Clinical Kidney Journal, 2020, vol. 13, no. 3, 287–290

doi: 10.1093/ckj/sfaa015
Advance Access Publication Date: 25 February 2020
Editorial Comment

EDITORIAL COMMENT

Blood pressure targets in patients with chronic kidney disease: MDRD and AASK now confirming SPRINT

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ABSTRACT

Recent American and European hypertension guidelines are not in agreement regarding blood pressure (BP) targets for persons with chronic kidney disease (CKD). Previous analyses from the African American Study on Kidney Disease (AASK) and Modification of Diet in Renal Disease (MDRD) trials suggested that strict BP control confers nephroprotection for patients with proteinuria, but a mortality benefit was not apparent. In contrast, an analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) subpopulation of CKD patients showed a mortality benefit with the systolic blood pressure (SBP) <120 mmHg versus the SBP <140 target. A recent analysis of the combined MDRD and AASK cohorts supports previous evidence on nephroprotection but also findings from the SPRINT trial on all-cause mortality benefits of intensive versus usual BP control in individuals with CKD.

Keywords: blood pressure targets, chronic kidney disease, end-stage kidney disease, hypertension, mortality, renal outcomes

Hypertension is the most common comorbidity accompanying chronic kidney disease (CKD), with prevalence estimated at 70–80% in Stage 1 and increasing to >90% in Stages 4 and 5, based on office blood pressure (BP) measurements [1, 2]. As in the case of diabetes mellitus, the target BP levels in CKD patients have been a matter of debate for years, with international guidelines over the past decades moving back and forth from <140/90 to <130/80 mmHg [3, 4]. So far, only two randomized trials have evaluated the effects of different BP targets on hard renal outcomes in patients with CKD, the Modification of Diet in Renal Disease (MDRD) study [5] and the African American Study on Kidney Disease (AASK) [6]; both of them included non-diabetic individuals.

The MDRD was a twin study [Study A, baseline glomerular filtration rate (GFR) 25–55 mL/min/1.73 m^2; Study B, baseline GFR 13–24 mL/min/1.73 m^2, median proteinuria 0.31–0.39 g/day] [5], in which 840 participants were randomized in a 2 × 2 factorial design to different dietary protein levels and a usual BP goal [mean arterial pressure (MAP) <107 and <113 mmHg for patients ≤60 and >60 years, respectively] or a low BP goal (MAP <92 and <98 mmHg for patients ≤60 and >60 years, respectively) for a mean follow-up of 2.2 years. The two BP arms showed similar projected GFR decline in 3 years (10.7 versus 11.5 mL/min/1.73 m^2) and risk of end-stage renal disease (ESRD) and death [0.85; 95% confidence interval (CI) 0.60–1.22 for low BP arm] [5]. A subsequent study, combining the randomized phase

Received: 7.1.2020. Editorial decision: 13.1.2020

and an observational phase of MDRD over a median 10.7-year follow-up (with no specific target BP recommended during the observational phase), showed that low BP goal was associated with reduced risk for ESRD [adjusted hazard ratio (HR) = 0.68; 95% CI 0.57–0.82] and the composite of ESRD or death (HR = 0.77; 95% CI 0.65–0.91) [7]. However, in subgroup analyses of both the randomized trial and the long-term study, the benefits of low BP target on GFR slope and the hard outcomes were evident only in patients with proteinuria, particularly those with proteinuria >1 g/day, which comprised 271 patients and were the subgroup with the highest incidence of events [7, 8].

The AASK trial randomized 1094 hypertensive African Americans with CKD (GFR 20–65 mL/min/1.73 m^2 and mean proteinuria, 0.6 g/day) in a 3 × 2 factorial design to treatment with metoprolol, ramipril or amlodipine, as well as to usual (MAP 102–107 mmHg) or low BP (MAP ≤92 mmHg) target. In the main trial, no significant differences between the two BP goals for any of the outcomes studied (GFR slope, composite of ≥50% or ≥25 mL/min/1.73 m^2 reduction in GFR from baseline, ESRD or death) was noted [6]. A further analysis in around 700 participants combining the trial phase and an additional observational phase, with a BP target of <130/80 mmHg for all participants for a total of 8.8–12.2 years, showed no significant difference between the usual and low BP goal groups in doubling of serum creatinine, ESRD or death (HR in low BP group, 0.91; 95% CI 0.77–1.08) [9]. Again, a significant interaction with the levels of baseline proteinuria was evident; i.e. patients with urine protein-to-creatinine ratio (UPCR) >0.22 g/g (about 320 mg/day) had lower risk for the primary outcome with intensive treatment (HR = 0.73; 95% CI 0.58–0.93), but there was no difference between BP arms for patients with UPCR ≤0.22 g/g (HR = 1.18; 95% CI 0.93–1.50) [9]. The incidence rate of events was 4.2-fold higher in the high proteinuria control group than in the low proteinuria controls. These findings from MDRD and AASK indicated that a low BP target can prolong renal survival in patients with non-diabetic kidney disease and proteinuria >0.25–0.3 g/day. Thus, with regards to renoprotection, a goal BP of <130/80 mmHg seemed justifiable for proteinuria >0.3 g/day, whereas a lower BP target of <125/75 mmHg could be helpful for patients with proteinuria >1 g/day [4, 10].

Despite the above evidence, a major question remained, i.e. whether a BP <130/80 mmHg would be able to also reduce cardiovascular events and mortality in patients with CKD. The Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9361 non-diabetic patients with systolic BP (SBP) ≥130 mmHg to intensive (SBP <120 mmHg) or standard treatment (SBP <140 mmHg) based on automated office BP measurements [11]. This trial was prematurely terminated (median follow-up 3.26 years) as the rate of the primary outcome (acute coronary syndrome with or without myocardial infarction, stroke, acute decompensated heart failure or death from cardiovascular causes) was significantly lower in the intensive treatment compared with the standard treatment group (HR = 0.75; 95% CI 0.64–0.89; P < 0.001). Importantly, the low BP target in this study produced a significant reduction in total mortality (HR = 0.73; 95% CI 0.60–0.90; P = 0.003), despite the premature termination of the study [11]. In SPRINT, 28% of the participants had estimated GFR (eGFR) <60 mL/min/1.73 m^2; this was an intended choice as patients with CKD have increased cardiovascular risk and the investigators wanted to include high-risk patient groups to increase the study power, especially since diabetes mellitus was an exclusion criterion. Results in the CKD subgroup suggested similar benefits for the primary outcome and all-cause mortality with low BP [11]. A pre-specified subgroup analysis in 2646 patients with CKD (eGFR 20–60 mL/min/1.73 m^2) from the SPRINT population showed non-significantly lower risk for the primary outcome (HR = 0.81; 95% CI 0.63–1.05) and lower mortality rate (HR = 0.72; 95% CI 0.53–0.99) in the intensive treatment compared with the standard treatment group [12]. The primary renal outcome (decrease in eGFR ≥50% or ESRD) occurred in 15/1330 intensive group and 16/1316 standard group participants (HR = 0.90; 95% CI 0.44–1.83) [12]. This, however, is not surprising as SPRINT was not powered to study renal outcomes, leading to very few hard renal events. Most importantly, increased albumin or protein excretion was not an inclusion criterion and thus, the majority of SPRINT participants with CKD had normoalbuminuria (median urinary albumin:creatinine ratio 13.3 mg/g). A low BP target is obviously not expected to confer renal benefits in the short follow-up of this group on low risk for renal disease progression, in accordance with the aforementioned findings of MDRD and AASK [7, 9].

Following this evidence favouring a low SBP target, the American College of Cardiology–American Heart Association High BP Clinical Practice Guidelines proposed BP thresholds of 130/80 mmHg for the diagnosis of hypertension in almost all individuals as well as a BP target of <130/80 mmHg for all hypertensive patients, including those with CKD [13]. In contrast, the recent European Society of Cardiology–European Society of Hypertension guidelines suggested a conservative SBP target range of 130–139 mmHg in CKD patients [14], which was higher than almost all other patient subgroups, without providing any clear rationale for this. Therefore, this recommendation rather confused the international nephrology community [15].

Recently, a very interesting observational study by Ku *et al.* compared the effects of intensive or usual BP control on renal outcomes and all-cause mortality in a cohort combining the MDRD and the AASK populations, adding to a total of 1907 patients with mean age of 53 ± 11 years, median GFR of 40 (28–52) mL/min/1.73 m^2 and urine protein excretion of 0.12 (0.04–0.62) g/day at baseline [16]. Over a median follow-up of 14.9 years, 438 deaths and 498 ESRD events in the strict BP control arm and 482 deaths and 526 ESRD events in the usual BP control arm occurred. This study showed that strict BP control was independently associated (after adjustment for age, sex, race, baseline proteinuria, GFR and body mass index) with lower risk of ESRD (HR = 0.88; 95% CI 0.78–0.99) compared with usual BP control. In subgroup analyses, low BP goal was associated with lower risk for ESRD in patients with proteinuria ≥0.44 g/g (HR = 0.77; 95% CI 0.64–0.92) but not in those with less baseline proteinuria (HR = 0.96; 95% CI 0.81–1.13), something totally expected as authors searched for the threshold at which effect modification by baseline proteinuria was present. The incidence of ESRD was 72% lower in the control group with lower baseline proteinuria than in controls with higher baseline proteinuria. What is, however, of major importance is that in this population, strict BP control was also associated with reduced risk of all-cause death in unadjusted (HR = 0.87; 95% CI 0.76–0.99) or adjusted (HR = 0.85; 95% CI 0.75–0.97) analyses. A trend towards lower mortality was observed for all studied subgroups, but it was significant for patients with higher proteinuria (HR = 0.77; 95% CI 0.62–0.96) and, interestingly, for those with GFR <30 mL/min/1.73 m^2 (HR = 0.73; 95% CI 0.59–0.92). Finally, the authors examined the risk of death before versus after the onset of ESRD, showing this to be 2- to 3-fold higher after onset of ESRD. Death rates after ESRD onset were significantly lower for patients in the strict (HR = 5.6; 95% CI 4.9–6.3) than those in the

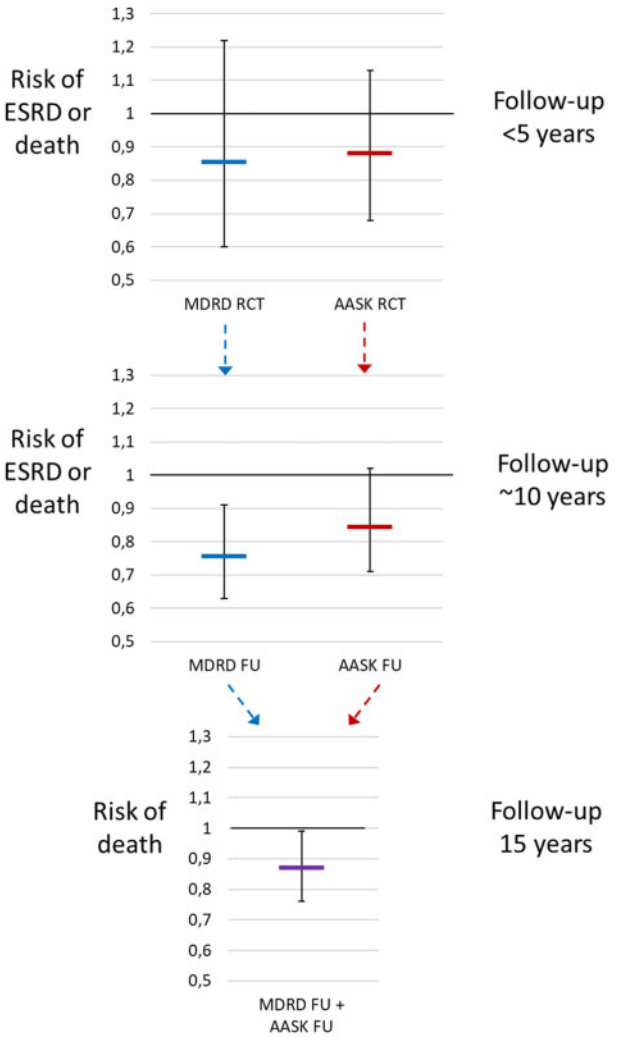

FIGURE 1: Impact of a low BP versus a conventional BP target on the risk of ESRD and/or death: data from the MDRD and AASK cohorts. Data are presented as published in the original publications for the MDRD (mean follow-up 2.2 years, relative risk shown) [5] and AASK randomized controlled trials (follow-up 3–6.4 years, adjusted risk reductions shown) [6], the MDRD (median follow-up 10.7 years, adjusted HR shown) [7] and AASK follow-up cohorts (follow-up 8.8–12.2 years, adjusted HR shown) [9], as well as for the combined MDRD and AASK follow-up cohorts (median follow-up 14.9 years, adjusted HR shown) [16]. Please note that only for the combined cohorts, death only data are presented alone. FU, follow-up.

usual BP control arm (HR = 7.1; 95% CI 6.4–8.0/100 person-years) [16].

Although clearly observational, the findings of the aforementioned study are an important addition to our knowledge, as they suggest that a low BP target can not only retard the progression of renal injury but also improve survival in a CKD population with an average GFR of 40 mL/min/1.73 m^2 and urine protein excretion of 0.12 g/day (Figure 1). This survival improvement may be more apparent in those most needed, i.e. patients with advanced CKD (Stage 4 or 5) and in the long term in those after ESRD onset. Based on this, it is rather obvious that the absence of significant effects of low BP target on mortality in each of the main MDRD and AASK was due to inadequate power (i.e. small sample size, short follow-up and young age of included participants) to assess differences in this outcome, simply because their primary aim was to investigate nephroprotection. This is a clear reminder that human studies should be interpreted within the appropriate context and that secondary analyses are also important, especially when studied phenomena need time to evolve. In this case, an objective reader would rather note that these results directly confirm the SPRINT findings, suggesting that a low BP target is not only safe but also beneficial with regards to mortality in the long-term in patients with non-diabetic CKD.

FUNDING

This article was not supported by any source and represents an original effort of the authors. Research by A.O. was supported by FIS PI16/02057, PI19/00588, PI19/00815, DTS18/00032, ERA-PerMed-JTC2018 (KIDNEY ATTACK AC18/00064 and PERSTIGAN AC18/00071), ISCIII-RETIC REDinREN RD016/0009 Fondos FEDER, FRIAT, Sociedad Española de Nefrología and Comunidad de Madrid B2017/BMD-3686 CIFRA2-CM.

CONFLICT OF INTEREST STATEMENT

A.O. has received research support, speaker fees or consultor fees from Sanofi, Amgen, Mundipharma, Servier, Kyowa-Kyrin and Otsuka. All other authors disclose that they do not have any financial or other relationships that might lead to a conflict of interest regarding this article.

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