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Assessment of statin-associated severe muscle toxicity in Japan: A cohort study by using a claims database and laboratory information

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ABSTRACT

Objective:

To evaluate whether the use of specific statins or concomitant use of interacting drugs is associated with an increased incidence of severe muscle toxicity in patients receiving statin therapy

Design:

Retrospective cohort study

Setting:

Sixteen medical facilities in Japan providing information on laboratory tests performed in, and claims received by, their facilities between 1 April 2004 and 31 December 2010

Participants:

A database representing a cohort of 35,903 adult statin (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) users was studied. Use of interacting drugs (fibrates, triazoles, macrolides, amiodarone, and ciclosporin) by these patients was determined.

Main outcome measure:

Severe muscle toxicity ('event') was identified by a diagnosis of muscle-related disorders and/or creatine kinase (CK) concentrations 10 times greater than the normal

upper limit. Events were excluded if patients had CK elevation-related conditions other than severe muscle toxicity. Incidence rates for severe muscle toxicity were determined per 1,000 person-years, with 95% confidence intervals (CI) determined by Poisson regression.

Results:

A total of 18,036 patients contributed 42,193 person-years of statin therapy, and 43 events were identified. Incidence of severe muscle toxicity in patients treated with statins ranged from 0.45 (95% CI, 0.19–1.08) with pravastatin to 1.73 (95% CI, 1.04–2.87) with rosuvastatin per 1,000 person-years. On using atorvastatin users as a reference, we found that there were no significant differences between statins with respect to incidence of severe muscle toxicity; 2,430 (13.5%) of the patients treated with statins received interacting drugs during their follow-up period. As a result of low numbers of events and of person-years of receiving interacting drugs, the 95% CI (wide) included the estimated incidence rate.

Conclusions:

This database study suggested that statin use is generally well tolerated and safe; however, the risk of severe muscle toxicity related to the use of interacting drugs requires further exploration.

ARTICLE SUMMARY

Article focus

- Asian populations are more sensitive to statins' clinical response than Western populations.
- Our objective was to evaluate the risk of severe muscle toxicity associated with statin and/or interacting drug use, by using claims database and laboratory information in Japan.

Key messages

- Patients receiving prescription statins were most often prescribed the lower limits of approved dosages, with rare concomitant use of interacting drugs that could increase steady-state statin concentrations.
- The number of adverse events was limited; the incidence of severe muscle toxicity was statistically indistinguishable among statins.
- This study has major implications for risk evaluation, given the information infrastructure available to validate claims-based estimations.

Strengths and limitations of this study

- This study is the first study to evaluate drug-associated risk by using claims database and laboratory information in Japan, indicating the potential applicability of electronic health information as a resource for applied analyses.
- Interacting drug use associated with increased risk of muscle toxicity requires further exploration because a low number of person-years of observations currently exists in the literature. Diagnostic information is slightly less complete than is prescription and laboratory test information; researchers should use caution when interpreting related information in database studies.

INTRODUCTION

Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor or HMG-CoA reductase inhibitor) are widely used for adults presenting with cardiovascular disease (CVD), and those with a 20% or greater 10-year risk of developing CVD,[1] to reduce the incidence of cardiovascular co-morbidity and mortality. Although statins are well-tolerated by the vast majority of patients, their use can lead to infrequent adverse muscle, renal, and hepatic events.[2, 3] Severe adverse events could lead to additional drug costs, increasing the burden of healthcare expenditures.[4] In addition, the concomitant use of interacting drugs could increase the risk of muscle toxicity.[5] The Asian population is more sensitive in its clinical response to statins than is the Western population. Therefore, the recommended doses of statin drugs are lower in Japan than those approved in Western countries.[6-8]

Clinical trials are restricted in the number and diversity of participants enrolled, such that the chances of detecting rare, adverse treatment effects are low. Regulatory bodies, including those in Japan, have long relied primarily on the voluntary reporting system to monitor post-marketing safety. In addition to voluntary reporting, which does not accurately reflect risk due to under-reporting, a major challenge for assessing the safety of statin use is a lack of comparative data. Given concerns about the

limitations of existing monitoring systems, the use of automatic databases such as claims or electronic healthcare records for post-marketing safety assessment has been well-structured and widely applied in the US and EU.[9, 10] Recently, the Sentinel System was launched by the US Food and Drug Administration (FDA) to develop active surveillance capabilities for evaluating post-market safety issues in regulated medical products.[11] In Japan, in order to complement this strategy for safety assessment, the Medical Information of Risk Assessment Initiative (MIHARI project) was launched by the Pharmaceutical and Medical Devices Agency (PMDA) in 2009. The MIHARI project aggregates electronic medical information with appropriate methodologies for risk evaluation, and ensures the accessibility and applicability of claims databases and electronic healthcare records for use.[12] The Japanese national claims database has been accessible to researchers by a peer-reviewed proposal process, beginning in April 2011.[13] In retrospective studies, a health outcome is defined by criteria that are restricted by the structure of a given database. Different definitions for explaining a certain adverse event could result in different conclusions. Before researchers and regulators begin working with the large automatic database in Japan, this database could be subjected to a pilot study to assess the applicability of electronic healthcare information for investigative research.

In early 2012, the FDA issued labelling changes for statin drugs based on updated safety information.[14] Administrative databases may be useful for identifying potential problems, such as assessment of risk factors and incidence of adverse treatment effects. Our study evaluated the rare adverse event of statin-associated muscle toxicity (e.g. myopathy or rhabdomyolysis), defined by two criteria, using the claims database with laboratory information.

METHODS AND ANALYSIS

Data resource

This retrospective cohort study analysed data from Medical Data Vision Co. Ltd. (MDV) in Tokyo, Japan. This commercial, electronic, record-based healthcare database provides information on ambulatory service, hospitalization, medication use, and laboratory tests for patients from 1 January 2004 through 31 December 2010. It contains the patients' demographic characteristics (e.g. age, sex), diagnoses (International Statistical Classification of Disease and Related Health Problems (ICD–10 codes)), prescription information (dose, quantity, and number of days of supply), and the results of laboratory tests for approximately 410,000 patients at 16 medical facilities across Japan.[15] Patients' identities have been encrypted for protection of privacy, but the data sets could be linked using unique, anonymous identifiers created by the data providers for research purposes. This study was approved by the Institutional Review Board at Meiji Pharmaceutical University and was conducted in compliance with the Japanese Ethical Guidelines for Epidemiological Research, updated in December 2008.[16]

Study cohort

Patients aged 18 or older that initiated statin therapy between 1 July 2004 and 30 June 2010 were included in this study. Statin initiation was defined for this cohort as no existing claim of statin prescription within three months after the first date of any claims. To be eligible for the study, new statin users were required to have undergone at least one blood test during statin therapy, for avoidance of information bias. To ensure the validity of information available for individuals undergoing statin therapy, the consistency between dyslipidaemia diagnoses (ICD-10 code E78) and laboratory results of cholesterol, triglyceride, and low-density lipoprotein (LDL) was determined.

Exposure of interest

The information on statin therapy was extracted from the claims database, and exposure time was estimated for each patient based on the amount of statin continuously received by the patient, reported as person-years. The statins commercially available in Japan during the investigation period were atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. The prescribing dosage was defined as the sum of prescribed doses divided by exposure time. Because medications might be changed or added for treatment purposes, patients were allowed to contribute to multiple cohorts. Exposure to interacting drugs that may cause muscle toxicity was analysed, excluding topical and ophthalmic preparations. Lists of potentially interacting drugs were compiled from package inserts for statin medications.[17] We determined whether patients had used any of the following interacting drugs while undergoing statin therapy: benzafibrate, fenofibrate, clinofibrate, clarithromycin, erythromycin, telithromycin, fluconazole, itraconazole, fosfluconazole, voriconazole cyclosporine, amiodarone, saquinavir/ritonavir, atazanavir, etraririne, and efavirenz.

Case identification

Previous studies generally defined severe muscle toxicity by diagnosis and/or by elevated creatine kinase (CK) concentration.[18, 19] Given concerns that the infrastructure of the database might restrict the presentation of information, the identification of severe muscle toxicity was conducted by using these two criteria separately. Criterion A was based on diagnosis of muscle-related disorders. Because there is no specific ICD-10 code to indicate severe muscle toxicity, the diagnosis contained the words 'myositis' or 'rhabdomyolysis', which were originally written in the Japanese language and were identified using a computer-assisted text searching method (FINDW function in SAS). Criterion B was based on laboratory results. A patient whose CK concentration was greater than ten times the upper limit of the normal range under statin therapy would be identified as a case. The normal range was given according to the sensitivity of the reference agents used in laboratory tests at each medical facility. The case was recognized as an event if no disease-related condition accompanied by CK elevation was confirmed. The disease-related conditions for CK elevation were as follows: any presence of diagnosis for myocardial infarction, myocarditis, trauma, or hypothyroidism, and any claim of nitrate and levothyroxine prescriptions being obtained within three days after the muscle toxicity event.[20] Statin therapy might be discontinued upon development of intolerable muscle symptoms, with or without CK elevation, in patients for whom other aetiologies were ruled out.[20] Physicians' management decisions about continuation or discontinuation of treatment were determined by compiling claims from patients' health records. Discontinuation was defined as no use of statin therapy in the six months following occurrence of muscle toxicity.

Statistical analyses

The incidence rate for severe muscle toxicity was presented per 1,000 person-years with 95% confidence intervals (CI) estimated by Poisson regression. The baseline period was defined as 180 days prior to statin initiation. Demographic (age, gender) and co-administration data were extracted from medical claims from the baseline period within the statin inception cohort. In addition to claims data, we identified the presence of co-morbidities from laboratory information for the baseline period. Renal impairment was defined by serum creatine concentrations (SCr) above the upper limit of the normal range; the hepatic impairment was indicated where laboratory values for alanine transaminase (ALT) and aspartate transaminase (APT) increased by more than three times the upper limit of normal during the baseline period. The cut-off of glycated haemoglobin (HbA1c) level for diabetes mellitus was set at greater than 6.1%, according to diagnostic criteria adopted in Japan.[21] To compare the characteristics of demographic and clinical variables between criteria, Kolmogorov-Smirnov tests were performed for continuous variables, and chi-square tests were used for dichotomous variables. Co-morbidity and co-administration of drugs were defined according to whether claims of a prescription were made prior to 180 days before occurrence of an event. In addition, to determine the muscle toxicity risk associated with drug-drug interactions, the incidence of muscle toxicity among patients that had concomitantly used interacting drugs was compared with those who did not. All statistical analyses were carried out using SAS software Version 9.3 (SAS Institute Inc., 2012, Cary NC, USA).

RESULTS

A total of 18,036 patients met all the criteria to be defined as new statin users (Figure 1). Of these patients, 11,468 (64%) were diagnosed as having dyslipidaemia, 14,355 (80%) had higher than normal levels of cholesterol, triglyceride or low-density lipoprotein, and 9,382 (52%) were diagnosed as having dyslipidaemia accompanied by higher than normal lipid levels. The mean (SD) age and follow-up month of patients in whom statin use was initiated were 66 (12) years and 29 (22) months, and 55% of patients were female. Atorvastatin was the most prevalent HMG-CoA reductase inhibitor and contributed to 37% of the total person-years in the inception cohort. The prescribed dosage was generally around the lower limit of the approved dose, with limited variation, regardless of the statin (Table 1).

Among new statin users, 43 cases (0.24%) were identified, of which 27, 20, and 4 cases were identified by criterion A, criterion B, and both A and B respectively. The proportion of discontinuation was similar among criteria A and B, where 7 and 6 cases of statin discontinuation were recorded respectively after occurrence of an event. Among them, 4 and 5 cases were hospitalized. Incidence (with 95% CI) of severe muscle toxicity in patients treated with statin monotherapy ranged from 0.45 (0.19–1.08) with pravastatin to 1.73 (1.04–2.87) with rosuvastatin per 1,000 person-years, with the summary risk estimate of 1.02 (0.76–1.37) per 1,000 person-years of use. Using atorvastatin – the most widely prescribed statin in Japan – as the reference, incidences of severe muscle toxicity were statistically indistinguishable among the statins, regardless of the criterion used (Table 2). Similarly, demographic and other characteristics of the cases did not differ for the two criteria (Table 3).

Of new statin users, 2,430 (13.5%) received interacting drugs during the follow-up period. Regarding the incidence rate of muscle toxicity with respect to interacting drug use, a low number of person-years of observation were contributed, representing limited use of interacting drugs, even when all statins and interacting drugs were aggregated. Because of the low number of events recorded, we found the wide 95% CI included the estimated incidence rate (Table 4).

DISCUSSION

This study extends previous work in measuring statin-associated severe muscle toxicity by using the claims database with laboratory information for actual patient records in Japan. Since the package insert suggests periodical laboratory tests during statin therapy, it is possible to assess the change of medical condition. With an estimated incidence of approximately 1 per 1,000 person-years of statin use, a low occurrence of severe muscle toxicity was found in the present study. Moreover, less than about one in five patients was found to have concomitant use of interacting drugs, implying that the use of statins is generally well tolerated and safe in Japan. The characteristics and incidences of severe muscle toxicity between statins were not significantly different. In addition, co-morbidity and co-administration occurred in similar proportions among cases defined by diagnosis and cases defined by laboratory results. However, the number of diagnoses of dyslipidaemia was slightly lower than the number of cases with concurrent elevated lipid levels, indicating an inconsistency between diagnosis and laboratory data.

Information on the incidence (% of users) of severe muscle toxicity is not provided in Japanese statin medication package inserts, with the exceptions of rosuvastatin (0.1%) and simvastatin (0.01%). The lower limit of the 95% confidence interval showed a value consistent with available package inserts; however, it is possible that adverse events would occur more frequently with widespread use of statins in clinical practice, because populations that participate in clinical trials are usually highly selected.[22] Comparing our analysis to statistics reported in previous studies (mostly from the US), the crude incidence of rhabdomyolysis ranged from 2.5 to 4.4 per 100,000 person-years among statin users, when identified by diagnosis and laboratory results combined.[18, 19] Since it is not applicable to compare the incidence of events defined by different parameters, we refined our event definition to take statin discontinuation after occurrence of an adverse event into consideration. Upon doing so, we found the crude incidence of rhabdomyolysis to be 7.1 per 100,000 person-years (3 cases per 42,193 person-years), suggesting a moderately high incidence in the present study. The incidence of rhabdomyolysis might differ among studies because the proportion of patients with risk factors is apparently different between the populations. Some case reports indicated that factors related to statin-associated severe muscle toxicity included older age, female gender, low body mass index, and diabetes mellitus,[23] characteristics that were common among patients in our study. However, evidence showed no increased rate of adverse events in Asian patients taking either lower or higher doses of statin,[24] despite racial differences in the pharmacokinetics of rosuvastatin between Asians and Caucasian.[25] After all the controversy over racial differences in pharmacokinetics and the clinical outcomes of statin (particularly rosuvastatin) use, the majority of prescribed doses were at the lower limits of approved dosage levels. Taking dosage levels into account, statins were well tolerated in the Japanese population, with a similar incidence of rhabdomyolysis as reported from Caucasian populations.

Using the claims database to evaluate potential drug interactions with statins is a useful complement to the limited information available from voluntary reports and clinical trials. A recent study found that the use of against label statin-fibrate combination therapy is decreasing annually, but that use of this therapy still persists in the US.[26] In the present study, only 2.8% of patients had been prescribed concomitant statin-fibrate therapy (data not shown). Although combination therapy may be attractive for patients with lipid disorders and without muscle complaints, the low prevalence of concomitant fibrate use implies that it is “generally contraindicated,” and that clinical practitioners are aware of the risks. Whether the risk is due to drug interactions remains controversial,[27, 28] but our study points to a higher incidence of severe muscle toxicity among patients taking interacting drugs. However, a low number of person-years of interacting drug use observations corresponded to a lack of statistical significance; this low prevalence of concomitant drug use might reduce the detection of severe muscle toxicity in current practice.

Our findings showed that the incidence of severe muscle toxicity varied according to the definition of an adverse event, suggesting that the infrastructure in which information is stored might greatly affect assessments of safe medical practice. The majority of cases with discontinuation of statin resulted in hospitalization. However, the outcome from severe muscle toxicity could not be ascertained since there is no information of death record in the database. Although diagnostic-based measures are inherently limited by weaknesses of administrative claims diagnostic data, including inaccuracy and incompleteness of discharge diagnoses,[29] the prescription claims have been shown to be fairly accurate and complete.[30] Thus, laboratory information was used as a surrogate indicator in this study when there was no corresponding treatment. The comparative characteristics between our two criteria imply that safety measures should be incorporated for a conservative interpretation of laboratory information. In order to avoid overestimating the risk of severe muscle toxicity, we identified the accompanying condition by both diagnosis and drugs when an event occurred, and excluded cases that were less likely to be related to statin use. Furthermore, the MDV database provided objective information that would not only complement the limitations of the claims database, but that would also provide the potential to monitor pharmacologic responses to therapeutic interventions using biomarkers. In addition, the MDV plans to enrol up to one hundred medical facilities to improve the applicability of using electronic health information in the near future. Limits to investigations imposed by small sample sizes could be overcome, and associations between the risk of adverse events and the use of statins with and without interacting drugs could be explored through this strategy. However, hospital-based data collection would be threatened by lost follow-up and lack of enrolment information such as patients' date of birth and geographic region. Since the database used in this study did not have enough power to evaluate rare events in Japanese clinical practice, the accessibility of a national claims database is expected to provide a complement to this limitation. In addition, the MIHARI project plans to aggregate information from 10 university hospitals (the Sentinel database) to confirm the signal with objective information based on appropriate methodology. Since the validity of claims-based information is often questioned, studies should be conducted to verify the validity[31] and explore the applicability of this information. From a regulatory perspective, great potential exists for evaluating risks for a population using validated information, with the goal of making efficient use of the resource. By using unique identification or indirect identifiers such as patient's date of birth, sex, hospital identification number, admission date, and discharge date, linkage between different databases is commonly used when clinical trial designs are not applicable.[32-34] Because the accessibility of healthcare information in Japan is strictly regulated by privacy protection, further discussion would be necessary to balance privacy protection with an active drug safety monitoring system.

CONCLUSIONS

The present study provides evidence of incidence of severe muscle toxicity with statin use, identified by diagnosis and objective laboratory information obtained from the claims database in Japan. Since the definition of safety measures varies according to the infrastructure of data resources, researchers should use caution when interpreting risk information that provides answers to uncertainties addressed before drug approval. While the use of combination therapy is relative low in patients with lipid disorders and without muscle complaints, the risks attributed to drug interactions in statin users require further exploration.

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FINANCIAL DISCLOSURE

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AUTHOR CONTRIBUTION

MA was the principal investigator for the grant. MK, TO and MA conceived the study. All authors contributed to study design. TO and MA were responsible for obtaining the data. CHC and MK conducted the initial data analysis. All authors contributed to decisions on the interpretation of results. CHC, KM, and MA contributed to the drafting the manuscript. All authors approved the final version of the manuscript prior to submission.

DATA SHARING STATEMENT

Technical appendix, statistical code, and dataset available from the corresponding author (makazawa@my-pharm.ac.jp). Inform consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

COMPETING INTERESTS STATEMENT

There are no competing interests.

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Figure 1. Flow-chart of study cohort

Table 1. Characteristics of new statin users (N = 18,036) for six drugs represented in this study.

	Atorvastatin (N = 7,052)	Rosuvastatin (N = 5,921)	Pravastatin (N = 5,110)	Pitavastatin (N = 1,774)	Simvastatin (N = 976)	Fluvastatin (N = 871)
Demographic variable						
Mean age, year (SD)	65 (12)	64 (12)	68 (11)	66 (12)	68 (12)	68 (10)
Male (%)	3,201 (45%)	3,092 (52%)	1,935 (38%)	785 (44%)	383 (39%)	421 (48%)
Statin use*						
Duration, month (range)	24 (6–42)	15 (4–28)	22 (6–41)	16 (5–32)	23 (7–41)	16 (6–32)
Daily prescribed dose, mg, where variable)	10	2.5	10	1.6 (1–2)	5	30 (20–30)
Co-morbidity						
Hepatic impairment† (%)	198 (3%)	213 (4%)	90 (2%)	30 (2%)	13 (1%)	18 (2%)
Renal impairment‡ (%)	1,778 (25%)	1,860 (31%)	1,126 (22%)	440 (25%)	151 (15%)	248 (28%)
HbA1c >6.1% (%)	1,209 (17%)	1,660 (28%)	700 (14%)	397 (22%)	125 (13%)	123 (14%)
Co-administration						
Calcium channel blockers (%)	2,554 (36%)	2,036 (34%)	1,981 (39%)	668 (38%)	390 (40%)	332 (38%)
ACE-I/ARB (%)	2,823 (40%)	2,444 (41%)	1,916 (38%)	703 (40%)	424 (43%)	332 (38%)
Insulin (%)	567 (8%)	562 (10%)	284 (6%)	138 (8%)	63 (7%)	45 (5%)
Oral hypoglycaemic agents (%)	1,452 (21%)	1,581 (27%)	902 (18%)	449 (25%)	182 (19%)	159 (18%)
Anti-platelet agents (%)	2,248 (32%)	1,748 (30%)	1,361 (27%)	448 (25%)	274 (28%)	348 (40%)
Nitrate (%)	1,297 (18%)	1,006 (17%)	814 (16%)	246 (14%)	137 (14%)	176 (20%)
H_2 receptor antagonist (%)	1,394 (20%)	928 (16%)	905 (18%)	275 (16%)	201 (21%)	162 (19%)

Proton Pump inhibitor (%)	1,223 (17%)	1,233 (21%)	700 (14%)	331 (19%)	126 (13%)	125 (14%)

* Data shown as median (Q1–Q3).

† Renal impairment: patients whose serum creatine levels increased by >1 × the upper limit of the normal range, prior to 180 days before statin initiation.

‡ Hepatic impairment defined patients whose alanine transaminase (ALT) or aspartate transaminase (APT) increased >3 x times the upper limit of the normal range prior to 180 days before statin imitation.

Note:

The approved daily dosage for each statin was listed as follows: atorvastatin 10–40 mg, rosuvastatin 2.5–20 mg, pravastatin 10–20 mg, pitavastatin 1–4 mg, simvastatin 5–20 mg, fluvastatin 20–60 mg.

Table 2. Risk of severe muscle toxicity among specific statin therapies

Generic statin name	# of events	Person-years	Incidence§	Incidence, Criterion A only§	Incidence, Criterion B only§	Incidence, Criterion A only§ (discontinuation)	Incidence, Criterion B only§ (discontinuation)
Atorvastatin	17	15,776	1.08 (0.67–1.73)	0.63 (0.34–1.18)	0.44 (0.21–0.93)	–	–
Rosuvastatin	15	8,655	1.73 (1.04–2.87)	1.15 (0.62–2.15)	0.81 (0.39–1.69)	0.46 (0.17–1.23)	0.35 (0.11–1.07)
Pravastatin	5	11,121	0.45 (0.19–1.08)	0.27 (0.09–0.84)	0.27 (0.09–0.84)	0.27 (0.09–0.84)	0.18 (0.04–0.72)
Pitavastatin	3	2,883	1.04 (0.34–3.23)	0.35 (0.05–2.46)	0.69 (0.17–2.77)	–	0.35 (0.05–2.46)
Simvastatin	2	2,123	0.94 (0.24–3.77)	0.94 (0.24–3.76)	0.47 (0.07–3.34)	–	–
Fluvastatin	1	1,635	0.61 (0.09–4.34)	0.61 (0.09–4.34)	–	–	–
All statins	43	42,193	1.02 (0.76–1.37)	0.64 (0.44–0.93)	0.47 (0.31–0.73)	0.17 (0.08–0.35)	0.14 (0.06–0.32)

§ Data shown as per 1,000 person-years with 95% confidence interval.

Note:

Criterion A: Defined by muscle related diagnosis.

Criterion B: Defined by creatine kinase (CK) concentration >10 x the upper limit of the normal range.

Discontinuation was defined as no use of statin therapy in the six months following occurrence of muscle toxicity.

Table 3. Characteristics of patients exhibiting Criterion A vs. Criterion B

	Criterion A only (N = 27)	Criterion B only (N = 20)	p-value
Demographic variable			
Female (%)	13 (48%)	9 (45%)	0.83
Mean age, years (SD)	60 (15)	69 (11)	0.07
Statin use at the event (%)			1.00
Atorvastatin	10 (37%)	7 (35%)	
Fluvastatin	1 (4%)	0	
Pitavastatin	1 (4%)	2 (10%)	
Pravastatin	3 (11%)	3 (15%)	
Rosuvastatin	10 (37%)	7 (35%)	
Simvastatin	2 (7%)	1 (5%)	
Discontinued statin use	7 (26%)	6 (30%)	0.76
Hospitalization with discontinuation	4 (15%)	5 (25%)	0.38
Mean dosage, defined daily dose (SD)	0.36 (0.18)	0.38 (0.19)	1.00
Mean interval after initiating Statin, month (SD)	18 (13)	19 (20)	0.98
Co-administrated drugs			
Hypoglycaemic agents (%)	8 (30%)	7 (35%)	0.69
Anti-platelet agents (%)	6 (22%)	8 (40%)	0.19
Calcium channel blocker (%)	11 (41%)	11 (55%)	0.33
Angiotensin Receptor Blocker (%)	9 (33%)	6 (30%)	0.81
GI protective agents (%)	9 (33%)	12 (60%)	0.07

Note:

Criterion A: Defined by muscle related diagnosis.

Criterion B: Defined by creatine kinase (CK) concentration >10 x times the upper limit of the normal range.

Four cases met both Criteria A and B.

The defined daily dose for atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin were 20 mg, 60 mg, 2 mg, 30 mg, 10 mg, and 30 mg, respectively.

Table 4. Risk of severe muscle toxicity from concomitant use of interacting drugs

	Concomitant use of interacting drugs*	No concomitant use of interacting drugs
N	2,430	15,606
Person-year	1,776	40,418
Number of events	3	40
Proportion of total events, %	0.12%	0.26%
Incidence per 1,000 person-years (95% CI)	1.69 (0.54–5.24)	0.99 (0.73-1.35)

* The number of patients who were exposed to specific interacting drugs in this study were as follows: benzafibrate (256), fenofibrate (262), clinofibrate (1), clarithromycin (1,688), erythromycin (77), telithromycin (2), fluconazole (22), itraconazole (125), fosfluconazole (31), voriconazole (11), cyclosporine (66), amiodarone (93), saquinavir/ritonavir (0), atazanavir (0), and etraririne (0), and efavirenz (0).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

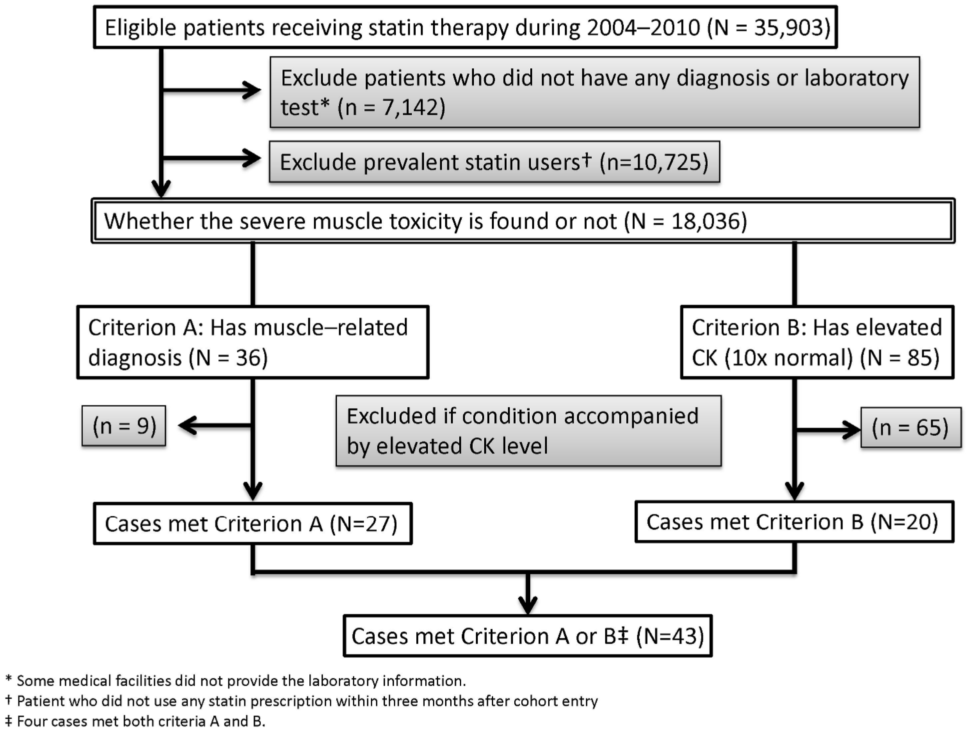
NA: Not applicable

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-9
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-12
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	13
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	14, Table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	14-15, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15, Table 2
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21-22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.



Flow-chart of study cohort
254x190mm (300 x 300 DPI)

Assessment of statin-associated severe muscle toxicity in Japan: A cohort study by using a claims database and laboratory information

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Assessment of statin-associated severe muscle toxicity in Japan: A cohort study by using a claims database and laboratory information

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ABSTRACT

Objective:

To evaluate whether the use of specific statins or concomitant use of interacting drugs is associated with an increased incidence of severe muscle toxicity in patients receiving statin therapy

Design:

Retrospective cohort study

Setting:

Sixteen medical facilities in Japan providing information on laboratory tests performed in, and claims received by, their facilities between 1 April 2004 and 31 December 2010.

Participants:

A database representing a cohort of 35,903 adult statin (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) users was studied. Use of interacting drugs (fibrates, triazoles, macrolides, amiodarone, and ciclosporin) by these patients was determined.

Main outcome measure:

Severe muscle toxicity ('event') was identified by a diagnosis of muscle-related disorders and/or creatine kinase (CK) concentrations 10 times greater than the normal

upper limit. Events were excluded if patients had CK elevation-related conditions other than severe muscle toxicity. Incidence rates for severe muscle toxicity were determined per 1,000 person-years, with 95% confidence intervals (CI) determined by Poisson regression.

Results:

A total of 18,036 patients contributed 42,193 person-years of statin therapy, and 43 events were identified. Incidence of severe muscle toxicity in patients treated with statins ranged from 0.45 (95% CI, 0.19–1.08) with pravastatin to 1.73 (95% CI, 1.04–2.87) with rosuvastatin per 1,000 person-years. On using atorvastatin users as a reference, we found that there were no significant differences between statins with respect to incidence of severe muscle toxicity; 2,430 (13.5%) of the patients treated with statins received interacting drugs during their follow-up period. As a result of low numbers of events and of person-years of receiving interacting drugs, the 95% CI (wide) included the estimated incidence rate.

Conclusions:

This database study suggested that statin use is generally well tolerated and safe; however, the risk of severe muscle toxicity related to the use of interacting drugs requires further exploration.

ARTICLE SUMMARY

Article focus

- Asian populations are more sensitive to statins' clinical response than Western populations.
- Our objective was to evaluate the risk of severe muscle toxicity associated with statin and/or interacting drug use, by using claims database and laboratory information in Japan.

Key messages

- Patients receiving prescription statins were most often prescribed the lower limits of approved dosages, with rare concomitant use of interacting drugs that could increase steady-state statin concentrations.
- The number of adverse events was limited; the incidence of severe muscle toxicity was statistically indistinguishable among statins.
- This study has major implications for risk evaluation, given the information infrastructure available to validate claims-based estimations.

Strengths and limitations of this study

- This study is the first study to evaluate drug-associated risk by using claims database and laboratory information in Japan, indicating the potential applicability of electronic health information as a resource for applied analyses.
- Interacting drug use associated with increased risk of muscle toxicity requires further exploration because a low number of person-years of observations currently exists in the literature. Diagnostic information is slightly less complete than is prescription and laboratory test information; researchers should use caution when interpreting related information in database studies.

INTRODUCTION

Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor or HMG-CoA reductase inhibitor) are widely used for adults presenting with cardiovascular disease (CVD), and those with a 20% or greater 10-year risk of developing CVD,[1] to reduce the incidence of cardiovascular co-morbidity and mortality. Although statins are well-tolerated by the vast majority of patients, their use can lead to infrequent adverse muscle, renal, and hepatic events.[2, 3] Severe adverse events could lead to additional drug costs, increasing the burden of healthcare expenditures.[4] In addition, the concomitant use of interacting drugs could increase the risk of muscle toxicity.[5] Moreover, the Asian population is more sensitive in its clinical response to statins than is the Western population, and approved statin doses in Japan are relatively low compared to those approved for use in the US. [6-9]

Clinical trials are restricted in the number and diversity of participants enrolled, such that the chances of detecting rare, adverse treatment effects are low. Regulatory bodies, including those in Japan, have long relied primarily on the voluntary reporting system to monitor post-marketing safety. In addition to voluntary reporting, which does not accurately reflect risk due to under-reporting, a major challenge for assessing the safety of statin use is a lack of comparative data. Given concerns about the

limitations of existing monitoring systems, the use of automatic databases such as claims or electronic healthcare records for post-marketing safety assessment has been well-structured and widely applied in the US and EU.[10, 11] Recently, the Sentinel System was launched by the US Food and Drug Administration (FDA) to develop active surveillance capabilities for evaluating post-market safety issues in regulated medical products.[12] In Japan, in order to complement this strategy for safety assessment, the Medical Information of Risk Assessment Initiative (MIHARI project) was launched by the Pharmaceutical and Medical Devices Agency (PMDA) in 2009. The MIHARI project aggregates electronic medical information with appropriate methodologies for risk evaluation, and ensures the accessibility and applicability of claims databases and electronic healthcare records for use.[13] The Japanese national claims database has been accessible to researchers by a peer-reviewed proposal process, beginning in April 2011.[14] In retrospective studies, a health outcome is defined by criteria that are restricted by the structure of a given database. Different definitions for explaining a certain adverse event could result in different conclusions. Before researchers and regulators begin working with large automated databases (including the MIHARI database) for drug safety monitoring, pilot studies are needed to evaluate the pros and cons of database studies under the Japanese healthcare system.

In early 2012, the FDA issued labelling changes for statin drugs based on updated safety information.[15] Administrative databases may be useful for identifying potential problems, such as assessment of risk factors and incidence of adverse treatment effects. Our study evaluated the rare adverse event of statin-associated muscle toxicity (e.g. myopathy or rhabdomyolysis), defined by two criteria, using the claims database with laboratory information.

METHODS AND ANALYSIS

Data resource

This retrospective cohort study analysed data from Medical Data Vision Co. Ltd. (MDV) in Tokyo, Japan. This commercial, electronic, record-based healthcare database provides information on ambulatory service, hospitalization, medication use, and laboratory tests for patients from 1 January 2004 through 31 December 2010. It contains the patients' demographic characteristics (e.g. age, sex), diagnoses (International Statistical Classification of Disease and Related Health Problems (ICD–10 codes)), prescription information (dose, quantity, and number of days of supply), and the results of laboratory tests for approximately 410,000 patients at 16 medical facilities across Japan.[16] Patients' identities have been encrypted for protection of privacy, but the data sets could be linked using unique, anonymous identifiers created by the data providers for research purposes. This study was approved by the Institutional Review Board at Meiji Pharmaceutical University and was conducted in compliance with the Japanese Ethical Guidelines for Epidemiological Research, updated in December 2008.[17]

Study cohort

Patients aged 18 or older that initiated statin therapy between 1 July 2004 and 30 June 2010 were included in this study. Because the median duration of statin prescription in the database was 28 days, a patient would be enrolled if there was no existing claim of statin prescription within 3 months after the first date of any claim. To avoid enrolling prevalent cases with muscle toxicity, patients who exhibited the following conditions would be excluded: a diagnosis of rhabdomyolysis/myositis; or the possibility of muscle-related CK elevation (i.e., patients whose CK elevation did not present with myocardial infarction, myocarditis, trauma, or hypothyroidism, and who had no claims of obtaining nitrate or levothyroxine prescriptions within 3 days after concurrent elevation of CK). In addition, the eligible population was required to have undergone at least one blood test during statin therapy, for avoidance of information bias. To ensure the validity of information available for individuals undergoing statin therapy, the consistency between dyslipidaemia diagnoses (ICD-10 code E78) and laboratory results of cholesterol, triglyceride, and low-density lipoprotein (LDL) was determined.

Exposure of interest

The information on statin therapy was extracted from the claims database, and exposure time was estimated for each patient based on the amount of statin continuously received by the patient, reported as person-years. We assumed that the patients received consecutive treatment from the initiation of statin therapy until the end of the last prescription, because the patients were monitored regularly. [18-19] The statins commercially available in Japan during the investigation period were atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. The prescribing dosage was defined as the sum total of the doses prescribed during the follow-up period, divided by exposure time. Because medications might be changed or added for treatment purposes, patients were allowed to contribute to multiple cohorts.

We also defined drugs that have some pharmacokinetic interactions with statins and that may increase risk of muscle toxicity. Lists of potentially interacting drugs were compiled from package inserts for statin medications, excluding topical and ophthalmic preparations.[20] We determined whether patients had used any of the following interacting drugs while undergoing statin therapy: fibrate (benzafibrate, fenofibrate, clinofibrate), macrolide antibiotics (clarithromycin, erythromycin, telithromycin), triazole antimycotics (fluconazole, itraconazole, fosfluconazole, voriconazole), immunosuppressant (cyclosporine), antiarrhythmic drug (amiodarone), and HIV/AIDS drugs (saquinavir/ritonavir, atazanavir, etravirine, and efavirenz). Statin therapy administrated concurrently with an interacting agent was treated as a time-varying covariate. Subjects could contribute person-time to the statin both with and without a concomitant interacting drug. Because the package inserts list the aforementioned interacting drugs as contraindicated or to be used with caution, concomitant use of these drugs with statins is rare. Therefore, we pooled all interacting drugs together rather than assessing specific drug interactions.

Case identification

Previous studies generally defined severe muscle toxicity by diagnosis and/or by elevated creatine kinase (CK) concentration.[21, 22] Since databases based on insurance claims do not contain laboratory results, differences in risk estimation would occur when the varying composition of available data. Therefore, we identified severe muscle toxicity using the following two criteria to explore the deviation between differing definitions. Therefore, we identified severe muscle toxicity using the following two criteria to explore the deviation between differing definitions. Criterion A was based on diagnosis of muscle-related disorders. Because there is no specific ICD-10 code to indicate severe muscle toxicity, the diagnosis contained the words 'myositis' or 'rhabdomyolysis', which were originally written in the Japanese language and were identified using a computer-assisted text searching method (FINDW function in SAS). Criterion B was based on laboratory results. A patient whose CK concentration was greater than ten times the upper limit of the normal range under statin therapy would be identified as a case. The normal range was given according to the sensitivity of the reference agents used in laboratory tests at each medical facility. The case was recognized as an event if no disease-related condition accompanied by CK elevation was confirmed. The disease-related conditions for CK elevation were as follows: any presence of diagnosis for myocardial infarction, myocarditis, trauma, or hypothyroidism, and any claim of nitrate and levothyroxine prescriptions being obtained within three days after the muscle toxicity event.[23] Statin therapy might be discontinued upon development of intolerable muscle symptoms, with or without CK elevation, in patients for whom other aetiologies were ruled out.[23] Physicians' management decisions about continuation or discontinuation of treatment were determined by compiling claims from patients' health records. Discontinuation was defined as no use of statin therapy in the six months following occurrence of muscle toxicity.

Statistical analyses

The incidence rate for severe muscle toxicity was presented per 1,000 person-years with 95% confidence intervals (CI) estimated by Poisson regression. The baseline period was defined as 180 days prior to statin initiation. Demographic (age, gender) and co-administration data were extracted from medical claims from the baseline period within the statin inception cohort. Patients were observed until occurrence of the first muscle toxicity event, and were censored when statin therapy was discontinued or when the end of the observational period was reached (31 December 2010). In addition to claims data, we identified the presence of co-morbidities from laboratory information for the baseline period. Renal impairment was defined by serum creatine concentrations (SCr) above the upper limit of the normal range; the hepatic impairment was indicated where laboratory values for alanine transaminase (ALT) and aspartate transaminase (APT) increased by more than three times the upper limit of normal during the baseline period. The cut-off of glycated haemoglobin (HbA1c) level for diabetes mellitus was set at greater than 6.1%, according to diagnostic criteria adopted in Japan.[24] To compare the characteristics of demographic and clinical variables between criteria, Kolmogorov-Smirnov tests were performed for continuous variables, and chi-square tests were used for dichotomous variables. Co-morbidity and co-administration of drugs were defined according to whether claims of a prescription were made prior to 180 days before occurrence of an event. In addition, to determine the muscle toxicity risk associated with drug-drug interactions, the incidence of muscle toxicity among patients that had concomitantly used interacting drugs was compared with those who did not. All statistical analyses were carried out using SAS software Version 9.3 (SAS Institute Inc., 2012, Cary NC, USA).

RESULTS

A total of 18,036 patients met all the criteria to be defined as new statin users (Figure 1). Of these patients, 11,468 (64%) were diagnosed as having dyslipidaemia, 14,355 (80%) had higher than normal levels of cholesterol, triglyceride or low-density lipoprotein, and 9,382 (52%) were diagnosed as having dyslipidaemia accompanied by higher than normal lipid levels. The mean (SD) age and follow-up month of patients in whom statin use was initiated were 66 (12) years and 29 (22) months, and 45% of patients were male. Atorvastatin was the most prevalent HMG-CoA reductase inhibitor and contributed to 37% of the total person-years in the inception cohort. The prescribed dosage was generally around the lower limit of the approved dose, with limited variation, regardless of the statin (Table 1).

Among new statin users, 43 cases (0.24%) were identified, of which 27, 20, and 4 cases were identified by criterion A, criterion B, and both A and B respectively (Tables 2 and 3). The proportion of discontinuation was similar among criteria A and B, where 7 and 6 cases of statin discontinuation were recorded respectively after occurrence of an event. Among them, 4 and 5 cases were hospitalized. Incidence (with 95% CI) of severe muscle toxicity in patients treated with statin monotherapy ranged from 0.45 (0.19–1.08) with pravastatin to 1.73 (1.04–2.87) with rosuvastatin per 1,000 person-years, with the summary risk estimate of 1.02 (0.76–1.37) per 1,000 person-years of use. Using atorvastatin – the most widely prescribed statin in Japan – as the reference, incidences of severe muscle toxicity were statistically indistinguishable among the statins, regardless of the criterion used. Similarly, demographic and other characteristics of the cases did not differ for the two criteria (Table 4).

Of new statin users, 2,430 (13.5%) received interacting drugs during the follow-up period. Regarding the incidence rate of muscle toxicity with respect to interacting drug use, a low number of person-years of observation were contributed, representing limited use of interacting drugs, even when all statins and interacting drugs were aggregated. Because of the low number of events recorded, we found the wide 95% CI included the estimated incidence rate (Table 5).

DISCUSSION

This study extends previous work in measuring statin-associated severe muscle toxicity by using the claims database with laboratory information for actual patient records in Japan. Since the package insert suggests periodical laboratory tests during statin therapy, it is possible to assess the change of medical condition. With an estimated incidence of approximately 1 per 1,000 person-years of statin use, a low occurrence of severe muscle toxicity was found in the present study. Moreover, less than about one in five patients was found to have concomitant use of interacting drugs, implying that the use of statins is generally well tolerated and safe in Japan. The characteristics and incidences of severe muscle toxicity between statins were not significantly different. In addition, clinical characteristics were similar among cases defined by diagnosis and cases defined by laboratory results. However, the number of diagnoses of dyslipidaemia was slightly lower than the number of cases with concurrent elevated lipid levels, indicating an inconsistency between diagnosis and laboratory data.

Information on the incidence (% of users) of severe muscle toxicity is not provided in Japanese statin medication package inserts, with the exceptions of rosuvastatin (0.1%) and simvastatin (0.01%). The lower limit of the 95% confidence interval showed a value consistent with available package inserts; however, it is possible that adverse events would occur more frequently with widespread use of statins in clinical practice, because populations that participate in clinical trials are usually highly selected.[25] Comparing our analysis to statistics reported in previous studies (mostly from the US), the crude incidence of rhabdomyolysis ranged from 2.5 to 4.4 per 100,000 person-years among statin users, when identified by diagnosis and laboratory results combined.[21, 22] Since it is not applicable to compare the incidence of events defined by different parameters, we refined our event definition to take statin discontinuation after occurrence of an adverse event into consideration. Upon doing so, we found the crude incidence of rhabdomyolysis to be 7.1 per 100,000 person-years (3 cases per 42,193 person-years), suggesting a moderately high incidence in the present study. The incidence of rhabdomyolysis might differ among studies because the proportion of patients with risk factors is apparently different between the populations. Some case reports indicated that factors related to statin-associated severe muscle toxicity included older age, female gender, low body mass index, and diabetes mellitus,[26] characteristics that were common among patients in our study. However, evidence showed no increased rate of adverse events in Asian patients taking either lower or higher doses of statin,[27] despite racial differences in the pharmacokinetics of rosuvastatin between Asians and Caucasian.[28] After all the controversy over racial differences in pharmacokinetics and the clinical outcomes of statin (particularly rosuvastatin) use, the majority of prescribed doses were at the lower limits of approved dosage levels, implying comparable potency among statins at the lowest effective dose. Taking dosage levels into account, statins were well tolerated in the Japanese population, with a similar incidence of rhabdomyolysis as reported from Caucasian populations.

Using the claims database to evaluate potential drug interactions with statins is a useful complement to the limited information available from voluntary reports and clinical trials. A recent study found that the use of against label statin-fibrate combination therapy is decreasing annually, but that use of this therapy still persists in the US.[29] In the present study, only 2.8% of patients had been prescribed concomitant statin-fibrate therapy (data not shown). Although combination therapy may be attractive for patients with lipid disorders and without muscle complaints, the low prevalence of concomitant fibrate use implies that it is "generally contraindicated," and that clinical practitioners are aware of the risks. Whether the risk is due to drug interactions remains controversial,[30, 31] but our study points to a higher incidence of severe muscle toxicity among patients taking interacting drugs. However, a low number of person-years of interacting drug use observations corresponded to a lack of statistical significance; this low prevalence of concomitant drug use might reduce the detection of severe muscle toxicity in current practice.

Our findings showed that the incidence of severe muscle toxicity varied according to the definition of an adverse event, suggesting that the infrastructure in which information is stored might greatly affect assessments of safe medical practice. The majority of cases of discontinuation of statins resulted in hospitalization accompanied by acute changes in renal function. However, the outcome from severe muscle toxicity could not be ascertained since there is no information of death record in the database. Although diagnostic-based measures are inherently limited by weaknesses of administrative claims diagnostic data, including inaccuracy and incompleteness of discharge diagnoses,[32] the prescription claims have been shown to be fairly accurate and complete.[33] Thus, laboratory information was used as a surrogate indicator in this study when there was no corresponding treatment. The comparative characteristics between our two criteria imply that safety measures should be incorporated for a conservative interpretation of laboratory information. In order to avoid overestimating the risk of severe muscle toxicity, we identified the accompanying condition by both diagnosis and drugs when an event occurred, and excluded cases that were less likely to be related to statin use. Furthermore, the MDV database provided objective information that would not only complement the limitations of the claims database, but that would also provide the potential to monitor pharmacologic responses to therapeutic interventions using biomarkers. In addition, the MDV plans to enrol up to one hundred medical facilities to improve the applicability of using electronic health information in the near future. Limits to investigations imposed by small sample sizes could be overcome, and associations between the risk of adverse events and the use of statins with and without interacting drugs could be explored through this strategy. However, hospital-based data collection would be threatened by lost follow-up and lack of enrolment information such as patients' date of birth and geographic region. Since the database used in this study did not have enough power to evaluate rare events in Japanese clinical practice, the accessibility of a national claims database is expected to provide a complement to this limitation. In addition, the MIHARI project plans to aggregate information from 10 university hospitals (the Sentinel database) to confirm the signal with objective information based on appropriate methodology. Since the validity of claims-based information is often questioned, studies should be conducted to verify the validity[34] and explore the applicability of this information. From a regulatory perspective, great potential exists for evaluating risks for a population using validated information, with the goal of making efficient use of the resource. By using unique identification or indirect identifiers such as patient's date of birth, sex, hospital identification number, admission date, and discharge date, linkage between different databases is commonly used when clinical trial designs are not applicable.[35-37] Because the accessibility of healthcare information in Japan is strictly regulated by privacy protection, further discussion would be necessary to balance privacy protection with an active drug safety monitoring system.

CONCLUSIONS

The present study provides evidence of incidence of severe muscle toxicity with statin use, identified by diagnosis and objective laboratory information obtained from the claims database in Japan. Since the definition of safety measures varies according to the infrastructure of data resources, researchers should use caution when interpreting risk information that provides answers to uncertainties addressed before drug approval. While the use of combination therapy is relative low in patients with lipid disorders and without muscle complaints, the risks attributed to drug interactions in statin users require further exploration.

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FINANCIAL DISCLOSURE

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AUTHOR CONTRIBUTION

MA was the principal investigator for the grant. MK, TO and MA conceived the study. All authors contributed to study design. TO and MA were responsible for obtaining the data. CHC and MK conducted the initial data analysis. All authors contributed to decisions on the interpretation of results. CHC, KM, and MA contributed to the drafting the manuscript. All authors approved the final version of the manuscript prior to submission.

DATA SHARING STATEMENT

Technical appendix, statistical code, and dataset available from the corresponding author (makazawa@my-pharm.ac.jp). Inform consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

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Figure 1. Flow-chart of study cohort

Table 1. Characteristics of new statin users (N = 18,036) for six drugs represented in this study.

	Atorvastatin (N = 7,052)	Rosuvastatin (N = 5,921)	Pravastatin (N = 5,110)	Pitavastatin (N = 1,774)	Simvastatin (N = 976)	Fluvastatin (N = 871)
Demographic variable						
Mean age, year (SD)	65 (12)	64 (12)	68 (11)	66 (12)	68 (12)	68 (10)
Male ,%	45%	52%	38%	44%	39%	48%
Statin use*						
Duration, month (range)	24 (6–42)	15 (4–28)	22 (6–41)	16 (5–32)	23 (7–41)	16 (6–32)
Daily prescribed dose, mg, where variable)	10	2.5	10	1.6 (1–2)	5	30 (20–30)
Co-morbidity						
Hepatic impairment†,%	3%	4%	2%	2%	1%	2%
Renal impairment‡,%	25%	31%	22%	25%	15%	28%
HbA1c >6.1%,%	17%	28%	14%	22%	13%	14%
Hypertension1	25%	53%	55%	28%	60%	57%
Diabetes mellitus2	55%	31%	21%	53%	22%	21%
Cardiovascular disease3	32%	30%	27%	25%	28%	40%
Ischemic heart disease4	18%	17%	16%	14%	14%	20%
Gastric ulcer5	34%	33%	30%	32%	32%	31%
Lipid profile						
TC >1x ULN	60%(2,248/3,773)	68%(2,547/3,719)	58%(1,436/2,467)	60%(541/909)	63%(261/419)	40%(165/408)
LDL >1x ULN	71%(1,639/2,295)	73%(3,019/4,118)	64%(969/1,524)	69%(664/969)	61%(147/243)	51%(104/202)

HDL < 1x LLN	16%(603/3,375)	18%(835/4,638)	13% (321/2,288)	15%(182/1,235)	13%(51/383)	15%(76/497)
TG > 1x ULN	54%(2,320/4,266)	58%(2,949/5,056)	45%(1,274/2,835)	52%(665/1,286)	48%(223/463)	46%(234/510)

* Data shown as median (Q1–Q3).

† Renal impairment: patients whose serum creatine levels increased by >1 × the upper limit of the normal range, prior to 180 days before statin initiation.

‡ Hepatic impairment defined patients whose alanine transaminase (ALT) or aspartate transaminase (APT) increased >3x times the upper limit of the normal range prior to 180 days before statin imitation.

a Patients with hypertension defined as the use of antihypertensive drugs, including CCB, ACEI, ARB, and alpha blocker

b Patients with diabetes mellitus defined as the use of hypoglycaemic agents, including bigunide, sulfonylurea,

c Patients with cardiovascular disease defined as the use of antiplatelet, including aspirin, clopidogrel, ticlopidine and dyperidamole.

d Patients with ischemic heart disease defined as the use of nitriate, including imdur, NTG and isodil

e Patients with the gastric ulcer defined as the use of gastrointestinal protective agents, including proton pump inhibitor and H_2 receptor antagonist.

Note:

The approved daily dosage for each statin was listed as follows: atorvastatin 10–40 mg, rosuvastatin 2.5–20 mg, pravastatin 10–20 mg, pitavastatin 1–4 mg, simvastatin 5–20 mg, fluvastatin 20–60 mg.

Table 2. Risk of severe muscle toxicity among specific statin therapies

Generic statin name	# of events†	Person-years	Incidence§
Atorvastatin	17	15,776	1.08 (0.67–1.73)
Rosuvastatin	15	8,655	1.73 (1.04–2.87)
Pravastatin	5	11,121	0.45 (0.19–1.08)
Pitavastatin	3	2,883	1.04 (0.34–3.23)
Simvastatin	2	2,123	0.94 (0.24–3.77)
Fluvastatin	1	1,635	0.61 (0.09–4.34)
All statins	43	42,193	1.02 (0.76–1.37)

† Cases were defined by either criterion A (muscle related diagnosis) or criterion B (creatine kinase concentration >10x the upper limit of the normal range).

§ Data shown as per 1,000 person-years with 95% confidence interval.

Note:

Table 3. Sensitivity analysis for risk of severe muscle toxicity among all statin users

Scenario	# of events	Incidence§
Met criterion A	27	0.64 (0.44–0.93)
Met criterion A with discontinuation	7	0.17 (0.08–0.35)
Met criterion B	20	0.47 (0.31–0.73)
Met criterion B with discontinuation	6	0.14 (0.06–0.32)
Met criteria A and B	4	0.09 (0.04–0.25)
Met criteria A and B, both with discontinuation	3	0.07 (0.02–0.22)
Met criterion A or B, but change CK>5xULN as case definition*	87	2.06 (1.67-2.53)

§ Data shown as per 1,000 person-years with 95% confidence interval.

Note:

Criterion A: Defined by muscle-related diagnosis.

Criterion B: Defined by creatine kinase (CK) concentration >10x the upper limit of the normal range (ULN).

Discontinuation was defined as no use of statin therapy in the six months following occurrence of muscle toxicity.

*Criterion B: 68 cases; Met criteria A and B: 8 cases.

Table 4. Characteristics of patients exhibiting Criterion A vs. Criterion B

	Criterion A (N = 27)	Criterion B (N = 20)	p-value
Demographic variable			
Male (%)	52%	55%	0.83
Mean age, years (SD)	60 (15)	69 (11)	0.07
Statin use at the event (%)			1.00
Atorvastatin	37%	35%	
Fluvastatin	4%	0	
Pitavastatin	4%	10%	
Pravastatin	11%	15%	
Rosuvastatin	37%	35%	
Simvastatin	7%	5%	
Discontinued statin use	26%	30%	0.76
Hospitalization with discontinuation	15%	25%	0.38
Mean interval after initiating Statin, month (SD)	18 (13)	19 (20)	0.98
Laboratory information			
SCr > 1x ULN	56% (9/16)	58% (11/19)	0.92
BUN > 1x ULN	44% (7/16)	50% (10/20)	0.71
APT > 1x ULN	56% (9/16)	80% (16/20)	0.12
ALT > 1x ULN	38% (6/16)	65% (13/20)	0.10

Abbreviations: SD, standard deviation; SCr, serum creatinine; BUN, blood urea nitrogen; APT, aspartate transaminase; ALT, alanine transaminase; ULN, upper limit of normal range.

Note:

Criterion A: Defined by muscle related diagnosis.

Criterion B: Defined by creatine kinase (CK) concentration >10x times the upper limit of the normal range.

Four cases met both Criteria A and B.

Table 5. Risk of severe muscle toxicity from concomitant use of interacting drugs

	Concomitant use of interacting drugs*	No concomitant use of interacting drugs
N	2,430	15,606
Person-year	1,776	40,418
Number of events	3	40
Proportion of total events, %	0.12%	0.26%
Incidence per 1,000 person-years (95% CI)	1.69 (0.54–5.24)	0.99 (0.73-1.35)

* The number of patients who were exposed to specific interacting drugs in this study were as follows: benzafibrate (256), fenofibrate (262), clinofibrate (1), clarithromycin (1,688), erythromycin (77), telithromycin (2), fluconazole (22), itraconazole (125), fosfluconazole (31), voriconazole (11), cyclosporine (66), amiodarone (93), saquinavir/ritonavir (0), atazanavir (0), and etraririne (0), and efavirenz (0).

Assessment of statin-associated severe muscle toxicity in Japan: A cohort study by using a claims database and laboratory information

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ABSTRACT

Objective:

To evaluate whether the use of specific statins or concomitant use of interacting drugs is associated with an increased incidence of severe muscle toxicity in patients receiving statin therapy

Design:

Retrospective cohort study

Setting:

Sixteen medical facilities in Japan providing information on laboratory tests performed in, and claims received by, their facilities between 1 April 2004 and 31 December 2010.

Participants:

A database representing a cohort of 35,903 adult statin (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) users was studied. Use of interacting drugs (fibrates, triazoles, macrolides, amiodarone, and ciclosporin) by these patients was determined.

Main outcome measure:

Severe muscle toxicity ('event') was identified by a diagnosis of muscle-related disorders and/or creatine kinase (CK) concentrations 10 times greater than the normal

upper limit. Events were excluded if patients had CK elevation-related conditions other than severe muscle toxicity. Incidence rates for severe muscle toxicity were determined per 1,000 person-years, with 95% confidence intervals (CI) determined by Poisson regression.

Results:

A total of 18,036 patients contributed 42,193 person-years of statin therapy, and 43 events were identified. Incidence of severe muscle toxicity in patients treated with statins ranged from 0.45 (95% CI, 0.19–1.08) with pravastatin to 1.73 (95% CI, 1.04–2.87) with rosuvastatin per 1,000 person-years. On using atorvastatin users as a reference, we found that there were no significant differences between statins with respect to incidence of severe muscle toxicity; 2,430 (13.5%) of the patients treated with statins received interacting drugs during their follow-up period. As a result of low numbers of events and of person-years of receiving interacting drugs, the 95% CI (wide) included the estimated incidence rate.

Conclusions:

This database study suggested that statin use is generally well tolerated and safe; however, the risk of severe muscle toxicity related to the use of interacting drugs requires further exploration.

ARTICLE SUMMARY

Article focus

- Asian populations are more sensitive to statins' clinical response than Western populations.
- Our objective was to evaluate the risk of severe muscle toxicity associated with statin and/or interacting drug use, by using claims database and laboratory information in Japan.

Key messages

- Patients receiving prescription statins were most often prescribed the lower limits of approved dosages, with rare concomitant use of interacting drugs that could increase steady-state statin concentrations.
- The number of adverse events was limited; the incidence of severe muscle toxicity was statistically indistinguishable among statins.
- This study has major implications for risk evaluation, given the information infrastructure available to validate claims-based estimations.

Strengths and limitations of this study

- This study is the first study to evaluate drug-associated risk by using claims database and laboratory information in Japan, indicating the potential applicability of electronic health information as a resource for applied analyses.
- Interacting drug use associated with increased risk of muscle toxicity requires further exploration because a low number of person-years of observations currently exists in the literature. Diagnostic information is slightly less complete than is prescription and laboratory test information; researchers should use caution when interpreting related information in database studies.

INTRODUCTION

Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor or HMG-CoA reductase inhibitor) are widely used for adults presenting with cardiovascular disease (CVD), and those with a 20% or greater 10-year risk of developing CVD,[1] to reduce the incidence of cardiovascular co-morbidity and mortality. Although statins are well-tolerated by the vast majority of patients, their use can lead to infrequent adverse muscle, renal, and hepatic events.[2, 3] Severe adverse events could lead to additional drug costs, increasing the burden of healthcare expenditures.[4] In addition, the concomitant use of interacting drugs could increase the risk of muscle toxicity.[5] Moreover, the Asian population is more sensitive in its clinical response to statins than is the Western population, and approved statin doses in Japan are relatively low compared to those approved for use in the US. [6-9]

Clinical trials are restricted in the number and diversity of participants enrolled, such that the chances of detecting rare, adverse treatment effects are low. Regulatory bodies, including those in Japan, have long relied primarily on the voluntary reporting system to monitor post-marketing safety. In addition to voluntary reporting, which does not accurately reflect risk due to under-reporting, a major challenge for assessing the safety of statin use is a lack of comparative data. Given concerns about the

limitations of existing monitoring systems, the use of automatic databases such as claims or electronic healthcare records for post-marketing safety assessment has been well-structured and widely applied in the US and EU.[10, 11] Recently, the Sentinel System was launched by the US Food and Drug Administration (FDA) to develop active surveillance capabilities for evaluating post-market safety issues in regulated medical products.[12] In Japan, in order to complement this strategy for safety assessment, the Medical Information of Risk Assessment Initiative (MIHARI project) was launched by the Pharmaceutical and Medical Devices Agency (PMDA) in 2009. The MIHARI project aggregates electronic medical information with appropriate methodologies for risk evaluation, and ensures the accessibility and applicability of claims databases and electronic healthcare records for use.[13] The Japanese national claims database has been accessible to researchers by a peer-reviewed proposal process, beginning in April 2011.[14] In retrospective studies, a health outcome is defined by criteria that are restricted by the structure of a given database. Different definitions for explaining a certain adverse event could result in different conclusions. Before researchers and regulators begin working with large automated databases (including the MIHARI database) for drug safety monitoring, pilot studies are needed to evaluate the pros and cons of database studies under the Japanese healthcare system.

In early 2012, the FDA issued labelling changes for statin drugs based on updated safety information.[15] Administrative databases may be useful for identifying potential problems, such as assessment of risk factors and incidence of adverse treatment effects. Our study evaluated the rare adverse event of statin-associated muscle toxicity (e.g. myopathy or rhabdomyolysis), defined by two criteria, using the claims database with laboratory information.

METHODS AND ANALYSIS

Data resource

This retrospective cohort study analysed data from Medical Data Vision Co. Ltd. (MDV) in Tokyo, Japan. This commercial, electronic, record-based healthcare database provides information on ambulatory service, hospitalization, medication use, and laboratory tests for patients from 1 January 2004 through 31 December 2010. It contains the patients' demographic characteristics (e.g. age, sex), diagnoses (International Statistical Classification of Disease and Related Health Problems (ICD–10 codes)), prescription information (dose, quantity, and number of days of supply), and the results of laboratory tests for approximately 410,000 patients at 16 medical facilities across Japan.[16] Patients' identities have been encrypted for protection of privacy, but the data sets could be linked using unique, anonymous identifiers created by the data providers for research purposes. This study was approved by the Institutional Review Board at Meiji Pharmaceutical University and was conducted in compliance with the Japanese Ethical Guidelines for Epidemiological Research, updated in December 2008.[17]

Study cohort

Patients aged 18 or older that initiated statin therapy between 1 July 2004 and 30 June 2010 were included in this study. Because the median duration of statin prescription in the database was 28 days, a patient would be enrolled if there was no existing claim of statin prescription within 3 months after the first date of any claim. To avoid enrolling prevalent cases with muscle toxicity, patients who exhibited the following conditions would be excluded: a diagnosis of rhabdomyolysis/myositis; or the possibility of muscle-related CK elevation (i.e., patients whose CK elevation did not present with myocardial infarction, myocarditis, trauma, or hypothyroidism, and who had no claims of obtaining nitrate or levothyroxine prescriptions within 3 days after concurrent elevation of CK). In addition, the eligible population was required to have undergone at least one blood test during statin therapy, for avoidance of information bias. To ensure the validity of information available for individuals undergoing statin therapy, the consistency between dyslipidaemia diagnoses (ICD-10 code E78) and laboratory results of cholesterol, triglyceride, and low-density lipoprotein (LDL) was determined.

Exposure of interest

The information on statin therapy was extracted from the claims database, and exposure time was estimated for each patient based on the amount of statin continuously received by the patient, reported as person-years. We assumed that the patients received consecutive treatment from the initiation of statin therapy until the end of the last prescription, because the patients were monitored regularly. [18-19] The statins commercially available in Japan during the investigation period were atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. The prescribing dosage was defined as the sum total of the doses prescribed during the follow-up period, divided by exposure time. Because medications might be changed or added for treatment purposes, patients were allowed to contribute to multiple cohorts.

We also defined drugs that have some pharmacokinetic interactions with statins and that may increase risk of muscle toxicity. Lists of potentially interacting drugs were compiled from package inserts for statin medications, excluding topical and ophthalmic preparations.[20] We determined whether patients had used any of the following interacting drugs while undergoing statin therapy: fibrate (benzafibrate, fenofibrate, clinofibrate), macrolide antibiotics (clarithromycin, erythromycin, telithromycin), triazole antimycotics (fluconazole, itraconazole, fosfluconazole, voriconazole), immunosuppressant (cyclosporine), antiarrhythmic drug (amiodarone), and HIV/AIDS drugs (saquinavir/ritonavir, atazanavir, etravirine, and efavirenz). Statin therapy administrated concurrently with an interacting agent was treated as a time-varying covariate. Subjects could contribute person-time to the statin both with and without a concomitant interacting drug. Because the package inserts list the aforementioned interacting drugs as contraindicated or to be used with caution, concomitant use of these drugs with statins is rare. Therefore, we pooled all interacting drugs together rather than assessing specific drug interactions.

Case identification

Previous studies generally defined severe muscle toxicity by diagnosis and/or by elevated creatine kinase (CK) concentration.[21, 22] Since databases based on insurance claims do not contain laboratory results, differences in risk estimation would occur when the varying composition of available data. Therefore, we identified severe muscle toxicity using the following two criteria to explore the deviation between differing definitions. Therefore, we identified severe muscle toxicity using the following two criteria to explore the deviation between differing definitions.

Criterion A was based on diagnosis of muscle-related disorders. Because there is no specific ICD-10 code to indicate severe muscle toxicity, the diagnosis contained the words 'myositis' or 'rhabdomyolysis', which were originally written in the Japanese language and were identified using a computer-assisted text searching method (FINDW function in SAS). Criterion B was based on laboratory results. A patient whose CK concentration was greater than ten times the upper limit of the normal range under statin therapy would be identified as a case. The normal range was given according to the sensitivity of the reference agents used in laboratory tests at each medical facility. The case was recognized as an event if no disease-related condition accompanied by CK elevation was confirmed. The disease-related conditions for CK elevation were as follows: any presence of diagnosis for myocardial infarction, myocarditis, trauma, or hypothyroidism, and any claim of nitrate and levothyroxine prescriptions being obtained within three days after the muscle toxicity event.[23] Statin therapy might be discontinued upon development of intolerable muscle symptoms, with or without CK elevation, in patients for whom other aetiologies were ruled out.[23] Physicians' management decisions about continuation or discontinuation of treatment were determined by compiling claims from patients' health records. Discontinuation was defined as no use of statin therapy in the six months following occurrence of muscle toxicity.

Statistical analyses

The incidence rate for severe muscle toxicity was presented per 1,000 person-years with 95% confidence intervals (CI) estimated by Poisson regression. The baseline period was defined as 180 days prior to statin initiation. Demographic (age, gender) and co-administration data were extracted from medical claims from the baseline period within the statin inception cohort. Patients were observed until occurrence of the first muscle toxicity event, and were censored when statin therapy was discontinued or when the end of the observational period was reached (31 December 2010). In addition to claims data, we identified the presence of co-morbidities from laboratory information for the baseline period. Renal impairment was defined by serum creatine concentrations (SCr) above the upper limit of the normal range; the hepatic impairment was indicated where laboratory values for alanine transaminase (ALT) and aspartate transaminase (APT) increased by more than three times the upper limit of normal during the baseline period. The cut-off of glycated haemoglobin (HbA1c) level for diabetes mellitus was set at greater than 6.1%, according to diagnostic criteria adopted in Japan.[24] To compare the characteristics of demographic and clinical variables between criteria, Kolmogorov-Smirnov tests were performed for continuous variables, and chi-square tests were used for dichotomous variables. Co-morbidity and co-administration of drugs were defined according to whether claims of a prescription were made prior to 180 days before occurrence of an event. In addition, to determine the muscle toxicity risk associated with drug-drug interactions, the incidence of muscle toxicity among patients that had concomitantly used interacting drugs was compared with those who did not. All statistical analyses were carried out using SAS software Version 9.3 (SAS Institute Inc., 2012, Cary NC, USA).

RESULTS

A total of 18,036 patients met all the criteria to be defined as new statin users (Figure 1). Of these patients, 11,468 (64%) were diagnosed as having dyslipidaemia, 14,355 (80%) had higher than normal levels of cholesterol, triglyceride or low-density lipoprotein, and 9,382 (52%) were diagnosed as having dyslipidaemia accompanied by higher than normal lipid levels. The mean (SD) age and follow-up month of patients in whom statin use was initiated were 66 (12) years and 29 (22) months, and 45% of patients were male. Atorvastatin was the most prevalent HMG-CoA reductase inhibitor and contributed to 37% of the total person-years in the inception cohort. The prescribed dosage was generally around the lower limit of the approved dose, with limited variation, regardless of the statin (Table 1).

Among new statin users, 43 cases (0.24%) were identified, of which 27, 20, and 4 cases were identified by criterion A, criterion B, and both A and B respectively (Tables 2 and 3). The proportion of discontinuation was similar among criteria A and B, where 7 and 6 cases of statin discontinuation were recorded respectively after occurrence of an event. Among them, 4 and 5 cases were hospitalized. Incidence (with 95% CI) of severe muscle toxicity in patients treated with statin monotherapy ranged from 0.45 (0.19–1.08) with pravastatin to 1.73 (1.04–2.87) with rosuvastatin per 1,000 person-years, with the summary risk estimate of 1.02 (0.76–1.37) per 1,000 person-years of use. Using atorvastatin – the most widely prescribed statin in Japan – as the reference, incidences of severe muscle toxicity were statistically indistinguishable among the statins, regardless of the criterion used. Similarly, demographic and other characteristics of the cases did not differ for the two criteria (Table 4).

Of new statin users, 2,430 (13.5%) received interacting drugs during the follow-up period. Regarding the incidence rate of muscle toxicity with respect to interacting drug use, a low number of person-years of observation were contributed, representing limited use of interacting drugs, even when all statins and interacting drugs were aggregated. Because of the low number of events recorded, we found the wide 95% CI included the estimated incidence rate (Table 5).

DISCUSSION

This study extends previous work in measuring statin-associated severe muscle toxicity by using the claims database with laboratory information for actual patient records in Japan. Since the package insert suggests periodical laboratory tests during statin therapy, it is possible to assess the change of medical condition. With an estimated incidence of approximately 1 per 1,000 person-years of statin use, a low occurrence of severe muscle toxicity was found in the present study. Moreover, less than about one in five patients was found to have concomitant use of interacting drugs, implying that the use of statins is generally well tolerated and safe in Japan. The characteristics and incidences of severe muscle toxicity between statins were not significantly different. In addition, clinical characteristics were similar among cases defined by diagnosis and cases defined by laboratory results. However, the number of diagnoses of dyslipidaemia was slightly lower than the number of cases with concurrent elevated lipid levels, indicating an inconsistency between diagnosis and laboratory data.

Information on the incidence (% of users) of severe muscle toxicity is not provided in Japanese statin medication package inserts, with the exceptions of rosuvastatin (0.1%) and simvastatin (0.01%). The lower limit of the 95% confidence interval showed a value consistent with available package inserts; however, it is possible that adverse events would occur more frequently with widespread use of statins in clinical practice, because populations that participate in clinical trials are usually highly selected.[25] Comparing our analysis to statistics reported in previous studies (mostly from the US), the crude incidence of rhabdomyolysis ranged from 2.5 to 4.4 per 100,000 person-years among statin users, when identified by diagnosis and laboratory results combined.[21, 22] Since it is not applicable to compare the incidence of events defined by different parameters, we refined our event definition to take statin discontinuation after occurrence of an adverse event into consideration. Upon doing so, we found the crude incidence of rhabdomyolysis to be 7.1 per 100,000 person-years (3 cases per 42,193 person-years), suggesting a moderately high incidence in the present study. The incidence of rhabdomyolysis might differ among studies because the proportion of patients with risk factors is apparently different between the populations. Some case reports indicated that factors related to statin-associated severe muscle toxicity included older age, female gender, low body mass index, and diabetes mellitus,[26] characteristics that were common among patients in our study. However, evidence showed no increased rate of adverse events in Asian patients taking either lower or higher doses of statin,[27] despite racial differences in the pharmacokinetics of rosuvastatin between Asians and Caucasian.[28] After all the controversy over racial differences in pharmacokinetics and the clinical outcomes of statin (particularly rosuvastatin) use, the majority of prescribed doses were at the lower limits of approved dosage levels, implying comparable potency among statins at the lowest effective dose. Taking dosage levels into account, statins were well tolerated in the Japanese population, with a similar incidence of rhabdomyolysis as reported from Caucasian populations.

Using the claims database to evaluate potential drug interactions with statins is a useful complement to the limited information available from voluntary reports and clinical trials. A recent study found that the use of against label statin-fibrate combination therapy is decreasing annually, but that use of this therapy still persists in the US.[29] In the present study, only 2.8% of patients had been prescribed concomitant statin-fibrate therapy (data not shown). Although combination therapy may be attractive for patients with lipid disorders and without muscle complaints, the low prevalence of concomitant fibrate use implies that it is "generally contraindicated," and that clinical practitioners are aware of the risks. Whether the risk is due to drug interactions remains controversial,[30, 31] but our study points to a higher incidence of severe muscle toxicity among patients taking interacting drugs. However, a low number of person-years of interacting drug use observations corresponded to a lack of statistical significance; this low prevalence of concomitant drug use might reduce the detection of severe muscle toxicity in current practice.

Our findings showed that the incidence of severe muscle toxicity varied according to the definition of an adverse event, suggesting that the infrastructure in which information is stored might greatly affect assessments of safe medical practice. The majority of cases of discontinuation of statins resulted in hospitalization accompanied by acute changes in renal function. However, the outcome from severe muscle toxicity could not be ascertained since there is no information of death record in the database. Although diagnostic-based measures are inherently limited by weaknesses of administrative claims diagnostic data, including inaccuracy and incompleteness of discharge diagnoses,[32] the prescription claims have been shown to be fairly accurate and complete.[33] Thus, laboratory information was used as a surrogate indicator in this study when there was no corresponding treatment. The comparative characteristics between our two criteria imply that safety measures should be incorporated for a conservative interpretation of laboratory information. In order to avoid overestimating the risk of severe muscle toxicity, we identified the accompanying condition by both diagnosis and drugs when an event occurred, and excluded cases that were less likely to be related to statin use. Furthermore, the MDV database provided objective information that would not only complement the limitations of the claims database, but that would also provide the potential to monitor pharmacologic responses to therapeutic interventions using biomarkers. In addition, the MDV plans to enrol up to one hundred medical facilities to improve the applicability of using electronic health information in the near future. Limits to investigations imposed by small sample sizes could be overcome, and associations between the risk of adverse events and the use of statins with and without interacting drugs could be explored through this strategy. However, hospital-based data collection would be threatened by lost follow-up and lack of enrolment information such as patients' date of birth and geographic region. Since the database used in this study did not have enough power to evaluate rare events in Japanese clinical practice, the accessibility of a national claims database is expected to provide a complement to this limitation. In addition, the MIHARI project plans to aggregate information from 10 university hospitals (the Sentinel database) to confirm the signal with objective information based on appropriate methodology. Since the validity of claims-based information is often questioned, studies should be conducted to verify the validity[34] and explore the applicability of this information. From a regulatory perspective, great potential exists for evaluating risks for a population using validated information, with the goal of making efficient use of the resource. By using unique identification or indirect identifiers such as patient's date of birth, sex, hospital identification number, admission date, and discharge date, linkage between different databases is commonly used when clinical trial designs are not applicable.[35-37] Because the accessibility of healthcare information in Japan is strictly regulated by privacy protection, further discussion would be necessary to balance privacy protection with an active drug safety monitoring system.

CONCLUSIONS

The present study provides evidence of incidence of severe muscle toxicity with statin use, identified by diagnosis and objective laboratory information obtained from the claims database in Japan. Since the definition of safety measures varies according to the infrastructure of data resources, researchers should use caution when interpreting risk information that provides answers to uncertainties addressed before drug approval. While the use of combination therapy is relative low in patients with lipid disorders and without muscle complaints, the risks attributed to drug interactions in statin users require further exploration.

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FINANCIAL DISCLOSURE

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AUTHOR CONTRIBUTION

MA was the principal investigator for the grant. MK, TO and MA conceived the study. All authors contributed to study design. TO and MA were responsible for obtaining the data. CHC and MK conducted the initial data analysis. All authors contributed to decisions on the interpretation of results. CHC, KM, and MA contributed to the drafting the manuscript. All authors approved the final version of the manuscript prior to submission.

DATA SHARING STATEMENT

Technical appendix, statistical code, and dataset available from the corresponding author (makazawa@my-pharm.ac.jp). Inform consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

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Figure 1. Flow-chart of study cohort

Table 1. Characteristics of new statin users (N = 18,036) for six drugs represented in this study.

	Atorvastatin (N = 7,052)	Rosuvastatin (N = 5,921)	Pravastatin (N = 5,110)	Pitavastatin (N = 1,774)	Simvastatin (N = 976)	Fluvastatin (N = 871)
Demographic variable						
Mean age, year (SD)	65 (12)	64 (12)	68 (11)	66 (12)	68 (12)	68 (10)
Male ,%	45%	52%	38%	44%	39%	48%
Statin use*						
Duration, month (range)	24 (6–42)	15 (4–28)	22 (6–41)	16 (5–32)	23 (7–41)	16 (6–32)
Daily prescribed dose, mg, where variable)	10	2.5	10	1.6 (1–2)	5	30 (20–30)
Co-morbidity						
Hepatic impairment†,%	3%	4%	2%	2%	1%	2%
Renal impairment‡,%	25%	31%	22%	25%	15%	28%
HbA1c >6.1%,%	17%	28%	14%	22%	13%	14%
Hypertension1	25%	53%	55%	28%	60%	57%
Diabetes mellitus2	55%	31%	21%	53%	22%	21%
Cardiovascular disease3	32%	30%	27%	25%	28%	40%
Ischemic heart disease4	18%	17%	16%	14%	14%	20%
Gastric ulcer5	34%	33%	30%	32%	32%	31%
Lipid profile						
TC >1x ULN	60%(2,248/3,773)	68%(2,547/3,719)	58%(1,436/2,467)	60%(541/909)	63%(261/419)	40%(165/408)
LDL >1x ULN	71%(1,639/2,295)	73%(3,019/4,118)	64%(969/1,524)	69%(664/969)	61%(147/243)	51%(104/202)

HDL < 1x LLN	16%(603/3,375)	18%(835/4,638)	13% (321/2,288)	15%(182/1,235)	13%(51/383)	15%(76/497)
TG > 1x ULN	54%(2,320/4,266)	58%(2,949/5,056)	45%(1,274/2,835)	52%(665/1,286)	48%(223/463)	46%(234/510)

* Data shown as median (Q1–Q3).

† Renal impairment: patients whose serum creatine levels increased by >1 × the upper limit of the normal range, prior to 180 days before statin initiation.

‡ Hepatic impairment defined patients whose alanine transaminase (ALT) or aspartate transaminase (APT) increased >3x times the upper limit of the normal range prior to 180 days before statin imitation.

a Patients with hypertension defined as the use of antihypertensive drugs, including CCB, ACEI, ARB, and alpha blocker

b Patients with diabetes mellitus defined as the use of hypoglycaemic agents, including bigunide, sulfonylurea,

c Patients with cardiovascular disease defined as the use of antiplatelet, including aspirin, clopidogrel, ticlopidine and dyperidamole.

d Patients with ischemic heart disease defined as the use of nitriate, including imdur, NTG and isodil

e Patients with the gastric ulcer defined as the use of gastrointestinal protective agents, including proton pump inhibitor and H_2 receptor antagonist.

Note:

The approved daily dosage for each statin was listed as follows: atorvastatin 10–40 mg, rosuvastatin 2.5–20 mg, pravastatin 10–20 mg, pitavastatin 1–4 mg, simvastatin 5–20 mg, fluvastatin 20–60 mg.

Table 2. Risk of severe muscle toxicity among specific statin therapies

Generic statin name	# of events†	Person-years	Incidence§
Atorvastatin	17	15,776	1.08 (0.67–1.73)
Rosuvastatin	15	8,655	1.73 (1.04–2.87)
Pravastatin	5	11,121	0.45 (0.19–1.08)
Pitavastatin	3	2,883	1.04 (0.34–3.23)
Simvastatin	2	2,123	0.94 (0.24–3.77)
Fluvastatin	1	1,635	0.61 (0.09–4.34)
All statins	43	42,193	1.02 (0.76–1.37)

† Cases were defined by either criterion A (muscle related diagnosis) or criterion B (creatine kinase concentration >10x the upper limit of the normal range).

§ Data shown as per 1,000 person-years with 95% confidence interval.

Note:

Table 3. Sensitivity analysis for risk of severe muscle toxicity among all statin users

Scenario	# of events	Incidence§
Met criterion A	27	0.64 (0.44–0.93)
Met criterion A with discontinuation	7	0.17 (0.08–0.35)
Met criterion B	20	0.47 (0.31–0.73)
Met criterion B with discontinuation	6	0.14 (0.06–0.32)
Met criteria A and B	4	0.09 (0.04–0.25)
Met criteria A and B, both with discontinuation	3	0.07 (0.02–0.22)
Met criterion A or B, but change CK>5xULN as case definition*	87	2.06 (1.67-2.53)

§ Data shown as per 1,000 person-years with 95% confidence interval.

Note:

Criterion A: Defined by muscle-related diagnosis.

Criterion B: Defined by creatine kinase (CK) concentration >10x the upper limit of the normal range (ULN).

Discontinuation was defined as no use of statin therapy in the six months following occurrence of muscle toxicity.

*Criterion B: 68 cases; Met criteria A and B: 8 cases.

Table 4. Characteristics of patients exhibiting Criterion A vs. Criterion B

	Criterion A (N = 27)	Criterion B (N = 20)	p-value
Demographic variable			
Male (%)	52%	55%	0.83
Mean age, years (SD)	60 (15)	69 (11)	0.07
Statin use at the event (%)			1.00
Atorvastatin	37%	35%	
Fluvastatin	4%	0	
Pitavastatin	4%	10%	
Pravastatin	11%	15%	
Rosuvastatin	37%	35%	
Simvastatin	7%	5%	
Discontinued statin use	26%	30%	0.76
Hospitalization with discontinuation	15%	25%	0.38
Mean interval after initiating Statin, month (SD)	18 (13)	19 (20)	0.98
Laboratory information			
SCr > 1x ULN	56% (9/16)	58% (11/19)	0.92
BUN > 1x ULN	44% (7/16)	50% (10/20)	0.71
APT > 1x ULN	56% (9/16)	80% (16/20)	0.12
ALT > 1x ULN	38% (6/16)	65% (13/20)	0.10

Abbreviations: SD, standard deviation; SCr, serum creatinine; BUN, blood urea nitrogen; APT, aspartate transaminase; ALT, alanine transaminase; ULN, upper limit of normal range.

Note:

Criterion A: Defined by muscle related diagnosis.

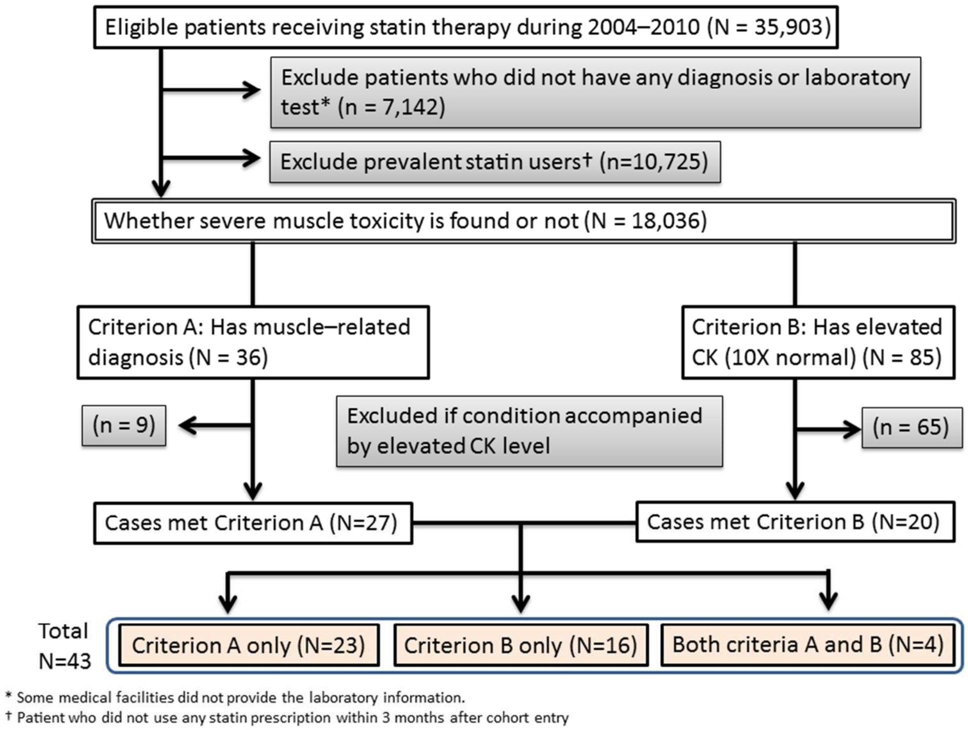
Criterion B: Defined by creatine kinase (CK) concentration >10x times the upper limit of the normal range.

Four cases met both Criteria A and B.

Table 5. Risk of severe muscle toxicity from concomitant use of interacting drugs

	Concomitant use of interacting drugs*	No concomitant use of interacting drugs
N	2,430	15,606
Person-year	1,776	40,418
Number of events	3	40
Proportion of total events, %	0.12%	0.26%
Incidence per 1,000 person-years (95% CI)	1.69 (0.54–5.24)	0.99 (0.73-1.35)

* The number of patients who were exposed to specific interacting drugs in this study were as follows: benzafibrate (256), fenofibrate (262), clinofibrate (1), clarithromycin (1,688), erythromycin (77), telithromycin (2), fluconazole (22), itraconazole (125), fosfluconazole (31), voriconazole (11), cyclosporine (66), amiodarone (93), saquinavir/ritonavir (0), atazanavir (0), and etraririne (0), and efavirenz (0).



Flow-chart of study cohort
254x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

NA: Not applicable

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-9
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-12
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	13
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	14, Table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	14-15, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15, Table 2
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21-22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Assessment of statin-associated muscle toxicity in Japan: A cohort study conducted using a claims database and laboratory information

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Assessment of statin-associated muscle toxicity in Japan: A cohort study conducted using a claims database and laboratory information

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Keywords: statin, interacting drugs, muscle toxicity, claims database, Japan

ABSTRACT

Objective:

To estimate the incidence of muscle toxicity in patients receiving statin therapy by examining study populations, drug exposure status, and outcome definitions.

Design:

Retrospective cohort study

Setting:

Sixteen medical facilities in Japan providing information on laboratory tests performed in and claims received by their facilities between 1 April 2004 and 31 December 2010.

Participants:

A database representing a cohort of 35,903 adult statin (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) users was studied. Use of interacting drugs (fibrates, triazoles, macrolides, amiodarone, and ciclosporin) by these patients was determined.

Main outcome measure:

Statin-associated muscle toxicity (the 'event') was identified based on a diagnosis of muscle-related disorders (myopathy or rhabdomyolysis) and/or abnormal elevation of creatine kinase (CK) concentrations. Events were excluded if the patients had CK elevation-related conditions other than muscle toxicity. Incidence rates for muscle toxicity were determined per 1,000 person-years, with 95% confidence intervals (CI) determined by Poisson regression.

Results:

A total of 18,036 patients accounted for 42,193 person-years of statin therapy, and 43 events were identified. The incidence of muscle toxicity in the patients treated with statins was 1.02 (95% CI: 0.76–1.37) per 1,000 person-years. The estimates varied when outcome definitions were modified from 0.09 per 1,000 person-years, which met both diagnosis and CK 10x greater than the upper limit of normal range (ULN) criteria, to 2.06 per 1,000 person-years, which met diagnosis or CK 5x ULN criterion. The incidence of muscle toxicity was also influenced by the statin therapies selected, but no significant differences were observed. Among 2,430 patients (13.5%) received interacting drugs with statins, only 3 muscle toxicity cases were observed (incidence: 1.69 per 1,000 person-years).

Conclusions:

This database study suggested that statin use is generally well tolerated and safe; however, the risk of muscle toxicity related to the use of interacting drugs requires further exploration.

ARTICLE SUMMARY

Article focus

- Asian populations are more sensitive to statins' clinical response than Western populations.
- Our objective was to evaluate the risk of muscle toxicity associated with statin and/or interacting drug use, by using claims database and laboratory information in Japan.

Key messages

- Patients receiving prescription statins were most often prescribed the lower limits of approved dosages, with rare concomitant use of interacting drugs that could increase steady-state statin concentrations.
- The number of adverse events was limited; the incidence of muscle toxicity was statistically indistinguishable among statins.
- This study has major implications for risk evaluation, given the information infrastructure available to validate claims-based estimations.

Strengths and limitations of this study

- This is the first study to evaluate drug-associated risk by using claims database and laboratory information in Japan, indicating the potential applicability of electronic health information as a resource for applied analyses.
- Interacting drug use associated with increased risk of muscle toxicity requires further exploration because a low number of person-years of observations currently exists in the literature. Diagnostic information is slightly less complete than is prescription and laboratory test information; researchers should use caution when interpreting related information in database studies.

INTRODUCTION

Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor or HMG-CoA reductase inhibitor) are widely used for adults presenting with cardiovascular disease (CVD), and those with a 20% or greater 10-year risk of developing CVD, [1] to reduce the incidence of cardiovascular co-morbidity and mortality. Although statins are well-tolerated by the vast majority of patients, their use can lead to infrequent adverse muscle, renal, and hepatic events. [2, 3] Severe adverse events could lead to additional drug costs, increasing the burden of healthcare expenditures. [4] In addition, the concomitant use of interacting drugs could increase the risk of muscle toxicity. [5] Moreover, the Asian population is more sensitive in its clinical response to statins than is the Western population, and approved statin doses in Japan are relatively low compared to those approved for use in the US. [6-9]

Clinical trials are restricted in the number and diversity of participants enrolled, such that the chances of detecting rare, adverse treatment effects are low. Regulatory bodies, including those in Japan, have long relied primarily on the voluntary reporting system to monitor post-marketing safety. In addition to voluntary reporting, which does not accurately reflect risk due to under-reporting, a major challenge for assessing the safety of statin use is a lack of comparative data. Given concerns about the limitations of existing monitoring systems, the use of automatic databases such as claims or electronic healthcare records for post-marketing safety assessment has been well-structured and widely applied in the US and EU. [10, 11] Recently, the Sentinel System was launched by the US Food and Drug Administration (FDA) to develop active surveillance capabilities for evaluating post-market safety issues in regulated medical products. [12] In Japan, in order to complement this strategy for safety assessment, the Medical Information of Risk Assessment Initiative (MIHARI project) was launched by the Pharmaceutical and Medical Devices Agency (PMDA) in 2009. [13, 14] In retrospective studies, a health outcome was defined by criteria that are restricted by the structure of a given database. Different definitions for explaining a certain adverse event could result in different conclusions. Before researchers and regulators begin working with large automated databases (including the MIHARI database) for drug safety monitoring, pilot studies are needed to evaluate the pros and cons of database studies under the Japanese healthcare system.

In early 2012, the FDA issued labelling changes for statin drugs based on updated safety information. [15] Administrative databases may be useful for identifying potential problems, such as assessment of risk factors and incidence of adverse treatment effects. Our study evaluated the rare adverse event of statin-associated muscle toxicity (e.g. myopathy or rhabdomyolysis), defined by two criteria, by using the claims database with laboratory information.

METHODS AND ANALYSIS

Data resource

This retrospective cohort study analysed data from Medical Data Vision Co. Ltd. (MDV) in Tokyo, Japan. This commercial, electronic, record-based healthcare database provides information on ambulatory service, hospitalization, medication use, and laboratory tests for patients from 1 January 2004 through 31 December 2010. It contains the patients' demographic characteristics (e.g. age and sex), diagnoses (International Statistical Classification of Disease and Related Health Problems (ICD–10 codes)), prescription information (dose, quantity, and number of days of supply), and the results of laboratory tests for approximately 410,000 patients at 16 medical facilities across Japan. [16] Although the source of information was limited to 16 facilities, the age and gender distribution of patients in the database was similar to that of the national demographics. Furthermore, the database had been used for various epidemiological studies including an observational study examining a national estimate of acute pancreatitis risk among diabetes patients in Japan. [17] Patients' identities have been encrypted for protection of privacy, but the data sets could be linked using unique, anonymous identifiers created by the data providers for research purposes. This study was approved by the Institutional Review Board at Meiji Pharmaceutical University and was conducted in compliance with the Japanese Ethical Guidelines for Epidemiological Research, updated in December 2008. [18]

Study cohort

Patients aged 18 or older who received initiated statin therapy between 1 July 2004 and 30 June 2010 were included in this study. Because the median duration of statin prescription in the database was 28 days, a patient would be enrolled if there was no existing claim of a statin prescription within 3 months after the first date of any claim. To avoid enrolling prevalent cases with muscle toxicity, patients who exhibited the following conditions during the 3 month period prior to statin initiation would be excluded: a diagnosis of rhabdomyolysis/myositis; or the possibility of muscle-related CK elevation (i.e., patients whose CK elevation did not present with myocardial infarction, myocarditis, trauma, or hypothyroidism, and who had no claims of obtaining nitrate or levothyroxine prescriptions within 3 days after concurrent elevation of CK). The eligible population was required to have undergone at least one blood test during statin therapy, to construct a cohort in which ascertainment of outcome was potentially equivalent.

Exposure of interest

The information on statin therapy was extracted from the claims database, and exposure time was estimated for each patient based on the amount of statin continuously received by the patient, reported as person-years. We assumed that the patients received consecutive treatment from the initiation of statin therapy until the end of the last prescription, because the patients were monitored regularly. [19, 20] The statins commercially available in Japan during the investigation period were atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. The prescribing dosage was defined as the sum total of the doses prescribed during the follow-up period, divided by exposure time. Because medications might be changed or added for treatment purposes, patients were allowed to contribute to multiple cohorts.

We also defined drugs that have some pharmacokinetic interactions with statins and that may increase risk of muscle toxicity. Lists of potentially interacting drugs were compiled from package inserts for statin medications, excluding topical and ophthalmic preparations. [21] We determined whether patients had used any of the following interacting drugs while undergoing statin therapy: fibrate (benzafibrate, fenofibrate, and clinofibrate), macrolide antibiotics (clarithromycin, erythromycin, and telithromycin), triazole antimycotics (fluconazole, itraconazole, fosfluconazole, and voriconazole), immunosuppressant (cyclosporine), antiarrhythmic drug (amiodarone), and HIV/AIDS drugs (saquinavir/ritonavir, atazanavir, etravirine, and efavirenz). Statin therapy administrated concurrently with an interacting agent was treated as a time-varying covariate. Subjects could contribute person-time to the statin both with and without a concomitant interacting drug. Because the package inserts list the aforementioned interacting drugs as contraindicated or to be used with caution, concomitant use of these drugs with statins is rare. Therefore, we pooled all interacting drugs together rather than assessing specific drug interactions.

Case identification

Previous studies generally defined statin-associated muscle toxicity by diagnosis and/or by elevated creatine kinase (CK) concentration. [22, 23] Since databases based on insurance claims do not contain laboratory results, differences in risk estimation would occur with the varying composition of available data. Therefore, we identified muscle toxicity by using the following two criteria to explore the deviation between differing definitions. Criterion A was based on diagnosis of muscle-related disorders. Because there is no specific ICD-10 code to indicate muscle toxicity, the diagnosis contained the words ‘myositis’ or ‘rhabdomyolysis’, which were originally written in the Japanese language and were identified using a computer-assisted text searching method (FINDW function in SAS). Criterion B was based on laboratory results. A patient whose CK concentration was greater than ten times the upper limit of the normal range under statin therapy would be identified as a case. The normal range was given according to the sensitivity of the reference agents used in laboratory tests at each medical facility. The case was recognized as an event if no disease-related condition accompanied by CK elevation was confirmed. The disease-related conditions for CK elevation were as follows: any presence of diagnosis for myocardial infarction, myocarditis, trauma, or hypothyroidism, and any claim of nitrate and levothyroxine prescriptions being obtained within three days after the muscle toxicity event. [24] Statin therapy might be discontinued upon development of intolerable muscle symptoms, with or without CK elevation, in patients for whom other aetiologies were ruled out. [24] Physicians’ management decisions about continuation or discontinuation of treatment were determined by compiling claims from patients’ health records. Discontinuation and switching were defined as no use of statin therapy or initiation of another statin therapy in the six months following occurrence of muscle toxicity.

Statistical analyses

The incidence rate for muscle toxicity was presented per 1,000 person-years with 95% confidence intervals (CI) estimated by Poisson regression. The baseline period was defined as 180 days prior to statin initiation. Demographic (age, gender) and co-administration data were extracted from medical claims from the baseline period within the statin inception cohort. Patients were observed until occurrence of the first muscle toxicity event, and were censored when statin therapy was discontinued or when the end of the observational period was reached (31 December 2010). In addition to claims data, we identified the presence of co-morbidities from laboratory information for the baseline period. Renal impairment was defined by serum creatine concentrations (SCr) above the upper limit of the normal range; hepatic impairment was indicated where laboratory values for alanine transaminase (ALT) and aspartate transaminase (APT) increased by more than three times the upper limit of normal during the baseline period. The cut-off of glycated haemoglobin (HbA1c) level for diabetes mellitus was set at greater than 6.1%, according to diagnostic criteria adopted in Japan. [25] To compare the characteristics of demographic and clinical variables between criteria, Kolmogorov-Smirnov tests were performed for continuous variables, and chi-square tests were used for dichotomous variables. Co-morbidity and co-administration of drugs were defined according to whether claims of a prescription were made prior to 180 days before occurrence of an event. In addition, to determine the muscle toxicity risk associated with drug-drug interactions, the incidence of muscle toxicity among patients who had concomitantly used interacting drugs was compared with that in patients who did not. Various sensitivity analyses were performed by modifying baseline periods (6 months and 12 months), statin exposure status (number of days on which statins were received as a denominator), and outcome definitions (abnormal range of CK values and switching, renal dysfunction, or hospitalization, with muscle toxicity). All statistical analyses were carried out using SAS software Version 9.3 (SAS Institute Inc., 2012, Cary NC, USA).

RESULTS

A total of 18,036 patients met all the criteria to be defined as new statin users (Figure 1). Of these patients, 11,468 (64%) were diagnosed as having dyslipidaemia, 14,355 (80%) had higher than normal levels of cholesterol, triglyceride or low-density lipoprotein, and 9,382 (52%) were diagnosed as having dyslipidaemia accompanied by higher than normal lipid levels. The mean (SD) age and follow-up month of patients in whom statin use was initiated were 66 (12) years and 29 (22) months, respectively, and 45% of patients were male. Atorvastatin was the most prevalent HMG-CoA reductase inhibitor and contributed to 37% of the total person-years in the inception cohort. The prescribed dosage was generally around the lower limit of the approved dose, with limited variation, regardless of the statin (Table 1).

Among the new statin users, 43 (0.24%) who met either criterion A or B were identified as base cases, and incidence (with 95% CI) of muscle toxicity was estimated as 1.02 (0.76–1.37) per 1,000 person-years (Table 2). According to various outcome definitions, the estimated incidences ranged from 0.09 (met both criteria A and B) to 2.06 (either met criterion A or demonstrated CK values > 5x ULN) per 1,000 person-years. When the strictest definition was selected (i.e., cases met both criteria A and B), 4 cases were identified, and most of these showed discontinuation, switching, renal dysfunction, or hospitalization after the occurrence of the adverse event (3, 1, 3, and 4 cases, respectively). No significant changes were observed when baseline periods or statin exposure status were modified. Incidence of muscle toxicity in the patients treated with statin monotherapy ranged from 0.45 with pravastatin to 1.73 with rosuvastatin per 1,000 person-years (Table 3). Using atorvastatin, the most widely prescribed statin in Japan, as the reference, incidences of muscle toxicity were statistically indistinguishable among the statins, regardless of the criterion used. Similarly, demographic and other characteristics of the cases did not differ for the two criteria (Table 4).

Of new statin users, 2,430 (13.5%) received interacting drugs during the follow-up period. Regarding the incidence rate of muscle toxicity with respect to interacting drug use, a low number of person-years of observation were contributed, representing limited use of interacting drugs, even when all statins and interacting drugs were aggregated. Because of the low number of events recorded, we found the wide 95% CI included the estimated incidence rate (Table 5).

DISCUSSION

This study extends previous work in measuring statin-associated muscle toxicity by using the claims database with laboratory information for actual patient records in Japan. Since the package insert suggests periodical laboratory tests during statin therapy, it is possible to assess the change of medical condition. With an estimated incidence of approximately 1 per 1,000 person-years of statin use, a low occurrence of muscle toxicity was found in the present study. Moreover, less than about one in five patients was found to show concomitant use of interacting drugs, implying that the use of statins is generally well tolerated and safe in Japan. The characteristics and incidences of muscle toxicity between statins were not significantly different. In addition, clinical characteristics were similar among cases defined by diagnosis and cases defined by laboratory results. However, the number of cases in which dyslipidaemia was diagnosed was slightly lower than the number of cases with concurrent elevated lipid levels, indicating an inconsistency between diagnosis and laboratory data.

Information on the frequency (% of users) of muscle toxicity is not provided in Japanese statin medication package inserts, with the exceptions of those of rosuvastatin (0.1%) and simvastatin (0.01%). The lower limit of the 95% confidence interval showed a value consistent with available package inserts; however, it is possible that adverse events would occur more frequently with widespread use of statins in clinical practice, because populations that participate in clinical trials are usually highly selected. [26] Comparing our analysis to statistics reported in previous studies (mostly from the US), the crude incidence of rhabdomyolysis ranged from 2.5 to 4.4 per 100,000 person-years among statin users, when identified by diagnosis and laboratory results combined. [22, 23] Since it is not applicable to compare the incidence of events defined by different parameters, we refined our event definition to consider statin discontinuation or switching and renal dysfunction or hospitalization after the occurrence of an adverse event. Under this revised definition, we found the crude incidence of rhabdomyolysis to be 7.1 to 9.5 per 100,000 person-years (3 to 4 cases per 42,193 person-years). The incidence of rhabdomyolysis might differ among studies because the proportion of patients with risk factors is apparently different between the populations. Some case reports indicated that factors related to statin-associated muscle toxicity included old age, female gender, low body mass index, and diabetes mellitus, [27] characteristics that were common among patients in our study. However, evidence showed no increase in the rate of adverse events in Asian patients taking either lower or higher doses of statin, [28] despite racial differences in the pharmacokinetics of rosuvastatin between Asians and Caucasian. [29] After all the controversy over racial differences in pharmacokinetics and the clinical outcomes of statin (particularly rosuvastatin) use, the majority of prescribed doses were at the lower limits of approved dosage levels, implying comparable potency among statins at the lowest effective dose. Taking dosage levels into account, statins were well tolerated in the Japanese population, with a similar incidence of rhabdomyolysis as that reported in Caucasian populations.

Using the claims database to evaluate potential drug interactions with statins is a useful complement to the limited information available from voluntary reports and clinical trials. A recent study found that the use of against label statin-fibrate combination therapy is decreasing annually, but that use of this therapy persists in the

US. [30] In the present study, only 2.8% of patients had been prescribed concomitant statin-fibrate therapy (data not shown). Although combination therapy may be attractive for patients with lipid disorders and without muscle complaints, the low prevalence of concomitant fibrate use implies that it is 'generally contraindicated', and that clinical practitioners are aware of the risks. Whether the risk is due to drug interactions remains controversial, [31, 32] but our study points to a higher incidence of muscle toxicity among patients taking interacting drugs. However, a low number of person-years of interacting drug use observations corresponded to a lack of statistical significance; this low prevalence of concomitant drug use might reduce the detection of muscle toxicity in current practice.

Our findings showed that the incidence of muscle toxicity varied according to the definition of an adverse event, suggesting that the infrastructure in which information is stored might greatly affect assessments of safe medical practice. The majority of cases of discontinuation or switching of statins resulted in hospitalization accompanied by acute changes in renal function. However, the outcome from severe muscle toxicity could not be ascertained since there is no information of death record in the database. Although diagnosis-based measures are inherently limited by weaknesses of administrative claims diagnostic data, including inaccuracy and incompleteness of discharge diagnoses, [33] the prescription claims have been shown to be fairly accurate and complete. [34] Thus, laboratory information was used as a surrogate indicator in this study when there was no corresponding treatment. The comparative characteristics between our two criteria imply that safety measures should be incorporated for a conservative interpretation of laboratory information. In order to avoid overestimating the risk of muscle toxicity, we identified the accompanying condition by both diagnosis and drugs when an event occurred, and excluded cases that were less likely to be related to statin use. Furthermore, the MDV database provided objective information that would not only complement the limitations of the claims database, but that would also provide the potential to monitor pharmacologic responses to therapeutic interventions using biomarkers. In addition, the MDV plans to enrol up to one hundred medical facilities to improve the applicability of using electronic health information in the near future. Limits to investigations imposed by small sample sizes could be overcome, and associations between the risk of adverse events and the use of statins with and without interacting drugs could be explored through this strategy. However, hospital-based data collection would be threatened by lost follow-up and lack of enrolment information such as patients' date of birth and geographic region. Since the database used in this study did not have enough power to evaluate rare events in Japanese clinical practice, the accessibility of a national claims database is expected to provide a complement to this limitation. In addition, the MIHARI project plans to aggregate information from 10 university hospitals (the Sentinel database) to confirm the signal with objective information based on appropriate methodology. Since the validity of claims-based information is often questioned, studies should be conducted to verify the validity [35] and explore the applicability of this information. From a regulatory perspective, great potential exists for evaluating risks for a population using validated information, with the goal of making efficient use of the resource. By using unique identification or indirect identifiers such as patient's date of birth, sex, hospital identification number, admission date, and discharge date, linkage between different databases is commonly used when clinical trial designs are not applicable. [36-38] Because the accessibility of healthcare information in Japan is strictly regulated by privacy protection, further discussion would be necessary to balance privacy protection with an active drug safety monitoring system.

CONCLUSIONS

The present study provides evidence of incidence of muscle toxicity with statin use, identified by diagnosis and objective laboratory information obtained from the claims database in Japan. Since the definition of safety measures varies according to the infrastructure of data resources, researchers should use caution when interpreting risk information that provides answers to uncertainties addressed before drug approval. While the use of combination therapy is relative low in patients with lipid disorders and without muscle complaints, the risks attributed to drug interactions in statin users require further exploration.

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FINANCIAL DISCLOSURE

This study was supported by a research grant from the Pfizer Health Research Foundation (Tokyo Japan).The sponsor had no role in study design, data collection, data analysis, data interpretation, or approval of the manuscript.

AUTHOR CONTRIBUTION

MA was the principal investigator for the grant. MK, TO and MA conceived the study. All authors contributed to study design. TO and MA were responsible for obtaining the data. CHC and MK conducted the initial data analysis. All authors contributed to decisions on the interpretation of results. CHC, KM, and MA contributed to the drafting the manuscript. All authors approved the final version of the manuscript prior to submission.

DATA SHARING STATEMENT

Technical appendix, statistical code, and dataset available from the corresponding author (makazawa@my-pharm.ac.jp). Inform consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

COMPETING INTERESTS

None

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Figure legend

Figure 1. Flow-chart of study cohort

Table 1. Characteristics of new statin users (N = 18,036) for six drugs represented in this study.

	Atorvastatin (N = 7,052)	Rosuvastatin (N = 5,921)	Pravastatin (N = 5,110)	Pitavastatin (N = 1,774)	Simvastatin (N = 976)	Fluvastatin (N = 871)
Demographic variable						
Mean age, year (SD)	65 (12)	64 (12)	68 (11)	66 (12)	68 (12)	68 (10)
Male ,%	45%	52%	38%	44%	39%	48%
Statin use*						
Duration, month (range)	24 (6–42)	15 (4–28)	22 (6–41)	16 (5–32)	23 (7–41)	16 (6–32)
Daily prescribed dose, mg, where variable)	10	2.5	10	1.6 (1–2)	5	30 (20–30)
Co-morbidity						
Hepatic impairment†,%	3%	4%	2%	2%	1%	2%
Renal impairment‡,%	25%	31%	22%	25%	15%	28%
HbA1c >6.1%,%	17%	28%	14%	22%	13%	14%
Hypertension [a]	25%	53%	55%	28%	60%	57%
Diabetes mellitus [b]	55%	31%	21%	53%	22%	21%
Cardiovascular disease [c]	32%	30%	27%	25%	28%	40%
Ischemic heart disease [d]	18%	17%	16%	14%	14%	20%
Gastric ulcer [e]	34%	33%	30%	32%	32%	31%
Lipid profile						
TC >1x ULN	60%(2,248/3,773)	68%(2,547/3,719)	58%(1,436/2,467)	60%(541/909)	63%(261/419)	40%(165/408)
LDL-C >1x ULN	71%(1,639/2,295)	73%(3,019/4,118)	64%(969/1,524)	69%(664/969)	61%(147/243)	51%(104/202)

HDL-C < 1x LLN	16%(603/3,375)	18%(835/4,638)	13% (321/2,288)	15%(182/1,235)	13%(51/383)	15%(76/497)
TG > 1x ULN	54%(2,320/4,266)	58%(2,949/5,056)	45%(1,274/2,835)	52%(665/1,286)	48%(223/463)	46%(234/510)

* Data shown as median (Q1–Q3), † Renal impairment: patients whose serum creatine levels increased by >1 × the upper limit of the normal range prior to 180 days before statin initiation, ‡ Hepatic impairment defined patients whose alanine transaminase (ALT) or aspartate transaminase (APT) increased >3x times the upper limit of the normal range prior to 180 days before statin imitation, [a] Patients with hypertension defined as the use of antihypertensive drugs, including CCB, ACEI, ARB, and alpha blocker, [b] Patients with diabetes mellitus defined as the use of hypoglycaemic agents, including bigunide and sulfonylurea, [c] Patients with cardiovascular disease defined as the use of antiplatelet, including aspirin, clopidogrel, ticlopidine, and dyperidamole, [d] Patients with ischemic heart disease defined as the use of nitriate, including imdur, NTG, and isodil, [e] Patients with the gastric ulcer defined as the use of gastrointestinal protective agents, including proton pump inhibitor and H_2 receptor antagonist.

Note: TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, and TG: triglyceride. The approved daily dosage for each statin was listed as follows: atorvastatin 10–40 mg, rosuvastatin 2.5–20 mg, pravastatin 10–20 mg, pitavastatin 1–4 mg, simvastatin 5–20 mg, and fluvastatin 20–60 mg.

Table 2: Risks of muscle toxicity by various case definitions

Outcome definitions	# of cases with events	# of eligible persons	Person -years	Incidence * [95% CI]
Base-case definition: criterion A (diagnosis of 'myositis' or 'rhabdomyolysis') or criterion B (CK >10x ULN)	**43**	**18,036**	**42,193**	**1.02 [0.76–1.37]**
with discontinuation	10			0.24 [0.13–0.44]
with switching	3			0.07 [0.02–0.22]
with renal dysfunction	17			0.40 [0.25–0.65]
with hospitalization	17			0.40 [0.25–0.65]
Criterion A or CK >5x ULN	87	**18,036**	**42,193**	2.06 [1.67–2.54]
with discontinuation	23			0.55 [0.36–0.82]
with switching	7			0.17 [0.08–0.35]
with renal dysfunction	39			0.92 [0.68–1.27]
with hospitalization	34			0.81 [0.58–1.13]
Criteria A and B	4	**18,036**	**42,193**	0.09 [0.04–0.25]
with discontinuation	3			0.07 [0.02–0.22]
with switching	1			0.02 [0.00–0.17]
with renal dysfunction	3			0.07 [0.02–0.22]
with hospitalization	4			0.09 [0.04–0.25]
Myositis (and criterion B)	0			--
Rhabdomyolysis (and criterion B)	4			0.09 [0.04–0.25]
Criterion A and CK > 5x ULN	8	**18,036**	**42,193**	0.19 [0.09–0.38]
with discontinuation	3			0.07 [0.02–0.22]
with switching	1			0.02 [0.00–0.17]
with renal dysfunction	6			0.14 [0.06–0.32]
with hospitalization	7			0.17 [0.08–0.35]
Myositis (and CK > 5x ULN)	0			--
Rhabdomyolysis	8			0.19 [0.09–0.38]

(and CK > 5x ULN)				
Criterion A	27	**18,036**	**42,193**	0.64 [0.44–0.93]
with discontinuation	7			0.17 [0.08–0.35]
with switching	3			0.07 [0.02–0.22]
with renal dysfunction	9			0.21 [0.11–0.41]
with hospitalization	8			0.19 [0.09–0.38]
Myositis	12			0.28 [0.16–0.50]
Rhabdomyolysis	15			0.36 [0.21–0.59]
Criterion B	20	**18,036**	**42,193**	0.47 [0.31–0.73]
with discontinuation	6			0.14 [0.06–0.22]
with switching	1			0.02 [0.00–0.17]
with renal dysfunction	11			0.26 [0.14-0.47]
with hospitalization	13			0.31 [0.18–0.53]
CK > 5x ULN	68			1.61 [1.27–2.04]
Baseline period				
Base case definition: 3months	**43**	**18,036**	**42,193**	**1.02 [0.76–1.37]**
6 months	40	16,649	38,645	1.04 [0.76–1.41]
12 months	31	13,693	29,387	1.05 [0.74–1.50]
Statin exposure status				
Base case definition: continuous exposure	**43**	**18,036**	**42,193**	**1.02 [0.76–1.37]**
Excluding stopping periods (days of statin supply)	39	18,036	38,027	1.03 [0.75–1.40]

* Data shown as per 1,000 person-years with 95% confidence interval.

Note: CK: creatine kinase, ULN: upper limit of the normal range. Discontinuation was defined as no use of statin therapy in the six months following occurrence of muscle toxicity. Switching was defined as patients who initiated another statin in the following period. Renal dysfunction was defined as serum creatinine increased above the upper limit of normal range within three days before or seven days after occurrence of an event.

Table 3. Risks of muscle toxicity among specific statin therapies

Generic statin name	# of cases with events *	Person-years	Incidence †
All statins	43	42,193	1.02 (0.76–1.37)
Atorvastatin	17	15,776	1.08 (0.67–1.73)
Rosuvastatin	15	8,655	1.73 (1.04–2.87)
Pravastatin	5	11,121	0.45 (0.19–1.08)
Pitavastatin	3	2,883	1.04 (0.34–3.23)
Simvastatin	2	2,123	0.94 (0.24–3.77)
Fluvastatin	1	1,635	0.61 (0.09–4.34)

* Cases were defined by either criterion A (diagnosis of 'myositis' or 'rhabdomyolysis') or criterion B (creatine kinase concentration >10x the upper limit of the normal range).

† Data shown as per 1,000 person-years with 95% confidence interval.

Table 4. Characteristics of patients exhibiting Criterion A vs. Criterion B

	Criterion A * (N = 27)	Criterion B * (N = 20)	p-value
Demographic variable			
Male (%)	52%	55%	0.83
Mean age, years (SD)	60 (15)	69 (11)	0.07
Statin use at the event (%)			1.00
Atorvastatin	37%	35%	
Fluvastatin	4%	0	
Pitavastatin	4%	10%	
Pravastatin	11%	15%	
Rosuvastatin	37%	35%	
Simvastatin	7%	5%	
Mean interval after initiating Statin, month (SD)	18 (13)	19 (20)	0.98
Laboratory information			
SCr > 1x ULN	56% (9/16)	58% (11/19)	0.92
BUN > 1x ULN	44% (7/16)	50% (10/20)	0.71
APT > 1x ULN	56% (9/16)	80% (16/20)	0.12
ALT > 1x ULN	38% (6/16)	65% (13/20)	0.10

* Criterion A is defined by diagnosis of 'myositis' or 'rhabdomyolysis' and criterion B is defined by creatine kinase (CK) concentration >10x times the upper limit of the normal range. Four cases met both Criteria A and B.

Note: SD: standard deviation, SCr: serum creatinine, BUN: blood urea nitrogen, APT: aspartate transaminase, ALT: alanine transaminase, ULN: upper limit of normal range.

Table 5. Risk of muscle toxicity from concomitant use of interacting drugs

	Concomitant use of interacting drugs *	No concomitant use of interacting drugs
N	2,430	15,606
Person-year	1,776	40,418
Number of events	3	40
Proportion of total events, %	0.12%	0.26%
Incidence per 1,000 person-years (95% CI)	1.69 (0.54–5.24)	0.99 (0.73–1.35)

* The number of patients who were exposed to specific interacting drugs in this study were as follows: benzafibrate (256), fenofibrate (262), clinofibrate (1), clarithromycin (1,688), erythromycin (77), telithromycin (2), fluconazole (22), itraconazole (125), fosfluconazole (31), voriconazole (11), cyclosporine (66), amiodarone (93), saquinavir/ritonavir (0), atazanavir (0), etraririne (0), and efavirenz (0).

Assessment of statin-associated muscle toxicity in Japan: A cohort study conducted using a claims database and laboratory information

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ABSTRACT

Objective:

To estimate the incidence of muscle toxicity in patients receiving statin therapy by examining study populations, drug exposure status, and outcome definitions.

Design:

Retrospective cohort study

Setting:

Sixteen medical facilities in Japan providing information on laboratory tests performed in and claims received by their facilities between 1 April 2004 and 31 December 2010.

Participants:

A database representing a cohort of 35,903 adult statin (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) users was studied. Use of interacting drugs (fibrates, triazoles, macrolides, amiodarone, and ciclosporin) by these patients was determined.

Main outcome measure:

Statin-associated muscle toxicity (the 'event') was identified based on a diagnosis of muscle-related disorders (myopathy or rhabdomyolysis) and/or abnormal elevation of creatine kinase (CK) concentrations. Events were excluded if the patients had CK

elevation-related conditions other than muscle toxicity. Incidence rates for muscle toxicity were determined per 1,000 person-years, with 95% confidence intervals (CI) determined by Poisson regression.

Results:

A total of 18,036 patients accounted for 42,193 person-years of statin therapy, and 43 events were identified. The incidence of muscle toxicity in the patients treated with statins was 1.02 (95% CI: 0.76–1.37) per 1,000 person-years. The estimates varied when outcome definitions were modified from 0.09 per 1,000 person-years, which met both diagnosis and CK 10x greater than the upper limit of normal range (ULN) criteria, to 2.06 per 1,000 person-years, which met diagnosis or CK 5x ULN criterion. The incidence of muscle toxicity was also influenced by the statin therapies selected, but no significant differences were observed. Among 2,430 patients (13.5%) received interacting drugs with statins, only 3 muscle toxicity cases were observed (incidence: 1.69 per 1,000 person-years).

Conclusions:

This database study suggested that statin use is generally well tolerated and safe; however, the risk of muscle toxicity related to the use of interacting drugs requires further exploration.

ARTICLE SUMMARY

Article focus

- Asian populations are more sensitive to statins' clinical response than Western populations.
- Our objective was to evaluate the risk of muscle toxicity associated with statin and/or interacting drug use, by using claims database and laboratory information in Japan.

Key messages

- Patients receiving prescription statins were most often prescribed the lower limits of approved dosages, with rare concomitant use of interacting drugs that could increase steady-state statin concentrations.
- The number of adverse events was limited; the incidence of muscle toxicity was statistically indistinguishable among statins.
- This study has major implications for risk evaluation, given the information infrastructure available to validate claims-based estimations.

Strengths and limitations of this study

- This is the first study to evaluate drug-associated risk by using claims database and laboratory information in Japan, indicating the potential applicability of electronic health information as a resource for applied analyses.
- Interacting drug use associated with increased risk of muscle toxicity requires further exploration because a low number of person-years of observations currently exists in the literature. Diagnostic information is slightly less complete than is prescription and laboratory test information; researchers should use caution when interpreting related information in database studies.

INTRODUCTION

Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor or HMG-CoA reductase inhibitor) are widely used for adults presenting with cardiovascular disease (CVD), and those with a 20% or greater 10-year risk of developing CVD, [1] to reduce the incidence of cardiovascular co-morbidity and mortality. Although statins are well-tolerated by the vast majority of patients, their use can lead to infrequent adverse muscle, renal, and hepatic events. [2, 3] Severe adverse events could lead to additional drug costs, increasing the burden of healthcare expenditures. [4] In addition, the concomitant use of interacting drugs could increase the risk of muscle toxicity. [5] Moreover, the Asian population is more sensitive in its clinical response to statins than is the Western population, and approved statin doses in Japan are relatively low compared to those approved for use in the US. [6-9]

Clinical trials are restricted in the number and diversity of participants enrolled, such that the chances of detecting rare, adverse treatment effects are low. Regulatory bodies, including those in Japan, have long relied primarily on the voluntary reporting system to monitor post-marketing safety. In addition to voluntary reporting, which does not accurately reflect risk due to under-reporting, a major challenge for assessing the safety of statin use is a lack of comparative data. Given concerns about the limitations of existing monitoring systems, the use of automatic databases such as claims or electronic healthcare records for post-marketing safety assessment has been well-structured and widely applied in the US and EU. [10, 11] Recently, the Sentinel System was launched by the US Food and Drug Administration (FDA) to develop active surveillance capabilities for evaluating post-market safety issues in regulated medical products. [12] In Japan, in order to complement this strategy for safety assessment, the Medical Information of Risk Assessment Initiative (MIHARI project) was launched by the Pharmaceutical and Medical Devices Agency (PMDA) in 2009. [13, 14] In retrospective studies, a health outcome was defined by criteria that are restricted by the structure of a given database. Different definitions for explaining a certain adverse event could result in different conclusions. Before researchers and regulators begin working with large automated databases (including the MIHARI database) for drug safety monitoring, pilot studies are needed to evaluate the pros and cons of database studies under the Japanese healthcare system.

In early 2012, the FDA issued labelling changes for statin drugs based on updated safety information. [15] Administrative databases may be useful for identifying potential problems, such as assessment of risk factors and incidence of adverse treatment effects. Our study evaluated the rare adverse event of statin-associated muscle toxicity (e.g. myopathy or rhabdomyolysis), defined by two criteria, by using the claims database with laboratory information.

METHODS AND ANALYSIS

Data resource

This retrospective cohort study analysed data from Medical Data Vision Co. Ltd. (MDV) in Tokyo, Japan. This commercial, electronic, record-based healthcare database provides information on ambulatory service, hospitalization, medication use, and laboratory tests for patients from 1 January 2004 through 31 December 2010. It contains the patients' demographic characteristics (e.g. age and sex), diagnoses (International Statistical Classification of Disease and Related Health Problems (ICD–10 codes)), prescription information (dose, quantity, and number of days of supply), and the results of laboratory tests for approximately 410,000 patients at 16 medical facilities across Japan. [16] Although the source of information was limited to 16 facilities, the age and gender distribution of patients in the database was similar to that of the national demographics. Furthermore, the database had been used for various epidemiological studies including an observational study examining a national estimate of acute pancreatitis risk among diabetes patients in Japan. [17] Patients' identities have been encrypted for protection of privacy, but the data sets could be linked using unique, anonymous identifiers created by the data providers for research purposes. This study was approved by the Institutional Review Board at Meiji Pharmaceutical University and was conducted in compliance with the Japanese Ethical Guidelines for Epidemiological Research, updated in December 2008. [18]

Study cohort

Patients aged 18 or older who received initiated statin therapy between 1 July 2004 and 30 June 2010 were included in this study. Because the median duration of statin prescription in the database was 28 days, a patient would be enrolled if there was no existing claim of a statin prescription within 3 months after the first date of any claim. To avoid enrolling prevalent cases with muscle toxicity, patients who exhibited the following conditions would be excluded: a diagnosis of rhabdomyolysis/myositis; or the possibility of muscle-related CK elevation (i.e., patients whose CK elevation did not present with myocardial infarction, myocarditis, trauma, or hypothyroidism, and who had no claims of obtaining nitrate or levothyroxine prescriptions within 3 days after concurrent elevation of CK). The eligible population was required to have undergone at least one blood test during statin therapy, to construct a cohort in which ascertainment of outcome was potentially equivalent.

Exposure of interest

The information on statin therapy was extracted from the claims database, and exposure time was estimated for each patient based on the amount of statin continuously received by the patient, reported as person-years. We assumed that the patients received consecutive treatment from the initiation of statin therapy until the end of the last prescription, because the patients were monitored regularly. [19, 20] The statins commercially available in Japan during the investigation period were atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. The prescribing dosage was defined as the sum total of the doses prescribed during the follow-up period, divided by exposure time. Because medications might be changed or added for treatment purposes, patients were allowed to contribute to multiple cohorts.

We also defined drugs that have some pharmacokinetic interactions with statins and that may increase risk of muscle toxicity. Lists of potentially interacting drugs were compiled from package inserts for statin medications, excluding topical and ophthalmic preparations. [21] We determined whether patients had used any of the following interacting drugs while undergoing statin therapy: fibrate (benzafibrate, fenofibrate, and clinofibrate), macrolide antibiotics (clarithromycin, erythromycin, and telithromycin), triazole antimycotics (fluconazole, itraconazole, fosfluconazole, and voriconazole), immunosuppressant (cyclosporine), antiarrhythmic drug (amiodarone), and HIV/AIDS drugs (saquinavir/ritonavir, atazanavir, etravirine, and efavirenz). Statin therapy administrated concurrently with an interacting agent was treated as a time-varying covariate. Subjects could contribute person-time to the statin both with and without a concomitant interacting drug. Because the package inserts list the aforementioned interacting drugs as contraindicated or to be used with caution, concomitant use of these drugs with statins is rare. Therefore, we pooled all interacting drugs together rather than assessing specific drug interactions.

Case identification

Previous studies generally defined statin-associated muscle toxicity by diagnosis and/or by elevated creatine kinase (CK) concentration. [22, 23] Since databases based on insurance claims do not contain laboratory results, differences in risk estimation would occur with the varying composition of available data. Therefore, we identified muscle toxicity by using the following two criteria to explore the deviation between differing definitions. Criterion A was based on diagnosis of muscle-related disorders. Because there is no specific ICD-10 code to indicate muscle toxicity, the diagnosis contained the words 'myositis' or 'rhabdomyolysis', which were originally written in the Japanese language and were identified using a computer-assisted text searching method (FINDW function in SAS). Criterion B was based on laboratory results. A patient whose CK concentration was greater than ten times the upper limit of the normal range under statin therapy would be identified as a case. The normal range was given according to the sensitivity of the reference agents used in laboratory tests at each medical facility. The case was recognized as an event if no disease-related condition accompanied by CK elevation was confirmed. The disease-related conditions for CK elevation were as follows: any presence of diagnosis for myocardial infarction, myocarditis, trauma, or hypothyroidism, and any claim of nitrate and levothyroxine prescriptions being obtained within three days after the muscle toxicity event. [24] Statin therapy might be discontinued upon development of intolerable muscle symptoms, with or without CK elevation, in patients for whom other aetiologies were ruled out. [24] Physicians' management decisions about continuation or discontinuation of treatment were determined by compiling claims from patients' health records. Discontinuation and switching were defined as no use of statin therapy or initiation of another statin therapy in the six months following occurrence of muscle toxicity.

Statistical analyses

The incidence rate for muscle toxicity was presented per 1,000 person-years with 95% confidence intervals (CI) estimated by Poisson regression. The baseline period was defined as 180 days prior to statin initiation. Demographic (age, gender) and co-administration data were extracted from medical claims from the baseline period within the statin inception cohort. Patients were observed until occurrence of the first muscle toxicity event, and were censored when statin therapy was discontinued or when the end of the observational period was reached (31 December 2010). In addition to claims data, we identified the presence of co-morbidities from laboratory information for the baseline period. Renal impairment was defined by serum creatine concentrations (SCr) above the upper limit of the normal range; hepatic impairment was indicated where laboratory values for alanine transaminase (ALT) and aspartate transaminase (APT) increased by more than three times the upper limit of normal during the baseline period. The cut-off of glycated haemoglobin (HbA1c) level for diabetes mellitus was set at greater than 6.1%, according to diagnostic criteria adopted in Japan. [25] To compare the characteristics of demographic and clinical variables between criteria, Kolmogorov-Smirnov tests were performed for continuous variables, and chi-square tests were used for dichotomous variables. Co-morbidity and co-administration of drugs were defined according to whether claims of a prescription were made prior to 180 days before occurrence of an event. In addition, to determine the muscle toxicity risk associated with drug-drug interactions, the incidence of muscle toxicity among patients who had concomitantly used interacting drugs was compared with that in patients who did not. Various sensitivity analyses were performed by modifying baseline periods (6 months and 12 months), statin exposure status (number of days on which statins were received as a denominator), and outcome definitions (abnormal range of CK values and switching, renal dysfunction, or hospitalization, with muscle toxicity). All statistical analyses were carried out using SAS software Version 9.3 (SAS Institute Inc., 2012, Cary NC, USA).

RESULTS

A total of 18,036 patients met all the criteria to be defined as new statin users (Figure 1). Of these patients, 11,468 (64%) were diagnosed as having dyslipidaemia, 14,355 (80%) had higher than normal levels of cholesterol, triglyceride or low-density lipoprotein, and 9,382 (52%) were diagnosed as having dyslipidaemia accompanied by higher than normal lipid levels. The mean (SD) age and follow-up month of patients in whom statin use was initiated were 66 (12) years and 29 (22) months, respectively, and 45% of patients were male. Atorvastatin was the most prevalent HMG-CoA reductase inhibitor and contributed to 37% of the total person-years in the inception cohort. The prescribed dosage was generally around the lower limit of the approved dose, with limited variation, regardless of the statin (Table 1).

Among the new statin users, 43 (0.24%) who met either criterion A or B were identified as base cases, and incidence (with 95% CI) of muscle toxicity was estimated as 1.02 (0.76–1.37) per 1,000 person-years (Table 2). According to various outcome definitions, the estimated incidences ranged from 0.09 (met both criteria A and B) to 2.06 (either met criterion A or demonstrated CK values > 5x ULN) per 1,000 person-years. When the strictest definition was selected (i.e., cases met both criteria A and B), 4 cases were identified, and most of these showed discontinuation, switching, renal dysfunction, or hospitalization after the occurrence of the adverse event (3, 1, 3, and 4 cases, respectively). No significant changes were observed when baseline periods or statin exposure status were modified. Incidence of muscle toxicity in the patients treated with statin monotherapy ranged from 0.45 with pravastatin to 1.73 with rosuvastatin per 1,000 person-years (Table 3). Using atorvastatin, the most widely prescribed statin in Japan, as the reference, incidences of muscle toxicity were statistically indistinguishable among the statins, regardless of the criterion used. Similarly, demographic and other characteristics of the cases did not differ for the two criteria (Table 4).

Of new statin users, 2,430 (13.5%) received interacting drugs during the follow-up period. Regarding the incidence rate of muscle toxicity with respect to interacting drug use, a low number of person-years of observation were contributed, representing limited use of interacting drugs, even when all statins and interacting drugs were aggregated. Because of the low number of events recorded, we found the wide 95% CI included the estimated incidence rate (Table 5).

DISCUSSION

This study extends previous work in measuring statin-associated muscle toxicity by using the claims database with laboratory information for actual patient records in Japan. Since the package insert suggests periodical laboratory tests during statin therapy, it is possible to assess the change of medical condition. With an estimated incidence of approximately 1 per 1,000 person-years of statin use, a low occurrence of muscle toxicity was found in the present study. Moreover, less than about one in five patients was found to show concomitant use of interacting drugs, implying that the use of statins is generally well tolerated and safe in Japan. The characteristics and incidences of muscle toxicity between statins were not significantly different. In addition, clinical characteristics were similar among cases defined by diagnosis and cases defined by laboratory results. However, the number of cases in which dyslipidaemia was diagnosed was slightly lower than the number of cases with concurrent elevated lipid levels, indicating an inconsistency between diagnosis and laboratory data.

Information on the frequency (% of users) of muscle toxicity is not provided in Japanese statin medication package inserts, with the exceptions of those of rosuvastatin (0.1%) and simvastatin (0.01%). The lower limit of the 95% confidence interval showed a value consistent with available package inserts; however, it is possible that adverse events would occur more frequently with widespread use of statins in clinical practice, because populations that participate in clinical trials are usually highly selected. [26] Comparing our analysis to statistics reported in previous studies (mostly from the US), the crude incidence of rhabdomyolysis ranged from 2.5 to 4.4 per 100,000 person-years among statin users, when identified by diagnosis and laboratory results combined. [22, 23] Since it is not applicable to compare the incidence of events defined by different parameters, we refined our event definition to consider statin discontinuation or switching and renal dysfunction or hospitalization after the occurrence of an adverse event. Under this revised definition, we found the crude incidence of rhabdomyolysis to be 7.1 to 9.5 per 100,000 person-years (3 to 4 cases per 42,193 person-years), suggesting a moderately high incidence in the present study. The incidence of rhabdomyolysis might differ among studies because the proportion of patients with risk factors is apparently different between the populations. Some case reports indicated that factors related to statin-associated muscle toxicity included old age, female gender, low body mass index, and diabetes mellitus, [27] characteristics that were common among patients in our study. However, evidence showed no increase in the rate of adverse events in Asian patients taking either lower or higher doses of statin, [28] despite racial differences in the pharmacokinetics of rosuvastatin between Asians and Caucasian. [29] After all the controversy over racial differences in pharmacokinetics and the clinical outcomes of statin (particularly rosuvastatin) use, the majority of prescribed doses were at the lower limits of approved dosage levels, implying comparable potency among statins at the lowest effective dose. Taking dosage levels into account, statins were well tolerated in the Japanese population, with a similar incidence of rhabdomyolysis as that reported in Caucasian populations.

Using the claims database to evaluate potential drug interactions with statins is a useful complement to the limited information available from voluntary reports and clinical trials. A recent study found that the use of against label statin-fibrate combination therapy is decreasing annually, but that use of this therapy persists in the

US. [30] In the present study, only 2.8% of patients had been prescribed concomitant statin-fibrate therapy (data not shown). Although combination therapy may be attractive for patients with lipid disorders and without muscle complaints, the low prevalence of concomitant fibrate use implies that it is 'generally contraindicated', and that clinical practitioners are aware of the risks. Whether the risk is due to drug interactions remains controversial, [31, 32] but our study points to a higher incidence of muscle toxicity among patients taking interacting drugs. However, a low number of person-years of interacting drug use observations corresponded to a lack of statistical significance; this low prevalence of concomitant drug use might reduce the detection of muscle toxicity in current practice.

Our findings showed that the incidence of muscle toxicity varied according to the definition of an adverse event, suggesting that the infrastructure in which information is stored might greatly affect assessments of safe medical practice. The majority of cases of discontinuation or switching of statins resulted in hospitalization accompanied by acute changes in renal function. However, the outcome from severe muscle toxicity could not be ascertained since there is no information of death record in the database. Although diagnosis-based measures are inherently limited by weaknesses of administrative claims diagnostic data, including inaccuracy and incompleteness of discharge diagnoses, [33] the prescription claims have been shown to be fairly accurate and complete. [34] Thus, laboratory information was used as a surrogate indicator in this study when there was no corresponding treatment. The comparative characteristics between our two criteria imply that safety measures should be incorporated for a conservative interpretation of laboratory information. In order to avoid overestimating the risk of muscle toxicity, we identified the accompanying condition by both diagnosis and drugs when an event occurred, and excluded cases that were less likely to be related to statin use. Furthermore, the MDV database provided objective information that would not only complement the limitations of the claims database, but that would also provide the potential to monitor pharmacologic responses to therapeutic interventions using biomarkers. In addition, the MDV plans to enrol up to one hundred medical facilities to improve the applicability of using electronic health information in the near future. Limits to investigations imposed by small sample sizes could be overcome, and associations between the risk of adverse events and the use of statins with and without interacting drugs could be explored through this strategy. However, hospital-based data collection would be threatened by lost follow-up and lack of enrolment information such as patients' date of birth and geographic region. Since the database used in this study did not have enough power to evaluate rare events in Japanese clinical practice, the accessibility of a national claims database is expected to provide a complement to this limitation. In addition, the MIHARI project plans to aggregate information from 10 university hospitals (the Sentinel database) to confirm the signal with objective information based on appropriate methodology. Since the validity of claims-based information is often questioned, studies should be conducted to verify the validity [35] and explore the applicability of this information. From a regulatory perspective, great potential exists for evaluating risks for a population using validated information, with the goal of making efficient use of the resource. By using unique identification or indirect identifiers such as patient's date of birth, sex, hospital identification number, admission date, and discharge date, linkage between different databases is commonly used when clinical trial designs are not applicable. [36-38] Because the accessibility of healthcare information in Japan is strictly regulated by privacy protection, further discussion would be necessary to balance privacy protection with an active drug safety monitoring system.

CONCLUSIONS

The present study provides evidence of incidence of muscle toxicity with statin use, identified by diagnosis and objective laboratory information obtained from the claims database in Japan. Since the definition of safety measures varies according to the infrastructure of data resources, researchers should use caution when interpreting risk information that provides answers to uncertainties addressed before drug approval. While the use of combination therapy is relative low in patients with lipid disorders and without muscle complaints, the risks attributed to drug interactions in statin users require further exploration.

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FINANCIAL DISCLOSURE

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AUTHOR CONTRIBUTION

MA was the principal investigator for the grant. MK, TO and MA conceived the study. All authors contributed to study design. TO and MA were responsible for obtaining the data. CHC and MK conducted the initial data analysis. All authors contributed to decisions on the interpretation of results. CHC, KM, and MA contributed to the drafting the manuscript. All authors approved the final version of the manuscript prior to submission.

DATA SHARING STATEMENT

Technical appendix, statistical code, and dataset available from the corresponding author (makazawa@my-pharm.ac.jp). Inform consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

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Figure 1. Flow-chart of study cohort

Table 1. Characteristics of new statin users (N = 18,036) for six drugs represented in this study.

	Atorvastatin (N = 7,052)	Rosuvastatin (N = 5,921)	Pravastatin (N = 5,110)	Pitavastatin (N = 1,774)	Simvastatin (N = 976)	Fluvastatin (N = 871)
Demographic variable						
Mean age, year (SD)	65 (12)	64 (12)	68 (11)	66 (12)	68 (12)	68 (10)
Male ,%	45%	52%	38%	44%	39%	48%
Statin use*						
Duration, month (range)	24 (6–42)	15 (4–28)	22 (6–41)	16 (5–32)	23 (7–41)	16 (6–32)
Daily prescribed dose, mg, where variable)	10	2.5	10	1.6 (1–2)	5	30 (20–30)
Co-morbidity						
Hepatic impairment†,%	3%	4%	2%	2%	1%	2%
Renal impairment‡,%	25%	31%	22%	25%	15%	28%
HbA1c >6.1%,%	17%	28%	14%	22%	13%	14%
Hypertension [a]	25%	53%	55%	28%	60%	57%
Diabetes mellitus [b]	55%	31%	21%	53%	22%	21%
Cardiovascular disease [c]	32%	30%	27%	25%	28%	40%
Ischemic heart disease [d]	18%	17%	16%	14%	14%	20%
Gastric ulcer [e]	34%	33%	30%	32%	32%	31%
Lipid profile						
TC >1x ULN	60%(2,248/3,773)	68%(2,547/3,719)	58%(1,436/2,467)	60%(541/909)	63%(261/419)	40%(165/408)
LDL-C >1x ULN	71%(1,639/2,295)	73%(3,019/4,118)	64%(969/1,524)	69%(664/969)	61%(147/243)	51%(104/202)

HDL-C < 1x LLN	16%(603/3,375)	18%(835/4,638)	13% (321/2,288)	15%(182/1,235)	13%(51/383)	15%(76/497)
TG > 1x ULN	54%(2,320/4,266)	58%(2,949/5,056)	45%(1,274/2,835)	52%(665/1,286)	48%(223/463)	46%(234/510)

* Data shown as median (Q1–Q3), † Renal impairment: patients whose serum creatine levels increased by >1 × the upper limit of the normal range prior to 180 days before statin initiation, ‡ Hepatic impairment defined patients whose alanine transaminase (ALT) or aspartate transaminase (APT) increased >3x times the upper limit of the normal range prior to 180 days before statin imitation, [a] Patients with hypertension defined as the use of antihypertensive drugs, including CCB, ACEI, ARB, and alpha blocker, [b] Patients with diabetes mellitus defined as the use of hypoglycaemic agents, including bigunide and sulfonylurea, [c] Patients with cardiovascular disease defined as the use of antiplatelet, including aspirin, clopidogrel, ticlopidine, and dyperidamole, [d] Patients with ischemic heart disease defined as the use of nitriate, including imdur, NTG, and isodil, [e] Patients with the gastric ulcer defined as the use of gastrointestinal protective agents, including proton pump inhibitor and H_2 receptor antagonist.

Note: TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, and TG: triglyceride. The approved daily dosage for each statin was listed as follows: atorvastatin 10–40 mg, rosuvastatin 2.5–20 mg, pravastatin 10–20 mg, pitavastatin 1–4 mg, simvastatin 5–20 mg, and fluvastatin 20–60 mg.

Table 2: Risks of muscle toxicity by various case definitions

Outcome definitions	# of cases with events	# of eligible persons	Person -years	Incidence * [95% CI]
Base-case definition: criterion A (diagnosis of 'myositis' or 'rhabdomyolysis') or criterion B (CK >10x ULN)	**43**	**18,036**	**42,193**	**1.02 [0.76–1.37]**
with discontinuation	10			0.24 [0.13–0.44]
with switching	3			0.07 [0.02–0.22]
with renal dysfunction	17			0.40 [0.25–0.65]
with hospitalization	17			0.40 [0.25–0.65]
Criterion A or CK >5x ULN	87	**18,036**	**42,193**	2.06 [1.67–2.54]
with discontinuation	23			0.55 [0.36–0.82]
with switching	7			0.17 [0.08–0.35]
with renal dysfunction	39			0.92 [0.68–1.27]
with hospitalization	34			0.81 [0.58–1.13]
Criteria A and B	4	**18,036**	**42,193**	0.09 [0.04–0.25]
with discontinuation	3			0.07 [0.02–0.22]
with switching	1			0.02 [0.00–0.17]
with renal dysfunction	3			0.07 [0.02–0.22]
with hospitalization	4			0.09 [0.04–0.25]
Myositis (and criterion B)	0			--
Rhabdomyolysis (and criterion B)	4			0.09 [0.04–0.25]
Criterion A and CK > 5x ULN	8	**18,036**	**42,193**	0.19 [0.09–0.38]
with discontinuation	3			0.07 [0.02–0.22]
with switching	1			0.02 [0.00–0.17]
with renal dysfunction	6			0.14 [0.06–0.32]
with hospitalization	7			0.17 [0.08–0.35]
Myositis (and CK > 5x ULN)	0			--
Rhabdomyolysis	8			0.19 [0.09–0.38]

(and CK > 5x ULN)				
Criterion A	27	**18,036**	**42,193**	0.64 [0.44–0.93]
with discontinuation	7			0.17 [0.08–0.35]
with switching	3			0.07 [0.02–0.22]
with renal dysfunction	9			0.21 [0.11–0.41]
with hospitalization	8			0.19 [0.09–0.38]
Myositis	12			0.28 [0.16–0.50]
Rhabdomyolysis	15			0.36 [0.21–0.59]
Criterion B	20	**18,036**	**42,193**	0.47 [0.31–0.73]
with discontinuation	6			0.14 [0.06–0.22]
with switching	1			0.02 [0.00–0.17]
with renal dysfunction	11			0.26 [0.14-0.47]
with hospitalization	13			0.31 [0.18–0.53]
CK > 5x ULN	68			1.61 [1.27–2.04]
Baseline period				
Base case definition: 3months	**43**	**18,036**	**42,193**	**1.02 [0.76–1.37]**
6 months	40	16,649	38,645	1.04 [0.76–1.41]
12 months	31	13,693	29,387	1.05 [0.74–1.50]
Statin exposure status				
Base case definition: continuous exposure	**43**	**18,036**	**42,193**	**1.02 [0.76–1.37]**
Excluding stopping periods (days of statin supply)	39	18,036	38,027	1.03 [0.75–1.40]

* Data shown as per 1,000 person-years with 95% confidence interval.

Note: CK: creatine kinase, ULN: upper limit of the normal range. Discontinuation was defined as no use of statin therapy in the six months following occurrence of muscle toxicity. Switching was defined as patients who initiated another statin in the following period. Renal dysfunction was defined as serum creatinine increased above the upper limit of normal range within three days before or seven days after occurrence of an event.

Table 3. Risks of muscle toxicity among specific statin therapies

Generic statin name	# of cases with events *	Person-years	Incidence †
All statins	43	42,193	1.02 (0.76–1.37)
Atorvastatin	17	15,776	1.08 (0.67–1.73)
Rosuvastatin	15	8,655	1.73 (1.04–2.87)
Pravastatin	5	11,121	0.45 (0.19–1.08)
Pitavastatin	3	2,883	1.04 (0.34–3.23)
Simvastatin	2	2,123	0.94 (0.24–3.77)
Fluvastatin	1	1,635	0.61 (0.09–4.34)

* Cases were defined by either criterion A (diagnosis of 'myositis' or 'rhabdomyolysis') or criterion B (creatine kinase concentration >10x the upper limit of the normal range).

† Data shown as per 1,000 person-years with 95% confidence interval.

Table 4. Characteristics of patients exhibiting Criterion A vs. Criterion B

	Criterion A * (N = 27)	Criterion B * (N = 20)	p-value
Demographic variable			
Male (%)	52%	55%	0.83
Mean age, years (SD)	60 (15)	69 (11)	0.07
Statin use at the event (%)			1.00
Atorvastatin	37%	35%	
Fluvastatin	4%	0	
Pitavastatin	4%	10%	
Pravastatin	11%	15%	
Rosuvastatin	37%	35%	
Simvastatin	7%	5%	
Mean interval after initiating Statin, month (SD)	18 (13)	19 (20)	0.98
Laboratory information			
SCr > 1x ULN	56% (9/16)	58% (11/19)	0.92
BUN > 1x ULN	44% (7/16)	50% (10/20)	0.71
APT > 1x ULN	56% (9/16)	80% (16/20)	0.12
ALT > 1x ULN	38% (6/16)	65% (13/20)	0.10

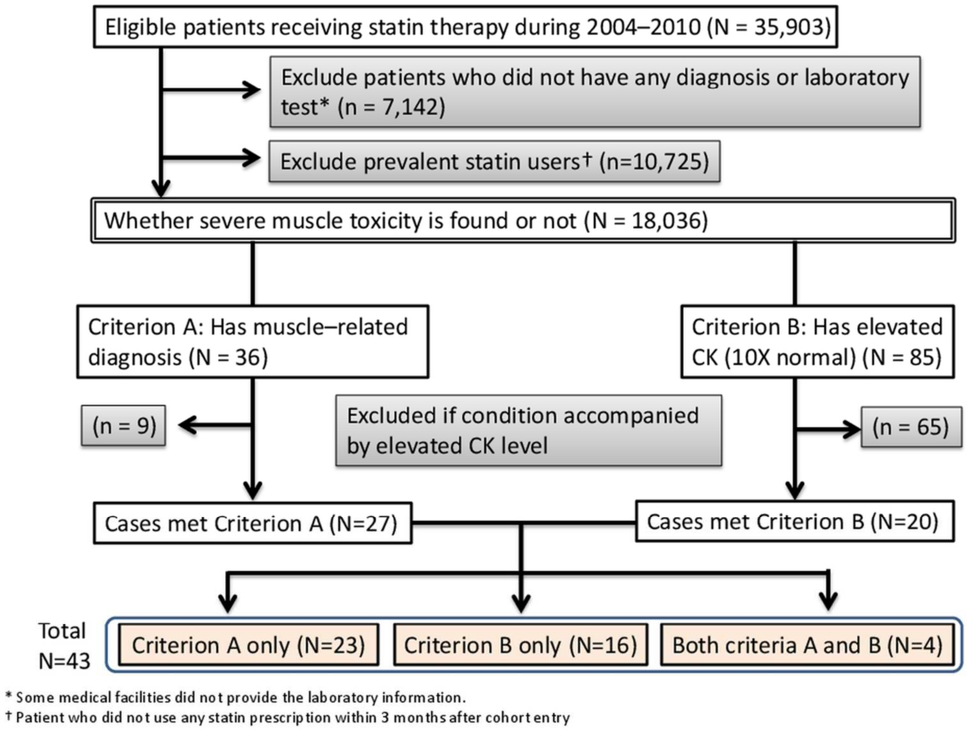
* Criterion A is defined by diagnosis of 'myositis' or 'rhabdomyolysis' and criterion B is defined by creatine kinase (CK) concentration >10x times the upper limit of the normal range. Four cases met both Criteria A and B.

Note: SD: standard deviation, SCr: serum creatinine, BUN: blood urea nitrogen, APT: aspartate transaminase, ALT: alanine transaminase, ULN: upper limit of normal range.

Table 5. Risk of muscle toxicity from concomitant use of interacting drugs

	Concomitant use of interacting drugs *	No concomitant use of interacting drugs
N	2,430	15,606
Person-year	1,776	40,418
Number of events	3	40
Proportion of total events, %	0.12%	0.26%
Incidence per 1,000 person-years (95% CI)	1.69 (0.54–5.24)	0.99 (0.73–1.35)

* The number of patients who were exposed to specific interacting drugs in this study were as follows: benzafibrate (256), fenofibrate (262), clinofibrate (1), clarithromycin (1,688), erythromycin (77), telithromycin (2), fluconazole (22), itraconazole (125), fosfluconazole (31), voriconazole (11), cyclosporine (66), amiodarone (93), saquinavir/ritonavir (0), atazanavir (0), etraririne (0), and efavirenz (0).



Flow-chart of study cohort
119x90mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

NA: Not applicable

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-9
Objectives	3	State specific objectives, including any prespecified hypotheses	8-9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	13-15
Bias	9	Describe any efforts to address potential sources of bias	14-15
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-15
		(*b*) Describe any methods used to examine subgroups and interactions	13-15
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	15
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	15
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	15, Table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	15-16, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16-17, Table 2, 3, 5
		(*b*) Report category boundaries when continuous variables were categorized	Table 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 2, 3, 5
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.