International Journal of Cardiology 201 (2015) 538–543

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Statin therapy lowers the risk of new-onset atrial fibrillation in patients with end-stage renal disease

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ARTICLE INFO

Article history:
Received 31 October 2014
Received in revised form 8 January 2015
Accepted 25 January 2015
Available online 26 January 2015

Keywords:
Statins
Atrial fibrillation
Dialysis
Propensity score

ABSTRACT

Objectives: The objective is to assess the effectiveness of statin use to prevent atrial fibrillation (AF) in dialysis patients.
Methods: We used a database from the Registry for Catastrophic Illness from the National Health Research Institute (NHRI), which encompasses almost 100% of the patients receiving dialysis started from 1997 to 2008 in Taiwan. All dialysis patients aged 18 or older without history of cardiovascular events in 1997 and 1998 were incorporated. Finally, 113,191 dialysis patients were enrolled. We used propensity score (PS) matching method and Cox's proportional hazard regression models to estimate hazard ratios for AF events for statin users vs. nonusers.
Results: In statin group, the incidence of developing new AF was significantly lower than that in control group (1.1% vs. 3.8%, $P < 0.001$). The PS-based selection process identified 2146 patients receiving statins and 2146 who did not receive statins. The incidence of developing AF remained lower in statin group than that in control group (2.4% vs. 4.9%, $P < 0.001$). After PS matching, Cox's proportional hazard regression analyses showed that there was a protective effect of developing AF in a dose-responsive manner. The protective effect was more obvious in subjects with younger age, female gender, hyperlipidemia, coronary artery disease and peripheral artery disease and in subjects without taking angiotensin converting enzyme inhibitor and angiotensin receptor blocker.
Conclusion: Our analyses showed that statin therapy was associated with lower risk of newly diagnosed AF in patients with dialysis.

1. Introduction

Chronic kidney disease (CKD), including end-stage renal disease (ESRD), is considered a coronary vascular disease (CVD) risk equivalent [1]. Evidence showed that renal dysfunction is associated with an increase in risk of CVD, especially in patients receiving dialysis therapy [1–3]. In 1998, the National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in Chronic Renal Disease issued a report emphasizing the high risk of CVD in CKD [2]. Patients with CKD often have numerous risk factors for the development of CVD, such as hypertension, diabetes and hyperlipidemia. Whether aggressive risk factor modification could reduce the risk of CVD is important in clinical practice.

Hyperlipidemia is known as a main risk factor of CVD. Lipid-lowering treatment with statin has demonstrated the cardiovascular benefit in various groups. SHARP trial showed that treatment of CKD patients not requiring dialysis with a statin lead to a significant reduction in cardiovascular events [4]. However, the 4D [5] and AURORA trials [6] failed to show a benefit with statin therapy in dialysis patients. Therefore, 2014 Kidney Disease Improving Global Outcome (KDIGO) guidelines stated that statin therapy is not routinely initiated in dialysis patients [7].

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and it is an independent risk factor for both morbidity and mortality [8–12]. CKD has been shown to increase the risk of developing AF [13,14]. The prevalence of AF is between 8 to 34% in patients on hemodialysis and approximately 7% in patients undergoing peritoneal dialysis [15–18],

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http://dx.doi.org/10.1016/j.ijcard.2015.01.040
0167-5273/

which is much higher than that in the general population. Many studies have shown that statin treatment might prevent onset or recurrence of AF in different patient populations [19,20]. Whether the statin treatment remains effective for the prevention of AF in dialysis patients is unclear. In the present study, we examine this hypothesis by using a nation-wide database which covered almost 100% of dialysis patients in Taiwan.

2. Methods

2.1. Registry data sources

A universal National Health Insurance (NHI) program was implemented in Taiwan in March 1995. Ninety-six percent of the total Taiwanese population has been enrolled in this program [21]. By the end of 1996, the Bureau of NHI (BNHI) had contracts with 97% of all Taiwanese hospitals and clinics to join the national health insurance system [22]. Although the BNHI accumulates all administrative and claims data for Taiwan, the National Health Research Institute (NHRI) collaborated with the BNHI to establish an NHI research database. The NHRI safeguards the privacy and confidentiality of all beneficiaries and provides health insurance data for research only after ethical approval has been obtained. Data including gender, date of birth, medications and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; www.icd9data.com/2007) were retrieved for the analyses performed in this study.

2.2. Study population and outcomes

For the current study, we used a database from the Registry for Catastrophic Illness from NHRI. The database encompasses almost 100% of the patients receiving renal replacement therapy which started from 1997 to 2008 in Taiwan (around 23 million people). By reviewing ambulatory and inpatient claims data, we included ESRD subjects under dialysis (including hemodialysis and peritoneal dialysis) and aged over 18. All subjects were then followed from 1997 to 2009 with a median follow-up time of 4.3 years (25–75%, 1.57–8.77 years). Subjects with valvular heart disease (ICD-9-CM codes: 394.X–396.X and 398.X) were excluded from the current study. The main exposure of interest was statin therapy, identified from prescription claims. We collected information on prescribed drug types and dosage, date of prescription, number of days of treatment and the total number of pills dispensed from the outpatient pharmacy prescription database (included in the claims database). There was a specific code for every visit of each patient. By searching the outpatient pharmacy prescription database, we were able to obtain these codes and collect information regarding the prescribed statins. Prescription data of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, two major drug categories to reduce risk of new-onset AF, were also collected. Each statin was assigned an appropriate equivalent dose according to the following formula: lovastatin 40 mg = pravastatin 40 mg = simvastatin 20 mg = atorvastatin 10 mg = fluvastatin 80 mg = rosuvastatin 5 mg. The study outcome was the recording of a new diagnosis of AF (ICD-9-CM codes: 427.31–427.32). New diagnosis of AF was defined as a new addition of ICD-9-CM codes. If a patient had new-onset AF noted by the physician, either he needed medication treatment or not, the physician would add the ICD-9-CM codes of AF as a record. According to the regulation of the BNHI, false diagnoses can result in a severe penalty. The BNHI conducts expert reviews on a random sample for every 50–100 ambulatory and inpatient claims on a quarterly basis [23].

2.3. Comorbidities

Comorbidities were defined by diagnoses at hospital discharge or in clinic records. For our study population, we searched the national registry database to identify the presence of hypertension (HTN; ICD-9-CM codes: 401.X–405.X), diabetes mellitus (DM; ICD-9-CM codes: 249.X, 250.X), hyperlipidemia (272.X), cardiovascular disease (CVD) including coronary artery disease (ICD-9-CM codes: 411.X-414.X, V17.3 and V81.0), peripheral arterial disease (ICD-9-CM codes: 250.7, 443.X and 444.2), heart failure hospitalization (ICD-9-CM codes: 428.0–428.3 and 428.9), or stroke (i.e., transient ischemic accident, ischemic stroke and hemorrhagic stroke; ICD-9-CM codes: 430.X–432.X, 434.X, 435.X, V12.54).

2.4. Propensity score-based matching

Propensity score (PS) matching is a method used to balance observed covariates in two treatment groups [16]. In the present study, the PS was the conditional probability of receiving statin treatment, as a binary dependent variable, under a set of measurements. Clinical risk factors, such as sex, age, HTN, DM, hyperlipidemia, heart failure, comorbidities and use of medications other than statins, were added into a nonparsimonious multivariable logistic regression model to predict the risk of use of statins. The predicted probability derived from the logistic equation was used as the PS for each individual. The two groups of subjects (taking and not statins) were combined and classified according to PS; subjects in the two groups were matched by PS. If an appropriate PS match could not be found for individual subjects within the two groups, they were excluded from further analysis. The remaining patients constituted a well-matched 1:1 prospective cohort.

2.5. Statistical analysis

Comparisons of baseline characteristics (categorical covariates) including the use of different statins were made using the chi-squared test between subjects with and without taking statins. To estimate the risk of a new diagnosis of AF associated with different doses of statins, we used Cox's proportional hazard models to adjust potential confounders including baseline demographic data, comorbid conditions and concomitant medications. Subjects who did not receive statin treatment served as the reference group for comparison with patients who received different doses of statins. To investigate a possible dose–response effect, we classified participants into tertiles according to total dosage after transforming statin use into equivalent doses. Because one patient might have taken more than one type of statin during the study period, when comparing the effect of different statins we excluded patients who had used more than one type of statin and used patients treated with atorvastatin as the reference group. The AF-free survival time was defined as the time from the day of enrolment to a new diagnosis of AF. If an event did not occur, the case was regarded as censorship at the end of the study or at the time of death, withdrawal from the insurance, loss contact and receiving kidney transplantation, whichever occurred first. To demonstrate consistency, we also performed subgroup analyses to determine whether the results remained robust in different age, gender and CVD subgroups. Kaplan–Meier curves were plotted to determine the event-free survival trend between patients with different total equivalent doses of statins. A logistic regression model was used for PS matching. All analyses were performed with SPSS 15.0 for WINDOWS 7 (SPSS Inc., Chicago, IL, USA). For all analyses, a two-tailed P value < 0.05 was considered statistically significant.

3. Results

3.1. Demographics

The basic demographic characteristics of the patient population are summarized in Table 1. A total of 113,191 subjects (58,124 women and 55,066 men) were included in the final analyses, with a median follow-up period of 4.29 years. By the end of the study, 3732 subjects had been diagnosed with AF. Initially, statins were prescribed to 21,073 subjects. The patients who received statins tended to be