Effects of Statin Treatment on the Development of Tendinopathy

A Nationwide Population-Based Cohort Study

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Background: Previous longitudinal cohort studies have reported the conflicting results of the relationship between statin use and the development of tendinopathy disorder. It is unclear if there is a relationship between statin use, particularly the type or cumulative doses, and the development of tendinopathy disorder.

Purpose: To investigate an association between statin treatment and the development of tendinopathy.

Study Design: Cohort study; Level of evidence, 3.

Methods: A total of 594,130 participants were enrolled in this study in 2002 and evaluated until 2015. There were 84,102 statin users and 168,204 nonusers (controls) selected at a ratio of 1:2 using propensity score matching analysis. The types of included tendinopathy were as follows: (1) trigger finger, (2) radial styloid tenosynovitis, (3) elbow epicondylitis, (4) rotator cuff tendinopathy, and (5) Achilles tendinitis. Cox proportional hazards models with time-varying covariates were constructed to identify the association between statin use and tendinopathy development.

Results: Statin treatments regardless of statin types were associated with a significantly greater risk of all types of tendinopathy development (hazard ratio, 1.435; 95% CI, 1.411-1.460) compared with no statin treatment. A trend toward risk reduction was observed according to cumulative statin doses, which was indicated by hazard ratios of 2.337 (95% CI, 2.269-2.406), 2.210 (95% CI, 2.132-2.290), and 1.1 (95% CI, 1.098-1.146) in patients with cumulative defined daily doses of 90, 91-180, and >180, respectively.

Conclusion: This nationwide population-based cohort study suggests that statin use regardless of the statin type was associated with a greater risk of tendinopathy compared with that of nonusers. The risk of tendinopathy development was diluted with the increasing cumulative defined daily dose.

Keywords: statin; dyslipidemia; tendon; tendinopathy; tendinitis; cohort study

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are commonly used to reduce serum cholesterol levels, preventing cardiovascular events and decreasing their related mortality rate. Although they have been widely accepted as safe medications, pre- and postmarketing studies alike have reported musculoskeletal side effects, such as statin-associated muscle symptoms (SAMSs) and tendon impairments.[17,26,29] Serious adverse effects of statins on muscles have consistently been shown, but there are inconsistencies among previous studies about statin-associated tendon impairments.

Several previous studies have found that statins increase the risk of development of tendon impairment, including tendinopathy and tendon rupture.[4,5,9,10,11,18,21] However, other studies failed to demonstrate an increased risk of tendon impairment in statin users.[1,2,7,14,24,28,32] Furthermore, some studies showed that statins reduce the risk of the development of tendon complications.[7,14] Contractor et al[7] determined that simvastatin use was associated with a lower risk of tendon rupture, and Lin et al[14] reported that statin use was associated with a lower risk of developing rotator cuff disease in patients with hyperlipidemia compared with no statin use.

Accordingly, in the present nationwide population cohort study, we evaluated a potential association between statin use and the risk of tendinopathy development. In particular, we investigated the following for each tendinopathy: (1) the risk of tendinopathy development according to the type of statin and (2) the risk of tendinopathy development according to the cumulative dose of statins. We hypothesized that statin use would be associated with an increased risk of tendinopathy development.

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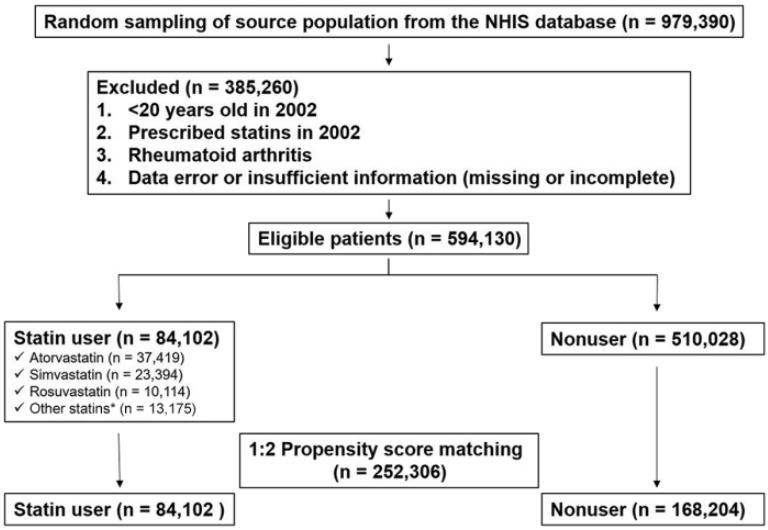

Figure 1. Flow diagram of the patient selection process. [a]Other statins included pitavastatin, pravastatin, lovastatin, and fluvastatin. NHIS, National Health Insurance Service.

METHODS

Data Sources

We obtained a 2002-2015 data set from the National Health Insurance Service–National Sample Cohort (NHIS-NSC) database in the Republic of Korea. The Republic of Korea has a single-payer universal health care system, and the NHIS provides health insurance to >99% of the Korean population.[13] The cohort is a representative random sample of approximately 2.2% of the total Korean population in 2002, followed for 13 years (until 2015) unless participants were disqualified because of death or immigration. Detailed information on and the quality of this cohort have been reported previously.[6,13,27] The information in the data set included sociodemographic variables; diagnosis statements defined by the International Classification of Diseases, 10th Revision (ICD-10); prescriptions; and hospital visit dates. Researchers can analyze NHIS-NSC data if their study is approved by the review committee. The protocol of this study was approved by our institutional review board. Written informed consent was not required because we only accessed the database for analysis purposes, and personal information was not used.

Study Population and Design

The NHIS-NSC data set comprises approximately 1 million participants, and those who met the following criteria were excluded from this study (n = 405,870): (1) <20 years of age in 2002, (2) prescribed statins in 2002, (3) diagnosed with rheumatoid arthritis during all follow-up periods, and (4) had missing or incomplete information or data errors. A total of 594,130 participants were included in the present study (Figure 1).

The study population was divided into 2 groups: (1) statin users and (2) statin nonusers. We selected atorvastatin, simvastatin, rosuvastatin, pitavastatin, pravastatin, lovastatin, and fluvastatin as the drugs of interest. The defined daily dose (DDD) recommended by the World Health Organization (WHO) is the assumed average maintenance dose per day of a drug. The cumulative DDD (cDDD) was calculated for each of the prescribed days according to the WHO definition according to the following formula: $cDDD = (Issued\ statin \times Dose\ of\ statin\ per\ issuance)/DDD$. Statin user was defined as a patient who used statins for ≥28 cDDD during admission and outpatient visits during the study period. To ensure that all study participants had ≥1 statin-free year, those who were prescribed statins in 2002 were excluded.

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Ethical approval for this study was obtained from Korea University Guro Hospital (reference No. 2021GR0262).

TABLE 1
Baseline Characteristics of the Nationwide Cohort of Patients Before and After 1:2 Propensity Score Matching, Stratified by Statin Use[a]

	Entire Cohort (N = 594,130)			Matched Cohort (N = 252,306)		
Characteristic	Statin Users (n = 84,102)	Nonusers (n = 510,028)	SMD	Statin Users (n = 84,102)	Nonusers (n = 168,204)	SMD
Age, y	49.78 ± 12.89	38.90 ± 13.84	0.815	49.78 ± 12.89	50.14 ± 14.11	–0.0519
Age group, y						
<30	4740 (5.64)	148,579 (29.13)		4740 (5.64)	9512 (5.66)	
30-39	13,862 (16.48)	149,040 (29.22)		13,862 (16.48)	27,771 (16.51)	
40-49	24,738 (29.41)	109,857 (21.54)		24,738 (29.41)	49,055 (29.16)	
50-59	19,763 (23.50)	50,170 (9.84)		19,763 (23.50)	35,150 (20.90)	
60-69	15,011 (17.85)	33,974 (6.66)		15,011 (17.85)	28,308 (16.83)	
≥70	5988 (7.12)	18,408 (3.61)		5988 (7.12)	18,408 (10.94)	
Female sex	38,358 (45.61)	242,835 (47.61)	–0.0402	38,358 (45.61)	73,612 (43.76)	0.0371
Comorbidities						
Diabetes mellitus	7939 (9.44)	12,576 (2.47)	0.2385	7939 (9.44)	11,884 (7.07)	0.0812
Dyslipidemia	4793 (5.70)	8644 (1.69)	0.1727	4793 (5.70)	6879 (4.09)	0.0694
CKD	257 (0.31)	429 (0.08)	0.0401	257 (0.31)	363 (0.22)	0.0163
Comedications						
Corticosteroids	27,560 (32.77)	109,532 (21.48)	0.2406	27,560 (32.77)	49,944 (29.69)	0.0656
Quinolone antibiotics	16,631 (19.77)	54,619 (10.71)	0.2276	16,631 (19.77)	**28,585 (16.99)**	**0.0698**

[a]Data are presented as mean ± SD or n (%). CKD, chronic kidney disease; SMD, standardized mean difference.

Outcomes and Follow-up Evaluation

The primary outcome of interest for this study was the development of tendinopathy. The ICD-10 system was used to identify patients with tendinopathy: trigger finger and radial styloid tenosynovitis (ICD-10 codes M65.3 and M65.4); tendinopathies of the shoulder, including rotator cuff tear, calcific tendinitis, bicipital tendinitis, impingement syndrome, and bursitis (ICD-10 codes M75.1-M75.5); medial or lateral elbow epicondylitis (ICD-10 codes M77.0 and M77.1); and Achilles tendinitis (ICD-10 code M76.6). Patients were included in the tendinopathy group if they had ≥1 outpatient visit or ≥1 inpatient stay. Further analysis was performed to identify the relationship between the development of tendinopathy and the type and cumulative dose of statins. The index date was the date a patient first received a prescription for statins. Baseline characteristics were gathered at the time of cohort entry date in 2002 or the closest date available. The follow-up period for each patient was calculated from the index date to the time of tendinopathy diagnosis or the last follow-up (December 31, 2015).

Covariates

Covariates that could affect the main outcomes during statin treatment were also abstracted from the NHIS-NCS database (Appendix Table A1). Patient covariates included age and sex. Underlying comorbidities, including diabetes mellitus, dyslipidemia, and chronic kidney disease (CKD), were selected as covariates. Among drugs, corticosteroids and quinolone antibiotics were chosen as covariates.[31]

Statistical Analysis

All patients who met the study eligibility criteria at baseline were included in the analyses, and their data were analyzed based on intention to treat. Continuous variables were compared using an unpaired 2-tailed *t* test, and categorical variables were compared using a chi-square test. Cox proportional hazards models with time-varying covariates were constructed to identify the relationship between statin use and tendinopathy development.

Propensity score matching (PSM) analysis was used to reduce the effect of selection bias and potential confounding between both groups. Propensity scores were computed using the following variables: age, sex, diabetes mellitus, dyslipidemia, CKD, use of steroids, and use of quinolone antibiotics. For PSM, a nearest-neighbor 1:2 matching scheme with a caliper size of 0.1 was used. In all subgroup analysis, the variables used in the PSM analysis were adjusted.

All statistical analyses were performed using the SAS software (Version 9.4; SAS Institute Inc) and R statistical software (Version 3.3.3; R Foundation for Statistical Computing; http://cran.r-project.org/). All reported *P* values are 2-sided, and $P < .05$ was considered to be statistically significant.

RESULTS

Baseline Patient Characteristics

Among the cohort of 594,130 patients in the NHIS-NCS data set, 84,102 were statin users and 510,028 were the nonusers of the unmatched cohort (Table 1). A 1:2 PSM

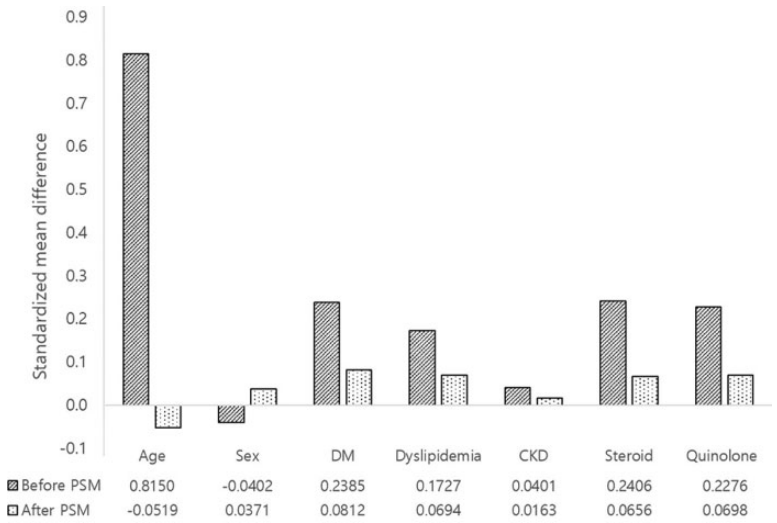

Figure 2. Standardized mean differences in the baseline characteristics for the entire cohort and matched cohort. CKD, chronic kidney disease; DM, diabetes mellitus; PSM, propensity score matching.

TABLE 2
Risk of Tendinopathy Development According to the Statin Treatment[a]

Tendinopathy Type	Events, n	Events per 10,000 Person-Years, n	HR (95% CI)	*P*
All types				
Nonuser	63,339	33.27	Reference	
Statin user	19,287	42.83	1.435 (1.411-1.460)	**<.0001**
Trigger finger				
Nonuser	4278	2.85	Reference	
Statin user	1567	4.10	1.609 (1.512-1.714)	**<.0001**
Radial styloid tenosynovitis				
Nonuser	2725	1.83	Reference	
Statin user	688	1.82	1.365 (1.247-1.495)	**<.0001**
Elbow epicondylitis				
Nonuser	22,442	13.90	Reference	
Statin user	5786	14.57	1.350 (1.309-1.393)	**<.0001**
Shoulder tendinopathy				
Nonuser	31,541	18.59	Reference	
Statin user	10,605	25.38	1.425 (1.392-1.459)	**<.0001**
Achilles tendinitis				
Nonuser	2353	1.59	Reference	
Statin user	641	1.69	1.516 (1.380-1.667)	**<.0001**

[a]Bolded *P* values indicate a statistically significant difference compared with the reference group ($P < .05$).

analysis was conducted, and the characteristics of pairs were balanced, with a standardized difference of <10% for all baseline variables (Figure 2). After PSM analysis, data from a total of 255,306 patients were included (statin users, 84,102; nonusers, 168,204). The mean ages of the statin user and nonuser groups were 49.78 ± 12.89 and 50.14 ± 14.11 years, respectively. In the statin user group, 45,744 participants (54.39%) were male, while 94,592 participants (56.24%) were male in the nonuser group. Among the statin users, atorvastatin users accounted for the majority (44.49%), followed by simvastatin users (27.82%), rosuvastatin users (12.03%), and users of other medications such as pitavastatin, pravastatin, lovastatin, and fluvastatin (15.67%).

Risk of Tendinopathy Development According to the Use of Statins

In the matched cohort, statin users had greater rates of tendinopathy development than nonusers (number of events per 10,000 person-years, 42.83 vs 33.27; hazard ratio [HR], 1.435; 95% CI, 1.411-1.460; $P < .0001$) (Table 2, Figure 3A). Consistent results were identified for all included tendinopathy types, including trigger finger

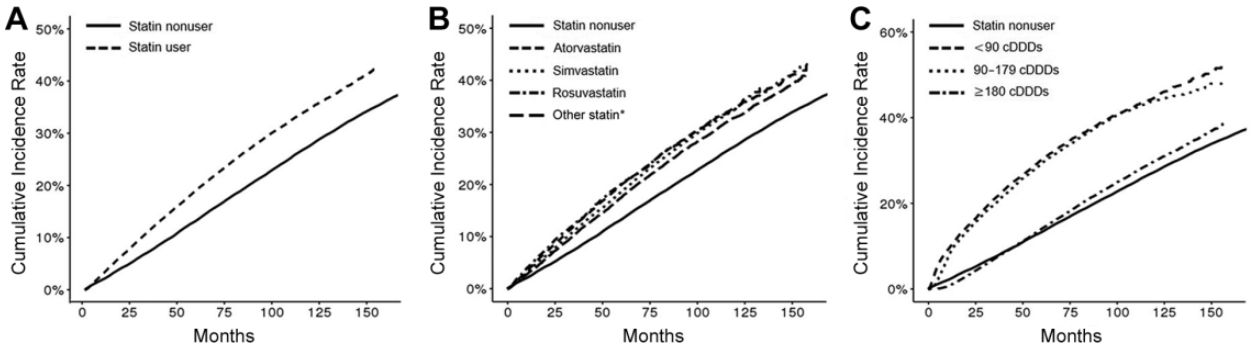

Figure 3. Cumulative incidence of the tendinopathy in matched cohort patients (statin users vs nonusers). (A) Overall, (B) by statin type, and (C) by cumulative doses of statin. [a]Pitavastatin, pravastatin, lovastatin, or fluvastatin. cDDD, cumulative defined daily dose.

(HR, 1.609; 95% CI, 1.512-1.714), radial styloid tenosynovitis (HR, 1.365; 95% CI, 1.247-1.495), elbow epicondylitis (HR, 1.350; 95% CI, 1.309-1.393), shoulder tendinopathy (HR, 1.425; 95% CI, 1.392-1.459), and Achilles tendinitis (HR, 1.516; 95% CI, 1.380-1.667) ($P < .0001$ for all).

Risk of Tendinopathy Development According to Statin Type

In the matched cohort, statin users had higher rates of tendinopathy development than nonusers regardless of statin type: atorvastatin (HR 1.431; 95% CI, 1.396-1.468), simvastatin (HR, 1.461; 95% CI, 1.424-1.498), rosuvastatin (HR, 1.460; 95% CI, 1.386-1.537), and other statins (HR, 1.388; 95% CI, 1.342-1.436) (Table 3, Figure 3B). Atorvastatin and simvastatin users had greater rates of tendinopathy development across all types of tendinopathy compared with nonusers. Among rosuvastatin users, trigger finger, elbow epicondylitis, and shoulder tendinopathy development showed significantly higher rates compared with those among nonusers. However, the rates of radial styloid tenosynovitis and Achilles tendinitis development were not significantly different (HR, 1.264; 95% CI, 0.942-1.698; $P = .1186$ for radial styloid tenosynovitis and HR, 1.348; 95% CI, 0.997-1.822; $P = .0526$ for Achilles tendinitis).

Risk of Tendinopathy Development According to Cumulative Dosage

In the matched cohort, statin users had greater incidence rates of tendinopathy compared with nonusers regardless of cumulative dosage: <90 cDDD (HR, 2.337; 95% CI, 2.269-2.406), 90-180 cDDD (HR, 2.210; 95% CI, 2.132-2.290), and >180 cDDD (HR, 1.122; 95% CI, 1.098-1.146) (Table 4, Figure 3C). As analyzed by type of tendinopathy, at <180 cDDD, statin users had higher rates of tendinopathy development than nonusers. Meanwhile, at >180 cDDD, statin users had higher rates of trigger finger and shoulder tendinopathy development than nonusers (HR, 1.314; 95% CI, 1.221-1.415 for trigger finger and HR, 1.115; 95% CI, 1.084-1.147 for shoulder tendinopathy). However, at >180 cDDD, the rates of radial styloid tenosynovitis, elbow epicondylitis, and Achilles tendinopathy development were not significant. A forest plot presents the association between statin use and tendinopathy development (Figure 4).

DISCUSSION

This study demonstrated that (1) statin use significantly increased the risk of tendinopathy development, (2) the risk of tendinopathy development was increased regardless of the type of statin used, and (3) the risk of developing tendinopathies was diluted with the increasing cumulative dose of statin.

Several previous longitudinal cohort studies have reported the relationship between statin treatment and tendinopathy. A population-based longitudinal cohort study from Taiwan showed that statin treatment had a protective effect on the development of shoulder tendinopathy in hyperlipidemia patients.[14] These authors showed that hyperlipidemia is a risk factor for shoulder tendinopathy and statin use provides a protective effect in patients with hyperlipidemia, but this protective effect may be due to an immortal time bias because the statin treatment group was confirmed based on observations made during follow-up.[28] In contrast, another longitudinal cohort study from Sweden reported that statin use increased the risk of trigger finger, shoulder tendinopathy, and Achilles tendinopathy.[9] Their findings are consistent with our findings. Furthermore, the present study also demonstrated consistent findings for other upper extremity tendinopathies, including radial styloid tenosynovitis and elbow epicondylitis. Eliasson et al[9,10] proposed, as a cause of tendinopathy development in statin users, that statin induces excessive matrix metalloproteinase (MMP) release in tendon tissue, followed by a weakened tendon matrix. They found that simvastatin administration increases protein levels of MMP-1 and MMP-13 in artificial tendons from

TABLE 3
Risk of Tendinopathy Development According to Statin Type[a]

Tendinopathy Type	Events, n	Events per 10,000 Person-Years, n	HR (95% CI)	*P*
All types of tendinopathy				
Nonuser	63,339	33.27	Reference	
Atorvastatin	7309	44.13	1.431 (1.396-1.468)	**<.0001**
Simvastatin	6850	42.63	1.461 (1.424-1.498)	**<.0001**
Rosuvastatin	1518	44.97	1.460 (1.386-1.537)	**<.0001**
Other statins[b]	3610	39.99	1.388 (1.342-1.436)	**<.0001**
Trigger finger				
Nonuser	4278	2.85	Reference	
Atorvastatin	576	3.99	1.568 (1.431-1.718)	**<.0001**
Simvastatin	579	4.35	1.693 (1.548-1.852)	**<.0001**
Rosuvastatin	131	4.43	1.801 (1.510-2.149)	**<.0001**
Other statins[b]	281	3.75	1.468 (1.299-1.660)	**<.0001**
Radial styloid tenosynovitis				
Nonuser	2725	1.83	Reference	
Atorvastatin	242	1.69	1.293 (1.126-1.484)	**.0003**
Simvastatin	259	1.97	1.437 (1.260-1.639)	**<.0001**
Rosuvastatin	46	1.57	1.264 (0.942-1.698)	.1186
Other statins[b]	141	3.82	1.397 (1.176-1.660)	**.0001**
Elbow epicondylitis				
Nonuser	22,442	13.90	Reference	
Atorvastatin	2180	14.63	1.346 (1.286-1.410)	**<.0001**
Simvastatin	2099	15.07	1.396 (1.334-1.462)	**<.0001**
Rosuvastatin	451	14.78	1.382 (1.258-1.519)	**<.0001**
Other statins[b]	1056	13.52	1.264 (1.187-1.345)	**<.0001**
Shoulder tendinopathy				
Nonuser	31,541	18.59	Reference	
Atorvastatin	4071	26.17	1.440 (1.392-1.490)	**<.0001**
Simvastatin	3674	24.93	1.421 (1.372-1.472)	**<.0001**
Rosuvastatin	846	26.65	1.485 (1.386-1.591)	**<.0001**
Other statins[b]	2014	24.21	1.383 (1.321-1.448)	**<.0001**
Achilles tendinitis				
Nonuser	2353	1.59	Reference	
Atorvastatin		1.68	1.496 (1.301-1.720)	**<.0001**
Simvastatin	239	1.81	1.618 (1.411-1.856)	**<.0001**
Rosuvastatin	44	1.50	1.348 (0.997-1.822)	.0526
Other statins[b]	118	1.59	1.436 (1.190-1.732)	**.0002**

[a]Bolded *P* values indicate a statistically significant difference compared with the reference group ($P < .05$).
[b]Pitavastatin, pravastatin, lovastatin, or fluvastatin.

human tendon fibroblasts and decreases mechanical strengths of the artificial tendon such as stiffness and maximal forces.

In the present study, the risk of tendinopathies was increased significantly in most cases for statin users regardless of the type of statin. Only rosuvastatin did not significantly increase the risk of radial styloid tenosynovitis and Achilles tendinitis development in the subgroup analysis. Rosuvastatin is a representative hydrophilic statin and has high hepato-selectivity, so it can be considered that adverse drug reactions may occur less in specific tendons. It is reported that hydrophilic statins are less likely to penetrate nonhepatic tissues because of their hepato-selectivity, and thus there are fewer general adverse drug reactions, such as SAMSs.[23] Further investigations may be required to identify the possible effects of statins on the specific tendons.

The most noteworthy finding in this study is that the risk of developing tendinopathy was high in the low-cDDD group, and the deleterious effect of statins was diluted as the cumulative dose increased. In other words, if a patient is going to have issues with tendinopathy from statin use, it will likely manifest in the first 180 days of use. It was reported that the myotoxicity and muscular symptom prevalence rates were lower in patients with statin treatment for >3 months compared with those with statin treatment for <3 months.[3] Our study shows similar results with the aforementioned studies of SAMSs. Predisposing factors, such as HMG-CoA reductase pathway–mediated effects or genetic factors, proposed as a mechanism of SAMSs, may be considered as the cause of dilution phenomenon in the present study.[8,19,30] In all types of tendinopathy, the deleterious effect of statins was diluted as the cumulative dose increased, and especially in certain types of tendinopathies

TABLE 4
Risk of Tendinopathy Development According to the Cumulative Dose of Statin[a]

Tendinopathy Type	Events, n	Events per 10,000 Person-Years, n	HR (95% CI)	*P*
All types				
Nonuser	63,339	33.27	Reference	
<90 cDDD statin	5076	70.50	2.337 (2.269-2.406)	**<.0001**
90-180 cDDD statin	3271	65.70	2.210 (2.132-2.290)	**<.0001**
>180 cDDD statin	10,940	33.30	1.122 (1.098-1.146)	**<.0001**
Trigger finger				
Nonuser	4278	2.85	Reference	
<90 cDDD statin	351	5.90	2.463 (2.203-2.754)	**<.0001**
90-180 cDDD statin	253	6.20	2.531 (2.224-2.880)	**<.0001**
>180 cDDD statin	963	3.42	1.314 (1.221-1.415)	**<.0001**
Radial styloid tenosynovitis				
Nonuser	2725	1.83	Reference	
<90 cDDD statin	172	2.92	2.312 (1.973-2.701)	**<.0001**
90-180 cDDD statin	117	2.89	2.249 (1.863-2.717)	**<.0001**
>180 cDDD statin	399	1.43	1.056 (0.945-1.180)	.3360
Elbow epicondylitis				
Nonuser	22,442	13.90	Reference	
<90 cDDD statin	1672	26.58	2.462 (2.339-2.591)	**<.0001**
90-180 cDDD statin	1067	24.78	2.316 (2.176-2.466)	**<.0001**
>180 cDDD statin	3047	10.47	0.967 (0.929-1.006)	.0938
Shoulder tendinopathy				
Nonuser	31,541	18.59	Reference	
<90 cDDD statin	2687	40.70	2.394 (2.300-2.493)	**<.0001**
90-180 cDDD statin	1730	38.39	2.218 (2.112-2.330)	**<.0001**
>180 cDDD statin	6188	20.17	1.115 (1.084-1.147)	**<.0001**
Achilles tendinitis				
Nonuser	2353	1.59	Reference	
<90 cDDD statin	194	3.28	2.837 (2.439-3.300)	**<.0001**
90-180 cDDD statin	104	2.57	2.285 (1.871-2.791)	**<.0001**
>180 cDDD statin	343	1.23	1.109 (0.985-1.249)	.0885

[a]Bolded *P* values indicate a statistically significant difference compared with the reference group ($P < .05$). cDDD, cumulative defined daily dose.

including radial styloid tenosynovitis, elbow tendinopathy, and Achilles tendinitis, the HRs were not significantly different from those of nonusers in high cumulative dose (>180 cDDD). Although reasons for these differential effects cannot be explained, it can be speculated that different pathologies for each tendinopathy could affect the HR of each tendinopathy differently in a high cumulative dose.

Limitations

There are several limitations in this study. First, the present study was performed in common types of tendinopathy including hand, wrist, elbow, shoulder, and Achilles tendinopathy. Other tendinopathy, such as knee tendinopathy, was not included in this study. However, rotator cuff tendinopathy and elbow epicondylitis are the most common types of tendinopathy in the upper extremity and Achilles tendinopathy is the most common in the lower extremity.[22,25] Second, tendon rupture is often considered as the final stage of causal pathway from tendinopathy. However, patients with tendon rupture were not included in this study because a certain portion of patients having ICD-10 diagnostic codes of tendon rupture may have traumatic causes. Third, there is a certain degree of residual confounding factors, since we could not control for factors generally thought to be related to the development of tendinopathy, such as smoking,[15] body mass index,[16] alcohol intake,[20] and other potential risk factors (eg, aromatase inhibitors[12]). However, most factors considered to be important, such as steroid use history and underlying diabetes, were included as covariates and analyzed. Fourth, the reverse causation phenomenon and immortal time bias may occur because of the nature of longitudinal cohort studies that track drug use for a long time. To minimize the phenomenon and bias, we used Cox proportional hazards modeling with time-varying covariates. Fifth, this study uses a database of a racially homogenous cohort, so it may be difficult to apply the results of the study broadly to a more diverse cohort. Sixth, there are inevitable limitations to using ICD-10 diagnostic codes and prescription records for research. Coding of tendinopathy depending on the decision of individual clinicians is not standardized, and a patient's compliance with prescription is not guaranteed.

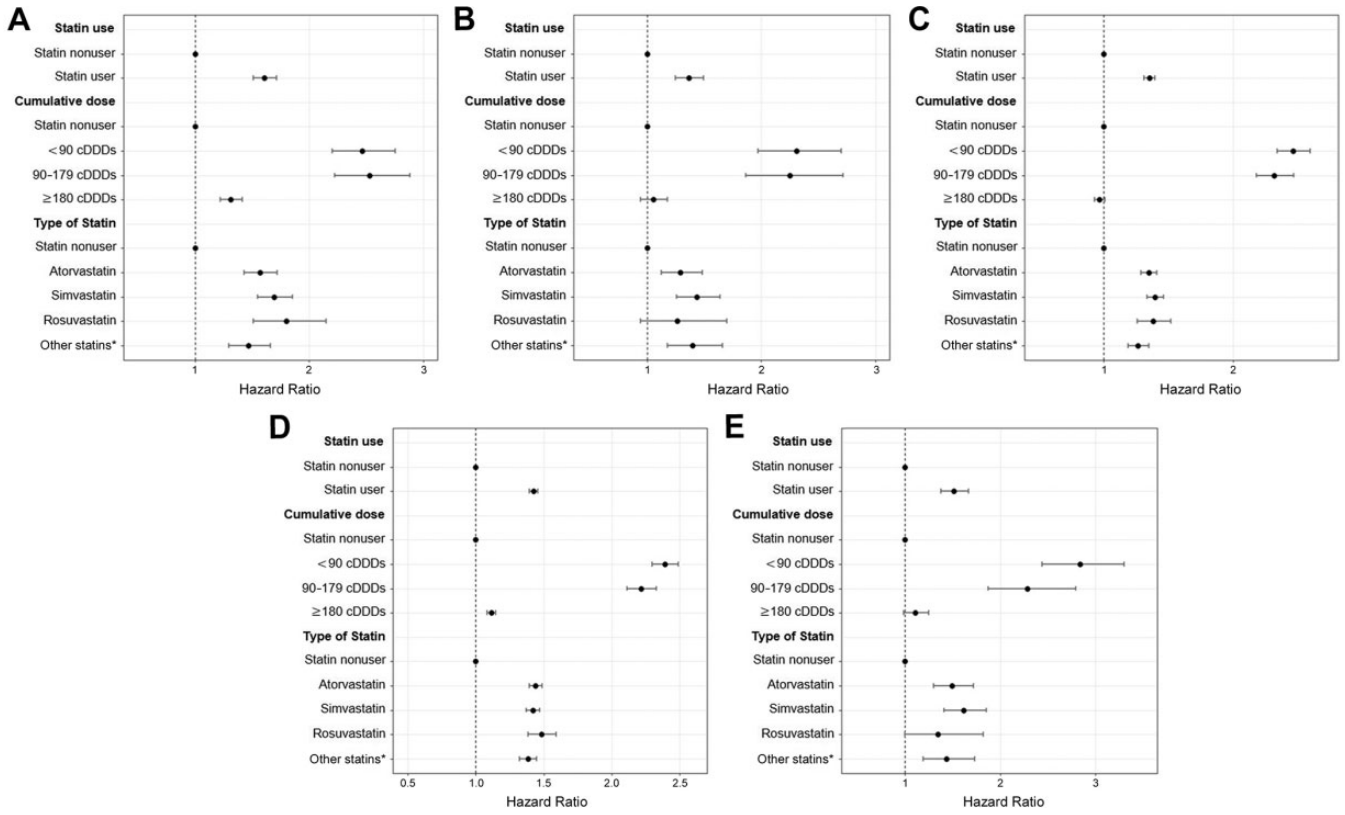

Figure 4. Forest plot portraying the hazard ratios and 95% CIs of the association between statin use and tendinopathy development according to statin use, cumulative defined daily dose (cDDD) of statin, and statin type for (A) trigger finger, (B) radial styloid tenosynovitis, (C) elbow epicondylitis, (D) shoulder tendinopathy, and (E) Achilles tendinopathy. *Pitavastatin, pravastatin, lovastatin, or fluvastatin

CONCLUSION

The results of our study revealed that statin use increased the incidence of tendinopathy regardless of the type of statin used. Our results also show that statin-related tendinopathies mainly occur in the low cumulative dose of statin treatment. Clinicians should be aware that tendinopathies may develop in patients taking statins, especially in the early stages of treatment.

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APPENDIX

TABLE A1
Definition of Diagnostic and Procedural Codes Based on Korean NHIS Database[a]

Variable	Definition
Exclusion criteria (disease)	
Rheumatoid arthritis	ICD-10 diagnosis codes: M05-M06
Clinical history or risk factor	
Diabetes mellitus	ICD-10 diagnosis codes: E10, E11, E14
Dyslipidemia	ICD-10 diagnosis code: E78
Chronic kidney disease	ICD-10 diagnosis codes: N18-N19
Concurrent medication	
Corticosteroid	Korea drug codes: 116401ATB, 140801ATB, 141901ATB, 141903ATB, 160201ATB, 170901ATB, 170906ATB, 193302ATB, 193305ATB, 217034ASY, 217035ASY, 217001ATB, 296900ATB, 296900ATB, 116530BIJ, 142030BIJ, 142230BIJ, 142232BIJ, 193601BIJ, 193603BIJ, 193604BIJ
Quinolone antibiotics	Korea drug codes: 134103ATB, 134105ATB, 134105ATR, 134108ATR, 134109ATB, 183201ATB, 183202ATB, 183203ATB, 183205ATB, 184901ATB, 184903ATB, 184904ATB, 203303ATB, 203901ATB, 203904ATB, 242201ATB, 380301ATB, 428901ATB, 442901ATB, 637101ATB, 134133BIJ, 134134BIJ, 134135BIJ, 183233BIJ, 183234BIJ, 183235BIJ, 203940BIJ, 380335BIJ, 442902BIJ, 801601BIJ
Statins	
Atorvastatin	Korea drug codes: 111501ATB, 502201ATB, 472300ATB, 614500ATB, 524000ATB, 527100ATB, 633800ATB, 671800ATR, 671900ATR, 673800ATR, 688100ATB, 688200ATB, 690500ATB, 690700ATB, 111502ATB, 502202ATB, 472400ATB, 518900ATB, 524100ATB, 527000ATB, 633900ATB, 672000ATR, 672100ATR, 688300ATB, 688400ATB, 690400ATB, 690600ATB, 111503ATB, 502203ATB, 472500ATB, 634800ATB, 688500ATB, 111504ATB, 502204ATB, 634600ATB
Simvastatin	Korea drug codes: 227806ATB, 227803ATB, 471000ATB, 227801ATB, 227801ATR, 631400ATB, 227802ATB, 507800ATB, 631500ATB, 227805ATB

(continued)

Table A1 (continued)

Variable	Definition
Rosuvastatin	Korea drug codes: 454003ATB, 640700ATB, 644200ATB, 526900ATB, 664600ATB, 629700ATB, 629800ATB, 631600ATB, 631700ATB, 655000ATB, 654800ATB, 663400ACS, 661800ATB, 673700ATB, 663900ATB, 664200ATB, 673900ATB, 671200ATB, 671300ATB, 677300ATB, 686800ATB, 680300ATB, 679700ATB, 684300ATB, 684500ATB, 672500ATR, 672600ATR, 683300ATR, 454001ATB, 640800ATB, 525000ATB, 525100ATB, 644100ATB, 526300ATB, 653200ATB, 629900ATB, 630100ATB, 654900ATB, 654700ATB, 661900ATB, 662000ATB, 664000ATB, 664300ATB, 664700ATB, 674000ATB, 671400ATB, 671500ATB, 671600ATB, 677400ATB, 677500ATB, 679500ATB, 679600ATB, 691400ATB, 684400ATB, 684600ATB, 672700ATR, 672800ATR, 683400ATR, 683000ATB, 683200ATB, 454002ATB, 640900ATB, 525200ATB, 525300ATB, 526400ATB, 526500ATB, 630000ATB, 630200ATB, 654600ATB, 662100ATB, 664100ATB, 664400ATB, 664800ATB, 674100ATB, 677000ATB, 677100ATB, 671700ATB, 677600ATB, 691500ATB, 684700ATB, 672900ATR, 673000ATR, 683100ATB
Pitavastatin	Korea drug codes: 470902ATB, 470901ATB, 635000ATB, 634900ATB, 679300ACH, 470903ATB, 635200ATB, 635100ATB
Pravastatin	Korea drug codes: 216602ATB, 216601ATB, 216603ATB, 216604ATB, 519300ACH
Lovastatin	Korea drug codes: 185801ATB
Fluvastatin	Korea drug codes: 162401ACH, 162402ACH, 162403ATR

[a]ICD-10, International Classification of Diseases, 10th Revision; NHIS, National Health Insurance Service.