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Continuation of statin therapy and a decreased risk of atrial fibrillation/flutter in patients with and without chronic kidney disease

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ABSTRACT

Background: To contain cost, Taiwan's previous National Health Insurance Reimbursement Policy requested that physicians discontinue their patients' statin therapy once the serum cholesterol had reached appropriate levels. This allowed us to evaluate the association between statin continuation and the occurrence of atrial fibrillation/flutter and whether it was modified by chronic kidney disease (CKD) status.

Methods: Patients who initiated statin therapy between January 1, 2001 and December 31, 2009 were identified from a random sample of one million subjects in the Taiwan National Health Insurance Research Database. The outcome was atrial fibrillation/flutter. A proportional hazard regression model with time-varying statin use was applied to estimate the hazard ratios (HR) and 95% confidence intervals (CIs) for atrial fibrillation/flutter according to current statin use versus treatment discontinuation, adjusted for baseline disease risk scores and time-varying covariates.

Results: A total of 6767 CKD and 63,678 non-CKD patients initiating statin therapy were included and followed for an average of 4.0 years. A total of 1118 participants experienced new-onset atrial fibrillation/flutter. The incidence of atrial fibrillation/flutter was approximately 2 fold higher in the CKD patients. Continuation of statin therapy was associated with a 22% (adjusted hazard ratio 0.78; 95% CI: 0.65–0.93) and 57% (adjusted HR 0.43; 95% CI: 0.27–0.68) decrease in atrial fibrillation/flutter hazard as compared with discontinuation in non-CKD and CKD patients, respectively.

Conclusions: Continuation of statin therapy was associated with a decreased risk of atrial fibrillation/flutter among CKD and non-CKD patients. However, further randomized studies are still needed to assess the association.

1. Introduction

Atrial fibrillation/flutter is a commonly seen arrhythmia in clinical practice that is associated with markedly increased morbidity and mortality [1]. A number of risk factors can predispose individuals to atrial fibrillation/flutter, including coronary artery disease (CAD), congestive heart failure (CHF), valvular heart disease, diabetes mellitus, hypertension, hyperthyroidism, and chronic kidney disease (CKD) [2–5]. Atrial fibrillation/flutter has been reported to occur in 7–27% of CKD patients [5].

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the most frequently prescribed lipid-lowering drugs,

Abbreviations: 95% CIs, 95% confidence interval; ATC, anatomical therapeutic chemical; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; NHIRD, National Health Insurance Research Database; NSAIDs, nonsteroidal anti-inflammatory drugs; Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

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which have been demonstrated to reduce cardiovascular events in both primary and secondary prevention [6,7]. In addition to their lipid-lowering properties, statins have also been found to reduce the risk for developing atrial fibrillation in patients with pre-existent CAD or CHF and in those who received cardiac and non-cardiac thoracic surgery [8–11]. However, a comprehensive systematic review and meta-analysis of randomized trials found that the beneficial effect of statins from short term studies enrolling these highly selected patients was not supported by the data from the long term trials [7–12]. While several methodological and clinical differences between the short-term and longer-term trials, and between studies comparing users with never users vs. those comparing high with low cumulative use may explain the inconsistent results [13–15], a possible immediate but not sustained effect of statins on the risk atrial fibrillation still cannot be excluded.

It is well established that patients with CKD experience high cardiovascular event rates [6]. Although it is generally recognized that statins may be beneficial to patients with mild to moderate CKD, the effect of statin therapy among patients with advanced CKD and end-stage renal disease (ESRD) on cardiovascular morbidity and mortality remains controversial [6,16–19]. Accordingly, we hypothesized that the effect of statin treatment on the occurrence of atrial fibrillation/flutter might be modified by the presence or absence of CKD. Thus, using data from the Taiwan National Health Insurance claims database, the aim of this study was to assess the association between statin treatment and the occurrence of atrial fibrillation/flutter in the general population, and whether the association would be different according to CKD status. Because laboratory results were not available in the claims database, patients with hypercholesterolemia but not receiving statin therapy could not be identified. Therefore, the comparison of statin users with non-users was susceptible to confounding by indication. Instead, we examined the effect of statin therapy on atrial fibrillation/flutter occurrence by comparing the risk of atrial fibrillation/flutter during statin continuation therapy with that during discontinuation among statin initiators. For cost containment, Taiwan's National Health Insurance Reimbursement Policy requested that physicians discontinue their patients' statin therapy or to reduce dosage once the serum cholesterol concentration had reached appropriate levels. This allowed us to evaluate the association of statin continuation and discontinuation on the risk of atrial fibrillation/flutter occurrence.

2. Methods

2.1. Data source

A single-payer and compulsory National Health Insurance program was implemented in Taiwan in 1995. By 2007, the program enrollment rate was 98.4%. The National Health Insurance Research Database (NHIRD) is a research database developed by the National Health Research Institute, with linked data from the demographic and enrollment records, hospital claims, ambulatory care visits, and pharmacy dispensing claims from hospitals, outpatient clinics, and community pharmacies. The Longitudinal Health Insurance Database 2005 comprises a random sample of one million subjects from the NHIRD with longitudinally linked data available from 1997 through 2009. Our source population comprised all beneficiaries from The Longitudinal Health Insurance Database 2005 who were at least 20 years of age on January 1, 2001. The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee.

2.2. Study population

From the source population, we identified patients who initiated statins, including lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, and rosuvastatin between January 1, 2001 and December 31, 2009. Initiation was defined as no prescription of statin therapy during the 12 months prior to the first prescription (index date). Exclusion criteria included the following: age over 100 years, lack of continuous insurance coverage during the 12 months preceding the index date, a record of receiving more than two types of statins on the index date, and an inpatient or outpatient diagnosis of atrial fibrillation/flutter during the year preceding the index date. To avoid erroneous inclusion of the patients who had atrial fibrillation/flutter, we excluded patients who received medical treatments consistent with atrial fibrillation/flutter (digoxin, anti-arrhythmic agents, and warfarin). Patients diagnosed with conduction disorders or cardiac dysrhythmias (ICD-9-CM code 426, 427) were also excluded.

2.3. Stratification by CKD

Study participants were further classified according to CKD at baseline based on the ICD-9-CM diagnostic codes during the year preceding the index date (Supplementary Table 1). The algorithm which uses ICD-9 diagnosis codes to identify CKD in claims databases has shown high positive predictive values (85.7%–97.5%) [20].

2.4. Use of study drugs

We collected information on the types, dosage, date of prescription, and supply days of prescribed drugs, as well as the total number of pills dispensed from the outpatient pharmacy prescription database. Every person-day during the study period was classified by continuation and discontinuation of statin therapy. Continuing statin use was defined as use during the period between the prescription start date and the end of the days of supply. Statins were classified into high cholesterol-lowering efficacy (atorvastatin and rosuvastatin) and low cholesterol-lowering efficacy (lovastatin, pravastatin, fluvastatin, and simvastatin). Discontinuation of statin therapy was defined by a lack of medication refill. Each patient was allowed to contribute person-days into different categories of statin continuation or discontinuation.

2.5. Study end points

The outcome of interest in this study was atrial fibrillation/flutter, defined by an ICD-9-CM diagnosis code of 427.3 in the inpatient or outpatient database. A previous validation study using a hospital administrative database reported a positive predictive value of 90% using this definition [21]. To increase accuracy, we also defined our study endpoint in the sensitivity analysis as having at least one hospital admission with a diagnostic code of atrial fibrillation/flutter or two or more outpatient visits with a diagnostic code of atrial fibrillation/flutter. Also, we conducted analyses on acute tonsillitis that was not likely to be associated with statin use as a "negative control". Patients were followed from the index date until outcome occurrence, death, disenrollment from the national health insurance, or December 31, 2009.

2.6. Covariate ascertainment and adjustment

We used inpatient and outpatient diagnosis and prescription files during the 12-month period before the index date to ascertain patients' history of hypertension, diabetes mellitus, cardiovascular, peripheral vascular, and cerebrovascular disease, chronic kidney, liver, and lung disease, neurological disorders, depression, thyroid, musculoskeletal, and gastrointestinal diseases, alcoholism and substance abuse (ICD-9-CM codes provided in Supplementary

Table 1). Similarly, medication history of using cyclooxygenase-2 selective and non-selective non-steroidal anti-inflammatory drugs, anti-platelet agents, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, calcium channel blockers, other anti-hypertensive agents, nitrates, insulin, oral anti-diabetics, fibrates, thyroid-therapy drugs, and diuretics were ascertained (ATC codes provided in Supplementary Table 1). We also collected information on patients' age, sex, and resource utilization (number of outpatient visits, number of hospitalizations, number of laboratory test measurements) during the 12 months before the index date.

To evaluate the accuracy of our algorithms to identify patients with atrial fibrillation/flutter and those with CKD, we conducted a validation study by randomly sampling records of 660 patients with ICD-9-CM code of 427.3 and 100 patients with CKD diagnostic codes in 2 hospitals. Their medical records were then reviewed by two physicians (YCL and CHC). Patients were ascertained to have atrial fibrillation/flutter if documented by ECG examinations, and to have CKD if the estimated glomerular filtration rate was less than 60 mL/min/1.73 m^2 for 3 months using Modification of Diet in Renal Disease formula. The positive predictive value was 89% for atrial fibrillation and 88% for CKD by using those criteria, suggesting a good diagnostic accuracy of our definition.

2.7. Statistical methods

Incidence rates of atrial fibrillation/flutter were calculated and their 95% confidence intervals (CIs) were estimated on a Poisson distribution.

We used a Cox regression model with a time-varying variable for statin use to estimate the hazard ratios (HR) of atrial fibrillation/flutter comparing patients continued on statin treatment with those who discontinued. Separate analyses were further conducted for statin initiators according to CKD status. Because the number of end points was small in comparison to the number of covariates, disease risk score deciles were included as summary measures of all covariates in the regression model to adjust for baseline imbalance [22]. Using logistic regression, we estimated the disease risk score, or the probability of atrial fibrillation occurrence based on patients' age, sex, initiation year, underlying diseases, concomitant medications, and resource utilization at 12 months prior to the index date (Supplementary Tables 2 and 3). In addition, time-varying use of anti-diabetic, anti-hypertensive, and anti-platelet medications was also adjusted for the potential change in risk during continuing statin use and discontinuation. In the primary analysis, we evaluated the effect of overall statin use versus discontinuation. Then, a Cox regression model accounting for baseline disease risk score deciles, time-varying use of anti-diabetics, antihypertensives, and anti-platelet agents was applied to find adjusted HRs. To increase study endpoint accuracy, a sensitivity analysis was performed using more strict criteria for atrial fibrillation/flutter outcome definition. Furthermore, we further evaluated the association of continued use of high cholesterol-lowering efficacy statin versus discontinuation, and continued use of low cholesterol-lowering efficacy statin versus discontinuation.

Stratified analyses were performed to evaluate the potential of effect modification. Participants with or without CKD were further stratified according to age (<65 or ≥65 years), hypertension (yes/no), diabetes mellitus (yes/no), and coronary artery disease (yes/no). A significant effect modification was considered if the confidence intervals between subgroups did not overlap. A two-tailed p value <0.05 was considered to denote statistical significance. All statistical analyses were performed with SAS 9.2 software (SAS Institute, Cary, NC).

3. Results

After excluding those who did not meet our study criteria, a total of 70,445 patients initiating statin therapy, including 6767 with CKD and 63,678 without CKD (Fig. 1). The study participants had a mean age of 57.9 years. The baseline characteristics of the total study population and the CKD and non-CKD patients initiating statin therapy are shown in Table 1. By comparison to non-CKD counterparts, patients with CKD were older and had a higher prevalence of diabetes, hypertension, ischemic heart disease, heart failure, gout, chronic liver and lung disease, osteoarthritis, upper gastrointestinal bleeding and peptic ulcer disease.

The total follow-up of study participants was 280,297 person-years, with an average length of follow-up of 4.0 years. During the study period, approximately 70% of the recorded person-time contributed to the discontinuation category. Similar person-time experiences were noted in the high and low cholesterol-lowering efficacy statin use groups.

A total of 1118 study participants had new-onset atrial fibrillation/flutter occurrence during the follow-up period. The absolute number of events and the crude incidence rate of atrial fibrillation/flutter according to statin use status are shown in Table 2. The incidence of atrial fibrillation/flutter was significantly lower in patients currently using statins as compared to those who discontinued treatment. Furthermore, among those discontinuing statin therapy, the incidence of atrial fibrillation/flutter incidence was approximately 2 fold higher in CKD than in non-CKD patients. (The associations of other baseline characteristics and atrial fibrillation/flutter were shown in Supplementary Table 4) Similar rates of atrial fibrillation/flutter were noted for high and low cholesterol-lowering efficacy statin use.

In the Cox regression analysis using time-varying statin use, continued statin use among overall study population was associated

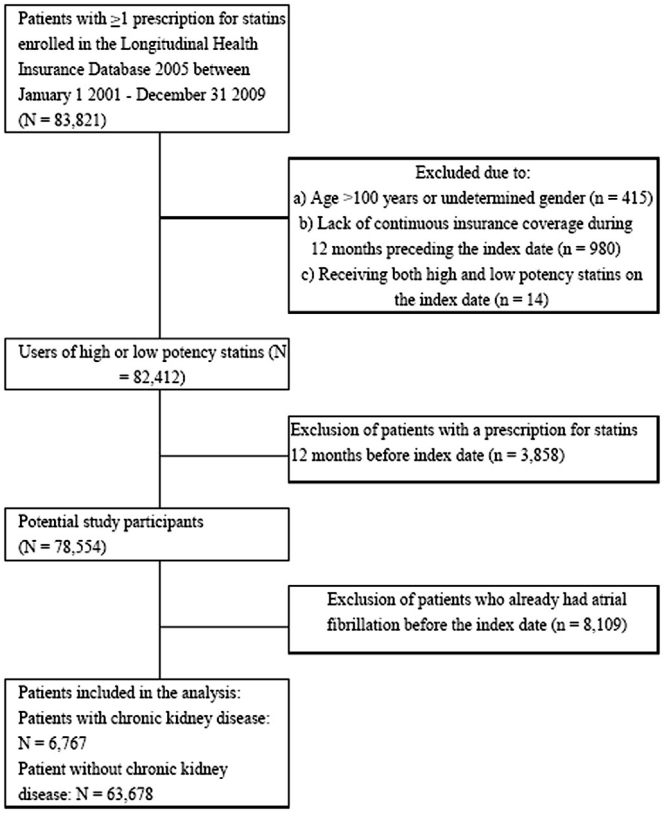

Fig. 1. Study flow.

Table 1
Baseline characteristics of the overall study population, and stratified by chronic kidney disease during the 12-month period before initiation of statin therapy.

	Overall population ($N = 70,445$)	Patients with chronic kidney disease ($N = 6767$)	Patients without chronic kidney disease ($N = 63,678$)
Patient characteristics			
Age at statin initiation (mean ± SD)	57.85 ± 12.55	60.01 ± 12.99	57.61 ± 12.48
Male (%)	47.68	49.52	47.48
Comorbidities (%)			
Diabetes mellitus	38.27	54.07	36.59
Hypertension	47.74	55.87	46.87
Hypertensive heart or renal disease	19.81	33.26	18.38
Ischemic heart disease	15.42	17.59	15.19
Myocardial infarction	1.88	1.38	1.93
Angina or unstable angina	7.19	8.14	7.10
Heart failure	2.53	4.85	2.28
Cerebrovascular disease	10.00	10.79	9.91
Intracranial hemorrhage	0.85	0.92	0.84
Transient ischemic attack	1.96	1.92	1.96
Gout	16.33	23.73	15.54
Chronic liver disease	17.12	19.51	16.87
Chronic lung disease, smoking	11.91	13.43	11.75
Upper gastrointestinal bleeding	30.69	34.86	30.25
Peptic ulcer disease	16.51	19.99	16.14
Medication use (%)			
COX-2 non-selective NSAIDs	75.6	75.08	75.66
COX-2 selective NSAIDs	5.32	7.2	5.12
Anti-platelet agents	35.3	48.53	33.9
ACE inhibitors/ARBs	36.76	56.92	34.61
Beta blockers	34.29	39.46	33.74
Calcium channel blockers	40.64	51.51	39.49
Other anti-hypertensive agents	8.89	14.05	8.34
Nitrates	11.26	14.13	10.95
Anti-diabetic agents	32.86	45.97	31.47
Insulin	3.93	10.85	3.19
Fibrates	13.12	15.93	12.82
Diuretics	21.08	37.65	19.32

SD: Standard deviation.

with a 19% decrease in atrial fibrillation/flutter risk as compared to treatment discontinuation (adjusted HR 0.81; 95% CI: 0.70–0.96; Table 3). The hazard ratio was 0.78 (95% CI: 0.65–0.93) in patients without CKD. A further reduction in atrial fibrillation/flutter risk with continued versus discontinued statin use was also noted among CKD patients (adjusted HR 0.43; 95% CI: 0.27–0.68) although the confidence intervals were overlapping between patients with and without CKD. The sensitivity analysis using a stricter outcome definition revealed similar results (Table 3). In secondary analyses, the continued use of both high and low cholesterol-lowering efficacy statins had an inverse association on atrial fibrillation/flutter risk by comparison to treatment discontinuation. We found no significant difference in the risk reduction of atrial fibrillation/flutter between patients on higher (≥0.5 DDD) and lower (<0.5 DDD) daily dose of statin. (Table 3). No association was found between statin continued/discontinued use and acute tonsillitis occurrence (adjusted HR 0.99; 95% CI: 0.95–1.03).

As outlined in Table 4, the negative association between continuing statin use and risk of atrial fibrillation/flutter was not modified by control for various baseline characteristics in subgroup analyses. Of note, although the confidence intervals were wide due to limited number of patients, statin use was associated with a significantly decreased risk estimate in CKD patients with age ≥65 years, without hypertension, and with coronary artery disease versus those of non-CKD patients.

4. Discussion

The current study revealed that the incidence of atrial fibrillation/flutter was significantly lower in patients with current statin use as compared with those who discontinued therapy regardless of CKD status and other underlying diseases. Although our analysis indicated an association of statin use to a decreased risk of AF, the absolute rate difference appeared to be very low.

While atrial fibrillation was assumed to be a consequence of myocardial ischemia, valvular insufficiency, or chronic heart failure with elevated intra-atrial pressure and atrial enlargement, a substantial proportion of patients with atrial fibrillation have no detectable heart disease. Accumulating data suggest that inflammation and abnormal oxidative stress is a pathophysiological feature involved in the development, recurrence, and persistence of atrial fibrillation [23]. Within the JUPITER trial cohort of individuals selected for underlying inflammation, increasing levels of high-sensitivity C-reactive protein were associated with an increased risk of incident atrial fibrillation and random allocation to rosuvastatin significantly reduced that risk [22]. Despite its beneficial effect on coronary atherosclerosis, emerging evidence suggested that statin had an effect beyond lipid-lowering which may acutely influence the risk of atrial fibrillation [24]. Researchers have

Table 2
Person-days, number of event, and incident rate of atrial fibrillation/flutter in total statin use, high cholesterol-lowering efficacy statin use, low cholesterol-lowering efficacy statin use, and discontinuation among total population, patients with and without chronic kidney disease.

	Total statin use	High cholesterol-lowering efficacy statin use	Low cholesterol-lowering efficacy statin use	Discontinuation
Total population ($N = 70,445$)				
Person-days	26,316,901	14,239,911	14,076,990	72,590,368
Number of events	186	102	84	932
Crude incident rate per 1,000,000 (95% CI)	7.07 (6.05–8.08)	7.16 (5.77–8.55)	5.97 (4.69–7.24)	12.8 (12.0–13.7)
Patients with chronic kidney disease ($N = 6767$)				
Person-days	3,285,709	1,715,367	1,570,342	7,130,946
Number of events	25	17	8	166
Crude incident rate per 1,000,000 (95% CI)	7.61(4.63–10.6)	9.91(5.20–14.6)	5.09(1.56–8.62)	23.3(19.7–26.8)
Patients without chronic kidney disease ($N = 63,678$)				
Person-days	25,031,192	12,524,544	12,506,648	65,459,422
Number of event	161	85	76	766
Crude incident rate per 1,000,000 (95% CI)	6.43(5.44–7.43)	6.79(5.34–8.23)	6.08(4.71–7.44)	11.7(10.9–12.5)

High cholesterol-lowering efficacy statin included atorvastatin and rosuvastatin.
Low cholesterol-lowering efficacy statin included lovastatin, pravastatin, fluvastatin, and simvastatin.

Table 3
Hazard ratios of atrial fibrillation/flutter comparing continued use of any statin, high cholesterol-lowering efficacy statin, and low cholesterol-lowering efficacy statin with discontinuation in patients with and without chronic kidney disease.

	Total population ($N = 70,445$)		Patients with chronic kidney disease ($N = 6767$)		Patients without chronic kidney disease ($N = 63,678$)	
	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Primary analysis						
Statin continued use vs. discontinuation	1.00 (0.85–1.18)	0.81 (0.70–0.96)	0.48 (0.30–0.76)	0.43 (0.27–0.68)	0.98 (0.82–1.17)	0.78 (0.65–0.93)
Sensitivity analysis[b]						
Statin continued use vs. discontinuation	0.93 (0.78–1.12)	0.74 (0.62–0.88)	0.43 (0.26–0.72)	0.38 (0.23–0.63)	0.89 (0.73–1.09)	0.70 (0.57–0.86)
Secondary analysis						
High cholesterol-lowering efficacy statin use vs. discontinuation	1.18 (0.98–1.45)	0.92 (0.75–1.12)	0.77 (0.47–1.28)	0.58 (0.34–0.99)	1.09 (0.87–1.37)	0.85 (0.67–1.07)
Low cholesterol-lowering efficacy statin use vs. discontinuation	0.83 (0.66–1.03)	0.69 (0.55–0.86)	0.33 (0.16–0.69)	0.27 (0.13–0.57)	0.87 (0.68–1.11)	0.71 (0.55–0.91)
Dosage effect						
<0.5 DDD	1.01 (0.81–1.26)	0.77 (0.62–0.97)	0.37(0.19–0.72)	0.32(0.16–0.62)	0.99(0.77–1.26)	0.76(0.60–0.98)
≥0.5 DDD	1.00 (0.81–1.22)	0.83 (0.68–1.02)	0.60(0.35–1.05)	0.56(0.32–0.97)	0.97(0.77–1.21)	0.79(0.63–1.00)

High cholesterol-lowering efficacy statin included atorvastatin and rosuvastatin.
Low cholesterol-lowering efficacy statin included lovastatin, pravastatin, fluvastatin, and simvastatin.
[a] Adjusted for baseline disease risk score deciles, time-varying use of anti-diabetics, antihypertensives, and anti-platelet agents.
[b] Outcome defined as ≥2 outpatient diagnostic codes or 1 discharge diagnostic code.

demonstrated that statins could exert some direct effect on transmembrane ion fluxes and interact with the channel proteins that may directly affect the electrophysiological properties of atrial muscle [25]. Therefore, it is pharmacologically reasonable to assume that statin withdrawal will adversely modulating these ionic currents and may precipitate atrial fibrillation occurrence.

Previously, we reported that the incidence of death was 621 per 100,000 person-years during statin discontinuation, but the rate decreased to 87 and 146 per person-years during lipophilic and hydrophilic statin use, respectively [26]. Atrial fibrillation/flutter might be one of the morbidities that statins could ameliorate before a major cardiovascular event or death took place or before censorship. There is a concern that the comparison between statin use and discontinuation may not be attributed solely to statin effect. Given that decisions to stop statin treatment are often related to clinical events or behavioral characteristics that may be related to the outcome of interest, statin discontinuation may actually serve as a health status indicator. In specific, it has been reported that current statin users are much less likely to experience a wide range of clinical events that are plausibly related to statin use, (for example, myocardial infarction and strokes) as well as other events that likely have little to do with this drug class, perhaps in part because statin users tend to be more health conscious and use more preventive health services. In our study, statin discontinuation comprised up to 70% of the total follow-up person-time. This data was compatible with Taiwan's previous insurance health care policy to encourage physicians to stop statin therapy when patients' serum cholesterol levels attaining the goal, which allowed the "natural" experiment to evaluate statin use on the risk of atrial fibrillation. Therefore, a typical prescription pattern among these statin initiators was repeated cycles of initiation and discontinuation [27]. On the other hand, statin therapy was generally well-tolerated; statin discontinuation due to patient preference or development of side effects did not follow this cyclic pattern, and the proportion was relatively small. Furthermore, it was also unlikely that the adverse reactions related to statins would cause atrial fibrillation. Also, we conducted analyses on acute tonsillitis that was not likely to be associated with statin use as a "negative control". The contrast of the findings that statin use versus discontinuation was associated with atrial fibrillation but not acute tonsillitis was in general support of our hypothesis in the association between drug effect and outcome occurrence.

Previous research suggested a possible dose–response relationship between statin therapy and risk of atrial fibrillation/flutter [6,28,29]. In this study, we reported that both high and low cholesterol-lowering efficacy statins were associated with a similar reduction in the risk of atrial fibrillation/flutter. This finding implies that the reduction in atrial fibrillation/flutter in response to statin therapy might be attributed to the pleiotropic, rather than the lipid-lowering effects of statins. For example, since inflammation is one of the mechanisms involved in the development of atrial fibrillation/flutter, the anti-inflammatory properties of statins may play a protective role [2,29]. Recent evidence illustrated that increasing atrial oxidative stress might induce and maintain an atrial fibrillation/flutter [4,12]. Additionally, the statin-induced inhibition of NADPH oxidase activity might be effective in preventing early atrial fibrillation/flutter-induced atrial remodeling or new-onset atrial fibrillation/flutter [30]. Statins might also improve atrial remodeling by altering collagen metabolism to adjust the antiarrhythmic efficacy [31].

The optimal treatment of dyslipidemic CKD patients would reduce cardiovascular risk as well as prevent the progression of renal dysfunction [6]. However, findings from randomized controlled trials are conflicting. For instance, the 4D and AURORA trials failed to show a beneficial effect of statins on CV risk among dialysis patients. However, the SHARP study showed that simvastatin plus ezetimibe safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced CKD [32]. Based on the above evidence, it is suggested that despite the fact that the cardio- and reno-protective effects of statins largely depend on their influence on the mevalonate pathway, numerous factors such as malnutrition and inflammation could interference with these benefits [6,33,34].

An issue is that the crude HR for statin use is reported as 1 but this changes to 0.81 in adjusted analysis (Table 3). Since the patients with statin continuation had a higher baseline risk score and were more likely to initiate anti-platelet, anti-hypertensive, and anti-diabetic therapy during the follow-up and these factors were

Table 4
Hazard ratios of atrial fibrillation/flutter associated with continued statin use vs. discontinuation among different subgroups of patients with and without chronic kidney disease.

	Total population ($N = 70,445$)			Patients with chronic kidney disease ($N = 6767$)			Patients without chronic kidney disease ($N = 63,678$)		
	Number of patients	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Number of patients	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Number of patients	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Age									
≥65 years	21,148	0.84(0.69–1.04)	0.77(0.63–0.95)	2572	0.26(0.13–0.53)	0.24(0.12–0.49)	18,576	0.83(0.66–1.05)	0.74(0.59–0.94)
<65 years	49,297	0.94(0.71–1.25)	0.72(0.55–0.96)	4195	0.39(0.16–0.94)	0.35(0.15–0.84)	45,102	0.78(0.56–1.08)	0.59(0.42–0.82)
Gender									
Male	33,587	0.81(0.63–1.04)	0.67(0.52–0.87)	3351	0.27(0.12–0.61)	0.23(0.10–0.53)	30,236	0.81(0.61–1.07)	0.63(0.47–0.83)
Female	36,858	0.90(0.72–1.14)	0.76(0.61–0.96)	3416	0.37(0.18–0.76)	0.33(0.16–0.67)	33,442	0.86(0.67–1.12)	0.70(0.54–0.90)
Hypertension									
Yes	33,628	0.87(0.71–1.06)	0.81(0.66–1.00)	3781	0.44(0.25–0.77)	0.43(0.24–0.76)	29,847	0.77(0.61–0.98)	0.69(0.54–0.87)
No	36,817	0.80(0.60–1.08)	0.61(0.46–0.82)	2986	0.12(0.04–0.41)	0.10(0.03–0.34)	33,831	0.89(0.65–1.22)	0.65(0.48–0.89)
Diabetes									
Yes	26,956	0.69(0.53–0.89)	0.64(0.50–0.82)	3659	0.23(0.11–0.51)	0.22(0.10–0.47)	23,297	0.65(0.48–0.87)	0.57(0.43–0.77)
No	43,489	1.04(0.83–1.31)	0.80(0.64–1.01)	3108	0.33(0.15–0.77)	0.32(0.14–0.71)	40,381	1.01(0.79–1.29)	0.75(0.58–0.96)
Coronary artery disease									
Yes	11,374	0.81(0.61–1.09)	0.75(0.56–1.01)	1219	0.18(0.06–0.54)	0.16(0.05–0.47)	10,155	0.76(0.55–1.06)	0.67(0.48–0.93)
No	59,071	0.86(0.70–1.06)	0.73(0.59–0.89)	5548	0.33(0.18–0.64)	0.31(0.16–0.58)	53,523	0.81(0.64–1.02)	0.65(0.52–0.82)

[a] Adjusted for baseline disease risk score deciles, and time-varying use of anti-diabetics, anti-hypertensives, and anti-platelet agents.

associated with an increased risk for atrial fibrillation/flutter, the "true" association turned negative after careful adjustment of these confounding factors (Supplementary Table 5).

In our analysis, the risk of atrial fibrillation/flutter was reduced with continued statin therapy in both CKD and non-CKD patients. Furthermore, stratification analyses revealed that the protective association of statins on atrial fibrillation/flutter were consistent independent of age (>65 versus <65 years), or the presence of diabetes mellitus, hypertension, and coexistent CAD. This finding suggested that statins could reduce cardiac arrhythmias across a wide spectrum of clinical conditions. Although the severity of CKD was previously regarded as a modifier of the protective effect of statins on cardiovascular risk [35], the present study shows that CKD had no influence on the association between statin use and atrial fibrillation/flutter risk. The results of the SHARP study also indicate similar treatment benefits in patients with CKD and ESRD [36]. Our findings support the notion that the safety profile of lipid-lowering therapy with statins in CKD is not different from that observed in people with normal renal function [37].

This study has a number of limitations that warrant mention. First, this is a non-randomized study design. Although we used time-varying analysis to adjust for the effects of anti-diabetic, anti-hypertensive, and anti-platelet medications, the results might be still confounded by other underlying diseases. However, the observed protective association between continuation of statin therapy and atrial fibrillation/flutter could not be solely due to these confounders because the patients continuing on statin use were mostly high-risk ones. Second, the health insurance claims databases lacked information on a number of key factors, including serum cholesterol and creatinine concentration, smoking status, and body mass index. Most of the discontinuation events occurred in compliance with national insurance policy that necessitated discontinuation when an optimal lipid level was reached. Therefore, the risk reduction in atrial fibrillation/flutter could be in part attributed to reaching optimal lipid levels. It is also possible that other life style factors which we do not know of (such as smoking abstinence and body weight reduction) drove the association achieving optimal lipids, statin discontinuation, and atrial fibrillation/flutter. Third, we were not able to assess the severity of comorbidities (e.g. blood pressure level, glycohemoglobin level, thyroid function, cardiac function), all of which could contribute to the development of atrial fibrillation/flutter. Fourth, renal function, as normally assessed by an estimated glomerular filtration rate and urinary albuminuria, could not be precisely determined from the claims database. Fifth, the difference between hydrophilic and lipophilic statins on reducing atrial fibrillation/flutter was not compared in this study. Finally, aside from policy requirement, the reasons for discontinuing statin therapy were not available in the claims database. However, factors such as adverse drug reactions or treatment non-adherence, despite infrequent, may precipitate the onset of atrial fibrillation.

5. Conclusions

In conclusion, as compared with treatment discontinuation, the continuation of statin therapy was associated with a reduction in the risk of atrial fibrillation/flutter among patients with and without CKD. The positive effect of statin therapy on the risk of atrial fibrillation/flutter was observed in patients of different ages and with different comorbidities. However, further studies are still needed to assess the effect of statins on the incidence of atrial fibrillation/flutter.

Contributorship

Study concept and design: Chang CH, Lin JW.
Acquisition of data: Lai MS.
Analysis and interpretation of data: Lee YC, Chang CH, Lin JW.
Drafting of the manuscript: Lee YC, Chang SN, Lin JW, Chang CH.
Critical revision of the manuscript for important intellectual content: Lee YC, Chang CH, Tsai CT, Chang SN, Chung YH, Lin MS, Lin JW, Lai MS.
Statistical analysis: Lee YC, Chung YH.
Obtained funding: Lai MS.
Study supervision: Lin MS, Lai MS.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2013.11.036.

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