How to search for the role and prevalence of defective fibrinolytic states as triggers of myocardial infarction? The haemostasis epidemiologist's view

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The most useful phenotypic measures of fibrinolysis in prediction of myocardial infarction currently appear to be tissue-type plasminogen activator (t-PA) antigen and fibrin D-dimer. Recent meta-analyses of prospective studies show significant associations with incident ischaemic heart disease (including myocardial infarction) after adjustment for classical risk factors. The odds ratio in the top third versus the bottom third for baseline values was 1.5 (95% confidence interval 1.2-1.8) for t-PA antigen, and 1.7 (95% confidence interval 1.3-2.2) for D-dimer. Further studies are required to establish with confidence the associations for plasminogen activator inhibitor type 1, urokinase-type plasminogen activator, and other fibrinolytic variables.

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What is the approach?

The approach which haemostasis epidemiologists should take is as follows:
• interact with haemostasis biologists, geneticists and cardiologists in order to understand their viewpoints;
• agree the key phenotypic and genetic measures as well as biological correlates (confounders) of the phenotypic measures and their relationships to myocardial infarction;
• agree the key sampling conditions for phenotypic measures (e.g. time of day, resting, fasting, venous occlusion, etc. – as discussed in Leiden Fibrinolytic Workshops, European Concerted Action against Thrombosis and International Society for Thrombosis and Haemostasis Scientific and Standardisation Committee meetings);
• accept that in epidemiological field studies, a pragmatic balance has to be made between scientifically desirable sampling conditions, and epidemiologically desirable need to ensure high recruitment rates;
• perform both cross-sectional studies and (preferably) prospective cohort studies in men and women, with and without defined baseline vascular disease, appropriately analysed and published;
• collaborate in meta-analyses of all relevant studies, and in discussion of their biological, clinical and public health significance.

What are the key genetic measures?

The geneticist will have provided the current catalogue of gene polymorphisms related to tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor type 1 (PAI-1), urokinase-type plasminogen activator (u-PA), plasminogen, etc. These will not account for the powerful environmental influences on risk of myocardial infarction.

What are the key phenotypic measures?

The most useful currently appear to be:
• t-PA antigen. This largely measures inactivate t-PA/PAI-1 complexes, which have recently been shown to predict recurrent myocardial infarction in the SHEEP study[1]. In a recent new prospective study and meta-analysis of seven previous relevant studies in general populations (involving 2119 coronary heart disease cases and 8832 controls), the odds ratio for coronary heart disease in the top third versus the bottom third for baseline t-PA antigen values was 2.18 (95% confidence interval-CI 1.77-2.69) adjusted for age and sex, falling to 1.5 (95% CI 1.2-1.8) after adjustment for baseline values of classical risk factors[2]. It is concluded that while t-PA antigen may be a coronary heart disease risk predictor, its association is substantially confounded by

serum lipids, body mass index, insulin, urea, blood pressure, alcohol consumption, markers of inflammation, haematocrit, lung function, and other markers of endothelial disturbance such as von Willebrand factor. Interpretation of the role of t-PA antigen in coronary heart disease is therefore complicated;

• PAI-1 activity/antigen. In a recent meta-analysis[2] of five prospective studies in general populations (involving 833 coronary heart disease cases and 3122 controls), the odds ratio for coronary heart disease in the top third versus the bottom third was 0.98 (95% CI 0.53-1.81). It is concluded that at present there is substantial uncertainty concerning the association of PAI-1 with coronary heart disease: further prospective studies are required;

• u-PA activity. In a recent prospective study, u-PA activity was associated with coronary heart disease risk[3]. Further prospective studies are again required to establish the strength of this association with confidence;

• fibrin D-dimer. In a recent meta-analysis of seven prospective studies (involving 1535 coronary heart disease cases) the odds ratio for coronary heart disease in the top third versus the bottom third was 1.7 (95% CI 1.3-2.2)[4]. While it is possible that the associations of t-PA antigen with coronary heart disease may reflect up-regulation of the endogenous fibrinolytic system as an appropriate response to hypercoagulability, resulting in the association of fibrin D-dimer with coronary heart disease (increased thrombin and plasmin activity causing increased turnover of cross-linked fibrin) the overall association of t-PA with D-dimer in the population is very weak[2].

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