Chapter 5

Concluding remarks

In this chapter, we summarize the findings from the three studies included in this thesis as well as the implications, suggestions, and limitations of those studies.

Acute coronary syndrome (ACS) encompases unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI).[1] ACS is an important clinical manifestation of CAD resulting in life treatening conditions.[2,3] Elevated LDL-C has been strongly associated with increased risk of developing CAD,[4] and well established research has shown that lowering LDL-C reduces the incidence of cardiovascular events.[5-10] Thus, LDL-C has been identified as the primary target for lipid lowering therapy by many guidelines for approximately two decades.[4] The established LDL-C target goals for individuals are determined based upon patient risk factors and the level of risk for future CAD events. The target LDL-C goal for patients with ACS is <70 mg/dL, as recommended by the ESC/EAS guidelines[11] and by the NCEP ATP III guidelines[12] for an optional goal for high risk patients.

Statins are cornerstones in reducing LDL-C levels.[4] Currently six statins are available in Thailand including simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin. All statins have a similar therapeutic effect but they differ in their potency, resulting in different lipid-lowering effects.[13] **In study I, entitled "Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency",** the potency of statins were classified in 2 groups (high or low potency of statins), and we found no differences in the LDL-C goal attainment between the two groups.[14] This might be possibly due to the definition of high or low potency of statins used in our study, i.e., our high potency statins were not as highly potent as in other studies or in guidelines such as the ACC/AHA guidelines.[15] High potency statins in our studies comprised simvastatin 40 mg, rosuvastatin 10 and 20 mg, atorvastatin 20 and 40 mg, and pitavastatin 2 mg, whereas low potency statins comprised simvastatin 10 and 20 mg, and pravastatin 40 mg. On the other hand, the high-intensity statins by the ACC/AHA guidelines include rosuvastatin 20-40 mg/day and atorvastatin 40-80 mg/day, which is expected to reduce LDL-C by ≥50%; the high potency statins in our study were expected to reduce LDL-C by ≥40%.

Although research has shown that reducing LDL-C levels is associated with reduced death and myocardial infarction in patients following ACS,[5-10] a large proportion of ACS patients using statins in real world clinical practices cannot achieve LDL-C goal as recommended by the NCEP ATP III guidelines. About one fourth of ACS patients in Thailand can achieve the target LDL-C goal of less than 70 mg/dl.[16,17] Study I showed that less than 30% of ACS patients could attain LDL-C <70 mg/dL after a follow-up period[14] which was higher than that found in previous studies.[16,17] In addition, our study was a retrospective cohort study, while the other two studies were cross-sectional studies.

Although treating to LDL-C target < 70 mg/dL in patients with ACS has been applied in real world clinical practices for more than a decade; later in November 2013, treating to LDL-C target became a debatable issue after the release of new cholesterol guidelines by the ACC/AHA. The ACC/AHA guidelines abandoned LDL-C goal for lipid management due to the lack of evidence from randomized controlled trials supporting the benefits of LDL-C target. Our study also investigated the effect of LDL-C goal on the first cardiovascular events among patients following ACS in **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".**[18] The results showed that ACS patients treated with statins who achieved LDL-C<70 mg/dL were more likely to have fewer first cardiovascular events than those with LDL-C≥100 mg/dL.[18] Our findings support the treat to LDL-C target approach as suggested by the NCEP/ATP III guidelines, ESC/EAS guidelines, and the National Lipid Association guidelines. Treating to target is also as a means to encourage communication between physicians and patients in helping patients to achieve their lipid therapy and also enhance their adherence to statin therapy.[19]

ACS patients are at high risk for recurrent cardiovascular events following the first event,[5-7] ranging from 1 to 9% of ACS patients experiencing subsequent cardiovascular events. **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",** showed that clinical

indicators associated with increased risk of recurrent cardiovascular outcomes in our cohort were not LDL-C goal attainment (<70 mg/dL), being male, not undergoing revascularization (either PCI or CABG), and decreased eGFR (<60 mL/min/1.73m^2).[20] Study III further suggested that treating to LDL-C<70 mg/dL not only prevents the first cardiovascular events but also all recurrent cardiovascular events among ACS patients.[20]

Our findings add to the current knowledge of statin therapy among high risk patients. Our studies are among the few in Thailand conducted among ACS patients, the very high cardiovascular risk patients, involving real world practices in terms of the attainment of LDL-C <70 mg/dL, the effect of LDL-C goal attainment and other clinical indicators on recurrence of cardiovascular events. It also included the first recurrent event and all further recurrent events, i.e., the second, the third. Previous studies have investigated reaching LDL-C<100, or <70 mg/dL in patients with cardiovascular risk. All patients were treated by a cardiologist in our studies. While previous studies in Thailand employed a cross-sectional design such that no causal relationship could be determined, our longitudinal study allowed causal associations to be made. We also investigated the effects of LDL-C goal on the risk of cardiovascular events, and clinical indicators of recurrent cardiovascular events.

Some limitations should be noted in our studies. First, its retrospective design may be distorted by confounding factors; however, we adjusted the confounders in the statistical analysis, e.g., by using the propensity score to control for confounding by indication or contraindication in study I.[14] The adjustment of confounders in the regression models was performed in study II[18] and III.[20] Nevertheless, some residual confounders may remain in this type of research. Second, inclusion of patients who had complete lipid profiles in their electronic medical records both at baseline and follow-up resulted in fewer patients being included. Therefore, selection bias could be found. However, as missing data is quite normal in real world studies particularly in a retrospective cohort study; we conducted a comparison between patients included and those excluded from the study; no significant difference was found, except age. Third, the sample size of our studies may be insufficient to evaluate the effect of statin

potency on LDL-C goal attainment. However, legitimately establishing an association between statin potency and LDL-C goal attainment in ACS patients is still possible. 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 be interpreted with caution for ACS patients treated by primary care physicians. Fifth, statin adherence and titration of the statin dose during treatment were beyond the scope of our studies. Further assessment of medication adherence in statin users and the effect of statin dose adjustment to meet LCL-C goals in practice settings is needed.

In summary, we found that less than 30% of ACS patients were found to attain LDL-C goal<70 mg/dL in our study; potency of statins was not associated with LDL-C goal attainment. In addition, those achieving LDL-C goal attainment were associated with fewer first recurrence of cardiovascular events compared with those with LDL-C≥100 mg/dL. Recurrent cardiovascular events, e.g., the first, the second to the seventh, were found higher among those who could not achieve LDL-C goal, being male, not undergoing revascularization, or decreased eGFR. Our thesis should be useful for increasing awareness of patients and practitioners of the importance of achieving LDL-C goal for better cardiovascular outcomes. The result should also help to design interventions to improve LDL-C goal attainment among patients that will lead to improve cardiovascular outcomes. Statin adherence, which is beyond the scope of our studies, should be assessed in further study as this is a vital part for patients to have better cardiovascular outcomes.

Implications and suggestions for further research: LDL-C goal attainment in ACS patients treated with statins was lower than 30%, though in line with other studies. This suggests some works needs to be conducted to raise the awareness of both physicians and patients to pay more intention on achieving LDL-C goal to reduce cardiovascular events. In our cohort study, low to moderate intensity of statins were used the most, while high-intensity statins were used by very few patients. The findings from our studies were in contrast to the ACC/AHA 2013 cholesterol guidelines that recommend using high-intensity statins - defined as rosuvastatin 20-40 mg/day

and atorvastatin 40-80 mg/day - for ACS patients immediately after a diagnosis of ACS. Thus, reasons should be investigated for this suboptimal use of high-intensity statins in our setting. Further research should focus on lowering LDL-C with high-intensity statins to create a higher percentage of patients who can reach LDL-C reduction of ≥50%. On the other hand, it would be interesting to investigate whether Thai patients do not need to use high-intensity statins, as reported in other Asians such as a Japanese population.

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