CARDIOLOGY DIALOGUES



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Lowering LDL in patients with heart disease: How aggressive should you be?

Editor's note—This article is based on a discussion held at the Cleveland Clinic Heart Center's "Controversies in Cardiology" conference.

HE IMPORTANCE OF reducing low-density lipoprotein (LDL) cholesterol in managing patients with coronary heart disease (CHD) is unquestioned. However, debate continues over how aggressive physicians should be in lowering LDL. Experts have not been able to agree on a target level that is both beneficial and practical.

In this month's Cardiology Dialogue, Dr. Thomas Pearson of the University of Rochester (NY) argues that lipid-lowering therapy should be individualized, not only on the basis of the LDL level but on other factors as well. Dr. Fredric Pashkow of the Cleveland Clinic, on the other hand, contends that aggressive therapy is warranted for all patients. Both discuss the merits and the failures of several recent high-profile studies and offer their personal insights on what constitutes rational therapy.

THE CASE FOR INDIVIDUALIZED TREATMENT

DR. PEARSON: In its current guidelines, the American Heart Association recommends that the goal LDL level in patients with CHD be less than 100 mg/dL.¹ This goal is based on the results of Rossouw's meta-analysis² of 14 cholesterol-lowering intervention studies; Rossouw calculated that plaque progression

ceases at an LDL level near 100 mg/dL. Coincidentally, 100 mg/dL is a nice round number.

But guidelines are only guidelines; they are not rules. Must every patient's LDL be lowered to less than 100 mg/dL? If not, how low should you take the LDL level?

I would suggest that the 100 mg/dL goal may be somewhat arbitrary, and that the ideal LDL level may actually be higher or lower in individual patients.

Rationale for treatment: To interrupt the disease process

In my view, the rationale for treatment is to interrupt the disease process of endothelial dysfunction leading to plaque initiation and growth, which progresses to plaque destabilization and thrombosis. I suspect it is not imperative to lower LDL to 100 mg/dL to treat endothelial dysfunction and prevent plaque destabilization, and therefore to prevent coronary events.

I base this argument on a number of small serial angiographic studies that Rossouw included in his meta-analysis.² In these studies, lipid-lowering treatment reduced the incidence of myocardial infarction (MI) between 24% and 82%, even though many patients still had LDL levels well above 100 mg/dL and had only minimal reductions in plaque growth. Other studies confirmed that the endothelium can stabilize at LDL levels higher than 100.

Clinical trials can be misleading

Clinical trials, as helpful and important as they are, have an element of artificiality. Researchers must cope with a variety of procedural, ethical, economic, and other consid-

The 100 mg/dL LDL goal for all CHD patients is arbitrary —Dr. Pearson

^{*}Disclosure: Dr. Pearson has indicated that he has received grant or research support and serves as a consultant and a member of the speakers' bureau for several companies that manufacture lipid-lowering drugs; Dr. Pashkow has also indicated that he serves on the speakers' bureau of several of these companies.

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erations, any of which can provide an incomplete picture of the actual natural course of disease. For example, in many trials, patient enrollment is highly selective. Moreover, the selection of only one or two endpoints from a wide variety of possible outcomes can skew the interpretation of results. Some studies test only one dose of a drug. And, for reasons of cost, many trials last only 5 years or less.

In real life, we don't treat our patients for only 5 years, we treat them for decades. Some studies show that it can take 8 years of treatment to begin to see a definite change in atherosclerotic growth. Therefore, patients with objectively documented coronary disease need a *long-term* LDL goal, but clinical trials cannot help us establish long-term LDL goals.

How many trials showed that patients with very high LDL levels—higher than 190 mg/dL—were able to lower them to less than 100 mg/dL? None. In the Scandinavian Simvastatin Survival Study (4S),³ LDL levels fell from 190 to 140 mg/dL, and in the Cholesterol and Recurrent Events (CARE) study,⁴ they fell from 140 to 110 mg/dL.

We have not yet conducted a trial to determine just how far we should lower LDL levels, and we ought to do so. Without a longterm LDL goal, the best we can do is treat endothelial dysfunction and prevent plaque destabilization, and this can be done without lowering LDL levels to 100 mg/dL.

Some patients may need extra-aggressive treatment

On the other hand, some patients may need their LDL levels lowered to considerably less than 100 mg/dL.

CHD patients with low LDL levels. When the guidelines for LDL goals in CHD patients were being discussed, they were accompanied by a minority opinion that recommended that all patients with CHD should have their LDL levels lowered, regardless of what their level is. In other words, no matter how low their level is, it's still too high.

Approximately 10% of CHD patients have LDL levels less than 100 mg/dL at baseline. The minority report said that we should not be satisfied that these patients have already achieved the AHA's LDL goal; their LDL should be lowered even further. The basis for this recommendation is that serial angiographic studies show that untreated coronary atherosclerosis naturally tends to progress, even if the LDL is low, if the patient has other risk factors such as diabetes, hypertension, or smoking. In addition, we need to consider other risk factors such as lipoprotein (a) (Lp[a]), fibrinogen, and homocysteine.

Patients with elevated homocysteine, fibrinogen, or Lp(a). At a given level of homocysteine (say, 15 mg/ μ mol/L), even a low LDL level is not sufficient. Likewise, a patient with low fibrinogen and LDL levels will experience only a small increase in risk if the LDL level gradually increases, but a patient with a high fibrinogen level and low LDL may experience a much greater increase in risk if the LDL level rises.

Patients with high Lp(a) levels benefit greatly from LDL lowering, according to the Familial Atherosclerosis Treatment Study (FATS).⁵ The implication is that patients with high Lp(a) levels should be targeted for more aggressive LDL lowering. When we see any patient at our institution who has a high Lp(a) level, we routinely begin treatment to lower the LDL level to 70 or 80 mg/dL. Unfortunately, not many drugs lower Lp(a).

Post-bypass patients. Finally, we must consider the concept of vulnerable vascular beds. In patients who have undergone bypass surgery, the grafted saphenous vein is more prone to atherosclerosis than are the native arteries. So although a target LDL level of 100 mg/dL might suffice for a patient with native coronary arteries, a level of 80 mg/dL is preferable for a patient with a saphenous vein graft. A bypass operation is a \$40,000 investment, so we ought to make sure that we prevent new plaque growth by being aggressive in lowering LDL.

THE CASE FOR AGGRESSIVE THERAPY ACROSS THE BOARD

DR. PASHKOW: I appreciate Dr. Pearson's elegant presentation, and I concede his main point that a goal LDL level of 100 mg/dL for all patients with CHD may be arbitrary and that a more individualized approach may be better. In fact, I would like to amplify some of his discussion a bit.

Patients are so obsessed with cholesterol that they ignore other risk factors —Dr. Pashkow Nevertheless, as far as practical recommendations to our colleagues are concerned, 100 mg/dL is still our best bet, because at present we have no way to adjust this number for individual patients with CHD and no data to show that this hypothetical approach would work. Furthermore, given the ubiquity of hyperlipidemia, perhaps our emphasis should not be so much on precise goals as on the need for lipid-lowering therapy in the first place fewer than half of high-risk patients who should be receiving a statin are in fact receiving one.⁶

In addition, the medical community has convinced patients to become so obsessed with their cholesterol levels that they are completely disinterested in other risk factors that may be even more critical, such as excessive caloric consumption and a lack of physical exercise.

Surrogate markers and end points are unreliable

We ought to beware of basing our recommendations on studies that used surrogate end points, which are often unreliable. For example, for many decades we judged the effectiveness of class IC antiarrhythmics on how well they reduced the frequency of ectopy, and this parameter turned out to be invalid. In fact, more patients died who received these drugs.⁷

That's why I'm afraid we may be mistaken in relying on the LDL level as a predictor of acute events, particularly with acute MI. LDL is only one facet of the story. Granted, it may be the most practical approach for our patients since we now have drugs that lower LDL effectively, but the issue is more complex than that.

Plaque regression does not necessarily mean improved survival

Another surrogate marker, the size of the plaque on angiography, may not be a good marker of risk, and regression of obstruction may not be a good measure of the success of lipid-lowering therapy. MIs usually evolve from plaques that were only marginally obstructive in the months or years leading up to them. Only about 15% of MIs arise from plaques causing more than 70% obstruction before the MI, whereas about two thirds arise from plaques previously causing less than 50% obstruction.

Rossouw's meta-analysis notwithstanding, the totality of studies shows that angiographic changes in response to LDL reduction are not necessarily predictive of cardiovascular events. In fact, results are widely divergent. For example, the post-CABG trial⁸ showed that lipid-lowering therapy led to a mean reduction in LDL levels of 39%, a 0.18-mm regression of plaque on angiography, and a 10% reduction in cardiac events. By contrast, the PLAC I9 study showed that lipid-lowering therapy led to a 26% reduction in LDL and only a 0.02-mm reduction in plaque regression, but an enormous 60% reduction in cardiac events. Furthermore, in the CARE study,⁴ patients with established CHD whose LDL levels were reduced by 10% to 20% had a greater reduction in events than those whose levels were reduced by 20% to 30% and more; they also had fewer events than patients whose LDL levels fell less than 10%. We saw much the same thing in West of Scotland Coronary Prevention Study (WOSCOPS),¹⁰ where investigators found that men who had a 23% reduction in LDL had fewer events than men whose LDL levels were reduced by 29%, 34%, or 41%.

Another significant finding of the West of Scotland trial was that pravastatin-treated patients whose LDL levels had been reduced to no lower than 152 to 157 mg/dL had fewer coronary events than placebo controls who had the same LDL level. The implication is that just the act of lowering LDL to some degree is more important than the final LDL level itself.

These studies may be showing us that lipids are only part of the story, however. Consider the etiology of acute coronary syndromes (MIs and unstable angina), which arise from the rupture of small, unstable plaques. Compared with stable, flow-obstructing plaque (which is responsible for stable angina), unstable plaque contains not only more lipids, but also more macrophages, T cells, collagen, and elastin as well. In an acute coronary syndrome, the fracture of the thin fibrous cap releases this matrix of substances into the circulation and precipitates the formation of thrombi. When a patient has a high Lp(a), we try to lower the LDL to 70 or 80 —Dr. Pearson

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It may be that statin therapy has other effects that result in plaque stabilization, such as anti-inflammatory effects, and that are just as important as lipid lowering.

WHAT IS THE MOST RATIONAL STRATEGY?

DR. PEARSON: In treating CHD, we ought to be setting our sights higher than we are now. Instead of settling for a one-third reduction in coronary events and deaths (as occurred in the major trials of lipid-lowering therapy), we ought to be thinking about how to stop the disease completely.

In the 4S trial,³ treatment reduced coronary events by 32% and deaths by 33% compared with placebo. However, at the end of 5.4 years, the mortality rate among treated patients was still 8%. Is 8% mortality acceptable? I contend that it is not. I don't think we have treated coronary disease as much as we can. We are not looking closely enough at risk factors to identify high-risk subgroups, and so we have not been aggressive enough in treating them.

Beware of basing on studies that used surrogate end points -Dr. Pashkow

Several clinical trials of aggressive therapy are now under way, including the TNT (Treating to New Targets) study. Until the results become available, we do not really recommendations know what the ideal goal LDL level should be. I believe, as I have said, that patients at higher risk should be treated more aggressively, while others might be treated less aggressively. **DR. PASHKOW:** We know that lowering LDL in the extreme will work, but we don't know if this is the best option. We hope the TNT study will finally determine whether lowering LDL levels to 100 mg/dL is worthwhile. If so, then we have to ask if a goal of 80 mg/dL would be even better. Would a difference of 20 mg/dL actually make a difference in all-cause mortality in the long run?

DR. PEARSON: I don't think that will happen, because I don't think it would be costeffective for everyone. At some point, prevention becomes a matter of cost-effectiveness. For example, the Air Force/Texas Coronary Atherosclerosis Prevention Study¹¹ was successful from a prevention standpoint, but not from a cost-effectiveness standpoint.

It would be very expensive to lower the

LDL levels of a very large group of CHD patients from 100 to 80 mg/dL. But even if we did, I believe the benefit would be minimal. We will have to reserve the 80 mg/dL target for specific subgroups of high-risk patients and aim for LDL levels between 100 and 130 mg/dL for the rest.

There are no stone tablets inscribed. Thou shalt lower LDL to less than 100. The key is to individualize therapy. We can answer the question How low should we go? by asking another question: How low do we need to go?

AUDIENCE COMMENT: The only appropriate end point is all-cause mortality. It is the only measurement that is completely unbiased and objective. Cardiac death is a soft end point. An extensive amount of literature now shows that many patients who are reported to have experienced sudden cardiac death actually died of other causes. The cause of death is not always as obvious as it seems. The danger of using end points other than total mortality is that one can end up with inaccurate results. DR. PEARSON: As I mentioned, studies can be confusing because clinical end points are measured in many ways, such as for example the need for angioplasty or revascularization or the incidence of angina, MI, or death. But I believe that the important outcome here is the prevention of endothelial dysfunction and plaque destabilization. These two pathologic factors can be prevented even when the LDL level is greater than 100 mg/dL. So in clinical practice, I believe that our end point should not be the prevention of events, but the successful treatment of the disease process itself.

AUDIENCE OUESTION: Is there an LDL level below which unintended effects become a problem? Depression and suicide had been mentioned, only to be debunked later. Perhaps there are unintended long-term neuronal effects with the statins that we haven't yet appreciated. Do you know of any hazards?

DR. PEARSON: There are some genetic abnormalities, such as hypobetalipoproteinemia, in which some patients are born with very low LDL levels, but these cases are rare. Some studies from Asia suggested that low LDL levels are associated with hemorrhagic stroke. But even so, we have to keep in mind

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that these patients have had low LDL levels all their lives. These are instances of develop-

mentally low LDL. It's not clear that we would

see the same problems in a 50-year-old patient who has just had his LDL level lowered from

190 to, say, 70 mg/dL. In the US population,

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