JACC: ADVANCES VOL. 3, NO. 11, 2024

ORIGINAL RESEARCH

Association Between Systolic Blood Pressure Time in Target Range Indices and Adverse Cardiovascular Outcomes

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ABSTRACT

BACKGROUND There is no consensus on optimal time points or systolic blood pressure (SBP) ranges for calculating SBP time in target range (TTR).

OBJECTIVES The purpose of this study was to examine the association between various SBP TTR metrics and long-term major adverse cardiovascular events (MACEs).

METHODS This post hoc analysis of SPRINT (Systolic Blood Pressure Intervention Trial) included participants with complete SBP records and excluded those with events in the initial 2 years. SBP TTR indices were calculated using 3 distinct time points and 3 SBP ranges. The SBP TTR index was the percentage of BP segments within the target SBP ranges. MACE, a composite of heart attack, stroke, heart failure, and cardiovascular death, was the primary outcome.

RESULTS The study included 7,134 participants, of which 280 had a MACE. The median follow-up was 3.91 years. The SBP TTR 110-140 mm Hg in the initial 3 months (3-month TTR 110-140) had the optimal association with incident MACEs (HR per SD increase: 0.898 [95% CI: 0.788-1.022], relative informativeness = 24,398%). Furthermore, a cutoff value of 0.65 for 3-month TTR 110 to 140 index was identified by threshold saturation analysis and used to evaluate early SBP control. No difference in MACE was seen between different mean SBP subgroups in those with good early control (3-month TTR >0.65) ($P = 0.88$), but in those with poor early control (3-month TTR ≤0.65), a higher mean SBP of 130 to 140 mm Hg was related to increased MACEs risk ($P = 0.019$).

CONCLUSIONS In nondiabetic hypertensive patients, the 3-month TTR 110 to 140 mm Hg index was independently associated with 2-year MACEs. A cutoff of TTR index as 0.65 indicated that the patient was within BP target range 65% of the time, combined with mean SBP, could potentially be used as a metric for early control stability and late cardiovascular risks. (Systolic Blood Pressure Intervention Trial [SPRINT]; NCT01206062) (JACC Adv. 2024;3:101350)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 19, 2024; revised manuscript received September 10, 2024, accepted September 16, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101350

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CV death = cardiovascular death

MACE = major adverse cardiovascular event

MI = myocardial infarction

RCS = restricted cubic spline

SBP = systolic blood pressure

TTR = time in target range

Hypertension, a pervasive cardiovascular risk factor, significantly contributes to severe outcomes like myocardial infarction (MI), stroke, and cardiovascular mortality.[1] Recent hypertension guidelines depended on one-time measurements like office, home, and ambulatory blood pressure (BP) measurements,[2,3] which failed to capture ongoing BP loads. Thus, there is an urgent for innovative indices that more accurately assess BP burden over time.

In recent years, systolic blood pressure (SBP) time in target range (TTR) has recently gained attention for its ability to measure the duration of SBP within the target range for hypertensive population.[2] SBP TTR is calculated by determining the percentage of time that a patient's SBP remains within a specified target range over a given period.[4] Numerous prior studies have consistently demonstrated that SBP TTR serves as a reliable and independent associated factor of adverse cardiovascular outcomes.[4-8]

In terms of time points, most studies calculate TTR with at least three BP readings over the initial 3 months,[4-7] while others use all readings across their study.[8,9]

In terms of target BP ranges, target BP ranges within 110 to 130 mm Hg for TTR are common,[10,11] but some post hoc studies,[4-7] utilizing the SPRINT (Systolic Blood Pressure Intervention Trial) database, set different SBP targets for intensive (110-130 mm Hg) and standard (120-140 mm Hg) treatment groups. Additionally, other studies calculated TTR using a target range of 110 to 140 mm Hg[6] or 120 to 130 mm Hg.[8] The various TTR calculation methods prevented its use in clinical practice. Therefore, understanding the optimal TTR metric and establishing a standardized measurement for TTR is needed.

In this study, we conduct a post hoc analysis of the SPRINT data set, calculating TTR across 3 distinct time points (1-3 months, 1-12 months, and 1-24 months) and according to 3 SBP ranges (110-130 mm Hg, 110-140 mm Hg, and group-specific criteria described like other post hoc analysis of SPRINT). This methodology allows for the derivation of nine discrete TTR indices, thereby enabling an assessment of the correlation between different TTR metrics and the incidence of long-term major adverse cardiovascular events (MACEs).

METHODS

This was a post hoc analysis of the SPRINT. We requested the anonymized, limited-access data sets of the SPRINT through the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Coordinating Center (NHLBI BioLINCC). This study protocol was approved by ethical Review Boards at Shanghai 10th People's Hospital (ID of the approval: SHSY-IEC-5.0/22K179/P01) and NHLBI BioLINCC. All participants provided informed consent in the SPRINT.

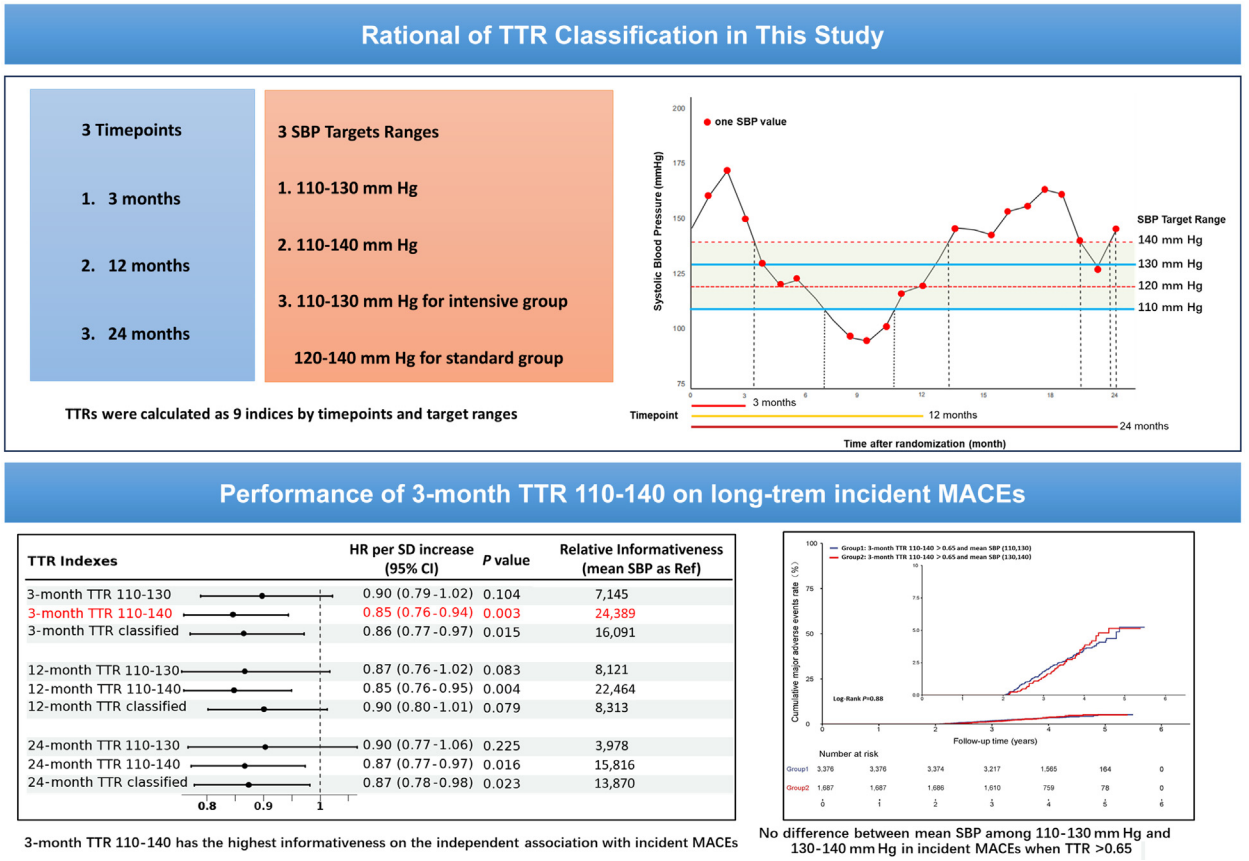
STUDY POPULATION. The SPRINT trial was a multicenter, open-label, randomized controlled study comparing intensive and standard SBP therapies. A total of 9,361 adults with hypertension and increased cardiovascular risk were enrolled, excluding those with diabetes or prior stroke. The details of the SPRINT have been reported previously.[12]

For this study, participants in SPRINT were enrolled if they had BP records at the 1st, 2nd, 3rd, 12th, and 24th month during the follow-up. Participants experiencing events of interest in the first 24 months or with missing baseline data were excluded. The details of subject screening process are shown in Supplemental Figure 1.

BLOOD PRESSURE MEASUREMENTS AND DEFINITION OF TIME IN TARGET RANGE. In SPRINT, BP was recorded at baseline and then monthly in the initial 3 months, and every 3 months thereafter. Trained staff measured BP three times per visit after participants had been seated for at least 5 minutes. The study utilized the average of these three BP readings.[12] Using these records from months 1 to 24, we calculated these SBP TTR indices, defined as the percentage of time that a patient's SBP remained within a specified target range over a given period.[4] We calculated nine TTR indices based on various time points (3, 12, 24 months) and SBP ranges (110-130 mm Hg for all, 110-140 mm Hg for all, or group-specific ranges including 110-130 mm Hg for intensive and 120-140 mm Hg for standard treatment groups). "TTR classified" refers to the index using group-specific ranges (**Central Illustration**). To calculate these TTR indices, we used Roosendaal's linear interpolation to estimate changes in SBP between measurements. Then, we divided the follow-up period into 10,000 segments, assigned SBP value to each, respectively, and calculated the SBP TTR index by determining the percentage of segments that within the target SBP ranges.

FOLLOW-UP AND STUDY OUTCOMES. Participants were followed until the study end or their first outcome event occurring 2 years later. The median follow-up was 3.91 years (95% CI: 3.47-4.44). MACEs, the primary outcome, included cardiovascular death (CV death), nonfatal MI, nonfatal stroke, and heart

CENTRAL ILLUSTRATION **Association Between Systolic Blood Pressure Time in Target Range Indices and Adverse Cardiovascular Outcomes**



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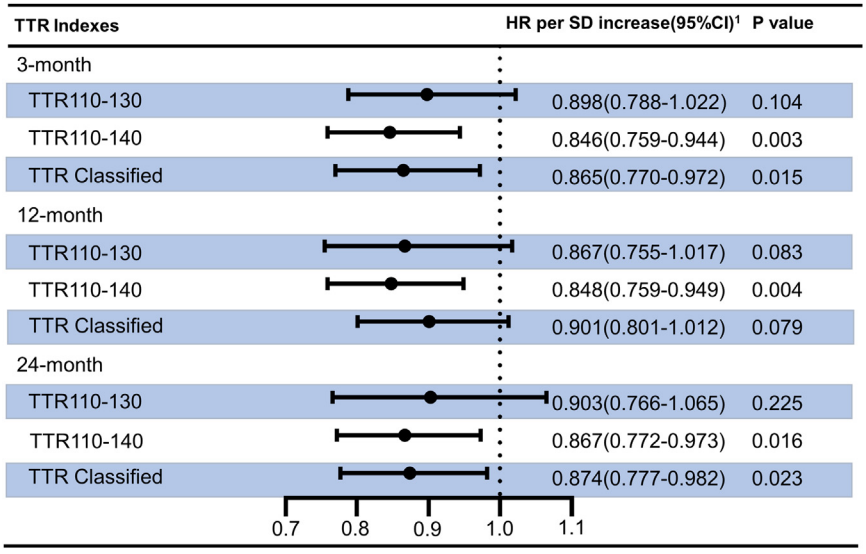
This figure depicts most common time points and target ranges for SBP TTR calculation (top left) and schematic plot (top right) of SBP TTR definition. SBP time in 110 to 140 mm Hg range of initial 3 months (3-month TTR 110-140) has independent association and greatest informativeness with MACEs incidence, adjusted for cardiovascular risk factors and baseline SBP (bottom left). No difference between mean SBP among 110-130 mm Hg and 130-140 mm Hg was shown in MACEs incidence when early SBP controlled well (3-month TTR 110-140 >0.65). Abbreviations as in Figures 1 and 3.

failure. Secondary outcomes were MACEs components and all-cause mortality. Outcomes were determined by an independent, blinded adjudication committee in SPRINT.

SENSITIVE ANALYSIS. To validate the stability of our results, we expanded our MACEs definition by including acute coronary syndrome without MI (NOMIACS), consistent with the primary outcome in SPRINT. Multivariable Cox models were utilized to examine the association between the 3-month TTR 110 to 140 index and new defined MACEs occurred after 3, 12, and 24 months. In parallel, aligning with the intensive target of SBP <120 mm Hg, we analyzed the association between TTR 100 to 120 indices and long-term MACEs occurring 2 years later. In the primary analysis, we set our primary outcomes after the maximum observation period to compare different TTR indicators with long-term cardiovascular risks. To address the potential bias caused by excluding participants with events occurring within the initial 24 months, we also analyzed the independent association between different TTR indices and incident MACEs after their observation periods, adjusted for priori cardiovascular risk factors by multivariable Cox regression.

STATISTICAL ANALYSIS. Participants were divided by sex for baseline demographic and clinical data. Categorical data are shown as numbers (percentages), while continuous data are reported as mean ± SD for normally distributed variables or as median (25th-

FIGURE 1 Association Between Various Time Point and Threshold-Derived Time in Target Ranges and Major Adverse Cardiovascular Event



Model[1] was adjusted by age, sex, race, BMI, eGFR, treatment group, framingham cardiovascular risk score, and baseline SBP. BMI = body mass index; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; TTR = time in target range.

75th percentile) for skewed data. Normality was assessed with the Shapiro-Wilk test. Statistical differences were evaluated using the Welch *t*-test for normally distributed variables, the Wilcoxon rank-sum test for non-normally distributed variables, and the Pearson chi-squared test for categorical variables.

To investigate the independent associations of MACEs with all SBP-TTR indices, we conducted multivariable Cox regression models, adjusting for a series of cardiovascular risk factors including age, sex, race, body mass index, estimated glomerular filtration rate, treatment group, Framingham cardiovascular risk score, and baseline SBP. We then established a basic Cox model for incident MACEs, using the same covariables as a benchmark for comparison. Subsequently, those TTR indices that showed significant independent associations were included as covariables in the basic Cox model for further analysis. C-statistics and model informativeness[13] were utilized to evaluate the incremental improvement of each SBP TTR index over the basic Cox model. The SBP TTR index with the highest C-statistic and informativeness was identified as the optimal TTR index, demonstrating the best independent correlation with MACEs occurrence after 2 years. Multivariable Cox models, incorporating this index alongside mean SBP or SBP SD, were conducted to assess its independent correlation with MACEs incidence. Subgroup analyses based on sex, age, race, chronic kidney disease and CV death history, and treatment groups at baseline were also conducted to explore the correlation between this TTR index and MACEs.

To evaluate the nonlinear relationship between the TTR index and MACEs HRs, we utilized restricted cubic spline (RCS) analysis, adjusted for covariables consistent with prior Cox models. The cutoff value for the TTR index was derived by identifying the inflection point on the RCS plot that corresponded to the maximum likelihood estimate. Subsequently, the

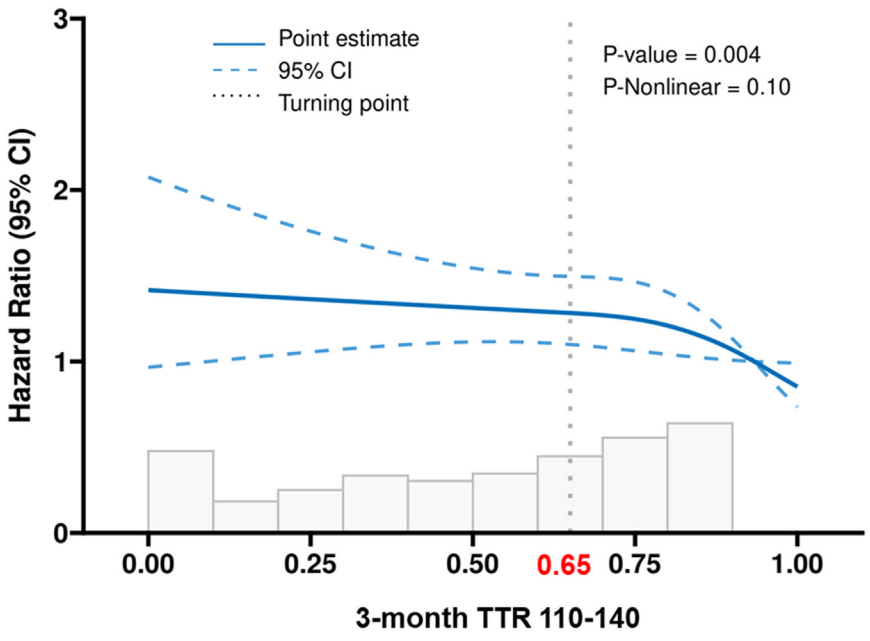
TABLE 1 Relationship Between Various Time in Target Range Indices and Major Adverse Cardiovascular Events

Model	C-Statistic	Informativeness	
		Chi-Square Statistics	Relative Informativeness
Base model (BM)[a]	0.65 (0.62-0.68)	/	/
BM + mean SBP	0.65 (0.62-0.68)	0.037	100%
BM + SBP SD	0.65 (0.61-0.68)	1.250	3,378%
BM + 3-mo TTR 110-140	0.66 (0.64-0.69)	9.024	24,389%
BM + 12-mo TTR 110-140	0.66 (0.63-0.69)	8.312	22,464%
BM + 24-mo TTR 110-140	0.66 (0.62-0.69)	5.852	15,816%
BM + 3-mo TTR classified	0.66 (0.62-0.69)	5.954	16,091%
BM + 24-mo TTR classified	0.65 (0.62-0.69)	5.132	13,870%

[a]Base model was adjusted for age, sex, race, BMI, eGFR, 10-y cardiovascular risk score, treatment group, and baseline SBP.

SBP = systolic blood pressure; TTR = time in target range.

FIGURE 2 Linear Association Between 3-Month Time in Target Range of 110 to 140 and HR



HR of long-term MACEs was adjusted for age, sex, race, BMI, eGFR, 10-year cardiovascular risk score, treatment group, and baseline SBP. Cutoff value were inferred by threshold saturation analysis in RCS curve. MACE = major adverse cardiovascular event; RCS = restricted cubic spline; other abbreviations as in Figure 1.

study population was stratified based on this cutoff value for baseline characterization. The clinical significance of this cutoff for MACEs incidence was ascertained by categorizing participants into early SBP controlled and uncontrolled groups. Group comparisons were conducted using multivariable Cox models, with the TTR index considered both as a binary and continuous variable. Furthermore, each group was subdivided into subgroups based on mean SBP ranges of 110 to 130 mm Hg and 130 to 140 mm Hg. Kaplan-Meier curves and log-rank tests were subsequently employed to assess differences in MACEs cumulative event rates among these subgroups. Additionally, multivariable Cox models were used to confirm statistical differences among subgroups. This stratification allowed for a more granular analysis of the impact of SBP control on MACEs incidence, adjusted for traditional cardiovascular risk factors within each subgroup.

All Cox model analyses were adjusted for a series of priori confounders in this study, verified for the proportional hazards assumption using Schoenfeld residuals with time plots. We conducted all analyses using R version 4.0.1 (developed by R Core Team, R Foundation for Statistical Computing) and SPSS version 26.0 (IBM Corporation).

RESULTS

BASELINE CHARACTERISTICS OF STUDY POPULATION. A total of 7,134 participants were enrolled in this study (Supplemental Figure 1), with a mean age of 68 years. Among them, 2,481 (34.7%) were female, and 870 (12.2%) were current smokers (Supplemental Table 1). The median follow-up period was 3.91 years, with a 95% CI of 3.47 to 4.44 years.

RELATIONSHIP BETWEEN SBP TTR INDICES AND LONG-TERM INCIDENT MACEs. We evaluated the independent correlation between various TTR indices and the incidence of MACEs, presenting HRs per SD increase in multiple multivariable Cox models (Figure 1). Notably, the 3-month TTR 110 to 140 ($P = 0.003$), 3-month TTR classified ($P = 0.015$), 12-month TTR 110 to 140 ($P = 0.004$), 24-month TTR 110 to 140 ($P = 0.016$), and 24-month TTR classified ($P = 0.023$) were associated with long-term incident MACEs, independent from conventional cardiovascular risk factors (Figure 1). Among these, the 3-month TTR 110 to 140 index provided the most substantial improvement to the basic cardiovascular Cox model for MACE incidence, with a C-statistic of 0.661 (95% CI: 0.628-0.694) and a relative informativeness of 24,389%, thus emerging as the optimal SBP TTR

TABLE 2 Patient Demographics and Baseline Characteristics According to Time in Target Range Groups (>0.65 and ≤0.65)

		TTR Groups		
	Overall (N = 7,134)	>0.65 (n = 5,127)	≤0.65 (n = 2,007)	*P* Value[a]
Age (y)	67 (61-75)	67 (61-75)	68 (61-76)	0.009
Group				<0.001
Standard	3,539 (50%)	2,392 (47%)	1,147 (57%)	
Intensive	3,595 (50%)	2,735 (53%)	860 (43%)	
Sex				<0.001
Male	4,653 (65%)	3,437 (67%)	1,216 (61%)	
Female	2,481 (35%)	1,690 (33%)	791 (39%)	
Race				0.004
Non-Black	4,989 (70%)	3,635 (71%)	1,354 (67%)	
Black	2,145 (30%)	1,492 (29%)	653 (33%)	
Smoking status				0.048
Current smoker	870 (12%)	596 (12%)	274 (14%)	
Former smoker	3,094 (43%)	2,251 (44%)	843 (42%)	
Never smoker	3,170 (44%)	2,280 (44%)	890 (44%)	
CV death history				0.031
No	5,725 (80%)	4,147 (81%)	1,578 (79%)	
Yes	1,409 (20%)	980 (19%)	429 (21%)	
CKD history				0.215
No	5,193 (73%)	3,753 (73%)	1,440 (72%)	
Yes	1,941 (27%)	1,374 (27%)	567 (28%)	
BMI (kg/m^2)	29.0 (26.0-32.9)	29.1 (26.1-32.9)	28.8 (25.7-32.9)	0.083
Baseline SBP (mm Hg)	140 (15)	138 (14)	144 (17)	<0.001
Baseline DBP (mm Hg)	78 (12)	78 (11)	79 (13)	0.003
10-y CV death risk	18 (12-25)	17 (12-25)	19 (13-28)	<0.001
Mean SBP (mm Hg)	129 (11)	126 (7)	135 (16)	<0.001
SBP SD	8.3 (4.9-12.5)	7.4 (4.5-11.3)	10.7 (6.7-16.3)	<0.001
SBP TTR (%)	0.93 (0.59-1.00)	1.00 (0.89-1.00)	0.34 (0.13-0.50)	<0.001

Values are median (IQR) or n (%). [a]Wilcoxon rank sum test; Pearson's chi-square test; Welch 2 sample *t*-test.
CKD = chronic kidney disease; DBP = diastolic blood pressure; other abbreviations as in Table 1.

index related to MACEs occurred 2 years later (Table 1). Furthermore, a multivariable Cox model, adjusted for conventional cardiovascular risk factors along with mean SBP or SBP SD, confirmed that the 3-month TTR 110 to 140 index was an independent associated factor of long-term MACEs ($P = 0.001$ along with mean SBP; $P = 0.005$ along with SBP SD) (Supplemental Figure 2). Additionally, subgroup analyses of the 3-month TTR 110 to 140 index in relation to MACEs were conducted across different baseline characteristics, with most subgroups reflecting trends consistent with the overall Cox analysis (Supplemental Figure 3).

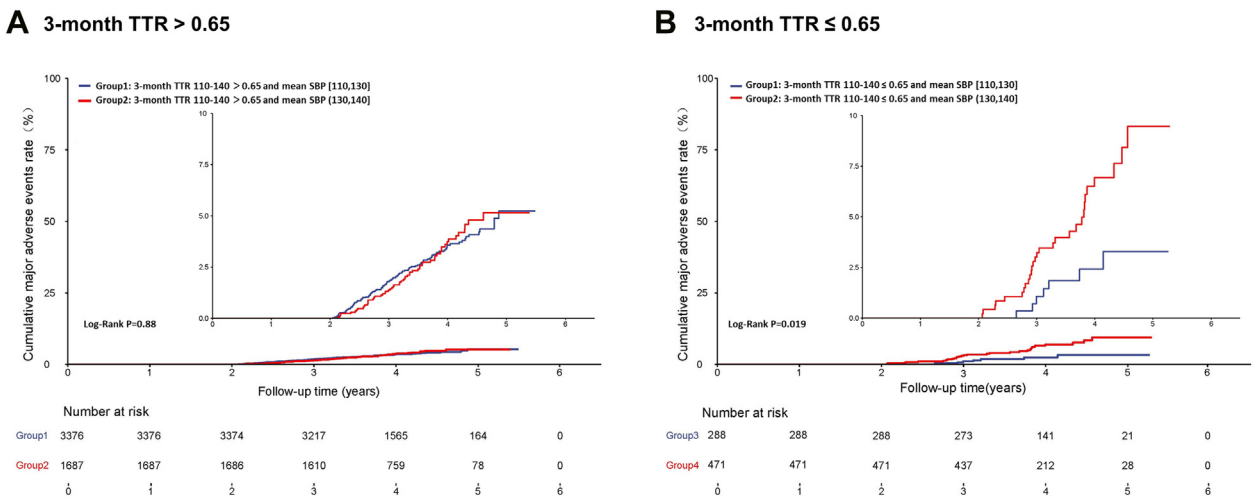
Furthermore, we utilized RCS curve to assess the potential nonlinear relationship between the 3-month TTR 110 to 140 index and the HRs for MACEs, adjusted for covariates from prior Cox models. Our results showed a linear trend consisted between 3-month TTR 110 to 140 index and incident MACEs (P for nonlinear = 0.10) (Figure 2). The inflection point of the RCS plot was identified as 0.65, which was considered as the cutoff value of the 3-month TTR 110 to 140 index (Figure 2). Subsequently, we re-evaluated the study population using this threshold (0.65) for the 3-month TTR 110 to 140 index. The subgroup with a lower TTR (3-month TTR 110-140 ≤0.65) predominantly comprised males, had a higher proportion of Black individuals, current smokers, and exhibited elevated 10-year cardiovascular risk scores, along with higher baseline SBP values and increased 3-month mean SBP and SBP SD (Table 2).

TABLE 3 Validation of the Cutoff Value for 3-Month Time in Target Range 110-140

	TTR as Categorical Variable		TTR as Continuous Variable	
Group	HR per SD Increase (95% CI)	*P* Value	HR per SD Increase (95% CI)	*P* Value
TTR ≤0.65	Ref.		0.88 (0.65-1.19)	0.407
TTR >0.65	0.76 (0.59-0.98)	0.033	0.50 (0.33-0.75)	0.001

HR per SD increase was adjusted for age, sex, race, BMI, eGFR, 10-y cardiovascular risk score, treatment group, and baseline SBP.
Abbreviation as in Table 1.

FIGURE 3 Cumulative Events Rate of Major Adverse Cardiovascular Events Among Various Mean Systolic Blood Pressure and 3-Month Time in Target Range Subgroups



Participants were stratified into different groups according to the cutoff value of 3-month TTR 110 to 140, then the difference in cumulative MACEs incidence between different mean SBP range subgroups were discussed. Statistical difference was tested by log-rank method. Abbreviations as in **Figures 1 and 2**.

THE IMPORTANCE OF EARLY SBP CONTROLLED. We divided participants based on their 3-month TTR 110 to 140 value into two groups: those with TTR ≤0.65 (poorer early SBP control) and those with TTR > 0.65 (better early SBP control). This classification showed an independent association with long-term MACEs risk (HR per SD increase: 0.76 [95% CI: 0.59-0.98], $P = 0.033$). Further analysis found a statistical difference in MACEs risk between the groups (TTR>0.65: $P = 0.407$; TTR ≤ 0.65: $P = 0.001$), as shown in **Table 3**. Subgroup analyses, stratified by mean SBP levels (110-130 mm Hg and 130-140 mm Hg) and early SBP control (3-month TTR >0.65 and ≤0.65), are presented in **Figure 3** and Supplemental Table 2. No MACEs risk difference was seen between different mean SBP subgroups in those with good early control (3-month TTR >0.65) (log-rank $P = 0.88$). But in those with poor early control (3-month TTR ≤0.65), a higher mean SBP of 130 to 140 mm Hg was related to increased MACEs risk (log-rank $P = 0.019$). Multivariable Cox analyses, adjusting for cardiovascular risk factors, confirmed these findings in Supplemental Tables 3 and 4, no matter in which treatment groups.

SENSITIVITY ANALYSIS RESULTS: TEMPORAL AND RANGE DYNAMICS OF TTR INDICES AND MACEs RISK. In alignment with the intensive BP control target of 120 mm Hg, we conducted a sensitivity analysis using a new target range of 100 to 120 mm Hg at 3 different time points. Our results indicated no independent association between the TTR 100 to 120 at 3, 12, and 24 months and MACEs after 2 years (Supplemental Table 5). Expanding the MACEs definition to include other acute coronary syndromes not resulting in MI, as the primary outcome in the SPRINT, the 3-month TTR 110 to 140 index maintained an independent association with MACEs occurred after different time points (Supplemental Table 6). Furthermore, we evaluated the independence of relationship between the corresponding TTR indicators and MACEs at different time points, we found the 3-month TTR 110 to 130 to be independently associated with MACEs after 3 months, with other TTR indicators consisted with the previous study findings shown in **Figure 1** (Supplemental Table 7).

DISCUSSION

TTR, the proportion of time that BP is within the target range during a certain period, has been considered an efficient index to reflect BP control in prior studies.[4-9] It was demonstrated to be independently association with various clinical adverse outcomes, including composite MACEs,[4] heart failure hospitalization,[8] CV death,[14] kidney events,[7,15] stroke,[16] incident atrial fibrillation,[6] and probable dementia.[5] Based on that data, the 2023 European Society of Cardiology hypertension management guidelines[2] included TTR as a recommended

assessment of BP control. However, variability in the calculation of TTR across above studies, in terms of methodology, timing, and BP thresholds, posed challenges for its clinical application. Hence, understanding the different time points and target SBP ranges in SBP TTR calculation to the relationship of TTR index and their association with MACEs is essential.

The time points when the TTR index is measured significantly impact its clinical relevance, with durations ranging from very short-term[17] (24 hours ambulatory blood pressure monitoring), short-term (3-6 months),[4,7,18] to longer-term (even up to 15 years)[14] in different studies. In this study, we selected 3 different time points to examine the influence of time points on the association between TTR indices and long-term incident MACEs. We found the 3-month TTR indices (including TTR 110-140, TTR classified) were associated with MACEs (**Figure 1**, Supplemental Table 7), even slightly better than some TTR indices calculated over 12 or 24 months. However, the BP measurement strategy in SPRINT, with monthly checks for the initial 3 months and then every 3 months, may explain our findings. Within the SPRINT study, the most significant fluctuations and reductions in mean SBP occurred during the first 3 months of the treatment phase, irrespective of the specific intervention, and were closely associated with the initiation of antihypertensive therapy. This result underscored the significance of BP control during the initial phase of antihypertensive therapy, particularly the initial 3 months, which not only relates to the early MACEs but also the long-term MACEs. In addition, because TTR is calculated by linear interpolation method, the BP sampling frequency may affect TTR calculation. Monthly BP intervention in the first 3 months may be essential for BP stability in patients. Achieving stable BP in target range within 3 months means effective antihypertensive treatment and early BP controlled, which is directly related to the decreased risk of long-term MACE. In this scenario, the lower risk of MACE may be due to better patient responsiveness and medical adherence, both of which are associated with better long-term outcomes.

Regarding the optimal target BP range, post hoc analysis of SPRINT applied 120 to 140 mm Hg for standard and 110 to 130 mm Hg for intensive group, whereas other studies usually adopt ranges such as 110 to 130 mm Hg, 120 to 130 mm Hg, and 120 to 140 mm Hg. Our findings suggest that the range of 110-140 mm Hg in TTR calculation may have the greatest informativeness for long-term MACEs incidence (**Figure 1, Central Illustration**). The reason could be that previous studies evaluating intensive BP control mainly focused on the mean SBP control, without considering the early stabilization of SBP.

Based on this hypothesis, our further analysis revealed a linear relationship between 3-month TTR 110 to 140 index and the incidence of MACE (*P* for nonlinearity = 0.10, shown in **Figure 2**). A cutoff value of 0.65 was inferred by maximum likelihood estimation with maximum slope change (**Figure 2**). We found no independent association between 3-month TTR 110 to 140 index with long-term incident MACE when TTR values ≤0.65 (**Table 3**), whereas TTR values >0.65 independently correlated with a reduction in MACE. Based on these findings, we inferred the TTR value >0.65 to define "good early BP control." The TTR value >0.65 indicates that the patient was within BP target range 65% of the time or more. However, its application in other populations may be limited and requires further study to validate.

To expand the application of this cutoff value, participants with good early BP control (TTR ≥0.65) were divided into two subgroups based on two mean SBP ranges: 110-130 mm Hg and 130-140 mm Hg. However, there was no significant difference in long-term MACEs between these subgroups was found, with good early BP control (3-month TTR 110-140 >0.65) (**Figure 3A, Central Illustration**). Notably, poor early BP control (3-month TTR 110-140 ≤ 0.65), coupled with a SBP of 130-140 mm Hg, was associated with the increased risk of long-term MACE (**Figure 3B**). Therefore, for patients who have poor early stable BP control, mean SBP should be maintained within the 110-130 mm Hg range. Notably, the mean systolic BP was 121.5 mm Hg in the intensive-treatment group and 134.6 mm Hg in the standard-treatment group in SPRINT. The overall control of mean SBP in the population is at the target range 110 to 140 mm Hg. However, different levels of early BP control were demonstrated to be directly related to long-term incident MACEs, particularly with the classification by 0.65 as TTR threshold. Consequently, alongside considering mean BP within the target range, the degree of early BP control is crucial. The 3-month TTR 110 to 140 index and its cutoff value worth to be considered as a recommend indicator in this situation.

CLINICAL APPLICATION. Our results suggest that the TTR metric in the early stages of antihypertensive treatment (3 months) is not only directly related to the occurrence of long-term MACEs (**Figure 1**) but also independently associated with MACEs occurring after the observation period (Supplemental Table 7). Hence, in the early stage (3-month) of

antihypertensive treatment, regular BP monitoring and timely medication adjustments are important for hypertensive patients to achieve stable BP control. Our study also suggests that for hypertensive patients without good early BP control, maintaining BP within the 110 to 130 mm Hg range may be directly associated with a lower risk of long-term MACEs. However, this conclusion is based on a single study population and further studies are needed. The BP control targets in the real-world may vary for different hypertensive populations, particularly those with other comorbidities. This study highlights the potential value of the 3-month TTR 110 to 140 index in early BP control and antihypertensive assessment, supporting the notion that antihypertensive programs for adjustment of medications could have an important impact on long-term cardiovascular health and potentially prevent long-term MACE. Furthermore, the TTR index cutoff of 0.65 was inferred to evaluate whether the early BP control was satisfactory. In people with poor early BP control (TTR 110-140 index ≤0.65 for 3-month), mean SBP control at 110 to 130 or 130 to 140 mm Hg had different for long-term MACE risk, suggesting that the combination of mean SBP and TTR may achieve a more precise stratification of cardiovascular risk in the hypertensive population to hint the adjustment of antihypertensive regimen for patients.

STUDY LIMITATION. First, this is a random controlled trial, transferred to cohort for analysis. The impact of treatment may be underestimated. Second, as an association study, whether the reduction of cardiovascular events caused by the decrement of SBP TTR was uncertain. In addition, the threshold of 0.65 in 3-month TTR 110 to 140 index was inferred and tested in the same data set and another cohort is needed to validate this value. However, our results were consistent with previous findings on the independent relationship between TTR indices and MACEs. Finally, our results should be verified in future cohort studies focused on BP control assessment.

CONCLUSIONS

The 3-month TTR with the 110 to 140 mm Hg range is associated with MACEs, indicating the importance of early BP control. The 3-month TTR index with a range of 110 to 140 mm Hg and its inferred cutoff value of 0.65, could serve as an assessment of early BP control to provide a further stratification of cardiovascular risk in the hypertensive population with the combination of mean SBP.

ACKNOWLEDGMENTS The authors appreciate the SPRINT study participants for their clinical data and the staff for data collection efforts.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was financially supported by the Health Youth Talent Project of Shanghai Municipal Health Commission (2022YQ023), Shanghai Municipal Health Commission Clinical Research Project (Youth, 20214Y0152), the National Nature Science Foundation of China (82170388, 82370300), Shanghai Technology Research Leader Program (21XD1434700), the cardiac rehabilitation fund by the International Medical Exchange Foundation (Z-2019-42-1908-3), and Grant for the construction of Innovative Flagship Hospital for Integrated Traditional Chinese and Western Medicine (No. ZY (2021-2023)-0205-05). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Systolic blood pressure time in target range (SBP TTR) is a new indicator to assess the reach and stability of blood pressure. Different computational definitions of SBP TTR have been linked to multiple clinical adverse events (cardiovascular death, non-fatal myocardial infarction, stroke, heart failure, nephro-related adverse events, atrial fibrillation, and dementia). However, at present, there are still disputes about the optimal time points and SBP target ranges of SBP TTR. Here, we report a strong independent association of TTR within 110-140 mmHg for 3 months with adverse cardiovascular events in hypertension populations, superior to other time points (12 months, 12 mm Hg, 12 mm Hg, 24 months) with other SBP target ranges (110-130 mm Hg, TTR-classified). We also suggest that achieving at least 65% of the time within the 110-140 mm Hg can be a useful goal for controlling blood pressure in the initial 3 months. This can be combined with mean SBP to assess and differentiate cardiovascular risk in hypertensive patients.

TRANSLATIONAL OUTLOOK: Our study demonstrates that maintaining a SBP TTR of 65% within 110-140 mm Hg for 3 months strongly associated to reduced MACEs in hypertensive populations, which suggested a potential target for early BP control and maybe optimize the treatment and management of blood pressure in clinical practice. However, these results should be validated in other cohort studies to confirm the generalizability and robustness of the 65% TTR threshold as a reliable indicator for cardiovascular risk stratification and early intervention in hypertension management.

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KEY WORDS blood pressure management, hypertension, time in target range

APPENDIX For supplemental tables and figures, please see the online version of this paper.