The Effects of Starting Statin Therapy Prior to Percutaneous Coronary Intervention with Drug-Eluting Stent on Postprocedural Myonecrosis and Clinical Outcome

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Background: Statin therapy prior to or soon after percutaneous coronary intervention (PCI) is associated with improved clinical outcome in those patients. Recent trials have demonstrated that drug-eluting stent (DES) can reduce stent failure due to restenosis. The objective of this study was to determine whether starting statin treatment prior to PCI with DES reduced periprocedural myonecrosis and improved clinical outcome.

Methods: A total of 161 patients (aged 66.2 ± 10.6 years, M/F = 116/45) with stable or unstable angina pectoris who underwent PCI with DES were enrolled. Statin therapy was administered at the discretion of the attending physician. We compared the peri-procedural serum levels of creatine phosphokinase (CPK) and MB-fraction of creatine phosphokinase (CK-MB), the incidence of myonecrosis, defined as elevation of peak CK-MB above upper limit of normal within 24 hours after the index procedure, and the major adverse cardiovascular event (MACE) rates up to 9 months between the statin-treated (statin group; n = 63) and non-statin-treated (non-statin group; n = 98) patients. Major adverse cardiovascular events were defined as cardiac death, nonfatal myocardial infarction or stroke, or re-intervention procedure.

Results: The baseline and procedural data were similar in both groups. However, statin-treated patients were more likely to have hyperlipidemia (81.0% vs. 62.2%; $P = 0.01$), younger age (61.9 years vs. 69.0 years; $P < 0.0001$), and longer lesion length (22.07 mm vs. 17.30 mm; $P = 0.05$) than non-statin-treated patients. Postprocedural peak levels of CK-MB (10.32 IU/L vs. 17.05 IU/L; $P = 0.04$) and the incidence of myonecrosis (24% vs. 46%; $P = 0.05$) were significant lower in the statin group than those in the non-statin group. Within a 9-month period, receiving statin therapy was not associated with a significant reduction of MACE (log rank test, $P = 0.44$).

Conclusion: Our data demonstrate that starting statin therapy before PCI with DES can reduce periprocedural myonecrosis. Whether statin therapy can improve long-term clinical outcome in those patients needs to be confirmed in larger prospective randomized trials.

Key Words: Statins • Drug-eluting stent • Percutaneous coronary intervention • Myonecrosis • Clinical outcome

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INTRODUCTION

Primary and secondary prevention with statins reduces major adverse cardiovascular events (MACE) in patients with coronary artery disease.[1-3] Percutaneous coronary intervention (PCI) is effective in relieving ischemic symptoms due to coronary atherosclerotic nar-

rowing in patients with coronary artery disease. However, although PCI effectively improves symptoms by restoring coronary perfusion, patients continue to have high rates of postprocedural cardiovascular events.[4] Recent studies have demonstrated that drug-eluting stent (DES) can significantly reduce restenosis in patients undergoing PCI.[5-8]

A few reports also suggest that statin therapy prior to or soon after PCI is associated with reduced periprocedural myocardial damage or infarction[9,10] and MACE with respect to cardiac death, non-fatal myocardial infarction and re-intervention procedure.[11-14] However, the impact of pretreatment with statins prior to PCI with DES is not well established. The aim of the present study was to determine whether starting statin therapy before PCI with DES could reduce peri-procedural myonecrosis and improve clinical outcome at 9 months.

METHODS

Study participants

Between November 2003 and August 2004, a total of 161 patients with stable or unstable angina who underwent PCI with DES (Cypher or Taxus stent) were recruited. Exclusion criteria were acute myocardial infarction (MI), recent myocardial infarction (within 7 days of procedure), cardiogenic shock, any increase in creatine phosphokinase (CPK), MB-fraction of creatine phosphokinase (CK-MB), or Troponin I above upper normal limit at the time of PCI, renal failure with creatinine > 3 mg/dl, or a history of liver or muscle disease.

Statin therapy was administered at the discretion of the attending physician. Patients were stratified into 2 groups: the statin group consisted of 63 patients who had been treated with statin therapy at least 3 days prior to PCI and thereafter; the non-statin group consisted of 98 patients who were not on statin therapy at the time of PCI or during a 9-month follow-up. The statins used in the present study included simvastatin in 11% of cases, atorvastatin in 71% of cases, pravastatin in 8% of cases and fluvastatin in 8% of cases. All patients without contra-indications were pretreated with aspirin (100 mg/day) and ticlopidine 200 mg twice a day for at least 3 days before the procedure or with clopidogrel 300 mg at least 6 hours before the procedure. All patients continued ticlopidine 200 mg twice daily or clopidogrel 75 mg once daily for at least 3 months. Procedural success was defined as a reduction of stenosis to <30% residual narrowing. Myonecrosis was defined as elevation of peak CK-MB above upper limit of normal within 24 hours after the index procedure. The normal value of CPK-MB is 7.9-17.3 IU/L and of CPK is 43-244 IU/L.

Access to hospital records was approved by the hospital human subjects review board at Cheng-Hsin General Hospital. Informed consent was obtained from all participants before the screening.

Data collection and blood sampling

The demographic and procedural data, including medication use, hemodynamic status, equipment use, and final result of each case and MACE, defined as cardiac death, nonfatal MI, stroke, or reintervention procedure (including coronary artery bypass grafting, repeat PCI, or PCI for a new lesion) data were collected by a cardiologist and research coordinators through patient interview, chart review, and serial telephone contacts. Subjects implanted with bare metal stents were excluded.

Before the index procedure and after PCI with DES, venous blood samples were collected serially at 6 to 8 hours and the morning after PCI (16 hours to 24 hours) to assay CPK and CK-MB. All cardiac enzyme measurements were done at the clinical chemistry laboratory of this hospital. CPK measurements were obtained using the Germany Society of Clinical Chemistry method (GSCC method, Autoanalyzer Hitachi 917). The CK-MB was measured with immunoinhibition combined GSCC method (Autoanalyzer Hitachi 917).

Statistical analysis

Statistical analysis was performed using SAS 8.1 (SAS Institute, Cary, NC, USA). In the univariate analysis, chi-square (χ^2) testing or two-sample independent Student's *t*-testing were applied, respectively, for discrete or continuous variables. The linear regression model was used to assess the independent effects of statin use on CPK or CK-MB values after controlling for age. The Kaplan-Meier method was used to estimate the cumulative event rates, with the study patients being stratified into two groups according to whether continuous statin therapy was administered. The differences between event rate curves were tested by a log rank test. A *p*-value of <

0.05 was considered statistically significant. The results are presented as means ± standard deviations (SDs). In addition, the Kolmogorov-Smirnov test was used to determine the normal (Gaussian) distribution of CPK and CK-MB before parametric statistical analyses.

RESULTS

Baseline characteristics of the study patients

In this study, 84.5% of subjects had implanted one stent, 13.0% two stents, and 2.5% three stents. The demographic data of the study population are presented in Table 1. There were no significant differences in baseline characteristics between the two groups with respect to gender, diabetes, smoking status, hypertension and so on. The cumulative incidences of statins and non-statins used were 13.47% and 10.57% (p value = 0.44 for log-rank test), respectively. However, as expected, the incidence of a history of hyperlipidemia was significantly higher in patients receiving continuous statin therapy compared with patients not taking a statin (81.0% vs. 62.2 %; $P = 0.01$). Furthermore, the mean age of the statin group was significantly younger than that of the non-statin group (61.9 years vs. 69.0 years, $P < 0.0001$). The levels of total cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides were similar between the two groups.

Procedural data of the study population

The procedural data of the two groups are presented in Table 2. There were no significant differences between the two groups in lesion location, lesion type, proportion of restenotic lesion, diameter of reference vessel and diameter stenosis of the target lesion. However, the lesion length was longer in the statin group

Table 1. Comparison of baseline characteristics between statin and non-statin patients prior to percutaneous coronary intervention (PCI)

Variable	PCI patients						P value for χ^2 test or t test
	Statins used		Non-statins used		Total		
	(n = 63)		(n = 98)		(n = 161)		
Categorical variables							
Gender (male)	48	76.2%	68	69.4%	116	72.0%	0.35
Smoking (yes)	26	41.2%	40	41.2%	66	41.0%	0.93
Regular exercise	26	41.3%	30	30.6%	56	34.8%	0.17
Hypertension	41	65.1%	74	75.5%	115	71.4%	0.20
Diabetes mellitus	21	33.3%	29	29.6%	50	31.1%	0.55
Hyperlipidemia	51	81.0%	61	62.2%	112	69.6%	0.01
Family history	3	4.8%	3	2.9%	6	3.7%	0.68
LVEF < 40	6	9.5%	7	7.1%	13	8.1%	0.51
Unstable angina	14	22.2%	18	18.4%	32	19.9%	0.79
Continuous variables							
Age (yrs)	61.9 ± 11.3		69.0 ± 9.1		66.2 ± 10.6		< 0.0001
BMI (Kg/m^2)	25.9 ± 3.6		25.8 ± 3.7		25.8 ± 3.7		0.94
BUN	18.4 ± 6.9		17.8 ± 5.0		18.2 ± 6.2		0.54
Creatinine	1.09 ± 0.28		1.13 ± 0.34		1.11 ± 0.32		0.46
Uric acid	6.3 ± 1.7		6.8 ± 1.8		6.6 ± 1.7		0.10
Triglyceride	150.2 ± 117.1		145.7 ± 83.1		147.5 ± 97.6		0.77
Total cholesterol	186.3 ± 44.9		195.7 ± 38.3		192.0 ± 41.2		0.16
LDL-cholesterol	117.8 ± 40.7		127.9 ± 33.8		124.0 ± 36.6		0.10
HDL-cholesterol	46.1 ± 11.6		45.7 ± 12.1		45.8 ± 11.9		0.84
Number of vessels treated	1.32 ± 0.47		1.30 ± 0.48		1.31 ± 0.48		0.73

LVEF = left ventricular ejection fraction; BMI = body mass index; LDL-cholesterol = low-density lipoprotein cholesterol; HDL-cholesterol = high-density lipoprotein cholesterol.

Table 2. Comparison of the procedural characteristics between statin and non-statin patients prior to percutaneous coronary intervention (PCI)

Variable	PCI patients			P value for χ^2 test or t test
	Statins used	Non-statins used	Total	
	(n = 63)	(n = 98)	(n = 161)	
Categorical variables				
Lesion location				
LAD	59.6%	57.5%	58.4%	0.11
LCX	25.0%	13.7%	18.4%	
RCA	15.4%	28.8%	23.2%	
Restenotic lesion				
Yes	15.1%	11.0%	12.6%	0.48
No	84.9%	89.0%	87.4%	
AHA lesion type				
A	4.0%	11.7%	8.7%	0.29
B1	20.0%	27.3%	24.4%	
B2	32.0%	26.0%	28.4%	
C	44.0%	35.1%	38.6%	
Continuous variables				
Lesion length	22.07 ± 15.27	17.30 ± 9.41	19.13 ± 12.18	0.05
Reference vessel diameter	3.13 ± 0.35	3.33 ± 2.56	3.25 ± 2.02	0.48
Analysis segment stenosis (%)	79.13 ± 16.03	75.88 ± 19.69	77.17 ± 18.33	0.32

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; AHA = American Heart Association.

compared with that in the non-statin group (22.07 mm vs. 17.30 mm, $P = 0.05$).

Post-procedural CPK and CK-MB changes

Post-procedural peak levels of CPK (79.71 IU/L vs. 112.81 IU/L, $P = 0.04$) and CK-MB (10.32 IU/L vs. 17.05 IU/L, $P = 0.04$) were significantly lower in the statin group than in the non-statin group (Table 3). The peak CK-MB level was significantly lower in the statin group compared to that of the non-statin group, even after adjustment for age ($P = 0.015$).

The incidence of myonecrosis, defined as elevation of peak CK-MB above upper limit of normal within 24 hours after the index procedure, was significantly lower in the statin group than in the non-statin group (24% vs. 46%, $P = 0.05$; Figure 1).

Clinical outcome at nine months

The MACE rates of the two groups are presented in Figure 2. At 9 months, there was a 13.47% (8 of 63) cu-

Table 3. Comparison of CPK and CK-MB between statin and non-statin patients prior to percutaneous coronary intervention (PCI)

Variable	PCI patients			P value for t test*	P value after adjusting for confounding factors**
	Statins used	Nonstatins used	Total		
	(n = 63)	(n = 98)	(n = 161)		
CPK (IU/L)	79.71 ± 42.51	112.81 ± 95.51	99.82 ± 80.53	0.04	0.127
CK-MB (IU/L)	10.32 ± 10.80	17.05 ± 17.71	14.41 ± 15.69	0.04	0.044

CPK = creatine phosphokinase; CK-MB = MB-fraction of creatine phosphokinase.

*P-values of Komogorov-Smirnov test of normal distribution for CPK and CK-MB were 0.07 and 0.10, respectively.

**Confounding factors included gender, age, drug medication, smoking, regular exercise, BMI, BUN, creatinine, uric acid, triglyceride, total cholesterol, unstable angina, and number of vessels treated.

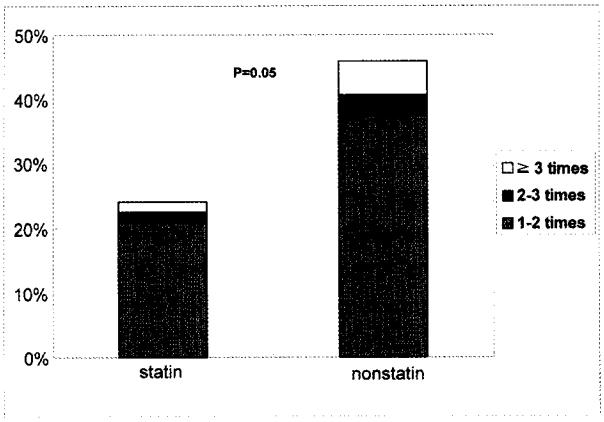

Figure 1. The distribution of CK-MB 1-2, 2-3, and ≧ 3 times above upper normal limit in statin and non-statin groups.

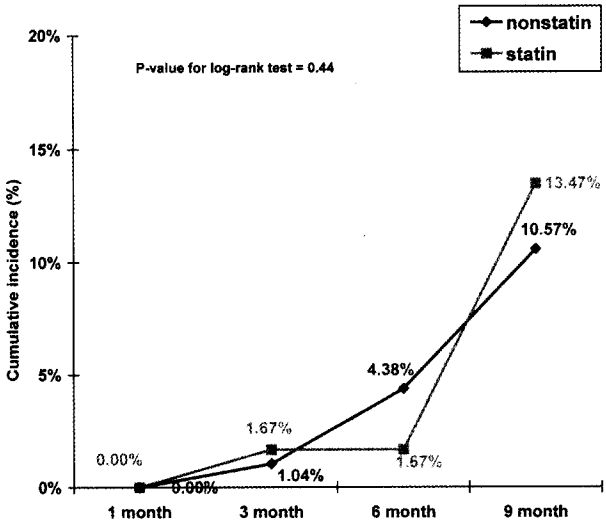

Figure 2. Cumulative incidence of major adverse cardiac events (death, stroke, MI, revascularization with PCI or CABG) between statin and non-statin groups.

mulative event rate in the statin group and a 10.57% (10 of 98) event rate in the non-statin group (log rank test, $P = 0.44$). Within the total combined patient population, MACE was the primary cause of death in 1, stroke in 2, and readmission for re-intervention in 15.

DISCUSSION

It is well known that PCI is an effective method of myocardial revascularization. During the past decade, PCI procedure volumes have been growing rapidly worldwide. However, although patients undergoing PCI experience short-term improvements in ischemic symptoms, rates of cardiovascular events following PCI remain high.[4] Although PCI effectively improves symptoms by restoring coronary perfusion, the vascular injury from PCI may induce platelet activation, thrombosis, and inflammation within the vessel wall and the distal microvasculature, resulting in systemic inflammatory and prothrombotic substrates, which have been postulated to be a major contributor to restenosis and cardiovascular events after PCI.[14,15] The first strategy that was shown to be effective in lowering restenosis following balloon angioplasty was stent implantation. However, in-stent restenosis, which is mainly due to neointimal proliferation, has been the Achilles' heel of interventional cardiology. In recent years, DES has shown promising results in the treatment of in-stent restenosis, with a low incidence of recurrent restenosis and adverse cardiac events.[5-8]

Statins have important lipid-lowering and anti-inflammatory effects, both in intro[16] and in vivo.[17] Several studies have suggested that statin therapy prior to or soon after PCI is associated with reduced periprocedural myocardial damage or infarction,[9,10,18] adverse cardiac events and mortality during follow-up.[11-14] Among them, the Lescol Intervention Prevention Study (LIPS) is the first large, randomized prospective trial to demonstrate the benefits of statin therapy in patients post-first PCI for reducing MACE. The results showed that early initiation of lipid-lowering treatment with fluvastatin at hospital discharge significantly reduced the incidence of MACE, with a risk reduction of 22%. The beneficial effects of fluvastatin have been observed in patients with unstable and stable angina alike. In a subpopulation analysis, greater benefits with the use of early fluvastatin treatment in post-PCI patients were seen in diabetics and those with multi-vessel disease.[12] The results of LIPS support the use of early lipid-lowering therapy in post-PCI patients, irrespective of the clinical presentation (stable or unstable angina), stent use or baseline lipid level.

Although the exact underlying mechanisms of the beneficial effect of statins are not completely clear, the anti-inflammatory effect of statins might contribute to the reduction of myocardial necrosis due to microembolization during coronary intervention.[14,15] Furthermore, aggressive LDL-C lowering itself should also be an im-

portant mechanism for event reduction by early statin treatment in patients undergoing PCI.[11-14] In the ESTABLISH trial, aggressive lipid-lowering by atorvastatin 40 mg daily immediately after acute coronary syndrome onset significantly reduced the plaque volume of a non-culprit lesion compared with the control group, even in patients with baseline LDL-C < 125 mg/dL.[19] For these reasons, the practice patterns with regard to adjuvant pharmacological therapy in patients undergoing PCI have changed in recent years. For example, in the Cleveland Clinic, only 26.5% of patients undergoing PCI between 1993 and 1999 were receiving statin treatment at the time of the procedure, but in the year 2000, 39.6% of patients had statins initiated before the procedure, and in 2002, 88.3% of non-statin-pretreated patients were started on a statin after PCI.[14]

However, in the DES era, whether pretreatment with statin can still significantly reduce procedural myocardial injury in elective PCI and improve clinical outcome has never been studied. In the ARMYDA (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) study, only 22% of the study patients underwent DES implantation.[9] Therefore, the aim of the present study was to determine whether starting statin therapy before PCI with DES could reduce peri-procedural myonecrosis and improve clinical outcome at 9 months. Although we did not check baseline CPK and MB levels, our data demonstrates that starting statin therapy prior to PCI with DES resulted in a significant reduction in the risk of periprocedural myocardial injury as measured by peak CPK and CK-MB levels. This is a limitation of this study. However, statin therapy was not associated with a significant reduction of future cardiac events at 9 months.

Since all trials regarding statin therapy in patients undergoing PCI have failed to demonstrate a reduction of restenotic complications at 6 months with statins,[11,12,20,21] it is not surprising that statin therapy was not associated with a significant reduction in MACE at 9 months in our study. Three earlier trials that focused on the effect of statins on angiographic restenosis failed to demonstrate an effect on angiographic outcome at the target site after PCI.[11,20,21] Even in the large, randomized LIPS, with early initiation of lipid-lowering treatment with fluvastatin at hospital discharge, a significant reduction in the incidence of MACE did not appear until approximately 1.5 years after the index procedure. When overlapping restenotic complications, that is, repeat PCI on index target lesion in the first 6 months, are not taken into account, separation of the fluvastatin MACE-free survival curve from the placebo control curve occurred at approximately 6 months.[12] The low number of patients, low rates of MACE, and the short follow-up periods in this study most likely explain the lack of the expected reduction of MACE at 9 months. However, a statistically significant reduction of peak CK-MB levels and the incidence of post-procedural myonecrosis was observed in patients receiving continuous statin therapy compared with patients not taking a statin in the current study. Whether this and other vascular protective effects of statins in combination with the promising anti-proliferative effect of DES are effective in improving long-term clinical outcomes in those who undergo PCI needs to be confirmed in larger and longer studies.

CONCLUSIONS

The present study shows that starting statin therapy before PCI with DES can reduce periprocedural myonecrosis but has a neutral effect on short-term clinical outcome. Whether statin therapy can improve long-term clinical outcome in those patients needs to be confirmed in larger prospective randomized trials.

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在裝置塗藥支架之介入治療術前即開始使用 Statin 類藥物對術後心肌受損及預後之影響

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背景 在冠狀動脈介入治療術前或稍後使用 Statin 類降血脂藥物可有效改善此類患者之臨床預後。裝置塗藥支架則證實可有效減少介入治療術後血管再狹窄的發生。然而若在置放塗藥支架前即開始使用 Statin 類藥物是否能減少術後之心肌受損且改善臨床預後則不得而知，也是本研究探討的主題。

方法 本研究收集本院 161 位因冠心症合併心絞痛而接受例行介入治療並裝置塗藥支架的患者進行分析，病患是否使用 Statin 類降血脂藥物由其主治醫師自行決定。病患依是否使用 Statin 類降血脂藥物分為兩組：自術前即開始使用 Statin 類藥物且術後持續使用者為 Statin 組 (N = 63)；自術前至術後第九個月止均未使用該類藥物者為 Non-Statin 組 (N = 98)。我們在術前及術後第 6 至 8 小時及第 16 至 24 小時共抽血三次測其血清中 CPK 及 CK-MB 的數值，以評估術後心肌受損的程度。所有病患並追蹤至術後第九個月，統計其是否發生死亡、復發心肌梗塞、腦中風及血管再阻塞而需重行介入治療等重大心血管事件之發生率。

結果 Statin 組患者與 Non-statin 組患者相較，其基本臨床及手術資料類似，然而前者之高血脂症發病率較高 (81.0% vs. 62.2%；$P = 0.01$)、年齡較輕 (61.9 歲 vs. 69.0 歲；$P < 0.0001$)、且血管病灶較長 (22.07 mm vs. 17.30 mm；$P = 0.05$)。Statin 組其代表心肌受損之術後 CK-MB 最高值明顯低於 Non-statin 組 (10.32 IU/L vs. 17.05 IU/L；$P = 0.04$)；其術後 CK-MB 超過正常值之心肌受損發生率也明顯少於 Non-statin 組 (24% vs. 46%；$P = 0.05$)。追蹤至術後第九個月時，Statin 組之重大心血管事件之發生率與 Non-statin 組相近 (log rank test, $P = 0.44$)。

結論 在裝置塗藥支架之介入治療術前即開始使用 Statin 類藥物可減少術後心肌受損。至於是否能改善長期臨床預後，仍須大型前瞻性隨機研究加以驗證。

關鍵詞： Statin 類降血脂藥物、塗藥支架、介入治療術、心肌受損、臨床預後。