Longer time in blood pressure target range improves cardiovascular outcomes among patients with Type 2 diabetes: A Secondary Analysis of a Randomized Clinical Trial

Running title: TIR among Type 2 diabetic patients

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Abstract

Aims: To examine the prognostic value of time in target range (TIR) with adverse outcomes and validate it with common blood pressure (BP) metrics among patients with Type 2 diabetes mellitus.

Methods:

We performed a post hoc analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial. TIR for each subject was calculated using linear interpolation and an SBP target range of 110 to 130 mm Hg. Cox models were used to assess the association of TIR and other BP metrics with the rate of clinical outcomes.

Results:

A higher TIR (61.9-100.0%) was associated with a 46% reduction in major adverse cardiovascular events (MACE) (hazard ratio [HR]:0.54; 95% CI: 0.43, 0.67) compared with TIR 0-22.9%. Results were similar for stroke (0.19; 0.10, 0.36), myocardial infarction (0.67; 0.51, 0.89), heart failure (0.47; 0.33, 0.66), cardiovascular death (0.63; 0.42, 0.93) and all-cause mortality (0.70; 0.54, 0.91). Further analyses suggested a curvilinear association of TIR with MACE, and this association was independent with baseline, final SBP, mean SBP, or visit-to-visit SBP variability.

Conclusions:

Longer TIR is associated with lower cardiovascular risk and may add value as an outcome measure for hypertension control studies among patients with diabetes.

Keywords: Diabetes mellitus; Hypertension, Blood pressure; Cardiovascular disease

Introduction

Diabetes increases the risk of developing cardiovascular disease (CVD), which is exaggerated with the co-existence of hypertension[1, 2]. Although blood pressure (BP) lowering has been proven to be an established strategy to prevent microvascular and macrovascular complications from patients with Type 2 diabetes mellitus (T2DM), BP targets are rarely met and maintained in practice, even in the setting of clinical trials with target BP[3-6].

Apart from well-recognized reasons for not meeting BP targets, such as underuse of combination therapy, treatment inertia, and undetected non-adherence[7, 8], investigators have argued that current guidelines unintentionally fail to warn clinicians for further treatment intensification after a single measure below a BP goal and no guidelines yet specify recommendations about the frequency to meet a BP target [3]. Some studies have examined the importance of average BP over time or cumulative BP burden in hypertension management[9-11]. Others have focused on measures of BP variability (BPV), such as standard deviation (SD), and found they were associated with adverse CVD events, renal disease, and mortality in patients with T2DM[12, 13]. However, these metrics had their own limitations. For example, mean BP is derived without regard to BPV and the exposure time of each BP level, and BPV could not link BP stability within specific ranges with adverse outcomes.

Time in range (TIR) from continuous glucose monitoring data has been popularized as a useful metric along hemoglobin A1c (HbA_{1c}) to assess glycemic control among both Type 1 and Type 2 diabetes[14, 15]. Likewise, researchers on hypertension management proposed to use the concept of TIR but derived from visit-to-visit BP measurements to elucidate the characteristics of BP control[16, 17]. Previous studies have indicated the prognosis value of TIR among various hypertensive populations including those with coronary heart disease or heart failure (HF) [16-20].

However, evidence regarding the TIR in diabetic patients has been lacking, particularly for those with well-controlled BP. Thus, the present study aimed to assess: 1) whether the relationship between TIR and diabetic complications existed among diabetic patients with well-controlled and relatively low BP, and 2) its performance compared with commonly studied BP metrics (i.e., baseline BP, last office BP, BPV and achieved BP).

Subjects, Materials and Methods

This was a post-hoc analysis of limited-access Action to Control Cardiovascular Risk in Diabetes (ACCORD) BioLINCC datasets obtained from the NIH upon approval. The design and conduct of the randomized, controlled ACCORD trials have been reported previously[21]. A total of 10,251 middle-aged and older men and women with T2DM were enrolled and randomized to either intensive (HbA_{1c} target <6.0%, n=5,128) or standard (HbA_{1c} target 7.0-7.9%, n=5,123) glycemic treatment groups. Of these randomized participants, 4733 participants were further randomly allocated to intensive therapy (systolic BP[SBP] target <120 mm Hg, n=2,362) or standard therapy (SBP target <140 mm Hg, n=2,371) groups. Subjects were followed up from 2001 through mid-2009.

For our current study, participants with a diagnosis of hypertension and at least 3 available SBP readings from the main ACCORD trials were included in the analysis. The trial protocol was approved by an independent review panel appointed by the NHLBI and by the institutional review board or ethics committee at each center. Each participant has provided written informed consent. This analysis was waived for ethical approval by ethical committee of Liverpool School of Tropical Medicine (No:20-077).

BP measurements

Seated systolic and diastolic BPs were measured for all eligible participants at baseline. The BP measurements at follow-up varied across treatment groups. For participants who received intensive BP treatment, BP was measured monthly for four months and every two months thereafter. For participants who received standard BP treatment, BP was measured at the first and fourth month and every 4 months thereafter.

TIR was calculated as the percentage of follow-up days with BP in the target range using the

Rosendaal method[22], which assumed a linear relationship existed between 2 consecutive BP values. We adopted a wide SBP target range of 110-130 mmHg after considering the inconsistency in current guidelines and realizing that only an upper limit of the hypertension treatment goal may place more weight on the risks of hypertension and less on the risks of potential overtreatment. In addition, the following BP metrics were computed: baseline SBP; last on-treatment SBP value before an event; mean SBP achieved on treatment, or SD across all BP measurements for BPV. To avoid the potential reverse causality, only SBP measures before an event (if observed) were used for the above BP parameters.

Primary and secondary outcomes

The pre-specified primary outcome for the ACCORD trial was major adverse cardiovascular events (MACE), which was a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Secondary outcomes were also explored, which included nonfatal stroke; nonfatal myocardial infarction (MI); HF; cardiovascular death; and all-cause mortality.

Statistical Analysis

Baseline characteristics were described as mean and SD (or median and interquartile if skewed) or number of participants (n) and percentage (%) by the quartile of TIR. Chi-squared tests for categorized variables or Analysis of Variance (ANOVA) tests for continuous variables were used to compare the difference across quartiles. The follow-up time of the primary or each secondary outcome was defined as the time from randomization to the first event or end of follow-up.

The differences in the TIR quartile on the time to the event were assessed by the Kaplan-Meier method and tested by the log-rank test. We also calculated the number of events and incidence rate per 100 person-year across each TIR strata for each outcome. Adjusted hazard ratio (HR) and 95% confidence intervals (CIs) from the Cox model were reported after testing the proportional hazard

assumption by scaled Schoenfeld residuals. We fitted two Cox models, one (minimally adjusted model) only included age, sex, race, and treatment assignments as covariates; and another (fully adjusted model) that further controlled for baseline covariates, namely, smoker, drinker, baseline SBP, body mass index, total cholesterol, high-density lipoprotein cholesterol, history of coronary heart disease, history of stroke, history of dyslipidemia and history of HF. To verify the robustness of our findings, we repeated our analyses among participants enrolled for the BP trial and non-BP trial, respectively. Also, a different SBP target range of 120-130 mm Hg was explored.

We further assessed the validation of TIR with the other four BP metrics (baseline SBP, last SBP, mean SBP, BPV) using the restricted cubic spline model. Then, we examined the predictive performance of five models, which included five SBP measures and adjusted for the same covariates from the fully adjusted model, for predicting the 5-year risk of MACE. Overall model performance was assessed by (Schwarz) Bayesian information criterion (BIC). Discrimination performance was compared by Harrell's C statistic, and calibration performance was assessed by Hosmer-Lemeshow test. In addition, reclassification performance of adding each BP metrics to the fully adjusted model was evaluated by absolute and relative integrated discrimination index (IDI). CIs and the comparison of Harrell's C statistics, absolute and relative IDI were based on 1,000 bootstrap samples. All analyses were done using SAS 9.4 (SAS Institute Inc, Cary, NC, USA) or STATA software version 15.0 (Stata Corporation). A two-sided p value < 0.05 were considered statistically significant.

Results:

Among those 10,251 diabetic patients from the ACCORD trial, there were 9,247 subjects having hypertension or receiving antihypertensive treatment. After further excluding 340 participants with less than 3 BP measures at follow-up, our analysis included a total of 8,907 participants (mean [SD] age, 63 [7] years; 5426 [60.9%] male) with a median follow-up of 4.94 (4.14-5.69) years. The mean SBP at baseline was 136.8 (17.2) mm Hg, and diastolic BP was 74.9 (10.7) mm Hg. The median number of BP measurements is 15 (12-20). The TIR with an SBP target of 110-130 mmHg across the follow-up was 43 (25) % for the overall analysis population but with a relatively higher rate of TIR>50% among those enrolled for BP trial than those not [1,896 (43.8%) vs 1,698 (37.1%)].

Table 1 shows the baseline characteristics of study participants according to the quartile of TIR. Participants from the highest quartile were more likely to be younger and white race, had lower systolic and diastolic BPs, higher proportion of intensive BP treatment, than those in the lowest quartile. However, the cumulative proportion of MACE was decreasing from the first (12.93%) to the fourth quartiles (7.28%) of TIR **(Figure 1)**.

Table 2 consistently indicated that participants from the fourth quartile had the lowest crude incidence rate (per 100 person-year) of MACE, nonfatal stroke, nonfatal MI, HF, cardiovascular death and all-cause mortality. Similar with the results from minimal adjusted model, the highest

quartile of TIR was significantly associated with a lower risk of MACE (HR:0.54; 95% CI: 0.43, 0.67), nonfatal stroke (0.19; 0.10, 0.36), nonfatal MI (0.67; 0.51, 0.89), HF (0.47; 0.33, 0.66), cardiovascular death (0.63; 0.42, 0.93), all-cause mortality (0.70; 0.54, 0.91), compared to the first quartile of TIR in the fully adjusted model. A linear trend was found for each clinical outcome across different quartiles (all $P_{\text{for trend}}<0.05$). This was consistently observed among patients from the ACCORD BP trial **(Appendix Table 1)** and non-BP trial subgroups **(Appendix Table 2)**.

When TIR was examined as a continuous variable, the multivariable adjusted HRs for each 10% increase in TIR all reached significance for primary outcome and secondary outcomes. Similar results were found if we chose the target range of SBP 120-130 mmHg (**Appendix Table 3**). Further spline analyses suggested the decreased tendency in MACE with the increase of TIR, but U-shaped associations with the baseline, final, mean achieved SBP and BPV **(Figure 2),** and the weak and non-monotonous association, particular for baseline and final SBP (**Appendix Table 4**). We also found a lower BIC value and similar C statistics for mean achieved SBP with TIR, but higher BIC and lower C statistics for baseline SBP, final SBP, and BPV compared with TIR (**Table 3**). This indicated the incremental predictive performance of single BP measurement may be smaller for predicting the risk of MACE. We also found that TIR remained significantly associated with CVD events despite adjustment for mean systolic blood pressure or systolic blood pressure variability (**Appendix Table 5**).

Discussion

This secondary analysis showed that higher TIR with a visit-to-visit SBP target of 110-130 mmHg was linearly associated with a lower risk of CVD events or mortality among patients with T2DM and on average well-controlled BP (baseline systolic and diastolic BP <140/90 mm Hg). This finding was consistently observed in both BP trial and non-BP trial participants from the ACCORD trial, and analyses redefining the SBP target range as 120-130 mmHg. Unlike the snapshot BP metrics (i.e., baseline or last BP), TIR had a similar model performance to the averaged SBP or BPV but remained a significant predictor of CVD events after adjusting for the averaged SBP or BPV. Additionally, in contrast to the U shape for mean SBP or BPV, a monotonous relationship between TIR and CVD risk may imply its potential for better feasibility in clinical practice.

Hypertension is common among patients with diabetes, which affects 50% to 80% of T2DM in the US[23]. Numerous studies have shown that lowering BP reduces CVD risk in diabetic individuals[4, 24, 25]; Yet, the proportion of patients meeting the BP target is still unacceptable low with approximately 30%[26]. Reasons for not achieving ideal BP control were complex, but researchers argued the commonly used single cross-sectional BP indicators from clinical guidelines and many previous observational studies might be one of the main drivers[3, 19]. The true picture of longitudinal BP status could be well captured with multiple measures, which were always specified for diagnosis of hypertension but seldom for BP control. Some BP indicators, which derived from longitudinal BP data, such as mean BP and visit-to-visit office BPV, were proposed and assessed with clinical outcomes. However, inconsistent results were reported, particularly for BPV[27-30], even though it took into account BP fluctuations comparing with the mean BP. The contradictory results may be because BPV only considered the variability of BP but ignored whether the BP was within the target range, apart from the inherent difference between

cohorts and study types.

The emerging metric of TIR could not only incorporate the average BP value and the degree of BP variability throughout the follow-up, but also the variation both within and out of target range. Clearly, TIR can largely improve the defect of above BP indicators, and its association with clinical outcomes has been confirmed by previous limited studies[16-20]. Our study was the first to explore the association between TIR and prognosis among patients with diabetes and BP, particularly in those with well-controlled BP. Overall, we observed a significant link of TIR with CVD risk, which was consistently confirmed both in the ACCORD BP trial and non-BP trial subgroups. Importantly, our study identified that the independent association of TIR and clinical outcomes was shown in a linear manner, which was in line with previous reports[17, 19] but contrasted to the J- or U- shaped curve for other BP management indicators [31-33]. This gradient of CVD risk across TIR not only demonstrated its capability to better quantify the attributable risk to differences in longitudinal BP management, but also its potential to better characterize the benefits of BP-lowering treatment in reducing CVD risk and mortality. Our study emphasized the need to reconsider the definition of BP target by including time course of achieving and maintaining ideal BP in current BP management guidelines[3, 8, 19]. Given that the achieved BP control rate was still lower than expected, even among those with relatively high-resource countries[34, 35], it seems the time to move the bar rather than solely advocating more aggressive treatment and lower BP targets. With advances in the electronic health records systems, BP recordings from home BP monitoring and apps could be feasibly uploaded and maintained. The BP profile over time and the derived TIR could be easily visualized to aid clinicians' decision.

Our study has several strengths including the rigorous BP measurements and standardized events adjudications in a well-designed clinical trial setting. There are also several limitations in this study.

First, TIR may be less accurately defined in subjects with fewer recorded BP measures, however, we standardize it by presenting it in percentage, which averaged over follow-up years. This approach could account for the influence from the number of BP measurements. Second, different SBP goals may be needed in certain patient groups, particularly for those elderly patients with comorbidities, complications, and limited life expectancy. However, similar results were observed after adopting the SBP target of 120-130 mmHg. Third, due to the observational design of this analysis in nature, the presence of residual confounding (e.g., classes of antihypertension drug) remained a possibility. Forth, our study only included macrovascular complications and mortality from diabetes. Further analysis for microvascular complications is needed. Finally, participants included in the analysis were patients with T2DM in a clinical trial setting, which may not be generalizable to other diabetic populations (e.g., Type 1 diabetes) from the real world. Further randomized trials evaluating interventions to increase the TIR to improve clinical outcomes would be necessary.

In summary, our study, in contrast to other BP metrics, found an independent and graded inverse relationship between TIR and the risks of CVD event or mortality among patients with T2DM with well-controlled and relatively low BP. Our finding suggested that future efforts to lower CVD risk among hypertensive patients should be encouraged to utilize multiple measurements of BP with aims for attaining a high TIR in both clinical practice and clinical studies[36, 37].

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Data Availability Statement

The data that support the findings of this study are available from BioLINCC but restrictions apply to the availability of these data, which were used under license for the current study, and so are not

publicly available. Data are however available from the authors upon reasonable request and with permission of BioLINCC.

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Figure Legends:

Figure 1. Incident rate of MACE by quartile of Time in Target Range

Q1(0% to ≤22.9%); Q2(22.9% to ≤43.4%); Q3(43.4% to ≤61.9%); Q4(61.9% to ≤100.0%).

MACE: major adverse cardiovascular events

Figure 2 Spline analyses of baseline SBP, final SBP, achieved SBP, BPV and time in target range

Hazards ratio for primary outcome (shadow represents upper and lower bounds of 95% confidence interval) is relative to 140 mm Hg for baseline SBP, last SBP and mean SBP, median SD for BPV, 0% for time in target range.

Knots are placed at 25th, 50th, and 75th centiles of time in target range, baseline SBP, last SBP, achieved SBP and BPV.

Multivariable model was adjusted for the variables of age, sex, race, and treatment assignments, smoker, drinker, baseline SBP, BMI, TC, HDL-C, history of CHD, history of stroke, history of dyslipidemia and history of heart failure.

SBP: systolic blood pressure; BPV: Blood pressure variability; BMI: Body mass index; TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; CHD; coronary heart disease.

Table 1 Baseline Demographics and Clinical Risk Factors, by quartile of Time in Target Range

	Q1 (0% to ≤22.9%)	Q2 (22.9% to ≤43.4%)	Q3 (43.4% to ≤61.9%)	Q4 (61.9% to ≤100.0%)
N	2,226	2,227	2,227	2,227
Age, years	63.2(6.9)	63.2 (6.6)	62.9(6.6)	62.1(6.6)
Male sex, n (%)	1,357 (61.0)	1,355(60.8)	1,319 (59.2)	1,395(62.6)
Race, n (%)				
Black	539(24.2)	460 (20.7)	455(20.4)	325(14.6)
Hispanic	180 (8.1)	156(7.0)	153(6.9)	148(6.7)
White	1,233(55.4)	1,396(62.7)	1,407 (63.2)	1,481(66.5)
Other	274(12.3)	215(9.7)	212(9.5)	273(12.3)
History of, n (%)				
CHD	648(29.1)	740(33.2)	728(32.7)	646(29.0)
Stroke	151(6.8)	148(6.7)	147 (6.6)	114(5.1)
Dyslipidemia	1,550(69.6)	1,584(71.1)	1,576(70.8)	1,600(71.9)
Heart failure	116(5.2)	131(5.9)	112(5.0)	95(4.3)
Smoker, n (%)				
Never	1013(45.5)	948(42.6)	904(40.6)	961(43.2)
Current	300(13.5)	296(13.3)	306(13.7)	275(12.4)
Past	913(41.0)	983(44.1)	1017(45.7)	991(44.5)
Current drinker, n (%)	492(22.1)	498(22.4)	551(24.7)	556(25.0)
BMI, kg/m^2,	32.0(5.4)	32.5(5.4)	32.6(5.3)	32.3(5.4)
SBP (mm Hg)	146.1(17.1)	137.2(16.9)	133.5(16.3)	130.7(14.3)
DBP (mm Hg)	77.2(11.0)	75.0 (11.0)	73.8(10.7)	73.6(9.9)
TC (mg/dL)	185.6(42.0)	180.1(40.0)	182.9(43.2)	181.9(41.8)

HDL-C (mg/dL)	41.9(12.1)	41.9(11.5)	42.1(11.8)	42.1(11.6)
Randomization group, n (%)				
Intensive glycemic treatment, %	1,056(47.4)	1,117(50.2)	1,130(50.7)	1,121(50.3)
Intensive lipid treatment, %	595(26.1)	566(24.8)	577(25.3)	544(23.8)
Intensive BP treatment, %	137(6.2)	367(16.5)	729(32.7)	951(42.7)

SBP: systolic blood pressure; BMI: Body mass index; TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; CHD; Coronary Heart Disease; BP: blood pressure

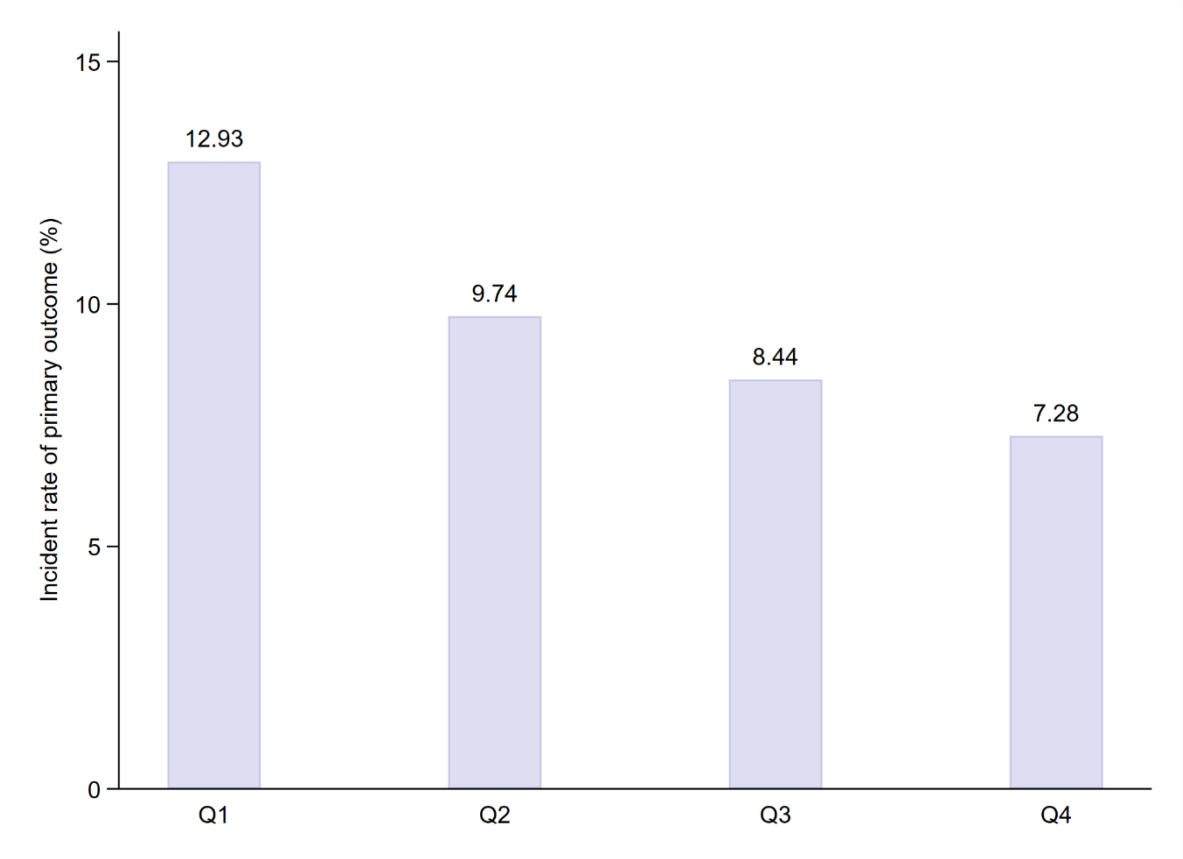

Figure 1. Incident rate of MACE by quartile of Time in Target Range

Q1(0% to ≤22.9%); Q2(22.9% to ≤43.4%); Q3(43.4% to ≤61.9%); Q4(61.9% to ≤100.0%).

MACE: major adverse cardiovascular events

Table 2 Association of TIR with cardiovascular events and death in Type 2 diabetic patients

Outcome	No of events	Incidence rate (100 person years)	HR (95%CI), p value	
			Minimally adjusted	Fully Adjusted
Primary outcome				
Q1	288	2.63	1.00 (ref)	1.00 (ref)
Q2	217	1.95	0.70 (0.59, 0.84), 0.0001	0.68 (0.57, 0.82), <0.0001
Q3	188	1.70	0.60 (0.50, 0.73), <0.0001	0.58 (0.47, 0.71), <0.0001
Q4	162	1.49	0.53 (0.43, 0.66), <0.0001	0.54 (0.43, 0.67), <0.0001
P for trend			<0.0001	<0.0001
Secondary outcomes				
Nonfatal stroke				
Q1	74	0.68	1.00 (ref)	1.00 (ref)
Q2	26	0.23	0.33 (0.21, 0.52), <0.0001	0.35 (0.22, 0.56), <0.0001
Q3	29	0.26	0.34 (0.22, 0.55), <0.0001	0.38 (0.23, 0.63), 0.0001
Q4	15	0.12	0.16 (0.08, 0.29), <0.0001	0.19 (0.10, 0.36), <0.0001
P for trend			<0.0001	<0.0001
Nonfatal MI				
Q1	156	1.42	1.00 (ref)	1.00 (ref)
Q2	140	1.26	0.85 (0.68, 1.07), 0.1675	0.82 (0.65, 1.04), 0.1051
Q3	110	1.00	0.68 (0.52, 0.87), 0.0025	0.63 (0.49, 0.83), 0.0007
Q4	109	1.00	0.68 (0.52, 0.89), 0.0047	0.67 (0.51, 0.89), 0.0054
P for trend			0.0013	0.0014
Heart failure				
Q1	126	1.15	1.00 (ref)	1.00 (ref)
Q2	122	1.09	0.92(0.71, 1.18), 0.4930	0.88 (0.68, 1.13), 0.3096
Q3	103	0.93	0.78 (0.60, 1.03), 0.0761	0.77 (0.58, 1.02), 0.0719
Q4	54	0.50	0.43 (0.31, 0.61), <0.0001	0.47 (0.33, 0.66), <0.0001
P for trend			<0.0001	<0.0001
Cardiovascular death				

Q1	85	0.78	1.00 (ref)	1.00 (ref)
Q2	64	0.57	0.72 (0.52, 0.99), 0.0468	0.66 (0.47, 0.93), 0.0167
Q3	61	0.55	0.68 (0.48, 0.95), 0.0252	0.65 (0.46, 0.93), 0.0186
Q4	53	0.49	0.62 (0.43, 0.90), 0.0121	0.63 (0.42, 0.93), 0.0186
P for trend			0.0103	0.0203
All-cause mortality				
Q1	178	1.63	1.00 (ref)	1.00 (ref)
Q2	143	1.28	0.77 (0.61, 0.96), 0.0182	0.73(0.58, 0.91), 0.0059
Q3	147	1.33	0.78 (0.62, 0.98), 0.0296	0.74 (0.59, 0.95), 0.0157
Q4	124	1.14	0.70 (0.55, 0.90), 0.0053	0.70 (0.54, 0.91), 0.0068
P for trend			0.0074	0.0114

The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes

We fitted two basic models: one (minimally adjusted model) that included only age, sex, race, and treatment assignments as independent variables and another (fully adjusted model) that also further controlled for baseline covariates, namely, smoker, drinker, baseline SBP, BMI, TC, HDL, history of CHD, history of stroke, history of dyslipidemia and history of heart failure,

Q1(0% to ≤22.9%); Q2(22.9% to ≤43.4%); Q3(43.4% to ≤61.9%); Q4(61.9% to ≤100.0%).

SBP: systolic blood pressure; BMI: Body mass index; TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; CHD; Coronary Heart Disease; MI: myocardial infarction; CVD: cardiovascular disease

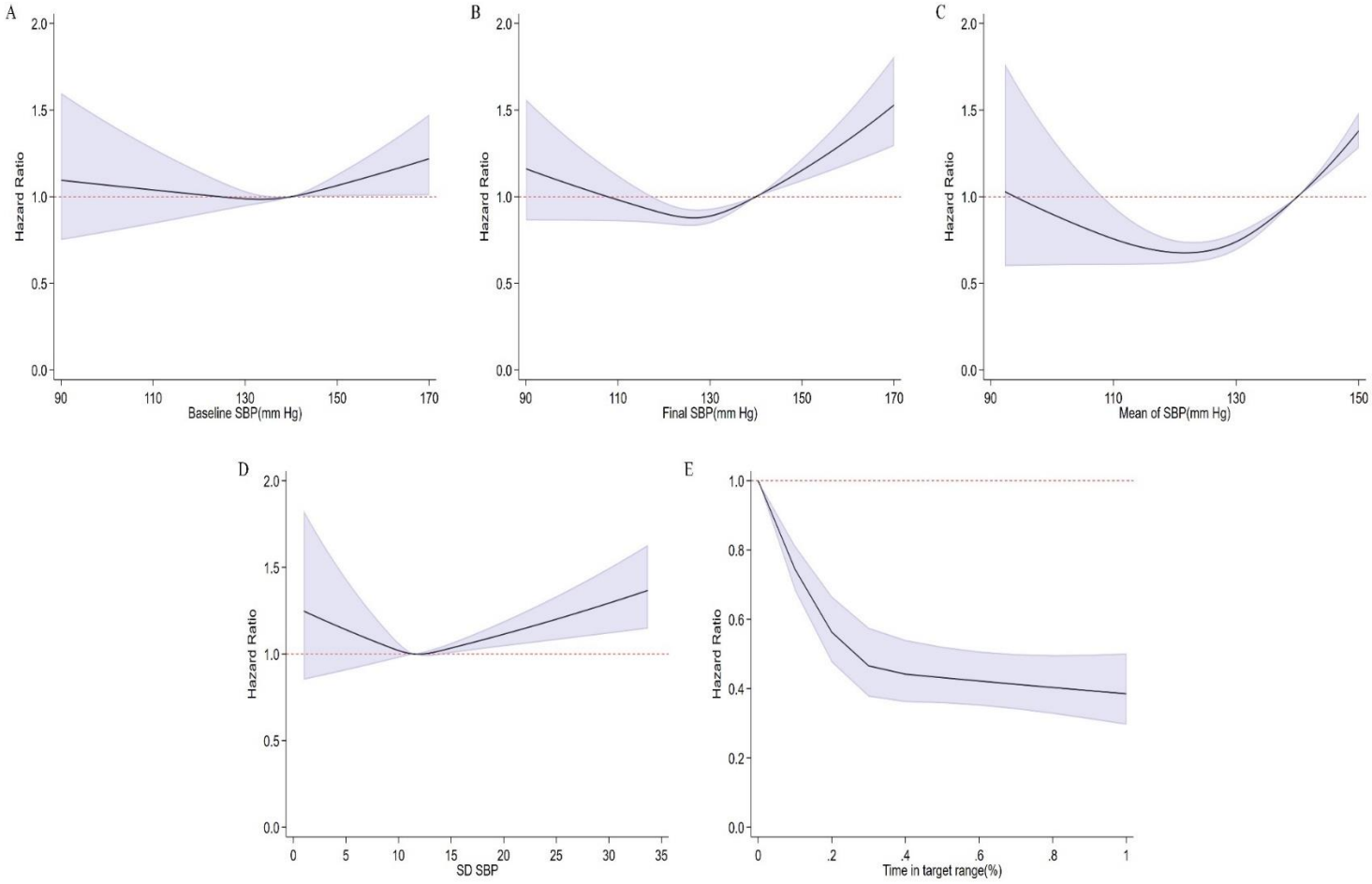

Figure 2 Spline analyses of baseline SBP, final SBP, achieved SBP, BPV and time in target range

Hazards ratio for primary outcome (shadow represents upper and lower bounds of 95% confidence interval) is relative to 140 mm Hg for baseline SBP, last SBP and mean SBP, median SD for BPV, 0% for time in target range.

Knots are placed at 25th, 50th, and 75th centiles of time in target range, baseline SBP, last SBP, achieved SBP and BPV.

Multivariable model was adjusted for the variables of age, sex, race, and treatment assignments, smoker, drinker, baseline SBP, BMI, TC, HDL-C, history of CHD, history of stroke, history of dyslipidemia and history of heart failure.

SBP: systolic blood pressure; BPV: Blood pressure variability; BMI: Body mass index; TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; CHD; coronary heart disease.

Table 3 Model performance of different BP metrics for MACE at 5 years*

Statistics	Baseline SBP (Base model)	Base model +Last office SBP	Base model +Achieved SBP	Base model +BPV	Base model +TIR
Model fit					
BIC	14781.833	14782.357	14724.445	14784.359	14738.464
Discrimination					
C statistics (95%CI)	0.660 (0.640, 0.679)	0.662 (0.642, 0.680)	0.679 (0.659, 0.697)	0.661 (0.642, 0.680)	0.671 (0.652, 0.691)
C difference (95%CI), p value†	Reference	0.002 (-0.001, 0.006), p=0.269	0.019 (0.009, 0.030), p=0.0003	0.002 (-0.0003, 0.004), p=0.112	0.011 (0.001, 0.022), 0.040
Calibration					
Hosmer-Lemeshow p value	0.060	0.001	0.226	0.008	0.148
Integrated discrimination index (IDI)					
Discrimination slope	0.035	0.036	0.044	0.036	0.042
Absolute IDI (95%CI), p value†	Reference	0.0008 (0.0003, 0.0014), p=0.003	0.0081 (0.0061, 0.0106), p<0.0001	0.0002 (-0.0006, 0.0050), p=0.701	0.0066 (0.0053, 0.0081), p<0.0001
Relative IDI (95%CI), p value†	Reference	0.0235 (0.0085, 0.0390), p=0.003	0.2299 (0.1664, 0.2961), p<0.0001	0.0050 (-0.0158, 0.0354), p=0.013	0.1862 (0.1457, 0.2288), p<0.0001

MACE was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

* Adjusted variables include age, sex, race, treatment assignments, smoker, drinker, baseline SBP, BMI, TC, HDL, history of CHD, history of stroke, history of dyslipidemia and history of heart failure.

†Based on 1,000 bootstrap samples for comparison of C indices: BIC, (Schwarz) Bayesian information criterion

SBP: systolic blood pressure; BMI: Body mass index; TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; CHD; Coronary Heart Disease; BPV: Blood Pressure Variability; TIR: Time in target range; MACE: Major adverse cardiovascular event

Additional file 1

Appendix Table 1. TTR (110-130) with primary and secondary outcomes – BP trial subgroup (n=4334)

Appendix Table 2 TTR (110-130) with primary and secondary outcomes - Not in BP trial (n=4573)

Appendix Table 3. TTR by different target range with primary and secondary outcomes (n=8907)

Appendix Table 4: HRs of Different BP metrics with MACE

Appendix Table 5: Association of TIR (per SD) with different outcomes with an adjustment for other BP metrics