ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #543B

l. Full Title: Association of Soluble Thrombomodulin Levels with Incident Coronary Heart Disease and Asymptomatic Carotid Atherosclerosis; the ARIC Study

Abbreviated Title: Thrombomodulin and CHD

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3. Timeline:
Soluble thrombomodulin (STM) measurements have been completed. Data analyses can begin as soon as data arrives at Chapel Hill. First draft of the manuscript should be ready during spring 1998.

4. Rationale:
Hemostatic factors play an important role in the pathogenesis of atherothrombotic diseases. In this study we propose to evaluate the association of plasma STM levels with incident coronary heart disease (CHD) and asymptomatic carotid atherosclerosis. Thrombomodulin is an endothelial integral membrane glycoprotein with a major role in the regulation of intravascular coagulation (1-3). It functions as a thrombin receptor and accelerates activation of protein C. Activated protein C in the presence of protein S,inactivates factors VIIIa and Va, thereby inhibiting thrombin formation.

Thrombomodulin also acts as a competetive inhibitor of fibrinogen clotting, inhibits thrombin activation of platelets and blocks thrombin binding to the platelet surface (1). It also accelerates the inactivation of prourokinase, suggesting a regulatory role in the cellular fibrinolytic system. The cell-surface expression of thrombomodulin has been reported to increase in vitro in response to CAMP, retinoic acid and thrombin and decrease in response to endotoxin, hypoxia, interleukin-l, tumor necrosis factor-a and homocysteine (4). Thrombomodulin can also be found in plasma as a soluble form, probably released by leukocyte proteases or activated proteolytic enzymes in the coagulation-fibrinolytic system; the soluble form is considered to be a marker of endothelial cell injury (5-6). Increased levels of antigenic component have been reported in thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, atherosclerosis, connective tissue diseases, pulmonary thromboembolism, acute respiratory distress syndrome, chronic and acute renal failure, acute hepatic failure, thalassemia, diabetic angiopathy (7-9). Few studies have reported plasma thrombomodulin levels in atherosclerosis and ischaemic heart disease (7,8), which gave inconsistent results. In order to attain sufficient power for valid analysis, prospective studies involving large sample size are needed. The ARIC Study is well suited for determining the potential role of plasma levels of thrombomodulin as a risk factor for acute ischaemic events (10). We propose to look at the inter-relations of thrombomodulin with the other hemostatic factors measured at baseline.

5. Main Hypothesis:
The plasma STM levels are associated positively with asymptomatic atherosclerosis and incident CHD, independent of other major risk factors.

6. Data (variables, time window, source, inclusions/exclusions):
STM measured by ELISA technique has been completed in 2048 baseline samples (carotid atherosclerosis cases, incident CHD cases and cohort random sample). These will be analysed using the case-cohort design. Persons with prevalent CHD or history of stroke or TIA at baseline will be excluded. Important covariates include age, race, field center, "standard" CVD risk factors, other hemostatic factors, esp. fibrinogen.

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