individuals with established ischaemic heart disease to progress to myocardial infarction. This, in theory at least, should give some insight on factors involved in plaque instability and rupture if the groups were adequately matched for atheroma burden and other features of ischaemic heart disease. The drawback in extrapolating these findings to the very important issues of plaque instability and rupture is related to the difficult problem of identifying this phenotype in population studies.

However, both tPA and elastase are enzymes that are indirectly or directly involved in the degradation of components of the extracellular matrix and it is an attractive hypothesis that the elevations in levels reported in this study may be related to increased plaque instability. This remains speculation at present but further information on these issues will be valuable in both our understanding of disease mechanisms and in the development of novel approaches towards therapeutic intervention.

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References
acute phase reactants. However, generalized atherosclerosis potentially results in vulnerable plaques not only in multiple wall segments of the coronary circulation but also in the aorta and carotid arteries. Under these circumstances there could be chronic expression of sufficient cytokines to stimulate the liver to generate increased quantities of phase reactants such as C-reactive protein, serum amyloid-A protein, fibrinogen, immunoglobulins and others.

The erythrocyte sedimentation rate has for over 50 years been a widely applied test for acute phase reactants. Acute and chronic inflammation, tissue injury, collagen disease and many malignancies result in its elevation and this reflects one of its deficiencies, namely, it may be abnormal in the presence of many different disease states. A major virtue is its simplicity and low cost. The Westergren technique uses a small 200 mm long calibrated glass tube with a diameter of 2.5 mm. The narrow column is filled with fresh whole blood anticoagulated with EDTA and left to stand. The distance red cells settle from the meniscus is measured after 1 h and reported in mm . h^{-1}. The erythrocyte sedimentation rate is primarily determined by fibrinogen and other major plasma proteins such as immunoglobulins. Coating of the red cells by these proteins helps to neutralize the surface negative charge of red cells which normally repel one from another, thus promoting aggregation and a faster settling rate. Similarly, anaemia, by increasing the ratio of serum protein concentrations to red cell volume also increases the erythrocyte sedimentation rate.

Earlier this year, Danesh, Collins, Peto and Lowe\[2\] published an analysis of pooled data from previously published prospective studies on the association of the erythrocyte sedimentation rate and the subsequent development of coronary heart disease. Of 1703 analysed fatal or non-fatal coronary heart disease cases, all but 65 came from two population-based studies, one in Sweden and the NHANES I Study in the United States. Comparing erythrocyte sedimentation rates in individuals in the top third with those in the bottom third at baseline revealed a risk ratio of 1.33 (95% CI 1.15 to 1.54, 2 P≤0.0001). A similar analysis of the relationship of haematocrit in 16 studies involving over 8000 patients who developed coronary heart disease was 1.16 (95% CI 1.05 to 1.29) and for plasma viscosity in four studies involving 1278 cases was 1.57 (95% CI 1.34 to 1.85). It is clear that rheological properties of blood correlate with the subsequent development of coronary heart disease among middle-aged populations. However, the value of measuring the erythrocyte sedimentation rate for this purpose has yet to be established.

The study by Eriksson et al. in this issue\[3\] provides erythrocyte sedimentation rate information on 243 coronary heart disease deaths and 240 non-fatal myocardial infarction cases among 2014 apparently healthy men aged 40–60 years followed for 23 years. It presents the longest follow-up period of any prior study. Of particular interest was a re-examination of the cohort 7 years later. The erythrocyte sedimentation rate became a strong predictor of subsequent coronary heart disease mortality among the 403 men who had developed angina pectoris and/or had a positive exercise ECG test by the time of the second survey.

Despite the observation that erythrocyte sedimentation rate clearly predicted coronary heart disease mortality by multivariate Cox-regression analysis, the present study has a number of significant limitations. First, despite the fact that associations with age, haemoglobin, smoking status, total cholesterol and systolic blood pressure were adjusted, no baseline measurements were made of serum fibrinogen, albumin, or immunoglobulins. Along with haematocrit, these proteins play a dominant role in determining the erythrocyte sedimentation rate. In particular, correction for fibrinogen would have been desirable since this phase reactant correlates strongly with the development of coronary heart disease and clearly plays a fundamental role in the thrombotic process\[4\]. It should be noted that the population studies pooled by Danesh and colleagues also failed to adjust for fibrinogen levels\[2\].

Secondly, the initial cohort was limited to males aged 40–60. Thus, the usefulness of the erythrocyte sedimentation rate in the older male where coronary heart disease is more prevalent and in women is not provided. An earlier longitudinal population study of erythrocyte sedimentation rates in women from Göteborg, Sweden, failed to predict subsequent myocardial infarction\[5\]. Similarly, in the NHANES I study no significant associations were seen in women in contrast to men\[6\]. It is difficult to understand why C-reactive protein was strongly predictive for the subsequent development of coronary heart disease in the Women’s Health Study\[7\] while the erythrocyte sedimentation rate was not. Clearly, more studies in women are needed.

Third, serum albumin was not measured. Serum albumin is inversely correlated with the risk of coronary heart disease and again, this represents another unadjusted variable.

Fourth, the overwhelming majority of subjects in the study by Eriksson et al\[3\], either dying from coronary heart disease or surviving after one or more myocardial infarcts, had normal baseline erythrocyte sedimentation rate values i.e. 76/106 and 192/240, respectively. Furthermore, the percent of subjects developing non-fatal myocardial infarctions in the
baseline erythrocyte sedimentation rate group of 15 to 29 mm h⁻¹ was similar to the event rate among those with normal baseline sedimentation rates. Only the group whose erythrocyte sedimentation rate was ≥ 30 had an elevated frequency of myocardial infarction, but the numbers in this subgroup were extremely small (eight non-fatal myocardial infarctions out of 36 subjects over an average 21 year follow-up). It would seem that the erythrocyte sedimentation rate had poor predictive accuracy for the subsequent development of a non-fatal myocardial infarction.

Long-term prospective studies of subjects with raised plasma C-reactive protein or low albumen have found an increased risk of coronary heart disease of about 50%[8]. Erikssen et al.[3] found that only 58 of 208 (27.9%) of their cohort with baseline elevations in erythrocyte sedimentation rate (> 14 mm h⁻¹) had either a non-fatal myocardial infarction or had died from coronary heart disease. Among 2014 men in the study, 240 subsequently developed one or more non-fatal myocardial infarctions. Of these, only 28 or 13.4% had a baseline elevation in erythrocyte sedimentation rate compared to 212 or 11.7% who had a normal erythrocyte sedimentation rate.

The above is not meant to question the observed correlation between erythrocyte sedimentation rate and the prediction of subsequent coronary heart disease mortality. Nevertheless, when one has relatively poor sensitivity of a possible marker to detect a first myocardial infarction, there should be reason above and beyond its simplicity of performance and low cost to justify its use.

Is there sufficient evidence to add the erythrocyte sedimentation rate to our list of markers in terms of prospective epidemiological studies that demonstrate its usefulness? There are very little data in women and only a restricted amount of data in men. Furthermore, some of the data are conflicting. In the study of Erikssen et al., the erythrocyte sedimentation rate failed to predict subsequent non-fatal myocardial infarctions in men, whereas in earlier studies it proved predictive. Certainly, a risk marker that is unable to predict the subsequent development of a first myocardial infarction, if such is the case, has limited value even if it does predict coronary heart disease mortality. Furthermore, a new marker for routine use should enhance the predictability of relative risk already available with currently established markers. One benefit of measuring hs-C-reactive protein is that when combined with measurements of the ratio of total cholesterol to HDL cholesterol, it significantly adds to the predictive value achievable by either alone[8].

Finally, there are no data on the response of the erythrocyte sedimentation rate to interventions designed to lower the risk of acute coronary events either in primary or secondary prevention. The present study did demonstrate that the erythrocyte sedimentation rate provided an enhanced ability to predict subsequent coronary heart disease mortality among the 403 patients who had developed angina pectoris and/or who had a positive ECG test at the second survey 7 years later. However, no data are available to indicate whether lessening risks with therapeutic interventions, such as statin therapy, alters the erythrocyte sedimentation rate.

In conclusion, the present study[3] adds to the epidemiological database on prospective studies of risk markers for coronary heart disease. However, even though the Erikssen et al.[3] study added to the earlier Danesh meta-analysis, this is insufficient reason to recommend routine use of the erythrocyte sedimentation rate in establishing individual risk factor profiles.

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