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CME

Clinical Predictors of Plaque Progression Despite Very Low Levels of Low-Density Lipoprotein Cholesterol

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Clinical Predictors of Plaque Progression Despite Very Low Levels of Low-Density Lipoprotein Cholesterol

Objectives The purpose of this study was to characterize the determinants of plaque progression despite achieving very low levels of low-density lipoprotein cholesterol (LDL-C).

Background Despite achieving very low levels of LDL-C, many patients continue to demonstrate disease progression and have clinical events.

Methods A total of 3,437 patients with coronary artery disease underwent serial intravascular ultrasound examination in 7 clinical trials. Patients who achieved an on-treatment LDL-C level of ≤70 mg/dl (n = 951) were stratified as progressors (n = 200) and nonprogressors (n = 751) and compared.

Results Despite achieving LDL-C ≤70 mg/dl, >20% of patients continued to progress. There were no demographic differences between groups. Progressors demonstrated higher baseline levels of glucose (117.1 ± 42.5 mg/dl vs. 112.1 ± 40.0 mg/dl, p = 0.02), triglycerides (157.5 mg/dl vs. 133.0 mg/dl, p = 0.004), and a smaller decrease of apolipoprotein B (−25.1 ± 3.4 mg/dl vs. −27.4 ± 3.35 mg/dl, p = 0.01) at follow-up. Multivariable analysis revealed that independently associated risk factors of progression in patients with LDL-C ≤70 mg/dl included baseline percent atheroma volume (p = 0.001), presence of diabetes mellitus (p = 0.02), increase in systolic blood pressure (p = 0.001), less increase in high-density lipoprotein cholesterol (p = 0.01), and a smaller decrease in apolipoprotein B levels (p = 0.001), but not changes in C-reactive protein (p = 0.78) or LDL-C (p = 0.84).

Conclusions Residual risk factors are associated with the likelihood of disease progression in patients who achieve very low LDL-C levels. In addition, the association between apolipoprotein B and atheroma progression highlights the potential importance of LDL particle concentration in patients with optimal LDL-C control. This finding highlights the need for intensive modification of global risk in patients with coronary artery disease. (J Am Coll Cardiol 2010;55:2736–42) © 2010 by the American College of Cardiology Foundation

Compelling evidence from observational and interventional studies highlight the pivotal role of hyperlipidemia in the pathogenesis of atherosclerotic cardiovascular disease. Virtually all such studies demonstrate a direct relationship between reduction in low-density lipoprotein cholesterol (LDL-C) and cardiovascular morbidity and mortality (1–3). Accordingly, current lipid-lowering guidelines focus on LDL-C reduction as a principal target for primary and secondary prevention of cardiovascular disease (4). Recent clinical trials have demonstrated an incremental benefit from use of more intensive lipid-lowering regimens (5,6), and more recent iterations of guidelines emphasize more aggressive target levels for LDL reduction (7).

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Arterial wall imaging with intravascular ultrasound (IVUS) enables serial quantitation of coronary atherosclerotic plaque burden. In clinical trials, IVUS has been employed to evaluate the effect of various medical therapies on disease progression. An initial study demonstrated the ability of intensive LDL-C lowering with high-dose statin therapy to arrest atheroma progression (3). A subsequent study demonstrated regression of atherosclerosis in patients who achieve LDL-C levels <70 mg/dl (8).

However, not all patients with a LDL-C level <70 mg/dl exhibit regression of coronary atherosclerosis on serial IVUS imaging. The residual risk factors associated with progression despite achieving very low LDL-C levels remain to be elucidated. Therefore, the objective of the current analysis was to characterize the clinical factors that correlate with atheroma progression in patients who achieve a LDL-C level <70 mg/dl.

Methods

Selection of subjects and study design. The current analysis pooled data from 7 prospective atherosclerosis progression/regression IVUS trials, including a total population of 3,437 patients with established coronary heart disease. Patients with an on-treatment LDL-C level <70 mg/dl were classified as progressors (≥5% increase in percent atheroma volume [PAV]) or nonprogressors. These 7 studies, which included a wide range of pharmacological interventions, were the CAMELOT (Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis) study (9), the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering) (6) study, the ACTIVATE (Acyl: Cholesterol Acyltransferase Intravascular Atherosclerosis Treatment Evaluation) study (10), the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial (8), the ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by Cholesteryl Ester Transfer Protein Inhibition and High-Density Lipoprotein Elevation) study (11), the PERISCOPE (Comparison of Pioglitazone Versus Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes) trial (12), and

Abbreviations and Acronyms

Apo = apolipoprotein
EEM = external elastic membrane
HDL-C = high-density lipoprotein cholesterol
IVUS = intravascular ultrasound
LDL-C = low-density lipoprotein cholesterol
PAV = percent atheroma volume
TAV = total atheroma volume

the STRADIVARIUS (Effect of Rimonabant on Progression of Atherosclerosis in Patients With Abdominal Obesity and Coronary Artery Disease) study (13). These were clinical trials that employed serial IVUS examination to assess the impact of intensive lipid lowering, antihypertensive therapy, acyl:cholesterol acyltransferase inhibition, cholesteryl ester transfer protein inhibition, oral glucose-lowering agents, and endocannabinoid type 1 receptor antagonists on the progression of coronary atherosclerosis. All patients were required to have coronary artery disease, defined as having at least 1 lumen narrowing >20% in a major epicardial coronary artery on a diagnostic coronary angiogram performed for a clinical indication.

Acquisition and analysis of IVUS images. The acquisition and analysis of ultrasonic images have been described in detail previously (8–13). In brief, after anticoagulation therapy and administration of intracoronary nitroglycerin, an imaging catheter containing a high-frequency ultrasound transducer (30 to 40 MHz) was inserted distally within a coronary artery. The target vessel for imaging was required to have a segment of at least 30 mm in length that contained no lumen narrowing >50%, had not undergone previous revascularization, and was not considered to be the culprit vessel for a prior myocardial infarction. Continuous ultrasonic imaging was acquired during withdrawal of the catheter through the segment of artery at a constant rate of 0.5 mm/s. Images were stored on videotape and subsequently digitized for analysis in a single core laboratory by persons who were blinded to the clinical characteristics and treatment status of the patients. Matching arterial segments were defined from the images acquired at the baseline and follow-up studies on the basis of the anatomic location of proximal and distal side branches (fiduciary points). Images spaced precisely 1 mm apart in the segment of interest were selected for analysis.

The leading edge of the lumen and the external elastic membrane (EEM) were defined by manual planimetry. The plaque area was defined as the difference in area occupied by the lumen and EEM borders. The total atheroma volume (TAV) was calculated by summation of the plaque area calculated for each measured image and subsequently normalized to account for differences in segment length between subjects:

$$TAV_{normalized} = \frac{\sum (EEM_{area} - Lumen_{area})}{\text{Number of images in Pullback}} \times \text{Median number of images in whole cohort}$$

The percent atheroma volume (PAV) was calculated as the proportion of vessel wall volume occupied by atherosclerotic plaque:

$$PAV = \frac{\sum (EEM_{area} - Lumen_{area})}{\sum (EEM_{area})} \times 100$$

Volumes occupied by the lumen and EEM were similarly calculated by summation of their respective areas in each measured image and subsequently normalized to account for differences in segment length between subjects.

Statistical analyses. Patients with an on-treatment follow-up LDL-C ≤70 mg/dl (n = 951) were classified as progressors (≥5% increase in PAV, n = 200) or nonprogressors (n = 751). Baseline demographics, medical history, baseline and follow-up biochemical data (lipids, C-reactive protein, blood pressure, glucose, and apolipoprotein B [apoB]), as well as IVUS measurements were compared between the groups. Two-sample *t* tests were performed for normally distributed continuous variables and Wilcoxon rank-sum tests for non-normally distributed continuous variables, and chi-square tests were run for categorical variables. Serial changes in biochemical data and in IVUS measurements between the groups were assessed using mixed modeling methodology adjusting for their baseline counterparts. Trial was considered a random effect in the mixed modeling. Generalized estimating equations models were constructed for obtaining clinical predictors of progressors, with the assumption that progression in different trials was statistically independent with each other whereas the progression data within each trial was uniformly correlated. A 2-sided probability value of <0.05 was considered statistically significant. All the analyses were performed using the SAS software version 9.1.3 (SAS Institute, Cary, North Carolina).

Results

Clinical and biochemical characteristics of subjects. No significant differences in clinical characteristics and use of medications at baseline and during the course of the studies were observed in patients stratified according to the presence or absence of atheroma progression (Table 1). The degree of risk factor control at baseline and follow-up are summarized in Table 2. At baseline, progressors had higher levels of triglycerides (157.5 mg/dl, interquartile range 107.0 to 212.5 mg/dl vs. 133.0 mg/dl, interquartile range 96.0 to 188.9 mg/dl, p = 0.004) and glucose (117.1 ± 42.5 mg/dl vs. 112.1 ± 40.0 mg/dl, p = 0.02). At follow-up, progressors demonstrated higher levels of triglycerides (121.1 mg/dl vs. 111.2 mg/dl, p = 0.03), systolic blood pressure (130.8 ± 14.8 mm Hg vs. 128.3 ± 13.8 mm Hg, p = 0.047), apoB (65.9 ± 16.6 mg/dl vs. 61.9 ± 16.0 mg/dl, p = 0.002), and LDL-C (58.4 ± 8.7 mg/dl vs. 56.5 ± 9.8 mg/dl, p = 0.02).

Measures of atheroma burden and vessel dimensions. Measures of atheroma burden and vessel dimensions at baseline and on serial evaluation are summarized in Table 3. Of interest, the mean duration of follow-up to the time of the second IVUS study was in fact shorter for patients who demonstrated progression (654.3 ± 105.2 days vs. 674.4 ± 107.3 days, p = 0.02). Progressors demonstrated less extensive disease at baseline, with a smaller PAV (34.5 ±

Table 1 Clinical Characteristics and Use of Established Medical Therapies in Patients, Progressors and Nonprogressors

Characteristic	Progressors (n = 200)	Nonprogressors (n = 751)	p Value
Age, yrs	59.3 ± 10.0	59.3 ± 9.3	0.87
Female	30.5	26.4	0.24
Hypertension	79.5	83.6	0.17
Current smoker	19.8	16.1	0.26
BMI, kg/m^2	31.2 ± 6.4	30.9 ± 5.9	0.68
Diabetes mellitus	32.5	29.8	0.47
Metabolic syndrome	59.0	54.9	0.30
History of MI	29.0	30.6	0.66
History of CABG	5.2	2.8	0.13
History of PCI	40.7	47.0	0.15
Statin use			
Baseline	69.5	69.9	0.91
Concomitant	97.0	98.3	0.26
Concomitant high dose	51.9	57.2	0.19
Beta-blocker use			
Baseline	75.5	77.6	0.52
Concomitant	77.0	79.6	0.42
ACE inhibitor use			
Baseline	48.5	51.0	0.53
Concomitant	58.0	55.1	0.47
Aspirin use			
Baseline	94.0	94.5	0.77
Concomitant	94.0	94.5	0.77

Values are mean ± SD or %. Concomitant high-dose statin therapy was defined as atorvastatin 40 or 80 mg, simvastatin 80 mg, or rosuvastatin 20 or 40 mg.

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention.

8.4% vs. 39.3 ± 8.8%, p < 0.001), TAV (169.2 ± 71.7 mm^3 vs. 192.4 ± 79.1 mm^3, p < 0.001), and larger lumen volume (322.7 ± 124.5 mm^3 vs. 293.9 ± 107.8 mm^3, p = 0.008). Despite the presence of less atherosclerosis, the EEM volume did not differ between the groups (491.9 ± 172.6 mm^3 vs. 486.3 ± 164.9 mm^3, p = 0.91). In addition to predictable greater progression of PAV (+3.83 ± 0.2% vs. −1.1 ± 0.2%, p < 0.001) and TAV (+8.4 ± 1.9 mm^3 vs. −10.4 ± 1.6 mm^3, p < 0.001), progressors demonstrated greater reductions in both EEM volume (−21.6 ± 3.8 mm^3 vs. −13.4 ± 3.0 mm^3, p = 0.01) and lumen volume (−31.7 ± 2.6 mm^3 vs. −2.8 ± 1.9 mm^3, p < 0.001).

In comparison of patients with an on-treatment LDL-C >70 mg/dl, patients with LDL-C ≤70 mg/dl demonstrated less progression of PAV (0.53 ± 0.24% vs. 0.05 ± 0.26%, p < 0.001) and TAV (−2.54 ± 2.0 mm^3 vs. −5.90 ± 2.1 mm^3, p < 0.001), and were less likely to undergo substantial disease progression (30.4% vs. 21%, p < 0.0001). Nevertheless, it is important to note that 1 in 5 subjects with LDL-C ≤70 mg/dl demonstrated substantial disease progression.

Independent predictors of atheroma progression at LDL-C ≤70 mg/dl. Multivariable analysis controlling for all univariate predictors revealed that independently associated risk factors of atheroma progression in patients with a LDL-C level <70 mg/dl included baseline PAV (p < 0.001), diabetes mellitus (p = 0.02), greater increases in systolic blood pressure (p < 0.001), a smaller increase in high-density lipoprotein cholesterol (HDL-C) (p = 0.01), and smaller decrease in apoB levels (p < 0.001). Neither changes in LDL-C (p = 0.84) or C-reactive protein (p = 0.78) were associated with the likelihood of atheroma progression in patients with very low LDL-C levels (Fig. 1). There was no difference in the composite end point of death, myocardial infarction, and stroke between progressors and nonprogressors (1.8% vs. 1.9%, p = 0.77).

Discussion

We investigated the predictors of plaque progression in patients achieving very low levels of LDL-C. Despite achieving intensive control of LDL-C (mean on-treatment level 58.4 mg/dl), 1 in 5 of these patients demonstrated ongoing disease progression. Multivariable analysis revealed that patients were more likely to progress if they had diabetes, greater increases in systolic blood pressure, smaller increases in HDL-C, and smaller decreases in apoB. These results have important implications for the understanding of the potential impact of residual risk factors that promote progression in patients with very low levels of LDL-C. This analysis highlights the importance of lipid and nonlipid factors, in addition to LDL-C in the prevention of coronary heart disease.

Clinical trials using statins to lower LDL-C have demonstrated reductions in cardiovascular events and atheroma progression (5,6). The reduction in events and atheroma progression were related to the magnitude of absolute reductions in LDL-C. Angiographic and IVUS studies have demonstrated regression of coronary disease with aggressive LDL-C lowering strategies (8,14). However, in all of these trials, many patients achieving very low levels of LDL-C subsequently experienced a cardiovascular event or demonstrated progression of coronary atherosclerosis.

The present analysis suggests that optimal control of LDL-C represents only 1 component of a successful strategy for secondary prevention in patients with established coronary artery disease. The current findings that additional risk factors predict the likelihood of undergoing disease progression support the concept that atherosclerosis is a multifactorial process and is likely to respond best to therapeutic approaches that modify global risk, rather than a strategy that targets 1 individual risk factor. As a result, lifestyle measures and pharmacological regimens are likely to have the most profound impact in reducing the burden of cardiovascular disease.

These observations highlight the importance of mixed dyslipidemia in the propagation of coronary artery disease, and support reports that these factors predict residual clinical risk in large clinical trials of statin therapy (15,16). That is particularly important in the setting of abdominal adiposity and the metabolic syndrome, which are each associated with the development of this atherogenic dyslipidemic phenotype (17). The potential impact of lowering triglycerides and raising

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Table 2 Measures of Risk Factor Control in Progressors and Nonprogressors

Parameter	Progressors (n = 200)	Nonprogressors (n = 751)	p Value
Triglycerides, mg/dl			
Baseline	157.5 (107.0, 212.5)	133.0 (96.0, 188.9)	0.004
Follow-up	121.1 (90.5, 181.4)	111.2 (85.3, 156.5)	0.03
Change	−17.9 ± 7.5	−21.4 ± 6.7	0.44
HDL cholesterol, mg/dl			
Baseline	42.4 ± 11.7	41.7 ± 11.3	0.59
Follow-up	49.9 ± 18.3	50.7 ± 18.2	0.37
Change	4.9 ± 2.6	5.4 ± 2.6	0.40
Systolic blood pressure, mm Hg			
Baseline	127.8 ± 17.3	127.1 ± 16.9	0.815
Follow-up	130.8 ± 14.8	128.3 ± 13.8	0.047
Change	2.5 ± 0.7	1.1 ± 0.43	0.08
Diastolic blood pressure, mm Hg			
Baseline	75.4 ± 9.3	74.6 ± 9.2	0.28
Follow-up	75.5 ± 7.3	74.9 ± 8.1	0.39
Change	−0.04.1 ± 0.5	−0.0 ± 0.4	0.93
Glucose, mg/dl			
Baseline	117.1 ± 42.5	112.1 ± 40.0	0.02
Follow-up	118.4 ± 39.7	114.7 ± 34.2	0.25
Change	8.7 ± 41.8	9.7 ± 34.1	<0.001
Apolipoprotein B, mg/dl			
Baseline	94.0 ± 37.0	90.0 ± 37.0	0.11
Follow-up	65.9 ± 16.6	61.9 ± 16.0	0.002
Change	−25.1 ± 3.4	−27.4 ± 3.35	0.01
LDL cholesterol, mg/dl			
Baseline	94.3 ± 37.0	90.2 ± 36.2	0.21
Follow-up	58.4 ± 8.7	56.5 ± 9.8	0.02
Change	−32.2 ± 2.5	−33.3 ± 2.4	0.11
C-reactive protein, mg/l			
Baseline	2.5 (1.2, 5.2)	2.4 (1.1, 5.2)	0.45
Follow-up	1.8 (0.9, 3.9)	1.6 (0.8, 3.7)	0.50
Change	−0.04 (−1.08, 0.99)	−0.00 (−0.80, 0.80)	0.70

Results expressed as mean ± SD or median (interquartile range) when not normally distributed (triglyceride, C-reactive protein); least squares mean ± SEM changes of parameters after controlling for baseline levels.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

HDL-C in statin-treated patients with coronary artery disease is currently being investigated in large clinical trials.

The importance of atherogenic dyslipidemic factors is also highlighted by the observation that smaller reductions in levels of apoB predict progression, despite achieving a very low LDL-C level. These findings underscore the potential importance of apoB, a measure of LDL particle concentration. Increasing interest has focused on the additional prognostic information that may be generated by assessment of measures of LDL particle size and concentration. Studies have shown that cholesterol-depleted small LDL particles often accompany low HDL-C and elevated triglyceride levels (18–20). Consistent with this, recent reports have demonstrated discordance between LDL particle numbers and LDL-C in subjects with the metabolic syndrome (21) and diabetes (22). Numerous investigators have reported that measures of apoB or LDL particle concentration predict residual risk in patients with apparent optimal control of LDL-C, and potentially highlight a patient who might benefit from more intensive lipid-lowering strategies (23,24). Furthermore, a large case-control study has demonstrated that the apoB/apoA1 ratio is the strongest biochemical predictor of incident myocardial infarction, underscoring the potential importance of measure of lipoprotein particles, in contrast to cholesterol content (25). The association between the presence of greater numbers of small, dense LDL particles in patients with hypertriglyceridemia and low HDL-C identifies a patient who harbors substantial cardiovascular risk even if LDL-C levels are below treatment goals. Further studies are required to determine whether specifically targeting patients with more intensive lipid-lowering therapy on the basis of abnormal measures of LDL particles.

Relatively small increases in blood pressure were found to independently predict atheroma progression. These small rises occurred within the blood pressure range currently considered to be well controlled, and further highlight that plaque can continue to accumulate within the artery wall in patients who are pre-hypertensive (26). These findings are consistent with observations from population studies that cardiovascular risk begins to increase once blood pressure

Table 3 Measures of Atheroma Burden and Vessel Wall Dimensions

Characteristic	Progressors (n = 200)	Nonprogressors (n = 751)	p Value
Baseline			
Percent atheroma volume	34.5 ± 8.4	39.3 ± 8.8	<0.001
Total atheroma volume, mm^3	169.2 ± 71.7	192.4 ± 79.1	<0.001
EEM volume, mm^3	491.9 ± 172.6	486.3 ± 164.9	0.91
Lumen volume, mm^3	322.7 ± 124.5	293.9 ± 107.8	0.008
Change from baseline			
Percent atheroma volume	3.83 ± 0.22	−1.14 ± 0.17	<0.001
Total atheroma volume, mm^3	8.36 ± 1.86	−10.38 ± 1.56	<0.001
EEM volume, mm^3	−21.62 ± 3.82	−13.42 ± 3.00	0.01
Mean follow-up duration, days	654.3 ± 105.2	674.4 ± 107.3	0.02

Measures of atheroma burden and vessel wall dimensions at baseline, and their least squares mean ± SEM change on serial evaluation.
EEM = external elastic membrane.

exceeds 115/75 mm Hg (27) and that intensive lowering of both LDL-C and blood pressure have an incremental impact on disease progression (28). Accordingly, the results of the current analysis further support findings from clinical trials of benefit of targeting both blood pressure and dyslipidemia to prevent cardiovascular events.

It is also important to note that baseline disease burden was a predictor of disease progression. The finding that substantial progression was more common among patients with less disease at baseline is consistent with previous observations (29). The relative contribution of more progression in these vessels or a greater likelihood of regression in extensively diseased arteries remains to be determined.

A number of caveats with regard to the current analysis should be noted. This analysis represents an observational study that used pooled data from clinical trials and makes no inferences about the use of specific treatment strategies. While there was some heterogeneity across studies, all trials were conducted by the same group, using identical imaging protocols and with analysis by 1 core laboratory. Use of a mixed model statistical approach was applied to account for potential differences between studies. Nevertheless, we cannot exclude the possibility that there is residual heterogeneity in the analysis despite adopting these measures. It should also be noted that although there was no relationship with events, that these studies are small and not sufficient and powered to examine the association between plaque progression and outcomes. This association requires ongoing exploration in larger studies.

Conclusions

Despite receiving intensive medical therapy and achieving very low LDL-C levels, >20% of patients with coronary artery disease continue to demonstrate atheroma progression. While achieving a very low LDL-C level is essential for cardiovascular prevention, the greatest impact is likely to be derived from the use of a combination of lifestyle and pharmacological therapies that reduce global risk, by targeting multiple risk factors. Furthermore, differences in terms of apoB may reflect that achieving a LDL-C level ≤70

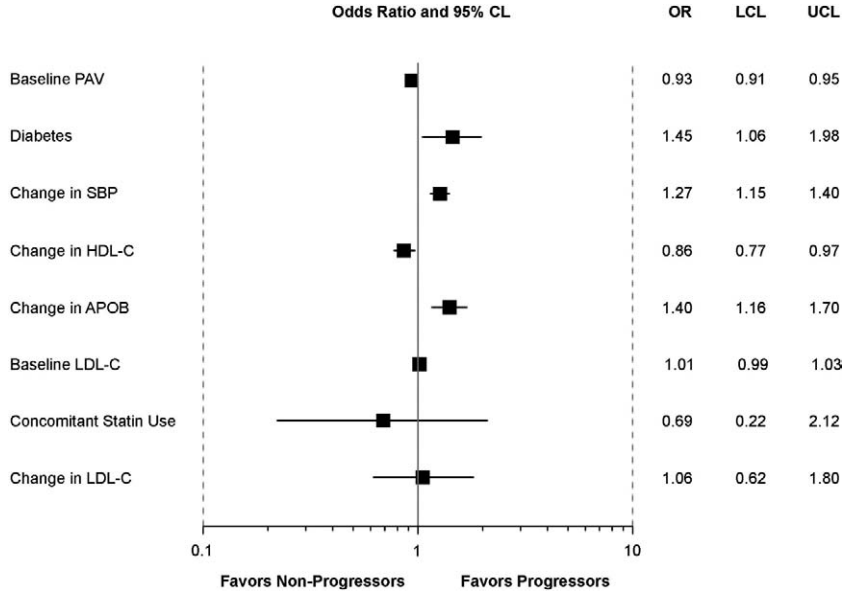

Figure 1 Forest Plot of Independent Predictors of Atheroma Progression

Forest plot illustrating the independent predictors of atheroma progression in patients with on-treatment low-density lipoprotein cholesterol (LDL-C) ≤70 mg/dl on multivariable analysis, including all univariate predictors and cardiovascular risk factors. Odds ratios (ORs) of the changes data were calculated from the changes per standard deviation. The x-axis was on a logarithmic scale. APOB = apolipoprotein B; CL = confidence limit; HDL-C = high-density lipoprotein cholesterol; LCL = lower confidence limit; PAV = percent atheroma volume; SBP = systolic blood pressure; UCL = upper confidence limit.

mg/dl may not indicate optimal lipid control in some patients. These findings further highlight the multifactorial nature of atherosclerotic cardiovascular disease and the ongoing need to improve current risk marker strategies.

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Key Words: low low-density lipoprotein ■ intravascular ultrasound ■ apolipoprotein B ■ atherosclerosis.

APPENDIX

For a description of the "poolability" of the 7 trials in this study, please see the online version of this article.