การเปรียบเทียบประสิทธิผลและความปลอดภัยของการใช้ยาพิทาวาสแททิน 1 มิลลิกรัม วันละครั้ง กับอะทอร์วาสแททิน 10 มิลลิกรัม วันละครั้ง ในผู้ป่วยนอกที่มีภาวะคอเลสเตอรอลสูงในเลือด

นายปวัฒน์ ผุดวาย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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COMPARATIVE EFFICACY AND SAFETY OF PITAVASTATIN 1 MG ONCE DAILY DOSE VERSUS ATORVASTATIN 10 MG ONCE DAILY DOSE IN OUTPATIENTS WITH HYPERCHOLESTEROLEMIA

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A Thesis Submitted in Partial Fulfillment of the Requirements
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Department of Pharmacy Practice
Faculty of Pharmaceutical Sciences
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Thesis Title	COMPARATIVE EFFICACY AND SAFETY OF PITAVASTATIN 1 MG ONCE DAILY DOSE VERSUS ATORVASTATIN 10 MG ONCE DAILY DOSE IN OUTPATIENTS WITH HYPERCHOLESTEROLEMIA
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Field of Study	Clinical Pharmacy
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ปวัฒน์ ผุดวาย : การเปรียบเทียบประสิทธิผลและความปลอดภัยของการใช้ยาพิทาวาสแททิน 1 มิลลิกรัม วันละครั้ง กับอะทอร์วาสแททิน 10 มิลลิกรัม วันละครั้ง ในผู้ป่วยนอกที่มีภาวะคอเลสเตอรอลสูงในเลือด. (COMPARATIVE EFFICACY AND SAFETY OF PITAVASTATIN 1 MG ONCE DAILY DOSE VERSUS ATORVASTATIN 10 MG ONCE DAILY DOSE IN OUTPATIENTS WITH HYPERCHOLESTEROLEMIA) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ.เรวดี ธรรมอุปกรณ์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: พอ.นพ.นครินทร์ คันสนยุทธ, รศ.ดร.ศุภกิจ วงศ์วิวัฒนนุกิจ, 98 หน้า.

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิผลและความปลอดภัยของการใช้ยาพิทาวาสแททิน 1 มิลลิกรัม วันละครั้ง กับอะทอร์วาสแททิน 10 มิลลิกรัม วันละครั้ง ในด้าน (1) การเปลี่ยนแปลงระดับไขมัน, hsCRP และไฟบริโนเจน (2) ประสิทธิผลในการลดระดับ LDL-C ให้ถึงเกณฑ์เป้าหมายของผู้ป่วยแต่ละราย ตามแนวทางของ NCEP ATP III (3) อาการไม่พึงประสงค์ และ (4) มูลค่ายาต่อปี

วิธีดำเนินการวิจัย: การวิจัยเชิงทดลองชนิด randomized open-label, parallel design ดำเนินการศึกษาที่แผนกตรวจโรคผู้ป่วยนอก โรงพยาบาลพระมงกุฎเกล้า ระหว่างเดือนพฤศจิกายน 2551 ถึง พฤษภาคม 2552 ผู้เข้าร่วมวิจัย 100 รายแบ่งเป็น 2 กลุ่มเท่าๆ กัน กลุ่มแรกได้รับยาพิทาวาสแททิน 1 มิลลิกรัม วันละครั้ง กลุ่มที่สองได้รับยาอะทอร์วาสแททิน 10 มิลลิกรัม วันละครั้ง เป็นระยะเวลา 8 สัปดาห์ การประเมินผลพิจารณาจากผลการตรวจทางห้องปฏิบัติการ การตรวจร่างกาย และการสัมภาษณ์ผู้ป่วย

ผลการวิจัย: ผู้ป่วยเข้าร่วมการทดลองทั้งหมด 100 คน พบว่ามี 98 คนที่อยู่จนครบระยะเวลาการวิจัย ข้อมูลพื้นฐานของผู้ป่วยทั้ง 2 กลุ่มไม่มีความแตกต่างกัน ยกเว้นระดับ AST ในกลุ่มพิทาวาสแททินที่พบว่ามีค่าสูงกว่ากลุ่มอะทอร์วาสแททินทางสถิติ แต่ก็พบว่าค่า AST ดังกล่าวไม่มีความแตกต่างทางคลินิก เมื่อรับประทานยาครบ 8 สัปดาห์ พบว่ายาพิทาวาสแททินลดระดับ LDL-C และ TC ได้ต่ำกว่ายาอะทอร์วาสแททิน (37.37% vs. 45.75%, p<0.001และ 27.55% vs. 32.31%, p=0.005 ตามลำดับ) แต่อย่างไรก็ตามพบว่าร้อยละการเปลี่ยนแปลงของ TG, HDL-C, hsCRP และไฟบริโนเจน ของยาทั้งสองชนิดนั้นไม่มีความแตกต่างกัน ผู้ป่วยที่รับประทานยาทั้งสองกลุ่มสามารถลดระดับ LDL-C ตามเกณฑ์เป้าหมายของ NCEP ATP III ได้ไม่แตกต่างกัน (74% vs. 84%, p=0.220) สำหรับอัตราการเกิดอาการไม่พึงประสงค์จากยาทั้งสองชนิดนั้นพบว่าไม่แตกต่างกัน (p>0.05) นอกจากนี้พบว่าผู้ป่วยที่ได้รับยาพิทาวาสแททิน 1 มิลลิกรัม วันละครั้ง มีค่ายาต่อปี น้อยกว่ากลุ่มที่ได้รับยาอะทอร์วาสแททิน 10 มิลลิกรัม วันละครั้ง 40.51% (5,856.00 บาท และ 14,457.00 บาท ตามลำดับ)

สรุปผลการวิจัย: หลังรับประทานยา 8 สัปดาห์ ยาพิทาวาสแททิน 1 มิลลิกรัม วันละครั้ง ลด LDL-C และ TC ได้น้อยกว่ายาอะทอร์วาสแททิน 10 มิลลิกรัม วันละครั้ง แต่มีสัดส่วนของผู้ป่วยที่สามารถลดระดับ LDL-C ตามเกณฑ์เป้าหมายของ NCEP ATP III ได้ไม่แตกต่างกัน และหากพิจารณามูลค่ายาต่อปี พบว่ายาพิทาวาสแททิน 1 มิลลิกรัม วันละครั้ง ถูกกว่ายาอะทอร์วาสแททิน 10 มิลลิกรัม วันละครั้ง

ภาควิชา เภสัชกรรมปฏิบัติ ลายมือชื่อนิสิต ปวัฒน์ ผุดวาย

สาขาวิชา เภสัชกรรมคลินิก ลายมือชื่ออ.ที่ปรึกษาวิทยานิพนธ์หลัก เรวดี ธรรมอุปกรณ์

ปีการศึกษา 2552 ลายมือชื่ออ.ที่ปรึกษาวิทยานิพนธ์ร่วม

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PAWAT PUTWAI : COMPARATIVE EFFICACY AND SAFETY OF PITAVASTATIN 1 MG ONCE DAILY DOSE VERSUS ATORVASTATIN 10 MG ONCE DAILY DOSE IN OUTPATIENTS WITH HYPERCHOLESTEROLEMIA. THESIS ADVISOR : ASSOC. PROF. RAWADEE DHUMMA-UPAKORN THESIS CO-ADVISOR : COLONEL NAKARIN SANSANAYUDH, M.D., ASSOC. PROF. SUPAKIT WONGWIWATTHANANUKIT, Ph.D., 98 pp.

Objectives: To compare the efficacy and safety of pitavastatin 1 mg once daily with atorvastatin 10 mg once daily in terms of: (1) serum lipids, hsCRP, and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals according to NCEP ATP III guidelines, (3) adverse event rates, and (4) annual cost of drug treatment.

Methods: A randomized, open-label, parallel study was conducted during November, 2008 to May, 2009 at outpatient department, Phramongkutklao Hospital, Bangkok, Thailand. One hundred patients were randomly assigned equally into the pitavastatin 1 mg once daily group and atorvastatin 10 mg once daily group for 8 weeks. Data were assessed using laboratory data (12-hour fasting blood), physical examination, and patients' interviews.

Results: Of 100 patients enrolled, 98 patients completed the study. There was no significant difference in baseline characteristics between groups except serum AST level. Although, mean AST in pitavastatin group was statistically higher than atorvastatin group but there was no clinically significant difference between groups. Pitavastatin 1 mg once daily reduced LDL-C and TC from baseline lower than atorvastatin 10 mg once daily (37.37% vs. 45.75%, $p<0.001$ for LDL-C and 27.55% vs. 32.31%, $p=0.005$ for TC), but there was no significant difference in percent TG, HDL-C, hsCRP, and fibrinogen change between groups ($p>0.05$). The percentage of patients who achieved their LDL-C goals was not significantly different between pitavastatin and atorvastatin group (74% vs. 84%, $p=0.220$). In addition, the number of patients who experienced adverse events was not significantly different between groups ($p>0.05$). Annual cost of drug treatment in pitavastatin 1 mg once daily group was lower than atorvastatin 10 mg once daily group by 40.51% (5,856.00 baht vs. 14,457.00 baht, respectively).

Conclusions: Although pitavastatin 1 mg once daily dose reduced TC and LDL-C lower than atorvastatin 10 mg once daily dose, but the percentage of patients who achieved their LDL-C goals was not significantly different between groups. Moreover, pitavastatin 1 mg once daily is an alternative regimen for cost saving than atorvastatin 10 mg once daily.

Department : Pharmacy Practice Student's Signature Pawat Putwai
Field of Study : Clinical Pharmacy Advisor's Signature R. Dhumma-upakorn
Academic Year : 2009 Co-Advisor's Signature

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LIST OF ABBREVIATIONS

A1C	Glycosylated hemoglobin A1C
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adult Treatment Panel
BMI	Body Mass Index
CHD	Coronary heart disease
CK	Creatine kinase
CRP	C- reactive protein
CVS	Cardiovascular disease
CYP	Cytochrome
DBP	Diastolic blood pressure
FBS	Fasting blood sugar
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
hsCRP	High-sensitivity C-reactive protein
IC50	The half maximal inhibitory concentration
ICER	Incremental cost effectiveness ratio
IDL-C	Intermediate density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
mg	Milligram
mg/dL	Milligram per decilitre
mg/L	Milligram per liter
mmHg	Millimeter of mercury
mRNA	Messenger ribonucleic acid
NCEP	National Cholesterol Education Program
SBP	Systolic blood pressure
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitors
TC	Total cholesterol
TG	Triglyceride
TLCs	Therapeutic lifestyle changes

ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

CHAPTER I

INTRODUCTION

1. Rationale and Background

Coronary heart disease (CHD), complications of atherosclerosis, is the leading cause of morbidity and mortality. Meanwhile, World Health Organization (WHO) reported that CHD had been the first common cause of death killing 7.2 million people in 2004 **[1]**. In Thailand, Cardiovascular disease (CVD) is also a major cause of death, about 62,827 people died in 2006 **[2]**. Accumulating evidence over the last decades has linked elevated total cholesterol, elevated low-density lipoprotein cholesterol (LDL-C), and low high-density lipoprotein cholesterol (HDL-C) to development of CHD. Premature coronary atherosclerosis is most common and significant consequence of hypercholesterolemia **[3, 4]**. Several clinical trials have demonstrated that reduction of LDL-C reduces CHD event rates in primary prevention and in secondary intervention **[5-9]**. In general, for every 1% reduction in LDL-C, there is a 1% reduction in CHD event rates. On the basis of this compelling evidence, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) issued treatment guidelines that identified elevated LDL-C as the primary target of cholesterol lowering therapy **[10, 11]**.

Cholesterol lowering therapy consists of non-pharmacologic therapy and pharmacologic therapy. Non-pharmacologic therapy or therapeutic lifestyle changes (TLCs) include reduction of intakes of saturated fats and cholesterol, weight reduction, and increase in physical activities. Statins or 3-Hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors are widely used as most effective agents for cholesterol lowering therapy which reduce LDL-C between 18% and 55% **[3, 10]**. The large statin trials have shown that statins are effective in both primary and secondary preventions, decrease coronary morbidity and mortality between 24% and 42% and reduce all cause mortality between 9% and 30% **[3, 10]**.

Although statins have been widely used to reduce the CHD risk but CHD is still a leading cause of death **[1-3, 12]**. There are partly because patients with hypercholesterolemia are not achieving their LDL-C goals. The Lipid Treatment Assessment Project (L-TAP) and Improve Persistence And Compliance with Therapy (ImPACT) trials have demonstrated that the only 38% to 62.5% of patients can attain

their LDL-C target levels **[13, 14]**. Previous studies in Thailand reported that the percentage of patients who reached the LDL-C targets was about 46.5% and 47.7%. In patients with CHD, only 34.6% and 35% of patients can achieve their LDL-C goals **[15, 16]**. Overall, more than half of patients treated with lipid-lowering drugs do not achieve LDL-C target levels. The strategies for improving percentage of patients who reached the LDL-C goals are desirable. Therefore, the powerful LDL-C lowering drugs have become a major role for more aggressive treatment of hypercholesterolemia.

Statins that are available in Thailand are simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin providing choices of agents for the treatment of patients to evidence-based targets. Atorvastatin and rosuvastatin are very effective in lowering LDL-C ranging from 37% to 54% and 43 to 62%, respectively **[10, 17]**. Strong suppression of cholesterol synthesis has resulted in adverse reactions such as hepatic dysfunction and rhabdomyolysis, and therefore, selection of safer statins is vital in this subset of patients. Drug-drug interaction is another factor related to safety, especially those mediated by the drug metabolizing enzymes of the CYP450 class. In addition, CYP3A4, CYP2C9 and CYP2D6 are most abundant CYP3A isoenzymes involved in the metabolism of the established statins **[18]**. The interaction can reduce statin efficacy or enhance the risk of adverse reaction. Many drugs undergoing hepatic metabolism via CYP3A4 (i.e., azole antifungals, corticosteroids, some benzodiazepines, grape fruit juice, immunosuppressant, macrolide antibiotics, protease inhibitors, and SSRI antidepressants) are very likely to increase plasma concentration of lipophilic statins including atorvastatin that increased risk of adverse reactions. Moreover, the disadvantage of atorvastatin and rosuvastatin is their high cost which may affect patient affordability, resulting in underuse of statins.

Since more than half of all coronary events occur in patients without hypercholesterolemia, the other emerging factors associated risk for coronary events have been explored, including inflammatory markers, fibrinogen, lipoprotein(a), apolipoprotein (apo) A-I, apo B-100, and homocysteine **[10]**. Recently, much attention has focused on the role of C-reactive protein (CRP), a marker of inflammation, and fibrinogen, as the independent predictors of CHD **[10, 19-26]**. The ability of pravastatin, lovastatin, cerivastatin, fluvastatin, simvastatin, atorvastatin and pitavastatin to reduce serum CRP has been demonstrated in a number of trials. These studies have indicated that serum CRP is decreased between 13.1% and 47.0%

($p<0.05$). This reduction does not relate to LDL-C reduction **[27-34]**. Conflicting results of the effect of statins on fibrinogen have been documented. Previous studies have shown that atorvastatin and lovastatin significantly increase serum fibrinogen between 19.3% and 26.0% ($p<0.05$), whereas pravastatin reduces serum fibrinogen between 7% and 19%, and simvastatin does not affect the serum fibrinogen **[35-38]**.

Pitavastatin is a novel, totally synthetic HMG-CoA reductase inhibitor, which has a strong LDL-C lowering action and safety profile **[39]**. In Phase II studies on the efficacy and safety of pitavastatin, LDL-C reduction was dose-dependent, significantly decreased by 34, 42 and 47% at dose of 1, 2 and 4 mg, respectively **[39-41]**. A significant decrease in TG and a significant increase in HDL-C occurred at all doses, although there were not dose correlations. Pharmacokinetic studies have shown that the mean inhibitory concentration (IC_{50}) is 6.8 nM, suggesting even more potency than rosuvastatin. The terminal elimination half-life of 11 hours suggests that pitavastatin is long-acting HMG-CoA reductase inhibitors. Studies on the metabolism via cytochrome isoenzymes revealed that pitavastatin undergoes only minimal transformation, mainly via CYP2C9 and, to a lesser extent, via CYP2C8, indicating minimal likelihood for serious metabolic drug interactions **[18]**. A large-scale prospective post marketing surveillance (Livalo effectiveness and Safety Study; LIVES) investigation in 19,921 patients with hypercholesterolemia reported similar incidence of adverse reactions in comparison with other statins, 10.4% of pitavastatin compared with 12.0% of atorvastatin and 11.1% of rosuvastatin **[42]**. In addition, most of the adverse drug reactions were mild in severity. Common adverse drug reactions were increase in serum creatine phosphokinase (2.74%), elevated alanine aminotransferase (1.79%), elevated aspartate aminotransferase (1.50%), myalgia (1.08%) and gamma-glutamyltransferase abnormal (1.00%).

Previous comparative studies in phase III have confirmed the efficacy in LDL-C reduction of pitavastatin. These results indicated that pitavastatin 2 mg once daily reduced LDL-C levels from baseline significantly greater than pravastatin 10 mg once daily (-37.6% vs. -18.4%; $p<0.05$), but there was no significant difference in the percent decrease in LDL-C levels between pitavastatin 2 mg once daily and simvastatin 20 mg once daily (-38.2% vs. 39.4%; $p=0.648$) or atorvastatin 10 mg once daily (-42.6% vs. -44.1%; $p=0.456$) **[43-45]**. The recommended starting dose of pitavastatin in current clinical practice is 2 mg once daily. However, Yoshitomi, et al. study, a 12-week, open-label, found that there were no significant differences in the

percent change of TC, HDL-C, and LDL-C levels between pitavastatin 1 mg once daily and atorvastatin 10 mg daily **[46]**. Although this result suggested that pitavastatin 1 mg once daily and atorvastatin 10 mg once daily were equivalent in potency of LDL-C reduction as the initial therapy, the study has a significant drawback from selection bias due to its potential of non-randomized design.

The purpose of this study was to compare the efficacy and safety of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily in patients with hypercholesterolemia and to compare the effect of both agents on serum hsCRP and fibrinogen level.

2. Objectives

To compare:

1. Efficacy of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily in terms of: (1) LDL-C reduction, (2) TC reduction, (3) TG reduction, (4) HDL-C elevation, (5) hsCRP reduction, (6) change in fibrinogen level, and (7) percentage of patients who achieve their LDL-C goals according to NCEP ATP III guidelines.
2. The adverse events of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily.
3. Annual cost of drug treatment in patients receiving pitavastatin 1 mg once daily and atorvastatin 10 mg once daily.

3. Hypotheses

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

4. Significance of the Study

This study would add to the knowledge base on the:

1. Efficacy and safety of pitavastatin 1 mg once daily when compared with atorvastatin 10 mg once daily that could be used to consider the appropriate regimen for each individual patient.
2. Efficacy of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily on hsCRP and fibrinogen which are the important predictors of CHD in clinical practice.
3. Annual cost of drug treatment in patients receiving pitavastatin 1 mg once daily compared with atorvastatin 10 mg once daily

5. Operational Definitions

1. Patient with hypercholesterolemia means: (1) patient with CHD or CHD risk equivalents [i.e., diabetes mellitus, other forms of clinical atherosclerotic disease (peripheral arterial disease, carotid artery disease, and abdominal aortic aneurysm), or patient with more than 20% of 10-year risk for developing major coronary events] who has LDL-C levels of 100 mg/dL or more, (2) patient with more than one major risk factor for CHD and equal or less than 20% of 10-year risk for developing major coronary events, who has LDL-C levels of 130 mg/dL or more, and (3) patient with less than two major risk factors for CHD who has LDL-C levels of 160 mg/dL or more.
2. Efficacy means the ability in lowering TC, LDL-C, TG, hsCRP, and fibrinogen levels, and increasing HDL-C levels from baseline. Also, the ability in lowering LDL-C of patients to achieve their LDL-C goals according to NCEP ATP III guidelines **[10]**. In this study, the efficacy will be evaluated after the patient has taken pitavastatin or atorvastatin for 8 weeks. The efficacy in lowering TC, LDL-C, TG, hsCRP, and fibrinogen levels, and increasing HDL-C levels from baseline are evaluated by the percent changes from baseline, which calculated by:

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

The efficacy in lowering LDL-C of patients to achieve their LDL-C goals is evaluated by the percentage of patients who achieve their LDL-C goals according to NCEP ATP III guidelines **[10]**.

3. LDL-C goals according to NCEP ATP III guidelines means: (1) LDL-C less than 100 mg/dL in patient with CHD or CHD risk equivalents [i.e., diabetes mellitus, other forms of clinical atherosclerotic disease (peripheral arterial disease, carotid artery disease, and abdominal aortic aneurysm), or more than 20% of 10-year risk for developing major coronary events], (2) LDL-C less than 130 mg/dL in patient with more than one major risk factor for CHD and equal or less than 20% of 10- year risk for developing major coronary events, and (3) LDL-C less than 160 mg/dL in patient with less than two major risk factors for CHD **[10]**.
4. Safety means rates of adverse events from pitavastatin or atorvastatin e.g., muscle pain, muscle weakness, rash, more than 3 times the upper limit of normal (ULN) of AST or ALT elevation and more than 10 times the ULN of CK elevation. Safety is evaluated throughout the study period by adverse events reporting, patient interview, physical examinations, and laboratory tests.
5. Patient who meets the criteria for starting statins according to NCEP ATP III guidelines means: (1) patient with CHD or CHD risk equivalents [i.e., diabetes mellitus, other forms of clinical atherosclerotic disease (peripheral arterial disease, carotid artery disease, and abdominal aortic aneurysm), or more than 20% of 10- year risk for developing major coronary events] who has LDL-C equally or more than 100 mg/dL, (2) patient with more than one major risk factor for CHD and 10% to 20% of 10-year risk for developing major coronary events, who has LDL-C equally or more than 130 mg/dL, (3) patient with more than one major risk factor for CHD and less than 10% of 10- year risk for developing major coronary events, who has LDL-C equally or more than 160 mg/dL or 130 mg/dL after TLCs, and (4) patient with less than two major risk factors for CHD, who has LDL-C equally or more than 190 mg/dL or 160 mg/dL after TLCs **[10]**.
6. Annual cost of drug treatment means cost of patients receiving pitavastatin 2 mg haft of tablet once daily or atorvastatin 10 mg tablet once daily for 366 days of treatment calculated by using pricelist cost.

CHAPTER II
LITERATURE REVIEW

This study aimed to compare the efficacy and safety between pitavastatin 1 mg once daily and atorvastatin 10 mg once daily in outpatients with hypercholesterolemia. This chapter is divided into 4 sections. As follow: (1) hypercholesterolemia, (2) pitavastatin, (3) C-reactive protein, and (4) fibrinogen. Each section provides the necessary information and shapes the knowledge base for this study.

1. Hypercholesterolemia

Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids and steroid hormones. Cholesterol travels in the blood indistinct particles containing both lipid and proteins (lipoproteins). Three major classes of lipoproteins are found in the serum of a fasting individual: LDL-C, HDL-C, and very low density lipoproteins (VLDL-C). Another lipoprotein class, intermediate density lipoprotein (IDL-C), resides between VLDL-C and LDL-C; in clinical practice, IDL-C is included in the LDL-C measurement. Abnormalities of plasma lipoproteins can result in a predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease. Hypercholesterolemia is a condition that elevated TC and LDL-C and reduced HDL-C. Accumulating evidence over the last decades had linked elevated of total and LDL-C and reduced of HDL-C to the development of CHD **[5-9].** These studies demonstrated that reduction of LDL-C and elevation of HDL-C reduces CHD event rates. In general, for 1% reduction in LDL-C, there is a 1% reduction in CHD event rates and elevations of HDL-C of 1% result in approximately 2% reduction in CHD events **[10, 47].**

1.1 Epidemiology

CHD is the major cause of global morbidity and mortality. World Health Organization (WHO) reported that CHD was the leading cause of death in many countries as shown in Table 1. It killed 7.2 million people in 2004, representing 12.2% of all death; such diseases caused 6.5% of all death in male and 5.7% in

female**[1]**. In Thailand, CVD is also a major cause of death, about 62,827 people died in 2006 **[2]**.

Table 1: Death by sex and WHO regions, estimates for 2004 **[1]**.

	Number of deaths caused by CHD x 1,000 people; (percent of all death)
Sex	
Both males and females	7,198 (12.2%)
Males	3,827 (6.5%)
Females	3,371 (5.7%)
WHO regions	
Africa	346
South East Asia	2,011
The Americas	925
Eastern Mediterranean	579
Europe	2,296
Western Pacific	1,029

1.2 Causes of Hypercholesterolemia

Causes of hypercholesterolemia can be categorized into two causes **[4]**.

1.2.1 Primary Hypercholesterolemia

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

1.2.2 Secondary Hypercholesterolemia

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

Table 2: Secondary causes of hypercholesterolemia **[3]**.

Hypothyroidism	Drug: progestins, thiazide diuretics,
Obstructive liver disease	glucocorticoids, β-blockers,
Nephrotic syndrome	isotretinoin, protease inhibitors,
Anorexia nervosa	cyclosporine, mirtazapine, and
Acute intermittent porphyria	sirolimus

1.3 Signs and Symptoms

Most patients with hypercholesterolemia are asymptomatic for many years prior to clinically evident disease (i.e., xanthomas, eruptions, and cornea arcus) **[3]**. Therefore, more accurate patient evaluation is based on serum lipid profile.

1.4 Patient Evaluation

The NCEP ATP III has recommended that a 12-hour fasting lipoprotein profile including TC, LDL-C, HDL-C and TG should be measured in all adults 20 years of age or older at least once every 5 years for lipid classification. After a lipid abnormality is confirmed (Table 3), risk determinants in addition to LDL-C should be identified. The risk determinants included the presence or absence of CHD, other clinical forms of atherosclerotic diseases, diabetes mellitus, and the major risk factors for CHD (Table 4). Based on these risk determinants, NCEP ATP III identifies three categories of risk that modify the goals and modalities of LDL lowering therapy as shown in Table 5.

Recently, NCEP ATP III issued an update NCEP report, implications of recent clinical trials for the ATP III guidelines, which recommend LDL-C goal of < 70 mg/dL as an optional goal in patients with high risk category (CHD or CHD risk equivalents) and < 100 mg/dL as a optional goal in patients with moderately high risk category (> 2 risk factors and 10-year risk 10% to 20%). This is because the results from five major clinical trials with statin therapy confirming the benefit of cholesterol-lowering therapy in high risk persons **[11]**.

1.5 Hypercholesterolemia Treatment

Establishing targeted changes and outcomes with consistent reinforcement of goals and measures at follow-up visits to attain goals are important to reduce barriers for optimizing non-pharmacologic therapy and pharmacologic therapy. Non-pharmacologic therapy or TLCs should be implemented in all patients prior to considering drug therapy.

Table 3: NCEP ATP III classification of lipid **[3]**.

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

Table 4: Major risk factors (exclusive of LDL-C) that modify LDL-C **[17].**

Positive risk factors
Age:
Men: ≥ 45 years
Women: ≥ 55 years or premature menopause without estrogen-replacement therapy
Family history of premature CHD:
definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative
Current cigarette smoking
Hypertension: ≥ 140/90 mmHg or on antihypertensive medication
Low high-density lipoprotein cholesterol: < 40 mg/dL
Negative risk factor
High high-density lipoprotein cholesterol: ≥ 60 mg/dL

Table 5: LDL-C goals and cut points for therapeutic lifestyle changes (TLCs) and drug therapy in different risk categories **[10, 11].**

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

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

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

** an update NCEP report **[11]**

1.5.1 Non-pharmacologic therapy

NCEP ATP III recommends a multifactorial lifestyle approach to reducing risk for CHD. This approach is designated TLCs and includes the following components:

- Reduced intakes of saturated fats and cholesterol
- Therapeutic dietary options for enhancing LDL lowering (plant stanols/sterols and increased viscous [soluble] fiber)
- Weight reduction
- Increased regular physical activity

Reduced intakes of saturated fats (< 7% of total calories) and cholesterol (< 200mg/dL) and other therapeutic dietary options for LDL-lowering (plant stanols/sterols and increased viscous fiber) are introduced first for the purpose of achieving the LDL-C goals. After maximum reduction of LDL-C is achieved with dietary therapy, emphasis shifts to management of the metabolic syndrome and its associated lipid risk factors (elevated triglycerides and low HDL-C). A high proportion of patients with the metabolic syndrome are overweight/obese and sedentary; for them, weight reduction therapy and physical activity guidance is

required to obtain further CHD risk reduction beyond that achieved by LDL-C lowering.

After 12 weeks, the response to dietary therapy should be evaluated. If the LDL-C goal is achieved, the current intensity of dietary therapy should be maintained indefinitely. If the patient is approaching the LDL-C goal, consideration should be given to continuing dietary therapy before adding LDL-C lowering drugs. If it appears unlikely that the LDL-C goal will be achieved with dietary therapy alone, drug therapy should be considered.

1.5.2 Pharmacologic Therapy

LDL-C is the primary target of treatment in clinical lipid management. The use of TLCs, including LDL-C lowering dietary options will achieve the therapeutic goal in many persons. Nonetheless, a portion of the population whose short-term and/or long-term risk for CHD will require LDL-C lowering drugs to reach the prescribed goal for LDL-C. When drugs are used, however, TLCs also should always be used concomitantly. Dietary therapy provides additional CHD risk reduction beyond drug efficacy.

The major classes of drugs for consideration are statins or HMG-CoA reductase inhibitors (i.e., lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin), bile acid sequestrants (i.e., cholestyramine, colestipol, and colesevelam), nicotinic acid (i.e., crystalline, timed-release preparations, and Niaspan®), fibric acid derivatives or fibrates (i.e., gemfibrozil, fenofibrate, and clofibrate), and cholesterol absorption inhibitor (i.e., ezetimibe). The efficacy of these drugs is shown in Table 6. The availability of statins allows attainment of the LDL-C goal in most of higher risk persons. Other agents—bile acid sequestrants, nicotinic acid, some fibrates, and cholesterol absorption inhibitor —also can moderately lower LDL-C levels.

Statins are the most powerful LDL-C lowering drugs which reduce LDL-C level by -18% to -55 %. Statins are effective in both primary and secondary preventions which decrease coronary morbidity and mortality between 24% and 42% and reduce all cause mortality between 9% and 30% **[10, 47]**. Treatment with statins is generally safe, although rarely persons experience abdominal discomfort, myalgia, myopathy, rash, and transient aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatine kinase (CK) elevation. The characteristics of various statins are summarized in Table 7.

Table 6: The efficacy on lipid profile of lipid-lowering drugs [10]**.**

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

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

The starting dose of statin will depend on the baseline LDL-C level. In persons with only moderate elevations of LDL-C, the LDL-C goals will be achieved with low or standard doses, and higher doses will not be necessary. The response to drug therapy should be checked in about 6 weeks. If the treatment goal has been achieved, the current dose can be maintained; if not, LDL-C lowering therapy can be intensified, either by increasing the statin dose or by combining a statin with other drug.

2. Pitavastatin

Pitavastatin, (+) – monocalcium bis (3R,5S,6E) – 7 - (2 – cyclopropyl – 4 -[4-fluorophenyl] -3-quinolyl- 3,5-dihydroxy-6-heptenoate (C50H46F2N2O8), is a totally synthetic statin with a molecular weight of 880.98 which was developed by Nissan Chemical Industries Ltd., Tokyo, Japan and later developed by Koya Co. Ltd., Tokyo, Japan (Figure 1).

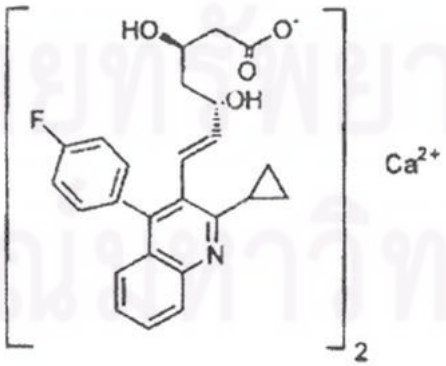

Figure 1: Structure of pitavastatin **[51]**

Table 7: Summary characteristics of various statins **[17, 41, 43-46, 48, 49]**

Statin	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Pitavastatin
LDL-C reduction (%)	10 mg: 21% 20 mg: 27% 40 mg: 31% 80 mg: 40%	10 mg: 22% 20 mg: 32% 40 mg: 34% 80 mg: 37%	10 mg: 30% 20 mg: 38% 40 mg: 41% 80 mg: 47%	20 mg: 22% 40 mg: 25% 80 mg: 36%	10 mg: 39% 20 mg: 43% 40 mg: 50% 80 mg: 60%	5 mg: 45% 10 mg: 52% 20 mg: 55% 40 mg: 63%	2 mg: 37-43% 4 mg: 48%
Molecular weight	405	446.5	418.5	433.5	1209	1001	881
Origin Synthetic	Microbial	Semi-synthetic (microbial origin)	Semi-synthetic (microbial origin)	Synthetic	Synthetic	Synthetic	Synthetic
Racemic	No	No	No	Yes	No	No	No
Prodrug	Yes	No	No	No	No	No	No
LogP	1.70	-0.84	1.60	1.27	1.11	-0.33	1.49
Absorption (%)	31	37	65–85	98	30	50	80
Hepatic excretion (%)	>70	66	78–87	68	>70	90	NA
Bioavailability (%)	<5	17	<5	10–35	12	20	>60

LDL-C = low-density lipoprotein cholesterol; LogP = logarithm to base 10 of the n-octanol/water partition coefficient of active hydroxyl forms of statins.

Table 7: Summary characteristics of various statins **[17, 41, 43-46, 48, 49]**

Statin	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Pitavastatin
Effect of food on bioavailability (%)	Yes (↑50)	Yes (↓30)	No	Yes(↓15–25)	Yes (↓13)	No	No
Protein binding (%)	96–98.5	43–54	>95	>98	>98	88	96
Tmax	2.8	0.9–1.6	1.3–2.4	0.5–1.5	2.0–4.0	3	0.5–0.8
T½	2.5–3.0	0.8–3.0	1.9–3.0	0.5–2.3	11–30	20	11
Renal excretion (%)	30	60	13	6	2	10	<2
50% inhibitory concentration (nmol/l)	2.7–11.1	55.1	18.1	17.9	15.2	12	6.8
Lipid-lowering metabolites	Yes	Yes Mainly inactive	Yes	Yes Mainly active	Yes Active	No	No
Range of dose (mg)	10–80	5–40	5–80	20–80	10–80	5–80	1–4
Primary metabolic pathway	CYP3A4	CYP3A4 Minimally	CYP3A	CYP2C9	CYP3A4	CYP2C9 Minimally	CYP2C9 Minimally

LDL-C = low-density lipoprotein cholesterol; logP = logarithm to base 10 of the n-octanol/water partition coefficient of active hydroxyl forms of statins.

Pitavastatin achieves its potent pharmacologic action by strong binding to the active site of HMG-CoA reductase consists of hydrophilic areas and hydrophobic areas, and pitavastatin is thought to form 10 hydrogen bonds with hydrophilic amino groups in this active pocket. The cyclopropyl group is an important feature of the structure-activity relationship, and this group fits hydrophobic areas of HMG-CoA reductase, thus retaining preferable space and form, so that pitavastatin shows inhibitory action. It is reported that inhibitory activity of pitavastatin analog, which has an isoprppyl group instead of a cycloproply group, was only about a fifth of that of pitavastatin, so pitavastatin may be regarded as a compound that is designed to fit the enzyme structure **[39, 48, 50]**

2.1 Pharmacodynamics and Pleiotropic Effects

Pitavastatin showed substrate-competitive type inhibition of HMG-CoA reductase with an IC_{50} of 6.8 nM, which is 2.4- and 6.8-times more potent than that of simvastatin and pravastatin, respectively **[52]**. Pitavastatin inhibited cholesterol synthesis from acetic acid with an IC_{50} of 5.8 nM in human liver cancer-derived cells (HepG2), which is 2.9- and 5.7-times stronger than that of simvastatin and atorvastatin, respectively **[53]**. In an in vitro studies in HepG2 cells, pitavastatin increased LDL-C receptor mRNA, LDL-C binding to the LDL-C receptor, LDL-C internalization into the cells, and degradation of apolipoprotein (apo) B **[53]**. Compared with simvastatin and atorvastatin, pitavastatin most effectively induced the expression of the LDL-C receptor mRNA. These results indicate that the effect of statins on the upregulation of mRNA expression for LDL receptor differs among the lipophilic statins **[39]**.

Statins possess multiple beneficial effects that are independent of LDL-C lowering, including reduction of inflammation, effect on the endothelium and the coagulation cascade. Various in vitro and in vivo studies have suggested that pitavastatin also has many pleiotropic effects: it reduces the inflammatory response and the generation of reactive oxygen species, improves endothelial function, increases nitric oxide production, inhibits cell adhesion, attenuated smooth muscle cell concentration, increases thrombomodulin expression, enhances angiogenesis and promotes apoA-I production **[54-63]**.

2.2 Pharmacokinetics and Metabolism

In pharmacokinetics studies, pitavastatin has shown high bioavailability, exceeding 80% in rat, and it is selectively distributed to the target organ liver (where its radioactivity level was about 54-times as high as in plasma in rat). Then, being affected little by CYP-mediated metabolism, it enters the enterohepatic circulation and is excreted mainly in the feces, with <2% of the dose excreted in the urine. Because it enters the enterohepatic circulation, pitavastatin has a longer half-life as compared with that of other statins which is considered to contribute to its LDL-C lowering effect (Table 7).

Pitavastatin is minimally influenced by CYP metabolism in spite of its lipid solubility; it is glucuronized and rapidly converted through the elimination reaction to the inactive lactone form (Figure 2). Pitavastatin is metabolized slightly by CYP2C9 to yield M-13, but the amount of M-13 produced is considered to be clinically negligible. As compared with other statins, which are mainly metabolized by CYP, pitavastatin has a unique metabolic pathway, so that CYP-mediated drug interactions between pitavastatin and concomitantly administered drugs metabolized by CYP may be minimal, which contributes significantly to the clinical use of pitavastatin.

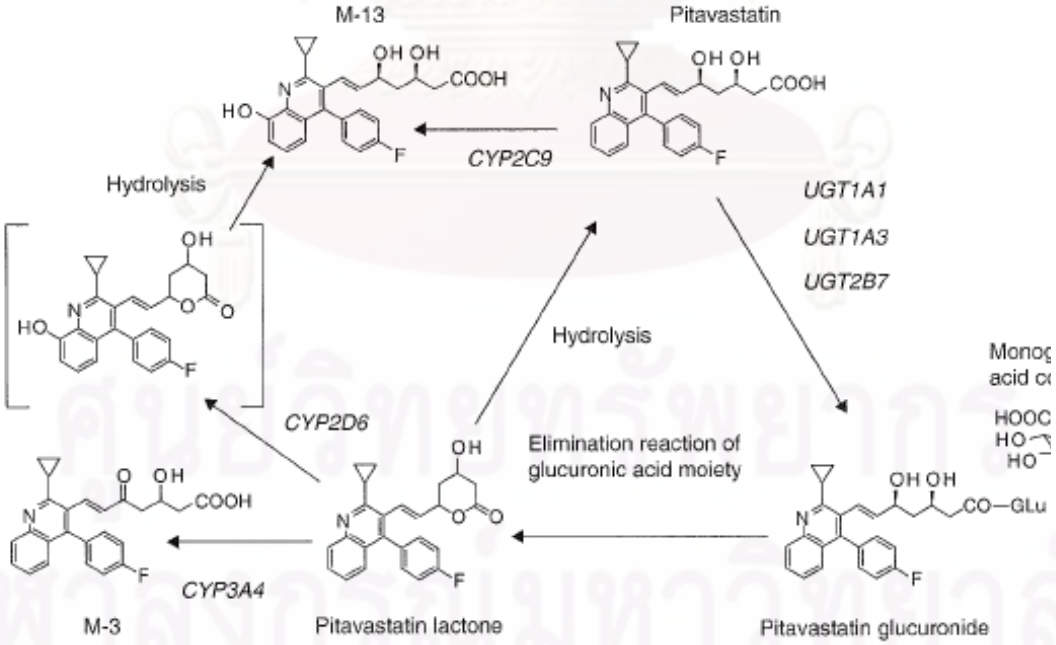

Figure 2: Metabolic pathway of pitavastatin **[39, 48, 50].**

2.3 Clinical Efficacy Data

Several studies of pitavastatin on the efficacy of lipid lowering in hyperlipidemic patients have showed that TC and LDL-C reduction were dose dependent. A significant decrease in TG and a significant increase in HDL-C occurred at all doses, although there was not a dose correlation **[39-41]**.

Saito, et al. (2002) conducted a 12-week, multicenter, double blind, and comparative study with 1, 2 or 4mg once daily evening of pitavastatin was performed in 264 patients with hyperlipidemia. The study indicated that pitavastatin reduced TC by -23.0%, -29.1% and -32.4% at 1, 2, and 4 mg, respectively. Similar to LDL-C reduction, pitavastatin reduced LDL-C by -33.6%, -41.8% and -47.0% at 1, 2, and 4 mg, respectively. The reduction rate of TC and LDL-C were significant in all groups as compared with the baseline level, and were significantly dose-dependent. In addition, a significant decrease in TG and a significant increase in HDL-C occurred at all doses, although there was not a dose correlation. Pitavastatin significantly reduced TG by -26.8%, -22.3% and -30.7% at 1, 2, and 4 mg, respectively and significantly increased HDL-C level by 6.8mg/dL, 5.9 mg/dL and 7.9 mg/dL at 1, 2, and 4 mg, respectively **[41]**.

Moreover, Noji, et al. (2002) reported that after 4-week placebo run-in period, 2 mg per day of pitavastatin was administered for 8 weeks and the dose was increased to 4 mg per day for up to 104 weeks in 25 patients with heterozygous familial hypercholesterolemia (FH). The study shown that TC decreased by 31% from baseline ($P<0.0001$) at the eighth week and furthermore decreased by 37% from the initial value ($P<0.0001$) during treatment with the higher dose at week 12. Similarly, the baseline LDL-C decreased by 41% at the eighth week, and furthermore decreased by 49% at week 12 from baseline ($P<0.0001$) **[40]**. These findings confirmed a dose-dependent effect of pitavastatin on TC and LDL-C reduction.

Previous comparative studies in phase III have confirmed the efficacy in LDL-C reduction of pitavastatin. These results indicated that pitavastatin 2 mg once daily was significantly lower LDL-C levels from baseline than pravastatin 10 mg once daily but there was no significant difference in the percent decrease in LDL-C levels compared with simvastatin 20 mg once daily or atorvastatin 10 mg once daily **[43-45]**. Tendency of the starting dose of pitavastatin in current clinical practice to initiate therapy is 2 mg once daily.

Saito, et al. (2002) conducted a 12-week, multi-center, randomized, double blind, controlled study to confirm the efficacy and safety of pitavastatin 2 mg once daily compared with pravastatin 10 mg once daily in Japan patients with hypercholesterolemia. At 12-week post-randomization, the pitavastatin group showed significantly lower LDL-C levels by -37.6% from baseline compared with -18.4% in the pravastatin group ($p<0.05$). Pitavastatin also significantly lowered TC by -28.2% compared with -14.0% of pravastatin ($p<0.05$). Moreover, it showed greater reduction of LDL-C in women than in men. The results are shown in Table 8.

Park, et al. (2005) carried out an 8-week, multicenter, prospective, randomized, open-label, phase III clinical trial to evaluate the efficacy and safety of pitavastatin 2 mg once daily compared with simvastatin 20 mg once daily in Korean patients with hypercholesterolemia. The study reported that there was no significant difference in the percent decrease in LDL-C levels (mean [SD], 38.2% [11.6%] decrease for the pitavastatin group vs. 39.4% [12.9%] decrease for the simvastatin group ($p=0.648$). Also, there were no significant differences between the 2 study groups in the percent changes in TC, TG, or HDL-C levels from baseline to study end as shown in Table 9 **[44]**.

Table 8: Mean percent changes from baseline at the twelfth week in comparative study of pitavastatin 2 mg daily and pravastatin 10 mg daily in Japan patients with primary hypercholesterolemia **[43]**.

Serum lipids	**Mean percent change from baseline (%)**				
	n	**Pitavastatin (2 mg)**	***N***	**Pravastatin (10 mg)**	**95% CI**
LDL-C	*120*	-37.6	*105*	-18.4	-22.5 to -15.9
TC	*120*	-28.0	*105*	-13.8	-16.5 to -11.8
HDL-C	*120*	8.9	*105*	9.8	-4.7 to -2.9
TG[a]	*50*	-23.3	*44*	-20.2	-16.1 to -9.8 (1); -∞ to -7.7 (2)

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

[a] TG represents the data of the patients with a baseline level of TG ≥ 150 mg/dL.

(1) the 95% CI of difference is shown in the upper line

(2) the non-inferiority is in the lower line

Table 9: Mean percent changes from baseline at the eighth week in comparative study of pitavastatin 2 mg daily and simvastatin 20 mg daily in Korean patients with primary hypercholesterolemia **[44]**.

Serum lipids	Mean percent change from baseline (%) (SD)				
	n	**Pitavastatin (2 mg)**	***N***	**Simvastatin (20 mg)**	**p-value**
LDL-C	*49*	-38.2 (11.6)	*46*	-39.4 (12.9)	0.648
TC	*49*	-26.9 (8.9)	*46*	-28.5 (8.7)	0.405
HDL-C	*49*	8.3 (13.4)	*46*	3.6 (16.2)	0.127
TG[a]	*28*	-29.8 (20.6)	*19*	-17.4 (36.9)	0.147

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

[a] Patients with baseline TG levels ≥ 150 mg/dL were included in the analysis. Significant was set at $p<0.05$

Yokote, et al. (2008) conducted collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA) study, a randomized, multi-center, open-label study, to compare the efficacy and safety of pitavastatin and atorvastatin in Japanese patients with hypercholesterolemia. After a 4-week dietary lead-in period, eligible patients were randomized to receive either 2 mg of pitavastatin or 10 mg of atorvastatin once daily for 12 weeks. At the end of treatment, there was no significant difference in percent change of LDL-C from baseline between pitavastatin and atorvastatin groups (-42.6% vs. -44.1%, p=0.456). Both pitavastatin and atorvastatin were also no significant difference in percent change of non-HDL-C, TC, and TG from baseline. HDL-C showed a significant increase at week 12 with pitavastatin group (3.2%, p=0.033 vs. baseline) but not with atorvastatin group (1.7%, p=0.221 vs. baseline). These results were shown in Table 10.

Similarly, an 8-week, multi-center, randomized, open-label, dose-titration study by Lee, et al., pitavastatin 2 mg/day (n=110) was found to be noninferior to atorvastatin 10 mg/day (n=112) in term of reducing LDL-C (-42.9 vs. -44.1, p=0.45). In addition, there were also no significant differences between groups in terms of the percent changes from baseline in TC, TG, and HDL-C **[34]**. These results confirmed that pitavastatin 2 mg/day and atorvastatin 10 mg/day were equivalent potency.

However, Tendency of the starting dose of pitavastatin in current clinical practice to initiate therapy is 2 mg once daily. On the other hand, Toshitomi, et al. study, a 12-week, open-label, non-randomized trial, found that there were no significant differences in the percent change of LDL-C levels between pitavastatin 1 mg once daily and atorvastatin 10 mg daily (38%±13 vs. 41%±12, P>0.05). In addition, pitavastatin group and atorvastatin group were no significant difference in percent change of TC and HDL-C as shown in Table 11 **[46]**. Although this result indicated that pitavastatin 1 mg once daily and atorvastatin 10 mg once daily were equivalent potency in LDL-C reduction as the initial therapy, it may be uselessness by selection bias from non-randomized design.

Table 10: Mean percent changes from baseline at the twelfth week in comparative study of pitavastatin 2 mg daily and atorvastatin 10 mg daily in Japanese patients with primary hypercholesterolemia (CHIBA study) **[45]**.

	Mean percent change from baseline (%) (SD)		
Serum lipids	**Pitavastatin 2 mg (N= 93)**	**Atorvastatin 10 mg (N= 98)**	**P value**
LDL-C	-42.6 (12.1)	-44.1 (11.1)	0.456
TC	-29.7 (8.9)	-31.1 (9.4)	0.341
TG	-17.3 (32.4)	-10.7 (33.7)	0.247
HDL-C	3.2 (13.0)	1.7 (12.7)	0.457
Non-HDL-C	-39.0 (11.1)	-40.3 (11.3)	0.456

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride; TC = total cholesterol
Significant was set at p<0.05

Table 11: Mean percent changes from baseline at the twelfth week in comparative study of pitavastatin 1 mg daily and atorvastatin 10 mg daily in Japanese patients with primary hypercholesterolemia **[46]**.

Serum lipids	Mean percent change from baseline (%) ±SD	
	Pitavastatin 1 mg (N= 70)	**Atorvastatin 10 mg (N= 67)**
LDL-C	-38.0 ± 13.0	-41.0 ± 12.0
TC	-28.0 ± 8.0	-29.0 ± 10
TG	-11.0 ± 30	-21.0 ± 25*
HDL-C	3.0 ±12.0	7 ± 12

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

2.4 Safety and Tolerability Data

Pitavastatin at dose of 1, 2 and 4 mg have been well tolerated with a safety profile that is comparable to other statins. The results of eight clinical trials in Japan summarized that the subjective symptoms and objective findings assessed as adverse drug reactions were noted in 5.6% (50/886 subjects), but none of the events occurred at a rate > 1%. Abnormal laboratory parameters assessed as adverse drug reactions by the investigators were noted in 18.8% (167/886 subjects). Major changes included increased γ-glutamyl transpeptidase in 5.3%, increased CK in 4.6%, increased glutamyl pyruvic transaminase in 3.6% and increased glutamyl oxaloacetic transminase in 3.2% of subjects. These adverse reactions were similar to those observed with already marketed statins. Severe adverse drug reactions occurred in 0.9% and the administration was discontinued due to adverse drug reactions in only 2.8% of subjects **[39]**.

A large scale prospective post marketing surveillance (Livalo effectiveness and Safety Study; LIVES) investigation analyzed from 19,921 patients with hypercholesterolemia in Japan reported that most of the adverse drug reactions were mild in severity. Common adverse drug reactions were blood creatine phosphokinase increased (2.74%), alanine aminotransferase increased (1.79%), aspartate aminotransferase increased (1.50%), myalgia (1.08%) and gamma glutamyltransferase increased (1.00%). In addition, incidences of adverse reactions

were also not high in comparison with other statins, 10.4% of pitavastatin compared with 12.0% of atorvastatin and 11.1% of rosuvastatin **[42]**. These results were shown in Table 12.

Moreover, pitavastatin did not affect the glucose parameters. Clinical trials reported that incidence of adverse reactions of increased plasma glucose and glycosylated hemoglobin A1C (A1C) was only 0.02% **[42]**. It is reported that glucose uptake in differentiated 3T3-L1 cells was unaffected by pitavastatin, whereas it was reduced by other statins **[64]**. Retrospective study by Sasaki, et al. demonstrated that diabetic patients receiving pitavastatin 2 mg/day for 3 months were not different in the change of glucose blood levels from baseline (from 155±53 to 154±51 mg/dL) and the change of A1C levels from baseline (from 7.2±1.0 to 7.3±10 mg/dL). There was no correlation between percent change of LDL-C and A1C from baseline **[65]**. Therefore, pitavastatin is useful for lowering LDL-C in diabetic patients without interference with blood glucose levels or A1C

Table 12: Adverse reactions and major abnormalities in LIVES study compared with other statins conducted in Japan **[39, 42]**

	Pitavastatin	**Atorvastatin**	**Rosuvastatin**
Number of cases investigated	19,925	4,805	8,795
Incidence of adverse reactions	10.4%	12.0%	11.1%
Increased CK (CPK)	2.74%	2.2%	2.3%
Increased ALT (GPT)	1.79%	1.8%	0.7%
Increased AST (GOT)	1.5%	1.1%	0.5%
Increased γ-GTP	1.0%	1.9%	0.6%
Increased plasma glucose	0.02%	0.37%	0.01%
Increased A1C	0.02%	0.25%	0.01%
Hematuria	0.01%	-	0.7%
Proteinuria	0.03%	0.2%	0.3%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CPK = creatine phosphokinase; GOT = glutamic oxaloacetic transaminase; GPT = glutamate pyruvate transaminase; GTP = glutamyltranspeptidase; A1C = glycosylated hemoglobin A1C

3. C-reactive Protein

C-reactive protein (CRP) is an acute phase reactant that is synthesized by hepatocytes, predominantly under transcriptional control by the cytokine IL-6. In healthy young adult volunteer blood donors, the median concentration of CRP is 0.8 mg/l, the 90^{th} centile is 3.0 mg/l, and the 99^{th} centile is 10 mg/l, but following an acute-phase stimulus, values may increase from less than 50 μg/l to more than 500 mg/l, that is, 10,000-fold. The hepatic synthesis starts very rapidly after a single stimulus, serum concentrations rising above 5 mg/l by about 6 hours and peaking around 48 hours. The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate (3), which thus directly reflects the intensity of the pathological process stimulating CRP production. When the stimulus for increased production completely ceases, the circulating CRP concentration falls rapidly, at almost the rate of plasma CRP clearance **[66, 67]**.

A sizable number of studies have examined that CRP is inflammation marker for consideration as predictors of cardiovascular risk. It is employable in clinical settings, after consideration of the stability for analysis, the commercial availability of assays, the standardization of those assays to allow comparison of results, and the precision of the assays as measured by the coefficient of variation. However, the CRP laboratory test was necessary to detect the low-grade inflammation associated with CVD. Therefore, high-sensitivity CRP (hsCRP) analytical method was developed to detect below 0.3 mg/L of CRP levels with acceptable precisions **[19, 67]**.

The coefficient of variation of hsCRP assays is generally <10% from the 0.3- to 10-mg/L range. Considerable within-individual variability exists for hsCRP. Sources of variation of inflammatory markers have been studied to varying degrees. There seems to be little seasonal or diurnal variation with hsCRP. Several factors have been identified as being associated with increased or decreased levels of hsCRP (Table 13); this list is likely incomplete. For example, body weight and the metabolic syndrome are consistently associated with elevated hsCRP, and weight loss is associated with reduction in hsCRP level. This association of hsCRP with these conditions is poorly defined from a mechanism standpoint, and is possibly due to co association with prevalent vascular disease. Individuals with evidence of active infection, systemic inflammatory processes, or trauma should not be tested until these

conditions have abated. An hsCRP level of >10 mg/L, for example, should be discarded and repeated in 2 weeks to allow acute inflammations to subside before retesting **[68, 69]**.

Atherosclerosis is considered to be an inflammatory response to injury. The major injurious factors that promote atherogenesis (e.g., cigarette smoking hypertension, atherogenic lipoproteins and hyperglycemia) are well established. This process begins with injury to vascular endothelium in response to these risk factors, leading to oxidation and macrophage uptake of LDL-C and formation of the fatty streak. The fatty streak is the initial building block in the development of the atherosclerotic plaque. These early steps of atherogenesis also involve the elicitation of proinflammatory cytokines causing hepatic stimulation and production of CRP. Moreover, CRP may contribute to atherosclerosis by facilitating macrophage uptake of LDL-C, thus accelerating fatty-streak formation. These findings have stimulated research examining the potential role of CRP as a predictive tool for future cardiovascular events **[19, 47, 70]**

Table 13: Patient characteristics and conditions associated with increased or decreased levels of hsCRP **[19, 67, 69].**

Increased Levels	**Decreased Levels**
Elevated blood pressure	Moderate alcohol consumption
Elevated body mass index	Increased activity/endurance exercise
Cigarette smoking	Weight loss
Metabolic syndrome/diabetes mellitus	Smoking cessation
Low HDL-C/high TG	Medications
Estrogen/progestogen hormone use	Statins
Chronic infections (gingivitis, bronchitis)	Fibrates
Chronic inflammation (rheumatoid arthritis)	Niacin
	Aspirin
	Tamoxifen
	Thiazolidinediones

Several studies have shown a dose-response relationship between the level of hsCRP and risk of incident coronary disease (i.e., coronary, and peripheral vascular disease), with minimal correlation to LDL-C **[19-26]**. This suggests that CRP may identify individuals who traditionally would not have met the criteria for treatment based solely on lipid levels. Therefore, a recent published review article and scientific statement by the American Heart Association and Centers for Disease Control and Prevention on "Markers of Inflammation and Cardiovascular Disease" recommends using hsCRP as an adjunct to the lipid panel to predict future cardiovascular events in patients who had 10-20% of 10-year risk for CHD **[19]**.

Statins are highly effective in reducing the risk of CVD. One of the potential mechanisms contributing to the beneficial effects of lipid lowering in patients with CVD is a reduction of inflammation. This effect may be due to extensive immunomodulatory properties that operate independently of lipid lowering (pleiotropic effect) **[47]**. Statins have been hypothesized to have direct anti-inflammatory effects by reduce macrophage content within atherosclerotic plaques, suppress the expression of metalloproteinases involved in the fibrous cap dissolution, and inhibit the expression of adhesion molecules critical for monocyte attachment and adhesion to the endothelial wall **[28]**. The ability of statins to reduce serum CRP has been demonstrated in a number of trials. These studies have indicated that serum CRP is decreased from baseline after receiving pravastatin 40 mg per day (13.1% to 20.3%), lovastatin 20 to 40 mg per day (12.5% to 17.4%), cerivastatin 0.4 to 0.8 mg per day (13.3% to 24.5%),fluvastatin 20 mg per day (15.9%), simvastatin 20 to 40 mg per day (22.8% to 37.2%), atorvastatin 10 to 80 mg per day (15.0% to 47.0%), and pitavastatin 2 mg per day (32.9%) (all $p<0.05$) **[27-29]**. However, the effect of pitavastatin 1 mg per day on hsCRP has not been studied yet.

4. Fibrinogen

Fibrinogen is a protein synthesized by liver which plays two essential roles in the body. One, it is a vital part of the "common pathway" of the coagulation process. The conversion of fibrinogen (factor I) to fibrin is the last step of the "coagulation cascade", a series of reactions in the blood triggered by tissue injury and platelet activation. And two, it is also a protein called an acute phase reactant that becomes elevated with tissue inflammation or tissue destruction. When fibrinogen acts as an "acute phase reactant", it rises sharply during tissue inflammation or injury. Most

acute myocardial infarctions (heart attack) are now known to be due to acute thrombosis, or the sudden formation of a blood clot at the site of an atherosclerotic plaque. It makes sense, therefore, that elevated levels of fibrinogen, an acute phase protein and is part of the coagulation cascade of proteins, would be associated with an increase in risk of heart attack**[19]**. There are many factors that affect the fibrinogen levels (Table 14).

Table 14: Patient characteristics and conditions associated with increased or decreased levels of fibrinogen **[73].**

Increased Levels	**Decreased Levels**
Cigarette smoking	Regular physical activity
Oral contraceptive drugs	Prostate cancer
Steroid hormones	Liver disease
Positive energy balance	Alcohol
Diabetes mellitus	Drugs:
Pregnancy	Ticlopidine
High dietary fat intake	Bezafibrate
Increasing age	Phenobarbital
Menopause	Valproic acid
Inflammation	Urokinase
Thrombin endotoxin	Streptokinase
Prostaglandins	
Stomatch, breast, or kidney cancers	
Vascular damage	

Several studies have demonstrated that fibrinogen is an independent risk factor for CHD **[10, 19, 71, 72]**. Meresca, et al. (1999) conducted a meta-analysis to examine the association between fibrinogen and CVS. This study showed that the overall risk of cardiovascular event in subjects with plasma fibrinogen levels in the higher tertile, was twice as high as that of subjects in the lower one (odds ratio, 1.99; 95% confidence interval, 1.85 to 2.13). The study also indicated that high plasma fibrinogen levels were associated with an increased risk of CVD in healthy as much as in high risk individuals **[73]**.

Experimental and clinical studies have indicated a relationship between hyperlipidemia and increased blood thrombogenicity. This implied that correction of hypercholesterolemia by statins could normalize blood thrombogenicity. However, conflicting findings on the effect of different statins on fibrinogen have been reported **[36, 37, 72]**. Most studies reported an increase of serum fibrinogen with atorvastatin and lovastatin (ranging from 19.3% to 26.0%), a neutral effect on serum fibrinogen with fluvastatin and simvastatin, and a decrease of serum fibrinogen with pravastatin (ranging from 7.0% to 19.0%) **[37, 38, 74, 75]**. Currently, the effect of new statins, pitavastatin, on serum fibrinogen has not been studied. Therefore, the study is needed to examine the effect of pitavastatin on serum fibrinogen.

CHAPTER III
RESEARCH METHODOLOGY

This study was carried out to compare the efficacy and safety of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily in outpatients with hypercholesterolemia in terms of: (1) serum lipids, hsCRP, and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals according to NCEP ATP III guidelines, (3) adverse event rates, and (4) Annual cost of drug treatment.

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

1. Patients

1.1 Patient Selection

The Subjects of this study were patients with hypercholesterolemia who visited outpatient department of Phramongkutklao Hospital between November 2008 to May 2009, who had never received statins, and met the following criteria:

Inclusion criteria:

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

Exclusion criteria:

1. diagnosed with secondary hypercholesterolemia.
2. took drugs known to affect the levels of lipids within 6 weeks before the study (i.e., progestin, estrogen, corticosteroids, isotretinoin, protease inhibitors, cyclosporine, sirolimus, mirtazapine, interferons, asparaginase, and azole antifungals).
3. took drugs known to affect the levels of hsCRP and fibrinogen within 6 weeks before the study (i.e., azole antifungals, bile acid resins, verapamil, cyclosporine, fusidic acid, grape fruit, azithromycin, clarithromycin, erythromycin, phenytoin, and protease inhibitors).

4. took drugs interacted with pitavastatin and atorvastatin within 6 weeks before the study (i.e., estrogen, fibrates, tamoxifen, ticlopidine, corticosteroids, thiazolidinedione, phenobarbital, valproic acid, urokinase, and streptokinase).
5. had an active liver disease or elevated liver enzymes (AST, ALT > 3 times the upper limit of normal).
6. had creatine kinase > 10 times the upper limit of normal.
7. had severe renal impairment (creatinine clearance < 30 mL/min).
8. had chronic inflammatory conditions (i.e., severe arthritis, lupus, or inflammatory bowel disease).
9. had cancer or history of cancer.
10. had recent infection or illness (within 2 weeks before the study).
11. had been hospitalized for acute coronary syndrome within 3 months before the study.
12. had pregnancy or lactation.
13. had TG level > 400 mg/dL
14. had serious medical or psychological conditions that may compromise successful participation in the study.

If the patients had an intolerable adverse event, serum AST, ALT > 3 times the upper limit of normal, or CK> 10 times the upper limit of normal, hypersensitivity to statins, or required other lipid lowering agent (i.e., fibrates, niacin, bile-acid sequestrants, and cholesterol absorption inhibitor) or required other drugs that interacted with pitavastatin and atorvastatin during the study period, these patients would be excluded.

1.2 Sample Size Estimation

An estimated sample of 100 subjects was calculated by using equation (1), at an α significance level of 0.05 (i.e., Type I error) and a power of 80% [83]. The differences of percent LDL-C reduction between pitavastatin 1 mg once daily and atorvastatin 10 mg once daily were assumed as Yoshitimi, et al. and Yokote, et al. studies, because there is, currently, no comparative study of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily in randomized design. Yoshitimi, et al. found that percent changes in LDL-C reduction of pitavastatin 1 mg group (n=70) and atorvastatin 10 mg group (n=67) were 38±13 and 41±12, respectively **[46]**. However,

these results may effected by selection bias from non-randomized design, then potency in LDL-C reduction of atorvastatin 10 mg conducted as randomized trial by Yokote, et al. was used to calculate sample size instead of by Yoshitimi, et al. Yokote, et al. found that percent changes in LDL-C reduction of atorvastatin 10 mg group (n=125) were 44.1±11 **[45]**.

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

No know σ^2, so used S_p^2 (pooled variance) instead that calculated by equation (2)

$$S_p^2 = \frac{(n_1-1) S_1^2 + (n_2-1) S_2^2}{n_1+ n_2-2} \quad \text{....equation (2)}$$

Determination: $n_1 = 70$ $n_2 = 125$,

$S_1 = 0.13$ $S_2 = 0.111$

$$S_p^2 = \frac{(70-1) (0.132) + (125-1) (0.1112)}{70+125 – 2}$$

$$= 0.014$$

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

$\beta = 0.20$ (one-sided); $Z_\beta = 0.84$

d = non-inferiority margin of LDL-C reduction **[44]** = 0.07

$$N/group = 2 (1.96+0.84)^2 (0.014)/0.07^2$$

$$= 44.8 \approx 45 \text{ subjects}$$

Estimate drop out 10%

$$N/group = 45/ (1-0.1) = 50 \text{ subjects}$$

Therefore, 100 patients were recruited for this study (50 subjects per group).

1.3 Patient Randomization

One hundred patients were randomly assigned equally into two groups using block of four randomization. One group received pitavastatin 1 mg once daily at 8.00

p.m. for 8 weeks and another group also received atorvastatin 10 mg once daily at 8.00 p.m. for 8 weeks. Then, simple random sampling was used to determine each group.

2 Methods

2.1 Study Design and Procedures

This randomized, open-label, parallel study was approved by the ethic committee of Phramongkutklao Hospital. Prior to study, the patient record forms (appendix A), research subject information sheets (appendix B), consent forms (appendix C), and Naranjo's algorithm (appendix D) had been developed. At study initiation, the patients diagnosed with hypercholesterolemia were screened by physicians and referred to the researcher for subject eligibility assessment. Subject eligibility was determined by laboratory data (TC, TG, HDL-C, LDL-C, AST, ALT, CK, and creatinine), patient interviews, and OPD cards review. If laboratory data had not been completed, the patients would have been given a detailed explanation of the study and asked for blood sampling appointment. All eligible patients were invited to participate in this study. After both verbal and non-verbal description of the study (e.g., an assurance of confidentiality and the right to refuse), patients provided written consent forms. The patient demographic data and laboratory data were recorded in the patient record forms. Blood pressure (BP) was also measured and recorded by using blood pressure monitoring machine (OMRON Digital Blood Pressure Monitor HEM-907, Japan). Then, all patients were educated about undesirable outcomes of hypercholesterolemia, risk factors for CHD, individual risk category and LDL-C goals, TLCs, and studying drug (e.g. name, regimens, indications, and adverse drug reactions). The researcher believed that this was the strategy that encouraged the patients to realize the dangers of hypercholesterolemia and to adhere to their drugs and TLCs, and this also made the patients be able to observe the adverse events, to record and to tell the physician or researcher. Patients who did not have data on hsCRP, fibrinogen, or fasting blood sugar (FBS) were also made an appointment to obtain these data.

The patients were randomly assigned to receive pitavastatin 2 mg (supplied by Livalo®; licensed to Kowa Company, Ltd. and Nissan Chemical Industries, Ltd. of Japan) half tablet once daily or atorvastatin 10 mg (Lipitor®; licensed to Pfizer (Thailand) Ltd.) once daily for 8 weeks by block randomization. In the pitavastatin

group, tablet splitting technique by pill splitter was used to improve compliance. The researcher followed up the patients via telephone at first, forth, and seventh week of the study to monitor adverse events and other problems. On the other hand, patients could phone the researcher directly at anytime. If the problems had occurred, patients would have been given the advices and/or invited to visit a hospital for further evaluation.

At the end of 8-week, the efficacy, safety, and compliance of pitavastatin and atorvastatin were evaluated. Twelve-hour fasting blood sample was obtained to evaluate changes in lipids, hsCRP, fibrinogen, and safety parameters. The percentages of patients achieving LDL-C goals as defined by NCEP ATP III guidelines and annual cost of drug treatment were also assessed. Blood sample was collected between 6.00 a.m. to 10.00 a.m. Safety and tolerability were evaluated throughout the study on the basis of adverse events reporting, patient interviews, physical examinations, and laboratory studies (i.e., AST, ALT, and CK levels). All adverse events were assessed the causality from the study drug using Naranjo's algorithm and reported to the Ministry of Public Health. Drug compliance was evaluated by using pill count technique. In addition, all patients were interviewed about their lifestyles, diet control, exercise, and other problems during the study period. The diagram of the study procedure is shown in Figure 3.

2.2 Laboratory Measurement

Fasting lipid panels, hepatic enzyme panels, CK, creatinine, hsCRP, and fibrinogen concentration were obtained as baseline data at random between 6.00 a.m. and 10.00 a.m. before the study period and again on the last day of the 8-week period. Cholesterol levels, hepatic transaminase enzymes, CK, creatinine, and hsCRP were measured by using the COBAS INTEGRA 800 Roche Diagnostic (GmbH D-68298, Mannheim, Germany) at the central laboratory of Phramongkutklao Hospital. hsCRP was assayed by particle enhanced immunoturbidimetric technique. Fibrinogen level was analyzed using turbidimetric method with the DigiSpec Helena Laboratories (Germany). Both instruments were calibrated and standardized daily by technical staffs.

2.3 Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 17.0. Intention to treat analysis was used by replacing the missing data with series mean for each group. Both descriptive and inferential statistics were determined. The level of significance was set at $\alpha = 0.05$ and the power of the test was set at $1-\beta = 0.8$.

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

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

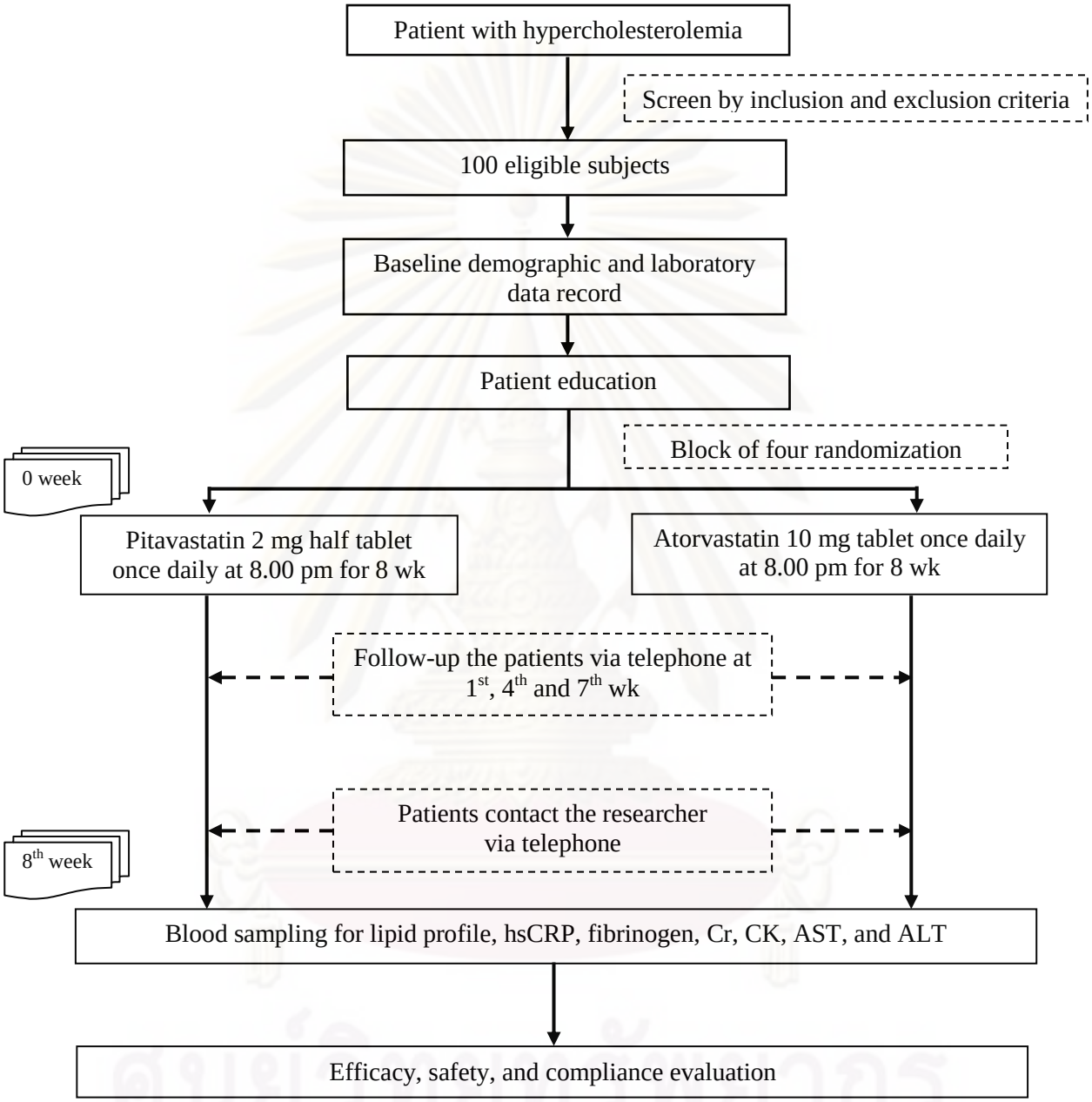

Figure 3: The study procedure diagram.

CHAPTER IV

RESULTS AND DISCUSSIONS

The study was a randomized, open-label, parallel trial. The purpose was to compare the efficacy and safety of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily in terms of: (1) serum lipids, hsCRP, and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals according to NCEP ATP III guidelines, (3) adverse event rates, and (4) annual cost of drug treatment.

This chapter is divided into 3 parts:

1. Baseline patient characteristics which consist of baseline patient demographics and clinical laboratory data.
2. Efficacy evaluation including the efficacy of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily on serum lipids, hsCRP, and fibrinogen changing from baseline, the percentage of patients who achieved their LDL-C goals according to NCEP ATP III guidelines, and annual cost of drug treatment.
3. Safety evaluation.

1. Baseline Patient Characteristics

1.1 Baseline Patient Demographics

Patients with hypercholesterolemia who met the inclusion criteria were recruited to participate in this study. Figure 4 depicts the patient flow diagram. Of 100 patients enrolled, 98 patients completed the 8-week study period (48 patients in pitavastatin group and 50 patients in atorvastatin group). Two patients on pitavastatin were excluded from the study, because they had adverse events (i.e., muscle pain, nausea, and vomiting).

Table 15 and Table 16 summarize the baseline patient demographic data. The result shows that 60.0% of patients were female. This finding agreed with previous studies in that the proportion of Thai women with hypercholesterolemia is higher than men (54.90% - 63.64% of female) **[15, 76]**. This is also similar to the results reported by Wongwiwatthananukit, et al. and Phruttisunakon in those 60.0% to 64.4% of hypercholesterolemic patients at Phramongkutklao Hospital were female **[16, 77]**.

The mean age of patients in this study was 58.74 ± 10.02 years, ranging from 35 to 81 years. This finding was similar to the results from two previous studies at Phramongkutklao Hospital indicated that mean age of hypercholesterolemic patients were 59.64 ± 9.89 years (ranging from 41 to 82 years) and 60.56 ± 9.57 years (ranging from 43 to 79 years) **[16, 77]**. Most common age range was 50 -59 years, representing 34% of patients. This age range is considered as one of the major risk factors for CHD. The average weight and height were 62.60 ± 11.37 kg and 159.78 ± 9.11 m, respectively. The mean body mass index (BMI) was 24.45 ± 3.51 kg/m^2 ranging from 16.63 to 32.87 kg/m^2. The common BMI range was 25 – 29.9 kg/m^2, representing 42% of patients, which was classified as obese patients according to the World Health Organization (WHO) criteria for Asia-Pacific region **[78]**.

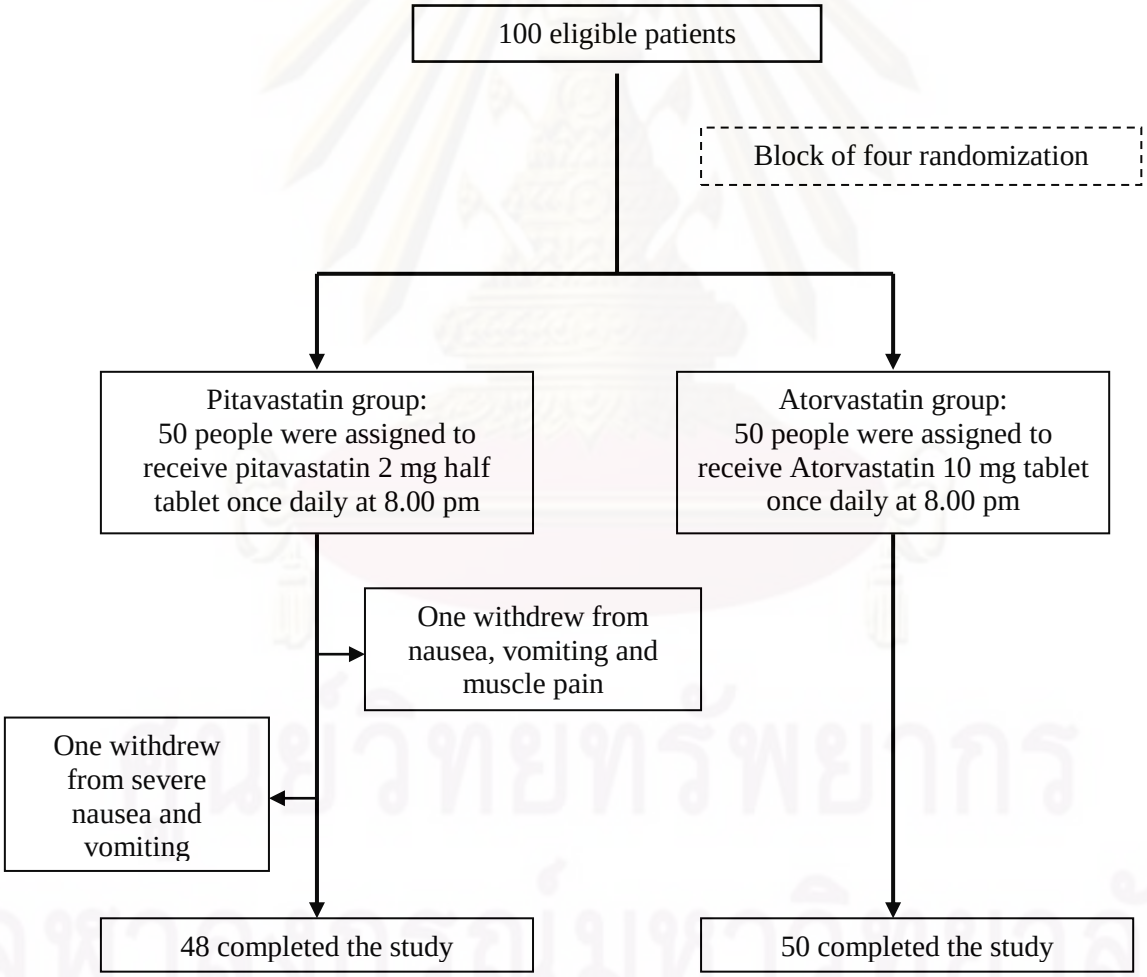

Figure 4: Patient flow diagrams**.**

Table 15: Baseline patient demographics in categorical data.

Variable	No. of patients (%)*			p- value[a]
	Pitavastatin group (N=50)	Atorvastatin group (N=50)	Total (N=100)	
Sex				
- Male	16 (32.0)	24 (48.0)	40 (40.0)	0.102
- Female	34 (68.0)	26 (52.0)	60 (60.0)	
AGE				
- 30-39 years	0 (0.0)	3 (6.0)	3 (3.0)	
- 40-49 years	9 (18.0)	7 (14.0)	16 (16.0)	
- 50-59 years	15 (30.0)	19 (38.0)	34 (34.0)	0.142 [b]
- 60-69 years	19 (38.0)	10 (20.0)	29 (29.0)	
- 70-79 years	7 (14.0)	10 (20.0)	17 (17.0)	
- ≥ 80 years	0 (0.0)	1 (2.0)	1 (1.00)	
BMI (kg/m^2)				
- <18.5 (underweight)	1 (2.0)	3 (6.0)	4 (4.0)	
- 18.5-22.9 (normal range)	15 (30.0)	16 (32.0)	31 (31.0)	0.853
- 23-24.9 (at risk)	10 (20.0)	7 (14.0)	17 (17.0)	
- 25-29.9 (obese I)	21 (42.0)	21 (42.0)	42 (42.0)	
- ≥ 30 (obese II)	3 (6.0)	3 (6.0)	6 (6.0)	
Waist circumference (inches)				
- > 36 inches in male	8 (50.0)	14 (58.3)	22.0 (55.0)	0.604
- > 32 inches in female	27 (79.4)	16 (61.5)	43 (71.7)	0.128
Underlying diseases				
- Hypertension	38 (76.0)	30 (60.0)	68 (68.0)	0.086
- Diabetes mellitus	9 (18.0)	9 (18.0)	18 (18.0)	1.000
- Coronary heart disease	3 (6.0)	3 (6.0)	6 (6.0)	1.000 [b]
- Cerebrovascular disease	1 (2.0)	3 (6.0)	4 (4.0)	0.617 [b]
- Gout	2 (4.0)	1 (2.0)	3 (3.0)	1.000 [b]
Number of concurrent drugs[c]				
- 0-5 drugs	39 (78.0)	39 (78.0)	78 (78.0)	1.000
- > 5 drugs	11 (22.0)	11 (22.0)	22 (22.0)	
Smoker	5 (10.0)	3 (6.0)	8 (8.0)	0.715 [b]

* percent each regimen for the pitavastatin and the atorvastatin group columns, or percent of all patients in a total column

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

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

[c] lists of concurrent drug are shown in Table 17.

Table 16: Baseline patient demographics in continuous data.

Variable	Mean ± SD (range)			p- value[a]
	Pitavastatin group (N=50)	Atorvastatin group (N=50)	Total (N=100)	
Age (years)	59.20 ± 9.04 (41 to 77)	58.28 ± 10.98 (35 to 81)	58.74 ± 10.02 (35 to 81)	0.648
Weight (kg)	61.98 ± 10.21 (40.20 to 84.00)	63.22 ± 12.50 (41.00 to 89.30)	62.60 ± 11.37 (40.20 to 89.30)	0.586
Height (m)	158.82 ± 9.18 (140.0 to 180.0)	160.74 ± 9.04 (143.0 to 178.0)	159.78 ±9.11 (140.0 to 180.00)	0.295
BMI (kg/m2)	24.55 ± 3.39 (16.95 to 32.87)	24.34 ± 3.66 (16.63 to 31.63)	24.45 ± 3.51 (16.63 to 32.87)	0.765
Waist circumference (inches)	35.08 ± 4.02 (25.50 to 45.00)	34.64 ± 4.24 (25.50 to 45.00)	34.86 ± 4.11 (25.50 to 45.00)	0.595
SBP (mmHg)	132.68 ± 18.22 (95 to 175)	135.02 ± 24.30 (82 to 198)	133.85 ± 21.40 (82 to 198)	0.587
DBP (mmHg)	79.74 ± 11.37 (53 to 103)	80.24 ± 12.48 (50 to 111)	79.99 ± 11.88 (50 to 111)	0.834
Number of concurrent drugs	3.44 ± 2.36 (0 to 8)	3.92 ± 3.32 (0 to 17)	3.68 ± 2.87 (0 to 17)	0.406

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

[a] using independent t-test to compare mean between pitavastatin group and atorvastatin group

The obesity was one of the problems in these patients and associated with CVD. However, obesity is a modifiable risk factor; therefore, the role of healthcare professionals on these patients should be initiated to control their weight. Overall, mean waist circumference was 34.86 ± 4.11 inches (ranging from 25.50 to 45.00 inches). The waist circumference (more than 36 inches in male and 32 inches in female) associated with the cardiovascular risk factors of the metabolic syndrome was identified in both male and female.

Most underlying diseases of patients in this study were hypertension (68%) and diabetes mellitus (18%). This finding is consistent with the result conducted by Phruttisunakon in that 71.2% had hypertension and 16.9% had diabetes mellitus **[77]**. Both hypertension and diabetes mellitus are the independent major risk factors for CHD. Therefore, NCEP ATP III recommended that treated hypertension should also count as a risk factor for setting goals of LDL-C in primary prevention and diabetes mellitus should be treated as a separate category of high risk **[10]**. The overall mean systolic blood pressure and diastolic blood pressure were 133.85 ± 21.40 mmHg

and 79.99 ± 11.88 mmHg, respectively which were classified as prehypertension according to JNC VII criteria **[79]**. In addition from subgroup analysis (Appendix E), mean systolic blood pressure and diastolic blood pressure of patients with hypertension who received drug therapy were 140.50 ± 20.19 mmHg and 81.71 ± 11.78 mmHg, respectively. These finding showed the failure of treatment and need more attention to achieve their goals, especially in patients who had both hypertension and diabetes mellitus.

Most patients (78%) got equal or less than five concurrent drugs (mean of the number of concurrent drugs were 3.68 ± 2.87 drugs). The number of patients who received each type of concurrent drug was not significantly different between the pitavastatin and atorvastatin groups (all $p>0.05$) (Table 17). Only eight patients (8%) currently smoked. These are small percentage which may be due to the success of the recent government campaign, increase in physician reinforcement and increase in awareness and concern of patients. The number of patients who smoked cigarettes was not significantly different between the pitavastatin and atorvastatin groups (Table 15).

Table 18 summarizes the major risk factors for CHD and patient risk category. The first most common major risk factor was age (male ≥ 45 years, or female ≥ 55 years or premature menopause without estrogen replacement therapy), representing 88% of patients. The second most common was hypertension, representing 72% of patients. These results are consistent with the previous studies in that age was most common major risk factor (85% to 90.5%) followed by hypertension (52.4% to 76.3%) **[16, 77, 80, 81]**. Sixty percent of patients had more than one major risk factor (45%, 14% and 1% of patients had two, three and four major risk factors, respectively). There was no significant difference in the number of patients each risk category. Patients in low, moderate, moderately high and high risk categories were accounted for 30%, 21%, 21% and 28%, respectively.

Comparison of patient baseline demographic data of the pitavastatin group with the atorvastatin group was tested by independent t-test for continuous data and Chi-square (χ^2) test or Fisher's exact test for categorical data. The results showed that there were no significant differences between two groups in terms of: sex, age, age ranges, weight, height, BMI, BMI ranges, waist circumference, waist circumference ranges, underlying diseases, SBP, DBP, number of concurrent drugs, smoker, type of

Table 17: Comparison of concurrent drugs between pitavastatin and atorvastatin groups.

Concurrent drugs**	Number of patients (%)*			p-value[a]
	Pitavastatin group (N=50)	Atorvastatin group (N=50)	Total (N=100)	
Acarbose	0 (0.0)	2 (4.0)	2 (2.0)	0.495
ACEIs/ARBs[†]	27 (54.0)	24 (48.0)	51 (51.0)	0.548
Allopurinol	2 (4.0)	1 (2.0)	3 (3.0)	1.000
Antianginal drugs[γ]	3 (6.0)	1 (2.0)	4 (4.0)	0.613
Aspirin	9 (18.0)	7 (14.0)	16 (16.0)	0.585
α-blockers[††]	3 (6.0)	1 (2.0)	4 (4.0)	0.617
β-blockers[†††]	11 (22.0)	10 (20.0)	21 (21.0)	0.806
Calcium channel blockers[††††]	21 (42.0)	14 (28.0)	35 (35.0)	0.142
Celecoxib	1 (2.0)	3 (6.0)	4 (4.0)	0.617
Clopidogrel	0 (0.0)	1 (2.0)	1 (1.0)	1.000
Colchicine	2 (4.0)	1 (2.0)	3 (3.0)	1.000
Diclofenac	1 (2.0)	0 (0.0)	1 (1.0)	1.000
Diltiazem	0 (0.0)	3 (6.0)	3 (3.0)	0.242
Diuretics[†††††]	15 (30.0)	7 (14.0)	22 (22.0)	0.054
Gabapentin	0 (0.0)	1 (2.0)	1 (1.0)	1.000
Gliclazide	1 (2.0)	2 (4.0)	3 (3.0)	1.000
Glipizide	6 (12.0)	3 (6.0)	9 (9.0)	0.487
Metformin	9 (18.0)	8 (16.0)	17 (17.0)	0.790
Paracetamol + orphenadrine	3 (6.0)	3 (6.0)	6 (6.0)	1.000
Piroxicam	1 (2.0)	0 (0.0)	1 (1.0)	1.000
Proton pump inhibitors[γγ]	4 (8.0)	7 (14.0)	11 (11.0)	0.617
Verapamil	0 (0.0)	1 (2.0)	1 (1.0)	1.000
Warfarin	0 (0.0)	2(4.0)	2 (2.0)	0.495

* percent each regimen for the pitavastatin and the atorvastatin group columns, or percent of all patients in a total column

** other concurrent drugs include amitryptyline (N =1), vitamin B1-6-12 (N =11), vitamin B complex (N =2), betahistine (N =3), clonazepam (N =1), diazepam (N =1), domperidone (N =1), finasteride (N =1), folic acid (N =2), glucosamine (N =6), lorazepam (N =1), mecobalamin (N =5), multivitamin (N =4), pracaterol (N =1), sertraline (N =2), and vitamin E (N =2) (all other drugs in the pitavastatin group were not significant different from the atorvastatin group; all $p>0.05$)

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

[†] ACEIs = angiotensin converting enzyme inhibitors (i.e., enalapril, lisinopril, perindopril, quinarapril, and ramipril) ARBs = Angiotensin II receptor blockers (i.e., candesartan, irbesatarn, telmesatarn, and valsatarn)

[††] α-blockers i.e., doxazosin, prazosin, tamsulosin

[†††] β-blockers i.e., atenolol, bisoprolol, and metoprolol

[††††] Cacium channel blockers i.e., amlodipine, felodipine, lercanidipine, manidipine, and nifedipine

[†††††] Diuretics i.e., hydrochlorothiazide, furosemide, and spironolactone

[γ] Antianginal drugs i.e., isosorbide mononitrate and isosorbide dinitrate

[γγ] Proton pump inhibitors i.e., esomeprazole, omeprazole, pantoprazole, and rabeprazole

Table 18: Risk factors for coronary heart disease

Variable	Number of patients (%)*			p-value
	Pitavastatin group (N=50)	**Atorvastatin group (N=50)**	**Total (N=100)**	
Major risk factors				
- Age**	44 (88.0)	44 (88.0)	88 (88.0)	1.000 [a]
- Family history***	0 (0.0)	4 (8.0)	4 (4.0)	0.118 [b]
- Hypertension	39 (78.0)	33 (66.0)	72 (72.0)	0.181 [a]
- Smoking	5 (10.0)	3 (6.0)	8 (8.0)	0.715 [b]
- HDL-C < 40 mg/dL	8 (16.0)	3 (6.0)	11 (11.0)	0.110 [a]
- HDL-C ≥ 60 mg/dL†	14 (28.0)	12 (24.0)	26 (26.0)	0.648 [a]
No. of major risk factor (s)				
- 0 factor	8 (16.0)	7 (14.0)	15 (15.0)	0.597 [a]
- 1 factor	11 (22.0)	14 (28.0)	25 (25.0)	
- 2 factors	21 (42.0)	24 (48.0)	45 (45.0)	
- 3 factors	9 (18.0)	5 (10.0)	14 (14.0)	
- 4 factors	1 (2.0)	0 (0.0)	1 (1.0)	
Risk category				
- High risk: CHD or CHD equivalents †† (10-year risk > 20%)	14 (28.00)	14 (28.0)	28 (28.0)	0.799 [a]
- Moderately high risk: ≥ 2 risk factors (10-year risk 10-20%)	9 (18.0)	12 (24.0)	21 (21.0)	
- Moderate risk: ≥ 2 risk factors (10-year risk < 10%)	10 (20.0)	11 (22.0)	21 (21.0)	
- Low risk: 0-1 risk factor	17 (34.0)	13 (26.0)	30 (30.0)	

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

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

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

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

† negative risk factor

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

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

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

major risk factor, number of major risk factors, and risk categories (all p>0.05). Moreover, the number of patients each age range was not significantly different between two groups (p=1.00).

1.2 Baseline Clinical Laboratory Data

Baseline clinical laboratory data are listed in Table 19 and Table 20. The differences of baseline laboratory data between the pitavastatin and atorvastatin groups were determined by independent t-test for normal distribution continuous data or Mann-Whitney U test for non-normal distribution continuous data and Chi-square (χ^2) test or Fisher's exact test for categorical data. It shows that all data except AST (i.e., FBS, TC, TG, HDL-C, LDL-C, hsCRP, fibrinogen, ALT, CK, and creatinine) was not significantly different between the pitavastatin and atorvastatin groups (all $p>0.05$).

The central tendency of baseline FBS was reported by median because of non-distribution data. The overall median baseline FBS was 97 mg/dL, ranging from 75 to 266 mg/dL. The median baseline FBS of the pitavastatin group (96 mg/dL, ranging from 75 to 266 mg/dL) was not significantly different with the atorvastatin group (98 mg/dL, ranging from 77 to 192 mg/dL) ($p=0.375$). These levels are normal range according to American Diabetes Association (ADA 2009) which classified these as normoglycemia **[82]**. In addition from subgroup analysis (Appendix E), the mean baseline FBS of patients with diabetes mellitus in pitavastatin group (N=9) was slightly higher than that in the atorvastatin group (N=9), but was not significantly different (157.56 ± 57.22 mg/dL vs. 139.67 ± 34.74 mg/dL; $p=0.435$). These FBS levels are higher than normal range and should be treated as a risk factor of metabolic syndrome.

Regarding baseline lipid profiles, the patients including in this study were dominant TC and LDL-C level regardless high TG and low HDL-C level. The mean baseline TC of all patients was 256.80 ± 40.60 mg/dL, ranging from 177 to 360 mg/dL. Similar to the results of Kitiyadisai and Phruttisunakon studies in that the mean baseline TC of all patients were 248.86 ± 35.32 mg/dL and 256.47 ± 48.54 mg/dL, respectively **[77, 83]**. There was no significant difference in baseline TC between pitavastatin group (258.44 ± 41.25 mg/dL, ranging from 183 to 360 mg/dL) and atorvastatin groups (255.16 ± 40.29 mg/dL, ranging from 177 to 355 mg/dL)

Table 19: Baseline clinical laboratory data.

Variable	Mean ± SD and Median (range)			p- value[a]
	Pitavastatin group (N=50)	**Atorvastatin group (N=50)**	**Total (N=100)**	
FBS (mg/dL)	106.34 ± 34.90 (75 to 266)	105.90 ± 24.97[#] (77 to 192)	106.12 ± 30.24 (75 to 266)	0.942
Median	*96**	*98**	*97**	0.375[b]
TC (mg/dL)	258.44 ± 41.25 (183 to 360)	255.16 ± 40.29 (177 to 355)	256.80 ± 40.60 (177 to 360)	0.688
TG (mg/dL)	145.22 ± 56.95 (44 to 308)	141.86 ± 49.08 (57 to 247)	143.54 ± 51.92 (44 to 308)	0.753
HDL-C (mg/dL)	53.40 ± 15.59 (23 to 112)	53.92 ± 13.05 (35 to 92)	53.66 ± 14.31 (23 to 112)	0.858
LDL-C (mg/dL)	175.99 ± 34.54 (111 to 259)	172.86 ± 34.53 (100 to 249)	174.43 ± 34.39 (100 to 259)	0.652
hsCRP (mg/L)	2.20 ± 2.09 (0.09 to 9.55)	1.95 ± 2.19 (0.06 to 12.00)	2.07 ± 2.14 (0.06 to 12.00)	0.340
Median	*1.31**	*1.10*	*1.24**	0.562[b]
Fibrinogen (mg/dL)	452 ± 80.66 (310 to 660)	439.80 ± 86.13 (280 to 730)	445.90 ± 83.24 (280 to 730)	0.467
AST (IU/L)	27.14 ± 13.68 (13 to 98)	22.54 ± 8.33 (9 to 61)	24.84 ± 11.50 (9 to 98)	0.045
Median	*23**	*21*	*22**	*0.039*[b]
ALT (IU/L)	25.88 ± 18.27 (7 to 96)	22.12 ± 11.67 (7 to 64)	24.00 ± 15.37 (7 to 96)	0.223
Median	*21**	*20*	*20.50**	*0.392*[b]
CK (IU/L)	109.82 ± 52.46 (10 to 243)	126.70 ± 94.68 (21 to 520)	118.26 ± 76.62 (10 to 520)	0.273
Median	*95.5*	*101.0*	*99**	*0.890*[b]
Creatinine; overall (μmol/L)	70.09 ± 17.13 (35.40 to 115.05)	79.30 ± 19.58 (44.25 to 132.75)	74.69 ± 18.88 (35.40 to 132.75)	*0.014*
Median	*70.80*	*79.65*	70.80*	*0.011*[b]
Creatinine; Male (μmol/L)	87.39 ± 13.28 (70.80 to 115.05)	91.82 ± 17.08 (70.80 to 132.75)	90.05 ± 15.64 (70.80 to 132.75)	*0.388*
Creatinine; Female (μmol/L)	61.95 ± 11.93 (35.40 to 97.35)	67.74 ± 13.92 (44.25 to 97.35)	64.46 ± 13.04 (35.40 to 97.35)	*0.089*
Median	*61.95**	*70.80*	61.95*	*0.081*[b]

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

\# missing data were replaced by series mean (1 missing value in atorvastatin)

* using median to represent the central tendency instead of mean because the data were not normal distribution

[a] using independent t-test to compare mean of FBS, TC, TG, HDL-C, LDL-C, fibrinogen, CK, and creatinine (male) between groups

[b] using Mann-Whitney U test to compare median of hsCRP, AST, ALT, and creatinine (female) between groups.

set a significant difference at $\alpha = 0.05$

Table 20: Number of patients in baseline laboratory category data.

Variable	No. of patients (%)			p-value[a]
	Pitavastatin group (N=50)	Atorvastatin group (N=50)	Total (N=100)	
TC (mg/dL)				
- < 200 (desirable)	3 (6.0%)	5 (10.0%)	8 (8.0%)	0.818
- 200 – 239 (borderline high)	14 (28.0%)	13 (26.0%)	27 (27.0%)	
- ≥ 240 (high)	33 (66.0%)	32 (64.0%)	65 (65.0%)	
TG (mg/dL)				
- < 150 normal	31 (62.0%)	27 (54.0%)	58 (58.0%)	
- 150 – 199 (borderline high)	11 (22.0%)	17 (34.0%)	28 (28.0%)	0.397
- 200 -499 (high)	8 (16.0%)	6 (12.0%)	14 (14.0%)	
- ≥ 500 (very high)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
HDL-C				
- < 40 mg/dL	8 (16.0%)	3 (6.0%)	11 (11.0%)	0.202
- 40 -59 mg/dL	28 (56.0%)	35 (70.0%)	63 (63.0%0	
- ≥ 60 mg/dL	14 (28.0%)	12 (24.0%)	26 (26.0%)	
LDL-C				
- < 100 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	
- 100 -129 mg/dL	5 (10.0%)	6 (12.0%)	11 (11.0%)	0.945
- 130-159 mg/dL	12 (24.0%)	11 (22.0%)	23 (23.0%)	
- 160-189 mg/dL	17 (34.0%)	15 (30.0%)	32 (32.0%)	
- ≥ 190 mg/dL	16 (32.0%)	18 (36.0%)	34 (34.0%)	
hsCRP (mg/L)				
- < 1 (low)	17 (34.0%)	20 (40.0%)	37 (37.0%)	0.250
- 1-3 (average)	18 (36.0%)	22 (44.0%)	40 (40.0%)	
- > 3 (high)	15 (30.0%)	8 (16.0%)	23 (23.0%)	
Fibrinogen (mg/dL)				
- < 200	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.529
- 200 - 400 (normal)	16 (32.0%)	19 (38.0%)	35 (35.0%)	
- > 400	34 (68.0%)	31 (62.0%)	65 (65.0%)	

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

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

[a] using Chi-square test to compare the number of patients in the pitavastatin group and atorvastatin group
set a significant difference at $\alpha = 0.05$

(p=0.688). Most common TC range was high level (≥ 240 mg/dL), representing 65% of patients. This level is higher than a desirable level as recommended by NCEP ATP III (TC should less than 200 mg/dL). Moreover, only 8% of patients had baseline TC in a desirable range.

Regarding the mean baseline TG, there was no significant difference between the pitavastatin and atorvastatin groups (p=0.753). The mean baseline TG in the

pitavastatin and atorvastatin groups were 145.22 ± 56.95 mg/dL (ranging from 44 to 308 mg/dL) and 141.86 ± 49.08 mg/dL (ranging from 57 to 247 mg/dL), respectively. The overall mean baseline TG was 143.54 ± 51.92 mg/dL (ranging from 44 to 308 mg/dL), which slightly lower than a previous results reported by Kitiyadisai (153.29 ± 76.50 mg/dL) and Phruttisunakon (163.57 ± 81.18 mg/dL) **[77, 83]**. According to TG levels are classified by NCEP ATP III guidelines, the common baseline TG range was normal level (lower than 150 mg/dL), representing 58% of all patients. The percentage of all patients who had baseline TG range higher than the normal level were 28% in borderline high level and 14% in high level. However, there was no significant difference in the number of patients each level between groups (p=0.397).

The overall mean baseline HDL-C was 53.66 ± 14.31 mg/dL (ranging from 23 to 112 mg/dL). Similar to the result of Kitiyadisai study in that the mean baseline HDL-C of all patients was 52.66 ± 15.96 mg/dL but this finding is slightly lower than reported in the Phruttisunakon study (57.25 ± 14.26 mg/dL) **[77, 83]**. The mean baseline HDL-C of the pitavastatin group (53.40 ± 15.59 mg/dL, ranging from 23 to 112 mg/dL) was not significantly different compared with the atorvastatin group (53.92 ± 13.05 mg/dL, ranging from 35 to 92 mg/dL) (p=0.858). According to HDL-C level classified by NCEP ATP III guidelines, there were 11% of all patients in low level (lower than 40 mg/dL) and 26% of all patients in high level (equal and more than 60 mg/dL). These results showed that most of patients (89%) were not included as the positive major risk factor for CHD, especially 26% of all patients was high level which counted as negative major risk factor for CHD. However, there was no significant difference in the number of patients each level between groups (p=0.202).

For baseline LDL-C, the overall mean was 174.43 ± 34.39 mg/dL (ranging from 100 to 259 mg/dL) which was classified as high level. This finding was consistent with the results of Kitiyadisai and Phruttisunakon studies in that the mean LDL-C were 176.03 ± 31.92 mg/dL and 174.80 ± 44.15 mg/dL, respectively. There was no significant difference in mean LDL-C between the pitavastatin and atorvastatin groups (175.99 ± 34.54 mg/dL, ranging from 111 to 259 mg/dL and 172.86 ± 34.53, ranging from 100 to 249 mg/dL, respectively; p=0.652). None of the patient had baseline LDL-C in the optimal range (< 100 mg/dL) because of the patients who had LDL-C greater than 100 mg/dL and required statin therapy according to NCEP ATP III guidelines were recruited in this study.

With regard to the baseline hsCRP, the distribution which determined by Kolmogorov Smirnov test of hsCRP was not normal. Therefore, median was used to represent the central tendency instead of mean. The median baseline hsCRP of the pitavastatin group (1.31 mg/dL, ranging from 0.09 to 9.55 mg/dL) was not significantly different with the atorvastatin group (1.10 mg/dL, ranging from 0.06 to 12.00 mg/dL) (p =0.562). The percentage of all patients each hsCRP category were 40% in average level (1-3 mg/L), 37% in low level (< 1 mg/L) and 23% in high level (> 3 mg/L). In addition, the number of patients each hsCRP category was not significantly different between groups (p=0.250).

For baseline fibrinogen (Table 19), the overall mean fibrinogen was 445.90 ± 83.24 mg/dL, ranging from 280 to 730 mg/dL. There was no significant difference between the pitavastatin and atorvastatin groups (p=0.467). The mean baseline fibrinogen in the pitavastatin and atorvastatin groups were 452.00 ± 80.66 mg/dL (ranging from 310 to 660 mg/dL) and 439.80 ± 86.13 mg/dL (ranging from 280 to 730 mg/dL), respectively. These levels were higher than normal range (200 – 400 mg/dL). Moreover, most patients (65%) had fibrinogen level more than 400 mg/dL, which was associated with an increase risk for CHD. The number of patients each fibrinogen category was not significantly different between groups (p=0.529).

Regarding the baseline laboratory data of safety profile (Table 19), the overall median of ASL, ALT, CK and creatinine were used to represent the central tendency instead of mean because the data were not normal distribution. The overall median of AST, ALT, CK and creatinine were 22.00 IU/L, 20.50 IU/L, 99.00 IU/L, and 70.80 μmol/L, respectively. The median baseline ALT in the pitavastatin group (21 IU/L, ranging from 7 to 96 IU/L) was not significantly different with the atorvastatin group (20 IU/L, ranging from 7 to 64 IU/L) (p=0.392). The mean baseline CK in the pitavastatin group (109.82 ± 52.46 IU/L, ranging from 10 to 243 IU/L) was slightly lower than the atorvastatin group (126.70 ± 94.68 IU/L, ranging from 21 to 520 IU/L), but it was not significantly different between groups (p=0.273). The mean baseline creatinine in male of the pitavastatin group (87.39 ± 13.28 μmol/L, ranging from 70.80 to 115.05 μmol/L) was not significantly different with the atorvastatin group (91.82 ± 17.08 μmol/L, ranging from 70.80 to 132.75 μmol/L) (p=0.388). Similarly, the median baseline creatinine in female of the pitavastatin group (61.95 μmol/L, ranging from 35.40 to 97.35 μmol/L) was not significantly different with the

atorvastatin group (70.80 μmol/L, ranging from 44.25 to 97.35 μmol/L) (p=0.081). In addition, there was significantly different in baseline median AST between groups (p=0.039). The median baseline AST in the pitavastatin group (23 IU/L, ranging from 13 to 98 IU/L) was significantly higher than the atorvastatin group (21 IU/L, ranging from 9 to 61 IU/L). However, baseline serum AST was classified as normal clinical range (0 - 37 IU/L).

2. Efficacy Evaluation

Of 100 patients assigned to the study, two patients (2%) in the pitavastatin group were excluded from the study. Intention to treat analysis was performed to determine the efficacy of all patients (50 patients per each group). The missing data were replaced by series mean of each group. As shown in Table 21, the demographic data (i.e., weight, waist circumference, SBP, and DBP) of patients at the study initiation (week 0) was not significantly different from that at the study completion (week 8^{th}) in both patient groups (both p>0.05), excepted BMI and FBS. The mean baseline BMI in pitavastatin group was significantly higher than BMI at the eighth week (24.55 ± 3.39 kg/m^2 vs. 24.39 ± 3.31 kg/m^2, p=0.027) , but was not shown the difference in atorvastatin group (24.34 ± 3.66 kg/m^2 vs. 24.36 ± 3.60 kg/m^2, p=0.827). Although, there was a statistically significant difference between baseline BMI and at the end of the study in pitavastatin group, but there was no clinically significant difference. Because these BMI values are classified in the same category, which are called "at risk range" (23.0 – 29.9 kg/m^2). Regarding FBS at the eighth week, the median FBS in the pitavastatin and atorvastatin groups were significantly lower than FBS from baseline (p=0.049 and p=0.031, respectively). The causes of these results might be giving education about diet control, increase in activity, and weight reduction to patients, which are not only be able to decrease serum lipid level but may also decrease blood glucose level.

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

The efficacy of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily on serum lipids, hsCRP and fibrinogen alteration were summarized in Table 22. Paired t-test was used to compare mean of TC, TG, HDL-C, LDL-C, and fibrinogen at baseline (week 0) with at the end of study (week 8^{th}). Because hsCRP distribution was

not normal, therefore, median hsCRP was used instead of mean. Wilcoxon signed-rank test was performed to compare median hsCRP at baseline and at the end of study. In addition, independent t-test was used to compare mean of serum TC, TG, HDL-C, LDL-C, and fibrinogen at the eighth week between the pitavastatin and atorvastatin groups. For hsCRP which was non-normal distribution, Mann-Whitney U test was performed to compare median hsCRP at the eighth week between groups.

At the eighth week of the pitavastatin group, mean baseline TC was significantly decreased from 258.44 ± 41.25 mg/dL to 187.65 ± 31.96 mg/dL ($p<0.001$). Mean baseline TG was also significantly decreased from 145.22 ± 56.95 mg/dL to 118.56 ± 37.02 mg/dL ($p=0.001$). Moreover, serum LDL-C was significantly decreased from 175.99 ± 34.54 mg/dL at baseline to 110.73 ± 26.68 mg/dL at the end of study ($p<0.001$). In addition, there was no significant difference in mean baseline HDL-C compared with that after the eighth week (53.40 ± 15.59 mg/dL vs. 53.21 ± 12.38 mg/dL, $p=0.879$). Median baseline hsCRP was slightly increased from 1.31 mg/L to 1.65 mg/L, but there was no significant difference ($p=0.654$). Mean fibrinogen was also slightly increased from 452.00 ± 80.66 mg/dL (baseline) to 471.62 ± 85.36 mg/dL (at the end of study), but there was no significant difference ($p=0.057$).

For the atorvastatin group, mean baseline TC was significantly decreased from 255.16 ± 40.29 mg/dL to 172.00 ± 30.52 mg/dL after the eighth week ($p<0.001$). Mean LDL-C was also decreased from 172.86 ± 34.53 mg/dL (baseline) to 92.86 ± 22.09 mg/dL (at the end of study) ($p<0.001$). However, there was no significant difference in baseline TG and HDL-C compared with at the end of study. Mean baseline TG was slightly decreased from 141.86 ± 49.08 mg/dL to 128.32 ± 62.26 mg/dL after the eighth week ($p=0.062$). Mean HDL-C was also slightly decreased from 53.92 ± 13.05 mg/dL (baseline) to 53.48 ± 13.47 mg/dL (at the end of study) ($p=0.601$). In addition, median baseline hsCRP was significantly decreased from 1.10 mg/L to 1.03 mg/L ($p=0.027$). Mean baseline fibrinogen was not significantly different with the level after the eighth week (439.80 ± 86.13 mg/dL vs. 448.80 ± 77.27mg/dL, $p=0.436$).

Table 21: Comparison of the demographic data between week 0 and 8 within patient groups and between two patient groups at the eighth week

Data	Pitavastatin group (N = 50)			Atorvastatin group (N = 50)			
	Mean ± SD (range)		p-value[a] (before-after)	Mean ± SD (range)		p-value[a] (before-after)	p-value [b] (between groups)
	Week 0	Week 8th		Week 0	Week 8th		
Weight (kg)	61.98 ± 10.21 (40.20 to 84.00)	61.87 ± 10.20 (39.20 to 83.00)	0.627	63.22 ± 12.50 (41.00 to 89.30)	63.27 ± 12.10 (42.00 to 87.40)	0.829	0.532
BMI (kg/m^2)	24.55 ± 3.39 (16.95 to 32.87)	24.39 ± 3.31 (16.53 to 32.87)	0.027*	24.34 ± 3.66 (16.63 to 31.63)	24.36 ± 3.60 (17.04 to 32.39)	0.827	0.966
Waist (inches) circumference	35.08 ± 4.02 (25.50 to 45.00)	35.81 ± 9.67 (25.00 to 97.50)	0.538	34.64 ± 4.24 (25.50 to 45.00)	34.49 ± 4.15 (25.00 to 42.00)	0.485	0.378
Median	*35.50*	*35.33*	*0.082*	*35.25*	*35.00*	*0.480*	*0.7931*
SBP (mgHg)	132.68 ± 18.22 (95.00 to 175.00)	128.10 ± 16.75 (85.00 to 160.00)	0.067	135.02 ± 24.30 (82.00 to 198.00)	131.72 ± 19.71 (90.00 to 186.00)	0.175	0.532
DBP (mgHg)	79.74 ± 11.37 (53.00 to 103.00)	77.20 ± 11.77 (45.00 to 103.00)	0.076	80.24 ± 12.48 (50.00 to 111.00)	76.72 ± 12.37 (47.00 to 105.00)	0.071	0.384
FBS (mg/dL)	106.34 ± 34.90 (75.00 to 266.00)	101.11 ± 24.97 (73.00 to 209.00)	0.053	105.90 ± 24.97[#] (77.00 to 192.00)	100.15 ± 23.09[#] (11.00 to 163.00)	0.038*	0.843
Median	*96.00*	*94.50*	*0.049**	*98.00*	*98.00*	*0.031**	*0.549*

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

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (1 missing in atorvastatin group).

[a] using paired t-test to compare mean at the study initiation (week 0) with at the end of study (week 8th) of each group and using Wilcoxon signed rank test to compare median at the baseline with at the end of study

[b] using independent t-test to compare mean of the pitavastatin group with the atorvastatin group at the eighth week and using Mann-Whitney U test to compare median at the eighth week of patients in the pitavastatin group with the atorvastatin group

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

Table 22: Comparison of clinical laboratory data between week 0 and 8 within patient groups and between two patient groups at the eighth week

Data	Pitavastatin group (N = 50)			Atorvastatin group (N = 50) [#]			
	Mean ± SD (range)		p-value[a] (before-after)	Mean ± SD (range)		p-value[a] (before-after)	p-value [b] (between groups)
	Week 0	Week 8[th#]		Week 0	Week 8[th]		
TC (mg/dL)	258.44 ± 41.25 (183.00 to 360.00)	187.65 ± 31.96 (115.00 to 256.00)	< 0.001*	255.16 ± 40.29 (177.00 to 355.00)	172.00 ± 30.52 (118.00 to 242.00)	< 0.001*	0.014*
TG (mg/dL)	145.22 ± 56.95 (44.00 to 308.00)	118.56 ± 37.02 (67.00 to 234.00)	0.001*	141.86 ± 49.08 (57.00 to 247.00)	128.32 ± 62.26 (47.00 to 357.00)	0.062	0.344
HDL-C (mg/dL)	53.40 ± 15.59 (23.20 to 112.00)	53.21 ± 12.38 (31.00 to 86.00)	0.879	53.92 ± 13.05 (35.00 to 92.00)	53.48 ± 13.47 (34.00 to 96.00)	0.601	0.918
LDL-C (mg/dL)	175.99 ± 34.54 (111.00 to 259.40)	110.73 ± 26.68 (53.40 to 161.20)	< 0.001*	172.86 ± 34.53 (100.02 to 248.60)	92.86 ± 22.09 (52.00 to 136.80)	< 0.001*	< 0.001*
hsCRP (mg/L)	2.20 ± 2.09 (0.09 to 9.55)	2.02 ± 1.68[##] (0.00 to 9.78)	0.468	1.75 ± 1.65[##] (0.06 to 7.81)	1.30 ± 1.07[##] (0.00 to 6.04)	0.023*	0.012*
Median	*1.31*	*1.65*	*0.654*	*1.10*	*1.03*	*0.028**	*0.008**
Fibrinogen (mg/dL)	452.00 ± 80.66 (310.00 to 660.00)	471.62 ± 85.36[###] (300.00 to 690.00)	0.057	439.80 ± 86.13 (280.00 to 730.00)	448.80 ± 77.27 (280.00 to 630.00)	0.436	0.164

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

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (2 missing in the pitavastatin group).

[##] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (3 missing in pitavastatin group; 2 missing in atorvastatin group).

[###] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (4 missing in pitavastatin group).

[a] using paired t-test to compare mean at the study initiation (week 0) with at the end of study (week 8[th]) of each group and using Wilcoxon signed rank test to compare median at the baseline with at the end of study

[b] using independent t-test to compare mean of the pitavastatin group with the atorvastatin group at the eighth week and using Mann-Whitney U test to compare median at the eighth week of patients in the pitavastatin group with the atorvastatin group

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

With regard to the difference at the end of study between groups reported in Table 22, mean TC and LDL-C at the eighth week in the pitavastatin group were significantly higher than the atorvastatin group ($p=0.014$ and $p<0.001$, respectively). Moreover, median hsCRP at the end of study in the pitavastatin group was also significantly higher than the atorvastatin group ($p=0.008$). However, there was no significant difference in mean TG and HDL-C at the end of study between groups. These findings indicated that the patients receiving atorvastatin 10 mg once daily for 8 weeks provided lower levels of TC, LDL-C, and hsCRP compared with the patients receiving pitavastatin 1 mg once daily. However at the end of study, atorvastatin 10 mg once daily and pitavastatin 1 mg once daily provide similar level of TG, HDL-C, and fibrinogen.

The percentage of change in serum lipids, hsCRP, and fibrinogen is summarized in Table 23, Table 24 and Figure 5. The overall mean percentage of reduction in serum TC of patients in the pitavastatin group was significantly lower than that in the atorvastatin group ($27.55 \pm 8.06\%$ vs. $32.31 \pm 8.37\%$, $p=0.005$). This finding disagrees with the study of Yoshitomi, et al. in that there was no significant difference in percent change of serum TC between the patients receiving pitavastatin 1 mg once daily and atorvastatin 10 mg once daily after 12-week period of the study ($28 \pm 8\%$ vs. $29 \pm 10\%$, $p>0.05$) **[46]**. This conflicting result may be effect from non randomized study causing selection bias. Although the percentage of serum TC change in the pitavastatin 1 mg once daily group is similar to the result of Yoshitomi, et al., but this percentage of serum TC change in the atorvastatin 10 mg once daily group is slightly higher than the result of Yoshitomi, et al. On the other hand, the percentage of TC change in the patients receiving atorvastatin 10 mg once daily from this finding consistent with previous randomized studies in Asia population reported that atorvastatin 10 mg once daily could reduce serum TC between 29.6% and 31.1% **[34, 45, 77]**. However, at the end of study, most of patients receiving either pitavastatin or atorvastatin had serum TC lower than 200 mg/dL which classified as desirable level (66% vs. 76%, $p=0.424$).

The percentage of reduction in serum TG in the pitavastatin group was slightly higher than the atorvastatin group but there was no significant difference ($10.37 \pm 38.92\%$ vs. $7.06 \pm 36.33\%$, $p=0.661$). This finding disagrees with the study of Yoshitomi, et al. in that the mean percent change of serum TG between the patients receiving pitavastatin 1 mg once daily was significantly lower than that receiving

atorvastatin 10 mg once daily (11 ± 30% vs. 21 ± 25%, p<0.05) **[46]**. This conflicting result may be effect from the difference of baseline TG level. Yoshitomi, et al. showed baseline TG level more than 150 mg/dL in both pitavastatin and atorvastatin groups (160 ± 77 mg/dL and 150 ± 66 mg/dL, respectively), whereas this study slowed normal baseline TG level in both groups (145.22 ± 56.95 mg/dL and 141.86 ± 49.08 mg/dL, respectively). The percentage of TG change in the pitavastatin group is similar to the result of Yoshitomi, et al., but not showed in atorvastatin group. Serum TG in the atorvastatin group was slightly lower level than the randomized studies in Asia population showed that atorvastatin 10 mg once daily provided the percent reduction of TG level between 10.75% and 15.91% **[34, 45, 77]**. This may be because some patients had more carbohydrate diet intake during the study period.

Table 23: The percentage of change in serum lipids from baseline

Percent change	**Mean ± SD (range)**			**p-value** [b]
	Pitavastatin group (N = 50) [#]	**Atorvastatin group (N = 50)**	**Total (N = 100)**	
TC	-27.55 ± 8.06 (-42.69 to -10.95)	-32.31 ± 8.37 (-50.00 to -11.69)	-29.93 ± 8.52 (-50.00 to -10.95)	0.005*
TG overall	-10.37 ± 38.92 (-70.45 to 188.64)	-7.06 ± 36.33 (-57.78 to 138.33)	-8.72± 37.50 (-70.45 to 188.64)	0.661
TG < 150 mg/dL	2.96 ± 42.07 (-33.82 to 188.64)	-3.50 ± 38.48 (-55.65 to 138.33)	-0.05 ± 40.21 (-55.65 to 188.64)	0.547
TG ≥ 150 mg/dL	-32.12 ± 19.22 (-70.45 to 13.25)	-11.25 ± 34.01 (-57.78 to 70.81)	-20.69 ± 29.89 (-70.45 to 70.81)	0.017*
HDL_C overall	2.76 ± 17.94 (-28.13 to 76.72)	-0.41 ± 11.41 (-21.15 to 35.56)	-1.17 ± 15.04 (-28.13 to 76+.72	0.294
HDL-C < 40 mg/dL	16.68 ± 27.44 (-10.26 to 76.72)	0.95 ± 8.89 (-5.41 to 11.11)	12.39 ± 24.43 (-10.26 to 76.72)	0.369
HDL-C ≥ 40 mg/dL	0.11 ± 14.52 (-28.13 to 26.67)	-0.50 ± 11.62 (-21.15 to 35.56)	-0.21 ± 13.00 (-28.13 to 35.56)	0.827
LDL-C	-37.37 ± 11.37 (-57.96 to -9.91)	-45.75 ± 10.60 (-70.56 to -18.19)	-41.56 ± 11.72 (-17.56 to -9.91)	< 0.001*

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

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (2 missing in the pitavastatin group).

[b] using independent t-test to compare mean of the pitavastatin group with the atorvastatin group at the eighth week

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

Table 24: The percentage of change in hsCRP and fibrinogen from baseline

Percent change	Mean ± SD (range)			p-value [b]
	Pitavastatin group (N = 50)	Atorvastatin group (N = 50)	Total (N = 100)	
hsCRP overall	66.47 ± 261.62[#] (-100 to 1628)	37.24 ± 263.70[#] (-100 to 1700)	51.86 ± 261.75 (-100 to 1700)	0.579
Median	*0.02*	*-17.16*	*-11.72*	*0.201*
hsCRP < 3 mg/L	107.15 ± 303.99 (-100 to 1628)	52.42 ± 281.62 (-100 to 1700)	76.98 ± 291.23 (-100 to 1700)	0.413
Median	*18.99*	*-9.30*	*0.00*	*0.115*
hsCRP ≥ 3 mg/L	-28.43 ± 36.86 (-82.56 to 60.43)	-56.04 ± 30.13 (-95.99 to 16.61)	-37.22 ± 36.58 (-95.99 to 60.43)	0.123
Median	-43.59	-50.45	-46.40	0.100
Fibrinogen	5.46 ± 16.20[##] (-36.17 to 56.41)	3.80 ± 17.01 (-39.73 to 40.63)	4.63 ± 16.55 (-39.73 to 56.41)	0.618

SD = standard deviation; hsCRP = high sensitivity C-reactive protein

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (3 missing in pitavastatin group; 2 missing in atorvastatin group).

[##] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (4 missing in pitavastatin group).

[b] using independent t-test to compare mean of the pitavastatin group with the atorvastatin group at the eighth week and using Mann-Whitney U test to compare median at the eighth week of patients in the pitavastatin group with the atorvastatin group

set a significant difference at $\alpha = 0.05$

Moreover on subgroup analysis, patients were divided into two groups according to their TG level at baseline (<150 or ≥ 150 mg/dL) and the percentage of TG reduction was compared between groups (Figure 6). These results showed that the patient who had TG ≥ 150 mg/dL in the pitavastatin group provided significant decrease in the percentage of TG change than the atorvastatin group (-32.12±19.22 % vs. -11.25 ± 42.01%, p=0.017), but there was no significant difference in the patients who had TG < 150 mg/dL between groups (2.96 ± 42.07% of the pitavastatin group vs. -3.50 ± 31.47%, p=0.547). This finding may indicated that pitavastatin 1 mg once daily had greater effect on TG reduction than atorvastatin 10 mg daily in the patients with high TG level.

The percentage of HDL-C change in the pitavastatin group and atorvastatin groups were 2.76 ± 17.94% and -0.41 ± 11.41%, respectively. There was no significant difference between groups (p= 0.294). This finding consistent with the study of Yoshitomi, et al. in that the mean percent change of serum HDL-C in the

pitavastatin 1 mg once daily group was not significantly different with the atorvastatin 10 mg once daily group (-3 ± 12% vs. -7 ± 12%, p>0.05) **[46]**.

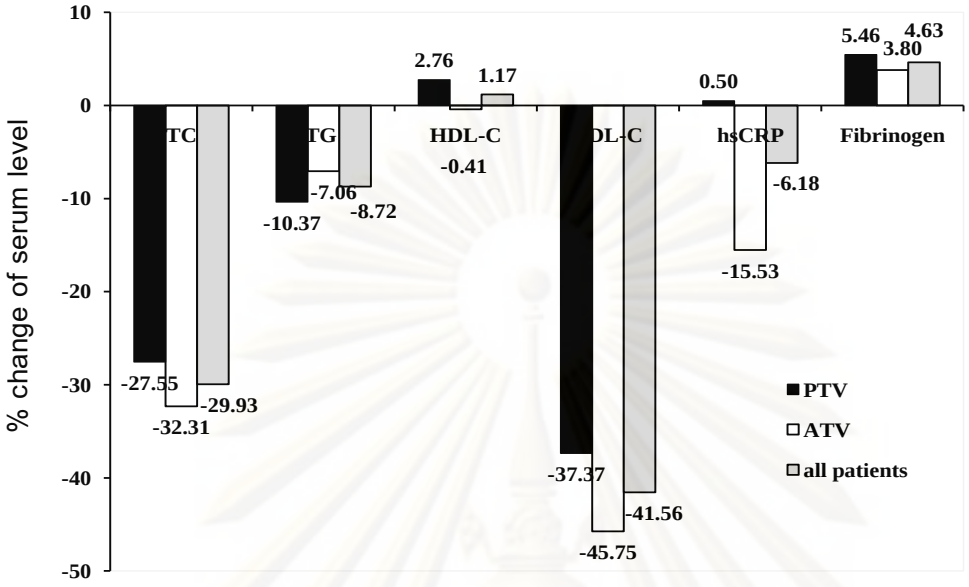

Figure 5: The mean percentage of change in serum TC, TG, HDL-C, hsCRP, and fibrinogen of the patients in the pitavastatin group (N = 50) [#], the atorvastatin group (N = 50) [#], and all patients (N = 100) [#].

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

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean.

Moreover, individual statins seem to increase HDL-C levels to different degree. Jones, et al. conducted a parallel-group, open-label, randomized, multicenter comparative study for 6 weeks reported that rosuvastatin was more effective in elevating HDL-C levels than atorvastatin, simvastatin, and pravastatin (all p<0.001) **[84]**. For atorvastatin, the results of prospective, multicentre, randomized clinical trials in hypercholesterolemic patients showed a pattern of decreasing HDL-C levels with increasing doses of atorvastatin. Mean percent increases in HDL-C ranged from 4.0% to 10.0% for atorvastatin 10 and 20 mg, decreased 3 to 6.4% with 40 mg, and approached 0% with the 80 mg dose **[85]**. This percentage of HDL-C change in atorvastatin group is consistent with previous studies in Asia population indicated that

atorvastatin 10 mg had effect on HDL-C change by -3.6% to 6.7% of patients without significant difference from baseline (all p>0.05) **[34, 45, 77]**.

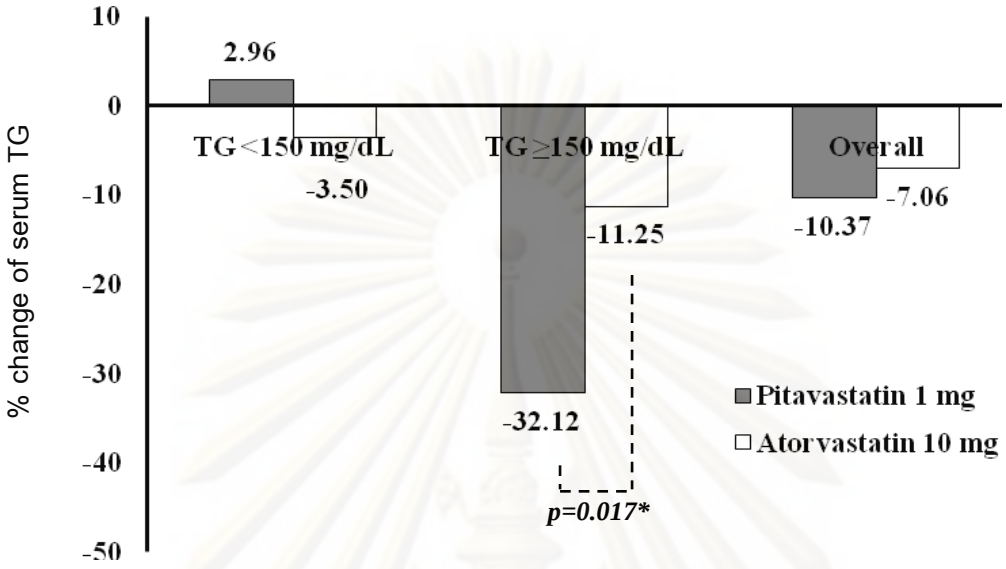

Figure 6: The mean percentage of change in serum TG of the patients in the pitavastatin group, the atorvastatin group, and all patients (N = 100).

TG = triglyceride; pitavastatin group (number of patients each category was 31 in TG <150 mg/dL[#] and 19 in TG ≥ 150 mg/dL); atorvastatin group (number of patients each category was 27 in TG <150 mg/dL and 23 in TG ≥ 150 mg/dL)

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (2 missing in the pitavastatin group).

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

With regarding pitavastatin, previous studies reported that at higher dose of pitavastatin (2 mg) increased serum HDL-C approximately 3.2% to 8.9% from baseline **[34, 43-45]**. However, there was also no significant difference in the percent change of serum HDL-C between the hypercholesterolemic patients receiving pitavastatin 2 mg once daily and atorvastatin 10 mg once daily **[34, 45]**. Moreover on subgroup analysis, patients were divided into two groups according to their HDL-C level at baseline (<40 or ≥ 40 mg/dL) and the percentage of HDL-C change was compared between groups (Figure 7). The percent HDL-C changes of patients with baseline HDL-C equal or more than 40 mg/dL in the pitavastatin and atorvastatin groups were not significantly different (0.11 ± 14.52% vs. -0.50 ± 11.62%, p=0.827). In case of patients with baseline HDL-C below 40 mg/dL, the percent HDL-C changes of the pitavastatin group (16.68 ± 27.44%) were slightly higher than the

atorvastatin group (0.95 ± 8.89%), but there was no statistically significant difference between groups (p=0.369). In patients who had baseline HDL-C below 40 mg/dL showed higher magnitude of the percent HDL-C change than patients who had baseline HDL-C equal or more than 40 mg/dL, especially in the pitavastatin group. Yokote, et al and Sasaki, et al. reported that a significant increase in HDL-C was observed only in the pitavastatin 2 mg once daily and not in the atorvastatin 10 mg once daily group **[45, 86]**. It may be because pitavastatin increases production of apolipoprotein A-I, an essential component of the HDL particle, in HepG2 cells at lower concentrations compared to atorvastatin **[62]**. Similary to Sasaki, et al. reported that the percent change in Apo A-I was also significantly greater in the pitavastatin group compared with the atorvastatin group (5.1 vs. 0.6, respectively; p=0.019) **[45]**. Moreover in vitro study, pitavastatin was shown to stimulate lipoprotein lipase (LPL) activity more potently than atorvastatin, which may facilitate an increase in HDL through the efficient metabolism of TG-rich lipoproteins**[87]**.

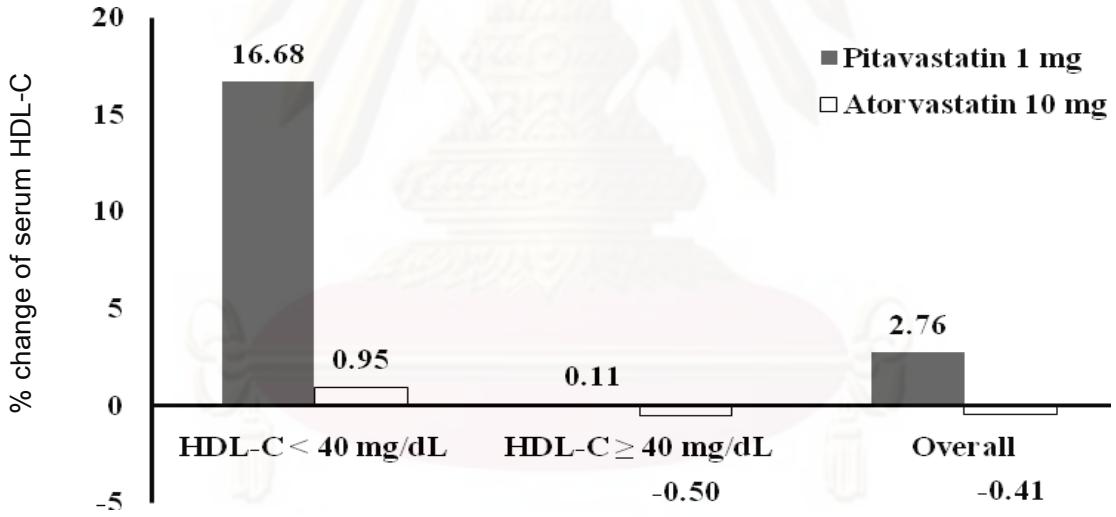

Figure 7 The mean percentage of change in serum HDL-C of the patients in the pitavastatin group, the atorvastatin group, and all patients (N = 100)

HDL-C = High density lipoprotein cholesterol; pitavastatin group (number of patients each category was 8 in HDL-C <40 mg/dL and 42 in HDL-C ≥ 40 mg/dL[#]); atorvastatin group (number of patients each category was 3 in HDL-C <40 mg/dL and 47 in HDL-C ≥ 40 mg/dL)

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (2 missing in the pitavastatin group).

The mean percentage of LDL-C reduction in the pitavastatin group was significantly lower than the atorvastatin group (37.37 ± 11.37% and 45.75 ± 10.60, $p<0.001$). This finding disagrees with the study of Yoshitomi, et al. in that there was no significant difference in the mean percent change of serum LDL-C between the patients receiving pitavastatin 1 mg once daily and atorvastatin 10 mg once daily (38 ± 13% vs. 41 ± 12%, $p>0.05$) **[46]**. Moreover, the randomized studies in hypercholesterolemic patients showed that the mean percentage of LDL-C reduction in the pitavastatin 2 mg once daily group was not significantly different with the atorvastatin 10 mg once daily **[34, 45]**. Many randomized studies in hypercholesterolemic patients for 8 to 12 weeks indicated that pitavastatin 2 mg and atorvastatin 10 mg had effect on LDL-C reduction by 32.6% to 42.9% and 39.9% to 44.10%, respectively **[34, 43-45, 77]**. This finding may be determined that the optimal dose of pitavastatin provided comparable effect on LDL-C reduction with atorvastatin 10 mg once daily was 2 mg of pitavastatin once daily.

As shown in Table 24 the patients in the pitavastatin group had an increase in median serum hsCRP by 0.02% and in the atorvastatin group had a decrease in median serum hsCRP by 17.16%. There was no significant difference between groups ($p=0.201$). For the efficacy of atorvastatin 10 mg on hsCRP alteration, this finding is consistent with previous studies in that the percentage of hsCRP reduction was approximately 15.4% to 25% **[34, 88, 89]**. However, this result of the pitavastatin group do not support the previous studies reported that pitavastatin had effect on hsCRP reduction like other statins. As in Lee, et al. study, the mean hsCRP concentrations was decreased from 24.6 to 16.5 mg/L (32.9%) in hypercholesterolemic patients receiving pitavastatin 2 mg once daily for 8 weeks **[34]**. Similar to the result of Koshiyama, et al. in that the hsCRP concentrations was decreased from 0.69 mg/L to 0.45 mg/L (34.8% reduction from baseline, $p<0.01$) in patients with hypercholesterolemia and type II diabetes mellitus receiving pitavastatin 1 to 2 mg once daily for 12 months **[90]**. However, it may be because of confounding factors such as variation in the single point of serum hsCRP measurement, virus infection in rainy season, and increase or endurance of exercise.

Because of wide range in the percentage of hsCRP change, subgroup analysis was performed. The patients were divided into two groups according to baseline hsCRP level (< 3 mg/L, and ≥3 mg/L) and the percentage of hsCRP change was compared between groups (Table 24). The patients with baseline hsCRP less than

3 mg/L, hsCRP change was occurred 18.99% in the pitavastatin group and -9.30% in atorvastatin group, but the difference was not statistically significance (p=0.115). For the patients with baseline hsCRP equal or more than 3 mg/L, hsCRP change was occurred -43.59% in the pitavastatin group and -50.45% in atorvastatin group, but the difference was not statistically significance (p=0.123). In patients who had baseline hsCRP equal or more than 3 mg/L showed higher magnitude of the percent hsCRP change than patients who had baseline hsCRP less than 3 mg/L. This finding consistent with Gensini, et al. in that there were significant reductions in hsCRP levels in subjects with baseline hsCRP levels ≥ 3 mg/L, but not in those with levels <3 mg/L, with the 10 to 40 mg atorvastatin doses compared to baseline **[89]**. In addition, recent study, Japan assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) study, reported that intensive statin therapy with pitavastatin 4 mg per day and atorvastatin 20 mg per day produced a significant regression of atheroma burden with negative vessel remodeling and showed the percent of hsCRP changes by -97.3% and -95.4%, respectively **[91]**.

With regard to fibrinogen, the mean percent change of serum fibrinogen in the pitavastatin group was not significantly different from that in the atorvastatin group (5.46 ± 16.20% vs. 3.80 ± 17.01%, p=0.618), but there was no significant difference in the mean serum fibrinogen between baseline and at the end of study in both the pitavastatin and atorvastatin groups (p=0.057 and p=0.436, respectively) as shown in Table 22. There have been no previous studies that determine the effect of pitavastatin on serum fibrinogen. However this finding is consistent with the neutral effect of simvastatin, fluvastatin, and rosuvastatin on fibrinogen levels **[38, 83]**. For the effect of atorvastatin on serum fibrinogen, this finding do not support the previous studies in that serum fibrinogen was increased by atorvastatin **[38]**.

These finding indicated that both pitavastatin 1 mg once daily and atorvastatin 10 mg once daily significantly reduced serum TC and LDL-C from baseline. For TG level, atorvastatin 10 mg once daily could not produce a significant decrease in serum TG from baseline, whereas, pitavastatin 1 mg once daily could. In addition, both pitavastatin 1 mg once daily and atorvastatin 10 mg once daily could not produce a significant difference in serum HDL-C and fibrinogen between baseline and at the end of study. Moreover, the percentage of TC and LDL-C reduction in patients receiving atorvastatin 10 mg once daily was significantly higher than that receiving

pitavastatin 1 mg once daily. Therefore, the pitavastatin 1 mg once daily had not equivalent potency on TC and LDL-C reduction compared with the atorvastatin 10 mg once daily.

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

The percentage of patients who achieved their LDL-C goals according to NCEP ATP III guidelines is summarized in Table 25 and Figure 8. Overall, 79% of patients in the study achieved their LDL-C goals. The percentages of patients who achieved LDL-C goals in the pitavastatin and atorvastatin groups were 74% and 84%, respectively. There was no significant difference between groups (p=0.220). There have been no previous study determined the percentage of patients who achieved LDL-C goals in pitavastatin 1 mg once daily. However, the percentage of patients achieving LDL-C goals of statin was dose-dependent response. The percentage of patients achieving LDL-C goals reported in this study was slightly lower than that in the pitavastatin 2 mg once daily. Lee, et al. and Park, et al. conducting an 8-week, multicenter, randomized, open-label studies in Korea patients with hypercholesterolemia reported that the percentages of patients who received pitavastatin 2 mg once daily and met the target level according to NCEP ATP III guidelines were 92.7% (102/110) and 93.9% (46/49), respectively **[34, 44]**. The finding in the atorvastatin group is consistent with the previous studies in that approximately 76% to 92% of patients in the atorvastatin 10 mg once daily group achieved their goals **[34, 77]**. This finding also supports the previous studies in that the pitavastatin 1 mg once daily and the atorvastatin 10 mg once daily reduced LDL-C sufficiently to allow most patients to achieve NCEP ATP III goals **[10, 13, 15, 92]**.

On subgroup analysis by risk category according to NCEP ATP III guidelines, LDL-C goals of patients in the pitavastatin group who were in low, moderate, moderately high and high risk category were achieved by 88.2%, 80%, 88.9%, and 42.9%, respectively. Likewise in the atorvastatin group, 92.3%, 90.9%, 83.3% and 71.4% of patients who were in low, moderate, moderately high and high risk category reached their LDL-C goals. These finding are consistent with the previous studies in that the percentage of patients who achieved LDL-C goals in high risk category seemed to be lower than that in the other risk groups. However, there was no significant difference in number of patients who achieved goals among risk groups

(p=0.168 for the pitavastatin group and p=0.963 for the atorvastatin group). Similarly, no significant difference in the number of patients who achieved goals between groups was found each risk category (all p>0.05). These findings indicated that although pitavastatin 1 mg once daily had lower effect on LDL-C reduction than atorvastatin 10 mg once daily, but it also had comparable effect in reaching LDL-C goals, regardless of risk category.

Table 25: The number of patients achieving and not achieving their LDL-C goals according to NCEP ATP III

Risk category	No. of patients achieved LDL-C goals (%) No. of patients not achieved LDL-C goals (%)			p-value[b]
	Pitavastatin group (N = 50)	Atorvastatin group (N = 50)	Total (N = 100)	
High risk[#]: CHD or CHD equivalents [†] (10-year risk > 20%)	6 (42.9) 8 (57.1)	10 (71.4) 4 (28.6)	16 (16.0) 12 (12.0)	0.127 [a]
Moderately high risk: ≥ 2 risk factors (10-year risk 10-20%)	8 (88.9) 1 (11.1)	10 (83.3) 2 (16.7)	18 (18.0) 3 (3.0)	1.000
Moderate risk: ≥ 2 risk factors (10-year risk < 10%)	8 (80.0) 2 (20.0)	10 (90.9) 1 (9.1)	18 (18.0) 3 (3.0)	0.587
Low risk[#]: 0-1 risk factor	15 (88.2) 2 (11.8)	12 (92.3) 1 (7.7)	27 (27.0) 3 (3.0)	1.000
Total	37 (74.0) 13 (26.0)	42 (84.0) 8 (16.0)	79 (79.0) 21 (21.0)	0.220 [a]

CHD = coronary heart disease

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (1 missing in the pitavastatin group).

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

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

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

set a significant difference at $\alpha = 0.05$

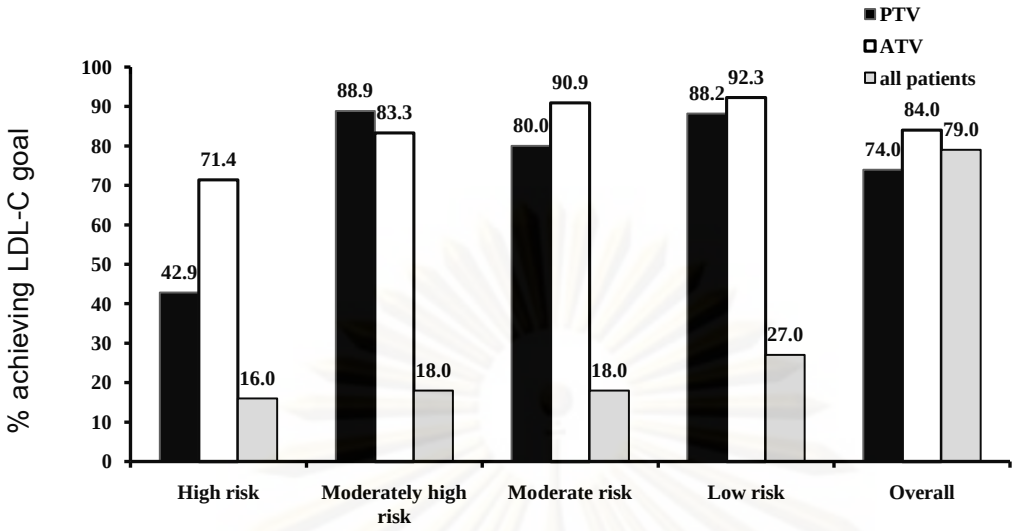

Figure 8: The percentage of patients who achieved LDL-C goals according to NCEP ATP III guidelines were categorized by risk category (N = 100[#] in all patients, N = 50[#] in the pitavastatin and atorvastatin groups).

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

Moderately high risk = patients who had more than one major risk factor and 10-year risk = 10%-20%

Moderate risk = patients who had more than one major risk factor and 10-year risk < 10%

Low risk[#] = patients who had less than one major risk factor

[#] Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (1 missing in the pitavastatin group).

2.3 Annual cost of drug treatment

The NCEP ATP III guidelines recommend maintaining lipid levels within particular targets to reduce the risk of CHD events. Most of patients require a life-long therapy with statins and these drugs (including pitavastatin and atorvastatin) are expensive, this can affect the patient affordability which can reduce compliance or fail to lower LDL-C adequately. Therefore, annual cost of drug treatment is one of the strategies to evaluate the cost effectiveness of statins therapy. This can help health providers select the appropriate regimen for each patient.

Because the pitavastatin are not available at Phramongkutklao Hospital, so that comparison of the annual cost of drug treatment between groups uses pricelist of Vajira Hospital instead (Medical hospital). The cost of Pitavastatin tablet 2 mg and

atorvastatin tablet 10 mg are 32 and 39.50 baht per tablet (pricelist at June 2009). The annual cost of drug treatment was calculated by:

The annual cost of drug treatment in pitavastatin 1 mg group

= Number of pitavastatin 2 mg tablet using in 366 days **x** pricelist cost of pitavastatin 2 mg tablet

= 183 x 32.00

= 5,856.00 baht

The annual cost of drug treatment in atorvastatin 10 mg group

= Number of atorvastatin 10 mg tablet using in 366 days **x** pricelist cost of atorvastatin 10 mg tablet

= 366 x 39.50

= 14,457.00 baht

The annual cost of drug treatment in patients receiving pitavastatin 2 mg half a tablet once daily was 5,856.00 baht, which is accounted for 40.51% of cost of the patients receiving atorvastatin 10 mg once daily (14,457.00 baht). Pitavastatin 2 mg half a tablet once daily (using Tablet splitting device) and atorvastatin 10 mg once daily provided LDL-C reuction by 37.37% and 45.75%, respectively. The diferential cost per year between regimens (pitavastatin 1 mg once daily and atorvastatin 10 mg once daily) was 8,601 baht. The incremental cost effectiveness ratio (ICER) has the implication in decision-making that higher cost of atorvastatin 10 mg once daily yields higher percent LDL-C reduction than pitavastatin 1 mg once daily. Here, the ICER of 1,026.37 baht means that the patient has to pay 1,026.37 baht for one percent increased in LDL-C reduction by atorvastatin 10 mg once daily over pitavastatin 1 mg once daily. ICER calculated by:

The incremental cost effectiveness ratio

= (annual cost atorvastatin 10 mg once daily - annual cost pitavastatin 10 mg once daily) / (percent LDL-C reduction of atorvastatin 10 mg once daily - percent LDL-C reduction of pitavastatin 1 mg once daily)

= (14,457.00 - 5,856.00) / (45.75 - 37.37)

= 1,026.37 baht

Several studies showed that cost-effectiveness is directly related to baseline population risk and inversely related to drug cost per unit of LDL-C lowering. As baseline risk increases and effective drug cost decreases, cholesterol lowering with statins becomes more cost-effective. Secondary prevention is clearly cost-effective, and almost always more cost-effective than primary prevention, except in higher-risk persons. However, they are made with the recognition that drug prices vary widely under different hospital and health care payment plans. Therefore, this finding indicates that pitavastatin 2 mg half a tablet once daily may be a suitable drug regimen for some patients who have financial problem and need 30 – 40% reduction in serum LDL-C.

3. Safety Evaluation

Of 100 patients enrolled, 98 patients completed the 8-week study period. Two patients on pitavastatin were excluded from the study, because they had adverse events (i.e., muscle pain, nausea, and vomiting).

First patient was Thai female aged 75 years old in the pitavastatin group. She experienced back pain and vomiting after pitavastatin 1 mg once daily for 8 days, and one day after that she had nausea. Because of drug intolerance, she discontinued for 7 days and the symptom disappeared. She concerned that she got these symptoms because of taking pitavastatin. Therefore, she made a decision to drop out from the study. The causality assessment by using Naranjo's algorithm showed this was a possible adverse event due to the drug.

The other patient was female aged 51 years old in the pitavastatin group. She experienced severe nausea and vomiting after pitavastatin 1 mg once daily for 7 days. She took domperidone tablet to relieve these symptoms for 2 days, but these symptoms did not cease. Therefore, she discontinued pitavastatin and the symptoms disappeared. She concerned that she got these symptoms because of taking pitavastatin, so that she asked for a withdrawal from the study without drug rechallenging. The causality assessment by using Naranjo's algorithm showed this was a possible adverse event due to the drug.

Table 26 summarizes the number of patient experienced adverse events. The number of patients each adverse event of the pitavastatin group was not significantly different from that in the atorvastatin group (all $p>0.05$). Overall, patient complaints were muscle pain (7%), vertigo (4%), nausea (4%), vomiting (2%), headache (2%),

muscle weakness (1%), and stomachache (1%). Renal related adverse events accounted for 17% of all patients (5 % of pitavastatin and 12% of atorvastatin). There was no patient experienced CK and AST more than 3 times the ULN. There were two patients who experienced ALT more than 3 times the ULN. Of these two patients, one, a 52-year-old male who had baseline serum ALT 95 IU/L was current smoker and took 7 drugs per day. The other, a 60-year-old female who had baseline serum ALT 96 IU/L was high serum TG (308 mg/dL). Both of them had high baseline serum ALT for a long time. It may be because of fatty liver, number of concurrent drugs, or smoking that elevated the baseline ALT level. After pitavastatin for 8 weeks their ALT levels were increased to 130 and 127 IU/L, respectively.

Table 26: The number of patient experienced adverse events

Variable	No. of patients (%)*			
	Pitavastatin group (N=50)#	**Atorvastatin group (N=50)#**	**Total (N=100)**	**p-value[a]**
Muscle pain [c]	5 (10)	2 (4)	7 (7)	0.436
Vertigo [c]	2 (4)	2 (4)	4 (4)	1.000
Nausea [c]	3 (6)	1 (2)	4 (4)	0.617
Vomiting [c]	1 (2)	1 (2)	2 (2)	1.000
Headache [c]	1 (2)	1 (2)	2 (2)	1.000
Muscle weakness [c]	1 (2)	0 (0)	1 (1)	1.000
Stomachache [c]	0 (0)	1 (2)	1 (1)	1.000
AST > 3 times the ULN**	0 (0)	0 (0)	0 (0)	1.000
ALT > 3 times the ULN**	2 (4)	0 (0)	2 (2)	0.495
CK > 3 times the ULN**	0 (0)	0 (0)	0 (0)	1.000
Creatinine > the ULN**	5 (10)	12 (24)	17 (17)	0.062 [b]

AST= aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase

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

** ULN (upper limit normal) of the laboratory range tested in Phramokutklao Hospital i.e., AST [0-37 IU/L], ALT [0-41 IU/L], CK [25-200 IU/L], and creatinine [62-106 μmol/L for male and 44-80 μmol/L for female]

Intention to treat analysis was used in data at the eighth week (2 patients in the pitavastatin group who withdrew from the study)

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

b using Chi-square test to compare the number of patients between groups

c possible adverse event assessed by using Naranjo's algorithm

Table 27 presents mean ± SD and median of the safety data. Because AST, ALT, CK and creatinine (female category in the pitavastatin group) were not normal distribution from Kolmogorov-Smirnov test, median was reported to represent the central tendency of these data. For liver–related adverse events, median of baseline

serum AST and ALT (Table 19) in the pitavastatin and atorvastatin groups were normal clinical range. Although baseline serum AST in the pitavastatin group was statistically higher than the atorvastatin group (23.0 vs. 21.0 IU/L, p=0.039), but there was no significant difference in median of baseline serum ALT between groups (21.0 vs. 20.0 IU/L, p=0.392). After 8-week (Table 27), serum AST and ALT in the pitavastatin group were not significantly different from baseline (p>0.05). Similarly, serum AST at eighth week in the atorvastatin group was not different from baseline (22.0 vs. 21.0IU/L, p=0.054), but there was significant increasing of serum ALT (from 20 to 24.5 IU/L, p=0.017) from baseline. However, serum AST and ALT at the end of study were not significantly different between the pitavastatin and atorvastatin groups (p>0.05) and these results were normal clinical range. Only two patients in pitavastatin group increased ALT more than 3 times the ULN after 8-week. These finding consistent with Sasaki, et al. in that no patient had serum AST more than 3 times and there were 2 patients in the pitavastatin group and none in the atorvastatin group had serum ALT more than 3 times the ULN **[86]**.

With regarding muscle-related adverse events, there was no significant difference in baseline serum CK between the pitavastatin and atorvastatin groups (109.82 ± 52.46 vs. 126.70 ± 76.62 IU/L, p=0.273) (Table 19). After 8-week of the study, mean serum CK was slightly increased from baseline in the pitavastatin (from 109.82 to 122.02 IU/L, p=0.069) and atorvastatin groups (from 126.70 to 133.96 IU/L, p=0.399), but was not significantly different each group (Table 27). In addition, median of serum CK at the end of study was not significantly different between the pitavastatin and atorvastatin groups (p=0.967). There was only one patient (2%) in the pitavastatin group experienced muscle weakness without elevated CK and creatinine. Although, five patients (10%) and two patients (4%) in the pitavastatin group and the atorvastatin group, respectively experienced muscle pain, but none of them had the elevated CK more than 3 times the ULN with symptom. Muscle-related adverse event form this study was slightly lower than previous study in terms of elevated CK, presenting 2.74% for pitavastatin and 2.2% for atorvastatin **[39, 42]**.

In term of renal function, the normal ranges of serum creatinine at Phramongkutklao Hospital were 62–106 μmol/L for male and 44-80 μmol/L for female. Mean serum baseline creatinine in the pitavastatin group was significantly lower than the atorvastatin group (70.09 ± 17.13 vs. 79.30 ± 19.58 μmol/L, p=0.014).

After patients were categorized into two groups by sex (male and female), baseline serum creatinine in male category was not significantly different between the pitavastatin and atorvastatin groups (87.39 ± 13.28 vs. 91.82 ± 17.08 μmol/L, p=0.388). Similarly, baseline serum creatinine in female category was not significantly different between groups (61.95 vs. 70.80 μmol/L, p=0.081). In male category, serum creatinine at 8-week in both the pitavastatin and atorvastatin groups were not significantly changed from baseline (p=0.173 and p=0.862, respectively). Similarly in female category, mean serum creatinine at 8-week in the atorvastatin groups was not significantly increased from baseline (p=0.588). Whereas serum creatinine at 8-week in female category of the pitavastatin group was significantly increased from baseline (from 61.95 to 65.41 μmol/L, p=0.029). It may be because the number of women aged more than 60 years old in the pitavastatin group (17/34) was higher than that in the atorvastatin group (10/26). The elderly patients may be susceptible to having elevated serum creatinine. However, each sex category, there was no significant difference in serum creatinine at the end of study between groups.

Throughout, both pitavastatin and atorvastatin were well tolerated, with a similar low incidence of treatment-emergent adverse events. The majority of adverse events were of a mild to moderate intensity. There was no reported case of rhabdomyolysis or acute renal failure. In addition, each adverse event that reported in this study was not significantly different between the patients receiving pitavastatin 1 mg once daily and atorvastatin 10 mg once daily (all p>0.05).

Table 27: Comparisons of laboratory data for safety profile between week 0 and the eighth week each patient group and between the pitavastatin and the atorvastatin groups at the eighth week

Data	Pitavastatin group (N = 50)			Atorvastatin group (N = 50)			p-value [b] (between groups)
	Mean ± SD (range)		p-value[a] (before-after)	Mean ± SD (range)		p-value[a] (before-after)	
	Week 0	Week 8th#		Week 0	Week 8th		
AST (IU/L)	27.14 ± 13.68 (13.00 to 98.00)	25.70 ± 11.71 (12.00 to 79.00)	0.466	22.54 ± 8.33 (9.00 to 61.00)	24.46 ± 8.84 (11.00 to 59.00)	0.042*	0.551
Median	*23.00*	*23.00*	0.928	*21.00*	*22.00*	0.054	0.431
ALT (IU/L)	25.88 ± 18.27 (7.00 to 96.00)	25.53 ± 23.02 (4.00 to 130.00)	0.836	22.12 ± 11.67 (7.00 to 64.00)	26.08 ± 13.83 (6.00 to 86.00)	0.022*	0.886
Median	*21.00*	*22.00*	0.457	*20.00*	*24.50*	0.017*	0.168
CK (IU/L)	109.82 ± 52.46 (10.00 to 243.00)	122.02 ± 60.93## (44.00 to 383.00)	0.068	126.70 ± 94.68 (21.00 to 520.00)	133.96 ± 94.17 (36.00 to 533.00)	0.399	0.453
Median	*95.50*	*115.00*	0.643	*101.00*	*118.00*	0.406	0.967
Cr; Overall (μmol/L)	70.09 ± 17.13 (35.40 to 115.05)	73.33 ± 17.14 (44.25 to 115.05)	0.009*	79.30 ± 19.58 (44.25 to 132.75)	79.65 ± 19.26 (44.25 to 132.75)	0.799	0.086

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

\# Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (2 missing in pitavastatin group).

\## Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (4 missing in pitavastatin group).

a using paired t-test to compare mean at the study initiation (week 0) with at the end of study (week 8th) of each group and using Wilcoxon signed rank test to compare median at the baseline with at the end of study

b using independent t-test to compare mean of the pitavastatin group with the atorvastatin group at the eighth week and using Mann-Whitney U test to compare median at the eighth week of patients in the pitavastatin group with the atorvastatin group

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

Table 27: Comparisons of laboratory data for safety profile between week 0 and the eighth week each patient group and between the pitavastatin and the atorvastatin groups at the eighth week (continued)

Data	Pitavastatin group (N = 50)			Atorvastatin group (N = 50)			p-value [b] (between groups)
	Mean ± SD (range)		p-value[a] (before-after)	Mean ± SD (range)		p-value[a] (before-after)	
	Week 0	Week 8th		Week 0	Week 8th		
Cr; Male (μmol/L)	87.39 ± 13.28 (70.80 to 115.05)	90.16 ± 14.53 (61.95 to 115.05)	0.173	91.82 ± 17.08 (70.80 to 132.75)	91.45 ± 17.64 (70.80 to 132.75)	0.8619	0.810
Cr; Female (μmol/L)	61.95 ± 11.93 (35.40 to 97.35)	65.41 ± 11.75# (44.25 to 88.50)	0.029*	67.74 ± 13.92 (44.25 to 97.35)	68.76 ± 13.55 (44.25 to 88.50)	0.588	0.310
Median	*61.95*	*61.95*	*0.027**	*70.80*	66.38	0.682	*0.352*

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

Intention to treat analysis was used in data at the eighth week and missing data were replaced by series mean (2 missing in pitavastatin group).

a using paired t-test to compare mean at the study initiation (week 0) with at the end of study (week 8th) of each group and using Wilcoxon signed rank test to compare median at the baseline with at the end of study

b using independent t-test to compare mean of the pitavastatin group with the atorvastatin group at the eighth week and using Mann-Whitney U test to compare median at the eighth week of patients in the pitavastatin group with the atorvastatin group

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

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

1. Conclusions

This randomized, open-label, parallel trial was designed to compare the efficacy and safety of pitavastatin 1 mg once daily and atorvastatin 10 mg once daily in outpatients with hypercholesterolemia in terms of: (1) serum lipids, hsCRP and fibrinogen alteration, (2) the percentage of patients who achieved their LDL-C goals, according to NCEP ATP III guidelines, (3) adverse event rates, and (4) annual cost of drug treatment. The study was conducted from November 2008 to May 2009 at outpatient department, Phramongkutklao Hospital. The subjects were patients with hypercholesterolemia who met the criteria for starting statin therapy according to NCEP ATP III guidelines and had never received statins. One hundred eligible patients were randomly assigned equally into the pitavastatin 1 mg once daily and atorvastatin 10 mg once daily groups for 8 weeks. Efficacy and safety were evaluated by laboratory data, physical examinations and patient interviews. Data were analyzed using intention to treat analysis with a significant level of 0.05. Descriptive and inferential statistics were used to evaluate data. The conclusions of this study are as follows;

1. All baseline demographic data of patients receiving pitavastatin 1 mg once daily and atorvastatin 10 mg once daily were not significantly different in terms of: sex, age, age ranges, weight, height, BMI, BMI ranges, waist circumference, waist circumference ranges, underlying diseases, SBP, DBP, number of concurrent drugs, smoker, type major risk factor, number of major risk factors, and risk category.
2. Baseline clinical laboratory data of patients receiving pitavastatin 1 mg once daily and atorvastatin 10 mg once daily were not significantly different in terms of: TC, TG, HDL-C, LDL-C, hsCRP, and fibrinogen.
3. At eighth week, both pitavastatin 1 mg once daily and atorvastatin 10 mg once daily reduced serum TC and LDL-C from baseline and presented a non significant difference in serum HDL-C, and fibrinogen. However, only pitavastatin 1 mg once daily significantly decreased serum TG from baseline, especially in case of patients with baseline serum TG equal and above 150 mg/dL.

4. Serum TC, LDL-C and hsCRP of patients receiving pitavastatin 1 mg once daily for 8 weeks were significantly higher than atorvastatin 10 mg once daily. However there were no significantly difference in TG, HDL-C and fibrinogen between groups at the end of study.
5. The percentage of change in serum TC and LDL-C of patients receiving pitavastatin 1 mg once daily were significantly lower than that of atorvastatin 10 mg once daily. Whereas, there was no significant difference of the percentage of change in serum TG, HDL-C, hsCRP and fibrinogen between groups.
6. Pitavastatin 1 mg once daily and atorvastatin 10 mg once daily had a comparable LDL-C lowering effect that allows the patients to achieve their LDL-C goals according to NCEP ATP III guidelines. (74% and 84% of patients in pitavastatin 1 mg once daily and atorvastatin 10 mg once daily, respectively)
7. The number of patients experienced the adverse events was not significantly different between the patients receiving pitavastatin 1 mg once daily and atorvastatin 10 mg once daily. However, serum ALT at the end of study in the atorvastatin group was significantly increased from baseline. Similarly, serum creatinine at the end of study in woman receiving pitavastatin was significantly increased from baseline. Whereas, there was no significant difference in serum AST, ALT, CK, and creatinine at the end of study between the pitavastatin and atorvastatin groups.
8. Annual cost of drug treatment in patients receiving pitavastatin 1 mg once daily was lower than that of the patients receiving atorvastatin 10 mg once (5,856.00 baht and 14,457.00 baht, respectively). Therefore, in case of patient who needs to achieve LDL-C goal using a moderate or intensive LDL-C lowering drug therapy (30% to 40%) and has a financial problem, pitavastatin 1 mg once daily may be a reasonable choice compared with atorvastatin 10 mg once daily.

2. Limitations

1. The small sample size was not enough power of a test for subgroup analysis in specific patients.
2. The open label study might be cause of measurement or selection bias.
3. This study had unequal baseline of AST and creatinine between patients receiving pitavastatin 1 mg once daily and atorvastatin 10 mg once daily. AST and creatinine may be confounding factors for adverse event rate of patients.

4. This study conducted in rainy season which may be cause of viral infection. Viral infection may be confounding factor for serum hsCRP and fibrinogen.
5. Because pitavastatin 1 mg tablet and pitavastatin 2 mg scored tablet were not available in Thailand, tablet splitting technique was applied in pitavastatin 2 mg tablet. Although investigator provided tablet splitting devices in all patients and educated them to use it correctly, individual perception may be confounding factor for drug compliance and drug efficacy.
6. The investigator could not contact two patients during study period because one of them had no own telephone and another one gave the wrong telephone number. Therefore, less intervention maybe affected achieving their goals or adverse event rates of patients.
7. Although, turbidimetric method often exhibits poor accuracy and precision than Clauss method, the turbidimetric is the only method used at Pharmongkutklao Hospital. Therefore, serum fibrinogen was measured using turbidimetric method.

3. Recommendations

Future studies should include:

1. Study the efficacy and safety of statins in specific patients (e.g. mixed dyslipidemic patient, high risk patient, patient with high hsCRP)
2. Conducting multicenter study to confirm the efficacy, safety, and cost effectiveness of pitavastatin 1 mg once daily compared with atorvastatin 10 mg once daily.
3. Using Clauss method to measure serum fibrinogen to increase the accuracy and precision of serum fibrinogen measurement.
4. Measuring at least two times of serum lipids, hsCRP, and fibrinogen should be conducted to assess the tendency of the parameters changing.
5. Using pitavastatin 1 mg tablet or pitavastatin 2 mg scored tablet to improve drug quality variation and drug compliance.
6. Determining the effect of statins on the other emerging risk factors for CHD (e.g., hemocysteine, lipoprotein (a) and apolipoprotein B-100) to investigate the other beneficial effects of statins.
7. Expanded time frame of the study more than 8 week period for long-term efficacy and safety monitoring.

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APPENDICES

วันที่เริ่ม .....
วันที่สิ้นสุด.....
โทร .....

Appendix A
แบบฟอร์มบันทึกข้อมูลผู้ป่วย

เลขที่ □□□

ID ..... HN ……. อายุ ..... ปี (วันเกิด .....)

เพศ ☒ชาย ☒หญิง อาชีพ .....

ประวัติแพ้ยา □ NKDA □ แพ้ยา..... อาการที่พบ.....

สิทธิการรักษา □ 30 บาท □ ประกันสังคม □ เบิกต้นสังกัด □ ชำระเงินเอง □ อื่นๆ.....

ยาที่ได้รับ □ **pitavastatin 2 mg ครึ่งเม็ด หลังอาหารเย็นวันละครั้ง**

□ **atorvastatin 10 mg 1 เม็ด หลังอาหารเย็นวันละครั้ง**

โรคระจำตัว □ โรคหลอดเลือดหัวใจ (AP, MI, coronary angioplasty, CABG, UA, ACS)

□ โรคเบาหวาน □ โรคตับ □ โรคไต ClCr ……

□ โรคหลอดเลือดแดงแข็งอื่น เช่น สมองขาดเลือดชั่วคราว โรคหลอดเลือดแดงส่วนปลาย หลอดเลือดแดงที่ท้องโป่ง□ โรคไทรอยด์ □ โรคเกาต์

□ โรคความดันโลหิตสูง □ ภาวะไขมันในเลือดสูง□ อื่นๆ ….....

ยา / อาหารเสริม / สมุนไพร อื่นๆ ที่ได้รับร่วมด้วย *จำนวนรายการยาทั้งหมด* ..... *รายการ*

ชนิดยา / ความแรง	วิธีใช้	ชนิดยา / ความแรง	วิธีใช้

ปัจจัยเสี่ยงสำคัญเชิงบวก

☐ อายุ (เพศชาย ≥ 45 ปี, เพศหญิง ≥ 55 ปี หรือประจำเดือนหมดก่อนอายุ 55 ปี และไม่ได้รับฮอร์โมนทดแทน)

□ ประวัติญาติสายตรง เป็นโรคหลอดเลือดหัวใจหรือเสียชีวิตก่อนอายุ 55 ปี ในเพศชาย และ 65 ปี ในเพศหญิง

□ ปัจจุบันสูบบุหรี่ (หรือสูบบุหรี่ภายใน 1 เดือนที่ผ่านมา) จำนวน .....มวน/ วัน

□ โรคความดันโลหิตสูง (ความดันโลหิต ≥140/90 mmHg หรือได้รับยาลดความดันโลหิต)

□ ระดับ HDL < 40 mg/dl

ปัจจัยเสี่ยงสำคัญเชิงลบ

O ระดับ HDL ≥ 60 mg/dl

รวม..... Risk factor (s)

10-year risk score = …… %

Risk category	**LDL-C goals**
□ High risk; CHD or CHD risk equivalent (10-year risk > 20%)	<100 mg/dl
□ Moderately high risk; ≥2 risk factors (10-year risk 10 - 20%)	<130 mg/dl
□ Moderate risk; ≥ 2 risk factors (10-year risk < 10%)	<130 mg/dl
□ Lower risk; 0-1 risk factor	<160 mg/dl

ผลการตรวจร่างกายและผลการตรวจทางห้องปฏิบัติการ

ข้อมูล	ข้อมูลพื้นฐาน	สิ้นสุดการวิจัย
	วันที่	วันที่ .....
น้ำหนัก (kg)		
ส่วนสูง (m)		
BMI (kg/m^2)		
เส้นรอบวงระดับเอว (นิ้ว)		
ความดัน (mmHg)		
FBS (mg/dL)		
TC (mg/dL)		
TG (mg/dL)		
LDL-C (mg/dL)		
HDL-C (mg/dL)		
hsCRP (mg/dL)		
Fibrinogen (mg/dL)		
AST (IU/L)		
ALT (IU/L)		
CK (IU/L)		
Cr (μmol/L)		
การควบคุมอาหาร		
การออกกำลังกาย		

อาการไม่พึงประสงค์จากยา	วันที่พบอาการ	การแก้ไข	ผลประเมินตาม Naranjo's algorithm
ปวดเมื่อยกล้ามเนื้อ, กล้ามเนื้ออ่อนแรง			
ปวดศีรษะ			
มึนศีรษะ			
คลื่นไส้			
อาเจียน			
ปวดท้อง, ท้องอืด			
ท้องเสีย			
AST, ALT, CK > 3 ULN			

LDL-C เมื่อสิ้นสุดการวิจัยเท่ากับ …….. Mg/dL

☐ **Achieve goal**

☐ **Not achieve goal**

Appendix B

เอกสารชี้แจงข้อมูลแก่ผู้เข้าร่วมโครงการวิจัย

(Research Subject Information sheet)

ชื่อโครงการวิจัย

การเปรียบเทียบประสิทธิผลและความปลอดภัยของการใช้ยาพิทาวา สแททิน 1 มิลลิกรัม วันละครั้ง กับ อะทอร์วาสแททิน 10 มิลลิกรัม วันละครั้ง ในผู้ป่วยนอกที่มีภาวะคอเลสเทอรอลสูงในเลือด

วันที่ชี้แจง .....

ชื่อและสถานที่ทำงานของผู้วิจัย

ชื่อ	พ.อ.นครินทร์ ศันสนยุทธ
ตำแหน่ง	อาจารย์แผนกโรคหัวใจและหลอดเลือด กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า
ที่ทำงาน	แผนกโรคหัวใจและหลอดเลือด กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า
โทรศัพท์	02-3547600 ต่อ 93327
ชื่อ	ภก.ปวัฒน์ ผุดวาย
ตำแหน่ง	นิสิตปริญญาโท ภาควิชาเภสัชกรรมคลินิก
ที่ทำงาน	คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
โทรศัพท์	089-6266158

ชื่อผู้วิจัยร่วม

พ.ต.หญิงนงลักษณ์ โตรักษา เภสัชกร กองเภสัชกรรม โรงพยาบาลพระมงกุฎเกล้า

ผู้ให้ทุนวิจัย

ทุนอุดหนุนวิทยานิพนธ์สำหรับนิสิต จากฝ่ายวิจัย จุฬาลงกรณ์มหาวิทยาลัย บัณฑิตวิทยาลัย

ท่านได้รับการเชิญชวนให้เข้าร่วมในโครงการวิจัยนี้ แต่ก่อนที่ท่านจะตกลง ใจเข้าร่วมหรือไม่ โปรดอ่านข้อความในเอกสารนี้ทั้งหมด เพื่อให้ทราบว่า เหตุใดท่านจึงได้รับเชิญให้เข้าร่วมในโครงการวิจัยนี้ โครงการวิจัยนี้ทำเพื่ออะไร หากท่านเข้าร่วมโครงการวิจัยนี้ท่านจะต้องทำอะไรบ้าง รวมทั้งข้อดีและข้อเสียที่อาจจะเกิดขึ้นในระหว่างการวิจัย

ในเอกสารนี้ อาจมีข้อความที่ท่านอ่านแล้วยังไม่เข้าใจ โปรดสอบถามผู้วิจัยหรือผู้ช่วยผู้วิจัยที่ทำโครงการนี้เพื่อให้อธิบายจนกว่าท่านจะเข้าใจ ท่านจะได้รับเอกสารนี้ 1 ชุด กลับไปอ่านที่บ้านเพื่อปรึกษาหารือกับญาติพี่น้อง เพื่อน หรือแพทย์ที่ท่านรู้จัก ให้ช่วยตัดสินใจว่าควรจะเข้าร่วมโครงการวิจัยนี้หรือไม่ การเข้าร่วมในโครงการวิจัยครั้งนี้จะต้องเป็น **ความสมัครใจ** ของท่าน ไม่มีการบังคับหรือชักจูง

ถึงแม้ท่านจะไม่เข้าร่วมในโครงการวิจัย ท่านก็จะได้รับการรักษาพยาบาลตามปกติ การไม่เข้าร่วมหรือถอนตัวจากโครงการวิจัยนี้ จะไม่มีผลกระทบต่อการได้รับบริการ การรักษาพยาบาลหรือผลประโยชน์ที่พึงจะได้รับของท่านแต่อย่างใด

โปรดอย่าลงลายมือชื่อของท่านในเอกสารนี้จนกว่าท่านจะแน่ใจว่ามีความประสงค์จะเข้าร่วมในโครงการวิจัยนี้ คำว่า "ท่าน" ในเอกสารนี้ หมายถึงผู้เข้าร่วมโครงการวิจัยในฐานะเป็นอาสาสมัครใ น โครงการวิจัยนี้ หากท่านเป็น**ผู้แทนโดยชอบธรรมตามกฎหมาย**ของผู้ที่จะเข้าร่วมในโครงการวิจัย และลงนามแทนในเอกสารนี้ โปรดเข้าใจว่า "ท่าน" ในเอกสารนี้หมายถึงผู้เข้าร่วมในโครงการวิจัยเท่านั้น

โครงการวิจัยนี้มีที่มาอย่างไร และวัตถุประสงค์ของโครงการวิจัย

ภาวะไขมันในเ ลือดผิดปกติ เป็นปัจจัยเสี่ยงสำคัญที่ทำให้เกิดโรคท่อเลือดแดงและหลอดเลือดแดงแข็ง และก่อให้เกิดโรคอื่นๆ ในระบบหัวใจหลอดเลือดตามมาได้ เช่น โรคหลอดเลือดสมอง โรคหลอดเลือดแดงส่วนปลาย และโรคหลอดเลือดหัวใจ เป็นต้น ซึ่งพบว่าระดับคอเลสเทอรอลรวม และแอลดีแอลคอเลสเทอรอลมีความสัมพันธ์โดยตรงกับอัตราการเกิดและอัตราการตายจากโรคหลอดเลือดหัวใจ ข้อมูลเชิงประจักษ์จากการทดลองทางคลินิกจำนวนมาก ชี้ชัดว่าการลดระดับแอลดีแอลคอเลสเทอรอลสามารถป้องกันการเกิดโรคหลอดเลือดหัวใจได้ ทั้งในผู้ป่วยที่ยังไม่มีประวัติเป็นโรคหลอดเลือดหัวใ จเพื่อป้องกันไม่ให้เกิดโรคหลอดเลือดหัวใจ และในผู้ป่วยที่มีประวัติเป็นโรคหัวใจอยู่แล้ว เพื่อป้องกันการเกิดโรคซ้ำ ซึ่งสามารถลดอัตราการเกิดและการตายจากโรคหลอดเลือดหัวใจได้ประมาณร้อยละ 24-50

ปัจจุบัน National Cholesterol Education Program (NCEP) จึงแนะนำให้กา รลดระดับแอลดีแอลคอเลสเทอรอล เป็นเป้าหมายแรกของแนวทางในการรักษา ซึ่งระดับแอลดีแอลคอเลสเทอรอลเป้าหมายจะขึ้นกับระดับความเสี่ยงต่อการเกิดโรคหลอดเลือดหัวใจในแต่ละบุคคลด้วย ในปัจจุบันการรักษาภาวะไขมันในเลือดผิดปกติประกอบด้วย การปรับเปลี่ยนพฤติกรรมการ ดำเนินชีวิต เช่น การออกกำลังกาย การควบคุมอาหาร และการลดน้ำหนัก เป็นต้น และการใช้ยาลดไขมัน ยากลุ่ม เอชเอ็มจี-โคเอ รีดักเทส อินฮิบิเตอร์ เป็นยากลุ่มที่มีฤทธิ์ในการลดระดับแอลดีแอลคอเลสเทอรอลอย่างมี ประสิทธิภาพเมื่อเทียบกับยาอื่น และสามารถลดอัตราการเกิดและการตายจากโรคหลอดเลือดหัวใจได้ประมาณร้อยละ 24-37 ดังนั้นจึงถูกใช้อย่างแพร่หลายในการป้องกันทั้งแบบปฐมภูมิและทุติยภูมิเพื่อลดอัตราการตายจากโรคหัวใจและหลอดเลือดตามแนวทางรักษาของ NCEP ATP III เพื่อลดระดับแอลดีแอลคอเลสเทอรอล

ผลการศึกษาของ L-TAP และ ImPACT พบว่าผู้ป่วยที่รับประทานยาลดไขมันชนิดต่างๆ ทั้งที่รับประทานยาเพียงชนิดเดียว และรับประทานร่วมกับยาอื่น สามารถควบคุมระดับแอลดีแอลคอเลสเทอรอลได้ตามเกณฑ์เป้าหมายของ NCEP มีจำนวนเพียงร้อยละ 38-62.5 สำหรับประเทศไทยมีผลสำรวจของชุติพรและคณะ ซึ่งเป็นการศึกษาเชิงพรรณนาแบบภาคตัดขวางในกลุ่มผู้ป่วยนอก โรงพยาบาลพระมงกุฎเกล้า พ.ศ.2547 พบว่าการใช้ยากลุ่ม เอชเอ็มจี-โคเอ รีดักเทส อินฮิบิเตอร์ เพียงชนิดเดียวสามารถลดระดับแอลดีแอลคอเลสเทอรอล ตามเกณฑ์เป้าหมายของ NCEP ATP III ได้ร้อยละ 47.7 และเมื่อ

พิจารณาแยกตามระดับความเสี่ยงในการเกิดโรคหลอดเลือดหัวใจเป็น ระดับต่ำ ปานกลาง และสูง พบว่าผู้ป่วยสามารถลดระดับแอลดีแอลคอเลสเทอรอล ได้ตามเกณฑ์เป้าหมายร้อยละ 83.7, 70 และ 35 ตามลำดับ จากข้อมูลดังกล่าวพอสรุปได้ว่ายากลุ่ม เอชเอ็มจี-โคเอ รีดักเทส อินฮิบิเตอร์ ทั้งที่รับประทานยาเพียงชนิดเดียว และให้ร่วมกับยาอื่น ยังมีสัดส่วนของผู้ป่วยที่ไม่สามารถควบคุมระดับแอลดีแอลคอเลสเทอรอลให้ได้ตามเป้าหมายอยู่มากกว่าร้อยละ 50 โดยเฉพาะ ผู้ป่วยในกลุ่มเสี่ยงสูง และยากลุ่มนี้มีโอกาสเกิดปฏิกิริยาระหว่างยาได้ง่าย เนื่องจากที่มีกระบวนการแปรรูปวิธีเดียวกันกับยาอื่น ซึ่งเพิ่มโอกาสเกิดอาการไม่พึงประสงค์จากยาได้ ดังนั้นจึงมีความพยายามศึกษาหากลยุทธ์ อื่นๆ เพื่อเพิ่มสัดส่วน ของผู้ป่วยที่สามารถลดระดับแอลดีแอลคอเลสเทอรอลให้ได้ตามเป้าหมายมากขึ้นและ มีการเกิด ปฏิกิริยาระหว่างยาน้อย วิธีการที่ผู้วิจัยสนใจคือการหายาชนิดใหม่ที่มีประสิทธิผลดีและมีความปลอดภัยแก่ผู้ป่วยมาทดแทน

ยาพิทาวาสแททิน เป็นยากลุ่มเอชเอ็มจี-โคเอ รีดักเทส อินฮิบิเตอร์ชนิดใหม่ที่มีประสิทธิผลและความปลอดภัยในการลดระดับแอลดีแอลคอเลสเทอรอลในเลือด จากการศึกษาประสิทธิผลทางคลินิกของ ยาพิทาวา สแททิน พบว่าการลดระดับคอเลสเทอรอลรวม และแอลดีแอลคอเลสเท อรอลมีความสัมพันธ์กับขนาดยาที่เพิ่มขึ้น คือ เมื่อรับประทานยาพิทาวาสแททิน ขนาด 1, 2 และ 4 มิลลิกรัม วันละครั้งพบว่าสามารถลดระดับแอลดีแอลคอเลสเทอรอลได้ร้อยละ 34, 42 และ 47 ตามลำดับและจากรายงานของ Livalo effectiveness and safety study (LIVES) พบว่าอัตราการเกิดอาการไม่พึงประสงค์ของยาพิทาวาสแททินโดยรวมคิดเป็นร้อยละ 10.4 ซึ่งไม่มากกว่าอะทอร์วาสแททิน และโรซูวาสแททินซึ่งพบว่ามีอัตราการเกิดอาการไม่พึงประสงค์โดยรวมร้อยละ 12.0 และ 11.1 ตามลำดับ นอกจากนี้ ยังมีการศึกษาเพื่อยืนยันประสิทธิผลในการลดระดับแอลดีแอลคอเลสเทอรอล ของยาพิทาวาสแททินโดยการเปรียบเทียบกับยาอื่นพบว่า ยาพิทาวาสแททิน 2 มิลลิกรัม สามารถลดระดับแอลดีแอลคอเลสเทอรอลได้มากกว่ายาพราวาสแททิน 10 มิลลิกรัม และมีประสิทธิผล ในการลดระดับแอลดีแอลคอเลสเทอรอลไม่แตกต่างกับซิมวาสแททิน 20 มิลลิกรัม และอะทอร์วาสแททิน 10 มิลลิกรัม

ในปี 2006 มีการศึกษาของ Yoshitomi และคณะ ซึ่งศึกษาเพื่อเปรียบเทียบประสิทธิผลและความปลอดภัยขอยาพิทาวา สแททิน 1 มิลลิกรัม กับยาอะทอร์วา สแททิน 10 มิลลิกรัม วันละครั้ง ในผู้ป่วยที่มีภาวะคอเลสเทอรอลสูงในเลือดจำนวน 137 คน เป็นระยะเวลา 12 สัปดาห์ พบว่ากลุ่มที่ได้ยาพิทาวาสแททิน 1 มิลลิกรัม วันละครั้ง สามารถลดระดับแอลดีแอลคอเลสเทอรอลในเลือดได้ไม่แตกต่างกับกลุ่มที่ได้ยาอะทอร์วา สแททิน 10 มิลลิกรัม วันละครั้ง อย่างมีนัยสำคัญ (38%±13 vs. 41%±12) แต่เนื่องจากรูปแบบการศึกษานี้ไม่เป็นแบบสุ่ม ทำให้ข้อมูลอาจมีอคติในการเลือกตัวอย่างได้ ผลสรุปที่ได้จึงไม่สามารถปรับใช้กับประชากรทั่วไปได้ ดังนั้นผู้วิจัยจึงต้องการศึกษาเพื่อยืนยันประสิทธิผลในการลดระดับแอลดีแอล คอเลสเทอรอล ในเลือดของยาพิทาวา สแททิน 1 มิลลิกรัม วันละครั้ง เปรียบเทียบกับยาอะทอร์วา สแททิน 10 มิลลิกรัม วันละครั้ง ในรู ปแบบการศึกษาแบบ สุ่ม เพื่อกำหนดขนาดยาเริ่มต้นของยาพิตาวาสแททิน ในการรักษาผู้ป่วยที่มีภาวะไขมันสูงในเลือดต่อไป

ท่านได้รับเชิญให้เข้าร่วมโครงการวิจัยนี้เพราะคุณสมบัติที่เหมาะสมดังต่อไปนี้

เป็นผู้ป่วยที่มีอายุมากกว่าหรือเท่ากับ 20 ปี ที่จำเป็นต้องได้รับยาลดไขมันตามแนวทางการรักษาของ NCEP ATP III และลงชื่อยินยอมเข้าร่วมการวิจัย

ท่านไม่สามารถเข้าร่วมโครงการวิจัยได้หากท่านมีคุณสมบัติดังต่อไปนี้

ผู้ป่วยมีภาวะหลอดเลือดหัวใจเฉียบพลันก่อนเข้าร่วมการวิจัย 3 เดือน หรือได้รับการวินิจฉัยว่าเป็นโรคดังต่อไปนี้ ภาวะขาดไทรอยด์ฮอร์โมน, โรคตับ, โรคไต, ภาวะการติดเชื้อ, ภาวะอักเสบเรื้องรัง หรือเป็นมะเร็ง หรือเป็นหญิงที่ตั้งครรภ์ หรือให้นมบุตรอยู่ หรือมีประวัติแพ้ยากลุ่ม เอชเอ็มจี- โคเอ รีดักเทส อินฮิบิเตอร์ หรือมีระดับไตร กลีเซอไรด์ สูงกว่า 400 มิลลิกรัมต่อเดซิลิตร หรือ ได้รับยาที่เกิดปฏิกิริยาระหว่างยากับยา พิตาวาสแททิน และยาอะทอร์วาสแททิน หรือได้รับยาร่วมมีผลต่อการเปลี่ยนแปลงของระดับไขมันในเลือด hsCRP และ fibrinogen หรือมีระดับเอนไซม์ AST, ALT เพิ่มสูงจากค่าสูงสุดปกติ 3 เท่า หรือ CK เพิ่มสูงจากค่าสูงสุดปกติ 10 เท่า หรือมีความผิดปกติทางจิตใจ ความจำเสื่อม หรืออยู่ในสภาพที่ไม่สามารถรับรู้ เข้าใจ หรือให้ความร่วมมือตามระเบียบวิธีวิจัยต่างๆ ได้

จะมีการทำโครงการวิจัยนี้ที่ใด และมีจำนวนผู้เข้าร่วมโครงการวิจัยทั้งสิ้นเท่าไร

ผู้เข้าร่วมการวิจัยคือ ผู้ป่วยนอกที่มีภาวะไขมันสูงในเลือด ซึ่งเข้ารับการรักษา ณ ห้องตรวจโรคผู้ป่วยนอก แผนกเวชศาสตร์ครอบครัว แผนกต่อมไร้ท่อ แผนกโรคหัวใจ และคลินิกพิเศษนอกเวลาราชการ โรงพยาบาลพระมงกุฎเกล้า ในช่วงเวลาที่ดำเนินการเก็บข้อมูล รวมทั้งสิ้น 100 คน

ระยะเวลาที่ท่านจะต้องร่วมโครงการวิจัยและจำนวนครั้งที่นัด

ผู้ป่วยที่เข้าร่วมการวิจัยจะได้รับการสัมภาษณ์ การตรวจร่างกาย และการตรวจทางห้องปฏิบัติการ โดยแพทย์ เพื่อจัดกลุ่มผู้ป่วยตามระดับความเสี่ยงของการเกิดโรคหลอดเลือดหัวใจ ผู้ป่วยจะมีระยะเวลาเข้าร่วมการวิจัยทั้งสิ้น 8 สัปดาห์ โดยนับวันที่ผู้ป่วยได้รับการสุ่มเลือกเพื่อรับประทานยาในแต่ละกลุ่มเป็นสัปดาห์ที่ 0 ของการวิจัย ซึ่งก่อนรับประทานยาผู้ป่วยจะได้รับการประเมินระดับไขมันในเลือด และผลทางห้องปฏิบัติการอื่นๆ ไว้เป็นข้อมูลพื้นฐาน และเมื่อครบ 8 สัปดาห์ แพทย์จะนัดพบผู้ป่วยอีกครั้งเพื่อทำการประเมินระดับไขมันในเลือด และผลทางห้องปฏิบัติการอื่นๆ เพื่อเปรียบเทียบประสิทธิผลของยา และประเมินอาการไม่พึงประสงค์จากการใช้ยา ในระหว่างช่วง 8 สัปดาห์ ผู้วิจัยโทรศัพท์ถึงผู้ป่วยในสัปดาห์ที่ 1, 3 และ 7 เพื่อค้นหาอาการไม่พึงประสงค์จากยา ปัญหาหรืออุปสรรคของผู้ป่วยที่อาจส่งผลต่อการวิจัยได้

หากท่านเข้าร่วมโครงการวิจัยครั้งนี้ ท่านจะต้องปฏิบัติตามขั้นตอน หรือได้รับการปฏิบัติอย่างไรบ้าง

ผู้ป่วยที่ผ่านเกณฑ์คัดเลือกเข้าร่วมการวิจัยแต่ละคนได้รับการอธิบายถึงวัตถุประสงค์ของการวิจัย และเงื่อนไขในการเข้าร่วมโครงการวิจัย และลงลายมือชื่อในหนังสือยินยอมเข้าร่วมการวิจัย การเก็บข้อมูลประวัติผู้ป่วยและครอบครัว ข้อมูลการใช้ยานอกโรงพยาบาล จะใช้วิธีสัมภาษณ์ซึ่งหน้าจากผู้วิจัย

การเก็บข้อมูลประวัติการใช้ยาในโรงพยาบาล ประวัติการเจ็บป่วยในอดีตจะได้จากการสืบค้นใน เวชระเบียนผู้ป่วย ส่วนการวินิจฉัยโรค การตรวจร่างกาย การตรวจทางห้องปฏิบัติการ จะดูแลโดยแพทย์ และในสัปดาห์ที่ 1, 3 และ 7 ของการวิจัยผู้วิจัยจะสอบถามข้อมูลเพื่อค้นหาอาการไม่พึงประสงค์จากยา ปัญหาหรืออุปสรรคของผู้ป่วยที่อาจส่งผลต่อการวิจัยเพิ่มเติมโดยการสำภาษณ์ทางโทรศัพท์

ความไม่สุขสบาย หรือความเสี่ยงต่ออันตรายที่อาจจะได้รับจากกรรมวิธีการวิจัยมีอะไรบ้าง และวิธีการป้องกัน/แก้ไขที่ผู้วิจัยเตรียมไว้หากมีเหตุการณ์ดังกล่าวเกิดขึ้น

ยาพิตาวา สแททิน หรือยาอะทอร์วา สแททิน มีรายงานอัตราการเกิดอาการไม่พึงประสงค์โดยรวม ร้อยละ 10.4 และ 12.0 ตามลำดับ อาการไม่พึงประสงค์ที่พบส่วนใหญ่เป็นแบบไม่รุนแรง เช่น คลื่นไส้ อาเจียน ปวดศีรษะ ปวดเมื่อกล้ามเนื้อ เป็นต้น ซึ่งหากผู้ป่วยเกิดอาการดังกล่าวผู้ป่วยสามารถโทรศัพท์ปรึกษาผู้วิจัยได้ตลอด 24 ชั่วโมง และจะได้รับการรักษาเพื่อแก้ไขอาการดังกล่ าวโดยแพทย์ผู้เชี่ยวชาญ และหากผู้ป่วยเกิดอาการไม่พึงประสงค์ชนิดรุนแรง เช่น มีภาวะตับอักเสบ หรือกล้ามเนื้ออักเสบ เป็นต้น ผู้ป่วยจะได้รับการพิจารณาหยุดยาและได้รับการรักษาโดยแพทย์ผู้มีความเชี่ยวชาญ

ประโยชน์ที่คาดว่าจะได้รับจากโครงการวิจัย

1. ผู้ป่วยได้รับความรู้และแนวปฏิบัติสำหรับการปรับเปลี่ยนการดำเนินชีวิต เพื่อลดระดับไขมัน เช่น การออกกำลังกาย การควบคุมอาหาร และการลดน้ำหนักเป็นต้น
2. ได้ข้อมูลเกี่ยวกับประสิทธิผล ความปลอดภัย ของพิทาวาสแททิน 1 มิลลิกรัม และ อะทอร์วาสแททิน 10 มิลลิกรัม ในผู้ป่วยที่มีภาวะไขมันในเลือดผิดปกติ
3. เป็นข้อมูลเพื่อใช้ในกระบวนการตัดสินใจทางเภสัชบำบัด (therapeutic decision making process) เพื่อลดภาวะเสี่ยงของการเกิดโรคหัวใจและหลอดเลือด ตามแนวทางของ NCEP ATP III
4. เป็นข้อมูลเพื่อใช้ประกอบในการพิจารณาคัดเลือกยาเข้าในเภสัชตำรับของโรงพยาบาล

ค่าใช้จ่ายที่ผู้เข้าร่วมในโครงการวิจัยจะต้องรับผิดชอบ

ไม่มี

ค่าตอบแทนที่จะได้รับเมื่อเข้าร่วมโครงการวิจัย

ไม่มี

หากท่านไม่เข้าร่วมโครงการวิจัยนี้ ท่านมีทางเลือกอื่นอย่างไรบ้าง

หากท่านไม่เข้าร่วมโครงการ ท่านสามารถรับบริการจากโรงพยาบาลพระมงกุฎเกล้า ตามแผนการรักษาเดิม โดยไม่มีผลเปลี่ยนแปลงใดๆ

หากเกิดอันตรายที่เกี่ยวข้องกับโครงการวิจัยนี้ จะติดต่อกับใคร และจะได้รับการปฏิบัติอย่างไร

พ.อ. นพ.นครินทร์ ศันสนยุทธ โทรศัพท์ 089-1130099 หรือ ภก.ปวัฒน์ ผุดวาย โทรศัพท์ 089-6266158 ได้ตลอด 24 ชั่วโมง ซึ่งหากผู้ป่วยเกิดอันตรายที่เกี่ยวข้องกับโครงการวิจัย ผู้ป่วยสามารถโทรศัพท์ปรึกษาผู้วิจัยได้ตลอด 24 ชั่วโมง และจะได้รับการรักษาเพื่อแก้ไขอาการดังกล่าวโดยแพทย์ผู้เชี่ยวชาญ และหากผู้ป่วยเกิดอาการไม่พึงประสงค์ชนิดรุนแรง เช่น มีภาวะตับอักเสบ หรือกล้ามเนื้ออักเสบ เป็นต้น ผู้ป่วยจะได้รับการพิจารณาหยุดยาและได้รับการรักษาโดยแพทย์ผู้มีความเชี่ยวชาญ ซึ่งค่าใช้จ่ายในการรักษาพยาบาลที่เกิดขึ้น ให้ใช้ตามสิทธิการรักษาพยาบาลของผู้ป่วย และที่เหลือจะเป็นความรับผิดชอบของผู้วิจัย

หากท่านมีคำถามที่เกี่ยวข้องกับโครงการวิจัย จะถามใคร ระบุชื่อผู้วิจัยหรือผู้วิจัยร่วม

พ.อ. นพ.นครินทร์ ศันสนยุทธ โทรศัพท์ 089-1130099 หรือ ภก.ปวัฒน์ ผุดวาย โทรศัพท์ 089-6266158 ได้ตลอด 24 ชั่วโมง

หากท่านรู้สึกว่าได้รับการปฏิบัติอย่างไม่เป็นธรรมในระหว่างโครงการวิจัยนี้ ท่านอาจแจ้งเรื่องได้ที่

สำนักงานพิจารณาโครงการวิจัย พบ. เบอร์โทร 02-3547600-28 ต่อ 94270

ข้อมูลส่วนตัวของท่านที่ได้จากโครงการวิจัยครั้งนี้จะถูกนำไปใช้ดังต่อไปนี้

การนำเสนอข้อมูลที่ได้จากโครงการวิจัย เพื่อประโยชน์ทางวิชาการจะไม่มีการเปิดเผยชื่อนามสกุล ที่อยู่ของผู้เข้าร่วมในโครงการวิจัยเป็นรายบุคคล และมีมาตรการในการเก็บรักษาข้อมูลส่วนตัวและข้อมูลที่ได้จากโครงการวิจัยอย่างปลอดภัย ข้อมูลจะถูกส่งให้คณะกรรมการจริยธรรมฯ และนักวิเคราะห์ข้อมูลสถิติเท่านั้น และจะมีการนำเสนอผลการวิจัยใน ภาควิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย และมีการตีพิมพ์เป็นวิทยานิพนธ์ของจุฬาลงกรณ์มหาวิทยาลัย

ท่านจะถอนตัวออกจากโครงการวิจัยหลังจากได้ลงนามเข้าร่วมโครงการวิจัยแล้วได้หรือไม่

ผู้เข้าร่วมในโครงการวิจัย สามารถถอนตัวออกจากโครงการวิจัยได้ตลอดเวลา โดยจะไม่มีผลเสียใดๆ เกิดขึ้น

หากมีข้อมูลใหม่ที่เกี่ยวข้องกับโครงการวิจัย ท่านจะได้รับแจ้งข้อมูลนั้นโดยผู้วิจัยหรือผู้วิจัยร่วมนั้นทันที

Appendix C

หนังสือแสดงเจตนายินยอมเข้าร่วมการวิจัย (Informed Consent)

รับรองโดยคณะอนุกรรมการพิจารณาโครงการวิจัย พบ.

ชื่อครงการวิจัย การเปรียบเทียบประสิทธิผลและความปลอดภัยของการใช้ยา พิทาวา สแททิน 1 มิลลิกรัม วันละครั้ง กับ อะทอร์วา สแททิน 10 มิลลิกรัม วันละครั้ง ในผู้ป่วยนอกที่มีภาวะคอเลสเทอรอลสูงในเลือด

วันที่ลงนาม.....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรืออาการที่อาจเกิดขึ้นจากการวิจัย หรือจากยาที่ใช้ รวมทั้งประโยชน์ที่คาดว่าจะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามที่ข้าพเจ้าสงสัยด้วยความเต็มใจ และไม่ปิดบังซ่อนเร้น จนข้าพเจ้าพอใจ

ข้าพเจ้าเข้าร่วมในโครงการวิจัยนี้ด้วยความสมัครใจ โดยปราศจากการบังคับหรือชักจูง

ข้าพเจ้ามีสิทธิที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยเมื่อใดก็ได้ และการบอกเลิกนี้จะไม่มีผลต่อการรักษาพยาบาลที่ข้าพเจ้าจะพึงได้รับในปัจจุบันและในอนาคต

ผู้วิจัยรับรองว่าจะ เก็บข้อมูลเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยเฉพาะในรูปของสรุปผลการวิจัยโดยไม่มีการระบุชื่อนามสกุลของข้าพเจ้า การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆ ที่เกี่ยวข้อง จะกระทำด้วยเหตุผลทางวิชาการเท่านั้น

ผู้วิจัยรับรองว่าหากเกิดอันตรายใ ดๆ จากการวิจัย ข้าพเจ้าจะได้รับการรักษาพยาบาล ตามที่ระบุในเอกสารชี้แจงข้อมูลแก่ผู้เข้าร่วมโครงการวิจัย

ข้าพเจ้าจะได้รับเอกสารชี้แจงและหนังสือยินยอมที่มีข้อความเดียวกันกับที่ผู้วิจัยเก็บไว้ เป็นส่วนตัวข้าพเจ้าเอง 1 ชุด

ข้าพเจ้าได้รับทราบข้อความข้างต้นแล้ ว มีความเข้าใจดีทุกประการ และลงนามในใบยินยอมด้วยความเต็มใจ

ลงชื่อ.....**ผู้เข้าร่วมโครงการวิจัย**
(.....**ชื่อ-นามสกุล ตัวบรรจง**)

ลงชื่อ .....**ผู้ดำเนินโครงการวิจัย**
(.....**ชื่อ-นามสกุล ตัวบรรจง**)

ลงชื่อ.....**พยาน**
(.....**ชื่อ -นามสกุล ตัวบรรจง**)

ลงชื่อ.....**พยาน**
(.....**ชื่อ -นามสกุล ตัวบรรจง**)

Appendix D

แบบประเมินอาการไม่พึงประสงค์จากการใช้ยา (Naranjo's Algorithm)

ชื่อ-สกุล..... HN…… อายุ.....ปี

ชื่อยาที่สงสัย..... ประวัติการแพ้ยา ☐ NKDA

วันที่เริ่มใช้ยา.....… ☐ แพ้ยา

.....

วันที่หยุดใช้ยา..... วันที่ประเมิน.....

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

ผลการประเมิน ☐ ใช่แน่นอน (Definite) > 9 คะแนน ☐ น่าจะใช่ (Probable) 5-8 คะแนน

☐ เป็นไปได้ (Possible) 1-4 คะแนน ☐ ไม่น่าจะใช่ (Doubtful) < 0 คะแนน

Appendix E

Subgroup analysis of baseline patient charecteristics in the pitavastatin and atorvastatin groups.

Variable	Mean ± SD (range)			p-value[a]
	Pitavastatin group	Atorvastatin group	Total	
SBP (mmHg) in HT patients	*N = 38* 136.82 ± 17.18 (95 to 175)	*N = 30* 145.17± 22.92 (102 to 198)	*N = 68* 140.50 ± 20.19 (95 to 198)	0.091
DBP (mmHg) in HT patients	*N = 38* 81.05 ± 10.51 (55 to 103)	*N = 30* 82.53 ± 13.37 (50 to 111)	*N = 68* 81.71 ± 11.78 (50 to 111)	0.611
FBS (mg/dL) in DM patients	N = 9 157.56 ± 57.22 (102 to 266)	N = 9 139.67 ± 34.74 (98 to 192)	N = 18 148.61 ± 46.84 (98 to 266)	0.435

SD = standard deviation; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBS = fasting blood sugar

[a] using independent t-test to compare mean of SBP, DBP, and FBS between groups

VITAE

Mr. Pawat Putwai was born in Krabi on October 7, 1980. He received his Bachelor of Science in Pharmacy from Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkla, Thailand since 2003. His current position is a pharmacist at Samutprakarn Hospital, Samutprakarn, Thailand.