#### Prognostic value of time in blood pressure target range among patients with heart failure

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**Total word counts:** 4219

**Author disclosures:** No relationships with industry related with this work

**Acknowledgments:** The TOCAPT and BEST Investigators and the National Heart, Lung, and Blood Institute investigators are greatly acknowledged for conducting the trials and making both data sets publicly available. Drs Kangyu Chen and Tao Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Short "tweet":** Time in blood pressure target range could independently predict adverse outcome in hypertensive patients with HF

**Abstract**

**Objectives** We assessed the prognostic value of time in blood pressure (BP) target range among hypertensive patients with heart failure (HF).

**Background** BP is a continuous and dynamic measure. However, standard BP control metrics may not reflect the variability in BP over time.

**Methods** We performed a post-hoc analysis of data from the Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) trial and the Beta-Blocker Evaluation of Survival Trial (BEST). Time in target range (TTR) for each patient was calculated using linear interpolation across study period with the target range of systolic BP 120-130 mmHg.

**Results** A total of 4789 hypertensive patients (n=1654 from BEST and n=3135 from TOPCAT) were included. The cumulative incidences of primary endpoint (i.e., cardiovascular death or HF hospitalization) were highest among the top quartile of TTR with a dose-dependent manner across quartiles (*Ptrend* <0.005). The top quartile of TTR was significantly associated with a lower risk of primary outcome using adjusted Cox regression model [hazard ratio 0.71; 95% confidence interval (CI): 0.60, 0.82], cardiovascular mortality (0.68: 0.55, 0.84), HF hospitalization (0.70: 0.58, 0.85), all-cause mortality (0.69: 0.58, 0.83), any hospitalization (0.76: 0.67, 0.85). Further analyses using restricted cubic spline indicated a linear relationship between TTR and primary outcome. Similar patterns were observed among the individual trial. Sensitivity analyses generated consistent results while redefining target range as 110-130 mmHg for systolic BP or 70-80 mmHg for diastolic BP.

**Conclusions** TTR could independently predict major adverse cardiovascular events in hypertensive patients with HF.

**Keywords**: hypertension; quality of care; time in target range; heart failure, cardiovascular event

**Abbreviations list:**

BP: Blood pressure

TTR: time in target range

HF: heart failure

TOPCAT: Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist

BEST: Beta-Blocker Evaluation of Survival Trial

LVEF: left ventricular ejection fraction

OBPV: office BP variability

**Introduction**

Hypertension is one of the most common comorbidities and risk factors for cardiovascular disease including heart failure (HF). Numerous studies have confirmed that effective blood pressure (BP) management can prevent the occurrence and progression of HF(1-3). Despite decades of endeavors in improvement on public awareness, guideline statements, and widely available and inexpensive antihypertension drugs, the prevalence of hypertension among patient with stable HF remains very high (>50%)(4,5).

BP is a continuous and dynamic variable. However, a single or average BP value is often used as a monitoring indicator in clinical practice and studies of hypertension, which makes it difficult to accurately assess the objective state of BP. In 2007, Giuseppe et al(6) found that continuous and effective BP control could provide additional benefits for hypertension treatment in the International VerapamilSR-Trandolapril Study. Therefore, it is recommended that doctors should pay attention to every point of BP monitoring instead of single value of BP.

Recently, researchers have proposed the concept of “time in target range” (TTR) in the field of hypertension management(7). This measurement can incorporate both the average BP value prevailing during long term follow-up and the degree of BP variability. Also, it can account for variation both within and out of target range. A number of limited studies have shown that a higher proportion of BP controlled within the target range was significantly associated with a decreased risk of cardiovascular event or mortality(7-9). This indicated that TTR may serve as an appropriate performance measure for population level monitoring of BP control or BP control interventions in clinical trials. It remains to be established that this would be a suitable measure for patients with HF given that paradoxical and controversial relationship between BP lowering with clinical outcomes often existed (4,10,11).

As such, in the present study, we aimed to assess the value of adopting time in BP target range by exploring its association with clinical outcomes among hypertensive patients with HF on the basis of a post-hoc analysis of two published randomized trials conducted at different centuries.

**Methods**

The present study was a secondary analysis using data from the Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT)  trial and the [Beta-Blocker](https://www.sciencedirect.com/topics/nursing-and-health-professions/beta-adrenergic-receptor-blocking-agent) Evaluation of Survival Trial (BEST)  obtained from the National Institutes of Heart, Lung, and Blood Institute’s Biologic Specimen and Data Repository Information Coordinating Center via an approved proposal.

**Study population**

The rationale, design and results of the randomized, controlled TOPCAT and BEST trials have been described elsewhere(12-15). The institutional review board of each site from each trial approved the protocol and all patients gave written informed consent. For the TOPCAT trial(13), a total of 3445 participants were randomized to receive spironolactone (n=1722) or matching placebo (n=1723) between 2006 and 2012. Patients were eligible if they were 50 years or older with left ventricular ejection fraction (LVEF) ≥45% and symptomatic HF, and either a hospitalization for HF within the prior year or an elevated natriuretic peptide level within the 60 days before randomization. A full list of inclusion and exclusion criteria could be found in its protocol paper(14). Overall, the patients were followed up an average of 3.3 years. For the BEST trial(12), 2708 patients with advanced chronic HF were recruited between 1995 and 1998 in the United States and Canada and were randomly assigned to receive either bucindolol (n=1354) or placebo (n=1354) with a mean follow up of 2.0 years. In this trial, all patients were 18 years old having New York Heart Association (NYHA) class III or IV HF with LVEF < 35%. The detailed inclusion and exclusion criteria was published elsewhere(15).

Clearly, a major difference between these two trials is that the BEST trial recruited HF patient with a reduced ejection fraction (HFrEF) and TOPCAT trial enrolled HF with a preserved ejection fraction (HFpEF). For the current study, to calculate the time in BP target range, we restricted our analyses to those hypertensive subjects with at least two BP measurements from the de-identified public-use copy of the BEST (n=2707) and TOPCAT(n=3445) dataset. We defined hypertension as reporting history of hypertension or systolic BP140 or diastolic BP90 at baseline. Given that the same BP target was recommended for both HFrEF and HFpEF from recent hypertension guidelines(16,17) and there were no differences in outcomes between the randomised groups within both trials(12,13), we firstly pooled the trial data to allow an adequately powered analysis and then separated them to take account of the possible difference of antihypertensive treatment effect across the spectrum of ejection fraction. This analysis was approved by The First Affiliated Hospital of USTC (Anhui Provincial Hospital) Medical Research Ethics Committee (REC Num: 2021-RE-029).

**BP and Other Measurements**

Patients from both trials underwent a detailed baseline evaluation including patient demographics, medical history, drug use history and laboratory test. Seated office BP was measured by trained staff during each visit with the mean number of visits per subject of 11(range, 2-16) for TOPCAT and 13 (range, 2-28) for BEST trial.

TTR for each patient was calculated by linear interpolation using the Rosendaal method(18). In contrast to the approach expressing the TTR as the percentage of BP measurements recorded within a certain window(7), this method takes into consideration both the frequency of BP measurements and the actual BP values. TTR reflects the magnitude of BP variability for patient during the follow-up period. In our primary analysis, we classified patients according to the quartiles of TTR (TTR for SBP window 120–130 mm Hg) for the combined and individual trial separately but redefining the BP target range while performing sensitivity analyses.

**Study Outcomes**

The original primary outcome is the combined end point of cardiovascular disease death, aborted cardiac arrest, or HF hospitalization for TOPCAT trial(13) and all-cause mortality for the BEST trial(12). In order to facilitate the comparisons between TOPCAT and BEST trials and other contemporary HF trials(19,20). We redefined the primary outcome as the combined end point of cardiovascular death or HF hospitalization. Our secondary outcomes included cardiovascular mortality, HF hospitalization, all-cause mortality and any hospitalization. All events were adjudicated by a clinical endpoint committee but not for hospitalizations in BEST trial.

**Statistical analysis**

The baseline characteristics of patients were expressed as mean ± standard deviation for continuous variables and counts and percentages for categorical variables. The intergroup differences across the quartile of TTR were assessed using Chi-square tests for categorized variables and ANOVA for continuous variables.

We plotted the cumulative incidence of primary endpoint according to the TTR strata for each trial and the combined data of both trials in Kaplan-Meier (KM) curves and compared the differences using the log-rank test. We also calculated the number of events and incidence rate per 100 person-years across each TTR strata for each outcome. A stratified Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for each clinical outcome with the lowest quartile as the reference. The Cox models were adjusted for age, sex, white race, treatment group (Model 1), NYHA, current smoker, history of myocardial infarction, history of peripheral arterial disease, dyslipidemia, atrial fibrillation, diabetes, systolic BP, heart rate, body mass index (BMI), creatinine, potassium, angiotensin-converting enzyme inhibitors (ACEI), diuretic (Model 2) but with CCB, ARB, β-blocker additionally for TOPCAT study. The interaction between treatment group and TTR strata was tested. We repeated the above analyses redefining the therapeutic range using diastolic BP of 70-80 mmHg or a wider threshold of SBP 110-130 mmHg after considering the inconsistent BP goal for HF treatment(16,17).

We also used the restricted cubic splines to explore the dose-response association between TTR expressed as the continuous variable (with 0% as the reference) with primary outcome adjusting for the variables from the above Model 2. Spline knots were placed at the 25th, 50th, and 75th centiles of the distribution of TTR overall and by study. We tested for potential non-linearity by a likelihood ratio test comparing the model with only a linear term against the model with linear and cubic spline terms. Data were analyzed with STATA software version 15.0 (Stata Corporation).

**Results**

After excluding 1302 non-hypertensive patients and 61 with less 2 BP measurements from the limited-access trial data, our analysis included a total of 4789 patients with 1654 from the BEST trial and 3135 from the TOPCAT trial. Overall, the incidence rates vary largely between trials (25.48 per 100 person-year for BEST and 5.67 per 100 person-year for TOPCAT) and the TTR is relatively low (18% for BEST and 26% for TOPCAT). The baseline characteristics of study participants from the combined BEST and TOPCAT trial according to quartile of TTR in systolic BP are shown in **Table** **1** and trial-specific baseline characteristics are indicated in **eTable 1 and 2**. In general, participants from the highest quartile were more likely to be female and white race, had lower rate of NYHA III or IV, atrial fibrillation, diabetes mellitus and diuretic use, lower level of systolic BP, heart rate, BMI, and creatinine, than participants in the lowest quartile.

As shown in **Figure 1A**, the cumulative incidences of primary endpoint were highest in the top quartile of TTR, compared with other quartiles. The difference across the four groups were statistically significant (*P*<0.001). This pattern was also found for each trial (all *P*<0.001) (**Figure 1B and C**). There was no evidence of an interaction between treatment group and TTR strata overall and by study with respect to the primary composite outcome (all *p* interaction >0.2). Further analyses indicated that patients from the upper quartile generally have the lowest crude incidence rate of the primary outcome, cardiovascular mortality, HF hospitalization, all-cause mortality and any hospitalization (**Table 2**). This was consistently observed among patients from the TOPCAT trial and the BEST with a higher event rate conducted last century (**eTable 3 and 4 and Figure 2**).

Consistent with result from adjustments for age, sex, white race, and treatment group, our results from full adjusted model indicated that top quartile of TTR was significantly associated with a lower risk of primary outcome (0.71; 95% CI: 0.60, 0.82; *P*<0.0001), cardiovascular mortality (0.68: 0.55, 0.84, *P*<0.0001), HF hospitalization (0.70:0.58,0.85; *P*=0.0003), all-cause mortality (0.69:0.58, 0.83; *P*<0.0001), any hospitalization (0.76: 0.67,0.85; *P*<0.0001). A linear trend was also found for each clinical outcomes across different quartiles (all *p* for trend <0.005). Our further analysis using restricted cubic spline model indicated that the association of TTR and primary outcome generally showed a linear relationship overall (**Figure 3A)** and by study (**Figure 3 B-C**). We did not find a significant non-linear trend (*p* non-linearity=0.058 overall; *p* non-linearity =0.079 for TOPCAT, *p* non-linearity =0.141 for BEST).

The significant associations with primary outcome and each secondary outcome were consistently observed overall and by study even after fully adjustment (**Table 1, Figure 2 and eTable 3 and 4**). Of note, in comparison with the association between TTR with all-cause or cardiovascular mortality, the magnitude of the relationship with hospitalization was weaker.

Our sensitivity analyses using different therapeutic range for systolic BP (110-130 mmHg) confirmed the clinical benefits from longer TTR (**eTable 5, 6 and 7**). Furthermore, we found that the significant association of the increase in TTR with improved clinical outcomes persisted if therapeutic range for diastolic BP (70-80 mmHg) was adopted (**eTable 8, 9 and 10**).

**Discussion**

This post hoc analysis has demonstrated that in patients with HF and hypertension, higher TTR with a systolic BP target of 120-130mmHg was associated with lower risk of cardiovascular death or HF hospitalization. This observation was consistent across all important clinical outcomes considered among HF patients. The results also held for systolic BP target of 110-130mmHg and diastolic BP target of 70-80mmHg. TTR was persistently found to have the same predictive value for outcome regardless of HF types (i.e., HFrEF and HFpEF), time of trial conducted (1995-1998 vs 2006-2012), clinical event rates (25 vs 5 per 100 person-year) and low TTR (18% vs 26%) across the BEST and TOPCAT trial. Meanwhile, a linear relationship was found between TTR and primary outcome, which suggested that the longer TTR, the better outcomes would be.

The systolic BP target used in this study was 120-130mmHg, which was in line with the current guidelines(17,21,22). The 2017 ACC /AHA hypertension guidelines recommend that in patients with HF and hypertension, systolic BP should be treated to below 130 mmHg(16). The 2018 ESC/ESH Hypertension Guideline suggests that systolic BP should not below 120 mmHg in HF patients(17). However, the BP target in HF patients remains controversial, as current evidence comes mostly from BP-lowering trials among hypertensive population with exclusion of HF patients typically(2,23). In contrast to the well-established linear relationship between elevated BP and cardiovascular events in the general population, a J-shaped association between systolic BP and all-cause and cardiovascular mortality among patients with HF were reported, especially among those with HFrEF(24,25). Taken together, we chose systolic BP of 120-130mmHg as the therapeutic range in our study. With TTR in this systolic BP range, TTR performed well as a good predictor of both mortality and HF hospitalization.

Unlike the treatment goal of hypertensive patients, which is to lower BP to improve prognosis, the focus of HF management is to improve prognosis by prescribing drugs that have demonstrated improved mortality rates. Standard HF therapy usually induces hypotension in clinical trials, which may be lower than that recommended in the guidelines. In the BEST trial, all patients had received optimal medical therapy, including the use of ACEI for at least one month(13). Current guidelines also recommend titration of drugs that have compelling indications for management of HF and also reduce BP(17,21). Accordingly, we tested the predictive value of TTR with a wider systolic BP target range (110-130 mmHg) and found the results were in line with that of systolic BP target range (120-130mmHg).

Since BP measurement is dynamic and varies from time to time, and from visit to visit, a single BP value may not reflect the full spectrum of hypertension-related cardiovascular risk. Studies have explored full spectrum approaches to monitor an individual patient’s BP control. In a cohort study, the mean value of higher 24-hour and higher nighttime BP were associated with greater risk of all-cause mortality and cardiovascular outcomes(26). Visit-to-visit office BP variability (OBPV) also seems to be an independent predictor of cardiovascular events, stroke, myocardial infarction, and cardiovascular mortality(27-29). However, other studies have failed to show an association of OBPV with clinical outcomes(30-32). This may be because OBPV could be narrow even if all BP measures exceed the target range. Also, the average of multiple BP measurements may be within target range even if none of the individual BP measurements fall within that range.

In a recent study, TTR was demonstrated to be a significant predictor of cardiovascular outcomes even after adjusting for mean systolic BP and systolic BP variability(9). Chung SC et al(8) used 1.64 million clinical BP readings to calculate the TTR based on current target BP levels among patients with newly diagnosed hypertension from UK. Their study found that the inverse associations between a higher TTR and lower risk of incident cardiovascular diseases were independent of BP variability or number of follow-up measures. Another study also demonstrated an inverse and gradual association between TTR and all-cause mortality in a large US veteran cohort(7). These studies together showed that TTR may add incremental value to current widely used BP ‘control’ indicators and could be of major clinical importance for the optimal management of patients with arterial hypertension in real-life clinical practice. Our study was the first attempt to explore the value of TTR in HF patients for BP control and found a significant association with cardiovascular death or HF hospitalization even among population with a relatively low TTR. Our study emphasizes the importance of monitoring BP in everyday clinical practice and maintaining the consistency of BP control over time.

**Limitation**

BP targets among HF patients with different comorbidities (eg, type 2 diabetes or renal dysfunction) may differ from those without. Our study did not examine the difference by disease comorbidities. Thus, use of TTR in specialized groups needs further validation. As TTR is relatively low in our study population, we are unsure whether higher TTR due to maximally tolerated guideline directed medical therapy would invalidate our findings. Our study was also limited to use the timepoints dictated by the two trials. There are more explorations of the timings of BP measurement time and frequency (eg, daytime or nighttime ambulatory BP) to optimize the predictive value of TTR. Since both trials were performed mainly in north America, further research is warranted in other regions, such as Asia, given that the BP management varied differently under different medical systems. This is a post-hoc analysis and we cannot completely rule out some effect of reverse causality and a properly designed prospective randomized clinical trial is needed to testify the performance of TTR in hypertension management among HF patients.

**Conclusion**

High TTR was found to be highly associated with major adverse cardiovascular events in a dose response manner among patients with HF and hypertension. This supports TTR as a measure for use in BP control. Efforts to lower cardiovascular risk among these patients should be taken, by attaining a high TTR of multiple measurements of BP in usual care or via self-monitoring.

**Clinical Perspectives**

TTR could independently predict major adverse cardiovascular events in patients with HF and hypertension. Our study supports TTR as a suitable BP control metric.

**TRANSLATIONAL OUTLOOK**

A prospective randomized clinical trial is needed where patients are randomly assigned to a strategy of using TTR to guide BP control.

**Acknowledgments**

The TOCAPT and BEST Investigators and the National Heart, Lung, and Blood Institute investigators are greatly acknowledged for conducting the trials and making both data sets publicly available. Drs Kangyu Chen and Tao Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Funding**

The National Heart, Lung, and Blood Institute sponsored the SPRINT and ACCORD trials. No specific fund supports the current analysis. This article does not necessarily reflect the opinions or views of the SPRINT and ACCORD trial or the NHLBI.

**Conflict of Interest**

None

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**Figure legends**

**Figure 1: KM curve for primary outcome, overall and by study**

1. For combine dataset Q1(0% to <2%), Q2(2% to <19%), Q3(19% to <38%) and Q4 (38% to 100%) for combined dataset,
2. For TOPCAT study, Q1(0% to <7%), Q2(7% to <23%), Q3(23% to <41%) and Q4 (41% to 100%)
3. For BEST Study, Q1(0%), Q2(1% to <14%), Q3(14% to <31%) and Q4 (31% to 100%)

**Figure 2 Study-specific Associations of Systolic Blood Pressure Time in Target Range and Clinical Outcomes**

Study specific quartile was used: Q1(0%), Q2(1% to <14%), Q3(14% to <31%) and Q4 (31% to 100%) for BEST study; Q1(0% to <7%), Q2(7% to <23%), Q3(23% to <41%) and Q4 (41% to 100%) for TOPCAT study.

Model was adjusted for age, sex, white race, treatment group, NYHA, Current smoker, Previous MI, Previous PAD, Dyslipidemia, Atrial fibrillation, Diabetes, SBP, Heart rate, BMI, Creatinine, Potassium, ACEI, Diuretic for BEST study but with CCB, ARB, β-blocker additionally for TOPCAT study.

PAD: Peripheral arterial disease; NYHA: New York Heart Association class; MI: Myocardial infarction; ACEI: angiotensin-converting enzyme inhibitors; CCB: Calcium-channel blockers; BMI: Body mass index; SBP: Systolic blood pressure.

**Figure 3, Spline curve between Time in rang to primary outcome overall and by study.**

1. For combine dataset,
2. For BEST Study
3. For TOPCAT study

Spline analysis was performed with 0% as the reference. Model was adjusted for age, sex, white race, treatment group, NYHA, Current smoker, Previous MI, Previous PAD, Dyslipidemia, Atrial fibrillation, Diabetes, SBP, Heart rate, BMI, Creatinine, Potassium, ACEI, Diuretic for BEST study but with CCB, ARB, β-blocker additionally for TOPCAT study.

**Central Illustration:**

**An inverse and gradual association between TTR and major adverse cardiovascular events**

Overall, Q1(0% to <2%), Q2(2% to <19%), Q3(19% to <38%) and Q4 (38% to 100%) for combined dataset,

For TOPCAT study, Q1(0% to <7%), Q2(7% to <23%), Q3(23% to <41%) and Q4 (41% to 100%)

For BEST Study, Q1(0%), Q2(1% to <14%), Q3(14% to <31%) and Q4 (31% to 100%)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 1. Baseline Characteristics of Study Participants according to Systolic Blood Pressure in TTR** | | | | | |
|  | Q1 | Q2 | Q3 | Q4 |  |
|  | 0% to <2% | 2% to <19% | 19% to <38% | 38% to 100% | *P* value |
| N | 1197 | 1197 | 1198 | 1197 | -- |
| Age, year | 64.81±10.96 | 66.47±11.45 | 66.92±10.78 | 65.62±10.43 | <0.01 |
| Male, n (%) | 730(60.99) | 720(60.15) | 704(58.76) | 642(53.63) | <0.01 |
| White race, n (%) | 887(74.1) | 949(79.28) | 987(82.39) | 1010(84.38) | <0.01 |
| Trial drug\*, n (%) | 580(48.45) | 596(49.79) | 599(50.00) | 623(52.05) | 0.37 |
| NYHA III or IV, n (%) | 799(66.75) | 725(60.57) | 615(51.34) | 567(47.37) | <0.01 |
| Current smoker, n (%) | 144(12.03) | 171(14.29) | 138(11.52) | 162(13.53) | 0.15 |
| Previous MI, n (%) | 386(32.25) | 400(33.42) | 383(31.97) | 403(33.67) | 0.76 |
| Previous PAD, n (%) | 169(14.12) | 167(13.95) | 147(12.27) | 135(11.28) | 0.11 |
| Atrial fibrillation, n (%) | 346(28.91) | 427(35.67) | 410(34.22) | 315(26.32) | <0.01 |
| Dyslipidemia, n (%) | 633(52.88) | 678(56.64) | 719(60.02) | 668(55.81) | 0.01 |
| Diabetes, n (%) | 453(37.84) | 490(40.94) | 445(37.15) | 349(29.16) | <0.01 |
| SBP, mmHg | 125.47±24.93 | 126.85±19.33 | 124.67±16.36 | 123.23±11.72 | <0.01 |
| DBP, mmHg | 72.84±13.89 | 73.37±11.87 | 72.63±10.83 | 73.91±9.82 | 0.04 |
| Heart rate, bpm | 74.72±12.95 | 73.83±13.53 | 72.63±12.11 | 71.94±11.63 | <0.01 |
| BMI, kg/m2 | 34.35±8.07 | 34.74±8.35 | 33.66±7.64 | 33.09±7.81 | <0.01 |
| Creatinine, mmol/L | 106.85±34.15 | 103.34±31.59 | 102.61±31.67 | 97.17±28.17 | <0.01 |
| Potassium, mmol/L | 4.27±0.51 | 4.28±0.44 | 4.27±0.46 | 4.23±0.50 | 0.07 |
| ACEI use, n (%) | 941(78.61) | 907(75.77) | 860(71.79) | 895(74.77) | <0.01 |
| ARB use, n (%)\*\* | 143(22.24) | 169(22.24) | 181(21.52) | 159(17.89) | 0.08 |
| β-blocker use, n (%)\*\* | 517(80.40) | 603(79.34) | 659(78.36) | 685(76.97) | 0.40 |
| CCB use, n (%)\*\* | 272(42.30) | 280(36.84) | 332(39.48) | 350(39.33) | 0.23 |
| Diuretic use, n (%) | 1079(90.14) | 1057(88.3) | 1052(87.81) | 963(80.45) | <0.01 |
| \*In TOPCAT study, the trial drug is Spironolactone; in BEST study, the trial drug is Bucindolol.  \*\* Data were only available for 3135 patients in TOPCAT study  Continuous data was presented as means± standard deviation  PAD: Peripheral arterial disease; NYHA: New York Heart Association class; MI: Myocardial infarction; ACEI: angiotensin-converting enzyme inhibitors; CCB: Calcium-channel blockers; BMI: body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure | | | | | |

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**Figure 1: KM curve for primary outcome, overall and by study**

1. For combine dataset Q1(0% to <2%), Q2(2% to <19%), Q3(19% to <38%) and Q4 (38% to 100%) for combined dataset,
2. For TOPCAT study, Q1(0% to <7%), Q2(7% to <23%), Q3(23% to <41%) and Q4 (41% to 100%)
3. For BEST Study, Q1(0%), Q2(1% to <14%), Q3(14% to <31%) and Q4 (31% to 100%)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 2. Associations of Systolic Blood Pressure Time in Target Range and Clinical Outcomes** | | | | | | |
|  | Number of events | Incidence Rate (100-person year) | Model 1\* | | Model 2\*\* | |
|  | Hazard Ratio (95% CI) | *P* value | Hazard Ratio (95% CI) | *P* value |
| Primary outcome |  |  |  |  |  |  |
| Q1(0% to <2%) | 461 | 16.26 | Reference | -- | Reference | -- |
| Q2(2% to <19%) | 377 | 10.01 | 0.73(0.63,0.83) | <0.0001 | 0.75(0.65,0.86) | <0.0001 |
| Q3(19% to <38%) | 345 | 8.98 | 0.73(0.64,0.84) | <0.0001 | 0.77(0.55,0.86) | 0.0004 |
| Q4(38% to 100%) | 261 | 7.37 | 0.63(0.54,0.73) | <0.0001 | 0.71(0.60,0.82) | <0.0001 |
| *P* for Trend |  |  |  | <0.0001 |  | <0.0001 |
| Cardiovascular mortality |  |  |  |  |  |  |
| Q1(0% to <2%) | 274 | 9.67 | Reference | -- | Reference | -- |
| Q2(2% to <19%) | 174 | 4.62 | 0.54(0.45,0.66) | <0.0001 | 0.58(0.47,0.70) | <0.0001 |
| Q3(19% to <38%) | 157 | 4.09 | 0.54(0.44,0.66) | <0.0001 | 0.56(0.46,0.68) | <0.0001 |
| Q4(38% to 100%) | 142 | 4.01 | 0.61(0.50,0.75) | <0.0001 | 0.68(0.55,0.84) | 0.0003 |
| *P* for Trend |  |  |  | <0.0001 |  | <0.0001 |
| HF hospitalization |  |  |  |  |  |  |
| Q1(0% to <2%) | 327 | 11.54 | Reference | -- | Reference | -- |
| Q2(2% to <19%) | 292 | 7.75 | 0.82(0.70,0.96) | 0.0135 | 0.86(0.73,1.01) | 0.0630 |
| Q3(19% to <38%) | 271 | 7.05 | 0.85(0.72,0.99) | 0.0469 | 0.91(0.77,1.07) | 0.2545 |
| Q4(38% to 100%) | 173 | 4.89 | 0.61(0.51,0.73) | <0.0001 | 0.70(0.58,0.85) | 0.0003 |
| *P* for Trend |  |  |  | <0.0001 |  | 0.0015 |
| All-cause mortality |  |  |  |  |  |  |
| Q1(0% to <2%) | 348 | 12.28 | Reference | -- | Reference | -- |
| Q2(2% to <19%) | 232 | 6.16 | 0.54(0.46,0.64) | <0.0001 | 0.56(0.47,0.66) | <0.0001 |
| Q3(19% to <38%) | 213 | 5.54 | 0.54(0.45,0.64) | <0.0001 | 0.54(0.45,0.65) | <0.0001 |
| Q4(38% to 100%) | 197 | 5.56 | 0.62(0.52,0.75) | <0.0001 | 0.69(0.58,0.83) | <0.0001 |
| *P* for Trend |  |  |  | <0.0001 |  | <0.0001 |
| Any hospitalization |  |  |  |  |  |  |
| Q1(0% to <2%) | 667 | 23.53 | Reference | -- | Reference | -- |
| Q2(2% to <19%) | 689 | 18.29 | 0.92(0.83,1.02) | 0.1204 | 0.90(0.80,0.99) | 0.0475 |
| Q3(19% to <38%) | 637 | 16.58 | 0.84(0.75,0.93) | 0.0014 | 0.83(0.74,0.92) | 0.0008 |
| Q4(38% to 100%) | 505 | 14.26 | 0.71(0.63,0.79) | <0.0001 | 0.76(0.67,0.85) | <0.0001 |
| *P* for Trend |  |  |  | <0.0001 |  | <0.0001 |
| \*Model 1 was adjusted for age, sex, white race, and treatment group | | | |  |  |  |
| \*\*Model 2 was adjusted for age, sex, white race, treatment group, NYHA, Current smoker, Previous MI, Previous PAD, Dyslipidemia, Atrial fibrillation, Diabetes, SBP, Heart rate, BMI, Creatinine, Potassium, ACEI, Diuretic.  PAD: Peripheral arterial disease; NYHA: New York Heart Association class; MI: Myocardial infarction; ACEI: angiotensin-converting enzyme inhibitors; BMI: Body mass index; SBP: Systolic blood pressure; | | | | | | |

Diagram, schematic

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**Figure 2 Study-specific Associations of Systolic Blood Pressure Time in Target Range and Clinical Outcomes**

Study specific quartile was used: Q1(0%), Q2(1% to <14%), Q3(14% to <31%) and Q4 (31% to 100%) for BEST study; Q1(0% to <7%), Q2(7% to <23%), Q3(23% to <41%) and Q4 (41% to 100%) for TOPCAT study.

Model was adjusted for age, sex, white race, treatment group, NYHA, Current smoker, Previous MI, Previous PAD, Dyslipidemia, Atrial fibrillation, Diabetes, SBP, Heart rate, BMI, Creatinine, Potassium, ACEI, Diuretic for BEST study but with CCB, ARB, β-blocker additionally for TOPCAT study.

PAD: Peripheral arterial disease; NYHA: New York Heart Association class; MI: Myocardial infarction; ACEI: angiotensin-converting enzyme inhibitors; CCB: Calcium-channel blockers; BMI: Body mass index; SBP: Systolic blood pressure.

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Chart, histogram

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**Figure 3, Spline curve between Time in rang to primary outcome overall and by study.**

1. For combine dataset,
2. For BEST Study
3. For TOPCAT study

Spline analysis was performed with 0% as the reference. Model was adjusted for age, sex, white race, treatment group, NYHA, Current smoker, Previous MI, Previous PAD, Dyslipidemia, Atrial fibrillation, Diabetes, SBP, Heart rate, BMI, Creatinine, Potassium, ACEI, Diuretic for BEST study but with CCB, ARB, β-blocker additionally for TOPCAT study.

PAD: Peripheral arterial disease; NYHA: New York Heart Association class; MI: Myocardial infarction; ACEI: angiotensin-converting enzyme inhibitors; CCB: Calcium-channel blockers; BMI: Body mass index; SBP: Systolic blood pressure.

Chart

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**Central Illustration: An inverse and gradual association between TTR and major adverse cardiovascular events**

1. Overall, Q1(0% to <2%), Q2(2% to <19%), Q3(19% to <38%) and Q4 (38% to 100%) for combined dataset,
2. For TOPCAT study, Q1(0% to <7%), Q2(7% to <23%), Q3(23% to <41%) and Q4 (41% to 100%)
3. For BEST Study, Q1(0%), Q2(1% to <14%), Q3(14% to <31%) and Q4 (31% to 100%)