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Association of statin therapy with ventricular arrhythmias among patients with acute coronary syndrome

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ABSTRACT

Background In addition to lowering cholesterol, statins stabilise atherosclerotic plaques and can potentially reduce the incidence of ventricular arrhythmias. We tested the hypothesis that prior statin therapy is associated with a lower incidence of inhospital ventricular arrhythmias among patients with acute coronary syndrome (ACS).

Methods The study population consisted of 2007 patients (mean age 64 years, 67.5% male) enrolled in the Thai Registry of Acute Coronary Syndrome, a prospective, multicentre, nationwide, observational study of patients with ACS. Patients were categorised as either statin users or non-users according to their reports of statin use before enrolment at their initial presentation. The primary endpoint was inhospital ventricular arrhythmias. The secondary endpoint was a composite endpoint of inhospital ventricular arrhythmias or inhospital cardiac death. A propensity-adjusted multivariate model was developed to assess the effects of statin use on the primary and secondary endpoints.

Results During a mean hospital stay of 7 days, a total of 96 patients (4.8%) died; 82 (4.1%) of the deaths were due to cardiac causes. The primary and secondary endpoints were reached in 163 patients (8.1%) and 194 patients (9.7%), respectively. A total of 525 patients (26.2%) had used statins prior to hospitalisation. After adjusting for the propensity scores and other relevant covariates, statin use was associated with lower risks of the primary (adjusted OR 0.505, 95% CI 0.276 to 0.923) and secondary endpoints (adjusted OR 0.498, 95% CI 0.276 to 0.897).

Conclusions The use of statins is associated with a reduced incidence of ventricular arrhythmias among patients with ACS.

INTRODUCTION

Previous studies have demonstrated that statins may possess antiarrhythmic properties[1 2] in addition to their lipid-lowering effect. Statins have been shown to stabilise atherosclerotic plaques, regulate the autonomic nervous system and reduce repolarisation heterogeneity.[2–6] Data from the Multicenter Automatic Defibrillator Implantation Trial II study indicated that statins were associated with a lower incidence of ventricular arrhythmias (VAs).[7]

The outcomes of patients with acute coronary syndrome (ACS) have markedly improved over the past decade.[8] However, the outcome of VAs during ACS remains extremely poor. VAs in ACS patients are associated with a 10-fold increase in inhospital mortality and a more than fivefold increase in 6-month mortality.[9 10]

The Thai Registry of ACS (TRACS) is a registry of 2007 patients with ACS. We examined the data from TRACS to determine whether prior statin use would reduce the incidence of inhospital VAs.

METHODS

TRACS is a multicentre, prospective, nationwide observational cohort study of adult patients (age ≥18 years) hospitalised for ACS. The study design and the inclusion and exclusion criteria have been described elsewhere.[11] Briefly, 39 hospitals in Thailand, private and government owned, voluntarily participated in the registry. Each hospital had to enrol 50–80 consecutive patients. Data regarding baseline characteristics, outcomes and events during hospitalisation were collected and centrally managed via a web-based application. Patients were categorised as statin users or non-users based on their reports of statin use of at least 7 days before the enrolment. The primary endpoint was VA, and the secondary endpoint was a composite endpoint of VA or cardiac death. The endpoints were not prespecified prior to the enrolment. The study received approval from the ethics committee of each participating hospital.

Definitions

ACS was diagnosed on the basis of the presence of chest pain lasting more than 20 min, an ECG change consistent with ACS or other symptoms that the participating physicians determined to be related to ACS. The onset of symptoms had to be within 14 days of admittance to the hospital.

ST segment elevation myocardial infarction (STEMI) was diagnosed on the basis of the presence of new or presumably new ST segment elevations >1 mm in two consecutive leads or the presence of a new left bundle branch block on the index or subsequent ECG with positive cardiac markers of necrosis. Non-STEMI (NSTEMI) was defined as the presence of positive cardiac markers of necrosis without new ST segment elevations on the index or subsequent ECG. Otherwise, when the cardiac markers were within normal ranges, unstable angina (UA) was diagnosed.

VAs included sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Sustained VA was defined as VA of 30 s or more or VA that resulted in haemodynamic instability.

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Statistical analysis

Pearson's χ^2 test and Student's t test were used to analyse differences between groups. A two-step approach was used to evaluate the effects of prior statin use on the primary and secondary endpoints. First, the probability of the patient being treated with statin-based therapy based on his/her pretreatment conditions was estimated with the propensity score method. The variables included in the model were age, sex, past medical history (myocardial infarction, congestive heart failure, stroke, diabetes, hypertension, dyslipidaemia, dysrhythmia and chronic kidney disease), smoking history (current smoker, ex-smoker or non-smoker) and medication use (aspirin, clopidogrel, β blockers, angiotensin-converting enzyme inhibitors and antiarrhythmic agents). Second, the effects of statin use on the primary and secondary outcomes were evaluated using a multivariate binary logistic regression analysis. The model was adjusted using the propensity score and the following relevant covariates: age, sex, type of ACS (STEMI, NSTEMI or UA), troponin T, the left ventricular ejection fraction, the presence of heart failure and the type of revascularisation (thrombolytic therapy, percutaneous coronary intervention or coronary bypass graft). ORs and 95% CIs were calculated. A p value ≤0.05 was considered statistically significant. All the analyses were performed using SPSS V.13.0 (IBM Corporation, USA).

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RESULTS

A total of 2007 patients (mean age 63.5 years, 67.5% male) were enrolled in the study. The most common type of ACS was STEMI (54%), followed by NSTEMI (32.4%) and UA (13.6%). There were 525 patients (26.2%) who had used statins prior to hospitalisation. The characteristics of the statin users and non-users are summarised in table 1. The statin users were older, had more medical illnesses, and had higher rates of aspirin, β blocker and angiotensin-converting enzyme inhibitor use. Compared with the non-users, the statin users were less likely to develop STEMI, to receive thrombolytic therapy or to undergo percutaneous coronary intervention.

Table 1 Characteristics of the statin users and non-users (N=2007)

Variables	Statin users (N=525)	Non-users (N=1482)	p Value
Mean Age	66.7±10.8	62.4±13.3	<0.0001
Male	309 (58.9%)	1046 (70.6%)	<0.0001
Previous MI	202 (38.5%)	111 (7.5%)	<0.0001
Peripheral arterial disease	8 (1.5%)	9 (0.6%)	0.13
Congestive heart failure	164 (31.2%)	100 (6.7%)	<0.0001
Ischaemic stroke	61 (11.6%)	66 (3.8%)	<0.0001
Diabetes	322 (61.3%)	696 (47%)	<0.0001
Hypertension	436 (83.0%)	759 (51.2%)	<0.0001
Dysrhythmia	28 (5.3%)	40 (2.7%)	0.02
Chronic renal failure	115 (21.9%)	78 (5.3%)	<0.0001
Current smoker	72 (13.7%)	572 (38.6%)	<0.0001
Medications used prior to the hospitalisation			
Aspirin	386 (73.5%)	170 (11.5%)	<0.0001
Clopidogrel	122 (23.2%)	29 (2.0%)	<0.0001
β Blocker	264 (50.3%)	138 (9.3%)	<0.0001
ACEI	191 (36.4%)	114 (7.7%)	<0.0001
Antiarrhythmic agent	8 (1.5%)	5 (0.3%)	0.004
Type of MI			<0.0001
STEMI	151 (28.8%)	951 (64.2%)	
NSTEMI	258 (49.1%)	406 (27.4%)	
Unstable angina	116 (22.1%)	125 (8.4%)	
Heart rate (beats/min)	85.4±23.2	82.3±24.7	0.02
Systolic blood pressure (mm Hg)	135.6±35.8	127.2±34.7	<0.0001
Diastolic blood pressure (mm Hg)	78.9±20.7	75.8±21.5	0.005
Troponin T (ng/ml)	1.56±3.7	2.79±5.4	<0.0001
CKMB (ng/ml)	46.7±89	109.3±156	<0.0001
Ejection fraction (%)	49.2±15	48.7±14	0.68
Medications used during the hospitalisation			
Aspirin	517 (98.5%)	1465 (98.9%)	0.504
Clopidogrel	399 (76.0%)	1173 (79.1%)	0.132
β Blocker	275 (52.4%)	741 (50%)	0.361
ACEI	262 (49.9%)	782 (52.7%)	0.2647
Antiarrhythmic agent	52 (9.9%)	146 (9.9%)	0.972
Thrombolytics Administered	41 (7.8%)	433 (29.22%)	<0.0001
PCI performed	148 (28.2%)	520 (35.1%)	0.004
CABG	25 (4.8%)	37 (2.5%)	0.01

ACEI, ACE inhibitors; CABG, coronary artery bypass graft; CKMB, creatine kinase MB isoenzyme; MI, myocardial infarction; NSTEMI, non-ST segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST segment elevation MI.

Inhospital outcomes

During the indexed hospitalisation (mean length of stay 7.4 ±8 days), 96 patients (4.8%) died; 82 of the deaths were due to cardiac causes. VA occurred in 163 patients (8.1%) and was more frequent among patients with STEMI and low ejection fractions (table 2). The mortality rate was higher among the patients with VA than those without VA (25.2% vs 2.9%, p<0.0001; table 2).

The primary endpoint and the secondary composite endpoint were reached in 163 (8.1%) and 194 (9.7%) patients, respectively. The incidences of both endpoints were significantly lower among the statin users (table 3).

A propensity-adjusted multivariate analysis revealed that statin use prior to hospitalisation for ACS was associated with lower risks of the primary (adjusted OR 0.505, 95% CI 0.276 to 0.923) and secondary endpoints (adjusted OR 0.498, 95% CI 0.276 to 0.897) (table 4).

DISCUSSION

In this study, the benefit of statin use for reducing VA was investigated in a large, nationwide cohort of patients with ACS. The statin users were sicker than the non-users. NSTEMI was the most common type of ACS among the statin users at the time of presentation at the hospital. After adjusting for the conditional probability of being treated with statins and the impacts of the background covariates on the endpoints, previous statin use was associated with greater than 40% decreases in the risks of VA and the composite endpoint of VA or cardiac death. VA among patients with ACS was associated with high incidences of inhospital cardiac death and death from any cause. Although statin use was not associated with a significant reduction in all-cause mortality or cardiovascular mortality, we did observe a decreasing trend.

Prior studies have shown an antiarrhythmic benefit of statin use in various settings. In animals, statin use shortened the

Table 2 Comparison of patients with and without inhospital ventricular arrhythmias

Variables	No VA (N=1844)	VA (N=163)	p Value
Statin users	496 (26.9%)	29 (17.8%)	0.01
Thrombolytics administered	46 (28.2%)	428 (23.2%)	0.31
Ejection fraction (%)	49.4±14.6	43.99±14.9	0.0001
Type of ACS			<0.0001
STEMI	967 (52.4%)	116 (71.2%)	
NSTEMI	608 (33.0%)	42 (25.8%)	
Unstable angina	269 (14.6%)	5 (3.1%)	
Inhospital death	55 (2.9%)	41 (25.2%)	<0.0001
Inhospital cardiac death	46 (2.5%)	36 (22.1%)	<0.0001

ACS, acute coronary syndrome; NSTEMI, non-STEMI; STEMI, ST segment elevation myocardial infarction; VA, ventricular arrhythmias.

duration of the action potential and suppressed trigger activity, thereby reducing the incidence of VAs.[5 6] In the Multicenter Automatic Defibrillator Implantation Trial II[7] and Sudden Cardiac Death in Heart Failure Trial studies,[12] statin use was associated with a decrease in implantable cardioverter defibrillator therapy for VT/VF. In the Global Registry of Acute Coronary Events (GRACE), a large cohort of patients admitted with ACS to hospitals in North America, South America, Europe, Australia and New Zealand, prior statin use was associated with lower risks of atrial fibrillation, atrial flutter, VT/VF and cardiac arrest. Limited data, however, was available in Asian population.

In this study, the presence of VA among patients with ACS was shown to be an independent predictor of inhospital mortality. Statin use was associated with a lower risk of VA (OR 0.505) compared with that observed in the GRACE study (OR 0.81). One possible explanation for this difference is that only half of the statin users in our study were receiving β blockers, and less than half were on angiotensin-converting enzyme inhibitors. In the GRACE study, more than 70% of the statin users were receiving β blockers, and more than 50% were on angiotensin-converting enzyme inhibitors. The incremental benefit of statin use found in our study is therefore likely to be more pronounced than that was observed in GRACE study.

Study limitations

A non-randomised study such as ours may be subject to selection bias. Several characteristics of the statin users were significantly different from those of the non-users. To correct for this imbalance between the groups, a propensity-adjusted multivariate analysis was used. However, the associations between statin use and the endpoints may have been confounded by other, uncontrolled factors. In addition, the effects of statins may depend on the type, dose and duration of statin use; these data were not collected in this study.

Table 3 Inhospital outcomes according to previous statin use (N=2007)

Outcome	Statin users (N=525)	Non-users (N=1482)	p Value
Inhospital death	20 (3.9%)	76 (5.1%)	0.187
Inhospital cardiac death	16 (3.1%)	66 (4.5%)	0.136
Primary endpoint (inhospital ventricular arrhythmias)	29 (5.5%)	134 (9%)	0.011
Secondary endpoint (inhospital ventricular arrhythmias or inhospital cardiac death)	35 (6.7%)	159 (10.7%)	0.004

Table 4 ORs and 95% CIs for the primary and secondary endpoints

	Unadjusted OR (95% CI, p value)	Adjusted OR* (95% CI, p value)
Primary endpoint	0.099 (0.083 to 0.119, p<0.0001)	0.505 (0.276 to 0.923, p=0.026)
Secondary endpoint	0.128 (0.109 to 0.151, p<0.0001)	0.498 (0.276 to 0.897, p=0.020)

*Adjusted for propensity score, age, sex, type of acute coronary syndrome, troponin T, the left ventricular ejection fraction, the presence of heart failure and the type of revascularisation.

Conclusions

VAs among patients with ACS are associated with an increased mortality rate. The use of statins appeared to have a protective effect against VAs.

Contributors SA wrote the statistical analysis plan, analysed the data and drafted and revised the paper. PS designed data collection tools, monitored data collection for the whole trial and revised the draft paper. TN, CS and PK drafted and revised the paper.

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Competing interests None.

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