Chapter 1

Introduction

Worldwide, coronary artery disease (CAD) is projected to be the first leading cause of mortality and disability in 2020,[1-3] and in 2030, with 13.4% of total deaths.[4] In Thailand, CAD was the second leading cause of mortality in 2005 (7.8%) following stroke (10.7%);[5] CAD is ranked as the fourth leading cause of death among males (7.3%) and second among females (8.6%).[5]

Acute coronary syndrome (ACS), a life-threatening condition, is an important clinical manifestation of coronary artery disease (CAD) mostly resulting from atheromatous plaque rupture.[6,7] ACS encompasses unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI).[8] Unstable angina and NSTEMI share a similar pathology of non-total obstruction of coronary artery of differing severity in which NSTEMI presents myocardial necrosis.[6] Unlike UA/NSTEMI, total occlusion of the infarct-related artery is found in patients with STEMI.[9]

Dyslipidaemia is an important risk factor of ACS.[10,11] Elevated low-density lipoprotein cholesterol (LDL-C) has been strongly associated with increasing risk of developing CAD.[10,11] Well-established research has shown that lowering LDL-C will lower the risk of CAD in both primary prevention, i.e., in people initially free from CAD[12-15] and secondary prevention, i.e., in patients with established atherosclerotic cardiovascular disease (ASCVD).[16-22] A meta-analysis of data from 26 randomized trials, by the Cholesterol Treatment Trialists' (CTT) collaborations, of more- vs. less-intense statin therapy showed that each 1.0 mmol/L (38.6 mg/dL) reduction in LDL-C resulted in a 22% relative risk reduction for major vascular events (hazard ratio of 0.78).[23]

LDL-C has been traditionally recommended as the primary target for lipid lowering therapy for two decades based on guidelines such as the 2004 NCEP/ATP III[11,24] (National Cholesterol Education Program Adult Treatment Panel III) guidelines and ESC/EAS Guidelines for the management of dyslipidaemias in 2011.[10] The established LDL-C 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[10] and the updated NCEP/ATP III guidelines in 2004.[24]

Statins, the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are the first line agents in lipid-lowering therapy.[10,11] Currently, six statins are available in Thailand: simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin. All statins have similar therapeutic effects but differ in their potency. The different potency of individual statins results in different lipid-lowering effects and a reduced mortality rate or cardiovascular events.[25] According to newly released guidelines such as the 2013 ACC/AHA cholesterol guidelines, the intensity or potency of statins can be divided in 3 groups based on the average expected LDL-C response to a specific statin and dose: high-intensity statins (≥50% LDL-C reduction), moderate-intensity statins (30 to <50% LDL-C reduction), and low-intensity statins (<30% LDL-C reduction).[26] Although efficacious statins are available, most patients cannot achieve their LDL-C goal, especially very high risk patients such as ACS patients. Little is known about the achieve rate of LDL-C targets in high-risk patients in Thailand, especially ACS patients. 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%[27] and the CEPHEUS (CEntralized Pan-Asian survey on tHE Under-treatment of hypercholeSterolemia) Thailand survey reported 16.7%[28]). Patients treated with high intensity statins should have a lower LDL-C level compared with those with lower-intensity statins. Thus, study I evaluated LDL-C goal attainment among ACS patients, and identified the association between patients using statins of different potency, high or low, and LDL-C goal attainment. However, definition of intensity of statins used in our studies differed from that used in the 2013 ACC/AHA guidelines.

Treating to LDL-C target has been used as a primary target in patients treated with lipid-lowering agents for approximately two decades. Recently, the newly released cholesterol guidelines by the ACC/AHA in November 2013 no longer recommend the target LDL-C as the treatment goal for patients due to the lack of evidence from RCT studies. In addition, ACS patients who achieve LDL-C goals should have a lower rate of cardiovascular outcomes when compared with those with higher LDL-C levels when the patients follow for an appropriate time such as 2 years. Hence,

study II investigated the effect of LDL-C goal on the first recurrent cardiovascular events in ACS patients.

ACS patients are at high risk for not only the first recurrent cardiovascular event but also additional recurrent events, e.g., the second, the third, the fourth,[29,30] with about 1 to 9% of ACS patients having subsequent cardiovascular events.[29,30] ACS patients with differing 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. Therefore, study III investigated what clinical indicators were associated with recurrent cardiovascular outcomes in our cohort.

All in all, this thesis comprises three studies with the objectives described below.

1. To investigate percentage of ACS patients treated with statins who achieved LDL-C target of <70 mg/dL (study I)
2. To investigate effect of potency of statins (high or low) on LDL-C goal attainment <70 mg/dL (study I)
3. To investigate effect of LDL-C goal attainment <70 mg/dL on the first recurrent cardiovascular event (study II)
4. To explore clinical indicators associated with all recurrent cardiovascular events (study III)

All of the three studies included in this dissertation were conducted retrospectively using data from the Maharaj Nakorn Chiang Mai Hospital. The first part of this dissertation introduces ACS in terms of epidemiology, pathology, and statin therapy in ACS in Chapter 2. Then the second part presents study I in Chapter 3, while studies II and III are presented in Chapter 4. Finally, the concluding remarks in Chapter 5 summarize all findings in this dissertation again including limitation and application for health care professionals in this field.

This dissertation applied the philosophical context of clinical epidemiology, and to answer all research questions requires dealing with three parts: theoretical design, data collection design, and the design of data analysis. Thus, philosophical context of clinical epidemiology including all three components for each study is described in Appendix A. All publications of studies I, II, and III are enclosed in Appendix B, C, and D, respectively.

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