Original Article

Increased Dose and Duration of Statin Use is Associated with Decreased Asthma-Related Emergency Department Visits and Hospitalizations

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What is already known about this topic? Statins have pleiotropic anti-inflammatory and immunomodulatory effects, yet the effect of statin use on asthma-related emergency department (ED) visits and hospitalization has remained unclear.

What does this article add to our knowledge? In line with some previous studies, this study suggests that statins may have a beneficial effect on preventing asthma exacerbations and are associated with a decreased risk of asthma-related ED visits and/or hospitalization in an Asian population.

How does this study impact current management guidelines? This study indicates that statin use is associated with decreased risk of asthma-related ED visits and/or hospitalization. Future randomized clinical trials would be of importance to examine the effect of statin therapy on asthma exacerbations.

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BACKGROUND: Statins have pleiotropic anti-inflammatory and immunomodulatory effects, yet the effect of statin use on asthma-related emergency department (ED) visits and hospitalizations has remained unclear, especially in Asian populations.
OBJECTIVE: We sought to examine the effect of statin therapy on asthma-related ED visits and/or hospitalizations.
METHODS: A cohort study was conducted using data from Taiwan's National Health Insurance Research Database from 2001 to 2013. A total of 117,595 adult patients with asthma were included. The outcomes were defined as asthma-related ED visits and/or hospitalizations. Multiple Cox proportional hazards models were applied to determine the effect of statin use on asthma-related ED visits and/or hospitalizations.
RESULTS: There were 3,417 asthma-related ED visits and/or hospitalizations among 117,595 subjects with asthma. Statin users were significantly less likely to experience asthma-related ED visits and/or hospitalizations (adjusted hazard ratio: 0.81; 95% confidence interval: 0.74-0.89) compared with nonstatin users. The risks of asthma-related ED visits and/or hospitalizations were decreased among those with a higher cumulative defined daily dose (DDD), greater average DDD, and longer cumulative-day users than the counterparts.
CONCLUSIONS: Our study suggests that statin use is associated with the decreased risk of asthma-related ED visits and/or hospitalizations in patients with asthma. A dose-response effect of statin use is also observed in this study. Therefore, future randomized clinical trials would be warranted to further evaluate the association. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)

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Asthma is a respiratory syndrome defined by variable, reversible airway obstruction and increased hyperreactivity of the airways to various sources of stimuli.[1] Approximately 300 million

Abbreviations used
AHR- Adjusted hazards ratio
cDDD- Cumulative DDD
CI- Confidence interval
DDD- Defined daily dose
ED- Emergency department
LHID- Longitudinal Health Insurance Database
NHI- National Health Insurance
NHIRD- National Health Insurance Research Database

people around the world suffer from asthma, and roughly 1,000 people die from asthma every day.[2-4] The estimated prevalence of adult asthma ranges from 0.8% to 13.4% worldwide.[5] Previous studies have reported that most asthmatic patients can maintain asthma control with regular treatment.[6,7] However, some studies have also documented that suboptimal asthma control is related to more emergency department (ED) visits, consequently leading to increased health care burden.[8,9]

Hydroxymethylglutaryl-coenzyme A reductase inhibitors, statins, are commonly prescribed for hyperlipidemia and administered for the primary and secondary prevention of cardiovascular disease.[10,11] Previous studies have provided evidence that statin therapy reduces high-sensitivity C-reactive protein level and causes pleiotropic anti-inflammatory and immunomodulatory effects.[12] Nevertheless, whether statin use can decrease the occurrence of asthma exacerbations has remained inconclusive.[13-15] For example, Zeki et al[16] suggested that simvastatin inhibits airway hyperreactivity and attenuates airway inflammation. However, Menzies et al[17] showed no evidence for therapeutic anti-inflammatory effects of simvastatin on the treatment of asthma.

Therefore, to evaluate effect of statin use on asthma-related outcomes, we conducted a cohort study using a representative sample of an Asian population from Taiwan's National Health Insurance Research Databases (NHIRD) from 2001 to 2013. The objectives of this study were to investigate the association between statin use and asthma-related outcomes, specifically, asthma-related ED visits and/or hospitalizations. We also examined whether there were dose-response effects of statin use on the aforementioned asthma-related outcomes.

METHODS

Data source

We used registry data derived from 3 different Longitudinal Health Insurance Databases (LHIDs) composed of medical claims data from the NHIRD in Taiwan. In brief, the National Health Insurance (NHI) program has provided mandatory medical care to residents in Taiwan since 1995. The NHIRD contains reimbursement claims data collected by the NHI program, including demographic characteristics, outpatient and inpatient claims data, and prescription records. Previous studies have reported that enrollees represent approximately 98% of the total population in Taiwan.[18] Specifically, each LHID was constructed by randomly selecting 1 million enrollees from the NHI program in 2000, 2005, and 2010, separately. As such, a total of roughly 3 million subjects and their medical claims data from January 1, 2002, to December 31, 2013, were included in the present study. The Institutional Review Board of the National Health Research Institutes, Taiwan, approved this study protocol.

Study cohort

In this retrospective cohort study, we included patients aged 20 years and older with asthma. We identified patients as having asthma if they had a diagnosis based on International Classification of Diseases, Ninth Revision, Clinical Modification codes for asthma (493.xx) plus 1 inpatient or 2 outpatient visits for asthma within 1 year during 2002-2013. Of note, the exclusion criteria in this study were as follows: (1) patients with asthma-related ED visits and/or hospitalizations before index date; (2) patients whose gender was missing in the databases; (3) patients whose records were duplicates in at least 2 of 3 LHID datasets; and (4) patients who passed away within 1 year between the diagnosis of asthma and the index date because we were not able to compute the Deyo-Charlson index that was used to control for comorbid conditions. Of note, we found 1 patient with inaccurate records from an LHID set and excluded the patient from the subsequent analyses. Figure 1 (*A*) illustrates the detailed flow chart regarding inclusion/exclusion criteria for the study patients.

Statin exposure

For statin users, we defined the statin index date as the first identified prescription date of statins. Statin users were included in subsequent analyses if were enrolled in the NHI program for the 24-month observation period after the index date (Figure 1, *B*). We defined the nonstatin users as patients without any statin prescription during the entire 36-month period. The corresponding index date of the nonstatin users was defined as the last date of the first 12 months during the 36-month period (Figure 1, *B*). We excluded patients with asthma diagnosed in the 12 months before the index date to make the baseline characteristics of the 2 groups comparable. Statins investigated in this study include lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, and rosuvastatin.

In this study, we examined 3 different kinds of statin dose effect, including cumulative drug days, cumulative defined daily dose (cDDD), and average DDD. More specifically, the average daily dose of statin use was assessed using DDD, which was defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults."[19] We summed up the total numbers of prescription days as cumulative drug days and classified the cumulative drug days into quartiles: 0 (nonuse; reference group), >0 days and ≤ 38 days, >38 days and ≤ 101 days, >101 days and ≤ 224 days, and >224 cumulative drug days, separately. We also computed the cDDD, and classified the cDDD into quartiles: 0 (nonuse; reference group), >0 cDDD and ≤ 28 cDDD, >28 cDDD and ≤ 74.67 cDDD, >74.67 cDDD and ≤ 172 cDDD, and >172 cDDD, individually. Of note, cumulative drug days and cDDD for each study patient were calculated based on the 24-month follow-up period. The statin users in this study may or may not continuously fill statin prescriptions over the 24-month period because physicians prescribed statin agents to patients and adjusted dosing based on their condition. The average DDD was computed by dividing the cDDD by the number of statin-use days, and categorized into tertiles: 0 (nonuse; reference group), >0 and ≤ 0.67, and >0.67 average DDD, respectively.

Data analysis

We compared the distributions of demographic and clinical characteristics between statin users and nonstatin users in our study cohort using the F test for continuous variables and the χ^2 test for categorical variables. The primary outcomes in this study were asthma-related ED visits and/or hospitalizations. Multiple Cox proportional hazards models with covariate adjustment were applied