EPIDEMIOLOGY

Possible link between statin and iron deficiency anemia: A South Korean nationwide population-based cohort study

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An extensive evaluation of disease occurrence after statin use based on a "hypothesis-free" approach remains scarce. To examine the effect of statin use on the potential risk of developing diseases, a propensity score–matched cohort study was executed using data from the National Sample Cohort in South Korea. A total of 7847 statin users and 39,235 nonstatin users were included in the final analysis. The period of statin use was defined as our main time-dependent exposure and was divided into three periods: current, recent, and past. The main outcomes were defined as new-onset diseases with ≥100 events based on the International Statistical Classification of Diseases, 10th Revision. We calculated the adjusted hazard ratios and 95% confidence intervals (CIs) using Cox regression. We found that statin use significantly increased the risk of developing iron deficiency anemia up to 5.04 times (95% CI, 2.11 to 12.03). Therefore, the iron levels of patients using statins should be monitored carefully.

INTRODUCTION

The number of adults diagnosed with dyslipidemia is on the rise in the Republic of Korea (hereafter, Korea). The age-standardized prevalence of hypercholesterolemia in individuals aged 20 years and above increased from 9.2% in 2008 to 18.0% in 2018 (*1*). Dyslipidemia contributes to the global burden of diseases, including ischemic heart disease and ischemic stroke, which are the leading causes of death (*2*). Statins—3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) inhibitors—have been popularly prescribed according to experts' guidelines to manage dyslipidemia (*3*–*5*), accounting for approximately 90% of dyslipidemia treatment in Korea since 2006 (*1*). As a result of the trend toward earlier initiation of statin therapy, more adults are being exposed to it, which could inevitably lead to increased risks of adverse effects (AEs).

Several unintended positive effects of statins have been identified, including anti-inflammation, anti-oxidative activity, anti-atherogenic activity, and improvement of endothelial function (*6*). However, in randomized controlled trials (RCTs) or meta-analyses (*4*, *5*, *7*, *8*), statin-associated AEs including muscle symptoms and liver toxicity are frequently reported. Moreover, numerous observational studies have associated statin use with an increase in the incidence of type 2 diabetes mellitus (T2DM) in many populations (*9*–*14*). Similarly, epidemiological studies (*15*–*18*) have also linked statin use with Parkinson's disease (PD).

Furthermore, patients' medication adherence is known to be influenced by potential AEs (*7*, *19*). However, comprehensive evaluation of the potential AEs that require long-term follow-up or those that are uncommon is challenging within the RCT framework. Various observational studies have suggested navigating these limitations and investigating real-world risks (*20*). A previous study (*21*) attempted to evaluate the broad-spectrum effects of statins by focusing on diseases likely associated with them as other studies (*9*, *15*, *22*) have done. This hypothesis-based study design could potentially overlook underlying AEs. A hypothesis-free data-mining approach (*23*) detected rosuvastatin-specific AEs including iron deficiency anemia (IDA) without considering causation and confounders. However, these studies are vulnerable to biases such as measured or unmeasured confounders (*24*), necessitating careful design. Hence, it is crucial to conduct real-world pharmacovigilance studies based on a hypothesis-free design using various methods to navigate each study's limitations.

Our study used a large-scale cohort database provided by the National Health Insurance Service (NHIS) in Korea, offering at least 10 years of follow-up data. The completeness of this database, collected independently of our study, ensured the representativeness of the real-world setting, minimized biases (*24*, *25*), and facilitated the evaluation and comparison of the disease-wise time-dependent effect of statin use in Korea. Therefore, we investigated statin-related AEs within a "hypothesis-free" or "agnostic" framework.

RESULTS

After applying the inclusion and exclusion criteria, 14,332 statin users with hyperlipidemia and 128,502 nonstatin users were eligible for the study (Fig. 1). We identified that the propensity score-based matched dataset consisted of 7847 statin users and 39,235 nonstatin users.

A total of 14 diagnoses with the International Statistical Classification of Diseases, 10th Revision (ICD-10) were identified from the cohort study (Fig. 2A): T2DM (ICD-10 code, E11), IDA (D50), gastric ulcer (GU; K25), migraine (G43), sleep disorder (G47), senile cataract (H25), disorders of vestibular function (H81), gastroesophageal reflux disease (GERD; K21) gout (M10), gonarthrosis (M17), spondylosis (M47), osteoporosis (M81),

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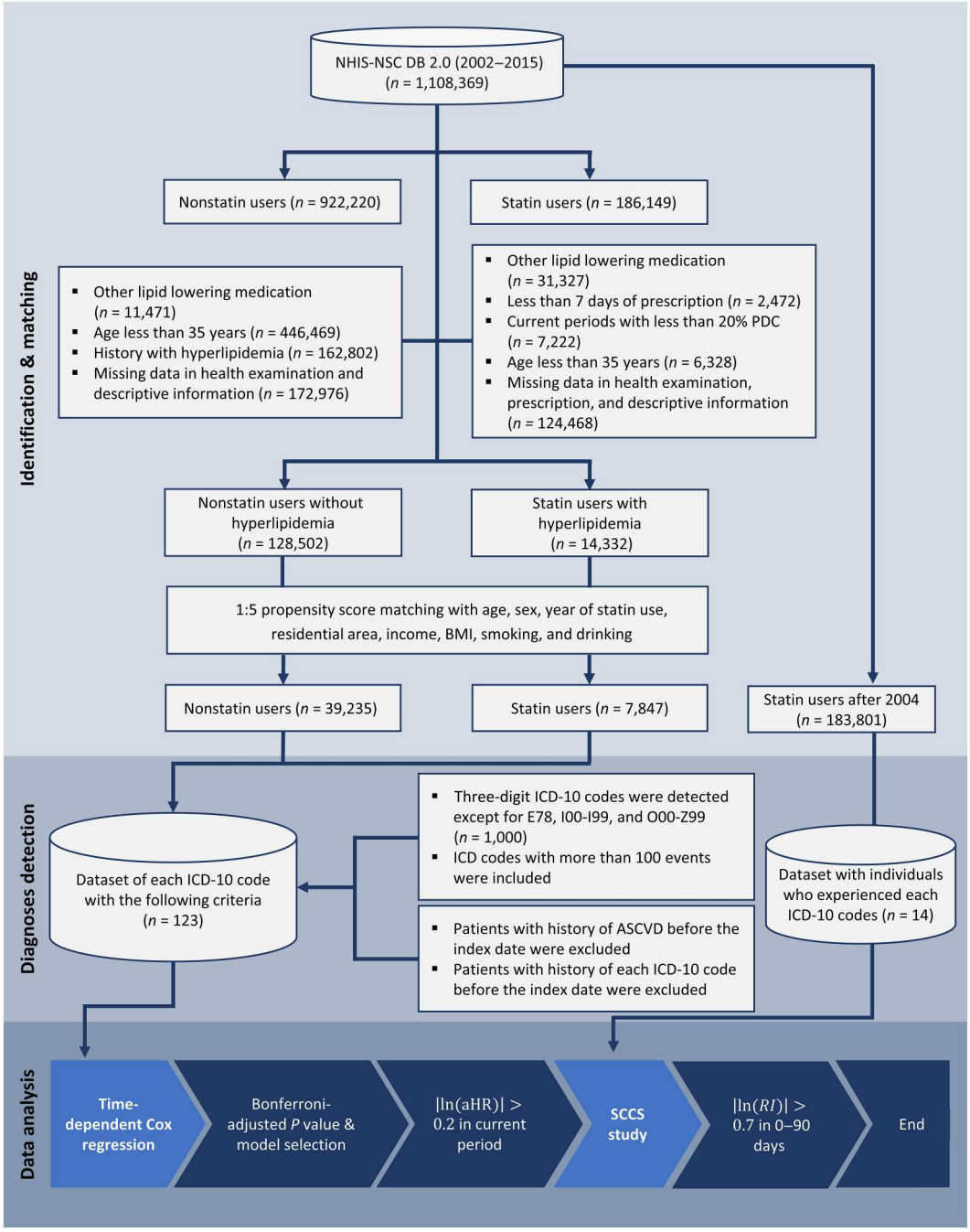

Fig. 1. Flowchart of the study process. aHR, adjusted hazard ratio; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; ICD-10, International Statistical Classification of Diseases, 10th Revision; NHIS-NSC, National Health Insurance Service–National Sample Cohort; PDC, possession days covered; RI, relative incidence; SCCS, self-controlled case series.

cystitis (N30), and hyperplasia of prostate (N40). Of these, only three, i.e., T2DM, IDA, and GU, satisfied the criteria for our self-controlled case series (SCCS) design (Fig. 2B).

In the retrospective cohort analysis, the exposure level to each statin prescription was categorized into three periods: current (up to 3 months from the prescription end date), recent (up to 12 months from the prescription end date), and past (more than 12 months after the prescription end date). In the case-only design, each observation period was divided similarly to the cohort study, with the past period as a baseline.

In the cohort analysis, we confirmed the strongly time-dependent relationship of T2DM risks in each period [adjusted hazard ratio (aHR) 7.30, 95% confidence interval (CI) 5.36 to 9.95 (for the "current period"); aHR 6.08, 95% CI 3.98 to 9.30 (for the "recent period"); and aHR 5.09, 95% CI 2.28 to 11.34 (for the "past period")]. The effect of statin use on IDA was also significant

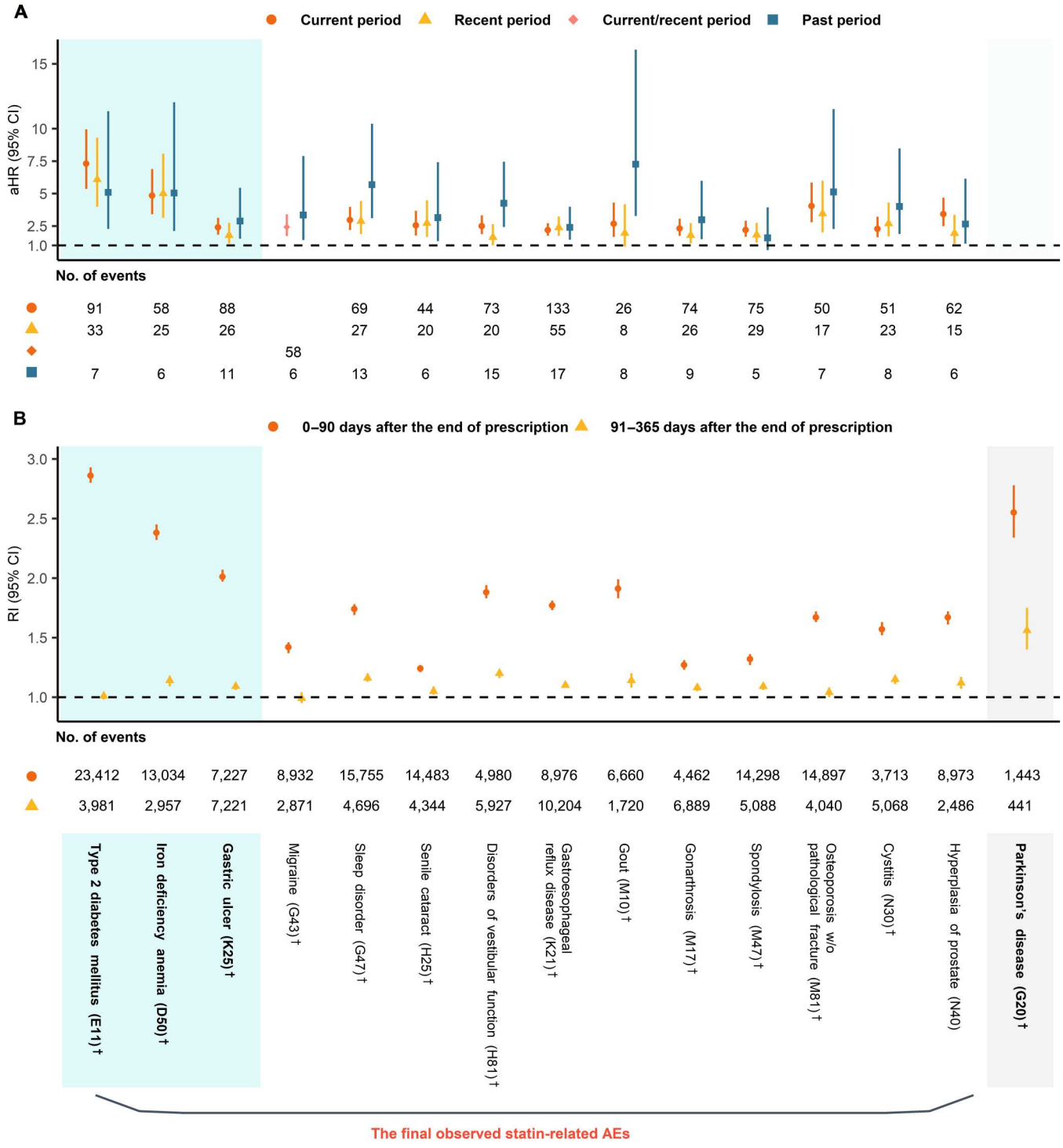

Fig. 2. Adjusted hazard ratios and relative incidences of candidate statin-related adverse effects. All aHRs were adjusted for total cholesterol and residential area as a random effect. PD was excluded in (A) because of the insufficient sample size. (**A**) Results of time-dependent Cox regression for candidate statin-related AEs with aHRs and 95% CIs for each period. (**B**) Results of SCCS design for candidate statin-related AEs, and PD with RIs and 95% CIs for each period. We detected 14 statin-related AEs using (A) and (B). †Diagnoses matched on the previously known AE. AE, adverse effect; aHR, adjusted hazard ratio; CI, confidence interval; PD, Parkinson's disease; RI, relative incidence; SCCS, self-controlled case series; w/o, without.

across the periods [aHR 4.84, 95% CI 3.40 to 6.89 (for the "current period"); aHR 5.01, 95% CI 3.12 to 8.06 (for the "recent period"); and aHR 5.04, 95% CI 2.11 to 12.03 (for the "past period")]. A slight increase in the trend of IDA risk was observed between the recent and past periods, with overlapping 95% CIs. The observed trend in GU risk fluctuated regardless of the exposure level to statins [aHR 2.39, 95% CI 1.83 to 3.13 (for the "current period"); aHR 1.78, 95% CI 1.16 to 2.73 (for the "recent period"); and aHR 2.88, 95% CI 1.52 to 5.44 (for the "past period")].

We found that the risk of T2DM was the highest in both designs [relative incidence (RI) 2.86, 95% CI 2.80 to 2.93 (for "0 to 90 days"); RI 1.01, 95% CI 0.98 to 1.04 (for "91 to 365 days")] followed by IDA [RI 2.38, 95% CI 2.32 to 2.45 (for "0 to 90 days"); RI 1.14, 95% CI 1.09 to 1.18 (for "91 to 365 days")] and GU [RI 2.01, 95% CI 1.97 to 2.07 (for "0 to 90 days"); RI 1.09, 95% CI 1.06 to 1.12 (for "91 to 365 days")], for current statin users versus no statin users in this cohort study. Their matched RIs in the SCCS design were similarly high, while the RI of GU in 0 to 90 days was high in the SCCS design compared to the result of Cox regression (Fig. 2).

In addition, the RI of PD in 0 to 90 days after the end of statin prescription was 2.55 (95% CI 2.34 to 2.78) and that of the next interval was 1.56 (95% CI 1.40 to 1.75) even though PD was excluded in the Cox regression owing to insufficient sample size (Fig. 2B).

Pearson's correlation coefficients between IDA and each ICD-10 code of diseases of the digestive system are shown in table S1. The absolute values of them were ranged from <0.01 to 0.19 and their mean (SD) was 0.04 (0.04). In particular, the magnitude of the correlation between IDA and GU was not strong (correlation coefficient = 0.12; table S1). After adjusting the history of GU in the analysis, a similar effect regarding IDA was observed (table S2). This confirms that statin use increased the risk of IDA regardless of GU.

In our sensitivity analyses, 9 of 14 ICD-10 codes, including T2DM and IDA, were detected when we accounted for total cholesterol, comorbidity, and comedications. Furthermore, when we limited our analysis to patients with a history of dyslipidemia, we found consistent results for T2DM, IDA, and GU (tables S3 and S4). For individuals of European ancestry, we also observed a considerable relationship between proxies of HMGCR inhibition and IDA or T2DM, respectively (see Supplementary Text, figs. S1 and S2, and tables S5 to S7).

DISCUSSION

We designed a hypothesis-free approach for identifying statin-related AEs by disease type based on time-dependent usage of statins by applying statistically appropriate methods on large-scale populations. It was successful in two aspects; most of the estimated risks were replicated on the basis of previously published literature and a prominent statin-related risk was found.

Validation with previous studies

To mitigate false-positive results, we concurrently adopted the retrospective cohort study and case-only design (SCCS). Findings of the former were in accordance with those of the previously published studies in 12 of the 14 statin-related AEs (*9*, *26*–*29*). Evaluation of the overall results of the two designs, including the case-only design, identified T2DM and GU as AEs.

Several previous studies (*9*, *26*, *30*) have repeatedly confirmed the increased risk of new-onset T2DM with statin use, and recent meta-analyses (*27*, *28*) have supported these results. We found that the risk of T2DM was higher than that of other observed AEs, and the extent of risk was reflected in the active status of therapy with statin use. This replicated result strengthens the validity of our study design.

An increased risk of GU was also observed in both designs. Previous observational and meta-analysis studies have not been in agreement (*31*–*33*) with some studies suggesting no effect (*34*–*36*); however, a nested case-control study (*29*) reported that statin use could increase the odds of peptic ulcer by 45% in Korea. We also identified 10 other known statin-related AEs in our study: migraine (*37*–*39*), sleep disorder (*40*–*42*), senile cataract (*21*, *22*), disorders of vestibular function (*43*), GERD (*44*), gouts (*45*), gonarthrosis (*46*, *47*), spondylosis (*48*), osteoporosis (*49*, *50*), and cystitis (*51*). However, all their associations with statin use were weak in both designs, and the biological shreds of evidence for these findings are unidentified.

In addition, the validity of our case-only design was confirmed in that given only statin-prescribed patients diagnosed with PD, it was likely to increase the risk of this diagnosis in both durations since exposure. Unfortunately, the risk for PD could not be evaluated in this cohort study owing to events being less than 100. Although the relationship between statin use and PD was unclear, the results obtained in this study were similar to those of previous studies with statin use (*15*, *16*) or low-density lipoprotein cholesterol (LDL-C) (*52*).

Potential association between statin use and IDA

A large population-based cohort study (*21*) in the United Kingdom reported no risk of anemia with statin use. Since our results indicated that the risks related to statin use increased consistently over time, the findings from the U.K. population may be partially attributed to the use of a time-independent risk model. The outcomes of our study were comparable to that of a data-mining approach study (*23*) on the signals of rosuvastatin for IDA compared to other statins in Korea. Meanwhile, our study had more achievements in connoting the causally related effects through our elaborate study designs. This was supported by our sensitivity analyses and two-sample Mendelian randomization (MR) results.

To the best of our knowledge, this is the first study that observed the risk of IDA as a possible AE related to statin use in real-world data. Our study suggested that statin could affect iron metabolism besides controlling LDL-C levels. In general, the effect of statins on atherosclerotic cardiovascular disease (ASCVD) is explained by lowering serum LDL-C levels. However, it has been proposed that statins have so-called pleiotropic effects, such as potential anti-inflammatory effects on the development of atherosclerotic plaque by reducing C-reactive protein concentrations (*53*, *54*). Iron was suggested as another mediator for the effect of anti-inflammation (*55*). An excess of non–transferrin-bound iron was reported to accelerate redox cycling mainly causing the inflammatory process (*56*, *57*). Therefore, iron deficiency leads to ameliorating oxidative stress (*58*). Statins have already been reported to inhibit hepcidin expression, the key hormonal regulator of iron distribution (*59*). Consequently, their use may have contributed to improved cardiovascular disease (CVD) risk through a reduction in iron levels. These

inferences are in line with the finding that ferritin levels could result in better CVD outcomes without interacting with LDL-C levels (*58*).

There was a supportive result that there could be another pathway causing statin-related IDA. The most common class of anemia is IDA, in which iron is deficient, making hemoglobin carry oxygen in serum (*60*). Since iron is mainly absorbed in the duodenum, gastrointestinal diseases are one of the causes of iron deficiency (*61*). We also found a negligible correlation between IDA and any diseases of the digestive system, and IDA risk due to statin use is similar even after adjusting the history of GU (table S1 and S2). Therefore, statins could affect iron homeostasis leading to IDA regardless of the risk of GU.

Our study had some limitations. First, we focused on relatively common diseases with more than 100 events in the population that occurred during the observation period, and rare statin-related AEs, such as rhabdomyolysis (*38*), were not evaluated in our study. Second, we adopted the SCCS design to increase the statistical validity; nonetheless, our estimates may be biased because of potential confounders that were not considered. Third, we sought to compare the results of cohort and case-only studies with the recommendation of Farrington *et al.* (*62*) However, a dose-response relationship could not be detected. Fourth, our result should be carefully interpreted since we evaluated three-letter ICD-10 codes, not meaningful categories. Last, we considered only the Korean population, which limits the generalization of our results for pharmacokinetic and pharmacogenetic properties to other populations (*63*).

Our modeling strategy in pharmacovigilance with a population-based cohort was validated using the increased, time-dependent risk of T2DM with statin use. Here, we found an association between statin use and the risk of developing IDA in real-world data that indicated that iron levels in patients receiving statin therapy need to be monitored regularly. Further preclinical and clinical studies are necessary to validate our findings.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board (no. E1910/001-001) of the Seoul National University, Korea. The need for informed consent was waived owing to the anonymized nature of the collected data.

Data collection

The National Sample Cohort (NSC) 2.0 from 1 January 2002 to 31 December 2015 was provided by NHIS in Korea and used in this study. NHIS, a single insurance institution, provides a universal healthcare coverage system to almost the entire population in Korea (*64*). This database randomly included approximately 2% of all citizens who qualified for this program for 1 year in 2006 or received medical aid (*64*). It contained electronic information regarding demographics, details of drug prescriptions, and medical records including diagnoses. Diagnoses were coded on the basis of the ICD-10.

Study population

Individuals aged over 36 years were selected for this study. Lipoprotein metabolism disorders and lipidemias were coded as E78, per the ICD-10.

We defined the respective study population and applied two methodologies:

Retrospective cohort study

E78 patients who used at least one type of statins were considered statin users, and individuals without dyslipidemia who had never been prescribed statins were considered nonstatin users (Fig. 1). The index date of each statin user was assigned as the first observed date of statin prescription, and the same was used as the index date for their matched nonstatin user. Each statin user was matched with five nonstatin users. Patients with ASCVD were excluded because ASCVD can confound the effect of statins.

Case-only design

Follow-ups began after the index date that was set as 1 January 2004. Since this study design could cancel out time-invariant confounding variables, we included all patients with an E78 diagnosis and at least one exposure to any of the statins.

Main exposure

The main exposure in our analysis was statin use. Statins included simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin. To isolate the effect of statins, other lipid-lowering medications and combinations, including fibrates, bile acid sequestrants, nicotinic acid and derivatives, other lipid-modifying agents, and statins in combinations with other agents, were excluded.

We separately specified the exposures (Fig. 3):

Retrospective cohort study

We excluded statin users with prescriptions <7 days and nonadherent statin users who used statins for <20% of the days required for adherence (*65*). To differentiate between statin-related AEs based on the follow-up period of statin use in the cohort study, the exposure level was divided into three periods: current, recent, and past (*66*). The period with successive prescriptions of ≤3 months from the end date of the prescription was considered "current." The period of up to 12 months from the end date of the current period was considered "recent," and the period from the end date of the recent period to the next current period was defined as "past."

Case-only design

Each period was split into two risk periods: a current risk period of 0 to 90 days after the end date of prescription, followed by a recent risk period of 91 to 365 days after the end date of prescription.

Outcome

ICD-10 codes have been developed since 1900 and are continuously updated to allow us to systematically record morbidity and mortality (*67*). For our clinical outcomes, different three-letter ICD-10 codes were considered separately. To achieve sufficiently large statistical power, codes with <100 events were excluded. E78 and diseases of the circulatory system, coded between I00 and I99, were excluded because of reverse causation. Codes O00 to Z99 were excluded because they were consequences of external causes (pregnancy and perinatal conditions, congenital anomalies, injuries, and poisoning). Consequently, a total of incident 123 diagnoses out of the 1000 ICD-10 codes were considered eligible. Death or when no outcome occurred was considered censored.

Statistical analyses

A multiple logistic regression model was used to calculate propensity scores, which considered confounding factors such as age, sex,

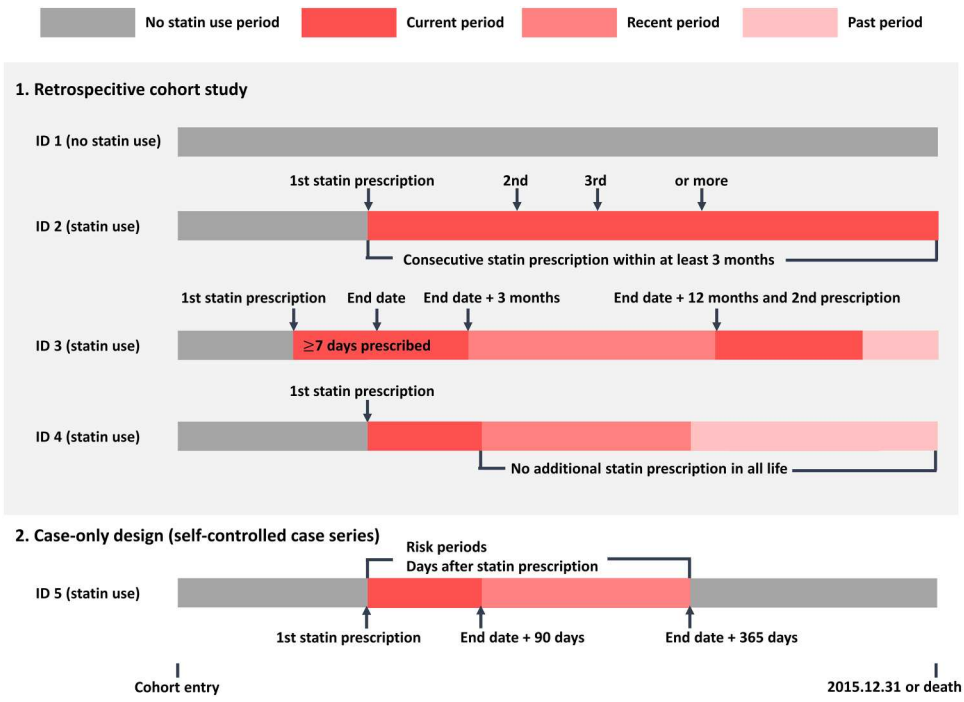

Fig. 3. Diagram for the definition of exposure. For the retrospective cohort study, exposure level to statin was divided into three periods: current, recent, and past. For the case-only design, each observation period was split into two risk periods: a current risk period of 0 to 90 days after the end date of prescription followed by a recent risk period of 91 to 365 days after the end date of prescription.

year of statin use, income, residential area, body mass index, history of tobacco smoking, and alcohol consumption. We set a caliper at 0.15 and examined the absolute standardized mean differences according to statin use in table S8. We estimated the aHRs with their 95% CIs using the Cox proportional hazard model for time-dependent exposures after adjusting for total cholesterol and residential area. Residential area was considered as a random variable, with a gamma distribution to account for heterogeneity in dwelling locations. We assumed that there were five different scenarios of statin exposure under other fixed conditions: (i) current, recent, and past period; (ii) current/recent and past period; (iii) current and recent/past period; (iv) current, recent, and past as linear; and (v) statin use and no use. Model selection for each selected diagnosis was performed using the Bayesian information criterion. Scaled Schoenfeld residual plots with the frailties as an offset and cumulative raw Schoenfeld residuals by Brownian motion (*68*) were examined for proportional hazard assumption.

We prepared an SCCS as a case-only design for each diagnosis with $|\ln(\text{aHR})| > 0.2$ in the current period in the cohort study. Because of a violation of the SCCS assumption, as evidenced by event-dependent exposure shown in the centered event plot, we used the standard SCCS, incorporating a pre-exposure period of 20 days and checked the crude incidences of main outcomes because of rarity (*62*, *69*). Last, statin-related AE was defined when $|\ln(\text{RI})| > 0.7$ for 0 to 90 days after the cessation of the prescribed use of statins.

Pearson's correlation coefficients were calculated to evaluate the relationship between IDA and diseases of the digestive system ("K" based on ICD-10), using NHIS-NSC data, where the results were summarized. Furthermore, we performed two sensitivity analyses: (i) considering total cholesterol, comorbidities, anticoagulants, and antiplatelet in 1:1 propensity score matching (PSM) and (ii) selecting only patients with dyslipidemia using the previous 1:1 PSM. In these cases, we adjusted only the residential area as a random effect in the Cox model. Last, a two-sample MR was conducted to investigate the causal association using an independent dataset. Details are provided in the Supplementary Materials.

The significance level was set at 0.05, and the problem of multiple testing was adjusted with Bonferroni correction. Statistical analyses were performed using the SAS enterprise guide (version 7.13; SAS Institute, Cary, NC, USA), R (version 3.3.3; The R Development Core Team, Vienna, Austria), and Rex (*70*) (version 3.5.3; Rexsoft, Seoul, Korea).

Supplementary Materials

This PDF file includes:

Supplementary Text
Figs. S1 and S2
Tables S1 to S8
Legend for data file S1
Legend for code file S1
References

Other Supplementary Material for this manuscript includes the following:

Data file S1
Code file S1

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