Association Between Blood Pressure and Adverse Renal Events in Type 1 Diabetes

Elaine Ku,[1,2] Charles E. McCulloch,[3] Michael Mauer,[4] Stephen E. Gitelman,[5] Barbara A. Grimes,[3] and Chi-yuan Hsu[1]

Diabetes Care 2016;39:2218–2224 | DOI: 10.2337/dc16-0857

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To compare different blood pressure (BP) levels in their association with the risk of renal outcomes in type 1 diabetes and to determine whether an intensive glycemic control strategy modifies this association.

RESEARCH DESIGN AND METHODS

We included 1,441 participants with type 1 diabetes between the ages of 13 and 39 years who had previously been randomized to receive intensive versus conventional glycemic control in the Diabetes Control and Complications Trial (DCCT). The exposures of interest were time-updated systolic BP (SBP) and diastolic BP (DBP) categories. Outcomes included macroalbuminuria (>300 mg/24 h) or stage III chronic kidney disease (CKD) (sustained estimated glomerular filtration rate <60 mL/min/1.73 m^2).

RESULTS

During a median follow-up time of 24 years, there were 84 cases of stage III CKD and 169 cases of macroalbuminuria. In adjusted models, SBP in the <120 mmHg range was associated with a 0.59 times higher risk of macroalbuminuria (95% CI 0.37–0.95) and a 0.32 times higher risk of stage III CKD (95% CI 0.14–0.75) compared with SBPs between 130 and 140 mmHg. DBP in the <70 mmHg range were associated with a 0.73 times higher risk of macroalbuminuria (95% CI 0.44–1.18) and a 0.47 times higher risk of stage III CKD (95% CI 0.21–1.05) compared with DBPs between 80 and 90 mmHg. No interaction was noted between BP and prior DCCT-assigned glycemic control strategy (all $P > 0.05$).

CONCLUSIONS

A lower BP (<120/70 mmHg) was associated with a substantially lower risk of adverse renal outcomes, regardless of the prior assigned glycemic control strategy. Interventional trials may be useful to help determine whether the currently recommended BP target of 140/90 mmHg may be too high for optimal renal protection in type 1 diabetes.

The Joint National Committee and American Diabetes Association guidelines currently recommend a blood pressure (BP) target of <140/90 mmHg for all adults with diabetes, regardless of type (1–3). However, evidence used to support this recommendation is primarily based on data from trials of type 2 diabetes (4–6). The relationship between BP and adverse outcomes in type 1 and type 2 diabetes may differ, given that the type 1 diabetes population is typically much younger at disease onset, hypertension is less frequently present at diagnosis (3), and the basis

[1]Division of Nephrology, Department of Medicine, University of California, San Francisco, San Francisco, CA
[2]Division of Pediatric Nephrology, Department of Pediatrics, University of California, San Francisco, San Francisco, CA
[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA
[4]Division of Pediatric Nephrology, Department of Pediatrics, University of Minnesota, Minneapolis, MN
[5]Division of Pediatric Endocrinology, Department of Pediatrics, University of California, San Francisco, San Francisco, CA

Corresponding author: Elaine Ku, elaine.ku@ucsf.edu.

Received 20 April 2016 and accepted 8 August 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0857/-/DC1.

for the pathophysiology and disease complications may differ between the two populations.

Prior prospective cohort studies (7,8) of patients with type 1 diabetes suggested that lower BP levels (<110–120/70–80 mmHg) at baseline entry were associated with a lower risk of adverse renal outcomes, including incident microalbuminuria. In one trial of antihypertensive treatment in type 1 diabetes (9), assignment to a lower mean arterial pressure (MAP) target of <92 mmHg (corresponding to ~125/75 mmHg) led to a significant reduction in proteinuria compared with a MAP target of 100–107 mmHg (corresponding to ~130–140/85–90 mmHg). Thus, it is possible that lower BP (<120/80 mmHg) reduces the risk of important renal outcomes, such as proteinuria, in patients with type 1 diabetes and may provide a synergistic benefit with intensive glycemic control on renal outcomes (10–12). However, fewer studies have examined the association between BP levels over time and the risk of more advanced renal outcomes, such as stage III chronic kidney disease (CKD) or end-stage renal disease (ESRD), during long-term follow-up. One recent report (13) in a large cohort of patients with type 1 diabetes with established diabetic nephropathy indicated that survival has improved and the loss of renal function has diminished over time, along with better control of modifiable risk factors such as BP. Given the typical long duration before the onset of more serious renal complications in type 1 diabetes, the use of observational data to help support or refute the potential use of future BP-lowering trials on the risk of renal outcomes would be useful in this population.

The primary objective of this study was to determine whether there is an association between lower BP levels and the risk of more advanced diabetic nephropathy, defined as macroalbuminuria or stage III CKD, within a background of different glycemic control strategies using data from the Diabetes Control and Complications Trial (DCCT). We hypothesized that exposure to BPs <120/80 mmHg would be associated with a lower risk of macroalbuminuria and CKD and that there would be a stepwise increase in the risk of adverse renal outcomes with stepwise increases in BP levels. We also hypothesized that the association of BP and outcomes would be weaker in participants formerly assigned to receive intensive glycemic control during the DCCT.

RESEARCH DESIGN AND METHODS

The DCCT randomized 1,441 participants between the ages of 13 and 39 years with type 1 diabetes to intensive (hemoglobin A_{1c} goal of <6% or 42 mmol/mol) versus conventional glycemic control between 1983 and 1993. A primary prevention cohort (diabetes for <5 years, albumin excretion rate <40 mg/24 h, and no retinopathy) and a secondary prevention cohort (diabetes duration of 1–20 years, albumin excretion rate ≤200 mg/24 h, and no more than moderate nonproliferative retinopathy) were included. Details of the trial have been described previously (14). Participants with a BP >140/90 mmHg or a history of treatment for hypertension during the 2 years prior to randomization were excluded.

At the conclusion of the DCCT, 96% of participants (*N* = 1,375) enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) observational phase of the study, which is still ongoing (15). All participants in the conventional glycemic control arm were offered instruction in intensive glycemic control, and participants in the intensive glycemic control arm were encouraged to continue intensive glycemic control. After the trial, all participants returned to their own providers for care. The current study includes DCCT and EDIC follow-up through 2012 (year 18 of the EDIC).

BP Measurements

During the DCCT and EDIC, BP was measured by trained observers in a standardized fashion after 5 min of rest every 3 months during the DCCT and annually during the EDIC (11). If BP was ≥140/90 mmHg, participants were asked to return in a month for repeat measurement during the DCCT and received a diagnosis of hypertension only if BP remained above this threshold. BPs <140/90 mmHg were not treated during the DCCT. Data on the use of antihypertensive medications, including the renin-angiotensin-aldosterone system (RAAS) blockers, were collected at all annual visits. The use of RAAS blockers was discouraged during the DCCT.

Predictors of Interest

Only BP measurements taken at the annual visits in the DCCT and EDIC were included for analysis. In our primary analysis, time-updated systolic BP (SBP) was categorized as <120 mmHg, 120 to <130 mmHg, 130 to <140 mmHg, and ≥140 mmHg. Time-updated diastolic BP (DBP) was categorized as <70 mmHg, 70 to <80 mmHg, 80 to <90 mmHg, and ≥90 mmHg. For all predictors of interest, a 1-year time lag was used to examine the association between BP and outcomes (e.g., year 0 BP measurements were used as predictors of year 1 outcomes). We chose to categorize BPs as our primary predictor to facilitate the comparison of results to current guideline-recommended BP targets. We selected SBPs in the range of 130 to <140 mmHg and DBPs in the range of 80 to <90 mmHg that would not warrant treatment according to current hypertension guidelines as the reference group. In a secondary analysis, time-updated SBP and DBP (with a 1-year lag) were also used as continuous predictors of all outcomes of interest.

Outcomes of Interest

The primary outcomes of interest were macroalbuminuria and stage III CKD. Urine albumin levels were measured yearly during the DCCT and every 2 years during the EDIC using 4-h timed collections that were expressed as 24-h rates, as previously described (10). As per prior DCCT and EDIC studies, macroalbuminuria was defined as the first visit where the urine albumin concentration was >300 mg/day (10). Stage III CKD was defined as a sustained estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 on two consecutive visits according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (10,16). Serum creatinine values were measured yearly and were retrospectively recalibrated to isotope dilution mass spectrophotometry-traceable values if values were obtained prior to 2007 (12).

Secondary outcomes of interest included incident sustained microalbuminuria, defined as two consecutive visits when the urine albumin level was ≥30 mg/24 h (16); sustained eGFR of <90 mL/min/1.73 m^2; and the onset of ESRD (receipt of dialysis or transplant).

Statistical Analysis

In primary analysis, time-updated Cox models were used to examine the

association between BP categories and outcomes of interest in separate models for SBP and DBP. The base model was stratified on primary versus secondary prevention cohorts (to accommodate nonproportionality in risk) and were controlled only for the assigned glycemic control strategy during the DCCT (model 1). We subsequently added fixed covariates measured at baseline entry, including age, sex, race, education, family history of hypertension, albuminuria, smoking status, and eGFR (model 2). We then additionally adjusted for time-updated covariates including BMI, smoking status, use of antihypertensive medications (yes/no), eGFR, albuminuria, hemoglobin A_{1c} level, and use of ACE inhibitors or angiotensin receptor blockers (ARBs) ascertained at the same time as the time-updated BP measurements (model 3). Our primary analysis was based on model 3, with a 1-year lag built into our Cox models between BP and outcome ascertainment. All time-dependent covariates were updated annually, and missing values were carried forward from the prior year. In additional analyses, we also performed adjusted Cox models with 4-year and 7-year lags built into our models (the approximate mean follow-up duration of the DCCT) between BP and outcome ascertainment to ensure that BP levels temporally precede the onset of kidney disease and are less likely to be a consequence of kidney disease.

We subsequently tested for the presence of interaction between SBP and DBP (as continuous predictors to maximize power) and assigned glycemic control strategy during DCCT to assess for effect modification.

In a secondary analysis, we repeated our models using 1-year lagged SBP and DBP as continuous predictors in fully adjusted models (model 3) for all outcomes. To assess for the presence of nonlinearities in the association between BP and outcomes of interest, quadratic BP terms (SBP or DBP) were added to adjusted Cox models and tested for statistical significance. To determine whether SBP or DBP was a more important predictor of adverse renal outcomes, we included both parameters as continuous predictors in the same Cox model. We also evaluated the association among baseline BP values as continuous predictors of our primary outcomes.

Finally, to attempt to isolate the association between treated BP levels and renal outcomes of interest, we used SBP and DBP as continuous predictors in Cox models restricted to the duration of follow-up when participants reported active use of antihypertensive agents. We also tested formally for the presence of interaction between antihypertensive therapy and SBP or DBP categories.

All data used were deidentified and obtained from the National Institute of Diabetes and Digestive and Kidney Diseases data repository. The University of California, San Francisco, Institutional Review Board considers this study "exempt" human subjects research. All analyses were conducted using Stata 13.

RESULTS

The baseline characteristics of participants at the time of enrollment in the DCCT are shown in Table 1. The mean age of participants was 27 years, and >96% were white. No participant had macroalbuminuria or stage III CKD at the time of entry into the DCCT. During the trial, the mean hemoglobin A_{1c} level was 7.3% (56 mmol/mol) in the intensive glycemic control arm and 9.1% (76 mmol/mol) in the conventional glycemic control arm and converged to 8% during the EDIC phase of the study (12,14). After a mean follow-up time of 6.5 years during the DCCT, intensive glycemic control was found to delay the onset of diabetic retinopathy, neuropathy, and nephropathy (14).

Macroalbuminuria developed in a total of 169 participants (0.54 cases/100 person-years) and stage III CKD developed in 84 participants (0.26 cases/100 person-years) during a median follow-up time of 24 years. Among those in whom CKD developed, the mean qualifying eGFR at incident CKD was 47.4 ± 11.6 mL/min/1.73 m^2. In our primary analysis, SBP <120 mmHg, but not DBP <70 mmHg, was associated with a statistically significant lower risk of macroalbuminuria and stage III CKD compared with reference BPs (Table 2). In fully adjusted models, SBPs in the range of 120 to <130 mmHg and DBPs in the range of 80 to <90 mmHg also trended toward a lower risk of macroalbuminuria, but these associations did not achieve statistical significance. BPs ≥140/90 mmHg

Table 1—Baseline characteristics at time of enrollment in DCCT by SBP category

Baseline characteristics at DCCT enrollment	SBP <120 mmHg (*N* = 908)	SBP 120 to <130 mmHg (*N* = 376)	SBP 130 to <140 mmHg (*N* = 135)	SBP ≥140 mmHg (*N* = 22)
Age, mean ± SD (years)	26.2 ± 7.3	27.6 ± 6.8	28.1 ± 6.2	29.4 ± 5.7
Female sex, *N* (%)	516 (56.8)	137 (36.4)	25 (18.5)	2 (9.1)
White, *N* (%)	871 (95.9)	366 (97.3)	132 (97.8)	22 (100.0)
Education, mean ± SD (years)	13.9 ± 2.3	14.3 ± 2.2	14.5 ± 2.1	15.0 ± 1.7
Family history of hypertension, *N* (%)	502 (55.3)	215 (57.2)	83 (61.5)	11 (50.0)
Duration of diabetes, median (IQR) (years)	3.9 (2.1–8.7)	4.3 (2.2–8.9)	4.7 (2.3–10.1)	9.7 (3.9–11.9)
Retinopathy at baseline, *N* (%)	428 (47.1)	191 (50.8)	78 (57.8)	18 (81.8)
BMI, mean ± SD (kg/m^2)	23.1 ± 2.7	23.8 ± 2.7	24.7 ± 2.8	24.7 ± 2.7
Hemoglobin A_{1c}, mean ± SD (%)	9.0 ± 1.6	8.8 ± 1.5	8.6 ± 1.5	8.8 ± 1.1
Serum creatinine, mean ± SD (mg/dL)	0.78 ± 0.15	0.82 ± 0.14	0.88 ± 0.15	0.90 ± 0.11
eGFR by CKD-EPI equation, mean ± SD (mL/min/1.73 m^2)	127.0 ± 14.9	125.4 ± 12.8	123.0 ± 13.0	120.5 ± 9.3
Microalbuminuria (≥30 mg/day), *N* (%)	89 (9.8)	46 (12.2)	16 (11.9)	6 (27.3)

All percentages are provided by category of BP. IQR, interquartile range.

Table 2—Risk of macroalbuminuria during long-term follow-up in DCCT and EDIC

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
SBP category						
≥140 mmHg	2.95 (1.84–4.74)	<0.001	3.12 (1.94–5.04)	<0.001	2.77 (1.68–4.57)	<0.001
130 to <140 mmHg	Reference		Reference		Reference	
120 to <130 mmHg	0.65 (0.42–1.02)	0.06	0.63 (0.40–0.99)	0.047	0.85 (0.53–1.36)	0.49
<120 mmHg	0.36 (0.23–0.56)	<0.001	0.37 (0.24–0.59)	<0.001	0.59 (0.37–0.95)	0.03
DBP category						
≥90 mmHg	2.16 (1.32–3.53)	0.002	2.00 (1.22–3.27)	0.006	1.79 (1.08–2.98)	0.03
80 to <90 mmHg	Reference		Reference		Reference	
70 to <80 mmHg	0.49 (0.34–0.70)	<0.001	0.51 (0.35–0.73)	<0.001	0.71 (0.48–1.04)	0.08
<70 mmHg	0.39 (0.25–0.61)	<0.001	0.45 (0.28–0.71)	0.001	0.73 (0.44–1.18)	0.20

Model 1, stratified on primary vs. secondary prevention cohort and adjusted for DCCT randomization arm (intensive glycemic control strategy), with reference group being SBP 130 to <140 mmHg or DBP 80 to <90 mmHg; model 2, adjusted additionally for baseline factors, including age, sex, race, education, family history of hypertension, albuminuria, smoking status (ever smoked, yes/no), and baseline eGFR (by CKD-EPI equation); model 3, additionally adjusted for time-dependent covariates including hemoglobin A_{1c}, BMI, use of any antihypertensive medication, smoking status, use of RAAS blockade (ACE inhibitor or ARB), albuminuria, and eGFR (all with 1-year lag). HR, hazard ratio.

were associated with a statistically significant higher risk of macroalbuminuria and stage III CKD compared with reference BPs (Tables 2 and 3). Tests for interaction between SBP or DBP (as continuous predictors) and glycemic control strategy did not achieve statistical significance (all $P > 0.05$).

In sensitivity analysis, the association between BP and outcomes using a 4-year or 7-year lag between BP categories and outcome ascertainment were attenuated in some cases, although SBP <120 mmHg and DBP <70 mmHg remained statistically significantly associated with a lower risk of stage III CKD (Supplementary Table 1). There was no statistically significant association between lower BP and macroalbuminuria in our sensitivity analysis when incorporating a 7-year lag.

In continuous models, lower SBP and DBP levels were also associated with a lower risk of macroalbuminuria and stage III CKD (Table 4). The test for nonlinearities in the association between BP and primary outcomes of interest did not achieve statistical significance (all $P > 0.10$). When SBP and DBP were both included in the same model, SBP, but not DBP, was associated with our primary outcomes (Table 4). There was no statistically significant association between baseline BP measurements at DCCT entry and our primary outcomes (Table 4).

In terms of secondary outcomes of interest, incident microalbuminuria developed in 363 participants (1.38 cases/100 person-years), 472 participants (1.60 cases/100-person-years) had eGFR decline to <90 mL/min/1.73 m^2, and ESRD developed in 26 participants (0.08 cases/100 person-years) during long-term follow-up. Every 10 mmHg increase in SBP was associated with a 1.25 times higher risk of microalbuminuria (95% CI 1.15–1.37), a 1.13 times higher risk of eGFR decline to <90 mL/min/1.73 m^2 (95% CI 1.05–1.21), and a 1.04 times higher risk of ESRD (95% CI 0.77–1.41) in adjusted Cox models. Every 10 mmHg increase in DBP was associated with a 1.17 times higher risk of microalbuminuria (95% CI 1.03–1.32), a 1.15 times higher risk of eGFR decline to <90 mL/min/1.73 m^2 (95% CI 1.04–1.29), and a 0.80 times higher risk of ESRD (95% CI 0.47–1.38) in adjusted models.

Finally, in an exploratory analysis using our fully adjusted model, the risk of macroalbuminuria during the follow-up that was attributed to active antihypertensive therapy ($N = 910$) was 1.56 times higher (95% CI 1.29–1.88) with every 10 mmHg increase in SBP and 1.37 times higher for every 10 mmHg increase in

Table 3—Risk of stage III CKD during long-term follow-up in DCCT and EDIC studies

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
SBP category						
≥140 mmHg	3.49 (1.95–6.27)	<0.001	3.45 (1.91–6.21)	<0.001	1.89 (1.00–3.57)	0.05
130 to <140 mmHg	Reference		Reference		Reference	
120 to <130 mmHg	0.75 (0.40–1.39)	0.36	0.75 (0.40–1.41)	0.38	1.46 (0.75–2.83)	0.27
<120 mmHg	0.15 (0.07–0.34)	<0.001	0.15 (0.07–0.34)	<0.001	0.32 (0.14–0.75)	0.009
DBP category						
≥90 mmHg	4.37 (2.40–7.95)	<0.001	4.33 (2.37–7.93)	<0.001	2.07 (1.03–4.17)	0.04
80 to <90 mmHg	Reference		Reference		Reference	
70 to <80 mmHg	0.72 (0.42–1.23)	0.23	0.69 (0.40–1.19)	0.18	1.11 (0.61–2.01)	0.73
<70 mmHg	0.33 (0.16–0.70)	0.004	0.30 (0.14–0.63)	0.002	0.47 (0.21–1.05)	0.07

Model 1, stratified on primary vs. secondary prevention cohort and adjusted for DCCT randomization arm (intensive glycemic control strategy), with reference group being SBP 130 to <140 mmHg or DBP 80 to <90 mmHg; model 2, adjusted additionally for baseline factors including age, sex, race, education, family history of hypertension, albuminuria, smoking status (ever smoked, yes/no), and baseline eGFR (by CKD-EPI equation); model 3, additionally adjusted for time-updated covariates including hemoglobin A_{1c}, BMI, use of any antihypertensive medication, smoking status, use of RAAS blockade (ACE inhibitor or ARB), albuminuria, and eGFR (all with 1-year lag). HR, hazard ratio.

Table 4—Comparison of risk of renal outcomes of interest using SBP and DBP as linear predictors

Model for SBP	HR (per 10 mmHg SBP increase) (95% CI)	*P* value	Model for DBP	HR (per 10 mmHg DBP increase) (95% CI)	*P* value
Macroalbuminuria					
Baseline SBP[1]	1.00 (0.86–1.17)	0.98	Baseline DBP[1]	1.04 (0.86–1.26)	0.69
Time-updated SBP	1.44 (1.28–1.62)	<0.001	Time-updated DBP	1.32 (1.10–1.59)	0.003
Time-updated SBP and DBP in same model	1.47 (1.28–1.69)	<0.001	Time-updated SBP and DBP in same model	0.95 (0.77–1.18)	0.64
Stage III CKD					
Baseline SBP[1]	0.96 (0.78–1.18)	0.68	Baseline DBP[1]	1.23 (0.94–1.61)	0.13
Time-updated SBP	1.34 (1.16–1.54)	<0.001	Time-updated DBP	1.41 (1.09–1.82)	0.009
Time-updated SBP and DBP in same model	1.32 (1.11–1.57)	0.002	Time-updated SBP and DBP in same model	1.04 (0.76–1.43)	0.78

All models were adjusted for age, race, sex, education, family history of hypertension, trial arm, and time-dependent covariates, including BMI, use of any antihypertensive medication, albuminuria, eGFR, smoking status, hemoglobin A_{1c}, and use of ACE inhibitors or ARB (all with 1-year lag), unless otherwise specified. HR, hazard ratio. [1]Models were adjusted for baseline age, sex, race, education level, family history of hypertension, smoking status, albuminuria, eGFR, trial arm, and BMI.

DBP (95% CI 1.01–1.84). The risk of stage III CKD among participants receiving antihypertensive treatment (*N* = 988) was 1.27 times higher (95% CI 1.10–1.47) for every 10 mmHg increase in SBP and 1.32 times higher (95% CI 1.01–1.72) for every 10 mmHg increase in DBP. Test results for the interaction between SBP and DBP and antihypertensive medication use did not achieve statistical significance for any primary outcome of interest (all $P > 0.10$).

CONCLUSIONS

The primary objective of this study was to determine the stepwise association between lower BPs (to levels <120/80 mmHg) and the risk of adverse renal outcomes. We also aimed to determine whether exposure to intensive glycemic control would modify any benefit associated with lower BPs. We hypothesized and found that SBPs <120 mmHg were associated with a statistically significant lower risk of our primary outcomes of macroalbuminuria and incident stage III CKD compared with reference BPs in the range of 130 to <140 mmHg range. DBPs <70 mmHg trended toward lower risk of macroalbuminuria and stage III CKD, although this finding did not achieve statistical significance. Contrary to our hypothesis, these results were independent of assigned glycemic control strategy during DCCT or achieved hemoglobin A_{1c} levels during the DCCT and EDIC. We also found that lower BPs were associated with a lower risk of microalbuminuria and milder declines in renal function.

Recently, both the Joint National Committee and the American Diabetes Association revised recommendations for BP targets in patients with type 1 and type 2 diabetes from <130/80 to <140/90 mmHg (1,2,17). The rationale for this change stemmed primarily from the lack of solid trial-based evidence to support the benefit of a lower BP target in patients with diabetes (1,2). For example, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive BP lowering (to an SBP goal of 120 vs. 140 mmHg) did not reduce the risk of a composite outcome of cardiovascular events and death among patients with type 2 diabetes (6). However, few trials have been conducted to test the benefit of alternate BP targets on the risk of adverse renal outcomes in the type 1 diabetes population. It is possible that patients with type 1 diabetes could have a different association between BP level and renal outcomes compared with patients with type 2 diabetes, given the younger age of disease onset, the earlier diagnosis, and the lower prevalence of comorbidities, such as obesity at the time of type 1 diabetes onset (18). In the absence of randomized controlled trials on outcomes, such as incident CKD in type 1 diabetes, the observational data in DCCT and EDIC could serve to provide support for the conduct of interventional trials to further test the hypothesis that tight BP control would delay the onset and progression of clinical renal disease in this population.

In randomized controlled trials of normotensive persons (defined as DBP of <90 mmHg) with type 1 diabetes treated with RAAS blockade, persons randomized to receive RAAS blockade (who achieved a 3–7 mmHg lower BP compared with the placebo arm) had a lower risk of worsening overt proteinuria, thus suggesting the benefit of lower BP levels on renal outcomes (19,20). Another small trial demonstrated a benefit to lowering MAP to <92 mmHg (corresponding to ~125/75 mmHg) on the reduction of proteinuria (mean 535 mg/24 h vs. 1,723 mg/24 h in the MAP target of 100–107 mmHg) but not on renal function decline during 2 years of follow-up (9). Observational studies (21) have shown that persistent microalbuminuria is more likely to develop in normotensive normoalbuminuric patients with higher baseline BP values who have type 1 diabetes during follow-up. Elevations in SBP during sleep have been found to precede the onset of microalbuminuria in otherwise normotensive normoalbuminuric adolescents and young adults with type 1 diabetes (21–23).

Our study expands upon the results from prior studies by providing data from a larger and well-characterized population on the risk of more advanced renal end points, including stage III CKD, during nearly 30 years of follow-up. Our study is also unique in the use of time-updated BPs and hemoglobin A_{1c} measures, which may reduce the misclassification bias of BP status and glycemic control during long-term follow-up. In fact, we found that baseline SBP and DBP values at DCCT entry were poorly predictive of the long-term risk of adverse renal outcomes in our study (24–27).

Multiple follow-up studies using the DCCT/EDIC cohort (10–12,24) have demonstrated the importance of glycemic control in preventing long-term renal sequelae, including the onset of hypertension, microalbuminuria, macroalbuminuria, and CKD. It is plausible, however, that intensive glycemic control and BP control may provide synergistic and additive renal protection in patients with type 1 diabetes. The results of animal studies (25,26) have suggested an additive interaction between diabetes and hypertension, in which both contribute to enhanced vascular permeability to albumin and monocyte adhesiveness to the endothelium (a first step in atherogenesis). Our study suggests that even in participants who had been previously exposed to intensive glycemic control, lower BP was still associated with a lower risk of adverse renal outcomes. We believe this finding to be important, as the traditional focus in type 1 diabetes research and clinical practice has been on the effects of intensive glycemic control (10,11). We would suggest that our finding between lower BP and renal outcomes supports the need for future interventional studies, because BP treatment may be less costly and more achievable than other treatment options.

The large effect size of lower BPs observed in our study may be due to the long duration of follow-up, and the accurate assessment of both the predictor of interest and other confounding factors that are likely to change over time, such as antihypertensive use, hemoglobin A_{1c} level, and BMI, all of which were prospectively collected per the research protocol. When restricting our analyses to the duration of follow-up when patients actively received antihypertensive drug therapy, we observed similar effect sizes for renal protection in those patients treated to lower BP levels, suggesting a potential benefit to antihypertensive therapy. We note that, in our sensitivity analysis with a 7-year imposed lag, the association between lower BP and lower risk of adverse outcomes only achieved statistical significance for incident CKD, and not for macroalbuminuria. Whether this attenuation is due to diminished power (given the obligatory exclusion of $>$25% events from our analysis when we enforce a 7-year lag between BP and outcome ascertainment), reverse causation (in that worsened renal injury and/or function can also lead to worsened BP) or the tendency for BP levels to have shorter-term associations with albuminuria (due to hemodynamic responses to BP changes or albuminuria-lowering effects of BP medications) are unclear.

Finally, our fully adjusted models may be overly conservative in their adjustment for time-updated albuminuria and eGFR, given that our primary outcomes of interest are macroalbuminuria and stage III CKD.

Although the results of this study are compatible with the hypothesis that lower BP targets may reduce complications in the younger type 1 diabetes population, other explanations are also possible. For example, it is known that there is a strong familial component to diabetic nephropathy risk in type 1 diabetes (27,28) and that a family history of hypertension is a significant predictor of diabetic nephropathy risk (29–31). It is possible that the propensity to hypertension is associated with a genetic predisposition to diabetic nephropathy through pathways that are, at least in part, independent of systemic BP (32).

The strengths of our study include the well-characterized cohort, the long duration and completeness of follow-up, the detailed collection of covariates that may potentially confound the association between BP and renal outcomes, and the use of models that account for changes in time-varying covariates.

We also recognize a number of limitations. Because these data are observational, they cannot prove causation. It remains possible that subtle kidney disease may lead to early elevations in BP, and we cannot rule out the potential for reverse causation in our findings. However, we note similar trends in our data even when imposing a 7-year lag between BP and CKD ascertainment. Other limitations include the use of a study cohort that is predominantly white, which may limit the ability to apply our results to other races. The urinary measurements may also be limited in their ability to capture potential diurnal variations in albumin excretion.

In conclusion, there is an association between BP levels that are significantly below the current treatment guidelines and the risk of adverse renal outcomes in patients with type 1 diabetes, independent of glycemic control. We believe that these data provide a rationale for future interventional trials designed to test the hypothesis that more aggressive lowering of BP could reduce the renal morbidities associated with type 1 diabetes.

Funding. This work was supported by National Institutes of Health (NIH) grant KL2-TR-00014 and National Heart, Lung, and Blood Institute grant K23-HL-131023 to E.K. and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant K24-DK-92291 to C.-y.H. The Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study were conducted by the DCCT/EDIC Research Group and supported by NIH grants and contracts and by the General Clinical Research Center Program (National Center for Research Resources). The data from the DCCT/EDIC study were supplied by the NIDDK Central Repositories.

The manuscript was not prepared under the auspices of the DCCT/EDIC study and does not represent the analyses or conclusions of the DCCT/EDIC study group, the NIDDK Central Repositories, or the NIH.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. E.K., C.E.M., M.M., S.G., B.G., and C.-y.H. participated in the design and conception of the study, the data analysis and interpretation, the drafting of the manuscript and its revisions, and final approval of the manuscript. E.K. and B.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the American Society of Nephrology Kidney Week 2016, Chicago, IL, 15–20 November 2016.

References

1. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520

2. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis 2014;64:510–533

3. American Diabetes Association. *Standards of Medical Care in Diabetes–2015*: summary of revisions. Diabetes Care 2015;38(Suppl. 1):S4

4. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713

5. Curb JD, Pressel SL, Cutler JA, et al.; Systolic Hypertension in the Elderly Program Cooperative Research Group. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. JAMA 1996;276:1886–1892

6. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585

7. Orchard TJ, Forrest KY, Kuller LH, Becker DJ; Pittsburgh Epidemiology of Diabetes Complications

Study. Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care 2001;24:1053–1059
8. Shankar A, Klein R, Klein BE, Nieto FJ, Moss SE. Relationship between low-normal blood pressure and kidney disease in type 1 diabetes. Hypertension 2007;49:48–54
9. Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ; Collaborative Study Group. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Am J Kidney Dis 1999;34:809–817
10. de Boer IH, Afkarian M, Rue TC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Renal outcomes in patients with type 1 diabetes and macroalbuminuria. J Am Soc Nephrol 2014;25:2342–2350
11. de Boer IH, Kestenbaum B, Rue TC, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med 2008;168:1867–1873
12. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011;365:2366–2376
13. Andrésdóttir G, Jensen ML, Carstensen B, et al. Improved prognosis of diabetic nephropathy in type 1 diabetes. Kidney Int 2015;87:417–426
14. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
15. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
16. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612
17. National High Blood Pressure Education Program. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. Bethesda, MD, National Heart, Lung, and Blood Institute, 2004
18. Kharroubi AT, Darwish HM. Diabetes mellitus: the epidemic of the century. World J Diabetes 2015;6:850–867
19. Viberti G, Mogensen CE, Groop LC, Pauls JF; European Microalbuminuria Captopril Study Group. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. JAMA 1994;271:275–279
20. The EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet 1997;349:1787–1792
21. Hovind P, Tarnow L, Rossing P, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. BMJ 2004;328:1105
22. Lurbe A, Redón J, Pascual JM, Tacons J, Alvarez V, Batlle DC. Altered blood pressure during sleep in normotensive subjects with type I diabetes. Hypertension 1993;21:227–235
23. Lurbe E, Redon J, Kesani A, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N Engl J Med 2002;347:797–805
24. DCCT/EDIC Research Group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol 2014;2:793–800
25. Tilton RG, Pugliese G, Faller AM, LaRose LS, Province MA, Williamson JR. Interactions between hypertension and diabetes on vascular function and structure in rats. J Diabetes Complications 1992;6:187–196
26. Tsao PS, Niebauer J, Buitrago R, et al. Interaction of diabetes and hypertension on determinants of endothelial adhesiveness. Arterioscler Thromb Vasc Biol 1998;18:947–953
27. Quinn M, Angelico MC, Warram JH, Krolewski AS. Familial factors determine the development of diabetic nephropathy in patients with IDDM. Diabetologia 1996;39:940–945
28. Seaquist ER, Goetz FC, Rich S, Barbosa J. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. N Engl J Med 1989;320:1161–1165
29. Walker JD, Tariq T, Viberti G. Sodium-lithium countertransport activity in red cells of patients with insulin dependent diabetes and nephropathy and their parents. BMJ 1990;301:635–638
30. Trevisan R, Fioretto P, Barbosa J, Mauer M. Insulin-dependent diabetic sibling pairs are concordant for sodium-hydrogen antiport activity. Kidney Int 1999;55:2383–2389
31. Viberti GC, Keen H, Wiseman MJ. Raised arterial pressure in parents of proteinuric insulin dependent diabetics. Br Med J (Clin Res Ed) 1987;295:515–517
32. Mauer SM, Sutherland DE, Steffes MW. Relationship of systemic blood pressure to nephropathology in insulin-dependent diabetes mellitus. Kidney Int 1992;41:736–740