

# Real-World Analyses of the Safety Outcome among a General Population Treated with Statins: An Asian Population-Based Study

Jia-Ling Lin<sup>1</sup>, Po-Sheng Chen<sup>1</sup>, Hui-Wen Lin<sup>1</sup>, Liang-Miin Tsai<sup>1,2</sup>, Sheng-Hsiang Lin<sup>3,4,5</sup> and Yi-Heng Li<sup>1</sup>

Jia-Ling Lin and Po-Sheng Chen contributed equally to this study.

Sheng-Hsiang Lin and Yi-Heng Li are joint senior authors and contributed equally to this work.

<sup>1</sup>Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

<sup>2</sup>Department of Internal Medicine, Tainan Municipal Hospital (Managed by Show Chwan Medical Care Corporation), Tainan, Taiwan

<sup>3</sup>Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

<sup>4</sup>Biostatistics Consulting Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

<sup>5</sup>Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

**Aim:** The safety concern of statins is still a major issue for Asians. The aim of this study is to compare the risk of statin-associated adverse events among potent statins.

**Methods:** We included patients from the Taiwan National Health Insurance Research Database who had been treated with atorvastatin, rosuvastatin, or pitavastatin and were without diabetes at baseline. They were classified into three groups: usual-dose statin (atorvastatin 10 mg/d or rosuvastatin 5–10 mg/d), high-dose statin (atorvastatin 20–40 mg/d and rosuvastatin 20 mg/d), and pitavastatin (2–4 mg/d). The primary endpoint is a composite of safety events, including hepatitis, myopathy, and new-onset diabetes mellitus (NODM). We matched age, sex, and year of recruitment among the three groups ( $n=50,935$  in each group) and then used the multivariate Cox proportional hazards model to evaluate the relation between the safety endpoint and different statin groups.

**Results:** After a mean follow-up of  $3.08 \pm 0.83$  years, the safety events occurred in 9.84% in the pitavastatin group, 10.88% in the usual-dose statin group, and 10.49% in high-dose statin group. The multivariate Cox proportional hazards model indicated that usual-dose statin and high-dose statin were associated with a higher risk of the composite safety events compared with pitavastatin (adjusted hazard ratio [aHR]: 1.12, 95% confidence interval [CI]: 1.08–1.17 for usual-dose statin and aHR: 1.06, 95% CI: 1.02–1.10 for high-dose statin). The risks of hepatitis requiring hospitalization and NODM were especially lower in pitavastatin group.

**Conclusions:** Compared with atorvastatin and rosuvastatin, pitavastatin might be associated with a lower risk of safety events in Asians.

**Key words:** Statin, Adverse events, Asians

## Introduction

Statin therapy that reduces low-density lipoprotein cholesterol (LDL-C) demonstrated

benefits in improving the cardiovascular (CV) outcome in primary and secondary prevention studies<sup>1-4</sup>. Statins are generally safe and tolerated well by most patients. However, statin-associated muscle

Address for correspondence: Yi-Heng Li, Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng Li Road, Tainan, Taiwan.  
E-mail: heng@mail.ncku.edu.tw

Received: May 26, 2021 Accepted for publication: August 6, 2021

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events and hepatitis are encountered occasionally. These events are common reasons of statin intolerance that is associated with an increased risk of recurrent myocardial infarction<sup>5, 6</sup>. Association of statins with new-onset diabetes mellitus (NODM) was also reported from several randomized clinical trials and observational studies<sup>7</sup>. In the real-world practice in Asia, the doses of statins are typically lower than those recommended in the western lipid guidelines, even in patients with atherosclerotic cardiovascular disease, because the safety issue of statin is always a major concern in the Asian population<sup>8, 9</sup>. Asians are more sensitive to atorvastatin and rosuvastatin. A pharmacokinetic study demonstrated that East Asian populations had 2-fold higher blood concentration of rosuvastatin than Caucasians after being given the same dose<sup>10</sup>. Therefore, the American Heart Association (AHA)/American College of Cardiology (ACC) Cholesterol Guideline recommends a lower starting dose of rosuvastatin for Asians<sup>11</sup>. NODM is another problem attracting attention in Asia because the increasing prevalence of diabetes has become a major public health issue and has a significant socioeconomic impact to most nations in this region<sup>12</sup>.

Pitavastatin is one of the potent statins in the market. Pitavastatin administered at 4 mg/d decreases LDL-C by 46%, meaning that it is roughly as efficacious as atorvastatin 20–30 mg/day<sup>13</sup>. A large-scale randomized clinical trial from Japan, the REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease) study, demonstrated that pitavastatin 4 mg/d was more effective in reducing CV events than pitavastatin 1 mg/d and that the risk of serious statin-associated adverse events, including rhabdomyolysis and NODM, were similar between the two treatment groups<sup>14</sup>. Unlike atorvastatin and rosuvastatin, the metabolism of pitavastatin is minimally dependent on hepatic enzyme cytochrome P450. Almost 99% pitavastatin is metabolized by glucuronidation, converted into the inactive lactone form and excreted in bile<sup>15</sup>. Therefore, the risk of a drug–drug interaction becomes negligible between pitavastatin and concomitantly administered drugs metabolized by cytochrome P450. Furthermore, there exists higher prevalence of functional polymorphisms of cytochrome P450 genes causing a decrease in the enzyme's activity in Asians<sup>16</sup>. Therefore, Asians could have higher blood concentrations of atorvastatin and rosuvastatin, but there were no differences in blood levels after exposure to pitavastatin between Caucasians and Asians<sup>17</sup>. Previous studies assessed the impact of different statins on glycemic control in

given populations and found that pitavastatin was associated with a favorable effect on glucose metabolism<sup>18–20</sup>. Based on the scientific evidence from these studies, we hypothesized that pitavastatin could have a lower risk of myopathy, hepatitis, and NODM in Asians compared to atorvastatin and rosuvastatin because of its unique metabolic pathway. We designed a population-based retrospective cohort study to compare the incidences of these statin-related adverse events among pitavastatin, atorvastatin, and rosuvastatin in a Taiwanese population.

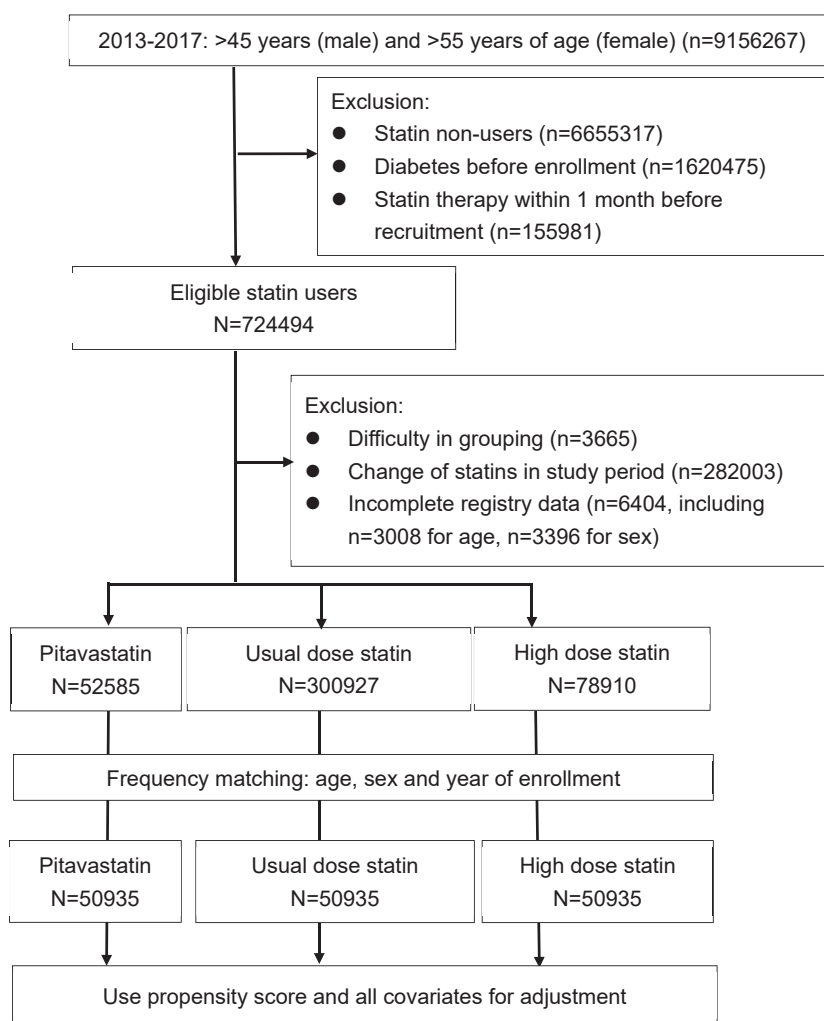
## Methods

### Data Source

In this study, we retrieved data from the Taiwan National Health Insurance Research Database (NHIRD) from the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taipei, Taiwan. This databank is derived from the claim data of the Taiwan National Health Insurance (NHI) program and includes demographic characteristics, medical diagnoses, procedures, expenditures, and prescriptions of all inpatient and outpatient services. Taiwan NHI is a mandatory-enrollment and single-payer insurance program that was launched since 1995 and provides comprehensive medical care in more than 99.5% of residents in Taiwan. Personal information of each subject in the databank has been encrypted for privacy. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (or ICD-10-CM after 2016) were used to identify demographic characteristics, concomitant medical diseases, and medications (**Supplemental Table 1**). The accuracy of ICD-9-CM diagnostic codes in Taiwan's NHIRD was verified in previous studies<sup>21–23</sup>. Although ICD-10-CM was used in Taiwan for only a few years, there also have been studies validating the diagnostic codes between ICD-9-CM and ICD-10-CM in NHIRD<sup>24, 25</sup>. All these study results indicated that records from NHIRD are accurate and consistent between ICD-9-CM and ICD-10-CM. This study was approved by the Institutional Review Board of our hospital (IRB No.: A-ER-109-153).

### Study Design and Population

This is a population-based retrospective cohort study. We included all male subjects  $\geq 45$  and female  $\geq 55$  years of age from January 2013 to December 2017 from the claim data of NHI for analysis. We set these age criteria to narrow down the population that is more likely to be treated with statins. We excluded those with preexisting diabetes recognized by using



**Fig. 1.** Flowchart of patient selection

In the exclusion criteria, difficulty in grouping indicated that subjects received two kinds of statins at the same time or subjects with statin switched during the initial 30-day period after enrollment, change of statins in the follow-up period indicated subjects with statin changes causing a shift between the three defined groups, and incomplete registry data indicated subjects with missing data of age and sex.

ICD diagnosis codes (ICD-9-CM code 250 and ICD-10 codes E08 to E13) or antidiabetic medication in data screening. To include only new statin users, we also excluded those who had already received statin therapy within 1 month before recruitment. Among the eligible subjects, statin users were defined as those who received atorvastatin, rosuvastatin, or pitavastatin for more than 90% of times in consecutive 30 days after enrollment, and these patients were included to form the base of this study ( $n=724,494$ ). Because high-intensity statins (atorvastatin  $\geq 40$  mg/d and rosuvastatin  $\geq 20$  mg/d) defined by AHA/ACC were not commonly used in Asia, we modified the definition of statin intensity for classification. All subjects were classified into three groups: (1)

pitavastatin 2–4 mg/d, (2) usual-dose statin (atorvastatin 10 mg/d, rosuvastatin 5 mg/d, and rosuvastatin 10 mg/d), and (3) high-dose statin (atorvastatin 20 mg/d, atorvastatin 40 mg/d, and rosuvastatin 20 mg/d). We excluded those with (1) difficulty in grouping (subjects who received two kinds of statins at the same time or subjects with statin switched during the initial 30-day period after enrollment), (2) change of statins in the follow-up period (subjects with statin changes causing a shift between the three defined groups), and (3) incomplete registry data (subjects with missing data of age and sex). The flowchart of categorization of the study subjects was presented in [Fig. 1](#).

## Study Outcomes and Follow-Up

We used a consistent encrypting procedure that could link and continuously follow all of the claims belonging to the same patient within the databank. Because ICD-9-CM codes were replaced by ICD-10-CM codes in NHI from 2016 in Taiwan, both ICD-9 and -10 codes were used to identify the primary outcome. The primary outcome was a composite endpoint of safety events, including myopathy requiring hospitalization (ICD-9-CM codes 729.1, 359.4, 359.8, and 359.9; ICD-10-CM codes M60.1, M60.8, M60.9, G72.0, G72.4, G72.8, and G72.9), hepatitis requiring hospitalization (ICD-9-CM code 573.3; ICD-10-CM codes K72.0, K72.9, K71.1, K71.2, K75.2, K75.9, and K76.9) and NODM (ICD-9-CM code 250; ICD-10-CM code E08-E13) defined as new diagnosis of diabetes, and new antidiabetic medications or insulin were prescribed. Myopathy or hepatitis needs to have a document of hospitalization with major discharge diagnosis of these diseases. NODM needs to have hospitalization with major discharge diagnosis of diabetes or diagnosis of diabetes in outpatient clinics for two consecutive times. Secondary outcomes were the individual components of the primary outcome. All patients were followed up until December 31, 2018, and the shortest follow-up time was at least 1 year.

## Statistical Analysis

In the initial analysis, we only used frequency matching with age, sex, and year of enrollment with a 1:1:1 ratio to select patients from the pitavastatin, usual-dose statin, and high-dose statin groups (**Fig. 1**). Continuous variables were presented as means  $\pm$  standard deviations, and categorical variables as numbers and percentages. Distributions of the clinical characteristics between the groups after frequency matching were evaluated using the absolute standardized mean difference (ASMD). ASMD was calculated as the mean or proportion of a variable divided by the pooled estimate of the standard deviation of that variable. An ASMD  $< 0.1$  indicates a negligible difference between the two comparison groups. Since randomization is not possible in observational studies, the three groups may be unbalanced for some demographic and clinical characteristics. The multivariate Cox proportional hazards model was used to examine the relationship between endpoint and different statin treatments. In this study, we calculated the propensity score for each study participant and performed covariate adjustment using the propensity score as one of the covariates in the multivariate model. The propensity score is the

probability of exposure to the different treatments and was computed using a multivariate logistic regression analysis conditional on baseline variables of study subjects. Then, we applied the propensity score as a variable to adjust the effect of treatment on the outcome in the multivariate Cox model along with the other baseline variables. Therefore, the Cox model was adjusted for the propensity score, age, sex, hypertension, heart failure, peripheral artery disease, atrial fibrillation, chronic obstructive lung disease, chronic liver disease, peptic ulcer disease, ischemic heart disease, chronic kidney disease, stroke, hemodialysis, and medications. In the Cox multivariate model, we also performed a time-dependent analysis by using statin exposure time as a segmented time-dependent covariate to avoid bias introduced by different drug treatment times. Kaplan–Meier curves were created to present the cumulative incidence and the time to the primary safety outcome in each statin group. Because mortality was not our interesting outcome but would be a competing event influencing the result of our analysis, we re-examined the relationship between different statins and clinical outcomes and compared the differences between these three groups using a competing risk regression model that excluded the influence of mortality in the follow-up period<sup>26, 27</sup>. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated from the Cox model after adjusting for all these potential confounders. SAS 9.4 for Windows (SAS Institute Inc., Cary, NC) was used for all data analyses.

## Results

**Fig. 1** is the flowchart of patient selection from January 2013 to December 2017. After exclusion and initial match with age, sex, and year of enrollment, there were 50,935 patients in each statin group. The initial numbers of the different statins with their dosages are described in **Supplemental Table 2**. **Table 1** presents the baseline characteristics and medications in the three statin groups. After initial matching with age, sex, and year of enrollment, most other clinical characteristics were also well balanced between the three groups, except that ASMD  $> 0.1$  was still observed in heart failure, ischemic heart disease, stroke, use of antiplatelet, and beta blocker between some groups. Patients in the high-dose statin group had the highest proportion of ischemic heart disease, stroke, and taking antiplatelet agents compared to the other groups. The other clinical characteristics and medications were well matched between the groups (**Table 1**).

**Table 1.** Baseline characteristics of patients with different statin therapy

	All (N=152805)	Pitavastatin (N=50935)	Usual dose statin (N=50935)	High dose statin (N=50935)	Absolute standardized mean difference (ASMD)		
					1 vs 2	1 vs 3	2 vs 3
Male	84618 (55.38)	28206 (55.38)	28206 (55.38)	28206 (55.38)	0.000	0.000	0.000
Age	64.50 ± 10.56	64.57 ± 10.63	64.39 ± 10.43	64.54 ± 10.61	0.018	0.003	0.014
Comorbidities							
Hypertension	96651 (63.25)	32965 (64.72)	32714 (64.23)	30972 (60.81)	0.010	0.081	0.071
*Heart failure	9509 (6.22)	3635 (7.14)	2269 (4.45)	3605 (7.08)	0.115	0.002	0.113
Peripheral artery disease	3876 (2.54)	1275 (2.50)	1188 (2.33)	1413 (2.77)	0.011	0.017	0.028
Atrial fibrillation	5367 (3.51)	2055 (4.03)	1308 (2.57)	2004 (3.93)	0.082	0.005	0.077
Chronic obstructive lung disease	15690 (10.27)	5457 (10.71)	4886 (9.59)	5347 (10.50)	0.037	0.007	0.030
Chronic liver disease	16464 (10.77)	5525 (10.85)	5826 (11.44)	5113 (10.04)	0.019	0.027	0.045
Peptic ulcer disease	20006(13.09)	7104 (13.95)	6425 (12.61)	6477 (12.72)	0.039	0.036	0.003
*Ischemic heart disease	42073 (27.53)	14981 (29.41)	11133 (21.86)	15959 (31.33)	0.174	0.042	0.216
Chronic Kidney Disease	10015 (6.55)	3006 (5.90)	3212 (6.31)	3797 (7.45)	0.017	0.062	0.045
*Stroke	15451 (10.11)	4578 (8.99)	4475 (8.79)	6398 (12.56)	0.007	0.115	0.123
Hemodialysis	1072 (0.70)	239 (0.47)	319 (0.63)	514 (1.01)	0.021	0.063	0.043
Medications							
*Antiplatelet	64986 (42.53)	21497 (42.2)	18591 (36.50)	24898 (48.88)	0.117	0.134	0.252
ACEI/ARB	75069 (49.13)	25928 (50.90)	24278 (47.66)	24863 (48.81)	0.065	0.042	0.023
*Beta blocker	60701 (39.72)	21615 (42.44)	18020 (35.38)	21066 (41.36)	0.145	0.022	0.123
NOAC	3018 (1.98)	1103 (2.17)	729 (1.43)	1186 (2.33)	0.055	0.011	0.066

Data are presented as number (percentages) or mean ± standard deviation.

\*ASMD >0.1 between some groups. 1, Pitavastatin; 2, Usual dose statin; 3, High dose statin

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NOAC, non-vitamin K antagonist oral anticoagulant.

**Table 2.** Outcomes of safety events

	Pitavastatin N=50935		Usual dose statin N=50935					High dose statin N=50935				
	N (%)	HR	N (%)	Crude HR (95% CI)	P	Adjusted HR (95% CI)	P	N (%)	Crude HR (95% CI)	P	Adjusted HR (95% CI)	P
Safety outcome	5014 (9.84)	Ref.	5542 (10.88)	1.08 (1.04-1.12)	<0.001	1.12 (1.08-1.17)	<0.001	5343 (10.49)	1.05 (1.01-1.09)	0.011	1.06 (1.02-1.10)	0.006
Hepatitis	240 (0.47)	Ref.	287 (0.56)	1.18 (0.99-1.40)	0.062	1.21 (1.02-1.44)	0.029	289 (0.57)	1.19 (1.01-1.42)	0.044	1.19 (1.01-1.42)	0.044
Myopathy	19 (0.04)	Ref.	28 (0.05)	1.46 (0.82-2.65)	0.204	1.49 (0.82-2.69)	0.189	24 (0.05)	1.25 (0.69-2.32)	0.461	1.26 (0.69-2.30)	0.463
NODM	4818 (9.46)	Ref.	5284 (10.37)	1.07 (1.03-1.12)	0.001	1.11 (1.07-1.16)	<0.001	5113 (10.04)	1.05 (1.01-1.09)	0.026	1.05 (1.01-1.09)	0.015

Model was adjusted for propensity score, statin exposure time as time-dependent covariate, age, sex, comorbidities (hypertension, heart failure, peripheral artery disease, atrial fibrillation, chronic obstructive lung disease, chronic liver disease, peptic ulcer disease, ischemic heart disease, chronic kidney disease, stroke, hemodialysis), and medications (antiplatelet, ACEI/ARB, beta blocker, NOAC).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; NODM, new-onset diabetes mellitus; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; P, p-value; Ref, reference.

After a mean follow-up time of 3.08 ± 0.83 years, the primary outcome of safety events occurred in 5,014 (9.84%) patients in the pitavastatin group, 5,542 (10.88%) in the usual-dose statin group, and

5,343 (10.49%) in the high-dose statin group. We compared the primary outcome between the groups and used pitavastatin as the reference group to estimate the risk (Table 2). In the multivariate Cox



proportional hazards model, usual- and high-dose statin groups had a higher risk of primary outcome (usual-dose statin vs. pitavastatin: adjusted HR, 1.12 and 95% CI, 1.08–1.17, high-dose statin vs. pitavastatin: adjusted HR, 1.06 and 95% CI, 1.02–1.10). In the analysis of secondary outcomes, usual- and high-dose statin groups had a higher risk of hepatitis requiring hospitalization (usual-dose statin vs. pitavastatin: adjusted HR, 1.21 and 95% CI, 1.02–1.44, high-dose statin vs. pitavastatin: adjusted HR, 1.19 and 95% CI, 1.01–1.42) and higher risk of NODM (usual-dose statin vs. pitavastatin: adjusted HR, 1.11 and 95% CI, 1.07–1.16, high-dose statin vs. pitavastatin: adjusted HR, 1.05 and 95% CI, 1.01–1.09) compared with pitavastatin. The incidence of myopathy requiring hospitalization was very low, and it occurred in 0.04% in pitavastatin, 0.05% in usual- and high-dose statin groups, respectively. There was no significant difference between pitavastatin vs. usual-statin dose and between pitavastatin vs. high-dose statin. When mortality was taken into consideration, the competing risk regression model (**Supplemental Table 3**) showed similar results to the findings of primary analysis from the multivariate Cox proportional hazards model. The cumulative incidence of the primary safety outcome in different statin groups is shown in **Supplemental Fig. 1**. **Fig. 2** shows the subgroup analysis of the primary safety outcome. Compared to usual-dose statin, no statistical heterogeneity was identified among most subgroups, except in patients with ischemic heart disease and those who received an antiplatelet and a beta blocker (**Fig. 2A**). However, compared to high-dose statin, pitavastatin carried a lower risk of primary composite safety events in more subgroups including patients with hypertension, heart failure, peripheral artery disease, ischemic heart disease, chronic kidney disease and those treated with an antiplatelet, an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and a beta blocker (**Fig. 2B**). Similar findings were observed among the subgroup analysis for NODM (**Supplemental Fig. 2**).

## Discussion

To the best of our knowledge, our study is the largest investigation about the safety of different statins in the Asian population. In the present study, we found that patients receiving pitavastatin had a lower risk of a composite outcome of safety events compared to those receiving atorvastatin and rosuvastatin. Severe hepatitis requiring hospitalization and NODM were significantly less in pitavastatin-treated patients. These results suggested that

pitavastatin may be a relatively safer choice of statin for Asians who are susceptible to statin-associated adverse events.

Statin-associated muscle events, including myalgia, myopathy, or rhabdomyolysis, and hepatitis are common adverse events that make patients unable or unwilling to continue with statins<sup>28</sup>). Our study found that the risk of severe muscular events was very low in statin users in this Asian population; this is consistent with previous study results from Western countries<sup>29, 30</sup>). Although we did not have the creatine kinase data in our study, the incidence of myopathy requiring hospitalization was only 0.04% in the pitavastatin group. In the REAL-CAD study, the incidence of rhabdomyolysis occurred in 2 out of 6,390 (0.03%) patients treated with pitavastatin 4 mg/d<sup>14</sup>). Our study also demonstrated that myopathy requiring hospitalization occurred in 0.05% in usual- and high-dose statin groups and that there was no significant difference compared to pitavastatin. This result was similar to our previous observation of myocardial infarction patients in Taiwan, showing that high-intensity statins did not increase the risk of severe myopathy requiring admission compared to that of other statins<sup>9</sup>). The risk of severe hepatitis requiring hospitalization was higher in usual- and high-dose statin groups compared to pitavastatin in our study. In Japan, there was a small randomized clinical trial that compared the clinical outcomes of hypercholesterolemic patients treated with pitavastatin 2 mg/d ( $n=332$ ) vs. outcomes of those treated with atorvastatin 10 mg/d ( $n=332$ )<sup>31</sup>). In a mean follow-up of 3.8 years, muscle complaints were reported more often in the atorvastatin group, but rhabdomyolysis was similar between pitavastatin and atorvastatin. The rate of hepatitis defined as elevation of transaminase >3 upper limit of normal (ULN) was similar between the groups (pitavastatin vs. atorvastatin: 2.2% vs. 2.6%,  $p=0.801$ )<sup>31</sup>). It has long been known that there exist different risks of adverse events among statins. In a meta-analysis of 18 randomized controlled trials of statins with 71,108 patients, fluvastatin and pravastatin had significantly fewer occurrences of myalgia and liver function change than those of atorvastatin, but the risks of any creatine kinase change were similar between the statins<sup>32</sup>). This meta-analysis also demonstrated that statin-associated serious muscular events (creatinine kinase >10 × ULN or rhabdomyolysis) were rare with an absolute risk of 0.03%, which was similar to our observation<sup>32</sup>). Another larger meta-analysis of 72 randomized controlled trials with 159,458 study participants found that atorvastatin was significantly more likely to lead to elevated transaminase level vs. pravastatin<sup>33</sup>).

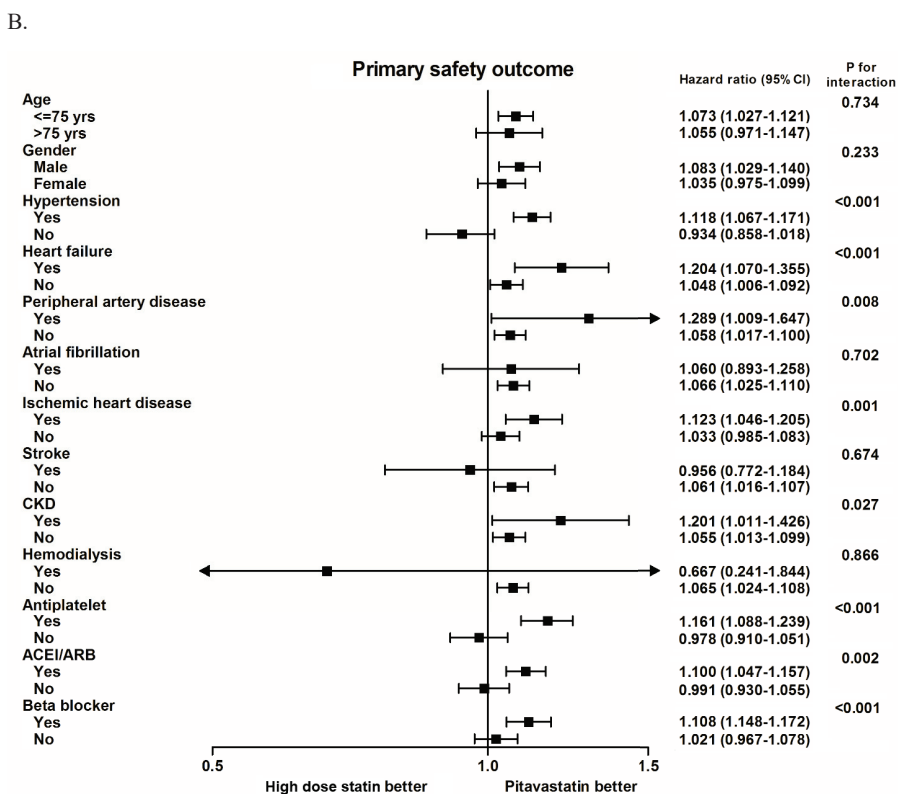
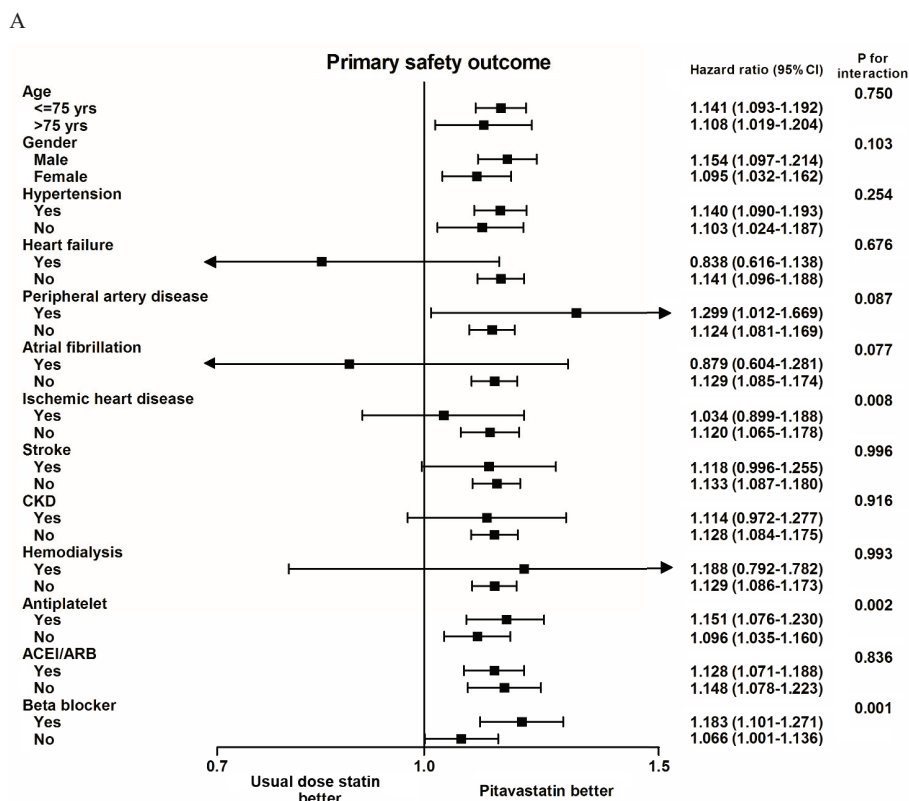


Fig. 2. Subgroup analysis of primary composite safety outcome

(A) pitavastatin vs. usual-dose statin (B) pitavastatin vs. high-dose statin. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

More than 70% medications need to be metabolized by hepatic cytochrome P450. Since pitavastatin minimally uses this enzyme for metabolism, the lower risk of drug–drug interaction could explain the less hepatic side effects we observed in this study. Among the potent statins that could reduce LDL-C  $\geq$  40%, pitavastatin may be a safer choice for Asian patients to avoid the development of statin-associated adverse events.

Statin therapy increases a small risk of incident diabetes, and the risk was associated with the duration and dose of statins<sup>34, 35</sup>). Although the risk is considered to be a drug class effect, the intensity of diabetogenicity seems to be different among statins. A previous study demonstrated that the risk of NODM was higher in users of atorvastatin and rosuvastatin compared to that in users of pravastatin<sup>36</sup>). Since pitavastatin is one of the potent statins, its influence on glucose homeostasis was investigated and compared with the other potent statins. In the REAL-CAD study from Japan, risks of NODM were similar between those treated with pitavastatin 4 mg/d ( $n=6,390$ ) and those treated with pitavastatin 1 mg/d ( $n=6,428$ ) after a median follow-up of 3.9 years<sup>14</sup>). In Korea, Choi *et al.* conducted another study to assess the diabetogenic effect of pitavastatin (2–4 mg/d,  $n=255$ ), atorvastatin (10–20 mg/d,  $n=1267$ ), and rosuvastatin (5–10 mg/d,  $n=961$ ) based on the data retrieved from the Korean Acute Myocardial Infarction Registry<sup>37</sup>). Compared with those treated with pitavastatin, patients treated with atorvastatin or rosuvastatin had a higher incidence of NODM (adjusted HR, 2.615, 95% CI, 1.163–5.879 and adjusted HR, 3.906, 95 CI, 1.756–8.689, respectively) in a 3-year follow-up<sup>37</sup>). A single-center, all-comer study performed in Taiwan compared the risk of NODM in pitavastatin (2 mg/d,  $n=1,312$ ), atorvastatin (10 mg/d,  $n=3,034$ ), and rosuvastatin (10 mg/d,  $n=3,991$ )<sup>38</sup>). The study found that pitavastatin users had higher probability of NODM-free (log-rank test,  $p=0.038$ ) than the other statins in a 4-year follow-up<sup>38</sup>). Because the case number was small in these previous studies, we decided to perform a larger one to re-evaluate this effect. Our study results indicated that pitavastatin ( $n=50,935$ ) was associated with a lower probability of NODM compared to that of atorvastatin and rosuvastatin. The mechanism explaining a lower risk of NODM in pitavastatin is not completely clear. A recent in-vitro study demonstrated that rosuvastatin had a more significant effect than pitavastatin in decreasing the insulin-induced protein kinase B phosphorylation and translocation of glucose transporter-4 to the plasma membrane in cultured adipocytes<sup>39</sup>). This observation

partially explains the difference of glucose uptake ability in adipocytes treated with different statins.

The strengths of our study include the nationwide population-based design and larger sample size. Among the potent statins, our findings suggest that pitavastatin carries a lower risk of statin-associated hepatitis and NODM compared with that carried by atorvastatin and rosuvastatin after adjustment of multiple clinical factors. There were several limitations of our study merit emphasis. First, our study was a non-randomized and observational study. Although we adjusted the propensity score and clinical characteristics in the multivariate analysis, other unmeasured confounding factors potentially may bias the study results. Second, we could not obtain the baseline laboratory data, such as liver function and sugar and hemoglobin A1C concentrations, that may influence the occurrence of the safety events. We also did not have other important risk factors for NODM, such as body weight and family history of diabetes. All these factors could not be adjusted in our analysis. Third, the exclusion criterion “change of statins during follow-up” could include subjects whose prescriptions were changed because of adverse events. However, we think only minor adverse events, such as myalgia, could be missed. Severe adverse events, such as myopathy and hepatitis requiring hospitalization, we observed in this study were documented in the medical records and would not be missed in our study. In the REAL-CAD study, although the risks of rhabdomyolysis were similar, muscle complaints were more frequent in pitavastatin 4 mg/d compared to those in pitavastatin 1 mg/d (1.9% vs. 0.7%,  $p<0.001$ ). Unfortunately, in our study, we could not compare the incidence of myalgia between the three groups because this complaint was not completely recorded in the claim data. We also did not have the baseline or follow-up creatine kinase levels in these patients. Because patients with statin discontinuation or switch were excluded in our study, it was difficult to estimate the occurrence of myalgia with these parameters between the groups. Fourth, the mean follow-up time was 3.08 years in our study. This duration of follow-up may be insufficient for observation of the long-term risk of these statins’ adverse events.

In conclusion, the results of our study suggest that the risk of the composite safety outcomes, especially hepatitis requiring hospitalization and NODM, was lower in an Asian population treated with pitavastatin compared to the risk in that treated with atorvastatin and rosuvastatin. In addition to treating LDL-C to target, prescription of appropriate statin according to the patients’ baseline conditions,



including liver function and sugar status, is important to avoid side effects and improve compliance.

### Funding Sources

This study was sponsored by Cheng-Hsing Medical Foundation, Tainan, Taiwan and Orient EuroPharma Co. Ltd, Taipei, Taiwan. The funders had no role in study design, data collection, decision to publish, or preparation of the manuscript.

We are grateful to the Health Data Science Center, National Cheng Kung University Hospital for providing administrative and technical support.

### Conflicts of Interests

The authors declare no conflicts of interests.

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**Supplemental Table 1.** ICD codes used in this study

Disease	ICD-9 Codes	ICD-10 Codes
Comorbidity		
Hyperlipidemia	272	E78
Hypertension	401, 402, 403, 404, 405	I10.xx -I16.xx
Heart failure	428	I09.81, I11.0, I13.0, I13.2, I42, I50, I97.13, O90.3, T86.52
Peripheral artery disease	440, 443, 444, 447.8, 447.9	I70.2-I70.9, I71, I73.9
Atrial fibrillation	427.3	I48
Chronic obstructive lung disease	490-496, 500, 502, 503, 504, 505	J40-J45, J47, J60-J65, J70.3, J84, J98
Chronic liver disease	V02.61, V02.62, 070, 571, 573.9	A52.7, B15-B19, K70-K75, K76.0, K76.9, K77, Z22.51, Z22.52, Z94.4, C22.0, Z85.05
Peptic ulcer disease	531-534, 530.2, V12.71	K25-K28, Z87.11
Ischemic heart disease	411, 413, 414	I20, I24, I25
Chronic kidney disease	403, 404, 585, V45.1, V56	I12, I13, N18, N19, N29, Z99.2, Z49, Q61, O10.2, O10.3
Stroke	433, 434, 436, 437.1, 437.9	I63, I67.8, I67.9
Outcome		
Diabetes mellitus	250	E08-E13
Hepatitis	573.3	K72.0, K72.9, K71.1, K71.2, K75.2, K75.9, K76.9
Myopathy	729.1, 359.8, 359.4, 359.9	M60.1, M60.8, M60.9, G72.0, G72.4, G72.8, G72.9

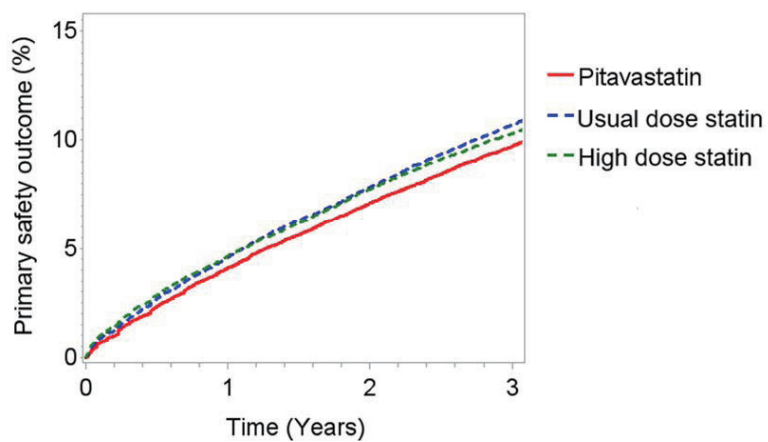
**Supplemental Table 2.** The initial numbers of the prescribed statins

	Pitavastatin N = 50935		Usual dose statin N = 50935			High dose statin N = 50935		
	2 mg	4 mg	Atorvastatin 10 mg	Rosuvastatin 5 mg	Rosuvastatin 10 mg	Atorvastatin 20 mg	Atorvastatin 40 mg	Rosuvastatin 20 mg
N	49475	1460	24108	4187	22640	40277	10589	69
%	97.13%	2.87%	47.33%	8.22%	44.45%	79.08%	20.79%	0.14%

**Supplemental Table 3.** Competing risk regression model of the safety outcome

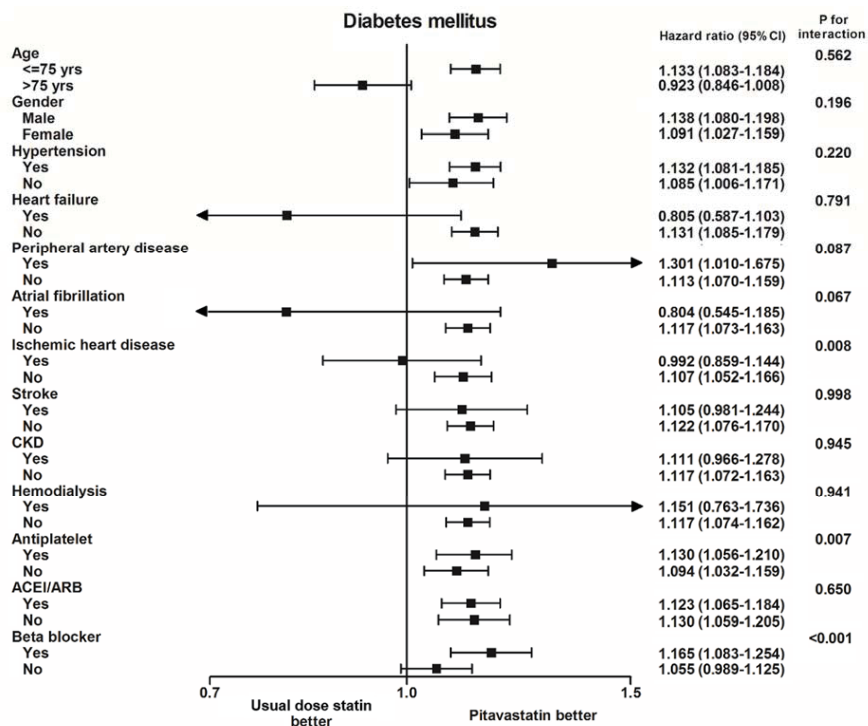
	Pitavastatin N = 50935		Usual dose statin N = 50935					High dose statin N = 50935				
	N (%)	SHR	N (%)	Crude SHR (95% CI)	P	Adjusted SHR (95% CI)	P	N (%)	Crude SHR (95% CI)	P	Adjusted SHR (95% CI)	P
Safety outcome	5014 (9.84)	Ref.	5542 (10.88)	1.08 (1.04-1.12)	<0.001	1.13 (1.08-1.17)	<0.001	5343 (10.49)	1.06 (1.02-1.10)	0.006	1.06 (1.02-1.10)	0.004
Hepatitis	240 (0.47)	Ref.	287 (0.56)	1.18 (0.99-1.40)	0.062	1.22 (1.03-1.45)	0.023	289 (0.57)	1.20 (1.01-1.43)	0.036	1.20 (1.01-1.43)	0.035
Myopathy	19 (0.04)	Ref.	28 (0.05)	1.46 (0.81-2.62)	0.205	1.49 (0.83-2.71)	0.185	24 (0.05)	1.26 (0.69-2.31)	0.452	1.26 (0.69-2.32)	0.450
NODM	4818 (9.46)	Ref.	5284 (10.37)	1.07 (1.03-1.11)	0.001	1.12 (1.07-1.16)	<0.001	5113 (10.04)	1.05 (1.01-1.09)	0.015	1.05 (1.01-1.10)	0.009

Model was adjusted for propensity score, statin exposure time as time-dependent covariate, age, sex, comorbidities (hypertension, heart failure, peripheral artery disease, atrial fibrillation, chronic obstructive lung disease, chronic liver disease, peptic ulcer disease, ischemic heart disease, chronic kidney disease, stroke, hemodialysis), and medications (antiplatelet, ACEI/ARB, beta blocker, NOAC). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; NODM, new-onset diabetes mellitus; SHR, Subdistribution hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; P, p-value; Ref, reference.

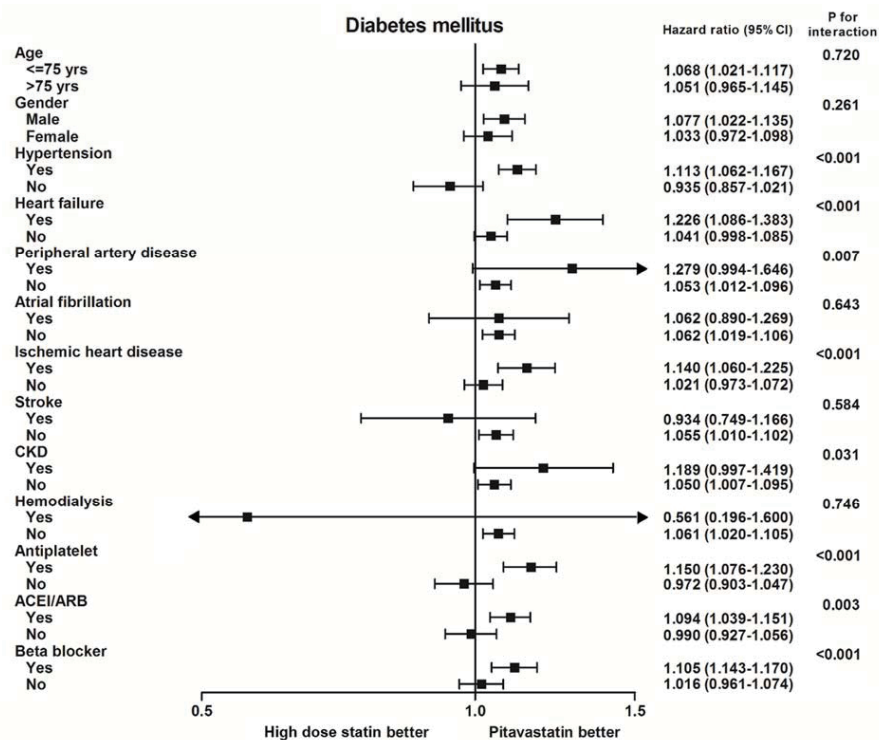


**Supplemental Fig. 1.** Kaplan–Meier curves showed the cumulative incidence of primary safety outcome in different statin groups

A.



B.



**Supplemental Fig. 2.** Subgroup analysis of new-onset diabetes mellitus

(A) pitavastatin vs. usual-dose statin (B) pitavastatin vs. high-dose statin. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.