Atherosclerosis in the HIV and non-HIV setting: detecting and modifying cardiovascular risk

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Atherosclerosis measured by B-mode ultrasonography: effect of statin therapy on disease progression

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Abstract

Changes in intima-media thickness (IMT) and arterial lumen diameter – as measured by B-mode high-resolution ultrasonography and quantitative coronary angiography, respectively – are currently the only surrogate markers for progression of atherosclerotic disease recognized by regulatory authorities in the United States and Europe. Because atherosclerosis is a disease of the arterial wall, the ability of B-mode ultrasonography to provide visualization of IMT offers significant advantages over angiography. These advantages, as well as the safety and noninvasive-ness of B-mode ultrasonography, have led to increasing use of this imaging technique in observational studies and interventional studies of lipid-lowering agents over the last decade. These observational studies clearly demonstrated an association between carotid IMT and atherosclerotic disease. Of the interventional studies, the recent Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial found that use of atorvastatin 80 mg daily for aggressive lowering of plasma low-density lipoprotein cholesterol (LDL-C) concentrations to below current target levels was associated with significant IMT regression compared with results obtained with less aggressive plasma LDL-C lowering. A new study – Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin (METEOR) – will examine the effects of aggressive lipid-lowering treatment with rosuvastatin 40 mg daily on IMT. The cohort in this study will be individuals with mild hypercholesterolemia whose standard risk assessment does not categorize them as at sufficient risk of clinical disease to warrant initiation of lipid-lowering therapy despite their relatively high IMT values.
Atherosclerosis is a dynamic disease process characterized by vessel wall remodeling that occurs over decades, ultimately becoming clinically manifest as acute cardiovascular events in many individuals.1 Epidemiologic and interventional studies using cardiovascular clinical end points require long study periods and large populations to establish the influence of risk factors and effects of therapeutic interventions in preventing such disease outcomes. B-mode (2-dimensional) ultrasonographic imaging permits noninvasive, real-time, high-resolution imaging of superficial artery walls, thus allowing visualization of the effects of atherosclerotic processes on the vessel wall at every stage from relative absence of disease to complete arterial occlusion. Because atherosclerosis is a disease of the arterial wall, the ability of B-mode ultrasonography to provide visualization of carotid intima-media thickness (IMT) offers significant advantages over angiography.2 In particular, B-mode ultrasonography permits visualization of the entire artery wall at all stages of disease progression, whereas angiography permits visualization of the lumen only and detects changes only at very late stages in the disease process. Moreover, B-mode ultrasonography is safe and noninvasive, and so it can be used in observational studies of healthy patients as well as in atherosclerosis regression trials.3 Several questions about B-mode ultrasonography remain unanswered, including the most appropriate vessel for measurement of IMT (e.g., internal carotid artery vs. common carotid artery), its applicability in younger patients, and standardization of imaging protocols.4–6 Overall, however, the weight of evidence strongly supports the use of B-mode ultrasonography as a research tool in clinical trials of lipid-lowering agents: it allows disease progression and interventional effects to be assessed in smaller patient populations and over relatively shorter periods than in studies using clinical end points. To date, changes in IMT measured by B-mode high-resolution ultrasonography and changes in arterial lumen diameter determined by quantitative coronary angiography are the only surrogate markers for progression of atherosclerotic disease recognized by the US Food and Drug Administration (FDA).

This article reviews evidence from observational studies demonstrating that carotid IMT is increased in patients with established clinical cardiovascular disease (CVD) and that increased IMT is predictive of new-onset clinical disease. An overview of key 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) interventional trials using B-mode ultrasonography is provided, and the implications of these studies for the treatment of patients with various risk profiles, including those at low risk of experiencing clinical events but with relatively high IMT values, are discussed. A more nuanced understanding of patient risk is particularly important in light of 2 recent reports: the final report of the third Adult Treatment Panel (ATPIII) of the US National Cholesterol Education Program (NCEP),7 which significantly revised the use of Framingham risk assessment and increased the number of patients eligible for plasma lipid lowering therapy; and the UK Medical Research Council/ British Heart Foundation (MRC/BHF) Heart Protection Study (HPS),8 which demonstrated that statin treatment may benefit a wider range of individuals than previously believed.
Observational intima-media thickness studies

Several observational studies have shown that individuals with CVD have greater IMT values and that greater IMT is associated with increased risk of clinical disease. In an early study, Geroulakos et al. compared 75 patients undergoing coronary angiography for symptomatic coronary artery disease (CAD) with 40 asymptomatic matched control subjects. These investigators found that common carotid IMT was greater in patients than in control subjects and was greater in patients with stenosis on coronary angiography than in those with “normal” angiograms.

Two large studies that assessed the association of IMT on B-mode ultrasonography and atherosclerotic disease in the general community are the Atherosclerosis Risk in Communities (ARIC) Study and the Rotterdam Study. In the ARIC Study, assessment of the far wall of the carotid artery in 13,870 black and white men and women revealed that the mean carotid IMT was greater in individuals with prevalent CVD than in disease-free individuals across all race and sex strata. A mean carotid IMT increase of 0.2 mm increased the relative risk of myocardial infarction (MI) by 33% and stroke by 28%, suggesting that B-mode ultrasonography is a noninvasive predictor of CAD. Similar results were demonstrated by the Rotterdam Study, a single-center prospective study in 8,000 individuals >55 years in a suburb of Rotterdam: documented associations between carotid IMT and MI, stroke, angina, intermittent claudication, and hypertension. Over a mean 2.7 years of follow-up, a case-control substudy in subjects with or without MI or stroke showed that a higher baseline IMT was associated with increased risk of MI (odds ratio OR, 1.43 per baseline IMT SD increment of 0.163) and that it increased the risk of stroke (OR, 1.41/SD increment). Greater risk of MI (OR, 1.51/SD increment) and stroke (OR, 1.57/SD increment) also was associated with higher baseline IMT in those subjects without a history of MI or stroke.

The association between IMT and CVD in asymptomatic patients was also seen in a study by the Cardiovascular Health Study Collaborative Research Group, which observed 4,476 patients without clinical CVD for a median follow-up of >6 years. Cumulative (unadjusted) cardiovascular event rates correlated with baseline carotid IMT quintile, with the rate of MI or stroke <5% in the lowest (first) quintile and >25% in the highest (fifth) quintile. The significant relation remained after adjustment for other risk factors; relative risk of MI or stroke increased to 1.54 in the second IMT quintile, 1.84 in the third quintile, 2.01 in the fourth quintile, and 3.15 in the fifth quintile.

These observational studies clearly demonstrate an association between carotid IMT and atherosclerotic disease. However, because carotid IMT is also strongly related to conventional risk factors, whether use of this biomarker improves the ability to stratify patients into high- and low-risk groups remains a matter of debate.


**Statin interventional studies**

The effects of statin therapy on atherosclerosis have been assessed by high-resolution ultrasonographic measurement of carotid IMT in a number of studies. It is important to keep in mind, however, that lack of a standardized protocol for measuring IMT change makes inter-study comparisons difficult. In particular, imaging protocols vary with respect to the carotid artery selected for IMT measurement, i.e., left or right common carotid artery, the carotid bulb, or the internal carotid artery, as well as the specific segment of the artery, i.e., near or far wall. Some trials have included both internal and common carotid arteries as outcome measures, whereas others have focused on the far wall of the common carotid artery.  

An example of variation due to the arterial segment selected occurred in the Asymptomatic Carotid Artery Progression Study (ACAPS)\textsuperscript{15}; 919 asymptomatic men and women (aged 40 to 79 years) with early carotid atherosclerosis received lovastatin 20 to 40 mg daily or placebo (all received aspirin) and had carotid IMT measured at 6-month intervals for 3 years. The mean values for maximum carotid IMT decreased by 0.009 mm/yr in the lovastatin group and increased by 0.006 mm/yr in the placebo group (P = 0.001) (Figure 1). Plasma levels of low-density lipoprotein cholesterol (LDL-C) were reduced by 28% in the lovastatin recipients (from 157 to 113 mg/dL) and were unchanged in the placebo group. However, it is instructive to note that the results for ACAPS would have been negative if only far-wall common carotid artery IMT had been used as an outcome measure, illustrating the difficulty in making comparisons with studies that do not include IMT of the internal carotid artery as an outcome measure.\textsuperscript{6}

*Figure 1* Change in mean values for maximum carotid intima-media thickness (IMT) measurements in patients receiving either lovastatin 20 to 40 mg or placebo daily in the Asymptomatic Carotid Artery Progression Study (ACAPS). (Reprinted with permission from *Circulation*.)\textsuperscript{15}
One such study is the Kuopio Atherosclerosis Prevention Study,\textsuperscript{16} which measured IMT in the right and left distal common carotid artery and the right and left carotid bulb but not in the internal carotid artery; 447 men (aged 44 to 65 years) with plasma levels of LDL-C $\geq 4.0$ mmol/L (154 mg/dL) and total cholesterol $< 7.5$ mmol/L (290 mg/dL) received pravastatin 40 mg or placebo daily for 3 years. Overall mean carotid IMT increased by 0.017 mm/yr in the pravastatin group and increased by 0.031 mm/yr in the placebo group ($P < 0.005$). Plasma LDL-C concentration was reduced by 27\% in the pravastatin group and remained unchanged in the placebo group. The study investigators suggested that the straight segment of the common carotid artery be used as the site for B-mode ultrasonography in future studies assessing atherosclerotic disease progression.

The importance of common carotid artery measurements was also demonstrated in the Monitored Atherosclerosis Regression Study (MARS).\textsuperscript{17} Distal common carotid IMT was measured at 6-month intervals for $\leq 4$ years in 188 adults (aged 37 to 67 years) with angiographic CAD and a plasma total cholesterol value of 190 to 295 mg/dL who received either placebo plus dietary therapy or lovastatin 80 mg daily. IMT was significantly reduced in the lovastatin recipients as early as 1 year after initiation of therapy (Figure 2). Mean reductions in IMT were 0.038 mm/yr at 2 years and 0.028 mm/yr at 4 years in the lovastatin group compared with mean increases of 0.019 mm/yr at 2 years and 0.015 mm/yr at 4 years in the placebo group ($P < 0.001$). Reductions in IMT were greater in lovastatin recipients with higher baseline IMT values, whereas increases in placebo recipients were similar irrespective of baseline values. On-treatment levels of plasma LDL-C and several other plasma lipid measures correlated with the rate of change in IMT. Plasma LDL-C concentration decreased by 45.4\%--from 4.03 to 2.20 mmol/L (156 to 85 mg/dL)--in the lovastatin group, and remained unchanged in the placebo group.

A substudy of the Regression Growth Evaluation Statin Study (REGRESS)\textsuperscript{18} showed that pravastatin has a treatment effect on both the carotid and femoral artery walls. In this report from REGRESS, 255 men (<70 years) with angiographic coronary disease and plasma total cholesterol levels of 155 to 310 mg/dL received pravastatin 40 mg daily or placebo and had carotid and femoral artery IMT measured at 6-month intervals for 2 years. The mean combined IMT decreased by 0.05 mm in the pravastatin group and remained unchanged in the placebo group, and the mean values for maximal IMT decreased by 0.005 mm and increased by 0.001 mm, respectively. The pravastatin treatment effects were highly significant (combined IMT, $P = 0.0085$; combined far-wall IMT, $P < 0.0001$; both vs. placebo). Plasma LDL-C concentration was reduced by 28.7\%--from 4.36 to 3.11 mmol/L (168 to 120 mg/dL)--in the pravastatin group and remained unchanged in the placebo group. Interestingly, a separate arm of the study that assessed pravastatin efficacy by means of coronary angiography failed to demonstrate improvement at the same level of statistical significance as did the ultrasonography arm of the study, despite the larger sample size in the angiography arm ($n=885$).\textsuperscript{19} The difference in the 2 study arms highlights the benefit of B-mode ultrasonography as a research tool in statin interventional trials.
In the Atorvastatin Versus Simvastatin on Atherosclerosis Progression (ASAP) trial, 325 patients (aged 30 to 70 years) with heterozygous familial hypercholesterolemia – which poses a high risk for accelerated and severe atherosclerotic disease – received daily atorvastatin 80 mg (aggressive lipid lowering) or simvastatin 40 mg (conventional lipid lowering) for 2 years. Patients either were previously untreated or had on-treatment plasma LDL-C levels >4.5 mmol/L (174 mg/dL). Carotid IMT was significantly reduced (− 0.031 mm) in the atorvastatin group and significantly increased (+0.036 mm) in the simvastatin group; the difference between groups was statistically significant (P =0.0001). Plasma levels of LDL-C were decreased by 51.5% with atorvastatin 80 mg treatment (from 8.00 to 3.88 mmol/L [309 to 150 mg/dL]) and by 42.3% with simvastatin 40 mg (from 8.33 to 4.81 mmol/L [322 to 186 mg/dL]). As in ACAPS, this trial combined common and internal carotid IMT as a primary outcome measure, so results are not easily comparable with other studies that did not include internal carotid IMT.

This ASAP trial demonstrated the advantages of aggressive plasma lipid lowering over conventional treatment with respect to progression of atherosclerosis. Does it follow that lowering plasma LDL-C concentrations even below the level recommended by ATP III guidelines provides additional treatment advantages? Results of the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study suggest that this may be the case. In this study, 161 patients (mean age, 60 years) who met ATP III criteria for plasma lipid-lowering therapy received atorvastatin 80 mg or pravastatin 40 mg daily for 1 year, with carotid IMT measured at 6 and 12 months. Plasma levels of LDL-C were reduced by 48.6% (from 148 to 76 mg/dL) with atorvastatin 80 mg and by 29.0% (from 155 to 110 mg/dL) with pravastatin 40 mg, whereas IMT was reduced by 0.034 mm in the atorvastatin group and increased by 0.025 mm in the pravastatin group at 12 months (P =0.03) (Figure 3).
Figure 3  Mean carotid intima-media thickness (IMT) measurements at baseline and 6 and 12 months in patients receiving pravastatin 40 mg or atorvastatin 80 mg daily in the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study. (Reprinted with permission from Circulation)²¹

Despite the difficulties in comparing IMT data across statin interventional trials, the weight of evidence indicates that a greater magnitude of plasma LDL-C lowering is associated with a greater beneficial impact in terms of atherosclerotic regression. These findings are clearly supported by, and lend support to, the ATP III report, which emphasizes the need for more aggressive treatment of patients at risk for CVD.⁷ In fact, the results of the ARBITER study suggest that plasma LDL-C lowering to below currently recommended target levels provides additional benefit in atherosclerotic regression.²¹

A new trial of rosuvastatin – the Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin (METEOR) study – is now exploring whether asymptomatic patients who are not candidates for plasma lipid-lowering therapy on the basis of ATP III risk assessment, but who have relatively high IMT values, can also benefit from statin treatment.²² Rosuvastatin is highly efficacious in reducing plasma concentrations of LDL-C as well as in improving other plasma lipid variables in hypercholesterolemic patients: when compared with atorvastatin, simvastatin, and pravastatin,²³,²⁴ rosuvastatin produced significantly greater reductions in plasma LDL-C values across the dose ranges of the drugs.²⁵ Rosuvastatin 40 mg daily reduces plasma levels of LDL-C by 63% in patients with mild to moderate hypercholesterolemia.²⁴ In METEOR,²² a target population of 840 patients is to be randomized in the proportion of 5:2 to receive either double blinded rosuvastatin 40 mg or placebo daily for 2 years, respectively, with carotid IMT measured at 6-month intervals. Eligible patients are men aged 45 to 70 years and women aged 55 to 70 years who meet the following criteria: plasma LDL-C level of 3.1 to 4.1 mmol/L (120 to 159 mg/dL) plus 10-year coronary heart
disease risk <10% or plasma LDL-C level ≤4.9 mmol/L (189 mg/dL) and no additional risk factors; plasma high-density lipoprotein cholesterol level >1.6 mmol/L (6.2 mg/dL); plasma triglyceride level ≤1.65 mmol/L (500 mg/dL); and maximal carotid IMT of 1.2 to 3.5 mm. Trial participants thus are not candidates for plasma lipid-lowering therapy on the basis of ATP III risk assessment, which allows placebo use in the trial, but they have relatively high carotid IMT values. Rosuvastatin treatment is expected to reduce plasma LDL-C concentrations to well below 100 mg/dL, the upper end of the target range in patients with the most aggressive plasma LDL-C goals, as did atorvastatin 80 mg daily in the ARBITER study.

The METEOR study should provide important information on the effects of aggressive lipid reduction on regression of increased IMT in patients considered to be at low risk of clinical disease. A positive outcome will provide support for the use of statin treatment in individuals who are at low risk on the basis of standard risk assessment while having evidence of advanced atherosclerotic disease determined by means of IMT measurements.

B-mode ultrasonography has also been used in clinical trials of other plasma lipid-lowering agents, such as ezetimibe. Because this technique allows disease progression and intervention effects to be assessed in smaller patient populations and over relatively shorter periods than in studies using clinical end points, B-mode ultrasonography is expected to be incorporated into the phase 3 programs of novel agents currently in development, including cholesteryl ester transfer protein inhibitors, acyl coenzyme A:cholesterol acyltransferase inhibitors, ileal bile acid transport inhibitors, microsomal triglyceride transfer protein inhibitors, and dual peroxisome proliferator-activated receptor–α and –γ agonists. For the full benefit of B-mode ultrasonography to be realized, however, several issues remain to be addressed, including further standardization of the imaging protocols.
References


