Intravascular Ultrasound Studies of Plaque Progression and Regression
Impact of Lipid-Modifying Therapies

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KEYWORDS

• Atherosclerosis • Lipids • Clinical trials • Intravascular ultrasound

KEY POINTS

- Intravascular ultrasound (IVUS) trials are performed in patients who have presented for a clinical indicated coronary angiogram.
- Serial IVUS imaging has provided important insights into the factors that are associated with progression of coronary atherosclerosis.
- When integrated into clinical trials, serial vascular imaging has permitted the assessment of the effect of medical therapies on disease progression.

INTRODUCTION

Over the course of the last 25 years, clinical trials have consistently demonstrated that lowering levels of low-density lipoprotein cholesterol (LDL-C) reduces cardiovascular events in high-risk patients.[1–3] This has led to widespread use of statins and increasing prescription of additional lipid-lowering agents in patients who are unable to achieve treatment targets.[4,5] There remains, however, a considerable residual risk of clinical events, suggesting the need to identify more effective strategies to achieve greater reductions in cardiovascular risk.[6] In parallel to these studies, technological advances in arterial wall imaging have enabled study of the factors associated with the natural history of progression of atherosclerosis.[7] When integrated into clinical trials, serial vascular imaging has permitted the assessment of the effect of medical therapies on disease progression.

EARLY IMAGING CLINICAL TRIALS

Coronary angiography generates a 2-D silhouette of the artery lumen, with the ability to quantify the extent of obstructive disease. This technique is widely used in clinical practice, with early evidence that the severity of angiographic disease associates with adverse clinical outcomes.[8,9] Early studies using serial quantitative coronary angiography demonstrated a favorable impact of statin therapy on progression of obstructive disease, with evidence of a direct relationship between the degree of lipid lowering and degree of

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angiographic benefit.[10–12] Extending beyond these benefits of LDL-C lowering, other studies have demonstrated that administration of fenofibrate in patients with diabetes can slow progression of obstructive disease[13] and that addition of niacin to background statin therapy produces regression of angiographic disease.[14] These later findings suggested that potentially targeting additional lipid parameters, beyond LDL-C, may provide further benefit for high-risk patients. A fundamental limitation of angiography is its inability to directly image the vessel wall.[15] Accordingly, it is unable to provide a comprehensive evaluation of the impact of medical therapies on the full burden of atherosclerotic disease.

Noninvasive B-mode ultrasound imaging of the carotid artery permits measurement of carotid intima-medial thickness (cIMT), representing an early change within the artery wall that correlates with cardiovascular risk factors, atherosclerotic disease burden and adverse cardiovascular outcomes.[16] Clinical trials have demonstrated a direct relationship between the degree of LDL-C lowering with statins and slowing of cIMT progression.[17] Later studies observed cIMT regression with use of high-intensity statin agents.[18,19] These findings provided insights into the impact of statin therapy on early changes in the artery wall.

INTRAVASCULAR ULTRASOUND

The ability to place high-frequency ultrasound transducers within the coronary artery lumen permits intravascular ultrasound (IVUS) to generate high-resolution imaging of the full thickness of the artery wall.[20] This enables visualization of the full burden of atherosclerotic plaque within the vessel wall, with quantitative techniques able to measure the area of plaque within each cross-sectional image. Continuous imaging during catheter withdrawal produces a series of cross-sectional images throughout a length of artery extending the quantitation of plaque burden to a volumetric measure. Comparison of imaging in anatomically matched segments, defined by the presence of proximal and distal side branches, permits measurement of changes in plaque volume over time.[21] This provides a unique opportunity to characterize the factors associated with plaque progression and to determine whether medical therapies can slow disease progression or promote regression of atherosclerotic plaque.[22–27] Subsequent studies have demonstrated that the burden and progression of coronary atherosclerosis are associated with the subsequent incidence of cardiovascular death, myocardial infarction, or coronary revascularization.[28,29] Several clinical trials have demonstrated important insights into the role of medical therapies modifying plasma lipoproteins and their impact on atherosclerotic plaque within the coronary vasculature.

STATIN ADMINISTRATION

An early study using serial IVUS imaging demonstrated no impact of intensive statin therapy on plaque progression yet reported a favorable impact on plaque characteristics, suggesting a potentially beneficial effect on plaque composition.[30] Subsequent studies, however, have consistently demonstrated that intensive statin therapy exerts a protective effect on disease progression.[25–27] The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study compared the effects of atorvastatin (80 mg) and pravastatin (40 mg) on progression of coronary atherosclerosis in 502 patients. Greater lowering of LDL-C (79 mg/dL vs 110 mg/dL) with intensive atorvastatin was associated with halting of plaque progression.[25] Subsequent analyses reported a direct relationship between slowing of disease progression with both lowering of LDL-C and the inflammatory marker, C-reactive protein (CRP).[31] The finding of an independent relationship between CRP lowering and slowing disease progression supported claims that statins may exert anti-inflammatory effects in vivo.

A Study to evaluate the Effect of Rosuvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) subsequently evaluated the impact of high-dose rosuvastatin for 24 months on coronary plaque burden.[26] Lowering LDL-C to 60 mg/dL and raising high-density lipoprotein cholesterol (HDL-C) by approximately 15% with rosuvastatin was associated with plaque regression. Although this study reinforced the direct relationship between LDL-C lowering and changes in plaque burden, further analyses also reported a direct relationship between HDL-C raising and slowing disease progression with statins.[32] The change in the ratio of apolipoprotein B/apolipoprotein A-I, reflecting the proportion of atherogenic to protective lipoproteins, emerged as the strongest predictor of disease progression in the setting of statin therapy.

These findings provided the impetus to perform the largest serial IVUS study of plaque progression. The Study of Coronary Atheroma by inTravascular Ultrasound: Effect of Rosuvastatin versus AtorvastatiN (SATURN) directly compared the impact of the 2 most intensive statins (atorvastatin 80 mg and rosuvastatin 40 mg) for