Blood Pressure Measurement Device, Number and Timing of Visits, and Intra-Individual Visit-to-Visit Variability of Blood Pressure

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Visit-to-visit variability (VVV) of blood pressure is associated with cardiovascular disease. The authors examined the effects of visit number and timing and automated or manual measurement device on VVV in the placebo arm of the Trial of Preventing Hypertension (TROPHY) (N=225) and simulations. VVV was assessed using intra-individual standard deviation (SD), range, maximum, coefficient of variation, successive variation, and average real variability of systolic blood pressure. VVV increased with number of visits used to calculate it in the TROPHY population (*P* for trend <.05 for all metrics) and simulations. Using consecutive visits in TROPHY, average SD was 5.6 mm Hg from 3 visits, 6.8 mm Hg from 7 visits, and 7.7 mm Hg from 18 visits. When 7 visits were spread out across 4 years, the average SD was higher (7.5 mm Hg) than when visits were consecutive over 18 months (*P*<.001). SD was higher using a single blood pressure measurement per visit (compared with the mean of 3 measurements per visit *P*<.001) and with automated vs manual devices (*P*<.001). In summary, number and timing of visits and device used to measure blood pressure influence VVV and need to be considered when designing, interpreting, and comparing studies. *J Clin Hypertens (Greenwich)*. 2012;14:744–750.

Associations between visit-to-visit variability (VVV) of systolic blood pressure (SBP) and stroke, coronary heart disease, and mortality have been reported in several recent publications.[1–5] In one study, VVV had a stronger association with cardiovascular events than mean blood pressure (BP).[3] This has inspired a great deal of interest in VVV as a novel risk factor for cardiovascular disease independent of mean BP. Antihypertensive medication classes have differential effects on VVV that parallel their effects on outcomes, suggesting that cardiovascular events could potentially be prevented by switching patients to antihypertensive medications that reduce VVV.[2,6,7]

VVV is a relatively new risk factor, however, and methods for assessing VVV have not been standardized. To investigate the effects of VVV on cardiovascular and mortality outcomes, investigators have used existing BP data from clinical trials and established cohorts.[1–5] The number and timing of BP measurements and the BP measurement protocols have differed from study to study. For example, some populations had one BP measurement per visit while others averaged multiple measurements.[1–5] Some of the prior studies have used automated BP measurement while others relied on manual BP measurement.[1–5] The minimal number of measurements needed to reliably estimate an individual's VVV is not known, and the impact of the time between visits on VVV has not been extensively studied. Prior studies have examined the association of VVV and outcomes using as few as 3 visits while other studies have used more visits. In addition, the effect of automated vs manual BP measurement device and number of BPs per visit on VVV is unclear. Information regarding the effects of BP assessment on VVV is necessary to appropriately design, interpret, and compare studies of VVV.

We therefore examined the effect of the number and timing of BP measurements and BP measurement device on VVV using data from the placebo arm of the Trial of Preventing Hypertension (TROPHY) and from simulation studies. In TROPHY, BP was measured every 1 to 3 months for 4 years. The simulation studies allowed us to examine the effect of the number of visits on VVV without complicating factors such as change in mean BP over time.

METHODS

Study Population

The design and results of the TROPHY trial have been presented previously.[8,9] Briefly, men and women aged 30 to 65 years with high-normal BP (average systolic/diastolic BP over 3 baseline visits of 130–139/≤89 mm Hg or ≤139/85–89 mm Hg) were randomized to 16 mg/d of candesartan (n=391) or placebo (n=381). After 2 years of follow-up, the active treatment group was switched to placebo. The primary

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endpoint was a composite of 3 visits with SBP ≥140 mm Hg or diastolic BP ≥90 mm Hg, 1 visit with SBP ≥160 mm Hg or diastolic BP ≥100 mm Hg, or target organ damage or other clinical reasons to start antihypertensive therapy as determined by the investigators. If a participant reached the endpoint, open-label antihypertensive treatment was initiated. Treatment with metoprolol or hydrochlorothiazide was provided to participants at no cost, but other medications, with the exception of angiotensin receptor blockers, could also be used. For this analysis, we included the 225 participants randomized to placebo who completed all 18 postbaseline visits. Institutional review boards at all participating centers approved the TROPHY protocol, and all participants provided written informed consent.

BP Measurement

At each clinic visit, BP was measured after 5 minutes of rest using a standardized protocol. BP was measured 3 times using an automated device (HEM-705CP; Omron Healthcare, Kyoto, Japan) and 3 times using a manual device. The order of the automated and manual BP measurement and the specific manual BP measurement device used were not specified in the TROPHY protocol.

Calculation of VVV of SBP

Although several metrics of VVV have been proposed, we focused on the intra-individual standard deviation (SD) of SBP because it has been previously associated with cardiovascular events and mortality[1,3] and it is easy to calculate and interpret. Because BP at the 3 baseline visits determined eligibility for study entry and was constrained to a narrow range, BP measurements from these visits were not used in any of the analyses. We calculated the BP at each visit using 4 different approaches: the mean of the 3 automated BP measurements, the first automated BP measurement, the mean of the 3 manual BP measurements, and the first manual BP measurement. Intra-individual SD was calculated using the formula $SD = \sqrt{\sum_{i=1}^{n} (x_i - \bar{x})^2/(\mathrm{n}-1)}$. In this formula, n is the number of visits, x_i is the individual's BP at visit i (the mean of 3 measurements or the first measurement), and $\bar{x}$ is the individual's average BP across visits. To examine whether the number of BP measurements influences the intra-individual SD, we calculated the intra-individual SD using the first 3 postbaseline visits, first 4 postbaseline visits, and up to all 18 postbaseline visits. Additionally, we calculated the intra-individual SD from 7 measurements spaced out across the 4-year follow-up period.

To examine whether the number of visits influences other metrics of VVV, we calculated the range, the maximum, the coefficient of variation, the successive variation, and the average real variability using the mean of 3 manual BP measurements per visit. The coefficient of variation was calculated as $SD/\bar{x}$, the successive variation was calculated as $\sqrt{\left(\sum_{i=1}^{n-1} (x_{i+1} - x_i)^2\right)/(n-1)}$, and the average real variability was calculated as $(\sum_{i=1}^{n-1} |x_{i+1} - x_i|)/(n-1)$.

Statistical Analysis

We first calculated means and SD or percentages of baseline characteristics of the TROPHY participants randomized to placebo by whether they initiated antihypertensive medications during the study period. We computed the correlations between intra-individual SD calculated from 7 visits using the mean of the 3 automated BP measurements per visit, the first automated BP measurement per visit, the mean of the 3 manual BP measurements per visit, and the first manual BP measurement per visit. We chose to examine the intra-individual SD calculated from 7 visits as this has been used in previous studies.[3,10] We compared the SD between participants who did and did not initiate antihypertensive medications using *t* tests. Additionally, we calculated the SD of SBP including only those measurements taken prior to the initiation of antihypertensive medications. For these calculations, an individual who initiated antihypertensive medications after 5 visits would have an SD calculated from 5 visits, would be censored after 5 visits, and would not have SDs calculated from 6 to 18 visits. We tested for the statistical significance of differences in SD calculated from 7 visits with automated vs manual devices and using 1 vs the mean of 3 BP measurements per visit using paired *t* tests. Tests of trend in SD and other VVV metrics by number of visit were performed using generalized estimating equations. To compare the intra-individual SD calculated using a limited number of visits (3–10 visits) with the intra-individual SD calculated using all 18 visits, we computed the percent difference as $100\% \times |\mathrm{SD_n} - \mathrm{SD_{18}}|/\mathrm{SD_{18}}$ where $\mathrm{SD_n}$ is the intra-individual SD calculated from n visits and $\mathrm{SD_{18}}$ is the intra-individual SD calculated from 18 visits. We tested for differences between SD calculated from 7 consecutive visits and 7 visits spread out across follow-up visit using paired *t* tests.

Simulation Study

To evaluate how the number of visits affects the intra-individual SD under ideal conditions of known "true" mean and intra-individual SD, we created simulated populations of 200 individuals and BP measurements from 100 visits. SBP was assumed to be normally distributed where all individuals had a mean SBP of 135 mm Hg and an intra-individual SD of 8.5 mm Hg. In the first simulated population, we assumed that BP measurements were uncorrelated between visits. We then modeled an autoregressive correlation structure, which assumed BP measurements were more closely correlated in adjacent visits with the correlation

decreasing over time.[11] In this correlation structure, adjacent visits had a correlation of r, a pair of visits with one intervening visit had a correlation of r^2, a pair of visits with 2 intervening visits had a correlation of r^3, and so on. We examined simulated populations with autocorrelation coefficients of 0.3, 0.5, and 0.7. As in the TROPHY study population, we calculated the intra-individual SD across visits (n=3–100). In the simulated population, we used a fractional polynomial algorithm[12] to examine the shape of the association between the intra-individual SD and the number of visits. Fractional polynomials take the form X^p+X^q where X is the variable of interest, in this case the number of visits. The powers p and q were chosen from the set of possible values −2, −1, −0.5, natural logarithm, 0.5, 1, 2, and 3 based on the best fit to the data. If p=q then the model is $X^p+X^p \ln(X)$. We also explored simpler polynomial curves within smaller, more plausible ranges of number of visits. Additionally, we examined the SD from 7 consecutive visits and 7 visits spaced throughout the 100 simulated visits. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and Stata version 11.2 (StataCorp, College Station, TX).

RESULTS

Study Population

Of the 225 participants in the TROPHY placebo arm who completed all 18 postbaseline study visits, 138 (61%) initiated antihypertensive medications during follow-up and 87 (39%) did not. There were no major differences in baseline characteristics between those who did and did not initiate antihypertensive medications (Table I).

TABLE I. Baseline Characteristics of the Study Population by Incident Antihypertensive Medication Use

		Incident Antihypertensive Medication Use	
	Overall Population (n=225)	Yes (n=138)	No (n=87)
Age, mean (SD), y	48.9 (8.1)	49.8 (8.0)	47.3 (8.1)
Race, No. (%)			
White	199 (88.4)	125 (90.6)	74 (85.1)
Black	13 (5.8)	8 (5.8)	5 (5.7)
Other	13 (5.8)	5 (3.6)	8 (9.2)
Male sex, No. (%)	130 (57.8)	83 (60.1)	47 (54.0)
Body mass index, mean (SD), kg/m^2	30.1 (5.8)	30.3 (5.8)	29.7 (5.8)
Systolic blood pressure, mean (SD), mm Hg	134 (4)	135 (4)	134 (4)
Diastolic blood pressure, mean (SD), mm Hg	85 (4)	85 (4)	84 (4)

Abbreviation: SD, standard deviation.

BP Measurement Technique and Intra-Individual SD

Correlations between intra-individual SD from 7 visits calculated from the first measurement per visit and the mean of 3 measurements per visit using the same type of device were high (r=0.85–0.94), but the correlations between intra-individual SD calculated from automated vs manual devices were lower (0.49–0.67) (Table II). In the overall TROPHY population, regardless of the number of visits used, intra-individual SD calculated using automated BP measurement was higher than manual measurement ($P<.001$ for SD calculated from 7 visits) (Table III). For both automated and manual measurements, using the first measurement taken at each visit resulted in a higher intra-individual SD compared with using the mean of 3 measurements taken at each visit ($P<.001$ for SD calculated from 7 visits). The same associations of device used and number of BP measurements per visit with intra-individual SD were observed in the subgroups that did and did not initiate antihypertensive medications ($P<.05$). For example, in the population who did not initiate antihypertensive medications, the SD calculated from 7 visits was 6.9 mm Hg for the mean of 3 automated measurements, 7.6 mm Hg for a single automated measurement, 5.8 mm Hg for the mean of 3 manual measurements, and 6.5 mm Hg for a single manual measurement.

Number of Visits and Intra-Individual SD

In the overall TROPHY population, the average intra-individual SD increased with the number of visits used to calculate it regardless of how BP was measured (Table III). The same pattern was observed in the participants who did and those who did initiate antihypertensive medications although the SD was lower in the individuals who did not initiate medication (for SD calculated from 7 visits $P<.001$ comparing those who initiated antihypertensives and those who did not) (Figure 1). When we censored participants at the time of antihypertensive medication initiation, the intra-individual SDs fell between those in the overall population and those who never initiated antihypertensive medications. As the number of visits increased, more individuals were censored and the intra-individual SD more closely corresponded to the population who never initiated antihypertensive medications.

In the overall TROPHY population, intra-individual SD calculated from 3 visits differed, on average, by 41% from the values calculated using 18 visits, regardless of BP measurement device or number of BP measurements per visit. With 7 visits, the intra-individual SD differed by 21% to 24% from the values calculated using 18 visits.

In the simulated data, we observed a nonlinear pattern of higher intra-individual SD with an increasing number of visits (Figure 2). The SD approached the true value of 8.5 mm Hg more quickly when BP had less between-visit correlation. Based on the best fit to the

TABLE II. Correlations Between Intra-Individual Standard Deviation in Systolic Blood Pressure Calculated Using Automated and Manual Blood Pressure Measurement Devices from 7 Visits

	Mean of 3 Automated Measurements	First Automated Measurement	Mean of 3 Manual Measurements	First Manual Measurement
Overall Population (N=225)				
Mean of 3 automated measurements 1				
First automated measurement	0.92	1		
Mean of 3 manual measurements	0.67	0.61	1	
First manual measurement	0.61	0.57	0.92	1
No incident antihypertensive medication use (n=87)				
Mean of 3 automated measurements	1			
First automated measurement	0.87	1		
Mean of 3 manual measurements	0.65	0.53	1	
First manual measurement	0.60	0.49	0.85	1
Incident antihypertensive medication use (n=138)				
Mean of 3 automated measurements	1			
First automated measurement	0.93	1		
Mean of 3 manual measurements	0.65	0.61	1	
First manual measurement	0.59	0.57	0.94	1

TABLE III. Intra-Individual Standard Deviation in Systolic Blood Pressure by Number of Visits, Number of Measurements Per Visit, and Blood Pressure Measurement Device in the Overall Population (N=225)

Number of Visits	Mean of 3 Automated Measurements	First Automated Measurement	Mean of 3 Manual Measurements	First Manual Measurement
3	6.2 (3.6)	6.9 (3.8)	5.6 (3.2)	6.4 (3.7)
4	6.7 (3.5)	7.3 (3.5)	6.0 (3.1)	6.7 (3.4)
5	7.1 (3.3)	7.7 (3.3)	6.3 (2.9)	6.9 (3.1)
6	7.5 (3.2)	8.1 (3.2)	6.7 (2.9)	7.3 (3.0)
7	7.5 (3.0)	8.2 (2.9)	6.8 (2.6)	7.4 (2.7)
8	7.7 (2.9)	8.4 (2.9)	7.0 (2.9)	7.6 (3.0)
9	7.8 (2.7)	8.5 (2.7)	7.1 (2.8)	7.7 (2.8)
10	7.9 (2.6)	8.5 (2.6)	7.0 (2.6)	7.7 (2.7)
11	7.9 (2.5)	8.6 (2.5)	7.1 (2.5)	7.7 (2.6)
12	8.0 (2.5)	8.6 (2.4)	7.1 (2.5)	7.7 (2.5)
13	8.1 (2.6)	8.7 (2.5)	7.2 (2.5)	7.8 (2.5)
14	8.2 (2.6)	8.8 (2.5)	7.3 (2.5)	7.9 (2.5)
15	8.3 (2.6)	8.9 (2.5)	7.4 (2.5)	8.0 (2.4)
16	8.3 (2.6)	8.9 (2.5)	7.6 (2.4)	8.1 (2.4)
17	8.4 (2.6)	9.0 (2.5)	7.6 (2.5)	8.2 (2.4)
18	8.5 (2.6)	9.1 (2.5)	7.7 (2.5)	8.2 (2.4)
P for trend	$< .001$	$< .001$	$< .001$	$<.001$

Values are expressed as mean intra-individual standard deviation (standard deviation of the intra-individual standard deviation).

data, the fractional polynomial algorithm selected the number of visits to powers −1 and 3 as the best predictors of the intra-individual SD when there was no correlation in BP between visits ($SD=\beta_0+\beta_1 n^{-1}+\beta_2 n^3$, where n=the number of visits used to calculated SD). The fractional polynomial algorithm selected the powers −0.5 and −0.5 when the autocorrelation coefficient was 0.3, −0.5 and 0.5 when the autocorrelation coefficient was 0.5, and natural logarithm and natural logarithm squared when the autocorrelation coefficient was 0.7. The number of visits and the square of the number of visits appeared to fit the shape of the curves acceptably in the range of 4 to 20 visits, based on the observation that the residuals from this model were not associated with the number of visits.

Number of Visits and Other Metrics of VVV

The range, maximum, coefficient of variation, average real variability, and successive variation all increased with the number of visits used to calculate the metric (Table IV).

Timing of Visits and Intra-Individual SD

Increasing the time between BP measurements was associated with higher intra-individual SD. In the overall TROPHY population, using the mean of 3 manual measurements at each visit, the average intra-individual SD calculated from 7 consecutive visits (total time=18 months, median time between visits=3 months) was 6.8 mm Hg. In comparison, the average intra-individual SD calculated from 7 visits spaced out across the 4-year follow-up period (median time between visits= 8 months) was 7.5 mm Hg ($P<.001$ as compared with 7 consecutive visits). The SD calculated from all 18 visits during the 4-year period was higher (7.7 mm Hg), but the difference did not reach statistical significance ($P=.12$).

In the simulated data without correlations between visits, the intra-individual SD calculated from 7 consecutive visits and 7 visits spread out across the 100 visits were similar (8.2 mm Hg and 8.3 mm Hg). When BP was assumed to be autocorrelated, the

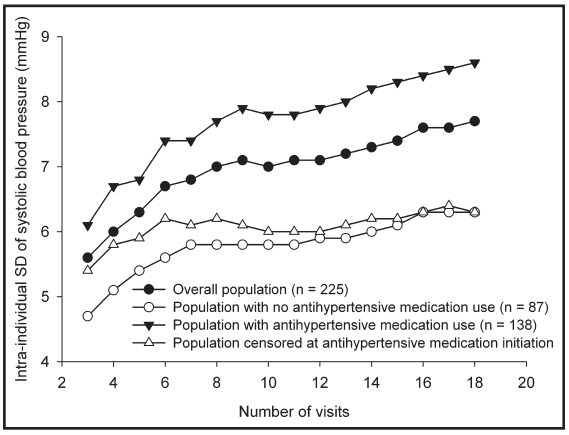

FIGURE 1. Intra-individual standard deviations (SDs) of systolic blood pressure (SBP) by number of visits among the overall population, those who did not initiate antihypertensive medications, those who did initiate antihypertensive medications, and censoring participants at the time of initiation of antihypertensive medications. Intra-individual SD calculated using the mean of 3 manual blood pressure measurements at each visit. Results were similar when visit blood pressure was determined using the first measurement or an automated measurement device.

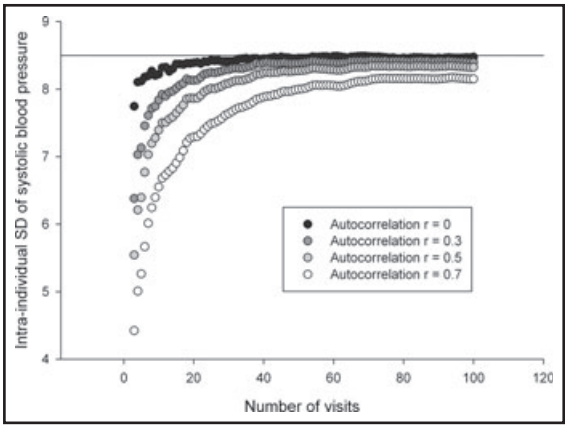

FIGURE 2. Average intra-individual standard deviations (SDs) of systolic blood pressure (SBP) by number of visits in simulated populations of 200 individuals with a mean blood pressure of 135 mm Hg and an intra-individual SD of 8.5 mm Hg.

intra-individual SD was higher when visits were not consecutive. With an autocorrelation coefficient of 0.3, the intra-individual SD from 7 consecutive visits was 7.6 mm Hg compared with 8.1 mm Hg when 7 measurements were distributed across the 100 visits. Corresponding values were 7.0 mm Hg and 8.0 mm Hg when the autocorrelation coefficient was 0.5 and 6.0 and 7.9 mm Hg when the autocorrelation coefficient was 0.7.

DISCUSSION

In this study, we determined that design factors such as the number and timing of visits with BP measurements and the BP measurement device used influence VVV. Of particular importance, the intra-individual SD of BP increased with the number of visits used to calculate it in a nonlinear fashion. We observed this pattern in the overall TROPHY population, in subgroups defined by initiation of antihypertensive medications, and in simulated data. The same pattern of increasing values with increasing number of visits was also observed with the other metrics of VVV that we examined: range, maximum, coefficient of variation, average real variability, and successive variation. Although we did not examine SD independent of the mean, because it is indexed to SD, it would also increase with an increasing number of visits. A higher intra-individual SD and coefficient of variation of BP with $\geq$7 visits compared with $\geq$3 visits was also noted in a previous study.[13] The association between the number of visits used to calculate the SD and the SD may be counterintuitive. However, it is a property of the usual formula for the SD when the number of measurements is small.[14,15] As described in the statistical literature, the bias in the SD formula decreases with increasing sample size and is related to the use of the t rather than z distribution with small sample sizes.[14,15]

When the number of visits used to calculate VVV is not consistent across individuals, the dependence of the SD on the number of visits could produce bias if characteristics associated with the number of visits are also associated with the outcome. For example, a patient who visits a doctor frequently because of diabetes will have a larger number of BP measurements, leading to a higher SD. Given the higher risk for outcomes such as stroke or coronary heart disease among individuals with diabetes, this could lead to a spurious or exaggerated association between VVV and these outcomes. Our results suggest that within a study the same number of BP measurements should be used for calculating VVV for all participants or that the number of measurements should be adjusted for statistically. The relationship between the number of visits used to calculate intra-individual SD and the SD values appeared to be well approximated by the linear and quadratic terms in the range of 4 to 20 visits. Alternatively, formulas for and tables of correction factors for the SD have been published[14,15]; however, these correction factors are not widely used in the biomedical literature and, to our knowledge, have not been used in research on VVV.

In large study populations, practical concerns limit the number of study visits. In addition, the visits used to calculate VVV should precede the follow-up period during which events occur to ensure that VVV is not affected by the events. This leads to a trade-off between using more visits to calculate VVV, resulting in a more accurate assessment of VVV but a shorter follow-up period, or using fewer visits to calculate VVV, resulting in a less accurate assessment of VVV but a longer follow-up period for events to accrue.

TABLE IV. Range, Maximum, Coefficient of Variation, Successive Variation, and Average Real Variability by Number of Visits in the Overall Population (N=225)[a]

Number of Visits	Range	Maximum	Coefficient of Variation, %	Successive Variation	Average Real Variability
3	10.7 (6.1)	134 (9)	4.4 (2.5)	8.2 (4.4)	7.1 (3.8)
4	13.4 (6.9)	135 (9)	4.7 (2.4)	8.5 (4.0)	7.2 (3.4)
5	15.5 (7.1)	136 (9)	4.9 (2.2)	8.8 (3.9)	7.3 (3.2)
6	17.7 (7.6)	138 (10)	5.2 (2.1)	9.0 (3.8)	7.4 (3.1)
7	19.1 (7.5)	138 (10)	5.3 (1.9)	9.2 (3.8)	7.5 (3.0)
8	20.6 (8.9)	139 (11)	5.4 (2.1)	9.4 (3.9)	7.6 (3.0)
9	21.6 (9.0)	139 (10)	5.5 (2.0)	9.3 (3.7)	7.5 (2.8)
10	22.1 (8.9)	140 (10)	5.5 (1.9)	9.2 (3.5)	7.4 (2.7)
11	23.0 (9.0)	140 (10)	5.5 (1.9)	9.3 (3.4)	7.4 (2.6)
12	24.1 (9.2)	140 (10)	5.6 (1.8)	9.3 (3.3)	7.4 (2.5)
13	24.8 (9.5)	141 (10)	5.6 (1.8)	9.4 (3.2)	7.5 (2.5)
14	25.6 (9.8)	141 (10)	5.7 (1.9)	9.6 (3.2)	7.6 (2.5)
15	26.4 (9.7)	142 (10)	5.8 (1.8)	9.7 (3.2)	7.7 (2.4)
16	27.4 (10.0)	142 (10)	5.9 (1.8)	9.7 (3.1)	7.7 (2.4)
17	28.2 (10.2)	142 (10)	6.0 (1.9)	9.7 (3.1)	7.7 (2.4)
18	28.9 (10.4)	142 (10)	6.1 (1.9)	N/A[b]	N/A[b]
P for trend	<.001	<.001	<.001	<.001	.04

Values are expressed as mean value (standard deviation). [a]Blood pressure assessed as the mean of 3 manual measurements per visit. [b]The formulas for successive variation and average real variability require n+1 visits to calculate.

Empirically, in one prior study, a larger number of visits used to calculate the intra-individual SD resulted in a higher hazard ratio for stroke.[3] We had hoped to determine the minimal number of visits needed to reliably and accurately estimate VVV. Our results suggest that there is no simple answer. In both the TROPHY study population and simulated data, the calculated intra-individual SD from 7 or 10 visits was less than the true value (the SD calculated from all 18 visits in the TROPHY population and the SD specified in the simulation). Previous work has demonstrated that higher intra-individual SD increases the number of measurements needed to accurately calculate an individual's true mean BP.[3] The effect of number of visits on the estimated intra-individual SD was not reported.

The other factors we studied also influenced the intra-individual SD. Visits spaced further apart were associated with a higher SD. This could be the result of underlying changes in BP due to aging, changes in medication use or other behaviors, and seasonal patterns in BP. Additionally within-person correlation in BP declining over time results in a higher intra-individual SD, as shown in the simulations. In TROPHY, the intra-individual SD calculated from 7 visits over 4 years was lower than the SD calculated from 18 visits over the same time period, though the difference did not reach statistical significance. This suggests that both the number and spacing of visits impacts intra-individual SD.

We found that averaging 3 BP measurements per visit resulted in a lower SD. This is similar to previous findings that averaging measurements across multiple visits reduced within-person variability of BP and that intra-individual variability was lower in when calculated using 24-hour average BP than clinic BP.[13,16] However, the SD calculated from a single measurement per visit was highly correlated with the SD calculated from the mean of 3 measurements per visit. This implies that if the intent is to rank individuals on degree of VVV, a single BP measurement per visit may provide similar information to the mean of three measurements per visit. However, when individuals have the same underlying degree of variability, those with more measurements per visit will have a lower intra-individual SD. This could lead to bias if the number of BP measurements taken per visit is related to the individuals' health status or other characteristics. To avoid this problem, the same number of measurements per visit should be used for all participants in a study.

Finally, the SD was higher when automated BP measurement devices were used as compared with manual devices. One possible explanation is that the errors introduced by oscillometric BP monitoring with automated devices led to excess variability. Alternatively, with manual measurement, observer bias and the practice of recording only even values may have lead to a reduction in variability. Manual BP measurements by well-trained observers continue to be recommended for routine clinical use.[17]

The observed SD of SBP was lower in this population than in other described populations.[1–5] As we have shown, comparing the variability of BP across populations is complicated by the influence of the study design. Additionally, individuals with higher SBP tend to have higher variability of SBP.[3] The TROPHY

population had relatively low BP in a narrow range, which likely contributed to the observed low SD of SBP. Previous studies have included individuals with frank hypertension and individuals with existing cardiovascular disease.[1–5]

In the TROPHY placebo arm, 61% of participants initiated antihypertensive medications. We observed higher SD in the participants who initiated antihypertensive medications than those who did not. A contributing factor could have been the decision rule used to initiate antihypertensive therapy (3 visits with SBP $\geq$140 mm Hg or diastolic BP $\geq$90 mm Hg, 1 visit with SBP $\geq$160 mm Hg or diastolic BP $\geq$100 mm Hg, or target organ damage or other clinical reasons to start antihypertensive therapy as determined by the investigators). This rule could have had the effect of selecting participants with higher VVV for treatment.

STUDY STRENGTHS AND LIMITATIONS

The use of high-quality BP measurements using automated and manual devices from a trial population randomized to placebo and followed for 4 years is a major strength of this study. However, there are also limitations including the initiation of antihypertensive medications in the majority of the participants. The current study was restricted to individuals with BP in a narrow, prehypertensive range at baseline and the impact of number of visits, timing of visits, and device used to measure BP on VVV should be investigated in additional populations, including hypertensive individuals receiving treatment. We focused primarily on intra-individual SD, and a more thorough investigation of other metrics is warranted.

CONCLUSIONS

The current study demonstrates that VVV is influenced by the number of visits used to calculate it, the timing of those visits, the BP measurement device, and the number of measurements per visit. It is important to recognize that factors besides intrinsic VVV may result in differences in VVV between study populations. When investigating the association of VVV and outcomes in a study population, VVV should be calculated using the same number of visits for all individuals or VVV should be adjusted for the number of visits used in its calculation. The current study indicates that care must be taken in the implementation and interpretation of VVV as this line of research matures.

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