Statins use and the risk of liver dysfunction: A Chinese cohort study in real world clinical practice

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ABSTRACT

Background: The risk of liver injury is greatly of concern in China due to higher prevalence of hepatitis. In this study, we evaluated the association between the use of statins and the elevation of aminotransferase (ALT) in "real-world" clinical practice.

Methods: 4489 patients were divided into statins group (62%) and no statins group (38%) according to their status of medications. Detections of ALT were performed within 24 h after admission. The association of elevation of ALT and statins was analyzed.

Results: The percentage of patients with ALT > 1 × ULN(Upper Limit of Normal), was higher in statins group than that in no statins group (OR = 1.27, 95%CI 1.08–1.493), but after adjusting risk factors the OR value was 1.043(95%CI 0.851–1.278) with no statistical difference. Similarly, no differences were found regarding percentages of patients with ALT > 3 × ULN. Types of statins were usual in clinical practice and dosages of statins used were moderate in >90% of patient. We failed to find differences among the types and the dosage of statins except lovastatin. In addition, the relation of statin use duration to elevated ALT was evaluated. The higher proportion of elevated ALT in patients with stain use <1 month was detected compared those with stain use ≥3 months (OR = 1.408, 95%CI 1.111–1.783).

Conclusion: The data, firstly, provided two important information regarding the real status of liver dysfunction in Chinese patients who used moderate statins: 1) no relations between statin variety and ALT elevation; 2)statin-induced liver dysfunction frequently found in <1 month. Further study may be needed to confirm our findings.

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1. Introduction

The HMG-CoA reductase inhibitors (statins) are widely prescribed for patients with hyperlipidemia and coronary heart disease. Statins reduce cardiovascular morbidity and mortality in high risk patients with or without hyperlipidemia [1]. As a result, statins are among the most frequently prescribed medications worldwide with over 143 million prescriptions annually dispensed in the United States alone [2].

Besides of the benefit impact of statins, the adverse effects such as liver dysfunction, myopathy and cognitive impairment have also been of greatly concern. Melissa Y, et al. found that the side effect of statins (complaining of muscle pain) was the primary reason for discontinuation (60%) [3]. Traditionally we test plasma aminotransferase (ALT) of the patients who use statins, so liver injury presented as plasma ALT elevations may also be the cause of discontinuation. Previous studies suggested that mild elevations in serum ALT arisen in up to 3% of treated patients, but clinically apparent drug-induced liver injury is rare [2]. In 2012, hence, the Food and Drug Administration (FDA) of the United States altered statin labeling such that unless clinically indicated for other reasons, after a pre-statin therapy baseline evaluation, follow-up liver enzyme testing was not uniformly required after statin initiation [4]. However, in HPS2-THRIVE study, excess of raised ALT was seen chiefly among the participants in China with excess of consecutive ALT > 3 × ULN(Upper Limit of Normal) of 0.24%/year compared with 0.02%/year in Europe [5]. As is known to all, the highest endemicity for HBV in the world is in the Western Pacific region. The north and central Asian countries including China have HBsAg prevalence rates as high as 10% to 12% [6]. This may be one of the reason that liver injury is more likely to occur in Chinese. Thus it can be seen that the data of the amount of patients who have statins-related liver dysfunction and the level of elevation of ALT were not available in Chinese population, especially a large cohort observation.

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2. Method

2.1. Study population

From March 2011 through February 2016, we consecutively recruited 8243 patients who were referred for diagnostic or interventional coronary angiography because of angina-like chest pain and/or positive treadmill exercise test or clinically indicated coronary computed tomography (CT) angiography. Patients with severe renal dysfunction (creatinine clearance rate <30 ml/min), active virus hepatitis, myocardial infarction related elevation of aminotransferase, heart failure (left ventricular ejection fraction <45%), significant instability of haemodynamics, infection or systemic inflammation, history or evidence of valvular heart disease, congestive heart failure, untreated thyroid disease, sinus node dysfunction or conduction disturbance, estrogen replacement therapy and carcinoma were excluded from the study. There were 4489 patients enrolled according to the exclusion criteria. The patients were divided into two groups. Group 1: patients who had taken statins before admission. Group 2: patients who had not taken statins before admission. Types of statins included simvastatin, atorvastatin, pravastatin, lovastatin, rosuvastatin, fluvastatin and pitavastatin. Patients who did not take statins were defined as those who did not take any lipid-lowering medicine including statins, fibrates, nicotinic acids, ezetimibe, probucol and omega-3 fatty acids for 3 months before admission (Fig. 1). The protocol was approved by Fu Wai hospital ethics committee. This study has been designed and conducted in accordance with the Declaration of Helsinki. All the patients have signed informed consents before enrolled in our study.

Informed consent was obtained from all individual participants included in the study. For this type of study formal consent of ethics approval is not required.

2.2. Laboratory examinations

Blood samples were obtained for all patients from the cubital vein after a 12-h overnight fast within 24 h after admission. All the samples were tested in the clinical laboratory of Fuwai Hospital. The main index of liver function was alanine aminotransferase(ALT). CAD was defined as 1) any of the coronary artery such as the left main coronary artery (LM), the left anterior descending artery (LAD), the left circumflex coronary artery (LCX), right coronary artery (RCA) or the main branch of the vascular diameter stenosis reaching 50% or more; 2) who had prior coronary revascularization treatment; 3) any of the coronary artery had moderate to severe stenosis in computerized tomographic angiography (CTA). Hypertension was defined as blood pressure >140/90 mm Hg (at least 2 measurements under different conditions) or taking antihypertensive treatment. Diabetes was defined as fasting blood glucose >7.0 mmol/l or taking insulin or oral antidiabetic medicine.

2.3. Statistical analysis

Data were analyzed using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD or median (Q1–Q3 quartile), and categorical variables were expressed as percentage. Comparison of categorical variables between the groups was performed using chi-square test. Comparison of
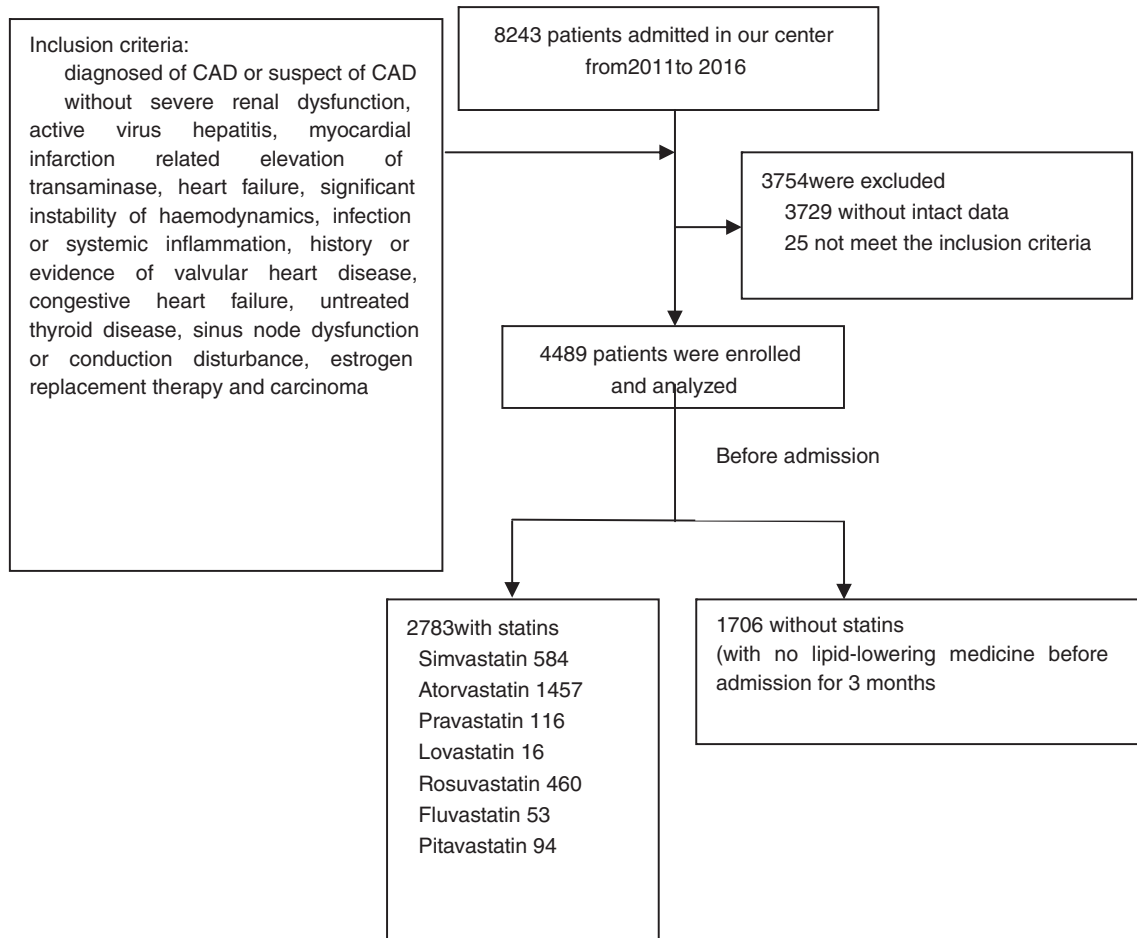
Fig. 1. Flowchart of patients enrolled in the study.