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After the Failure of ENHANCEd Cholesterol Lowering in Familial Hypercholesterolemia, SEAS of Problems with Ezetimibe

In a recent issue of the Journal, Whayne[1] analyzed the results of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial,[2] and proposed several explanations to the lack of effect of a more intensive low-density lipoprotein (LDL) cholesterol lowering with ezetimibe (beyond the level achieved with simvastatin) in patients with familial hypercholesterolemia. Furthermore, he pointed out that the ENHANCE trial lasted only 24 months, and a longer period could be required to see benefit from cholesterol lowering by ezetimibe.[1] However, he did not consider that the concentration of cholesterol by itself seems to be unimportant in familial hypercholesterolemia, and that a long-lasting therapy with ezetimibe and statin may raise some safety concerns.

Mounting evidence suggests that in familial hypercholesterolemia neither the incidence[3] nor the prevalence[4] of cardiovascular disease is associated with the lipid levels. This striking observation has been explained by the narrow range of LDL concentrations.[3] The argument is untenable, however, because total and LDL cholesterol in some individuals with familial hypercholesterolemia may be more than twice as high as in others.

A possible cause of cardiovascular disease in familial hypercholesterolemia may be inborn errors of the coagulation system. Indeed, in cohorts of people with familial hypercholesterolemia, it has been found that plasma fibrinogen and factor VIII were significantly higher in those with coronary heart disease than in those without,[5] whereas total and LDL cholesterol did not differ significantly. It has also been documented that polymorphism in the prothrombin gene is strongly associated with cardiovascular risk in people with this disorder.[6] The reason why statin treatment is of benefit in familial hypercholesterolemia may therefore be mediated by their well-known antithrombotic effects, not their effect on cholesterol.

However, the results of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial have been recently published.[7] During a follow-up of 52.2 months, simvastatin and ezetimibe, as compared with placebo, did not reduce the composite outcome of combined aortic valve events and ischemic events in patients with aortic stenosis. But, of more concern, an excess of incident cancers was observed in the simvastatin–ezetimibe group, with 105 in that group as compared with 70 in the placebo group ($P = .01$). In addition, deaths from cancer were more frequent in the active treatment group (39 deaths vs. 23 in the placebo group), achieving a borderline statistical significance ($P = .05$).[7] Of note, the average age in the ENHANCE trail was 46 years, and in the SEAS trial 68 years.

It is well known that statins are immunomodulatory drugs,[8] which might promote growth increase of occult cancers, especially in the elderly individuals[9] who already harbor cancers. Furthermore, ezetimibe inhibits the absorption of phytosterols and other phytonutrients that are linked to protection against cancer.[10] Therefore, the increased cancer incidence associated with cholesterol-lowering treatment cannot be dismissed as being coincidental, also because many observations from the statin trials are in accord.[11]

Although the ENHANCE trial was a treatment failure, it has contributed valuable knowledge about

the pathogenesis of premature coronary disease in familial hypercholesterolemia. A relevant question to answer in future research is whether attempts to normalize the coagulation system may be more useful than cholesterol lowering, given the safety issues raised in the SEAS trial.

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