Serial Intravascular Ultrasound Assessment of Atherosclerosis Progression and Regression

— State-of-the-Art and Limitations —

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Coronary heart disease remains a leading cause of morbidity and mortality. Surrogate imaging endpoints may allow smaller sample sizes and shorter study durations to expedite the process of drug development and testing, and to evaluate potential benefits of novel antiatherosclerotic drugs before clinical endpoint data are available—an approach that may reduce cost and effort. Intravascular ultrasound (IVUS) is particularly suitable because it is readily available and because of its relatively high image resolution, accurate and reproducible measurements, ability to detect mild, angiographically silent atherosclerotic disease that can be a precursor of future coronary events, and suitability for serial (baseline and follow-up) imaging and analysis. However, there are significant limitations to the use of IVUS as an endpoint in progression/regression studies that must be considered when evaluating the results of such studies. (*Circ J* 2009; 73: 1557–1560)

Key Words: Atherosclerosis; Coronary artery disease; Imaging; Intravascular ultrasound; Ischemic heart disease

Coronary heart disease remains a leading cause of morbidity and mortality. Established preventive pharmacological therapies reduce cardiovascular event rates, but only by 30–40%. The assessment of morbidity and mortality as primary endpoints in conventional large-scale clinical trials of established and novel agents is associated with a substantial financial burden.^{1–3} Surrogate endpoints, on the other hand, may allow smaller sample sizes and shorter study durations to expedite the process of drug development and testing, and to evaluate potential benefits of novel anti-atherosclerotic drugs before clinical endpoint data are available—an approach that may reduce cost and effort.^{1,3–5}

Intravascular ultrasound (IVUS) is particularly suitable because it is readily available and because of its relatively high image resolution, accurate and reproducible measurements, ability to detect mild, angiographically silent atherosclerotic disease that can be a precursor of future coronary events, and suitability for serial (baseline and follow-up) imaging and analysis.⁶ Conversely, angiographic studies of progression/regression are limited because angiography shows the opacified silhouette of only the lumen; furthermore, the variability of vascular remodeling prevents reliable assessment of the plaque dimensions on the basis of lumen narrowing.

Using planar, not volumetric IVUS analysis, the relation between low-density lipoprotein-cholesterol (LDL-C) levels and the progressive enlargement of coronary plaques was demonstrated in 2003.⁷ In that study there was a direct linear relationship between changes in left main plaque area vs LDL-C levels ($r=0.41$, $P<0.0001$). An LDL-C value of 75 mg/dl was the threshold below which

regression analysis predicted, on average, no increase in atherosclerotic plaque. This observational study also revealed a significant negative correlation between high-density lipoprotein-cholesterol (HDL-C) and atherosclerotic plaque progression; low HDL-C was on average associated with greater plaque progression. During follow-up, adverse non-left main related cardiovascular events occurred mainly in patients with the greatest rate of left main plaque progression ($P<0.001$).⁸

State-of-the-Art

Since then, serial IVUS analysis has become standardized. In contemporary progression/regression studies an untreated 30–40 mm or longer, moderately diseased untreated coronary artery segment is identified angiographically, a guidewire is positioned into the distal vessel, intracoronary nitroglycerin is administered, the IVUS catheter is inserted over the guidewire into the coronary artery beyond a distal fiducial point (ie, a well-defined side branch), motorized transducer pullback through a stationary imaging sheath is initiated and continues for at least 30–40 mm until a well-defined proximal fiducial point is reached, and then the IVUS catheter is removed. In the core laboratory the lumen and external elastic membrane contours are drawn and areas measured at pre-specified intervals (ie, every 1 mm), plaque & media areas are calculated as external elastic membrane minus lumen, and volumes are calculated using Simpson's rule and then normalized for pullback length. Baseline and follow-up analyses of the entire segment between the proximal and distal fiducial points are compared as the primary endpoint; comparative analysis of

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the “worst segment” is reserved for a secondary endpoint because the reproducibility is worse.

Two large-scale pharmacological intervention trials using serial volumetric IVUS analysis studied the effects of statin therapy on coronary plaque progression-regression.^{9,10} The LDL-C threshold that was associated with no disease progression in the earlier, aforementioned observational study was confirmed by the much larger “Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial”, a prospective randomized study that tested the effect of 18 months of intensive vs moderate lipid-lowering therapy on coronary plaque progression.⁹ The “Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID)” demonstrated that very high-intensity statin therapy to a mean LDL-C level of 60.8 mg/dl resulted in overall regression of atherosclerotic plaque; however, there was no control group for comparison.¹⁰ Third, a small, randomized trial suggested that 5-week infusions of the HDL-mimic, Apo-A1 Milano, induced significant plaque regression in patients with acute coronary syndrome.¹¹ Conversely, 2 serial IVUS studies showed no significant difference in plaque progression between patients treated with acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors vs placebo; cholesterol esterification by the enzyme ACAT plays an important role in atherosclerotic plaque formation.^{12,13} Thus, negative IVUS studies can prevent needless large-scale clinical trials if negative studies accurately reflect clinical events.

Study Limitations

Nevertheless, there are significant limitations to those studies that must be considered when evaluating their findings.

Calcium shadows deeper arterial structures. When present, significant calcium precludes identification of the external elastic membrane and, therefore, measurement of atherosclerotic plaque.

Non-uniform rotation distortion, which is an imaging artifact unique to the mechanical, rotating, high-frequency transducers typically used in progression/regression studies, is difficult and sometimes impossible to recognize.

There often are discrepancies between baseline and follow-up pullback lengths that affect volumetric analyses.

Poor imaging techniques necessitating rejection of segments and/or patients can introduce bias.

The most common primary endpoint in IVUS-based progression/regression studies is the absolute change in normalized % atheroma volume (also called plaque burden) that is calculated as plaque&media volume divided by external elastic membrane volume over the entire analysis segment. This endpoint has become the “industry standard” because it is associated with the smallest variance. However, changes in % atheroma volume are small (median of 1.6% in the pravastatin group and 0.2% in the atorvastatin group in REVERSAL, median of -0.8% in the combined treatment groups of the Apo-A1 Milano study, and median -0.8% in ASTEROID). More importantly, population variances are large (standard deviation of 4.9% in the pravastatin group and 5.1% in the atorvastatin group in REVERSAL, 3.2% in the combined treatment groups of the Apo-A1 Milano study, and 3.2% in ASTEROID); if a study is “positive,” slightly more than 50% regress and slightly less than 50% progress. This also emphasizes the importance of a control group in all such studies.

Because % atheroma volume is calculated as plaque&

media volume divided by external elastic membrane volume, it can also be influenced by remodeling; positive remodeling (increase external elastic membrane volume) could reduce % atheroma volume with no absolute change in plaque mass, and negative remodeling (or an increase in vessel tone) would decrease external elastic membrane volume to increase % atheroma volume with no absolute change in plaque mass. Several serial IVUS observations have confirmed a broad spectrum of serial remodeling responses (changes in external elastic membrane) in mild-to-moderate atherosclerotic coronary lesions.^{14,15} Schoenhagen et al have observed negative remodeling of the coronary vessel wall during plaque stabilizing therapy that appeared to be related to its antiinflammatory effects.¹⁶ Scharlt et al have showed that positive remodeling was diminished in patients with plaque progression, despite intensive lipid-lowering therapy.¹⁷ Tardif et al concluded that regression of atherosclerotic plaques was accompanied by negative remodeling without an increase in lumen dimensions.¹⁸ Thus, on the one hand an inward shift of the remodeling pattern may be considered a sign of plaque stabilization, on the other negative remodeling might also affect the primary IVUS endpoint in the absence of actual regression.

IVUS cannot predict which segments will change most (or least) or even which segments will progress or regress, other than the fact that calcified segments change the least.

Arterial segments are selected for analysis based on coronary angiography. These segments may not be representative of segments prone to causing clinical events. Clinical events are most commonly the result of rupture of vulnerable plaques with superimposed thrombus formation. Pathologic studies have shown relatively few “unstable” lesions (ie, vulnerable plaques), even in high-risk patients,^{19,20} making it unlikely that a “blindly” selected 30–40 mm coronary artery segment based on coronary angiography will, fortuitously, contain even 1 vulnerable plaque. Furthermore, there seems to be a contradiction between the clinical benefit of certain pharmacological interventions, such as statins, and their more limited effect on plaque size. This discrepancy can be explained by stabilization of plaque composition rather than a reduction in plaque mass. However, conventional grayscale IVUS has significant limitations in the assessment of plaque composition and lesion phenotype and their changes over time. Therefore, spectral analysis of IVUS radiofrequency (RF) data was developed to quantify individual coronary plaque components or assess plaque deformability (stability).^{21–24} In a serial RF-IVUS study of patients treated with statins, Kawasaki et al demonstrated stabilization of plaque composition (decrease in lipidic tissue and increase in fibrotic tissue), despite no change in plaque burden.²⁵ The Integrated Biomarker And Imaging Study 2 (IBIS 2) trial tested darapladib inhibition of the enzyme lipoprotein-associated phospholipase A2 (Lp-PLA2) on plaque geometry and composition. Necrotic core volume, a key determinant of plaque vulnerability, continued to increase among control patients, but not in patients treated with darapladib; however, the primary endpoint (changes in plaque strain by palpography) was not different between the 2 groups, nor there was a change in plaque burden.²⁶ Because its resolution is 100–150 μ m, IVUS with or without RF analysis is unable to visualize the <65 μ m fibrous cap thickness or macrophage infiltration typical of a rupture-prone thin-cap fibroatheroma. Conversely, the superior 10 μ m resolution of optical coherence tomography (OCT) makes it an ideal technique for identifying these defining

features of a vulnerable plaque.^{27–29} In a serial OCT imaging study there was a significant increase in fibrous cap thickness during statin therapy.³⁰

Finally, a prerequisite for adoption of an imaging technique in progression/regression trials is evidence that this endpoint is a true surrogate for clinical events. Quantitative coronary angiographic studies have shown that progressive obstruction of the coronary lumen is associated with an increased risk of adverse cardiovascular events.^{31–33} Although there are no equivalent IVUS data, an IVUS-based trial reported that intensive antihypertensive therapy with amlodipine reduced coronary plaque progression and adverse cardiovascular events.¹² The clinical “Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial” used the same treatment regimen as REVERSAL and reported a significantly greater reduction in 2-year cardiovascular events in patients with acute coronary syndromes after treatment with intensive vs moderate lipid-lowering therapy.^{9,34} REVERSAL and PROVE-IT were distinct studies in different patient populations, but when considered together they provide inferential evidence that atherosclerotic progression measured by IVUS would predict an increased risk of cardiovascular events. Conversely, the companion studies Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUSTRATE) and Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) showed how complex can be the relationship between IVUS-measured progression/regression and clinical events. These 2 studies compared statins + torcetrapib to statins alone. Although there was no difference in the primary imaging endpoint, the absolute change in % atheroma volume comparing treatment and control groups in ILLUSTRATE,³⁵ ILLUMINATE reported more clinical events including cardiovascular mortality in the treatment group.³⁶

Conclusion

As the global burden of cardiovascular disease increases, there is need for surrogate imaging endpoints to maximize efficiency in the evaluation of new anti-atherosclerotic therapies. Despite its limitations, invasive imaging with IVUS remains the gold standard. RF-based IVUS analysis permits quantitative assessment of atherosclerotic plaque composition to supplement the grayscale IVUS assessment of overall plaque burden, and OCT allows measurement of fibrous cap thickness and detection of macrophages. A single catheter that permits simultaneous imaging with both IVUS (including RF analysis) and OCT during a single pullback is under development. Nevertheless, the definitive link between imaging and clinical endpoints is currently lacking.

Disclosure

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