Lipids, Biomarkers, and Noninvasive Imaging of Atherosclerotic Disease Activity in Clinical Trials

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There is great interest in developing a reliable measure of atherosclerotic disease activity that can serve as a measurement of the response to anti-atherosclerotic therapies. The epidemiologic relationship between lipid measures, most notably low-density lipoprotein cholesterol (LDL-C) and binary cardiovascular (CV) events, has been confirmed in treatment trials reliably demonstrating that a reduction in LDL-C translates into improved CV outcomes. Conversely, measures of atherosclerotic disease, such as carotid intima-media thickness and coronary calcification, while serving as a proxy for the burden and severity of atherosclerosis, have not performed well as disease activity measures that relate to responses to therapy or changes in CV events. Newer approaches, including blood biomarkers of cellular activity (lipoprotein-associated phospholipase A2, myeloperoxidase), visualization of plaque

composition with magnetic resonance imaging (MRI), and assessment of the metabolic activity of atherosclerosis with positron emission tomography (PET), hold promise in combination as a measure of atherosclerosis disease activity.

Enhancing Our Sophistication in Measuring Atherosclerosis in Clinical Trials

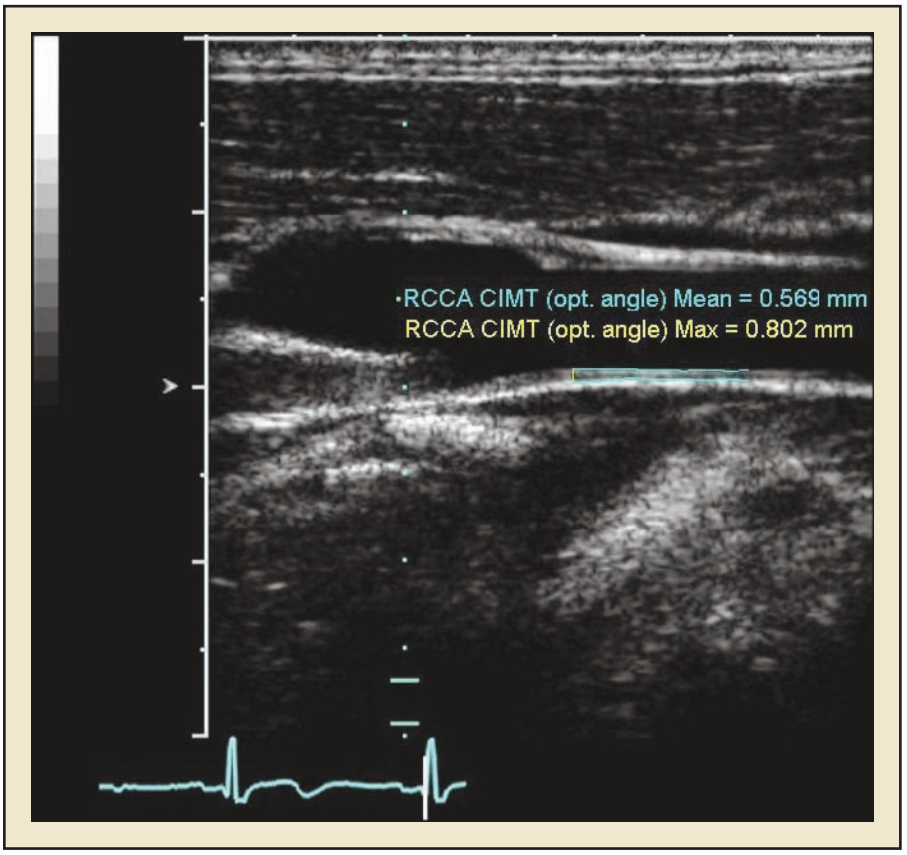
The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial was the most recent clinical trial to question the value of anatomic measures of atherosclerosis in randomized studies.[1] This trial randomized 720 patients, average age 46 years, with familial hypercholesterolemia (FH) by genotyping or World Health Organization criteria (which cite multiple definitions but in general use LDL-C values > 190 mg/dL). The ENHANCE subjects had LDL-C values of at least 210 mg/dL when off medication. Approximately 80% had previously been taking statins (3-hydroxy-3-methyl-glutaryl-CoA [HMG-CoA] reductase inhibitors). Importantly, the authors did not report the duration of statin therapy, the use of other lipid-lowering medications, or the degree of LDL-C control during adulthood. These factors clearly influence the degree and stability of anatomic atherosclerosis over a long period of time.

Of the 1180 patients who were screened, 408 did not meet entry criteria (of whom 288 had LDL-C values presumably too low for inclusion). The remaining patients were randomized to simvastatin 80 mg/d plus ezetimibe 10 mg/d (n = 357) versus simvastatin 80 mg/d alone (n = 363). The lost to follow-up rates of 10% in the simvastatin plus ezetimibe group and 12% in the simvastatin monotherapy group were acceptable. The primary outcome measure was the mean change in carotid artery intima-media thickness (CIMT) (calculated as the mean of 6 ultrasound measurements of the far wall intima-media distance of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries) at 24 months (Figure 1). The trial had 90% power to detect a difference of 0.05 mm in CIMT, with a large standard deviation of 0.20 (4 times the mean) at a 2-sided alpha of 0.05. It is presumed that the authors compared paired differences as opposed to unpaired differences, although this distinction is not clarified. A point of reference was the annual CIMT progression rates of 0.03 mm to 0.05 mm seen in large epidemiologic studies that have been modestly associated with CV events (relative risk [RR], 1.11-1.43).

At baseline, the mean CIMT of 6 segments was 0.69 ± 0.13 mm for the simvastatin plus ezetimibe group and 0.70 ± 13 mm for the simvastatin monotherapy group (P = .64). These patients with FH appeared to have been very well treated over the course of their lives, as these CIMT values would fall within the second most favorable category in the Atherosclerosis in Communities at Risk (ARIC) study, corresponding to a 5 per 1000 person-years risk of coronary heart disease (CHD) (Figure 2).[2] The group at highest risk in ARIC, patients with CIMT greater than 1.0 mm, had a 12 per 1000 person-years rate of CHD events.

The LDL-C reductions were from 319.0 ± 65.0 mg/dL to 141.3 ± 52.6 mg/dL (55.6%) in the simvastatin plus ezetimibe patients and from 317.8 ± 66.1 mg/dL to 192.7 ±

Figure 1. *Example of CIMT measurement by B-mode ultrasound. CIMT, carotid artery intima-media thickness; RCCA, right common carotid artery; opt., optimum.*



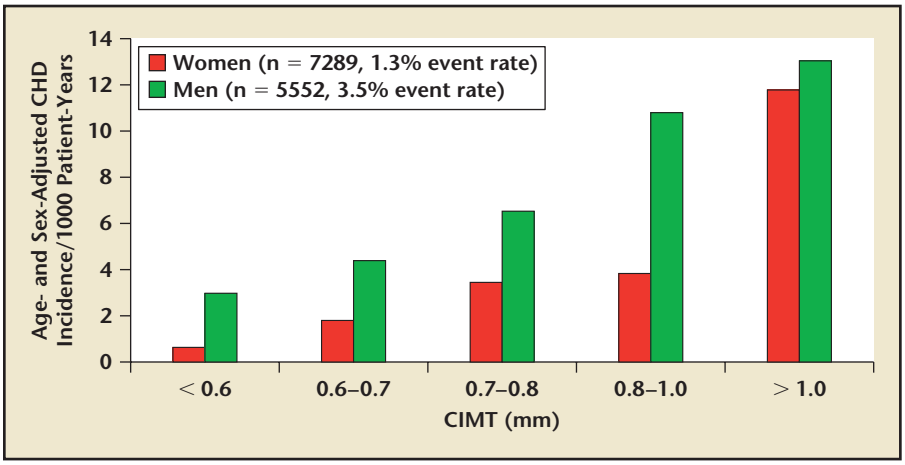


Figure 2. *Baseline CIMT and risk of cardiovascular events in the ARIC study. The mean follow-up was 5.2 years. The CHD incidence included myocardial infarction and cardiac death. CIMT, carotid artery intima-media thickness; ARIC, Atherosclerosis in Communities at Risk; CHD, coronary heart disease; MI, myocardial infarction. Data from Chambless LE et al.*[2]

60.3 mg/dL (39.1%) in the simvastatin monotherapy patients ($P < .01$) (Figure 3). The CIMT values were essentially unchanged from baseline, with the mean of 6 carotid segments being 0.71 ± 0.15 mm in the simvastatin plus ezetimibe patients and 0.70 ± 0.14 mm in the simvastatin alone patients ($P = .29$). The mean differences from baseline were 0.0111 ± 0.0038 in the simvastatin plus ezetimibe group and 0.0058 ± 0.0037 in the simvastatin alone group ($P = .29$). The annualized progression rate of CIMT in this trial was about 0.004 mm, which is about a tenth of the rate of progression of healthy volunteers and similar to that of FH patients undergoing lipid apheresis.[3] Thus, LDL-C reduction with a statin, even without achievement of levels less than 100 mg/dL or less than 70 mg/dL, can halt the anatomic progression of atherosclerosis. Because the difference in the presumably paired differences between the groups was 0.0111−0.0058 = 0.0053, the authors overestimated the effect size of 0.05 by a factor of 10. Thus, ENHANCE was severely underpowered to compare very small mean differences between the groups, given the relatively low baseline CIMT—a reflection of good, and likely prolonged, background treatment for hypercholesterolemia.

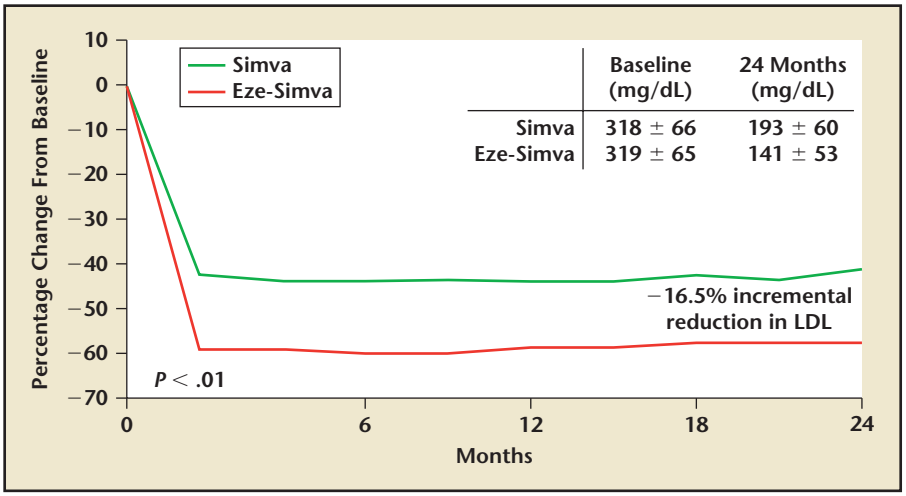
Comments

The ENHANCE trial demonstrated a significant difference in LDL-C reduction with simvastatin 80 mg plus ezetimibe 10 mg compared with simvastatin 80 mg monotherapy. This finding confirms that reduction in cholesterol synthesis (with a statin) combined with attenuation of enterohepatic circulation of cholesterol (with ezetimibe) is superior to the statin alone at the highest dose in patients with FH. Low CIMT values at baseline and very small changes in CIMT over 24 months left the trial severely underpowered to draw conclusions regarding the differential rate of anatomic progression of atherosclerosis. When presented with a well-validated biomarker associated with CV events, such as LDL-C (90,056 participants in 14 randomized trials), and a large effect size in a clinical trial such as ENHANCE, the most appropriate inference would be that combination treatment is beneficial.[4] Conversely, although the observation of a fundamental halt of progression of CIMT in both groups is gratifying in terms of treatment response, one cannot make inferences on drug effect given the ENHANCE limitations in low baseline CIMT values, the very small effect differential, and the severe lack of power at that effect size.

Other Studies of Carotid Atherosclerosis as a Disease Measure

There have been numerous trials using the change in CIMT (measured in various ways) as an endpoint. It is

Figure 3. *Reductions in LDL-C in the ENHANCE trial. LDL-C, low-density lipoprotein cholesterol; ENHANCE, Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; Simva, simvastatin 80 mg; Eze, ezetimide 10 mg. Reprinted with permission from Kastelein JJ et al.*[1] *Copyright © 2008 Massachusetts Medical Society. All rights reserved.*



beyond the scope of this article to review all of these trials, but a few points can be made on CIMT and treatment response. As a general rule, from both epidemiologic studies and clinical trials, a 0.03 to 0.05 mm annual increase in CIMT has been associated with a modest increase in CV events.[2-5] There have been relatively small treatment effects on CIMT progression, even when statins have created large LDL-C reductions compared with placebo.[6] In the Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II) trial, 151 patients were randomized to pravastatin 40 mg/d versus placebo, and differences in maximal CIMT in the 6 carotid segments were compared for 3 years.[7] Statin treatment resulted in a nonsignificant reduction in annual progression of the mean-maximum CIMT: 0.068 mm for the pravastatin group versus 0.059 mm for the placebo group. The LDL-C values achieved were 120 mg/dL for the treatment group versus 167 mg/dL for the control group, which translated into a reduction in fatal and nonfatal coronary events ($P = .09$) and of any fatal event plus nonfatal myocardial infarction ($P = .04$). Thus, the PLAC-II trial is another one in which a difference in CIMT did not correspond to LDL-C reduction and its translation to reduced CV events. As a measure of systemic atherosclerosis, why does CIMT progression have such a weak relationship with treatment effects on LDL-C and CV events? It has been demonstrated in 5640 subjects from the Cardiovascular Health Study that specific carotid structural geometric patterns are associated with the development of new CV events, independently of age, gender, traditional risk factors, and carotid CIMT.[8] Thus, the mean thickness of 6 segments is not capturing important information about outward and inward vascular remodeling and plaque vulnerability.

Newer MRI techniques of the carotid arteries have demonstrated that statins do not impact the overall atherosclerotic burden, but rather, the composition of atherosclerotic plaque. The randomized, double-blind Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: A Magnetic Resonance Imaging Observation (ORION) trial used 1.5-tesla MRI to image carotid atherosclerotic plaques at baseline and after 24 months of treatment.[9] Forty-three patients with fasting LDL-C between 100 and 250 mg/dL and 16% to 79% carotid stenosis as assessed by duplex ultrasound were randomized to receive rosuvastatin at either a low dose (5 mg) or a high dose (40 mg for 4 weeks and 80 mg thereafter, unless the patient did not tolerate the 80 mg dose or LDL-C dropped below 50 mg/dL). After 24 months, LDL-C was significantly reduced in the high-dose group as compared with the low-dose group (59.9% vs 38.2% [$P < .001$]). Despite the difference in LDL-C, there were no significant changes in carotid plaque volume for either dosage group. In all patients with a lipid-rich necrotic core at baseline, the mean proportion of the vessel wall composed of this material decreased by 41.4% ($P = .005$).

Finally, the use of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) coregistered with computed tomography is yielding important information on the progression and destabilization of atherosclerotic plaque. ^{18}FDG-PET imaging is capable of visualizing atherosclerotic plaque inflammation, as its accumulation corresponds to the macrophage-rich area of the plaque. In a small study, 43 consecutive subjects were randomized to either simvastatin (n = 21) or dietary management only (n = 22).[10] Positron emission tomography (PET) revealed 117 ^{18}FDG-positive plaques in the statin group and 123 such plaques in the diet group. At 3 months, simvastatin, but not diet alone, attenuated plaque ^{18}FDG uptakes and decreased the maximum uptake of ^{18}FDG in carotid and aortic plaque ($P < .01$). Simvastatin reduced LDL-C by 30% ($P < .01$) and increased high-density lipoprotein cholesterol (HDL-C) by 15% ($P < .01$). In the diet group, LDL-C and HDL-C levels were not changed. In the statin group, the decrease in signal intensity was correlated with the HDL-C elevation ($P < 0.01$), but not with the LDL-C reduction.

Comments

As we can see, noninvasive imaging of the carotid arteries with B-mode ultrasound, MRI, and PET, as singular measures, can have pitfalls with respect to making inferences on the progression of atherosclerosis and its relationship to lipid values. Thus, LDL-C should remain the biological measure of interest for clinical purposes at this time.

Coronary Artery Calcification and Statin Trials

Two nonrandomized studies using statins have demonstrated that attenuation of progression in coronary artery calcification (CAC), as measured by electron beam computed tomography (EBCT) (Agatston score or coronary calcium volume), is associated with LDL-C reduction.[11-13] The annualized relative change of the CAC score in 32 of 66 patients who achieved an LDL-C level of less than 100 mg/dL with cerivastatin 0.3 mg decreased from 27% to −3.4% ($P < .0001$) on serial EBCT exams.[11] In a report on 149 patients with coronary artery disease (CAD), Callister and colleagues[12] demonstrated that patients who

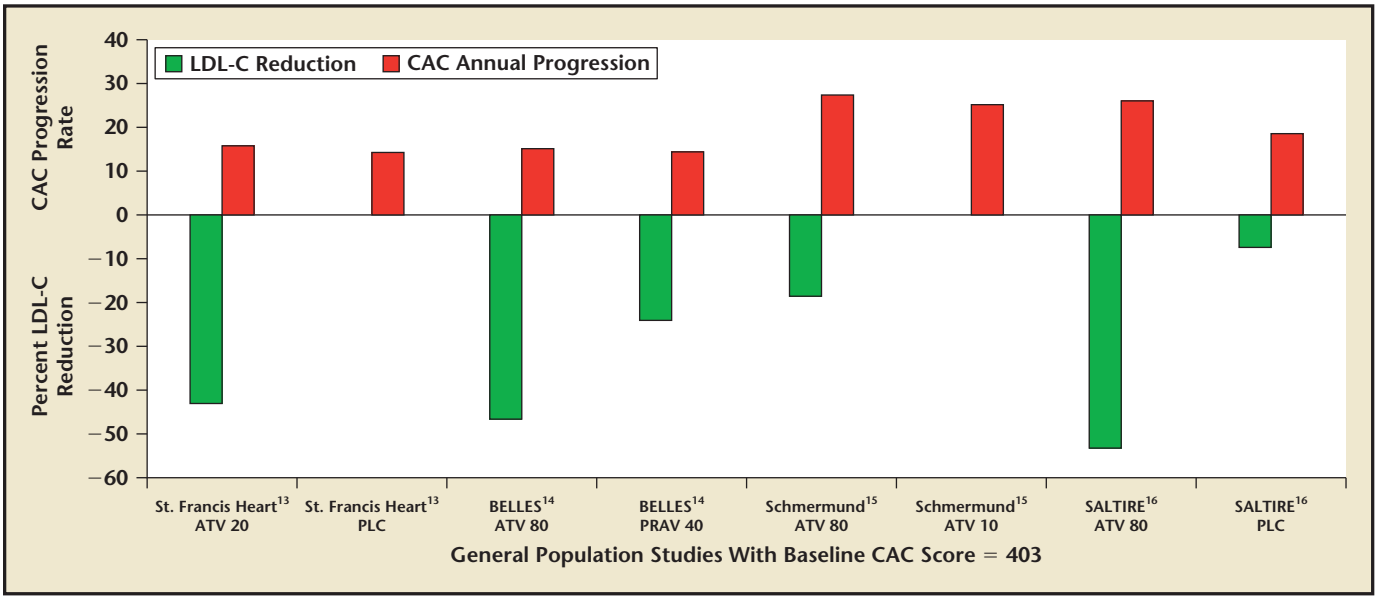


Figure 4. *Achieved LDL-C reduction and annualized rate of CAC in 4 randomized trials in the general population showing no impact of LDL-C reduction on the rate of CAC progression. Baseline mean CAC score was calculated as the weighted mean of the 2 groups of trials. LDL-C, low-density lipoprotein cholesterol; CAC, coronary artery calcification; ATV, atorvastatin; PRAV, pravastatin; PLC, placebo; BELLES, Beyond Endorsed Lipid Lowering with EBT Scanning; SALTIRE, Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression.*

achieved an LDL-C of less than 120 mg/dL had a regression of CAC as shown by EBCT when measured 12 to 15 months apart. There was a correlation (r = 0.50) between the reduction in LDL-C and the change in CAC as shown by EBCT, with regression in CAC beginning to occur on the line of best fit at an approximate LDL-C level of less than 100 mg/dL. Some patients in these studies had arrest or reversal in the calcification process; however, the determinants beyond LDL-C reduction of this reversal process are not completely understood.

There have been 5 randomized, prospective, comparative trials of statins in the general population attempting to show attenuation or reversal of CAC as measured by EBCT.[13-17] All of these trials, which have a total of 2273 patients, have failed to demonstrate that LDL-C reduction can modify the rate of progression of CAC, which is on average about 25% per year. However, in the larger studies with sufficient follow-up time, as expected there has been a decrease in CV events associated with LDL-C reduction with statins. Additionally, the Coronary Artery Calcification Treatment with Zocor (CATZ) study testing simvastatin 80 mg/d versus placebo for 12 months in 80 patients failed to demonstrate a difference in the progression of abdominal aortic calcification measured by CT.[17] Finally, the Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression (SALTIRE) trial tested atorvastatin 80 mg/d (n = 77) versus placebo (n = 78) during 25 months and found annual progression in aortic valvular calcification to be 22.3% ± 21.0% in the atorvastatin group and 21.7% ± 19.8% in the placebo group (P = .93).[18]

Summary

Taken as a whole, it appears that LDL-C reduction does not influence the rate of progressive atherosclerotic calcification (Figure 4). However, despite the advancement of calcification, it appears that LDL-C reduction, as expected, reduces rates of myocardial infarction and CV death. Thus, as with CIMT measurement, monitoring the progression of CAC is not a valid approach for detecting a change in the risk for atherosclerotic events.

Convergence of Imaging and Biomarkers as Measures of Atherosclerotic Disease Activity

Table 1 lists some of the noninvasive imaging technologies and blood biomarkers measured in the clinical trials attempting to make inferences regarding atherosclerotic disease activity. The most promising approach would appear to combine an imaging measure of plaque composition and/or biologic activity (MRI or PET) with blood biomarkers of macrophage and leukocyte activity within the plaque (lipoprotein phospholipase A2, myeloperoxidase).[19-21]

Table 1
Strengths and Weaknesses of Noninvasive Atherosclerotic Disease Activity Measures in Clinical Trials

Issue	CIMT	EBCT CAC	MRI	PET	Blood Biomarkers
Standardized measurement	+++++	+++++	+	+	+++++
Atherosclerotic burden	++++	++++	++	+	–
Plaque composition	+	+	++++	++	–
Vessel remodeling	+	+	+++	++	–
Macrophage activity	–	–	+	++++	LpPLA2
Leukocyte activity	–	–	–	–	MPO
Predicts future CV events	+++	++++	+	+	+++++ LDL-C ++ HDL-C ++ TG +++ hs-CRP ++++ LpPLA2 ++ MPO
Proven treatment target	Small effect size Inconsistent across trials	Failed	ND	+	+++++ LDL-C +++ HDL-C ++ TG + hs-CRP + LpPLA2

CIMT, carotid intimal medial thickness; EBCT, electron beam computed tomography; CAC, coronary artery calcification; MRI, magnetic resonance imaging; PET, positron emission tomography; LpPLA2, lipoprotein phospholipase A2; MPO, myeloperoxidase; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein; ND, no data available at this time.

These measurements together may be able to identify atherosclerotic lesions undergoing growth and changes that lead to progressive occlusion or plaque rupture. High-sensitivity C-reactive protein (hs-CRP), a product of hepatocytes in response to signals from adipokines, is too confounded by visceral adiposity and other CV risk factors (LDL-C) to emerge as a clear treatment target for pharmacotherapy.[22] However, it may be useful in assessing the impact of weight loss on the CV system because this intervention has been shown to cause very large (> 50%) reductions in hs-CRP.[23] Clearly, the lipid measurements of LDL-C, total cholesterol, HDL-C, and triglycerides, in descending order, are the most reliable treatment targets we have for clinical trials that relate to binary CV events.[24] The relationship of LDL-C reduction and translation into reduction in binary CV events has been the most consistent (Figure 5). At this time, it is important to keep these issues in perspective. Clinical trials that demonstrate LDL-C lowering without a concordant change in noninvasive imaging are prone to misinterpretation and confusion in the research and clinical communities, as witnessed by the ENHANCE and PLAC-II trials.

Conclusion

Anatomic assessment of atherosclerosis by B-mode ultrasound at multiple sites in the carotid arteries and calculation of CIMT do not accurately reflect changes in plaque morphology that relate to the development of future CV events. However, patients who have greater CIMT measures, as a proxy of the overall burden of systemic atherosclerosis, have modestly increased CV risk, as shown in ENHANCE and PLAC-II. In addition, many other trials suggest that CIMT is an inappropriate outcome measure and cannot supplant the information revealed in the LDL-C level. Likewise, serial measurement of CAC by computed tomography in the coronary arteries cannot be relied upon as an index of responsiveness to statins or change in LDL-C. Like CIMT, CAC is a reflection of the overall burden of atherosclerosis, and compared with people who have little or no measurable atherosclerosis, patients with high levels of CAC can be expected to have higher risks for myocardial infarction and cardiac death. The use of coronary computed tomography angiography has

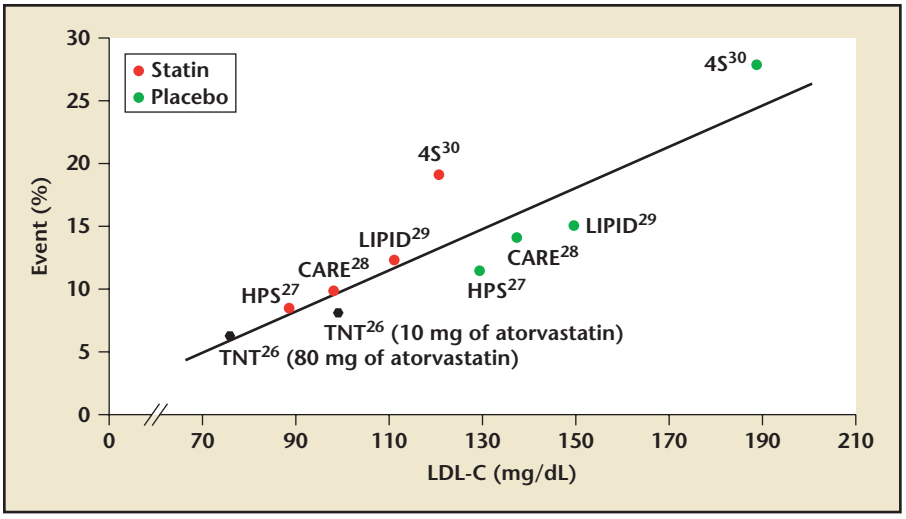


Figure 5. *Relationship between LDL-C reduction and cardiovascular events in major statin trials. LDL-C, low-density lipoprotein cholesterol; TNT, Treating to New Targets; HPS, Heart Protection Study; CARE, Cholesterol and Recurrent Events Trial; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; 4S, Scandinavian Simvastatin Survival Study. Reprinted with permission from LaRosa JC et al.[26] Copyright © 2005 Massachusetts Medical Society. All rights reserved.*

not yet been evaluated as a treatment target in clinical trials with respect to either severity of stenosis or plaque morphology. We can anticipate from the prior quantitative angiography trials that regression of the severity of stenosis will not be a useful measure in future trials using CTA.[25] However, assessment of plaque morphology and potential vulnerability are research ideas worth exploring with this technology. Newer techniques using MRI or PET hold promise for allowing inferences regarding atherosclerotic disease progression, which appears to be seen as changes in plaque morphology and not in overall artery thickness or calcification. These imaging techniques, combined with blood biomarkers of cellular activity within the atherosclerotic plaque, hold the most promise for establishing an index of atherosclerotic disease activity for use in future clinical trials. Until enhanced models of endpoint(s) of patient and plaque vulnerability are developed that correlate with CV events, one must use caution in using single surrogate markers of atherosclerosis activity, such as CIMT, to compare the effectiveness of risk factor intervention strategies on known important endpoints, such as LDL-C, as was the case in the ENHANCE trial. New and reliable assessments of atherosclerosis progression and patient/plaque vulnerability will likely include a combination of anatomic, morphologic, and biomarker inputs. ■

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