Control of Blood Pressure in Chronic Kidney Disease: How Low to Go?

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BP Goal in Diabetic CKD

The potential benefit of aggressive lowering of BP on diabetic nephropathy was first suggested in an uncontrolled trial on 11 subjects with insulin-dependent diabetes in the early 1980s by Parving et al. [12], in which a significant reduction in rate of decline in glo-
merular filtration rate (GFR) was observed before the treatment (0.89 ml/min/month) to during the treatment (0.22 ml/min/month) with a mean achieved BP of 129/84 mm Hg.

Subsequently, four primary randomized controlled trials (RCTs) with BP-lowering intervention in patients with type 2 diabetes aimed to address this question (table 1): the Hypertension Optimal Treatment (HOT) study, United Kingdom Prospective Diabetes Study (UKPDS), the Appropriate BP Control in Diabetes (ABCD) trial, and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. In the HOT study, 18,790 subjects with hypertension (≤10% were diabetics with no specified level of serum creatinine or urine albumin) were randomized to three diastolic BP (DBP) target subgroups (<90, <85, or <80 mm Hg), and the results demonstrated a mortality benefit of lower levels (<80 vs. 90 mm Hg or higher DBP) [13]. However, there were no significant differences in serum creatinine levels at the end of the 3.8 years. Moreover, the incidence of major cardiovascular events did not differ in patients with a baseline serum creatinine level >133 μmol/l (n = 470) among the three BP target groups.

The UKPDS was the first large-scale RCT conducted during the 1980s to determine the impact of intensive (<150/85 mm Hg) versus conventional (<180/105 mm Hg) control on the development and progression of CKD due to type 2 diabetes [14, 15]. Over 8.4 years of follow-up, significant risk reductions in macrovascular (34%) and microvascular (37%) outcomes were observed in the intensive BP control group. However, it should be noted that the target BP goal (<150/80 mm Hg) and the minimum achieved BP (144/82 mm Hg) in tight control were higher than the conventional targets recommended in the current JNC-7 guidelines [16]. Thus, the UKPDS was not designed to answer the question of whether reduction of BP to levels <140/90 mm Hg would be beneficial.

However, secondary analysis of UKPDS data revealed that each 10 mm Hg decrease in mean systolic BP (SBP) was associated with reductions in risk of 12% for any complication related to diabetes, 17% for deaths related to diabetes, 11% for myocardial infarction and 13% for microvascular complications. Any reduction in BP was likely to reduce the risk of complications, with no threshold level, the lowest risk being in those with SBP <120 mm Hg [14]. Thus the notion of keeping BP as low as possible in patients with diabetic CKD was recommended, albeit based on post-hoc analysis with inherent limitations.

The ABCD trial also aimed to examine the role of intensive versus moderate BP reduction on the prevention of CVD-related events, and progression of nephropathy, neuropathy, and retinopathy in individuals with type 2 diabetes [17]. The normotensive group that received intensive therapy to lower BP had a mean BP of 128 ± 0.8/75 ± 0.3 mm Hg, as compared with a mean BP of 137 ± 0.7/81 ± 0.3 mm Hg in the group that received standard therapy (p < 0.001). There was no significant change in the primary outcome of mean renal function (as assessed by 24 h creatinine clearance) between the randomized groups during 5 years. The intensive therapy group had less progression from normoalbuminuria to microalbuminuria (p = 0.01) and from microalbuminuria to overt albuminuria (p = 0.03), less progression of diabetic retinopathy (p = 0.02), and a lower incidence of stroke (p = 0.02). Thus, while the primary outcomes were inconclusive, the secondary outcomes of the ABCD trial indicated some benefit of lower BP goals. Moreover, while albuminuria at baseline was associated with faster progression of kidney disease and onset of CVD, a differential effect of intensive versus standard levels of BP by levels of albuminuria on these adverse outcomes were not reported.

More recently, in the ACCORD study, a total of 4,733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting an SBP <120 mm Hg, or standard therapy, targeting an SBP <140 mm Hg [18, 19]. Despite the fact that there was a significant and sustained difference in BP between intensive therapy (119.3 mm Hg) and standard therapy (133.5 mm Hg), the results showed no difference in overall CVD events after a follow-up of 4.7 years. However, the analysis of secondary endpoints showed a decrease in stroke (p = 0.01) and macroalbuminuria (p = 0.009) in the intensive BP group. It remains possible that the differential effect of low achieved BP on the latter secondary outcomes was due to more effective cerebral and renal autoregulation. It is important to note that subjects with serum creatinine >1.5 mg/dl were excluded from ACCORD, thus risk of progression to hard renal outcomes was low, as is the generalizability to the population seen in routine nephrology practices. Moreover, while about 40% of subjects in ACCORD had urine albumin levels >30 mg/day, data on outcomes by baseline level of albuminuria have not been reported. Moreover, the intensive therapy group had significantly higher rates of serious adverse events attributed to antihypertensive treatment, as well as higher rates of hypokalemia and elevations in serum creatinine level.
### Table 1. BP lowering in CKD

<table>
<thead>
<tr>
<th>Trial/year</th>
<th>Design</th>
<th>Primary endpoint</th>
<th>Number</th>
<th>Follow-up years</th>
<th>Achieved mean BP</th>
<th>Results</th>
<th>Authors’ conclusion</th>
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<tbody>
<tr>
<td><strong>Diabetic BP lowering studies</strong></td>
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<tr>
<td>HOT [13]</td>
<td>PROBE DBP &lt;90 vs. DBP &lt;85 vs. DBP &lt;80 mm Hg</td>
<td>Composite, CVD</td>
<td>18,790 (1,501 with diabetes)</td>
<td>3.8</td>
<td>DBP &lt; 20.3 mm Hg</td>
<td>DBP &lt; 22.3 mm Hg</td>
<td>DBP &lt; 24.3 mm Hg</td>
</tr>
<tr>
<td>UKPDS [14]</td>
<td>PROBE BP &lt;150/85 vs. &lt;180/105 mm Hg</td>
<td>Composite diabetic complications, CVD, renal</td>
<td>1,148</td>
<td>8.4</td>
<td>144/82 mm Hg</td>
<td>154/87 mm Hg</td>
<td>↓ Diabetic microvascular complications, diabetic mortality, stroke, microvascular with low BP goal</td>
</tr>
<tr>
<td>ABCD [17]</td>
<td>RCT DBP 80–89 vs. &lt;75 mm Hg</td>
<td>Change in creatinine clearance</td>
<td>950</td>
<td>5</td>
<td>138/86 mm Hg</td>
<td>132/78 mm Hg</td>
<td>24 h creatinine clearance remained stable in both intensive and usual BP control groups</td>
</tr>
<tr>
<td>ACCORD [18, 19]</td>
<td>RCT &lt;120 mm Hg vs. &lt;140 mm Hg</td>
<td>Composite of non-fatal myocardial infarct, stroke, and CVD death</td>
<td>4,733</td>
<td>3.5</td>
<td>119.3 mm Hg</td>
<td>133.5 mm Hg</td>
<td>No significant difference in composite outcome between randomized groups</td>
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<td><strong>Antihypertensive trials – secondary analysis</strong></td>
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<tr>
<td>RENAAL [20]</td>
<td>RCT PLCB vs. ARB</td>
<td>Doubling of creatinine ESRD or death</td>
<td>1,513</td>
<td>3.4</td>
<td>ARB 140/74 mm Hg</td>
<td>PLCB 142/74 mm Hg</td>
<td>Treated SBP values of ≥140 mm Hg in those with nephropathy from type 2 diabetes significantly increases risk of nephropathy progression compared with values &lt;130 mm Hg</td>
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<tr>
<td>IDNT [21]</td>
<td>RCT PLCB vs. CCB PLCB vs. ARB</td>
<td>Doubling of serum creatinine ESRD or death</td>
<td>1,715</td>
<td>2.6</td>
<td>135/85 mm Hg or less in all groups</td>
<td></td>
<td>Lower BP correlated with slower renal progression Progressively lower achieved SBP to 120 mm Hg were associated with a decrease in secondary outcome of cardiovascular mortality and congestive heart failure in subgroup with high serum creatinine</td>
</tr>
<tr>
<td>ADVANCE [22]</td>
<td>RCT Intensive or standard glucose control</td>
<td>Composites of macro- and microvascular events</td>
<td>11,140</td>
<td>5</td>
<td>135.5 vs. 137.9 mm Hg</td>
<td></td>
<td>Reduced the risk of renal events by 21%</td>
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<td><strong>Non-diabetic Primary</strong></td>
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<tr>
<td>MDRD [24]</td>
<td>RCT</td>
<td>Proteinuria and decline in GFR</td>
<td>840</td>
<td>3+</td>
<td>Usual BP goal (target MAP, &lt; or = 107 mm Hg) or a low BP goal (target MAP, &lt; or = 92 mm Hg)</td>
<td></td>
<td>In those with baseline proteinuria &lt;1 g/day, no significant difference in rate of decline in GFR between usual vs. low BP goal</td>
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- **DBP**: Diastolic Blood Pressure
- **CVD**: Cardiovascular Disease
- **MAP**: Mean Arterial Pressure
- **ESRD**: End Stage Renal Disease
- **GFR**: Glomerular Filtration Rate
- **SBP**: Systolic Blood Pressure
- **PLCB**: Placebo
- **ARB**: Angiotensin II Receptor Blocker
- **CCB**: Calcium Channel Blocker
- **RENAAL**: Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study
- **IDNT**: International Data Network study
- **ADVANCE**: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation study
### Table 1 (continued)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>MDRD post-trial follow-up [25]</td>
<td>RCT</td>
<td>Kidney failure (defined as initiation of dialysis or kidney transplantation) and a composite outcome of kidney failure or all-cause mortality</td>
<td>840</td>
<td>6+ years of post-trial follow-up</td>
<td>Lower by 5.1 mm Hg in the low BP group</td>
<td>Adjusted HRs were 0.68 (95% CI 0.57–0.82; p &lt; 0.001) for kidney failure and 0.77 (CI 0.65–0.91; p = 0.0024) for the composite outcome in the low target BP group compared with the usual target BP group. No significant interaction by level of proteinuria</td>
<td>Low BP better for CKD progression regardless of the level of proteinuria</td>
</tr>
<tr>
<td>AASK in trial plus cohort phase [26, 27]</td>
<td>RCT</td>
<td>Doubling of the serum creatinine level, a diagnosis of ESRD, or death</td>
<td>1,094</td>
<td>8.8–12.2 years, including post-trial follow-up</td>
<td>In trial phase: 130/78 mm Hg in the intensive control group and 141/86 mm Hg in the standard control group. Cohort phase: 131/78 and 134/78 mm Hg, respectively</td>
<td>Lower BP goal did not significantly reduce the rate of the clinical composite outcome in the overall group, however the effects differed according to the baseline level of proteinuria (p = 0.02 for interaction). In those with a protein:creatinine ratio ≥0.22, HR = 0.73 (95% CI 0.58–0.93); p = 0.01. In those with a protein:creatinine ratio &lt;0.22 or more, HR = 1.18 (95% CI 0.93–1.50); p = 0.16</td>
<td>No additional benefit of lower BP goal was observed on slowing progression of hypertensive nephrosclerosis in those without clinical proteinuria. Lower BP goal may be beneficial in those with baseline proteinuria ≥300 mg/day</td>
</tr>
<tr>
<td>REIN-2 [28]</td>
<td>RCT</td>
<td>Change in GFR, ESRD or death, proteinuria, CVD events</td>
<td>338</td>
<td>1.6</td>
<td>130/80 mm Hg 134/82 mm Hg</td>
<td>(23%) patients assigned to intensified BP control and 34/168 (20%) allocated to conventional control progressed to ESRD (HR 1.00 (95% CI 0.61–1.64); p = 0.99. All subjects were proteinuric (urine protein excretion ≥1 g/day)</td>
<td>No additional benefit of lower BP goal was observed on slowing progression of non-diabetic proteinuric nephropathy against a background of ACE inhibitor therapy</td>
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</table>

### Antihypertensive trials – secondary analysis

| AIPRD study group [30] | Individual patient data meta-analysis Comparing the efficacy of antihypertensive regimens with or without ACEI in 11 RCTs | Doubling of baseline serum creatinine or ESRD | 1,860 | 2.2 | Mean follow-up BP 142/86 mm Hg | No benefit of intensive BP lowering in those without proteinuria (<1 g/day). Lowest risk for kidney disease progression at SBP levels of between 110 and 129 mm Hg in patients with proteinuria ≥1 g/day | No benefit of lower BP goal was observed on slowing progression of non-diabetic kidney disease in those without or low levels of proteinuria (<1 g/day). A SBP goal between 110 and 129 mm Hg may be beneficial in patients with urine protein excretion >1.0 g/day |

HOT = Hypertension Optimal Treatment; UKPDS = United Kingdom Prospective Diabetes; ABCD = Appropriate Blood Pressure Control in Diabetes; ACCORD = Action to Control Cardiovascular Risk in Diabetes; RENAAL = Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II antagonist Losartan; IDNT = Irbesartan Diabetic Nephropathy Trial; ADVANCE = Action In Diabetes And Vascular Disease; MDRD = Modification of Diet in Renal Disease; AASK = African American Study of Kidney Disease and Hypertension Study Group.

HR = Hazard ratio; MAP = mean arterial pressure; CVD = cardiovascular disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; Cr = creatinine; NS = not significant; PLCB = placebo; PROBE = prospective, randomized, open-label, blinded endpoint; RCT = randomized, controlled trial.
Evidence from secondary analysis of trials designed to study the impact of blockers of the renin-angiotensin system, including the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and Irbesartan Diabetic Nephropathy Trial (IDNT) in patients with clinical proteinuria (>500 mg/day in RENAAL and >900 mg/day in IDNT) and type 2 diabetes, suggests that lower achieved SBP was more protective of kidney and CVD outcomes than higher levels [20, 21]. The lowest risk was at lowest achieved BP, with no threshold level, suggesting that achieving <120/80 mm Hg would be advisable. Likewise, secondary analysis of the Action In Diabetes And Vascular Disease (ADVANCE) study on 11,140 patients aged 55 years or older with type 2 diabetes to undergo either standard glucose control or intensive glucose control with no prespecified BP targets, achieved a mean 5.6/2.2 mm Hg greater reduction in BP, which resulted in a significant 9% reduction in relative risk of a major macro- or microvascular event and 21% reduction in renal events (new or worsening nephropathy), that is the development of macroalbuminuria, defined as a urinary albumin:creatinine ratio >300 μg of albumin per milligram of creatinine, or doubling of the serum creatinine level to at least 200 μmol/l (2.26 mg/dl), the need for renal-replacement therapy, or death due to renal disease [22]. However, as patients were on active treatment of perindopril/indapamide, it is debatable whether this effect was due to the renoprotective effect of ACE inhibitors or BP lowering only.

Thus, the overall weight of evidence from results of BP-lowering trials in type 2 diabetes indicates a possible benefit of intensive BP reduction based on results of UKPDS (in which BP goal was not intensive), subgroup analysis of diabetic subjects in HOT, or secondary analysis of data (UKPDS, ADVANCE). Clearly, these data are rather suboptimal for any firm recommendations to support target of <130/80 mm Hg in non-proteinuric diabetics, especially when primary outcomes of primary RCTs (ABCD, ACCORD) in with patients randomized to intensive versus conventional BP goals do not support benefit of kidney progression or cardiovascular outcomes. For diabetic patients with proteinuric CKD (>500 to 900 mg/day), evidence from secondary analysis of RENAAL and IDNT suggests a possible benefit of lower targets (i.e. <120/80 mm Hg). However, the relationship between BP and CKD is complex, and the issue of ‘reverse causality’ in secondary analysis always remains a high possibility — i.e. those less likely to progress due to non-BP related factors had lower BP, rather than intensive BP lowering leading to slower progression. Thus, future studies of BP targets in patients with type 2 diabetes must also stratify by the level of albuminuria for clearer guidance.

**BP Goal in Non-Diabetic CKD**

Three primary RCTs have evaluated target BP levels in patients with predominantly non-diabetic CKD [23]. In addition, evidence from secondary analysis of antihypertensive medications of achieved BP levels on CKD progression also provides some clues.

The Modification of Diet in Renal Disease (MDRD) study was a 2 × 2 factorial design, in which patients were randomly assigned to a low (<125/75 mm Hg) or usual BP target and one of two types of diet with different levels of protein intake. During the main trial period of over 3 years, although there was no difference in risk of decline in GFR between the low and normal BP target in the overall groups, the low BP target was beneficial in the high proteinuria subgroup (>1 g) [24]. However, it is worth noting that the effects of BP control in the MDRD study may have been partly confounded by the renoprotective effect of ACE inhibitors, which were taken by 54% of the patients in the low BP group, but only by 34% in the usual BP group. More recently, post-trial follow-up of the MDRD study participants over 6+ years was performed in which the result for the hard outcome of kidney failure (defined as initiation of dialysis or kidney transplantation and a composite outcome of kidney failure or all-cause mortality) was favorable for the low BP target, for all patients regardless of the level of proteinuria [25]. However, the presence of a potential interaction between BP level and proteinuria on CKD progression, a categorical outcome of kidney failure, cannot be ruled out due to limited power, despite the longer duration of post-trial follow-up.

In the African American Study Kidney Disease (AASK) trial, 1,094 participants with mild to moderate chronic renal insufficiency (mean GFR 45.7 ml/min/1.73 m²) caused by hypertension were divided into two groups with two BP interventions – mean arterial pressure (MAP) <92 mm Hg and MAP 102–107 mm Hg. Additionally, patients were randomized to one of three classes of antihypertensive agents – calcium channel blocker (amlodipine), converting enzyme inhibitor (ramipril), or β-blocker (metoprolol) [26]. Lower BP did not reduce the rate of GFR decline. After completing the trial phase of just over 4 years in which there was no dif-
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those with low GFR, albeit there may be power to detect a potential interaction between BP and clinical proteinuria on renal and CVD outcomes.

Conclusions

BP lowering is an important therapeutic goal in patients with diabetic and non-diabetic CKD. The spectrum of the disease is wide, with benefit of strategies influenced by patient characteristics that determine the rate of progression and onset of CVD. However, evidence on BP reduction that accounts for the heterogeneity of clinical presentation is rather scarce. In diabetic kidney disease, while data support lowering BP to levels <140/90 mm Hg, evidence in favor of pushing the levels to <130/80 mm Hg is largely driven by subgroup (HOT) or secondary analysis (UKPDS, ADVANCE), and primary RCT data do not favor further intensive targets (i.e. <120/80 mm Hg) in all subjects with diabetes (ABCD, ACCORD). More research is needed to determine whether a lower BP target confers additional benefit to diabetic patients in the presence of clinical albuminuria, especially since secondary analyses are suggestive (IDNT, RENAL) that such a goal might be associated with additional benefit.

Thus, aiming for a BP of <130/80 mm Hg in patients with diabetic CKD may be justifiable, especially in the presence of clinical proteinuria of ≥1 g/day.

In patients with non-diabetic CKD without albuminuria, the weight of evidence for BP target is in favor of <140/90 mm Hg. For non-diabetic CKD with albuminuria, evidence suggests different cut-off levels to stratify albuminuria for BP goals ≥300 mg/day in Blacks or ≥1 g/day in non-Blacks, and aiming for a target BP of <130/80 mm Hg at these levels would be reasonable. However, in all patients with CKD, it is best to avoid reduction of SBP to levels <110 mm Hg since there has been no benefit documented with such levels of intensive lowering even in secondary analysis; on the contrary, there may be risk of harm with such an aggressive approach.

Clearly, evidence-based medicine aims to apply the best available scientifically collected evidence to arrive at clinical decision-making. Thus, consistent results from adequately powered and well-conducted RCTs randomizing patients with key characteristics relevant to the clinical practice of nephrology (diabetic and non-diabetic CKD with different levels of albuminuria, kidney function, and race) and to BP targets for hard kidney and cardiovascular outcomes would provide the highest level of evidence for clinical practice guidelines. Since conclusive evidence from RCT is limited for the entire spectrum of patients encountered by nephrologists, subgroup and secondary analysis provide useful information for the outcomes of interest albeit recognizing that individual judgment and caution be exercised with strict regimens, especially where the strength of evidence is less than optimal.

It is therefore important to underscore that there is clearly a need for well-designed RCTs stratified by patient characteristics such as albuminuria and race to determine the optimal level of BP for slowing the progression of CKD and preventing CVD in patients with diabetic and non-diabetic kidney disease. It is also vital that in addition to serious adverse events, information on quality of life and cost effectiveness be also collected for a comprehensive assessment from the patients’ and health-planners’ perspectives.

References

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Editorial Comment
Meguid El Nahas, Sheffield

The minireview by A. Faqah and T.H. Jafar exposes the issues related to BP target values in CKD. Numerous statements suggested that the lower the BP, the slower the progression of CKD. A number of guidelines have stipulated target values around 130/80 mm Hg and even lower in patients with diabetes and those with proteinuria. The evidence upon which these guidelines were based relied primarily on observational data as well as secondary or post hoc analyses of clinical trials and systematic and meta-analyses of heterogeneous data. This review exposes the weakness of such evidence. As so often in nephrology, evidence is gathered from observational studies that remain unsubstantiated by subsequent attempts at confirmation by RCTs. So often in nephrology, evidence is sought from secondary and post hoc analyses not intended or powered to answer the question raised...! So often in nephrology, dogma prevails enforced by unsubstantiated guidelines...!

Most RCTs mentioned in the review that attempted to answer whether intensive BP control is beneficial in slowing the progression of CKD failed to show a significant difference in renal functional outcomes. Furthermore,
concern about harm has been raised in those submitted to intensive treatment with increased morbidity and mortality.

Finally, the assumption that one size fits all with target systolic levels of <130 or 120 mm Hg is preposterous. Age, race and comorbidities may dictate different target levels. This is becoming apparent in patients on hemodialysis where older and diabetic individuals had higher mortality rates at lower (<140/70 mm Hg) BP levels. More remarkable was the observation in this cohort analysis that survival did not seem to be harmed by higher systolic and diastolic values [1]. In conclusion, it is high time that BP-related guidelines in CKD are reviewed; this is currently underway by KDIGO. It is also high time that nephrologists base their practice on substantiated guidelines…. It is also high time that nephrologists critically appraise the data submitted to them by 'experts' and refute assertions based on secondary and post hoc analyses as weak at best. We have a long way to go!

Reference