ARIC Manuscript Proposal #988

PC Reviewed: 01/20/04	**Status: A**	**Priority: 2**
SC Reviewed: 01/20/04	**Status: A**	**Priority: 2**

1.a. Full Title: Are atherosclerosis and venous thromboembolism associated?

b. Abbreviated Title (Length 26 characters):
Atherosclerosis and venous thrombosis

2. Writing Group (list individual with lead responsibility first):

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3. Timeline: Analysis to begin Fall, 2003 with manuscript submission Mar/Apr, 2004

4. Rationale:

Traditionally, atherosclerotic arterial disease and venous thrombosis were considered to occur in patient populations with distinctly different risk factors. However, in as many as one-third of patients with venous thromboembolism, the precipitating cause is unknown. In addition, many investigations have demonstrated that atherosclerosis is associated with activation of the coagulation system, leading to the question of whether this clotting propensity could be a contributing factor in the development of venous thromboembolic disease.

Venous thromboembolic disease results from activation of the coagulation system so that the homeostatic balance between bleeding and clotting is disrupted in favor of pathologic thrombosis. Similarly, atherosclerotic arteries display coagulation system activation. Stimulation of platelets and hemostatic factors in atherosclerotic arteries creates a procoagulant environment with a principal component of atherosclerotic ischemia being clot formation at the site of the atherosclerotic plaque. Several studies have demonstrated this hemostatic marker elevation in individuals with coronary heart disease. Fibrinogen, von Willebrand factor antigen, tissue plasminogen activator antigen, and factor VII activity were all elevated in subjects with a history of ischemic coronary heart disease and predicted an increased risk of future cardiac and cerebral events (1,2,3,4). Moreover, subjects with peripheral arterial disease demonstrated elevated fibrinogen and D-dimer levels (5,6,7).

It is possible that this atherosclerosis associated coagulation activation acts systemically to promote clot formation in the venous circulation. Data obtained from studies exploring a possible link between atherosclerosis and venous thrombosis suggests that both entities are likely to occur in the same individual. Libertiny and Hands found that subjects suffering from symptomatic peripheral arterial disease with a decreased ankle-brachial index had an increased risk of venous thrombotic events (8). Prandoni et al reported that subjects with a history of venous thrombosis had a higher prevalence of carotid plaques (9). However, despite the fact that both disease processes display coagulation activation, there is little investigation into this connection.

The ARIC cohort and the LITE ancillary contain ample data to explore this subject. Analysis of both carotid intima-media thickness and ankle-brachial index in relation to venous thrombosis rates could contribute valuable insight into this question and provide a direction for further investigation into this largely unexplored subject.

References

1. Wilhelmsen L, Bray PF, Tayback M et al. Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med 1984;311:501-5.
2. Meade TW, Mellows S, Brozovic M et al. Haemostatic function and ischemic heart disease; results of the Northwick Park Heart Study. Lancet 1986;2:533-7.
3. Thompson SG, Kienast J, Pyke SD et al. Haemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. N Engl J Med 1995;332:635-41.
4. Miller JG, Bauer KA, Barzeger S et al. Increased activation of the haemostatic system in men at risk of fatal coronary heart disease. Thromb Haemost 1996;75:767-71.
5. Strano A, Hoppensteadt D, Walenga JM et al. Plasma levels of the molecular markers of coagulation and fibrinolysis in patients with peripheral vascular disease. Semin Thromb hemost 1996;22(suppl 1):35-40.
6. De Buyzere M, Phillipe J, Duprez D et al. Coagulation system activation and increase D-dimer levels in peripheral arterial occlusive disease. Am J Hematol 1993;43:91-4.
7. Lowe GDO, Fowkes FGR, Dawes J et al. Blood viscosity, fibrinogen, and activation of coagulation and leukocytes in peripheral arterial disease and the normal population in the Edinburgh Artery Study. Circ 1993;87:1915-20.
8. Libertiny G, Hands L. Deep venous thrombosis in peripheral vascular disease. Br J Surg 1999;86(7):907-10.
9. Prandoni P, Bilora F, Marchiori A et al. An association between atherosclerosis and venous thrombosis. N Engl J Med 2003;348(15):1435-1441.

5. Main Hypothesis/Study Questions:

1. To determine whether decreased ABI (<.90 in males, <.85 in females) is associated with increased incidence of venous thrombosis.
2. To determine whether increased carotid intima-media thickness is associated with increased incidence of venous thrombosis.

6. Data (variables, time window, source, inclusions/exclusions):

Inclusion: For both hypotheses, the full ARIC dataset will be used.

Exclusion: Participants with a history of prevalent CHD, stroke, DVT, or PE at baseline, subjects on warfarin at baseline, subjects with incident secondary VTE

Analysis: The primary measure of association will be the hazard ratio for the diagnosis of venous thromboembolism. Routine proportional hazards will be used for both hypotheses, with and without covariates.

- Independent variables: baseline ABI, IMT
- Dependent variable: incidence of VTE, subclassified as idiopathic (n=85 at present but will be approximately 150 after inclusion of new cases)

Covariates: Age, gender, race, BMI, diabetes mellitus, hormone replacement therapy (as a time-dependent covariate)

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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

___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

11. 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.