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Impact of low dose atorvastatin on development of new-onset diabetes mellitus in Asian population: Three-year clinical outcomes

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ABSTRACT

Background: High dose atorvastatin is known to be associated with new onset diabetes mellitus (NODM) in patients with high risk for developing diabetes mellitus (DM). However, low dose atorvastatin is more commonly used as compared with high dose atorvastatin. The aim of this study is to investigate the impact of low dose atorvastatin (LDA, 10 mg or 20 mg) on the development of NODM up to three years in Asian patients.
Methods: From January 2004 to September 2009, we investigated a total of 3566 patients who did not have DM. To adjust for potential confounders, a propensity score matching (PSM) analysis was performed using the logistic regression model. After PSM (C-statistics: 0.851), a total of 818 patients (LDA group, n = 409 patients and control group, n = 409 patients) were enrolled for analysis.
Results: Before PSM, the cumulative incidence of NODM (5.8% vs. 2.1%, $p < 0.001$), myocardial infarction (0.5% vs. 0.1%, p-value = 0.007), and major adverse cardio-cerebral event (MACCE, 1.8% vs. 0.7%, p-value = 0.012) at three-years were higher in the LAD group. However, after PSM, there was a trend toward higher incidence of NODM (5.9% vs. 3.2%, p = 0.064) in the LDA group, but the incidence of MACCE (1.2% vs. 1.5%, p-value = 1.000) was similar between the two groups. In multivariable analysis, the LDA administration was tended to be an independent predictor of NODM (OR: 1.99, 95% CI: 1.00–3.98, p-value 0.050).
Conclusions: In this study, the use of LDA tended to be a risk factor for NODM in Asian patients and reduced clinical events similar to the control group. However, large-scale randomized controlled trials will be needed to get the final conclusion.

1. Introduction

Recently, statins have been the most widely used medication to reduce the risk of cardiovascular event in patients with a variety of risk factors [1,2]. However, recent studies reveal a possible association between the use of statin and an increased risk of new onset diabetes mellitus (NODM). Previous studies showed a 27% increased risk of diabetes with rosuvastatin [2]. However, taking pravastatin lowered the risk by 30% [3]. These findings suggest that the statin effect on glucose homeostasis may not be a "class" effect, but rather differential among various agents of the class [4].

Atorvastatin is a lipophilic statin, and previous clinical studies showed that there were contradictory findings with regard to the effect of atorvastatin on glucose homeostasis in patients with hypertension, hyperlipidemia, and prediabetes. In the "real world," low dose atorvastatin is more commonly used as compared with high dose atorvastatin, particularly among Asian populations having smaller body weights. Therefore, in the present study, we retrospectively investigated the impact of low dose (10 mg or 20 mg) atorvastatin on the development of NODM based on a database of three-year clinical outcomes in a series of all-comer Asian populations.

2. Methods

We investigated a total of 3566 consecutive patients who visited Korea University Guro Hospital, Seoul, Korea, between January 2004 and September 2009, and who had at least one cardiovascular disease or cardiovascular risk without history of DM. The patients were divided into two groups either those who had been treated with low dose atorvastatin or no lipid lowering agents (LDA group, n = 566 patients,

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control group, n = 3000 patients). Among a total of 566 patients, patients who received 10 mg atorvastatin were 88% (498/566 patients) and patients who received 20 mg atorvastatin were 12% (68/566 patients), respectively. To adjust for potential confounders, propensity score matching (PSM) analysis was performed using the logistic regression model, testing the propensity to have the LDA group rather than the control group. We tested all available variables that could be of potential relevance: Age, gender, body mass index, history of cardiovascular risk (hypertension, dyslipidemia, cerebrovascular disease, cardiac arrhythmia, intracoronary spasm, angina pectoris, chest pain, current smokers, and current alcoholics) baseline laboratory findings (hemoglobin A1c%, fasting blood glucose, total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol) and co-medication treatments (aspirin, beta blockers, calcium channel blockers, angiotensin receptor blockers, angiotensin co-enzyme inhibitors, diuretics, and nitrates). The LDA group was then matched to the control group on the propensity scores with the nearest available pair matching method. Subjects were matched with a caliper width equal to 0.05. The procedure yielded 409 well-matched pairs (overall balance test; $x^2 = 12.24$, p = 0.997). The logistic model by which the propensity score was estimated showed predictive value well (C statistic = 0.851).

After PSM, a total of 818 patients were enrolled for this analysis (LDA group, n = 409 patients, control group, n = 409 patients). The primary end point is the cumulative incidence of NODM during the three years clinical follow up. NODM is defined as having a fasting blood glucose ≥126 mg/dl or HbA1c ≥6.5% [5]. The secondary end point is the clinical outcomes including total death, cardiac death, myocardial infarction (MI), cerebrovascular accidents (CVA), and the major adverse cerebrocardiovascular accidents (MACCE) during three years clinical follow up. Mean follow up duration was 976 ± 278 days in all groups before baseline adjustment, and 993 ± 240 days in PSM groups.

2.1. Statistics

All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviation and were compared using Student's t-test. Categorical data were expressed as percentages and were compared using chi-square statistics or Fisher's exact test. A p-value < 0.05 was considered statistically significant. Moreover, multivariate cox-regression analysis adjusted with following variables was performed to determine the different impact of LDA on the incidence of NODM. The following factors were co-analyzed in the multivariable analysis: gender (male), age, hypertension, cardiovascular disease, coronary spasm, dyslipidemia, angiotensin II receptor blocker (ARB)s, angiotensin converting enzyme inhibitor (ACEI)s, calcium channel blocker, beta blockers, diuretics, nitrates, and statins.

Table 1
Baseline clinical characteristics, laboratory findings, and previous medical treatment before baseline adjustment using propensity score matching.

Variables, n (%)	LDA (n = 566)	Control (n = 3000)	p-Value
Baseline clinical characteristics			
Gender (male)	316 (55.8)	1488 (49.6)	0.007
Age	60.7 ± 10.5	54.3 ± 13.4	<0.001
Body mass index (kg/m^2)	24.6 ± 3.1	24.4 ± 3.4	0.129
Hypertension	305 (53.8)	1706 (56.8)	0.190
Dyslipidemia	124 (21.9)	460 (15.3)	<0.001
Cardiovascular disease	102 (18.0)	238 (7.9)	<0.001
Coronary artery spasm	37 (6.5)	176 (5.8)	0.537
Cerebrovascular disease	48 (8.4)	219 (7.3)	0.328
Heart failure	19 (3.3)	128 (4.2)	0.318
Atrial fibrillation	28 (4.9)	130 (4.3)	0.515
Smoking history	237 (41.8)	576 (19.2)	<0.001
Baseline laboratory findings			
Fasting glucose	60.7 ± 10.5	54.3 ± 13.4	<0.001
HbA1c	5.6 ± 0.2	5.5 ± 0.3	<0.001
Total cholesterol	175.3 ± 43.9	175.1 ± 30.4	0.906
Triglyceride	131.4 ± 79.6	127.8 ± 93.54	0.334
HDL-cholesterol	50.4 ± 13.8	52.4 ± 13.8	0.002
LDL-cholesterol	99.0 ± 40.4	97.9 ± 26.3	0.540
Hemoglobin	13.6 ± 1.5	13.8 ± 1.6	0.058
Creatinine	0.93 ± 0.45	0.84 ± 0.40	<0.001
Previous medical treatment			
Beta blockers	189 (33.3)	540 (18)	<0.001
CCBs	269 (47.5)	1243 (41.4)	0.007
Diuretics	136 (24)	623 (20.7)	0.082
RAAS inhibitor	1315 (36.7)	296 (33.9)	<0.001

LDA: Low dose atorvastatin, HDL: High density lipoprotein, LDL: low density lipoprotein, CCB: calcium channel blocker, RAS: renin–angiotensin–aldosterone system.

Table 2
Baseline clinical characteristics, laboratory findings, and previous medical treatment after baseline adjustment using propensity score matching.

Variables, n (%)	LDA (n = 409)	Control (n = 409)	p-Value
Baseline clinical characteristics			
Gender (male)	208 (50.8)	208 (50.8)	1.000
Age	60.3 ± 10.5	61.6 ± 11.3	0.083
Body mass index (kg/m^2)	24.6 ± 3.1	24.7 ± 4.2	0.951
Hypertension	222 (54.2)	219 (53.5)	0.833
Dyslipidemia	80 (19.5)	79 (19.3)	0.930
Cardiovascular disease	57 (13.9)	63 (15.4)	0.553
Coronary artery spasm	29 (7.0)	29 (7.0)	1.000
Cerebrovascular disease	29 (7.0)	30 (7.3)	0.892
Heart failure	15 (3.6)	16 (3.9)	0.855
Atrial fibrillation	19 (4.6)	13 (3.1)	0.279
Smoking history	145 (35.4)	152 (37.1)	0.611
Baseline laboratory findings			
Fasting glucose	93.7 ± 7.9	93.3 ± 8.2	0.547
HbA1c	5.6 ± 0.2	5.6 ± 0.2	0.824
Total cholesterol	175.7 ± 43.0	175.4 ± 30.9	0.884
Triglyceride	131.9 ± 84.2	137.6 ± 104.3	0.385
HDL-cholesterol	51.3 ± 13.5	50.8 ± 13.5	0.665
LDL-cholesterol	98.6 ± 39.3	97.7 ± 26.2	0.707
Hemoglobin	13.7 ± 1.5	13.6 ± 1.6	0.714
Creatinine	0.92 ± 0.49	0.90 ± 0.61	0.787
Previous medical treatment			
Beta blockers	116 (28.3)	119 (29)	0.817
CCBs	196 (47.9)	197 (48.1)	0.944
Diuretics	105 (25.6)	109 (26.6)	0.750
RAAS inhibitor	187 (47.3)	185 (45.1)	0.419

LDA: Low dose atorvastatin, HDL: High density lipoprotein, LDL: low density lipoprotein, CCB: calcium channel blocker, RAS: renin–angiotensin–aldosterone system.

3. Results

Mean follow-up duration was 976 ± 278 days in all groups, and 993 ± 240 days in PSM group. After PSM, a total of 818 patients (LDA group = 409 patients and control group = 409 patients) were enrolled for this analysis.

Before baseline adjustment, clinical characteristics showed that male gender (55.8% vs. 49.6%, p-value = 0.007) and elderly patients (60.7 ± 10.5 years vs. 54.3 ± 13.4 years, p-value < 0.001) were more prevalent in the LDA group as compared with the control group.

Table 3
NODM and clinical outcomes up to 3 years before baseline adjustment using PSM.

Variables, n (%)	LDA (n = 566)	Control (n = 3000)	p-Value
Cumulative incidence of NODM	33 (5.8)	62 (2.1)	<0.001
Follow up days, mean ± SD	976.4 ± 278.1	809.8 ± 405.9	<0.001
Clinical outcomes up to 3 years			
Mortality	6 (1.1)	13 (0.4)	0.060
Cardiac death	2 (0.4)	3 (0.1)	0.191
Myocardial infarction	3 (0.5)	2 (0.1)	0.007
Cerebrovascular accidents	2 (0.4)	2 (0.4)	0.871
MACCE	10 (1.8)	21 (0.7)	0.012

NODM: new-onset diabetes mellitus, PSM: propensity score matching, SD: standard deviation, ACEI: angiotensin converting enzyme inhibitor, MACCE: major adverse cardio-cerebrovascular accidents.