Cell adhesion molecules, simvastatin and hormone replacement therapy, in coronary artery disease

See page 975 for the article to which this Editorial refers

The paper by Sbarouni et al. in this issue[1] deals with several very timely topics. First of all, the magnitude of lipid lowering obtained by hormone replacement therapy is less than with established simvastatin therapy, but hormone replacement therapy is also associated with significant lowering of total cholesterol as well as LDL-cholesterol. Secondly, hormone replacement therapy is associated with a decrease in lipoprotein(a), an effect which in the clinic might imply a reduction in atherogenesis and an improvement in spontaneous thrombolysis. These effects were not obtained by simvastatin. The main difference in action was, however, seen in relation to the soluble adhesion molecules ICAM-1, VCAM-1 and E-selectin, all claimed to be involved in the inflammatory response leading to increased atherogenicity. Inflammatory markers have been claimed to be associated with increased risk of severe outcome in angina pectoris, such as myocardial infarction and sudden death[2]. The study is small but meticulously conducted and the results are in accordance with other findings.

However, the study deals with surrogate end-points and it may be superfluous to remind readers that cardiological practice has repeatedly been misled by such observations. The most flagrant examples are the studies with prophylactic antiarrhythmic therapy after myocardial infarction. The HERS study (Heart Estrogen/progestin Replacement Study) also illustrates this since hormone replacement therapy in this study was not associated with improved prognosis in a mixed group of women with coronary heart disease, which was in contrast to several impressive observational studies. The study of Sbarouni et al.[1] underlines that the hormone replacement therapy issue is not yet resolved and that further experimental and clinical studies need to be done. If these findings were concurrent with clinical effects, leading to a slowing down of the atherosclerotic process and a reduction of the risk of severe manifestations of the disease, both therapeutic and preventive strategies would appear. That there is reason to believe that this might be the case is the fact that women with angina pectoris have better prognosis than men, even if adjustments are made for age and concomitant diseases[3].

The female hormones may be positive modulating factors and reduce the effect of situations eliciting an acute event. The right patient population and treatment has yet to be identified. It may be pertinent to stress that hormone replacement therapy given with the purpose of improving prognosis in women with coronary heart disease is quite complicated, since the other hormonal aspects need to be taken into account, i.e. the risk for endometrial and breast cancer as well as venous thrombosis. These considerations must also be taken into account when cost-effectiveness of such treatment is discussed. Also, in a priority setting other measures for preventing a negative outcome of the disease are much more evidence-based and cost effective. From a clinical point of view, this study however, confirms the recommendations that women already on hormone replacement therapy, in coronary artery disease.
replacement therapy developing coronary heart disease need not stop their replacement therapy, but that it may in fact postpone complications although this is not proven.

Another interesting feature of the study is that it sheds some light on the topic of whether the inflammation and inflammatory response seen in patients with hyperlipidaemia and atherosclerotic disease is the result of the hyperlipidaemia or a separate issue. In my mind this study implies that simvastatin treatment in itself is not antiinflammatory on a short-term basis. Whether true reduction in plaques associated with longer duration of simvastatin treatment is a result of only lipid lowering or if an adjuvant antiinflammatory effect cannot be resolved by this study. The question remains, does the inflammatory response, seen in patients with atherosclerotic disease and associated with poorer prognosis, come before or after.

A third observation in this study was the diverging effects on lipoprotein(a). The authors do not deal in depth with this issue, but the findings are of interest in the context of how to influence progression of disease. Again the risk of severe complications i.e. myocardial infarction and sudden death, in both of which thrombosis is involved, either in the large epicardial vessels or in areas supplied by smaller vessels where severe ventricular arrhythmias may originate. Sudden death is a ‘male’ complication and although most of it may be attributed to increased sympathetic tone or autonomous imbalance, microthrombi are often found at autopsy. Whether lipoprotein (a) is involved in this is of course only speculative from this study’s point of view.

In conclusion, this study underlines the importance of the need for further experimental and clinical studies aimed at an improved description of the various background factors and processes leading to atherosclerotic disease and its complications in women. It also argues for therapeutic studies, with surrogate end-points, but preferably studies where mechanisms are studied concomitantly or as a part of the intervention and where women are considered.

N. REHNQVIST
National Board of Health and Welfare, Stockholm, Sweden

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Is SHORT hospital treatment safe for patients with acute myocardial infarction?

See page 992 for the article to which this Editorial refers

Duration of hospital treatment for acute myocardial infarction has decreased substantially over the last decades but still appears to be determined rather by tradition than by scientifically founded reasons. It should cover the time required for treating and stabilizing the patient and performing the diagnostic tests deemed necessary. In the early, unstable days after acute myocardial infarction, patients are threatened by reinfarction, myocardial rupture, infarct extension and death due to pump failure or ventricular fibrillation. But, how can we be sure when this period of instability ends? Repeat myocardial ischaemia in the early post-myocardial infarction period may be caused by incompletely resolved thrombus in the culprit lesion or coexistent unstable plaques. Yamaguchi et al.[1] have detected thrombi angioscopically in 24% and Goldstein et al.[2] have observed complex lesions in 39% of patients by angiography in non-culprit vessels after acute myocardial infarction. These patients had an increased risk of repeat ischaemia, reinfarction and early revascularization procedures.

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