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ARTICLE

Effects of statins in patients with coronary artery spasm: A nationwide population-based study

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Abstract

Controversies regarding the benefits of statin treatment on clinical outcomes in coronary artery spasm (CAS) without obstructive coronary artery disease (CAD) persist due to limited data. In this retrospective nationwide population-based cohort study from the Taiwan National Health Insurance Research Database during the period 2000–2012, the matched cohorts consisted of 12,000 patients with CAS. After propensity score matching with 1:1 ratio, 2216 patients were eligible for outcome analysis in either statin or nonstatin group, with the mean follow-up duration of 4.8 and 4.6 years, respectively. Statin users versus nonusers had a

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CAS, coronary artery spasm; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; INOCA, ischemia with nonobstructive coronary artery disease; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; NHI, National Health Institute; NHIRD, National Health Insurance Research Database; PCI, percutaneous coronary intervention; SHR, subdistribution hazard ratio.

Yu-Ching Lee and Ming-Jui Hung contributed equally to this work.

There have been no previous presentations of the whole or part of the work presented in the article.

significantly reduced risk of major adverse cardiovascular events (MACEs) (6.7% vs. 9.5%, hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.55–0.84) and all-cause mortality (6.0% vs. 7.6%; HR 0.77; 95% CI 0.61–0.96). While the results of MACEs were mainly contributed by cardiovascular death (1.9% vs. 3.2%; HR 0.56; 95% CI 0.38–0.83) and ischemic stroke (3.8% vs. 5.4%; subdistribution HR 0.69; 95% CI 0.52–0.91), they were primarily driven by reductions in ischemic but not hemorrhagic stroke. The benefit of statins was significantly pronounced in patients with hypertension and diabetes. Nevertheless, the effect on MACEs was consistent irrespective of age, sex, dyslipidemia, and mental disorder. Statins significantly reduced the risk of MACEs and all-cause mortality in CAS patients. The benefit of statin therapy in reducing MACEs appeared to be linear, with greater risk reduction with higher doses and longer duration without upper threshold, reflecting the dose-dependent relationship of statins with MACEs in CAS patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

It is debatable whether administration of statins improves prognosis of coronary artery spasm (CAS).

WHAT QUESTION DID THIS STUDY ADDRESS?

This nationwide population-based cohort study explored whether the effects of statins are fixed or change over time in reducing adverse cardiovascular events in CAS patients but without obstructive coronary artery disease.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Statin users versus nonusers had a significantly reduced risk of major adverse cardiovascular events (MACEs) and all-cause mortality, mainly contributed by reduced cardiovascular death and ischemic stroke but not hemorrhagic stroke. While the benefit of statins was significantly pronounced in patients with hypertension and diabetes, the effects, irrespective of age, sex, dyslipidemia, and mental disorder, appeared to be positively linear without upper threshold, reflecting the dose-dependent relationship of statins with MACEs in CAS patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Because the risk of stroke and cardiovascular mortality is not low in CAS, clinicians should be more aggressive in treating CAS patients to ensure timely and personalized provision of care.

INTRODUCTION

Ischemia with nonobstructive coronary artery disease (INOCA), including epicardial coronary artery spasm (CAS), microvascular CAS, or mixed epicardial/microvascular CAS, is a nonbenign condition with an equal incidence of major adverse cardiovascular outcomes and effects on quality of life as obstructive coronary artery disease (CAD).[1,2] Patients with myocardial ischemia due to nonobstructive CAD was associated with a significantly greater 1-year risk of acute myocardial infarction (AMI) and all-cause mortality.[3] In this regard, INOCA comprises up to 70% of angina patients undergoing coronary angiography,[2] and endothelial dysfunction makes up two thirds of symptomatic INOCA and a smaller percentage of "myocardial infarction with nonobstructive CAD." CAS, an excessive coronary vasoconstriction, is associated with inflammation[4] and can cause total or subtotal vascular occlusion, leading to syncope, heart failure syndromes, arrhythmic syndromes, and myocardial ischemic syndromes including asymptomatic ischemia, angina, infarction, and sudden cardiac death.[5] In CAS with minimal atherosclerosis, the survival rates are as high as 99% at 1 year and 94% at 5 years, while the survival in CAS

with nonobstructive multivessel atherosclerosis falls to 87% and 77% at 1 and 5 years, respectively,[6] suggesting drugs available to treat ischemic heart disease might be considered in the management of CAS without obstructive CAD. Despite the established first-line therapy using calcium channel blockers,[7] treatment of CAS with a statin in addition to a calcium channel blocker may help inhibit vascular contractility.[8]

Statins have a biphasic lipid-independent and dose-dependent effect on atherosclerotic angiogenesis related to alterations in endothelial apoptosis, which is proangiogenic at low concentrations, but angiostatic at high concentrations that are reversed by geranylgeranyl pyrophosphate.[9] At clinically relevant doses, statins may modulate angiogenesis in humans via effects on geranylated proteins,[9] suggesting statin therapies may have direct clinical significance on coronary morbidity and mortality. Furthermore, although endothelial dysfunction is not always present in CAS,[10,11] dysfunctional endothelial nitric oxide synthase resulting in inefficient release of nitric oxide has been shown to be strongly associated with CAS.[12] In this context, statin is associated with improvement in endothelial dysfunction, increases in nitric oxide bioavailability, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques,[13] all of which may contribute to cardiovascular benefits beyond low-density lipoprotein cholesterol reduction alone in CAS.[14] Among studies of statin therapy in CAS, statins decrease cardiovascular events[15] and CAS development[16,17] in three studies, while the other four studies[18–21] showed no association of statins with reduced cardiac death and recurrent AMI in CAS. As a result, time–course studies are required to dissect the impact of statins on the prognosis of patients with CAS.

It is currently debatable whether long-term administration of statins improves prognosis of CAS.[22] This issue has not been settled due to some major limitations of prior clinical studies: limited population, relatively short follow-up, and hence, the absence of appreciable association between the doses of statin and benefits of clinical outcomes. Furthermore, although men have a higher overall prevalence of and mortality from cardiovascular disease and women experience higher mortality from certain cardiovascular events, such as stroke,[23] in men and women at an equivalent risk of cardiovascular disease, statin therapy is similarly effective for the prevention of major cardiovascular events and all-cause mortality regardless of sex.[24] Because these data in CAS are limited and whether the benefits of statins are fixed or change over time has considerable implications for clinical and public health care, we, therefore, investigated the efficacy of long-term administration and the dose–response effect of statins, with and without regard to sex, in reducing adverse cardiovascular events in CAS patients but without obstructive CAD in a nationwide population-based cohort and retrospective case–control study.

METHODS

Data source

This was designed as a prospective cohort study of retrospectively collected data from the Taiwan National Health Insurance Research Database (NHIRD). In Taiwan, joining the National Health Institute (NHI) program is compulsory for all residents, and the Taiwanese government is the single payer. Thus, over 99.8% of the approximately 24 million people living in Taiwan are included in the NHIRD. The Taiwan NHI has been launched since 1995 and provides affordable and high-quality health care to all beneficiaries. Upon our application, data of outpatient and inpatient services, including diagnoses, medications, interventions, operations, hospitalizations, and emergency visits on patients with CAS between 1995 and 2013 are available in this study. Diagnosis is recorded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.[25] In order to match our previous CAS research design,[26,27] we used a similar database from 2000 to 2012. While the management of dyslipidemia has barely changed in the past decade in Taiwan, statins remained the cornerstone of therapy as no new statin has been approved for clinical use. Although proprotein convertase subtilisin/kexin type 9 inhibitors became available in Taiwan after 2015, their use was infrequent. Additionally, the twice-yearly Leqvio® (inclisiran) injections are anticipated to become available in Taiwan by 2025. As a result, the usability and scalability of the database from 2000 to 2012 do not have a statistically significant impact on the findings of this study. Data obtained from the NHIRD are deidentified from all personal information and therefore this study was exempted obtaining informed consent from patients and was waived from a full review of the study protocol by the Ethics Institutional Review Board of Chang Gung Memorial Hospital, Keelung (approval reference number: 103-0248B). This study conformed to the tenets of the Declaration of Helsinki.

Study patients

Patients with a diagnosis of CAS between 2000 and 2012 were identified in the NHIRD. To ascertain the accuracy of CAS diagnosis, we restricted the patients to fulfill with at least three outpatient or any one inpatient diagnoses.[26]

The disease was registered by the ICD-9-CM codes of 413.1. Patients with an old diagnosis of CAS before 2000, missing demographics (including age and sex) and age < 20 years were excluded. We further excluded patients with indications for statins, including a history of AMI, coronary revascularization (including percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]), and ischemic or hemorrhagic strokes. Furthermore, patients whose follow-up less than 180 days due to all reasons and who developed major outcomes (AMI, stroke, and coronary revascularization) during the first 180-day follow-up were excluded. Patients were then categorized into two groups according to whether they received statins during the first 180-day follow-up (Figure 1). The index date was defined as the diagnostic date of CAS.

Covariates

The covariates in this study were demographics (age and sex), proxy for socioeconomic status (urbanization level of the residence, geographical region of the living area, and monthly income), comorbidities, and concomitant medications. The comorbidities assessed in this study, including hypertension, diabetes, dyslipidemia, chronic kidney disease, dialysis, atrial fibrillation, peripheral arterial disease, asthma, chronic obstructive pulmonary disease, malignancy, heart failure hospitalization, valve disease, cardiomyopathy, alcohol disorder, gout, hepatitis C virus infection, and mental disorder (e.g., anxiety, depression). The concomitant medications were classified into four classes, including glucose-lowering, antihypertensive, lipid-lowering, and antithrombotic agents. Comorbidities were detected when at least two outpatient diagnoses or any single discharge diagnosis in the previous year preceding to the index date. The information of drugs was captured by any prescription in the first 180-day follow-up in the outpatient claims data or long-term medication refills.

Outcomes

The primary outcome in this study was major adverse cardiovascular events (MACEs), which was a composite of cardiovascular death, AMI, and ischemic stroke. Secondary outcomes were all-cause death, individual components of MACEs, spontaneous intracerebral hemorrhage, coronary revascularization (PCI or CABG), and heart failure hospitalization. Dates and causes of death were included in the NHIRD. CV death was defined according to the criteria established by the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials by the United States Food and Drug Administration. AMI, ischemic stroke, spontaneous intracerebral hemorrhage, and heart failure hospitalization were detected using the principal discharge diagnosis. We also investigated major adverse limb events, including revascularization (i.e.,

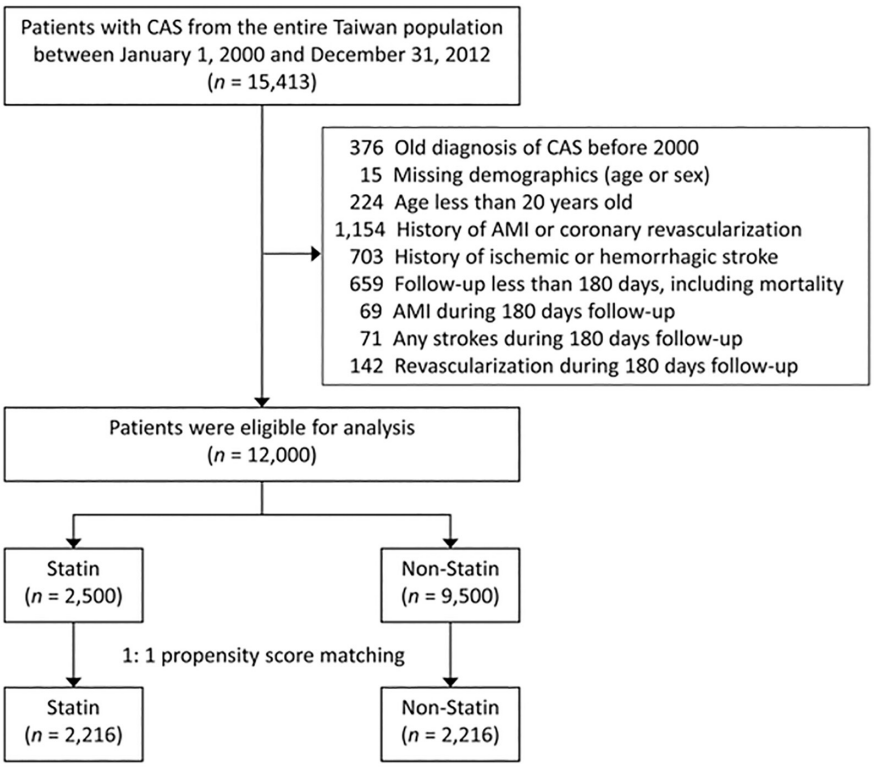


FIGURE 1 The flowchart for the inclusion and exclusion of the study patients.

endovascular therapy and peripheral bypass) and amputation. Most of the diagnostic codes for outcomes used in this study are validated in previous NHIRD studies.[28] For the analysis of each outcome, patients were followed until the day of outcome occurrence, death, or the end of database (December 31, 2013), whichever came first.

Statistical analysis

To make a comparability of outcomes between the study groups (statin vs. nonstatin), a propensity score matched cohort was created. The propensity score was the conditional probability given the values of the baseline covariates (Table 1), which was calculated using a multivariable logistic regression model where the study groups were regressed on all covariates (except the follow-up year was replaced by the index date). Each patient in the statin group was matched to a counterpart in the nonstatin group. The matching was processed using a greedy nearest neighbor algorithm with a caliper of 0.2 times the standard deviation of the logit of the propensity score. In addition, a random matching order was adopted, and replacement were not allowed. The balance of baseline covariates between groups was assessed using the standardized difference (STD), where a value of less than 0.1 was considered negligible.

The risks of fatal outcomes (i.e., MACEs, cardiovascular death, and all-cause death) between groups were compared using the Cox proportional hazard model. The incidences of nonfatal outcomes (e.g., AMI or ischemic stroke) between groups were compared using the Fine and Gray subdistribution hazard model, which considered all-cause mortality as a competing risk. The study groups (statin vs. no-statin) were the only explanatory variable in the abovementioned survival models. The potential outcome dependency of the two individuals among the same matching pair was dealt with using the robust standard error. Subgroup analysis of the primary outcome (MACEs) was further conducted by several clinically relevant variables, including age (<65 vs. ≥65 years), sex, hypertension, diabetes, dyslipidemia, mental disorder, concomitant use of aspirin, and lipid-lowering drugs other than statins (i.e., ezetimibe, fibrates, niacin, and cholestyramine).

Other analyses were conducted in the statin group before matching. First, we compared the risk of MACEs in patients receiving different intensities of statins (low, moderate, and high). Of note, only two statins were classified as high potency: rosuvastatin 20–40 mg and atorvastatin 40–80 mg. Statins with low potency included simvastatin 10 mg, pravastatin 10–20 mg, lovastatin 20 mg, fluvastatin 20–40 mg, and pitavastatin 1 mg. The other statins were classified as moderate potency. Second, the statins were divided into lipophilic versus hydrophilic statins. Third, we compared the risk of MACEs among the different brands of statins. Moreover, we conducted a dose–response analysis of statin compliance on the risk of MACEs using the whole cohort before matching. Statin compliance was assessed by counting the prescribed days within the first 180 days after CAS diagnosis. Patients were divided into several subgroups according to the days prescribed with statins during the first 180-day follow-up: nonstatin, <3 months, 3–5 months, and ≥6 months. The linear trend for statin compliance over the risk of MACEs was also tested. Multivariable covariates adjustments were made in the aforementioned analyses, including the covariates listed in Table 1. A $p < 0.05$ was considered significant. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Ethics statement

The Institutional Review Board of Chang Gung Medical Foundation approved the study protocol (approval number: 103-0248B) and waived the requirement for informed consent because patient information was deidentified and anonymized before analysis.

RESULTS

Inclusion of the patients

A total of 15,413 patients with a diagnosis of CAS were identified in the NHIRD between 2000 and 2012. After applying the exclusion criteria as mentioned previously, 12,000 patients remained. Of them, 2500 patients received at least one prescription of statins during the first 180-day follow-up and 9500 patients did not. After propensity score matching with 1:1 ratio, 2216 patients were eligible for outcome analysis in either group (Figure 1).

Patient characteristics

Among the 12,000 patients, the mean age was 56.4 years (standard deviation: 14 years) and 5771 (48.1%) patients were male. Compared to patients in the nonstatin group, those in the stain group were elder (58.1 vs. 55.9 years), had higher prevalence of hypertension, diabetes, dyslipidemia, and gout, were more likely to be prescribed with all glucose-lowering drugs except insulin, had more prescriptions of angiotensin-converting enzyme inhibitor/

TABLE 1 Baseline characteristics of the patients with coronary artery spasm who received statin versus who did not.

Variable	Before matching			After matching		
	Statin ($n=2500$)	Nonstatin ($n=9500$)	STD	Statin ($n=2216$)	Nonstatin ($n=2216$)	STD
Age, year (median, IQR)	58.1 ± 11.5	55.9 ± 14.6	0.17	57.8 ± 11.6	58.5 ± 13.1	−0.06
Male	1118 (44.7)	4653 (49.0)	−0.09	1011 (45.6)	1062 (47.9)	−0.05
Urbanization level of the residence						
Low	405 (16.2)	1443 (15.2)	0.03	346 (15.6)	361 (16.3)	−0.02
Moderate	936 (37.4)	3977 (41.9)	−0.09	836 (37.7)	821 (37.0)	0.01
High	739 (29.6)	2575 (27.1)	0.05	658 (29.7)	682 (30.8)	−0.02
Very high	420 (16.8)	1505 (15.8)	0.03	376 (17.0)	352 (15.9)	0.03
Geographical region of the residence						
North	514 (20.6)	1891 (19.9)	0.02	467 (21.1)	446 (20.1)	0.02
Central	919 (36.8)	3807 (40.1)	−0.07	814 (36.7)	831 (37.5)	−0.02
South	1014 (40.6)	3600 (37.9)	0.05	887 (40.0)	894 (40.3)	−0.01
East	53 (2.1)	202 (2.1)	<0.01	48 (2.2)	45 (2.0)	0.01
Monthly income, NTD						
≤17,880	758 (30.3)	2902 (30.5)	<0.01	663 (29.9)	665 (30.0)	<0.01
17,881–22,800	823 (32.9)	3396 (35.7)	−0.06	732 (33.0)	737 (33.3)	<0.01
>22,800	919 (36.8)	3202 (33.7)	0.06	821 (37.0)	814 (36.7)	0.01
Comorbidity						
Hypertension	1403 (56.1)	4223 (44.5)	0.23	1199 (54.1)	1219 (55.0)	−0.02
Diabetes mellitus	594 (23.8)	1045 (11.0)	0.34	461 (20.8)	442 (19.9)	0.02
Dyslipidemia	1454 (58.2)	1683 (17.7)	0.92	1170 (52.8)	1142 (51.5)	0.03
Chronic kidney disease	195 (7.8)	582 (6.1)	0.07	167 (7.5)	171 (7.7)	−0.01
Dialysis	19 (0.8)	73 (0.8)	<0.01	18 (0.8)	17 (0.8)	0.01
Atrial fibrillation	70 (2.8)	259 (2.7)	<0.01	61 (2.8)	68 (3.1)	−0.02
Peripheral arterial disease	72 (2.9)	251 (2.6)	0.01	65 (2.9)	65 (2.9)	<0.01
Asthma	175 (7.0)	660 (6.9)	<0.01	154 (6.9)	147 (6.6)	0.01
Chronic obstructive pulmonary disease	231 (9.2)	1055 (11.1)	−0.06	218 (9.8)	219 (9.9)	<0.01
Malignancy	70 (2.8)	283 (3.0)	−0.01	64 (2.9)	65 (2.9)	<0.01
Heart failure hospitalization	73 (2.9)	265 (2.8)	0.01	66 (3.0)	69 (3.1)	−0.01
Valve disease	288 (11.5)	1232 (13.0)	−0.04	269 (12.1)	278 (12.5)	−0.01
Cardiomyopathy	32 (1.3)	126 (1.3)	<0.01	28 (1.3)	25 (1.1)	0.01
Alcohol disorder	42 (1.7)	206 (2.2)	−0.04	38 (1.7)	38 (1.7)	<0.01
Gout	262 (10.5)	701 (7.4)	0.11	222 (10.0)	243 (11.0)	−0.03
Hepatitis C virus infection	24 (1.0)	196 (2.1)	−0.09	24 (1.1)	17 (0.8)	0.03
Mental disorder (e.g., anxiety, depression)	1103 (44.1)	3885 (40.9)	0.07	971 (43.8)	955 (43.1)	0.01
Glucose-lowering drug						
Metformin	375 (15.0)	550 (5.8)	0.31	274 (12.4)	278 (12.5)	−0.01
Sulfonylurea	293 (11.7)	523 (5.5)	0.22	225 (10.2)	208 (9.4)	0.03
Dipeptidyl peptidase-4 inhibitor	42 (1.7)	37 (0.4)	0.13	27 (1.2)	25 (1.1)	0.01
Alpha glucose inhibitor	62 (2.5)	89 (0.9)	0.12	41 (1.9)	44 (2.0)	−0.01
Thiazolidinedione	64 (2.6)	70 (0.7)	0.14	42 (1.9)	38 (1.7)	0.01

TABLE 1 (Continued)

Variable	Before matching			After matching		
	Statin ($n=2500$)	Nonstatin ($n=9500$)	STD	Statin ($n=2216$)	Nonstatin ($n=2216$)	STD
Glinide	52 (2.1)	67 (0.7)	0.12	35 (1.6)	37 (1.7)	−0.01
Insulin	52 (2.1)	132 (1.4)	0.05	41 (1.9)	44 (2.0)	−0.01
Anti-hypertensive drug						
ACEi/ARB	893 (35.7)	2482 (26.1)	0.21	750 (33.8)	764 (34.5)	−0.01
Beta-blocker	967 (38.7)	3784 (39.8)	−0.02	854 (38.5)	862 (38.9)	−0.01
dCCB	1086 (43.4)	3382 (35.6)	0.16	937 (42.3)	942 (42.5)	<0.01
Loop diuretics	154 (6.2)	571 (6.0)	0.01	142 (6.4)	144 (6.5)	<0.01
Mineralocorticoid receptor antagonist	44 (1.8)	136 (1.4)	0.03	42 (1.9)	34 (1.5)	0.03
Thiazide	174 (7.0)	603 (6.3)	0.02	153 (6.9)	166 (7.5)	−0.02
Alpha blocker	98 (3.9)	315 (3.3)	0.03	85 (3.8)	102 (4.6)	−0.04
Vasodilator	28 (1.1)	59 (0.6)	0.05	22 (1.0)	27 (1.2)	−0.02
Nitrates	1330 (53.2)	4573 (48.1)	0.10	1153 (52.0)	1179 (53.2)	−0.02
Lipids-lowering drug						
Fibrate	173 (6.9)	420 (4.4)	0.11	164 (7.4)	169 (7.6)	−0.01
Other lipids-lowering agents	193 (7.7)	437 (4.6)	0.13	173 (7.8)	177 (8.0)	−0.01
Antithrombotic agent						
Aspirin	1588 (63.5)	4063 (42.8)	0.43	1331 (60.1)	1362 (61.5)	−0.03
Clopidogrel	136 (5.4)	219 (2.3)	0.16	104 (4.7)	107 (4.8)	−0.01
Anticoagulant	58 (2.3)	159 (1.7)	0.05	50 (2.3)	63 (2.8)	−0.04
Follow-up year	4.6 ± 2.9	5.8 ± 3.3	−0.38	4.8 ± 2.9	4.6 ± 2.9	0.04

Note: Data are presented in terms of frequency (percentage) or mean ± standard deviation.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; dCCB, dihydropyridine calcium channel blocker; IQR, interquartile range; NTD, New Taiwan Dollar; STD, standardized difference.

angiotensin II receptor blocker and dihydropyridine calcium channel blocker and nitrates, were more likely to be prescribed with fibrates and other lipids-lowering agents, and had more prescriptions of aspirin and clopidogrel (the absolute values of STD >0.1; Table 1). Before matching, the mean follow-up duration was 4.6 and 5.8 years in the statin and nonstatin groups, respectively. After matching, all of the baseline characteristics were well-balanced between groups with the absolute values of STD <0.1.

Outcomes

After matching, the mean follow-up duration was 4.8 and 4.6 years in the statin and nonstatin groups, respectively. The result demonstrated that statin users had a significantly reduced risk of MACEs compared with nonstatin users (6.7% vs. 9.5%, hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.55–0.84; Table 2 and Figure 2a). While the results of MACEs were mainly contributed by cardiovascular death (1.9% vs. 3.2%; HR 0.56, 95% CI 0.38–0.83) and ischemic stroke (3.8% vs. 5.4%; subdistribution HR 0.69, 95% CI 0.52–0.91) (Figure 2b,c), the reduction in MACEs was primarily driven by reductions in ischemic stroke but not hemorrhagic stroke in statin users versus nonusers. As to other outcomes, the result showed that patients in the statin group had a significantly lower all-cause mortality risk (6.0% vs. 7.6%; HR 0.77, 95% CI 0.61–0.96) (Figure 2d). However, the use of statin was not significantly associated with the risk of AMI, spontaneous intracerebral hemorrhage, coronary revascularization, heart failure hospitalization, and major adverse limb events (Table 2).

Subgroup analysis of MACEs

We further stratified the analysis of MACEs by several clinically relevant subgroup variables. The results suggested

TABLE 2 Follow-up outcomes of the patients with coronary artery spasm who received statin versus who did not in the propensity score matched cohort.

Outcome	Statin ($n=2216$)	Nonstatin ($n=2216$)	HR/SHR (95% CI) of statin	p
All-cause death	134 (6.0)	169 (7.6)	0.77 (0.61–0.96)	0.021
Major adverse cardiovascular events				
Cardiovascular death	41 (1.9)	70 (3.2)	0.56 (0.38–0.83)	0.003
Acute myocardial infarction	37 (1.7)	43 (1.9)	0.84 (0.54–1.31)	0.439
Ischemic stroke	85 (3.8)	120 (5.4)	0.69 (0.52–0.91)	0.009
Composite outcome	148 (6.7)	211 (9.5)	0.68 (0.55–0.84)	<0.001
Spontaneous intracerebral hemorrhage	17 (0.8)	19 (0.9)	0.87 (0.46–1.66)	0.681
Coronary revascularization (PCI or CABG)	86 (3.9)	69 (3.1)	1.24 (0.90–1.71)	0.185
Heart failure hospitalization	49 (2.2)	56 (2.5)	0.86 (0.58–1.27)	0.443
Major adverse limb events				
Revascularization	4 (0.18)	5 (0.23)	0.80 (0.21–2.97)	0.735
Amputation	1 (0.05)	6 (0.27)	0.16 (0.02–1.36)	0.094
Composite outcome	5 (0.23)	10 (0.45)	0.50 (0.17–1.45)	0.200

Note: Data are presented in terms of frequency (percentage).

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; SHR, subdistribution hazard ratio.

that the observed benefit of statins was more pronounced in patients with hypertension (HR: 0.58 vs. 0.97; p for interaction = 0.026) and diabetes (HR: 0.46 vs. 0.79; p for interaction = 0.022) than those without (Figure 3). Despite this, the impact of statins on MACEs remained consistent across various subgroups, including those defined by age, sex, presence of dyslipidemia, mental disorders, and concomitant use of aspirin and other lipid-lowering medications besides statins.

Miscellaneous analysis

In the analysis using the 2500 patients with CAS before matching, the results showed that there were no significant difference in the risk of MACEs for patients with different intensities of statins, lipophilicities, and brands of statins (Table 3). In the analysis using the whole cohort ($n=12{,}000$), the result revealed an apparent dose–response effect of the statins compliance (Table 3). The event rate of MACEs at the end of follow-up was 10%, 8.3%, 7.0%, and 4.5% in the nonstatin group, statins with <3 months, statins with 3–5 months, and statins with ≥6 months. The fitted (adjusted) one minus survival rates of MACEs for all compliance groups were plotted and the result clearly exhibited the greater compliance was associated with more risk reduction (Figure 4).

DISCUSSION

In this large cohort study, statins significantly reduced the risk of all-cause mortality and MACE, including cardiovascular death, AMI, and ischemic stroke, in CAS patients without obstructive CAD. The benefits for MACE risk were mainly attributed to the decreased risk to develop ischemic stroke. The benefit of statin therapy in reducing MACEs appeared to be linear, with greater risk reduction with higher doses and longer duration without upper threshold, reflecting the dose-dependent relationship of statins with MACEs in CAS patients. Although the benefit of statin therapy in reducing MACEs remained consistent irrespective of age, sex, dyslipidemia, and mental disorder, the benefit was more apparent in the subgroups of CAS patients with type 2 diabetes (diabetes) and hypertension.

Notwithstanding in CAD patients with borderline cholesterol levels, it has demonstrated that reducing cholesterol alone does not consistently decrease CAD mortality,[29] benefits of cholesterol lowering in high-risk patients or those with established CAD is well established. Furthermore, although primary prevention trials and meta-analyses provide evidence in favor of statins in CAD,[30] statin therapy did not reduce all-cause mortality, cardiovascular mortality, and CAD mortality,[30] because coronary heart disease, including CAD and CAS, is an extremely complex malady with the true fatal complications independent of

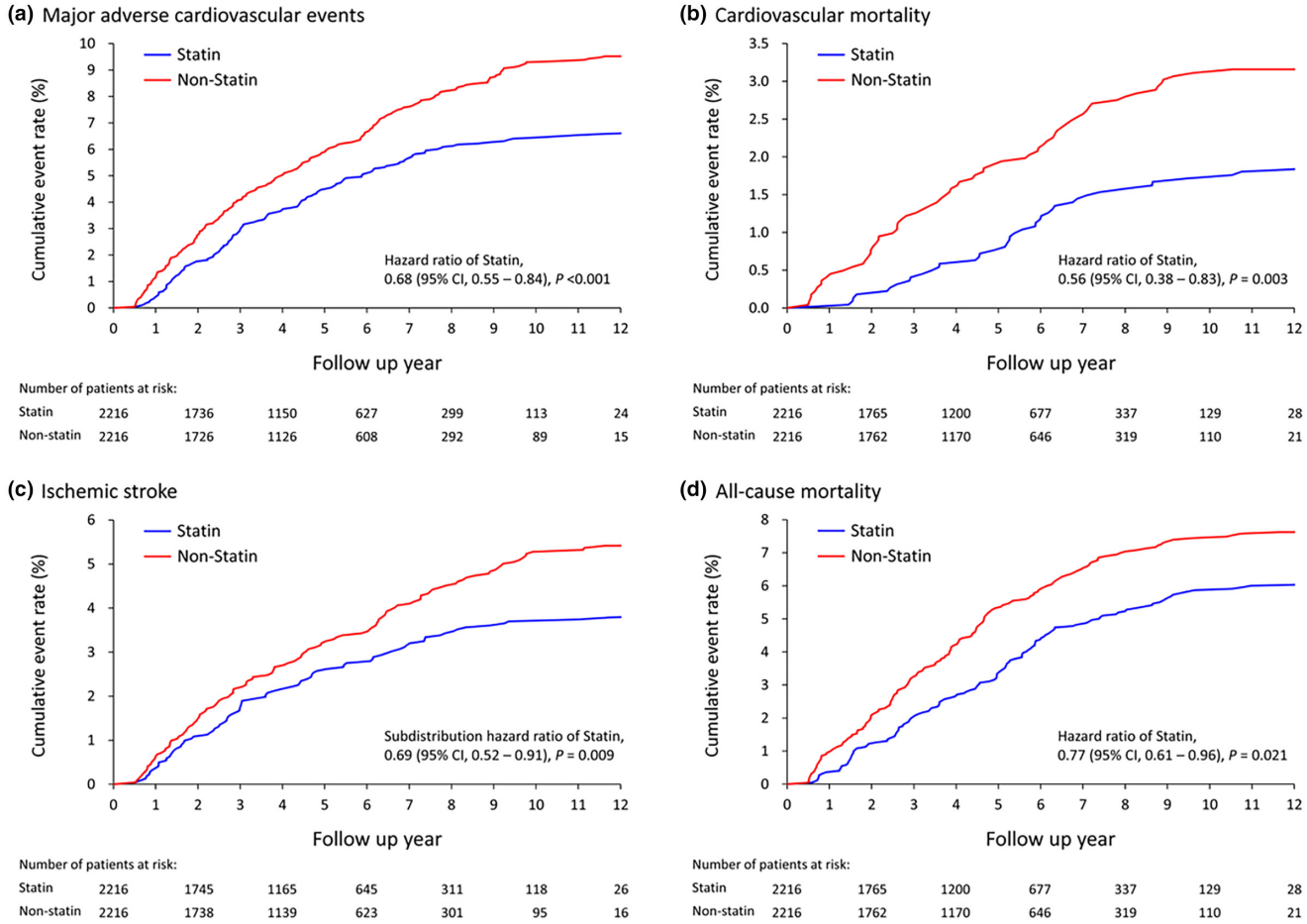


FIGURE 2 The cumulative event rates. (a) Major adverse cardiovascular events, (b) cardiovascular mortality, (c) ischemic stroke, and (d) all-cause mortality for statin and nonstatin groups in the propensity score matched cohort. CI, confidence interval.

cholesterol metabolism. However, the evidence provided by clinical trials is often not reproducible in population-based studies,[31] probably attributable to difficulty in controlling biases, one of which is statin nonadherence in clinical practice. In a meta-analysis, 50% of the CAD patients receiving newly prescribed statins discontinued therapy in <1 year.[32] On the other hand, while CAS has been demonstrated to be a precursor of obstructive CAD,[33] the phenomenon that endothelial dysfunction is not always present in patients with CAS[10,11] might explain why statins may not consistently work as well as expected against CAS-related adverse clinical outcomes, as since 2005, statin trials of coronary heart disease have failed to demonstrate a congruous mortality benefit.[29]

In INOCA, statins have been shown to reduce exercise-induced ischemia and improve flow-mediated dilation[34,35] probably through inhibiting oxidative stress and inflammation[14] and improving coronary flow reserve and coronary microcirculation.[36] Moreover, statins are effective in suppressing CAS by inhibiting the vascular smooth muscle cell contraction.[15] While previous shorter (<3.5 years)[37–40] primary prevention and randomized controlled trials with >90% of participants free of CAD failed to demonstrate the benefit of statins in major cerebrovascular events and major coronary events, they have shown only marginally significant benefits on mortality, which might be because a <5-year follow-up make the relevant mortality benefits unlikely to arise for the primary prevention trials. Our study showed that the advantages of the statins in reducing MACE among CAS patients became evident after at least 3 months of treatment. A long follow-up period >10 years showed a clear benefit in all-cause mortality, cardiovascular mortality, and ischemic stroke, with the risk lower by 23%, 44%, and 31%, respectively, in CAS patients on statin. Furthermore, among all-cause mortality, 31% and 41% were due to cardiovascular mortality in statin users and nonusers, respectively, suggesting the beneficial effects of statins on cardiovascular outcome among CAS patients. Notably, as opposed to that the statin-associated reduction in all-cause mortality in atherosclerotic cardiovascular disease is primarily driven by reductions in deaths due to CAD (20% relative reduction) and other cardiac causes (10% relative reduction),[41] the benefits for MACE risk in CAS were mainly driven by the decreased risk to

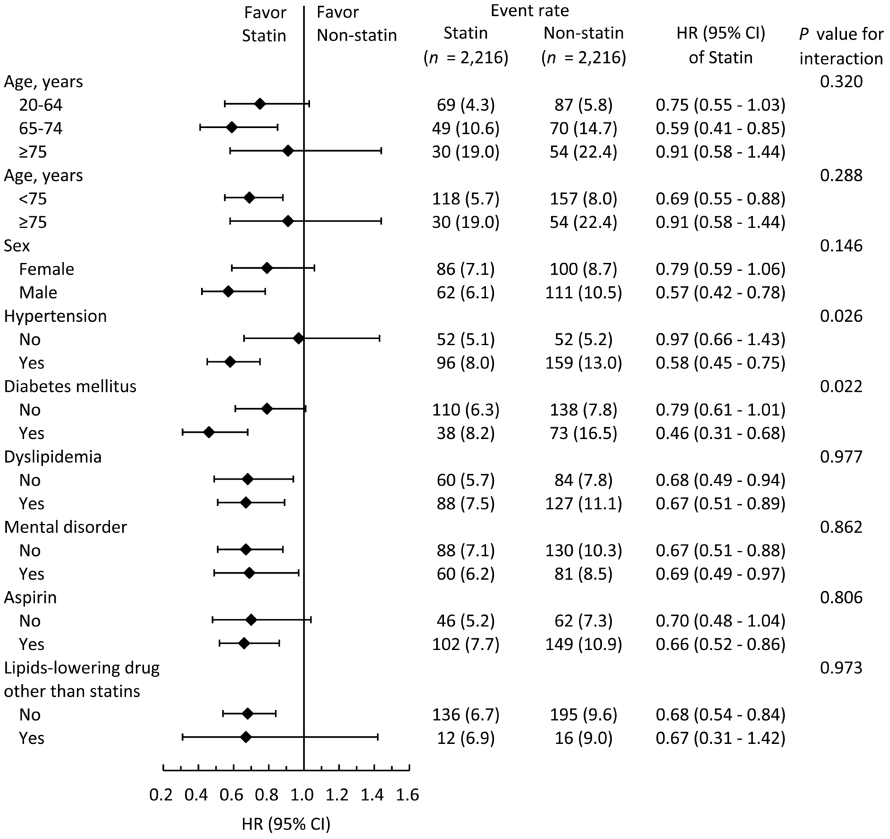


FIGURE 3 Subgroup analysis of major adverse cardiovascular events stratified by prespecified variables in the matched cohorts. CI, confidence interval; HR, hazard ratio.

develop ischemic stroke but not hemorrhagic stroke in statin users versus nonusers, which is in line with previous studies showing that statins reduce the overall risk of first or recurrent stroke despite the small increase in hemorrhagic stroke.[42] In our study, the overall ischemic and hemorrhagic stroke prevalence among patients with CAS were 1.1% (646/12,000/4.7 follow-up years) and 0.2% (126/12,000/4.7 follow-up years), which, for all stroke types combined, is higher than the crude point prevalence per year of 0.6% in general Taiwanese population[43] and 1% in the world population.[44] Although there is geographic variation in the lifetime risk of stroke, with the highest risks in East Asia, Central Europe, and Eastern Europe,[45] our results have important implications for East Asian countries such as Korea and Taiwan, because stroke has a higher mortality than CAD in East Asia, as opposed to findings in Western and other Asian countries.[46] Taken together, the favorable risk–benefit balance in long-term MACEs for statin treatment in CAS without obstructive CAD might be mediated through the pleiotropic effects beyond lipid-lowering and restoration of endothelial functions, which likely translate into a lower risk of cardiovascular events, including mortality.

While evidence shows endothelial dysfunction plays a significant role in CAS, clinical observations question its exclusive contribution. Endothelial dysfunction is often associated with common cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, and atherosclerosis, whereas the prevalence of endothelial dysfunction in CAS is comparatively lower. Thus, it is not surprising that ACh-induced CAS occurs less frequently in angina associated with hypertension, uncontrolled blood pressure, or diabetes than in angina without these factors.[47,48] A previous study using substance P, a pure endothelial-dependent vasodilator, demonstrates that in patients with variant angina, endothelial dysfunction at sites of CAS is not necessarily present.[10] Therefore, an impairment of endothelium-mediated vasodilation appears unlikely to cause CAS by itself, though it might facilitate the effects of coronary vasoconstrictors in "CAS prone" individuals.[49] The clinical findings by Kaski et al. support the hypothesis that focal CAS in variant angina primarily arises from VSMC hyperreactivity to vasoactive stimuli, which showed that in patients with documented spontaneous CAS, ergonovine-induced CAS was seen at the same site, indicating local coronary hyperreactivity despite a generalized stimulus.[50] While epicardial atherosclerosis may induce endothelial dysfunction leading to CAS, this CAS can also in reverse accelerate epicardial atherosclerosis through decreased blood flow and wall shear stress.[51] Altogether, these observations imply that statins might reduce or stabilize plaque in areas of nonobstructive atherosclerosis, thereby reducing CAS and plaque progression, including rupture.

TABLE 3 The association between intensity, lipophilicity, statin drug and compliance, and the risk of major adverse cardiovascular event in the whole cohort.

Variable	Numbers	Event (*n*, %)	Adjusted HR (95% CI)[e]	*p*
Intensity[a]				
Low	295	44 (14.9)	Reference	—
Moderate	1717	108 (6.3)	0.88 (0.61–1.29)	0.520
High	288	10 (3.5)	0.93 (0.45–1.93)	0.847
p trend				0.636
Lipophilicity[b]				
Lipophilic statin	1785	120 (6.7)	Reference	—
Hydrophilic statin	600	44 (7.3)	1.22 (0.84–1.77)	0.306
Statin drug[c]				
Rosuvastatin	357	16 (4.5)	1.37 (0.53–3.53)	0.521
Atorvastatin	920	63 (6.9)	1.04 (0.47–2.33)	0.920
Simvastatin	393	22 (5.6)	0.85 (0.36–2.02)	0.715
Fluvastatin	312	24 (7.7)	1.10 (0.44–2.75)	0.845
Pravastatin	238	28 (11.8)	1.16 (0.48–2.77)	0.745
Lovastatin	71	8 (11.3)	Reference	—
Pitavastatin	1	0 (0.0)	NA	NA
Compliance[d]				
Nonstatin	9500	947 (10.0)	Reference	—
<3 months	847	70 (8.3)	0.91 (0.70–1.17)	0.447
3–5 months	1032	72 (7.0)	0.77 (0.60–0.99)	0.038
≥6 months	621	28 (4.5)	0.57 (0.39–0.83)	0.004
p trend				<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable.

[a]200 patients were excluded due to switching between different intensities during the 6-month follow-up.

[b]115 patients were excluded due to switching between hydrophilic and lipophilic statins during the 6-month follow-up.

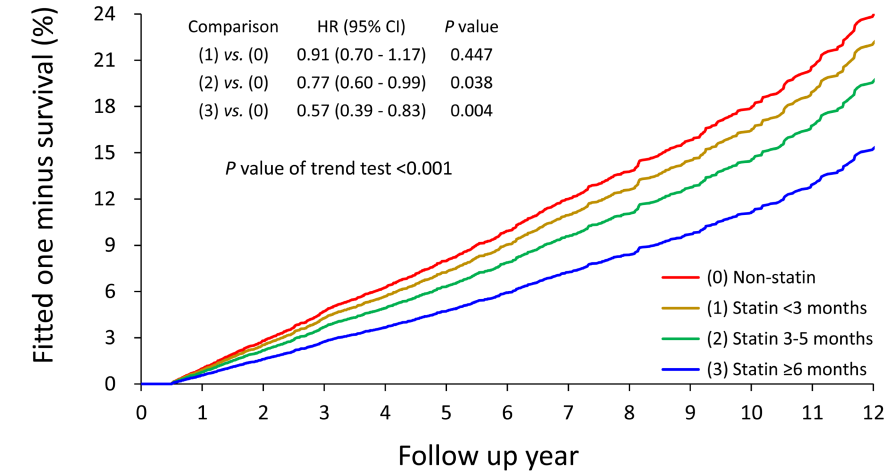
[c]208 patients were excluded due to switching between different statin drugs during the 6-month follow-up.

[d]The sample size was 12,000, including the nonstatin patients.

[e]Adjusted for all of the covariates listed in Table 1.

On the other hand, while another large-scale study has shown that statin was associated with a significant reduction in mortality for individuals with nonobstructive CAD, the statin intensity was not evaluated.[52] For most adults, consideration of the time to benefit is critical before starting therapy. Although most clinical trials suggest that the benefits of statins are recognized within 2 to 5 years, the association between statin and lower mortality can become evident within 2 years.[53] We demonstrated for the first time that statins were associated with a highly steady duration- and dose-dependent decreased risk of MACEs without threshold irrespective of different intensities, lipophilicities, and brands, suggesting statin therapy duration may be more critical than statin intensity for the reduction of MACEs in CAS patients. Therefore, the continued use of statins is critical in reducing MACEs of CAS patients.

Although the updated 2018 American Heart Association/American College of Cardiology cholesterol guidelines recommend statins as a reasonable primary prevention of atherosclerotic cardiovascular disease for people aged ≥75 years,[54] many other guidelines remain unclear on their role for people aged ≥75 years due to insufficient evidence. Our study demonstrated that statins in CAS decreased the risk of MACE in patients aged ≥65 or ≥75 years as well as in those aged <65 or <75 years, suggesting that age should not be the determinant to start or discontinue statins. Although early meta-analyses suggested that statins may not be as efficacious in women as they are in men for the primary prevention of cardiovascular disease,[55] which was largely due to women's underrepresentation and were therefore underpowered to analyze efficacy in women in early statin studies, multiple studies have since disproven a sex-based difference



Number of patients at risk:

Non-statin	9500	7918	5928	3934	2401	1235	348
<3 months	847	702	456	253	125	52	11
3-5 months	1032	785	511	281	126	47	9
≥6 months	621	439	270	122	52	14	4

FIGURE 4 The fitted (adjusted) one minus survival rates of major adverse cardiovascular events in patients with different compliances of statins in the whole cohort before matching. The greater compliance was associated with more risk reduction.

in efficacy. Out of 4432 CAS patients participating in our study, 2359 (53%) were women and 2073 (47%) were men, among which the reductions in MACEs were similar in men versus women.

The US Preventive Services Task Force indicates that adults with diabetes or hypertension should be offered a low- to moderate-dose statin for the primary prevention of cardiovascular disease events and mortality.[23] In CAS, compared with nonhypertensive patients, statins reduced MACE by 39% in hypertensive patients. When compared with nondiabetic CAS patients, statins reduced MACE by 33% in diabetic CAS patients. Our results are in line with the US Preventive Services Task Force recommendation statement. Despite type 2 diabetes prevalence more than doubling since the 1970s, heart disease prevalence has only modestly increased in diabetic individuals and remained stable in nondiabetics.[56] In CAS with no or one-vessel atherosclerosis, the prognosis is benign, with a 99% survival rate at 1 year and 94% at 5 years; however, for CAS with multivessel atherosclerosis common in diabetes and hypertension, survival drops to 87% at 1 year and 77% at 5 years.[6] Moreover, coronary atherosclerosis correlates with major cardiovascular events in CAS,[57] suggesting drugs available to treat ischemic heart disease might benefit CAS without obstructive CAD. Dyslipidemia in diabetes, characterized by hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, elevated levels of low-density lipoprotein (LDL) cholesterol and apo B levels, and the accumulation of small, dense LDL particles (associated with increased oxidative stress), significantly contribute to diabetic atherosclerotic cardiovascular disease, which poses high or very high cardiovascular risk.[58] To date, no other lipid-lowering therapies have demonstrated more profound effects than statins in preventing cardiovascular events in diabetes. As a result, international guidelines (ESC/EASD, ESC/EAS, AHA/ACC) support statins as the mainstay treatment for diabetes to target apo B-containing lipoproteins.[58] In hypertension, a meta-analysis of randomized trials found a 25% relative risk reduction in cardiovascular events with statin therapy in a primary prevention population.[59] Hence, for those with intermediate cardiovascular risk but no overt cardiovascular disease, statin may offer benefits beyond LDL cholesterol reduction. Pharmacological research of hypertension in the past 20 years has suggested pleiotropic effects of statins beyond LDL cholesterol reduction. Notably, these effects include antioxidative, anti-inflammatory, and antifibrotic properties.[60,61] Consequently, clinical guidelines[62,63] recommend a risk-based approach to statin use, rather than solely focusing on LDL levels.

However, some limitations need to be acknowledged. First, the major limitation is the use of diagnoses in an electronic health record, which lack meticulous objective definitions in research and data validity issues. The validity of different diseases in electronic health records can vary within and between datasets. The first step toward validation is to clearly define the requirements for data and data models. Some diseases, such as asthma, might be coded using combinations of diagnoses and/or less specific symptoms, whereas the validity of diagnoses with very specific signs and/or symptoms, such as CAS, is likely to be higher. Hence, to align with our previous study design[26,27] and reduce misclassification

bias from coding errors, patients with CAS must have at least three outpatient diagnoses or one inpatient diagnosis. Second, while controlling for confounding by multivariate modeling, personal data such as smoking habits and substance use, laboratory data, including platelet counts and leukocyte counts, and biomarkers inclusive of C-reactive protein and interleukin-6 were not accessible because of the data privacy policy. Considering these confounders, socioeconomic indicators such as sex, monthly income, and residential areas were adjusted in the regression analyses. However, Taiwanese adults have a particularly high male and much lower female smoking prevalence with the male-to-female ratio of 11 (46.8% and 4.3%, respectively).[64] Hence, sex could be a reliable proxy for smoking. Third, a limitation of matching is that unexposed individuals not matched to exposed individuals, and possibly some unmatched exposed individuals, are excluded from the analysis, resulting in a decrease in the estimated association. However, while matching can give less precise estimates for unmatched exposed individuals, the propensity score is a powerful and effective technique in balancing pretreatment covariates and reducing confounding in studies with many covariates. Fourth, oxidative stress can be exacerbated by smoking habits, which can undermine the anti-inflammatory and antioxidant action of statins. However, this effect can vary depending on the specific statin used, suggesting that the protective effects of statins might be underestimated. Although primary prevention trials show that untreated nonsmokers and smokers on statins have similar event risks,[65] these trials do not indicate a preferred statin for smokers due to differences in patient inclusion criteria, smoking status definitions, concurrent treatments, trial durations, and the number of smokers/ex-smokers studied. The lack of ability to comment on this issue is further demonstrated by two secondary prevention trials, CARE[66] and LIPID,[67] which used pravastatin at the same dose (40 mg/day). In CARE, the percentage risk reduction in primary end points was 33% in smokers and 22% in nonsmokers. In LIPID, the corresponding figures were 27% and 11%. Various mechanisms may independently affect each smoker, including dyslipidemia, platelet dysfunction, impaired fibrinolysis, high blood pressure, increased carotid artery intima-media thickness, insulin resistance, endothelial damage, and unhealthy lifestyle choices. In contrast, during instances of acute lung inflammation induced by cigarette smoke in C57BL/6 male mice, atorvastatin and pravastatin showed minimal effects on inflammation and oxidative stress, while rosuvastatin and simvastatin exhibited the most significant anti-inflammatory and antioxidant effect, respectively.[68]

CONCLUSIONS

Clinicians should aggressively treat CAS patients to ensure timely provision of care due to the high risk of stroke and cardiovascular mortality. The benefits for MACE risk in CAS were primarily driven by the decreased risk to develop ischemic stroke but not hemorrhagic stroke in statin users versus nonusers. Statin therapies were associated with decreased risk of MACEs without threshold in a highly steady duration- and dose-dependent manner, regardless of intensity, lipophilicity, or brand, supporting the principle that "longer is better" in CAS. Furthermore, statins consistently reduced MACEs across all groups, irrespective of age, sex, dyslipidemia, and mental disorder, but its benefits became more evident in CAS patients with hypertension or diabetes.

AUTHOR CONTRIBUTIONS

Y.-C.L., M.-J.H., and M.-Y.H. wrote the manuscript, designed the research. T.-H.C., C.-T.M., and C.-T.Y. performed the research. N.G.K., I.Y.C., P.H., and M.-Y.H. analyzed the data. Y.-C.L. and M.-J.H. contributed equally to this work.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

The data underlying this article are not publicly available because of information governance restrictions and held by the Taiwan Ministry of Health and Welfare, which must approve an application to access these data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Contact the staff of the Ministry of Health and Welfare (e-mail: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886–2–8590-6848.

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