Supplementary Online Content

Silverman DN, Plante TB, Infeld M, et al. Association of β-blocker use with heart failure hospitalizations and cardiovascular disease mortality among patients with heart failure with a preserved ejection fraction: a secondary analysis of the TOPCAT trial. *JAMA Netw Open.* 2019;2(12):e1916598. doi:10.1001/jamanetworkopen.2019.16598

eTable 1. Sensitivity Analysis, Hazard Ratios for Heart Failure Hospitalizations by Ejection Fraction Among Those Not Changing Baseline Beta-Blocker Status During Follow-up
eTable 2. Sensitivity Analysis, Hazard Ratios for Heart Failure Hospitalizations by Ejection Fraction Among Those Not Changing Baseline Beta-Blocker Status During Follow-up Using the Propensity Score Matched Cohort
eTable 3. Baseline Characteristics of Propensity Score Matched Patients That Did Not Change Baseline Beta-Blocker Status During Follow-up
eTable 4. Beta-blocker Utilization in Contemporary HFpEF Cohorts
eTable 5. Median and Interquartile Ranges for BNP and NT-proBNP Levels
eTable 6. Hazard Ratios for Cardiovascular Disease Mortality by Ejection Fraction
eFigure 1. Cumulative Incidence Plot for Cardiovascular Disease Mortality by Beta-Blocker Use in Patients With an EF ≥50%
eFigure 2. Quartile Ranges of BNP and NT-proBNP Levels by Beta-Blocker Use

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Sensitivity Analysis, Hazard Ratios for Heart Failure Hospitalizations by Ejection Fraction Among Those Not Changing Baseline Beta-Blocker Status During Follow-up*

	Unadjusted	Minimally Adjusted**	Fully adjusted***
All EF	1.66 (1.20, 2.30)	1.54 (1.11, 2.15)	1.55 (1.11, 2.17)
EF <50%	0.53 (0.23, 1.21)	0.51 (0.22, 1.18)	0.49 (0.21, 1.17)
EF ≥50%	1.90 (1.33, 2.71)	1.74 (1.21, 2.49)	1.76 (1.22, 2.53)
EF ≥55%	2.24 (1.47, 3.42)	2.04 (1.32, 3.12)	2.08 (1.35, 3.21)
EF ≥60%	2.29 (1.38, 3.78)	2.07 (1.24, 3.45)	2.06 (1.23, 3.47)
EF ≥65%	3.09 (1.34, 7.11)	2.83 (1.20, 6.64)	2.68 (1.13, 6.34)

*This analysis excludes the 284 participants who did not receive beta-blockers at baseline who had documented beta-blocker use during medication reconciliation at any follow-up visit (n=103) and those who received beta-blockers at baseline who had follow-up visits at which medication reconciliation documented no beta-blocker use (n=181). We censored at the time of first heart failure hospitalization for these comparisons. The interaction between an EF threshold of 50% and beta-blocker use and incident HF hospitalizations in the fully adjusted model achieved statistical significance (p=0.007).

*Adjusted for age, sex, race/ethnicity, and treatment assignment
** Minimally adjusted model plus prior myocardial infarction, atrial fibrillation, chronic obstructive pulmonary disease, asthma, and hypertension

eTable 2. Sensitivity Analysis, Hazard Ratios for Heart Failure Hospitalizations by Ejection Fraction Among Those Not Changing Baseline Beta-Blocker Status During Follow-up Using the Propensity Score Matched Cohort

	Hazard Ratios
All EF	1.36 (0.94, 1.97)
EF ≥50%	1.51 (0.99, 2.29)
EF ≥55%	1.71 (1.03, 2.83)
EF ≥60%	2.20 (1.06, 4.57)
EF ≥65%	2.66 (0.71, 9.93)

This analysis excludes participants who did not receive beta-blockers at baseline who had documented beta-blocker use during medication reconciliation at any follow-up visit and those who received beta-blockers at baseline who had follow-up visits at which medication reconciliation documented no beta-blocker use. We censored at the time of first heart failure hospitalization for these comparisons. The interaction between EF and beta-blocker use and incident HF hospitalizations was statistically significant (p=0.046).The hazard ratios for patients with an EF 45-49 could not be estimated due to the small number of matched sets.

eTable 3. Baseline Characteristics of Propensity Score Matched Patients That Did Not Change Baseline Beta-Blocker Status During Follow-up

		Beta Blocker		
		No	Yes	P value*
N		260	640	
Treatment	N (%) spironolactone	133 (51%)	323 (50%)	0.84
Age	Mean (SD) years	73 (10)	73 (10)	0.92
Sex	N (%) female	148 (57%)	352 (55%)	0.97
Race	N (%) white non-hispanic	145 (56%)	371 (58%)	0.88
NYHA class ≥3	N (%)	90 (35%)	222 (35%)	0.73
Height	Mean (SD) cm	166 (11)	165 (11)	0.47
Weight	Mean (SD) kg	92 (26)	92 (25)	0.78
BMI	Mean (SD)	33.5 (9.2)	33.5 (8.1)	0.93
Waist	Mean (SD) cm	110 (19)	108 (17)	0.15
HR	Mean (SD) bpm	71 (12)	70 (11)	0.90
SBP	Mean (SD) mmHg	129 (16)	128 (16)	0.89
DBP	Mean (SD) mmHg	73 (13)	72 (11)	0.78
Baseline Medications/ Natriuretic Peptides				
ACE/ARB/Aliskirin	N (%)	205 (79%)	486 (76%)	0.27
Statin	N (%)	123 (47%)	347 (54%)	0.95
Other lipid medication	N (%)	18 (7%)	47 (7%)	0.72
Aspirin	N (%)	118 (45%)	316 (49%)	0.98
Other antiplatelet agent	N (%)	20 (8%)	52 (8%)	0.74
Anticoagulation	N (%)	90 (35%)	244 (38%)	0.61
Thiazide diuretic	N (%)	76 (29%)	179 (28%)	0.99
Loop diuretic	N (%)	182(70%)	487 (76%)	0.51
Other K sparing	N (%)	1 (<1%)	4 (1%)	0.44
CAI diuretic	N (%)	0 (0%)	1 (<1%)	0.48
Any diuretic	N (%)	225 (87%)	569 (89%)	0.80
Ca channel blocker	N (%)	119 (46%)	270 (42%)	0.84
Digoxin	N (%)	32 (12%)	79 (12%)	0.73
BNP	Mean (SD)	307 (226)	407 (486)	0.10
NT-proBNP	Mean (SD)	1787 (2296)	1807 (2159)	0.77
BNP quartile	N(%) 1	17 (19%)	61 (23%)	0.13
	N(%) 2	32 (36%)	62 (24%)	
	N(%) 3	23 (26%)	75 (29%)	
	N(%) 4	18 (20%)	65 (25%)	
NT-proBNP quartile	N(%) 1	10 (19%)	25 (17%)	0.31
	N(%) 2	11 (21%)	39 (27%)	
	N(%) 3	18 (34%)	27 (19%)	
	N(%) 4	14 (26%)	54 (37%)	

Past Medical History				
MI	N (%)	27 (10%)	80 (13%)	0.83
Angina	N (%)	44 (17%)	124 (19%)	0.99
Stroke	N (%)	26 (10%)	48 (8%)	0.19
COPD	N (%)	53 (20%)	120 (19%)	0.94
Asthma	N (%)	37 (14%)	85 (13%)	0.90
HTN	N (%)	220 (85%)	560 (88%)	0.87
PAD	N (%)	23 (9%)	52 (8%)	0.58
Dyslipidemia	N (%)	152 (58%)	405 (63%)	0.96
Atrial fibrillation	N (%)	100 (38%)	278 (43%)	0.56
Thyroid	N (%)	50 (19%)	124 (19%)	0.86
Diabetes mellitus	N (%)	96 (37%)	250 (39%)	0.92
Smoking	N (%)	20 (8%)	37 (6%)	0.33
CABG	N (%)	24 (9%)	71 (11%)	0.93
PCI	N (%)	31 (12%)	84 (13%)	0.84
ICD	N (%)	3 (1%)	19 (3%)	0.17
Pacemaker	N (%)	43 (17%)	97 (15%)	0.81
EF	Mean (SD)	59.2 (7.7)	58.7 (7.9)	0.73
EF >50%	N (%)	236 (91%)	571 (89%)	0.71
EF >55%	N (%)	201 (77%)	479 (75%)	0.60
EF >60%	N (%)	143 (55%)	317 (50%)	0.21
EF >65%	N (%)	69 (27%)	177 (28%)	0.53
Outcomes				
HF hospitalization	N (%)	41 (16%)	147 (23%)	0.04
CVD death	N (%)	33 (13%)	87 (14%)	0.71
MI	N (%)	10 (4%)	31 (5%)	0.67
Stroke	N (%)	6 (2%)	25 (4%)	0.26
*** Cochran-Mantel-Haenszel chi square test for categorical variables;**				
conditional logistic regression for continuous variables				

Baseline characteristics of the propensity score matched cohort of patients that did not change their beta-blocker status during follow-up. ACE-I, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; BMI, body mass index; CABG, Coronary Artery Bypass Grafting; CAI, Carbonic anhydrase Inhibitor; COPD, Chronic Obstructive Pulmonary Disease; DBP; diastolic blood pressure; EF, Ejection Fraction; HR, Heart Rate, HTN, Hypertension; ICD, Implantable Cardioverter Defibrillator; K, Potassium; MI, Myocardial Infarction; NYHA, New York Heart Association; PAD, Peripheral Artery Disease; PCI, Percutaneous Coronary Intervention.

eTable 4. Beta-blocker Utilization in Contemporary HFpEF Cohorts

Study	Treatment Arms	Major Endpoints	Inclusion Criteria	Mean EF	Baseline beta-blocker use
CHARM-P 2003 (n=3,023)	Candesartan Placebo	CV Mortality HF Hospitalization	LVEF >40% NYHA II-IV	54%	**56%**
PEP-CHF 2006 (n=850)	Perindopril Placebo	All-cause Mortality HF Hospitalization	Clinical DHF	65%	**54%**
I-PRESERVE 2008 (n=4,128)	Irbesartan Placebo	All-cause Mortality CV Hospitalization	LVEF ≥45% NYHA II-IV	60%	**59%**
RELAX 2013 (n= 216)	Sildenafil Placebo	Change in Peak VO_2 on CPET	LVEF ≥50% NYHA II-IV	60%	**76%**
TOPCAT 2014 (n=3,445)	Spironolactone Placebo	CV Mortality, RSD HF Hospitalization	LVEF ≥45%, clinical DHF	56%	**79%**
NEAT-HFpEF 2015 (n=110)	Isosorbide mononitrate Placebo	Exercise Capacity QOL measure	LVEF ≥50% NYHA II-III	63%	**70%**
INDIE-HFpEF 2018 (n=105)	Inorganic nitrate Placebo	Peak Oxygen consumption	LVEF ≥50%, clinical DHF	61%	**63%**
PARAGON-HF 2018 (n=4,822)	Sacubitril/Valsartan Valsartan	CV Mortality HF Hospitalization	LVEF ≥45% NYHA II-IV	58%	**80%**

CHARM-P, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity-Preserved; CPET, cardiopulmonary exercise test; CV, cardiovascular; DHF, diastolic heart failure; HF, heart failure; INDIE-HFpEF, Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure With Preserved Ejection Fraction; I-PRESERVE, Irbesartan in Heart Failure With Preserved Ejection Fraction; EF, left ventricular ejection fraction; NEAT-HFpEF, Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction; PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction; PEP-CHF, Perindopril in Elderly People With Chronic Heart Failure; RSD, resuscitated sudden death; QOL, quality of life

eTable 5. Median and Interquartile Ranges for BNP and NT-proBNP Levels

	All EFs			EF <50%			EF ≥50%		
	No Beta-blocker	Beta-Blocker	p-value	No Beta-blocker	Beta-Blocker	p-value	No Beta-blocker	Beta-Blocker	p-value
BNP	205 (139-326)	273 (153-475)	0.001	240 (234-298)	364 (249-516)	0.14	198 (138-331)	261 (150-465)	0.002
NT-proBNP	889 (621-1694)	972 (554-2148)	0.20	1839 (1380-7333)	967 (526-1630)	0.01	847 (551-1520)	989 (554-2213)	0.03

Median (IQR) of BNP and NT-proBNP by beta-blocker use at baseline in the entire population and stratified by an EF threshold of 50%. P-values compare log-transformed BNP or NT-proBNP values at baseline by beta-blocker use.

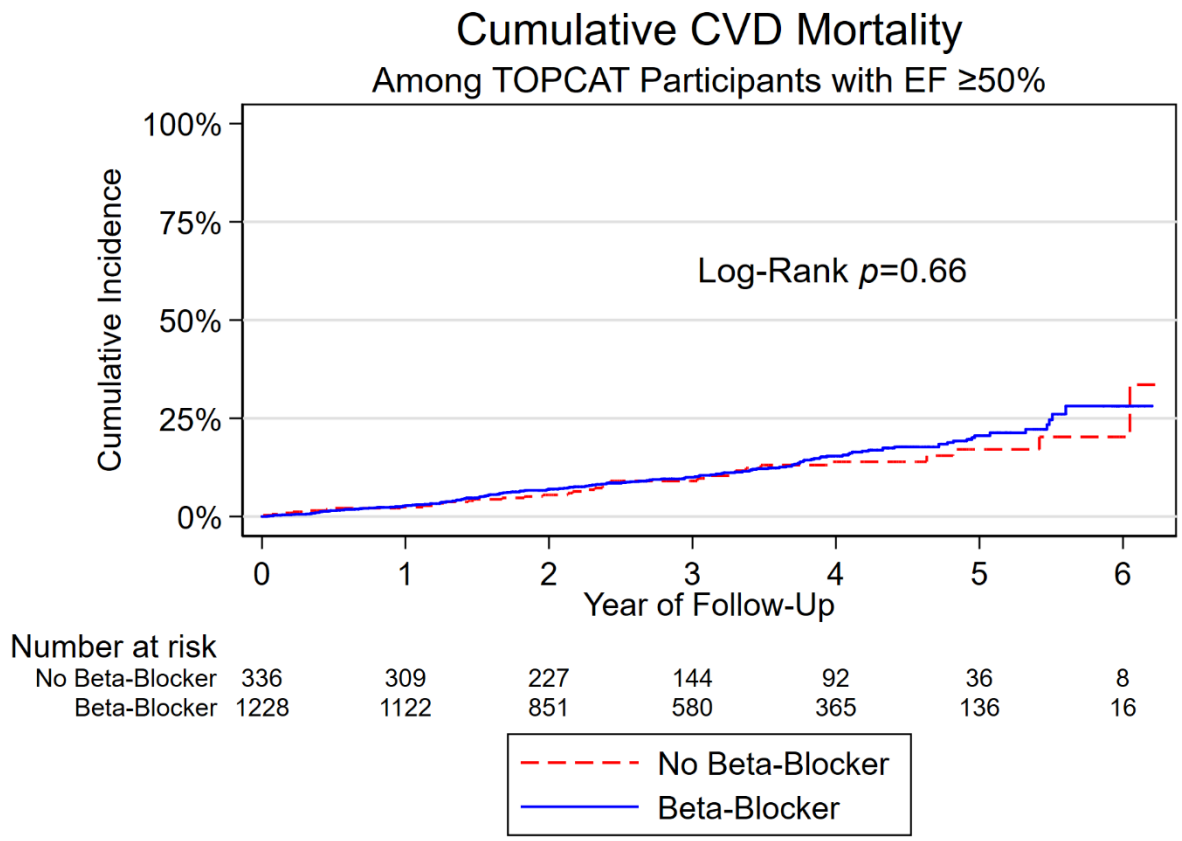
eTable 6. Hazard Ratios for Cardiovascular Disease Mortality by Ejection Fraction

	Unadjusted	Minimally Adjusted*	Fully adjusted**
All EF	1.08 (0.77, 1.50)	1.11 (0.80, 1.56)	1.16 (0.82, 1.62)
EF <50%	0.69 (0.30, 1.58)	0.67 (0.28, 1.62)	0.62 (0.25, 1.58)
EF ≥50%	1.14 (0.79, 1.64)	1.21 (0.84, 1.76)	1.24 (0.85, 1.79)

*Adjusted for age, sex, race/ethnicity, and treatment assignment
**Minimally adjusted model plus prior myocardial infarction, atrial fibrillation, chronic obstructive pulmonary disease, asthma, and hypertension

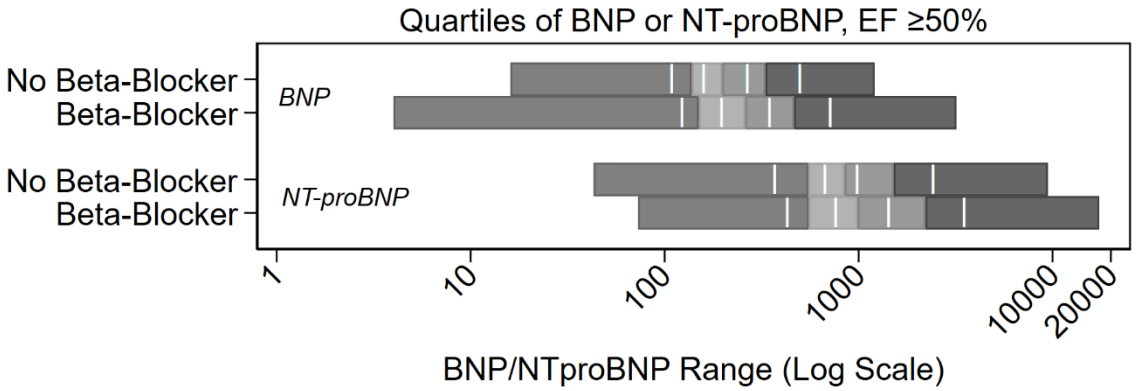
Hazard ratios for cardiovascular disease mortality for beta-blocker use at baseline versus no beta-blocker use at baseline.
.

eFigure 1. Cumulative Incidence Plot for Cardiovascular Disease Mortality by Beta-Blocker Use in Patients With an EF ≥50%



Kaplan Meier plots for CVD mortality by beta-blocker use at baseline stratified by an ejection fraction ≥50%.

eFigure 2. Quartile Ranges of BNP and NT-proBNP Levels by Beta-Blocker Use



Baseline brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) levels by beta-blocker at baseline use in patients with an EF ≥50%. Midpoints of the quartiles are indicated by vertical lines.