Chapter 4

Recurrent cardiovascular events and the association with LDL-C goal, sex, eGFR, and revascularization

Publications of short communication in this chapter are listed below.

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.

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

This chapter focuses on recurrent cardiovascular events and its association with LDL-C goal attainment and other clinical indicators.

Survivors of ACS

Survivors of ACS are at very high risk of further cardiovascular events and need quality intensive risk factor evaluation and management including lifestyle adaptations and the use of drug therapy. As high cholesterol is a vital risk factor for ACS; early use of intensive statin therapy is supported by major clinical trials, such as the MIRACL study,[1] and the PROVE IT study.[2] Thus, worldwide guidelines recommend using high dose statins soon after ACS is diagnosed irrespective of baseline LDL-C levels, such as during the first 1-4 days of hospitalization with ACS.[3] If basal LDL-C levels are known, doses of statins should reach the LDL-C target of <70mg/dL (approximately 1.8 mmol/L). For patients at increased risk of side effects with high potency of statins (such as the elderly and people with renal impairment, hepatic impairment, or potential interaction with other concomitant therapy), the use of lower potency statins should be considered.[3] After initiation statin therapy in patients presenting with ACS, lipids should be followed 4-6 weeks to evaluate reaching LDL-C target as well as safety aspect; adaption of statin dose can be conducted consequently.[3]

Treating to LDL-C target is associated with fewer cardiovascular events

An LDL-C goal of <70 mg/dL has been used as the target of therapy in dyslipidaemia management in very high risk patients such as ACS patients for more than 10 years. As discussed earlier, using high-intensity statins with higher risk patients has been debated among experts and physicians, instead of treating to LDL-C<70 mg/dL.[4,5] The lack of evidence from RCTs intended to demonstrate treating to an LDL-C target associated with improved clinical outcomes does not mean a lack of benefit of LDL-C goal.[4,5] However, post-hoc studies of RCTs have shown the benefit of lowering LDL-C to a target level associated with improved cardiac events.[6,7] Also, evidence from observational studies has indicated a relationship between the levels of atherogenic cholesterol and cardiovascular risk.[8-10]

Study II was a retrospective cohort study to investigate the effect of LDL-C goal attainment on cardiovascular events. Although not a randomized controlled study, as preferred by the 2013 ACC/AHA guidelines, it could provide evidence from real world practice. Similar to study I, it was conducted among ACS patients treated with statin therapy during hospitalization or at discharge. Patients were followed up for at least 1 year from the date of measuring LDL-C goal attainment after initial LDL-C level during hospitalization until the first recurrent cardiovascular event. The recurrent cardiovascular events in our study were defined as nonfatal ACS (MI or UA), nonfatal stroke, or all-cause death. We found that ACS patients treated with statins who achieved an LDL-C goal of <70mg/dL had a 58% reduction in the risk of the first cardiovascular event (HR=0.42, 95%CI: 0.18-0.95).[11] Study II showed the usefulness of treating to target approach; the short communication of study II is explained below.

Supporting research[11]

Study II entitled, "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," aimed to investigate whether LDL-C goal attainment was associated with reduced cardiovascular events in real-world practices in northern Thailand (Appendix C).

Background

Achieving an LDL-C goal of <70 mg/dL in ACS patients is suboptimal. Less than 45% of high-risk patients can reach LDL-C of <70 mg/dL.[12-25] with approximately 24% of ACS patients achieving this goal in study I.[26] Whether those with LDL-C <70 mg/dL are at lower risk of cardiovascular events is questionable, as compared with those at higher levels of LDL-C.

Objective

This study aimed to assess the association between LDL-C goal attainment of <70 mg/dL and the first recurrent cardiovascular event in ACS patients treated with statins in routine clinical practice in Thailand.

Methods

Study population and setting

Study II was performed retrospectively at the Maharaj Nakorn Chiang Mai Hospital by reviewing the medical profiles charts and electronic database of ACS patients hospitalized at the hospital. ACS patients included in the study are described below. Patients were aged ≥18 year; hospitalized with a diagnosis of ACS, including UA, NSTEMI, and STEMI, according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, code of I20 (angina pectoris) and I21 (acute MI). All patients were treated with statins in hospital or on discharge date until 2012; had LDL-C measurement at least twice: at baseline during admission and at follow-up between 14 days and 1 year; and were followed up for at least 12 months from the date of measuring 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. Time to cardiovascular events was the interval between the dates of measuring the LDL-C goal to the date of the first cardiovascular event.

LDL-C goal attainment and cardiovascular events

Patients were divided in three groups based on their LDL-C levels at the first follow-up: <70 mg/dL (achieved LDL-C goal), 70–99 mg/dL, and ≥100 mg/dL (reference). The primary outcome was the first recurrence of the composite of cardiovascular events, including nonfatal ACS (MI or UA), nonfatal stroke, or all-cause death.

Statistical analysis

Characteristics of patients were displayed with descriptive statistics, and 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, 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), were used to determine the

effect of LDL-C goal attainment on cardiovascular events. The two-tailed test was used, and *P*-value<0.05 was considered statistically significant.

Results and discussions

Of 405 patients, 27% 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.

Forty-six patients experienced the first recurrence of 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 of cardiovascular outcomes in the LDL-C <70 mg/dL, LDL-C 70–99 mg/dL, and the LDL-C ≥100 mg/dL group were 43, 66 and 88 per 1,000 person-years, respectively. ACS patients on statins who achieved an LDL-C of <70 mg/dL had a 58% reduction in 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. 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 although this was not significant (adjusted HR=0.73; 95% CI=0.37–1.42).

Table 4.1 Univariable and multivariable Cox proportional hazards model of LDL-C goal attainment affecting first event of composite outcomes of myocardial infarction, stroke or death (n=405)

	Crude HR[a] (95%CI)	p-value	Adjusted HR[ab] (95%CI)	p-value
LDL-C levels				
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

Note: [a]Stratified analysis by spectrum of acute coronary syndrome, [a]djusted with age, sex, diabetes, hypertension, serum creatinine, ACEI/ARB, revascularization (PCI or CABG), baseline LDL-C
Abbreviations: HR, hazard ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; mg/dL, milligrams per deciliter; ACEI / ARB, angiotensin-converting enzyme inhibitors /angiotensin II receptor blockers.

Our findings showed that patients treated to LDL-C target (<70 mg/dL) were more likely to have fewer cardiovascular events by approximately 58% as compared with those having LDL-C 100 mg/dL or over. Our finding supports the benefit of the treating to LDL-C target approach. Although this was an observational study, the results reflect the real-world clinical practice of cardiologists in lipid management of patients at very high risk of cardiovascular events.

Importance of treating to LDL-C goal in ACS patients

Much debate has occurred on the replacement of the fire and forget approach instead of treating to target since the newly released lipid management guidelines of ACC/AHA in 2013.[4] Abandoning the LDL-C goal target is perhaps the most controversial change among experts and physicians in the new 2013 ACC/AHA guidelines.[4,5,27-31]

Our finding in study II highlights that achieving LDL-C target of <70 mg/dL is vital for ACS patients; thus, those achieving the LDL-C goal are more likely to have fewer cardiovascular events. Continuously using the LDL-C goal as a target therapy will help to identify those who cannot achieve the LDL-C goal, producing a higher risk of cardiovascular events. This will lead to a physician-patients communication in the patient-centered approach to enhance the rate of achieving LDL-C goal as well as the adherence to statin therapy. This patient-centered approach encourages physicians and patients to discuss treatment objectives and use the treatment goal to follow patients' progress and to maximize long-term adherence to the treatment plan.[4] A study in Singapore found that more than 80% of patients with coronary artery disease 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.[32] However, a study found reluctance among physicians in clinical practice in using high-intensity statins, instead of using the treating to LDL-C target, as recommended by the 2013 ACC/AHA guidelines with patients.[29]

Conclusion

In short, study II demonstrates the importance of treating to LDL-C target of <70 mg/dL as this was found to reduce the first cardiovascular event in ACS patients.

Recurrent cardiovascular events following an ACS

Recurrent cardiovascular events following an ACS in this context meant any cardiovascular events occurring to ACS patients after their hospitalization of ACS. Patients with established cardiovascular disease such as ACS patients are at high risk for recurrent cardiovascular events following the first event,[33-35] with about 1% (140/13,608)[34] to 9% (380/4,162)[35] of ACS patients having subsequent cardiovascular events. The risk of recurrent cardiovascular events is 2-6 times higher compared with those with stable CAD during the first 6 months following an ACS, after which it slowly declines.[36] In our cohort study, some survivors from ACS experience no recurrence of cardiovascular events; some experience only the first occurrence of events; some experience 2 further events, some experience 3 further events; and some experience 7 recurrent events. Recurrent cardiovascular events associated with statins have been studied in survivors of established heart disease. Treatment with statins reduced not only the first cardiovascular event but also the recurrent, e.g., second, third, and fourth cardiovascular events.[37] 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 MI.[38] An International Model to Predict Recurrent Cardiovascular Disease[39] found that traditional risk factors, burden of disease, lack of treatment, and geographic location are associated with recurrent cardiovascular disease. However, little is known, to the best of our knowledge, whether lowering LDL-C with statins to reach goal (<70 mg/dL) is associated with a reduction in all recurrent cardiovascular events. In addition, other clinical indicators associated with all recurrent cardiovascular events remain unknown. Thus, study III was designed to answer this research question; the short communication of study III is provided below.

Supporting research

Study III entitled, "Clinical indicators for recurrent cardiovascular events in acute coronary syndrome patients treated with statins under routine practice in Thailand: an observational study," aimed to investigate the clinical predictors, including lowering LDL-C to reach goal, associated with recurrent cardiovascular events.

Rationale of the study

Survivors of ACS, after discharge from the hospital, are at higher risk of recurrent cardiovascular events. That is, some patients have no cardiovascular events, while others have recurrent cardiovascular events ranging from 1 to 9%.[34,35] ACS patients may experience only one recurrent event, i.e., the first recurrent event, while others may experience at least two recurrent events, e.g., second, third, fourth. Most randomized controlled trials and observational studies use the first occurrence of cardiovascular event, usually a composite endpoint, as the primary outcome,[1,40,41] ignoring all other recurrent events. However, ignoring the occurrence of all other events will not represent real-world practices and may miss some important information of patients. In addition, doctors and patients both knowing all recurrence, including the first and all other recurrences of events, is a better means to monitor their health conditions. In addition, ACS patients with different frequencies of recurrent cardiovascular events 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 MI.[38] However, little is known on the clinical indicators associated with recurrent cardiovascular events, especially in Thailand.

Thus, study III aimed to explore clinical indicators collected in routine clinical practice that were associated with recurrent cardiovascular events in patients with ACS.

Methods

The methods were similar to study II. Briefly, medical records and electronic database of ACS patients were reviewed from 2009 to 2012 for their clinical indicators, e.g., age, sex, comorbidity, medication, lipid profiles including achieving LDL-C goal <70 mg/dL. However, in addition to study II, all recurrent cardiovascular events, not only the first recurrent event, were considered as the outcomes of this study. As we also wanted to assess whether achieving LDL-C goal was a clinical indicator associated with all recurrent cardiovascular events, the recurrent cardiovascular events in our study were defined as nonfatal ACS (MI or UA), nonfatal stroke, or all-cause death following the assessment of LDL-C goal attainment. Patients were divided in 3 groups based on their frequency of recurrent cardiovascular events: 0 recurrent events, 1 recurrent event, at least 2 recurrent events (called as "multiple recurrent events" in this study). The frequency of recurrent events was the outcome of interest in study III.

In addition to the descriptive statistics to describe patients included in the study, nonparametric tests for trends across ordered groups were used to investigate differences across the three groups of patients. As the outcome variable, the frequency of recurrent events (0, 1, ≥2 recurrent events), was ordered naturally; ordinal logistic regression was used.[42,43] Ordinal logistic regression (clustered with type of ACS [UA, NSTEMI, STEMI] and adjusted with the length of follow-up time was carried out to explore the clinical indicators associated with recurrent cardiovascular events.

Results and discussion

The median time of follow-up was 810 days (Interquartile range [IQR]: 489–1093) for all 405 included in the analysis. Of 405 patients, 359 (88.6%) patients had no recurrent events; 36 (8.9%) patients had a single recurrent event, and 10 (2.5%) patients had at least 2 recurrent events. Of those subjects with ACS with at least one recurrent cardiovascular event, the most common was nonfatal ACS; ten patients died. Ten patients had at least 2 recurrent cardiovascular events, and one patient had seven cardiovascular events (all nonfatal ACS).

In our study, 2.5% of ACS patients experienced multiple recurrent cardiovascular events, i.e., at least 2 cardiovascular events occurred in patients, in line with previous studies reporting ranges of 1–9 %.[34, 35] We found four clinical indicators associated with recurrent cardiovascular events: two protective factors (achieving LDL-C goal of less than 70 mg/dL, and undergoing revascularization (either PCI or CABG) during admission, and two risk factors (male sex and decreased eGFR <60 mL/min/1.73m^2).

Table 4.2 Univariable and Multivariable analysis of clinical indicators for recurrent cardiovascular events (n=405)

Clinical indicators	Univariable 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/1.73m^2	3.24 (2.74 – 3.82)	<0.001	2.46 (2.21 – 2.75)	<0.001
Male sex	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

Note: [a]time from index hospitalization to the last medical contact
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

LDL-C goal attainment

As expected, those with LDL-C<70 mg/dL were associated with a decrease in recurrent cardiovascular events (OR: 0.43, 95% CI: 0.27 – 0.69) compared with those with LDL-C≥100 mg/dL. This finding also supports treating to LDL-C target. Our finding adds to the current knowledge that achieving LDL-C goal <70 m/dL not only reduces the first

recurrence of cardiovascular event, as found in study II[11] and other studies,[6,7,44] but also reduces the likelihood of further recurrence of cardiovascular events.

Our finding of study III and the results from the two post-hoc analyses from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22)[6,7] also support the treat to target approach, although these are not clinical trials studies. Nonetheless, observational studies such as our study reflect real world practices. The post-hoc analysis of the PROVE IT-TIMI 22 study showed ACS patients with a lower of LDL-C (≤40 mg/dL and >40 to 60 mg/dL groups) were associated with reduced cardiac events, as compared with the reference group with higher LDL-C levels (>80 to 100 mg/dL).[6] Similar results in similar studies with a post hoc analysis were found among the elderly with ACS aged ≥70 years. Among these elderly patients, the achievement of LDL-C<70 mg/dL was associated with a 40% relatively lower risk of cardiac events (composite of death, MI, or UA).[7] Further, the just released results from the IMPROVE-IT study confirmed that lower LDL-C was associated with lower cardiovascular events.[45] The IMPROVE-IT study, conducted in 18,144 patients with post-ACS, showed that patients with LDL-C <60 mg/dL had reduced cardiovascular events.

Revascularization

We found an association between undergoing revascularization, either with PCI or CABG, and fewer subsequent cardiovascular events. Previous studies showed that ACS patients undergoing revascularization procedures during hospitalization are associated with an improvement in clinical outcomes.[46-51] For instance, ACS patients undergoing revascularization within 14 days of hospitalization had a significant 30% lower risk of 1-year mortality.[46] The Canadian ACS Registry showed the benefit of revascularization among patients with non–ST elevation acute coronary syndrome; hospital revascularization is associated with improved 1-year survival.[47]

Compared with studies conducted in Thailand, study III had a higher prevalence of revascularization than the two registries of ACS patients in Thailand. [52,53] This may be possibly due to the variety of hospitals included in both registries, from

different parts in Thailand, but our study was conducted in only one teaching hospital in northern Thailand.

Male sex

The association between sex and cardiovascular events is inconclusive among patients with cardiovascular disease.[39,54-57] We found that males were more likely to have recurrent cardiovascular events, similar to a study by Wilson et al[58] showing that being male was a significant predictor of recurrent cardiovascular events.[58] However, a study by Movahed et al found that women undergoing percutaneous coronary intervention had a higher mortality rate.[55]

Decreased eGFR

Research showed that increased serum creatinine or decreased eGFR was associated with major adverse cardiac events.[57,59-66] Study III showed that renal dysfunction, based on eGFR <60 mL/min/1.73m^2 was associated with recurrent cardiovascular events. This observation is similar to previous studies showing renal dysfunction was a predictor of the likelihood of recurrent cardiovascular disease.[38,58]

Limitation of the study

To investigate clinical factors on recurrent cardiovascular events, ACS patients were followed from the date of measuring LDL-C goal attainment, a period of two weeks to one year after initial LDL-C at baseline during their hospitalization. Using this method, ACS patients who died after hospitalization but before the date of LDL-C goal assessment were excluded. This may result in selection bias; therefore, the results should be interpreted with this caution in mind. Further research should be conducted if all deaths after hospitalization due to ACS are included for analysis.

Summary

In conclusion, recurrent cardiovascular events, i.e., the first and the second, occurred among 46 ACS patients in our study. Those ACS patients achieved LDL-C goal of <70 mg/dL, associated with a reduction in the first cardiovascular events as shown in study

II. Study III showed that four clinical indicators associated with recurrent cardiovascular events are LDL-C goal attainment, being male, undergoing revascularization (either with PCI or CABG), and reduced eGFR. LDL-C goal attainment and undergoing revascularization are protective factors: ACS patients who achieved LDL-C goal or were undergoing revascularization were associated with reduced recurrent cardiovascular events. Being male and reduced eGFR constituted risk factors: ACS patients who were males or had reduced eGFR (<60 mL/min/1.73m^2) were more likely to have recurrent cardiovascular events. This chapter highlights that ACS patients achieving LDL-C goal were associated with a decrease in total recurrent cardiovascular events, including the first recurrent events and further recurrent events, supporting the treat to target approach in lipid management.

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