Statin Use Is Associated With Decreased Osteoporosis and Fracture Risks in Stroke Patients

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Context: Poststroke osteoporosis and consequent fractures increase the risk of morbidity and mortality and cause considerable socioeconomic burden.

Objective: To evaluate the association between statin use and risks of osteoporosis and fracture in stroke patients.

Design: Population-based propensity score–matched cohort study.

Setting: Taiwan's National Health Insurance Research Database.

Patients: Patients newly diagnosed with a stroke between 2000 and 2012 were identified. After propensity score matching, 5254 patients were included, with 2627 patients in the statin and nonstatin cohorts, respectively.

Main Outcome Measures: Hazard ratios (HRs) for poststroke osteoporosis, hip fracture, and vertebral fracture (together, the primary outcome) were calculated using Cox proportional hazards regression models according to statin use status.

Results: Poststroke statin use was associated with a lower overall risk of the primary outcome [adjusted hazard ratio (aHR) = 0.66; $P < 0.001$]. In subanalyses, statin use was associated with a decreased risk of all individual outcomes, including osteoporosis (aHR = 0.68; $P < 0.001$), hip fracture (aHR = 0.59; $P < 0.001$), and vertebral fracture (aHR = 0.73; $P = 0.003$). A dose-effect relationship was identified. The aHRs for developing the primary outcome were 0.96, 0.86, and 0.34 for patients who used 1 to 90, 91 to 365, and >365 cumulative defined daily doses of statins, respectively. These dose-effect relationships were maintained on subgroup analyses stratified by age, sex, and stroke type and sensitivity analyses conducted without propensity score matching.

Conclusions: Statin use is associated with decreased risks of osteoporosis, hip fracture, and vertebral fracture in stroke patients. (***J Clin Endocrinol Metab*** **103: 3439–3448, 2018)**

Osteoporosis is a systemic skeletal disease characterized by impairment of bone density, strength, and microarchitecture. Osteoporosis can increase the risk of fragility fractures and therefore is associated with considerable medical and socioeconomic burdens. Hip and vertebral fractures are the most common sites of osteoporotic fracture, with both having the potential to significantly increase the risks for disability, morbidity, and mortality (1–3).

Stroke is a major risk factor for osteoporosis and fractures owing to substantial loss of bone mineral density (BMD), gait disability, balance impairment, immobilization, and increase in fall risk after the stroke (4–7). Fractures, which are a common complication of

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Abbreviations: aHR, adjusted hazard ratio; BMD, bone mineral density; cDDD, cumulative defined daily dose; DDD, defined daily dose; HR, hazard ratio; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; LHID, Longitudinal Health Insurance Database; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; NIHSS, National Institutes of Health Stroke Scale; SSI, stroke severity index.

stroke, can further reduce functional recovery, prolong disability, and increase the mortality risk among stroke patients (8, 9). Thus, it is imperative to develop strategies for osteoporosis and fracture prevention among stroke survivors.

Statins, also known as 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors, were developed to treat hyperlipidemia, with a proven therapeutic benefit for the prevention and treatment of cardiovascular disease (10–12). Some studies have indicated a further therapeutic role of statins in decreasing the risk of osteoporosis and bone fracture (13, 14), but conflicting results have been reported (15, 16). Because statins control dyslipidemia and prevent cardiovascular disease recurrence (17), a considerable proportion of stroke survivors receive statins in clinical practice. However, previous studies evaluating the association between the use of statins and the risks of osteoporosis and bone fractures have typically been performed in a general population. Moreover, no recent study assessing this relationship has focused specifically on stroke patients.

To date, it is unclear whether the use of statins can decrease the risk of osteoporosis and bone fracture after a stroke. Therefore, we aimed to evaluate the association of statin use and the risk of osteoporosis, hip fracture, and vertebral fracture in patients after a stroke.

Materials and Methods

Data sources

We conducted a population-based, propensity-matched, retrospective cohort study of adult patients aged ≥20 years with a diagnosis of new-onset stroke between 2000 and 2012 who were registered in Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program in Taiwan, which has been operating since March 1995, is a single-payer mandatory health insurance system that covers >99% of Taiwan's population and reimburses medical fees for almost all outpatient, inpatient, and emergency services. The Longitudinal Health Insurance Database (LHID), developed by the National Health Research Institute of Taiwan for research purposes, contains a randomly and systematically selected representative subset of 1,000,000 people from the NHIRD registry of all NHI beneficiaries in the year 2000. The LHID includes patient demographics and medical claims for all inpatient, outpatient, and emergency care services. As reported by the National Health Research Institute, there was no statistically significant difference in age, sex, or medical care use between the LHID sample cohort and all NHI beneficiaries in Taiwan. To protect patient privacy and data security, the National Health Research Institute encrypted all personal identification information before releasing the LHID. This study was conducted in accordance with the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. The Tzu-Chi General Hospital Research Ethics Committee approved this study (REC No: IRB107-05-C).

Study population

Patients registered in the LHID and hospitalized with the principal diagnosis of stroke were included [*International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 433, 434, and 436 (ischemic stroke) and 430 to 432 (hemorrhagic stroke)]. The date of stroke diagnosis and corresponding hospitalization were defined as the index date and index hospitalization, respectively. Our exclusion criteria were previous stroke before the year 2000; history of osteoporosis, hip fracture, or vertebral fracture; osteoporosis treatment before the index date; diagnosis of osteoporosis, hip fracture, or vertebral fracture during the index hospitalization; death during the index hospitalization; and previous statin treatment before the index date or initiation of statin treatment at >6 months after the index date (Fig. 1).

Exclusion for a stroke history ensured that we enrolled only patients with a new-onset stroke. Exclusion of patients with previous osteoporosis, hip fracture, vertebral fracture, or use of osteoporosis treatment before the index date was necessary because these were our primary outcomes. Exclusion of patients who developed osteoporosis, hip fracture or vertebral fracture during the index hospitalization was necessary to accurately determine the occurrence of our primary outcomes after the stroke. Exclusion of patients who died during the index hospitalization ensured a sufficient follow-up observation period for accurate assessment of the outcomes. Exclusion for use of statin treatment before the index date or the initiation of statin

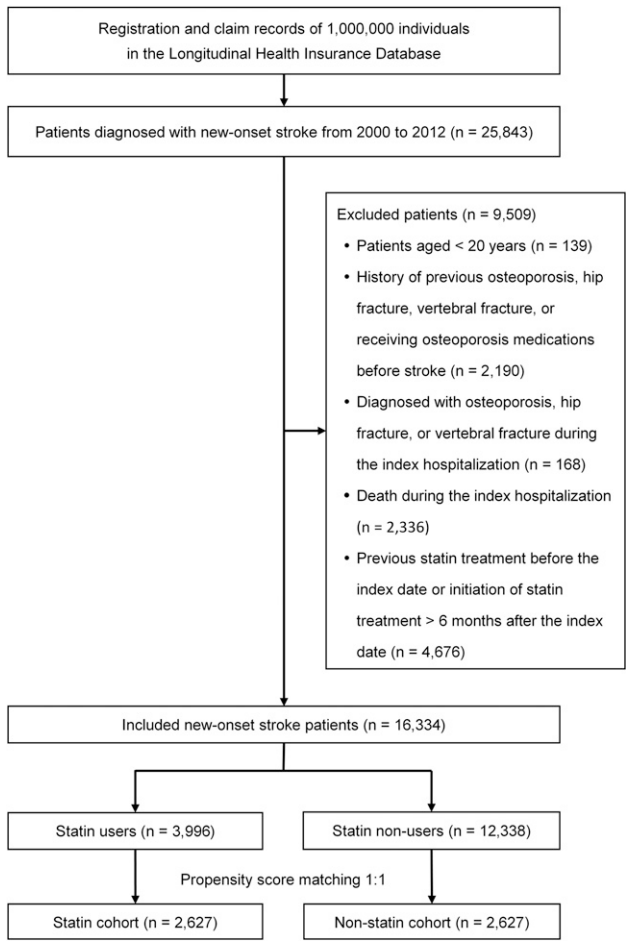

Figure 1. Study flow diagram.

treatment >6 months (180 days) after the index date was necessary to avoid selection bias.

Statin exposure

Statins are available only by prescription in Taiwan. We identified all prescriptions for statins (including atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, and pitavastatin) in the enrolled patients. The statin cohort included patients who had been prescribed statins after the index date (but <6 months after the index date). Those who did not receive any statin prescription after the index date were included in the nonstatin cohort (control cohort). To further evaluate the possible dose-effect relationship, we performed subanalyses after dividing the statin cohort into groups on the basis of cumulative defined daily doses (cDDDs) of statins. The statin cDDD was calculated as the sum of dispensed defined daily doses (DDDs) of all prescribed statins during the follow-up period and was used to establish three subgroups: 1 to 90, 91 to 365, and >365 cDDDs. The DDD methodology is widely used in studies investigating pharmacy claims data. According to the World Health Organization, the DDD is a unit that allows measurement of the average daily maintenance dose of a drug prescribed for its main indication in an adult (18).

Study outcomes

As described in our previous report (19), we defined the primary outcome as any new diagnosis of osteoporosis (*ICD-9-CM* diagnostic codes 733.0 and 733.1), hip fracture (820.x), or vertebral fracture (733.13, 805.x). The *ICD-9-CM* diagnostic code 806.x for vertebral fracture was not a primary outcome because this almost always represents a major traumatic injury rather than an osteoporosis-related fracture. In addition, to increase the diagnostic accuracy of a fracture event, only patients with a fracture diagnosis who underwent an imaging examination (X-ray examination, computed tomography, or magnetic resonance imaging) were included as fracture cases. All individuals were followed up from the index date to the development of the primary outcome, death, or 31 December 2013 (the last date of our study database). Death was defined as the date a patient was withdrawn from the Taiwan NHI program, a definition that has been validated as an accurate and reliable proxy for the date of death (20–22). In addition to evaluating the primary outcome, we analyzed the three diagnoses (osteoporosis, hip fracture, and vertebral fracture) separately. Analyses were also conducted after stratifying patients by age, sex, and stroke type (ischemic or hemorrhagic).

Covariates

Baseline characteristics and clinical details recorded as *ICD-9-CM*/procedure codes and medication prescription data were obtained from both outpatient and inpatient reimbursement claims for all subjects. Charlson comorbidity index scores were calculated on the basis of preexisting comorbidities and clinical conditions according to each patient's records (23). Preexisting comorbidity was defined as a disease diagnosed at least once as an inpatient or twice as an outpatient within the year before the index date. A baseline medication was defined as a drug prescribed for at least 30 days within the year before the index date. Baseline comorbidities and medications that we considered potential confounders are listed in Table 1.

Proxy variables of stroke severity were identified according to the clinical condition from index hospitalization records, including diagnosis codes for hemiplegia and aphasia and procedure codes for mechanical ventilation, intensive care unit utilization, and neurosurgery, to eliminate the possible confounding effect caused by differences in stroke severity. Moreover, we used a claims-based stroke severity index (SSI) score to estimate the National Institutes of Health Stroke Scale (NIHSS) for each stroke inpatient. The claims-based SSI was developed to estimate a patient's stroke severity using claims-based data from the NHIRD (24) and was validated by previous studies that showed it was highly correlated with the NIHSS and functional outcomes after stroke (24–26). We used the SSI score obtained for each stroke inpatient to calculate the patient's estimated NIHSS score, using the formula developed by Hsieh *et al.* (27) (estimated NIHSS = $1.1722 \times \text{SSI} - 0.7533$) to predict stroke severity and neurologic deficit.

We used income and housing urbanization levels to identify each patient's socioeconomic status. Income-related NHI premiums were used to determine income levels, which were categorized into four income brackets (New Taiwan dollars ≥40,000; 20,000 to 39,999; 1 to 19,999; and financially dependent). Housing urbanization levels were categorized into five groups, with level 1 indicating the most urbanized areas and level 5 the least (28). More detailed descriptions of our method for assessing income and urbanization levels were published previously (19).

Propensity score matching and sensitivity analyses

We minimized selection bias between the statin and nonstatin cohorts by conducting propensity score matching to balance all baseline characteristics listed in Table 1, including age, sex, income and urbanization levels, comorbidities, stroke severity proxies, and baseline medications. A propensity score that estimated the probability of receiving a statin prescription was calculated for each statin and nonstatin user using logistic regression models based on all covariates in Table 1. Each statin and nonstatin user pair was matched using a nearest-neighbor matching algorithm without replacement, with a caliper width equal to 0.2 of the SD of the logit of the propensity score (29). Although propensity score matching can help balance baseline characteristics, some subjects will be excluded because they cannot be matched to a suitable case or control. These exclusions may cause bias. Therefore, to confirm our study results, a sensitivity analysis (sensitivity analysis A) was conducted by including all eligible stroke patients and without matching procedures.

In addition, two more sensitivity analyses were performed to explore for evidence of selection bias. The first of these sensitivity analyses did not exclude patients with statin exposure before the index date, using propensity score matching and multivariate Cox proportional hazards regression models to control for previous statin exposure (sensitivity analysis B). The second of these analyses included patients for whom statin treatment was initiated within 12 months of the index date, as in the statin cohort (therefore including those for whom statins were prescribed >6 months after the index date), but excluding those in whom statin treatment was initiated at >12 months from the index date (sensitivity analysis C).

Statistical analysis

Continuous variables were compared using independent *t* tests, with categorical variables compared using a χ^2 test. Event-free rates were estimated using the Kaplan-Meier

Table 1. Baseline Characteristics of Stroke Patients According to Statin Use After Propensity Score Matching

	Statin Use		
	Yes (n = 2627)	No (n = 2627)	*P* Value
Demographic factors			
Age, y	66.5 ± 12.4	66.2 ± 13.6	0.381
Sex			0.572
Male	1581 (60.2%)	1601 (60.9%)	
Female	1046 (39.8%)	1026 (39.1%)	
Socioeconomic factors			
Income level (NTD)			0.043
Financially dependent	724 (27.6%)	681 (25.9%)	
1–19,999	1370 (52.2%)	1355 (51.6%)	
20,000–39,999	358 (13.6%)	364 (13.9%)	
≥40,000	175 (6.7%)	227 (8.6%)	
Urbanization level			0.834
1 (most urbanized)	653 (24.9%)	665 (25.3%)	
2	693 (26.4%)	716 (27.3%)	
3	483 (18.4%)	476 (18.1%)	
4	440 (16.7%)	412 (15.7%)	
5 (least urbanized)	358 (13.6%)	358 (13.6%)	
Comorbidities			
Charlson comorbidity index	2.5 ± 1.7	2.6 ± 1.8	0.106
Hypertension	1983 (75.5%)	2001 (76.2%)	0.562
Diabetes mellitus	978 (37.2%)	1067 (40.6%)	0.012
Coronary artery disease	538 (20.5%)	546 (20.8%)	0.785
Congestive heart failure	198 (7.5%)	193 (7.3%)	0.793
COPD	270 (10.3%)	285 (10.8%)	0.501
Cirrhosis	173 (6.6%)	168 (6.4%)	0.779
Chronic kidney disease	191 (7.3%)	218 (8.3%)	0.164
Hyperlipidemia	928 (35.3%)	949 (36.1%)	0.545
Thyroid dysfunction	27 (1.0%)	25 (1.0%)	0.780
Rheumatoid arthritis	17 (0.6%)	18 (0.7%)	0.865
Dementia	98 (3.7%)	86 (3.3%)	0.368
Depression	87 (3.3%)	74 (2.8%)	0.298
Parkinsonism	60 (2.3%)	54 (2.1%)	0.570
Epilepsy	34 (1.3%)	42 (1.6%)	0.355
Malignancy	121 (4.6%)	136 (5.2%)	0.337
Stroke type			0.664
Ischemic stroke	2332 (88.8%)	2322 (88.4%)	
Hemorrhagic stroke	295 (11.2%)	305 (11.6%)	
Stroke severity proxies			
Estimated NIHSS	7.5 ± 5.2	7.5 ± 5.3	0.732
ICU utilization	469 (17.9%)	488 (18.6%)	0.497
Mechanical ventilation	130 (4.9%)	144 (5.5%)	0.385
Hemiplegia	429 (16.3%)	425 (16.2%)	0.881
Aphasia	41 (1.6%)	38 (1.4%)	0.734
Neurosurgery	63 (2.4%)	76 (2.9%)	0.264
Baseline medication use			
Corticosteroids	143 (5.4%)	149 (5.7%)	0.718
Thiazide diuretics	400 (15.2%)	395 (15.0%)	0.847
Loop diuretics	180 (6.9%)	174 (6.6%)	0.741
NSAIDs	718 (27.3%)	704 (26.8%)	0.664
Antiepileptics	97 (3.7%)	110 (4.2%)	0.357
Antiparkinsonian	52 (2.0%)	51 (1.9%)	0.921
Antipsychotics	93 (3.5%)	77 (2.9%)	0.212
Anxiolytics	473 (18.0%)	469 (17.9%)	0.886
Hypnotics and sedatives	266 (10.1%)	289 (11.0%)	0.302
Antidepressants	136 (5.2%)	133 (5.1%)	0.851
Proton pump inhibitors	94 (3.6%)	96 (3.7%)	0.883
Estrogen	23 (0.9%)	21 (0.8%)	0.762
Thyroxine	19 (0.7%)	18 (0.7%)	0.869
Antithyroid drugs	5 (0.2%)	9 (0.3%)	0.284

Continuous data and categorical data are expressed as mean ± SD and number (%), respectively.

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NIHSS, National Institutes of Health Stroke Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan dollar.

method, and the differences between survival curves were compared by log-rank tests. Hazard ratios (HRs) and 95% CIs for developing outcomes (including any events and osteoporosis, hip fracture, and vertebral fracture, respectively) were calculated using univariate and multivariate Cox proportional hazards regression models. The multivariate Cox proportional hazards regression models were performed after adjusting for all covariates listed in Table 1. We also corrected for the immortal time when calculating incidence rates and HRs for the comparison between the statin and nonstatin groups (30). To control for immortal time, we conducted a time-dependent analysis in which we classified the follow-up time as untreated (nonuser) until the statin use definition was met and as treated (statin user) thereafter. The detailed methods used for the correction of the immortal time bias have been previously described (30). Moreover, to eliminate the possible confounding effect caused by competing mortality, the Cox proportional hazards regression models were conducted with the addition of competing risk events (competing mortality) (31). Results with a two-sided probability value of <0.05 were considered statistically significant. Statistical analyses were performed using Stata version 13 (Stata Corporation, College Station, TX).

Results

Patient characteristics

We initially identified 25,843 patients with a new-onset stroke in our study population. After application of our exclusion criteria, 16,334 were enrolled for propensity score matching (statin cohort, 3996; nonstatin cohort, 12,338) (Fig. 1). After propensity score matching, 5254 patients were included, with 2627 patients each in the statin and nonstatin cohorts. The statin and nonstatin cohorts had significant differences in many baseline characteristics before matching (Supplemental Table 1). After propensity score matching, almost all covariates were balanced (Table 1).

Risk of osteoporosis, hip fracture, and vertebral fracture

During the mean follow-up period of 4.2 years, 390 patients in the statin cohort and 535 in the nonstatin cohort developed a hip or vertebral fracture or osteoporosis after their stroke (Table 2). Kaplan-Meier curves revealed a lower cumulative incidence of any event (osteoporosis, hip fracture, or vertebral fracture) in the statin cohort than in the nonstatin cohort (35.1 *vs* 48.0 per 1000 person-years, respectively; log-rank test, $P < 0.001$) (Fig. 2a). Overall, statin use after a stroke was associated with a lower risk of developing osteoporosis, hip fracture, or vertebral fracture in both univariate (crude HR = 0.72; 95% CI = 0.63 to 0.82; $P < 0.001$) and multivariate Cox proportional hazards regression models (adjusted hazard ratio [aHR] = 0.66; 95% CI = 0.58 to 0.76; $P < 0.001$) (Table 2).

In subanalyses for each event, statin use was associated with a decreased risk of osteoporosis (aHR = 0.68; 95% CI = 0.58 to 0.79; $P < 0.001$), hip fracture (aHR = 0.59; 95% CI = 0.47 to 0.75; $P < 0.001$), and vertebral fracture (aHR = 0.73; 95% CI = 0.60 to 0.90; $P = 0.003$) (Table 2). The osteoporosis, hip fracture, and vertebral fracture event-free survival curves are shown in Fig. 2b, 2c, and 2d, respectively.

Analyses of the dose-effect relationship based on statin cDDD

Our subanalyses of the association between the statin cDDD and primary outcomes identified a dose-effect relationship between statin use and the risk of developing any event (osteoporosis, hip fracture, or vertebral fracture). In patients with 1 to 90 cDDDs of statins, the aHR was 0.96 (95% CI = 0.81 to 1.15; $P = 0.688$); in those with 91 to 365 cDDDs, the aHR was 0.86 (95% CI = 0.71 to 1.03; $P = 0.109$); and in those with >365 cDDDs, the aHR was 0.34 (95% CI = 0.27 to 0.43; $P < 0.001$) (Table 3).

The event subanalyses also revealed a dose-effect relationship, and as the statin cDDD increased, the risks of osteoporosis, hip fracture, and vertebral fracture decreased. The estimated aHRs for osteoporosis risk were 0.95, 0.87, and 0.35; for hip fracture risk, 0.85, 0.79, and 0.26; and for vertebral fracture risk, 0.90, 0.97, and 0.45 in each statin cDDD stratum (1 to 90, 91 to 365, and >365 cDDDs), respectively (Table 3).

Analyses stratified by age, sex, and stroke type

The association between statin use and decreased risk of osteoporosis, hip fracture, and vertebral fracture was retained on subgroup analyses stratified by age, sex and stroke type, including young patients, old patients, males, females, and ischemic stroke patients; however, this association was not statistically significant for patients who had sustained a hemorrhagic stroke. A dose-effect relationship was also identified, with an increase in statin cDDD being associated with decreased risk of osteoporosis, hip fracture, and vertebral fracture (Table 4). Of note, although the association between statin use and decrease in the risk of osteoporosis and fractures did not reach statistical significance among patients with hemorrhagic stroke (most likely because of an insufficient number of cases in this category), a similar trend for dose-effect relationship was observed (Table 4).

Results of sensitivity analyses

Sensitivity analysis A without propensity score matching revealed a similar association between statin

Table 2. Osteoporosis, Hip Fracture, and Vertebral Fracture Risks in Stroke Patients According to Statin Use

			Univariate Model		Multivariate Model[b]	
	Events	Incidence Rate[a]	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Any event[c]						
Nonusers	535	48.0	1 (ref.)		1 (ref.)	
Statin users	390	35.1	0.72 (0.63–0.82)	<0.001	0.66 (0.58–0.76)	<0.001
Osteoporosis						
Nonusers	371	31.6	1 (ref.)		1 (ref.)	
Statin users	277	24.1	0.75 (0.64–0.88)	<0.001	0.68 (0.58–0.79)	<0.001
Hip fracture						
Nonusers	195	15.1	1 (ref.)		1 (ref.)	
Statin users	114	9.4	0.62 (0.49–0.78)	<0.001	0.59 (0.47–0.75)	<0.001
Vertebral fracture						
Nonusers	219	17.3	1 (ref.)		1 (ref.)	
Statin users	162	13.5	0.78 (0.63–0.95)	0.012	0.73 (0.60–0.90)	0.003

We included 2627 statin users and 2627 statin nonusers after propensity score matching.

Abbreviation: ref., reference.

[a]Per 1000 person-years.

[b]Multivariate Cox proportional hazards regression model with adjustment for all baseline characteristics listed in Table 1 and competing mortality.

[c]Any event was defined as developing any of the following: osteoporosis, hip fracture, or vertebral fracture.

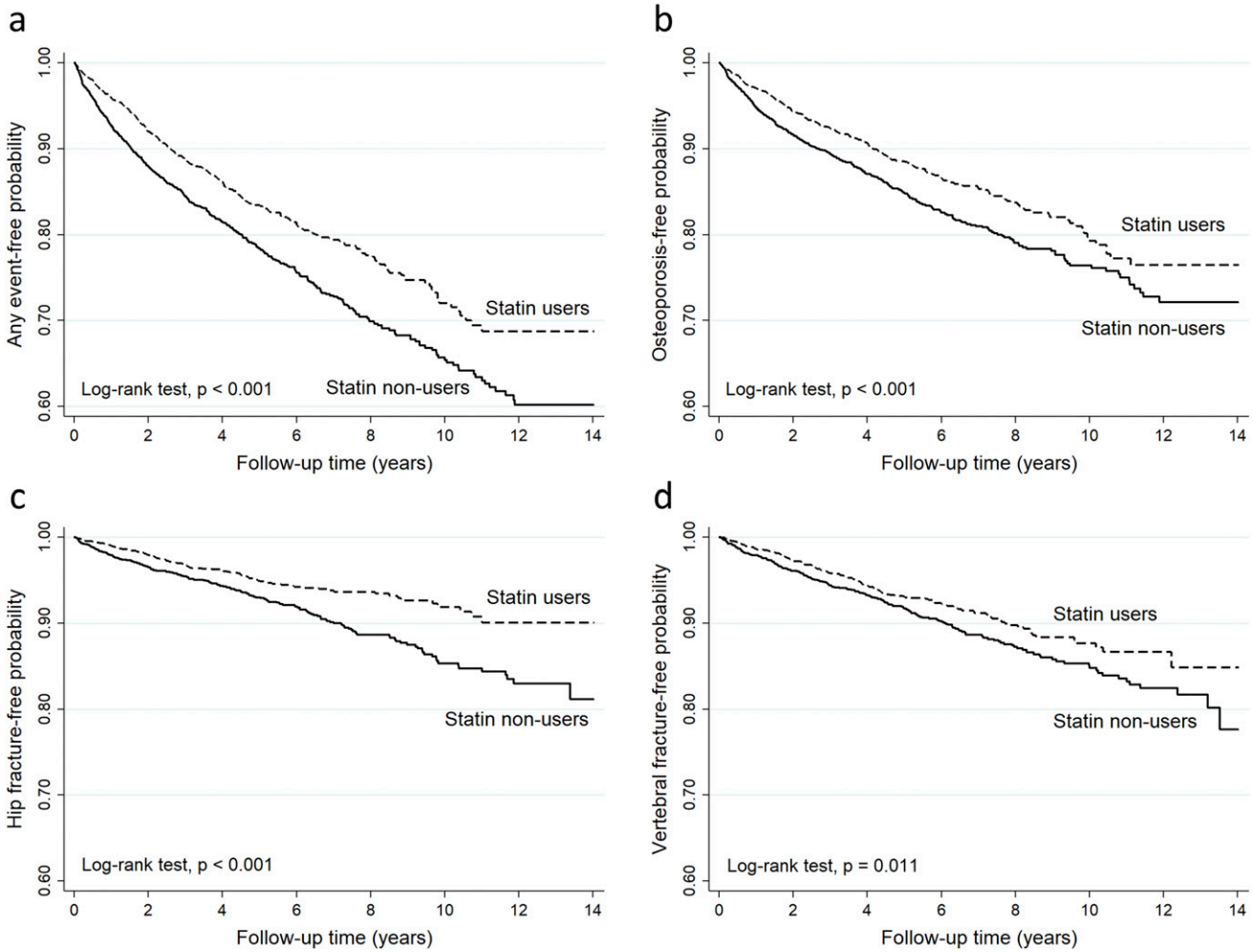

Figure 2. Kaplan-Meier curves comparing the estimated event-free probability in statin users and nonusers after a stroke for (a) any primary event diagnosis (osteoporosis, hip fracture, or vertebral fracture); (b) osteoporosis; (c) hip fracture; and (d) vertebral fracture.

use and decreased risk of osteoporosis or fractures (aHR = 0.71; 95% CI = 0.64 to 0.80; $P < 0.001$) (Supplemental Table 2). The previously identified trends were maintained for each individual event, including the dose-effect relationship (Supplemental Tables 2 and 3). Sensitivity analysis B, which did not exclude patients with previous statin exposure before the index date, and sensitivity analysis C, which included all patients who initiated statin treatment <12 months after the index date, confirmed the previous trends, including the dose-effect relationship. The detailed results for sensitivity analyses B and C are presented in Supplemental Table 4.

Discussion

In this population-based, propensity-matched cohort study, we found that statin use was associated with decreased risks of osteoporosis, hip fracture, and vertebral fracture in stroke patients. Moreover, a dose-effect relationship was observed between statin cDDD and decreased risks of osteoporosis and fractures.

Previous studies demonstrated that osteoporosis and consequent fractures after a stroke could interfere with functional recovery and increase morbidity, mortality, and the socioeconomic costs of poststroke care (5, 7–9, 32, 33). Numerous studies have identified osteoporosis and bone fracture risk factors and prevention strategies in stroke survivors (5, 33, 34). However, to our knowledge, the potential of statin treatment in preventing osteoporosis and fracture has not been previously reported in this clinical population, and the current large-scale investigation addresses this knowledge gap. The public health implications of our findings could be substantial because of the high incidence and prevalence of stroke, osteoporosis, and bone fractures.

Our study results were consistent with those of several previous studies that focused on general populations (13, 14). A recent meta-analysis that included clinical trials and observational studies indicated that statin use was significantly associated with increased BMD and a decreased risk of hip fracture, with an OR of 0.75 for statin users compared with nonusers. A tendency toward a

Table 3. Osteoporosis, Hip Fracture, and Vertebral Fracture Risks in Stroke Patients According to Cumulative Statin Doses

			Univariate Model		Multivariate Model[b]	
	Events	Incidence Rate[a]	Crude HR[c] (95% CI)	*P* Value	Adjusted HR[c] (95% CI)	*P* Value
Any event[d]						
1–90 cDDDs	163	57.6	1.16 (0.97–1.38)	0.106	0.96 (0.81–1.15)	0.688
91–365 cDDDs	142	47.6	0.95 (0.79–1.14)	0.588	0.86 (0.71–1.03)	0.109
>365 cDDDs	85	16.0	0.34 (0.27–0.43)	<0.001	0.34 (0.27–0.43)	<0.001
Osteoporosis						
1–90 cDDDs	117	39.2	1.19 (0.97–1.47)	0.098	0.95 (0.77–1.17)	0.619
91–365 cDDDs	103	33.2	1.00 (0.80–1.24)	0.995	0.87 (0.70–1.08)	0.212
>365 cDDDs	57	10.6	0.34 (0.26–0.45)	<0.001	0.35 (0.26–0.46)	<0.001
Hip fracture						
1–90 cDDDs	51	15.4	1.01 (0.74–1.37)	0.970	0.85 (0.62–1.16)	0.299
91–365 cDDDs	43	12.9	0.84 (0.60–1.16)	0.287	0.79 (0.56–1.10)	0.157
>365 cDDDs	20	3.6	0.24 (0.15–0.38)	<0.001	0.26 (0.16–0.41)	<0.001
Vertebral fracture						
1–90 cDDDs	60	18.4	1.05 (0.79–1.40)	0.721	0.90 (0.67–1.20)	0.473
91–365 cDDDs	61	18.6	1.07 (0.80–1.42)	0.655	0.97 (0.73–1.30)	0.847
>365 cDDDs	41	7.5	0.44 (0.31–0.61)	<0.001	0.45 (0.32–0.63)	<0.001

Statin cDDDs groups: 1–90, n = 852; 91–365, n = 831; >365, n = 944.

[a]Per 1000 person-y.

[b]Multivariate Cox proportional hazards regression model with adjustment for all baseline characteristics listed in Table 1 and competing mortality.

[c]The HR of each cDDD category was calculated using statin nonusers as reference.

[d]Any event was defined as developing any of the following: osteoporosis, hip fracture, or vertebral fracture.

reduced risk of vertebral fracture (OR = 0.81) was also reported, but this trend was not significant (13). Another meta-analysis also reported a significant association between statin use and decreased risk of overall fracture, with an OR of 0.80 (14). Our study, which specifically focused on stroke patients, revealed compatible but more significant results, with ~30% to 40% decreased risk of osteoporosis, hip fracture, and vertebral fracture with statin use. We also identified a dose-effect relationship between this risk and the use of statins. Differences in results between studies may be explained by the characteristics of our study population, including a much higher risk for osteoporosis and fracture than that of the general population. This increased vulnerability could have caused the effects of statins to be much more significant in our cohort than in other study populations. On the other hand, another recent meta-analysis that included only clinical trials reported that although increased BMD was associated with statin use, there was no significant association between statin use and fracture risk (15). However, this meta-analysis included only two clinical trials that evaluated fracture risk, and neither performed an analysis in stroke patients (35, 36).

In our subanalyses for different statin cumulative doses, only patients with high cDDDs of statin had a significant reduction in the risk of osteoporosis and fractures; the effect was not significant for the remaining two lower cDDD categories. These findings can be explained by the fact that it takes substantial doses/duration of statin use to observe its possible effects on the related risk of osteoporosis/fractures. Improvement in BMD and bone health involves a long-term, continuous process and thus theoretically cannot be rapidly achieved by insufficient statin exposure via the possible underlying mechanism described in the following text.

The mechanisms underlying the possible association between statins and osteoporosis and fracture risks have not yet been clarified (13). Previous studies identified some pathways through which statins may influence bone metabolism (11, 37). Statins can upregulate bone morphogenetic protein-2 through the ras/phosphoinositide 3-kinase/protein kinase B/mitogen-activated protein kinase signaling pathway, and this upregulation further increases runt-related transcription factor 2 expression and induces osteoblast differentiation (11, 37). Osteoblast differentiation and proliferation can also be enhanced by statins through the inhibition of farnesyl pyrophosphate and geranylgeranyl pyrophosphate synthesis. In addition, statins protect osteoblasts from apoptosis by regulating the transforming growth factor-β/SMAD3 signaling pathway. Moreover, statins can suppress osteoclastogenesis via the osteoprotegerin/receptor activator of nuclear factor κB ligand/receptor activator of nuclear factor κB signaling pathway by stimulating estrogen receptor-α expression (11, 13, 37). These mechanisms can increase new bone formation (11). Further, they could contribute

Table 4. Osteoporosis, Hip Fracture, and Vertebral Fracture Risks According to Cumulative Statin Doses in Stroke Patients Stratified by Age, Sex, and Stroke Type

	Univariate Model		Multivariate Model[a]	
	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age <65 y				
Nonusers	1 (ref.)		1 (ref.)	
All statin users	0.57 (0.43–0.74)	<0.001	0.55 (0.42–0.72)	<0.001
1–90 cDDDs	1.05 (0.72–1.52)	0.798	1.02 (0.69–1.49)	0.934
91–365 cDDDs	0.68 (0.45–1.03)	0.069	0.68 (0.44–1.04)	0.074
>365 cDDDs	0.31 (0.20–0.47)	<0.001	0.29 (0.19–0.45)	<0.001
Age ≥65 y				
Nonusers	1 (ref.)		1 (ref.)	
All statin users	0.75 (0.65–0.88)	<0.001	0.70 (0.60–0.82)	<0.001
1–90 cDDDs	1.08 (0.89–1.32)	0.437	0.97 (0.79–1.19)	0.766
91–365 cDDDs	0.99 (0.80–1.22)	0.926	0.91 (0.74–1.13)	0.409
>365 cDDDs	0.36 (0.28–0.47)	<0.001	0.35 (0.27–0.46)	<0.001
Male				
Nonusers	1 (ref.)		1 (ref.)	
All statin users	0.67 (0.55–0.83)	<0.001	0.64 (0.52–0.79)	<0.001
1–90 cDDDs	1.16 (0.88–1.53)	0.299	0.99 (0.74–1.32)	0.936
91–365 cDDDs	0.89 (0.66–1.21)	0.462	0.86 (0.63–1.16)	0.323
>365 cDDDs	0.29 (0.20–0.42)	<0.001	0.29 (0.20–0.43)	<0.001
Female				
Nonusers	1 (ref.)		1 (ref.)	
All statin users	0.73 (0.62–0.86)	<0.001	0.66 (0.55–0.78)	<0.001
1–90 cDDDs	1.11 (0.88–1.39)	0.376	0.93 (0.74–1.18)	0.574
91–365 cDDDs	0.94 (0.74–1.19)	0.621	0.84 (0.66–1.07)	0.159
>365 cDDDs	0.37 (0.28–0.49)	<0.001	0.36 (0.27–0.47)	<0.001
Ischemic stroke				
Nonusers	1 (ref.)		1 (ref.)	
All statin users	0.71 (0.62–0.82)	<0.001	0.66 (0.58–0.76)	<0.001
1–90 cDDDs	1.14 (0.95–1.37)	0.150	0.97 (0.80–1.17)	0.731
91–365 cDDDs	0.96 (0.79–1.16)	0.668	0.88 (0.72–1.07)	0.184
>365 cDDDs	0.33 (0.26–0.42)	<0.001	0.33 (0.26–0.42)	<0.001
Hemorrhagic stroke				
Nonusers	1 (ref.)		1 (ref.)	
All statin users	0.80 (0.50–1.28)	0.349	0.74 (0.43–1.27)	0.274
1–90 cDDDs	1.31 (0.70–2.46)	0.399	1.16 (0.56–2.42)	0.686
91–365 cDDDs	0.95 (0.50–1.81)	0.871	0.82 (0.38–1.78)	0.618
>365 cDDDs	0.40 (0.18–0.90)	0.027	0.43 (0.17–1.03)	0.058

Abbreviation: ref., reference.

[a]Multivariate Cox proportional hazards regression model with adjustment for all baseline characteristics listed in Table 1 and competing mortality.

to the decreased risk of developing osteoporosis and subsequent bone fracture observed in this study in stroke patients receiving statins.

The main strength of our study is its nationwide population-based design, large sample size, and sufficient follow-up period. Similar results revealed in sensitivity analyses further strengthen our findings. Nevertheless, some limitations should be addressed. First, some clinical data were not present in the LHID, such as lifestyle factors and physical, psychiatric, and laboratory examination reports (*e.g.*, calcium and vitamin D levels). These might be confounding factors of the measured study outcomes. Although our study included propensity score matching, sensitivity analyses without matching, and multivariate Cox proportional hazards regression models adjusting for many confounding factors and competing mortality to eliminate possible confounding effects, bias related to unknown or unmeasured confounders might exist in this nonrandomized observational study. Second, because we used de-identified claims as our data set, it was not possible to include medical details of the fracture, such as the mechanism of injury or resulting symptoms (*e.g.*, numbness and back pain). As such, we could not determine whether a fracture event resulted from a low-trauma injury or whether a vertebral fracture was a clinical vertebral fracture. Further research is required to evaluate these issues. Third, we analyzed outcomes using cDDDs to represent cumulative overall statin exposure, and so the effects of different types or potencies of statins were not assessed or compared. Further studies are necessary to evaluate this issue specifically. Fourth, because the National Health Research Institute encrypted all

personal identifiers before releasing the database, it was impossible to confirm the accuracy of any diagnosis by direct patient evaluation. However, only patients who were hospitalized with a principal diagnosis of stroke were included, and the accuracy of the diagnostic code for stroke was validated in previous studies (38–40). Further, the accuracy of the diagnostic codes for hip and vertebral fractures were also previously validated in both inpatients and outpatients (41). Moreover, hospitals and doctors in Taiwan are heavily fined for incorrect diagnoses and coding errors. Thus, the diagnostic validity in this study can be considered satisfactory.

In summary, this population-based, propensity-matched cohort study revealed that statin use was associated with a decreased risk of osteoporosis, hip fracture, and vertebral fracture in stroke patients, with a dose-effect relationship observed. Further prospective clinical trials are needed to confirm our findings.

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