CHEST

A Population-Based Cohort Study on the Drug-Specific Effect of Statins on Sepsis Outcome

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BACKGROUND: Whether statin treatment, proved by recent experimental studies to have an antimicrobial activity, exerts a drug- or a class-specific effect in sepsis remains unknown.

METHODS: Short-term mortality in patients with sepsis was analyzed using data from the National Health Insurance Research Database. Use of statins was defined as the cumulative use of a specific statin (atorvastatin, simvastatin, or rosuvastatin) for > 30 days prior to the index sepsis admission. We determined the association between statin and sepsis outcome by multivariate-adjusted Cox models and propensity score (PS)-matched analysis, using a 1:1:1 PS matching technique.

RESULTS: A total of 52,737 patients with sepsis fulfilled the inclusion criteria, of which 1,855 were prescribed atorvastatin, 916 were prescribed simvastatin, and 732 were prescribed rosuvastatin. Compared with nonusers, simvastatin (hazard ratio [HR], 0.72; 95% CI, 0.58-0.90) and atorvastatin (HR, 0.78; 95% CI, 0.68-0.90) were associated with an improved 30-day survival, whereas rosuvastatin was not (HR, 0.87; 95% CI, 0.73-1.04). Using rosuvastatin as the reference, atorvastatin (HR, 0.79; 95% CI, 0.64-0.99) and simvastatin (HR, 0.77; 95% CI, 0.59-0.99) had superior effectiveness in preventing mortality.

CONCLUSIONS: Compatible with in vitro experimental findings, our results suggest that the drug-specific effect of statins on sepsis is not correlated to their lipid-lowering potency.

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KEY WORDS: atorvastatin; rosuvastatin; sepsis; simvastatin; statin

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ABBREVIATIONS: HR = hazard ratio; ICD-9-CM = *International Classification of Diseases–9th Revision–Clinical Modification*; LHID = Longitudinal Health Insurance Database; PS = propensity score

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Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection. Despite major advancements in medical care, the mortality of sepsis remains high, with a case-fatality rate around 17% to 26%.[1-4] Empirical antibiotic and organ supportive care have been the cornerstones of sepsis management. However, the global escalation in antimicrobial-resistant bacteria is increasingly compromising the effectiveness of antimicrobial therapy. Therefore, therapies that can attenuate the dysregulated immune response in sepsis have been intensively studied in the last decade.

Because of the pleiotropic immunomodulatory effects of statins demonstrated in animal models of sepsis, several clinical observational studies and randomized controlled trials have investigated whether the use of statins could improve the outcome of sepsis in humans.[5-8] Most observational studies have found that preadmission use of statin improves the outcome of sepsis, and a meta-analysis of 27 observational studies has concluded that statin treatment can decrease sepsis mortality by 35% (relative risk, 0.65; 95% CI, 0.57-0.75).[9-11] In contrast with observational studies, randomized controlled trials, however, did not observe beneficial effects of postadmission use of statins in patients with sepsis.[12-16] It has been controversially debated if the observed protective effect of preadmission use of statin was solely because of the healthy user effect. The healthy user effect describes the phenomenon in which patients prescribed with statins tend to have a constellation of healthier behaviors and therefore improved outcomes in most systemic diseases.

Just when the enthusiasm in the potential role of statins in improving sepsis outcome has tempered, emerging new evidence demonstrates that statins may have direct antibacterial effects and modulate the bacterial virulence.[17-19] The antibacterial or antivirulence effects may be statin-specific, not directly correlating with their lipid-lowering potency.[17,20] For example, although simvastatin was associated with better antibacterial effects than rosuvastatin, the latter was found to have a more potent lipid-lowering capacity.[21,22] Therefore, the primary aim of this research is to determine if the protective effects of statins are drug- or class-specific. In addition, a head-to-head comparison on different types of statins may provide insights on whether the protective effect of statins is solely caused by the healthy user effect.

Methods

Data Source

Taiwan's National Health Insurance program is a single-payer government-operated compulsory health insurance program, which covers > 98.4% of the 23 million people that reside in Taiwan. Specific data subsets were constructed for different research purposes. We used the year 2000 version of the Longitudinal Health Insurance Database (LHID) for this analysis, which used a systematic approach to randomly sample 1 million beneficiaries from the Registry for Beneficiaries of the National Health Insurance Research Database at 2000 to ensure the selected sample represents demographic and geographic region distribution of the entire Taiwanese population. The selected participants were followed from 2000 to 2011 to form a longitudinal close cohort for research use. The longitudinal nature of the LHID permits to identify a cohort based on diagnoses, health services, and drugs utilization, to track medical history, to establish a prescription drug profile, and to determine the end point of drug treatments. The LHID included detailed information on patient demographics, inpatient and outpatient electronic claims records, individual diagnoses, surgical and medical operations, dispositions, and detailed data on prescribed medication, such as brand/generic name of the prescribed drugs, route, quantity, and number of days of administration. This study was approved by the National Taiwan University Hospital Research Ethics Committee (No. 201311044RINB), and patient consent was waived for this anonymized electronic research database.

Study Cohort and Identification of Patients With Sepsis

The study cohort consisted of all the LHID participants hospitalized for sepsis between year 2001 and 2011. Year 2000 was used for assessment of covariates and statin use of patients with sepsis identified in 2001. Compatible with the sepsis-3 definition, sepsis was defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection. However, because the laboratory test results for the Sequential Organ Failure Assessment score were not available in a health claims database, we identified sepsis cases using a validated *International Classification of Diseases–9th Revision–Clinical Modification* (ICD-9-CM) coding system proposed by Angus et al,[3] in which at least one acute organ dysfunction and a diagnosis of bacterial or fungal infections is required to define an episode of sepsis. Acute organ dysfunctions used for this study were cardiovascular/shock, respiratory, central nervous system, hematologic, hepatic, renal, and metabolic system dysfunctions. e-Appendix 1 lists the ICD-9-CM codes used to identify patients with bacterial and fungal infections and acute organ dysfunctions. We defined the index date as the first day of an ED or hospital visit because of sepsis within 1 given year, and recurrent sepsis admissions in the same year were not considered in our analysis. Patients were followed from the index admission date to the occurrence of death, termination of health insurance coverage, or the end of the study period, whichever came first.

Outcomes and Covariates

The primary end point for the analysis is 30-day all-cause mortality; the secondary end points are 90-day all-cause mortality and acute respiratory failure. Acute respiratory failure was defined by the requirement of ventilation during the index sepsis admission episode. Based on the literature review, we collected a total of 61 covariates in the following dimensions: demographics, sources of infection, preexisting comorbidities, proxies for lifestyle factors, health care facilities utilization, and use of specific medications.