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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Intravascular Ultrasound-Derived Measures of Coronary Atherosclerotic Plaque Burden and Clinical Outcome

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Objectives The aim of this study was to investigate the relationship between intravascular ultrasound (IVUS)-derived measures of atherosclerosis and cardiovascular outcomes.

Background IVUS has been used in clinical trials to evaluate the effect of medical therapies on coronary atheroma progression.

Methods Coronary plaque progression was evaluated in 4,137 patients in 6 clinical trials that used serial IVUS. The relationship between baseline and change in percent atheroma volume (PAV) and total atheroma volume with incident major adverse cardiovascular events (MACE) was investigated.

Results PAV increased by 0.3% ($p < 0.001$), and 19.9% of subjects experienced MACE (0.9% death, 1.8% myocardial infarction, 18.9% coronary revascularization). Greater baseline PAVs were observed in patients who experienced myocardial infarctions (42.2 ± 9.6% vs. 38.6 ± 9.1%, $p = 0.001$), coronary revascularization (41.2 ± 9.3% vs. 38.1 ± 9.0%, $p < 0.001$), or MACE (41.3 ± 9.2% vs. 38.0 ± 9.0%, $p < 0.001$). Each standard deviation increase in PAV was associated with a 1.32-fold (95% confidence interval: 1.22 to 1.42; $p < 0.001$) greater likelihood of experiencing a MACE. During follow-up (21.1 ± 3.7 months), greater increases in PAV, but not total atheroma volume, were observed in subjects who experienced MACE compared with those who did not (0.95 ± 0.19% vs. 0.46 ± 0.16%, $p < 0.001$). Each standard deviation increase in PAV was associated with a 1.20-fold (95% confidence interval: 1.10 to 1.31; $p < 0.001$) greater risk for MACE. Multivariate analysis revealed that factors associated with MACE included baseline PAV ($p < 0.0001$), change in PAV ($p = 0.002$), smoking ($p = 0.0002$) and hypertension ($p = 0.01$).

Conclusions A direct relationship was observed between the burden of coronary atherosclerosis, its progression, and adverse cardiovascular events. The relationship between disease progression and outcomes largely reflected the need for coronary revascularization. These data support the use of atherosclerosis imaging with IVUS in the evaluation of novel antiatherosclerotic therapies. (J Am Coll Cardiol 2010;55:2399–407) © 2010 by the American College of Cardiology Foundation

Vascular imaging has been used for more than 30 years to define the natural history of the atherosclerotic disease process and to assess the effects of interventions on the progression of this disease (1–5). The rationale for this approach is based on the concept that atherosclerotic plaque represents the fundamental pathological substrate

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JACC Vol. 55, No. 21, 2010
May 25, 2010:2399–407

Abbreviations and Acronyms

IVUS = intravascular ultrasound

MACE = major adverse cardiovascular event(s)

underlying the occurrence of ischemic cardiovascular events. Theoretically, interventions that slow the progression of atherosclerotic disease should also improve clinical outcomes. Previous studies using coronary angiography and carotid ultrasound have established a strong relationship between the extent of disease, its rate of progression, and subsequent cardiovascular morbidity and mortality (6–9). These findings have prompted regulatory authorities to permit labeling of therapies on the basis of their effects on atherosclerosis progression.

Intravascular ultrasound (IVUS) enables high-resolution imaging of the coronary artery wall with precise quantification of atherosclerotic disease burden. Although this imaging modality is now commonly used in clinical trials, the relationship between atheroma volume, the rate of disease progression, and clinical outcomes has not been fully elucidated. This knowledge gap exists largely because individual IVUS trials are too small and too short in duration to have adequate statistical power to establish the relationship between disease burden and clinical outcomes. Furthermore, the invasive nature of IVUS imaging does not permit routine prospective imaging and follow-up in large patient populations. The objective of the present analysis was to pool the results of several recent IVUS trials to clarify the relationship between the extent and progression of coronary atherosclerosis and the subsequent risk for adverse cardiovascular outcomes.

Methods

Selection of subjects. The present analysis included patients participating in 6 clinical trials that assessed the impact of medical therapies on changes in coronary atheroma burden using IVUS that also included adjudication of clinical events. The trials included assessment of the effects of intensive lipid lowering (REVERSAL [Reversal of Atherosclerosis With Aggressive Lipid Lowering]) (10), antihypertensive therapies (CAMELOT [Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis]) (11), acyl-coenzyme A:cholesterol acyltransferase inhibition (ACTIVATE [ACAT Intravascular Atherosclerosis Treatment Evaluation]) (12), cholesteryl ester transfer protein inhibition (ILLUSTRATE [Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation]) (13), the peroxisome proliferator-activated receptor-gamma agonist pioglitazone in type 2 diabetes (PERISCOPE [Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation]) (14), and the endocannibanoid antagonist rimonabant (STRADIVARIUS [Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant–The Intravascular Ultrasound Study]) (15). In each of these studies, subjects were required to have coronary artery disease, defined as the presence of at least one luminal narrowing >20% in an epicardial coronary artery on coronary angiography performed for a clinical indication.

Acquisition and analysis of IVUS images. The acquisition and analysis of IVUS images has been described in detail previously (10–15). Briefly, a target vessel containing no luminal stenosis >50% within a segment of at least 30 mm in length was selected for imaging. To evaluate the impact on the natural history of coronary atherosclerosis progression, the target vessel was required to not have undergone previous revascularization or represent the culprit vessel from a prior myocardial infarction. After the administration of anticoagulation and nitroglycerin, an imaging catheter containing a high-frequency (30 to 40 MHz) ultrasound transducer was placed as distal as possible within the coronary artery. Ultrasound images were continuously recorded on videotape during withdrawal of the catheter at a constant rate of 0.5 mm/s. Imaging was performed within the same coronary artery at baseline and at the end of the study, which ranged from 18 to 24 months.

The recorded images were digitized for subsequent analysis. An anatomically matched segment was defined at the 2 time points on the basis of proximal and distal side branches (fiduciary points). Cross-sectional images spaced precisely 1 mm apart were selected for measurement. The leading edges of the lumen and external elastic membrane (EEM) were traced by manual planimetry. Plaque area was defined as the area occupied between these leading edges. Total atheroma volume was calculated as the summation of plaque area in each measured image, normalized to account for differences in segment length between different subjects:

$$\text{Total atheroma volume}_{\text{normalized}} = \frac{\sum (\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\text{number of images in pullback}} \times \text{median number of images in cohort}$$

Percent atheroma volume was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque, throughout the segment of interest:

$$\text{Percent atheroma volume} = \frac{\sum (\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\sum \text{EEM}_{\text{area}}} \times 100$$

The remodeling index at the most diseased site was calculated as the ratio of the EEM area at the diseased site compared with the least diseased site within the proximal 10 mm.

Statistical analysis. Major adverse cardiovascular events (MACE) were defined as the combination of death from all causes, myocardial infarction, and coronary revascularization. Myocardial infarctions were recorded as spontaneous events, not secondary to percutaneous coronary intervention. Similarly, revascularization events were not planned, as patients who are expected to undergo revascularization are not enrolled in these studies. One event was recorded per

patient for the present analysis. Least squares means for baseline plaque burden from an unadjusted model are presented by whether or not a subject experienced 1 of the MACE. Similarly, least squares means from an analysis of covariance controlling for baseline plaque were used to summarize changes in measures of atheroma burden by event status. Unadjusted Cox proportional hazards models were used to assess the association between baseline percent atheroma volume and clinical events, and unadjusted logistic regression models were used to assess the association between change in percent atheroma volume and clinical events. Hazard ratios and odds ratios, respectively, are expressed per SD. Given that each trial's duration varied between 18 and 24 months, the change in atheroma burden was annualized by dividing the change by the number of days between IVUS measurements and multiplying by 365 days. A multivariate logistic model to assess the association between change in percent atheroma volume and MACE after controlling for important baseline characteristics was also developed. All baseline demographics (age, sex, race, history of risk factors [hypertension, smoking, diabetes, and hypercholesterolemia], and history of cardiovascular disease [myocardial infarction, stroke, coronary revascularization, and peripheral vascular disease]), concomitant medication use (aspirin, statins, angiotensin-converting enzyme inhibitors, and beta-blockers), biochemical parameters (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, apolipoprotein A-I, apolipoprotein B, and C-reactive protein) and vital signs (pulse and systolic and diastolic blood pressure) were considered for inclusion into an adjusted model. A stepwise elimination procedure was used to determine the final model, which was then stratified by study. A bootstrapping technique was used to draw 500 samples from the original data and rerun the stepwise modeling process to confirm the model. As a continuous variable, the change in percent atheroma volume was modeled nonparametrically by a spline function with 6 knots, and the model also included its interaction with the baseline volume. A sensitivity analysis was performed by imputing the missing values for follow-up atheroma volume, and similar results were obtained. All statistical analysis were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

Results

Clinical characteristics. The clinical characteristics, medication use, and laboratory values of patients at baseline are summarized in Tables 1 to 3. Patients had a mean age of 57.7 years, 69.1% were male, they had a high prevalence of risk factors (hypercholesterolemia 77.4%, hypertension 77.4%, metabolic syndrome 59.3%, diabetes 35.2%, previous percutaneous coronary intervention 42.9%), and they had a high rate of use of established medical therapies (statins 92.4%, aspirin 93.4%, beta-blockers 75.5%, angiotensin-converting enzyme inhibitors 55.3%). Forty-two percent of patients underwent percutaneous coronary intervention in another coronary artery immediately before the acquisition of baseline IVUS imaging. Significant reductions in levels of atherogenic lipoproteins and high-sensitivity C-reactive protein and elevations in levels of high-density lipoprotein cholesterol and blood pressure were observed during serial evaluation. A total of 3,130 patients (75.7%) underwent serial ultrasonic imaging at both baseline and follow-up. A mean increase in percent atheroma volume from 38.6% to 39.0% ($p < 0.001$) and decreases in both total atheroma volume from 190.0 to 187.8 mm^3 ($p < 0.001$) and remodeling index from 0.95 to 0.92 ($p < 0.001$) were observed during follow-up of 21.1 ± 3.7 months. During the courses of the studies, 19.9% of patients experienced cardiovascular events (death in 0.9%, myocardial infarction in 1.8%, and coronary revascularization in 18.9%).

Table 1 Clinical Characteristics and Medication Use of Subjects

Parameter	Cohort (n = 4,137)
Age (yrs)	57.7 ± 9.6
Men	69.1
Caucasian	90.3
Body mass index (kg/m^2)	31.7 ± 6.0
Smokers	22.3
Diabetes	35.2
Hypertension	77.4
Metabolic syndrome	59.3
Previous CABG	3.1
Previous PCI	42.9
Hypercholesterolemia	77.4
Baseline medication use	
Aspirin	92.7
Beta-blockers	73.8
ACE inhibitors	49.5
Statins	79.2
Medication use during trials	
Aspirin	93.4
Beta-blockers	75.5
ACE inhibitors	55.3
Statins	92.4
Baseline angiographic data	
Maximum percent diameter stenosis	31.3 ± 12.2
Minimum luminal diameter (mm)	2.1 ± 0.5
Subjects with maximum stenosis >50%	62.7
Subjects with 3-vessel disease >20%	49.4

Data are expressed as mean ± SD for continuous variables and as percentages for categorical variables.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; PCI = percutaneous intervention.

Baseline atheroma burden and clinical outcomes. The baseline measures of atheroma burden in subjects stratified according to the incidence of clinical events during the studies are summarized in Table 4. Greater percent atheroma volumes at baseline were present in subjects who subsequently experienced myocardial infarctions (42.2 ± 9.6% vs. 38.6 ± 9.1%, $p = 0.001$), coronary revascularization (41.2 ± 9.3% vs. 38.1 ± 9.0%, $p < 0.001$), or the composite MACE end point (41.3 ± 9.2% vs. 38.0 ± 9.0%,

JACC Vol. 55, No. 21, 2010
May 25, 2010:2399–407

Table 2 Biochemical, Hemodynamic, and Atheroma Measures at Baseline and on Treatment and Their Changes in All Subjects

Parameter	Baseline	On Treatment	Median Change (IQR)	p Value
Total cholesterol (mg/dl)	178.9 ± 43.8	168.7 ± 32.5	−2.5 (−27.0 to 14.0)	<0.001
LDL cholesterol (mg/dl)	100.7 ± 35.6	89.9 ± 27.2	−5.2 (−25.0 to 8.8)	<0.001
HDL cholesterol (mg/dl)	42.4 ± 11.6	47.6 ± 15.7	3.0 (−1.2 to 9.0)	<0.001
Triglycerides (mg/dl)	142.0 (102.8 to 203.7)	134.7 (98.0 to 184.5)	−7.4 (−39.4 to 20.8)	<0.001
CRP (mg/l)	2.7 (1.2 to 5.7)	2.0 (1.0 to 4.6)	−0.3 (−1.9 to 0.6)	<0.001
Systolic BP (mm Hg)	127.3 ± 16.1	128.6 ± 12.8	2.0 (−6.1 to 9.7)	<0.001
Diastolic BP (mm Hg)	75.8 ± 9.4	76.2 ± 7.3	0.5 (−4.3 to 5.2)	<0.001
Percent atheroma volume (%)	38.6 ± 9.1	39.0 ± 9.1	0.3 (−1.3 to 2.1)	<0.001
Total atheroma volume (mm^3)	190.0 ± 83.7	187.8 ± 82.8	−2.4 (−12.7 to 7.9)	<0.001
Remodeling index	0.95 ± 0.20	0.92 ± 0.19	−0.03 (−0.1 to 0.1)	<0.001

Data are expressed as mean ± SD or as median (IQR).
BP = blood pressure; CRP = C-reactive protein; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.

$p < 0.001$). Although percent atheroma volumes were also greater in those subjects who subsequently died (41.1 ± 8.6% vs. 38.6 ± 9.2%, $p = 0.10$), this failed to reach conventional levels of statistical significance. Although total atheroma volumes were greater in patients who experienced the composite end point (199.0 ± 87.8 mm^3 vs. 187.9 ± 82.5 mm^3, $p = 0.001$) and coronary revascularization (197.6 ± 88.0 mm^3 vs. 188.3 ± 82.5 mm^3, $p = 0.006$), no difference was observed with regard to either death or myocardial infarction. Similar findings were observed when patients treated with experimental antiatherosclerotic therapies (pactimibe, torcetrapib, and rimonabant) were excluded. The remodeling index did not differ in patients who experienced cardiovascular events (0.94 ± 0.19 vs. 0.94 ± 0.20, $p = 0.67$).

Each standard deviation increase in percent atheroma volume at baseline was associated with a 1.34-fold increase (95% confidence interval [CI]: 1.00 to 1.80; $p = 0.05$) in the risk for myocardial infarction, a 1.31-fold (95% CI: 1.21 to 1.41; $p < 0.001$) greater risk for coronary revascularization, and a 1.32-fold (95% CI: 1.22 to 1.42; $p < 0.001$) greater risk for MACE (Table 5). Survival curves demonstrated that the excess rate of clinical events in subjects with the highest quartile of percent atheroma volume at baseline became apparent within a few months of follow-up (Fig. 1).

Change in atheroma burden and clinical outcomes. Changes in measures of atheroma burden in subjects stratified according to the incidence of clinical end points during the studies are summarized in Table 6. Greater increases in percent atheroma volume were observed in subjects who underwent coronary revascularization (0.96 ± 0.19% vs. 0.46 ± 0.16%, $p < 0.001$) or experienced the composite MACE end point (0.95 ± 0.19% vs. 0.46 ± 0.16%, $p < 0.001$). In contrast, changes in total atheroma volume (−2.5 ± 0.8 mm^3 vs. −1.9 ± 0.4 mm^3, $p = 0.52$) and the remodeling index at the most diseased site (−0.02 ± 0.01 vs. −0.03 ± 0.00, $p = 0.17$) did not differ between groups stratified according to the incidence of cardiovascular events. Similar findings were observed when patients treated with experimental antiatherosclerotic therapies (pactimibe, torcetrapib, and rimonabant) were excluded. Analysis of the relationship between changes in atheroma burden and clinical events is confounded by the finding that baseline burden is associated with both disease progression and clinical outcome ($p = 0.03$ for statistical interaction). However, modeling revealed that regardless of the baseline level, a direct relationship was observed between annual changes in percent atheroma volume (Fig. 2). In particular, a greater increase in clinical risk was observed per unit change in atheroma burden in those subjects with the least amount of disease at baseline. Each standard deviation increase in change in percent atheroma volume was associated with a 1.20-fold (95% CI: 1.10 to 1.31; $p < 0.001$) greater risk for coronary revascularization and a 1.20-fold (95% CI: 1.10 to 1.31; $p = 0.002$) greater risk for MACE (Table 7). Multivariate analysis revealed that risk factors associated with incident MACE included baseline percent atheroma volume ($p < 0.0001$), change in percent atheroma volume ($p = 0.002$), smoking ($p = 0.0002$), and history of hypertension ($p = 0.01$) (Table 8).

Discussion

Despite the widespread application of established medical and surgical therapies, coronary artery disease continues to present a major global public health challenge. To address residual cardiovascular risk, considerable research has focused on the development of new therapeutic strategies designed to prevent or delay the progression of coronary disease. Although large prospective clinical trials are essential to establish both the efficacy and safety of new cardiovascular therapies, increasing interest has focused on the use of imaging studies during the early stages of development to select the most promising therapies for further study (12,16–20). Imaging trials can potentially improve the efficiency of drug development by identifying therapies most likely to succeed in outcomes trials, while permitting the early termination of development programs unlikely to demonstrate clinical efficacy.

The concept of using atherosclerosis imaging to determine the efficacy of therapies originally evolved through studies conducted using traditional imaging methods, such

Table 3 Cardiovascular Events and Changes in Measures of Coronary Atheroma Burden in Each Study, Stratified According to Treatment Group

Variable	ACTIVATE		CAMELOT			ILLUSTRATE		PERISCOPE		REVERSAL		STRADIVARIUS	
	Pactimibe (n = 265)	Placebo (n = 260)	Amlodipine (n = 131)	Enalapril (n = 133)	Placebo (n = 132)	Torcetrapib (n = 587)	Placebo (n = 593)	Glimepiride (n = 273)	Pioglitazone (n = 273)	Atorvastatin (n = 323)	Pravastatin (n = 325)	Rimonabant (n = 421)	Placebo (n = 416)
MACE (%)	26.1	26.2	13.7	16.5	18.2	20.3	17.4	12.8	12.3	34.7	34.5	13.1	12.7
Mortality (%)	0.8	1.6	3.1	2.3	1.5	1.4	1.0	0.7	1.1	0.3	0.3	0	0.5
Myocardial infarction (%)	1.6	2.4	2.3	1.5	1.5	2.2	2.7	1.5	0.7	1.5	1.5	2.1	1.0
Revascularization (%)	25.3	24.6	11.5	15.2	17.4	19.3	16.0	11.0	10.8	34.4	34.2	12.4	11.8
Baseline percent atheroma volume (%)	39.3 ± 8.9	39.1 ± 9.0	40.7 ± 10.3	41.4 ± 9.3	41.4 ± 9.9	37.1 ± 8.7	37.7 ± 8.4	40.6 ± 8.5	40.5 ± 8.7	38.2 ± 11.5	39.6 ± 10.7	37.1 ± 8.0	37.6 ± 7.6
Change in percent atheroma volume	0.7 ± 0.2	0.6 ± 0.2	0.3 ± 0.3	0.6 ± 0.3	1.0 ± 0.3	0.1 ± 0.1	0.15 ± 0.1	0.7 ± 0.2	−0.1 ± 0.2	0.5 ± 0.3	2.0 ± 0.3	0.3 ± 0.1	0.5 ± 0.1
Baseline total atheroma volume (mm^3)	186.6 ± 83.7	187.8 ± 86.9	218.8 ± 94.5	216.6 ± 82.3	207.6 ± 78.6	174.2 ± 79.0	181.4 ± 76.5	200.7 ± 86.3	192.9 ± 82.0	201.5 ± 93.2	215.6 ± 97.0	175.7 ± 73.7	181.8 ± 74.7
Change in total atheroma volume (mm^3)	−1.2 ± 1.4	−5.4 ± 1.4	−0.4 ± 2.1	0.7 ± 2.1	1.7 ± 2.0	−6.4 ± 0.7	−4.2 ± 0.7	−1.8 ± 1.4	−6.4 ± 1.4	−0.6 ± 2.0	6.2 ± 2.0	−1.9 ± 0.9	0.9 ± 0.9
Baseline remodeling index	0.94 ± 0.18	0.94 ± 0.19	0.96 ± 0.21	0.94 ± 0.22	0.96 ± 0.20	0.95 ± 0.18	0.94 ± 0.19	0.96 ± 0.20	0.93 ± 0.20	0.94 ± 0.21	0.96 ± 0.22	0.94 ± 0.18	0.94 ± 0.20
Change in remodeling index	−0.03 ± 0.01	−0.02 ± 0.01	−0.04 ± 0.02	−0.06 ± 0.02	−0.05 ± 0.01	−0.02 ± 0.01	−0.02 ± 0.01	−0.02 ± 0.01	−0.03 ± 0.01	−0.03 ± 0.01	−0.03 ± 0.01	−0.02 ± 0.01	−0.01 ± 0.01

Data are expressed as percentages or mean ± SD.

ACTIVATE = ACAT Intravascular Atherosclerosis Treatment Evaluation; CAMELOT = Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis; ILLUSTRATE = Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation; PERISCOPE = Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; REVERSAL = Reversal of Atherosclerosis With Aggressive Lipid Lowering; STRADIVARIUS = Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—The Intravascular Ultrasound Study.

as coronary angiography and ultrasonic measurement of carotid intima-media thickness (1–5). However, unlike other methods, coronary IVUS imaging permits the direct measurement of coronary atheromatous plaque, which represents a theoretically appealing method for assessing the effects of therapies (21,22). In initial IVUS trials, interventions that targeted established risk factors demonstrated favorable effects on the rate of progression of coronary atherosclerosis (10,11,16,17,23). Although these findings have stimulated considerable scientific interest, the relationship between atheroma burden, the rate of progression, and cardiovascular outcomes remained to be elucidated. We sought to close this knowledge gap by pooling results from 6 serial IVUS imaging trials involving 4,137 patients with established coronary artery disease followed for an average of 21 months and analyzed at the same core laboratory.

The present analysis demonstrates a relationship between increasing burden of coronary atherosclerosis, as determined by IVUS, and subsequent clinical outcomes. Approximately 20% of patients experienced MACE, and these subjects who had adverse outcomes had slightly more than 3% greater percent atheroma volume during initial imaging ($p < 0.001$) (Table 4). Similarly, patients who experienced myocardial infarctions or subsequent coronary revascularization had greater initial plaque burden ($p < 0.001$). There were only 38 deaths, but nonetheless, a trend toward a greater baseline atheroma burden was observed in patients who died during follow-up ($p = 0.10$). Although the present analysis cannot discriminate events resulting from complications of native atherosclerotic plaque or the clinical sequelae of restenosis, these findings demonstrate that a greater atheroma burden is associated with unfavorable cardiovascular outcomes.

The magnitude of the increased risk was further evaluated by examining the hazard ratio associated with an increasing extent of disease burden. Each standard deviation increase in percent atheroma volume had a more than 1.3-fold higher risk for a MACE, myocardial infarction, or coronary revascularization (Table 5). The effects of increasing disease burden on death were not evident in this analysis, which likely reflects the finding that there were few mortal events. Examination of event-free survival curves shows an early separation between patients in the lowest and highest quartiles, with progressively worse outcomes over time for patients with greater disease burden. The totality of these findings demonstrates a link between the extent of disease burden measured by IVUS and adverse cardiovascular outcomes.

We also endeavored to explore the relationship between serial changes in atheroma burden and cardiovascular events. The relationship between the rate of disease progression and clinical outcome is considerably more complicated. The present study and prior analyses (24) have convincingly demonstrated that the rate of progression measured by IVUS is strongly influenced by the extent of baseline atheroma volume. In particular, the greatest degree of disease progression was observed in those

JACC Vol. 55, No. 21, 2010
May 25, 2010:2399–407

Table 4 Measures of Atheroma Burden at Baseline in Subjects Stratified According to the Incidence of Cardiovascular Events During the Studies for the Entire Cohort and After the Exclusion of Patients Treated With Experimental Therapies (Torcetrapib, Pactimibe, and Rimonabant)

Clinical Event	Percent Atheroma Volume (%)			Total Atheroma Volume (mm^3)		
	No	Yes	p Value	No	Yes	p Value
Entire cohort						
Death, myocardial infarction, coronary revascularization (n = 819)	38.0 ± 9.0	41.3 ± 9.2	<0.001	187.9 ± 82.5	199.0 ± 87.8	0.001
Death (n = 38)	38.6 ± 9.2	41.1 ± 8.6	0.10	189.9 ± 83.7	203.6 ± 81.1	0.14
Myocardial infarction (n = 75)	38.6 ± 9.1	42.2 ± 9.6	0.001	189.9 ± 83.6	199.1 ± 87.0	0.38
Coronary revascularization (n = 775)	38.1 ± 9.0	41.2 ± 9.3	<0.001	188.3 ± 82.5	197.6 ± 88.0	0.006
Excluding experimental therapies						
Death, myocardial infarction, coronary revascularization (n = 578)	38.4 ± 9.2	41.7 ± 9.5	<0.001	192.9 ± 84.8	206.6 ± 86.8	<0.001
Death (n = 28)	39.1 ± 9.4	41.4 ± 8.5	0.08	195.6 ± 85.4	201.8 ± 79.3	0.41
Myocardial infarction (n = 49)	39.0 ± 9.3	43.8 ± 9.7	<0.001	182.6 ± 85.4	215.0 ± 78.6	0.07
Coronary revascularization (n = 545)	38.5 ± 9.2	41.6 ± 9.6	<0.001	193.3 ± 84.7	205.3 ± 87.3	0.001

Data are expressed as mean ± SD.

subjects with the least amount of plaque at baseline. Accordingly, simple relationships do not accurately describe the relationship between change in atheroma volume and clinical outcomes. Nonetheless, the 20% of patients with MACE had a 0.95% increase in atheroma volume during these trials, while those without events had a 0.46% increase. Thus, a 0.5% difference in progression rate identified a group with adverse clinical outcomes. Interestingly, this difference is similar in magnitude to the differences in progression rate noted for effective antiatherosclerotic therapies in several IVUS trials (10,11,14,23). The predominance of coronary revascularization among the clinical events and the relatively low rate of myocardial infarction are likely to underscore the observation of a closer relationship between disease progression and revascularization in the present analysis.

To account for the complex relationship between baseline plaque volume and the progression rate, a model was developed that describes the association between the risk for cardiovascular events and the annual rate of disease progression for patients stratified according to baseline plaque volume (Fig. 2). From these curves, it can be observed that for any level of baseline disease burden, the hazard ratio for MACE is related to the rate of progression. Furthermore, using multivariate analysis, both the extent of disease at baseline ($p < 0.0001$) and its rate of progression ($p = 0.005$) were found to be independently associated with adverse outcomes. These findings demonstrate the importance of disease progression in serial IVUS studies in association with clinical outcomes and support the use of coronary atherosclerosis imaging in clinical trials to evaluate novel antiatherosclerotic therapies.

Table 5 Relationship Between Increasing SDs of Baseline Percent Atheroma Volume and Cardiovascular Events

Event	HR (95% CI)	p Value
Death, myocardial infarction, coronary revascularization	1.32 (1.22–1.42)	<0.001
Death	0.73 (0.16–3.31)	0.69
Myocardial infarction	1.34 (1.00–1.80)	0.05
Coronary revascularization	1.31 (1.21–1.41)	<0.001

CI = confidence interval; HR = hazard ratio.

The association between the extent of coronary atherosclerosis and clinical outcomes on IVUS complements a large body of evidence that links atheroma burden and clinical events. Necropsy studies have demonstrated the presence of more extensive atherosclerosis within the coronary arteries of victims of sudden cardiac death compared with those who died from noncardiac causes (25). Large registries of patients undergoing coronary angiography demonstrate an association between more extensive or severe luminal stenoses and adverse cardiovascular outcomes (6,7). Prior studies have demonstrated a relationship be-

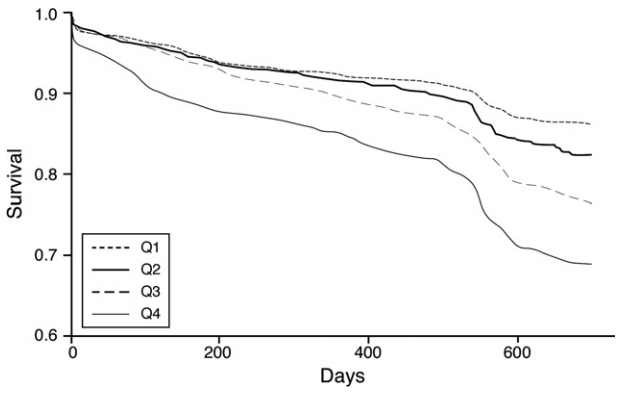

Figure 1 Baseline Plaque Burden and Cardiovascular Events

Survival from cardiovascular events (death, myocardial infarction, and coronary revascularization) in patients stratified according to quartiles (Q) of percent atheroma volume at baseline.

Table 6 Changes in Measures of Atheroma Burden, Controlling for Baseline Values, in Subjects Stratified According to the Incidence of Cardiovascular Events During the Studies for the Entire Cohort and After the Exclusion of Patients Treated With Experimental Therapies (Torcetrapib, Pactimibe, and Rimonabant)

	Percent Atheroma Volume (%)			Total Atheroma Volume (mm^3)		
Clinical Event	No	Yes	p Value	No	Yes	p Value
Entire cohort						
Death, myocardial infarction, coronary revascularization	0.46 ± 0.16	0.95 ± 0.19	<0.001	−1.9 ± 0.4	−2.5 ± 0.8	0.52
Death	0.56 ± 0.17	−0.60 ± 1.55	0.45	−2.0 ± 0.4	−3.5 ± 14.6	0.92
Myocardial infarction	0.56 ± 0.17	0.61 ± 0.44	0.90	−2.0 ± 0.4	−7.1 ± 3.0	0.10
Coronary revascularization	0.46 ± 0.16	0.96 ± 0.19	<0.001	−2.0 ± 0.4	−2.3 ± 0.8	0.72
Excluding experimental therapies						
Death, myocardial infarction, coronary revascularization	0.44 ± 0.16	1.06 ± 0.20	<0.001	−1.6 ± 1.5	−1.7 ± 1.7	0.89
Death	0.56 ± 0.16	−1.89 ± 2.14	0.25	−1.6 ± 1.5	−8.7 ± 14.8	0.63
Myocardial infarction	0.56 ± 0.16	0.76 ± 0.59	0.73	−1.5 ± 1.5	−7.0 ± 4.0	0.14
Coronary revascularization	0.44 ± 0.16	1.08 ± 0.20	<0.001	−1.6 ± 1.5	−1.3 ± 1.7	0.79

Data are expressed as least squares mean ± SE.

tween the degree of carotid intima-media thickness (8,9) or coronary calcification (26,27), both surrogate measures of coronary disease burden, and cardiovascular morbidity and mortality. A small IVUS study previously suggested a relationship between progression at the most diseased site in the left main coronary artery and clinical outcomes, although to date there has been very little investigation into this association in other cohorts (28). The finding of a more consistent relationship between outcomes and measures of percent atheroma volume, compared with total atheroma volume, highlights the potential importance of arterial wall remodeling, in addition to atheroma burden, in promoting cardiovascular events. Although the remodeling index, which reflects the response of the vessel wall at the most diseased site, was not associated with outcomes, it was important to note that percent atheroma volume, reflecting the interaction between the artery wall and plaque throughout the imaged segment, did associate with the likelihood of having a clinical event. It is important to note that the findings were observed in the entire cohort and in subjects who were treated only with therapies used in contemporary clinical practice. This further supports the concept of the systemic, as opposed to focal, nature of coronary heart disease.

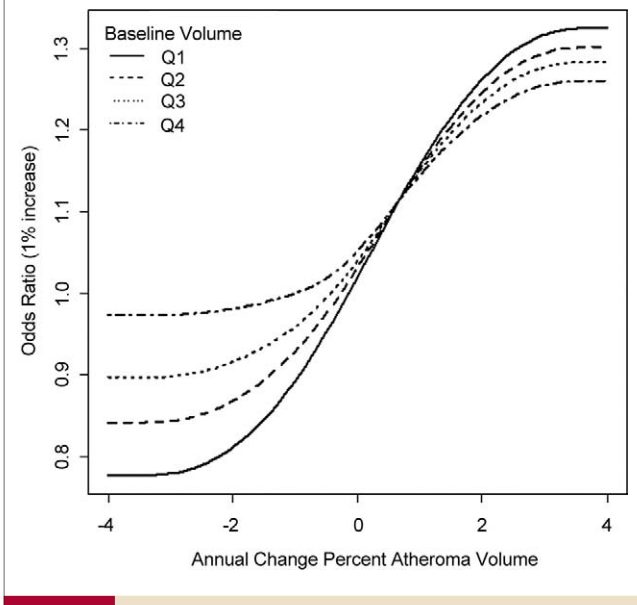

Figure 2 Change in Plaque Burden and Cardiovascular Events

Relationship between annual change in percent atheroma volume and odds ratio for cardiovascular events (death, myocardial infarction, and coronary revascularization) stratified according to quartiles (Q) of percent atheroma volume at baseline.

A number of caveats should be noted. The present findings result from the pooling of individual patient data from a number of clinical trials. Although these studies were similar in terms of patient populations, imaging acquisition, and core laboratory analysis, it is possible that there could be residual heterogeneous confounding factors, despite the use of mixed modeling statistical approaches to deal with pooling of the data. Similarly, although there may be differences between individual trials with regard to directions of disease progression and event rates with different treatment groups, it is important to note that each of these studies was small and not powered to evaluate clinical events.

All patients were required to have some degree of obstructive disease evident on coronary angiography per-

Table 7 Relationship Between Increasing SDs of Change in Percent Atheroma Volume, Controlling for Baseline Values and Study, and Cardiovascular Events Expressed

Event	OR (95% CI)	p Value
Death, myocardial infarction, coronary revascularization	1.20 (1.10 to 1.31)	<0.001
Death	0.49 (0.12 to 1.95)	0.31
Myocardial infarction	0.98 (0.73 to 1.32)	0.90
Coronary revascularization	1.20 (1.10 to 1.31)	<0.001

CI = confidence interval; OR = odds ratio.

JACC Vol. 55, No. 21, 2010
May 25, 2010:2399–407

Table 8 Multivariate Model With Risk Factors Associated With Major Adverse Cardiovascular Events, Controlling for Study

Variable	OR (95% CI)	p Value
Baseline PAV per SD	1.45 (1.32 to 1.59)	<0.0001
Change PAV per SD	1.15 (1.05 to 1.26)	0.002
History of hypertension	1.34 (1.06 to 1.68)	0.01
Current smoker	1.49 (1.21 to 1.84)	0.0002

CI = confidence interval; OR = odds ratio; PAV = percent atheroma volume.

formed for a clinical indication. Therefore, the present population represents a narrower spectrum of risk compared with previous studies of carotid intima-media thickness or coronary calcification. Furthermore, the relatively young age, high rate of use of established therapies, and lack of severe obstructions in the imaged vessels may have further influenced the overall risk in this cohort, which was reflected by the low incidence of death and myocardial infarction and the predominance of revascularization in clinical events. The present findings cannot be applied to subjects with subclinical coronary atherosclerosis, although the invasive nature of IVUS makes it unlikely that this imaging modality would ever be used in randomized clinical trials in low-risk populations.

Approximately 25% of patients did not undergo imaging at follow-up. In some of these cases, this was due to the occurrence of clinical events that precluded the ability to image at the follow-up as originally scheduled, which may introduce bias in defining the relationship between progression and outcomes. However, such bias would tend to weaken the relationship between progression and subsequent ischemic events. Furthermore, imputation of results for noncompleters did not alter the conclusions of these analyses. The present study pooled the results for a heterogeneous group of clinical trials involving many different therapies. Ideally, a single large prospective trial would offer the best evidence for a relationship between disease burden and clinical outcome.

Given that it is unknown whether the clinical events were directly related to the imaged vessel or another artery that may have previously undergone revascularization, it is uncertain to what degree the present findings reflect a relationship with the progression of native atherosclerosis or restenosis within a vessel that has previously undergone revascularization. This is an important point given that nearly half of patients underwent percutaneous coronary intervention immediately before the acquisition of baseline IVUS images. It is also unknown how many of these procedures involved the placement of bare-metal versus drug-eluting stents and therefore what influence that may have had on the demonstrated relationship with outcomes. The findings support previous reports of a relationship between underlying disease burden and clinical outcome after percutaneous intervention (29). The relationship between disease progression and outcomes related to native and restenotic phenomena requires ongoing investigation in large prospective studies.

Although the present findings indicate an association between disease burden and cardiovascular events and its progression with need for coronary revascularization, this does not diminish the potential importance of plaque composition. Increasing evidence has recognized that atherosclerosis is a chronic inflammatory process, with episodes of acute ischemia often occurring in the setting of rupture of an inflamed and necrotic lipid-rich plaque. Considerable interest has focused on the ability to characterize plaque components with arterial wall imaging. Although some groups have investigated ultrasonic echogenicity as a surrogate of composition, these data were not collected in the present cohort. The relationship between these factors and their serial changes with clinical outcomes remains to be determined as these imaging approaches are increasingly validated. Nevertheless, it is unlikely that plaque burden and composition are mutually exclusive factors and that they in combination with the remodeling response of the artery wall are important in determining a patient's likelihood of ultimately having an adverse cardiovascular outcome.

Despite these limitations, the present analysis demonstrates a relationship between the extent and progression of coronary atherosclerosis, as determined by IVUS, and the prospective risk for cardiovascular events. These observations support the use of IVUS clinical trials in the early development of novel antiatherosclerotic agents. Although IVUS is not a substitute for definitive clinical outcomes trials, this imaging modality is useful to select those agents most suitable for subsequent investigation in larger, more expensive long-term studies.

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Key Words: atherosclerosis ■ intravascular ultrasound ■ risk factors ■ imaging.