JACC: HEART FAILURE VOL. 10, NO. 6, 2022
© 2022 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/).

MINI-FOCUS ISSUE: BLOOD PRESSURE AND HEART FAILURE

Prognostic Value of Time in Blood Pressure Target Range Among Patients With Heart Failure



Kangyu Chen, PhD,[a] Chao Li, PhD,[b] Victoria Cornelius, PhD,[c] Dahai Yu, PhD,[d] Qi Wang, MD,[a] Rui Shi, PhD,[e] Zhenqiang Wu, PhD,[f] Hao Su, PhD,[a] Ji Yan, MD,[a,*] Tao Chen, PhD,[g,*] Zhixin Jiang, PhD[h,*]

ABSTRACT

BACKGROUND Blood pressure (BP) is a continuous and dynamic measure. However, standard BP control metrics may not reflect the variability in BP over time.

OBJECTIVES This study assessed the prognostic value of time in BP target range among hypertensive patients with heart failure (HF).

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

RESULTS A total of 4,789 hypertensive patients (n = 1,654 from BEST and n = 3,135 from TOPCAT) were included. The cumulative incidences of primary endpoint (ie, cardiovascular death or HF hospitalization) were highest among the top quartile of TTR with a dose-dependent manner across quartiles (P_{trend} <0.005). The top quartile of TTR was significantly associated with a lower risk of primary outcome using adjusted Cox regression model (HR: 0.71; 95% CI: 0.60-0.82), cardiovascular mortality (HR: 0.68; 95% CI: 0.55-0.84), HF hospitalization (HR: 0.70; 95% CI: 0.58-0.85), all-cause mortality (HR: 0.69; 95% CI: 0.58-0.83), and any hospitalization (HR: 0.76; 95% CI: 0.67-0.85). Further analyses using restricted cubic spline indicated a linear relationship between TTR and primary outcome. Similar patterns were observed in the individual trial. Sensitivity analyses generated consistent results while redefining target range as 110 to 130 mm Hg for systolic BP or 70 to 80 mm Hg for diastolic BP.

CONCLUSIONS TTR could independently predict major adverse cardiovascular events in hypertensive patients with HF. (J Am Coll Cardiol HF 2022;10:369-379) © 2022 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/).

From the [a]Department of Cardiology, Department of Cardiology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China; [b]Department of Epidemiology and Health Statistics, School of Public Health, Xi'an Jiaotong University Health Science Centre, Xi'an, China; [c]Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, United Kingdom; [d]Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Keele, United Kingdom; [e]Heart Rhythm Centre, The Royal Brompton and Harefield National Health Service Foundation Trust, National Heart and Lung Institute, Imperial College London, London, United Kingdom; [f]Department of Geriatric Medicine, The University of Auckland, Auckland, New Zealand; [g]Department of Public Health, Policy & Systems, Institute of Population Health, Whelan Building, Quadrangle, The University of Liverpool, Liverpool, United Kingdom; and the [h]Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China. *Drs Tao Chen, Ji Yan, and Zhixin Jiang are joint senior authors.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2022.01.010

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

HF = heart failure

OBPV = office blood pressure variability

TTR = time in target range

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 patients 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, Mancia et al[6] found that continuous and effective BP control could provide additional benefits for hypertension treatment in the International Verapamil SR Trandolapril Study. Therefore, it is recommended that doctors should pay attention to every point of BP monitoring instead of single value of BP.

SEE PAGE 393

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 outside 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 2 published randomized trials conducted in different centuries.

METHODS

The present study was a secondary analysis using data from the TOPCAT (Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist) trial and the BEST (Beta-Blocker Evaluation of Survival Trial) 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, a total of 3,445 participants were randomized to receive spironolactone (n = 1,722) or matching placebo (n = 1,723) between 2006 and 2012.[13] Patients were eligible if they were 50 years of age or older with left ventricular ejection fraction ≥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 after an average of 3.3 years. For the BEST trial, 2,708 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 = 1,354) or placebo (n = 1,354) with a mean follow-up of 2.0 years.[12] In this trial, all patients were 18 years old having New York Heart Association (NYHA) functional class III or IV HF with left ventricular ejection fraction <35%. The detailed inclusion and exclusion criteria were published elsewhere.[15]

Clearly, a major difference between these 2 trials is that the BEST trial recruited HF patients with reduced ejection fraction (HFrEF) and TOPCAT trial enrolled HF patients with 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 2 BP measurements from the de-identified public-use copy of the BEST

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

Manuscript received November 16, 2021; revised manuscript received January 12, 2022, accepted January 13, 2022.

TABLE 1 Baseline Characteristics of Study Participants According to Systolic Blood Pressure in TTR

	Q1	Q2	Q3	Q4	
	0% to <2% (n = 1,197)	2% to <19% (n = 1,197)	19% to <38% (n = 1,198)	38% to 100% (n = 1,197)	*P* Value
Age, y	64.81 ± 10.96	66.47 ± 11.45	66.92 ± 10.78	65.62 ± 10.43	<0.01
Male	730 (60.99)	720 (60.15)	704 (58.76)	642 (53.63)	<0.01
White race	887 (74.1)	949 (79.28)	987 (82.39)	1,010 (84.38)	<0.01
Trial drug[a]	580 (48.45)	596 (49.79)	599 (50.00)	623 (52.05)	0.37
NYHA functional class III or IV	799 (66.75)	725 (60.57)	615 (51.34)	567 (47.37)	<0.01
Current smoker	144 (12.03)	171 (14.29)	138 (11.52)	162 (13.53)	0.15
Previous MI	386 (32.25)	400 (33.42)	383 (31.97)	403 (33.67)	0.76
Previous PAD	169 (14.12)	167 (13.95)	147 (12.27)	135 (11.28)	0.11
Atrial fibrillation	346 (28.91)	427 (35.67)	410 (34.22)	315 (26.32)	<0.01
Dyslipidemia	633 (52.88)	678 (56.64)	719 (60.02)	668 (55.81)	0.01
Diabetes	453 (37.84)	490 (40.94)	445 (37.15)	349 (29.16)	<0.01
SBP, mm Hg	125.47 ± 24.93	126.85 ± 19.33	124.67 ± 16.36	123.23 ± 11.72	<0.01
DBP, mm Hg	72.84 ± 13.89	73.37 ± 11.87	72.63 ± 10.83	73.91 ± 9.82	0.04
Heart rate, beats/min	74.72 ± 12.95	73.83 ± 13.53	72.63 ± 12.11	71.94 ± 11.63	<0.01
BMI, kg/m^2	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	941 (78.61)	907 (75.77)	860 (71.79)	895 (74.77)	<0.01
ARB[b]	143 (22.24)	169 (22.24)	181 (21.52)	159 (17.89)	0.08
Beta-blocker[b]	517 (80.40)	603 (79.34)	659 (78.36)	685 (76.97)	0.40
CCB[b]	272 (42.30)	280 (36.84)	332 (39.48)	350 (39.33)	0.23
Diuretic	1,079 (90.14)	1,057 (88.3)	1,052 (87.81)	963 (80.45)	<0.01

Values are mean ± SD or n (%), unless otherwise indicated. [a]In the TOPCAT study, the trial drug is spironolactone; in the BEST study, the trial drug is bucindolol. [b]Data were only available for 3,135 patients in the TOPCAT study.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BEST = Beta-Blocker Evaluation of Survival Trial; BMI = body mass index; CCB = calcium channel blocker; DBP = diastolic blood pressure; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral artery disease; SBP = systolic blood pressure; TOPCAT = Treatment of Preserved Cardiac Function HF With an Aldosterone Antagonist; TTR = time in target range.

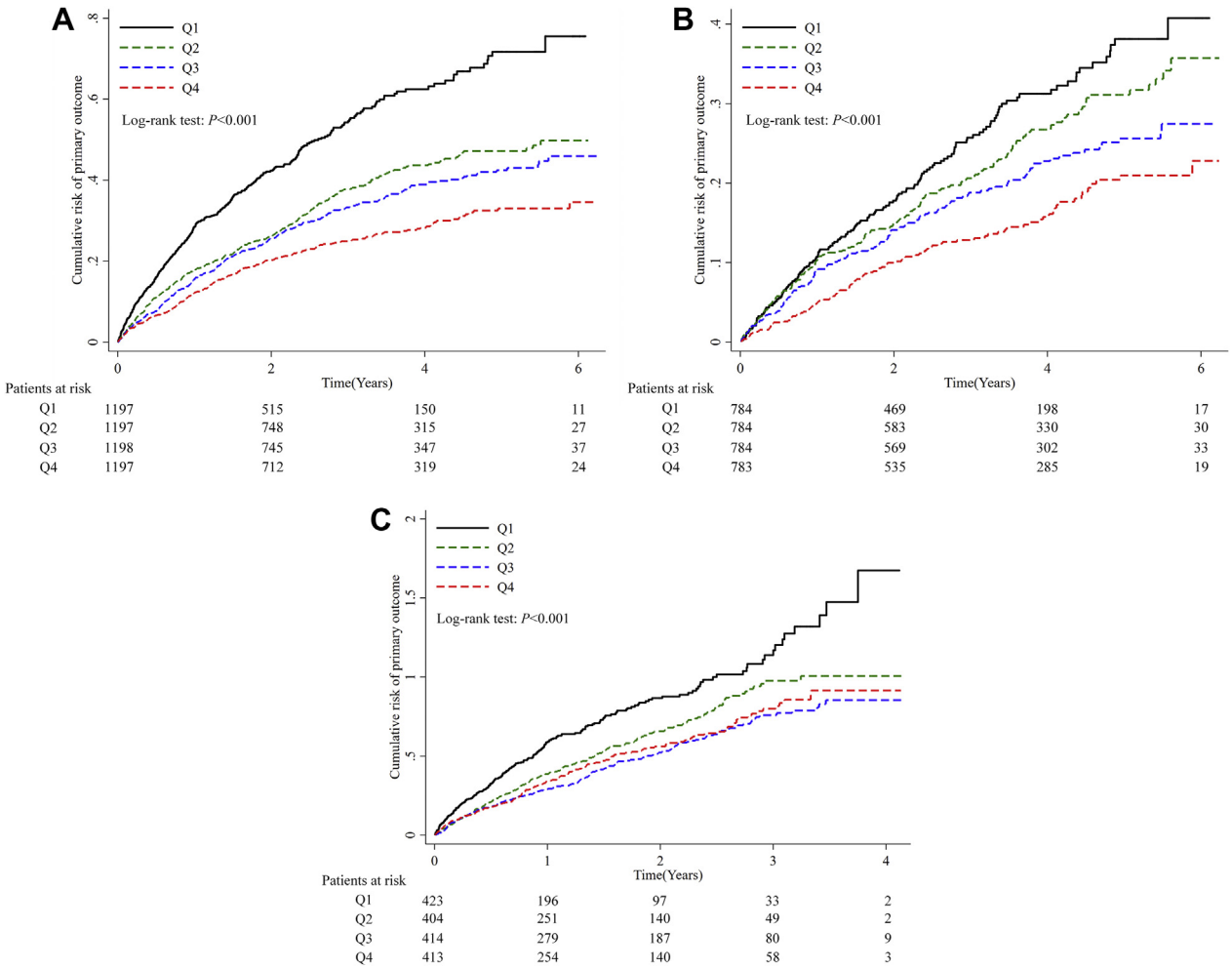
(n = 2,707) and TOPCAT (n = 3,445) datasets. We defined hypertension as reporting history of hypertension or systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg at baseline. Given that the same BP target was recommended for both HFrEF and HFpEF from recent hypertension guidelines and there were no differences in outcomes between the randomized groups within both trials, we first pooled the trial data to allow an adequately powered analysis, then separated them to take account of the possible difference of antihypertensive treatment effect across the spectrum of ejection fraction.[12,13,16,17] 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 to 16) for the TOPCAT and 13 (range, 2 to 28) for the 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, this method takes into consideration both the frequency of BP measurements and the actual BP values.[7] 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 systolic blood pressure [SBP] window 120 to 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 endpoint of cardiovascular disease death, aborted cardiac arrest, or HF hospitalization for the TOPCAT trial and all-cause mortality for the BEST trial.[12,13] To facilitate the comparisons between the TOPCAT and BEST trials and other contemporary HF trials, we redefined the primary outcome as the combined endpoint of cardiovascular death or HF hospitalization.[19,20] Our secondary outcomes included cardiovascular mortality, HF

FIGURE 1 Kaplan-Meier Curve for Primary Outcome, Overall, and by Study



(A) For combined dataset Q1 (0% to <2%), Q2 (2% to <19%), Q3 (19% to <38%), and Q4 (38% to 100%). **(B)** For TOPCAT study, Q1 (0% to <7%), Q2 (7% to <23%), Q3 (23% to <41%), and Q4 (41% to 100%). **(C)** For BEST study, Q1 (0%), Q2 (1% to <14%), Q3 (14% to <31%), and Q4 (31% to 100%). BEST = Beta-Blocker Evaluation of Survival Trial; TOPCAT = Treatment of Preserved Cardiac Function HF With an Aldosterone Antagonist.

hospitalization, all-cause mortality, and any hospitalization. All events were adjudicated by a clinical endpoint committee but not for hospitalizations in the BEST trial.

STATISTICAL ANALYSIS. The baseline characteristics of patients were expressed as mean ± SD 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 analysis of variance 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 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 HRs and 95% 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 (ACEIs), diuretic (model 2) but with calcium-channel

TABLE 2 Associations of SBP, TTR, and Clinical Outcomes

	No. of Events	Incidence Rate (100 Person-Years)	Model 1[a]		Model 2[b]	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Primary outcome						
Q1 (0% to <2%)	461	16.26	Ref	—	Ref	—
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 value for trend				<0.0001		<0.0001
Cardiovascular mortality						
Q1 (0% to <2%)	274	9.67	Ref	—	Ref	—
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 value for trend				<0.0001		<0.0001
HF hospitalization						
Q1 (0% to <2%)	327	11.54	Ref	—	Ref	—
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 value for trend				<0.0001		0.0015
All-cause mortality						
Q1 (0% to <2%)	348	12.28	Ref	—	Ref	—
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 value for trend				<0.0001		<0.0001
Any hospitalization						
Q1 (0% to <2%)	667	23.53	Ref	—	Ref	—
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 value for trend				<0.0001		<0.0001

[a]Model 1 was adjusted for age, sex, white race, and treatment group [b]Model 2 was adjusted for age, sex, white race, treatment group, NYHA functional class, current smoker, previous MI, previous PAD, dyslipidemia, atrial fibrillation, diabetes, SBP, heart rate, BMI, creatinine, potassium, ACEI, and diuretic.

HF = heart failure; Ref = reference; other abbreviations as in Table 1.

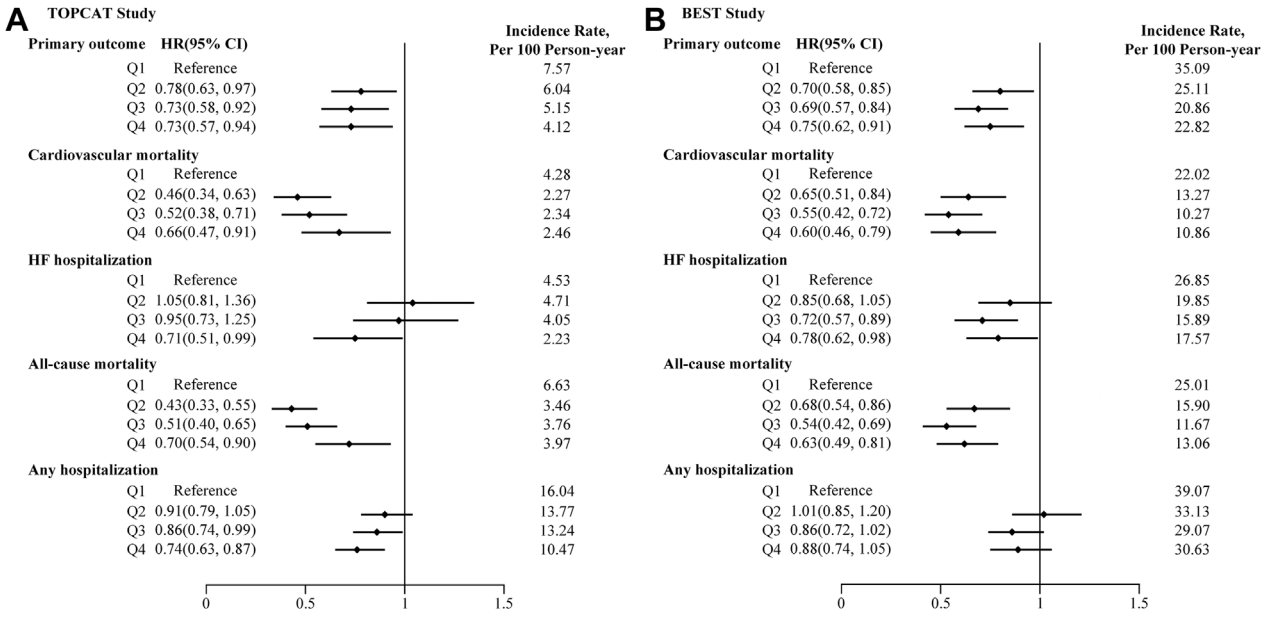
blockers, angiotensin receptor blockers, and β-blocker for the TOPCAT study. The interaction between treatment group and TTR strata was tested. We repeated the above analyses redefining the therapeutic range using diastolic BP of 70 to 80 mm Hg or a wider threshold of SBP 110 to 130 mm Hg after considering 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-described 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 nonlinearity 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 1,302 nonhypertensive patients and 61 with <2 BP measurements from the limited-access trial data, our analysis included a total of 4,789 patients with 1,654 from the BEST trial and 3,135 from the TOPCAT trial. Overall, the incidence rates vary largely between trials (25.48 per 100 person-years for BEST and 5.67 per 100 person-years for TOPCAT) and the TTR rate 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

FIGURE 2 Study-Specific Associations of Systolic Blood Pressure Time in Target Range and Clinical Outcomes



Study specific quartiles were used: Q1 (0%), Q2 (1% to <14%), Q3 (14% to <31%), and Q4 (31% to 100%) for the BEST study; and Q1 (0% to <7%), Q2 (7% to <23%), Q3 (23% to <41%), and Q4 (41% to 100%) for the TOPCAT study. The model was adjusted for age, sex, white race, treatment group, New York Heart Association functional class, current smoker, previous myocardial infarction, previous peripheral artery disease, dyslipidemia, atrial fibrillation, diabetes, systolic blood pressure, heart rate, body mass index, creatinine, potassium, angiotensin-converting enzyme inhibitor, diuretic for the BEST study but with calcium channel blockers, angiotensin receptor blocker, and beta-blocker additionally for the TOPCAT study. Abbreviations as in Figure 1.

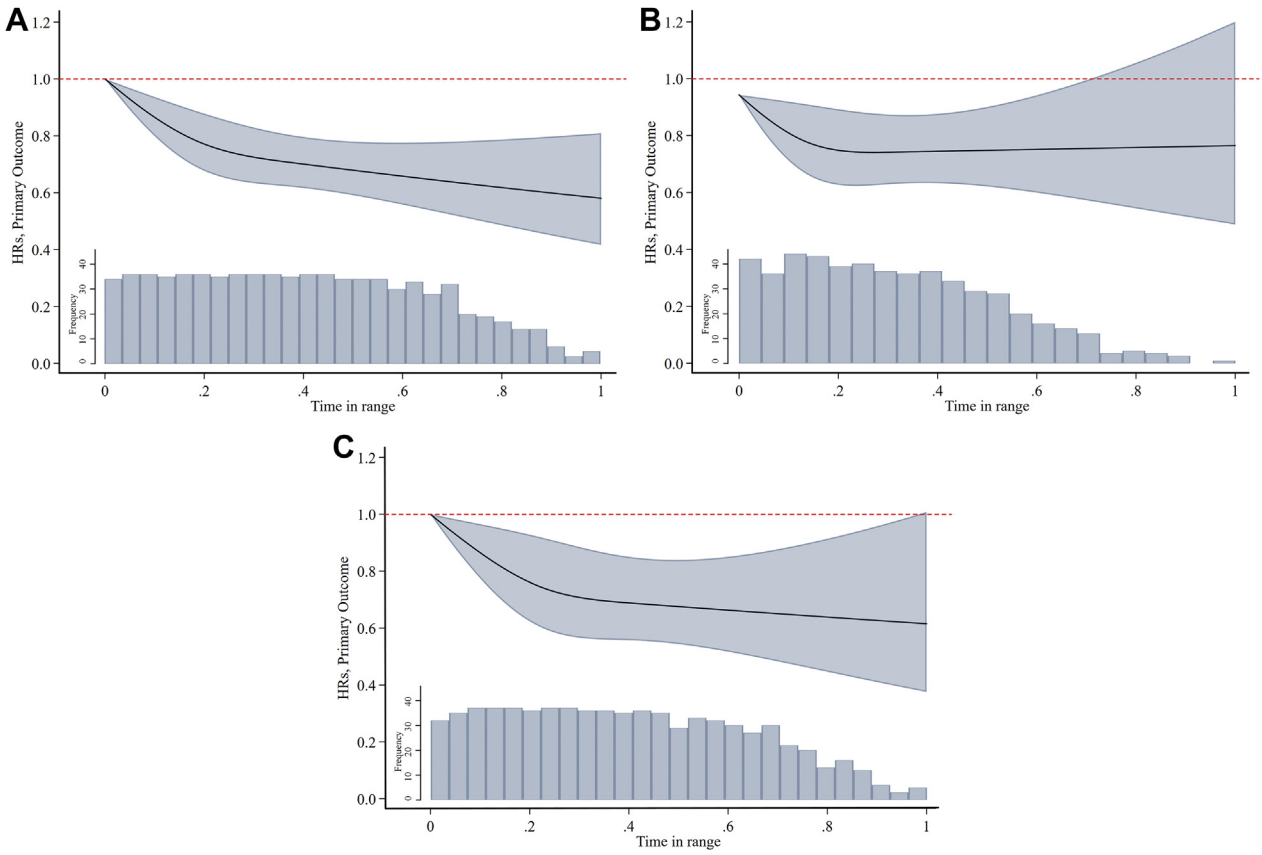
Supplemental Tables 1 and 2. In general, participants from the highest quartile were more likely to be female and White race, had lower rate of NYHA functional class III or IV, atrial fibrillation, diabetes mellitus, diuretic use, and lower levels of systolic BP, heart rate, BMI, and creatinine, than 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 4 groups was statistically significant ($P <$ 0.001). This pattern was also found for each trial (all $P < 0.001$) (**Figures 1B and 1C**). 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 $P_{\text{interaction}} > 0.20$). 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 and the BEST trials with a higher event rate conducted in the last century (Supplemental Tables 3 and 4, **Figure 2**).

Consistent with results from adjustments for age, sex, white race, and treatment group, our results from the full-adjusted model indicated that the top quartile of TTR was significantly associated with a lower risk of primary outcome (HR: 0.71; 95% CI: 0.60-0.82; $P < 0.0001$), cardiovascular mortality (HR: 0.68; 95% CI: 0.55-0.84; $P < 0.0001$), HF hospitalization (HR: 0.70; 95% CI: 0.58-0.85; $P = 0.0003$), all-cause mortality (HR: 0.69; 95% CI: 0.58-0.83; $P < 0.0001$), and any hospitalization (HR: 0.76; 95% CI: 0.67-0.85; $P < 0.0001$). A linear trend was also found for each clinical outcome across different quartiles (all P for trend <0.005). Our further analysis using a restricted cubic spline model indicated that the association of TTR and primary outcome generally showed a linear relationship overall (**Figure 3A**) and by study (**Figures 3B and 3C**). We did not find a significant nonlinear trend ($P_{\text{nonlinearity}} = 0.058$ overall; $P_{\text{nonlinearity}} = 0.079$ for TOPCAT, and $P_{\text{nonlinearity}} = 0.141$ 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**, Supplemental Tables 3 and 4). In comparison with the association between

FIGURE 3 Spline Curves Between Time in Range to Primary Outcome Overall and by Study



(A) For the combined dataset. **(B)** For the BEST study. **(C)** For the TOPCAT study. Spline analysis was performed with 0% as the reference. The model was adjusted for age, sex, white race, treatment group, New York Heart Association functional class, current smoker, previous myocardial infarction, previous peripheral artery disease, dyslipidemia, atrial fibrillation, diabetes, systolic blood pressure, heart rate, body mass index, creatinine, potassium, angiotensin-converting enzyme inhibitor, diuretic for the BEST study but with calcium channel blockers, angiotensin receptor blocker, and beta-blocker additionally for the TOPCAT study. Abbreviations as in **Figure 1**.

TTR with all-cause or cardiovascular mortality, the magnitude of the relationship with hospitalization was weaker.

Our sensitivity analyses using different therapeutic ranges for systolic BP (110 to 130 mm Hg) confirmed the clinical benefits from longer TTR (Supplemental Tables 5 to 7). Furthermore, we found that the significant association of the increase in TTR with improved clinical outcomes persisted if the therapeutic range for diastolic BP (70 to 80 mm Hg) was adopted (Supplemental Tables 8 to 10).

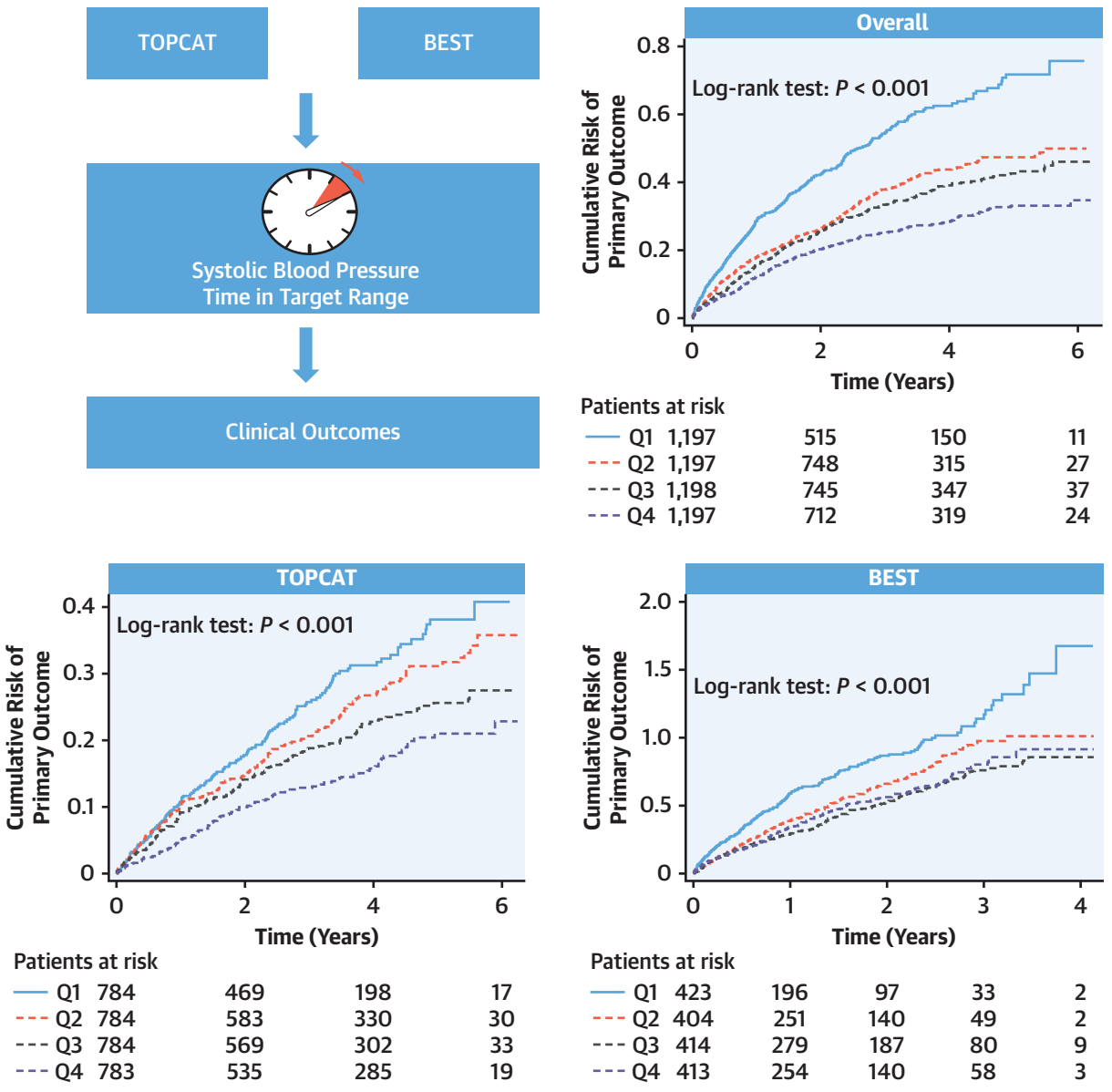
DISCUSSION

This post hoc analysis has shown that in patients with HF and hypertension, higher TTR with a systolic BP target of 120 to 130 mm Hg 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 an SBP target of 110 to 130 mm Hg and diastolic BP target of 70 to 80 mm Hg. TTR was persistently found to have the same predictive value for outcome regardless of HF types (ie, HFrEF and HFpEF), time of trial conducted (1995-1998 vs 2006-2012), clinical event rates (25 vs 5 per 100 person-years), and low TTR (18% vs 26%) across both the BEST and TOPCAT trials. Meanwhile, a linear relationship was found between TTR and primary outcome, which suggested that longer TTR is associated with better outcomes (**Central Illustration**).

The SBP target used in this study was 120 to 130 mm Hg, which was in line with the current guidelines.[16,17,21] The 2017 American College of Cardiology/American Heart Association hypertension guidelines recommend that in patients with HF and

JACC: HEART FAILURE VOL. 10, NO. 6, 2022
JUNE 2022:369–379

CENTRAL ILLUSTRATION **An Inverse and Gradual Association Between Time in Target Range and Major Adverse Cardiovascular Events**



Chen K, et al. J Am Coll Cardiol HF. 2022;10(6):369–379.

For overall, Q1 (0% to <2%), Q2 (2% to <19%), Q3 (19% to <38%), and Q4 (38% to 100%) for the combined dataset. For the TOPCAT study, Q1 (0% to <7%), Q2 (7% to <23%), Q3 (23% to <41%), and Q4 (41% to 100%). For the BEST study, Q1 (0%), Q2 (1% to <14%), Q3 (14% to <31%), and Q4 (31% to 100%). BEST = Beta-Blocker Evaluation of Survival Trial; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

hypertension, SBP should be treated to below 130 mm Hg.[16] The 2018 European Society of Cardiology/European Society of Hypertension guideline suggests that SBP should not be below 120 mm Hg in HF patients.[17] However, the BP target in HF patients remains controversial, as current evidence comes mostly from BP-lowering trials in a hypertensive population with exclusion of HF patients typically.[2,22] In contrast to the well-established linear relationship between elevated BP and cardiovascular events in the general population, a J-shaped association between SBP and all-cause and cardiovascular mortality

among patients with HF were reported, especially among those with HFrEF.[23,24] Taken together, we chose an SBP of 120 to 130 mm Hg as the therapeutic range in our study. With TTR in this SBP 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 shown 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 ACEIs for at least 1 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 SBP target range (110-130 mm Hg) and found that the results were in line with that of the SBP target range (120-130 mm Hg).

Because 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.[25] Visit-to-visit office BP variability (OBPV) also seems to be an independent predictor of cardiovascular events, stroke, myocardial infarction, and cardiovascular mortality.[26-28] However, other studies have failed to show an association of OBPV with clinical outcomes.[29-31] 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 shown to be a significant predictor of cardiovascular outcomes even after adjusting for mean SBP and SBP variability.[9] Chung 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 the United Kingdom. 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 showed an inverse and gradual association between TTR and all-cause mortality in a large U.S. 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.

STUDY LIMITATIONS. 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 using the timepoints dictated by the 2 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. Because both trials were performed mainly in North America, further research is warranted in other regions, such as Asia, given that 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.

CONCLUSIONS

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.

ACKNOWLEDGMENTS The authors thank TOPCAT and BEST Investigators and the National Heart, Lung, and Blood Institute investigators for conducting the trials and making both data sets publicly available.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

No specific fund supports the current analysis. This paper does not necessarily reflect the opinions or views of the TOPCAT and BEST trial or the NHLBI. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESSES FOR CORRESPONDENCE: Dr Tao Chen, Department of Public Health, Policy & Systems, Institute of Population Health, Whelan Building, Quadrangle, The University of Liverpool, Liverpool L69 3GB, United Kingdom. E-mail: Tao.chen@liverpool.ac.uk. OR Dr Ji Yan, Department of Cardiology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, China. E-mail: yanji111111@126.com. OR Dr Zhixin Jiang, Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing 210029, China. E-mail: zhixin_jiang@njmu.edu.cn.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: 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.

REFERENCES

1. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957–967.

2. Group SR, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.

3. Pinho-Gomes AC, Azevedo L, Bidel Z, et al. Effects of blood pressure-lowering drugs in heart failure: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens*. 2019;37:1757–1767.

4. Oh GC, Cho HJ. Blood pressure and heart failure. *Clin Hypertens*. 2020;26:1.

5. Nichols GA, Reynolds K, Kimes TM, Rosales AG, Chan WW. Comparison of risk of re-hospitalization, all-cause mortality, and medical care resource utilization in patients with heart failure and preserved versus reduced ejection fraction. *Am J Cardiol*. 2015;116:1088–1092.

6. Mancia G, Messerli F, Bakris G, Zhou Q, Champion A, Pepine CJ. Blood pressure control and improved cardiovascular outcomes in the International Verapamil SR-Trandolapril Study. *Hypertension*. 2007;50:299–305.

7. Doumas M, Tsioufis C, Fletcher R, Amdur R, Faselis C, Papademetriou V. Time in therapeutic range, as a determinant of all-cause mortality in patients with hypertension. *J Am Heart Assoc*. 2017;6(11):e007131.

8. Chung SC, Pujades-Rodriguez M, Duyx B, et al. Time spent at blood pressure target and the risk of death and cardiovascular diseases. *PLoS One*. 2018;13:e0202359.

9. Fatani N, Dixon DL, Van Tassell BW, Fanikos J, Buckley LF. Systolic blood pressure time in target range and cardiovascular outcomes in patients with hypertension. *J Am Coll Cardiol*. 2021;77:1290–1299.

10. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. *J Am Coll Cardiol HF*. 2017;5:543–551.

11. Georgiopoulou VV, Kalogeropoulos AP, Butler J. Dilemmas of blood pressure management for heart failure prevention. *Circ Heart Fail*. 2011;4:528–533.

12. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659–1667.

13. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.

14. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J*. 2011;162:966–972 e10.

15. The BEST Steering Committee. Design of the Beta-Blocker Evaluation Survival Trial (BEST). *Am J Cardiol*. 1995;75:1220–1223.

16. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:2199–2269.

17. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104.

18. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69:236–239.

19. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.

20. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

21. Chow SL, Maisel AS, Anand I, et al. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. *Circulation*. 2017;135:e1054–e1091.

22. Group AS, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585.

23. Schmid FA, Schlager O, Keller P, et al. Prognostic value of long-term blood pressure changes in patients with chronic heart failure. *Eur J Heart Fail*. 2017;19:837–842.

24. Raphael CE, Whinnett ZI, Davies JE, et al. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. *Heart*. 2009;95:56–62.

25. Yang WY, Melgarejo JD, Thijs L, et al. Association of office and ambulatory blood pressure with mortality and cardiovascular outcomes. *JAMA*. 2019;322:409–420.

26. Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. *Hypertension*. 2011;57:160–166.

27. Diaz KM, Tanner RM, Falzon L, et al. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. *Hypertension*. 2014;64:965–982.

28. Wei FF, Zhou Y, Thijs L, et al. Visit-to-visit blood pressure variability and clinical outcomes in patients with heart failure with preserved ejection fraction. *Hypertension*. 2021;77:1549–1558.

29. Schutte R, Thijs L, Liu YP, et al. Within-subject blood pressure level — not variability — predicts fatal and nonfatal outcomes in a general population. *Hypertension*. 2012;60:1138–1147.

30. Hara A, Thijs L, Asayama K, Jacobs L, Wang JG, Staessen JA. Randomised double-blind comparison of placebo and active drugs for effects on risks associated with blood pressure variability in the Systolic Hypertension in Europe trial. *PLoS One*. 2014;9:e103169.

31. Chang TI, Reboussin DM, Chertow GM, et al. Visit-to-visit office blood pressure variability and cardiovascular outcomes in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension*. 2017;70:751–758.

KEY WORDS cardiovascular event, heart failure, hypertension, quality of care, time in target range

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