Low-Density Lipoprotein Reduction and Cancer
Not Definitive But Provocative*

Anthony N. DeMaria, MD, MACC, Ori Ben-Yehuda, MD, FACC
San Diego, California

In this issue of the Journal, Alsleikh-Ali et al. (1) present data suggesting an inverse relationship between the absolute level of low-density lipoprotein cholesterol (LDL-C) reached in randomized clinical trials (RCTs) of statins and the incidence of cancer. As acknowledged by the authors, and emphasized in an accompanying editorial, the findings are not definitive but rather are hypothesis generating and require further investigation. Nevertheless, they are certainly provocative, and have considerable potential to alter the prescription of and compliance with drug therapy of proven efficacy. Therefore, we thought it would be worthwhile to review the process taken and considerations in reaching a decision to publish this manuscript.

See pages 409 and 419

Alsleikh-Ali et al. (1) initially submitted an analysis that examined the relationship of the degree of LDL-C lowering to liver toxicity and rhabdomyolysis in RCTs assessing statin therapy. The effect of drug dosage was also examined. Both reviewers and editors believed that the subject was important in light of recent evidence that intense LDL reduction yields superior benefits to moderate lowering. However, the editors requested that the authors include the incidence of cancer, since this was the other major side effect often feared from statin therapy. Upon complying with this request, the authors uncovered what was to them (and to us) the unexpected relation of LDL level achieved and incidence of cancer. Recognizing that their data were far from definitive, they sought advice from the editors, who recommended submission of the analysis in full.

From the onset of the review, it was clear that the data were imperfect. The authors themselves listed numerous limitations, including the retrospective use of summary data, the use of data from clinical trials rather than “real-world” experience, and the lack of standardization of adverse events in individual trials. Except for the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial, no individual statin trial showed an increase of cancer. Moreover, the report excluded data from 4 large statin RCTs (PROVE-IT [Pravastatin or Atorvastatin Evaluation and Infection Therapy], A to Z [Aggrastat to Zocor], TNT [Treating to New Targets], and IDEAL [Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering]). The study analyzed the relationship between LDL-C levels achieved and incident cancer rates and does not contain data to implicate statins themselves as the cause. Even if true, the increased risk of cancer would apply only at very low levels of LDL, and would be offset by the major benefits demonstrated for statin therapy in numerous clinical studies. The cardiovascular benefit translates into an overall mortality reduction in high-risk patients (30% and 13% decrease in all-cause mortality in the 4S [Scandinavian Simvastatin Survival Study Group] and Heart Protection study, respectively).

Given the above limitations, and the potential for misinterpretation of the data, many people would argue (and several associate editors did) that we had adequate grounds to reject the manuscript. In fact, this paper provoked spirited discussions at 3 of our weekly meetings, additional reviews, and several revisions. It was acknowledged that the misinterpretation by physicians, portrayal by the media, and the response of patients to the findings could all result in harm. However, in the final analysis, the consensus was that these findings could not be ignored, that they did indeed warrant further investigation, and that they should be aired in public.

Having decided to publish the paper, it was clear that we should do so in the most responsible way possible. We invited an editorial to put the findings in proper perspective. La Rosa’s (2) recommendation that a systematic analysis of RCTs not included in this study be funded and performed is right on target, and trials that treat patients to specific LDL-C goals, rather than compare 2 statin doses, are needed as well. We prepared this essay explaining our rationale and process. Finally, we plan to be as cautious, balanced, and responsible in discussing this material with the lay media as possible.

In the 5 years that we have been stewards of the Journal, no other manuscript has stimulated such intense scrutiny and discussion. Given the growing public angst regarding the safety of prescription medications, all were concerned that the paper contained great potential both for harm and good. In the end, we agreed to publish the article with as much caution and perspective as possible. This decision was bolstered largely by great confidence in the ability of our readers to interpret the data accurately and to act on the findings appropriately. Until additional data are available, we believe adherence to existing National Cholesterol Education Program guidelines is appropriate, especially with

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Division of Cardiovascular Medicine, University of California, San Diego Medical Center, San Diego, California.
regard to the recommendation that lower LDL-C goals to approximately 70 mg/dl apply only to high-risk patients.

Reprint requests and correspondence: Dr. Anthony N. De-Maria, Editor-in-Chief, Journal of the American College of Cardiology, 3655 Nobel Drive, Suite 400, San Diego, California 92122. E-mail: ademaria@acc.org.

REFERENCES
