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

PRINCIPAL INVESTIGATOR: Mark T. Dransfield, MD

CONTRACTING ORGANIZATION: University of Alabama, Birmingham, AL

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13. SUPPLEMENTARY NOTES

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. We completed the primary project early, and the New England Journal of Medicine published our finding in October 2019. The results strongly indicate that patients with COPD and at risk for exacerbation should not be prescribed beta-blockers in the absence of an established indication for the drugs such as recent myocardial infarction or heart failure. These results raise important questions about the use of beta- blockers in patients with COPD and myocardial infarction. To address these questions and bolster the findings of the primary project, we are conducting an observational study of beta-blockers in patients with COPD and myocardial infarction as an additional task to the approved statement of work. Major activities for this reporting period centered on concluding enrollment and follow-up at all clinical sites.

15. SUBJECT TERMS

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

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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.

The study was stopped early due to futility for the primary endpoint and safety concerns. We randomized 532 participants with a mean (±SD) age of 65.0±7.8 years and FEV_1 of 41.1±16.3 % predicted. There was no difference in time to first exacerbation between groups and the hazard ratio (HR) for assignment to metoprolol was 1.05 (95%CI: 0.84-1.32; p=0.66). Metoprolol was associated with a higher risk of exacerbation requiring hospitalization (HR 1.91, 95%CI: 1.29-2.83). Patient reported possible beta-blocker side effects were similar between groups as was the overall rate of non-respiratory serious adverse events. During the treatment period, we observed 11 deaths in the metoprolol group and 5 in the placebo group. The results of the study strongly indicate that patients with COPD and at risk for exacerbation should not be prescribed beta blockers in the absence of an established indication for the drugs such as recent myocardial infarction or heart failure.

As noted above, retrospective observational studies have suggested that the benefits of beta-blockers in patients with recent myocardial infarction and heart failure extend to those with COPD, however, this has not been prospectively confirmed and randomized trials in those settings may be needed to assess overall risk-benefit. Though such trials are beyond the scope of the current award, we do have the opportunity to conduct a prospective, observational cohort study to examine cardiac and pulmonary outcomes in COPD patients hospitalized for acute myocardial infarction who are and are not treated with beta-blockers. Prior observational studies examining this issue were retrospective studies and have been limited by poor characterization of the COPD patients enrolled and a lack of follow-up data about pulmonary outcomes including COPD exacerbations. The results of this observational study would provide more robust data regarding the overall risk-benefit of beta-blockers in this population and provide preliminary data about the feasibility of recruitment for a subsequent randomized trial. This study has been added and approved as an additional task.

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

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 clinical trial was halted on March 21, 2019 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. Since the early stoppage, sites have completed missing forms and answered data queries. The database has been locked. A manuscript was published by the New England Journal of Medicine.

Major activities during this reporting period have centered on the following activities:

- Additional analysis and manuscript preparation.
- An ancillary Observational Study protocol that was developed and accepted by the DOD. Major activities this protocol are outlined following the summary of the clinical trial.

Clinical Trial Activities

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**

Specific Aims to accomplished through the conduct of the proposed observational study

Specific Aim 1. 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.

Patients admitted to the hospital with myocardial infarction (both ST-elevation and non-ST-elevation) will be identified through the electronic medical record and approached for participation in the study. Baseline characterization will include demographics, smoking history, presence of COPD by patient self-report and by physician documentation, prior history of exacerbations in the year before admission, supplemental oxygen use, respiratory and cardiac medication use, comorbidities and pulmonary

function data as available in the EMR. Results of this Aim will provide data about the prevalence and clinical characteristics of COPD in the hospitalized population with MI in our network. The Aim will also provide an estimate of the number of annual admissions for patients with COPD and MI.

Specific Aim 2. To determine the association between beta-blocker use at discharge and cardiopulmonary outcomes in patients with COPD and myocardial infarction.

Patients with self-reported or physician-diagnosed COPD will be followed prospectively from the time of discharge using both review of the electronic medical record as well as periodic phone calls at 3 months, 6 months, 9 months and 1 year. We will determine the associations between beta-blocker use at discharge and the risk for all-cause mortality, recurrent ischemic events, and hospitalization for COPD exacerbation adjusting for baseline characteristics and COPD severity.

What was accomplished under these goals?

Major activities during this reporting period have centered on the following activities:

- Continuation of IRB and HRPO submissions and approvals for the observational study at sub-sites.
- Continued enrollment and follow up in the observational study at all sites with IRB and HRPO approval.

Activity	Timeline	Achieved
Develop study protocol	48-51 months	31 JAN 2020
IRB and HRPO approvals	51-54 months	08 APR 2022 with 90% (18 of 20) participating sites having obtained approvals
Subject recruitment	54-70 months	18 MAY 2022.
Data analysis	70-72 months	
Submission of publication	72 months	

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 randomized controlled study protocol. PMID: 27267111.

During the fourth reporting period, the following article was published 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, efforts will focus on the 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. We will complete follow up efforts in the observational study at approved sites, conduct data analysis and development of manuscript(s) for publication.

IMPACT:

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

In the 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. 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 NEJM article

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

See NEJM article

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Because the clinical 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. The ancillary observational study protocol was developed during the COVID -19 pandemic and therefore includes options for enrolling participants that take into consideration the possibility of limited access to hospitalized patients. Option 1 or 2 are preferable if local guidance permits.

> Option 1: A total of 3 visits including 1 in person visit in the hospital and 2 follow up phone calls with EMR review at 3 and 6 months after discharge. Sites may consider alternatives to in person consent and data collection including by telephone or video conference.

Option 2: EMR review at the time of hospital admission followed by post-discharge telephone consent and 2 follow up phone calls with EMR review at 3 and 6 months.

Option 3: EMR review at the time of hospital admission and follow-up review of the EMR at 3 and 6 months after discharge.

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 was been approved, year 5 budgets were revised to reflect changes to accommodate final analysis and presentation/publication of results at all sub sites. A one-year no cost extension was approved to conduct the observational study, and two additional one year no cost extensions were subsequently approved to extend the performance period to September 29, 2023.

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

The additional observational study protocol has been 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

Fifth Reporting period:

Nothing to report

Sixth Reporting period:

Nothing to report

Seventh Reporting period:

1. Heart Rate Variability on 10-Second Electrocardiogram and Risk of Acute Exacerbation of COPD: A Secondary Analysis of the BLOCK COPD Trial.
   MacDonald DM, Mkorombindo T, Ling SX, Adabag S, Casaburi R, Connett JE, Helgeson ES, Porszasz J, Rossiter HB, Stringer WW, Voelker H, Zhao D, Dransfield MT, Kunisaki KM.
   Chronic Obstr Pulm Dis. 2022 Apr 29;9(2):226-236. doi: 10.15326/jcopdf.2021.0264.
   PMID: 35403415 **Free PMC article.**

2. Lung Function and the Risk of Exacerbation in the β-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease Trial.

Parekh TM, Helgeson ES, Connett J, Voelker H, Ling SX, Lazarus SC, Bhatt SP, MacDonald DM, Mkorombindo T, Kunisaki KM, Fortis S, Kaminsky D, Dransfield MT.
Ann Am Thorac Soc. 2022 Oct;19(10):1642-1649. doi: 10.1513/AnnalsATS.202109-1042OC.
PMID: 35363600 Clinical Trial.

3. Beta-blocker use in patients with chronic obstructive pulmonary disease: A systematic review: A systematic review of βB in COPD.
Ruzieh M, Baugh AD, Al Jebbawi L, Edwards ES, Jia KQ, Dransfield MT, Foy AJ.
Trends Cardiovasc Med. 2021 Nov 29:S1050-1738(21)00139-0. doi: 10.1016/j.tcm.2021.11.004. Online ahead of print.
PMID: 34856338 Review.

4. Chronotropic Index and Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Secondary Analysis of BLOCK COPD.
MacDonald DM, Helgeson ES, Adabag S, Casaburi R, Connett JE, Stringer WW, Voelker H, Dransfield MT, Kunisaki KM.
Ann Am Thorac Soc. 2021 Nov;18(11):1795-1802. doi: 10.1513/AnnalsATS.202008-1085OC.
PMID: 33784233

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 developed an informational website for participants and providers. This site provided a broad overview of the trial including contact information for UAB, the DCC, the research pharmacy and all clinical sites. It is now closed

url: http://blockcopd.org/

Second reporting period:

Nothing to report.

Third reporting period:

Nothing to report

Forth-reporting period:

Nothing to report

Fifth-reporting period:

Nothing to report

Sixth-reporting period:

Nothing to report

Seventh-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

Fourth 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.

Fifth Reporting period:

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

Sixth Reporting period:

Nothing to report.

Seventh Reporting period:

Nothing to report.

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: 1.8
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: 6
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: .762
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.

Name: Vera Bittner
Project Role: Consultant
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Dr. Bittner is a cardiologist who provides expertise for the ancillary observational study.

Name: Abimbola Samuel Akinseye-Kolapo
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.48
Contribution to Project: Research Coordinator

Samuel is a research coordinator. He assists with recruiting for and conducting study related procedures for this research project.

Name: Arnissa Goggins
Project Role: Research Coordinator

Research Identifier: N/A
Nearest Person Month worked: 4.8
Contribution to Project: Arnissa is a research coordinator. She assisted with recruitment for the DoD Beta Blocker Observational Study.

Name: Cynthia Kirkesy
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 12
Contribution to Project: Cynthia is a research specialist and assists the research coordinators with phone calls and recruitment.

Minnesota DCC

Name: Erika Helgeson, Ph.D.
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Dr. Helgeson Contributes to the data analysis and authorship of papers on study outcomes.

Name: Dr. John Connett
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.9
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: 2.6
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: 2.6
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: KD Bohara Irene Olson
Project Role: Data Quality Control

Research Identifier: N/A
Nearest Person Month worked: 3
Contribution to Project: Ms. Bohara assists Ms. Voelker in creating schemas and databases for forms. She also sets up error correction and logging procedures.

Name: Kien Quan
Project Role: Tech Supp
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Kien maintains all workstation hardware, the electronic mail system, security, and statistical software. Mr. Quan provides assistance to staff on computer network applications.

University of Michigan

Name: MeiLan Han
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .42
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: 5.04
Contribution to Project: Mary Kay is a research coordinator at the University of Michigan site. She assists with recruiting for this research project.

Weil Cornell Medical College

Name: Robert J. Kaner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
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: Matthew Marcelino
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
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.

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: .45
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: .12
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: Jenny Hixon
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Jenny is the research coordinator at the Northwestern University site. She oversees the clinic visits.

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.

Name: Rhonda Lincoln
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Rhonda is the research coordinator for the University of Pittsburgh site. Rhonda is responsible for study set-up, regulatory submission recruiting and screening, and randomization study visits.

Name: Paula Consolaro
Project Role: Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Paula is the research coordinator for the University of Pittsburgh site Paula is responsible for study set-up, regulatory submission recruiting and screening, and randomization study visits.

Temple University

Name: Gerard Criner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .60
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: Delors Fehrle
Project Role: RN, Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
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: 1.2
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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Brigham and Women's Hospital

Name: Carolyn Come
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
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: .12
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: 1.2
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: .6
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.

National Jewish Health

Name: Jennifer Underwood
Project Role: Clinical Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Jennifer is the research coordinator at the National Jewish Health site. She is the point of contact for NJH queries and is responsible for resolution and data clean-up.

Mayo Clinic

Name: Megan Dulohery Scrodin
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
Contribution to Project: Dr. Scrodin is the PI for the Mayo Clinic Site. Dr. Scrodin 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: 1.2
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: Julian Silva
Project Role: Clinical Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.20
Contribution to Project: Julian maintains the research database at the UCSF site and is responsible for all ongoing communications with study participants.

UCSF - Fresno

Name: Vipul Jain
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .48
Contribution to Project: Dr. Jain is the PI for the UCSF (University of California, Fresno) site. She oversees the day-to-day research activities at this site.

Name: Yasmina Hernandez
Project Role: Clinical Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 4.6
Contribution to Project: Yasmina maintains the research database at the UCSF Fresno site and is responsible for all ongoing communications with study participants.

LA BIOMED

Name: William W. Stringer
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
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: Leticia Diaz
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Leticia is the study coordinator for this site and is responsible for screening and enrolling patients in this study.

Cleveland Clinic Foundation

Name: Umur Hatipoglu
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6

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: 1.2
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.

University of Vermont

Name: David A. Kaminsky
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
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.

North Florida Foundation for Research and Education, Inc.

Name: Peruvemba Sririam
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
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: 1.2
Contribution to Project: Paige is the study coordinator for this site. She will assist in patient recruitment and patient visits at this site.

Providence Health & Services - Washington

Name: Allison Lambert
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
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:	Joni Baxter
Project Role:	Study Coordinator
Research Identifier:	N/A
Nearest Person Month worked:	1.2
Contribution to Project:	Joni 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:

none

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 - 9/29/2023

Study Goals:

(1) Carry out a clinical trial to examine the potential role of beta-blockers in the treatment of chronic obstructive pulmonary disease (COPD).
(2) Carry out an observational study of beta-blockers in patients with COPD and myocardial infarction as an additional task.

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.

(2) Additional Observational Study Aims: A) 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 B) To determine the association between beta-blocker use at discharge and cardiopulmonary outcomes in patients with COPD and myocardial infarction.

Key Accomplishments:

- Clinical trial completed, database locked, and manuscript published in N Engl J Med (2019 DEC)
- Ancillary Observational Study approved.
- Observational study enrollment complete.
  - Total enrolled 597 enrolled, and 3548 screened.

Key Outcomes:

Publications: 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.BMJ Open. 2016 Jun 7;6(6):e012292. doi: 10.1136/bmjopen-2016-012292.PMID: 27267111

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.N Engl J Med. 2019 Dec 12;381(24):2304-2314. doi: 10.1056/NEJMoa1908142. Epub 2019 Oct 20.PMID: 31633896

Heart Rate Variability on 10-Second Electrocardiogram and Risk of Acute Exacerbation of COPD: A Secondary Analysis of the BLOCK COPD Trial.MacDonald DM, Mkorombindo T, Ling SX, Adabag S, Casaburi R, Connett JE, Helgeson ES, Porszasz J, Rossiter HB, Stringer WW, Voelker H, Zhao D, Dransfield MT, Kunisaki KM.Chronic Obstr Pulm Dis. 2022 Apr 29;9(2):226-236. doi: 10.15326/jcopdf.2021.0264.PMID: 35403415 **Free PMC article.**

Lung Function and the Risk of Exacerbation in the β-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease Trial.Parekh TM, Helgeson ES, Connett J, Voelker H, Ling SX, Lazarus SC, Bhatt SP, MacDonald DM, Mkorombindo T, Kunisaki KM, Fortis S, Kaminsky D, Dransfield MT.Ann Am Thorac Soc. 2022 Oct;19(10):1642-1649. doi: 10.1513/AnnalsATS.202109-1042OC.PMID: 35363600

Beta-blocker use in patients with chronic obstructive pulmonary disease: A systematic review: A systematic review of βB in COPD.Ruzieh M, Baugh AD, Al Jebbawi L, Edwards ES, Jia KQ, Dransfield MT, Foy AJ.Trends Cardiovasc Med. 2021 Nov 29:S1050-1738(21)00139-0. doi: 10.1016/j.tcm.2021.11.004. Online ahead of print.PMID: 34856338

Chronotropic Index and Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Secondary Analysis of BLOCK COPD.MacDonald DM, Helgeson ES, Adabag S, Casaburi R, Connett JE, Stringer WW, Voelker H, Dransfield MT, Kunisaki KM.Ann Am Thorac Soc. 2021 Nov;18(11):1795-1802. doi: 10.1513/AnnalsATS.202008-1085OC.PMID: 33784233

Patents: N/A **Funding Obtained:** N/A