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# Reproducibility of visit-to-visit variability of blood pressure measured as part of routine clinical care

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## Abstract

**Objectives—**Secondary analysis of clinical trial data suggests visit-to-visit variability (VVV) of blood pressure is strongly associated with the incidence of cardiovascular disease. Measurement of blood pressure in usual practice settings may be subject to substantial error, calling into question the value of VVV in real-world settings.

**Methods—**We analyzed data on adults ≥ 65 years of age with diagnosed hypertension who were taking antihypertensive medication from the Cohort Study of Medication Adherence among Older Adults (n=772 with 14 or more blood pressure measurements). All blood pressure measurements, taken as part of routine out-patient care over a median of 2.8 years, were abstracted from patients' medical charts.

**Results—**Using each participant's first 7 systolic blood pressure (SBP) measurements, the mean intra-individual standard deviation was 13.5 mmHg. The intra-class correlation coefficient for the standard deviation based on the first 7 and second 7 SBP measurements was 0.28 (95% CI: 0.20 – 0.34). Individuals in the highest quintile of standard deviation of SBP based on their first 7 measurements were more likely to be in the highest quintile of VVV using their second 7 measurements (observed/expected ratio = 1.71, 95% CI: 1.29 – 2.22). Results were similar for other metrics of VVV. The intra-class correlation coefficient was lower for diastolic blood pressure (DBP) than SBP.

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Conflicts of interest: None

This work has not been presented or published previously

**Conclusions—**These data suggest VVV of SBP measured in a real-world setting is not random. Future studies are needed to assess the prognostic value of VVV of SBP assessed in routine clinical practice.

### Keywords

Blood pressure; variability; reproducibility; health services research

Several recent studies have reported a strong and graded association between visit to visit variability (VVV) of blood pressure and the incidence of coronary heart disease, stroke, and all-cause mortality[1, 2]. These associations were present after adjustment for several potential confounders, including mean blood pressure level. Furthermore, VVV has been demonstrated to be reproducible, suggesting it may have value as a predictor of cardiovascular disease risk[3]. While these data may have profound implications for the treatment of hypertension, they were derived from large randomized controlled trials and observational cohort studies wherein blood pressure measurements were performed as part of a research protocol at set time periods following standardized procedures.

The use of electronic medical records provides an opportunity to make VVV of blood pressure available for use in routine clinical practice. However, blood pressure measurement in the office setting is often criticized for having systematic and random error[4, 5]. The degree to which VVV of blood pressure, calculated using clinic measurements, reflects real variability versus measurement error is uncertain. If VVV using clinic measurements is reproducible, it may provide an important tool for assessing a patient's future cardiovascular disease risk and guiding treatment decisions.

The goal of this analysis was to determine the degree to which VVV is reproducible when using blood pressure measured as part of routine care in the out-patient setting. Additionally, we sought to identify patient factors associated with a lack of reproducibility. We analyzed blood pressure data, obtained through the abstraction of electronic medical records from a large managed care organization for participants in the Cohort Study of Medication Adherence among Older Adults (CoSMO). *A priori, we* chose to determine the reproducibility of VVV based on the first 4 versus second 4 and first 7 versus second 7 blood pressure measurements to match a study which calculated reproducibility of VVV in the setting of two clinical trials[3].

## METHODS

### Study Population and Timeline

The CoSMO study design, recruitment flowchart, and baseline characteristics of participants have been previously described[6]. In brief, adults, 65 years and older who were receiving treatment for essential hypertension were randomly selected from the roster of a large managed care organization in southeastern Louisiana. Recruitment was conducted from August 21, 2006 to September 30, 2007, and 2,194 participants were enrolled. Participants were actively followed through February 2010. All participants provided verbal informed

consent, and CoSMO was approved by the Ochsner Clinic Foundation's Institutional Review Board and the Privacy Board of the managed care organization.

### Study Measures

Recruitment and survey data were collected via telephone by trained interviewers. Participant characteristics, including demographics, cigarette smoking and duration of hypertension were assessed through self-report. Based on ICD-9 codes recorded in the managed care organization's administrative database, a weighted comorbidity score was generated using the Charlson comorbidity index[7]. The number and classes of antihypertensive medications being taken by each participant were downloaded from the managed care organization's pharmacy database.

### Blood pressure data

Trained research staff abstracted blood pressure data from electronic medical records for outpatient clinic visits occurring the year prior to the baseline interview through the completion of the second CoSMO follow-up interview (median time = 2.8 years; maximum = 4 years). All blood pressure measurements included in this study were obtained as part of clinical care and no structured measurement approaches were prescribed. Data abstraction included systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels, patient position, and date of blood pressure measurement. For the current analysis, only seated blood pressure measurements were used. In our sample, 79% of visits had only 1 recorded blood pressure measurement while 19% of visits had 2 recordings, and < 3% of visits had 3 or more recordings. Blood pressure levels were averaged for visits with more than one measurement taken. Blood pressure data were available for 2,130 CoSMO participants.

### VVV of blood pressure

VVV metrics were calculated for the first 4 and second 4 blood pressure measurements and again for the first 7 and second 7 blood pressure measurements. The first 4 blood pressure measurements occurred over a median period of 7.2 months (range: 2 weeks to 34 months), while the second 4 blood pressure measurements occurred over a median period of 7.4 months (range: 1 week to 30 months). The first 7 and second 7 blood pressure measurements occurred over a median period of 11.5 months (range: 2 months to 28 months) and 11.0 months (range: 2 months to 29 months), respectively. For the current analyses, we evaluated seven VVV metrics: standard deviation, standard deviation independent of the mean (SDIM), coefficient of variation, peak size, trough size, successive variation (SV), and average real variability (ARV) (see Appendix for formulas)[3]. Standard deviation has been used in prior studies as the primary measure of VVV. Because standard deviation is correlated with mean SBP, we also evaluated SDIM. Coefficient of variation provides a normalized measure of variability. Peaks and troughs in blood pressure were defined as the difference between the mean and the maximum blood pressure (for peak) and mean and the minimum blood pressure (for trough). The SV and ARV take the order of the blood pressure measurements into account and quantify variability between adjacent readings.

### Statistical Analysis

Participant characteristics were calculated for the overall CoSMO study population and for individuals with at least 8 and at least 14 blood pressure measurements. Herein, we describe the analysis for individuals with 8 or more blood pressure measurements (n=1,580) comparing the first 4 and second 4 blood pressure measurements. Analogous analyses were conducted for individuals with 14 or more blood pressure measurements (n=772) and comparing the first 7 and second 7 blood pressure measurements. Using the first 4 and second 4 abstracted measurements separately, the mean blood pressure level and each of the seven VVV metrics were calculated. Additionally, the Spearman correlation coefficient between the seven VVV metrics and the mean blood pressure level was calculated. Next, the intra-class correlation coefficients (ICC) for the mean blood pressure level and each of the seven VVV metrics between the first 4 and second 4 measurements were calculated. The 95% confidence interval for each ICC was calculated using a 10,000 iteration bootstrap. Two sensitivity analyses were conducted to determine the reproducibility of VVV using alternate time periods. First, we calculated the ICC limited to blood pressure measurements that occurred at least one week apart (n=1,547 participants with 8 or more measurements and n=677 with 14 or more measurements separated by one or more week). Second, we calculated the ICC comparing VVV of blood pressure during the first 18 months of follow-up with the second 18 months of follow-up (n=1,180 participants with 4 or more measurements and n=453 with 7 or more measurements in each 18 month time period). The above analyses for reproducibility of VVV were performed for SBP and DBP, separately.

Next, the population was divided into quintiles based on the distribution of standard deviation using the first 7 SBP values and, separately, using the second 7 SBP values. Weighted Kappa statistics were used to calculate the agreement between these categories[8]. Amongst individuals in the highest quintile of standard deviation of SBP based on their first 7 SBP measurements, we calculated the observed and expected number of participants in the highest quintile of standard deviation based on their second 7 SBP measurements. Additionally, the observed and expected number of participants in the lowest quintile of standard deviation of SBP was calculated. The categorical analyses of reproducibility (i.e., weighted Kappa and observed-to-expected ratios) were also performed using SDIM as the VVV metric.

Finally, we determined patient characteristics associated with low levels of VVV reproducibility. For this analysis, individuals whose standard deviation of SBP based on their second 7 measurements was 8 or more mmHg higher or −8 or more lower than the standard deviation of SBP for their first 7 measurements were defined as having a low level of reproducibility. The cut-point of 8 mmHg was chosen to represent the highest quintile of change in standard deviation of SBP over the two time periods. Using logistic regression, the odds ratio for low reproducibility was calculated in unadjusted and age, race, gender, and mean SBP adjusted models. All analyses were conducted in SAS version 9.2 (SAS Institute, Cary NC).

## RESULTS

The mean age of CoSMO study participants was 75.0 (standard deviation = 5.6) years, 59% were women and 31% were African-American (Table 1). The majority of participants had hypertension for ≥ 10 years and was taking 3 or more classes of antihypertensive medications. Compared to the overall CoSMO population, participants with ≥ 8 and ≥ 14 blood pressure measurements were more likely to have diabetes mellitus, a history of myocardial infarction or stroke, a Charlson comorbidity score ≥ 2, and to be taking more antihypertensive medication classes. Digit preference was present in these data. For those with at least 8 blood pressure measurements, 47% of all SBP readings end in zero and 49% of all DBP readings end in zero. Additionally, for those with at least 14 blood pressure measurements, 48% of all SBP readings end in zero and 49% of all DBP readings end in zero Of all SBP recordings, 9% were exactly 140 mmHg, and 5% of all DBP readings were exactly 90 mmHg.

Based on the first 4 measurements, the mean SBP was 135.4 mmHg, the intra-individual standard deviation was 12.2 mmHg and the SDIM was 12.1 mmHg (Table 2). Each VVV metric except SDIM was correlated with mean SBP. Results were similar using the first 7 SBP measurements. The mean DBP, based on the first 4 measurements, was 75.6 mmHg and the intra-individual standard deviation and SDIM were 7.0 mmHg and 7.1 mmHg, respectively. For DBP, only the coefficient of variation was correlated with mean DBP ($\rho = -0.18$). Similar patterns were present when considering the first 7 DBP measurements.

The top panel of Table 3 shows the ICC for the first 4 versus second 4 measurements and first 7 versus second 7 measurements of mean SBP and each VVV metric for SBP. The ICC was highest for comparing the first 4 and second 4 and first 7 and second 7 intra-individual mean SBP levels. For the VVV measures, the ICC was highest for standard deviation of SBP (0.19, 95% CI: 0.13 – 0.25 comparing the first versus second 4 measurements and 0.28, 95% CI: 0.20 – 0.34 for the first versus second 7 measurements). The ICCs for DBP are shown in the bottom panel of Table 3. For DBP, the highest ICC for the VVV measures was for coefficient of variation (0.15, 95% CI: 0.10 – 0.20 comparing the first versus second 4 measurements and 0.21, 95% CI: 0.14 – 0.27 for the first versus second 7 measurements). The ICCs were similar in sensitivity analyses limited to blood pressure measurements taken one or more week apart (Supplemental Table 1). The ICC was higher for VVV metrics calculated using all blood pressure measurements available from two consecutive 18 month time periods (Supplemental Table 2). For example, amongst individuals with 7 or more blood pressure measurements in each time period, the ICC comparing the standard deviation of blood pressure based on all measurements from months 0 to 18 with months 19 through 36 was 0.36 (95% CI: 0.26 – 0.45).

The weighted kappa assessing the concordance of quintile of standard deviation based on the first 7 and second 7 SBP measurements was 0.14 (95% CI: 0.09 – 0.19; Table 4 top panel). The analogous weighted kappa statistic for SDIM was 0.10 (95% CI: 0.05 – 0.15; Table 4 bottom panel). Participants in the highest quintile of standard deviation of SBP based on their first 7 measurements were more likely to be in the highest quintile based on their second 7 measurements (observed-to-expected ratio =1.71, 95% CI: 1.29 – 2.22). The

observed-to-expected ratio for being in the lowest quintile of standard deviation of SBP was 1.40 (95% CI: 1.02 – 1.86). For SDIM, the observed-to-expected ratio for being in the highest quintile was 1.53 (95% CI: 1.14 – 2.03) and for the lowest quintile was 1.24 (95% CI: 0.89 – 1.69).

In unadjusted models, female gender, higher mean SBP and pulse pressure, and the use of angiotensin receptor blockers were associated with lower reproducibility of VVV of blood pressure (Table 5). After adjustment for age, race, and gender, higher mean SBP remained associated with a higher odds ratio for low reproducibility of VVV of blood pressure. Additionally, after adjustment for age, race, gender, and mean SBP, use of angiotensin receptor blockers was associated with an increased odds ratio for low reproducibility.

## DISCUSSION

Data from the current study provide insight into the reliability of VVV calculated based on blood pressure measurements taken for the purpose of providing clinical care. Using blood pressure measurements taken for routine care and not research purposes, intra-individual VVV was not random. Comparing the first and second 7 SBP measurements, the ICC was 0.28 for standard deviation and 0.22 for SDIM. Furthermore, individuals in the highest quintile of VVV based on their initial 7 measurements were significantly more likely to be in the highest VVV quintile based on their second 7 measurements.

The reproducibility of VVV of blood pressure in the current study using non-standardized clinic-based measurements is consistent with results generated from two prior research studies, the UK-TIA and the European Carotid Surgery Trial (ECST)[3]. Participants in UK-TIA and ECST, all of whom had a transient ischemic attack (TIA) or minor ischemic stroke, were followed a mean of 4 and 6.1 years, respectively, with blood pressure measured at regular intervals: every four months in the UK-TIA and at a four month follow-up visit and annually thereafter in ECST. The ICC for standard deviation of SBP based on four measurements was 0.25 and 0.16 in the UK-TIA and ECST, respectively (compared to 0.19 in the current study) and 0.32 and 0.18, respectively, based on 7 measurements (compared to 0.28 in the current study). The current study extends these data from patients with TIA to a population with hypertension and from blood pressure measured as part of a study protocol to measurements taken as part of clinical care. While future studies on the prognostic importance of VVV in outpatient settings on outcomes are needed, the current study provides important new data highlighting the reproducibility of VVV using routine outpatient visit data.

The lower degree of reproducibility for VVV compared to mean SBP identified in the current study has important implications for both future research and, possibly, for patient care. First, studies estimating the risk for outcomes (e.g., stroke) associated with VVV may provide biased estimates[9]. The error involved in estimating mean blood pressure levels based on a single measurement is well established and substantial research has documented the importance of correction for regression dilution[10, 11]. The lower ICC for VVV metrics, compared to mean blood pressure levels, in the current study suggests correction for

regression dilution bias may be important for studies evaluating the relation of VVV with subsequent outcomes.

Second, in the current study, reproducibility of VVV was higher when based on a larger number of measurements. For example, the ICC for standard deviation was 1.19 when based on 4 measurements and 0.28 based on 7 measurements. Therefore, investigators should be cautious in undertaking and interpreting data from studies based on only a few blood pressure measurements per person. In such situations, the lack of an association between VVV and outcomes (e.g., stroke) may be due to an unreliable estimate of VVV. However, as an association between VVV and all-cause mortality has been detected with as few as three blood pressure measurements, understanding the limitations of using few data points requires more study[2].

Third, future studies are needed to determine the optimal number of blood pressure measurements needed to obtain reliable and valid estimates of VVV. In a simulation, Rothwell showed the difference between an individual's observed and true blood pressure differed by level of intra-individual VVV. Also, the absolute difference between observed and true mean blood pressure level was less than 5 mmHg using 5 or more blood pressure measurements[1]. However, the Rothwell study did not address reproducibility of VVV metrics. Using more blood pressure measurements provides a greater degree of reliability[12]. There are limitations to using a greater number of blood pressure measurements to estimate VVV. In the clinical setting, many individuals may have a limited number of blood pressure measurements and, thus, may be excluded from the calculation of VVV. In the current study of hypertensive older adults, those with 14 or more blood pressure measurements had more comorbidities than the population as a whole. Excluding individuals with only a few blood pressure measurements may lead to a smaller study sample which is systematically different from the source population. It would beneficial for future studies to evaluate the optimal number of blood pressure measurements needed to reliably estimate VVV.

With the advent and wider use of electronic medical records and computer applications, the reporting of VVV in routine outpatient settings may be feasible. Calculating VVV in the setting of outpatient care may have important implications. A recent meta-analysis of data from randomized trials comparing antihypertensive regimens (with each other and with placebo) suggested that use of calcium channel blockers and thiazide-type diuretics lead to lower VVV of blood pressure, whereas use of ACE-inhibitors and beta blockers lead to greater variability[13]. If VVV measured in the clinical setting is determined to be related to adverse outcomes and specific antihypertensive medications differentially affect VVV of blood pressure, these findings may impact the approach used for blood pressure measurement and patient monitoring. In those patients with both high average blood pressure levels (i.e. SBP/DBP ≥ 140/90 mmHg) and high VVV of blood pressure, an additional treatment target (i.e., lower VVV of blood pressure) beyond a reduction in average blood pressure may be recommended to reduce their risk for cardiovascular events. Additionally, low medication adherence has been suggested as a possible factor explaining the link between antihypertensive medication use and higher VVV of blood pressure[2]. While there are other biological reasons for high VVV of blood pressure (e.g., arterial

stiffness, inflammation, sympathetic nervous system overactivity), capturing VVV in the outpatient clinical setting may be useful for identifying low antihypertensive medication adherence for some patients[12, 14, 15]. Future research is needed on the relation between VVV and outcomes in the clinic setting.

The goal of the current analysis was to assess the reproducibility of VVV of blood pressure based on measurements taken for patient care. However, there are several important aspects of VVV of blood pressure assessed in clinical practice that were beyond the scope of this analysis. These include assessing the impact of antihypertensive medication adherence, drug classes, and changes in prescription regimen on VVV of blood pressure. Additionally, the association of VVV of blood pressure on outcomes including cardiovascular and renal disease warrants investigation.

The current results should be interpreted in the context of certain limitations. First, while almost all CoSMO participants had blood pressure measurements available, only 772 of the 2,194 CoSMO study participants had 14 or more blood pressure measurements taken during the study period. Second, the CoSMO study was restricted to participants ≥ 65 years of age with hypertension and taking antihypertensive medications. Evaluation of the reproducibility of VVV in younger adults and those without hypertension, especially those not taking antihypertensive medications, is needed. However, studying the reproducibility of VVV in these adults was beyond the scope of the current study. Third, blood pressure measurements were not taken at set time periods and only a median of 2.8 years of blood pressure data (maximum of 4 years) were available. Fourth, only a single blood pressure measurement was recorded in patients' charts for 79% of visits. Having multiple blood pressure measurements at each visit may increase the reproducibility of VVV of blood pressure. Data were not available on whether blood pressure was taken manually or with automated devices. However, at the time of the study, manual blood pressure was the primary mode of measurement in the outpatient clinics. Additionally, the high degree of digit preference also is indicative of manual blood pressure measurement. Prior studies have suggested there is higher reliability in blood pressure measurements, especially among patients with hypertension, when taken by automated measurement devices[16]. Therefore, it can be posited that higher reproducibility will be present when automated devices are used. Future studies of blood pressure measurement technique (manual or automatic) on reproducibility of VVV are needed. Despite these limitations, the current study has several notable strengths. These include a well characterized study population with a substantial number of African-Americans and whites and men and women. Additionally, the results were markedly consistent, regardless of VVV metric analyzed.

Intra-individual VVV derived using outpatient blood pressure measurements taken as part of routine patient care is not a random phenomenon. The level of reproducibility observed in the current study is consistent with data obtained from randomized controlled trials of individuals with cerebrovascular disease wherein blood pressure was measured following protocols at set time intervals. Future studies on the prognostic value of VVV of blood pressure measured for routine outpatient care on cardiovascular and renal disease outcomes are warranted.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Appendix. Formulas used to calculate VVV metrics

| | | |
|---|---|---|
| Formula 1<br>Standard deviation (SD) | $SD = \sqrt{\frac{\sum (x_i - \bar{x})^2}{n-1}}$ | |
| Formula 2<br>Standard deviation independent of the mean (SDIM) | $SDIM = \frac{SD}{\bar{x}_i^{\,a}}$ | [a] is derived by fitting a curve to $SD = k \times x^a$, where k is a constant |
| Formula 3<br>Coefficient of variation (CV) | $CV = \frac{SD}{\bar{x}_i}$ | |
| Formula 4<br>Peak size | $\text{Peak size} = \max x_i - \bar{x}$ | |
| Formula 5<br>Trough size | $\text{Trough size} = \bar{x} - \min x_i$ | |
| Formula 6<br>Successive variation (SV) | $SV = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}\left(B_{i+1} - BP_i\right)^2}$ | where $BP_i$ represents the *ith* BP measure-ment for i = 1, 2, …, n. |
| Formula 7<br>Average real variability (ARV) | $ARV = \frac{1}{n-1}\sum_{i=1}^{n-1} \lvert BP_{i+1} - BP_i \rvert$ | |

An explanation of these metrics is provided in Reference 3 (Howard SC, 2009)

## Abbreviation definition list

| | |
|---|---|
| **VVV** | visit-to-visit variability |
| **SBP** | systolic blood pressure |

| | |
|---|---|
| **CoSMO** | Cohort Study of Medication Adherence among Older Adults |
| **SDIM** | standard deviation independent of the mean |
| **CV** | coefficient of variation |
| **SV** | successive variation |
| **ARV** | average real variability |
| **ICC** | Intraclass correlation coefficient |
| **ECST** | European Carotid Surgery Trial |

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**Table 1**

Characteristics of the overall CoSMO study population and those with 8 or more and 14 or more blood pressure measurements available for analysis.

| | **Overall (n=2,194)** | **At least 8 BP measurements (n=1,580)** | **At least 14 BP measurements (n=772)** |
|---|---|---|---|
| Age, years, mean (SD) | 75.0 (5.6) | 75.2 (5.5) | 75.4 (5.4) |
| Women, % | 59% | 59% | 59% |
| African-American, % | 31% | 32% | 33% |
| Current smoking, % | 6% | 5% | 4% |
| Diabetes mellitus, % | 42% | 45% | 47% |
| History of MI, % | 12% | 13% | 16% |
| History of stroke, % | 13% | 14% | 18% |
| Charlson co-morbidity score ≥ 2, % | 50% | 54% | 63% |
| Hypertension duration ≥ 10 years | 63% | 64% | 67% |
| Anti-hypertensive medication classes | | | |
| Mean (SD) | 2.6 (1.1) | 2.7 (1.2) | 2.9 (1.2) |
| ≥ 3 | 51% | 55% | 63% |

SD – standard deviation, BP – blood pressure, MI –myocardial infarction

## Table 2

Mean values of systolic and diastolic blood pressure variability metrics based on the first four measurements and first seven measurements.

| | Systolic blood pressure | | | | | |
|---|---|---|---|---|---|---|
| | First 4 measurements | | | First 7 measurements | | |
| | Mean ± SD | Correlation with mean | p-value | Mean ± SD | Correlation with mean | p-value |
| Mean | 135.4 ± 12.2 | -- | -- | 135.2 ± 11.7 | -- | -- |
| SD | 12.2 ± 6.4 | 0.29 | <0.001 | 13.5 ± 5.3 | 0.36 | <0.001 |
| SDIM | 12.1 ± 6.0 | −0.02 | 0.500 | 13.4 ± 4.9 | −0.03 | 0.403 |
| CV | 9.0 ± 4.5 | 0.11 | <0.001 | 9.9 ± 3.7 | 0.13 | <0.001 |
| Peak size | 13.9 ± 8.4 | 0.30 | <0.001 | 20.1 ± 9.7 | 0.31 | <0.001 |
| Trough size | 13.2 ± 7.4 | 0.24 | <0.001 | 18.0 ± 7.4 | 0.29 | <0.001 |
| SV | 16.6 ± 9.2 | 0.27 | <0.001 | 17.9 ± 7.8 | 0.33 | <0.001 |
| ARV | 14.5 ± 8.4 | 0.26 | <0.001 | 14.9 ± 6.7 | 0.33 | <0.001 |

| | Diastolic blood pressure | | | | | |
|---|---|---|---|---|---|---|
| | First 4 measurements | | | First 7 measurements | | |
| | Mean ± SD | Correlation with mean | p-value | Mean ± SD | Correlation with mean | p-value |
| Mean | 75.6 ± 7.6 | -- | -- | 74.8 ± 7.1 | -- | -- |
| SD | 7.0 ± 3.4 | 0.04 | 0.154 | 7.7 ± 2.7 | 0.03 | 0.339 |
| SDIM | 7.1 ± 3.4 | −0.03 | 0.165 | 7.8 ± 2.8 | −0.06 | 0.126 |
| CV | 9.3 ± 4.6 | −0.18 | <0.001 | 10.3 ± 3.8 | −0.23 | <0.001 |
| Peak size | 7.7 ± 4.3 | 0.03 | 0.216 | 10.9 ± 5.0 | 0.03 | 0.343 |
| Trough size | 7.7 ± 4.25 | 0.04 | 0.145 | 10.4 ± 4.5 | 0.07 | 0.052 |
| SV | 9.6 ± 5.0 | 0.03 | 0.199 | 10.3 ± 4.1 | 0.01 | 0.702 |
| ARV | 8.3 ± 4.6 | 0.03 | 0.173 | 8.6 ± 3.6 | 0.01 | 0.788 |

SD – standard deviation, SDIM – standard deviation independent of the mean, CV – coefficient of variation, SV – successive variation, ARV – average real variation.

## Table 3

The reproducibility of measures of blood pressure variability based on the first four and second four measurements and the first seven and second seven measurements.

| | Systolic blood pressure | | | |
|---|---|---|---|---|
| | First 4 versus second 4 measurements | | First 7 versus second 7 measurements | |
| | ICC (95% CI) | p-value | ICC (95% CI) | p-value |
| Mean | 0.57 (0.53, 0.60) | <0.001 | 0.64 (0.59, 0.68) | <0.001 |
| SD | 0.19 (0.13, 0.25) | <0.001 | 0.28 (0.20, 0.34) | <0.001 |
| SDIM | 0.13 (0.07, 0.18) | <0.001 | 0.22 (0.15, 0.28) | <0.001 |
| CV | 0.14 (0.09, 0.20) | <0.001 | 0.23 (0.16, 0.29) | <0.001 |
| Peak size | 0.14 (0.08, 0.19) | <0.001 | 0.18 (0.10, 0.25) | <0.001 |
| Trough size | 0.17 (0.11, 0.23) | <0.001 | 0.23 (0.16, 0.29) | <0.001 |
| SV | 0.16 (0.11, 0.22) | <0.001 | 0.26 (0.18, 0.32) | <0.001 |
| ARV | 0.14 (0.09, 0.20) | <0.001 | 0.25 (0.19, 0.32) | <0.001 |

| | Diastolic blood pressure | | | |
|---|---|---|---|---|
| | First 4 versus second 4 measurements | | First 7 versus second 7 measurements | |
| | ICC (95% CI) | p-value | ICC (95% CI) | p-value |
| Mean | 0.66 (0.63, 0.69) | <0.001 | 0.70 (0.65, 0.73) | <0.001 |
| SD | 0.12 (0.07, 0.17) | <0.001 | 0.19 (0.11, 0.26) | <0.001 |
| SDIM | 0.12 (0.07, 0.17) | <0.001 | 0.18 (0.11, 0.25) | <0.001 |
| CV | 0.15 (0.10, 0.20) | <0.001 | 0.21 (0.14, 0.27) | <0.001 |
| Peak size | 0.09 (0.04, 0.14) | <0.001 | 0.14 (0.06, 0.21) | <0.001 |
| Trough size | 0.11 (0.06, 0.16) | <0.001 | 0.11 (0.04, 0.18) | <0.001 |
| SV | 0.11 (0.06, 0.16) | <0.001 | 0.12 (0.04, 0.19) | <0.001 |
| ARV | 0.10 (0.05, 0.15) | <0.001 | 0.11 (0.04, 0.18) | <0.001 |

## Table 4

Cross tabulation of quintiles of standard deviation (top panel) and standard deviation independent of the mean (bottom panel) for systolic blood pressure between the first seven versus second seven measurements.

| | | **Quintile of SD, second 7 SBP measurements** | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | Total |
| Quintile of SD, first 7 SBP measurements | 1 | 43 | 35 | 26 | 33 | 17 | 154 |
| | 2 | 45 | 30 | 27 | 27 | 25 | 154 |
| | 3 | 29 | 32 | 35 | 34 | 27 | 157 |
| | 4 | 24 | 28 | 43 | 25 | 33 | 153 |
| | 5 | 13 | 29 | 24 | 35 | 53 | 154 |
| | Total | 154 | 154 | 155 | 154 | 155 | 772 |

| | | **Quintile of SDIM, second 7 SBP measurements** | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | Total |
| Quintile of SDIM, first 7 SBP measurements | 1 | 38 | 36 | 33 | 30 | 18 | 155 |
| | 2 | 43 | 23 | 31 | 27 | 29 | 153 |
| | 3 | 32 | 30 | 35 | 28 | 31 | 156 |
| | 4 | 23 | 36 | 31 | 35 | 29 | 154 |
| | 5 | 18 | 29 | 25 | 35 | 47 | 154 |
| | Total | 154 | 154 | 155 | 155 | 154 | 772 |

Weighted kappa = 0.14 95% CI = (0.09, 0.19)

Weighted kappa = 0.10 95% CI = (0.05, 0.15)

SBP – systolic blood pressure, SD – standard deviation, SDIM – standard deviation independent of the mean

## Table 5

Association of patient characteristics with low reproducibility of visit-to-visit variability of blood pressure between the first seven versus second seven measurements.

| | Unadjusted | | Adjusted* | |
|---|---|---|---|---|
| | **Odds Ratio (95% CI)** | **p-value** | **Odds Ratio (95% CI)** | **p-value** |
| Age, years | 1.02 (0.99, 1.05) | 0.251 | 1.02 (0.99, 1.06) | 0.261 |
| Women | 1.50 (1.03, 2.17) | 0.034 | 1.31 (0.89, 1.94) | 0.167 |
| African-American | 1.38 (0.96, 1.99) | 0.087 | 1.20 (0.81, 1.77) | 0.370 |
| Mean SBP, mmHg | 1.05 (1.03, 1.06) | <0.001 | 1.04 (1.03, 1.06) | <0.001 |
| Mean pulse pressure, mmHg | 1.04 (1.02, 1.05) | <0.001 | 0.99 (0.96, 1.02) | 0.627 |
| Diabetes mellitus | 0.94 (0.66, 1.33) | 0.717 | 0.95 (0.66, 1.38) | 0.796 |
| History of myocardial infarction | 0.87 (0.53, 1.44) | 0.597 | 0.97 (0.58, 1.64) | 0.914 |
| History of stroke | 0.84 (0.52, 1.37) | 0.488 | 0.95 (0.57, 1.58) | 0.845 |
| History of heart failure | 0.73 (0.38, 1.39) | 0.341 | 0.83 (0.43, 1.62) | 0.585 |
| Antihypertensive medication class | | | | |
| ACE Inhibitors | 0.93 (0.65, 1.33) | 0.691 | 0.97 (0.67, 1.40) | 0.862 |
| Beta blockers | 1.19 (0.83, 1.70) | 0.347 | 1.25 (0.86, 1.82) | 0.234 |
| Calcium channel blockers | 1.29 (0.91, 1.84) | 0.158 | 1.08 (0.74, 1.56) | 0.711 |
| Angiotensin receptor blockers | 1.73 (1.20, 2.50) | 0.004 | 1.58 (1.07, 2.32) | 0.020 |
| Diuretics | 0.93 (0.64, 1.34) | 0.698 | 0.85 (0.58, 1.24) | 0.400 |

Low reproducibility was defined as an absolute difference in the standard deviation of systolic blood pressure ≥ 8 mmHg between the first seven and second measurements. This outcome was observed in 20.0% (N=154) patients.

*Adjusted for age, gender, race, and mean systolic blood pressure