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Discussion

Prof. Peter Libby: Professor Esper, you made a very provocative statement in the summary of your paper: that one should institute primary prevention therapy regardless of the age of the patient and that the desirable level of cholesterol is 'as low as possible'. Would you elaborate further on the type of patients in whom you would start therapy? In particular, would you initiate lipid lowering in patients who had not sustained a myocardial infarction and who had no other evidence of atherosclerosis?

Prof. Ricardo J. Esper: The benefit of primary prevention has been demonstrated in select patient groups. However, we do not as yet know at precisely what plasma cholesterol level further reduction becomes beneficial. It probably varies between patients. But it is relatively easy to initiate some aspects of primary prevention, particularly dietary and lifestyle education, in young patients. It seems likely that these types of risk reduction strategies will be most effective when people incorporate them into their lives at a relatively young age. In older patients in whom lifestyle interventions are unsuccessful, pharmacological therapy may be necessary.

Question: I would like to ask Professor Libby whether he would choose the aggressive use of lipid-lowering drugs in patients with unstable angina, on the basis of the premise that these agents are likely to stabilise vulnerable atherosclerotic lesions.

Prof. Libby: We are unsure about the effect of lipid lowering on the smooth muscle cells involved in repairing the fissures in plaques. On the other hand, Professor Esper has presented evidence that aggressive lipid lowering can very quickly improve endothelial vasodilator function. Thus, this is probably a question that will ultimately be resolved only in clinical trials. One such study, the MIRACL trial,[1] is currently focusing on this particular hypothesis and is examining the effects of a potent HMG-CoA reductase inhibitor in patients who have sustained a non–Q-wave myocardial infarction or an episode of unstable angina.

Dr Pablo Werba: Professor Libby, I would like to know whether you would consider choosing between HMG-CoA reductase inhibitors on the basis of drug effects other than lipid lowering that have been demonstrated in pharmacodynamic studies.

Prof. Libby: No. At this time, much of the available data is from *in vitro* studies, which have used exaggerated doses of individual agents. I think that, instead of debating class effects versus agent-specific effects, we should focus on what we do know. And that is that lipid lowering – whether dietary or pharmacological – can reduce events and prevent heart attacks. Once we achieve a situation whereby 80 or 90% of patients who are eligible for lipid-lowering therapy are actually being treated, then we can begin to consider the differences between individual agents. I can think of situations in my own practice where I might choose one agent over another – on, for instance, the basis of its drug interaction profile. However, I think the important message is that lipid lowering reduces heart attacks, regardless of the pathway by which it is achieved.

Prof. Libby: Dr Stein, in view of its evident lack of effect on the skeletal muscles, could you tell us where cerivastatin is on the spectrum of hydrophilicity to hydrophobicity in terms of some of the other statins? Is it likely to cross the membranes of peripheral cells?

Dr Evan A. Stein: Cerivastatin is tightly bound to protein, and its peripheral levels are very low. Dr Mück has studied this extensively, so perhaps he will comment futher.

Dr Wolfgang Mück: Cerivastatin is more than 99% bound to plasma proteins, and its peripheral levels are, indeed, very low. The drug has little affinity for any peripheral tissues other than its target site, the liver.

Reference

1. Schwartz GG, Oliver MF, Ezekowitz MD, et al. Rationale and design of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study that evaluates atorvastatin in unstable angina pectoris and in non–Q-wave acute myocardial infarction. Am J Cardiol 1998; 81 (5): 578-81