1. Full Title: Plasminogen as a Predictor of Incident Coronary Heart Disease and Asymptomatic Carotid Atherosclerosis; the ARIC Study
Abbreviated Title: Plasminogen and CHD

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3. Timeline:
Plasminogen 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:
Plasminogen is a precursor of the primary fibrinolytic enzyme, plasmin, which plays an important role in maintaining vascular patency and has an effect also on cell migration (1). Plasmin activity is tightly controlled by plasminogen activators and inhibitors (2). Binding of plasminogen to fibrin or cell surfaces is the key event in regulating the activity of plasminogen-plasmin system. Bound plasminogen is more readily activated and is protected from inactivation by inhibitors. Lipoprotein (a), which is assumed to be an atherogenic molecule and has a considerable structural similarity with plasminogen, competes with plasminogen for binding to fibrin and cell surfaces (3,4). In vitro it can, depending on conditions, either prevent or promote plasminogen activation. Interestingly, plasminogen and apolipoprotein (a) are genetically closely linked and localized to chromosome 6 at band 6q26-27 (5). The transcription of plasminogen clearly increases in response to
interleukin-6 suggesting that it can behave as an acute phase reactant (2,6). Correlates of plasminogen are poorly known. Its levels are assumed to be similar in men and women, but in women a decrease with age has been reported (7). Several reports have shown that oral contraceptive use and hormone replacement therapy are associated with higher plasminogen levels in women (8-10). No prospective studies on plasminogen as a predictor of coronary events have been published and cross-sectional studies have given conflicting results. A report from Germany (11) has found a positive association between plasminogen and the extent of coronary atherosclerosis in angiography, whereas in Finland no association between prevalent CHD and plasminogen was found (12). The large material and prospective nature of the ARIC Study provides a possibility to obtain a more definitive answer on the relationship of plasminogen with incident CHD and asymptomatic carotid atherosclerosis. We propose to investigate also, whether the predictive power of plasminogen is dependent on the levels of Lp(a), tissue plasminogen activator, or plasminogen activator inhibitor-1.

5. Main hypothesis:
The plasma plasminogen levels are positively associated with incident CHD events and asymptomatic carotid atherosclerosis, independently of "standard" CVD risk factors.

6. Data (variables, time window, source, inclusions/exclusions):
Plasminogen measurements have been completed in incident CHD cases, carotid atherosclerosis cases and in cohort random sample. These will be analyzed using the case-cohort design. Persons with prevalent CHD or history of stroke or TIA at baseline will be excluded. Main covariates include age, race, field center, "standard" CHD risk factors, Lp(a), t-PA, PAI-1, fibrinogen, other hemostatic risk factors, WBC, CRP.

REFERENCES:
9) Meilahn EN, Kuller LH, Matthews KA, Kiss JE. Hemostatic factors according to

