九州大学学術情報リポジトリ
Kyushu University Institutional Repository

Statin Therapy May Prevent Restenosis After Successful Coronary Intervention, Independent of Lipid-lowering Effect and CRP Level

Yamawaki, Tohru
Division of cardiovascular medicine, Aso-Iizuka Hospital

Yamada, Akira
Division of cardiovascular medicine, Aso-Iizuka Hospital

Fukumoto, Yoshihiro
Division of cardiovascular medicine, Aso-Iizuka Hospital

Kishi, Takuya
Division of cardiovascular medicine, Aso-Iizuka Hospital

他

https://doi.org/10.15017/6199

出版情報：福岡醫學雜誌. 98 (6), pp.260-269, 2007-06-25. 福岡医学会
バージョン：
権利関係：

Statin Therapy May Prevent Restenosis After Successful Coronary Intervention, Independent of Lipid-lowering Effect and CRP Level

Tohru YAMAWAKI, Akira YAMADA, Yoshihiro FUKUMOTO, Takuya KISHI, Atsushi SOBASHIMA, Koichi KUWATA, Ryo NAKAMURA, Masatoshi SEKIYA, Hiroshi ANDO and Shuichi OKAMATSU

From the Division of cardiovascular medicine, Aso-Iizuka Hospital, Fukuoka, Japan

Abstract **Background**: As statins have the anti-atherosclerotic pleiotropic effects, we retrospectively examined the effects of statins on restenosis after percutaneous coronary intervention (PCI).
Methods: We reviewed consecutive 341 patients who underwent successful PCI and follow-up angiography six months after the procedure between January 2002 and December 2004. Statins were initiated in 207 patients (statin group), but not in the other 134 (control group). We compared the angiographic findings, low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP) between the two groups.
Results: LDL-C level in statin group was significantly higher than those in control group at baseline (116.0 ± 35.8 vs 103.1 ± 24.5 mg/dL, $p < 0.01$); however, the values were inverted between the two groups at follow-up (99.9 ± 29.5 vs 107.6 ± 26.0 mg/dL, $p = 0.015$). CRP levels were comparable between these two groups. Statin group showed significantly lower angiographic restenosis (defined as ≥ 50% stenosis at the target site) rate (35.3 vs 46.3 %, $p = 0.042$) and target lesion revascularization (TLR) rate (14.5 vs 23.9 %, $p = 0.018$) than control group. Multivariate analysis indicated that the prescription of statin, but not LDL-C level at follow-up and % reduction of LDL-C during the follow-up period, predict the restenosis prevention.
Conclusions: Statins can decrease restenosis and TLR rate after PCI, independent of lipid-lowering effect and CRP level in this study.

Introduction

Percutaneous coronary intervention (PCI) is a widely accepted treatment for coronary artery disease (CAD). However, the restenosis after PCI has been a significant clinical problem, which occurs in 30-40% of patients within 3-6 months after the procedure[1)2)]. Although drug eluting stents (DES) dramatically reduce angiographic restenosis, DES are not suitable for all CAD patients, especially in cases who cannot receive long-term anti-platelet therapy, and also emergent cases of acute myocardial infarction (MI)[3)~6)].

3-Hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are lipid-lowering agents, showing favorable effects on primary and secondary prevention of MI, and survival rate of CAD patients in many mega-study[7)~9)]. Beyond the lipid-lowering effect, statins provide various anti-atherosclerotic effects, such as improvement endothelial function, reduction of C-reactive protein (CRP), tissue factor, plasminogen activator inhibitor-1 expression and smooth muscle cells (SMCs) proliferation[10)~12)]. Walter et al. have demonstrated for the first time that statin therapy significantly reduced restenosis after coronary stent implantation[13)], while other recent studies have shown no significant

difference between statin and conventional treatment[14)15)]. As we sometimes experience the benefit of statins not only in lipid-lowering effect but also in longer angina-free periods in patients with CAD, we examined the retrospective study to assess the effects of statins on restenosis after successful PCI.

Methods

Patients Population

We retrospectively evaluated a total of 341 consecutive patients (mean age 67.1 ± 10.4 years old) who underwent successful PCI for CAD and follow-up angiography to assess the restenosis at 6 months after PCI or when symptom recurred between January 2002 and December 2004 in Aso-Iizuka Hospital, Fukuoka, Japan. There were 258 men and 83 women. For each patient, baseline demographic, clinical, procedural, and outcome data were collected by use of the standard medical records. Serum levels of CRP, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured at the time of PCI and follow-up angiography. We started statin treatment before or immediately after PCI, and continued during the follow-up period in patients of LDL-C ≥ 100 mg/dl, according to the guideline of Japanese atherosclerosis society for secondary prevention of CAD[16)].

PCI Procedure and Anti-platelet Therapy

All patients had been receiving chronic 100 mg/day of aspirin or received 200 mg of aspirin once prior to the procedure. PCI was performed via the femoral or radial approach using 6～8F guide catheters. Intravenous heparin (10,000 U) was administered at the beginning of the procedure and, if necessary, a repeat bolus of 5,000 U was administered to maintain the activated clotting time to > 250 seconds. Coronary stenting were planed before the PCI procedure or indicated for coronary dissection or suboptimal results after balloon angioplasty using bare metal stents. We used cutting balloon for in-stent restenosis[17)], rotablator for calcificated lesion[18)], and directional coronary atherectomy for eccentric proximal lesion[19)]. The balloon or stent diameter was chosen to ensure a balloon-to-artery ratio of 1.1 as estimated by quantitative coronary angiography. Patients continued 100 mg of aspirin once daily, and additionally 100 mg of ticlopidine twice daily for > 4 weeks in case of stent implantation.

Quantitative Coronary Angiography and Target Lesion Revascularization

Experienced cardiologists assessed quantitative angiographic measurements with computer-based densitometric system (Philips Medical Systems, The Netherlands). The nearest normal reference diameter, minimal lumen diameter (MLD), and lesion length were measured before and immediately after the procedure, and at follow-up. The restenosis was defined as a ≥ 50% diameter stenosis at follow up. Target lesion revascularization (TLR), defined as repeated intervention at restenotic sites, was performed at the presence of ischemia, which was indicated either by the recurrence of angina or positive stress test.

Outcomes

The primary end points were the follow-up angiographic MLD, restenosis and TLR rates. Secondary end points were major adverse coronary events, which were

defined as cardiac death, MI, unstable angina, and worsened effort angina.

Statistical Analysis

The results were expressed as the mean ± standard deviation (SD). Differences between the 2 groups with or without statin treatment were assessed with unpaired Student's t test, and χ^2 test for categorical variables. Paired data were analyzed by paired Student's t test. A p value of < 0.05 was considered to be statistically significant. Multivariate analysis was performed using the logistic regression model. All potential risk factors for restenosis were included. Odds ratios and 95% confidence intervals were calculated.

Result

Baseline characteristics and Procedural Data

Two hundred seven out of 341 patients received statin therapy (statin group) and 134 did not (control group). In statin group, 120 patients (58.0 %) received atorvastatin (11.0 ± 3.5 mg), 43 (20.8 %) did pravastatin (8.6 ± 3.0 mg), 31 (15.0 %) did fluvastatin (24.2 ± 8.9 mg), and 13 (6.2%) did simvastatin (5.0 ± 0.0 mg). There were significantly larger number of patients with hypercholesterolemia in statin group than that in control group (72.9 vs 15.6 %, p < 0.01) (Table 1). There was no significant difference in other coronary risk factors, such as age, sex, medications except statins, indications for PCI, and number of target vessels between the groups. PCI was performed for 213 lesions in statin group, and 139 lesions in control group. There were no significant differences in target vessels, performed procedure, reference diameter and minimal lumen diameter before and immediately after procedure between the two groups (Table 2).

Lipid profiles and CRP level at Baseline and Follow-Up

In statin group, all patients continued statin therapy until follow-up. TC and LDL-C levels in statin group were significantly higher than those in control group at baseline, and were significantly decreased

Table 1 Baseline Characteristics of the Study Subjects

	Control (n=134)	Statin (n=207)	p
Age, y	67.9±9.9	66.6±10.8	0.237
Men, n (%)	104 (77.6)	154 (74.4)	0.501
Diabetes, n (%)	38 (28.3)	66 (31.9)	0.491
Hypertension, n (%)	93 (69.4)	144 (69.6)	0.975
Smoking, n (%)	70 (52.2)	122 (58.9)	0.224
Hypercholesterolemia, n (%)	21 (15.6)	151 (72.9)*	<0.01
Statin			
Atorvastatin, n (%)	-	120 (58.0)	
pravastatin, n (%)	-	43 (20.8)	
fluvastatin, n (%)	-	31 (15.0)	
simvastatin, n (%)	-	13 (6.2)	
Medication during FU			
Aspirin	134 (100)	206 (99.5)	0.422
ACE inhibitor or ARB	112 (83.5)	178 (85.9)	0.543
Beta blocker	91 (67.9)	157 (75.8)	0.108
Indication for PCI, n (%)			0.345
Emergent	63 (47.0)	103 (47.8)	
Urgent	23 (17.2)	24 (11.6)	
Elective	48 (35.8)	80 (38.6)	
Target vessels, n (%)			0.769
1 vessel	127 (94.8)	196 (94.7)	
2 vessels	5 (3.7)	6 (2.9)	
LMT	2 (1.5)	5 (2.4)	
FU period, days	174.4±57.2	180.0±59.0	0.381

FU=follow-up; ACE=angiotensin converting enzyme; ARB=angiotensin II receptor bocker; PCI=percutaneous coronary intervention; LMT=left main trunk. Values are mean ± SD when appropriate. Values of $p < 0.05$ were considered statistically significant. *$p < 0.05$ Control vs Statin.

Table 2 Target Lesion Characteristics and Procedural Data

	Control (n=139)	Statin (n=213)	p
FU period, days	174.4±57.2	180.0±59.0	0.381
Target vessel, n (%)			0.772
RCA	55 (39.6)	79 (37.1)	
LAD	55 (39.6)	93 (43.7)	
LCx	27 (19.4)	36 (16.9)	
LMT	2 (1.4)	5 (2.3)	
Procedural data, n (%)			0.808
POBA	14 (10.1)	23 (10.8)	
Stent	116 (83.4)	177 (83.1)	
Cutting balloon	5 (3.6)	6 (2.8)	
Rotablator	4 (2.9)	5 (2.3)	
DCA	0 (0.0)	2 (1.0)	
Lesion length, mm	13.99±6.70	14.11±6.00	0.875
Reference diameter, mm	2.91±0.57	2.91±0.62	0.977
Pre-PCI MLD, mm	0.34±0.44	0.27±0.36	0.109
Post-PCI MLD, mm	2.67±0.62	2.66±0.65	0.934
FU MLD, mm	1.43±0.92	1.74±0.87*	<0.01

RCA=right coronary artery; LAD=left anterior descending artery; LCx=left circumflex artery; POBA=plain old balloon angioplasty; DCA=directional coronary atherectomy; PCI=percutaneous coronary intervention; MLD=minimal lumen diameter; FU=follow-up. Values are mean ± SD when appropriate. Values of $p < 0.05$ were considered statistically significant. *$p < 0.05$ Control vs Statin.

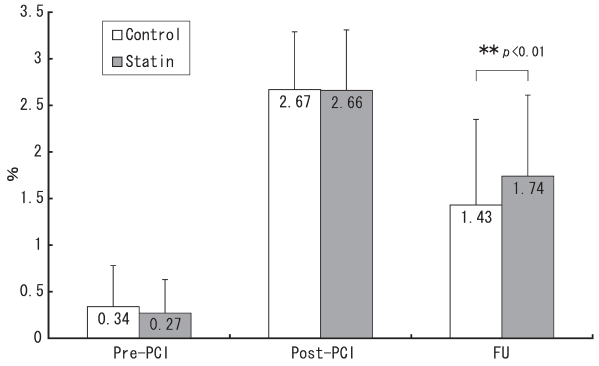

Fig. 1 Coronary minimal lumen diameters at PCI sites before, immediately after angioplasty, and at follow-up. Statin therapy significantly prevented the reduction of MLD at follow-up. Bars indicated SD

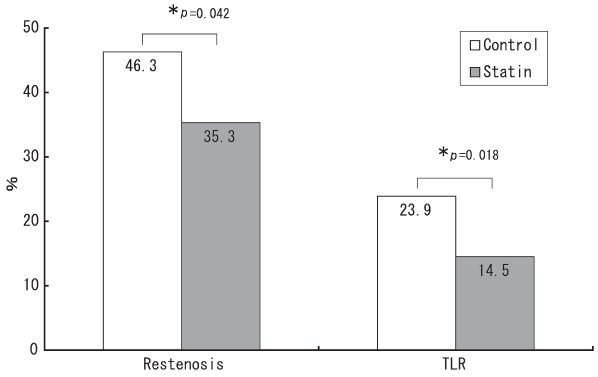

Fig. 2 Coronary angiographic restenosis and target lesion revascularization rates. Statin therapy significantly reduced restenosis and TLR rates.

Table 3 Lipid Profile and CRP

	Baseline			Follow-Up		
	Control (n=134)	Statin (n=207)	*p*	Control (n=134)	Statin (n=207)	*p*
TC, mg/dL	172.1±31.0	189.0±41.9	< 0.01	185.3±34.0**	179.5±36.0**	0.137
(%Change of TC, %)				(+7.7)	(-5.0)	
HDL-C, mg/dL	48.5±13.9	45.5±14.3	0.076	50.4±17.6	47.1±18.7	0.107
LDL-C, mg/dL	103.1±24.5	116.0±35.8	< 0.01	107.6±26.0	99.9±29.5**	0.015
(%Change of LDL-C, %)				(+4.4)	(-13.4)	
CRP, mg/dL	0.65±1.11	0.53±1.29	0.407	0.36±0.54	0.32±0.82	0.695

TC=total cholesterol; HDL-C=HDL cholesterol; LDL-C=LDL cholesterol; CRP=C-reactive protein. Values are mean ± SD when appropriate. Values of $p < 0.05$ were considered statistically significant. *$p < 0.05$, **$p < 0.01$ Baseline vs follow-up.

at follow-up (Table 3). LDL-C level in statins group was lower than that in control group at follow-up. HDL-C and CRP levels showed no significant differences during the follow-up period in these two groups.

Angiographic Analysis and Major Adverse Coronary Events

There was no significant difference in the follow-up period, 174.4 ± 57.2 days in control group and 180.0 ± 59.0 days in statin group (Table 2). Reference diameter was 2.91 ± 0.57 mm in control group and 2.91 ± 0.62 mm in statin group (Table 2 and Figure 1). At the procedure, minimal lumen diameter was 0.34 ± 0.44 mm in control group and 0.27 ± 0.36 mm in statin group, increasing to 2.67 ± 0.62 mm and 2.66 ± 0.65, respectively, showing no significant differences between the groups. At follow-up, minimal lumen diameter in statin group was larger than that in control group (1.74 ± 0.87 vs 1.43 ± 0.92 mm, $p < 0.01$), and angiographic restenosis rate was significantly lower in statin group than in control group (35.3 vs 46.3 %, $p = 0.042$). TLR rate was also significantly lower in statins group (14.5 vs 23.9 %, $p = 0.018$) (Figure 2). Unexpectedly, in statin group, restenosis rate and TLR rate were lower in LDL-C ≥ 100mg/dl patients compared with LDL-C < 100 mg/dl patients (Table 4).

MI related to target vessel was significantly lower in statin group , but the incidences of other major adverse coronary events during the follow-up period showed no significant difference between the groups (Table 5).

Table 4 LDL-C levels and Restenosis with or without statins

	Control			Statin		
	LDL-C Levels at FU			LDL-C Levels at FU		
	<100mg/dL (n=50)	≥100mg/dL (n=84)	*p*	<100mg/dL (n=115)	≥100mg/dL (n=92)	*p*
Restenosis, n (%)	25 (50.0)	37 (44.0)	0.508	45 (39.1)	28 (30.4)	0.195
TLR, n (%)	12 (24.0)	20 (23.8)	0.980	23 (20.0)	7 (7.6)	0.012

LDL-C=LDL cholesterol; FU=follow-up; TLR=target lesion revascularization. Values of $p < 0.05$ were considered statistically significant.

Table 5 Major Adverse Coronary Event for Follow-Up Period

	Control (n=134)	Statin (n=207)	*p*
All event, n (%)	30 (22.4)	36 (17.4)	0.255
Cardiac death, n (%)	0 (0.0)	0 (0.0)	-
MI			
target vessel, n (%)	3 (2.2)	0 (0.0)	0.031
non-target vessel, n (%)	0 (0.0)	2 (1.0)	0.255
Unstabe angina			
target vessel, n (%)	1 (0.7)	5 (2.4)	0.253
non-target vessel, n (%)	2 (1.5)	1 (0.5)	0.331
Effort angina			
target vessel, n (%)	20 (14.9)	17 (8.2)	0.052
non-target vessel, n (%)	4 (3.0)	11 (5.3)	0.307

MI=myocardial infarction. Values of $p<0.05$ were considered statistically significant.

Table 6 Multivariate Analysis of Factors Associated With Restenosis

	Odds ratio (95% CI)	*p*
Statin	0.63 (0.41-0.98)	0.042
Age>70 years	1.07 (0.69-1.66)	0.751
Male	1.06 (0.64-1.76)	0.825
Diabetes	1.17 (0.74-1.88)	0.497
Hypertension	1.41 (0.88-2.28)	0.153
Smoking	1.17 (0.74-1.88)	0.862
ACE inhibitor or ARB	1.02 (0.55-1.87)	0.953
Beta blocker	0.82 (0.51-1.33)	0.429
LDL-C<100mg/dL at follow-up	1.26 (0.81-1.94)	0.300
LDL-C>10% reduction at follow-up	1.07 (0.69-1.66)	0.755

CI=confidence interval; ACE=angiotensin converting enzyme; ARB=angiotensin II receptor bocker; LDL-C=LDL cholesterol. Values of $p < 0.05$ were considered statistically significant.

Multivariate Analysis

Multivariate analysis indicated that the prescription of statins was associated with reduced restenosis rate ($p = 0.042$) (Table 6). LDL-C level at follow-up, % reduction of LDL-C during the follow-up period, other coronary risk factors and medications except statins did not predict the restenosis development.

Discussion

This retrospective study demonstrated that statin therapy significantly reduced restenosis and TLR after successful PCI, independent of lipid-lowering effect and CRP level. Although DES can dramatically reduce angiographic restenosis, they have not completely eliminated restenosis in the real world[3)~5)20)], Japanese Ministry of Health, Labour and Welfare dose not recommend DES emergent cases of acute MI, because of its thrombogenicity. Additionally, the incidences of late cardiac death and non-fatal MI after the discontinuation of anti-platelet therapy are greater in DES treated patients as compared with BMS treated patients. Therefore DES are not suitable for the CAD patients who cannot receive long-term anti-platelet therapy[6)]. For such patients, the effect of statin on restenosis after PCI will be still of value.

Statins provide not only lipid-lowering effect but also additional pleiotropic effects, including anti-inflammatory and anti-thrombotic effects such as improvement of endothelial function and plaque stabilization[10)~12)21)]. Statins also have a direct anti-proliferative effect[22)] including inhibition of platelet derived growth factor (PDGF)-induced DNA synthesis in SMCs[23)]. Since statins can inhibit intimal hyperplasia after arterial injury[24)25)] in animal models, we can expect statins reduce restenosis after PCI in humans. Although the FLuvastatin Angioplasty Restenosis (FLARE) trial, a randomized placebo-controlled trial, did not show the beneficial effect of statin therapy on restenosis after coronary balloon angioplasty[26)], Walter et al. demonstrated that statin therapy signif-

Table 7 Comparison of the Effect of Statin therapy to Restenosis after PCI

Study	Method	Medication	Patients, n	Stent Use, %	Restenosis rate (statin vs contorl)
FLARE 1999	prospective	fluvastatin	836	0%	28% vs 31%, p=0.42
Walter et al. 2000	retrospective	various statins	525	100%	25.4% vs 38%, p<0.005
Present study	retrospective	various statins	352	83%	35.3% vs 46.3%, p=0.042

icantly reduced restenosis after coronary stent implantation[13]. Restenosis after PCI is associated with not only neointimal formation caused by SMCs proliferation and migration but also geometric remodeling[27)~29)], which can be inhibited by stent implantation[30]. These two clinical studies suggest that statin therapy may suppress neointimal formation but not geometric remodeling. The results of the present study, showing the beneficial effect of statins on restenosis after PCI, are compatible to previous studies, given that more than 80% of the patient population received coronary stent implantation (Table 7).

We have not fully understood mechanisms of the anti-proliferative effect of statin treatment in neointimal formation after PCI. Walter et al. demonstrated that baseline total cholesterol and relative change of cholesterol were not related to restenosis rate[13]. Our study also demonstrated that serum LDL-C level and its reduction rate by statins were not associated with reduction of restenosis after PCI. Additionally, in statin group, restenosis and TLR rates were lower in LDL-C ≥ 100mg/dl patients compared with those in LDL-C < 100 mg/dl patients. Even through LDL-C < 100mg/dl might be inappropriate as a cut-off value, these results may suggest that the preventive effects of statins on restenosis after PCI might not be dependent on lipid-lowering effect or LDL-C level. In addition, the present study showed that restenosis after PCI is not associated with CRP level in the follow-up period. We also consider that our low doses of statins could not directly inhibit SMCs proliferation in neointimal formation[21)22)]. Although we have no data on endothelial function in our study population, several studies indicated it is involved in the mechanism mediating suppression of the neointimal formation. Regenerated endothelial function at PCI site may play an important role in the prevention of restenosis, because nitric oxide (NO) derived from endothelium mediates not only vascular relaxation but also SMC mitogenesis and proliferation[31]. Statins increase endothelium dependent NO bioavailability by stimulating and up-regulating endothelium NO synthase in vitro[32] and in vivo[33]. More recently, Laufs et al. showed that statins suppress PDGF-induced SMC proliferation and up-regulate endothelial nitric oxide synthase by inhibiting Rho / Rho-kinase pathway[34)35)]. On the other hand, chronic oral nitrate therapy was not performed in this study because there was no evidence indicated its beneficial effect of PCI[36].

This study showed that statin therapy did not reduce major adverse coronary events except target-vessel related myocardial infarction, many clinical trials, however, have shown that lipid-lowering by statins can prevent recurrent ischemic coronary events[7)~9)37)38)], probably due to stabilization coronary atherosclerotic plaques and suppression of macrophage activity[21)39)40)]. This discrepancy may be due to a short-term assessment for 6 months with relatively low dose statin treatment.

Study Limitations

According to the guideline of Japanese atherosclerosis society for secondary prevention of CAD[16], we indicated statin therapy for patients of LDL-C levels ≥ 100 mg/dl, even if TC levels were under 220 mg/dl. Therefore, mean TC level at the procedure was relatively low even in statin group. It was unknown if the low TC level affected the results of this study or not. We need CAD patients with higher LDL-C levels to see the effects of statins depending on the lipid lowering.

References

1) Popma JJ and Topol EJ : Factors influencing restenosis after coronary angioplasty. Am J Med 88 : 1N-16N, 1990.
2) Hillegass AB, Ohman EM and Calif RM : Restenosis : the clinical issues. Philadelphia : Saunders ; 1994.
3) Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL and Kuntz RE : Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 349 : 1315-1323, 2003.
4) Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ and Russell ME : A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 350 : 221-231, 2004.
5) Ardissino D, Cavallini C, Bramucci E, Indolfi C, Marzocchi A, Manari A, Angeloni G, Carosio G, Bonizzoni E, Colusso S, Repetto M and Merlini PA : Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries : a randomized trial. Jama 292 : 2727-2734, 2004.
6) Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S and Kaiser C : Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents : an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol 48 : 2584-2591, 2006.
7) Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 339 : 1349-1357, 1998.
8) Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, Branzi A, Bertolami MC, Jackson G, Strauss B and Meier B : Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention : a randomized controlled trial. Jama 287 : 3215-3222, 2002.
9) Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA and Skene AM : Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 350 : 1495-1504, 2004.
10) Vaughan CJ, Murphy MB and Buckley BM : Statins do more than just lower cholesterol. Lancet 348 : 1079-1082, 1996.
11) Takemoto M and Liao JK : Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. Arterioscler Thromb Vasc Biol 21 : 1712-1719, 2001.
12) Davignon J : Beneficial cardiovascular pleiotropic effects of statins. Circulation 109 : III39-43, 2004.
13) Walter DH, Schachinger V, Elsner M, Mach S, Auch-Schwelk W and Zeiher AM : Effect of statin therapy on restenosis after coronary stent implantation. Am J Cardiol 85 : 962-968, 2000.
14) Horlitz M, Amin FR, Boerrigter G, Sigwart U and Clague JR : Restenosis after successful ostial stent implantation : the role of statins compared with conventional treatment. J Interv Cardiol 17 : 301-306, 2004.
15) Bae JH, Bassenge E, Kim KY, Synn YC, Park KR and Schwemmer M : Effects of low-dose atorvastatin on vascular responses in patients undergoing percutaneous coronary intervention with stenting. J Cardiovasc Pharmacol Ther 9 : 185-192, 2004.

16) Hata Y, Mabuchi H, Saito Y, Itakura H, Egusa G, Ito H, Teramoto T, Tsushima M, Tada N, Oikawa S, Yamada N, Yamashita S, Sakuma N and Sasaki J : Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults. J Atheroscler Thromb 9 : 1-27, 2002.
17) Albiero R, Silber S, Di Mario C, Cernigliaro C, Battaglia S, Reimers B, Frasheri A, Klauss V, Auge JM, Rubartelli P, Morice MC, Cremonesi A, Schofer J, Bortone A and Colombo A : Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis : results of the restenosis cutting balloon evaluation trial (RESCUT). J Am Coll Cardiol 43 : 943-949, 2004.
18) MacIsaac AI, Bass TA, Buchbinder M, Cowley MJ, Leon MB, Warth DC and Whitlow PL : High speed rotational atherectomy : outcome in calcified and noncalcified coronary artery lesions. J Am Coll Cardiol 26 : 731-736, 1995.
19) Baim DS, Cutlip DE, Sharma SK, Ho KK, Fortuna R, Schreiber TL, Feldman RL, Shani J, Senerchia C, Zhang Y, Lansky AJ, Popma JJ and Kuntz RE : Final results of the Balloon vs Optimal Atherectomy Trial (BOAT). Circulation 97 : 322-331, 1998.
20) Wong A and Chan C : Drug-eluting stents : the end of restenosis? Ann Acad Med Singapore 33 : 423-431, 2004.
21) Fukumoto Y, Libby P, Rabkin E, Hill CC, Enomoto M, Hirouchi Y, Shiomi M and Aikawa M : Statins alter smooth muscle cell accumulation and collagen content in established atheroma of watanabe heritable hyperlipidemic rabbits. Circulation 103 : 993-999, 2001.
22) Corsini A, Pazzucconi F, Pfister P, Paoletti R and Sirtori CR : Inhibitor of proliferation of arterial smooth-muscle cells by fluvastatin. Lancet 348 : 1584, 1996.
23) Yang Z, Kozai T, van der Loo B, Viswambharan H, Lachat M, Turina MI, Malinski T and Luscher TF : HMG-CoA reductase inhibition improves endothelial cell function and inhibits smooth muscle cell proliferation in human saphenous veins. J Am Coll Cardiol 36 : 1691-1697, 2000.
24) Gellman J, Ezekowitz MD, Sarembock IJ, Azrin MA, Nochomowitz LE, Lerner E and Haudenschild CC : Effect of lovastatin on intimal hyperplasia after balloon angioplasty : a study in an atherosclerotic hypercholesterolemic rabbit. J Am Coll Cardiol 17 : 251-259, 1991.
25) Soma MR, Donetti E, Parolini C, Mazzini G, Ferrari C, Fumagalli R and Paoletti R : HMG CoA reductase inhibitors. In vivo effects on carotid intimal thickening in normocholesterolemic rabbits. Arterioscler Thromb 13 : 571-578, 1993.
26) Serruys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M, Branzi A, Shepherd J, Suryapranata H, de Feyter PJ, Melkert R, van Es GA and Pfister PJ : A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty ; final results of the fluvastatin angiographic restenosis (FLARE) trial. Eur Heart J 20 : 58-69, 1999.
27) Currier JW and Faxon DP : Restenosis after percutaneous transluminal coronary angioplasty : Have we been aiming at the wrong target? J Am Coll Cardiol 25 : 516-520, 1995.
28) King SB, 3rd : Vascular stents and atherosclerosis. Circulation 79 : 460-462, 1989.
29) Serruys PW, Beatt KJ, Giessen WJ : Stenting of Coronary arteries : are we the sorcerer's apprentice? Eur Heart J 10 : 774-782, 1989.
30) Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, Kent KM, Griffin J and Leon MB : Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation 94 : 1247-1254, 1996.
31) Garg UC and Hassid A : Nitric oxide -generating vasodilators and 8-bromo -cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. J Clin Invest 83 : 1774-1777, 1989.
32) Laufs U, La Fata V, Plutzky J, Liao JK : Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 97 : 1129-1135, 1998.
33) Egashira K, Hirooka Y, Kai H, Sugima-

chi M, Suzuki S, Inou T and Takeshita A : Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. Circulation 89 : 2519-2524, 1994.
34) Laufs U, Marra D, Node K and Liao JK : 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors attenuate vascular smooth muscle proliferation by preventing rho GTPase-induced down-regulation of p27(Kip1). J Biol Chem 274 : 21926-21931, 1999.
35) Laufs U, Liao JK : Targeting Rho in cardiovascular disease. Circ Res 87 : 526-528, 2000.
36) Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC, Jr. : ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction --executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). J Am Coll Cardiol 44 : 671-719, 2004.
37) Manzato E : Scandinavian simvastatin study (4S). Lancet 344 : 1767 ; author reply 1767-1768, 1994.
38) Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR and Braunwald E : The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 335 : 1001-1009, 1996.
39) Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, Shiomi M, Schoen FJ and Libby P : An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro. Circulation 103 : 276-283, 2001.
40) Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H and Daida H : 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 110 : 1061-1068, 2004.

(Received for publication February 8, 2007)

Abbreviation List

PCI = percutaneous coronary intervention
CAD = coronary artery disease
DES = drug eluting stents
MI = myocardial infarction
CRP = C-reactive protein
SMCs = smooth muscle cells
TC = total cholesterol
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
TLR = target lesion revascularization
MLD = minimal lumen diameter
PDGF = platelet derived growth factor
NO = nitric oxide

(和文抄録)

経皮的冠動脈形成術後患者におけるスタチンの再狭窄予防効果の検討

麻生飯塚病院 循環器科
山脇 徹，山田 明，福本義弘，岸 拓弥，側島淳史，桑田孝一，
中村 亮，関屋正俊，安藤洋志，岡松秀一

背景：スタチンには様々な抗動脈硬化作用があることが知られているが，我々は経皮的冠動脈形成術の再狭窄にスタチンが影響を与えるか，後ろ向きに検討を行った．
方法：当院で2002年1月から2004年12月までの期間で経皮的冠動脈形成術を施行し，約6ケ月後に経過観察のための冠動脈造影を施行された341例を対象とした．207例がスタチン投与を受け(スタチン群)，それ以外の134例は投与を受けていなかった(コントロール群)．両群間で冠動脈造影所見とLDLコレステロール，CRPについて比較検討を行った．
結果：ベースラインではLDLコレステロール値はスタチン群で有意に高かった（116.0 ± 35.8 vs 103.1 ± 24.5 mg/dL，p < 0.01)．しかし6ケ月後の経過観察の時点では逆転していた（99.9 ± 29.5 vs 107.6 ± 26.0 mg/dL，p=0.015)．CRPは両群間で差はなかった．スタチン群ではコントロール群に比べて再狭窄率は有意に低下していた．(35.3 vs 46.3 %，p = 0.042)．また再治療率も同様であった．(14.5 vs 23.9 %，p = 0.018)．多変量解析では経過観察時のLDLコレステロール値やLDLコレステロール低下率は再狭窄率とは相関を認めなかった．
結論：本研究ではスタチンがコレステロール低下効果やCRPとは関係なく経皮的冠動脈形成術後の再狭窄率や再治療率を減少させうることを示した．