ARIC Manuscript Proposal #2085

PC Reviewed: 2/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. **Full Title:** Inappropriate Avoidance? Beta-Blockers and Lung Disease

b. **Abbreviated Title (Length 26 characters):** Beta-Blockers and COPD

2. **Writing Group:**
   Writing group members: Allison Meyer, PharmD, Deborah Minor, PharmD, Kenneth Butler, PhD, Alan Penman, MD, PhD, MPH, Marcy Petrini, PhD, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AMM_ [please confirm with your initials electronically or in writing]

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3. **Timeline:** Data analysis will be conducted from February – April and a manuscript written by June.

4. **Rationale:**  
Chronic obstructive pulmonary disease (COPD) affects more than 14 million Americans and was the third leading causes of death in the US in 2007.\(^1\,^2\) Studies indicate that many patients with COPD have chronic comorbidities, including hypertension, ischemic heart disease, heart failure, and subclinical atherosclerosis.\(^3\,^5\) Management of cardiovascular conditions is vital as they contribute to increased mortality in with COPD.\(^6\) Appropriate therapy for these conditions may include beta-blockers (BB); however, these agents are...
often not prescribed for fear of worsening the patient’s lung function\textsuperscript{7} despite evidence that BB, particularly cardioselective BB, are typically well tolerated in these patients.\textsuperscript{8,9} Evidence suggests that withholding beta-blockers in COPD patients hospitalized for acute MI or heart failure exacerbation contributes to poor outcomes, including increased mortality.\textsuperscript{10-12} It has been suggested that some beta-blockers may even reduce the risk of COPD exacerbations and decrease mortality in COPD patients without cardiovascular disease.\textsuperscript{13} Due to confusion regarding appropriateness of BB therapy in patients with COPD, more evidence is needed to clarify recommendations, particularly in patients with comorbid cardiovascular conditions who would likely benefit from beta-blocker therapy.

The purpose of this study is to analyze Atherosclerosis Risk in Communities (ARIC) data with particular interests in participants with COPD and existing cardiovascular disease (i.e. CHD, heart failure, hypertension) for the presence or absence of beta-blocker use and other potential factors that may influence morbidity and mortality. Participants will also be evaluated for any documented history of COPD exacerbation or hospitalization associated with COPD or cardiovascular disease.

References


5. Main Hypothesis/Study Questions:

1. Participants with COPD and cardiovascular disease may not be prescribed beta-blockers appropriately, despite evidence that beta-blocker use would be associated with fewer hospitalizations and lower mortality.
2. Participants with CVD and COPD or COPD only who are prescribed beta-blockers will have improved outcomes compared to those with CVD and COPD or COPD only and not prescribed beta-blockers for hospitalization for COPD exacerbations, hospitalization or death from CHD/HF, and all-cause mortality.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

This will be a longitudinal study using data from the ARIC study visits 1 (1987-89) through visit 4 (1996-98). Participant data collected for this analysis will include: pulmonary history, respiratory symptoms and signs, measures of spirometry, medication history (beta-blocker use), blood pressure, hypertension status, prevalent and incident CHD and HF, and all-cause mortality. The primary outcome will be the frequency of beta blocker use. Secondary outcomes include hospitalization for COPD exacerbations, hospitalization or death from CHD/HF, and all-cause mortality. Limitations of this study include the retrospective, observational design; the use of self-reported annual follow-up data (on chronic lung disease and medication use) for classifying participants; the lack of information on reasons for beta-blocker use; and the difficulty in determining whether the COPD status of participants changed over subsequent visits (2-4).

Groups:
At visit 1 participants will grouped by self-reported COPD and CVD status into 4 groups:
- 1. COPD and CVD
- 2. COPD, no CVD
- 3. CVD, no COPD
- 4. No COPD or CVD

Definitions
For this study “COPD” will be defined in 2 ways:
- 1. currently have chronic bronchitis/emphysema = ever had, and still have, chronic bronchitis/emphysema;
- 2. currently have confirmed chronic bronchitis/emphysema = ever had, and still have, chronic bronchitis/emphysema confirmed by a doctor.

For this study “CVD” will be defined as currently having CHD and/or heart failure and/or hypertension.
Visit 1 variables to be used:

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>Visit 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>“ever had chronic bronchitis?”</td>
<td>rpaa27</td>
</tr>
<tr>
<td>“still have chronic bronchitis”</td>
<td>rpaa28</td>
</tr>
<tr>
<td>“doc confirmed chronic bronchitis”</td>
<td>rpaa29</td>
</tr>
<tr>
<td>“ever had chronic emphysema?”</td>
<td>rpaa31</td>
</tr>
<tr>
<td>“still have chronic emphysema”</td>
<td>rpaa32</td>
</tr>
<tr>
<td>“doc confirmed chronic emphysema”</td>
<td>rpaa33</td>
</tr>
<tr>
<td>Prevalent CHD</td>
<td>prvchd01</td>
</tr>
<tr>
<td>Prevalent HF</td>
<td>prevHF1</td>
</tr>
<tr>
<td>Hypertension (140/90 or higher and/or HT med use)</td>
<td>hypert05</td>
</tr>
</tbody>
</table>

MTC codes used for identifying beta-blocker use: 330000, 331000, 332000, 333000, and 369220.

Preliminary analysis:
The (unadjusted) proportion of participants using beta-blockers at each visit, by visit 1 group, is shown in the corresponding figure.

Statistical methods
Using SAS v9, we will estimate the difference among groups (using group #4 (no COPD or CVD) as the reference group) in the log-odds of using a beta-blocker (without and with adjustment for covariates):
1. using generalized linear mixed models (proc glimmix)
2. using GEE models (proc genmod)

In both cases an appropriate covariance structure will be estimated to account for the non-independence of participant outcome data over time. We will test the group*time interaction term for statistical significance.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes  
       X No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  _____ Yes  _____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)
8.a. Will the DNA data be used in this manuscript?
   ____ Yes    _X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?
   ____ Yes   ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscce.unc.edu/ARIC/search.php
   ___x___ Yes      _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)? There are no manuscript proposals related to this topic.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?
   ____ Yes    _X_ No

11.b. If yes, is the proposal
   ___ A. primarily the result of an ancillary study (list number* __________)
   ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscce.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscce.unc.edu/aric/index.php, under Publications, Policies & Forms, http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.