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ORIGINAL RESEARCH

Systolic Blood Pressure Time in Target Range and Cardiovascular Disease and Premature Death

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ABSTRACT

BACKGROUND Previous research has suggested that time-in-target range (TTR) for systolic blood pressure (SBP) was associated with adverse cardiovascular events, but real-world data studies remain limited.

OBJECTIVES The purpose of this study was to estimate the SBP-TTR associated with cardiovascular disease (CVD) and premature death among the employed individuals with hypertension.

METHODS This study included 9,552 participants from the workplace hypertension management program initiated by the Kailuan Study in 2009. TTR was calculated using linear interpolation with the target range of SBP between 120 and 140 mm Hg. Multivariable Cox regression was used to evaluate the HR and CI for the association among SBP-TTR and CVD, premature CVD, and premature death.

RESULTS Participants with higher TTR exhibited a reduced number of cardiovascular risk factors. For a 1-SD increment in SBP-TTR, the HR was 0.81 (95% CI: 0.74-0.88) for CVD, 0.76 (95% CI: 0.67-0.86) for premature CVD, and 0.83 (95% CI: 0.74-0.92) for premature death. Furthermore, SBP-TTR was associated with a lower risk of ischemic stroke (HR: 0.81; 95% CI: 0.74-0.90) and hemorrhagic stroke (HR: 0.72; 95% CI: 0.56-0.93), but not myocardial infarction (HR: 0.84; 95% CI: 0.68-1.03). Results were similar when the target range of SBP was redefined as 110 to 130 mm Hg, but there was no significant association between SBP-TTR and hemorrhagic stroke (HR: 0.84; 95% CI: 0.64-1.10).

CONCLUSIONS SBP-TTR was associated with a decreased risk of CVD, premature CVD, and premature death among the employed individuals. (JACC Asia. 2024;4:987-996) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cardiovascular disease (CVD) represents one of the most significant causes of death worldwide and is widely acknowledged as a significant public health issue. In 2016, 71% of the 56.9 million global deaths were attributed to noncommunicable diseases (NCDs), including CVD. It is noteworthy that 42% of these deaths occurred in individuals under the age of 70 years.[1] One of the United Nations' Sustainable Development Goals is to reduce premature death from NCDs by one-third by 2030.[2] To achieve this goal, it is crucial to urgently identify the risk factors contributing to CVD and premature death and to prioritize interventions accordingly. Hypertension is a significant modifiable risk

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure
CVD = cardiovascular disease
MI = myocardial infarction
SBP = systolic blood pressure
TTR = time in target range

factor for CVD and premature death. Meta-analyses predicated on an extensive array of randomized controlled clinical trials have elucidated that for every decrement of 5 mm Hg in systolic blood pressure (SBP), the risks of stroke, heart failure, ischemic heart disease, and cardiovascular-related death diminish by 13%, 13%, 8%, and 5%, respectively.[3] Hypertension guidelines advocate for reducing blood pressure (BP) levels to below 140/90 mm Hg to enhance prognostic outcomes.[4] However, assessing BP control based on a single outpatient measurement is challenging in clinical practice because of the fluctuating nature of BP over time. Prior research has found an association between BP variability and CVD risk, which remains independent of baseline BP measurements.[5,6] Consequently, there arises a pressing need for a comprehensive metric to evaluate the state of BP management.

Time in target range (TTR) serves as a novel metric for BP management, representing the proportion of time during which BP remains within a specified target range relative to the total exposure period.[7] TTR encapsulates both the mean and variability of BP, incorporating variations both within and outside the target range, along with periods of well-maintained BP control. Recent investigations have unveiled associations between SBP-TTR and all-cause death, adverse cardiovascular events, and cognitive impairments among hypertensive patients.[7-9] However, the majority of these studies rely on post hoc analyses of pharmacological intervention trials, evaluating the association between SBP-TTR and the risk of CVD and all-cause death only over relatively short follow-up periods. At present, there is a paucity of evidence from real-world settings with extended follow-up periods, and it remains unclear whether SBP-TTR can be used to predict premature death. In light of this, the present study explores the longitudinal association between SBP-TTR and the risks of CVD and premature death using BP monitoring data from the Kailuan Study, which encompasses a cohort of employed individuals.

METHODS

STUDY POPULATION. This study was conducted as part of the Kailuan Study, a large and dynamic community-based cohort study in Tangshan, China.[10,11] Briefly, the Kailuan Study cohort consists of current and retired employees of the Kailuan Group, a large state-owned coal mining enterprise in China. These participants undergo biennial health examinations at 11 affiliated hospitals of the Kailuan Group. In 2009, the Kailuan Group initiated a population-based occupational health program for workers engaged in coal-related occupations with the objective of improving their overall health status. This program includes measuring BP, distributing medication, and conducting health education sessions, with follow-ups every 2 weeks. The study included participants who had been receiving antihypertensive medication and had participated in the BP monitoring program for a minimum of 6 months. The research followed the Helsinki Declaration principles and received approval from the Institutional Review Board of Kailuan General Hospital.

In this study, 9,744 active employees from the Kailuan cohort who were receiving antihypertensive medication had their BP monitored for a minimum of 6 months, with a minimum of 4 months of BP data collected during the exposure period. We excluded participants with a history of CVD or who had experienced a CVD event within the first 6 months (n = 192), leaving 9,552 participants in the final analytic cohort. The flowchart is shown in Supplemental Figure 1.

BP MEASUREMENTS. BP measurements were conducted according to standardized procedures using calibrated standard mercury sphygmomanometers by health care personnel from the health maintenance hospital. Participants were seated comfortably and observed to rest quietly for 5 minutes before their BP was measured on the right upper arm. The SBP was determined by the first Korotkoff sound, and the diastolic BP was indicated by the fifth Korotkoff sound. Three consecutive measurements were taken, with intervals of 1 to 2 minutes between each reading, and the average value was recorded. Subsequent BP follow-ups occurred every 2 weeks. Following current guidelines,[4] this study established the TTR for SBP as 120 to 140 mm Hg. SBP-TTR was calculated using the linear interpolation method.[12] The linear interpolation assumes a linear change in SBP between the measured SBP readings and utilizes the measured and linearly interpolated SBP changes to calculate TTR. The mean and variability of SBP were determined by calculating the weighted average (SBP-Mean) and the weighted SD (SBP-SD), respectively, of all SBP measurements taken in the preceding 6 months.

ANTIHYPERTENSIVE MEDICATION USE. According to current guidelines,[4] individuals with BP readings of 140/90 mm Hg or higher are recommended to undergo antihypertensive medication therapy. In this study, active employees from the Kailuan group who participated in BP management were given the autonomy to decide whether to accept complimentary medications provided by the health maintenance

hospital. The antihypertensive medications offered included nifedipine, captopril, spironolactone, and hydrochlorothiazide. Clinicians prescribed 1 or a combination of these drugs based on individual health profiles and made necessary adjustments during follow-up visits. For participants who decline the provided medications and opted for self-administration, clinicians verified their medication adherence and offered guidance. All participants were provided with comprehensive health education by health care professionals. The health education emphasized lifestyle modifications, such as weight reduction, low-sodium diets, limited alcohol consumption, increased physical activity, and smoking cessation.

OUTCOMES AND FOLLOW-UP TIME. The primary outcomes were CVD events and premature death. CVD was defined as a composite endpoint consisting of fatal or nonfatal myocardial infarctions (MIs) and strokes. For individuals with 2 or more events during follow-up, only time to first event was considered for each individual. Premature CVD was defined as the occurrence of CVD before the age of 55 years in men and the age of 65 years in women.[13,14] Premature death was defined as death before age 70 years.[15] Baseline time for follow-up was defined as 6 months after managing hypertension. The follow-up time was from baseline time to the date of outcomes, death, loss to follow-up, or December 31, 2020, whichever occurred first.

We used International Classification of Diseases-10th Revision (ICD-10) codes to identify CVD cases (I21 for MI, I60 to I63 for stroke). All participants were part of the Kailuan health care system and had unique medical insurance numbers. The incidence of diseases among these participants was monitored annually by tracking their hospitalization data through their medical insurance numbers. Specialized medical personnel trained by our research team reviewed health care records, auxiliary examination results, medical orders, and nursing documentation from the Kailuan General Hospital and various other hospitals in Tangshan City. The CVD case was documented using an event investigation form designed collaboratively by epidemiologists and clinical medicine experts. The diagnosis of MI was based on the presence of clinical symptoms, alterations in the serum concentrations of cardiac enzymes and biomarkers, and electrocardiographic results.[16] Incident stroke was diagnosed on the basis of neurological signs, clinical symptoms, and neuroimaging tests, including computed tomography or magnetic resonance.[17] Death information was linked to the municipal death registries and checked annually against local residential records, with active confirmation of survival through subdistrict offices.

ASSESSMENT OF PARTICIPANT CHARACTERISTICS. This study is based on the Kailuan cohort. On the day of the Kailuan cohort follow-up, trained professionals administered standardized questionnaires to collect information on individual characteristics such as age and sex, lifestyle factors such as smoking and alcohol consumption, and personal history including medical history and medication usage. Weight, height, and waist circumference were measured by trained field workers during surveys, and body mass index (BMI) was calculated.

All biochemical samples were measured at the central laboratory of the Kailuan General Hospital. Triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured by an enzymatic method using an autoanalyser (Hitachi 747; Hitachi). High-sensitivity C-reactive protein (hsCRP) was measured by high-sensitivity particle-enhanced immunonephelometry assay (Cias Latex CRP-H, Kanto Chemical). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.[18] Chronic kidney disease was defined as an eGFR <60 mL/min/1.73 m^2 or the presence of proteinuria.[19] The CVD risk was evaluated using the China-par model.[20] The baseline characteristics of the participants were determined by contemporaneous follow-up data at month 6 of hypertension management program in the current year.

STATISTICAL ANALYSIS. Baseline characteristics were presented based on the quartiles of SBP-TTR. Continuous variables were evaluated for normality using Shapiro-Wilk test and histograms. Normally distributed continuous variables were expressed as mean $\pm$ SD, and intergroup comparisons were conducted using analysis of variance test. Skewed distributed continuous variables were represented by the median (Q1, Q3), and intergroup comparisons were made using the Mann-Whitney U test. Frequencies and percentages were used to present categorical data, and intergroup differences were assessed through the chi-square test. The Pearson correlation coefficient was used to assess the relationship between SBP-TTR and SBP-Mean, as well as SBP-SD. Kaplan-Meier curves were used to compare the cumulative incidence rates of CVD, premature CVD, and premature death across SBP-TTR groups, followed by the log-rank test for significance. Multivariable Cox proportional hazards regression models were used to analyze the associations among SBP-

TTR categories; each 1-SD increase in SBP-TTR; and the risks of CVD, premature CVD, and premature death. Furthermore, we tested for trend by treating the SBP-TTR categories as continuous in the model. The models were adjusted for variables such as age, sex, baseline SBP, BMI, LDL-C, HDL-C, hsCRP, eGFR, smoking status, alcohol consumption, physical exercise, diabetes, educational level, and family history of CVD. Covariates were chosen a priori based on previous research and clinical knowledge.[7,8] In addition, we repeated the analysis while controlling TTR within the range of 110 to 130 mm Hg. Furthermore, separate analyses were conducted for each individual cardiovascular outcome. The Cox model Schoenfeld residuals test did not indicate any violation of the proportional hazard assumption.

Several sensitivity analyses were conducted to evaluate the robustness of the association between SBP-TTR and the risks of CVD, premature CVD, and premature death. First, we conducted lagged analyses by excluding endpoint events that occurred within the first 2 years of follow-up. Second, we also examined whether the duration of the exposure period affected the association between SBP-TTR and endpoint events by calculating SBP-TTR using BP records within a 12-month timeframe for analysis. Third, to investigate whether SBP-TTR predicted CVD, premature CVD, and premature death independently of SBP-Mean and SBP-SD, we included SBP-Mean and SBP-SD in fully adjusted Cox proportional hazards regression models separately. Fourth, we divided the follow-up period into 2 stages to explore potential differences in the impact of SBP-TTR on short- and long-term prognosis: one within the initial 5 years and the other for the remaining follow-up period. We analyzed the associations among SBP-TTR and the risks of CVD, premature CVD, and premature death for each respective period.

Stratified analyses were conducted by baseline characteristics, including age groups (<45 and ≥45 years),[21] sex (male and female), BMI status (<24 and ≥24 kg/m^2),[22] hsCRP groups (<2 and ≥2 mg/dL),[23] China-par score (<10% and ≥10%), and renal function.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc) and Stata software version 16.1 (StataCorp). Statistical significance was defined as a 2-sided P value <0.05.

RESULTS

The study participants had an average age of 47.60 ± 6.92 years, and 9,198 individuals (96.29%) were men. The median SBP-TTR was 56% (Q1, Q3: 18%, 86%). The mean SBP level during the initial measurement was 142.47 mm Hg, which decreased to 136.46 mm Hg 6 months later. At baseline, quartile 4 had significantly lower baseline SBP, BMI, HDL-C, FBG, hsCRP, SBP-Mean, SBP-SD, and smoking, drinking, diabetes mellitus, high education rates compared with quartile 1. Conversely, LDL-C levels were higher in quartile 3 than in quartile 1, as shown in **Table 1**. The frequency of BP measurements during the exposure period ranged from 4 to 13 times, with a median of 11 (Q1, Q3: 9, 12) measurements. The correlation coefficient between SBP-TTR and SBP-Mean was $r = -0.74$, while it was $r = -0.10$ with SBP-SD.

ASSOCIATION OF SBP-TTR WITH CVD EVENTS. Of the 808 participants who experienced a CVD event (the average age of onset was 55.44 years), 345 cases (42.70%) were premature CVD. The quartile 1 group with low SBP-TTR had a higher cumulative incidence rate of CVD and premature CVD compared with the quartile 4 group (**Figure 1**). In the fully adjusted model, the HRs for CVD risk were 0.86 (95% CI: 0.71-1.03) for quartile 2, 0.64 (95% CI: 0.51-0.80) for quartile 3 and 0.61 (95% CI: 0.49-0.77) for quartile 4, compared with quartile 1. Similarly, compared with the quartile 1, the HR of having a high premature CVD risk for the quartiles 2, 3, and 4 were statistically significant. After converting SBP-TTR into a continuous variable, an increase of 1 SD in SBP-TTR was associated with a 19% decrease in the risk of CVD (HR: 0.81; 95% CI: 0.74 to 0.88), and a 24% decrease in premature CVD (HR: 0.76; 95% CI: 0.67 to 0.86), as shown in **Table 2**.

ASSOCIATION OF SBP-TTR WITH PREMATURE DEATH. During the follow-up period, 489 participants experienced premature death events, with an average age of death of 56.52 years. Cumulative incidence of premature death was lower in the quartile 3 group compared with quartile 1 group (**Figure 1**). The HRs comparing the reference category of quartile 1 against quartiles 2, 3, and 4 were 0.80 (95% CI: 0.63-1.01), 0.61 (95% CI: 0.46-0.81), and 0.65 (95% CI: 0.49-0.87), respectively. Additionally, for each 1-SD increase in SBP-TTR, there was a 17% decrease in the risk of premature death (HR: 0.83; 95% CI: 0.74-0.92) (**Table 2**).

SENSITIVITY ANALYSES. We performed a series of sensitivity analyses to assess our primary results, and found similar results in some analysis (Supplemental Tables 1 and 2). However, when simultaneously adjusting for baseline SBP and SBP-Mean, the association among SBP-TTR and CVD, premature CVD, and premature death events disappeared

TABLE 1 Baseline Characteristics

	Quartile 1 TTR <18% (n = 2,365)	Quartile 2 TTR 18%-<56% (n = 2,385)	Quartile 3 TTR 56%-<85% (n = 2,357)	Quartile 4 TTR ≥85% (n = 2,445)	*P* Value
Age, y	48.41 ± 6.66	48.00 ± 6.97	47.30 ± 6.91	46.74 ± 7.03	<0.001
Male	2,301 (97.29)	2,298 (96.35)	2,247 (95.33)	2,352 (96.20)	0.005
SBP, mm Hg	147.36 ± 12.75	137.37 ± 12.07	131.90 ± 10.55	129.44 ± 7.85	<0.001
BMI, kg/m^2	26.35 ± 12.75	26.06 ± 3.24	25.89 ± 3.32	25.79 ± 3.00	<0.001
FBG, mmol/L	6.18 ± 1.92	5.95 ± 2.15	5.94 ± 2.99	5.87 ± 2.32	<0.001
LDL-C, mmol/L	2.56 ± 0.78	2.60 ± 0.78	2.62 ± 0.74	2.66 ± 0.70	<0.001
HDL-C, mmol/L	1.54 ± 0.48	1.48 ± 0.44	1.48 ± 0.43	1.44 ± 0.40	<0.001
HsCRP, mg/dL	1.50 (0.70, 2.79)	1.30 (0.60, 2.50)	1.22 (0.52, 2.40)	1.20 (0.50, 2.30)	<0.001
eGFR, mL/min·1.73 m^2	93.91 ± 19.44	94.75 ± 18.98	94.91 ± 19.30	93.82 ± 19.67	0.113
China-par, %	11.52 ± 5.48	8.90 ± 4.60	7.45 ± 3.95	6.69 ± 3.40	<0.001
SBP-Mean, mm Hg	150.12 ± 10.33	139.75 ± 8.40	132.53 ± 6.60	128.81 ± 4.39	<0.001
SBP-SD, mm Hg	12.39 ± 10.35	14.64 ± 10.74	14.65 ± 9.96	9.11 ± 7.42	<0.001
Smoking	1,331 (56.28)	1,237 (51.87)	1,196 (50.74)	1,180 (48.26)	<0.001
Drinking	1,354 (57.25)	1,332 (55.85)	1,257 (53.33)	1,238 (50.63)	<0.001
Exercising	248 (10.49)	254 (10.65)	244 (10.35)	211 (8.63)	0.067
Diabetes mellitus	196 (8.29)	159 (6.67)	168 (7.13)	148 (6.05)	0.019
High school and above	493 (20.85)	544 (22.81)	524 (22.23)	640 (26.18)	<0.001
Family history of cardiovascular disease	442 (18.69)	450 (18.87)	468 (19.86)	409 (16.73)	0.042

Values are mean ± SD or n (%).

BMI = body mass index; China-par = cardiovascular risk assessment based on the China-par model; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; SBP-Mean = the mean of systolic blood pressure; SBP-SD = the SD of systolic blood pressure.

(Supplemental Table 3). When dividing the follow-up duration into 2 phases, SBP-TTR was not found to be associated with premature death events within the initial 5-year period. When excluding data from the initial 5-year period to predict long-term outcomes, the observed trends remained consistent with the primary analysis and achieved statistical significance (Supplemental Table 4).

ADDITIONAL ANALYSES. When SBP was controlled within the range of 110 to 130 mm Hg, SBP-TTR was associated with a lower risk of CVD, premature CVD, and premature death, independent of baseline SBP and SBP-Mean (Supplemental Table 5). In addition, it was observed that maintaining SBP levels within 110 to 130 mm Hg associated with a lower risk of MI and ischemic stroke, but not with hemorrhagic stroke (**Table 3**).

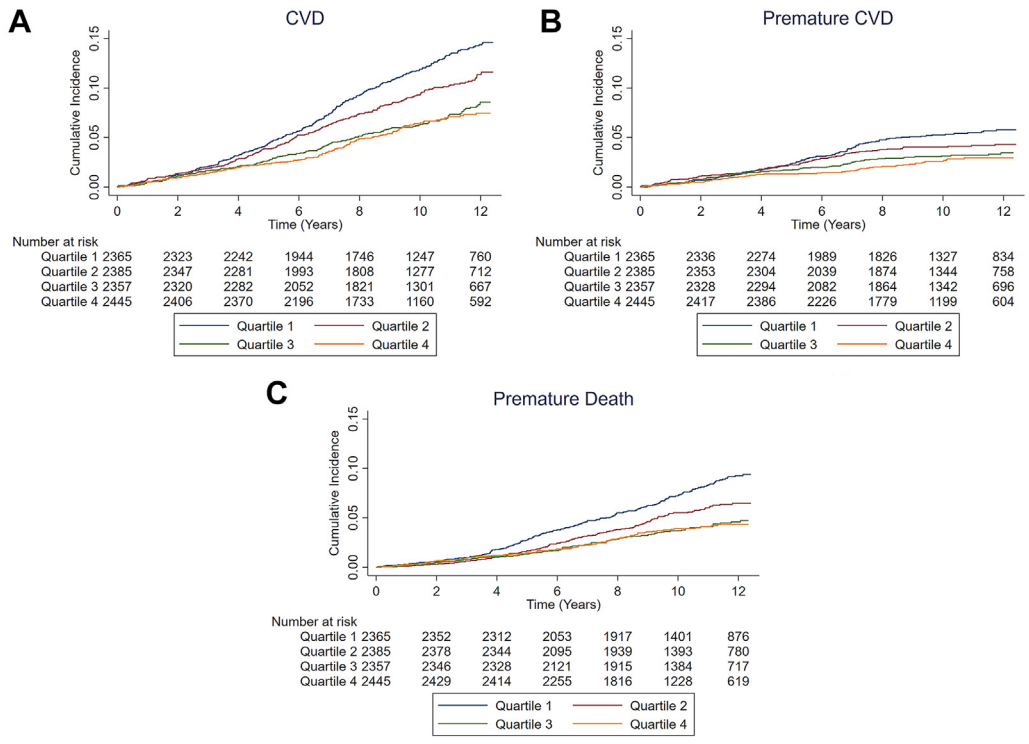
SUBGROUP ANALYSIS. Subgroup analysis result showed that the benefit of a high SBP-TTR on CVD was more prominent in women than in men (*P* for interaction <0.05). Additionally, an increase of 1 SD in SBP-TTR was significantly associated with a lower risk of premature death among participants with a high cardiovascular risk score (*P* for interaction <0.05). However, the associations attenuated or even became insignificant in participants with a low cardiovascular risk score (Supplemental Table 6).

DISCUSSION

This study focused on employed individuals as an observational cohort, using workplace SBP data to calculate TTR. The results showed that, after adjustment for traditional cardiovascular risk factors, higher TTR with an SBP target of 120 to 140 mm Hg was associated with a lower risk of CVD, premature CVD, and premature death. Furthermore, controlling SBP within the range of 110 to 130 mm Hg was associated with additional reductions in the risks of CVD, premature CVD, and premature death (**Central Illustration**).

Based on current guidelines,[4] this study defined the SBP target range for analysis as 120 to 140 mm Hg when calculating SBP-TTR. The results showed that, compared with the quartile 1 group, the quartile 4 group had a 39% reduction in the risk of CVD and a 51% reduction in the risk of premature CVD. For every 1-SD increase in SBP-TTR, there was a 19% reduction in the risk of CVD and a 24% reduction in the risk of premature CVD. Our results are consistent with several previous studies. A post hoc analysis of the

FIGURE 1 Cumulative Incidence of Endpoints Events



The figure shows the cumulative risk of cardiovascular disease (CVD) (A), premature CVD (B), and premature death (C) according to quartiles of systolic blood pressure time in target range.

SPRINT study showed that during a median follow-up of 3.3 years, each 1-SD increase in SBP-TTR was associated with a 19% reduction in the risk of adverse cardiovascular outcomes, including cardiovascular death, MI, non-MI acute coronary syndrome, stroke, or acute decompensated heart failure.[7] Buckley et al[24] used BP data from both the SPRINT (Systolic Blood Pressure Intervention Trial) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) trials and showed that, compared with the group with an SBP-TTR of 0%, the SBP-TTR 70% to <100% and SBP-TTR = 100% groups had 31% and 45% reductions in adverse cardiovascular outcomes, respectively.

Compared with these 2 post hoc analyses, our study had a longer duration of BP monitoring, allowing for a more comprehensive assessment of BP control over time. We also had a larger number of BP recordings, which enabled us to calculate TTR more accurately, providing a more precise measure of BP control effectiveness. Furthermore, our study population consisted of young working individuals from an industrial environment, which was a unique demographic not extensively studied in similar analyses. This population was often exposed to specific occupational hazards and health challenges, making our findings particularly relevant to this group.

Additionally, it was observed that a higher SBP-TTR was associated with a lower risk of premature death. Specifically, for each 1-SD increase in SBP-TTR, there was a 17% decrease in the risk of premature death. Doumas et al[25] also found that hypertensive patients with a longer SBP-TTR experienced a lower all-cause death risk. However, this study did not provide detailed demographic and clinical characteristics, such as BMI, lipid profiles, and medical history. This limitation restricts the interpretation of the relationship between SBP-TTR and death risk. In contrast, our study accounted for a more comprehensive set of confounding factors, providing a more nuanced understanding of the association between SBP-TTR and death risk. Our results highlight that hypertensive patients with a high SBP-TTR

TABLE 2 Associations of SBP-TTR and Cardiovascular Outcomes

	n	Incidence Density	Model 1	*P* Value	Model 2	*P* Value
CVD						
Quartile 1	2,365	12.43	Reference		Reference	
Quartile 2	2,385	9.75	0.80 (0.67-0.95)	0.011	0.86 (0.71-1.03)	0.111
Quartile 3	2,357	6.83	0.58 (0.48-0.71)	<0.001	0.64 (0.51-0.80)	<0.001
Quartile 4	2,445	6.27	0.55 (0.45-0.67)	<0.001	0.61 (0.49-0.77)	<0.001
1-SD			0.78 (0.72-0.83)	<0.001	0.81 (0.74-0.88)	<0.001
P value for trend			<0.001		<0.001	
Premature CVD						
Quartile 1	2,365	5.12	Reference		Reference	
Quartile 2	2,385	3.97	0.75 (0.57-0.98)	0.035	0.79 (0.59-1.05)	0.111
Quartile 3	2,357	3.09	0.55 (0.41-0.75)	<0.001	0.60 (0.43-0.83)	0.002
Quartile 4	2,445	2.59	0.44 (0.33-0.61)	<0.001	0.49 (0.34-0.70)	<0.001
1-SD			0.73 (0.66-0.82)	<0.001	0.76 (0.67-0.86)	<0.001
P value for trend			<0.001		0.001	
Premature death						
Quartile 1	2,365	7.67	Reference		Reference	
Quartile 2	2,385	5.34	0.71 (0.57-0.89)	0.003	0.80 (0.63-1.01)	0.061
Quartile 3	2,357	3.80	0.54 (0.42-0.69)	<0.001	0.61 (0.46-0.81)	<0.001
Quartile 4	2,445	3.68	0.54 (0.42-0.70)	<0.001	0.65 (0.49-0.87)	0.004
1-SD			0.77 (0.70-0.84)	<0.001	0.83 (0.74-0.92)	<0.001
P value for trend			<0.001		<0.001	

Model 1 adjusted for age and sex; model 2 adjusted for model 1 and further adjustment for baseline systolic blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, estimated glomerular filtration rate, smoking, drinking, exercising, diabetes mellitus, education, and family history. Incidence density values were per 1,000 person-years.

CVD = cardiovascular disease; SBP-TTR = systolic blood pressure time in target range.

experience a significant survival advantage, further supporting the usefulness of TTR as a metric for BP management. However, it is important to note that results from the SPRINT and ACCORD trials did not demonstrate a significant association between SBP-TTR and death risk.[7,25] This may be because of the relatively short duration of follow-up, which may have influenced the incidence of mortality outcomes.

Furthermore, when the treatment target for SBP was set in the range of 110-130 mmHg, there was a significant association between SBP-TTR and the reduced risk of CVD, premature CVD, and premature death. It is noteworthy that in-depth analysis of individual cardiovascular outcomes revealed that intensified BP control had significant benefits only in terms of MI and ischemic stroke, with no further reduction observed in the risk of hemorrhagic stroke. The subgroup analysis results indicate that associations of a higher SBP-TTR with attenuated risk of incident CVD were more prominent in women. As previously reported, sex hormones such as estrogen and testosterone, as well as supplementation of sex chromosomes, were likely to play a role in the sex differences observed in CVD.[26,27] However, it is important to note that the interpretation of these results should be cautious because of the relatively small proportion of women included in this study. In addition, the inverse association between SBP-TTR and the risk of premature death was more pronounced in individuals with high cardiovascular risk. This highlights the potential clinical value of SBP-TTR in high-risk populations.

Mean BP and its variability were important metrics for assessing BP control. They provide insights into long-term trends and fluctuations in BP levels. Our results showed that adjusting for SBP-Mean weakened the association between SBP-TTR and the risks

TABLE 3 Association of SBP-TTR and Individual Cardiovascular Outcomes

	n	HR (95% CI)[a]	*P* Value	HR (95% CI)[b]	*P* Value
MI	132	0.84 (0.68-1.03)	0.092	0.76 (0.60-0.97)	0.028
IS	614	0.81 (0.74-0.90)	<0.001	0.76 (0.68-0.85)	<0.001
HS	93	0.72 (0.56-0.93)	0.011	0.84 (0.64-1.10)	0.196

Model adjusted for age, sex, baseline systolic blood pressure (SBP), body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, estimated glomerular filtration rate, smoking, drinking, exercising, diabetes mellitus, education, and family history. [a]The target SBP is set between 120 and 140 mm Hg, the risk for each 1-SD increase in time in target range (TTR). [b]The target SBP is set between 110 and 130 mm Hg, the risk for each 1-SD increase in TTR.

HS = hemorrhagic stroke; IS = ischemic stroke; MI = myocardial infarction.

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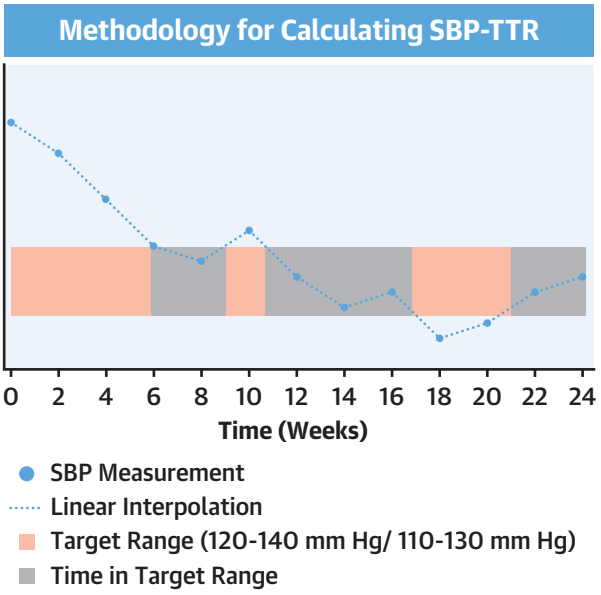
CENTRAL ILLUSTRATION **Systolic Blood Pressure Time in Target Range and Endpoint Events**



HR (95% CI) of SBP-TTR for Cardiovascular Events

The target SBP is set between 120-140 mm Hg, the risk for 1-SD in SBP-TTR	
CVD	0.81 (0.74-0.88)
Premature CVD	0.76 (0.67-0.86)
Premature death	0.83 (0.74-0.92)

The target SBP is set between 110-130 mm Hg, the risk for 1-SD in SBP-TTR	
CVD	0.77 (0.70-0.84)
Premature CVD	0.70 (0.60-0.81)
Premature death	0.73 (0.66-0.80)

Han X, et al. JACC Asia. 2024;4(12):987–996.

The blood pressure data collected from the workplace was used to calculate the systolic blood pressure time in target range (SBP-TTR) over a 6-month period using linear interpolation. The results suggest an association between SBP-TTR and cardiovascular disease (CVD), premature CVD, and premature death.

of CVD, premature CVD, and premature death. However, TTR with an SBP target of 110 to 130 was associated with lower risk of CVD, premature CVD and premature death, irrespective of SBP-Mean and SBP-SD. These analyses highlight potential differences in the effects of intensified and standard BP control interventions, with SBP-TTR showing better predictive performance in the context of intensified BP strategies.

Furthermore, we conducted a separate investigation into the impact of SBP-TTR on short- and long-term prognoses. Our findings indicate that the association among SBP-TTR and the risks of CVD, premature CVD, and premature death was only evident in the analyses focusing on long-term outcomes. It is worth noting that, although not statistically significant, the trends observed for SBP-TTR in short-term prognoses were consistent with the primary analysis. This result could be attributed to the relatively younger age of the study participants included in our research, leading to a lower incidence rate of CVD events within the short-term follow-up period. The study suggests that the benefits of elevated TTR may persist and become more pronounced over time. Additionally, the exposure period was extended to 12 months to investigate whether a longer duration of elevated SBP-TTR would yield greater benefits.

STUDY STRENGTHS AND LIMITATIONS. Our study has several strengths. First, we used BP data collected in the workplace, with an extended follow-up duration and more frequent BP monitoring. The workplace is a crucial setting for managing key risk factors for hypertension and other chronic diseases.[28] The study suggests that TTR may be a potential target and management indicator for SBP treatment in implementing workplace-based BP intervention strategies. Second, the study's data were obtained in a normalized work environment, which mitigated the white-coat hypertension effect and better reflected the participants' everyday BP levels.[29,30] Third, we adjusted for a comprehensive set of covariates to potentially minimize any unmeasured residual confounding.

However, there also exist some limitations for our study. First, because this was an observational study, it cannot definitively establish causality. Nonetheless, we conducted a lagged analysis over a 2-year period to mitigate potential causal associations. Second, comorbidities may introduce variability in BP targets for hypertensive patients. Due to sample size constraints, we were unable to thoroughly investigate

the association among TTR and the risks of CVD, premature CVD, and premature death across different hypertensive subgroups. Last, the study cohort was predominantly composed of factory employees, with the majority being under 50 years of age, and a relatively small proportion of female participants, so the generalization of the findings may be limited. Therefore, further research is necessary to validate these findings in diverse demographic groups.

CONCLUSIONS

We observed a dose-response relationship between the TTR of SBP and major adverse cardiovascular events among hypertensive employees. These findings highlight the significance of managing hypertension in the working population and propose the use of SBP-TTR as an indicator to evaluate the quality of BP management in workplace hypertension programs.

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PERSPECTIVES

COMPETENCY IN PROFESSIONALISM: The study findings, based on real-world data, highlight the importance of TTR as a predictive indicator for cardiovascular adverse events. Long-term maintenance of optimal TTR levels was associated with a reduction in cardiovascular events and death in working populations.

TRANSLATIONAL OUTLOOK: The utilization of multiple BP recordings in routine care or self-monitoring can facilitate the development of treatment strategies to achieve high TTR and thus reduce cardiovascular risk in hypertensive patients. In addition to its application in the workplace, TTR could be utilized as an automatic indicator for effective BP control, inherently integrated into calibrated wearable BP measurement devices for use in the general population.

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