Long-Term Variability of Blood Pressure, Cardiovascular Outcomes, and Mortality: The Look AHEAD Study

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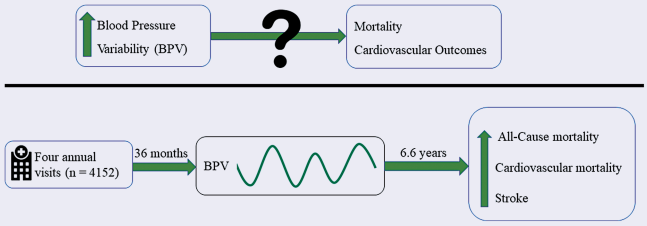
BACKGROUND
We evaluated the associations of visit-to-visit blood pressure (BP) variability with incident cardiovascular disease (CVD) and deaths in adults with type 2 diabetes.

METHODS
We analyzed 4,152 participants in Look AHEAD (Action for Health in Diabetes) free of CVD events and deaths during the first 36 months of follow-up. Variability of systolic BP (SBP) and diastolic BP (DBP) across 4 annual visits was assessed using the intraindividual SD, variation independent of the mean, and coefficient of variation. Cox regression was used to generate the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for CVD (myocardial infarction [MI], stroke, or CVD-related deaths) and mortality.

RESULTS
Over a median of 6.6 years, there were 220 MIs, 105 stroke cases, 62 CVD-related deaths, and 236 deaths. After adjustment for confounders including average BP, the aHRs for the highest (vs. lowest) tertile of SD of SBP were 1.98 (95% CI 1.01–3.92), 1.25 (95% CI 0.90–1.72), 1.26 (95% CI 0.96–1.64), 1.05 (95% CI 0.75–1.46), and 1.64 (95% CI 0.99–2.72) for CVD mortality, all-cause mortality, CVD, MI, and stroke, respectively. The equivalent aHRs for SD of DBP were 1.84 (95% CI 0.98–3.48), 1.43 (95% CI 1.03–1.98), 1.19 (95% CI 0.91–1.56), 1.14 (95% CI 0.82–1.58), and 0.97 (95% CI 0.58–1.60), respectively.

CONCLUSIONS
In a large sample of individuals with type 2 diabetes, a greater variability in SBP was associated with higher cardiovascular mortality and CVD events; a higher variability in DBP was linked to increased overall and cardiovascular mortality.

GRAPHICAL ABSTRACT



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Hypertension and type 2 diabetes are common and tend to coexist in the same individuals.[1,2] Among individuals with type 2 diabetes, the presence of hypertension and the degree of its control are major predictors of adverse cardiovascular disease (CVD) events such as coronary artery disease and stroke.[3] As such, optimal blood pressure (BP) control remains a top priority in the management of individuals with type 2 diabetes.[3] Emerging evidence suggests that visit-to-visit variability of BP may be positively associated with risks of future CVD events independent of average BP and other CVD risk factors.[4–11] This is relevant especially for people with diabetes mellitus who may inherently have increased BP variability partly due to their propensity to develop autonomic dysfunction and increased arterial stiffness.[12,13]

Although studies have evaluated the effect of visit-to-visit variability of BP with CVD events and deaths, the evidence in individuals with type 2 diabetes is overall scant, as these studies were limited in several ways including a retrospective

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design,[14] the lack of diverse study samples,[6,14–17] small sample size,[18] or short duration of follow-up.[6,11,15] Therefore, we used data from the Look AHEAD (Action for Health in Diabetes) study—a large community-based cohort of adults with type 2 diabetes in whom several annual recordings of BP were obtained at the outset.[19,20] We hypothesized that a higher variability in systolic BP (SBP) or diastolic BP (DBP) would be associated with greater risks of CVD events and mortality.

METHODS

Study design

We conducted a secondary analysis of the Look AHEAD, a multicenter randomized clinical trial of the effects of intensive lifestyle interventions on CVD outcomes. Details about the rationale and design of Look AHEAD have been reported elsewhere.[19,20] Briefly, a total of 5,145 participants were recruited from August 2001 to April 2004 across 16 locations in the United States and randomly assigned to participate in either the intensive lifestyle intervention or to receive diabetes support and education. Eligible participants were aged 45–76 years with a self-report diagnosis of type 2 diabetes confirmed by measured glucose levels, use of antidiabetic medication, or medical records.[19,20]

For the current study, we used the publicly available Look AHEAD dataset obtained through the NHLBI Biorepository (BioLINCC). We excluded participants with consent restrictions (n = 244), and those who experienced CVD events or died during the first 36 months of follow-up (n = 749). After these exclusions, 4,152 participants were included in our analyses.

The research protocol was approved by the Institutional Review Board at participating centers and each participant gave an informed consent.

Assessment of long-term variability of BP

At each study visit, BP was measured twice from the right arm by certified staff with participants in a seated position using an automated device (Dinamap Monitor Pro 100, Chicago, IL). The first BP was obtained after the participant had rested for 5 minutes, and the second BP was measured after waiting at least 30 seconds. The average of the 2 readings was used as the examination BP.[19,20] Long-term variability of BP was defined as the variability of SBP or DBP measured at the 4 visits. Variability was assessed using 3 metrics: (i) the SD of the longitudinal intraindividual BP measurements in each participant; (ii) the variability independent of the mean (VIM) calculated as $100 \times SD/mean^{\beta}$ where β is the regression coefficient based on the natural logarithm of SD as a function of the natural logarithm of the mean; (iii) the coefficient of variation (CV) calculated as SD/mean.[7] Given that there is no consensus on the ideal measure of variability, we chose to assess several variability indices in an attempt to capture the entire spectrum or various aspects of BP variability.

Ascertainment of incident cardiovascular events

Participants free of CVD events or deaths during the first 36 months were followed and queried for incident outcomes through annual visits and semiannual phone calls. These queries were enhanced via searches of relevant records and national databases for deaths. Outcomes were classified by an event adjudication committee.[19,20] The outcomes assessed in this study included: (i) all-cause mortality; (ii) cardiovascular mortality; (iii) CVD (composite of myocardial infarction [MI], stroke, and death from cardiovascular causes); (iv) MI events; and (v) stroke cases.

Covariates

At baseline, data on covariates including age, sex, race/ethnicity, duration of diabetes, history of CVD, use of antihypertensive medication (updated at subsequent follow-up visits), current smoking, and alcohol use were collected using standardized questionnaires.[19,20] Weight and height were measured certified clinic staff in duplicate using a digital scale and a standard stadiometer, respectively; and the average of the duplicate measures were used for the analyses. Body mass index was calculated as weight in kilograms divided by square of height in meters.[19,20] At each of the 4 first annual visits, blood samples were collected from each participant after 12 hours of fasting. Blood assays were performed at the Look AHEAD Central Biochemistry Laboratory.[19,20]

Plasma total cholesterol was measured using enzymatic methods standardized to the Center for Disease Control and Prevention reference methods.[20,21] High-density lipoprotein cholesterol was measured by the treatment of whole plasma with dextran sulfate-magnesium to precipitate all of the apolipoprotein B-containing lipoproteins.[22] Glycosylated hemoglobin (HbA_{1C}) was measured using ion exchange high-performance liquid chromatography (Biorad Variant II). Serum creatinine was assayed by the Jaffe method on Hitachi 917 analyzer,[20] and the estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[23]

Statistical analyses

We created tertiles of intraindividual SD of SBP and DBP and compared participants across those tertiles using the analysis of variance or Kruskal–Wallis test (for continuous variables) or the χ^2 test (for categorical variables).

The follow-up time was calculated from the fourth visit to the earliest of date of outcome, death, or trial's termination (14 September 2012). Cox proportional hazards models were used to generate hazard ratios and associated 95% confidence intervals for outcomes. Each variability metric was assessed as a continuous variable and tertiles using the lowest tertile as reference group. We constructed nested regression models with the first model (model 1) adjusted for age, sex, race/ethnicity, and treatment arm; the second model (model 2) accounted for covariates in model 1 plus body mass index, current smoking, alcohol drinking, use of antihypertensive

Table 1. Characteristics of study participants by tertiles of SD of systolic blood pressure

Characteristic	Entire sample	Tertiles of SD of systolic blood pressure, mm Hg			
		T1 (<7.01)	T2 (7.01–10.97)	T3 (>10.97)	
	N = 4,152	*N* = 1,384	*N* = 1,384	*N* = 1,384	*P* value
At baseline					
Age, years	58.9 (6.8)	58.3 (6.8)	58.8 (6.8)	59.7 (6.7)	<0.001
Women, %	58.8	55.2	59.4	61.7	0.002
Randomization arm, %					0.008
Diabetes support and education	49.2	49.9	51.7	45.9	
Intensive lifestyle intervention	50.8	50.1	48.3	54.1	
Race/ethnicity, %					0.356
White	67.7	69.7	66.8	66.7	
Non-Hispanic Black	16.7	15.8	17.4	16.8	
Hispanic	12.0	11.6	12.1	12.3	
Body mass index, kg/m^2	35.9 (5.9)	35.2 (5.7)	35.9 (5.9)	36.6 (6.0)	<0.001
Current smoking, %	3.9	3.8	3.8	4.1	0.919
Alcohol drinking, %	34.1	34.7	34.8	32.9	0.483
History of cardiovascular disease, %	13.3	11.7	12.6	15.6	0.006
Duration of diabetes, years	5.0 (2.0–10.0)	5.0 (2.0–9.0)	5.0 (2.0–9.0)	5.0 (2.0–10.0)	0.004
eGFR, ml/min/1.73 m^2	89.9 (16.0)	90.4 (15.4)	90.5 (16.2)	88.8 (16.3)	0.007
During follow-up					
Average hemoglobin A_{1C}	7.0 (1.0)	7.0 (0.9)	7.0 (1.0)	7.1 (1.1)	0.035
Average total-to-HDL cholesterol ratio	4.2 (1.2)	4.2 (1.2)	4.2 (1.1)	4.3 (1.1)	0.563
Use of antihypertensive medication, %	83.1	75.4	82.9	90.9	<0.001
Average systolic blood pressure, mm Hg	125.6 (14.1)	122.6 (13.8)	124.8 (13.3)	129.5 (14.3)	<0.001
Average diastolic blood pressure, mm Hg	68.2 (8.0)	68.0 (7.9)	68.1 (8.1)	68.6 (7.8)	0.094

Data are mean (SD), median (interquartile range), or proportion as appropriate. Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

medication, history of CVD, estimated glomerular filtration rate, duration of diabetes, mean total to high-density lipoprotein cholesterol ratio, and mean HbA_{1C}; the final model (model 3) adjusted for variables in model 2 with additional adjustment for average SBP when evaluating the variability of SBP or average DBP when evaluating DBP variability. Of note, for models evaluating the VIM of SBP (or DBP), we did not adjust for mean SBP (or DBP) as VIM already accounts for the mean in its calculation.

A 2-sided *P* value <0.05 was considered statistically significant. All analyses were conducted using STATA 14.2 (Stata, College Station, TX).

RESULTS

Characteristics of study participants

Table 1 displays the characteristics of participants by tertiles of SD of SBP. On average, participants in the top tertile of SD of SBP were older, more likely to be women, and had longer duration of diabetes, lower estimated glomerular filtration rate, as well as higher body mass index, hemoglobin A_{1C}, and BP measures.

Participants in the highest tertile of DBP variability were more likely to be Hispanic and to have lower estimated glomerular filtration rate, as well as higher body mass index, total to high-density lipoprotein cholesterol ratio, and BP measurements (Supplementary Table S1 online).

Long-term variability of BP and clinical outcomes

Over a median follow-up period of 6.6 years (interquartile range: 5.9–7.3), there were a total of 62 CVD-related deaths, 236 all-cause deaths, 220 MI events, 105 stroke cases, and 350 experienced the CVD composite. The cumulative Kaplan–Meier curves of clinical outcomes by SD of SBP or DBP are displayed in Figure 1 and Supplementary Figure S1 online, respectively.

Variability of SBP and outcomes

The adjusted hazard ratios by intraindividual SD of SBP are displayed in Table 2. After maximal adjustment including the average SBP, each SD increment in intraindividual SD of SBP was associated with increased hazards of cardiovascular mortality, all-cause mortality, composite CVD as well as stroke, but not MI. When assessed as categories, participants in the highest of SD of SBP (compared with lowest tertile) had statistically significant increased risks of cardiovascular mortality, but not of all-cause mortality, composite CVD, MI, or stroke.

Variability of DBP and outcomes

Table 3 displays the associations of long-term variability of DBP (assessed as intraindividual SD) of DBP and clinical

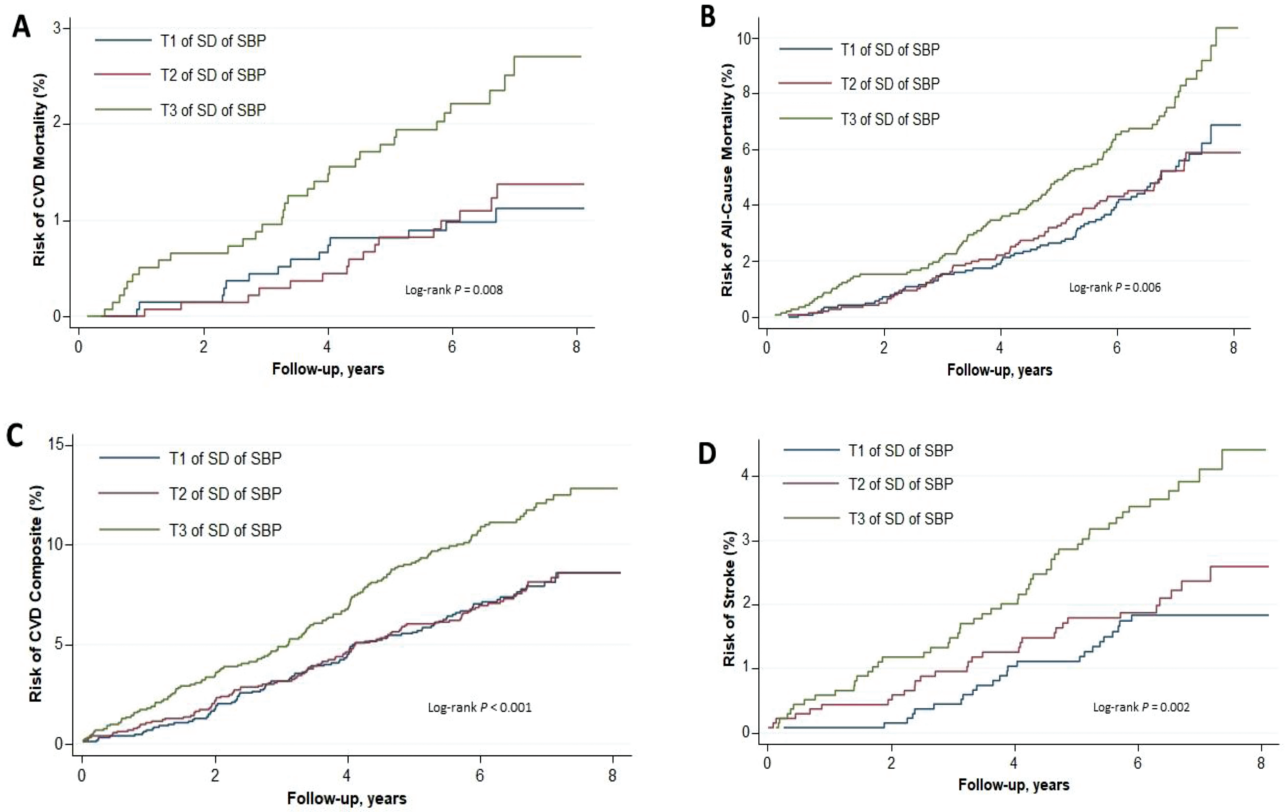

Figure 1. Unadjusted cumulative hazards of cardiovascular mortality (**a**), all-cause mortality (**b**), CVD (**c**), and stroke (**d**) by tertiles of intraindividual SD of systolic blood pressure. CVD was defined as a composite of myocardial infarction, stroke, and/or death from cardiovascular causes. Abbreviations: CVD, cardiovascular disease; SBP, systolic blood pressure; T, tertile.

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Table 2. Incidence and hazard ratios of cardiovascular outcomes by SD of systolic blood pressure

Outcome	Tertile of SD of systolic blood pressure, mm Hg			P_{trend}	Per SD
	T1 (<7.01)	T2 (7.01–10.97)	T3 (>10.97)		
Cardiovascular mortality					
No events/no at risk	14/1,384	16/1,384	32/1,384	…	62/4,152
Rate/1,000 person-years	1.5 (0.9–2.6)	1.8 (1.1–2.9)	3.6 (2.5–5.0)	…	2.3 (1.8–2.9)
Model 1	Reference	1.14 (0.55–2.33)	2.26 (1.20–4.25)*	0.007	1.52 (1.23–1.86)‡
Model 2	Reference	1.12 (0.52–2.39)	2.10 (1.07–4.13)*	0.018	1.46 (1.18–1.81)†
Model 3	Reference	1.09 (0.51–2.35)	1.98 (1.01–3.92)*	0.030	1.41 (1.13–1.76)†
All-cause mortality					
No events/no at risk	68/1,384	67/1,384	101/1,384	…	236/4,152
Rate/1,000 person-years	7.5 (5.9–9.5)	7.4 (5.8–9.4)	11.2 (9.2–13.6)	…	8.7 (7.6–9.9)
Model 1	Reference	0.95 (0.68–1.33)	1.38 (1.01–1.88)*	0.031	1.18 (1.05–1.33)†
Model 2	Reference	0.90 (0.64–1.28)	1.28 (0.93–1.76)	0.099	1.14 (1.01–1.29)*
Model 3	Reference	0.90 (0.63–1.27)	1.25 (0.90–1.72)	0.144	1.12 (0.99–1.27)
CVD[a]					
No events/no at risk	101/1,384	100/1,384	149/1,384	…	350/4,152
Rate/1,000 person-years	11.4 (9.4–13.9)	11.4 (9.4–13.9)	17.3 (14.7–20.3)	…	13.3 (12.0–14.8)
Model 1	Reference	0.98 (0.74–1.29)	1.47 (1.14–1.89)†	0.002	1.23 (1.11–1.35)‡
Model 2	Reference	0.92 (0.69–1.23)	1.33 (1.02–1.74)*	0.021	1.18 (1.07–1.31)†
Model 3	Reference	0.90 (0.68–1.20)	1.26 (0.96–1.64)	0.066	1.14 (1.03–1.26)*
Myocardial infarction					
No events/no at risk	70/1,384	64/1,384	86/1,384	…	220/4,152
Rate/1,000 person-years	7.9 (6.2–9.9)	7.2 (5.7–9.2)	9.8 (8.0–12.2)	…	8.3 (7.3–9.5)
Model 1	Reference	0.91 (0.65–1.27)	1.24 (0.90–1.70)	0.178	1.13 (0.99–1.28)
Model 2	Reference	0.86 (0.61–1.22)	1.12 (0.81–1.56)	0.448	1.09 (0.96–1.24)
Model 3	Reference	0.84 (0.60–1.19)	1.05 (0.75–1.46)	0.722	1.05 (0.92–1.19)
Stroke					
No events/no at risk	24/1,384	30/1,384	51/1,384	…	105/4,152
Rate/1,000 person-years	2.7 (1.8–4.0)	3.3 (2.3–4.8)	5.8 (4.4–7.6)	…	3.9 (3.2–4.7)
Model 1	Reference	1.23 (0.72–2.10)	2.02 (1.24–3.29)†	0.003	1.33 (1.13–1.57)†
Model 2	Reference	1.14 (0.65–1.98)	1.80 (1.09–2.99)*	0.015	1.28 (1.08–1.52)†
Model 3	Reference	1.12 (0.64–1.94)	1.64 (0.99–2.72)	0.043	1.20 (1.01–1.43)*

Data are hazard ratios (95% confidence interval) unless otherwise specified. Model 1 adjusted for age, sex, race/ethnicity, and randomization arm; model 2 includes variables in model 1 with further adjustment for body mass index, current smoking, alcohol drinking, use of antihypertensive medications during follow-up, average ratio of total to high-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes, average HbA_{1C}, and history of cardiovascular disease; model 3 includes variables in model 2 with further adjustment for average systolic blood pressure. Abbreviation: CVD, cardiovascular disease.

[a]CVD was a composite of myocardial infarction, stroke, and death for cardiovascular causes.

*$P < 0.05$.

†$P < 0.01$.

‡$P < 0.001$.

outcomes. After multivariable adjustment, each SD increase in the intraindividual SD of DBP was associated with statistically significant higher risks of cardiovascular mortality, all-cause mortality, but not composite CVD, MI, and stroke. Likewise, individuals in the highest (vs. lowest) tertile of SD of DBP had increased hazards of cardiovascular mortality and all-cause mortality, but not composite CVD, MI, and stroke, respectively.

Supplementary analyses

We tested the robustness of our results by performing additional analyses assessing BP variability using the VIM and CV. Consistent with our main analyses, each SD increase in the VIM of SBP was associated with higher risks of cardiovascular mortality, all-cause mortality, composite CVD, and stroke, but not MI (Supplementary Table S2 online). After adjusting for relevant confounders, each SD increment in the VIM of DBP was associated with statistically significant increased hazards of cardiovascular mortality as well as all-cause mortality, but not composite CVD, MI, or stroke (Supplementary Table S3 online). When variability was measured using the CV, each SD increase in CV of SBP led to increased risks of cardiovascular mortality, all-cause mortality, CVD composite, and stroke (Supplementary Table S4 online). Moreover, each SD increment in CV of DBP was related to increased hazards of cardiovascular mortality and all-cause mortality; but not CVD composite, MI, or stroke (Supplementary Table S5 online).

DISCUSSION

We evaluated the associations of long-term variability in BP with cardiovascular outcomes and mortality among individuals with type 2 diabetes. We made several observations. First, higher levels of variability in SBP were associated with greater cardiovascular mortality and CVD events. Second, a higher variability in DBP was associated with increased overall and cardiovascular mortality. These associations were independent of average BP levels. Our findings confirm the importance of BP variability in the assessment of CVD risk in adults with type 2 diabetes and underscore the necessity of consistent BP control in this high-risk population.

Our study complements the available body of evidence by performing a comprehensive assessment of the relations of long-term variability in BP with CVD outcomes and deaths in a large and racially diverse sample of adults with type 2 diabetes. Individuals with type 2 diabetes have greater rates of autonomic dysfunction and arterial stiffness, which might result in high BP variability,[12,13] yet there is a dearth of epidemiological data exploring BP variability and CVD outcomes in this population. Indeed, a recent systematic review showed that prior epidemiologic studies exploring these associations in type 2 diabetes are scarce and have several limitations including the lack of diverse sample, smaller sample sizes, and shorter duration of follow-up.[11] Additionally, our study explored multiple outcomes and attempted to capture the full spectrum of BP variability by assessing multiple variability indices. Our findings of a positive association between visit-to-visit variability with CVD and deaths are agreement with prior studies conducted in both the general population,[4,5,7–9,24] and the few reports of individuals with type 2 diabetes.[6,11,14–18] Additionally, the positive association between variability of SBP and cerebrovascular accidents is consistent with prior studies from the general population although these reports were not specific to people with diabetes.[5,8,9]

A number of mechanisms may explain the positive relationship between higher visit-to-visit variability in BP and CVD events and mortality among people with type 2 diabetes. First, type 2 diabetes is positively related to poor arterial compliance. Indeed, BP variability is increased with arterial stiffness which may reduce the ability to adjust for greater fluctuations in stroke volume (due to autonomic dysfunction), leading to amplified variations of SBP and therefore increasing the rates of adverse vascular events.[25,26] Second, the rate of autonomic dysfunction is elevated in type 2 diabetes which increases BP variability.[27] The resulting heightened sympathetic response has been shown to increase the rates of CVD events and mortality.[27,28] Third, mechanistic studies have shown that high BP variability is associated with several end-organ complications including aortic hypertrophy, myocardial damage (inflammation and apoptosis of cardiac myocytes), direct endothelial damage, and activation of renin–angiotensin system.[29] Finally, the stronger association between BP variability and mortality in our study is potentially related to the higher rates of microvascular disease which are known to be associated with greater mortality rates in individuals with diabetes.[30,31]

A few limitations to our study should be acknowledged. First, this was an observational study, hence there is a possibility of residual confounding. Second, our study sample was limited to people with type 2 diabetes, hence our results are not generalizable to other hyperglycemic states including type 1 diabetes. Third, our study lacked data on adherence to antihypertensive medication, which may affect BP variability over time. Finally, given that our study relied on only 4 time points to assess BP variability, we may have underestimated BP variability and consequently the magnitude of our effect estimates. Indeed, Levitan *et al.* have previously established that visit-to-visit variability of BP increases with the number of visits used to calculate it.[32] Despite these few limitations, strengths of this study include a large and diverse prospective cohort, the recording of BP values at regular preset intervals spread over a 36-month period for the entire cohort, the long duration of follow-up, the standardized assessment of BP and other covariates, as well the blinded adjudication of outcomes.

The clinical and research implications of our findings are manifold for patients with type 2 diabetes. Visit-to-visit fluctuations of BP appear as an independent predictor of adverse outcomes in this population. More research is needed to establish practical and reliable ways of assessing long-term variability of BP in clinical practice. Additionally, considerable debate remains about the ideal therapeutic strategies for individuals with type 2 diabetes known to have elevated BP variability. Although

Table 3. Incidence and hazard ratios of cardiovascular outcomes by SD of diastolic blood pressure

Outcome	Tertile of SD of diastolic blood pressure, mm Hg			P_{trend}	Per SD
	T1 (< 3.58)	T2 (3.58–5.54)	T3 (> 5.54)		
Cardiovascular mortality					
No events/no at risk	16/1,384	16/1,384	30/1,384	…	62/4,152
Rate/1,000 person-years	1.8 (1.1–2.9)	1.8 (1.1–2.9)	3.3 (2.3–4.7)	…	2.3 (1.8–2.9)
Model 1	Reference	1.07 (0.53–2.14)	1.93 (1.05–3.54)*	0.027	1.36 (1.12–1.66)†
Model 2	Reference	1.02 (0.50–2.09)	1.89 (1.01–3.57)*	0.035	1.34 (1.08–1.66)†
Model 3	Reference	1.04 (0.50–2.13)	1.84 (0.98–3.48)	0.046	1.29 (1.05–1.59)*
All-cause mortality					
No events/no at risk	65/1,384	74/1,384	97/1,384	…	236/4,152
Rate/1,000 person-years	7.2 (5.6–9.2)	8.2 (6.5–10.2)	10.7 (8.8–13.1)	…	8.7 (7.6–9.9)
Model 1	Reference	1.20 (0.86–1.67)	1.49 (1.09–2.04)*	0.012	1.19 (1.06–1.34)†
Model 2	Reference	1.18 (0.84–1.65)	1.44 (1.05–2.00)*	0.024	1.17 (1.04–1.32)*
Model 3	Reference	1.18 (0.84–1.66)	1.43 (1.03–1.98)*	0.029	1.16 (1.03–1.30)*
CVD[a]					
No events/no at risk	104/1,384	118/1,384	128/1,384	…	350/4,152
Rate/1,000 person-years	11.9 (9.8–14.4)	13.5 (11.2–16.1)	14.7 (12.3–17.4)	…	13.3 (12.0–14.8)
Model 1	Reference	1.19 (0.91–1.54)	1.25 (0.97–1.63)	0.088	1.12 (1.01–1.24)*
Model 2	Reference	1.13 (0.86–1.47)	1.20 (0.92–1.57)	0.172	1.09 (0.98–1.21)
Model 3	Reference	1.13 (0.86–1.48)	1.19 (0.91–1.56)	0.196	1.08 (0.98–1.20)
Myocardial infarction					
No events/no at risk	69/1,384	72/1,384	79/1,384	…	220/4,152
Rate/1,000 person-years	7.8 (6.2–9.9)	8.1 (6.4–10.2)	9.0 (7.2–11.2)	…	8.3 (7.3–9.5)
Model 1	Reference	1.09 (0.79–1.52)	1.18 (0.85–1.63)	0.321	1.06 (0.93–1.21)
Model 2	Reference	1.01 (0.72–1.42)	1.15 (0.83–1.59)	0.409	1.04 (0.91–1.19)
Model 3	Reference	1.01 (0.72–1.42)	1.14 (0.82–1.58)	0.432	1.04 (0.91–1.18)
Stroke					
No events/no at risk	31/1,384	40/1,384	34/1,384	…	105/4,152
Rate/1,000 person-years	3.5 (2.4–4.9)	4.5 (3.3–6.1)	3.8 (2.7–5.3)	…	3.9 (3.2–4.7)
Model 1	Reference	1.32 (0.83–2.11)	1.10 (0.67–1.79)	0.721	1.09 (0.91–1.31)
Model 2	Reference	1.27 (0.79–2.05)	0.99 (0.60–1.64)	0.942	1.03 (0.85–1.25)
Model 3	Reference	1.27 (0.79–2.05)	0.97 (0.58–1.60)	0.870	1.01 (0.83–1.23)

Data are hazard ratios (95% confidence interval) unless otherwise specified. Model 1 adjusted for age, sex, race/ethnicity, and randomization arm; model 2 includes variables in model 1 with further adjustment for body mass index, current smoking, alcohol drinking, use of antihypertensive medications during follow-up, average ratio of total to high-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes, average HbA_{1C}, and history of cardiovascular disease; model 3 includes variables in model 2 with further adjustment for average diastolic blood pressure. Abbreviation: CVD, cardiovascular disease.

[a]CVD was a composite of myocardial infarction, stroke, and death for cardiovascular causes.

*$P < 0.05$.

†$P < 0.01$.

antihypertensive classes such as calcium-channel blockers and non-loop diuretics have been suggested to be partially effective at controlling BP variability, optimal approaches remain to be determined. Indeed, reduction of BP variability may contribute to the end-organ protective effects of certain BP-lowering medications.[29]

In conclusion, in a large community-based sample of adults with type 2 diabetes, a higher long-term variability of SBP was independently associated with a greater risk of CVD events and cardiovascular mortality; whereas a higher variability in DBP was associated with greater overall and cardiovascular mortality. Our findings highlight the relevance of visit-to-visit variability of BP in the prediction of CVD outcomes and deaths in people type 2 diabetes and underscore the necessity of stable and consistent BP control in this population.

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DISCLOSURE

The authors declared no conflict of interest.

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