ประสิทธิผลและความปลอดภัยของยาโรซูวาสทาทิน ขนาด 10 มิลลิกรัม วันละครั้ง เทียบกับวันเว้นวัน ในผู้ป่วยนอกที่มีภาวะคอเลสเทอรอลในเลือดสูง

เรือเอกหญิง ชุติพร กิติยาดิศัย

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EFFECTIVENESS AND SAFETY OF ROSUVASTATIN 10 MG ONCE DAILY VERSUS EVERY OTHER DAY IN OUTPATIENTS WITH HYPERCHOLESTEROLEMIA

Lieutenant Chutiporn Kitiyadisai

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy in Clinical Pharmacy
Department of Pharmacy
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By	Lieutenant Chutiporn Kitiyadisai
Field of Study	Clinical Pharmacy
Thesis Advisor	Assistant Professor Supakit Wongwiwatthananukit, Pharm.D., Ph.D.
Thesis Co-advisor	Lieutenant Colonel Nakarin Sansanayudh, M.D.

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

……Dean of the Faculty of Pharmaceutical Sciences

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……Thesis Advisor

(Assistant Professor Supakit Wongwiwatthananukit, Pharm.D., Ph.D.)

……..…… Thesis Co-advisor

(Lieutenant Colonel Nakarin Sansanayudh, M.D.)

……Member

(Assistant Professor Sarinee Krittiyanunt, M.Sc.)

……Member

(Assistant Professor Suree Jianmongkol, Ph.D.)

ชุติพร กิติยาดิศัย: ประสิทธิผลและความปลอดภัยของยาโรซูวาสทาทิน ขนาด 10 มิลลิกรัมวันละครั้ง เทียบกับ วันเว้นวัน ในผู้ป่วยนอกที่มีภาวะคอเลสเทอรอลในเลือดสูง. (EFFECTIVENESS AND SAFETY OF ROSUVASTATIN 10 MG ONCE DAILY VERSUS EVERY OTHER DAY IN OUTPATIENTS WITH HYPERCHOLESTEROLEMIA) อ.ที่ปรึกษา: ผศ.ดร.ศุภกิจ วงศ์วิวัฒนนุกิจ, อ.ที่ปรึกษาร่วม: พ.ท.นพ. นครินทร์ ศันสนยุทธ. 108 หน้า. ISBN 974-53-2136-2.

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิผลและความปลอดภัยของยาโรซูวาสทาทินขนาด 10 มิลลิกรัมวันละครั้ง และขนาด 10 มิลลิกรัมวันเว้นวัน ในด้าน (1) การเปลี่ยนแปลงระดับไขมัน, hsCRP และไฟบริโนเจน (2) ประสิทธิผลในการลดระดับ LDL-C ให้ถึงเกณฑ์เป้าหมายของผู้ป่วยแต่ละราย ตามแนวทางของ NCEP-ATP III (3) อาการไม่พึงประสงค์ และ (4) มูลค่ายา rosuvastatin ใน 1 เดือนต่อร้อยละของ LDL-C ที่ลดลง

วิธีดำเนินการวิจัย: การวิจัยเชิงทดลองชนิด randomized open-labeled, parallel design ดำเนินการศึกษาที่แผนกตรวจโรคผู้ป่วยนอก โรงพยาบาลพระมงกุฎเกล้า ระหว่างเดือนกันยายน 2547 ถึง กุมภาพันธ์ 2548 ผู้เข้าร่วมวิจัย 80 ราย ถูกสุ่มเป็น 2 กลุ่มเท่าๆกัน คือ กลุ่มควบคุมและกลุ่มศึกษาโดยวิธี block of four randomization โดยกลุ่มควบคุมและกลุ่มศึกษาได้รับ rosuvastatin 10 มิลลิกรัมวันละครั้ง และ 10 มิลลิกรัมวันเว้นวัน เป็นเวลา 8 สัปดาห์ ตามลำดับ เปรียบเทียบผลในด้าน (1) ร้อยละของการเปลี่ยนแปลงระดับไขมันในเลือด, hsCRP และไฟบริโนเจน (2) ร้อยละของผู้ป่วยที่สามารถลดระดับ LDL-C ได้ถึงเป้าหมายตามเกณฑ์ของ NCEP-ATP III (3) อาการไม่พึงประสงค์ และ (4) มูลค่ายา rosuvastatin ใน 1 เดือนต่อร้อยละของ LDL-C ที่ลดลง การประเมินผลพิจารณาจากผลตรวจทางห้องปฏิบัติการ ผลการตรวจร่างกาย และการสัมภาษณ์ผู้ป่วย สถิติที่ใช้เปรียบเทียบคือ Chi-square test, independent t-test, paired t-test, Mann-Whitney U test, Wilcoxon signed-rank test, และ Two-way ANOVA with repeated measures on one factor

ผลการวิจัย: ผู้ป่วย 2 กลุ่ม มีข้อมูลพื้นฐานแตกต่างกันในด้าน อายุเฉลี่ย และ ระดับ hsCRP เริ่มต้น โดยผู้ป่วยกลุ่มศึกษามีอายุเฉลี่ยและระดับ hsCRP เริ่มต้นสูงกว่ากลุ่มควบคุม ($p < 0.05$) ผลการศึกษาพบว่า ผู้ป่วยกลุ่มควบคุมสามารถลดระดับ TC, TG และ LDL-C ได้มากกว่ากลุ่มศึกษาอย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) แต่การเพิ่มระดับ HDL-C และการลดระดับ hsCRP และไฟบริโนเจนไม่แตกต่างกัน ($p > 0.05$) อย่างไรก็ตามผู้ป่วยกลุ่มควบคุมและกลุ่มศึกษาสามารถลดระดับ LDL-C ได้ถึงเป้าหมายตามเกณฑ์ของ NCEP-ATP III ไม่แตกต่างกัน ($p = 0.180$) นอกจากนี้การศึกษาพบว่า ผู้ป่วยกลุ่มควบคุมและกลุ่มศึกษามีอัตราการเกิดอาการไม่พึงประสงค์ไม่แตกต่างกัน ($p = 0.439$) ผู้ป่วยกลุ่มศึกษามีมูลค่ายา rosuvastatin ใน 1 เดือนต่อร้อยละของ LDL-C ที่ลดลง น้อยกว่ากลุ่มควบคุม (17.77 บาท และ 28.62 บาท ตามลำดับ)

สรุปผลการวิจัย: การใช้ยา rosuvastatin ขนาด 10 มิลลิกรัม วันเว้นวัน เป็นทางเลือกหนึ่งที่ช่วยประหยัดค่าใช้จ่ายในการรักษาซึ่งมีอัตราการเกิดอาการไม่พึงประสงค์และประสิทธิผลในการลดระดับ LDL-C ของผู้ป่วยได้ถึงเกณฑ์เป้าหมาย ไม่แตกต่างจากการใช้ยาวันละครั้ง ถึงแม้ว่าประสิทธิผลในการลดระดับ LDL-C จะน้อยกว่าการใช้ยาวันละครั้งก็ตาม

ภาควิชา .....เภสัชกรรม.....	ลายมือชื่อนิสิต .....
สาขาวิชา .....เภสัชกรรมคลินิก.....	ลายมือชื่ออาจารย์ที่ปรึกษา .....
ปีการศึกษา .....2547.....	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม .....

4676561033: MAJOR CLINICAL PHARMACY
KEY WORD: EFFECTIVENESS / SAFETY / ROSUVASTATIN / EVERY OTHER DAY / HYPERCHOLESTEROLEMIA

CHUTIPORN KITIYADISAI: EFFECTIVENESS AND SAFETY OF ROSUVASTATIN 10 MG ONCE DAILY VERSUS EVERY OTHER DAY IN OUTPATIENTS WITH HYPERCHOLESTEROLEMIA. THESIS ADVISOR: ASST. PROF. SUPAKIT WONGWIWATTHANANUKIT, Pharm.D., Ph.D., THESIS COADVISOR: LT. COL. NAKARIN SANSANAYUDH, M.D., 108 pp. ISBN: 974-53-2136-2.

Objectives: To compare the effectiveness and safety of rosuvastatin 10 mg once daily with every other day in terms of: (1) serum lipids, hsCRP, and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals according to NCEP-ATP III guidelines, (3) adverse event rates, and (4) monthly cost per %LDL-C reduction.

Methods: A randomized, open-labeled, parallel study was conducted during September, 2004 to February, 2005 at outpatient department, Phramongkutklao hospital, Bangkok, Thailand. Eighty patients were randomly assigned equally into the control and study groups by block of four randomization. The patients in the control and study groups received rosuvastatin 10 mg once daily and 10 mg every other day for 8 weeks, respectively. Outcome variables were evaluated in terms of: (1) percentage of change from baseline in serum LDL-C, TC, TG, HDL-C, hsCRP, and fibrinogen, (2) percentage of patients who achieved their LDL-C goals according to NCEP-ATP III guidelines, (3) adverse event rates, and (4) monthly cost per %LDL-C reduction of each patient group. Data were assessed using laboratory data (12-hour fasting blood and urine samples), physical examinations, and patient interviews. Chi-square test, independent t-test, paired t-test, Mann-Whitney U test, Wilcoxon signed-rank test, and Two-way ANOVA with repeated measures on one factor were used to analyze data.

Results: There were statistically significant differences in baseline characteristics of mean age and hsCRP between the control and study groups. Mean age and hsCRP in the study group were significantly higher than those in the control group ($p < 0.05$). The percentage of change in serum TC, TG, and LDL-C in the control group was significantly higher than that in the study group ($p < 0.05$). But, there was no significant difference in the percentage of change in serum HDL-C, hsCRP, and fibrinogen between the control and study groups ($p > 0.05$). The percentage of patients who achieved LDL-C goals according to NCEP-ATP III guidelines was not significantly different between the control and study groups ($p = 0.180$). In addition, the number of patients who experienced adverse events was not significantly different between both groups ($p = 0.439$). Monthly cost per %LDL-C reduction in the study group was lower than that in the control group (17.77 baht and 28.62 baht, respectively).

Conclusions: Every other day dosing of rosuvastatin is an alternative regimen for cost saving. It provides comparable adverse event rates and LDL-C lowering effect with once daily dosing, which allows the patients to achieve their LDL-C goals, despite less reduction in LDL-C.

Department ……...Pharmacy…….. Student's signature …….

Field of study ……..Clinical Pharmacy…….. Advisor's signature ……....

Academic year ……...2004…… Co-advisor's signature…….....

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TABLE OF CONTENTS

Page

Page

LIST OF TABLES

Table Page

Table Page

Table Page

LIST OF FIGURES

Figure Page

LIST OF ABBREVIATIONS

ALT	=	alanine aminotransferase
AST	=	aspartate aminotransferase
ATP	=	Adult Treatment Panel
BMI	=	body mass index
CHD	=	coronary heart disease
CK	=	creatine kinase
CVS	=	cardiovascular disease
DBP	=	diastolic blood pressure
FBS	=	fasting blood sugar
HDL-C	=	high-density lipoprotein cholesterol
HMG-CoA	=	3-hydroxy-3-methylglutaryl coenzyme A
hsCRP	=	high-sensitivity C-reactive protein
LDL-C	=	low-density lipoprotein cholesterol
mg	=	milligram
mg/dL	=	milligram per decilitre
mg/L	=	milligram per litre
NCEP	=	National Cholesterol Education Program
SBP	=	systolic blood pressure
SD	=	standard deviation
TC	=	total cholesterol
TG	=	triglyceride
TLC	=	therapeutic lifestyle change
ULN	=	upper limit of normal

CHAPTER I
INTRODUCTION

Coronary heart disease (CHD) is the first leading cause of global death, killing approximately 6,880,000 people in 2001 **[1]**. In Thailand, cardiovascular disease (CVS) is also a major cause of death. According to data from the Ministry of Public Health, about 40,000 people died of CVS in 2003 **[2]**. Moreover, the CVS mortality rate of Thai people tends to increase from 52.3 per 100,000 persons in 2000 to 63.7 per 100,000 persons in 2003 **[2]**. Since many studies have indicated that elevated low-density lipoprotein cholesterol (LDL-C) is a major cause of CHD and LDL-C lowering therapy can reduce CHD morbidity and mortality, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) has identified elevated LDL-C as the primary target of cholesterol-lowering therapy **[3-8]**.

Recently, results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 (PROVE IT – TIMI 22) and Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trials have demonstrated that lowering LDL-C to markedly below 100 mg/dL more significantly reduces death or major cardiovascular events ($p = 0.005$) and slow progression of coronary atherosclerosis ($p = 0.02$) than lowering LDL-C to marginally below 100 mg/dL in patients with CHD **[9-13]**. These findings lead to issuing of an update NCEP report from ATP III, which recommend LDL-C less than 70 mg/dL and less than 100 mg/dL as a optional goal in high risk patients (CHD or CHD risk equivalents) and moderately high risk patients ($\geq$ 2 risk factors and 10-year risk 10% to 20%), respectively **[14-15]**.

Lipid-lowering therapy consists of therapeutic lifestyle changes (TLC) and drug treatment. Currently, the available lipid-lowering drugs include 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, fibric acid derivatives, bile acid resin, niacin, and cholesterol absorption inhibitor. The most effective LDL-C lowering drugs are statins, which can reduce LDL-C between 18% and 55% **[4]**. Statins are effective in both primary and secondary preventions which decrease coronary morbidity and mortality between 24% and 37%

and reduce all cause mortality by 22% **[3-4,6,8]**. In addition, most patients are well tolerated to statins therapy. The infrequent adverse events are abdominal discomfort, myalgia, rash, and transient aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatine kinase (CK) elevation **[8]**.

Although statins trials have shown a reduction of CHD risk, CHD is still a major cause of death **[2,16-18]**. This is partly because many patients with hypercholesterolemia can not achieve their LDL-C goals **[5,8,19-20]**. The Lipid Treatment Assessment Project (L-TAP), European Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE), and Improve Persistence And Compliance with Therapy (ImPACT) trials have demonstrated that the overall of 37.5% to 62% of patients can not attain their LDL-C goals **[5,8,19]**. Similar to a study in Thailand, the percentage of patients who reached the LDL-C targets is 40.5, of which only 11.9% of patients with CHD can achieve their LDL-C goal **[21]**. Therefore, the powerful LDL-C lowering drugs have become a major role for more aggressive therapy.

Atorvastatin 10 to 80 mg and rosuvastatin 5 to 40 mg are very effective in lowering LDL-C ranging from 37% to 54% and 43% to 62%, respectively **[22-23]**. However, the major disadvantage of these agents is their high costs (about 46 to 70 baht per tablet). The high costs may affect patient affordability, resulting in underuse of statins. Thus, the strategies for reducing costs without diminishing efficacy or increasing side effects are desirable. Those include tablet-splitting and every other day dosing techniques. Most currently available statins tablets are not scored and cutting tablet in half may be problematic for patients who are visually, physically, or mentally impaired, so many every other day dosing studies have been conducted **[17,24-31]**. Studies have demonstrated that lovastatin, fluvastatin, simvastatin, and atorvastatin in every other day regimen significantly reduce LDL-C from baseline between 20% and 34% ($p < 0.05$) **[17,24,26,28-30]**. Moreover, the studies have shown that there is no statistically significant difference in LDL-C lowering effect between once daily dosing and every other day dosing ($p > 0.05$), except the results reported by Phruttisunakon, *et al*. **[17,26,28,30]**. Nevertheless, Phruttisunakon, *et al*. has found that the percentage of patients achieving LDL-C goal is not different between two regimens **[28]**. Regarding safety and compliance, studies have shown

that patients receiving every other day regimen are well tolerated and there is no significant difference in patient compliance **[17,24,26,28-30]**. However, to date, there has been no study that compares the efficacy and safety between every other day dosing and once daily dosing of rosuvastatin despite long half-life of rosuvastatin (19 hours).

Since more than half of all coronary events occur in patients without hypercholesterolemia, the other emerging factors associated risk for coronary events have been explored, including inflammatory markers, fibrinogen, lipoprotein(a), apolipoprotein (apo) A-I, apo B-100, and homocysteine **[4,32]**. Recently, much attention has focused on the role of C-reactive protein (CRP), a marker of inflammation, and fibrinogen, as the independent predictors of CHD **[32-38]**. The ability of pravastatin, lovastatin, cerivastatin, fluvastatin, simvastatin and atorvastatin to reduce serum CRP has been demonstrated in a number of trials. These studies have indicated that serum CRP is decreased between 13.1% and 47.0% ($p < 0.05$). This reduction does not relate to LDL-C reduction **[33,36,39-45]**. Conflicting results of the effect of statins on fibrinogen have also been documented. These studies have shown that atorvastatin and lovastatin significantly increase serum fibrinogen between 19% and 26% ($p < 0.05$), whereas pravastatin reduces serum fibrinogen between 7% and 19%, and simvastatin does not affect the serum fibrinogen **[46-53]**. However, there is no study of the effect of rosuvastatin on serum CRP and fibrinogen in both once daily and every other day regimens.

The purpose of this study was to compare the effectiveness and safety of rosuvastatin every other day with once daily regimen in altering lipids, high sensitivity C-reactive protein (hsCRP), and fibrinogen level, including adverse event rates of rosuvastatin in patients with hypercholesterolemia. Moreover, efficacy of rosuvastatin on the percentage of patients who achieved NCEP-ATP III goals and monthly cost per %LDL-C reduction in each regimen were also evaluated.

Objectives

To compare:

1. Effectiveness of rosuvastatin 10 mg once daily with every other day in terms of: (1) LDL-C reduction, (2) TC reduction, (3) TG reduction, (4) HDL-C elevation,

(5) hsCRP reduction, (6) fibrinogen reduction, and (7) percentage of patients who achieve their LDL-C goals according to NCEP-ATP III guidelines.

2. The adverse events of rosuvastatin 10 mg once daily with every other day regimen.
3. Monthly cost per %LDL-C reduction of patients receiving rosuvastatin 10 mg once daily with every other day.

Hypotheses

1. Efficacy of rosuvastatin 10 mg every other day in TC, LDL-C, TG, hsCRP, and fibrinogen reductions and HDL-C elevation is not different from rosuvastatin 10 mg once daily.
2. Efficacy of rosuvastatin 10 mg every other day in lowering LDL-C of patients to achieve their LDL-C goals according to NCEP-ATP III guidelines, is not different from rosuvastatin 10 mg once daily.
3. Adverse event rates of rosuvastatin 10 mg every other day is lower than rosuvastatin 10 mg once daily.

Significance of the Study

This study would add to the knowledge base on the:

1. Effectiveness and safety of rosuvastatin 10 mg every other day when compared with once daily regimen that could be used to consider the appropriate regimen for each individual patient.
2. Efficacy of both rosuvastatin 10 mg once daily and every other day on hsCRP and fibrinogen which are the important predictors of CHD in clinical practice.
3. Cost of rosuvastatin compared with its effectiveness when taking rosuvastatin 10 mg once daily versus every other day.

Operational Definitions

1. *Patient with hypercholesterolemia* means: (1) patient with CHD or CHD risk equivalents [i.e., diabetes mellitus, other forms of clinical atherosclerotic disease (peripheral arterial disease, carotid artery disease, and abdominal aortic aneurysm), and more than 20% of 10-year risk for developing major coronary events] who has equally or more than 100 mg/dL of LDL-C levels, (2) patient with more than one

major risk factor for CHD and equal or less than 20% of 10-year risk for developing major coronary events, who has equally or more than 130 mg/dL of LDL-C levels, and (3) patient with less than two major risk factors for CHD who has equally or more than 160 mg/dL of LDL-C levels.

2. *Effectiveness* means the ability in lowering TC, LDL-C, TG, hsCRP, and fibrinogen levels, and increasing HDL-C levels from baseline. Also, the ability in lowering LDL-C of patients to achieve their LDL-C goals according to NCEP-ATP III guidelines **[4]**. In this study, the effectiveness will be evaluated after the patient has taken rosuvastatin for 8 weeks.

   The effectiveness in lowering TC, LDL-C, TG, hsCRP, and fibrinogen levels, and increasing HDL-C levels from baseline are evaluated by the percent changes from baseline, which calculated by:

$$\frac{\text{Differences of the levels at the end of study from baseline x 100}}{\text{Baseline levels}}$$

   The effectiveness in lowering LDL-C of patients to achieve their LDL-C goals is evaluated by the percentage of patients who achieve their LDL-C goals according to NCEP-ATP III guidelines **[4]**.

3. *LDL-C goals according to NCEP-ATP III guidelines* means: (1) LDL-C less than 100 mg/dL in patient with CHD or CHD risk equivalents [i.e., diabetes mellitus, other forms of clinical atherosclerotic disease (peripheral arterial disease, carotid artery disease, and abdominal aortic aneurysm), or more than 20% of 10-year risk for developing major coronary events], (2) LDL-C less than 130 mg/dL in patient with more than one major risk factor for CHD and equal or less than 20% of 10-year risk for developing major coronary events, and (3) LDL-C less than 160 mg/dL in patient with less than two major risk factors for CHD **[4]**.

4. *Safety* means rates of adverse events from rosuvastatin e.g., muscle pain, muscle weakness, proteinuria, hematuria, and more than 3 times the upper limit of normal (ULN) of AST, ALT or CK elevation. Safety is evaluated throughout the study period by adverse events reporting, patient interview, physical examinations, and laboratory tests.

5. *Patient who meets the criteria for starting statins according to NCEP-ATP III guidelines* means: (1) patient with CHD or CHD risk equivalents [i.e., diabetes

mellitus, other forms of clinical atherosclerotic disease (peripheral arterial disease, carotid artery disease, and abdominal aortic aneurysm), or more than 20% of 10-year risk for developing major coronary events] who has LDL-C equally or more than 130 mg/dL or 100 mg/dL after lifestyle modifications, (2) patient with more than one major risk factor for CHD and 10% to 20% of 10-year risk for developing major coronary events, who has LDL-C equally or more than 130 mg/dL, (3) patient with more than one major risk factor for CHD and less than 10% of 10-year risk for developing major coronary events, who has LDL-C equally or more than 160 mg/dL or 130 mg/dL after therapeutic lifestyle changes, and (4) patient with less than two major risk factors for CHD, who has LDL-C equally or more than 190 mg/dL or 160 mg/dL after therapeutic lifestyle changes **[4]**.

6. *Monthly cost per %LDL-C reduction* means cost of 30 tablets (for once daily dosing) or 15 tablets (for every other day dosing) of rosuvastatin 10 mg divided by %LDL-C reduction in each patient group.

CHAPTER II
LITERATURE REVIEW

This study was conducted to compare the effectiveness on serum lipids, hsCRP, and fibrinogen and the safety of rosuvastatin 10 mg once daily with every other day in outpatients with hypercholesterolemia. Therefore, this chapter is divided into 5 sections. They are as follow: (1) hypercholesterolemia, (2) rosuvastatin, (3) C-reactive protein, (4) fibrinogen, and (5) every other day statins therapy. Each section is necessary to provide information and shape the knowledge base in the methods of the study.

1. Hypercholesterolemia

Hypercholesterolemia is a condition that elevated serum LDL-C or TC. Several clinical and epidemiological studies clearly establish the link between hypercholesterolemia and CHD, the leading cause of global deaths **[1,3-6]**. These studies have demonstrated a direct relationship between serum LDL-C or TC and CHD morbidity and mortality. They have also demonstrated an inverse relationship between HDL-C and risk for CHD. In general, these studies have shown that every 1% increase in cholesterol level, there is a 2% increase in the incidence of CHD and for every 1% decrease in HDL-C level, there is a 2% to 3% increase in the incidence of CHD **[3,6]**.

Epidemiology

Since CHD is a leading cause of global death that causes approximately 6,880,000 deaths in 2001, hypercholesterolemia becomes a major healthcare problem of the world **[1]**. Likewise, CHD is also a major cause of death in Thailand which kills about 40,000 people in 2003 (Table 1). Moreover, the CVS mortality rate of Thai people tends to increase from 52.3 per 100,000 persons in 2000 to 63.7 per 100,000 persons in 2003 **[2]**. Therefore, hypercholesterolemia is a major healthcare problem in Thailand.

Table 1 The number and death rates per 100,000 population of cardiovascular disease **[2]**

Year	2000	2001	2002	2003
Number of dead people (persons)	32,331	34,903	32,895	40,090
Death rates per 100,000 population	52.3	56.2	52.6	63.7

Based on the National Health and Nutrition Examination Survey (NHANES IV 1999 to 2000), an estimated 104,700,000 American adults (50.7% of Americans age 20 and older) had serum TC of 200 mg/dL or higher **[6,16]**. In Thailand, the International Collaborative Study of Cardiovascular Disease in Asia (InterASIA) study (2002) estimated that 4,400,000 Thai people had high serum TC ($\geq$ 200 mg/dL) **[54]**.

The prevalence of hypercholesterolemia in western world had gradually declined during the past four decades. The average total cholesterol in United States has fallen from 220 mg/dL between 1960 and 1962 to 203 mg/dL between 1988 and 1994. Moreover, the number of Americans with a desirable blood cholesterol level (< 200 mg/dL) has risen from 45% (1976) to 49% (1980) **[6]**. In the contrary, three large cross-sectional studies in Thailand assessing prevalence of cardiovascular risk factors, National Health Examination Survey I (NHES I 1991), NHES II (1996) and InterASIA (2000) studies have revealed that age-adjusted mean cholesterol level is significantly increased from 189 mg/dL to 201 mg/dL during this period **[55]**. This may be because many Thai people have had more unhealthy lifestyle (e.g., eating fast food diet and lack of exercise). Therefore, Thai people should realize the danger of hypercholesterolemia and seek the proper management to reduce CHD risk, including therapeutic lifestyle changes and drug therapy.

Causes of Hypercholesterolemia

Causes of hypercholesterolemia can be categorized into two causes **[56]**.

1. Primary hypercholesterolemia

   Primary hypercholesterolemia is associated with disorder of lipid metabolism (i.e., overproduction and/or impaired removal of lipoproteins).

2. Secondary hypercholesterolemia

Secondary hypercholesterolemia is caused by "non-lipid" factors. Secondary causes of hypercholesterolemia are shown in Table 2.

Table 2 Secondary causes of hypercholesterolemia **[6,56]**

Hypothyroidism
Obstructive liver disease
Nephrotic syndrome
Anorexia nervosa
Active intermittent porphyria
Drugs: progestrins, thiazide diuretics, glucocorticoids, β-blockers, isotretinoin, protease inhibitors, cyclosporin, mirtazapine, and sirolimus

Signs and Symptoms

Most patients with hypercholesterolemia have no symptoms or clinical manifestations of genetic lipid disorders (i.e., xanthomas, eruptions, and cornea arcus) **[6]**. Therefore, more accurate patient evaluation is based on serum lipid profile.

Hypercholesterolemia Managements

The NCEP ATP III has recommended that a 12-hour fasting lipid profiles be used in the initial lipid classification (Table 3). Then risk determinants in addition to LDL-C should be identified. The risk determinants include the presence or absence of CHD, diabetes mellitus, other clinical forms of atherosclerotic disease, and the major risk factors for CHD (Table 4). Based on these risk determinants, ATP III identifies three categories of risk that recommend LDL-C goal and LDL-C levels of initiation of therapeutic lifestyle changes (TLC) or drug therapy in each risk category (Table 5) **[3-4,6]**.

Table 3 ATP III classification of lipid profiles **[4]**

Low-density lipoprotein cholesterol	
< 100 mg/dl	Optimal
100-129 mg/dl	Near optimal or above optimal
130-159 mg/dl	Borderline high
160-189 mg/dl	High
≥ 190 mg/dl	Very high
Total cholesterol	
< 200 mg/dl	desirable
200-239 mg/dl	Borderline high
≥ 240 mg/dl	High
High-density lipoprotein cholesterol	
< 40 mg/dl	Low
≥ 60 mg/dl	High
Triglyceride	
< 150 mg/dl	Normal
150-199 mg/dl	Borderline high
200-499 mg/dl	High
≥ 500 mg/dl	Very high

Table 4 Major risk factors for CHD **[4]**

Positive risk factors

- Age: Male ≥ 45 years
  Female ≥ 55 years or premature menopause without estrogen replacement therapy
- Family history of a premature CHD (definite myocardial infarction or sudden death) before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative
- Current cigarette smoking
- Hypertension (≥ 140/90 mmHg or on antihypertensive drugs)
- Low HDL-C (< 40 mg/dL)

Negative risk factor

- High HDL-C (≥ 60 mg/dL)

Table 5 LDL-C goals and cutpoints for therapeutic lifestyle changes (TLC) and drug therapy **[4,14]**

Risk category	LDL-C goal (mg/dL)	LDL-C level to start TLC (mg/dL)	LDL-C level to consider drug therapy (mg/dL)
High risk: CHD or CHD equivalents† (10-year risk > 20%)	< 100 (< 70: optional)*	≥ 100	≥ 130 (100-129: optional)
Moderately high risk: ≥ 2 risk factors (10-year CHD risk 10-20%)	< 130 (< 100: optional)*	≥ 130	≥ 130 (100-129: optional)*
Moderate risk: ≥ 2 risk factors (10-year CHD risk for CHD < 10%)	< 130	≥ 130	≥160
Low risk: 0-1 risk factor	< 160	≥ 160	≥ 190 (160-189: optional)

CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; TLC = therapeutic lifestyle changes

† CHD risk equivalents = other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery), diabetes mellitus, and 10-year risk for CHD > 20%

* an update NCEP report

Recently, ATP III issued an update NCEP report, implications of recent clinical trials for the NCEP III guidelines, which recommend LDL-C goal of < 70 mg/dL as an optional goal in patients with high risk category (CHD or CHD risk equivalents) and < 100 mg/dL as a optional goal in patients with moderately high risk category (≥ 2 risk factors and 10-year risk 10% to 20%). This is because the results from five major clinical trials with statin therapy confirming the benefit of cholesterol-lowering therapy in high risk persons **[14]**.

Hypercholesterolemia managements consist of TLC and drug therapy.

1. Therapeutic lifestyle changes (TLC)

ATP III recommends a multifaceted lifestyle approach to reduce risk for CHD **[4]**. Its essential features are:

1) Reduced intake of saturated fats (< 7% of total calories) and cholesterol (< 200 mg/dL).
2) Therapeutic options for enhancing LDL-C lowering such as plant stanols/ sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d).
3) Weight reduction.
4) Increased physical activity.

2. Drug therapy

Currently, there are many available lipid-lowering drugs, including statins, fibric acid derivatives, bile acid resin, niacin, and cholesterol absorption inhibitor. The efficacy of these drugs is shown in Table 6.

Table 6 Average effects on lipid profiles of lipid-lowering drugs **[3-4]**

Drug	LDL-C	HDL-C	TG
Statins	- 18% to -55 %	+ 5% to +15 %	- 7% to -30 %
Fibric acid derivatives	- 5% to -20%	+ 10% to +20%	- 20% to -50 %
Niacin	- 5% to -25 %	+ 15% to +35 %	- 20% to -50 %
Bile acid resin	- 15% to -30 %	+ 3 % to 5%	+ 3% to +10 %
Cholesterol absorption inhibitor	- 18% to -22 %	+ 0% to +2 %	- 0% to +5 %

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride

The most effective LDL-C lowering drugs are statins, which can reduce LDL-C between 18% and 55% **[4]**. Statins are effective in decreasing coronary morbidity and mortality between 24% and 37% and reducing all cause mortality by 22% for both primary and secondary preventions **[3-4,6,8]**. In addition, most patients are well tolerated to statins therapy. The infrequent adverse events are abdominal discomfort, myalgia, rash, and transient aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatine kinase (CK) elevation **[8]**. The characteristics of various statins are summarized in Table 7.

Table 7 Summary characteristics of various statins **[57]**

Drug name (Trade name)	**Lovastatin (Mevacor)**	**Pravastatin (Prevachol)**	**Simvastatin (Zocor)**	**Fluvastatin (Lescol)**	**Atorvastatin (Lipitor)**	**Rosuvastatin (Crestor)**
Potency: Average decrease in LDL-C	20 mg: 29% 40 mg: 31% 80 mg: 40-48%	10 mg: 19% 20 mg: 24% 40 mg: 34% 80 mg: 40%	10 mg: 28% 20 mg: 35% 40 mg: 40% 80 mg: 48%	20 mg: 17% 40 mg: 23% 80 mg: 33%	10 mg: 38% 20 mg: 46% 40 mg: 51% 80 mg: 54%	5 mg: 43% 10 mg: 50% 20 mg: 53% 40 mg: 62%
Renal function	Use lower doses fore severe renal impairment (creatinine clearance < 30 ml/min)	Use lower doses for significant renal impairment (reduce initial dose to 10 mg daily)	Use lower doses for severe renal impairment (reduce initial dose to 5 mg daily)	No dose adjustment necessary for reduced renal function (not studied at doses > 40 mg in patients with severe renal impairment)	No dose adjustment necessary for reduced renal function.	Use lower doses for severe renal impairment (creatinine clearance < 30 ml/min)
Liver function monitoring	LFTs at baseline. Also, at 6 and 12 weeks after start of therapy or elevation of dose. Then every 6 months thereafter	LFTs at baseline. Also, prior to elevation of dose, and when otherwise clinically indicated.	LFTs at baseline and thereafter when clinically indicated. Patients titrated to 80 mg should receive an additional test before titration, 3 months after titration, and every 6 months for the 1st year.	LFTs at baseline. Also, at 12 weeks after initiation or elevation of dose.	LFTs at baseline. Also at 12 weeks following both the initiation of therapy and dose elevation. Check every 6 months thereafter.	LFTs at baseline. Also, at 12 weeks after initiation or elevation of dose. Then every 6 months thereafter.

Table 7 Summary characteristics of various statins **[57]** *(continued)*

Drug name (Trade name)	Lovastatin (Mevacor)	Pravastatin (Prevachol)	Simvastatin (Zocor)	Fluvastatin (Lescol)	Atorvastatin (Lipitor)	Rosuvastatin (Crestor)
Drug interactions	Metabolized by CYP3A4 enzyme system. Watch for interactions with drugs that inhibit this enzyme including: erythromycin, clarithromycin, Ketoconazole, Verapamil, diltiazem, nefazodone, fluvoxamine, cyclosporine, grapefruit juice, etc.	Not significantly metabolized by cytochrome P450 and may be less likely to be involved in drug interactions. Cyclosporine can increase pravastatin levels.	Metabolized by CYP3A4 enzyme system. Watch for interactions with drugs that inhibit this enzyme including: erythromycin, clarithromycin, Ketoconazole, Verapamil, diltiazem, nefazodone, fluvoxamine, cyclosporin, grapefruit juice, etc.	Metabolized primarily by CYP2C9 enzyme system and may be less likely to be involved in drug interactions. Fluvastatin can increase levels of phenytoin. Rifampin can lower fluvastatin level	Metabolized by CYP3A4 enzyme system, but less than lovastatin and simvastatin. Some drugs that inhibit CYP3A4 include:	Not significantly metabolized by cytochrome P450 and may be less likely to be involved in drug interactions. Use lower doses for patients taking cyclosporin or gemfibrozil (both drugs increase rosuvastatin levels). Rosuvastatin with warfarin results in increased INR
Food interactions	Take with dinner.	Take without regard to meals.	Take without regard to meals.	Take without regard to meals.	Take without regard to meals.	Take without regard to meals.

2. Rosuvastatin

Rosuvastatin calcium (Crestor®; licensed to AstraZeneca), the seventh drug in the statin class, was approved by the United States Food and Drug Administration (US FDA) in August 2003 for the reduction of cholesterol levels in patients with hypercholesterolemia. It is a synthetic lipid-lowering agent containing a sulphonyl moiety introduced to lower lipophilicity and to improve selectivity for the liver (Figure 1) **[20]**. Rosuvastatin is a potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis **[58]**.

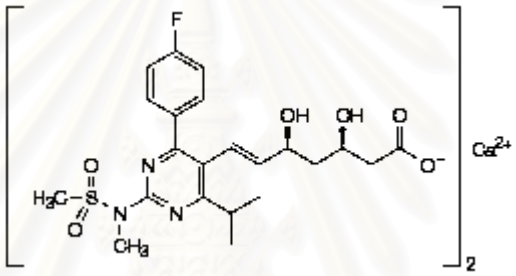


Figure 1 Rosuvastatin structure **[20]**

Indications

Rosuvastatin is indicated by US FDA that used:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable **[58]**.

Pharmacokinetics

Rosuvastatin is administered orally, once daily. Pharmacokinetic parameters of rosuvastatin are presented in Table 8. No clinically relevant differences in pharmacokinetics are observed between older (> 65 years) and younger (18 to 35 years) patients, between male and female patients, or between morning and evening dosing **[58-59]**. However, AstraZeneca Pharmaceuticals released a revised package insert for rosuvastatin on March 2nd, 2005 because of the result from a pharmacokinetic study. This study involving a diverse population of Asians residing in the United States, rosuvastatin drug levels were found to be elevated approximately two-fold compared with a Caucasian control group. As a result of these findings, the 5 mg dose of rosuvastatin should be considered as the starting dose for Asian patients **[60]**. Effect of race, gender, geriatric, and renal insufficiency on plasma rosuvastatin concentration are shown in Table 9.

Table 8 Pharmacokinetic parameters of rosuvastatin **[58-59]**

Parameters	
T_{max}	3-5 hours
C_{max} (40 mg x 7 days)	37.0 ng/mL
AUC	255.9 (ng x h)/mL
Bioavailability	20%
Effect of food on bioavailability	20%
Volume of distribution	134 L
Protein binding	88%
Metabolism	Cytochrome P450 2C9
Elimination half-life	19 hours
Excretion - feces - urine	 90% 10%

T_{max} = time to peak plasma concentration; C_{max} = peak plasma concentration; AUC = area under the plasma concentration-time curve

Table 9 Effect of race, gender, geriatric, and renal insufficiency on plasma rosuvastatin concentration **[58]**

Race	Approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group.
Gender	No differences in plasma concentrations of rosuvastatin between men and women.
Geriatric	No differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age $\geq$ 65 years).
Renal insufficiency - $Cl_{cr} \geq 30$ mL/min/1.73m^2 - $Cl_{cr} < 30$ mL/min/1.73m^2	-No influence on plasma concentrations of rosuvastatin -Plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment ($Cl_{cr} < 30$ mL/min/1.73 m^2) compared with healthy subjects ($Cl_{cr} > 80$ mL/min/1.73 m^2)

C_{max} = peak plasma concentration; AUC = area under the plasma concentration-time curve; Cl_{cr} = creatinine clearance

Drug Interactions

Cytochrome (CYP) P450 metabolism of rosuvastatin appears to be minimal and is principally mediated by the CYP 2C9 enzyme, with little involvement of CYP 3A4. This finding is consistent with the absence of clinically significant pharmacokinetic drug-drug interactions between rosuvastatin and other drugs known to inhibit CYP 3A4 enzymes **[58-59]**. Significant drug-drug interactions of rosuvastatin are shown in Table 10.

Table 10 Drug-drug interactions of rosuvastatin **[58]**

Drugs	Results
Cyclosporin	C_{max} and AUC of rosuvastatin are increased 11- and 7-fold, respectively, compared with historical data in healthy subjects.
Warfarin	Rosuvastatin does not change warfarin plasma concentrations, but increases International Normalized Ratio (INR).
Gemfibrozil	Coadministration of gemfibrozil (600 mg twice daily for 7 days) with rosuvastatin (80 mg) results in a 90% and 120% increase for AUC and C_{max} of rosuvastatin, respectively.
Antacid	Coadministration of an antacid (aluminum and magnesium hydroxide combination) with rosuvastatin (40 mg) results in a decrease in plasma concentrations of rosuvastatin by 54%.
Oral contraceptives (ethinyl estradiol and norgestrel)	An increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.

C_{max} = peak plasma concentration; AUC = area under the plasma concentration-time curve

Dosage Forms, Administration and Contraindications

Dosage forms, administration, and contraindications of rosuvastatin are shown in Table 11.

Table 11 Dosage forms, administration, and contraindications of rosuvastatin **[58]**

Dosage forms	Tablets 5 mg, 10 mg, 20 mg, and 40 mg (only 10 mg and 20 mg tablets are available in Thailand)
Administration	Rosuvastatin can be administered as a single dose at any time of day, with or without food.
Contraindications	- Patients with a known hypersensitivity - Patients with active liver disease or with unexplained persistent elevations of serum transaminases - Pregnancy and lactation (Pregnancy category X)

Dosage

The dose range for rosuvastatin is 5 mg to 40 mg once daily. Therapy with rosuvastatin should be individualized according to the goal of therapy and response. The usual recommended starting dose of rosuvastatin is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and for special populations such as patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency (Table 12) **[58,60]**.

Table 12 Dosage of rosuvastatin **[58,60]**

Population	Recommended doses
General population	Dose range 5 to 40 mg once daily (Starting at 10 mg once daily)
Asian patients	Starting at 5 mg once daily
Patients taking cyclosporin	Limit to 5 mg once daily
Concomitant lipid-lowering therapy	Limit to 10 mg once daily
Patients with severe renal insufficiency (Cl_{cr} < 30 mL/min/1.73m^2) not on hemodialysis	Starting at 5 mg once daily and not to exceed 10 mg once daily

Cl_{cr} = creatinine clearance

Clinical Efficacy Data

Rosuvastatin reduces TC, LDL-C, and TG and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within one week, and maximum response is usually achieved within four weeks and maintained during long-term therapy **[58]**. Several studies have been conducted to examine the efficacy of rosuvastatin. In a variety of dose-ranging and comparative trials in patients with hypercholesterolemia, 5 mg and 10 mg dose of rosuvastatin reduced LDL-C by up to 47% and 53%, respectively and by as much as 63% at 40 mg **[59,61]**.

Olsson, *et al*. (2001) conducted a randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy of rosuvastatin across the dose

range. Patients with hypercholesterolemia were randomly assigned to receive placebo or various doses of rosuvastatin as a single daily dose for six weeks. The results are shown in Table 13 **[58-59,61-63]**. In addition, the study also showed that most patients receiving rosuvastatin 5 and 10 mg reached their LDL-C goals according to NCEP guidelines (67% and 81%, respectively) **[62]**.

Table 13 Mean percentage of change from baseline at week 6 in rosuvastatin dose-ranging study **[58-59]**

Serum lipids	Mean % change from baseline (%)				
	Placebo (N = 13)	Rosuvastatin (N = 69)			
		5 mg (N = 17)	10 mg (N = 17)	20 mg (N =17)	40 mg (N = 18)
LDL-C	-7	-45**	-52**	-55**	-63**
TC	-5	-33**	-36**	-40**	-46**
HDL-C	+3	+13*	+14*	+8	+10
TG	-3	-35*	-10	-23	-28

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride

* $p < 0.05$ vs. placebo; ** $p < 0.001$ vs. placebo

In two 12-week randomized, double-blind comparative studies, one study compared effect of rosuvastatin 5 mg and 10 mg with simvastatin 20 mg and pravastatin 20 mg in hypercholesterolemic patients by Paolett, *et al* (2001). In another study, Davidson, *et al*. (2002) compared effect of rosuvastatin 5 mg and 10 mg with atorvastatin 10 in hypercholesterolemic patients **[59,61]**. The results are shown in Table 14 and Table 15, respectively.

Knopp, *et al*. (2002) carried out a six-week randomized, double-blind, dose-ranging study to compare rosuvastatin and atorvastatin across a range of doses in patients with hypercholesterolemia. The study indicated that at dose of 10 mg to 80 mg, percent reductions in LDL-C were 47% to 62% with rosuvastatin and 38% to 54% with atorvastatin. The LDL-C lowering response with rosuvastatin was significantly greater than with atorvastatin ($p < 0.01$) **[59,61]**.

Table 14 Mean percentage of change from baseline at week 12 in comparative study of rosuvastatin versus simvastatin and pravastatin in hypercholesterolemic patients **[59]**

Serum lipids	Mean % change from baseline (%)			
	Rosuvastatin 5 mg (N = 119)	Rosuvastatin 10 mg (N = 111)	Simvastatin 20 mg (N = 129)	Pravastatin 20 mg (N = 136)
LDL-C	-42*	-49**	-37	-28
TC	-30*	-34**	-26	-20
HDL-C	+6	+7	+4	+4
TG	-12	-18	-14	-13

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride
* $p < 0.001$ vs. pravastatin, $p < 0.005$ vs. simvastatin
** $p < 0.001$ vs. pravastatin, $p < 0.001$ vs. simvastatin

Table 15 Mean percentage of change from baseline at week 12 in comparative study of rosuvastatin versus atorvastatin in hypercholesterolemic patients **[59]**

Serum lipids	Mean % change from baseline (%)		
	Rosuvastatin 5 mg (N = 128)	Rosuvastatin 10 mg (N = 129)	Atorvastatin 10 mg (N = 127)
LDL-C	-40*	-43***	-35
TC	-28**	-30***	-25
HDL-C	+13*	+12**	+8
TG	-17	-19	-19

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride
* $p < 0.01$ vs. atorvastatin; ** $p < 0.05$ vs. atorvastatin; *** $p < 0.001$ vs. atorvastatin

Olsson, *et al*. (2002) conducted a 52-week dose-titration study to compare the efficacy of rosuvastatin with atorvastatin. Four-hundred and twelve patients received rosuvastatin 5 mg or 10 mg or atorvastatin 10 mg for 12 weeks. Then, does were sequentially doubled at 8-week intervals to a maximum of 80 mg if patients failed to achieve NCEP-ATP II LDL-C goal. The results are shown in Table 16. At 52 weeks, mean doses in the initial rosuvastatin 5 mg and 10 mg groups were 9.3 mg and 13.4 mg, respectively. The mean dose in the atorvastatin group was 20.8 mg **[59,61]**.

Table 16 Mean percentage of change from baseline at week 12 and week 52 and percentage of patients who achieved LDL-C goal according to NCEP-ATP II guidelines in comparative study of rosuvastatin versus atorvastatin in hypercholesterolemic patients **[59]**

Serum lipids / follow-up duration	Rosuvastatin 5 mg (N = 138)	Rosuvastatin 10 mg (N = 134)	Atorvastatin 10 mg (N = 140)
	Mean % change from baseline (%)		
LDL-C			
12 weeks	-46*	-50*	-39
52 weeks	-47**	-53*	-44
TC			
12 weeks	-32*	-35*	-28
52 weeks	-34	-38*	-38
HDL-C			
12 weeks	+6	+8	+6
52 weeks	+2	+3**	-1
TG			
12 weeks	-15	-19	-16
52 weeks	-20	-21	-19
	% patients who achieved LDL-C goal (%)††		
All patients			
12 weeks	86	89	73
52 weeks	88	98	87
High-risk patients†			
12 weeks	62	78	27
52 weeks	65	97	61

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride

† patients with CHD or CHD risk equivalents [other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery), diabetes mellitus, and 10-year risk for CHD > 20%]

†† no statistical comparison was performed between group for goal achievement

* $p < 0.001$ vs. atorvastatin

** $p < 0.05$ vs. atorvastatin

Similar to Olsson, *et al*. study, Brown, *et al*. (2002) also conducted a 52-week dose-titration study. This study compared effect of rosuvastatin with simvastatin and pravastatin. In this study, 477 patients received rosuvastatin 5 mg or 10 mg, simvastatin 20 mg, and pravastatin 20 mg for 12 weeks. After that, does were sequentially doubled at 8-week intervals (to a maximum of 80 mg of rosuvastatin and simvastatin and 40 mg for pravastatin) for failure to achieve ATP II LDL-C goals. The results are shown in Table 17. At 52 weeks, mean doses in the initial rosuvastatin 5 mg and 10 mg groups were 9.5 mg and 13.8 mg, respectively. Whereas, the mean dose in the simvastatin and pravastatin group were 36.3 mg and 32.6 mg, respectively **[59,61]**.

Jones, *et al*. (2003) conducted the Statin Therpaies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) study. This study was a six-week, randomized, parallel-group, open-label, comparator-controlled study. It was carried out to compare rosuvastatin with atorvastatin, pravastatin, and simvastatin across dose ranges for changing in serum LDL-C and other serum lipids. The results are reported in Table 18. In addition, this study also indicated that LDL-C goals of NCEP-ATP III were achieved between 82% and 89% of patients treated with rosuvastatin 10 mg to 40 mg compared with 69% to 85% of patients treated with atorvastatin 10 mg to 80 mg **[22]**.

Jame, *et al*. (2003) and Shepherd, *et al*. (2003) analyzed pooled data from five 12-week randomized, double-blind studies in patients with hypercholesterolemia. The purpose was to: (1) compare efficacy of rosuvastatin 5 mg and 10 mg with atorvastatin 10 mg (data from three of the five studies), (2) compare efficacy of rosuvastatin 5 mg and 10 mg with simvastatin 20 mg and pravastatin 20 mg (data from two of the five studies), and (3) summarize overall efficacy of rosuvastatin on serum lipids over 12 weeks (data from five studies) **[64-65]**. The results are shown in Table 19 –22.

Table 17 Mean percentage of change from baseline at week 12 and week 52 and percentage of patients who achieved LDL-C goal according to NCEP-ATP II guidelines in comparative study of rosuvastatin versus simvastatin and pravastatin in hypercholesterolemic patients **[59]**

Serum lipids / follow-up duration	Rosuvastatin 5 mg (N = 123)	Rosuvastatin 10 mg (N = 116)	Simvastatin 20 mg (N = 120)	Pravastatin 20 mg (N = 118)
	Mean % change from baseline (%)			
LDL-C				
12 weeks	-39 [a, b]	-47 [a, b]	-35	-27
52 weeks	-42 [a]	-48 [a, b]	-38	-32
HDL-C				
12 weeks	+8	+12 [a]	+9	+8
52 weeks	+4	+8	+6	+4
TG				
12 weeks	-18 [b]	-22 [a, b]	-10	-11
52 weeks	-16	-18 [a]	-14	-9
	% patients who achieved LDL-C goal (%)[††]			
All patients				
12 weeks	80	90	69	53
52 weeks	88	88	73	60
High-risk patients[†]				
12 weeks	48	63	30	9
52 weeks	84	71	30	6

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride

† patients with CHD or CHD risk equivalents [other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery), diabetes mellitus, and 10-year risk for CHD > 20%]

†† no statistical comparison was performed between group for goal achievement

[a] $p < 0.05$ vs. pravastatin

[b] $p < 0.05$ vs. simvastatin

Table 18 Mean percentage of change from baseline at week 6 in STELLAR study **[22]**

Serum lipids / dose of study drugs	Mean % change from baseline (%)			
	Rosuvastatin (N = 480)	Atorvastatin (N = 641)	Simvastatin (N = 655)	Pravastatin (N = 492)
LDL-C				
10 mg	-45.8	-36.8 [a]	-28.3 [a]	-20.1 [a]
20 mg	-52.4	-42.6 [b]	-35.0 [a,b]	-24.4 [a, b]
40 mg	-55.0	-47.8 [b, c]	-38.8 [a, b, c]	-29.7 [a, b, c]
80 mg	NA	-51.1	-45.8 [b, c]	NA
TC				
10 mg	-32.9	-27.1 [a]	-20.3 [a]	-14.7 [a]
20 mg	-37.6	-31.8 [b]	-25.7 [a, b]	-17.2 [a, b]
40 mg	-40.2	-35.8 [c]	-27.9 [a, b, c]	-21.5 [a, b, c]
80 mg	NA	-38.9	-32.9 [b, c]	NA
HDL-C				
10 mg	+7.7	+5.7	+5.3	+3.2 [a]
20 mg	+9.5	+4.8 [b]	+6.0	+4.4 [b]
40 mg	+9.6	+4.4 [b, c]	+5.2 [b, c]	+5.6 [b, c]
80 mg	NA	+2.1 [b, c]	+6.8	NA
TG				
10 mg	-19.8	-20.0	-11.9	-8.2 [a]
20 mg	-23.7	-22.6	-17.6	-7.7 [a, b]
40 mg	-26.1	-26.8	-14.8 [b, c]	-13.2 [b, c]
80 mg	NA	-28.2	-18.2	NA

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride; NA = data not available

[a] $p < 0.002$ vs. rosuvastatin 10 mg

[b] $p < 0.002$ vs. rosuvastatin 20 mg

[c] $p < 0.002$ vs. rosuvastatin 40 mg

Table 19 Pooled data analysis: Mean percentage of change from baseline at week 12 in comparative studies of rosuvastatin versus atorvastatin **[64]**

Serum lipids	Mean % change from baseline (%)		
	Rosuvastatin 5 mg (N = 390)	Rosuvastatin 10 mg (N = 389)	Atorvastatin 10 mg (N = 393)
LDL-C	-41.9*	-46.7*	-36.4
TC	-29.6*	-33.0*	-26.7
HDL-C	+8.2**	+8.9*	+5.5
TG	-16.4	-19.2	-17.6

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride
* $p < 0.001$ vs. atorvastatin; ** $p < 0.01$ vs. atorvastatin

Table 20 Pooled data analysis: Mean percentage of change from baseline at week 12 in comparative studies of rosuvastatin versus simvastatin and pravastatin **[64]**

Serum lipids	Mean % change from baseline (%)			
	Rosuvastatin 5 mg (N = 240)	Rosuvastatin 10 mg (N = 226)	Simvastatin 20 mg (N = 249)	Pravastatin 20 mg (N = 252)
LDL-C	-40.6*	-48.1*	-35.7	-27.1
TC	-29.1*	-34.0*	-25.1	-19.2
HDL-C	+6.9	+9.1**	+6.2	+6.2
TG	-14.9	-20.2***	-12.2	-12.4

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride
* $p < 0.001$ vs. simvastatin and pravastatin
** $p < 0.05$ vs. simvastatin and pravastatin
*** $p < 0.01$ vs. simvastatin and pravastatin

Table 21 Pooled data analysis: Mean percentage of change from baseline at week 12 of all patients in comparative studies of rosuvastatin versus atorvastatin and versus simvastatin and pravastatin **[64]**

Serum lipids	Mean % change from baseline (%)	
	Rosuvastatin 5 mg (N = 630)	Rosuvastatin 10 mg (N = 615)
LDL-C	-41.4	-47.2
TC	-29.4	-33.4
HDL-C	+7.7	+9.0
TG	-15.8	-19.6

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride

Table 22 Pooled data analysis: Percentage of patients achieving ATP III LDL-C goals at initial doses in comparative studies of rosuvastatin versus atorvastatin and versus simvastatin and pravastatin **[69,65]**

Risk group target	% achieved LDL-C goal (%)†			
	<100 mg/dL	<130 mg/dL	<160 mg/dL	All
Comparative studies vs. atorvastatin				
Rosuvastatin 5 mg (N = 390)	40.0[a]	86.0	95.0	67.0[b]
Rosuvastatin 10 mg (N = 389)	60.0[a]	88.0	96.0	76.0[b]
Atorvastatin 10 mg (N = 393)	19.0	80.0	91.0	53.0
Comparative studies vs. simvastatin and pravastatin				
Rosuvastatin 5 mg (N = 240)	39.0[c,e]	80.0[c]	91.0	71.0[c,f]
Rosuvastatin 10 mg (N = 226)	63.0[c,g]	89.0[c,f]	99.0[d,f]	86.0[c,g]
Simvastatin 20 mg (N = 249)	22.5	74.0	90.0	64.0
Pravastatin 20 mg (N = 252)	5.0	40.0	88.0	49.0

† LDL-C goal defined by NCEP-ATP III as follows: (1) < 100 mg/dL in patients with CHD or CHD risk equivalents [other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery), diabetes mellitus, and 10-year risk for CHD > 20%], (2) < 130 mg/dL in patients without CHD and with ≥ 2 risk factors and 10-year risk for CHD ≤ 20%, and (3) < 160 mg/dL in patients without CHD and with < 2 risk factors

[a] $p < 0.001$ vs. atorvastatin; [b] $p < 0.01$ vs. atorvastatin

[c] $p < 0.001$ vs. pravastatin; [d] $p < 0.05$ vs. pravastatin

[e] $p < 0.01$ vs. simvastatin; [f] $p < 0.05$ vs. simvastatin; [g] $p < 0.001$ vs. simvastatin

Rosuvastatin has been assessed in many dose-ranging studies and comparative studies with other statins in hypercholesterolemic patients. Dose-ranging studies with rosuvastatin have demonstrated marked dose-related reduction in LDL-C of up to 63% at 40 mg. A comparative dose-ranging study with atorvastatin has shown that rosuvastatin produces a significantly greater reduction in LDL-C across the dose range. Moreover, rosuvastatin 5 mg to 40 mg improves LDL-C lowering effect and LDL-C goal achievement compared with widely used doses of atorvastatin, simvastatin, and pravastatin. The effects of rosuvastatin on LDL-C have been accompanied by beneficial changes in a number of important lipid measures in addition to LDL-C, including serum TC, HDL-C, and TG **[63]**. These findings indicate that LDL-C lowering effect of rosuvastatin may help patients who require lipid-lowering therapy to achieve their recommended LDL-C goals.

Safety Data

Rosuvastatin is generally well tolerated. The most common adverse events thought to be related to rosuvastatin were myalgia, constipation, headache, abdominal pain, diarrhea, pharyngitis, flu syndrome, asthenia, and nausea **[8,58-59,61,66]**. In placebo-controlled trials, adverse events those considered related to trial treatment by the investigators occurred in 16.0% of patients who received rosuvastatin 5 mg to 40 mg (N = 744) and in 17.8% of patients who received placebo (N = 382) **[66]**. Moreover, rates of adverse events leading to withdrawal, nonfatal serious adverse events, and adverse events leading to death were similar to the patients who received rosuvastatin or placebo. In fixed-dose controlled trials, rosuvastatin 5 mg to 40 mg was well tolerated and had an adverse event profile similar to those of atorvastatin 10 mg to 80 mg, simvastatin 10 mg to 80 mg, and pravastatin 10 mg to 40 mg **[61,66]**. The adverse event rates of rosuvastatin are shown in Table 23.

Like the other statins, rosuvastatin is associated with biochemical abnormalities of liver function. In most cases, the elevations were transient and resolved or improved on continuing therapy or after a brief interruption of therapy. However, it is recommended

that liver function tests should be performed before and at 12 weeks following both the initiation of therapy and after any increases of dosage. Liver enzyme changes generally occur in the first three months of treatment with rosuvastatin. Patients who develop an increase in serum transaminase enzymes (i.e., AST or ALT) should be monitored until the abnormalities resolve. If an increase in serum AST or ALT > 3 times the upper limit of normal (ULN) persists, reduction of dose or withdrawal of rosuvastatin should be recommended **[58,62]**.

Table 23 Adverse event rates of rosuvastatin **[22,58-59,61,63,66-67**]

Adverse events	Rate (%)
Nausea	3.4 – 11.8
Myalgia	3.1 – 7.0
Pharyngitis	5.0 – 9.0
Headache	3.0 – 5.9
Dry mouth	5.9
Diarrhea	3.4
Dyspepsia	3.4
Asthenia	2.7
Back pain	2.6
Flu syndrome	2.3
Peripheral edema	$\geq$ 2
Myopathy	$\leq$ 0.03
AST/ALT > 3 times the ULN	0.1 – 0.8
CK > 10 times the ULN	0.1– 0.4
Rhabdomyolysis	< 0.01
Proteinuria	9.7 – 12.6
Hematuria	6 - 10

Myopathy (defined as muscle symptoms with serum CK > 10 times the ULN) and rare cases of rhabdomyolysis (defined as muscle symptoms with serum CK > 10 times the ULN and with creatinine elevation), which can lead to acute renal failure and death, have been reported for all currently approved statins, including rosuvastatin. Like the other statins, reports of rhabdomyolysis with rosuvastatin are rare, but the incidence is higher with the highest marketed dose (40 mg). In addition, risks of myopathy at 5 mg to 40 mg of rosuvastatin appear comparable to the other statins **[58,62]**.

In contrast to currently approved statins, rosuvastatin is associated with renal damage which has not previously been reported as a major event with other statins. Rosuvastatin has been noted to cause proteinuria and hematuria. Dipstick-positive proteinuria and microscopic hematuria are observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (80 mg). This is also noted to occur in a higher rate in patients taking 40 mg compared with patients taking either lower doses of rosuvastatin or comparator statin agents. In clinical trials, this effect was transient, and did not predict worsening of renal function. However, proteinuria has been also reported with the other statins, although at a lower incidence **[58,62,67]**.

Overall, rosuvastatin is a new statin with a number of advantageous pharmacological properties, including enhanced HMG-CoA reductase binding characteristics, relative hydrophillicity, and selective uptake into hepatic cells. CYP metabolism of rosuvastatin appears to be minimal and is principally mediated by 2C9 enzymes. Therefore, the clinically significant pharmacokinetic drug-drug interactions with other drugs known to inhibit CYP 3A4 enzymes have not been observed. In addition, rosuvastatin has been shown to be highly effective in reducing LDL-C and improving other lipid profiles. Moreover, it is well tolerated and has a safety profile similar to the other marketed statins.

3. C-reactive Protein

C-reactive protein (CRP) is a non specific acute-phase reactant. It is synthesized by hepatocytes, predominantly under transcriptional control by the interleukin-6 **[68-71]**. De novo hepatic synthesis starts very rapidly after a single stimulus. Serum CRP rises above 5 mg/L approximately 6 hours and reaches its peak around 48 hours after stimulus. The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate. When the stimulus for increased production completely ceases, the circulating CRP concentration falls rapidly, at almost the rate of plasma CRP clearance **[68,70]**. Two studies have indicated that in the absence of inflammatory stimulation, CRP reverts significantly toward normal within 24 hours to few days **[70-71]**.

Infection, allergic complications of infection, necrosis, trauma, malignancy, and inflammatory diseases can precipitate the release of CRP **[68]**. In addition, there are some factors that can affect the CRP levels such as statins, smoking and weight loss (Table 24) **[32,70]**.

Table 24 Factors that alter CRP levels **[32,70]**

Increase CRP	Decrease CRP
Chronic infections	Aspirin
Chronic inflammation	Fibrates
Diabetes mellitus	Niacin
Hypertension	Moderate alcohol intake
Metabolic syndrome	Selective estrogen receptor modulators
Obesity	Smoking cessation
Low HDL-C/ high TG	Statins
Oral estrogen	Tamoxifen
Smoking	Thiazolidinediones
	Weight loss

Refinement of the CRP laboratory test was necessary to detect the low-grade inflammation associated with cardiovascular disease. Therefore, high-sensitivity CRP (hsCRP) analytical method was developed to detect low CRP levels **[32]**. The advantages of hsCRP include the ability to standardize the assay, minimal variation among assay (<10%), lack of seasonal or diurnal variation, acceptable cost (300 baht), and the ability to have samples drawn regardless of food intake **[32,68,72]**.

Atherosclerosis, which was initially thought to be purely a disease of arterial lipid deposition, is also now considered an inflammatory disease. This process begins with injury to the vascular endothelium in response to major risk factors (e.g., hypertension, smoking, and diabetes), leading to oxidation and macrophage uptake of LDL-C and formation of the fatty streak. The fatty streak is the initial building block in the development of the atherosclerotic plaque. These early steps of atherogenesis also involve the elicitation of proinflammatory cytokines causing hepatic stimulation and production of CRP. Moreover, CRP may contribute to atherosclerosis by facilitating macrophage uptake of LDL-C, thus accelerating fatty-streak formation. These findings have stimulated research examining the potential role of CRP as a predictive tool for future cardiovascular events **[32]**.

Several studies have shown a moderate to strong association between hsCRP levels and future vascular events (i.e., coronary, cerebrovascular, and peripheral vascular disease), with minimal correlation to LDL-C **[32,34-38,76]**. This suggests that CRP may identify individuals who traditionally would not have met the criteria for treatment based solely on lipid levels **[32]**. Therefore, a recent published review article and scientific statement by the American Heart Association and Centers for Disease Control and Prevention on "Markers of Inflammation and Cardiovascular Disease" recommends using hsCRP as an adjunct to the lipid panel to predict future cardiovascular events in patients who had 10-20% of 10-year risk for CHD **[38]**.

Although numerous forms of lipid-lowering therapy can alter levels of hsCRP (Table 1), the most extensively studies agents are statins, which highly effective in reducing the risk of cardiovascular disease **[32,36]**. Statins have been hypothesized to

have direct anti-inflammatory effects by reduce macrophage content within atherosclerotic plaques, suppress the expression of metalloproteinases involved in the fibrous cap dissolution, and inhibit the expression of adhesion molecules critical for monocyte attachment and adhesion to the endothelial wall **[33]**. Treatment with statins has been found to produce median reductions in hsCRP of 15% to 25% within six weeks of starting treatment. These reductions appear to be unrelated to the magnitude of LDL-C reduction **[36]**. The ability of pravastatin, lovastatin, cerivastatin, fluvastatin, simvastatin and atorvastatin to reduce hsCRP levels has been demonstrated in a number of trials. These studies have revealed that serum hsCRP is significantly reduced from baseline after receiving pravastatin 40 mg per day (13.1% to 20.3%), lovastatin 20 to 40 mg per day (12.5% to 17.4%), cerivastatin 0.4 to 0.8 mg per day (13.3% to 24.5%), fluvastatin 20 mg per day (15.9%), simvastatin 20 to 40 mg per day (22.8% to 37.2%), and atorvastatin 10 to 80 mg per day (15.0% to 47.0%) (all $p < 0.05$) **[33,39-44,73]**. However, the effect of rosuvastatin on hsCRP has not been studied yet.

Recently, the substudies of PROVE IT – TIMI 22 and REVERSAL have shown that patients who have low CRP levels after statin therapy have better clinical outcomes and slower rate of atherosclerosis progression than those with higher CRP levels, regardless of the resultant level of LDL-C **[74-75]**. These findings support the aggressive use of statins to achieve target levels of both LDL-C and CRP for reduction of coronary events in post acute coronary syndrome patients. In addition, these studies suggest that monitoring CRP and LDL-C should be performed in lowering cardiovascular risks with statin therapy **[69]**.

To date, the efficacy of every other day statins therapy on serum CRP has not yet been conducted. However, Jialal, *et al*. suggested that the effect of statins on CRP might be sustained with every other day dosing. Jialal, *et al*. investigated the effect of atorvastatin 10 mg, pravastatin 40 mg, and simvastatin 20 mg on hsCRP. In this study there was a 3-week washout period between drugs. During the washout phase, LDL-C increased significantly ($p < 0.001$) but there was no significant increase in hsCRP ($p = 0.21$). This study also suggested that the CRP-lowering effect of statins is more

prolonged than their effect on LDL-C. Therefore, every other day dosing of statins therapy probably would not compromise their effect on CRP **[34,40]**. To definitively answer of every other day statins effect on hsCRP, the prospective studies are required.

4. Fibrinogen

Fibrinogen is a protein synthesized by liver which plays two essential roles in the body. One, it is a vital part of the "common pathway" of the coagulation process. The conversion of fibrinogen (factor I) to fibrin is the last step of the "coagulation cascade", a series of reactions in the blood triggered by tissue injury and platelet activation. And two, it is also a protein called an acute phase reactant that becomes elevated with tissue inflammation or tissue destruction. When fibrinogen acts as an "acute phase reactant", it rises sharply during tissue inflammation or injury. Most acute myocardial infarctions (heart attack) are now known to be due to acute thrombosis, or the sudden formation of a blood clot at the site of an atherosclerotic plaque. It makes sense, therefore, that elevated levels of fibrinogen, an acute phase protein and is part of the coagulation cascade of proteins, would be associated with an increase in risk of heart attack **[77]**. There are many factors that affect the fibrinogen levels (Table 25)

Several studies have demonstrated that fibrinogen is an independent risk factor for CHD **[72,76,78-81]**. Meresca, *et al*. (1999) conducted a meta-analysis to examine the association between fibrinogen and CVS. This study showed that the overall risk of cardiovascular event in subjects with plasma fibrinogen levels in the higher tertile, was twice as high as that of subjects in the lower one (odds ratio, 1.99; 95% confidence interval, 1.85 to 2.13). The study also indicated that high plasma fibrinogen levels were associated with an increased risk of cardiovascular disease in healthy as much as in high-risk individuals **[81]**.

Table 25 Factors affecting plasma fibrinogen level **[77,81]**

Increases	Decrease
Cigarette smoking	Ticlopidine
Oral contraceptive drugs	Bezafibrate
Estrogen	Phenobarbital
Pregnancy	Valproic acid
Diabetes mellitus	Urokinase
High dietary fat intake	Streptokinase
Increasing age	Alcohol
Menopause	Liver disease
Inflammation	Prostate cancer
Inflammatory disorder	
Thrombin endotoxin	
Prostaglandins	
Stomach, breast, or kidney cancers	
Vascular damage	

Experimental and clinical studies have indicated a relationship between hyperlipidemia and increased blood thrombogenicity. This implied that correction of hypercholesterolemia by statins could normalize blood thrombogenicity **[82]**. However, conflicting findings on the effect of different statins on fibrinogen have been reported **[49-53,82]**. Most studies reported an increase of serum fibrinogen with atorvastatin and lovastatin (ranging from 19.3% to 26.0%), a neutral effect on serum fibrinogen with fluvastatin and simvastatin, and a decrease of serum fibrinogen with pravastatin (ranging from 7.0% to 19.0%) **[49-53,82]**. Currently, the effect of new statins, rosuvastatin, on serum fibrinogen has not been studied. Therefore, the study is needed to examine the effect of rosuvastatin on serum fibrinogen.

5. Every Other Day Statins Therapy

Despite evidence of safety and effectiveness of statins, they are greatly underused due to high costs and fear of toxicity **[31]**. In addition, most patients require long-term statins therapy **[27]**. Therefore, the strategies for reducing drug costs without hindering therapeutic efficacy or increase side effects are desirable **[17,27]**. These strategies include tablet splitting method and every other day dosing method. However, most available statins are unscored tablets or in capsule form and cutting tablet in half may be problematic for patients who are visually, physically, or mentally impaired **[17,30]**. Therefore, every day dosing may be more desirable. Since rosuvastatin has a long half life, 19 hours, it is conceivable that the every other day dosing might be effective in maintaining the lipid-lowering efficacy **[58-59]**. Currently, the efficacy of rosuvastatin in every other day dosing has not yet been conducted. However, there are many studies that debate over whether statins might still produce a significant effect on serum LDL-C by administering them every other day instead of once daily **[17,24,26,28-31]**.

Rindone, *et al*. (1995) conducted an open-labeled, nonrandomized, before-after comparison trial to examine the efficacy of administering lovastatin 20 mg every other day in patients with hypercholesterolemia. The subjects were patients who had serum LDL-C more than 160 mg/dL, calculated using the Friedewald equation, despite following a three-month trial of an American Heart Association (AHA) Step I diet. Patients were excluded if they had serum TG more than 400 mg/dL, evidence of hepatic disease, previous lovastatin intolerance, or concurrent use of a lipid-lowering agent. All eligible patients were given lovastatin 20 mg every other day for six weeks. Of the 21 eligible patients, 19 patients completed the study. One patient withdrew from developing angioedema, another was lost to follow-up. After six weeks of therapy, 19 patients (17 men) had mean reduction in serum TC by 15% and LDL-C by 20% (both $p = 0.001$). There was no statistically significant difference in the mean change from baseline of serum TG (8% reduction; $p = 0.07$) and HDL-C (5% elevation; $p = 0.52$). The adverse event was reported only one patient with muscle cramping which did not require discontinuation of therapy **[27,29]**. Although this study showed that every other day

appeared to be effective. Several aspects of the trial design are worth exploring. First, this study did not have an intention to treat analysis for dropout patients. Second, there was no comparator group. Finally, this study had small patient population and included only two women. This makes it difficult to extrapolate the results to the general population.

Dennis, *et al*. (1997) conducted a retrospective review to evaluate the therapeutic effects of lovastatin 20 mg every other day and to determine whether this regimen represent a cost-effective alternative to the conventional once daily dosing. The subjects were outpatients who received lovastatin 20 mg every other day for primary hypercholesterolemia with a follow-up of every six weeks to four months. Patients were excluded if they had serum TG more than 400 mg/dL due to a decrease in the reliability of LDL-C estimation by the Friedewald equation. The cost-effective analysis was performed in terms of monthly cost per percent LDL-C reduction, using data of lovastatin 10 mg once daily reported by Rubinstein. Twenty male patients met all criteria and were analyzed. The study reported that mean serum TC and LDL-C were significantly decreased from baseline by 14.0% and 21.5%, respectively (both $p < 0.05$). Four of the 20 patients (20%) attained their LDL-C goals. No significant change was noted in serum TG or HDL-C. The monthly cost per percent LDL-C reduction per patient was $0.63 in patients receiving lovastatin 20 mg every other day and $0.87 in patients receiving lovastatin 10 mg once daily **[24,27]**. However, there were many limitations in this study. First, this study was a small retrospective review and included patients with follow-up periods as short as three month. Therefore, the investigators could not evaluate effects of continued every other day of lovastatin therapy overtime. Moreover, bias in patient selection may occur because the physician might select every other day dosing for patients who would respond positively. Second, it is difficult to determine whether undocumented adverse events were the cause of discontinued therapy. Finally, all patients were male, which difficult to generalized the results across different patient population.

Rindone, *et al*. (1998) carried out a randomized, nonblinded, crossover study to assess the efficacy of fluvastatin administered every other day versus an equivalent dose given once daily in patients with hypercholesterolemia. Thirty patients who had calculated LDL-C more than 160 mg/dL, using a Friedewald equation, after three months of the AHA Step I diet, were recruited in this study. The patients were excluded if they were taking concomitant lipid-lowering agents, had a baseline serum TG of 400 mg/dL or greater, or had previous intolerance to any statin. Of 30 patients enrolled, 23 completed the protocol (22 men). Ten patients were randomized to receive fluvastatin 20 mg once daily for six weeks followed by fluvastatin 40 mg every other day for six more weeks. Conversely, the other 13 patients received fluvastatin 40 mg every other day first. The study showed that fluvastatin 20 mg once daily and 40 mg every other day significantly reduced LDL-C from baseline by 24% and 21%, respectively (both $p < 0.05$) and reduced TC from baseline by 18% and 15%, respectively (both $p < 0.05$). There was no statistically significant difference in the reduction of TG or HDL-C from baseline in both regimens. This study also revealed that there was no statistically significant difference in serum lipids between regimens **[27,30-31]**. However, there are some limitations in this study. First, the possibility of a carryover effect exists since there was no washout period. However, six weeks should be adequate for a new steady-state in LDL-C reduction. Second, this small study of only 23 subjects does not eliminate the possibility of type II error. Finally, the presence of only one woman makes extrapolation beyond the male population difficult.

Matalka, *et al*. (2002) conducted a double-blind, placebo-controlled trial to evaluate the efficacy and cost-effectiveness between every other day dosing and once daily dosing of atorvastatin in patients with hypercholesterolemia. Thirty-five eligible patients who met the NCEP-ATP II guidelines for drug therapy were randomly assigned to received atorvastatin 10 mg once daily (17 patients) or every other day (18 patients). Patients were excludes if they had serum TG more than 400 mg/dL; myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within last three months; elevated liver enzymes or active liver disease (AST,

ALT, GGT $\geq$ 3 times the upper limit of normal); or were receiving immunosuppressant drugs, azole antifungal agents or warfarin. Of the 35 patients enrolled, 26 completed the 12-weeks study period (14 in every other day group and 12 in once daily group). There were five patients dropped out from once daily group. Of these, two patients had gastrointestinal disturbance and one experienced muscle weakness with mild CK elevation. Four patients in every other day group dropped out from the study, which two patients experienced flu-like symptoms. At six weeks, patients receiving atorvastatin 10 mg every other day had a 27% LDL-C reduction, while patients receiving atorvastatin 10 mg once daily had a 38% LDL-C reduction. If the patients in both groups did not meet their LDL-C goals by week six, they would take double dose of their starting dosage until the end of study. By week 12, the difference in LDL-C lowering between the every other day (35%) and once daily groups (38%) was not statistically significant ($p = 0.49$). The mean dose was 18 mg (9 mg/day) in the every other day dosing group and 12 mg/day in the once daily group at the end of the 12 weeks ($p = 0.001$). The monthly cost analysis based on 1% LDL-C reduction per patient at week 12 of the study was $1.22 versus $1.71 in the every other day and once daily groups, respectively **[26]**. The limitation of this study was that the study had a small sample size and high drop out rate, leading to an increase in type II error. In addition, most patients in this study were male (100% in once daily group and 89% in every other day group). This may reduce the ability to extrapolate these findings to the general population.

Copher, *et al*. (2002) conducted a nonrandomized, before-after comparison trial to compare the efficacy of simvastatin once daily with every other day in double dose of once daily regimen. The simvastatin regimen for eligible patients (15 men) with hyperlipidemia who met their LDL-C goals by NCEP guidelines was converted from once daily dosing to double the daily dose given every other day for 8 weeks. Patients were excluded if they had an active prescription for more than 40 mg/day of simvastatin, were receiving a protease inhibitor, or taking combination antihyperlipidemic therapy requiring a dosage change during the study period. The study showed that of the 14 patients completing the study, 12 remained at or below their LDL-C goals. The serum

TC, LDL-C, HDL-C, and TG after patients receiving simvastatin once daily was not significantly different from patients receiving every other day regimen (all $p > 0.05$). This study revealed that no patients had complaints of musculoskeletal toxicity or significantly elevated serum CK, AST, or ALT during the study period **[17]**. However, there were some limitations in this study. The study had only small number of elderly male patients (ranging in age from 59 to 82 years). Therefore, it was difficult to generalize the results to the general population.

Phruttisunakon, *et al*. (2003) conducted a randomized double-blind, parallel trial to assess the efficacy of atorvastatin 10 mg administered every other day versus once daily in hypercholesterolemic patients for the primary prevention of CHD. Sixty-eight patients without CHD were enrolled in the 8 weeks of therapeutic lifestyle change period. After that, the patients were randomized to received atorvastatin 10 mg once daily (N = 30) or every other day (N = 31) for 8 weeks. Of these, 59 patients completed the study, 30 in once daily group and 29 in every other day group. The study showed that at week 16, atorvastatin 10 mg once daily significantly reduced LDL-C (39%), TC (30%), and TG (18%) from baseline (all $p < 0.001$). Also, atorvastatin 10 mg every other day significantly reduced LDL-C (31%), TC (21%), and TG (5%) from baseline ($p < 0.05$). However, both regimens showed a non significant change in serum HDL-C ($p > 0.05$). The study also revealed that atorvastatin 10 mg once daily significantly produced greater percent reductions from baseline in LDL-C and TC than every other day dosing (39% vs 31%; $p < 0.001$ and 30% vs 21%; $p < 0.01$, respectively). However, the percentage of patients who achieved their LDL-C goals in patients receiving atorvastatin 10 mg once daily (73%) was not significantly different from patients receiving atorvastatin 10 mg every other day (65%) ($p = 0.135$). There were three adverse events in four patients (7%). These were gastrointestinal disturbance (one patient in every other day group), AST and ALT elevation more than three times the upper limit of normal (one patient in every other day group), and CK elevation more than three times the upper limit of normal (two patients in once daily group) **[28,85]**. However, this study only focused on patients

with primary hypercholesterolemia. Therefore, the results could not be generalized to all hypercholesterolemia patients.

Currently, only lovastatin, fluvastatin, simvastatin, and atorvastatin have been shown to significantly reduce serum LDL-C from baseline when given every other day. The efficacy of pravastatin and rosuvastatin on every other day dosing has not yet been carried out. Despite the seeming efficacy for every other day dosing in the previous study, various study limitations warrant further explorations. All of these studies were small, with a male predominance. The absence of females and lack of age distribution greatly reduces the ability of extending these findings to the general population. Therefore, larger, randomized, controlled trials, including men and women of various ages, are warranted. Moreover, none of studies have conducted the role of every other day statins therapy on CRP and fibrinogen level, the emerging risk factors in coronary events. Therefore, this randomized open-labeled, parallel study was conducted to compare the effectiveness and safety of rosuvastatin, a new powerful LDL-C lowering agent, 10 mg once daily with every other day in terms of: (1) serum lipids, hsCRP, and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals according to NCEP-ATP III guidelines, (3) adverse event rates, and (4) monthly cost per %LDL-C reduction.

CHAPTER III
METHODS

This study was carried out to compare the effectiveness and safety of rosuvastatin 10 mg once daily with every other day in outpatients with hypercholesterolemia in terms of: (1) serum lipids, hsCRP, and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals according to NCEP-ATP III guidelines, (3) adverse event rates, and (4) monthly cost per %LDL-C reduction.

This chapter describes in detail how the study was conducted. It is devided into two sections. The first section describes the patients in this study, including patient selection, sample size estimation, and patient randomization. The second section describes methods, including study design and procedures, laboratory measurement, and statistical analysis.

1. Patients

1.1 Patient Selection

Subjects in this study were patients with hypercholesterolemia who visited outpatient department of Phramongkutklao hospital between September 2004 to February 2005, who had never received statins, and met the following criteria:

Inclusion criteria:

1. aged $\geq$ 18 years.
2. met the criteria for starting statins therapy according to NCEP-ATP III guidelines.
3. gave written informed consent.

Exclusion criteria:

1. diagnosed with secondary hypercholesterolemia.
2. took drugs known to affect the levels of lipids, hsCRP, and fibrinogen, or interacted with rosuvastatin (i.e., estrogen, corticosteroids, tamoxifen, phenobarbital, urokinase, streptokinase, cyclosporine, gemfibrozil, erythromycin, warfarin, heparin, low-molecular weight heparin, and valproic acid).

3. had an active liver disease or elevated liver enzymes (AST, ALT > 3 times the upper limit of normal).
4. had creatine kinase > 3 times the upper limit of normal.
5. had severe renal impairment (creatinine clearance < 30 mL/min).
6. had chronic inflammatory conditions (i.e., severe arthritis, lupus, or inflammatory bowel disease).
7. had cancer or history of cancer.
8. had recent infection or illness (within 2 weeks before the study).
9. had been hospitalized for acute coronary syndrome within 3 months before the study.
10. had pregnancy or lactation.
11. had serious medical or psychological conditions that may compromise successful participation in the study.

If the patients had an intolerable adverse event, serum AST, ALT, or CK > 3 times the upper limit of normal, hypersensitivity to statins, or required other lipid-lowering agent (i.e., fibrates, niacin, bile-acid sequestrants, and cholesterol absorption inhibitor) during the study period, these patients would be excluded.

1.2 Sample Size Estimation

An estimated sample of 80 subjects was calculated by using equation (1), at an α significance level of 0.05 (i.e., Type I error) and a power of 80% **[83]**. The differences of percent LDL-C reduction by atorvastatin between once daily and every other day regimens were assumed as rosuvastatin, because there is, currently, no comparative study of rosuvastatin and half-life of rosuvastatin is not much different from atorvastatin (19 hours and 14 hour, respectively). Phruttisunakon, *et al.* found that Thai patients receiving atorvastatin 10 mg once daily could reduce LDL-C more than atorvastatin 10 mg every other day by 8 % **[28]**. The standard deviation in this study was assumed as 10.72 according to the finding in efficacy of rosuvastatin 10 mg once daily on LDL-C reduction (i.e., serum LDL-C was reduced from 190 mg/dL to 95.4 mg/dL) **[62]**.

$$N = \frac{2 (Z_\alpha + Z_\beta)^2 \sigma^2}{d^2} \quad \text{.....equation (1)}$$

Determination: $\alpha = 0.05$ (two-sided); $Z_\alpha = 1.96$

$\beta = 0.2$ (one-sided); $Z_\beta = 0.84$

$\sigma = 10.72$

d = the differences of LDL-C reduction between regimens

$= 0.08 \times 95.4 = 7.632$ mg/dL

So, N/ group $= \frac{2 (1.96 + 0.84)^2 (10.72)^2}{(7.632)^2}$

$= 30.9 \approx 31$ subjects

Estimate drop out 20%, N/ group $= \frac{31}{(1 - 0.2)} \approx 40$ subjects

Therefore, 80 patients were recruited for this study (40 subjects per group).

1.3 Patient randomization

Eighty patients were randomly assigned equally into two groups using block of four randomization. One group received rosuvastatin 10 mg once daily at 8.00 p.m. for 8 weeks (control group) and another group received rosuvastatin 10 mg every other day at 8.00 p.m. for 8 weeks (study group). Then, simple random sampling was used to determine the control and the study groups.

2. Methods

2.1 Study Design and Procedures

This randomized, open-labeled, parallel trial was approved by the ethic committee of Phramongkutklao hospital. Prior to study, the patient record forms (appendix A), research subject information sheets (appendix B), consent forms (appendix C), and Naranjo's algorithm (appendix D) had been developed. At study initiation, the patients diagnosed with hypercholesterolemia were screened by physicians and referred to the researcher for subject eligibility assessment. Subject eligibility was determined by laboratory data (TC, TG, HDL-C, LDL-C, AST, ALT, CK, and creatinine), patient interviews, and OPD cards review. If laboratory data had

not been completed, the patients would have been given a detailed explanation of the study and asked for blood sampling appointment. All eligible patients were invited to participate in this study. After both verbal and non-verbal description of the study (e.g., an assurance of confidentiality and the right to refuse), patients provided written consent forms. The patient demographic data and laboratory data were recorded in the patient record forms. Blood pressures (BP) were also measured and recorded by using blood pressure monitoring machine (OMRON Digital Blood Pressure Monitor HEM-907, Japan). Then, all patients were educated about undesirable outcomes of hypercholesterolemia, risk factors for CHD, individual risk category and LDL-C goal, TLC, and studying drug (e.g. name, regimens, indications, and adverse drug reactions). The researcher believed that this was the strategy that encouraged the patients to realize the dangers of hypercholesterolemia and to adhere to their drugs and TLC, and this also made the patients be able to observe the adverse events, to record and to tell the physician or researcher. Patients who did not have data on hsCRP, fibrinogen, fasting blood sugar (FBS), or urine analysis were also made an appointment to obtain these data.

The patients were randomly assigned to receive rosuvastatin 10 mg (supplied by Crestor®; licensed to AstraZeneca from IPR Pharmaceuticals Inc., Canovanas, Puerto Rico, Lot. No. CA 352) once daily (control group) or 10 mg every other day (study group) for 8 weeks by block randomization. In the study group, odd- or even-day dosing technique was used to improve compliance. The reason for choosing 10 mg once daily and 10 mg every other day (average 5 mg/day) regimens was that rosuvastatin 5 mg and 10 mg per day could reduce LDL-C between 39% and 45%, which were standard doses according to NCEP-ATP III (2004) recommendations. The standard doses of statins would allow an approximate 30% to 40% reduction in LDL-C levels and reduce coronary risk with a similar percentage over a five-year period **[14]**. The researcher followed up the patients via telephone every week during the study period to monitor adverse events and other problems. On the other hand, patients could phone the researcher directly at anytime. If the problems had occurred, patients would have been given the advices and/or invited to visit a hospital for further evaluation.

At the end of 8 weeks, the efficacy and safety of rosuvastatin were evaluated in each group of the patients. Twelve-hour fasting blood and urine samples were obtained to evaluate changes in lipids, hsCRP, fibrinogen, and safety parameters. The percentage of patients achieving LDL-C goals as defined by NCEP-ATP III guidelines and monthly cost per % LDL-C reduction were also assessed. Blood and urine samples were collected between 7.00 a.m. to 10.00 a.m. For the study group, this was the time in which the patients did not take the study medicine the day before following-up day. Safety and tolerability were evaluated throughout the study on the basis of adverse events reporting, patient interviews, physical examinations, and laboratory studies (i.e., AST, ALT, CK levels, and urine analysis for proteinuria or hematuria). All adverse events were assessed the causality from the study drug using Naranjo's algorithm and reported to the Ministry of Public Health. In addition, all patients were interviewed about their lifestyles, compliance, and other problems during the study period. The diagram of the study procedure is shown in Figure 2

2.2 Laboratory Measurement

Fasting lipid panels, hepatic enzyme panels, CK, creatinine, hsCRP, fibrinogen concentration and urine analysis were obtained as baseline data at random between 7.00 a.m. and 10.00 a.m. before the study period and again on the last day of the 8-week period. Cholesterol levels, hepatic transaminase enzymes, CK, creatinine, and hsCRP were measured by using the COBAS INTEGRA 800 Roche Diagnostic (GmbH D-68298, Mannheim, Germany) at the central laboratory of Phramongkutklao hospital. HsCRP was assayed by particle enhanced immunoturbidimetric technique. Fibrinogen level was analyzed using turbidimetric method with the DigiSpec Helena Laboratories (Germany). Both instruments were calibrated and standardized daily by technical staffs.

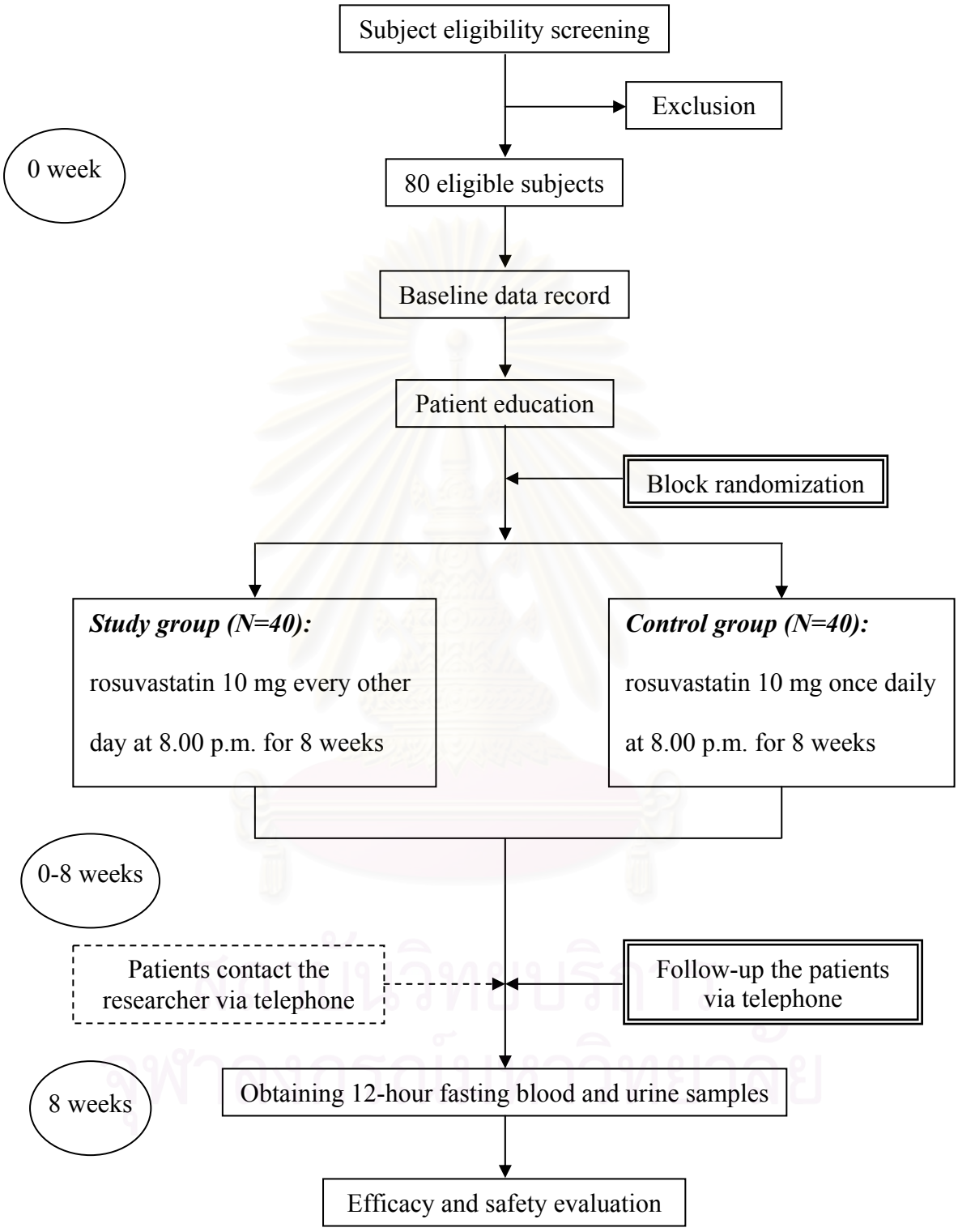


Figure 2 The diagram of the study procedure

2.3 Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 12.0. Intention to treat analysis was used by replacing the missing data with series mean for each group. Both descriptive and inferential statistics were determined. The level of significance was set at an $\alpha = 0.05$.

Descriptive statistics (e.g., mean, standard deviation, median, percentage, and frequency) were used to evaluate the baseline characteristics, efficacy data (i.e., lipids, hsCRP, and fibrinogen altering), and safety data.

Kolmogorov-Smirnov test and Levene's test were used to determine the distribution of data and homogeneity of variance, respectively. Statistical comparisons between study and control group for categorical variables were performed using Chi-square tests or Fisher's exact test in the analysis of baseline patient characteristics, laboratory data, percentage of patients achieving LDL-C goal, and percentage of patients experienced adverse events. Continuous variables between baseline and at the end of study for each patient group were compared by using paired t-test when data were normal distribution or using Wilcoxon signed-rank test when data were non-normal distribution. In addition, continuous variables between study and control groups were compared by using independent t-test or Mann-Whitney U test for normal and non normal distribution data, respectively. Moreover, if baseline data are different between the patient groups, two-way ANOVA with repeated measures on one factor would be performed to determine the interaction between groups and time and to examine the main effects of group and time. Main effect of group would suggest that there was an overall difference between the control and study groups with respect to the mean of the data. Main effect of time would suggest that there was a significant difference between data obtained at one time and data obtained at another time during the study period.

CHAPTER IV
RESULTS AND DISCUSSIONS

The study was a randomized, open-labeled, parallel trial. The purpose was to compare the effectiveness and safety of rosuvastatin 10 mg once daily with every other day in terms of: (1) serum lipids, hsCRP, and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals according to NCEP-ATP III guidelines, (3) adverse event rates, and (4) monthly cost per %LDL-C reduction.

This chapter is divided into 3 parts:

1. Baseline patient characteristics which consist of baseline patient demographics and clinical laboratory data.
2. Efficacy evaluation including the efficacy of rosuvastatin 10 mg once daily and every other day on serum lipids, hsCRP, and fibrinogen changing from baseline, the percentage of patients who achieved their LDL-C goals according to NCEP-ATP III guidelines, and monthly cost per %LDL-C reduction.
3. Safety evaluation.

1. Baseline Patient Characteristics

1.1 Baseline Patient Demographics

Subjects were recruited from patients with hypercholesterolemia who met the inclusion criteria and were willing to participate in the study. Figure 3 depicts the patient flow diagram. Of 80 patients enrolled, 76 patients completed the 8-week study period (38 patients in each group). One patient died of sepsis, three asked for withdrawal due to adverse events (i.e., headache, malaise, and myalgia).

Table 26 – 27 present baseline patient demographic data. Most patients (60%) were female. This finding is consistent with the proportion of Thai adults with hypercholesterolemia (i.e., 57.83% female) **[54]**. This is also similar to the results reported by Kitiyadisai, *et al*. and Phruttisunakon in those 51.7% to 64.4% of hypercholesterolemia patients at Phramongkutklao hospital were female **[84-85]**.

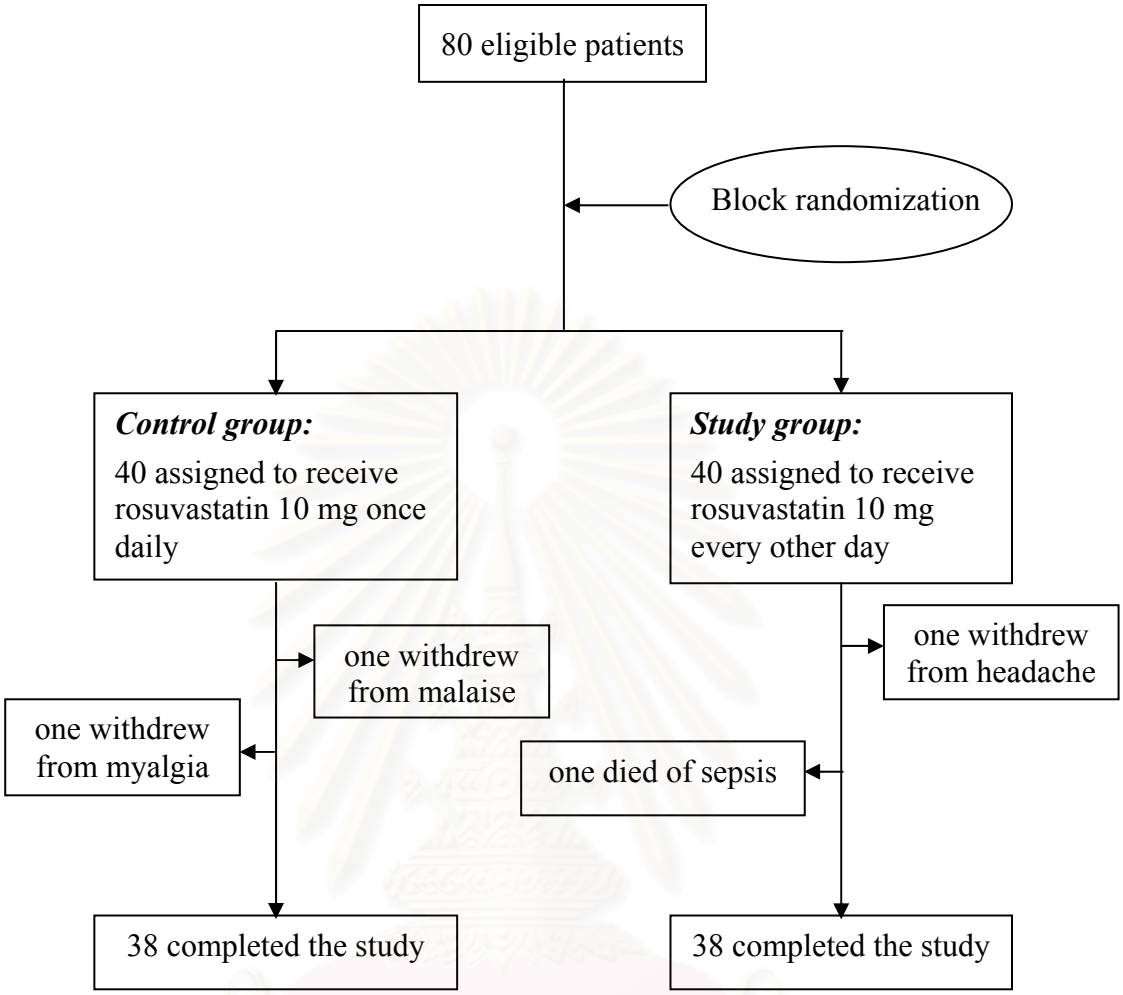


Figure 3 Patient flow diagram

The mean age of patients (mean ± SD) was 59.64 ± 9.89 years (ranging from 41 to 82 years). This is similar to the results from three previous studies at Phramongkutklao hospital which indicate that mean age of hypercholesterolemic patients were 63.47 ± 10.85 years (ranging from 28 to 90 years), 61.87 ± 9.66 years (ranging from 35 to 83 years), and 60.56 ± 9.75 years (ranging from 43 to 79 years) **[84-86]**. The most common age range was 50 – 59 years, representing 40% of patients. This age range is considered as one of the major risk factors for CHD. The average weight and height were 66.37 ± 12.00 kg and 1.60 ± 0.08 m, respectively. The mean body mass index (BMI) was 25.69 ± 3.70 kg/m^2 (ranging from 18.5 to 34.6 kg/m^2). This is similar to the results reported by Samphao-Ngern (25.2 ± 2.9 kg/m^2) and Phruttisunakon (25.84 ± 3.80 kg/m^2) **[85,87]**. Most patients (36.3%) were in

Table 26 Baseline patient demographics in categorical data

Data	No. of patients (%)*			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
Sex				
- Male	17 (42.5)	15 (37.5)	32 (40.0)	0.819
- Female	23 (57.5)	25 (62.5)	48 (60.0)	
Age				
- 40 – 49 years	9 (22.5)	4 (10.0)	13 (16.2)	
- 50 – 59 years	17 (42.5)	15 (37.5)	32 (40.0)	0.390
- 60 – 69 years	6 (15.0)	9 (22.5)	15 (18.8)	
- 70 – 79 years	8 (20.0)	11 (27.5)	19 (23.8)	
- $\geq$ 80 years	0 (0.0)	1 (2.5)	1 (1.2)	
BMI (kg/m^2)				
- < 18.5 (underweight)	0 (0.0)	0 (0.0)	0 (0.0)	
- 18.5 – 22.9 (normal range)	11 (27.5)	10 (25.0)	21 (26.3)	0.975
- 23.0 – 24.9 (at risk)	9 (22.5)	8 (20.0)	17 (21.3)	
- 25.0 – 29.9 (obese I)	14 (35.0)	15 (37.5)	29 (36.3)	
- $\geq$ 30 (obese II)	6 (15.0)	7 (17.5)	13 (16.3)	
Waist circumference (inches)				
- > 36 inches in male	7 (17.5)	9 (22.5)	16 (20.0)	0.780
- > 32 inches in female	13 (32.5)	11 (27.5)	24 (30.0)	0.807
Underlying diseases				
- Hypertension	26 (65.0)	34 (85.0)	60 (75.0)	0.071
- Diabetes mellitus	11 (27.5)	11 (27.5)	22 (27.5)	1.000
- Gout	3 (7.5)	3 (7.5)	6 (7.5)	1.000
- Others**	9 (22.5)	11 (27.5)	20 (25.0)	0.796
Number of concurrent drugs				
- 0 – 5 drug(s)	33 (82.5)	30 (75.0)	63 (78.8)	0.585
- > 5 drugs	7 (17.5)	10 (25.0)	17 (21.2)	
Metabolic syndrome	14 (35.0)	18 (45.0)	32 (40.0)	0.494

Table 26 Baseline patient demographics in categorical data *(continued)*

Data	No. of patients (%)*			*p* value
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
Occupation				
- Government officer	18 (45.0)	17 (42.5)	35 (43.8)	0.151[a]
- Housekeeper	11 (27.5)	10 (25.0)	21 (26.2)	
- None	2 (5.0)	9 (22.5)	11 (13.8)	
- Commerce	3 (7.5)	2 (5.0)	5 (6.2)	
- Others***	6 (15.0)	2 (5.0)	8 (10.0)	
Health insurance rights				
- Refundable	27 (67.5)	28 (70.0)	55 (68.8)	0.932[a]
- Non refundable	4 (10.0)	3 (7.5)	7 (8.8)	
- Social security	3 (7.5)	2 (5.0)	5 (6.2)	
- National health insurance (30 baht scheme)	6 (15.0)	7 (17.5)	13 (16.2)	
Smoker	3 (7.5)	2 (5.0)	5 (6.2)	1.000[b]
Alcoholic drinker	8 (20.0)	2 (5.0)	10 (12.5)	0.091[a]

[a] using Chi-square test to compare the number of patients in the control group with the study group

[b] using Fisher's exact test to compare the number of patients in the control group with the study group

* % in each regimen for the control and the study group columns, or % of all patients in a total column

** CHD, cerebrovascular disease, asthma, arrhythmia, heart failure, parkinsonism, and benign prostatic hyperplasia

*** state enterprise, employee, and farmer

Table 27 Baseline patient demographics in continuous data

Data	Mean ± SD (range)			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
Age (years)	57.18 ± 1.48 (41, 73)	62.10 ± 1.57 (41, 82)	59.64 ± 9.89 (41, 82)	0.025*
Weight (kg)	66.14 ± 9.59 (50, 90)	66.60 ± 14.14 (40, 96)	66.37 ± 12.00 (40, 6)	0.868
Height (m)	1.61 ± 0.01 (1.50, 1.76)	1.60 ± 0.01 (1.40, 1.75)	1.60 ± 0.08 (1.40, 1.76)	0.548
BMI (kg/m^2)	25.53 ± 3.39 (20.7, 33.0)	25.85 ± 4.02 (18.5, 34.6)	25.69 ± 3.70 (18.5, 34.6)	0.702
Waist circumference (inches)	33.68 ± 3.24 (27.0, 40.0)	34.14 ± 5.08 (24.0, 45.5)	33.91 ± 4.20 (24.0, 45.5)	0.630
SBP (mgHg)	137.90 ± 21.28 (98, 210)	144.07 ± 27.08 (81, 220)	140.99 ± 24.96 (81, 220)	0.058
DBP (mgHg)	84.83 ± 19.07 (52, 160)	83.88 ± 11.15 (56, 110)	84.35 ± 15.53 (52, 160)	0.787
Number of concurrent drugs	3.45 ± 2.17 (0, 8)	4.28 ± 2.33 (1, 10)	3.86 ± 2.28 (0, 10)	0.106

SD = standard deviation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure

[a] using independent t-test to compare mean of the control group with the study group

* having a statistically significant difference at $\alpha = 0.05$

25.0 – 29.9 kg/m^2 BMI range which was classified as obese patients according to the World Health Organization (WHO) criteria for Asia-Pacific region **[88]**. This indicates that obesity was one of the problems in these patients and associated with cardiovascular diseases. However, obesity is a modifiable risk factor, therefore, the role of healthcare professionals on these patients should be initiated to control their weight. The mean waist circumference was 33.91 ± 4.20 inches (ranging from 24.0 to

45.5 inches). The abdominal obesity (defined as weight circumference more than 36 inches in male and 32 inches in female) associated with the cardiovascular risk factors of the metabolic syndrome was identified in both male (20%) and female (30%) **[88]**.

Most underlying diseases in the study populations were hypertension (HTN, 75.0%) and diabetes mellitus (DM, 27.5%). This finding is congruent with the result reported by Phruttisunakon which also showed that 71.2% of patients had HTN and 16.9% had DM **[85]**. Both HTN and DM are the major risk factors for CHD. Therefore, these factors should also be considered when caring the patients. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 140.99 ± 24.96 and 84.35 ± 15.53, respectively. Despite evidence of HTN in most patients, the mean DBP appears to be lower than the HTN range. This may be because many patients were taking antihypertensive drugs and most patients were elderly with isolated systolic hypertension. Nearly half of patients (40%) had metabolic syndrome which was associated with substantial increase in CHD risk. These patients should be educated and encouraged to improve their BP, FBS, TG, HDL-C, and waist circumference. Most patients got equal or less than five concurrent drugs (i.e., mean of the number of concurrent drugs were 3.86 ± 2.28 drugs). The number of patients who received each type of concurrent drug was not significantly different between the control and the study groups (all $p > 0.05$) (Table 28).

Most patients were government officers (43.8%) and housekeeper (26.2%) because most of them were soldiers and their families. Most patients (68.8%) could refund their healthcare expenditure. This finding is consistent with the previous studies which showed that 70.2% to 77.6% of patients could refund their healthcare expenditure **[84-86]**. Only five patients (6.2%) currently smoked cigarettes, and 10 patients (12.5%) drank alcohol. These are small percentage which may be due to the success of the recent government campaign, increase in physician reinforcement and increase in awareness and concern of the patients. The numbers of patients who smoked cigarettes and drank alcohol were not different between the control and the study groups (Table 26).

Table 28 Comparison of the concurrent drugs in the control with the study group

Concurrent drugs*	No. of patients (%)**			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
Allopurinol	1 (2.5)	1 (2.5)	2 (2.5)	1.000
Amiloride + HCTZ (Moduretic®)	1 (0.0)	0 (0.0)	1 (1.2)	1.000
Amlodipine	4 (10.0)	3 (7.5)	7 (8.8)	1.000
Aspirin	9 (22.5)	10 (25.0)	19 (23.8)	1.000
Atenolol	10 (25.0)	18 (45.0)	28 (35.0)	0.101
Bisoprolol	1 (2.5)	0 (0.0)	1 (1.2)	1.000
Candesartan	1 (2.5)	2 (5.0)	3 (3.8)	1.000
Clopidogrel	0 (0.0)	2 (5.0)	2 (2.5)	0.494
Colchicine	2 (5.0)	2 (5.0)	4 (5.0)	1.000
Digoxin	1 (2.5)	0 (0.0)	1 (1.2)	1.000
Diltiazem	1 (2.5)	2 (5.0)	3 (3.8)	1.000
Doxazosin	1 (2.5)	2 (5.0)	3 (3.8)	1.000
Enalapril	10 (25.0)	13 (32.5)	23 (28.8)	0.621
Felodipine	0 (0.0)	2 (5.0)	2 (2.5)	0.494
Furosemide	1 (2.5)	0 (0.0)	1 (1.2)	1.000
Glibenclamide	3 (7.5)	1 (2.5)	4 (5.0)	0.615
Gliclazide	4 (10.0)	2 (5.0)	6 (7.5)	0.675
Glipizide	3 (7.5)	7 (17.5)	10 (12.5)	0.310
HCTZ	12 (30.0)	18 (45.0)	30 (37.5)	0.248
Irbesartan	1 (2.5)	1 (2.5)	2 (2.5)	1.000
Isosorbide-5-mononitrate	1 (2.5)	2 (5.0)	3 (3.8)	1.000
Isosorbide dinitrate	0 (0.0)	2 (5.0)	2 (2.5)	0.494
Manidipine	1 (2.5)	2 (5.0)	3 (3.8)	1.000
Metformin	9 (22.5)	9 (22.5)	18 (22.5)	1.000
Metoprolol	1 (2.5)	0 (0.0)	1 (1.2)	1.000
Nifedipine	3 (7.5)	6 (15.0)	9 (11.2)	0.481
Perindopril	2 (5.0)	1 (2.5)	3 (3.8)	1.000

Table 28 Comparison of the concurrent drugs in the control with the study group *(continued)*

Concurrent drugs*	No. of patients (%)**			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
Prazosin	0 (0.0)	1 (2.5)	1 (1.2)	1.000
Propranolol	0 (0.0)	1 (2.5)	1 (1.2)	1.000
Quinapril	1 (2.5)	0 (0.0)	1 (1.2)	1.000
Ramipril	2 (5.0)	0 (0.0)	2 (2.5)	0.494
Spironolactone	0 (0.0)	2 (5.0)	2 (2.5)	0.494
Terazosin	0 (0.0)	1 (2.5)	1 (1.2)	1.000

* other concurrent drugs include alprazolam (N = 7), amitriptyline (N = 1), betahistine (N = 2), calcium carbonate (N = 9), carbidopa + levodopa (N = 1), cetirizine (N = 1), cinnarizine (N = 1), dimenhydrinate (N = 5), entacapone (N = 1), flunarizine (N = 4), folic acid (N = 3), levodopa + benserazide (N = 1), lorazepam (N = 2), multivitamin (N = 1), omeprazole (N = 9), ranitidine (N = 2), vitamin $B_{1\text{-}6\text{-}12}$ (N = 4), and vitamin B complex (N = 8) (all other drugs in the control group were not significant different from the study group; all $p > 0.05$)

** % in each regimen for the control and the study group columns, or % of all patients in a total column

[a] using Chi-square test to compare the number of patients taking a drug and not taking that drug in the control with the study group

As regards risk factors for CHD, the major risk factors for CHD and patient risk categories are presented in Table 29. The most common major risk factor was age (i.e., male $\geq$ 45 years, or female $\geq$ 55 years or premature menopause without estrogen replacement therapy) which accounted for 93.8% of the patients. The second most common was hypertension, which accounted for 75% of patients. These results are consistent with the previous studies in which age was the most common major risk factor (85% to 90.5%) followed by hypertension (52.4% to 76.3%) **[84-87]**. Sixty-five percent of patients had more than one major risk factors (i.e., 37.5% and 27.5% of patients had two and three major risk factors, respectively). Consequently, most patients (40%) were in moderate risk category (i.e., had more than one major risk factor and 10-year risk equal or less than 20% without experienced CHD) which required lowering of LDL-C levels to less than 130 mg/dL to achieve LDL-C goal

Table 29 Risk factors for coronary heart disease

Data	No. of patients (%)*			*p* value
	Control group (N = 38)	Study group (N = 38)	Total (N = 76)	
Major risk factors				
- Age**	37 (92.5)	38 (95.0)	75 (93.8)	1.000[b]
- Family history***	5 (12.5)	3 (7.5)	8 (10.0)	0.712[b]
- Hypertension	26 (65.0)	34 (85.0)	60 (75.0)	0.071[a]
- Smoking	3 (7.5)	2 (5.0)	5 (6.2)	1.000[b]
- HDL-C < 40 mg/dL	7 (17.5)	11 (27.5)	18 (22.5)	0.422[a]
- HDL-C ≥ 60 mg/dL†	14 (35.0)	9 (22.5)	23 (28.8)	0.323[a]
No. of major risk factor(s)				
- 0 factor	8 (20.0)	4 (10.0)	12 (15.0)	
- 1 factor	9 (22.5)	7 (17.5)	16 (20.0)	0.359[a]
- 2 factors	15 (37.5)	15 (37.5)	30 (37.5)	
- 3 factors	8 (20.0)	14 (35.0)	22 (27.5)	
Risk categories				
- High; CHD or CHD risk equivalents††	11 (27.5)	16 (40.0)	27 (33.8)	0.347[a]
- Moderate; ≥ 2 risk factors	16 (40.0)	16 (40.0)	32 (40.0)	
- Low; 0-1 risk factor	13 (32.5)	8 (20.0)	21 (26.2)	

HDL-C = high-density lipoprotein cholesterol; CHD = coronary heart disease

* % in each regimen for the control and the study group columns, or % of all patients in a total column

** male ≥ 45 years; female ≥ 55 years or premature menopause without estrogen replacement therapy

*** family history of premature CHD (CHD in male first-degree relative < 55 years; CHD in female first-degree relative < 65 years)

† negative risk factor

†† CHD risk equivalents = other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery), diabetes mellitus, and 10-year risk for CHD > 20%

[a] using Chi-square test to compare the number of patients in the control with the study group

[b] using Fisher's exact test to compare the number of patients in the control with the study group

according to NCEP-ATP III guidelines **[4]**. Patients in high (i.e., had CHD or CHD risk equivalents) and low (i.e., had less than two major risk factors) risk categories were accounted for 33.8% and 26.2% of all patients, respectively.

Comparison of patient baseline characteristics of the study with the control group was tested by independent t-test for continuous data and Chi-square (χ^2) test or Fisher's exact test for categorical data. The results showed that there were no significant differences between two groups in terms of: sex, age ranges, weight, height, BMI, BMI ranges, waist circumference, waist circumference ranges, underlying diseases, SBP, DBP, number of patients with metabolic syndrome, number of concurrent drugs, occupation, health insurance rights, smoker, alcoholic drinker, type of major risk factor, number of major risk factors, and risk categories (all $p > 0.05$). However, the mean age of patients in the study groups was significantly higher than that in the control group (62.10 ± 1.57 years, and 57.18 ± 1.48 years, respectively; $p = 0.025$). It is possible that an increasing age might affect patient self-care, compliance, or adverse event rates. However, the number of patients in each age range was not significantly different between two groups ($p = 0.390$).

1.2 Baseline Clinical Laboratory Data

Baseline clinical laboratory data are presented in Table 30 – 31. Independent t-test and Chi-square test were used to determine the difference of baseline laboratory data between the control and study groups. It was found that all data except hsCRP (i.e., FBS, TC, TG, HDL-C, LDL-C, fibrinogen, AST, ALT, CK, and creatinine) were not significantly different between the control and study groups (all $p > 0.05$).

The overall mean baseline FBS was 114.69 ± 44.17 mg/dL (ranging from 66.6 to 324.0 mg/dL). Mean baseline FBS in the control group (117.92 ± 50.62, ranging from 75.0 to 324.0 mg/L) was slightly higher than that in the study group (111.46 ± 36.99 mg/dL, ranging from 66.6 to 221.4 mg/dL), but was not significantly different ($p = 0.517$). These levels are higher than the normal range according to the American Diabetes Association (ADA 2005) which classified these as impaired fasting glucose. These FBS levels are one of the components of metabolic syndrome **[88-89]**.

Mean baseline TC in the control and study groups were 256.20 ± 35.47 mg/dL (ranging from 176 to 331 mg/dL) and 241.52 ± 34.04 mg/dL (ranging from 181 to

Table 30 Baseline clinical laboratory data

Data	Mean ± SD and median* (range)			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
FBS (mg/dL)	117.92 ± 50.62 (75.0, 324.0)	111.46 ± 36.99 (66.6, 221.4)	114.69 ± 44.17 (66.6, 324.0)	0.517
TC (mg/dL)	256.20± 35.47 (176, 331)	241.52 ± 34.04 (181, 320)	248.86 ± 35.32 (176, 331)	0.063
TG (mg/dL)	155.27 ± 79.44 (60, 382)	151.30 ± 74.41 (50, 362)	153.29 ± 76.50 (50, 382)	0.818
HDL-C (mg/dL)	52.73 ± 14.86 (26, 80)	52.60 ± 17.17 (31, 104)	52.66 ± 15.96 (26, 104)	0.972
- Male	47.29 ± 15.70 (26, 80)	44.93 ± 7.60 (31, 57)	46.19 ± 12.44 (26, 80)	0.600
- Female	56.74 ± 13.13 (33, 80)	57.20 ± 19.66 (31, 104)	56.98 ± 16.68 (31, 104)	0.925
LDL-C (mg/dL)	181.73 ± 34.65 (121 – 256)	170.33 ± 28.22 (120 – 252)	176.03 ± 31.92 (120 – 256)	0.111
hsCRP (mg/L)	3.103 ± 2.916 (0.301, 15.564)	4.233 ± 3.123 (0.453, 13.076)	3.668 ± 3.055 (0.301, 15.564)	0.099
Median	*2.013*	*3.107*	*2.586*	*0.030***
Fibrinogen (mg/dL)	415.75 ± 116.51 (200, 900)	460.25 ± 123.76 (190, 740)	438.00 ± 121.50 (190, 900)	0.102
AST (IU/L)	22.87 ± 7.55 (14, 47)	25.28 ± 11.76 (14, 73)	24.08 ± 9.894 (14, 73)	0.281
Median	*20.0*	*20.5*	*20.0*	*0.609*
ALT (IU/L)	25.45 ± 9.82 (14, 53)	28.28 ± 22.09 (7, 108)	26.86 ± 17.044 (7, 108)	0.463
Median	*23.0*	*19.0*	*22.0*	*0.256*

Table 30 Baseline clinical laboratory data *(Continued)*

Data	Mean ± SD or median* (range)			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
CK (IU/L)	141.00 ± 101.60 (43, 484)	103.83 ± 65.87 (26, 351)	122.41 ± 87.10 (26, 484)	0.124
Median	*109.5*	*88.0*	*98.0*	*0.077*
Creatinine (μmol/L)	73.38 ± 18.05 (42, 104)	78.50 ± 23.14 (44, 128)	75.94 ± 20.78 (42, 128)	0.273

SD = standard deviation; FBS = fasting blood sugar; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase

* using mean ± SD for FBS, TC, TG, HDL-C, LDL-C, and fibrinogen because of normal distribution, and using median for hsCRP, AST, ALT, and CK due to non-normal distribution

** having a statistically significant difference at α = 0.05

[a] using independent t-test to compare mean of FBS, TC, TG, HDL-C, LDL-C, and fibrinogen in the control with the study group, and using Mann-Whitney U test to compare median of hsCRP, AST, ALT, and CK in the control with the study group

320 mg/dL), respectively ($p = 0.063$). Similar to the result of baseline serum TC in Phruttisunakon study (256.47 ± 48.54 mg/dL), mean TC of all patients in this study was 248.86 ± 35.32 mg/dL (ranging from 176 to 331 mg/dL) **[85]**. These levels are higher than a desirable level as recommended by NCEP-ATP III (TC should less than 200 mg/dL). Moreover, only 5% of patients had baseline TC in a desirable range (Table 31).

With regard to the baseline TG, there was no statistically significant difference between the control and study groups ($p = 0.818$). Mean baseline TG in the control and study groups were 155.27 ± 79.44 mg/dL (ranging from 60 to 382 mg/dL) and 151.30 ± 74.41 mg/dL (ranging from 50 to 362 mg/dL), respectively. Mean baseline TG of all patients was 153.29 ± 76.50 mg/dL (ranging from 50 to 382 mg/dL), which slightly lower than a previous result reported by Phruttisunakon (163.57 ± 81.18

Table 31 Number of patients who had baseline laboratory data in normal range

Data	No. of patients (%)*			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
TC (mg/dL)				
- < 200 (desirable)	2 (5.0)	2 (5.0)	4 (5.0)	1.000
- ≥ 200	38 (95.0)	38 (95.0)	76 (95.0)	
TG (mg/dL)				
- < 150 (normal)	26 (65.0)	22 (55.0)	48 (60.0)	0.494
- ≥ 150	14 (35.0)	18 (45.0)	32 (40.0)	
HDL-C (mg/dL)				
- < 40 (low)	11 (27.5)	12 (30.0)	23 (28.8)	1.000
- ≥ 60 (high)	14 (35.0)	9 (22.5)	23 (28.8)	0.323
LDL-C (mg/dL)				
- < 100 (optimal)	0 (0.0)	0 (0.0)	0 (0.0)	
- 100-129 (above optimal)	2 (5.0)	2 (5.0)	4 (5.0)	0.438
- 130-159 (borderline high)	8 (20.0)	12 (30.0)	20 (25.0)	
- 160-189 (high)	17 (42.5)	19 (47.5)	36 (45.0)	
- ≥ 190 (very high)	13 (32.5)	7 (17.5)	20 (25.0)	
hsCRP (mg/L)				
- ≤ 5 (normal)	32 (80.0)	26 (65.0)	58 (72.5)	0.211
- > 5	8 (20.0)	14 (35.0)	22 (27.5)	
Fibrinogen (mg/dL)				
- < 200	0 (0.0)	2 (5.0)	2 (2.5)	0.260
- 200 – 400 (normal)	15 (37.5)	11 (27.5)	26 (32.5)	
- > 400	25 (62.5)	27 (67.5)	52 (65.0)	

TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein

* % in each regimen for the control and the study group columns, or % of all patients in a total column

** having a statistically significant difference at $\alpha = 0.05$

[a] using Chi-square test to compare the number of patients in the control with the study group

mg/dL) **[85]**. The percentage of patients who had baseline TG higher than the normal range (i.e., more than 150 mg/dL) were 35% and 45% in the control and study groups, respectively ($p = 0.209$). Overall, forty percent of patients had baseline TG above the normal range, as shown in Table 31.

For baseline HDL-C, the overall mean was 52.66 ± 15.96 mg/dL (ranging from 26 to 104 mg/dL). This level is slightly lower than that reported in the Phruttisunakon study (57.25 ± 14.26 mg/dL) **[85]**. Mean HDL-C in the control group was 52.73 ± 14.86 mg/dL (ranging from 26 to 80 mg/dL), which was similar to 52.60 ± 17.17 mg/dL (ranging from 31 to 104 mg/dL) in the study group ($p = 0.972$). Since male generally has lower level than female, serum HDL-C was categorized by sex. Mean HDL-C of male patients was 47.29 ± 15.70 mg/dL (ranging from 26 to 80 mg/dL) and 44.93 ± 7.60 mg/dL (ranging from 31 to 57 mg/dL) in the control and study groups, respectively. There was no statistically significant difference of mean HDL-C between two groups ($p = 0.600$). Similarly, there was also no significant difference in mean HDL-C of female patients between the control (mean was 56.74 ± 13.13 mg/dL; ranging from 33 to 80 mg/dL) and study groups (mean was 57.20 ± 19.66 mg/dL; ranging from 31 to 104 mg/dL) ($p = 0.925$). For all patients, mean baseline HDL-C of male and female patients were 46.19 ± 12.44 mg/dL (ranging from 26 to 80 mg/dL) and 56.98 ± 16.68 mg/dL (ranging from 31 to 104 mg/dL), respectively. Of 80 patients, 28.8% had low serum HDL-C less than 40 mg/dL. High serum HDL-C also accounted for 28.8% of the patients (Table 31).

Regarding the baseline LDL-C, the overall mean LDL-C was 176.03 ± 31.92 mg/dL (ranging from 120 to 256 mg/dL) which was categorized as high level. This finding is in a similar fashion to the result reported by Phruttisunakon in that mean LDL-C of hypercholesterolemic patients at Phramongkutklao hospital was 174.80 ± 44.15 mg/dL **[85]**. There was no a significant difference of mean LDL-C between the control and study groups (181.23 ± 34.65 mg/dL, ranging from 121 to 256 mg/dL, and 170.33 ± 28.22 mg/dL, ranging from 120 to 252 mg/dL, respectively; $p = 0.111$). As shown in Table 31, none of the patients had baseline LDL-C in the optimal range because only patients who had high LDL-C level and required statins therapy were recruited in this study.

For baseline hsCRP, the distribution which determined by Kolmogorov-Smirnov test of hsCRP was not normal. Therefore, median was used to represent the central tendency instead of mean. The median hsCRP of the study group (3.170 mg/L, ranging from 0.453 to 13.076 mg/L) was significantly higher than that in the control group (2.013 mg/L, ranging from 0.301 to 15.564 mg/L) ($p = 0.030$). It may be because patients in the study group were older than the control group. HsCRP levels tend to be higher in elderly patients. Most patients (72.5%) had serum hsCRP in the normal range (Table 31). In addition, the number of patients who had hsCRP in normal range or above normal was not significantly different between the control and study groups ($p = 0.211$).

Regarding the baseline fibrinogen, the overall mean fibrinogen was 438.00 ± 121.50 mg/dL (ranging from 190 to 900 mg/dL). No significant difference in mean baseline fibrinogen was observed between two groups ($p = 0.102$). Mean fibrinogen in the control and study groups were 415.75 ± 116.51 mg/dL (ranging from 200 to 900 mg/dL) and 460.25 ± 123.76 mg/dL (ranging from 190 to 740 mg/dL), respectively. These levels were higher than normal range (200 to 400 mg/dL). Moreover, most patients (65%) had fibrinogen level more than 400 mg/dL (Table 5), which was associated with an increase risk for CHD. The number of patients in each fibrinogen category was not significantly different between the control and study groups ($p = 0.260$).

For baseline laboratory data of safety profile, median AST, ALT, and CK were reported because the data were not normal distribution. The overall median of AST, ALT, and CK were 20.0, 22.0, and 98.0 IU/L, respectively. Median AST of patients in the control group (20.0 IU/L) was not significantly different ($p = 0.609$) when compared with the study group (20.5 IU/L). Median ALT of patients in the control group was higher than in the study group (23.0 vs 19.0 IU/L, respectively), but was not statistically significant ($p = 0.256$). Also, there was no a statistically significant difference of median CK in the control and study groups ($p = 0.077$). Median CK in the control and study groups were 109.5 and 88.0 IU/L, respectively. The overall mean creatinine was 75.94 ± 20.78 IU/L (ranging from 42 to 128 IU/L). Mean creatinine in the study group (78.50 ± 23.14 IU/L, ranging from 44 to 128 IU/L)

was slightly higher than in the control group (73.38 ± 18.05 IU/L, ranging from 42 to 104 IU/L), but was not significantly different ($p = 0.273$).

2. Efficacy Evaluation

Of 40 patients in the control and study groups, two patients (5%) in each group withdrew from the study. Intention to treat analysis was performed to determine the efficacy of all patients (40 patients per each group). The missing data were replaced by series mean of each group. As shown in Table 32, the demographic data of patients (i.e., weight, BMI, waist circumference, SBP, DBP, and FBS) at the study initiation (week 0) was not significantly different from that at the study completion (week 8) in both patient groups (both $p > 0.05$).

2.1 Efficacy on Serum Lipids, hsCRP, and Fibrinogen Changing from Baseline

Table 33 presents the efficacy of rosuvastatin 10 mg once daily and every other day on serum lipids, hsCRP, and fibrinogen alteration. Paired t-test was used to compare mean of TC, TG, HDL-C, LDL-C, and fibrinogen at baseline (week 0) with at the end of study (week 8). Because hsCRP distribution which determined by Kolmogorov-Smirnov test was not normal. Therefore, median hsCRP was used instead of mean. Wilcoxon signed-rank test was performed to compare median hsCRP at baseline and at the end of study. In addition, independent t-test was used to compare mean of serum TC, TG, HDL-C, LDL-C, and fibrinogen at week 8 between the control and study groups. For hsCRP, baseline hsCRP in the control group was significantly different from the study group ($p = 0.030$) (Table 30). Therefore, two-way ANOVA with repeated measures on one factor was performed to adjust this difference.

In the control group, mean TC was significantly decreased from 256.20 ± 35.47 mg/dL (baseline) to 161.52 ± 42.34 mg/dL (at the end of study) ($p < 0.001$). Serum TG was also significantly decreased from 155.27 ± 79.44 mg/dL (baseline) to 116.66 ± 53.09 mg/dL (at the end of study) ($p < 0.001$). Moreover, there was a significant decrease in serum LDL-C from 181.73 ± 34.65 mg/dL (baseline) to 94.10 ± 40.16 mg/dL (at the end of study) ($p < 0.001$). In addition, median hsCRP was significantly reduced from 2.013 mg/L (baseline) to 1.802 mg/L (at the end of study)

Table 32 Comparison of the demographic data between week 0 and 8 within patient groups and between two patient groups at week 8

Data	Control group (N = 40)*			Study group (N = 40)*			p value†† (between groups)
	Mean ± SD (range)		p value† (before-after)	Mean ± SD (range)		p value† (before-after)	
	week 0	week 8		week 0	week 8		
Weight (kg)	66.14 ± 9.59 (50, 90)	65.35 ± 8.47 (49, 88)	0.258	66.60 ± 14.14 (40, 96)	66.17 ± 13.44 (41, 95)	0.517	0.747
BMI (kg/m^2)	25.53 ± 3.39 (20.7, 33.0)	25.40 ± 3.25 (20.7, 33.2)	0.426	25.85 ± 4.02 (18.5, 34.6)	25.81 ± 3.94 (18.9, 35.4)	0.802	0.615
Waist circumference (inches)	33.68 ± 3.24 (27.0, 40.0)	33.67 ± 3.06 (27.0, 40.0)	0.945	34.14 ± 5.08 (24.0, 45.5)	34.04 ± 4.96 (24.0, 45.4)	0.423	0.686
SBP (mgHg)	137.90 ± 21.28 (98, 210)	133.18 ± 15.60 (100, 180)	0.592	144.07 ± 27.08 (81, 220)	135.21 ± 18.32 (85, 191)	0.053	0.596
DBP (mgHg)	84.83 ± 19.07 (52, 160)	79.46 ± 9.60 (55, 99)	0.105	83.88 ± 11.15 (56, 110)	77.91 ± 11.15 (54, 102)	0.070	0.507
FBS (mg/dL)	117.92 ± 50.62 (75.0, 324.0)	117.07 ± 42.42 (79.2, 298.8)	0.891	111.46 ± 36.99 (66.6, 221.4)	107.53 ± 37.96 (72.0, 306.0)	0.400	0.292

SD = standard deviation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBS = fasting blood sugar

* intention to treat analysis was used in data at week 8 and missing data were replaced by series mean

† using paired t-test to compare mean at the study initiation (week 0) with at the end of study (week 8) of each group

†† using independent t-test to compare mean of the control group with the study group at week 8

Table 33 Comparison of clinical laboratory data between week 0 and 8 within patient groups and between two patient groups at week 8

Data	Control group (N = 40)[#]			Study group (N = 40)[#]			p value[b] (between groups)
	Mean ± SD or Median* (range)		p value[a] (before-after)	Mean ± SD or Median* (range)		p value[a] (before-after)	
	week 0	week 8		week 0	week 8		
TC (mg/dL)	256.20 ± 35.47 (176, 331)	161.52 ± 42.34 (103, 329)	< 0.001**	241.52 ± 34.04 (181, 320)	174.22 ± 27.85 (127, 243)	< 0.001**	0.117
TG (mg/dL)	155.27 ± 79.44 (60, 382)	116.66 ± 53.09 (41, 289)	< 0.001**	151.30 ± 74.41 (50, 362)	131.56 ± 63.08 (42, 315)	0.026**	0.247
HDL-C (mg/dL)	52.73 ± 14.86 (26, 80)	56.05 ± 14.52 (25, 100)	0.038**	52.60 ± 17.17 (31, 104)	55.13 ± 15.22 (34, 89)	0.114	0.782
LDL-C (mg/dL)	181.73 ± 34.65 (121, 256)	94.10 ± 40.16 (51, 241)	< 0.001**	170.33 ± 28.22 (120, 252)	105.07 ± 26.30 (49, 173)	< 0.001**	0.153
hsCRP (mg/L)	3.103 ± 2.916 (0.301, 15.564)	1.842 ± 1.264 (0.222, 4.845)	0.003**	4.233 ± 3.123 (0.453, 13.076)	2.699 ± 1.989 (0.584, 10.913)	< 0.001**	0.024**
Median	*2.013*	*1.802*	*< 0.001***	*3.170*	*2.331*	*< 0.001***	*0.025***
Fibrinogen (mg/dL)	415.75 ± 116.51 (200 – 900)	413.37 ± 89.83 (220, 660)	0.867	460.25 ± 123.76 (190, 740)	458.18 ± 165.81 (150, 1080)	0.908	0.137

SD = standard deviation; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein

[#] intention to treat analysis was used in data at week 8 and missing data were replaced by series mean

* using mean ± SD for TC, TG, HDL-C, LDL-C, and fibrinogen because of normal distribution, and using median for hsCRP due to non-normal distribution

** has a significant difference at $\alpha = 0.05$

[a] using paired t-test to compare mean of TC, TG, HDL-C, LDL-C, and fibrinogen at baseline (week 0) with at the end of study (week 8), and using Wilcoxon signed ranks test to compare median of hsCRP at baseline with at the end of study

[b] using independent t-test to compare mean of TC, TG, HDL-C, LDL-C, and fibrinogen at week 8 of the patients in the control group with the study group, and using Mann-Whitney U test to compare median of hsCRP at week 8 of patients in the control group with the study group

($p < 0.001$). The patients in this control group had a significant increase in serum HDL-C from 52.73 ± 14.86 mg/dL (baseline) to 56.05 ± 14.52 mg/dL (at the end of study) ($p = 0.038$). However, there was no significant difference in serum fibrinogen between baseline and that at the end of study (415.75 ± 116.51 mg/dL vs 413.37 ± 89.93 mg/dL; $p = 0.867$).

For the study group, serum TC was significantly reduced from 241.52 ± 34.04 mg/dL (baseline) to 174.22 ± 27.85 mg/dL (at the end of study) ($p < 0.001$). Also, mean TG at the end of study was significantly decreased from baseline (from 151.30 ± 74.11 mg/dL to 131.56 ± 63.08 mg/dL; $p = 0.041$). In addition, there was a significant decrease in serum LDL-C from 170.33 ± 28.22 mg/dL (baseline) to 105.07 ± 26.30 mg/dL (at the end of study) ($p < 0.001$). Moreover, median hsCRP was also significantly decreased from 3.170 mg/L (baseline) to 2.331 mg/L (at the end of study) ($p < 0.001$). However, there was no significant difference in serum HDL-C between baseline and at the end of study (52.60 ± 17.17 mg/dL vs 55.13 ± 15.22 mg/dL; $p = 0.114$). Also, mean fibrinogen at baseline (460.25 ± 123.76 mg/dL) was not significantly different from the level at the end of study (458.18 ± 165.81 mg/dL) ($p = 0.908$).

As shown in Table 33, serum TC, TG, HDL-C, LDL-C, and fibrinogen at the end of study were not significantly different between the control and study groups (all $p > 0.05$). This finding indicates that patients receiving rosuvastatin 10 mg once daily and every other day for 8 weeks provided similar levels of serum TC, TG, HDL-C, LDL-C, and fibrinogen. For hsCRP, the result from two-way ANOVA with repeated measures on one factor is shown in Figure 4 and Table 34. The Group x Time interaction was not significant, $F_{1,78} = 0.29$, $p = 0.592$. This finding indicates that the relationship between time and hsCRP levels was not different for each group. The main effect of group was significant difference, $F_{1,78} = 4.225$, $p = 0.043$. This means that there was a significant difference of hsCRP levels between the control and study groups during the 8-week period. This finding is consistent with the results using Mann-Whitney U test in that hsCRP levels at the end of study was significantly higher than that in the study group ($p = 0.025$) (Table 33). This analysis also revealed a significant effect for time, $F_{1,78} = 30.54$, $p < 0.001$. This finding indicates that baseline hsCRP in each group was significantly different from that at the end of study

(i.e., serum hsCRP at baseline was significantly higher than that at the end of study). This is congruent with the results determined by using Wilcoxon signed-rank test in that the median hsCRP of the patients in both control and study groups were significantly reduced from baseline ($p < 0.001$ in both groups) (Table 33).

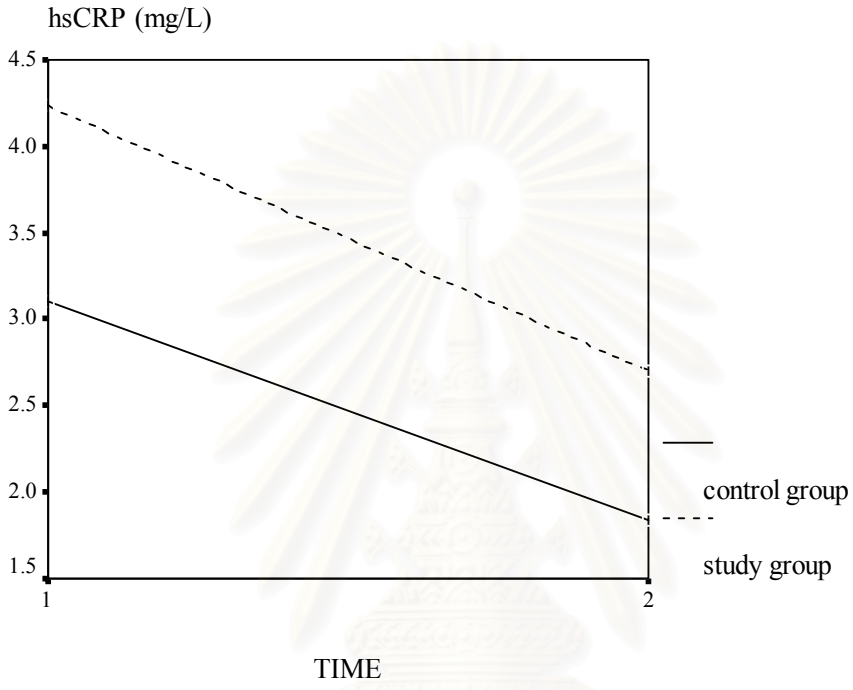


Figure 4 Comparison of hsCRP levels between the control and study groups

Table 34 ANOVA summary table for the change in serum hsCRP following rosuvastatin 10 mg once daily and every other day for 8 weeks

Dependent variable: hsCRP

Source	Sum of squares	df	Mean squares	F-ratio	*p* value
Between subjects					
Group	39.48	1	39.48	4.225	0.043*
Residual between	728.91	78	9.34		
Within subjects					
Time	78.14	1	78.14	30.54	0.000*
Group x Time interaction	0.74	1	0.74	0.29	0.592
Residual within	199.58	78	2.559		

* having a significant difference at $\alpha = 0.05$

The percentage of change in serum lipids, hsCRP, and fibrinogen is shown in Table 35 and Figure 5. The mean percentage of reduction in serum TC was 36.76% and 28.08% in the control and study groups, respectively. The percentage of reduction in serum TC of the patients in the control group is similar to the pervious studies. Those studies reported that rosuvastatin 10 mg once daily could reduce serum TC between 30% and 38% **[22,58-59,61-65]**. The percentage of reduction in serum TC of the patients in the study group is lower than that reported in the patients receiving rosuvastatin 10 mg once daily. But it is similar to the percentage of TC reduction of patients receiving rosuvastatin 5 mg once daily (28% to 34%), which is an equivalent dose of rosuvastatin 10 mg every other day **[58-59,61-65]**. The percentage of change in TC in the study group were significantly lower than that in the control group ($p = 0.002$). This may be due to lower rosuvastatin concentration. This finding indicates that rosuvastatin 10 mg every other day seemed to be less effective in lowering TC levels than 10 mg once daily regimen.

The patients in the control group had significantly greater percentage of reduction in serum TG than that in the study group (20.95% and 8.59% in the control and the study group, respectively; $p = 0.018$). The percentage of reduction in serum TG in the control group is similar to the previous studies in that rosuvastatin 10 mg once daily reduced TG between 10% and 22% **[22,58-59,61-65,90]**. The patients in the study group had lower percentage of reduction in serum TG than that reported in the previous studies (i.e., 10% to 20% for rosuvastatin 10 mg and 12% to 35% for rosuvastatin 5 mg) **[22,58-59,61-65,90]**. This may be because some patients had more carbohydrate diet intake during the study period.

Mean percentage of elevation in serum HDL-C of the patients in the control and study groups were 8.60% and 5.79%, respectively. This finding is consistent with those previous studies in that patients taking rosuvastatin 10 mg and 5 mg once daily had a 3% to 14% and 2% to 13% HDL-C elevation, respectively **[22,58-59,61-65,90]**. The percentage of HDL-C elevation of the patients in the control group was not significantly different from that in the study group ($p = 0.501$). This finding indicates that rosuvastatin 10 mg once daily and every other day had a comparable effect on HDL-C.

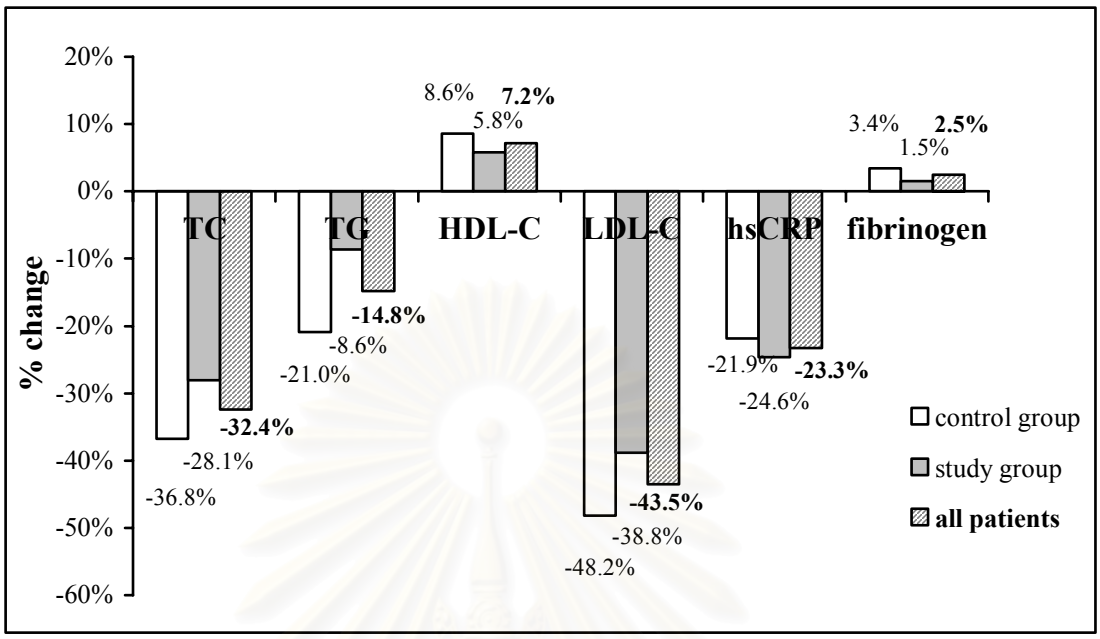
Table 35 Mean percentage of change in serum lipids, hsCRP, and fibrinogen from baseline

Data	Mean % change ± SD* (range)			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
TC change (%)	-36.76 ± 13.49 (-59.29, 5.26)	-28.08 ± 10.65 (-46.79, 4.29)	-32.42 ± 12.85 (-59.29, 21.55)	0.002*
TG change (%)	-20.95 ± 18.03 (-58.16, 25.00)	-8.59 ± 26.80 (-68.51, 60.53)	-14.77 ± 23.53 (-68.51, 60.53)	0.018*
HDL-C change (%)	8.60 ± 18.42 (-33.87, 54.55)	5.79 ± 18.73 (-16.00, 83.72)	7.19 ± 18.51 (-33.87, 83.72)	0.501
LDL-C change (%)	-48.22 ± 19.06 (-73.11, 10.88)	-38.83 ± 12.42 (-61.76, -0.59)	-43.53 ± 16.67 (-73.11, 10.88)	0.011*
hsCRP change (%)	-25.87 ± 44.03 (-90.15, 157.72)	-25.99 ± 39.70 (-74.78, 148.10)	-25.93 ± 41.66 (-90.15, 157.72)	0.990
Fibrinogen change (%)	3.41 ± 28.06 (-38.89, 125.00)	1.50 ± 26.18 (-31.43, 84.85)	2.46 ± 26.98 (-38.89, 125.00)	0.754

SD = standard deviation; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein

* intention to treat analysis was used in data at week 8 and missing data were replaced by series mean

[a] using independent t-test to compare mean % change of patients in the control with the study group



TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein

* intention to treat analysis was used by replacing missing data with series mean

Figure 5 The mean percentage of change in serum TC, TG, HDL-C, LDL-C, hsCRP, and fibrinogen of the patients in the control group (N = 40), the study group (N = 40), and all patients (N = 80)*

The percentage of LDL-C reduction in the control group (48.22%) was significantly higher than that in the study group (38.83%) ($p = 0.011$). It might be that the rosuvastatin concentrations of patients receiving 10 mg every other day regimen was not effective enough to lower LDL-C similar to 10 mg once daily regimen. The percentage of LDL-C reduction of the patients in the control group is similar to the previous studies that reported 43% to 53% of LDL-C reduction in patients receiving rosuvastatin 10 mg **[22,58-59,61-65,90]**. On the other hand, the percentage of LDL-C reduction of the patients in the study group is lower than those previously reported in the rosuvastatin 10 mg (43% to 53%), but is similar to rosuvastatin 5 mg (39% to 47%) **[22, 58-59,61-65,90]**. This may be because rosuvastatin 10 mg every other day is an equivalent dose of rosuvastatin 5 mg once daily.

The patients in the control and study groups had a decrease in serum hsCRP by 25.87% and 25.99%, respectively. This was not significantly different ($p = 0.754$).

The result supports the finding of an earlier study by Jialal, *et al* which demonstrated that every other day dosing of statins probably would not compromise their effect on hsCRP **[34,40]**. The effect of rosuvastatin on percentage of hsCRP reduction has never been addressed yet. However, the percentage of hsCRP reduction in this study is similar to other statins (i.e., pravastatin, cerivastatin, lovastatin, simvastatin, and atorvastatin) that can reduce hsCRP between 13.1% and 47.0% **[33,39-44,73,91]**.

For fibrinogen, the percentage of change in serum fibrinogen in the control group (3.41%) was not significantly different from that in the study group (1.50%) ($p = 0.754$). There have been no previous studies that determine the effect of rosuvastatin on serum fibrinogen. However, this finding is consistent with the effect of simvastatin and fluvastatin on fibrinogen levels (i.e., both simvastatin and fluvastatin did not have an effect on fibrinogen) **[47,49-51,53,82]**. On the other hand, this finding is inconsistent with the findings in those pravastatin, atorvastatin, and lovastatin affected the serum fibrinogen (i.e., serum fibrinogen was decreased by pravastatin and increased by atorvastatin and lovastatin) **[46,49,51-53]**.

These findings indicate that both rosuvastatin 10 mg once daily and every other day significantly reduced serum TC, TG, LDL-C, and hsCRP from baseline. For HDL-C, rosuvastatin 10 mg every other day could not produce a significant increase in serum HDL-C from baseline, whereas, rosuvastatin 10 mg once daily could. In addition, both rosuvastatin 10 mg once daily and every other day could not produce a significant decrease in serum fibrinogen. This study also shows that serum TC, TG, HDL-C, LDL-C, and fibrinogen of patients receiving rosuvastatin 10 mg once daily for 8 weeks were not significantly different from those of patients receiving rosuvastatin 10 mg every other day. In contrast, there was a significant difference of serum hsCRP between once daily and every other day dosing after the patients had taken rosuvastatin for 8 weeks. Moreover, this study reveals that the percentage of change in serum TC, TG, and LDL-C of patients receiving rosuvastatin 10 mg once daily was significantly higher than that of patients receiving rosuvastatin 10 mg every other day. But, no statistically significant difference of the percentage of change in serum HDL-C, hsCRP, and fibrinogen was observed between patients receiving rosuvastatin 10 mg once daily and every other day.

2.2 The Percentage of Patients who Achieved LDL-C Goals According to NCEP-ATP III Guidelines

The percentage of patients who achieved their LDL-C goals according to NCEP-ATP III guidelines are presented in Table 36 and Figure 6. Overall, 77.5% of all patients in this study achieved their LDL-C goals. The percentage of patients who reached LDL-C goals in the control and study groups were 85% and 70%, respectively, which was not significantly different between groups ($p = 0.180$). This finding is consistent with the previous study in that 76% to 86% and 67% to 88% of patients receiving rosuvastatin 10 mg and 5 mg once daily achieved their LDL-C goals, respectively **[22,52,61-62,65]**. In addition, these percentages are higher than those found in other statins, which only half of patients (38% to 64%) could achieve their LDL-C goals **[5,8,19,65]**. This finding also supports the previous study in that rosuvastatin 10 mg once daily reduced LDL-C sufficiently to allow most patients to achieve NCEP-ATP III goals **[65]**. Among the patients in control group, LDL-C goals were achieved by 76.9%, 93.8%, and 81.8% of patients who were in low, moderate, and high risk category, respectively. Likewise, 100.0%, 75.0%, and 50.0% of patients in the study group who were in low, moderate, and high risk category, reached their LDL-C goals. These findings are also consistent with the previous studies in which 97%, 89%, and 61% of patients who achieved their LDL-C goals after receiving rosuvastatin 10 mg once daily were in low, moderate, and high risk category, respectively, **[65]**.

The percentage of patients who received rosuvastatin 10 mg once daily and achieved LDL-C goal in the low risk category (76.9%) was lower than that in the other risk groups, despite the highest LDL-C goal in low risk category. This may be because two patients who dropped out from the control group were in the low risk category. Therefore, the result may be underestimated by using intention to treat analysis [i.e., the percentage of patients who achieved LDL-C goal in each group were calculated from the number of patients who achieved goal in each group divided by the number of all patients (including dropped out patients) in that group]. Also, two patients who dropped out from the study group were in the high risk category, therefore, the percentage of patients who achieved goal in high risk category seemed to be lower than that in the other risk groups. However, LDL-C goal in the high risk

group is lower than that in the other risk groups and more patients in the high risk category were in the study group. Therefore, it may be more difficult to help the patients to reach their LDL-C goal. Despite these results, no significant difference in the number of patients who achieved LDL-C goal between the control and study groups was found in each risk category (all $p > 0.05$). These findings indicate that rosuvastatin 10 mg once daily and every other day had a comparable LDL-C lowering effect in reaching LDL-C goal, regardless of risk category. Therefore, every other day dosing of rosuvastatin 10 mg may be an alternative therapy that allows the patients to achieve their LDL-C goals, especially in the low risk category.

Table 36 The number of patients achieving and not achieving their LDL-C goals according to NCEP-ATP III

Risk category	No. of patients achieved LDL-C goal (%)* *No. of patients not achieved LDL-C goal (%)**			*p* value[a]
	Control group† (N = 40)	Study group† (N = 40)	Total† (N = 80)	
High; CHD or CHD risk equivalents††	9 (81.8) *2 (18.2)*	8 (50.0) *8 (50.0)*	17 (63.0) *10 (37.0)*	0.124
Moderate; ≥ 2 risk factors	15 (93.8) *1 (6.2)*	12 (75.0) *4 (25.0)*	27 (84.4) *5 (15.6)*	0.333
Low; 0-1 risk factor	10 (76.9) *3 (23.1)*	8 (100.0) *0 (0.0)*	18 (85.7) *3 (14.3)*	0.257
Total	**34 (85.0)** ***6 (15.0)***	**28 (70.0)** ***12 (30.0)***	**62 (77.5)** ***18 (22.5)***	**0.180**

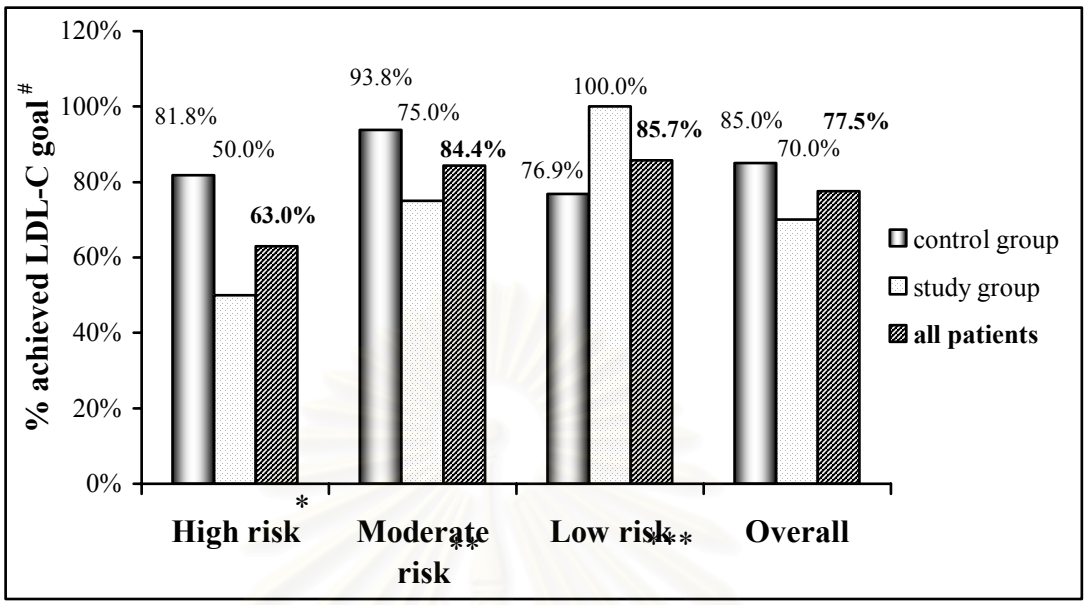
LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease

* % of patients in each group and each risk category

† intention to treat analysis was used for two dropped out patients in low risk group of the control group and for two dropped out patients in high risk group of the study group

†† CHD risk equivalents = other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery), diabetes mellitus, and 10-year risk for CHD > 20%

[a] using Fisher's exact test to compare the number of patients who achieved and not achieved LDL-C goal in the control with the study group



intention to treat analysis was used for two dropped out patients in low risk group of the control group and for two dropped out patients in high risk group of the study group

* patients who had CHD or CHD risk equivalents (other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery), diabetes mellitus, and 10-year risk for CHD > 20%)

** patients who had more than one major risk factor and 10-year risk equal or fewer than 20% without experienced CHD

*** patients who had fewer than two major risk factor

Figure 6 The percentage of patients who achieved LDL-C goals according to NCEP-ATP III guidelines were categorized by risk categories (N = 80 in all patients, N = 40 in the control and the study group)

2.3 Monthly Cost per %LDL-C Reduction

Since most patients require a life-long therapy with statins and these drugs (including rosuvastatin) are expensive, this can affect the patient affordability which can reduce compliance or fail to lower LDL-C adequately. Therefore, monthly cost per %LDL-C reduction is one of the strategies to evaluate the cost effectiveness of statins therapy. This can help providers select the appropriate regimen for each patient.

The cost of rosuvastatin 10 mg at Phramongkutklao hospital (2004) is 46 baht per tablet. Patients receiving rosuvastatin 10 mg once daily and every other day could

reduce their LDL-C by 48.22% and 38.83%, respectively. The monthly cost per %LDL-C reduction was calculated by:

The monthly cost per % LDL-C reduction of rosuvastatin 10 mg once daily

$$= \frac{\text{cost of 30 tablets of rosuvastatin 10 mg}}{\text{\%LDL-C reduction of patients receiving rosuvastatin 10 mg once daily}}$$

$$= \frac{46 \times 30}{48.22}$$

$$= 28.62 \text{ baht}$$

The monthly cost per % LDL-C reduction of rosuvastatin 10 mg every other day

$$= \frac{\text{cost of 15 tablets of rosuvastatin 10 mg}}{\text{\%LDL-C reduction of patients receiving rosuvastatin 10 mg once daily}}$$

$$= \frac{46 \times 15}{38.83}$$

$$= 17.77 \text{ baht}$$

The monthly cost per %LDL-C reduction of patients receiving rosuvastatin 10 mg every other day was 17.77 baht, which accounted for 37.9% lower cost than the patients receiving rosuvastatin 10 mg once daily (28.62 baht). Therefore, patients who need a 30% to 40% reduction in serum LDL-C, have to pay about 858.56 to 1144.75 baht per month for once daily regimen and 533.09 to 710.79 baht per month for every other day regimen. This finding is consistent with a previous study that reported 34% lower of annual drug cost saving in every other day regimen of atorvastatin therapy compared with once daily regimen **[26]**.

This study shows that the every other day regimen seems to help the patients save their healthcare costs when compared with the once daily regimen. However, several factors (e.g., high baseline serum lipids, low LDL-C goal, and poor compliance) should be also considered when managing individual patient with hypercholesterolemia.

3. Safety Evaluation

During 8-week study period, three patients withdrew from the study due to adverse events. Two patients in the control group experienced malaise and muscle pain without CK elevation (myalgia). One patient in the study group experienced headache.

The patient who experienced mild malaise had an event when she had taken the study drug for three days and did not wish to participate in the study. The patient refused to go to the hospital for further evaluation. Two days after drug discontinuation, the symptom disappeared. The causality assessment by using Naranjo's algorithm showed this was a possible adverse event due to the study drug.

The patient who experienced myalgia had an event at week 6 of the study. All laboratory data were in normal range including CK. The physician diagnosed myofasciitis for this patient. However, the study drug was discontinued and restarted with atorvastatin one month later. The causality assessment by using Naranjo's algorithm showed this was a possible adverse event due to the study drug.

Finally, the patient who experienced headache had an event after he had taken the study drug for two days. The patient discontinued the study drug for five days and then restarted again. After the study drug had been restarted for one day, the patient experienced headache again. Therefore, the patient discontinued the study drug and asked for a withdrawal from the study. The causality assessment by using Naranjo's algorithm showed this was a probable adverse event due to the study drug.

Table 37 presents the number of patients experienced adverse events. All adverse events were reported about 25% of patients. The adverse event rates in the study group was higher than the control group, but were not significantly different ($p = 0.439$). This may be because of more advanced age, more female sex, more concurrent drugs, and higher baseline serum creatinine in the study group. These factors might increase risk of the adverse events. In addition, the number of each adverse event in the control group was not significantly different from that in the study group (all $p > 0.05$). Renal-related adverse events accounted for 15% of all patients. Patient complaints (i.e., headache, muscle pain, muscle weakness, dry mouth, foot edema, and mild malaise) and musculoskeletal-related adverse events (i.e., CK > 3 times the ULN, muscle pain, and muscle weakness) were found about

8.75% and 3.75%, respectively. However, liver-related adverse events (i.e., AST and ALT increase more than 3 times the ULN) were not found in this study. Table 38 – 39 present mean ± SD and median of the safety data. Because AST, ALT, and CK were not normal distribution from Kolmogorov-Smirnov test, median was reported to represent the central tendency of these data

.

Table 37 The numbers of patients who experienced adverse events*

Adverse events	No. of patients (%)**			*p* value[a]
	Control group (N = 40)	Study group (N = 40)	Total (N = 80)	
AST > 3 times the ULN	0 (0.0)	0 (0.0)	0 (0.00)	1.000
ALT > 3 times the ULN	0 (0.0)	0 (0.0)	0 (0.00)	1.000
CK > 3 times the ULN[b]	1 (2.5)	0 (0.0)	1 (1.25)	1.000
Creatinine elevation > the ULN[b]	0 (0.0)	2 (5.0)	2 (2.50)	0.494
Proteinuria increase 1 level[# c]	0 (0.0)	1 (2.5)	1 (1.25)	1.000
Hematuria increase 1 level[# c]	2 (5.0)	3 (7.5)	5 (6.25)	1.000
Hematuria increase 2 levels[# c]	2 (5.0)	2 (5.0)	4 (5.00)	1.000
Headache[b]	0 (0.0)	2 (5.0)	2 (2.50)	0.494
Muscle pain[c]	1 (2.5)	0 (0.0)	1 (1.25)	1.000
Muscle weakness[c]	1 (2.5)	0 (0.0)	1 (1.25)	1.000
Dry mouth[c]	0 (0.0)	1 (2.5)	1 (1.25)	1.000
Foot edema[c]	0 (0.0)	1 (2.5)	1 (1.25)	1.000
Mild malaise[c]	1 (2.5)	0 (0.0)	1 (1.25)	1.000
Total	**8 (20.0)**	**12 (30.0)**	**20 (25.0)**	**0.439**

AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase; ULN = upper limit of normal

* one patient could have more than 1 events

** % in each regimen for the control and the study group columns, or % of all patients in total column

[#] increase from baseline in normal range

[a] using Fisher's exact test to compare the number of patients in the control with the study group for each event, and using Chi-square test to compare total events of each patient group

[b] probable adverse event assessed by using Naranjo's algorithm

[c] possible adverse event assessed by using Naranjo's algorithm

Table 38 Laboratory data for safety profile of all patients (N = 80)

Data [normal range]††	Mean ± SD and median* (range)		*p* value†
	week 0	week 8	
AST (IU/L) [0 – 37]	24.08 ± 9.89 (14, 73)	25.63 ± 8.54 (15, 51)	0.108
Median	*20.0*	*24.0*	*0.024***
ALT (IU/L) [0 – 41]	26.86 ± 17.04 (7, 108)	27.21 ± 15.49 (7, 85)	0.815
Median	*22.0*	*24.0*	*0.423*
CK (IU/L) [25 – 200]	122.41 ± 87.10 (26, 484)	137.47 ± 105.06 (42, 714)	0.109
Median	*98.0*	*110.5*	*0.080*
Creatinine (μmol/L) [62 – 106 (male), 44 – 80 (female)]	75.94 ± 20.78 (42, 128)	73.28 ± 21.51 (41, 169)	0.051

SD = standard deviation; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase

* using median for AST, ALT, and CK due to non-normal distribution, and using mean ± SD for creatinine because of normal distribution

** having a significant difference at $\alpha = 0.05$

† compare week 0 with week 8 by using Wilcoxon signed-rank test for AST, ALT, and CK, and using paired t-test for creatinine

†† normal range of Phramongkutklao hospital

Table 39 Comparisons of laboratory data for safety profile between week 0 and week 8 in each patient group and between the control and the study groups at week 8

Data	Control group (N = 40)			Study group (N = 40)			*p* value†† (between group)
	Mean ± SD and Median* (range)		*p* value† (before-after)	Mean ± SD and Median* (range)		*p* value† (before-after)	
	week 0	week 8		week 0	week 8		
AST (IU/L)	22.88 ± 7.55 (14, 47)	26.73 ± 9.39 (16, 51)	0.002**	25.28 ± 11.76 (14, 73)	24.53 ± 7.55 (15, 45)	0.612	0.252
Median	*20.0*	*25.0*	*0.002***	*20.5*	*22.2*	*0.909*	*0.319*
ALT (IU/L)	25.45 ± 9.82 (14, 53)	29.61 ± 14.06 (12, 75)	0.011**	28.28 ± 22.09 (7, 108)	24.81 ± 16.62 (7, 85)	0.158	0.167
Median	*23.0*	*27.1*	*0.021***	*19.0*	*19.0*	*0.327*	*0.024***
CK (IU/L)	141.00 ± 101.60 (43, 484)	166.82 ± 133.99 (44, 714)	0.148	103.82 ± 65.87 (26, 351)	108.12 ± 56.38 (42, 262)	0.489	0.013**
Median	*109.5*	*124.0*	*0.133*	*88.0*	*104.0*	*0.323*	*0.036***
Creatinine (μmol/L)	73.38 ± 18.05 (42, 104)	70.96 ± 17.96 (43, 108)	0.087	78.50 ± 23.14 (44, 128)	75.59 ± 24.57 (41, 169)	0.207	0.339

SD = standard deviation; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase

* using median for AST, ALT, and CK due to non-normal distribution, and using mean ± SD for creatinine because of normal distribution

** having a significant difference at $\alpha = 0.05$

† compare week 0 with week 8 within group by using Wilcoxon signed-rank test for AST, ALT, and CK, and using paired t-test for creatinine

†† compare the control with the study group at week 8 by using Mann-Whitney U test for AST, ALT, and CK, and using independent t-test for creatinine

Regarding the renal-related adverse events, two patients (5.0%) in the study group had an increase in serum creatinine from normal range at baseline to above the ULN, whereas no patient in the control group had. This may be because baseline serum creatinine of patients in the study group was higher than that in the control group. In addition, more patients who older (i.e., aged $\geq$ 60 years) were in the study group than those in the control group (Table 26 – 27). These patients were more susceptible to having the adverse events. However, as shown in Table 38 – 39, there

was no significant difference in mean serum creatinine between baseline and at the end of study of all patients and patients in both the control and study groups (p = 0.051, p = 0.087, and p = 0.339, respectively). Mean serum creatinine of all patients decreased from 75.94 ± 20.78 μmol/L (week 0) to 73.28 ± 21.51 μmol/L (week 8), which accounted for 3.5% reduction. Similarly, mean serum creatinine of patients in the control and study groups were also decreased from baseline by 3.3% and 3.7%, respectively. This finding is consistent with the previous studies in that mean serum creatinine either remained the same or slightly decreased from baseline about 1% to 4% in patients receiving rosuvastatin 10 mg to 40 mg **[58,61-62]**.

Proteinuria and hematuria elevations were found about 1.25% and 11.25% of all patients, respectively. The percentage of patients who had the one grade increase in proteinuria and hematuria in the study group was more than that in the control group, but was not significantly different (all p = 1.000). This may be because there were more elderly patients in the study group. In addition, more patients with hypertension were found in the study group. This can result in an increase in proteinuria or hematuria in the study group. The one grade increase in proteinuria was found about 2.5% in the study group. This result is lower than a previous study in that 7.6% of patients receiving rosuvastatin had one grade increase in proteinuria **[62]**. Perhaps the sample size of this study was small and rosuvastatin concentrations was lower due to every other day dosing. The percentage of patients who had an increase in one or two grades hematuria in this study was 11.25%, which was more than the previous study (7%) **[62]**. This may be partly because in the previous study there was a report of more than two grades increase in hematuria, whereas this study was not. Both more than one grade increase in proteinuria and more than two grades increase in hematuria were not found in this study. This is not similar to the other studies in which the patients receiving rosuvastatin 10 mg had more than one grade increase in proteinuria from baseline about 2% to 3% and more than two grades hematuria elevation about 7% to 10% **[62]**. This phenomenon may be due to sample specificity or insufficient of representative sample size to detect these events. In addition, the patients who had creatinine clearance less than 30 mL/min were excluded from the study.

When the complaints of the adverse effect were considered, rosuvastatin was generally well tolerated in both patient groups. There were 8.75% of patients who had complaints and no significant differences between the control and study groups were found ($p > 0.05$). The most common complaint of the adverse effect was headache, which accounted for 5.0% in the study group. This finding is consistent with a previous study that found 5.5% of patients receiving rosuvastatin had headache **[58]**. The other complaints were muscle pain, muscle weakness, dry mouth, foot edema, and mild malaise. Of these, each event occurred in 1.25% of patient. Muscle pain, muscle weakness, and mild malaise were found in the control group. While, headache, dry mouth, and foot edema were reported in the study group. These adverse event rates are similar to the previous studies [muscle pain and muscle weakness (2.8%), dry mouth and malaise (<1%), and peripheral edema (≥ 2%)] **[58]**. However, the complaints of the adverse effect may be just a feeling or subjective data, not objective. The patients might be anxious that they occurred these events. Moreover, the patients who received every other day regimen might have a nocebo effect. The patients also thought that they received relatively less treatment and drug, which may result in undesirable events.

The musculoskeletal-related adverse events only occurred in the control group. The events consisted of myalgia (2.5% of all patients or 5.0% in the control group) and CK elevation more than 3 times the ULN (1.25% of all patients or 2.5% in the control group). None of the patient had more than 10 times the ULN of CK elevation, while the previous studies reported an incidence of 0.1% to 0.2% **[62,66]**. This may be due to small number of the study population and low incidence of this adverse event. Higher dosage of rosuvastatin and higher baseline CK concentration of the patients in the control group may contribute to higher rate of musculoskeletal-related adverse events. Consequently, serum CK at the end of study in the control group was significantly higher than that in the study group ($p = 0.036$). However, serum CK was not significantly increase from baseline in both the control and study groups ($p = 0.133$ and $p = 0.323$, respectively).

There were no AST or ALT elevation more than 3 times the ULN. This finding does not support the previous studies reported that patients receiving rosuvastatin 5 mg and 10 mg had AST or ALT elevation more than 3 times the ULN

about 0.5% and 0.1% to 0.8%, respectively **[62,66]**. Serum AST of all patients at the end of study was significantly higher than that at baseline, 24.0 and 20.0 IU/L, respectively ($p = 0.024$). In the control group, serum AST at the end of study was also significantly higher than that at baseline, 25.0 and 20.0 IU/L, respectively ($p = 0.002$). Unlike the control group, baseline AST in the study group was not significantly different from that at the end of study ($p = 0.909$). These findings indicate that patients receiving rosuvastatin 10 mg once daily had a significant increase in serum AST from baseline, while patients receiving rosuvastatin 10 mg every other day did not. However, serum AST at the end of study between the control and study groups was not significantly different ($p = 0.339$). With regard to the serum ALT, median ALT of all patients at the end of study was not significantly increased from baseline, 24.0 and 22.0 IU/L at week 8 and week 0, respectively ($p = 0.423$). However, serum ALT at the end of study in the control group was significantly increased from baseline, 27.1 and 23.0 IU/L at week 8 and week 0, respectively ($p = 0.021$). Moreover, it was also significantly higher than that in the study group ($p = 0.024$). In contrast, median ALT at the end of study in the study group was equal to baseline, both was 19.0 IU/L ($p = 0.327$). These findings indicate that serum ALT of patients receiving rosuvastatin 10 mg once daily for 8 weeks significantly increased from baseline and higher than patients receiving rosuvastatin 10 mg every other day. Although a statistically significant increase in serum AST and ALT was found in the control group, this difference might not be clinically significant. This may be because these levels are still in the normal range and long term follow-up is needed to evaluate this side effect.

Overall, rosuvastatin was well tolerated. The adverse event rates of patients receiving rosuvastatin 10 mg once daily and every other day were not significantly different. In addition, each adverse event that reported in this study was not significantly different between the patients receiving rosuvastatin 10 mg once daily and every other day (all $p > 0.05$).

CHAPTER V
CONCLUSIONS AND RECOMMENDATIONS

This randomized, open-labeled, parallel trial was designed to compare the effectiveness and safety of rosuvastatin 10 mg once daily with every other day in outpatients with hypercholesterolemia in terms of: (1) serum lipids, hsCRP, and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals, according to NCEP-ATP III guidelines, (3) adverse event rates, and (4) monthly cost per %LDL-C reduction. The study was conducted from September 2004 to February 2005 at outpatient department, Phramongkutklao hospital. The subjects were patients with hypercholesterolemia who met the criteria for starting statins therapy according to NCEP-ATP III guidelines and they had never received statins. Eighty eligible patients were randomly assigned equally into the control and study groups. The patients in the control and study groups received rosuvastatin 10 mg once daily and 10 mg every other day for 8 weeks, respectively. Effectiveness and safety were evaluated by laboratory data, physical examinations, and patient interviews. Data were analyzed using intention to treat analysis with a significant level of 0.05. Descriptive and inferential statistics were used to evaluate data. The conclusions of this study are as follows:

1. Baseline patient demographics of both patient receiving rosuvastatin 10 mg once daily and every other day were not significantly different in terms of: sex, weight, height, BMI, waist circumference, SBP, DBP, number of concurrent drugs, underlying diseases, number of patients with metabolic syndrome, occupation, health insurance rights, alcoholic drinker, type of major risk factors, number of major risk factors, and risk categories. However, mean age of patients receiving rosuvastatin 10 mg every other day was significantly higher than patients receiving rosuvastatin 10 mg once daily.
2. All baseline clinical laboratory data of patients receiving rosuvastatin 10 mg once daily were not significantly different from patients receiving rosuvastatin 10 mg every other day, except hsCRP. Baseline hsCRP of patients receiving rosuvastatin

10 mg every other day was significantly higher than patients receiving rosuvastatin 10 mg once daily.

3. Both rosuvastatin 10 mg once daily and every other day at week 8 significantly reduced serum TC, TG, LDL-C, and hsCRP from baseline and produced a non-significant decrease in serum fibrinogen. However, only rosuvastatin 10 mg once daily significantly increased serum HDL-C from baseline.
4. Serum TC, TG, HDL-C, LDL-C, and fibrinogen at week 8 were not significantly different between patients receiving rosuvastatin 10 mg once daily and every other day. However, serum hsCRP at week 8 of patients receiving rosuvastatin 10 mg every other day was significantly higher than patients receiving rosuvastatin 10 mg once daily.
5. The percentage of change in serum TC, TG, and LDL-C of patients receiving rosuvastatin 10 mg once daily for 8 weeks was significantly higher than that of patients receiving rosuvastatin 10 mg every other day. Whereas, there was no significant difference of the percentage of change in HDL-C, hsCRP, and fibrinogen between patients receiving rosuvastatin 10 mg once daily and every other day.
6. Rosuvastatin 10 mg once daily and every other day had a comparable LDL-C lowering effect that allows the patients to achieve their LDL-C goals according to NCEP-ATP III guidelines (85% and 70% of patients in once daily and every other day regimens, respectively).
7. The number of patients experienced the adverse events was not significantly different between patients receiving rosuvastatin 10 mg once daily and every other day. However, serum AST and ALT at week 8 of patients receiving rosuvastatin 10 mg once daily were significantly increased from baseline. Whereas, there was no significant difference of serum AST and ALT between baseline and week 8 in patients receiving rosuvastatin 10 mg once daily. In addition, serum ALT and CK at week 8 of patients receiving rosuvastatin 10 mg once daily were significantly higher than those of patients receiving rosuvastatin 10 mg every other day.
8. Monthly cost per %LDL-C reduction of the patients receiving rosuvastatin 10 mg every other day was lower than that of the patients receiving rosuvastatin 10 mg once daily (17.77 baht and 28.62 baht, respectively).

Limitations

1. This study had an unequal baseline of mean age between patients receiving rosuvastatin 10 mg once daily and every other day. Age may be a confounding factor which might affect the adverse event rates of the patients.
2. The researcher could not contact one patient during the study period because this patient did not have own telephone. Despite less intervention, this patient achieved his LDL-C goal according to NCEP-ATP III after 8-week study period and did not have any adverse events.
3. Although, turbidimetric method often exhibits poor accuracy and precision than Clauss method, the turbidimetric is the only method used at Phramongkutklao hospital. Therefore, serum fibrinogen was measured using turbidimetric method.

Recommendations

Future studies should include:

1. Measuring at least three times of serum lipids, hsCRP, and fibrinogen should be conducted to assess the tendency of the parameters changing and expanding time more than 8 weeks period to evaluate long-term effect of every other day dosing of rosuvastatin therapy.
2. Using Clauss method to measure serum fibrinogen to increase the accuracy and precision of serum fibrinogen measurement.
3. Using the Asian dose of rosuvastatin (i.e., 5 mg) to evaluate the appropriateness regimen for Thai patients.
4. Conducting multicenter study to confirm the effectiveness and safety of rosuvastatin every other day when compared with once daily regimen.
5. Determining the effect of statins on the other emerging risk factors for CHD (e.g., homocysteine, lipoprotein(a) and apolipoprotein B-100) to investigate the other beneficial effects of statins.
6. Studying pharmacogenomics in patients receiving once daily and every other day regimen to determine the effectiveness and safety of the drug in individual patient.
7. Using the compliance aids (e.g., reminder cards and micro-electronic bottle cap that have alarms and flashing indicators to alert a patient when a dose is due) to improve the compliance of patients who received every other day regimen.

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Appendices

วันที่เริ่มได้รับยา….....
วันสิ้นสุดการวิจัย.....

เลขที่ ☐☐☐

Appendix A

แบบฟอร์มบันทึกข้อมูลผู้ป่วย

ชื่อ-สกุล..... HN…… อายุ.....ปี อาชีพ.....

ที่อยู่..... โทรศัพท์.....

สิทธิการรักษา ☐ เบิกได้ ☐ เบิกไม่ได้ ☐ อื่นๆ..... ประวัติแพ้ยา ☐ NKDA

รูปแบบยา Rosuvastatin ที่ได้รับ ☐ 10 mg OD ☐ 10 mg AD ☐ แพ้ยา.....

วันที่สะดวกให้โทร.สอบถาม .....

โรคประจำตัว ☐ โรคหลอดเลือดหัวใจ ☐ โรคเบาหวาน ☐ โรคตับ

☐ โรคหลอดเลือดแดงแข็งอื่น เช่น สมองขาดเลือดชั่วคราว โรคหลอดเลือดแดงส่วนปลาย หลอดเลือดแดงที่ท้องโป่ง☐ โรคไทรอยด์ ☐ โรคเกาต์

☐ โรคความดันโลหิตสูง ☐ ภาวะไขมันในเลือดสูง ☐ โรคไต Cl_{Cr}……..

☐ โรคอื่นๆ.....

ยา/อาหารเสริม/สมุนไพรที่ได้รับร่วมด้วยขณะวิจัย

Metabolic syndrome

☐ ภาวะอ้วนลงพุง M > 90 cm (36 inches)
F > 80 cm (32 inches)

☐ TG ≥ 150 mg/dL

☐ HDL M < 40 mg/dL
F < 50 mg/dL

☐ BP ≥ 130/85 mmHg

☐ FBS ≥ 110 mg/dL

○ **Yes**
○ **No**

ปัจจัยเสี่ยง ☐ อายุ (เพศชาย ≥ 45 ปี เพศหญิง ≥ 55 ปี หรือประจำเดือนหมดก่อนวัยและไม่ได้รับฮอร์โมนเอสโตรเจนชดเชย)

☐ ประวัติญาติสายตรงเป็นโรคหลอดเลือดหัวใจก่อนอายุ 55 ปีในเพศชายและ 65ปีในเพศหญิง

☐ ปัจจุบันสูบบุหรี่ (หรือสูบบุหรี่ภายในเดือนที่ผ่านมา)

☐ โรคความดันโลหิตสูง (ความดันโลหิต ≥ 140/90 mmHg หรือได้รับยาลดความดันโลหิต)

☐ ระดับ HDL < 40 mg/dL

○ ระดับ HDL ≥ 60 mg/dL รวม …… risk factor(s)

10-year risk = ……..%

risk category	*LDL Goal*
☐ CHD or CHD risk equivalent (10-year risk > 20%)	< 100 mg/dL (2.58 mmol/L)
☐ ≥ 2 risk factors (10-year risk ≤ 20%)	< 130 mg/dL (3.36 mmol/L)
☐ 0-1 risk factor	< 160 mg/dL (4.13 mmol/L)

เลขที่ ☐☐☐

ผลการตรวจร่างกาย พฤติกรรมการดำเนินชีวิต และผลการตรวจทางห้องปฏิบัติการ

ข้อมูล	วันที่……..	วันที่.....	% Change
น้ำหนัก (kg)			
ส่วนสูง (m^2)			
BMI (kg/m^2)			
เส้นรอบเอว (inches)			
BP (mmHg)			
การสูบบุหรี่			
การดื่มสุรา			
การออกกำลังกาย			
การคุมอาหาร			
Glu (mg/dL)			
TC (mg/dL)			
TG (mg/dL)			
HDL (mg/dL)			
LDL (mg/dL)			
hsCRP (mg/L)			
Fibrinogen (mg/dL)			
AST (IU/L)			
ALT (IU/L)			
CK (IU/L)			
Cr (μmol/L)			
Proteinuria/ Hematuria			

Cost per %LDL reduction = ……..……

LDL เมื่อสิ้นสุดการวิจัยเท่ากับ ..... mg/dL ☐ **achieve goal**

☐ **not achieve goal**

ผู้ป่วย ☐ **เกิด ADR**…….

☐ **ไม่เกิด ADR**

Appendix B

เอกสารชี้แจงข้อมูลแก่ผู้เข้าร่วมโครงการวิจัย (Research Subject Information Sheet)

ชื่อโครงการวิจัย

ประสิทธิผลและความปลอดภัยของยาโรซูวาสทาทิน ขนาด 10 มิลลิกรัมวันละครั้ง เทียบกับ 10 มิลลิกรัมวันเว้นวัน ในผู้ป่วยนอกที่มีภาวะคอเลสเทอรอลในเลือดสูง ณ โรงพยาบาลพระมงกุฎเกล้า

วันที่ชี้แจง

ชื่อและสถานที่ทำงานของหัวหน้าโครงการวิจัย

พันโทนายแพทย์นครินทร์ ศันสนยุทธ หน่วยหทัยวิทยา ภาควิชาอายุรศาสตร์ ร.พ.พระมงกุฎเกล้า โทร. 0-2354-7600

ชื่อผู้วิจัยร่วม

ผศ.ดร.ศุภกิจ วงศ์วิวัฒนนุกิจ และเรือโทหญิงชุติพร กิติยาดิศัย โครงการจัดตั้งภาควิชาเภสัชกรรมคลินิก ภาควิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร. 0-1848-5897

ท่านได้รับการเชิญชวนให้เข้าร่วมการวิจัยเรื่องนี้ แต่ก่อนที่ท่านจะตกลงใจเข้าร่วมโครงการวิจัยหรือไม่ โปรดอ่านข้อความในเอกสารนี้ทั้งหมด เพื่อให้ทราบว่า เหตุใดท่านจึงได้รับการเชิญให้เข้าร่วมโครงการวิจัยนี้ โครงการวิจัยนี้ทำเพื่ออะไร หากท่านเข้าร่วมโครงการวิจัยนี้ท่านจะต้องทำอะไรบ้าง รวมทั้งข้อดีและข้อเสียที่อาจจะเกิดขึ้นในระหว่างโครงการวิจัยนี้

ในเอกสารนี้ อาจมีข้อความที่ท่านอ่านแล้วไม่เข้าใจ โปรดสอบถามหัวหน้าโครงการหรือผู้ช่วยที่ทำโครงการวิจัยนี้ ให้ช่วยอธิบายจนกว่าจะเข้าใจตลอด ท่านอาจขอเอกสารนี้กลับไปอ่านที่บ้านเพื่อปรึกษาหารือกับญาติพี่น้อง เพื่อน หรือแพทย์ที่ท่านรู้จัก ให้ช่วยคิดว่าควรจะเข้าร่วมโครงการวิจัยครั้งนี้หรือไม่ การเข้าร่วมโครงการวิจัยครั้งนี้จะต้องเป็นความสมัครใจของท่าน ไม่มีการบังคับหรือชักจูง ถึงแม้ท่านจะไม่เข้าร่วมในโครงการวิจัยท่านก็จะได้รับการรักษาพยาบาลตามปกติ การไม่เข้าร่วมหรือถอนตัวจากโครงการวิจัยนี้จะไม่มีผลกระทบต่อการได้รับบริการ การรักษาพยาบาล หรือผลประโยชน์ที่พึงจะได้รับของท่านแต่อย่างใด

โปรดอย่าลงลายมือชื่อของท่านในเอกสารนี้ จนกว่าท่านจะแน่ใจว่ามีความประสงค์จะเข้าร่วมโครงการวิจัยนี้จริง คำว่า “ท่าน” ในเอกสารนี้ หมายถึงผู้เข้าร่วมโครงการวิจัยในฐานะเป็นอาสาสมัครในโครงการวิจัยนี้ หากท่านเป็นผู้แทนโดยชอบธรรมตามกฎหมายของผู้ที่จะเข้าร่วม

โครงการวิจัย และจะลงนามแทนในเอกสารนี้ โปรดเข้าใจว่า “ท่าน” ในเอกสารนี้ หมายถึงผู้เข้าร่วมโครงการวิจัยเท่านั้น

โครงการวิจัยนี้มีที่มาอย่างไร และวัตถุประสงค์ของโครงการ

ปัจจุบันผู้ป่วยภาวะคอเลสเทอรอลในเลือดสูงจำนวนมาก ไม่สามารถควบคุมระดับไขมันได้ตามเกณฑ์ ส่งผลให้ประชากรจำนวนมากเสียชีวิตจากโรคหัวใจและหลอดเลือดซึ่งเป็นสาเหตุการตายที่สำคัญสาเหตุหนึ่งของประชากรไทย ยาลดระดับคอเลสเทอรอลในเลือดที่มีประสิทธิผลสูงและนิยมใช้ในปัจจุบัน ได้แก่ ยาอะทอวาสทาทิน และยาโรซูวาสทาทิน เป็นต้น แต่เนื่องจากยาเหล่านี้ราคาแพงและต้องใช้เป็นระยะเวลานาน ทำให้เกิดปัญหาด้านค่าใช้จ่ายแก่ผู้ป่วย และเศรษฐกิจของประเทศ ผู้วิจัยจึงทำการวิจัยเพื่อหาแนวทางการรักษาที่สามารถลดค่าใช้จ่ายโดยคงประสิทธิผลและความปลอดภัยของยา โดยศึกษาการใช้ยารูปแบบวันเว้นวัน และนอกเหนือจากระดับไขมันในเลือดที่มีความสัมพันธ์กับการเกิดโรคหลอดเลือดหัวใจแล้ว ปัจจุบันพบว่ามีปัจจัยเสี่ยงอื่นที่เกี่ยวข้องกับโรคหลอดเลือดหัวใจเช่นกัน ได้แก่ ซีรีแอ็กทีฟโปรตีน และไฟบริโนเจน ดังนั้นการวิจัยนี้จึงมีวัตถุประสงค์เพื่อ เปรียบเทียบประสิทธิผลและความปลอดภัยของยาโรซูวาสทาทินรูปแบบรับประทานทุกวันกับวันเว้นวัน และศึกษาบทบาทของยาโรซูวาสทาทินต่อ ซีรีแอ็กทีฟโปรตีน และไฟบริโนเจน ซึ่งใช้เป็นตัวทำนายการเกิดโรคหลอดเลือดหัวใจ

ท่านได้รับเชิญให้เข้าร่วมโครงการวิจัยนี้เพราะคุณสมบัติที่เหมาะสมดังต่อไปนี้

1. ได้รับการวินิจฉัยว่ามีภาวะคอเลสเทอรอลในเลือดสูงและยังไม่เคยได้รับยาลดไขมันกลุ่มสทาทิน
2. อายุไม่น้อยกว่า 18 ปี
3. มีคุณสมบัติเข้าตามเกณฑ์ที่ต้องเริ่มการรักษาด้วยยาลดไขมันในเลือด

ท่านไม่สามารถเข้าร่วมโครงการวิจัยได้หากท่านมีคุณสมบัติดังต่อไปนี้

1. ตั้งครรภ์หรืออยู่ระหว่างการให้นมบุตร
2. มีโรคประจำตัวคือ โรคตับ โรคมะเร็ง หรือโรคที่มีการอักเสบเรื้อรัง ได้แก่ โรคข้ออักเสบ และโรคลำไส้อักเสบ
3. มีภาวะติดเชื้อ
4. ได้รับยาที่มีผลต่อระดับไขมันในเลือด ซีรีแอ็กทีฟโปรตีน ไฟบริโนเจน หรือยาที่อาจเกิดปฏิกิริยาระหว่างยากับยาโรซูวาสทาทิน ได้แก่ ยาคุมกำเนิดชนิดรับประทาน ยาสเตียรอยด์ ยากันชักฟีโนบาร์บิทอล (phenobarbital) ยากันชักวาโพรอิกแอซิด (valproic acid) ยากดภูมิคุ้มกันไซโคสปอริน (cyclosporine) และยาต้านการแข็งตัวของเลือดวาร์ฟาริน (warfarin)
5. จำเป็นต้องได้รับยาลดไขมันอื่นที่นอกเหนือจากการวิจัย

6. เกิดอาการไม่พึงประสงค์ เช่น ปวดเมื่อยกล้ามเนื้อ หรือกล้ามเนื้ออ่อนแรง จนไม่สามารถทนได้ หรือมีระดับเอ็นไซม์ตับหรือกล้ามเนื้อสูงเกินกว่า 3 เท่าของค่าสูงสุดของค่าปกติ

สถานที่ทำโครงการวิจัย และจำนวนผู้เข้าร่วมโครงการวิจัย

สถานที่ทำโครงการวิจัยนี้คือ กองอายุรกรรมและกองตรวจโรคผู้ป่วยนอก โรงพยาบาลพระมงกุฎเกล้า โดยมีจำนวนผู้เข้าร่วมโครงการวิจัยทั้งสิ้น 80 คน

ระยะเวลาที่ท่านจะต้องร่วมโครงการวิจัยและจำนวนครั้งที่นัด

ระยะเวลาที่ท่านจะต้องเข้าร่วมโครงการวิจัยคือ 8 สัปดาห์ ซึ่งจะต้องพบผู้วิจัยจำนวน 2 ครั้ง ครั้งแรกเมื่อเริ่มต้นการวิจัย และครั้งที่ 2 คือสัปดาห์ที่ 8 ของการวิจัย โดยระหว่างที่ท่านเข้าร่วมโครงการวิจัยผู้วิจัยจะโทรศัพท์ถึงท่าน เพื่อสอบถามถึงอาการไม่พึงประสงค์ หรือปัญหาต่างๆที่อาจเกิดขึ้นกับท่าน

หากท่านเข้าร่วมโครงการวิจัยครั้งนี้ ท่านจะต้องปฏิบัติตามขั้นตอน หรือได้รับการปฏิบัติอย่างไรบ้าง

เมื่อท่านเข้าร่วมโครงการวิจัยท่านจะได้รับการเจาะเลือดเพื่อตรวจวัดระดับไขมัน ซีรีแอ็กทีฟโปรตีน ไฟบริโนเจน เอนไซม์ตับและกล้ามเนื้อ และตรวจปัสสาวะ เพื่อเป็นข้อมูลพื้นฐานก่อนการวิจัย และได้รับความรู้ด้านโรค ยา และการปรับเปลี่ยนพฤติกรรมการดำเนินชีวิต จากนั้นท่านจะได้รับการสุ่มให้ได้รับยาซึ่งโดยปกติแล้วผู้เข้าร่วมโครงการวิจัยจะถูกแบ่งเป็น 2 กลุ่ม กลุ่มละ 40 คน ด้วยวิธีการสุ่ม โดยกลุ่มแรกจะได้รับยาโรซูวาสทาทินขนาด 10 มิลลิกรัม รับประทานวันละ 1 ครั้งทุกวัน เป็นเวลา 8 สัปดาห์ และกลุ่มที่สองจะได้รับยาโรซูวาสทาทินขนาด 10 มิลลิกรัม รับประทานวันเว้นวัน เป็นเวลา 8 สัปดาห์ ซึ่งโอกาสที่ผู้เข้าร่วมการวิจัยจะอยู่กลุ่มใดนั้นมีอัตราส่วนเท่ากันคือ 1 ต่อ 1 ท่านจะได้รับการนัดหมายให้มาพบผู้วิจัยเมื่อท่านได้รับยาครบ 8 สัปดาห์ โดยระหว่างที่ท่านได้รับยานั้นผู้วิจัยจะโทรศัพท์ถึงท่านเพื่อสอบถามถึงอาการไม่พึงประสงค์ ตลอดจนปัญหาต่างๆของท่าน เมื่อท่านมาพบผู้วิจัยตามนัดท่านจะได้รับการเจาะเลือดและตรวจปัสสาวะอีกครั้งเพื่อประเมินประสิทธิผลและความปลอดภัยของยา หลังสิ้นสุดการวิจัยแพทย์จะพิจารณาปรับเปลี่ยนยาลดไขมันตามความเหมาะสมของผู้ป่วยต่อไป

ความไม่สุขสบาย หรือความเสี่ยงต่ออันตรายที่อาจจะได้รับจากกรรมวิธีการวิจัย และวิธีการป้องกัน/แก้ไขที่หัวหน้าโครงการวิจัยเตรียมไว้หากมีเหตุการณ์ดังกล่าวเกิดขึ้น

ความไม่สุขสบาย หรือความเสี่ยงต่ออันตรายที่ท่านอาจจะได้รับคือ การเกิดอาการไม่พึงประสงค์จากการใช้ยาโรซูวาสทาทิน โดยอาจมีอาการปวดเมื่อยกล้ามเนื้อ กล้ามเนื้ออ่อนแรง หรือมีระดับเอ็นไซม์ตับ และ/หรือเอ็นไซม์กล้ามเนื้อสูงขึ้น ซึ่งผู้วิจัยดำเนินการป้องกันโดยการให้ความรู้แก่ผู้เข้าร่วมโครงการวิจัยถึงอาการไม่พึงประสงค์ที่อาจเกิดขึ้น เพื่อให้ผู้เข้าร่วมโครงการวิจัย

สามารถสังเกตและแจ้งแพทย์หรือผู้วิจัยทันทีที่เกิดอาการ นอกจากนี้ผู้วิจัยมีการโทรศัพท์สอบถามและติดตามอาการและปัญหาต่างๆระหว่างการใช้ยาของผู้เข้าร่วมโครงการวิจัย

ประโยชน์ที่อาจจะได้รับจากการวิจัย

ประโยชน์ที่ผู้เข้าร่วมโครงการวิจัยจะได้รับจากการวิจัย คือ ได้รับความรู้เรื่องภาวะไขมันในเลือดผิดปกติ พฤติกรรมการดำเนินชีวิตที่เหมาะสม และการใช้ยาอย่างถูกต้อง เพื่อลดระดับไขมันในเลือดให้อยู่ในเกณฑ์ปกติ และประหยัดค่าใช้จ่ายด้านยาลดไขมันในเลือด ตลอดจนได้รับการติดตามปัญหาต่างๆอย่างใกล้ชิด

ประโยชน์ที่อาจจะได้รับจากการวิจัยต่อส่วนรวมคือ สามารถนำข้อมูลที่ได้มาประกอบการพิจารณารูปแบบการสั่งใช้ยาที่เหมาะสมกับการรักษาผู้ป่วยแต่ละรายตามประสิทธิผลในการรักษา ความปลอดภัย และเศรษฐฐานะของผู้ป่วย และทราบข้อมูลประสิทธิผลของยาโรซูวาสทาทินต่อปัจจัยที่ใช้ทำนายการเกิดโรคหลอดเลือดหัวใจ คือ ซีรีแอ็กทีฟโปรตีน และไฟบริโนเจน เพื่อใช้ในทางปฏิบัติต่อไป

ค่าใช้จ่ายที่ท่านจะต้องรับผิดชอบระหว่างโครงการวิจัย

ค่าใช้จ่ายที่ท่านจะต้องรับผิดชอบระหว่างโครงการวิจัยคือ ค่าใช้จ่ายด้านยา และการรักษาอื่นๆที่ไม่เกี่ยวข้องกับโครงการวิจัย ส่วนที่ท่านจะได้รับจากโครงการวิจัยโดยไม่เสียค่าใช้จ่ายคือ ค่ายาลดไขมันในเลือดโรซูวาสทาทิน และค่าตรวจทางห้องปฏิบัติการของระดับไขมันในเลือด ซีรีแอ็กทีฟโปรตีน ไฟบริโนเจน เอนไซม์ตับ เอนไซม์กล้ามเนื้อ และค่าตรวจปัสสาวะ

หากท่านไม่เข้าร่วมโครงการวิจัยนี้ท่านมีทางเลือกอื่นอย่างไรบ้าง

หากท่านไม่เข้าร่วมโครงการวิจัยนี้ท่านมีทางเลือกอื่นคือ

1. การปรับเปลี่ยนพฤติกรรมการดำเนินชีวิต เช่น การเลิกสูบบุหรี่ การควบคุมอาหาร และการออกกำลังกาย เป็นต้น
2. การที่แพทย์พิจารณาเปลี่ยนยาลดไขมันในเลือดเป็นยาชนิดอื่นที่ให้ผลดีในการรักษาเช่นเดียวกัน

หากมีอันตรายที่เกี่ยวข้องกับโครงการวิจัยนี้เกิดขึ้นจะติดต่อกับใคร และจะได้รับการปฏิบัติอย่างไร

หากมีอันตรายที่เกี่ยวข้องกับโครงการวิจัยนี้เกิดขึ้นท่านสามารถติดต่อกับ พันโทนายแพทย์นครินทร์ ศันสนยุทธ หน่วยหทัยวิทยา ภาควิชาอายุรศาสตร์ โรงพยาบาลพระมงกุฎเกล้า หัวหน้าโครงการวิจัย โทร. 0-2354-7600 หรือ เรือโทหญิงชุติพร กิติยาดิศัย ผู้วิจัยร่วม ได้ที่โครงการจัดตั้งภาควิชาเภสัชกรรมคลินิก ภาควิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร. 0-1848-5897 ตลอด 24 ชั่วโมง กรณีที่มีเหตุการณ์ฉุกเฉินท่านสามารถโทรศัพท์ติดต่อหัวหน้าโครงการวิจัยหรือผู้วิจัยร่วมได้ทันที ซึ่งจะให้คำแนะนำในขณะนั้น และรับผิดชอบค่าใช้จ่ายที่

เกิดขึ้น พร้อมชดเชยรายได้ที่สูญเสียไประหว่างการรักษา พยาบาลดังกล่าว ตลอดจนเงินทดแทนความพิการที่อาจเกิดขึ้นตามความเหมาะสม

หากท่านมีคำถามที่เกี่ยวข้องกับโครงการวิจัย จะสอบถามได้จากใคร

1. พันโทนายแพทย์นครินทร์ ศันสนยุทธ หน่วยหทัยวิทยา ภาควิชาอายุรศาสตร์ โรงพยาบาลพระมงกุฎเกล้า หัวหน้าโครงการวิจัย โทร. 0-2354-7600 หรือ
2. เรือโทหญิงชุติพร กิติยาดิศัย โครงการจัดตั้งภาควิชาเภสัชกรรมคลินิก ภาควิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ผู้วิจัยร่วม โทร. 0-1848-5897

หากท่านรู้สึกว่าได้รับการปฏิบัติอย่างไม่เป็นธรรมในระหว่างโครงการวิจัยนี้ ท่านอาจแจ้งเรื่องได้ที่

สำนักงานพิจารณาโครงการวิจัย พบ. โทร. 0-2354-7600 ต่อ 93681

ข้อมูลส่วนตัวของท่านที่ได้จากโครงการวิจัยครั้งนี้จะถูกนำไปใช้ดังต่อไปนี้

ผู้วิจัยจะนำเสนอข้อมูลจากโครงการวิจัยนี้ในรูปที่เป็นสรุปผลการวิจัยโดยรวม เพื่อประโยชน์ทางวิชาการ โดยไม่เปิดเผย ชื่อ นามสกุล ที่อยู่ ของผู้เข้าร่วมโครงการวิจัยเป็นรายบุคคล และมีมาตรการในการเก็บรักษาข้อมูลทั้งส่วนตัวและข้อมูลที่ได้จากโครงการวิจัย โดยการเปิดเผยข้อมูลต่อหน่วยงานต่างๆที่เกี่ยวข้อง กระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ท่านจะถอนตัวออกจากโครงการวิจัยหลังจากได้ลงนามเข้าร่วมโครงการวิจัยแล้วได้หรือไม่

ท่านสามารถถอนตัวออกจากโครงการวิจัยได้ตลอดเวลา โดยไม่เกิดผลเสียใดๆตามมา และท่านอาจถูกขอให้ออกจากโครงการวิจัยโดยหัวหน้าโครงการวิจัย ในกรณีที่ท่านได้รับยาที่อาจเกิดปฏิกิริยาระหว่างยากับยาโรซูวาสทาทิน ได้รับยาลดไขมันชนิดอื่นที่นอกเหนือจากการวิจัย หรือเกิดอาการไม่พึงประสงค์จากยา

หากมีข้อมูลใหม่ที่เกี่ยวข้องกับโครงการวิจัย ท่านจะได้รับแจ้งข้อมูลนั้นโดยหัวหน้าโครงการวิจัยหรือผู้ร่วมวิจัยทันที

หากผู้วิจัยมีข้อมูลเพิ่มเติมทั้งด้านประโยชน์และโทษที่เกี่ยวข้องกับการวิจัยนี้ ผู้วิจัยจะแจ้งให้ท่านทราบทันทีโดยไม่ปิดบัง

Appendix C

หนังสือแสดงเจตนายินยอมเข้าร่วมการวิจัย (Consent form)

รับรองโดยคณะอนุกรรมการพิจารณาโครงการวิจัย พบ.

วันที่ลงนาม.....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรืออาการที่อาจเกิดขึ้นจากการวิจัย หรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามต่างที่ข้าพเจ้าสงสัยด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้ามีสิทธิที่จะบอกเลิกเข้าร่วมในโครงการวิจัยเมื่อใดก็ได้ และเข้าร่วมโครงการวิจัยนี้โดยสมัครใจ และการบอกเลิกการเข้าร่วมการวิจัยนี้ จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ผู้วิจัยรับรองว่าหากเกิดอันตรายใดๆจากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่คิดมูลค่า และจะได้รับการชดเชยรายได้ที่สูญเสียไประหว่างการรักษาพยาบาลดังกล่าว ตลอดจนเงินทดแทนความพิการที่อาจเกิดขึ้นตามความเหมาะสม

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว และมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงชื่อ.....ผู้เข้าร่วมโครงการวิจัย

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....ผู้ดำเนินการโครงการวิจัย

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....พยาน

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....พยาน

(.....ชื่อ-นามสกุล ตัวบรรจง)

ในกรณีที่ผู้เข้าร่วมโครงการวิจัยไม่สามารถลงลายมือชื่อด้วยตนเองได้ ให้ผู้แทนโดยชอบตามกฎหมายซึ่งมีส่วนเกี่ยวข้องเป็น.....ของผู้เข้าร่วมโครงการวิจัย เป็นผู้ลงนามแทน

ลงชื่อ.....ผู้แทนโดยชอบธรรม

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....พยาน

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....พยาน

(.....ชื่อ-นามสกุล ตัวบรรจง)

Appendix D เลขที่ ☐☐☐

แบบประเมินอาการไม่พึงประสงค์จากการใช้ยา (Naranjo's Algorithm)

ชื่อ-สกุล..... HN…… อายุ.....ปี
ชื่อยาที่สงสัย..... ประวัติการแพ้ยา ☐ NKDA
วันที่เริ่มใช้ยา..... ☐ แพ้ยา.....
วันที่หยุดใช้ยา..... วันที่ประเมิน.....

รายการประเมิน	ใช่	ไม่ใช่	ไม่ทราบ
1. เคยมีสรุปหรือรายงาน ADR เกี่ยวกับยาที่สงสัยมาแล้ว	+1	0	0
2. อาการไม่พึงประสงค์เกิดขึ้นหลังได้รับยาที่สงสัย	+2	-1	0
3. อาการไม่พึงประสงค์ดีขึ้นเมื่อหยุดยาที่สงสัยหรือเมื่อให้ยาต้านที่เฉพาะเจาะจง	+1	0	0
4. อาการไม่พึงประสงค์ดังกล่าวเกิดขึ้นอีกเมื่อได้รับยาที่สงสัยเข้าไปใหม่	+2	-1	0
5. อาการไม่พึงประสงค์สามารถเกิดจากสาเหตุอื่นนอกเหนือจากยาที่สงสัย	-1	+2	0
6. อาการไม่พึงประสงค์เกิดขึ้นได้ใหม่เมื่อได้รับยาหลอก	-1	+1	0
7. สามารถตรวจวัดระดับยาในเลือดหรือของเหลวในร่างกายว่ามีความเข้มข้นที่ทำให้เกิดพิษ	+1	0	0
8. อาการไม่พึงประสงค์รุนแรงขึ้นเมื่อเพิ่มขนาดยาหรือลดลงเมื่อลดขนาดยา	+1	0	0
9. ผู้ป่วยเคยเกิดอาการไม่พึงประสงค์เช่นนี้มาแล้วเมื่อได้รับยาในครั้งก่อน	+1	0	0
10. อาการไม่พึงประสงค์นั้นมีหลักฐานที่ได้รับการยืนยันโดยวิธีอันเหมาะสม	+1	0	0
รวมคะแนน			

ผลการประเมิน ☐ ใช่แน่นอน (Definite) ≥ 9 คะแนน ☐ น่าจะใช่ (Probable) 5-8 คะแนน
☐ เป็นไปได้ (Possible) 1-4 คะแนน ☐ ไม่น่าจะใช่ (Doubtful) ≤ 0 คะแนน

VITA

Lieutenant Junior Grade Chutiporn Kitiyadisai was borned on June 26th, 1979 in Bangkok, Thailand. She has graduated Bachelor of Science in Pharmacy from Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand since 2000. She works at pharmacy department of Somdedpranangjaosirikit hospital, Royal Thai Navy, Chonburi, Thailand