**ARIC Manuscript Proposal # 1272**

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| **PC Reviewed: _7_/10_/07** | **Status: _A___** | **Priority: _2__** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Association of High-Density Lipoprotein Cholesterol and Venous Thromboembolism in the Longitudinal Investigation of Thromboembolism Etiology (LITE) Study

**b. Abbreviated Title (Length 26 characters)**: HDL-c and VTE in LITE

**2. Writing Group**:

Writing group members: Alanna Chamberlain, MPH
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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**:

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| Statistical Analysis: | July 2007 – August 2007 |
| Manuscript Preparation: | August 2007 – September 2007 |
| Manuscript Revision: | September 2007 |
| Manuscript Submission: | October 2007 |

**4. Rationale**:

Plasma levels of high-density lipoprotein cholesterol (HDL-c) are inversely related to risk of coronary heart disease (CHD). Mechanisms through which high levels of HDL-c may reduce the risk of CHD include reduced formation of atherosclerotic lesions by mediation of reverse cholesterol transport, anti-inflammatory and anti-oxidant effects, and attenuation of endothelial dysfunction.[1] However, typical CHD risk factors (such as elevated cholesterol, hypertension, and cigarette smoking) do not increase risk of venous thromboembolism (VTE).[2,3] A prospective study using LITE data found that lipid levels (total cholesterol, LDL, HDL, and TG) were not associated with VTE incidence.[3]

Despite the lack of association between traditional CHD risk factors and VTE, two recent case-control studies have suggested that HDL-c levels are inversely associated with risk of VTE. A first study compared HDL and low-density lipoprotein (LDL) particles, as well as a ratio of apolipoproteinB/apolipoprotein AI in 49 male VTE patients under the age of 55 to 49 matched controls from the Scripps Venous Thrombosis Registry. The authors concluded that VTE in these men < 55 years of age is associated with lower levels of HDL particles, and elevated levels of LDL particles and aplipoprotein B/apolipoprotein AI.[4] A second case-control study compared 71 recurrent VTE patients with 142 matched controls who had a history of one VTE within the Austrian Study on Recurrent Venous Thromboembolism on 10 major lipoprotein subclasses and HDL-c. This study found that patients with high levels of apolipoprotein AI and HDL had a decreased risk of recurrent VTE after an average follow-up of 48 months.[5]

Although these two case-control studies have suggested an inverse association between HDL-c and VTE, there were many limitations to these studies. First, the number of VTE patients included in both studies was very small. Second, only males were included in the first study. Finally, both studies were case-control studies. Also, the previous study in LITE reported only associations of VTE with HDL-c, and did not look at HDL subfractions or apolipoprotein AI. Additional VTE events have also occurred in the five years since the previous LITE study was published. We propose to determine prospectively, the risk of incident VTE by baseline HDL-c levels, as well as subfractions of HDL ($HDL_2$ and $HDL_3$) and apolipoprotein AI level in the LITE study.

References:


1. Rosenson RS. Low HDL-C: A secondary target of dyslipidemia therapy. *Am J Med*. 2005;118:1067-1077.

2. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol*. 2005;162:975-982.

3. Tsai AW, Cushman M, Rosamond W, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med*. 2002;162:1182.

4. Deguchi H, Pecheniuk NM, Elias DJ, Averell PM, Griffin JH. High-density lipoprotein deficiency and dyslipoproteinemia associated with venous thrombosis in men. *Circulation*. 2005;112:893-99.

5. Eichinger S, Pecheniuk NM, Hron G, Deguchi H, Schemper M, Kyrle PA, Griffin JH. High-density lipoprotein and the risk of recurrent venous thromboembolism. *Circulation*. 2007;115:1609-1614.

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

We hypothesize that high levels of HDL-c are associated with decreased incidence of VTE in a large combined dataset from the ARIC and CHS studies. We also wish to determine if HDL subfractions or apolipoprotein AI are better determinants of the risk of incident VTE compared to HDL-c.

**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).**

Independent variables in this study include HDL-c, and in the ARIC cohort only HDL subfractions ($HDL_2$ and $HDL_3$), and apolipoprotein AI. The dependent variable is incidence of VTE. Men and women from LITE who have no history of VTE or warfarin use at baseline will be included in this study. Participants will be categorized by quartile of HDL-c level at baseline. Incidence rates of VTE will be calculated using Poisson regression models, and hazard ratios of VTE will be compared between participants in different HDL-c quartiles using Cox proportional hazards models in SAS. The association between HDL-c and incident VTE will be adjusted for the following covariates: age, sex, race, study (ARIC, CHS), body mass index, diabetes, and use of cholesterol medication. Interaction tests by sex and study will be conducted, and analyses will be reported separately by sex and/or study if evidence of heterogeneity by sex or study is present. We will also examine idiopathic and secondary VTE separately in supplemental analyses and we may also conduct time-dependent analyses using HDL-c as the time-dependent variable.

**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)?**

**CHS/ARIC Proposal # 708:** Cardiovascular risk factors and venous thromboembolism incidence: The Longitudinal Investigation of Thromboembolism Etiology (LITE) Study

**ARIC Proposal # 1236:** Metabolic syndrome and risk of venous thromboembolism

**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.**