Supplementary Appendix

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

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Supplementary Appendix

Trial of Beta-Blockers for the Prevention of Acute Exacerbations of COPD

Mark T. Dransfield MD, Helen Voelker BA, Surya P. Bhatt MD, Keith Brenner MD, Richard Casaburi MD, Carolyn E. Come MD, J. Allen D. Cooper MD, Gerard J. Criner MD, Jeffrey L. Curtis MD, MeiLan K. Han MD, Umur Hatipoğlu MD, Erika S. Helgeson PhD, Vipul V. Jain MD, Ravi Kalhan MD, David Kaminsky MD, Robert Kaner MD, Ken M. Kunisaki MD, Allison A. Lambert MD, Matthew R. Lammi MD, Sarah Lindberg MPH, Barry J. Make MD, Fernando J. Martinez MD, Charlene McEvoy MD, Ralph J. Panos MD, Robert M. Reed MD, Paul D. Scanlon MD, Frank C. Sciurba MD, Anthony Smith MD, P.S. Sriram MD, William W. Stringer MD, Jeremy A. Weingarten MD, J. Michael Wells MD, Elizabeth Westfall MPH, Stephen C. Lazarus MD, and John E. Connett PhD for the BLOCK COPD Study Group

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List of Investigators and Study Acknowledgements

Birmingham VA
Allen Cooper (PI), Patti Smith (Coordinator).

Boston-Brigham and Women's Hospital and West Roxbury VA
Carolyn E. Come (PI), Christina M. Mercugliano, Erick S. MacLean, Emily A. Holmes (Research Coordinators), Kevin M. Zinchuk (Research Pharmacist)

Cincinnati VA Medical Center
Ralph Panos (PI), Kimberly Kersey, Laura Lach (Coordinators).

Cleveland Clinic
Umur Hatipoglu (PI), Amy Attaway, Anu Suri, Mohammed Al-Jaghbeer, Sudhir Dudekonda, Muhammad Raza (Co-Investigators), Richard Rice, Jenna Brinker (Coordinators).

Columbia University
Keith Brenner (PI), Immani Easthausen, M. Atif Choudhury, Maahika Srinivasan, Sana Sajjad, Onumara Opara (Coordinators).

Health Partners
Charlene E McEvoy (PI), Pamela J Neuenfeldt, Cheryl Sasse (Coordinators).

LABIOMED-Harbor-UCLA Medical Center
W. Stringer (PI), R. Casaburi, H. Rossiter, J. Porszasz (Co-investigators), L. Diaz, R. Indelicato, C. Lopez-Garcia, R. Calmelat, D. Cavanaugh - (Coordinators).

Louisiana State University
Matthew R. Lammi (PI), Connie Romaine, Marie Sandi, Paula Lauto (Coordinators).

Mayo Clinic
Paul D. Scanlon (PI), Jeremy Clain, Alexander Niven, Megan Dulohery Scrodin (Co-Investigators), Boleyn Andrist, Alana English, Tami S. Krpata (Coordinators).

Minneapolis VA Health Care System
Ken Kunisaki (PI) Megan Campbell, Miranda DeConcini (Coordinators) Anne Melzer, Chris Wendt, Erin Wetherbee (Co-Investigator), Doug DeCarolis (Research Pharmacist).

National Jewish
Barry Make (PI), Steven Lommatzsch, Amen Sergew (Co-Investigators), Jennifer Underwood (Coordinator).

New York-Presbyterian Weill Cornell Medical College
Robert J. Kaner (PI), Fernando J. Martinez, Ben-Gary Harvey, Daniel Libby, Laura Libby, Brian Gelbman, David Chappell Weir, Andrea Shioleno, Jamuna Krishnan, William Zhengyang Zhang (Co-Investigators), Elizabeth Peters, Alicia J. Morris, Matthew Marcelino (Coordinators).

New York-Presbyterian Brooklyn Methodist Hospital
Jeremy Weingarten (PI), Anthony Saleh, Saleem Shahzad, Liziamma George, Liam Gross (Co-PIs), Puja Chadha, Christina Edwards (Coordinators).

New York-Presbyterian Queens
Anthony Smith (PI), Susan Ingenito (Coordinator)

Northwestern University
Ravi Kalhan (PI). Sharon Rosenberg, Lewis Smith, Jenny Hixon, Allison Rogowski, Alyssa Frederick (Coordinators).

Providence Medical Group, Spokane
Allison A. Lambert (PI), Radica Alicic, Thomas DeCato (Co-investigators), Lisa Davis (Coordinator).

Temple School of Pharmacy
David Lebo, Michael Jacobs.

Temple University
Gerard Criner (PI), Nathaniel Marchetti (co-investigator), Helga Criner, Dee Fehrle, Joseph Lambert (Coordinators).

University of Alabama at Birmingham
Mark Dransfield (PI), Surya Bhatt, J. Michael Wells, Anand Iyer, Trisha Parekh, Steven Lloyd, Gregory Payne, Samuel McElwee (Co-Investigators), Elizabeth Westfall (Project Manager), Keenya Mathews, Renita Holmes (Coordinators).

University of California, Fresno
Vipul Jain (PI), Dennis Richard Allison, John McClain (Co-investigators), Janna Blaauw, Griselda Aguilar, Alexa Lopez (Coordinators).

University of California San Francisco (UCSF)
Stephen C. Lazarus, (PI), Prescott G. Woodruff, (Co-Investigator), Julian Silva (Coordinators).

University of Maryland
Robert Reed (PI), Giora Netzer (Co-investigator), Archana Patel, Maura Deeley, (Coordiantors), Saif M Borgan, Sadam Haddadin, Hasan Radhi, Hassan A Haji, Nirali Marvania (Research assistants).

University of Michigan
MeiLan K. Han (PI), Wassim Labaki (co-investigator), Mary Kay Hamby (Coordinator).

University of Minnesota (Data Coordinating Center)
John E. Connett (PI), Chris Wendt (Co-PI), Sarah Lindberg, Helen Voelker (Study Coordinators), Irene Olson (Quality Control).

University of Pittsburgh
Frank Sciurba (PI), Divay Chandra, Jessica Bon Field, Michael Emmet O'Brien, Craig Riley, (Co-Investigators), Paula Consolaro, Megan D'Innocenzo, Kelsey Elliott, Christina Ledezma, Jenna Smith , Elizabeth Stempkowski (Coordinators), Daniel Arminavage, Robert Wilson (PFT Technicians), Rhonda Lincoln (Project Administrator).

University of Vermont
David A. Kaminsky (PI), Erika Gonyaw, Chloe Housenger, Kevin Hodgdon, Heidi Pecott-Grimm (Coordinators)

VA Ann Arbor Healthcare System, Ann Arbor, MI
Jeffrey L. Curtis (PI), Lisa McCloskey (Coordinator).

Data and Safety Monitoring Committee
Nadia Hansel (Research Monitor), Vera Bittner, James Tonascia.

Congressionally Directed Medical Research Programs (CDMRP)
Sandy Snyder (Science Officer) and Usamah Kayyali (Science Officer)

Supplementary Methods

Conditional Power Analyses

The original alternative hypothesis for the trial was that 65% of participants in the placebo group would have at least 1 exacerbation in 1 year, whereas 55% of those in the metoprolol group would have at least 1 exacerbation in 1 year. The primary outcome was time to occurrence of a first exacerbation (mild, moderate, severe, or very severe).

The original projected sample size, allowing for 12% dropout, was N = 1028. This assumes a treatment effect for the primary outcome as noted above (65% vs. 55%), and a power of 90%.

With 520 participants contributing data, there was no evidence of a treatment effect favoring the beta-blocker.

As was done at the previous DSMB meeting, we carried out simulation studies to investigate conditional probabilities of seeing a significant difference between the groups if the trial continued with evaluation of N = 1028 participants. Conditional here means that we accept all of the outcome data that we have observed up to the present time for 520 participants. The simulation studies made assumptions regarding the probabilities of future primary outcome events, as follows:

Simulation study #1: Conditional on the current observed data, and assume the future probabilities of events agree with the original alternative hypothesis (65% vs. 55%).

Simulation study #2: Conditional on the current observed data, and assume the future probabilities of having an exacerbation are the same as what we have observed so far.

Simulation study #3: Conditional on the current observed data, and assume the future probabilities of having an exacerbation are the same for both groups (65%).

All three studies involved 10,000 simulated trials. The simulations also required simulations of deaths and withdrawals (based on observed rates).

Conditional Power for the three scenarios:

Simulation study #1: The estimated probability of seeing a significant difference between the two groups is 6.1%.

Simulation study #2: The estimated probability of seeing a significant difference between the two groups is 30.0% but in favor of placebo.

Simulation study #3: The estimated probability of seeing a significant difference between the two groups is 7.2%.

Analysis of Secondary Endpoints

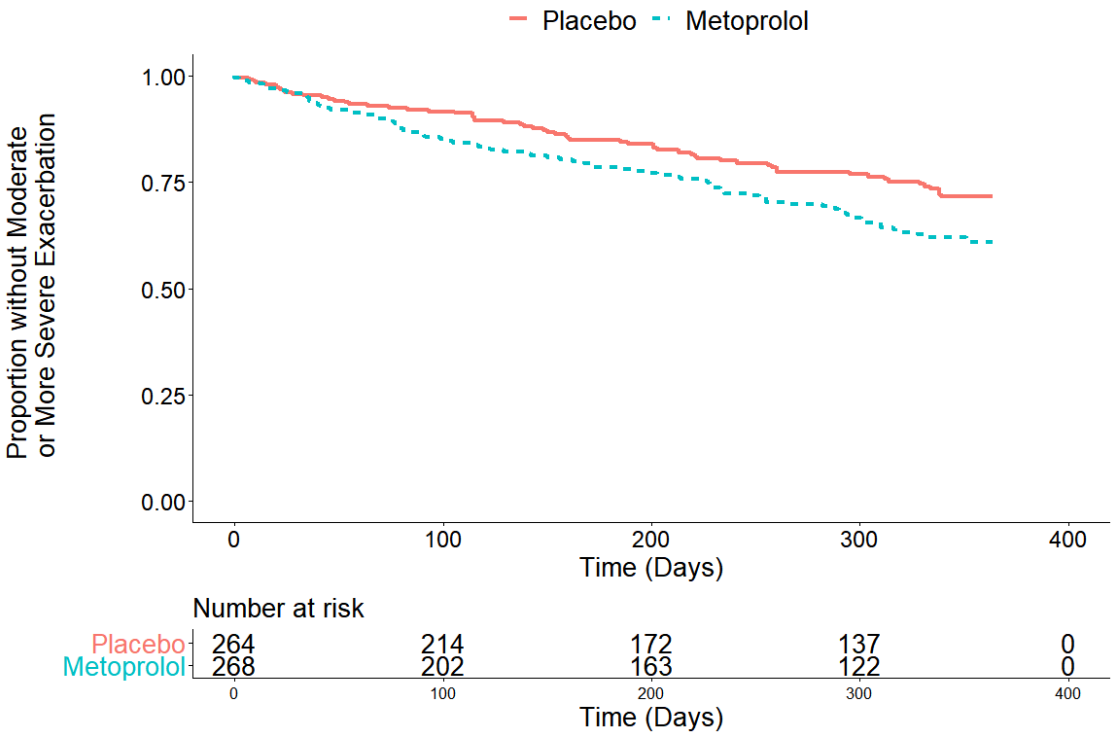
For evaluation of secondary study endpoints (FEV_1, six-minute walk distance, SGRQ, CAT, SOBQ) and cardiac measures (heart rate, systolic and diastolic blood pressure), close-out visit measurements from participants who ended the study early were analyzed as if they were measured at the next scheduled study visit. Due to differences in time on metoprolol or placebo, cardiac measurements taken during the weaning period from individuals who ended the study early were not included in the analysis of secondary endpoints.

Study Design, Data Collection, Analysis, and Manuscript Preparation.

The study was designed by MTD and SPB in conjunction with the Steering Committee members who are listed as authors. The data were gathered by all participating centers as listed in the acknowledgements. The data were analyzed by the Data Coordinating Center (JEC, ESH, HV, SL) and vouched for by both the DCC and MTD. MTD wrote the first draft of the manuscript. The DCC, MTD and the Steering Committee approved the decision to publish the paper and

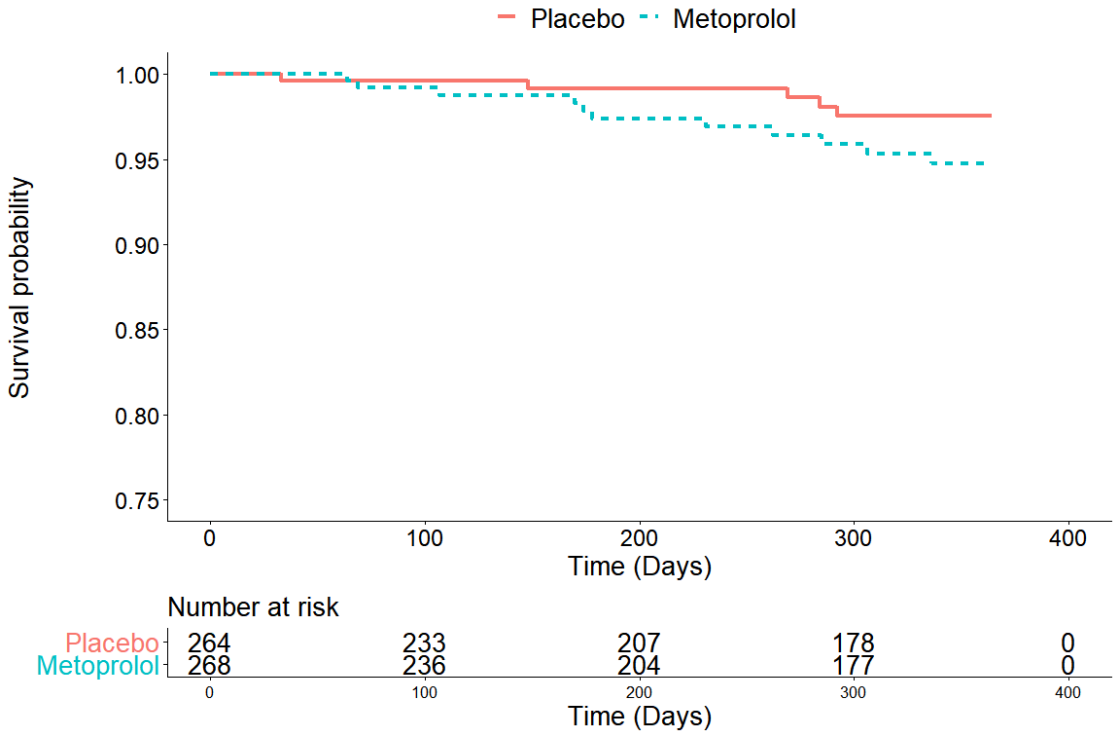
approved the final submitted version. There were no agreements concerning confidentiality of the data between the sponsor and the authors or the participating institutions.

Supplemental Figure S1a. Effect of Metoprolol on the Time to the First Chronic Obstructive Pulmonary Disease Exacerbation of Moderate Severity or Greater (Exacerbation Leading to a Visit to an Emergency Department, Hospitalization, or Hospitalization with Intubation and Mechanical Ventilation.



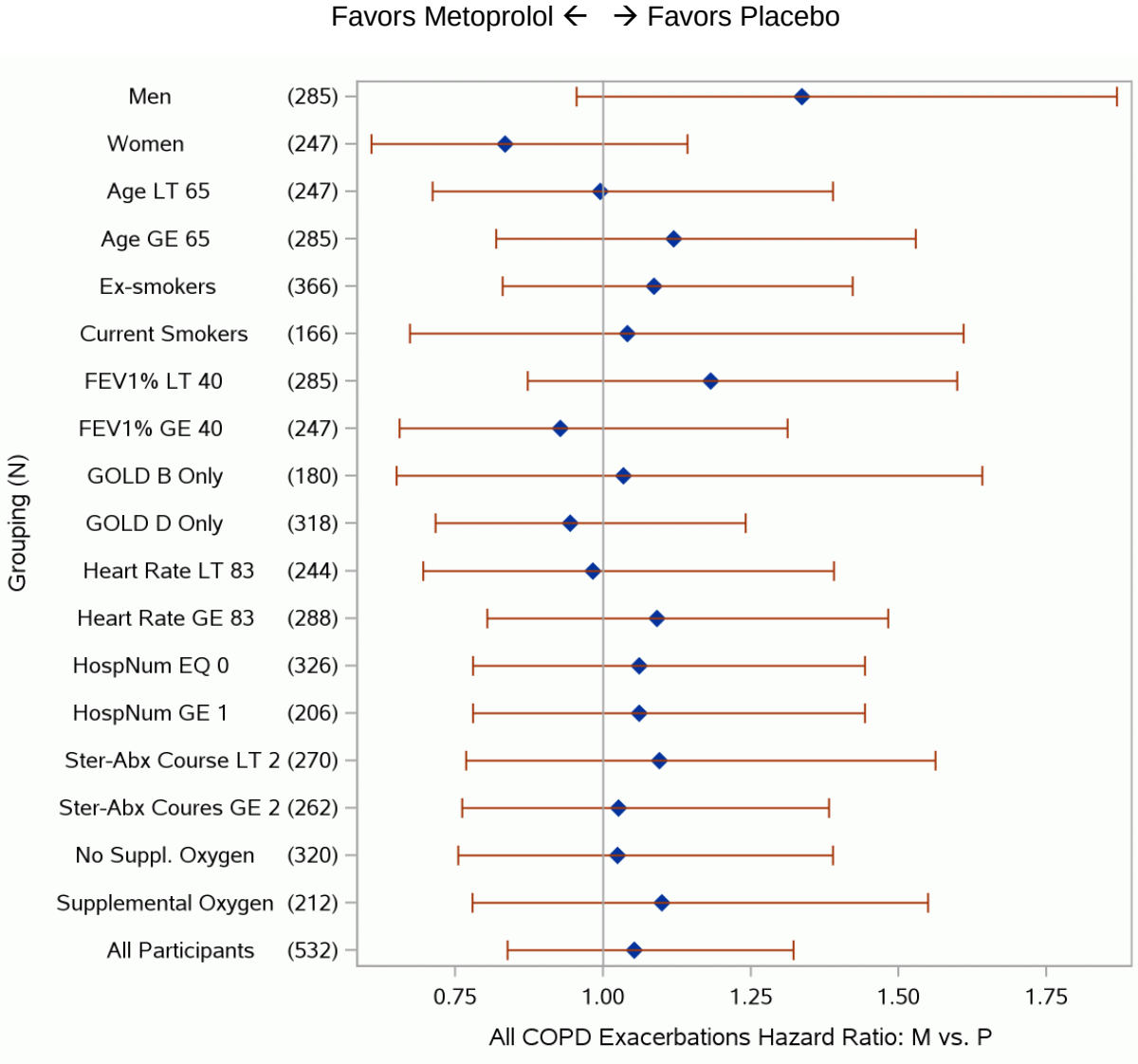
Exacerbations of moderate severity or greater occurred in 86/268 (32.1%) of participants assigned to metoprolol and 61/264 (23.1%) of participants assigned to placebo.

Supplemental Figure S1b. Effect of Metoprolol on Survival.



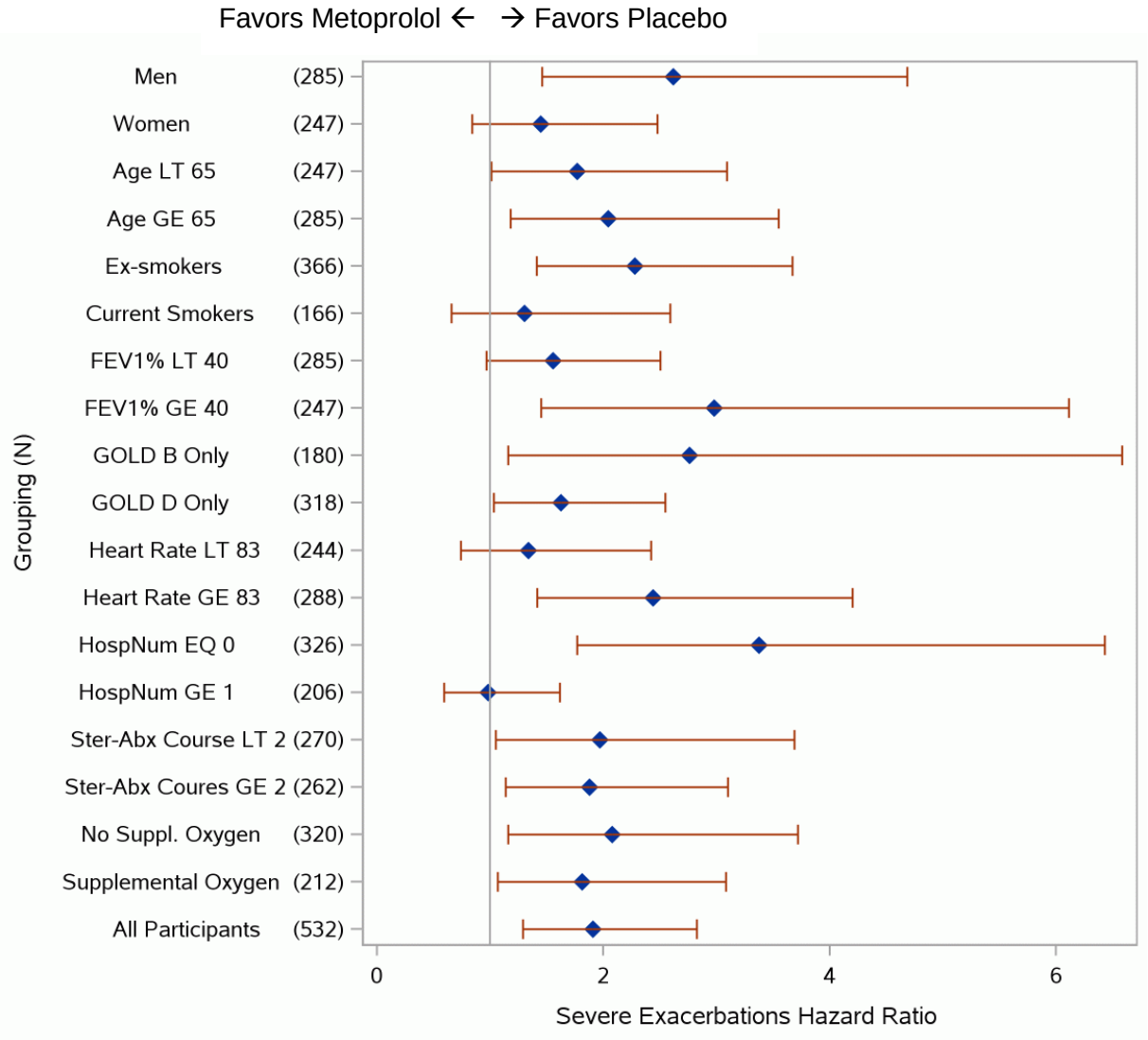
Deaths during the treatment period occurred in 11/268 (4.1%) of participants assigned to metoprolol and 5/264 (1.9%) of participants assigned to placebo.

Supplemental Figure S2a. Hazard Ratios with 95% Confidence Intervals for the Risk of Any Exacerbation in Those Assigned to Metoprolol Compared with Placebo By Subgroup.



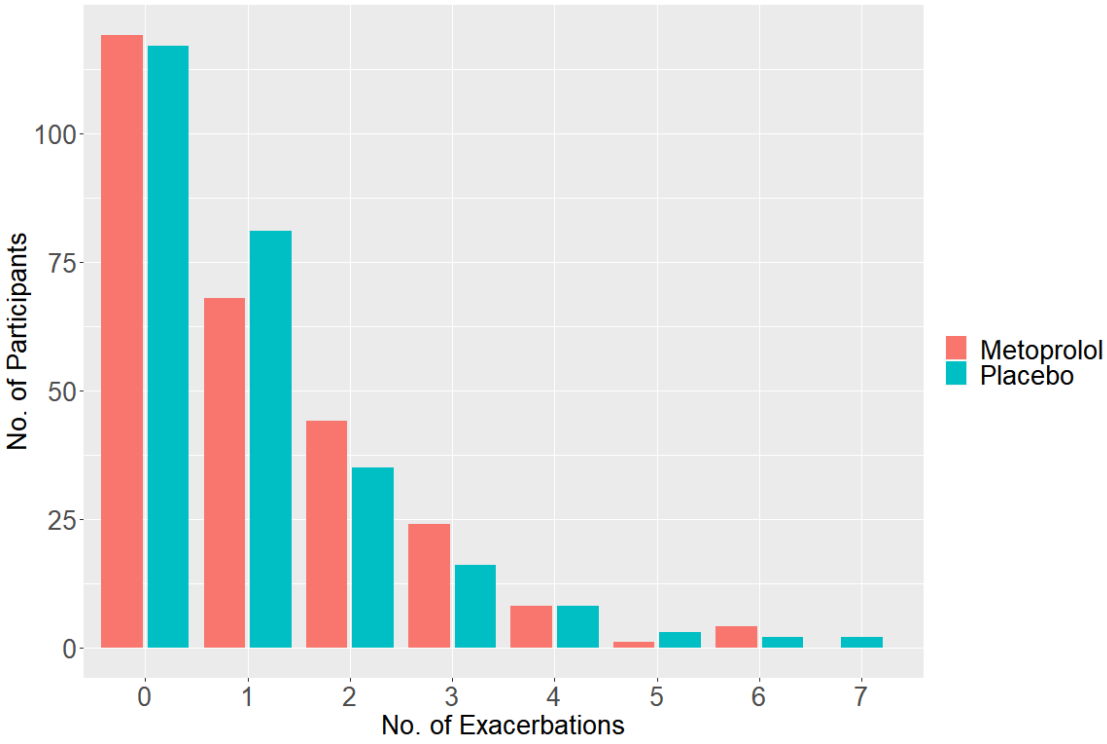
Abbreviations: GOLD (Global Initiative for Chronic Obstructive Lung Disease), LT (less than), GE (greater than or equal to), EQ (equal to), Ster-Abx (receipt of steroids and/or antibiotics for respiratory problems in the year prior), FEV_1% (forced expiratory volume %predicted).

Supplemental Figure S2b. Hazard Ratios with 95% Confidence Intervals for the Risk of Severe or Very Severe Exacerbation in Those Assigned to Metoprolol Compared with Placebo By Subgroup.

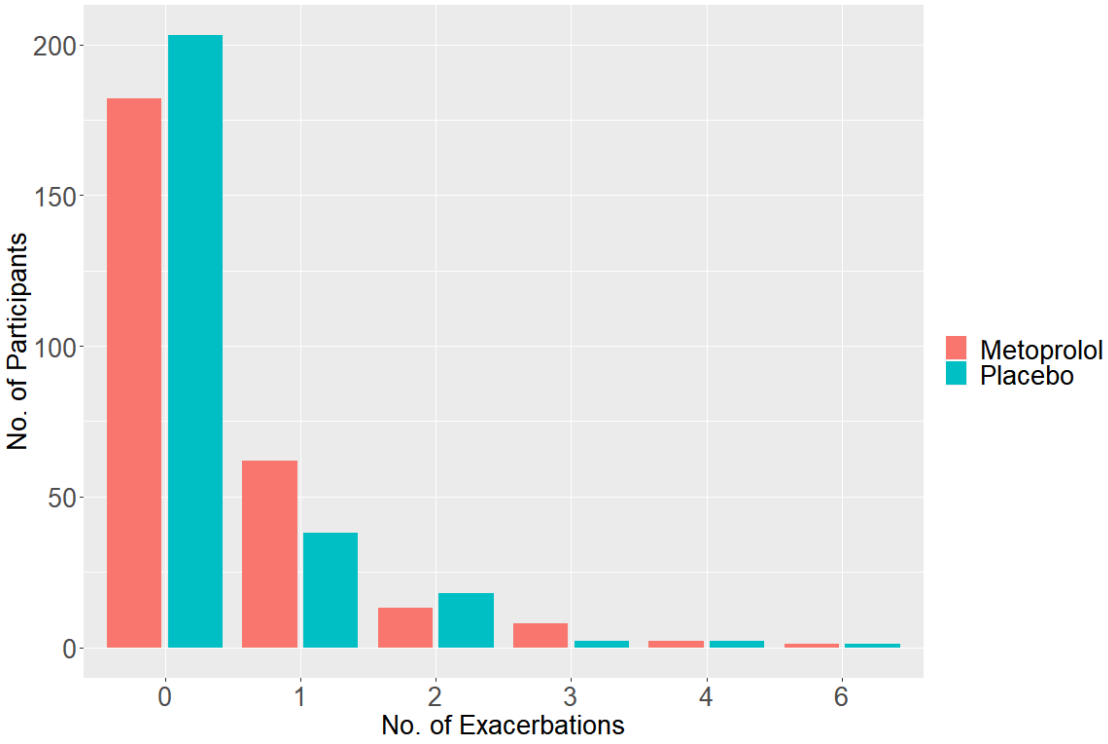


Abbreviations: GOLD (Global Initiative for Chronic Obstructive Lung Disease), LT (less than), GE (greater than or equal to), EQ (equal to), Ster-Abx (receipt of steroids and/or antibiotics for respiratory problems in the year prior), FEV_1% (forced expiratory volume %predicted).

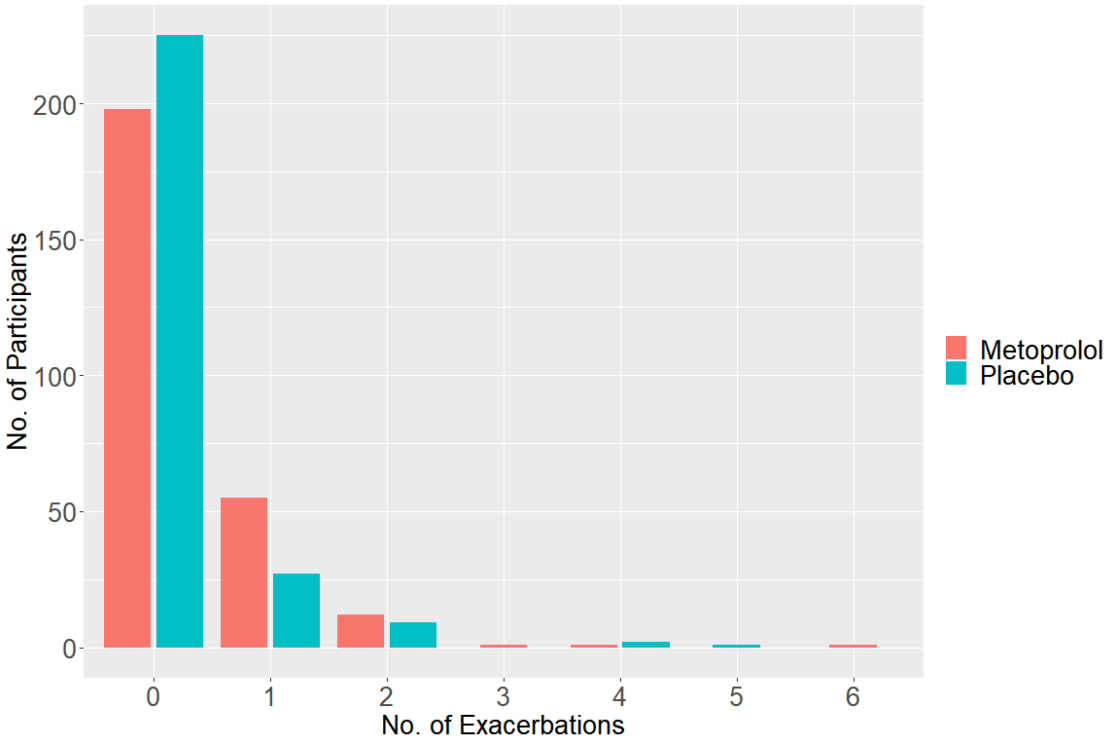
Supplemental Figure S3a. Histogram of all Exacerbations by Study Group.



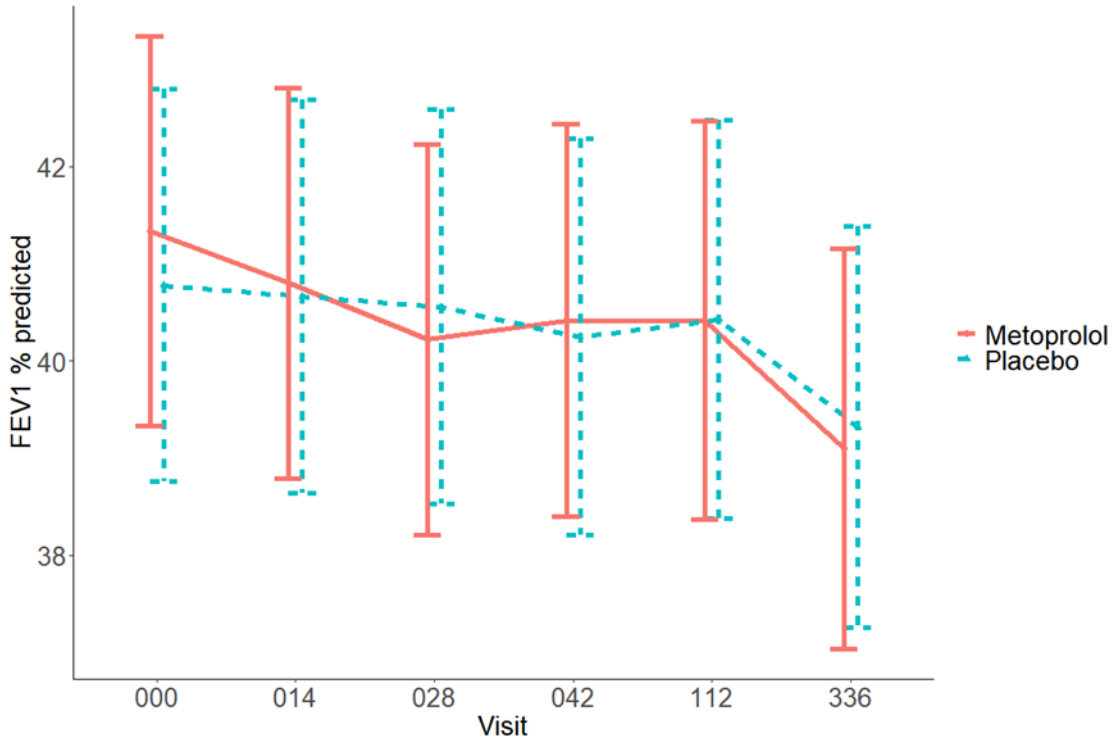
Supplemental Figure S3b. Histogram of Exacerbations of Moderate Severity or Greater by Study Group.



Supplemental Figure S3c. Histogram of Severe or Very Severe Exacerbations by Study Group.



Supplemental Figure S4. Forced expiratory volume in 1 second (FEV1) %predicted with 95% confidence intervals.



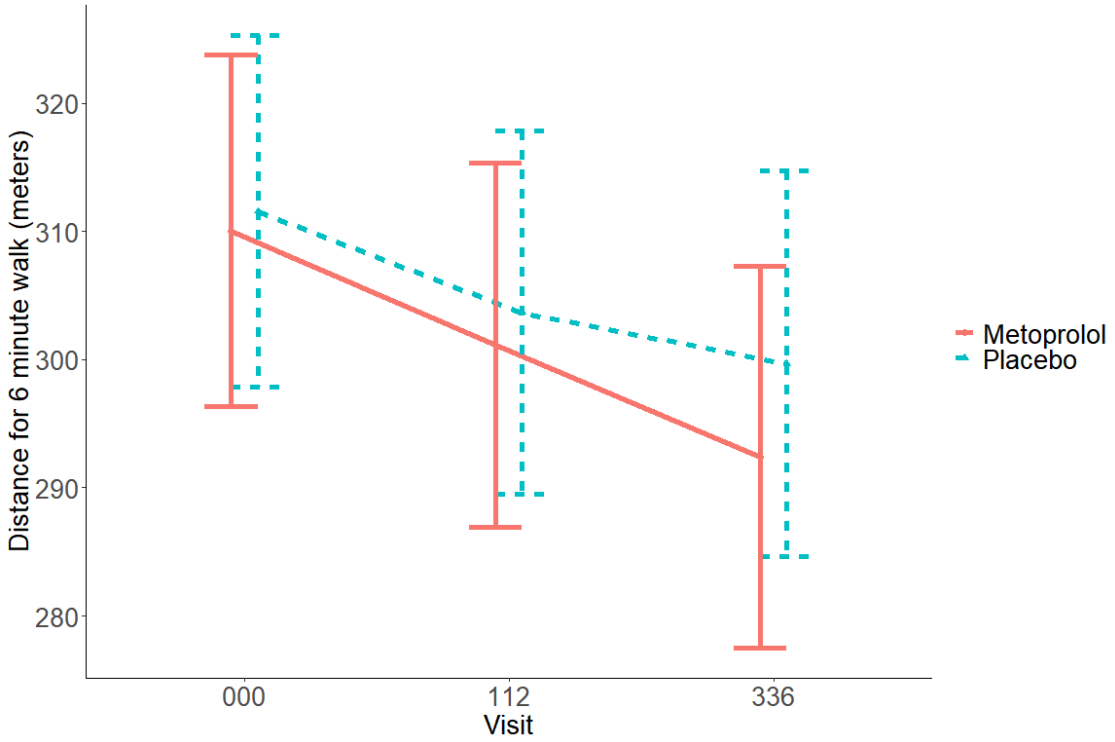
Count of participants by assignment and visit day

	000	014	028	042	112	336
Placebo	264	254	247	238	216	197
Metoprolol	268	258	255	243	203	193

Estimated difference in change from baseline FEV_1 %predicted between groups

Difference in change: metoprolol minus placebo	Estimate (95% CI)
Baseline to day 014 visit	-0.42 (-1.76, 0.92)
Baseline to day 028 visit	-0.89 (-2.25, 0.46)
Baseline to day 042 visit	-0.39 (-1.76, 0.98)
Baseline to day 112 visit	-0.57 (-2.00, 0.87)
Baseline to day 336 visit	-0.78 (-2.25, 0.69)

Supplemental Figure S5. Six-minute walk distance with 95% confidence intervals.



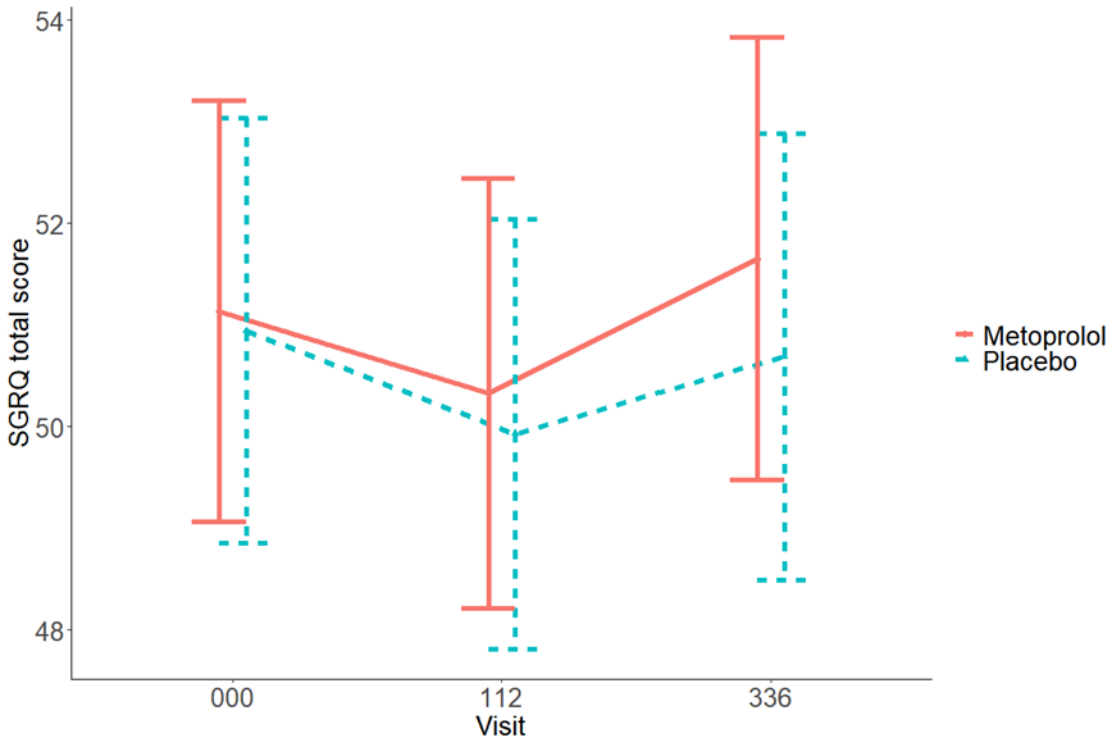
Count of participants by assignment and visit day

	000	112	336
Placebo	259	220	166
Metoprolol	259	216	174

Estimated difference in change from baseline in six-minute walk distance (meters) between groups

Difference in change: metoprolol minus placebo	Estimate (95% CI)
Baseline to day 112 visit	-1.03 (-15.39, 13.33)
Baseline to day 336 visit	-5.77 (-21.59, 10.06)

Supplemental Figure S6. St. George's Respiratory Questionnaire (SGRQ) score with 95% confidence intervals.



Count of participants by assignment and visit day

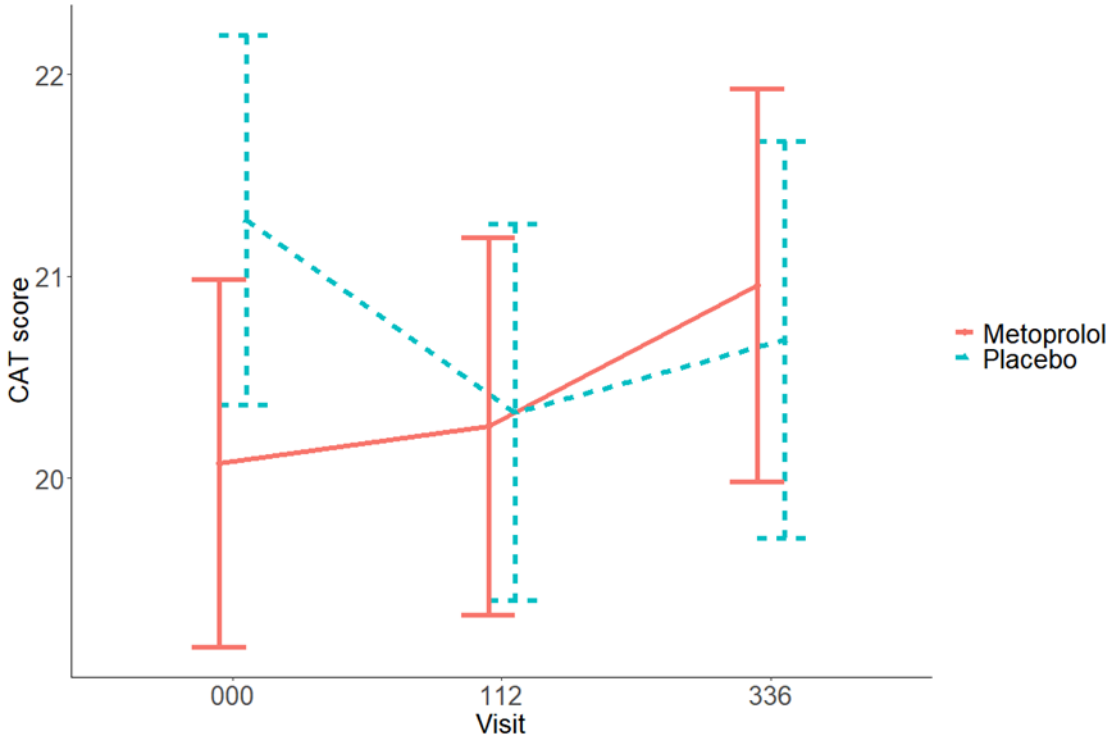
	000	112	336
Placebo	263	248	200
Metoprolol	268	241	203

Estimated difference in change from baseline SGRQ between groups

Difference in change: metoprolol minus placebo	Estimate (95% CI)
Baseline to day 112 visit	0.21 (-1.80, 2.21)
Baseline to day 336 visit	0.77 (-1.38, 2.92)

Scores on the SGRQ range from 0 to 100, with lower scores indicating better functioning and with a minimal clinically important difference (MCID) of 4 points[1].

Supplemental Figure S7. COPD Assessment Test (CAT) score with 95% confidence intervals.



Count of participants by assignment and visit day

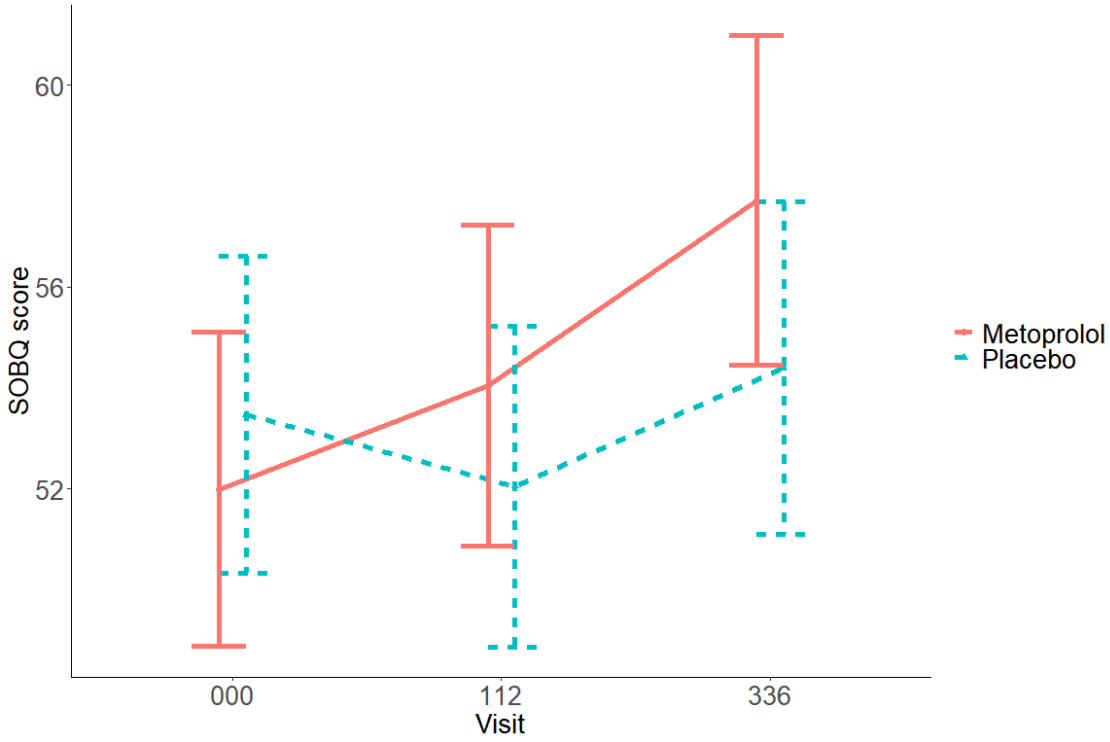
	000	112	336
Placebo	264	248	200
Metoprolol	268	241	206

Estimated difference in change from baseline in CAT between groups

Difference in change: metoprolol minus placebo	Estimate (95% CI)
Baseline to day 112 visit	1.13 (0.06, 2.20)
Baseline to day 336 visit	1.47 (0.32, 2.62)

Scores on the CAT range from 0 to 40, with lower scores indicating better functioning and with a MCID of 2 points[2].

Supplemental Figure S8. San Diego Shortness of Breath Questionnaire (SOBQ) score with 95% confidence intervals.



Count of participants by assignment and visit day

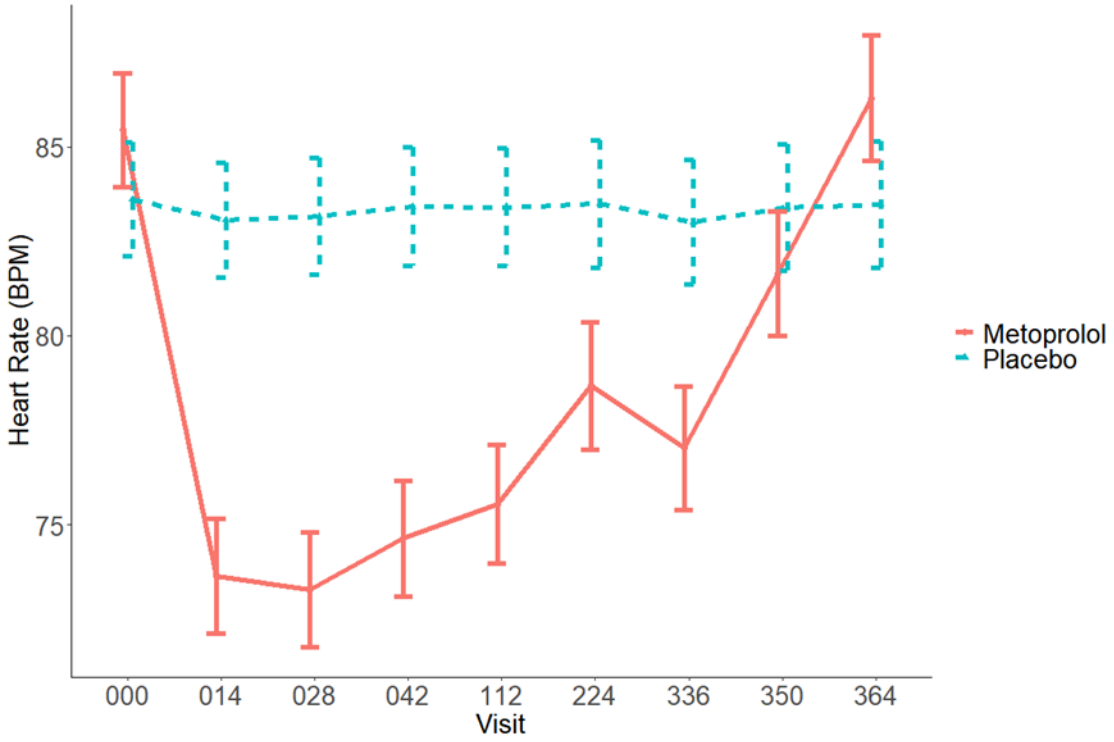
	000	112	336
Placebo	262	247	199
Metoprolol	265	240	204

Estimated difference in change from baseline in SOBQ between groups

Difference in change: metoprolol minus placebo	Estimate (95% CI)
Baseline to day 112 visit	3.47 (0.42, 6.52)
Baseline to day 336 visit	4.80 (1.52, 8.07)

Scores on the SOBQ range from 0 to 120, with lower scores indicating less dyspnea and with an MCID of 5 points[3].

Supplemental Figure S9a. Heart rate with 95% confidence interval.



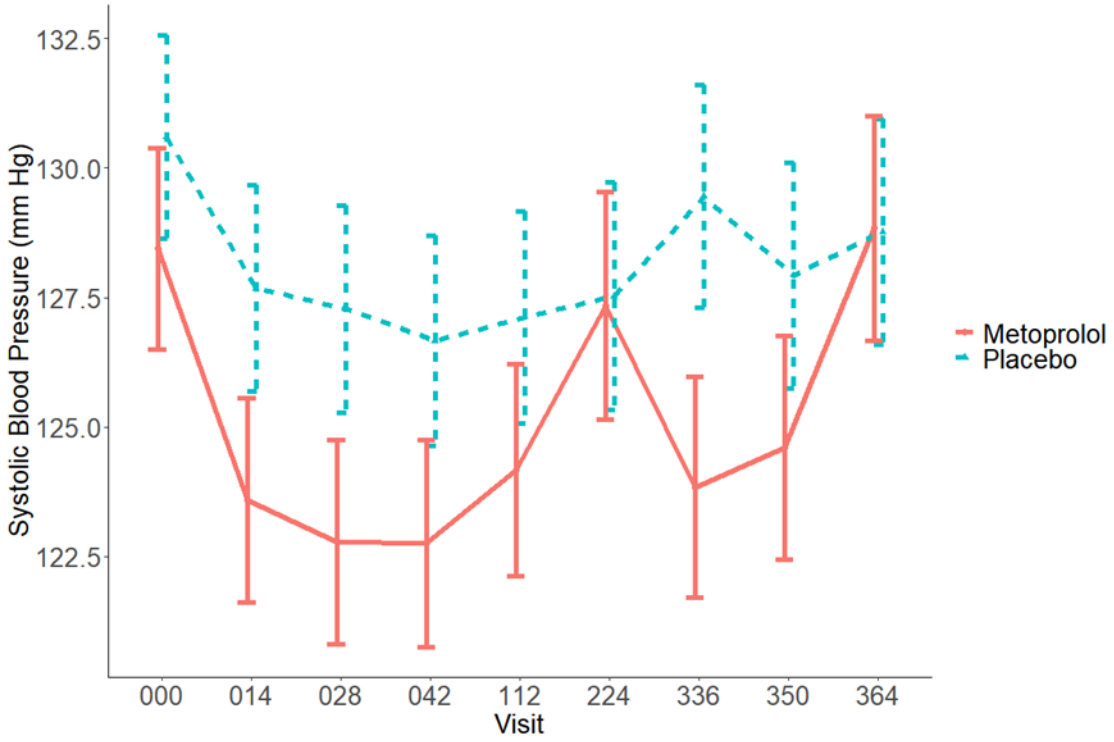
Count of participants by assignment and visit day

	000	014	028	042	112	224	336	350	364
Placebo	264	255	250	238	234	183	197	189	187
Metoprolol	268	260	259	248	227	180	200	193	189

Estimated difference in change from baseline in heart rate between groups

Difference in change: metoprolol minus placebo	Estimate (95% CI)
Baseline to day 14 visit	-11.26 (-13.34, -9.19)
Baseline to day 28 visit	-11.73 (-13.81, -9.64)
Baseline to day 43 visit	-10.64 (-12.75, -8.52)
Baseline to day 112 visit	-9.71 (-11.85, -7.56)
Baseline to day 224 visit	-6.66 (-8.98, -4.35)
Baseline to day 336 visit	-7.83 (-10.08, -5.58)
Baseline to day 350 visit	-3.59 (-5.87, -1.32)
Baseline to day 364 visit	0.96 (-1.33, 3.25)

Supplemental Figure S9b. Systolic blood pressure with 95% confidence interval.



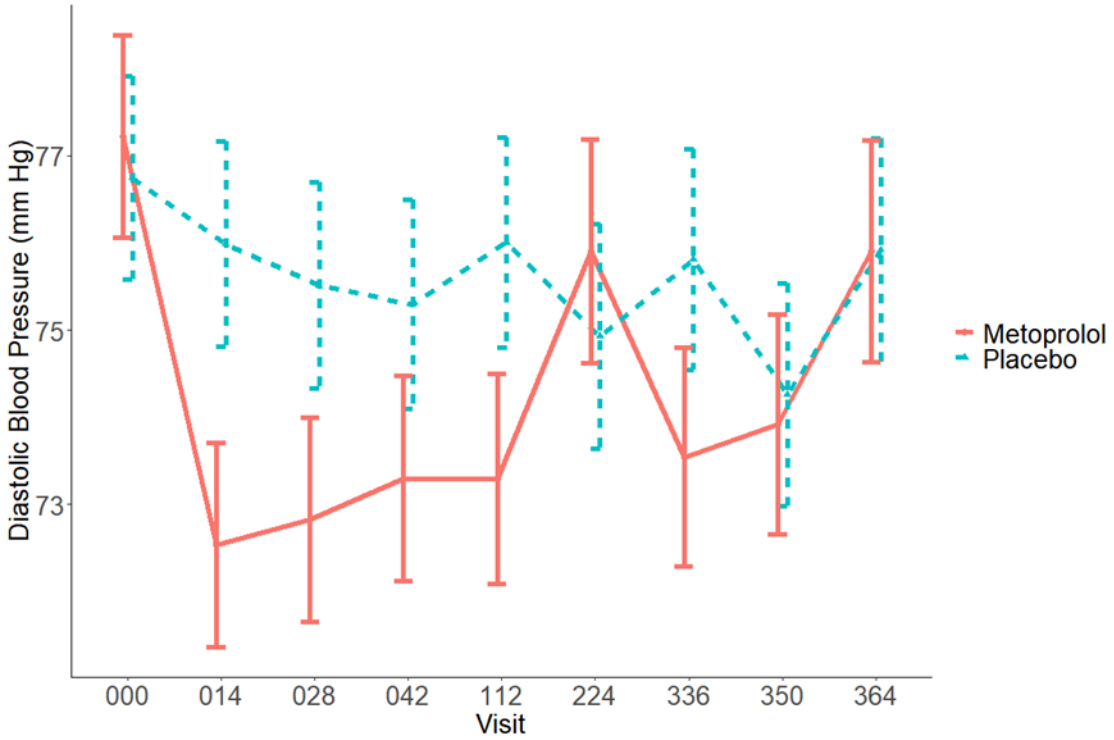
Count of participants by assignment and visit day

	000	014	028	042	112	224	336	350	364
Placebo	263	255	250	238	234	183	196	189	187
Metoprolol	268	260	259	248	228	180	199	193	189

Estimated difference in change from baseline in systolic blood pressure between groups

Difference in change: metoprolol minus placebo	Estimate (95% CI)
Baseline to day 14 visit	-1.94 (-4.68, 0.80)
Baseline to day 28 visit	-2.34 (-5.09, 0.41)
Baseline to day 42 visit	-1.75 (-4.54, 1.04)
Baseline to day 112 visit	-0.80 (-3.64, 2.04)
Baseline to day 224 visit	1.97 (-1.08, 5.03)
Baseline to day 336 visit	-3.47 (-6.44, -0.49)
Baseline to day 350 visit	-1.18 (-4.19, 1.83)
Baseline to day 364 visit	2.23 (-0.80, 5.25)

Supplemental Figure S9c. Diastolic blood pressure with 95% confidence interval.



Count of participants by assignment and visit day

	000	014	028	042	112	224	336	350	364
Placebo	263	255	250	238	234	183	196	189	187
Metoprolol	268	260	259	248	228	180	199	193	189

Estimated difference in change from baseline in diastolic blood pressure between groups

Difference in change: metoprolol minus placebo	Estimate (95% CI)
Baseline to day 14 visit	-3.93 (-5.45, -2.42)
Baseline to day 28 visit	-3.17 (-4.69, -1.65)
Baseline to day 42 visit	-2.48 (-4.02, -0.93)
Baseline to day 112 visit	-3.19 (-4.76, -1.62)
Baseline to day 224 visit	0.50 (-1.19, 2.19)
Baseline to day 336 visit	-2.75 (-4.39, -1.10)
Baseline to day 350 visit	-0.82 (-2.49, 0.84)
Baseline to day 364 visit	-0.49 (-2.16, 1.19)

Supplemental Table S1. Characteristics of the Participants.

Characteristic	Metoprolol	Placebo	Total
	N=268	N=264	N=532
Age, years	65.2 ± 7.6	64.8 ± 7.9	65.0 ± 7.8
Race			
White	178 (66.4)	194 (73.5)	372 (69.9)
Black	83 (31.0)	60 (22.7)	143 (26.9)
Other	7 (2.6)	10 (3.8)	17 (3.2)
Female sex, no. (%)	124 (46.3)	123 (46.6)	247 (46.4)
FEV_1 after bronchodilator, L	1.1±0.5	1.1±0.5	1.1±0.5
FEV_1 after bronchodilator, % of predicted value	41.3 ± 16.3	40.8 ± 16.2	41.1 ± 16.3
FEV_1/FVC, %	44.2 ± 11.7	45.2 ± 21.6	44.7 ± 17.3
GOLD Spirometric Classification, no. (%)			
1	1 (0.4)	1 (0.4)	2 (0.4)
2	84 (31.3)	75 (28.4)	159 (29.9)
3	98 (36.6)	110 (41.7)	208 (39.1)
4	85 (31.7)	78 (29.5)	163 (30.6)
GOLD 2019 Classification, no. (%)			
A	6 (2.2)	5 (1.9)	11 (2.1)
B	56 (20.9)	86 (32.6)	142 (26.7)

C	14 (5.2)	9 (3.4)	23 (4.3)
D	192 (71.6)	164 (62.1)	356 (66.9)
Smoking history, pack-years	50.7 ± 28.7	49.5 ± 29.6	50.1 ± 29.1
Current smoking, no. (%)	95 (35.4)	71 (26.9)	166 (31.2)
COPD Medication, no. (%)			
Inhaled glucocorticoids, LABA, and LAMA	154 (57.5)	160 (60.6)	314 (59.0)
Inhaled glucocorticoids and LABAs only	45 (16.8)	51 (19.3)	96 (18.0)
LAMAs only	20 (7.5)	17 (6.4)	37 (7.0)
LABAs and LAMAs only	11 (4.1)	13 (4.9)	24 (4.5)
Inhaled glucocorticoids and LAMAs only	8 (3.0)	6 (2.3)	14 (2.6)
Inhaled glucocorticoids only	5 (1.9)	2 (0.8)	7 (1.3)
Other	25 (9.3)	15 (5.7)	40 (7.5)
BMI, kg/m^2	26.9 ± 6.9	27.4 ± 6.1	27.2 ± 6.5
Heart rate, beats per minute	85.5 ± 10.8	83.6 ± 11.7	84.5 ± 11.3
Systolic blood pressure, mm Hg	128.4 ± 16.5	130.6 ± 15.9	129.5 ± 16.2
Diastolic blood pressure, mm Hg	77.2 ± 9.2	76.8 ± 9.1	77.0 ± 9.1
Coronary artery disease, no. (%)	40 (14.9)	39 (14.8)	79 (14.8)
Diabetes, no. (%)	44 (16.4)	40 (15.2)	84 (15.8)
Hypertension, no. (%)	118 (44.0)	129 (48.9)	247 (46.4)
Statin use, no. (%)	97 (36.2)	96 (36.4)	193 (36.3)

Number of courses of systemic glucocorticoid or antibiotic use within previous 12 months	1.9 ± 1.5	1.9 ± 1.7	1.9 ± 1.6
Number of hospitalizations within previous 12 months	0.7 ± 1.0	0.5 ± 1.2	0.6 ± 1.1
Baseline COPD Assessment Test Score	20.1 ± 7.3	21.3 ± 7.3	20.7 ± 7.3
Baseline Modified Medical Research Council score >1, no. (%)	164 (61.2)	169 (64.0)	333 (62.6)
Entry criteria, no. (%)			
Systemic glucocorticoid or antibiotic use within previous 12 months	246 (91.8)	228 (86.4)	474 (89.1)
COPD exacerbation leading to ED visit or hospitalization within previous 12 months	168 (62.7)	133 (50.4)	301 (56.6)
Prescription or use of supplemental oxygen within previous 12 months	106 (39.6)	106 (40.2)	212 (39.8)

Abbreviations: COPD (chronic obstructive pulmonary disease), GOLD (Global Initiative for Obstructive Lung Disease), FEV_1 (forced expiratory volume), FVC (forced vital capacity), LABA (long acting beta agonist), LAMA (long acting muscarinic antagonist), ED (emergency department), BMI (body mass index); mm Hg (millimeters of mercury)

Plus minus differences are mean ± standard deviation; co-morbid conditions are self-reported

Supplemental Table S2. Non-fatal and Fatal Serious Adverse Events by Study Group in the Metoprolol Group Compared with the Placebo Group.

Event	Metoprolol (N=268)	Placebo (N=264)	P Value
Cardiovascular			
Myocardial infarction	0.009	0.004	0.51
Heart failure	0.008	0.014	0.57
Stroke	0.004	0.008	0.65
Arrhythmias	0.012	0.008	0.71
Hypotension	0	0.004	0.31
Other Cardiovascular	0.004	0.004	0.99
Respiratory			
COPD Exacerbation*	0.43	0.19	0.018
Pneumonia	0.084	0.057	0.34
Other Respiratory	0.020	0.004	0.16
Gastrointestinal	0.025	0.049	0.52
Musculoskeletal	0.008	0.005	0.69
Cancer			
Lung Cancer	0.004	0.008	0.55
Other Cancer	0.010	0.004	0.45
Infections, non-pneumonia	0	0.026	0.24
Head, eyes, ears, nose and throat	0.004	0.016	0.45
Trauma/Falls	0.008	0.012	0.66
Neurologic, non-stroke	0.004	0.004	0.91

Psychiatric	0.004	0	0.32
Chest Pain, not otherwise specified	0.004	0.004	0.99
Endocrine	0.004	0	0.32
Other	0.008	0.008	0.97
Total	0.65	0.43	0.065
Fatal event — no. of participants (%)			
COPD	7 (2.6)	1 (0.4)	
Sudden Cardiac Death	0 (0)	1 (0.4)	
Lung Cancer	1 (0.4)	0 (0)	
Sepsis	1 (0.4)	1 (0.4)	0.17[#]
Unknown	1 (0.4)	2 (0.8)	
Other	1 (0.4)	0 (0)	
Total	11 (4.1)	5 (1.9)	0.14[##]

Note: Serious adverse events are as reported by the clinical site investigator. *COPD exacerbations listed here may not meet the protocol-defined criteria for the primary endpoint. [#]Fisher exact test comparing cause of death between groups. [##]Log-rank test. There were 4 additional deaths in the placebo group (COPD – 1, unknown - 2, lung cancer – 1) and 3 additional deaths in the metoprolol group (COPD – 2, pneumonia - 1) after the treatment period.

Supplemental Table S3: Participant-Reported Possible Beta-Blocker Side Effects by Study Group.

	Metoprolol	Placebo	Total	P-value
Total Number of Participants	268	263	531	
Depression				
Yes (%)	28 (10.4)	39 (14.8)	67	0.13
Severity				
Mild	17 (6.3)	28 (10.6)	45	
Moderate	10 (3.7)	10 (3.8)	20	
Severe	1 (0.4)	1 (0.4)	2	
No Depression	240 (89.6)	224 (85.2)	464	
Headache				
Yes (%)	71 (26.5)	78 (29.7)	149	0.42
Severity				
Mild	53 (19.8)	53 (20.2)	106	
Moderate	16 (6.0)	23 (8.7)	39	
Severe	2 (0.7)	2 (0.8)	4	
No Headache	197 (73.5)	185 (70.3)	382	
Fainting/Passing out				
Yes (%)	4 (1.5)	8 (3.0)	12	0.23
Severity				
Mild	3 (1.1)	3 (1.1)	6	
Moderate	0 (0.0)	3 (1.1)	3	
Severe	1 (0.4)	2 (0.8)	3	
No Fainting/Passing	264 (98.5)	255 (97.0)	519	
Daytime Sleepiness				
Yes (%)	58 (21.6)	70 (26.6)	128	0.18
Severity				
Mild	42 (15.7)	56 (21.3)	98	
Moderate	12 (4.5)	13 (4.9)	25	
Severe	4 (1.5)	1 (0.4)	5	
No Daytime	210 (78.4)	193 (73.4)	403	
Memory Loss				
Yes (%)	20 (7.5)	21 (8.0)	41	0.82
Severity				
Mild	15 (5.6)	18 (6.8)	33	
Moderate	5 (1.9)	3 (1.1)	8	
Severe	0 (0.0)	0 (0.0)	0	
No Memory Loss	248 (92.5)	242 (92.0)	490	
Loss of sexual desire				
Yes (%)	10 (3.7)	6 (2.3)	16	0.33
Severity				

Mild	9 (3.4)	5 (1.9)	14	
Moderate	1 (0.4)	1 (0.4)	2	
Severe	0 (0.0)	0 (0.0)	0	
No Loss desire	258 (96.3)	257 (97.7)	515	
Lack of energy				
Yes (%)	91 (34.0)	77 (29.3)	168	0.25
Severity				
Mild	54 (20.1)	51 (19.4)	105	
Moderate	29 (10.8)	22 (8.4)	51	
Severe	8 (3.0)	4 (1.5)	12	
No Lack of energy	177 (66.0)	186 (70.7)	363	
Rash				
Yes (%)	17 (6.3)	21 (8.0)	38	0.46
Severity				
Mild	13 (4.9)	20 (7.6)	33	
Moderate	4 (1.5)	1 (0.4)	5	
Severe	0 (0.0)	0 (0.0)	0	
No Rash	251 (93.7)	242 (92.0)	493	
Itching				
Yes (%)	30 (11.2)	22 (8.4)	52	0.27
Severity				
Mild	24 (9.0)	19 (7.2)	43	
Moderate	5 (1.9)	3 (1.1)	8	
Severe	1 (0.4)	0 (0.0)	1	
No Itching	238 (88.8)	241 (91.6)	479	
Tongue or facial swelling				
Yes (%)	7 (2.6)	5 (1.9)	12	0.58
Severity				
Mild	5 (1.9)	3 (1.1)	8	
Moderate	1 (0.4)	2 (0.8)	3	
Severe	1 (0.4)	0 (0.0)	1	
No Tongue or facial	261 (97.4)	258 (98.1)	519	
Vomiting				
Yes (%)	11 (4.1)	18 (6.8)	29	0.17
Severity				
Mild	10 (3.7)	14 (5.3)	24	
Moderate	1 (0.4)	3 (1.1)	4	
Severe	0 (0.0)	1 (0.4)	1	
No Vomiting	257 (95.9)	245 (93.2)	502	
Nausea				
Yes (%)	45 (16.8)	42 (16.0)	87	0.80
Severity				
Mild	36 (13.4)	37 (14.1)	73	
Moderate	9 (3.4)	4 (1.5)	13	

Severe	0 (0.0)	1 (0.4)	1	
No Nausea	223 (83.2)	221 (84.0)	444	
Constipation				
Yes (%)	30 (11.2)	32 (12.2)	62	0.73
Severity				
Mild	24 (9.0)	25 (9.5)	49	
Moderate	6 (2.2)	6 (2.3)	12	
Severe	0 (0.0)	1 (0.4)	1	
No Constipation	238 (88.8)	231 (87.8%)	469	
Wheezing				
Yes (%)	88 (32.8)	79 (30.0)	167	0.49
Severity				
Mild	39 (14.6)	26 (9.9)	65	
Moderate	31 (11.6)	42 (16.0)	73	
Severe	18 (6.7)	11 (4.2)	29	
No Wheezing	180 (67.2)	184 (70.0)	364	
Shortness of breath				
Yes (%)	115 (42.9)	112 (42.6)	227	0.94
Severity				
Mild	31 (11.6)	39 (14.8)	70	
Moderate	54 (20.1)	56 (21.3)	110	
Severe	30 (11.2)	17 (6.5)	47	
No SOB	153 (57.1)	151 (57.4)	304	
Chest tightness				
Yes (%)	81 (30.2)	80 (30.4)	161	0.96
Severity				
Mild	37 (13.8)	38 (14.4)	75	
Moderate	28 (10.4)	37 (14.1)	65	
Severe	16 (6.0)	5 (1.9)	21	
No Chest tightness	187 (69.8)	183 (69.6)	370	
Heart skipping or irregular				
Yes (%)	16 (6.0)	15 (5.7)	31	0.90
Severity				
Mild	13 (4.9)	10 (3.8)	23	
Moderate	2 (0.7)	3 (1.1)	5	
Severe	1 (0.4)	2 (0.8)	3	
No Heart skipping	252 (94.0)	248 (94.3)	500	
Dizziness/light				
Yes (%)	74 (27.6)	64 (24.3)	138	0.39
Severity				
Mild	53 (19.8)	41 (15.6)	94	
Moderate	17 (6.3)	19 (7.2)	36	
Severe	4 (1.5)	4 (1.5)	8	
No Dizziness/light	194 (72.4)	199 (75.7)	393	

Supplemental Table S4. Permanent Discontinuation of Study Drug by Treatment Group.

Reason for Discontinuation, no. (%)	Metoprolol N=268	Placebo N=264	Total N=532
Cardiac event*	5 (1.9)	2 (0.8)	8 (1.5)
Respiratory symptoms	8 (3.0)	3 (1.1)	11 (2.1)
Incompatible medications	5 (1.9)	4 (1.5)	9 (1.7)
Allergy	1 (0.4)	0 (0)	1 (0.2)
Other reason**	11 (4.1)	7 (2.7)	17 (3.2)
Total	30 (11.2)	16 (6.1)	46 (8.7)

*Cardiac events, Metoprolol: Arrhythmias (1), Myocardial infarction (1), Congestive heart failure (2), Chest pain (1); Placebo: arrhythmias (2)

**Other reason detail, Metoprolol: Depression/cognitive issues (2), Decreased blood pressure or heart rate (2), Lightheadedness, dizziness, fatigue (3), PCP discretion (1), Peripheral vascular disease (2); Placebo: Depression/cognitive issues (2), Decreased blood pressure or heart rate (1), Lightheadedness, dizziness, fatigue (1), Moderate itching (1), General health decline (1), Stroke (1)

Supplemental Table S5. Estimated Compliance by Study Group.

Visit Period	Metoprolol Compliance (%)	Placebo Compliance (%)
Randomization to day 14 visit	90	92
Day 14 visit to day 28 visit	87	88
Day 28 visit to day 42 visit	89	84
Day 42 to day 112 visit	85	83
Day 112 to day 224 visit	81	83
Day 224 to day 336 visit	87	90

Compliance was calculated as the number of doses taken divided by the number of prescribed doses in the given study period and is reported as a percentage.

References

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