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Report

Decreased Risk of Fragility Fractures associated with Statin Use in the Older Japanese Population: a Nationwide Case–crossover Study

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The association between statin use and fractures has been investigated by several cohort and case–control studies, with inconsistent results, but no case–crossover study has been conducted. This case–crossover study aimed to analyze the association between statin use and fragility fractures in a large older cohort using the National Database of Health Insurance Claims and Specific Health Checkups of Japan. In this study, 446,101 patients aged ≥65 years in Japan who sustained fragility fractures from May 2013 to September 2014 were evaluated. Statin use was compared between the case window (3 days just before the date of the fragility fracture) and three control windows (31–33, 34–36, and 37–39 days before the fragility fracture), and the association between statin use and the occurrence of fragility fractures was estimated using a conditional logistic regression model with 1:3 matching of cases to controls. The adjusted odds ratio for the association between statin use and fragility fractures was 0.86 (95% confidence interval 0.83–0.89). Stratified analyses showed a tendency for a decreased risk of fractures with statin use; females (versus males), very old (versus old) individuals, and those with fractures in the vertebrae (versus proximal humerus, distal radius, or femoral neck) had substantially decreased risks of fractures. The results suggest a decreased risk of fragility fractures associated with statin use in older Japanese individuals, but further studies are needed.

Key words fragility fracture, statins, case–crossover, older, fracture

INTRODUCTION

Statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, are widely used as cholesterol-lowering medications. Since the report by Mundy *et al.*[1] in 1999 showing increased expression of the bone morphogenetic protein-2 gene in bone cells treated with statins, several clinical studies with cohort and case–control designs have investigated the association between statin use and the risk of fractures, but the results have been inconsistent.[2,3] This inconsistency is thought to be attributed to the presence of confounders, small cohort sizes, and the presence of few very old people in the population.

A case–crossover design,[4] with self-matched controls, has a unique advantage in that it can eliminate measurable and unmeasurable time-invariant confounders such as sex, age, underlying disease, frailty, and genetics.[5] However, to the best of our knowledge, no case–crossover study has investigated the association between statin use and fractures.

This case–crossover study aimed to evaluate the association between statin use and fragility fractures, targeting almost all citizens aged ≥65 years in Japan who had lived without hospitalization for some time but sustained fragility fractures, using the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB Japan).

MATERIALS AND METHODS

Study Design, Data Source, and Study Population This case–crossover study, which targeted only subjects who experienced fragility fractures, was conducted as part of the Polypharmacy and Fracture in Older People Study, approved by the ethics committee of Tokushima Bunri University in September 2015 (no. H27-8). Using claims data from April 2012 to September 2014 from the NDB Japan generated by the Ministry of Health, Labour and Welfare, this study evaluated patients aged ≥65 years who (1) sustained fragility fractures in any of four locations (proximal humerus, distal radius, vertebrae, and/or femoral neck) during the follow-up period (May 2013 to September 2014) and (2) had not been hospitalized at least 13 months prior to the fracture. Patients who had no medication record or opioid use prior to the fracture were excluded. The follow-up period ended when the patient experienced any fracture or was hospitalized, or on September 30, 2014, whichever came first.

Measures and Statistical Analyses Fragility fractures are caused by a slight external force such as a fall from standing height or lower.[6] The detailed definitions of the fragility fractures incurred and patient characteristics such as complications and Charlson Comorbidity Index[7] in this study have been described elsewhere.[8] Consistent with the previously

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described definition and procedure,[8] fragility fractures were determined by independent judgements by two physicians who used diagnostic and modifier codes added to the diagnostic codes. Fracture occurrence was identified by radiographic examination on the date of diagnosis at the institution where the diagnosis was made.

Medication use was compared between the case window (3 days before the date of the fragility fracture) and three control windows (31–33, 34–36, and 37–39 days before the date of the fragility fracture) based on the standard procedure used for case–crossover studies[4] (Fig. 1). This study included oral formulations, patches with systemic action (rotigotine, rivastigmine, estrogen, nitrates, and beta-blocking agents), and injected formulations, including statins (Anatomical Therapeutic Chemical code: C10AA), 11 classes of medications related to bone-metabolism, and 15 classes related to falls. Statins included atorvastatin, fluvastatin, simvastatin, pitavastatin, pravastatin, and rosuvastatin. Medications related to bone metabolism included proton pump inhibitors (A02B), steroids (H02A and H02B), thyroid hormones (H03A), anti-estrogens (L02AE, fulvestrant [L02BA], and L02BG), vitamin D (A11C), calcium agents (A12A), anabolic steroids (A14A), vitamin K (B02B), estrogen agonists (G03A, G03C, G03E, G03F, G03G, G03X, H01C, and L02BA excluding fulvestrant), calcium homeostasis agents and somatropin (H01AC, teriparatide [H05A], and H05BA), and bisphosphonates and RANKL (receptor activator of NF-kappa B ligand)-targeted antibody (M05B). Medications related to falls included antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), antiepileptics (N03A), anti-Parkinson agents (N04), anti-dementia agents (N06D), insulins (A10A), hypoglycemic agents excluding insulin (A10B), nitrates and erectile dysfunction agents (C01DA and G04BE), antiadrenergic agents and vasodilators relaxing vascular smooth muscle (C02A, C02C, C02DB, and G04C), diuretics (C03), beta-blocking agents (C07), calcium channel blockers (C08 and C10BX), and renin–angiotensin-system-acting agents (C09).

Medication use was expressed in daily-units. The dates of oral formulation use were defined by the dispensing date and administration period. The dates of patch use was identified by dividing the total number of patches by the standard daily maintenance dose. The dates of injection formulation use were defined exclusively by the dispensing date; the exception was self-injection agents such as insulin and glucagon-like peptide-1, for which the dates of self-injection were defined as the dispensing date and 365 days from that date.

The association between statin use and fragility fractures was assessed using conditional logistic regression models with 1:3 matching of cases to controls. The multivariate model included all of the above medication classes. Stratified analyses were also conducted according to sex, age class, and fracture location. Two-tailed P-values < 0.05 were defined *a priori* indicating statistical significance. SAS Enterprise Guide 7.13 and SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) were used for the data processing and statistical analyses.

RESULTS

A total of 446,101 patients who sustained fragility fractures were evaluated. Their characteristics are summarized in Table 1. Females and patients aged ≥85 years made up approximately 80% and 30% of the study cohort, respectively. Approximately 60% of patients sustained vertebral fractures, and 17% and 17% sustained distal radius and femoral neck fractures, respectively.

The number of patients who used statins according to study window was 102,040 (22.9%) during the case window (3 days before the fracture) compared with 102,665 (23.0%), 102,822 (23.0%), and 102,758 (23.0%) during the 31–33 day, 34–36 day, and 37–39 day control windows, respectively. The adjusted odds ratio (OR) for incurring a fragility fracture with statin use was 0.86 (95% confidence interval 0.83–0.89) for all patients (Table 2). In the stratified analyses by sex, age class, and fracture location (Table 2), the adjusted OR for a decreased fracture risk was significant for females (0.85 [0.82–0.88]), but not for males. Patients aged ≥85 years had a lower OR (0.75 [0.69–0.81]) than those of relatively younger patients (aged 65–69, 70–74, 75–79, and 80–84 years: 0.89 [0.81–0.99], 0.88 [0.81–0.95], 0.91 [0.84–0.98], and 0.85 [0.79–0.92], respectively). Vertebral location decreased the risk of fragility fractures (0.81 [0.77, 0.85]) compared with other locations (proximal humerus, distal radius, or femoral neck).

More detailed analyses stratified by both sex and age class showed that the ORs for incurring a fragility fracture were not significant for younger male patients (Table 3). In the analyses stratified by all of sex, age class, and fracture location, a significantly decreased fragility fracture risk was observed for vertebral fractures in male patients aged 80–84 and ≥85 years and for female patients of all age classes, but the other fracture locations did not show significance for the most part (Table 4).

DISCUSSION

Two strengths of this study support the decreased risk of fragility fractures that was observed with statin use: (1) the case–crossover design, which naturally excludes time-invariant confounders, and (2) the large cohort including very old patients aged ≥85 years, using data from the NDB Japan, which covers approximately 31 million patients aged ≥65 years. The findings support previous evidence of an association between statin use and a decreased risk of fractures found in both cohort[9-12] and case–control[13-17] studies.

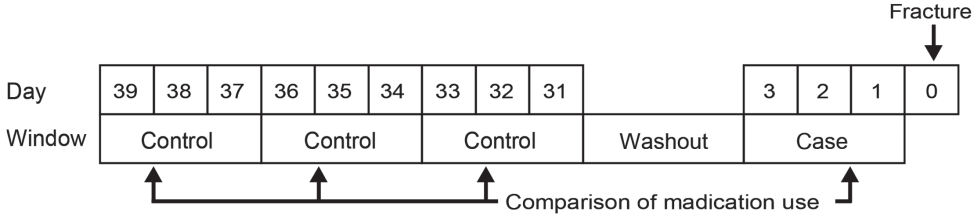

Fig. 1. Definition of the Windows Used in This Case–Crossover Study

Table 1. Patient Characteristics

Characteristics	*n* (%) *N*=446,101
Sex	
Male	83,656 (18.8)
Female	362,445 (81.2)
Age, years	
65–69	47,589 (10.7)
70–74	70,327 (15.8)
75–79	91,794 (20.6)
80–84	101,476 (22.7)
≥85	134,915 (30.2)
Complication: code[a]	
Malignant neoplasm: C00–97	43,610 (9.8)
Anemia: D50–64	75,871 (17.0)
Diabetes mellitus: E10–14	137,338 (30.8)
Hyperlipidemia: E78.0–78.5	210,952 (47.3)
Schizophrenia: F20	13,241 (3.0)
Depression: F32–33	42,607 (9.6)
Parkinson's disease: G20	14,543 (3.3)
Alzheimer's disease: G30	55,687 (12.5)
Epilepsy: G40–41	12,214 (2.7)
Sleep disorder: G47	156,090 (35.0)
Polyneuropathy and peripheral nervous system: G60–64	92,141 (20.7)
Essential hypertension: I10	291,876 (65.4)
Angina: I20	84,650 (19.0)
Heart failure: I50	92,706 (20.8)
Cerebral infarction: I63 and I69.3	95,450 (21.4)
Cerebrovascular disease excluding I63 and I69.3: I60–69	46,133 (10.3)
Allergic rhinitis: J30	109,538 (24.6)
Asthma: J45–46	56,152 (12.6)
Rheumatoid arthritis: M05–06	21,057 (4.7)
Arthrosis: M15–19	162,596 (36.5)
Osteoporosis: M80–82	190,575 (42.7)
Charlson comorbidity index	
0	104,923 (23.5)
1–2	171,055 (38.3)
3–4	112,121 (25.1)
≥5	58,002 (13.0)
Fracture history[b]	
No	354,375 (79.4)
Yes	91,726 (20.6)
Fracture location[c]	
Proximal humerus	23,832 (5.4)
Distal radius	75,256 (17.0)
Vertebrae	268,702 (60.5)
Femoral neck	76,296 (17.2)

[a] ICD-10 code.
[b] This was defined as any disease code for a fracture predating the fracture date per the claims data from April 2012; therefore, these data do not reveal fracture history from birth.
[c] Patients with only one fragility fracture location. The percentage was estimated by dividing the number of indicated patients by 444,086.

Table 2. Adjusted Odds Ratios (ORs) for Fragility Fractures with Statin Use[a]

Strata	*n*	Adjusted OR (95% CI)[b]
All	446,101	**0.86 (0.83–0.89)**
Sex		
Male	83,656	0.91 (0.81–1.01)
Female	362,445	**0.85 (0.82–0.88)**
Age, years		
65–69	47,589	**0.89 (0.81–0.99)**
70–74	70,327	**0.88 (0.81–0.95)**
75–79	91,794	**0.91 (0.84–0.98)**
80–84	101,476	**0.85 (0.79–0.92)**
≥85	134,915	**0.75 (0.69–0.81)**
Fracture history		
No	354,375	**0.85 (0.82–0.89)**
Yes	91,726	**0.86 (0.80–0.94)**
Fracture location		
Proximal humerus	23,832	0.99 (0.84–1.16)
Distal radius	75,256	0.96 (0.88–1.04)
Vertebrae	268,702	**0.81 (0.77–0.85)**
Femoral neck	76,296	**0.87 (0.78–0.97)**

CI, confidence interval
[a] All analyses except the fracture location analyses were conducted in all patients (*n*=446,101). Fracture location was evaluated for patients with only one fragility fracture location (*n*=444,086).
[b] All analyses were adjusted for 11 classes of medications related to bone metabolism and 15 classes of medications related to falls. Bold letters indicate statistical significance.

Table 3. Adjusted Odds Ratios (ORs) for Fragility Fractures with Statin Use Stratified by Sex and Age Class[a]

Strata	*n*	Adjusted OR (95% CI)[b]
Males		
65–69 years	9557	1.63 (1.20–2.21)
70–74 years	13,305	0.85 (0.66–1.09)
75–79 years	17,831	1.18 (0.93–1.48)
80–84 years	19,806	**0.67 (0.54–0.83)**
≥85 years	23,157	**0.71 (0.56–0.89)**
Females		
65–69 years	38,032	**0.84 (0.76–0.93)**
70–74 years	57,022	**0.88 (0.81–0.96)**
75–79 years	73,963	**0.88 (0.81–0.95)**
80–84 years	81,670	**0.87 (0.81–0.95)**
≥85 years	111,758	**0.75 (0.69–0.82)**

CI, confidence interval
[a] All patients (*n*=446,101).
[b] All analyses were adjusted for 11 classes of medications related to bone metabolism and 15 classes of medications related to falls. Bold letters indicate statistical significance.

The following two findings of this study are very important and require further investigation. First, it is unclear whether the results of the stratified analyses, in which no significant effects on fragility fracture risk were found in relatively younger males and in those with fracture locations other than the vertebrae, were attributed to weak statistical power. However, the findings that statins have a beneficial effect on fractures in females, very old patients, and those with vertebral fractures are likely true. Second, this study showed that patients with fragility fractures used statins often during the control windows but relatively less often during the case window. The interval between the case and control windows was only approximately 30 days, and it is possible that the beneficial effect of statins disappears after 30 days.

The findings of this study need careful interpretation as described above. However, this is the first case–crossover study to analyze the association between statin use and fractures, and the findings suggest a decreased risk of fragility fractures associated with statin use in older Japanese individuals. Further studies are needed to confirm these findings.

Table 4. Adjusted Odds Ratios (ORs) for Fragility Fractures with Statin Use Stratified by Sex, Age Class, and Fracture Location[a]

Strata	*n*	Adjusted OR (95% CI)[b]
Males		
65–69 years		
Proximal humerus	721	0.74 (0.24–2.25)
Distal radius	2423	0.86 (0.50–1.48)
Vertebrae	5451	2.33 (1.53–3.55)
Femoral neck	940	1.66 (0.48–5.68)
70–74 years		
Proximal humerus	739	0.82 (0.31–2.19)
Distal radius	2333	1.20 (0.68–2.12)
Vertebrae	8732	0.79 (0.58–1.09)
Femoral neck	1458	0.91 (0.38, 2.18)
75–79 years		
Proximal humerus	753	1.38 (0.46–4.12)
Distal radius	2135	0.74 (0.40–1.40)
Vertebrae	12,539	1.32 (1.00–1.74)
Femoral neck	2356	0.95 (0.44–2.08)
80–84 years		
Proximal humerus	735	0.48 (0.14–1.61)
Distal radius	1843	0.80 (0.39–1.64)
Vertebrae	13,863	**0.65 (0.50–0.83)**
Femoral neck	3311	0.83 (0.44–1.55)
≥85 years		
Proximal humerus	830	2.55 (0.42–15.59)
Distal radius	1486	1.25 (0.55–2.82)
Vertebrae	15,364	**0.72 (0.54–0.95)**
Femoral neck	5389	**0.47 (0.27–0.83)**
Females		
65–69 years		
Proximal humerus	2499	1.21 (0.79–1.87)
Distal radius	14,170	**0.80 (0.68–0.95)**
Vertebrae	18,847	**0.77 (0.66–0.89)**
Femoral neck	2388	1.85 (1.10–3.13)
70–74 years		
Proximal humerus	3203	1.01 (0.68–1.48)
Distal radius	15,305	1.05 (0.89–1.24)
Vertebrae	34,250	**0.82 (0.74–0.92)**
Femoral neck	4066	**0.57 (0.39–0.83)**
75–79 years		
Proximal humerus	3916	**0.68 (0.47–0.98)**
Distal radius	13,478	0.94 (0.79–1.13)
Vertebrae	48,605	**0.86 (0.78–0.94)**
Femoral neck	7668	0.98 (0.74, 1.31)
80–84 years		
Proximal humerus	4314	1.26 (0.88–1.82)
Distal radius	11,548	1.22 (0.99–1.50)
Vertebrae	51,823	**0.80 (0.72–0.88)**
Femoral neck	13,605	**0.79 (0.62–1.00)**
≥85 years		
Proximal humerus	6122	0.90 (0.62–1.30)
Distal radius	10,535	0.84 (0.65–1.08)
Vertebrae	59,228	**0.68 (0.61–0.76)**
Femoral neck	35,115	0.90 (0.76–1.08)

CI, confidence interval

[a] Patients with only one fragility fracture location (n=444,086).

[b] All analyses were adjusted for 11 classes of medications related to bone metabolism and 15 classes of medications related to falls. Bold letters indicate statistical significance.

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Conflict of interest The authors declare no conflict of interest.

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