REVIEW

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# Intravascular ultrasonography: Using imaging end points in coronary atherosclerosis trials

## ABSTRACT

Intravascular ultrasonography (IVUS) can precisely measure plaque burden and is being used to test new drug therapies. Other imaging tests may also prove useful to monitor treatment of atherosclerosis and identify populations at risk for coronary artery disease (CAD).

## KEY POINTS

New markers of early cardiovascular disease are needed: if clinical event rates are used as end points, trials must be extremely large.

Lipoprotein concentrations are good surrogate markers but may not be directly altered by potential new therapies, such as those targeting inflammation.

Measuring plaque burden with imaging tests allows one to directly monitor atherosclerosis.

Plaque progression cannot be accurately assessed by measuring arterial lumen dimensions because complex remodeling occurs as a plaque enlarges.

Volumetric analysis of plaque progression, using IVUS during cardiac catheterization, has been successfully used in clinical trials of CAD therapy.

Ultrasonography, computed tomography, and magnetic resonance imaging are increasingly used to identify apparently healthy patients at high risk for CAD.

The authors have indicated that they have received research support from the Pfizer, Merck, AstraZeneca, Sankyo, and Takeda corporations.

NEW IMAGING TECHNIQUES to detect and measure atherosclerosis offer great potential in evaluating new drug therapies, monitoring treatment of patients with coronary artery disease (CAD), and identifying people without symptoms who are at high risk for acute coronary events.

In this article we discuss intravascular ultrasonography (IVUS), which is a test performed during cardiac catheterization that has been used successfully to evaluate new drug therapies for atherosclerosis in patients with known CAD. We also discuss noninvasive computed tomographic (CT) imaging of plaque, which may in the future be used to identify subclinical disease as the basis for primary prevention of acute cardiovascular events.

## ATHEROSCLEROSIS STILL EPIDEMIC

CAD is still the single largest cause of death of men and women in industrialized societies,[1–3] although survival rates of patients with symptoms have improved with drug treatment and percutaneous and surgical revascularization.

But the positive trends of the last decade may be reversed because of increasingly widespread physical inactivity and high-fat diets, leading to an epidemic of obesity, dyslipidemia, and insulin resistance. Increased efforts in disease prevention are urgently needed,[4] aimed at modifying diet and life style and developing new classes of drugs that alter the development and progression of atherosclerosis.

## PROBLEMS IN STUDYING CAD

It is often difficult to detect CAD early in its course because of the characteristics of atherosclerotic lesion development.[5] Acute coronary events, including myocardial infarction and sudden cardiac death, are often the first signs of disease: they are usually initiated by the abrupt rupture of preexisting lesions that were only mildly stenotic.[6,7]

However, CAD begins to develop many years before clinical events occur.[8] Because the event rate in the apparently healthy population is low, drug trials with the traditional end points of myocardial infarction and death require extremely large populations and long follow-up.

Similarly, because patients with documented CAD now have better treatment (including the wider use of statins), there are fewer events, and secondary prevention trials require increasingly large study populations to attain sufficient statistical power.

## SURROGATE END POINTS FOR CORONARY EVENTS

**Positive trends in CAD may be offset by the rise in obesity, dyslipidemia, and insulin resistance**

Disease markers other than coronary events are commonly used as end points in studies that assess new medications for CAD.

Total cholesterol was identified by the Framingham Heart Study[9] as a major contributor to CAD and as strongly related to disease progression. Many subsequent studies of lipid-lowering medications demonstrated a link between reducing low-density lipoprotein cholesterol (LDL-C) and preventing cardiovascular morbidity and mortality.[10–16] Accordingly, the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) identified LDL-C as the primary target for disease prevention.[17]

Other pathophysiologic processes are becoming targets for pharmacological intervention. Recent areas of intense research include the role of high-density lipoprotein cholesterol (HDL-C) and systemic inflammatory changes associated with CAD.[5,18–21]

Because these experimental classes of medications may have little or no effect on LDL-C, new markers are needed to develop and evaluate them. However, the presence of disease markers and how they change during drug therapy typically reflect only part of the complex pathophysiology of CAD and may be mere epiphenomena. New markers must be carefully evaluated by directly comparing them with clinical end points in serial studies.

## ATHEROSCLEROSIS IMAGING

Emerging markers of CAD are lesion morphology and plaque burden, which are assessed by in vivo imaging and which allow one direct observation of the vascular effects associated with antiatherosclerotic agents.[22,23] Detecting and quantifying subclinical coronary atherosclerosis and plaque vulnerability may help identify high-risk patients before coronary events occur and allow serial monitoring during therapy.

**Quantitative coronary angiography** to measure luminal dimensions was the first imaging technique used to serially assess atherosclerotic disease.[24] Clinical trials using medications effective against atherosclerosis typically demonstrated that treated patients showed regression or less progression.[25,26]

However, the angiographic differences associated with significantly fewer clinical events were surprisingly small.[26–28] Cardiovascular events correlate poorly with angiographic lumen size because of characteristics of disease progression: early on, the vessel expands at the lesion site, allowing the plaque to enlarge without obstructing the lumen.[29,30] Because of this complex remodeling, angiography underestimates the extent of atherosclerosis compared with postmortem or IVUS measurements.[31] Although angiographic lesions appear as a focal disease process, CAD is actually diffusely distributed in the coronary tree.[32]

**IVUS** allows direct observation of a vessel's plaque burden rather than its lumen size. It is performed during cardiac catheterization[33,34]: a small catheter (< 3 French or < 1.0 mm) is advanced into a coronary artery, allowing real-time intraluminal imaging of the vessel wall and measurement of the atheroma.[35]

The first serial studies using IVUS were small, and they monitored plaque area at the most diseased site during drug treatment.

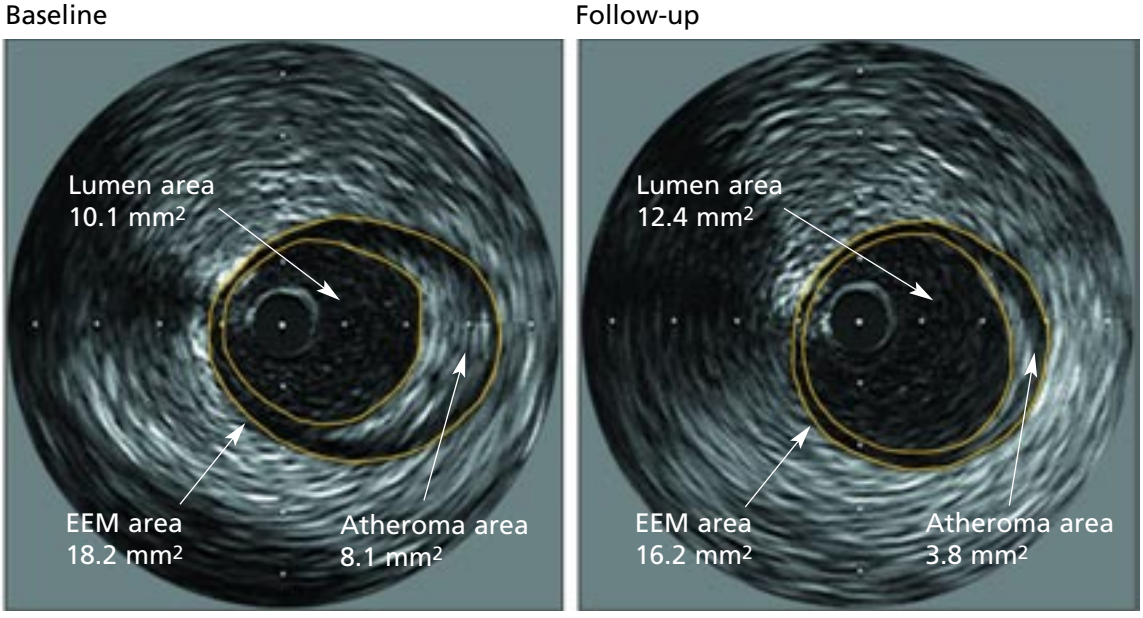


**FIGURE 1.** Coronary intravascular ultrasonographic (IVUS) images at baseline (**left**) and after 18 months of statin treatment (**right**) in a patient in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial.[43] Atheroma area is calculated by subtracting the lumen area from the area of the external elastic membrane (EEM).

Plaque size progressed more slowly or regressed in the treatment groups.[36,37] This approach, however, is difficult to reproduce: it is hard to exactly match an individual lesion site, which may change in size and morphology between baseline and follow-up. Another shortcoming is that single lesion sites are insufficient measures of the diffuse, heterogeneous disease accumulation found in patients with CAD.

To address these concerns, recent coronary IVUS trials used quantitative volumetric analysis.[38,39] Plaque area is measured at consecutive 1-mm intervals along a vessel segment between two characteristic side branches, and the results are integrated to calculate plaque burden. In serial studies, patients typically return for a repeat IVUS examination after 12 to 24 months. Because a segment is matched rather than individual sites, small changes in atheroma volume (the primary efficacy measure) can be assessed with considerable statistical power.[39–41] Important aspects of measurement variability and required sample size were discussed in recent studies.[41–44]

## IVUS STUDIES IN PATIENTS WITH KNOWN DISEASE

**IVUS shows plaque burden, rather than lumen size**

### Lowering LDL-C with statins

**Schartl et al**[42] evaluated plaque volume and morphology in a serial IVUS study in 131 patients with CAD, who were randomized to undergo either treatment with atorvastatin or "usual care" (including other statin therapy).

After 12 months, the mean LDL-C concentration had fallen from 155 to 86 mg/dL in the atorvastatin group and from 166 to 140 mg/dL in the usual care group. The mean absolute plaque volume increased 1.2 ± 30.4 $mm^3$ in patients taking atorvastatin compared with 9.6 ± 28.1 $mm^3$ in the usual care group, although the difference was not statistically significant ($P = .19$). Plaque echogenicity increased more in those treated with atorvastatin, presumably reflecting lipid depletion of atherosclerotic lesions.

Several other multicenter IVUS studies using volumetric analysis of plaque burden have recently been published (see below).[39]

**The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)**

**trial**[43] randomly assigned 502 patients with angiographically documented CAD to undergo treatment for 18 months with either atorvastatin 80 mg or pravastatin 40 mg. IVUS was performed at baseline and at study completion and analyzed in a blinded core laboratory (**FIGURE 1**).

At baseline, the mean LDL-C concentration was 150.2 mg/dL (range 125–210 mg/dL), which was reduced to 110 mg/dL with pravastatin and 79 mg/dL with atorvastatin ($P < .001$). C-reactive protein levels decreased 5.2% with pravastatin and 36.4% with atorvastatin ($P < .001$).

The primary end point was the percent change in atheroma volume. Atheroma increased in volume by a median of 2.7% in the pravastatin group ($P = .001$) but decreased by 0.4% in the atorvastatin group ($P = .98$ compared with baseline, $P = .02$ compared with the pravastatin group), indicating absence of progression with high-dose atorvastatin. The lower rate was independent of baseline LDL-C levels.

These results show that intensive treatment of hypercholesterolemia using atorvastatin 80 mg can arrest progression of coronary atherosclerosis.

## Raising HDL-C

In addition to high LDL-C, low HDL-C levels are also associated with increased cardiovascular risk, and pharmacological interventions aimed at increasing HDL-C are emerging.[18,45] In animal models, intravenous infusion of recombinant apolipoprotein A-I Milano/phospholipid complex, a variant of the apolipoprotein A-I protein normally present in HDL, is associated with plaque regression.[18]

**The apolipoprotein A-I Milano trial**[44] randomized 47 patients to receive five weekly intravenous infusions of placebo or recombinant apolipoprotein A-I Milano/phospholipid complexes (ETC-216) at 15 mg/kg or 45 mg/kg in a double-blind fashion, in a ratio of 1:2:2. IVUS was performed within 2 weeks after an episode of acute coronary syndrome and was repeated after the five weekly treatments. The primary efficacy measure was the change from baseline in percent atheroma volume in the combined ETC-216 cohort.

The mean atheroma volume decreased by 1.06% (SD 3.17%) in the combined ETC-216 group (median –0.81%; 95% confidence interval [CI] –0.34% to –1.53%, $P = .02$ compared with baseline). In the placebo group, the mean atheroma volume increased by 0.14% (SD 3.09%, median 0.03%, $P = 0.97$ compared with baseline). The absolute reduction in atheroma volume in the combined treatment groups was 14.1 $mm^3$, a 4.2% decrease from baseline ($P < .001$).

This study demonstrated for the first time that plaque regression can be achieved with a systemic pharmacological intervention and identified HDL as an important therapeutic target.

## Calcium blocker and ACE inhibitor?

The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study examined the effect of antihypertensive drugs on cardiovascular events in patients with angiographically documented CAD and normal blood pressure.[46] A total of 1,991 patients were randomized to 24-month treatment with amlodipine, enalapril, or placebo. A substudy of 274 patients measured atherosclerosis progression by IVUS.

**New therapies will aim at targets other than LDL-C**

Baseline blood pressure averaged 129/78 mm Hg for all patients; it increased by 0.7/0.6 mm Hg in the placebo group and decreased by 4.8/2.5 mm Hg in the amlodipine group and by 4.9/2.4 mm Hg in the enalapril group, respectively ($P < .001$ for both vs placebo).

Cardiovascular events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients (hazard ratio [HR] 0.69, 95% CI 0.54–0.88, $P = .003$), and in 136 (20.2%) enalapril-treated patients (HR 0.85, 95% CI 0.67–1.07, $P = .16$). The incidence of cardiovascular events in the enalapril vs amlodipine groups was not significantly different (HR 0.81, 95% CI 0.63–1.04, $P = .10$).

Compared with baseline, IVUS showed progression in the placebo group ($P < .001$), a trend toward progression in the enalapril group ($P = .08$), and no progression in the amlodipine group ($P = .31$). There was significantly less progression of atherosclerosis in the amlodipine-treated vs placebo-treated patients in the subgroup with systolic blood pressures greater than the mean ($P = .02$). Although only significant in the subgroup

with elevated systolic blood pressure, the concordance of reduced clinical events and less progression of plaque burden suggests the validity of imaging end points in disease prevention.

## ATHEROSCLEROSIS IMAGING FOR PRIMARY PREVENTION

Noninvasive imaging methods will eventually be needed to study primary disease prevention of people with subclinical CAD.[22]

**B-mode ultrasonography** and **magnetic resonance imaging** are noninvasive and have been used to demonstrate regression of plaque burden in femoral arteries, carotid arteries, and the aorta during lipid-lowering treatment.[47–49]

**CT calcium scoring** has been used in small studies to evaluate treatment with drugs that lower LDL-C and their effect on the calcified coronary plaque burden.[50,51] LDL-C reduction was associated with less calcified atherosclerotic plaque, but the significance of these findings is incompletely understood.

Distinguishing between calcified and noncalcified plaque has recently become possible with contrast-enhanced multidetector CT imaging, and may in the future allow noninvasive assessment of overall coronary plaque burden.[52,53] Larger studies are needed to elucidate the complex role of calcified and noncalcified plaque in CAD progression.

**Disease markers reflect only part of the complex pathophysiology of CAD**

If a large plaque burden is found to increase the chance of future clinical events, assessing plaque burden could become an important component in evaluating cardiovascular risk. This scenario is supported by the concordance of imaging and clinical end points in the REVERSAL and PROVE-IT trials,[54] the latter of which also randomized patients with acute coronary syndromes to treatment with either atorvastatin 80 mg or pravastatin 40 mg, but used a clinical composite of death, myocardial infarction, unstable angina, and stroke as an end point. After a mean follow-up of 24 months, the rate of the combined end point was 16% lower in the atorvastatin group, and the mortality rate was 28% lower.

However, the relationship between plaque burden and clinical events is likely complex and modified by disease activity, particularly inflammatory processes, which play a central role in the progression to acute coronary events. Assessing disease activity has become possible with biochemical markers.[20,21]

Recent data from the REVERSAL and PROVE-IT trials provide preliminary insights into the correlation between inflammatory markers, plaque burden, and clinical events.[55,56] In the REVERSAL substudy, a decrease in C-reactive protein (CRP) levels during lipid-lowering treatment was independently and significantly correlated with the rate of progression of plaque burden.[55] Similarly, the CRP substudy from PROVE-IT demonstrated that a decrease in CRP levels during statin treatment correlated with better clinical outcomes independent of the level of LDL-C achieved.[56]

Similar data do not yet exist for multidetector CT imaging or other noninvasive techniques but will be examined in future studies. Novel imaging approaches using nanotechnology are also being explored.[57,58] Future studies with clinical, biochemical, and imaging end points will need to examine the relationship between plaque burden, markers of disease activity, and clinical events.

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