ORIGINAL RESEARCH

Effect of Intensive and Standard Clinic-Based Hypertension Management on the Concordance Between Clinic and Ambulatory Blood Pressure and Blood Pressure Variability in SPRINT

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Background—Blood pressure (BP) varies over time within individual patients and across different BP measurement techniques. The effect of different BP targets on concordance between BP measurements is unknown. The goals of this analysis are to evaluate concordance between (1) clinic and ambulatory BP, (2) clinic visit-to-visit variability and ambulatory BP variability, and (3) first and second ambulatory BP and to evaluate whether different clinic targets affect these relationships.

Methods and Results—The SPRINT (Systolic Blood Pressure Intervention Trial) ambulatory BP monitoring ancillary study obtained ambulatory BP readings in 897 participants at the 27-month follow-up visit and obtained a second reading in 203 participants 293±84 days afterward. There was considerable lack of agreement between clinic and daytime ambulatory systolic BP with wide limits of agreement in Bland-Altman plots of −21 to 34 mm Hg in the intensive-treatment group and −26 to 32 mm Hg in the standard-treatment group. Overall, there was poor agreement between clinic visit-to-visit variability and ambulatory BP variability with correlation coefficients for systolic and diastolic BP all <0.16. We observed a high correlation between first and second ambulatory BP; however, the limits of agreement were wide in both the intensive group (−27 to 21 mm Hg) and the standard group (−23 to 20 mm Hg).

Conclusions—We found low concordance in BP and BP variability between clinic and ambulatory BP and second ambulatory BP. Results did not differ by treatment arm. These results reinforce the need for multiple BP measurements before clinical decision making. **(*J Am Heart Assoc*. 2019;8:e011706. DOI: 10.1161/JAHA.118.011706.)**

Key Words: ambulatory blood pressure monitoring • circadian rhythm • concordance • variability

Hypertension is typically defined in clinical practice and in research settings based on blood pressure (BP) readings during clinic visits. However, BP is a dynamic phenomenon and varies over 24 hours and from day to day, particularly in older adults.[1] BP is variable within an individual patient over time and between measurement techniques

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Accompanying Tables S1 through S7 and Figures S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011706

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Clinical Perspective

What Is New?

- This is the first study to examine the concordance between clinic and ambulatory blood pressure and to evaluate whether different clinic blood pressure targets affect this association.
- Using the Systolic Blood Pressure Intervention Trial cohort, we found low concordance in blood pressure and blood pressure variability between clinic and ambulatory blood pressure measurements.

What Are the Clinical Implications?

- We propose using both clinic and ambulatory blood pressure measurements to diagnose patients with hypertension.
- We emphasize the importance of properly measuring blood pressure and obtaining repeat blood pressure measurements.

obtained within a narrow period of time. Diurnal BP patterns in individual patients are common, reproducible,[2] and have been well characterized using ambulatory BP monitoring (ABPM), a noninvasive technique that provides a 24-hour snapshot of BP and BP variability.[3] Unlike traditional clinic-based BP measurement, which captures BP at 1 clinic visit, ABPM has the ability to assess BP throughout the day and night and provides an assessment of 24-hour variability in BP.

Previous observational studies, mainly in hypertensive patients, have reported that daytime ambulatory BP or home BPs are usually lower than clinic BP measures.[4-6] Several recent studies have found that this association is age dependent; daytime or awake ambulatory BP is more likely to be higher than office BP in adults >50 years of age.[7-9] However, results from a large Spanish ambulatory cohort showed that clinic BP was higher than daytime ambulatory BP at all ages.[10] They also reported that hypertension diagnosis was misclassified in 40% of the cases using clinic BP. These results highlight the importance of out-of-office BP in diagnosing hypertension.

Visit-to-visit variability (VVV) in BP provides a temporal measure of the consistency of BP control and potentially also treatment adherence.[11] Both VVV[12] and, to a lesser extent, ambulatory BP variability[13] have been associated with higher cardiovascular risk. Prior observational studies in people not taking antihypertensive medications[14] and in people treated for hypertension[15,16] have demonstrated a notable lack of strong correlation between VVV and ambulatory BP variability, suggesting that they are related to different aspects of cardiovascular health. These data come from observational studies and do not allow an examination of how different in-clinic targets may differentially affect these metrics of variability.

Additionally, clinic and ambulatory BPs can be used to define normotensive individuals (normal clinic and ambulatory BP) and individuals who experience a white-coat effect (high clinic BP relative to ambulatory BP) or a masked effect (high ambulatory BP relative to clinic BP). These BP categories have clinical significance. Patients with masked hypertension are at a higher risk for adverse clinical events and all-cause mortality than patients with controlled clinic and ambulatory BP and white-coat hypertension.[17] Recent reports have found an independent increased risk for adverse events with white-coat hypertension compared with normotensive participants.[18-21] As with BP variability, the effect of different in-clinic BP targets on white-coat and masked effects is unknown.

The SPRINT (Systolic Blood Pressure Intervention Trial) ABPM ancillary study obtained ambulatory BP readings in a subset of 897 participants in the SPRINT study at selected clinical sites at the 27-month visit; a second ABPM was obtained 3 to 12 months after completion of the first ABPM on a subset of 203 participants.[22] A previous analysis by Drawz et al using the same SPRINT cohort assessed the effect of clinic-based intensive and standard BP-lowering strategies on ambulatory BP. Compared with standard treatment, intensive clinic-based hypertension treatment lowered nighttime systolic BP, daytime systolic BP, and 24 hour systolic BP but did not change the diurnal BP pattern.[22] The goals of this analysis are to evaluate concordance (1) between clinic and ambulatory BP, (2) between VVV and ambulatory BP variability, and (3) between first and second ABPM, and further, to evaluate whether different clinic targets affect these relationships.

Methods

Data Availability

Some anonymized data and materials have been made publicly available through the National Heart, Lung, and Blood Institute at https://biolincc.nhlbi.nih.gov/studies/sprint/ for reproducing/replicating the results of this analysis. The Statistical Analyses section provides details of analytical methods.

Study Participants

Details of the SPRINT study have been published previously.[23,24] SPRINT was a multicenter clinical outcome trial that assigned 9361 participants to intensive BP-lowering treatment (systolic BP target of <120 mm Hg) or standard treatment (systolic BP target of <140 mm Hg). Participants were at least 50 years old with systolic BP 130 to 180 mm Hg, depending on the intensity of antihypertensive treatment at baseline, and were at increased risk of

cardiovascular disease (CVD), defined as established CVD (excluding stroke), age ≥75 years, chronic kidney disease, or a 10-year Framingham CVD risk score of >15%. Exclusion criteria included diabetes mellitus, previous stroke, polycystic kidney disease, symptomatic heart failure in the past 6 months, left ventricular ejection fraction <35%, known cause of secondary hypertension, any organ transplant, severe chronic kidney disease (estimated glomerular filtration rate <20 mL/min per 1.73 m^2), dialysis, proteinuria >1 g/d, dementia, and systolic BP <110 mm Hg after 1 minute of standing. Mean achieved systolic BP in the intensive group was 121.4 mm Hg versus 134.6 mm Hg in the standard group during a median follow-up of 3.26 years.[23]

SPRINT participants were recruited at 15 clinical sites to participate in the ambulatory BP ancillary study at the 27-month follow-up visit. The protocol was approved by the institutional review board at each of the participating sites. Informed consent for the ancillary study was obtained from eligible SPRINT participants. Participants were excluded from the ambulatory BP ancillary study for the following reasons: arm circumference >50 cm, shift worker or work regularly scheduled at night, history of breast cancer requiring mastectomy or radiation on the nondominant arm (to avoid frequent BP measurements in patients with lymphedema), or end-stage renal disease. Clinical and laboratory data were obtained from the 24- and 27-month study visits.[23]

Clinic Blood Pressure Measurement

At each SPRINT visit, trained clinical staff measured BP using an automated oscillometric measurement device (HEM-907 XL, Omron Healthcare, Lake Forest, IL) and standardized procedures.[24] BP measurement requirements included measuring BP early in the visit and not following stressful exam components such as blood draws, proper positioning of the participant in a chair with back support, and proper cuff size determination. The *Manual of Procedures* stated that participants should be resting, not completing questionnaires, and not speaking with study staff during the 5-minute rest period or while BP measurements were being taken. The *Manual of Procedures* recommended that staff should leave the room during the 5-minute rest period but return to take the BPs at the end of the 5-minute rest. The *Manual of Procedures* did not require staff attendance or absence during BP measurement.[25] BP was averaged over 3 consecutive measurements obtained at 1-minute intervals.[24,26]

Ambulatory Blood Pressure Measurement

Ambulatory BP was measured within 3 weeks of the 27-month study visit using SpaceLabs (Snoqualmie, WA) Medical Model 90207 monitors. The monitor was placed on the participants' nondominant arm, measured BP every 30 minutes, and was set so that readings were not displayed. Participants were given written instructions, and staff recorded antihypertensive medication dosage and timing. Based on the British Hypertension Society, a recording was deemed to be acceptable if there were at least 14 readings between 6:00 AM and 12:00 midnight and at least 6 readings between 12:00 midnight and 6:00 AM.[27-30] Consecutive participants who completed the first ABPM were approached to obtain a second measurement at the next follow-up visit. In this convenience sample of 203 participants, the second ABPM was obtained 3 to 12 months after completion of the first ABPM. Nighttime systolic BP was defined as the average of all systolic BP readings during the 1 AM–to–6 AM window; daytime systolic BP was defined as the average of all systolic BP readings during the 9 AM–to–9 PM window.[31] Daytime ambulatory BP was used for primary analyses.

Blood Pressure Variability

For clinic BP, we defined VVV using the average of the 3 BPs measured at each of the 21-month through 33-month clinic visits. We required clinic BP to be measured for at least 4 out of 5 of these visits in order to calculate VVV. VVV was defined as the coefficient of variation (standard deviation of mean BPs from the 21-month through 33-month clinic visits divided by the overall mean BP from all those visits).

For ambulatory BP, variability was defined by coefficient of variation and the average real variability (ARV).[32] ARV is typically utilized to assess changes in BP that occur over short time intervals; it is the average of the absolute difference between consecutive BP readings.

Statistical Analyses

We compared baseline characteristics and BP variability measures between the intensive- and standard-treatment groups. Continuous variables are presented as mean (SD), and categorical variables as n (%). Statistical significance for categorical variables was tested using the chi-squared method and t test for continuous variables. Spearman correlations, Bland-Altman plots, and intraclass correlation coefficients were used to evaluate association, concordance, and agreement, respectively, between clinic and ambulatory BP, clinic VVV and ambulatory variability (ARV and coefficient of variation), and between the first and second ambulatory BP measurements.[33] Bland-Altman plots show the average of 2 measures on the *x*-axis and the difference between the 2 measures on the *y*-axis. This method is used to evaluate agreement between the 2 measurement methods.[33,34]

Table 1. Characteristics of SPRINT Participants in the Ambulatory BP Ancillary Study at the 27-Months SPRINT Study Visit

Variable	Total n=897	Intensive n=453	Standard n=444	*P* Value
Age, y (27 mo)	71.5 (9.5)	71.6 (9.3)	71.5 (9.7)	0.898
Female	257 (28.6%)	132 (29.1%)	125 (28.2%)	0.801
Race				0.502
Black	251 (27.9%)	124 (27.9%)	127 (28.0%)	
White	604 (67.3%)	304 (68.4%)	300 (66.2%)	
Other	21 (2.3%)	8 (1.8%)	13 (2.9%)	
Hispanic	21 (2.3%)	8 (1.8%)	13 (2.9%)	
Body mass index, kg/m^2 (24 mo)	29.5 (5.6)	29.6 (5.7)	29.4 (5.5)	0.57
Smoking				0.597
Never	414 (46.2%)	210 (46.5%)	204 (45.9%)	
Former	391 (43.6%)	192 (42.5%)	199 (44.8%)	
Current	91 (10.1%)	50 (9.2%)	41 (11.1%)	
Alcohol				0.098
Heavy drinker	103 (11.5%)	43 (9.5%)	60 (13.5%)	
Light drinker	180 (20.1%)	91 (20.1%)	89 (20.0%)	
Moderate drinker	216 (24.1%)	31 (6.8%)	18 (14.1%)	
Nondrinker	349 (38.9%)	171 (37.7%)	178 (40.1%)	
Unknown	49 (5.5%)	31 (6.8%)	18 (4.1%)	
History of CVD, baseline	195 (21.7%)	94 (20.8%)	101 (22.7%)	0.520
Experienced CVD event before ABPM*	29 (3.2%)	15 (3.3%)	14 (3.2%)	1.000
Diabetes mellitus	21 (2.3%)	9 (2%)	12 (2.7%)	0.625
Stroke	1 (0.1%)	1 (0.2%)	0 (0.0)	1.000
Cancer	129 (14.4%)	61 (13.5%)	68 (15.3%)	0.488
eGFR, mL/min per 1.73 m^2 (24 mo)	70.3 (20.9)	67.3 (20.2)	73.4 (21.1)	<0.001
Urine albumin/creatinine, mg/g (24 mo)	8.8 [5.4–20.6]	7.9 [4.9–15.2]	10.6 [6.1–28.4]	<0.001
Number of antihypertensive medications (27 mo)	2.3 (1.3)	2.9 (1.2)	1.8 (1.1)	<0.001
β blocker	307 (34.3%)	182 (40.2%)	125 (28.2%)	<0.001
Calcium channel blockers	416 (46.4%)	271 (59.8%)	145 (32.7%)	<0.001
ACE inhibitors	291 (32.5%)	163 (36%)	128 (28.9%)	0.023
Angiotensin receptor blockers	331 (36.9%)	190 (41.9%)	141 (31.8%)	0.002
α blockers	80 (8.9%)	47 (10.4%)	33 (7.4%)	0.156
Diuretics	530 (59.2%)	342 (75.5%)	188 (42.4%)	<0.001
Vasodilators	36 (4%)	26 (5.7%)	10 (2.3%)	0.013

Continuous variables presented as mean (SD), categorical variables as n (%), $P<0.05$ considered statistically significant; 24 mo indicates data collected at 24-month annual visit; 27 mo, data collected at 27-month study visit; ABPM indicates ambulatory blood pressure monitoring; ACE, angiotensin-converting enzyme; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SPRINT, Systolic Blood Pressure Intervention Trial.
*After randomization; eGFR based on the Modification of Diet in Renal Disease study equation.

Agreement can be assessed based on the average and the 95% limits of agreement, which are 1.96 times the standard deviation of the differences between the 2 measurements. A priori, we considered any mean difference >|5| mm Hg to be clinically significant and to demonstrate wide variation. The difference between clinic BP and daytime ambulatory BP by treatment group was evaluated using linear regression, adjusting for clinic site. In secondary analyses we adjusted for potential confounders of the association between difference in clinic and daytime ambulatory BP and treatment arm. These included estimated glomerular filtration rate, age, sex, and race. Additionally, a test for interaction was performed

to examine effect modification by each of these variables. We conducted further analysis looking into the difference between clinic BP and daytime ambulatory BP in the prespecified subgroups for SPRINT: previous chronic kidney disease (estimated glomerular filtration rate based on the Modification of Diet in Renal Disease study equation <60 mL/min per 1.73 m^2), sex, race (black versus nonblack), previous CVD, and baseline systolic BP tertiles (<133, 133 to <145, or ≥145 mm Hg). In sensitivity analysis the κ statistic, a measure of the agreement for categorization of BP (masked, white-coat, controlled and sustained hypertension) at times of first ABPM and second ABPM, was calculated. κ values of 0.4 to 0.6, 0.6 to 0.8, and 0.8 to 1 indicate moderate, substantial, and almost perfect agreement, respectively.[35] Statistical analyses were conducted using RStudio (RStudio: Integrated Development for R. RStudio, Inc., Boston, MA, Version 3.0).

Results

We included 897 SPRINT participants who had acceptable ABPM readings, of whom 453 were in the intensive-treatment group and 444 in the standard-treatment group. Characteristics of participants are shown in Table 1. Overall, at the time of the first ABPM, participants averaged 71.5 years of age; 28.6% were female, and 28% were black. There were no differences in baseline demographic characteristics. Participants in the intensive-treatment group were on more antihypertensive medications at the 27-month visit. As expected, participants in the intensive-treatment group at the time of ABPM had lower clinic and 24 hour ambulatory BP (Table S1). In addition, participants in the intensive-treatment group had a lower estimated glomerular filtration rate (mean 67.3 versus 73.4 mL/min per 1.73 m^2, $P<0.0001$) and a lower urine albumin-to-creatinine ratio (median 7.9 versus 10.6 mg/g, $P<0.0001$) at the visit before ABPM. Baseline characteristics were similar between participants who had ABPM measured compared with those who did not and between participants who had a second ABPM compared with only 1 ABPM measurement (Table S2).[22] Of note, 57% (511/897), 33.8% (303/897), and 9.2% (83/897) of the participants had their clinic BPs taken when study staff were never in the room (unattended), when study staff were in the room during BP measurement and resting period (attended), and when study staff were not in the room during the resting period but were in the room during BP measurement (Table S3). Clinic BP did not differ among these different clinic measurement techniques in the overall cohort and in each of the treatment arms.

Concordance Between Clinic and Ambulatory Blood Pressure

There was poor agreement between daytime systolic ambulatory BP and 27-month clinic systolic BP as indicated by a

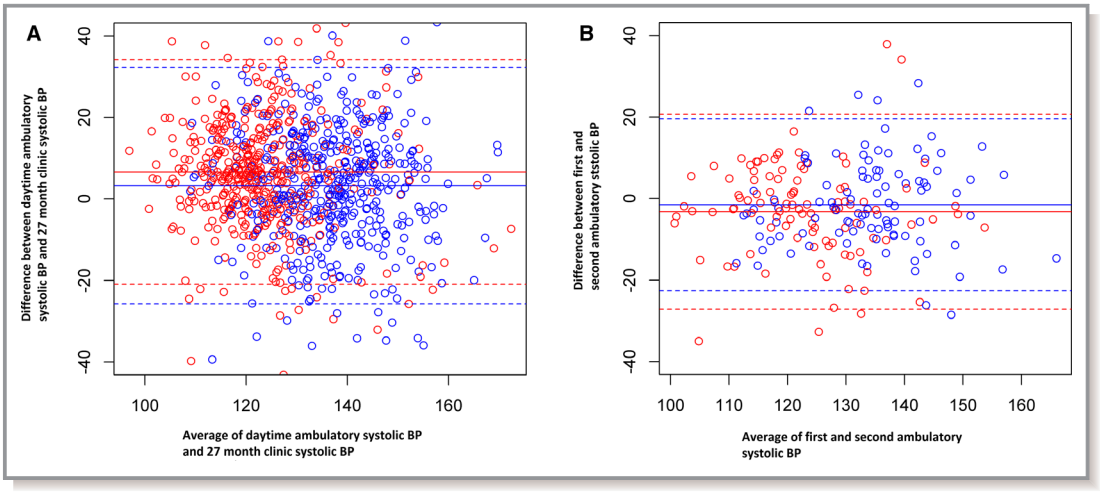

Figure 1. **A**, Bland-Altman plot comparing 27-month clinic SBP to daytime ambulatory SBP. Solid lines represent mean difference in blood pressure, and dashed lines represent limits of agreement (±1.96×SD of difference). Red represents intensive-treatment arm; blue represents the standard-treatment arm. Bland-Altman plots indicate poor agreement with limits of agreement ranging from −20.94 to 34.21 mm Hg for the intensive-treatment group and −25.74 to 32.26 mm Hg for the standard-treatment group. **B**, Bland-Altman plot comparing first ambulatory SBP to second ambulatory SBP. Solid lines represent mean difference in blood pressure, and dashed lines represent limits of agreement (±1.96×SD of difference). Red represents intensive-treatment arm; blue represents the standard-treatment arm. Bland-Altman plots indicate poor agreement with limits of agreement ranging from −27.16 to 20.72 mm Hg for the intensive-treatment group and −22.62 to 19.60 mm Hg for the standard-treatment group. BP indicates blood pressure.

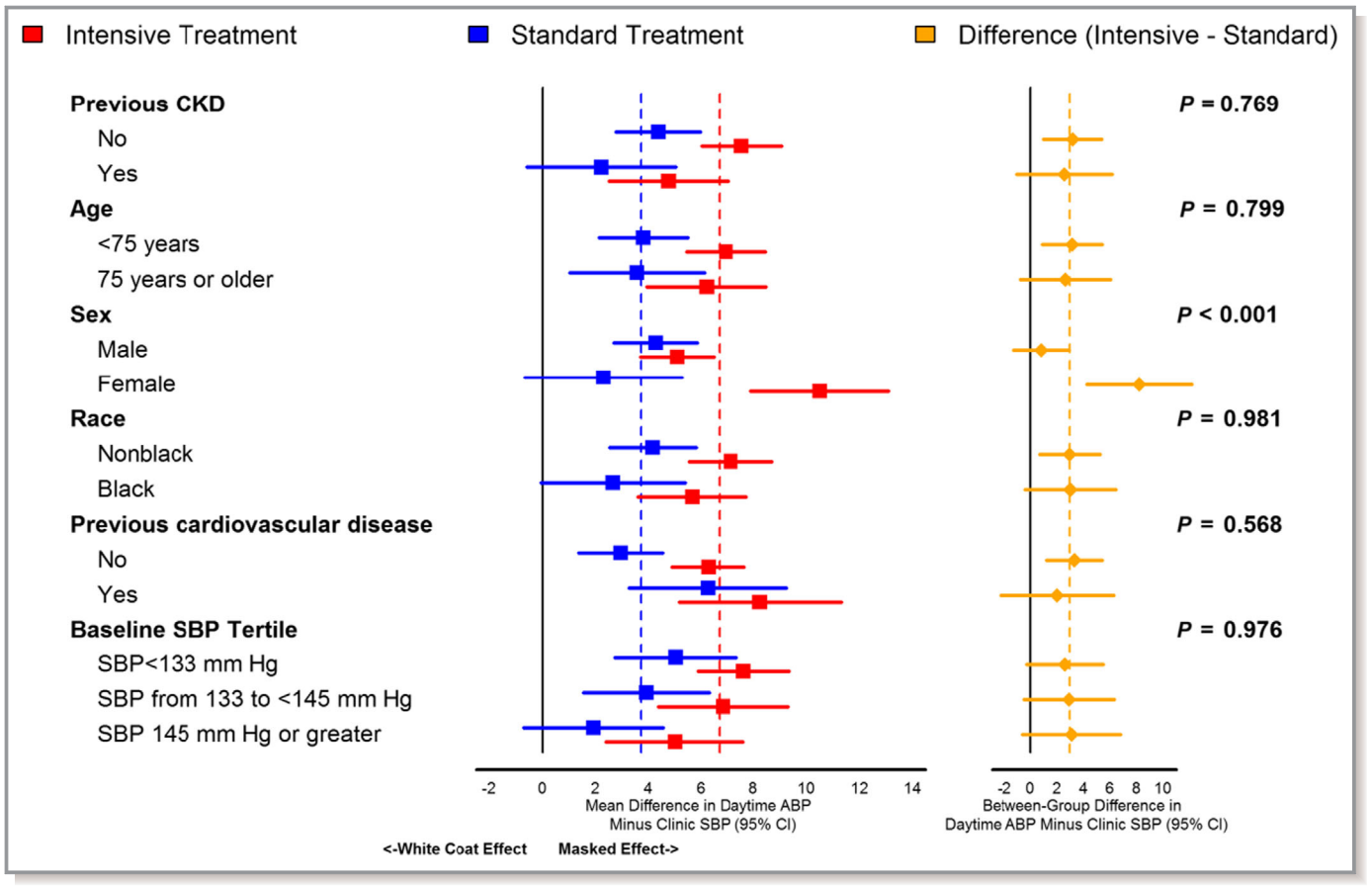

Figure 2. Difference between daytime ambulatory systolic blood pressure (BP) and clinic systolic BP by subgroups in the standard and intensive treatment groups. ABP indicates ambulatory BP; CKD, chronic kidney disease; SBP, systolic BP.

Bland-Altman plot with limits of agreement ranging from −21 to 34 mm Hg for the intensive-treatment group and −26 to 32 mm Hg for the standard-treatment group (Figure 1A). Intraclass correlation coefficient comparing daytime systolic ambulatory BP and 27-month clinic systolic BP was 0.31 (95% CI 0.22-0.29) in the intensive-treatment arm and 0.35 (95% CI 0.27-0.43) in the standard-treatment arm, indicating poor agreement. We observed a masked effect in the intensive-treatment group where the daytime ambulatory systolic BP was 6.6 mm Hg higher than clinic systolic BP. In the standard-treatment group there was a small, masked effect as well (daytime ambulatory systolic BP 3.3 mm Hg higher than clinic systolic BP; Figure S1). Similarly, in adjusted analyses, we observed a greater difference between ambulatory and clinic BP in the intensive-treatment group compared with the standard-treatment group (Table S4). Similar results were observed in each of the following subgroup categories: age above and below 75 years, history of chronic kidney disease at baseline, race, previous CVD, and baseline systolic BP tertile (Figure 2). However, this difference between ambulatory and clinic systolic BP across treatment groups differed by sex, with a more pronounced masked effect among women in the intensive group (Figure 2).

Clinic and Ambulatory Blood Pressure Variability

Overall, there was poor agreement between clinic VVV and ambulatory BP variability, as measured by the coefficient of

Table 2. Correlation Between Ambulatory Blood Pressure and Clinic Visit to Visit Variability

	ABPM ARV-Systolic BP	ABPM ARV-Diastolic BP	ABPM Coefficient of Variation-Systolic BP	ABPM Coefficient of Variation-Diastolic BP
VVV-systolic BP	0.13*	−0.0001	0.064	0.024
VVV-diastolic BP	0.16*	−0.039	0.071*	0.035

ABPM indicates ambulatory blood pressure monitor; ARV, average real variability; BP, blood pressure in mm Hg; coefficient of variation, SD of mean BP/mean BP; VVV, visit-to-visit variability.
*Significant values (P<0.05).

Table 3. Clinic and Ambulatory Variability Results at 27 Months

	Intensive	Standard	*P* Value
Clinic			
VVV between 21 to 33 months visits*			
Clinic systolic BP	0.08 [9.6/118.6]	0.08 [10.7/135.6]	0.796†
Clinic diastolic BP	0.15 [9.6/65.9]	0.15 [10.7/73.9]	0.567†
Ambulatory blood pressure			
24 hour ARV‡			
Systolic BP	9.91 (2.18)	10.44 (2.23)	0.00015†
Diastolic BP	7.35 (1.60)	7.79 (1.81)	0.00023†
Coefficient of variation (24 h)‡			
Systolic BP	0.11 (0.03)	0.11 (0.03)	0.819†
Diastolic BP	0.14 (0.04)	0.14 (0.04)	0.384†

*Values presented as VVV mean value [standard deviation of mean BPs from 21-month to 33-month clinic visit/mean overall mean of BP from 21-months to 33-months visits]. All values presented as mean (SD).
‡ARV indicates average real variability (average of the absolute difference between consecutive BP readings); BP, blood pressure in mm Hg; coefficient of variation, SD of mean BP/mean BP; VVV, visit-to-visit variability (standard deviation of mean BPs from the 21-month through 33-month clinic visits divided by the overall mean BP from those visits).
†*P*-values from t test of the log-transformed values.

variation and ARV, respectively: correlation coefficients are all ≤0.16 (Table 2). The results were consistent when analyzed within randomized groups (Tables S5 and S6). Clinic BP variability and ambulatory BP coefficient of variation did not differ between treatment groups; however, ambulatory BP ARV was significantly higher in the standard-treatment group compared with the intensive-treatment group (Table 3).

Concordance Between First and Second ABPM

In the 203 participants with a second ABPM, the average time between ABPM measurements was 293±84 days. We found a relatively high correlation between 24-hour ambulatory systolic BP at 27 months and the second ABPM for both the intensive- and standard-treatment groups (Table S7). However, Bland-Altman plots show that the limit of agreement ranged from −27 to 21 mm Hg for the intensive-treatment group (mean difference=−3.2 mm Hg) and −23 to 20 mm Hg for the standard-treatment group (mean difference=−1.5 mm Hg) (Figure 1B). Intraclass correlation coefficient comparing first and second ambulatory systolic BP was 0.50, 95% CI (0.34-0.63) in the intensive-treatment arm and 0.61, 95% CI (0.47-0.72) in the standard-treatment arm, indicating moderate agreement. The results were similar for diastolic and daytime ambulatory BPs. The time difference between the first and second ABPM was not significantly associated with BP difference between the first and second ABPM.

In sensitivity analysis we found that BP categorization (masked, white-coat, controlled, and sustained hypertension) did not remain stable between the time of the first and second ABPM, κ=0.38 (95% CI 0.28–0.48) (Figure S2). For instance, of 57 participants with masked hypertension in the first ABPM, 28 maintained that categorization in the second ABPM. The κ remained the same irrespective of the time between ABPMs.

Discussion

Our results demonstrate low concordance between clinic and ambulatory BP as well as low concordance between clinic and ambulatory BP variability. In addition, there was poor agreement in both treatment groups between the first and second ABPMs, which occurred on average 293 days apart. Our study also demonstrated a more pronounced masked effect in the intensive-treatment arm compared with the standard-treatment arm.

Multiple factors affect BP measurement reproducibility and level of agreement, including BP technique, device accuracy, setting, and patient factors.[36,37] Inaccuracy of BP measurements could lead to misclassification of BP control, which is particularly significant for patients who are on treatment or near diagnostic thresholds. Accurate BP measurement is also of increasing importance given new guidelines recommending a lower threshold to treat and target systolic BP of ≤130 mm Hg.[38] This lower threshold is closer to the peak of the bell curve of routine clinic BPs and therefore increases the number of patients whose true BP is within 5 to 10 mm Hg of the threshold. We demonstrated poor concordance between carefully measured clinic and ambulatory BP and BP variability as well as between 2 ambulatory BP

measurements. These results demonstrate the variable nature of BP and reinforce the recommendation from the American College of Cardiology/American Heart Association Task Force to utilize an average of ≥2 readings obtained on ≥2 occasions to estimate an individual's level of BP.[38]

Individuals with masked hypertension, both treated and untreated, are associated with increased CVD risk compared with normotensive individuals.[18,39] Observational studies have shown that 25% of patients with high clinic BP have normal BP outside of clinic, known as "white-coat hypertension."[36] Most studies have demonstrated that patients with white-coat hypertension are at low risk of adverse events; however, several recent reports have found that individuals with white-coat hypertension are at increased risk for cardiovascular disease and all-cause mortality.[18-21] The United States Preventive Services Task Force and the recent American College of Cardiology/American Heart Association guidelines recommend measurement of home or ambulatory BP in patients with high clinic BP to confirm the diagnosis of hypertension before starting treatment (grade A recommendation).[38,40,41] The effect of different clinic BP targets on white-coat and masked effects was unknown before SPRINT. We have shown that there was a more pronounced masked effect in the intensive-treatment arm compared with the standard-treatment arm. However, this observation is based on only 1 ABPM; categorization of white-coat hypertension may vary over time for ≈25% of patients.[42]

Previous studies have shown that BP reduction is greater for clinic BP than ambulatory BP.[43] A recent meta-analysis of 52 studies with 9500 patients by Soranna et al studied the differences in BP reduction on office and ambulatory BP.[44] They confirmed previous findings in which clinic BP was reduced by 33% to 36% more than ambulatory BPs. The authors conclude that this difference is not a fixed ratio; rather, it differs by patient characteristics. They cite 3 possible reasons for antihypertensive treatment affecting BP differently, including (1) white-coat effect varying among patients and affecting only office BP, (2) BP reduction being directly related to baseline BP, and (3) regression to the mean that affects office BP readings more than several ambulatory BP readings.[44] These findings could possibly explain why we found a masked effect in both treatment groups, as clinic BP is more likely to decrease than ambulatory BP with antihypertensive treatment.

In our analyses, despite a relatively high correlation between first and second ambulatory BPs, we observed wide limits of agreement in both treatment arms. This discordance between correlation and limits of agreement can be observed when there is a wide range of values because they measure 2 different constructs: association and concordance, respectively. Time difference between ABPMs did not affect BP differences between measurements. We also found that BP categorization did not remain stable between the first and second ABPM (κ=0.38). Our results are consistent with that of Ben-Dov et al. They found that among 196 subjects who underwent a second ABPM within a mean interval of 1.5 years, diagnosis of white-coat and masked hypertension were reasonably reproducible (test-retest agreement for BP was good, κ=0.64).[45] Current recommendations are for repeat ABPM within 6 to 8 months in patients with white-coat hypertension.[46] Other studies found that masked hypertension seems to have fair reproducibility when assessed using ABPM and office BP measures 1 week apart in untreated borderline hypertensive patients.[47,48] De la Sierra et al report that BP phenotypes (both masked and white-coat hypertensive) are only reproducible over the short term (during 1 week) and shift to sustained hypertension over long term follow up among untreated patients.[49]

The strengths of our study include the ability to demonstrate the impact of different BP targets on concordance between ABPM and clinic BP and BP variability by using a relatively large subset from a randomized clinical trial with diverse participants. Also, the availability of a second ambulatory BP measurement allowed us to assess concordance between 2 ABPMs at 2 different clinic BP targets. Our study had several limitations, including that ambulatory BP was not measured at the baseline SPRINT visit, which therefore limited our ability to assess ambulatory BP trajectories within each treatment group. Only a subset of SPRINT subjects participated in the SPRINT ancillary study, and of those, 23% had a second ABPM; this may limit the generalizability of our results and increased variability of our estimates. However, participants included in the ancillary study had generally similar baseline characteristics to those who were not part of the ancillary study, and participants who had a second ABPM were generally similar to those who only had 1 ABPM (Table S2).[22] Furthermore, one of the inherent limitations of the standard ABPM protocols is that BP is measured every 30 minutes, an interval that does not allow for assessment of beat-to-beat BP variability. This lack of beat-to-beat assessment may explain the observed lack of concordance between clinic and ambulatory BP variabilities. Our results are still subject to selection bias, as participants were not randomized to participate in the ancillary study. Additionally, acceptable readings were consistent with the British Hypertension Society (14 valid daytime readings and 6 valid nighttime readings) rather than using 20 valid daytime and 7 valid nighttime as recommended by the European Society of Hypertension.[29,31] However, 95% of our participants had more than 70% valid readings and >20 daytime readings and >7 nighttime readings, as recommended by the European Society of Hypertension. In SPRINT, whether BP measurement was attended or unattended, there was no evidence that attendance led to lower clinic BP measurements at baseline or follow-up. The difference in systolic BP between

standard and intensive groups was the same regardless of staff attendance.[25] These results emphasize that proper BP technique (trained staff, proper cuff size, quiet rest period, using validated automated BP device) is more important than staff attendance. Therefore, we conclude that staff attendance likely did not affect our results.

We conclude that in the SPRINT ambulatory BP ancillary study there was low concordance in BP and BP variability between clinic and ambulatory BP and between 2 separate ambulatory BPs. Results were consistent in the intensive- and standard-treatment groups. These results highlight the variability in BP and the importance of obtaining BP measurements on multiple occasions for diagnosing and treating hypertension. It is reasonable to obtain out-of-office BPs to identify patients with masked and white-coat hypertension as recommended by the United States Preventive Services Task Force and the American College of Cardiology/American Heart Association guidelines. It is also more practical to obtain repeated measures with home BPs versus ABPM.

Perspectives

The effect of different BP targets on concordance between clinic and ambulatory BP is unknown. The SPRINT ambulatory BP ancillary study provides evidence of poor concordance between clinic and ambulatory BP in the intensive- and the standard-treatment groups. There was also poor agreement between clinic visit-to-visit variability and ambulatory BP variability with correlation coefficients for systolic and diastolic BP <0.16. Although the 2 ambulatory BP measurements were highly correlated, there were wide limits of agreement of −27 to −21 mm Hg in the intensive group and −23 to −20 mm Hg in the standard-treatment arm. In conclusion, the SPRINT ambulatory BP ancillary study demonstrated that there was low concordance in BP and BP variability between clinic and ambulatory BP irrespective of treatment target. This emphasizes the need to properly measure BP and to obtain repeat BP measurements and argues for using both clinic and out-of-clinic BP to classify patients before diagnosing hypertension and determining the best course of treatment. We are unable to make specific recommendations on the number of separate occasions BP should be measured to correctly classify patients' "true" BP. Future analyses will compare BP measurements taken in routine clinical settings to BPs obtained in the research setting. Also, studies are needed to determine the number of high BP readings in clinical practice that typically trigger physicians to intensify therapy.

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Disclosures

None.

References

1. Mancia G. Short- and long-term blood pressure variability: present and future. *Hypertension*. 2012;60:512–517.
2. Wendelin-Saarenhovi M, Isoaho R, Hartiala J, Helenius H, Kivelä SL, Hietanen E. Long-term reproducibility of ambulatory blood pressure in unselected elderly subjects. *Clin Physiol*. 2001;21:316–322.
3. Li Y, Wang JG, Dolan E, Gao PJ, Guo HF, Nawrot T, Stanton AV, Zhu DL, O'Brien E, Staessen JA. Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. *Hypertension*. 2006;47:359–364.
4. Little P, Barnett J, Barnsley L, Marjoram J, Fitzgerald-Barron A, Mant D. Comparison of agreement between different measures of blood pressure in primary care and daytime ambulatory blood pressure. *BMJ*. 2002;325:254.
5. Staessen JA, Bieniaszewski L, O'Brien ET, Imai Y, Fagard R. An epidemiological approach to ambulatory blood pressure monitoring: the Belgian Population Study. *Blood Press Monit*. 1996;1:13–26.
6. Mancia G, Sega R, Bravi C, De Vito G, Valagussa F, Cesana G, Zanchetti A. Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens*. 1995;13:1377–1390.
7. Ishikawa J, Ishikawa Y, Edmondson D, Pickering TG, Schwartz JE. Age and the difference between awake ambulatory blood pressure and office blood pressure: a meta-analysis. *Blood Press Monit*. 2011;16:159–167.
8. Conen D, Aeschbacher S, Thijs L, Li Y, Boggia J, Asayama K, Hansen TW, Kikuya M, Björklund-Bodegård K, Ohkubo T, Jeppesen J, Gu YM, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Schoen T, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Mena L, Maestre GE, Filipovský J, Imai Y, O'Brien E, Wang JG, Risch L, Staessen JA. Age-specific differences between conventional and ambulatory daytime blood pressure values. *Hypertension*. 2014;64:1073–1079.
9. Stergiou GS, Ntineri A, Kollias A, Destounis A, Nasothimiou E, Roussias L. Changing relationship among clinic, home, and ambulatory blood pressure with increasing age. *J Am Soc Hypertens*. 2015;9:544–552.
10. Banegas JR, Ruilope LM, de la Sierra A, Vinyoles E, Gorostidi M, de la Cruz JJ, Segura J, Oliveras A, Martell N, García-Puig J, Williams B. Clinic versus daytime ambulatory blood pressure difference in hypertensive patients: the impact of age and clinic blood pressure. *Hypertension*. 2017;69:211–219.
11. Mancia G. Visit-to-visit blood pressure variability: an insight into the mechanisms. *Hypertension*. 2016;68:32–33.
12. Muntner P, Whittle J, Lynch AI, Colantonio LD, Simpson LM, Einhorn PT, Levitan EB, Whelton PK, Cushman WC, Louis GT, Davis BR, Oparil S. Visit-to-visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality: a cohort study. *Ann Intern Med*. 2015;163:329–338.
13. Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, Richart T, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Wang J, Ibsen H, O'Brien E, Staessen JA; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension*. 2010;55:1049–1057.
14. Muntner P, Shimbo D, Diaz KM, Newman J, Sloan RP, Schwartz JE. Low correlation between visit-to-visit variability and 24-h variability of blood pressure. *Hypertens Res*. 2013;36:940–946.
15. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905.
16. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability in the European Lacidipine Study on Atherosclerosis: methodological aspects and effects of antihypertensive treatment. *J Hypertens*. 2012;30:1241–1251.
17. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. *J Hypertens*. 2007;25:2193–2198.
18. Banegas JR, Ruilope LM, de la Sierra A, Vinyoles E, Gorostidi M, de la Cruz JJ, Ruiz-Hurtado G, Segura J, Rodríguez-Artalejo F, Williams B. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med*. 2018;378:1509–1520.
19. Ntineri A, Kalogeropoulos PG, Kyriakoulis KG, Aissopou EK, Thomopoulou G, Kollias A, Stergiou GS. Prognostic value of average home blood pressure and variability: 19-year follow-up of the Didima study. *J Hypertens*. 2018;36:69–76.
20. Tientcheu D, Ayers C, Das SR, McGuire DK, de Lemos JA, Khera A, Kaplan N, Victor R, Vongpatanasin W. Target organ complications and cardiovascular events associated with masked hypertension and white-coat hypertension: analysis from the Dallas Heart Study. *J Am Coll Cardiol*. 2015;66:2159–2169.
21. Kushiro T, Kario K, Saito I, Teramukai S, Sato Y, Okuda Y, Shimada K. Increased cardiovascular risk of treated white coat and masked hypertension in patients with diabetes and chronic kidney disease: the HONEST Study. *Hypertens Res*. 2017;40:87–95.
22. Drawz PE, Pajewski NM, Bates JT, Bello NA, Cushman WC, Dwyer JP, Fine LJ, Goff DC, Haley WE, Krousel-Wood M, McWilliams A, Rifkin DE, Slinin Y, Taylor A, Townsend R, Wall B, Wright JT, Rahman M. Effect of intensive versus standard clinic-based hypertension management on ambulatory blood pressure: results from the SPRINT (Systolic Blood Pressure Intervention Trial) ambulatory blood pressure study. *Hypertension*. 2017;69:42–50.
23. Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
24. Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, Fine LJ, Goff DC, Johnson KC, Killeen AA, Lewis CE, Oparil S, Reboussin DM, Rocco MV, Snyder JK, Williamson JD, Wright JT, Whelton PK. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials*. 2014;11:532–546.
25. Johnson KC, Whelton PK, Cushman WC, Cutler JA, Evans GW, Snyder JK, Ambrosius WT, Beddhu S, Cheung AK, Fine LJ, Lewis CE, Rahman M, Reboussin DM, Rocco MV, Oparil S, Wright JT. Blood pressure measurement in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension*. 2018;71:848–857.
26. Excerpt from the SPRINT Manual of Procedures. November 1, 2010. Available at: https://www.sprinttrial.org/public/MOP_Excerpt_about_BP_Measurement.pdf. Accessed July 10, 2018.
27. Drawz PE, Alper AB, Anderson AH, Brecklin CS, Charleston J, Chen J, Deo R, Fischer MJ, He J, Hsu CY, Huan Y, Keane MG, Kusek JW, Makos GK, Miller ER, Soliman EZ, Steigerwalt SP, Taliercio JJ, Townsend RR, Weir MR, Wright JT, Xie D, Rahman M; Chronic Renal Insufficiency Cohort Study Investigators. Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. *Clin J Am Soc Nephrol*. 2016;11:642–652.
28. Gabbai FB, Rahman M, Hu B, Appel LJ, Charleston J, Contreras G, Faulkner ML, Hiremath L, Jamerson KA, Lea JP, Lipkowitz MS, Pogue VA, Rostand SG, Smogorzewski MJ, Wright JT, Greene T, Gassman J, Wang X, Phillips RA. Relationship between ambulatory BP and clinical outcomes in patients with hypertensive CKD. *Clin J Am Soc Nephrol*. 2012;7:1770–1776.
29. O'Brien E, Coats A, Owens P, Petrie J, Padfield PL, Littler WA, de Swiet M, Mee F. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. *BMJ*. 2000;320:1128–1134.
30. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens*. 2003;21:821–848.
31. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Lurbe E, Mallion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Omboni S, Palatini P, Redon J, Ruilope LM, Shennan A, Staessen JA, vanMontfrans G, Verdecchia P, Waeber B, Wang J, Zanchetti A, Zhang Y; European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens*. 2014;32:1359–1366.
32. Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens*. 2005;23:505–511.
33. Bland JM, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. *Lancet*. 1995;346:1085–1087.
34. Myles PS, Cui J. Using the Bland-Altman method to measure agreement with repeated measures. *Br J Anaesth*. 2007;99:309–311.
35. McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, Guyatt G; for the Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic). *CMAJ*. 2004;171:1369–1373.
36. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart

Association Council on High Blood Pressure Research. *Hypertension*. 2005;45:142–161.

37. Vinyoles E, Blancafort X, López-Quiñones C, Arqué M, Brau A, Cerdán N, de la Figuera M, Díaz F, Pujol E. Blood pressure measurement in an ambulatory setting: concordance between physician and patient self-measurement. *J Hum Hypertens*. 2003;17:45–50.
38. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD, Wright JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324.
39. Stergiou GS, Asayama K, Thijs L, Kollias A, Niiranen TJ, Hozawa A, Boggia J, Johansson JK, Ohkubo T, Tsuji I, Jula AM, Imai Y, Staessen JA; International Database on HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) Investigators. Prognosis of white-coat and masked hypertension: International Database of Home blood pressure in relation to Cardiovascular Outcome. *Hypertension*. 2014;63:675–682.
40. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Whitlock EP. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2015;162:192–204.
41. Siu AL; US Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;163:778–786.
42. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Grant FC, Kaczorowski J. Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: randomised parallel design controlled trial. *BMJ*. 2011;342:d286.
43. Mancia G, Parati G. Office compared with ambulatory blood pressure in assessing response to antihypertensive treatment: a meta-analysis. *J Hypertens*. 2004;22:435–445.
44. Soranna D, Zambon A, Corrao G, Zanchetti A, Parati G, Mancia G. Different effects of antihypertensive treatment on office and ambulatory blood pressure: a meta-analysis. *J Hypertens*. 2019;37:467–475.
45. Ben-Dov IZ, Ben-Arie L, Mekler J, Bursztyn M. Reproducibility of white-coat and masked hypertension in ambulatory BP monitoring. *Int J Cardiol*. 2007;117:355–359.
46. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; European Society of Hypertension Working Group on Blood Pressure Monitoring. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens*. 2005;23:697–701.
47. Viera AJ, Hinderliter AL, Kshirsagar AV, Fine J, Dominik R. Reproducibility of masked hypertension in adults with untreated borderline office blood pressure: comparison of ambulatory and home monitoring. *Am J Hypertens*. 2010;23:1190–1197.
48. Viera AJ, Lin FC, Tuttle LA, Olsson E, Stankevitz K, Girdler SS, Klein JL, Hinderliter AL. Reproducibility of masked hypertension among adults 30 years or older. *Blood Press Monit*. 2014;19:208–215.
49. de la Sierra A, Vinyoles E, Banegas JR, Parati G, de la Cruz JJ, Gorostidi M, Segura J, Ruilope LM. Short-term and long-term reproducibility of hypertension phenotypes obtained by office and ambulatory blood pressure measurements. *J Clin Hypertens (Greenwich)*. 2016;18:927–933.

Supplemental Material

Table S1. Clinic and Ambulatory Blood Pressure Results.

Variable, mean (sd)	Total n= 897	Intensive n= 453	Standard n= 444	p-value
Blood Pressure				
27 mo clinic systolic BP	127.6 (15.6)	119.9 (13.3)	135.5 (13.7)	<0.001
27 mo clinic diastolic BP	69.7 (12)	65.9 (10.5)	73.6 (12.2)	<0.001
24-hr systolic BP	128.3 (13.2)	122.7 (12)	134 (11.8)	<0.001
24-hr diastolic BP	71.7 (9.5)	68.8 (8)	74.7 (10)	<0.001
Daytime systolic BP	132.6 (13.9)	126.52 (12.32)	138.78 (12.57)	<0.001
Daytime diastolic BP	75.26 (10.2)	72.03 (8.51)	78.56 (10.68)	<0.001

27 mo, data collected at 27-mo study visit; BP, blood pressure. P-value compares intensive vs standard treatment arms.

Table S2. Baseline characteristics of SPRINT subjects that did and did not have a second ABPM measurement.

Variable	Participants with one ABPM measurement N=694	Participants with two ABPM measurements N=203	p-value
Intensive-treatment group	350 (50.4)	103 (50.7)	1.000
Age (years)	71.4 ± 9.3	71.8 ± 10.0	0.677
Female sex	192 (27.7)	65 (32.0)	0.263
Race / Ethnicity			0.803
White	472 (68.0)	132 (65.0)	
Black	189 (27.2)	62 (30.5)	
Hispanic	17 (2.4)	4 (2.0)	
Other	16 (2.3)	5 (2.5)	
Body Mass Index (kg/m^2)	29.5 ± 5.6	29.3 ± 5.6	0.629
Smoking status			0.797
Never smoker	320 (46.2)	94 (46.3)	
Former smoker	305 (44.0)	86 (42.4)	
Current smoker	68 (9.8)	23 (11.3)	
Alcohol consumption			0.792
Non-drinker	268 (38.6)	81 (39.9)	
Light drinker	139 (20.0)	41 (20.2)	
Moderate drinker	172 (24.8)	44 (21.7)	
Heavy drinker	80 (11.5)	23 (11.3)	
History of CVD	22 (3.2)	7 (3.4)	1.000
eGFR, mL min^{-1} per 1.73 m^2 (24 mo)	70.1 ± 21.2	70.7 ± 19.5	0.752
Urine albumin/Cr (mg/g)	8.5 (5.4 to 21.6)	9.5 (5.4 to 19.9)	<0.001
Diabetes	17 (2.4)	4 (2.0)	0.894
Stroke	1 (0.1)	0 (0.0)	1.000
Cancer	101 (14.6)	28 (13.8)	0.875
Number of antihypertensive medications	1.9 ± 1.1	1.9 ± 1.0	0.990
Beta-blockers	227 (32.8)	80 (39.4)	0.094
Calcium channel blockers	329 (47.5)	87 (42.9)	0.280
ACE inhibitors	228 (32.9)	63 (31.0)	0.679
Angiotensin receptor blockers	257 (37.1)	74 (36.5)	0.935
Vasodilators	12 (1.3)	18 (1.8)	0.889
Alpha-blockers	59 (8.5)	21 (10.3)	0.667
Diuretics	418 (60.3)	112 (55.2)	0.219
In-clinic systolic BP (mm Hg)	127.9 ± 15.7	126.4 ± 15.1	0.191
In-clinic diastolic BP (mm Hg)	69.9 ± 12.1	69.1 ± 11.7	0.452

Table S3. Comparing clinic blood pressures by blood pressure measuring techniques used.

	Never alone (Attended) n=303	Always alone (Unattended) n=511	Alone at rest n=83	p-value
Systolic BP (27M) [mm Hg]				
Overall:	127 ± 15.8	128 ± 15.5	127 ± 15.8	0.81
Intensive:	119 ± 13.6	121± 13.2	119 ± 12.4	0.46
Standard:	135 ± 13.8	136± 13.4	134 ± 14.9	0.86
Daytime systolic ambulatory BP [mm Hg]				
Overall:	131 ± 13.6	133 ± 13.4	134 ± 16.8	0.06
Intensive:	124 ± 11.0	128 ± 12.7	126 ± 12.8	0.002
Standard:	138 ± 12.1	139 ± 12.1	142 ± 16.2	0.15

Table S4. Mean difference for daytime systolic BP and clinic systolic BP.

	Estimate (95%CI)	p-value
Intensive treatment group	1.68 (-0.53, 3.89)	0.135
eGFR	0.04 (-0.01, 0.09)	0.132
Age	-0.04 (-0.15, 0.07)	0.503
Black	-0.78 (-7.15, 5.58)	0.809
Hispanic	-2.29 (-10.94, 6.34)	0.602
White	1.47 (-4.75, 7.69)	0.642
Female	-0.96 (-3.95, 2.03)	0.528
Female*intensive treatment	6.09 (1.96, 10.22)	0.004

Estimates denote mean difference between daytime ambulatory systolic blood pressure (BP) and clinic systolic BP based on general linear model. Model adjusted for clinic site, estimated glomerular filtration rate, continuous age, race, sex, and interaction between sex and treatment arm. Positive values indicate a masked effect.

Table S5. Correlation between ambulatory blood pressure variability and clinic visit to visit variability in intensive treatment group.

	ABPM ARV-Systolic BP	ABPM ARV-Diastolic BP	ABPM coefficient of variation-Systolic BP	ABPM coefficient of variation-Diastolic BP
VVV- Systolic BP	**0.127**	**0.007**	-0.007	-0.025
VVV- Diastolic BP	**0.151**	-0.037	-0.0004	-0.023

ABPM, ambulatory blood pressure monitor; VVV, visit to visit variability; BP, blood pressure in mm Hg; ARV, average real variability; coefficient of variation= SD of mean BP/ mean BP
Bolded: significant values

Table S6. Correlation between ambulatory blood pressure variability and clinic visit to visit variability in standard treatment group.

	ABPM ARV-Systolic BP	ABPM ARV-Diastolic BP	ABPM coefficient of variation-Systolic BP	ABPM coefficient of variation-Diastolic BP
VVV- Systolic BP	**0.130**	-0.010	**0.137**	0.071
VVV- Diastolic BP	**0.156**	-0.046	**0.144**	0.092

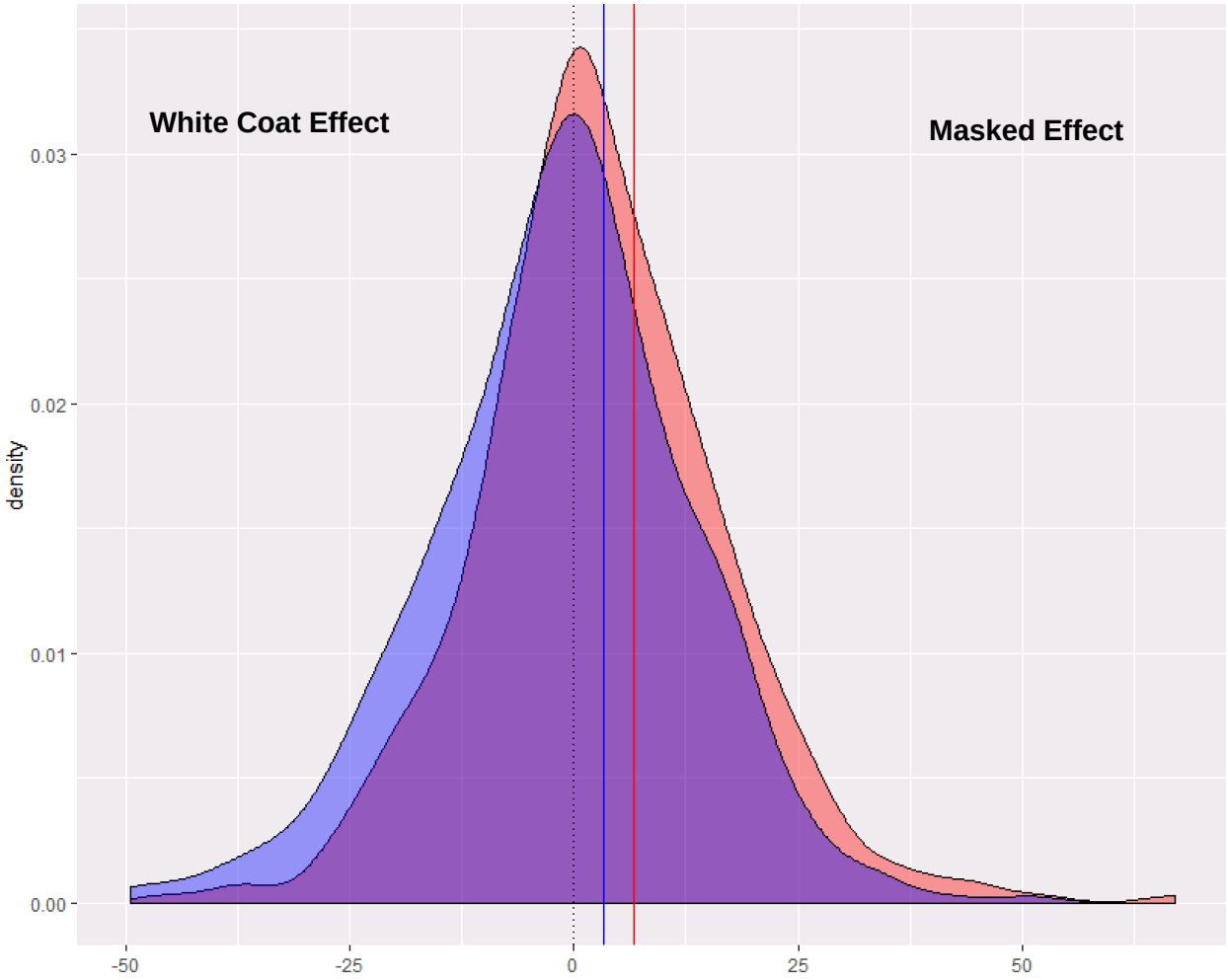
ABPM, ambulatory blood pressure monitor; VVV, visit to visit variability; BP, blood pressure in mm Hg; ARV, average real variability; coefficient of variation= SD of mean BP/ mean BP
Bolded: significant values

Table S7. Comparison of BP measurement on patients with a second ABPM (n= 203).

	Intensive (n=103)			Standard (n=100)		
	ABPM at 27 month	Second ABPM	Corr-elation	ABPM at 27 month	Second ABPM	Corr-elation
24 hour						
Systolic BP-mean(sd)	121.24(13.39)	124.45(13.80)	**0.55**	133.09(14.63)	134.60(14.31)	**0.57**
Diastolic BP-mean(sd)	68.71(9.76)	69.28(9.82)	**0.73**	74.06(10.59)	74.43(10.35)	**0.79**
Daytime						
Systolic BP-mean(sd)	125.84(11.67)	128.55(12.27)	**0.51**	138.05(12.72)	139.03(12.89)	**0.53**
Diastolic BP-mean(sd)	72.45(8.27)	72.69(8.51)	**0.72**	78.11(8.86)	78.03(9.03)	**0.74**
Nighttime						
Systolic BP-mean(sd)	113.43(9.51)	117.14(9.96)	**0.25**	123.67(10.58)	125.77(9.88)	**0.20**
Diastolic BP-mean(sd)	62.33(7.23)	63.38(7.62)	**0.33**	66.80(8.15)	67.77(7.16)	**0.32**

ABPM, ambulatory blood pressure monitor; Bolded: indicates significant correlation

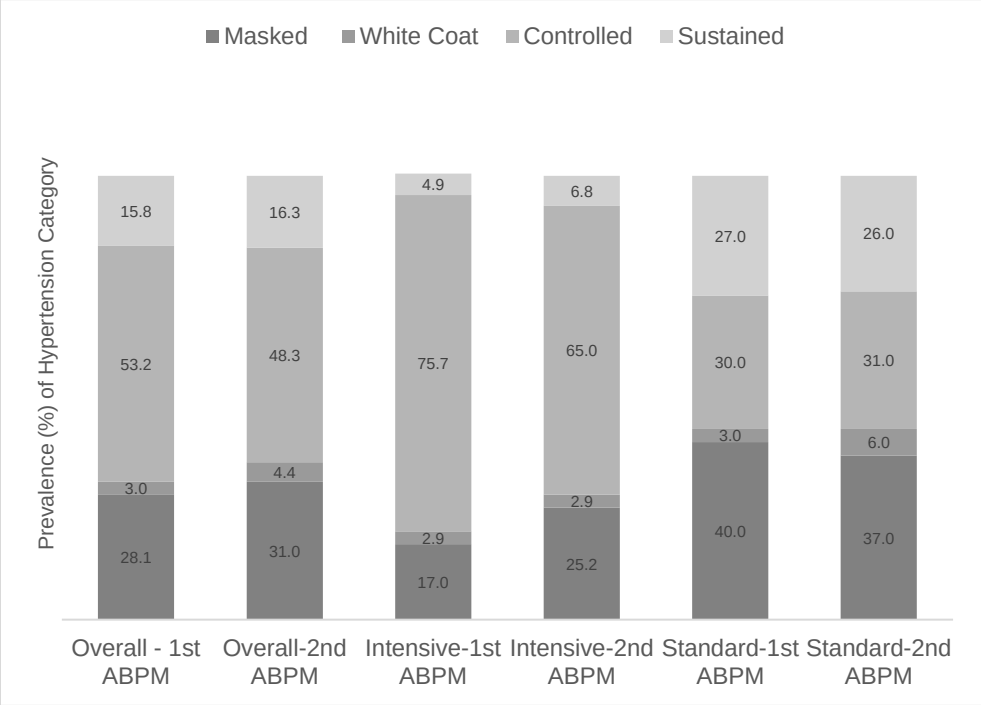
Figure S1. Plot comparing difference between daytime systolic BP and clinic systolic BP in standard and intensive treatment arm.



Difference in daytime systolic BP and clinic systolic BP at 27 month visit

Red represents intensive treatment arm, while blue represents the standard treatment arm. Vertical lines represent mean difference for each treatment group.

Figure S2. Prevalence of sustained hypertension, masked hypertension, controlled blood pressure and white coat hypertension among participants who had 2 ABPM.



	First ABPM – Hypertension Categorization (overall)			
	Masked	White Coat	Controlled	Sustained
Second ABPM- Hypertension Categorization (overall)				
Masked	**28**	3	20	12
White Coat	3	**1**	4	1
Controlled	13	1	**80**	4
Sustained	13	1	4	**15**

Masked hypertension: 24 hour BP ≥ 130/80mm Hg and clinic BP (nearest clinic visit) <140/90 mm Hg
White coat hypertension: 24 hour systolic BP < 130/80 mm Hg and clinic BP (nearest clinic visit) ≥140/90 mm Hg
Controlled hypertension: 24 hour systolic BP < 130/80mm Hg and clinic systolic BP (nearest clinic visit) <140/90 mm Hg
Sustained hypertension: 24 hour systolic BP ≥ 130/80 mm Hg and clinic BP (nearest clinic visit) ≥140/90 mm Hg