

# Is Medication Adherence Predictive of Cardiovascular Outcomes and Blood Pressure Control? The Systolic Blood Pressure Intervention Trial (SPRINT)

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## BACKGROUND

Adherence to study medications is crucial to evaluating treatment effects in clinical trials. To assess whether in the SPRINT trial, adherence and cardiovascular outcomes are associated regardless of intervention assignment.

## METHODS

This study included 9,361 participants aged  $\geq 50$  years, recruited from 102 clinics. Participants were randomized to a Standard Treatment Group (targeted systolic blood pressure [SBP]  $< 140$  mm Hg) or an Intensive Treatment Group (targeted SBP  $< 120$  mm Hg) and followed for incident cardiovascular events until the study was halted early for benefit. The 8-item Morisky Medication Adherence Scale (MMAS-8) was administered at baseline, and at the 12- and 48-month (or close out) visit.

## RESULTS

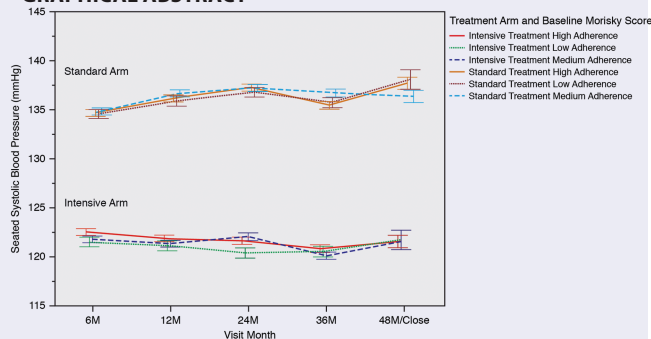
Adjusting for covariates, there was no association between the baseline 8-item MMAS-8 and the likelihood of the primary composite endpoint, any of the secondary endpoints, or blood pressure (BP) control. Low adherence was associated with a higher body mass index, SBP, diastolic BP, and Patient Health Questionnaire, and high adherence was associated with a higher Montreal Cognitive Assessment. There was no difference in the MMAS-8 over time by treatment arm assignment. For the primary outcome (a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes), baseline odds ratios (95% confidence intervals) for the Low vs. Medium and vs. High; and, for Medium

vs. High MMAS-8 were 1.02 (0.82–1.28), 1.07 (0.85–1.34), and 1.05 (0.88–1.250).

## CONCLUSIONS

In SPRINT, medication adherence as measured using the MMAS-8 was not associated with outcomes or BP control.

## GRAPHICAL ABSTRACT



Each error bar is constructed using 1 standard error from the mean.

In this analysis of the SPRINT Trial, it was found that medication adherence did not predict cardiovascular outcomes or BP control when using a common method of measuring adherence (The Morisky Score). Reasons for this are discussed, one of which could be the limitations of the Score itself, and another being clinical trial participation.

**Keywords:** blood pressure; hypertension; medication adherence; predictors; SPRINT.

<https://doi.org/10.1093/ajh/hpab145>

\*This work was initiated when he was at the Colorado School of Public Health.

A list of the SPRINT Research Group is available in the data supplement, which can be accessed at <https://www.ahajournals.org/doi/suppl/HYPERTENSION.120.15868>.

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Initially submitted May 12, 2021; date of first revision July 6, 2021; accepted for publication September 13, 2021; online publication September 16, 2021.

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Medication nonadherence is common and is associated with adverse outcomes and higher costs of care.<sup>1-5</sup> In 2003, a World Health Organization statement suggested that improved medication adherence “may have a far greater impact on the health of the population than any improvement in specific medical treatments.”<sup>2</sup> As former Surgeon General Dr C. Everett Koop famously said, “Drugs don’t work in patients who don’t take them.”<sup>3</sup>

We anticipated that participants in the intensive arm of the SPRINT trial might have lower adherence to the blood pressure (BP) intervention than participants in the standard arm since they were likely to require more medication to reach their target BP. In SPRINT, the primary measure of adherence was the 8-item Morisky Medication Adherence Scale (MMAS-8). Using a cut-point of less than 6 on the MMAS-8, the sensitivity and specificity of the 8-item scale for identifying low vs. higher adherers were estimated to be 93% and 53%, respectively.<sup>6</sup> One of the *a priori* areas of focus in the SPRINT trial was the influence of medication adherence on clinical outcomes, so we assessed whether lower medication adherence was predictive of worse BP control and more frequent cardiovascular outcomes, regardless of the intervention assignment.

## METHODS

### Study design and oversight

SPRINT was a prospective, open-label, multicenter, randomized controlled trial conducted at 102 clinical sites (organized into 5 clinical center networks) in the United States, and Puerto Rico that compared standard (target systolic blood pressure [SBP] of <140 mm Hg) to intensive (target SBP of <120 mm Hg) BP control in hypertensive adults who were at high risk for cardiovascular disease (CVD) events. The primary composite endpoint was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. The protocol for the trial is publicly available as is detailed inclusion and exclusion criteria and BP measurement methodology.<sup>7,8</sup>

SPRINT was sponsored by the NHLBI, with cosponsorship by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the National Institute on Aging. An independent data and safety monitoring board monitored unblinded trial results and safety events. The study was approved by the institutional review board at each participating study site.

The MMAS-8 was administered to all participants at the baseline, 12-, and 48-month (or close out) visit (use of the MMAS is protected by the US and International copyright laws. Permission for use is required). At every medication management visit, participants were administered a single-item Visual Analogue Scale (VAS) that was used to screen for adherence. If the participant’s response to this item indicated a possible problem with adherence or if the participant was not at the appropriate BP target at a given visit, study personnel addressed the specific issues and barriers for each study participant that might have been preventing

optimal adherence.<sup>7</sup> In addition, a checklist of behavioral “red flags” was provided to clinic staff to enable identification of participants who may be at risk for problems with adherence. Participants’ responses on the adherence measures and/or observation of “red flags” by clinic staff required specific actions to be taken by clinic staff.<sup>7</sup>

### Study population

This study included 9,361 SPRINT participants aged  $\geq 50$  years (Figure 1). Participants were recruited from 102 clinics (3,331 women, 2,648 with chronic kidney disease, 1,877 with a history of CVD, 3,962 minorities, and 2,636  $\geq 75$  years of age) between November 2010 and March 2013 (Figure 1). Participants were required to meet all the following criteria: an age of at least 50 years, a SBP of 130–180 mm Hg and an increased risk of CVD events. Increased cardiovascular risk was defined by 1 or more of the following: clinical or subclinical CVD other than stroke; chronic kidney disease, excluding polycystic kidney disease, with an estimated glomerular filtration rate (ml/min/1.73 m<sup>2</sup>) of 20 to less than 60 ml/min/1.73 m<sup>2</sup> of body surface area (calculated with the use of the 4 variable Modification of Diet in Renal Disease equation); a 10-year risk of CVD of 15% or greater (on the basis of a Framingham Risk Score >13 (men); >16 (women)); or an age of 75 years or older. Patients with diabetes mellitus, polycystic kidney disease, or prior stroke were excluded. All participants provided written informed consent.

### Randomization blinding and interventions

Eligible participants were assigned to a SBP target of either <140 mm Hg (the Standard Treatment Group) or <120 mm Hg (the Intensive Treatment Group).

Randomization was stratified according to clinical site. Participants and study personnel were aware of the study-group assignments, but outcome adjudicators were not.

### Baseline data collected

Demographic characteristics included age, sex, race, ethnicity, smoking and alcohol use history, body mass index, and level of education; the presence of clinical CVD (coronary and/or peripheral arterial disease, including carotid artery disease or previous carotid endarterectomy or stenting); chronic kidney disease defined as estimated glomerular filtration rate <60 ml/min/1.73 m<sup>2</sup> estimated by the MDRD equation; urinary protein level; systolic and diastolic BP; antihypertensive use and fasting glucose and low-density lipoprotein and high-density lipoprotein cholesterol.

**Outcomes** Clinical events were ascertained every 3 months during follow-up using a structured interview to minimize ascertainment bias. Deaths were investigated at any time the clinical site staff became aware of a potential death. Additional sources, including searches of the National Death Index (NDI), were used to augment death ascertainment.

**Primary SPRINT endpoint** The primary endpoint for SPRINT was a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

Secondary outcomes included individual CVD events (fatal and nonfatal myocardial infarction, stroke, and heart failure; acute coronary syndrome, and death attributable to CVD); all-cause mortality, congestive heart failure (CHF) death, and readmission for CHF.

**Definition of outcomes** CVD outcomes were ascertained primarily through surveillance for self-reported events, review of pertinent medical records, and ECG collection and classification by members of the Morbidity and Mortality subcommittee masked to treatment assignment. Myocardial infarction was defined by assessing elements of the clinical presentation (signs and symptoms), results of cardiac enzyme determinations, and ECG readings, and was based on a 2003 Scientific Statement by the American Heart Association, World Heart Federation Council on Epidemiology and Prevention, the European Society of Cardiology, the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute.<sup>9</sup> The diagnosis of non-myocardial infarction ACS required hospitalization for evaluation, with documented new or changing cardiac ischemic symptoms. Furthermore, confirmatory evidence of CAD was required. Stroke was defined as the rapid onset of focal neurologic symptoms, headache, or meningism not due to other conditions (e.g., central nervous system infection), plus a lesion on brain imaging consistent with symptoms except when death occurs within 24 hours without resolution of symptoms. CVD death included fatal coronary heart disease, sudden cardiac death, CHF, stroke, and other noncardiac cardiovascular events adjudicated centrally as the underlying cause of death. Death from CHF was based on hospital records and interviews with families. To verify self-reported diagnoses, copies were requested of all death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses. If patients were admitted multiple times for CHF during the study period, only the first admission was utilized in the analyses. Atrial fibrillation or flutter in SPRINT was primarily detected from the scheduled study ECGs using Minnesota ECG classification.<sup>10</sup> Other sources of detection included hospital discharge ICD code (ICD-10 code I48 or ICD-9 code 427.3) and self-report.

**Exposure** Medication adherence defined by the MMAS-8 score, as it has been shown that the MMAS-8 is a reliable indicator of adherence to a medication regimen and, has been significantly associated with BP control ( $P < 0.05$ ).<sup>11,12</sup> The level of adherence per the MMAS-8 score was as follows: Low <6 points, Medium 6–7 points, and High 8 points.<sup>11</sup>

### Statistical analyses

For inclusion in this analysis, participants randomized in SPRINT had to have a completed MMAS-8, Patient Health Questionnaire (PHQ-9), and Montreal Cognitive Assessment (MoCA) scores at baseline for inclusion in this

analysis (Figure 1). The PHQ-9 is the major depressive disorder module of the full PHQ. PHQ is used to provisionally diagnose depression and grade severity of symptoms in general medical and mental health settings. For PHQ-9, those with one to two missing responses, the average of nonmissing responses was used for the missing responses. The MoCA is a cognitive screening test designed to assist in the detection of mild cognitive impairment and Alzheimer's disease. Depression status and severity and cognitive function have been associated with adherence.

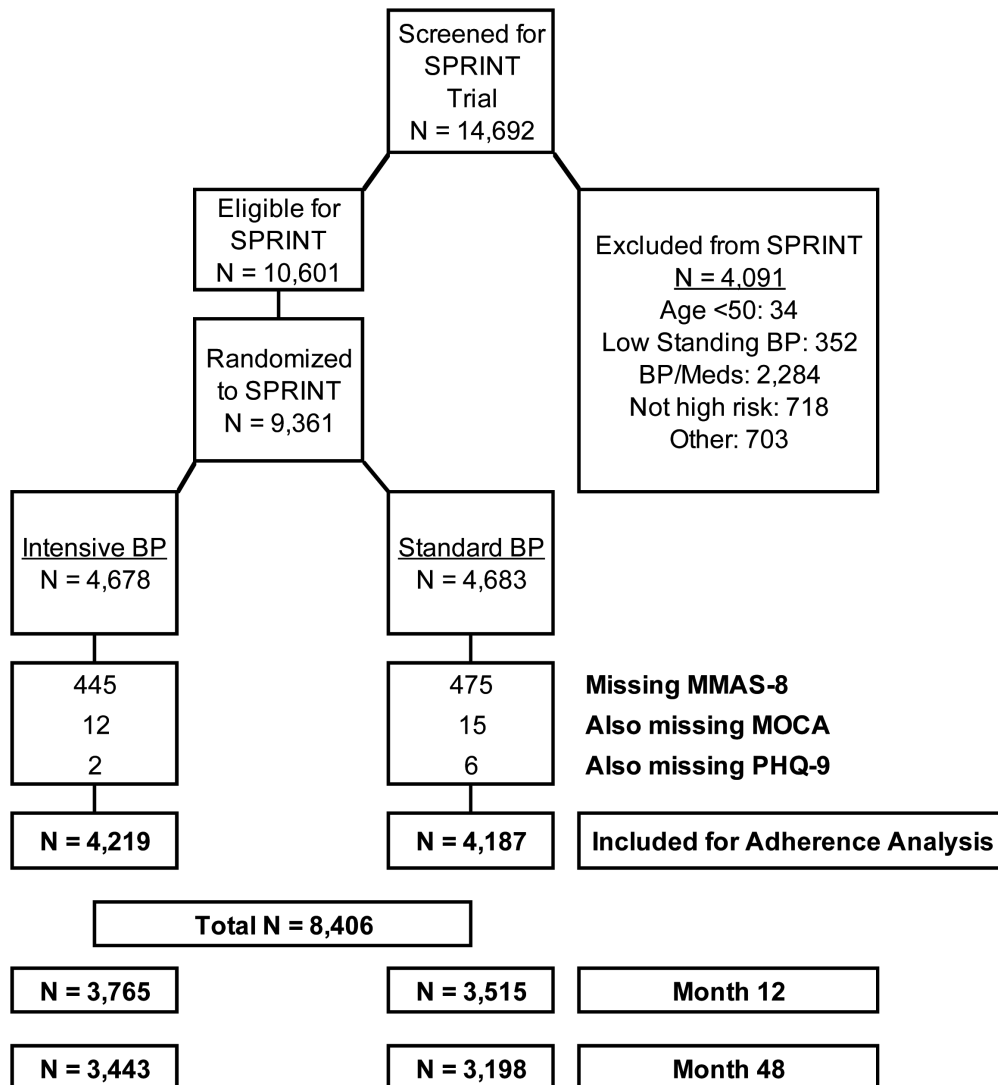
For cohort characterization, descriptive statistics were calculated for all variables:  $n$  (%) for categorical variables, mean (SD)/median (interquartile range) for continuous variables. Associations with baseline adherence level, unadjusted chi-square analysis was conducted for categorical variables, and ANOVA with Tukey's HSD or a Wilcoxon with Steel–Dwass for continuous variables and follow-up adherence group comparisons, as applicable. In addition to baseline systolic BP (mm Hg), and intervention arm (standard or intensive BP control), covariates previously shown to be related to adherence were considered for covariate adjusted models: age (in years) at randomization, gender (female or male), race/ethnicity (White only, African American, Hispanic, or Other), body mass index ( $\text{kg}/\text{m}^2$ ), and smoking status (never, former, or current). Due to high association with MMAS-8, the PHQ-9 and MoCA scores were not considered as covariates. The rationale for covariates in the model testing the association between MMAS and outcomes is not provided.

Log-rank chi-square statistics from covariate adjusted nominal logistic regression to determine association of baseline MMAS with outcomes of interest (Yes or No): BP control, primary composite outcome of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes; and secondary outcomes of individual CVD events of fatal and nonfatal myocardial infarction, stroke, and heart failure; acute coronary syndrome, and death attributable to CVD, all-cause mortality, CHF death, and readmission for CHF. Unadjusted Kaplan–Meier analysis was used to assess median time to BP control and primary and secondary events by MMAS-8 baseline level, and Cox proportional hazards models were used to assess MMAS-8 level while adjusting for covariates.

Due to the secondary nature of this data analysis, other than for the scoring of the PHQ-9, no imputation methods were utilized for any missing data, other than the outcomes as described in the SPRINT trial, and no adjustments were made for multiple testing.  $P$  values of  $<0.05$  were considered significant. All analyses were performed using JMP Pro 14/15 or SAS 9.4 (SAS Institute, Cary, NC, USA).

### RESULTS

At baseline, 21.3% were categorized as Low adherence using the MMAS-8, with 39.9% Medium, and 38.8% High adherence (Table 1). Low adherence was associated with a higher body mass index, SBP, diastolic BP, and PHQ-9, and high adherence was associated with a higher MoCA. Overall, there was no difference in the MMAS-8 over time by treatment arm assignment and, the score improved from baseline to 12 months (6.9–7.3) and at 48 months were similar to the 12-month MMSA-8.



**Figure 1.** Cohort disposition. Abbreviation: BP, blood pressure; MMAS-8, 8-item Morisky Medication Adherence Scale; MoCA, Montreal Cognitive Assessment; PHQ-9, Patient Health Questionnaire.

For the primary analysis after adjustment for covariates, there was no association between baseline MMAS-8 and the primary outcome (Table 2). There was also no association of the baseline MMAS-8 and the likelihood of a primary outcome. After adjustment for covariates, there was still no association between baseline MMAS-8 and likelihood of a Primary Event. There was also no association between the baseline MMAS-8 and timing of the Primary Event. Neither the baseline MMAS-8, nor the MMAS-8 over time was predictive of BP control. Tables 3 and 4 show the results of the MMAS-8 by SBP control in the standard and intensive arms.

Figure 2 shows the baseline MMAS-8 by SBP and Figure 3 SBP control by MMAS-8 category, over time. No significant differences are noted either in SBP from baseline to closeout or the % whose BP was controlled over time. Specifically, in the Standard Treatment Group, the composite primary event occurred in 8.3%, 9.5%, and 9.0% in the Low, Medium, and High adherence groups, respectively; and, in the Intensive Treatment Group 6.4%, 7.0%, and 7.5%, respectively ( $P = 0.20$ ).

Supplementary Table S1 online lists the odds ratio (95% confidence interval [CI]) for the covariate adjusted models. For the primary outcome, baseline odds ratios for the Low vs. Medium and vs. High; and, for Medium vs. High MMAS-8 were 1.02 (0.82, 1.28); 1.07 (0.85, 1.34); 1.05 (0.88, 1.25) all NS.

#### Secondary events

There was no association between the baseline MMAS-8 and any secondary event (CVD, stroke, heart failure, vascular events, and death) (Supplementary Table S2 online).

#### DISCUSSION

Medication adherence is critical to the validity and generalizability of any clinical trial and is a common and refractory problem. In this analysis of SPRINT, we did not observe any evidence that medication adherence as measured by the MMAS-8 varied by treatment arm, nor was it predictive of BP control or clinical outcome.

**Table 1.** Baseline clinical characteristics by baseline Morisky score

Baseline characteristic Mean (SD) or N (%)	All (8,406)	Baseline Morisky Scale Adherence			P value
		Low: <6 (n = 1,787, 21.3%)	Medium: 6 < 8 (n = 3,357, 39.9%)	High: 8+ (n = 3,262, 38.8%)	
Intensive treatment	4,219 (50.2)	900 (50.4)	1,660 (49.5)	1,659 (50.9)	0.5112
Age (years)	68.1 (9.4)	65.0 (9.3)	68.4 (9.3)	69.5 (9.1)	<b>&lt;0.0001</b>
Age ≥75	2,422 (28.8)	345 (19.3)	991 (29.5)	1,086 (33.3)	<b>&lt;0.0001</b>
Female	3,083 (36.7)	705 (39.5)	1,213 (36.1)	1,165 (35.7)	<b>0.0224</b>
Race/ethnicity					
Hispanic	906 (10.8)	209 (11.7)	323 (9.6)	374 (11.5)	<b>&lt;0.0001</b>
African American	2,586 (30.7)	822 (46.0)	990 (29.5)	774 (23.7)	
White Only	4,781 (56.9)	721 (40.4)	1,990 (59.3)	2,070 (63.5)	
Other	133 (1.6)	35 (2.0)	54 (1.6)	44 (1.4)	
Education level <sup>a</sup>					
Less than high school (HS)	718 (8.6)	193 (10.9)	286 (8.6)	239 (7.4)	<b>&lt;0.0001</b>
HS diploma or GED	1,379 (16.6)	316 (17.9)	538 (16.2)	525 (16.3)	
Post HS/some college	2,970 (35.7)	689 (39.0)	1,176 (35.5)	1,105 (34.2)	
College graduate or higher	3,244 (39.0)	567 (32.1)	1,317 (39.7)	1,360 (42.1)	
Smoking status <sup>a</sup>					
Never	3,710 (44.4)	766 (43.2)	1,479 (44.3)	1,465 (45.1)	<b>&lt;0.0001</b>
Former	3,608 (43.1)	648 (36.5)	1,487 (44.6)	1,473 (45.3)	
Current	1,045 (12.5)	361 (20.3)	372 (11.1)	312 (9.6)	
Pack years of smoking (including never): mean (SD)	12.2 (20.1)	11.4 (19.3)	12.7 (20.7)	12.2 (20.5)	0.4856 <sup>c</sup>
Lives with other adults <sup>a</sup>	5,976 (71.1)	1,268 (71.0)	2,355 (70.2)	2,353 (72.1)	0.2177
Health insurance	7,628 (90.7)	1,531 (85.7)	3,038 (90.5)	3,059 (93.8)	<b>&lt;0.0001</b>
Any drug benefits	6,519 (77.6)	1,286 (72.0)	2,570 (76.6)	2,663 (81.2)	<b>&lt;0.0001</b>
Alcohol abuse <sup>a</sup>	338 (4.0)	106 (5.9)	118 (3.5)	114 (3.5)	<b>&lt;0.0001</b>
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	29.9 (5.6)	30.6 (5.9)	29.9 (5.5)	29.5 (5.5)	<b>&lt;0.0001<sup>b</sup></b>
BMI category					
Underweight	41 (0.5)	9 (0.5)	17 (0.5)	15 (0.5)	<b>&lt;0.0001</b>
Normal	1,482 (17.8)	272 (15.3)	587 (17.6)	623 (19.2)	
Overweight	3,249 (38.9)	644 (36.3)	1,285 (38.5)	1,320 (40.7)	
Obese	1,284 (42.9)	848 (47.8)	1,446 (43.4)	1,284 (39.6)	
Cardiovascular disease	1,771 (21.1)	343 (19.2)	751 (22.4)	677 (20.8)	<b>0.0243</b>
Framingham 10-yr CVD risk <sup>a</sup>	17.5 (2.5)	17.5 (2.5)	17.5 (2.5)	17.5 (2.5)	0.8660
Chronic kidney disease	2,501 (29.8)	447 (25.0)	1,038 (30.9)	1,016 (31.2)	<b>&lt;0.0001</b>
Systolic blood pressure (BP) <sup>a</sup>	139.0 (15.4)	139.9 (16.0)	138.6 (15.4)	139.1 (15.1)	<b>0.0148<sup>b</sup></b>
Diastolic BP <sup>a</sup>	77.5 (11.7)	80.5 (12.1)	77.2 (11.6)	76.2 (11.3)	<b>&lt;0.0001<sup>b</sup></b>
No. anti-hypertensive medications, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.1714
Systolic BP					
<140	4,583 (54.5)	947 (53.0)	1,884 (56.1)	1,752 (53.7)	<b>0.0188</b>
140–160	3,022 (36.0)	643 (36.0)	1,160 (34.6)	1,219 (37.4)	
160	801 (9.5)	197 (11.0)	313 (9.3)	291 (8.9)	

**Table 1.** Continued

Baseline characteristic Mean (SD) or N (%)	All (8,406)	Baseline Morisky Scale Adherence			P value
		Low: <6 (n = 1,787, 21.3%)	Medium: 6 < 8 (n = 3,357, 39.9%)	High: 8+ (n = 3,262, 38.8%)	
PHQ-9 score, median (IQR)	2 (0, 4)	3 (1, 7)	2 (0, 4)	1 (0, 3)	<b>&lt;0.0001<sup>c</sup></b>
MoCA (0–30)	22.7 (4.4)	22.5 (4.4)	22.8 (4.4)	22.8 (4.3)	<b>0.0214<sup>b</sup></b>
MMAS-8, median (IQR)	7 (6.5, 8)	5.5 (4.5, 5.6)	7 (6.8, 7.8)	8 (8, 8)	NA

Bolded *P* values indicate statistical significance.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; IQR, interquartile range; MMAS-8, 8-item Morisky Medication Adherence Scale; MoCA, Montreal Cognitive Assessment; PHQ-9, Patient Health Questionnaire.

<sup>a</sup>*N* for education (8,311), smoking status (8,363), BMI (8,350), alcohol abuse (8,402), drug benefits (8,401), lives with other adults (8,403), and Framingham Risk Score (8,401).

<sup>b</sup>Equal variance *F*-test with Tukey's HSD:

BMI: Low vs. Medium and High (both *P* < 0.0001), Medium vs. High (0.0072); systolic BP: Low vs. Medium (0.0104); diastolic BP: Low vs. Medium and High (both *P* < 0.0001), Medium vs. High (0.0010); MoCA: High vs. Low (0.0264), Medium vs. Low (0.0387).

<sup>c</sup>Wilcoxon with Steel–Dwass median comparisons: PHQ-9: Low vs. Medium and High (both *P* < 0.0001), Medium vs. High (<0.0001).

**Table 2.** Primary Event (a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) by baseline Morisky score and treatment (*N* = 8,311)

Treatment	Primary Event	Overall ( <i>N</i> = 8,311)	Baseline Morisky score		
			Low ( <i>N</i> = 1,761)	Medium ( <i>N</i> = 3,319)	High ( <i>N</i> = 3,231)
Standard ( <i>N</i> = 4,133)	Yes	374 (9.1)	73 (8.3)	159 (9.5)	142 (9.0)
	No	3,759 (91.0)	803 (91.7)	1,516 (90.5)	1,440 (91.0)
Intensive ( <i>N</i> = 4,178)	Yes	295 (7.1)	57 (6.4)	115 (7.0)	123 (7.5)
	No	3,883 (92.9)	828 (93.6)	1,529 (93.0)	1,526 (92.5)

Abbreviations: BMI, body mass index; BP, blood pressure; MI, myocardial infarction. Adjusting for covariates (race/ethnicity, baseline BP, BMI), there is no association between baseline Morisky adherence score and likelihood of primary outcome. Number for analysis: 8,311 participants with all baseline covariates (669 with event): myocardial infarction 181, non-MI acute coronary syndrome 74, cardiovascular death 71, stroke 140. No difference in type of event and Morisky category, *P* = 0.1969.

**Table 3.** SPRINT Morisky score by SBP control at month 12 (standard arm)

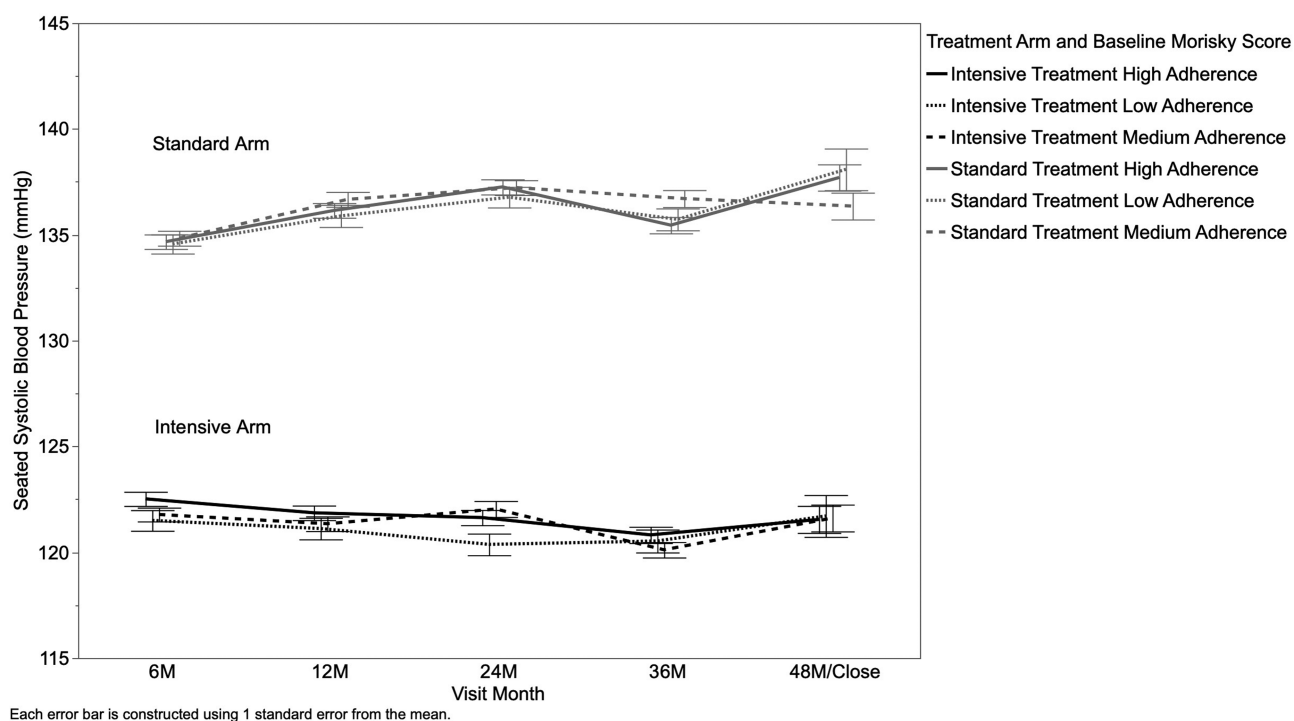
Number (%)	Overall ( <i>N</i> = 3,738)	Month 12 SBP controlled status Standard arm ≤140 mm Hg		P value
		Not controlled ( <i>N</i> = 1,243)	Controlled ( <i>N</i> = 2,495)	
Baseline				
Low adherence	769 (20.6)	235 (18.9)	534 (21.4)	0.1985
Medium adherence	1,504 (40.2)	513 (41.3)	991 (39.7)	
High adherence	1,465 (39.2)	495 (39.8)	970 (66.2)	
Month 12				
Low adherence	431 (12.4)	149 (12.8)	282 (12.2)	0.8409
Medium adherence	1,319 (37.9)	443 (38.0)	876 (37.8)	
High adherence	1,734 (49.8)	574 (49.2)	1,160 (50.0)	
Change from baseline to month 12				
Decrease in Morisky score	545 (15.6)	201 (17.2)	344 (14.8)	0.1629
No change in Morisky score	1,839 (52.8)	610 (52.3)	1,229 (53.0)	
Increase in Morisky score	1,100 (31.6)	355 (30.5)	745 (32.1)	

Abbreviation: SBP, systolic blood pressure.

**Table 4.** SPRINT Morisky score by SBP control at month 12 (intensive arm)

Number (%)	Overall (N = 3,747)	Month 12 SBP controlled status		P value
		Intensive arm ≤120 mm Hg		
		Not controlled (N = 1,584)	Controlled (N = 2,163)	
Baseline				
Low adherence	775 (20.4)	319 (19.8)	456 (20.9)	0.1499
Medium adherence	1,514 (39.9)	624 (38.7)	890 (40.8)	
High adherence	1,507 (39.7)	669 (41.5)	838 (38.4)	
Month 12				
Low adherence	505 (13.5)	241 (15.2)	264 (12.2)	0.0212
Medium adherence	1,385 (37.0)	585 (36.9)	800 (37.0)	
High adherence	1,857 (49.6)	758 (47.9)	1,099 (50.8)	
Change from baseline to month 12				
Decrease in Morisky score	629 (16.8)	299 (18.9)	330 (15.3)	<0.0001
No change in Morisky score	1,961 (52.3)	850 (53.7)	1,111 (51.4)	
Increase in Morisky score	1,157 (30.9)	435 (27.5)	722 (33.4)	

Abbreviation: SBP, systolic blood pressure.



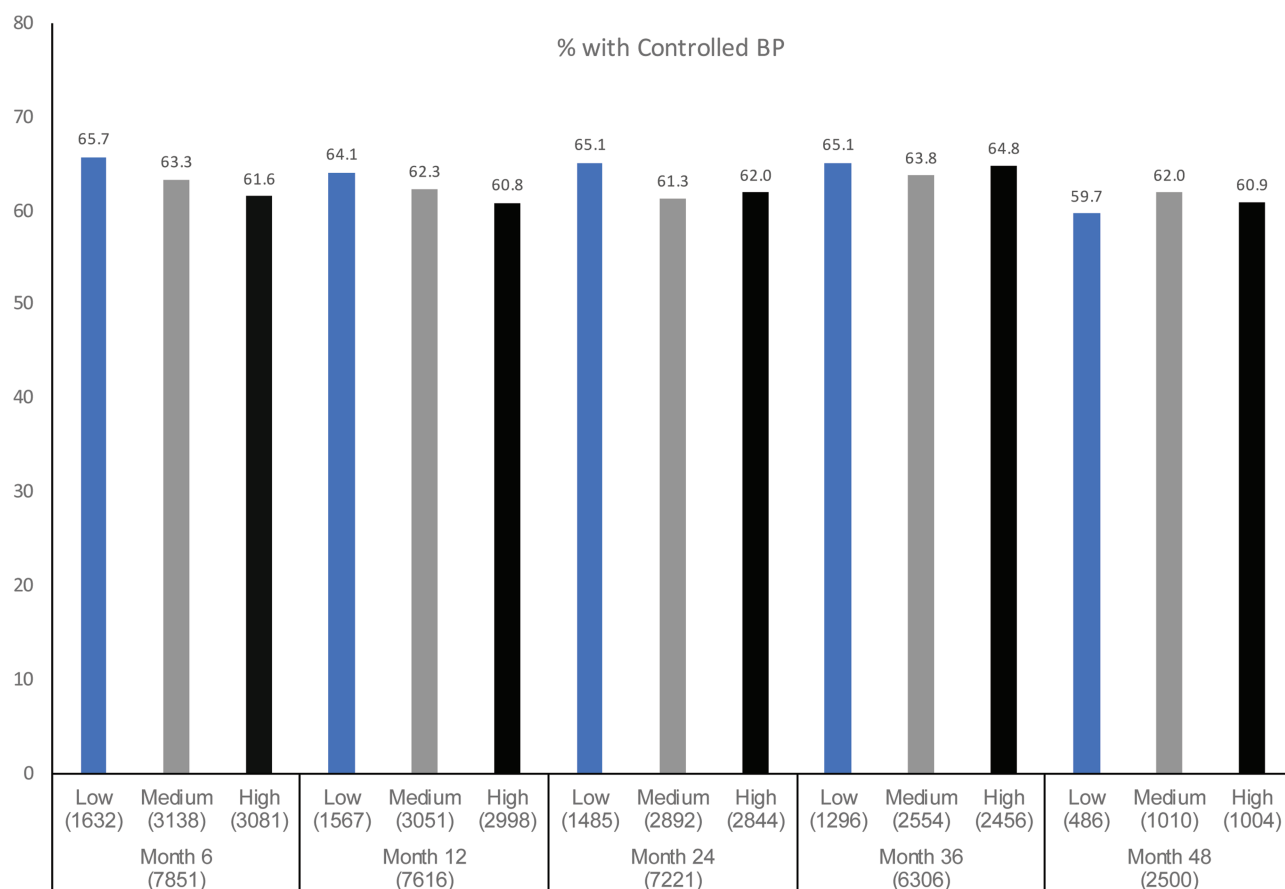
**Figure 2.** Mean systolic BP over time (baseline [BL] to closeout) in the intensive and standard groups by baseline Morisky score (category [Cat], N = 8,311). Abbreviation: BP, blood pressure.

### Medication adherence

Long-term adherence to statins, angiotensin converting enzyme inhibitors, and  $\beta$ -blockers hovers around 50%–60%, regardless of insurance status, clinical indication, and setting.<sup>13,14</sup> Even in the period immediately after acute myocardial infarction, a time during which one might expect patients to be particularly attuned to the importance of taking medications as prescribed, adherence is surprisingly low.<sup>15,16</sup>

### Morisky score and outcomes

Adherence and outcomes have been associated in many studies, so the absence of this relationship in SPRINT is interesting.<sup>17–19</sup> In 2011, the NIH convened a panel of experts which was assembled by the NIH Adherence Network—a consortium of science officers working at many different NIH institutes, centers, and offices to review the current evidence-base behind self-report measures of medication



**Figure 3.** BP control and adherence over time (N = 8,311). Abbreviation: BP, blood pressure.

adherence with an eye toward optimizing their selection and use. The panel was charged with reviewing the evidence base for self-report measures across major fields of chronic illness prevention and treatment and making best practice recommendations. They concluded that “self-report adherence measures are readily integrated into clinical research visits and represent a low burden assessment approach that may be more acceptable to patients than alternatives. Unique types of self-report measures may be needed at different junctures within a clinical trial. For example, single-item measures including Visual Analogue Scales (VAS) can be useful as brief adherence screens at medication management visits. Self-report measures that can indicate reasons for nonadherence such as the Morisky adherence measure may be administered at baseline and during selected visits to ascertain adherence barriers to inform interventions to address and improve these challenges.”<sup>20</sup> Other adherence measures, such as the nonproprietary Krousel-Wood and Hill-Bone Compliance measures, were also discussed.<sup>20</sup> In summary, they noted that most evidence indicates that self-report adherence measures show moderate correspondence to other adherence measures and can significantly predict clinical outcomes.<sup>20</sup> Since its development in 2009, the MMAS-8 has been used in more than 200 studies, although it has not been well studied in relation to cardiovascular events. Over the past 2–3 years, use of the MMAS-8 in RCTs of medical adherence intervention

regarding numerous chronic diseases has increased. Finally, the MMAS-8 has been used in 12 RCTs of treatments for acute coronary syndrome, diabetes mellitus, hypertension, chronic heart failure, and malignant neoplasms.<sup>6</sup> There have been some criticisms of the MMAS-8. Moon *et al.* stated, “for a cut-off value of 6, the MMAS-8 in a meta-analysis showed the pooled sensitivity and specificity in 12 studies were 0.43 (95% CI, 0.33 to 0.53) and 0.73 (95% CI, 0.68 to 0.78), respectively,” so as with any other score, there is not a uniform association with outcomes.<sup>6</sup> Finally, Muntner *et al.* assessed what was the minimal detectable change for scores on the MMAS-8; and, their results suggested that within-person changes in MMAS-8 scores of 2 or more points over time might represent a real change in antihypertensive medication adherence.<sup>21</sup>

There are several possibilities to account for the lack of association of adherence and outcomes in SPRINT. It is possible that the lack of association of outcomes, BP and adherence, as measured by MMAS-8, was related to aspects of the study design. That is, perhaps the MMAS-8 was not associated with outcomes in SPRINT because participants were seen frequently (monthly for the first 3 months, then at least every 3 months, and more often in those not meeting BP goal), and if poor compliance as assessed by MMAS-8 or VAS was observed at a visit, the importance of adherence was emphasized by study staff. Since this would have been



the same for both treatment groups, it could lead to a null finding. In addition, any potential participants with characteristics judged by the clinic team to be likely to limit adherence to interventions, including alcohol or substance abuse, lack of family support, and/or a history of poor adherence, were excluded from SPRINT. Participants were randomized to standard (<140 mm Hg) vs. intensive (<120 mm Hg) treatment groups. The trial provided free medications and visits with highly trained and emphatic staff. As noted in the previously published baseline assessment of medication adherence in SPRINT (20), the participant selection process did not represent a random sample with respect to BP and antihypertensive medication numbers. Eligibility criteria for SBP at screening were 130–180, and furthermore those with higher baseline SBP were excluded unless the number of such meds at screening was relatively low; and those with SBP <130 at screening were also excluded. Taken together, the foregoing could be expected to attenuate the effect of medication adherence on outcomes in SPRINT. Additionally, the study was stopped early for benefit (the Intensive Treatment Group demonstrating fewer clinical events compared with the Standard Treatment Group), so it is possible that a longer study duration might have differentiated the low vs. high adherence subjects. It should be noted that interaction between the MMAS-8 adherence levels and the number of BP-lowering medications on SBP control at baseline in a prior SPRINT manuscript, was assessed and found to be nonsignificant, and this held for the Interaction effects of MMAS levels of adherence with gender, age (senior subgroup), race/ethnicity, and chronic kidney disease. Also, as Moon *et al.* stated, “for a cut-off value of 6, the MMAS-8 in a meta-analysis showed the pooled sensitivity and specificity in 12 studies were 0.43 (95% CI, 0.33 to 0.53) and 0.73 (95% CI, 0.68 to 0.78), respectively,” so as with any other score, there is not a uniform association with outcomes.<sup>6</sup> Another issue is the validity of the MMAS in chronic disease (and more particularly in chronic kidney disease) and correlation to specific clinical outcomes.

### Strengths and limitations

The strengths of the SPRINT STUDY include a large randomized rigorously performed trial that had a hypotheses that could easily be answered; and, that it used validated score system to measure adherence. This lent itself well to analyze the relationship of medication adherence and outcome.

Limitations include the open-label design, and lack of a placebo control group, and the use of self-report for some variables. The main SPRINT trial was not designed to test the relationship between medication adherence and clinical outcomes. Inclusion and exclusion criteria impact generalizability and must be considered in the interpretation.

In conclusion, within setting of a large randomized controlled trial with well-defined protocols addressing medication management, we did not observe any association between the MMAS-8 and clinical outcomes or BP control. Adherence to study medications and dosing protocols is crucial to evaluating the effects of clinical trials, and one of the

goals of SPRINT was the implementation of strategies that maximized participant adherence for the duration of the trial. We believe that was achieved in SPRINT and could act as a model to improve adherence in general.

### SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

### FUNDING

The Systolic Blood Pressure Intervention Trial was funded with Federal funds from the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS), under Contract Numbers HHSN268200900040C, HSN268200900046C, HHSN268200900047C, HHSN268200900048C, HHSN268200900049C, and Inter-Agency Agreement Number A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. The SPRINT investigators acknowledge the contribution of study medications (azilsartan and azilsartan combined with chlorthalidone) from Takeda Pharmaceuticals International. This study was also supported by the following CTAs (Clinical and Translational Science Awards) funded by NCATS (National Center for Advancing Translational Sciences): CWRU: UL1TR000439, OSU: UL1RR025755, U Penn: UL1RR024134 and UL1TR000003, Boston: UL1RR025771, Stanford: UL1TR000093, Tufts: UL1RR025752, UL1TR000073, and UL1TR001064, University of Illinois: UL1TR000050, University of Pittsburgh: UL1TR000005, UT Southwestern: 9U54TR000017-06, University of Utah: UL1TR000105-05, Vanderbilt University: UL1 TR000445, George Washington University: UL1TR000075, University of CA, Davis: UL1 TR000002, University of Florida: UL1 TR000064, University of Michigan: UL1TR000433, Tulane University: P30GM103337 COBRE Award NIGMS.

### ACKNOWLEDGMENTS

All components of the SPRINT study protocol were designed and implemented by the investigators. The investigative team collected, analyzed, and interpreted the data. All aspects of manuscript writing and revision were carried out by the coauthors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the NHLBI; the National

Institutes of Health; or the U.S. Department of Health and Human Services.

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## DISCLOSURE

Dr Cofield has received consulting fees from the Department of Defense for grant review. Stephen P. Glasser, Mara Vitolins, Michael V. Rocco, Carolyn Harmon Still, William E. Haley, and David Goff have no conflicts to report.

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