LIST OF PUBLICATIONS

Study I

Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, Phrommintikul A. Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency. Ther Clin Risk Manag. 2015;11:127-136.

Study II

Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, Phrommintikul A. Low-density lipoprotein cholesterol of less than 70 mg/dL is associated with fewer cardiovascular events in acute coronary syndrome patients: a real-life cohort in Thailand. Ther Clin Risk Manag. 2015;11:659-667.

Study III

Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, Phrommintikul A. Clinical indicators for recurrent cardiovascular events in acute coronary syndrome patients treated with statins under routine practice in Thailand: an observational study. BMC Cardiovasc Disord. 2015;15(1):55.

Appendices

Appendix A

Philosophical context of clinical epidemiology design in this thesis

Philosophical context of clinical epidemiologic study design in this thesis[1,2]

This part presents how the three studies were conducted based on the philosophical context of clinical epidemiologic study design.

Clinical epidemiology is epidemiology with the application of epidemiologic methods relevant to patient care.[1] The three components in study design in clinical epidemiology include 1) the theoretical design, 2) the design of data collection and 3) the design of data analysis.[1,2]

The first step of each clinical study is the theoretical design, in which a research question is formulated and translated to an occurrence relation. The elements in an occurrence relation comprise an outcome and determinants. Two types of occurrence relation: causal relation and descriptive relation. The causal relation research is to explain associations between one or more determinants and an outcome. Confounders play an important role in this type of research; therefore, adjustment of confounders is needed to reflect the true relationship between the determinants and an outcome. Thus, for causal association, the relationship between a determinant and an outcome must be present conditional on the existence of confounders. On the other hand, the descriptive relation research is aimed to predict rather than to explain. Confounders play no roles in a descriptive research; all determinants are acting for the best prediction of an outcome of interest. The occurrence relation showing the relationship between an outcome and determinants can be summarized in a mathematic function (f) as described below.[1,2]

A causal occurrence relation

Outcome = f (D|Confounders)

A descriptive occurrence relation

Outcome = f (D1 + D2 + D3+……)

(D is a determinant)

The second step in conducting a clinical research is the design of data collection - to design of the conceptual and operational collection of data to document the empirical occurrence relation in a study population. The last step is the design of data analysis, which includes a description of how data will be analyzed to reflect the relationship of determinants and an outcome.

Ethics approval of all of three studies was obtained from the Faculty of Medicine, Chiang Mai University, before commencement of the study.

Table 6.1: Summary of study design of three studies

Study	Type of study	Theoretical design (Occurrence relations)	Data collection	Data analysis
I	A therapeutic causal research	LDL-C goal attainment = f (Statin potency | confounders)	Data were retrospectively collected from medical records of ACS patients treated with statins from 2009-2011.	- Cox's Proportional regression analysis, stratified with spectrum of ACS and adjusted with propensity score
II	A prognostic causal research	First recurrent cardiovascular event = f (LDL-C goal attainment | confounders)	Data were retrospectively collected from medical records of ACS patients treated with statins from 2009-2012.	- Cox's Proportional regression analysis, stratified with spectrum of ACS.
III	A prognostic descriptive research	Recurrent cardiovascular events= f (LDL-C goal attainment +revascularization+ eGFR+sex+age+hypertension+ diabetes+ACEI/ARB)	Data were retrospectively collected from medical records of ACS patients treated with statins from 2009-2012.	- Ordinal logistic regression

Study I

Title: Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency

Theoretical design

The research questions were "What are success rate of ACS patients treated with statins in achieving LDL-C goal of <70 mg/dL?" and "What are the differences in effect of high potency statins versus low potency statins on LDL-C goal attainment (LDL-C<70 mg/dL) in ACS patients treated with statins?" This leads to the therapeutic causal research. The domain in this study comprised ACS patients hospitalized at Maharaj Nakorn Chiang Mai Hospital, otherwise known as Chiang Mai University (CMU) Hospital, who were treated with statin therapy for the secondary prevention of cardiovascular risk.

Study I was a therapeutic causal research aiming to assess the effect of high potency statins versus low potency statins on LDL-C goal attainment. This study is to explain causal relation between potency of statins and LDL-C goal attainment; thus, all potential confounding factors played crucial roles in this study design that needed to be adjusted. The occurrence relation of study I can be displayed as shown below.

LDL-C goal attainment = f (Statin potency | confounders)

The design of data collection

The study setting was CMU Hospital, which is part of Chiang Mai University. The hospital has 1,400 patient beds to serve 1,300,000 outpatients and 48,000 inpatients annually. This university-affiliated hospital serves patients in Chiang Mai Province (a population of approximately 1,600,000) as well as patients referred from 17 other provinces in northern Thailand.

All included patients in our cohort were those diagnosed with ACS – including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI) – aged at least 18 years, treated

with statin therapy, and admitted to the hospital from January 2009 to December 2011. An International Classification of Diseases, 10th Revision (ICD-10) code of I20 (angina pectoris) or I21 (acute myocardial infarction) was used to diagnose ACS at discharge.

This study was a retrospective cohort study. All relevant information of included patients was retrieved by a trained nurse and a researcher, from the medical records and hospital database.

The design of data analysis

The principal analysis was performed on patients, who were included from January 2009 to December 2011. We excluded 693 patients due to missing data on LDL-C levels either at baseline (during hospitalization or at discharge) or at first follow-up visit, or patients with LDL-C at baseline lower than 70 mg/dL (Figure 6.1). Finally, a total of 396 patients were included in the final analysis. A comparison between the two groups included and excluded from the final analysis was performed. We found no significant difference in most characteristics between the two groups, except for age.

The main interest was the causal relationship between potency of statins, high or low, and the LDL-C goal attainment; therefore, the potential confounders were adjusted with a covariate of propensity score. The potential confounders in this study were age, sex, diabetes mellitus, hypertension, serum creatinine, alanine aminotransferase, LDL-C at baseline, health insurance of patients, and smoking status. A retrospective cohort study such as this study is prone to have a problem of confounding by indication or contraindication. The propensity score methods could be used to control for these confounders. Thus, we used the propensity score to adjust for confounders with technique of covariate adjustment of propensity score. [3-5]

The steps of analysis are described below.

1. Describe characteristics of patients in the two groups, high or low potency statin groups, with descriptive statistics; the categorical variables were reported with counts and percentages, while the continuous variables were reported with means and standard deviations.

2. Compare the two groups with Fisher's exact test for categorical variables or the independent t-test for continuous variables.
3. Use logistic regression to calculate for a propensity score of each patient. A propensity score was generated to estimate the probability of receiving high or low potency statins. Variables included for estimation of the propensity score were age, sex, diabetes mellitus, hypertension, serum creatinine, alanine aminotransferase, LDL-C at baseline, health insurance of patients, and smoking status.
4. Univariable Cox proportional hazard regression stratified by spectrum of ACS at discharge was carried out. Then multivariable Cox proportional hazard regression stratified by spectrum of ACS at discharge, and adjusted with the propensity score was performed to assess the effect of potency of statins on LDL-C goal attainment.
5. In all cases, the statistical significance level was set as two-tailed and at a P-value <0.05.
6. Stata version 12.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

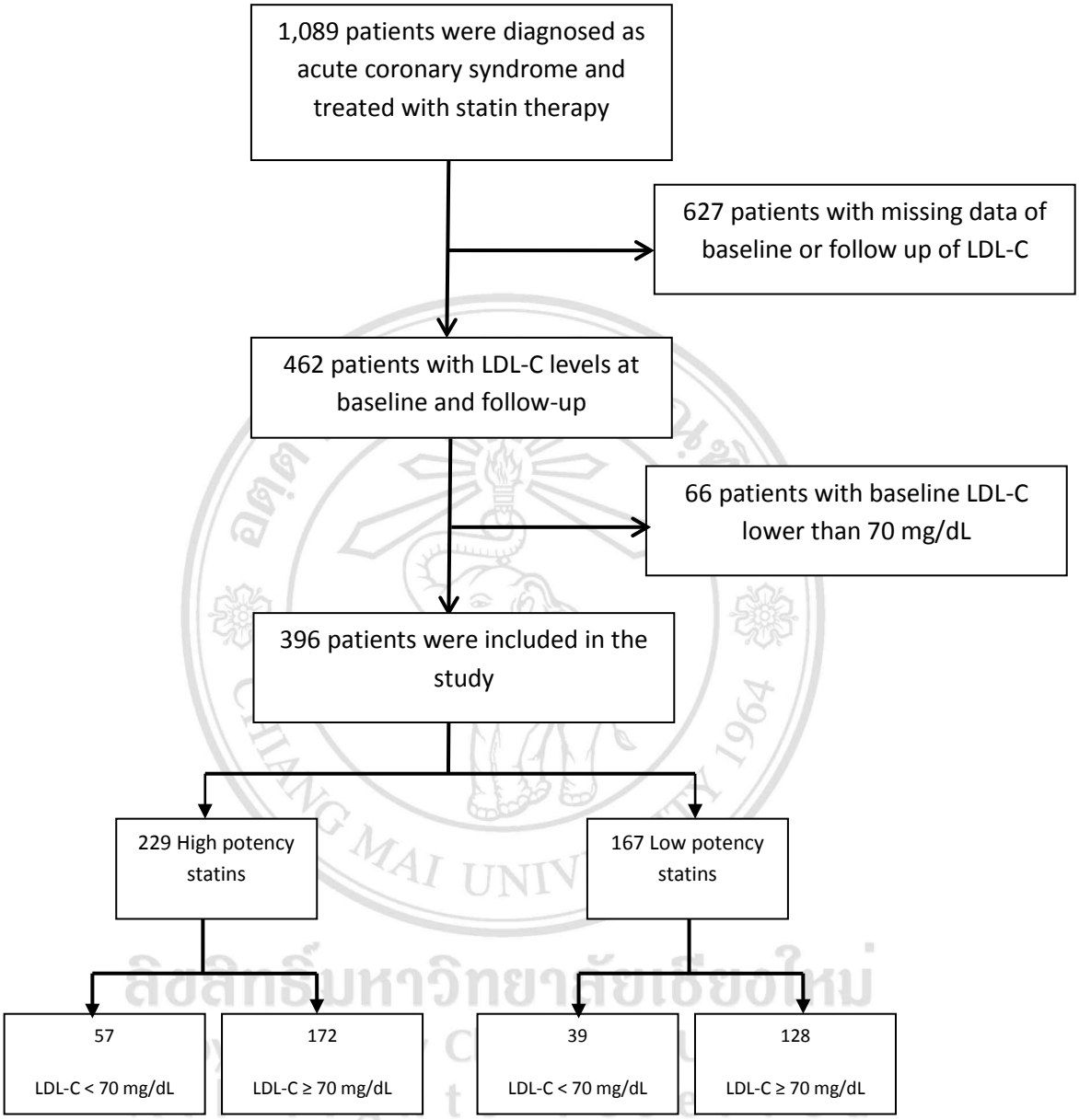

Figure 6.1: Study flow

Study II

Tile: Low-density lipoprotein cholesterol of less than 70 mg/dL is associated with fewer cardiovascular events in acute coronary syndrome patients: a real-life cohort in Thailand

Theoretical design

The research questions was "What is the effect of reaching an LDL-C goal of <70 mg/dL (<1.8 mmol/L) on the first composite cardiovascular outcomes in routine clinical practice in Thailand? The domain of this study constituted ACS patients admitted to CMU hospital and who were treated with statins.

Study II was a prognostic causal research. This study was designed to explain causal relation between LDL-C goal attainment and the first recurrence of cardiovascular events. Only the first recurrent event was considered in study II. All potential confounding factors played important roles in this study design; thus, all confounders needed to be adjusted. The occurrence relation is presented below.

First recurrent cardiovascular event = f (LDL-C goal attainment | confounders)

The design of data collection

The study setting was the same as study I, CMU Hospital. Same as study I, all included patients in our cohort were those diagnosed with ACS (UA, NSTEMI, and STEMI), aged at least 18 years, treated with statin therapy, and were admitted to the hospital from January 2009 to December 2012, one year longer than study I. This study was also a retrospective study. A well-trained nurse and a researcher collected all relevant information of included patients from the medical records and hospital database of individual patients.

The design of data analysis

The principal analysis was performed on the patients who were included from January 2009 to December 2012. A total of 684 patients were excluded from the analysis because of the lack of LDL-C levels (either at baseline or at follow-up), leaving 405 patients in the final analysis. However, we compared the characteristics of two groups of patients, those included and excluded from the analysis. The two groups did not differ significantly in most characteristics, except age.

The main interest was the causal relationship between LDL-C goal attainment and the first recurrent cardiovascular events; thus, the potential confounders (age, sex, diabetes mellitus, hypertension, serum creatinine, ACEI/ARB, revascularization [either PCI or CABG], and baseline LDL-C level were adjusted.

The steps of analysis are delineated below.

1. Describe characteristics of patients in the three groups based on the LDL-C levels at the first follow up visit: <70mg/dL (achieved goal), 70-99 mg/dL, and ≥100 mg/dL (reference group), with descriptive statistics. The categorical variables were reported with counts and percentages, while the continuous variables were reported with means and standard deviations.
2. Compare the three groups with Fisher's exact test for categorical variables or one-way analysis of variance for continuous variables.
3. Univariable Cox proportional hazard regression, stratified by type of ACS (UA, NSTEMI, and STEMI), was carried out. Then multivariable Cox proportional hazard regression stratified by type of ACS (UA, NSTEMI, and STEMI) and adjusted with the confounding factors was performed to assess the effect of LDL-C goal attainment on the first recurrent cardiovascular event.
4. In all cases, the statistical significance level was set as two-tailed and at a P-value <0.05.
5. Stata version 12.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

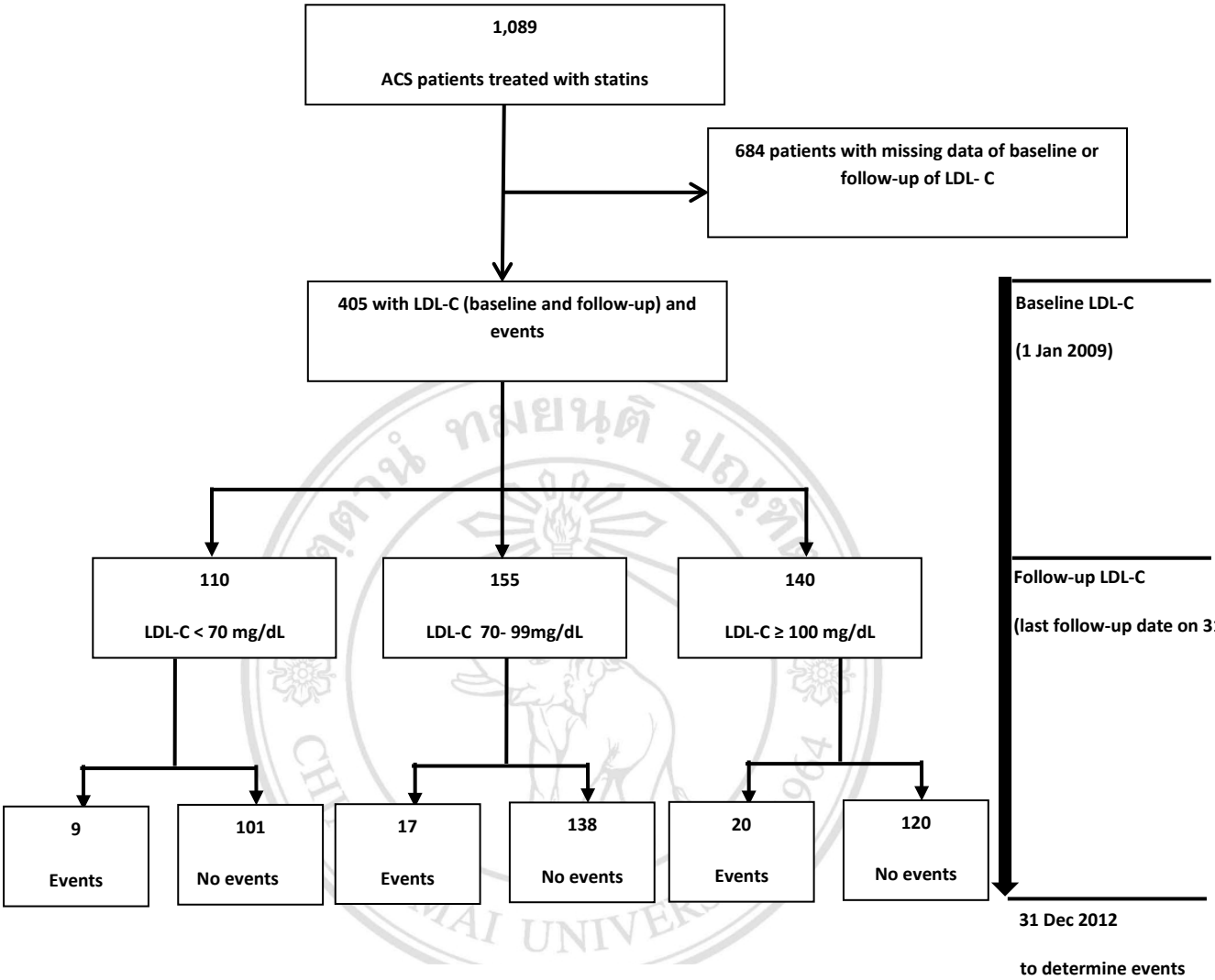

Figure 6.2: Flowchart of patient selection and study timeline.

Study III

Title: Clinical indicators for recurrent cardiovascular events in acute coronary syndrome patients treated with statins under routine practice in Thailand: an observational study

Theoretical design

The research question was "What clinical indicators were associated with all recurrent cardiovascular events?" This leads to the prognostic descriptive research. The domain comprised patients with ACS admitted to CMU hospital and who were treated with statin therapy.

Study III was a prognostic descriptive research. It constituted a non-causal element where interested determinants acted as predictors of an interested event. The interested events in this study were all recurrent cardiovascular events in this study; therefore, all recurrent cardiovascular events were considered in study III. Recurrent cardiovascular events were defined as nonfatal ACS (MI or UA), nonfatal stroke, or all-cause death happening after the assessment of LDL-C goal attainment. The outcome of this study included the frequencies of recurrent events, defined as no recurrent event (0), single recurrent event (1), and multiple recurrent events ($\geq$2) (Figure 6.3). For instance, when a patient experienced only a nonfatal MI, this was classified as having a single recurrent event. When a patient had a nonfatal MI, and subsequently had a stroke, this patient was characterized as having multiple recurrent events. Thus all recurrent events were weighted equally, i.e., death, recurrent MI, or nonfatal stroke was weighted equally. The occurrence relation of this study could be displayed as shown below.

Recurrent cardiovascular events = f (LDL-C goal attainment + revascularization
+ eGFR +sex+age+diabetes mellitus
+hypertension+ ACEI/ARB)

The design of data collection

The study setting was the same as the study I and II, CMU Hospital. All included patients in study III were the same as in study II – ACS patients (UA, NSTEMI, and STEMI) from 2009 to 2012, at least 18 years of age and were treated with statin therapy. An ICD-10 code of I20 (angina pectoris) or I21 (acute myocardial infarction) was used for a discharge diagnosis of ACS. All information of patients was tracked from the admission to the hospital until the last occurrence of recurrent cardiovascular event or until 31 December 2012, the last date of study period.

This study was a retrospective study. All relevant information of included patients was retrieved by a trained nurse and a researcher, from the medical records and hospital database.

The design of data analysis

The principal analysis was performed on patients who were included from January 2009 to December 2012, excluding 684 patients because of unavailable data of LDL-C levels (either at baseline or at follow-up). A total of 405 patients remained in the final analysis. We compared those included in the analysis with those excluded from the analysis; we found no significance difference between the two groups, except age.

The main interest was the descriptive relationship among determinants (clinical indicators) and the outcome (all recurrent cardiovascular events as defined by frequencies of recurrent events: 0, 1, ≥2).

The steps of analysis are shown below.

1. Describe characteristics of patients in the three groups based on the frequencies of events (0, 1, ≥2 events) with descriptive statistics. The categorical variables were reported with counts and percentages, while the continuous variables were reported with means and standard deviations.
2. Compare the three groups with a nonparametric test for trend.
3. Univariable and multivariable ordinal logistic regression adjusted with the length of follow-up were carried out to explore the clinical indicators for recurrent cardiovascular events. The outcome of interest in this study included the frequencies of cardiovascular recurrent events, defined as 0, 1, ≥2

recurrent events. Thus, we used the ordinal logistic regression because the outcome of interest was an ordinal variable.[6,7]

4. In all cases, the statistical significance level was set as two-tailed and at a P-value <0.05.
5. Stata version 12.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

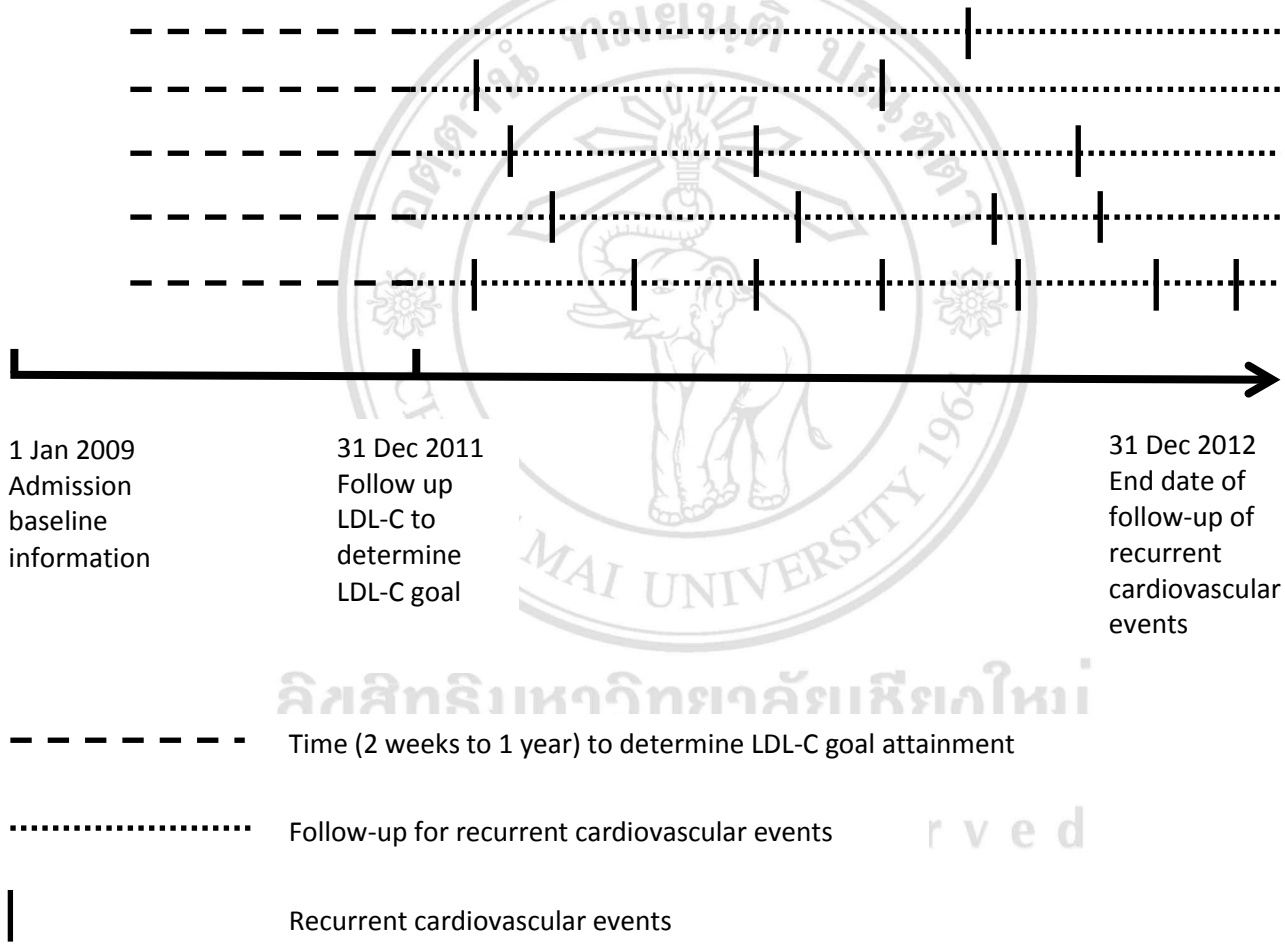

Figure 6.3: Index date, study period, and recurrent cardiovascular events.

REFERENCES

1. Grobbee DE. Clinicai epidemiology: principle, methods, and applications for clinical research The US: Jones and bartlett publishers; 2009.
2. Patumanond J. Clinical Epidemiology:Theoretical Concepts. Bangkok: Amarin Printing & Publishing Public Company Limited; 2011.
3. Rosenbaum PR, Rubin DB. The Central Role of the Propensity Score in Observational Studies for Causal Effects. Biometrika 1983;70:41-55.
4. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research 2011;46:399-424.
5. D'Agostino RB. Propensity scores in cardiovascular research. Circulation 2007;115:2340-3.
6. Armstrong BG, Sloan M. Ordinal regression models for epidemiologic data. American journal of epidemiology 1989;129:191-204.
7. Ananth CV, Kleinbaum DG. Regression models for ordinal responses: a review of methods and applications. International journal of epidemiology 1997;26:1323-33.

Appendix B

Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, Phrommintikul A. Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency. Ther Clin Risk Manag. 2015;11:127-136.

Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency

Dujrudee Chinwong[1,2]
Jayanton Patumanond[3]
Surarong Chinwong[1]
Khanchai Siriwattana[4]
Siriluck Gunaparn[5]
John Joseph Hall[6]
Arintaya Phrommintikul[5]

[1]Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [2]Clinical Epidemiology Program, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [3]Center of Excellence in Applied Epidemiology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand; [4]Division of Medicine, Nakornping Hospital, Chiang Mai, Thailand; [5]Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [6]Centre for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health, Faculty of Health, University of Newcastle, Callaghan, NSW, Australia

Background: Elevated low-density lipoprotein cholesterol (LDL-C) is associated with an increased risk of coronary artery disease. Current guidelines recommend an LDL-C target of <70 mg/dL (<1.8 mmol/L) for acute coronary syndrome (ACS) patients, and the first-line treatment to lower lipids is statin therapy. Despite current guidelines and the efficacious lipid-lowering agents available, about half of patients at very high risk, including ACS patients, fail to achieve their LDL-C goal. This study assessed LDL-C goal attainment according to use of high and low potency statins in routine practice in Thailand.

Methods: A retrospective cohort study was performed by retrieving data from medical records and the electronic hospital database for a tertiary care hospital in Thailand between 2009 and 2011. Included were ACS patients treated with statins at baseline and with follow-up of LDL-C levels. Patients were divided into high or low potency statin users, and the proportion reaching the LDL-C goal of <70 mg/dL was determined. A Cox proportional hazard model was applied to determine the relationship between statin potency and LDL-C goal attainment. Propensity score adjustment was used to control for confounding by indication.

Results: Of 396 ACS patients (60% males, mean age 64.3±11.6 years), 229 (58%) were treated with high potency statins and 167 (42%) with low potency statins. A quarter reached their target LDL-C goal (25% for patients on high potency statins and 23% on low potency statins). High potency statins were not associated with increased LDL-C goal attainment (adjusted hazards ratio 1.22, 95% confidence interval 0.79–1.88; P=0.363).

Conclusion: There was no significant effect of high potency statins on LDL-C goal attainment. Moreover, this study showed low LDL-C goal attainment for patients on either low or high potency statins. The reasons for the low LDL-C goal attainment rate warrants further investigation.

Keywords: LDL-C goal attainment, statins, potency statins, high risk, propensity score

Introduction

Coronary artery disease is the leading cause of death globally,[1] including in Thailand.[2] The association between elevated low-density lipoprotein cholesterol (LDL-C) and increased risk of coronary artery disease is well established.[3,4] Acute coronary syndrome (ACS) is an important clinical manifestation of coronary artery disease[5] and usually occurs as a result of one of three problems, ie, unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction, which is diagnosed by electrocardiography. Patients with ACS are at very high risk of further life-threatening cardiac events, so intensive LDL-C-lowering therapy is needed soon after diagnosis.[3,4,6–8] Current guidelines therefore recommend more aggressive LDL-C targets for ACS patients compared with healthy patients (<200 mg/dL

Correspondence: Arintaya Phrommintikul
Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, 50200, Thailand
Tel +66 5394 6716
Fax +66 5328 9177
Email arintayap@gmail.com

or <5.2 mmol/L) as per the updated National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) guideline,[3] and the guidelines of the European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS)[9] recommend an LDL-C goal of <70 mg/dL (<1.8 mmol/L).

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are considered the first-line pharmacological therapy for reducing LDL-C levels to prevent progression of coronary artery disease.[3,9,10] Six statins are currently available in Thailand, including simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin. Although all statins have a similar therapeutic effect (class effect) by lowering lipids, their potency differs.[11] Combination therapy with statins and other lipid-lowering agents (eg, ezetimibe, bile acid resins, or niacin) is recommended to achieve optimal reduction in LDL-C and minimize the risk of adverse effects from statin use. In addition, statins are one of the top groups with regard to drug expenditure in Thailand. Not all statins are listed in the National List of Essential Medicines (NLEM), which is used by public health insurance schemes in Thailand as the reference for the pharmaceutical benefit package.[12,13] About 96% of the Thai population are covered by one of three public insurance schemes: a civil servant medical benefit scheme for government officers and their dependants; a social security scheme for private sector employees; and universal coverage for people who are not eligible for either the civil servant medical benefit scheme or social security scheme.[12] Thus, the NLEM influences physicians' choices of statins for LDL-C control in ACS patients.

Despite the current guidelines and efficacious lipid-lowering agents available, about half of very high-risk patients, including ACS patients, fail to achieve their LDL-C goal of <70 mg/dL.[14–25] The highest success rate in achieving this goal came from a study in Hong Kong (83.1%),[26] while the lowest reported success rate was in Greece (10%).[22] However, studies of compliance with LDL-C levels of <70 mg/dL in very high-risk patients, especially ACS patients, are limited in Asia, especially in Thailand. Two observational studies in Thailand have shown a low proportion of attainment of an LDL-C goal <70 mg/dL in patients at very high risk for developing cardiovascular disease (Silaruks et al reported a rate of 11.6%[21] and the CEPHEUS (CEntralized Pan-Asian survey on tHE Under-treatment of hypercholeSterolemia) Thailand survey reported 16.7%[17]).

Little is known about the effects of statins of differing potency with regard to achieving a target LDL-C <70 mg/dL in the real-world setting in Asia. This study investigated the success of ACS patients in achieving this goal, as well as any difference in effect of high potency statins versus low potency statins.

Materials and methods

Data source and data collection

This retrospective cohort study was performed at the Maharaj Nakorn Chiang Mai Hospital in the north of Thailand. This tertiary hospital serves patients in Chiang Mai province, which has a population of 1,600,000, and receives patients with complicated conditions referred from 17 other provinces in northern Thailand. The hospital has 1,400 patient beds, and provides care for an average of 1,300,000 outpatients and 48,000 inpatients annually. This study was approved by the research ethics committee, Faculty of Medicine, Chiang Mai University, Thailand, before commencement, and included patients diagnosed with ACS between January 2009 and December 2011.

Data were collected by a study nurse aware of the research protocol and a researcher. Patient information, including demographic data, comorbidities, risk factors for coronary artery disease, current medication, and laboratory results including lipid profiles (total cholesterol, LDL-C, high-density lipoprotein, and triglycerides) were retrieved from medical charts and the electronic hospital database.

We retrospectively selected all patients aged 18 years and over who were diagnosed with an ICD-10 (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision) code of I20 (angina pectoris) or I21 (acute myocardial infarction) who were treated with statins during admission or from the discharge date between January 2009 and December 2011. All included patients needed to have two assessments of their LDL-C levels and had to have remained on statin therapy between the two assessments, ie, one assessment at baseline during their hospital admission (index date) and one at follow-up within 2 weeks to 1 year following the index date. Patients with a baseline LDL-C <70 mg/dL were excluded from the analysis (Figure 1).

Exposure and outcome measurement

Patients were divided into two groups, as either high or low potency statin users. Patients in the high potency statin group were treated with simvastatin 40 mg, rosuvastatin 10 mg or 20 mg, atorvastatin 20 mg or 40 mg, or pitavastatin 2 mg

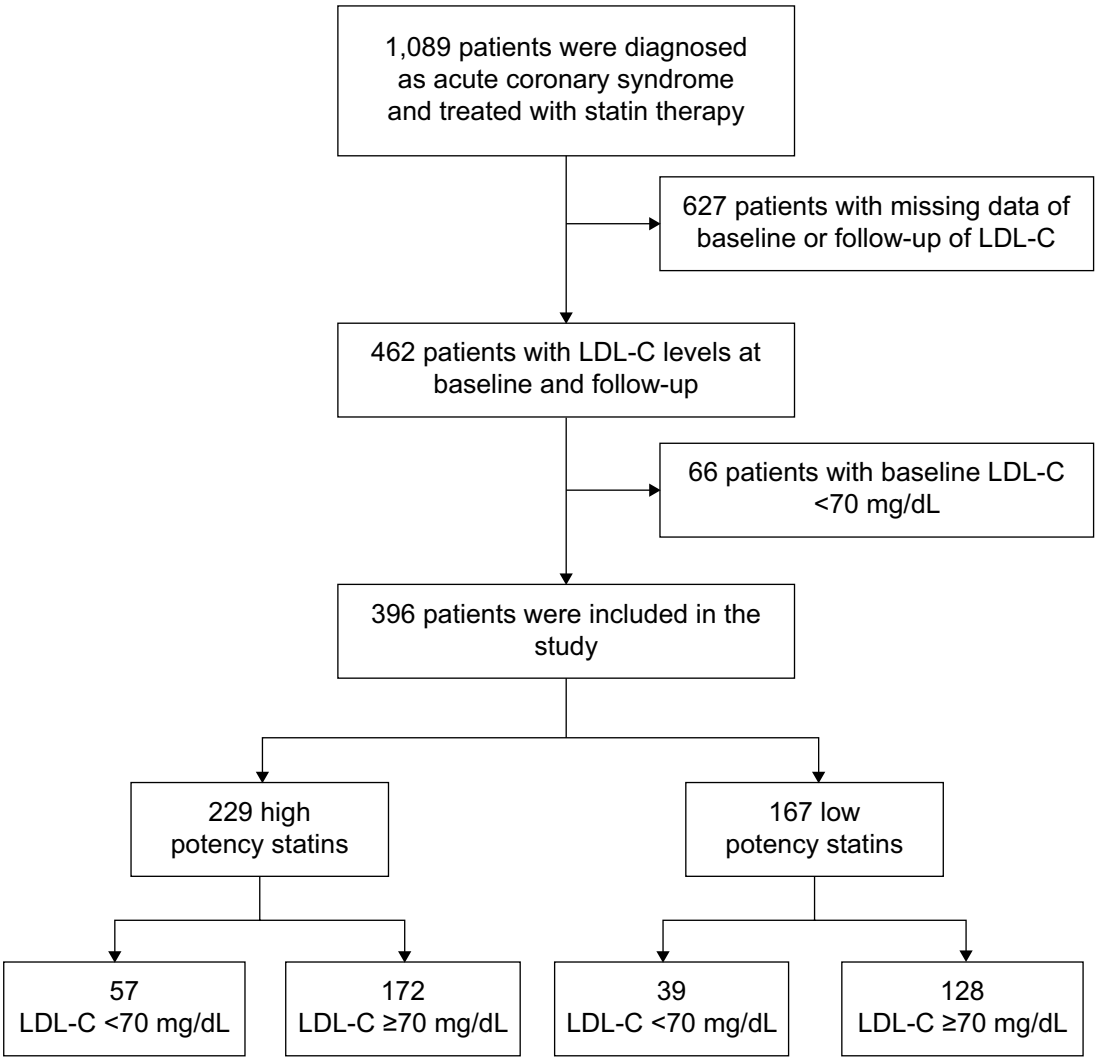

Figure 1 Flow chart of patient selection.
Abbreviation: LDL-C, low-density lipoprotein cholesterol.

daily which, based on previous studies, could be expected to achieve an LDL-C reduction of ≥40%.[11,27,28] Patients on simvastatin 10 mg or 20 mg or pravastatin 40 mg daily were in the low potency statin group and had an expected LDL-C reduction <40%.[11,27,28]

The outcome target was achieving an LDL-C goal of less than 70 mg/dL (<1.8 mmol/L) according to the updated NCEP/ATP III[3,10] and ESC/EAS guidelines[9] during the follow-up period of 2 weeks to 1 year.

Data analysis

Applying a descriptive method, counts and percentages were reported for categorical variables, and the mean and standard deviation for continuous variables. Differences between groups were compared using Fisher's Exact test for categorical variables or the independent *t*-test for continuous variables. Due to our use of an observational study design, which is prone to confounding factors, propensity scoring was used to adjust for confounding by indication.[29–31] Using logistic regression, a propensity score was generated to estimate the probability of receiving high or low potency statins. The variables included in the propensity score were age, sex, diabetes mellitus, hypertension, serum creatinine, alanine aminotransferase, LDL-C at baseline, health insurance status of patients, and smoking status. The Cox proportional hazard model (adjusted for propensity score and stratified by spectrum of ACS) was used to assess the effect of statin potency on LDL-C goal attainment. In all cases, the statistical significance level was set as two-tailed and at a *P*-value <0.05. All statistical analyses were carried out using Stata version 12 software (StataCorp LP, College Station, TX, USA).

Results

A total of 1,089 patients diagnosed with ACS were identified. After excluding 693 patients (627 with missing data on LDL-C levels, and 66 patients with a baseline LDL-C <70 mg/dL), 396 patients were included in the final analysis (Figure 1). A comparison between the groups included and excluded from the final analysis showed no significant difference in demographics between the two groups, except that the included patients were younger than the excluded patients (64.4±11.9 years versus 67.8±12.7 years, respectively, $P<0.001$).

Sixty percent of the patients were men, about 60% were covered by the universal coverage scheme, and one-fifth were current smokers. Fifty-five percent were diagnosed as having ST segment myocardial infarction, 28% as having non-ST segment myocardial infarction, and 16% as having unstable angina. The top three reported atherosclerotic risk factors were hypertension (60%), dyslipidemia (38%), and diabetes mellitus (28%). Two-fifths were treated with percutaneous coronary intervention during their hospital stay. The most frequently used current medications were antiplatelet/anticoagulant drugs (97%), beta-blockers (84%), and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (65%, Table 1). The baseline lipid profiles were 122.8±37.8 mg/dL for LDL-C, 40.3±11.1 mg/dL for high-density lipoprotein cholesterol, 143.4±79.1 mg/dL for triglycerides, and 191.5±46.3 mg/dL for total cholesterol (Table 2). Simvastatin was the most commonly prescribed statin and statin monotherapy was predominantly used in this study (Table 3).

Of the 396 ACS patients, 229 (57.8%) were treated with high potency statins and 167 (42.2%) with low potency statins. Both groups were similar with regard to demographic characteristics and risk factors for coronary artery disease. Patients covered by the universal coverage scheme were more often prescribed low potency statins, while those covered by the civil servant medical benefit scheme were more likely to receive high potency statins. Patients given high potency statins were more likely to have hypertension and dyslipidemia. Their pathology results and lipid profiles were similar, except that patients on high potency statins had higher total cholesterol and LDL-C levels at baseline (Tables 1 and 2). This suggests that the patients treated with high potency statins had more severe illness than those on low potency statins.

A quarter (24%) of the patients reached their target LDL-C, and there was no difference in LDL-C goal attainment between the high (24.9%) and low (23.4%) potency statin groups (Figure 2). The incidence rate of achieving the LDL-C goal was 2.0 per 1,000 person-days in patients with high potency statins and 1.7 per 1,000 person-days for those with low potency statins (Table 4). Patients using high potency statins were no more likely to reach their LDL-C target than patients on low potency statins (hazards ratio 1.15, 95% confidence interval 0.76–1.73, $P=0.516$), and the results remained the same after adjusting for propensity score (adjusted hazards ratio 1.22, 95% confidence interval 0.79–1.88, $P=0.363$, Table 5).

Discussion

LDL-C goal attainment

This clinic-based study in Thailand revealed that only a quarter of ACS patients (24%) attained their LDL-C goal of <70 mg/dL. Although the success rate of ACS patients achieving this goal was higher than in previous studies in Thailand,[17,21] most did not achieve their LDL-C target with the statin therapy available at the hospital. These results are consistent with other studies in Asian countries and worldwide, ie, that less than half of patients at very high risk for cardiovascular disease attain their LDL-C target, even though there are several efficacious lipid-lowering medications available.[14–25] Some studies have shown that less than 30% of high-risk patients reach their target LDL-C,[17,21–24,32,33] while other studies reported that target LDL-C was achieved by 30%–45% of patients at high risk of cardiovascular disease.[14–16,18–20,25]

Inadequate statin therapy for lowering LDL-C might play a role in the failure of achieving target LDL-C. Most (98%) of the patients in our study used statin monotherapy, and simvastatin was the drug used most often, which is in line with other studies.[17,18,26,34,35] According to the updated NCEP/ATP III and ESC/EAS guidelines, if the LDL-C goal is not achieved with statin monotherapy, combination therapy is recommended.[3,9,10] Combination therapy that includes a statin plus another lipid-lowering agent (eg, ezetimibe, bile acid resins, or niacin) can achieve a considerable reduction in LDL-C levels, while also limiting the risk of dose-related adverse effects from statin therapy.[3,9,10] Published studies have shown that the combination of a statin and ezetimibe is more effective than statin monotherapy in terms of lowering LDL-C and achieving the target of <70 mg/dL.[36–42] Approximately 25% of patients in this study with LDL-C higher than 140 mg/dL at baseline would require combination therapy including a statin to achieve their target LDL-C. However, only seven patients (1.8%) were prescribed combination therapy. This is consistent with other studies reporting that statin combination therapy was used less frequently in routine practice.[18,35,39,42] Although all treating physicians in this study were cardiologists, they were possibly reluctant to titrate statin doses upwards; there may be two reasons for this, ie, concern regarding potential adverse events, eg, an

Table 1 Baseline characteristics of patients classified by statin potency (n=396)

Characteristics	High potency statins (n=229)	Low potency statins (n=167)	*P*-value
Sex			
Male to female	144 (62.9):85 (37.1)	92 (55.1):75 (44.9)	0.122
Age (years)	63.9±12.0	64.8±11.0	0.453
Health insurance			
Universal coverage scheme	117 (51.1)	112 (67.1)	0.008
Civil servant medical benefit scheme	99 (43.2)	49 (29.3)	
Social security scheme	11 (4.8)	4 (2.4)	
Self-pay	2 (0.9)	2 (1.2)	
Smoking status			
Nonsmoker	143 (62.5)	92 (55.1)	0.315
Ex-smoker	41 (17.9)	34 (20.4)	
Current smoker	45 (19.7)	41 (24.6)	
Diagnosis at discharge			
Unstable angina	36 (15.7)	29 (17.4)	0.470
NSTEMI	61 (26.6)	52 (31.1)	
STEMI	132 (57.6)	86 (51.5)	
Atherosclerotic risk factors			
Diabetes mellitus	70 (30.6)	42 (25.2)	0.260
Hypertension	151 (66.0)	89 (53.3)	0.013
Chronic kidney disease	26 (11.4)	24 (14.4)	0.444
Dyslipidemia	97 (42.4)	52 (31.1)	0.027
Family history of premature atherosclerosis	6 (2.6)	1 (0.6)	0.247
Previous history of cardiovascular events			
Chronic stable angina	19 (8.3)	12 (7.2)	0.710
Myocardial infarction or unstable angina	48 (21.0)	31 (18.6)	0.611
Stroke (ischemic)	18 (7.9)	7 (4.2)	0.150
Peripheral vascular disease	1 (0.4)	1 (0.6)	1.000
Previous history of cardiovascular intervention			
PCI	15 (6.6)	8 (4.8)	0.520
CABG	11 (4.8)	7 (4.2)	0.813
Revascularization of peripheral vascular disease	2 (0.9)	0 (0.0)	0.511
Carotid intervention	3 (1.3)	0 (0.0)	0.267
Treatment during admission			
PCI	103 (45.0)	59 (35.3)	0.063
CABG	2 (0.9)	3 (1.8)	0.654
Thrombolytic indicated	26 (11.4)	22 (13.2)	0.641
Current medications			
Lipid-lowering drugs (non-statins)	5 (2.2)	2 (1.2)	0.704
Antiplatelet/anticoagulant drugs	223 (97.4)	164 (98.2)	0.739
Beta-blockers	191 (83.4)	143 (85.6)	0.578
ACEI/ARB	159 (69.4)	100 (59.9)	0.054
CCB	40 (17.5)	34 (20.4)	0.515
Diuretics	67 (29.3)	48 (28.7)	1.000

Note: Numbers are n (%) or mean ± standard deviation (SD).
Abbreviations: NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCB, calcium channel blockers.

increase in muscle toxicity, and/or doubling the dose of a statin results in lowering LDL-C by only an additional 6%, ie, the "rule of 6".[43,44]

The Thailand policy promoting the rational use of medicines may also play a role in the low rate of achievement of the LDL-C target. Thailand has adopted the NLEM to encourage rational drug use and to control drug cost in the country, so medicines listed in the NLEM can be prescribed for patients under the health insurance schemes, but patients have to pay for drugs not listed in the NLEM.[12,13] Simvastatin was the only statin listed in the NLEM during the study period from 2009 to 2011.[45] However, simvastatin 40 mg (the most commonly used high potency statin) can only reduce LDL-C by about 43%[46] and cannot decrease the LDL-C level to <70 mg/dL in patients with a level >140 mg/dL at baseline. In this situation, atorvastatin, rosuvastatin or statin

Table 2 Baseline laboratory and lipid values of patients by statin potency (n=396)

Characteristics	High potency statins (n=229)	Low potency statins (n=167)	*P*-value
Baseline laboratory			
Serum creatinine (mg/dL)	1.5±2.2	1.3±0.7	0.344
ALT (U/L)	31.6±38.7	34.9±30.4	0.356
Fasting blood glucose (mg/dL)	132.1±50.5[a]	142.8±97.4[b]	0.164
Baseline lipid values			
Total cholesterol (mg/dL)	195.1±45.4	186.8 ±47.2	0.089
Triglycerides (mg/dL)	147.7±79.1	137.7±79.1	0.233
High-density lipoprotein (mg/dL)	39.9±10.3	40.8±12.2	0.428
Low-density lipoprotein (mg/dL)	127.1±38.6	116.8±35.9	0.007
Propensity score	0.61±0.13	0.54±0.13	<0.001

Notes: Numbers are mean ± standard deviation. [a]n=222, [b]n=161.
Abbreviation: ALT, alanine aminotransferase.

combination therapy should be used to lower LDL-C to the target level, but rosuvastatin and atorvastatin are not included in the NLEM. Our study suggests that physicians may have limited choices with regard to statin therapy for ACS patients, which impacts on LDL-C outcomes due to the regulations of the NLEM. A similar finding has been reported for Iceland, where a new reimbursement regulation was introduced in 2009 requiring patients to switch from atorvastatin, rosuvastatin, and pravastatin to simvastatin for the treatment of hyperlipidemia. After one year, the new reimbursement regulation resulted in an increase in cholesterol levels and decrease in the proportion of heart disease patients reaching the treatment goal.[47]

Poor adherence to statin therapy might explain the failure to attain the LDL-C goal in this real-world practice study, given that adherence to statins is positively related to achieving the LDL-C goal.[48–50] Patients on statin therapy tend to decline in adherence after the initial prescription, and the 2-year adherence rate in ACS patients was reported to be only 40%.[51] Patient adherence to statin therapy was not measured in this study, so further investigation of medication adherence in our population is warranted.

Table 3 Statin therapy in this study (n=396)

Statins (n, % of LDL-C reduction)	n (%)
High potency statins (229, ≥40)	
Simvastatin 40 mg	149 (65.1)
Rosuvastatin 10 mg	15 (6.6)
Rosuvastatin 20 mg	9 (3.9)
Atorvastatin 20 mg	33 (14.4)
Atorvastatin 40 mg	21 (9.2)
Pitavastatin 2 mg	2 (0.9)
Low potency statins (167, <40)	
Simvastatin 10 mg	11 (6.6)
Simvastatin 20 mg	155 (92.8)
Pravastatin 40 mg	1 (0.6)
Monotherapy/combination therapy	
Statin monotherapy	389 (98.2)
Statin combination therapy	7 (1.8)
Statin + ezetimibe 10 mg	2
Statin + gemfibrozil 300 mg	2
Statin + gemfibrozil 900 mg	1
Statin + fenofibrate cap 160 mg	1
Statin + niacin 375 mg	1

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Effect of statin potency on LDL-C goal attainment

This study showed that treatment with a high potency statin was not associated with an increased likelihood of attaining the LDL-C goal in routine clinical practice. The effect of statin potency on reduction of LDL-C remains controversial in observational studies, although a positive relationship between statin potency and LDL-C goal attainment is well established in randomized controlled trials.[7,8]

This study is in agreement with certain other studies showing that the potency of the statin used does not increase the likelihood of reaching the recommended goal.[15,18,35,52] However, the results from yet other studies indicate that

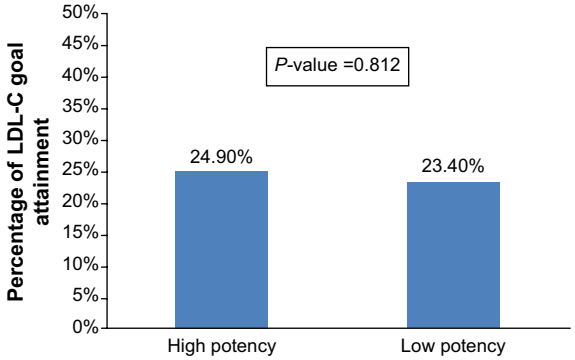

Figure 2 Percentage of LDL-C goal attainment of <70 mg/dL by high and low potency statins (n=396).
Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Table 4 Incidence of LDL-C goal attainment by statin potency (n=396)

Outcomes	High potency statins (n=229)	Low potency statins (n=167)	*P*-value
Total of person-days of follow-up	28,603	22,551	
Median survival time (days)	298	301	
LDL-C goal attainment (<70 mg/dL)			
Number of patients with goal attainment	57	39	
Incidence (per 1,000 person-days)	2.0	1.7	0.243

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

patients treated with high potency statins are significantly more likely to achieve LDL-C control.[22,32,53,54] The difference in results between these carious studies might reflect differences in the definition of high or low potency of statins used in the studies, which could affect the percent of LDL-C reduction and lead to differences in successful goal attainment. For instance, a study by Rallidis et al[32] showed a positive relationship between the potency of the statin and LDL-C control, and the definition of intensive lipid-lowering medication was a medication that could lower LDL-C by more than 50%. These drugs include rosuvastatin 20–40 mg, atorvastatin 40–80 mg, simvastatin 80 mg daily, and the combination of a statin at a moderate or high dose with ezetimibe, a bile acid sequestrant, or niacin. In our study, high potency statins were defined as simvastatin 40 mg, atorvastatin 20–40 mg, rosuvastatin 10–20 mg, and pitavastatin 2 mg daily, based on a percent LDL-C reduction of ≥40%.[11,27,28] These treatment regimens fall mostly into the low to moderate potency category used in the study by Rallidis et al.[32]

Other factors may have also influenced the results, such as comorbidities (particularly hypertension and dyslipidemia), individual variation in response to statin therapy, and variation in lifestyle and food modification. Patients on high-intensity statins had higher baseline LDL-C levels and a higher prevalence of hypertension and dyslipidemia, resulting in poorer LDL-C control. Individual patients may respond to statin therapy differently even at the same statin dose, resulting in different degrees of LDL-C reduction. Further, patients may differ significantly in their extent of lifestyle and food modification, which can also result in differing degrees of LDL-C reduction.

The timing of the follow-up visit may have influenced the results with regard to LDL-C goal attainment. A single follow-up visit between 2 weeks and 1 year after hospitalization for ACS was used in this study, whereas the follow-up duration in a study conducted in Europe and Canada was at least 3 months.[53] We carried out a further analysis examining the relationship between statin potency and LDL-C goal attainment by varying follow-up duration (eg, 1 month, 2 months, 3 months, and 6 months), but the results remained the same. As mentioned earlier, the nonlinear decline in statin adherence after the initial prescription is a concern that could affect LDL-C goal attainment.[51]

Further, high potency statins are recommended in the new 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline for the treatment of blood cholesterol to reduce the atherosclerotic cardiovascular risk in adults (ie, the 2013 ACC/AHA Cholesterol Guidelines)[55] and lipid modification in the National Institute for Health and Care Excellence (NICE) clinical guideline 181,[56] due to the results of randomized controlled trials considered by the guideline writers. Uncertainty appears to remain with regard to this policy. Our findings are at odds with the recommendations of the 2013 ACC/AHA Cholesterol Guidelines[55] and the latest NICE guidelines from the UK,[56] which no longer recommend use of both LDL-L goals and ongoing monitoring of LDL-C levels. Rather, our findings support the ESC/EAS[9] and 2014 National Lipid Association[57] recommendation that maintaining the LDL-C goal and monitoring of LDL-C levels are beneficial for physicians and patients in following the patient's progress. In this study, for example, monitoring of LDL-C was essential for identifying the 75%

Table 5 Effect of statin potency on LDL-C goal attainment (n=396)

Outcomes	Crude HR (95% CI)[a]	*P*-value	Adjusted HR (95% CI)[a,b]	*P*-value
LDL-C goal attainment (<70 mg/dL)				
High potency statins	1.15 (0.76–1.73)	0.516	1.22 (0.79–1.88)	0.363
Low potency statins	1.00		1.00	

Notes: [a]Stratified analysis by diagnosis at discharge. [b]Adjusted for propensity score including age, sex, diabetes mellitus, hypertension, serum creatinine, ALT, LDL-C at baseline, health insurance of patients, and smoking status.
Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HR, hazards ratio; LDL-C, low-density lipoprotein cholesterol.

of patients who fail to achieve their LDL-C goal, and without monitoring, many ACS patients will be at increased risk of future cardiovascular events.

Strengths and limitations

To the best of our knowledge, this is the first study in Thailand that assesses the attainment of LDL-C <70 mg/dL in those patients with ACS in routine clinical practice. Previous studies investigated reaching LDL-C <100, or <70 mg/dL in patients with cardiovascular risk. All patients were treated by a cardiologist. While previous studies in Thailand have had a cross-sectional design such that no causal relationship could be determined, our longitudinal study allows associations to be made.

This study has some limitations. First, its retrospective design may be distorted by confounding factors; however, we attempted to adjust for this by use of the propensity score to control for confounding. Second, inclusion of patients who had complete lipid profiles in their electronic medical records at both at baseline and follow-up resulted in fewer patients being included. However, a comparison between patients included and those excluded from the study found no significant difference. Third, the sample size in this study is too small for evaluation of the effect of statin potency on LDL-C goal attainment. However, it is still possible to legitimately establish an association between statin potency and LDL-C goal attainment in ACS patients. Fourth, these findings are limited in terms of their generalizability given that all patients were from a university affiliated hospital and all were managed by cardiologists. Therefore, our findings should not be generalized to ACS patients who were managed by primary care physicians or are from other parts of Thailand. Nonetheless, these findings are applicable in other Asian countries where physicians predominantly use statin monotherapy at low to medium potency in patients at high cardiovascular risk.[24] Fifth, statin adherence and titration of the dose during treatment were beyond the scope of this study. If extremely low adherence is equally distributed between high and low potency statin users, our finding of no significant difference in LDL-C goal attainment between these two groups could be anticipated. There is a need for further assessment of medication adherence in statin users and the effect of statin dose adjustment to meet LCL-C goals in practice settings.

Conclusion

Three-quarters of ACS patients failed to achieve their recommended LDL-C goal of <70 mg/dL, and use of high potency statins was not associated with increased LDL-C control. We believe that this study reflects the real-world practice situation of suboptimal LDL-C goal achievement in ACS patients who are at high cardiovascular risk. Hence, we encourage cardiologists to use LDL-C goal attainment as a target for therapy, and to monitor LDL-C levels in ACS patients in order to prevent further cardiovascular events. Improvement in achieving the LDL-C goal is required in clinical practice to improve outcomes in ACS patients. Further studies are needed to identify the reasons for low LDL-C control rates. In addition, the impact of the NLEM on LDL-C control in very high-risk patients (eg, those with ACS) needing more intensive statin therapy requires further evaluation.

Acknowledgments

The authors thank the Graduate School, Chiang Mai University, Thailand, for its financial support of this study, the authorities of Maharaj Nakorn Chiang Mai Hospital for their permission to use the data, Claudia Koller for assistance with editing this manuscript, and Yodi Christiani, Research Centre for Gender, Health and Ageing, University of Newcastle, for her valuable suggestions regarding preparation of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet.* 2006;367(9524):1747–1757.
2. Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Popul Health Metr.* 2010;8:14.
3. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110(2):227–239.
4. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA.* 2001;285(13):1711–1718.
5. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation.* 2005;111(25):3481–3488.
6. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350(15):1495–1504.
7. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA.* 2004;292(11):1307–1316.
8. Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 Trial. *J Am Coll Cardiol.* 2005;46(8):1405–1410.
9. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J.* 2011;32(14):1769–1818.

10. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486–2497.
11. Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. *J Clin Pharm Ther.* 2010;35(2):139–151.
12. Tarn YH, Hu S, Kamae I, et al. Health-care systems and pharmacoeconomic research in Asia-Pacific region. *Value Health.* 2008;11 Suppl 1: S137–S155.
13. Anothaisintawee T, Leelahavarong P, Ratanapakorn T, Teerawattananon Y. The use of comparative effectiveness research to inform policy decisions on the inclusion of bevacizumab for the treatment of macular diseases in Thailand's pharmaceutical benefit package. *Clinicoecon Outcomes Res.* 2012;4:361–374.
14. Chin CW, Gao F, Le T, Tan R. Lipid goal attainment and prescription behavior in asian patients with acute coronary syndromes: experience from a tertiary hospital. *Clin Med Insights Cardiol.* 2013;7:51–57.
15. Kauffman AB, Olson KL, Youngblood ML, Zadvorny EB, Delate T, Merenich JA. Attainment of low-density lipoprotein cholesterol goals in coronary artery disease. *J Clin Lipidol.* 2010;4(3):173–180.
16. Kitkungvan D, Lynn Fillipon NM, Dani SS, Downey BC. Low-density lipoprotein cholesterol target achievement in patients at high risk for coronary heart disease. *J Clin Lipidol.* 2010;4(4):293–297.
17. Sukonthasarn A, Homsanit M, Prommete B, Chotinaiwattarakul C, Piamsomboon C, Likittanasombat K. Lipid-lowering treatment in hypercholesterolemic patients: the CEPHEUS Thailand survey. *J Med Assoc Thai.* 2011;94(12):1424–1434.
18. Karalis DG, Victor B, Ahedor L, Liu L. Use of lipid-lowering medications and the likelihood of achieving optimal LDL-cholesterol goals in coronary artery disease patients. *Cholesterol.* 2012;2012:861924.
19. Karalis DG, Subramanya RD, Hessen SE, Liu L, Victor MF. Achieving optimal lipid goals in patients with coronary artery disease. *Am J Cardiol.* 2011;107(6):886–890.
20. Park JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolaemic patients: the CEPHEUS Pan-Asian survey. *Eur J Prev Cardiol.* 2012;19(4):781–794.
21. Silaruks S, Sriratanasathavorn C, Rawdaree P, Kunjara-Na-Ayudhaya R, Thinkhamrop B, Sritara P. Lipid-lowering therapy using statins in patients with cardiovascular risk in clinical practice in Thailand. *Heart Asia.* 2011;3:99–103.
22. Xanthopoulou I, Davlouros P, Siahos S, Perperis A, Zaharioglou E, Alexopoulos D. First-line treatment patterns and lipid target levels attainment in very high cardiovascular risk outpatients. *Lipids Health Dis.* 2013;12(170):12–170.
23. Andrikopoulos G, Tzeis S, Nikas N, et al. Short-term outcome and attainment of secondary prevention goals in patients with acute coronary syndrome-Results from the countrywide TARGET study. *Int J Cardiol.* 2013;168(2):922–927.
24. Kim HS, Wu Y, Lin SJ, et al. Current status of cholesterol goal attainment after statin therapy among patients with hypercholesterolemia in Asian countries and region: the Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY-Asia) study. *Curr Med Res Opin.* 2008;24(7):1951–1963.
25. Melloni C, Shah BR, Ou FS, et al. Lipid-lowering intensification and low-density lipoprotein cholesterol achievement from hospital admission to 1-year follow-up after an acute coronary syndrome event: results from the Medications AppIIed aNd SusTAINed Over Time (MAINTAIN) registry. *Am Heart J.* 2010;160(6):1121–1129.
26. Chan RH, Chan PH, Chan KK, et al. The CEPHEUS Pan-Asian survey: high low-density lipoprotein cholesterol goal attainment rate among hypercholesterolaemic patients undergoing lipid-lowering treatment in a Hong Kong regional centre. *Hong Kong Med J.* 2012;18(5):395–406.
27. Mukhtar RY, Reid J, Reckless JP. Pitavastatin. *Int J Clin Pract.* 2005;59(2):239–252.
28. Masana L. Pitavastatin – from clinical trials to clinical practice. *Atheroscler Suppl.* 2010;11(3):15–22.
29. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70(1): 41–55.
30. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399–424.
31. D'Agostino RB. Propensity scores in cardiovascular research. *Circulation.* 2007;115(17):2340–2343.
32. Rallidis LS, Kotakos C, Sourides V, et al. Attainment of optional low-density lipoprotein cholesterol goal of less than 70 mg/dL and impact on prognosis of very high risk stable coronary patients: a 3-year follow-up. *Expert Opin Pharmacother.* 2011;12(10):1481–1489.
33. Hermans MP, Castro Cabezas M, Strandberg T, et al. Centralized Pan-European survey on the under-treatment of hypercholesterolaemia (CEPHEUS): overall findings from eight countries. *Curr Med Res Opin.* 2010;26(2):445–454.
34. Chaiyakunapruk N, Asuphol O, Dhippayom T, Poowaruttanawiwit P, Jeanpeerapong N. Statins utilisation pattern: a retrospective evaluation in a tertiary care hospital in Thailand. *Int J Pharm Pract.* 2011;19(2): 129–135.
35. Van Ganse E, Laforest L, Alemao E, Davies G, Gutkin S, Yin D. Lipid-modifying therapy and attainment of cholesterol goals in Europe: the Return on Expenditure Achieved for Lipid Therapy (REALITY) study. *Curr Med Res Opin.* 2005;21(9):1389–1399.
36. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J.* 2004;148(3):447–455.
37. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol.* 2002;40(12):2125–2134.
38. Friedman HS, Rajagopalan S, Barnes JP, Roseman H. Combination therapy with ezetimibe/simvastatin versus statin monotherapy for low-density lipoprotein cholesterol reduction and goal attainment in a real-world clinical setting. *Clin Ther.* 2011;33(2):212–224.
39. Foody JM, Toth PP, Tomassini JE, et al. Changes in LDL-C levels and goal attainment associated with addition of ezetimibe to simvastatin, atorvastatin, or rosuvastatin compared with titrating statin monotherapy. *Vasc Health Risk Manag.* 2013;9:719–727.
40. Davidson MH. Reducing residual risk for patients on statin therapy: the potential role of combination therapy. *Am J Cardiol.* 2005; 96(9A):3K–13K.
41. Mikhailidis DP, Lawson RW, McCormick AL, et al. Comparative efficacy of the addition of ezetimibe to statin vs statin titration in patients with hypercholesterolaemia: systematic review and meta-analysis. *Curr Med Res Opin.* 2011;27(6):1191–1210.
42. Toth PP, Foody JM, Tomassini JE, et al. Therapeutic practice patterns related to statin potency and ezetimibe/simvastatin combination therapies in lowering LDL-C in patients with high-risk cardiovascular disease. *J Clin Lipidol.* 2014;8(1):107–116.
43. Vaughan CJ, Gotto AM Jr. Update on statins: 2003. *Circulation.* 2004; 110(7):886–892.
44. Illingworth DR. Management of hypercholesterolemia. *Med Clin North Am*. 2000;84(1):23–42.
45. National Drug Committee. *National List of Essential Medicines 2008*. Bangkok, Thailand: Sri-muang Kanpim; 2008.
46. Ose L, Budinski D, Hounslow N, Arneson V. Comparison of pitavastatin with simvastatin in primary hypercholesterolaemia or combined dyslipidaemia. *Curr Med Res Opin.* 2009;25(11):2755–2764.
47. Gizurarson S, Bjornsdottir LR, Einarsdottir R, Halldorsson M, Andersen K. Clinical consequences following regulatory changes in respect to reimbursement of statins cost by the Icelandic Social Insurance Administration. *Scand J Public Health.* 2012;40(7):663–667.

48. Parris ES, Lawrence DB, Mohn LA, Long LB. Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. *Diabetes Care.* 2005;28(3):595–599.
49. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* 2009;119(23):3028–3035.
50. Bermingham M, Hayden J, Dawkins I, et al. Prospective analysis of LDL-C goal achievement and self-reported medication adherence among statin users in primary care. *Clin Ther.* 2011;33(9):1180–1189.
51. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA.* 2002;288(4):462–467.
52. Laforest L, Moulin P, Souchet T, et al. Correlates of LDL-cholesterol goal attainment in patients under lipid lowering therapy. *Atherosclerosis.* 2008;199(2):368–377.
53. Gitt AK, Drexel H, Feely J, et al. Persistent lipid abnormalities in statin-treated patients and predictors of LDL-cholesterol goal achievement in clinical practice in Europe and Canada. *Eur J Prev Cardiol.* 2012;19(2):221–230.
54. Ho KT, Chin KW, Ng KS, Alemao E, Rajagopalan S, Yin D. The A-SACT (Achievement in Singapore of Cholesterol Targets) study in patients with coronary heart disease. *Am J Cardiovasc Drugs.* 2006;6(6):383–391.
55. Stone NJ, Robinson JG, Lichtenstein AH, et al. 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. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889–2934.
56. National Institute for Health and Care Excellence. Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. London, UK: National Clinical Guideline Centre; 2014. Available from: http://www.nice.org.uk/guidance/cg181/resources/guidance-lipid-modification-cardiovascular-risk-assessment-and-the-modification-of-blood-lipids-for-the-primary-and-secondary-prevention-of-cardiovascular-disease-pdf. Accessed November 27, 2014.
57. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary. *J Clin Lipidol.* 2014;8(5):473–488.

Dove Medical Press Ltd. LICENSE TERMS AND CONDITIONS

Nov 30, 2015

This is a License Agreement between Dujrudee Chinwong ("You") and Dove Medical Press Ltd. ("Dove Medical Press Ltd.") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Dove Medical Press Ltd., and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

License Number	3754851136873
License date	Nov 23, 2015
Licensed content publisher	Dove Medical Press Ltd.
Licensed content title	Therapeutics and Clinical Risk Management
Licensed content date	Jan 1, 2005
Type of Use	Thesis/Dissertation
Requestor type	Academic institution
Format	Electronic
Portion	chapter/article
Title or numeric reference of the portion(s)	1 articles with 57 references, 5 tables and 2 figures.
Title of the article or chapter the portion is from	Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency
Editor of portion(s)	N/A
Author of portion(s)	N/A
Volume of serial or monograph.	N/A
Issue, if republishing an article from a serial	Volume 2015:11 Pages 127Ã¢ÂÂ136
Page range of the portion	None
Publication date of portion	23 January 2015
Rights for	Main product and any product related to main product
Duration of use	Current edition and up to 5 years
Creation of copies for the disabled	no
With minor editing privileges	yes
For distribution to	Worldwide
In the following language(s)	Original language plus one translation
Specific languages	English, Thai
With incidental promotional use	yes
The lifetime unit quantity of new product	Up to 499
Made available in the following markets	Education
The requesting person/organization is:	Dujrudee Chinwong

Order reference number	None
Author/Editor	Dujrudee Chinwong
The standard identifier	an internal reference
Title	Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency
Publisher	Chiang Mai University
Expected publication date	Nov 2015
Estimated size (pages)	80
Total (may include CCC user fee)	0.00 USD
Terms and Conditions	

TERMS AND CONDITIONS

The following terms are individual to this publisher:

None

Other Terms and Conditions:

STANDARD TERMS AND CONDITIONS

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

3.1 All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

3.2 General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, Dept 001, P.O. Box 843006, Boston, MA 02284-3006. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the

Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.
3.3 Unless otherwise provided in the Order Confirmation, any grant of rights to User (i) is "one-time" (including the editions and product family specified in the license), (ii) is non-exclusive and non-transferable and (iii) is subject to any and all limitations and restrictions (such as, but not limited to, limitations on duration of use or circulation) included in the Order Confirmation or invoice and/or in these terms and conditions. Upon completion of the licensed use, User shall either secure a new permission for further use of the Work(s) or immediately cease any new use of the Work(s) and shall render inaccessible (such as by deleting or by removing or severing links or other locators) any further copies of the Work (except for copies printed on paper in accordance with this license and still in User's stock at the end of such period).
3.4 In the event that the material for which a republication license is sought includes third party materials (such as photographs, illustrations, graphs, inserts and similar materials) which are identified in such material as having been used by permission, User is responsible for identifying, and seeking separate licenses (under this Service or otherwise) for, any of such third party materials; without a separate license, such third party materials may not be used.
3.5 Use of proper copyright notice for a Work is required as a condition of any license granted under the Service. Unless otherwise provided in the Order Confirmation, a proper copyright notice will read substantially as follows: "Republished with permission of [Rightsholder's name], from [Work's title, author, volume, edition number and year of copyright]; permission conveyed through Copyright Clearance Center, Inc. " Such notice must be provided in a reasonably legible font size and must be placed either immediately adjacent to the Work as used (for example, as part of a by-line or footnote but not as a separate electronic link) or in the place where substantially all other credits or notices for the new work containing the republished Work are located. Failure to include the required notice results in loss to the Rightsholder and CCC, and the User shall be liable to pay liquidated damages for each such failure equal to twice the use fee specified in the Order Confirmation, in addition to the use fee itself and any other fees and charges specified.
3.6 User may only make alterations to the Work if and as expressly set forth in the Order Confirmation. No Work may be used in any way that is defamatory, violates the rights of third parties (including such third parties' rights of copyright, privacy, publicity, or other tangible or intangible property), or is otherwise illegal, sexually explicit or obscene. In addition, User may not conjoin a Work with any other material that may result in damage to the reputation of the Rightsholder. User agrees to inform CCC if it becomes aware of any infringement of any rights in a Work and to cooperate with any reasonable request of CCC or the Rightsholder in connection therewith.
4. Indemnity. User hereby indemnifies and agrees to defend the Rightsholder and CCC, and their respective employees and directors, against all claims, liability, damages, costs and expenses, including legal fees and expenses, arising out of any use of a Work beyond the scope of the rights granted herein, or any use of a Work which has been altered in any unauthorized way by User, including claims of defamation or infringement of rights of copyright, publicity, privacy or other tangible or intangible property.
5. Limitation of Liability. UNDER NO CIRCUMSTANCES WILL CCC OR THE RIGHTSHOLDER BE LIABLE FOR ANY DIRECT, INDIRECT, CONSEQUENTIAL OR INCIDENTAL DAMAGES (INCLUDING WITHOUT LIMITATION DAMAGES FOR LOSS OF BUSINESS PROFITS OR INFORMATION, OR FOR BUSINESS INTERRUPTION) ARISING OUT OF THE USE OR INABILITY TO USE A WORK, EVEN IF ONE OF THEM HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. In any event, the total liability of the Rightsholder and CCC (including their respective employees

and directors) shall not exceed the total amount actually paid by User for this license. User assumes full liability for the actions and omissions of its principals, employees, agents, affiliates, successors and assigns.

6. Limited Warranties. THE WORK(S) AND RIGHT(S) ARE PROVIDED "AS IS". CCC HAS THE RIGHT TO GRANT TO USER THE RIGHTS GRANTED IN THE ORDER CONFIRMATION DOCUMENT. CCC AND THE RIGHTSHOLDER DISCLAIM ALL OTHER WARRANTIES RELATING TO THE WORK(S) AND RIGHT(S), EITHER EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. ADDITIONAL RIGHTS MAY BE REQUIRED TO USE ILLUSTRATIONS, GRAPHS, PHOTOGRAPHS, ABSTRACTS, INSERTS OR OTHER PORTIONS OF THE WORK (AS OPPOSED TO THE ENTIRE WORK) IN A MANNER CONTEMPLATED BY USER; USER UNDERSTANDS AND AGREES THAT NEITHER CCC NOR THE RIGHTSHOLDER MAY HAVE SUCH ADDITIONAL RIGHTS TO GRANT.

7. Effect of Breach. Any failure by User to pay any amount when due, or any use by User of a Work beyond the scope of the license set forth in the Order Confirmation and/or these terms and conditions, shall be a material breach of the license created by the Order Confirmation and these terms and conditions. Any breach not cured within 30 days of written notice thereof shall result in immediate termination of such license without further notice. Any unauthorized (but licensable) use of a Work that is terminated immediately upon notice thereof may be liquidated by payment of the Rightsholder's ordinary license price therefor; any unauthorized (and unlicensable) use that is not terminated immediately for any reason (including, for example, because materials containing the Work cannot reasonably be recalled) will be subject to all remedies available at law or in equity, but in no event to a payment of less than three times the Rightsholder's ordinary license price for the most closely analogous licensable use plus Rightsholder's and/or CCC's costs and expenses incurred in collecting such payment.

8. **Miscellaneous.**

8.1 User acknowledges that CCC may, from time to time, make changes or additions to the Service or to these terms and conditions, and CCC reserves the right to send notice to the User by electronic mail or otherwise for the purposes of notifying User of such changes or additions; provided that any such changes or additions shall not apply to permissions already secured and paid for.

8.2 Use of User-related information collected through the Service is governed by CCC's privacy policy, available online here:
http://www.copyright.com/content/cc3/en/tools/footer/privacypolicy.html.

8.3 The licensing transaction described in the Order Confirmation is personal to User. Therefore, User may not assign or transfer to any other person (whether a natural person or an organization of any kind) the license created by the Order Confirmation and these terms and conditions or any rights granted hereunder; provided, however, that User may assign such license in its entirety on written notice to CCC in the event of a transfer of all or substantially all of User's rights in the new material which includes the Work(s) licensed under this Service.

8.4 No amendment or waiver of any terms is binding unless set forth in writing and signed by the parties. The Rightsholder and CCC hereby object to any terms contained in any writing prepared by the User or its principals, employees, agents or affiliates and purporting to govern or otherwise relate to the licensing transaction described in the Order Confirmation, which terms are in any way inconsistent with any terms set forth in the Order Confirmation and/or in these terms and conditions or CCC's standard operating procedures, whether such writing is prepared prior to, simultaneously with or subsequent to the Order Confirmation, and whether such writing appears on a copy of the Order Confirmation or in a separate instrument.

8.5 The licensing transaction described in the Order Confirmation document shall be governed by and construed under the law of the State of New York, USA, without regard to the principles thereof of conflicts of law. Any case, controversy, suit, action, or proceeding arising out of, in connection with, or related to such licensing transaction shall be brought, at CCC's sole discretion, in any federal or state court located in the County of New York, State of New York, USA, or in any federal or state court whose geographical jurisdiction covers the location of the Rightsholder set forth in the Order Confirmation. The parties expressly submit to the personal jurisdiction and venue of each such federal or state court.If you have any comments or questions about the Service or Copyright Clearance Center, please contact us at 978-750-8400 or send an e-mail to info@copyright.com.
v 1.1

Appendix C

Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, Phrommintikul A. Low-density lipoprotein cholesterol of less than 70 mg/dL is associated with fewer cardiovascular events in acute coronary syndrome patients: a real-life cohort in Thailand. Ther Clin Risk Manag. 2015;11:659-667.

.

Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Low-density lipoprotein cholesterol of less than 70 mg/dL is associated with fewer cardiovascular events in acute coronary syndrome patients: a real-life cohort in Thailand

Dujrudee Chinwong[1,2]
Jayanton Patumanond[3]
Surarong Chinwong[1]
Khanchai Siriwattana[4]
Siriluck Gunaparn[5]
John Joseph Hall[6]
Arintaya Phrommintikul[5]

[1]Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [2]Clinical Epidemiology Program, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [3]Center of Excellence in Applied Epidemiology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand; [4]Division of Medicine, Nakornping Hospital, Chiang Mai, Thailand; [5]Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [6]Centre for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health, Faculty of Health, University of Newcastle, Callaghan, NSW, Australia

Background: Elevated low-density lipoprotein cholesterol (LDL-C) is associated with an increased risk of cardiovascular disease or mortality; however, the LDL-C goal for therapy in acute coronary syndrome (ACS) patients is controversial and varies among guidelines. This study aimed to assess the effect of reaching an LDL-C goal of <70 mg/dL (<1.8 mmol/L) on first composite cardiovascular outcomes in routine clinical practice in Thailand.

Methods: A retrospective cohort study was conducted using medical charts and the electronic hospital database of patients diagnosed with ACS and treated with statins at a tertiary care hospital in Thailand between 2009 and 2012. After admission, patients were followed from the date of LDL-C goal assessment until the first event of composite cardiovascular outcomes (nonfatal ACS, nonfatal stroke, or all-cause death). Cox proportional hazard models adjusted for potential confounders were used.

Results: Of 405 patients, mean age was 65 years (60% males). Twenty-seven percent of the patients attained an LDL-C goal of <70 mg/dL, 38% had LDL-C between 70 and 99 mg/dL, and 35% had LDL-C ≥100 mg/dL. Forty-six patients experienced a composite cardiovascular outcome. Compared with patients with an LDL-C ≥100 mg/dL, patients achieving an LDL-C of <70 mg/dL were associated with a reduced composite cardiovascular outcome (adjusted hazard ratio [HR]=0.42; 95% confidence interval [CI]=0.18–0.95; *P*-value=0.037), but patients with an LDL-C between 70 and 99 mg/dL had a lower composite cardiovascular outcome, which was not statistically significant (adjusted HR=0.73; 95% CI=0.37–1.42; *P*-value=0.354).

Conclusion: ACS patients who received statins and achieved an LDL-C of <70 mg/dL had significantly fewer composite cardiovascular outcomes, confirming "the lower the better" and the benefit of treating to LDL-C target in ACS patient management.

Keywords: LDL-C goal attainment, achieving LDL-C goal, statins, acute coronary syndrome, composite cardiovascular events

Introduction

Coronary artery disease (CAD) is one of the leading causes of death worldwide[1] and also in Thailand.[2] Well-established research demonstrates that a reduction in low-density lipoprotein cholesterol (LDL-C) is associated with a reduced risk of developing cardiovascular events and of mortality.[3–7] The main stem in LDL-C reduction is the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, also known as statins.[4,7,8] Recommending a treatment target for LDL-C for patients at very high cardiovascular risk, such as patients with acute coronary syndrome (ACS), is based on substantial evidence. Many commonly used guidelines (eg, the National

Correspondence: Arintaya Phrommintikul
Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand 50200
Tel +66 5394 6716
Fax +66 5328 9177
Email arintayap@gmail.com

Cholesterol Education Program/Adult Treatment Panel III [NCEP/ATP III][4] and the guidelines of the European Society of Cardiology and the European Atherosclerosis Society [ESC/EAS])[7] recommend a goal of <70 mg/dL in these very high-risk patients. By contrast, recent guidelines (the 2013 American College of Cardiology/American Heart Association [ACC/AHA] on cholesterol management,[9] as well as the National Institute for Health and Care Excellence [NICE] guidelines on lipid modification released in July 2014)[10] use the "fire and forget approach", which does not recommend LDL-C goal attainment because of a lack of randomized controlled trials (RCTs) establishing the benefit of the effect of treating to LDL-C target on cardiovascular morbidity and mortality. These later guidelines recommend the use of high-intensity statins for secondary prevention in ACS patients, with repeated measurement of lipid profiles being used to monitor patient compliance rather than LDL-C goal attainment.

It is common that very high cardiovascular risk patients such as ACS patients have difficulty in achieving an LDL-C goal of <70 mg/dL. Less than 45% of high-risk patients can reach LDL-C of <70 mg/dL,[11–24] with only 10% of patients achieving this goal in a study conducted in Greece.[13] Patients not achieving the desired LDL-C goal are at greater risk of cardiovascular events. The treat to target approach has greater benefit in identifying those ACS patients who fail to attain the LDL-C goal. In contrast, the fire and forget approach fails to recognize those ACS patients not achieving the desired goal; these ACS patients are at higher risk of cardiovascular events. As per the 2013 ACC/AHA guidelines, which recommend treatment according to patient risk and statin potency, a reduction in LDL-C of at least 50% is expected with high-intensity statins; however, variations in response to medications from patient to patient are common. Without follow-up lipid profiles, there is difficulty in evaluating the patients' cardiovascular risks. Elimination of the LDL-C goal target is perhaps the most controversial change among experts and physicans since the new 2013 ACC/AHA guidelines were released in November 2013.[25,26] This study therefore aimed to assess the association between LDL-C goal attainment of <70 mg/dL and cardiovascular outcomes in ACS patients treated with statins in routine clinical practice in Thailand.

Methods

Study population and setting

This retrospective cohort study was performed at a university-affiliated hospital, the Maharaj Nakorn Chiang Mai Hospital, in northern Thailand. This hospital provides services to patients in Chiang Mai province (a population of 1,600,000) as well as those patients referred from hospitals from 17 other provinces in the north. The hospital has 1,400 patient beds and an average of 1,300,000 outpatients and 48,000 inpatients each year. The study protocol was reviewed and approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, before commencement of the study.

A study nurse aware of the protocol and a researcher retrospectively selected all patients (aged ≥18 years) hospitalized with a diagnosis of ACS according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, code of I20 (angina pectoris) and I21 (acute myocardial infarction [MI]) who were treated with statins from 2009 to 2012. The patients' information, including demographic data, comorbidities, CAD risk factors, current medication, and laboratory results, including lipid profiles (total cholesterol, LDL-C, high-density lipoprotein, and triglycerides), was retrieved from medical charts and from the electronic hospital database. Patients were included in the analysis based on the following criteria: 1) admission date between January 1, 2009 and December 31, 2012; 2) diagnosis at discharge from medical charts as ACS patients, classified into three groups: unstable angina (UA), non ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI); 3) treated with statins during admission or on discharge date; 4) had LDL-C measurement both at admission (baseline) and at follow-up between 14 days and 1 year, as long as they remained on statins throughout this period of time; and 5) were followed for at least 12 months from the date of achieving the LDL-C goal of <70 mg/dL (index date) until the first event of cardiovascular outcomes occurred or until December 31, 2012, whichever came first, or the last entry on the medical record of a patient. Time to cardiovascular events was the interval between the dates of measuring the LDL-C goal to the date of the first cardiovascular event (Figure 1).

Achieved LDL-C levels and cardiovascular events

Patients were divided into three groups by lipid levels at 2 weeks to 1 year of follow-up after admission: <70 mg/dL, 70–99 mg/dL, and ≥100 mg/dL. According to the updated NCEP/ATP III[4] and the ESC/EAS guidelines,[7] those patients with LDL-C <70 mg/dL (<1.8 mmol/L) were classified as achieving LDL-C goal.

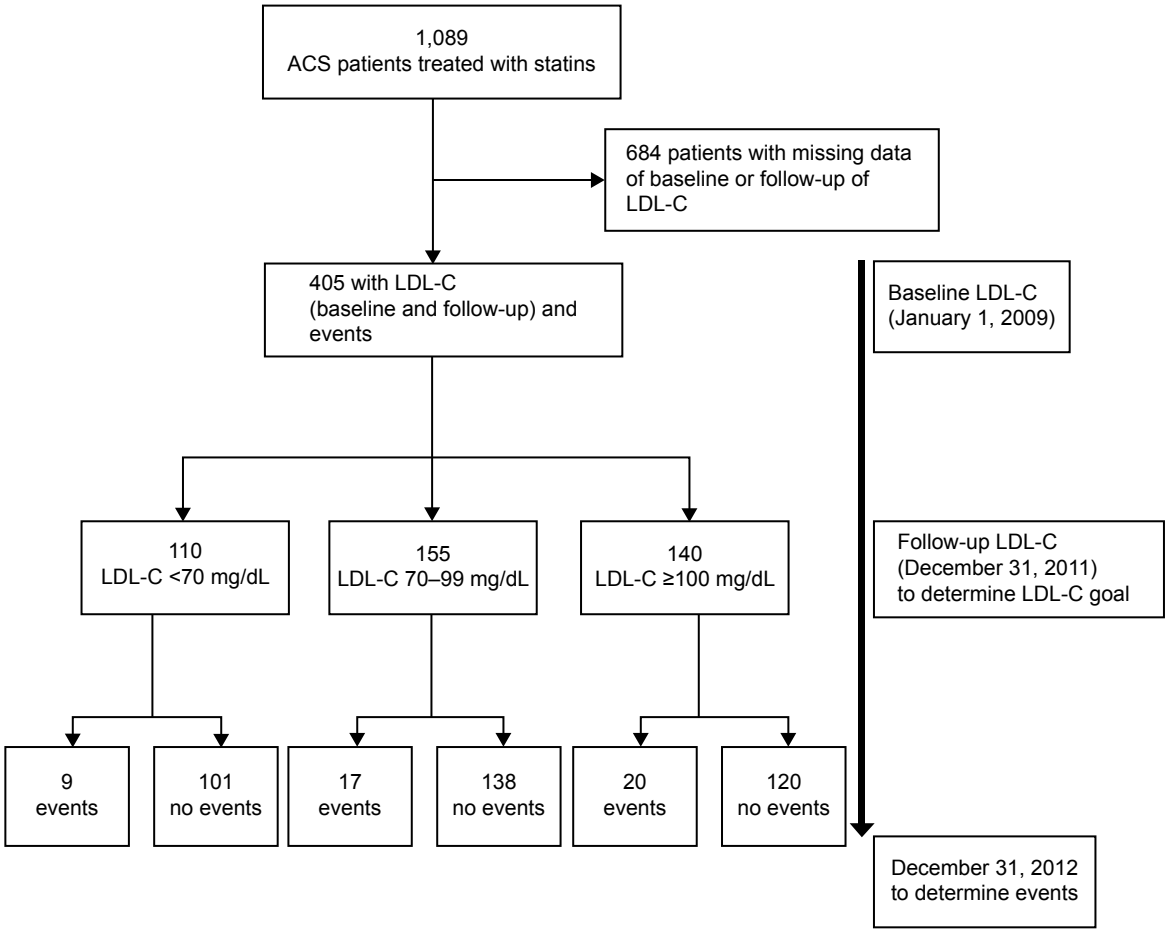

Figure 1 Flowchart of patient selection and study timeline.
Abbreviations: ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholestrol.

The primary end point was the first occurrence of any component of the composite of cardiovascular events, including nonfatal ACS (MI or UA), nonfatal stroke, or all-cause death.

Statistical analysis

We carried out all analyses with STATA software, version 12 (StataCorp LP, College Station, TX, USA). Using descriptive statistical methods, categorical variables were reported as counts and percentages, and continuous variables were presented as means with standard deviations. Differences between groups were compared using Fisher's exact tests for categorical variables or one-way analysis of variance for continuous variables. Univariable and multivariable Cox proportional hazard models were used to determine the effect of LDL-C goal attainment on cardiovascular events. The multivariable analysis were adjusted with potential confounders (age, sex, diabetes mellitus, hypertension, serum creatinine, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, revascularization, and baseline LDL-C level) and stratified by spectrum of ACS (UA, NSTEMI, STEMI). Patients with LDL-C ≥100 mg/dL were the reference group. The two-tailed test was used, and P-value<0.05 was considered statistically significant.

Results

We identified a total of 1,089 patients diagnosed with ACS from 2009 to 2012. We excluded 684 patients from the analysis because of unavailable data of LDL-C level at baseline or follow-up, resulting in 405 patients in the final analysis. Comparison between patients included and excluded from the analysis indicated that the two groups were not significantly different in their baseline characteristics, except that included patients were younger than excluded patients (64.9±11.5 vs 67.2±12.9; P-value=0.003).

Of 405 patients, 403 patients (99.5%) were treated with statins for the whole follow-up period, which was from baseline until the dates of first cardiovascular event occurring or until December 31, 2012, whichever came first. Statin therapy in two patients (0.5%) was discontinued during

their follow-up period because of their low LDL-C levels, about 40–45 mg/dL. Table 1 shows the baseline characteristics of the three groups as defined by their LDL-C level: <70 mg/dL, 70–99 mg/dL, and ≥100 mg/dL. Twenty-seven percent of the patients attained an LDL-C goal of <70 mg/dL, 38% had LDL-C between 70 and 99 mg/dL, and 35% had LDL-C ≥100 mg/dL. These three groups were similar in demographic characteristics, statin therapy, and coronary artery risk factors, except that patients with LDL-C <70 mg/dL were older and lower in total cholesterol and LDL-C levels at baseline compared with the other two groups (Tables 1–3).

Table 1 Baseline characteristic of patients classified by LDL-C levels (n=405)

Characteristics	LDL-C <70 mg/dL (n=110)	LDL-C 70–99 mg/dL (n=155)	LDL-C ≥100 mg/dL (n=140)	*P*-value
Male sex	64 (58.2)	100 (64.5)	81 (57.9)	0.425
Age (years)	67.4±10.8	64.6±11.9	63.3±11.4	0.016
Health insurance				
Universal coverage scheme	59 (53.6)	88 (56.8)	78 (55.7)	0.552
Civil servant medical benefit scheme	45 (40.9)	59 (38.1)	55 (39.3)	
Social security scheme	3 (2.7)	7 (4.5)	7 (5.0)	
Self-pay	3 (2.7)	1 (0.6)	0 (0.0)	
Smoking				
Nonsmoker	77 (70.0)	85 (54.8)	77 (55.0)	0.094
Ex-smoker	13 (11.8)	32 (20.7)	28 (20.0)	
Current smoker	20 (18.2)	38 (24.5)	35 (25.0)	
Diagnosis at discharge				
Unstable angina	21 (19.1)	29 (18.7)	28 (20.0)	0.368
NSTEMI	28 (25.5)	35 (22.6)	45 (32.1)	
STEMI	61 (55.5)	91 (58.7)	67 (47.9)	
Atherosclerotic risk factors				
Diabetes mellitus	31 (28.2)	46 (29.7)	40 (28.6)	0.970
Hypertension	71 (64.6)	92 (59.4)	88 (62.9)	0.675
Chronic kidney disease	17 (15.5)	17 (11.0)	17 (12.1)	0.551
Dyslipidemia	42 (38.2)	59 (38.1)	63 (45.0)	0.400
Family history of premature atherosclerosis	0 (0.0)	2 (1.3)	5 (3.6)	0.102
Previous history of cardiovascular events				
Chronic stable angina	11 (10.0)	11 (7.1)	13 (9.3)	0.696
Myocardial infarction or unstable angina	21 (19.1)	37 (23.9)	29 (20.7)	0.644
Stroke (ischemic)	4 (3.6)	15 (9.7)	5 (3.6)	0.057
Peripheral vascular disease	0 (0.0)	1 (0.7)	0 (0.0)	1.000
Previous history of cardiovascular intervention				
PCI	4 (3.6)	13 (8.4)	9 (6.4)	0.301
CABG	5 (4.6)	9 (5.8)	6 (4.3)	0.842
Revascularization of peripheral vascular disease	0 (0.0)	1 (0.7)	0 (0.0)	1.000
Carotid intervention	1 (0.9)	1 (0.7)	0 (0.0)	0.735
Treatment during admission				
PCI	39 (35.5)	59 (38.1)	61 (43.6)	0.392
CABG	0 (0.0)	2 (1.3)	3 (2.1)	0.382
Thrombolytic indicated	15 (13.6)	22 (14.2)	13 (9.3)	0.393
Medications				
Lipid-lowering drugs (nonstatins)	2 (1.8)	6 (3.9)	3 (2.1)	0.586
Antiplatelet/anticoagulant drugs	105 (95.5)	153 (98.7)	137 (97.9)	0.256
Beta-blockers	86 (78.2)	129 (83.2)	121 (86.4)	0.235
ACEI/ARB	71 (64.6)	95 (61.3)	91 (65.0)	0.780
CCB	31 (28.2)	28 (18.1)	26 (18.6)	0.107
Diuretics	39 (35.5)	43 (27.7)	33 (23.6)	0.119
Diabetic drugs	20 (18.2)	24 (15.5)	21 (15.0)	0.784

Note: Numbers are n (%) or mean ± standard deviation.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; NSTEMI, non ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CCB, calcium channel blocker.

Table 2 Baseline laboratory and lipid values of patients classified by LDL-C levels (n=405)

Characteristic	LDL-C <70 mg/dL (n=110)	LDL-C 70–99 mg/dL (n=155)	LDL-C ≥100 mg/dL (n=140)	*P*-value
Baseline laboratory				
Serum creatinine (mg/dL)	1.7±2.3	1.4±1.9	1.3±0.9	0.240
ALT (U/L)	31.9±23.6	32.5±30.9	42.5±76.0	0.150
Fasting blood glucose (n=387)	128.7±50.3	138.9±56.7	137.4±99.3	0.520
Baseline lipid values				
Total cholesterol (mg/dL)	165.8±50.1	180.8±49.2	192.1±46.0	<0.001
Triglyceride (mg/dL)	127.6±67.7	133.9±78.5	150.5±92.4	0.064
High-density lipoprotein (mg/dL)	39.6±12.2	40.8±12.0	39.7±9.9	0.656
Low-density lipoprotein (mg/dL)	97.7±41.5	112.6±39.8	123.3±39.7	<0.001

Note: Numbers are mean ± standard deviation.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase.

Forty-six patients experienced cardiovascular outcomes (35 nonfatal ACS, one stroke, ten deaths). Median follow-up time from the date of measuring LDL-C goal attainment (index date) to the date of occurrence of the cardiovascular event was 1.74 years (interquartile range of 0.74–2.53). The incidence rates (per 1,000 person-years) of cardiovascular outcomes were 43 in the LDL-C <70 mg/dL group, 66 in the LDL-C 70–99 mg/dL group, and 88 in the LDL-C ≥100 mg/dL group (Table 4). Multivariable Cox proportional hazard models showed that ACS patients treated with statins who achieved LDL-C of <70 mg/dL had fewer cardiovascular events compared with patients with an LDL-C ≥100 mg/dL (adjusted hazard ratio [HR]=0.42; 95% confidence interval [CI]=0.18–0.95; *P*-value=0.037). Similarly, patients with an LDL-C between 70 and 99 mg/dL were less likely to have cardiovascular events compared with patients with an LDL-C ≥100 mg/dL, but this was not statistically significant (adjusted HR=0.73; 95% CI=0.37–1.42; *P*-value=0.354) (Table 5).

Discussion

LDL-C goal attainment of <70 mg/dL has been used as a target for therapy to reduce further progression of cardiovascular events in ACS patients, as recommended by many guidelines since 2004. Recently, the treating to target approach has been a controversial issue in lipid management for physicians. Some guidelines – 2013 ACC/AHA guidelines on cholesterol management,[9] as well as NICE guidelines on lipid modification[10] – have abandoned the LDL-C goal due to the lack of RCT studies confirming the benefit of treating to LDL-C target on cardiovascular morbidity or mortality. Most RCTs of cholesterol-lowering medication were conducted testing drug treatment against a placebo control or a high-intensity drug with a lower-intensity drug.[9,10] In contrast, some guidelines – the 2011 ESC/EAS guidelines for the management of dyslipidemias,[7] as well as those of the 2014 National Lipid Association[27] – support using an LDL-C goal as a target for therapy in ACS patients. This clinical-based study in Thailand demonstrates that achieving

Table 3 Statin therapy on discharge date (n=405)

Statins	LDL-C <70 mg/dL (n=110)	LDL-C 70–99 mg/dL (n=155)	LDL-C ≥100 mg/dL (n=140)	*P*-value
Simvastatin 10 mg	3 (2.7)	6 (3.8)	6 (4.3)	0.927
Simvastatin 20 mg	40 (36.4)	61 (39.4)	54 (38.6)	
Simvastatin 40 mg	37 (33.6)	57 (36.8)	50 (35.7)	
Rosuvastatin 10 mg	6 (5.4)	5 (3.2)	8 (5.7)	
Rosuvastatin 20 mg	2 (1.8)	4 (2.6)	4 (2.9)	
Atorvastatin 20 mg	14 (12.7)	12 (7.7)	11 (7.8)	
Atorvastatin 40 mg	6 (5.4)	9 (5.8)	6 (4.3)	
Pitavastatin 2 mg	0 (0.0)	1 (0.6)	1 (0.7)	
Pravastatin 40 mg	2 (1.8)	0 (0.0)	0 (0.0)	

Note: Numbers are n (%).
Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Table 4 Person-time and incidence rate of outcomes by LDL-C levels (n=405)

Outcomes	LDL-C <70 mg/dL (n=110)	LDL-C 70–99 mg/dL (n=155)	LDL-C ≥100 mg/dL (n=140)	*P*-value
Total of person-years follow-up (total =690.34)	208.53	255.83	225.98	
Median time of follow-up, IQR (years)	1.96, 1.01–2.67	1.56, 0.71–2.51	1.52, 0.68–2.41	0.041
Mean time of follow-up ± SD (years)	1.89±1.04	1.65±1.05	1.61±1.06	0.045
Composite first events of nonfatal ACS, nonfatal stroke, death				
Number of patients (n=46)	9	17	20	
Incidence rate (per 1,000 person-years)	43	66	88	0.099
Nonfatal ACS				
Number of patients (n=35)	7	13	15	
Incidence rate (per 1,000 person-years)	33	51	66	0.875
Nonfatal stroke				
Number of patients (n=1)	0	1	0	
Incidence rate (per 1,000 person-years)	0	4	0	
Death				
Number of patients (n=10)	5	3	5	
Incidence rate (per 1,000 person-years)	22	12	22	0.231

Abbreviations: ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation.

an LDL-C goal of <70 mg/dL is associated with a reduction in cardiovascular events, a finding that supports the treating to LDL-C target approach. The findings also highlight that lower LDL-C is associated with better clinical outcomes. Although this is an observational study, the results represent the real-world clinical practice of cardiologists taking care of patients with very high cardiovascular risk.

Interestingly, our findings, which support treating to LDL-C target and the lower the LDL-C the fewer the cardiovascular events, are in line with the recently released results of the study Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).[28–30] This study was conducted in 18,144 patients with post-ACS and conducted over 9 years in 39 countries. It was found that the mean LDL-C at baseline was reduced from 95 mg/dL to 53.2 mg/dL at 1 year in patients receiving ezetimibe 10 mg plus simvastatin 40 mg, compared with 69.9 mg/dL in patients who received simvastatin 40 mg alone. The primary end point – a composite of cardiovascular death, MI, UA requiring rehospitalization, coronary revascularization, or stroke – in the ezetimibe plus simvastatin group was decreased by 6.4% over 7 years when compared with only simvastatin 40 mg (*P*-value =0.016). Further, our findings are also consistent with the results from three post hoc analyses

Table 5 Univariable and multivariable Cox proportional hazards model of LDL-C goal attainment affecting first event of composite outcomes of nonfatal ACS, nonfatal stroke, or death (n=405)

	Crude HR[a] (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value
LDL-C goal attainment				
LDL-C ≥100 mg/dL	1.00		1.00	
LDL-C 70–99 mg/dL	0.84 (0.44–1.62)	0.605	0.73 (0.37–1.42)	0.354
LDL-C <70 mg/dL	0.55 (0.25–1.21)	0.140	0.42 (0.18–0.95)	0.037
Age (years)	1.02 (0.99–1.05)	0.142	1.02 (0.99–1.04)	0.280
Male sex	1.33 (0.72–2.44)	0.367	1.55 (0.83–2.89)	0.170
Diabetes mellitus	1.67 (0.92–3.04)	0.091	1.42 (0.76–2.63)	0.271
Hypertension	1.89 (0.91–3.94)	0.088	1.69 (0.80–3.56)	0.171
Serum creatinine (mg/dL)	2.30 (1.27–4.17)	0.006	1.92 (1.00–3.70)	0.051
ACEI/ARB	0.63 (0.35–1.13)	0.119	0.91 (0.48–1.70)	0.758
Revascularization	0.43 (0.20–0.93)	0.032	0.49 (0.22–1.09)	0.079
Baseline LDL-C (mg/dL)	1.00 (0.99–1.01)	0.932	1.00 (0.99–1.01)	0.908

Note: [a]Stratified analysis by spectrum of acute coronary syndrome.
Abbreviations: ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

of data from two RCTs.[31–33] A post hoc analysis of the Treating to New Target (TNT) study, where patients were divided into quintiles according to their LDL-C levels, revealed that the patients who attained LDL-C levels <64 mg/dL had the lowest rate of major cardiovascular events (ie, CAD death, nonfatal MI, and stroke).[31] The risk was reduced in proportion to reductions in LDL-C levels.[31] In a further post hoc analysis from the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) study,[32] ACS patients were divided by 4-month LDL-C levels into four groups (≤40, >40–60, >60–80, and >80–100 mg/dL). The two groups with lower LDL-C values (≤40 mg/dL and >40–60 mg/dL groups) had fewer cardiac events (death, MI, stroke, recurrent ischemia, revascularization) when compared with the reference group (>80–100 mg/dL): ≤40 mg/dL, HR=0.61, and >40–60 mg/dL, HR=0.67.[32] Another post hoc analysis of the PROVE IT-TIMI 22 study among elderly patients with ACS found that the achievement of LDL-C <70 mg/dL was associated with a 40% relative lower risk of events (acute cardiac clinical events of death, MI, or UA requiring rehospitalization): HR=0.60.[33]

In addition, an observational study reported by Rallidis et at[16] found similar results that LDL-C goal attainment is associated with a reduction in cardiovascular events. Patients at very high risk with stable CAD who achieved an LDL-C goal of <70 mg/dL were less likely to have cardiovascular events (HR=0.34, 95% CI=0.17–0.70; *P*-value =0.003).[16]

Our findings underscore the importance of achieving LDL-C target goals for patients at very high risk of cardiovascular events. LDL-C goal attainment is associated with reduced cardiovascular outcomes; therefore, it is essential to continue using LDL-C <70 mg/dL as a target goal for treatment in very high cardiovascular risk patients. Moreover, the treat to target approach is beneficial for a patient-centered approach where physicians and patients discuss treatment objectives and use the treatment goal in order to follow patients' progress and to maximize long-term adherence to the treatment plan.[27] A study in Singapore found that >80% of CAD patients did not know their LDL-C target because of poor, or lack of, communication regarding LDL-C targets between physicians and patients, suggesting that patients may not achieve their treatment targets.[34] Besides, many studies show a positive relationship between adherence to taking statins and achieving the LDL-C goal.[35–37] However, adherence to statin therapy declines over time; ACS patients had a 2-year adherence rate with statins of about 40%.[38] Therefore, discussion with the patient of the importance of achieving and maintaining the LDL-C goal to reduce the risk of a cardiovascular event is vital.

In addition, and similar to previous studies, our findings demonstrate the difficulty in achieving an LDL-C goal of <70 mg/dL in patients with ACS; these patients are at higher risk of further cardiovascular events. Although only 27% of ACS patients in our study achieved LDL-C levels <70 mg/dL, the success rate of patients achieving this goal was higher than in previous studies in Thailand that showed <20% attaining the goal.[11,12] The finding is consistent with other studies that found that less than half of patients at very high risk for cardiovascular disease attain the LDL-C target.[11–24] Failure to achieve the LDL-C goal in ACS patients is due to some factors as discussed in a previous study,[39] such as inadequate lipid therapy,[39] health care policy,[39,40] or poor adherence to statin therapy.[35–37] Since using the treat to target approach can identify ACS patients who fail to attain the LDL-C goal (about three-quarters in this study), these patients can be identified as at greater risk of cardiovascular events; thus, LDL-C goal attainment is essential and also a means for doctors to follow up patients' progress.

Strengths and limitations

To the best of our knowledge, this study is possibly the first study in Asia to confirm that treating to LDL-C target of <70 mg/dL reduces cardiovascular events in very high cardiovascular risk ACS patients in real-world clinical practice.

However, the present study has some limitations. First, as it is a retrospective study, the results should be interpreted with caution due to possible confounders and lack of some information. Although we attempted to adjust for potential confounders in the statistical methods, residual unknown confounding factors could remain with this study design. No data on statin therapy prior to admission are available in about half of the patients because of various reasons (eg, some patients were referred from other hospitals in northern Thailand without information of statin therapy before their admission). However, all patients received statin therapy on their discharge dates. Second, it may not reflect the situation in other areas in Thailand or other countries because 1) all patients were from a university-affiliated hospital and 2) all patients were managed by cardiologists. Nevertheless, we believe that our finding – treating to LDL-C target of <70 mg/dL decreases cardiovascular events – is applicable for ACS patient management in other countries, because our findings are quite consistent with the IMPROVE IT study, which enrolled ACS patients from 39 countries with different clinical practice patterns as well as social and

economic background.[28–30] Finally, statin adherence, statin dose titration, and lifestyle therapies such as diet or exercise during treatment may have had an impact on LDL-C goal attainment and cardiovascular outcomes, but these were beyond the scope of our study. However, the effects of statin adherence, statin dose adjustment, and lifestyle therapies on cardiovascular outcomes warrant further analysis.

Conclusion

All in all, ACS patients who received statins and achieved an LDL-C of <70 mg/dL were more likely to have fewer cardiovascular outcomes, confirming the concept "the lower the better". However, about three-quarters of ACS patients in this study had difficulty achieving the LDL-C target; patients not achieving the LDL-C target are at greater risk of cardiovascular events compared with those achieving the goal. The treating to LDL-C target approach is supported by our finding, the 2011 ESC/EAS guidelines for the management of dyslipidemias,[7] and the 2014 National Lipid Association guidelines.[27] Thus, the use of the LDL-C goal of <70 mg/dL should be continued for lipid therapy and as a means of communication of patients' progress between physicians and patients.

Acknowledgments

This study was partially supported by the Graduate School, Chiang Mai University, Thailand. We thank the authorities of the Maharaj Nakorn Chiang Mai Hospital for their permission to use their data. The authors thank Claudia Koller for her assistance with editing this manuscript. Dujrudee Chinwong would like to express her gratitude to the Australian Government for awarding her with a 2014 Endeavour Research Fellowship undertaking at the University of Newcastle, Australia.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet.* 2006;367(9524):1747–1757.
2. Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Popul Health Metr.* 2010;8:14.
3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005;366(9493):1267–1278.
4. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110(2):227–239.
5. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA.* 2001;285(13):1711–1718.
6. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol.* 2006;48(3):438–445.
7. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J.* 2011;32(14):1769–1818.
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486–2497.
9. Stone NJ, Robinson JG, Lichtenstein AH, et al. 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. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889–2934.
10. National Institute for Health and Care Excellence. *Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease.* London, UK: National Clinical Guideline Centre; 2014.
11. Silaruks S, Sriratanasathavorn C, Rawdaree P, Kunjara-Na-Ayudhaya R, Thinkhamrop B, Sritara P. Lipid-lowering therapy using statins in patients with cardiovascular risk in clinical practice in Thailand. *Heart Asia.* 2011;3:99–103.
12. Sukonthasarn A, Homsanit M, Prommete B, Chotinaiwattarakul C, Piamsomboon C, Likittanasombat K. Lipid-lowering treatment in hypercholesterolemic patients: the CEPHEUS Thailand survey. *J Med Assoc Thai.* 2011;94(12):1424–1434.
13. Xanthopoulou I, Davlouros P, Siahos S, Perperis A, Zaharioglou E, Alexopoulos D. First-line treatment patterns and lipid target levels attainment in very high cardiovascular risk outpatients. *Lipids Health Dis.* 2013;12:170.
14. Andrikopoulos G, Tzeis S, Nikas N, et al. Short-term outcome and attainment of secondary prevention goals in patients with acute coronary syndrome – results from the countrywide TARGET study. *Int J Cardiol.* 2013;168(2):922–927.
15. Kim HS, Wu Y, Lin SJ, et al. Current status of cholesterol goal attainment after statin therapy among patients with hypercholesterolemia in Asian countries and region: the Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY-Asia) study. *Curr Med Res Opin.* 2008;24(7):1951–1963.
16. Rallidis LS, Kotakos C, Sourides V, et al. Attainment of optional low-density lipoprotein cholesterol goal of less than 70 mg/dL and impact on prognosis of very high risk stable coronary patients: a 3-year follow-up. *Expert Opin Pharmacother.* 2011;12(10):1481–1489.
17. Hermans MP, Castro Cabezas M, Strandberg T, et al. Centralized Pan-European Survey on the Under-treatment of Hypercholesterolaemia (CEPHEUS): overall findings from eight countries. *Curr Med Res Opin.* 2010;26(2):445–454.
18. Chin CW, Gao F, Le T, Tan R. Lipid goal attainment and prescription behavior in asian patients with acute coronary syndromes: experience from a tertiary hospital. *Clin Med Insights Cardiol.* 2013;7:51–57.
19. Kauffman AB, Olson KL, Youngblood ML, Zadvorny EB, Delate T, Merenich JA. Attainment of low-density lipoprotein cholesterol goals in coronary artery disease. *J Clin Lipidol.* 2010;4(3):173–180.
20. Kitkungvan D, Lynn Fillipon NM, Dani SS, Downey BC. Low-density lipoprotein cholesterol target achievement in patients at high risk for coronary heart disease. *J Clin Lipidol.* 2010;4(4):293–297.
21. Karalis DG, Victor B, Ahedor L, Liu L. Use of lipid-lowering medications and the likelihood of achieving optimal LDL-cholesterol goals in coronary artery disease patients. *Cholesterol.* 2012;2012:861924.

22. Karalis DG, Subramanya RD, Hessen SE, Liu L, Victor MF. Achieving optimal lipid goals in patients with coronary artery disease. *Am J Cardiol.* 2011;107(6):886–890.
23. Park JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolaemic patients: the CEPHEUS pan-Asian survey. *Eur J Prev Cardiol.* 2012;19(4):781–794.
24. Melloni C, Shah BR, Ou FS, et al. Lipid-lowering intensification and low-density lipoprotein cholesterol achievement from hospital admission to 1-year follow-up after an acute coronary syndrome event: results from the Medications ApplIed aNd SusTAINed Over Time (MAINTAIN) registry. *Am Heart J.* 2010;160(6):1121–1129, 1129.e1.
25. Ray KK, Kastelein JJ, Boekholdt SM, et al. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. *Eur Heart J.* 2014;35(15):960–968.
26. Lopez-Jimenez F, Simha V, Thomas RJ, et al. A summary and critical assessment of the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: filling the gaps. *Mayo Clin Proc.* 2014;89(9):1257–1278.
27. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary. *J Clin Lipidol.* 2014;8(5):473–488.
28. Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J.* 2008;156(5):826–832.
29. Blazing MA, Giugliano RP, Cannon CP, et al. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. *Am Heart J.* 2014;168(2):205–212.e1.
30. O'Riordan M. *IMPROVE-IT: 'Modest' Benefit When Adding Ezetimibe to Statins in Post-ACS Patients. Medscape Pharmacist Website*. Available from: http://www.medscape.com/viewarticle/835030. Accessed February 23, 2015.
31. LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H. Safety and efficacy of Atorvastatin-induced very low-density lipoprotein cholesterol levels in Patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). *Am J Cardiol.* 2007;100(5):747–752.
32. Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. *J Am Coll Cardiol.* 2005;46(8):1411–1416.
33. Ray KK, Bach RG, Cannon CP, et al. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. *Eur Heart J.* 2006;27(19):2310–2316.
34. Tan NC, Ho SC. Treat-to-target approach in managing modifiable risk factors of patients with coronary heart disease in primary care in Singapore: what are the issues? *Asia Pac Fam Med.* 2011;10:12.
35. Parris ES, Lawrence DB, Mohn LA, Long LB. Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. *Diabetes Care.* 2005;28(3):595–599.
36. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* 2009;119(23):3028–3035.
37. Bermingham M, Hayden J, Dawkins I, et al. Prospective analysis of LDL-C goal achievement and self-reported medication adherence among statin users in primary care. *Clin Ther.* 2011;33(9):1180–1189.
38. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA.* 2002;288(4):462–467.
39. Chinwong D, Patumanond J, Chinwong S, et al. Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency. *Ther Clin Risk Manag.* 2015;11:127–136.
40. Gizurarson S, Bjornsdottir LR, Einarsdottir R, Halldorsson M, Andersen K. Clinical consequences following regulatory changes in respect to reimbursement of statins cost by the Icelandic Social Insurance Administration. *Scand J Public Health.* 2012;40(7):663–667.

Dove Medical Press Ltd. LICENSE TERMS AND CONDITIONS

Nov 30, 2015

This is a License Agreement between Dujrudee Chinwong ("You") and Dove Medical Press Ltd. ("Dove Medical Press Ltd.") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Dove Medical Press Ltd., and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

License Number	3754851140520
License date	Nov 23, 2015
Licensed content publisher	Dove Medical Press Ltd.
Licensed content title	Therapeutics and Clinical Risk Management
Licensed content date	Jan 1, 2005
Type of Use	Thesis/Dissertation
Requestor type	Academic institution
Format	Electronic
Portion	chapter/article
Title or numeric reference of the portion(s)	1 article with 40 references, 5 tables and 1 figure.
Title of the article or chapter the portion is from	Low-density lipoprotein cholesterol of less than 70 mg/dL is associated with fewer cardiovascular events in acute coronary syndrome patients: a real-life cohort in Thailand
Editor of portion(s)	N/A
Author of portion(s)	N/A
Volume of serial or monograph.	N/A
Issue, if republishing an article from a serial	Volume 2015:11 Pages 659â667
Page range of the portion	None
Publication date of portion	24 April 2015
Rights for	Main product and any product related to main product
Duration of use	Current edition and up to 5 years
Creation of copies for the disabled	no
With minor editing privileges	yes
For distribution to	Worldwide
In the following language(s)	Original language plus one translation
Specific languages	English, Thai
With incidental promotional use	yes
The lifetime unit quantity of new product	Up to 499
Made available in the following markets	Education
The requesting person/organization is:	Dujrudee Chinwong

Order reference number	None
Author/Editor	Dujrudee Chinwong
The standard identifier	an internal reference
Title	Low-density lipoprotein cholesterol of less than 70 mg/dL is associated with fewer cardiovascular events in acute coronary syndrome patients: a real-life cohort in Thailand
Publisher	Chiang Mai University
Expected publication date	Nov 2015
Estimated size (pages)	80
Total (may include CCC user fee)	0.00 USD
Terms and Conditions	

TERMS AND CONDITIONS

The following terms are individual to this publisher:

None

Other Terms and Conditions:

STANDARD TERMS AND CONDITIONS

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

3.1 All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

3.2 General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, Dept 001, P.O. Box 843006, Boston, MA 02284-3006. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the

Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.
3.3 Unless otherwise provided in the Order Confirmation, any grant of rights to User (i) is "one-time" (including the editions and product family specified in the license), (ii) is non-exclusive and non-transferable and (iii) is subject to any and all limitations and restrictions (such as, but not limited to, limitations on duration of use or circulation) included in the Order Confirmation or invoice and/or in these terms and conditions. Upon completion of the licensed use, User shall either secure a new permission for further use of the Work(s) or immediately cease any new use of the Work(s) and shall render inaccessible (such as by deleting or by removing or severing links or other locators) any further copies of the Work (except for copies printed on paper in accordance with this license and still in User's stock at the end of such period).
3.4 In the event that the material for which a republication license is sought includes third party materials (such as photographs, illustrations, graphs, inserts and similar materials) which are identified in such material as having been used by permission, User is responsible for identifying, and seeking separate licenses (under this Service or otherwise) for, any of such third party materials; without a separate license, such third party materials may not be used.
3.5 Use of proper copyright notice for a Work is required as a condition of any license granted under the Service. Unless otherwise provided in the Order Confirmation, a proper copyright notice will read substantially as follows: "Republished with permission of [Rightsholder's name], from [Work's title, author, volume, edition number and year of copyright]; permission conveyed through Copyright Clearance Center, Inc. " Such notice must be provided in a reasonably legible font size and must be placed either immediately adjacent to the Work as used (for example, as part of a by-line or footnote but not as a separate electronic link) or in the place where substantially all other credits or notices for the new work containing the republished Work are located. Failure to include the required notice results in loss to the Rightsholder and CCC, and the User shall be liable to pay liquidated damages for each such failure equal to twice the use fee specified in the Order Confirmation, in addition to the use fee itself and any other fees and charges specified.
3.6 User may only make alterations to the Work if and as expressly set forth in the Order Confirmation. No Work may be used in any way that is defamatory, violates the rights of third parties (including such third parties' rights of copyright, privacy, publicity, or other tangible or intangible property), or is otherwise illegal, sexually explicit or obscene. In addition, User may not conjoin a Work with any other material that may result in damage to the reputation of the Rightsholder. User agrees to inform CCC if it becomes aware of any infringement of any rights in a Work and to cooperate with any reasonable request of CCC or the Rightsholder in connection therewith.
4. Indemnity. User hereby indemnifies and agrees to defend the Rightsholder and CCC, and their respective employees and directors, against all claims, liability, damages, costs and expenses, including legal fees and expenses, arising out of any use of a Work beyond the scope of the rights granted herein, or any use of a Work which has been altered in any unauthorized way by User, including claims of defamation or infringement of rights of copyright, publicity, privacy or other tangible or intangible property.
5. Limitation of Liability. UNDER NO CIRCUMSTANCES WILL CCC OR THE RIGHTSHOLDER BE LIABLE FOR ANY DIRECT, INDIRECT, CONSEQUENTIAL OR INCIDENTAL DAMAGES (INCLUDING WITHOUT LIMITATION DAMAGES FOR LOSS OF BUSINESS PROFITS OR INFORMATION, OR FOR BUSINESS INTERRUPTION) ARISING OUT OF THE USE OR INABILITY TO USE A WORK, EVEN IF ONE OF THEM HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. In any event, the total liability of the Rightsholder and CCC (including their respective employees

and directors) shall not exceed the total amount actually paid by User for this license. User assumes full liability for the actions and omissions of its principals, employees, agents, affiliates, successors and assigns.

6. Limited Warranties. THE WORK(S) AND RIGHT(S) ARE PROVIDED "AS IS". CCC HAS THE RIGHT TO GRANT TO USER THE RIGHTS GRANTED IN THE ORDER CONFIRMATION DOCUMENT. CCC AND THE RIGHTSHOLDER DISCLAIM ALL OTHER WARRANTIES RELATING TO THE WORK(S) AND RIGHT(S), EITHER EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. ADDITIONAL RIGHTS MAY BE REQUIRED TO USE ILLUSTRATIONS, GRAPHS, PHOTOGRAPHS, ABSTRACTS, INSERTS OR OTHER PORTIONS OF THE WORK (AS OPPOSED TO THE ENTIRE WORK) IN A MANNER CONTEMPLATED BY USER; USER UNDERSTANDS AND AGREES THAT NEITHER CCC NOR THE RIGHTSHOLDER MAY HAVE SUCH ADDITIONAL RIGHTS TO GRANT.

7. Effect of Breach. Any failure by User to pay any amount when due, or any use by User of a Work beyond the scope of the license set forth in the Order Confirmation and/or these terms and conditions, shall be a material breach of the license created by the Order Confirmation and these terms and conditions. Any breach not cured within 30 days of written notice thereof shall result in immediate termination of such license without further notice. Any unauthorized (but licensable) use of a Work that is terminated immediately upon notice thereof may be liquidated by payment of the Rightsholder's ordinary license price therefor; any unauthorized (and unlicensable) use that is not terminated immediately for any reason (including, for example, because materials containing the Work cannot reasonably be recalled) will be subject to all remedies available at law or in equity, but in no event to a payment of less than three times the Rightsholder's ordinary license price for the most closely analogous licensable use plus Rightsholder's and/or CCC's costs and expenses incurred in collecting such payment.

8. **Miscellaneous.**

8.1 User acknowledges that CCC may, from time to time, make changes or additions to the Service or to these terms and conditions, and CCC reserves the right to send notice to the User by electronic mail or otherwise for the purposes of notifying User of such changes or additions; provided that any such changes or additions shall not apply to permissions already secured and paid for.

8.2 Use of User-related information collected through the Service is governed by CCC's privacy policy, available online here:
http://www.copyright.com/content/cc3/en/tools/footer/privacypolicy.html.

8.3 The licensing transaction described in the Order Confirmation is personal to User. Therefore, User may not assign or transfer to any other person (whether a natural person or an organization of any kind) the license created by the Order Confirmation and these terms and conditions or any rights granted hereunder; provided, however, that User may assign such license in its entirety on written notice to CCC in the event of a transfer of all or substantially all of User's rights in the new material which includes the Work(s) licensed under this Service.

8.4 No amendment or waiver of any terms is binding unless set forth in writing and signed by the parties. The Rightsholder and CCC hereby object to any terms contained in any writing prepared by the User or its principals, employees, agents or affiliates and purporting to govern or otherwise relate to the licensing transaction described in the Order Confirmation, which terms are in any way inconsistent with any terms set forth in the Order Confirmation and/or in these terms and conditions or CCC's standard operating procedures, whether such writing is prepared prior to, simultaneously with or subsequent to the Order Confirmation, and whether such writing appears on a copy of the Order Confirmation or in a separate instrument.

8.5 The licensing transaction described in the Order Confirmation document shall be governed by and construed under the law of the State of New York, USA, without regard to the principles thereof of conflicts of law. Any case, controversy, suit, action, or proceeding arising out of, in connection with, or related to such licensing transaction shall be brought, at CCC's sole discretion, in any federal or state court located in the County of New York, State of New York, USA, or in any federal or state court whose geographical jurisdiction covers the location of the Rightsholder set forth in the Order Confirmation. The parties expressly submit to the personal jurisdiction and venue of each such federal or state court.If you have any comments or questions about the Service or Copyright Clearance Center, please contact us at 978-750-8400 or send an e-mail to info@copyright.com.
v 1.1

Appendix D

Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, Phrommintikul A. Clinical indicators for recurrent cardiovascular events in acute coronary syndrome patients treated with statins under routine practice in Thailand: an observational study. BMC Cardiovasc Disord. 2015;15(1):55.

Chinwong et al. BMC Cardiovascular Disorders (2015) 15:55
DOI 10.1186/s12872-015-0052-y

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Clinical indicators for recurrent cardiovascular events in acute coronary syndrome patients treated with statins under routine practice in Thailand: an observational study

Dujrudee Chinwong[1,2], Jayanton Patumanond[3], Surarong Chinwong[1], Khanchai Siriwattana[4], Siriluck Gunaparn[5], John Joseph Hall[6] and Arintaya Phrommintikul[5*]

Abstract

Background: Acute coronary syndrome (ACS) patients are at very high cardiovascular risk and tend to have recurrent cardiovascular events. The clinical indicators for subsequent cardiovascular events are limited and need further investigation. This study aimed to explore clinical indicators that were associated with recurrent cardiovascular events following index hospitalization.

Methods: The data of patients hospitalized with ACS at a tertiary care hospital in northern Thailand between January 2009 and December 2012 were retrospectively reviewed from medical charts and the electronic hospital database. The patients were classified into three groups based on the frequency of recurrent cardiovascular events (nonfatal ACS, nonfatal stroke, or all-cause death) they suffered: no recurrent events (0), single recurrent event (1), and multiple recurrent events (≥2). Ordinal logistic regression was performed to explore the clinical indicators for recurrent cardiovascular events.

Results: A total of 405 patients were included; 60 % were male; the average age was 64.9 ± 11.5 years; 40 % underwent coronary revascularization during admission. Overall, 359 (88.6 %) had no recurrent events, 36 (8.9 %) had a single recurrent event, and 10 (2.5 %) had multiple recurrent events. The significant clinical indicators associated with recurrent cardiovascular events were achieving an LDL-C goal of < 70 mg/dL (Adjusted OR = 0.43; 95 % CI = 0.27–0.69, p-value < 0.001), undergoing revascularization during admission (Adjusted OR = 0.44; 95 % CI = 0.24–0.81, *p*-value = 0.009), being male (Adjusted OR = 1.85; 95 % CI = 1.29–2.66, *p*-value = 0.001), and decrease estimated glomerular filtration rate (Adjusted OR = 2.46; 95 % CI = 2.21–2.75, *p*-value < 0.001).

Conclusion: The routine clinical practice indicators assessed in ACS patients that were associated with recurrent cardiovascular events were that achieving the LDL-C goal and revascularization are protective factors, while being male and having decreased estimated glomerular filtration rate are risk factors for recurrent cardiovascular events. These clinical indicators should be used for routinely monitoring patients to prevent recurrent cardiovascular events in ACS patients.

Keywords: Subsequent cardiovascular events, LDL-C < 70 mg/dL, LDL-C goal, Multiple recurrent cardiovascular events, Acute coronary syndrome, eGFR, Revascularization

* Correspondence: arintayap@gmail.com
[5]Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand50200
Full list of author information is available at the end of the article

Background

Acute coronary syndrome (ACS) is one of the clinical manifestations of cardiovascular diseases considered to be life threatening [1]. Comparing with the Global Registry of Acute Coronary Events (GRACE) [2] that showed an in-hospital mortality rate of 4.6 %; the in-hospital death rate was higher in the first [3] and second [4] Thai registries of ACS patients. Both are multi-center, prospective, nation-wide registries that collect relevant information in Thailand. The first Thai Acute Coronary Syndrome (TACS) registry [3] conducted between 2002 and 2004 in 17 provinces showed an in-hospital mortality rate of 12.6 %. Later, between 2007 and 2008, the second registry (the Thai Registry of Acute Coronary Syndrome, TRACS) was conducted in 39 provinces; it showed a reduced in-hospital morality of 4.8 %, but the mortality rates at 6-months and 1-year were still high (14.1 % and 17.7 %, respectively) [4].

Patients with established cardiovascular disease such as ACS patients are at higher risk for recurrent cardiovascular events following the first event [5–7], with about 1 % (140/13,608) [6] to 9 % (380/4,162) [7] of ACS patients having subsequent cardiovascular events. The first event of the composite of cardiovascular events was widely used in efficacy analyses for the Randomized Controlled Trials (RCTs) [8, 9], but the subsequent events following the first event are generally not considered in a primary end point analysis. However, in routine clinical practice both the patients and physicians are concerned not only about the first event but also about subsequent events. ACS patients with different frequency of recurrent cardiovascular events following their index hospitalization may differ in their clinical indicators. Investigating recurrent events, rather than only the first event, can provide more evidence for physicians and patients on how best to monitor patients' progress. Some predictors of subsequent cardiovascular events such as age, high serum creatinine, and low high-density lipoprotein cholesterol were reported in survivors of first hospitalized myocardial infarction [10].

There are limited data available about the clinical indicators for recurrent cardiovascular events in Thailand. This study aims to explore if any of the information that is collected as part of routine clinical practice is associated with recurrent cardiovascular events in patients with ACS in Thailand.

Methods

Setting and study population

The study setting was the Maharaj Nakorn Chiang Mai Hospital, which is part of Chiang Mai University, with 1,400 patient beds to serve 1,300,000 outpatients and 48,000 inpatients annually [11]. This tertiary teaching hospital provides services to patients from Chiang Mai province (a population of approximately 1,600,000) and from 17 other provinces in northern Thailand that refer patients with complicated conditions such as ACS for specialist treatment. The hospital provides services in every medical discipline through a number of centers including the Northern Thailand Heart Center, the Northern Neuroscience Center, the Trauma Center, the Cancer Treatment and Research Center, the Respiratory Research Center, and the Lung Health Center. The research protocol was reviewed and approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, prior to commencement of data collection for the study.

We included all patients diagnosed with ACS - including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI) - aged 18 years and over, treated with statins, and were admitted to the hospital between January 2009 and December 2012. A diagnosis of ACS was based on an ICD-10 (International Classification of Diseases, 10th Revision) code of I20 (angina pectoris) or I21 (acute myocardial infarction). We retrospectively reviewed and retrieved the information for the clinical indicators of interest and cardiovascular events of the included patients from medical charts and from the electronic hospital database.

Clinical indicators of interest

Clinical indicators of interest based on routinely clinical practice were collected: demographic data, co-morbidities, atherosclerotic risk factors, current medications, and laboratory results including lipid profiles (total cholesterol, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and triglycerides), alanine aminotransferase (ALT), fasting blood glucose, and serum creatinine. The degree of renal function of patients was classified according to the estimated glomerular filtration rate (eGFR) during admission with the use of CKD-EPI Creatinine 2009 Equation, which estimated eGFR from serum creatinine, age, sex, and race, into two groups: < 60 mL/min/1.73 m^2 and ≥ 60 mL/min/1.73 m^2 [12]. LDL-C goal attainment was determined at the first follow-up visit of patients which occurred between 2 weeks and 1 year from the admission date. LDL-C levels were categorized into one of three groups: LDL-C < 70 mg/dL, 70–99 mg/dL, and $\geq$ 100 mg/dL; LDL-C < 70 mg/dL (<1.8 mmol/L) was classified as achieving the LDL-C goal according to the guidelines [13]; LDL-C ≥ 100 mg/dL was used as the reference group in the analysis. Revascularization was defined as undergoing percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) during admission of patients.

Recurrent cardiovascular events

In our study, recurrent cardiovascular events were defined as nonfatal ACS (myocardial infarction (MI) or unstable angina), nonfatal stroke, or all-cause death following the index hospitalization. Patients were categorized into three groups based on the frequency of recurrent cardiovascular events: no recurrent event (0), single recurrent event (1), and multiple recurrent events (≥2, Fig. 1). For example, if a patient experienced only a nonfatal MI, this was classified as having a single recurrent event. If a patient had a nonfatal MI, and the same patient subsequently had a stroke, the patient was characterized as having multiple recurrent events. Using this method, all events were weighted equally (i.e. death and recurrent MI or stroke were weighted equally).

Statistical analysis

Descriptive statistics were examined to describe variables with counts and percentages reporting for categorical variables, and means with standard deviations for continuous variables. We used nonparametric tests for trends across ordered groups to investigate differences across the three groups of patients. Due to the ordinal nature of the outcome variable (0, 1, ≥2 recurrent events), we used ordinal logistic regression [14, 15]. Univariable and multivariable ordinal logistic regression (clustered with stratum of ACS [UA, NSTEMI, STEMI] and adjusted with the length of follow-up time) were performed to explore the clinical indicators for recurrent cardiovascular events. The two-tailed test was used and p-value < 0.05 was considered statistically significant. All analyses were carried out using STATA software, version 12 (StataCorp LP, College Station, TX, USA).

Results

A total of 1,089 medical records of patients diagnosed with ACS were reviewed. Due to the incompleteness of the essential data for analysis, lack of LDL-C level at baseline and follow-up, we excluded 684 patients' records, resulting in 405 patients being included in the final analysis. We performed a comparison analysis between those patients excluded and included in the analysis and found that the two groups were not significantly different in their baseline characteristics; but the excluded patients were older than the included patients (67.2 ± 12.9 vs 64.9 ± 11.5; p-value = 0.003).

In our study, the median time of follow-up from index hospitalization to the last medical contact, or until 31 December 2012, was 810 days (Interquartile range [IQR]: 489–1093). For those with a single recurrent event (36 patients), the median time from index hospitalization to the first recurrent event was 278 days (IQR: 159–522). Of the 405 patients, 359 (88.6 %) patients did not experience any recurrent event; 36 (8.9 %) patients experienced a single recurrent event, and 10 (2.5 %) patients experienced ≥ 2 recurrent events. The three groups were similar in gender, age, health insurance status, smoking status, having dyslipidaemia, having a family history of premature atherosclerosis, having a previous history of chronic stable angina, stroke, and

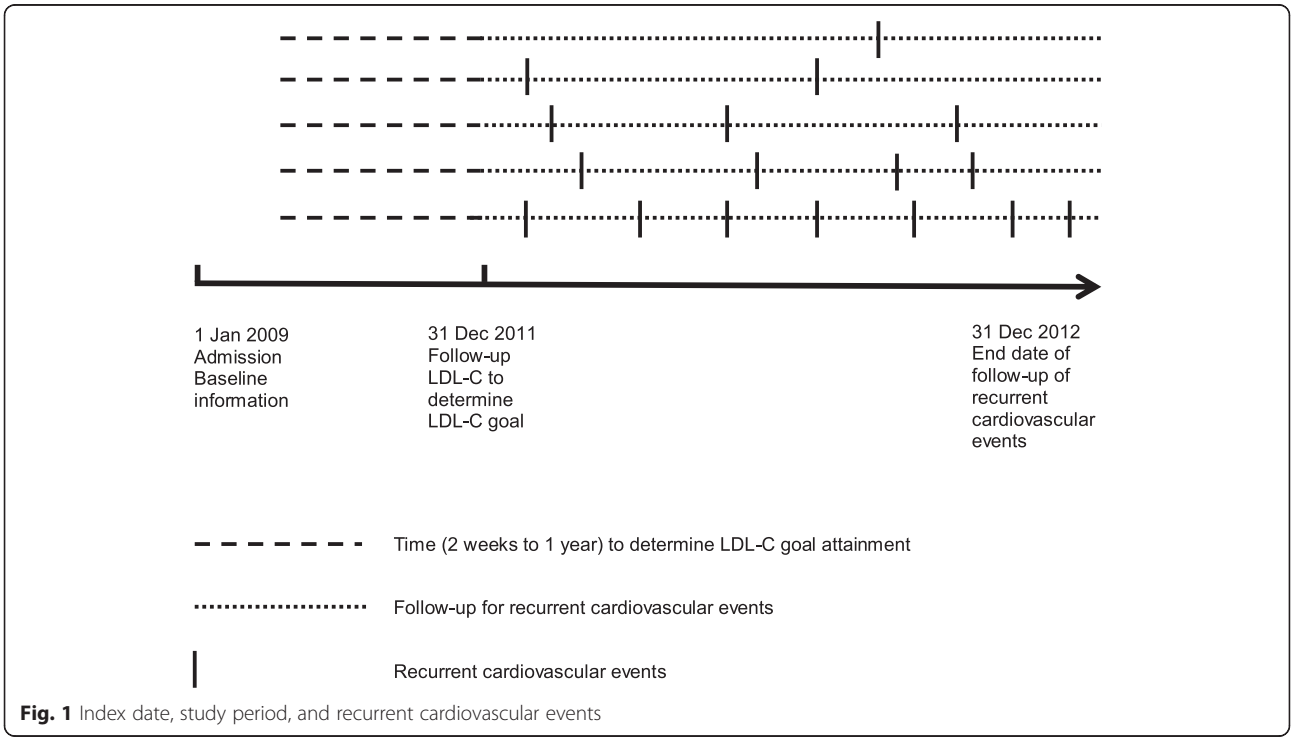

Fig. 1 Index date, study period, and recurrent cardiovascular events

peripheral vascular disease, having a history of CABG and carotid intervention, and current medication use. They also were similar in most of the laboratory findings except for serum creatinine and eGFR. Characteristics that differed among groups were diagnosis at discharge, diabetes mellitus, hypertension, chronic kidney disease, previous histories of MI or UA, previous histories of percutaneous coronary intervention (PCI), undergoing PCI during admission, current medication with diabetic drugs and calcium channel blocker (CCB) (Table 1). Of those who had a recurrent cardiovascular event, nonfatal ACS was the most common; ten patients died; ten patients had multiple recurrent cardiovascular events; one patient had seven cardiovascular events (all nonfatal ACS) (Table 2).

The univariable ordinal logistic regression showed that the significant clinical indicators associated with recurrent cardiovascular outcomes were achieving LDL-C goal of < 70 mg/dL, revascularization, eGFR <60 mL/min/1.73 m^2, increased age, hypertension, use of angiotensin-converting enzyme inhibitors (ACEI/ARB) (Table 3). With multivariable ordinal logistic regression, four clinical factors (2 protective factors and 2 risk factors) associated with recurrent cardiovascular events were achieving LDL-C goal of < 70 mg/dL (Adjusted OR = 0.43; 95 % CI = 0.27–0.69, *p*-value < 0.001), undergoing revascularization during admission (Adjusted OR = 0.44; 95 % CI = 0.24–0.81, *p*-value = 0.009), being male (Adjusted OR = 1.85; 95 % CI = 1.29–2.66, *p*-value = 0.001), and eGFR < 60 mL/min/1.73 m^2 (Adjusted OR = 2.46; 95 % CI = 2.21–2.75, *p*-value < 0.001) (Table 3). In our study, there were five non-cardiovascular deaths; nevertheless, the results of clinical indicators on recurrent cardiovascular events were consistent when using cardiovascular death instead of all-cause death. In addition, ACEI/ARB was found to be a protective factor for recurrent events (the data not shown).

Discussion

In our study, multiple recurrent cardiovascular events occurred in 2.5 % of ACS patients, which are in line with previous studies that 1–9 % of patients had multiple recurrent cardiovascular events. Our study to investigate the clinical factors that were associated with recurrent cardiovascular events identified two protective factors – achieving LDL-C goal of less than 70 mg/dL, and undergoing revascularization (either PCI or CABG) during admission. The study also found two risk factors for further events – male gender and decreased eGFR.

Achieving LDL-C goal of less than 70 mg/dL

Our finding shows that patients with ACS who achieve the LDL-C goal of less than 70 mg/dL have fewer recurrent cardiovascular events compared to those not achieving goal. To our knowledge, there is no other study that investigates the association between LDL-C goal achievement and recurrent cardiovascular events. However, some studies [16–18], including our former study [19], demonstrated that lowering LDL-C to less than 70 mg/dL resulted in reducing the incidence of cardiovascular events. Our previous study revealed that ACS patients treated with statins who achieved an LDL-C goal of <70 mg/dL had significantly fewer composite cardiovascular outcomes [19]. Similarly, the results from the two post-hoc analyses from the PROVE IT-TIMI 22 RTC (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) [17, 18] showed that ACS patients with the lower LDL-C values (≤40 mg/dL and >40 to 60 mg/dL groups) had a reduction in cardiac events (death, MI, stroke, recurrent ischemia, revascularization) when compared with the reference group (>80 to 100 mg/dL) [17]. The same study found that elderly patients with ACS who attained LDL-C levels < 70 mg/dL had a 40 % relative lower risk of acute cardiac clinical events of death, MI, or UA requiring rehospitalisation [18].

Further, a recently released result of a RCT study, the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [20–22], conducted over 9 years on 18,144 patients with post-ACS from 39 countries, showed that an LDL-C less than 60 mg/dL is associated with a reduction in cardiovascular events. The primary end point of that study was a composite of cardiovascular death, MI, unstable angina requiring rehospitalisation, coronary revascularization, or stroke. The primary endpoint in the ezetimibe plus simvastatin group, with LDL-C of about 53 mg/dL after 1 year of follow-up, was decreased by 6.4 % over 7 years when compared with the simvastatin (40 mg) only group, with LDL-C of about 69 mg/dL (p = 0.016).

Many guidelines, such as the ESC/EAS Guidelines for the management of dyslipidemias [13], and the 2014 National Lipid Association [23], recommend an LDL-C goal of less than 70 mg/dL as a target for therapy in ACS patients. Recently, some guidelines – 2013 ACC/AHA on cholesterol management [24] and the NICE guidelines on lipid modification [25] – does not recommend the LDL-C goal because they found no evidence from RCTs studies to confirm an association between treating to the LDL-C target and cardiovascular events or mortality. As a result, the treating to target approach has been debatable in lipid management for some physicians. Our finding supports that treating to an LDL-C target of less than 70 mg/dL is beneficial because patients who do not achieve this goal are more likely to have subsequent cardiovascular events. This suggests that physicians should discuss with patients the importance of getting their LDL-C goal below 70 mg/dL to reduce their risk of further cardiovascular events.

Table 1 Baseline characteristics of acute coronary syndrome patients with no cardiovascular events, a single event, or multiple events (n = 405)

Characteristics	Recurrent cardiovascular events			*p*-value for trend
	0	**1**	**≥2**	
	(n = 359)	**(n = 36)**	**(n = 10)**	
Gender				
Male	215 (60.0)	24 (66.7)	6 (60.0)	0.600
Age, (year)	64.5 ± 11.5	68.1 ± 11.7	66.7 ± 11.6	0.128
Health insurance				
Universal coverage scheme	201 (56.0)	19 (52.8)	5(50.0)	0.630
Civil servant medical benefit scheme	139 (38.7)	16 (44.4)	4 (40.0)	
Social security scheme	15 (4.2)	1 (2.8)	1 (10.0)	
Self- pay	4 (1.1)	0 (0.0)	0 (0.0)	
Smoking				
Non smoker	208 (57.9)	23 (63.9)	8 (80.0)	0.204
Ex-smoker	67 (18.7)	6 (16.7)	0 (0.0)	
Current smoker	84 (23.4)	7 (19.4)	2 (20.0)	
Diagnosis at discharge				
Unstable angina	66 (18.4)	5 (13.9)	7 (70.0)	0.001
NSTEMI	90 (25.1)	16 (44.4)	2 (20.0)	
STEMI	203 (56.6)	15 (41.7)	1 (10.0)	
Atherosclerotic risk factors				
Diabetes mellitus	97 (27.0)	15 (41.7)	5 (50.0)	0.019
Hypertension	215 (59.9)	29 (80.6)	7 (70.0)	0.039
Chronic kidney disease	37 (10.3)	12 (33.3)	2 (20.0)	0.001
Dyslipidemia	141 (39.3)	17 (47.2)	6 (60.0)	0.119
Family history of premature atherosclerosis	7 (1.9)	0 (0.0)	0 (0.0)	0.369
Previous history of cardiovascular events				
Chronic stable angina	30 (8.4)	2 (5.6)	3 (30.0)	0.174
Myocardial infarction or unstable angina	71 (19.8)	11 (30.6)	5 (50.0)	0.008
Stroke (Ischemic)	22(6.1)	1 (2.8)	1 (10.0)	0.870
Peripheral vascular disease	1 (0.3)	0 (0.0)	0 (0.0)	0.736
Previous history of cardiovascular intervention				
PCI	19 (5.3)	4 (11.1)	3 (30.0)	0.002
CABG	17 (4.7)	0 (0.0)	3 (30.0)	0.071
Revascularization of peripheral vascular disease	1 (0.3)	0 (0.0)	0 (0.0)	0.736
Carotid intervention	2 (0.6)	0 (0.0)	0 (0.0)	0.633
Treatment during admission				
PCI	151 (42.1)	7 (19.4)	1 (10.0)	0.001
CABG	4 (1.1)	1 (2.8)	0 (0.0)	0.735
Thrombolytic indicated	43 (12.0)	6 (16.7)	1 (10.0)	0.690
Medications				
Lipid lowering drugs (non-statins)	9 (2.5)	1 (2.8)	1 (10.0)	0.271
Antiplatelet/Anticoagulant drugs	350 (97.5)	35 (97.2)	10 (100.0)	0.766
Beta-blockers	296 (82.5)	31 (86.1)	9 (90.0)	0.414
ACEI/ARB	235 (65.5)	18 (50.0)	5 (50.0)	0.054

Table 1 Baseline characteristics of acute coronary syndrome patients with no cardiovascular events, a single event, or multiple events (n = 405) *(Continued)*

CCB	71 (19.8)	7 (19.4)	7 (70.0)	0.006
Diuretics	100 (27.9)	14 (38.9)	1 (10.0)	0.979
Diabetic drugs	53 (14.8)	8 (22.2)	4 (40.0)	0.021
Baseline laboratory results				
Serum creatinine (mg/dL)	1.4 ± 1.8	1.8 ± 1.1	1.3 ± 0.4	0.003
eGFR (mL/min/1.73 m^2)	62.7 ± 25.7	46.3 ± 23.0	58.5 ± 21.8	0.004
ALT (U/L)	35.4 ± 45.5	41.5 ± 88.8	26.6 ± 10.0	0.142
Fasting blood glucose (mg/dL)[a]	135.1 ± 75.3	134.1 ± 47.7	164.4 ± 70.5	0.230
Total cholesterol (mg/dL)	181.1 ± 50.4	185.4 ± 43.5	169.8 ± 46.8	0.757
Triglyceride (mg/dL)[b]	137.0 ± 81.2	158.7 ± 89.5	196.4 ± 153.9	0.086
High density lipoprotein (mg/dL)[c]	40.4 ± 11.7	38.0 ± 7.5	34.8 ± 9.7	0.168
Low density lipoprotein (mg/dL)	112.6 ± 41.9	114.0 ± 37.9	92.3 ± 29.6	0.300
Median follow-up time (day)[d]	808 (490–1,073)	782 (306–1,146)	1,088 (674–1,239)	0.609

Abbreviations: LDL-C, low-density lipoprotein cholesterol; mg/dL, milligrams per deciliter; NSTEMI, non –ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; U/L, units/liter

Notes: Numbers are n (%) or mean ± standard deviation (SD) or median (Interquartile range); the data were missing for some variables, [a]fasting blood glucose, n = 343, 35, 9; [b]triglyceride, n = 335, 32, 5; [c] high density lipoprotein, n = 335, 32, 5; [d] time form index hospitalization to last medical contact

Revascularization

Our findings show that undergoing revascularization, either with PCI or CABG, is associated with fewer subsequent cardiovascular events. To our knowledge, no studies have been conducted to assess the impact of revascularization on recurrent cardiovascular events. Nevertheless, previous studies [26–31] showed improvement in the clinical outcomes of ACS patients who underwent revascularization procedures during hospitalization. For example, a study conducted by Held et al. revealed that revascularization within 14 days of hospital admission for ACS was associated with a significant 30 % reduction in 1-year mortality [26]. The results of the Canadian ACS Registry showed that in-hospital revascularization was associated with better 1-year survival only among patients with high-risk non–ST- elevation acute coronary syndrome [27]. Vanasse et al. demonstrated that patients with myocardial infarction who underwent revascularization had a better 2-year cardiovascular survival rate compared to patients without revascularization, regardless of pharmacological treatments [31].

Table 2 Summary of recurrent cardiovascular events

Recurrent events (n = 46)	Patients with event
Single recurrent event (n = 36)	
MI	26
Stroke	0
Cardiovascular death	5
Non-cardiovascular death	5
Multiple recurrent events (n = 10)	
Two recurrent events	6
MI, stroke	1
Stroke, MI	1
MI, MI	4
Three recurrent events (all nonfatal ACS)	2
Four recurrent events (all nonfatal ACS)	1
Seven recurrent events (all nonfatal ACS)	1

Abbreviations: MI, myocardial infarction; ACS, acute coronary syndrome

It has to be noted that there was higher prevalence of revascularization in this study than in the two registries of ACS patients in Thailand, possibly because this study was conducted in a University hospital where all patients were managed by cardiologists, while the two Thai ACS registries reported on a variety of hospitals with different capabilities [3, 4]. Also, the proportion of ACS patients that underwent revascularization is higher than that in a study in Sri Lanka where no patients presenting with STEMI underwent PCI or CABG [32].

Male gender

The association between gender and mortality among the patients with cardiovascular disease is inconclusive [33–37]. In our study more males died than females; of ten deaths, six were males. However, this total is too low for generalizations. We also found that males were more likely to have recurrent cardiovascular events; this is consistent with a study by Wilson et al. that being male was a significant predictor of recurrent cardiovascular events [34]. However, Movahed et al. found a higher mortality rate among women undergoing percutaneous

Table 3 Univariable and multivariable analysis of clinical indicators for recurrent cardiovascular events (n = 405)

Clinical indicators	OR (95 % CI)	*p*-value	Multivariable OR (95 % CI)	*p*-value
LDL-C goal attainment				
LDL-C ≥ 100 mg/dL	1.00		1.00	
LDL-C 70–99 mg/dL	0.75 (0.36–1.58)	0.448	0.67 (0.35–1.30)	0.240
LDL-C < 70 mg/dL	0.55 (0.33–0.91)	0.019	0.43 (0.27–0.69)	<0.001
Revascularization	0.32 (0.17–0.63)	0.001	0.44 (0.24–0.81)	0.009
eGFR < 60 mL/min/1.73 m^2	3.24 (2.74–3.82)	<0.001	2.46 (2.21–2.75)	<0.001
Male gender	1.25 (0.79–1.96)	0.337	1.85 (1.29–2.66)	0.001
Age (year)	1.03 (1.01–1.04)	<0.001	1.00 (0.99–1.03)	0.258
Hypertension	2.39 (1.20–4.73)	0.013	1.66 (0.70–3.95)	0.249
ACEI/ARB	0.53 (0.35–0.81)	0.003	0.72 (0.49–1.06)	0.101
Diabetes mellitus	2.09 (0.67–6.50)	0.202	1.56 (0.52–4.73)	0.428
Follow-up time (day)[a]	1.00 (1.00–1.00)	0.908	1.00 (1.00–1.00)	0.890

Abbreviations: OR, odds ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; mg/dL, milligrams per deciliter; eGFR, estimated glomerular filtration rate; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers
Note: [a]time from index hospitalization to the last medical contact

coronary intervention in comparison to men [35]. Singh et al. reported no significant differences between men and women patients after PCI in short-term (30-day mortality) or long-term mortality, after accounting for risk factors [36]. Similarly, a study by D'Ascenzo et al. found similar long-term major adverse cardiac events between the female and male patients undergoing PCI [33].

Decreased eGFR

Elevated serum creatinine and decreased eGFR suggest impaired renal function, with eGFR being a more reliable indicator [1]. Studies showed that increased serum creatinine or decreased eGFR was associated with major adverse cardiac events [38–46]. Our finding adds to that knowledge i.e. renal dysfunction, based on eGFR < 60 mL/min/1.73 m^2, is associated with recurrent cardiovascular events. This observation is in line with previous studies that renal dysfunction was found to predict the likelihood of recurrent cardiovascular disease [10, 47].

Limitations

Due to the limitations of this study, the results should be interpreted with caution. The first limitation is related to the nature of retrospective study design, in that residual and/or unknown confounding factors could exit, and some data were unavailable. For example, the time from hospital admission of the ACS patients to the assessment of LDL-C goal attainment varied from 2 weeks to one year, depending on the availability of the patients' lipid profiles on the first follow-up visit. As per the ESC/EAS Guidelines for the management of dyslipidaemias [13], patients' lipids should be tested 4–12 weeks after starting lipid-lowering treatment. In our study, few patients (25, 6.2 %) had an LDL-C measurement before 4 weeks. Second, all patients included in the study had a very high cardiovascular risk (ACS patients), so the findings may not apply to patients with less severe disease. In addition, all patients were treated by cardiologists at a University hospital where the level of care exceeds that in lower level hospitals. Third, the number of patients with the occurrence of recurrent events was also very low (36 patients or 8.9 % with single recurrent event, and 10 patients or 2.5 % with multiple recurrent events), so that larger scale studies are required before the relationships found here can be generalized. Fourth, although some biomarkers have been shown to be independent prognostic markers for morbidity and mortality in ACS patients, e.g., B-type natriuretic peptide and high-sensitivity C-reactive protein [48, 49], these biomarkers have not been routinely measured in clinical practice in our setting. Biomarkers therefore were not included as potential clinical indicators for recurrent events in our study.

However, only a few studies have assessed the relationship between LDL-C goal attainment and cardiovascular events, and even fewer looked at subsequent cardiovascular events in a real-world setting; our study provides information about the factors associated with recurrent cardiovascular events in ACS patients in real world practice based on information collected as part of routine clinical practice. Our findings will be of use to physicians to identify ACS patients at higher risk of recurrent cardiovascular events who should be intensively followed up to prevent subsequent cardiac events, namely those ACS patients who do not achieve the LDL-C goal of < 70 mg/dL, did not undergoing revascularization, are male, and have decreased eGFR.

Conclusion

In conclusion, this study of routine clinical practice in ACS patients found that achieving an LDL-C goal of less than 70 mg/dL and undergoing revascularization are protective factors, whereas male gender and an eGFR less than 60 mL/min/1.73 $m^2$are risk factors for recurrent cardiovascular events. These clinical indicators should be used for routine-monitoring of patients to prevent recurrent cardiovascular events in ACS patients.

Abbreviations

ACS: Acute coronary syndrome; GRACE: Global Registry of Acute Coronary Events; TACS: Thai Acute Coronary Syndrome; TRACS: Thai Registry of Acute Coronary Syndrome; ICD-10: International Classification of Diseases, 10th Revision; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; IMPROVE-IT: IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; UA: Unstable angina; NSTEMI: Non-ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass surgery; ACEI/ARB: Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CCB: Calcium channel blocker.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Study concept and design: DC, CP, SC, AP. Acquisition of data: SG, DC. Statistical analysis and interpretation of data: DC, CP, SC, AP. Drafting of the manuscript:DC. Critical revision of the manuscript for important intellectual content: DC, CP, SC, KS, JJH, AP. Study supervision: AP. English language reviewing and editing: JJH. Final approval of the manuscript: DC, CP, SC, KS, SG, JJH, AP.

Acknowledgments

This study was partly supported by the Graduate School, Chiang Mai University, Thailand. The authors wish to thank the authorities of Maharaj Nakorn Chiang Mai Hospital for providing data for this study. The authors also would like to thank Claudia Koller for assistance with editing this manuscript. Dujrudee Chinwong would like to express her gratefulness to the Australian Government for awarding her the 2014 Endeavour Research Fellowship undertaken at the University of Newcastle, Australia.

Author details

[1]Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand. [2]Clinical Epidemiology Program, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [3]Center of Excellence in Applied Epidemiology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand. [4]Division of Medicine, Nakornping Hospital, Chiang Mai, Thailand. [5]Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand50200. [6]Centre for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health, Faculty of Health, University of Newcastle, Callaghan, NSW, Australia.

Received: 20 February 2015 Accepted: 1 June 2015
Published online: 16 June 2015

References

1. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(23):2999–3054.
2. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163(19):2345–53.
3. Srimahachota S, Kanjanavanit R, Boonyaratavej S, Boonsom W, Veerakul G, Tresukosol D. Demographic, management practices and in-hospital outcomes of Thai Acute Coronary Syndrome Registry (TACSR): the difference from the Western world. J Med Assoc Thai. 2007;90 Suppl 1:1–11.
4. Srimahachota S, Boonyaratavej S, Kanjanavanit R, Sritara P, Krittayaphong R, Kunjara-Na-ayudhya R, et al. Thai Registry in Acute Coronary Syndrome (TRACS)–an extension of Thai Acute Coronary Syndrome registry (TACS) group: lower in-hospital but still high mortality at one-year. J Med Assoc Thai. 2012;95(4):508–18.
5. Pocock S, Bueno H, Licour M, Medina J, Zhang L, Annemans L, Danchin N, Huo Y, Van de Werf F. Predictors of one-year mortality at hospital discharge after acute coronary syndromes: A new risk score from the EPICOR (long-tErm follow uP of antithrombotic management patterns In acute CORonary syndrome patients) study. Eur Heart J Acute Cardiovasc Care. 2014.Epub ahead of print.
6. Murphy SA, Antman EM, Wiviott SD, Weerakkody G, Morocutti G, Huber K, et al. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. Eur Heart J. 2008;29(20):2473–9.
7. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial. J Am Coll Cardiol. 2009;54(25):2358–62.
8. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495–504.
9. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292(11):1307–16.
10. Kaplan RC, Heckbert SR, Furberg CD, Psaty BM. Predictors of subsequent coronary events, stroke, and death among survivors of first hospitalized myocardial infarction. J Clin Epidemiol. 2002;55(7):654–64.
11. Maharaj Nakorn Chiang Mai Hospital [http://www.med.cmu.ac.th/2013/academic-departments-2/maharaj-nakorn-chiang-mai-hospital.html] Accessed 10 Feb 2015.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
13. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32(14):1769–818.
14. Armstrong BG, Sloan M. Ordinal regression models for epidemiologic data. Am J Epidemiol. 1989;129(1):191–204.
15. Ananth CV, Kleinbaum DG. Regression models for ordinal responses: a review of methods and applications. Int J Epidemiol. 1997;26(6):1323–33.
16. LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H. Safety and efficacy of Atorvastatin-induced very low-density lipoprotein cholesterol levels in Patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). Am J Cardiol. 2007;100(5):747–52.
17. Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: A PROVE IT-TIMI 22 Substudy. J Am Coll Cardiol. 2005;46(8):1411–6.
18. Ray KK, Bach RG, Cannon CP, Cairns R, Kirtane AJ, Wiviott SD, et al. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. Eur Heart J. 2006;27(19):2310–6.
19. Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, Phrommintikul A. Low-density lipoprotein cholesterol of less than 70 mg/dL is associated with fewer cardiovascular events in acute coronary syndrome patients: a real life cohort in Thailand. Ther Clin Risk Manag. Ther Clin Risk Manag. 2015; 11:659-67.
20. Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008;156(5):826–32.
21. Blazing MA, Giugliano RP, Cannon CP, Musliner TA, Tershakovec AM, White JA, et al. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes:

final baseline characteristics of the IMPROVE-IT study population. Am Heart J. 2014;168(2):205–12. e201.
22. O'Riordan, M. IMPROVE-IT: 'Modest' Benefit When Adding Ezetimibe to Statins in Post-ACS Patients [Available from: http://www.medscape.com/viewarticle/835030] Accessed 19 Nov 2014
23. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 - executive summary. J Clin Lipidol. 2014;8(5):473–88.
24. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 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. J Am Coll Cardiol. 2014;63(25 Pt B):2889–934.
25. National Institute for Health and Care Excellence. Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. London: National Clinical Guideline Centre; 2014.
26. Held C, Tornvall P, Stenestrand U. Effects of revascularization within 14 days of hospital admission due to acute coronary syndrome on 1-year mortality in patients with previous coronary artery bypass graft surgery. Eur Heart J. 2007;28(3):316–25.
27. Yan AT, Yan RT, Tan M, Eagle KA, Granger CB, Dabbous OH, et al. In-hospital revascularization and one-year outcome of acute coronary syndrome patients stratified by the GRACE risk score. Am J Cardiol. 2005;96(7):913–6.
28. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med. 2001;344(25):1879–87.
29. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Lancet 1999, 354(9180):708–715.
30. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet. 2002;360(9335):743–51.
31. Vanasse A, Courteau J, Niyonsenga T. Revascularization and cardioprotective drug treatment in myocardial infarction patients: how do they impact on patients' survival when delivered as usual care. BMC Cardiovasc Disord. 2006;6:21.
32. Bandara R, Medagama A, Munasinghe R, Dinamithra N, Subasinghe A, Herath J, et al. Management and outcomes of acute ST-segment-elevation myocardial infarction at a tertiary-care hospital in Sri Lanka: an observational study. BMC Cardiovasc Disord. 2015;15(1):1.
33. D'Ascenzo F, Gonella A, Quadri G, Longo G, Biondi-Zoccai G, Moretti C, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. Am J Cardiol. 2011;107(5):651–4.
34. Wilson PW, D'Agostino Sr R, Bhatt DL, Eagle K, Pencina MJ, Smith SC, et al. An international model to predict recurrent cardiovascular disease. Am J Med. 2012;125(7):695–703. e691.
35. Movahed MR, Hashemzadeh M, Jamal MM, Ramaraj R. Decreasing in-hospital mortality of patients undergoing percutaneous coronary intervention with persistent higher mortality rates in women and minorities in the United States. J Invasive Cardiol. 2010;22(2):58–60.
36. Singh M, Rihal CS, Gersh BJ, Roger VL, Bell MR, Lennon RJ, et al. Mortality differences between men and women after percutaneous coronary interventions. A 25-year, single-center experience. J Am Coll Cardiol. 2008;51(24):2313–20.
37. Srichaiveth B, Ruengsakulrach P, Visudharom K, Sanguanwong S, Tangsubutr W, Insamian P. Impact of gender on treatment and clinical outcomes in acute ST elevation myocardial infarction patients in Thailand. J Med Assoc Thai. 2007;90 Suppl 1:65–73.
38. Walsh CR, O'Donnell CJ, Camargo Jr CA, Giugliano RP, Lloyd-Jones DM. Elevated serum creatinine is associated with 1-year mortality after acute myocardial infarction. Am Heart J. 2002;144(6):1003–11.
39. Facila L, Nunez J, Bodi V, Sanchis J, Bertomeu-Gonzalez V, Consuegra L, et al. Prognostic value of serum creatinine in non-ST-elevation acute coronary syndrome. Rev Esp Cardiol. 2006;59(3):209–16.
40. Jose P, Skali H, Anavekar N, Tomson C, Krumholz HM, Rouleau JL, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. J Am Soc Nephrol. 2006;17(10):2886–91.
41. Krumholz HM, Chen J, Chen YT, Wang Y, Radford MJ. Predicting one-year mortality among elderly survivors of hospitalization for an acute myocardial infarction: results from the Cooperative Cardiovascular Project. J Am Coll Cardiol. 2001;38(2):453–9.
42. Sooklim K, Srimahachota S, Boonyaratavej S, Kanjanavanit R, Siriviwattanakul N, Piamsomboon C, et al. Renal dysfunction as an independent predictor of total mortality after acute coronary syndrome: the Thai ACS Registry. J Med Assoc Thai. 2007;90 Suppl 1:32–40.
43. Kang YU, Jeong MH, Kim SW. Impact of renal dysfunction on clinical outcomes of acute coronary syndrome. Yonsei Med J. 2009;50(4):537–45.
44. Mielniczuk LM, Pfeffer MA, Lewis EF, Blazing MA, de Lemos JA, Shui A, et al. Estimated glomerular filtration rate, inflammation, and cardiovascular events after an acute coronary syndrome. Am Heart J. 2008;155(4):725–31.
45. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med. 2004;351(13):1285–95.
46. Al Suwaidi J, Reddan DN, Williams K, Pieper KS, Harrington RA, Califf RM, et al. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation. 2002;106(8):974–80.
47. Wattanakit K, Folsom AR, Chambless LE, Nieto FJ. Risk factors for cardiovascular event recurrence in the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2005;149(4):606–12.
48. Brugger-Andersen T, Ponitz V, Staines H, Pritchard D, Grundt H, Nilsen DW. B-type natriuretic peptide is a long-term predictor of all-cause mortality, whereas high-sensitive C-reactive protein predicts recurrent short-term troponin T positive cardiac events in chest pain patients: a prognostic study. BMC Cardiovasc Disord. 2008;8:34.
49. Zamani P, Schwartz GG, Olsson AG, Rifai N, Bao W, Libby P, et al. Inflammatory biomarkers, death, and recurrent nonfatal coronary events after an acute coronary syndrome in the MIRACL study. J Am Heart Assoc. 2013;2(1):e003103.

00600496 re:Ask for permission to use a paper

"Ricardo Sison Jr." <info@biomedcentral.com>

Tue 11/24/2015 11:49 PM

To:DUJRUDEE CHINWONG <dujrudee.c@cmu.ac.th>;

Dear Dr. Chinwong,

Thank you for contacting BioMed Central.

The article you refer to is an open access publication. Therefore you are free to use the article for the purpose required, as long as its integrity is maintained and its original authors, citation details and publisher are identified.

For detailed information about the terms please refer to the open access license:

http://www.biomedcentral.com/about/license.

If the above link gives an error message, please try to use the alternative link below:

http://www.biomedcentral.com/about/policies/licence-agreement

If you have any questions please do not hesitate to contact me.

Best wishes

Ricardo Sison Jr.
Customer Services
info@biomedcentral.com
www.biomedcentral.com
----------Your Question/Comment ----------

To whom it may concern,

I am the first author of the paper entitled “Clinical indicators for recurrent cardiovascular events in acute coronary syndrome patients treated with statins under routine practice in Thailand: an observational study ” that was published in BMC Cardiovascular Disorders 2015, 15:55 (16 June 2015). This paper is part of my PhD thesis and I have to include it in my thesis as part of appendices.

Therefore, I would like to kindly ask you to provide a formal letter to give permission in doing this. Please kindly suggest if I do not have to ask for permission but I can use this paper to include it in my PhD thesis right away.

I would greatly appreciate if you could reply within two days or as soon as you can.

Sincerely yours,

Dujrudee Chinwong
ref:_00D20CUt._50020srJ5cAAE:ref

CURRICULUM VITAE

Name	Mrs. Dujrudee Chinwong
Date of birth	26 April 1971
Place of Birth	Roi-Et Province, Thailand

Education

1990 - 1995	B.Sc.(Pharm) Khon Kaen University, Khon Kaen, Thailand
1995 - 1997	M.Sc.in Pharm (Pharmacy Administration), Mahidol University, Bangkok, Thailand
2002 – 2003	MIPH, Master of International Public Health, University of Sydney, Australia
2010 - 2015	Ph.D. candidate in Clinical Epidemiology Program, Faculty of Medicine, Chiang Mai University, Thailand

Scholarships & Awards

1995-1997	University Developing and Commission Grant for Master of Pharmacy, at Mahidol University, Bangkok, Thailand
2000	The Youth Invitation Program by the JICA (Japan International Cooperation Agency) under the International Cooperation Program of the Government of Japan to Visit Japan for one Month in order to Exchange Culture and Professional Career.
2001	The Group Study Exchange of the Rotary International to visit Massachusetts for one month in order to Exchange Culture and Professional Career.
2002-2003	Australian Development Scholarships for Master of International Public Health at the University of Sydney, Australia
2014	Endeavour Research Fellowship awarded by the Australian Government to undertake a fellowship for 6 month, from July to December 21014, at the University of Newcastle

Publications

1. Chinwong D, Patumanond J, Chinwong S, et al. Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency. *Ther Clin Risk Manag.* 2015;11:127-136.

2. Chinwong D, Patumanond J, Chinwong S, et al. Low-density lipoprotein cholesterol of less than 70 mg/dL is associated with fewer cardiovascular events in acute coronary syndrome patients: a real-life cohort in Thailand. *Ther Clin Risk Manag.* 2015;11:659-667.

3. Chinwong D, Patumanond J, Chinwong S, et al. Clinical indicators for recurrent cardiovascular events in acute coronary syndrome patients treated with statins under routine practice in Thailand: an observational study. *BMC Cardiovasc Disord.* 2015;15(1):55.

Presentation

The effect of low-density lipoprotein cholesterol goal attainment on cardiovascular outcomes in patients with acute coronary syndrome: a real world practice in Thailand. Poster presentation at the ISPOR 19th Annual International Meeting, Palais des congrès de Montréal, Montreal, QC, Canada. May 31-June 4, 2014.