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Original Article

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Clinical Characteristics of Patients With Statin Discontinuation in Korea: A Nationwide Population-Based Study

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ABSTRACT

Objective: To investigate the clinical characteristics of patients with statin discontinuation in Korea, using a nationwide database.
Methods: We analyzed 1,308,390 patients treated with statin for the first time in their life between 2016 and 2017 using the Korean National Health Information Database. The patients participated in the Korean National Health Screening Program within two years before taking statin. Patients with statin discontinuation were defined as those who were not prescribed statin between 365 days and 730 days after the initial statin prescription.
Results: The overall prevalence of statin discontinuation was 39.44%. Patients with statin discontinuation were younger, had lower body mass index (BMI), included a higher number of smokers and drinkers, did not exercise regularly, with fewer cases of hypertension and diabetes mellitus than those without statin discontinuation (p<0.001). Compared with patients aged 20–29 years, the risk of statin discontinuation showed a U-shaped relationship with age (odds ratios [ORs]: 0.619 in 30–39 years; 0.454 in 40–49 years; 0.345 in 50–59 years; 0.307 in 60–69 years; 0.324 in 70–79 years; and 0.415 in ≥80 years). In addition, increased BMI was associated with decreased risk of statin discontinuation (ORs: 0.969 with 25.0–29.9 kg/m^2, and 0.890 with ≥30.0 kg/m^2). Patients with hypertension and diabetes mellitus were at a lower risk of statin discontinuation (OR: 0.414 for hypertension; 0.416 for diabetes mellitus).
Conclusion: The prevalence of patients with statin discontinuation in Korea was 39.44% at 1 to 2 years after initial statin treatment.

Keywords: Compliance; Dyslipidemia; Lipid; Statin

INTRODUCTION

Dyslipidemia is an important risk factor for cardiovascular disease (CVD) and increases global healthcare burden.[1,2] Treatment with statins is effective in reducing lipid levels and is an essential component of CVD prevention.[3-5] Currently, it is one of the most widely studied and used medications in the world.[6] It is well known that statins reduce the risk of CVD in terms of primary and secondary prevention.[7,8] Almost all dyslipidemia treatment guidelines recommend statins for primary prevention in high-risk patients and for secondary

Conflict of Interest
The authors have no conflicts of interest to declare. The funding source had no role in the collection of the data or in the decision to submit the manuscript for publication.

Data Availability Statement
The data that support the findings of this study are available from the National Health Insurance Sharing Service (NHISS, https://nhiss.nhis.or.kr/) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the NHISS.

Author Contributions
Conceptualization: Kim KS, Hong S, Han K, Park CY; Formal analysis: Han K; Investigation: Kim KS, Hong S, Park CY; Methodology: Kim KS, Hong S, Han K, Park CY; Project administration: Kim KS; Resources: Kim KS; Supervision: Hong S, Han K, Park CY; Validation: Kim KS, Hong S, Han K, Park CY; Writing - original draft: Kim KS; Writing - review & editing: Kim KS, Hong S, Han K, Park CY.

prevention in patients with CVDs.[9,10] However, studies suggest an increased number of patients who do not adhere to regular statin treatment.[11] The proportion of patients with statin discontinuation was only 4–11% in clinical trials,[12,13] but the real-world prevalence was significantly higher ranging from 11% to 53%.[14,15]

The effectiveness of statins depends on a patient's level of adherence, which is bound to affect lipid control and CVD outcomes. Many observational studies have reported a protective relationship between statin adherence and CVD outcomes in both primary and secondary prevention strategies.[16,17] In addition, high levels of adherence decreased hospitalization, which reduced future healthcare costs.[18,19] Consequently, it is important to increase adherence to statin treatment to save patients and reduce healthcare burden.

Previous studies investigating the factors underlying statin discontinuation, which is an extreme form of poor adherence, reported mixed results. Some studies showed that young (<50 years) or old (>70 years) patients,[15,20] smokers,[21] and those with intensive dose therapy[22] tended to carry a higher risk for statin discontinuation. Although many guidelines recommend statins for nearly all patients with type 2 diabetes,[9,10,23] an increased risk of statin discontinuation has also been reported for patients with diabetes.[21,24] However, some studies have shown that continuation of lipid-lowering drugs was associated with diabetes.[25] Other studies reported lack of association between statin discontinuation and age,[21,26] diabetes,[27,28] or smoking.[28] The clinical characteristics of patients with statin discontinuation in Korea at the national level have yet to be reported. Therefore, this study aimed to investigate the clinical characteristics of patients with statin discontinuation in Korea, using a nationwide database.

MATERIALS AND METHODS

1. Study database and participants

This analysis was conducted using the National Health Information Database (NHID), which is produced by the National Health Insurance Service (NHIS) associated with the National Health Screening Program. The NHIS is a single-payer health care system that is managed by the Korean government and covers >97% of the Korean population. The NHID contains information pertaining to sociodemographic variables, diagnoses (as defined by the International Classification of Diseases, 10th revision [ICD-10]), prescriptions, and hospital visit dates. The National Health Screening Program includes a medical interview, anthropometric measurements, blood tests, urine test, and additional assessments. Based on the NHID, we identified 1,837,610 patients who were treated with statin for the first time in their life between 2016 and 2017. They participated in the Korean National Health Screening Program within two years prior to statin treatment. We excluded patients without health data two years before 2016 (n=477,014) those with missing variables (n=35,082), and those who died before 730 days after initial statin prescription (n=17,124). Finally, 1,308,390 patients were included (**Fig. 1**). This study was performed according to the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of CHA Bundang Medical Center (2020-03-038-007). The requirement for informed consent was waived by the IRB because we did not access personal identifying information.

2. Measurements

Anthropometric and laboratory data were gathered from the National Health Screening Program. Patients' smoking status, alcohol consumption, and regular exercise levels were

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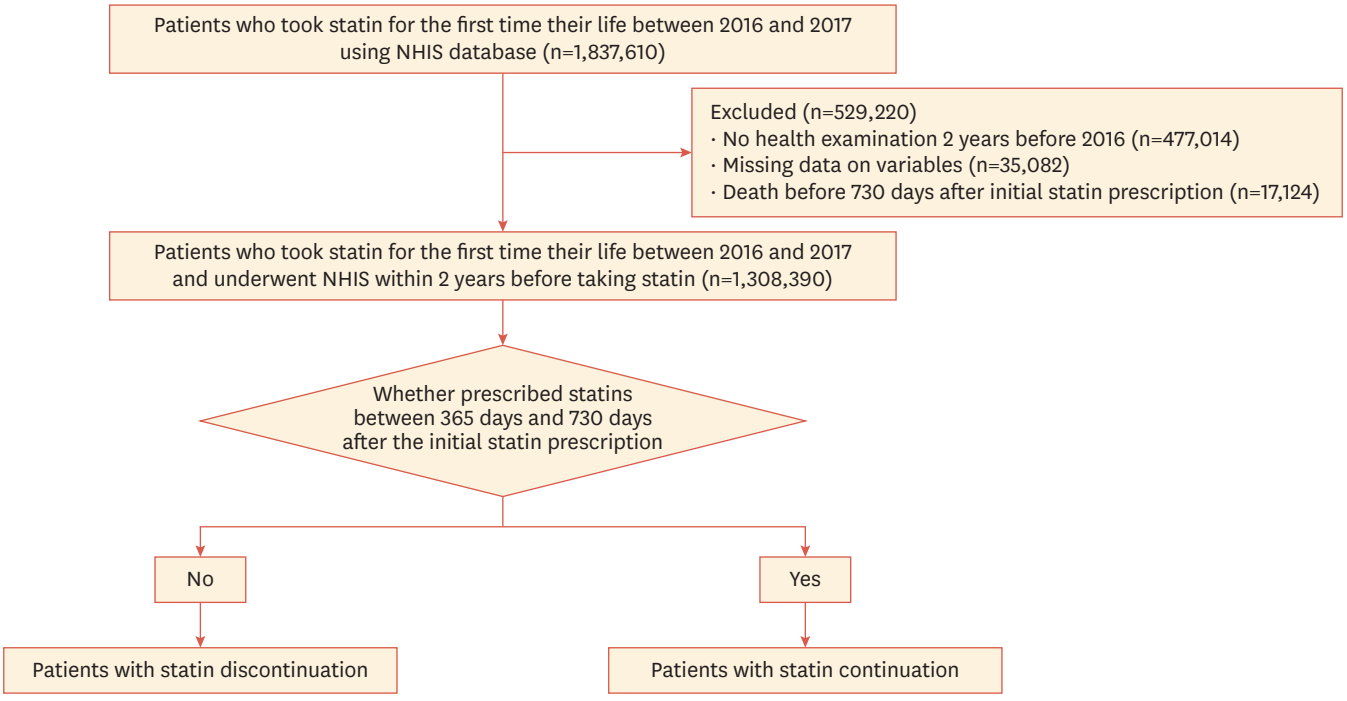

Fig. 1. Flowchart outling study population selection and design.
NHIS, The National Health Insurance Service.

determined using a standardized self-assessment questionnaire. Heavy alcohol consumption was defined as drinking more than 30 g/day. Regular exercise was defined as >30 minutes of moderate physical activity performed at least five times per week or >20 minutes of strenuous physical activity performed at least three times per week. Low income was defined by the lowest quartile for income and meeting criteria for medical aid benefit. Levels of glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, and creatinine levels were measured in venous blood samples after an overnight fast of at least eight hours. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

3. Definitions

Abdominal obesity was defined as waist circumference ≥90 cm in men and ≥85 cm in women.[29] Glycemic status was classified as follows: normal, if fasting plasma glucose (FPG) <100 mg/dL; impaired fasting glucose, FPG 100–125 mg/dL; diabetes mellitus (DM), FPG ≥126 mg/dL or prescriptions for anti-diabetic drugs under ICD-10 codes E11-E14. Blood pressure status was classified as follows: normal, if blood pressure <120/80 mmHg; prehypertension, if the systolic pressure was 120–139 mmHg or the diastolic pressure was 80–89 mmHg; hypertension was defined as blood pressure ≥140/90 mmHg or prescriptions for anti-hypertensive drugs under ICD-10 codes I10-13 or I15. Chronic kidney disease (CKD) was defined as eGFR <60 mL/min/1.73 m^2. Myocardial infarction (MI) was defined as ICD-10 code I21 or I22 during hospitalization. Ischemic stroke was defined as ICD-10 code I63 or I64 during hospitalization with claims for brain magnetic resonance imaging or computed tomography. Patients with statin discontinuation were defined as those who never be prescribed statin between 365 days and 730 days after the initial statin prescription.

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4. Statistical analysis

Data for continuous variables are presented as means ± standard deviation or geometric mean (95% confidence interval [CI]). Categorical variables are reported as number (%). The significance of differences in measurements between groups was assessed using the independent sample *t*-test, and χ^2 test. The odds ratios (ORs) and 95% CIs for statin discontinuation were calculated using multivariable logistic regression analysis. The multivariable models were adjusted for age, sex, body mass index (BMI), abdominal obesity, smoking status, alcohol consumption, low income, regular exercise, DM, hypertension, and CKD. Statistical significance was defined as a two-sided *p* value <0.05. Analyses were performed with SAS version 9.4 (SAS Institute).

RESULTS

Baseline characteristics of study population are presented in **Table 1**. The overall prevalence of patients with statin discontinuation was 39.44%. Patients with statin discontinuation were younger, more likely to be male and had lower BMI. They included a higher number of smokers and drinkers and did not exercise regularly. However, fewer patients with statin discontinuation earned low income than those continuing with statin therapy. Patients with statin discontinuation had less hypertension, DM, CKD, MI, and ischemic stroke than those

Table 1. Baseline characteristics of study population

Variables	Patients with statin discontinuation	Patients with statin continuation	*p*-value
No.	515,987	792,403	
Age (yr)	53.83±11.70	57.12±11.04	<0.001
Male	262,838 (50.94)	391,731 (49.44)	<0.001
Height (cm)	162.93±9.30	162.02±9.19	<0.001
Weight (kg)	65.54±12.44	65.70±12.34	<0.001
Body mass index (kg/m^2)	24.56±3.29	24.90±3.36	<0.001
Waist circumference (cm)	82.59±9.03	83.79±9.06	<0.001
Smoking status			<0.001
Nonsmoker	311,432 (60.36)	490,106 (61.85)	
Ex-smoker	89,325 (17.31)	150,003 (18.93)	
Current smoker	115,230 (22.33)	152,294 (19.22)	
Alcohol consumption			<0.001
None	288,608 (55.93)	469,174 (59.21)	
Mild (<30 g/day)	184,887 (35.83)	264,519 (33.38)	
Heavy (≥30 g/day)	42,492 (8.24)	58,710 (7.41)	
Regular exercise	102,881 (19.94)	163,490 (20.63)	<0.001
Low income	106,180 (20.58)	168,726 (21.29)	<0.001
Diabetes mellitus	55,517 (10.76)	183,023 (23.10)	<0.001
Hypertension	156,310 (30.29)	409,932 (51.73)	<0.001
Chronic kidney disease	19,549 (3.79)	43,506 (5.49)	<0.001
MI or ischemic stroke	21,186 (4.11)	64,964 (8.20)	<0.001
MI	5,401 (1.05)	18,812 (2.37)	<0.001
Ischemic stroke	16,382 (3.17)	47,911 (6.05)	<0.001
Systolic blood pressure (mmHg)	124.42±15.12	128.31±16.15	<0.001
Diastolic blood pressure (mmHg)	77.63±10.26	79.40±10.85	<0.001
Fasting plasma glucose (mg/dL)	102.49±27.73	111.22±38.77	<0.001
Total cholesterol (mg/dL)	230.80±37.37	225.41±38.38	<0.001
Triglyceride (mg/dL)	128.97 (128.77–213.51)	133.23 (133.07–216.59)	<0.001
HDL-cholesterol (mg/dL)	54.91±15.78	53.48±14.87	<0.001
LDL-cholesterol (mg/dL)	146.58±35.65	141.81±35.40	<0.001
eGFR (mL/min/1.73 m^2)	92.92±16.53	90.77±16.98	<0.001

Data are presented as mean ± standard deviation or, geometric mean (95% confidence interval), or number (%).
MI, myocardial infarction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

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with statin continuation. Levels of total cholesterol, HDL-cholesterol, LDL-cholesterol, and eGFR were higher in patients with statin discontinuation than in those with statin continuation, whereas levels of FPG, systolic and diastolic blood pressure, and TG were lower.

Statin discontinuation decreased with increasing age, except in patients aged more than 80 years (20–29 years, 68.48%; 30–39 years, 55.64%; 40–49 years, 46.53%; 50–59 years, 38.82%; 60–69 years, 33.35%, 70–79 years, 30.79%, ≥80 years, 34.21%; *p* for trend <0.05) (**Fig. 2A**). The prevalence of statin discontinuation decreased with increasing BMI (<18.5 kg/m^2, 45.13%; 18.5–22.9 kg/m^2, 42.29%; 23.0–24.9 kg/m^2, 39.79%; 25.0–29.9 kg/m^2, 37.62%; ≥30.0 kg/m^2, 34.73%; *p* for trend <0.05) (**Fig. 2B**). The prevalence of statin discontinuation was the lowest in patients with normal glucose status, impaired fasting glucose, and DM, in that order (normal, 44.37%; impaired fasting glucose, 40.77%; DM, 23.27%; *p* for trend <0.05) (**Fig. 2C**). In addition, the prevalence of statin discontinuation was the lowest in patients with normal blood pressure, prehypertension, and hypertension, in that order (normal, 50.98%; prehypertension, 46.74%; hypertension, 27.60%; *p* for trend <0.05) (**Fig. 2D**).

Compared with those aged 20–29 years, the ORs for patients discontinuing statin treatment aged 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years were 0.619 (95% CI, 0.593–0.646), 0.454 (95% CI, 0.436–0.472), 0.345 (95% CI, 0.331–0.359), 0.307 (95% CI, 0.295–0.320), 0.324 (95% CI, 0.311–0.338), and 0.415 (95% CI, 0.395–0.435), respectively, after adjustment for age, sex, BMI, abdominal obesity, smoking status, alcohol consumption, low income,

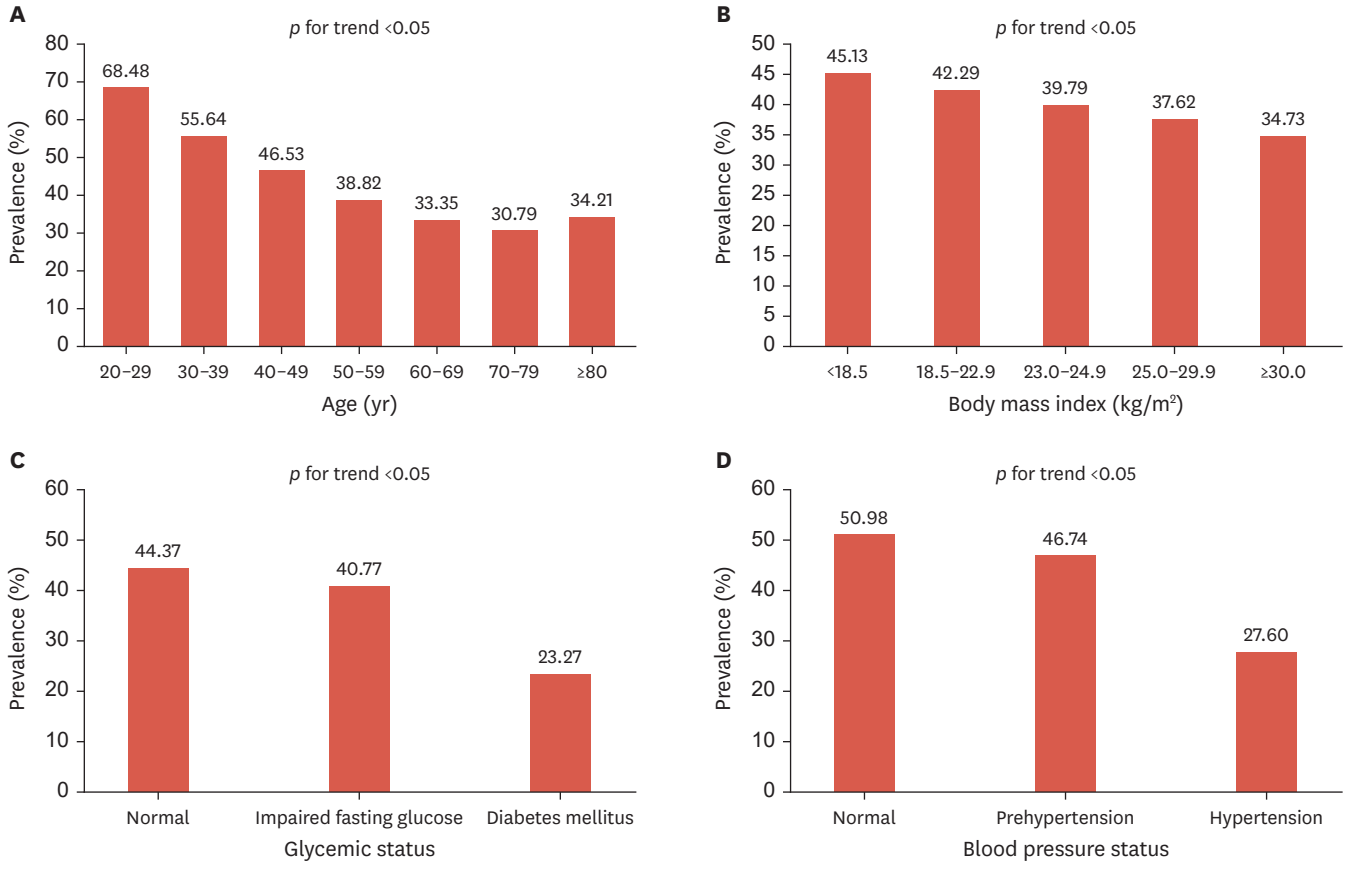

Fig. 2. Prevalence of statin discontinuation among patients according to (A) age, (B) body mass index, (C) status of diabetes mellitus, and (D) status of hypertension.

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regular exercise, DM, hypertension, and CKD (**Table 2**). In addition, the risk of statin discontinuation in women was 10.3% lower than in men. Compared with patients with a BMI of 18.5–22.9 kg/m^2, the risk for statin discontinuation was 7.8% higher in patients with BMI <18.5 kg/m^2, but 2.5%, 3.1%, and 11.0% lower in those with BMI values of 23.0–24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥30 kg/m^2, respectively. The risks for statin discontinuation were lower in ex-smokers (OR, 0.915; 95% CI, 0.904–0.927) than nonsmoker, but not different in current smoker (OR, 1.010; 95% CI, 0.998–1.022). The risks for statin discontinuation were higher in heavy drinkers (OR, 1.168; 95% CI, 1.150–1.186), but lower in patients with regular

Table 2. The risk of statin discontinuation according to the subgroup

Variables	No. of patients	No. of event	Odds ratio (95% confidence interval)	
			Unadjusted	Adjusted*
Age (yr)				
20–29	12,073	8,268	1.000 (reference)	1.000 (reference)
30–39	74,287	41,337	0.577 (0.554–0.602)	0.619 (0.593–0.646)
40–49	277,135	128,963	0.401 (0.385–0.417)	0.454 (0.436–0.472)
50–59	468,619	181,916	0.292 (0.281–0.304)	0.345 (0.331–0.359)
60–69	304,251	101,481	0.230 (0.221–0.240)	0.307 (0.295–0.320)
70–79	140,979	43,401	0.205 (0.197–0.213)	0.324 (0.311–0.338)
≥80	31,046	10,621	0.239 (0.229–0.250)	0.415 (0.395–0.435)
Sex				
Male	654,569	262,838	1.000 (reference)	1.000 (reference)
Female	653,821	253,149	0.942 (0.935–0.948)	0.897 (0.887–0.907)
Body mass index (kg/m^2)				
<18.5	18,804	8,487	1.123 (1.090–1.156)	1.078 (1.046–1.112)
18.5–22.9	375,134	158,643	1.000 (reference)	1.000 (reference)
23.0–24.9	338,312	134,619	0.902 (0.893–0.910)	0.975 (0.966–0.985)
25.0–29.9	488,784	183,901	0.823 (0.816–0.830)	0.969 (0.959–0.980)
≥30.0	87,356	30,337	0.726 (0.715–0.737)	0.890 (0.873–0.907)
Abdominal obesity				
No	906,193	374,308	1.000 (reference)	1.000 (reference)
Yes	402,197	141,679	0.773 (0.767–0.779)	0.943 (0.933–0.952)
Smoking status				
Nonsmoker	801,538	311,432	1.000 (reference)	1.000 (reference)
Ex-smoker	239,328	89,325	0.937 (0.928–0.946)	0.915 (0.904–0.927)
Current smoker	267,524	115,230	1.191 (1.180–1.201)	1.010 (0.998–1.022)
Alcohol consumption				
None	757,782	288,608	1.000 (reference)	1.000 (reference)
Mild (<30 g/day)	449,406	184,887	1.136 (1.128–1.145)	1.042 (1.033–1.051)
Heavy (≥30 g/day)	101,202	42,492	1.177 (1.161–1.192)	1.168 (1.150–1.186)
Regular exercise				
No	1,042,019	413,106	1.000 (reference)	1.000 (reference)
Yes	266,371	102,881	0.958 (0.950–0.967)	0.975 (0.966–0.984)
Low income				
No	1,033,484	409,807	1.000 (reference)	1.000 (reference)
Yes	274,906	106,180	0.958 (0.950–0.966)	1.007 (0.998–1.016)
Glycemic status				
Normal	674,450	299,247	1.000 (reference)	1.000 (reference)
Impaired fasting glucose	395,400	161,223	0.863 (0.856–0.870)	0.949 (0.941–0.957)
Diabetes mellitus	238,540	55,517	0.380 (0.376–0.384)	0.416 (0.411–0.421)
Blood pressure status				
Normal	302,061	153,987	1.000 (reference)	1.000 (reference)
Prehypertension	440,087	205,690	0.844 (0.836–0.852)	0.873 (0.865–0.881)
Hypertension	566,242	156,310	0.367 (0.363–0.370)	0.414 (0.410–0.418)
Chronic kidney disease				
No	1,245,335	496,438	1.000 (reference)	1.000 (reference)
Yes	63,055	19,549	0.678 (0.666–0.690)	0.960 (0.943–0.978)

*Adjusted for age, sex, body mass index, abdominal obesity, smoking status, alcohol consumption, low income, regular exercise, diabetes mellitus, hypertension, and chronic kidney disease.

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exercise (OR, 0.975; 95% CI, 0.966–0.984). Patients with impaired fasting glucose and DM were at a lower risk for statin discontinuation compared with those presenting with normal glucose status (impaired fasting glucose: OR 0.949, 95% CI 0.941–0.957; DM: OR 0.416, 95% CI 0.411–0.421). According to blood pressure status, the ORs for statin discontinuation were 0.873 (95% CI, 0.865–0.881) in prehypertension and 0.414 (95% CI, 0.410–0.418) in hypertension. Patients with CKD were at a lower risk for statin discontinuation compared with those presenting without CKD (OR, 0.960; 95% CI, 0.943–0.978).

Especially, 6.58% of study population has MI or ischemic stroke (**Table 1**). The prevalence of statin discontinuation was 40.48% in patients without MI or ischemic stroke, but 24.59% in patients with MI or ischemic stroke (**Supplementary Table 1**). Baseline characteristics of patients without MI or ischemic stroke were similar with those of total study population according to the statin discontinuation. However, patients with statin discontinuation were more likely to be female, less current smoker, more likely to have low income, and had lower total cholesterol and LDL-cholesterol than those with statin continuation in population with previous MI or ischemic stroke. Across all subsets, the prevalence of statin discontinuation tended to be lower in patients with previous MI or ischemic stroke than in those without previous MI or ischemic stroke (**Table 3**). The ORs for statin discontinuation in patients with and without previous MI or ischemic stroke were also similar patterns with those of total study population, except that the OR for statin discontinuation in patients with previous MI or ischemic stroke was higher in women.

DISCUSSION

This study investigated the clinical characteristics of Korean patients with statin discontinuation using information from a national database. The prevalence of patients with statin discontinuation was 39.44% at 1–2 years after initial statin treatment from 2016 to 2017. The prevalence of statin discontinuation decreased with increasing BMI and age except in patients aged above 80 years. In addition, a lower prevalence of statin discontinuation was found in patients with DM or hypertension compared with individuals with normal glucose or blood pressure status. The risk of statin discontinuation was elevated by factors such as young age, male gender, low BMI, heavy drinking, absence of regular exercise, and in patients without DM or hypertension after adjustment for covariates.

Although statin is a very important medication for preventing CVD or death, discontinuation of statin is not rare in the clinical setting. Many studies have investigated the rate of statin discontinuation, which varied from 10% to more than 50%.[30] A meta-analysis of both randomized controlled trials and observational studies showed that adherence to statin treatment at one year reported in randomized controlled trials was on average significantly higher (90.3%) than in those reported in observational studies (49%).[31] The Incremental Decrease in End Points through Aggressive Lipid Lowering study including 8,888 patients with a history of confirmed acute MI reported less than 80% adherence in 11% of patients.[13] A retrospective cohort study of 34,501 patients who were 65 years of age and older, and treated with statins between 1990 and 1998, reported that statin discontinuation rate increased substantially over time and reached 75% after 5 years.[32] Another study including 22,340 Australians aged ≥65 years who underwent statin therapy from 2014 to 2015 reported that the first-year discontinuation rate was 44.7%.[33] In our study, we investigated statin discontinuation rates in more than 1.3 million patients at 1–2 years after initial statin

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Table 3. The risk of statin discontinuation according to the presence of previous myocardial infarction or ischemic stroke

Variables	Previous myocardial infarction or ischemic stroke (–)				Previous myocardial infarction or ischemic stroke (+)			
	No. of patients	No. of event (%)	Odds ratio (95% confidence interval)		No. of patients	No. of event (%)	Odds ratio (95% confidence interval)	
			Unadjusted	Adjusted*			Unadjusted	Adjusted*
Age (yr)								
20–29	11,812	8,137 (68.89)	1.000 (reference)	1.000 (reference)	261	131 (50.19)	1.000 (reference)	1.000 (reference)
30–39	72,495	40,718 (56.17)	0.579 (0.555–0.603)	0.617 (0.591–0.644)	1,792	619 (34.54)	0.524 (0.403–0.680)	0.600 (0.460–0.783)
40–49	268,297	126,521 (47.16)	0.403 (0.387–0.419)	0.460 (0.441–0.479)	8,838	2,442 (27.53)	0.379 (0.296–0.485)	0.422 (0.328–0.542)
50–59	448,019	176,861 (39.48)	0.295 (0.283–0.306)	0.353 (0.339–0.368)	20,600	5,055 (24.54)	0.323 (0.253–0.412)	0.358 (0.279–0.460)
60–69	280,412	96,278 (34.33)	0.236 (0.227–0.246)	0.319 (0.306–0.333)	23,839	5,203 (21.83)	0.277 (0.217–0.354)	0.321 (0.250–0.412)
70–79	118,139	38,016 (32.18)	0.214 (0.206–0.223)	0.347 (0.332–0.362)	22,840	5,385 (23.58)	0.306 (0.240–0.391)	0.359 (0.280–0.462)
≥80	23,066	8,270 (35.85)	0.252 (0.241–0.265)	0.455 (0.433–0.478)	7,980	2,351 (29.46)	0.414 (0.324–0.531)	0.471 (0.365–0.607)
Sex								
Male	602,708	251,336 (41.70)	1.000 (reference)	1.000 (reference)	51,861	11,502 (22.18)	1.000 (reference)	1.000 (reference)
Female	619,532	243,465 (39.30)	0.905 (0.899–0.912)	0.858 (0.848–0.868)	34,289	9,684 (28.24)	1.381 (1.338–1.425)	1.252 (1.198–1.307)
Body mass index (kg/m^2)								
<18.5	16,657	7,775 (46.48)	1.138 (1.103–1.174)	1.078 (1.043–1.113)	2,147	712 (33.16)	1.360 (1.238–1.494)	1.287 (1.170–1.416)
18.5–22.9	348,351	151,482 (43.49)	1.000 (reference)	1.000 (reference)	26,783	7,161 (26.74)	1.000 (reference)	1.000 (reference)
23.0–24.9	315,712	129,228 (40.93)	0.901 (0.892–0.909)	0.974 (0.964–0.984)	22,600	5,391 (23.85)	0.858 (0.824–0.894)	0.910 (0.872–0.949)
25.0–29.9	458,234	176,910 (38.61)	0.817 (0.810–0.825)	0.968 (0.957–0.978)	30,550	6,991 (22.88)	0.813 (0.783–0.845)	0.887 (0.848–0.929)
≥30.0	83,286	29,406 (35.31)	0.709 (0.698–0.721)	0.889 (0.872–0.907)	4,070	931 (22.87)	0.813 (0.752–0.879)	0.854 (0.781–0.935)
Abdominal obesity								
No	847,053	359,265 (42.41)	1.000 (reference)	1.000 (reference)	59,140	15,043 (25.44)	1.000 (reference)	1.000 (reference)
Yes	375,187	135,536 (36.12)	0.768 (0.762–0.774)	0.939 (0.929–0.949)	27,010	6,143 (22.74)	0.863 (0.834–0.893)	0.982 (0.941–1.026)
Smoking status								
Nonsmoker	752,997	298,439 (39.63)	1.000 (reference)	1.000 (reference)	48,541	12,993 (26.77)	1.000 (reference)	1.000 (reference)
Ex-smoker	222,431	85,600 (38.48)	0.953 (0.944–0.962)	0.912 (0.900–0.923)	16,897	3,725 (22.05)	0.774 (0.742–0.807)	0.907 (0.862–0.954)
Current smoker	246,812	110,762 (44.88)	1.240 (1.229–1.251)	1.042 (1.029–1.055)	20,712	4,468 (21.57)	0.753 (0.724–0.782)	0.787 (0.749–0.827)
Alcohol consumption								
None	703,415	274,838 (39.07)	1.000 (reference)	1.000 (reference)	54,367	13,770 (25.33)	1.000 (reference)	1.000 (reference)
Mild (<30 g/day)	423,910	179,027 (42.23)	1.140 (1.131–1.149)	1.039 (1.030–1.049)	25,496	5,860 (22.98)	0.880 (0.850–0.911)	0.996 (0.956–1.036)
Heavy (≥30 g/day)	94,915	40,936 (43.13)	1.183 (1.166–1.199)	1.159 (1.141–1.178)	6,287	1,556 (24.75)	0.970 (0.913–1.030)	1.202 (1.123–1.286)
Regular Exercise								
No	972,412	395,778 (40.70)	1.000 (reference)	1.000 (reference)	69,607	17,328 (24.89)	1.000 (reference)	1.000 (reference)
Yes	249,828	99,023 (36.64)	0.957 (0.948–0.965)	0.974 (0.965–0.983)	16,543	3,858 (23.32)	0.918 (0.882–0.955)	0.964 (0.925–1.004)
Low income								
No	965,631	393,267 (40.73)	1.000 (reference)	1.000 (reference)	67,853	16,540 (24.38)	1.000 (reference)	1.000 (reference)
Yes	256,609	101,534 (39.57)	0.953 (0.945–0.962)	1.007 (0.998–1.017)	18,297	4,646 (25.39)	1.056 (1.017–1.096)	1.080 (1.039–1.122)
Glycemic status								
Normal	631,752	287,816 (45.56)	1.000 (reference)	1.000 (reference)	42,698	11,431 (26.77)	1.000 (reference)	1.000 (reference)
Impaired fasting glucose	369,356	154,764 (41.90)	0.862 (0.855–0.869)	0.946 (0.938–0.954)	26,044	6,459 (24.80)	0.902 (0.871–0.935)	0.970 (0.935–1.006)
Diabetes mellitus	221,132	52,221 (23.62)	0.369 (0.365–0.374)	0.397 (0.392–0.402)	17,408	3,296 (18.93)	0.639 (0.612–0.667)	0.725 (0.693–0.758)
Blood pressure status								
Normal	290,264	150,096 (51.71)	1.000 (reference)	1.000 (reference)	11,797	3,891 (32.98)	1.000 (reference)	1.000 (reference)
Prehypertension	417,352	199,565 (47.82)	0.856 (0.848–0.864)	0.882 (0.873–0.890)	22,735	6,125 (26.94)	0.749 (0.714–0.786)	0.793 (0.755–0.833)
Hypertension	514,624	145,140 (28.20)	0.367 (0.363–0.370)	0.408 (0.404–0.413)	51,618	11,170 (21.64)	0.561 (0.537–0.586)	0.604 (0.576–0.632)
Chronic kidney disease								
No	1,167,576	477,277 (40.88)	1.000 (reference)	1.000 (reference)	77,759	19,161 (24.64)	1.000 (reference)	1.000 (reference)
Yes	54,664	17,524 (32.06)	0.682 (0.670–0.695)	0.951 (0.933–0.970)	8,391	2,025 (24.13)	0.973 (0.923–1.025)	1.034 (0.979–1.093)

Number of event was expressed as number (%).

*Adjusted for age, sex, body mass index, abdominal obesity, smoking status, alcohol consumption, low income, regular exercise, diabetes mellitus, hypertension, and chronic kidney disease.

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treatment using the Korean nationwide database. Although we included all age groups and evaluated at 1 to 2 years after statin treatment, the statin discontinuation rate of 39.44% was similar to other real-world data.

Several studies found that younger and older patients, women, ethnic minorities, smokers, patients with lower BMI, and patients without hypertension or DM have lower levels of adherence to statin treatment, but most studies were not representative of the general population and were inconsistent overall in terms of study design, definitions of exposure, and outcome.[34] Age tended to show a U-shaped relationship with the risk of statin nonadherence.[20] A population-based study conducted in Northern Denmark reported that nonpersistent patients were more likely to be very young (aged <45 years) or very old (aged >75 years).[15] Another study of adults aged 18–34 years as the reference reported that the odds for statin nonadherence were 0.68 (95% CI, 0.56–0.85) among 35–44-year olds, 0.41 (95% CI, 0.34–0.50) among 45–54-year olds, 0.34 (95% CI, 0.28–0.41) among 55–64-year olds, 0.44 (95% CI, 0.36–0.53) among 65–74-year olds and 0.46 (95% CI, 0.38–0.57) among those ≥75 years old.[35] Some studies that did not include younger populations have reported a more steady improvement in adherence with older age.[36] In our study, compared with those aged 20–29 years, the ORs for patients with statin discontinuation also showed a U-shaped relationship that decreased with increasing age and increased after more than 70 years of age. Obesity (adjusted OR, 0.86; 95% CI, 0.74–0.99) and overweight (adjusted OR, 0.88; 95% CI, 0.79–0.98) predicted a reduced risk of nonadherence in a study of 9,285 participants in the Finnish Public Sector Study.[37] In addition, obesity in male population has been shown to decrease the odds of nonadherence (OR, 0.87; 95% CI, 0.81–0.94).[38] Our study also showed that the risk of patients with statin discontinuation decreased with increasing BMI. We could not investigate the underlying factors, but we assumed that relatively healthier patients (younger or with lower BMI) might prefer to use other methods of lowering cardiovascular risk, such as lifestyle modification including diet or exercise. Furthermore, in this study, the risks for statin discontinuation were lower in ex-smokers than nonsmoker. We think that ex-smokers may be paying more attention to their health, so they are more likely to take their medication well. Because patients with hypertension or DM have a high risk for CVD, statins are indicated for prevention of CVD in many cases. Mixed results suggested the association between statin discontinuation and diabetes or hypertension.[28,39] However, a prospective open cohort study including 570,337 patients reported that patients with hypertension and type 2 DM were less likely to discontinue treatment and more likely to restart if they did discontinue.[34] Our study results were consistent with the aforementioned study of patients with hypertension or DM, who were at a lower risk of statin discontinuation. In the study using data from New Zealand community pharmacies, the secondary prevention group was 0.67 (95% CI, 0.65–0.69) times as likely to discontinue statin treatment than the primary prevention group between 2006 and 2011 involving 289,666 new statin users.[40] In our study, the prevalence of statin discontinuation was also lower in patients with MI or ischemic stroke than those without MI or ischemic stroke.

There are several limitations to consider when interpreting the results of this study. First, the factors contributing to discontinuation of statin therapy or drug-related adverse effects in the patient database were unknown. Second, we used the prescription database to estimate actual pill intake, without confirming that a patient actually took the medicine. Finally, the statin treatment intensity or individual statin treatments were not investigated. This study, however, was valuable because it assessed members of the general population and included more than 1.3 million people, using Korean national-level data.

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In conclusion, the prevalence of patients with statin discontinuation in Korea was 39.44% at 1 to 2 years after initial statin treatment. The risk for statin discontinuation was high in patients at young age, especially among males, those with low BMI, who were heavy drinkers, those who did not exercise regularly, and those without DM or hypertension. These data suggest that patients discontinuing statin therapy can be identified and monitored carefully.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Baseline characteristics of study population according to the presence of previous myocardial infarction or ischemic stroke

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