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Progression of coronary atherosclerosis in stable patients with ultrasonic features of high-risk plaques

Yu Kataoka[1]*, Kathy Wolski[2], Craig Balog[2], Kiyoko Uno[3], Rishi Puri[3], E. Murat Tuzcu[3], Steven E. Nissen[3], and Stephen J. Nicholls[1]

[1]South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia; [2]C5 Research, Cleveland Clinic, Cleveland, OH, USA; and [3]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH, USA

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Aim Large plaque burden, expansive vascular remodelling, and spotty calcification have been considered as important morphologies of high-risk plaques causing acute coronary events. Although non-occlusive rupture of high-risk plaques has been proposed as a mechanism for disease progression in post-mortem studies, the natural history of coronary atherosclerosis in stable patients with high-risk plaques has not been fully elucidated. We sought to evaluate coronary atheroma progression in stable patients with greyscale intravascular ultrasound (IVUS)-derived high-risk plaques.

Methods and results We analysed 4477 patients with stable coronary artery disease underwent serial greyscale IVUS imaging in eight clinical trials. We compared volumetric intravascular ultrasound (IVUS) data in the non-culprit segments between patients with and without high-risk plaques, defined as the combination of per cent atheroma volume (PAV) >63%, positive remodelling and spotty calcification. High-risk plaques were observed in 201 (4.5%) of patients. Patients with high-risk plaques exhibited a greater PAV (47.1 ± 8.4 vs. 37.7 ± 8.7%, $P < 0.001$) at baseline. On serial evaluation, however, regression of PAV (−0.26 ± 0.39 vs. 0.24 ± 0.32%, $P = 0.03$) was observed. In patients with high-risk plaques, the non-statin use was associated with the accelerated atheroma progression, whereas atheroma regression was observed under statin therapy (change in PAV: 1.87 ± 0.68% vs. −0.83 ± 0.53%, $P = 0.01$).

Conclusions Patients with high-risk plaques exhibit extensive atheroma burden, which is modifiable with anti-atherosclerotic therapies. These findings underscore risk modification using a statin in patients with high-risk plaques.

Keywords Intravascular ultrasound • Statin • Plaque progression • Coronary • Atherosclerosis

Introduction

Coronary artery disease (CAD) is highly prevalent in Western countries.[1] In particular, acute coronary syndrome (ACS) and sudden cardiac death are responsible for much of the mortality and morbidity occurring due to CAD.[2] Atherosclerotic plaque that results in acute coronary events has been considered as a high-risk plaque[3,4] and consequently there has been considerable effort to identify its features as they represent an important target for the prevention of future coronary events.

Autopsy studies have demonstrated the culprit lesions in victims of sudden cardiac death to harbour a large lipid core, macrophage infiltrate, and necrotic material, covered by a thin fibrous cap and associated with expansive arterial remodelling, neovascularity, and spotty calcification.[5–7] While these features have been reported to associate with plaque instability leading to plaque rupture,[5–8] non-occlusive silent plaque rupture has been demonstrated as a mechanism associated with disease progression in a post-mortem study.[9] These observations may indicate the potential relationship between high-risk plaques containing morphological features related to plaque instability and atheroma progression. However, high-risk plaques have been evaluated only after the occurrence of acute coronary events in these studies, and it remains to be determined how disease substrate behaves in stable patients with high-risk plaques.

* Corresponding author. Tel: +61 881164426, Email: jimmyk67@yahoo.co.jp

In addition, while identification of such lesions has been proposed to mandate more aggressive therapy, the disease response in this setting has not been studied.

Greyscale IVUS permits precise quantitation of plaque volume and has been employed in clinical trials that evaluate anti-atherosclerotic therapies.[10–20] IVUS has also enhanced our understanding of the factors that influence the atheroma progression and its response to the use of medical therapies such as statin.[11–20] IVUS does not directly discriminate individual plaque components, whereas it does illustrate features that are consistent with high-risk plaques, including a large plaque burden, positive remodelling, and spotty calcification. These ultrasonographic features have been already identified in culprit lesions in patients with ACS.[21–23] Accordingly, the objective of the current study was to investigate atheroma progression in stable patients with high-risk plaques and determine the impact of anti-atherosclerotic medical therapies on plaque progression.

Methods

Study population

We analysed 4477 stable patients with angiographic CAD from eight clinical trials that evaluated the effect of medical therapies on the progression of coronary atherosclerosis using serial IVUS imaging.[11–18] All the patients were required to have at least one 20% stenosis in a major epicardial coronary artery on a clinically indicated coronary angiogram. The target vessel for IVUS interrogation 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 infraction. All imaging analysis was performed in the same core laboratory. Each study was approved by the institutional review board of the participating clinical trial sites, and all the participants are provided informed written consent before enrolment.

Acquisition and analysis of IVUS images

The methods for acquisition and analysis of IVUS images have been previously described.[11–20] In brief, after anticoagulation therapy and administration of intracoronary nitroglycerine, an IVUS catheter (30–40 MHz) was inserted distally within the coronary artery. IVUS images were continuously recorded during the withdrawal of the catheter at a constant rate of 0.5 mm/s. Images were digitized, and analysis of each segment was selected by using proximal and distal side branches as reference points to enable subsequent analysis of the same segment at follow-up. Imaging was performed within the same coronary artery at baseline and at the end of the study, which ranged from 18 to 24 months. 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. The plaque area was defined as the area occupied between these leading edges. The total atheroma volume (TAV) was calculated as the summation of the plaque area in each measured image, normalized to account for differences in segment length between different subjects:

$$\mathrm{TAV}_{\mathrm{normalized}}(\mathrm{mm}^3) = \left[\frac{\Sigma(\mathrm{EEM}_{\mathrm{area}} - \mathrm{LUMEN}_{\mathrm{area}})}{\text{Number of slices in pullback}}\right] \times \text{Median number of slices in study population.}$$

The per cent atheroma volume (PAV) was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque

$$\mathrm{PAV}(\%) = \left[\frac{\Sigma(\mathrm{EEM}_{\mathrm{area}} - \mathrm{LUMEN}_{\mathrm{area}})}{\Sigma\,\mathrm{EEM}_{\mathrm{area}}}\right] \times 100$$

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.

High-risk plaque identification

Based on previous observations of greyscale IVUS, high-risk plaques were defined as a focal lesion containing spotty calcification, with the associated lesion plaque area >63% and positive remodelling.[21–24] Spotty calcification was defined as one to four consecutive images containing calcification with an arc of shadowing <90°. The remodelling index was calculated as the ratio of the EEM area at the most diseased site showing the largest plaque area compared with the EEM area at the least diseased site, within the proximal 10 mm that contained the lowest plaque area. Positive remodelling was defined as an index >1.05. We compared clinical characteristics and atheroma burden of entire imaged segments in patients with and without high-risk plaques.

Statistical analysis

Continuous variables were expressed as means ± SD if normally distributed (or median and inter-quartile range if not normally distributed) and categorical variables as percentage. Clinical characteristics, medication use, and atherosclerotic plaque burden at baseline and during the follow-up were compared by using two-sample *t* tests for normally distributed continuous variables and Wilcoxon rank-sum tests for non-normally distributed continuous variables, and χ^2 tests for categorical variables. Serial changes in plaque burden (expressed as least squared means ± SEM) were assessed with a random effect mixed model adjusting for baseline plaque burden, with trial set as a random factor to control for heterogeneity across the eight studies. A two-sided probability value of <0.05 was considered statistically significant. All statistical analyses were performed using the SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Baseline clinical characteristics

High-risk plaques were observed in 201 (4.5%) of patients. Baseline clinical characteristics of patients with and without high-risk plaques are summarized in *Table 1*. Patients with high-risk plaques were more likely to be male (82.1 vs. 71.0%, $P = 0.001$), and have diabetes (43.8 vs. 28.3%, $P < 0.001$) and receive a beta-blocker at baseline (83.1 vs. 73.6%, $P = 0.003$). Patients with high-risk plaques were also more likely to have a lower body mass index (30.2 ± 5.1 vs. 30.9 ± 5.9, $P = 0.09$), a history of hypertension (82.1 vs. 77.1%, $P = 0.09$), dyslipidaemia (78.6 vs. 72.6%, $P = 0.06$), percutaneous coronary intervention (45.0 vs. 38.7%, $P = 0.08$), and myocardial infarction (36.8 vs. 28.3%, $P = 0.009$) although these failed to meet statistical significance. Patients with high-risk plaques demonstrated lower levels of high-density lipoprotein cholesterol (HDL-C: 1.0 ± 0.2 vs. 1.1 ± 0.3 mmol/L, $P = 0.005$) and higher levels of triglyceride (1.7 vs. 1.6 mmol/L, $P = 0.006$) and fasting glucose (6.8 ± 3.3 vs. 6.1 ± 2.1 mmol/L, $P = 0.002$).

Of patients with high-risk plaques, 22 (10.9%) had evidence of multiple plaques at baseline. There were no significant differences

Table 1 Baseline clinical characteristics

	Patients without high-risk plaques ($n = 4276$)	Patients with high-risk plaque ($n = 201$)	*P*-value
Age (years)	57.8 ± 9.2	57.4 ± 9.3	0.59
Caucasian (%)	93.0	90.5	0.18
Male (%)	71.0	82.1	0.001
BMI (kg/m^2)	30.9 ± 5.9	30.2 ± 5.1	0.09
Hypertension (%)	77.1	82.1	0.09
Hyperlipidaemia (%)	72.6	78.6	0.06
Diabetes (%)	28.3	43.8	<0.001
Previous percutaneous coronary intervention (%)	38.7	45.0	0.08
Previous myocardial infarction (%)	28.3	36.8	0.009
Current tobacco use (%)	24.1	25.7	0.63
Baseline medications (%)			
Statin use	72.2	78.1	0.07
Beta-blocker use	73.6	83.1	0.003
Aspirin use	93.0	94.0	0.57
ACE inhibitor use	48.9	52.7	0.29
Calcium-channel blocker use	33.3	33.8	0.87
Baseline parameters			
LDL-cholesterol (mmol/L)	2.8 ± 0.9	2.8 ± 0.9	0.85
HDL-cholesterol (mmol/L)	1.1 ± 0.3	1.0 ± 0.2	0.005
Triglyceride (mmol/L)[a]	1.6 (1.1, 2.2)	1.7 (1.3, 2.4)	0.006
CRP (mg/L)[a]	2.3 (1.1, 5.2)	2.5 (1.0, 5.3)	0.67
Fasting glucose (mmol/L)	6.1 ± 2.1	6.8 ± 3.3	0.002
Systolic blood pressure (mmHg)	128.2 ± 16.9	126.3 ± 17.1	0.10
Diastolic blood pressure (mmHg)	76.1 ± 9.8	75.5 ± 9.6	0.41

ACE, angiotensin-converting enzyme; BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Median (inter-quartile range).

between patients with one and multiple high-risk plaques (data not shown).

Volumetric IVUS findings in entire imaged segments with and without high-risk plaques at baseline are summarized in *Table 2*. Patients with high-risk plaques had a greater PAV (47.1 ± 8.4 vs. 37.7 ± 8.7%, $P < 0.001$) and TAV (219.6 ± 84.3 vs. 187.8 ± 81.8 mm^3, $P < 0.001$), in association with a larger EEM (492.8 ± 170.2 vs. 464.1 ± 151.0 mm^3, $P = 0.04$) and a smaller lumen volume (244.5 ± 87.2 vs. 305.0 ± 110.2 mm^3, $P < 0.001$) throughout the length of imaged vessel. These patients demonstrated more diffuse disease, as evidenced by greater percentage of images containing plaque (83.6 vs. 72.1%, $P < 0.001$). A higher remodelling index (1.1 ± 0.2 vs. 0.9 ± 0.2, $P < 0.001$) and greater percentage of images containing calcium (33.6 vs. 28.6%, $P < 0.001$) were also observed. The length of analysed segment was comparable between patients with and without high-risk plaques (37.2 ± 15.3 vs. 35.7 ± 15.1 mm, $P = 0.10$).

Medical therapies and risk factor control

Medication use and degree of risk factor control at follow-up are summarized in *Table 3*. Over 90% of both patients with and without high-risk plaques were treated with statin during the course of the study (90.5 vs. 90.8%, $P = 0.84$); 12.4 and 18.6% of each group's patients commenced a statin during the follow-up ($P = 0.07$). While patients with high-risk plaques were more likely to receive a beta-blocker therapy (84.6 vs. 75.4%, $P = 0.003$), the use of aspirin, ACE inhibitor and calcium-channel blocker was comparable between two groups. At follow-up, on-treatment level of LDL-C, CRP, and systolic blood pressure in both groups was controlled <2.6 mmol/L, 2.0 mg/L, and 130 mmHg, respectively. In patients with high-risk plaques, a lower level of on-treatment HDL-C (1.2 ± 0.3 vs. 1.3 ± 0.4 mmol/L, $P = 0.008$) and a higher level of on-treatment triglyceride (1.5 vs. 1.4 mmol/L, $P = 0.04$) were observed.

Atheroma progression in patients with high-risk plaques

Serial changes in measures of atheroma burden within the entire imaged vessel are illustrated in *Table 4*. Under the frequent use of anti-atherosclerotic medical therapies (90.6% statin, 93.9% aspirin, 80.0% beta-blocker, and 54.9% ACE inhibitor) and the presence of controlled multiple risk factors in both groups, patients with high-risk plaques exhibited less atheroma progression of PAV (−0.26 ± 0.39 vs. 0.24 ± 0.32%, $P = 0.03$) and TAV (−8.25 ± 2.48 vs. −3.90 ± 2.05 mm^3, $P = 0.003$). There were no significant differences with

Table 2 Baseline atheroma burden

	Patients without high-risk plaques ($n = 4276$)	Patients with high-risk plaques ($n = 201$)	*P*-value
Baseline PAV (%)	37.7 ± 8.7	47.1 ± 8.4	<0.001
Baseline TAV (mm^3)	187.8 ± 81.8	219.6 ± 84.3	<0.001
EEM (mm^3)	464.1 ± 151.0	492.8 ± 170.2	0.04
Lumen (mm^3)	305.0 ± 110.2	244.5 ± 87.2	<0.001
Percentage of images containing plaque (%)	72.1 ± 27.8	83.6 ± 20.7	<0.001
Remodelling index	0.9 ± 0.2	1.1 ± 0.2	<0.001
Percentage of images containing calcium (%)	28.6 ± 23.9	33.6 ± 21.2	<0.001
Length of analysed vessel (mm)	35.7 ± 15.1	37.2 ± 15.3	0.10

EEM, external elastic membrane; PAV, per cent atheroma volume; TAV, total atheroma volume.

Table 3 On-treatment risk control

	Patients without high-risk plaques ($n = 4276$)	Patients with high-risk plaques ($n = 201$)	*P*-value
Statin (%)	90.8	90.5	0.84
Aspirin (%)	93.8	94.0	0.89
Beta-blocker (%)	75.4	84.6	0.003
ACE inhibitor (%)	54.2	55.7	0.68
Calcium channel blocker (%)	38.5	43.3	0.18
LDL-cholesterol (mmol/L)	2.1 ± 0.7	2.2 ± 0.7	0.22
HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	0.008
Triglyceride (mmol/L)[a]	1.4 (1.1, 1.9)	1.5 (1.1, 2.2)	0.04
CRP (mg/L)[a]	1.6 (0.7, 3.8)	1.7 (0.7, 4.2)	0.62
Fasting glucose (mmol/L)	6.4 ± 2.3	6.8 ± 2.7	0.05
Systolic blood pressure (mmHg)	129.4 ± 14.1	129.4 ± 15.7	0.94
Diastolic blood pressure (mmHg)	76.5 ± 8.1	76.3 ± 7.8	0.75

ACE, angiotensin-converting enzyme; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Median (inter-quartile range).

regard to changes in EEM (−14.56 ± 3.74 vs. −12.43 ± 2.38 mm^3, $P = 0.49$) and lumen volume (−7.52 ± 2.85 vs. −8.52 ± 1.74 mm^3, $P = 0.67$). The remodelling index at follow-up was greater in patients with high-risk plaques (1.0 ± 0.1 vs. 0.9 ± 0.1, $P < 0.001$). This is consistent with the finding that patients with high-risk plaques were more likely to show expansive remodelling (64.3 vs. 23.6%, $P = 0.01$). In addition, a significant correlation was observed between the change in PAV at the focal site of high-risk plaque and throughout the entire arterial segment evaluated ($r = 0.39$, $P < 0.0001$). Newly developed high-risk plaques were observed at follow-up in 4 (2.0) and 113 (2.6%) of patients with and without high-risk plaques at baseline, respectively ($P = 0.62$).

Statin therapy and atheroma progression in patients with high-risk plaques

In the current analysis, the impact of statin therapy on atheroma progression was investigated (*Figure 1*). The use of a statin was associated with slower disease progression in both patients with (change in PAV: −0.83 ± 0.53 vs. 1.87 ± 0.68%, $P = 0.01$) and without high-risk plaques (change in PAV: 0.20 ± 0.31% vs. 1.13 ± 0.37%, $P = 0.001$). In particular, high-risk plaque patients without a statin therapy exhibited an accelerated progression of PAV. In contrast, the greatest regression of PAV was observed in patients with high-risk plaques receiving a statin (change in PAV: high-risk plaque patients with a statin vs. non- high-risk plaque patients with and without a statin, $P = 0.001$ and $P < 0.001$, respectively).

Clinical outcome during 2-year follow-up

During a 2-year observational period, two patients with a high-risk plaque developed myocardial infarction, whereas 61 and 3 patients without high-risk plaque developed myocardial infarction and death, respectively. There were no significant differences in the occurrence of myocardial infarction (1.0 vs. 1.4%, $P = 1.00$) and death (0.0 vs. 0.1%, $P = 1.00$) between patients with and without high-risk plaque.

Table 4 Serial change in atheroma burden and vessel remodelling

	Patients without high-risk plaques ($n = 4276$)	Patients with high-risk plaques ($n = 201$)	*P*-value
PAV (%)	0.24 ± 0.32	−0.26 ± 0.39	0.03
Adjusted PAV (%)[a]	0.23 ± 0.33	−0.30 ± 0.39	0.02
TAV (mm^3)	−3.90 ± 2.05	−8.25 ± 2.48	0.003
Adjusted TAV (mm^3)[a]	−3.98 ± 2.02	−8.52 ± 2.47	0.002
Lumen volume (mm^3)	−8.52 ± 1.74	−7.52 ± 2.85	0.67
EEM volume (mm^3)	−12.43 ± 2.38	−14.56 ± 3.74	0.49
Remodelling ratio at follow-up	0.9 ± 0.1	1.0 ± 0.1	<0.001
Constrictive remodelling (%)	50.8	18.9	
No remodelling (%)	25.6	16.8	
Positive remodelling (%)	23.6	64.3	

[a]Adjusted for differences in clinical characteristics and baseline atheroma burden.

Discussion

In the current study, we characterized a burden and progression of a atherosclerotic plaque throughout a length of the coronary artery in patients with and without evidence of high-risk plaques. Under a frequent use of anti-atherosclerotic medical therapies, patients with high-risk plaques harboured less atheroma progression despite the presence of more extensive disease at baseline. Additionally, statin use attenuated atheroma progression in these patients. Our findings emphasize the modifiability of disease in patients with high-risk plaques through using anti-atherosclerotic medical therapies including statins.

Histopathological studies have elucidated the culprit plaque morphology causing plaque rupture that leads to ACS and sudden coronary death.[5–7] The importance of plaque instability in these studies has stimulated efforts to develop imaging modalities for risk prediction and the efficacious therapeutic strategies for the prevention of future ischaemic events. While a range of imaging modalities have been developed to characterize plaque composition,[25–32] some of these techniques still require ongoing development and validation study. Greyscale IVUS, despite its limited resolution to visualize plaque composition, enables us to illustrate a large plaque burden, positive remodelling, and spotty calcification that have been reported to associate with plaque vulnerability. Greyscale IVUS has identified these characteristics at culprit lesion in patients with ACS.[21–23] However, serial evaluation of high-risk plaques before the occurrence of acute coronary events in stable patients is limited. In addition, it remains to be fully characterized the natural history of coronary atherosclerosis in stable patients having focal high-risk plaques throughout an imaging length. In the current study, our findings suggest that in patients with stable symptoms, high-risk plaques are identified in only 4.5% which is consistent with observation of plaques analysed by multislice computed tomography in 1059 patients with stable or suspected CAD.[27] The most striking features of these patients are regression of atheroma burden during the course of study. Particularly, the presence of more extensive atherosclerotic plaque, which progress at the greatest rate unless statin therapy is applied. When medical therapies including a statin are used, they profoundly regress, emphasizing the relative modifiability of the patient with evidence of high-risk plaques.

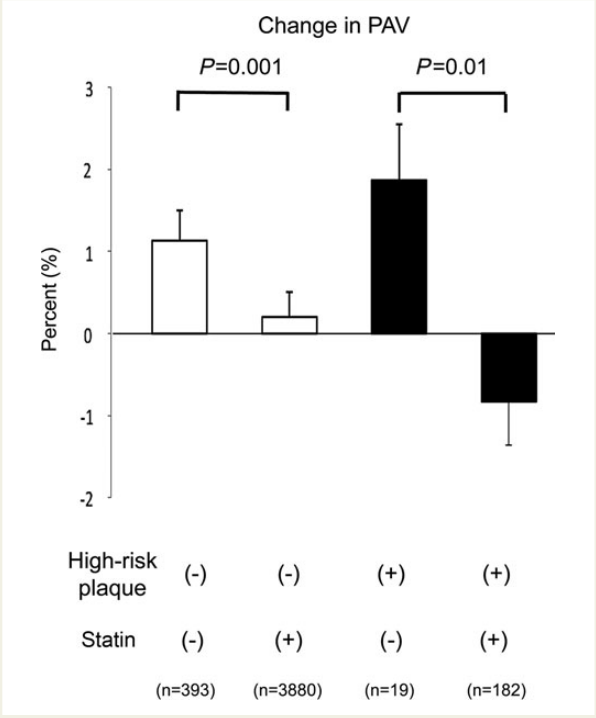

Figure 1: Statin therapy and atheroma progression. Progression of PAV, stratified according to the presence or absence of high-risk plaques and the use of statin therapy.

The current analysis provides insights into the beneficial impact of a statin therapy on atheroma progression in the presence of a high-risk plaque. Various interventional studies have demonstrated that lowering of the LDL-C level by using a statin is associated with less disease progression.[12,33–36] Another study using an intravascular angioscopy showed a favourable plaque stabilization effect of statin therapy at more vulnerable lesions reflected by yellow colour

plaques.[37] Considering that high-risk plaques pathologically contain more inflammatory materials and atherogenic lipoproteins,[8,38–40] patients with high-risk plaques would respond well to a statin therapy potentially modifying these materials and therefore, would be the important therapeutic target for the prevention of future cardiovascular events. While some have advocated that identification of a high-risk lesion on imaging may warrant the use of novel focal-based interventions, the findings of this analysis support the evidence highlighting the benefits of systemic-based medical interventions.

We did not observe any differences in the incidence of myocardial infarction and death between patients with and without high-risk plaques. In the current study, over 90% of study subjects received a statin therapy at follow-up. In addition, disease progression was significantly reduced under statin therapy in both groups. The beneficial effect of statin on coronary atherosclerosis might prevent clinical events, resulting in a very low prevalence of death and myocardial infarction. A high use of statin might also make it difficult to detect any significance in clinical events between two groups.

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 modelling statistical approaches to deal with pooling of the data. The current analysis reflects the relationship between the presence of high-risk plaques and disease progression. However, the resultant impact on clinical events remains to be fully determined. Because of the relatively small number of patients having high-risk plaques, a larger study is required to elucidate the effect of IVUS-derived high-risk plaques on clinical outcome. Given previous reports of an association between atheroma progression and adverse cardiovascular events,[41] it is possible that intensive medical intervention in patients with high-risk plaques may result in less cardiovascular morbidity. The current study does not collect the information about culprit vessels and lesions causing myocardial infarction during the follow-up. We followed up the occurrence of clinical events in the study subjects for 2 years only. Longer follow-up periods would be needed to further evaluate the association between high-risk plaques and adverse cardiovascular events.

In summary, patients with evidence of high-risk plaques harbour more extensive atherosclerotic plaque, a finding that supports reports from a number of imaging modalities. While disease progression is the greatest in these patients without a statin, they also demonstrate the greatest benefit from the use of a statin. These findings reflect that patients with high-risk plaques exhibit an extensive and progressive but modifiable form of disease.

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References

1. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997;**349**:1498–504.
2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM *et al.* American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation* 2011;**123**:e18–209.
3. Davies MJ. The pathophysiology of acute coronary syndromes. *Heart* 2000;**83**:361–6.
4. Schaar JA, Muller JE, Falk E, Virmani R, Fuster V, Serruys PW *et al.* Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, San-torini, Greece. *Eur Heart J* 2004;**25**:1077–82.
5. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;**92**:657–71.
6. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, Strauss HW. Arithmetic of vulnerable plaques for noninvasive imaging. *Nat Clin Pract Cardiovasc Med* 2008;**5**:S2–10.
7. Kolodgie FD, Burke AP, Farb A, Gold HK, Yuan J, Narula J *et al.* The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol* 2001;**16**:285–92.
8. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J* 2013;**34**:719–28.
9. Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J *et al.* Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation* 2001;**103**:934–40.
10. Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Nissen SE. Intravascular ultrasound in cardiovascular medicine. *Circulation* 2006;**114**:e55–9.
11. 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.
12. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D *et al.* CAMELOT Investigators. 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.
13. Nissen SE, Tuzcu EM, Brewer HB, Sipahi I, Nicholls SJ, Ganz P *et al.* ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) Investigators. Effect of ACAT inhibition on the progression of coronary atherosclerosis. *N Engl J Med* 2006;**354**:1253–63.
14. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM *et al.* ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;**295**:1556–65.
15. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT *et al.* ILLUSTRATE Investigators. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007;**356**:1304–16.
16. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A *et al.* PERISCOPE Investigators. 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.
17. Nissen SE, Nicholls SJ, Wolski K, Rodés-Cabau J, Cannon CP, Deanfield JE *et al.* STRADIVARIUS Investigators. 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.
18. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P *et al.* Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011;**365**:2078–87.
19. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J *et al.* 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.
20. 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.
21. Fujii K, Mintz GS, Carlier SG, Costa JD Jr, Kimura M, Sano K *et al.* Intravascular ultrasound profile analysis of ruptured coronary plaques. *Am J Cardiol* 2006;**98**:429–35.

22. 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.
23. Ehara S, Kobayashi Y, Yoshiyama M, Shimada K, Shimada Y, Fukuda D *et al.* Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. *Circulation* 2004;**110**:3424–9.
24. 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 an acute coronary syndrome. *J Am Coll Cardiol* 2000; **35**:106–11.
25. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH *et al.* The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998;**128**:262–9.
26. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000;**36**: 1253–60.
27. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T *et al.* Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009;**54**:49–57.
28. 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.
29. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH *et al.* Characterization of human atherosclerosis by optical coherence tomography. *Circulation* 2002;**106**:1640–5.
30. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N *et al.* Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. *Circulation* 2002;**105**:2708–11.
31. Ueda Y, Ogasawara N, Matsuo K, Hirotani S, Kashiwase K, Hirata A *et al.* Acute coronary syndrome: insight from angioscopy. *Circ J* 2010;**74**:411–7.
32. Madder RD, Smith JL, Dixon SR, Goldstein JA. Composition of target lesions by near-infrared spectroscopy in patients with acute coronary syndrome versus stable angina. *Circ Cardiovasc Interv* 2012;**5**:55–61.
33. Ballantyne CM. Clinical trial endpoints: angiograms, events, and plaque instability. *Am J Cardiol* 1998;**82**:5M–11M.
34. Jensen LO, Thayssen P, Pedersen KE, Stender S, Haghfelt T. Regression of coronary atherosclerosis by simvastatin: a serial intravascular ultrasound study. *Circulation* 2004;**110**:265–70.
35. 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.
36. Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S *et al.* COSMOS Investigators. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). *Circ J* 2009;**73**: 2110–7.
37. Hirayama A, Saito S, Ueda Y, Takayama T, Honye J, Komatsu S *et al.* Plaque-stabilizing effect of atorvastatin is stronger for plaques evaluated as more unstable by angioscopy and intravascular ultrasound. *Circ J* 2011;**75**:1448–54.
38. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R. Concept of vulnerable/unstable plaque. *Arterioscler Thromb Vasc Biol* 2010;**30**:1282–92.
39. Libby P. Atherosclerosis: disease biology affecting the coronary vasculature. *Am J Cardiol* 2006;**98**:3Q–9.
40. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol* 2005;**46**:937–54.
41. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A *et al.* Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 2010;**55**:2399–407.