Low-Density Lipoprotein Treatment Targets: How Strong Is the Evidence?

Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. Ann Intern Med 2006;145:520–30.

Study Overview

Objective. To determine if the existing medical literature supports titrating lipid-lowering therapy to the 2004 National Cholesterol Education Program (NCEP) goals for low-density lipoprotein (LDL) cholesterol.

Design. Narrative review of all controlled clinical trials, cohort studies, and case-control studies examining the relationship between LDL cholesterol and cardiovascular outcomes in patients with LDL cholesterol < 130 mg/dL.

Methods. Reports cited in the 2004 NCEP report [1], the American College of Physicians lipid guidelines [2], a meta-analysis [3], and the Cochrane database as well as studies found on MEDLINE were examined, yielding 1214 articles. Articles were reviewed to see if they assessed an independent association between LDL cholesterol level and major cardiovascular outcomes in patients with LDL levels < 130 mg/dL. No study met these criteria; thus, the authors examined the methodologic limitations to answering this question in the studies found.

Main results. There was no direct evidence suggesting that the extent of LDL cholesterol reduction below 130 mg/dL was an independent predictor of the degree of cardiovascular risk reduction. One large study suggested that patients with small, intermediate, and large LDL responses to a statin derived similar cardiovascular benefit. Studies that addressed the benefits of achieving specific LDL cholesterol goals had avoidable limitations such as failure to account for confounders, reliance on ecological rather than patient-level analyses, and failure to adequately address the hypothesis that the non–LDL-lowering effects of statins accounted for the observed benefits.

Conclusion. Strong evidence suggests that patients at high cardiovascular risk benefit from the fixed statin doses used in clinical trials, but there is no evidence that titrating LDL cholesterol–lowering therapy to achieve the proposed target LDL goals is preferable to fixed-dose statin therapy. This question could be at least partially answered using currently available data if specific limitations are addressed.

Commentary

Trials comparing statin regimens have generally found that more powerful doses (in terms of LDL lowering) produced greater cardiovascular risk reduction, but Hayward et al point out that existing studies provide, at best, indirect and potentially flawed evidence that cholesterol-lowering therapies should be adjusted to reach currently recommended LDL targets. It is not clear that LDL lowering per se was the direct mechanism through which this risk reduction was

achieved, and it has not yet been shown that an alternative strategy of adjusting drug dosages or using drugs in combination would provide additional improvements in cardiovascular outcomes without added risks compared with a fixed dose of a single drug. Hayward et al provide a convincing critique of the existing literature and challenge physicians not to rush to apply proposed treatment goals for LDL lowering, particularly for patients who are near their LDL goals on high-dose statin therapy.

Why is this such an important distinction? Many patients at high cardiovascular risk will not have LDL cholesterol levels lower than 100 mg/dL despite taking 40 or 80 mg/day of a potent statin. Even more patients will fail to reach levels below 70 mg/dL with single drug treatment even if they have an average LDL response to the drug [4]. The costs, complexity, and potential risks of treatment would be expected to rise as additional drugs are added, but the marginal benefits (if any) of changing treatment in this setting are not yet clear. Conversely, there is the question of whether physicians should be satisfied that a high-risk patient with an LDL cholesterol level just below the optional guideline threshold of 70 mg/dL on a low-dose statin is achieving maximal benefit. Current clinical evidence supports selecting a treatment and dosage that achieve the best results in high-risk patients even if a lower-dose statin would achieve an LDL cholesterol level below the specified target. Randomized trials are needed to compare the effects on clinical outcomes of strategies involving addition of drugs to existing potent statin therapy.

Applications for Clinical Practice

Moderate or high doses of potent statins (eg, atorvastatin 80 mg daily or simvastatin 40 or 80 mg daily) as used in clinical trials treating high-risk patients result in large cardiovascular risk reductions and should be widely used in these patients. It is not yet clear whether any change in treatment should be made for high-risk patients receiving high-dose statin therapy who fall modestly short of the LDL target thresholds defined by the NCEP.

—Review by Stephen D. Persell, MD, MPH

References

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