ARIC Manuscript Proposal # 843

PC Reviewed: 11/29/01	**Status: ____A__**	**Priority: ____2___**
SC Reviewed: 12/03/01	**Status: ____A__**	**Priority: ____2___**

ARIC Manuscript Proposal

1. Full Title: Heparin Cofactor II Deficiency and Atherosclerosis Risk
   Abbreviated Title: HCII and Atherosclerosis

2. Writing Group

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3. Timeline: 1 year from receipt of plasma samples to completion of manuscript

4. Rationale:

Heparin cofactor (HC) II is a serine protease inhibitor that acts as substrate by trapping the target protease in a stable complex (1-3). HCII inhibits both thrombin and chymotrypsin and the inhibitory activity for thrombin is enhanced by the presence of heparin, heparan sulfate or dermatan sulfate by more than 1000-fold. Congenital deficiency of HCII associated with thrombosis has been reported in several families. Bertina et al (4) indicated that the prevalence of heterozygous deficiency in population was similar between healthy subjects and patients with venous thromboembolism. Thus, HCII deficiency has been thought to represent a modest clinical risk factor for venous thrombosis. However, in view of the fact that HCII is activated by its binding to dermatan sulfate present in vascular walls, HCII may also play a role in preventing thrombin action and protecting from atherosclerotic changes of injured arterial walls. Kanagawa Y et al (5) reported a case with type I congenital HCII deficiency

manifesting multiple atherosclerotic lesions at coronary artery, internal carotid arteries, renal artery and abdominal artery. In addition, mice with deficiency of the thrombin inhibitor heparin cofactor II have a significantly shorter time to thrombotic occlusion of the carotid artery after photochemical injury to the endothelium.

5. Main hypothesis/study questions:

   Is heparin cofactor II deficiency a risk factor for atherosclerosis in humans?

6. Data: We propose to determine HCII activity and antigen levels in baseline plasma samples of subjects who have developed coronary heart disease and in a stratified random sample of the entire ARIC cohort.

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

8. Will the DNA data be used in this manuscript? No

9. Review of existing ARIC Study manuscript proposals:

References:

1. Tollefsen DM et al. Heparin cofactor II. Purification and properties of a heparin-dependent inhibitor of thrombin in human plasma. J Biol Chem 1982;257:2162-9.
2. Ragg H. A new member of the plasma protease inhibitor gene family. Nucleic Acids Res 1986;14:1073-88.
3. Tollefsen DM. Insight into the mechanism of action of heparin cofactor II. Thromb Haemost 1995;74:1209-14.
4. Bertina RM et al. Hereditary heparin cofactor II deficiency and the risk of development of thrombosis. Thromb Haemost 1987;57:196-200.
5. Kanagawa Y et al. Molecular mechanism of type I congenital heparin cofactor (HC) II deficiency caused by missense mutation at reactive P2 site: HCII Tokushima. Thromb Haemost 2001;85:101-7.