Relation of Low-Density Lipoprotein Cholesterol Level to Plaque Rupture

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Statin therapy reduces low-density lipoprotein cholesterol (LDL-C), inflammation, and atherosclerotic cardiovascular disease. We investigated the association between LDL-C and statin therapy on the prevalence of plaque rupture (PR). Patients with acute coronary syndromes who underwent optical coherence tomography imaging of the culprit lesion were divided into 4 groups based on LDL-C level and statin use (Group 1: LDL-C ≤ 100 without statin; Group 2; LDL-C ≤ 100 with statin; Group 3: LDL-C > 100 with statin; Group 4: LDL-C > 100 without statin), and the prevalence of PR was compared between the groups. Among 896 patients, PR was diagnosed in 444 (49.6%) patients. The prevalence of PR was significantly different among the 4 groups (p = 0.007): it was highest in the high LDL-C without statin group and lowest in the low LDL-C without statin group (53.9% and 39.2%, respectively). Compared with the high LDL-C without statin group, the low LDL-C without statin and low LDL-C with statin groups had a significantly lower prevalence of PR (p = 0.001, p = 0.040, respectively), and the low LDL-C with statin group had a significantly higher prevalence of calcification (p = 0.037). The patients with naturally low LDL-C have the lowest risk of PR. The patients with low LDL-C achieved by statin therapy had a higher prevalence of calcification. When LDL-C level is elevated, early and aggressive treatment with statin may help to prevent PR by stabilizing plaques through calcification. **(Am J Cardiol 2020;134:48−54)**

A high plasma level of low-density lipoprotein cholesterol (LDL-C) is an important risk factor for atherosclerotic cardiovascular disease (ASCVD).[1] Large clinical trials have shown that statin therapy reduces both the circulating levels of LDL-C and the incidence of ASCVD.[2−4] Previous studies using intracoronary imaging have shown that statin therapy reduces the lipid content of plaques and thickens fibrous caps,[5−7] possibly preventing plaque rupture (PR) in the future. The guidelines for prevention of ASCVD recommend statin use for primary prevention.[8] However, there are few studies on the relationship between LDL-C levels and statin therapy on the incidence of PR. To evaluate the association between LDL-C levels and statin therapy on PR, we divided acute coronary syndrome (ACS) patients into 4 groups based on LDL-C levels on admission and the use of statin prior to admission, and the prevalence of PR was compared.

Methods

This study was an international collaborative effort to investigate pathobiology of ACS (NCT03479723). Patients presenting with ACS who underwent optical coherence tomography (OCT) imaging of the culprit lesion were eligible. Among 1,241 patients, those without statin data or LDL-C levels on admission (n = 345) were excluded. Ultimately, a total of 896 cases were included in the analysis. Demographic and OCT findings of the culprit lesions were evaluated. All images were coded, digitally stored, and sent to Massachusetts General Hospital (Boston, Massachusetts). The protocol was approved by the institutional review board at each site. The methods of OCT image acquisition and analysis have been previously described in detail,[9] and are summarized in the supplemental methods. The patients were divided into 4 groups based on LDL-C levels on admission and the use of statin prior to admission. Patients who had LDL-C levels ≤100 on admission were classified into the low LDL-C group, and patients who had LDL-C levels >100 on admission were classified into the high LDL-C group.[8,10] Group1 was defined as low LDL-C without statin; Group 2 as low LDL-C with statin; Group 3 as high LDL-C with statin; Group 4 as high LDL-C without statin. The definitions of coronary risk factors, including hypertension, hyperlipidemia, diabetes mellitus and chronic

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See page 53 for disclosure information.

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kidney disease (CKD) are summarized in the supplemental methods. The methods of statistical analysis are also summarized in the supplemental methods.

Results

A total of 896 patients were divided into 4 groups: Group 1: 163 (18.2%) patients, Group 2: 109 (12.2%) patients, Group 3: 119 (13.3%) patients, and Group 4: 505 (56.3%) patients. The baseline characteristics of the 4 groups are summarized in Table 1. Patients on statin were older, had higher prevalence of hypertension, hyperlipidemia, and prior myocardial infarction, and were more frequently on aspirin. Group 4 more frequently presented with ST-segment-elevation myocardial infarction (STEMI) and Group 2 frequently presented with non ST-segment−elevation acute coronary syndrome (NSTE-ACS). Among 896 patients, PR was diagnosed in 444 (49.6%) patients. Figure 1 shows that 312 (58.5%) out of 533 patients had PR during STEMI, while 132 (36.3%) out of 363 patients had PR during NSTE-ACS patients. PR is the main underlying pathology in STEMI, whereas ACS without PR is the predominant mechanism in NSTE-ACS ($p < 0.001$). Figure 2 shows the prevalence of PR among the 4 groups. The prevalence of PR was 64 (39.2%) in Group 1; 48 (44.0%) in Group 2; 60 (50.4%) in Group 3; 272 (53.9%) in Group 4 ($p = 0.007$). There were 77 patients (8.6%) who had LDL-C <70 mg/dl. The prevalence of PR was significantly lower in patients with LDL-C <70 mg/dl than in those with LDL-C ≥70 mg/dl (sTable 1). OCT findings of the 4 groups are summarized in Table 1. Plaque characteristics were significantly different among the 4 groups, with the exception of the prevalence of cholesterol crystal. The prevalence of lipid rich plaque (LRP) was higher in high LDL-C groups. The prevalence of macrophage was the highest in Group 4. The prevalence of calcification was high in patients on statin. Table 2 shows the logistic regression analyses for PR, plaque erosion (PE) and calcified plaque (CP). In the multivariable logistic regression analysis, Groups 1 and 2 were associated with low prevalence of PR. PE was associated with younger age and non-CKD as well as Group 1. CP was associated with advanced age, hypertension and CKD as well as low LDL-C. Table 3 shows the logistic regression analyses for each plaque characteristic. Low prevalence of LRP was significantly associated with low LDL-C. Low prevalence of macrophages was also significantly associated low LDL-C. Calcification was significantly associated with advanced age and diabetes mellitus as well as

Table 1
Baseline characteristics

Variable	Group 1 (n = 163)	Group 2 (n = 109)	Group 3 (n = 119)	Group 4 (n = 505)	p Value
Age (years)	64.2 ± 13.0	66.6 ± 11.7	67.2 ± 11.2	64.3 ± 11.9	0.038
Men	129 (79%)	82 (75%)	88 (74%)	405 (80%)	0.383
Hypertension	112 (69%)	78 (72%)	88 (74%)	307 (61%)	0.011
Hyperlipidemia	83 (51%)	108 (99%)	119 (100%)	396 (78%)	<0.001
Diabetes mellitus	52 (32%)	44 (40%)	42 (35%)	157 (31%)	0.274
Prior myocardial infarction	6 (4%)	23 (21%)	12 (10%)	20 (4%)	<0.001
Smoker	102 (63%)	61 (56%)	64 (54%)	361 (72%)	<0.001
Chronic kidney disease	41 (25%)	26 (24%)	19 (16%)	77 (15%)	0.012
Clinical presentation					<0.001
ST segment elevation myocardial infarction	92 (56%)	36 (33%)	69 (58%)	336 (67%)	
Non ST segment elevation acute coronary syndrome	71 (44%)	73 (67%)	50 (42%)	169 (33%)	
Medication					
Aspirin	15 (9%)	76 (70%)	62 (52%)	38 (8%)	<0.001
Laboratory data					
Total cholesterol (mg/dl)	148.6 ± 26.2	145.8 ± 28.6	198.5 ± 40.2	207.7 ± 35.8	<0.001
Low-density lipoprotein cholesterol (mg/dl)	76.1 ± 17.7	75.3 ± 17.1	136.3 ± 29.6	145.2 ± 34.5	<0.001
High-density lipoprotein cholesterol (mg/dl)	46.3 ± 18.7	46.8 ± 16.0	47.3 ± 11.8	46.7 ± 12.0	0.938
Triglyceride (mg/dl)	106.7 ± 106.6	106.3 ± 78.7	123.0 ± 91.8	121.4 ± 100.4	0.209
Hemoglobin A1c (%)	6.2 ± 1.2	6.4 ± 1.0	6.5 ± 1.3	6.3 ± 1.2	0.188
Creatinine (mg/dl)	1.09 ± 1.12	1.03 ± 0.98	0.92 ± 0.46	0.94 ± 0.76	0.190
Optical coherence tomography findings					
Plaque rupture	64 (39%)	48 (44%)	60 (50%)	272 (54%)	0.007
Without plaque rupture	99 (61%)	61 (56%)	59 (50%)	233 (46%)	
Plaque erosion	71(44%)	33 (30%)	40 (34%)	185 (37%)	
Calcified plaque	28 (17%)	28 (26%)	19 (16%)	48 (9%)	
Plaque characteristics					
Lipid rich plaque	82 (50%)	58 (53%)	77 (65%)	323 (64%)	0.005
Macrophage	90 (55%)	65 (60%)	76 (64%)	354 (70%)	0.003
Cholesterol crystal	29 (18%)	24 (22%)	32 (27%)	117 (23%)	0.317
Calcification	76 (47%)	67 (62%)	65 (55%)	225 (45%)	0.006

Values are numbers (%) or means ± standard deviation.

Group 1 = Low-density lipoprotein cholesterol levels ≤100 without statin, Group 2 = Low-density lipoprotein cholesterol levels ≤100 with statin, Group 3 = Low-density lipoprotein cholesterol levels >100 with statin, Group 4 = Low-density lipoprotein cholesterol levels >100 without statin.

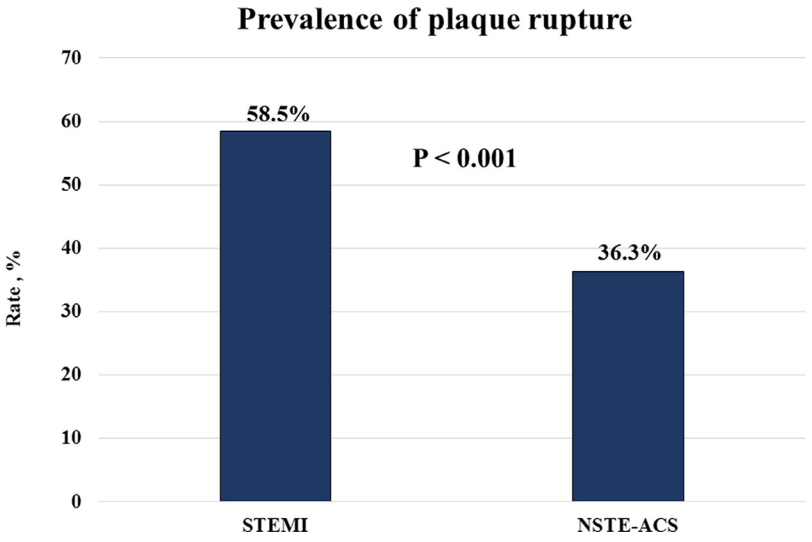

Figure 1. Prevalence of plaque rupture in patients with STEMI versus NSTE-ACS. Plaque rupture was more frequently found in STEMI patients than in NSTE-ACS patients (58.5% vs 36.3%; p < 0.001). STEMI = ST segment elevation myocardial infarction; NSTE-ACS = non ST segment elevation acute coronary syndrome.

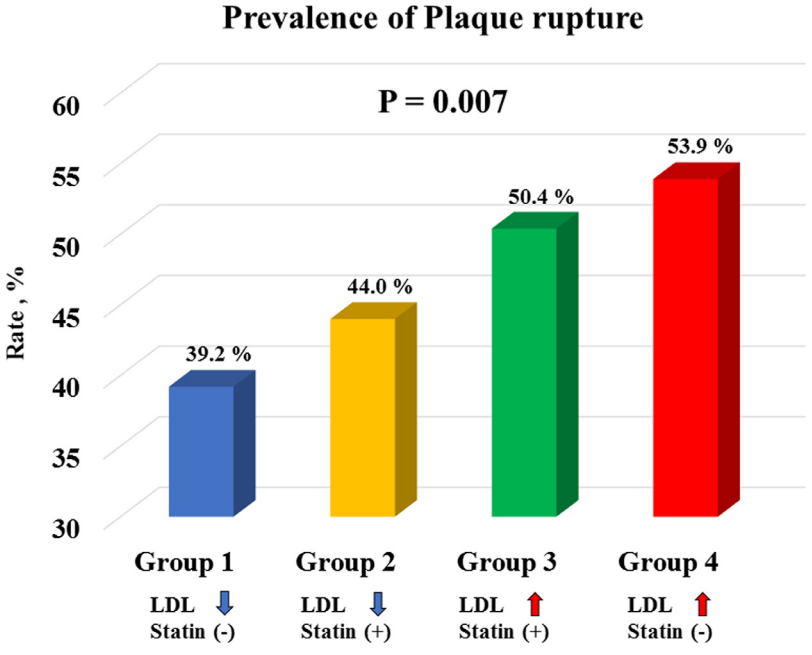

Figure 2. Prevalence of plaque rupture among the 4 groups. The prevalence of plaque rupture was significantly different among the 4 groups (39.2% in low LDL without statin; 44.0% in low LDL with statin; 50.4% in high LDL with statin; 53.9% in high LDL without statin; p = 0.007). LDL-C = low-density lipoprotein cholesterol.

Group 2. Table 4 shows the proportion of underlying pathology between men and women. There were significant differences between the 4 groups in men (p < 0.001), but not in women (p = 0.821). The sample size might not have been sufficient for testing the interaction, and it was not significant (p = 0.603).

Discussion

The present study demonstrates that the prevalence of PR was highest in the high LDL-C without statin group and lowest in the low LDL-C without statin group. Compared with the high LDL-C without statin group, the low LDL-C with statin group had lower prevalence of PR. In our study, we also found that PR was more frequently found in STEMI than in NSTE-ACS, and the use of statin independently reduced the risk for STEMI (sTable 2), a finding consistent with previous studies.[9,11,12] However, previous reports did not directly investigate the underlying mechanism.

The strongest risk for PR is hyperlipidemia,[13] and the plasma levels of LDL-C relate to the plaque composition and plaque volume.[14,15] In our study, the prevalence of PR was higher in the high LDL-C groups than in the low LDL-

Table 2
Logistic regression analyses for pathogenesis

	Unadjusted			Adjusted		
Variable	Odds ratio	95% confidence interval	p Value	Odds ratio	95% confidence interval	p Value
Plaque rupture						
Age (per 1-yr increment)	1.006	0.995-1.017	0.256	1.004	0.992-1.016	0.555
Men	0.834	0.606-1.148	0.264	0.861	0.600-1.234	0.414
Smoker	0.899	0.682-1.185	0.450	0.912	0.667-1.245	0.561
Hypertension	0.983	0.746-1.294	0.901	0.953	0.713-1.273	0.745
Hyperlipidemia	1.008	0.790-1.499	0.606	1.004	0.705-1.430	0.983
Diabetes mellitus	1.125	0.851-1.486	0.408	1.120	0.841-1.490	0.439
Chronic kidney disease	1.206	0.858-1.694	0.281	1.265	0.886-1.808	0.196
Risk classification						
Group 4 (Reference)						
Group 1	0.554	0.386-0.794	0.001	0.538	0.369-0.785	0.001
Group 2	0.674	0.444-1.022	0.064	0.638	0.415-0.980	0.040
Group 3	0.871	0.584-1.299	0.499	0.842	0.557-1.273	0.414
Plaque erosion						
Age (per 1-yr increment)	0.971	0.960-0.982	< 0.001	0.978	0.966-0.991	< 0.001
Men	1.244	0.887-1.743	0.206	1.077	0.733-1.581	0.705
Smoker	1.216	0.911-1.623	0.185	1.047	0.753-1.457	0.784
Hypertension	0.703	0.530-0.933	0.015	0.861	0.637-1.163	0.329
Hyperlipidemia	0.938	0.674-1.306	0.705	1.072	0.740-1.552	0.714
Diabetes mellitus	0.680	0.506-0.915	0.011	0.766	0.564-1.041	0.089
Chronic kidney disease	0.408	0.273-0.610	< 0.001	0.466	0.307-0.707	< 0.001
Risk classification						
Group 4 (Reference)						
Group 1	1.335	0.933-1.911	0.114	1.508	1.023-2.222	0.038
Group 2	0.751	0.480-1.174	0.209	0.854	0.535-1.364	0.510
Group 3	0.876	0.575-1.335	0.537	0.960	0.617-1.495	0.857
Calcified plaque						
Age (per 1-yr increment)	1.049	1.031-1.068	<0.001	1.041	1.021-1.062	< 0.001
Men	0.965	0.609-1.529	0.879	1.138	0.668-1.941	0.634
Smoker	0.858	0.579-1.273	0.448	1.120	0.704-1.781	0.632
Hypertension	2.302	1.449-3.657	<0.001	1.635	1.006-2.657	0.047
Hyperlipidemia	0.950	0.599-1.506	0.828	0.861	0.498-1.490	0.593
Diabetes mellitus	1.597	1.083-2.356	0.018	1.328	0.880-2.003	0.177
Chronic kidney disease	2.668	1.750-4.068	<0.001	1.838	1.168-2.893	0.009
Risk classification						
Group 4 (Reference)						
Group 1	1.975	1.193-3.269	0.008	1.752	1.013-3.031	0.045
Group 2	3.291	1.952-5.550	<0.001	2.937	1.674-5.152	< 0.001
Group 3	1.809	1.019-3.210	0.043	1.659	0.903-3.046	0.103

Group 1 = Low-density lipoprotein cholesterol levels ≤100 without statin, Group 2 = Low-density lipoprotein cholesterol levels ≤100 with statin, Group 3 = Low-density lipoprotein cholesterol levels >100 with statin, Group 4 = Low-density lipoprotein cholesterol levels >100 without statin.

C groups. PR is commonly associated with a lipid-rich plaque with necrotic core and abundant macrophages.[16,17] We also found that the prevalence of LRP and macrophages was higher in the high LDL-C groups than in the low LDL-C groups. Group 1 had the lowest prevalence of LRP and macrophages. Compared with Group 1, the prevalence of PR was higher in Group 2, despite similar LDL-C levels. This result indicates that patients with naturally low LDL-C levels have lower risk of PR, as compared with those with low LDL-C levels achieved by statin therapy. Accumulated LDL-C during a lifetime may be an important factor for PR, since patients in the low LDL-C achieved by statin therapy would have had longer exposure to high LDL-C level over their lifetime than those with naturally low LDL. A previous study showed that sequence variations in proprotein convertase subtilisin/kexin 9 associated with lower levels of LDL-C conferred protection against ASCVD and even relatively moderate reductions in LDL-C level in this population would markedly reduce the incidence of ASCVD if sustained over a lifetime.[18] These data may indicate that earlier implementation of lipid management should be recommended to prevent PR.

Recent guidelines for cholesterol management recommended statin therapy not only for secondary but also for primary prevention of ASCVD for patients with hyperlipidemia.[8,19] Our data supports this recommendation. When the two groups treated with statin were compared, Group 2 with low LDL showed lower prevalence of PR, lipid rich plaque, and macrophages. Previous prospective, randomized studies using OCT comparing the effect of high and low dose statin therapy demonstrated that high dose statin therapy induced rapid and more robust plaque stabilization

Table 3
Logistic regression analyses for plaque characteristics

	Unadjusted			Adjusted		
Variable	Odds ratio	95% confidence interval	p Value	Odds ratio	95% confidence interval	p Value
Lipid rich plaque						
Age (per 1-yr increment)	1.013	1.002-1.025	0.021	1.013	1.001-1.026	0.037
Men	0.792	0.568-1.104	0.169	0.869	0.599-1.263	0.462
Smoker	0.876	0.660-1.163	0.360	0.920	0.668-12.66	0.608
Hypertension	0.910	0.686-1.207	0.910	0.831	0.616-1.119	0.223
Hyperlipidemia	1.264	0.915-1.748	0.156	1.201	0.839-1.719	0.317
Diabetes mellitus	1.141	0.857-1.519	0.367	1.153	0.859-1.548	0.344
Chronic kidney disease	1.057	0.746-1.497	0.755	1.060	0.735-1.528	0.756
Risk classification						
Group 4 (Reference)						
Group 1	0.570	0.399-0.815	0.002	0.598	0.411-0.871	0.007
Group 2	0.641	0.422-0.973	0.037	0.587	0.381-0.904	0.016
Group 3	1.033	0.680-1.568	0.879	0.953	0.619-1.469	0.829
Macrophage						
Age (per 1-yr increment)	0.994	0.982-1.005	0.284	0.993	0.980-1.005	0.246
Men	0.776	0.550-1.096	0.150	0.767	0.521-1.128	0.177
Smoker	0.966	0.723-1.292	0.817	0.941	0.678-1.306	0.716
Hypertension	0.966	0.723-1.290	0.813	1.052	0.775-1.428	0.744
Hyperlipidemia	1.100	0.788-1.537	0.575	0.987	0.680-1.434	0.947
Diabetes mellitus	1.173	0.872-1.576	0.291	1.259	0.928-1.707	0.139
Chronic kidney disease	0.689	0.487-0.975	0.035	0.752	0.522-1.083	0.126
Risk classification						
Group 4 (Reference)						
Group 1	0.526	0.366-0.756	0.001	0.529	0.361-0.776	0.001
Group 2	0.630	0.411-1.005	0.034	0.627	0.403-0.975	0.038
Group 3	0.754	0.495-1.147	0.187	0.740	0.479-1.143	0.175
Cholesterol crystal						
Age (per 1-yr increment)	1.004	0.991-1.017	0.548	1.002	0.988-1.017	0.757
Men	1.231	0.829-1.828	0.304	1.434	0.921-2.234	0.110
Smoker	0.856	0.618-1.186	0.349	0.756	0.524-1.090	0.134
Hypertension	1.157	0.829-1.616	0.391	1.109	0.781-1.573	0.564
Hyperlipidemia	1.117	0.756-1.650	0.579	0.991	0.646-1.519	0.965
Diabetes mellitus	1.461	1.056-2.021	0.022	1.157	1.046-2.029	0.026
Chronic kidney disease	1.055	0.705-1.577	0.795	0.756	0.524-1.090	0.134
Risk classification						
Group 4 (Reference)						
Group 1	0.718	0.457-1.127	0.150	0.689	0.429-1.105	0.122
Group 2	0.936	0.569-1.541	0.796	0.864	0.516-1.115	0.577
Group 3	1.220	0.774-1.922	0.392	1.145	0.713-1.838	0.575
Calcification						
Age (per 1-yr increment)	1.039	1.027-1.051	<0.001	1.032	1.019-1.045	< 0.001
Men	0.625	0.453-0.862	0.004	0.818	0.566-1.184	0.287
Smoker	0.648	0.491-0.855	0.002	0.859	0.624-1.182	0.350
Hypertension	1.734	1.311-2.294	<0.001	1.321	0.981-1.778	0.067
Hyperlipidemia	1.436	1.038-1.986	0.029	1.366	0.947-1.972	0.096
Diabetes mellitus	1.473	1.113-1.949	0.007	1.352	1.008-1.814	0.044
Chronic kidney disease	1.702	1.207-2.402	0.002	1.311	0.908-1.892	0.149
Risk classification						
Group 4 (Reference)						
Group 1	1.087	0.763-1.549	0.644	1.106	0.753-1.625	0.608
Group 2	1.838	1.207-2.801	0.005	1.608	1.029-2.514	0.037
Group 3	1.498	1.003-2.238	0.048	1.191	0.778-1.823	0.421

Group 1 = Low-density lipoprotein cholesterol levels ≤100 without statin, Group 2 = Low-density lipoprotein cholesterol levels ≤100 with statin, Group 3 = Low-density lipoprotein cholesterol levels >100 with statin, Group 4 = Low-density lipoprotein cholesterol levels >100 without statin.

by increasing fibrous cap thickness and reducing macrophage accumulations.[20,21] The effect of plaque stabilization is mediated through not only reduction in lipids but also macrophages.[22] These results showed that it is important to reduce LDL-C levels by aggressive statin therapy for prevention of future PR. Our data showed that plaque calcification was more frequent in patients with statin therapy, particularly in those with low LDL. Recent studies showed that statin therapy was associated with increased coronary plaque calcification.[23,24] Pathology studies have pointed to

Table 4
Proportion of underlying pathology between men and women

Variable	Group 1 (n = 163)	2 (n = 109)	3 (n = 119)	4 (n = 505)	p Value
Men (n = 704)	129	82	88	405	0.603
Plaque rupture	48 (37%)	34 (42%)	46 (52%)	214 (53%)	<0.001
Plaque erosion	59 (46%)	24 (29%)	29 (33%)	154 (38%)	
Calcified plaque	22 (17%)	24 (29%)	13 (15%)	37 (9%)	
Women (n = 192)	34	27	31	100	
Plaque rupture	16 (47%)	14 (52%)	14 (45%)	58 (58%)	0.821
Plaque erosion	12 (35%)	9 (33%)	11 (36%)	31 (31%)	
Calcified plaque	6 (18%)	4 (15%)	6 (19%)	11 (11%)	

Values are numbers (%).
Group 1 = Low-density lipoprotein cholesterol levels ≤100 without statin, Group 2 = Low-density lipoprotein cholesterol levels ≤100 with statin, Group 3 = Low-density lipoprotein cholesterol levels >100 with statin, Group 4 = Low-density lipoprotein cholesterol levels >100 without statin.

a central role of vascular smooth muscle cells and macrophage apoptosis driving plaque calcification,[25,26] and statins stimulated vascular smooth muscle cells apoptosis and subsequent calcification in an in vitro study.[27] A previous serial observation study using intravascular ultrasound comparing the effect of high dose statin, low dose statin, and non-statin therapy demonstrated that statin therapy increased plaque calcification, and the greatest increase in calcium was evident in the high dose group.[28] It has been shown that larger, denser calcium structures are associated with plaque stabilization and better outcomes.[29–31] Taken together, plaque calcification induced by statin therapy may represent plaque stabilization.

Patients with naturally low LDL-C levels have the lowest risk of PR, followed by those with low LDL-C levels achieved by statin. Accumulated low LDL-C during a lifetime may be an important factor for plaque destabilization. Among ACS patients, having naturally low LDL increases the likelihood of finding other plaque morphologies underlying ACS rather than PR. Early and aggressive cholesterol management may be beneficial for prevention of PR. On the other hand, PE was associated with low LDL-C without statin and CP was associated with low LDL-C with statin. Because the underlying mechanism of thrombus formation remains less well understood in PE and CP patients, further studies are needed to clarify the influence of LDL-C and statin to thrombus formation in these 2 conditions.

This study has several limitations. First, this study was a retrospective analysis from a recently established database. Although consecutive patients were enrolled at each institution, the decision to perform OCT was left at the discretion of each operator. All patients presented with ACS. During the acute phase of ACS, it is often difficult to image the culprit lesion prior to PCI and to obtain high quality images. Second, duration of statin therapy and LDL-C levels prior to admission were not recorded. Third, the sample size is relatively small. To our knowledge, this is the first and largest study showing patients with naturally low LDL-C levels have the lowest risk of PR.

Authors Contribution

Ik-Kyung Jang: Conceptualization, Writing - Review & Editing, Supervision. Osamu Kurihara: Investigation, Formal analysis, Writing - Original Draft. Hyung Oh Kim: Investigation. Michele Russo: Investigation. Makoto Araki: Writing - Review & Editing. Akihiro Nakajima: Writing - Review & Editing. Hang Lee: Formal analysis. Masamichi Takano: Writing - Review & Editing. Kyoichi Mizuno: Writing - Review & Editing.

Disclosures

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.08.016.

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