Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 9, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.12.014

Is Intravascular Ultrasound the Gold Standard Surrogate for Clinically Relevant Atherosclerosis Progression?

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Are progressive changes in intravascular ultrasound (IVUS)-derived indexes of plaque size sufficiently predictive of in-trial or future cardiovascular event risk that IVUS can serve as an efficient surrogate for clinical events in coronary disease trials? This question remains unanswered by clinical trials reported to date. Indeed, the answer may well be "yes." Nevertheless, there are enough concerns about the physical limitations, the fundamental assumptions, and the interpretation of the IVUS measurements that the answer cannot be taken for granted. Here, we review the evidence to date, discuss some of the concerns, and compare IVUS results with those of quantitative arteriography. (J Am Coll Cardiol 2007;49:933–8) © 2007 by the American College of Cardiology Foundation

Be not the first by whom the new is tried, nor yet the last to cast the old aside.

Alexander Pope (1)

In this issue of the *Journal*, Böse et al. (2) present the rationale and data supporting the use of intravascular ultrasound (IVUS) as a surrogate measure for evaluating therapeutic interventions in atherosclerotic coronary disease. Given the growing use of IVUS, it is appropriate to establish a dialog examining current uses of, and assertions about, this invasive technology. The fundamental assertion by proponents of IVUS has been that measurement of the growth in segmental coronary plaque is a better predictor of future cardiovascular events and therefore, as a surrogate, superior to the measured progression of coronary luminal obstruction from the arteriogram (2,3). If there were no assertion of superiority, why would IVUS be pronounced the "gold standard," and be advocated despite its substantial added cost, invasive nature, and extensive postprocessing analysis? This assertion requires careful scrutiny, in part, because the U.S. Food and Drug Administration may soon review results obtained with IVUS for approval of new drugs. As a counterpoint to the report by Böse et al. (2), the present brief review compares the evidence supporting IVUS for evaluating coronary atherosclerosis therapies with evidence for an older technique, quantitative coronary arteriography (QCA).

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Manuscript received August 15, 2006, accepted August 26, 2006.

The logic of IVUS for documentation of atherosclerosis progression is that serial measurement of plaque volume in a single mildly to moderately diseased segment of 1 coronary artery provides a reasonable approximation of plaque growth in all proximal coronary beds and thus, hypothetically, an estimate of clinical risk (2–4).

The different logic of QCA is that serial measurement of focal diameter stenosis in defined standard segments of all proximal vessels provides an average per-patient estimate of stenosis change that reasonably reflects the rate of progression of the patient's coronary obstruction and therefore, hypothetically, of risk (5–7).

Mechanisms of Atherosclerosis Leading to Clinical Events

A successful intervention operates on the disease process in a way that reduces the frequency of future adverse vascular events. By extension, to successfully replace the large long clinical trials upon which we now depend, a surrogate outcome measure would need to examine the vasculature in a way that characterizes the disease process(es) leading to clinical events. Although patients dying of heart disease usually have a large coronary atherosclerotic burden (8,9), it remains to be proved that growth of plaque volume trumps progressive luminal obstruction for testing the efficacy of a therapeutic intervention.

Clinical events usually occur when the degree of obstruction at a focal stenosis abruptly worsens. Indeed, it is common that patients presenting with severe angina or an acute myocardial infarction (MI) have, on angiography, a readily identified severe stenosis or total occlusion (the

Abbreviations and Acronyms

IVUS = intravascular ultrasound
LDL = low-density lipoprotein
MI = myocardial infarction
QCA = quantitative coronary arteriography
%S = percent stenosis

"culprit lesion"), often complicated by thrombosis. Yet, often the remainder of their coronary tree shows only minor luminal irregularities. It is well understood, based on the work of Glagov et al. (8) and Kragel et al. (9), that those arteries with seeemingly near-normal lumen contours are often extensively involved with plaque, and the clinical event (myocardial infarction or unstable angina) is precipitated by disruption, thrombosis, and new severe narrowing of a short segment of an initially mild to moderate focal stenosis (10–13). The critical question is whether measured worsening of luminal obstruction (QCA) or measured growth in plaque volume (IVUS) is a more relevant index of clinical risk.

Key Questions and Discussion Points: The Evidence

A first question is whether IVUS techniques provide different and more useful information than arteriographic techniques. Clearly, the information obtained from ultrasound measures of coronary disease differs qualitatively from that of arteriography. Quantitative coronary arteriography does not accurately measure plaque volume, and IVUS has not been used to estimate focal luminal obstruction. There are other differences of consequence.

Differences in Dealing With Severe Obstructions

QCA. Direct injection of contrast into the coronary ostia provides full visualization of the coronary tree and its narrowings, with a spatial resolution of ±0.1 mm on lumen diameter estimates and ±3% on estimates of percentage stenosis (%S) (5,14,15). When a focal arterial lesion progresses from a moderate to a severe narrowing or total occlusion, the change in stenosis severity can be measured precisely. Indeed (see subsequent), much of the mean stenosis progression, per patient, is due to a single lesion, initially in the range of 30%S to 60%S, that abruptly progresses to 70%S to 100%S, precipitating an ischemic event (16).

IVUS. The IVUS catheter cannot pass through severely narrowed or occluded arteries. Therefore, the effect of major progression or new total occlusion on plaque volume cannot be serially measured and must be imputed or be excluded from analysis. To date, such imputation methods have not been described. Furthermore, when a plaque abruptly develops severe new focal narrowing, if it can be accurately crossed and measured in follow-up, the increase in total plaque volume of the long segment measured at baseline would not show a large fractional increase in size concordant with the large increase in stenosis severity.

Differences in the Effects of Remodeling

QCA. The early effects of plaque growth are compensated by outward (positive) remodeling (8) with preservation of the lumen. As a consequence, the average annual worsening of luminal narrowing is <1%S, or 0.02 mm diameter, per year, among untreated coronary disease patients. This seems trivially small to most clinicians. Yet <1%S/year is entirely consistent with the observation that the average stenosis severity is 35%S among the 9 proximal coronary segments of a typical 50-year-old patient (17,18). Atherosclerosis is a slowly growing process until it focally erupts.

IVUS. A central hypothesis encouraging the development of IVUS has been that, owing to early outward remodeling of the artery (3,8), plaque growth should actually be more rapid than that inferred from the arteriogram. Therefore, plaque growth, if measured directly, would be more rapid and, hypothetically, more revealing of the underlying pathologic processes. But, surprisingly, the magnitude of changes in plaque volume and in luminal stenosis in clinical trials is relatively small (19–22), especially when adjusting for the fact that lumen measurements are based on diameter, whereas those for plaque size are based on area (diameter squared). For example, in the REVERSAL (Reversing Atherosclerosis With Aggressive Lipid Lowering) trial (19), median percentage change in plaque volume was +2.6% over 1.5 years with pravastatin, and −0.4% (decrease) with high-dose atorvastatin—further confirmation that, however measured, atherosclerosis is a slowly growing process. Indeed, IVUS studies show remodeling to be a heterogeneous process and have challenged the original Glagov et al. (8) observations that arteries with small plaques remodel outward, whereas larger plaques (>40% of external elastic lamina area) grow into the lumen (23,24).

Differences in Estimates of Plaque Structure and Composition

Neither QCA nor IVUS can reliably identify characteristics of the plaque that render it vulnerable (11). Although IVUS has a theoretical advantage in this regard, especially using radiofrequency backscatter analysis (25,26), at present neither technique can quantify macrophage clusters, the large core lipid pool, or the dangerously thin fibrous cap (27).

A critical second question is whether rates of QCA stenosis progression or IVUS plaque volume growth during a trial correlate best with the patient's risk of coronary events.

Future Events

QCA. Early studies (28–30) confirmed that more rapid progression of luminal obstruction during a trial correlates significantly with more frequent cardiovascular events after the trial.

IVUS. After heart transplant, the "silent" 1-year growth of coronary plaque in initially mildly diseased graft hearts has been found to predict future mortality and the composite of

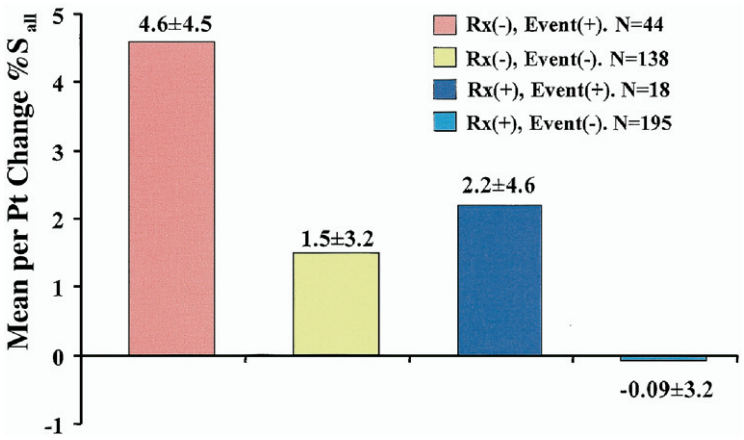

Figure 1 **Mean Stenosis Change by QCA: Effects of Therapy and In-Trial Events**

Impact of intensive therapy and of an in-trial cardiovascular event on the average in-trial change in coronary stenosis (%S) in all coronary stenoses (n = 4,450) measured in 393 patients participating in 3 pooled trials (16,17,38) that compared intensive combination therapy (niacin + colesipol, lovastatin + colestipol, simvastatin + niacin, or niacin + gemfibrozil + cholestyramine) against placebo. In treated and in placebo patients, the measured mean stenosis progression was significantly greater among patients with events than among those without events (p = 0.005 and p = 0.0001, respectively). Forty-four of 182 placebo-treated and 18 of 213 intensively treated patients had events, a 65% risk reduction with treatment versus placebo (p = 0.0001). Pt = patient; QCA = quantitative coronary arteriography; Rx = treatment.

death and MI over 6 years of follow-up (31). Whether these events were due to immunologic cardiomyocyte rejection or vascular ischemia was not clear. Furthermore, severe intimal thickening after transplant (>0.5 mm/year) is fundamentally different from native coronary disease; it is unlikely to be a good model for typical atherosclerosis. A study of left main coronary plaque growth in relation to cardiovascular risk indices and future events in 56 patients (32), provides encouraging early evidence that plaque growth, as measured by IVUS in this short coronary segment, is driven by traditional risk factors and predicts future vascular events.

In-Trial Events

QCA. Analysis of 6 placebo-controlled statin trials (33–38) of 2.3 years average duration showed highly significant and consistent slowing, by about 50%, of stenosis progression rates (from about 1%S/year with placebo to 0.5%/year with statins), with statins. In these trials, the average reduction in event rate was 27%, significant in all but 1 of the 6 trials.

To further address this question, we pooled data from 3 QCA lipid therapy trials (17,18,39) of 2.8 years average duration, in which the coronary stenosis measurements were made in our laboratory using the same prospective fully blinded methods and in which the event classification was blindly and independently adjudicated. Figure 1 shows the results. Progression of the average stenosis among placebo patients with versus without events was 4.6%S versus 1.5%S, respectively ($p < 0.0001$). Among treated patients, this difference was 2.2%S versus −0.1%S, respectively ($p < 0.005$). In all 213 intensively treated patients, the rate of CV events (death, MI, progressive ischemia) was reduced by 64% relative to the 180 control (placebo) patients ($p = 0.0001$). The mechanism of this strong relationship between events and average progression of stenosis is that virtually every patient with a coronary event had an identifiable culprit lesion that progressed from average 56%S to 82%S, resulting in an ischemic event (18). Thus, for a patient with such substantial progression in a single lesion, the average change among 10 measured lesions would be increased by 2.6%S owing to the culprit. Although nonculprit lesions progress significantly more slowly (or actually regress) with intensive therapy (40), the principal impact on progression is via the culprit lesion for an ischemic coronary event. Thus, for QCA, progression of obstruction and in-trial events are strongly linked. Because of the favorable effect of therapy, on average, in all measured stenoses and for prevention of coronary events, stenosis progression with QCA is an extremely statistically efficient measure of therapy benefit, being mechanistically linked with both slowing of natural progression and reduction in events. As a consequence, typical sample sizes needed to prove clinical benefit of statin in 5-year event trials have been in the >4,000-patient range, whereas the 6 average 2.3-year statin trials mentioned (33–38) averaged 455 patients each.

IVUS. The weakest link in the rationale for IVUS as an imaging surrogate for event trials is the lack of a clear evidence base showing a relationship between plaque growth and events in the trials reported to date (19,20,22). It should be emphasized that IVUS trials have been disadvantaged relative to QCA in this regard. On average they have been shorter (1.5 to 2 years) than the typical QCA trial (2 to 3 years), and have compared an intensive regimen with a conventional one of proven benefit. As examples, in the REVERSAL trial, the number of events in 502 evaluable patients treated for 1.5 years with atorvastatin was 1

death and 4 MI; in contrast, those treated with pravastatin at lower dose experienced 1 death and 7 MI (19), and in the REVERSAL trial there was a significant difference in median percentage change in plaque volume. In the CAMELOT (Comparison of Amlodipine and Enalapril to Limit Occurrences of Thrombosis) study (21), among 1,991 patients randomized to placebo, enalapril, or amlodipine for 2 years, 274 patients entered an IVUS substudy. Overall, relative to placebo, there was a 31% reduction with amlodipine in the angina-driven composite cardiovascular end point ($p = 0.003$); but in the IVUS cohort, there was a nonsignificant trend toward less progression ($p = 0.12$). In ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) (22), an uncontrolled trial, low-density lipoprotein (LDL) cholesterol reduction to 60 mg/dl was associated with a reduction in percentage atheroma volume (−0.79% change; $p = 0.001$) which appears well predicted by LDL cholesterol levels across trials.

Finally, are there other concerns about these methodologies?

Partial Sampling

IVUS. As currently performed, the IVUS estimate is based on plaque volume change in a relatively mildly to moderately diseased segment of only 1 of the 3 main coronary arteries through which the IVUS catheter can be passed. Thus, IVUS does not evaluate the entire coronary bed as arteriography does, just a single 30 mm, or longer, segment of 1 mildly to moderately diseased artery.

Image Spatial Resolution

QCA. In the late 1990s virtually all catheterization laboratories switched from film to digital image storage. This transition substantially degraded image quality. Film resolution is equivalent to 3,000 × 3,000 pixels; the digital images have about 500 × 500 pixels of full-field resolution after compression for storage. Although this loss of image spatial resolution can be largely compensated by averaging repeated measurements and, to a limited extent, by gray-scale manipulation, it has discouraged some QCA investigators. However, other investigators remain active in this field (7).

Appropriate Measurement End Points

IVUS. There has been a variable choice of reported IVUS end points (19,20) (atheroma volume, percent atheroma volume, atheroma volume in 10 mm subsegment with greatest disease severity, and normalized atheroma volume) in reports from different clinical trials; for each of them, mean and median values have been generated in the statistical analyses. The reported "primary" end point often provided a statistical result that appeared most favorable to the intervention under study. For example, in the REVERSAL trial (19), 80 mg atorvastatin was compared with 40 mg pravastatin in terms of IVUS-measured coronary disease change. The IVUS primary end point, prespecified in the protocol, was the "average percentage change in atheroma volume." Both mean and median percentage changes in atheroma volume were reported (atorvastatin vs. pravastatin: mean +4.1% vs. +5.4% [p = NS]; median −0.4% vs. +2.7% [$p = 0.02$]). But the median values were designated, without further justification, as the "prespecified primary end point," and thus the trial was considered to show a significant benefit from atorvastatin in terms of atherosclerosis progression.

In the saline-controlled study (20) of apoA-I Milano infusion in acute coronary syndrome, the primary end point was "change in percent atheroma volume" of the interrogated segment (essentially the ratio of atheroma volume to total artery volume, expressed as a percentage and computed very differently than "percentage change in atheroma volume"). The results indicate a median −0.81%; (yes, <1%) change from baseline ($p = 0.02$) in percentage atheroma volume in the combined apoA-I Milano group—which could be due to plaque shrinkage or to lumen enlargement (not specified)—and a median +0.03% ($p = 0.97$) in the placebo group. Again, the use of median change rather than mean was not justified, although the variance of the means appeared to be greater. The 2 groups were not statistically compared, but the conclusion was that apoA-I Milano, in 5 weekly infusions, produced significant regression of coronary atherosclerosis.

Another IVUS variable, the percentage change in plaque volume in the most heavily involved 10 mm of the segment examined, has been reported (19) as a secondary end point; it also appears to provide more statistical power, perhaps because it is an examination of the more lipid-rich portion of the plaque.

It is fair to conclude that exceptionally small changes from baseline in these several variables are statistically significant, as are between-group differences in 1 of these 4 trials, and appear to be predicted by LDL cholesterol levels in therapy. However, the choice of different measurement criteria in different studies could be viewed as cherry-picking. This is perhaps appropriate in the evolutionary stages of a new technique, but should not be an option for an established method grounded in a well defined pathophysiologic rationale.

Study Dropout Rates

IVUS. Of the 1,221 patients randomized and studied at baseline in 3 trials (19,20,22), an evaluable follow-up study was not obtained, largely owing to patient withdrawal, in 323 (26%).

Discussion

À la Pope, we may be accused of clinging too long to the "old" QCA technique. In fact, this is not so; our laboratories have, for the past 5 years, abandoned QCA for other pursuits (41). Indeed, we have great interest in, and admiration for IVUS as a technologic feat, for the insights it has

provided into atherosclerosis mechanisms (31,42) and stent deployment (43), and for the promise it may hold for useful estimation of plaque composition and structure.

Nevertheless, the present review finds the IVUS clinical trials to date to be too short, too underpowered, and lacking sufficient between-group differential treatment effects to establish a clear relationship between reduction in specified indices of plaque growth, measured as proposed, and reduction in clinical cardiovascular events. This may be due, in part, to the power issues mentioned in the preceding. But there are also real concerns about handling of new severe stenosis, and about whether the selected segmental IVUS exam provides representative information on the patient's overall plaque growth. More fundamentally, there are concerns whether overall plaque growth, given remodeling, is a good marker for in-trial or future event risk and, if so, which IVUS-derived index is most effective in risk prediction.

The principal question remains: whether progressive change in plaque size (or in other IVUS-derived indexes of plaque or lumen volume [42] provide better prediction of clinical events than progressive changes in luminal obstruction throughout the coronary tree. This question has yet to be answered, but the data to date do not compare favorably with the findings in trials measuring progressive lumenal obstruction. For reasons given, we believe that methods to estimate luminal obstruction and plaque composition provide the most useful surrogates for clinical benefit.

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