ARIC Manuscript Proposal # 3161

PC Reviewed: 5/8/18    Status: _____    Priority: 2
SC Reviewed: _________    Status: _____    Priority: _____

1.a. Full Title: The effects of platelet activation and aspirin use in COPD

b. Abbreviated Title (Length 26 characters): Platelets, Aspirin in COPD

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

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3. Timeline: Analysis to start immediately
4. **Rationale:**

Despite being the third leading cause of death in the United States,\(^1\) routinely prescribed medications for COPD have been limited to inhaled rather than systemic medications even though COPD is now recognized as a disease associated with systemic inflammation and its manifestations.\(^2\,^3\) Recent observational studies, including a meta-analysis have demonstrated reduced all-cause mortality among stable and exacerbated COPD patients on aspirin therapy.\(^4\,^7\) In addition, aspirin use in the general population has been associated with slower progression of emphysema, which was stronger in those with airflow obstruction.\(^8\) To our knowledge the effect of aspirin therapy on respiratory outcomes in stable COPD has not been previously explored. Aspirin inhibits platelet activity by blocking conversion of arachidonic acid and has both direct and indirect anti-inflammatory properties. Our study aims to investigate the association of aspirin use (including dose and frequency) with exacerbations, lung function decline, and mortality (all-cause mortality, respiratory and cardiovascular specific mortality) in participants with COPD. By utilizing propensity score methodology and matching, we will be better able to control for confounding by indication and unmeasured confounding in this analysis.

Furthermore, the role of platelets in the manifestation of COPD is not yet understood. Previous animal studies have documented the role of platelets and platelet activation in bronchoconstriction, bronchial reactivity, airway inflammation, and remodeling and have corroborated clinical studies suggesting a role of increased platelet activity in allergic and non-allergic asthmatics.\(^9\) COPD case status has been associated with elevation in platelet counts and platelet activation, though the implication of these findings on disease outcomes remains unclear. In a study of 109 patients with stable COPD, platelet count was significantly higher than that of 51 healthy controls and did not differ by smoking status.\(^10\) A strong correlation between platelet count and elevated levels of P-selectin, a glycoprotein expressed and secreted by activated platelets, has been reported,\(^11\) and a few studies have reported increased platelet activation in stable COPD measured directly as platelet-monocyte aggregates or as soluble markers of platelet activation.\(^12\,^15\) A recent study of patients hospitalized for COPD exacerbation found that thrombocytosis was associated with increased risk of in-hospital and 1-year mortality independent of cardiovascular events and correlated with respiratory failure and exacerbation severity.\(^4\) Our group has recently reported an association of thrombocytosis with worse COPD morbidity, including higher likelihood of prior exacerbation, worse patient reported outcomes, and GOLD group D classification in meta-analysis of two large observational cohorts of participants with stable COPD (SPIROMICS and COPDGene).\(^16\) To our knowledge no prior study has directly investigated the association between platelet activation and COPD outcomes. Our study aims to investigate the association of degree of platelet activation using serum thromboxane B2 with exacerbations, lung function decline, and mortality among participants with COPD and the general cohort.

5. **Main Hypothesis/Study Questions:**

We hypothesize that:

1. Aspirin users with COPD (defined as presence of both FEV\(_1\)/FVC ratio and FEV\(_1\) less than the lower limit of normal and constituting 11-12% of the ARIC cohort)\(^17\,^19\) at visit 1 will have fewer COPD exacerbations, reduced all-cause mortality, and slower lung function decline than non-users with COPD.
2. Participants without airflow obstruction at visit 1 who use aspirin will have slower lung function decline and reduced COPD incidence compared to non-users without airflow obstruction.
3. Higher levels of thromboxane B2 among participants with COPD at visit 1 will be associated with more frequent COPD exacerbations, increased all-cause mortality, and more rapid lung function decline.
4. Higher serum levels of thromboxane B2 among participants without airflow obstruction at baseline will be associated with more rapid lung function decline and increased incidence of COPD.

If our hypotheses are confirmed then this paper would stimulate additional research into the role that platelet activation plays in COPD and the mechanism underlying the association of aspirin with improved outcomes in COPD.

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).

**Study design:** Secondary analysis of longitudinal data using all ARIC participants consenting to non-cardiovascular studies

**Inclusion/exclusion:**

**Inclusion criteria:**
ARIC participants who completed baseline spirometry

**Exclusion criteria:**
Missing data on relevant exposure metrics (aspirin use, thromboxane B2)
Missing baseline spirometry
Potential contraindication to aspirin use such as history of upper gastrointestinal bleed
For exacerbation/mortality analyses: Missing hospitalization and/or vital status data

**Outcomes:**

**Primary Outcome:**
Hospitalizations during follow-up with diagnosis code consistent with COPD exacerbation

**Secondary Outcomes (to be explored):**
- Difference in FEV1 percent predicted between baseline and follow-up (visit two and five) measurements
- All-cause and cause-specific mortality

**Variables of Interest (including timing)**
- Aspirin use at baseline
- Serum Thromboxane B2
- Spirometry data including FEV1, FVC, and FEV1/FVC ratio at baseline and follow-up (visits two and five)
- All-cause and cause-specific mortality data
- Demographic variables (age, race, ethnicity, gender, center) at baseline assessment, as well as socio-economic variables including educational attainment
- Medical comorbidities including individual cardiovascular, metabolic, hematologic, hepatobiliary, and gastrointestinal comorbidities
- Other medication use at baseline such as statin, beta-blocker, and inhalers
- Anthropometric data including BMI
- Smoking status at baseline and number of years smoked
- Occupation and secondhand smoke exposure
- Physical activity (modified Baecke Physical Activity questionnaire)

Data analysis:
- Baseline characteristics will be compared among participants based on baseline aspirin use using t-test and chi-squared.
- A propensity score for the probability of aspirin use will be constructed using logistic regression analysis with multiple independent covariates including baseline demographics, COPD severity, smoking status, cardiovascular comorbidities, additional cardiovascular medication use and body mass index.
- For the main analysis, participants will be matched in a 1:1 ratio without replacement based on propensity score with caliper width of 0.2 times the standard deviation of the logit of the propensity score. Unconditional regression analysis will be performed on the matched sample to investigate the association of aspirin use with incidence rate of COPD exacerbations. Representation of the exacerbation variable and appropriate modeling will be determined based on exploration of the data present once dataset is received. Linear mixed models will used to model decline in lung function and mortality will be modeled as time to death using cox proportional hazards models for all-cause mortality and a competing risk analysis for cause-specific mortality.
- Covariates will be including in all longitudinal models to address residual confounding including time-varying covariates for variables that were collected at follow-up visits (such as smoking status). Additional adjustment for secondhand smoke exposure among non-smokers, occupation, and physical activity to account for time spent indoors and deconditioning will be explored.
- Effect modification by baseline COPD severity will be tested
- Sensitivity analyses investigating the association of aspirin use with COPD exacerbations, lung function decline and exacerbations during follow-up will be performed using multivariable regression, including the propensity score as a covariate, using inverse probability of treatment weighting, and stratification by propensity score quintile.
- Serum thromboxane B2 will be used to subset the participants reporting aspirin use into aspirin responders (with low or undetectable thromboxane B2)
- Association of thromboxane B2 (as a continuous variable and split into quartiles) with cross-sectional and longitudinal lung function and exacerbations (among participants with COPD at baseline) will be investigated using similar methods as described above.
- Sensitivity analysis using multiple imputation of missing values and application of weighted generalized estimating equations will be considered based on distribution and extent of missing data and loss to follow-up.
Anticipated limitations or challenges:
Misclassification of aspirin use at baseline or discontinuation over follow-up. Decreased power when performing a matched analysis. Unmeasured confounding.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes  ____ 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? __X__ 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.cscc.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)?

None identified

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.cscc.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.

References

