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EDITORIAL COMMENT

Low LDL-C Levels and Cancer

Reassuring But Still Not Definitive*

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Atherosclerosis and its complications, coronary heart disease, stroke, and peripheral arterial disease, remain the leading cause of death and are increasing in incidence in the developing world (1). Treatment of dyslipidemia, particularly lowering of low-density lipoprotein cholesterol (LDL-C), is currently the cornerstone in the prevention and treatment of atherosclerosis. Not surprisingly, therefore, millions of patients worldwide are being treated with lipid-lowering agents, particularly statins. And while the beneficial effects of LDL-C lowering have been validated in multiple clinical trials, there remains uncertainty regarding LDL-C targets. Moreover, knowing whether adverse noncardiovascular events are associated with low LDL-C levels is of great clinical importance as physicians and patients balance risk versus benefit.

See pages 1141 and 1148

In this issue of the *Journal*, Alsheikh-Ali et al. (2) present a meta-regression analysis of data from 15 randomized clinical trials. They conclude that, while an inverse association between on-treatment LDL-C and incident cancer occurs, there was no evidence that statins themselves increased the risk of cancer. This analysis was prompted by an earlier study published in the *Journal* in which the same investigators identified evidence of increased incident cancers in relation to lower LDL-C levels achieved in various statin trials (3). In an accompanying editorial, Dr. Daniel Steinberg (4) concludes that indeed statin treatment does not cause cancer. Among explanations for the LDL-C level's association with incident cancer, he emphasizes the possible role of subclinical cancers as well as the confounding effect of other diseases that may lower LDL-C as well as increase risk for cancers.

Is the issue completely resolved? As this article and accompanying editorial were going to press, the preliminary results of the SEAS (Effects of Simvastatin and Ezetimibe on Clinical Outcomes in Patients with Aortic Stenosis) study were released (5). In this placebo-controlled study of patients with aortic stenosis, LDL-C was reduced by 61% to a mean of 52 mg/dl in the active arm (6). The study failed to meet its primary end point in reducing major cardiovascular events (atherosclerotic disease events were reduced significantly, while aortic valve disease events were not reduced). Of concern was the finding that cancer rates were increased significantly in the active arm of the study, with 102 cases versus 67 cases in the control arm. The press release for the study was accompanied by an analysis from 2 other ongoing large trials with simvastatin/ezetimibe combination (IMPROVE-IT [IMProved Reduction of Outcomes: Vytorin Efficacy International Trial] and SHARP [Study of Heart and Renal Protection]), which in a pooled analysis showed no excess of cancers (5). Several important limitations of this analysis need to be highlighted: 1) duration of treatment experience in these ongoing trials is significantly shorter than in the SEAS study; 2) while SHARP is a placebo-controlled trial, the larger IMPROVE-IT study is a comparison of 2 active arms (simvastatin/ezetimibe vs. simvastatin alone); and 3) LDL-C levels (both starting and on treatment) for these trials were not reported—entry criteria for the IMPROVE-IT study, however, mandate relatively low starting LDL-C levels (≤125 mg/dl for treatment naïve subjects) and both treatment arms are expected to have low LDL-C levels, possibly obscuring any potential adverse effect of low LDL-C levels (7).

So while statin treatment in itself appears not to increase risk of cancer, the issue of a possible link between very low LDL-C levels and cancer has not been fully resolved. If indeed background disease (whether subclinical cancers or other comorbidities that lower cholesterol and also increase cancer risk) is to account for the link, one would expect a lower LDL-C to be apparent on entry into the study. Moreover, statins result in a very prompt reduction in cholesterol and LDL-C levels. As trials routinely monitor response to therapy in addition to collecting clinical events, the effect of drug-induced LDL-C reductions versus background low LDL-C level could be differentiated on a patient-level analysis. Indeed, the major limitation in both the original article by Alsheikh-Ali et al. (3) and the present, more complete analysis (2), is the lack of patient-level data. As there is a spectrum of LDL-C levels within each trial (both due to

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different baseline levels as well as differing responses to the lipid lowering agents), focusing only on mean levels may obscure an important link that can only be ascertained by analyzing patient-level data.

The reporting of cancer rates in many of the clinical trials has been incomplete. For example, the main Treat to New Targets publication reported a statistically insignificant increase in cancer deaths (85 cases vs. 75 cases) in the intensive 80-mg atorvastatin arm versus the 10-mg arm, but did not report overall cancer incidence (8). Given the importance of the topic, it is paramount that the Food and Drug Administration and the pharmaceutical industry promptly analyze and report the cancer incidence in the various trials with a patient-level analysis.

When the initial report by Alsheikh-Ali et al. (3) was published, we accompanied it by an editorial titled "Low-Density Lipoprotein Reduction in Cancer: Not Definitive But Provocative" (9). We highlighted the wisdom of present guidelines that emphasize a link between baseline cardiovascular risk and LDL-C goals and cautioned that the analysis needed to be viewed as hypothesis generating. Similarly, while reassured by their present analysis (2), we still believe that further study is mandated. The findings from the SEAS study, while not definitive, support this need. We also reaffirm our belief that the present guidelines adequately balance the clear benefit of LDL-C lowering with potential risks.

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