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STATE-OF-THE-ART PAPER AND COMMENTARY

Intravascular Ultrasound for the Evaluation of Therapies Targeting Coronary Atherosclerosis

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Many cardiovascular events are clinical manifestations of underlying atherosclerotic disease. The progression of atherosclerosis, traditionally measured by angiography, is predictive of future clinical events and is a valid surrogate marker of cardiovascular (CV) disease. There is growing interest in using novel surrogate end points in clinical trials to expedite the development of new CV therapies. Innovative imaging technologies, such as intravascular ultrasound (IVUS), may carry advantages for the evaluation of coronary atherosclerotic burden and disease progression. Unlike angiography, which displays only the opacified luminal "silhouette," IVUS provides transmural imaging of the entire arterial wall and permits both detection of early-stage atherosclerosis and accurate cross-sectional and even 3-dimensional quantification of plaques. Intravascular ultrasound is now used to guide therapeutic interventions and for diagnostic purposes, primarily for the evaluation of ambiguous lesions and left main coronary artery disease. In addition, clinical studies are using IVUS serially to measure plaque progression, which appears to be related to future CV events. Although the probative force of clinical end point studies still is stronger, IVUS is catching up. Currently, several trials of CV therapies use IVUS-determined plaque progression as the end point. The rationale for using IVUS-based surrogate end points in clinical trials is discussed in the present review. Key advantages of using IVUS-based surrogate end points versus clinical outcome include smaller patient numbers and substantially shorter trial durations; this reduces costs and may expedite the development and testing of new drugs. We expect in the near future a further increase of the use of IVUS-based surrogate end points in trials that evaluate novel CV therapies targeting on coronary atherosclerosis. (J Am Coll Cardiol 2007; 49:925–32) © 2007 by the American College of Cardiology Foundation

Although the use of pharmacotherapy for primary and secondary prevention of cardiovascular disease (CVD) is widely accepted, a considerable number of patients still experience cardiovascular (CV) events. Consequently, the development of more effective treatment of CVD remains a key objective of CV research. A key stage in the development of novel therapies is the demonstration of a significant clinical benefit in terms of a reduction in CV morbidity and mortality. Clinical end point trials with sufficient statistical power to detect differences between an established and a novel therapeutic regimen are inevitably large and require a long study duration, often necessitating the follow-up of several thousand patients (1). This has economic and logistical implications, as highlighted in a recent editorial (2), and has encouraged the consideration of alternative trial designs and end points for the evaluation of novel CV therapies.

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A surrogate end point may be defined as a measure of a pathophysiologic process that is characteristic of future clinical outcome or end points. A surrogate end point allows correctly inferring the effect of a therapeutic intervention on an unobserved clinical end point. Using appropriate surrogate end points in trials can enable the detection of statistically significant differences between therapeutic regimens with substantially smaller sample sizes within a shorter period of time (1). Thus, use of surrogate end points can potentially expedite drug development, providing benefits for both the medical community and patients. The objective of the present review is to present evidence supporting IVUS assessment of atherosclerotic plaque progression as a surrogate marker for CV events.

Angiography, Atherosclerotic Progression, and CV Events

Most coronary events are clinical manifestations of underlying atherosclerotic disease. Traditionally, coronary angiography has been used for imaging of CVD; it has demonstrated that atherosclerotic plaque progression, inferred by progressive angiographic luminal obstruction, is associated with an increased rate of CV events.

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Abbreviations and Acronyms

CHD = coronary heart disease
CI = confidence interval
CSA = cross-sectional area
CV = cardiovascular
CVD = cardiovascular disease
%DS = percentage diameter stenosis
EEM = external elastic membrane
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
IVUS = intravascular ultrasound
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction

In the Cholesterol-Lowering Atherosclerosis Study (3), 162 patients with previous coronary artery bypass graft (CABG) surgery were randomized to lipid-lowering therapy with colestipol/niacin or to placebo. Coronary angiograms were conducted at baseline and after 2 years. Atherosclerotic disease was assessed qualitatively by a consensus panel evaluation (global change score) and quantitatively by measuring the mean change in percentage diameter stenosis (%DS) and the minimum lumen diameter. Atherosclerotic progression at 2 years by global change score, %DS, or minimum lumen diameter was associated with a significantly increased rate of coronary events ($p < 0.05$). In mild to moderate lesions (<50%DS), every increase of 10%DS or 0.3 mm decrease in minimum lumen diameter was associated with a relative risk of 2.1 (95% CI 1.4 to 3.0; $p < 0.001$) and 1.8 (95% CI 1.4 to 2.4; $p < 0.001$), respectively, for any future coronary event.

In a clinical trial of nicardipine in 335 patients without previous or planned CABG surgery or angioplasty (4), atherosclerosis was assessed by angiography at baseline and after 2 years. Plaque progression, defined as an increase of at least 15%DS in 1 or more coronary lesions, was observed in 141 patients and was significantly associated with future coronary events. During the follow-up period, 16 of 19 cardiac deaths occurred in patients with plaque progression, representing a relative risk of 7.3 (95% CI 2.2 to 24.7; $p < 0.001$) versus patients with no evidence of plaque progression. Patients with disease progression also had an increased risk of cardiac death or nonfatal infarction (relative risk 2.3, 95% CI 1.3 to 4.2; $p = 0.009$) (4).

Angiographic evidence from trials suggests that stabilization of atherosclerosis is associated with reduced rates of CV events. In the High-Density Lipoprotein Atherosclerosis Treatment Study, 160 patients with coronary heart disease (CHD) were randomized to 1 of 4 treatment regimens, including the combination of simvastatin and/or niacin, or placebo (5). Coronary angiography was conducted at baseline and after 3 years; at follow-up, mean percentage stenosis in proximal arteries had increased by an average of 3.9% in patients receiving placebo but had decreased by 0.4% in patients receiving simvastatin plus niacin therapy ($p < 0.001$ vs. placebo). The frequency of the composite primary end point (death from coronary causes, confirmed myocardial infarction [MI], stroke, and revascularization for worsening ischemia symptoms) was 90% lower in patients on simvastatin plus niacin than on placebo (3% vs. 24%; $p = 0.04$).

Limitations of Coronary Angiography

Over the past 2 decades, a new paradigm for atherogenesis has emerged. Atherosclerosis primarily affects the arterial wall, with atherosclerotic plaque growth initially accommodated in an outwardly expanding vessel wall (positive remodeling) (6). Owing to this process, angiographically detectable stenosis does not occur during the early stages of plaque accumulation when the increasing total vessel occupies the increasing amount of plaque mass (6). Although positively remodeled lesions do not restrict blood flow, they may be unstable and may contribute to the onset of acute coronary syndromes (7–9). The increased understanding of atherogenesis has highlighted inherent limitations of coronary angiography as a technique for the assessment of coronary atherosclerosis (10).

Angiography provides a 2-dimensional view of the arterial lumen, but with no visualization of the vessel wall. Therefore, as a result of positive remodeling, angiography frequently fails to detect the early stages of atherosclerosis (6,11). Furthermore, owing to its reliance on comparing putative sites of stenosis with an apparently normal (reference) arterial segment, angiography often fails to detect diffuse disease in which the entire artery may be impacted by atherosclerotic disease (12). Visual assessment of angiograms is subject to significant variation in image interpretation (observer bias) which may lead to a significant underestimation of lesion severity, as determined by postmortem histologic analysis (12,13).

IVUS and the Imaging of Atherosclerotic Disease

Owing to the limitations of angiography, a variety of alternative invasive and noninvasive diagnostic techniques have been explored for a more accurate imaging of atherosclerotic coronary vessels. Intravascular ultrasound, for example, is a catheter-based technique that provides high-resolution cross-sectional images of the coronary vessel in vivo. In daily clinical practice, IVUS is a widespread method for the visualization of coronary lumen, vessel wall, and atherosclerotic plaque formation (14). The coronary artery is subselectively cannulated by a catheter incorporating a miniature transducer which emits high-frequency ultrasound (usually in the range of 20 to 50 MHz). As the transducer is moved through the artery, ultrasonic reflections are electronically converted to cross-sectional images.

Qualitative and quantitative IVUS analyses are usually performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (15). Lumen cross-sectional area (CSA) is quantified by planimetry of the leading edge of the blood-intima acoustic interface. The outer vessel border (external elastic membrane [EEM] CSA) is detected as the interface between media and adventitia. Atheroma-CSA is calculated as the difference between EEM-CSA and lumen-

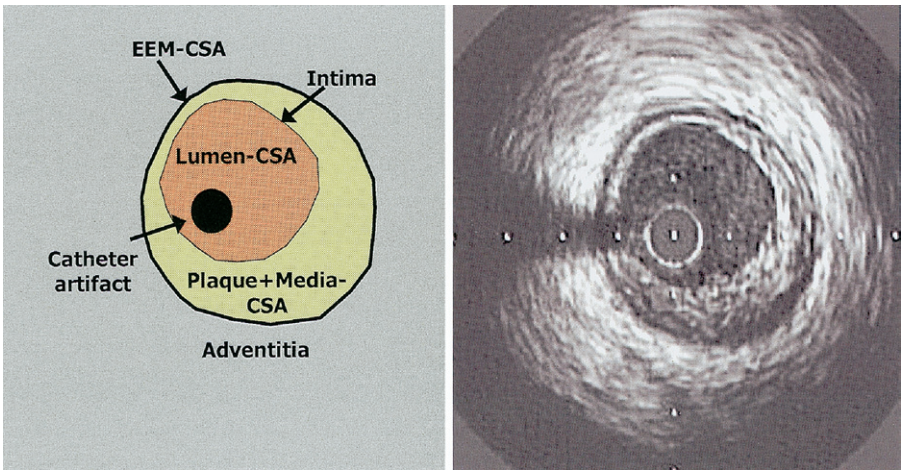

Figure 1 IVUS Cross-Sectional Image of an Atherosclerotic Human Coronary Artery

Determination of plaque cross-sectional area using intravascular ultrasound (IVUS): external elastic membrane (EEM)–cross-sectional area (CSA) − Lumen-CSA = Plaque + Media-CSA.

CSA (Fig. 1). The use of a motorized pull-back device with a defined pull-back speed (0.5 to 1 mm/s) is the established method to image the entire vessel. This permits a volumetric assessment of vessel and plaque dimensions after longitudinal or 3-dimensional computer-assisted reconstruction (15) (Fig. 2).

Because IVUS is fundamentally different from angiography, it is not subject to the same limitations as angiography. Intravascular ultrasound can identify diffuse disease and remodeling of the vessel wall, both of which may be common in atherosclerotic progression and may be determinants of clinical outcome (11). Furthermore, IVUS is normally more sensitive than angiography for the detection of stenosis (16). For these reasons, there is frequently a discrepancy between the extent and severity of CHD as diagnosed by IVUS versus angiography (17,18).

In addition, IVUS may be helpful in the detection of plaques with a high risk of spontaneous plaque rupture. Some typical morphologic criteria of these vulnerable rupture-prone plaques can be identified by IVUS (8,9,19). Plaque ruptures typically occur in proximal vessel segments, in eccentric lesions with positive and expansive remodeling,

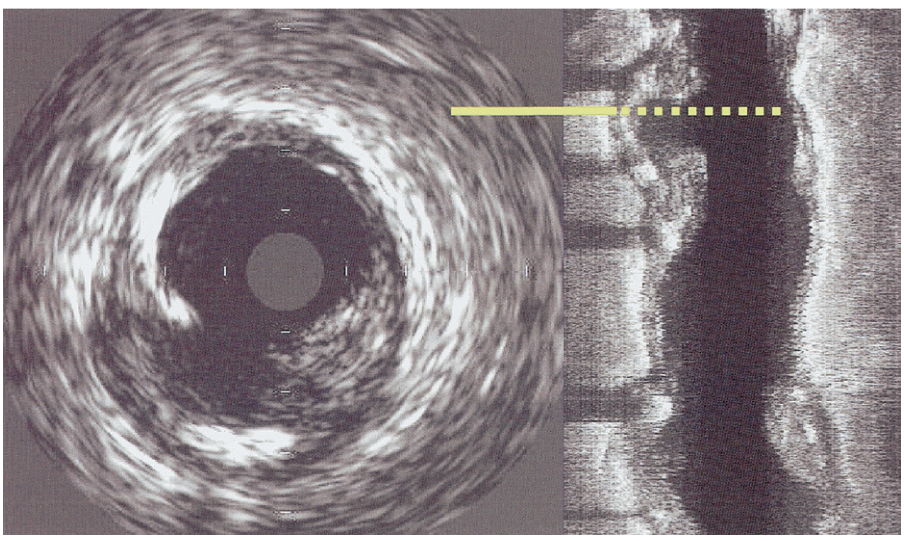

Figure 2 IVUS Cross-Sectional Image and Longitudinal Reconstruction of an Atherosclerotic Coronary Artery With a Plaque Rupture

(Left) Intravascular ultrasound (IVUS) cross-sectional image; **(right)** longitudinal reconstruction. The **line** indicates the position of the cross-sectional image and thus the site of plaque rupture in the longitudinal reconstruction.

and even in plaques with large plaque mass (8,9) (Fig. 2). In some cases, an echolucent zone, representing a lipid-rich core, can be identified within the plaque by IVUS (9).

Although IVUS offers many advantages over angiography, its widespread use in clinical practice may be partially limited by its invasive nature, which carries a certain level of risk. For this reason, the safety of IVUS has been rigorously investigated, and data from almost 3,500 examinations indicate a low overall rate of acute complications (20–22). The major complications are dissection and vessel closure, which may occur in <0.5% of procedures (nearly always in patients undergoing simultaneous intracoronary interventions) (21,22). Importantly, IVUS does not appear to accelerate atherosclerosis in nontransplant nonintervened coronary arteries (20). Coronary angiography is still regarded by many as the principal imaging technique for guiding coronary interventions. Nevertheless, IVUS is proving to be a valuable addition, particularly in the identification of angiographically silent atherosclerosis and ambiguous lesions.

Detection of Coronary Plaque Composition Based on IVUS

Initially, conventional grayscale IVUS was used to characterize coronary plaque composition qualitatively by the echogenicity of different plaque structures. Coronary calcification especially can be well detected (15). Nevertheless, IVUS is limited in the detection and quantification of specific plaque components, e.g., lipid-rich tissue and necrotic core (15). Recent technical developments, such as integrated backscatter and virtual histology, have focused on further mathematical analysis of the radiofrequency signal underlying the IVUS grayscale image. These techniques allow identification and quantification of different plaque components, such as lipid, fibrous tissue, calcification, and necrotic core. In addition, color-coded visualization of different plaque components can be performed (23,24). In a study by Fujii et al. (25), IVUS virtual histology-derived plaque composition of positively remodeled vessels showed more fibrofatty content than that of negatively remodeled lesions. Future studies will have to evaluate the potential additional values of these new imaging techniques and whether these methods are able to detect changes in plaque composition in addition to the changes in plaque volume. In the future, these techniques may have the potential to assess the effects of pharmacologic therapies on plaque composition. In addition, the possibility of identifying and quantifying the lipid-rich plaque components or the necrotic core may open a new window in the detection and analysis of vulnerable plaques.

Association Between Coronary Plaque Progression, as Measured by IVUS, and CV Events

Because plaque progression, inferred by progressive angiographic luminal obstruction, has been shown to be associated with an increased risk of CV events (3,4), it can be expected that plaque progression, as measured by IVUS, should show a similar and perhaps even stronger association.

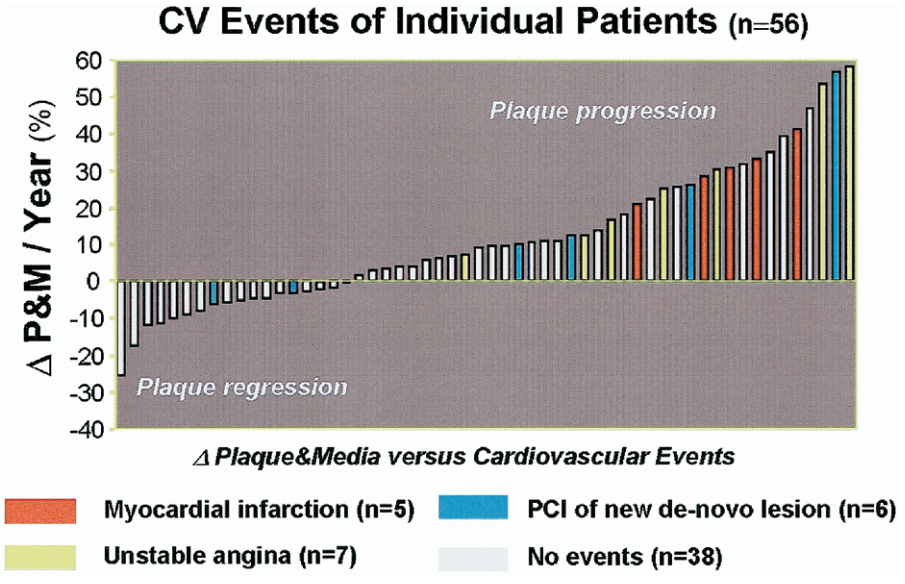

Figure 3 Plaque Progression/Regression Versus CV Events

Higher rate of cardiovascular (CV) events in patients with plaque progression during follow-up.
Modified from von Birgelen et al. (27). PCI = percutaneous coronary intervention; P&M = plaque and media.

An emerging body of evidence provides support for this supposition.

In a study of patients that underwent percutaneous coronary intervention (26), obstructive left main coronary artery disease, detectable by IVUS but angiographically silent, was an independent predictor of future cardiac events. The IVUS imaging was conducted during percutaneous coronary intervention in 107 patients with normal or mild left main coronary artery disease by both visual (<20%DS) and quantitative angiography (mean 4.8%DS). The IVUS mean area stenosis was 30.2%. Major adverse cardiac events in 102 patients followed for a median of 29 months were death (n = 6), MI (n = 4), repeat percutaneous coronary intervention (n = 13), and CABG (n = 16). By univariate analysis, these events were significantly associated with IVUS minimum and mean lumen area, angiographic minimum lumen diameter, female gender, and diabetes. For every 5 mm^2 increase in IVUS minimum and mean lumen area, the hazard ratio (HR) was 0.59 ($p = 0.01$) and 0.62 ($p = 0.01$), respectively. For every 1 mm increase in angiographic minimum lumen diameter, the HR was 0.59 ($p = 0.04$). By multivariate analysis, only minimum lumen area by IVUS (HR 0.59 for every 5 mm^2 increase; $p = 0.015$) and diabetes (HR 2.69; $p = 0.014$) were significant independent predictors of cardiac events.

A recent retrospective analysis of serial IVUS examinations of patients with established CVD published by von Birgelen et al. (27) demonstrated that plaque progression as measured by IVUS was associated with a significantly increased risk of clinical events as predicted by established risk-scoring systems. The IVUS examination of the left main coronary artery was conducted in 56 patients during an initial coronary angiography and in a repeat procedure after 18 months. Because no validated risk score for secondary prevention was available, the risk of CV events was estimated using 3 established algorithms for determining CVD risk in primary prevention: Prospective Cardiovascular Münster, European Systematic Coronary Risk Evaluation, and Framingham risk score). By all 3 algorithms, patients at greatest risk of CV events exhibited significantly greater plaque progression by IVUS than patients at lowest risk ($p < 0.01$ and $p < 0.05$ for absolute and percentage increases in atheroma CSA, respectively). Furthermore, the estimated risk of clinical events by all three algorithms exhibited a positive linear correlation with percentage increases in atheroma CSA ($r = 0.41$ to $r = 0.60$; $p < 0.002$ to $p < 0.0001$). During the follow-up period, actual adverse CV events occurred in 18 patients, in whom the annual plaque progression was significantly greater than in the remaining asymptomatic patients ($p < 0.001$) (Fig. 3). The aforementioned data were obtained from a relatively small retrospective analysis and may be considered only "hypothesis-generating." Nevertheless, various recent prospective trials also provided evidence that supports such a hypothesis, as discussed in the following section.

Use of IVUS-Measured Changes in Atheroma Dimensions as a Surrogate End Point

In accordance with the hypothesis that plaque progression detected by IVUS is a valid predictive marker for CV events, several clinical trials of CV drugs have used IVUS-measured changes in atheroma dimensions as surrogate end points (28–32).

The CAMELOT (Comparison of Amlodipine and Enalapril to Limit Occurrences of Thrombosis) and NORMALISE (Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation) studies (28) showed that antihypertensive therapy with amlodipine reduced IVUS-detected coronary plaque progression and CV events. In the CAMELOT study, 1,991 patients with angiographically documented CHD (>20%DS) and normal blood pressure were randomized to receive either 10 mg amlodipine, 20 mg enalapril, or placebo daily. In a subgroup of 274 patients (NORMALISE), IVUS was conducted at baseline and at study completion. After 24 months of therapy, the incidence of CV events was significantly lower in amlodipine-treated patients versus placebo (16.6% vs. 23.1%, HR 0.69, 95% CI 0.54 to 0.88; $p = 0.003$) but not in the enalapril-treated

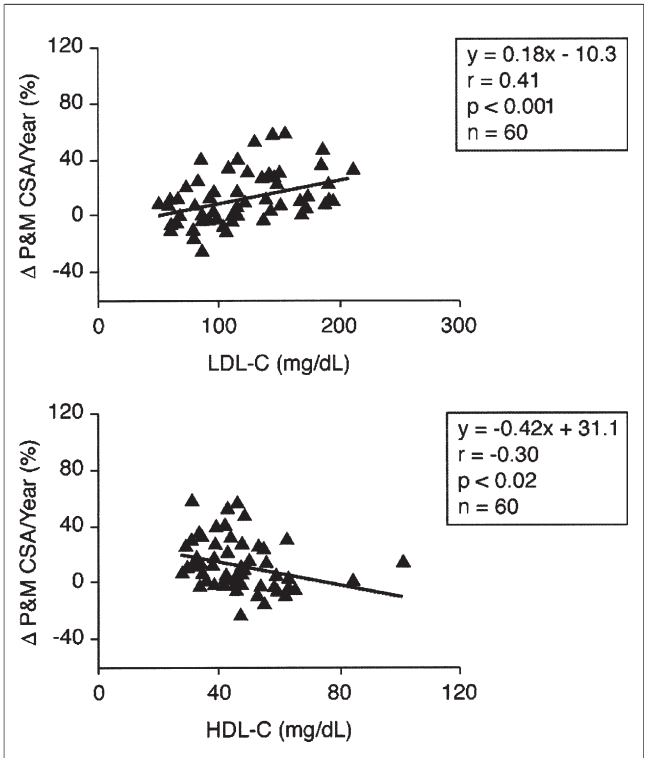

Figure 4 Cholesterol Levels Versus Plaque Progression Regression

(Top) Positive relation between plaque progression, defined as change in plaque plus media cross-sectional area/year (ΔP&M CSA/year), versus LDL-C levels. **(Bottom)** Negative relation between plaque progression (ΔP&M CSA/year) versus HDL-C levels. Modified from von Birgelen et al. (33). CSA = cross-sectional area; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; P&M = plaque and media.

group (20.3%, HR 0.85, 95% CI 0.67 to 1.07; p = 0.16). Mirroring these differences in CV event incidence, there was no significant change from baseline in mean percentage IVUS-measured atheroma volume in the amlodipine group (p = 0.31), a trend toward an increase in the enalapril group (p = 0.08), and a significant increase in the placebo group (p < 0.001).

The linear relation between cholesterol levels and coronary plaque progression as assessed with serial IVUS measurements was first shown in an observational study by von Birgelen et al. (33). Nonstenotic left main coronary arteries were examined by IVUS and after 18.3 ± 9.4 months. In this retrospective analysis, a positive linear relation between low-density lipoprotein cholesterol (LDL-C) and plaque progression was found (r = 0.41; p < 0.0001) (Fig. 4). An LDL-C cut-off value of 75 mg/dl was found at which there was no increase in plaque-CSA (Fig. 5). An inverse relationship between high-density lipoprotein cholesterol (HDL-C) levels and the annual changes in plaque size was also indicated (r = −0.32; p < 0.01).

Later on, these results were supported by the volumetric IVUS data of the prospective REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering) trial. In that study, IVUS examination demonstrated significantly more reduction of plaque progression in patients with intense lowering of LDL-C versus moderate lowering of LDL-C (29). In the REVERSAL trial, 654 patients with angiographically established CHD (>20%DS in at least 1 lesion) and elevated LDL-C (mean 150.2 mg/dl) were randomized to receive 80 mg/day atorvastatin or 40 mg/day pravastatin. The IVUS was conducted at baseline and after 18 months of therapy. With regard to the primary end point of percentage change in atheroma volume, disease progression was significantly lower in the atorvastatin group than in the pravastatin group (p = 0.02). Atheroma volume increased from baseline by a mean of 2.4% (95% CI 0.2% to 4.7%; p = 0.001) in the pravastatin group compared with a mean decrease of 0.4% in the atorvastatin group (95% CI −2.4% to 1.5%; p = 0.98). Baseline LDL-C levels were reduced to a mean of 110 mg/dl and 79 mg/dl in the pravastatin and atorvastatin groups, respectively (p < 0.001). This LDL-C value of patients on atorvastatin who had virtually no change in plaque dimensions is almost identical to the threshold at which no progression occurred in the observational study by von Birgelen et al. (33) (Fig. 5).

The REVERSAL study used the same treatment regimen as the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study, which reported a significantly greater reduction in CV events in patients with acute coronary syndromes after treatment for 2 years with 80 mg/day atorvastatin compared with 40 mg/day pravastatin (34). Although the REVERSAL and PROVE IT studies were distinct studies, when considered together their results provide further evidence that atherosclerotic progression measured by IVUS is predictive of an increased risk of CV events.

There are other studies that indicate that lipid-lowering therapy may not only slow down plaque progression but may even induce plaque regression. Okazaki et al. (30) analyzed the impact of aggressive lipid-lowering therapy on coronary plaque volume in patients with acute coronary syndrome with serial IVUS. In the ESTABLISH study, the patients were randomized to a lipid-lowering therapy (20 mg/day atorvastatin) or no lipid-lowering therapy (control group). After therapy with atorvastatin for 6 months, there was a

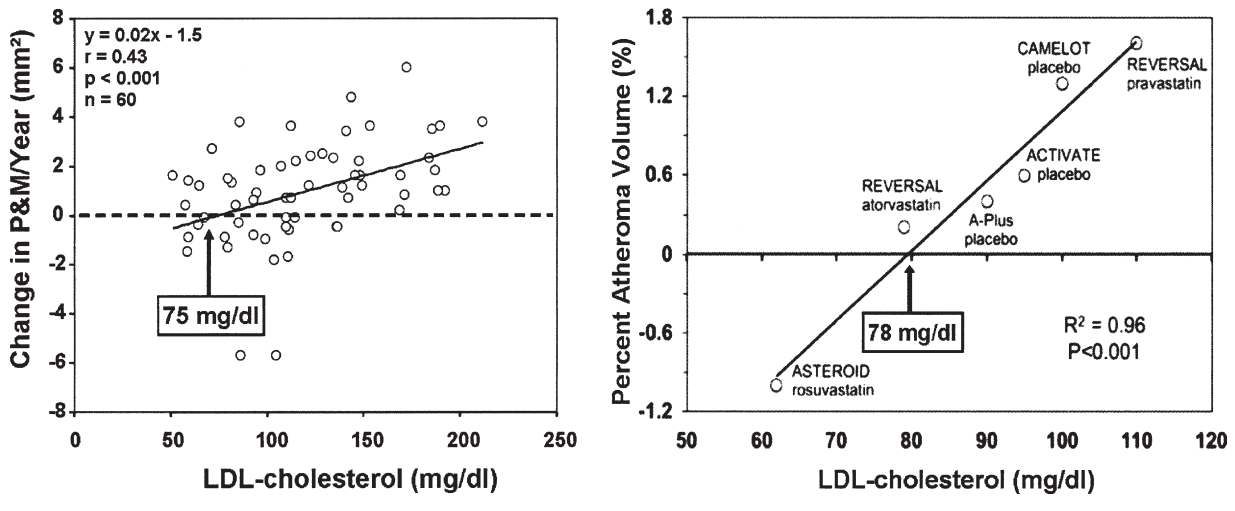

Figure 5 LDL-C Versus Coronary Plaque Progression/Regression

(Left) First demonstration of the positive correlation between coronary plaque progression by intravascular ultrasound and LDL-C levels in an observational study. Modified from von Birgelen et al. (33). **(Right)** Confirmation of the relation between LDL-C and coronary plaque progression by data derived from various large randomized trials. Modified from Nissen SE et al. (36). LDL-C = low-density lipoprotein cholesterol; P&M = plaque and media.

significant plaque volume reduction by IVUS (−13.1% ± 12.8%) and a significant positive relation between the LDL-C reduction and the reduction in plaque volume ($r = 0.612$; $p < 0.0001$) (30).

The relationship between LDL-C lowering and the IVUS-measured regression of atherosclerotic plaque volume could also be demonstrated in the LACMART (Low-Density Lipoprotein Apheresis Coronary Morphology and Reserve Trial) (35), which assessed the effect of LDL-C lowering by medication alone or in combination with LDL-apheresis on coronary atherosclerosis in patients with familial hypercholesterolemia. The patients treated with LDL-apheresis showed a significant lowering of total cholesterol (−28.4%) and LDL-C (−34.3%), whereas the medication group showed no changes in cholesterol levels (35). At 12 months follow-up, IVUS measurements showed a decrease in plaque area in patients treated by aggressive lipid-lowering therapy (LDL-apheresis group) versus an increase in plaque area in the medication group ($p = 0.008$).

Those results were emphasized by ASTEROID (A Study To Evaluate the Effect of Rouvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden), which evaluated the effect of maximally intensive statin therapy with 40 mg/day rosuvastatin on coronary plaque progression or regression as assessed with serial IVUS examination (36). A total of 507 patients were included in this study, and 349 patients had a follow-up examination after 24 months. Under therapy, the mean baseline LDL-C levels were reduced from 130.4 ± 34.3 mg/dl to 60.7 ± 20.1 mg/dl (mean reduction of 53.2%), and the HDL-C levels showed an increase from 43.1 ± 11.1 mg/dl to 49.2 ± 12.6 mg/dl (mean increase of 14.6%). The IVUS measurements demonstrated a reduction of total plaque volume by 6.8% (−14.7 ± 25.7 mm^3) after lipid-lowering therapy of 24 months ($p < 0.001$ compared with baseline) (Fig. 5).

Advantages of Using IVUS-Based Surrogate End Points for Evaluation of Novel Therapies Targeting Atherosclerosis

The assessment of morbidity and mortality as end points of large clinical trials is associated with a substantial burden in terms of resources (1). The recent development of effective pharmacotherapies that further reduce the incidence of CV events aggravates this problem, because novel agents must now prove to be superior to those therapies rather than to placebo. Thus, demonstrating greater efficacy for a novel therapy versus an existing therapy in a clinical end point trial has become more challenging and may require further increases in study sample size, duration, or both.

In contrast, surrogate end points allow trials of novel CVD therapies to be conducted within a shorter time frame and with fewer participants. Consequently, the use of surrogate end points as an alternative to clinical end points may expedite the process of drug development and testing. As a consequence, this approach reduces costs, which is beneficial for both patients and the medical community. Even as a complement to clinical end points, the use of surrogate markers enables pharmaceutical companies and regulatory bodies to evaluate the potential benefits of novel drugs until clinical end point data become available.

The emerging body of evidence validating IVUS-detected progression of coronary atherosclerosis as a surrogate marker of future CV events suggests its use in clinical trials (37). Indeed, IVUS may be a particularly suitable technique for this purpose, given its ability to detect early-stage disease (i.e., angiographically silent atherosclerosis) which can be a precursor of future coronary events.

Conclusions

As the global burden of CVD increases in the aging population, the need for surrogate end points to maximize efficacy in the evaluation of new CVD therapies is likely to grow. Most coronary events are a consequence of underlying atherosclerosis, so that measuring the progression of this pathophysiologic state has attracted much attention for predicting clinical outcomes. Currently, the inherent limitations of angiography in providing a clinically relevant picture of arterial disease are clearly recognized. Intravascular ultrasound, on the other hand, provides a different means of imaging coronary arteries and is not subject to the same limitations of coronary angiography. There is growing evidence from clinical studies that IVUS-measured increases in coronary plaque dimensions predict future CV events, which supports its validity as a surrogate end point in trials that assess novel pharmacologic therapies.

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