Beta-Blocker Use in Hypertension and Heart Failure (A Secondary Analysis of the Systolic Blood Pressure Intervention Trial)

Daniel N. Silverman, MD[a], Jeanne du Fay de Lavallaz, MD[b], Timothy B. Plante, MD, MHS[c], Margaret M. Infeld, MD, MS[c], Parag Goyal, MD, MSc[d], Stephen P. Juraschek, MD, PhD[e], Geoff B. Dougherty, PhD, MPH[f], Peter W. Callas, PhD[g], and Markus Meyer, MD[h,*]

Given the concern that beta-blocker use may be associated with an increased risk for heart failure (HF) in populations with normal left ventricular systolic function, we evaluated the association between beta-blocker use and incident HF events, as well as loop diuretic initiation in the Systolic Blood Pressure Intervention Trial (SPRINT). SPRINT demonstrated that a blood pressure target of <120 mm Hg reduced cardiovascular outcomes compared with <140 mm Hg in adults with at least one cardiovascular risk factor and without HF. The lower rate of the composite primary outcome in the 120 mm Hg group was primarily driven by a reduction in HF events. Subjects on a beta blocker for the entire trial duration were compared with subjects who never received a beta blocker after 1:1 propensity score matching. A competing risk survival analysis by beta-blocker status was performed to estimate the effect of the drug on incident HF and was then repeated for a secondary end point of cardiovascular disease death. Among the 3,284 propensity score−matched subjects, beta-blocker exposure was associated with an increased HF risk (hazard ratio 5.86; 95% confidence interval 2.73 to 13.04; p <0.001). A sensitivity analysis of propensity score −matched cohorts with a history of coronary artery disease or atrial fibrillation revealed the same association (hazard ratio 3.49; 95% confidence interval 1.15 to 10.06; p = 0.028). In conclusion, beta-blocker exposure in this secondary analysis was associated with increased incident HF in subjects with hypertension without HF at baseline. Published by Elsevier Inc. (Am J Cardiol 2022;165:58−64)

Hypertension is prevalent and a major driver of cardiovascular disease (CVD) morbidity and mortality,[1] including heart failure (HF), stroke, and coronary artery disease (CAD).[2,3] The Systolic Blood Pressure Intervention Trial (SPRINT) was designed to evaluate whether a systolic blood pressure (BP) target of <120 mm Hg in patients without HF and ≥1 CVD risk factor would reduce cardiovascular events.[4] The trial was stopped early after interim analyses indicated that the primary composite outcome was reduced in the lower BP arm.[4] Although patients with symptomatic HF were generally excluded from enrollment, the main benefit of a lower BP was a marked reduction in incident HF (Figure 1).[4] The SPRINT protocol encouraged participating investigators to use antihypertensive medications supported by evidence from large randomized trials as first-line agents. The use of beta blockers was reserved for the presence of a secondary indication. Nonetheless, at the conclusion of SPRINT, more than a third of the participants were receiving beta blockers.[4] Data from randomized trials and secondary analyses suggest an association between beta-blocker use and decompensated HF in patient populations with predominantly normal ejection fractions (EFs).[5−7] The objective of our study was to investigate whether beta-blocker exposure was a risk factor for incident HF in a trial cohort with predominantly normal EFs and cardiac risk factors.

Methods

The SPRINT design and results have been described in detail.[4] In brief, the trial was a multicenter, open-label, randomized trial enrolling 9,361 subjects in the United States and Puerto Rico with a systolic BP of ≥130 mm Hg who had no history of diabetes or stroke but who had ≥1 CVD risk factor. Subjects were enrolled to either (1) intensive BP control with a target systolic BP of ≤120 mm Hg (lower BP

[a]Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; [b]Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland; [c]Departments of Medicine and; [g]Biostatistics, University of Vermont Larner College of Medicine, Burlington, Vermont; [d]Divisions of Cardiology and General Internal Medicine, Department of Medicine, Weill Cornell Medicine, New York, New York; [e]Department of Medicine, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, Massachusetts; [f]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and [h]Department of Medicine, Lillehei Heart Institute, University of Minnesota College of Medicine, Minneapolis, Minnesota. Manuscript received August 19, 2021; revised manuscript received and accepted October 22, 2021.

Daniel N. Silverman and Jeanne du Fay de Lavallaz contributed equally to this work.

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See page 63 for disclosure information.

*Corresponding author: Tel: (612)-625-9538; fax: (612)-301-8298.

E-mail address: meye3249@umn.edu (M. Meyer).

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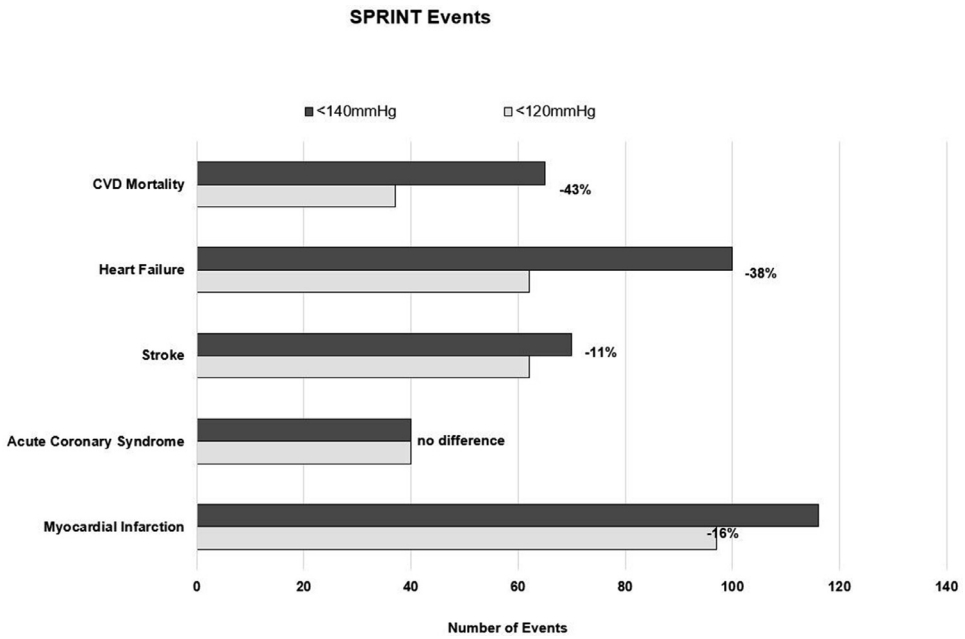

Figure 1. Cumulative incidence of events contributing to primary composite outcome. Cumulative incidence of events contributing to the SPRINT primary composite outcome stratified by treatment group and higher BP target (<140 mm Hg) versus lower BP target (<120 mm Hg). Percentages to the right of the lower BP target bars represent the relative difference between lower BP and higher BP targets.

arm), or (2) standard BP control with target systolic BP of ≤140 mm Hg (higher BP arm). Included subjects were ≥50 years of age and met prespecified BP criteria with accompanying requirements for number of antihypertensive medications.

CVD risk factors could include 1 or more of the following: (1) known presence of clinical or subclinical CVD (other than stroke), (2) stable chronic kidney disease with an estimated glomerular filtration rate 20 to 59 ml/min/1.73 m^2, (3) Framingham Risk Score for 10-year CVD risk ≥15%, and/or (4) age ≥75 years. Clinical CVD included previous myocardial infarction (MI) or acute coronary syndrome (ACS), previous vascular intervention or surgery for obstructive arteriosclerosis, an established ≥50% arterial stenosis, or an abdominal aortic aneurysm ≥5 cm with or without repair. Subclinical CVD included patients with a coronary artery calcium score ≥400 Agatston units within the previous 2 years, ankle brachial index <0.90 within the previous 2 years, or left ventricular hypertrophy by electrocardiography (ECG), echocardiogram report, or other cardiac imaging modality within the previous 2 years. Participants with symptomatic HF in the 6 months preceding enrollment or who were known to have EF <35% were excluded.[4]

A specific antihypertensive medication regimen was not prescribed. Instead, a treatment algorithm emphasizing initiation of a 2- or 3-drug regimen preferentially using a combination of a thiazide-type diuretic and/or an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) and/or calcium channel blocker (CCB) was recommended based on clinical trial data. The use of beta blockers as part of the hypertension treatment regimen was only advised in specific clinical scenarios including the setting of underlying CAD, as a heart rate−controlling agent with atrial fibrillation (AF), impaired renal function, or electrolyte abnormalities that would preclude ACE-I/ARB/thiazide diuretics. Hypertension remained the primary indication for the use of all medication classes, with further selection based on concomitant co-morbidities. For study follow-up visits, titration of agents already in use or addition of preferred agents was recommended.[4]

The baseline visit included laboratory testing, vital signs, anthropomorphic data, ECG, medical history, demographic characteristics, medication inventory, and quality of life surveys. For the next 3 months, participants returned for monthly follow-up visits, which included a comprehensive medical history, assessments of vital signs, and medication inventories for the first 3 months. Thereafter, interval study visits occurred every 3 months for the remainder of the first year, and then annually. A medication inventory was included at each visit.[4]

The deidentified SPRINT database was obtained from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repositories Information Coordinating Center. The database included 9,361 randomized subjects. Of those, 17 subjects were excluded based on incomplete medication inventories. Because it was our goal to examine incident HF, we also excluded the 332 subjects with a history of HF (enrolled in the trial based on a history of HF without symptoms in the preceding 6 months and with EF documented above 35%). The remaining analyzed population included 9,012 subjects as shown in Figure 2. Baseline and follow-up medication inventories were used to determine the use of beta blockers and other major antihypertensive classes such as ACE-I/ARB, thiazides, and CCBs.

The primary end point of this secondary analysis was incident HF defined as hospitalization or emergency department visit for HF requiring intravenous loop diuretics.[4] The secondary end point was death from CVD with causes

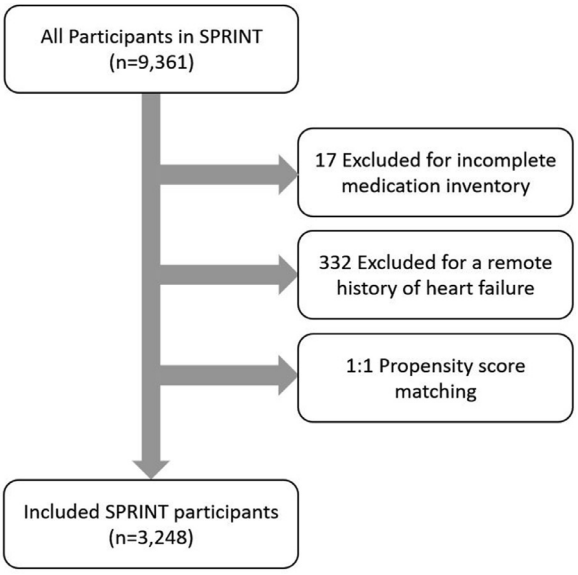

Figure 2. Flow diagram of analyzed population. Flow diagram of patient inclusions and exclusions leading to the analyzed population.

including MI, stroke, or postmortem findings of an acute CVD event.

For the primary analysis, we compared subjects on a beta blocker for the entire trial with subjects who never received a beta blocker to assess the risk of incident HF and beta-blocker status. To correct for a maximal number of confounding variables, we created propensity score−matched (PSM) cohorts. After estimation of the propensity score, subjects within the subgroups were matched in a 1:1 ratio to the controls accounting for 27 confounding variables: age, gender, race, previous MI, previous ACS, carotid artery disease, peripheral artery disease (PAD), aortic stenosis, abdominal aortic aneurysm ≥5 cm, calcium score >400, low ankle brachial index, left ventricular hypertrophy on ECG, study arm, Framingham risk, systolic BP, diastolic BP, number of antihypertensive agents at enrollment, smoking status, aspirin use, estimated glomerular filtration rate, high-density lipoprotein, total cholesterol, body mass index, statin use, and antihypertensive class use. We used the "nearest neighbor" matching algorithm with a caliper size of 1% of the SD of the estimated propensity score to construct a matched-paired sample.[8] This caliper size is more stringent than typically recommended for observational studies[9] and allows for optimal matching of co-morbidities, that is, MI and antihypertensive medication use. After the PSM, we conducted a competing risk survival analysis by beta-blocker status to estimate the effect of the drug on incident HF accounting for acute MI and all-cause death as competing risk. We repeated the analysis for the secondary end point of CVD death.

The PSM analysis was repeated for the subjects with a potential beta-blocker indication such as history of MI, ACS, coronary revascularization, and history of AF or AF on the baseline ECG. To compare the impact of the other major antihypertensive classes on HF, we repeated the PSM analyses for patients who did not change ACE-I/ARB, thiazide, or CCB status during the trial. The impact of beta blockers on objective variables, such as heart rate and systolic BP, was analyzed using linear mixed-effect models controlling for multiple co-morbidities (fixed effects). As multiple data points were available for each subject, a patient identifier was used as random effect.

Results

This secondary analysis of SPRINT included 9,012 participants with a median age of 67 years (interquartile range 61 to 75). Median follow-up was 3.3 years, with 8,736 subjects (96.93%) followed after 1 year, 8,736 subjects followed after 2 years, and 6,076 subjects followed after 3 years. Of these, 4,501 (50%) had been randomized to the lower BP arm, 3,218 (36%) were women, and 3,803 (42%) were non-White (Table 1). A history of acute MI was present in 576 subjects (6%), and 397 (4%) had a history of ACS. Most of the trial participants were using between 1 and 3 antihypertensive medications at baseline. Overall, 3,248 subjects (36%) were on a beta blocker at the beginning of the trial, and 2,813 (31%) received beta blockers for the entire trial. In addition, 3,284 subjects were matched using a propensity score.

An analysis of subjects who received beta blockers for the entire trial compared with subjects who never received a beta blocker was well balanced in terms of concomitant BP medications (Table 2). The types of beta blockers used and dosing was similar to the overall cohort (Supplementary Tables 1 and 2). In the matched group that never received beta blockers, there were 6 incident HF events, and in the group that received beta blockers for the entire trial, there were 41 HF events. The cumulative incidence of HF and competing events are shown in Figure 3. This analysis confirmed a positive association between beta blocker use and incident HF (hazard ratio [HR] 5.86, confidence interval [CI] 2.63 to 13.04; p <0.001) (Table 3).

The analysis of patients with a potential indication for beta-blocker use (i.e., history of MI, ACS, and previous coronary revascularization or AF) demonstrated a positive association of beta-blocker use and incident HF in the PSM analysis (Supplementary Table 3). In the PSM cohort of subjects who remained on an antihypertensive drug class for the trial versus subjects who were never exposed, no significant association was seen between beta blockers and risk of CVD death (Supplementary Table 4).

Beta-blocker use versus nonuse was associated with a lower heart rate (−5.09 beats per minute, p <0.001; Supplementary Table 5). Systolic BP was not different between beta-blocker users and nonusers.

Discussion

In this secondary analysis of SPRINT of hypertensive subjects with at least 1 CVD risk factor but without HF, beta-blocker use was associated with a higher risk of incident HF including in those subjects for whom a traditional indication was identified.

The enrollment criteria ensured that most patients had a normal EF and would not receive concealed benefits from HF medications such as ACE-I/ARBs or beta blockers. The SPRINT results suggest that the major benefit of a lower BP is a reduction of HF (HR 0.62, CI 0.45 to 0.84,

Table 1
Baseline characteristics of subjects with hypertension and without heart failure in SPRINT

Variable	Overall cohort n (%)
(n = 9,012)	
Age, median [IQR]	67.0 [61.0 to 75.0]
Women	3,218 (36%)
Black	2,669 (30%)
Hispanic	965 (11%)
Other	169 (2%)
White	5,209 (58%)
Lower BP target arm	4,501 (50%)
10 y Framingham risk, median [IQR]	17.7 [12.0, 25.6]
SBP, median [IQR], mm Hg	138.0 [130.0, 149.0]
DBP, median [IQR], mm Hg	78.0 [70.0, 86.0]
Number of antihypertensive agents	
0	868 (10%)
1	2,700 (30%)
2	3,178 (35%)
3	1,795 (20%)
4	455 (5%)
5	15 (0%)
6	1 (0%)
Current smoker	1,192 (13)
Aspirin	4,530 (50)
Statin	3,850 (43)
Cholesterol, median [IQR]	187.0 [162.0 to 215.0]
BMI, median [IQR], kg/m^2	29.0 [25.8 to 32.9]
History of acute myocardial infarction	576 (6%)
History of acute coronary syndrome	397 (4%)
Coronary revascularization	790 (9%)
LVH on ECG	396 (4%)
Beta blocker	
At baseline	3,248 (36%)
Sometimes	4,626 (51%)
Never	4,386 (49%)
Entire trial duration	2,813 (31%)
ACE-I/ARB	
At baseline	5,853 (65%)
Sometimes	7,705 (85%)
Never	1,307 (15%)
Always	5,128 (57%)
CCB	
At baseline	3,612 (40%)
Sometimes	6,184 (69%)
Never	2,828 (31%)
Always	3,152 (35%)
Thiazide	
At baseline	4,516 (50%)
Sometimes	6,754 (75%)
Never	2,258 (25%)
Always	3,260 (36%)

ACE-I = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMI = body mass index; CCB = calcium channel blocker; DBP = diastolic blood pressure; ECG = electrocardiogram; IQR = interquartile range; LVH = left ventricular hypertrophy; SBP = systolic blood pressure.

p = 0.002). This result may not be surprising because hypertension and age are the most important risk factors for the development of HF,[10,11] and BP reduction has been consistently shown to have a protective effect.[10] In contrast, beta-blocker use was consistently associated with a higher risk of HF including in the cohort with recommended beta-blocker use (e.g., history of ACS, MI, and AF).

The prevalence of CAD in the SPRINT population was below 20%, and the prevalence of AF was <10%; however, more than 50% of subjects received beta blockers at some point during the study. Alternative reasons for beta-blocker use, such as renal disease limiting the use of first-line agents or resistant hypertension on >3 first-line agents, were also not common in this population (Table 2).[4] In our analyses, we attempted to correct for co-morbidities and clinical scenarios that could favor beta-blocker use. Nonetheless, beta blockers were consistently associated with an increased risk for incident HF. Adverse or neutral effects of beta blockers on HF and other cardiovascular outcomes in subjects with normal EFs have previously been documented in hypertension trials, prospective and observational CAD studies in the reperfusion era, and in HF with preserved EF.[12−15]

Randomized trials that directly compared beta blockers with other antihypertensive medications have not yielded such clear results. Subjects in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) randomized to atenolol had significantly more CVD events compared with losartan. Similarly, atenolol was less efficacious than amlodipine in preventing major cardiovascular events in Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), mostly riven by an excess in strokes. Nonetheless, incident HF was uncommon and statistically not different.[13,16] Whereas LIFE and ASCOT excluded patients older than 80 and 79 years of age, respectively, SPRINT did not have an upper age limit. The median age for HF events in SPRINT was 77 years, and 25% were older than 81 years. SPRINT was also enriched with HF emergency room visits, raising statistical power.[4,13,16] Previous analyses of patient cohorts with presumably normal EFs receiving beta blockers similarly have shown inconsistent results with respect to the effect of beta blockers on HF outcomes,[17−19] probably influenced by factors such as baseline patient CVD risk, inclusion and exclusion criteria, sample size, and study duration.

Some of the adverse outcomes associated with beta blockers may be explained by their heart rate−lowering effects. Lower heart rates are known to increase central BP because of reflected systemic arterial pressure waves that coincide with the ongoing systolic ejection. In addition, lower heart rates prolong diastolic filling that can only be accomplished at higher filling pressures as left ventricular compliance declines. These effects combine to increase ventricular wall stress, which explains why natriuretic peptide levels are higher with beta blockers in historic hypertension studies and in HF with preserved EF.[4,20,21] Subjects with higher BPs have a higher HF risk and are therefore more susceptible to the adverse effect of beta blockers as suggested in our individual analyses of the SPRINT treatment arms.[10,22,23]

Previous studies of beta blockers in populations with preserved EFs have also varied considerably in their conclusions regarding their effects on CVD mortality.[6,13,23−27] It may be possible that the anti-ischemic and antiarrhythmic effects of beta blockers convey some mortality benefits in specific subgroups of patients with normal EFs. Mechanisms by which such subgroups may derive benefit from

Table 2
Baseline characteristics and propensity score−matched cohorts of subjects on beta blocker (beta blocker) for the entire trial versus those never on a beta blocker for the duration of the trial (no beta blocker)

	Before propensity score matching			After propensity score matching		
Variable	No beta blocker	Beta blocker	p value	No beta blocker	Beta blocker	p value
Number of patients	6,199	2,813		1,642	1,642	
Age, median [IQR]	66.0 [60.0, 75.0]	68.0 [61.0, 76.0]	<0.001	67.0 [61.0, 76.0]	67.0 [61.0, 76.0]	0.822
Female	2,182 (35%)	1,036 (37%)	0.141	600 (37%)	599 (36%)	1.000
Race			<0.001			0.966
Black	1,920 (31%)	749 (27%)		453 (28%)	453 (28%)	
Hispanic	698 (11%)	267 (9%)		184 (11%)	175 (11%)	
Other	119 (2%)	50 (2%)		33 (2%)	33 (2%)	
White	3,462 (56%)	1,747 (62%)		972 (59%)	981 (60%)	
Acute myocardial infarction	205 (3%)	371 (13%)	<0.001	78 (5%)	81 (5%)	0.871
Acute coronary syndrome	159 (3%)	238 (8%)	<0.001	63 (4%)	63 (4%)	1.000
Carotid revascularization	111 (2%)	150 (5%)	<0.001	43 (3%)	43 (3%)	1.000
PAD	60 (1%)	61 (2%)	<0.001	25 (2%)	20 (1%)	0.548
Stenosis >50% of artery	108 (2%)	154 (5%)	<0.001	43 (3%)	41 (2%)	0.912
Ascending aortic aneurysm >=5 cm without repair	30 (0%)	25 (1%)	0.032	14 (1%)	9 (1%)	0.403
Calcium score>400	13 (0%)	13 (0%)	0.063	7 (0%)	7 (0%)	1.000
Low ABI ≤ 90	26 (0%)	22 (1%)	0.042	8 (0%)	7 (0%)	1.000
LVH on ECG	233 (4%)	163 (6%)	<0.001	73 (4%)	76 (5%)	0.867
Lower BP target arm control arm	2,909 (47%)	1,592 (57%)	<0.001	885 (54%)	881 (54%)	0.916
10 y Framingham Risk >15%	3,771 (61%)	1,778 (63%)	0.042	1,017 (62%)	1,032 (63%)	0.614
SBP, median [IQR]	138.0 [129.0, 148.0]	139.0 [130.0, 151.0]	0.001	139.0 [130.0, 149.0]	139.0 [130.0, 150.0]	0.688
DBP, median [IQR]	79.0 [71.0, 86.0]	77.0 [69.0, 85.0]	<0.001	78.0 [70.0, 85.0]	78.0 [70.0, 86.8]	0.849
Number of antihypertensive agents			<0.001			0.577
0	778 (13%)	90 (3%)		90 (5%)	86 (5%)	
1	2,194 (35%)	506 (18%)		431 (26%)	432 (26%)	
2	2,156 (35%)	1,022 (36%)		676 (41%)	716 (44%)	
3	886 (14%)	909 (32%)		386 (24%)	352 (21%)	
>3	185 (3%)	286 (10%)		59 (4%)	56 (3%)	
Smoking category			0.001			0.552
Never	2,818 (46%)	1,180 (42%)		723 (44%)	704 (43%)	
Former	2,545 (41%)	1,267 (45%)		715 (44%)	714 (43%)	
Current	830 (13%)	362 (13%)		204 (12%)	224 (14%)	
Aspirin	2,849 (46%)	1,681 (60%)	<0.001	889 (54%)	874 (53%)	0.624
EGFR, median [IQR]	72.6 [60.2, 85.7]	68.8 [54.9, 82.3]	<0.001	71.3 [57.8, 83.9]	71.6 [57.9, 84.4]	0.778
HDL, median [IQR]	51.0 [44.0, 62.0]	48.0 [41.0, 58.0]	<0.001	50.0 [43.0, 60.0]	49.0 [42.0, 60.0]	0.168
Cholesterol, median [IQR]	190.0 [166.0, 217.0]	181.0 [154.0, 210.0]	<0.001	187.0 [162.0, 213.0]	186.0 [159.0, 214.0]	0.738
BMI, median [IQR]	28.9 [25.8, 32.7]	29.1 [25.9, 33.1]	0.065	29.1 [26.1, 33.0]	29.1 [25.7, 33.0]	0.402
Statin	2,335 (38%)	1,515 (54%)	<0.001	732 (45%)	761 (46%)	0.326
ACE-I at baseline or initiated during the trial	5,362 (86%)	2,343 (83%)	<0.001	1,396 (85%)	1,370 (83%)	0.231
CCB at baseline or initiated during the trial	4,289 (69%)	1,895 (67%)	0.088	1,113 (68%)	1,095 (67%)	0.527
Thiazide at baseline or initiated during the trial	4,708 (76%)	2,042 (73%)	0.001	1,252 (76%)	1,241 (76%)	0.683

AAA = abdominal aortic aneurysm; ABI = ankle brachial index; ACE-I = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMI = body mass index; CCB = calcium channel blocker; DBP = diastolic blood pressure; EGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; IQR = interquartile range; LVH = left ventricular hypertrophy; PAD = peripheral artery disease; SBP = systolic blood pressure.

Table 3
Hazard ratios from the survival analysis modeling for incident heart failure decompensation accounting for the competing risk of cardiovascular death and acute MI in propensity score−matched cohorts of patients who did not change the antihypertensive class for the whole duration of the trial (always or never); matched cohorts for each antihypertensive class were generated

Antihypertensive class	HR	2.5% CI	97.5% CI	p value
Beta blocker	5.86	2.63	13.04	<0.001
ACE-I/ARB	1.71	0.86	3.38	0.12
CCB	1.68	0.87	3.24	0.12
Thiazide	0.71	0.40	1.24	0.23

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HR = hazard ratio.

beta blockade include attenuation of ischemia, modest suppression of ventricular arrhythmias, or by prevention of tachycardia-induced cardiomyopathy, though these hypotheses have not been formally evaluated.

Patients were randomized to a BP target and not a specific medication class with the SPRINT protocol, allowing for multiple antihypertensive agents to be prescribed at the discretion of the participating provider. As beta blockers vary in selectivity and pharmacokinetics, a dose-effect analysis is not possible. Although propensity score matching attempted to equalize baseline risks among subjects, it is not a substitute for prospective randomization. To mitigate the risk of including patients with reduced EFs, we excluded all patients with a remote history of HF. However, subjects with a reduced EF who may have been inadvertently enrolled or subjects who developed a reduced EF

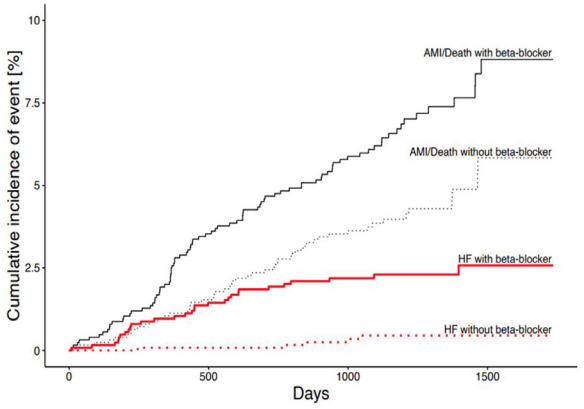

Figure 3. Events by beta-blocker use or nonuse for the entire trial in the propensity score−matched cohort. Cumulative incidence plot of acute heart failure exacerbation *(in red)* in the propensity score−matched cohort of patients who stayed on a beta blocker during the whole trial *(full line)* versus patient who were never on the drug *(dotted line)*. The competing risk of all-cause death and acute MI for both groups is represented *(in black)*. In the matched group without beta blockers, there were 6 events of incident heart failure decompensation and 72 competing events. In the matched group with beta blockers, there were 41 incident heart failure events and 133 competing events.

during the trial should have derived benefits from beta-blocker therapy.

In conclusion, our findings demonstrate a positive association between beta-blocker use and incident HF in a cohort of patients with baseline hypertension. Given the high prevalence of beta-blocker use in patients with hypertension and their association with HF, prospective clinical trials that examine both the safety and efficacy of beta blockers in populations with normal EFs are needed.

Disclosures

Dr. Meyer has licensed patents on the use of pacemakers to prevent and treat heart failure with preserved ejection fraction; the relationship is modest. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.10.049.

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