การบรรลุเป้าหมายระดับไขมันในเลือดของยาอะทอร์วาสทาทิน, โรซูวาสทาทิน, และซิมวาสทาทิน ในผู้ป่วยโรคหัวใจขาดเลือดและผู้ป่วยที่มีความเสี่ยงเทียบเท่าโรคหัวใจขาดเลือด ณ โรงพยาบาลสรรพสิทธิประสงค์

นางอุษณีย์ กิตติวงศ์สุนทร

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Lipid Goal Achievement of Atorvastatin, Rosuvastatin and Simvastatin among Coronary Heart Disease / Coronary Heart Disease Risk Equivalent Patients at Sappasittiprasong Hospital

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A Thesis Submitted in Partial Fulfillment of the Requirements

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อุษณีย์ กิตติวงศ์สุนทร: การบรรลุเป้าหมายระดับไขมันในเลือดของยาอะทอร์วาสทาทิน, โรซูวาสทาทิน และซิมวาสทาทิน ในผู้ป่วยที่มีประวัติโรคหัวใจขาดเลือดและผู้ป่วยที่มีความเสี่ยงเทียบเท่าโรคหัวใจขาดเลือด ณ โรงพยาบาลสรรพสิทธิประสงค์ (Lipid Goal Achievement of Atorvastatin, Rosuvastatin and Simvastatin among Coronary Heart Disease/Coronary Heart Disease Risk Equivalent Patients at Sappasittiprasong Hospital) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ดร. วิทยา กุลสมบูรณ์, 70 หน้า

การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบประสิทธิผลของยาอะทอร์วาสทาทิน, โรซูวาสทาทิน และซิมวาสทาทิน ของผู้ป่วยที่มีประวัติโรคหัวใจขาดเลือดและผู้ป่วยที่มีความเสี่ยงเทียบเท่าโรคหัวใจขาดเลือดในเวชปฏิบัติ โดยใช้วิธีการศึกษาแบบตัดขวางและเก็บข้อมูลย้อนหลังจากฐานข้อมูล ในกลุ่มผู้ป่วยที่ได้รับยาสทาทินครั้งแรก ระหว่างเดือนตุลาคม 2547 – เดือนกันยายน 2550 และไม่เคยได้รับยาลดไขมัน 6 เดือนก่อนรับยาที่ศึกษา กลุ่มผู้ป่วยที่ศึกษามีอายุ ≥ 35 ปี, มีประวัติโรคหัวใจขาดเลือดหรือมีความเสี่ยงเทียบเท่าโรคหัวใจขาดเลือด, และมีระดับ LDL-C แรกเริ่ม > 100 มก./ดล ระยะเวลาได้รับยาสทาทินต้องไม่น้อยกว่า 90 วัน วัดผลจากร้อยละของผู้ป่วยที่บรรลุเกณฑ์เป้าหมายของระดับ LDL-C ตามแนวทางของ NCEP ATP III และค่าเฉลี่ยของร้อยละการเปลี่ยนแปลงของการลดระดับ LDL-C รวมทั้งประเมินผลทางเศรษฐศาสตร์โดยคิดต้นทุนเฉพาะค่ายาเท่านั้น สถิติที่ใช้คือ Chi-square test และ ANOVA

ผู้ป่วยที่มีคุณสมบัติตรงตามเงื่อนไขที่ศึกษา 1,024 ราย เป็นผู้ป่วยที่ได้รับยาซิมวาสทาทิน 794 ราย , ยาอะทอร์วาสทาทิน 109 ราย และยาโรซูวาสทาทิน 121 ราย มีอายุเฉลี่ย 62 ปี เพศชาย 47.9% ผลการศึกษาพบว่า การบรรลุเป้าหมายระดับ LDL-C < 100 มก./ดล.ตามแนวทางของ NCEP ATP III ของยาโรซูวาสทาทิน (78%), ยาซิมวาสทาทิน(68%), และยาอะทอร์วาสทาทิน(62.4%)ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (P=0.078) ค่าเฉลี่ยของร้อยละการเปลี่ยนแปลงของการลดระดับLDL-C ของยาโรซูวาสทาทินดีที่สุดเมื่อเปรียบเทียบกับยาซิมวาสทาทินและยาอะทอร์วาสทาทินอย่างมีนัยสำคัญทางสถิติ (-46.1%,-38.5%และ-38.2% ตามลำดับ, P<0.05) ยาซิมวาสทาทินมีความคุ้มค่าทางเศรษฐศาสตร์มากที่สุดเมื่อเปรียบเทียบกับยาโรซูวาสทาทินและยาอะทอร์วาสทาทิน (376บาท, 16,670 บาท, และ 29,417 บาท ตามลำดับต่อผู้ป่วย 1 รายที่บรรลุเป้าหมายระดับไขมันในเลือด) โดยสรุปยาซิมวาสทาทินให้ผลบรรลุเป้าหมายระดับไขมันในเลือดตามแนวทางของ NCEP ATP III ที่มีความคุ้มค่าด้านเศรษฐศาสตร์มากที่สุดเมื่อเปรียบเทียบกับยาโรซูวาสทาทินและยาอะทอร์วาสทาทิน จึงควรเลือกใช้เป็นยาลำดับแรกสำหรับผู้ป่วยโรคหัวใจขาดเลือดและผู้ป่วยที่มีความเสี่ยงเทียบเท่าโรคหัวใจขาดเลือด ยกเว้นผู้ป่วยที่มีข้อห้ามใช้กับยาซิมวาสทาทิน

สาขาวิชา: .....เภสัชศาสตร์สังคมและบริหาร.... ลายมือชื่อนิสิต.....

ปีการศึกษา: .....2551..... ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....Vithya. KL

497 68644 33: MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEY WORD: LIPID GOAL ACHIEVEMENT/ATORVASTATIN/ROSUVASTATIN/SIMVASTATIN/
CORONARY HEART DISEASE

USANEE KITTIWONGSUNTHORN: LIPID GOAL ACHIEVEMENT OF ATORVASTATIN, ROSUVASTATIN, AND SIMVASTATIN AMONG CORONARY HEART DISEASE/CORONARY HEART DISEASE RISK EQUIVALENT PATIENTS AT SAPPASITTIPRASONG HOSPITAL. THESIS PRINCIPAL ADVISOR: ASSOCIATE PROFESSOR VITHAYA KULSOMBOON, Ph.D., 70 pp.

The objectives of this study were to compare the effectiveness of atorvastatin, rosuvastatin, and simvastatin among CHD/CHD risk equivalent patients in usual clinical practice. A Cross-sectional retrospective study was conducted by using electronic database among patients who were newly prescribed statin therapy during October 2004 to September 2007 and didn't receive dyslipidemic drugs in the preceding 6 months. Patients aged 35 years or older with CHD/CHD-risk equivalent and LDL-C baseline > 100 mg/dL were included. Patients must receive statins not less than 90 days. Outcome measurements were the percentage of patients who achieved LDL-C goal according to NCEP ATP III guideline and mean of percent change in LDL C – reduction including economic assessment for drug costs only. Chi-square test and ANOVA were used for statistic analysis.

Of the 1,024 patients who met the study criteria, 794 taking simvastatin, 109 taking atorvastatin and 121 taking rosuvastatin. Patients had average age of 62 years and 47.9% were male. The results showed that lipid goal achievement based on NCEP ATP III goal of LDL-C <100 mg/dL of rosuvastatin (78%), simvastatin (68%), and atorvastatin (62.4%) were not statistically different (P=0.078). The mean of percent change in LDL-C reduction of rosuvastatin was the greatest compared with simvastatin and atorvastatin significantly (-46.1%, -38.5%, and -38.2%, P<0.05). Simvastatin was the most cost-effectiveness compared with rosuvastatin and atorvastatin (376, 16,670, and 29,417 Baht per patient at goal per year). In conclusion, simvastatin is the most cost -effectiveness in achieving LDL-C goals according to NCEP ATP III guideline compared with rosuvastatin and atorvastatin among CHD/CHD-risk equivalent patients. Therefore, simvastatin should be the first choice for CHD/CHD-risk equivalent patients except the patients who has contra-indication with simvastatin.

Field of study: Social and Administrative Pharmacy. Student's signature.....

Academic year:..... 2008..... Thesis Principal Advisor's signature.....

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LIST OF ABBREVIATIONS

ALT	=	Alanine aminotransferase
AST	=	Aspartate aminotransferase
ATPIII	=	Adult Treatment Panel III
ATV	=	Atorvastatin
BP	=	Blood pressure
CHD	=	Coronary heart disease
CK	=	Creatine kinase
Cr Cl	=	Creatinine clearance
CVD	=	Cardiovacular disease
CYP3A4	=	Cytochrome P 3A4
HDL-C	=	High density lipoprotein cholesterol
HMG-CoA	=	3-Hydroxy-3-methylglutaryl coenzyme A
LDL-C	=	Low density lipoprotein cholesterol
MI	=	Myocardial infarction
mg/dL	=	milligram/deciliter
NCEP	=	National Cholesterol Education Program
RCTs	=	Randomized control trials
RSV	=	Rosuvastatin
SVT	=	Simvastatin
TC	=	Total cholesterol
TG	=	Triglyceride
VLDL	=	Very low density lipoprotein
WHO	=	World Health Organization

CHAPTER I

INTRODUCTION

Cardiovascular disease (CVD), especially coronary heart diseases (CHD), hypertension, and stroke, is the most common cause of death in many countries including Thailand.[1,2,3] World Health Organization (WHO) estimated that 17 million people death from CVD each year. WHO also predicts that in 2020, 11.1 million people will die from CHD.[4] In Thailand, data from the Ministry of Public Health reported that heart disease was the third cause of death for many years. Death from hypertension and stroke increased from 18.9:100,000 population in 2000 to 34.8 : 100,000 population in 2004.[3] Hypercholesterolemia is a crucial risk factor to cause of CVD.[1,2,5] In 2002, The International Collaborative Study of Cardiovascular disease in Asia (InterASIA), estimated that 4.4 million Thai people had high serum total cholesterol (TC$\geq$ 200 mg/dL) which indicated a high-risk for CVD. This may be the result from unhealthy lifestyle, such as eating fast food and lack of exercise.[6]

Results from clinical trials and meta-analysis of trial results clearly showed that statins reduced total cholesterol (TC) and low-density-lipoprotein cholesterol (LDL-C) levels, thereby reducing CHD risk and total mortality. More recently, clinical data demonstrated that more intensive lipid lowering provides additional clinical benefits. Evidence-based guidelines issued by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) underline the importance of hyperlipidemia treatment with an aggressive LDL-C goal of <100 mg/dL for high-risk patients. Moreover, updated optional recommendations to the ATP III guidelines, published in July 2004, now recommend an optional LDL-C goal of <70 mg/dL in very high-risk patients. Since LDL-C is the primary target of

therapy, ATP III identified persons according to cardiovascular risk into three classes: high, moderate and low. Patients with established CHD and CHD risk equivalent (patients who have type 2 diabetes without CHD; non - coronary forms of clinical atherosclerotic disease; and patients who have multiple risk factors with 10-year risk of CHD >20%) are called high risk. If the patients have established CHD and plus diabetes mellitus, acute coronary syndrome, or metabolic syndrome, they are called very high risk.[5,7]

The statins are the most effective drugs for lowering LDL-C levels and known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Statins can reduce LDL-C 18%-55%; triglycerides(TG) generally range from 7%–30%, but will generally rise HDL-C by 5%–15%.[2,5,8] Results from five clinical trials (CARE[9], LIPID[10], 4S[11], WOSCOPS[12], and AFCAPS/TexCAPS[13]) have documented that statins can decrease the risk for CHD and total mortality (decrease coronary morbidity and mortality 24%-37%; and reduce all cause mortality by 22%).[5,8] The statins are well-tolerated by most persons because of less adverse events. The infrequent adverse events are abdominal discomfort, rash, myalgia, transient aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and creatine kinase (CK) elevation.

Three statins mostly used in many hospital of Thailand, including Sappasittiprasong Hospital, are atorvastatin (ATV), simvastatin (SVT) and rosuvastatin (RSV). Several evidences showed that these statins are different in effectiveness of hypercholesterolemia management. In clinical trials, three studies: STELLAR trial (2003),[14] DISCOERY trial (2006),[15] and SOLAR trial (2007)[16] showed that rosuvastatin significantly reduced LDL-C levels (50% vs 42% for ATV and 40% for SVT) and achieved NCEP goal (76% vs 58% for ATV and 53% for SVT) greater than atorvastatin and simvastatin in high-risk patients with LDL-C baseline > 130 mg/dL and length of statin therapy 12 weeks in high rate. Recent

observational studies demonstrated that in usual care setting number of patients who were prescribed statin therapy achieved the NCEP goal less than in clinical trial. The Lipid Treatment Assessment Project (L-TAP),[17] Achievement in Singapore of Cholesterol Targets (A-SACT),[18] and REALITY-PHARMO study[19] showed that the patients achieved LDL-C goals range from 30%to38%. Similar to a study in Thailand, the percentage of high risk patients who reached LDL-C target (<100 mg/dL) was 34.6%. The difference between clinical trial efficacy and real-life effectiveness may be due to the lack of patient follow-up, failure to titrate to an effective dose or switching to a more potent statins, high baseline cholesterol levels, cost, and lack of patient motivation as well as factors driven by reimbursement.[20]

In opposite, some evidences of effectiveness of rosuvastatin compared with atorvastatin or simvastatin in usual care setting (out of clinical trials) showed the results as the same as clinical trials, rosuvastatin was greater reduction in LDL-C and achievement LDL-C goal than atorvastatin and simvastatin. Using data from patient medical record, Ohsfeldt and others (2006)[21] compared the effectiveness of rosuvastatin with atorvastatin and simvastatin in high-risk patients who were newly prescribed statin therapy for 18 months of treatment. While Fox and others (2007)[22]used data from electronic medical records database to compare the effectiveness of statins between aged $\geq$ 65 years and < 65 years patients who were newly prescribed statin therapy at least 90 days. Two studies showed that rosuvastatin had the percentage of LDL-C reduction (37% vs 28% for ATV and 27% for SVT) and attaining NCEP ATP III goal higher than atorvastatin and simvastatin (69.7% vs 54.8% for ATV and 51.2% for SVT), but the rate was lower than in clinical trials. Rosuvastatin was more effective than atorvastatin and simvastatin. It has cost less than atorvastatin but greater than generic simvastatin.

Sappasittiprasong Hospital is a 1,000-beds, a regional hospital in North-east of Thailand. There are three statins in the hospital formulary: atorvastatin (official in

2000), simvastatin (official in 2001) and rosuvastatin (official in 2005). Atorvastatin and rosuvastatin are innovative drugs and higher price than simvastatin which is generic drug (50.29 Baht for ATV, 34.71 Baht for RSV and 0.70 Baht for SVT). Statins are prescribed in the highest top ten drug expenditures for several years at Sappasittiprasong hospital. Overall drug expenditures of three statins took about 30 million bath in 2007 and trend to increase in high rate. Simvastatin and atorvastatin are placed in National Essential Drug Lists (NEDL), but in 2008, atorvastatin is released from NEDL, while rosuvastatin is not placed in NEDL. Because of the difference of drug prices, high drug expenditures and debating in effectiveness of statins between clinical trials and usual clinical practices, it is difficult to decide which statins are the most cost-effectiveness to select for hospital formulary. In additionally, the study about comparison in effectiveness between three statins in Thailand was not provided. Therefore, this study is applied to compare the effectiveness of rosuvastatin, atorvastatin, and simvastatin in achieving LDL-C goal according to NCEP ATP III guidelines and reducing serum LDL-C levels among CHD/CHD-risk equivalent patients in usual clinical practice of Sappasittiprasong hospital. Moreover, the economic values among atorvastatin, rosuvastatin and simvastatin therapies in CHD and CHD risk equivalent patients were also assessed.

Objectives:

1. To compare the effectiveness of atorvastatin, rosuvastatin, and simvastatin among CHD and CHD risk equivalent patients in usual clinical practice at Sappasittiprasong Hospital in terms of:

    1.1 The percentage of patients who achieved their LDL-C goal (LDL-C <100 mg/dL) according to NCEP ATP III guidelines.

    1.2 The mean of percent change in LDL-C reduction.

2. To assess economic values among atorvastatin, rosuvastatin and simvastatin therapies in CHD and CHD risk equivalent patients at Sappasittiprasong Hospital.

Hypotheses :

1. The proportion of patients who achieved LDL-C goal according to NCEP ATP III guideline among atorvastatin, rosuvastatin and simvastatin are not different.

$$H_0 : P_{atorvastatin} = P_{rosuvastatin} = P_{simvastatin}$$

$$H_1 : P_{atorvastatin} \neq P_{rosuvastatin} \neq P_{simvastatin}$$

2. The means of percent change in LDL-C reduction among atorvastatin, rosuvastatin, and simvastatin are not different.

$$H_0 : \mu_{atorvastatin} = \mu_{rosuvastatin} = \mu_{simvastatin}$$

$$H_1 : \mu_{atorvastatin} \neq \mu_{rosuvastatin} \neq \mu_{simvastatin}$$

Operational definitions:

1. Patients with CHD defined by NCEP ATP III: Persons who had a history of acute myocardial infarction, evidence of silent myocardial infarction , history of unstable angina and stable angina pectoris, history of coronary angioplasty and coronary artery surgery.

2. Patients with CHD risk equivalents defined by NCEP ATP III: Persons who are peripheral artery disease, abdominal aortic aneurysm, carotid artery disease (such as transient ischemic attack or stroke of carotid origin, or >50% stenosis on angiography or ultrasound), likely other forms of clinical atherosclerotic disease (e.g., renal artery disease), and type II diabetes mellitus.

3. High-risk patients defined by NCEP ATP III: Persons with CHD and CHD risk equivalents.

4. Very high-risk patients defined by NCEP ATP III: Persons with the presence of established CHD plus diabetes mellitus (In this study, the researcher did not evaluate for metabolic syndrome because some data such as blood pressure and abdominal obesity, was not available in electronic database).

5. LDL-C goal according to NCEP ATP III: NCEP ATP III provided evidenced-based treatment guidelines for hypercholesterolemia management based on risk for CHD and LDL-C level baseline before starting therapy. The recommended LDL-C goal for high-risk patients is < 100 mg/dL. If patients are very high-risk, the recommended LDL-C goal < 70 mg/dL is provided.

Expected Benefits:

1. The result of this study will be used for economic assessment of statin therapies in CHD and CHD risk equivalent patients at Sappasittiprasong Hospital.

2. The differences of clinical outcomes among these statins can be used as criteria in drug selection for the Pharmacy and Therapeutic Committee.

CHAPTER II

LITERATURE REVIEW

This study was conducted to compare the effectiveness of atorvastatin, rosuvastatin and simvastatin in terms of LDL-C goal achievement according to NCEP guideline and LDL-C reduction among CHD / CHD risk equivalent patients in usual clinical practice. Therefore, this chapter provided the information based on previous published studies into 3 sections: (1) Hypercholesterolemia management according to NCEP guideline (2) Characteristics of statins (3) Articles related statin therapy.

I. Hypercholesterolemia management

Coronary heart disease (CHD) is one of the major health problems and the leading cause of death worldwide including Thailand.[1,2,3] The CVD mortality rate of Thai people trends to increase in the future. In 2002, the International Collaborative Study of Cardiovascular Disease in Asia (InterAsia) estimated that 4,400,000 Thai people had high serum cholesterol (TC>200mg/dL).[6] Hypercholesterolemia is an important risk factor of CHD. Several epidemiological studies reported that serum total cholesterol levels are continuously correlated with CHD risk over a broad range of cholesterol values. This relationship has been observed in many populations throughout the world. The results from recent trials indicated that in every 1% increased in cholesterol level, there is a 2% increased in the incidence of CHD. [1,5]

Hypercholesterolemia is a condition that elevated serum LDL-C or total cholesterol (TC) levels. Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids and steroid hormones. Cholesterol consists of lipid and proteins (lipoproteins). There are three major classes of lipoproteins, such as low density lipoproteins (LDL-C), high density lipoproteins (HDL-C), and very

low density lipoproteins (VLDL-C). LDL-C typically makes up 60%–70% of the total cholesterol and contains a single apolipoprotein, namely apo B-100 (apo B). LDL-C is the major atherogenic and has long been identified by NCEP as the primary target of cholesterol-lowering therapy. HDL-C normally makes up 20%–30% of the total cholesterol and contains apo A-I and apo A-II. HDL-C levels are inversely correlated with risk for CHD. VLDL is triglyceride-rich lipoprotein, but contains 10%–15% of the total cholesterol. The major apo lipoproteins of VLDL are apo B-100, apo Cs (C-I, C-II, and C-III), and apo E. VLDL remnants will promote atherosclerosis similar to LDL. [5]

LDL-C is routinely estimated from measurements of total cholesterol, total triglycerides and HDL-C in the fasting state. If the triglyceride (TG) level is < 400 mg/dL, the value of LDL-C can calculate from this formula: [5]

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - \text{TG}/5 \quad \text{(all measures in mg/dL)}$$

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) presents the National Cholesterol Education Program (NCEP) updated recommendations for cholesterol testing and management which focuses on the role of the clinical approach to prevention of coronary heart disease (CHD). All ATP reports have identified low-density lipoprotein cholesterol (LDL-C) as the primary target of cholesterol lowering therapy. Many prospective studies have shown that high serum concentrations of LDL-C are a major risk factor for coronary heart disease (CHD). A large number of randomized control trials (RTCs), moreover, have documented that lowering of LDL-C levels will reduce the risk for major coronary events.

NCEP ATP III has recommended that a 12- hour fasting lipids test to classify lipid profiles and risk determination. (see Table 2.1)

Table 2.1 ATP III classification of lipid profiles

LDL Cholesterol (mg/dL)	
<100	Optimal
100–129	Near optimal/ above optimal
130–159	Borderline High
160–189	High
≥ 190	Very High
Total Cholesterol	
< 200	Desirable
200–239	Borderline High
≥ 240	High
Triglycerides	
< 150 mg/dL	Normal
150–199 mg/dL	Borderline-high
200–499 mg/dL	High
≥ 500 mg/dL	Very high
High density lipoprotein cholesterol (HDL-C)	
<40 mg/dL	Low
≥60 mg/dL	High

The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management. *ATP I* outlined a strategy for primary prevention of CHD in persons with high LDL-C (>160 mg/dL) or in those with borderline-high LDL-C (130–159 mg/dL) and multiple (2+) other risk factors. *ATP II* affirmed the importance of this approach and added a new feature: the intensive management of LDL-C in persons with established CHD, lower LDL-C goal of <100 mg/dL. *ATP III* maintains attention to intensive treatment of patients with CHD; its major new feature is a focus on primary prevention in persons with

multiple risk factors. New features of ATP III are : Raises diabetic persons without CHD (most of whom display multiple risk factors) to the risk level of CHD risk equivalent; uses Framingham risk scoring for assessment of 10-year absolute CHD risk to identify certain patients with multiple (2+) risk factors for more intensive treatment; identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes; and raises categorical low HDL cholesterol from <35 mg/dL to <40 mg/dL because the latter is a better measure of a depressed HDL.[5]

ATP III reviewed new data from 5 large RCTs with statins. Five large RCTs are the Heart Protection Study (HPS),[23] the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER),[24] Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial (ALLHAT-LLT),[25] Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA),[26] and the Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 Trial (PROVE-IT).[27]

However, both HPS and PROVE-IT study suggested that additional benefit may be obtained by reducing LDL levels to substantially below 100 mg/dL. Thus several other clinical trials (TNT,[28] IDEAL,[29] and A-to-Z[30] trials) are underway to probe the efficacy of lowering LDL to very low levels.[7] Until these trials are completed, prudence requires that setting an LDL-C goal of < 70 mg/dL for high-risk patients must be left as a therapeutic option on the basis of clinical trial evidence, whereas a goal of < 100 mg/dL can be retained as a strong recommendation. Patients who are considered to reduce LDL-C levels < 70 mg/dL are categorized into very high-risk. The criteria for placing the patients in the very high risk are the presence of established CHD plus (1) multiple major risk factors especially diabetes, (2) severe and poorly controlled risk factors such as continued cigarette smoking, (3) multiple risk factors of the metabolic syndrome such as high

triglycerides > 200 mg/dL plus non-HDL-C > 130 mg/dL with low HDL-C (<40 mg/dL), and (4) patients with acute coronary syndromes. [5, 7]

Thus, ATP III had proposed the updated management of patients with lipid disorders, particularly for high-risk patients. Persons are categorized into 3 risk categories; all summaries are showed in Table 2.2.[5, 7]

(1) *Established CHD and CHD risk equivalents*. CHD risk equivalents include non-coronary forms of clinical atherosclerotic disease, diabetes and multiple (2+) CHD risk factors with 10-year risk for CHD > 20%. All persons in this category can be called *high risk*. The goal for LDL-lowering therapy is an LDL-C level <100 mg/dL but when risk is very high, an LDL-C goal of < 70 mg/dL, is a therapeutic option based on the available clinical trial evidence. When baseline LDL-C is ≥ 130 mg/dL, an LDL-lowering drug should be started simultaneously with dietary therapy. If the baseline LDL-C level is in the range of 100 to 129 mg/dL, ATP III suggested intensive dietary therapy whereas LDL-lowering drug was said to be optional.

(2) *Multiple (2+) risk factors*. ATP III added new patients with multiple (2+) CHD risk factors by counting of risk factors. ATP III recommended that Framingham risk scoring be carried out in individuals with 2+ risk factors so as to triage them into 3 levels of 10-year risk for hard CHD events (myocardial infarction + CHD death) : >20%, 10-20%, and <10%. Persons with a 10-year risk >20% were elevated to the high-risk category; for them, the LDL-C goal is < 100 mg/dL. Persons with 2+ risk factors and a 10-year risk 10%-20% can be called *moderate high- risk*, the LDL-C goal is < 130 mg/dL and LDL- lowering drug therapy should be considered if the LDL-C level is above the goal level. If persons with 10-year risk is < 10% were called *moderate risk*, the LDL-C goal is < 130 mg/dL and LDL-lowering drug can be considered if the LDL-C level is ≥ 160 mg/dL after a trial of dietary therapy.

(3) *Zero to one (0-1) risk factor*. Persons with 0-1 risk factor were called *low risk*; LDL-C management is the same too. If the LDL-C level is ≥ 160 mg/dL, the LDL-C goal is < 160 mg/dL. When LDL-C is ≥ 190 mg/dL and dietary therapy is adequately used, drug should be considered. If serum LDL-C ranges from 160-189 mg/dL, introduction of a cholesterol-lowering drug is a therapeutic option when severe risk factor is present.

Table 2.2 LDL-C goals and cut point for therapeutic lifestyle change and drug therapy. [5,7]

Risk Categories	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 and CHD risk equivalent (10-year risk > 20%)	< 100 (<70 is optional)*	≥ 100	≥ 130 (100-129 is optional)*
Moderate high risk: 10-year risk 10%-20%	< 130 (<100 is optional)	≥ 130	≥ 130 (100-129 is optional)*
Moderate risk: 10-year risk <10%	< 130	≥ 130	≥ 160
Low risk: 0-1 risk	< 160	≥ 160	≥ 190 (160-189 is option)*

Remark : CHD = coronary heart disease, TLC = Therapeutic lifestyle change, LDL-C = Low – density lipoprotein cholesterol

* an update NCEP ATP III

Persons with established CHD as a risk indicator

The previous literature suggested that having coronary disease increase future CHD event risk approximately 7 fold compared with healthy individuals, with an absolute risk of 50%-60% per decade. From the recent secondary prevention trials (CARE,[9] LIPID,[10] 4S,[11] and WOSCOPS[12]) indicated that persons with any clinical evidence of CHD have a risk for recurrent myocardial infarction and CHD death that exceed 20 percent over 10 years. Several clinical patterns constitute a diagnosis of CHD: acute myocardial infarction, evidence of silent myocardial infarction or myocardial ischemia, unstable and stable angina pectoris, and history of coronary procedures (coronary angioplasty and coronary artery surgery).[5]

Persons with CHD risk equivalents

Persons without established CHD who have developed major coronary events, equal to could be considered as persons with CHD. It can be said that they have a CHD risk equivalent. Several groups of persons with CHD risk equivalents are identified: peripheral arterial disease (PAD), carotid artery disease, abdominal aortic aneurysm (AAA), diabetes mellitus (DM), and persons who have an absolute 10-year risk for hard CHD > 20 %.[5]

Peripheral artery disease (PAD) was diagnosed by the ankle/brachial blood pressure index (ABI). If ABI is less than 0.9, an annual event rate for major coronary events is 2.4-3.8 percent per year. In the Multi-center Study of Osteoporosis Fractures, 497 ABI was measured in 1,027 women without CHD. Those with ABI <0.9 had an annual rate for total CHD mortality of 2.9 percent per year. In the San Diego cohort of the Lipid Research Clinic Study, persons with documented PAD (without CHD) had a total CHD mortality of 2 percent per year.[5]

Carotid artery disease, when persons had > 75% carotid stenosis, rates of transient ischemic attacks (TIAs), stroke and CHD events were very high

(8.3%per year for CHD events), and were high even when stenosis was > 50%. These studies show that persons with symptomatic carotid artery disease are at high risk for major coronary events and can be considered CHD risk equivalents.[5]

Abdominal aortic aneurysm (AAA), from the study of Hertzer who reported the incidence of myocardial infarction following AAA resection in 343 persons followed 6-11 years post-operatives, persons without previous CHD events had CHD mortality averaged 1.9 % per year. This study thus supported the concept that AAA is a CHD risk equivalent.[5]

Diabetes mellitus, persons with type 1 or type 2 diabetes are at increased risk for CHD. Most literature relating diabetes to CHD risk considers type 2 diabetes, although cardiovascular complications are important for persons with type 1 as well because of the many differences between the two forms of diabetes. *Type 2 diabetes* is normally characterized by insulin resistance, variable levels of endogenous insulin, and typically by overweight/obesity and the metabolic syndrome. Many evidences supported that persons with type 2 diabetes are as CHD risk equivalent. In a Finnish population-based study indicated that persons with type 2 diabetes without prior CHD have a risk for myocardial infarction as high as persons without diabetes with previous myocardial infarction. Similar, the results from the recent OASIS study, persons with type 2 diabetes without CHD, average age 65, had rates of CHD events equal to that of persons with established CHD. Nonetheless, some studies found that the combined risk factors of age plus diabetes appear to raise absolute risk for CHD to above 20 percent per decade. Normally, persons with type 2 diabetes have a 10-year risk for major coronary events (myocardial infarction and CHD death) over 20%, so persons with type 2 diabetes can be considered as CHD risk equivalent.[5]

Persons with type 1 diabetes are clearly at increased risk for CHD, but no study has specifically examined whether type 1 diabetic subjects have a risk

of CHD as high as age- and sex-matched non-diabetic subjects with pre-existing CHD. Persons with type 1 diabetes often develop diabetes at early age and some persons have a 10-year risk for CHD less than 15-20 percent, thus LDL-lowering therapy depends on clinical judgment. However, the ATP III panel favored starting LDL-lowering drug therapy in persons with type 1 diabetes when LDL-C levels are ≥130 mg/dL. [5]

Persons without clinical atherosclerotic disease and have *a 10-year risk for hard CHD > 20%* are still at high risk because of advanced coronary atherosclerosis. Thus, it's appropriate to employ intensive risk-reduction therapy similar to that used in persons with established CHD. The most reliable method have been used to identify these high-risk persons, is assessment of absolute risk with Framingham risk scoring. Approaches to risk assessment is to count the number of *major independent risk factors* for CHD and then carry out 10-year risk assessment for hard CHD (MI + CHD death) which divided into three categories : *> 20%* (CHD risk equivalent), *10-20%* and *<10%* according to Framingham risk scoring. The major independent risk factors identified in risk factor counting include: [5]

- Cigarette smoking (any cigarette smoking in the past month)
- Hypertension (BP≥ 140/90 mmHg or taking antihypertensive medication)
- Family history of premature CHD (CHD in male 1st- degree relative < 55 years; CHD in female 1st- degree relative < 65 years)
- Low HDL-C (< 40 mg/dL)
- Age (men≥ 45 years; woman ≥ 55 years)

If a person has a high HDL-C (≥ 60 mg/dL), one risk factor is subtracted from the count.

Risk assessment for determining 10-year risk is carried out according to Framingham risk scoring. Risk factor scoring in ATP III derived from an update of Framingham database and methodology reported by Wilson et al, the revised scoring applies specifically to hard CHD. The risk factors in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL-C, systolic blood pressure, treatment for hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor and sum total risk score, then estimate 10-year risk for men or women in listed Table 2 .3 and 2.4.[5]

Table 2.3 Estimate of 10-year Risk for Men (Framingham point scores)

Age (yrs)	Points	Total Cholesterol	Points at ages 20-39	Points at ages 40-49	Points at ages 50-59	Points at ages 60-69	Points at age 70-79
20-34	-9	<160	0	0	0	0	0
35-39	-4	160-199	4	3	2	1	0
40-44	0	200-239	7	5	3	1	0
45-49	3	240-279	9	6	4	2	1
50-54	6	≥280	11	8	5	3	1
55-59	8						
60-64	10		Point at ages 20-39	Points at ages 40-49	Points at ages 50-59	Points at ages 60-69	Points at age 70-79
65-69	11						
70-74	12	Nonsmoker	0	0	0	0	0
75-79	13	Smoker	8	5	3	1	1

HDL-C	Points	Systolic BP	If Untreated	If Treated
≥60	-1	<120	0	0
50-59	0	120-129	0	1
40-49	1	130-139	1	2
<40	2	140-159	1	2
		≥160	2	3

Table 2.3 Estimate of 10-year Risk for Men (Framingham point scores)

(continue)

Point Total	10-year Risk	Point Total	10-year Risk
< 0	<1%	9	5%
0	1%	10	6%
1	1%	11	8%
2	1%	12	10%
3	1%	13	12%
4	1%	14	16%
5	1%	15	20%
6	2%	16	25%
7	3%	≥ 17	≥ 30%
8	4%		

Table 2.4 Estimate of 10-year Risk for Women (Framingham point scores)

Age (yrs)	Points	Total Cholesterol	Points at ages 20-39	Points at ages 40-49	Points at ages 50-59	Points at ages 60-69	Points at age 70-79
20-34	-7	<160	0	0	0	0	0
35-39	-3	160-199	4	3	2	1	1
40-44	0	200-239	8	6	4	2	1
45-49	3	240-279	11	8	5	3	2
50-54	6	≥280	13	10	7	4	2
55-59	8						
60-64	10		Point at ages 20-39	Points at ages 40-49	Points at ages 50-59	Points at ages 60-69	Points at age 70-79
65-69	12						
70-74	14	Nonsmoker	0	0	0	0	0
75-79	16	Smoker	9	7	4	2	1

Table 2.4 Estimate of 10-year Risk for Women (Framingham point scores)

(continue)

HDL-C	Points	Systolic BP	If Untreated	If Treated
≥ 60	-1	< 120	0	0
50-59	0	120-129	1	3
40-49	1	130-139	2	4
< 40	2	140-159	3	5
		≥ 160	4	6

Point Total	10-year Risk	Point Total	10-year Risk
< 9	<1%	17	5%
9	1%	18	6%
10	1%	19	8%
11	1%	20	11%
12	1%	21	14%
13	2%	22	17%
14	2%	23	22%
15	3%	24	27%
16	4%	≥ 25	≥ 30%

II. Characteristics of Statins

Statins known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors which works by blocking an enzyme HMG-CoA reductase that is the rate-limiting step in the hepatic cholesterol synthesis. Therefore, statins increased LDL receptor expression on the hepatocyte surface, increased uptake of LDL-C, decreased circulating LDL-C, decreased triglycerides and also increased HDL-C levels. Statins can reduce LDL-C between 18% and 55%; triglycerides (TG) generally range from 7%–30 %, but will generally rise HDL-C by 5–15 %. All statins have the

same mechanism of action but differ in terms of chemistry, pharmacokinetics, potency, safety, and cost.[2,5,8] The characteristic of the three statins are summarized in Table 5.

Table 2.5 Summary characteristics of three statins [2,5,8]

Characteristics	Atorvastatin	Rosuvastatin	Simvastatin
Chemistry	- synthetic - lipophilic (cross the blood-brain barrier which may lead to central nervous system complain)	- synthetic - hydrophilic (greater hepatoselectivity and less influence on smooth muscle proliferation)	-Semisynthetic (derived from fungi) - lipophilic (cross the blood-brain barrier which may lead to central nervous system complain)
Pharmacokinetics	- food affect to absorption of drug - active hydroxyl acid - metabolized via CYP 3A4 - eliminate in the bile - long t ½	- food don't affect to drug absorption - active hydroxyl acid - not significantly metabolized via CYP 3A4 - eliminate in the feces - long t ½	- food don't affect to drug absorption - prodrug - metabolized via CYP 3A4 - eliminate in the feces - short t ½
Usual starting daily dose	10 mg	10 mg	20 mg
Maximum approved daily dose	80 mg	40 mg	80 mg
Potency : average decrease in LDL-C	10 mg : 38% 20 mg : 46% 40 mg : 51% 80 mg : 54%	5 mg : 43% 10 mg : 50% 20 mg : 53% 40 mg : 62%	10 mg : 28% 20 mg : 35 % 40 mg : 40 % 80 mg : 48%

Table 2.5 Summary characteristics of three statins [2,5,8] (continue)

Characteristics	Atorvastatin	Rosuvastatin	Simvastatin
Renal function Patients	- no dose adjustment	- use low doses for severe renal impairment (Cr Cl < 30 ml/min)	-use low doses for severe renal impairment (reduce initial dose to 5 mg daily)
Drug interactions	Metabolized by CYP 3A4 enzyme system. Monitoring for interaction with drugs that inhibit this enzyme, including erythromycin, clarithromycin, ketoconazole, diltiazem, cyclosporine, etc.	Not significantly metabolized by cytochrome P450. It may be less involved in drug interactions. Use lower doses for patients taking cyclosporine or gemfibrozil because of increasing rosuvastatin levels.	Same as atorvastatin.
Food interactions	No effect. It can administer at any time of day.	No effect. It can administer at any time of day.	It should administer in the evening meal or at bedtime.

Statins are well-tolerated by most patients. Elevated hepatic transaminases generally occur in 0.5–2.0 % of cases and are dose – dependent. [2,5] Statins can produce myopathy which an elevation of creatine kinase is the best indicator of statin-induced myopathy. Clinical significant myopathy are muscle aches, soreness, or weakness and elevated creatine kinase levels, generally greater than 10 times the upper limit of normal. Overall, the incidence of myopathy with elevations in serum

creatine kinase during statin therapy is low and rhabdomyolysis found very rarely. [2,5] Myopathy is mostly occurred in older patients and persons with multiple medication, especially drug-drug interaction involve with the CYP 3A4 such as fibrate, macrolide antibiotics. However all persons started on statins should be instructed to report muscle pain and weakness or brown urine, and a creatine kinase measurement should be done.[2] . All statins are contraindicated in pregnancy (category X).[2]

III. Articles related statin therapy

3.1 Five major clinical trials of statin therapy evaluated clinical end point in reducing risk of CHD and suggested therapeutic options for reducing LDL goals to < 100 mg/dL for high-risk patients according to NCEP ATP III guideline: HPS, PROSPER, ALLHAT-LLT, ASCOT-LLT, and PROVE-IT

The Heart Protection Study (HPS) [23]

The HPS was a randomized, 2 x 2 factorial trial of lipid lowering and antioxidant vitamins, of 20,536 high-risk patients, defined as those who had at least 1 of the following: (1) coronary disease, (2) occlusive disease of the non-coronary arteries, or (3) diabetes mellitus. Subjects were randomized to simvastatin 40 mg or placebo and mean followed up 5 years. Approximately 28% (n = 5806) of the subjects included were composed of persons aged 70 years or older at entry. Regardless of the entry levels of LDL -C below 116 mg/dL or total cholesterol below 193 mg/dL. Patients who took simvastatin resulted in the lowering of LDL-C levels from 116 mg/dL to below 77 mg/dL results in significant reductions in vascular events. Specifically, all-cause mortality was significantly reduced by 12.9% for those assigned simvastatin vs 14.7% for those assigned placebo (P = 0.0003) primarily due to a highly significant 18% reduction in coronary death (5.7% vs 6.9%, respectively; P = 0.0005) and a marginally significant reduction in other

vascular deaths (1.9% vs 2.2%, respectively; P = 0.07). The first-event rates for nonfatal MI or coronary death (8.7% vs 11.8%, P <0.0001), for nonfatal or fatal stroke (4.3% vs 5.7%, P < 0.0001), and for coronary or non-coronary revascularization (9.1% vs 11.7%, P <0.0001) were reduced significantly for those assigned to atorvastatin as compared with placebo.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [24]

PROSPER was a randomized controlled trial of elderly patients (aged 70-82) with either a history of, or risk factors for, CVD and stroke. A total of 5804 patients (2804 men, 3000 women) were randomly assigned to either pravastatin 40 mg daily (n = 2891) or placebo (n = 2913), and followed for a mean of 3.2 years. At 3-month follow-up, LDL-C was 34% low, HDL-C 5% higher, and TG 13% lower in the pravastatin group. At 2-year follow-up, patients who were assigned pravastatin experienced a reduction in LDL-C of 33% (27% in all patients assigned pravastatin). Pravastatin significantly lowered the risk for a primary endpoint (a composite of definite or suspect death from CHD, nonfatal MI, and fatal or nonfatal stroke) by 15% (P = 0.014), and the risk for a secondary endpoint, CHD death, or nonfatal MI by 19% (P = 0.006). Pravastatin also significantly reduced other outcomes, including the risk for all cardiovascular events (including primary endpoint or coronary artery bypass graft, percutaneous tran luminal coronary angioplasty or peripheral arterial surgery, or angioplasty) by 15% (P = 0.012) and risk for death from CHD by 24% (P = 0.043).

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial (ALLHAT-LLT) [25]

ALLHAT-LLT was a multicenter, randomized, nonblinded trial conducted from 1994 through 2002 in a subset of 10,355 patients, aged 55 years and older with LDL cholesterol of 120-189 mg/dL (100-129 mg/dL if known CHD),

from ALLHAT. Patients were randomized to receive pravastatin 40 mg or usual care, and were followed for 8 years (mean follow-up, 4.8 years). With respect to these older patients with well-controlled hypertension and moderately elevated LDL cholesterol, all-cause mortality, the primary outcome, or CHD, a secondary outcome, were not reduced significantly by pravastatin when compared with usual care. Specifically, all-cause mortality was similar for the 2 groups: 14.9% for the pravastatin group as compared with 15.3% for the usual care group (P = 0.88). Additionally, CHD event rates were 9.3% and 10.4%, respectively (P = 0.16).

Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) [26]

ASCOT was a randomized, double-blind, placebo-controlled, 2 x 2 factorial primary prevention trial of blood pressure lowering and lipid lowering. 19,342 hypertensive patients (aged 40-70 years with at least 3 other cardiovascular risk factors) were randomized to 1 of 2 antihypertensive regimens. A total of 10,297 European patients with non-fasting total cholesterol concentrations of < 250 mg/dL or less were randomly assigned to receive 10 mg of atorvastatin. Atorvastatin reduced LDL-C by 35% and TC by 24% after 1 year of follow-up. ASCOT-LLT was terminated early after about 3 years by the independent Data and Safety Monitoring Board (DSMB) due to the emergence of a statistically extreme 36% reduction in the primary outcome of CHD events (P = 0.0005). At that time, there was also a statistically significant 27% reduction in the secondary outcome of fatal and nonfatal stroke (P =0.0236); a statistically significant 21% reduction in total cardiovascular events, including revascularization procedures (P = 0.0005); and a statistically extreme 29% reduction in total coronary events (P = 0.0005).

The Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 Trial (PROVE-IT) [27]

The PROVE-IT trial randomized 4162 post acute coronary syndrome patients to atorvastatin 80 mg or pravastatin 40 mg with a mean follow-up of 2 years. Patients randomized to high-dose atorvastatin achieved an average LDL-C of 62 mg/dL, and those assigned pravastatin achieved an average LDL –C of 95 mg/L ($P < 0.001$). In regard to the secondary endpoint, those who were assigned high-dose atorvastatin had significant reductions in subsequent CHD events, including a 25% reduction in death due to CHD, MI, or revascularization ($P < 0.001$), as compared with those who were assigned to standard-dose pravastatin who experienced a 14% reduction in these events ($P = 0.029$). In regard to the individual components of the primary endpoint, high-dose atorvastatin was more beneficial than standard-dose pravastatin. Specifically, there was a 14% decrease in the need for revascularization ($P =0.04$) and a 29% decrease in the risk for recurrent unstable angina ($P = 0.02$), with possible but nonsignificant reductions in rates of death from any cause or MI.

3.2 Three studies concerning intensive Statin Therapy supported that high-dose statins are more effective than standard dose statins for reducing cardiovascular events which implicate to intensive statin therapy for very high-risk patients(LDL-C target < 70 mg/dL) : TNT, IDEAL and A to Z.

Treating to New Targets (TNT) [28]

TNT was conducted to assess the efficacy and safety of lowering LDL-C levels below 100 mg/dL in 10,001 patients with stable CHD and had LDL - C levels of less than 130 mg/dL, were randomly assigned to double-blind therapy and received either 10 mg or 80 mg of atorvastatin per day. Patients were followed for a median of 4.9 years. The primary end point was the occurrence of a first major

cardiovascular event, defined as death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. The mean LDL-C levels were 77 mg/dL during treatment with 80 mg of atorvastatin and 101 mg/dL during treatment with 10 mg of atorvastatin. The incidence of persistent elevations in liver aminotransferase levels was 0.2 %in the group given 10 mg of atorvastatin and 1.2% in the group given 80 mg of atorvastatin (P<0.001). A primary event occurred in 434 patients (8.7%) receiving 80 mg of atorvastatin, as compared with 548 patients (10.9%) receiving 10 mg of atorvastatin, representing an absolute reduction in the rate of major cardiovascular events of 2.2% and a 22 % relative reduction in risk (hazard ratio, 0.78; 95% CI, 0.69-0.89; P<0.001). There was no difference between the two treatment groups in overall mortality.

Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) [29]

IDEAL trial was conducted to compare the effects of 2 strategies of lipid lowering on the risk of cardiovascular disease among patients with a previous myocardial infarction (MI). The study design was a prospective, randomized, open-label, blinded end-point evaluation trial conducted at 190 ambulatory cardiology care and specialist practices in northern Europe between March 1999 and March 2005 with a median follow-up of 4.8 years, which enrolled 8888 patients aged 80 years or younger with a history of acute MI. Patients were randomly assigned to receive a high dose of atorvastatin (80 mg/d; n=4439), or usual-dose simvastatin (20 mg/d; n=4449). Main outcome measurement was occurrence of a major coronary event, defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation. The mean LDL-C levels were 104 mg/dL in the simvastatin group and 81 mg/dL in the atorvastatin group. A major coronary event occurred in 463 simvastatin patients (10.4%) and in 411 atorvastatin patients (9.3%) (Hazard ratio [HR], 0.89; 95% CI, 0.78-1.01; P=0.07). Nonfatal acute MI occurred in 321

(7.2%) and 267 (6.0%) in the 2 groups (HR, 0.83; 95% CI, 0.71-0.98; P = 0.02), but no differences were seen in the 2 other components of the primary end point. Major cardiovascular events occurred in 608 and 533 in the 2 groups, respectively (HR, 0.87;95% CI, 0.77-0.98; P=0.02). Occurrence of any coronary event was reported in 1059 simvastatin and 898 atorvastatin patients (HR, 0.84; 95% CI, 0.76-0.91; P=0.001). Noncardiovascular death occurred in 156 (3.5%) and 143 (3.2%) in the 2 groups (HR, 0.92; 95% CI, 0.73-1.15; P= 0.47). Death from any cause occurred in 374 (8.4%) in the simvastatin group and 366 (8.2%) in the atorvastatin group (HR, 0.98; 95% CI, 0.85-1.13;P=0.81). Patients in the atorvastatin group had higher rates of drug discontinuation due to nonserious adverse events; transaminase elevation resulted in 43 (1.0%) vs 5 (0.1%) withdrawals (P=0.001). Serious myopathy and rhabdomyolysis were rare in both groups.

Aggreastat to Zocor (A to Z) [30]

A to Z trials was assigned to compare early initiation of an intensive statin regimen with delayed initiation of a less intensive regimen in patients with ACS. The study design was randomized, double-blind trial. Patients were randomized into 2 arms, one received 40 mg/d of simvastatin for 1 month followed by 80 mg/d(n = 2265) and another received placebo for 4 months followed by 20 mg/d of simvastatin (n = 2232), studied between December 29, 1999, and January 6, 2003. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke. Follow-up was for at least 6 months and up to 24 months. The median LDL-C level achieved while taking placebo was 122 mg/dL at 1 month and was 77 mg/dL at 8 months while taking 20 mg/d of simvastatin. Among the patients in the simvastatin only group, the median LDL-C level achieved at 1 month while taking 40 mg/d of simvastatin was 68 mg/dL and was 63 mg/dL at 8 months while taking 80 mg/d of simvastatin. A total of 343 patients (16.7%) in the placebo plus simvastatin group experienced the

primary end point compared with 309 (14.4%) in the simvastatin only group (40 mg/80 mg) (hazard ratio, 0.89; 95% CI 0.76-1.04; $P = 0.14$). Cardiovascular death occurred in 109 (5.4%) and 83 (4.1%) patients in the 2 groups (HR, 0.75; 95% CI, 0.57-1.00; $P = 0.05$) but no differences were observed in other individual components of the primary end point. No difference was evident during the first 4 months between the groups for the primary end point (HR, 1.01; 95% CI, 0.83-1.25; $P = 0.89$), but from 4 months through the end of the study the primary end point was significantly reduced in the simvastatin only group (HR, 0.75; 95% CI, 0.60-0.95; $P = 0.02$).

3.3 Three studies compared the achievement of LDL-C goal and LDL-C reduction among statins in clinical trials. The design of three studies was a randomized, open-label, parallel-group and multi-center trial. Three studies were the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin, 2003 (STELLAR), the Direct Statin Comparison of LDL-C Values; an Evaluation of Rosuvastatin therapy, 2006 (DISCOVERY), and the Satisfying Optimal LDL-C ATP III goals with Rosuvastatin, 2007 (SOLAR). The results from these trials showed that rosuvastatin is greater in LDL-C reduction and achievement of LDL-C goal < 100 mg/dL than atorvastatin and simvastatin. *All summary see in Table 2.6.*

Table 2.6 Summary of three studies in clinical trials for comparisons of the effectiveness of statin therapy.

Details	STELLAR[14]	DISCOVERY[15]	SOLAR[16]
Design	- randomized, open-label - multi-center, parallel-group	- randomized, open-label -multi-center, parallel-group	- randomized, open-label - multi-center
Population	- Adults with hypercholesterolemia. -LDL baseline 160-250 mg/dL, TG < 400 mg/dL	- High risk with hypercholesterolemia. - aged ≥ 18 yrs. - LDL baseline ≥ 3.5 mmol/L (130 mg/dL), TG < 4.52 mmol/L (400 mg/dL)	-High risk of CHD - aged ≥ 18 yrs. - LDL baseline 130-250 mg/dL, TG < 400 mg/dL
Sample size	2268	1760	1494
Drugs	-ATV10,20, 40 and 80 mg per day -RSV10,20,40 and 80 mg per day - SVT 10,20,40 and 80 mg per day (across doses)	- ATV 10 mg / day - RSV 10 mg/day - SVT 20 mg/day (fixed dose)	- ATV 10 mg/ day - RSV 10 mg/day - SVT 20 mg/day (double doses if not achieved goals)
Duration of statin therapy	6 weeks	12 weeks	6 weeks and titrated to double if not achieved goals for 6 weeks

Table 2.6 Summary of three studies in clinical trials for comparisons of the effectiveness of statin therapy. (continue)

Details	STELLAR[14]	DISCOVERY[15]	SOLAR[16]
Results	Subgroup in high-risk of CHD= 665 patients Achieving LDL-C goal: - 58% in RSV 10 mg - 29% in ATV 10 mg, -14%SVT 20mg (P<0.002) Reduction LDL-C level: - 46% in RSV 10 mg, - 37% in ATV10 mg, - 35%in SVT 20 mg (P<0.002)	Achieving LDL-C goal : -76% in RSV , - 55% in ATV, - 50% in SVT (P<0.001) Reduction LDL-C level : - 50% in RSV, - 42% in ATV, - 40% in SVT (P<0.001)	Achieving LDL-C goal <u>at 6 weeks</u> : - 66% in RSV , - 41% in ATV , - 39% in SVT (P<0.001) <u>at 12 weeks</u> : - 76% in RSV, - 58% in ATV - 53 % in SVT (P<0.001) Reduction LDL-C level <u>at 6 weeks</u> : - 45% in RSV, - 36% in ATV, - 34% in SVT (P<0.002) <u>at 12 weeks</u> : - 48% in RSV, - 41% in ATV - 40% in STV (P<0.001)

3.4 Studies in usual clinical practice concerning NCEP goals achievement. The results from three studies in usual clinical practice debate to clinical trials. The results reported that the patients taking statins achieved NCEP goals less than in clinical trial with in the range of 30% - 38%.

In 1997, Pearson TA, Laurora I, Chu H, and Kafonek S determine the percentage of patients in the multi-center Lipid Treatment Assessment Project (L-TAP) receiving lipid-lowering therapy who are achieving LDL-C goals with 4,888 adult dyslipidemic patients, who had been receiving the same lipid-lowering therapy for at least 3 months. Lipid levels were determined once in each patient at the time of enrollment. The primary end point was the success rate, defined as the proportion of patients who achieved their LDL-C target level as specified by NCEP guidelines. The results found that Overall, only 38% of patients achieved NCEP-specified LDL-C target levels; success rates were 68% among low-risk patients, 37% among high-risk patents, and 18% among patients with CHD. However, many patients treated with lipid-lowering drugs did not achieve LDL-C target levels. [17]

In Singapore, Ho KT, Chin KW, NG KS, Alemao E, Rajagopalan S, and Yin D. (2006), conducted the Achievement in Singapore of Cholesterol Targets (A-SACT) study to determine the proportion of patients with CHD who achieved LDL-C goal and factors influencing goal attainment by using records from the Singapore Cardiac Databank, found that approximately 70% did not achieve serum LDL-C target of < 100 mg/dL and majority (94%) of patients at very high risk did not achieve serum LDL-C target of < 70 mg/dL. Patients receiving higher potency statins were significantly more likely to achieve LDL-C goals, whereas those with higher baseline LDL-C levels or Malaysian ethnicity were less to achieve LDL-C goals. Efforts to enhance medication adherence, well tolerated therapies such as using high-equipotency or high-dose statins and dose titration will help to improve achievement LDL-C goals. [18]

Goettsch WG, Yin DD, Alemao E, Klungel OH, Stanlenhoef AF and Herings RMC (REALITY-PHARMO study) studied the use and effectiveness of lipid-lowering drugs with respect to lowering of cholesterol levels in routine daily practice with 20,392 hypercholesterolemia patients by retrospective population based cohort study from computer data found that only about 30.2% of all treated patients achieved goal after one year and the percentage of patients achieving guideline recommended goal is low in real-life even in patients treated with high dose statins.[19]

3.5 Two studies in usual clinical practice compared the effectiveness of rosuvastatin, atorvastatin and simvastatin in reducing LDL-C levels and achieving LDL-C goals according to NCEP ATP III by reviewing medical records or using electronic medical database. *The results were the similar as in clinical trials.*

Table 2.7 Summary of two studies in usual clinical practice for comparisons of the effectiveness of statin therapy.

Details	Ohsfeldt and et al (2006) [21]	Fox and et al (2007) [22]
Design	retrospective study	retrospective cohort study
Setting	-Routine clinical practice in the Midwest of USA - use patient medical record	- use General Electric Medical System (GEMS) electronic medical records database of patients treated in physician practices
Objectives	estimate the effectiveness and cost-effectiveness of RSV compared with ATV and SVT among high-risk group	Compare effectiveness of RSV with other statins among patients aged ≥65 yrs and patients aged < 65 yrs.

Table 2.7 Summary of two studies in usual clinical practice for comparisons of the effectiveness of statin therapy. (continue)

Details	Ohsfeldt and et al (2006) [21]	Fox and et al (2007) [22]
Population	- aged 18-79 years with CHD or CHD risk equivalent patients. - newly statin therapy. - no dyslipidemic drugs prior 6 month. - no switch to other statins. - baseline lipid 90 days before start statins and final lipid 4 weeks after start statins.	- aged ≥65 yrs and < 65 yrs - newly statin therapy. - no dyslipidemic drugs prior 12 months. - no switch to other statin. - baseline lipid 90 days before start statins and final lipid > 30 days after start statins.
Duration of statin therapy	18 months	≥ 90 days
Sample size	775 patients - 63 taking RSV - 480 taking ATV - 232 taking SVT	Patients aged≥65 yrs: n=5,958 - 235 taking RSV, 3195 taking ATV, and 1432 taking SVT Patients aged < 65 yrs. : n= 5326 - 353 taking RSV, 3340 taking ATV, and 944 taking SVT
Results	*Achievement LDL-C goal*: 69.7% for RSV, 54.8% for ATV, and 51.2% for SVT, P<0.05 *Reduction in LDL-C level* : - 41.3% for RSV, 28.1% for ATV, and 25.4% for SVT, P<0.05	Patients aged≥65 yrs: *Achievement LDL-C goal*: 76.0% for RSV, 73.0% for ATV, and 64.1% for SVT, P<0.05 *Reduction in LDL-C level*: - 24.3% for RSV, 17.5% for ATV, and 14.8% for SVT, P<0.05

Table 2.7 Summary of two studies in usual clinical practice for comparisons of the effectiveness of statin therapy. (continue)

Details	Ohsfeldt and et al (2006) [21]	Fox and et al (2007) [22]
Results		Patients aged < 65 yrs: *Achievement LDL-C goal* :78.4% for RSV, 71.5% for ATV, and 66.9% for SVT, P<0.05 *Reduction in LDL-C level*: - 28.5% for RSV, 21.3% for ATV, and 18.4% for SVT, P<0.05

CHAPTER III

METHODOLOGY

This chapter has 2 sections. The first section describes study population, including inclusion criteria, exclusion criteria, and sample size. The second section describes methods, including study design, data collection, conceptual framework, outcome measurement, statistical analysis, ethical licenses, and limitation of study.

I. Study Population:

Study population were patients who firstly prescribed atorvastatin, rosuvastatin, or simvastatin during October 2004 to September 2007, had no prior use of dyslipidaemic medications (bile acid sequestrants, fibrate, nicotinic acid, ezetimibe or statins) within the 6 months before starting statin therapy, and met the following criteria.

1.1 *Inclusion criteria:*

1. Patients aged 35 years or older. (We include the patients aged 35 or older because CHD is generally rare in younger adults). [5]
2. Patients who were diagnosed CHD or CHD risk equivalents according to NCEP ATP III guidelines.
3. Patients who had serum LDL-C level at baseline > 100 mg/dL.

1.2 *Exclusion criteria:*

1. Patients who were switched to another statins or received other dyslipidemic medications (bile acid sequestrants, fibrate, nicotinic acid and ezetimibe) after using statins. However, the titration of the statins dosage is permitted, if LDL-C level target did not achieve.
2. Patients who discontinued statin therapy.

3. Patients who didn't have the final lipid measurement.

1.3 *Sample size:* The study included all patients who met the inclusion and exclusion criteria in this study. Each group must not be less than 100 patients.

II. Methods

2.1 *Study Design*: Cross-sectional retrospective study was designed for this study by using data from electronic database (Hom C system) of Sappasittiprasong hospital during April 2004 to April 2008.

2.2 *Data collection:*

The patient's data were extracted from electronic database of medical record, pharmacy, and Laboratory unit into excel file before analysis. The procedures started from:

1. For Pharmacy database: Drug Codes were utilized to identify use of dyslipidemia medications. Pharmacy dispensing data were used to estimate the first dispensed prescription for considering the starting date of statin therapy, statin types, co-administrated drugs, dosage, frequency, quantity, date of received drugs, age of patients, sex, and medical benefit schemes. All dispensing data will be captured both outpatient and inpatient.

2. For medical record database: CHD and its risk equivalents were defined by *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) codes for diabetes mellitus(E10-E11), ischemic heart disease (I25.1, I25.2, I25.4, I25.9), myocardial infarction(I21.0, I21.1, I21.4, I21.9), angina pectoris(I20.0, I20.9), abdominal aortic aneurysm(I71.4), peripheral vascular disease (I73.9), carotid stenosis (I65.2), and cerebral infarction (I63.9, I64). Additionally, ICD-9 codes were used for (PTCA nos) single percutaneous transluminal coronary angioplasty(36.01), (Coronary Atherectomy) Multiple PTCA

(36.05), insert of coronary artery stents (36.06), insertion of drug-eluting coronary artery stents (36.07), and coronary arteriography using two catheters (88.56). Identification number (HN and AN), sex, age, and medical benefit scheme of the patients were also used to extract the data related to diseases.

3. For laboratory database, lipid results and test dates obtained from clinical laboratory database for total cholesterol (TC), LDL-C, HDL-C, and triglyceride (TG). The patients must have at least one complete lipid panel result before and after initiating statin therapy. The LDL-C baseline was defined as the lipid value closest to the start date of statin therapy (up to 90 days before). If lipid panel results were not available within 3 months before initiating statin therapy, the patient was excluded from the study. The final lipid value was defined as the lipid measures obtained closest the end of the study period while the patient was still taking the same statin as at the start of treatment. The final lipid value had to be obtained at least 30 days after initiating statin therapy and not more than 90 days after the end of study. The patients who didn't have the final lipid value after starting statin therapy over 6 months were excluded from the study.

4. Duration of statin therapy was limited at least 3 months after initiating statin therapy. The patients were required to have a minimum of 3-month supply of statin therapy because previous evidence showed that statins produced outcome achievement goals in high rate within 12 weeks after starting statins. (DISCOVERY-UK, and SOLAR trial) Additionally, high-risk patients would have highest benefit from lipid-lowering therapy when LDL-C goal achievement met in the short period.

5. The patients who discontinued statin therapy will be defined as the lack of a prescription or refill order within 15 days after the period of the prescription supply. For example, if the patient was ordered a 60-day statin prescription, the patient have to refill within 75 days of the initial prescription to consider that the patient still persistent on the statin therapy. If patient was titrated dose of statin, the last dose was computed for statin daily dose.

6. The outcome measures were computed for each individual statin. Change in total cholesterol. HDL-C and triglycerides were also computed.

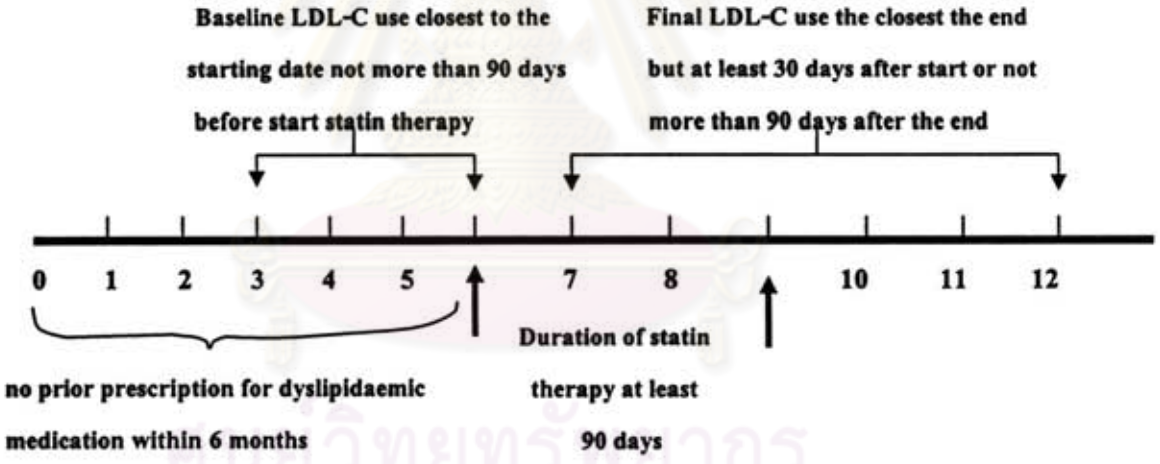

Figure 1. The diagram of data collection for LDL-C values and time of statin therapy

2.3 *Conceptual Framework:*

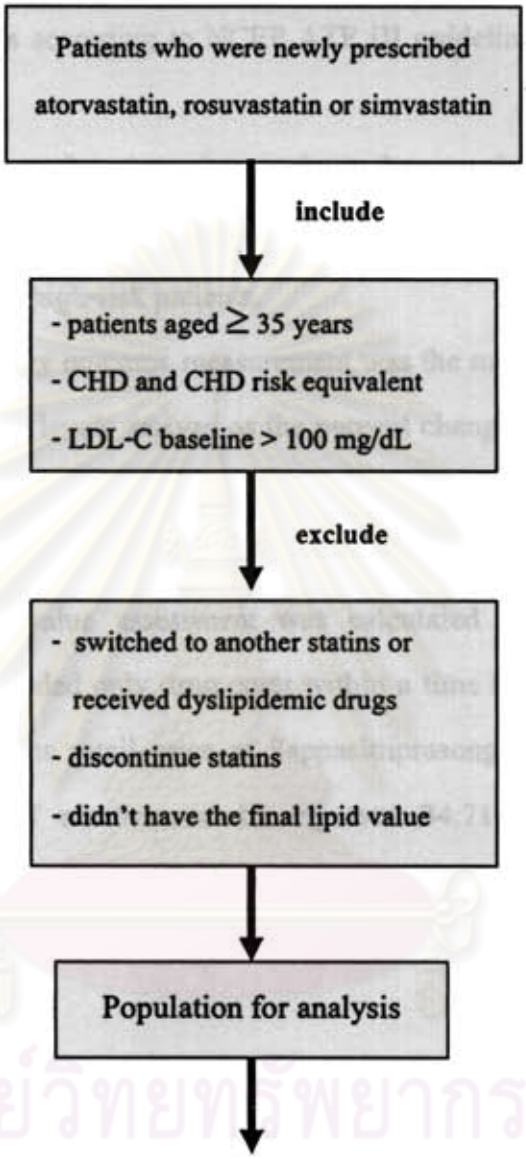

Figure 2. The diagram of study population.

2.4 *Outcome measurement:*

Main outcome measurement was the proportion of patients who achieved LDL-C goals according to NCEP ATP III guideline (final serum LDL-C levels <100 mg/dL).

However, the researcher performed an exploratory analysis of the proportion of patients who reached the recommended optional LDL-C goal of less than 70 mg/dL for very high-risk patients.

Secondary outcome measurement was the mean of percent change in reducing serum LDL-C levels derived as the percent change in serum LDL-C level of patients taking studied statins from baseline to final lipid panel results in each patient.

An economic value assessment was calculated based on the provider perspective. Costs included only drug costs within a time horizon of 1 year. Drug costs were based on the retail price at Sappasittiprasong Hospital in 2007. The branded drug price of rosuvastatin 10 mg was 34.71 Baht; 50.29 Baht for atorvastatin 20 mg; and 0.70 Baht for simvastatin 20 mg in generic drug. Incremental cost-effectiveness ratio per patient at goal was computed from this formula:

$$\text{Incremental cost-effectiveness ratio per patients at goal} = \frac{\text{[Cost of statin A – Cost of statin B] X 100}}{\text{\% patients at goal of statin A - \% patients at goal of statin B}}$$

In additionally, incremental cost-effectiveness ratio per unit of LDL-C reduction was computed from this formula:

$$\text{Incremental cost-effectiveness ratio of 1\% LDL-C reduction} = \frac{\text{[Cost of statin A – Cost of statin B]}}{\text{\% LDL-C reduction of statin A - \% LDL-C reduction of statin B}}$$

2.5 *Statistical Analysis:*

1. Descriptive statistics were used to report population characteristics. Frequencies and percentages were reported for categorical variables, and continuous variables were reported as means and their standard deviations.

To compare the difference of patient characteristics between statin groups, one-way ANOVA was used for continuous variables and Chi-square test was used for categorical variables.

2. Differences in the proportion of patients with LDL-C goal achievement for patients receiving atorvastatin, rosuvastatin, and simvastatin was analyzed by using Chi-square test.

3. Differences in the mean percent change of the patients with lowering LDL-C level for patients receiving atorvastatin, rosuvastatin, and simvastatin were analyzed by using ANOVA and Post Hoc test for multiple comparisons among statin therapies.

4. Statistical analyses were performed by using SSPS version 14.0.

2.6 *Ethical Licenses:*

The proposal was approved the process by the Faculty Committee and was approved by the Sappasittiprasong Hospital Ethics Committee again before starting the study.

2.7 *Limitations of the study:*

Because of using retrospective data from electronic computer, some data can not retrieve such as blood pressure, family history of patients, and smoking history. Thus, the risk assessment for determining 10-year risk according to Framingham risk scoring was not evaluated. Patients with cardiovascular risk were only provided by ICD-10 and ICD-9.

The discontinuation of statin therapy and receiving co-dyslipidemic drugs or switching to another statins was assessed from pharmacy dispensing data only. Therefore, patients received statins from other hospitals or medical clinic were not detected in this study.

CHAPTER IV

RESULTS

The purposes of the study were to compare the effectiveness of atorvastatin, rosuvastatin and simvastatin among CHD and CHD-risk equivalent in usual clinical practice of Sappasittiprasong Hospital in terms of: LDL-C goal achievement according to NCEP ATP III guideline, LDL-C reduction, and to conduct economic assessment. This chapter has 4 parts including (1) Patient characteristics (2) Achievement of LDL-C goals (3) Change in Lipid parameters and (4) Economic value assessment.

I. Patient characteristics:

From electronic medical records database (Hom C system) of Sappasittiprasong hospital, 15,033 patients who firstly prescribed statins were identified including 11,948 taking simvastatin, 1,581 taking atorvastatin and 1,504 taking rosuvastatin. These patients were selected based on the inclusion criteria (aged $\geq$ 35 years, CHD/ CHD risk equivalent and baseline LDL-C > 100 mg/dL): 4,715 taking simvastatin, 307 taking atorvastatin and 312 taking rosuvastatin. The patients were excluded because of switching to another statins or received other dyslipidemic medication, discontinuing statins therapy and didn't have final lipid test, so the number of patients selected into this study were 1,024 patients: 794 taking simvastatin, 109 taking atorvastatin and 121 taking rosuvastatin. (see figure 3.)

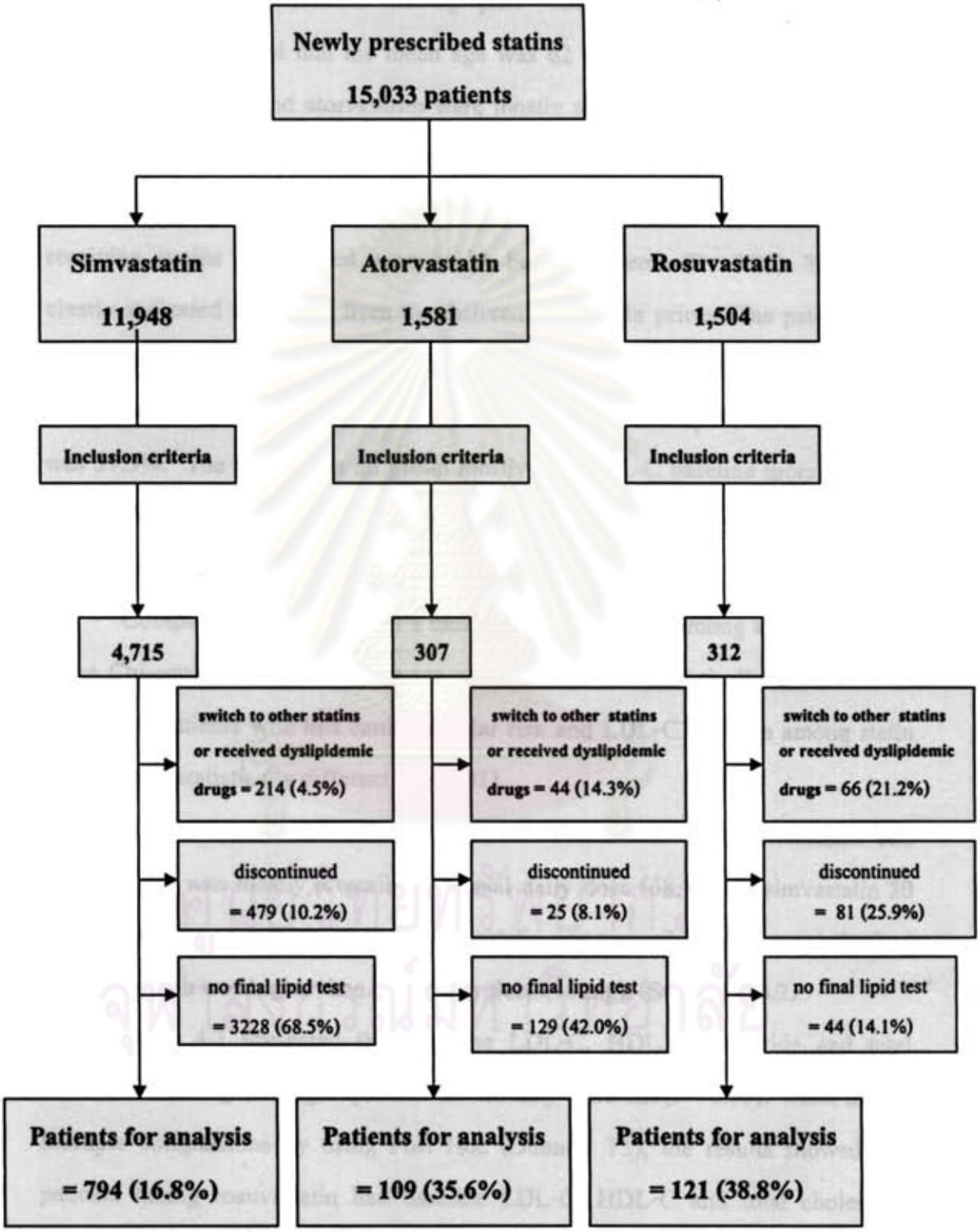

Figure 3. Patients flow diagram

Table 4.1 presented demographic data of the patients. Patient's characteristics showed that the mean age was 62 ± 10.5 years and 47.9 % were male. Rosuvastatin and atorvastatin were mostly prescribed for out of pocket and Civil Service Medical Benefit Scheme (CSMBS) patients, while simvastatin was mostly prescribed for Universal Coverage (UC) scheme patients. The differences of receiving statins were based upon health benefit scheme ($P < 0.05$). This result clearly indicated the effect from the difference of statin prices. The patients with CHD–risk equivalent were more likely to be in every statins group (60.2%) and 10.6 % were very high-risk patients. The percentage of diabetes patients in all groups was 57.3%. The patients in all group mostly had LDL-C baseline more than 130 mg/dL. Patients taking atorvastatin and rosuvastatin had LDL-C baseline higher than simvastatin which most of them were more than 160 mg/dL.

Comparisons of the patient's baseline characteristics among statin groups by using Chi-square test showed that sex and age were not statistically different ($P > 0.05$). But patients who had cardiovascular risk and LDL-C baseline among statin groups were statistically different ($P < 0.01$).

The mean of statin daily dose was 17.7± 7.6 mg. Simvastatin and Rosuvastatin was mostly prescribed at usual daily dose (68.1% for simvastatin 20 mg, 85.1% for rosuvastatin 10 mg). Atorvastatin was prescribed in 20 mg daily dose (50.5%) which was higher than usual daily dose (10 mg). (See Table 4.2)

Table 4.3 presented that baseline LDL-C, HDL, triglyceride and total cholesterol among statin groups were statistically different ($P < 0.05$). When testing multiple comparisons by using Post Hoc (Dunnett T3), the results showed that patients taking rosuvastatin had baseline LDL-C, HDL-C and total cholesterol higher than patients taking simvastatin ($P<0.05$), while other comparisons were not ($P>0.05$). However, patients taking rosuvastatin had baseline triglyceride higher

baseline triglyceride between atorvastatin and simvastatin was not statistically significant. (see Table 4.4)

Table 4.1 Demographic of patient characteristics compared among statin groups

Characteristics	Simvastatin (N = 794)	Atorvastatin (N = 109)	Rosuvastatin (N= 121)	Total (N= 1,024)	P value
Sex : male	366 (46.1%)	63 (57.8%)	61 (50.4%)	490 (47.9%)	0.060
female	428 (53.9%)	46 (42.2%)	60 (49.6%)	534 (52.1%)	
Age : 35 - 50 years	126 (15.9%)	13 (11.9%)	15 (12.4%)	154 (15.0%)	0.643
51 - 65 years	383 (48.2%)	53 (48.6%)	64 (52.9%)	500 (48.8%)	
> 65 years	285 (35.9%)	43 (39.4%)	42 (34.7%)	370 (36.1%)	
Mean ± SD (years)	61.9±10.6	63.1 ±10.6	61.4 ± 10.0	62 ± 10.5	0.456
Health benefit scheme#:					
- Out of pocket and CSMBS [a]	276 (34.8%)	99 (90.8%)	120 (99.2%)	495 (48.3%)	0.000*
- SSS [b]	14 (1.8%)	3 (2.8%)	0 (0%)	17 (1.7%)	
- UC [c]	504 (63.4%)	7 (6.4%)	1 (0.8%)	512 (50.0%)	
Cardiovascular risk:					
- High risk patients					
: *CHD patients*	237 (29.8%)	41 (37.6%)	21 (17.4%)	299 (29.2%)	0.001*
: CHD risk equivalent	466 (58.7%)	57 (52.3%)	93 (76.9%)	616 (60.2%)	
- Diabetes mellitus (DM)	354 (44.6%)	46 (42.2%)	78 (64.5%)	478 (46.7%)	
- Others	112 (14.1%)	11 (10.1%)	15 (12.4%)	138 (13.5%)	
- Very high risk patients (CHD + DM)	91 (11.5%)	11 (10.1%)	7 (5.8%)	109 (10.6%)	
LDL-C baseline groups:					
- < 130 mg/dL	217 (27.3%)	15 (13.8%)	26 (21.5%)	258 (25.2%)	0.006*
- 130 – 160 mg/dL	292 (36.8%)	43 (39.4%)	38 (31.4%)	373 (36.4%)	
- > 160 mg/dL	285 (35.9%)	51 (46.8%)	57 (47.1%)	393 (38.4%)	

Remark: * Significant at P < 0.05 # using Fisher's extract test

a = CSMBS means Civil Service Medical Benefit Scheme. b = SSS means Social Service Scheme

c = UC means Universal Coverage scheme

Table 4.2 Comparisons of statin daily dose among statin groups.

Statin daily doses	Simvastatin (N = 794)	Atorvastatin (N = 109)	Rosuvastatin (N= 121)	Total (N= 1,024)
Mean ± SD (mg)	19.0±7.4	17.0±7.8	10.0±2.6	17.7±7.6
Range (mg)	(10, 60)	(10, 40)	(5, 20)	(5, 60)
No. of patients (%)				
- 5 mg	0 (0.0%)	0 (0.0%)	12 (9.9%)	12 (1.2%)
- 10 mg	194 (24.4%)	47 (43.1%)	103 (85.1%)	344 (33.6%)
- 15 mg	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.1%)
- 20 mg	541 (68.1%)	55 (50.5%)	5 (4.1%)	601 (58.7%)
- 30 mg	7 (0.9%)	0 (0.0%)	0 (0.0%)	7 (0.7%)
- 40 mg	49 (6.2%)	7 (6.4%)	0 (0.0%)	56 (5.5%)
- 60 mg	3 (0.4%)	0 (0.0%)	0 (0.0%)	3 (0.3%)

Table 4.3 Comparisons of baseline Lipid parameters among statin groups.

Baseline lipid parameters	Mean ± SD (range) Simvastatin (N = 794)	Atorvastatin (N = 109)	Rosuvastatin (N= 121)	Total (N= 1,024)	P value
LDL-C (mg/dL)	153.7 ± 34.4 (100.8, 328)	162.5 ± 36.2 (103, 300)	167.3 ± 45.7 (106, 363)	156.2 ± 36.4 (100.8, 363)	0.001*
HDL-C (mg/dL)	38.0 ± 9.8 (13, 88)	39.8 ± 12.6 (14, 98)	40.7 ± 11.1 (20,89)	38.5 ± 10.3 (13, 98)	0.023*
Triglyceride (mg/dL)	159.0 ± 72.1 (44, 469)	156.9 ± 74.3 (43, 493)	184.1 ± 92.2 (46, 501)	161.8 ± 75.4 (43, 501)	0.016*
Total cholesterol (mg/dL)	224.7 ± 40.5 (142, 425)	234.8 ± 47.0 (117.6, 448)	244.6 ± 52.0 (159, 433)	228.1 ± 43.2 (117.6, 448)	0.000*

Remark : using one-way ANOVA to compare the mean of patients between statin groups.

* Significant at $P < 0.05$

Table 4.4 Multiple comparisons of baseline lipid parameters among statin groups.

Lipid parameters	Statin comparisons	Mean difference (mg/dL)	95 % CI	P value
LDL-C	Rosuvastatin vs Atorvastatin	4.8	-8.2, 17.8	0.758
	Rosuvastatin vs Simvastatin	13.6	3.1, 24.0	0.006*
	Atorvastatin vs Simvastatin	8.8	-0.1,17.7	0.052
HDL-C	Rosuvastatin vs Atorvastatin	0.9	-2.9, 4.7	0.918
	Rosuvastatin vs Simvastatin	2.7	-0.1, 5.3	0.039*
	Atorvastatin vs Simvastatin	1.8	-1.3, 4.8	0.408
Triglycerides	Rosuvastatin vs Atorvastatin	27.2	-0.7, 53.7	0.042*
	Rosuvastatin vs Simvastatin	25.1	3.9, 46.3	0.014*
	Atorvastatin vs Simvastatin	-2.1	-20.4, 16.2	0.989
Total cholesterol	Rosuvastatin vs Atorvastatin	9.8	-5.9, 25.5	0.351
	Rosuvastatin vs Simvastatin	20.0	8.0, 31.9	0.000*
	Atorvastatin vs Simvastatin	10.2	-1.3, 21.6	0.097

Remark: * Significant at $P < 0.05$

Using Post Hoc test (Dunnett T3) for multiple comparisons among statin groups.

II. Achievement of LDL-C goals

NCEP ATP III guidelines recommended a goal of LDL-C <100 mg/dL for high-risk patients and optional goal of LDL-C <70 mg/dL for very high-risk patients. The result showed that in usual clinical practice, CHD/CHD risk equivalent patients taking rosuvastatin achieved LDL-C goals greater than patients taking

atorvastatin or simvastatin but the difference were not statistically significant. (76.0% versus 62.4% and 68.0% respectively, P = 0.078). (see Table 4.5 and Figure 4)

Table 4.5 Comparisons of the number and percentage of patients achieving their LDL-C goal according to NCEP guideline (LDL-C level < 100 mg/dL) among statin groups

Statin Types	No. of patients (%) achieving NCEP goals		Total
	yes	no	
Simvastatin	540 (68.0%)	254 (32.0%)	794
Atorvastatin	68 (62.4%)	41 (37.6%)	109
Rosuvastatin	92 (76.0%)	29 (24.0%)	121
Total	702 (68.6%)	322 (31.4%)	1024

Remark: using Chi- square test , P value = 0.078, not significant difference.

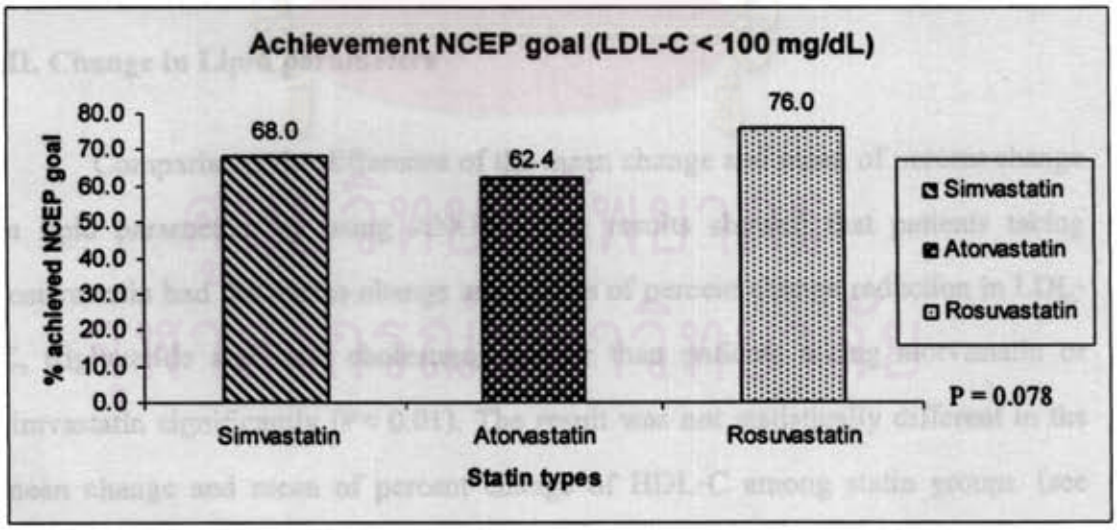

Figure 4. The percentage of patients achieving their LDL-C goals according to NCEP guideline (LDL-C level < 100 mg/dL) compared among statin groups

There were 109 patients of which were at very high risk from 1,024 patients (10.6%). Overall the patients achieving optional NCEP goals (LDL-C < 70 mg/dL) were only 22 cases (20.2%). The study could not compare these high risk patients among statin groups because the sample size in atorvastatin and rosuvastatin group were too small. (see Table 4.6)

Table 4.6 The numbers and percentage of patients achieving optional NCEP goal for very high risk patients (LDL-C level < 70 mg/dL)

Statin Types	Number of patients	Number of patients who achieved optional NCEP goals at LDL-C level <70 mg/dL (%)*
Simvastatin	91	20 (22.0%)
Atorvastatin	11	0 (0%)
Rosuvastatin	7	2 (28.6%)
Total	109	22 (20.2%)

III. Change in Lipid parameters

Comparisons the difference of the mean change and mean of percent change in lipid parameters by using ANOVA, the results showed that patients taking rosuvastatin had the means change and means of percent change reduction in LDL-C, triglyceride and total cholesterol greater than patients taking atorvastatin or simvastatin significantly (P< 0.01). The result was not statistically different in the mean change and mean of percent change of HDL-C among statin groups. (see Table 4.7 and Figure 5)

Table 4.7 Mean and mean of percent change in lipid parameters among CHD/ CHD risk equivalent patients compared among statin groups.

Lipid Values	change in Lipid parameters (mg/dL) Simvastatin (95% CI) (N = 794)	Atorvastatin (95% CI) (N = 109)	Rosuvastatin (95% CI) (N= 121)	Total (95% CI) (N= 1024)	P value
LDL-C:					
mean±SD change	-60.6 ± 31.4	-64.8 ± 42.8	-78.5 ± 37.8	-63.2 ± 34.1	0.000*
	(-62.8, -58.4)	(-72.4, -56.0)	(-85.3, - 71.7)	(65.2, -61.1)	
mean±SD % change	-38.5 ± 15.9	-38.2 ± 21.0	-46.1 ± 16.5	-39.4 ± 16.7	0.000*
	(-39.6, -37.4)	(-42.2, -34.2)	(-49.1, -43.2)	(-40.4, -38.3)	
HDL-C:					
mean±SD change	0. 2 ± 8.2	1.4 ± 12.8	1.0 ± 8.3	0.4 ± 8.8	0.267
	(-0.7, +0.7)	(-0.9, +3.9)	(-0.51, +2.5)	(-0.3, 0.9)	
mean±SD % change	2.6 ± 22.6	6.4 ± 34.4	4.8 ± 20.4	3.3 ± 23.9	0.226
	(1.0, 4.2)	(-0.1, 12.9)	(1.1, 8.4)	(1.8, 4.7)	
Triglyceride:					
mean±SD change	-6.1 ± 75.8	-13.9 ± 78.5	-38.6 ± 73.1	-10.8 ± 76.4	0.000*
	(-11.4, -0.8)	(-28.8, -1.0)	(-51.8, -25.4)	(-15.4,-6.1)	
mean±SD % change	7.1 ± 53.1	-0.01 ± 43.7	-14.9 ± 33.2	3.7 ± 50.7	0.000*
	(3.4,10.8)	(-8.3, 8.3)	(-20.9, -9)	(0.6, 6.8)	
Total Cholesterol:					
mean±SD change	-61.7 ± 38.1	-65.6 ± 50.3	-84.6 ± 44.2	-64.8 ± 40.9	0.000*
	(-64.4, -59.1)	(-75.1, -56.1)	(-92.5, -76.6)	(-67.3, -62.3)	
mean±SD % change	-26.5 ± 14.4	-26.2 ± 18.7	-33.6 ± 14.2	-27.3 ± 15.0	0.001*
	(-27.5, -25.5)	(-29.7, -22.7)	(36.1, -31)	(-28.2, -26.4)	

Remark : using one-way ANOVA.

* Significant at $P < 0.01$

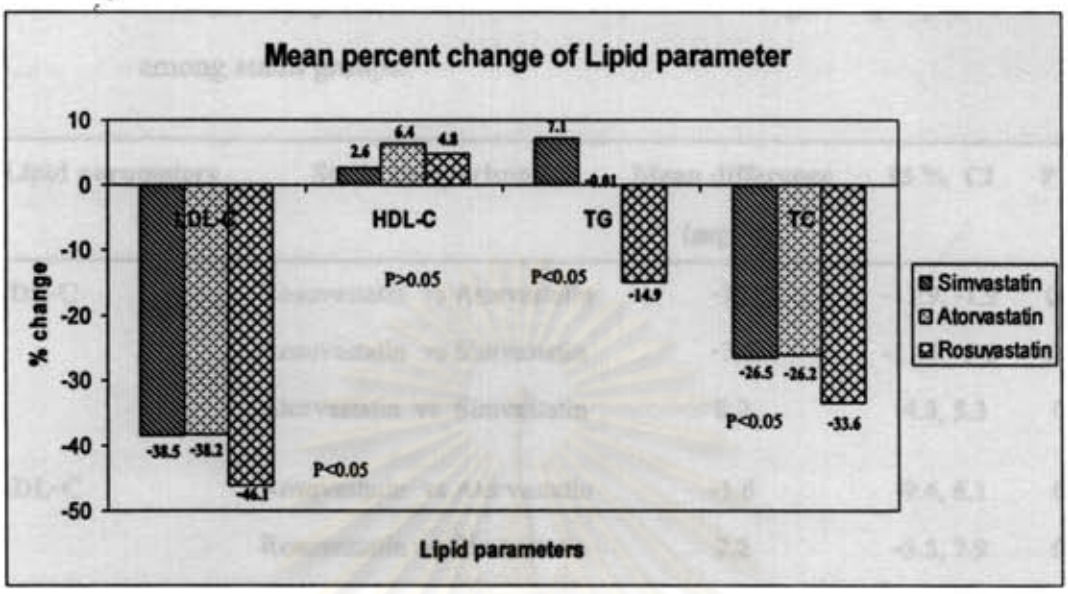

Figure 5. Means of percent change in lipid parameters of patients compared among statin groups

When testing multiple comparisons of the mean of percent change of lipid parameters by using Post Hoc test (Dunnett T3), the results showed that rosuvastatin reduced LDL-C, triglyceride and total cholesterol levels greater than atorvastatin or simvastatin significantly ($P < 0.05$). The reduction in LDL-C, triglyceride and total cholesterol levels of simvastatin and atorvastatin were not statistically different. (See Table 4.8)

Table 4.8 Multiple comparisons of the mean of percent change in lipid parameters among statin groups.

Lipid parameters	Statin comparisons	Mean difference (mg/dL)	95 % CI	P value
LDL-C	Rosuvastatin vs Atorvastatin	-7.9	-13.9, -1.9	0.006*
	Rosuvastatin vs Simvastatin	-7.6	-11.5, -3.8	0.000*
	Atorvastatin vs Simvastatin	0.2	-4.8, 5.3	0.999
HDL-C	Rosuvastatin vs Atorvastatin	-1.6	-9.4, 6.1	0.873
	Rosuvastatin vs Simvastatin	2.2	-3.5, 7.9	0.650
	Atorvastatin vs Simvastatin	3.8	-2.2, 9.8	0.297
Triglycerides	Rosuvastatin vs Atorvastatin	-15.0	-27.4, -2.6	0.012*
	Rosuvastatin vs Simvastatin	-22.4	-31, -13.8	0.000*
	Atorvastatin vs Simvastatin	-7.4	-18.5, 3.7	0.293
Total cholesterol	Rosuvastatin vs Atorvastatin	-7.4	-12.4, -2.1	0.003*
	Rosuvastatin vs Simvastatin	-7.7	-11.3, -4.1	0.000*
	Atorvastatin vs Simvastatin	-0.3	-5.0, 4.4	0.997

Remark : Multiple comparisons by using Post Hoc (Dunnette T3) test .

* Significant at $P < 0.05$

Subgroup Analysis

Out of pocket and Civil Service Medical Benefit Scheme (CSMBS) Patients

Because almost all of the patients in Out of pocket and CSMBS group received rosuvastatin and atorvastatin, the study conducted subgroup analysis of outcome of the three statins to compare the treatment outcome. The results showed that patients taking rosuvastatin had the baseline LDL-C higher than atorvastatin and simvastatin patients. The number of patients who achieved LDL-C goal (< 100 mg/dL) according to NCEP ATP III in rosuvastatin group was greater

than atorvastatin and simvastatin, but the difference was not statistically different. The mean of percent change in LDL-C reduction of rosuvastatin group was greater than atorvastatin and simvastatin, but the mean of percent change in LDL-C reduction between atorvastatin and simvastatin was not statistically different. (see Table 4.9 and 4.10)

Table 4.9 Comparisons of the LDL-C goal achievement and LDL-C reduction in Out of pocket and CSMBS patients among statin groups.

Characteristics	Simvastatin (N= 276)	Atorvastatin (N= 99)	Rosuvastatin (N= 120)	Total (N= 495)	P value
LDL-C baseline:					
mean ±SD (mg/dL)	154.8±31.4	162.5±34.0	167.6±45.8	159.4±36.2	0.004*
Statin daily dose:					
mean±SD (mg)	18.0±6.0	17.1±7.6	10.0±2.6	15.9±6.7	0.000*
Achievement LDL-C goal: No. of patients (%)	185 (67.0%)	62 (62.6%)	91 (75.8%)	338 (68.3%)	0.090
LDL-C reduction:					
Mean % change (mg/dL)	-38.9±15.6	-38.5±21.5	-46.2±16.6	-40.6±17.4	0.000*

Remark : * Significant at $P < 0.05$

Table 4.10 Multiple comparisons of the mean of percent change in LDL-C reduction in Out of pocket and CSMBS patients among statin groups.

Lipid parameters	Statin comparisons	Mean difference (mg/dL)	95 % CI	P value
LDL-C	Rosuvastatin vs Atorvastatin	-7.7	-14.0, -1.3	0.012*
	Rosuvastatin vs Simvastatin	-7.2	-11.5, -2.9	0.000*
	Atorvastatin vs Simvastatin	0.5	-5.2, 6.2	0.996

Remark : * Significant at $P < 0.05$

CHD and CHD-risk equivalent Patients

Because the number of patients in very high risk was so small, the patients were included into established CHD group. In patients with established CHD, the results showed that mean LDL-C baseline among statin groups was not statistically different (P>0.05). The number of patients who achieved NCEP goals in rosuvastatin group was greater than simvastatin and atorvastatin groups respectively, but the difference was not statistical significance. In the same way, the mean of percent change in LDL-C reduction of rosuvastatin patients was greater than simvastatin and atorvastatin patients significantly, but the mean of percent change in LDL-C reduction between atorvastatin and simvastatin was not statistical difference. (see Table 4.11)

In CHD risk equivalent patients, the patients had the mean LDL-C baseline higher than the patients with established CHD. However, the patients having CHD risk equivalent and taking rosuvastatin had the mean LDL-C baseline in the same as atorvastatin patients and were higher than simvastatin patients. The number of patients who achieved LDL-C goal in rosuvastatin group was greater than atorvastatin and simvastatin group, but the difference was not statistical significance. The mean of percent change in LDL-C reduction of rosuvastatin and atorvastatin were not different and were higher than simvastatin group. (see Table 4.12)

Table 4.11 Comparisons of the LDL-C goal achievement and LDL-C reduction in established CHD patients among statin groups.

Characteristics	Simvastatin (N= 328)	Atorvastatin (N= 52)	Rosuvastatin (N= 28)	Total (N= 408)	P value
LDL-C baseline:					
mean ±SD (mg/dL)	147.5±36.1	152.6 ±30.9	154.8±49.3	148.7±36.5	0.429
Statin daily dose:					
mean±SD (mg)	20.5±7.8	18.1±7.9	10.7±3.8	19.5±8.0	0.000*
Achievement LDL-C					
goal: No. of patients (%)	240 (73.2%)	31 (59.6%)	23 (82.1%)	294 (72.1%)	0.060
LDL-C reduction:					
Mean % change (mg/dL)	-37.2±16.2	-34.7±17.9	-45.7±16.9	-37.4±16.6	0.014*

Remark : * Significant at $P < 0.05$

Table 4.12 Comparisons of the LDL-C goal achievement and LDL-C reduction in CHD risk equivalent patients among statin groups.

Characteristics	Simvastatin (N= 466)	Atorvastatin (N= 57)	Rosuvastatin (N= 93)	Total (N= 616)	P value
LDL-C baseline:					
mean ±SD (mg/dL)	158.1±32.8	171.6 ±38.6	171.1±44.1	161.3±35.7	0.000*
Statin daily dose:					
mean±SD (mg)	18.0±7.0	16.0±7.5	9.7±2.1	16.6±7.2	0.000*
Achievement LDL-C					
goal: No. of patients (%)	300 (64.4%)	37 (64.9%)	69 (74.2%)	406 (65.9%)	0.187
LDL-C reduction:					
Mean % change (mg/dL)	-39.4±15.6	-41.5±23.2	-46.2±16.4	-40.6±16.7	0.001*

Remark : * Significant at $P < 0.05$

LDL-C baseline Groups

When subgroup analysis for LDL-C baseline group was conducted, the mean statin daily dose among them were similar. The percent of patients who achieved LDL-C goal in the high LDL-C baseline (> 160 mg/dL) group was lower than in the low LDL-C baseline (< 130 mg/dL) group. However, the patients with taking rosuvastatin in all LDL-C baseline groups achieved LDL-C goal greater than atorvastatin and simvastatin patients, but the difference was not statistical significance. In the same way, the mean of percent change in LDL-C reduction of rosuvastatin patients was greater than atorvastatin and simvastatin patients. But the mean of percent change in LDL-C reduction of the high LDL-C baseline (> 160 mg/dL) group between statin therapy in the vicinity (P> 0.05) and was higher than the low LDL-C baseline (< 130 mg/dL) group.

Table 4.13 Comparisons of the LDL-C goal achievement and LDL-C reduction in LDL-C baseline groups among statin groups.

Characteristics	Simvastatin (N= 794)	Atorvastatin (N=109)	Rosuvastatin (N=121)	Total (N=1024)	P value
LDL-C baseline< 130 mg/dL					
No. of patients	217	15	26	258	
Statin daily dose:					
mean±SD (mg)	18.6±6.8	16.0±8.3	10.0±2.4	17.6±7.1	0.000*
Achievement LDL-C goal:					
No. of patients (%)	177 (81.6%)	11 (73.3%)	22 (84.6%)	210 (81.4%)	0.672
LDL-C reduction:					
Mean % change (mg/dL)	-32.2±16.2	-23.5±21.3	-38.2±18.9	-32.3±17.0	0.027*
LDL-C baseline 130 – 160 mg/dL					
No. of patients	292	43	38	373	
Statin daily dose:					
mean±SD (mg)	19.3±8.0	17.2±7.0	9.6±2.7	18.1±8.0	0.000*
Achievement LDL-C goal:					
No. of patients (%)	207 (70.9%)	32 (74.4 %)	33 (86.8%)	272 (72.9%)	0.111
LDL-C reduction:					
Mean % change (mg/dL)	-37.6±14.6	-37.0±16.8	-47.3±14.7	-38.6±15.1	0.001*
LDL-C baseline > 160 mg/dL					
No. of patients	285	51	57	393	
Statin daily dose:					
mean±SD (mg)	19.1±7.3	17.1±8.3	10.2±2.7	17.5±7.6	0.000*
Achievement LDL-C goal:					
No. of patients (%)	156 (54.7%)	25 (49.0%)	37 (64.9%)	218 (55.5%)	0.230
LDL-C reduction:					
Mean % change (mg/dL)	-44.1±15.6	-43.5±22.3	-48.9±15.5	-44.7±16.2	0.102

Remark : * Significant at P < 0.05

IV. Economic value assessment

The study used the provider perspective. Costs included only drug cost. Drug costs came from the retail price of Sappasittiprasong Hospital in 2007. Types of pharmacoeconomic study was cost-effectiveness analysis and incremental cost-effectiveness ratio (ICER) was also conducted. Outcomes came from the results of this study. The percent of patients who achieved NCEP goal (LDL-C < 100 mg/dL) and the mean of percent change in LDL-C reduction were as effectiveness. The results showed that simvastatin had the lowest annual cost of 256 Baht, followed by rosuvastatin (12,669 Baht) and atorvastatin (18,356 Baht). Simvastatin was the most cost-effectiven therapy among CHD/CHD risk equivalent patients with the lowest annual cost per patient treated to achieve NCEP LDL-C goal of <100 mg/dL (376 Baht), and the lowest annual cost of 1% LDL-C reduction(7 Baht). The incremental cost – effectiveness of rosuvastatin was 155,163 Baht per patient treated to achieve NCEP LDL-C goal of <100 mg/dL and 1,633 Baht of 1% LDL-C reduction, compared with simvastatin. Atorvastatin had highest annual cost in achievement of NCEP goals and LDL-C reduction. With the lowest effectiveness and highest cost, atorvastatin was least cost-effective based upon the outcomes in this study.

Table 4.14 Comparisons of the cost – effectiveness in achievement of LDL-C goal according to NCEP guideline and LDL-C reduction among statin groups.

Statin Therapy	Effectiveness* (%)	Annual costs ** (Baht)	Cost-effectiveness ratio (cost per unit of effectiveness)	Incremental Cost-effectiveness ratio
NCEP LDL-C Goal (effectiveness as % of patients at goal)				
Rosuvastatin 10 mg	76.0	12,669	16,670	155,163‡
Simvastatin 20 mg	68.0	256	376	dominated
Atorvastatin 20 mg	62.4	18,356	29,417	-
LDL-C reduction (effectiveness as % LDL-C reduction)				
Rosuvastatin 10 mg	46.1	12,669	275	1,633‡‡
Simvastatin 20 mg	38.5	256	7	dominated
Atorvastatin 20 mg	38.2	18,356	481	-

Remark : * Effectiveness based on the effectiveness of statin daily dose in each statin: simvastatin 20mg, rosuvastatin 10 mg and atorvastatin 20 mg.

** Statin prices based on retail price at Sappasittiprasong Hospital in 2007 : simvastatin = 0.70 Baht, atorvastatin = 50.29 Baht, and rosuvastatin = 34.71 Baht.

Thus, annual costs = price x 365

‡ Incremental cost-effectiveness ratio of patients at goal $= \frac{(\text{cost of RSV} - \text{cost of SVT}) \times 100}{\%\text{patients at goal of RSV} - \%\text{ patients at goal of SVT}}$

‡‡ Incremental cost-effectiveness ratio of 1 % LDL-C reduction $= \frac{(\text{cost of RSV} - \text{cost of SVT})}{\%\text{ LDL-C reduction of RTV} - \%\text{ LDL-C reduction of SVT}}$

CHAPTURE V

DISCUSSION AND CONCLUSION

This section consists of 4 parts including discussion, limitation of this study, conclusion, and recommendations. Discussion was mentioned in 5 topics: the difference in the number of patients who were excluded from the study, difference in LDL-C baseline, subgroup analysis, economic assessment, and a comparison with related researches. The discussion of this study follows:

1. The difference in the number of patients who were excluded from the study among statin groups. The high number of patients taking rosuvastatin or atorvastatin was excluded because of switching to other statin, receiving dyslipidemic drugs or discontinuation. These results may be explained that most of patients taking rosuvastatin or atorvastatin were in the group of out of pocket and CSMBS patients. Most of them had high level of education and high level of economic status. Some patients had to pay for therapy by themselves leading to discontinuation of the drugs because rosuvastatin and atorvastatin was expensive. The number of patients taking atorvastatin was excluded less than patients taking rosuvastatin because atorvastatin was in essential drug (ED) list but rosuvastatin was not.

2. The difference of LDL-C baseline may affect the effectiveness of statins. Patients taking rosuvastatin or atorvastatin had LDL-C baseline higher than simvastatin. Therefore, it was more difficult to reduce LDL-C baseline of rosuvastatin and atorvastatin to target LDL-C goal than simvastatin. For this reason, it may affect the probability of LDL-C goal achievement among statin groups.

3. Subgroup analysis. Patients with established CHD had the mean LDL-C baseline lower than patients with CHD risk equivalent because most of them were

diabetes patients. Thus, the percent of LDL-C goal achievement of patients with established CHD was greater than patients with CHD risk equivalent. In opposite, the mean percent change in LDL-C reduction of patients with established CHD was lower than patients with CHD risk equivalent. These results were in the same as patients with subgroup in both the low and high LDL-C baseline group. For this reason, patients with CHD risk equivalent and high LDL-C level including very high risk patients when they need to achieve LDL-C goal of < 100 mg/dL and < 70 mg/dL, rosuvastatin may be considered.

4. Relationship between economic assessment and achievement of LDL-C goal. Rosuvastatin group showed slightly effective in achievement of LDL-C goal according to NCEP guideline but the result was not significant. It also had more LDL-C reduction than atorvastatin and simvastatin group. However, rosuvastatin take the highest annual cost per unit of effectiveness in achievement of LDL-C goal and LDL-C reduction, compared with simvastatin. In additional, rosuvastatin had incremental cost-effectiveness of 155,163 Baht per patients treated to achieve LDL-C goal and 1,633 Baht per 1 % of LDL-C reduction compared with simvastatin. If one hundred patients need to achieve LDL-C goals, fifteen million baht has to be paid. In the same way, if patients need to lower LDL-C level 50% from baseline to achieve LDL-C goal, eighty thousand baht has to be paid for one patient. Thus, generic simvastatin was the most cost-effectiveness for CHD and CHD risk equivalent patients because it had the lowest annual cost 376 Baht per patient at goal and 7 Baht per unit of LDL-C reduction.

5. Comparisons with related researches. The results of this study were similar to the results from randomized controlled trials (STELLAR,[14] DISCOVERY,[15] and SOLAR trials[16]) and from the study in of Ohsfeldt and others (2006),[21] and Fox and others (2007).[22] In DISCOVERY-UK and SOLAR trials showed that achieving LDL-C goal rate (76% vs 58% for ATV and 53% for SVT)

and percent of LDL-C reduction (48% vs 41% for ATV and 40% for SVT) for 12 weeks in rosuvastatin group were greater than atorvastatin and simvastatin. The study of Fox and others (2007) showed that achieving LDL-C goal rate (78.4% vs 71.5% for ATV and 66.9% for SVT) and percent of LDL-C reduction (28.5% vs 21.3% for ATV and 18.4% for SVT). This study found that rosuvastatin has achieved NCEP goal rate (76% vs 62.4% for ATV and 68.3% for SVT) near the study of Fox, and others. But the percent change of LDL-C reduction in this study (46.1% vs 37.9% for ATV and 38.5% for SVT) greater than the study of Fox, and others. In additional, atorvastatin group in this study had in LDL-C goal achievement and LDL-C reduction lower than simvastatin. This result was opposite to the study of Fox, and others. The reason of this difference may come from LDL-C baseline of study population. In this study, patients taking statins had LDL-C baseline (167.3 mg/dL for RSV, 162.5 mg/dL for ATV and 153.7 mg/dL for SVT) higher than patients in the study of Fox, and others (143.5 mg/dL for RSV, 124.4 mg/dL for ATV, and 118.9 mg/dL for SVT).

Limitations of this study

Because this study collected retrospective data from electronic database, several data were not available. Several factors can not control and some patient demographic characteristics were different. Data on race, other risk of CHD, or drug compliance were not available. Another limitation is that some dyslipidemic therapies could be obtained without a prescription (e.g., niacin, fish oil). Determining whether patients receiving such products were difficult to ascertain from our data sources. Furthermore, diet and exercise could also influence the results of patients' lipid levels. Although inferential statistic analyses were used to evaluated and controlled the differences in demographic characteristics, generalizability of the results has to be concerned regarding this limitation.

The present study was observational study and it evaluated only intermediate outcome (percent in achievement LDL-C goal and reduction in LDL cholesterol) of statins at the doses prescribed in routine clinical practice. Due to the observational nature of this study, comparisons between simvastatin, rosuvastatin and atorvastatin relied mainly on the sample available in each of the comparator groups. Because the small number of patients was taking atorvastatin or rosuvastatin in this study, no comparison could be made on dose-to-dose basis among statin groups.

Conclusion

The lipid goal achievement based on NCEP ATP III goal of LDL-C <100 mg/dL of rosuvastatin (78%), simvastatin (68%), and atorvastatin (62.4%) were not statistically different (P=0.078). The mean of percent change in LDL-C reduction of rosuvastatin was the greatest compared with simvastatin and atorvastatin but it had high annual cost-effective. Simvastatin had mean of percent change in LDL-C reduction less than rosuvastatin but it had lowest annual cost effective. The findings indicated that patients with simvastatin are the most cost- effectiveness compared with rosuvastatin and atorvastatin (at current prices). These findings reflect treatment effectiveness as observed in clinical practice for CHD/ CHD-risk equivalent patients treated with statin therapy rather than the efficacy demonstrated in clinical trials. Thus, in usual clinical practice, simvastatin should be the first choice to be selected for CHD/CHD-risk equivalent patients except the patients has some problem such as having contra-indication or taking drug interaction with simvastatin.

Recommendation

The finding from this study should be proposed to the Pharmacy and Therapeutic Committee of Sappasittiprasong Hospital to improve the guidelines for appropriate and cost-effective use of statins in the hospital. The pattern of this study should be applied for evaluation of other drugs use in usual clinical practice.

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