Effect of intensive blood pressure on the progression of non-diabetic chronic kidney disease at varying degrees of proteinuria

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ABSTRACT

The ideal blood pressure (BP) target for renoprotection is uncertain in patients with non-diabetic chronic kidney disease (CKD), especially considering the influence exerted by pre-existing proteinuria. In this pooled analysis of landmark trials, we coalesced individual data from 5001 such subjects randomized to intensive versus standard BP targets. We employed multivariable regression to evaluate the relationship between follow-up systolic blood pressure (SBP) and diastolic blood pressure (DBP) on CKD progression (defined as glomerular filtration rate decline by 50% or end-stage renal disease), focusing on the potential for effect modification by baseline proteinuria or albuminuria. The median follow-up was 3.2 years. We found that SBP rather than DBP was the primary predictor of renal outcomes. The optimal SBP target was 110–129 mm Hg. We observed a strong interaction between SBP and proteinuria such that lower SBP ranges were significantly linked with progressively lower CKD risk in grade A3 albuminuria or ≥0.5–1 g/day proteinuria (relative to SBP 110–119 mm Hg, the adjusted HR for SBP 120–129 mm Hg, 130–139 mm Hg, and 140–149 mm Hg was 1.5, 2.3, and 3.3, respectively; all p<0.05). In grade A2 microalbuminuria or proteinuria near 0.5 g/day, a non-significant but possible connection was seen between tighter BP and decreased CKD (aforementioned HRs all <2; all p>0.05), while in grade A1 albuminuria or proteinuria <0.2 g/day no significant association was apparent (HRs all <1.5; all p>0.1). We conclude that in non-diabetic CKD, stricter BP targets <130 mm Hg may help limit CKD progression as proteinuria rises.

Significance of this study

What is already known about this subject?

- ► Recent evidence from the Systolic Blood Pressure Intervention Trial (SPRINT) indicates that a tighter blood pressure (BP) target is associated with improved mortality and cardiovascular outcomes in patients without diabetes, with further analyses suggesting the benefits extend to chronic kidney disease (CKD).
- ► Kidney outcome improvement in patients with non-diabetic CKD has not been previously confirmed by this practice except potentially in individuals with proteinuria.
- ► The extent to which CKD was aided by intensive BP control varied based on the degree of proteinuria.
- ► The precise levels of BP and proteinuria associated with renoprotection remain unclear.

What are the new findings?

- ► The relationship between BP and proteinuria on CKD progression was characterized in a more precise manner by pooling individual patient data from landmark goal BP trials (including SPRINT).
- ► This study found that tighter systolic blood pressure (SBP) control <130 mm Hg was associated with better preservation of renal function as proteinuria escalated.
- ► Evidence that strict BP control was linked with reduction in CKD progression was robust at higher degrees of albuminuria (grade A3) or proteinuria (above 1 g/day) but less clear at lower quantities.

INTRODUCTION

Hypertension (HTN) is an important contributor to progression of non-diabetic chronic kidney disease (CKD). Ever since the Systolic Blood Pressure Intervention Trial (SPRINT) published in 2015 demonstrated superior survival and cardiovascular (CV) outcomes targeting a systolic blood pressure (SBP) <120 mm Hg in patients without diabetes at high risk for cardiovascular disease (CVD), there has been a subsequent trend toward tighter blood pressure (BP) targets in clinical practice.[1] However, the effect of more aggressive BP control on progression of renal disease in individuals with non-diabetic CKD is less clear, especially considering the potential impact of pre-existing proteinuria. For instance, although analyses of SPRINT limited to CKD

Significance of this study

How might these results change the focus of research or clinical practice?

- The results of this paper suggest that in patients who have non-diabetic CKD, an intensive BP goal (defined as SBP <130 mm Hg) may help preserve kidney function better in cases with higher degrees of albuminuria or proteinuria, and in such instances institution of a more intensive BP target may be more strongly indicated.
- It is hoped this study stimulates further investigation into the role that proteinuria may play in modifying the effect of a tighter BP target.

confirmed a mortality reduction with this practice, it was suggested that CV benefit diminishes and the risk–benefit profile differs at poorer levels of renal function.[2 3]

From a renal standpoint, intensive BP control (eg, SBP <120–130 mm Hg) has not been conclusively shown by various clinical trials and meta-analyses to result in an improvement in kidney outcomes; however, in individuals with proteinuria, the possibility of benefit has often been raised.[4–6] The purpose of this study is to further investigate the role of intensive BP control in non-diabetic CKD at varying degrees of proteinuria by combining the data from several landmark goal BP trials performed within this arena. Trial data will be pooled in this analysis because this approach may best clarify the precise BP and proteinuria levels associated with renoprotection in this population.

MATERIALS AND METHODS

Study design

This was a pooled, patient-level analysis of randomized controlled trials (RCTs) which compared intensive versus standard BP targets in non-diabetic, predialysis CKD. The primary reasoning behind aggregating clinical trial data on an individual basis was to most precisely determine the interplay between achieved BP levels and baseline proteinuria on CKD progression. Pooling was deemed reasonable given the similarity of study designs and patient populations. Trials were eligible if they included subjects with ≥90% non-diabetic CKD, defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, or a GFR ≥60 mL/min/1.73 m^2 with albuminuria (≥30 mg/g of creatinine or equivalent) or proteinuria (≥150 mg/g of creatinine or equivalent). Trials were required to report albuminuria or proteinuria at baseline and kidney disease outcomes. Trials with fewer than 100 subjects per BP group or follow-up duration shorter than 1 year were excluded. All subjects in eligible trials were randomly assigned to either an intensive or regular BP target based on the design of the individual trials. All participating data repositories or study centers agreed to grant access to research materials. Only de-identified data were used for the current analyses and informed consent was previously documented for all patients per trial protocols.

Study population

Following the application of inclusion/exclusion criteria mentioned above, 5001 subjects were pooled from five HTN trials spanning the years 1994–2017: Modification of Diet in Renal Disease (MDRD), African American Study of Kidney Disease and Hypertension (AASK), Ramipril Efficacy In Nephropathy 2 (REIN-2), SPRINT, and HALT Progression of Polycystic Kidney Disease (HALT-PKD). The majority of subjects stemmed from SPRINT, which comprised about half the census. All subjects were aged 18 years or older. Etiologies of CKD were diverse in the trials that reported them (eg, hypertensive nephrosclerosis, glomerular diseases). In keeping with non-diabetic definitions of each trial, a very small minority of patients with diabetes were included (43 from the MDRD trial, constituting 0.9% of cases); apart from this, all other patients were known to have a CKD due to a non-diabetic etiology. Polycystic kidney disease (PKD) was present in at least 378 cases, representing 7% of the cohort (178 from HALT-PKD, 200 from MDRD, unknown from REIN-2, none from SPRINT and AASK where PKD was excluded). Patients with diabetes were later excluded in a sensitivity analysis. Only subjects with reduced GFR <60 mL/min/1.73 m^2 or a preserved GFR ≥60 mL/min/1.73 m^2 with an abnormal amount of albuminuria (≥30 mg/day or equivalent) or proteinuria (≥150 mg/day or equivalent) at baseline were included.

Study measurements/definitions

GFR was determined preferentially by a direct clearance measurement method (iothalamate clearance adjusted for body surface area with Dubois formula); if not available, GFR was estimated with serum creatinine using the four-variable MDRD equation.[7] Baseline GFR was defined as the mean of two GFR measurements immediately prior to randomization. Urinary albumin and protein were assessed preferentially by a 24-hour urine collection; if not available, a spot urine albumin or protein to creatinine ratio was used. Baseline urine albumin or protein was defined as the last known value prior to randomization.

Specifics regarding the technique of BP acquisition varied depending on the trial. All trials reported BP as the average of two or more readings. Baseline BP was defined as the last known BP immediately prior to randomization. The number of distinct antihypertensive drug classes was assessed at baseline (just prior to randomization) and at trial start (immediately following randomization).

Follow-up BP was modeled as a time-dependent covariate based on time segments of 3-month durations in the first year of follow-up and 6-month periods thereafter. The closest BP reading to the start of the time segment was selected, giving preference for a value recorded after the start of the interval over the one which preceded it. If no BPs were available during the time segment, the last known value from the prior time period was carried forward.

Average follow-up BP was used to group patients into various categories of follow-up BP and was defined as the mean of all unique follow-up BP values (excluding those carried forward) obtained at or beyond 6 months; if no BPs were available then, the last known BP value prior to 6 months was used. Groups were divided in this manner for several reasons: (1) the definition of intensive versus standard BP varied considerably between trials; (2) we wished to stratify BP into multiple clinically relevant ranges

that approach the continuous, J-shaped relationship BP is known to exhibit with outcomes[8–10]; (3) most patients achieved the target BP (or most trials observed good separation in BP between intervention arms) by 6 months; (4) time-averaged BP is known to be a stronger predictor of outcomes than single-point measurements[11 12]; and (5) we wished to minimize potential skewing of results related to number of BP readings actually submitted by each patient. However, because BP here was ascertained during treatment rather than prior to randomization, our study should be considered an 'on-treatment', observational analysis of randomized clinical trial data.

Study outcomes

The primary outcome was CKD progression—a composite of ≥50% reduction in GFR from baseline or the development of end-stage renal disease (ESRD) requiring renal replacement therapy, defined as long-term dialysis need or renal transplantation. Patients were censored at the end of the trial unless they were lost to follow-up, died, or reached ESRD before that date.

Statistical analyses

Statistical analysis was conducted using R V.3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria) and Statistical Package for Social Sciences (SPSS) V.25.0. Crude, unadjusted comparisons were accomplished with Kaplan-Meier method, with log-rank test to estimate statistical significance. We employed Cox proportional hazard regression to determine the risks that follow-up BP, proteinuria, or other covariates exerted on CKD progression. The proportionality assumption was verified by visual inspection of Schoenfeld residual plot and log–log survival curves against time. A two-tailed p value of <0.05 was considered significant.

Given its J-shaped relationship with outcomes, mean follow-up BP was expressed as ordinal variables in the following manner: SBP in 10 mm Hg increments from 110 to 150 mm Hg; diastolic blood pressure (DBP) in a 5 mm Hg increment from 55 to 60 mm Hg, then 10 mm Hg increments from 60 to 90 mm Hg. We deliberately chose not to base our analysis on the intensive versus standard BP comparison because the definition of intensive BP varied from study to study, and because this approach would have difficulty elucidating the precise BP range associated with clinical benefit.

In the adjusted multivariable model, CKD progression was a function of follow-up BP, age, sex, race/ethnicity, body mass index (BMI), diabetes mellitus, CVD, smoking status, baseline GFR, albuminuria/proteinuria category, baseline SBP, baseline DBP, time-updated SBP, time-updated DBP, and antihypertensive regimen (number of antihypertensive drug classes and ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, or diuretic use at baseline and trial start). We adjusted for BP both at baseline and during follow-up as a time-varying covariate. Trial was entered as a stratification variable. We did not adjust for assignment to intensive BP arm given marked collinearity with designated follow-up BP group. By convention, the BP range that resulted in the lowest HR in the adjusted model was selected as the reference range.

Each trial measured either proteinuria or albuminuria (but not both) using the same method. Albuminuria or proteinuria was graded based on the Kidney Disease Improving Global Outcomes guidelines to unify different methods of quantification. This related categories of urine albumin to creatinine ratio (UACR), urine albumin excretion rate (UAER), urine protein to creatinine ratio (UPCR), and urine protein excretion rate (UPER).[13] Criteria were as follows: normal to mildly increased (A1), UAER/UACR <30 or UPER/UPCR <150; moderately increased (A2), UAER/UACR ≥30–<300 or UPER/UPCR ≥150–<500; severely increased (A3), UAER/UACR ≥300 or UPER/UPCR ≥500; excretion rates were in mg/day and ratios in mg/g.

We tested for interactions by assessing the significance of interaction terms—the product of average follow-up BP and either baseline GFR, CKD stage, or baseline albuminuria/proteinuria classification—on the CKD deterioration outcome. In order to more closely inspect how baseline proteinuria alters the effect of intensive BP control (considered to be an SBP 110–129 mm Hg) on CKD progression, we developed an interaction plot that used spline terms in the Cox model.[14] Here, an intensive SBP range of 110–129 mm Hg was compared with the reference standard SBP of 130–149 mm Hg. Proteinuria was entered in the model as a natural cubic spline term with 1 internal knot point (allowing for slope change) placed at the median and 2 boundary knots (beyond which the spline is linear) at the first and third quartile. The reference value for HR was median proteinuria (234 mg/day).

Missing data were handled in the following manner: cases lacking any albuminuria or proteinuria measurement were excluded by listwise deletion (92 cases from SPRINT). Baseline BP, baseline GFR, and baseline proteinuria were imputed with next observation carried backward (6 cases). BMI was imputed with expectation–maximization algorithm (19 cases). Number of agents and race were imputed by mode for trial (3 cases). Unknown category was designated for missing smoking data (5 cases). Missing follow-up BP data were imputed with last observation carried forward (55 cases). We performed several sensitivity analyses: (1) omitting all subjects with imputed data (101 cases representing 2.0% of data set); (2) defining average follow-up BP as the mean of follow-up BP readings at or beyond 12 months; (3) defining average follow-up BP as the mean of all follow-up BP readings; (4) excluding cases with diabetes (43 from MDRD trial constituting 0.9% of cases); and (5) excluding the HALT-PKD trial whose subjects had earlier kidney disease.

RESULTS

In total, 5001 subjects with non-diabetic CKD enrolled in five trials were randomized in 1:1 fashion to intensive BP control or standard BP control. Descriptive baseline characteristics are presented in table 1. The median BP follow-up time was 3.2 years. The average age of the cohort was 62±15 years old, with most cases being at or above age 50 (3995 persons or 80% of cohort). Female gender made up 39% of cases. The mean baseline GFR was approximately 45±15 mL/min/1.73 m^2. Most patients had a GFR ranging from ≥30 to <60 mL/min/1.73 m^2 (3729 constituting 74.6% of population); 906 individuals (18.1%) had

Table 1 Study and patient characteristics of goal blood pressure trials included in pooled analysis

Trial	AASK	HALT-PKD	MDRD	REIN-2	SPRINT	Total
Date of publication	2002	2014	1994	2005	2017	1994–2017
Number of patients included	1094	178	840	335	2554	5001
GFR criteria (mL/min/1.73 m^2)	20–65	>60	13–55	<70, excluding ESRD	20–59	<60 or ≥60 with abnormal albuminuria or proteinuria
GFR assessment method	Renal clearance of ^{125}I-iothalamate	eGFR from SCr	Renal clearance of ^{125}I-iothalamate	Renal clearance of non-radioactive iohexol	eGFR from SCr	(per trial)
Albuminuria/proteinuria criteria	UPCR ≤2.5 g/g	UAER ≥30 mg/day	UPER <10 g/day	UPER ≥1 g/day	UACR <600 mg/g	(per trial)
Standard BP target (mm Hg)	MAP 102–107 (≈140/90)	120–130/70–80	MAP ≤107 (≈140/90)	DBP <90	SBP <140	(per trial)
Intensive BP intervention (mm Hg)	MAP ≤92 (≈125/75)	95–110/60–75	MAP ≤92 (≈125/75)	<130/80	SBP <120	(per trial)
Intensive treatment, n (%)	540 (49.4)	91 (51.1)	432 (51.4)	167 (49.9)	1284 (50.3)	2514 (50.3)
Age, years	54.1±10.7	35.7±8.3	51.3±12.4	53.5±15.3	71.9±9.3	62.0±15.0
Female sex, n (%)	424 (38.8)	83 (46.6)	332 (39.5)	84 (25.1)	1005 (39.4)	1928 (38.6)
Race or ethnicity, n (%)						
Non-Hispanic black	1094 (100.0)	7 (3.9)	66 (7.9)	0 (0.0)	616 (24.1)	1783 (35.7)
Non-Hispanic white	0 (0.0)	162 (91.0)	714 (85.0)	331 (98.8)	1715 (67.1)	2922 (58.4)
Hispanic	0 (0.0)	3 (1.7)	39 (4.6)	0 (0.0)	183 (7.2)	225 (4.5)
Other	0 (0.0)	6 (3.4)	21 (2.5)	4 (1.2)	40 (1.6)	71 (1.4)
BMI, kg/m^2	30.6±6.6	27.2±5.4	27.1±4.4	26.4±4.3	29.4±5.8	29.0±5.8
Comorbidities, n (%)						
HTN	1094 (100)	178 (100)	724 (86.2)	335 (100)	2554 (100)	4885 (97.7)
DM	0 (0)	0 (0)	43 (5.1)	0 (0)	0 (0)	43 (0.9)
CVD	564 (51.6)	0 (0)	81 (9.6)	80 (23.9)	627 (24.5)	1352 (27)
Smoking status, n (%)						
Never smoked	461 (42.1)	103 (57.9)	400 (47.6)	196 (58.5)	1161 (45.5)	2321 (46.4)
Former smoker	312 (28.5)	51 (28.7)	82 (9.8)	81 (24.2)	1176 (46.0)	1702 (34.0)
Current smoker	321 (29.3)	24 (13.5)	358 (42.6)	54 (16.1)	216 (8.5)	973 (19.5)
Missing data	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.2)	1 (0.0)	5 (0.1)
Baseline BP, mm Hg						
Systolic	150.3±23.9	127.9±14.9	131.9±17.6	136.7±16.9	139.1±16.0	139.8±19.3
Diastolic	95.5±14.2	81.3±10.9	81.0±10.1	84.1±9.7	75.0±12.2	81.3±14.6
Number of follow-up BP readings evaluated	12,344	1850	6889	2169	22,882	46,134
Number of antihypertensive agents						
At baseline	2.4±1.2	0.2±0.5	1.6±1.1	2.0±1.1	2.1±1.0	2.0±1.1
In standard BP arm	2.1±0.9	1.6±0.7	1.7±1.2	2.2±1.2	2.2±1.1	2.1±0.2
In intensive BP arm	2.2±1.0	1.7±0.8	1.6±1.2	3.0±1.0	2.5±1.0	2.3±1.1
Mean follow-up SBP, mm Hg*						
In standard BP arm	141.2±12.8	120.5±9.1	134.4±15.9	134.7±14.4	136.0±9.2	136.3±6.7
In intensive BP arm	129.4±13.7	113.3±11.3	127.1±14.3	130.8±12.0	123.3±10.2	125.4±12.5
Mean follow-up DBP, mm Hg*						
In standard BP arm	85.7±7.9	77.6±7.0	81.0±7.2	82.5±7.6	72.6±10.0	77.8±3.8
In intensive BP arm	78.2±9.2	71.6±8.8	77.4±6.8	79.8±6.1	66.3±9.1	71.8±10.4
Baseline GFR, mL/min/1.73 m^2	46.4±13.6	77.7±19.4	33.0±11.7	29.1±15.8	47.8±9.5	44.8±14.9
Median baseline albuminuria, mg/day or mg/g (IQR)		49.9 (33.1–91.0)			13.3 (6.4–43.0)	14.7 (6.7–48.5)
Median baseline proteinuria, mg/day or mg/g (IQR)	80.8 (29.8–358.8)		320.0 (70.0–1502.5)	1923.6 (1178.1–2849.7)		233.9 (50.0–1250.0)
Median follow-up, years	4.2	6.0	2.7	1.6	3.2	3.2
Lost to follow-up or withdrawal, n (%)†	9 (0.8)	36 (20.2)	16 (1.9)	49 (14.6)	126 (4.9)	236 (4.7)
Completed study, n (%)	980 (89.6)	141 (79.2)	790 (94.0)	281 (83.9)	2266 (88.7)	4458 (89.1)

Continued

Table 1 Continued

Trial	AASK	HALT-PKD	MDRD	REIN-2	SPRINT	Total
Outcomes, n (%)						
CKD progression‡	300 (27.4)	1 (0.6)	298 (35.5)	86 (25.7)	28 (1.1)	713 (14.3)
GFR decrease by ≥50%	243 (22.2)	0 (0.0)	237 (28.2)	53 (15.8)	20 (0.8)	553 (11.1)
ESRD or transplant	179 (16.4)	1 (0.6)	194 (23.1)	72 (21.5)	16 (0.6)	462 (9.2)
Death	105 (9.6)	1 (0.6)	34 (4.0)	5 (1.5)	162 (6.3)	307 (6.1)
AKI	20 (1.8)	14 (7.9)	2 (0.2)	0 (0.0)	190 (7.4)	226 (4.5)

Numerical data are reported as mean±SD, unless otherwise specified.
*Defined as mean of all follow-up values beginning 6 months after randomization; if not available then the last known BP was used.
†Excludes patients who died.
‡Composite of ≥50% reduction in GFR from baseline or ESRD requiring RRT (long-term dialysis or renal transplantation).
AASK, African American Study of Kidney Disease and Hypertension; AKI, acute kidney injury; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HALT-PKD, HALT Progression of Polycystic Kidney Disease; HTN, hypertension; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; REIN-2, Ramipril Efficacy In Nephropathy 2; RRT, renal replacement therapy; ; SBP, systolic blood pressure; SCr, serum creatinine; SPRINT, Systolic Blood Pressure Intervention Trial; UACR, urine albumin to creatinine ratio; UAER, urine albumin excretion rate; UPCR, urine protein to creatinine ratio; UPER, urine protein excretion rate.

GFR ≥60 mL/min/1.73 m^2, while 366 patients (7.3%) had GFR <30 mL/min/1.73 m^2. Urinary protein excretion was reported in 2269 patients from three trials (AASK, MDRD, and REIN-2); in these cases, the median baseline proteinuria was about 234 (IQR 50–1250) mg/day or equivalent. Urinary albumin was reported in 2732 patients from two trials (SPRINT and HALT-PKD); the median albuminuria was about 15 (IQR 7–49) mg/day or equivalent.

Outcomes

The incidence of CKD progression as well as its individual components for the prespecified categorized follow-up SBP ranges are shown in table 2. SBP 110–119 mm Hg was associated with the lowest incidence of CKD progression. Hazards regression analysis is presented in table 3. In both the unadjusted and adjusted models, SBP 110–119 mm Hg was associated with lowest risk. After adjustment for clinically important variables, SBP 110–119 mm Hg and SBP 120–129 mm Hg were found to provide the least hazard, with all other ranges imparting significantly higher risk (HRs ≥1.7, p<0.05).

In an unadjusted Cox regression, follow-up DBP appeared to display a similar pattern as SBP on CKD progression, with a DBP range of 55–59 mm Hg being linked with the lowest risk of CKD and other DBP strata resulting in progressively higher risk (data not shown). However, in the adjusted multivariable model, all DBP strata posed statistically similar renal risk (all p>0.1), with only the extremes of DBP displaying a non-significant trend toward renal harm (for DBP <55 mm Hg, HR 2.49, p=0.136; for DBP >90 mm Hg, HR 1.51, p=0.42).

The incidence and risk of CKD progression according to albuminuria or proteinuria category are given in tables 4 and 5. Normal to mildly increased (A1) albuminuria or proteinuria was associated with the least risk of CKD progression, with risk expectedly mounting as proteinuria classification worsened. Relative to microalbuminuria or proteinuria in the grade A1 category, the adjusted HR of CKD advancement was 1.51 (95% CI 1.17 to 1.93) for A2 and 3.09 (95% CI 2.49 to 3.83) for A3 categories.

We found no substantial differences from the main results in all sensitivity analyses which sought to ensure no meaningful error arose from imputation, inclusion of diabetic or HALT-PKD cases, or BP classification scheme (online supplemental file 1).

Interactions

We detected a prominent interaction between follow-up SBP and baseline albuminuria or proteinuria classification (eg, $p_{interaction}$=0.019 for grade A2 and $p_{interaction}$=0.001 for

Table 2 Incidence of renal outcomes according to follow-up SBP

Follow-up SBP, mm Hg*	Follow-up BP readings evaluated (n)	Patients (n)	CKD progression, n (%)†‡	≥50% reduction in GFR, n (%)‡	ESRD or transplant, n (%)‡
<110	1669	183	18 (9.8)	16 (8.7)	9 (4.9)
110–119	9071	949	68 (7.2)	53 (5.6)	36 (3.8)
120–129	12,011	1281	159 (12.4)	136 (10.6)	87 (6.8)
130–139	13,141	1426	191 (13.4)	140 (9.8)	130 (9.1)
140–149	7278	781	148 (19.0)	118 (15.1)	100 (12.8)
≥150	2964	381	129 (33.9)	90 (23.6)	100 (26.2)
Total	46,134	5001	713 (14.3)	553 (11.1)	462 (9.2)

*Defined as mean of all follow-up values beginning 6 months after randomization; if not available then last known BP was used.
†Composite of ≥50% reduction in GFR from baseline or ESRD requiring RRT (long-term dialysis or renal transplantation).
‡Percentage is relative to specified BP stratum.
BP, blood pressure; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RRT, renal replacement therapy; SBP, systolic blood pressure.

Table 3 Risk of chronic kidney disease progression according to follow-up SBP

Follow-up SBP, mm Hg*	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†	P value‡
<110	1.3 (0.77 to 2.18)	1.75 (1.03 to 2.97)	0.038
110–119	1	1	Reference
120–129	1.85 (1.39 to 2.46)	1.35 (1.01 to 1.81)	0.043
130–139	2.04 (1.55 to 2.69)	1.67 (1.23 to 2.26)	0.001
140–149	2.94 (2.21 to 3.93)	2.03 (1.45 to 2.86)	<0.001
≥150	7.01 (5.22 to 9.41)	3.01 (2.01 to 4.5)	<0.001

*Defined as mean of all follow-up values beginning 6 months after randomization; if not available then last known BP was used.
†Adjusted for age, sex, race/ethnicity, body mass index, diabetes mellitus, cardiovascular disease, smoking status, baseline glomerular filtration rate, albuminuria/proteinuria category, baseline SBP, baseline DBP, time-updated SBP, time-updated DBP, and antihypertensive regimen (number of antihypertensive drug classes, ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, or diuretic use at baseline and trial start).
‡For adjusted analysis.
BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

grade A3, both relative to grade A1 and treating follow-up SBP as a continuous variable). A Kaplan-Meier plot also provided rough evidence of a differential effect on outcomes dependent on these parameters (figure 1). We could not identify any significant interactions between follow-up SBP (expressed as both a continuous and a categorical variable) and baseline GFR or CKD stage (all $p_{interaction} > 0.05$).

To further explore interaction effects, we carried out the Cox regression analysis in subgroups of baseline albuminuria or proteinuria. The incidence of CKD progression for SBP 110–129 mm Hg (identified as the ideal range in our study) was similar to that for SBP 130–149 mm Hg at normal levels of microalbuminuria or proteinuria but diverged at higher grades (figure 2A). We followed this by a depiction of HR according to follow-up SBP and albuminuria/proteinuria classification (figure 2B). Here, the lowest risk occurred at SBP ranges 110–119 mm Hg and 120–129 mm Hg. However, beginning at an SBP of 130 mm Hg, only patients with higher levels of albuminuria or proteinuria experienced higher risk. Risk trended toward harm for grade A2 and was significantly deleterious for grade A3, in which case it was 2.3 times higher at SBP 130–139 mm Hg and 3.3 times at SBP 140–149 mm Hg. By contrast, for grade A1, risk remained relatively similar over a wide range of BPs. Therefore, in patients with larger degrees of albuminuria or proteinuria, an SBP 110–129 mm Hg was associated with the most favorable renal survival.

Table 4 Incidence of chronic kidney disease progression according to baseline albuminuria or proteinuria

Albuminuria/proteinuria category*	Follow-up BP readings evaluated (n)	Patients (n)	CKD progression, n (%)†
Normal to mildly increased (A1)	26,802	2763	160 (5.8)
Moderately increased (A2)	10,632	1135	124 (10.9)
Severely increased (A3)	8700	1103	429 (38.9)
Total	46,134	5001	713 (14.3)

*Categories for albuminuria and proteinuria are based on the Kidney Disease Improving Global Outcomes guidelines.
†Composite of ≥50% reduction in GFR from baseline or ESRD requiring RRT (long-term dialysis or renal transplantation). Percentage is relative to specified albuminuria/proteinuria stratum.
BP, blood pressure; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RRT, renal replacement therapy.

Table 5 Risk of chronic kidney disease progression according to baseline albuminuria or proteinuria

Albuminuria/proteinuria category*	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†	P value‡
Normal to mildly increased (A1)	1	1	Reference
Moderately increased (A2)	1.85 (1.46 to 2.34)	1.51 (1.17 to 1.93)	0.001
Severely increased (A3)	11.43 (9.51 to 13.72)	3.09 (2.49 to 3.83)	<0.001

*Categories for albuminuria and proteinuria are based on the Kidney Disease Improving Global Outcomes guidelines.
†Adjusted for age, sex, race/ethnicity, body mass index, diabetes mellitus, cardiovascular disease, smoking status, baseline glomerular filtration rate, baseline SBP, baseline DBP, time-updated SBP, time-updated DBP, and antihypertensive regimen (number of antihypertensive drug classes, ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, or diuretic use at baseline and trial start).
‡For adjusted analysis.
DBP, diastolic blood pressure; SBP, systolic blood pressure.

We strove to more precisely determine the threshold level of proteinuria above which rigorous BP control began to display a beneficial relationship with CKD progression. Interaction plots portraying how proteinuria modifies the effect of strict and standard SBP ranges on CKD progression are given in figure 3. Results were displayed up to first 1 g of proteinuria as they were relatively robust within the IQR but less reliable outside this range. We found that an intensive SBP of 110–129 mm Hg was significantly linked with less CKD progression at or above a proteinuria level of approximately 0.7 g/day. Alternative spline models for proteinuria (eg, penalized spline or linear spline) found the transition point of benefit to be roughly 0.5–1 g/day. We attempted a similar plot for albuminuria but were not able to generate this due to a lower event rate for CKD progression in this group attributable to lower grades of albuminuria overall.

DISCUSSION

This pooled analysis of non-diabetic kidney disease found that the optimal SBP range associated with the least CKD progression was 110–129 mm Hg. Lower SBP <110 mm Hg was linked with an increased risk of CKD, as was higher SBP ≥130 mm Hg in a successive fashion. Here, it was not possible to exclude some degree of reverse causality (ie, more significant renal dysfunction contributing to HTN). Consistent with other reports, we perceived a robust, graded relationship between SBP and proteinuria such that the importance of maintaining SBP <130 mm Hg heightened as proteinuria scaled higher.[5 6 15 16] In patients having albuminuria in the grade A3 range or total proteinuria ≥0.5–1 g/day, a strong connection was observed between stricter SBP control and limitation in CKD advancement. In patients with grade A2 microalbuminuria or proteinuria near 0.5 g/day, lower SBP goals may have been non-significantly related to lower CKD progression, although the relationship was inconclusive. In patients with grade A1 albuminuria or proteinuria <0.2 g/day, tighter BP control did not seem to be significantly related to CKD. We also did not find that DBP was linked with risk of CKD progression.

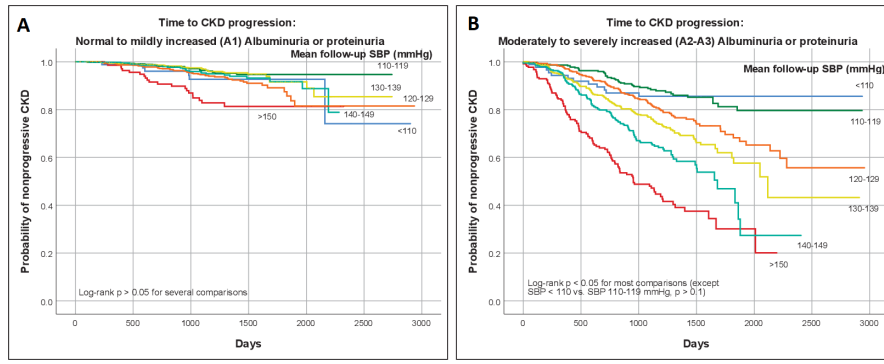

Figure 1 Kaplan-Meier estimates of chronic kidney disease (CKD) progression according to systolic blood pressure (SBP) target for (A) normal to mildly increased (A1) albuminuria or proteinuria and (B) moderately to severely increased (A2–A3) albuminuria or proteinuria.

This pattern aligns with the prevalent view that DBP is a less important determinant of outcomes than SBP in older adults, who comprised the majority of this cohort.[17 18] It possibly also reflects the belief that DBP tends to be more of a marker of general health status or comorbidity burden rather than a causal factor in relation to outcomes.[19 20]

Our study is surely not without limitations. First, this is pooled analysis rather than a typical meta-analysis. As such, it may be more susceptible to concerns surrounding homogeneity of patient populations and uniformity of study designs and methods.[21 22] The fact that our analysis was based on achieved BP (received treatment during during follow-up) rather than initial assignment to a goal BP (intended treatment prior to randomization) represents another shortcoming. Lack of the intention-to-treat principle may introduce selection bias due to crossover (eg, inability to reach BP goals in some hypertensive subjects assigned to intensive therapy) and non-random dropout. We also realize that division of a few continuous variables (BP and proteinuria) into clinically relevant categories may be accompanied by loss of some power. It should be emphasized that all studies were designed as goal BP trials, not albuminuria or proteinuria trials. Moreover, albuminuria or proteinuria assessment was limited only to that at baseline due to lack of available data during follow-up.

Our study should be interpreted heavily in the context of the population under investigation. The vast majority of our cohort were older adults, with four out of five being at or above the age of 50. Plenty of literature exists discussing the prospect of differential HTN targets according to age.[23 24] Notably, most cases of CKD were moderately advanced, with over 90% being at stages 3–4 and a relative minority being at other stages (7% stages 1–2, 2% stage 5). Consequently, the applicability of our results to patients with very mild or severe CKD is less certain. For instance, a post-hoc analysis of SPRINT subjects with more advanced CKD (estimated GFR 20–45 mL/min/1.73 m^2) found that CV benefit attained by an intensive BP target attenuated with lower GFR.[3] Moreover, HALT-PKD subjects made up a significant proportion of earlier CKD (93% of CKD stage 1 and 30% of stage 2). Results derived from patients with autosomal dominant PKD (ADPKD), especially in the early stage, are less likely to be generalizable to non-diabetic CKD stemming from another etiology. This may be particularly relevant in ADPKD as tighter goal BPs than usual are advocated to help reduce the rate of cyst growth.[25 26] We addressed this issue to some extent by excluding HALT-PKD in a sensitivity analysis. As PKD was not highly represented overall (close to 7%), its inclusion would not be expected to alter results substantially. Additionally, the spectrum of

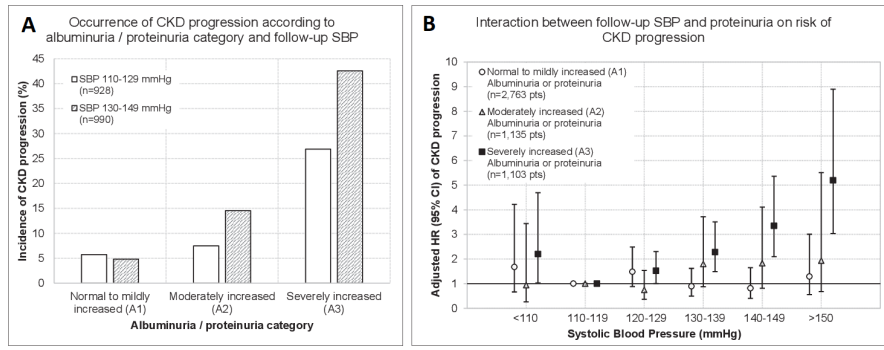

Figure 2 (A) Fraction of patients encountering CKD progression event according to albuminuria/proteinuria category and follow-up SBP in paired categories of SBP 110–129 mm Hg and 130–149 mm Hg. (B) Risk of the composite CKD outcome for various follow-up SBP ranges, stratified by albuminuria/proteinuria classification. The reference group was SBP 110–119 mm Hg. The points represent adjusted HRs. The error bars represent 95% CIs. Adjustments include trial center, age, sex, race/ethnicity, body mass index, diabetes mellitus, cardiovascular disease, smoking status, baseline glomerular filtration rate, baseline SBP, baseline DBP, time-updated SBP, time-updated DBP, and antihypertensive regimen (number of antihypertensive drug classes and ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, or diuretic use at baseline and trial start). CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

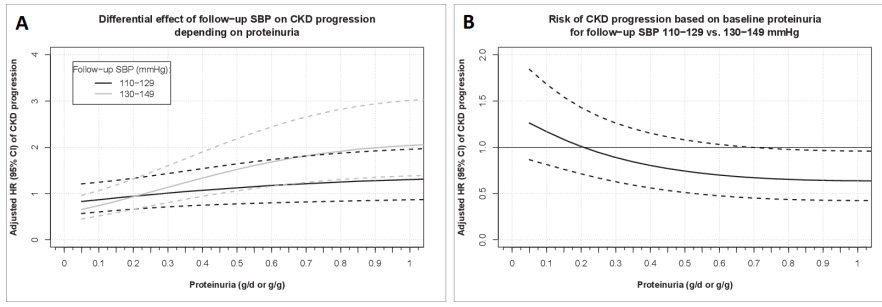

Figure 3 (A) Risk of CKD progression according to proteinuria and follow-up SBP in paired categories of SBP 110–129 mm Hg and 130–149 mm Hg. Data were fit by a Cox proportional hazards regression model and hazard was plotted using natural cubic splines. The reference standard was a median proteinuria of 234 mg/day. The solid lines represent HRs. The dotted lines represent 95% CIs. (B) Risk of CKD progression according to proteinuria for follow-up SBP 110–129 mm Hg in comparison with the reference category 130–149 mm Hg. The solid line represents HR. The dotted lines represent the 95% CI. For A and B, adjustments include trial center, age, sex, race/ethnicity, body mass index, diabetes mellitus, cardiovascular disease, smoking status, baseline glomerular filtration rate, baseline SBP, baseline DBP, time-updated SBP, time-updated DBP, and antihypertensive regimen (number of antihypertensive drug classes and ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, or diuretic use at baseline and trial start). CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

albuminuria and proteinuria in our study was limited to that of trial subjects required to meet certain recruitment criteria (ie, some trials recruited individuals with lower proteinuria, others recruited subjects with more proteinuria). This may also limit generalizability.

Despite limiting studies to those with common designs and patient populations, disparate methodologies between studies could have served as a source for error. For instance, regarding BP measurement technique, whereas SPRINT employed an automated oscillometric method after 5 min of rest in an unattended environment, AASK used an auscultatory, manual sphygmomanometer measurement after 5 min of relaxing. As a result, BP readings derived from SPRINT mimicked ambulatory BP monitoring and were likely ≈5–10 mm Hg lower than traditional office-based BP measurements; in contrast, those obtained in AASK were more typical of inoffice measurements.[27–29] Other examples include discrepancies between studies in methods for proteinuria or albuminuria quantification (eg, 24-hour collection vs random spot ratio to creatinine) or GFR measurement (eg, direct clearance of a filtration marker vs creatinine-based estimation using MDRD equation).

Overall, our pooled analysis in non-diabetic CKD, in agreement with prior findings, confirmed that a tighter BP target (SBP <130 mm Hg rather than SBP <140 mm Hg or higher) was associated with better preservation of renal function in patients with larger amounts of albuminuria (grade A2–A3) or proteinuria (≥0.5–1 g/day) who were likely at a greater risk of disease progression. The relationship was clear at higher degrees of urine albumin or protein excretion but weaker at lesser degrees. Although reverse causation could not be excluded, the observed trends aligned with expectations and correlated highly with previous studies.[5 6 15 16] It would serve the HTN field well if future RCTs were to specifically, by study nature, explore the optimal BP target in the face of pre-existing proteinuria.

Contributors PJDM was the lead author of this study and is primarily responsible for conceptualization/planning, methodology, data acquisition, data curation, investigation, analysis, and writing. EOG supervised the project administration and supported in planning, methodology, analysis, investigation, writing, and review. GS provided support in planning, methodology, writing, and review of this article. All other authors reviewed and helped finalize the paper. AP also provided data access. All authors read and approved the final manuscript.

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Patient consent for publication Not required.

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Data availability statement Data may be obtained from a third party and are not publicly available. De-identified, individual participant data (IPD) were obtained from the following sources: Modification of Diet in Renal Disease (MDRD), African American Study of Kidney Disease and Hypertension (AASK), and HALT Progression of Polycystic Kidney Disease (HALT-PKD) trials (study data sets are available from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository, part of the National Institutes of Health (NIH), at https://repository.niddk.nih.gov/studies/mdrd/https://repository.niddk.nih.gov/studies/aask-trial and https://repository.niddk.nih.gov/studies/halt-pkd/), Systolic Blood Pressure Intervention Trial (SPRINT) (study data sets are available from the National Heart, Lung, and Blood Institute (NHLBI) Data Repository, part of the National Institutes of Health (NIH), at https://biolincc.nhlbi.nih.gov/studies/sprint/), and Ramipril Efficacy In Nephropathy 2 (REIN-2) trial (study data sets are available from the Clinical Research Center for Rare Diseases in the Mario Negri Institute for Pharmacological Research, at http://clintrials.marionegri.it/index.php/main-trials/61.html). IPD obtained from these sources (repository or third party) are not publicly available. As per the data transfer agreements, IPD may not be transferred to other parties. IPD may be requested from the original sources mentioned above, if necessary. Only aggregate or summary data derived from these studies are available in public form.

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