Atherosclerosis Imaging in Progression/Regression Trials: Surrogate Marker or Direct Window into the Atherosclerotic Disease Process?

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Summary

CAD remains a major global cause of morbidity and mortality. Comprehensive drug development programs of novel pharmacological treatment strategies frequently utilize traditional mortality/morbidity endpoints studies and additional surrogate endpoints trials. This parallel approach allows an assessment of efficacy several years in advance of the availability of data from clinical endpoint trials. Several atherosclerosis imaging markers have been introduced into these drug-development strategies, including angiography, carotid ultrasound, IVUS, MRI, and CT. This review will discuss the current status of atherosclerosis imaging as an endpoint in progression/regression trials, with an emphasis on evidence-based data. In addition to a discussion of the results of individual imaging modalities, the emerging data comparing different modalities and approaches are presented.

Introduction

Atherosclerotic cardiovascular disease remains a major global cause of morbidity and mortality. Subclinical atherosclerosis develops and progresses slowly over many decades, before suddenly causing clinical manifestations. The remaining clinical challenge is the identification and modification of the disease process in the early subclinical stages. Current comprehensive approaches to risk reduction, including diet, exercise, and pharmacological intervention, decrease cardiovascular risk but do not prevent a substantial number of life-threatening cardiovascular events. Further improvements will require earlier diagnosis, a better understanding of the genetic predisposition, and the development of novel pharmacological strategies to modify disease progression. Novel therapies require eventual proof of effectiveness in traditional mortality/morbidity endpoints trials, with large patient populations and long-term follow-up. However, current comprehensive drug development programs frequently utilize additional clinical trials and trials with surrogate endpoints/biomarkers of disease progression. This parallel approach allows an assessment of the efficacy of new therapies several years in advance of the availability of data from clinical endpoint trials. The best-established example is the role of LDL as a surrogate in pharmacological intervention trials.

Over the last decade, the use of imaging markers has been introduced into these drug-development strategies (Figure 1, Table 1). Imaging endpoints include changes in luminal stenosis assessed with angiography, carotid intima-media thickness using ultrasound, coronary calcium content assessed with computed tomography, and coronary atheroma volume using intravascular ultrasound. Emerging approaches are evaluating endothelial function, plaque composition, and imaging with novel, non-invasive modalities, including CT and MRI.

These tests measure a wide variety of characteristics of vascular anatomy and physiology, which all reflect the atherosclerotic disease process, progression/regression, and plaque stability. However, the correlation of these approaches to one another is incompletely understood. This review will discuss the current status of atherosclerosis imaging as an endpoint in progression/regression trials, with an emphasis on evidence-based data. In addition to a discussion of the results of individual imaging modalities, the emerging data comparing different modalities and approaches are presented.
Atherosclerosis imaging and luminal stenosis

Coronary artery disease can be described by the changes of the arterial wall and by the associated luminal narrowing. After the introduction of coronary angiography, quantitative coronary lumen imaging has been the first approach to atherosclerosis imaging. Based on extensive data from various patient populations, it is well established that angiographically determined disease progression reflects clinical prognosis. Results from serial angiographic multicenter trials during lipid-modifying treatment demonstrate that change in...
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These limitations have been the rational for vessel wall imaging using invasive modalities, specifically IVUS, and non-invasive modalities including CT calcium scoring and CIMT. The data collected with these modalities are summarized in the following paragraphs.

CT Calcium scoring

Computed tomography without contrast administration allows the quantification of coronary calcification, which is a pathognomonic sign of chronic atherosclerosis. Total calcium load in the coronary tree can be quantified with several calcium scoring algorithms. Most data have been collected with EBCT, but MDCT has recently emerged as an alternative.

The association between conventional risk factors for coronary artery disease and calcium score is well documented. In a study of 30,908 asymptomatic individuals aged 30 to 90 years, conventional clinical risk factors were significantly associated with the presence of detectable coronary calcium. The mean calcium score increased in proportion to the number of CAD risk factors. In age-adjusted (multivariable) logistic regression analysis, cigarette use, histories of hypercholesterolemia, diabetes, and hypertension were each significantly associated with mild to extensive calcium scores.

The predictive value of the overall calcium score for future coronary events is well established and an incremental value of calcium scores over clinical risk-assessment in selected patient groups with intermediate risk has been shown. In one study, 10,377 asymptomatic individuals were followed with the objective of developing risk-adjusted multivariable models that included risk factors and coronary calcium scores for the prediction of all-cause mortality. During a mean follow-up of 5.0 years, the death rate was 2.4%. In a risk-adjusted model (p < 0.001), coronary calcium was an independent predictor of mortality (p < 0.001). Five-year risk-adjusted survival was 99.0% for a calcium score of 10 or less and 95.0% for a score of greater than 1,000 (p < 0.001). With a receiver operating characteristic curve, the concordance index increased from 0.72 for cardiac risk factors alone to 0.78 (p < 0.001) when the calcium score was added to a multivariable model for prediction of death.

A prospective observational study of 1312 asymptomatic adults with coronary risk factors examined whether the calcium score (CACS) combined with clinical risk assessment (Framingham Risk Score, FRS) provided prognostic information superior to either method alone. Participants underwent calcium scoring and were contacted yearly. During a median of 7.0 years of follow-up, 84 patients experienced myocardial infarction (MI) or cardiovascular death; 70 patients died of any cause. Compared with an FRS of less than 10%, an FRS of more than 20% predicted the risk of MI or CHD death (hazard ratio [HR], 14.3; p = 0.009). Compared with a CACS of zero, a CACS of more than 300 was predictive (HR, 3.9; p<0.001). Across categories of FRS, CACS was predictive of risk among patients with an FRS higher than 10% (p<0.001) but not with an FRS of less than 10%.

Although calcium predicts risk, it does not localize the site of plaques prone to rupture. High-grade stenotic lesions causing chronic, stable angina pectoris often demonstrate dense calcifications. In contrast, high-risk culprit lesions causing acute coronary events are frequently not calcified or minimally calcified and may not be reflected by calcium scoring. It is also not well understood how plaque stabilization affects individual lesion calcification during progression/regression, and results of CT studies examining dynamic changes in the calcium volume score during pharmacological therapy have been inconclusive.

In a retrospective study, 149 patients with no history of coronary artery disease underwent calcium scoring at baseline and after a minimum of 12 months. Treatment with statins was begun at the discretion of the referring physician in 105 patients (70 percent). At follow-up, a net reduction in the calcium-volume score was observed only in the 65 treated patients whose final LDL cholesterol levels were less than 120 mg per deciliter (mean [± SD] change in the score, -7+/−23 percent; p=0.01). Untreated patients had an average LDL cholesterol level of at least 120 mg per deciliter and at the time of follow-up had a significant net increase in mean calcium-volume score (mean change, +52+/−36 percent; p<0.001). The 40 treated patients who had average LDL cholesterol levels of at least 120 mg per deciliter had a measurable increase in mean calcium-volume score (25+/−22 percent, p<0.001), although it was smaller than the increase in the untreated patients.

In a cohort study of 66 patients with LDL cholesterol >130 mg/dL, and no lipid-lowering treatment, a CT scan was performed at baseline and after a mean interval of 14 months. Then treatment with cerivastatin was initiated (0.3 mg/day). After 12 months of treatment, a third EBT scan was
performed. Coronary calcifications were quantified using a volumetric score. Cerivastatin therapy lowered the mean LDL cholesterol level from 164+/-30 to 107+/-21 mg/dL. The median calcified volume was 155 mm³ (range, 15 to 1849) at baseline, 201 mm³ (19 to 2486) after 14 months without treatment, and 203 mm³ (15 to 2569) after 12 months of cerivastatin treatment. The median annual absolute increase in coronary calcium was 25 mm³ during the untreated versus 11 mm³ during the treatment period (p<0.01). The median annual relative increase in coronary calcium was 25% during the untreated versus 8.8% during the treatment period (p<0.0001). In 32 patients with an LDL cholesterol level <100 mg/dL during treatment, the median relative change was 27% during the untreated versus -3.4% during the treatment period (p=0.001).

Off-the-record-note: cerivastatin was pulled from the market because of an association with rhabdomyolysis.

In a multicenter, randomized trial, 471 patients without history of coronary artery disease but with cardiovascular risk factors were randomized to receive 80 mg or 10 mg of atorvastatin per day over 12 months. During the 12-month drug treatment, LDL cholesterol decreased from 106+/-22 to 87+/-33 mg/dL in the 80-mg atorvastatin group (p<0.001), whereas levels remained stable in the 10-mg group (108+/-23 at baseline, 109+/-28 mg/dL at the end of the study, p=NS). The mean progression of CAC volume scores, corrected for the baseline CAC volume score, was 27% in the 80-mg atorvastatin group and 25% in the 10-mg atorvastatin group (p=0.65). CAC progression showed no relationship with on-treatment LDL cholesterol levels.

In summary, CT calcium scoring is an established tool for initial risk assessment, but has currently limited value as an endpoint in serial progression/regression trials.

**B-mode ultrasound carotid intima-media thickness**

B-mode ultrasonography of the carotid arteries quantifies carotid intima-media thickness (CIMT) as a marker of atherosclerotic burden. Under standardized conditions, the reproducibility is suitable for application in large, multicenter clinical trials.

Various studies have shown a strong correlation between IMT and cardiovascular risk factors. Over the past decade, several large observational studies have demonstrated that baseline CIMT is an independent predictor of future clinical cardiovascular events. This has been shown in symptomatic and asymptomatic patients across all age groups, including healthy young adults. In the ARIC study, which examined about 12,800 individuals aged 45-64 years without CVD, a mean CIMT of >1 mm at baseline was associated with a significantly increased risk for clinical coronary events in >4-7 years of follow-up when compared with a mean CIMT of ≤1 mm. In a prospective trial of 1288 Finnish men followed for up to 2.5 years, intimal-medial thickening was associated with a 2.2-fold (p = NS), small carotid plaques with a 4.2-fold (p < 0.01), and large (“stenotic”) plaques with a 6.7-fold (p < 0.01) risk of acute myocardial infarction compared with men free of any structural changes in the carotid artery wall at baseline.

The Rotterdam study followed about 8000 individuals at least 55 years of age after a baseline carotid ultrasound. After an average follow-up of 2.7 years, baseline CIMT was significantly greater in those who experienced events than in asymptomatic individuals. A difference in CIMT of 0.163 mm was associated with an odds ratio of 1.41 for stroke and 1.43 for MI. The Cardiovascular Health Study of 5858 individuals aged at least 65 years with no history of CVD found that those with the greatest CIMT at baseline experienced a significantly higher incidence of cardiovascular events over 6 years of follow-up.

Serial intervention trials have demonstrated the value of CIMT as an endpoint in serial pharmacological intervention trials. Placebo-controlled clinical trials showed that statin therapy slowed or reversed progression of CIMT and reduced the incidence of cardiovascular events. Both the ASAP and ARBITER-I trial showed that aggressive lipid lowering with statins was associated with a decrease in CIMT as opposed to no change or progression in the comparative low-dose-statin arms. In the ARBITER study, 161 patients with hypercholesterolemia were treated with atorvastatin 80 mg or pravastatin 40 mg daily. After 1 year, CIMT had decreased by a mean of 0.034 mm in atorvastatin patients but had not significantly changed in pravastatin recipients. The METEOR study assessed the impact of rosuvastatin in 984 asymptomatic subjects at low risk of CAD. The results showed that treatment with rosuvastatin 40 mg/day halted progression of atherosclerosis. A recent meta-analysis of statin progression/regression trials has revealed a statistical link between progression of CIMT and incidence of cardiovascular events. A mean annual decrease in CIMT thickness of 0.012 mm was associated with an odds ratio of 0.48 for cardiovascular events.

Other studies employing CIMT endpoints examined the effect of HTN treatment, the effects of cannabinoid-1 receptor rimonabant (AUDITOR) antagonist on atherosclerotic progression in obese patients with metabolic syndrome. Other studies employing CIMT endpoints examined the effect of HTN treatment, the effects of cannabinoid-1 receptor rimonabant (AUDITOR) antagonist on atherosclerotic progression in obese patients with metabolic syndrome. ClinicalTrials.gov Identifier: NCT00228176), and the effect of HTN treatment 55, the effects of cannabinoid-1 receptor rimonabant (AUDITOR) antagonist on atherosclerotic progression in obese patients with metabolic syndrome. ClinicalTrials.gov Identifier: NCT00228176).

**Intravascular ultrasound**

Similar to CIMT, there is extensive experience with intravascular ultrasound (IVUS). In contrast to CIMT, IVUS directly examines coronary arteries but is a highly invasive modality, which is performed during cardiac catheterization using small, intracoronary ultrasound catheters. Although its safety is well established, the invasive nature restricts IVUS to higher risk populations, typically patients with clinically indicated PCI. IVUS allows precise measurement of the atheroma (intima-media area) by planimetry of the blood-intima and media-adventitia border. Atheroma volume is calculated as the sum of the differences in cross-sectional area between sequential cross-sections of the vessel at a given site.
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IVUS studies have examined the relationship between plaque burden and future cardiovascular events. In a study of 107 patients with angiographically insignificant coronary atherosclerosis, left main coronary artery disease detected by IVUS was significantly associated with future coronary events. IVUS studies have shown that the rate of plaque growth in the left main coronary artery correlates with traditional risk factors. Patients at greatest risk of cardiovascular events, as determined by the PROCAM, SCORE, and Framingham CVD algorithms, exhibited significantly greater plaque progression between baseline and follow-up (median 14 months).

For the use as an endpoint in progression/regression trials, volumetric-analysis approaches integrate consecutive plaque-area measurements at 0.5–1 mm intervals along long vessel segments. Because the segment rather than individual sites are matched at baseline and follow up, assessment of small percentage changes in atheroma volume is possible with considerable statistical power. In a recent randomized trial, intra-observer variability was analyzed in 1177 images from 18 patients. The mean (±SD) differences were negligible for both EEM (0.76 ± 0.93 mm²) and lumen areas (-0.07 ± 0.75 mm²). Linear regression analysis showed close correlations between the original and re-analysis (r = 0.99 and 0.98 for EEM and lumen areas, respectively). Interobserver variability was evaluated in 2151 images from 30 patients. The mean (SD) differences were negligible for both EEM (0.07 ± 0.93 mm²) and lumen areas (-0.07 ± 0.93 mm²). Regression analysis showed close correlations between the original and re-analysis (r = 0.99 and 0.98 for EEM and lumen areas, respectively).

IVUS surrogate endpoints have been employed in several trials of statin-based treatment regimens in patients with acute or stable CHD. In the REVESAL trial, 654 patients were imaged at baseline and after 18 months of therapy. Atheroma volume decreased by 0.4% (p = 0.98) in those receiving atorvastatin 80 mg but increased by 2.7% (p = 0.001) in those receiving pravastatin 40 mg. In the ASTEROID trial, 346 patients were imaged before and after 24-month single-arm therapy with rosuvastatin 40 mg. Rosuvastatin was associated with a significant reduction from baseline in LDL-C (-53%) and also a significant increase from baseline in HDL-C (15%). The two IVUS-derived primary endpoints change in percent atheroma volume and change in atheroma volume in the 10 mm subsegment most seriously affected showed a significant reduction in both endpoints compared with baseline.

Pooled data from ASTEROID and other IVUS studies suggest an independent role of HDL raising. In a small study examining the effect of HDL, a total of 57 patients with acute coronary syndromes were randomized to double-blind treatment with weekly infusions of recombinant Apo A-I Milano or placebo. After 6 weeks, atheroma volume measured by IVUS had decreased by a mean of 4.2% (p < 0.001) in patients receiving Apo A-I Milano, but had not changed significantly in those receiving placebo. In the ERASE study, the efficacy of infusion of reconstituted HDL in patients with acute coronary syndromes was examined. In contrast to the Apo A-I Milano study, the results showed that short-term infusions of reconstituted HDL did not result in a significantly greater percent change in atheroma volume than did infusions of saline placebo.

Other recently completed and ongoing trials employing IVUS endpoints to evaluate novel CVD therapies include the use of rimonabact in patients with CHD and abdominal obesity and of rosiglitazone vs. glipizide in patients with type-2 diabetes and CHD (APPROACH study ClinicalTrials.gov identifier: NCT00116831). The comparison of these intravascular-ultrasound trials with outcome studies using similar pharmacological interventions provide indirect data correlating plaque burden to clinical outcomes. In the CAMELOT study, 1991 normotensive patients with QCA-documented coronary atherosclerosis were randomized to 24 months of therapy with amlodipine, enalapril or placebo. At study end, the cumulative incidences of cardiovascular events in the amlodipine, enalapril, and placebo groups were 16.6% (HR = 0.69 vs. placebo; p = 0.003), 20.2% (HR = 0.85 vs. placebo; p = 0.16), and 23.1%, respectively. IVUS was conducted at baseline and at study completion in a subgroup of 274 patients (the NORMALIZE sub-study). There was no progression of IVUS-assessed atherosclerotic burden in the amlodipine group (p = 0.31), a trend towards progression in the enalapril group (p = 0.08), and progression in the placebo group (p < 0.001). Based on these results, IVUS plaque burden is a valid endpoint in pharmacological intervention trials.

Emerging techniques:

There is intensive research into the role of non-invasive coronary atherosclerosis imaging. However, non-invasive visualization of the coronary arteries remains challenging, because the coronaries are small and tortuous, and respiratory motion and the continuous cardiac motion distort the image.

Multidetector Computed tomography

Computed-tomography coronary angiography (CTA) allows identification and quantification of calcified and non-calcified coronary plaques. Based on the presence or distribution of plaques (one-, two- or three-vessel disease) and stenosis severity (>50% diameter stenosis), the plaque burden of the entire coronary tree can be established. The prevalence of different disease patterns has recently been described. The prevalence and characteristics of coronary plaques in a patient population with suspected significant coronary artery disease (CAD) was examined. 64-slice coronary CT was performed in 161 consecutive patients with an intermediate risk of CAD. Computed tomography data sets were evaluated for presence of coronary calcifications, noncalcified plaques, and/or lumen narrowing. Noncalcified coronary plaques were detected in 48 (29.8%) of 161 enrolled patients. In 28 of these patients (23.6% of overall group) noncalcified plaques were associated with coronary calcifications. The presence of noncalcified plaques as the only manifestation of CAD was found in 10 patients (6.2% of the overall group of 161 patients). Patients with noncalcified plaques were characterized by significantly higher total cholesterol, low-density lipoprotein, and C-reactive protein levels as well as by a trend for more diabetes

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mellitus. The majority of noncalcified plaques resulted in a lumen narrowing of <50%. CAD and coronary calcifications were ruled out in 53 of 161 (32.9%) patients, whereas 60 of 161 (37.3%) patients presented with calcifications in the absence of noncalcified plaque.

Precise quantification is limited and it is unclear whether the Computed-tomography assessment of the coronary plaque burden is accurate in stratifying cardiac risk and whether it adds to the calcium score. An initial study sought to determine the prognostic value of CT coronary angiography in 100 patients (73 men, age 59 +/- 12 years) who were referred for cardiac catheterization due to suspicion of significant CAD. These patients underwent additional CTA and were followed up for the occurrence of cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and coronary revascularization. Coronary plaques were detected in 80 (80%) patients. During a mean follow-up of 16 months, 33 events occurred in 26 patients, most of which were revascularization. In patients with normal coronary arteries on CT, the first-year event rate was 0% versus 30% in patients with any CT evidence of CAD. The observed event rate was highest in the presence of obstructive lesions (63%) and when obstructive lesions were located in the left main (LM)/left anterior descending (LAD) coronary arteries (77%). Nonetheless, an elevated event rate was also observed in patients with nonobstructive CAD (8%). In multivariate analysis, significant predictors of events were the presence of CAD, obstructive CAD, obstructive CAD in LM/LAD, number of segments with plaques, number of segments with obstructive plaques, and number of segments with mixed plaques.

Another study examined the association of all-cause mortality with CTA-defined extent and severity of coronary artery disease (CAD) in a cohort of 1,127 patients. Stenosis by CT was scored as minimal (<30%), mild (30% to 49%), moderate (50% to 70%), or severe (> 70%) for each coronary artery. Plaque was assessed as: 1) moderate or obstructive plaque; 2) CTA score modified from Duke coronary artery score; and 3) simple clinical scores grading plaque extent and distribution. A 15.3 +/- 3.9-month follow-up of all-cause mortality was assessed using Cox proportional hazards models adjusted for pretest CAD likelihood and risk factors. Deaths were verified by the Social Security Death Index. The CTA predictors of death included proximal left anterior descending artery stenosis and number of vessels with > 50% and > 70% stenosis (all p < 0.0001). A modified Duke CAD index, an angiographic score integrating proximal CAD, plaque extent, and left main (LM) disease, improved risk stratification (p < 0.0001). Patients with <50% stenosis had the highest survival, 99.7%. Survival worsened with higher-risk Duke scores, ranging from 96% survival for 1 stenosis > 70% or 2 stenoses > 50% (p = 0.013) to 85% survival for > 50% LM artery stenosis (p < 0.0001). Clinical scores measuring plaque burden and distribution predicted 5% to 6% higher absolute death rate (6.6% vs. 1.6% and 8.4% vs. 2.5%; p = 0.05 for both).

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance (CMR) allows the imaging of the vessel wall. Most work has been performed in the carotid artery and aorta, because of its closeness to the surface and larger size, respectively. Studies with carotid MRI demonstrated an interstudy reproducibility of 4.4%.

A number of serial studies in humans have assessed CMR in the longitudinal measurement of aortic and carotid atherosclerotic plaques and atherosclerotic plaque in thoracic and abdominal aortic plaques in 40 hypercholesterolemic patients. Treatment effects were evaluated as changes in vessel wall thickness (VWT) and vessel wall area (VWA) of atherosclerotic lesions from baseline to 12 months of treatment. The 20-mg dose induced a greater low-density lipoprotein (LDL) cholesterol reduction than did the 5-mg dose (-47% vs. -34%, p < 0.001). Although the 20-mg and 5-mg doses reduced C-reactive protein (CRP) levels (-47% and -20%, respectively), the degree of CRP reduction did not differ between the two doses. The 20-mg dose reduced VWT and VWA of thoracic aortic plaques (-12% and -18%, respectively, p < 0.001), whereas the 5-mg dose did not (+1% and +4%), respectively. Notably, the degree of plaque regression in thoracic aorta correlated with LDL cholesterol (r = 0.64) and CRP (r = 0.49) reductions. Regarding abdominal aortic plaques, the 20-mg dose could not reduce VWT or VWA (-1% and +3%, respectively), and progression was observed with the 5-mg treatment (+5% and +12%, respectively, p < 0.01).
In conclusion, atheroma CMR and CT are used for longitudinal follow up of patients to investigate atheroma progression and regression. Additional studies are needed to further explore the ability of multidetector Computed tomography and magnetic resonance imaging to assess disease progression, stabilization or even regression following specific therapy.

Other approaches beyond luminal stenosis and plaque burden

Lumen (angiography) and plaque (IVUS, CIMT) describe arterial dimensional attributes. However, clinical significance is probably also related to plaque composition and vascular reactivity.

Plaque composition with IVUS

Using intravascular ultrasound (IVUS) the internal ultrasound reflection from the vessels wall/ plaque allow atheroma characterization91,92. Initial description of plaque morphology focused on culprit lesions in patients presenting with acute or stable coronary syndromes93,94. Based on these studies, a prospective invasalvular ultrasound study hypothesized that certain features would be associated with the development of acute coronary syndromes during follow-up95. The authors examined morphologic features of vulnerability in mild-to-moderately stenotic plaques at baseline and during 2-year follow-up period. Twelve patients had an acute coronary event at a previously examined coronary site. The preexisting plaques, related to the subsequent acute events, demonstrated an eccentric pattern and the mean percent plaque area was greater here than in the patients without acute events. However, there was no statistically significant difference in lumen area between the two patient groups. Serial trials during statin treatment showed that lipid-lowering therapy is associated with an increase in echogenicity67.

However, standard grayscale IVUS imaging is limited to the analysis of plaque composition and only represents a fraction of the data of the reflected ultrasound signal. Advanced mathematical algorithms including radiofrequency analysis (RFA) and elastography allow a more detailed analysis96,97. IVUS-derived RFA (virtual histology, VH-IVUS) displays the reconstructed data as a color coded tissue map of plaque composition based on validation to histology98,99. VH-IVUS displays plaque components into four basic tissue types: fibrous (dark-green), fibro-fatty (light-green), necrotic core (red), and dense calcium (white)100. In a recent study, IVUS backscatter data from 51 left anterior descending coronary arteries were tested ex vivo and compared to the histological interpretation of the matched site. The overall predictive accuracies were 93.5% for fibrotic tissue, 94.1% for fibro-fatty tissue, 95.8% for necrotic core and 96.7% for dense calcium101.

Based on further analysis of this compositional data, classification of plaque types is performed in analogy to histopathological classification. These plaque types include pathological intimal thickening, fibroatheroma, and fibrotic-calcific plaque96.

While these post-processing techniques provide additional information about plaque composition, spatial resolution of VH-IVUS (100-200 µm) is too low to detect critical fibrous cap thickness, which by histology is defined as 65 µm. There is ongoing research to define the IVUS derived fibroatheroma (ID TCFA), based on size and confluence of the necrotic core, absence of evidence of a visible fibrous cap, presence of small amounts of calcium, length of the necrotic core against the lumen surface, occurrence of multiple, confluent necrotic cores and positive remodeling102,103. In the Carotid Artery Plaque Virtual Histology Evaluation (CAPITAL) study, a correlation between VH-IVUS plaque characterization and the true histological examination of the plaque following endarterectomy was found. Specifically, there was a high predictive accuracy for the identification of TCFA104.

The emerging results with VH-IVUS are encouraging. Similar to IVUS plaque burden, confirmation of its usefulness as an endpoint in clinical trials will be necessary in large multicenter progression/regression trials. The ongoing PROSPECT trial (ClinicalTrials.gov identifier: NCT00180466) is a natural history study to assess the relationship of unexpected acute coronary events and plaque burden, composition, and type in intermediate lesions. It is the first prospective study that is aimed at detecting high-risk lesions using both grayscale and VH IVUS technologies.

Based on the differences of the Hounsfield unit (Computed tomography) and appearance in different MRI sequences, CT and MRI provide some input in plaque composition78,79,105. However, the experience is limited.

Flow-mediated dilatation

The vascular endothelium has a central role in atherosclerosis progression, and endothelial dysfunction is one of the earliest stages of atherogenesis, preceding the occurrence of atherosclerotic lesion formation105-107. Major cardiovascular risk factors, including hypertension, smoking, hypercholesterolemia and diabetes mellitus have been shown to contribute to the onset of endothelial dysfunction107,108. More recently, endothelial dysfunction has also been shown to have predictive value for cardiovascular events109.

The gold standard to measure endothelial function are invasive techniques using intra-arterial infusion of selective endothelial agonists. The introduction of non-invasive tests of endothelial function has been critical for wider application110,111. The basic principle of flow-mediated dilatation (FMD) is the induction of increased blood flow in the brachial artery, following deflation of an occluding forearm cuff. The ensuing reactive hyperemia causes a diameter increase of the brachial artery which can be measured using ultrasound diameter measurements. The advantages of this technique are its non-invasive and readily applicable nature. Careful standardization of the protocol, including the implementation of automated real-time vessel-boundary detection, has contributed to reducing the variability. However, substantial variation in reproducibility has been described, due to both differences in technical protocols and the impact of physiological factors on FMD110. The large interindividual variation limits the use of FMD as an individual cardiovascular risk marker. Initial studies to evaluate changes in endothelial function are ongoing.
levels decreased 16.3 mg/dL vs. an increase of 3.3 mg/dL (p < 0.001 for both comparisons). Median fasting insulin levels decreased with pioglitazone and increased with glimepiride (p < 0.001). Repeat intravascular ultrasonography examination was performed in 360 patients at study completion. The main outcome measure was a change in percent atheroma volume (PAV) from baseline to study completion. Least squares mean PAV increased 0.73% with glimepiride and decreased 0.16% with pioglitazone (p = 0.002).

Similar comprehensive data were collected for torcetrapib, an inhibitor of cholesteryl ester transfer protein (CETP) that elevates HDL-C levels\textsuperscript{115,116}. Based on pre-clinical data, a beneficial effect on plaque regression was postulated. However, the clinical development of torcetrapib was halted, after the independent Data and Safety Monitoring Board of the ILLUMINATE trial recommended terminating the study because of a statistically significant imbalance in all-cause mortality between patients receiving torcetrapib/atorvastatin and those receiving atorvastatin alone\textsuperscript{117,118}.

The ILLUMINATE trial investigated whether torcetrapib might reduce major cardiovascular events\textsuperscript{119,120}. A total of 15,067 patients at high cardiovascular risk were randomized to torcetrapib plus atorvastatin or atorvastatin alone. The primary outcome was the time to the first major cardiovascular event, which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina. At 12 months, there was an increase of 72.1% in high-density lipoprotein cholesterol and a decrease of 24.9% in low-density lipoprotein cholesterol in patients who received torcetrapib, as compared with baseline (p<0.001 for both comparisons), in addition to an increase of 5.4 mm Hg in systolic blood pressure, a decrease in serum potassium, and increases in serum sodium, bicarbonate, and aldosterone (p<0.001 for all comparisons). There was also an increased risk of cardiovascular events (hazard ratio, 1.25; p=0.001) and death from any cause (hazard ratio, 1.38; p=0.006). Post hoc analyses showed an increased risk of death in patients treated with torcetrapib whose reduction in potassium or increase in bicarbonate was greater than the median change.

Two randomized, CIMT trials (RADIANCE 1 and 2) comparing the effects of torcetrapib/atorvastatin vs. atorvastatin monotherapy were completed before clinical development of torcetrapib was halted\textsuperscript{119,120}. The results from RADIANCE 1, in which 850 patients with heterozygous familial hypercholesterolemia were randomized, indicated that treatment with torcetrapib/atorvastatin did not result in a reduction of progression of atherosclerosis\textsuperscript{119}. Similarly, the results from RADIANCE 2, in which 752 patients with mixed dyslipidemia were randomized, failed to demonstrate a beneficial effect of torcetrapib treatment on atherosclerosis assessed by CIMT despite an increase in HDL-C by 63.4%, and a decrease in LDL-C by 17.7%, relative to atorvastatin treatment alone\textsuperscript{120}.

Similarly, the ILLUSTRATE trial, which used IVUS endpoints to compare the effects of torcetrapib/atorvastatin vs. atorvastatin alone, found no beneficial effect of torcetrapib treatment on progression of atherosclerosis, despite a significant increase in HDL levels in the torcetrapib/atorvastatin treatment group relative to the atorvastatin alone group\textsuperscript{121}.
Correlation between lumen and plaque burden

As described above, the rationale for plaque imaging has been the limitations of angiography. However, the above-described results demonstrate that both change in lumen and plaque are valid markers in serial progression/regression trials. The relationship between changes in plaque and lumen during progression and regression is poorly understood. A recent study investigated the relationship between changes in lumen and plaque volume from baseline to follow-up (9.13 vs. 0.20 mm³, p=0.028). Importantly, when QCA results were analyzed as a dichotomous variable, patients with evidence of angiographic progression had both larger plaque volumes on the initial IVUS examination and a significant increase in plaque volume from baseline to follow-up (9.13 vs. 0.20 mm³, p=0.028).

Interestingly, in this comparison of QCA and IVUS, the correlations with QCA were better for IVUS-determined percent atheroma volume than for plaque volume. This is probably because both percent atheroma volume on IVUS and QCA parameters take into account changes in plaque burden as well as vascular remodeling. Serial IVUS studies confirmed that remodeling is an important process during disease progression/regression. These studies demonstrate that plaque-stabilizing therapy is associated with constrictive remodeling.

A similar analysis was performed in the ASTEROID trial, which assessed the effects of 2 years of therapy with 40 mg/day rosuvastatin on coronary atherosclerosis measured with both IVUS and QCA. Rosuvastatin reduced low-density lipoprotein cholesterol by 53.3% to 61.1 ± 20.3 mg/dL and increased high-density lipoprotein cholesterol by 13.8% to 48.3 ± 12.4 mg/dL. Examining a major coronary artery that was angiographically normal or had <50% stenosis at baseline, IVUS assessment of change in percent atheroma volume, change in atheroma volume in the 10-mm subsegment with the greatest disease severity at baseline, and change in normalized total atheroma volume for the entire artery showed regression. The effects of rosuvastatin on discrete coronary stenoses by QCA were a secondary endpoint of the study. Blinded quantitative coronary angiography analyses of percent diameter stenosis and minimum lumen diameter were performed for up to 10 segments of coronary arteries and major branches with >25% diameter stenosis at baseline. For each patient, the mean of all matched lesions at baseline and study end was calculated. There were 292 patients with 613 matched stenoses. Mean±SD percent diameter stenosis decreased from 37.3±8.4% to 36.0±10.1%. Minimum lumen diameter increased from 1.65±0.36 mm to 1.68±0.38 mm.

The angiographic changes were in the same direction as the IVUS findings of a decrease in plaque burden. The results demonstrate concordant improvements in angiographic measurements of lumen dimension and IVUS measurements of atheroma volume consistent with regression of atherosclerosis with intensive statin therapy.

In contrast, the CAMELOT trial found no correlation between IVUS and QCA parameters. The authors examined the relationship between quantitative coronary angiography parameters, baseline characteristics, and clinical events in a large trial of CAD regression with antihypertensive agents. Patients were randomized to amlopine, enalapril, or placebo and followed for 24 months for major ischemic events. Among 431 patients participating in the angiographic and intravascular ultrasound substudy NORMALISE, 298 (99 receiving amlopine, 96 enalapril, and 103 placebo) had complete angiographic and intravascular ultrasound data. The patients did not differ significantly with respect to baseline characteristics (except for diabetes) or extent of CAD. After 24 months, the change in minimal lumen diameter (MLD) was -0.02 +/- 0.13 for amlopine, -0.03 +/- 0.12 for enalapril, and -0.03 +/- 0.17 mm for placebo (p = 0.40). Major ischemic events occurred in 20.2%, 24%, and 25.2%, respectively (p = 0.68). There was no significant correlation between change in MLD and age, sex, statin therapy, or systolic blood pressure at baseline. The changes in MLD did not differ in patients with and without cardiovascular events, regardless of treatment assignment (p = 0.54). Only the extent of CAD was independently predictive of ischemic events.

Conclusion

The significant global burden of CAD requires development of more effective pharmacological therapies. New compounds need to be tested in carefully designed development programs. Surrogate endpoints can evaluate efficacy ahead of the availability of clinical endpoint data. Atherosclerosis imaging surrogate endpoints allow assessment of progression of pathology at stages of disease prior to those that precipitate clinical symptoms and events and therefore provide a window into the disease process.

However, recent data using established surrogate endpoint are reason for caution. Results from the ENHANCE trial, demonstrated that ezetimibe added to statin therapy failed to have an effect on the rate of atherosclerotic disease progression, despite significant further reductions in LDL-cholesterol levels. Equally unexpected, in the ACCORD trial, intensive glucose control was associated with increased mortality. These results are at odds with the otherwise close relationship between LDL cholesterol and atherosclerosis and between glucose control and mortality.
Comprehensive drug development programs increasingly evaluate new therapies with more than one surrogate endpoint, in trials which are conducted while clinical endpoint studies are ongoing.

Potential Conflict of Interest
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Study Association
This study is not associated with any graduation program.
Atherosclerosis imaging in progression/regression trials

References


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