Review Article

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

Paul Schoenhagen and E. Murat Tuzcu
Cleveland Clinic, Imaging Institute and Heart & Vascular Institute, Cleveland - USA

Abbreviations

CAD - coronary artery disease
CABG - coronary artery bypass surgery
CIMT - carotid intima-media thickness
CMR - cardiovascular magnetic resonance
CT - Computed tomography
CTA - computed tomographic angiography
EBCT - electron-beam computed tomography
EEM - external elastic membrane
FMD - flow-mediated dilatation
IMT - intima-media thickness
IVUS - intravascular ultrasound
MDCT - multi-detector computed tomography
MI - myocardial infarction
MRI - magnetic resonance imaging
PCI - percutaneous coronary intervention
QCA - quantitative coronary angiography
RFA - radio frequency analysis

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.

Key Words

Atherosclerosis; diagnostic imaging; coronary diseases; disease progression.

Mailing Address: Paul Schoenhagen •
Cleveland Clinic, Imaging Institute and Heart & Vascular Institute, 9500 Euclid Avenue, Desk HB-6, 44195, Cleveland - USA
E-mail: schoenp1@ccf.org
Manuscript received July 1, 2008; received manuscript revised July 3, 2008; accepted July 3, 2008.

Introduction

Atherosclerotic cardiovascular disease remains a major global cause of morbidity and mortality[1]. Subclinical atherosclerosis develops and progresses slowly over many decades, before suddenly causing clinical manifestations[2]. 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[3,4], 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 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[5,6]. 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[7,8] (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.

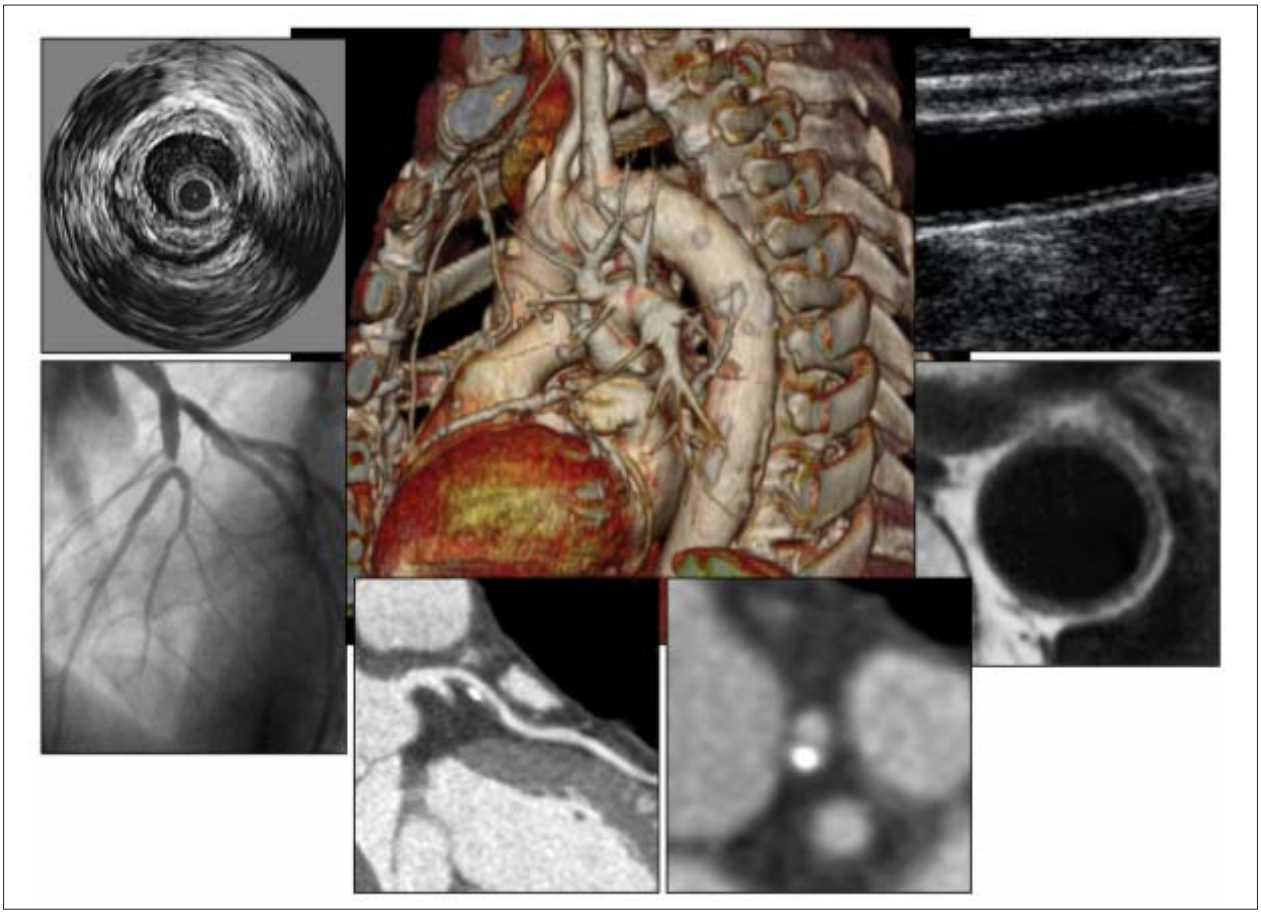

Figure 1 - Atherosclerosis is a systemic disease, which affects the entire arterial tree; In the center of the figure a volume-rendered image of the chest is shown; The ascending and descending thoracic aorta, aortic arch with the arch branch vessels, and the coronary arteries are seen; Starting from the left upper panel and continuing counter-clock wise, an IVUS image of a coronary artery, a coronary angiogram, a coronary CT angiogram and its cross-section, a cross-sectional MRI image of the descending aorta, and a CIMT image of the carotid artery are shown.

Table 1 - **Overview of current atherosclerosis imaging modalities**

	Lumen	Plaque Burden	Plaque Composition	Established Endpoint	Comment
Angiography	SM	-	-	change in lumen	
CT calcium scoring	-	S	-/+	-	
CIMT	+	SM	+	change in wall thickness	carotid
IVUS	+	SM	+/-	change in plaque burden	
IVUS/RFA	+/-	+	+	-	
CT	+	+	+	-	
MRI	+	S	+	-	carotid aorta
Vascular reactivity	-	-	-	-	Vascular function

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[9,10]. Results from serial angiographic multicenter trials during lipid-modifying treatment demonstrate that change in

luminal stenosis is a valid surrogate marker for cardiovascular risk[11-15]. This experience is summarized in a meta-analysis of QCA studies describing data of a total of 3674 patients with coronary disease who were treated with different drug classes[16,17]. A small reduction in mean proximal diameter stenosis progression corresponded to a significant reduction in event rate in these trials.

While these data with coronary angiography demonstrate an association between atherosclerotic progression, luminal dimensions, and risk of cardiovascular events, the evolving understanding of atherogenesis has demonstrated fundamental limitations of "luminography"[2,18]. Early subclinical stages of coronary plaques develop over decades within the arterial wall, which initially expands outwards (positive remodelling)[19,20]. This process allows accommodating the growing plaque with preservation of the lumen. Consequently, early-stages of coronary atherosclerosis are angiographically undetectable, or underestimated when compared to postmortem pathological studies[21]. While positively remodeled lesions may have minimal stenotic effect, these plaques have been shown to be significantly associated with acute coronary syndromes[22,23]. Lumen imaging is also limited when long segments are diffusely affected by atherosclerotic changes, because the detection of angiographic stenosis relies on a comparison to a normal reference site[24].

Atherosclerosis imaging and plaque burden

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[25-27]. Most data have been collected with EBCT, but MDCT has recently emerged as an alternative[28].

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[29]. 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[30-33]. 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[32]. 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[33]. 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[34]. 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[35-38].

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[36]. 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[37]. 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 mm^3 (range, 15 to 1849) at baseline, 201 mm^3 (19 to 2486) after 14 months without treatment, and 203 mm^3 (15 to 2569) after 12 months of cerivastatin treatment. The median annual absolute increase in coronary calcium was 25 mm^3 during the untreated versus 11 mm^3 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=0.0001).

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[38]. 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[39,40].

Various studies have shown a strong correlation between IMT and cardiovascular risk factors[41-43]. Over the past decade, several large observational studies have demonstrated that baseline CIMT is an independent predictor of future clinical cardiovascular events[44-50]. This has been shown in symptomatic and asymptomatic patients across all age groups, including healthy young adults[44,45]. In the ARIC study, which examined about12,800 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[46]. 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[47]. The Rotterdam study followed about 8000 individuals at least 55 years of age after a baseline carotid ultrasound[48]. After an average follow-up of 2.7 years, baseline CIMT was compared in those with and without cardiovascular events during follow-up. 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[49].

Serial intervention trials have demonstrated the value of CIMT as an endpoint in serial pharmacological intervention trials[50-59]. Placebo-controlled clinical trials showed that statin therapy slowed or reversed progression of CIMT and reduced the incidence of cardiovascular events. Both the ASAP[51] and ARBITER-I trial[52] 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[52]. The METEOR study assessed the impact of rosuvastatin in 984 asymptomatic subjects at low risk of CAD[53]. 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[54]. 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[55], 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 treatment with simvastatin plus ezetimibe vs. simvastatin alone in familial hypercholesterolemia patients[56].

Based on these results, CIMT is a valid surrogate marker for cardiovascular disease. The advantage of CIMT is its non-invasiveness, which allows data collection in lower risk populations. However, the data are collected in the carotid and not directly in the coronary arteries.

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[57-60], 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)[61,62], by planimetry of the blood-intima and media-adventitia border. Atheroma volume is calculated as the sum of the differences in cross-sectional

area for all evaluable cross-sectional images along coronary segments.

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[63]. IVUS studies have shown that the rate of plaque growth in the left main coronary artery correlates with traditional risk factors[64,65]. 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[66]. The mean (±SD) differences were negligible for both EEM (-0.16 ± 0.68 mm^2) and lumen areas (-0.02 ± 0.75 mm^2). 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 mm^2). 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[66-72]. In the REVERSAL trial, 654 patients were imaged at baseline and after 18 months of therapy[66]. 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[69]. 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[70]. In a small study examining the effect of HDL[71], 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-1 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[72].

Other recently completed and ongoing trials employing IVUS endpoints to evaluate novel CVD therapies include the use of rimonabant in patients with CHD and abdominal obesity[73] 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[66,74]. In the CAMELOT study, 1991 normotensive patients with QCA-documented coronary atherosclerosis were randomized to 24 months of therapy with amlodipine, enalapril or placebo[75]. 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[76-79]. 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[80]. The prevalence of different disease patterns has recently been described[81]. 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

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[82,83]. 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[82]. 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[83]. 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[84]. 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%[85]. A number of serial studies in humans have assessed CMR in the longitudinal measurement of aortic and carotid atheroma[86-90].

In a double-blind study, newly diagnosed hypercholesterolemic patients (n = 51) with asymptomatic aortic and/or carotid atherosclerotic plaques were randomized to 20 mg/day (n = 29) or 80 mg/day (n = 22) simvastatin[88]. Mean follow-up was 18.1 months. A total of 93 aortic and 57 carotid plaques were detected and sequentially followed up by MRI every six months after lipid-lowering initiation. The primary MRI end point was change in vessel wall area (VWA). Total cholesterol decreased by 26% versus 33% and LDL-C by 36% versus 46% in the conventional (20 mg) versus aggressive (80 mg) simvastatin groups, respectively. Although the simvastatin 80mg group had significantly higher baseline TC and LDL-C levels, both groups reached similar absolute values after treatment. A significant reduction in VWA could already be observed at 12 months. No difference on vascular effects was detected between the randomized doses. Post-hoc analysis showed that patients reaching mean on-treatment LDL-C < or = 100 mg/dL had larger decreases in plaque size.

Atherosclerotic plaque in thoracic aorta were measured by combined surface/transesophageal MRI in 27 patients (treated with simvastatin 20 to 80 mg daily) before and after 6 months of therapy[89]. Plaque volume and luminal dimensions were measured from 6 cross sections used to construct a 2.4-cm 3D volume of the aorta that included plaque and lumen. Plaque volume was reduced from 3.3+/-0.1.4 to 2.9+/-1.4 cm^3 at 6 months ($p<0.02$), whereas luminal volume increase was less accentuated (from 12.0+/-3.9 to 12.2+/-3.7 cm^3, $p<0.06$). LDL cholesterol decreased by 23% (from 125+/-32 to 97+/-27 mg/dL, $p<0.05$) in 6 months. Plaque regression was significantly related to LDL cholesterol reduction ($p<0.02$ and $p<0.005$, respectively), and luminal volume increase was inversely related to LDL cholesterol reduction ($p<0.04$). Plaque volume measurement was highly reproducible (intraclass correlation R=0.98 and variability=4.8%). Intraobserver (0.91) and interobserver (0.81) concordances were documented for plaque volume assessment.

Another study investigated the effects of 20-mg versus 5-mg atorvastatin on thoracic and abdominal aortic plaques in 40 hypercholesterolemic patients[90]. 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 -28%, 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%). 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 anatomic dimensions. 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 characterization[91,92]. Initial description of plaque morphology focused on culprit lesions in patients presenting with acute or stable coronary syndromes[93,94]. Based on these studies, a prospective intravascular ultrasound study hypothesized that certain features would be associated with the development of acute coronary syndromes during follow-up[95]. 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 echogenicity[67].

However, standard grayscale IVUS imaging is limited to the analysis of the 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 analysis[96,97]. IVUS-derived RFA (virtual histology, VH-IVUS) displays the reconstructed data as a color coded tissue map of plaque composition based on validation to histology[98-100]. VH-IVUS classifies plaque components into four basic tissue types: fibrous (dark-green), fibro-fatty (light-green), necrotic core (red), and dense calcium (white)[101]. 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 calcium[101].

Based on further analysis of this compositional data, classification of plaque types is performed in analogy to histopathological classification. These plaque types include pathologic intimal thickening, fibroatheroma, and fibrotic-calcific plaque[96].

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 remodeling[102,103]. 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 TCFA[104].

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 composition[78,79,105]. 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 formation[106]. Major cardiovascular risk factors, including hypertension, smoking, hypercholesterolemia and diabetes mellitus have been shown to contribute to the onset of endothelial dysfunction[107,108]. More recently, endothelial dysfunction has also been shown to have predictive value for cardiovascular events[109]. 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 application[110,111]. 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 FMD[110]. 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.

Correlation between modalities and approaches

The above described atherosclerotic imaging 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 each other is poorly understood.

Correlation between IVUS and CIMT

The two vascular ultrasound imaging techniques - carotid CIMT and IVUS of the coronary arteries - are increasingly being used as integral components of larger trial programs to assess novel cardiovascular therapies in surrogate endpoint trials. Recent examples are the experience with pioglitazone and CETP-inhibitors.

Pioglitazone is an agonist of peroxisome proliferator-activated receptor gamma (PPAR gamma). In a prospective, randomized controlled trial, 5238 patients with type 2 diabetes and evidence of macrovascular disease were assigned to oral pioglitazone titrated from 15 mg to 45 mg (n=2605) or matching placebo (n=2633)[112]. The primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, and endovascular or surgical intervention in the coronary or leg arteries. The average time of observation was 34.5 months. A total of 514 patients in the pioglitazone group and 572 patients in the placebo group had at least one event in the primary composite endpoint (p=0.095). The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. A total of 301 patients in the pioglitazone group and 358 in the placebo group reached this endpoint (p=0.027).

An associated imaging study evaluated the effect of pioglitazone vs. glimepiride on changes in CIMT[113]. In that study, 462 adults with type-2 DM (mean duration, 7.7 years; mean HbA1c value, 7.4%) were randomized to pioglitazone hydrochloride (15-45 mg/day) or glimepiride (1-4 mg/day). The treatment period was 72 weeks. The main outcome measure was an absolute change from baseline to final visit in mean CIMT. Mean change in CIMT was less with pioglitazone vs. glimepiride. At week 72, the primary endpoint of progression of mean CIMT was less with pioglitazone vs. glimepiride (-0.001 mm vs. +0.012 mm, respectively; p = 0.02). Pioglitazone also slowed progression of maximum CIMT compared with glimepiride (0.002 mm vs. 0.026 mm, respectively, at 72 weeks; p = 0.008). The beneficial effect of pioglitazone on mean CIMT was similar across prespecified subgroups.

A randomized, multicenter IVUS trial examined 543 patients with coronary disease and type-2 diabetes[114]. Patients were randomized to receive pioglitazone 15 to 45 mg, or glimepiride 1 to 4 mg for 18 months with titration to maximum dosage, if tolerated. Mean (SD) baseline HbA(1c) levels were 7.4% (1.0%) in both groups and declined during treatment an average 0.55% with pioglitazone and 0.36% with glimepiride (between-group p = 0.03). In the pioglitazone group, compared with glimepiride, high-density lipoprotein levels increased 5.7 mg/dL vs. 0.9 mg/dL, and median triglyceride 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[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[117,118].

The ILLUMINATE trial investigated whether torcetrapib might reduce major cardiovascular events[118]. 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, 1.58; 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[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[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[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[121].

Correlation between lumen and plaque burden

As described above, the rational 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[122,123] investigated the relationships between QCA and IVUS at single time points and also for the changes over time. For matched segments at baseline, statistically significant correlations were observed between a composite QCA coronary artery score and IVUS-derived lumen volume ($r=0.65$, $p<0.0001$) and also for total vessel volume ($r=0.55$, $p<0.0001$). Similar relationships were found between the QCA cumulative coronary stenosis score and percent atheroma volume on IVUS ($r=0.32$, $p<0.0001$). For global (all segments) QCA-derived and single-vessel IVUS-derived data, a similar pattern of correlations was observed. Between baseline and follow-up, there were statistically significant but weak correlations between the changes over time in lumen dimensions on QCA and IVUS ($P=0.005$) and between the change in cumulative coronary stenosis score on QCA and percent atheroma volume on IVUS ($r=0.14$, $p=0.01$). 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 mm^3, $p=0.028$).

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[124].

A similar analysis was performed in the ASTEROID trial[125], 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[126]. 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 amlodipine, 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 amlodipine, 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 amlodipine, -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 change 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[127-129].

However, recent data using established surrogate endpoint are reason for caution[56,130]. 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[56]. Equally unexpected, in the ACCORD trial, intensive glucose control was associated with increased mortality[130]. These results are at odds with the otherwise close relationship between LDL cholesterol and atherosclerosis and between glucose control and mortality, respectively.

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

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any graduation program.

References

1. World Health Organization. Cardiovascular disease: prevention and control. http://www.who.int/dietphysicalactivity/publications/facts/cvd/en.
2. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005; 111: 3481-8.
3. Wang L, Fan C, Topol SE, Topol EJ, Wang Q. Mutation of MEF2A in an inherited disorder with features of coronary artery disease. Science. 2003; 302: 1578-81.
4. Chen M, Capps C, Willerson JT, Zoldhelyi P. E2F-1 regulates nuclear factor-kappaB activity and cell adhesion: potential antiinflammatory activity of the transcription factor E2F-1. Circulation. 2002; 106: 2707-13.
5. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med. 1989; 8: 431-40.
6. Wittes J, Lakatos E, Probstfield J. Surrogate endpoints in clinical trials: cardiovascular diseases. Stat Med. 1989; 8: 415-25.
7. Sankatsing RR, de Groot E, Jukema JW, de Feyter PJ, Pennell DJ, Schoenhagen P, et al. Surrogate markers for atherosclerotic disease. Curr Opin Lipidol. 2005; 16: 434-41.
8. Waters D, Craven TE, Lesperance J. Prognostic significance of progression of coronary atherosclerosis. Circulation. 1993; 87: 1067-75.
9. Mack WJ, Xiang M, Selzer RH, Hodis HN. Serial quantitative coronary angiography and coronary events. Am Heart J. 2000; 139: 993-9.
10. Azen SP, Mack WJ, Cashin-Hemphill L, LaBree L, Shircore AM, Selzer RH, et al. Progression of coronary artery disease predicts clinical coronary events: long-term follow-up from the Cholesterol Lowering Atherosclerosis Study. Circulation. 1996; 93: 34-41.
11. Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). Circulation. 1995; 91: 2528-40.
12. Waters D, Higginson L, Gladstone P, Kimball B, Le May M, Boccuzzi SJ, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography: the Canadian Coronary Atherosclerosis Intervention Trial. Circulation. 1994; 89: 959-68.
13. MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). Lancet. 1994; 344: 633-8.
14. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): reduction in atherosclerosis progression and clinical events. J Am Coll Cardiol. 1995; 26: 1133-9.
15. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin J-T, Kaplan C, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990; 323: 1289-98.
16. Brown BG, Stukovsky KH, Zhao XQ. Simultaneous low-density lipoprotein-C lowering and high-density lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomized lipid trials. Curr Opin Lipidol. 2006; 17: 631-6.
17. Waters D, Lesperance J. Regression of coronary atherosclerosis: an achievable goal? Review of results from recent clinical trials. Am J Med. 1991; 91: S10–S17.
18. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation. 1995; 92: 2333-42.
19. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987; 316: 1371-5.
20. Schoenhagen P, Ziada KM, Vince DG, Nissen SE, Tuzcu EM. Arterial remodeling and coronary artery disease: the concept of "dilated" versus "obstructive" coronary atherosclerosis. J Am Coll Cardiol. 2001; 38: 297-306.
21. Marcus ML, Armstrong ML, Heistad DD, Eastham CL, Mark AL. Comparison of three methods of evaluating coronary obstructive lesions: postmortem arteriography, pathologic examination and measurement of regional myocardium perfusion during maximal vasodilation. Am J Cardiol. 1982; 49: 1699–1706.
22. Pasterkamp G, Schoneveld AH, van der Wal AC, Haudenschild CC, Clarijs RJ, Becker AE, et al. Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox. J Am Coll Cardiol. 1998; 32: 655-62.
23. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. Circulation. 2000; 101: 598-603.
24. Mintz GS, Painter JA, Pichard AD, Kent KM, Satler LF, Popma JJ, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. J Am Coll Cardiol. 1995; 25: 1479-85.
25. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15: 827-32.
26. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with and electron-beam CT volumetric method. Radiology. 1998; 208: 807-14.
27. Detrano R, Tang W, Kang X, Mahaisavariya P, McCrae M, Garner D, et al. Accurate coronary calcium phosphate mass measurements from electron beam computed tomograms. Am J Card Imaging. 1995; 3: 167-73.
28. Becker CR, Kleffel T, Crispin A, Knez A, Young J, Schoepf UJ, et al. Coronary artery calcium measurement: agreement of multirow detector and electron beam CT. Am J Roentgenol. 2001; 176: 1295-8.
29. Hoff JA, Daviglus ML, Chomka EV, Krainik AJ, Sevrukow A, Kondos GT. Conventional coronary artery disease risk factors and coronary artery calcium detected by electron beam tomography in 30.908 healthy individuals. Ann Epidemiol. 2003; 13: 163-9.
30. Secci A, Wong N, Tang W, Wang S, Doherty T, Detrano R. Electron beam computed tomographic coronary calcium as a predictor of coronary events. Circulation. 1997; 96: 1122-9.
31. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. Arch Intern Med. 2004; 164: 1285–92.
32. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology. 2003; 228: 826-33.
33. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA. 2004; 291: 210-5.
34. Schmermund A, Erbel R. Unstable coronary plaque and its relation to coronary calcium. Circulation. 2001; 104: 1682-7.
35. Budoff MJ, Raggi P. Coronary artery disease progression assessed by electron-beam computed tomography. Am J Cardiol. 2001; 88: 46E-50E.
36. Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ. Effect of HMG-CoA reductase inhibitors on coronary artery disease by electron-beam computed tomography. N Engl J Med. 1998; 339: 1972-8.
37. Achenbach S, Ropers D, Pohle K, Leber A, Thilo C, Knez A, et al. Influence of lipid-lowering therapy on the progression of coronary artery calcification: a prospective evaluation. Circulation. 2002; 106: 1077-82.
38. Schmermund A, Achenbach S, Budde T, Buziashvili Y, Förster A, Friedrich G, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation. 2006; 113: 427-37.
39. Bots ML, Grobbee DE. Intima media thickness as a surrogate marker for generalised atherosclerosis. Cardiovasc Drugs Ther. 2002; 16: 341-51.
40. Touboul PJ, Vicaut E, Labreuche J, Belliard JP, Cohen S, Kownator S, et al. Design, baseline characteristics and carotid intima-media thickness reproducibility in the PARC study. Cerebrovasc Dis. 2005; 19:57-63.

41. Wiegman A, de Groot E, Hutten BA, Rodenburg J, Gort J, Bakker HD, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. Lancet. 2004; 363: 369-70.

42. van Dam MJ, de Groot E, Clee SM, Hovingh GK, Roelants R, Brooks-Wilson A, et al. Association between increased arterial-wall thickness and impairment in ABCA1-driven cholesterol efflux: an observational study. Lancet. 2002; 359: 37-42.

43. Hovingh GK, Brownlie A, Bisoendial RJ, Dube MP, Levels JH, Petersen W, et al. A novel apoA-I mutation (L178P) leads to endothelial dysfunction, increased arterial wall thickness, and premature coronary artery disease. J Am Coll Cardiol. 2004; 44: 1429-35.

44. Oren A, Vos LE, Uiterwaal CS, Grobbee DE, Bots ML. Cardiovascular risk factors and increased carotid intima-media thickness in healthy young adults: the Atherosclerosis Risk in Young Adults (ARYA) Study. Arch Intern Med. 2003; 163: 1787-92.

45. Krishnan P, Balamurugan A, Urbina E, Srinivasan SR, Bond G, Tang R, et al. Cardiovascular risk profile of asymptomatic healthy young adults with increased carotid artery intima-media thickness: the Bogalusa Heart Study. J La State Med Soc. 2003; 155: 165-9.

46. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987- 1993. Am J Epidemiol. 1997; 146: 483-94.

47. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb. 1991; 11: 1245-9.

48. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation. 1997; 96: 1432-7.

49. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999; 340: 14-22.

50. de Groot E, Jukema JW, Montauban van Swijndregt AD, Zwinderman AH, Ackerstaff RG, van der Steen AF, et al. B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). J Am Coll Cardiol. 1998; 31: 1561-7.

51. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP): a prospective, randomised, double-blind trial. Lancet. 2001; 357: 577-81.

52. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. Circulation. 2002; 106: 2055-60.

53. Crouse JR, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007; 297: 1344-53.

54. Espeland MA, O'Leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. Curr Control Trials Cardiovasc Med. 2005; 6: 3.

55. Terpstra WF, May JF, Smit AJ, de Graeff PA, Crijns HJ. Effects of nifedipine on carotid and femoral arterial wall thickness in previously untreated hypertensive patients. Blood Press Suppl. 2003; 1: 22-9.

56. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008; 358: 1431-43.

57. Batkoff BW, Linker DT. Safety of intracoronary ultrasound: data from a Multicenter European Registry. Catheter Cardiovasc Diagn. 1996; 38: 238-41.

58. Hausmann D, Erbel R, Alibelli-Chemarin MJ, Boksch W, Caracciolo E, Cohn JM, et al. The safety of intracoronary ultrasound: a multicenter survey of 2207 examinations. Circulation. 1995; 91: 623-30.

59. Guedes A, Keller PF, L'Allier PL, Lesperance J, Gregoire J, Tardif JC. Long-term safety of intravascular ultrasound in nontransplant, nonintervened, atherosclerotic coronary arteries. J Am Coll Cardiol. 2005; 45: 559-64.

60. Ramasubbu K, Schoenhagen P, Balghith MA, Brechtken J, Ziada KM, Kapadia SR, et al. Repeated intravascular ultrasound imaging in cardiac transplant recipients does not accelerate transplant coronary artery disease. J Am Coll Cardiol. 2003; 41: 1739-43.

61. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology clinical expert consensus document on standards for aCGQuisition, measurement and reporting of intravascular ultrasound studies (IVUS). J Am Coll Cardiol. 2001; 37: 1478-92.

62. Di Mario C, Görge G, Peters R, Kearney P, Pinto F, Hausmann D, et al. Clinical application and image interpretation in intracoronary ultrasound. Study Group on Intracoronary Imaging of the Working Group of Coronary Circulation and of the Subgroup on Intravascular Ultrasound of the Working Group of Echocardiography of the European Society of Cardiology. Eur Heart J. 1998; 19: 207-29.

63. Ricciardi MJ, Meyers S, Choi K, Pang JL, Goodreau L, Davidson CJ. Angiographically silent left main disease detected by intravascular ultrasound: a marker for future adverse cardiac events. Am Heart J. 2003; 146: 507-12.

64. von Birgelen C, Hartmann M, Mintz GS, van Houwelingen KG, Deppermann N, Schmermund A, et al. Relationship between cardiovascular risk as predicted by established risk scores versus plaque progression as measured by serial intravascular ultrasound in left main coronary arteries. Circulation. 2004; 110: 1579-85.

65. von Birgelen C, Hartmann M, Mintz GS, Baumgart D, Schmermund A, Erbel R. Relation between progression and regression of atherosclerotic left main coronary artery disease and serum cholesterol levels as assessed with serial long-term (&12 months) follow-up intravascular ultrasound. Circulation. 2003; 108: 2757-62.

66. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004; 291: 1071-80.

67. Schartl M, Bocksch W, Koschyk DH, Voelker W, Karsch KR, Kreuzer J, et al. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. Circulation. 2001; 104: 387-92.

68. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH study. Circulation. 2004; 110: 1061-8.

69. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006; 295: 1556-65.

70. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA. 2007; 297: 499-508.

71. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA. 2003; 290: 2292–300.

72. Tardif JC, Grégoire J, L'Allier PL, Ibrahim R, Lespérance J, Heinonen TM, et al. Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) Investigators. JAMA. 2007; 297: 1675-82.

73. Nissen SE, Nicholls SJ, Wolski K, Rodés-Cabau J, Cannon CP, Deanfield JE, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. JAMA. 2008; 299: 1547-60.

74. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350: 1495-504.

75. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, et al. Effect

of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004; 292: 2217-25.

76. Schoenhagen P, Tuzcu EM, Stillman AE, Moliterno DJ, Halliburton SS, Kuzmiak SA, et al. Non-invasive assessment of plaque morphology and remodeling in mildly stenotic coronary segments: comparison of 16-slice computed tomography and intravascular ultrasound. Coron Artery Dis. 2003; 14: 459-62.

77. Achenbach S, Ropers D, Hoffmann U, MacNeill B, Baum U, Pohle K, et al. Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. J Am Coll Cardiol. 2004; 43: 842-7.

78. Leber AW, Knez A, Becker A, Becker C, von Ziegler F, Nikolaou K, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. J Am Coll Cardiol. 2004; 43: 1241-7.

79. Achenbach S, Moselewski F, Ropers D, Ferencik M, Hoffmann U, MacNeill B, et al. Improved detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. Circulation. 2004; 109: 14-7.

80. Mollet NR, Cademartiri F, Nieman K, Saia F, Lemos PA, McFadden EP, et al. Non-invasive assessment of coronary plaque burden using multislice computed tomography. Am J Cardiol. 2005; 95: 1165-9.

81. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schömig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. J Am Coll Cardiol. 2006; 48: 312-8.

82. Pundziute G, Schuijf JD, Jukema JW, Boersma E, de Roos A, van der Wall EE, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J Am Coll Cardiol. 2007; 49: 62-70.

83. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol. 2007; 50: 1161-70.

84. Crowe LA, Gatehouse P, Yang GZ, Mohiaddin RH, Varghese A, Charrier C, et al. Volume-selective 3D turbo spin echo imaging for vascular wall imaging and distensibility measurement. J Magn Reson Imaging. 2003; 17: 572-80.

85. Varghese A, Crowe LA, Mohiaddin RH, Gatehouse PD, Yang GZ, Nott DM, et al. Interstudy reproducibility of three dimensional volume-selective fast spin echomagnetic resonance for quantifying carotid artery wall volume. J Magn Reson Imaging. 2005; 21: 187-91.

86. Mohiaddin RH, Burman ED, Prasad SK, Varghese A, Tan RS, Collins SA, et al. Glagov remodeling of the atherosclerotic aorta demonstrated by cardiovascular magnetic resonance: the CORDA asymptomatic subject plaque assessment research (CASPAR) project. J Cardiovasc Magn Reson. 2004; 6: 517-25.

87. Corti R, Fuster V, Fayad ZA, Worthley SG, Helft G, Smith D, et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by highresolution noninvasive magnetic resonance imaging. Circulation. 2002; 106: 2884-7.

88. Corti R, Fuster V, Fayad ZA, Worthley SG, Helft G, Chaplin WF, et al. Effects of aggressive versus conventional lipid-lowering therapy by simvastatin on human atherosclerotic lesions: a prospective, randomized, double-blind trial with high-resolution magnetic resonance imaging. J Am Coll Cardiol. 2005; 46: 106-12.

89. Lima JA, Desai MY, Steen H, Warren WP, Gautam S, Lai S. Statin-induced cholesterol lowering and plaque regression after 6 months of magnetic resonance imaging-monitored therapy. Circulation. 2004; 110: 2336-41.

90. Yonemura A, Momiyama Y, Fayad ZA, Ayaori M, Ohmori R, Higashi K, et al. Effect of lipid-lowering therapy with atorvastatin on atherscleroticaortic plaques detected by noninvasive magnetic resonance imaging. J Am Coll Cardiol. 2005; 45: 733-42.

91. Nissen SE, Gurley JC, Grines CL, Booth DC, McClure R, Berk M, et al. Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. Circulation. 1991; 84: 1087-99.

92. Gussenhoven EJ, Essed CE, Lancée CT, Mastik F, Frietman P, van Egmond FC, et al. Arterial wall characteristics determined by intravascular ultrasound imaging: an in vitro study. J Am Coll Cardiol. 1989; 14: 947-52.

93. Hodgson JM, Reddy KG, Suneja R, Nair RN, Lesnefsky EJ, Sheehan HM. Intracoronary ultrasound imaging: correlation of plaque morphology with angiography, clinical syndrome and procedural results in patients undergoing coronary angioplasty. J Am Coll Cardiol. 1993; 21: 35-44.

94. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable and unstable coronary syndromes. Circulation. 2000; 101: 598-603.

95. Yamagishi M, Terashima M, Awano K, Kijima M, Nakatani S, Daikoku S, et al. Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before and acute coronary syndrome. J Am Coll Cardiol. 2000; 35: 106-11.

96. König A, Klauss V. Virtual histology. Heart. 2007; 93: 977-82.

97. de Korte CL, Pasterkamp G, van der Steen AF, Woutman HA, Bom N. Characterization of plaque components with intravascular ultrasound elastography in human femoral and coronary arteries in vitro. Circulation. 2000; 102: 617-23.

98. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation. 2002; 106: 2200-6.

99. Kawasaki M, Takatsu H, Noda T, Ito Y, Kunishima A, Arai M, et al. Noninvasive quantitative tissue characterization and two-dimensional color-coded map of human atherosclerotic lesions using ultrasound integrated backscatter: comparison between histology and integrated backscatter images. J Am Coll Cardiol. 2001; 38: 486-92.

100. Takiuchi S, Rakugi H, Honda K, Masuyama T, Hirata N, Ito H, et al. Quantitative ultrasonic tissue characterization can identify high-risk atherosclerotic alteration in human carotid arteries. Circulation. 2000;102: 766-70.

101. Nair A. Automated coronary plaque characterisation with intravascular ultrasound backscatter: ex vivo validation. Eurointervention. 2007; 3: 113-20.

102. Rodriguez-Granillo GA, García-García HM, Mc Fadden EP, Valgimigli M, Aoki J, de Feyter P, et al. In vivo intravascular ultrasound-derived thin cap fibroatheroma detection using ultrasound radiofrequency data analysis. J Am Coll Cardiol. 2005; 46: 2038-42.

103. Rodriguez-Granillo GA, Serruys PW, Garcia-Garcia HM, Aoki J, Valgimigli M, van Mieghem CA, et al. Coronary artery remodelling is related to plaque composition. Heart. 2006; 92: 388-91.

104. Diethrich EB, Margolis PM, Reid DB. Virtual histology intravascular ultrasound assessment of carotid artery disease: the carotid artery plaque virtual histology evaluation (CAPITAL) study. J Endovasc Ther. 2007; 14: 676-86.

105. Yuan C, Mitsumori LM, Beach KW, Maravilla KR. Carotid atherosclerotic plaque: noninvasive MR characterization and identification of vulnerable lesions. Radiology. 2001; 221: 285-99.

106. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992; 340: 1111-5.

107. Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation. 1993; 88: 2149-55.

108. Clarkson P, Celermajer DS, Donald AE, Sampson M, Sorensen KE, Adams M, et al. Impaired vascular reactivity in insulin-dependent diabetes mellitus is related to disease duration and low density lipoprotein cholesterol levels. J Am Coll Cardiol. 1996; 28: 573-9.

109. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation. 2000; 101: 1899-906.

110. Anderson EA, Mark AL. Flow-mediated and reflex changes in large peripheral artery tone in humans. Circulation. 1989; 79: 93-100.

111. Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, et al. Close relation of endothelial function in the human coronary and peripheral circulations. J Am Coll Cardiol. 1995; 26: 1235-41.

112. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005; 366: 1279-89.

113. Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino RB et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA. 2006; 296: 2572-81.

114. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA. 2008; 299: 1561-73.

115. Clark RW, Sutfin TA, Ruggeri RB, Willauer AT, Sugarman ED, Magnus-Aryitey G, et al. Raising high-density lipoprotein in humans through inhibition of cholesteryl ester transfer protein: an initial multidose study of torcetrapib. Arterioscler Thromb Vasc Biol. 2004; 24: 490-7.

116. Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW, et al. Effects of aninhibitor of cholesteryl ester transfer protein on HDL cholesterol. N Engl J Med. 2004; 350: 1505-15.

117. Cholesterol: the good the bad the stopped trials. Lancet. 2006; 368: 2034.

118. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, et al. The ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007; 357: 2109-22.

119. Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N Engl J Med. 2007; 356: 1620-30.

120. Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH, et al. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, doubleblind trial. Lancet. 2007; 370: 153-60.

121. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, et al. Effect of Torcetrapib on the progression of coronary atherosclerosis. N Engl J Med. 2007; 356: 1304-16.

122. Berry C, L'Allier PL, Grégoire J, Lespérance J, Levesque S, Ibrahim R, et al. Comparison of intravascular ultrasound and quantitative coronary angiography for the assessment of coronary artery disease progression. Circulation. 2007; 115: 1851-7.

123. Brown BG. A direct comparison of intravascular ultrasound and quantitative coronary arteriography: implications for measures of atherosclerosis as clinical surrogates. Circulation. 2007; 115: 1824-6.

124. Schoenhagen P, Tuzcu EM, Apperson-Hansen C, Wang C, Wolski K, Lin S, et al. Determinants of arterial wall remodeling during lipid-lowering therapy: serial intravascular ultrasound observations from the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial. Circulation. 2006; 113: 2826-34.

125. Ballantyne CM, Raichlen JS, Nicholls SJ, Erbel R, Tardif JC, Brener SJ, et al. The ASTEROID Investigators. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography. a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. Circulation. 2008; 117: 2458-66.

126. Brener SJ, Ivanc TB, Poliszczuk R, Chen M, Tuzcu EM, Hu T, et al. Antihypertensive therapy and regression of coronary artery disease: insights from the Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) and Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation (NORMALISE) trials. Am Heart J. 2006; 152: 1059-63.

127. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002; 347: 1557-65.

128. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005; 352: 29-38.

129. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. Creactive protein levels and outcomes after statin therapy. N Engl J Med. 2005; 352: 20-8.

130. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358: 2545-59.