ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #596

1. Full Title: Association of thrombomodulin amino acid dimorphism (Ala455Val) with risk of myocardial infarction: the ARIC Study
Abbreviated Title (length 26): TM Dimorphism and MI

2. Writing Group (list individual with lead responsibility first):
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3. Timeline:
Measurement of TM gene polymorphism is in progress in the approved ARIC CRS and CHD incident events as by the CC.

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| Preliminary analysis | 06/98 |
| Manuscript preparation | 08/98 |
| Circulation to co-authors | 09/98 |
| Submission to journal | 10/98 |

4. Rationale:
Thrombomodulin is an integral endothelial cell membrane receptor for thrombin (1). Thrombin binding to TM results in a conformation change of thrombin which activates the protein C (PC) anticoagulant pathway. The impairment of the PC pathway is likely to contribute to risk factors for thrombosis. It has been suggested that mutations in TM or impaired TM expression might also contribute to risk factors for MI (2). It was supported by recent studies of C/T dimorphism within the coding region of the TM gene(4). This dimorphism is located in the region of TM responsible for thrombin binding and PC activation. In a Dutch investigation (4) TM dimorphism was neutral with respect to venous thrombus. At present, it is unknown what impact Ala455Val substitution has on TM function, but the possibility that dimorphism is an additional predictor of early MI deserves additional attention. Recent analysis shows that soluble TM levels are inversely correlated with incident MI and this inverse correlation was considered to be related to

TM expression. We propose to determine the frequency of C/T dimorphism (Ala455 to Val replacement) in the ARIC CHD cases and cohort random samples and its association with incident MI cases.

5. Main Hypothesis:
Presence of C/T dimorphism in TM gene is associated with an increased risk for acute myocardial infarction. Furthermore, the C/T dimorphism is correlated with the level of soluble TM.

6. Data (variables, time window, source, inclusions/exclusions):
Data will be sent to the CC and also analyzed locally by Dr Chul Ahn, with supervision from the CC.

REFERENCES:
1. Suzuki K et al. Structure and expression of human thrombomodulin, a thrombin receptor on endothelium acting as a cofactor for protein C activation.
EMBO J 6, 1891-7, 1987.
2. Ireland H. et al. Thrombomodulin gene mutations associated with myocardial infarction. Circulation 96, 15-18, 1997.
3. Norlund L, Holm J, Zoller B, Ohlin A. A common thrombomodulin amino acid dimorphism is associated with myocardial infarction. Thromb Haemost 77,
248-51 (1977)
4. van der Velden PA, Krommenhoek-Van Es T et al. A frequent thrombomodulin amino acid dimorphism is not associated with thrombophilia. Thromb
Haemost 65, 511-3, 1991.