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Original Article

Association of statin use and the risk of end-stage renal disease: A nationwide Asian population-based case–control study

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ABSTRACT

Background: Although experimental models have shown that statins could alleviate glomerular damage and decrease urinary protein excretion, the renal effects of statins remain unclear. A case–control study was conducted using data from Taiwan's National Health Insurance system.
Methods: An end-stage renal disease (ESRD) group comprising 11,486 patients was established. Each patient was frequency-matched by age, sex, and comorbidities with one person without ESRD from the general population. Logistic regression analysis was performed to estimate the influence of statin use on ESRD risk.
Results: The overall adjusted odds ratios (ORs) of ESRD among patients who received statins was 1.59 (95% confidence interval = 1.50–1.68). The raised ESRD risk of statin remained consolidated regardless of statin type ($P < .001$), except lovastatin. Further, while stratified by cumulative define daily dose, the risk of ESRD increased with accumulative dosage of statins (P for trend < .001).
Conclusion: This population-based case–control study showed that statin use might be associated with increased ESRD risks. Large-scale randomized clinical trial encompassing statins of different kinds and populations of different comorbidities would be helpful to clarify the potential ESRD risks of statin users

1. Introduction

Statins (3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors) have revolutionized the treatment of dyslipidemic and cardiovascular diseases. Given the success of statins in reducing the incidence of CHD-related morbidity, mortality, and stroke, their use is growing, particularly in patients with diabetes and its major comorbidities [1]. In contrast to the major benefits of statins in improving cardiovascular outcomes, claims of renal benefits of statins are controversial.

Studies of animal models have shown that treatment with statins could ameliorate the pathological changes of glomeruli, including decrease hypercellularity and fibrosis, as well as proteinuria [2,3]. However, while translating into clinical studies, these significant renoprotective effects of statin could not be demonstrated clearly. Some studies have shown that statins treatment could reduce urinary excretion of albumin in diabetic or nephrotic patients [4,5], although other studies did not note similar effects [6,7]. With regard to estimated glomerular filtration rate (eGFR), the benefits of statins also remained inconclusive. Notably, results of these clinical trials are inconsistent because of intratrial variability in evaluating outcomes, statistical methods, heterogeneity of studying population, types of statin prescription, and duration of follow-up [1,8,9].

End-stage renal disease (ESRD) refers to terminal overall renal function failure, generating an economic burden for the whole healthcare system [10]. The risk factors of ESRD is multifaceted, including cardiovascular disease (CVD), diabetes, hyperlipidemia, hypertension, and aging. In preventing the progression of chronic kidney disease (CKD) and further entering the status of ESRD, the core aim is reducing urinary protein excretion and retarding GFR decline. Meta-analyses and clinical trials have investigated the effect of statin use on urine protein excretion and eGFR [11–14]. However, no definitive population-based case–control study has investigated whether statin use could cause ESRD.

Accordingly, we conducted a nationwide, population-based case–control study to evaluate the renal safety of statin use by investigating the association between statin use and ESRD risk.

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2. Methods

2.1. Data source

This study used data retrieved from the National Health Insurance Research Database (NHIRD) of Taiwan's National Health Insurance (NHI) program. Participation in the system is obligatory; the NHI program provides coverage to more than 99% of the 23.74 million residents in the country and is contracted with 97% of all hospitals and clinics in Taiwan [15]. The NHIRD includes complete information on inpatient care, ambulatory care, dental care, and prescribed drugs and provides researchers with scrambled identification numbers associated with the relevant claim information, including each patient's sex, date of birth, registry of medical services, and prescriptions. This data set contains deidentified secondary data; therefore, no information could be used to identify any patient. This study was approved by the Ethics Review Board of China Medical University (CMUH104-REC2-115). The diagnoses and procedures were based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

2.2. Strength of data source

The strengths of our study are its population-based design, generalizability of findings, and use of population-based data and NHIRD records using a large sample size and having low loss to follow-up in the longitudinal design, including study and control cohorts. In addition, NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single buyer, the government in Taiwan. All insurance claims should be scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria in the study. If these doctors or hospitals make wrong diagnoses or coding, they will be punished with a lot of penalties. Therefore, the diagnoses of ESRD [16–18] and hyperlipidemia [19–21] based on ICD-9 codes in this study should be highly reliable.

2.3. Patients selected

Patients were identified from 2 subsets of the NHIRD. Subjects with hyperlipidemia (ICD-9-CM code 272) constituted the base population. We first identified patients aged at least 20 years and with renal diseases (ICD-9-CM code 580–589) and incident ESRD (ICD-9-CM code 585) by using the 2006–2009 records of the NHIRD Registry of Catastrophic Illnesses Patient Database. The first-time ESRD diagnosis date served as the index date. Finally, we extracted 11486ESRD patients with complete age or sex information and without a history of statin use before hyperlipidemia diagnosis to comprise the ESRD group. Control patients were also identified from the Longitudinal Health Insurance Database 2000 (LHID 2000), which contains the claims data of one million people sampled randomly from the NHIRD 2000 enrollment file. No significant difference exists in sex, age, or health care costs between cohorts in the LHID2000 and all insurance enrollees. For each patient with ESRD, we randomly selected one patient with renal diseases but without ESRD from the same period. We selected 1 control subject for each case from the LHID2000 matched on age within 10 years, gender, medications including angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blockers (ARB), NSAID (nonsteroid anti-inflammatory drugs), ezetimibe, fenobirate/gembibrozil, and resins, and comorbidity of diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), coronary artery disease (CAD; ICD-9-CM codes 410–414), congestive heart failure (CHF; ICD-9-CM code 428), and cancer (ICD-9-CM codes 140–208), proteinuria (ICD-9-CM code 581, 791.0), year of diagnosis of renal diseases, and year of diagnosis of ESRD.

2.4. Variables of interest

We considered major comorbidities such as diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), coronary artery disease (CAD; ICD-9-CM codes 410–414), congestive heart failure (CHF; ICD-9-CM code 428), cancer (ICD-9-CM codes 140–208), and proteinuria (ICD-9-CM codes 791.0) as baseline covariates. Six statin drugs available commercially in Taiwan were analyzed: simvastatin, fluvastatin, lovastatin, atorvastatin, pravastatin, and rosuvastatin. Medication use records were retrieved from ambulatory and inpatient claims data. We calculated patients' cumulative defined daily dose (cDDD) of each type of statin, namely, simvastatin (ATC C10AA01), lovastatin (ATC C10AA02), pravastatin (ATC C10AA03), fluvastatin (ATC C10AA04), atorvastatin (ATC C10AA05), and rosuvastatin (ATC C10AA07). For each type of statin, the cDDD was partitioned into 2 levels according to their median dose.

2.5. Statistical analysis

The baseline characteristics between the ESRD and the non-ESRD groups were compared using the chi-square test. We used the *t*-test to analyze continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with ESRD risk were estimated using conditional logistic regression models. All analyses were performed using SAS statistical software for Windows (Version 9.3; SAS Institute, Inc., Cary, NC, USA), and the significance level was set at .05.

3. Results

Table 1 summarizes the baseline characteristics profiles of the patients. A total of 22,972 patients with hyperlipidemia were enrolled in this study. The duration from diagnosis of CKD to diagnosis of ESRD is

Table 1
Baseline characteristics between end-stage renal disease group and non-end-stage renal disease group.

	ESRD				
	No, $N = 11,486$		Yes, $N = 11,486$		
	n	%	*n*	%	*P* value*
Gender					0.95
Women	5828	50.7	5833	50.8	
Men	5658	49.3	5653	49.2	
Age group (year)					0.03
≤64	4961	43.2	4775	41.6	
65–74	3474	30.3	3524	30.7	
≥75	3051	26.6	3187	27.8	
Mean (SD) (year)*	65.9	11.8	66.0	12.2	0.75
Medications					
Statin	6683	58.2	7845	68.3	<0.001
ACEI/ARB	10,282	89.5	10,262	89.3	0.67
NSAID	10,654	92.8	10,648	92.7	0.88
Ezetimibe	367	3.20	374	3.26	0.79
Fenobirate and gembibrozil	4908	42.7	4991	43.5	0.27
Resin	152	1.32	161	1.40	0.61
Baseline comorbidities					
Diabetes	6795	59.2	6832	59.5	0.62
Hypertension	10,917	95.1	10,882	94.7	0.29
Chronic obstructive pulmonary disease	4697	40.9	4687	40.8	0.89
CAD	6151	53.6	6187	53.9	0.63
CHF	1872	16.3	1874	16.3	0.97
Cancer	787	6.85	801	6.97	0.72
Proteinuria	1720	15.0	1864	16.2	0.01

Chi-square test and *t-test comparing subjects with and without end-stage renal disease. Data are presented as the number of subjects in each group, with percentages given in parentheses.
ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; NSAID, nonsteroid anti-inflammatory drugs.