Atherosclerosis 283 (2019) 61–68

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Associations between statins and coronary artery disease and stroke risks in patients with asthma–chronic obstructive pulmonary disease overlap syndrome: A time-dependent regression study

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HIGHLIGHTS

- The effect of statins on the risk of CAD and stroke among an ACOS cohort has not been reported.
- The ACOS cohort with statins use had a lower risk of CAD and ischemic stroke.
- The risk of stroke was lower in this cohort for statins with long duration.

ARTICLE INFO

Keywords:
Coronary artery disease
Stroke
Asthma–chronic obstructive pulmonary disease overlap syndrome

ABSTRACT

Backgound and aims: We aimed at determining the effects of statin use on coronary artery disease (CAD) and stroke risks in patients with asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS).
Methods: We retrospectively enrolled patients with ACOS treated with (N = 916) and without (N = 6338) statins. The cumulative incidence of CAD and stroke (ischemic and hemorrhagic) was analyzed through time-dependent Cox proportional regression. After adjustment for sex, age, comorbidities, inhaled corticosteroid steroid (ICS) use, and oral steroid (OS) use, we calculated the adjusted hazard ratios (aHRs) and their 95% confidence intervals (CIs) for CAD or stroke in the statin users (long-term [> 600 days] and short-term [≤ 600 days]) compared with the non-users.
Results: Among the statin users, aHRs (95% CIs) for CAD and stroke were 0.50 (0.41–0.62) and 0.83 (0.63–1.09), respectively; moreover, aHRs were 0.30 (0.09–0.99) and 0.90 (0.68–1.20) for ischemic and hemorrhagic stroke, respectively. aHRs (95% CIs) for CAD and stroke were 0.58 (0.47–0.71) and 0.93 (0.70–1.23), respectively, in the short-term users and 0.23 (0.13–0.41) and 0.42 (0.19–0.89), respectively, in the long-term users.
Conclusions: CAD risk was lower in all statin users, regardless of the duration of use, whereas ischemic stroke risk was lower only in the long-term statin users. No association was observed between hemorrhagic stroke risk and statin use.

Abbreviations: CAD, coronary artery disease; ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; aHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

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https://doi.org/10.1016/j.atherosclerosis.2019.02.007
Received 22 June 2018; Received in revised form 21 January 2019; Accepted 1 February 2019
Available online 11 February 2019
0021-9150/

1. Introduction

Coronary artery disease (CAD) and stroke are major causes of mortality in developing countries [1]. Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), in which asthma and COPD occur concurrently [2], is associated with inflammation of the airways [2] and blood vessels, such as the pulmonary [3], coronary, and cerebrovascular arteries [4,5]. Acute exacerbation of ACOS may aggravate hypoxemia and inflammation of blood vessels, which are the key risk factors for CAD and stroke [6–8]. Thus, the incidence of CAD and stroke is high among patients with ACOS [4,5].

Statins are widely used for treatment of hypercholesterolemia because they inhibit 3-hydroxy-3-methylglutaryl coenzymes and exhibit anti-inflammatory and immunomodulatory effects. They can attenuate airway inflammation [9,10] and reduce the levels of systemic inflammatory markers, such as C-reactive protein [11]. Therefore, statins may ameliorate asthma and COPD comorbidities [12,13], such as pulmonary embolism. However, whether statin use reduces cardiovascular disease (CVD) risk in patients with asthma and COPD remains unclear [14]. Moreover, the effects of statins on hemorrhagic stroke remain unclear. Huisa et al. reported that statins are associated with hemorrhagic stroke, whereas Martí-Fàbregas et al. reported no association between statins and hemorrhagic stroke [15,16].

Patients with ACOS who use inhaled hydrocortisone steroids (ICSs) may have relatively less pulmonary or coronary artery inflammation and low CVD incidence [3–5]. The percentage of patients using ICS increased from < 40% at the point of diagnosis to 53.48% during follow-up in a recent ACOS cohort study [8]. Thus, ICS use is critical for patients with ACOS [17]. Few studies have focused on the associations between the use of a combination of statin and oral steroid (OS) or ICS and the risks of CAD and stroke in patients with ACOS [17,18]. Therefore, we investigated these risks with particular focus on their association with OS and ICS use.

2. Materials and methods

2.1. Data source

We designed a retrospective cohort study by using data from the Longitudinal Health Insurance Database of 1 million enrollees in the Taiwan National Health Insurance (NHI) program between 2000 and 2011. Since its implementation in 1995, the NHI program has been providing comprehensive medical care, including ambulatory and inpatient care, to nearly all residents of Taiwan; consequently, the NHI program has previously been described in detail [19]. The program uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for defining diseases. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH104-REC2-115-CR3) and specifically waived the requirement for consent.

2.2. Sampled patients

Because no criterion for direct ACOS detection is currently available, we used the ICD-9-CM codes and prescribed drugs recorded in the patient data, as reported previously [20–23]. The demographic characteristics revealed that most patients with COPD were smokers (82.9%), had abnormal chest X-rays (CXR; 84.7%) and pulmonary function test results (58.4%), and had cough with sputum (79%) [24–26]. Physicians provide continuous prescriptions of ICSs, OSs, or statins to patients with COPD and asthma; these prescriptions become valid from the day the prescription is written. Moreover, the physicians assess patients with COPD and asthma at follow-up visits based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification and statin guidelines [27]. The GOLD classification includes the use of Modified Medical Research Council (mMRC) scores and COPD assessment test (CAT) scores. Drug use is also analyzed based on the GOLD classification [25]. Moreover, statins are prescribed depending on the patients' cholesterol levels [23]. These clinical policies are well validated in Taiwan [28,29].

Based on these criteria, we identified patients aged at least 20 years with ACOS and diagnosed with COPD (ICD-9-CM codes 491, 492, and 496) between January 1, 2000, and December 31, 2010 [8]. The date of the first asthma diagnosis (ICD-9-CM code 493) was defined as the index date [30]. We excluded patients with a history of CAD (ICD-9-CM codes 410–414) or stroke (ICD-9-CM codes 430–438) before the asthma diagnosis. The patients were followed up from the index date until the patient left the NHI program, experienced a CAD or stroke event, or until December 31, 2011. Next, based on their first stroke diagnosis, the patients with stroke were grouped into two cohorts, namely hemorrhagic stroke (ICD-9-CM 430–432) and ischemic stroke (ICD-9-CM 433–438). Our exposure of interest was new statin use for ≥30 days; these patients were defined as statin users and did not receive statins before entry into the study cohort. Because drug use is dynamic during the follow-up period, drug exposure was analyzed every 6 months [31,32]. Noyes et al. reported that statin use for approximately 600 days (~19.7 weeks) is associated with regression of atherosclerotic plaque in the arteries [33]. Thus, patients should receive aggressive treatment for reducing lipid levels for approximately 2 years before reduction in statin use is considered. Nicholls et al. reported lower CAD and stroke risks in patients who were long-term (> 600 days; e.g., 104 weeks) statin users [34]. Based on the total statin treatment duration (days), we calculated the cumulative days of statin use by each user during the study period. The cumulative days of statin use were divided into four levels according to quartiles and divided into two levels according to the third quartile (75th percentile).

We also considered the effects of comorbidities and other medications. The patients were defined as having comorbidities if they received disease diagnosis recorded before the endpoint of the study. In this study, the comorbidities were sleep disorders, diabetes, hypertension, hyperlipidemia, mental disorders, alcohol-related illness, and chronic kidney disease. Other medications, namely ICSs and OSs, were also considered.

Stratification by disease severity has been mentioned in previous studies [3,8,29]. The more severe the ACOS, the higher is the frequency of ICS, OS, and statin prescription [4,5,8,25] (Supplemental Fig. 1).

2.3. ACOS cohort validation

In a recent ACOS study based on the NHI Research Database (NHIRD) [8], Su et al. reported that ICS use was 36.14% at the time of initial diagnosis and 53.48% during follow-up. Moreover, Shantakumar et al. reported that ICS and OS use were 46.1% and 85.5% at the 1-year follow-up point, respectively [21]. Therefore, we used the ICS− and OS-use statuses of the patients [35] as tools for further confirming ACOS. Furthermore, pulmonary function testing (PFT) results [36] and clinical symptoms, such as chronic productive cough for 3 months in two successive years, wheezing, and dyspnea [37], aid early ACOS detection. Moreover, CXR, particularly with 90% sensitivity and 98% specificity for emphysema [38], can aid ACOS confirmation; 51.0% of patients with ACOS undergo CXR [21]. Thus, in addition to ICS and OS use, clinical symptoms and CXR are the two main auxiliary methods used for ACOS identification and follow-up [35,39].

According to an American study, patients with ACOS can be classified as A (low risk, few symptoms, and an mMRC score of 0–1 or a CAT score of < 10), B (low risk, many symptoms, and an mMRC score of > 2 or a CAT score of > 10), C (high risk, few symptoms, and an mMRC score of 0–1 or a CAT score of < 10), or D (high risk, many symptoms, and an mMRC score of > 2 or a CAT score of > 10) [39]. Similarly, Japanese and Korean studies have identified and followed up patients with ACOS and determined drug use based on the aforementioned classification [37,40]; this method is also commonly used in Taiwan.

Table 1
Demographic characteristics and clinical comorbidity statuses of the cohorts.

	ACOS						*p*-value
	Statin						
	All (N = 7254)		No (N = 6338)		Yes (N = 916)		
	n	%	n	%	n	%	
Age, years							< 0.001
< 50	1825	25.2	1614	25.5	211	23.0	
50-64	2327	32.1	1945	30.7	382	41.7	
65+	3102	42.8	2779	43.9	323	35.3	
Mean ± SD[a]	60.4	15.0	60.6	15.3	59.1	11.9	0.004
Gender							< 0.001
Women	3146	43.4	2665	42.1	481	52.5	
Men	4108	56.6	3673	58.0	435	47.5	
Comorbidity							
Sleep disorder	2887	39.8	2442	38.5	445	48.6	< 0.001
Diabetes	1150	15.9	849	13.4	301	32.9	< 0.001
Hypertension	4055	55.9	3385	53.4	670	73.1	< 0.001
Hyperlipidemia	2290	31.6	1543	24.4	747	81.6	< 0.001
Mental disorders	3766	51.9	3231	51.0	535	58.4	< 0.001
Alcohol-related illness	699	9.64	591	9.32	108	11.8	0.02
Chronic kidney disease	350	4.82	295	4.65	55	6.00	< 0.001
Medication							
Inhaled corticosteroids (ICSs)	1768	24.4	1519	24.0	249	27.2	< 0.001
Oral steroids (OSs)	5175	71.3	4452	70.2	723	78.9	< 0.001

Chi-square test.
[a] Student *t*-test.

Su et al. reported that in the NHIRD, sensitivity for asthma (92.0%) and COPD (86.2%) diagnosis is high [8]; thus, deriving ACOS diagnosis from the COPD cohort in the NHIRD is reasonable. Furthermore, in our study, 98.4% (approximately 7141 of 7254) of the patients with ACOS received a COPD- or asthma-related examination, such as CXR (32001C and 32002C), computed tomography (33070B, 33071B, 33072B), or PFT (17001C [Wright's peak flow meter], 17002B [P_i max and P_e max], 17003C [flow–volume curve], 17004B [lung volume with functional residual capacity], 17005B [single-breath nitrogen washout test], 17006B [bronchodilator test], 17007B [standard bronchodilator test], 17008B [polysomnography], 17009B [carbon monoxide diffusing capacity], 17010B [pressure–volume curve], 17011B [pressure–flow curve], 17012B [pressure–volume curve and pressure–flow curve], 17013B [carbon dioxide stimulation test and mouth occlusion pressure], 17014B [closing volume], 17015B [hypoxic stimulation test], 17016B [exercise pulmonary function test or stress test], 17017B [haloscale respiration], 17018B [basal metabolic rate], 17019C [bronchial provocation], and 17020B [multiple-breath nitrogen washout test]). Therefore, the NHIRD data for ACOS are representative of the real-world status of this disorder in Taiwan.

2.4. Sensitivity analyses

Cumulative days of statin use were divided into two levels according to the third quartile or four levels according to quartiles. We also calculated the proportion of statin use during the study period, denoted as PDC, according to the cumulative days of statin use divided by the follow-up period. The PDC was divided into three levels according to the tertile. The statin users cohort and nonusers cohort were matched at a 1:1 ratio based on propensity scores using nearest neighbor matching, initially to the eighth digit and then, as needed, to the first digit. We employed logistic regression to calculate the propensity scores for drug status by estimating the assignment probability based on baseline variables, such as age, sex, comorbidity of sleep disorders, diabetes, hypertension, hyperlipidemia, mental disorders, alcohol-related illness, chronic kidney disease, and medication (ICS and OS) use. Potential bias was reduced by propensity-score matching.

2.5. Statistical analysis

Demographic factors, comorbidities, and medication were compared between the statin users and nonusers using the chi-square and Student *t*-test for categorical and continuous variables, respectively. The cumulative incidence of CAD or stroke was estimated and plotted for the statin users and nonusers using the Kaplan–Meier method, and the difference was assessed using the log-rank test.

The incidence density of CAD or stroke was calculated using the number of CAD or stroke events divided by the total person-years for each group. Because the ACOS patients and statin users may not have been taking their medication regularly during the study period, the effect of the drug may have been overestimated. Therefore, we considered statin use as a time-dependent covariate in the Cox proportional hazard model to illustrate the effect as hazard ratios (HRs) and their 95% confidence intervals (CIs). In the time-dependent covariates of statin use, the comparison represented each 6-month period for a single patient, and drug exposure variables were presented as yes or no (binary) variables. Adjusted HRs (aHRs) were calculated after adjustment for age, sex, comorbidities, and medication use. The incidence rates and HRs for CAD and stroke in statin users were calculated relative to nonusers and stratified by sex, age, ICS-use status, and OS-use status. Additional sensitivity analysis was conducted to assess whether different cumulative doses of statin affected CAD or stroke outcomes. Cox models were also used to estimate the HR and 95% CI of CAD or stroke risk in the propensity-matched statin users compared with the nonusers. SAS (version 9.4; SAS Institute, Cary, NC, USA) was used for all data management and analyses. The significance level was set at $p < 0.05$.

2.6. Ethical approval

The Research Ethics Committee of China Medical University and Hospital, Taiwan approved this study (CMUH104-REC2-115-CR3).

3. Results

In this study, we included 7254 patients with ACOS; among them, 916 patients were statin users (Table 1). A comparison between the

Table 2
Overall CAD and stroke incidence (per 1000 person-years) and estimated HRs in statin users compared with non-users using the time-dependent regression model.

Variables	Statin	
	No (N = 6338)	Yes (N = 916)
CAD		
Person-years	34,968	6976
Follow-up time (y), mean ± SD	5.52 ± 3.46	7.62 ± 2.93
Event, n	1089	117
Rate	31.1	16.8
cHR (95% CI)	1 (Reference)	0.58 (0.48, 0.70)***
aHR (95% CI)[a]	1 (Reference)	0.50 (0.41, 0.62)***
Stroke		
Person-years	39,565	7210
Follow-up time (y), mean ± SD	7.87 ± 2.82	6.24 ± 3.41
Event, n	531	67
Rate	13.4	9.29
cHR (95% CI)	1 (Reference)	0.70 (0.55, 0.91)**
aHR (95% CI)[a]	1 (Reference)	0.83 (0.63, 1.09)
Ischemic stroke		
Person-years	39,566	7210
Event, n	65	3
Rate	1.64	0.42
cHR (95% CI)	1 (Reference)	0.25 (0.08, 0.80)*
aHR (95% CI)[a]	1 (Reference)	0.30 (0.09, 0.99)*
Hemorrhagic stroke		
Person-years	39,566	7210
Event, n	466	64
Rate	11.8	8.88
cHR (95% CI)	1 (Reference)	0.77 (0.59, 0.99)*
aHR (95% CI)[a]	1 (Reference)	0.90 (0.68, 1.20)

*$p < 0.05$, ***$p < 0.001$.
CAD, coronary artery disease; cHR, crude hazard ratio; aHR, adjusted hazard ratio; ICS, inhaled corticosteroid; OS, oral steroid.
[a] Adjusted for age, sex, comorbidity (sleep disorders, diabetes, hypertension, hyperlipidemia, mental disorders, alcohol-related illness, and chronic kidney disease), and ICS and OS use.

mean ages of the statin users and non-users revealed that users were significantly younger than non-users (59.1 *vs.* 60.6 years, $p < 0.001$); moreover, 52.5% and 42.1% of the statin users and non-users, respectively, were women. The prevalence of all comorbidities was significantly higher in statin users than in non-users. ICS and OS use was more frequent in statin users than non-users.

The cumulative incidence of CAD and stroke was lower in statin users than non-users (log-rank test, $p < 0.001$ and $p = 0.006$, respectively; Supplemental Figs. 2A and B). In statin users and non-users, the mean follow-up duration was 7.62 and 5.52 years, respectively, and CAD event incidence was 117 and 1089, respectively (Table 2). CAD incidence density rate was lower by 42% in statin users than non-users (16.8 *vs.* 31.1 per 1000 person-years). After adjustments for all covariates, statin users had an aHR (95% CI) of 0.50 (0.41–0.62) for CAD events compared with non-users.

The incidence density rates of ischemic stroke were 0.42 and 1.64 per 1000 person-years in statin users and non-users, respectively. Compared with statin non-users, aHRs (95% CIs) for ischemic and hemorrhagic stroke were 0.30 (0.09–0.99) and 0.90 (0.68–1.20), respectively, in statin users.

Table 3 presents CAD and stroke risks in statin users and non-users stratified by sex and age. For all the groups (male or female and age < 50 or ≥50 years), CAD or stroke risk was considerably lower in statin users than in non-users. Table 4 presents CAD and stroke risks among statin users and non-users stratified by ICS and OS use. Regardless of ICS or OS use, statin users exhibited a considerably lower CAD or stroke risk than did non-users. However, the reductions in stroke risks were not statistically significant.

We subsequently evaluated the effects of statin therapy duration (≤600 or > 600 days) on CAD and stroke risks. Regardless of the duration, statin users had a lower CAD risk than non-users (aHR [95% CI] = 0.58 [0.47–0.71] and 0.23 [0.13–0.41] for ≤600 and > 600 days, respectively; Table 5). We also noted a dose-dependent decrease in CAD risk in users; aHRs progressively decreased as the cumulative statin dose decreased over a quartile. The patients who used statins for > 600 days exhibited a significantly lower stroke risk (aHR = 0.42 [95% CI = 0.19–0.89]) than non-users; moreover, compared with the statin non-users, the stroke risk decreased from 1.56 (95% CI = 1.09–1.23) in those using statins for ≤60 days to 0.40 (95% CI = 0.19–0.86) in those using statins for > 600 days. The variations in the lengths of exposure and their effects on stroke and CAD risk are also shown in Table 5.

Based on their adherence to statin use during the study period (or PDC), we divided our patients with ACOS into low- (33%), medium- (33%–66%), and high-adherence (> 66%) groups. The low-, medium-, and high-adherence statin users exhibited lower risk of CAD than did the reference group of non-users. However, when the low-adherence group was the reference group, CAD and stroke risks did not differ significantly between the medium- and high-adherence groups (Supplemental Table 1). This result may be associated with the use of different baselines in the study cohort. To balance these confounding factors, we used propensity-score matching to reduce the differences between the two cohorts and compare statin–CAD risk associations, which generated findings similar to those of the primary model (Supplemental Tables 2 and 3).

4. Discussion

In this study, statin users exhibited low CAD and stroke risks. This result was contrary to the result of a study that reported no notable stroke-related benefits of statin use in patients with diabetes mellitus [41]. After stratification by stroke type (ischemic or hemorrhagic), the risk of ischemic stroke was lower in statin users than non-users, but no such result was observed for hemorrhagic stroke risk. Consistent with our results, Chou et al. reported that in adults with a high risk of CVD but no prior CVD events, statin use is associated with a low risk of CVD events, and patients at a high baseline risk have relatively greater absolute benefits (e.g., those with hypercholesterolemia) [42]. A study that focused on stroke prevention through aggressive reduction in cholesterol levels revealed that in patients without known CAD, daily statin use reduced the overall incidence of ischemic stroke and CAD but slightly increased the incidence of hemorrhagic stroke [16]; these findings were partly consistent with our results. Our results regarding the relationship between statin use and hemorrhagic stroke risk require further confirmation through randomized control trials.

The patients with long-term (104 weeks) statin use exhibited significantly lower CAD [33] and stroke risks than did non-users. Similarly, a systematic review reported that long-term (e.g., 19.7 months) statin use is associated with atherosclerotic plaque regression [34]. In addition, short-term statin use is associated with a relatively low CAD risk. A meta-analysis revealed that statin users exhibited 20%–30% lower mortality and major CAD event risks than did placebo-treated patients; the reduction was noticeable within as early as 1 year (short-term statin use) of treatment initiation [43], which corroborated our findings. Moreover, ultrashort-term statin use (e.g., perioperative statin therapy for patients undergoing coronary artery bypass grafting) can reduce CAD risks [44,45]. The effects of statin use on CAD risk in patients with ACOS warrant additional research [46].

Cytokines are involved in atherosclerosis-related disorders (e.g., CAD and stroke) as well as small airway disorders and pulmonary artery inflammation (e.g., ACOS) [10,47]; for example, interleukin (IL)-6 may aggravate atherosclerosis, whereas IL-10 may attenuate it [48]. In ACOS, high IL-6 and low IL-10 levels aggravate inflammation and

Table 3
Sex- and age-stratified overall CAD and stroke incidence (per 1000 person-years) and estimated HRs in statin users compared with non-users using the time-dependent regression model.

	Men		Women	
	Statin		Statin	
	No (N = 3673)	Yes (N = 435)	No (N = 2665)	Yes (N = 481)
CAD				
No. of event	659	68	8.25430	49
Incidence rate	33.6	21.0	28.0	13.1
cHR (95% CI)	1 (Reference)	0.67 (0.52, 0.86)**	1 (Reference)	0.51 (0.38, 0.69)***
aHR (95% CI)[a]	1 (Reference)	0.59 (0.45, 0.77)***	1 (Reference)	0.42 (0.31, 0.57)***
Stroke				
No. of event	352	35	179	32
Incidence rate	15.9	10.5	10.3	8.25
cHR (95% CI)	1 (Reference)	0.67 (0.47, 0.95)*	1 (Reference)	0.82 (0.56, 1.19)
aHR (95% CI)[a]	1 (Reference)	0.82 (0.56, 1.19)	1 (Reference)	0.85 (0.56, 1.28)
	Age < 50 Statin No (N = 1614)	**Yes (N = 211)**	**Age≧50 Statin No (N = 4724)**	**Yes (N = 705)**
CAD				
No. of event	124	12	965	105
Incidence rate	11.2	6.60	40.5	20.4
cHR (95% CI)	1 (Reference)	0.60 (0.33, 1.09)	1 (Reference)	0.55 (0.45, 0.67)***
aHR (95% CI)[a]	1 (Reference)	0.33 (0.17, 0.61)***	1 (Reference)	0.51 (0.41, 0.63)***
Stroke				
No. of event	23	2	508	65
Incidence rate	1.96	1.09	18.3	12.1
cHR (95% CI)	1 (Reference)	0.54 (0.13, 2.29)	1 (Reference)	0.67 (0.52, 0.87)**
aHR (95% CI)[a]	1 (Reference)	0.27 (0.06, 1.26)	1 (Reference)	0.85 (0.64, 1.13)

CAD, coronary artery disease; cHR, crude hazard ratio; aHR, adjusted hazard ratio; ICS, inhaled corticosteroid; OS, oral steroid.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Adjusted for age, sex, comorbidity (sleep disorders, diabetes, hypertension, hyperlipidemia, mental disorders, alcohol-related illness, and chronic kidney disease), and ICS and OS use.

atherosclerosis in the pulmonary, coronary, and cerebrovascular arteries [49]. These findings may explain the high incidence of CAD and stroke in our patients with ACOS. Both ICSs and OSs may exhibit anti-inflammatory effects; thus, they may attenuate the effects of IL-6 and enhance those of IL-10 [50,51]. A cumulative ICS dose of ≥0.13 g may have a protective effect against cardiovascular-related diseases, such as stroke, as supported by our previous results [5]. Moreover, the use of ICS or OS with statins has an additive effect [17]. Therefore, in the later course of ACOS, the combined use of statins and ICS or OS was associated with lower incidence of CAD events, even in the short-term statin users.

In a study on rats, statins and steroids increased IL-10 levels and reduced IL-6 levels, thus improving cardiac function after acute myocardial infarction [52]. Coronary artery bypass grafting is associated with a strong systemic inflammatory response that is related to postoperative complications. Preoperative administration of either methylprednisolone or atorvastatin reduces the release of proinflammatory cytokines (e.g., IL-6) in patients undergoing coronary revascularization; consequently, these patients experience few postoperative complications [53]. These findings support our results. The combined use of steroids and statins is a common anti-inflammatory strategy. In our ACOS cohort, the long-term use of a combination of statins and ICS or OS was associated with a reduction in CAD and stroke risk, but short-term use was associated with a reduction in only CAD risk.

The time-dependent and propensity-score analyses revealed the association between statins and a relatively low CAD risk. However, CAD and stroke risks did not differ significantly in the patients with low adherence and those with high adherence to statin treatment. Adherence, or PDC, was estimated from data in filled prescriptions, but filled prescriptions do not necessarily indicate that the prescribed drugs are used as intended [54,55]. However, the effects of statins are dose dependent [56]; thus, long-term use of statins or high adherence reduces the risk of CAD. In this study, of the 916 statin users, only 183 used statins for > 600 days, and 200 had high adherence. Thus, no patient with long-term (> 600 days) statin use exhibited low adherence. Therefore, all the 183 satin users exhibited a relatively low risk of CAD and stroke in this study. However, the degree of ACOS severity may modulate the effects of statins. Consequently, the patients with mild ACOS (e.g., GOLD grade A) with relatively low adherence (e.g., PDC = 30%) had relatively low CAD risk.

Lifestyle may play a role in CAD and stroke risk reduction. Adherence to physical activity guidelines may increase high-density lipoprotein cholesterol levels and reduce low-density lipoprotein cholesterol (LDL-C) levels, thus reducing the incidence of CAD and stroke [57]. Therefore, patients with low statin adherence but high physical activity may exhibit low CAD and stroke incidence, which is similar to that noted in patients with high statin adherence. Moreover, 42.3% of patients with high statin adherence in one study did not achieve a > 30% reduction in LDL-C levels [58]. Therefore, physical activity is more effective than statin adherence in reducing CAD and stroke incidence in patients with ACOS. In summary, these findings indicate that the therapeutic control of LDL-C levels requires statin adherence and lifestyle modification; thus, the incidence rates of CAD and stroke can be reduced more efficiently by lowering LDL-C levels by using a combination of drugs and healthy lifestyle [59]. These results warrant additional research.

Table 4
ICS and OS use–stratified overall CAD and stroke incidence (per 1000 person-years) and estimated HRs in statin users compared with non-users using the time-dependent regression model.

	With ICSs		Without ICSs	
	Statin		Statin	
	No (N = 1519)	Yes (N = 249)	No (N = 4819)	Yes (N = 667)
CAD				
No. of event	152	22	934	95
Incidence rate	16.3	10.8	36.7	19.2
cHR (95% CI)	1 (Reference)	0.67 (0.43, 1.05)	1 (Reference)	0.57 (0.46, 0.70)***
aHR (95% CI)[a]	1 (Reference)	0.60 (0.37, 0.98)*	1 (Reference)	0.49 (0.39, 0.61)***
Stroke				
No. of event	80	17	451	50
Incidence rate	7.97	8.28	15.3	9.69
cHR (95% CI)	1 (Reference)	1.02 (0.60, 1.72)	1 (Reference)	0.65 (0.48, 0.87)**
aHR (95% CI)[a]	1 (Reference)	1.10 (0.61, 1.97)	1 (Reference)	0.77 (0.56, 1.05)
	With OSs Statin No (N = 4452)	**Yes (N = 723)**	**Without OSs Statin No (N = 1886)**	**Yes (N = 193)**
CAD				
No. of event	632	85	457	32
Incidence rate	24.7	15.2	48.5	23.0
cHR (95% CI)	1 (Reference)	0.65 (0.52, 0.81)***	1 (Reference)	0.53 (0.37, 0.75)***
aHR (95% CI)[a]	1 (Reference)	0.56 (0.44, 0.71)***	1 (Reference)	0.40 (0.27, 0.58)***
Stroke				
No. of event	347	51	184	16
Incidence rate	12.5	8.86	15.6	11.0
cHR (95% CI)	1 (Reference)	0.72 (0.54, 0.96)*	1 (Reference)	0.72 (0.43, 1.20)
aHR (95% CI)[a]	1 (Reference)	0.82 (0.59, 1.13)	1 (Reference)	0.82 (0.48, 1.43)

CAD, coronary artery disease; cHR, crude hazard ratio; aHR, adjusted hazard ratio; ICS, inhaled corticosteroid; OS, oral steroid.
*$p < 0.05$, **$p < 0.001$, ***$p < 0.001$.
[a] Adjusted for age, sex, comorbidity (sleep disorders, diabetes, hypertension, hyperlipidemia, mental disorders, alcohol-related illness, and chronic kidney disease), and ICS and OS use.

Table 5
Therapy duration–stratified overall CAD and stroke incidence (per 1000 person-years) and estimated HRs in statin users compared with non-users using the time-dependent regression model.

Statin exposed	N	Event	Person-year	Incidence rate	cHR (95% CI)	aHR (95% CI)[a]
CAD						
Duration on statin						
None	6338	1089	34968	31.1	1.00	1.00
≤600 days[#]	733	105	5354	19.6	0.67 (0.55, 0.82)***	0.58 (0.47, 0.71)***
> 600 days	183	12	1622	7.40	0.27 (0.15, 0.47)***	0.23 (0.13, 0.41)***
≤60 days[§]	258	46	1798	25.6	0.66 (0.64, 1.16)	0.76 (0.56, 1.02)
61–210 days	252	38	1845	20.6	0.70 (0.51, 0.97)*	0.61 (0.43, 0.84)**
211–600 days	223	21	1711	12.3	0.42 (0.27, 0.65)***	0.35 (0.23, 0.55)***
> 600 days	183	12	1622	7.40	0.27 (0.15, 0.47)***	0.23 (0.13, 0.40)***
Stroke						
Duration on statin						
None	6338	531	39566	13.4	1.00	1.00
≤600 days[#]	733	60	5578	10.8	0.81 (0.62, 1.06)	0.93 (0.70, 1.23)
> 600 days	183	7	1633	4.29	0.33 (0.16, 0.69)**	0.42 (0.19, 0.89)*
≤60 days[§]	258	33	1857	17.8	1.34 (0.94, 1.90)	1.56 (1.09, 2.23)*
61–210 days	252	14	1969	7.11	0.54 (0.32,0.92)*	0.59 (0.34, 1.01)
211–600 days	223	13	1751	7.42	0.56 (0.32,0.97)*	0.62 (0.35, 1.09)
> 600 days	183	7	1633	4.29	0.33 (0.16, 0.69)**	0.40 (0.19, 0.86)*

CAD, coronary artery disease; cHR, crude hazard ratio; aHR, adjusted hazard ratio; ICS, inhaled corticosteroid; OS, oral steroid.
*$p < 0.05$, **$p < 0.001$, ***$p < 0.001$.
[#]Cumulative days of statin use during the study period were divided into two levels according to the third quartile (75th percentile).
[§]Cumulative days of statin use during the study period were divided into four levels according to quartiles.
[a] Adjusted for age, sex, comorbidity (sleep disorders, diabetes, hypertension, hyperlipidemia, mental disorders, alcohol-related illness, and chronic kidney disease), and ICS and OS use.

4.1. Strengths

The importance of simulation studies is increasing with the development of additional extensions of the Cox proportional hazards model with time-dependent covariates. This study developed a method for generating survival times by using a Cox proportional hazards model with time-dependent covariates [60]. This method relies on simple transformation of random variables generated according to a truncated piecewise exponential distribution, which provides practitioners with considerable flexibility and control over the number of time-dependent covariates and periods in the duration of follow-up measurements. The use of this model may prevent time-related bias and immortal time bias.

The accuracy of medical records in the NHIRD is high, which makes it a valid resource for population research regarding CAD and stroke [61]. Statin use in Taiwan is in accordance with international guidelines. The NHIRD-based identification of ACOS [8] and pneumonia [62] has been validated in several reports [4,5,20–23]. Therefore, the use of this well-established method prevented all potential biases in this study.

4.2. Limitations

Pharmacogenetics is defined as the study of genetic variation as a determinant of drug response. It can provide complementary information regarding clinical factors and disease subphenotypes to optimize predictions of treatment response. The possible limitations of this study are biases and confounding variables, such as the choice of exposure risk window (risk windows may be validated or sensitivity analysis may be conducted based on varying lengths of the exposure risk windows); confounding by indication (randomization helps to prevent selection bias by the clinician); protopathic bias (can be controlled by adding a lag time into the exposure, which implies excluding the exposure in a time period before outcome occurrence); and surveillance bias (can be controlled by using evidence-based clinical guidelines specifying which at-risk patients should be studied and clearly conveying exact testing modalities and frequencies) [63].

Although we used a new-user design, with propensity score matching and a time-dependent model for analysis, the results were not as accurate as those of randomized control trials were. In the general population, untreated dyslipidemia is a risk factor for both CAD and stroke; nevertheless, in patients with dyslipidemia, statins reduce CAD and stroke risks by 30% [43]. However, we did not consider lipid levels in our analyses. Therefore, the additive effects of statins with ICSs or OSs might partly reflect the burden of untreated hyperlipidemia (24.4%) among our statin nonusers. Cytokine data are unavailable in the NHIRD. We used these methods for evaluating healthy user bias. However, data on lifestyle changes (exercise and diet) in low-, medium-, or high-adherence patients are unavailable in the NHIRD; these confounding factors may have caused some biases in this study.

4.3. Conclusion

CAD risk was lower in all the statin-using patients with ACOS, regardless of the duration of statin use, whereas ischemic stroke risk was lower only in the patients with long-term statin use. However, no association between hemorrhagic stroke risk and statin use was noted.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

This work was supported by grants from the Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW108-TDU-B-212-133004); China Medical University Hospital (CMU106-ASIA-12, DMR-107-192); Academia Sinica Stroke Biosignature Project (BM10701010021); MOST Clinical Trial Consortium for Stroke (MOST 107-2321-B-039 -004-); Tseng-Lien Lin Foundation, Taichung, Taiwan; and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Author contributions

All authors have contributed significantly and agree with the manuscript content: Concept/Design: Jun-Jun Yeh, Chia-Hung Kao; Provision of study materials: Chia-Hung Kao; Collection and/or assembly of data: All authors; Data analysis and interpretation: All authors; Manuscript writing: All authors; Final approval of manuscript: All authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.02.007.

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