ARIC Manuscript Proposal # 1295

PC Reviewed: 10/09/07	**Status: __A__**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Chronic Obstructive Pulmonary Disease with Venous Thromboembolism in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): COPD and VTE in ARIC

2. Writing Group:

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

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3. Timeline:

Statistical Analysis:	September 2007 – October 2007
Manuscript Preparation:	October 2007 – November 2007
Manuscript Revision:	November 2007
Manuscript Submission:	December 2007

4. Rationale:

Chronic obstructive pulmonary disease (COPD) encompasses chronic bronchitis and emphysema, and is the fifth leading cause of death worldwide.[1] Symptoms of COPD include wheezing, dyspnea, sputum production, airflow obstruction, decreased expiratory flow, loss of lung elasticity, hyperinflation, and inflammatory narrowing of airways due to infiltration by neutrophils, macrophages, and CD8-positive T cells.[1,2,3]

Patients hospitalized for acute exacerbations of COPD may be at risk for developing venous thromboembolism (VTE) because of the presence of bronchial infection and decreased mobility.[4] VTE comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). Risk factors for VTE include prolonged immobility, trauma, surgery, cancer, previous VTE, increasing age, estrogen use, and congenital and acquired thrombophilic disorders.[4,5]

Few studies have shown an association between COPD and incidence of VTE. A review article reported that approximately 10% of patients with acute exacerbations of COPD suffer from DVT. The prevalence of PE has been mostly reported in autopsy series where up to 30% of cases who died from acute exacerbations of COPD had PE.[4] A study of 56 patients, 46 men and 10 women, found DVT and/or PE in 9 (~16%) cases. The investigators of this study did not find a relationship between DVT and/or PE with pulmonary function, arterial blood gas, height, weight, or disease duration,[6] which suggests decreased mobility from COPD may have contributed to DVT and PE in these patients.

The limited number of studies that have investigated the association between COPD and VTE, as well as a lack of information from large prospective studies, warrants further examination of the association between COPD and incident VTE. Therefore, we propose to examine the relationship between COPD and incident VTE in the ARIC cohort.

References:

1. Pauwels PRA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *The Lancet*. 2004/8/14;364:613-620.

2. De Palo VA. Pulmonary disease: Pneumonia, chronic obstructive pulmonary disease, asthma, and thromboembolic disease. *J Am Podiatr Med Assoc*. 2004;94:157-167.

3. Snoeck-Stroband JB, Postma DS, Lapperre TS, et al. Airway inflammation contributes to health status in COPD: A cross-sectional study. *Respir Res*. 2006;7:140.

4. Ambrosetti M, Ageno W, Spanevello A, Salerno M, Pedretti RFE. Prevalence and prevention of venous thromboembolism in patients with acute exacerbations of COPD. *Thrombosis Research*. 2003;112:203-207.

5. Tapson VF. The role of smoking in coagulation and thromboembolism in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;2:71-77.

6. ERELEL M, ÇUHADARO G Ç, ECE T, ARSEVEN O. The frequency of deep venous thrombosis and pulmonary embolus in acute exacerbation of chronic obstructive pulmonary disease. *Respiratory Medicine*. 2002/7;96:515-518.

5. Main Hypothesis/Study Questions:

We hypothesize that the incidence of VTE among participants in the ARIC cohort will be significantly higher among those with prevalent COPD compared to those without 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).

Participants from ARIC who have no history of VTE or warfarin use at baseline will be included in this study. The independent variable will be prevalence of COPD as determined by chronic symptoms (cough and sputum production) and lung function tests (FEV_1 as a percentage of predicted value, FVC as a percentage of predicted value, and FEV_1/FVC ratio). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[7] will be used to define prevalent COPD in five categories: none, stage 0, mild, moderate, and severe as shown below.

No COPD	FEV_1/FVC > 70% FEV_1 > 80% No chronic symptoms
Stage 0 COPD	FEV_1/FVC > 70% FEV_1 > 80% Chronic symptoms (cough and/or sputum production)
Mild COPD	FEV_1/FVC < 70% $FEV_1 \geq$ 80% With or without chronic symptoms
Moderate COPD	FEV_1/FVC < 70% FEV_1 < 80% With or without chronic symptoms
Severe COPD	FEV_1/FVC < 70% FEV_1 < 30%

Baseline data for chronic symptoms and lung function will be used for participants who have a VTE event between baseline and visit 2. For the remaining participants, lung function will be averaged over baseline and visit 2, and cough and/or sputum production at either one or both visits will be used to define presence of chronic symptoms. Also, we may combine moderate and severe COPD into a single category depending on the number of participants with moderate and severe COPD. Additionally, if there are not adequate numbers in the COPD categories, we may use quartiles of FEV_1 and FVC as the

independent variables. The dependent variable in this study will be incidence of VTE; however, those who have a cancer-related VTE event will be excluded from the analysis. Cox proportional hazards regression will be used to determine the hazard ratios of VTE by prevalence and severity of COPD, as well as quartiles of FEV_1 and FVC if necessary. If confounding is observed, the associations will be adjusted for the following covariates at baseline: age, sex, race, body mass index, diabetes, factor VIII and smoking status and amount. An interaction test by sex will be conducted, and analyses will be reported separately if evidence of heterogeneity by sex is present. We will also describe the percentage of VTE hospitalizations among the COPD exposure categories (COPD and no COPD at baseline/visit 2) who also had a COPD discharge diagnosis during their VTE hospitalization. Finally, we will examine the main effect of smoking on VTE and test an interaction between smoking and COPD on incidence of VTE. If the smoking-COPD interaction is significant, we will report analyses stratified by smoking status or categories of pack-years of smoking**.**

7. Pauwels RA, Buist AS, Calverley PMA, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. *Am J Respir Crit Care Med*. 2001;163:1256-1276.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

MS #708: Cardiovascular risk factors and venous thromboembolism incidence: the Longitudinal Investigation of Thromboembolism Etiology

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

11.b. If yes, is the proposal

__X_ A. primarily the result of an ancillary study (list number* __1998.03_)

___ 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/

12. 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.