EDITORIAL

James V. Felicetta, MD, *Editor-in-Chief*

How Low Is Too Low?

Aha! I was hoping that the title of this little essay might grab your attention. But what exactly am I referring to here? Blood pressure? Blood sugar? Stress levels? I'll fess up: I'm talking about whether it's possible to have circulating low-density lipoprotein cholesterol (LDL-C) concentrations that are too low.

Many of you may be surprised that this issue could ever be a cause for concern. After all, for years we have wholeheartedly accepted that LDL-C is an unequivocal villain, responsible for the inexorable acceleration of atherosclerosis. Over time, this atherosclerosis then leads to severe vascular disease, be it coronary artery disease, cerebral artery disease, or peripheral arterial disease. Indeed, epidemiologic evidence from widely disparate areas around the globe has consistently demonstrated a very close association between LDL-C levels and cardiovascular risk.

Even more persuasive are the multiple, well-done randomized clinical trials, which have demonstrated that LDL-C reductions with various statins lead to very meaningful reductions in the rate of cardiovascular events (CEs), both in primary and in secondary settings. These reductions are typically in the range of a 25% to 40% reduction in risk after just 3 or 4 years of statin therapy. Some of the best of these studies are the 4S (Scandinavian Simvastatin Survival Study), the HPS (Heart Protection Study), and the TexCAPS/AFCAPS (Texas/Air Force Coronary Atherosclerosis Prevention Study). So it seems beyond any doubt that lowering LDL-C levels with statins can produce clinically meaningful reductions in CEs even after a relatively short duration of therapy.

But we also know that statins are hardly perfect therapy, as if such a thing existed in the real world. We originally worried about hepatotoxicity from statins, but over time we came to understand that serious liver problems are quite uncommon. However, we know now that muscle aches and soreness are disturbingly frequent adverse effects of statin therapy, even in the absence of creatine phosphokinase enzyme elevations; a few unlucky patients even go on to develop life-threatening rhabdomyolysis. Coenzyme Q may or may not afford some degree of protection from myopathy; it is well established that statin usage does indeed deplete levels of ubiquitin (coenzyme Q). There have also been isolated but persistent reports of uncertain credibility, suggesting that statins may impair cognitive function, perhaps leading to faulty thinking or to unfortunate dreams. Most of us put little or no stock in the possibility of cognitive problems. However, we do have to reluctantly acknowledge that statins can very definitely push an individual with insulin resistance from a prediabetic state into full-blown diabetes. These medications push people along the insulin-resistance spectrum, just as thiazide diuretics and beta blockers often do.

Thus, the search has been intense for other classes of medication that could lower LDL-C without the issues associated with statin therapy. In recent years, researchers have developed an extremely promising new class of LDL-C-lowering drugs, the PCSK-9 inhibitors. These synthetic monoclonal antibodies work by binding to the PCSK-9 enzyme, which is responsible for metabolizing LDL-C receptors on hepatocytes. When these LDL-C receptors are protected from being metabolized by this new medication, they last for a much longer duration and, hence, are able to remove much more LDL-C from the bloodstream than would normally be the case. This then creates the potential for reaching very low levels of LDL-C that have previously been unobtainable. I should note that these drugs are given by subcutaneous injection, either every 2 weeks or every 4 weeks.

We can also remember that populations with pristine, healthy diets, such as what Japan had in the pre-McDonald's era, typically enjoy mean LDL-C levels in the 30s and 40s.

In November 2013, the results of 1 year of therapy with Amgen's PCSK-9 inhibitor, evolocumab, were presented at the annual meeting of the American Heart Association in Dallas, Texas. For an old-timer like me, the results were truly amazing. About a quarter of the cadre who re-

ceived the new drug added on top of their existing therapy (basically statins) wound up with LDL-C levels below 25 µg/dL! It's unheard of to see such levels produced by medications, and thus, it's hard to know whether to celebrate or to start worrying big-time. On the one hand, we can remind ourselves of the very strong association alluded to earlier between LDL-C levels and cardiovascular risk. We can also remember that populations with pristine, healthy diets, such as what Japan had in the pre-McDonald's era, typically enjoyed mean LDL-C levels in the 30s and 40s.

But it's still a bit scary to think about the potential harm we might be doing to someone who is used to living with a considerably higher LDL-C level. After all, cholesterol delivered by LDL-C is a major stabilizing component of cell membranes throughout the body. That may explain why a modest increase in hemorrhagic strokes was seen in the observational Honolulu Heart Study in subjects who had both very low LDL-C levels and hypertension. And cholesterol is also a major synthetic building block for steroid hormones, including glucocorticoids, mineralocorticoids, and sex steroids. However, it turns out most of the cholesterol that goes into hormone synthesis is derived from circulating very low-density lipoprotein cholesterol (VLDL-C) rather than from LDL-C.

So how well did the subjects in the Amgen-sponsored study do with their levels of LDL-C under 25? They actually did remarkably well, with only a very modest increase in headaches and bad dreams, both of which could easily have been the play of chance and hence unrelated to the study medication. Certainly nothing disastrous happened to these research volunteers, and that is indeed quite reassuring. So the short-term data do seem to suggest that these agents are reasonably safe.

The larger question, though, is whether there is truly any cardiovascular benefit to driving LDL-C levels down so drastically. We've seen dramatic "improvements" in lipid levels with other agents that turned out not to translate into improvements in what we really care about, which is the rate of heart attacks, strokes, and overall cardiovascular deaths. The cholesteryl ester transfer protein inhibitors, such as torcetrapib and dalcetrapib, produced extremely impressive rises in high-density lipoprotein cholesterol (HDL-C) levels, and yet there was no reduction in cardiovascular risk whatsoever, perhaps because the HDL-C was of a dysfunctional variety. So it's important to be skeptical even when we see what seems to be quite impressive changes in lipid levels in what we would consider a favorable direction.

The new class of PCSK-9 inhibitors is unlikely to obtain U.S. Food and Drug Administration approval until some positive cardiovascular outcomes data have been generated, most likely in the very high-risk group of patients with familial hyperlipidemia. These folks typically have LDL-C levels routinely in the 250- to 400-µg/dL range and are at extremely high risk of untoward cardiovascular events. But even if cardiovascular benefits are demonstrated in that group, the question will remain whether there is also value in drastically reducing LDL-C levels in patients with much more modest elevations in LDL-C. There is also the issue of whether the risk reductions we have seen with statins are primarily related to the LDL-C reductions themselves, or to the so-called pleiotropic effect of the statins. The pleiotropic effects include improvement in endothelial function, reduction in thrombus formation, and vasodilatory effects, among others. The HPS showed that statins produced roughly the same degree of risk reduction regardless of the starting LDL-C level, suggesting that pleiotropic effects may be much more important than the LDL-C reduction. If statins primarily reduce cardiovascular risk through these mechanisms, it could well be that newer agents, such as PCSK-9 inhibitors, which do a bang-up job of lowering LDL-C but which may not have much in the way of pleiotropic effects, may not really do much to reduce cardiac risk.

So in conclusion, we really don't know at this point whether it's possible to lower LDL-C concentration to an excessively low level. And we also must remember that we don't even know for sure whether simply lowering LDL-C in isolation is really of much cardiovascular benefit at all. As in most areas of medicine, the more we learn, the more we realize how little we truly know. ●

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the author and do not necessarily reflect those of Federal Practitioner, *Frontline Medical Communications Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*