ARIC Manuscript Proposal #747

PC Reviewed: 10/17/00	**Status: __A__**	**Priority: __1__**
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1.a. Full Title: Effect of interaction between plasma soluble thrombomodulin (sTM) and soluble intercellular adhesion molecule-1 (sICAM-1) on predicting risk of incident coronary heart disease (CHD).

b. Abbreviated Title (Length 26 characters): sTM/sICAM-1 and CHD.

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

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3. Timeline: 9/00 analysis
12/00 begin writing

4. Rationale: Thrombomodulin (TM) is constitutively expressed on endothelial surface (1). It binds to thrombin and alters its conformation which converts it from a pro-thrombotic and pro-fibrinolytic to an anti-thrombotic and anti-fibrinolytic molecule (1-3). Thus, thrombomodulin is considered as an important vasoprotective molecule. TM is normally cleaved and its fragments circulate in the blood as soluble TM (4). Plasma sTM levels have been considered a marker of endothelial injury (5-8). However, recent ARIC analysis has shown that plasma sTM levels are inversely associated with risk of incident CHD (9). The adjusted risk ratio of the highest quintile of sTM ($\geq$55.3 ng/ml) compared with the lowest quintile (<24.7 ng/ml) was 0.29 (95% CI 0.15 – 0.57). These results have led us to postulate that in subjects without cardiovascular or other illnesses, a high plasma sTM reflects a high level of cellular TM expression and therefore protects against acute arterial thrombosis. Experimental data have shown that cellular TM expression is downregulated by proinflammatory mediators such as tumor necrosis factor, interleukin-1 and endotoxins (10,11) and cleavage of TM may be accelerated by activated neutrophil enzymes. Thus, plasma sTM levels are determined by multiple mechanisms. Analysis of the relationship of CHD with sTM alone may be masked by inflammation. We, therefore, propose to evaluate the effect of interaction between sTM and sICAM-1 on risk of incident CHD. The rationale

is that sICAM-1, a cleaved product of cellular ICAM-1 is a marker of inflammatory endothelial injury and is shown in the ARIC nested CHD case-cohort study to be positively associated with incident CHD (12). We reason that individuals with high level of sTM will be associated with a low CHD risk regardless of sICAM-1 level. Furthermore, individuals with a low sTM and high sICAM-1 will have a marked increase in CHD risk. To examine this, we will analyze interaction between sTM and sICAM in ARIC is nested CHD case-cohort study (i.e. Table 2).

5. Main Hypothesis/Study Questions:

a. There is an interaction between plasma sTM and sICAM-1 levels.

b. The top tertile of sTM is associated with low CHD risk regardless of sICAM-1 levels, and a low sTM with a high sICAM-1 is associated with high CHD risk.

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

CHD cases and random cohort sample

For this analysis, we will include 317 incident CHD and 726 individuals from the cohort random sample (follow-up period ended December 31, 1996). Their plasma sTM and sICAM-1 levels had been measured by the Central Hemostasis and Central Lipid Laboratory, respectively. These cases and cohort random sample have been described in sTM paper by Salomaa et al (9) and in sICAM-1 paper by Hwang et al (12).

Analysis

Interaction between the upper and lower tertiles of sTM and sICAM-1 will be analyzed by Chul Ahn. To evaluate the effects of interaction between sTM and sICAM-1 on CHD risk, we will perform weighted proportional hazard analysis to determine the adjusted risk ratio of the following three groups shown in the table below compared with the high sTM/low sICAM-1 group. The sample size for each group is also shown in the following table.

Table

	STM (tertile)	sICAM (tertile)	N
Reference Group	Upper	Lower	103
Group 1	Lower	Upper	143
Group 2	Upper	Upper	116
Group 3	Lower	Lower	108

sTM:	Upper tertile (≥43.3 ng/ml)
	Lower tertile (28.3 ng/ml)
SICAM-1:	Upper tertile (≥263 ng/ml)
	Lower tertile (<206 ng/ml)

The analysis will be performed by Chul Ahn in consultation with statisticians at the coordinating center.

References

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9. Salomaa V, Matei C, Aleksic N, et al. Soluble thrombomodulin as a predictor of incident coronary heart disease and symptomless carotid artery atherosclerosis in the ARIC study: A case-cohort study. Lancet 1999; 355: 1729-1734.
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11. Moore KL, Andreoli SP, Esmon CT, Bang NU. Endotoxin enhances tissue factor and suppresses thrombomodulin expression of human vascular endothelium in vitro. J Clin Invest 1987; 79: 124-130.
12. Hwang S-J, Ballantyne CM, Sharrett AJ, et al. circulating adhesion molecules VCAM-1, ICAM-1 and E-selectin in carotid atherosclerosis and incident coronary heart disease cases. The ARIC Study. Circulation 1997; 96: 4219-4225.

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 ICTDER01 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 ICTDER01 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 ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No