Prognostic Value of Variability in Systolic Blood Pressure Related to Vascular Events and Premature Death in Type 2 Diabetes Mellitus

The ADVANCE-ON Study

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See Editorial Commentary, pp 227–228

Abstract—Visit-to-visit variability in systolic blood pressure (SBP) is a risk factor for cardiovascular events. However, whether it provides additional predictive information beyond traditional risk factors, including mean SBP, in the long term is unclear. The ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) was a randomized controlled trial in patients with type 2 diabetes mellitus; ADVANCE-ON (ADVANCE-Observational) followed-up patients subsequently. In these analyses, 9114 patients without major macrovascular or renal events or death during the first 24 months were included. Data on SBP from 6 visits during the first 24 months after randomization were used to estimate visit-to-visit variability in several ways: the primary measure was the standard deviation. Events accrued during the following 7.6 years. The primary outcome was a composite of major macrovascular and renal events and all-cause mortality. Standard deviation of SBP was log-linearly associated with an increased risk of the primary outcome (P<0.001) after adjustment for mean SBP and other cardiovascular risk factors. The hazard ratio (HR; 95% confidence interval [CI]) in the highest, compared with the lowest, tenth of the standard deviation was 1.39 (1.15–1.69). Results were similar for major macrovascular events alone and all-cause mortality alone (both P<0.01). Addition of standard deviation of SBP significantly improved 8-year risk classification (continuous net reclassification improvement, 5.3%). Results were similar for other measures of visit-to-visit variability, except maximum SBP. Visit-to-visit variability in SBP is an independent predictor of vascular complications and death, which improves risk prediction beyond that provided by traditional risk factors, including mean SBP. **(*Hypertension*. 2017;70:461-468. DOI: 10.1161/HYPERTENSIONAHA.117.09359.)** ● **Online Data Supplement**

Key Words: blood pressure variability ■ cardiovascular disease ■ diabetes mellitus ■ mortality ■ myocardial infarction ■ stroke

Every cardiovascular disease (CVD) risk score, from the earliest[1] to the present day,[2] across the world, has included a measure of blood pressure (BP). For men and women, systolic blood pressure (SBP) is likely to be the next most important CVD factor to age. However, unlike age, SBP is prone to both short- and long-term variation, so that the inclusion of a single value of SBP in a risk score will underestimate its true effect because of regression dilution bias.[3] Multiple measurements are, therefore, recommended to calculate usual BP, but visit-to-visit variability (VVV) in SBP has also been identified as an independent risk factor for CVD, with greater VVV leading to greater risk.[4–6] Whether this means that VVV in SBP should

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be included in CVD risk scores is unknown. Furthermore, few studies of VVV in SBP have been conducted in patients with diabetes mellitus, who may be particularly susceptible to increased BP variability, given the high prevalence of arterial stiffness and autonomic dysfunction in this high-risk group.

SBP is also a major risk factor for renal disease[7,8] and premature death (henceforth referred to as death).[7,8] Hence, the same question of the additional predictive worth of VVV in SBP also arises for these outcomes.

We previously reported that increased VVV in SBP was a risk factor for macrovascular and microvascular events and death, independent of mean SBP and other cardiovascular risk factors, in the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation).[9] However, the short-term follow-up period (median 2.4 years) did not allow us to assess the suitability of including VVV in SBP in a CVD risk score beyond traditional risk factors, including mean SBP.

The objective of the present study was, thus, to examine the long-term impact of SBP variability and its predictive ability for vascular complications and mortality in patients with type 2 diabetes mellitus.

Methods

Study Design

ADVANCE was a factorial randomized controlled trial evaluating the effects of BP lowering and intensive blood glucose–lowering treatment on vascular outcomes in patients with type 2 diabetes mellitus. A detailed description of the design has been published previously.[10–12] In brief, a total of 11 140 individuals with type 2 diabetes mellitus at high risk of cardiovascular events were enrolled from 215 centers in 20 countries. Participants were randomly assigned to either a fixed-dose combination of perindopril (4 mg) and indapamide (1.25 mg) or matching placebo and to either a gliclazide (modified release)-based intensive glucose control regimen aiming to achieve a hemoglobin A_{1c} ≤6.5% or standard glucose control based on local guidelines of participating countries after a 6-week active run-in period. The ADVANCE-ON study (ADVANCE-Observational) was a post-trial follow-up study of the ADVANCE trial. Post-trial follow-up was obtained from 8494 patients out of a total of 10 082 patients alive when the randomized treatment phase of the ADVANCE trial was completed.[13] Participants were followed up for an overall median duration of 9.9 years. Patients with major macrovascular or renal events or death during the first 24 months, those with missing SBP values at any of the 6 occasions (3, 4, 6, 12, 18, and 24 months after randomization), and those with missing values in covariates were excluded from the present analysis. Approval for the study was obtained from the institutional review board of each center, and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, and the procedures followed were in accordance with the institutional guidelines.

BP Measurements and Visit-to-Visit Variability

BP was measured in duplicate, with an interval of at least 1 minute, after 5 minutes of rest in the seated position, by using a standardized automated sphygmomanometer (Omron HEM-705CP, Tokyo, Japan) and then averaged. BP recordings were taken at registration, randomization, 3, 4, and 6 months after randomization, and at every 6 months thereafter. Standard deviation (SD), coefficient of variation, variation independent of mean, average successive variability, residual standard deviation, and range of SBP were determined using values measured on 6 occasions (3, 4, 6, 12, 18, and 24 months after randomization), and maximum value were used as VVV parameters.[4,9,14] Mean of SBP during the 24-month measurement period, averaged over the 6 occasions, was taken as a covariate.

Follow-Up and Study Outcomes

Participants were followed up from their 24-month visit until the first event or the end of follow-up (Figure 1). The primary outcome was a composite of major macrovascular events, major renal events, and all-cause mortality. Major macrovascular events were defined as myocardial infarction (nonfatal and fatal), stroke (nonfatal and fatal), or cardiovascular death. Major renal events were defined as requirement for chronic renal-replacement therapy and death from renal disease. Secondary outcomes were components of primary outcome. Through to the end of randomized treatment, an independent end point advisory committee adjudicated all the outcomes. Outcomes occurring during post-trial follow-up were reported by the study centers using the standardized definitions adopted during the trial, without central adjudication.[13]

Statistical Analysis

Pearson's correlation coefficients were estimated between measures of VVV of SBP and mean SBP during the first 24 months and between measures of VVV of SBP adjusted for mean SBP. VVV of SBP was compared between the active treatment group and the placebo group by analysis of covariance after adjustment for mean SBP during the first 24 months. The effect of SBP parameters on outcomes was estimated by Cox proportional hazards model using groups defined by the tenths and for an increase of 1 SD for each SBP parameter. The proportional hazards assumption was verified through cumulative hazard plots. Adjustments were made for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure–lowering intervention, and randomized glucose control intervention (model 1), or variables in model 1 plus mean SBP (model 2). Unless invariant over time, these covariates were as measured at the 24-month visit. When data at the 24-month visit were missing, the latest data before the 24-month visit were used. A linear trend across tenths was tested taking the tenths as a continuous variable ranging from 1 to 10.

We repeated all analyses using after imputing missing values of BP and the covariates among 1375 patients using multiple imputation by Monte Carlo Markov Chains (n=10 489), with 10 imputations.[3] We also performed sensitivity analyses, which added pulse pressure or estimated glomerular filtration rate (using the CKD-EPI equation [Chronic Kidney Disease Epidemiology Collaboration][15]) as covariates. We also conducted subgroup analysis stratified by randomized blood pressure–lowering intervention, by mean SBP during the measurement period (<140 mm Hg or ≥140 mm Hg), and by sex.

For the primary outcome and its 3 major components, discrimination was evaluated using C statistics for 8-year risk, accounting for censoring,[16] and compared between model 2 and when adding each SBP parameter individually. In addition, the ability to reclassify the 8-year risk was assessed by the integrated discrimination index (IDI) and the net reclassification improvement (NRI), using methods suitable for survival data.[3] The C statistic estimates discrimination, and IDI and NRI estimate the added prognostic power when a new variable (such as VVV) is added to an existing model.[3,17] All analyses were performed using SAS Enterprise Guide 7.11 (SAS Institute Inc, Cary, NC) or Stata software (release 13; StataCorp, College Station, TX). A 2-sided $P<0.05$ was considered to be statistically significant in all analyses.

Results

Baseline Characteristics

Of the 11 140 patients who participated in the ADVANCE trial, 9114 patients were included in the primary analyses (Figure 1 and Table 1; Figure S1 in the online-only Data Supplement). For those in the current study, the mean age at the 24-month visit was 68 years, 42% were female, and 37% were recruited in Asia. BP at 24-month visit was 137/77 mm Hg. Mean 10-year predicted risk of major vascular events in the present study estimated by the AD-ON score[18] was 23.3%.

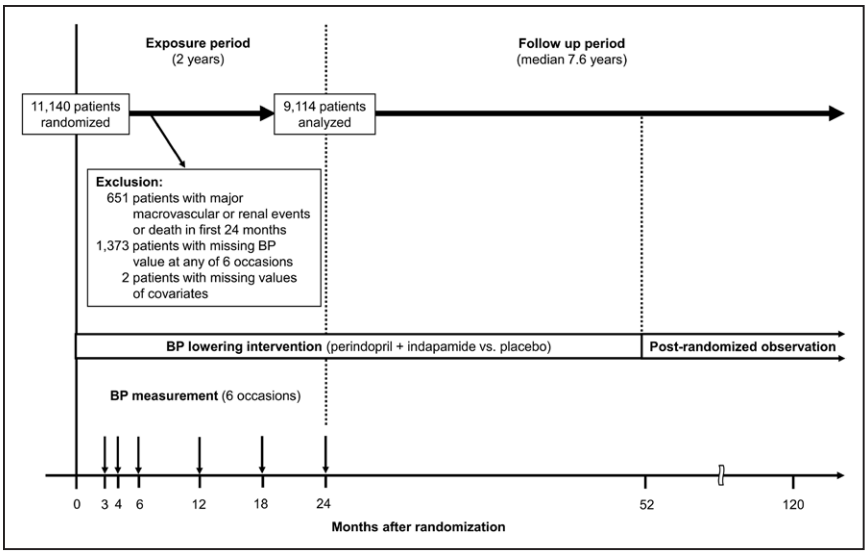

Figure 1. Flow diagram for study participants. Blood pressure (BP), measured at 6 occasions (3, 4, 6, 12, 18, and 24 months after randomization), was used to determine the mean, visit-to-visit variability, and maximum of systolic BP. After excluding 651 patients who had experienced major macrovascular or renal events or death within 24 months, 1373 patients with missing BP values at any of 6 occasions, and 2 patients with missing values of covariates, 9114 patients were eligible for the present study.

Blood Pressure Variability

All the measures of VVV of SBP, except the maximum value, were strongly correlated (r between 0.78 and 0.99) with each other (Table S1). After controlling for mean SBP, all measures of VVV of SBP, including the maximum value, were highly correlated (r between 0.71 and 1) with each other, and the correlations between our primary measure, SD, and the other measures of VVV were all strong (r between 0.83 and 0.99; Table S2). There was no statistically significant difference in VVV of SBP between the active treatment group and the placebo group, after adjustment for mean SBP (Table S3).

Effect of VVV in SBP on Outcomes

During a median of 7.6 years of follow-up, 1476 patients developed a major macrovascular event, 122 experienced a major renal event, and there were 1550 deaths. Higher mean SBP during the measurement period was associated with increased risk of the primary outcome and its components after adjusting for cardiovascular risk factors (Figure S2).

The risk of the primary outcome increased log-linearly with increasing SBP SD after adjustment for mean SBP and other cardiovascular risk factors (P for trend <0.001), with the highest tenth associated with a 39% greater risk of the primary outcome compared with the lowest tenth (HR, 1.39; 95% CI, 1.15–1.69; Figure 2). Similar statistically significant adjusted trends were observed for all-cause mortality (P for trend <0.001) and major macrovascular events (P for trend =0.007); the corresponding HRs (95% CIs) for the highest tenth compared with the lowest tenth of SBP SD were 1.67 (1.31–2.14) and 1.17 (0.92–1.49), respectively. After controlling for mean SBP and other cardiovascular risk factors, there was no statistically significant trend in the risk of either cardiovascular death or major renal events (Figures 2 and 3; P values were 0.07 and 0.11, respectively). However, in both cases, there was a statistically significant difference between the extreme tenths: the HRs (95% CIs) for the highest tenth compared with the lowest tenth were 1.53 (1.001–2.33) and 2.97 (1.10–8.01), respectively. For myocardial infarction and stroke, there was no evidence of either a trend (P values were 0.13 and 0.33, respectively) or a difference in risk between those in the top and bottom 10% of the distribution of SDs (HRs [95% CIs], 1.08 [0.72–1.63] and 1.08 [0.77–1.53], respectively; Figure 3). Similar results were present for all but one other measures of VVV in SBP: coefficient of variation, variation independent of mean, average successive variability, residual standard deviation, and range of SBP (Figures S3 through S7). For maximum of SBP, similar statistically significant trends for all 7 outcomes were seen using model 1, but were attenuated and became nonsignificant after additional adjustment for mean SBP in model 2 (Figure S8). The analyses for mean SBP and a variety of indices of VVV in SBP as continuous variables, instead of tenths, showed similar results (Table 2; Table S4).

Results remained unchanged when (1) missing values were imputed (Figure S9) and (2) models were adjusted for pulse pressure (Figure S10) or estimated glomerular filtration rate (Figure S11) as covariates, and the pattern of association between SD of SBP and each of the outcomes analyzed was also similar whether or not adjustment was made for the mean of SBP (Figure S12). Subgroup analyses, stratified by randomized blood pressure–lowering intervention or mean SBP levels during the measurement period, showed no significant heterogeneity in the associations between SD of SBP and the risks of each outcome considered (Figures S13 and S14). Similar associations were also observed by sex (Figure S15).

Discrimination and Reclassification

For the primary outcome, addition of SBP SD to the model with established cardiovascular risk factors, including mean SBP, significantly improved the C statistic (from 0.6459 to 0.6499; P=0.003), IDI (relative IDI, 4.18 [95% CI, 2.94–5.47]; P<0.001), continuous NRI (0.053 [95% CI, 0.003–0.107]; P=0.03), and categorical NRI (0.017 [95% CI, 0.006–0.029]; P=0.002; Table 3). Coefficient of variation, variation independent of mean, average successive variability, residual standard deviation, range, and maximum of SBP showed broadly similar improvements in the prediction metrics (Table S5). For macrovascular disease and death, discrimination of events was significantly improved by adding SBP SD to the prediction model; for major renal disease, the change in C statistic was

Table 1. Characteristics of ADVANCE-ON Participants Overall and Those Included in the Present Study

Variable	Overall Baseline (n=11 140)	Included in the Present Study	
		Baseline (n=9114)	24-Month Visit (n=9114)
Demographic factors			
Age, y	66 (6)	66 (6)	68 (6)
Female, %	4735 (43)	3849 (42)	
Resident in Asia, %	4136 (37)	3392 (37)	
Asian, %	4242 (38)	3476 (38)	
Non-Asian, %	6898 (62)	5638 (62)	
Medical and lifestyle history			
Duration of diabetes mellitus, y	7.9 (6.4)	7.8 (6.3)	9.8 (6.3)
Current smoking, %	1682 (15)	1356 (15)	919 (10)*
Current alcohol drinking, %	3396 (30)	2812 (31)	2541 (28)*
Clinical measurements			
Systolic blood pressure, mm Hg	145 (22)	145 (21)	137 (19)
Diastolic blood pressure, mm Hg	81 (11)	81 (11)	77 (10)
Pulse pressure, mm Hg	64 (17)	64 (17)	61 (15)
Heart rate, bpm	74 (12)	74 (12)	73 (12)*
Hemoglobin A_{1c}, %	7.5 (1.6)	7.5 (1.5)	7.0 (1.2)*
Total cholesterol, mmol/L	5.2 (1.2)	5.2 (1.2)	4.9 (1.1)*
Triglycerides, mmol/L	1.6 (1.2–2.3)	1.6 (1.2–2.3)	1.6 (1.1–2.2)*
Body mass index, kg/m^2	28.3 (5.2)	28.4 (5.2)	28.3 (5.2)*
eGFR, mL/min per 1.73 m^2	73 (17)	74 (17)	70 (18)*
Oral hypoglycemic agents, %	10 129 (91)	8281 (91)	8629 (95)*
Insulin, %	159 (1)	133 (1)	1605 (18)*
10-year risk of major vascular events, %	21.9 (12.6)	21.4 (12.0)	23.3 (12.6)*
Randomized treatments			
Perindopril–indapamide	5569 (50)	4567 (50)	
Intensive blood glucose control	5571 (50)	4547 (50)	
Additional BP-lowering treatments			
β-Blocker, %	2729 (25)	2242 (25)	2713 (30)*
Calcium-channel blocker, %	3427 (31)	2758 (30)	3116 (34)*
Diuretics, %†	2640 (24)	2138 (23)	1312 (14)*
Angiotensin-converting enzyme inhibitors, %†	4790 (43)	3963 (43)	4698 (52)*
Angiotensin II receptor blockers, %	609 (5)	469 (5)	635 (7)*
Other antihypertensive agents, %	1383 (12)	1102 (12)	946 (10)*
Any BP-lowering agents, %†	8366 (75)	6822 (75)	6976 (77)*
Visit-to-visit variability in systolic blood pressure‡			
Mean, mm Hg			137 (15)
SD, mm Hg			11.0 (5.0)
CV, %			8.0 (3.4)
VIM, mm Hg			11.0 (4.7)
ASV, mm Hg			12.0 (6.1)
RSD, mm Hg			10.2 (5.0)
Range, mm Hg			29 (14)
Maximum, mm Hg			152 (19)

Values are mean (SD) for continuous variables (except for triglycerides), median (interquartile range) for triglycerides, and number (%) for categorical variables. ADVANCE-ON indicates Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation–Observational; ASV, average successive variability; BP, blood pressure; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; RSD, residual standard deviation; SBP, systolic blood pressure; SD, standard deviation; and VIM, variation independent of the mean.

*When data at the 24-month visit were missing, the latest data before the 24-month visit were used.

†Randomized treatment with perindopril–indapamide was not included.

‡Defined using SBP values at 3, 4, 6, 12, 18, and 24 mo after randomization.

similar but not statistically significant. IDI was significantly positive in all 3 cases, with relative IDI highest for major renal disease. For NRI, results were mainly positive but not significant.

Discussion

This study showed that increased VVV in SBP was linearly associated with the increased risk of a composite of major macrovascular events, major renal events, and all-cause mortality in patients with type 2 diabetes mellitus over an 8-year period. This association remained statistically significant after multivariate adjustment for mean SBP and other cardiovascular risk factors. A similar trend was observed when macrovascular events and all-cause mortality were analyzed separately. Addition of VVV in SBP significantly improved the prediction of major outcomes beyond that obtained from mean SBP and traditional risk factors.

Several studies have examined the association between VVV in BP and the risk of CVD. A recent systematic review and meta-analysis of prospective studies has demonstrated that increased long-term variability in SBP (such as monitoring of BP in clinics) was significantly associated with increased risk of all-cause mortality, CVD mortality, CVD events, coronary heart disease, and stroke.[19] However, most of these studies were conducted in general populations, patients with hypertension, or those with CVD, whereas few studies have investigated the associations with vascular complications in patients with diabetes mellitus. While we have previously

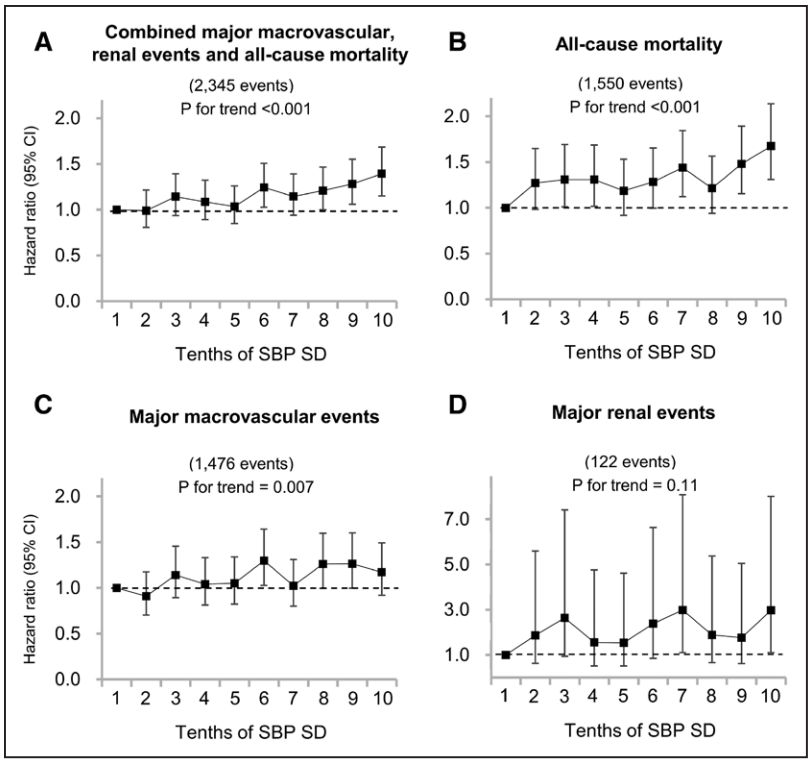

Figure 2. Hazard ratios and 95% confidence intervals (CIs) for major macrovascular and renal events and all-cause mortality according to tenths of standard deviation (SD) of systolic blood pressure (SBP). SBP SD was categorized according to the tenths. The ranges of SBP SD were 0.49 to 5.15, 5.16 to 6.79, 6.80 to 7.99, 8.00 to 9.13, 9.14 to 10.26, 10.27 to 11.47, 11.48 to 12.90, 12.91 to 14.79, 14.80 to 17.61, and 17.62 to 47.20 mm Hg. Hazard ratios were adjusted for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure–lowering intervention, randomized glucose control intervention, and mean SBP during the measurement period (the same covariates as model 2 in Table 2).

reported that VVV was positively associated with vascular outcomes in patients with type 2 diabetes mellitus,[9] the present study confirms and extends that evidence from a relatively short median 2.4 years of follow-up to a much longer period of median 7.6 years.

Regarding the components of macrovascular disease, neither myocardial infarction nor stroke showed a linear association with VVV in SBP. In contrast, a recent meta-analysis found a significant positive association between increases in VVV in SBP and coronary heart disease and stroke, although with significant heterogeneity in the magnitude of the association across studies.[19] Although we cannot be certain of the reasons for the lack of significant association in our study, it seems likely that sample size and the small number of events (only 478 myocardial infarction events and 668 stroke events) in our cohort might explain the discrepancy versus the positive association seen in our study for the primary outcome (2345 events), all-cause mortality (1550 events), and major macrovascular events (1476 events; Figure 2 and 3). Sample size considerations may also explain the difference between our findings and the report from the meta-analysis.[19] Further studies, such as individual participant data meta-analyses, are needed to elucidate this issue.

Although a significant association between VVV in BP and vascular events has been reported several times, only one previous study is known to have examined whether VVV in BP provides additional predictive information for future vascular events beyond the traditional risk factors, including mean BP. This study conducted among 2501 patients with a history of CVD showed that addition of coefficient of variation of SBP significantly improved IDI (0.0048; P=0.03) for CVD, but did not improve the area under the receiver-operating characteristic curve.[20] Our study of primary prevention of CVD and other outcomes, among patients with diabetes mellitus, provides evidence that addition of measures of VVV in SBP also improved the NRI, as well as the C statistic and IDI. Although the improvements in statistics were modest, even a small improvement in risk prediction could be important, especially in the management of high-risk patients.

The potential pathophysiologic mechanisms underlying the association between VVV in SBP and vascular events and death have not been fully clarified. Higher variability of BP may reflect reductions in large elastic artery compliance. An increase in BP variability has shown to be associated with arterial stiffness,[21,22] which may explain the increased incidence of vascular events. In addition, fluctuation of BP may reflect

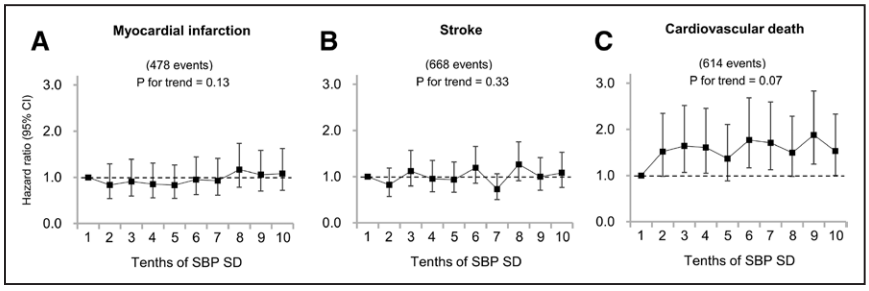

Figure 3. Hazard ratios and 95% confidence intervals (CIs) for components of major macrovascular events according to tenths of standard deviation (SD) of systolic blood pressure (SBP). SBP SD was categorized according to the tenths, same as in Figure 2. Hazard ratios were adjusted for the same covariates as in Figure 2.

Table 2. Effects of 1-SD Increment in Mean and SD of SBP on Primary Outcome (Combination of Major Macrovascular Events, Renal Events, and All-Cause Mortality) and Its Components

SBP Parameter	No. of Events	Model 1*			Model 2†		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value
Combined macrovascular, renal events, and all-cause mortality							
Mean SBP	2345	1.11	1.06–1.16	<0.001			
SD SBP		1.14	1.09–1.18	<0.001	1.11	1.07–1.16	<0.001
All-cause mortality							
Mean SBP	1550	1.09	1.04–1.15	0.001			
SD SBP		1.14	1.09–1.20	<0.001	1.13	1.07–1.19	<0.001
Major macrovascular events							
Mean SBP	1476	1.13	1.07–1.20	<0.001			
SD SBP		1.11	1.06–1.17	<0.001	1.08	1.03–1.14	0.004
Major renal events							
Mean SBP	122	1.52	1.27–1.81	<0.001			
SD SBP		1.27	1.08–1.50	0.005	1.15	0.97–1.37	0.11
Myocardial infarction							
Mean SBP	478	1.21	1.10–1.33	<0.001			
SD SBP		1.15	1.05–1.26	0.002	1.11	1.01–1.21	0.03
Stroke							
Mean SBP	668	1.14	1.05–1.23	0.002			
SD SBP		1.08	1.00–1.17	0.04	1.05	0.97–1.14	0.20
Cardiovascular death							
Mean SBP	614	1.16	1.06–1.26	<0.001			
SD SBP		1.12	1.03–1.21	0.006	1.08	0.998–1.18	0.06

HR (95% CI) per increase of 1 SD for each parameter was shown. SD values were 15.2 mm Hg for mean SBP and 5.0 mm Hg for SD SBP. CI indicates confidence intervals; HR, hazard ratio; SBP, systolic blood pressure; and SD, standard deviation.

*Model 1 was adjusted for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure–lowering intervention, and randomized glucose control intervention.

†Model 2 was adjusted for all variables in model 1 and mean SBP.

abnormal autonomic regulation. End-organ damage resulting from BP variability has been reported in animal models.[23] BP variability showed significant association with endothelial dysfunction and markers of inflammation in humans.[24,25] Although VVV in BP was associated with CVD independent of medication adherence,[26] poor adherence to medication may partly explain the association.[27] Further studies are needed to clarify the mechanisms responsible.

The strengths of the present study are the large sample size, the long-term follow-up, and the rigorous evaluation of VVV in SBP by using a variety of measures, in particular the variation independent of mean, which is not correlated with mean SBP. In addition, to the best of our knowledge, this is the first study to use a comprehensive set of discrimination and reclassification statistics to show the additional impact of VVV in SBP beyond mean SBP and other risk factors on the risk prediction of CVDs. However, limitations of our study should be noted. First, the end points during the post-trial follow-up were not adjudicated by central adjudication committee. However, we have previously shown that the end point adjudication process in the ADVANCE trial had no discernible effect on the observed HRs for any outcomes.[28] Second, selection bias might have arisen by excluding patients with missing BP value at any of 6 measurement occasions. However, the sensitivity analyses using imputation of missing values of BP did not materially change the results. Third, our study population was enrolled in a clinical trial, which may limit the generalizability of the results to unselected populations. Fourth, this is a post hoc observational study, and there may be residual confounding factors other than those included in the present analysis. Fifth, we were only able to follow-up 84% of the patients alive when the original trial period was completed, but it is unlikely that selective dropout could have resulted in any major bias, while baseline characteristics of patients included in the post-trial follow-up were similar to those of the entire trial population.[13] Sixth, previous reports[29,30] have found heterogeneity in the effects of VVV in SBP on stroke across drug classes. ADVANCE lacks reliable data regarding the effectiveness of the various drug classes in reducing VVV in SBP. Seventh, it is possible that treatment exposure varied during the observational post-trial follow-up period, which may have affected the association between VVV in

Table 3. Discrimination and Reclassification Statistics (95% Confidence Intervals) for Standard Deviation of Systolic Blood Pressure and Primary Outcome (Combination of Major Macrovascular Events, Renal Events, and All-Cause Mortality) and Its Major Components

Model	C Statistic	IDI	Relative IDI, %	NRI	
				Continuous	Categorical*
Combined macrovascular, renal events and all-cause mortality					
Base model†	0.6459 (0.6339–0.6580)				
Plus SD SBP	0.6499 (0.6379–0.6619)	0.0029 (0.0021–0.0038)	4.18 (2.94–5.47)	0.053 (0.003–0.107)	0.017 (0.006–0.029)
	P=0.003	*P*<0.001		*P*=0.03	*P*=0.002
All-cause mortality					
Base model†	0.6976 (0.6836–0.7117)				
Plus SD SBP	0.7009 (0.6870–0.7149)	0.0026 (0.0014–0.0039)	2.68 (1.40–3.98)	0.074 (0.017–0.134)	–0.0024 (–0.019 to 0.015)
	P=0.01	*P*<0.001		*P*=0.02	*P*=0.75
Major macrovascular events					
Base model†	0.6280 (0.6125–0.6435)				
Plus SD SBP	0.6312 (0.6158–0.6466)	0.0014 (0.0010–0.0019)	4.11 (2.84–5.33)	0.010 (–0.051 to 0.070)	0.002 (–0.014 to 0.017)
	P=0.02	*P*<0.001		*P*=0.47	*P*=0.42
Major renal events					
Base model†	0.7079 (0.6590–0.7568)				
Plus SD SBP	0.7175 (0.6708–0.7642)	0.0018 (0.0010–0.0030)	11.54 (6.31–17.24)	0.150 (–0.023 to 0.342)	–0.029 (–0.073 to 0.007)
	P=0.11	*P*<0.001		*P*=0.09	*P*=0.10

IDI indicates integrated discrimination index; NRI, net reclassification improvement; SBP, systolic blood pressure; and SD, standard deviation.

*Using cutoff points of 10% and 20% 8-year risk.

†Base model included age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure–lowering intervention, randomized glucose control intervention, and mean SBP.

SBP and study outcomes. Finally, event numbers were likely insufficient to provide reliable, consistent information on the additional prognostic value of VVV in SBP for the major components of the primary outcome, particularly, major renal disease. Nevertheless, there was sufficient information to conclude that VVV in SBP does seem to be a prime candidate for addition to CVD, and possibly renal, risk scores, at least in the context of diabetes mellitus.

Perspectives

VVV in SBP was significantly associated with increased 8-year risk of vascular events and all-cause mortality, independent of mean SBP and other traditional risk factors in patients with type 2 diabetes mellitus. In addition, VVV in SBP provided additional predictive information beyond that obtained from mean SBP and the traditional risk factors.

With the advent of linked clinical records, and home monitoring of BP, it is becoming practical to use VVV in SBP to improve individual risk stratification, beyond using mean SBP and other factors. Our findings suggest that reduced VVV in SBP may be an important therapeutic target in patients with type 2 diabetes mellitus.

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Novelty and Significance

What Is New?

- This is the first study to show that visit-to-visit variability (VVV) in systolic blood pressure (BP) provides additional predictive information on vascular events beyond that from mean BP and traditional risk factors, using a variety of measures of VVV and discrimination and reclassification statistics.

What Is Relevant?

- VVV in BP is associated with increased risk of cardiovascular events, but the additional utility of VVV in BP for the risk prediction of events in diabetes mellitus has not previously been clarified.

Summary

VVV in systolic blood pressure was significantly associated with an increased risk of vascular events and all-cause mortality independent of mean systolic BP and other traditional risk factors in patients with type 2 diabetes mellitus for an 8-year period and improved risk prediction beyond that provided by traditional risk factors for the next 8 years. Assessment of VVV in BP can be incorporated into clinical practice.