MDRD Study, a longer follow-up interval showed a beneficial effect in subgroups in which a benefit was not observed during the trial (4).

WHAT SHOULD CLINICIANS DO?

“Nondiabetic kidney disease” includes glomerular, vascular (including hypertensive nephrosclerosis), tubulointerstitial, and cystic diseases, which can usually be distinguished by the patient’s history, level of proteinuria, urinalysis, and ultrasonography of the kidneys (9). Proteinuria is particularly important to assess, as higher levels of proteinuria are associated with more rapid progression of kidney disease and increased risk for cardiovascular disease. In patients with proteinuria (spot urine total protein-to-creatinine ratio greater than 200 mg/g), clinicians should

prescribe an ACE inhibitor to slow progression of kidney disease (2). Some uncertainty remains about whether a lower blood pressure goal is beneficial and, if it is, which additional antihypertensive agents should be used to achieve it. Primarily on the basis of the MDRD Study, we think a lower blood pressure is reasonable; recent guidelines recommend a goal less than 130/80 mm Hg (2). The same goal is recommended to reduce cardiovascular disease in high-risk patients, including those with chronic kidney disease (2, 10). Clinicians should also prescribe diuretics, since most patients will require more than one medication. Additional antihypertensive agents can be selected on the basis of other compelling indications (for example, concomitant angina) and adverse effects. Based on the REIN-2 Trial, dihydropyridine calcium-channel blockers may not provide additional protection against kidney disease progression. Agents that lower proteinuria, such as angiotensin-receptor blockers, nondihydropyridine calcium-channel blockers, and β -blockers, may be preferable.

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