Relationship Between Statin Use and Outcomes in Patients Having Cardiac Arrest (from a Nationwide Cohort Study in Taiwan)

Chien-Hua Huang, MD, PhD[a,d], Ping-Hsun Yu, MD[b,c], Min-Shan Tsai, MD, PhD[a], Hui-Chun Huang, MD[d], Tzung-Dau Wang, MD, PhD[d], Wei-Tien Chang, MD, PhD[a], Chao-Hsiun Tang, PhD[c], and Wen-Jone Chen, MD, PhD[a,d,*]

Pretreatment with statins is associated with improved outcomes in severe sepsis, acute coronary syndrome, and stroke. Patients with cardiac arrest experience sepsis-like syndrome and ischemia reperfusion injuries in the heart and brain. The objective of this study was to investigate the effects of statin use before cardiac arrest on outcomes in cardiac arrest patients. Medical records of 142,131 adult patients who experienced nontraumatic cardiac arrest and were resuscitated between 2004 and 2011 were analyzed. Patients were grouped into 2 groups: the "statin group" comprised patients who had received statin treatment for at least 30 days before the cardiac arrest event; the "never statin group" comprised patients who had no statin use within 30 days before the event. Patients with previous statin treatment had better chance of survival to hospital discharge (6.1% vs 4.3%, p <0.0001) and 1-year survival (4.8% vs 3.2%, p <0.0001) after propensity score matching. Previous statin use was an independent predictor for 1-year survival (adjusted odds ratio 1.41, 95% confidence interval 1.16 to 1.71; p = 0.001). A favorable outcome effect of statin on 1-year survival was observed in the presence of diabetes mellitus, chronic kidney disease, and Charlson Comorbidity Index score greater than 5 in the subgroup analysis. In conclusion, statin use before cardiac arrest is associated with 1-year survival in a propensity score-matched nationwide cohort study. **(Am J Cardiol 2019;123:1572−1579)**

Statins are a widely used class of drugs that are primarily intended to treat hypercholesterolemia. In addition to lipid-lowering effects, statins have been shown to have pleiotropic properties of anti-inflammatory and antithrombotic effects on vascular endothelial cells.[1−3] Statin use before acute events has been associated with lower risks of having severe and fatal sepsis.[2,4−6] Statin treatment before ischemia reperfusion injuries, including acute coronary events and ischemic cerebral vascular events, are associated with better outcomes.[7−9] Cardiac arrest patients experience complex pathophysiological processes including ischemia reperfusion injuries in heart and brain in addition to a sepsis-like syndrome with cytokine storms in postresuscitation period.[10] The effects of previous statin use on cardiac arrest outcomes are rarely reported in published literature. We analyzed a nationwide cohort to test the hypothesis that statin use before cardiac arrest is associated with improved 1-year survival outcomes in resuscitated patients.

Methods

The National Health Insurance (NHI) program was launched in 1995, and it now provides coverage for more than 99% of the Taiwanese population of 23.74 million people.[11] The NHI database contains all claims data from the program in Taiwan and it details all patient demographics and orders for medical care. Taiwan's NHI Bureau is responsible for the comprehensive review of medical records and examination reports,[12] and it also publishes anonymous secondary data for research purposes. This study included the retrieval and review of medical records and reports from the Taiwan NHI Research Database that were accrued between 2004 and 2011. Disease diagnoses were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification. The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee (study no. 201404063W).

This observational, retrospective, and nationwide population-based cohort study of patients with nontraumatic cardiac arrest was designed to investigate the impact of pre-event statin use on survival outcomes. We enrolled patients receiving cardiopulmonary resuscitation (CPR) during short emergency room stays including out-of-hospital cardiac arrest patients with CPR in emergency room and cardiac arrest occurred in emergency department during short staying between January 2004 and December

[a]Department of Emergency Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; [b]Department of Emergency Medicine, Taipei Hospital, Ministry of Health and Welfare, Taipei, Taiwan; [c]School of Health Care Administration, College of Management, Taipei Medical University, Taipei, Taiwan; and [d]Department of Internal Medicine (Cardiology), College of Medicine, National Taiwan University, Taipei, Taiwan.
Manuscript received November 27, 2018; revised manuscript received and accepted February 6, 2019.

Funding: This study was supported by National Taiwan University Hospital, Taipei, Taiwan, grant number: 102TNY04.

See page 1578 for disclosure information.

*Corresponding author: Tel:+886223562831.

E-mail address: wjchen1955@ntu.edu.tw (W.-J. Chen).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.02.018

2011. Exclusion criteria included (1) age younger than 18 years, (2) trauma-related event, (3) emergency room stay longer than 6 hours, and (4) nonlevel 1 triage. Patients with an emergency department stay longer than 6 hours were excluded to decrease possible confounding effects on outcomes of inadequate postcardiac arrest care. Patients were followed from the index date of cardiac arrest until 1-year survival or death.

The Taiwan National Health Research Institute defines 4 tiers of urbanization that range from level 1, which indicates the most urbanized areas, to level 4, which indicates the least urbanized or most rural areas.[13] Illness severity was scored using the Charlson Comorbidity Index (CCI).[14] Hospitals were classified as medical centers if the specific requirements for medical staff and ability for specific treatment were qualified in regular hospital accreditation.[15] Criteria for qualification as a medical center include (1) 70% of total emergency physicians are fixed in and more than 50% of total fixed physicians are emergency medicine specialists, (2) the chief of emergency department should be emergency medicine specialist, (3) more than 75% of total stuff (including physicians and nurses) have qualified advanced cardiac life support training, (4) cardiologists and cardiovascular surgeons are available any time for managing the acute coronary syndrome, and (5) more than 75% of total ST elevation myocardial infarction (STEMI) patients have door-to-balloon time <90 minutes.

Cardiac arrest patients who had used statins continuously for 30 days before the index date were included in the "statin group." The control group or "never statin group" comprised patients without statin use in the 30 days before the cardiac arrest event. To clarify the effects of statin potency, statins were categorized according to potency to investigate the interactions in subgroup analyses. High-potency statins were rosuvastatin greater than or equal to 10 mg and atorvastatin greater than or equal to 20 mg; all other statins were considered low-potency drugs.[16]

Propensity scoring was used to reduce selection bias between the statin and never statin groups. The propensity score (PS) of the probability of receiving a statin was estimated using a logistic regression model drawn from pertinent characteristics, including age, gender, comorbidities, drug use, urbanization level, and year that the cardiac arrest occurred.[17] Results of logistic regression for PS estimation are reported in Table 1. Statin and never statin patients were then matched by PS at a 1:3 ratio without replacement.

The primary clinical outcome was 1-year survival. All patients were followed for 1 year after the day of the cardiac arrest or until loss to follow-up or death. Definition of survival to admission was survival to admit to intensive care unit in the hospital. Survival to hospital admission and survival to discharge were also analyzed.

To compare baseline characteristics of the 2 groups, the chi-square test was applied for categorical variables and the *t* test was applied for parametric continuous variables. Multiple logistic regression analysis was used to estimate the independent effects of statin use on survival outcomes. Variables, including baseline characteristics, comorbidities and risk factors, CCI scores, the use of resuscitation drugs (e.g., epinephrine, amiodarone, and lidocaine), or the completion of coronary angiography were included in the backward stepwise multiple logistic regression model and then verified by a forward stepwise method. The Kaplan-Meier method was applied for plotting the 1-year survival curve by applying the stratified log-rank test to evaluate the statin effect. Subgroup analyses of 1-year survival were based on demographic characteristics and management of cardiac arrest and resuscitation for the statin and never statin groups. All computations were completed with standard software (SAS v 9.4; SAS Institute, Cary, North Carolina), and statistical significance was established at a p-value of less than 0.05.

Table 1
Logistic regression of propensity matching of total patients

	Odds ratio (95 % CI)	p Value
Age, per year	0.99 (0.991−0.997)	<0.0001
Male	0.96 (0.90−1.03)	0.268
History of medication		
Antiplatelet agents	1.51 (1.40−1.62)	<0.0001
Angiotensin-converting enzyme inhibitors	0.89 (0.81−0.98)	0.022
Angiotensin receptor blockers	1.38 (1.27−1.50)	<0.0001
Beta-blocker	1.21 (1.12−1.31)	<0.0001
Urbanization Level		
1	1	
2	0.93 (0.86−1.00)	0.057
3	0.71 (0.62−0.82)	<0.0001
4 (Rural)	0.71 (0.65−0.78)	<0.0001
Charlson comorbidity index	0.97 (0.94−0.99)	0.001
History of comorbidities		
Diabetes mellitus	3.35 (3.09−3.63)	<0.0001
Hypertension	1.88 (1.73−2.04)	<0.0001
Coronary artery disease	2.65 (2.46−2.85)	<0.0001
Congestive heart failure	1.03 (0.94−1.12)	0.526
Atrial fibrillation	0.74 (0.65−0.86)	<0.0001
Chronic kidney disease	0.95 (0.85−1.06)	0.342
Malignancy	0.68 (0.58−0.79)	<0.0001
Chronic obstructive pulmonary disease	0.56 (0.51−0.63)	<0.0001
Asthma	0.97 (0.83−1.12)	0.631
Year or resuscitation		
2004	1	
2005	1.04 (0.89−1.21)	0.618
2006	1.22 (1.06−1.42)	0.007
2007	1.41 (1.23−1.63)	<0.0001
2008	1.52 (1.33−1.75)	<0.0001
2009	1.42 (1.24−1.64)	<0.0001
2010	1.67 (1.45−1.92)	<0.0001
2011	1.61 (1.40−1.85)	<0.0001

Results

There were 142,131 patients included for the analysis (Figure 1). Comorbidities of diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, and chronic kidney disease were more prevalent in the statin group than in the never statin group (Table 2). The presence of shockable rhythm (26.4% vs 20.3%), total epinephrine use during resuscitation, and the CCI score were higher in the statin group than in the never statin group. After PS matching, there were no significant differences in gender, urbanization, year of resuscitation, or most comorbidities

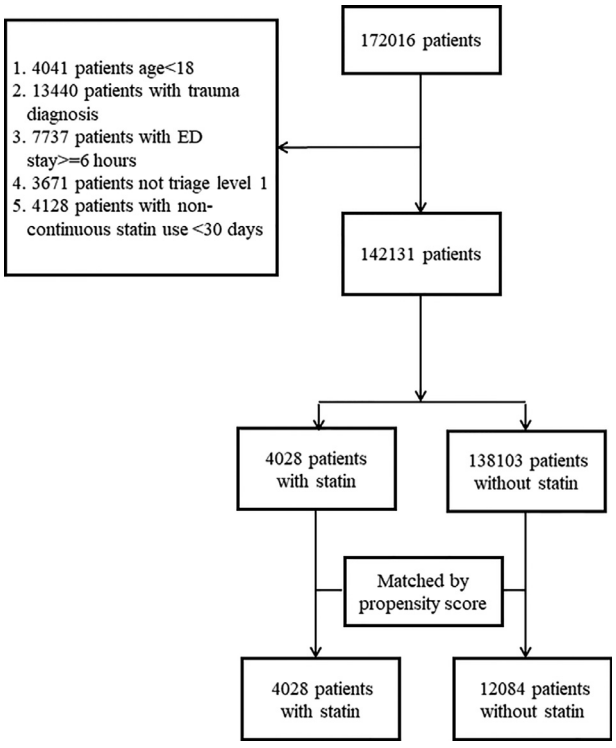


Figure 1. Flow chart of patient selection.

and characteristics. The exceptions were that age was older, the CCI score was higher, and hypertension was more prevalent in the never statin group (Table 3).

After PS matching, the statin group had better outcomes of survival to admission (21.1% vs 17.2 %; p <0.0001), survival to hospital discharge (6.1% vs 4.3%; p <0.0001), and 1-year survival (4.8% vs 3.2%; p <0.0001). The Kaplan-Meier survival curve showed better survival in the statin group through 1 year (Figure 2, stratified log-rank test; p <0.0001). When accounting for independent predictors for 1-year survival in the multiple logistic regression model, the previous use of statins was associated with a higher chance of 1-year survival (odds ratio [OR]: 1.41, 95% confidence interval [CI] 1.16 to 1.71; p = 0.001). Additionally, patients with younger age and a history of β blocker use had better chances of 1-year survival. Patients with higher CCI scores had lower chances of 1-year survival in multivariate analysis (Table 4). Cardiac arrest and resuscitation events that used less epinephrine, more amiodarone, and more lidocaine were associated with better chances of 1-year survival than events that used more epinephrine and less amiodarone and lidocaine. Patients who received coronary angiography during hospitalization also had improved chances of 1-year survival compared to patients who did not receive coronary angiography.

When patients were categorized according to statin potency, both the high-potency group (n = 1,150) and the low-potency group (n = 2,878) had better chances of survival to hospital admission (adjusted OR: 1.36, 95% CI 1.16 to 1.59, and adjusted OR: 1.30, 95% CI 1.16 to 1.44, respectively; both p <0.0001), survival to discharge (adjusted OR: 1.43, 95% CI 1.07 to 1.90, p = 0.015, and adjusted OR: 1.34, 95% CI 1.09 to 1.65, p = 0.005,

Table 2
Baseline characteristics, managements and outcomes of patients with/without statin use before matching

	Before propensity score matching		
Variables	Statin N = 4,028	Non-statin N = 138,103	p Value
Mean age, (SD)*, (years)	69.5 (11.8)	68.1 (17.6)	<0.0001
Male	2317 (57.5%)	87317 (63.2%)	<0.0001
Urbanization levels†			<0.0001
1	1137 (28.2%)	33340 (24.1%)	
2	1796 (44.6%)	57506 (41.6%)	
3	291 (7.2%)	12248 (8.9%)	
4 (Rural)	804 (20.0%)	35009 (25.4%)	
Charlson comorbidity index, (SD)	5.9 (2.4)	5.1 (3.0)	<0.0001
Medication			
Antiplatelet agents	1862 (46.2%)	29565 (21.4%)	<0.0001
Angiotensin converting enzyme inhibitors	583 (14.5%)	12774 (9.3%)	<0.0001
Angiotensin receptor blockers	874 (21.7%)	11774 (8.5%)	<0.0001
β-blockers	1255 (31.2%)	21477 (15.6%)	<0.0001
Comorbidities			
Diabetes mellitus	2527 (62.7%)	35830 (25.9%)	<0.0001
Hypertension	2985 (74.1%)	62191 (45.0%)	<0.0001
Coronary artery disease	1912 (47.5%)	25117 (18.2%)	<0.0001
Congestive heart failure	937 (23.3%)	18199 (13.2%)	<0.0001
Atrial fibrillation	241 (6.0%)	7332 (5.3%)	0.060
Chronic kidney disease	628 (15.6%)	11620 (8.4%)	<0.0001
Malignancy	246 (6.1%)	15486 (11.2%)	<0.0001
Chronic obstructive pulmonary disease	467(11.6%)	25081(18.2%)	<0.0001
Asthma	221 (5.5%)	9144 (6.6%)	0.004
Year of resuscitation			<0.0001
2004	335 (8.3%)	16074 (11.6%)	
2005	378 (9.4%)	17535 (12.7%)	
2006	448 (11.1%)	17109 (12.4%)	
2007	533 (13.2%)	17723 (12.8%)	
2008	579 (14.4%)	18177 (13.2%)	
2009	548 (13.6%)	17605 (12.8%)	
2010	609 (15.1%)	16888 (12.2%)	
2011	598 (14.9%)	16992 (12.3%)	
Shockable rhythm	1062 (26.4%)	28017 (20.3%)	<0.0001
Resuscitation in medical center	1128 (28.0%)	29204 (21.2%)	<0.0001
Managements			
Epinephrine	3903 (96.9%)	132451(95.9%)	0.002
Epinephrine dose (SD), mg	9.8 (6.9)	9.2 (16.5)	<0.0001
Amiodarone	519 (12.9%)	10311 (7.5%)	<0.0001
Lidocaine	179 (4.4%)	3899 (2.8%)	<0.0001
Coronary angiography	113 (2.8%)	1515 (1.1%)	<0.0001
Outcomes			
Survival to hospital admission	850 (21.1%)	21233 (15.4%)	<0.0001
Survival to hospital discharge	248 (6.1%)	5179 (3.8%)	<0.0001
One-year survival	193 (4.8%)	4621 (3.4%)	<0.0001

* SD = standard deviation.
† Urbanization levels: the urbanization level of inhabitants were categorized into 4 levels. The level 1 was the most urbanized area and level 4 was the most rural area.

Table 3
Baseline characteristics, managements and outcomes of patients with/without statin use after matching

Variables	After propensity score matching		
	Statin n = 4,028	No statin n = 12,084	p Value
Mean age, (SD)*, (year)	69.5 (11.8)	70.3 (14.2)	0.001
Male	2317 (57.5%)	6872 (56.9%)	0.485
Urbanization levels†			0.965
1	1137 (28.2%)	3414 (27.4%)	
2	1796 (44.6%)	5486 (45.4%)	
3	291 (7.2%)	839 (6.9%)	
4 (Rural)	804 (20.0%)	2445 (20.2%)	
Charlson comorbidity index, (SD)	5.9 (2.4)	6.0 (2.7)	0.008
Medication			
Antiplatelet agents	1862 (46.2%)	5443 (45.0%)	0.191
Angiotensin converting enzyme inhibitors	583 (14.5%)	1803 (14.9%)	0.489
Angiotensin receptor blockers	874 (21.7%)	2485 (20.5%)	0.125
β-blockers	1255 (31.2%)	3673 (30.4%)	0.364
Comorbidities			
Diabetes mellitus	2527 (62.7%)	7831 (64.8%)	0.018
Hypertension	2985 (74.1%)	9276 (76.8%)	0.001
Coronary artery disease	1912 (47.5%)	5543 (45.9%)	0.078
Congestive heart failure	937 (23.3%)	2745 (22.7%)	0.475
Atrial fibrillation	241 (6.0%)	773 (6.4%)	0.349
Chronic kidney disease	628 (15.6%)	1897 (15.7%)	0.871
Malignancy	246 (6.1%)	794 (6.6%)	0.300
Chronic obstructive pulmonary disease	467 (11.6%)	1454 (12.0%)	0.457
Asthma	221 (5.5%)	704 (5.8%)	0.423
Year of resuscitation			0.897
2004	335 (8.3%)	988 (8.2%)	
2005	378 (9.4%)	1144 (9.5%)	
2006	448 (11.1%)	1425 (11.8%)	
2007	533 (13.2%)	1515 (12.5%)	
2008	579 (14.4%)	1761 (14.6%)	
2009	548 (13.6%)	1667 (13.8%)	
2010	609 (15.1%)	1782 (14.8%)	
2011	598 (14.9%)	1802 (14.9%)	
Shockable rhythm	1062 (26.4%)	2637 (21.8%)	<0.0001
Resuscitation in medical center	1128 (28.0%)	2764 (23.0%)	<0.0001
Managements			
Epinephrine	3903 (96.9%)	11628 (96.2%)	0.048
Epinephrine dose (SD), mg	9.80 (6.9)	9.39 (6.7)	0.001
Amiodarone	519 (12.9%)	1118 (9.25%)	<0.0001
Lidocaine	179 (4.4%)	396 (3.3%)	0.001
Coronary angiography	113 (2.8%)	168 (1.4%)	<0.0001
Outcomes			
Survival to hospital admission	850 (21.1%)	2073 (17.2%)	<0.0001
Survival to hospital discharge	245 (6.1%)	514 (4.3%)	<0.0001
One-year survival	193 (4.8%)	386(3.2%)	<0.0001

* SD = standard deviation.
† Urbanization levels: the urbanization level of inhabitants were categorized into 4 levels. The level 1 was the most urbanized area and level 4 was the most rural area.

respectively), and 1-year survival (adjusted OR: 1.42, 95% CI 1.04 to 1.94, p = 0.028, and adjusted OR: 1.43, 95% CI 1.15 to 1.79, p = 0.002, respectively) compared to the never statin control group in multiple logistic regression model analysis (Figure 2).

Subgroup analyses were performed to investigate the interactions among previous statin use, comorbidities, and resuscitation variables. A favorable outcome effect of statin on 1-year survival was observed in the presence of diabetes mellitus (adjusted OR: 1.83 vs 1.14, p-value of interaction = 0.010), chronic kidney disease (adjusted OR: 2.61 vs 1.36, p-value of interaction = 0.005), and CCI score greater than 5 (OR: 2.00 vs 1.19, p-value of interaction = 0.004) (Figure 3). The remaining subgroups did not show significantly different effects of statin use on 1-year survival outcomes.

Discussion

The main finding in the PS-matched analysis was that previous use of statins was associated with better outcomes

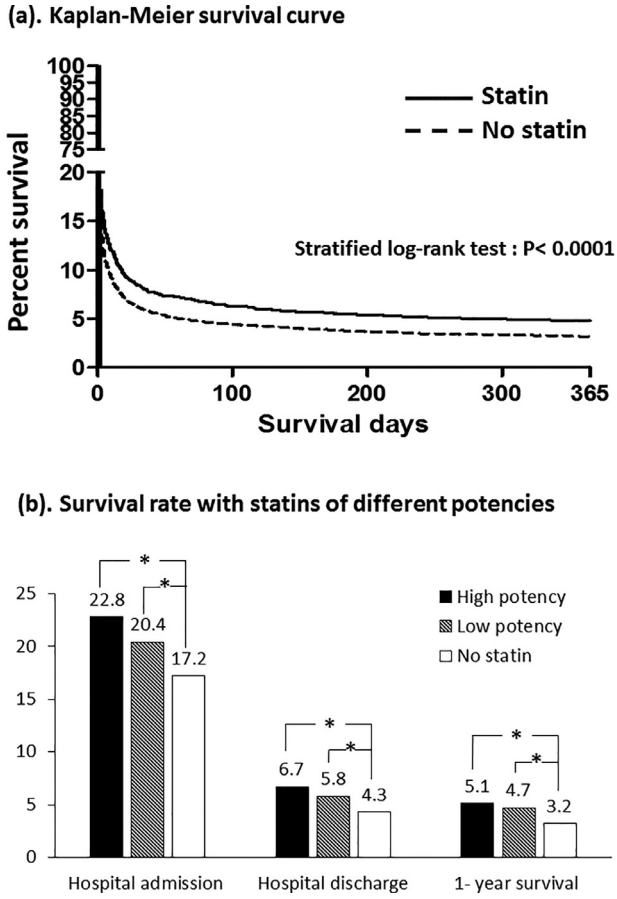


Figure 2. One-year survival outcomes in the statin and never statin groups. *(A)* Kaplan-Meier survival curves of statin and never statin groups. *(B)* One-year survival rates of patients receiving different potencies of statins (*p <0.05 by stratified log-rank test). Both the high-potency group (n = 1,150) and the low-potency group (n = 2,878) had better chances of survival to hospital admission (both p <0.0001), survival to discharge (p = 0.015 and 0.005, respectively), and 1-year survival (p = 0.028 and p = 0.002, respectively) compared to the never statin control group (n = 12,084) in multiple logistic regression model analysis.

of survival to admission, survival to hospital discharge, and 1-year survival. When adjusted in the multiple logistic regression model, the use of statins before an event was still an independent factor associated with improved 1-year survival outcomes. One strength of the study is the nationwide scale of the cohort, which included an adequate number of cardiac arrest patients in the analysis. PS matching helped to eliminate the effects of confounding variables when evaluating observational data.[18] Survival, which was followed for 1 year, provides more valuable information about long-term outcomes for cardiac arrest patients than outcomes only at hospital discharge. Additionally, the beneficial effects of previous statin treatment were consistent across different subgroups of patients, as well as between patients who received high-potency and low-potency statins.

The effects of previous statin use on survival outcomes in cardiac arrest patients is a novel issue. Cardiac arrest patients experience sepsis-like syndrome after successful initial resuscitation,[10] and as many as 70% of patients experience infection after cardiac arrest and resuscitation.[19] Several studies have focused on the effects of statin use on outcomes of sepsis and septic shock. Statin treatment before the sepsis event is associated with less severe sepsis and better outcomes of survival to hospital discharge and 1-year survival.[4,5,20] Statin pretreatment can reduce sepsis-related cytokine production, inflammatory cell activation, and overproduction of reactive oxygen species. Excessive vasodilation and circulatory collapse can be mitigated and cardiac output can be preserved with statin treatment.[21,22] However, the de novo administration of statins after the sepsis event has shown no benefit in several randomized trials.[2,3,23,24] The activation of cytokines after cardiac arrest could be at the time point of hospital admission whereas sepsis-like syndrome would keep going hours or days after the events. The saves associated with statin use may relate to the modulating of cytokine over-activation and subsequent sepsis-like syndrome. These findings support the beneficial effects of statin pretreatment against sepsis-related pathophysiological injuries from cardiac arrest.

Cardiac arrest patients experience postcardiac arrest syndrome, which may include more complicated pathophysiological changes than sepsis alone. The cessation of blood circulation and a probable acute coronary event lead to ischemia reperfusion injuries in major organs, including the brain and heart. According to several reports, the beneficial effects of statin use before ischemia-related brain injuries include a milder stroke severity and 58% lower mortality.[9] According to the Global Registry of Acute Coronary

Table 4
Univariate and multivariate analyses of variables for 1-year survival in propensity score-matched groups

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, pear year	0.98 (0.97−0.98)	<0.0001*	0.98 (0.97−0.99)	<0.0001*
Male	0.99 (0.84−1.18)	0.919	0.85 (0.71−1.02)	0.084
History of medication use				
Statins	1.53 (1.27−1.82)	<0.0001*	1.41 (1.16−1.71)	0.001*
Antiplatelet agents	0.89 (0.75−1.06)	0.187		
Angiotensin-converting enzyme inhibitors	0.69 (0.52−0.91)	0.007*	0.71 (0.53−0.94)	0.019*
Angiotensin receptor blockers	1.32 (1.08−1.60)	0.005*	1.24 (1.00−1.55)	0.050*
Beta-blockers	1.40 (1.17−1.66)	0.0001*	1.41(1.16−1.72)	0.001*
Urbanization level				
1	1.28 (1.00−1.63)	0.048*	1.32 (0.99−1.75)	0.061
2	1.01 (0.80−1.27)	0.959	1.00 (0.77−1.30)	0.975
3	1.37 (0.97−1.94)	0.070	1.47 (1.01−2.13)	0.044*
4 (rural)	1		1	
Charlson comorbidity index	0.88 (0.85−0.91)	<0.0001*	0.91(0.87−0.95)	<0.0001*
History of comorbidities				
Diabetes mellitus	0.81 (0.68−0.96)	0.013*		
Hypertension	0.84 (0.69−1.02)	0.065		
Coronary artery disease	0.96 (0.81−1.14)	0.616		
Congestive heart failure	0.68 (0.54−0.85)	0.001*		
Atrial fibrillation	0.66 (0.42−1.00)	0.046*		
Chronic kidney disease	1.06 (0.84−1.33)	0.620		
Malignancy	0.62 (0.39∼0.93)	0.021*		
Chronic obstructive pulmonary disease	0.60 (0.43−0.82)	0.001*		
Asthma	0.83 (0.54−1.22)	0.340		
Year of resuscitation				
2004	1		1	
2005	1.04 (0.70−1.54)	0.857	0.98 (0.65−1.48)	0.924
2006	1.12 (0.77−1.62)	0.561	0.91(0.61−1.35)	0.635
2007	1.05 (0.72−1.52)	0.811	0.84 (0.56−1.24)	0.370
2008	0.79 (0.54−1.15)	0.220	0.58 (0.38−0.87)	0.008*
2009	1.12 (0.78−1.61)	0.528	0.89 (0.61−1.32)	0.565
2010	1.00 (0.70−1.44)	0.997	0.72 (0.49−1.07)	0.100
2011	1.02 (0.71−1.47)	0.910	0.70 (0.47−1.04)	0.079
Shockable rhythm	1.55 (1.29−1.86)	<0.0001*	1.10 (0.87−1.41)	0.425
Resuscitation in medical center	1.47 (1.22−1.77)	<0.0001*	1.10 (0.88−1.37)	0.420
Epinephrine dose (per mg)	0.81 (0.79−0.83)	<0.0001*	0.82 (0.80−0.84)	<0.0001*
Amiodarone	2.31(1.85−2.86)	<0.0001*	1.84 (1.36−2.49)	<0.0001*
Lidocaine	2.51 (1.80−3.43)	<0.0001*	1.75 (1.18−2.59)	0.005*
Coronary angiography	31.52 (24.26−40.86)	<0.0001*	13.84 (10.23−18.71)	<0.0001*

CI = confidence interval; OR = odds ratio.

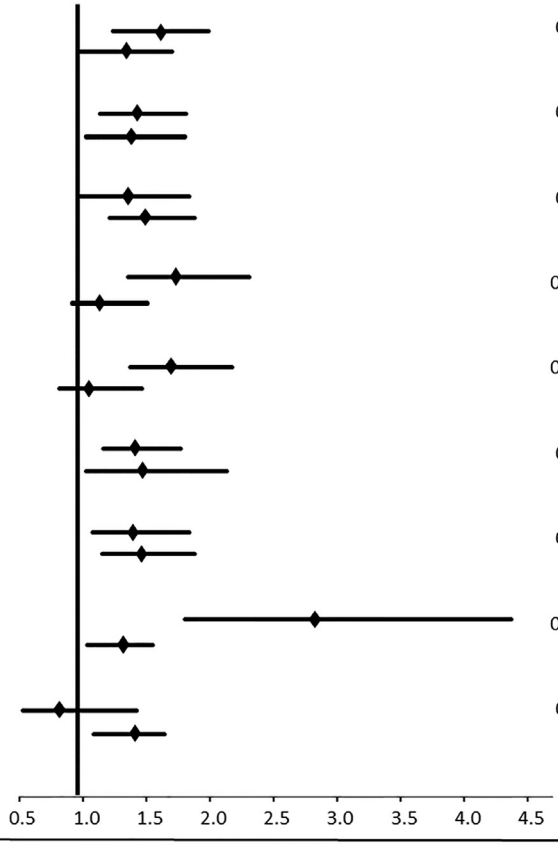
* p value <0.05.All factors on univariate analyses were included in multivariate analyses. Backward selection was used until a variable's p value was less than 0.1 in multivariate regression.

Events, pretreatment with statins is associated with a 21% reduction in the risk of ST segment elevation and a 22% reduction in the risk of myocardial infarction with acute coronary syndrome.[25] Experimental studies have shown that statin treatment decreases lipid oxidation and vascular inflammation, upregulates endothelial nitric oxide synthase, protects the myocardial ischemia reperfusion injuries, and promotes vascular fibrinolysis after plaque rupture.[26–28] These biologic effects of statins can be helpful in cardiac arrest patients who experience endothelial dysfunction, disturbance of the coagulation system, and impaired microcirculation.[29]

The study has some limitations. Detailed and personal data for every instance of CPR in the registry data was not available, although nonbiased and broad records were collected and reviewed for this nationwide cohort study. Resuscitation variables at the scene were not assessable in the NHI research database. However, the use of statins with different potencies before cardiac arrest events were not related to the occurrence of the cardiac arrest events and the performance of resuscitation efforts. The study evaluated a homogenous Asian population, so caution is advised in extrapolating results to other races. Another issue is that neurologic outcomes of subjects who survived out-of-hospital cardiac arrest are unknown. Reportedly, the chance of 1 year survival after cardiac arrest was higher in patients with favorable neurologic outcomes at hospital discharge.[30] As the primary end point of this study, 1-year survival rate should correlate well with favorable functional neurologic outcome.

In conclusion, statin use before cardiac arrest is associated with 1-year survival in a PS-matched nationwide

Characteristics	Statin No. of event/No. of patients	Non-statin No. of event/No. of patients	Adjusted[1] Odds ratio (95% CI)	Interaction p value
Gender				
Male	113/2316	218/6872	1.57 (1.23~1.98)	0.309
Female	80/1711	189/5209	1.30 (0.98~1.71)	
Age				
<70	117/1885	222/5019	1.43 (1.13~1.81)	0.806
>=70	76/2142	185/7062	1.37 (1.03~1.80)	
Shockable rhythm				
Yes	60/1061	136/3127	1.32 (0.95~1.82)	0.493
No	133/2966	271/8954	1.50 (1.21~1.87)	
Charlson comorbidity index				
>5	94/2099	175/6823	1.78 (1.36~2.31)	0.020*
<=5	99/1928	232/5258	1.17 (0.91~1.50)	
Diabetes mellitus				
Yes	126/2526	228/7722	1.73 (1.37~2.17)	0.013*
No	67/1501	179/4359	1.09 (0.81~1.46)	
Hypertension				
Yes	143/2985	315/9288	1.43 (1.16~1.76)	0.878
No	50/1042	92/2793	1.48 (1.02~2.13)	
Coronary artery disease				
Yes	87/1911	183/5601	1.41 (1.08~1.84)	0.815
No	106/2116	224/6480	1.47 (1.15~1.87)	
Chronic kidney disease				
Yes	43/628	49/1928	2.82 (1.81~4.38)	0.001*
No	150/3399	358/10153	1.26 (1.03~1.54)	
Coronary angiography				
Yes	56/113	92/171	0.84 (0.51~1.40)	0.082
No	137/3914	315/11910	1.34 (1.08~1.64)	



1. Adjusted for propensity score; 2. Asterisk (*) means p value < 0.05

Figure 3. Subgroup analysis for interactions among statin use before cardiac arrest, clinical characteristics, and 1-year survival (*p <0.05).

cohort study. These findings may provide opportunities for improving long-term outcomes in cardiac arrest patients.

Disclosures

The authors declare that they have no competing interests.

1. Albert MA, Danielson E, Rifai N, Ridker PM. Investigators P. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001;286:64–70.
2. Kruger P, Bailey M, Bellomo R, Cooper DJ, Harward M, Higgins A, Howe B, Jones D, Joyce C, Kostner K, McNeil J, Nichol A, Roberts MS, Syres G, Venkatesh B. Group AN-SI-ACT. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. *Am J Respir Crit Care Med* 2013;187:743–750.
3. National Heart L, Blood Institute ACTN, Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, Brower RG, Shanholtz C, Rock P, Douglas IS, deBoisblanc BP, Hough CL, Hite RD, Thompson BT. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014;370:2191–2200.
4. Hackam DG, Mamdani M, Li P, Redelmeier DA. Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis. *Lancet* 2006;367:413–418.
5. Ou SY, Chu H, Chao PW, Ou SM, Lee YJ, Kuo SC, Li SY, Shih CJ, Chen YT. Effect of the use of low and high potency statins and sepsis outcomes. *Intensive Care Med* 2014;40:1509–1517.
6. Fernandez R, De Pedro VJ, Artigas A. Statin therapy prior to ICU admission: protection against infection or a severity marker? *Intensive Care Med* 2006;32:160–164.
7. Fonarow GC, Wright RS, Spencer FA, Fredrick PD, Dong W, Every N, French WJ. National Registry of Myocardial Infarction I. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality. *Am J Cardiol* 2005;96:611–616.
8. Mytas D, Zairis M, Karanasos A, Kosma L, Arsenos P, Tentolouris C, Pitsavos C, Foussas S, Stefanadis C, Cokkinos D. Effect of statin pretreatment on the outcome of ST-segment elevation myocardial infarction in patients without prior history of coronary artery disease. *Hellenic J Cardiol* 2013;54:422–428.
9. Hong KS, Lee JS. Statins in acute ischemic stroke: a systematic review. *J Stroke* 2015;17:282–301.
10. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. *Circulation* 2002;106:562–568.
11. Cheng SH, Chiang TL. The effect of universal health insurance on health care utilization in Taiwan. Results from a natural experiment. *JAMA* 1997;278:89–93.
12. Shih CJ, Chu H, Chao PW, Lee YJ, Kuo SC, Li SY, Tarng DC, Yang CY, Yang WC, Ou SM, Chen YT. Long-term clinical outcome of major adverse cardiac events in survivors of infective endocarditis: a nationwide population-based study. *Circulation* 2014;130:1684–1691.
13. Lin YJ, Tian WH, Chen CC. Urbanization and the utilization of outpatient services under National Health Insurance in Taiwan. *Health Policy* 2011;103:236–243.
14. Charlson ME, Sax FL, MacKenzie CR, Fields SD, Braham RL, Douglas RG Jr. Resuscitation: how do we decide? A prospective

study of physicians' preferences and the clinical course of hospitalized patients. *JAMA* 1986;255:1316–1322.
15. Huang CH, Yu PH, Tsai MS, Chuang PY, Wang TD, Chiang CY, Chang WT, Ma MH, Tang CH, Chen WJ. Acute hospital administration of amiodarone and/or lidocaine in shockable patients presenting with out-of-hospital cardiac arrest: a nationwide cohort study. *Int J Cardiol* 2017;227:292–298.
16. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr., Tomaselli GF. American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:S1–45.
17. Tsai MS, Chuang PY, Yu PH, Huang CH, Tang CH, Chang WT, Chen WJ. Glucocorticoid use during cardiopulmonary resuscitation may be beneficial for cardiac arrest. *Int J Cardiol* 2016;222:629–635.
18. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.
19. Tsai MS, Chiang WC, Lee CC, Hsieh CC, Ko PC, Hsu CY, Su CP, Chen SY, Chang WT, Yuan A, Ma MH, Chen SC, Chen WJ. Infections in the survivors of out-of-hospital cardiac arrest in the first 7 days. *Intensive Care Med* 2005;31:621–626.
20. Liappis AP, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. *Clin Infect Dis* 2001;33:1352–1357.
21. Merx MW, Liehn EA, Janssens U, Lutticken R, Schrader J, Hanrath P, Weber C. HMG-CoA reductase inhibitor simvastatin profoundly improves survival in a murine model of sepsis. *Circulation* 2004;109:2560–2565.
22. Almog Y, Shefer A, Novack V, Maimon N, Barski L, Eizinger M, Friger M, Zeller L, Danon A. Prior statin therapy is associated with a decreased rate of severe sepsis. *Circulation* 2004;110:880–885.
23. Deshpande A, Pasupuleti V, Rothberg MB. Statin therapy and mortality from sepsis: a meta-analysis of randomized trials. *Am J Med* 2015;128:410–417. e411.
24. Brealey DA, Singer M, Terblanche M. Potential metabolic consequences of statins in sepsis. *Crit Care Med* 2011;39:1514–1520.
25. Spencer FA, Allegrone J, Goldberg RJ, Gore JM, Fox KA, Granger CB, Mehta RH, Brieger D, Investigators G. Association of statin therapy with outcomes of acute coronary syndromes: the GRACE study. *Ann Intern Med* 2004;140:857–866.
26. Koh KK, Son JW, Ahn JY, Jin DK, Kim HS, Choi YM, Kim DS, Jeong EM, Park GS, Choi IS, Shin EK. Comparative effects of diet and statin on no bioactivity and matrix metalloproteinases in hypercholesterolemic patients with coronary artery disease. *Arterioscler Thromb Vasc Biol* 2002;22:e19–e23.
27. Laufs U, Gertz K, Huang P, Nickenig G, Bohm M, Dirnagl U, Endres M. Atorvastatin upregulates type III nitric oxide synthase in thrombocytes, decreases platelet activation, and protects from cerebral ischemia in normocholesterolemic mice. *Stroke* 2000;31:2442–2449.
28. Bell RM, Yellon DM. Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway. *J Am Coll Cardiol* 2003;41:508–515.
29. Bro-Jeppesen J, Johansson PI, Hassager C, Wanscher M, Ostrowski SR, Bjerre M, Kjaergaard J. Endothelial activation/injury and associations with severity of post-cardiac arrest syndrome and mortality after out-of-hospital cardiac arrest. *Resuscitation* 2016;107:71–79.
30. Maynard C, Longstreth WT Jr., Nichol G, Hallstrom A, Kudenchuk PJ, Rea T, Copass MK, Carlbom D, Deem S, Olsufka M, Cobb LA, Kim F. Effect of prehospital induction of mild hypothermia on 3-month neurological status and 1-year survival among adults with cardiac arrest: long-term follow-up of a randomized, clinical trial. *J Am Heart Assoc* 2015;4:e001693.