A Call for Development of Comprehensive Therapy for Dyslipidemia

Treatment of hyperlipidemia with statins has become an integral part of management of vascular disease today. However, numerous gray areas exist in the treatment algorithm. The meta-analysis by Cannon et al. (1) refers to usage of high-dose statin therapy for low-density lipoprotein (LDL) reduction in the treatment of cardiovascular diseases. The title of the study uses the term “Intensive Versus Moderate Statin Therapy,” which apparently is a new term being coined for high-dose statin therapy. None of the trials included in the meta-analysis use this term to define the dose of atorvastatin. In all these trials the prime focus was the level of LDL achieved and event reduction following that. The atorvastatin dosage has never been shown to be an independent predictor of long-term outcome in multivariate analysis. Thus, any dose of atorvastatin or any other statin that achieves the desired level of LDL of about 70 mg/dl would be considered as optimal statin therapy according to the current knowledge. Whether the term “intensive” relates to a high dose of atorvastatin or to a dose of statin that reduces LDL to about 70 mg/dl is not clear. Hence, the new term of “intensive statin therapy” is probably not required in today’s clinical jargon.

Whether adequate LDL reduction if achieved using a smaller dose of statins will confer similar benefit as that with high-dose statins is not clear due to lack of data. As the pleiotropic effect cannot be easily measured in clinical practice, the real target for a clinician today is LDL cholesterol. Most of the large-scale trials also use the same target and compare the long-term outcomes with LDL reduction or levels achieved. It would be interesting to perform a subgroup analysis of patients receiving 10 mg of atorvastatin and reaching an LDL target of 70 mg/dl in the trials included in the researchers’ meta-analysis.

It is also very important to understand the same dose of a drug may not be required in all races to achieve the desired effect. In clinical practice in India, most of our colleagues have been able to maintain LDL levels close to 70 mg/dl with much lower doses of atorvastatin. As of today no important trial data is available to us from the region, and thus we rely heavily on Western literature. In this case, what would be an “intensive statin therapy” for an Asian Indian remains a very difficult question to answer. Thus, a term of “optimal lipid-lowering therapy” seems more useful and less confusing than intensive statin therapy.

Low high-density lipoprotein (HDL) is another important contributor to development of atherosclerotic vascular disease. In fact, rapid regression of atheroma has only been shown with infusion of apolipoprotein A-I milano (2). Further, results from the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study (3) involving 3,086 patients have shown that HDL and not LDL cholesterol levels influence short-term prognosis after acute coronary syndrome (ACS). It is also documented that HDL modulation is better with lower doses of atorvastatin than with higher doses and even better when low-dose atorvastatin is combined with ezetimibe.

Reduction in C-reactive protein is probably the only measurable pleiotropic effect of statins. Comparable C-reactive protein reduction has also been shown with combination of low-dose simvastatin and ezetimibe to that of high-dose atorvastatin, although in a short-term study (4). Reduction in LDL with a combination of low-dose atorvastatin and ezetimibe has been comparable to that with high-dose atorvastatin alone, again in a short-term study (5).

In light of these facts, it is very important that we develop a comprehensive hyperlipidemia therapy that encompasses adequate LDL reduction along with reduction in total cholesterol and triglycerides and elevation of HDL at the same time, rather than harping on high-dose statin therapy.

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Reply

We would like to thank Drs. Deshpande, Mardikar, and Deo for their important comments regarding our study (1). The term “intensive” statin therapy has recently been used to identify statin regimens that lower low-density lipoprotein cholesterol (LDL-C) by approximately 50%, as we did in the PROVE IT–TIMI-22...
PRINCIPAL CONFERENCE INTERVENTION (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial: “Intensive Versus Moderate Lipid Lowering With Statins After Acute Coronary Syndromes” (2). On the active debate regarding whether the appropriate treatment should be based on the dose of the statin or the achieved LDL, we agree that there have not been trials that directly compare 2 strategies of titrating to a specific LDL-C goal. All the trials use different, largely fixed regimens of a specific statin dose (either with intensive vs. moderate, or of statin therapy vs. placebo). In PROVE-IT TIMI-22, we designed the trial very specifically to have 2 different levels of achieved LDL-C so as to be able to compare patients who reached an average of <100 mg/dl, as recommended in the National Cholesterol Education Program (NCEP) III guidelines, versus a much lower LDL-C with a more intensive regimen, with the final median LDL-C values of 95 and 62 mg/dl, respectively.

Almost a decade ago, the NCEP Guideline committee adopted a practical approach to lipid lowering—where members specified target levels for LDL-C and other lipid levels. This was believed to be a means of having physicians identify high cholesterol values in patients and adjust treatment accordingly. The evidence directly supporting this approach does not exist, as recently lamented (3), but can be inferred from all the randomized trials.

For clinical care, we take a practical view. If we have a patient with an LDL <70 mg/dl on a moderate dose of a statin, we do not feel compelled to increase the dose. However, we are currently conducting the IMPROVE IT trial to address this question, to ascertain whether an even lower LDL is even better. It compares strategies using simvastatin versus simvastatin plus ezetimibe, which are anticipated to have achieved LDL levels of 65 versus 50 mg/dl, respectively. When the trial is completed in several years, we may have evidence to support an even lower target level for LDL.

For additional targets of therapy, we agree, and published the prospective analysis relating clinical event rates to levels of achieved C-reactive protein (4). We similarly have recently found triglycerides to be an important target for therapy (5). We agree that HDL is an important target as well, and we anticipate new approaches to address this important risk factor. All these data support the call for comprehensive management of all components of dyslipidemia.

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Depression and Heart Failure: Why the Link Continues to Elude Us

Rutledge et al.’s (1) important and comprehensive review of depression in heart failure highlights the relative neglect in investigating the key parameters of this important association in the literature. The researchers remind us there remains as yet no investigation of the effects of a depression intervention on objective clinical outcomes such as survival or secondary cardiac events in a heart failure (HF) population.

However, although their useful review emphasized the biological connections between HF and depression, some of the emerging key issues on the link between depression and heart disease possibly emphasize more the social and perceptual impacts of effect.

For example, we know that depression has a negative impact on social networks, and it could be that it partially mediates its effects on cardiovascular systems via this variable. It is now a well-established finding that those individuals who are more socially integrated—for example, in long-term relationships or connected to communities or organizations—display lower risks of premature all-cause mortality than do those who are not so well integrated socially (2).

Piferi and Lawler (2) have recently demonstrated that social support not only had a positive impact on blood pressure but giving social support appears to represent a separate construct from receiving social support and may exert a uniquely positive effect on health. It might be that future studies on depression and HF, particularly intervention ones, would need to take this kind of social mediating variable into account, and be highly specific as to whether giving or receiving social support was measured.

Another key aspect of depression, which should be part of the future of research into depression and HF, is the specific impact of low mood on perception. For example, Ruo et al. (3) recently established that depression has a clinically significant effect on self-rated health among women with coronary disease, even after adjustment for clinical diagnoses. The magnitude of this impact of depression on self-rated health was similar to that of major cardiovascular events such as angina, myocardial infarction, angio-plasty, HF, or coronary bypass surgery.

Whether depressed individuals are less compliant with treatments and medical advice, and whether they are unlikely to attend follow-up, are recalcitrant over exercise, losing weight, improving diet, and quitting smoking remain open questions. Thus, the precise pathway via how their depression impacts on their physical health continues to be a mystery.

This gap in our current knowledge probably accounts for the recent failure to demonstrate a significant impact on physical outcomes for treating depression following myocardial infarction (4).