Low-Density Lipoprotein Lowering and Atherosclerosis Progression
Does More Mean Less?

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Statins (hydroxymethylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) have been shown to significantly reduce cardiovascular clinical events in a variety of patient categories, ranging from patients with established cardiovascular disease to those at risk for cardiovascular disease.1-6 Clinical benefits of statin therapy have also been shown across a wide range of pretreatment cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, warranting recent recommendations that statin therapy should be considered in all high-risk subjects, regardless of baseline cholesterol levels.6 While it is generally agreed that most of the clinical benefits of statins are related to cholesterol/LDL-C lowering, other biological effects of statins that do not depend on LDL-C lowering, the so-called pleiotropic effects, including effects on non-LDL lipid fractions, have also been implicated, mostly based on indirect data and preclinical findings.7,8 Two important questions with respect to the statins are 1) is the magnitude of clinical benefit from statins related to the magnitude of LDL-C lowering, or, in other words, does a lower LDL-C mean greater benefit, and if so, what is the lowest LDL-C level below which no further benefit can be expected? and 2) do statins differ from each other in terms of clinical benefit, and if so, is that related to unique properties of a statin or simply due to differing potencies in LDL-C lowering?

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In this issue of Circulation, Taylor and colleagues9 attempted to address the issue of magnitude of LDL-C lowering and its effect on changes in carotid-intima media thickness (IMT) in a cohort of patients with hyperlipidemia in need of pharmacotherapy, as defined by National Cholesterol Education Panel–Adult Treatment Panel II (NCEP-ATPII) guidelines. The investigators randomized 161 patients (139 completed 1-year follow-up) to pravastatin 40 mg/d or atorvastatin 80 mg/d and followed their carotid IMT using B-mode ultrasound over the subsequent year. As predicted, atorvastatin-treated patients experienced a greater reduction (−48.5% versus −27.5%) and lower final LDL-C level (76±23 versus 110±30 mg/dL) than patients in the pravastatin group. Atorvastatin-treated patients demonstrated a net regression of mean carotid IMT (−0.038±0.021 mm), whereas the pravastatin group showed stabilization with no significant change (0.026±0.017 mm). These differences became significant at 12 months but not at 6 months after randomization. The authors9 therefore suggest that more aggressive LDL-C lowering, compared with more modest LDL-C lowering, may have greater benefits against atherosclerosis, and by inference, clinical events since changes in IMT have generally paralleled changes in clinical events in previous trials. These findings are generally consistent with results reported in the Post-Coronary Artery Bypass Grafting trial, where more aggressive LDL-C reduction was associated with less progression of saphenous vein-graft disease and left main-stem disease, as well as the trial comparing the effects of simvastatin to atorvastatin on carotid IMT in patients with familial hypercholesterolemia.10-12 In contrast, these findings differ from those from the Cholesterol And Recurrent Events (CARE) and West Of Scotland Coronary Prevention Study (WOSCOPS) trials, where no clinical benefit was observed with pravastatin in patients with either an LDL-C level below 125 mg/dL (CARE) or with greater than 24% decrease in LDL-C (WOSCOPS); however, the post-hoc nature of such analysis has raised concerns about their validity.13,14 The data provided by Taylor et al9 are of potential interest and could have significant implications for clinical practice. However, before we definitively conclude that “more” (LDL-C lowering) means “less” (atherosclerosis progression/clinical events), several points deserve emphasis. First, the authors measured changes in carotid IMT rather than changes in advanced atherosclerotic plaque; therefore, any conclusions about atherosclerosis regression remains inferential rather than proven. The currently ongoing trials evaluating the effect of varying degrees of LDL-C lowering on atherosclerotic plaque burden, using electron beam computed tomography (Beyond Endorsed Lipid Lowering with EBCT Scannings [BELLES] trial) or intravascular ultrasound (REVERSAl of Atherosclerosis with Lipitor [REVERSAL] trial) are likely to provide additional useful information in this regard. Second, the present study9 evaluated a relatively small cohort of patients for a relatively short follow-up period using carotid IMT, a surrogate measurement, rather than clinical events as the primary endpoint. Use of surrogate endpoints can, at times, be misleading and must be corroborated by event-based clinical trials. The currently ongoing PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE IT)
trial may provide a more direct answer with respect to clinical benefits of aggressive versus modest LDL-C lowering. Third, while the authors show major differences in mean LDL-C levels and mean carotid IMT changes between the atorvastatin and pravastatin groups, the possibility that the differences in carotid IMT changes may be related in part to unique properties of statins that are unrelated to the magnitude of LDL-C lowering cannot be confidently ruled out.\textsuperscript{15} Had the authors used different doses of the same drug to achieve variable LDL-C lowering, this confounding may have been less of an issue. Fourth, despite directionally different and significant changes in mean carotid IMT between the atorvastatin and pravastatin groups, regression was not confined to the atorvastatin group.\textsuperscript{8} In fact, patients in both groups showed regression, although the frequency was somewhat greater in the atorvastatin group (54.4\% of patients) compared with the pravastatin group (38.6\% of patients). These findings suggest the possibility that regression could occur without marked LDL-C lowering. Examination of individual data points comparing changes in LDL-C to changes in carotid IMT could have provided additional valuable information regarding the relationship of the magnitude of LDL-C lowering to IMT regression. Unfortunately, such data are not provided in the present study.\textsuperscript{9} It is also conceivable that longer-term follow-up may attenuate (or possibly magnify) differences observed between atorvastatin and pravastatin in this study. Fifth, more aggressive lowering of LDL-C with higher doses or use of more potent statins may be counter-balanced by an increased risk for adverse effects; this was recently highlighted by the increased risk of rhabdomyolysis seen with cerivastatin, a potent statin, leading to its withdrawal from the market. For the clinician, the important questions remains how to initiate and titrate lipid-lowering therapy with statins: to a specific LDL-C target or to a specific % change in LDL-C, or should the decision be solely based on pretreatment LDL levels or pretreatment estimated clinical risk?\textsuperscript{16} The recent data from the very large Heart Protection Study (HPS) using 40 mg of simvastatin/d shows that the magnitude of proportional risk reduction is the same whether the baseline LDL-C levels are <116, 116 to 135, or over 135 mg/dL in patients at high risk, indirectly raising questions about the “more” (LDL-C lowering) means “less” (atherosclerosis progression or clinical events) hypothesis.\textsuperscript{6} Furthermore, in the HPS, the response of patients to simvastatin was assessed in the prerandomization phase of the study, and the magnitude of relative risk reduction was not related to the magnitude of LDL-C reduction observed during this prerandomization phase.\textsuperscript{4} The relative risk reduction with simvastatin was similar in patients with <38\%, average, or >48\% LDL-C reduction.\textsuperscript{6} The HPS also provided reassuring data to suggest that high-risk subjects may benefit from statin therapy even when their baseline LDL-C levels are at or below 100 mg/dL, and that any threshold of LDL-C below which no benefit can be expected is likely to be much lower than 100 mg/dL and closer to 77 mg/dL or less.\textsuperscript{6} Finally, focusing solely on LDL-C reduction as a means to an end should not distract us from looking for other ways and non-LDL targets for anti-atherogenic intervention.\textsuperscript{17,18} While we sort these issues out with additional investigations, it is, nevertheless, sound advice that all patients at risk for vascular disease or with established vascular disease should be treated with statins regardless of baseline LDL-C levels, preferably using agents with proven benefits at doses with proven clinical efficacy and safety.\textsuperscript{6}

References


Key Words: Editorials | lipoproteins | atherosclerosis | statins
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Circulation. 2002;106:2039-2040
doi: 10.1161/01.CIR.000037742.25731.3D

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/106/16/2039

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