Title

Effect of Blood Pressure Control on Long-Term Risk of End-Stage Renal Disease and Death Among Subgroups of Patients With Chronic Kidney Disease

Journal

Journal of the American Heart Association, 8(16)

ISSN

2047-9980

Authors

Ku, Elaine
Sarnak, Mark J
Toto, Robert
et al.

Publication Date

2019-08-20

DOI

10.1161/jaha.119.012749

ORIGINAL RESEARCH

Effect of Blood Pressure Control on Long-Term Risk of End-Stage Renal Disease and Death Among Subgroups of Patients With Chronic Kidney Disease

Elaine Ku, MD, MAS; Mark J. Sarnak, MD; Robert Toto, MD; Charles E. McCulloch, PhD; Feng Lin, MS; Miroslaw Smogorzewski, MD; Chi-yuan Hsu, MD, MSc

***Background*—**Our objective was to explore the effect of intensive blood pressure (BP) control on kidney and death outcomes among subgroups of patients with chronic kidney disease divided by baseline proteinuria, glomerular filtration rate, age, and body mass index.

***Methods and Results*—**We included 840 MDRD (Modification of Diet in Renal Disease) trial and 1067 AASK (African American Study of Kidney Disease and Hypertension) participants. We used Cox models to examine whether the association between intensive BP control and risk of end-stage renal disease (ESRD) or death is modified by baseline proteinuria (≥0.44 versus <0.44 g/g), glomerular filtration rate (≥30 versus <30 mL/min per 1.73 m^2), age (≥40 versus <40 years), or body mass index (≥30 versus <30 kg/m^2). The median follow-up was 14.9 years. Strict (versus usual) BP control was protective against ESRD (hazard ratio $[HR]_{ESRD}$, 0.77; 95% CI, 0.64–0.92) among those with proteinuria ≥0.44 g/g but not proteinuria <0.44 g/g. Strict (versus usual) BP control was protective against death (HR_{death}, 0.73; 95% CI, 0.59–0.92) among those with glomerular filtration rate <30 mL/min per 1.73 m^2 but not glomerular filtration rate ≥30 mL/min per 1.73 m^2 (HR_{death}, 0.98; 95% CI, 0.84–1.15). Strict (versus usual) BP control was protective against ESRD among those ≥40 years (HR_{ESRD}, 0.82; 95% CI, 0.71–0.94) but not <40 years. Strict (versus usual) BP control was also protective against ESRD among those with body mass index ≥30 kg/m^2 (HR_{ESRD}, 0.75; 95% CI, 0.61–0.92) but not body mass index <30 kg/m^2.

***Conclusions*—**The ESRD and all-cause mortality benefits of intensive BP lowering may not be uniform across all subgroups of patients with chronic kidney disease. But intensive BP lowering was not associated with increased risk of ESRD or death among any subgroups that we examined. **(*J Am Heart Assoc*. 2019;8:e012749. DOI: 10.1161/JAHA.119.012749.)**

Key Words: chronic kidney disease • end-stage renal disease • hypertension • mortality

The 2017 American Heart Association guidelines recently lowered the blood pressure (BP) level that defines hypertension from 140/90 to 130/80 mm Hg for all patients with chronic kidney disease (CKD).[1] These guidelines were strongly influenced by the results of the recent SPRINT (Systolic Blood Pressure Intervention Trial), which demonstrated lower cardiovascular morbidity and all-cause mortality among patients with and without CKD at elevated cardiovascular risk who were randomized to a lower systolic BP target of <120 mm Hg.[1–3] However, the results of SPRINT have sparked considerable debate over optimal BP targets for individuals with different risk factors.[4–6]

Despite the cardiovascular and mortality benefit seen with intensive BP lowering, SPRINT did not demonstrate a benefit of strict BP control on renal outcomes before the trial was stopped early by the Data Safety and Monitoring Board. But there were only a small number of kidney events in SPRINT.[7] The results of SPRINT are consistent with those of other trials in nondiabetic CKD, which also failed to demonstrate in their primary analyses a benefit to intensive BP lowering over a relatively short time period on renal or mortality outcomes.[8–11] Post hoc analyses of SPRINT have suggested potential harm with an intensive BP-lowering approach among patients with

From the Division of Nephrology, Department of Medicine (E.K., C.-y.H.), Division of Pediatric Nephrology, Department of Pediatrics (E.K.), and Department of Epidemiology and Biostatistics (C.E.M., F.L.), University of California, San Francisco, San Francisco, CA; Division of Nephrology, Department of Medicine, Tufts University, Boston, Massachusetts (M.J.S.); University of Texas Southwestern Medical Center, Dallas, TX (R.T.); and Division of Nephrology and Hypertension, Department of Medicine, University of Southern California, Los Angeles, CA (M.S.).

Accompanying Tables S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012749

Correspondence to: Elaine Ku, MD, MAS, Division of Nephrology, University of California, San Francisco, 533 Parnassus Ave, U404, Box 0532, San Francisco, CA 94143-0532. E-mail: elaine.ku@ucsf.edu

Received March 22, 2019; accepted July 17, 2019.

Clinical Perspective

What Is New?

- Intensive blood pressure lowering has variable effects on the risk of end-stage renal disease and mortality, depending on the presence or absence of baseline risk factors among patients with chronic kidney disease.

What Are the Clinical Implications?

- Intensive blood pressure lowering appears to be especially beneficial in reducing risk of end-stage renal disease among patients who are older, are obese, or have more proteinuria.
- Intensive blood pressure lowering is also especially beneficial in reducing the risk of death among those with advanced chronic kidney disease.

CKD, including a higher risk for acute kidney injury, although most patients with CKD did recover from these acute kidney injury episodes, and acute kidney injury was not a primary outcome in SPRINT.[2,12]

Because the duration of most clinical trials of intensive BP control have been short (mean duration, ≈3 years),[8–11] trials that are stopped early may have exaggerated effect sizes,[13,14] and lower BP targets may be difficult to achieve in all patients with CKD, there is a need for longer-term studies of the effect of intensive BP control on CKD and mortality outcomes, which may occur over many years. In particular, there is a paucity of trial-based evidence to support appropriate BP targets among patients with advanced CKD (stage 4 or beyond) and among young patients with CKD (eg, 18–40 years of age) because of their underrepresentation in most clinical trials. There have also been few studies that have examined whether the effect of intensive BP lowering is more pronounced among patients who have other concurrent metabolic or cardiovascular risk factors, such as obesity, a known risk factor for both CKD progression and death.[15–18] Furthermore, current guidelines suggest that selection of BP targets be based on the estimated atherosclerotic cardiovascular disease risk, but the available risk estimators have not been validated and may not be applicable to patients <40 years of age.[1,19]

The objective of this study was to explore the long-term effects of intensive BP lowering on the risk of end-stage renal disease (ESRD) or death among CKD subgroups of interest. We were specifically interested in determining: (1) the threshold of baseline proteinuria that associates with renal or mortality benefit given prior post hoc analysis of trials that have noted at least a renal benefit from intensive BP control among patients with varying degrees of proteinuria[20–23]; (2) whether intensive BP lowering has differential effects on the risk of ESRD or death in those with advanced (glomerular filtration rate [GFR] <30 mL/min per 1.73 m^2) versus earlier stages of CKD; and (3) whether intensive BP lowering has differential effects in younger patients (<40 years of age) or among obese patients (body mass index [BMI] ≥30 kg/m^2). In addition, we were also interested in whether the impact of intensive BP lowering on mortality risk was primarily noted during the CKD phase of illness versus after the onset of ESRD (overall and by subgroups of interest). To enhance our ability to perform subgroup analyses, we pooled participants from 2 completed randomized controlled trials with long-term follow-up for study: the AASK (African American Study of Kidney Disease and Hypertension) and the MDRD (Modification of Diet in Renal Disease) trial.[8,10,20,24]

Methods

Study Population

AASK was a large 2×3 factorial randomized controlled study that assessed the effect of strict BP control and antihypertensive agents on the progression of CKD in blacks (N=1094). Details of the trial design and results have been published.[10,20,24] Between 1995 and 2001, participants between 18 and 70 years of age with measured GFR 20 to 65 mL/min per 1.73 m^2 were randomized to either strict (mean arterial pressure [MAP] ≤92 mm Hg) versus usual (MAP 102–107 mm Hg) 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-line antihypertensive agent in 2:2:1 assignment, respectively. Patients with a history of malignant hypertension, diabetes mellitus, causes of renal disease other than hypertensive nephrosclerosis, pregnancy, clinical evidence of heart failure, or proteinuria ≥2.5 g/d were excluded from study. At trial closure, 689 participants (of the original 1094) who had not developed ESRD or died continued in the observational cohort study, which began in April 2002 and ended June 30, 2007.[23,25] 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 mm Hg, which was modified in 2004 to <130/80 mm Hg as a result of publication of the Joint National Committee 7 guidelines.[23,26]

The MDRD trial was a large 2×2 factorial design randomized controlled trial of the effect of strict BP control and dietary protein restriction on the progression of CKD (N=840). Details of the study design and results have been previously published.[8] Briefly, between 1989 and 1993, CKD patients between 18 and 70 years of age with measured GFR 13 to 55 mL/min per 1.73 m^2 were randomized to either strict or usual BP control.[8,27] Strict BP control was defined as a target

MAP ≤92 mm Hg (corresponds to 125/75 mm Hg) for participants <61 years of age and a target MAP ≤98 mm Hg (corresponds to 135/80 mm Hg) for participants ≥61 years of age. Usual BP control was defined as a target MAP ≤107 mm Hg (corresponds to 140/90 mm Hg) for participants <61 years of age and a target MAP ≤113 mm Hg (corresponds to 160/90 mm Hg) for participants ≥61 years of age.[8] Angiotensin-converting enzyme inhibitors with or without diuretics were encouraged as first-line antihypertensive agents. Patients with urine protein ≥10 g/d, diabetes mellitus requiring insulin, class 3 or 4 heart failure, doubtful compliance, pregnancy, or serum albumin <3 g/dL were excluded. At trial closure, no specific BP targets were recommended, and data on long-term BP control after trial closure are not available.

The MDRD trial and AASK primary data have been made publicly available at the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository and can be accessed at https://repository.niddk.nih.gov/home/.[28]

Outcome

The primary outcomes of interest in our study were ESRD and mortality. To extend ascertainment of ESRD and vital status through 2012, we performed linkage of AASK and MDRD trial participants with the US Renal Data System, the national ESRD registry, and the national death indexes, as previously described.[29–32] Patients were censored as of June 30, 2012, if they had not developed ESRD or died by this date. For this study, to ensure uniform ascertainment, we defined ESRD as receipt of chronic dialysis or kidney transplant, according to the US Renal Data System database, over the entire study duration. AASK patients without identifiers available for linkage to external databases (N=27) were excluded from analyses, leaving 1067 participants for inclusion in the present study. No MDRD trial participants were excluded from study. Institutional review board approval was obtained for data linkage at the University of California, San Francisco, and the Cleveland Clinic.

Statistical Analysis

We included 1067 AASK participants and 840 MDRD trial participants for study, and we pooled both trials for analysis to enhance generalizability and power among the subgroups of interest after testing for and finding no interaction between BP arm assignment and trial data source for both outcomes of interest. We tested for differences between characteristics of patients in subgroups of interest using *t* tests, Wilcoxon rank-sum tests, and χ^2 tests.

To preserve the original randomization scheme, all primary analyses were conducted in an intention-to-treat manner using BP arm assignment as the primary predictor, but all primary models allowed for different baseline hazards for each trial in our Cox models. Risk factors of interest that we thought could modify the effect of intensive BP control on outcomes included level of GFR ≥30 or <30 mL/min per 1.73 m^2 (according to Kidney Disease Improving Global Outcomes guidelines for CKD staging),[33] age (≥40 or <40 years), and BMI (≥30 or <30 kg/m^2): these cutoffs were selected as clinically relevant thresholds for each factor of interest. Thus, we first performed stratified analysis by the risk factor of interest (eg, stage 4–5 CKD versus stage 3 CKD) using unadjusted Cox models for the outcomes of ESRD and death in separate models, pooling data from both trials and allowing separate baseline hazards for each trial. Both pre-ESRD and post-ESRD deaths were included. In Cox models with ESRD as the outcome, deaths occurring before ESRD were treated as a censoring event. In sensitivity analysis, we treated death as a competing risk in Fine-Gray models focused on ESRD. We considered unadjusted models our primary analysis given that we were testing the effect of the randomized intervention among subgroups of interest.

In secondary analysis, we repeated these analyses, adjusting for age, sex, race, measured GFR, BMI, and proteinuria category, but still allowed separate baseline hazards for each trial.

Next, we explored whether interactions were present between randomized BP goal assignment and kidney function, age, or BMI categories using our primary models for the risk of ESRD and death using pooled trial data. Tests for interaction were performed in separate models for each risk factor of interest.

We also tested for the presence of interaction between the logarithm of proteinuria (as a continuous variable) and the BP target assignment. Once we found the presence of an interaction, we determined the threshold of proteinuria at which intensive BP lowering was associated with risk of ESRD by using Cox models with 0.1g/g incremental thresholds of proteinuria to find the exact magnitude of proteinuria at which strict BP control became associated with benefit for the outcome of ESRD (ie, such that there was an interaction between BP arm assignment and proteinuria categories; Table S1). We found a difference in the risk of ESRD when proteinuria levels were <0.44 g/g. We then performed unadjusted and adjusted Cox models stratified by proteinuria categorized as ≥0.44 or <0.44 g/g as described above, and explored whether an interaction was present between BP arm assignment and proteinuria category.

Finally, we examined whether there was a difference in the effect of strict versus usual BP control on risk of death during the pre-ESRD phase of illness versus after the onset of ESRD.

We tested for interaction between BP arm assignment and ESRD onset (as a time-dependent covariate) for the risk of death.

We then examined the death rate during the CKD compared with the ESRD phase of illness overall and by subgroups of interest. Log-rank tests were used to determine whether the rate of death differed by BP arm assignment among all groups of interest.

All analyses were conducted using Stata 14 and verified by separate analyst using SAS. Institutional Review Board approval was obtained at University of California, San Francisco, for data linkage and secondary data analysis. Informed consent was obtained from all subjects for participation in the MDRD trial and AASK and AASK cohort studies.

Results

The baseline characteristics of MDRD trial and AASK participants included in this study (N=1907) are shown in Table 1. The mean age of participants was 53 years, median proteinuria was 0.12 g/g, and median GFR was 40 mL/min per 1.73 m^2 (Table 1). The characteristics of participants stratified by proteinuria, GFR, BMI, and age categories in the intensive and usual BP treatment arms are shown in Table 2.

Median follow-up starting from the time of randomization until death or administrative censoring was 14.9 (interquartile range, 9.6–15.8) years. There were 482 deaths and 526 ESRD cases among those randomized to the usual BP control arm and 438 deaths and 498 ESRD cases in the strict BP control arm. We did not find the presence of any interaction between BP arm assignment and trial data source (P>0.10) for the outcomes of ESRD or death.

Overall, there was a statistically significant benefit from strict versus usual BP control in unadjusted analysis for the outcomes of death and ESRD (Figure A and B), as previously described.[29–31] Similar findings were noted in adjusted analyses for the outcome of ESRD (Table S2).

For the outcome of death, in stratified analysis, the unadjusted risk of death was lower among those assigned to strict versus usual BP control if the participant had a baseline GFR <30 mL/min per 1.73 m^2 (hazard ratio [HR], 0.73; 95% CI, 0.59–0.92; FigureA). In contrast, those with higher baseline GFR had no statistically significant mortality benefit from strict (versus usual) BP control (FigureA). Similarly, those with more proteinuria at baseline tended to have lower risk of death from intensive BP lowering (FigureA), although there was not a statistically significant interaction (P>0.05). Results from adjusted analyses are shown in Table S2. For the outcome of death, we noted a statistically significant interaction between BP arm assignment and GFR category (P=0.02). There appeared to be no statistically significant difference in the risk of death by baseline proteinuria, BMI category, or age category (Figure A).

For the outcome of ESRD, we found a protective effect of strict (versus usual) BP control (HR, 0.77; 95% CI, 0.64–0.92) among those with more proteinuria (FigureB). This was not seen among participants with less baseline proteinuria (HR, 0.95; 95% CI, 0.81–1.12), as would be expected given that we searched for the threshold at which effect modification was present by baseline proteinuria. There was a statistically significant beneficial effect of strict (versus usual) BP control among older participants (HR, 0.82; 95% CI, 0.71–0.94) but not among younger participants (FigureB). There was also a statistically significant beneficial effect of strict (versus usual) BP control among obese (HR, 0.75; 95% CI, 0.61–0.92) but not among nonobese participants (FigureB). Results from adjusted analyses are shown in Table S2. The effect of strict BP control appeared to differ depending on age category (P=0.006 for interaction) and BMI category (P=0.03 for test for interaction), but not baseline GFR (P=0.87 for test for interaction) in unadjusted analysis.

In sensitivity analysis, even after accounting for the competing risk of death in Fine-Gray models, strict (versus usual) BP control was associated with a lower risk of ESRD among those with more proteinuria, older age, or obesity at baseline (Table 3).

Finally, we examined the risk of death before versus after the onset of ESRD. Death rates were 2- to 3-fold higher after onset of ESRD than during the CKD phase of illness (Table 4). Differences in death rates among those assigned to strict versus usual BP control were more pronounced after ESRD

Table 1. Overall Characteristics of MDRD Trial and AASK Participants at Baseline (N=1907)

Characteristic	Value
Age, y	53±11
Women	746 (39)
Black	1133 (59)
Baseline MAP, mm Hg	107±16
Baseline proteinuria, g/d	0.12 (0.04–0.62)
Baseline GFR, mL/min per 1.73 m^2	40 (28–52)
Baseline BMI, kg/m^2	29±6
Assignment to strict BP control	954 (50)
Assignment to ACE inhibitor in AASK only	425/1067 (40)

Data are given as mean±SD, number (percentage), or median (interquartile range). AASK indicates African American Study of Kidney Disease and Hypertension; ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease.

Table 2. Baseline Characteristics by CKD Subgroups of Interest

Characteristic	Usual BP	Strict BP	*P* Value	Usual BP	Strict BP	*P* Value
Proteinuria, g/g	<0.44			≥0.44		
Age, y	55±11	54±11	0.86	50±12	50±13	0.53
Women	254 (39)	271 (41)	0.45	126 (42)	95 (33)	0.02
Black	434 (66)	424 (64)	0.36	143 (48)	132 (46)	0.55
Baseline MAP, mm Hg	107±15	107±17	0.57	107±15	108±15	0.36
Baseline GFR, mL/min per 1.73 m^2	46 (33–56)	45 (33–55)	0.29	28 (22–38)	31 (23–44)	0.03
Baseline proteinuria, g/d	0.06 (0.03–0.12)	0.06 (0.03–0.14)	0.54	1.19 (0.71–1.87)	1.11 (0.68–1.82)	0.78
BMI, kg/m^2	28 (25–32)	28 (25–32)	0.39	28 (25–33)	28 (24–32)	0.72
GFR, mL/min per 1.73 m^2	≥30			<30		
Age, y	54±11	54±11	0.42	52±12	50±13	0.03
Women	250 (38)	258 (37)	0.74	130 (44)	108 (41)	0.57
Black	463 (71)	475 (69)	0.42	114 (38)	81 (31)	0.07
Baseline MAP, mm Hg	108±15	109±16	0.22	104± 14	103± 15	0.51
Baseline GFR, mL/min per 1.73 m^2	47 (39–56)	47 (38–55)	0.17	24 (20–27)	23 (19–27)	0.19
Baseline proteinuria, g/d	0.07 (0.03–0.29)	0.07 (0.03–0.36)	0.40	0.59 (0.12–1.44)	0.46 (0.13–1.41)	0.82
BMI, kg/m^2	29 (25–33)	29 (25–33)	0.73	27 (24–31)	26 (23–30)	0.06
Age category, y	<40			≥40		
Age, y	33±5	33±5	0.97	56±8	56±9	0.76
Women	57 (45)	47 (33)	0.053	323 (39)	319 (39)	0.96
Black	58 (46)	61 (43)	0.69	519 (63)	495 (61)	0.42
Baseline MAP, mm Hg	105±17	108±20	0.17	107±15	108±15	0.68
Baseline proteinuria, g/d	0.37 (0.09–1.21)	0.40 (0.1–1.29)	0.34	0.10 (0.03–0.54)	0.10 (0.03–0.49)	0.55
Baseline GFR, mL/min per 1.73 m^2	37 (27–48)	32 (24–47)	0.12	40 (28–53)	42 (30–53)	0.29
BMI, kg/m^2	26 (23–30)	27 (23–33)	0.20	28 (25–33)	28 (25–32)	0.26
BMI category, kg/m^2	<30			≥30		
Age, y	53±12	53±12	0.93	54±10	53±11	0.51
Women	235 (39)	219 (37)	0.52	145 (42)	147 (41)	0.77
Black	315 (52)	291 (49)	0.33	262 (76)	265 (74)	0.51
Baseline MAP, mm Hg	105±15	106±16	0.91	110±15	112±17	0.14
Baseline proteinuria, g/d	0.11 (0.04–0.65)	0.11 (0.04–0.63)	0.64	0.12 (0.03–0.65)	0.14 (0.04–0.55)	0.58
Baseline GFR, mL/min per 1.73 m^2	37 (26–50)	38 (26–50)	0.85	44 (31–55)	45 (34–54)	0.43
BMI, kg/m^2	26 (24–28)	26 (23–28)	0.11	35 (32–38)	34 (32–38)	0.26

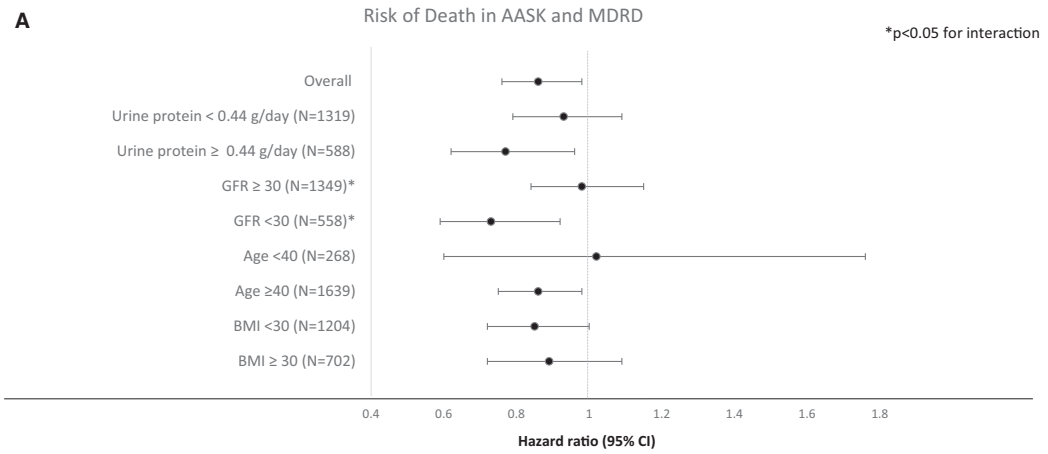
Data are given as column mean±SD, number (percentage), or median (interquartile range). BMI indicates body mass index; BP, blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate; MAP, mean arterial pressure.

onset compared with during the CKD phase of illness (Table 4).

Discussion

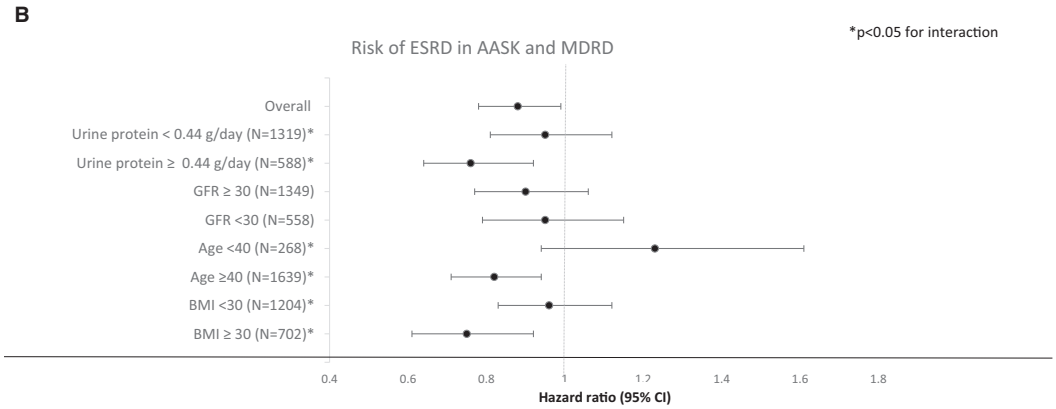
In this study, we pooled 2 completed trials of intensive BP lowering to examine its effect on risk of ESRD or death on the basis of baseline proteinuria, GFR, age, and BMI. For the outcome of mortality, we found that intensive BP control was especially beneficial among those with lower GFR at baseline. For the outcome of ESRD, intensive BP lowering was especially beneficial among those with more baseline proteinuria, older age, and higher BMI. We identified that presence of ≥0.44 g/g of proteinuria may help identify individuals who may especially benefit from intensive BP lowering. We also found that intensive BP lowering appeared to have particularly large benefits for the risk of death after the onset of ESRD, as opposed to during the CKD phase of illness. We believe our study is unique in its

A



MDRD and AASK N=1907	N	Number of deaths	Usual BP Death per 100 person-years	Strict BP Death per 100 person-years	Unadjusted HR (95% CI) Strict vs Usual
Overall	1907	920	3.7	3.3	0.87 (0.76-0.99)
Urine protein < 0.44 g/day	1319	591	3.3	3.1	0.93 (0.79-1.09)
Urine protein ≥ 0.44 g/day	588	329	4.7	3.7	0.77 (0.62-0.96)
GFR ≥ 30 mL/min/1.73 m²	343	592	3.2	3.1	0.98 (0.84-1.15)
GFR < 30 mL/min/1.73 m²	249	328	5.0	3.6	0.73 (0.59-0.92)
Age <40 years	268	53	1.1	1.2	1.02 (0.60-1.76)
Age ≥ 40 years	1639	867	4.3	3.7	0.86 (0.75-0.98)
BMI <30 kg/m²	1204	578	3.6	3.1	0.85 (0.72-1.00)
BMI ≥ 30 kg/m²	702	341	3.9	3.5	0.88 (0.71-1.09)

B



MDRD and AASK N=1907	N	Number of ESRD events	Usual BP ESRD per 100 person-years	Strict BP ESRD per 100 person-years	Unadjusted HR (95% CI) Strict vs Usual
Overall	1907	1024	6.0	5.4	0.88 (0.78-1.00)
Urine protein < 0.44 g/day	1319	569	4.0	4.0	0.95 (0.81-1.12)
Urine protein ≥ 0.44 g/day	588	455	14.1	10.8	0.77 (0.64-0.92)
GFR ≥ 30 mL/min/1.73 m²	1349	572	4.0	3.7	0.90 (0.77-1.06)
GFR < 30 mL/min/1.73 m²	558	452	14.6	14.4	0.95 (0.79-1.15)
Age <40 years	268	213	9.1	11.0	1.23 (0.94-1.61)
Age ≥ 40 years	1639	811	5.5	4.7	0.82 (0.71-0.94)
BMI <30 kg/m²	1204	665	6.0	5.9	0.96 (0.83-1.12)
BMI ≥ 30 kg/m²	702	358	6.0	4.7	0.75 (0.61-0.92)

Figure. **A**, Unadjusted risk of death by blood pressure (BP) arm assignment comparing strict vs usual BP control. **B**, Unadjusted risk of end-stage renal disease (ESRD) by BP arm assignment comparing strict vs usual BP control. AASK indicates African American Study of Kidney Disease and Hypertension; BMI, body mass index; GFR, glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease.

Table 3. Risk of ESRD Accounting for the Competing Risk of Death

MDRD Trial and AASK (N=1907)	Unadjusted Sub-HR (95% CI) Strict vs Usual
Overall	0.90 (0.80–1.02)
Urine protein <0.44 g/g*	0.99 (0.84–1.17)
Urine protein ≥0.44 g/g*	0.76 (0.63–0.91)
GFR ≥30 mL/min per 1.73 m^2	0.94 (0.80–1.10)
GFR <30 mL/min per 1.73 m^2	0.93 (0.77–1.12)
Age <40 y*	1.18 (0.90–1.54)
Age ≥40 y*	0.85 (0.74–0.98)
BMI <30 kg/m^2	0.97 (0.83–1.13)
BMI ≥30 kg/m^2	0.79 (0.65–0.98)

AASK indicates African American Study of Kidney Disease and Hypertension; BMI, body mass index; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease.
*P<0.05 for interaction.

provision of long-term follow-up that extends beyond the mean duration of most clinical trials (2–3 years).

In contrast to large observational studies suggesting that lower BP levels are associated with higher risk of mortality in patients with CKD,[34,35] we did not find evidence of harm in any subgroups explored when this intervention was tested in a randomized trial. We found the effect of intensive BP lowering to be especially protective from a mortality standpoint among those with advanced CKD at baseline enrollment. We believe this finding may be related to the higher cardiovascular risk among patients with advanced CKD and, therefore, greater derived benefit from intensive BP lowering and its cardiovascular benefits, although we are limited in the lack of data on cardiovascular events posttrial closure.[2] Intensive BP lowering during the CKD phase of illness may also serve to improve the cardiovascular health of patients once they transition to ESRD and, thereby, lower the risk of death after onset of ESRD (when cardiovascular mortality risk is at its peak).[31] Our data offer reassurance that intensive BP lowering did not appear to be associated with harm in any of the subgroups we analyzed in the trial settings and are overall consistent with the results of SPRINT, although the MDRD trial and AASK enrolled a population with greater severity of kidney disease and proteinuria compared with SPRINT and targeted MAP as opposed to systolic BP.

Although a few prior post hoc analyses of clinical trials have suggested a renal benefit with an intensive BP-lowering strategy among patients with significant proteinuria, most of these studies have focused on change in the slope of kidney function decline as an outcome and not ESRD onset.[20,21,36] Recent studies have suggested that slopes of renal function decline or albuminuria may not be associated with risk of ESRD as strongly as would be needed for these outcomes to serve as surrogate end points.[37] In prior post hoc trial analyses and meta-analyses, the level of proteinuria needed for intensive BP lowering to be associated with renal benefit varied considerably and ranged from a protein/creatinine ratio of 0.22 to 1.5 g/g.[21,23,36,38,39] In our study, we found that proteinuria ≥0.44 g/g may serve as a threshold that identifies patients who would benefit from intensive BP control because of the presence of proteinuria.

We note that there was significant heterogeneity in the effect of intensive BP lowering, depending on the characteristics of patients at baseline enrollment into the MDRD trial and AASK. Traditionally, most trials have not routinely reported the heterogeneity in the effect of the intervention being tested by baseline risk for outcomes of interest.[40,41] A network meta-analysis of randomized trials recently

Table 4. Death Rate Before and After ESRD by Subgroups of Interest

Variable	Death Rate (per 100-Person Years) During CKD (95% CI)		Death Rate (per 100-Person Years) during ESRD (95% CI)	
	Usual BP	Strict BP	Usual BP	Strict BP
Overall	2.1 (1.8–2.4)	2.2 (1.9–2.5)	7.1 (6.4–8.0)*	5.6 (4.9–6.3)*
Urine protein <0.44 g/d	2.2 (1.9–2.6)	2.1 (1.8–2.5)	7.2 (6.1–8.4)	6.2 (5.2–7.3)
Urine protein ≥0.44 g/d	1.7 (1.2–2.5)	2.3 (1.7–3.1)	7.1 (6.0–8.3)*	4.9 (4.0–6.0)*
GFR ≥30 mL/min per 1.73 m^2	2.2 (1.9–2.5)	2.2 (1.9–2.5)	6.9 (5.8–8.2)	6.8 (5.7–8.0)
GFR <30 mL/min per 1.73 m^2	1.7 (1.2–2.5)	2.2 (1.6–3.1)	7.3 (6.3–8.5)*	4.5 (3.7–5.5)*
Age <40 y	0.5 (0.2–1.2)	0.8 (0.4–1.5)	1.8 (1.1–2.8)	1.4 (0.9–2.2)
Age ≥40 y	2.3 (2.0–2.7)	2.3 (2.0–2.7)	9.0 (8.0–10.2)	7.6 (6.6–8.7)
BMI <30 kg/m^2	2.1 (1.7–2.5)	2.3 (1.9–2.7)	6.7 (5.8–7.7)*	4.6 (3.9–5.4)*
BMI ≥30 kg/m^2	2.1 (1.7–2.7)	2.0 (1.6–2.6)	8.1 (6.7–9.8)	8.1 (6.6–9.9)

BMI indicates body mass index; BP, blood pressure; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate.
*Statistically significantly different comparing strict vs usual BP arm assignment (P<0.05).

demonstrated that, although intensive BP lowering was effective in reducing the risk of cardiovascular outcomes, the risk of serious adverse events was higher with lower BP targets.[42] Our study explores patient characteristics that would favor intensification of BP control (eg, those with advanced CKD for survival benefit and those who are older, are obese, or have proteinuria for reduction in ESRD risk).

The strengths of our study include the large number of ESRD events and deaths and the availability of nearly 2 decades of follow-up in AASK and MDRD trial participants. In addition, we provide pooled data from 2 separate trials with a racially diverse group of participants and are able to provide data on the effect of an intervention delivered pre-ESRD on outcomes after the onset of ESRD.

However, there are several limitations to our study. Our results may not apply to people with CKD attributed to diabetes mellitus. Although we had prespecified interest in the subgroups divided by GFR, BMI, and age thresholds, we recognize the potential for multiple hypothesis testing and that not all risk factors were noted to be statistically significant effect modifiers. We do not have detailed data surrounding cardiovascular events (eg, stroke or new-onset heart failure) that may have developed with each of the treatment strategies during long-term follow-up. We acknowledge that our study is post hoc and observational and that our results may reflect the "legacy effect"[43] of BP lowering during these trials. Because of this, we believe that the findings in our study likely underestimate the true potential impact of intensive BP lowering, given the likely convergence of BP levels between the strict and usual BP arms posttrial closure, which would have attenuated the effects that we report and were most of our follow-up period.

In recognition of the challenges of achieving adequate BP control in the CKD population,[44–46] targeting patients who may have the greatest kidney and mortality benefits for the achievement of aggressive BP lowering is important. We suggest that patients with more proteinuria (>0.44 g/g) may particularly benefit from achievement of lower BP targets. Long-term benefits of intensive BP lowering after the transition from CKD to ESRD may also be a factor for consideration when selecting BP treatment targets. Further studies are needed to individualize the approach to BP target selection and balance the risk of ESRD with that of mortality and other adverse effects of treatment.

Acknowledgments

Research idea and study design: Drs Ku and Hsu; data acquisition: Drs Ku, Sarnak, Toto, Smogorzewski, and Hsu; data analysis/interpretation: Drs Ku, Sarnak, Toto, Smogorzewski, McCulloch, and Hsu and F. Lin; statistical analysis: Drs Ku, McCulloch, and Hsu and F. Lin. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Sources of Funding

This work was supported by the National Institutes of Health (NIH) (K23 HL131023 to Ku and K24 DK92291 to Hsu). The funding source did not have any role in manuscript preparation. The AASK (African American Study of Kidney Disease and Hypertension) and MDRD (Modification of Diet in Renal Disease) trial were conducted by AASK and MDRD trial investigators and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The data from the AASK and MDRD trial reported herein were supplied in part by the NIDDK Central Repositories. This manuscript does not necessarily reflect the opinions or views of the AASK and MDRD trial and cohort studies, the NIDDK Central Repositories, or the NIDDK grants MD000182, UL1TR000124, and P30AG021684. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The interpretation and reporting of the data presented herein are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

Disclosures

None.

References

1. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. 2017;72:e33.
2. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
3. Greenland P, Peterson E. The new 2017 ACC/AHA guidelines "up the pressure" on diagnosis and treatment of hypertension. *JAMA*. 2017;318:2083–2084.
4. Bhatt H, Ghazi L, Calhoun D, Oparil S. BP targets in hypertension: what should we do now that sprint is out? *Curr Cardiol Rep*. 2016;18:98.
5. Chertow GM, Beddhu S, Lewis JB, Toto RD, Cheung AK. Managing hypertension in patients with CKD: a marathon, not a sprint. *J Am Soc Nephrol*. 2016;27:40–43.
6. de Boer IH, Bakris G, Cannon CP. Individualizing blood pressure targets for people with diabetes and hypertension: comparing the ADA and the ACC/AHA recommendations. *JAMA*. 2018;319:1319–1320.
7. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, Oparil S, Rocco MV, Sink KM, Whelton PK, Wright JT Jr, Basile J, Beddhu S, Bhatt U, Chang TI, Chertow GM, Chonchol M, Freedman BI, Haley W, Ix JH, Katz LA, Killeen AA, Papademetriou V, Ricardo AC, Servilla K, Wall B, Wolfgram D, Yee J. Effects of intensive BP control in CKD. *J Am Soc Nephrol*. 2017;28:2812–2823.

8. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease: modification of diet in renal disease study group. *N Engl J Med*. 1994;330:877–884.
9. Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, Lesti M, Perticucci E, Chakarski IN, Leonardis D, Garini G, Sessa A, Basile C, Alpa M, Scanziani R, Sorba G, Zoccali C, Remuzzi G; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*. 2005;365:939–946.
10. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421–2431.
11. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, Winklhofer FT, Brosnahan G, Czarnecki PG, Hogan MC, Miskulin DC, Rahbari-Oskoui FF, Grantham JJ, Harris PC, Flessner MF, Bae KT, Moore CG, Chapman AB. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371:2255–2266.
12. Rocco MV, Sink KM, Lovato LC, Wolfgram DF, Wiegmann TB, Wall BM, Umanath K, Rahbari-Oskoui F, Porter AC, Pisoni R, Lewis CE, Lewis JB, Lash JP, Katz LA, Hawfield AT, Haley WE, Freedman BI, Dwyer JP, Drawz PE, Dobre M, Cheung AK, Campbell RC, Bhatt U, Beddhu S, Kimmel PL, Reboussin DM, Chertow GM. Effects of intensive blood pressure treatment on acute kidney injury events in the systolic blood pressure intervention trial (SPRINT). *Am J Kidney Dis*. 2017;71:352–361.
13. Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, Lacchetti C, Leung TW, Darling E, Bryant DM, Bucher HC, Schunemann HJ, Meade MO, Cook DJ, Erwin PJ, Sood A, Sood R, Lo B, Thompson CA, Zhou Q, Mills E, Guyatt GH. Randomized trials stopped early for benefit: a systematic review. *JAMA*. 2005;294:2203–2209.
14. Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, Heels-Ansdell D, Walter SD, Guyatt GH, Flynn DN, Elamin MB, Murad MH, Abu Elnour NO, Lampropulos JF, Sood A, Mullan RJ, Erwin PJ, Bankhead CR, Perera R, Ruiz Culebro C, You JJ, Mulla SM, Kaur J, Nerenberg KA, Schunemann H, Cook DJ, Lutz K, Ribic CM, Vale N, Malaga G, Akl EA, Ferreira-Gonzalez I, Alonso-Coello P, Urrutia G, Kunz R, Bucher HC, Nordmann AJ, Raatz H, da Silva SA, Tuche F, Strahm B, Djulbegovic B, Adhikari NK, Mills EJ, Gwadry-Sridhar F, Kirpalani H, Soares HP, Karanicolas PJ, Burns KE, Vandvik PO, Coto-Yglesias F, Chrispim PP, Ramsay T. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA*. 2010;303:1180–1187.
15. Modification of Diet in Renal Disease Study Group. Short-term effects of protein intake, blood pressure, and antihypertensive therapy on glomerular filtration rate in the modification of diet in renal disease study. *J Am Soc Nephrol*. 1996;7:2097–2109.
16. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Ann Intern Med*. 2006;144:21–28.
17. Lea J, Cheek D, Thornley-Brown D, Appel L, Agodoa L, Contreras G, Gassman J, Lash J, Miller ER III, Randall O, Wang X, McClellan W. Metabolic syndrome, proteinuria, and the risk of progressive CKD in hypertensive African Americans. *Am J Kidney Dis*. 2008;51:732–740.
18. Toto RD, Greene T, Hebert LA, Hiremath L, Lea JP, Lewis JB, Pogue V, Sika M, Wang X. Relationship between body mass index and proteinuria in hypertensive nephrosclerosis: results from the African American Study of Kidney Disease and Hypertension (AASK) cohort. *Am J Kidney Dis*. 2010;56:896–906.
19. American College of Cardiology. ASCVD risk estimator plus. http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/. Accessed May 8, 2019.
20. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, Charleston J, Cheek D, Cleveland W, Douglas JG, Douglas M, Dowie D, Faulkner M, Gabriel A, Gassman J, Greene T, Hall Y, Hebert L, Hiremath L, Jamerson K, Johnson CJ, Kopple J, Kusek J, Lash J, Lea J, Lewis JB, Lipkowitz M, Massry S, Middleton J, Miller ER III, Norris K, O'Connor D, Ojo A, Phillips RA, Pogue V, Rahman M, Randall OS, Rostand S, Schulman G, Smith W, Thornley-Brown D, Tisher CC, Toto RD, Wright JT Jr, Xu S; African American Study of Kidney Disease and Hypertension (AASK) Study Group. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA*. 2001;285:2719–2728.
21. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, King AJ, Klahr S, Massry SG, Seifter JL. Blood pressure control, proteinuria, and the progression of renal disease: the modification of diet in renal disease study. *Ann Intern Med*. 1995;123(10):754–762.
22. Remuzzi G, Chiurchiu C, Ruggenenti P. Proteinuria predicting outcome in renal disease: nondiabetic nephropathies (REIN). *Kidney Int Suppl*. 2004;66(Suppl 92):S90–S96.
23. Appel LJ, Wright JT Jr, Greene T, Agodoa LY, Astor BC, Bakris GL, Cleveland WH, Charleston J, Contreras G, Faulkner ML, Gabbai FB, Gassman JJ, Hebert LA, Jamerson KA, Kopple JD, Kusek JW, Lash JP, Lea JP, Lewis JB, Lipkowitz MS, Massry SG, Miller ER, Norris K, Phillips RA, Pogue VA, Randall OS, Rostand SG, Smogorzewski MJ, Toto RD, Wang X; AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010;363:918–929.
24. Gassman JJ, Greene T, Wright JT Jr, Agodoa L, Bakris G, Beck GJ, Douglas J, Jamerson K, Lewis J, Kutner M, Randall OS, Wang SR. Design and statistical aspects of the African American study of kidney disease and hypertension (AASK). *J Am Soc Nephrol*. 2003;14:S154–S165.
25. Appel LJ, Middleton J, Miller ER III, Lipkowitz M, Norris K, Agodoa LY, Bakris G, Douglas JG, Charleston J, Gassman J, Greene T, Jamerson K, Kusek JW, Lewis JA, Phillips RA, Rostand SG, Wright JT. The rationale and design of the AASK cohort study. *J Am Soc Nephrol*. 2003;14:S166–S172.
26. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
27. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, Levey AS. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med*. 2005;142:342–351.
28. NIDDK. NIDDK Central Repository. https://repository.niddk.nih.gov/home/. Accessed May 1, 2018.
29. Ku E, Bakris G, Johansen KL, Lin F, Sarnak MJ, Campese VM, Jamerson K, Gassman JJ, Smogorzewski M, Hsu CY. Acute declines in renal function during intensive BP lowering: implications for future ESRD risk. *J Am Soc Nephrol*. 2017;28:2794–2801.
30. Ku E, Gassman J, Appel LJ, Smogorzewski M, Sarnak MJ, Glidden DV, Bakris G, Gutierrez OM, Hebert LA, Ix JH, Lea J, Lipkowitz MS, Norris K, Ploth D, Pogue VA, Rostand SG, Siew ED, Sika M, Tisher CC, Toto R, Wright JT Jr, Wyatt C, Hsu CY. BP control and long-term risk of ESRD and mortality. *J Am Soc Nephrol*. 2017;28:671–677.
31. Ku E, Glidden DV, Johansen KL, Sarnak M, Tighiouart H, Grimes B, Hsu CY. Association between strict blood pressure control during chronic kidney disease and lower mortality after onset of end-stage renal disease. *Kidney Int*. 2015;87:1055–1060.
32. Xie D, Shlipak M, Hyre Anderson A, Chen J, Go AS, He J, Horwitz EJ, Rahman M, Ricardo AC, Sondheimer JH, Townsend RR, Hsu CY. Change in measured GFR versus eGFR and CKD outcomes. *J Am Soc Nephrol*. 2015;27:2196–2204.
33. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158:825–830.
34. Kovesdy CP, Lu JL, Molnar MZ, Ma JZ, Canada RB, Streja E, Kalantar-Zadeh K, Bleyer AJ. Observational modeling of strict vs conventional blood pressure control in patients with chronic kidney disease. *JAMA Intern Med*. 2014;174:1442–1449.
35. Kovesdy CP, Bleyer AJ, Molnar MZ, Ma JZ, Sim JJ, Cushman WC, Quarles LD, Kalantar-Zadeh K. Blood pressure and mortality in U.S. veterans with chronic kidney disease: a cohort study. *Ann Intern Med*. 2013;159:233–242.
36. Ruggenenti P, Perna A, Remuzzi G. Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. *Kidney Int*. 2003;63:2254–2261.
37. Palmer SC, Ruospo M, Teixeira-Pinto A, Craig JC, Macaskill P, Strippoli GFM. The validity of drug effects on proteinuria, albuminuria, serum creatinine, and estimated GFR as surrogate end points for ESKD: a systematic review. *Am J Kidney Dis*. 2018;72:779–789.
38. ESCAPE group, Wuhl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, Testa S, Jankauskiene A, Emre S, Caldas-Afonso A, Anarat A, Niaudet P, Mir S, Bakkaloglu A, Enke B, Montini G, Wingen AM, Sallay P, Jeck N, Berg U, Caliskan S, Wygoda S, Hohbach-Hohenfellner K, Dusek J, Urasinski T, Arbeiter K, Neuhaus T, Gellermann J, Drozdz D, Fischbach M, Moller K, Wigger M, Peruzzi L, Mehls O, Schaefer F. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med*. 2009;361:1639–1650.
39. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, Foote C, Rodgers A, Zhang H, Wang H, Strippoli GF, Perkovic V. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ*. 2013;185:949–957.
40. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. *JAMA*. 2007;298:1209–1212.

41. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials*. 2010;11:85.

42. Bangalore S, Toklu B, Gianos E, Schwartzbard A, Weintraub H, Ogedegbe G, Messerli FH. Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. *Am J Med*. 2017;130:707–719.e8

43. Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, Karter AJ. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the diabetes & aging study). *Diabetes Care*. 2019;42:416–426.

44. Plantinga LC, Miller ER III, Stevens LA, Saran R, Messer K, Flowers N, Geiss L, Powe NR; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Blood pressure control among persons without and with chronic kidney disease: US trends and risk factors 1999–2006. *Hypertension*. 2009;54:47–56.

45. Sarafidis PA, Li S, Chen SC, Collins AJ, Brown WW, Klag MJ, Bakris GL. Hypertension awareness, treatment, and control in chronic kidney disease. *Am J Med*. 2008;121:332–340.

46. Owen WF Jr. Patterns of care for patients with chronic kidney disease in the united states: dying for improvement. *J Am Soc Nephrol*. 2003;14:S76–S80.

SUPPLEMENTAL MATERIAL

Table S1. Thresholds for statistically significant interaction between BP arm assignment and baseline proteinuria for the outcome of ESRD.

MDRD and AASK N=1907	P-value
Urine protein < 0.3 g/g (versus ≥ 0.3 g/g)	0.09
Urine protein < 0.4 g/g (versus ≥ 0.4 g/g)	0.07
Urine protein < 0.43 g/g (versus ≥ 0.43 g/g)	0.056
Urine protein < 0.44 g/g (versus ≥ 0.44 g/g)	0.044
Urine protein < 0.45 g/g (versus ≥ 0.45 g/g)	0.04
Urine protein < 0.5 g/g (versus ≥ 0.5 g/g)	0.02
Urine protein < 0.6 g/g (versus ≥ 0.6 g/g)	0.02

Table S2. Risk of ESRD or death in Cox models comparing strict versus usual BP arms (HR = hazard ratio).

		Death		ESRD	
MDRD and AASK N=1907	N	Unadjusted HR(95% CI)	Adjusted* HR (95% CI)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Overall	1907	0.87 (0.76-0.99)	0.85 (0.75-0.97)	0.88 (0.78-1.00)	0.88 (0.78-0.99)
Urine protein < 0.44 g/day	1319	0.93 (0.79-1.09)	0.93 (0.79-1.09)	0.95 (0.81-1.12)	0.96 (0.81-1.13)
Urine protein ≥ 0.44 g/day	588	0.77 (0.62-0.96)	0.77 (0.61-0.96)	0.77 (0.64-0.92)	0.79 (0.65-0.96)
GFR ≥ 30 mL/min/1.73 m^2	1349	0.98 (0.84-1.15)	0.90 (0.77-1.06)	0.90 (0.77-1.06)	0.88 (0.75-1.04)
GFR < 30 mL/min/1.73 m^2	558	0.73 (0.59-0.92)	0.82 (0.66-1.03)	0.95 (0.79-1.15)	0.92 (0.76-1.11)
Age <40 years	268	1.02 (0.60-1.76)	0.88 (0.51-1.53)	1.23 (0.94-1.61)	1.00 (0.76-1.33)
Age ≥ 40 years	1639	0.86 (0.75-0.98)	0.88 (0.77-1.01)	0.82 (0.71-0.94)	0.85 (0.74-0.98)
BMI < 30 kg/m^2	1204	0.85 (0.72-1.00)	0.86 (0.73-1.01)	0.96 (0.83-1.12)	0.98 (0.84-1.15)
BMI ≥ 30 kg/m^2	702	0.88 (0.71-1.09)	0.90 (0.73-1.11)	0.75 (0.61-0.92)	0.67 (0.54-0.82)

*Adjusted for age, sex, race, proteinuria (≥ versus < 0.5 g/g), GFR (≥ 30 versus < 30 mL/min/1.73 m^2), BMI, and stratified for trial data source.