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Effects of Intensive Systolic Blood Pressure Lowering on End-Stage Kidney Disease and Kidney Function Decline in Adults With Type 2 Diabetes Mellitus and Cardiovascular Risk Factors: A Post Hoc Analysis of ACCORD-BP and SPRINT

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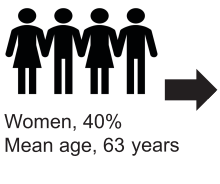
Why did we undertake this study?

- Higher SBP is associated with higher risk of CKD progression
- Intensive SBP lowering (<120 mmHg) reduces the risk of ASCVD but at the expense of more eGFR declines
- Intensive SBP lowering does not increase levels of urinary kidney tubular injury biomarkers
- The effect of intensive SBP lowering on major adverse kidney events remains incompletely understood

Study Design

ACCORD-BP participants in the standard glucose-lowering arm with CVD risk factors required for SPRINT eligibility:

- CVD or subclinical CVD
- CKD (eGFR 20-59 mL/min/1.73 m^2)
- 10-year ASCVD risk ≥15%
- Age >75 years

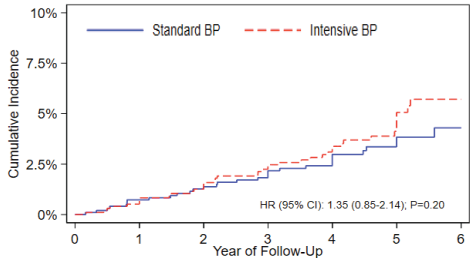


Women, 40%
Mean age, 63 years

SBP Target <120 mmHg (n=991)

SBP Target <140 mmHg (n=975)

Primary Composite Outcome



Sustained eGFR decline ≥57%, dialysis, kidney transplant, eGFR <15 mL/min/1.73 m^2 or SCr >3.3 mg/dL

UACR Outcome	Intensive	Standard	HR (95% CI)
	Events	Events	
30-300 mg/g	148	150	0.96 (0.76-1.20)
>300 mg/g	70	74	0.92 (0.66-1.28)

Conclusions: This post hoc subgroup analysis suggests that intensive SBP lowering may not increase the risk of major adverse kidney events or albuminuria in individuals with T2DM and CVD risk factors.

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SBP, systolic blood pressure; SCr, serum creatinine; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

ARTICLE HIGHLIGHTS

- The effects of intensive systolic blood pressure (SBP) lowering on end-stage kidney disease (ESKD) and on albuminuria in patients with type 2 diabetes mellitus or prediabetes remain uncertain.
- We hypothesized that intensive SBP lowering would decrease the risk of major adverse kidney events.
- This study did not find evidence that intensive SBP lowering increases the risk of ESKD or moderately or severely increased albuminuria.
- Our hypothesis-generating results suggest that the cardiovascular benefits of intensive SBP lowering can be achieved without an unacceptable risk of ESKD.

ORIGINAL ARTICLE

Effects of Intensive Systolic Blood Pressure Lowering on End-Stage Kidney Disease and Kidney Function Decline in Adults With Type 2 Diabetes Mellitus and Cardiovascular Risk Factors: A Post Hoc Analysis of ACCORD-BP and SPRINT

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OBJECTIVE

To determine the effects of intensive systolic blood pressure (SBP) lowering on the risk of major adverse kidney outcomes in people with type 2 diabetes mellitus (T2DM) and/or prediabetes and cardiovascular risk factors.

RESEARCH DESIGN AND METHODS

This post hoc ACCORD-BP subgroup analysis included participants in the standard glucose-lowering arm with cardiovascular risk factors required for SPRINT eligibility. Cox proportional hazards regression models compared the hazard for the composite of dialysis, kidney transplant, sustained estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, serum creatinine >3.3 mg/dL, or a sustained eGFR decline ≥57% between the intensive (<120 mmHg) and standard (<140 mmHg) SBP-lowering arms.

RESULTS

The study cohort included 1,966 SPRINT-eligible ACCORD-BP participants (40% women) with a mean age of 63 years. The mean SBP achieved after randomization was 120 ± 14 and 134 ± 15 mmHg in the intensive and standard arms, respectively. The kidney composite outcome occurred at a rate of 9.5 and 7.2 events per 1,000 person-years in the intensive and standard BP arms (hazard ratio [HR] 1.35 [95% CI 0.85–2.14]; *P* = 0.20). Intensive SBP lowering did not affect the risk of moderately (HR 0.96 [95% CI 0.76–1.20]) or severely (HR 0.92 [95% CI 0.66–1.28]) increased albuminuria. Including SPRINT participants with prediabetes in the cohort did not change the overall results.

CONCLUSIONS

This post hoc subgroup analysis suggests that intensive SBP lowering does not increase the risk of major adverse kidney events in individuals with T2DM and cardiovascular risk factors.

Individuals with type 2 diabetes mellitus (T2DM) have an increased risk of cardiovascular disease (CVD) and end-stage kidney disease (ESKD) (1). Hypertension is a

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common comorbidity in T2DM that is also associated with an increased risk of both CVD and ESKD (2,3). Although intensive systolic blood pressure (SBP) lowering (target SBP of <120 mmHg) significantly reduced the risk of major adverse CVD in the Systolic Blood Pressure Intervention Trial (SPRINT), which excluded participants with T2DM, the same SBP target did not reduce the risk of major adverse CVD events among individuals with T2DM in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD-BP) (4,5). Post hoc analyses of SPRINT participants with prediabetes (6) and ACCORD-BP participants with SPRINT-like high-risk features (7), as well as subgroup analysis from the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial (8), support the cardiovascular benefits of intensive SBP lowering in high-risk (defined using SPRINT criteria) individuals with prediabetes or T2DM (8).

The effects of intensive SBP lowering on adverse kidney outcomes remain unclear. Intensive SBP lowering increased the risk of incident chronic kidney disease (CKD), defined as a decline from baseline of ≥30% in estimated glomerular filtration rate (eGFR) to a value of <60 mL/min/1.73 m^2, in a pooled analysis of SPRINT and ACCORD-BP participants without prevalent CKD (9). This risk was increased further by the presence of T2DM (9). In the context of intensive SBP lowering, however, changes in eGFR of 20–30% may reflect a correction of glomerular hyperfiltration rather than loss of functional nephrons (10). Moreover, renin-angiotensin-aldosterone system inhibitors may exert their cardiorenal benefits by reducing intraglomerular pressure, which would manifest initially as a decline in eGFR. Additionally, the effects of intensive SBP lowering on clinical outcomes, such as dialysis and kidney transplant, larger declines in eGFR, and stage G5 CKD, remain uncertain. Thus, analysis of the effects of intensive SBP lowering on ESKD events may help to clarify the balance between kidney risk and cardiovascular benefit of intensive SBP lowering.

This post hoc study sought to determine the effects of intensive SBP lowering on the risk of major adverse kidney outcomes, including ESKD events, in people with T2DM and/or prediabetes and cardiovascular risk factors.

RESEARCH DESIGN AND METHODS

Study Design

The ACCORD-BP and SPRINT designs have been published previously (4,5). ACCORD-BP was a randomized, multicenter, two-by-two factorial clinical trial. Patients were randomly assigned to either an intensive SBP-lowering strategy (target SBP <120 mmHg) or a standard SBP-lowering strategy (target SBP <140 mmHg) and, in patients with T2DM, an intensive (hemoglobin A_{1c} [HbA_{1c}] goal <6.0%) or standard glucose-lowering strategy (HbA_{1c} goal 7.0–7.9%). SPRINT was a randomized, multicenter clinical trial that compared an intensive SBP-lowering strategy (target SBP <120 mmHg) against standard SBP lowering (target SBP <140 mmHg) in patients with an increased risk for CVD, excluding individuals with T2DM or prior stroke.

Participants

Because of heterogeneity in the effects of intensive SBP lowering on CVD outcomes in T2DM according to SPRINT eligibility status and concomitant intensive glucose lowering, we studied a previously reported subgroup of ACCORD-BP participants who met SPRINT eligibility criteria (7). Individuals from ACCORD-BP were eligible for this analysis if they were in the standard glucose-lowering arm and had at least one of the following risk factors: presence of clinical or subclinical CVD other than stroke; CKD, defined as eGFR of 20–59 mL/min/1.73 m^2 (calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation); estimated 10-year atherosclerotic CVD risk of ≥15% (calculated using the American College of Cardiology/American Heart Association pooled cohort equations); or aged >75 years (11,12). In two separate sensitivity analyses, we repeated the analyses in a pooled cohort of SPRINT-eligible ACCORD-BP participants and SPRINT participants with prediabetes, defined as fasting blood glucose ≥100 mg/dL (6), and in ACCORD-BP participants in the standard glucose-lowering arm (regardless of the presence of the risk factors above).

Intervention

In ACCORD-BP and SPRINT, participants were randomly assigned to either an intensive SBP-lowering strategy (target SBP <120 mmHg) or a standard BP-lowering strategy (target SBP <140 mmHg) as previously described (4,5). Preferred antihypertensive medications included thiazide- or thiazide-like diuretics, β-blockers, nondihydropyridine calcium channel blockers, and ACE inhibitors or angiotensin receptor blockers (ARBs). SBP was measured as the average of three seated measurements using an automated device (OMRON 907XL) after 5 min of observed or unobserved rest (13).

Outcomes

The primary outcome of this analysis was major adverse kidney events, defined as the composite of a sustained (two consecutive measurements that were at least 4 weeks apart) eGFR decline of ≥57% (calculated using the 2021 CKD-EPI equation), sustained eGFR <15 mL/min/1.73 m^2, serum creatinine >3.3 mg/dL, chronic dialysis, or kidney transplant (11). Serum creatinine was measured at baseline, at 4-month intervals, and then annually in ACCORD-BP and at baseline; months 1, 3, and 6; 1 year; 18 months; and 2, 3, and 4 years in SPRINT. Study staff ascertained dialysis and kidney transplant during study visits at 4-month intervals during the study.

Secondary outcomes included individual components of the primary outcome analyzed separately, ESKD (chronic dialysis, kidney transplant, eGFR <15 mL/min/1.73 m^2, or serum creatinine >3.3 mg/dL), the composite of all-cause death or major adverse kidney event, all-cause death alone, sustained eGFR decline of ≥40%, sustained eGFR decline of ≥30%, moderately increased albuminuria (urine albumin-to-creatinine ratio [UACR] of 30–300 mg/dL), and severely increased albuminuria (UACR >300 mg/dL). For the SPRINT participants with prediabetes, albuminuria was defined as a doubling of UACR ratio from <10 mg/g at baseline to >10 mg/g during follow-up. Additonally, we assessed all-cause mortality in the observational postintervention ACCORD Follow-on (ACCORDION) study (14).

Estimated Numbers of Cardiovascular Events and Sustained eGFR Declines Attributable to Intensive SBP Lowering Among SPRINT-Eligible Adults With T2DM in the U.S.

We sought to clarify the relative risks and benefits of intensive SBP lowering among individuals with T2DM at the population level. We estimated the numbers of cardiovascular events and sustained eGFR declines potentially attributable to intensive SBP lowering among SPRINT-eligible adults with T2DM in the U.S., overall and

separately among those with and without CKD. The total number of adults with T2DM who potentially met SPRINT eligibility criteria in the U.S. was estimated using the 2017–2018 cohort cycle of the National Health and Nutrition Examination Survey (NHANES) (15). T2DM was defined as ever being told by a doctor of a diagnosis of diabetes or an HbA_{1c} of 6.5% or higher and age at diabetes diagnosis of at least 40 years (16). SPRINT eligibility was defined as a self-reported history of coronary heart disease; myocardial infarction, or angina; an eGFR of 20–59 mL/min/1.73 m^2; or age ≥75 years. We excluded participants who were aged <18 years, were missing serum creatinine values, or had an eGFR <20 mL/min/1.73 m^2. CVD events potentially attributable to intensive SBP lowering included the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, any revascularization, and heart failure. The number of sustained eGFR declines of ≥40% and ≥30% were estimated among SPRINT-eligible adults with T2DM in the U.S. Incidence rates for cardiovascular events and sustained eGFR declines were derived from the present analyses of the SPRINT-eligible ACCORD-BP cohort.

Statistical Analysis

Baseline characteristics were summarized as means and SDs for continuous variables and numbers and proportions for categorical variables. We used independent-sample *t* tests to compare continuous variables and χ^2 tests to compare categorical variables between the intensive and standard SBP-lowering arms. Longitudinal changes in SBP were compared using linear mixed-effects models with a random-effects term for time, fixed-effects terms for treatment arm and the interaction of treatment arm and time, a randomly varying intercept, and an unstructured covariance matrix. For the primary and secondary outcomes, we estimated the hazard ratio (HR) for each outcome of interest comparing intensive with standard SBP lowering using a Cox proportional hazards regression model. Deviation from proportionality was assessed by visual inspection of scaled Schoenfeld residuals. Effect modification by age (≥75 years), sex, baseline albuminuria (≥30 mg/g), baseline eGFR <60 mL/min/1.73 m^2, and use of ACE inhibitor or ARB therapy was evaluated using multiplicative interaction terms in the primary cohort of SPRINT-eligible ACCORD-BP participants. In the sensitivity analysis cohort that included all ACCORD-BP participants in the standard glucose-lowering arm, we assessed effect modification by SPRINT eligibility status (as defined above).

Sample weights were used in all NHANES estimates to account for the complex, multistage probability sampling design and rates of survey nonresponse. The estimated numbers of cardiovascular and sustained eGFR decline events potentially attributable to intensive SBP lowering over a 3-year period were calculated as the products of *1*) the estimated number of adults in the U.S. who have T2DM and are SPRINT eligible, *2*) the absolute difference in incidence rates for intensive and standard SBP lowering, and *3*) 3 years. These estimates were calculated for all SPRINT-eligible adults in the U.S. with T2DM and according to CKD status (eGFR of <60 mL/min/1.73 m^2).

$P < 0.05$ was considered statistically significant. Stata 17.0 software (StataCorp LLC, College Station, TX) was used to conduct all analyses.

Data and Resource Availability

Access to the data for this analysis was obtained through the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center and NHANES.

RESULTS

Participant Characteristics

Of the 4,733 ACCORD-BP participants, we excluded 2,371 who were randomly assigned to intensive glucose lowering, 13 who were missing baseline serum creatinine measures, and 383 who did not meet SPRINT eligibility criteria, leaving 1,966 eligible participants (Supplementary Fig. 1). The mean age of the participants was 63 years, 40% were women, and the baseline mean eGFR was 80 mL/min/1.73 m^2 (Table 1). The mean SBP achieved after random assignment was significantly lower in the intensive BP-lowering arm compared with the standard BP-lowering arm (120 ± 14 vs. 134 ± 15 mmHg, $P <$ 0.001) (Supplementary Fig. 2).

Effect of Intensive SBP Lowering on Major Adverse Kidney Events

Over a median follow-up of 4.7 years, the primary composite outcome of ESKD or sustained eGFR decline of ≥57% occurred in 42 participants (9.6 events per 1,000 person-years) in the intensive SBP-lowering arm compared with 31 participants (7.2 events per 1,000 person-years)

Table 1—Baseline characteristics

Characteristic	Intensive SBP-lowering group (*n* = 991)	Standard SBP-lowering group (*n* = 975)	*P*
Age, years	63.0 ± 7.0	63.0 ± 7.0	0.64
Female sex, *n* (%)	391 (39.5)	386 (39.6)	0.95
Criteria for SPRINT eligibility, *n* (%)			
History of CVD	389 (39.3)	389 (39.9)	0.77
History of CKD*	156 (15.7)	132 (13.5)	0.17
Age of at least 75 years	56 (5.7)	59 (6.1)	0.71
10-year ASCVD risk score ≥15%	591 (59.6)	581 (59.6)	0.98
Current smoking, *n* (%)	122 (12.3)	119 (12.2)	0.94
Heart failure, *n* (%)	51 (5.1)	50 (5.1)	0.99
Baseline SBP, mmHg	139 ± 16.0	141 ± 16.0	0.056
Baseline DBP, mmHg	76 ± 10.0	76 ± 10.0	0.41
eGFR, mL/min/1.73 m^2*	80.0 ± 17.0	80.0 ± 16.0	0.76
LDL, mg/dL	112.9 ± 38.6	109.2 ± 36.2	0.032
HbA_{1c}, %	8.3 ± 1.0	8.3 ± 1.0	0.11
UACR, mg/dL, median (IQR)	16 (8–49)	18 (8–66)	0.19
10-year ASCVD risk score, %	30.4 ± 12.6	30.7 ± 12.3	0.65
BMI, kg/m^2	32.2 ± 5.5	32.1 ± 5.1	0.63

ASCVD, atherosclerotic cardiovascular disease; DBP, diastolic blood pressure; IQR, interquartile range. *Calculated based on the 2021 CKD-EPI equation.

in the standard SBP-lowering arm (HR 1.35 [95% CI 0.85–2.14]; $P = 0.20$) (Fig. 1). Intensive SBP lowering did not reduce the risk of ESKD (25 vs. 24 events; HR 1.03 [95% CI 0.58–1.80]) or a sustained eGFR decline of ≥57% (18 vs. 14 events; HR 1.29 [95% CI 0.64–2.59]) (Table 2).

Intensive SBP lowering did not reduce the risk of the composite of all-cause death or major adverse kidney event (100 vs. 101 events; HR 0.99 [95% CI 0.74–1.30]), all-cause death alone in the main study (60 vs. 71 events; HR 0.85 [95% CI 0.60–1.20]) or the ACCORDION study (194 vs. 193 events; HR 0.97 [95% CI 0.80–1.10]), moderately increased albuminuria (148 vs. 150 events; HR 0.96 [95% CI 0.76–1.20], or severely increased albuminuria (70 vs. 74 events; HR 0.92 [95% CI 0.66–1.28]) (Table 2). There was a greater number of eGFR declines of ≥40% (170 vs. 72 events; HR 2.46 [95% CI 1.87–3.25]) and of ≥30% (328 vs. 156 events; HR 2.32 [95% CI 1.91–2.80]) in the intensive SBP-lowering arm compared with the standard SBP-lowering arm (Table 2). There were no significant interactions between the effect of intensive SBP lowering on the primary composite outcome and age ($P_{interaction}$ = 0.23), sex ($P_{interaction}$ = 0.43), baseline albuminuria ($P_{interaction}$ = 0.33), baseline eGFR <60 mL/min/1.73 m^2 ($P_{interaction}$ = 0.18), or use of ACE inhibitors or ARBs ($P_{interaction}$ = 0.23) (Supplementary Table 1).

The overall results were consistent when SPRINT participants with prediabetes were included in the cohort with ACCORD-BP participants (Supplementary Table 2) and in ACCORD-BP participants in the standard glucose-lowering arm who did and did not meet SPRINT eligibility criteria (Supplementary Table 3).

Estimated Numbers of Kidney and Cardiovascular Events Potentially Attributable to Intensive SBP Lowering Among Adults With T2DM in the U.S.

An estimated 12.7 (95% CI 10.2–15.3) million American adults with T2DM potentially meet SPRINT eligibility criteria. The estimated mean age of the SPRINT-eligible adults with T2DM was 69 (95% CI 68–71) years, and the estimated proportion of women was 39% (95% CI 33–46%) (Supplementary Table 4). Intensive SBP lowering among these 12.7 million adults is estimated to prevent 952,500 (95% CI 765,500–1,147,500) cardiovascular events at the expense of 1.5 (95% CI 1.2–1.8) million sustained eGFR declines of ≥40% or 3.3 (95% CI 2.6–3.9) million sustained eGFR declines of ≥30% (Supplementary Table 5). Among the estimated 4.1 (95% CI 3.0–5.1) million SPRINT-eligible American adults with T2DM and CKD, intensive SBP lowering is estimated to potentially prevent 395,841 (95% CI 291,060–501,352) cardiovascular events at the expense of 318,729 (95% CI 234,360–402,318) sustained eGFR declines of ≥40% or 729,504 (95% CI 536,400–920,820) sustained eGFR declines of ≥30% (Supplementary Table 5).

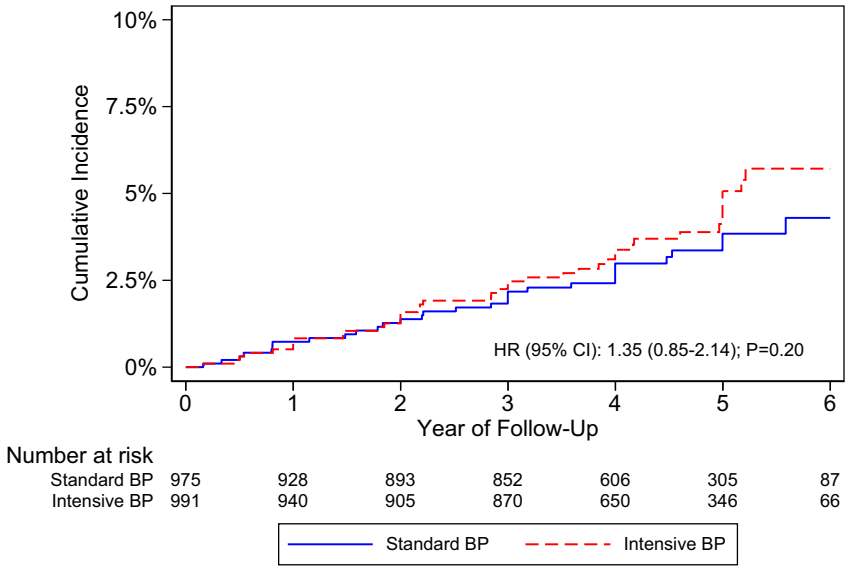

Figure 1—Incidence of major adverse kidney outcomes according to SBP-lowering strategy. The cumulative incidence of the primary composite outcome of sustained eGFR decline ≥57%, sustained eGFR <15 mL/min/1.73 m^2, serum creatinine >3.3 mg/dL, dialysis, or kidney transplant between the intensive SBP-lowering group and the standard SBP-lowering group is shown.

CONCLUSIONS

Previous research suggests that intensive SBP lowering in individuals with T2DM may increase the risk of incident CKD, defined as an eGFR decline of ≥30% to a value <60 mL/min/1.73 m^2 (9). The effects of intensive SBP lowering on ESKD events, as opposed to changes in eGFR, was previously unknown. Since intensive SBP lowering reduced the risk of major CVD events in individuals with T2DM who were SPRINT eligible, we hypothesized that intensive SBP lowering would decrease the risk of major adverse kidney events in the same individuals. Our analysis, however, did not find evidence that intensive SBP lowering decreases the risk of major adverse kidney events or moderately or severely increased albuminuria in patients with T2DM who meet SPRINT eligibility criteria. Results were consistent in an analysis that pooled SPRINT-eligible ACCORD-BP participants with SPRINT participants who had prediabetes and in ACCORD-BP participants in the standard glucose-lowering arm regardless of SPRINT eligibility. Our results argue against intensive SBP lowering as an intervention to slow the progression of CKD, suggest that the cardiovascular benefits of intensive SBP lowering can be achieved without an unacceptable risk of major adverse kidney events, and highlight important considerations for the interpretation of eGFR changes as clinical trial end points.

The 2021 Kidney Disease: Improving Global Outcomes guidelines for the management of BP in CKD recommend a target SBP goal of <120 mmHg based on the CVD event and all-cause mortality risk reduction observed in SPRINT, including within the prespecified subgroup of patients with CKD (17,18). The evidence on the potential long-term beneficial and harmful kidney effects of intensive SBP lowering in patients with CKD remains unclear, especially in patients with T2DM. A previous analysis from ACCORD-BP and SPRINT raised concern that intensive SBP lowering may increase the risk for incident CKD (9). This study focused on individuals without prevalent CKD and, therefore, did not analyze ESKD events (9). Our study builds upon this prior work with an analysis of ESKD events and eGFR-based

Table 2—Effects of intensive vs. standard SBP lowering on adverse kidney outcomes

Outcome	People with event, *n*		Events/1,000 person-years, *n*		HR (95% CI)	*P*
	Intensive (*n* = 991)	Standard (*n* = 975)	Intensive (*n* = 991)	Standard (*n* = 975)		
Primary composite outcome						
Sustained eGFR decline ≥57%, sustained eGFR <15 mL/min/1.73 m^2, serum creatinine >3.3 mg/dL, dialysis, or kidney transplant	42	31	9.58	7.18	1.35 (0.85–2.14)	0.20
Components of primary outcome						
Sustained eGFR decline ≥57%	18	14	3.85	3.07	1.29 (0.64–2.59)	0.47
ESKD	25	24	5.66	5.54	1.03 (0.58–1.80)	0.91
Secondary outcomes						
Death or major adverse kidney event	100	101	22.82	23.41	0.99 (0.74–1.30)	0.93
All-cause death	60	71	12.28	14.61	0.85 (0.60–1.20)	0.37
All-cause death during extended follow-up	194	193	21.28	21.69	0.97 (0.80–1.19)	0.83
Sustained eGFR decline ≥30%	328	156	85.50	36.81	2.32 (1.91–2.80)	<0.001
Sustained eGFR decline ≥40%	170	72	39.63	16.24	2.46 (1.87–3.25)	<0.001
Moderately increased albuminuria (UACR 30–300 mg/g)	148	150	58.62	60.97	0.96 (0.76–1.20)	0.72
Severely increased albuminuria (UACR >300 mg/g)	70	74	17.37	18.84	0.92 (0.66–1.28)	0.64

surrogate outcomes in CKD and non-CKD. While intensive SBP lowering increased the risk of modest sustained eGFR declines (≥30% and ≥40%), there was no difference between intensive and standard SBP lowering with respect to ESKD events or albuminuria 30–300 mg/g or >300 mg/g. The lack of effect of intensive SBP lowering on albuminuria, a predictor of ESKD risk, has particular importance in our analyses because our study had greater power to detect an effect on this outcome, which occurred in 442 participants, compared with the primary outcome, which occurred in 73 participants (19).

We sought to characterize the risk-benefit ratio for intensive SBP lowering at the population level by estimating the number of cardiovascular events potentially avoidable and the number of sustained eGFR declines potentially caused by intensive SBP lowering. While the number of eGFR declines of ≥30% or ≥40% would exceed the number of prevented cardiovascular events, the clinical significance of a clinical cardiovascular event exceeds that of a potentially reversible change in eGFR. Moreover, a post hoc analysis of SPRINT found that the effects of intensive SBP lowering on CVD events and overall mortality were independent of the initial eGFR decline (20).

We evaluated the effects of intensive SBP lowering on kidney outcomes in patients with T2DM using both clinical (ESKD) and eGFR-based outcomes (a sustained eGFR decline ≥57% from baseline), including different eGFR decline thresholds based on recommendations from the International Society of Nephrology (21). An eGFR-based surrogate outcome was included in the primary composite outcome to maximize the number of events. A sustained eGFR decline of ≥57% was chosen for the primary composite outcome instead of lower thresholds (≥30% or ≥40%) to approximate the risk of ESKD as closely as possible and to exclude the short-term effects of intensive SBP lowering on kidney hemodynamics (22,23). Interpretation of eGFR changes that occur while treating hypertension with an intensive SBP-lowering target to achieve a cardiovascular benefit in patients with T2DM should consider the underlying etiology, as certain BP-lowering agents (ACE inhibitors and ARBs) slow CKD progression by decreasing intrarenal hypertension and, accordingly, eGFR (24–26). In our study, intensive SBP lowering did not increase the risk of moderately or severely increased albuminuria, suggesting that the eGFR declines reflected a change in intrarenal hemodynamics rather than irreversible kidney damage. Furthermore, two post hoc studies of ACCORD-BP and SPRINT demonstrated that intensive SBP lowering was not associated with an increase in kidney tubule injury biomarker levels (27,28).

The African American Study of Kidney Disease (AASK) found that a mean arterial pressure target of ≤92 mmHg significantly reduced the risk of doubling of serum creatinine, ESKD, or death compared with a mean arterial pressure target of 102–106 mmHg in a subgroup with UACR of ≥0.22 (29). Our analysis of ACCORD-BP did not replicate this interaction, possibly because ACCORD-BP excluded individuals with UACR of ≥0.7. Since the absolute risk of CKD progression is highest among individuals with T2DM and albuminuria, further research on intensive SBP lowering in these individuals is needed.

The primary limitations of our analysis include the small number of events, lack of long-term event follow-up, and post hoc design. ACCORD-BP was not designed to test the effects of intensive SBP lowering on kidney outcomes in participants with T2DM and additional CVD risk factors. In the absence of long-term ESKD data, our analysis of ACCORDION found no difference in all-cause mortality between intensive and standard SBP lowering. Furthermore, a bidirectional Mendelian randomization analysis suggested that lifelong exposure to genetically instrumented higher kidney function associates with lower BP, but lifelong genetically instrumented lower BP does not associate with higher kidney function (30). Although our study was not a prespecified analysis of ACCORD-BP or SPRINT, our research was hypothesis driven, the selection of the study cohort was based on prior research, and the analyses maintained the original randomization allocation. In summary, these results suggest that intensive SBP

lowering to a target of <120 mmHg does not reduce the risk of major adverse kidney events or moderately or severely increased albuminuria in patients with T2DM and additional risk factors.

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