Tohoku J. Exp. Med., 2024, **263**, 105-113

Risk of Hemorrhagic Stroke among Patients Treated with High-Intensity Statins versus Pitavastatin-Ezetimibe: A Population Based Study

Po-Sheng Chen,[1,*] Jia-Ling Lin,[1,*] Hui-Wen Lin,[1,2] Sheng-Hsiang Lin[2,3,4] and Yi-Heng Li[1]

[1]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Biostatistics Consulting Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[3]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

High-intensity statin (HIS) is recommended for high-risk patients in current guidelines. However, the risk of hemorrhagic stroke (HS) with HIS is a concern for Asians. Pitavastatin carries pharmacological differences compared with other statins. We compared the risk of HS in patients treated with pitavastatin-ezetimibe vs. HIS. We conducted a population-based, propensity score–matched cohort study using data from the Taiwan National Health Insurance Research Database. From January 2013 to December 2018, adults (≥ 18 years) who received pitavastatin 2-4 mg/day plus ezetimibe 10 mg/day (combination group, N = 3,767) and those who received atorvastatin 40 mg/day or rosuvastatin 20 mg/day (HIS group, N = 37,670) were enrolled. The primary endpoint was HS. We also assessed the difference of a composite safety endpoint of hepatitis or myopathy requiring hospitalization and new-onset diabetes mellitus. Multivariable Cox proportional hazards model was used to evaluate the relationship between study endpoints and different treatment. After a mean follow-up of 3.05 ± 1.66 years, less HS occurred in combination group (0.74%) than in HIS group (1.35%) [adjusted hazard ratio (aHR) 0.65, 95% confidence interval (CI) 0.44-0.95]. In subgroup analysis, the lower risk of HS in combination group was consistent among all pre-specified subgroups. There was no significant difference of the composite safety endpoint between the 2 groups (aHR 0.91, 95% CI 0.81-1.02). In conclusion, pitavastatin-ezetimibe combination treatment had less HS compared with high-intensity atorvastatin and rosuvastatin. Pitavastatin-ezetimibe may be a favorable choice for Asians who need strict lipid control but with concern of HS.

Keywords: diabetes mellitus; hemorrhagic stroke; lipids; myopathy; statins
Tohoku J. Exp. Med., 2024 June, **263** (2), 105-113.
doi: 10.1620/tjem.2024.J019

Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) reduces the risk of cardiovascular (CV) events. The degree of risk reduction is proportional to the level of LDL-C reduction and the duration of exposure to a lower LDL-C level (Cholesterol Treatment Trialists' (CTT) Collaboration et al. 2010; Ference et al. 2017, 2018). Statin is the first-line therapy and high-intensity statins (HIS), including atorvastatin 40 mg/day and rosuvastatin 20 mg/day with the ability of ≥ 50% LDL-C reduction, is recommended in current guidelines for high-risk patients (Grundy et al. 2019;

Received November 28, 2023; revised and accepted February 11, 2024; J-STAGE Advance online publication February 22, 2024
*These two authors contributed equally to this work.
Correspondence: Dr. Yi-Heng Li, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng Li Road, Tainan 704, Taiwan.
e-mail: heng@mail.ncku.edu.tw
Sheng-Hsiang Lin, Biostatistics Consulting Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, and Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, 138 Sheng Li Road, Tainan 704, Taiwan.
e-mail: shlin922@mail.ncku.edu.tw

Mach et al. 2020; Chen et al. 2022). However, several recent studies found that statins, but not other lipid lowering drugs, increase the risk of hemorrhagic stroke (HS), especially in those who had a previous history of stroke and were under treatment with higher dose or potency statins (Teoh et al. 2019; Sanz-Cuesta and Saver 2021; Lee et al. 2022). In patients with lobar intracerebral hemorrhage (ICH) and suspected cerebral amyloid angiopathy, using ezetimibe instead of statins is suggested (Shoamanesh and Selim 2022). If statin is considered after ICH, HIS should be avoided (Shoamanesh and Selim 2022). HS is a concern for Asian statin users because the risk and prevalence of HS are much higher in Asian populations compared with white ethnicity (van Asch et al. 2010; Tsai et al. 2013). Asians are more sensitive to statins and HIS-associated muscle and liver side effects are another concern in Asia (Liao 2007; Naito et al. 2017). As a result, statin-ezetimibe therapy becomes another choice for patients at high risk of statin-associated side effects or with intolerance to HIS.

Although categorized as moderate-intensity statin, pitavastatin is another potent statin. Pitavastatin 2-4 mg/day provides 42-47% reduction of LDL-C which approximately equals to LDL-C lowering effect of atorvastatin 20-30 mg/day or rosuvastatin 10 mg/day (Hayashi et al. 2007). Pitavastatin 2-4 mg/day plus ezetimibe 10 mg/day could provide > 50% LDL-C reduction and achieved roughly the similar reduction of LDL-C to HIS because ezetimibe provides an additional 15-23% LDL-C reduction on top of statin. Unlike atorvastatin and rosuvastatin, pitavastatin is minimally metabolized by hepatic cytochrome P450 (CYP) enzymes and has lower risk of drug-drug interaction (Hayashi et al. 2007; Catapano 2010). Asian studies showed that pitavastatin was associated with less statin-associated side effects, including hepatitis and new-onset diabetes mellitus (NODM), compared with atorvastatin and rosuvastatin (Lin et al. 2022; Seo et al. 2022). The randomized clinical trial, REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease) study, demonstrated that pitavastatin 4 mg/day, compared with pitavastatin 1 mg/day, provided more LDL-C reduction and improved clinical outcomes in patients with coronary artery disease (Taguchi et al. 2018). In this study, the risk of HS for high dose pitavastatin 4 mg/day was similar to low dose pitavastatin 1 mg/day (Takahashi et al. 2020).

Based on the above evidence, we hypothesized that the risk of HS may be different between pitavastatin-ezetimibe and HIS, while they provide similar level of LDL-C reduction. We designed a population-based study to compare the risk of HS between pitavastatin 2-4 mg/day plus ezetimibe 10 mg/day and HIS (atorvastatin 40 mg/day and rosuvastatin 20 mg/day) in an Asian population. The incidences of safety events, including myopathy, hepatitis and NODM, were also evaluated between the two groups.

Methods

Data source

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. National Health Insurance (NHI) is a compulsory state-run medical insurance program launched in Taiwan since 1995 and covers medical care for more than 99% of the 23 million residents in Taiwan. NHIRD is derived from the NHI program's claim database and provides data including demographic characteristics, medical diagnoses, procedures, and prescriptions from both inpatient and outpatient services. To keep the study participants' privacy, identification number was encrypted. We used the International Classification of Diseases, Ninth and Tenth (after 2016) Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes to identify all the subjects' diagnosis. Previous studies had confirmed the diagnostic accuracy of both ICD-9-CM and ICD-10-CM codes in Taiwan's NHIRD (Cheng et al. 2014; Hsieh et al. 2015, 2019, 2020). The codes of ICD9-CM and ICD-10-CM used in this study were listed in Supplementary Table S1. The Institutional Review Board of National Cheng Kung University Hospital approved this study (IRB No: A-EX-111-003).

Study design

This was a population-based and retrospective cohort study. From January 1, 2013 to December 31, 2018, all adult patients (≥ 18 years old) who received pitavastatin 2-4 mg/day plus ezetimibe 10 mg/day (combination group) and patients who received atorvastatin 40 mg/d or rosuvastatin 20 mg/day (HIS group) for any reason were enrolled in this study (237,863 individuals). In Taiwan, the recommended HIS doses are atorvastatin 40 mg/day and rosuvastatin 20 mg/day which are similar to the recommendations in Japan (Naito et al. 2017). For fear of side effects, atorvastatin 80 mg/day is very rarely prescribed in Taiwan and rosuvastatin 40 mg/day does not have drug permit license from the Taiwan Food and Drug Administration. Subjects were included for analysis if they received medication for more than 90% of times in a consecutive 30 days after enrollment. For combination group, subjects were eligible if their prescription of pitavastatin and ezetimibe overlapped for more than 28 days. We excluded those who had: (1) incomplete registry data (missing data of sex or age); (2) diagnosis of diabetes or taken anti-diabetic medications before enrollment; (3) taken any other statin within one month before enrollment; and (4) age less than 18 years. In HIS group, subjects were excluded if they received ezetimibe after enrollment. The information of age, sex, medical history, and concomitant medications within the previous 3 months before enrollment were captured from the database as the baseline characteristics.

Study endpoints

The primary endpoint was HS (ICD-9 CM code 430, 431, 432; ICD-10 CM code I60, I61, I62). The composite safety endpoint included hepatitis requiring hospitalization (ICD-9 CM code 573.3; ICD-10 CM code K72.0, K72.9, K71.1, K71.2, K75.2, K75.9, K76.9), myopathy requiring hospitalization (ICD-9 CM code 359.4, 359.8, 359.9, 729.1; ICD-10 CM code M60.1, M60.8, M60.9, G72.0, G72.4, G72.8, G72.9), and NODM (ICD-9 CM code 250; ICD-10 CM code E08-E13) that needed to start antidiabetic medications. Identification of the endpoints of HS, myopathy or hepatitis required to have document of hospitalization with major discharge diagnosis of these diseases. Identification of NODM needed to have hospitalization with a new discharge diagnosis of diabetes or new diagnosis of diabetes in outpatient clinics for 2 times consecutively and starting anti-diabetic medications. The risk of individual component of the composite safety endpoint was also calculated. We continuously followed up all of the claim data belonging to the same patient within the NHIRD till December 31, 2019, and the shortest follow-up time was at least one year.

Statistical analysis

Continuous variables were presented as means ± standard deviations and categorical variables as numbers and percentages. To avoid the bias arising from non-randomization, we used propensity score matching of 1:10 for combination group to HIS group. The propensity score for the likelihood of receiving pitavastatin-ezetimibe vs. HIS was computed using multivariate logistic regression analysis, conditional on the covariates including index year, age, sex, medications, and comorbidities. After matching, we calculated the absolute standardized mean difference (ASMD) to assess distributions of clinical characteristics in the two groups. ASMD is the mean or proportion of a variable divided by the pooled estimate of the standard deviation of the variable. When ASMD < 0.1, the difference of this variable between the two groups is negligible. Multivariable Cox proportional hazards model was used to examine the relationship between endpoint and different treatment. The same covariates used for multivariate logistic regression analysis of propensity score matching were also used in the multivariable Cox proportional hazards model, including age, sex, comorbidities [hypertension, heart failure, peripheral artery disease (PAD), atrial fibrillation, chronic obstructive pulmonary disease (COPD), chronic liver disease, cancer, peptic ulcer disease, myocardial infarction, ischemic heart disease (IHD), chronic kidney disease (CKD), previous ischemic stroke, previous HS, hemodialysis], and medications [antiplatelet, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), beta-blocker, and non-vitamin K antagonist oral anticoagulant]. The hazard ratio (HR) and 95% confidence interval (CI) were calculated from the Cox models after adjusting for all these potential confounders.

A major sensitivity analysis was performed using the R package "obsSens" to estimate the range of HRs between the treatment groups for HS. A hypothetical unmeasured confounder with a favorable protective effect to observe the range of HRs that were confounded by this add-on factor with different prevalence in combination treatment and HIS groups. We also conducted another 3 sensitivity analyses with different inclusion and exclusion criteria: The first included diabetic patients but excluded patients with previous history of stroke (both ischemic and hemorrhagic), the second included all patients with diabetes and previous history of stroke and the third excluded patients with diabetes and previous history of stroke. We additionally used prespecified subgroup analyses to determine if the association between different treatment and HS varied by age, sex, previous ischemic stroke, previous HS, hypertension, heart failure, PAD, atrial fibrillation, COPD, IHD, CKD, use of antiplatelet, ACEI/ARB, and beta-blocker. We used SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) for data analyses.

Results

Overall, we identified 237,863 patients who were taking pitavastatin-ezetimibe or HIS in the database. After exclusions, 3,767 patients were in the pitavastatin-ezetimibe group and 103,851 patients in the HIS group. After 1:10 matching, there were 3,767 subjects in the combination group and 37,670 patients in the HIS group (Fig. 1). Table

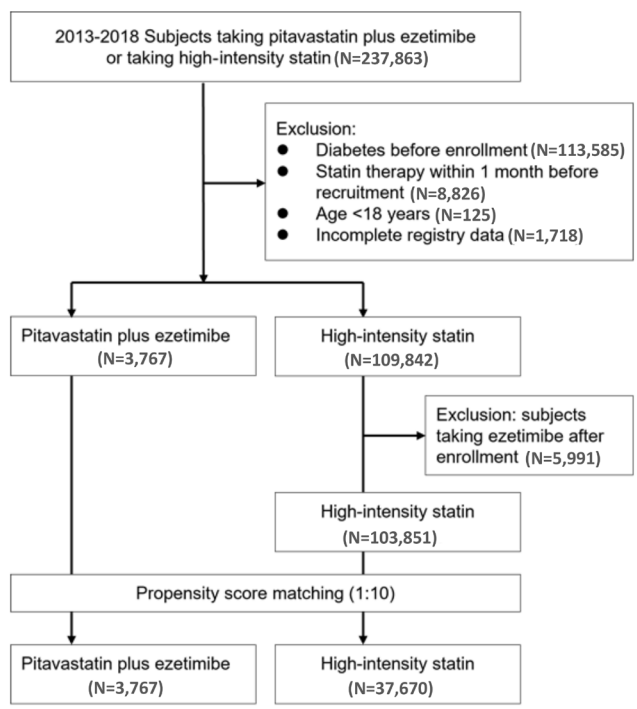

Fig. 1. Flowchart of patient selection.
In the exclusion criteria, incomplete registry data indicated subjects with missing data of age and sex. After 1:10 propensity score matching, there were 3,767 subjects in the combination group and 37,670 patients in the high-intensity statin group.

Table 1. Baseline characteristics.

	Propensity score matching							
	Before				After			
	All N = 107,618	Pitavastatin-ezetimibe N = 3,767	High-intensity statin N = 103,851	ASMD	All N = 41,437	Pitavastatin-ezetimibe N = 3,767	High-intensity statin N = 37,670	ASMD
Year				1.00				0.00
2013	44,343 (41.20)	299 (7.94)	44,044 (42.41)		3,289 (7.94)	299 (7.94)	2,990 (7.94)	
2014	14,569 (13.54)	337 (8.95)	14,232 (13.70)		3,707 (8.95)	337 (8.95)	3,370 (8.95)	
2015	11,027 (10.25)	371 (9.85)	10,656 (10.26)		4,081 (9.85)	371 (9.85)	3,710 (9.85)	
2016	11,160 (10.37)	524 (13.91)	10,636 (10.24)		5,764 (13.91)	524 (13.91)	5,240 (13.91)	
2017	12,303 (11.43)	1,042 (27.67)	11,261 (10.84)		11,462 (27.66)	1,042 (27.67)	10,420 (27.67)	
2018	14,216 (13.21)	1,194 (31.70)	13,022 (12.54)		13,134 (31.70)	1,194 (31.70)	11,940 (31.70)	
Male	56,584 (52.58)	2,068 (54.90)	54,516 (52.49)	0.05	22,054 (53.22)	2,068 (54.90)	19,986 (53.06)	0.04
Age	61.62 ± 12.94	59.77 ± 11.74	61.69 ± 12.98	0.16	60.30 ± 12.75	59.77 ± 11.74	60.35 ± 12.84	0.05
Comorbidities								
Hypertension	63,167 (58.70)	2,187 (58.06)	60,980 (58.72)	0.01	23,183 (55.95)	2,187 (58.06)	20,996 (55.74)	0.05
Heart failure	5,937 (5.52)	329 (8.73)	5,608 (5.40)	0.13	2,714 (6.55)	329 (8.73)	2,385 (6.33)	0.09
PAD	2,489 (2.31)	81 (2.15)	2,408 (2.32)	0.01	854 (2.06)	81 (2.15)	773 (2.05)	0.01
Atrial fibrillation	3,114 (2.89)	89 (2.36)	3,025 (2.91)	0.03	1,091 (2.63)	89 (2.36)	1,002 (2.66)	0.02
COPD	9,576 (8.90)	301 (7.99)	9,275 (8.93)	0.03	3,487 (8.42)	301 (7.99)	3,186 (8.46)	0.02
Chronic liver disease	12,099 (11.24)	549 (14.57)	11,550 (11.12)	0.10	5,297 (12.78)	549 (14.57)	4,748 (12.60)	0.06
Cancer*	58,890 (54.72)	1,318 (34.99)	57,572 (55.44)	0.42	11,927 (28.78)	1,318 (34.99)	10,609 (28.16)	0.15
PUD	14,618 (13.58)	547 (14.52)	14,071 (13.55)	0.03	5,437 (13.12)	547 (14.52)	4,890 (12.98)	0.05
MI	6,919 (6.43)	182 (4.83)	6,737 (6.49)	0.07	2,697 (6.51)	182 (4.83)	2,515 (6.68)	0.08
IHD*	27,089 (25.17)	1,528 (40.56)	25,561 (24.61)	0.35	11,333 (27.35)	1,528 (40.56)	9,805 (26.03)	0.31
CKD*	8,551 (7.95)	187 (4.96)	8,364 (8.05)	0.13	3,175 (7.66)	187 (4.96)	2,988 (7.93)	0.12
Previous ischemic stroke*	13,678 (12.71)	174 (4.62)	13,504 (13.00)	0.30	3,000 (7.24)	174 (4.62)	2,826 (7.50)	0.12
Previous hemorrhagic stroke	2,589 (2.41)	21 (0.56)	2,568 (2.47)	0.16	451 (1.09)	21 (0.56)	430 (1.14)	0.06
Hemodialysis	1,044 (0.97)	8 (0.21)	1,036 (1.00)	0.10	138 (0.33)	8 (0.21)	130 (0.35)	0.03
Medications								
Antiplatelet*	30,550 (28.39)	1,281 (34.01)	29,269 (28.18)	0.13	11,108 (26.81)	1,281 (34.01)	9,827 (26.09)	0.17
ACEI/ARB*	37,335 (34.69)	1,511 (40.11)	35,824 (34.50)	0.12	14,186 (34.24)	1,511 (40.11)	12,675 (33.65)	0.13
Beta blocker*	28,546 (26.53)	1,224 (32.49)	27,322 (6.31)	0.14	10,843 (26.17)	1,224 (32.49)	9,619 (25.53)	0.15
NOACs	712 (0.66)	33 (0.88)	679 (0.65)	0.03	465 (1.12)	33 (0.88)	432 (1.15)	0.03

Data are presented as number (percentages) or mean ± standard deviation.
*ASMD > 0.1 between matching groups.
ASMD, absolute standardized mean difference; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; PUD, peptic ulcer disease.

1 shows the baseline characteristics between the combination and HIS groups before and after matching. More than half of the subjects were enrolled in the last one-thirds of the enrollment years. The average age was similar in both groups (59.77 ± 11.74 years in pitavastatin-ezetimibe group and 60.35 ± 12.84 years in HIS group). The percentage of male was also similar (54.90% in pitavastatin-ezetimibe group and 53.06% in HIS group). After propensity score matching, subjects in combination group had more cancer, IHD, higher proportion of using antiplatelet, ACEI/ARB, and beta-blocker comparing to those in HIS group. Additionally, they also had less CKD, and ischemic stroke. All other characteristics were similar between the two groups. Most subjects in combination group received pitavastatin 2 mg/day while most subjects in HIS group had atorvastatin 40 mg/day (Supplementary Table S2).

The mean duration of follow-up was 3.05 ± 1.66 years. Table 2 shows clinical outcome events between the two groups. The primary endpoint, HS occurred in 28 subjects of the pitavastatin-ezetimibe combination group (0.74%) and in 507 subjects of the HIS group (1.35%). Multivariable Cox proportional hazards model demonstrated that the risk of HS was significantly lower in pitavastatin-ezetimibe group compared with HIS group [adjusted HR (aHR) 0.65, 95% CI 0.44-0.95]. The events of composite safety endpoint occurred in 309 patients in combination group (8.20%) and in 3,186 patients in HIS group (8.46%). The composite safety endpoint did not make statistical significance between the two groups (aHR 0.91, 95% CI 0.81-1.02). In the individual component of the composite safety endpoint, there was a non-significant 24% risk reduction of hepatitis requiring hospitalization (aHR 0.76, 95% CI 0.48-1.20) and 8% risk reduction of NODM (aHR 0.92, 95% CI 0.81-1.04) in the pitavastatin-ezetimibe group compared with the HIS group. The risk of myopathy requiring hospitalization was very low and occurred in 0.08% in pitavastatin-ezetimibe group and 0.06% in HIS group.

Fig. 2 shows the plot of major sensitivity analysis which assessed the influence of add-on an unmeasured confounder for HS. For example, when the unmeasured confounders were added for the HIS group (prevalence = 1.0) but not for the combination group (prevalence = 0), the HR was 0.3, indicating a lower HS risk. In contrast, when the unmeasured confounders were not added for the HIS group (prevalence = 0) but were added for the combination group (prevalence = 1.0), the HR was 1.5. Most of the HRs in different conditions were < 1.0 indicating consistency of a lower risk of HS in subjects receiving pitavastatin-ezetimibe than those having HIS. We further conducted another 3 sensitivity analyses. There was little attenuation of the lower HS risk with pitavastatin-ezetimibe by including diabetic patients. The lower risk of HS in pitavastatin-ezetimibe group was observed by including diabetic patients but excluding patients with previous history of stroke (Supplementary Table S3A) and also by including diabetic patients and patients with previous history of stroke (Supplementary Table S3B). When excluding all patients who had diabetes and with previous history of stroke, there was somewhat attenuation of the lower HS risk (aHR 0.66, 95% CI 0.41-1.09) (Supplementary Table S3C). When including all patients with diabetes and previous history of stroke for analysis (Supplementary Table S3B), there was also a borderline significant reduction of the composite safety endpoint (aHR 0.75, 95% CI 0.55-1.02) and it was mainly driven by the decreased risk of hepatitis requiring hospitalization (aHR 0.73, 95% CI 0.52-1.01). Subgroup analysis showed that the beneficial effect of pitavastatin-ezetimibe for a lower risk of HS was consistent among all prespecified subgroups, including patients with previous ischemic stroke and patients with previous HS (Fig. 3).

Discussion

This population-based study demonstrated that patients with pitavastatin-ezetimibe treatment had a lower risk of HS than those with HIS. The risk of composite safety endpoint, including hepatitis or myopathy requiring hospitalization and NODM, was similar between the two groups.

Table 2. Risk of hemorrhagic stroke and composite safety outcome.

	Pitavastatin-ezetimibe N = 3,767	High-intensity statin (reference) N = 3,7670	Crude HR (95% CI)	*P value*	Adjusted HR (95% CI)	*P value*
Hemorrhagic stroke	28 (0.74)	507 (1.35)	0.55 (0.38-0.81)	< 0.01	0.65 (0.44-0.95)	0.03
Safety outcome	309 (8.20)	3,186 (8.46)	0.97 (0.86-1.09)	0.58	0.91 (0.81-1.02)	0.12
Hepatitis	20 (0.53)	264 (0.70)	0.76 (0.48-1.20)	0.24	0.76 (0.48-1.20)	0.23
Myopathy	3 (0.08)	23 (0.06)	1.30 (0.39-4.33)	0.67	1.15 (0.34-3.87)	0.82
NODM	290 (7.70)	2,956 (7.85)	0.98 (0.87-1.10)	0.72	0.92 (0.81-1.04)	0.17

Data are presented as number of events (percentages). Model was adjusted for age, sex, comorbidities [hypertension, heart failure, peripheral artery disease (PAD), atrial fibrillation, chronic obstructive pulmonary disease (COPD), chronic liver disease, cancer, peptic ulcer disease, myocardial infarction (MI), ischemic heart disease (IHD), chronic kidney disease (CKD), previous ischemic stroke, previous hemorrhagic stroke, hemodialysis] and medications [antiplatelet, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), beta blocker, non-vitamin K antagonist oral anticoagulant (NOAC)].
CI, confidence interval; HR, hazard ratio.

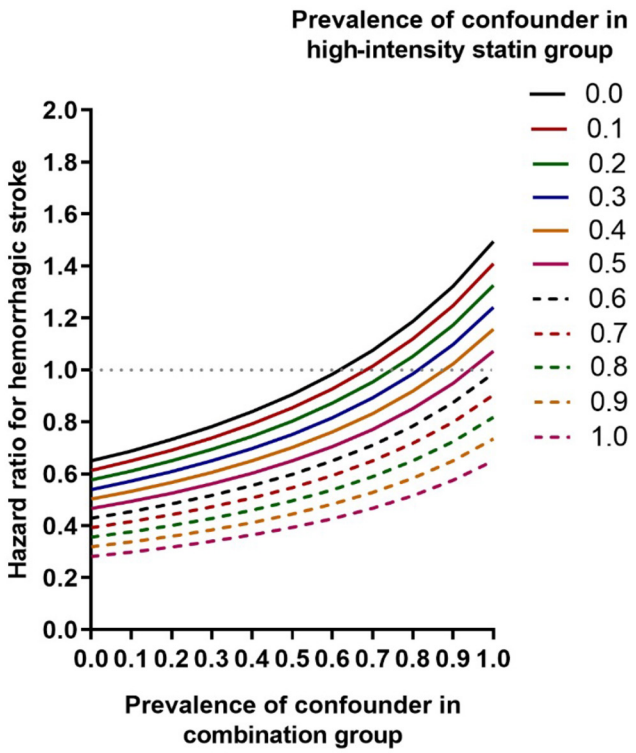

Fig. 2. Sensitivity analysis of an unmeasured confounder for hemorrhagic stroke.
Sensitivity analysis with add-on of an unmeasured confounder and the trend estimates of the hazard ratios for hemorrhagic stroke using a multivariable Cox regression model. The model showed that hazard ratios of hemorrhagic stroke were < 1.0 in most conditions, indicating consistency of a lower risk of hemorrhagic stroke in combination group.

Previous clinical trials, including HPS (Heart Protection Study) study and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study demonstrated an increased risk of HS in subjects with prior cerebrovascular disease treated with simvastatin 40 mg/day or atorvastatin 80 mg/day (Collins et al. 2004; Amarenco et al. 2006). However, the subsequent studies showed inconsistent results regarding the risk of HS with statins (Lei et al. 2014; Pandit et al. 2016; Ziff et al. 2019; Cheng et al. 2020). The association of HS and statin treatment remained controversial.

Initially, the low LDL-C level caused by statins was considered to be associated with HS (Ma et al. 2019; Sun et al. 2019). But recent analyses of the clinical trials with combination treatment of statin and non-statin lipid lowering therapies, including ezetimibe and proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors, did not demonstrate increased HS risk in patients with very low LDL-C levels achieved with the combination treatment (Giugliano et al. 2017, 2020). In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study with simvastatin plus ezetimibe, the HS risk was not increased among patients with an LDL-C < 30 mg/dL compared with patients with an LDL-C > 70 mg/dL (Giugliano et al. 2017). In FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) study, evolocumab plus statin reduced the baseline LDL-C level from 92 mg/dL to a median of 30 mg/mL and the risk of HS did not increase in evolocumab plus statin group compared with statin monotherapy (Giugliano et al. 2020).

Several studies have found the potential association between statin intensity and HS. In a meta-analysis of 36 statin randomized clinical trials (204,918 patients) and 5 PCSK9 inhibitor randomized clinical trials (76,140 patients), statins were associated with increased risk of HS (relative risk 1.15, $P < 0.05$) but not PCSK9 inhibitors ($P = 0.77$) (Sanz-Cuesta and Saver 2021). Higher dose/potency statins and prior stroke were associated with magnified risk of HS (Sanz-Cuesta and Saver 2021). Another meta-analysis also demonstrated that more intensive statin-based therapies were associated with an increased risk of HS with the effect possibly exacerbated by using HIS (Lee et al. 2022). Although the mechanism of increased HS risk is not clear, it seems that it is not caused by low LDL-C level or the magnitude of LDL-C reduction, but more likely related to the antithrombotic properties of statins that activate both coagulation and platelet systems (Violi et al. 2013).

Clinical trials demonstrated that pitavastatin-ezetimibe could provide 52% LDL-C reduction which is approximately equal to the effect of atorvastatin 40 mg/day or rosuvastatin 20 mg/day (Watanabe et al. 2015; Hagiwara et al. 2017). Our study found, with roughly similar LDL-C reduction, subjects receiving pitavastatin-ezetimibe had significantly lower risk of HS than those with high-intensity atorvastatin and rosuvastatin. In subgroup analysis, the lower HS risk was observed in patients with prior ischemic stroke or HS which were considered as major risk factors of HS in statin users (Amarenco et al. 2006; Sanz-Cuesta and Saver 2021; Lee et al. 2022). The exact mechanism accounting for the difference of HS risk among various statins was unknown. The direct antithrombotic effect of statins is considered to be a possible cause of HS. Stronger influence of HIS on coagulation system than pitavastatin might be a potential explanation. A previous study demonstrated that rosuvastatin, but not pitavastatin, enhanced the anticoagulation effect of warfarin (Yu et al. 2012). In that study, because the total plasma concentration of warfarin was similar between rosuvastatin and pitavastatin group, the difference of anticoagulation enhancement did not appear to be related to CYP-related drug-drug interaction, but more likely due to the different antithrombotic effect of statins (Yu et al. 2012). Currently, there is lack of evidence-based suggestions regarding the optimal lipid-lowering treatment strategy for subjects vulnerable to HS. Further randomized clinical trials are needed to solve this problem.

In the present study, although there were numerically lower NODM cases in combination group (7.85% vs. 7.70%), the difference of NODM risk between the two

groups did not reach statistical significance (aHR 0.92, 95% CI 0.81-1.04). We previously demonstrated that patients treated with high dose atorvastatin (20-40 mg/day) or rosuvastatin (20 mg/day) had a higher risk of NODM (aHR 1.05, 95% CI 1.01-1.10) than pitavastatin (Lin et al. 2022). Although the risk reduction was similar in our two studies, the smaller sample size of pitavastatin-ezetimibe in the current study caused the problem of statistical power. Another Asian study showed the same finding that there was no statistical significance about the NODM risk between pitavastatin and high-intensity atorvastatin or rosuvastatin due to the problem of smaller case number in HIS group (Seo et al. 2022).

The strength of our study was the data coming from general population in a national database which include more than 23 million residents in Taiwan. The longitudinal medical claims contained sufficient information on diagnosis, health service utilization, prescription information and all follow-up results. However, several study limitations need to be addressed. First, since the study was an observational study but not a randomized trial, some unmeasured confounding factors could not be excluded completely. We reduced the bias as far as possible using propensity matching to balance all observed covariates and the results were retested in multiple sensitivity analyses. Second, there was no laboratory data recorded in the database and we could not obtain the baseline and on-treatment LDL-C levels. Theoretically, the magnitude of LDL-C reduction would be similar between the groups, but the potential difference of LDL-C levels could exist and affect clinical outcomes. Third, we did not know the blood pressure levels of the study participants. Although the clinical outcome was similar between those with and without hypertension (Fig. 3), inability to analyze the blood pressure levels is a major limitation of our study. Fourth, we did not have the data of liver function, creatine phosphokinase, sugar, and hemoglobin A1c between the groups. However, the safety events, such as hepatitis or myopathy, required documented hospitalization and recorded in the discharge diagnosis. NODM needed to have new diagnosis of diabetes and begin any anti-diabetic medication. These events would not be missed in our study. Fifth, not like the diagnosis of ischemic stroke and myocardial infarction, the diagnosis of HS was not validated in Taiwan NHIRD. However, we believed that HS is

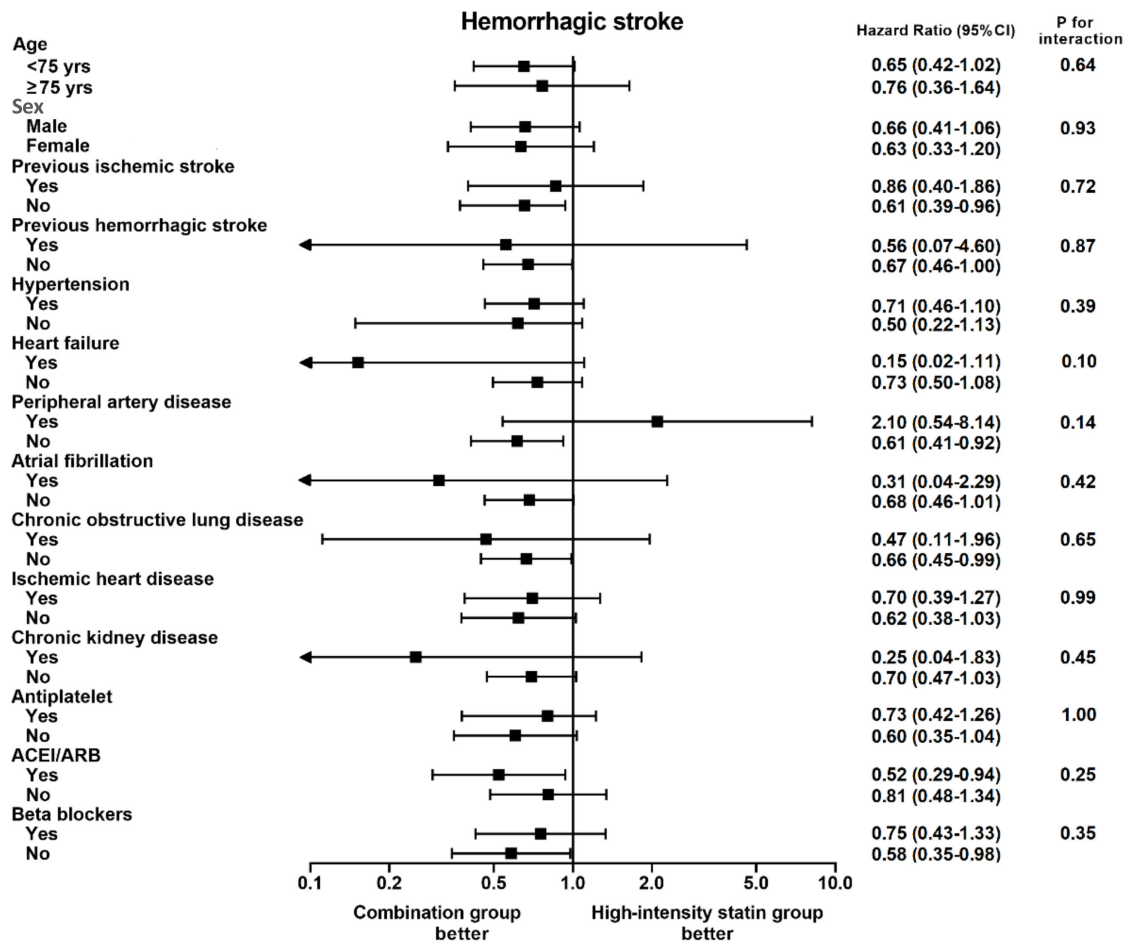

Fig. 3. Subgroup analysis of the treatment effect on hemorrhagic stroke.
The beneficial effect of pitavastatin-ezetimibe combination group for a lower risk of hemorrhagic stroke was consistent among all pre-specified subgroups. ACE1, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

a catastrophic illness and not easy to misdiagnose or misclassified from the image studies. Sixth, we did not have the data of some clinical characteristics that contribute to the development of HS, such as body mass index and alcoholism due to the information limitation of NHIRD. Finally, the use of statins or statin-ezetimibe was based on redemptions of prescriptions and the actual drug adherence was unknown. But a previous study showed that prescription registry data of statins correspond well with actual use of the medications after examining the statin concentrations (Riis et al. 2019).

In conclusion, the risk of HS was different among the intensive lipid-lowering strategies. Our study indicated Asians with pitavastatin-ezetimibe had lower risk of HS compared to high-intensity atorvastatin and rosuvastatin. Pitavastatin-ezetimibe may be an alternative choice of lipid lowering therapy for Asians who need intensive LDL-C reduction but at high risk of HS.

Acknowledgments

We are grateful to the Health Data Science Center, National Cheng Kung University Hospital for providing administrative and technical support. This study was sponsored by Cheng-Hsing Medical Foundation, Tainan, Taiwan. The funders had no role in study design, data collection, decision to publish, or preparation of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1620/tjem.2024.J019