

# Blood Pressure Control in Chronic Kidney Disease: Is Less Really More?

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## ABSTRACT

BP control is critical in the treatment of patients with chronic kidney disease. Recent guidelines now recommend a BP goal of <130/80 mmHg. Clinical trials using a randomized, intention-to-treat design have not established the benefits of this goal; rather, observational data and secondary or subgroup analyses drove the development of the new guidelines. A variety of observations suggest potential adverse events associate with achieving too low a BP in patients with chronic kidney disease, and ongoing randomized trials will have to establish the benefits or risks of meeting this goal.

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“A mind is a terrible thing to change” brings up the problem of confirmation bias. In a recent analysis of nearly 8000 participants, people were twice as likely to seek information confirming what they already believed rather than consider evidence that would challenge those beliefs.<sup>1</sup> Indeed, medicine is not immune to this bias; people reviewing the same data can reach dramatically different conclusions on the basis of preexisting beliefs. For many years, observational studies suggested patients who had renal disease and were on erythropoietin-stimulating agents had better outcomes with higher hemoglobin levels. This belief that a normal hemoglobin level was a good thing persisted despite early evidence to the contrary and eventually drove the formation of widely used guidelines.<sup>2</sup> Did confirmation bias contribute to the sad fact that the guidelines did not change until after multiple clinical trials demonstrated harm?

Now we have the BP problem. New BP goals significantly <140/90 mmHg may or may not be good for patients with chronic kidney disease (CKD). What is

unarguably true is that despite well-intended guidelines and passionate beliefs, no well-powered, randomized, intention-to-treat clinical trials have demonstrated a clinically significant benefit of achieving a BP target of  $\leq$ 130/80 mmHg in the setting of CKD.

Multiple landmark studies demonstrated unequivocally that lowering BP in individuals who are of any age and have moderate to severe hypertension reduces risk for stroke and, less consistently, other cardiovascular events.<sup>3–12</sup> Patients from these studies were randomly assigned to various antihypertensive regimens, resulting in different achieved BP. Of note, in all of those trials, patients in low-BP groups, on average, did not achieve mean BP <140/90 mmHg, and many showed benefit at considerably higher BP (Table 1). No adequately powered, randomized, controlled trials have demonstrated cardiovascular benefit with BP goals <140/90 mmHg. Only epidemiologic observations that patients who achieve lower BP have fewer cardiovascular events supports the hypothesis that BP goals

<140/90 mmHg may have cardiovascular benefit. This hypothesis will be tested in the ongoing Systolic Blood Pressure Intervention (SPRINT) trial sponsored by the National Institutes of Health, which will randomly assign >10,000 patients to one of two BP goals: <120/80 or <140/90 mmHg.

Patients with CKD were systematically excluded from the majority of early BP trials, and, consequently, few trials provided renal outcomes<sup>3–12</sup>; however, secondary analyses of these trials yielded some hypothesis-generating information. In the Hypertension Detection and Follow-up Program, patients who entered the trial with baseline serum creatinine (SCr) level of 1.50 to 1.69 mg/dl benefited from lower BP in the stepped-care group with fewer hypercreatininemic events.<sup>13</sup> In contrast, in the European Working Party on High Blood Pressure in the Elderly trial, SCr increased significantly in the patients who achieved lower BP compared with placebo.<sup>14</sup> In the Multiple Risk Factor Intervention Trial (MRFIT), 32,544 men were enrolled in a prevention trial to study the effects of BP control, lowering of serum cholesterol, and cessation of smoking on

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**Table 1.** Placebo-controlled hypertension trials

Trial	N	Low BP Achieved	Comparison Arms	Primary Results
SHEP <sup>4</sup>	4736	143/68	Diuretic-based regimen versus placebo	36% RRR in stroke
STOP <sup>6</sup>	1627	166/85	$\beta$ blocker and diuretic regimen versus placebo	29% RRR in stroke
Syst-Eur <sup>3</sup>	4695	153/77	CCB-based regimen versus placebo	42% RRR in stroke
Syst-China <sup>5</sup>	2394	150/81	CCB-based regimen versus placebo	38% RRR in stroke

CCB, calcium channel blocker; RRR, relative risk reduction.

coronary artery disease. After 16 years of follow-up, there were 814 cases of ESRD, and elevated BP was a strong independent risk factor.<sup>15,16</sup> The major cardiovascular trials establishing the benefit of a systolic BP (SBP) goal of <140 mmHg on reducing cardiovascular outcomes did not consistently suggest renal benefit. These trials were not designed to enroll patients with CKD or carefully measure renal outcomes.

Numerous observational studies also reported an association between higher levels of BP and ESRD.<sup>17–20</sup> More recently, the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, a study of intensive blood sugar control—not BP control—was conducted of 11,140 patients with type 2 diabetes. In a secondary analysis of BP in these patients, there were fewer renal events in patients with lower SBP over a range of 110 to 170 mmHg.<sup>21,22</sup>

Although observational data sets support the hypothesis that there is a continuous benefit of reducing BP to lower and lower levels, they are problematic: Patients were not randomly assigned to BP goals in these studies. As a result, there is the potential for confounding factors to account for the observed association of lower BP and better renal outcomes rather than a cause-and-effect relationship. As renal disease worsens, BP rises and is more difficult to control, so the observation in a study in which patients with worse renal function may on average have higher BP and those with less severe renal disease have lower BP and patients are not randomly assigned to different BP goals may not be due to a lower BP slowing the rate of loss of renal function. One cannot distinguish whether patients with less severe renal disease have lower BP because they have less severe

renal disease or lower BP leads to fewer adverse renal outcomes. There may also be common factors that both worsen renal disease and cause higher BP. Again there might be a strong relationship between higher BP and worse kidney disease, but this would not be due to a cause-and-effect relationship.

Last, drugs used to lower BP, such as inhibitors of the renin-angiotensin system, may benefit the kidney beyond lowering BP<sup>23–25</sup>; that is, lower BP would associate with better renal outcomes, but it would not be the cause of better renal outcomes. The only way to exclude these confounding factors is to conduct a trial in which patients are randomly assigned to different BP goals and the renal event rate is examined. Thus, studies that simply observe an association between achieved BP and renal events are open to interpretation and irresolvable concern.

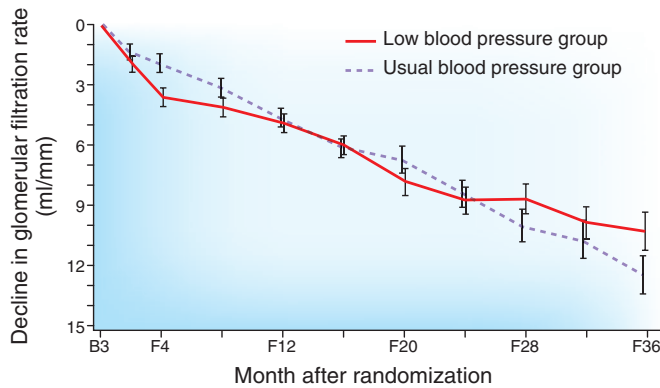
The classic study by Parving *et al.*<sup>26</sup> was one of the first to demonstrate that early antihypertensive treatment reduced the rate of declining renal function in 12 patients who had diabetes and served as their own controls. Several other small studies similarly revealed a benefit to randomly assigning patients to lower BP goals but also had too few patients to be definitive and used decreasing albuminuria as an outcome rather than a change in estimated GFR.<sup>27–30</sup> More recently, the Ramipril Efficacy in Nephropathy 2 (REIN-2) study randomly assigned 338 patients to either a diastolic BP (DBP) of <90 mmHg (conventional group) or BP <130/80 mmHg (intensified group) and reported no decrease in ESRD events in the intensified group.<sup>31</sup>

The Modification of Diet in Renal Disease (MDRD) study and the African American Study of Kidney Disease and Hypertension (AASK) are two large,

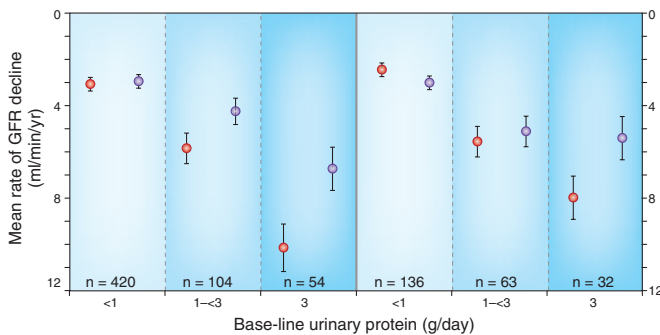
well-controlled clinical trials that examined the hypothesis that being randomly assigned to a mean arterial BP (MAP) of  $\leq 92$  versus 107 mmHg would slow the rate of decline in renal function as measured by I<sup>125</sup>-iothalamate GFR.<sup>32</sup> MDRD bears careful review because the results of that trial, along with other observational studies, drove the current guideline recommendation for a BP goal of <130/80 mmHg in patients who have CKD and proteinuria  $\geq 1$  g/24 h.

In MDRD, 840 patients with a GFR of either 25 to 55 ml/min (study A) or 13 to 24 ml/min (study B) were randomly assigned to a MAP goal of  $\leq 92$  or <107 mmHg. Of note, because MAP is calculated as DBP + one third pulse pressure, the patients who were randomly assigned to a MAP of  $\leq 92$  mmHg (roughly equivalent to 125/75 mmHg) had SBP between 98 and 154 mmHg, and the usual BP group with a MAP of 107 mmHg (roughly equivalent to 140/90 mmHg) had SBP between 103 and 163 mmHg. As can be seen in Figure 1, by the intention-to-treat design, there was no significant benefit on slowing the rate of decline of GFR in the group of patients who were randomly assigned to a MAP of  $\leq 92$  mmHg.<sup>32</sup> Analysis of other outcomes such as time to doubling of SCr or ESRD similarly showed no benefit of the low BP goal; however, a significant benefit of the low BP goal was seen in 54 patients who entered the study with proteinuria >3 g/24 h. Although the 104 patients with proteinuria of 1 to 3 g/24 h did not benefit as a group from the low BP goal, when grouped with patients with proteinuria >3 g/24 h, there was benefit. Furthermore, no significant benefit was associated with the low BP goal in any group of patients in study B (GFR 13 to 24 ml/min; Figure 2).<sup>32,33</sup>

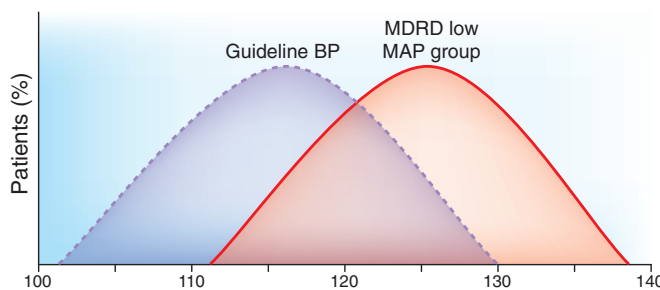
There were significant interactions in



**Figure 1.** Estimated mean  $\pm$  SE decline in the GFR from baseline (B) to selected follow-up times (F) in MDRD. The patients who were assigned to the usual-BP group (dashed line) are compared with those assigned to the low-BP group (solid line). Adapted from Klahr et al.,<sup>32</sup> with permission.



**Figure 2.** Decline in the GFR according to baseline urinary protein excretion and BP group in MDRD. The mean  $\pm$  SE rate of decline per year in the GFR from baseline to 3 years, for study A and study B categorized by baseline urine protein, is projected. ●, patients with usual BP; ○, patients with low BP. The number at the bottom of each panel indicates the total number of patients with follow-up GFR measurements in the two BP groups combined. Adapted from Klahr et al.,<sup>32</sup> with permission.



**Figure 3.** The solid line is the hypothetical representation of the average mean SBP and 1 SD on either side of that mean found in the MDRD study low-MAP group. Dashed line is the hypothetical representation of distribution of average SBP if guidelines target all SBP at  $<130$  mmHg.

MDRD between BP interventions and baseline proteinuria, and there was a reduction in proteinuria in patients who were randomly assigned to a MAP of  $\leq 92$  mmHg in both study A and study B; however, a major confounding factor

was the more frequent use of renin-angiotensin inhibitors, known modifiers of renal progression, in the low-BP group.<sup>33</sup> The primary result of the BP study in the MDRD was negative: There was no benefit in slowing the rate of decline of renal

function. Only a secondary analysis in the subgroup with proteinuria supports the low BP goal and is confounded by imbalance in the use of the renin-angiotensin inhibitors.

The MDRD results and the results of the observational studies noted formed the basis for the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline of  $<130/80$  mmHg for patients with CKD and proteinuria  $\geq 1$  g/24 h.<sup>34</sup> Guideline committees tend to use available evidence to make best practical recommendations, but a careful review of the data confirms that real uncertainty remains on appropriate BP goals for patients with CKD. Another quirk of the KDOQI guidelines is that they were largely based on the MDRD study, in which the low-BP group was randomly assigned to a MAP of  $\leq 92$  mmHg. A MAP goal allows a wide range of SBP and DBP combinations. Although never published, the actual mean follow-up systolic and diastolic BP in the usual group were  $132.7 (\pm 1.0 \text{ to } 14.9)/80.2 (\pm 1.0 \text{ to } 7.5)$  mmHg and in the low-BP group were  $125.6 (\pm 1.0 \text{ to } 13.8)/76.7 (\pm 1.0 \text{ to } 6.8)$  mmHg (Tom Greene, PhD, personal communication, October 2009). The low-MAP group had a wide range of SBP, approximately 98 to 154 mmHg. Achieving SBP in this range is a very different intervention than targeting all patients' SBP to  $<130$  mmHg (Figure 3).

Other evidence has become available since the appearance of these KDOQI guidelines. At the completion of the MDRD study, the patients were returned to the care of their usual physician, and there was no longer any BP separation between the two randomly assigned groups. After 7 years in routine care, fewer of those patients who were originally randomly assigned to a MAP  $\leq 92$  versus  $<107$  mmHg reached ESRD or the composite end point of ESRD or death.<sup>35</sup>

The second large study, the AASK, was completed by randomly assigning 1094 black patients with hypertension and a urine protein-creatinine ratio of  $<2.5$  to a MAP of  $\leq 92$  versus 102 to 107 mmHg. There was no significant benefit of being randomly assigned to the low-BP group for the full cohort.<sup>36</sup> In

contrast to the MDRD study, there also was no benefit in any subgroup, including those with proteinuria  $>1$  g/24 h.<sup>36</sup> There was, however, a reduction in proteinuria in the low-BP group of the full cohort.

After the AASK was completed, the majority of participants entered an observational cohort study. Ironically, although no benefit of the low BP goal was demonstrated in these same patients, the data safety committee asked all participants in the AASK cohort study to have a BP goal of  $\leq 130/80$  mmHg to comply with current guidelines. Seven years after the completion of the AASK, during which time there was no difference in BP between the two originally randomly assigned groups, those who originally were randomly assigned in the trial to a MAP of  $\leq 92$  mmHg had fewer ESRD events but only in the prespecified subgroup of patients, approximately 33% of those enrolled with urine protein-creatinine ratio  $>0.22$ .<sup>37</sup>

It is fair to ask whether these results from two trials are compelling evidence to support a low BP goal when the benefits of that goal are not apparent at the time BP is actually lowered but are apparent only in a subgroup of patients 7 years after there is no longer any difference in the BP. Although there is indirect evidence to support the hypothesis that BP  $<130/80$  mmHg may benefit the kidney, uncertainty abounds. Well-designed studies were unable to demonstrate that benefit in their full cohorts.<sup>32,36</sup> Of note, in 385 children in the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial, those who were randomly assigned to the MAP goal of  $<50$ th percentile had 50% fewer events (50% decreases in GFR or ESRD) as compared with those who were randomly assigned to a MAP in the 50th to 95th percentiles.<sup>38</sup> Although it supports lower BP as renoprotective, this trial in children is difficult to align with treatment goals in adults.

Not all hypotheses need be tested in clinical trials. For example, it would not be prudent to test the hypothesis that it is safer to jump out of an airplane with a

parachute than without one.<sup>39</sup> Although a few poor souls have survived the jump without an open chute, common sense will always prevail; however, if an intervention has the potential for a harmful effect rather than beneficial or is costly or a burden to patients, then a valid clinical trial is desirable, appropriate, and required. Lowering the SBP goal from 140 to 130 mmHg will require our nation of patients with hypertension to take one or possibly two additional antihypertensive medications with a considerable increase in cost and potential for medication-associated adverse effects. Furthermore, in the case of low BP goals, there is evidence they may be associated with clinical harm.

Observational studies have suggested the risk for stroke and death in patients with CKD may actually be greater among those with SBP levels  $\leq 120$  mmHg compared with higher levels.<sup>40</sup> Of concern, individuals with CKD have a J-shaped relationship with stroke outcomes, such that those with SBP  $<120$  mmHg are at significantly increased risk compared with those with CKD and SBP of 120 to 129 mmHg; the risk for stroke increases, of course, for SBP  $>130$  mmHg. This J shape was not seen for patients without CKD.<sup>41</sup> This latter finding suggests the possibility that if studies targeting lower BP goals are conducted on populations of patients who do *not* include patients with CKD, then the results may be misleading, because the risk-benefit relationship is different for patients with CKD. As is the case with observational studies supporting lower BP goals, these observational studies regarding risk are limited, because patients with more severe overall illness have lower BP, or drugs used to achieve lower BP levels may independently increase the risk for stroke. The few BP-lowering trials that have analyzed the effects of BP lowering in the subgroup of patients with CKD reported mixed results: Some showed benefit in reducing cardiovascular outcomes, whereas others were unable to show benefit.

In the Irbesartan in Diabetic Nephropathy Trial (IDNT), patients who had CKD and achieved SBP  $<120$  mmHg had a

higher risk for all-cause mortality than any other BP level, and this mortality risk was comparable to that seen in those with SBP  $>180$  mmHg.<sup>42</sup> A careful analysis of all comorbidities was unable to account for the increased mortality in patients who achieved SBP  $<120$  mmHg. Furthermore, a recent meta-analysis of trials that examined the effects of regimens targeting low BP goals in patients with CKD demonstrated no clear benefit for cardiovascular or CKD outcomes.<sup>43</sup> The recently reported ONgoing Telmisartan Alone and in combination with Ramipril Global EndpointT (ONTARGET) trial also shows that negative outcomes associate with very low SBP. In ONTARGET, 25,620 patients (9595 of whom had diabetes and 6157 of whom had stage 3 or 4 CKD) were randomly assigned to receive ramipril 10 mg/d, telmisartan 80 mg/d, or both.<sup>44</sup> Telmisartan was equivalent to ramipril with respect to the primary outcome, but in the combination group, there were more adverse events without an increase in benefit for the combined primary outcome of death from any cardiovascular cause, myocardial infarction, stroke, or hospitalization for heart failure. This lack of increased benefit is despite patients on combination therapy having a 2- to 3-mmHg reduction in SBP as compared with the ramipril group. This magnitude of change in SBP is predicted to result in a risk reduction of 4 to 5% on the basis of previous observational studies.<sup>45-47</sup> In this trial, the secondary renal outcome (dialysis or doubling of SCr) was similar in the telmisartan and ramipril groups but occurred more frequently with combination therapy. Combination therapy did reduce proteinuria to a greater extent than monotherapy but overall significantly worsened major renal outcomes.<sup>48</sup> This result was in large part due to an increase in dialysis for acute kidney injury in the combination group. In addition, patients in ONTARGET who achieved SBP  $<120$  mmHg had an *increase* in the primary outcome of cardiovascular mortality but *not* stroke compared with the 120- to 129-mmHg group.<sup>49</sup> It is certainly not difficult to imagine that elderly patients who have CKD and multiple comorbidities and

with an SBP goal of <130 mmHg, perhaps achieving BP far lower, might also develop severe enough hypotension to have acute kidney injury during an intercurrent illness. This large study did not randomly assign patients to two levels of BP, and interpretation of these latter results must be cautious because of inherent biases introduced by examining achieved results. This outcome, however, is not in any way dissimilar from the biases associated with the observational data supporting low BP goals.

Where does all this leave us? Fortunately, more data have been forthcoming. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomly assigned 4733 patients who had type 2 diabetes and either cardiovascular disease or risk factors for cardiovascular disease including albuminuria to a intensive therapy targeting an SBP of <120 mmHg or standard therapy targeting an SBP of <140 mmHg.<sup>50,51</sup> The mean SBP in the intensive group was 119.3 mmHg and in the standard group was 133.5 mmHg, for a mean difference of 14.2 mmHg. There were no significant differences between the two groups in the annual rate of the primary cardiovascular outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular disease. Importantly, only serious adverse events attributed to BP medications were collected by the local sites and were significantly more frequent in the intensive group. Of particular note, the intensive group had higher rates of elevated SCr and lower GFRs, so not only was there no cardiovascular benefit to intensive BP control, but also there was evidence of increased renal risk. Patients with SCr levels >1.5 mg/dl were excluded from this trial, and data suggest that patients with CKD may differ from patients without CKD.

Current guidelines reflect only conventional wisdom; however, there are several cautionary notes. What data there are to support lower BP goals are based on studies using MAP goals with a wide range of achieved SBP. If physicians begin receiving report cards that are based on guidelines, then their goal will be for all patients to have SBP <130

mmHg, likely resulting in a major shift leftward in the bell-shaped curve of SBP with unknown clinical consequences. This is reminiscent of the very high hemoglobin levels achieved in patients with CKD as a result of a similar bell-shaped curve effect with guidelines and report cards targeting all patient hemoglobin levels to >11 g/dl (Figure 3).

Lower BP goals may be beneficial in general, and there is a body of evidence to support this, but this is not confirmatory evidence from primary analyses from a definitive trial in patients with CKD. Even in the subset of patients with proteinuria >1 g/24 h, no primary analysis of any trial supports lower BP goals.

Uncertainty remains a reminder of risk and vigilance. For now, we should individualize BP control in our patients pending further data. The SPRINT trial will randomly assign approximately 10,000 patients to an SBP of <120 versus <140 mmHg and will include by intent a substantial number of patients with stage 3 CKD. We should make every effort to support robust recruitment of patients with CKD into this trial to obtain more data to help guide their care.

## DISCLOSURES

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