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BLOOD PRESSURE TARGETS FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

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Introduction

Hypertension is a major risk factor for the development and progression of chronic kidney disease (CKD) and can also be a consequence of kidney injury [1]. Several observational studies have shown a strong relationship between high blood pressure (BP) and increased risk for renal function decline or progression to end-stage renal disease (ESRD) in patients with or without diabetes, while in clinical trials patients with achieved BP below the conventional thresholds had longer renal survival [1, 2]. Thus, for more than a decade relevant guidelines have recommended a BP target of < 130/80 mm Hg for all individuals with CKD (and possibly < 125/75 for patients with proteinuria > 1 gr/day) [2–5], although evidence from trials with hard renal outcomes randomising patients to different BP targets was scarce [4]. In recent years, long-term extension data from such trials has appeared in the literature but, simultaneously, major cardiovascular studies have called into question the beneficial effects of a low BP goal for diabetic patients [6, 7], making selection of appropriate BP targets by the clinician a very complicated issue. Herein, we attempt to briefly clarify this field by presenting the available evidence for non-diabetic and diabetic CKD.

Blood pressure targets in non-diabetic kidney disease

The specific effects of different BP targets on hard renal end-points have been evaluated by two clinical trials in patients with non-diabetic CKD. The Modification of Diet in Renal Disease (MDRD) program included two sub-studies in patients with CKD of various aetiologies, of which 585 were in study A (glomerular filtration rate, [GFR] 25–55 mL/min/1.73 m^2) and 255 in study B (GFR 13–24 mL/min/1.73 m^2) [8]. Diabetic patients requiring insulin were excluded by protocol; thus, only 26 patients with diabetic nephropathy participated. In a 2 × 2 factorial design, patients were randomised into different levels of dietary protein consumption in both studies, as well as to a usual BP goal [mean arterial pressure (MAP) < 107 mm Hg for patients ≤ 60 years (roughly corresponding to < 140/90 mm Hg) and < 113 mm Hg for patients ≥ 61 years] or a low BP goal [MAP < 92 mm Hg for patients ≤ 60 years (corresponding to < 125/75 mm Hg) and < 98 mm Hg for patients ≥ 61 years]. The primary outcome was the rate of change in GFR (GFR slope) and the mean follow-up 2.2 years. Neither the projected decline in GFR (10.7 [95%CI, 9.1–12.4] vs. 11.5 [95%CI, 10.3–12.7) mL/min/1.73 m^2] nor the risk of ESRD and death (0.85, 95%CI, 0.60–1.22 for the low BP group) differed significantly between the groups [8]. However, in detailed analyses dividing patients by baseline proteinuria, the low target BP was associated with a slower GFR decline in patients with urine protein excretion > 0.25 g/day in study A and > 1 g/day in study B [8, 9], even after adjustment for numerous covariates.

The above findings were confirmed in a patient-level meta-analysis of trials comparing the efficacy ACE-inhibitors in patients with predominantly non-diabetic CKD, showing that SBP levels of 110–119 and 120–129 mm Hg were associated with lower risk of kidney disease progression in patients with proteinuria > 1 gr/day whereas in those with proteinuria < 1 gr/day this association was not evident [10]. A subsequent analysis examined long-term outcomes of the MDRD study adding the trial phase (1989–1993) to a cohort period between 1993–2000, with a potential median follow-up of 10.7 years during which no specific target BP was recommended [11]. In the long run the low target BP was associated with a reduced risk of kidney failure (adjusted hazard ratio [HR] 0.68; 95%CI, 0.57–0.82) and composite outcome of ESRD or death (HR 0.77; 95%CI, 0.65–0.91), compared with the usual target BP. In subgroup analyses the benefits from low target BP for ESRD and the composite end-point were again significant for patients with proteinuria > 1 gr/day. These findings indicated that a low-target BP may be particularly beneficial in proteinuric patients and led to the recommendations for target BP described above.

The second study on the field was the African-American Study on Kidney Disease (AASK), a 3 × 2 factorial trial of 1094 African-Americans with hypertensive renal disease (GFR, 20–65 mL/min/1.73 m^2) randomized to goal MAP of 102–107 mm Hg or ≤ 92 mm Hg, and to initial treatment with metoprolol, ramipril or amlodipine. The main outcomes were GFR slope and the composite of reduction in GFR by 50% or more (or ≥ 25 mL/min/1.73 m^2), ESRD or death. The mean achieved BP was 128/78 mm Hg in the lower BP group and 141/85 in the usual BP group. After a median follow-up of 3.8 years, neither the mean GFR slope (–2.21 ± 0.17 vs. –1.95 ± 0.17 mL/min/1.73 m^2 per year; P = 0.24) nor the composite outcome (risk reduction for intensive BP group 2%; 95%CI, –22% to 21%; P = 0.85) differed significantly between the BP groups whereas ramipril was associated with slower progression of renal disease [12].

After completing the trial phase of AASK, around 700 subjects were enrolled in a cohort phase in which the BP target was < 130/80 mm Hg, with total follow-up from 8.8 to 12.2 years. In the two phases together, there was no significant between-group difference in the risk of the composite outcome of doubling of serum creatinine (SCr), ESRD or death (HR in the intensive-control group, 0.91; 95%CI, 0.77–1.08). However, the outcome differed according to baseline proteinuria, as patients with urine protein-to-creatinine ratio (UPCR) > 0.22 in 24-hour collections (roughly equivalent to 300 mg/day) had lower risk of the primary outcome with intensive treatment (HR 0.73; 95%CI, 0.58––0.93) whereas in those with UPCR ≤ 0.22 there was no difference between BP groups (HR, 1.18; 95%CI, 0.93–1.50) [13].

Taken together, the findings from MDRD and AASK indicate that a low BP target is beneficial for long-term renal survival in patients with non-diabetic proteinuric kidney disease. It must be noted, however, that all available evidence derives either from sub-group analyses or from combination of randomized phases with long-term observational phases of these trials, and still no direct evidence is available on this issue. Further, both of these trials randomized to MAP levels, which correspond on average, but not for every patient, to specific levels of systolic and diastolic BP. With that in mind, a goal BP of < 130/80 (i.e. that of the AASK cohort study) seems justifiable for patients with urine protein excretion above 0.25–0.3 gr/day (equivalent to urine albumin around 0.15 gr/day) whereas a lower BP target of < 125/75 may be applicable for patients with proteinuria > 1 gr/day (Table 1).

Blood pressure targets in diabetic kidney disease

There are currently no clinical trials comparing the effects of different target BP levels on ESRD incidence in diabetic patients. Earlier randomized studies in patients with diabetes and varying levels of renal function and albumin excretion that compared different BP goals showed no difference in change of creatinine clearance but higher reductions of proteinuria and slower progression from micro- to macroalbuminuria with "intensive" versus "moderate" BP control [14, 15]. An analysis of controlled trials of diabetic kidney disease also suggested that lowering SBP to 130 mm Hg may be associated with a decrease in GFR loss down to 2 ml/min/1.73 m^2 per year [2]. A post hoc analysis of the RENAAL study (which included 1513 patients with type 2 diabetes, hypertension and macroalbuminuria and compared the effects of losartan versus placebo on renal disease progression) showed that baseline SBP of 140––159 mm Hg increased the risk for ESRD or death by 38%, compared to SBP < 130 mm Hg. Furthermore, every 10 mm Hg rise in baseline SBP increased the risk for ESRD or death by 6.7%, whereas the same rise in DBP decreased the risk by 10.9%; the authors concluded that patients with the highest baseline SBP and PP have the highest risk for nephropathy progression and the greatest benefit with aggressive reduction [16]. Similarly, a post-hoc analysis of the IDNT study [17] (including 1590 patients with type 2 diabetes, hypertension and urine protein excretion > 900 mg/d, to compare the effects of irbesartan, amlodipine and placebo) showed that SBP >149 mm Hg was associated with

Table 1. Blood pressure targets for patients with CKD based on available evidence from renal and cardiovascular trials

Type of kidney disease	Protein excretion < 0.3 g/day (normoalbuminuria, microalbuminuria, 30–150 mg/day)	Protein excretion 0.3–1 g/day (microalbuminuria 150–300 mg/day, macroalbuminuria 300–500 mg/day)	Protein excretion > 1 g/day (macroalbuminuria > 500 mg/day)
Non-diabetic kidney disease	< 140/90 mm Hg	< 130/80 mm Hg	<125/75 mm Hg*
Diabetic kidney disease	SBP < 130–140 mm Hg** DBP < 80 mm Hg**	< 130/80 mm Hg***	<130/80 mm Hg*** (<125/75 mm Hg*** for young patients with heavy proteinuria)

*As evident from MDRD study B trial phase and MDRD long-term study (*see text*); **from cardiovascular outcome trials (*see text*); ***through extrapolation from data in non-diabetic CKD and post-hoc or observational analyses in diabetic CKD (*see text*)

a 2.2-fold increase in the risk for doubling serum creatinine or ESRD compared with SBP < 134 mm Hg and follow-up achieved SBP most strongly predicted renal outcomes; moreover, progressive lowering of SBP to 120 mm Hg improved renal and patient survival, but below 120 mm Hg all-cause mortality increased.

Based on data like the above, and as the progression of renal injury appears to follow the same pathways once proteinuria develops, it has been argued that in patients with diabetes and proteinuria, the above BP targets for non-diabetic CKD should also apply [2]. This argument is generally accepted by the nephrology community, but large population studies suggest that the prevalence of macroalbuminuria (equivalent to proteinuria > 0.5 gr/day) in adult patients with diabetes is only around 10%, whereas another 20% have microalbuminuria and 70% have normoalbuminuria. Furthermore, around 11% of diabetic patients (rising to 26% of those > 65 years of age) have eGFR < 60 ml/min/1.73 m^2 [18]. Thus, an important amount of diabetic patients (especially elderly type 2 diabetics with concomitant hypertension) would have CKD Stage 3 or higher, without proteinuria. For these individuals a BP of < 130/80 mm Hg may not be required for renoprotection. However, a lower BP target could be warranted for cardiac and all-cause mortality benefits, as is evident from major cardiovascular trials in diabetes.

For more than 10 years all relevant guidelines have recommended a target BP of < 130/80 mmHg for patients with diabetes. The first evidence pointing towards a lower BP target derived from the UKPDS 38 study, which randomised 1148 hypertensive type 2 diabetic patients to a target BP of < 150/85 or < 180/105 mm Hg (and achieved mean BPs of 144/82 and 154/87 during 8.4 years); the "tight control" group had significant reductions of 38% in diabetes-related deaths and 24% in all diabetes-related endpoints [19]. Likewise, in the HOT study, which randomised 18,790 hypertensives to diastolic BP targets of ≤ 90, ≤ 85 or ≤ 80 mm Hg and showed no difference between groups in the total study-population, a 51% reduction in major cardiovascular events between ≤ 80 and ≤ 90 mm Hg was observed in the subgroup of 1501 diabetic patients [20]. Observational studies supported that SBP < 120 mm Hg in diabetes was related to reduced cardiovascular complications [21]. On this basis, a recommendation of target BP < 130/80 mm Hg in diabetes appeared in guidelines, although an SBP target < 130 mm Hg had not been examined in outcome trials, the "tight" control arms in UKPDS and HOT achieved mean SBPs > 140 mm Hg [19, 20] and this SBP target was difficult to achieve in clinical practice.

Further outcome trials attempted to examine this issue. The ADVANCE trial randomised 11,140 type 2 diabetics to fixed perindopril-indapamide combination or placebo, on top of background therapy. The mean BP was 135/74 vs. 140/76 in the two groups in 4.3 years of follow-up. Differences of 9% in major macrovascular or microvascular events, 18% in cardiovascular death and 14% in mortality favouring active treatment were noted [22]. These results indicated a favourable effect of further SBP lowering, but should be interpreted with caution as the main comparison was for a drug intervention. The ACCORD-BP trial randomized 4733 high-risk patients with type 2 diabetes to target SBP of < 120 mm Hg or < 140 mm Hg [23]. After 4.7 years no differences between groups were observed in the primary outcome of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death (HR 0.88; 95%CI: 0.73–1.06; $P = 0.20$) and all-cause mortality (HR 1.07; 95%CI: 0.85–1.35; $P = = 0.55$). Tight SBP control was associated with a 40% reduction in stroke but also with more serious adverse events (3.3% vs. 1.3%). Of note, the risk of any eGFR drop < 30 ml/min/1.73 m^2 increased with intensive treatment, but the risk of ESRD or dialysis was identical between groups. These findings were considered by many as conclusive evidence against the 130/80 BP target, but careful interpretation suggests differently for three reasons: first, the intensive SBP goal in ACCORD-BP was < 120 and not < 130 mmHg; second, after 1-year and until the study-end the mean SBPs were 119.3 and 133.5 mm Hg, respectively; and third, the event-rate was much lower than expected, leading to reduced power. Thus, the conclusion from ACCORD-BP was rather that a SBP target < 120 mm Hg in diabetes is not justified but the issue of optimal SBP target remained unresolved [6, 7].

Recent meta-analyses attempted to delineate the optimal SBP target in diabetes, showing insignificant decreases in mortality and myocardial infarction, and significant decreases in stroke with intensive targets [24, 25]. The main problem of these attempts was that they could not draw conclusions regarding specific targets but only comment on the comparative effectiveness of intensive versus standard BP-lowering "strategies". Furthermore, even with the stricter criteria, the mix-up of the "target" with actually "achieved" BPs in "standard" arms included led to problems similar to those of the ACCORD-BP study [7]. Of importance, both in the ACCORD and these meta-analyses the relative risks of all studied outcomes pointed strongly towards benefit with "intensive" BP lowering; thus, higher power could have led to significant differences favouring "intensive" goals. Overall, the DBP target of < 80 mm Hg seems justified for all patients with diabetes for reasons of reduction in cardiovascular end-points and mortality, especially since in the ACCORD trial the average DBP in the "standard care" group was much lower than 80 mm Hg. The critical question on the optimal SBP target remains unanswered but could be resolved by an adequately powered trial comparing < 130 versus < 140 mm Hg SBP goals and ensuring relevance of achieved BP to target BP levels. Until such evidence appears, caution in data interpretation and individualization of treatment is required. For example, a target level of < 125/75 may be easily tolerated and confer retardation of CKD progression in younger patients with type 1 diabetes, but in the elderly it could lead to frequent episodes of hypotension and acute renal failure (especially with concomitant aggressive RAS blockade or diuretic use, and atherosclerotic renal artery lesions), resulting in faster than expected renal function loss.

In conclusion, based on available data from observational analyses and surrogate outcomes and through extrapolation of evidence from non-diabetic proteinuric kidney disease, a BP < 130/80 mm Hg seems to protect kidney function in patients with diabetes and proteinuria > 0.3 gr/day (equivalent to albuminuria > 0.15 gr/day), Table 1. For the rest of patients with diabetic CKD, cardioprotection is the main determinant of BP targets; a diastolic target of < 80 mm Hg is somewhat warranted whereas the optimal SBP goal can be anywhere between 125 and 140 mmHg and should be decided on an individual basis according to anticipated benefits (proteinuria reduction) and risks (hypotension and acute renal failure).

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