Hypertension Control in Adults With Diabetes Mellitus and Recurrent Cardiovascular Events

Global Results From the Trial Evaluating Cardiovascular Outcomes With Sitagliptin

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Abstract—Systolic blood pressure (SBP) treatment targets for adults with diabetes mellitus remain unclear. SBP levels among 12 275 adults with diabetes mellitus, prior cardiovascular disease, and treated hypertension were evaluated in the TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) randomized trial of sitagliptin versus placebo. The association between baseline SBP and recurrent cardiovascular disease was evaluated using multivariable Cox proportional hazards modeling with restricted cubic splines, adjusting for clinical characteristics. Kaplan–Meier curves by baseline SBP were created to assess time to cardiovascular disease and 2 potential hypotension-related adverse events: worsening kidney function and fractures. The association between time-updated SBP and outcomes was examined using multivariable Cox proportional hazards models. Overall, 42.2% of adults with diabetes mellitus, cardiovascular disease, and hypertension had an SBP ≥140 mm Hg. The association between SBP and cardiovascular disease risk was U shaped, with a nadir ≈130 mm Hg. When the analysis was restricted to those with baseline SBP of 110 to 150 mm Hg, the adjusted association between SBP and cardiovascular disease risk was flat (hazard ratio per 10-mm Hg increase, 0.96; 95% confidence interval, 0.91–1.02). There was no association between SBP and risk of fracture. Above 150 mm Hg, higher SBP was associated with increasing risk of worsening kidney function (hazard ratio per 10-mm Hg increase, 1.10; 95% confidence interval, 1.02–1.18). Many patients with diabetes mellitus have uncontrolled hypertension. The U-shaped association between SBP and cardiovascular disease events was largely driven by those with very high or low SBP, with no difference in cardiovascular disease risk between 110 and 150 mm Hg. Lower SBP was not associated with higher risks of fractures or worsening kidney function. **(*Hypertension*. 2017;70:907-914. DOI: 10.1161/HYPERTENSIONAHA.117.09482.)** ● **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular disease ■ diabetes mellitus ■ hypertension ■ hypotension

Worldwide, ≈1 in 10 adults has diabetes mellitus, and the global prevalence of diabetes mellitus continues to rise.[1] Diabetes mellitus is a potent risk factor for cardiovascular disease (CVD), doubling the risk of both coronary heart disease and ischemic stroke.[2,3] In the United States, 22% of adults with diabetes mellitus have coronary heart disease and 9% have prior stroke.[4] This group is at particularly high risk of recurrent CVD events and should be targeted for aggressive risk factor modification for secondary prevention.

One of the most prevalent and modifiable cardiac risk factors in adults with diabetes mellitus is hypertension.[5] Although the prevalence of hypertension among those with diabetes mellitus is high, systolic blood pressure (SBP) treatment targets remain unclear. Prior guidelines from the Seventh Joint National Committee recommended that adults with diabetes mellitus be tightly controlled with a goal of <130/80 mm Hg. However, the authors noted that available data are somewhat sparse to justify the low target level.[6]

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Subsequent guidance from the panel members appointed to the Eighth Joint National Committee raised the threshold to 140/90 mm Hg in patients with diabetes mellitus, citing lack of randomized controlled trial evidence for more stringent goals.[7] The ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial found that patients with diabetes mellitus had similar cardiovascular outcomes when randomized to SBP targets of 140 versus 120 mm Hg.[8] Epidemiological studies have actually suggested a possible U shape to the association between SBP and CVD events, with a possible increase in hazard among those in patients with lower on-treatment SBPs.[9] In contrast, SPRINT (Systolic Blood Pressure Intervention Trial) found in a nondiabetic but high cardiovascular risk population that aggressive SBP lowering (<120 mm Hg) significantly reduced the risk of CVD and overall mortality.[10] The American Diabetes Association recently recommended that an optional target for hypertension management was <130 mm Hg, based on data that lower SBP targets in adults with diabetes mellitus may reduce risk of stroke and albuminuria.[11]

Our study goals were to use longitudinal data from TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin)[12] to (1) describe current patterns in SBP control among patients with diabetes mellitus and hypertension on a global scale; (2) determine the unadjusted and risk-adjusted association between on-treatment SBP and cardiovascular outcomes; and (3) determine whether lower on-treatment SBP was associated with adverse clinical events, including bone fractures and renal insufficiency (both overall and among older individuals).

Methods

TECOS was a double-blind, randomized clinical trial of sitagliptin or placebo added to usual care in adults age ≥50 years with diabetes mellitus and prevalent CVD (prior coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease) between December 2008 and July 2012. Overall, 14 671 patients were randomized and included in the intention-to-treat population. Of these, we included adults with a clinical diagnosis of hypertension and confirmed CVD at baseline and who were on at least 1 antihypertensive medication at trial enrollment. All TECOS trial participants provided informed consent to participate, and the protocol was approved by the ethics committee at each participating trial site. Blood pressures were collected in clinic at baseline and at study follow-up visits at enrolling sites per local clinic protocols.

Our primary effectiveness outcome was the composite CVD end point, including cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or hospitalization for heart failure. This composite was also assessed excluding hospitalization for heart failure (nonheart failure CVD).

Two safety outcomes, potential adverse events associated with too aggressive blood pressure lowering, were also assessed: bone fractures (potentially associated with falls) and worsening kidney function. Kidney function was defined using site-reported estimated glomerular filtration rate (eGFR) estimated with the Modification of Diet in Renal Disease method.[13] Worsening kidney function was defined in 2 ways: (1) for those with baseline chronic kidney disease (site-reported eGFR <90 mL/min per 1.73 m^2) as a decrease in site-reported eGFR ≥50% or development of end-stage renal disease requiring dialysis or transplantation, and (2) for those without chronic kidney disease as development of end-stage renal disease or a decrease in eGFR of ≥30% to a value of <60 mL/min per 1.73 m^2.

Statistical Analysis

The study population was divided into 5 groups based on their baseline SBP: <120 mm Hg, 120 to <130 mm Hg, 130 to <140 mm Hg, 140 to <160 mm Hg, and ≥160 mm Hg. Categorical and continuous baseline characteristics for these groups were described.

Unadjusted Kaplan–Meier curves were used to determine associations between baseline SBP and the effectiveness/safety end points of interest. The shape of the association between SBP at baseline and effectiveness/safety end points was evaluated using multivariable-adjusted Cox proportional hazards models to generate a plot of the predicted event rates at 48 months by baseline SBP. We then evaluated the association between SBP as a time-updated variable using all SBP measurements obtained during follow-up study visits and CVD events. If the test for nonlinearity for baseline SBP was significant based on the Wald χ^2 test, the risk for SBP was approximated using a piecewise linear spline, with clinical input and visual inspection of the shape of the adjusted association between SBP and end point of interest used to identify the cut points. Cox models were stratified by region and adjusted for the following risk factors: age, sex, race, prior stroke or transient ischemic attack, prior congestive heart failure, prior coronary disease, prior peripheral arterial disease, eGFR, hemoglobin A1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, smoking status, prior chronic obstructive pulmonary disease, prior atrial fibrillation or atrial flutter, albumin:creatinine ratio, creatinine, body mass index, hemoglobin, statin use, and treatment arm (sitagliptin or placebo).

Missing data for risk factors used in multivariable modeling were imputed using the fully conditional specification method,[14] and missing SBP measurements at follow-up were imputed using the last observation carried forward for measurements obtained ≤1 year before the missing observation. Missing SBP at baseline was not imputed.

Subgroup and Sensitivity Analyses

To further evaluate the shape of the association between baseline SBP and CVD events, multivariable spline and Cox models were repeated for adults with baseline SBP between 110 and 150 mm Hg. These ranges were selected because they eliminated the potential effects of those with outlier low or high SBP and were more representative of SBP ranges recommended by hypertension guidelines.

To evaluate the impact of preexisting heart failure on the results, the association between SBP and nonheart failure CVD events was evaluated excluding adults with heart failure at baseline. To evaluate whether the association between SBP and CVD end points varied with age, we looked at the association between baseline SBP and CVD outcomes, stratified by age group (>70 and ≤70 years), and tested the interaction between treated SBP and age (continuous) in Cox proportional hazards modeling used to determine association between time-updated SBP and CVD.

Safety Analyses

Safety end points were analyzed as described above; however, the multivariable analyses included the risk factors mentioned above in addition to diuretic usage for Cox proportional hazards models using time to development of bone fracture as the outcome. For worsening kidney failure, the multivariable model included use of an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor.

Results

Of the 14 671 patients in the intention-to-treat population for TECOS, 12 275 (83.7%) had a clinical diagnosis of hypertension and were on at least 1 blood pressure–lowering medication at baseline; 373 of these adults were excluded because of lack of SBP values at baseline. The average age of adults was 66.0 years, 30.7% were women, and 30.0% were non-white. Coronary artery disease was the most common type of CVD (present in 74.8%), and 19.5% of patients had prior congestive heart failure.

Table 1. Characteristics of Adults in TECOS With Treated Hypertension and Prior Cardiovascular Disease by Baseline SBP

Characteristic	SBP, mm Hg					All Patients (n=12 275)
	<120 (n=1613)	120–129 (n=2287)	130–139 (n=3192)	140–159 (n=4000)	≥160 (n=1183)	
Age	65.0 (60.0, 71.0)	65.0 (59.0, 71.0)	65.0 (60.0, 71.0)	66.0 (60.0, 72.0)	67.0 (61.0, 73.0)	66.0 (60.0, 71.0)
Female	25.2%	29.1%	30.5%	32.5%	36.3%	30.7%
Race						
White	67.3%	68.6%	69.7%	73.2%	66.7%	70.0%
Black	4.0%	3.7%	2.6%	3.0%	5.1%	3.3%
Asian	22.6%	21.2%	21.0%	17.5%	18.9%	19.9%
Other	6.2%	6.4%	6.7%	6.4%	9.3%	6.7%
Coronary artery disease	84.3%	77.8%	74.0%	71.4%	69.1%	74.8%
Cerebrovascular disease	22.1%	24.6%	25.4%	27.9%	28.5%	25.9%
Peripheral arterial disease	12.7%	13.1%	16.7%	17.6%	20.1%	16.1%
Prior myocardial infarction	48.7%	44.8%	42.8%	42.3%	36.9%	43.2%
Prior congestive heart failure	18.6%	18.4%	18.9%	21.3%	18.8%	19.5%
Prior stroke	15.7%	17.0	18.1%	20.1%	20.3%	18.4%
Atrial fibrillation/atrial flutter	11.5%	9.1%	7.7%	8.4%	5.7%	8.5%
eGFR, mL/min per 1.73 m^2	71.0 (59.0, 86.0)	72.0 (60.0, 87.0)	73.0 (60.0, 88.0)	72.0 (60.0, 87.5)	70.0 (57.0, 86.8)	72.0 (60.0, 87.0)
Hemoglobin, g/L	136.0 (125.0, 146.0)	136.0 (125.0, 146.0)	137.0 (127.0, 148.0)	138.0 (127.3, 148.0)	135.0 (125.0, 145.0)	137.0 (126.0, 147.0)
Diastolic blood pressure, mm Hg	68.0 (60.0, 72.0)	75.0 (69.0, 80.0)	80.0 (70.0, 82.0)	80.0 (76.0, 90.0)	87.0 (80.0, 94.0)	80.0 (70.0, 84.0)
BMI, kg/m^2	29.2 (26.1, 33.4)	29.8 (26.4, 33.6)	29.8 (26.6, 33.3)	30.2 (27.0, 33.9)	30.2 (26.9, 34.0)	29.9 (26.7, 33.7)
No. of BP medications	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
Total cholesterol, mmol/L	3.8 (3.3, 4.5)	4.0 (3.4, 4.7)	4.1 (3.5, 5.0)	4.3 (3.6, 5.2)	4.3 (3.6, 5.3)	4.1 (3.5, 4.9)
LDL cholesterol, mmol/L	1.9 (1.5, 2.5)	2.1 (1.6, 2.7)	2.1 (1.7, 2.8)	2.3 (1.8, 3.0)	2.3 (1.8, 3.1)	2.2 (1.7, 2.8)
HDL cholesterol, mmol/L	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)
Aspirin	81.1%	80.9%	78.6%	77.5%	76.8%	78.8%
ACE inhibitor or ARB	83.6%	84.9%	83.4%	86.0%	86.9%	84.9%
β-Blocker	72.2%	68.3%	66.6%	66.3%	65.7%	67.5%
Thiazide diuretic	22.9%	24.9%	26.6%	28.6%	29.3%	26.7%
Calcium channel blocker	29.1%	35.0%	38.1%	40.7%	46.1%	37.9%
Nitrate	26.2%	20.8%	19.2%	18.4%	15.9%	19.8%
α-1 blocker	10.6%	6.7%	7.2%	8.1%	9.0%	8.0%
Aldosterone antagonist	9.5%	7.1%	5.3%	5.3%	5.2%	6.2%
Hydralazine	0.7%	0.5%	0.8%	0.8%	1.4%	0.8%
Renin inhibitor (eg, aliskerin)	0.3%	0.4%	0.6%	0.6%	0.8%	0.6%
Other antihypertensive	5.0%	6.0%	5.2%	6.8%	8.4%	6.1%

eGFR by site-reported Modification of Diet in Renal Disease equation. Continuous variables presented as median (interquartile range). Categorical variables presented as %. The characteristics displayed in this table are not imputed but rather the original values. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; and TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

Rates of Blood Pressure Control

At baseline, 42.2% of individuals had an SBP ≥140 mm Hg, and 9.6% had an SBP ≥160 mm Hg, while 31.8% had an SBP <130 mm Hg and 13.1% an SBP <120 mm Hg. Characteristics of the overall population by baseline SBP are described in Table 1. Patients with higher SBP levels were older, more often women, more likely to have prior stroke, and less likely to have coronary artery disease. The median number of blood pressure medications used was the same (2.0) across all groups. Of those with SBP <120 mm Hg (n=1613) at baseline, 69.3% (n=1118) had SBP ≥110 and <120 mm Hg, 24.2% (n=390) had SBP ≥100 and <110 mm Hg, and 6.5% (n=105) had SBP <100 mm Hg.

Association of Blood Pressure Control and Cardiovascular Outcomes

The median duration of follow-up was 3.0 years. Overall, the composite cardiovascular event rate was 13.4%, or 4.9% per 100 person-years. In unadjusted analyses, time to development of CVD differed by baseline SBP (P<0.0001). The risk of development of CVD appeared to be higher for those with baseline SBP ≥140 mm Hg when compared with the lower SBP groups (Figure 1).

Restricted cubic spline analysis revealed that the association between SBP at baseline and predicted CVD risk was nonlinear, with a U-shaped association observed in both univariable (Figure S1A in the online-only Data Supplement) and multivariable analyses (Figure 2A). Based on the shape of this curve and clinical input, the association between time-updated SBP and CVD events was modeled with a piecewise linear spline: Above 130 mm Hg, every 10-mm Hg increase in SBP was associated with a 7% increase in the hazard of CVD (hazard ratio [HR], 1.07; 95% confidence interval [CI], 1.02–1.11). Below 130 mm Hg, every further 10-mm Hg decrease was associated with a 12% increase in hazard of CVD (HR, 1.12; 95% CI, 1.05–1.20).

However, further examination of the association between baseline SBP and CVD events restricted to those in the SBP range of 110 to 150 mm Hg eliminated the U-shaped association (unadjusted curve Figure S1A; adjusted curve Figure 2B; P for nonlinearity=0.18). When formally tested in the time-updated multivariable model, there was no association between SBP and CVD in adults with an SBP of 110 to 150 mm Hg (P=0.20; HR per 10-mm Hg increase, 0.96; 95% CI, 0.91–1.02; Table 2).

Sensitivity Analysis

The U shape of the association between baseline SBP and CVD was similar when applied to nonheart failure CVD events after excluding adults with heart failure at baseline (Figure S2). Specifically, in the overall population, there was a U-shaped association, but this was not apparent when limited to adults with an SBP of 110 to 150 mm Hg.

The shapes of the associations between baseline SBP and CVD were also similar in both younger (age ≤70 years) and older (age >70 years) adults (Figures S3 and S4). In multivariable modeling, the association between time-varying SBP and CVD did not differ by age (interaction P value 0.11).

Association Between SBP and Safety Outcomes

Kaplan–Meier curves showed a significant association between baseline SBP and development of worsening kidney function (P<0.001; Figure 3). Adults with a baseline SBP ≥160 mm Hg appeared to be at higher risk of development of worsening kidney failure when compared with the other 4 SBP groups at baseline. In multivariable modeling, the shape of the association between baseline SBP and worsening kidney function appeared flat until baseline SBP was ≥150 mm Hg, at which point the risk of worsening kidney function increased (multivariable-adjusted spline shown in Figure 4, unadjusted curve shown in Figure S5). Therefore, SBP of 150 mm Hg was used as the cutpoint for the linear splines of SBP included in the

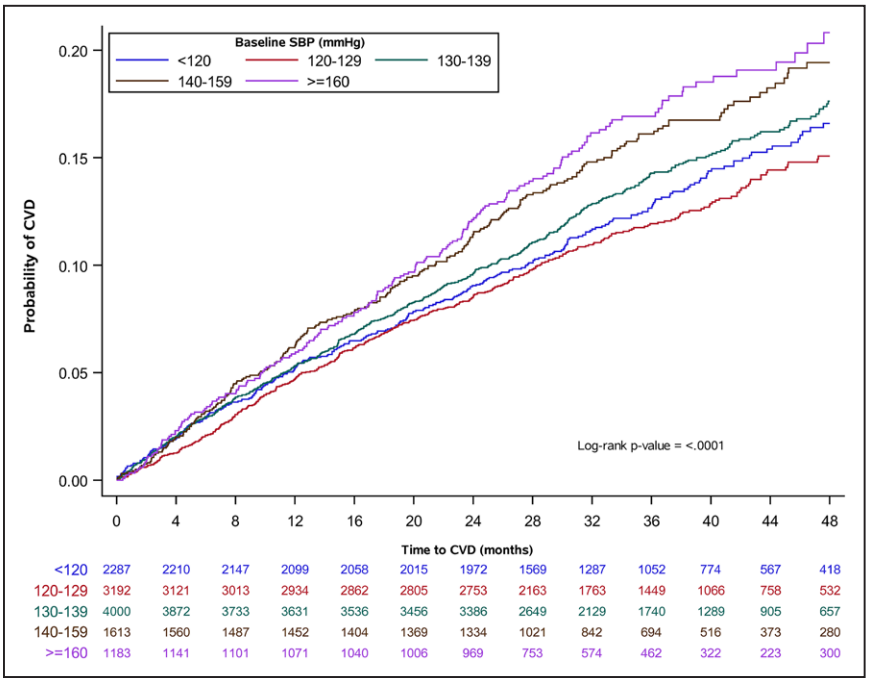

Figure 1. Systolic blood pressure (SBP) at baseline and time to cardiovascular disease (CVD) in adults with diabetes mellitus, treated hypertension, and prior CVD in TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin). Unadjusted Kaplan–Meier CVD event rates for adults with prior CVD, hypertension, and on blood pressure treatment. Numbers below the *x* axis are the number at risk at the time point, stratified by SBP group of interest.

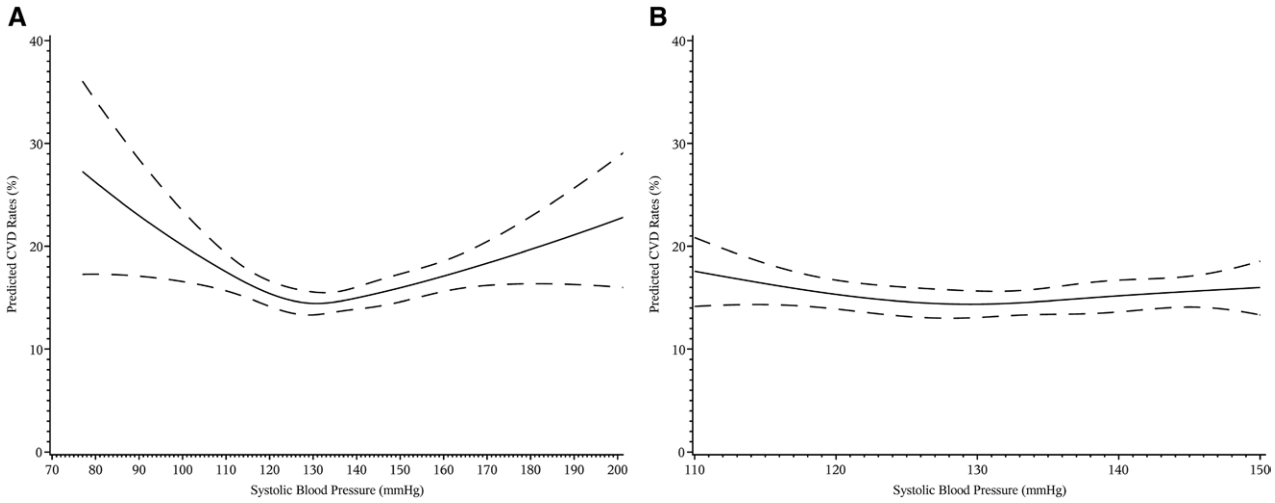

Figure 2. Multivariable-adjusted predicted cardiovascular disease (CVD) event rates at 48 mo in adults with diabetes mellitus, hypertension, and prior CVD by systolic blood pressure (SBP) at baseline: (**A**) SBP 70 to 200 mm Hg and (**B**) SBP 110 to 150 mm Hg. Predicted CVD event rates by baseline SBP adjusting for sex, age, race (white, black, Asian, and other), history of coronary disease, history of stroke/transient ischemic attack, history of peripheral artery disease, history of chronic obstructive pulmonary disease, history of congestive heart failure, history of atrial fibrillation/flutter, estimated glomerular filtration rate (eGFR), baseline hemoglobin A1c, albumin:creatinine ratio, creatinine, hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, smoking status (never, current, or former), statin use, body mass index, eGFR, and randomized treatment. Predicted event rates represent predicted rates from an average subject and are calculated from the Cox model based on an individual with mean values for each variable in the equation.

multivariable modeling. After adjustment for baseline factors, there was an association between time-varying SBP and time to development of worsening kidney function for SBP >150 mm Hg (HR per 10-mm Hg decrease for SBP ≤150 mm Hg, 1.04; 95% CI, 0.996–1.08; HR per 10-mm Hg increase for SBP >150 mm Hg, 1.10; 95% CI, 1.02–1.18).

No relationship could be detected between SBP at baseline and time to development of bone fractures using the unadjusted Kaplan–Meier event rates (log-rank *P* value, 0.23; Figure S6) or in multivariable analysis evaluating time-updated SBP (HR per 10-mm Hg increase, 0.95; 95% CI, 0.89–1.02; *P*=0.15).

Discussion

Adults with diabetes mellitus and hypertension have high longitudinal risks for cardiovascular and non-cardiovascular adverse outcomes. Our study of TECOS data has several important findings. First, we found that SBP control in patients with diabetes mellitus from a global perspective is suboptimal. Up to 40% of these individuals with high CVD risk had an SBP ≥140 mm Hg, and ≈10% had an SBP ≥160 mm Hg. Second, although there appeared to be a U-shaped association between on-treatment SBP at baseline and CVD events in the overall TECOS population, this apparent association was being driven by the extremes of SBP. Within the SBP range targeted by many guidelines (110–150 mm Hg), there was no apparent difference in risk of CVD events by SBP level. Finally, we found no evidence that lower SBP (<130 mm Hg) was associated with increased rates of bone fractures or worsening kidney function.

Regardless of the specific target used, SBP was a major undertreated but highly modifiable risk factor in this high-risk

Table 2. Hazard Ratios for the Association Between Time-Updated SBP and CVD End Points

End Point	Population	HR ≤130 mm Hg per 10-mm Hg Decrease	HR >130 mm Hg per 10-mm Hg increase
Overall			
Composite CVD	All adults with hypertension	1.12 (1.05–1.20)	1.07 (1.02–1.11)
Composite CVD	Excluding baseline HF	1.12 (1.03–1.21)	1.08 (1.03–1.13)
Non-HF CVD	All adults with hypertension	1.12 (1.02–1.22)	1.10 (1.04–1.15)
Non-HF CVD	Excluding baseline HF	1.10 (1.02–1.22)	1.07 (1.04–1.15)
SBP 110–150 mm Hg		HR per 10-mm Hg increase	
Composite CVD	All adults with hypertension	0.96 (0.91–1.02), *P*=0.20	
Composite CVD	Excluding baseline HF	0.96 (0.90–1.02), *P*=0.20	
Non-HF CVD	All adults with hypertension	0.97 (0.92–1.03), *P*=0.32	
Non-HF CVD	Excluding baseline HF	0.96 (0.90–1.04), *P*=0.32	

HR presented with 95% confidence interval. CVD indicates cardiovascular disease; HF, heart failure; HR, hazard ratio; and SBP, systolic blood pressure.

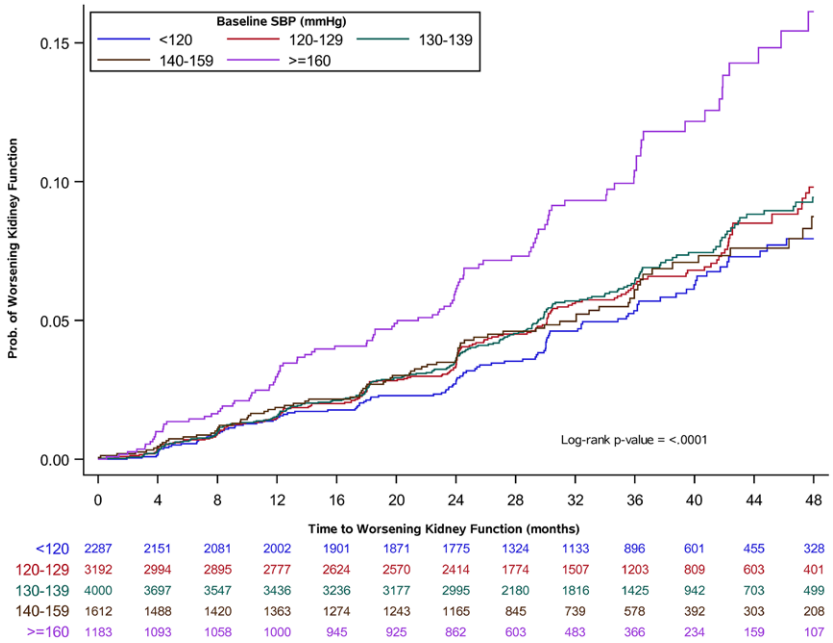

Figure 3. Systolic blood pressure (SBP) at baseline and time to worsening kidney function in adults with diabetes mellitus, treated hypertension, and prior cardiovascular disease in TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin). Unadjusted Kaplan–Meier event rates of worsening kidney function by baseline SBP category. Numbers below the *x* axis are the number at risk at the time point, stratified by SBP group of interest.

population. Nearly half of TECOS participants had elevated SBP ≥140 mm Hg, an area where there is little controversy on the benefits of blood pressure lowering in high-risk adults with diabetes mellitus. This highlights the important difference between what is recommended and what is achieved in a population. Given that 100% goal attainment is unlikely, 1 unintended consequence of lower SBP-recommended targets may be to shift the entire distribution of SBPs downward, thus decreasing the numbers of adults with extremely high SBPs.

The U-shaped association seen between SBP and CVD outcomes has raised concern about the risks of potentially overtreating SBP. For example, a recently reported analysis of adults with coronary artery disease in a large multicountry registry reported that on-treatment SBP <120 mm Hg was associated with increased risks of CVD events for both diabetic and nondiabetic adults.[9] However, all adults with SBP <120 mm Hg were analyzed together; the influence of outliers in this analysis may have been substantial. Although our analysis also demonstrated this association, we also showed that this U shape was largely influenced by adults with extremely low SBP.

Some of our findings are consistent with what has been observed previously. We found no strong association between macrovascular cardiovascular outcomes among those with on-treatment SBPs at baseline ranging from 110 to 150 mm Hg. Although trials have shown benefit in treatment of hypertension in adults with diabetes mellitus,[15] there have been limited

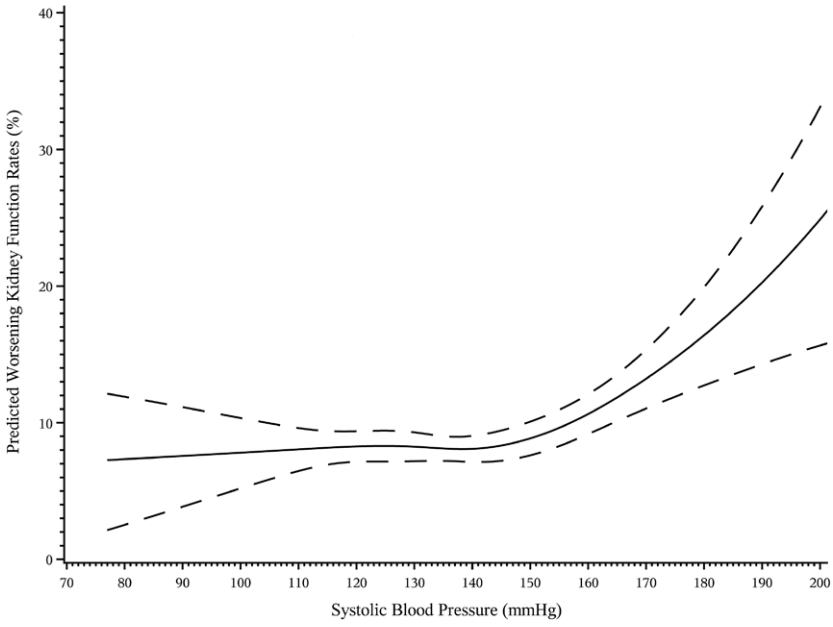

Figure 4. Multivariable-adjusted predicted rates of worsening kidney function at 48 mo in adults with diabetes mellitus, hypertension, and prior cardiovascular disease by systolic blood pressure (SBP) at baseline. Predicted event rates for worsening kidney function at 48 mo by baseline SBP adjusting for sex, age, race (white, black, Asian, and other), history of coronary disease, history of stroke/transient ischemic attack, history of peripheral artery disease, history of chronic obstructive pulmonary disease, history of congestive heart failure, history of atrial fibrillation/flutter, estimated glomerular filtration rate, baseline hemoglobin A1c, albumin:creatinine ratio, creatinine, hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, smoking status (never, current, or former), statin use, body mass index, and randomized treatment. Predicted event rates represent predicted rates from an average subject and are calculated from the Cox model based on an individual with mean values for each variable in the equation.

data supporting improved macrovascular outcomes <140 mm Hg. In ACCORD, the intensive treatment group achieving a mean SBP of 119.3 mm Hg had nonsignificantly lower cardiovascular event rates relative to the standard treatment arm who achieved a mean SBP of 133.5 mm Hg.[8] In this analysis, we chose to focus on the association between SBP and cardiovascular events given the moving target for SBP for adults with diabetes mellitus. Other studies have shown a U-shaped association for diastolic blood pressure and CVD events,[16] which was also seen in our sample (Figure S7). SBP and diastolic blood pressure are correlated; novel modeling approaches are needed to simultaneously evaluate the effect of SBP, diastolic blood pressure, and pulse pressure on CVD risk.

In addition to the focus on SBP, our analysis has several limitations. First, this is an observational analysis of trial data, and treatment biases may not have been fully accounted for by adjustment variables at baseline. It is possible that adults with lower on-treatment SBP had more comorbidities and, therefore, had more aggressive approaches to their blood pressure. In addition, blood pressure measurements were taken at outpatient clinic visits, which cannot detect white coat hypertension or masked hypertension and can be affected by measurement error.[17] However, this can also be interpreted as a strength because it reflects blood pressures that clinicians use in practice. This differs from blood pressures in the SPRINT trial, which used methods that led to systematically lower blood pressure readings than are seen in clinical practice.[18] Given the observational nature of this study, our findings should be interpreted with caution. The association between SBP and CVD may not imply that changes in treatment would change outcomes. Although we were unable to account for dosing, the number of blood pressure medication classes used did not substantially vary by baseline blood pressure. Thus, it is possible that the differences seen reflect more of the patients' vascular biology and response to blood pressure medications than their actual achieved blood pressure. Next, the TECOS population includes adults with relatively well-controlled diabetes mellitus, and thus these results may not be generalizable to all adults with diabetes mellitus. Finally, this analysis only included adults with prior CVD, thus showing the relationship between treated SBP and recurrent CVD events.

Perspectives

Globally, hypertension control remains suboptimal in adults with diabetes mellitus and CVD, demonstrating the need for further efforts to treat elevated blood pressure to prevent recurrent CVD events. The U-shaped curve seen between SBP and CVD events was largely driven by increased risk at extremes of SBP and indicates a wide margin for safety for treatment of SBP <140 mm Hg. Among those with SBP between 110 and 150 mm Hg, we could detect no increased risk of CVD events. We also found no risks for CVD, fractures, or worsening kidney function among those with on-treatment SBP down to 110 mm Hg. Given the potential microvascular improvements and lack of observed increase in macrovascular complications in both randomized trials and observational data, targeting SBP <130 mm Hg as currently optionally recommended by the American Diabetes Association guidelines seems safe. Our data heighten the need for improved hypertension treatment in high-risk adults with diabetes mellitus and CVD in community practice. Regardless of the target used, there remains substantial room for improvement in blood pressure control in adults with diabetes mellitus to reduce the risk of CVD.

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Novelty and Significance

What Is New?

- Although other studies have shown the U-shaped relationship between systolic blood pressure (SBP) and cardiovascular events, this analysis demonstrates how the shape of that curve is largely driven by extremely low SBPs. Between 110 and 150 mm Hg, the risk of cardiovascular disease (CVD) events in patients with diabetes mellitus and cardiovascular disease was similar.

What Is Relevant?

- Hypertension is a leading modifiable cause of events in adults with diabetes mellitus and CVD, yet control remains suboptimal globally.

Summary

Many patients with diabetes mellitus, CVD, and hypertension have uncontrolled blood pressure. Although there was a U-shaped association between baseline SBP and CVD events in the overall population, this was largely driven by those with very high or low baseline SBPs. There was a wide safety margin for on-treatment SBPs; between 110 and 150 mm Hg, we observed no difference in CVD risk.