Risk of Diabetes in Patients Treated with HMG-CoA Reductase Inhibitors

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The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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December 2013

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December 2013

ACKNOWLEDGEMENTS

First, I wish to express my sincere gratitude to my supervisor, Professor Eun Seok Kang, M.D., Ph.D., who gave me a lot of advice and guidance throughout my years at graduate school. He inspired me greatly to carry out this work.

In addition, I would like to convey thanks to Professor Bong Soo Cha, M.D., Ph.D. and Chul Hoon Kim, M.D., Ph.D. for support, encouragement and teachings in completing this paper.

Finally, I would like to give very special thanks to my family members, for their love, understanding and support, through the duration of my studies.

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ABSTRACT

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(Directed by Professor Eun Seok Kang)

Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (statins) are used to control blood cholesterol levels and reduce cardiovascular disease. It has been repeatedly reported that statins may cause new-onset diabetes mellitus (DM). However, limited evidence exists from direct head to head comparisons of statins on whether the risk of DM differs among statins. We investigated the risk of development of new-onset diabetes in subjects treated with different statins.

Our study enrolled 1,160 patients without DM or impaired fasting glucose (IFG) who were receiving statin treatment for cholesterol control. We evaluated the incidence of new-onset diabetes according to the type of statin. The mean duration of follow-up was 54.6 ± 10.6 months. The incidence of DM was significantly higher in the pitavastatin group (10.7%) compared to that in the other statin groups [atorvastatin (4.0%), rosuvastatin (6.1%), simvastatin (4.1%), and pravastatin (3.7%); p=0.003]. The risk of diabetes was the highest in the

pitavastatin group compared with that in the atorvastatin group [hazard ratio (HR)=2.68, p=0.004]. Other statins showed no significant risk differences compared to that for atorvastatin. Fasting blood glucose level at baseline was associated with the development of diabetes (HR=1.06, p=0.031). Other factors including age, gender, body-mass index, duration of statin use, and total cholesterol level at baseline showed no association with the development of DM.

Among the five statins, pitavastatin showed the strongest effect on the development of new-onset diabetes.

Key words : HMG CoA reductase inhibitors, statin, diabetes mellitus, hypercholesterolemia

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I. INTRODUCTION

Statins [inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase] are widely used to prevent cardiovascular disease (CVD) by lowering serum cholesterol[1]. Recently, the use of statins was addressed in the JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, which was a randomized, double-blind, placebo-controlled, and multicenter trial. The trial outcome showed that use of rosuvastatin for the prevention of CVD induced an increase in the development of new-onset diabetes mellitus (DM)[2]. Several other studies have reported similar results. In the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm) study, atorvastatin provided significant reductions in major cardiovascular events. However, the incidence of new-onset DM also increased compared with that in the placebo group [3.0% in the atorvastatin group vs. 2.6% in the placebo group; hazard ratio (HR)=1.15; 95% confidence interval (CI), 0.91–1.44; p=0.25][3]. The heart protection study (HPS) study

revealed that simvastatin reduced the incidence of first major vascular events in diabetic patients, but it increased the risk of development of new-onset DM (4.6% in the simvastatin group vs. 4.0% in the placebo group, p=0.10)[4]. In the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study, 40 mg of pravastatin increased the risk of new-onset DM by 32% [6.6% in the pravastatin group vs. 5.1% in the placebo group; odds ratio (OR)=1.32; 95% CI, 1.03–1.69)[5,6]. In these studies, statins increased the risk of development of DM, although the results were not statistically significant in all the studies. However, the WOSCOPS trial (West of Scotland Coronary Prevention Study) suggested that pravastatin lowered diabetes risk by 30%[7].

Statin treatment has been shown to modestly increase the risk of diabetes compared with that for placebo according to a recent meta-analysis[6]. Although statins share a similar mechanism of action, there are differences in chemical structure, metabolism, lipophilicity, and lipid-lowering potency. Several studies compared the diabetogenic effects among several types of statins. However, only limited data are available for the direct comparisons of statins[8-10]. In this study, we investigated the association between use of individual statins and new-onset DM.

II. MATERIALS AND METHODS

1. Participants

Our study included 1,160 patients with a history of statin medication use for managing hypercholesterolemia who were 20 years of age or older. Only new users who had not used a statin in a preceding year were enrolled. Patients with established DM or impaired fasting glucose (IFG, fasting plasma glucose level ≥ 100 mg/dl) before statin treatment were excluded. All patients had been prescribed one kind of statin for four years between January 2007 and January 2013. The 1,160 patients were grouped as follows: 375 patients in the atorvastatin group, 289 patients in the pitavastatin group, 345 patients in the rosuvastatin group, 97 patients in the simvastatin group, and 54 patients in the pravastatin group. Participants were excluded if they met any of the following criteria: history of intolerance for statins, or treatment with hormone replacement therapy (including steroids). The primary end point of this study was new-onset DM, defined as a fasting plasma glucose level ≥ 126 mg/dl on two consecutive tests, HbA1c level ≥ 6.5%, or starting glucose-lowering medication(s).

2. Methods

We evaluated the incidence of DM and dysglycemia (IFG and/or DM)

according to the statin used and any associated risk factors. Data from patients who switched to a different statin were excluded from analysis. All analyses used subjects treated with atorvastatin as the reference (comparison group), because atorvastatin has been used most widely.

The BMI, fasting blood glucose (FBG), and lipid profiles were examined for baseline at the start of statin medication. The LDL cholesterol concentration was calculated using the Friedewald formula as follows: LDL cholesterol = (total cholesterol – HDL cholesterol – triglycerides)/5. The mean dose of statin until the primary end point was calculated, and the mean dose of statin between patients with new-onset DM and without DM was compared in each statin group.

3. Statistical analysis

All statistical analyses were performed using the SPSS statistical analysis program (SPSS v. 20.0, SPSS Inc., Chicago, IL). All values are reported as means ± standard deviation, and the real numbers of participants with the percentage immediately follows in parentheses. Between-group differences of the means were compared using analysis of variance for parametric data. Between-group differences of numbers and percentages were evaluated using a $\chi 2$ test. Additional post-hoc analyses were performed to determine what parameters were involved in the origin of group differences. We performed time-to-event analyses using Cox proportional hazards regression to estimate the association between statin use and

development of new-onset DM. Kaplan-Meier survival curves were used to compare the time to new-onset DM in each statin group. The relative risk factor for new-onset DM and dysglycemia (IFG and/or DM) was obtained using univariate and multivariate Cox regression, and the risk is reported in the form of HR and 95% CI. For all tests, $p<0.05$ was considered as statistically significant.

III. RESULTS

1. Clinical characteristics of the study population

Table 1 shows the clinical characteristics of patients. The atorvastatin group included 32.32% of patients, followed by rosuvastatin (29.74%), pitavastatin (24.91%), simvastatin (8.36%), and pravastatin (4.66%). The ratio of female gender was higher in the simvastatin and pitavastatin groups compared with that in the atorvastatin group. Older patients were more likely to be included in the pitavastatin group than in the atorvastatin group (pitavastatin group, 62.7 ± 10.2 years; atorvastatin group, 60.7 ± 10.1 years; p=0.017).

Baseline values for BMI and fasting blood glucose at the start of statin treatment were not different among the groups. The total cholesterol level was higher in the pitavastatin and rosuvastatin groups, and triglyceride level was higher in the rosuvastatin group. HDL-cholesterol was higher in the pitavastatin and simvastatin groups, whereas LDL-cholesterol was higher in the pitavastatin group (Table 1). All factors that showed group differences were included in univariate and multivariate Cox regression analyses.

Table 1–Baseline characteristics for new statin users

	Total (N=1,160) (%)	Atorvastatin (n=375) (32.32%)	Pitavastatin (n=289) (24.91%)	Rosuvastatin (n=345) (29.74%)	Simvastatin (n=97) (8.36%)	Pravastatin (n=54) (4.66%)	*p-value*
Age at start of statin treatment (years)	61.4±10.4	60.5±10.8[1]	62.7±10.2[2]	60.7±10.1[1,2]	63.2±9.5[1,2]	61.6±11.3[1,2]	0.017
n female (%)	513 (44.2%)	145 (38.7%)[1]	148 (51.2%)[2]	135 (39.1%)[1]	58 (59.8%)[2]	27 (50.0%)[1,2]	<0.001
BMI (kg/m^2)	24.8±10.1	25.3±14.8	24.2±3.0	24.9±8.7	24.2±2.7	24.4±2.9	0.679
FBG (mg/dl)	91.0±5.6	90.5±5.7	91.5±5.3	91.3±5.6	91.3±5.9	90.5±5.9	0.122
Total cholesterol (mg/dl)	192.3±48.4	184.1±47.8[1]	196.2±45.3[2]	195.2±52.6[2]	193.7±41.4[1,2]	203.9±46.6[1,2]	0.003
Triglyceride (mg/dl)	146.6±93.3	136.9±75.6[1]	144.4±67.8[1,2]	158.5±126.5[2]	141.9±73.1[1,2]	157.7±100.6[1,2]	0.035
HDL-cholesterol (mg/dl)	47.6±11.9	45.9±10.9[1]	50.3±12.5[2]	46.0±11.9[1]	50.0±10.1[2]	50.3±15.0[1,2]	<0.001
LDL-cholesterol (mg/dl)	122.9±40.9	115.9±38.2[1]	129.0±38.3[2]	123.4±46.9[1,2]	126.2±38.4[1,2]	127.9±36.9[1,2]	0.001
Triglyceride/ HDL-cholesterol (ratio)	1.35±1.19	1.28±0.88[1]	1.24±0.87[1]	1.52±1.6[2]	1.27±1.02[1,2]	1.45±1.61[1,2]	0.027

All values are reported as means ± standard deviations (SD) and real numbers of participants with the percentage in parentheses. Between-group differences of the averages were compared using an analysis of variance (ANOVA) for parametric data. Between-group differences of numbers and percentages were compared using a χ^2 test. Additional post-hoc analyses were performed (2 > 1). FBG, fasting blood glucose.

2. Association between new-onset DM and the type of statin

Over the 7-year study period of 1,160 patients, the mean follow-up duration of 54.6 ± 10.6 months, we observed 69 subjects (5.95%) that developed new-onset DM and 356 subjects (30.7%) that developed dysglycemia (IFG or DM, Table 2). The incidence of new-onset DM was significantly higher in the pitavastatin group (10.7%) compared to that in the other statin groups [atorvastatin (4.0%), rosuvastatin (6.1%), and simvastatin (4.1%), p=0.003]. The incidence of new-onset DM appeared to be the lowest in the pravastatin group (3.7%), although this was not statistically significant (Table 2). There was no significant difference in incidence of dysglycemia(IFG or DM) development between different types of statins.

3. Analyses of risk factors for development of new-onset DM

In our multivariate Cox regression model, the diabetogenic effect of pitavastatin was the most significant (HR, 2.68; p=0.004; Figure 1) when compared to that of the atorvastatin group. Other statin groups showed no significant differences when compared to the atorvastatin group [rosuvastatin (HR, 1.11, p=0.780); simvastatin (HR, 1.39, p=0.568); and pravastatin (HR, 0.56, p=0.572); Figure 1]. Fasting glucose level at baseline was associated with the development of DM (HR, 1.06, p=0.031). Age, gender, BMI, use of angiotensin-converting enzyme inhibitors or

Table 2-Development of dysglycemia (IFG and/or DM) in new statin users

	Total (N=1,160) (%)	Atorvastatin (n=375) (32.32%)	Pitavastatin (n=289) (24.91%)	Rosuvastatin (n=345) (29.74%)	Simvastatin (n=97) (8.36%)	Pravastatin (n=54) (4.66%)	*p-value*
Duration of statin treatment (months)	54.6±10.6	55.2±10.2[2]	54.6±12.8[2]	53.1±9.7[1]	56.7±9.3[2]	55.8±7.5[1,2]	0.017
No. of subjects who developed dysglycemia (IFG + DM) (%)	356 (30.7%)	102 (27.2%)	96 (31.8%)	116 (33.6%)	27 (27.8%)	15 (22.2%)	0.210
No. of subjects who developed DM (%)	69 (5.95%)	15 (4.0%)[1]	31 (10.7%)[2]	17 (6.1%)[1]	4 (4.1%)[1]	2 (3.7%)[1,2]	0.003
No. of outcomes (IFG + DM) per 1000 person-years	90.18	83.85	90.67	109.32	71.10	64.77	
No. of outcomes (DM) per 1000 person-years	13.08	8.70	23.56	11.12	8.73	7.97	

All values are reported as means ± standard deviations (SD) and real numbers of participants with the percentage in parentheses. Between-group differences of the averages were compared using an analysis of variance (ANOVA) for parametric data. Between-group differences of numbers and percentages were compared using a χ^2 test. Additional post-hoc analyses were performed (2 > 1). IFG, impaired fasting glucose; DM, diabetes mellitus.

angiotensin-receptor blockers, total cholesterol, and triglyceride levels at baseline showed no association with the development of DM after adjustment for other risk factors (Table 3). However, comparing the development of dysglycemia (IFG or DM), the effect of pitavastatin was not significant (HR, 1.15; p=0.390; table 4) when compared to that of the atorvastatin group.

Men and women were separately analyzed. The diabetogenic effect of pitavastatin was not significant in men (HR, 1.02; p=0.960; Appendix table 5). However, in women, pitavastatin had an higher HR for new-onset DM of 7.22 (p=0.002; Appendix table 6). Age of the subject was also associated with the development of DM in men (HR, 1.04, p=0.034; Appendix table 5).

Table 3–Independent risk factors for development of DM

	Unadjusted		Adjusted	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Statin				
Atorvastatin	Reference		Reference	
Pitavastatin	2.74 (1.48–5.08)	0.001	2.68 (1.38–5.19)	**0.004**
Rosuvastatin	1.25 (0.63–2.51)	0.523	1.11 (0.53–2.35)	0.780
Simvastatin	1.01 (0.34–3.01)	0.980	1.39 (0.45–4.29)	0.568
Pravastatin	0.91 (0.21–3.98)	0.901	0.56 (0.07–4.24)	0.572
Age	1.03 (1.01–1.06)	0.010	1.02 (1.00–1.05)	0.113
Gender (Female)	1.15 (0.72–1.85)	0.562	1.16 (0.68–2.00)	0.606
BMI (kg/m^2)	1.00 (0.99–1.02)	0.644	1.01 (0.99–1.03)	0.446
Duration of observation (years)	1.00 (0.97–1.03)	0.992	0.99 (0.96-1.03)	0.711
FBG (mg/dl)	1.07 (1.02–1.12)	0.008	1.06 (1.01–1.17)	0.031
Total cholesterol (mg/dl)	1.00 (0.99–1.01)	0.572		
Triglyceride (mg/dl)	1.00 (1.00–1.00)	0.036	1.00 (1.00–1.00)	0.213
HDL-cholesterol (mg/dl)	0.98 (0.96–1.00)	0.046	0.98 (0.95-1.00)	0.051
Triglyceride/ HDL-cholesterol (ratio)	1.10 (0.96-1.27)	0.172		
LDL-cholesterol (mg/dl)	1.00 (1.00–1.01)	0.318		
ACEi/ ARB use	0.92 (0.55–1.54)	0.920		

The relative risk factor for development of diabetes was compared by using a multivariate Cox regression adjusted for age, gender, BMI, total cholesterol level, and triglyceride levels.
HR, hazard ratio; CI, confidence interval; FBG, fasting blood glucose; DM, diabetes mellitus; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

Table 4–Independent risk factors for development of dysglycemia (IFG and/or DM)

	Unadjusted		Adjusted	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Statin				
Atorvastatin	Reference		Reference	
Pitavastatin	1.03 (0.77–1.36)	0.852	1.15 (0.84–1.56)	0.390
Rosuvastatin	1.29 (0.99–1.68)	0.061	1.19 (0.89–1.58)	0.242
Simvastatin	0.86 (0.56–1.31)	0.470	0.98 (0.61–1.59)	0.940
Pravastatin	0.62 (0.34–1.13)	0.118	0.69 (0.36–1.33)	0.691
Age	1.00 (0.99–1.01)	0.636	1.00 (0.99–1.02)	0.599
Gender (Female)	0.91 (0.73–1.12)	0.358	1.00 (0.78–1.29)	0.983
BMI (kg/m^2)	1.01 (0.99–1.01)	0.226	1.01 (0.99–1.01)	0.160
Duration of observation (years)	0.96 (0.95–0.98)	<0.001	0.96 (0.94-0.98)	<0.001
FBG (mg/dl)	1.07 (1.05–1.10)	<0.001	1.06 (1.03–1.08)	<0.001
Total cholesterol (mg/dl)	1.00 (1.00–1.00)	0.732		
Triglyceride (mg/dl)	1.00 (1.00–1.00)	0.469		
HDL-cholesterol (mg/dl)	0.98 (0.97–0.99)	<0.001	0.98 (0.97-0.99)	0.002
Triglyceride/ HDL-cholesterol (ratio)	1.03 (0.95-1.12)	0.435		
LDL-cholesterol (mg/dl)	1.00 (1.00–1.00)	0.195		
ACEi/ ARB use	1.00 (0.80–1.25)	0.978		

The relative risk factor for development of diabetes was compared by using a multivariate Cox regression adjusted for age, gender, BMI, total cholesterol level, and triglyceride levels.
HR, hazard ratio; CI, confidence interval; FBG, fasting blood glucose; DM, diabetes mellitus; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

4. Comparison of the statin dose in each statin group

The mean statin dosages in this study were as follows: atorvastatin, 11.9 ± 5.2 mg/day; pitavastatin, 2.1 ± 1.3 mg/day; rosuvastatin, 10.7 ± 3.5 mg/day; simvastatin, 25.0 ± 9.3 mg/day; and pravastatin, 25.6 ± 8.8 mg/day. There was no difference in the dose of any single statin within a study group between patients that retained normal glucose levels and patients that developed new-onset DM (Table 5).

Table 5–Mean daily statin dose in each statin group

	Not DM developed	DM developed	*p-value*
Atorvastatin (mg/day)	11.8±5.0 (n=360)	14.2±8.1 (n=15)	0.082
Pitavastatin (mg/day)	2.1±1.4 (n=258)	2.0±0.5 (n=31)	0.560
Rosuvastatin (mg/day)	10.6±3.5 (n=328)	12.3±3.6 (n=17)	0.065
Simvastatin (mg/day)	25.1±9.4 (n=93)	25.0±5.0 (n=4)	0.986
Pravastatin (mg/day)	25.5±8.8 (n=52)	30.0 (n=2)	0.491

All values are reported as means ± standard deviations (SD). Between-group differences were compared using Student's *t*-test. DM, diabetes mellitus.

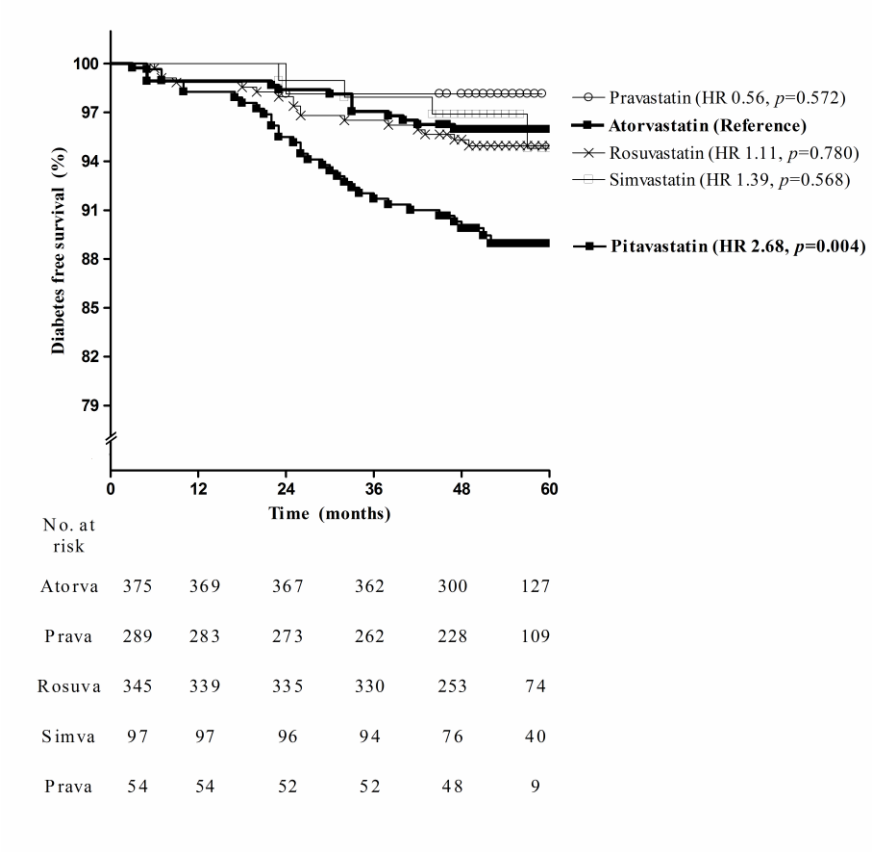

Figure 1. Survival curve of DM development.

Disease-free survival analysis according to type of statins. Kaplan-Meier curves for disease-free survival were stratified according to the type of statin.

IV. DISCUSSION

In a meta-analysis of 13 placebo-controlled statin trials with more than 90,000 patients, statin treatment was associated with a 9% higher risk of developing DM[6]. This raises the question whether all statins are equally diabetogenic? There is controversy about whether the risk of development of DM differs among statins. There are seven statins available in real clinical practice (atorvastatin, rosuvastatin, pravastatin, simvastatin, pitavastatin, lovastatin, and fluvastatin). The selection of a statin in clinical practice is usually based on the individual physician's preference for these medications, such as efficacy for lowering LDL-cholesterol, drug-food interactions, pharmacokinetic properties, and cost[11].

In previous meta-analysis studies, the diabetogenic effects of several statins were discussed simultaneously[6,9,12]. In a recent meta-analysis study, the diabetogenic effects of atorvastatin and rosuvastatin were found to be comparable at a moderate dose. Pravastatin showed a lower risk of new-onset DM compared with that for rosuvastatin[8]. In a current population-based cohort study, atorvastatin and simvastatin had an increased risk of new-onset DM compared with that for pravastatin[9]. In general, pravastatin produce less diabetogenic effect than other statins[8,9]. In this study, we found that pitavastatin shows the most powerful diabetogenic effect compared to that of other statins. Compared with atorvastatin (mean dosage of 11.9 ± 5.2 mg/day), pitavastatin

had an HR for new-onset DM of 2.68 (p=0.004) in association with pitavastatin (2.1 ± 1.3 mg/day). Rosuvastatin and simvastatin showed a trend of increased risk of DM, whereas pravastatin had a tendency to reduce the risk of DM.

Statins can be divided into natural or fully synthetic statins, and they have significant structural differences[13]. Pravastatin and simvastatin are natural fungal metabolites; atorvastatin, rosuvastatin, and pitavastatin are fully synthetic compounds. In our study, there was no statistically significant difference between natural and fully synthetic statins with respect to diabetes risk (OR, 0.54 vs. 1.86, respectively; p=0.144).

Statins are either lipophilic (simvastatin, atorvastatin, and pitavastatin) or hydrophilic (pravastatin and rosuvastatin). One study reported that there was no significant difference in diabetes risk between hydrophilic and lipophilic statins (OR, 1.10 vs. 1.08, respectively)[6]. Similarly, our study reveals that there is no significant difference between hydrophilic and lipophilic statins (OR, 1.28 vs. 0.78, respectively; p=0.318). Therefore, the structure and bioavailability of statins apparently has no significant impact on the diabetogenic effect.

Although the exact molecular mechanism(s) underlying the diabetogenic effect of statins is not known, many studies suggest plausible mechanisms. Deregulation of cellular cholesterol can lead to impaired insulin secretion by disrupting the function of voltage-gated calcium channels in pancreatic β cells[14]. The disruption of mitochondrial function in pancreatic β cells[15], myocytes[16], and adipocytes[17] can affect the serum glucose level. A decrease in the expression of

adipocyte insulin-responsive glucose transporter-4[18], and statin-induced sarcopenia[19] and muscle destruction[20,21], can be associated with the development of DM.

Statins exert their effects mainly in the liver. Cholesterol biosynthesis is mainly conducted in the liver. Therefore, it is plausible that statin treatment may induce hepatic insulin resistance. One study shows that statins increase the expression of hepatic gluconeogenic enzymes in human primary hepatocytes[22]. There are statin-induced differences in the expression of ATP-binding cassette transporter A1 (ABCA1) in hepatocytes[23], and in the changes in concentration of adiponectin[24] that vary according to the type of statins. However, the exact molecular mechanisms underlying these differences need to be determined. Pitavastatin is a lipophilic statin that is metabolized via CYP3A4[25] instead of cytochrome P450, which metabolizes the other statins. Pitavastatin is reported to increase the expression of ABCA1[23], apoA-I[26], and lipoprotein lipase[27]. The J-PREDICT clinical trial is currently underway in Japan[28] to study the effect of pitavastatin on new-onset DM in patients with impaired glucose tolerance.

A recent study reported a dose-dependent diabetogenic effect of statins[29]. This meta-analysis of five studies reported that intensive-dose statin therapy could increase the risk for development of diabetes compared to that conferred by moderate-dose statin therapy[29]. Asian populations were more sensitive to the statin dose than Western populations, probably due to genetic differences in statin metabolism[30]. Several studies reported that the effect of lowering

LDL-cholesterol may be associated with the diabetogenic effect of statins[31]. In the present study, the average dose of atorvastatin was 11.8 ± 5.0 mg/day, whereas that of pitavastatin was 2.1 ± 1.4 mg/day. A previous report showed that atorvastatin at 10 mg/day and pitavastatin at 2 mg/day had similar efficacies in lowering LDL-cholesterol[32]. Another study reported that rosuvastatin at 2.5 mg/day, atorvastatin at 10 mg/day, and pitavastatin at 2 mg/day all had similar efficacies for lowering LDL-cholesterol. The dose of rosuvastatin was relatively high in our study compared with dosages reported in previous studies, whereas the other statin doses were consistent with those of previous studies.

In our study, when separately analyzed according to sex, difference of diabetogenic effect among statins was more significant in women and was not significant in men (Appendix Table 5,6). An observational study of postmenopausal women found that the risk for development of diabetes increased more in Asian and Pacific Islander populations than in Western populations (HR, 1.78 vs. 1.49, respectively)[12]. Elderly and Asian women were significantly more vulnerable to the increased risk of development of DM caused by statin use[33].

There were several limitations in this study. First, we could not control all founding factors because it was a retrospective observational study, and there were some differences in the baseline characteristics of each group. We included all these variables as factors in a multivariate Cox regression model to minimize any confounding variables among participants who had used the same kind of

statin for more than four years. Second, newer statins such as pitavastatin may have been used in patients at higher risk for development of DM, due to the prescribing physician's preferences. And it could be related to higher diagnosis rate of diabetes. Third, the dose of each statin could not be controlled. Although the final mean dose of the statin was not different between the groups, a different relative dose of each type of statin could have affected the incidence of new-onset DM. Finally, the cohort sizes in the pravastatin and simvastatin groups were relatively small for analysis of statistical significance. Our study also had strengths. We identified several risk factors for development of DM, including age, gender, BMI, FBG, and lipid profile. We were able to adjust for these factors to determine the diabetogenic effects of different types of statins above and beyond these factors.

V. CONCLUSION

In conclusion, pitavastatin is associated with a greater risk of new-onset DM when compared with that for atorvastatin. Fasting blood glucose level at the start of statin treatment is another important risk factor. Although statins are the cornerstone of modern cardiovascular pharmacology, caution should be given for patients who receive statins for a prolonged time.

REFERENCES

1. Gotto AM, Moon JE. Management of Cardiovascular Risk: The Importance of Meeting Lipid Targets. The American journal of cardiology 2012;110:3A-14A.
2. Ridker PM, Danielson E, Fonseca F, Genest J, Gotto Jr AM, Kastelein J, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine 2008;359:2195.
3. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Drugs 2004;64:43-60.
4. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005.
5. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. The Lancet 2002;360:1623-30.
6. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. The Lancet 2010;375:735-42.
7. Freeman DJ, Norrie J, Sattar N, Neely RDG, Cobbe SM, Ford I, et al. Pravastatin and the development of diabetes mellitus evidence for a protective treatment effect in the West of Scotland Coronary

Prevention Study. Circulation 2001;103:357-62.

8. Navarese EP, Buffon A, Andreotti F, Kozinski M, Welton N, Fabiszak T, et al. Meta-Analysis of Impact of Different Types and Doses of Statins on New-Onset Diabetes Mellitus. The American journal of cardiology 2013.

9. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. BMJ: British Medical Journal 2013;346.

10. Zaharan NL, Williams D, Bennett K. Statins and risk of treated incident diabetes in a primary care population. British Journal of Clinical Pharmacology 2013;75:1118-24.

11. Chong PH, Seeger JD, Franklin C. Clinically relevant differences between the statins: implications for therapeutic selection. The American journal of medicine 2001;111:390-400.

12. Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, Wactawski-Wende J, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Archives of internal medicine 2012;172:144.

13. Bełtowski J, Wójcicka G, Jamroz-Wiśniewska A. Adverse effects of statins-mechanisms and consequences. Curr Drug Saf 2009;4:209-28.

14. Xia F, Xie L, Mihic A, Gao X, Chen Y, Gaisano HY, et al. Inhibition of cholesterol biosynthesis impairs insulin secretion and voltage-gated calcium channel function in pancreatic β-cells. Endocrinology 2008;149:5136-45.

15. Mulder H, Ling C. Mitochondrial dysfunction in pancreatic β-cells in type 2 diabetes. Molecular and cellular endocrinology 2009;297:34-40.

16. Kwak H-B, Thalacker-Mercer A, Anderson EJ, Lin C-T, Kane DA, Lee N-S, et al. Simvastatin impairs ADP-stimulated respiration and increases mitochondrial oxidative stress in primary human skeletal

myotubes. Free Radical Biology and Medicine 2011.

17. Kusminski CM, Scherer PE. Mitochondrial dysfunction in white adipose tissue. Trends in Endocrinology & Metabolism 2012.

18. Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, Yada T. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. Diabetologia 2006;49:1881-92.

19. Khamseh ME, Malek M, Aghili R, Emami Z. Sarcopenia and diabetes: pathogenesis and consequences. The British Journal of Diabetes & Vascular Disease 2011;11:230-4.

20. Draeger A, Monastyrskaya K, Mohaupt M, Hoppeler H, Savolainen H, Allemann C, et al. Statin therapy induces ultrastructural damage in skeletal muscle in patients without myalgia. The Journal of pathology 2006;210:94-102.

21. Golomb BA, Evans MA, Dimsdale JE, White HL. Effects of statins on energy and fatigue with exertion: Results from a randomized controlled trial. Archives of internal medicine 2012;172:1180-2.

22. Hafner M, Juvan P, Rezen T, Monostory K, Pascussi JM, Rozman D. The human primary hepatocyte transcriptome reveals novel insights into atorvastatin and rosuvastatin action. Pharmacogenet Genomics 2011;21:741-50.

23. Maejima T, Sugano T, Yamazaki H, Yoshinaka Y, Doi T, Tanabe S, et al. Pitavastatin increases ABCA1 expression by dual mechanisms: SREBP2-driven transcriptional activation and PPARα-dependent protein stabilization but without activating LXR in rat hepatoma McARH7777 cells. Journal of pharmacological sciences 2011;116:107.

24. Wanders D, Plaisance EP, Judd RL. Pharmacological effects of lipid-lowering drugs on circulating adipokines. World journal of diabetes 2010;1:116.

25. Fujino H, Yamada I, Shimada S, Nagao T, Yoneda M. Metabolic Fate of Pitavastatin (NK-104), a New Inhibitor of 3-Hydroxy-3-methyllutaryl Coenzyme A Reductase. Arzneimittelforschung 2011;52:745-53.
26. Maejima T, Yamazaki H, Aoki T, Tamaki T, Sato F, Kitahara M, et al. Effect of pitavastatin on apolipoprotein AI production in HepG2 cell. Biochemical and biophysical research communications 2004;324:835-9.
27. Saiki A, Murano T, Watanabe F, Oyama T, Miyashita Y, Shirai K. Pitavastatin enhanced lipoprotein lipase expression in 3T3-L1 preadipocytes. Journal of atherosclerosis and thrombosis 2005;12:163.
28. Yamazaki T, Kishimoto J, Ito C, Noda M, Odawara M, Terauchi Y, et al. Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (the J-PREDICT study): rationale, study design, and clinical characteristics of 1269 patients. Diabetology international 2011;2:134-40.
29. Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy. JAMA: The Journal of the American Medical Association 2011;305:2556.
30. Liao JK. Safety and efficacy of statins in Asians. The American journal of cardiology 2007;99:410-4.
31. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart J-C, Haffner S, et al. Effect of Lowering LDL Cholesterol Substantially Below Currently Recommended Levels in Patients With Coronary Heart Disease and Diabetes The Treating to New Targets (TNT) study. Diabetes Care 2006;29:1220-6.
32. Yokote K, Bujo H, Hanaoka H, Shinomiya M, Mikami K, Miyashita Y, et al. Multicenter collaborative randomized parallel group comparative

study of pitavastatin and atorvastatin in Japanese hypercholesterolemic patients: collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). Atherosclerosis 2008;201:345-52.

33. Goldstein MR, Mascitelli L. Do Statins Cause Diabetes? Current Diabetes Reports 2013:1-10.

Appendix Table 1–Baseline characteristics for new statin users in men

	Total (N=647) (%)	Atorvastatin (n=230) (35.55%)	Pitavastatin (n=141) (21.79%)	Rosuvastatin (n=210) (32.46%)	Simvastatin (n=39) (6.03%)	Pravastatin (n=27) (4.17%)	*p-value*
Age at start of statin treatment (years)	59.8±10.9	58.4±11.3[1]	62.0±11.3[2]	59.4±9.9[1,2]	62.5±10.5[1,2]	58.9±12.4[1,2]	0.012
BMI (kg/m^2)	25.0±11.7	26.1±18.7	24.2±2.7	24.5±2.9	24.0±2.2	24.3±3.0	0.557
FBG (mg/dl)	91.3±5.6	90.7±5.9	92.3±5.2	91.4±5.3	91.4±5.3	90.0±6.8	0.075
Total cholesterol (mg/dl)	181.6±47.8	178.6±47.4	181.2±43.8	184.0±52.5	182.0±37.5	186.2±46.6	0.822
Triglyceride (mg/dl)	148.3±107.1	140.0±84.1	139.0±70.6	158.9±144.4	151.5±82.4	178.3±124.2	0.168
HDL-cholesterol (mg/dl)	44.1±11.0	43.0±10.4[1]	47.4±11.9[2]	42.8±11.1[1]	46.4±8.9[1,2]	42.6±9.7[1,2]	0.001
LDL-cholesterol (mg/dl)	115.8±39.2	114.8±37.3	120.6±37.4	114.1±43.1	111.8±39.0	118.6±39.0	0.541
Triglyceride/ HDL-cholesterol (ratio)	1.44±1.37	1.31±0.99[1]	1.26±0.89[1]	1.64±1.79[2]	1.54±1.27[1,2]	1.83±2.09[1,2]	0.028

All values are reported as means ± standard deviations (SD) and real numbers of participants with the percentage in parentheses. Between-group differences of the averages were compared using an analysis of variance (ANOVA) for parametric data. Between-group differences of numbers and percentages were compared using a χ^2 test. Additional post-hoc analyses were performed (2 > 1). FBG, fasting blood glucose

Appendix Table 2–Baseline characteristics for new statin users in women

	Total (N=513) (%)	Atorvastatin (n=145) (28.27%)	Pitavastatin (n=148) (28.85%)	Rosuvastatin (n=135) (26.32%)	Simvastatin (n=58) (11.31%)	Pravastatin (n=27) (5.26%)	*p-value*
Age at start of statin treatment (years)	63.4±9.4	63.8±9.2	63.4±9.0	62.8±10.1	63.6±8.8	64.3±9.7	0.897
BMI (kg/m^2)	24.6±7.5	24.2±3.1	24.2±3.3	25.7±13.5	24.3±3.1	24.4±2.8	0.510
FBG (mg/dl)	90.7±5.6	90.1±5.4	90.8±5.3	91.1±5.9	91.3±6.3	91.0±4.9	0.571
Total cholesterol (mg/dl)	205.2±46.0	192.1±47.4[1]	209.6±42.4[2]	212.6±48.2[2]	201.4±42.4[1,2]	220.5±40.0[1,2]	0.001
Triglyceride (mg/dl)	144.4±72.2	131.9±59.5[1]	149.4±64.9[2]	158.0±92.5[2]	135.6±66.1[1,2]	132.1±55.6[1,2]	0.028
HDL-cholesterol (mg/dl)	52.1±11.5	50.6±10.0[1]	53.1±12.4[2]	51.0±11.5[1]	52.5±10.2[1,2]	58.8±15.0[1,2]	0.013
LDL-cholesterol (mg/dl)	131.9±41.3	117.8±39.6[1]	137.1±37.6[2]	138.1±46.4[2]	135.7±38.5[2]	137.7±31.4[1,2]	<0.001
Triglyceride/ HDL-cholesterol (ratio)	1.22±0.91	1.21±0.68	1.22±0.85	1.33±1.24	1.10±0.79	1.00±0.46	0.376

All values are reported as means ± standard deviations (SD) and real numbers of participants with the percentage in parentheses. Between-group differences of the averages were compared using an analysis of variance (ANOVA) for parametric data. Between-group differences of numbers and percentages were compared using a χ^2 test. Additional post-hoc analyses were performed (2 > 1). FBG, fasting blood glucose

Appendix Table 3-Development of dysglycemia (IFG and/or DM) in new statin users, men

	Total (N=647) (%)	Atorvastatin (n=230) (35.55%)	Pitavastatin (n=141) (21.79%)	Rosuvastatin (n=210) (32.46%)	Simvastatin (n=39) (6.03%)	Pravastatin (n=27) (4.17%)	*p-value*
Duration of statin treatment (months)	54.4±10.5	54.5±10.7[1,2]	56.1±11.6[2]	52.6±10.2[1]	54.8±8.6[1,2]	56.4±6.6[1,2]	0.030
No. of subjects who developed dysglycemia (IFG + DM) (%)	199 (30.8%)	66 (28.7%)	45 (31.9%)	74 (35.2%)	9 (23.1%)	5 (18.5%)	0.256
No. of subjects who developed DM (%)	36 (5.6%)	12 (5.2%)	10 (7.1%)	12 (5.7%)	1 (2.6%)	1 (3.7%)	0.821
No. of outcomes (IFG + DM) per 1000 person-years	92.3	92.1	88.5	113.2	56.5	42.6	
No. of outcomes (DM) per 1000 person-years	12.3	11.5	15.2	13.0	5.6	7.9	

All values are reported as means ± standard deviations (SD) and real numbers of participants with the percentage in parentheses. Between-group differences of the averages were compared using an analysis of variance (ANOVA) for parametric data. Between-group differences of numbers and percentages were compared using a χ^2 test. Additional post-hoc analyses were performed (2 > 1). IFG, impaired fasting glucose; DM, diabetes mellitus.

Appendix Table 4-Development of dysglycemia (IFG and/or DM) in new statin users, women

	Total (N=513) (%)	Atorvastatin (n=145) (28.27%)	Pitavastatin (n=148) (28.85%)	Rosuvastatin (n=135) (26.32%)	Simvastatin (n=58) (11.31%)	Pravastatin (n=27) (5.26%)	*p-value*
Duration of statin treatment (months)	54.9±10.7	56.2±9.1[2]	53.2±13.8[1]	53.9±8.8[1]	57.9±9.6[2]	55.2±8.4[1,2]	0.021
No. of subjects who developed dysglycemia (IFG + DM) (%)	150 (29.2%)	36 (24.8%)	47 (31.8%)	42 (31.1%)	18 (31.0%)	7 (25.9%)	0.210
No. of subjects who developed DM (%)	33 (6.4%)	3 (2.1%)[1]	21 (14.2%)[2]	5 (3.7%)[1]	3 (5.2%)[1]	1 (3.7%)[1,2]	<0.001
No. of outcomes (IFG + DM) per 1000 person-years	83.7	72.0	85.4	103.1	81.7	61.3	
No. of outcomes (DM) per 1000 person-years	14.1	4.4	32.0	8.2	10.7	8.1	

All values are reported as means ± standard deviations (SD) and real numbers of participants with the percentage in parentheses. Between-group differences of the averages were compared using an analysis of variance (ANOVA) for parametric data. Between-group differences of numbers and percentages were compared using a χ^2 test. Additional post-hoc analyses were performed (2 > 1). IFG, impaired fasting glucose; DM, diabetes mellitus.

Appendix Table 5–Independent risk factors for development of DM in men

	Unadjusted		Adjusted	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Statin				
Atorvastatin	Reference		Reference	
Pitavastatin	1.35 (0.58–3.12)	0.488	1.02 (0.42–2.50)	0.960
Rosuvastatin	1.11 (0.50–2.50)	0.793	1.21 (0.54–2.72)	0.652
Simvastatin	0.49 (0.06–3.74)	0.488	0.53 (0.07–4.11)	0.544
Pravastatin	0.69 (0.09–5.34)	0.726	0.85 (0.11–6.54)	0.873
Age	1.04 (1.00–1.07)	0.031	1.04 (1.00–1.07)	0.034
BMI (kg/m^2)	1.00 (0.99–1.02)	0.666	1.01 (0.99–1.03)	0.327
Duration of observation (years)	1.02 (0.97–1.06)	0.476	1.02 (0.97-1.06)	0.461
FBG (mg/dl)	1.06 (0.99–1.14)	0.073	1.07 (1.00–1.14)	0.061
Total cholesterol (mg/dl)	1.00 (0.99–1.01)	0.557		
Triglyceride (mg/dl)	1.00 (1.00–1.00)	0.101		
HDL-cholesterol (mg/dl)	0.97 (0.94–1.01)	0.112		
Triglyceride/ HDL-cholesterol (ratio)	1.11 (0.94-1.30)	0.224		
LDL-cholesterol (mg/dl)	1.00 (0.99–1.01)	0.656		
ACEi/ ARB use	0.81 (0.38–1.72)	0.579		

The relative risk factor for development of diabetes was compared by using a multivariate Cox regression adjusted for age, gender, BMI, total cholesterol level, and triglyceride levels.
HR, hazard ratio; CI, confidence interval; FBG, fasting blood glucose; DM, diabetes mellitus; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

Appendix Table 6–Independent risk factors for development of DM in women

	Unadjusted		Adjusted	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Statin				
Atorvastatin	Reference		Reference	
Pitavastatin	7.30 (2.18–24.49)	0.001	7.22 (2.13–24.54)	0.002
Rosuvastatin	1.84 (0.44–7.69)	0.405	1.04 (0.21–5.22)	0.964
Simvastatin	2.48 (0.50–12.31)	0.265	2.90 (0.58–14.53)	0.196
Pravastatin	1.78 (0.19–17.09)	0.618	1.85 (0.19–17.77)	0.595
Age	1.03 (0.99–1.07)	0.182	1.01 (0.97–1.05)	0.586
Gender (Female)	1.00 (0.97–1.05)	0.838	1.02 (0.97–1.07)	0.499
BMI (kg/m^2)	0.98 (0.94–1.03)	0.444	0.98 (0.93-1.03)	0.453
Duration of observation (years)	1.08 (1.00–1.16)	0.040	1.07 (0.99–1.16)	0.070
FBG (mg/dl)	1.00 (0.99–1.01)	0.963		
Total cholesterol (mg/dl)	1.00 (1.00–1.01)	0.192		
Triglyceride (mg/dl)	0.97 (0.94–1.01)	0.092		
HDL-cholesterol (mg/dl)	1.10 (0.81-1.50)	0.526		
Triglyceride/ HDL-cholesterol (ratio)	1.00 (1.00–1.01)	0.409		
LDL-cholesterol (mg/dl)	1.01 (0.50–2.06)	0.970		
ACEi/ ARB use				

The relative risk factor for development of diabetes was compared by using a multivariate Cox regression adjusted for age, gender, BMI, total cholesterol level, and triglyceride levels.
HR, hazard ratio; CI, confidence interval; FBG, fasting blood glucose; DM, diabetes mellitus; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

ABSTRACT(IN KOREAN)

HMG-CoA 환원효소 억제제 치료 환자에서의 당뇨병 위험

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3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) 환원효소 억제제(스타틴)는 혈중 콜레스테롤 농도를 조절하고 이를 통해 심혈관 질환의 발생을 예방한다. 이러한 스타틴이 새로운 당뇨병 발생 위험을 증가시킬 수 있다는 연구 결과들이 최근 들어 계속 발표되었다. 그러나 스타틴 종류 간 당뇨 발생 위험도 차이가 있는지에 대해서는 아직 논란의 여지가 있다. 우리는 본 연구에서 스타틴 약제 간에 새로운 당뇨병 발생의 위험도 차이 여부를 확인하고자 하였다.

기존에 당뇨병을 진단받지 않고 공복혈당 검사에서도 당뇨병이나 공복혈당 장애(Impaired fasting glucose) 소견을 보이지 않는 환자들 중에서 고콜레스테롤 혈증 치료를 위해 동일 스타틴 약제를 4년 이상 유지한 총 1,160명의 환자를 대상으로 하였다. 이들 환자를 대상으로 스타틴 종류에 따라 당뇨병의 발생률 차이를 비교하였다. 평균 추적관찰 기간은 54.6 ± 10.6 개월이었다. 당뇨병 발생률은 피타바스타틴(pitavastatin, 10.7%) 사용 그룹에서 다른 그룹에 비해 통계학적으로 유의미하게 높게 나타났다. [아토르바스타틴(atorvastatin, 4.0%), 로수바스타틴(rosuvastatin, 6.1%), 심바스타틴(simvastatin, 4.1%),

프라바스타틴(pravastatin, 3.7%); p=0.003].

아토르바스타틴을 기준으로 하여 비교하였을 때 피타바스타틴 치료 그룹에서 당뇨병 발생 위험도가 가장 높았다 [위험비 (hazard ratio, HR)=2.68, p=0.004]. 다른 종류의 스타틴은 당뇨병 발생 위험도에서 아토르바스타틴과 비교 시 통계학적 유의미한 차이를 보이지 않았다.

스타틴 사용 환자의 사용 시점에서의 공복혈당 수치는 당뇨 발생과 관련이 있었으며 그 값이 클수록 그 위험도가 큰 것으로 나타났다 (HR=1.06, p=0.031). 연령, 성별, 체질량지수(body-mass index, BMI), 스타틴 사용기간, 약제 시작 시점의 혈중 콜레스테롤 농도 등은 당뇨병 발생과 상관관계를 보이지 않았다.

본 연구에서는 피타바스타틴이 당뇨병 발생에 있어 가장 밀접한 연관성을 보였으나 이는 후향적인 관찰 연구의 결과로, 이에 대한 보다 많은 연구가 필요할 것이다.

핵심되는 말 : HMG CoA 환원효소 억제제, 스타틴, 당뇨병, 고콜레스테롤혈증