Effect of Statin Therapy on Mortality in Patients With Infective Endocarditis

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The aim of our study was to determine whether pre-emptive statin therapy was associated with improved outcome of infective endocarditis (IE). We conducted a nationwide, population-based, propensity score-matched cohort study with the Taiwan's National Health Insurance Research Database. All patients with IE between January 2000 and December 2010 were enrolled. The primary outcome was in-hospital mortality. The secondary outcome included all-cause mortality within the first 3 months, 6 months, and one year after the diagnosis of IE. Among 13,584 patients with IE, we applied propensity score-matching on a 1:4 ratio, in which 370 statin users were matched to 1,480 statin non-users. Compared with statin non-users, statin users had a significantly lower risk of in-hospital mortality (adjusted hazard ratio [aHR] 0.65, 95% confidence interval [CI], 0.49−0.86). The reduction in mortality from IE remained significant for follow-up 3 months (aHR 0.68, 95% CI, 0.53−0.88), 6 months (aHR 0.73, 95% CI, 0.58−0.91), and 12 months (aHR 0.68, 95% CI, 0.55−0.84). Statin therapy was associated with a reduced risk of ICU admission rates, shock events, the need for mechanical ventilation, but not significantly with the need for heart valvular replacement surgery. In conclusion, our study found that statin therapy is associated with a reduced risk of in-hospital and subsequent mortality of IE. **(Am J Cardiol 2014;114:94−99)**

A retrospective cohort of 283 patients with a diagnosis of IE conducted by Anavekar and colleagues first reported prior statin therapy were associated with reduced subsequent embolic events, but not significantly with reduced risks of mortality.[1] However, the independent association of statin use on mortality may be limited by small sample size, inclusion and the relatively short follow-up period. Thus, whether subjects complicated with IE before exposure of statin therapy gain the benefits of mortality at different time points in clinical practice need to be elucidated. Above-mentioned observations prompted us to test the hypothesis whether prior statin therapy could improve the outcome of IE. To reduce the impact of potential confounding elements stemming from inadequate controls for comorbidities, we conducted a nationwide population-based, propensity score-matched study of patients with IE by using Taiwan's National Health Insurance Research Database (NHIRD). The aim of this study was to evaluate whether statins influence subsequent adverse consequence or outcome in patients first admitted to the hospital with IE who were taking statins before hospital admission.

Method

In the current study, we used the National Health insurance Research database. In Taiwan, the National Health insurance (NHI) program was launched since 1995, which covers 99% of the population of 23 million people now. The NHI is a mandatory universal health insurance program, offering comprehensive medical care coverage, including outpatient, inpatient, emergency, dental, traditional Chinese medicine services, and prescription drugs. In 1999, the Bureau of National Health Insurance began to release patient data in electronic form. The multiple NHI databases provide comprehensive utilization and enrollment information for all patients under the NHI program. The diseases were coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, 2001 edition. The accuracy of diagnoses in the NHIRD has been validated for several diseases.[2,3] All information that would potentially expose a specific individual patient to be identified has been encrypted. The confidentiality of the data abides by the data regulations of the Bureau of National Health Insurance and the National Health Research Institute.

We designed a nationwide population-based, observational retrospective cohort study in Taiwan to determine the association between the prior statin use and the mortality in patients with IE. The study cohort comprised of all patients who had hospitalization with the diagnosis of IE and receiving antibiotic treatments between January 2000 and

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Table 1
Demographic and clinical characteristics of patients

Characteristic	Before Propensity Score-Matched			Propensity Score-Matched		
	Statin Users	Non-Users	p Value	Statin Users	Matched Non-Users	p Value
Patient (no.)	370	13,214		370	1,480	
Mean age (SD), year	64.9 (12.7)	56.6 (19.2)	<0.001	64.9 (12.7)	65.0 (13.7)	0.879
Male	193 (52%)	8,651 (66%)	<0.001	193 (52%)	762 (52%)	0.816
Income			<0.001			0.998
Dependent	128 (35%)	3,285 (25%)		128 (35%)	509 (34%)	
NT$ <19,100	72 (19%)	4,366 (33%)		72 (19%)	294 (20%)	
NT$ 19,100−42,000	154 (42%)	5,104 (39%)		154 (42%)	615 (42%)	
>NT$ 42,000	16 (4.3%)	459 (3.5%)		16 (4.3%)	62 (4.2%)	
Urbanization*			0.003			0.976
Level 1	211 (57%)	6557 (50%)		211 (57%)	832 (56%)	
Level 2	115 (31%)	5290 (40%)		115 (31%)	466 (32%)	
Level 3	34 (9.2%)	1,151 (8.7%)		34 (9.2%)	136 (9.2%)	
Level 4 (rural area)	10 (2.7%)	216 (1.6%)		10 (2.7%)	46 (3.1%)	
Charlson comorbidity score†			<0.001			0.890
0 score	3 (0.8%)	1,595 (12%)		3 (0.8%)	18 (1.2%)	
1 score	13 (3.5%)	1,960 (15%)		13 (3.5%)	61 (4.1%)	
2 score	30 (8.1%)	1,759 (13%)		30 (8.1%)	116 (7.8%)	
3 score	36 (9.7%)	1,531 (12%)		36 (9.7%)	128 (8.6%)	
≥4 score	288 (78%)	6,369 (48%)		288 (78%)	1,157 (78%)	
Concomitant medications						
Aspirin	155 (42%)	1,796 (14%)	<0.001	155 (42%)	622 (42%)	0.962
Clopidogrel	30 (8.1%)	201 (1.5%)	<0.001	30 (8.1%)	94 (6.4%)	0.227
Ticolpidine	11 (3.0%)	81 (0.6%)	<0.001	11 (3.0%)	43 (2.9%)	0.945
Cilostazole	6 (1.6%)	66 (0.5%)	0.003	6 (1.6%)	30 (2.0%)	0.614
Warfarin	26 (7.0%)	609 (4.6%)	<0.001	26 (7.0%)	116 (7.8%)	0.600
Dipyridamole	33 (8.9%)	560 (4.2%)	<0.001	33 (8.9%)	123 (8.3%)	0.707
ACE inhibitor or ARB	132 (36%)	1,617 (12%)	<0.001	132 (36%)	517 (35%)	0.789
Beta blocker	60 (16%)	1,174 (8.9%)	<0.001	60 (16%)	237 (16%)	0.924
Calcium-channel blocker	152 (41%)	1,917 (15%)	<0.001	152 (41%)	586 (40%)	0.601
Hypoglycemic drug	150 (41%)	1,345 (10%)	<0.001	150 (41%)	592 (40%)	0.850
Coexisting conditions						
Cerebrovascular disease	188 (51%)	4,570 (35%)	<0.001	188 (51%)	727 (49%)	0.561
Receiving heart valvular replacement surgery	26 (7.0%)	673 (5.1%)	0.097	26 (7.0%)	95 (6.4%)	0.672
Hypertension	339 (92%)	7,144 (54%)	<0.001	339 (92%)	1,356 (92%)	1.000
Myocardial infarction	74 (20%)	911 (6.9%)	<0.001	74 (20%)	269 (18%)	0.419
Coronary artery disease	269 (73%)	5,082 (38%)	<0.001	269 (73%)	1,078 (73%)	0.958
Chronic pulmonary disease	209 (56%)	5,891 (45%)	<0.001	209 (56%)	811 (55%)	0.559
Asthma	109 (29%)	2,617 (20%)	<0.001	109 (29%)	424 (29%)	0.758
Heart failure	186 (50%)	4,746 (36%)	<0.001	186 (50%)	745 (50%)	0.981
Valvular heart disease	161 (44%)	5,806 (44%)	0.871	161 (44%)	630 (43%)	0.742
Atrial fibrillation	51 (14%)	1,561 (12%)	0.248	51 (14%)	233 (16%)	0.350
Peripheral vascular disease	91 (25%)	1,253 (9.5%)	<0.001	91 (25%)	336 (23%)	0.440
Dyslipidemia	322 (87%)	3,434 (26%)	<0.001	322 (87%)	1,316 (89%)	0.307
DM	271 (73%)	4,390 (33%)	<0.001	271 (73%)	1,087 (73%)	0.937
DM, complicated with organ failure	154 (42%)	1,741 (13%)	<0.001	154 (42%)	640 (43%)	0.573
Rheumatoid disease	37 (10%)	870 (6.6%)	0.009	37 (10%)	159 (11%)	0.678
Cancer	64 (17%)	2,113 (16%)	0.499	64 (17%)	251 (17%)	0.877
AIDS	1 (0.3%)	165 (1.2%)	0.091	1 (0.3%)	3 (0.2%)	0.802
Chronic liver disease	113 (31%)	4,068 (31%)	0.920	113 (31%)	477 (32%)	0.533
Chronic renal disease	171 (46%)	3,487 (26%)	<0.001	171 (46%)	717 (48%)	0.443
Chronic dialysis	12 (3.2%)	176 (1.3%)	0.002	12 (3.2%)	58 (3.9%)	0.542
Drug abuse	11 (3.0%)	1,284 (9.7%)	<0.001	11 (3.0%)	34 (2.3%)	0.450
Propensity score (SD)	0.113 (0.048−0.227)	0.004 (0.002−0.018)	<0.001	0.113 (0.048−0.227)	0.113 (0.048−0.227)	0.999

ACE = angiotensin-converting-enzyme; AIDS = Acquired immune deficiency syndrome; ARB = Angiotensin II receptor blocker; DM = Diabetes mellitus; NT$ = new Taiwan dollars; SD = standard deviation.

* Urbanization levels in Taiwan are divided into four strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.

† Charlson Comorbidity Index (CCI) score is used to determine overall systemic health. With each increased level of CCI score, there are stepwise increases in the cumulative mortality.

Table 2
Association between statin use and risk of mortality in patients with infective endocarditis

	No. of Event/No. of Patients		Crude		Adjusted*	
	Statin Users	Non-Users	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Before propensity Score−Matched						
In-hospital mortality	56/370	2384/13,214	0.74 (0.57−0.97)	0.029	0.65 (0.49−0.86)	0.003
3-month Mortality	69/370	2782/13,214	0.86 (0.67−1.09)	0.203	0.74 (0.58−0.96)	0.022
6-month Mortality	87/370	3440/13,214	0.87 (0.71−1.08)	0.214	0.76 (0.60−0.95)	0.015
1-year Mortality	100/370	4098/13,214	0.84 (0.69−1.03)	0.090	0.70 (0.57−0.87)	<0.001
Propensity Score−Matched						
In-hospital mortality	56/370	321/1,480	0.60 (0.45−0.80)	0.001	0.60 (0.45−0.80)	<0.001
3-month Mortality	69/370	380/1,480	0.68 (0.53−0.88)	0.003	0.68 (0.53−0.88)	0.003
6-month Mortality	87/370	447/1,480	0.73 (0.58−0.91)	0.006	0.73 (0.58−0.91)	0.006
1-year Mortality	100/370	543/1,480	0.68 (0.55−0.84)	<0.001	0.68 (0.55−0.84)	<0.001

CI = confidence interval.
* Adjusted for propensity score.

Table 3
Association between statin use and adverse outcome in patients with infective endocarditis

	No. of Event/No. of Patients		Crude		Adjusted*	
	Statin Users	Non-Users	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Before propensity Score−Matched						
ICU admission	147/370	5,906/13,214	0.82 (0.66−1.01)	0.058	0.73 (0.59−0.92)	0.007
Shock event	110/370	4,606/13,214	0.79 (0.63−0.99)	0.041	0.74 (0.58−0.93)	0.012
Mechanical ventilation	116/370	4,817/13,214	0.80 (0.64−0.99)	0.045	0.77 (0.61−0.98)	0.032
Heart valvular replacement surgery	39/370	1,922/13,214	0.69 (0.50−0.97)	0.032	0.82 (0.8−1.17)	0.268
Propensity Score−Matched						
ICU admission	147/370	693/1,480	0.75 (0.59−0.94)	0.014	0.75 (0.59−0.94)	0.014
Shock event	110/370	541/1,480	0.73 (0.57−0.94)	0.014	0.73 (0.57−0.94)	0.014
Mechanical ventilation	116/370	547/1,480	0.78 (0.61−0.99)	0.045	0.78 (0.61−0.99)	0.045
Heart valvular replacement surgery	39/370	170/1,480	0.91 (0.63−1.31)	0.607	0.91 (0.63−1.31)	0.608

CI = confidence interval; ICU = intensive care unit.
* Adjusted for propensity score.

December 2010. Patients entered the cohort on the first day of hospitalization of IE and were followed up to death, lost to follow-up, or until December 31, 2011, whichever came first.

Baseline demographic data included age, sex, income, and urbanization. Charlson Comorbidity Index (CCI) score was used to determine overall systemic health.[4] Other systemic diseases not included in the CCI and concomitant medications associated with anti-inflammatory effects, patient's physical condition and underlying immune condition were extracted were also examined. We also identified patients who had a history of receiving heart valulvar replacement surgery. The statin users were defined as those who had received the continued prescription of statins for $\geq$ 30 days before the index date.

In order to reduce selection bias, we performed 1:4 case control matching analysis. For each statin user, we identified one such control patient with the most similar demographic characteristics, which were matched according to propensity score ($\pm$0.1 score) for the likelihood of statin use that was calculated from baseline covariates by using multivariate logistic regression analysis.

The primary outcome was in-hospital mortality. The secondary outcome was all-cause mortality within the first 3 months, 6 months, and one year of diagnosis of IE. Other adverse consequences including intensive care unit (ICU) admission rates, shock events, the need for mechanical ventilation and heart valvular replacement surgery during hospitalization were also included in our analysis.

Descriptive statistics were used to describe the baseline characteristics of our cohort. Baseline characteristics of the two groups were compared using Pearson χ^2 tests for categorical variables; the independent t-test for parametric continuous variables. The propensity score for the likelihood of statin use was calculated by multivariate logistic regression analysis, conditional on the baseline covariates in Table 1. Cox regression models were used to calculate the adjusted hazard ratio (HR) and 95% confidence intervals (CI) for the association between statin use and mortality. We also used multivariate logistic regression to calculate adjusted odds ratios (aOR) and 95% CI for the association between statin use and ICU admission rates, shock events, the need for mechanical ventilation and heart valvular replacement surgery. Adjustments were made for clinically relevant variables and for those that showed a statistically significant difference between the two groups at baseline. Finally, we performed subgroup analyses based on age, sex, CCI score, cerebrovascular disease, using antiplatelet drugs,

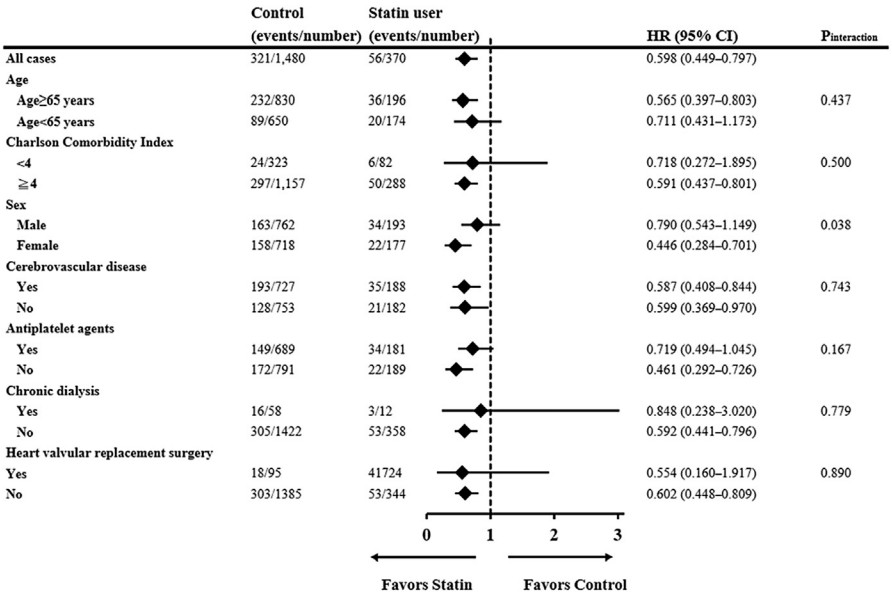

Figure 1. Subgroup analyses for statin use and risk of in-hospital mortality in patients with infective endocarditis.

and receiving heart valvular replacement surgery. Tests of interactions were performed for those subgroups by the likelihood ratio test. Microsoft SQL Server 2012 (Microsoft Corp., Redmond, Washington, USA) was used for data linkage, processing, and sampling. The propensity score and adjusted absolute incidence rate was calculated with SAS version 12.0 (SAS Campus Drive, Cary, North Carolina, USA). All other statistical analyses were conducted using STATA statistical software (version 12.0; StataCorp., Texas, USA). Statistical significance was defined as a p value of <0.05.

Results

Between January 2000 and December 2010, we identified 13,584 patients with a diagnosis of IE, including 370 statin users and 13,214 statin non-users. After 1:4 propensity score-matched, we identified 1,480 matched non-users. The detailed of baseline characteristics was shown in Table 1.

The main clinical outcome was shown in Table 2. Among 13,584 patients with IE, the overall cohort had an in-hospital mortality of 18%. Compared with statin non-users, statin users had a lower risk of in-hospital mortality, 3-month mortality, 6-month mortality, and 1-year mortality. Before matching, statin users were associated with a 31% reduction of in-hospital mortality compared with statin non-users. This similar tendency of reduced mortality associated with statin use was also observed after propensity-score matching. Among other secondary outcomes, statin users had a significantly lower risk of ICU admission rates, shock events, and the need for mechanical ventilation, but not the risk of the need for heart valvular replacement surgery. The detailed results are shown in Table 3.

As shown in Figure 1, in the subgroup analyses, compared with the matched control, the lower risk of mortality of IE in statin users were consistent. Tests of interaction were only significant for statin use and sex ($p = 0.038$). Compared with the matched control, statin only significantly reduced the risk of mortality for IE in female patients.

Discussion

In this nationwide propensity-score matching cohort study, we provide the new evidence that statin use as part of the management strategy for the primary prevention of IE was associated with a beneficial effect on subsequent mortality. Prior statin use for ≥ 1 month before the diagnosis of IE was associated with a 36% risk reduction of in-hospital mortality and the subsequent mortality was also significantly reduced (27% at 3 months, 22% at 6 months, 26% at 12 months, respectively). Furthermore, chronic statin use significantly reduced the adverse consequences caused by IE, including ICU admission rates, shock events, and the need for mechanical ventilation but not heart valvular replacement surgery. In subgroup analyses, the association between prior statin use and in-hospital mortality of IE remained consistent across subgroups of patients regardless of age, sex, CCI, cerebrovascular disease, chronic dialysis, using antiplatelet agents and receiving heart valvular replacement surgery.

It has been well documented that statins have highlighted their benefits in primary and secondary prevention of cardiovascular disease (CVD).[5,6] Intriguingly, all-cause mortality including non-fetal cardiovascular disease was also reduced. The phenomenon indirectly supports the additional benefits of statins independent of lipid lowering effect. In fact, statins inhibit the intermediate products in the mevalonate pathway, including mevalonate, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate, which involve in intracellular signaling pathways that responsible for innate and adaptive immune systems.[7] Results of recent research have provided further preclinical evidence for the pleiotrophic effects of statins on anti-inflammation,[8] anti-thrombosis[9] and immunomodulation.[10] Knowledge of the pleiotropic effects of statins has prompted a number of clinical studies in different settings, including sepsis,[11,12] community acquired pneumonia,[13]

bacteremia[14] or mixed infection.[15] However, inconsistent results of previous studies were noted, possibly due to nonrandomized heterogeneous or selected populations with small-scale sample size. Up to date, there was still lack of information regarding the effects of statin use on IE because of its uncommon nature. Anavekar et al[1] first reported continuous statin therapy has a benefit in symptomatic embolic event; however, no significant difference was found in the propensity-adjusted rate of 6-month mortality. The findings were limited by the small sample size and short-follow-up period. Thus, with the data set we used in this study, our results may better reflect the real protective effect of statins on patients with IE.

In this study, we focused on patients with IE who received pre-emptive statin therapy from a national population-based claims database. We believed that this definition of statin use served as an ideal group to test our hypothesis. For several years, statins have been studied extensively and the role of statin in these trials could be analyzed separately between the prevention and treatment cohorts.[16–18] Prior statin use (prevention cohorts) was associated with reduced sepsis rate.[19] However, the benefit may be offset by current or late statin therapy (treatment cohorts).[17,18] Some possible explanations were noted. First, when sepsis progressed to a more severe condition, it usually came to the state of immunosuppression. Therefore, the potential benefit of anti-inflammatory effects of statins may be diminished in such circumstances. Second, impairment of statin metabolism caused by critical illness contributes to decreased ubiquinone levels and thus exacerbates mitochondrial and organ dysfunction.[20]

For the other important IE-related outcomes, previous studies reported prior statin use was associated with a reduced rate of severe sepsis, ICU admission and fewer mechanical ventilation days.[12,19,21] Similar to previous reports, our study found that prior statin therapy was associated with a reduced rate of ICU admission, shock events and the need for mechanical ventilation after the diagnosis of IE. A possible explanation is that statin therapy improved survival in a septic murine model,[22,23] primarily via decline in monocyte adhesion and increased nitric oxide release from endothelium. Another proposed mechanism is that statin may have direct inhibition on inflammatory response induced by bacterial toxin and lipopolysaccharide.[24,25] However, current research did not show a significant correlation between reduced rates of valve surgery and prior statin therapy.

IE still carries a poor prognosis despite improvement in antibiotic and surgical techniques as well as advances in diagnosis, probably due to difficult eradiation and easy recurrence of culprit pathogen. Novel therapy may be warranted to strengthen the anti-inflammatory and anti-thrombotic effects as main preventive strategies for IE. Although antiplatelet and anticoagulant therapies were tested, previous studies have put out conflicting results, adding to concern about the potential risks of cerebral hemorrhage.[26,27] Our findings provide a basis for the new concept that prior statin use may have a protective role in subsequent outcome of patients with IE—at a stage of disease when pleiotrophic effects of statins may be most effective. Because high recurrent rates of IE were noted even after a successful treatment course,[28] at least 12-month close follow-up period with timely intervention was recommended by European guidelines.[29] Our study found the protective effects of statins seemed to persist for 1 year beyond the end treatment of IE.

Our study has several limitations. First, our study was retrospective and observational in nature. Ideally, randomized controlled trials (RCTs) have been advocated as the "gold standard" of epidemiologic studies. However, it is logistically difficult to conduct RCTs to evaluating the effects of prior statin use on IE outcome. These difficulties result from the low incidence of IE and the large numbers of participants with extended period of follow-up that carries a huge financial cost. Nevertheless, to eliminate the inherent confounders in observational studies, we used a propensity score-based algorithm to mimic an RCT design.[30] Second, several unmeasured biases including culprit pathogen and location of IE, were not available in our analyses. Third, causal relationship could not be answered in current study, but only association between statin therapy and reduced mortality of IE was able to be reported.

Disclosure

The authors have no conflicts of interest to disclose.

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