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Moderate to high intensity statin in dialysis patients after acute myocardial infarction: A national cohort study in Asia

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ABSTRACT

Background and aims: Statin is not beneficial for dialysis patients but moderate to high intensity statin is beneficial for patients after acute myocardial infarction (MI). The aim of this study was to evaluate the effect of moderate to high intensity statin on mortality, cardiovascular outcomes in dialysis patients after acute MI.

Methods: Data on dialysis patients were retrieved from the National Health Insurance Research Database in Taiwan. Dialysis patients admitted for MI were selected and divided into two groups according to statin prescription or not after MI. All-cause mortality and cardiovascular outcomes after a 4-year follow-up were analyzed after propensity score matching (PSM).

Results: We identified 790 patients who received moderate to high intensity statin therapy and 1788 patients who did not receive any statins after acute MI and clinical outcomes were analyzed after 1:1 PSM. The benefit of statin on mortality therapy appeared from 1 year to the end of the 4-year follow-up period after hospitalization (statin group *versus* non-statin group: 22.9% *vs.* 31.1% at 1 year (HR: 0.70; 95% CI: 0.58–0.85); 48.0% *vs.* 55.1% at the end of the 4 years (HR: 0.76; 95% CI: 0.67–0.88)). In addition, the impact of statin therapy was stronger in patients with shock at admission ($p = 0.035$). There were no differences in any individual cardiovascular outcome or adverse event.

Conclusions: Moderate to high intensity statin therapy might lower all-cause mortality in dialysis patients after acute MI, especially those with shock, but not influence cardiovascular outcomes and any adverse events.

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1. Introduction

Acute myocardial infarction (MI) is a life-threatening cardiovascular event [1], and the incidence increases with time and is higher in developed countries than in developing countries [2]. Statins are commonly prescribed during MI, and the efficacy of moderate to high intensity statin therapy in the secondary prevention of MI has been well established [3].

In terms of statin on dialysis patients, the reported effect of statins in preventing cardiovascular disease in dialysis patients has been disappointing. Die Deutsche Diabetes-Dialyse-Study (4D) and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis (AURORA) trials failed to show any beneficial effects of statin therapy, and the Study of Heart and Renal Protection (SHARP) trial did not show any benefits on total mortality or vascular death from reducing low-density lipoprotein cholesterol in patients undergoing hemodialysis [4–6]. This implies that mortality and cardiovascular events may not be prevented by statins in patients undergoing dialysis despite significantly lowering serum lipid levels.

However, dialysis patients have a higher risk of cardiovascular disease than those without chronic kidney disease, including MI [7]. In clinical practice, acute MI is a catastrophic clinical event in

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dialysis patients [8,9], and more than half of all patients die within the first year after its occurrence [10,11]. Therefore, the effect of statin therapy in dialysis patients with MI is an important issue.

According to the 4D and AURORA trials, statins may have no effect on cardiovascular outcomes in dialysis patients, whereas the Vytorin Efficacy International Trial (IMPROVE-IT) study [12] reported that statins might have a beneficial effect on cardiovascular outcomes in patients after acute coronary syndromes. Therefore, whether the beneficial effects of statins in the general population after acute MI can be extrapolated to dialysis patients with acute MI is unclear. To address this question, we performed this nationwide case-control study of dialysis patients with acute MI.

2. Materials and methods

2.1. Data source and study population

This national cohort study derived data from the National Health Insurance Research Database (NHIRD). The NHIRD is based on the National Health Insurance program in Taiwan, which covers over 99% of the population in Taiwan and includes around 23 million enrolees. The NHIRD prospectively records all submitted standardized data of healthcare services, including complete outpatient visits, hospitalization, medication prescriptions, disease, and vital status. The enrolee's original identification numbers are encrypted in the NHIRD to protect the patients' privacy, but the encrypting procedure is consistent so that linking claims belonging to the same enrolee is possible and can be followed longitudinally. Patients with end-stage renal disease requiring dialysis were identified according to an end-stage renal disease catastrophic illness certificate that specifically defines dialysis patients who need long-term maintenance dialysis and 24-h urine creatinine clearance rate of less than 5 ml/min. Therefore, patients with dialysis were included in the Registry for Catastrophic Illness database, which encompassed almost 100% of all patients with chronic kidney disease who received renal replacement therapy from 1995 to 2011 in Taiwan. The Research Ethics Committee of Chang-Gung Memorial Hospital approved the study protocol (201600983B0).

2.2. Patient enrolment and study design

This study is a population-based longitudinal cohort study. A total of 195,543 dialysis patients were initially identified, of whom 8572 were admitted for a first acute MI event. The high accuracy of diagnosis of acute MI based on ICD-9-CM was reported previously [13], but a validation study of acute MI in dialysis patients was also conducted in our center. After reviewing the medical records of randomly sampling 202 dialysis patients admitted for acute MI (ICD-9-CM code: 411, diagnosed as principal diagnosis) by a cardiologist (Y-S Lin), the positive predictive rate of diagnosis of acute MI was 99%. The index date was defined as the date of hospitalization for acute MI. The exclusion criteria were patients: 1) younger than 20 years and older than 100 years; 2) patients who took any lipid lowering agent in the 3 months before the index date, to reduce a possible influence of statin before AMI; 3) those prescribed with a low intensity statin or non-statin lipid-lowering medication after the index date; 4) those initially prescribed with statins 30 days after the index date and who were followed for less than 30 days after discharge, to reduce selection bias and balance the influence of statin. The remaining patients were then classified into two groups according to whether they did (statin group) or did not (non-statin group) receive statin therapy. To reduce potential confounding and selection bias due to the lack of randomization, we performed propensity scoring matching (PSM). The detailed study flowchart is shown in Fig. 1.

2.3. Definition of co-morbidities and drug exposure

Diseases are registered in the NHIRD using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. In this study, the diagnoses of diseases were defined as those recorded in any hospitalization before or during the index hospitalization or in more than two consecutive outpatient visits. The accuracy of diagnoses according to ICD-9-CM codes in claims data has been validated in a previous study [14]. Moreover, hypertension and diabetes mellitus were further confirmed by the prescription of long-term associated medications. The definitions of diseases are listed in Supplementary Table 1. Data on drug prescriptions were obtained from the out-patient pharmacy prescription database, including drug type, date of prescription, and duration of use. Long-term drug use was defined as use for at least 6 months after the index date (Supplementary Table 2).

Statins can be classified into three categories as low, moderate and high intensity according to the average expected low-density lipoprotein cholesterol response, dose and type of statin outlined in the 2013 American College of Cardiology/American Heart Association guidelines [3] and it recommends that patients with MI should be prescribed with moderate or high intensity statins. Therefore, patients who were prescribed with at least one moderate or high intensity statin after the index date were classified into the statin group, and those with no statin prescription into the non-statin group.

2.4. Outcome assessment

The observation period was from January 1, 2001 to December 31, 2013. The end of follow-up was 4 years after the index date or the date of a cardiovascular event or death within 4 years after the index date. Cardiovascular outcomes included non-fatal MI, hospitalization for heart failure and ischemic stroke, coronary intervention (percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG)) and cardiovascular death. MI (ICD-9-CM: 410), hospitalization for heart failure (ICD-9-CM: 428) and ischemic stroke (ICD-9-CM: 433–437) were defined as the principal diagnosis on admission. The accuracy of diagnoses in a claims database has been validated in previous studies [13,15]. The safety outcomes included new-onset diabetes mellitus, new-onset dementia, myopathy or rhabdomyolysis, newly diagnosed malignancy, hepatitis, and atrial fibrillation.

2.5. Statistical analysis

To minimize potential selection bias due to the non-randomized design of database research, we performed PSM. We calculated the propensity score according to age, sex, characteristics of dialysis (dialysis mode and duration of dialysis), baseline co-morbidities, prior coronary intervention (PCI or CABG), history of events, long-term drug use after the index date, management during the index admission and the index year of enrolment. We matched each patient in the statin group with one in the non-statin group.

Comparisons of the patients' characteristics between the statin and non-statin groups were performed using the Chi-square test for categorical variables and the independent sample *t*-test for continuous variables. The risk of a primary outcome (including all-cause mortality and cardiovascular event) during predefined follow-up periods (i.e. 3 months, 6 months, 1 year and 4 years) between the study groups was compared using Cox regression analysis with adjustments of the propensity score. Likewise, the risk of secondary safety outcomes during the 4-year follow-up period was also compared using Cox regression analysis between the statin and non-statin groups. Finally, the distribution of causes of death during the 4-year follow-up period between the two groups was compared using the Chi-square test. All data analyses

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