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Impact of Statin Therapy on Coronary Intervention for Non-ST Elevation Acute Coronary Syndrome With Decreased Low-Density Lipoprotein Cholesterol

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Abstract

Objectives. The benefits of treating patients with acute coronary syndrome (ACS) with statins are well established. This study investigated the effects of statins on patients who presented with low levels of low-density lipoprotein (LDL) cholesterol, were diagnosed with non-ST elevation ACS, and subsequently underwent percutaneous coronary interventions (PCI).

Methods. From 2000 to 2003, 87 patients (mean age 68 ± 10 years, 69 males, 18 females) underwent PCI because of non-ST elevation ACS, and had low LDL cholesterol on presentation. These patients were divided into two groups: those who had been taking statins (S-group, $n = 46$), and those not taking statins, or controls (C-group, $n = 41$). Only patients whose LDL cholesterol was < 100 mg/d*l* at admission (average: 82 ± 12 mg/d*l*) were included in the study. Troponin-T (TnT), creatine kinase (CK), CK-MB, and high-sense C reactive protein (hs-CRP) were measured before and 6 hr after PCI. The two groups were

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evaluated at 6 months clinical follow-up.

Results. There was no difference in these markers before PCI in both groups. TnT and CK-MB in the S-group at 6 hr post-PCI were significantly decreased compared to those of the C-group (0.45 ± 1.34 vs 1.40 ± 2.37 ng/m*l*, respectively, for TnT, $p = 0.04$; 17.2 ± 45.5 vs 81.3 ± 157.2 IU/*l*, respectively, for CK-MB, $p = 0.02$). Major adverse cardiac events (MACE) defined as death, myocardial infarction, congestive heart failure and target lesion revascularization were evaluated after 6 months. There was no difference in MACE between the two groups.

Conclusions. Statin treatment before PCI in patients with non-ST elevation ACS demonstrated beneficial effects such as less myocardial damage, even though both groups presented with low LDL cholesterol levels. However, no significant effect on MACE was seen at 6 months after PCI.

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Key Words

■Coronary artery disease ■Lipoproteins, LDL ■Lipid modifying agents
■Angioplasty ■ST segments

INTRODUCTION

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have been shown to reduce ischemic cardiovascular events by 25 to 30%, and to reduce low-density lipoprotein (LDL) cholesterol levels by 25 to 35%.[1–3] Some of the beneficial effects of statins may be due to the pleiotropic effects on anti-inflammation,[4–8] antithrombosis,[9, 10] and vasculature.[11] Acute coronary syndrome (ACS) is considered to be an indicator for high risk of early recurrent cardiovascular events.[12, 13] Therefore, we investigated the effect of statin therapy on patients with non-ST elevation ACS who presented with low levels of LDL cholesterol on admission.

SUBJECTS AND METHODS

Patient population

We evaluated 87 patients (69 males, 18 females, mean age 68 ± 10 years) who underwent percutaneous coronary interventions (PCI) at Toho University Ohashi Medical Center from September 2000 to March 2003. All patients had low LDL cholesterol on admission. All patients had non-ST elevation ACS that included high-risk unstable angina and non-ST elevation myocardial infarction, except for serum creatine kinase (CK) level ≥ 3 times than upper limit of normal on admission. We excluded patients based on the following criteria: left bundle-branch block or paced ventricular rhythm, severe congestive heart failure, cardiogenic shock, severe anemia, renal failure requiring dialysis, hepatic dysfunction, and administration of other cholesterol-lowering drugs before admission. In addition, patients with obvious side branch occlusion after PCI were excluded. We divided the study group patients into two groups: previously treated with statin treatment group (S-group, $n = 46$), and non-statin treatment control group (C-group, $n = 41$). The clinical course after PCI was monitored.

Percutaneous coronary intervention procedure

PCI was performed in a standard manner. Angiographic success was defined by a final result of $< 50\%$ residual stenosis by visual estimation. Stent implantation was performed according to current clinical practice, and limited to bare metal stents. All patients received aspirin 81 mg/d*l* or more before PCI, and ticlopidine 200 mg/d*l* or cilostazol 200 mg/d*l* for at least 2 weeks after stent placement. All patients received 100 IU/kg bolus of intravenous heparin before PCI, and activated clotting time was maintained at > 250 sec during the procedure. Thrombolysis in Myocardial Infarction (TIMI) grade was assessed at the end of the procedure.

Quantitative coronary angiographic analysis

Quantitative angiographic measurements were performed with an automated computer-based system (CMS, Medis Medical Imaging System) by experienced interventional cardiologists. Quantitative coronary angiography was performed before and immediately after the procedure using edge detection algorithms. Minimal luminal diameter, reference vessel diameter, and diameter of stenosis were measured.

Measurement of lipid profile and inflammatory markers

LDL cholesterol was measured on admission and

only patients with LDL <100 mg/d*l* were included in this study. Troponin-T (TnT), high-sense C-reactive protein (hs-CRP), CK, and CK-myocardial band (CK-MB) were measured before and 6 hr after PCI.

Clinical follow-up

Clinical follow-up for major adverse cardiac events (MACE) was assessed at 6 months after PCI. The definition of MACE was death, acute myocardial infarction (AMI), congestive heart failure (CHF), and target lesion revascularization (TLR). Aspirin 81 mg/d*l* or more was prescribed during follow-up except for intolerance. Management of statin treatment was left to individual physicians after PCI.

Statistical analysis

Statistical analysis was performed using commercial software (Statview™, Version 5.0, SAS Institute Inc). All data were analyzed as mean ± 1 standard deviation. Categorical variables were compared by the χ^2 or Fisher's exact test. Unpaired Student's *t*-test was performed to compare continuous variables between the two groups (**Table 1**). A probability value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Patient characteristics are compared between the two groups in **Table 1**. There was no difference in terms of age, sex, prevalence of diabetes mellitus and hypertension. The level of total cholesterol at admission was 161 ± 19 mg/d*l* in the S-group and 154 ± 17 mg/d*l* in the C-group (NS). High-density lipoprotein (HDL) cholesterol level was slightly higher in the S-group than in the C-group, but was not statistically significant (52 ± 14 vs 46 ± 14 mg/d*l*, respectively; $p = 0.09$). LDL cholesterol level was 82 ± 13 mg/d*l* in the S-group, and 82 ± 12 mg/d*l* in the C-group (NS) on admission, and triglyceride level was 135 ± 65 and 129 ± 74 mg/d*l*, respectively, which were also not different (NS). Statins known and taken by the patients in the S-group were as follows: atorvastatin in 10 patients (21.7%), pravastatin in 10 (21.7%), simvastatin in 3 (6.5%), and fluvastatin in 3 (6.5%). Left ventricular ejection fraction was not statistically different.

Table 1 Baseline patient characteristics

	S-group ($n=46$)	C-group ($n=41$)	*p* value
Age (yr)	69 ± 10	68 ± 12	0.71
Male	34 (73.9)	35 (85.4)	0.19
Smoking	22 (47.8)	21 (51.2)	0.75
Diabetes mellitus	24 (52.2)	16 (39.0)	0.22
Hypertension	32 (69.6)	32 (78.1)	0.37
Total cholesterol (mg/d*l*)	161 ± 19	154 ± 17	0.11
HDL cholesterol (mg/d*l*)	52 ± 14	46 ± 14	0.09
LDL cholesterol (mg/d*l*)	82 ± 13	82 ± 12	0.90
Triglyceride (mg/d*l*)	135 ± 65	129 ± 74	0.68
Prior-MI	13 (28.3)	8 (19.5)	0.38
LVEF (%)	59 ± 11	57 ± 18	0.56

Continuous values are mean $\pm$ SD. ( ): %.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; LVEF = left ventricular ejection fraction.

Angiographic results

The reference diameter in the S-group and C-group before angioplasty was not significantly different (2.9 ± 0.7 vs 3.0 ± 0.8 mm, respectively; NS). Minimal luminal diameter before PCI was also not significant (0.9 ± 0.3 vs 0.7 ± 0.5 mm, respectively; NS). Left anterior descending artery, left main coronary artery, and saphenous vein graft were treated in more patients in the S-group compared to the C-group, but there was no statistical difference between the two groups (**Table 2**). The right coronary artery was treated in more patients in the C-group, but no significant difference was found (29.3% vs 10.9%, respectively; $p = 0.06$). Regarding devices used in the procedure (**Table 3**), stent implantation was used more in the C-group than the S-group, though there was no significant statistical difference (65.9% vs 54.3%, respectively; NS). Rotational atherectomy was used more frequently in the C-group than the S-group (19.5% vs 13.0%, respectively; NS), whereas directional coronary atherectomy was used more frequently in the S-group than the C-group (15.2% vs 2.4%; respectively, $p = 0.07$). Both interventions were not significantly different between the two groups. Aspiration catheter and/or distal protection devices were used more in the S-group than the C-group, but no significance was found between the two groups (28.3% vs 22.0%, respectively; NS). Most treated lesions were de novo, and the prevalence of de novo lesion was lower in

Table 2 Lesion characteristics and procedural data

	S-group (n=46)	C-group (n=41)	p value
QCA analysis (mm)			
Pre-PCI reference	2.9±0.7	3.0±0.8	0.21
Pre-PCI MLD	0.9±0.3	0.7±0.5	0.69
Post-PCI reference	3.2±0.9	3.3±0.7	0.16
Post-PCI MLD	2.9±0.9	2.8±1.0	0.19
Type of lesion			
De novo	36(78.3)	35(85.4)	0.39
Type B2, C	26(56.5)	29(70.7)	0.17
Culprit vessel			
LAD	25(54.3)	15(36.6)	0.09
RCA	5(10.9)	12(29.3)	0.06
LCX	11(23.9)	13(31.7)	0.57
LMT	3(6.5)	0	0.10
SVG	2(4.3)	1(2.4)	0.62
Post-PCI TIMI grade	2.8±0.5	2.8±0.5	0.82

Continuous values are mean ± SD. ( ): %.
QCA = quantitative coronary angiography ; PCI = percutaneous coronary intervention ; MLD = minimal luminal diameter ; LAD = left anterior descending artery ; RCA = right coronary artery ; LCX = left circumflex artery ; LMT = left main trunk ; SVG = saphenous vein graft ; TIMI = Thrombolysis in Myocardial Infarction.

Table 3 Procedural characteristics

	S-group (n=46)	C-group (n=41)	p value
BA	29(63.0)	33(80.5)	0.14
Stent	25(54.3)	27(65.9)	0.27
CBA	15(32.6)	7(17.1)	0.13
RA	6(13.0)	8(19.5)	0.55
DCA	7(15.2)	1(2.4)	0.07
Aspiration/distal protection	13(28.3)	9(22.0)	0.52

( ): %.
BA=balloon angioplasty ; CBA=cutting balloon angioplasty; RA=rotational atherectomy; DCA=directional coronary atherectomy

the S-group than the C-group, but did not reach statistical difference(78.3% vs 85.4%, respectively; NS). The prevalence of type B2, C lesion was higher in the C-group, but there was no statistical significance(56.5% vs 70.7%; NS). Post angioplasty TIMI grade was the same in both groups (2.8±0.5 vs 2.8±0.5; NS).

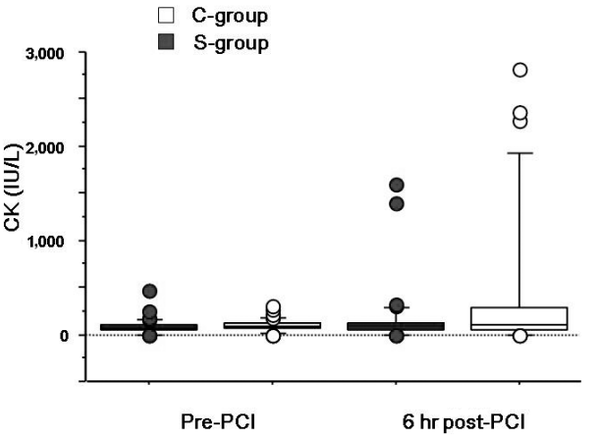

Fig. 1 Comparison of box plots illustrating creatine kinase levels in the control group(C-group), and the statin treatment group(S-group)
Both groups were compared in the pre-percutaneous coronary intervention and 6 hr post-PCI periods.
CK = creatine kinase. Other abbreviation as in Table 2.

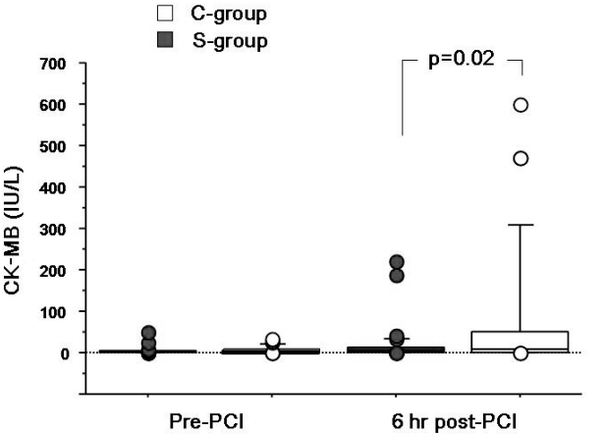

Fig. 2 Comparison of creatine kinase midband between the S-group and the C-group in the pre-PCI and 6 hr post PCI periods
CK-MB = creatine kinase midband. Other abbreviation as in Table 2.

Myocardial enzyme and inflammation marker

CK and CK-MB were measured in both groups before and 6 hr after PCI(**Figs. 1, 2**). The CK value was similar pre-PCI(137 ±331 IU/*l*, S-group vs 111 ±110 IU/*l*, C-group; NS), but higher in the C-group post PCI(295±882 vs 452±783 IU/*l*; NS), but this did not reach statistical difference. CK-MB showed no difference in the groups pre-PCI, but CK-MB was significantly higher in the C-group than in the S-group(81.3± 157.2 vs 17.2±45.5 IU/*l*, respectively, p=0.02)

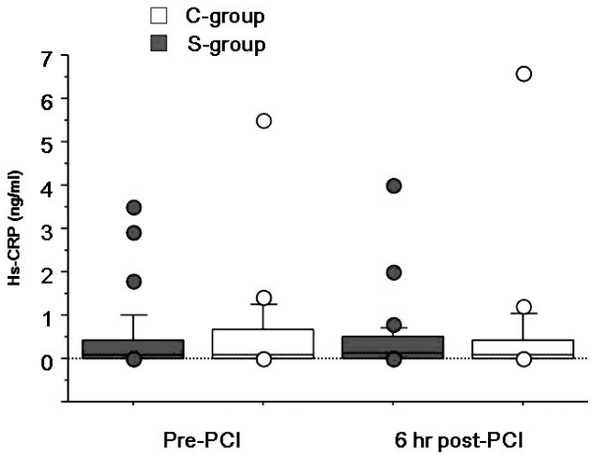

Fig. 3 High-sense C-reactive protein in the S-group and the C-group in the pre-PCI and 6 hr post-PCI periods
Hs-CRP = high-sense C-reactive protein. Other abbreviation as in Table 2.

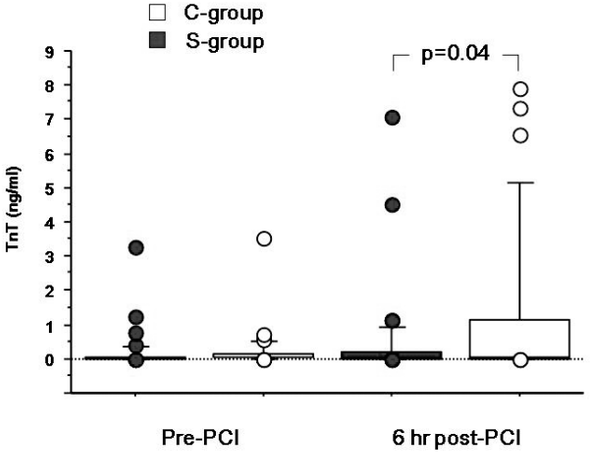

Fig. 4 Comparison of troponin-T in the S-group and the C-group in the pre-PCI and 6 hr post-PCI periods
TnT = troponin-T. Other abbreviation as in Table 2.

post-PCI. The hs-CRP was measured before and 6 hr after PCI in both groups. The value of hs-CRP was a little higher in the S-group than the C-group pre-PCI(**Fig. 3**), but there was no significant difference between the two groups(0.57 ± 1.22 vs 0.45 ± 1.01 ng/m*l*, respectively; NS). Hs-CRP value at 6 hr after PCI was higher in the C-group than the S-group, but was not significant(0.63 ± 1.71 vs 0.47 ± 1.02 ng/m*l*; NS). TnT was also measured before and 6 hr after PCI(**Fig. 4**). No difference was seen in the both groups pre-PCI, but TnT in the S-group was significantly less than that in the C-group post-PCI(0.45 ± 1.34 vs 1.40 ± 2.37 IU/*l*, respectively, $p = 0.04$).

Table 4 Comparison of medication during follow-up

	S-group (n=46)	C-group (n=41)	p value
Aspirin	44(95.7)	39(95.1)	0.91
Ticlopidine	29(63.0)	21(51.2)	0.27
Cilostazol	5(10.9)	6(14.6)	0.60
Nitrates	13(28.3)	10(24.4)	0.68
Calcium blocker	19(41.3)	13(31.7)	0.35
Beta-blocker	12(26.1)	12(29.3)	0.74
ACE-I/ARB	30(65.2)	32(78.1)	0.19
Nicorandil	13(28.3)	5(12.2)	0.07
Statin use during follow-up	40(87.0)	6(14.6)	<0.0001

( ): %.
ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Comparison of medical treatment during follow-up

Medical treatments during follow-up are shown in **Table 4**. Most patients kept taking aspirin during follow-up except for intolerance(95.7% in S-group vs 95.1% in C-group; NS). Ticlopidine or cilostazol were used for at least for 2 weeks after PCI, but were discontinued in some cases. So 63.0% of patients in the S-group and 51.2% in the C-group continued ticlopidine during the follow-up period. There was no significant difference between the S-group and the C-group regarding the use of medical treatments such as cilostazol, nitrates, calcium blocker, beta-blocker, and angiotensin converting enzyme inhibitor/angiotensin receptor blocker. The usage of nicorandil was more frequent in the S-group, but was not significant statistically(28.3% vs 12.2%, respectively; $p = 0.07$). Six patients (14.6%)started statin treatment in the C-group, and 40 patients(87.0%)continued statin therapy during follow-up($p < 0.0001$). The 6 patients who started statin treatment had 2 TLR(33.3%)during follow-up, and the 35 patients in the C-group who did not receive statin had 13 MACE(37.1%; 1 AMI, 2 CHF, and 10 TLR), so there was no difference in the frequency of MACE between these two groups (33.3% vs 37.1%, respectively; NS).

Clinical follow-up after 6 months

The characteristics of clinical follow-up 6

Table 5 Major adverse cardiac events at 6-month follow-up

	S-group (n=46)	C-group (n=41)	p value
Death	0	0	1.00
AMI	2(4.3)	1(2.4)	0.63
CHF	1(2.2)	2(4.9)	0.49
TLR	9(19.6)	12(29.3)	0.29

( ): %.
AMI=acute myocardial infarction ; CHF=congestive heart failure ; TLR=target lesion revascularization.

months after PCI are shown in **Table 5**. There was no death in both groups. Acute myocardial infarction, which was defined as CK value greater than 3 times the upper limit of normal, occurred in 2 patients(4.3%)in the S-group, and 1 patient(2.4%) in the C-group. There was no significant difference between the two groups. Congestive heart failure resulting in hospital re-admission occurred less in the S-group than the C-group, but there was no difference(2.2% vs 4.9%, respectively; NS). TLR in the S-group was less than in the C-group, but this did not reach statistical significance(19.6% vs 29.3%, respectively; NS).

DISCUSSION

Our results from this study demonstrate that patients who took statin before their non-ST elevation ACS event had a more favorable post PCI course, compared to those who were not taking statin, even though both groups of patients presented with low levels of LDL cholesterol. These results support recent studies on the benefits of statin administration before coronary intervention.[14, 15] While the precise underlying mechanism of inhibition of elevated myocardial enzymes by statins is not yet known, many hypothesize that the pleiotropic effects of statins contribute, by reducing inflammation, improving vascular endothelial functions, inhibiting thrombosis, and remodeling of plaque composition in the diseased vessel.[4–11] Our results did not reveal any difference in inflammatory markers such as hs-CRP after PCI. Although the value of hs-CRP in the S-group tended to be lower than that in the C-group, this did not reach statistical significance, likely because of the small study population.

In this study, statins inhibited the rise in CK-MB and TnT, likely through favorable remodeling on plaque composition and volume.[16] Coronary microembolization occurs more frequently among ACS patients.[17] Statins may not only reduce this phenomenon, but also improve endothelial function in the microcirculation, as well as provide direct myocardial protection.[18]

During coronary intervention, myocardial injury is estimated to occur in 10 to 40% of cases, and the myocardial injury sustained during the procedure is often characterized by a slight increase of markers of myocardial necrosis without symptoms, electrocardiographic changes or impairment of cardiac function.[19] However, even small increases of CK-MB signify a real and measurable myocardial injury and may be associated with a higher follow-up mortality.[20] Most instances of minor CK-MB elevation occur in patients with uncomplicated procedures with excellent final angiographic results, as shown by the final TIMI flow grade. This was the case with our study. Myocardial injury seen during successful PCI may be explained by distal microembolization of plaque components, an enhanced inflammatory state or total plaque burden and/or instability.[21]

Different treatments have been proposed to prevent myocardial injury during coronary intervention, including nitrate infusion, intracoronary beta-blockers,[22] adenosine, verapamil,[23] nicorandil[24] and b/ a inhibitors,[25] but none of these have been routinely introduced into clinical practice. The ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty)trial evaluated the effects of atorvastatin on post-procedural release of markers of myocardial damage in patients with stable angina, and the results suggest a beneficial effect of pre-treatment with statins.[26]

Our study design differed from ARYMDA, in that we exclusively studied a population with low level of LDL cholesterol. We enrolled non-ST elevation ACS patients who presented with low LDL cholesterol, and had a control group not being treated with statins. Our study subjects presented with ACS, and consequently had more coronary risk factors such as hypertension, diabetes mellitus, and smoking history, compared to the general population used in mega-trials.[27, 28] Most of the patients in the S-group had hypercholesterolemia, as they were receiving statin treatment before PCI. Despite this additional risk factor, the S-group had more favorable results post PCI, compared with the control group.

The results of the present study did not show any significant difference in terms of 6 months clinical outcome between two groups, but CHF and TLR tended to occur more in the C-group. This trend may reach statistical significance with a larger patient population and a longer follow-up duration.

Study limitations

This was a non-randomized, retrospective study at a single center, with a small number of subjects, and the follow-up period was limited to 6 months. The two groups had comparable patient demographics and lesion characteristics. The lipid profile was similar in both groups. We were unable to obtain the data regarding duration and dosage of statin treatment before PCI. However, the results of this study emphasize the favorable effect of statins on reducing myocardial injury after PCI, regardless of type, dosage, and duration of administration.

CONCLUSIONS

Statin treatment before PCI appears to confer benefits on patients with low LDL cholesterol who present with non-ST elevation ACS. Patients who took statins prior to their ACS event had less myocardial damage, compared with those who did not take statin. However, there was no significant difference in MACE between the two groups at 6 months follow-up.

Acknowledgment

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要　　約

LDLコレステロール低値の非ST上昇型急性冠症候群に対する冠動脈インターベンション: スタチン療法の効果

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目　的: 急性冠動脈症候群に対するスタチン療法は有用であることが知られている．我々は低比重リポ蛋白(LDL)コレステロール低値でありながら，非ST上昇急性冠動脈症候群を生じ経皮的冠動脈形成術(PCI)を施行された患者群に対し，以前からスタチン療法を行われていた群とそうでない群とを比較し，その効果を検討した．

方　法: 2000−2003年に，非ST上昇急性冠動脈症候群を生じたが，入院時のLDLコレステロール値100 mg/d*l*未満の87例の患者(平均年齢68±10歳，男性69例，女性18例，平均LDL 82±12 mg/d*l*)を調査した．スタチン治療群(46例)，および非スタチン治療対照群(41例)の2群に分け，PCI術前，術後6時間にクレアチンキナーゼ(CK), CK-MB, およびトロポニンT, 高感度C反応性蛋白を測定した．また，PCI施行6カ月後の主要心事故(死亡，急性心筋梗塞，心不全，病変部の再血行再建術)の割合を両群について調べた．

結　果: PCI施行前では両群に各測定項目の差異を認めなかった．しかし，トロポニンTとCK-MBに関し，治療6時間後の値はスタチン治療群が有意に対照群よりもおのおの低値をとった(トロポニンT値: 0.45±1.34 vs 1.40±2.37 ng/m*l*, $p=0.04$; CK-MB値: 17.2±45.5 vs 81.3±157.2 IU/*l*, $p=0.02$)．6ヵ月後の主要心事故には両群で差を認めなかった．

結　論: LDLコレステロール低値の患者群において，非ST上昇急性冠動脈症候群に対して行われるPCI施行前のスタチン療法は，術後心筋障害を軽減し有用であることが示唆された．しかし，6ヵ月後の主要心事故には有意な差は認められなかった．

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