Impact of Statin Use on Development of New-Onset Diabetes Mellitus in Asian Population

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There have been several reports showing that the statin use is associated with new-onset diabetes mellitus (DM). The aim of the present study was to evaluate the impact of chronic statin use on development of new-onset DM in a series of Asian population. The patients were retrospectively enrolled using the electronic database of Korea University Guro Hospital from January 2004 to February 2010. A total of 10,994 patients without a history of diabetes were analyzed. Baseline lipid profiles, fasting glucose, Hemoglobin (Hb) A1c, and glucose tolerance tests were measured in all patients before statin treatment. Included patients had HbA1c ≤5.7% and fasting glucose level ≤100 (mg/dl). The patients were divided into 2 groups according to the use of statins (the statin group, n = 2,324 patients and the nonstatin group, n = 8,670 patients). To adjust baseline potential confounders, a propensity score−matched analysis was performed using logistic regression model. After propensity score matching, 2 propensity-matched groups (1,699 pairs, n = 3,398, C statistic = 0.859) were generated and analyzed. After propensity score matching, baseline characteristics of both groups were balanced except that the statin group was older and had higher rate of coronary artery disease compared with the nonstatin group. During a 3-year follow-up, the statin group had higher incidence of new-onset DM compared with the nonstatin group (hazard ratio 1.99, 95% CI 1.36 to 2.92, p <0.001), but the statin group showed lower incidence of major adverse cerebral-cardiovascular events compared with the nonstatin group (hazard ratio 0.40, 95% CI 0.19 to 0.85, p <0.001). In the present study, although the use of statins was associated with higher rate of new-onset DM, it markedly improved 3-year cardiovascular outcomes in Asian population. **(Am J Cardiol 2016;117:382−387)**

The statins are widely used for cardiovascular disease prevention and which are clearly supported by clinical evidence. However, there have been several debates,[1−3] and there have been several reports showing that the statin use is associated with a slightly higher incidence of new-onset diabetes mellitus (DM).[4−12] However, there are limited data regarding the impact of chronic statin use on the development of new-onset DM in Asian population, especially in patients without DM.[10,13] Therefore, the aim of the present study was to evaluate the impact of chronic statin use on the development of new-onset DM in patients without DM and impaired glucose tolerance (IGT) in a series of Asian population.

Methods

A total of 65,686 consecutive patients who visited cardiovascular center of Korea University Guro Hospital

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Drs. Rha and Choi contributed equally to this study.

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See page 386 for disclosure information.

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Table 1
Baseline clinical characteristics and medication treatments

Variables, N (%) or mean ± SD	Overall Patients			Matched Patients		
	Statin Use (n = 2324)	No Use (n = 8670)	p Value	Statin Use (n = 1699)	No Use (n = 1699)	P Value
Gender (men)	1318 (56.7 %)	4033 (46.5 %)	< 0.001	883 (51.9 %)	879 (51.7 %)	0.891
Age, (years)	60.6 ± 10.8	51.1 ± 14.9	< 0.001	59.8 ± 10.8	60.7 ± 12.4	0.027
Body mass index, kg/m^2	24.4 ± 3.0	24.3 ± 3.4	0.091	24.5 ± 3.1	24.4 ± 3.6	0.576
Hypertension	1273 (54.7 %)	3149 (36.3 %)	< 0.001	888 (52.2 %)	904 (53.2 %)	0.582
Dyslipidemia	597 (25.6 %)	1125 (12.9 %)	< 0.001	388 (22.8 %)	408 (24 %)	0.418
Coronary artery disease	693 (29.8 %)	386 (4.4 %)	< 0.001	253 (14.8 %)	178 (10.4 %)	< 0.001
Myocardial infarction	208 (8.9 %)	40 (0.4 %)	< 0.001	44 (2.5 %)	31 (1.8 %)	0.129
Coronary revascularizations	436 (18.7 %)	63 (0.7 %)	< 0.001	73 (4.2 %)	53 (3.1 %)	0.069
Coronary spasm	101 (4.3 %)	280 (3.2 %)	0.009	79 (4.6 %)	92 (5.4 %)	0.308
Cerebrovascular accidents	438 (18.8 %)	670 (7.7 %)	< 0.001	311 (18.3 %)	329 (19.3 %)	0.430
Heart failure	93 (4.0 %)	259 (2.9 %)	0.014	68 (4.0 %)	69 (4.0 %)	0.931
Angina pectoris	634 (27.2 %)	1877 (21.6 %)	< 0.001	425 (25 %)	412 (24.2 %)	0.605
Chest pain	131 (5.6 %)	729 (8.4 %)	< 0.001	96 (5.6 %)	84 (4.9 %)	0.358
Arrhythmia	178 (7.6 %)	520 (5.9 %)	0.004	122 (7.1 %)	122 (7.1 %)	ns
Atrial fibrillation	119 (5.1 %)	267 (3.0 %)	< 0.001	82 (4.8 %)	81 (4.7 %)	0.936
Cardiac arrhythmia	95 (4.0 %)	340 (3.9 %)	0.715	64 (3.7 %)	61 (3.5 %)	0.785
Fasting glucose, mg/dl	94.1 ± 8.1	93.1 ± 8.0	< 0.001	94.2 ± 7.8	94.2 ± 7.9	0.900
Hemoglobin A1c, (%)	5.5 ± 0.2	5.4 ± 0.2	< 0.001	5.5 ± 0.2	5.5 ± 0.2	0.464
Insulin, (ng/ml)	7.5 ± 4.9	7.1 ± 5.3	0.072	7.6 ± 5.0	7.6 ± 5.4	0.945
Total cholesterol, (mg/dL)	179 ± 45	178 ± 33	0.100	181 ± 44	182 ± 34	0.664
Triglyceride, (mg/dL)	135 ± 93	122 ± 88	< 0.001	135 ± 97	136 ± 118	0.866
High-density lipoprotein cholesterol, (mg/dL)	50 ± 13	53 ± 13	< 0.001	52 ± 13	51 ± 14	0.508
Low-density lipoprotein cholesterol, (mg/dL)	113 ± 41	110 ± 29	0.008	114 ± 41	114 ± 30	0.733
Medication treatment						
Beta blockers	641 (27.5 %)	807 (9.3 %)	< 0.001	356 (20.9 %)	350 (20.6 %)	0.800
Calcium channel blockers	1160 (49.9 %)	1816 (20.9 %)	< 0.001	794 (46.7 %)	814 (47.9 %)	0.492
Angiotensin receptor blockers	756 (32.5 %)	1218 (14.0 %)	< 0.001	516 (30.3 %)	511 (30.0 %)	0.852
Angiotensin converting enzyme inhibitors	335 (14.4 %)	279 (3.2 %)	< 0.001	137 (8.0 %)	145 (8.5 %)	0.619
Diuretics	534 (22.9 %)	1039 (11.9 %)	< 0.001	383 (22.5 %)	385 (22.6 %)	0.935
Nitrates	974 (41.9 %)	798 (9.2 %)	< 0.001	490 (28.8 %)	450 (26.4 %)	0.125
Type of Statins						
Atorvastatin	811 (34.8 %)	-	-	605 (35.6 %)	-	-
Fluvavastatin	133 (5.7 %)	-	-	106 (6.2 %)	-	-
Pitavastatin	241 (10.3 %)	-	-	161 (9.4 %)	-	-
Pravastatin	252 (10.8 %)	-	-	196 (11.5 %)	-	-
Rosuvastatin	344 (14.8 %)	-	-	220 (12.9 %)	-	-
Simvastatin	543 (23.3 %)	-	-	411 (24.1 %)	-	-
Fibrates	29 (1.2 %)	98 (1.1 %)	0.638	25 (1.4 %)	34 (2.0 %)	0.237

Data are presented as N (%) or mean ± SD unless otherwise indicated.

(KUGH) from January 2004 to February 2010 were retrospectively enrolled using the electronic database of KUGH. All patients did lipid profiles, fasting glucose, Hemoglobin (Hb) A1c level, and glucose tolerance tests before statin treatment. Inclusion criteria included both HbA1c $\leq$5.7% and fasting glucose level $\leq$100 (mg/dl). Finally, a total of 10,994 patients without DM and IGT were analyzed. The study protocol was approved by the Institutional Review Board of KUGH.

New-onset DM was defined as fasting blood glucose $\geq$126 (mg/dl), HbA1c $\geq$6.5%, or the current use of hypoglycemic agents depending on the physician's discretion.[14] Major adverse cardiac and cerebral events (MACCEs) were defined as the composite of total death, nonfatal myocardial infarction, and cerebrovascular accidents. New-onset DM−related MACCE was defined as both new-onset DM and MACCE occurring at the same follow-up period. The primary study end point was the cumulative incidence of new-onset DM during 3-year clinical follow-up.

For continuous variables, differences between 2 groups were evaluated by unpaired *t* test or Mann−Whitney rank test. Data are expressed as mean ± SD. For discrete variables, differences were expressed as counts and percentages and analyzed with chi-square or Fisher's exact test between the groups as appropriate. To adjust for potential confounders, propensity score−matched analysis was performed using the logistic regression model. We tested all available variables that could be of potential relevance: age, men, cardiovascular risk factors (hypertension, diabetes, heart failure, chronic kidney disease, coronary artery disease, and cerebrovascular accidents), comedication treatment (angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, β blockers, diuretics, and warfarin), and laboratory findings