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TITLE: Beta Blockers for the Prevention of Acute Exacerbations of COPD

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CONTRACTING ORGANIZATION: University of Alabama at Birmingham
Birmingham, AL 35294

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14. ABSTRACT

We conducted a multicenter, randomized, placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate and severity of COPD exacerbations. The trial planned to enroll 1028 patients over a 3-year period. Study enrollment was halted early on March 21, 2019 based on DSMC recommendation after review of both the futility analysis and emerging safety concerns. Major activities for this reporting period centered on enrollment at clinical sites through March 21, 2019. Final enrollment was 532 subjects. Since March 21, 2019, major activities focused on notifying study participants and efficiently exiting all active study participants. The database has been locked. Initial analysis showed no difference in the risk of COPD exacerbations between the metoprolol and placebo group. The results showed that participants who took metoprolol had a higher risk of hospitalizations for COPD than those that took placebo. A manuscript was submitted to and accepted for publication by the New England Journal of Medicine.

15. SUBJECT TERMS

beta blockers , cardiovascular disease, COPD, exacerbation , metoprolol succinate, placebo-controlled, randomized

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INTRODUCTION:

A substantial majority of chronic obstructive pulmonary disease (COPD)-related morbidity, mortality, and healthcare costs are due to acute exacerbations, but existing medications have only a modest effect on reducing their frequency, even when used in combination. Observational studies suggest β-blockers may reduce the risk of COPD exacerbations; thus, we are conducting a randomized, placebo-controlled trial to definitively assess the impact of metoprolol succinate on the time to first, rate, and severity of COPD exacerbations. This is a multicenter, placebo-controlled, double-blind, prospective randomized trial that will enroll 1028 patients with at least moderately severe COPD over a 3-year period. Participants with at least moderate COPD will be randomized in a 1:1 fashion to receive metoprolol or placebo; the cohort will be enriched for patients at high risk for exacerbations. Patients will be screened and then randomized over a 2-week period and will then undergo a dose titration period for the following 6 weeks. Thereafter, patients will be followed for 42 additional weeks on their target dose of metoprolol or placebo followed by a 4-week dose weaning period. The primary endpoint is time to first occurrence of an acute exacerbation during the treatment period. Secondary end points include rates and severity of COPD exacerbations; rate of major cardiovascular events (MACE); all-cause mortality; lung function (forced expiratory volume in 1 s (FEV1)); dyspnea; quality of life; exercise capacity as measured by 6 minute walk test; markers of cardiac stretch (pro-NT brain natriuretic peptide) and systemic inflammation (high-sensitivity C reactive protein and fibrinogen). Analyses will be performed on an intent-to-treat basis.

KEYWORDS:
beta blockers
cardiovascular disease
COPD exacerbation
metoprolol succinate
placebo-controlled
randomized

ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aims to be achieved through the conduct of the proposed clinical trial:
Primary: To determine the effect of once daily metoprolol succinate compared with placebo on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and who do not have absolute indications for beta-blocker therapy.
Secondary: To estimate the effect of metoprolol succinate compared with placebo on the rate and severity of COPD exacerbations over 12 months, major adverse cardiac events (MACE), combined exacerbations and MACE, incidence and severity of metoprolol-related side effects including those that require cessation of drug, lung function, dyspnea, quality of life, exercise capacity, hospitalization rates, and all-cause mortality.

What was accomplished under these goals?

The DSMC reviewed the March 21, 2019 BLOCK-COPD Data Monitoring Report prepared by Dr. Connett and his Data Coordinating Center team. The report focused on conditional power futility analyses and updated interim serious adverse event data. Based on this review, the DSMC recommended that randomizations be stopped as soon as possible and that study medications be discontinued as soon as practically and safely possible. The decision to terminate the trial early before its planned end was based on both the futility analysis and emerging safety concerns. Given the interim data, the probability of finding a significant

difference between the metoprolol and placebo groups with respect to the primary outcome was highly unlikely were the trial to continue. Furthermore, the interim safety data suggested that use of the beta-blocker metoprolol increases the rate of severe exacerbations requiring hospitalizations compared to placebo.

Major activities for this reporting period centered on enrollment at clinical sites through March 21, 2019. Final enrollment was 532 subjects. Since March 21, 2019, major activities focused on notifying study participants and efficiently exiting all active study participants. The database has been locked. Initial analysis showed no difference in the risk of COPD exacerbations between the metoprolol and placebo group. The results showed that participants who took metoprolol had a higher risk of hospitalizations for COPD than those that took placebo. A manuscript was submitted to and accepted for publication by the New England Journal of Medicine.

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Screen 4-6 subjects/month	**6-42 months**	**Screening ended on March 21, 2019 (month 42)**
Randomize 2-3 subjects per site /month	**6-42 months**	**The first subject was randomized in May 2016, two months later than anticipated based on delays in regulatory approvals. Randomization ended March 21, 2019 (month 42)**
Complete study visits for 1 year + 1 month washout following enrolment	**6-55 months**	**Study visits were completed early. All visits completed by month 47**
Data entry	**6-55 months**	**complete month 47**
Issue queries	**6-56 months**	**complete month 48**
Resolve queries	**6-56 months**	**complete month 48**
Adverse event assessment and reporting	**6-55 months**	**complete month 47**
Maintain IRB approval	**6-60 months**	**Ongoing**
Develop reports for DSMB	**6-60 months**	**DSMB meetings have been held on 2 DEC 2016, 25 MAY 2017, 01 DEC 2017 and 29 MAY 2018, 30 NOV 2018 and 21 MAR 2019 The DCC has developed reports as necessary and recommended stopping the trial**
Conduct monthly coordinator calls	**6-56 months**	**Calls have been conduct monthly since August 2016. Monthly calls have also been conducted with PIs and other study staff since April 2016**
Provide drug and placebo as needed to sites	**6-55 months**	**complete month 42**
Return unused drug and placebo to DPMD	**56-58 months**	**complete month 48**

Perform key primary and secondary analyses	**56-57 months**	**Primary Complete month 48, secondary ongoing**
Share/discuss data with investigators	**57 months**	**Complete month 47**
Present key findings at National/International Meeting	**58-60 months**	**ongoing**
Submit primary manuscript	**60 months**	**Complete month 48**

What opportunities for training and professional development has the project provided?

Numerous pulmonary fellows and junior faculty have been involved in the study across sites providing experience and education regarding clinical trial execution.

How were the results disseminated to communities of interest?

During the first reporting period, the following article was published: β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol. PMID: 27267111.

During the fourth reporting period, the following article was accepted for publication and is include as Appendix 1: Metoprolol for the Prevention of Acute Exacerbations of COPD.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, upon obtaining approval from the DOD Science Officer, efforts will focus on an updated SOW that includes the addition of an observational study with the following specific aims: To determine the prevalence of COPD in patients admitted to the hospital with myocardial infarction and to characterize the phenotypic expression and severity of their underlying lung disease and 2) To determine the association between beta-blocker use at discharge and cardiopulmonary outcomes in patients with COPD and myocardial infarction. With the following timeline:

Activity	Timeline	CCRN Sites	DCC	DPMD
Develop study protocol	48-51 months	X	X	
IRB and HRPO approvals	51-54 months	X	X	
Subject recruitment	54-70 months	X	X	
Data analysis	70-72 months	X	X	
Submission of publication	72 months	X	X	

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

In this prospective, multicenter, randomized trial, we did not find evidence of a difference in the risk of COPD exacerbation between the metoprolol group and the placebo group, although the use of metoprolol was associated with a higher risk of exacerbation leading to hospitalization. These results differ from previously reported findings from observational studies suggesting that beta-blockers reduce the risks of exacerbation and death from any cause in patients with COPD. The full article is included as Appendix 1. N Engl J Med. 2019 Dec 12;381(24):2304-2314. doi: 10.1056/NEJMoa1908142. Epub 2019 Oct 20

What was the impact on other disciplines?

See appendix 1 for NEJM article

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

See appendix 1 for NEJM article

CHANGES/PROBLEMS:

Changes in approach and reasons for change

The DSMC reviewed the March 21, 2019 BLOCK-COPD Data Monitoring Report prepared by Dr. Connett and his Data Coordinating Center team. The report focused on conditional power futility analyses and updated interim serious adverse event data. Based on this review, the DSMC recommends that randomizations be stopped as soon as possible and that study medications be discontinued as soon as practically and safely possible. The decision to terminate the trial early before its planned end was based on both the futility analysis and emerging safety concerns. Given the interim data, the probability of finding a significant difference between the metoprolol and placebo groups with respect to the primary outcome is highly unlikely were the trial to continue. Furthermore, the interim safety data suggests that use of the beta-blocker metoprolol increases the rate of severe exacerbations requiring hospitalizations compared to placebo.

Because the trial was stopped early, an observational ancillary study entitled Beta-Blocker Use in Patients with Chronic Obstructive Pulmonary Disease (COPD) and Acute Myocardial Infarction has been approved.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes that had a significant impact on expenditures

Because the trial was stopped early, and an observational ancillary study entitled Beta-Blocker Use in Patients with Chronic Obstructive Pulmonary Disease (COPD) and Acute Myocardial Infarction has been approved, year 5 budgets have been revised to reflect changes to accommodate final analysis and presentation/publication of results at all sub sites. Furthermore,

a sub-set of existing sites will be identified to participate in the observational trial and budgets will be adjusted accordingly.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

During this forth-reporting period IRBs were notified that the study was stopping early. Development of the additional observational study protocol is underway and will be provided to local IRBs and DOD HRPO for review.

Significant changes in use or care of vertebrate animals.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

PRODUCTS:

Publications, conference papers, and presentations

First reporting period:

Journal publications

BMJ Open, vol. 6(6) pp. e012292

β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol.

Bhatt, SP; Connett, JE; Voelker, H; Lindberg, SM; Westfall, E; Wells, JM; Lazarus, SC; Criner, GJ; Dransfield, MT
PMID: 27267111
URL - http://www.ncbi.nlm.nih.gov/pubmed/27267111?dopt=Citation

acknowledgement of federal support – yes

Second Reporting period:

Nothing to report.

Third Reporting period:

Nothing to report

Forth Reporting period:

N Engl J Med. 2019 Dec 12;381(24):2304-2314. doi: 10.1056/NEJMoa1908142. Epub 2019 Oct 20

Metoprolol for the Prevention of Acute Exacerbations of **COPD**.

Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, Cooper JAD, Criner GJ, Curtis JL, Han MK, Hatipoğlu U, Helgeson ES, Jain VV, Kalhan R, Kaminsky D, Kaner R, Kunisaki KM, Lambert AA, Lammi MR, Lindberg S, Make BJ, Martinez FJ, McEvoy C, Panos RJ, Reed RM, Scanlon PD, Sciurba FC, Smith A, Sriram PS, Stringer WW, Weingarten JA, Wells JM, Westfall E, Lazarus SC, Connett JE; BLOCK **COPD** Trial Group.

PMID: 31633896

URL: https://www.ncbi.nlm.nih.gov/pubmed/?term=beta+blockers+copd

acknowledgement of federal support – yes

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers, and presentations.

Nothing to report.

Website(s) or other Internet site(s)

First reporting period:

The trial has been listed on ClinicalTrials.gov. The NCT number is NCT02587351.

url: https://clinicaltrials.gov/

We have developed an informational website for participants and providers. This site provides a broad overview of the trial including contact information for UAB, the DCC, the research pharmacy and all clinical sites.

url: http://blockcopd.org/

Second reporting period:

Nothing to report.

Third reporting period:

Nothing to report

Forth-reporting period:

Nothing to report

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

First reporting period:

We have developed a separate protocol for the collections and storage of serum, plasma and whole blood samples. The protocol has been approved by the UAB IRB. We ask other interested clinical sites that have the internal resources available to participate in the specimen collection protocol as well.

Second Reporting period:

Nothing to report.

Third Reporting period:

Nothing to Report

Forth Reporting period:

Observational ancillary study entitled Beta-Blocker Use in Patients with Chronic Obstructive Pulmonary Disease (COPD) and Acute Myocardial Infarction protocol is under development.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

University of Alabama at Birmingham

Name: Mark T. Dransfield
Project Role: PI
Research Identifier: 0000-0003-0346-1956
Nearest Person Month worked: 2.4
Contribution to Project: Dr. Dransfield is the PI of the Project. He oversees protocol related activities at all research sites and is the local site PI at UAB.

Name: Elizabeth Westfall
Project Role: Program Director
Research Identifier: N/A
Nearest Person Month worked: 3
Contribution to Project: Ms. Westfall assists in the regulatory and financial administration of this grant. This includes initiating subcontracts and overseeing disbursement of payments to subaward sites as well as overseeing human subject approvals.

Name: Steven G. Lloyd
Project Role: Consultant
Research Identifier: N/A
Nearest Person Month worked: 6.35
Contribution to Project: Consultant

Dr. Lloyd is the consultant on this g project. He provides cardiology expertise including review of EKGs and adjudication of adverse events that might require trial discontinuation.

Minnesota DCC

Name: Dr. John Connett
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.8

Contribution to Project: Dr. Connett oversees the project at the DCC site. He supervises the day-to-day operation of the Data Coordinating Center. Dr. Connett oversees the development of data collection procedures and methods for data transmission and management.

Name: Helen Voelker
Project Role: Information Technologies Manager
Research Identifier: N/A
Nearest Person Month worked: 4.2
Contribution to Project: Ms. Voelker develops database schemas, edits, and updates procedures for study data. Ms. Voelker develops the distributed data entry and data transmission system.

Name: Sarah Lindberg
Project Role: Protocol Manager
Research Identifier: N/A
Nearest Person Month worked: 3.7
Contribution to Project: Ms. Lindberg assists with writing sections of the Manual of Procedures, designing study data forms, and analyzing data for Steering Committee and DSMB meeting.

Name: Irene Olson
Project Role: Data Quality Control
Research Identifier: N/A
Nearest Person Month worked: 3
Contribution to Project: Ms. Olson assists Ms. Voelker in creating schemas and databases for forms.

Temple University School of Pharmacy

Name: David Lebo
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Lebo is the PI for the Temple Pharmacy site.
Dr. Lebo is responsible for producing, labeling, and distributing the study drug for this project. Mr. Lebo oversees the supply chain of the medication and monitors it for labeling and packaging deviations.

Temple University School of Pharmacy

Name: Susan Owaisat
Project Role: Research Scientist
Research Identifier: N/A
Nearest Person Month worked: 8.6
Contribution to Project: Susan coordinates the cGMP activities for the study. These include: label auditing, batch record authoring, inventory audits, track shipments, draft chain of custody documents, and conduct out of specification investigations.

University of Michigan

Name: MeiLan Han

Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Han is the PI for the University of Michigan site.
Dr. Han oversees day-to-day research activities at this site.

University of Michigan

Name: Mary Kay Hamby
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.44
Contribution to Project: Mary Kay is a research coordinator at the University of Michigan site.
She assists with recruiting for this research project.

University of Michigan

Name: Lisa McCloskey
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Lisa is a research coordinator at the University of Michigan site and assists Drs. Han and Curtis with recruitment and other day to day duties for this study.

University of Michigan

Name: Gretchen Bautista
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 4.8
Contribution to Project: Gretchen is a research coordinator at the University of Michigan site and assists Drs. Han and Curtis with recruitment and other day to day duties for this study.

Weil Cornell Medical College

Name: Robert J. Kaner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .18
Contribution to Project: Dr. Kaner is the PI for the Weil Cornell Medical College site. Dr. Kaner oversees day to day research activities at this site.

Weil Cornell Medical College

Name: Fernando Martinez
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .12

Contribution to Project: Dr. Martinez is the Co-Investigator for the Weil Cornell Medical College site.

Weil Cornell Medical College

Name: Keith Brenner
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .37
Contribution to Project: Dr. Brenner is the PI for Columbia University, a subsite of Weil Cornell Medical College site. Dr. Brenner assists in recruiting and evaluating patients for this study at the Columbia subsite.

Weil Cornell Medical College

Name: Elizabeth Peters
Project Role: Study coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Elizabeth is the study coordinator for the Weil Cornell Medical College site. She assists the PI with recruitment and study visits as outlined in the protocol. She will also act as a representative between the primary site (Cornell) and the subsites.

Weil Cornell Medical College

Name: Matthew Marcelino
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: .6.9
Contribution to Project: Matthew assists the Study Coordinator with the preparation, submission, and maintenance of clinical trials regulatory data and documentation. This includes assisting with the maintenance of Human Subjects and Regulatory documents necessary for submission to the Institutional Review Board, prime site and study sponsor in order to obtain initial and continued approval of the clinical research study. Matthew wiII assist with preparing responses to the IRB and to the primary site in accordance with internal and external policies and procedures.

Weil Cornell Medical College

Name: Sergio Alvarez
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 5.4
Contribution to Project: Sergio assists the Study Coordinator with the preparation, submission, and maintenance of clinical trials regulatory data and documentation. This includes assisting with the maintenance of Human Subjects and Regulatory documents necessary for submission to the Institutional Review Board, prime site and study sponsor in order to obtain initial and continued approval of the clinical research study. Sergio will assist with preparing responses

to the IRB and to the primary site in accordance with internal and external policies and procedures

New York Presbyterian Queens (NYPQ)

Name: Anthony Smith
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Smith is the PI at the New York Presbyterian Queens site. This is a subsite of Weill Cornell Medical College. Dr. Smith will oversee recruitment at this site.

New York Methodist (NYM)

Name: Jeremy Weingarten
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Weingarten is the PI at the New York Methodist site. This is a subsite of Weill Cornell Medical College. Dr. Weingarten will oversee recruitment at this site.

University of Maryland

Name: Robert M. Reed
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.44
Contribution to Project: Dr. Reed is the PI for the University of Maryland, Baltimore site. Dr. Reed oversees day to day research activities at this site.

Northwestern University

Name: Ravi Kalhan
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .36
Contribution to Project: Dr. Kalhan is the PI for the Northwestern University site. Dr. Kalhan oversees day to day research activities at this site.

Northwestern University

Name: Sharon Rosenberg
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .18
Contribution to Project: Dr. Rosenberg is the Co-Investigator for the Northwestern University site. Dr. Rosenberg assists Dr. Kalhan with day to day research activities at this site and supervise in data analysis and preparation of manuscripts.

University of Pittsburgh

Name: Frank Sciurba
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
Contribution to Project: Dr. Sciurba is the PI for the University of Pittsburgh site. Dr. Sciurba oversees day to day research activities at this site.

Temple University

Name: Gerard Criner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .47
Contribution to Project: Dr. Criner is the PI for the Temple University – Clinical site. Dr. Criner oversees day to day research activities at this site.

Temple University

Name: Nathaniel Marchetti
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .24
Contribution to Project: Dr. Marchetti is the Co-Investigator for the Temple University – Clinical site. Dr. Marchetti assists Dr. Criner with day to day research activities at this site. In addition Dr. Marchetti assists with recruitment, enrollment, and retention.

Temple University

Name: Dee Fehrle
Project Role: RN, Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.98
Contribution to Project: Dee Fehrle is the Research Nurse Coordinator at the Temple University Clinical site. Dee manages day to day study activities at this site. Dee recruit and enroll patients as well as see patients at each visit as outlined in the protocol. Dee also collects patient data.

Minneapolis VA

Name: Christine Wendt
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .60
Contribution to Project: Dr. Wendt is the Co-Investigator for the Minnesota Veterans Research and Education Foundation site. Dr. Wendt assists Dr. Niewoehner with protocol related activities at this site.

Minneapolis VA

Name: Ken Kunisaki
Project Role: PI

Research Identifier: N/A
Nearest Person Month worked: ..6
Contribution to Project: Dr. Kunisaki is the PI for the Minnesota Veterans Research and Education Foundation site. Dr. Kunisaki oversees day to day research activities at this site.

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Name: Dennis Niewoehner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Dr. Niewoehner is the Co-Investigator for the Minnesota Veterans Research and Education Foundation site. Dr. Niewoehner will be involved with data analysis and interepretation and results along with the site investigator. He will also assist with manuscript writing and presentations.

Minneapolis VA

Name: Susan Johnson
Project Role: Project Coordinator/ Data Analyst
Research Identifier: N/A
Nearest Person Month worked: 1.44
Contribution to Project: Susan is the Project Coordinator/ Data Analyst for the Minnesota Veterans Research and Education Foundation site. Susan is responsible for the preparation of the IRB application, renewal and amendments as well as patient screening and data analysis throughout the study.

Brigham and Women's Hospital

Name: Carolyn Come
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 2.8
Contribution to Project: Dr. Come is the PI for the Brigham and Women's Hospital site. Dr. Come oversees the day to day research activities at this site.

Health Partners Institute

Name: Charlene McEvoy
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 36
Contribution to Project: Dr. McEvoy is the PI for the HealthPartners Institute site. Dr. McEvoy oversees the day to day research activities at this site.

Health Partners Institute

Name: Cheryl Sasse
Project Role: Project Manager
Research Identifier: N/A
Nearest Person Month worked: 1.55
Contribution to Project: Cheryl is responsible for the day-to-day activities associated with the project. She is also responsible for regulatory

documentation to the local IRB and prime site.

National Jewish Health

Name: Barry Make
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Make is the PI for the National Jewish Health site. Dr. Make Oversees the day to day research activities at this site.

Mayo Clinic

Name: Paul Scanlon
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Scanlon is the PI for the Mayo Clinic Site. Dr. Scanlon oversees the day to day research activities at this site.

Mayo Clinic

Name: Tami Krpata
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.27
Contribution to Project: Tami performs all study coordinator duties including but not limited to recruiting, consenting patients, administering questionnaires, maintaining regulatory documents, entering data, etc.

UCSF

Name: Stephen Lazarus
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .56
Contribution to Project: Dr. Lazarus is the PI for the UCSF (University of California, San Francisco) site. He oversees the day to day research activities at this site.

UCSF

Name: Prescott Woodruff
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Prescott is the Co-Investigator at the UCSF (University of California, San Francisco) site. He assists with the development and implementation of the protocol, data analysis, and presentation of results.

LA BIOMED

Name: William W. Stringer
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .5
Contribution to Project: Dr. Stringer is the PI for the Los Angeles Biomedical Research site. He oversees the day to day research activities at this site.

LA BIOMED

Name: Richard Casaburi
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .3
Contribution to Project: Dr. Casaburi is the Co-Investigator at the Los Angeles Biomedical Research site. He assists with data analysis and manuscript preparation.

LA BIOMED

Name: Leticia Diaz
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3
Contribution to Project: Leticia is the study coordinator for this site and is responsible for screening and enrolling patients in this study.

Louisiana State University

Name: Matthew Lammi
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .72
Contribution to Project: Dr. Lammi is the PI at the Louisiana State University site. He is responsible for the overall supervision and direction of the project at LSUHSC.

Louisiana State University

Name: Connie Romaine
Project Role: Clinical Research Nurse
Research Identifier: N/A
Nearest Person Month worked: .72
Contribution to Project: Connie screens potential participants and assists Dr. Lammi with data and sample collection, staff education, meetings and teleconferences.

Cleveland Clinic Foundation

Name: Umur Hatipoglu
Project Role: PI
Research Identifier: N/A

Nearest Person Month worked: .12
Contribution to Project: Dr. Hatipoglu is the PI at the Cleveland Clinic Foundation site. He is responsible for the overall supervision and direction of the project at Cleveland Clinic Foundation.

Cleveland Clinic Foundation

Name: Rick Rice
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.0
Contribution to Project: Rick is responsible for obtaining informed consent on all subjects enrolled. He is responsible for screening/enrolling participants as well as collect and enter data.

Cincinnati VA Medical Center

Name: Ralph Panos
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Panos is the PI at the Cincinnati VA (CERV) site. He is responsible for the overall supervision and direction of this project at CERV.

UCSF Fresno

Name: Vipul Jain
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
Contribution to Project: Dr. Jain s is the PI at the UCSF Fresno site. He is responsible for the overall supervision and direction of this project at UCSF Fresno.

Name: Janna Blaauw
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 2.28
Contribution to Project: Janna Blaauw is the research coordinator for the UCSF-Fresno Site. Janna will assist in study recruitment and patient visits.

University of Vermont

Name: David A. Kaminsky
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Kaminsky is the PI at the University of Vermont & State Agricultural college site. He is responsible for the overall supervision and direction of this project at the University of Vermont.

University of Utah

Name: Richard Kanner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Kaminsky is the PI at the University Utah site. He is responsible for the overall supervision and direction of this project at the University of Utah.

North Florida Foundation for Research and Education, Inc.

Name: Peruvemba Sririam
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .60
Contribution to Project: Dr. Sririam is the PI at the North Florida Foundation for Research and Education site. He is responsible for the overall supervision and direction of this project at NFFRE. He will oversee the study and perform physical examinations on study participants.

North Florida Foundation for Research and Education, Inc.

Name: Paige Gustad
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.6
Contribution to Project: Paige is the study coordinator for this site. She will assist in patient recruitment and patient visits at this site.

North Florida Foundation for Research and Education, Inc.

Name: Angie Smith
Project Role: Regulatory Specialist
Research Identifier: N/A
Nearest Person Month worked: 1.56
Contribution to Project: Angie is the regulatory specialist at NFFRE site. Angie performs regulatory set-up and IRB continuation tasks related to this study.

Providence Health & Services - Washington

Name: Allison Lambert
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .2
Contribution to Project: Dr. Lambert is the PI at the Providence Health & Services – Washington site. She is responsible for the overall supervision and direction of this project at Providence. She will oversee the study and perform physical examinations on study participants.

Providence Health & Services - Washington

Name: Lisa Davis
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 3.1
Contribution to Project: Lisa is the clinical research coordinator at the Providence Health & Services – Washington site. She will perform the required patient visit procedures as outlined in the study protocol.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to Report

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable

QUAD CHARTS: See attachment 1

APPENDICES:

Forth-reporting period: NEJM article

PR140170: Beta Blockers for the Prevention of Acute Exacerbations of COPD

PI: Mark Dransfield, University of Alabama at Birmingham

Budget: $11,241,567 **Topic Area:** Respiratory Health **Mechanism:** Clinical Trial Award

Research Area: Chemoprevention, Chemotherapy **Award Status:** Open; 9/30/2015 - 9/29/2020

Study Goals:

Carry out a clinical trial to examine the potential role of beta-blockers in the treatment of chronic obstructive pulmonary disease (COPD).

Specific Aims:

(1) Determine the effect of once-daily metoprolol succinate, compared with placebo, on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and do not have absolute indications for beta-blocker therapy. (2) Estimate the effect of metoprolol succinate, compared with placebo, on the rate and severity of COPD exacerbations over 12 months, incidence and severity of metoprolol-related side effects, lung function, dyspnea, exercise tolerance, quality of life, hospitalization rates, rate of combined cardiovascular events (myocardial infarction, percutaneous coronary intervention, sudden death, stroke), and all-cause mortality.

Key Accomplishments:

- DSMC recommended enrollment be halted on March 21, 2019, and study medications be discontinued based on both the futility analysis for the primary endpoint and emerging safety concerns.
- Ended enrollment on March 21, 2019 at 52% of projected target randomized but with adequate sample size to analyze primary outcome.
- HRPO and IRBs have been notified of the decision to stop the trial.
- All early termination visits have been completed and all subjects have been weaned off study drug.
- Database has been locked
- Manuscript submitted to and published in NEJM.
- Ancillary Observational Study approved and detailed protocol, site selection, and IRB/HRPO applications under development.

Key Outcomes:

Publications: BMJ Open, vol. 6(6) pp. e012292, β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol. Bhatt, SP; Connett, JE; Voelker, H; Lindberg, SM; Westfall, E; Wells, JM; Lazarus, SC; Criner, GJ; Dransfield, MT. PMID: 27267111 URL - http://www.ncbi.nlm.nih.gov/pubmed/27267111?dopt=Citation

N Engl J Med. 2019 Dec 12;381(24):2304-2314. Epub 2019 Oct 20, Metoprolol for the Prevention of Acute Exacerbations of COPD. Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, Cooper JAD, Criner GJ, Curtis JL, Han MK, Hatipoğlu U, Helgeson ES, et al. PMID: 31633896 URL- https://www.ncbi.nlm.nih.gov/pubmed/?term=beta+blockers+copd

Patents: N/A

Funding Obtained: N/A

ORIGINAL ARTICLE

Metoprolol for the Prevention of Acute Exacerbations of COPD

M.T. Dransfield, H. Voelker, S.P. Bhatt, K. Brenner, R. Casaburi, C.E. Come, J.A.D. Cooper, G.J. Criner, J.L. Curtis, M.L.K. Han, U. Hatipoğlu, E.S. Helgeson, V.V. Jain, R. Kalhan, D. Kaminsky, R. Kaner, K.M. Kunisaki, A.A. Lambert, M.R. Lammi, S. Lindberg, B.J. Make, F.J. Martinez, C. McEvoy, R.J. Panos, R.M. Reed, P.D. Scanlon, F.C. Sciurba, A. Smith, P.S. Sriram, W.W. Stringer, J.A. Weingarten, J.M. Wells, E. Westfall, S.C. Lazarus, and J.E. Connett, for the BLOCK COPD Trial Group*

ABSTRACT

BACKGROUND

Observational studies suggest that beta-blockers may reduce the risk of exacerbations and death in patients with moderate or severe chronic obstructive pulmonary disease (COPD), but these findings have not been confirmed in randomized trials.

METHODS

In this prospective, randomized trial, we assigned patients between the ages of 40 and 85 years who had COPD to receive either a beta-blocker (extended-release metoprolol) or placebo. All the patients had a clinical history of COPD, along with moderate airflow limitation and an increased risk of exacerbations, as evidenced by a history of exacerbations during the previous year or the prescribed use of supplemental oxygen. We excluded patients who were already taking a beta-blocker or who had an established indication for the use of such drugs. The primary end point was the time until the first exacerbation of COPD during the treatment period, which ranged from 336 to 350 days, depending on the adjusted dose of metoprolol.

RESULTS

A total of 532 patients underwent randomization. The mean (±SD) age of the patients was 65.0±7.8 years; the mean forced expiratory volume in 1 second (FEV_1) was 41.1±16.3% of the predicted value. The trial was stopped early because of futility with respect to the primary end point and safety concerns. There was no significant between-group difference in the median time until the first exacerbation, which was 202 days in the metoprolol group and 222 days in the placebo group (hazard ratio for metoprolol vs. placebo, 1.05; 95% confidence interval [CI], 0.84 to 1.32; P=0.66). Metoprolol was associated with a higher risk of exacerbation leading to hospitalization (hazard ratio, 1.91; 95% CI, 1.29 to 2.83). The frequency of side effects that were possibly related to metoprolol was similar in the two groups, as was the overall rate of nonrespiratory serious adverse events. During the treatment period, there were 11 deaths in the metoprolol group and 5 in the placebo group.

CONCLUSIONS

Among patients with moderate or severe COPD who did not have an established indication for beta-blocker use, the time until the first COPD exacerbation was similar in the metoprolol group and the placebo group. Hospitalization for exacerbation was more common among the patients treated with metoprolol. (Funded by the Department of Defense; BLOCK COPD ClinicalTrials.gov number, NCT02587351.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Dransfield at the University of Alabama at Birmingham, 422 Tinsley Harrison Tower, 1900 University Blvd., Birmingham, AL 35294, or at mdransfield@uabmc.edu.

*A complete list of the BLOCK COPD trial group members is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 20, 2019, at NEJM.org.

N Engl J Med 2019;381:2304-14.
DOI: 10.1056/NEJMoa1908142

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. Most of COPD-related morbidity, mortality, and health care costs are driven by exacerbations, particularly those leading to hospitalization.[1,2] Since many patients have such exacerbations despite maintenance therapy, new approaches to treatment are needed.[2]

An exacerbation of COPD may be triggered or made more severe by underlying cardiovascular disease.[3] Patients with COPD have up to five times the risk of cardiovascular disease as age-matched controls,[4] and cardiovascular disease has been shown to be a risk factor for COPD exacerbations,[5] hospitalization for exacerbations,[6] in-hospital death,[7,8] and reduced survival.[9,10]

It is well established that beta-blockers reduce mortality in patients after myocardial infarction[11] and in those with heart failure.[12] Patients with COPD are often not treated with this class of medications, even when they have an evidence-based indication for the use of such drugs, because of concern about possible adverse effects on lung function.[13,14] This practice pattern persists despite multiple observational studies suggesting that beta-blockers benefit patients with COPD and coexisting cardiovascular disease, with outcomes similar to those observed in patients without COPD.[13,15,16] Several nonrandomized observational studies involving patients with COPD have also suggested that beta-blockers reduce the risk of exacerbations and death, regardless of the presence of cardiac disease.[17-20] However, these observational data are subject to biases, which has precluded determinations regarding cause and effect.[21]

In the BLOCK COPD (Beta-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) trial, we investigated the effect of the beta-blocker metoprolol, as compared with placebo, on the risk of COPD exacerbations among patients who were at high risk for such events.[22] We hypothesized that the use of metoprolol would lower the risk of exacerbations in these patients without having an adverse effect on lung function, results on a 6-minute walk test, dyspnea, or quality of life.

Methods

Trial Design and Oversight

We conducted this placebo-controlled, double-blind, prospective, randomized trial at 26 centers in the United States. The trial protocol, which was approved by the data and safety monitoring committee and the institutional review board at each trial center, is available with the full text of this article at NEJM.org. The Department of Defense funded the trial but had no role in its design, in the accrual or analysis of the data, or in the preparation of the manuscript. No commercial entity was involved in the trial. Written informed consent was obtained from all the patients.

Inclusion and Exclusion Criteria

We enrolled patients between the ages of 40 and 85 years who had received a clinical diagnosis of COPD and who had at least moderate airflow limitation, as defined by the Global Initiative for Obstructive Lung Disease (GOLD),[2] as follows: a forced expiratory volume in 1 second (FEV_1) of less than 80% of the predicted value after bronchodilation and a ratio of the FEV_1 to the forced vital capacity (FVC) of less than 0.70. We recruited patients who were at increased risk for exacerbations as indicated by at least one of the following factors: the receipt of a course of systemic glucocorticoids or antibiotic agents for respiratory problems during the previous year, a visit to an emergency department or hospitalization for a COPD exacerbation during the previous year, or the receipt of a prescription for supplemental oxygen for use at home for the treatment of COPD. The inclusion criteria were a resting heart rate between 65 and 120 beats per minute and a resting systolic blood pressure of more than 100 mm Hg. We excluded patients who had a proven indication for the use of a beta-blocker, including a history of myocardial infarction or revascularization within the previous 36 months or heart failure with a known left ventricular ejection fraction of less than 40%.[23,24]

Randomization and Intervention

Randomization was performed by a computer algorithm by means of an interactive website linked to the data coordinating center. The starting dose was one 50-mg tablet of metoprolol or matching placebo taken orally daily. Metoprolol was purchased for use in the trial; matching placebo was manufactured at the Current Good Manufacturing Practices Facility at the Temple University School of Pharmacy. For 42 days after randomization, patients underwent a dose-adjustment period on the basis of their

heart rate, systolic blood pressure, changes in FEV_1, and assessment of possible beta-blocker side effects. This dose adjustment resulted in a final daily dose of 25 mg, 50 mg, or 100 mg. Patients were followed until completion of the day 336 visit, after which they were weaned off either metoprolol or placebo, and were monitored for symptoms of beta-blocker withdrawal until the day 378 visit.

PRIMARY AND SECONDARY END POINTS

The primary end point was the median time until the first COPD exacerbation of any severity during the treatment period, which was defined as the period from randomization to day 336 for the patients receiving a final dose of 25 mg of metoprolol or placebo or until day 350 for those receiving a dose of 50 mg or 100 mg. This difference in treatment period according to dose was due to the additional time necessary to wean patients from the 50-mg and 100-mg dose levels.

An exacerbation of COPD was defined as an increase in or a new onset of two or more of the following symptoms: cough, sputum production, wheezing, dyspnea, or chest tightness that led to treatment with antibiotics or systemic glucocorticoids for at least 3 days.[25,26] The severity of the exacerbation was graded according to the following scale: mild (involving only home management, with or without contact with a health care provider), moderate (leading to a visit to an emergency department), severe (leading to hospitalization), and very severe (leading to intubation and mechanical ventilation). Key secondary end points included the rate of COPD exacerbations, all-cause mortality, all-cause hospitalization, results of spirometry, distance on the 6-minute walk test, dyspnea assessments, and measures of quality of life.

TRIAL VISITS

During in-clinic visits and telephone calls, the patients were queried regarding the efficacy and safety of the trial treatment, including providing details regarding any possible beta-blocker side effects. Spirometry and 6-minute walk tests were performed according to American Thoracic Society–European Respiratory Society guidelines.[27,28] Data regarding spirometry that was performed after bronchodilation are presented as a percentage of predicted reference values.[29] We evaluated the patients' disease-specific quality of life using scores on the St. George's Respiratory Questionnaire[30] and the COPD Assessment Test[31] and assessed the level of dyspnea using the modified Medical Research Council (mMRC) scale[32] and the San Diego Shortness of Breath Questionnaire[33] (SOBQ). In addition, we measured the 6-minute walk distance at baseline, at the day 112 visit, and at the day 336 visit. (Scores on the St. George's Respiratory Questionnaire range from 0 to 100, with lower scores indicating better functioning and with a minimal clinically important difference [MCID] of 4 points.[30] Scores on the COPD Assessment Test range from 0 to 40, with lower scores indicating better functioning and with a MCID of 2 points.[31] Scores for dyspnea on the mMRC scale range from 0 to 4, with higher scores indicating more severe breathlessness.[32] Scores on the San Diego Shortness of Breath Questionnaire range from 0 to 120, with higher scores indicating more severe breathlessness and with an MCID of 5 points.[33])

MONITORING PLAN, INTERIM ANALYSIS, AND EARLY TERMINATION

The data and safety monitoring committee met approximately every 6 months to review recruitment, follow-up rates, safety, and efficacy results. Reviews of outcome data involved multiple statistical testing procedures performed on a set of accumulating data, with the use of a sequential monitoring plan based on the alpha spending approach.[34]

After the first interim analysis on November 30, 2018, the committee recommended that the trial be continued but planned to reconvene before the second interim analysis to review serious adverse events. On March 21, 2019, the committee recommended that the trial be stopped on the basis of the conditional power analyses and concern about safety. (Details regarding the power analyses are provided in the Supplementary Appendix, available at NEJM.org.) Patients who had not yet completed the day 336 visit were contacted early to undergo final assessments and begin weaning from metoprolol or placebo, according to the protocol.

STATISTICAL ANALYSIS

We based the sample size and considerations for statistical power on the primary end point of the time until the first exacerbation of COPD. On the basis of data from previous clinical trials of a similar design,[25,26] we estimated that 65% of the patients in the placebo group would have an

exacerbation during the 1-year trial and that metoprolol would reduce this risk to 55%. Sample-size calculations that included a two-sided alpha level of 0.05 and a trial power of 90% indicated we would need to enroll 1028 patients on the assumption of a loss to follow-up of approximately 12%.

The primary analysis was based on Kaplan–Meier survival curves that described the probability of remaining exacerbation-free in each of the two groups. We used the log-rank test to compare the two curves. As secondary analyses, we used both unadjusted and adjusted Cox proportional-hazards models to assess the association between the trial-group assignment and the time until the first COPD exacerbation. Adjusted models included the covariates of race, sex, baseline age, FEV_1 as a percentage of the predicted value, smoking status, heart rate greater than the median value, number of hospitalizations for COPD during the previous year, number of exacerbations treated with glucocorticoids or antibiotics during the previous year, use of supplemental oxygen, scores on the COPD Assessment Test and the mMRC scale, and trial center.

We used Kaplan–Meier methods and Cox models to perform similar analyses of overall survival and used negative binomial regression models to analyze exacerbation rates. We used Student's t-tests to compare annualized rates of hospitalization and nonfatal serious adverse events and used mixed-effects models with patient-specific random intercepts to compare between-group differences in changes in continuous measures of secondary end points. All the analyses are based on the intention-to-treat principle.

RESULTS

PATIENTS

From May 2016 through March 2019, a total of 532 patients underwent randomization (268 to the metoprolol group and 264 to the placebo group). The most common reasons for exclusion were not meeting the spirometric criteria for COPD or a resting heart rate that was out of the mandated range. Details regarding screening, randomization, and follow-up are provided in Figure 1.

The demographic and clinical characteristics of the patients at baseline are provided in Table 1, with a full list provided in Table S1 in the Supplementary Appendix. The mean (±SD) age of the patients was 65.0±7.8 years, the mean FEV_1 was 41.1±16.3% of the predicted value, and the mean smoking exposure was 50.1±29.1 pack-years.

COPD EXACERBATIONS

There was no significant between-group difference in the median time until the first exacerbation, which was 202 days (95% confidence interval [CI], 162 to 282) in the metoprolol group and 222 days (95% CI, 189 to 295) in the placebo group (Fig. 2A). The unadjusted hazard ratio for the comparison between metoprolol and placebo was 1.05 (95% CI, 0.84 to 1.32; P=0.66), which was similar after adjustment (hazard ratio, 1.12; 95% CI, 0.88 to 1.42). For the time until the first exacerbation of moderate severity or greater, the unadjusted hazard ratio was 1.47 (95% CI, 1.06 to 2.04) and the adjusted hazard ratio was 1.46 (95% CI, 1.03 to 2.06) (Fig. S1A). For severe or very severe exacerbations, the unadjusted and adjusted hazard ratios were 1.91 (95% CI, 1.29 to 2.83) and 2.08 (95% CI, 1.37 to 3.14), respectively (Fig. 2B). The result of the subgroup analysis of the risk of exacerbation is provided in Figure S2.

We found no evidence of a between-group difference in the overall rates of exacerbation, with a rate per person-year of 1.40 (95% CI, 1.21 to 1.61) in the metoprolol group and 1.33 (95% CI, 1.15 to 1.54) in the placebo group (rate ratio, 1.05; 95% CI, 0.85 to 1.28). There was evidence that the metoprolol group had a higher rate of more severe exacerbation than the placebo group, with a rate ratio of 1.51 (95% CI, 1.00 to 2.29) for severe exacerbation and 3.71 (95% CI, 1.10 to 16.98) for very severe exacerbation (Table 2 and Fig. S3).

MORTALITY

During the treatment period, there were 11 deaths in the metoprolol group and 5 in the placebo group, with unadjusted and adjusted hazard ratios for death of 2.18 (95% CI, 0.76 to 6.29) and 2.13 (95% CI, 0.69 to 6.42), respectively (Fig. S1B). The majority of deaths in the metoprolol group were attributed to COPD (7, vs. 1 in the placebo group) (Table 3). After the treatment period, there were 3 additional deaths in the metoprolol group (at 10 to 277 days after the last dose) and 4 additional deaths in the placebo group (at 10 to 26 days after the last dose).

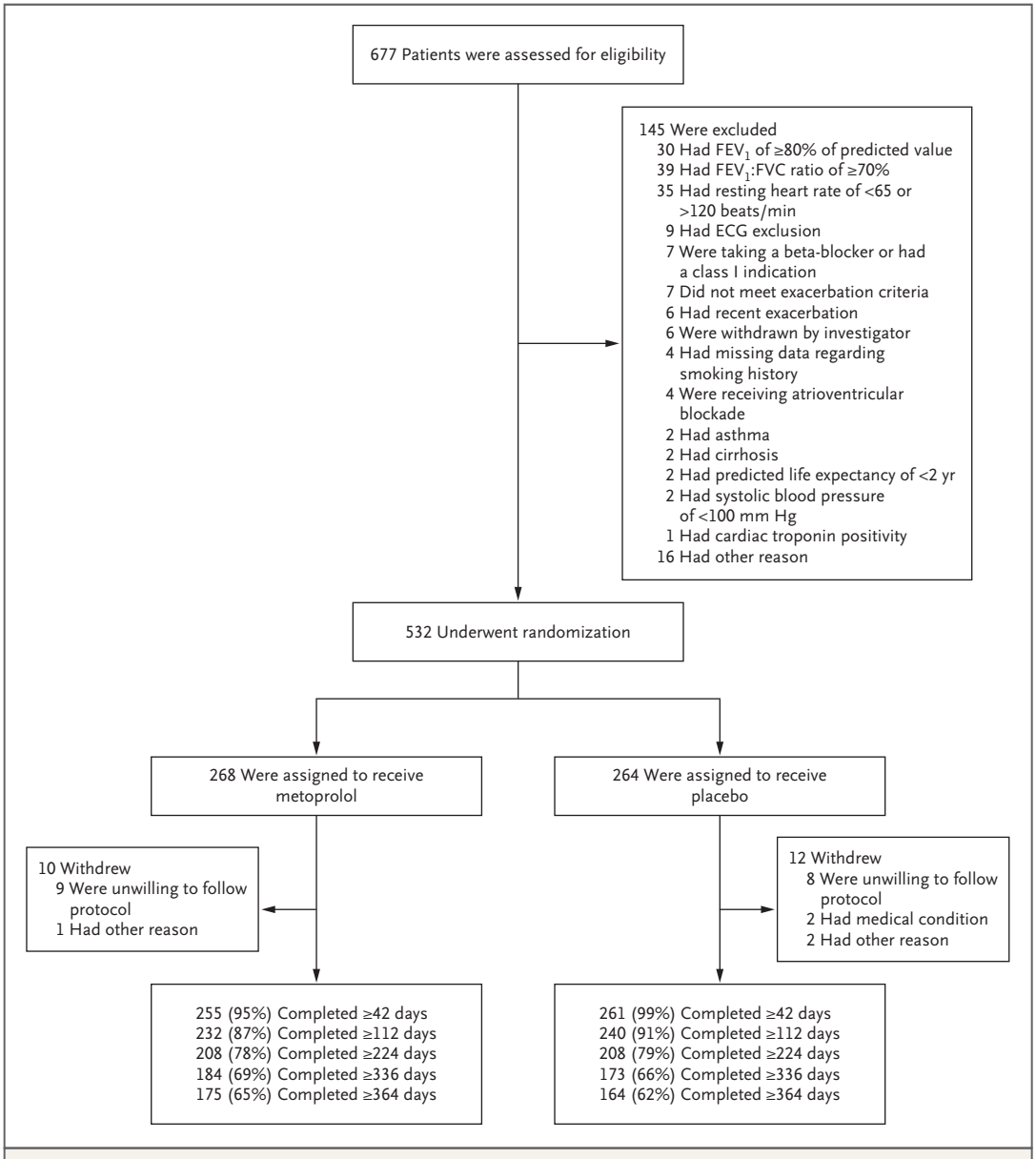

Figure 1. Screening, Randomization, and Follow-up.

Among the 145 patients who were excluded from the trial, several had more than one reason for exclusion. Patients were excluded from the trial if they had a class I indication for receipt of a beta-blocker (a history of myocardial infarction or revascularization within the previous 36 months or heart failure with a known left ventricular ejection fraction of less than 40%), according to the guidelines of the American College of Cardiology and the American Heart Association. ECG denotes electrocardiography, FEV_1 forced expiratory volume in 1 second, and FVC forced vital capacity.

HOSPITALIZATION AND NONFATAL SERIOUS ADVERSE EVENTS

The rate of hospitalization for any cause was 0.66 per person-year (95% CI, 0.47 to 0.86) in the metoprolol group and 0.42 per person-year (95% CI, 0.30 to 0.55) in the placebo group. The rate of overall nonfatal serious adverse events was 0.65 per person-year in the metoprolol group and 0.43 per person-year in the placebo group. Nonfatal, serious COPD exacerbations occurred at a rate of 0.43 per person-year and 0.19 per person-year, respectively (Table 3 and Table S2).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Metoprolol (N=268)	Placebo (N=264)
Age — yr	65.2±7.6	64.8±7.9
Race — no. (%)†		
White	178 (66.4)	194 (73.5)
Black	83 (31.0)	60 (22.7)
Other	7 (2.6)	10 (3.8)
Female sex — no. (%)	124 (46.3)	123 (46.6)
FEV_1 after bronchodilation — % of predicted value	41.3±16.3	40.8±16.2
FEV_1:FVC ratio — %	44.2±11.7	45.2±21.6
Smoking history		
No. of pack-yr	50.7±28.7	49.5±29.6
Current smoker — no. (%)	95 (35.4)	71 (26.9)
COPD medication — no. (%)		
Inhaled glucocorticoid, LABA, and LAMA	154 (57.5)	160 (60.6)
Inhaled glucocorticoid and LABA	45 (16.8)	51 (19.3)
LAMA only	20 (7.5)	17 (6.4)
LABA and LAMA	11 (4.1)	13 (4.9)
Inhaled glucocorticoid and LAMA	8 (3.0)	6 (2.3)
Inhaled glucocorticoid only	5 (1.9)	2 (0.8)
Other	25 (9.3)	15 (5.7)
Heart rate — beats/min	85.5±10.8	83.6±11.7
Blood pressure — mm Hg		
Systolic	128.4±16.5	130.6±15.9
Diastolic	77.2±9.2	76.8±9.1
No. of courses of systemic glucocorticoids or antibiotic use in previous 12 mo	1.9±1.5	1.9±1.7
No. of hospitalizations in previous 12 mo	0.7±1.0	0.5±1.2
Score on COPD Assessment Test‡	20.1±7.3	21.3±7.3
Score of >1 on modified Medical Research Council scale — no. (%)§	164 (61.2)	169 (64.0)
Enrollment criteria — no. (%)		
Systemic glucocorticoid or antibiotic use in previous 12 mo	246 (91.8)	228 (86.4)
COPD exacerbation leading to emergency department visit or hospitalization in previous 12 mo	168 (62.7)	133 (50.4)
Prescription or use of supplemental oxygen in previous 12 mo	106 (39.6)	106 (40.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. COPD denotes chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, LABA long-acting beta agonist, and LAMA long-acting muscarinic antagonist.
† Race was reported by the patients.
‡ Scores on the COPD Assessment Test range from 0 to 40, with lower scores indicating better functioning and with a minimal clinically important difference of 2 points.
§ Scores for dyspnea on the modified Medical Research Council scale range from 0 to 4, with higher scores indicating more severe breathlessness.

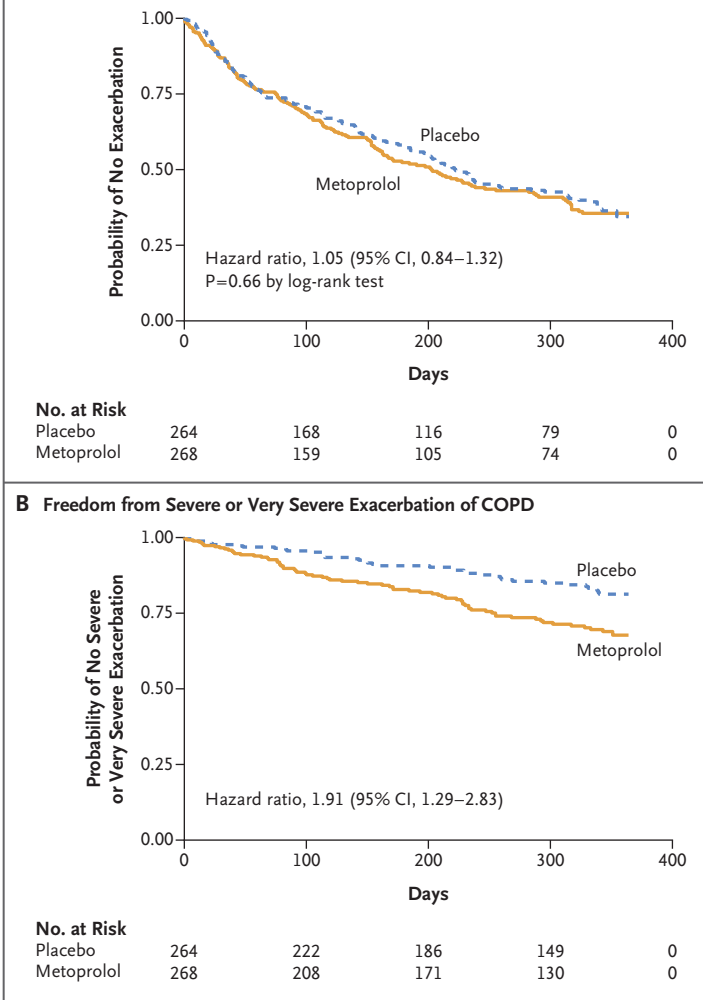

Figure 2. Exacerbations of Chronic Obstructive Pulmonary Disease (COPD).
Panel A shows the Kaplan–Meier estimate of freedom from exacerbation of COPD in the two trial groups. The median time until the first exacerbation was 202 days in the metoprolol group and 222 days in the placebo group. Panel B shows the probability of freedom from either a severe exacerbation (leading to hospitalization) or a very severe exacerbation (leading to hospitalization with intubation and mechanical ventilation). Severe or very severe exacerbations occurred in 26.1% of the patients in the metoprolol group and in 14.8% of those in the placebo group.

OTHER PRESPECIFIED MEASURES

There were no significant between-group differences in several prespecified measurements, including the change from baseline in the FEV_1, in the 6-minute walk distance, and in the score on the St. George's Respiratory Questionnaire (Figs. S4, S5, and S6). The patients in the metoprolol group had a greater increase (indicating worse control) from baseline in the score on the COPD Assessment Test than those in the placebo group, with a difference of 1.13 points (95% CI, 0.06 to 2.20) at day 112 and a difference of 1.47 points (95% CI, 0.32 to 2.62) at day 336 (Fig. S7). The metoprolol group also had a greater increase in SOBQ scores from baseline, indicating a worsening in shortness of breath. The between-group difference in the change from baseline was 3.47 points (95% CI, 0.42 to 6.52) at day 112 and 4.80 points (95% CI, 1.52 to 8.07) at day 336 (Fig. S8).

ADVERSE EVENTS AND DISCONTINUATIONS

We observed no evidence of between-group differences in the frequency of patient-reported adverse events that were potentially related to metoprolol (Table S3). Patients in the metoprolol group had a lower mean heart rate than those in the placebo group (difference, 6 to 10 beats per minute) (Fig. S9). Smaller and less consistent effects were seen for systolic and diastolic blood pressure. The discontinuation of metoprolol or placebo occurred more frequently in the metoprolol group than in the placebo group (11.2% vs. 6.1%). The most common reason for discontinuation was an increase in respiratory symptoms (Table S4).

DISCUSSION

In this prospective, multicenter, randomized trial, we did not find evidence of a difference in the risk of COPD exacerbation between the metoprolol group and the placebo group, although the use of metoprolol was associated with a higher risk of exacerbation leading to hospitalization. These results differ from previously reported findings from observational studies suggesting that beta-blockers reduce the risks of exacerbation and death from any cause in patients with COPD.[17-19] A meta-analysis of 9 studies showed that patients taking beta-blockers had a lower risk of COPD-related death than those not taking beta-blockers (relative risk, 0.69; 95% CI, 0.62 to 0.78).[18] Another meta-analysis of 15 studies also showed a lower risk of death from any cause (relative risk, 0.72; 95% CI, 0.63 to 0.83) or from COPD exacerbation (relative risk, 0.63; 95% CI, 0.57 to 0.71).[19] These observational studies have methodologic limitations inherent to their design, including the possibility of residual confounding and immortal time bias, which may have had an effect on the findings.[21]

Table 2. Rate of Exacerbation of COPD, According to Severity.

Severity of Exacerbation	Metoprolol (N=268)		Placebo (N=264)		Rate Ratio (95% CI)
	Events	Rate (95% CI)	Events	Rate (95% CI)	
	no.	*no. of events/person-yr*	*no.*	*no. of events/person-yr*	
Any severity	289	1.40 (1.21–1.61)	272	1.33 (1.15–1.54)	1.05 (0.85–1.28)
Mild	163	0.78 (0.65–0.94)	178	0.88 (0.74–1.05)	0.89 (0.69–1.15)
Moderate	34	0.17 (0.11–0.25)	36	0.18 (0.12–0.26)	0.94 (0.53–1.65)
Severe	81	0.40 (0.30–0.52)	55	0.26 (0.19–0.36)	1.51 (1.00–2.29)
Very severe	11	0.05 (0.03–0.10)	3	0.01 (0.00–0.05)	3.71 (1.10–16.98)
Moderate or greater	126	0.62 (0.50–0.77)	94	0.45 (0.35–0.58)	1.36 (0.98–1.91)
Severe or very severe	92	0.45 (0.35–0.58)	58	0.28 (0.21–0.38)	1.63 (1.10–2.42)

Table 3. Nonfatal and Fatal Serious Adverse Events.*

Event	Metoprolol (N=268)	Placebo (N=264)	P Value†
Nonfatal adverse events — no. of events per person-yr‡			
All events	0.650	0.430	0.07
Cardiovascular event			
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 event	0.004	0.004	0.99
Respiratory event			
COPD exacerbation§	0.430	0.190	0.02
Pneumonia	0.084	0.057	0.34
Other respiratory event	0.020	0.004	0.16
Fatal events — no. of patients (%)¶			
All events	11 (4.1)	5 (1.9)	0.14
COPD	7 (2.6)	1 (0.4)	—
Sudden cardiac death	0	1 (0.4)	—
Lung cancer	1 (0.4)	0	—
Sepsis	1 (0.4)	1 (0.4)	—
Unknown	1 (0.4)	2 (0.8)	—
Other	1 (0.4)	0	—

* Listed are adverse events that were reported as serious by the investigator.
† For nonfatal adverse events, P values were calculated by Student's t-test. For fatal adverse events, the P value for the overall between-group comparison was calculated by the log-rank test; P=0.17 by Fisher's exact test for the overall comparison among the causes of death.
‡ Nonfatal events are reported as rates per person-year because the patients could have had more than one event. A complete list of nonfatal serious adverse events is provided in Table S2.
§ COPD exacerbations that are listed here may not meet the protocol-defined criteria for the primary end point.
¶ After the treatment period, three additional deaths occurred in the metoprolol group (two from COPD and one from pneumonia) and four in the placebo group (one from COPD, one from lung cancer, and two from unknown causes).

A primary concern about the use of beta-blockers in patients with COPD is that the drugs may cause a worsening in lung function. We did not observe this effect, and none was reported in a meta-analysis on the subject.[35] We also found no evidence of between-group differences in the 6-minute walk distance or in patients' reports of possible beta-blocker side effects. However, metoprolol was associated with worsening of dyspnea and of the overall burden of COPD symptoms, as measured by the shortness-of-breath questionnaire and the COPD Assessment Test (although not on the St. George's Respiratory Questionnaire). In addition, more discontinuations occurred in the metoprolol group than in the placebo group, which suggests the presence of adverse respiratory effects not captured by spirometry.

Our trial has several limitations. First, although the investigators and patients were unaware of trial-group assignments, it was not possible to fully blind the effects of beta blockade, which resulted in reductions in heart rate and blood pressure. Second, our trial population had moderate or severe COPD with a high prevalence of supplemental oxygen use and previous hospitalization for COPD. Thus, we do not know whether our results would apply to patients with mild airflow obstruction or a lower exacerbation risk. Third, in part because the trial was stopped early, we had limited power to detect differences in the risk of severe exacerbation between subgroups and could not identify specific factors that predisposed patients to adverse outcomes when treated with metoprolol. Fourth, we do not know whether these results would be similar for other cardioselective beta-blockers or for noncardioselective agents, although concern regarding adverse respiratory effects is greater with the latter.[36] Finally, we did not enroll patients who had a proven indication for the use of a beta-blocker or who were already taking the drugs, so our results do not inform the risk of COPD exacerbations with metoprolol in such patients.

The risk of exacerbations of COPD was similar in the metoprolol group and the placebo group among patients with moderate or severe COPD who were at increased risk for exacerbations and had no proven indication for beta-blockers. Although observational studies have suggested that the benefits of beta-blockers in patients with recent myocardial infarction and heart failure extend to those with COPD,[15,19] this hypothesis has not been prospectively confirmed, and randomized trials to determine the overall risk–benefit ratio in such patients may be needed.

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APPENDIX

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