BP Control and Long-Term Risk of ESRD and Mortality

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ABSTRACT

We recently showed an association between strict BP control and lower mortality risk during two decades of follow-up of prior participants in the Modification of Diet in Renal Disease (MDRD) trial. Here, we determined the risk of ESRD and mortality during extended follow-up of the African American Study of Kidney Disease and Hypertension (AASK) trial. We linked 1067 former AASK participants with CKD previously randomized to strict or usual BP control (mean arterial pressure ≤92 mmHg or 102–107 mmHg, respectively) to the US Renal Data System and Social Security Death Index; 397 patients had ESRD and 475 deaths occurred during a median follow-up of 14.4 years from 1995 to 2012. Compared with the usual BP arm, the strict BP arm had unadjusted and adjusted relative risks of ESRD of 0.92 (95% confidence interval [95% CI], 0.75 to 1.12) and 0.95 (95% CI, 0.78 to 1.16; *P*=0.64), respectively, and unadjusted and adjusted relative risks of death of 0.92 (95% CI, 0.77 to 1.10) and 0.81 (95% CI, 0.68 to 0.98; *P*=0.03), respectively. In meta-analyses of individual-level data from the MDRD and the AASK trials, unadjusted relative risk of ESRD was 0.88 (95% CI, 0.78 to 1.00) and unadjusted relative risk of death was 0.87 (95% CI, 0.76 to 0.99) for strict versus usual BP arms. Our findings suggest that, during long–term follow-up, strict BP control does not delay the onset of ESRD but may reduce the relative risk of death in CKD.

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Several large randomized, controlled trials have tested the use of lower BP targets (to goals lower than the conventional target of 140/90 mmHg) in adult patients with CKD. The primary results of the Modification of Diet in Renal Disease (MDRD) Study, the African American Study of Kidney Disease and Hypertension (AASK), and the Ramipril Efficacy in Nephropathy-2 (REIN-2) Study showed that targeting these lower goals did not delay progression of CKD to ESRD.[1–3] As a result, the panel appointed to the Eighth Joint National Committee (JNC 8) and multiple other national and international guidelines currently recommend a BP goal of 140/90 mmHg for patients with CKD.[4–7] However, the typical duration of follow-up in prior BP trials in CKD was 2.2 years in MDRD, 3.7 years in AASK, and 1.6 years in REIN-2 Study. The long–term renal and mortality benefits of strict BP control beyond the end of major BP trials in CKD have been controversial.[8–11] In observational studies that provide longer follow-up for adverse outcomes of interest, lower BP levels have been shown to associate with higher rates of all-cause mortality in patients with CKD.[8,12–14]

The Systolic Blood Pressure Intervention Trial (SPRINT) recently reported that lowering BP to a systolic BP target <120 mmHg reduced the risk of a composite cardiovascular disease outcome and total mortality in a diverse study population enriched with patients with CKD.[15] There was no evidence that the benefits observed in the SPRINT differed by CKD status during a median follow-up duration of 3.3 years. However, intensive BP lowering in the SPRINT was also associated with a higher risk of orthostatic hypotension, AKI, and electrolyte abnormalities; the long-term consequences of these adverse events are unclear.[15] In a recent *post hoc* analysis of the Secondary Prevention of Small Subcortical Strokes Trial, which randomized persons with a history of stroke to a lower systolic BP target of <130 mmHg during a mean follow-up of 3.7 years, intensive BP lowering was found to associate with more rapid renal function decline.[16] Understanding the long-term sequelae of intensive BP lowering beyond the typical duration of BP trials is important as clinical practice shifts toward more aggressive BP treatment following the results of the SPRINT.

Previously, we published data from two decades of follow-up of participants assigned to strict BP control during MDRD.[1,11] We showed that participants previously randomized to strict BP control had lower risk of all-cause mortality (hazard ratio [HR], 0.82; 95% confidence interval [95% CI], 0.68 to 0.98; P=0.03), but no difference in long-term risk of ESRD compared with usual BP control was noted. This association was only apparent after follow-up for deaths was extended into the ESRD phase of disease.[11]

To further inform the discussion about the long-term benefit of strict BP control in CKD, including assessing whether treatment to <140/90 mmHg is associated with long–term ESRD and mortality risk, we performed extended follow-up of the AASK enrollees who were previously randomized to strict versus usual BP control using a combination of direct follow-up and administrative data. In exploratory analyses, we also performed a meta-analysis of the long-term risk of ESRD and death using individual-level data from MDRD and AASK, two of the largest CKD trials that now provide two decades of follow-up for outcomes of interest.

RESULTS

The baseline characteristics of the AASK participants included in this study (n=1067) are shown in Table 1. Those randomized to strict versus usual BP control were balanced in terms of demographic characteristics and comorbidities, with the exception of smoking status at baseline (Table 1).

Median follow-up starting from the time of randomization until death was 14.4 (interquartile range, 9.6–15.8) years. This long–term follow-up for the 1067 (of 1094 original AASK participants) with available health identifiers is complete through June of 2012 given that our follow-up is achieved by linkage to administrative databases. There were 397 AASK participants who developed ESRD (Figure 1), including 207 in the usual BP control arm (incidence =3.71 per 100 person-years; 95% CI, 3.23 to 4.25) and 190 in the strict BP control arm (incidence =3.44 per 100 person-years; 95% CI, 2.98 to 3.96). The risk of ESRD in unadjusted Cox model was 0.92 (95% CI, 0.75 to 1.12) and 0.95 (95% CI, 0.78 to 1.16; P=0.64) in adjusted Cox models, comparing strict versus usual BP arms (Figure 2A).

There were 249 deaths among those randomized to the usual BP control arm (incidence =3.70 per 100 person-years; 95% CI, 3.27 to 4.19) and 226 in the strict BP control arm (incidence =3.42 per 100 person-years; 95% CI, 3.00 to 3.90). There was no statistically significant difference in the risk of death between strict versus usual BP arms in unadjusted Cox model (HR, 0.92; 95% CI, 0.77 to 1.10; P=0.36) (Figure 2B). In adjusted Cox models, the risk of death was 0.81 (95% CI, 0.68 to 0.98; P=0.03).

There were no significant interactions noted between BP goal assignment and proteinuria, baseline GFR, or antihypertensive drug assignment (all P>0.05) for the outcome of mortality. There was also no statistically significant interaction between BP goal assignment and baseline GFR or antihypertensive drug assignment (all P>0.05) for the outcome of ESRD. However, there was a statistically significant interaction between BP assignment and proteinuria for the risk of ESRD (P=0.02). For participants who had <1 g/d proteinuria at baseline (n=892), risk of ESRD was 1.05 (95% CI, 0.83 to 1.32) comparing strict versus usual BP arms. In participants who had ≥1 g/d proteinuria at baseline (n=175), risk of ESRD was 0.59 (95% CI, 0.41 to 0.85) comparing strict versus usual BP arms in unadjusted analysis.

Characteristics of the study population in meta-analysis of individual-level data from AASK and MDRD are shown in Supplemental Table 1. During median follow-up duration of 14.9 years (interquartile range, 10.2–17.2 years) from time of

Table 1. Characteristics of participants in AASK with long–term follow-up by BP arm assignment at time of randomization

Characteristics at Time of Randomization	Strict BP, *n*=522	Usual BP, *n*=545	*P* Value
Mean age ± SD, yr	54.3±10.8	54.2±10.4	0.78
Men	321 (61.5)	332 (60.9)	0.85
Systolic BP ± SD, mmHg	151.6±24.9	149.1±22.6	0.09
Diastolic BP ± SD, mmHg	96.2±14.8	94.9±13.7	0.14
Mean GFR ± SD, ml/min per 1.73 m^2	46.8±13.3	46.1±14.0	0.40
Median proteinuria [interquartile range], g/d	0.12 [0.04, 0.53]	0.11 [0.04,0.59]	0.75
Current smoker	176 (33.7)	135 (24.8)	0.004
Heart disease[a]	282 (54.0)	264 (48.4)	0.07
Drug arm assignment			0.91
Angiotensin–converting enzyme inhibitor	207 (39.7)	218 (40.0)	
β-Blocker	209 (40.0)	222 (40.7)	
Calcium channel blocker	106 (20.3)	105 (19.3)	

All values are provided as *N* (%) unless otherwise specified.
[a]Heart disease was determined at baseline on the basis of a combination of self-report, chart review, or baseline electrocardiogram reading.

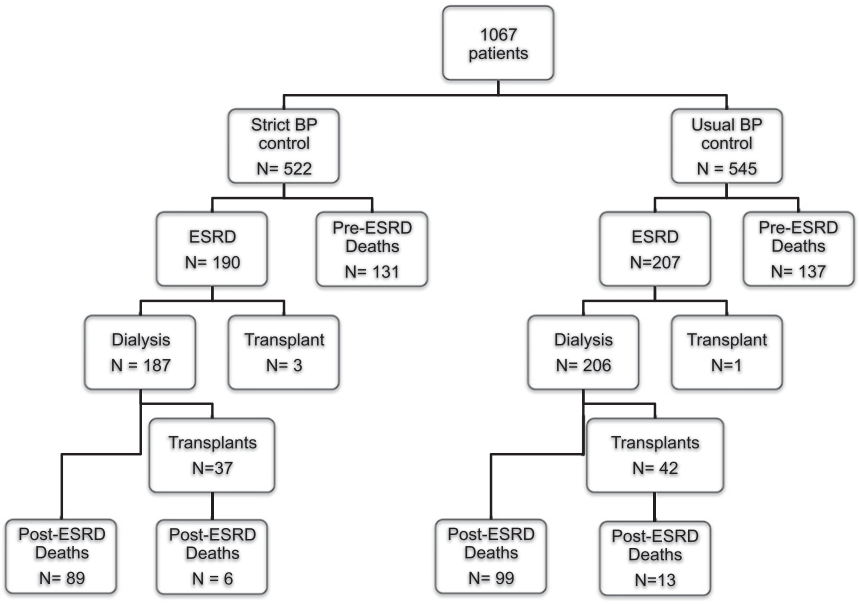

Figure 1. Long-term follow-up in AASK. Distribution of ESRD and deaths by BP study arm assignment in AASK.

randomization until death, a total of 1024 participants developed ESRD (Supplemental Figure 1). Risk of ESRD in unadjusted pooled analysis was 0.88 times lower in the strict versus usual BP arms (95% CI, 0.78 to 1.00; *P*=0.04) (Supplemental Figure 2A). Of the 1024 patients with ESRD, 39% occurred in AASK, and 61% occurred in MDRD. Of the 920 deaths that occurred, 52% of deaths occurred in AASK, and 48% occurred in MDRD. Participants previously randomized to strict BP control had a lower risk of death, regardless of ESRD status (unadjusted HR, 0.87; 95% CI, 0.76 to 0.99) (Supplemental Figure 2B).

DISCUSSION

There has been significant debate over the optimal BP target for persons with CKD, and BP targets have changed with each recent update of the JNC guidelines.[5,17–21] Most of the evidence to date on BP control in patients with CKD but without diabetes has been from trials using GFR decline or ESRD onset as their primary outcome.[1–3] However, important end points other than retarding CKD progression, such as all-cause mortality, may also inform the debate regarding BP targets and the safety of intensive BP lowering in patients with CKD. In our previous analysis of MDRD, we concluded that strict BP control during CKD could potentially offer a mortality benefit, which became evident when deaths after ESRD were included in long–term follow-up.[11] Our observations in MDRD are consistent with the results of SPRINT but not with recent observational studies that have suggested that strict BP control may paradoxically increase risk of death.[8,12–14]

Our analysis of long–term follow-up in 98% of formal AASK enrollees provides reassuring data that intensive BP control was not associated with significant harm in terms of risk of ESRD or death in our primary AASK analysis (which included deaths before and after ESRD), and we observed a tendency toward benefit for both outcomes of interest in our primary analysis. In sensitivity analysis using adjusted models, there was a statistically significant benefit to strict BP control for the outcome of all-cause mortality in AASK. Although the duration of BP intervention in AASK was only during the trial phase of AASK compared with the total duration of follow-up in our study, we had previously showed the potential for trial interventions to have long-lasting effects in MDRD, and similar effects of other trial interventions have been shown in contexts outside of nephrology.[10,11,22–25] However, we do note that the benefit of a strict BP control strategy was less robust in its effect size in AASK compared with our prior MDRD results.[11]

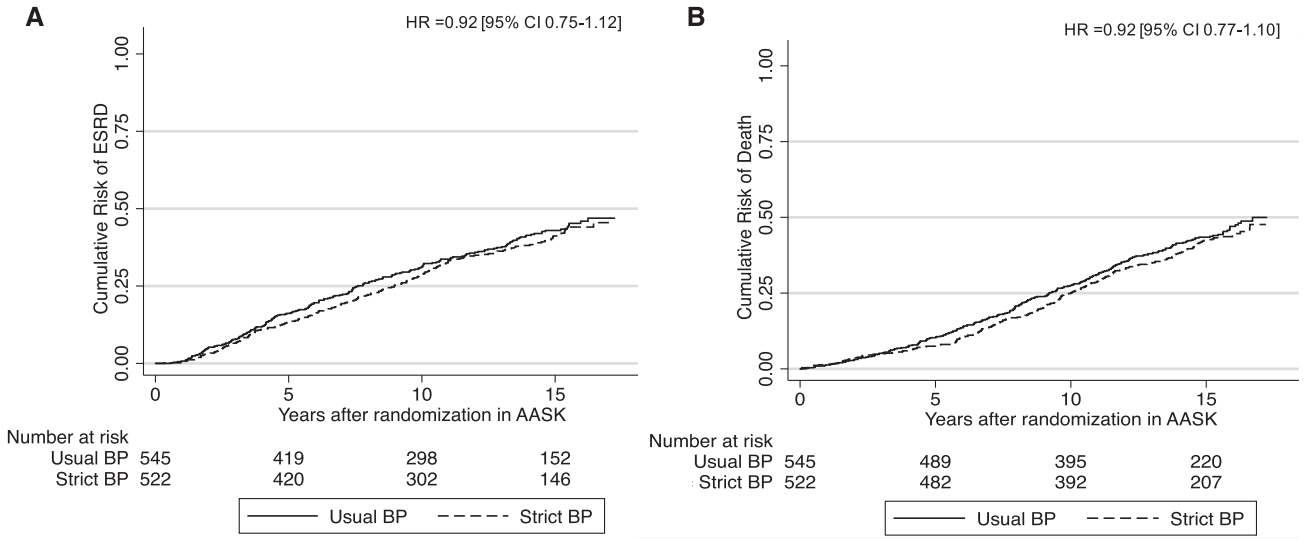

Figure 2. Long-term risk of adverse outcomes in AASK. Risk of (A) ESRD and (B) death during long–term extended follow-up of participants in the AASK.

There are several reasons why the association between BP treatment strategy and mortality risk may have been less robust in AASK compared with our prior findings in MDRD. First, there may be racial differences in the response to pharmacologic BP treatment and its benefit on long–term (post–ESRD) mortality risk.[26,27] MDRD was a predominantly white cohort, whereas AASK only enrolled blacks. The benefit of intensive BP control during CKD may not extend to mortality benefits in similar fashion in both blacks and whites. It is also important to note that the overall rate of cardiovascular events was low during the AASK trial and cohort studies,[28] and patients at elevated cardiovascular risk were excluded. This may account for some of the differences in our findings behind MDRD and AASK.

Second, the distribution of deaths was different in MDRD and AASK. Although a higher number of deaths occurred in AASK (n=475) compared with MDRD (n=445), the majority of deaths in AASK occurred before ESRD onset, whereas the majority of deaths in MDRD occurred after ESRD, possibly because of the lower baseline GFR in MDRD.[11] The benefit of strict BP control was noted to be especially prominent after ESRD onset in our prior MDRD analysis. Because AASK had a smaller number of deaths occur after ESRD, this may have contributed to the differences in our results.

Third, unlike in MDRD, where no specific BP treatment strategy was specified after the end of the trial, 63% of AASK trial participants were enrolled in AASK cohort study after trial closure if they had not developed ESRD or died. During the AASK cohort, BP was managed per protocol to a target of <130/80 mmHg.[9] Thus, the crossover of the patients in AASK previously randomized to the usual BP control arm to a more strict BP control strategy may have attenuated the differences in the two arms.

Fourth, the AASK participants all had hypertensive nephrosclerosis as the cause of their CKD, whereas the MDRD participants were a more heterogeneous population (including approximately 20% of participants with polycystic kidney disease). Cause of CKD could potentially be important in the effect of strict BP control on mortality risk after ESRD.

Our long–term observational follow-up of the effect of the delivered BP intervention during AASK should be interpreted in the context of the results of SPRINT, which was terminated after showing that, among patients without diabetes at high risk for cardiovascular events, targeting a systolic BP of <120 mmHg compared with <140 mmHg resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause.[15] This cardiovascular and mortality benefit was not different in patients with and without CKD, with risk of death being 0.82 times lower (95% CI, 0.63 to 1.07) in the intensive versus standard treatment arm in the CKD subgroup and similar to our effect sizes in both MDRD and AASK. However, it should again be highlighted that our study differs from SPRINT in that we included deaths before and after ESRD in our analysis.

Of note, we could not provide consistent evidence that strict BP control lowers the long-term risk of ESRD in either the AASK or the MDRD Trials when analyzed separately, although in subgroup analysis, the AASK participants with higher levels of proteinuria (≥1 g/d) did seem to have a benefit from strict BP control.[9] In our primary mortality analysis of the MDRD data, sensitivity analysis of the AASK data using adjusted models, and meta-analysis of the two data sources, there was a consistent and statistically significant reduction in the risk of mortality during long–term follow-up.[11] Although the historical focus in prior trials conducted in patients with CKD has been on the role of intensive BP control in delaying risk of ESRD, the long-term benefit of nonrenal outcomes may be

more sensitive to this intervention. Thus, our study does provide some reassurance that—not withstanding any acute rises in serum creatinine associated with more intensive BP lowering (such as that observed in the SPRINT)[15,29]—there was no evidence of an increased risk of ESRD during long–term follow-up.

The strengths of our study include the preservation of the intention to treat analysis on the basis of the original randomized control trial design and the ascertainment of long–term hard outcomes on 98% of the original AASK enrollees. In addition, we include deaths both before and after ESRD in our study, which is unique. Limitations to this study include the lack of follow-up data on BP levels after the end of AASK. We also acknowledge that the racial background and cause of CKD differ significantly between MDRD and AASK, which may complicate the interpretation of the combined study results. In addition, trial participants represent a select group of patients, and therefore, results from trials may not always generalize to the general CKD population. Nevertheless, randomized trials provide the best internal validity regarding the effect of interventions and are the best guide to both potential benefits and harms of treatment.

In conclusion, strict BP control in black clinical trial participants was not associated with increased risk of all-cause mortality, a concern raised by a number of observational studies.[8,12,14] There was also no evidence of a difference in the risk of ESRD in association with an intensive BP control strategy during long–term follow-up of AASK participants overall, although those with significant proteinuria may benefit from this strategy. Overall, our data suggest that strict BP control strategy may lead to a mortality benefit and are consistent with those of SPRINT. We believe that our data offer useful evidence of the long-term association between intensive BP control and renal and nonrenal outcomes.

CONCISE METHODS

The AASK

The AASK was a large 2×3 factorial randomized, controlled trial that assessed the effect of strict BP control and antihypertensive agents on the progression of CKD in blacks. Details of the trial design and results have been published.[3,30,31] Between 1995 and 2001, participants between 18 and 70 years of age with GFR=20–65 ml/min per 1.73 m^2 were randomized to either strict (mean arterial pressure [MAP] ≤92 mmHg) or usual (MAP=102–107 mmHg) BP control. Patients were also simultaneously randomized to an angiotensin–converting enzyme inhibitor (ramipril), sustained release β-blocker (metoprolol), or calcium channel blocker (amlodipine) as their first antihypertensive agent in 2:2:1 assignment, respectively. The amlodipine arm was stopped early in September of 2000 because of an interaction between BP intervention and proteinuria.[30] During the trial, the mean differences between the strict and usual BP control arms in systolic BP, diastolic BP, and MAP were 12, 7, and 10 mmHg, respectively.[3]

At trial closure, 689 participants (of the original 1094) who had not developed ESRD or died continued in the AASK cohort phase of the study, which began in April of 2002 and ended June 30, 2007.[9,32] All AASK cohort participants were switched as first-line therapy to an angiotensin–converting enzyme inhibitor or angiotensin receptor blocker if angiotensin–converting enzyme inhibitor could not be tolerated with a target BP of <140/90 mmHg, which was modified in 2004 to <130/80 mmHg as a result of the JNC 7 guidelines.[9,33] During the AASK cohort phase (mean follow-up of 3.4 years), the mean BP was 131/78 mmHg in participants previously assigned to strict BP control and 134/78 mmHg in participants previously assigned to usual BP control.[9]

Outcome

The primary outcomes of interest in our study were ESRD and all-cause mortality, including deaths before and after ESRD onset. To extend ascertainment of ESRD and vital status through June 30, 2012, we performed linkage of the AASK participants with the US Renal Data System (USRDS), the national ESRD registry, and the Social Security Death Index (SSDI), which compiles national death data. For this study, to ensure uniform ascertainment over the entire study duration, we defined ESRD as receipt of chronic dialysis or kidney transplant according to the USRDS database. For participants who developed ESRD, death dates after ESRD were obtained from the USRDS database. For patients who did not develop ESRD, death dates were ascertained using the AASK trial and cohort data if these deaths occurred before June 30, 2007. For the AASK trial and cohort participants who were not known to have died or developed ESRD, a search of the SSDI was undertaken to ascertain deaths. Patients were administratively censored if they were alive as of June 30, 2012, the most recent year of the USRDS data available at the time of study performance. The USRDS and SSDI have been validated previously as accurate data sources for ESRD onset and death dates, respectively, and have been used in other studies.[10,34–38]

Patients without identifiers available for linkage to external databases (n=27) were excluded from analyses. Institutional review board approval was obtained for data linkage at all 21 original AASK clinic centers, Cleveland Clinic Data Coordinating Center, and University of California, San Francisco.

Statistical Analyses

We tested for differences between characteristics at the time of randomization and ESRD onset using t test, chi-squared test, or Kruskal–Wallis test as appropriate. To preserve the original randomization scheme, all primary analyses were conducted in an intention to treat fashion. The primary outcomes, ESRD and all-cause mortality, were assessed by BP goal assignment in an unadjusted Cox model starting at the time of randomization.

In sensitivity analysis, we repeated these analyses adjusting for age, sex, baseline heart disease, baseline log–transformed proteinuria, and baseline smoking history (because of an imbalance between randomization arms between the strict and usual BP arms) at time of randomization.[11]

We tested for interactions between randomized BP goal and baseline GFR or log-transformed proteinuria as continuous variables

for the outcomes of ESRD and death.[11] Because of an interaction between BP goal and proteinuria for the outcome of ESRD, we then performed subgroup analysis by baseline urine protein <1 versus ≥ 1 g/d.[10] We also tested for interactions between BP arm assignment and antihypertensive drug class assignment in AASK for both primary outcomes.[3]

Individual–Level Meta–Analysis: The AASK and the MDRD Trial

After completion of our preplanned analysis, we performed a supplementary meta-analysis of individual-level data from MDRD and AASK and repeated our unadjusted Cox models examining the risk of ESRD and all-cause mortality (including deaths before and after ESRD) with stratification by data source. Stata 13 (StataCorp., College Station, TX) and SAS (SAS Institute Inc., Cary, NC) were used for the performance of all statistical analyses. P values <0.05 were considered statistically significant for all analyses, including interaction terms.

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DISCLOSURES

None.

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