

Low Levels of Low-Density Lipoprotein Cholesterol and Blood Pressure and Progression of Coronary Atherosclerosis

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- Objectives** We investigated coronary atheroma progression in patients with low levels of low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP).
- Background** Low LDL-C and SBP beneficially impact coronary atherosclerosis. However, the association between intensive control of both risk factors and coronary plaque progression remains unclear.
- Methods** Changes in atheroma burden monitored by intravascular ultrasound were studied in 3,437 patients with coronary artery disease (CAD) who were stratified according to on-treatment LDL-C and SBP.
- Results** Patients with very low LDL-C (≤ 70 mg/dl) and normal SBP (≤ 120 mm Hg) had less progression in percent atheroma volume (PAV) ($p < 0.001$) and total atheroma volume (TAV) ($p < 0.001$), more frequent plaque regression ($p = 0.01$), and less frequent plaque progression ($p < 0.001$). In patients with SBP > 120 mm Hg, very low LDL-C was associated with less progression of PAV ($+0.30\%$, 95% confidence interval [CI]: -0.17% to 0.77% vs. $+0.61\%$, 95% CI: 0.17% to 1.05% , $p = 0.01$) and TAV (-3.9 mm³, 95% CI: -7.24 to -0.63 mm³ vs. -1.2 mm³, 95% CI: -4.31 to 1.92 mm³, $p = 0.001$). In patients with LDL-C > 70 mg/dl, normal SBP was not associated with less progression of PAV ($+0.51\%$, 95% CI: 0.04% to 0.99% vs. $+0.61\%$, 95% CI: 0.17% to 1.05% , $p = 0.159$) or TAV (-2.3 mm³, 95% CI: -5.59 to 1.05 mm³ vs. -1.2 mm³, 95% CI: -4.31 to 1.92 mm³, $p = 0.617$).
- Conclusions** Very low LDL-C and normal SBP are associated with the slowest progression of coronary atherosclerosis. Although a greater beneficial association is observed in patients with very low LDL-C, these findings suggest the need for intensive control of global risk in patients with CAD. (J Am Coll Cardiol 2009;53:1110-5) © 2009 by the American College of Cardiology Foundation

Low density lipoprotein cholesterol (LDL-C) plays a pivotal role in the progression of atherosclerotic coronary artery disease (CAD). Clinical trials have demonstrated that low-

ering LDL-C with statins prevents cardiovascular events (1,2) and that intensive LDL-C lowering is associated with additional benefit in terms of clinical events and plaque progression (3,4). Accordingly, the National Cholesterol Education Program (NCEP) guidelines now include an LDL-C goal < 100 mg/dl for patients with CAD and an optional goal < 70 mg/dl for very high-risk patients (5).

See page 1116

Similarly, blood pressure (BP) plays an important role in the promotion of CAD. In epidemiological studies, cardiovascular event rates increase with BP $> 115/75$ mm Hg (6). Given that relatively mild increases in BP can increase cardiovascular risk, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) defines “pre-hypertension” as a BP of 120 to 139/80 to 89 mm Hg (7)

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and recommends consideration of pharmacological therapy for pre-hypertensive patients with compelling indications, including chronic kidney disease or diabetes. Interestingly, established CAD is not regarded as a compelling indication for drug therapy in pre-hypertensive patients. The observation that normotensive patients have less coronary plaque progression than hypertensive and pre-hypertensive patients (8) suggests that more intensive BP lowering than currently recommended may be beneficial.

Animal studies have indicated that BP and cholesterol-lowering therapy in combination may slow the progression of aortic atherosclerosis (9,10). However, the impact of simultaneous optimal control of LDL-C and BP in humans has not been defined. The current study characterizes the relationship between low levels of both LDL-C and systolic blood pressure (SBP) and coronary plaque progression.

Methods

Patients with established CAD who underwent serial intravascular ultrasound (IVUS) examination in 7 clinical trials were included for analysis (Table 1) (4,11-16). Each study was approved by the institutional review boards of the participating clinical trial sites, and all participants in the trials provided informed written consent before enrollment. Follow-up IVUS examination was performed between 18 and 24 months.

The methods for acquisition and analysis of IVUS images have been described previously (4,11-16). Lumen and external elastic membrane volumes, normalized total atheroma volume (TAV), and percent atheroma volume (PAV) in the target segment were calculated in each patient at baseline and at follow-up. Substantial plaque progression

and regression were pre-specified as a >5% relative increase or decrease in PAV.

Statistical analysis. Continuous variables are expressed as mean ± SD and categorical variables as percentage. Patients were stratified into 4 subgroups based on average on-treatment SBP > or <120 mm Hg and average on-treatment LDL-C level > or <70 mg/dl. Groups were compared with respect to clinical characteristics, medication use, and atherosclerotic plaque burden at baseline and during follow-up with use of the chi-square statistic. Comparisons between least squared mean ± SEM changes in PAV and TAV were performed with the use of a random effects mixed model with baseline plaque burden as a covariate and with trial as a random factor to control for any heterogeneity across the 7 studies. A test for trend across the 4 groups also was performed. Potential confounding factors such as baseline atheroma burden, age, diabetes, previous myocardial infarction, baseline LDL-C, and baseline SBP were controlled. Statistical analyses were performed with SAS version 8.2 (SAS Institute, Cary, North Carolina). A value of p < 0.05 was considered significant.

Abbreviations and Acronyms

- BP** = blood pressure
- CAD** = coronary artery disease
- CI** = confidence interval
- IVUS** = intravascular ultrasound
- JNC-7** = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
- LDL-C** = low-density lipoprotein cholesterol
- NCEP** = National Cholesterol Education Panel
- PAV** = percent atheroma volume
- SBP** = systolic blood pressure
- TAV** = total atheroma volume

Table 1 Drug Regimens Used in Each Constituent Trial

Trial	n	Study Group(s)
REVERSAL (11)	502	1. Atorvastatin 2. Pravastatin
CAMELOT (12)	249	1. Enalapril 2. Amlodipine 3. Placebo
ACTIVATE (13)	408	1. Pactimibe 2. Placebo
ASTEROID (4)	349	Rosuvastatin
ILLUSTRATE (14)	897	1. Atorvastatin + torcetrapib 2. Atorvastatin + placebo
PERISCOPE (15)	360	1. Pioglitazone 2. Glimepiride
STRADIVARIUS (16)	672	1. Rimonabant 2. Placebo

ACTIVATE = ACAT Intravascular Atherosclerosis Treatment Evaluation; ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; CAMELOT = Comparison of Amlodipine vs 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 = Reversing Atherosclerosis with Aggressive Lipid Lowering; STRADIVARIUS = Strategy To Reduce Atherosclerosis Development Involving Administration of Rimonabant—the Intravascular Ultrasound Study.

Results

Patient characteristics. Clinical characteristics and baseline atheroma burden are summarized in Table 2. Patients were predominantly male (70.6%) with a high prevalence of hypertension (79.2%), hyperlipidemia (75.4%), and diabetes (31.3%). Aspirin use was similar across groups at baseline; however, there were differences in statin, beta-blocker, angiotensin-converting enzyme inhibitor, and calcium-channel blocker use across groups. Baseline atheroma volume was greatest in patients with poor risk factor control.

Degree of risk factor control with treatment. Clinical characteristics during follow-up are summarized in Table 3. Mean LDL-C in groups III and IV was <100 mg/dl, in accordance with current NCEP guidelines. In contrast, mean LDL-C in groups I and II was significantly lower, approaching 55 mg/dl. Mean blood pressures in groups II and IV were 135/77 and 134/78 mg/dl, respectively, falling into the “pre-hypertension” category of the JNC-7 guidelines. However, mean blood pressures in groups I and III were 113/70 and 114/71 mg/dl, respectively, within the normal range.

Table 2 Baseline Clinical Characteristics

	Group I (n = 263)	Group II (n = 688)	Group III (n = 622)	Group IV (n = 1,864)	p Value
	SBP ≤120 mm Hg LDL-C ≤70 mg/dl	SBP >120 mm Hg LDL-C ≤70 mg/dl	SBP ≤120 mm Hg LDL-C >70 mg/dl	SBP >120 mm Hg LDL-C >70 mg/dl	
Age (yrs)	56 ± 9	61 ± 9	54 ± 9	58 ± 9	<0.01
Caucasian	94.7%	93.6%	92.3%	90.9%	0.04
Male sex	75.3%	71.8%	71.9%	69.2%	0.13
Hyperlipidemia	65.4%	67.2%	75.7%	79.7%	<0.01
Hypertension	74.9%	85.8%	62.4%	83.0%	<0.01
Previous percutaneous coronary intervention	48.5%	44.4%	42.8%	44.2%	0.57
Previous myocardial infarction	38.4%	27.2%	37.0%	27.4%	<0.01
Previous coronary bypass surgery	2.0%	3.9%	2.7%	3.2%	0.50
Diabetes mellitus	27.4%	31.5%	23.8%	34.3%	<0.01
Current tobacco use	21.1%	15.4%	26.8%	21.8%	<0.01
Statin use	75.3%	67.7%	81.8%	76.5%	<0.01
Beta-blocker use	81.4%	75.6%	73.5%	73.0%	0.02
ACE inhibitor use	55.9%	48.4%	44.4%	50.1%	0.01
Calcium-channel blocker use	35.0%	36.8%	24.1%	34.0%	<0.01
Aspirin use	95.8%	93.9%	94.4%	92.4%	0.09
Systolic BP (mm Hg)	116 ± 13	131 ± 16	117 ± 13	131 ± 16	<0.01
Diastolic BP (mm Hg)	71 ± 9	76 ± 9	72 ± 8	77 ± 9	<0.01
LDL-C (mg/dl)	88 ± 35	92 ± 37	105 ± 35	109 ± 36	<0.01
High-density lipoprotein cholesterol (mg/dl)	42 ± 11	42 ± 12	43 ± 12	43 ± 12	0.35
Baseline TAV (mm ³)	183.0 ± 82.2	189.3 ± 76.6	182.4 ± 82.1	195.7 ± 85.4	0.01
Baseline PAV (mm ³)	37.5 ± 8.6	38.6 ± 9.1	37.3 ± 9.1	39.1 ± 9.1	<0.01
From REVERSAL	9.5%	15.3%	12.5%	15.8%	<0.01
From CAMELOT	1.5%	2.3%	11.9%	8.3%	<0.01
From ACTIVATE	8.0%	6.2%	10.4%	15.0%	<0.01
From ASTEROID	22.4%	22.4%	6.1%	5.3%	<0.01
From ILLUSTRATE	38.0%	28.6%	34.1%	20.8%	<0.01
From PERISCOPE	7.2%	7.0%	9.3%	12.6%	<0.01
From STRADIVARIUS	13.3%	18.2%	15.6%	22.3%	<0.01

ACE = angiotensin-converting enzyme; BP = blood pressure; LDL-C = low-density lipoprotein cholesterol; PAV = percent atheroma volume; SBP = systolic blood pressure; TAV = total atheroma volume; other abbreviations as in Table 1.

Effect on atheroma progression. Serial changes in atheroma burden are illustrated in Figure 1. Lower levels of LDL-C and SBP were associated with less progression of PAV and TAV (p < 0.001 for trend), less frequent substantial atheroma progression (p < 0.001 for trend), and more frequent substantial atheroma regression (p = 0.01 for

trend). In patients with SBP >120 mm Hg, very low LDL-C (≤70 mg/dl) was associated with less progression in PAV (+0.30%, 95% confidence interval [CI]: -0.17% to 0.77% vs. +0.61%, 95% CI: 0.17% to 1.05%, p = 0.01) and TAV (-3.9 mm³, 95% CI: -7.24 to -0.63 mm³ vs. -1.2 mm³, 95% CI: -4.31 to 1.92 mm³, p = 0.001). In patients with

Table 3 On-Treatment Clinical Characteristics

	Group I	Group II	Group III	Group IV	p Value
	SBP ≤120 mm Hg LDL-C ≤70 mg/dl	SBP >120 mm Hg LDL-C ≤70 mg/dl	SBP ≤120 mm Hg LDL-C >70 mg/dl	SBP >120 mm Hg LDL-C >70 mg/dl	
Systolic BP (mm Hg)	113 ± 6	135 ± 11	114 ± 5	134 ± 11	<0.01
Diastolic BP (mm Hg)	70 ± 7	77 ± 7	71 ± 5	78 ± 7	<0.01
LDL-C (mg/dl)	57 ± 9	57 ± 10	95 ± 19	99 ± 23	<0.01
High-density lipoprotein cholesterol (mg/dl)	51 ± 18	50 ± 18	47 ± 14	47 ± 15	<0.01
Statin use	98.9%	97.7%	94.5%	93.0%	<0.01
Beta-blocker use	81.7%	78.1%	75.6%	75.3%	0.08
ACE inhibitor use	61.2%	53.6%	51.1%	56.1%	0.02
Calcium-channel blocker use	33.5%	43.0%	26.7%	41.1%	<0.01
Aspirin use	95.8%	93.9%	95.2%	93.9%	0.42

Abbreviations as in Table 2.

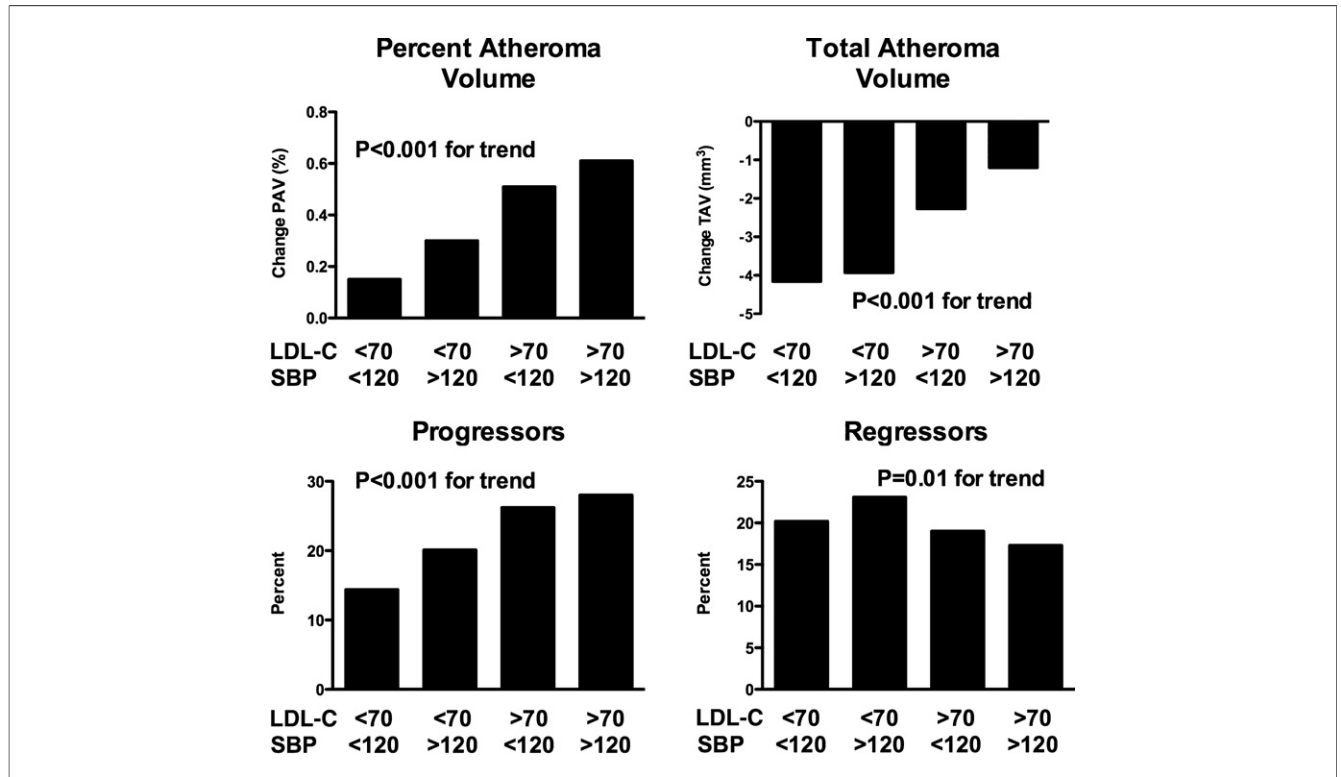


Figure 1 Serial Changes in Atheroma Burden

Change in percent atheroma volume (PAV) and total atheroma volume (TAV) and percentage of subjects undergoing substantial atheroma progression and regression, stratified according to on-treatment low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP).

normal SBP (≤ 120 mm Hg), very low LDL-C was associated with less progression in PAV (0.15%, 95% CI: -0.38% to 0.67% vs. 0.51% , 95% CI: 0.04% to 0.99% , $p = 0.05$), and no significant reduction in TAV (-2.3 mm³, 95% CI: -5.6 to 1.05 mm³ vs. -4.2 mm³, 95% CI: -7.83 to -0.49 mm³, $p = 0.141$). In the setting of LDL-C >70 mg/dl, normal SBP was associated with no greater reduction in PAV ($+0.51\%$, 95% CI: 0.04% to 0.99% vs. $+0.61\%$, 95% CI: 0.17% to 1.05% , $p = 0.159$) or in TAV (-1.2 mm³, 95% CI: -4.31 to 1.92 mm³

vs. -2.3 mm³, 95% CI: -5.59 to 1.05 mm³, $p = 0.617$), suggesting that lower levels of LDL-C had a greater impact on progression of CAD than SBP.

Serial changes in lumen and external elastic membrane volumes are illustrated in Figure 2. No change in lumen volume was observed, whereas lower levels of LDL-C and SBP were associated with a reduction in external elastic membrane volume ($p = 0.03$ for trend), suggestive of negative remodeling.

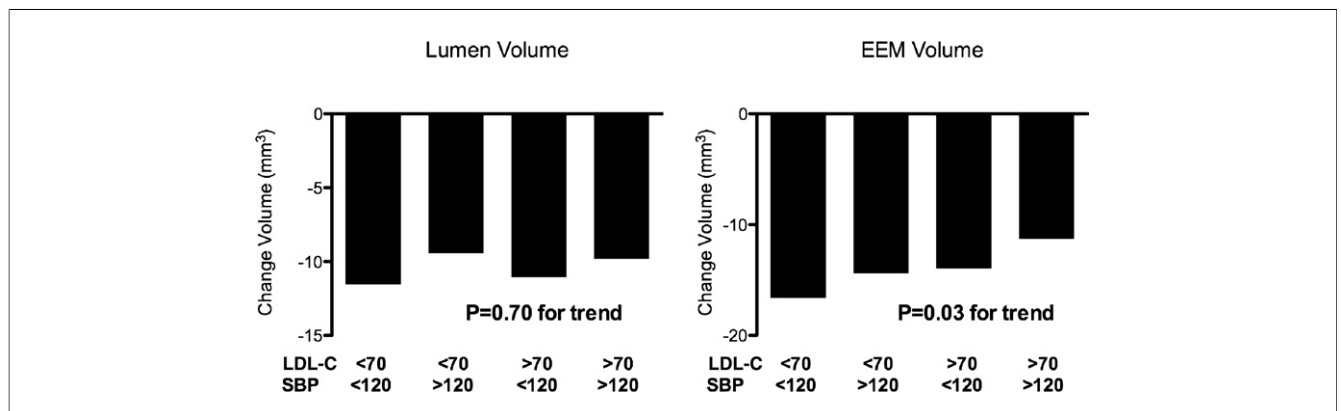


Figure 2 Serial Changes in Vessel Wall Volumes

Change in lumen and external elastic membrane (EEM) volumes, stratified according to on-treatment LDL-C and SBP. Abbreviations as in Figure 1.

Discussion

Increasing evidence suggests that intensive risk factor management beyond that currently proposed by guidelines has a beneficial impact in patients at risk for cardiovascular events. The current analysis demonstrated the slowest CAD progression in subjects with the lowest levels of both LDL-C and SBP. These results suggest the need to achieve optimal management of global risk in patients with established CAD.

Early studies demonstrated that lowering LDL-C slows the rate of progression of CAD on serial coronary angiography (17). Precise quantification of atheroma volume using IVUS has demonstrated that intensive lowering of LDL-C can halt progression of CAD (11) or even promote atherosclerotic regression (4). These observations complement studies demonstrating a reduction in cardiovascular events with LDL-C-lowering therapy and suggest a potential mechanism underlying this benefit. However, despite the compelling evidence regarding the benefits of lowering LDL-C, the optimal LDL-C goal for high-risk patients remains unclear.

Hypertension is highly prevalent in patients with CAD, and increasing evidence has challenged the concept that BP need only be treated when $>140/90$ mm Hg. Clinical events and plaque progression are reduced when BP is within the normal range. Pre-hypertension confers a 2-fold increase in event rates compared with normal BP (18), emphasizing the heightened cardiovascular risk in patients with even mild BP elevations. Despite these observations, the JNC-7 guidelines do not recommend initiation of BP lowering agents in pre-hypertensive patients with CAD.

Despite the evidence demonstrating the cardiovascular benefits of LDL-C and BP lowering, patients are suboptimally treated. Antihypertensive medication is prescribed in only 25% to 50% of cases of hypertension in North America and Europe (19), and global rates of hypertension control to $<140/90$ mm Hg range from only 5.4% in Korea to 58% in Barbados (20). The management of LDL-C remains suboptimal even in patients at high cardiovascular risk, with only 40% to 50% of patients achieving LDL-C targets in the U.S. (21) and Europe (22).

Interestingly, the current findings suggest that very low LDL-C levels are associated with less atheroma progression than normal SBP, supporting the evidence that intensively lowering LDL-C has a beneficial impact on plaque progression and clinical events in randomized controlled trials. In fact, LDL-C may be a stronger promoter of plaque progression than elevated SBP. Accordingly, very low LDL-C may have a more rapid or profound impact than normal SBP on attenuation of atheroma progression by slowing accumulation of lipid in the arterial wall.

The incremental effect of low SBP is less well understood. Although normal SBP alone was not associated with attenuated atheroma progression, fewer patients with normal SBP and very low LDL-C in combination (group I)

demonstrated substantial plaque progression. Importantly, mean SBP in groups II and IV and LDL-C in groups III and IV was in accordance with the current JNC-7 and NCEP guidelines. However, patients in group I demonstrated the greatest attenuation in coronary plaque progression. This trend was observed in all IVUS measurements evaluated in this study. Furthermore, correction for baseline SBP and LDL-C in our model had no impact on these findings. These data support the notion that global risk factor modification can slow the progression of CAD even when these risk factors are near the normal range.

Alternatively, the stronger association between very low LDL-C and attenuated atheroma progression may reflect the constituent clinical trials in the pooled analysis. The inclusion of 5 studies of lipid lowering and only 1 trial of blood pressure lowering in a small cohort may have contributed to the findings. The relative difference in LDL-C between groups was approximately 40%, with the difference in SBP only 15%. Therefore, a large clinical trial of antihypertensive therapy in patients with CAD may better define the impact of low levels of SBP on plaque progression.

This study is the first to demonstrate that normal BP and very low LDL-C in combination is associated with attenuated progression of CAD in humans. A small study reported that simvastatin, but not enalapril, had a beneficial effect on CAD in humans; however, the degree of BP and LDL-C control in that study were not optimal by current standards (23). Furthermore, the previous study assessed plaque progression by the use of coronary angiography rather than IVUS and, therefore, did not evaluate the impact of therapy on the full extent of disease.

The authors of SANDS (Stop Atherosclerosis in Native Diabetics Study) recently evaluated an aggressive strategy of BP and cholesterol management, reporting improvements in carotid intimal medial thickness and cross-sectional area with aggressive risk factor management (24); however, post hoc analysis suggested that this improvement was more closely correlated with cholesterol lowering than BP lowering. Our findings are complementary, suggesting that very low LDL-C and normal SBP impact coronary as well as carotid atherosclerosis, and that the impact of very low LDL-C may be greater than that of normal SBP.

Although these data reflect the relationship among LDL-C, SBP, and coronary atheroma progression, the resultant impact on clinical events remains to be determined. This analysis represents an observational study that used pooled data from clinical trials and makes no inferences about the use of specific strategies to lower BP or LDL-C. Furthermore, the number of patients achieving very low LDL-C and normal SBP in combination was relatively small and some of the group-to-group comparisons failed to reach statistical significance. Therefore, these findings should be more rigorously tested in the setting of a randomized clinical trial. The effects of risk factors outside of SBP and LDL-C, including glycemic control, tobacco use, and obesity, were not evaluated in this study. Patients who

achieved normal SBP and very low LDL-C in this study may have been more compliant with medical therapy or with healthy lifestyle modifications. Nevertheless, the results of this analysis suggest that a global risk factor modification strategy may optimize outcomes in patients with established CAD.

In this study, the greatest attenuation of coronary plaque progression was observed in patients with very low LDL-C and normal SBP in combination. Importantly, these data demonstrate that intensive BP and cholesterol control are associated with attenuation of plaque progression even when these values are near the normal range. These findings provide important mechanistic information about the effects of LDL-C and SBP on cardiovascular disease and support the need for intensive management of global risk in patients with CAD. A randomized controlled trial to directly test the clinical benefit obtained via intensive management of multiple risk factors would provide further support for this concept.

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