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Dosage of statin, cardiovascular comorbidities, and risk of atrial fibrillation: A nationwide population-based cohort study

Chen-Ying Hung [a], Ching-Heng Lin [b,*], Kuo-Yang Wang [a,d], Jin-Long Huang [a,c,d], Yu-Cheng Hsieh [a,c], El-Wui Loh [e], Tsuo-Hung Lan [b], Pesus Chou [f], Chih-Tai Ting [a,c], Tsu-Juey Wu [a,c,d,*]

[a] Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan
[b] Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan
[c] Department of Internal Medicine, Faculty of Medicine, Institute of Clinical Medicine, Cardiovascular Research Center, National Yang-Ming University School of Medicine, Taipei, Taiwan
[d] School of Medicine, Chung Shan Medical University, Taichung, Taiwan
[e] Institute of Population Health Sciences, National Health Research Institutes, Taiwan
[f] Community Medicine Research Center & Institute of Public Health, National Yang-Ming University, Taipei, Taiwan

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ABSTRACT

Background: Statin has potential protective effects against atrial fibrillation. Clinically, there is a need to predict the atrial fibrillation protective effects in statin-treated patients. The purpose of this study was to investigate if cardiovascular co-morbidities or cumulative defined daily doses (cDDDs) of statin use could predict statin efficacy in atrial fibrillation prevention.

Methods: Patients aged ≥50 years were identified from the Taiwan National Health Insurance Research Database. Medical records of 171,885 patients were used in this study, and 40,001 (23.3%) of the patients received statin therapy (≥28 cDDDs). Risk of new-onset atrial fibrillation in statin users and non-users (<28 cDDDs) was estimated.

Results: During the 9-year follow-up period, 6049 patients experienced new-onset atrial fibrillation. Overall, statin therapy reduced the risk of atrial fibrillation by 28% (adjusted hazard ratio [HR] 0.72; 95% CI 0.68 to 0.77). There was a dose–response relationship between statin use and the risk of atrial fibrillation. The adjusted HRs for atrial fibrillation were 1.04, 0.85, and 0.50 when cDDDs ranged from 28 to 90, 91 to 365, and more than 365, respectively. Subgroup analysis showed that statin use was more beneficial in patients with higher $CHADS_2$ and CHA_2DS_2VASc scores than those with a score of 0 (P value for interaction<0.001). The therapy provided no obvious beneficial effect in those with a $CHADS_2$ score of 0, a CHA_2DS_2VASc score of 0, or cDDDs less than 91.

Conclusions: Statin therapy reduces the risk of new-onset atrial fibrillation in a dose-dependent manner, and is beneficial in patients with cardiovascular co-morbidities.

1. Introduction

Atrial fibrillation (AF) is the most common serious arrhythmia and is associated with increased stroke, heart failure, mortality, and economic burden [1–3]. Old age, male gender, heart failure, hypertension, diabetes mellitus, vascular disease, pulmonary disease, chronic renal disease, and valvular heart disease have been reported as risk factors for the development of AF [2–7]. This arrhythmia has become more prevalent with the increase of the elderly population in recent years. Therefore, a major focus on the disease management is to effectively prevent the occurrence of new-onset AF.

Because classic antiarrhythmic drugs have limited long-term efficacy and several side effects, current focus of AF primary prevention has shifted to upstream therapies that target AF substrate, such as statins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), aldosterone antagonists, and omega-3 polyunsaturated fatty acids [8]. A recent guideline suggests that statins could be used for AF prevention in patients undergoing cardiac surgery or those with heart failure [8]. However, the number of current studies focusing on other high-risk groups, especially those with multiple cardiovascular co-morbidities, is still insufficient.

Meta-analyses of randomized controlled trials have consistently showed a protective effect of statin in the primary prevention of AF [9–11]. However, possibly because of the heterogeneity of study designs, specific patient groups that obtain more benefits from the treatment have not yet been identified. Furthermore, no clear dose–response relationship has been reported. The purpose of the present study was to determine if cardiovascular co-morbidities or cumulative

* Corresponding authors at: Cardiovascular Center, Taichung Veterans General Hospital, 160, Section 3, Chung-Kang Road, Taichung 407, Taiwan. Tel.: +886 4 24614049; fax: +886 4 24618922.
E-mail addresses: epid@vghtc.gov.tw (C.-H. Lin), tjwu@vghtc.gov.tw (T.-J. Wu).

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defined daily doses (cDDDs) of statin use could predict the effectiveness of statin on primary AF prevention in a nationwide population-based cohort. Established cardiovascular co-morbidity scoring systems ($CHADS_2$ score [12] and CHA_2DS_2VASc score [8]) were also used to evaluate the efficacy of statin treatment for AF prevention.

2. Methods

2.1. Study population and end-point

The National Health Insurance program in Taiwan has been operating since 1995, and covers about 99% of the island's population and all forms of health care services. The National Health Research Institute (NHRI) of Taiwan has established a National Health Insurance Research Database. In this study, we used a systemic sampling of patient data from 2000 to 2009 with a total of 1,000,000 subjects, which was released by the NHRI as the Longitudinal Health Insurance Database. These random samples have been confirmed by the NHRI to be representative of the general Taiwanese population. There were no statistically significant differences in age and gender between the sample and overall population.

Patients' information and characteristics were included in the database. These files also contain information about prescriptions, including the names of drugs, prescribed dosage, and drug use duration. The information about diagnoses and prescriptions is of high quality, and has previously been used for epidemiological researches [13,14]. The NHRI made data at the individual level available to us in an anonymous format, in which specific individuals cannot be identified. The NHRI safeguards the privacy of individuals and provides the data to researchers after ethical approval has been obtained. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital. The authors of this manuscript have certified that they comply with the principles of ethical publishing in the International Journal of Cardiology [15].

The present study was a population-based cohort study, in which all patients aged ≥50 years in 2001 were identified from the research databases. Patients were not eligible for enrollment if they had a history of cardiac dysrhythmias (including AF), thyrotoxicosis, or valvular heart disease in 2000. This study included 171,885 patients for analysis. The study endpoint was defined as new-onset AF (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 427.31) or death during the 9-year follow-up period (2001–2009). All occurrences of AF were confirmed by the claims data. To ensure the diagnostic validity, only patients with at least 3 consensus AF diagnoses at outpatient departments (to avoid misclassification by including patients with tentative diagnosis for exams and those retrieving exam reports) or at least 1 inpatient hospitalization AF diagnosis were identified. The date of the end-point event (AF or death) was defined as the index date.

2.2. Data collection

Statin use records were retrieved from ambulatory and inpatient claims data. The prescription dates and the number of pills per prescription were collated. Patients were divided into statin user group and non-user group according to their statin use between January 1, 2001, and the index date (if end-point event occurred) or December 31, 2009. We collected information on simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and rosuvastatin, which are the currently available statins in Taiwan. According to the payment regulations of the National Health Insurance program in Taiwan, statins were used in patients 1) with manifest cardiovascular disease of atherosclerotic origin, and low-density lipoprotein [LDL]≧100 mg/dL or total cholesterol [TC]≧160 mg/dL; 2) without manifest cardiovascular disease of atherosclerotic origin, but with ≧2 cardiovascular risk factors (including hypertension, diabetes mellitus, family history of premature coronary artery disease, male aged ≧45 years, female aged ≧55 years, and smoking) and LDL≧130 mg/dL or TC≧200 mg/dL; or 3) without manifest cardiovascular disease of atherosclerotic origin, but with hypercholesterolemia (LDL≧160 mg/dL or TC≧240 mg/d). The regulations incorporated not only laboratory but also clinical criteria. Therefore, statins were prescribed more in patients with apparent atherosclerotic diseases and multiple cardiovascular risk factors in this study (see Table 1).

The defined daily dose (DDD), recommended by the World Health Organization, is the assumed average maintenance dose per day of a drug. In this study, we used DDD for measuring the prescribed amount of statin, and compared individual statin based on the same standard by using the following formula: (total amount of drug)/(amount of drug in a DDD) = number of DDDs [13]. Cumulative DDDs (cDDDs), the sum of DDDs of any statin, were served as the exposed duration of statins. We classified statin use into four categories (<28, 28 to 90, 91 to 365, and >365 cDDDs) because the duration of the refill period for chronic disease is 3 months in Taiwan. Patients who used statins for less than 28 cDDDs were defined as non-users.

We identified many cardiovascular co-morbidities as potential confounders by ICD-9-CM diagnostic code between January 1, 2000, and December, 31, 2000. Patients were defined as having hypertension only when they had a diagnosis of hypertension (ICD-9-CM codes 401–405) and had used at least 1 antihypertensive drug. According to the payment regulations of the National Health Insurance program and guidelines of the Taiwan Society of Cardiology [16], antihypertensive agents should be prescribed for those with systolic and diastolic blood pressure more than 140/90 mm Hg (or 130/80 mm Hg for high-risk patients). Other co-morbidities were confirmed by ICD-9-CM diagnostic code (with at least 3 consensus diagnoses at an outpatient department or at least 1 inpatient hospitalization diagnosis): heart failure, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease (defined as myocardial infarction or peripheral vascular disease), chronic obstructive pulmonary disease (COPD), and chronic renal disease. The $CHADS_2$ score was calculated for each patient by assigning 1 point each for the presence of heart failure, hypertension, age≥75 years, and diabetes mellitus, and 2 points for a history of stroke or TIA [12]. The CHA_2DS_2VASc score was calculated for each patient by assigning 1 point each for the presence of heart failure, hypertension, age 65–74 years, diabetes mellitus, vascular disease, and female gender, and 2 points for a history of stroke or TIA, and age≥75 years [8]. Medications (ACEIs, ARBs, and aldosterone antagonists), which potentially could be used for AF prevention, and other cardiovascular medications were also identified between January 1, 2000, and December 31, 2000 (see Table 1).

Table 1
Baseline characteristics.

Variables	All patients (n = 171,885)		Statin users (≧28 cDDDs; n = 40,001)		Non-users (<28 cDDDs; n = 131,884)		P value
	No.	%	No.	%	No.	%	
Age at entry, years							
Mean ± SD	62.7 ± 9.1		62.3 ± 8.1		62.8 ± 9.4		<0.001
50–64	111,134	64.7	26,327	65.8	84,807	64.3	<0.001
65–74	41,784	24.3	10,695	26.7	31,089	23.6	
≧75	18,967	11.0	2979	7.5	15,988	12.1	
Female	86,714	50.5	23,206	58.0	63,508	48.2	<0.001
Medical disease							
Heart failure	1332	0.8	419	1.1	913	0.7	<0.001
Hypertension	47,860	27.8	17,440	43.6	30,420	23.1	<0.001
Diabetes mellitus	16,376	9.5	8429	21.1	7947	6.0	<0.001
Stroke or TIA	7404	4.3	2482	6.2	4922	3.7	<0.001
Vascular disease	1978	1.2	819	2.1	1159	0.9	<0.001
COPD	7907	4.6	1994	5.0	5913	4.5	<0.001
Chronic renal disease	3368	2.0	1202	3.0	2166	1.6	<0.001
Upstream therapy							
ACEIs and ARBs	24,025	14.0	9490	23.7	14,535	11.0	<0.001
Aldosterone antagonists	1577	0.9	443	1.1	1134	0.9	<0.001
Other medications							
Aspirin	81,381	47.4	28,052	70.1	53,329	40.4	<0.001
Warfarin	4150	2.4	1465	3.7	2685	2.0	<0.001
Alpha blocking agents	50,267	29.2	13,724	34.3	36,543	27.7	<0.001
Beta blocking agents	93,302	54.3	29,234	73.1	64,068	48.6	<0.001
Calcium channel blockers	103,384	60.2	31,879	79.7	71,505	54.2	<0.001
Diuretics	93,159	54.2	27,773	69.4	65,386	49.6	<0.001
Antiarrhythmics	8909	5.2	2704	6.8	6205	4.7	<0.001
Digoxin	11,840	6.9	3189	8.0	8651	6.6	<0.001
$CHADS_2$ score							
Mean ± SD	0.6 ± 0.9		0.9 ± 1.0		0.5 ± 0.8		<0.001
Score = 0	105,210	61.2	17,707	44.3	87,503	66.4	<0.001
Score = 1	44,413	25.8	14,010	35.0	30,403	23.1	
Score = 2	14,625	8.5	5603	14.0	9022	6.8	
Score = 3	5206	3.0	1817	4.5	3389	2.6	
Score = 4–6	2431	1.4	864	2.2	1567	1.2	
CHA_2DS_2VASc score							
Mean ± SD	1.4 ± 1.3		1.8 ± 1.3		1.3 ± 1.2		<0.001
Score = 0	40,794	23.7	5873	14.7	34,921	26.5	<0.001
Score = 1	63,317	36.8	13,141	32.9	50,176	38.1	
Score = 2	35,890	20.9	10,485	26.2	25,405	19.3	
Score = 3	19,554	11.4	6173	15.4	13,381	10.2	
Score = 4–5	11,086	6.5	3915	9.8	7171	5.4	
Score = 6–9	1244	0.7	414	1.0	830	0.6	
Statin use (≧28 cDDDs)							
28–90 cDDDs	10,750	6.3	10,750	26.9	–	–	
91–365 cDDDs	15,671	9.1	15,671	39.2	–	–	
>365 cDDDs	13,580	7.9	13,580	34.0	–	–	
Simvastatin	13,780	8.0	13,780	34.4	–	–	
Lovastatin	8857	5.2	8857	22.1	–	–	
Atorvastatin	19,655	11.4	19,655	49.1	–	–	
Fluvastatin	8329	4.9	8329	20.8	–	–	
Pravastatin	5713	3.3	5713	14.3	–	–	
Rosuvastatin	9435	5.5	9435	23.6	–	–	

cDDDs = cumulative defined daily doses; SD = standard deviation; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin-receptor blockers.