Original Article

Long-Term Efficacy of Pravastatin Therapy in Diabetic Patients Undergoing Complete Coronary Revascularization

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Aim: The long-term effect of statin therapy in diabetic patients after coronary revascularization is not well established. Accordingly, we sought to determine if whether statin therapy initiated at the time of complete revascularization including percutaneous coronary intervention (PCI) and/or bypass surgery reduces total and cardiac mortality among diabetic patients.

Methods: We collected data from 1,138 consecutive patients who underwent complete revascularization (PCI and/or bypass surgery). We then compared all-cause and cardiac mortality rates in 499 patients with diabetes mellitus of whom 149 (29.9%) were treated with statin at the time of revascularization. To adjust the variables that would have been related to the decision regarding statin administration, a propensity score was computed and multivariate Cox regression was carried out.

Results: During follow-up (8.8 ± 2.6 years), 103 patients died (including 43 who died of cardiac causes). The Multivariate analysis showed statin therapy to be significantly associated with reduced cardiac mortality (HR 0.39, 0.16 – 0.95; $p=0.039$), but not with all-cause mortality.

Conclusion: Statin therapy was associated with a significantly reduced risk of cardiac mortality in patients with diabetes mellitus and coronary artery disease after complete revascularization.

J Atheroscler Thromb, 2010; 17:350-355.

Key words; Diabetes, Statin, Long-term follow-up, Coronary intervention

Introduction

The long-term mortality rate after coronary intervention is two times higher among diabetic patients than non-diabetic patients¹. However, recent large-scale clinical trials have demonstrated that intensive glucose lowering therapy had insufficient power to reduce the incidence of major cardiovascular events^{2, 3}. Because patients with diabetes are more likely to have coronary risk factors than non-diabetic patients⁴, the control of other risk factors is an alternative therapeutic strategy for ameliorating cardiovascular events⁵. Clinical trials have shown that statins reduce the frequency of adverse cardiac events and rate of mortality

as secondary prevention⁶. This beneficial effect is more exaggerated in high risk patients. However, the long-term effect of statin therapy in diabetic patients after coronary revascularization is less well established. Accordingly, we investigated whether statin therapy initiated at the time of complete revascularization including percutaneous coronary intervention (PCI) and/or bypass surgery is associated with a reduced risk of total mortality and cardiac mortality among diabetic patients.

Methods

Subjects and Baseline Data Collection

We analyzed data from consecutive patients who had undergone surgical revascularization and/or PCI at Juntendo University Hospital between November 1987 and December 1992. Patients who met the following inclusion criteria were enrolled: 1) complete revascularization, defined as no un-bypassed major

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Received: February 26, 2009

Accepted for publication: October 6, 2009

vessels with $\geq 50\%$ stenosis and 2) diabetes mellitus defined as a fasting blood glucose concentration ≥ 126 mg/dL or treatment with oral hypoglycemic drugs or insulin injections at the time of complete revascularization. Patients who had other known life-threatening diseases at baseline and those who had undergone complex cardiac procedures, such as valve replacement or aneurysm repair at the time of surgical revascularization, were excluded.

Demographic data, including age, gender, and body mass index (BMI), coronary risk factors (blood pressure, lipid profile, fasting plasma glucose, smoking status, and family history of coronary artery disease), medication use, revascularization procedure-related factors, and co-morbidity (prior myocardial infarction or stroke, on dialysis, and atrial fibrillation) were collected from our institutional database.

For all analyses, patients were divided into 2 groups according to statin use at the time of complete revascularization. Each patient was further categorized based on the presence of coronary risk factors using the following criteria during the study period: hypertension defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or treatment with antihypertensive medications. A current smoker was defined as one who was smoking at the time of complete revascularization or who had quit smoking within 1 year of the complete revascularization. Atrial fibrillation was defined as persistent or permanent atrial fibrillation at the time of the procedure. Patients with isolated PCI comprised those in whom revascularization was completed by PCI without bypass grafting.

This study was performed according to the ethics policies of the institution, and approved by the internal review board.

Outcomes

Survival data were collected by serial contact (every 5 years) with the patients or their families until September 30, 2000 and from the medical records of patients who had died and of those who continued to be followed at our hospital. Information about the continuation of statin use and the circumstances and date of death was obtained from the families of patients who had died at home, and details of cardiac events or causes of death were supplied by other hospitals or clinics where the patients had been admitted. Mortality data were categorized according to the cause of death, such as death from all causes, cardiac death due to coronary artery disease or cardiogenic shock, and sudden death.

Statistical Analysis

Continuous variables are expressed as the mean $\pm$ SD and were compared using Student's *t*-test. Categorical data are displayed as frequencies and percentages and were compared using the Chi-square test or Fisher's exact test. Survival was estimated using the Kaplan-Meier method with the log-rank test and Cox proportional hazards models. To adjust the variables that would have been related to the decision regarding statin therapy at the time of revascularization, a propensity analysis was used.

A propensity analysis aims to identify patients with similar probabilities of receiving statins on the basis of observed clinical characteristics. Variables in the stepwise multivariate logistic regression analysis included: age, gender, BMI, total and HDL cholesterol levels, triglyceride level, hypertension, current smoker, family history of CAD, previous MI, previous stroke, on dialysis, atrial fibrillation, use of insulin, oral hypoglycemic drugs, nitrate, nicorandil, angiotensin converting enzyme inhibitors, beta blockers, calcium channel blockers, aspirin, other lipid lowering drugs, number of diseased vessels, left ventricular ejection fraction, and revascularization procedure date (before or after the median procedure date: October 26, 1990).

Based on the results of this logistic regression analysis, a propensity score was calculated for each patient. The propensity score was related to the probability of receiving statin therapy, a higher score indicating a higher probability of being allocated to the statin group in the present study. The goodness of fit of the propensity score was assessed using an area under the receiver operating characteristic curve (c-statistics).

In addition to the crude model, the benefits of statin therapy against all-cause and cardiovascular death were determined using three multivariate Cox proportional hazards models (Model 1, adjusted for propensity score; Model 2, adjusted for arterial bypass graft to LAD, whether complete revascularization was achieved by isolated PCI; Model 3, adjusted for variables included in Model 2 and propensity score.)

P-values < 0.05 were considered significant. All data were analyzed using Dr. SPSS II for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

Overall, complete revascularization was achieved during the study period in 1,138 patients, 499 (43.9%) of whom had diabetes. Baseline characteristics and

Table 1. Baseline characteristics

	No-Statins <i>n</i> = 350	Statins <i>n</i> = 149	<i>p</i> value
Age, years old	60.0 ± 9.2	61.7 ± 8.7	0.054
Male, <i>n</i> (%)	294 (84.0)	120 (80.5)	0.417
BMI, kg/m ²	23.8 ± 2.8	23.9 ± 2.8	0.669
Hypertension, <i>n</i> (%)	236 (67.4)	104 (69.8)	0.678
Total cholesterol, mg/dL	210.7 ± 49.0	208.4 ± 48.8	0.632
HDL cholesterol, mg/dL	40.1 ± 12.0	40.6 ± 10.3	0.330
Triglyceride, mg/dL	167.1 ± 114.9	157.8 ± 83.0	0.372
Current smoker, <i>n</i> (%)	253 (72.3)	102 (68.5)	0.450
Family history of CAD, <i>n</i> (%)	113 (32.3)	55 (36.9)	0.369
Prior MI, <i>n</i> (%)	165 (47.1)	54 (36.2)	0.032
Prior Stroke, <i>n</i> (%)	19 (5.4)	3 (2.0)	0.144
Atrial fibrillation, <i>n</i> (%)	50 (14.3)	17 (11.4)	0.472
On dialysis, <i>n</i> (%)	11 (3.1)	2 (1.3)	0.396
LVEF, %	63.1 ± 13.8	66.4 ± 12.6	0.013
LMT lesion, <i>n</i> (%)	27 (7.7)	8 (5.4)	0.455
Arterial bypass graft to LAD, <i>n</i> (%)	165 (47.1)	45 (30.2)	0.001
Number of diseased vessels	2.3 ± 0.83	2.1 ± 0.86	0.014
Multivessel disease, <i>n</i> (%)	266 (76.0)	101 (67.8)	0.073
Isolated PCI, <i>n</i> (%)	243 (69.4)	72 (48.3)	<0.001
Procedure date ≥ median, <i>n</i> (%)	172 (49.1)	78 (52.3)	0.577

BMI, body mass index; CAD, coronary artery disease; MI myocardial infarction; LVEF, left ventricular ejection fraction; LMT, left main trunk; LAD, left anterior descending, PCI, percutaneous coronary intervention

Table 2. Use of medications

	No-Statins <i>n</i> = 383	Statins <i>n</i> = 146	<i>p</i> value
Insulin, <i>n</i> (%)	25 (7.1)	8 (5.4)	0.594
Oral hypoglycemic drugs, <i>n</i> (%)	86 (24.6)	35 (23.5)	0.886
Nitrates, <i>n</i> (%)	323 (92.3)	136 (91.3)	0.841
Nicorandil, <i>n</i> (%)	73 (20.9)	34 (22.8)	0.712
ACE inhibitors, <i>n</i> (%)	24 (6.9)	10 (6.7)	0.947
Calcium channel blockers, <i>n</i> (%)	127 (36.3)	48 (32.2)	0.442
Beta blockers, <i>n</i> (%)	106 (30.3)	51 (34.2)	0.446
Other lipid lowering, <i>n</i> (%)	58 (16.6)	11 (7.4)	0.010
Aspirin, <i>n</i> (%)	200 (57.1)	107 (71.8)	0.003

clinical events during follow-up (mean, 8.8 ± 2.6 years) were collected for all of the patients with diabetes. Among the 499, 149 (29.9%) received statins when complete revascularization was achieved. Pravastatin at 10 or 20 mg/day was administered at least 2 weeks prior to the revascularization procedure in all of these cases. During the total follow-up period, 10 patients (6.7%) in the statin group stopped statin therapy, and 61 patients (17.4%) in the non-statin group started statin therapy. The baseline characteristics of the

patients with and without statins are shown in **Table 1**. More patients with an arterial bypass graft to LAD and lower LVEF were included in the non-statin group, whereas more patients underwent complete revascularization by isolated PCI in the statin group. More patients were given aspirin in the statin group; however, fewer were given other lipid-lowering drugs (**Table 2**). There were no significant differences between the 2 groups in any other variables. All patients underwent PCI with balloon angioplasty; no patients were

Fig. 1. Survival curves (all-cause death) of patients with and without Statin therapy.

There was no significant difference between patients taking statin and patients not taking statin when complete revascularization was achieved ($p=0.180$).

implanted with stents, which were not yet available at the time. All CABG procedures were performed under on-pump conventional cardiopulmonary bypass, and 42.1% involved arterial grafts.

Survival Analyses

In the propensity score analysis, independent variables associated with pravastatin use at the time of complete revascularization included: LVEF, currently taking aspirin, and other lipid lowering drugs, and whether complete revascularization was achieved by isolated PCI. The discriminatory power of the logistic regression model that derived the adequacy of the propensity score was confirmed by the area under the receiver operating characteristics curve, which was 0.74. Patients on statin therapy had a propensity score of 0.462 [0.385] (median [interquartile range]), while patients not on statin therapy had a median propensity score of 0.193 [0.116]. The suitability of the propensity score for adjusting baseline covariates of statin therapy was evaluated by testing for differences in these covariates within quintiles of the propensity score; the values for important variables associated with statin therapy were found not to differ significantly between the statin group and non-statin group.

Overall, 103 patients died during follow-up (79 in the non-statin group and 24 in the statin group); of these, 43 were cardiovascular deaths (37 in the non-statin group and 6 in the statin group). Based on the survival curve, statin use at the time of complete revas-

Fig. 2. Survival curves (cardiac death) of patients with and without statin therapy.

A statistically significant difference was observed between patients taking statin and patients not taking statin when complete revascularization was achieved ($p=0.030$).

cularization was significantly associated with a reduction in long-term mortality of cardiac death, although there was no significant association between statin use and all-cause mortality (**Fig. 1, 2**). In several Cox proportional hazards models, statin use at the time of complete revascularization was an independent and significant predictor of long-term survival with respect to cardiac death (**Table 3**). To assess the adequacy of the propensity score, numbers of statin users and cardiac deaths according to quintiles of the propensity score were determined (**Table 4**), showing that if the probability of being prescribed statin is high, the probability of cardiac death is low.

Discussion

This study showed that long-term pravastatin treatment was effective in reducing cardiac mortality among diabetic patients after complete revascularization. This effect was significant even after adjustments for several covariates that are established predictors for increased mortality following revascularization.

The MEGA study demonstrated that long-term pravastatin treatment was effective against cardiovascular events for primary prevention whereas statins did not reduce cardiac death⁷. The MUSASHI study also showed that statins decreased the frequency of cardiovascular events in patients with acute myocardial infarction, but did not reduce the incidence of cardiac death among high-risk patients⁸. This is prob-

Table 3. Hazard ratio of statin use for all-cause and cardiac mortality

	All-cause death			Cardiac death		
	HR	95%CI	<i>p</i>	HR	95%CI	<i>p</i>
Crude	0.73	0.46–1.15	0.175	0.40	0.17–0.94	0.035
Model 1	0.97	0.59–1.58	0.901	0.47	0.19–0.91	0.034
Model 2	0.86	0.54–1.38	0.533	0.45	0.19–0.91	0.031
Model 3	0.98	0.65–1.69	0.786	0.49	0.19–0.9	0.036

In model 1, HRs and 95% CIs were adjusted for propensity score.

In model 2, HRs and 95% CIs were adjusted for arterial bypass graft to LAD, whether complete revascularization was achieved by isolated PCI.

In model 3, HRs and 95% CIs were adjusted for variables included in model 2 and propensity score.

HR, hazard ratio; CI, confidence interval; LAD, left anterior descending; PCI, percutaneous coronary intervention

Table 4. Numbers of statin users and cardiac deaths according to the quintile of propensity score

	Quintile (Range) of Propensity Score				
	1 (0.032–0.152)	2 (0.153–0.189)	3 (0.191–0.245)	4 (0.247–0.534)	5 (0.538–0.674)
Number of statin users	14	14	21	38	62
Probability of statin use %	14.1	14.0	21.0	38.0	62.0
Number of cardiac deaths	15	8	8	8	4
Probability of cardiac death %	15.2	8.0	8.0	8.0	4.0

ably due to the lower rate of critical events among Japanese patients than in Western populations⁹). Furthermore, statin therapy was associated with reduced total and cardiovascular mortality after valvular heart surgery¹⁰ or coronary artery bypass grafting surgery¹¹). However, these studies included patients with and without diabetes. Our study was extended to diabetic patients after complete revascularization.

Long-term observation and numbers patients are required to confirm the effectiveness of drug treatment against hard end points in secondary prevention studies in Japan because of a low death rate. Long-term and large-scale outcome studies have been published in Japan. For example, Nagashima *et al.*, who registered 4,075 patients with AMI and observed them during a mean follow-up period of 4.1 years¹², found that statin use reduced long-term mortality. We too collected data from 575 consecutive patients who underwent PCI and were followed up for a mean of 11.0 years¹³, and found that pravastatin was associated with a reduction in the cardiac death rate. The present study strengthens the notion that pravastatin is effective long-term in diabetic patients and following complete revascularization including bypass surgery. We believe that this is the first long-term follow-up of diabetic patients after complete revascularization.

The present findings were consistent with several clinical studies that have shown benefits of statin therapy with respect to mortality among diabetic patients. In primary prevention¹⁴, the CARD trial showed that atorvastatin improved the clinical outcome of diabetic patients. A beneficial effect of statins on mortality in diabetic patients in secondary prevention was demonstrated in a subanalysis of large clinical trials and a meta-analysis¹⁵). However, there is scant data regarding long-term observations after complete revascularization in Japanese diabetic patients. To our knowledge, this is the first report to show that pravastatin prevented cardiac mortality in the era of choice between PCI and bypass surgery.

Study Limitations

This was a single center, observational study of daily clinical practice. Although propensity analyses are powerful, they are inherently limited by the number and accuracy of the variables evaluated. Furthermore, recent evidence suggests that propensity scores can not be used to adjust confounding factors¹⁶). Therefore, our findings should be interpreted with caution. Another limitation is the absence of precise information about the duration of diabetes and the level of HbA1c at the time of complete revasculariza-

tion, which might have influenced prognosis. Further studies are required to address whether or not statins confer a long-term benefit for this subgroup of diabetic patients.

Additionally, in our study, the total duration of statin use after complete revascularization was not examined and there was some crossover between the two groups. However, this crossover bias would probably have led to an underestimation of the association between statin administration and survival. Therefore, this further emphasizes that statin therapy at the time of complete revascularization is associated with improved long-term cardiac mortality. Although this might have affected our findings, it would appear that the effect was minimal.

Conclusion

The present study showed that use of pravastatin was associated with a significantly reduced risk of long-term cardiac mortality after complete revascularization among consecutive patients with diabetes mellitus.

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