ARIC MANUSCRIPT PROPOSAL FORM

Manuscript # 437

1. a. Title: Association of Factor XII activation with risk of coronary heart disease: The ARIC Study

b. Abbreviated title: FXIIa and CHD

2. Writing group:

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3. Timeline:

Activated coagulation factor XII (XIIa) will be measured in incident coronary heart disease (CHD) cases and carotid thin-walled controls (about 737 samples) by an enzyme-immunoassay. Methodology is established and works well in terms of intralaboratory assay variability. Measurement will be completed in approximately one month, beginning in February 1996.

4. Rationale:

The contact system of blood coagulation is an important defense system in the human organism (1). In response to negatively charged surfaces, factor XII (Hageman factor) is activated to produce XIIa, that has been shown to enhance fibrinolytic system, and both the intrinsic and extrinsic clotting systems (2). Excessive activity of the two pathways of coagulation may thus contribute to a state of hypercoagulability and enhanced risk of arterial thromboembolism.

Fibrinogen is now recognized as a risk factor for atherosclerotic events such as MI. Factor VII may be associated with MI related mortality (3). It has been postulated that factor VII activation requires activation of factor XII. Factor XII level is reported to be associated with thrombosis, but the relationship between factor XIIa and thrombotic disorders has not been yet determined.

The goal of the proposed writing group is to evaluate if individuals with incident CHD have significantly higher levels of factor XIIa, due to increased activation of factor XII, than controls, after statistical adjustment for other risk factors for atherosclerosis. We propose to study about 313 incident CHD cases and 343 carotid thin-walled controls. Measurement of factor XIIa will be performed using recently designed direct enzyme immunoassay with monoclonal antibody specific for XIIa (Shield Diagnostics, Dundee, UK).

This study will gain insight into the role of XII activation in arterial thrombotic diseases and may shed light on the interaction between XII and VII activation.

5. Main hypothesis:

The increased rate of activation of factor XII is associated with higher risk of incident CHD.

6. Data analysis:

All the laboratory data will be transmitted to the Coordinating Center. Data will be anslyzed at the CC. In the analyzing data, special attention will be paid to the incident case-control nature of selection.

REFERENCES:

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2. Wachtfogel, Y.T., DeLa Cadena, R.A., Coman, R.W. Structural biology, cellular interactions and pathophysiology of the contact system. Thromb Res 72: 1021, 1993.

3. Meade,T.W., Mellows, S., Brozovic, M., Miller G.J., Chakrabarti, R.R., North, W.R.S., Haines, A.P., Stirling, Y., Imeson, J.D., Thompson, S.G. Haemostatic function and ischaemic heart disease: Principal results of the Northwick Park Heart Study. Lancet, 2: 533-37, 1986.