A Direct Comparison of Intravascular Ultrasound and Quantitative Coronary Arteriography
Implications for Measures of Atherosclerosis as Clinical Surrogates

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Several established methods for the imaging of atherosclerosis (quantitative coronary arteriography [QCA], carotid intima-media thickness, magnetic resonance imaging, and intravascular ultrasound [IVUS]) have been used in clinical trials to determine whether defined therapeutic interventions slow the rate of progression of plaque size or composition, or reduce severity of luminal obstruction, and whether change in these measures predicts in-trial or future cardiovascular (CV) events. The report by Berry et al in this issue of Circulation, which compares simultaneously-obtained QCA measures of luminal obstruction with IVUS measures of plaque and luminal volume or percent plaque volume and their in-trial changes is a timely comparison between IVUS and QCA. The present editorial comment addresses the emerging evidence on the relative utility of measurements by these 2 techniques for use as surrogates for efficacy in clinical trials.

Proponents of these atherosclerosis imaging methods seek to establish their role as reasonable surrogates for CV event end points. Success holds the promise of a substantial decrease in the size and duration (ie, cost) of the large, long, clinical trials needed to confirm significant therapeutic benefits. In this regard, results with these techniques have been encouraging. With carotid intima-media thickness, single estimates of carotid plaque thickness have correlated with future CV event rates; furthermore, rates of plaque thickening over 1 year have tended to correlate with frequency of in-trial events. With QCA, progressive luminal obstruction has predicted in-trial event frequency and subsequent post-trial events. With magnetic resonance imaging, diminished plaque size and plaque lipid composition have been associated with lipid therapies that have greatly reduced event frequency. For an imaging method to provide an early assessment of in-trial therapeutic effects, it ought to characterize 1 or more key mechanisms of the atherosclerotic process that results in either abrupt or gradual progression of clinical ischemia. These mechanisms include progressive luminal obstruction, plaque rupture (associated with plaque lipid and inflammatory cell accumulation and thin fibrous cap), and endothelial dysfunction (associated with vasospasm and prothrombotic states). One measurable aspect of atherosclerosis is the size of the plaque. Kragel and colleagues have shown that patients who died as a result of clinical coronary events/diagnoses usually have extensive diffuse atherosclerosis and lipid accumulation in all coronary branches. This has led to the hypothesis that measurements of plaque volume or related variables and/or their rates of growth may provide indices that would serve as useful early-manifest surrogates for subsequent clinical events. To date, however, the IVUS trials of therapeutic intervention have yet to provide compelling evidence of an association between in-trial clinical events and the several measures of plaque volume or its growth. This may, in part, be the result of the short duration of these trials (typically 18 to 24 months) and the current ethical requirement that there be an active control group. Indeed, van Birgelen et al have shown that the rate of growth of plaque volume in the left main coronary segment correlates well with traditional risk factors. Furthermore, the rate of diffuse coronary intimal growth in posttransplant plant hearts is related to mortality prognosis, although this accelerated pathology differs substantially from that of native coronary atherosclerosis. Thus, although it is an attractive hypothesis, the evidence that IVUS is a useful surrogate for coronary events in clinical trials is incomplete.

The report by Berry et al is the first large-scale comparison of the 2 techniques in the context of a clinical trial. The major findings of this analysis are that measures of lumen size (diameter, volume) by IVUS and QCA are reasonably well-correlated (r=0.58 to 0.68; P<0.0001) within the same arterial segments. The correlation decreases considerably when the same segments are compared in terms of plaque volume by IVUS and lumen size by QCA (r=0.18 to 0.22; P=0.0003 to 0.0001). This low probability value is primarily a reflection of the number of patients studied rather than the amount of QCA variance explained by IVUS (R²=0.04). The authors refer to this as a “significant” correlation rather than an essential contradiction of the proposal that these 2 approaches provide comparable estimates of disease severity. When the techniques are compared in their commonly used modes, for all arterial segments (QCA) versus a single vessel segment (IVUS) the correlations between lumen size by QCA and plaque volume by IVUS become quite weak (r=0.08 to 0.13; P=0.11 to 0.03). Furthermore, changes by QCA over 2 years in any luminal measure of arterial disease are totally uncorrelated with change in plaque volume by IVUS.
was seen to occur only in lesions of coronary disease who were treated with 1 of 5 different drug regimens. The key question is how to interpret these findings. This is important because the US Food and Drug Administration will eventually be asked to approve new drugs, in part on the basis of IVUS measurements from controlled clinical trials. One interpretation of this reported lack of IVUS and QCA correlation may be that, despite plaque growth, lumen dimensions are preserved because of outward arterial remodeling, as described by Glagov et al. However, such remodeling was seen to occur only in lesions of <20% in diameter stenosis. A second interpretation might be that stenosis change by QCA is not a useful index of CV event risk. As a third alternative, the same interpretation may be proposed for IVUS.

Although less is known about the prognostic value of IVUS in native atherosclerosis trials, there is a substantial body of evidence with QCA that slowed disease change and risk reduction are each well and independently correlated with low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol changes, and that stenosis progression by QCA during a trial is a strong correlate of clinical event frequency during the trial. The evidence for this statement is summarized in a recent meta-analysis of 11 QCA studies conducted among a total of 3674 patients with coronary disease who were treated with 1 of 5 different drug classes (placebo, statins, fibrates, combined niacin and LDL-lowering drugs, and combined statins and resins). In this analysis, measured stenosis progression and event reduction relative to placebo were averaged within each treatment class. The relationship between stenosis progression rate by QCA and relative event reduction was computed from these data and is plotted in Figure 1. Over the full range of commercially available lipid therapies, from placebo to fibrates, to statins, to drug combinations that substantially lower LDL-C and raise high-density lipoprotein cholesterol, a 4% reduction in mean proximal diameter stenosis progression linearly corresponds to an approximate 70% reduction in event rate in these trials. Thus, each 1% reduction in diameter stenosis progression over the course of a study proportionately reduces event rate by nearly 20%. Given this evidence, it seems unreasonable to expect a measure (change in plaque volume by IVUS) to provide clinically useful information if it is virtually uncorrelated with QCA estimates of change in lumen narrowing.

Indeed, the weakest link in the rationale for IVUS as an imaging surrogate for event trials is the lack of a clear base of evidence that shows a relationship between plaque growth and events in the native coronary disease trials reported to date. It should be emphasized that IVUS trials have been at a disadvantage relative to QCA in this regard. On average IVUS trials have been shorter (1.5 to 2 years) than the typical QCA trial (2 to 3 years), and they have compared an intensive regimen with a conventional one of proven benefit. As examples, in the Reversal of Atherosclerosis with Aggressive Lipid-Lowering (REVERSAL) trial, the number of events in 502 patients treated for 1.5 years with atorvastatin was 1 death and 4 myocardial infarctions; by contrast, those treated with pravastatin at lower dose experienced 1 death and 7 myocardial infarctions. Yet, in REVERSAL there was a significant, albeit small, difference in median percent change in plaque volume. In the Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial, among 1991 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 CV end point ($P=0.003$), but in the IVUS cohort there was a nonsignificant trend toward less plaque growth ($P=0.12$). In the Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID), an uncontrolled trial, LDL-C reduction to 60 mg/dL was associated with a tiny reduction in percent atheroma volume ($-0.79%$ change; $P<0.001$), which appears to be well predicted by LDL-C levels.

In summary, the report of Berry et al finds little or no relationship between commonly used IVUS measures of change in plaque volume and established and clinically relevant QCA measures of change in coronary obstruction. As discussed in detail in a recent commentary on this subject, there are certain concerns about IVUS as a surrogate measure for use in clinical trials. Principal among these is that plaque volume is measured with IVUS in a single, often mildly narrowed 10-cm segment of 1 of the 3 coronary arteries. When that patient experiences a clinical coronary event, it is usually caused by focal plaque rupture with abrupt and severe atherothrombotic obstruction, with a low likelihood of occurrence in the originally interrogated artery segment. If it does occur there, the short segment of occlusion will add little to the originally measured plaque volume. Indeed, this obstructed segment may not technically or safely be crossed by the ultrasound catheter. Each of these scenarios...

### Figure 1

**Relationship between mean % stenosis change and % reduction in primary trial event rate relative to placebo.**

\( r = -0.002 \) to 0.06; \( P = 0.97 \) to 0.24. Even the IVUS variable, the volume change in the 5-mm segment that contains the greatest amount of plaque, was uncorrelated with the QCA lumen measures. In summary, there were reasonably good correlations between lumen size measures by both techniques; but plaque volume and its change by IVUS, currently in use in IVUS trials, were totally unrelated to minimum lumen diameter or percent stenosis or their changes as measured by QCA.
demonstrates the potential for discordance between the IVUS measure and the pathophysiology (obstruction) of the ischemic event.

There is widespread agreement that IVUS provides the best diagnostic measure of segmental atherosclerotic plaque burden. However, the sample in the clinical setting is limited to a fraction of the anatomy, a fraction that may not behave as its counterparts in the rest of the anatomy. Furthermore, Mother Nature has given us a mechanism, arterial remodeling,16 that compensates in varying degrees for plaque growth. As a consequence, we are justified in questioning the premise that indices based on segmental plaque volume, or their counterparts in the rest of the anatomy. Furthermore, there is widespread agreement that IVUS provides the best diagnostic measure of segmental atherosclerotic plaque burden. However, the sample in the clinical setting is limited to a fraction of the anatomy, a fraction that may not behave as its counterparts in the rest of the anatomy. Furthermore, Mother Nature has given us a mechanism, arterial remodeling,16 that compensates in varying degrees for plaque growth. As a consequence, we are justified in questioning the premise that indices based on segmental plaque volume, or their counterparts in the rest of the anatomy.

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References


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