IMPACT OF PHYSICIAN-PHARMACIST COLLABORATION ON DYSLIPIDEMIA MANAGEMENT IN TYPE 2 DIABETIC PATIENTS

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IMPACT OF PHYSICIAN-PHARMACIST COLLABORATION ON DYSLIPIDEMIA MANAGEMENT IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

The objective of this prospective, non-randomized, controlled trial was to determine the impact of physician-pharmacist collaboration on lipid management in diabetic patients at the Bangkok Metropolitan Administration General Hospital compared with usual care. The primary outcome was the achievement rate of LDL-C goal. The secondary outcomes included changes in lipid parameters, changes in usage rate of lipid modifying agents, types and acceptance rates of pharmacist's interventions. One hundred and 108 patients were enrolled into the usual care and the intervention groups, respectively. Baseline demographics and lipid parameters were similar between two groups. At the end of the study, the mean LDL-C was significantly lower in the intervention group (111.8±33 mg/dL vs 124.8 ±37 mg/dL; p = 0.008). The proportion of patients who reached the LDL-C target of < 100 mg/dL in the intervention group was significantly higher than those in the usual care group (39.8% vs 25.0%; p = 0.023). Beneficial changes in other lipid parameters in favor of the intervention group were also observed. Overall, clinical pharmacists made 60 interventions regarding the modification of lipid lowering therapy, 21 of these were accepted. Sixty interventions on treatment monitoring were made, 32 were accepted by physicians. Significantly more patients in the intervention group received statin therapy. The intensity of statin therapy was also significantly higher in the intervention group. In conclusion, physician-pharmacist collaboration could effectively increase the achievement rate of LDL-C targets in diabetic patients compared with the usual care. The findings of our study support the benefits of multidisciplinary approach in dyslipidemia management.

KEY WORDS : DYSLIPIDEMIA / TYPE 2 DIABETIC PATIENTS / LDL-C
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ผลของความร่วมมือระหว่างแพทย์และเภสัชกรในการจัดการภาวะไขมันผิดปกติในผู้ป่วยเบาหวานชนิดที่ 2 (IMPACT OF PHYSICIAN-PHARMACIST COLLABORATION ON DYSLIPIDEMIA MANAGEMENT IN TYPE 2 DIABETIC PATIENTS.)

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บทคัดย่อ

การศึกษานี้เป็นการศึกษาแบบไปข้างหน้าเพื่อประเมินผลความร่วมมือระหว่างแพทย์และเภสัชกรในการรักษาภาวะไขมันผิดปกติในผู้ป่วยเบาหวานชนิดที่ 2 ของผู้ป่วยนอกโรงพยาบาลกลางเปรียบเทียบระหว่างกลุ่มทดลองกับกลุ่มควบคุม ตัวชี้วัดชนิดปฐมภูมิของการศึกษาคือ อัตราที่ผู้ป่วยบรรลุเป้าหมายของ LDL-C ส่วนตัวชี้วัดชนิดทุติยภูมิคือ การเปลี่ยนแปลงของระดับไขมันต่างๆ อัตราการใช้ยาลดไขมัน ชนิดและอัตราการยอมรับคำแนะนำที่เภสัชกรส่งต่อให้แพทย์ ผลการศึกษาพบว่ากลุ่มควบคุมจำนวน 100 คนและกลุ่มทดลองจำนวน 108 คนมีลักษณะโดยทั่วไปและระดับไขมันในเลือดในเบื้องต้นไม่แตกต่างกัน เมื่อสิ้นสุดการศึกษาพบว่า LDL-C เฉลี่ยของกลุ่มทดลองน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (111.8 ± 33 mg/dL เทียบกับ 124.8 ± 37 mg/dL; p = 0.008) สัดส่วนของผู้ป่วยในกลุ่มทดลองมีอัตราการบรรลุเป้าหมายของ LDL-C ที่น้อยกว่า 100 mg/dL สูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 39.8 ในกลุ่มทดลองและร้อยละ 25 ในกลุ่มควบคุม, p = 0.023) ระดับไขมันอื่นๆ ในกลุ่มทดลองมีการเปลี่ยนแปลงไปในทางที่ดีขึ้นมากกว่ากลุ่มควบคุม อัตราการใช้ยาและขนาดยา statin ที่ใช้ในกลุ่มทดลองสูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ เภสัชกรให้คำแนะนำเกี่ยวกับการปรับเปลี่ยนยาลดไขมันในผู้ป่วยทั้งหมด 60 ครั้งและได้รับการยอมรับ 21 ครั้ง และให้คำแนะนำแก่แพทย์ในการติดตามระดับไขมันในเลือดของผู้ป่วยจำนวน 60 รายและได้รับการยอมรับ 32 ราย โดยสรุปความร่วมมือระหว่างแพทย์และเภสัชกรช่วยเพิ่มประสิทธิภาพในการรักษาภาวะไขมันในเลือดผิดปกติในผู้ป่วยเบาหวานชนิดที่ 2 โดยเพิ่มจำนวนผู้ป่วยที่บรรลุเป้าหมาย LDL-C ผลการศึกษานี้สนับสนุนให้เห็นถึงประโยชน์ของการรักษาภาวะไขมันในเลือดผิดปกติแบบสหสาขาวิชาชีพ

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LIST OF ABBREVIATION

ADA	American Diabetes Association
ACEIs	Angiotensin-converting enzyme inhibitors
ACQUIP	The Ambulatory care quality improvement project
ALLHAT-LLT	The Antihypertensive and lipid lowering treatment to prevent heart attack trial lipid lowering treatment
ASCOT-LLA	The Anglo-Scandinavian cardiac outcome trial-lipid lowering arm
BMA	Bangkok Metropolitan Administration
CAD	Coronary artery disease
CARE	The cholesterol and recurrent events
CARDS	The collaborative atorvastatin in diabetes study
CETP	Cholesterol ester transfer protein
CHD	Coronary heart disease
CYP	Cytochrome P
DTP	Drug therapy problem
DUE	Drug use evaluation
FFA	Free fatty acid
HDL-C	High-density lipoprotein cholesterol
HL	Hepatic lipase
HMG coA	3-hydroxy-3-methyglutaryl coenzyme A
HPS	The Heart protection study
ImPACT	Improve persistence and compliance with therapy
IMPROVE	Impact of managed pharmaceutical care on resource utilization and outcomes in veterans affairs medical center
LDL-C	Low-density lipoprotein cholesterol

LIST OF ABBREVIATION (continued)

LIPID	The Long-term Intervention with pravastatin in ischemic disease
LIPS	The Lescol intervention prevention study
LPL	Lipoprotein lipase
MCO	Managed care organization
MI	Myocardial infarction
NCEP	National cholesterol education program
Non HDL-C	Non high-density lipoprotein cholesterol
OR	Odd ratio
SCRIP	Study of cardiovascular risk intervention by pharmacists
TC	Total cholesterol
TG	Triglyceride
TLC	Therapeutic lifestyle change
VLDL	Very low-density lipoprotein
WOSCOP	The West of Scotland Coronary Prevention Study
4S	The Scandinavian Simvastatin Survival study

CHAPTER I
INTRODUCTION

Diabetes is a chronic disease that needs continuing medical care to prevent serious complications. Type 2 diabetes mellitus is the most common form of diabetes affecting more than two millions adults in Thailand (1). Most adverse diabetes outcomes are a result of vascular complications which are generally classified as microvascular (retinopathy, nephropathy and neuropathy) or macrovascular (coronary artery disease, cerebrovascular disease and peripheral vascular disease) complications. Coronary heart disease (CHD) is the leading cause of death among patients with type 2 diabetes. Haffner and colleagues found that diabetic patients without prior history of CHD have similar risk for future myocardial infarction as non-diabetic patients with established CHD (2). As a result, diabetes is now considered as a coronary heart disease equivalent or CHD-risk equivalent. In order to prevent and manage diabetes complications effectively, a variety of preventive measures beyond glycemic control are required. These include both non-pharmacological and pharmacological based treatments. For drug therapy, therapy with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), antiplatelets, and statins are strongly recommended for type 2 diabetes patients when indicated (3).

Lipid abnormalities contribute to an increased CHD risk of diabetic patients and are twice as common in type 2 diabetes compared with the general population. Insulin resistance leads to the inhibition of lipoprotein lipase enzyme, which causes elevated triglyceride, low levels of high-density lipoprotein (HDL) cholesterol and predominance of small dense LDL-C particle. Each of these dyslipidemia features is associated with an increased risk of cardiovascular disease. Although behavioral interventions such as diet control and exercise can improve diabetic dyslipidemia, for most diabetes patients, pharmacological therapy is needed to reach treatment goals. (4-5) According to the American Diabetic Association (ADA) and the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, and Treatment of High Blood Cholesterol in Adults or Adult Treatment Panel III (ATP III)

(6-8), the LDL-C cholesterol of lower than 100 mg/dl is the primary target in diabetic patients. Drug therapy should be initiated when baseline LDL-C is more than 130 mg/dL. In addition, the American College of Physicians recommends that statins should be used for primary prevention against macrovascular complications in patients with type 2 diabetes and other cardiovascular risk factors and for secondary prevention of cardiovascular mortality and morbidity for all patients with known coronary artery disease and type 2 diabetes patients (9-10).

Statins have been shown to reduce cardiovascular morbidity and mortality in a number of populations including diabetes. Earlier evidence of statins benefit in type 2 diabetes came from subgroup analysis of 5 large secondary prevention trials (11-15). In primary prevention setting, 3 large trials included large subgroups of patients with diabetes, mostly type 2 diabetes (13,16-17). In the Heart Protection Study or HPS (13), treatment with simvastatin 40 mg daily significantly reduced the risk of coronary heart disease and total cardiovascular events in patients with diabetes with or without prior history of coronary heart disease. Recently, the Collaborative Atorvastatin in Diabetes Study (CARDS) was the first large randomized, double-blinded, placebo-controlled trial conducted exclusively in type 2 diabetes. The results of the study indicated that statin therapy was effective and safe to be used as a primary prevention measure of CVD in diabetes patients (18).

Despite evidence from clinical trials and recommendations from guidelines, many studies reveal that many diabetic patients fail to achieve LDL-C goal (19-20). A number of studies evaluated the impact of pharmacist's participation in lipid management. Pharmacist can play an active role in providing education about diet and drug therapy, treatment goals, benefits of therapy, the importance of compliance, and monitoring of adverse effects (21-26).

In Thailand, there have been a number of studies conducted in diabetic patients in different aspects. However, there are only two studies that related to statins therapy including studies by Supapsophon and Pokhagul which were drug use evaluation studies (27-28). These studies demonstrated that a high proportion of statin therapy was prescribed in discordance with criteria established by the hospitals. Sampaogheun (29) conducted a study evaluating the role of pharmacists in the management of

hypercholesterolemia. It was found that pharmacist can increase medication adherence in these patients through patient education and counseling.

Recently, the Diabetes Care Clinic (DCC) was established at the Bangkok Metropolitan Administration (BMA) General Hospital in June 2004 with the collaboration between the Pharmacy Department and Internal Medicine Department. There were 3 clinical pharmacists and 7 physicians participating in this clinic. The objective of the clinic is to improve the quality of care in diabetes patients with the focus on the utilization of proven preventive measures including both non-pharmacological and pharmacological therapies. In addition, pharmacists provide one-on-one patient education regarding diet/exercise, conduct patient interview to identify drug therapy problems (DTP) and suggest appropriate interventions to physicians. Pharmacists also give presentation on drug therapy in the monthly multidisciplinary group education session held by the DCC.

The aim of this study was to determine the impact of the DCC with the focus on lipid management compared with the usual care group (control). The primary outcome was the achievement rate of LDL-C goal. The secondary outcomes included changes in lipid parameters, changes in usage rate of lipid modifying agents, types of pharmacist's interventions and the acceptance rate of such interventions.

CHAPTER II
LITERATURE REVIEW

1. Dyslipidemia in diabetes

Lipid abnormalities contribute to an increased CAD risk of diabetic patients and are twice as common in type 2 diabetes compared with the general populations. Insulin resistance leads to the inhibition of lipoprotein lipase enzyme, which causes elevated triglyceride, low levels of high-density lipoprotein (HDL) cholesterol and predominance of small dense LDL-C particle. Each of these dyslipidemia features is associated with an increased risk of cardiovascular disease. Although behavioral interventions such as diet control and exercise can improve diabetic dyslipidemia, for most diabetes patients, pharmacological therapy is needed to reach treatment goals (4-5).

Type 2 diabetes mellitus is a vascular disease and increases the risk for coronary artery disease by 2 to 4 times in the overall population. Haffner and colleagues found that diabetic patients with no history of coronary artery disease have the same risk for future myocardial infarction as do nondiabetic patients with known disease (Figure 1). More recently, researchers have recognized that patients with diabetes have cardiovascular event risk that is similar to patients with documented atherosclerosis (2, 30-31). Two thirds of the deaths in patients with diabetes are caused by atherosclerosis vascular disease. The National Cholesterol Education Program considers diabetes to be a coronary disease equivalent in their lipid guidelines (NCEP III) (8). In the East-West study, people with diabetes who did not have a previous of MI had a 20.2% incidence of MI at 7-year follow-up evaluation compared with an 18.8% incidence in people without diabetes with a history of MI, helping to establish diabetes as a CAD risk equivalent.

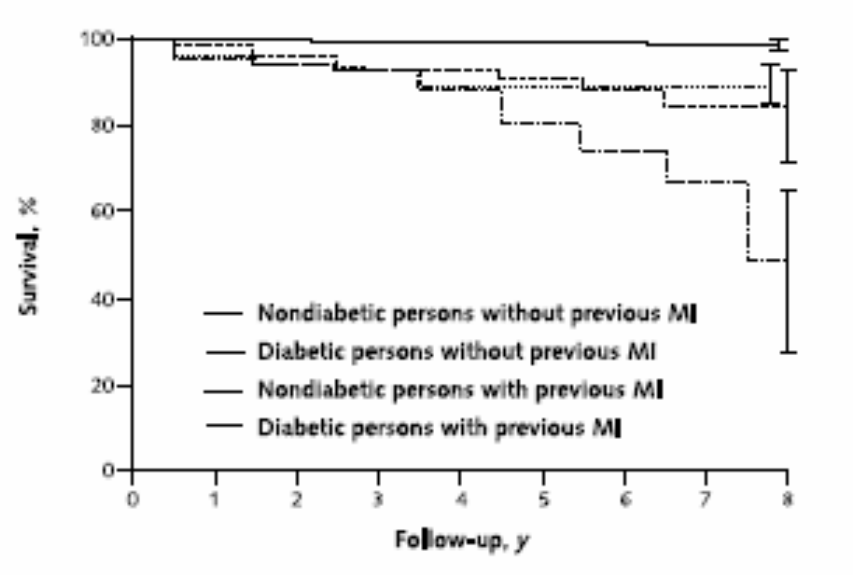

Figure 1 Kaplan-Meier estimates of the probability of death from coronary heart disease in 1059 patients with type 2 diabetes and 1378 non-diabetic patients with and without previous myocardial infarction (MI) (2).

2. Mechanisms of vascular disease

The mechanism for the development of atherosclerosis in patients with type 2 diabetes is becoming better defined (32). Table 1 shows the proposed pathophysiologic mechanisms that explain the independent risk factor status for coronary artery disease in diabetes.

Table 1 Mechanisms of increased atherosclerosis in diabetic patients (32).

Endothelial dysfunction
Diabetic dyslipidemia
Hypercoagulability
Oxidative stress
Impaired fibrinolysis
Platelet hyperaggregability
Autonomic neuropathy
Toxic effects of hyperglycemia

Patients with diabetes often present with abnormal lipid profiles because insulin regulate several of the steps of lipid metabolism. Dyslipidemia in type 2 diabetes is characterized by several strictly linked abnormalities (5). "Diabetic dyslipidemia" is characterized in the plasma component by normal to borderline LDL cholesterol level with small dense particles that are associated with increased apolipoprotein (apo) B, reduced HDL, and high triglyceride levels; increased VLDL of altered composition and increased level of remnant particles; and abnormal HDL2 particles. In the arterial wall, lipoproteins are excessively retained and oxidized, leading to the development of atherosclerosis (table 2) (33).

Table 2 Dyslipidemia in type 2 diabetes (5)

↑	Fasting plasma VLDL and TG
↑	Postprandial lipaemia
↑	Small, dense LDL-C
↓	HDL-C
↑	Small, dense HDL-C

3. Pathophysiology of diabetic dyslipidemia

Insulin resistance likely underlies the lipid changes associated with type 2 diabetes. Increasing resistance to insulin, even in persons considered to have "normal" insulin sensitivity, has been associated with higher concentration of cholesterol and TG and lowering concentration of HDL cholesterol. Importantly, insulin resistance and type 2 diabetes often occur along with other metabolic abnormalities such as obesity, hypertension, and hypercoagulability. This grouping of abnormalities has been referred to as the metabolic syndrome or "syndrome X" and has been associated with an increased risk for atherosclerosis. Other abnormalities may be associated with poorly controlled, for example, glycosylation of lipoproteins and other proteins involved in lipoprotein metabolism.

Links between endothelial dysfunction, atherosclerosis and diabetes have been increasingly recognized. One of the earliest discernible atherogenic changes in diabetes is endothelial dysfunction, which is characterizes by inhibited vasodilatation, vascular smooth-muscle proliferation, increased thrombogenesis and proatherogenic

cellular process (34). Abnormal endothelium-dependent vasodilatation also occurs in the microcirculation of patients with diabetes, where it may contribute to ischemia and its sequelae (35). Hyperglycemia and atherosclerosis in type 2 diabetes are related. Hyperglycemia causes glycosylation of virtually proteins, including collagen cross-linking with other extra cellular matrix proteins in the arterial wall. Long term exposure to elevated glucose levels alone can cause the endothelial cell dysfunction. The pathogenesis of atherosclerosis also involves oxidation of LDL cholesterol. Exposure to glycosylation end products can prolong the half-life of LDL cholesterol, increasing the likelihood that it will be trapped in the vascular wall where it is more susceptible to oxidation (36). Atherosclerosis is accelerated in patients with diabetes, and the development of coronary heart disease worsens the prognosis. Control of predisposing risk factors is an effective strategy for both cardiovascular disease and diabetes (table 3). With the exception of smoking, all reversible risk factors for coronary heart are more prevalent in patients with diabetes than in the general population. Based on the outcomes of major interventional trials in large cohort of diabetes patients, aggressive treatment of lipid abnormality is warranted. Because one half of patients with type 2 diabetes already have evidence of coronary heart disease at the time their diabetes diagnosed, the distinction between primary prevention in high-risk patients and secondary prevention in those with clinical coronary heart disease may be arbitrary in patients with diabetes (37).

Table 3 Risk factors for cardiovascular disease in patients with diabetes (37).

Modifiable major risk factors
Cigarette smoking
Hypertension
Low HDL cholesterol levels
Albuminuria
Hyperglycemia
Hyperinsulinemia
Predisposing risk factors
Obesity, fat distribution
Lack of physical activity
Genetic factors (family history)
Patients age
Disease duration

Most type 2 diabetic patients have some degree of insulin resistance. Insulin resistance is also strongly associated with many risk factors for coronary artery disease, such as hypertension, increased plasma triglyceride levels and low HDL cholesterol levels. Control of predisposing risk factors is an effective strategy for both cardiovascular disease and diabetes.

3.1 Association of insulin resistance and hepatic very low-density lipoprotein secretion

Resistance to insulin may contribute to the atherogenic dyslipidemia of diabetes by increasing the hepatic secretion of very low-density lipoprotein (VLDL). Metabolic tracer studies have documented overproduction of VLDL TG in insulin-resistant patients with hypertriglyceridemia. Additionally, several recent studies demonstrate increased secretion of apolipoprotein (apo) B in type 2 diabetes. The increased secretion of apo B-containing lipoprotein particles may be the result of increased free fatty acid (FFA) flux to the liver. Also, insulin-resistant persons have shown to lack sensitivity to the suppression effects of insulin on apoB secretion. This resistance to insulin may be at transfer protein activity, a protein identified as a key component of

the VLDL assembly process. Because of increased endogenous secretion of apoB-containing lipoprotein particles, the increased plasma levels of TG can drive a metabolic process that results in reduced HDL cholesterol levels and LDL particles that are smaller and denser. In a substrate-driven reaction, cholesterol ester transfer protein (CETP) exchanges TG of VLDL particles with cholesterol in the HDL particles. TG-rich HDL particles are then hydrolyzed by hepatic lipase (HL) and, as a result, are rapidly catabolized and cleared from plasma. HDL particles are heterogeneous and are classified by particle sizes that range from small, dense HDL_3 to larger HDL_2. The reduced plasma level of HDL in patients with type 2 diabetes manifests as reductions in the HDL_2 subspecies with relative or absolute increase in HDL_3. Increased concentrations of VLDL in plasma also result in the increased production of small, dense LDL particles. As many as seven distinct LDL subspecies, which differ in metabolic behaviors and pathologic roles, have been identified (Figure 2). Plasma VLDL levels correlate positively with increased density and decreased size of LDL. Increased concentrations of small, dense LDL, in turn, have been shown to be associated with reduced plasma HDL levels. Importantly, the residence time of small, dense LDL in plasma may be prolonged, given their relatively reduced affinity for the LDL receptor (38).

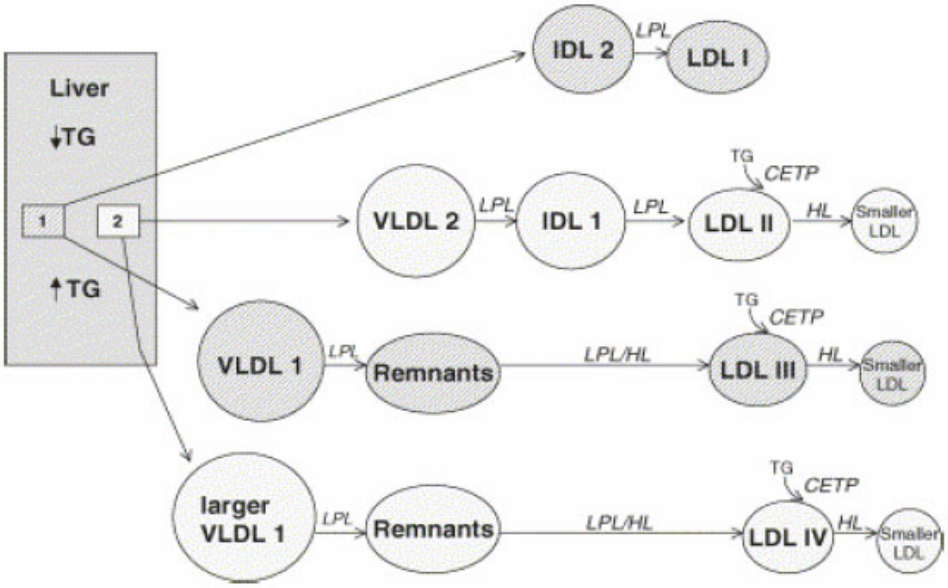

Figure 2 Hypothetical metabolic scheme incorporating proposed pathways for the production of major LDL subclass (38)

3.2 Effects of insulin resistance on lipid and lipoprotein clearance

Impaired clearance of lipid and lipoprotein particles represents another important mechanism by which insulin resistance can lead to abnormal lipid profiles. Insulin resistance has been associated with impaired lipoprotein lipase (LPL) and increased HL activity. LPL is synthesized in muscle and adipose tissue and interact with TG-rich lipoproteins in capillary endothelial cell beds where it hydrolyzes TG into FFA. The result lipoprotein particles are reduced in both at the core volume and surface and are either cleared through remnant removal pathways or moved along the delipidation pathway where they are converted into less LDL particles. HL is responsible for the hydrolysis of phospholipids in LDL and HDL particles. Its increased activity in the setting of insulin resistance has been associated with smaller and denser LDL particles and a decrease in HDL_2 particles because the latter are more rapidly cleared from plasma.

3.3 Lipid effects on insulin sensitivity

Insulin resistance and type 2 diabetes mellitus are often characterized by increased plasma FFA concentration because of increased adipose tissue efflux or impaired insulin-mediated skeletal muscle uptake. The fact that FFA levels are elevated in individual with increased FFA levels occurs before the onset of hyperglycemia. Elevation of plasma FFA concentration may interfere with glucose metabolism by impairing glucose uptake and by use in muscle. At the level of the pancreatic β-cell, FFA acutely increases glucose-stimulated insulin secretion, whereas chronic exposure has been associated with relatively impaired insulin secretion. Finally, in the presence of insulin resistance, FFA in the form of TG is deposited in muscle and the liver, heart, and pancreas where it may impair organ function.

4. Management of diabetic dyslipidemia

According to the American Diabetic Association (ADA) (6-7) and the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) (8), identify diabetes as a CHD risk equivalent and recommend the same aggressive treatment in diabetic individuals as in patients with established CHD.

This means that a diabetic patient with an LDL cholesterol level ≥ 130 mg/dL will likely require pharmacologic treatment to reach a goal lower than 100 mg/dl. For individuals with an LDL cholesterol concentration of 100-129 mg/dL, drug therapy is optional, but therapeutic lifestyle changes TLC involving both diet and physical activity are essential. Because poor diet can undermine the effects of lipid-lowering therapy, all patients must continue TLC even after they have begun drug treatment. For individuals with the high triglyceride concentration characteristic of diabetes, it is particularly important to monitor carbohydrate and fat intake of total calories. The primary goal is to lower LDL cholesterol. The ATP guideline recommends weight loss and physical activity as first-line therapy. Physical activity reduced levels of very-low-density lipoprotein cholesterol, which contains TG, and increase HDL concentration. Triglyceride levels < 150 mg/dL are consider normal. Although HDL cholesterol levels < 40 mg/dL are classified as a major CHD risk factor, the NCEP III guideline do not set a goal for HDL-raising therapy (Table 4).

Table 4 Comparison of lipid goals values from the American Diabetes Association (ADA) and the National Cholesterol Education Program (NCEP)* in mg/dL

Lipoproteins	**ADA**	**NCEP III**
LDL cholesterol	< 100	< 100
Total cholesterol	-	-
TG	< 150	<150
HDL cholesterol	> 40 (men) > 50(women)	≥ 40
Non HDL cholesterol	-	< 130

Table 5 shows the order of priorities for treatment of dyslipidemia. Treatment of LDL cholesterol is considered the first priority for pharmacological therapy of dyslipidemia (7).

Table 5 Order of priorities for treatment of diabetic dyslipidemia in adults (7)

I. LDL cholesterol lowering Lifestyle intervention Preferred HMG CoA reductase inhibitor (statin) Others Bile acid binding resin (resin) Cholesterol absorption inhibitor fenofibrates or niacin
II. HDL cholesterol raising Lifestyle interventions Nicotinic acid or fibrates
III. Triglyceride lowering Lifestyle interventions Glycemic control Fibric and derivative (gemfibrozil, fenofibrate) Niacin High-dose statins (in those who also have high LDL cholesterol)
IV. Combined hyperlipidemia First choice Improved glycemic control plus high-dose statin Second choice Improve glycemic control plus statin plus fibric acid derivative Third choice glycemic control plus statin plus nicotinic acid

In addition, the American College of Physicians recommends that statins should be used for primary prevention against macrovascular complication in patients with type 2 diabetes and other cardiovascular risk factors and for secondary prevention of cardiovascular mortality and morbidity for all patients with known coronary artery disease and type 2 diabetes patients (39-40).

The targets for weight loss should be sufficient to reduce triglyceride below 200 mg/dL. The associated improvement in glucose and HbA1C are important indicators of successful lipid management. LDL-C is often responsive to reductions of saturated fat and cholesterol intake. The target for saturated fat is less than 7% of calories and less than 200 mg/dL for cholesterol (8). Thirty minute of moderate exercise each day can significantly improve the success of weight loss regimen and associated with triglyceride reduction. The appropriate adjustment of oral hypoglycemic therapy or insulin should be the first step in treating patients with diabetes. After glucose control has been maximized for a given patient, the lipoprotein lipids should be re-evaluated. In those patients with triglyceride above 300 mg/dL, a triglyceride-reducing drug should be considered first. In such patients with hypertriglyceridaemia, the LDL-C values are often misleadingly low because the LDL-C is small and dense (2) and as triglyceride levels fall, LDL-C will often rise. This is usually associated with increased cholesterol content in each LDL-C particle, while the total number of particles may not change (41). If the triglyceride remains above 200 mg/dL or the LDL-C remains above 100 mg/dL after treatment with fibrates, the addition of a statin at low dose is appropriate.

Moderate LDL-C elevation above 100 mg/dL should be considered an important determinant of risk in diabetes, and if the patient is not responsive to 8 weeks of dietary change, drug treatment should be considered. Statin should be considered the first line therapy for elevated LDL-C. Reduction into the range of 70-100 mg/dL seems justified by current evidence. Five statin drugs are currently available in Thailand, including pravastatin, simvastatin, fluvastatin, atorvastatin and rosuvastatin. However, rosuvastatin was not available at the BMA hospital during the study period. This group of drugs offers several advantages, including proven prevention of clinical events of vascular disease in multiple clinical trials and in patients both with and without pre-existing diagnosis of atherosclerosis. Another advantage is that the statins are consider safe, although rhabdomyolysis occurs rarely (one in 10,000), and predictable but reversible elevations in the hepatic enzymes ALT and/or AST are observed in the approximately 2-3% of patients at the higher dose levels (42). Additional drugs may be needed to achieve the target LDL-C in some patients. These include ezetimibe, the first drug that appears to specifically reduce the absorption of

cholesterol into the blood stream from the intestine. Bile acid binding resins such as cholestyramine is also available for this purpose.

For patients with goal LDL-C less than 100 mg/dL and elevated triglyceride, the appropriate non-HDL-C goal is less than 130 mg/dL. The dose of statin may need to be increased to achieve this goal. The combination of statins and fibrates was questioned by the frequent occurrence of myopathy with elevated creatinine phosphokinase when cerivastatin and gemfibrozil were used together. Gemfibrozil is an effective competitor of glucuronidation process; fenofibtare and bezafibrate appear not to compete in this process and may be a safer choice for use in combination with statins. However, it is important to carefully consider other drugs which might be added to these combinations and might interfere with metabolic enzymes involved in the hepatic metabolism of the statins, primarily competitors and inhibitors of the cytochrome P 450 enzymes (most commonly CYP3A4).

4.1 Statins

Statins is the term applied to 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Statins are the first-line agents for LDL-C reduction and have been shown to reduce cardiovascular morbidity and mortality in a number of patient populations including diabetes. There is a well-recognized linear relation between LDL-C levels and the events rate in all the major statin secondary prevention trial. However, in the diabetic subgroups, the events rate in the statin-treated patients exceeds those of the placebo-treated patients without diabetes (Figure 3)

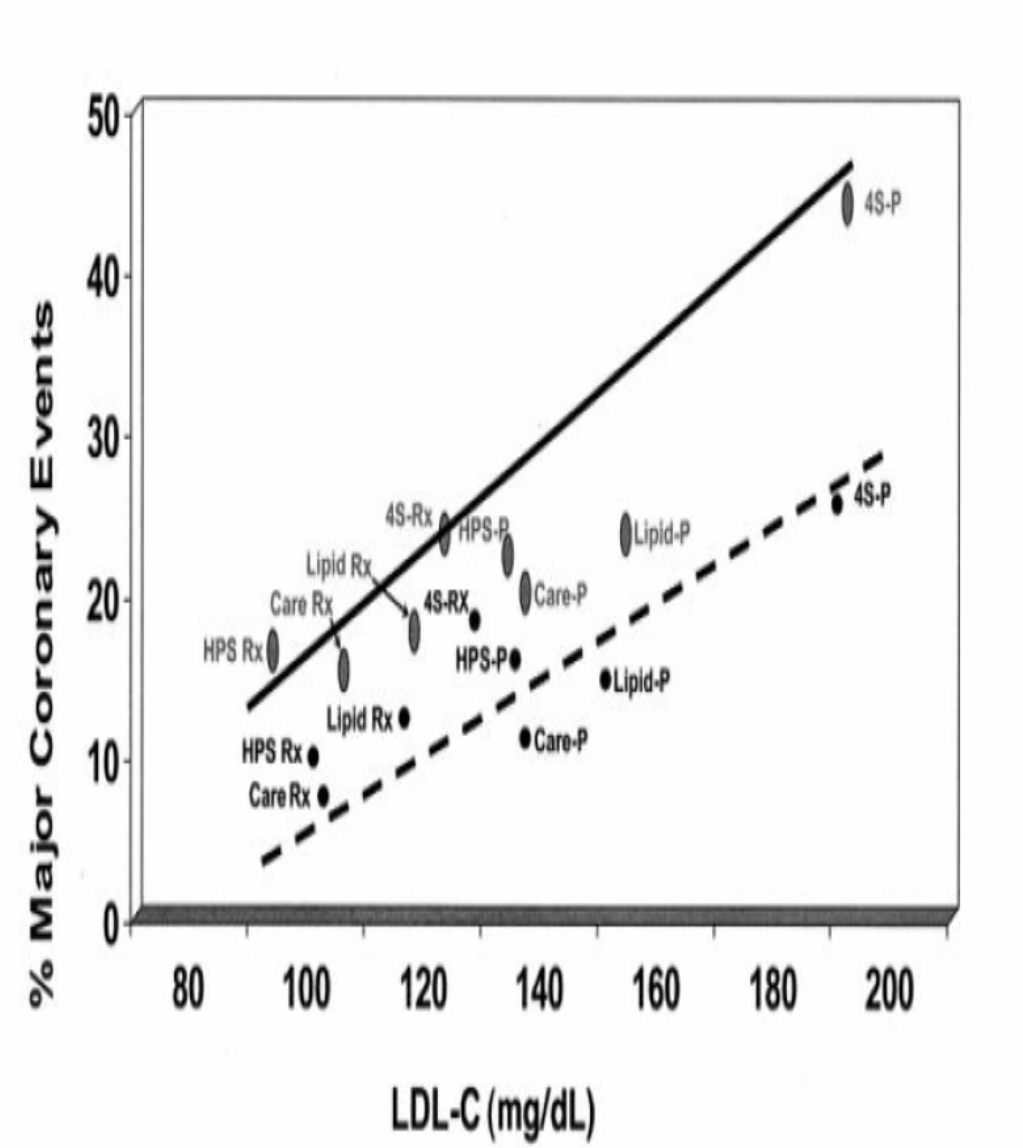

Figure 3 Comparative correlation of low-density cholesterol (LDL-C) and event rate in the treatment arms of the major secondary prevention statin trials in patients with and without diabetes mellitus (44)

Table 6 Priorities for the treatment of dyslipidemia in adult patients with diabetes (45)

Priorities in descending order of importance	Goal level, mg/dL	Therapy
Lower LDL-C levels	< 100 in patients with CHD < 130 in patients without CHD	Statin; bile acid sequestrant added if needed
Raise HDL-C levels	> 45	Behavioral intervention; glycemic control. Difficult to increase HDL-C level except with nicotinic acid
Lower triglyceride levels	< 200	Glycemic control; fibric acid derivative (fibrate); statin in patients who also have high LDL-C levels
Combined hyperlipidemia treat	Same as above	Improved glycemic control and one of the following: a statin and fibrate; a binding resin and a fibrate; a statin and nicotinic acid

4.1.1 Primary prevention.

In the primary prevention setting, 3 large trials included large subgroups of patients with diabetes, mostly were type 2 diabetes patients. These trials included the Heart Protection Study (HPS), the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) and the Anglo-Scandinavian Cardiac Outcome Trial-Lipid Lowering Arm (ASCOT-LLA) (13, 16-17). The HPS was prospectively designed to assess the effects of treatment in a large subpopulation of patients with diabetes mellitus. As shown in Figure 4, analysis of outcome in the 5,963 patients with diabetes enrolled demonstrated that simvastatin treatment produced 27% reduction in first major coronary events compared with placebo (95% confidence interval [CI], 15-38; $p < 0.001$) and a significant 22 % reduction in first major vascular

events (95%CI, 13-30; p < 0.0001) . These reductions were identical to those seen in the total population. (13)

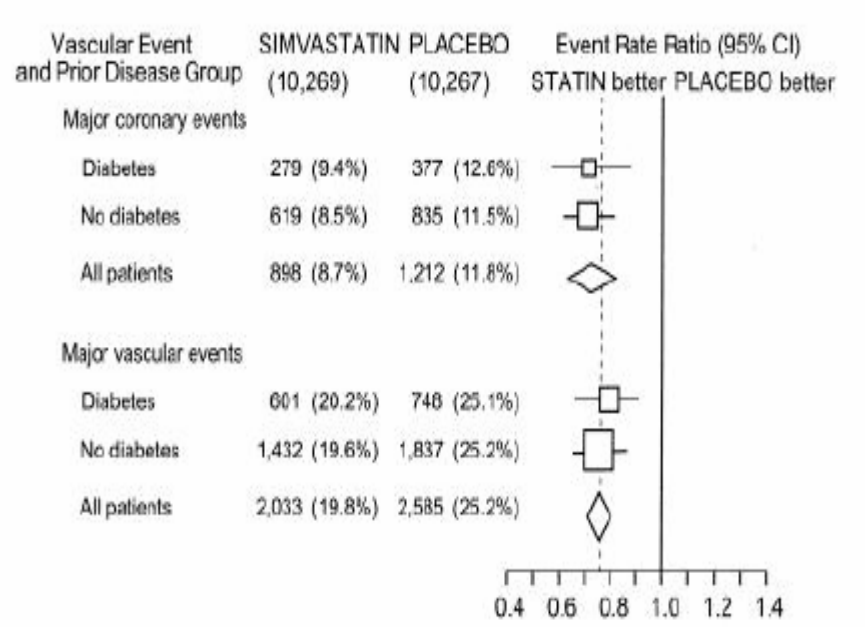

Figure 4 Analysis of outcome in the 5,963 patients with diabetes enrolled in the Heart Protection Study (13).

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) included 3,638 patients with diabetes, mostly type 2 diabetes. ALLHAT-LLT was non-blinded and pravastatin 40 mg per day did not reduce incidence of non-fatal myocardial infarction and coronary heart disease deaths in patients with diabetes; however, only 0.4-0.6 mmole/L reduction in LDL cholesterol concentration was achieved in the treated versus usual-care group (16).

In the ASCOTT-LLA included 2,532 patients with diabetes. Despite a reduction of 1.1-1.3 mmole/L in LDL cholesterol comparable to that observed in the CARDS, atorvastatin 10 mg per day did not to reduce the risk of non-fatal myocardial infarction and coronary heart disease death in the patients with diabetes and hypertension who had no pre-existing coronary heart disease (17).

Recently, the Collaborative Atorvastatin in Diabetes Study (CARDS) is the first large randomized, double-blinded, placebo-control trial conducted exclusively in type 2 diabetes. This objective of the study is to assess the effectiveness of atorvastatin 10

mg daily in the primary prevention of major cardiovascular events in over 2,800 type 2 diabetic patients who did not have high LDL-C (less than 3.0 mmole/L). The results of the study indicate that statin therapy is effective and safe to be used as a primary prevention measure of CVD in diabetes patients. (18)

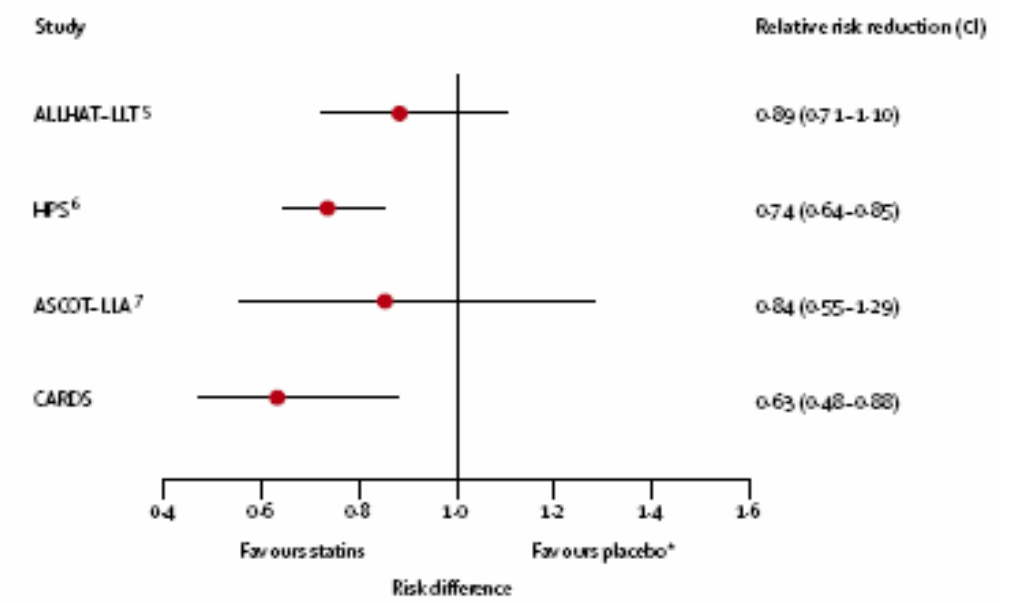

Figure 5 Relative risk reduction by statin therapy for primary of coronary heart disease in patients with diabetes in the four major trials (46).

4.1.2 Secondary prevention

Earlier evidence of statins benefit in type 2 diabetes came from subgroup analysis of 5 large secondary prevention trials. The Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) trial, the Heart Protection Study, the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) and the Lescol Intervention Prevention Study (LIPS) all reported the benefit of statins in the reduction of major cardiovascular events and CHD mortality (11-15).

The landmark Scandinavian Survival Study (4S) was the first randomized, controlled trial to demonstrate that coronary events and total mortality were decreased by a reduction in low-density lipoprotein cholesterol (LDL-C). In the 4S, simvastatin treatment was associated with 55% reduction in the risk for a major CHD events ($p=0.02$) among 202 diabetic patients (34% risk reduction in the overall study sample).

A more recent 4S analysis using 1997 ADA criteria for the diagnosis of diabetes found a 42% risk reduction ($p = 0.001$) with statin treatment among 483 diabetic patients (11, 47-48). Thereafter, the Cholesterol and Recurrents Events (CARE) and In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trials extended these results by demonstrating benefit in patients with relatively average total cholesterol and LDL-C levels and CHD. The CARE trial randomized 4,159 participants with prior MI and LDL-C ranging from 115 to 175 mg/dL. Participants received 40 mg /d of pravastatin or placebo for 5 years. Death from CHD or non fatal MI was decreased by 24% in the treatment group. Patients with baseline levels exceeding 150 mg/dL had 35% reduction in coronary events, compared with 26% reduction in those with baseline value of 100 to 150 mg/dL (12). In similar fashion, the LIPID trial also evaluated treatment of coronary patients with moderately elevated LDL-C levels. Pravastatin 40 mg was compared with placebo in 9,014 CHD patients over 6-years period. Median LDL-C decreased from 150 to 112 mg/dL. Major coronary events were reduced by 29%, coronary deaths by 24%, and total mortality by 23%. Pravastatin treatment led to a non significant 19% reduction in CHD risk among 782 patients with diabetes (25% risk reduction in the overall population) (14).

Analysis of outcomes with pravastatin treatment in the Pravastatin Pooling Project, which included patients from CARE, LIPID and WOSCOPS, showed that pravastatin treatment was associated with 26% reduction ($p = 0.002$) in CHD death, non fatal MI, percutaneous coronary intervention, or coronary artery bypass graft surgery among a total of 1,444 diabetic patients (23% risk reduction, $p < 0.001$, among 18,342 nondiabetic patients) (49). In addition to lowering cardiovascular risk in diabetic subgroups, statin treatment in the primary prevention WOSCOPS was linked to a significant 30% reduction in the risk for developing diabetes on both univariate and multivariate analysis (Figure 7,8) (50).

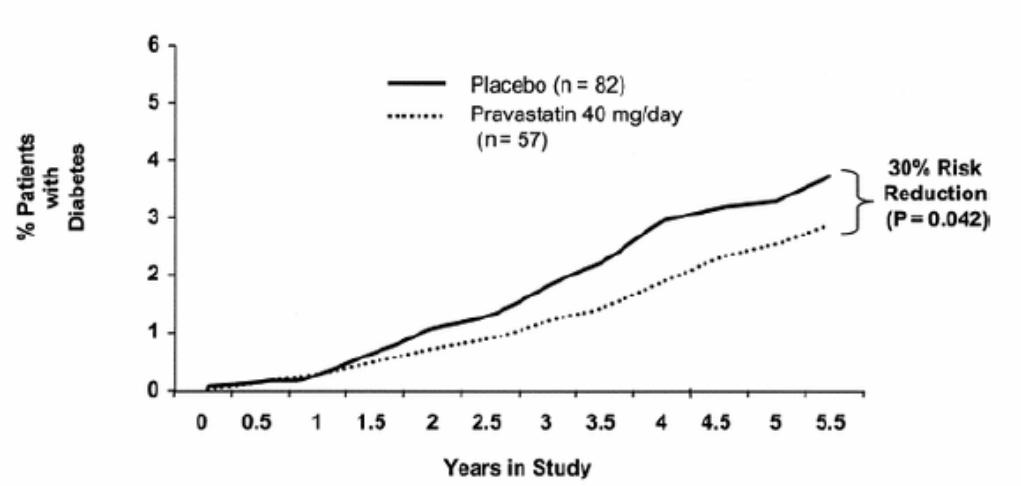

Figure 6 Risk for developing diabetes for pravastatin (n = 57) or placebo (n = 82) recipients participating in the West of Scotland Coronary Prevention Study (50)

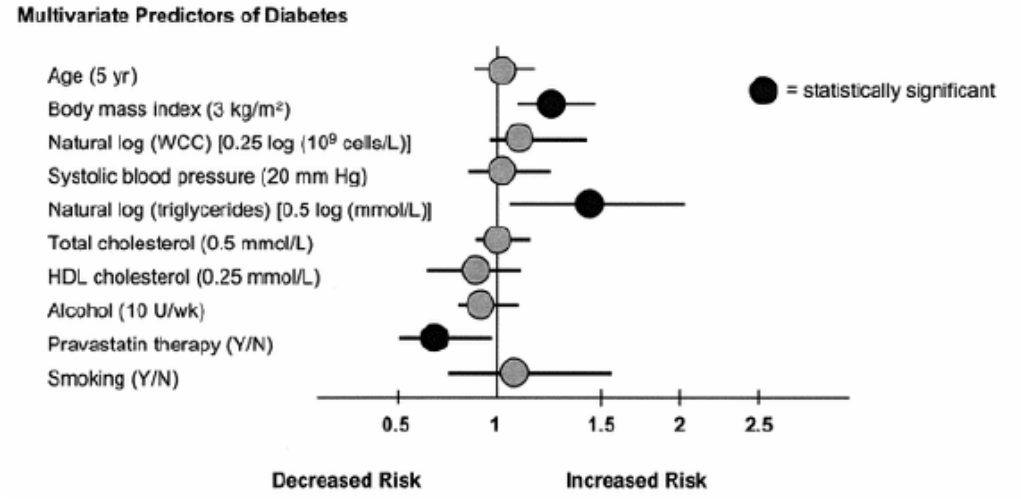

Figure 7 Multivariate analysis of risk factors for developing diabetes (50)

5. Inadequate treatment in diabetic dyslipidemia

Despite strong evidence from clinical trials and recommendations from guidelines, many studies reveal that significant proportion of diabetic patients fail to achieve LDL-C goal (19-20). Putzer and colleagues conducted a retrospective chart review on 239 type 2 diabetes patients. He found that only 93 (47%) patients had achieved LDL goal, 87 0f 207(42.0%) patients had achieved HDL goal and 142 of 206 (70%) attained triglyceride less than 200 mg/dl. Only 30 of 206(14.6%) patients achieved all three lipid goals. This study shows that the majority of diabetes patients

fail to attain lipid goals set forth by American Diabetes Association. (19) Similar to this study, Brown and colleagues conducted a cohort study of 12,106 patients with type 2 diabetes with symptomatic atherosclerosis (mean age 64 years, 55% male, mean follow-up 5 years). The aims of this study were to determine the extent to which medication proven to reduce cardiovascular mortality i.e. antiplatelet agents, statins and angiotensin-converting enzyme inhibitors (ACEIs) were prescribed for these patients. The investigators founded that fewer than 25% received an antiplatelet or statins. This study concluded that diabetes patients with symptomatic atherosclerotic disease are undertreated with medications known to reduce cardiovascular morbidity and mortality (20).

Beaton and colleagues conducted a retrospective study to evaluate the adequacy of glycemic, lipid, and blood pressure management for diabetic patients in a managed care organization (MCO) in New Mexico. A total of 7,114 patients were identified, 409 patients were randomly selected and included in the data analysis. Over a 2-year study period, testing rates for LDL-C was only 54.0%. Lipid lowering therapies were prescribed to 27.5% of patients, 21.4% of patients received statin therapy. For lipid level, only 22.5% were at LDL-C goal of < 100 mg/dL and 67.1% were at LDL-C of less than 130 mg/dL. About 37% had HDL-C > 45 mg/dL and 34% had triglyceride < 150 mg/dL. The results of this study show that within the managed care setting, diabetic patients still continue to be untreated or undertreated for lipid which in turn is associated with a low rate of goal attainment (51).

In a study by Massing and colleagues, the patients was randomly selected using outpatient medical record from 47,813 coronary artery disease (CAD) patients seen at 295 medical practices participating in the Quality Assurance Program II between 1996 and 1998. This study examined lipid management trends for CAD patients with or without diabetes in order to determine whether those with diabetes were beginning to receive aggressive lipid management consistent with their elevated risk. Lipid profile tests were performed in approximately 52% of the patients. LDL-C and non HDL-C values were documented in 61% and 58%, respectively. Lipid-lowering drugs prescriptions were documented in 45% of the patients. Lipid testing and treatment rates increased and mean lipid levels decreased markedly overtime. Of those, 26% of patients with diabetes were less likely to have lipid profile measured and 17% less

likely to receive a lipid-lowering medication than nondiabetic counterparts, and this disparity did not diminish over time. Among treated patients, mean non-HDL-C and LDL-C declined less rapidly over time for patients with diabetes. This study showed that although impressive progress was made in the outpatient management of CAD patients, lipid management for CAD with diabetes improved no more rapidly, and in some cases less rapidly, than for nondiabetic patients. Most effort is needed to ensure that patients with CAD and diabetes receive aggressive lipid management consistent with their high risk (52).

Erdman and colleagues conducted a retrospective study in 345 patients (91% African-American and 95% with type 2 diabetes) at outpatients' diabetic clinic to determine the impact of diabetes care on serum lipids and examine the independent effects of lipid-directed pharmacotherapy. The patients who presented in the diabetes treatment program during 1991 to 1998 with a 1-year follow-up visit and had lipid test at the initial and 1-year visit were selected from a computerized registry. This study founded that in 243 patients who do not taking dyslipidemia medications, all lipid values were similar to initial values. In 102 patients receiving pharmacotherapy, lipid levels were all significantly lowered at 1 year relative to baseline ($p < 0.001$). Use of lipid-directed therapy was associated with a significant decline in LDL cholesterol level (27 mg/dL vs 2 mg/dL), which was statistically greater than that detected in individuals not given therapy ($p = 0.003$). Most patients (94%) were using statins with an average dose of 22 mg. The proportion with LDL cholesterol levels ≥ 160 mg/dL decreased from 60% at the initial visit to 30% at 1 year, whereas the number with values < 130 mg/dL increased from 21 to 39 % (53).

From these studies, it is clear that while diabetic patients at high risk for cardiovascular diseases, a large proportion of these patients are undertreated. Therefore, measures aiming to improve treatment quality are greatly needed.

6. Pharmacist and management of dyslipidemia in type 2 diabetes.

Because of poor adherence rate, NCEP ATPIII places more emphasis on the importance of patient adherence with lipid-lowering therapy (both lifestyle changes and pharmacotherapy), and sets forth intervention to address this well documented problem. Table 7 describes the various intervention recommended by ATPIII to

improve adherence to therapy. The recommendations represent potential areas of involvement of the pharmacist. These recommendations offer an opportunity, as never before, for pharmacists to be involved in the care of patients with hyperlipidemia at multiple levels.

The American Society of Health-System Pharmacists published role of the pharmacist in diabetes management in 2002. Pharmacists can help identify patients with diabetes through screening and should targets patients at high risk, people with a family history of the disease. Patient education should be provided immediately after diagnosis, at a second stage at which time a patient assessment can be performed, and a third stage during with patients can receive continuing education to reinforce concepts and a motivational boost. One of the pharmacist's most important roles is the referral of patients to other members of the diabetes care team (55) A number of studies evaluate the impact of pharmacist's participation in lipid management. Pharmacist can play an active role in providing education about diet and drug therapy, treatment goals, benefits of therapy, the importance of compliance, and monitoring of adverse effects. (21-26).

Table 7 Intervention to improve adherence to therapy (8, 54)

Focus on patient	Focus on the physician and medical office	Focus on the health-delivery system
-Simplify medication regimen -Provide explicit instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment -Encourage the use of prompts to help patients remember treatment regimens -Use system to reinforce adherence and maintain contact with the patient -Encourage the support of family and friends - Reinforce and reward adherence -Increase the visits for patients unable to achieve treatment goal -Increase the convenience and access to care -Involve patients in their care through self-monitoring	-Teach physicians to implement lipid treatment guidelines -Use reminder to prompt physicians to attend to lipid management -Identify a patient advocate in the office to deliver or prompt care -Develop a standardized treatment plan to structure care -Use feedback from past performance to foster change in future care -Remind patients of appointment and follow up missed appointment	-Provide lipid management through lipid clinic -Deploy telemedicine -Utilize the collaborative care of pharmacists -Execute critical pathways in hospitals

6.1 Community pharmacy practice.

A prospective study was conducted by Shibley and Pugh to evaluate pharmaceutical care services to hyperlipidmia patients in two community pharmacies in Richmond, Virginia. USA. Pharmacists participated in a pre-study training program on the clinical management of dyslipidemia, including a pharmaceutical care protocol based on NCEP guidelines. Pharmacists performed point of care lipid screening, and then assisted patients in goal setting. Fasting lipid profiles were repeated at 6 and 12 months. Patients received education regarding dyslipidemia, CHD, and lifestyle modification focusing on diet. Pharmacist contacted physicians by phone or mail to recommend initiating or modifying drug therapy. There were 25 patients who completed the 12-month study. At 6 months, there were no statistically significance difference in lipid values between initial and 6 months assessments. However, both mean total cholesterol (225.8 mg/dL vs 241.2 mg/dL) and mean LDL-C (145.6 mg/dL vs 166.7 mg/dL) levels were significantly decreased at 12 months ($p<0.02$). No significant changes were detected in either HDL or triglyceride levels. Shibley and Pugh's study suggests that community-based pharmaceutical care programs might improve lipid values (21).

In Jafari's study, a pharmacist walk-in lipid screening program was a collaborative effort between a clinical pharmacist and a clinical pathologist. A fingerstick point-of-care lipid panel was performed in patients participating in a walk-in lipid screening program. The pharmacist reviewed results of the lipid profiles and questionnaire with patients, and provided a brief intervention. A follow-up letter with results and recommendations was sent to each participant. A total of 301 patients participated in the program from 1998 to 2000. Of those patients, 150 (50%) required intervention, 52 (34%) of whom were previous undiagnosed. Of the 301 patients, 87 (29%) had LDL levels above NCEP ATPIII guidelines, where as 69 (23%) had higher than recommend triglyceride levels. This program showed that easily accessible walk-in screening and consultation is a promise model for pharmacist disease state management in hyperlipidemia (56).

Project ImPACT (Improve Persistence and Compliance with Therapy), was a randomized observational study conducted during 1996-1999 in 32 US community pharmacies. The project's objectives were to improve patients' persistence and

compliance with lipid-lowering therapy, increase communication between patients, pharmacists, and physicians and improve both cholesterol levels and the percentage of patients at NCEP goal. Patients with newly diagnosed hyperlipidemia or those currently on lipid lowering medications were enrolled. Patients were seen monthly for three visits, then quarterly for 2 years subsequently. A total of 26 pharmacies in 12 states completed the study. Of the 574 patients who enrolled, 397 (69%) completed the entire 2-year study. Of the 345 patients on lipid-lowering medication, 323 continued throughout the study. Of the 2,817 visits, 2,539 occurrences of compliance were documented. Statistically changes were observed in mean values for each component of the fasting lipid profile. The mean reduction in total cholesterol level was 12.8%; triglyceride levels decreased by 10%. The mean decrease in LDL levels was 22.1% whereas the mean increase in HDL levels was 14.2%. Overall, 290 patients (62.5%) reached NCEP ATPII goals. This study suggests that pharmacists can, in collaboration with physicians and patients, identify patients with dyslipidemia and support them in their efforts to improve persistence, compliance, and NCEP goal attainment (22).

The largest study to date evaluating impact of pharmacists in the management of hyperlipidemia was the SCRIP (Study of Cardiovascular Risk Intervention by Pharmacists). This randomized controlled trial was conducted in 54 community pharmacies in Canada during 1998-2000. The study object was to compare a program of pharmacist intervention with usual care in patients at high risk for cardiovascular events. Potential study patients were identified through pharmacist review of medication history. Patients with coronary artery disease (CAD), cerebral or peripheral vascular disease were included as were those with diabetes plus one additional cardiovascular risk factor. Patients were randomized to either the pharmacist intervention group or usual care. Each patient in the pharmacist intervention group received a point-of-care total cholesterol measurement and was interviewed to determine cardiovascular risk. In addition to discussing an individual's lab results, pharmacists provided education and a brochure on cardiovascular risk factors and encouraged physician follow-up for further assessment of cardiovascular risk. A form was faxed to each patient's physician that included lab results, cardiovascular risk factors, blood pressure, and recommendation for management. Patients received regular follow-up either by phone or in person for 16 weeks. The usual care group

received the same brochure with general advice and minimal follow-up. The primary end points were composite measure of a fasting lipid profile by the primary care physician or the addition or increase in dosage of cholesterol-lowering medication. Secondary end points included the individual component of the primary end points as well as patient's satisfaction and health status. A total of 675 patients were randomized to either the intervention (344) or control (331) groups. After a preliminary analysis of the first 400 patients, the study was terminated early because of the striking benefits observed in the intervention group. In the intervention group, 196 patients (57%) reached the primary end point compared to 102 (31%) in the usual care group (odds ratio [OR] = 3.0; 95% confidence interval, 2.2-4.1; p<.001). In the intervention group, fasting lipid profile were performed in 53% of patients by the primary care physicians compared with 29% in the usual care group (OR = 2.8, p < 0.001). In the intervention group, 10% of patients received a new prescription for cholesterol-lowering medication compared with 4% in the usual care group (OR = 2.5, p < 0.003). Dosage cholesterol-lowering medications were increased by 3% and 1% in the intervention and usual care groups. (OR = 3.0, p = 0.07)

A diabetes subgroup analysis of SCRIP study was also analyzed and reported. There were 294 patients in the subgroup, 138 and 156 patients were in the control and intervention groups, respectively. Overall, the benefits seen in the diabetes subgroup were greater than the overall SCRIP population. In the intervention group, 62% of patients reached the primary end point compared to only 25% of patients in the usual care group (odds ratio [OR] = 4.8; 95% confidence interval, 3.0-7.9; p<0.01). (23-24)

The SCRIP trial convincingly demonstrated the value of community pharmacists in cholesterol risk management in patients at high risk of cardiovascular disease. Benefit of this intervention program included increased testing of fasting lipid profiles, decreased CHD risk, and increase use and titration of cholesterol-lowering medications at reasonable costs. Based on this evidence, it can be concluded that community pharmacy-base programs have the potential to positively impact patients with hyperlipidemia.

6.2 Primary care clinic

There are a number of retrospective studies evaluating the effectiveness of pharmacist in lipid clinic. During 1996-1998, Carson and colleague evaluated the pharmacist coordinated program for coronary risk reduction in 317 patients at a family health center adult medicine clinic. The program involved written coronary risk assessment and recommendations for intervention by pharmacist. This communication was accomplished through the medical record with minimal interaction between pharmacist and the patient. There were 61 (19%) patients classified as secondary prevention patients while another 60 (19%) were considered as high-risk primary prevention (LDL-C < 130 mg/dL). Both the secondary and primary prevention groups had significant reduction in LDL levels (26% and 27%, respectively, $p < 0.0001$). The percentage of patients in the secondary prevention group reached their NCEP ATPII LDL level goal of < 100 increased from 6% to 27% ($p < 0.04$). The percentage of primary prevention patient attaining their LDL level target of < 130 mg/dL increased from 20% to 51% ($p < 0.006$). This study shows that even minimal patient contact, the pharmacist can have a beneficial impact on lipid values and goal attainment in patients at relatively high cardiovascular risk (57).

A retrospective chart review was conducted in the Bay Pines Veterans Affairs Medical Center to determine the percentage of patients attaining LDL level goals who were in a pharmacist-managed chronic disease versus those managed by primary care provider. A total of 120 medical records were reviewed; 60 treated in the pharmacist-managed clinic and another 60 by primary care provider. Of the pharmacist-managed patients, 49 (82%) reached their NCEP ATPII LDL level goals compared with 38 (63%) of those managed by primary care practitioners ($p < 0.024$). While the LDL level goal attainment was high in both groups, significantly more patients in the pharmacist-managed group reached their LDL level goal. This study demonstrates that pharmacists can help promote the attainment of LDL-C goal compared to usual care (58).

O'Donnell and colleagues retrospectively reviewed medical records from 1996 to 1999 to determine the percentage of patients who attained and maintained their LDL goals after discharge from multidisciplinary lipid clinic at an integrated health care system. The lipid clinic operated under an NCEP ATPII based protocol with a

pharmacist and a dietitian evaluating, initiating, monitoring life style changes and pharmacotherapeutic interventions. This included education on diet, exercise, smoking cessation, hypertension and diabetes management. A total of 68 charts were reviewed. Most patients (n = 61) were Caucasian and the majority (n=50) were referred for secondary prevention. Statin were the most frequency prescribed class of lipid-lowering drugs and were initiated or modified in 52 (76%) of patients. Of the 56 patients who were on medications requiring laboratory monitoring of liver function tests, 53(94.6%) had aminotransferase monitoring at least annually while enrolled in the lipid clinic. This number fell to 26 (56.5%) after clinic discharge. A total of 44 (73%) patients achieved their goal after discharge. The findings supported the role of pharmacist in a protocol-driven lipid clinic in an integrated health system. The rate of goal-attainment more than 70% was significant higher than that reported in the usual group. The ability of pharmacist to initiate and manage drug therapy in this study may explain the higher rate of goal attainment when compared with community pharmacy-based studies where pharmacists only contacted the physician with recommended change in therapy (26).

Geber and colleagues conducted a retrospective medical record review in Veteran Affairs Medical Center primary care clinic to access the role of pharmacist-managed pharmacotherapy clinic in optimizing therapy in 150 patients with cardiovascular disease. Pharmacists responsible for operation in this clinic were required to possess a Doctor of Pharmacy degree with postgraduate residency training in hospital or ambulatory care. Pharmacists were granted prescriptive authority with the ability to starting, adjusting and/or discontinuing drugs as well as ordering and interpreting laboratory tests necessary for monitoring of drug therapy. Primary endpoints were the percentage of patients attaining LDL levels <100±5%, the percentage reaching NCEP ATPIII LDL goal < 100 mg/dL, change in lipid values, and additional cardiovascular outcomes and pharmacotherapy. A total of 150 electronic medical records of patients with CAD were reviewed; 75 patients were managed by primary care provider alone and 75 had been referred to clinical pharmacy specialists. Of these, 146 were included in the final analysis: 72 and 74 patients in the primary care and the clinical pharmacy group, respectively. The average duration of follow-up was 1.9 years for the primary care group and 1.7 years for the clinical pharmacy group. The result of this study

showed that appropriate treatment of hypercholesterolemia occurred in 96 % of patients referred to clinical pharmacist clinic compared with 68 % of those followed by primary care provider alone (P<0.0001). Of the clinical pharmacist-managed group, 85% achieved LDL-C goal levels of < 105 mg/dL compared with 50% of the primary care group (p < 0.0001). In addition, 72% of the clinical pharmacy group and 39% of the primary care group attained the NCEP ATPIII LDL level goal of < 100 (p < 0.0001), which was higher than the national average in both groups. Total cholesterol was decreased by 26.3% in the clinical pharmacy group compared with a reduction of 23.4% in the primary care group (p < 0.05). LDL levels decreased by 40.4% in the clinical pharmacy group compared to 16.2% in the primary care group (p < 0.05). The result of this study indicates that clinical pharmacist's participation on lipid management increase the LDL-C goal achievement rate in coronary artery disease patients. (25)

The Naval Medical Center San Diego performed a retrospective review to evaluate a pharmacist-managed lipid clinic. Clinical pharmacists saw patients in the clinic where they obtained a medical history, review fasting lipid profile results and goals, and discussed hyperlipidemia and cardiovascular disease with patients. Treatment interventions include both lifestyle changes and pharmacotherapeutic approaches. After 12 months, medical records of 115 of 146 active patients were evaluated (1999-2000). Beneficial effects were observed in each components of the fasting lipid profile. Compared with the baseline, mean total cholesterol levels was decreased by 12%, mean LDL-C levels decreased by 20%, mean HDL-C levels increased by 19%. Overall, 70% of patients attained NCEP ATPII LDL-C goals (59).

Bozovich and colleagues assessed the impact of pharmacist-managed clinic in patient with CHD. Interventions included patient education, drug therapy management and monitoring (n = 104). Patients were followed for 6 months and received aggressive treatment, educations, and fasting lipid profiles measurements (every 4-6 weeks) by the pharmacist. For control group, 101 patients with CAD were selected from one cardiologist's patient base to serve as control. During the study period, the clinical pharmacist made 79 recommendations directly related to hyperlipidemia and the cardiologist accepted all of these recommendations. At baseline, NCEP ATPII LDL-C level goals were met by 33% of the lipid clinic patients compared with 25% of

the control group ($p = 0.035$). After 6 months, 69 % of lipid clinic patients attained NCEP ATPII LDL-C level goals ($p < 0.0001$ vs. baseline) compared with 50% of the control group ($p < 0.0009$ vs. baseline). Lipid clinic patients more likely to reach their LDL-C goals than in the control group ($p < 0.016$). CHD patients in the lipid clinic were more likely to achieve LDL-C goal than those in the control group (60).

The IMPROVE (Impact of Managed Pharmaceutical care on Resource utilization and Outcomes in Veterans affairs medical center) trial is a large, randomized, controlled, multicenter study examining the effects of pharmacist in the management of patients with dyslipidemia. Patients in the intervention group received medical assessment by ambulatory care clinical pharmacists. Pharmacist interventions included drug therapy assessment, monitoring and adjustments, including ordering laboratory measures and medication in some sites. Intervention patients were seen at least three times; at baseline, 6 months and 12 months. There were 78 pharmacists at nine Veteran Affairs Medical Center who participated in caring for intervention patients. A total of 437 patients were randomized to either the intervention ($n = 208$) or control ($n = 229$) groups. There was a statistically significant increase in the assessment of lipid profiles after enrollment (87%) compared with before enrollment (71%) [$p < 0.02$]. Mean LDL levels decreased from 134.7 mg/dL to 111.3 mg/dL (-13.2% mean change) in the intervention group compared with a decrease from 131.8 mg/dL to 119.0 mg/dL (-5.5% mean change) in the control group ($p < 0.04$ between groups). Mean total cholesterol levels were decreased from 209.5 mg/dL to 191.8 mg/dL in the intervention group (-6.56% mean change) compared with decrease from 204.1 mg/dL to 196.7 mg/dL (-1.21% mean change) in the control group ($p< 0.03$ between groups). Changes in other component of the lipid profile (HDL and triglyceride levels) were not significant. In the subset of patients with CHD or diabetes (i.e. secondary prevention) mean LDL levels decreased by 12.5% (129.4 mg/dL to 107.0 mg/dL) in the intervention group versus 4.3% (128.3 mg/dL to 117.2 mg/dL) in the control group ($p < 0.069$ between groups). Mean total cholesterol levels decreased by 7.0% (206 mg/dL to 186.8 mg/dL) for intervention patients and by 1.1% (199.9 mg/dL to 192.1 mg/dL) for control ($p < 0.05$ between groups). Compared with baseline, the percentage of secondary prevention patients who attained NCEP ATPII goals for LDL levels

increased significantly in both the intervention and control group; there were no between-group difference.

Lee and colleagues conducted a prospective controlled study on the benefits of pharmacists' individualized counseling on drug compliance, cholesterol concentration reduction, attainment of NCEPIII LDL-c goals in a private community hospital in Hong Kong. Fifty patients were newly prescribed with lipid-lowering drugs for primary prevention and were divided into two groups. The patients in the individualized counseling group received "intense" counseling and follow-up of cholesterol concentration by a pharmacist for 3 months. The control group received routine counseling. At the end of the study, 80.8% of patient in the individualized group and 58.3%of patients in the control group had achieved reduction in LDL-C (p value < 0.05). This study demonstrated that pharmacists' individualized counseling, together with the assessment of cholesterol concentrations, had positive impacts on the management of hyperlipidemia, including improved drug compliance and better treatment endpoints (62).

Cioffi et al conducted a non-randomized, prospective study to compare diabetes outcomes prior to and after the establishment of a pharmacist-managed clinic in 70 poorly controlled diabetic patients at Veteran Affairs Hospital in Connecticut. Pharmacist's intervention encompassed patient education, medication counseling, monitoring and management of drug therapy. Pharmacists were provided limited prescribing authority on oral antidiabetic drugs and insulin. Patients were seen by the pharmacist every 6-8 weeks for a period of 9-12 months. The primary outcome of the study was changes in hemoglobin A_{1C} while secondary outcome included changes in weight, lipid parameters, blood pressure and level of microalbuminuria. The result of this study showed that glucose control improved significantly along with a significant reduction in microalbuminuria and blood pressure. In addition, LDL-C, TC, TG levels were reduced by 12.5%, 11% and 22.8%, respectively. The important limitations of this study are the lack of control and small sample size.

In Thailand, there are a number of studies conducted in diabetic patients in different aspects. Prueksaritanond et al (64) conducted a quasi-experimental design before-after intervention study in a university hospital to evaluate the efficacy of patients-centered care on type 2 diabetes. The primary outcome in this study was

changes in glycemic control. The healthcare team comprised with physicians, nutritionist and physical therapist. Pharmacist was not included into this team. The team provided group counseling every Wednesday morning for 6-8 weeks. There were 78 patients (68% were female) included into this 12-month long study. The result of this study showed that patients receiving care from the team had a mean fasting plasma glucose reduction of 43.07±76.32 mg/dL. With regards to lipid parameters, LDL-C, TC and TG did not change significantly from baseline while a slight yet significant increase in HDL-C was observed. The reason for this little to no changes in lipid parameters may relate to the study primary objective which was on glycemic control. As a result, interventions used mostly in the study may focus only on measures to improve glycemic control.

Nathisuwan et al conducted a cross-sectional study to assess the achievement rate of lipid goals based on ATPIII in the tertiary care hospital from June to August 2003. a total of 190 patients were included in this study. The average aged was 58±11 years. Approximately 60% of patients were female and with diabetes. For patients requiring LDL-C goal of less than 100 mg/dL, only 24.3% met this goal. For patients requiring LDL-C goal of less than 130 mg/dL and 160 mg/dL, the achievement rates were 46% and 63%, respectively. The most commonly adverse drug reaction was myalgia (3.2%). This study suggests that there is still a need for the improvement in achieving lipid goals and interventions aiming to improve treatment quality are warranted (65).

There were two studies that relates to statins therapy including studies by Supapsophon and Pokhagul (27-28) which were drug use evaluation studies. In Supapsophon's study (27), drug use evaluation (DUE) of HMG CoA reductase inhibitors were conducted at the Outpatient Department of Ramathibodi Hospital. This was quasi-experiment with pre- and post-intervention evaluation. The aims of this study was to establish guideline, study patterns of prescribing statins and access outcomes of DUE interventions. Aging, hypertension and diabetes were the predictors for prescribing statin. Only 62-66% of the prescriptions adhered to the developed guideline in terms of appropriate LDL cholesterol level (27). In Pokhagul's study (28), the aim of this study was to evaluate statins use in the Outpatient Clinic at Ratchaburi hospital using the drug use evaluation (DUE) criteria approved by the hospital committee. The drug use was evaluated in term of indication, contraindication, drug

therapy monitoring and dosage administration. The intervention was performed when DUE criteria were not met and/or drug interaction and adverse drug reaction were detected. Of the 247 patients, 55.99% and 44.01% were received statins for secondary and primary prevention respectively. Diabetes is the most common indication for statin prescribing (50.94%). These studies demonstrate that a high proportion of statin therapy was prescribed in discordance with criteria established by the hospitals. (28) In a study by Sampaogheun, the role of pharmacist in patients with hypercholesterolemia was evaluated. The results of the study showed that pharmacist can provide education, drug counseling and increase medication adherence in these patients (29).

In summary, although various studies evaluated different endpoints, the effect of pharmacist involvement appears to be positive. Clinic-based pharmacist disease management programs in hyperlipidemia help promote the achievement of NCEP lipid goals in 60-70% of patients. Clinic-based programs appear to most successfully impact lipid profiles and attain NCEP goals in setting where pharmacists can actively initiate and adjust drug therapy rather than only making recommendation to primary care providers, as is more often the case in community pharmacy-based programs. Medical record and physicians are generally more readily accessible to a clinic-based pharmacist than a community pharmacist, which may contribute to the more positive endpoints in the clinic-based studies. Both the community and clinic based research support the beneficial role of the pharmacist in dyslipidemia management.

Although there are a number of diabetes clinics with pharmacist's participation in Thailand, limited amount of evidence is available on the impact of these clinics on patient outcomes. Moreover, no previous study has been conducted to evaluate the impact of physician-pharmacist collaboration on dyslipidemia management in Thai diabetic patients. As a result, this study is aimed to evaluate whether such approach can help improve the achievement of lipid goals which may lead to a reduction in cardiovascular morbidity and mortality in diabetic patients. In addition, the results of this study may be used to support the establishment of multidisciplinary approach in the management of chronic diseases with a pharmacist as an active participant.

CHAPTER III
MATERIALS AND METHODS

1. Study design

This study was a prospective, non-randomized, controlled trial. The primary objective of the study was to evaluate the impact of physician-pharmacist collaboration on the achievement rate of LDL-C goal. The secondary outcomes of interest were changes in lipid parameters, usage rate of lipid modifying agents, types of pharmacist interventions and the acceptance rates of such interventions. This study was conducted during June – December 2004.

2. Patients populations

Type 2 diabetes at the Outpatient Department of the Bangkok Metropolitan Administration General Hospital served as our pool population. The patients in this study were recruited according to the inclusion and exclusion criteria as follows.

2.1 Inclusion criteria:

Patients eligible for this study included those with type 2 diabetes being followed-up by the Internal Medicine Department at the Bangkok Metropolitan Administration (BMA) General Hospital. Patients were enrolled into the study if they meet the following criteria.

- Age older than 40 years old
- Treated with either oral anti-diabetic agents or insulin therapy
- Received medication from the Pharmacy Department of BMA hospital
- With at least 2 outpatient visits to BMA hospital relating to diabetes during the study period with all types of health insurance except the government's universal coverage (30-baht health plan)

2.1.1 Intervention group

- Patients treated by 7 physicians of the Internal Medicine Department who participated in the DCC. There were 3 cardiologists, 2 internists, a nephrologist and an infectious diseases specialist.

2.1.2 Control group

- Patients treated by other physicians of the Internal Medicine Department who did not participate in the DCC. There were a cardiologist, 2 nephrologists, an oncology specialist, a hematologist and an infectious diseases specialists.
- Visited on the same date as patients in the intervention group.

2.2 Exclusion criteria:

The exclusion criteria included:

- Patients with government's universal coverage (30 baht) health plan were not included into the study since these patients were treated by physicians outside of the Internal Medicine Department.
- Loss follow-up after first visit or unwilling to participate to the study
- Patients with other types of diabetes for example; type 1 diabetes or gestational diabetes mellitus
- Patients with documented psychiatric problems

2.3. Determination of sample size

Calculation was based on the result from pilot retrospective study. Sample size was estimated using the following formula. (31)

$$2N = \frac{4 (Z_{\alpha} + Z_{\beta})^2 \bar{p} (1- \bar{p})}{(p_C - p_I)^2}$$

Where

N = number of sample

Z_{α} = Z score at probability of $\alpha/2 \leq 0.025$ (1.96)

Z_{β} = Z score at probability of 80% power (0.84)

$\bar{p}$ = $(p_C + p_I) / 2$

p_C = achievement rate of LDL-C goal in control group (0.3).

p_I = achievement rate of LDL-C goal in intervention group (0.6).

According to previous studies, pharmacist's involvement in dyslipidemia clinic could increase the achievement rate of LDL-C less than 100 mg/dL between 50-70 % (23, 24). We determined to detect a 50% improvement in the LDL-C achievement rate compare to the control group.

Ratio of achievement rate of LDL-C goal were

- Control group (p_c) = 0.3
- Intervention group. = 0.45

Replace these values to the formula

$$2N = \frac{4\,(1.96+0.84)^2\,0.375\,(1-0.375)}{(0.3-0.45)^2}$$

$2N$ = 396 patients

N = 168 patients

Therefore, the number of recruited patients in this study should be at least 43 patients in each group.

3. Methodology

For the purpose of completeness, brief detail of the development and process of the Diabetes Care Clinic at BMA hospital was presented as follows.

Development and Process of the Diabetes Care Clinic

1. Clinical pharmacists conducted literature review, designed clinic protocol, developed the guideline (Appendix A, Figure 8, 9) and presented protocol and guideline to the Medical Committee of the Internal Medicine Department for approval.

2. Protocol and guideline were modified and approved by the Internal Medicine Department. Seven out of 14 physicians agreed to join the clinic.

3. The project was submitted and approved by the Administration Board of the BMA hospital. The project received full funding from the BMA hospital.

4. Three clinical pharmacists who participated in this clinic were trained by the senior clinical pharmacist.

5. Process of the DCC includes the followings.

- Three clinical pharmacists screened type 2 diabetic patients who presented to the Medical Outpatient Clinic after a nurse measured blood pressure and weight of the patients. (Figure 9)

3.1 Intervention group

3.1.1 The medical chart of patients who are cared for by seven participating physicians were tacked with a card to identify potential patients for intervention group.

3.1.2 Pharmacists provided one-on-one patient and then asked patients for their willingness to participate in the study. Patient who denied was excluded from the study.

3.1.3 At initial visit

- The clinical pharmacist assessed time the patients had been diagnosed with diabetes, the patient's basic knowledge of diabetes and lifestyle patterns.
- General diabetes education was provided to the patient (Appendix D).
- Patient interview was conducted to identify drug therapy problems. The patient's medications and medication history were reviewed.
- Previous lipid profiles obtained from the medical record were evaluated. The patient's baseline lipid profile was also reviewed or obtained at the first visit. The pharmacist explained the lipid values, discussed with the patients and informed patients about their lipid goals. All new information obtained was documented in the patient's medical record.
- The clinical pharmacist provided recommendations to physician through pharmacist notes (Appendix B, C).

3.1.4 At subsequent follow-up.

- Pharmacist spent about twenty minutes for education, assessed and reinforced adherence to the medications, diet and lifestyle changes.
- The pharmacists explained the lipid profile results, inquired about side effects, and reviewed the patient's drug regimen compliance and potential drug interactions. Any significant findings were documented in the patient's medical record through pharmacist notes. If lipid goals

were not achieved, lifestyle modifications were intensified and recommendations were made to the physicians for modification of lipid drug therapy as appropriate. Recommendations to perform laboratory tests to monitor medication therapy were also provided to the physician. These recommendations were conveyed to physicians through pharmacist notes.

3.1.5 After completing a visit with pharmacist, patient was subsequently seen by physicians.

3.1.6 After completing a visit with physician, patient picked up his/her medications at the pharmacy department.

3.1.7 The clinical pharmacists collected a patient's data from patient's medical record and summarized interventions into the patient's profile(Appendix C).

3.2 Control group

3.2.1 The patients cared by non-participating physicians were randomly selected into the control group by using a block of five until reaching the number of patients equal to number of patients in the intervention group.

3.2.2 Patients' medical records were reviewed. Relevant data were collected into the patient's profile. (Appendix C)**.**

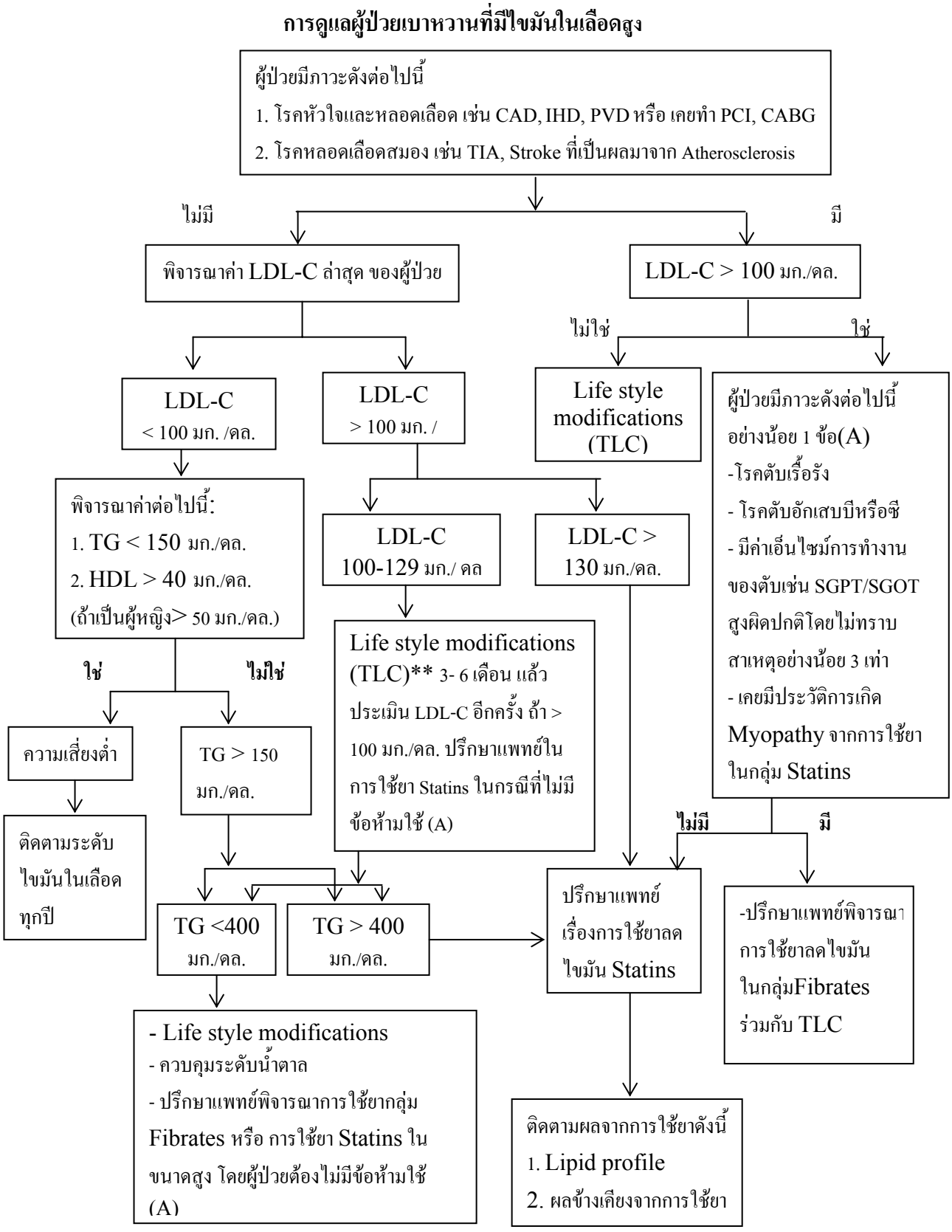

Figure 8. Diabetic dyslipidemia management

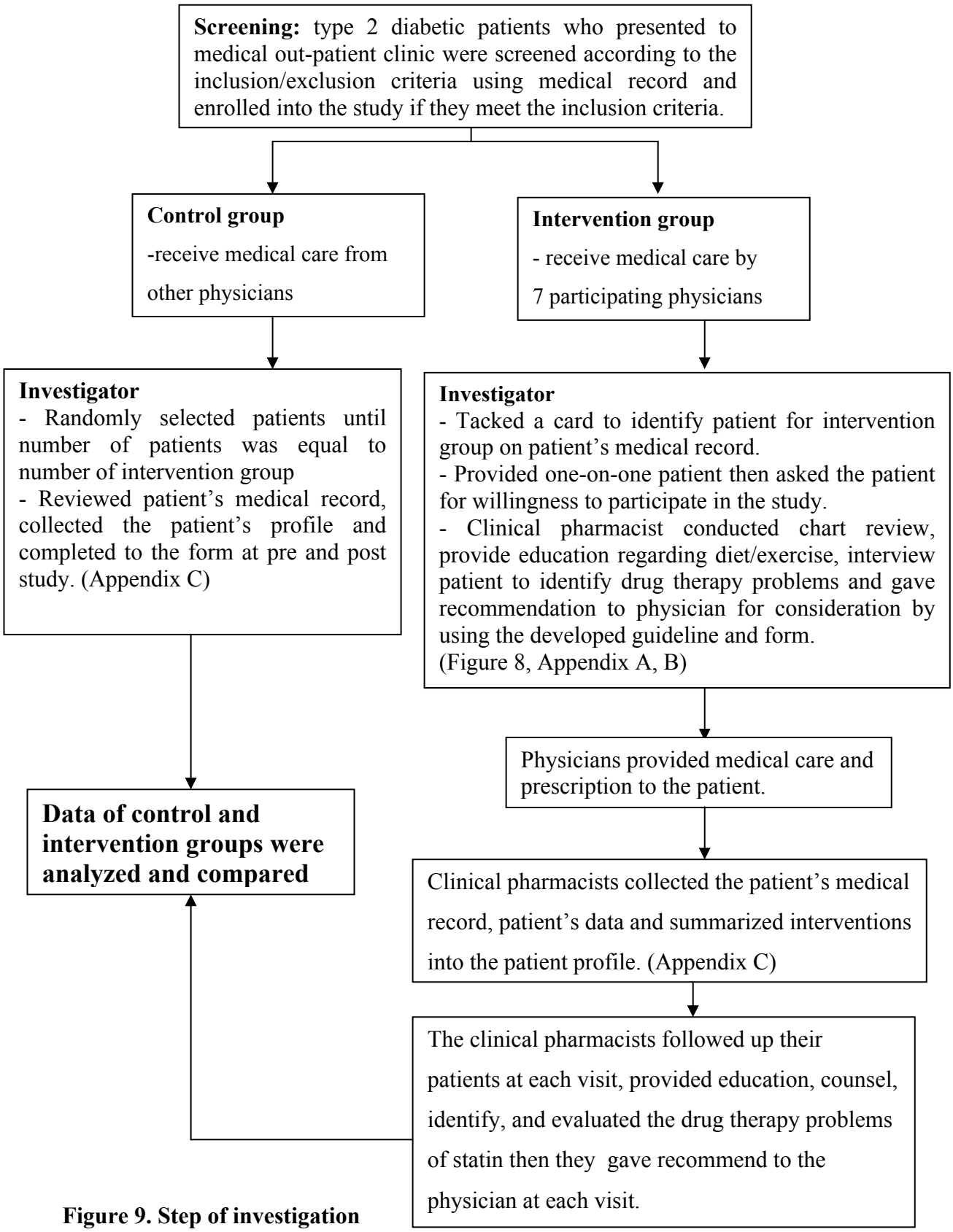

Figure 9. Step of investigation

4. Data collection

The following data were collected and recorded in the data collecting form (Appendix C).

4.1 Demographic data include

- Age
- Gender
- Hospital number
- Weight
- Blood pressure and pulse
- Underlying disease and doctor's diagnosis.

4.2 Pharmacotherapeutic data

- Fasting blood sugar
- Lipid profile
- The percentage of changes between baseline and last visit in each lipid parameters
- Achievement rates of lipid goals (LDL-C < 100 mg/dL, TC < 200 mg/dL, TG < 150 mg/dL, HDL-C > 40 mg/dL, non-HDL-C < 130 mg/dL)
- Types of others drugs which may interfere with lipid parameters including metformin, thiazolidinediones, beta-blockers, hydrochlorothiazide and alpha-blockers at baseline and last visit.
- Type of lipid lowering therapies at baseline and last visit
- The doses of statin therapy prescribed at baseline and last visit were collected. A "simvastatin equivalent dose" was used to compare the intensity of statin therapy. Only simvastatin and atorvastatin were used in our study population due to their availability on the hospital's formulary. For ease of comparison, atorvastatin doses were converted to "simvastatin equivalent doses" using the following conversion ratio: 10 mg of atorvastatin is equal to 20 mg of simvastatin since these two doses have been shown to produce identical LDL-C reduction in a large prospective randomized trial. (66)

4.3 Pharmacist's interventions

Information regarding pharmacist's interventions were collected and presented follow.

- Types of pharmacist interventions; initiation of statin therapy and dosage increase.
- The acceptance of the interventions by participating physicians.

5. Data analysis

All patients who had at least one follow-up after baseline visit with complete information were included and analyzed. The differences between groups were tested using chi-square for categorical variables and the Student's *t* test for continuous variables. For analysis of changes of continuous variables within group, the Student's paired *t* test was used. Non-parametric tests including Mann Whitney U and Wilcoxon's Sign Rank test were used when appropriate. A p value of less than or equal 0.05 was considered to be significant for all statistical values.

5.1 Demographic data were displayed as mean $\pm$ SD.

- Percentage of patient categorized by gender was compared using Student's *t* test
- Mean age at baseline in the control and intervention groups were analyzed for differences between groups using Student's *t* test.
- Prevalence of underlying diseases between the two groups were compared using chi-square test.
- Mean pharmacist's follow-up time.
- Mean weight and blood pressure at baseline in the control and intervention groups were analyzed for differences between groups using Student's *t* test.
- Lipid follow-up time between the two groups were compared using Student's *t* test.
- Fasting blood sugar
- Within-group comparison: Student's paired *t* test was used to analyze changes in lipid parameters and mean changes at baseline and last visit within the same group.

- Between-group comparison: Student's *t* test was used to compare differences in lipid parameters and mean changes of lipid parameters between two groups both at baseline and last visit.

5.2 Pharmacotherapeutic data

5.2.1 Lipid parameters

5.2.1.1 Within-group comparison: Student's paired *t* test was used to analyze changes in lipid parameters and mean changes at baseline and each visit within the same group.

5.2.1.2 Between-group comparison: Student's *t* test was used to compare differences in lipid parameters and mean changes of lipid parameters between two groups both at baseline and each visit.

5.2.1.3 The percentage of changes: Student's t test was used to compare differences in percentage of changes of lipid parameters between two groups between baseline and each visit.

5.2.2 Achievement in lipid goals

5.2.2.1 LDL-C < 100 mg/dL, TC < 200 mg/dL, TG < 150 mg/dL, HDL-C > 40 mg/dL, non-HDL-C < 130 mg/dL were considered as lipid goals in the present study.

5.2.2.2 The achievement rates of each lipid goals between the two groups both at baseline and last visit were compared using chi-square tests.

5.2.4 Other drugs which may interfere with lipid parameters

5.2.4.1 Drugs which may interfere with lipid parameters were metformin, thiazolidinediones, beta-blockers, hydrochlorothiazide and alpha-blockers.

5.2.4.2 Usage rates of these drugs at baseline and last visit between two groups were compared using chi-square test.

5.2.5 Lipid lowering therapies

5.2.5.1 Lipid lowering therapies were sub-classified as statin monotherapy, combination of statin and fibrate and fibrate monotherapy.

5.2.5.2 Usage rates of lipid lowering therapies at baseline and last visit between the two groups were compared using chi-square test.

5.2.5.3 Simvastatin equivalent dose within and between groups at baseline and last visit were analyzed using Wilcoxon's Sign Rank and Mann Whitney U tests, respectively.

5.2.6 Pharmacist's interventions were reported by descriptive statistics.

CHAPTER IV
RESULTS

This study was conducted at the Outpatient Department of the Bangkok Metropolitan Administration (BMA) General Hospital during June 2004 – December 2004. The results are presented as follow:

1. Baseline demographics
2. Pharmacotherapeutic data
3. Pharmacists' interventions

1. Baseline demographics

A total of 208 patients with type 2 diabetes mellitus with completed lipid data for at least 2 visits were included into the data analysis (100 and 108 patients in the control and the intervention group, respectively). The baseline demographic characteristics of the study population were presented in Table 8. There were no significant differences between the two groups on age, weight, sex, fasting blood sugar, blood pressure and comorbidities. Mean ± SD of ages were 63.0±10.3 and 62.2±10.5 years for patients in the control and intervention groups, respectively. About two-thirds of patients in each group were female. More than 80% of patients in both groups had hypertension. Macro- and microvascular complications were present in approximately one-fifth and one-fourth of patients in the control and intervention groups, respectively

The mean follow-up time was slightly longer in the control than the intervention groups (4.9±1.6 vs 4.0±1.4 months; $p < 0.0001$).

Table 8. Demographic and clinical characteristics

	Control group	Intervention group	p value **between group**
N	100	108	
Female (%) Male (%)	66(66.0) 34 (34.0)	70(64.8) 38 (35.2)	0.858
Age, mean ± SD range, y	63.0± 10.3 43-85	62.2±10.5 40-84	0.584
Weight, mean ± SD (kg)	63.2±10.5	64.6±11.7	0.405
Blood pressure, mean ± SD (mmHg) Systolic blood pressure Diastolic blood pressure	 141.1±18.0 80.2±12.3	 140.5±17.5 80.9±10.5	 0.796 0.668
Underlying disease, (%) - Hypertension - Coronary artery disease - Chronic renal failure - Stroke or Cerebrovascular disease - Peripheral vascular disease	 83 (83.0) 6 (6.0) 4 (4.0) 5 (5.0) 3 (3.0)	 92 (85.2) 14 (13.0) 11 (10.2) 5 (4.6) 1 (0.9)	 0.666 0.089 0.085 0.901 0.516

Student's *t* tests and Chi-square tests showed no statistically significant difference between the two groups, p value > 0.05.

2. Demographic characteristic at last visit

Data on changes in weight and blood pressure from baseline to last visit are presented in Table 9. At last visit, there were no differences in weight between two groups (63.1±10.7 vs 64.4±11.9 kg, p = 0.421). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were similar in control and intervention groups (139.4±16.1 vs 141.4±18.3 and 78.9±12.9 vs 81.8±11.4 mmHg). Compared to baseline values, blood pressure did not change significantly in both groups.

Table 9. Weight and blood pressure at last visit

	Control group	Intervention group	p value **between group**
Weight, mean ± SD (kg)	63.1±10.7	64.4±11.9	0.421
Blood pressure, mean ± SD (mmHg)			
Systolic blood pressure	139.4±16.1	141.4±18.3	0.414
Diastolic blood pressure	78.9±12.9	81.8±11.4	0.092

Student's *t* tests showed no statistically significant difference.

Fasting blood glucose levels were presented in Table 10. At baseline, FBS levels were similar in the control and intervention groups (164.6±55.8 vs 167.8±52.0 mg/dL). No significant changes in FBS were observed in the control group. However, there was a significant reduction in the mean FBS in the intervention group compared to baseline (167.8±52.0 vs 154.5±47.0; p = 0.005)

Table 10. **Fasting blood sugar levels of control and intervention groups at baseline and last visit**

Fasting blood sugar	Mean ± SD, mg/dL		p value **within group**	Mean change		p value **of percent mean changes between group**
	Baseline	Last visit		mg/dL	Δ%	
Control	164.6±55.8	161.8±61.9	0.692	2.8±69.0	↑7.7±81.5	0.143
Intervention	167.8±52.0	154.5±47.0	0.005†	13.3±48.7	↓4.6±28.2	
p value **between group**	0.628	0.341				

†Statistically significant difference within each group (Student's paired *t* test; p value < 0.05) between the two groups, p value > 0.05.

3. Pharmacotherapeutic data

3.1. Lipid profile

3.1.1. Baseline lipid profile

Baseline lipid profiles of patients in this study were presented in Table 11. Lipid parameters of the study population were consistent with classic dyslipidemic pattern of type 2 diabetes characterized by slightly elevated LDL-C, normal total cholesterol and elevated triglyceride levels. Overall, there were no significant differences between the two groups on any lipid parameters at baseline.

Table 11. Baseline lipid profiles

Lipid profiles	Mean SD ± SD, mg/dL		p value **between group**
	Control (N = 100)	Intervention (N = 108)	
LDL-C	123.4±44.9	122.6±40.0	0.886
TC	200.0±47.1	199.8±44.4	0.970
TG	185.0±90.2	198.6±84.3	0.263
HDL-C	58.2±14.4	56.8±12.9	0.478
Non HDL-C	144.9±48.9	142.7±43.0	0.733

Student's *t* tests showed no statistically significant difference between two groups, p value > 0.05.

3.1.2 Post-enrollment Lipid profile

3.1.2.1 Within-group comparison

Data on changes in lipid parameters from baseline to last visits within each group were presented in Table 12. Overall, favorable changes in lipid parameters from baseline were observed in both groups. In the control group, TC, TG and non-HDL-C were significantly decreased from baseline. There was also a slight yet significant increase in HDL-C compared to baseline. Despite favorable changes in these lipid parameters, no significant change in LDL-C was observed in the control group. On the contrary, a significant decrease in LDL-C was observed in the intervention group while the magnitude of reduction in TC, TG and non-HDL-C levels in the intervention

group were approximately doubled those of the control group. There was also a small yet significant increase in HDL-C similar to that observed in the control group.

3.1.2.2 Between-group comparison

Lipid profiles at the last follow-up visit were shown in Table 12 and depicted in Figure 10. At the end of follow-up, patients in the intervention group had significantly lower LDL-C levels than the control group (111.8±33.1 mg/dL vs 124.8±37.3 mg/dL; p value= 0.008). In addition, there is a non-significant trend in favor of the intervention group on total cholesterol levels (179.3±33.4 mg/dL vs 188.8±41.1 mg/dL; p value = 0.070). Triglyceride and non-HDL-C levels were slightly lower in the intervention group than the control group but this difference did not reach statistical significance. HDL-C levels were almost identical between the two groups (59.1±12.3 mg/dL vs 60.9±14.2 mg/dL in the intervention and control groups, respectively).

Table 12. Lipid profiles of control and intervention groups at baseline and last visit

Lipid profile	Control			Intervention			p value **between group at last visit**
	Mean ± SD, mg/dL		p value **within group**	Mean ± SD, mg/dL		p value **within group**	
	Baseline	Last visit		Baseline	Last visit		
LDL-C	123.4±44.9	124.8±37.3	0.746	122.6±40.0	111.8±33.1	0.003†	0.008*
TC	200.0±47.1	188.8±41.1	0.018†	199.8±44.4	179.3±33.4	<0.001†	0.070
TG	185.0±90.2	160.7±70.1	0.007†	198.6±84.3	158.1±74.1	<0.001†	0.796
HDL-C	58.2±15.1	60.9±14.2	0.006†	56.8±12.9	59.1±12.3	0.015†	0.332
Non HDL-C	144.9±48.9	127.6±40.1	<0.001†	142.7±43.0	120.5±30.9	<0.001†	0.156

* Student's *t* tests showed statistically significant difference between two groups, p value < 0.05.

† Student's paired *t* tests showed statistically significant difference within each group, p value < 0.05

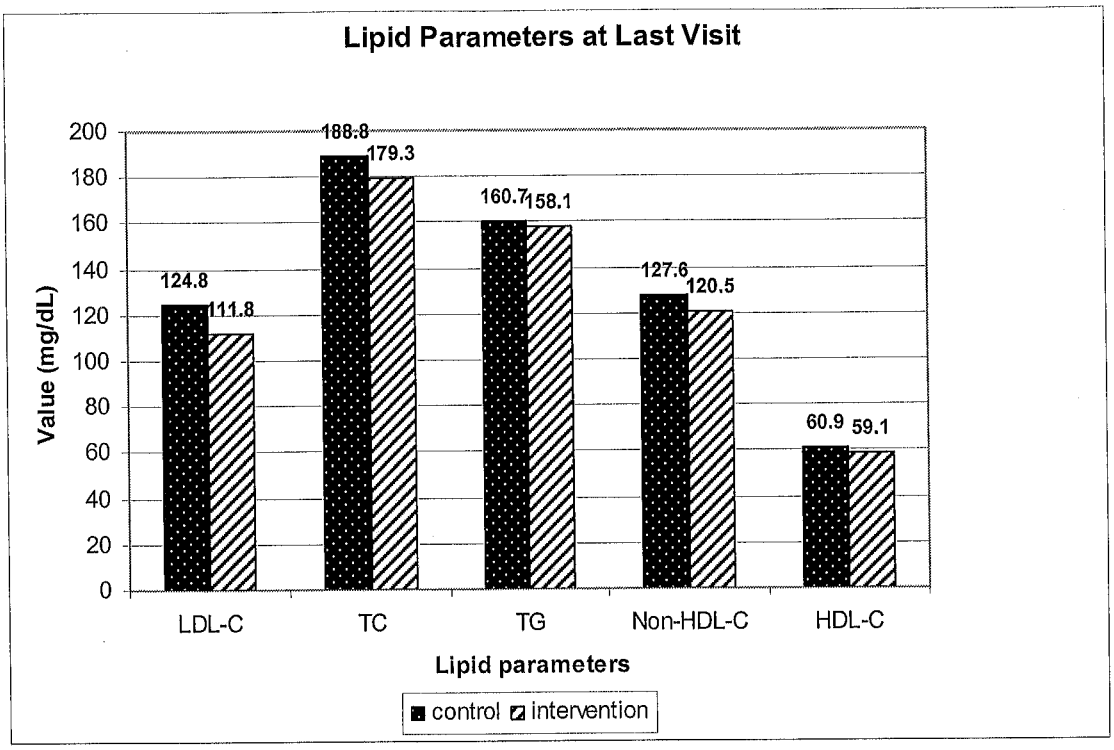

Figure 10. Lipid parameters at last visit between the intervention and control groups.

The mean changes from baseline of these lipid parameters between the two groups were also compared by Student's *t* test. Data is presented in Table 13 and depicted in Figure 11. In the intervention group, there was a mean reduction in LDL-C of 10.8 mg/dL from baseline. On the contrary, there was a mean increase in LDL-C of 1.4 mg/dL from baseline in the control group. The percent mean LDL-C changes between two groups were significantly different in favor of the intervention group (+10.9±46.1 vs –2.4±34.5 %; p = 0.018). The percent mean TG reduction in the intervention group was significantly greater than the control group (-13.3±41.9 vs -1.0±47.6 %; p = 0.047). The percent mean reduction in TC and non-HDL-C were approximately two times greater in the intervention than the control groups (TC/non-HDL-C: -7.7/-10.8 vs -2.5/-5.3 %). However, such differences did not reach statistical significance. For HDL-C, there was an almost identical increase in HDL-C in both groups.

Table 13. Lipid profiles of control and intervention groups at baseline and last visit with mean changes from baseline

Lipid profiles	Mean ± SD, mg/dL		Mean changes		p value **of percent mean changes between group**
	Baseline	Last F/U	mg/dL	Δ%	
LDL-C					
Control	123.4±44.9	124.8±37.5	↑1.4±42.6	↑10.9±46.1	0.018*
Intervention	122.6±40.0	111.8±33.1	↓10.8±37.4	↓2.4±34.5	
TC					
Control	200.0±47.1	188.8±41.2	↓11.3±46.8	↓2.5±22.4	0.071
Intervention	199.8±44.4	179.3±33.4	↓20.5±38.0	↓7.7±18.9	
TG					
Control	185.0±90.2	161.4±70.1	↓24.4±88.4	↓1.0±47.6	0.047*
Intervention	198.6±84.3	158.1±74.1	↓40.6±81.6	↓13.3±41.9	
HDL-C					
Control	58.2±14.4	60.9±14.2	↑2.7±9.5	↑6.6±18.8	0.932
Intervention	56.8±12.9	59.1±12.3	↑2.4±10.0	↑6.3±19.6	
Non HDL-C					
Control	144.9±48.9	127.6±40.1	↓17.3±47.3	↓5.3±32.3	0.187
Intervention	142.7±43.0	120.5±30.9	↓22.2±37.6	↓10.8±26.8	

* Student's *t* tests showed statistically significant different of percent mean changes between two groups, p value < 0.05

† Statistically significant difference within each group (Student's paired *t* tests; p value < 0.05)

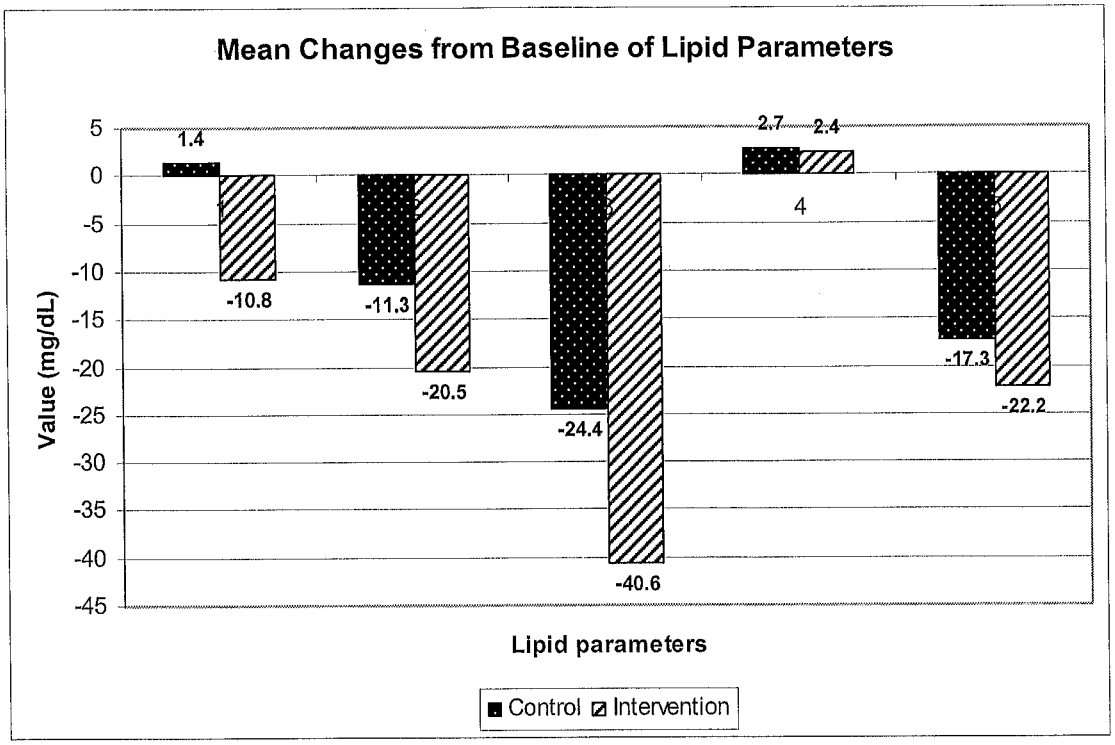

Figure 11. Mean difference of all lipid values between baseline and last follow-up (1 = LDL-C, 2 = TC, 3 = TG, 4 = HDL-C, 5 = Non-HDL-C)

Comparison within and between groups on lipid parameters at 1st, 2nd and 3rd visits are presented in Table 14, 15 and 16, respectively. Overall, LDL-C, TC, TG and non-HDL-C of patients in the intervention group were lower than the control group in every visit. However, only differences of LDL-C, TC and non-HDL-C levels at the 2nd visit reached statistical significance. Changes in lipid parameters at each visit of both control and intervention groups are presented in Table 17.

Table 14. Lipid profiles at baseline and 1st follow-up (N control = 100, N intervention = 108)

Lipid profiles	Mean ± SD, mg/dL		p value **within group**	Mean Changes		p value **of percent mean changes between group**
	Baseline	1st F/U		mg/dL	Δ%	
LDL-C						
Control	123.6±44.8	121.3±40.6	0.564	↓2.4±40.2	↑6.0±45.3	0.330
Intervention	122.6±40.0	115.0±33.6	0.040†	↓7.5±37.6	↑0.5±35.2	
TC						
Control	200.0±47.1	190.8±44.2	0.042	↓9.2±44.6	↓2.0±22.3	0.116
Intervention	199.8±44.4	181.4±35.6	<0.001†	↓18.4±39.9	↓6.6±19.7	
TG						
Control	185.0±90.2	174.9±75.5	0.245	↓10.1±86.6	↑7.3±52.2	0.015*
intervention	198.6±84.3	166.2±77.1	<0.001†	↓32.5±86.4	↓8.6±41.4	
HDL-C						
Control	57.9±14.5	60.8±15.7	0.009†	↑2.8±10.5	↑6.5±21.0	0.985
Intervention	56.8±12.9	59.5±12.9	0.010†	↑2.7±10.5	↑6.6±20.0	
Non HDL-C						
Control	145.3±49.0	130.7±41.7	0.002†	↓14.7±44.9	↓3.8±36.1	0.168
Intervention	142.7±43.0	121.5±31.4	<0.001†	↓21.2±38.2	↓9.9±27.1	

* Student's *t* tests showed statistically significant different of percent mean changes between two groups, p value < 0.05

† Statistically significant difference within each group (Student's paired *t* test; p value < 0.05)

Table 15. Lipid profiles at baseline and 2nd follow-up (N control = 42, N intervention = 40)

Lipid profiles	Mean ± SD, mg/dL		P value within group	Mean changes		P value **of percent mean changes between group**
	Baseline	2nd F/U		mg/dL	Δ%	
LDL-C						
Control	117.8±37.5	122.2±28.5	0.517	↑4.4±43.5	↑13.1±37.4	0.076
Intervention	116.7±34.4	110.0±33.8	0.259	↓6.7±37.7	↓1.3±35.9	
TC						
Control	198.3±44.4	188.6±31.0	0.163	↓9.7±46.0	↓1.1±22.1	0.095
Intervention	190.0±37.5	167.7±38.4	0.004†	↓22.3±46.6	↓9.2±22.5	
TG						
Control	195.2±90.3	182.7±87.7	0.327	↓12.5±84.6	↑1.6±42.8	0.177
Intervention	197.7±84.9	166.2±87.1	0.014†	↓31.4±79.8	↓10.4±39.5	
HDL-C						
Control	58.6±16.9	61.6±17.7	0.076	↑3.0±10.3	↑6.5±21.1	0.300
Intervention	56.0±12.6	61.3±13.8	0.004†	↑5.3±11.0	↑11.6±22.7	
Non HDL-C						
Control	143.2±47.0	125.9±30.2	0.020†	↓17.3±51.2	↓3.5±32.5	0.084
Intervention	134.2±36.0	107.8±38.1	0.001†	↓26.5±45.0	↓15.2±31.3	

† Statistically significant difference within each group (Student paired *t* test; p value < 0.05)

Table 16. Lipid profiles at baseline and 3rd follow-up (N control = 17, N intervention = 9)

Lipid profiles	Mean ± SD, mg/dL		P value within group	Mean Changes		p value **of percent mean changes between group**
	Baseline	3rd F/U		mg/dL	Δ%	
LDL-C						
Control	123.8±30.7	121.2±40.8	0.848	↓2.5±53.3	↓4.1±40.2	0.528
Intervention	104.8±41.8	91.9±39.6	0.323	↓12.9±36.7	↓5.8±32.3	
TC						
Control	216.3±37.4	184.3±44.1	0.024	↓32.0±58.5	↓12.4±23.4	0.858
Intervention	177.7±44.1	149.3±42.3	0.064	↓28.3±39.6	↓14.0±19.7	
TG						
Control	223.6±93.6	178.0±82.2	0.051	↓45.6±97.9	↓11.6±43.9	0.390
Intervention	222.0±101.2	152.8±67.6	0.043	↓69.2±86.4	↓25.8±31.6	
HDL-C						
Control	57.2±19.4	60.3±18.1	0.147	↑3.1±9.2	↑8.5±25.2	0.685
intervention	51.4±8.7	53.3±9.0	0.492	↑1.9±7.9	↑4.7±16.3	
Non HDL-C						
Control	153.8±51.7	117.8±39.8	0.007†	↓36.0±59.8	↓15.5±33.4	0.876
intervention	126.9±42.5	101.0±40.0	0.056	↓25.8±37.3	↓17.4±24.9	

† Statistically significant difference within each group (Student's paired *t* test; p value < 0.05)

Table 17. Lipid profile in each visit between two groups

Lipid profile	Mean ± SD, mg/dL				
	Baseline	1st follow up	2nd follow up	3rd follow up	Last follow up
N (control)	100	100	42	17	100
N(intervention)	108	108	40	9	108
LDL-C					
Control	123.4±44.9	121.3±40.6	122.2±28.5	121.2±40.8	124.8±37.2
Intervention	122.6±40.0	114.8±35.6	108.9±34.0	91.9±39.6	111.8±33.1
p value	0.886	0.213	0.056	0.051	0.008*
TC					
Control	200.0±47.1	190.8±44.2	188.6±31.0	184.3±44.1	188.8±41.2
Intervention	199.8±44.4	181.4±35.7	167.7±38.4	149.3±42.3	179.3±33.4
p value	0.970	0.092	0.006*	0.056	0.070
TG					
Control	185.0±90.2	174.9±75.5	182.7±87.7	178.0±82.2	160.7±70.1
Intervention	198.6±84.3	166.1±77.1	166.2±87.1	152.8±67.6	158.1±74.1
p value	0.263	0.408	0.381	0.428	0.796
HDL-C					
Control	58.2±14.4	60.8±15.7	61.6±17.7	60.3±18.1	60.9±14.2
Intervention	56.8±12.9	59.3±13.0	60.9±13.8	53.3±9.0	59.1±12.3
p value	0.478	0.474	0.839	0.285	0.332
Non HDL-C					
Control	144.9±49.0	130.7±41.7	125.9±30.2	117.8±39.8	127.6±40.1
Intervention	142.7±42.9	121.6±31.3	108.8±38.2	101.0±40.0	120.6±30.8
p value	0.733	0.077	0.018*	0.270	0.156

* Statistically significant difference between two groups (Student's *t* tests; p value < 0.05)

3.2 Achievement rates of lipid goals

3.2.1 At baseline

Baseline achievement rates of lipid profiles are presented in Table 18. At the beginning of this study, 31.0% and 28.7% of patients in the control and intervention groups had attained LDL-C goal of less than 100 mg/dL. Twenty nine percent and 27.8% of patients in the control and intervention groups had LDL-C levels between 100-129 mg/dL. Forty percent and 43.5% of patients in the control and intervention

groups had LDL-C levels of 130 mg/dL or higher. The proportions of patients with total cholesterol less than 200 mg/dL were 55.0% and 54.6% in the control and intervention group, respectively. Forty five percent and 33.3% of patients in the control and intervention group had triglyceride levels less than 150 mg/dL while more than 90% of both groups had HDL-C levels of 40 mg/dL or higher. For non-HDL-C, approximately 40% of patients in both groups had non-HDL-C of less than 130 mg/dL. Overall, there were no significant differences in the achievement rate of lipid goals at baseline.

Table 18. Achievement rate of lipid goals at baseline

Lipoproteins	Number (% of patients)		p value **between group**
	Control (N = 100)	Intervention (N = 108)	
LDL-C < 100 mg/dL	31(31.0)	31(28.7)	0.718
TC < 200 mg/dL	55(55.0)	59(54.6)	0.957
TG < 150 mg/dL	45(45.0)	36(33.3)	0.085
HDL-C ≥ 40 mg/dL	93(93.0)	100(92.6)	0.910
Non HDL-C < 130 mg/dL	41(41.0)	38(35.2)	0.388

Chi-square test shows no statistically significant between two groups, p value > 0.05.

3.2.2 At last visit

The achievement rates of lipid goals at last visit of both groups are presented in Table 19 and depicted in Figure 12. There were 25% and 39.8% of patients in the control and intervention groups who achieved the LDL-C goal of less than 100 mg/dL, respectively. This difference reaches statistical significance with a p value of 0.023. Such increase represents approximately 40% and 60% increase in the LDL-C goal attainment compared to baseline and the control group, respectively. While there was no difference in the proportion of patients with LDL-C between 100-129 mg/dL, fewer patients in the intervention group had LDL-C of 130 mg/dL or higher compared to the control group. Although this difference was not statistically significant, a non-

significant trend can be observed (27.8% vs 40%; p 0.062). The achievement rates of total cholesterol, triglyceride and non HDL-C were higher in the intervention groups. However, these differences did not reach statistical significance.

Table 19. Achievement rate of lipid goal at last visit

Lipoproteins	Number (% of patients)		p value between group
	Control (N = 100)	Intervention (N = 108)	
LDL-C < 100 mg/dL	25 (25.0)	43(39.8)	0.023‡
TC < 200 mg/dL	69(69.0)	85(78.7)	0.111
TG < 150 mg/dL	47(47.0)	58(53.7)	0.334
HDL-C > 40 mg/dL	97(97.0)	104(96.3)	0.779
Non HDL-C < 130 mg/dL	57(57.0)	72(66.7)	0.151

‡Chi-square test shows statistically significant between two groups, p value <0.05.

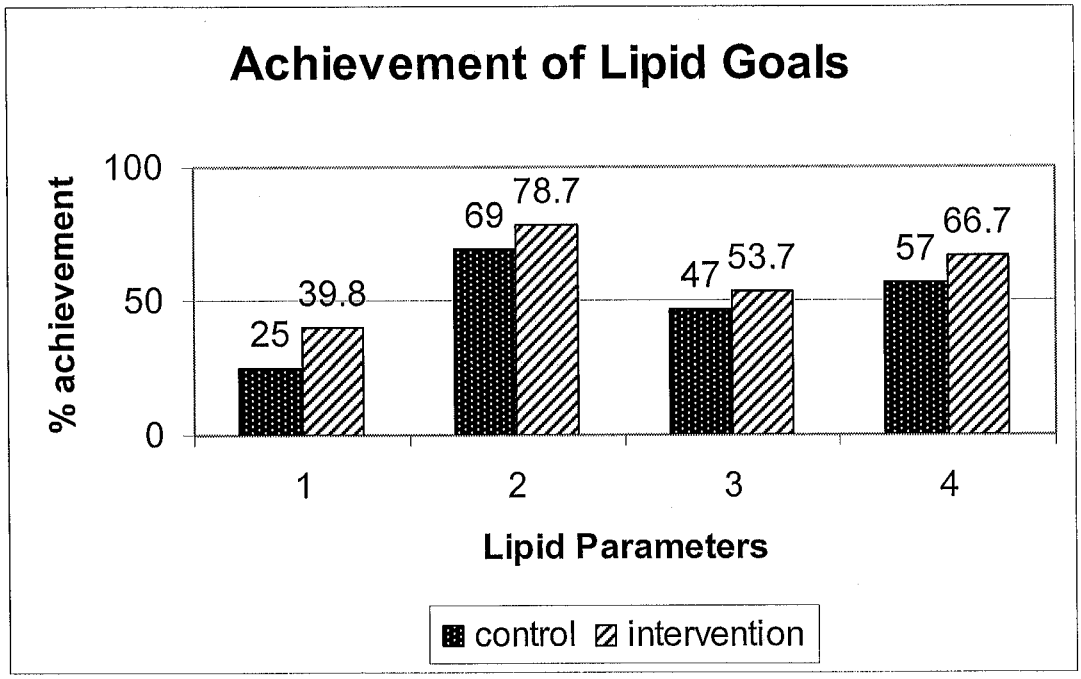

Figure 12. Achievement rates of lipid goals at last visit (1 = LDL-C, 2 = TC, 3 = TG, 4 = non-HDL-C)

Changes in proportion of patients achieving lipid goals are presented in Table 20 and Figure 13. Compared to baseline, there is a 19.4% decrease in the proportion of patients with LDL-C of less than 100 mg/dL. This is in contrary to the intervention group where 38.7% more patients achieved such LDL-C goal. For those with LDL-C between 100-129 mg/dL, there were 20.7% and 16.7% increase in the control and intervention groups, respectively. For the proportion of patients with LDL-C of 130 mg/dL or higher, there was no change in the control group while there were a 36.2% reduction in these population in the intervention group. For other lipid parameters, both groups experienced increases in the proportion of patients achieving TC, TG, HDL-C and non-HDL-C. With the exception of HDL-C, all changes observed with the intervention group were greater than those of the control group. These differences however did not reach statistical significance.

Table 20. Difference in number of patients who achieved lipid goal between baseline and last visit

Lipoproteins	Number (% of changes)	
	Control group	Intervention group
LDL-C < 100 mg/dL	↓6 (19.4)	↑12 (38.7)
TC < 200 mg/dL	↑14 (25.5)	↑26 (44.1)
TG < 150 mg/dL	↑2 (4.4)	↑22 (61.1)
HDL-C > 40 mg/dL	↑4 (4.3)	↑4 (4.0)
Non HDL-C < 130 mg/dL	↑16 (39.0)	↑34 (89.5)

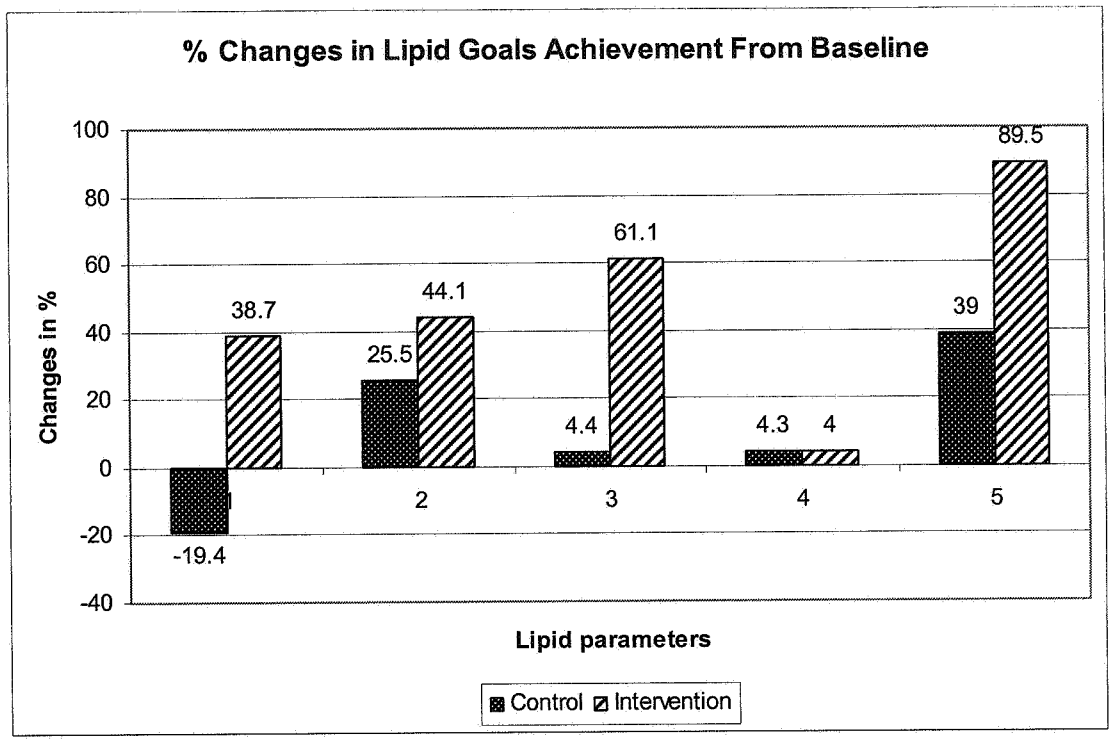

Figure 13. Changes (%) in lipid goals achievement from baseline to last visit in the control and intervention groups (1 = LDL-C, 2 = TC, 3 = TG, 4 = HDL-C, 5 = non-HDL-C)

3.3 Concurrent drugs with lipid modifying properties

In this study, we collected the data on concurrent drugs that may interfere with lipid parameters including metformin, beta-blockers, thiazolidinediones, hydrochlorothiazide and alpha-blockers. The usage rates of these drugs were represented in Table 21. With the exception of beta-blockers, these drugs were used at similar rates in both groups at baseline and last visit. About 60% of patients received metformin, 20% received hydrochlorothiazide and 4-7% received alpha-blockers, respectively. The usage rates of beta-blockers in the intervention group were higher than the control group both at baseline and last visit.

Table 21. Concurrents drugs with lipid modifying properties

Usage rate of other medicines	Baseline (%)		p value **between group**	Last visit (%)		p value **between group**
	Control	Intervention		Control	Intervention	
Metformin	66(66.0)	71 (65.7)	0.969	65(64.0)	74(68.5)	0.590
Thiazolidinediones	5 (5.0)	2 (1.9)	0.208	8 (8.0)	4 (3.7)	0.184
Beta-blockers	16 (16.0)	34 (31.5)	0.009‡	16 (16.0)	37 (34.3)	0.003‡
Hydrochlorothiazide	20 (20.0)	20 (18.0)	0.786	20 (20.0)	20 (18.6)	0.786
Alpha-blockers	3 (3.0)	7 (6.5)	0.241	3 (3.0)	8 (7.4)	0.156

‡Chi-square test shows statistically significant between two groups, p value <0.05.

3.4 Lipid lowering therapy

The usage rates of statins at baseline are depicted in Table 22. Thirty-two percent and 40.7% of patients in the control and intervention groups received monotherapy with statins, respectively. Combination therapy of statin and fibrate was prescribed to 7.0% and 12.0% of patients in the control and intervention groups, respectively. Twenty one percent and 13% of patients in the control and intervention groups received monotherapy with fibrates, respectively. Overall, there were no significant differences on the usage rate of any lipid-lowering therapies among the two groups. The usage rates of lipid lowering agents at the last visit are presented in Table 23. Thirty-six percent and 53.7% of patients in the control and intervention groups received monotherapy with statins, respectively. Approximately thirteen percent of patients in each group were prescribed combination therapy of statin and fibrate. Twenty three percent and 8.3% of patients in the control and intervention groups received monotherapy with fibrates, respectively. Overall, there were significant differences on the usage rate of statin monotherapy and fibrate monotherapy among the two groups with p value less than 0.05. Changes in proportion of patients received lipid lowering therapies are presented in Table 24. Compared to baseline, there was a 12.5% and 31.8% increase in the proportion of patients with statin monotherapy in the control and intervention groups, respectively. For those with combination of statin and fibrate, there were 85.7% and 15.4% increase in the control and intervention groups, respectively. For the proportion of patients with fibrate monotherapy, there was 9.5%

increasing in the control group while there was a 35.7% reduction in these populations in the intervention group.

Table 22. The usage rates of lipid lowering therapies at baseline

Usage of lipid lowering agents	Control (%)	Intervention (%)	p value **between group**
Statin only	32 (32.0)	44 (40.7)	0.191
Combination statin and fibrates	7 (7.0)	13 (12.0)	0.218
Fibrates only	21 (21.0)	14 (13.0)	0.122

Chi-square for categorical variables shows no statistically significant difference between the two groups, p value > 0.05.

Table 23. The usage rates of lipid lowering therapies at last visit

Usage of lipid lowering agents	Control (%)	Intervention (%)	p value **between group**
Statin only	36 (36.0)	58 (53.7)	0.010‡
Combination statin and fibrates	13 (13.0)	15 (13.9)	0.851
Fibrates only	23 (23.0)	9 (8.3)	0.003‡

‡Chi-square for categorical variables shows statistically significant difference between the two groups, p value < 0.05.

Table 24. **Difference in number of patients who received lipid lowering therapies between baseline and last visit**

Usage of lipid lowering agents	Number (% of changes)	
	Control group	Intervention group
Statin only	4 (12.5)	14 (31.8)
Combination statin and fibrates	6 (85.7)	2 (15.4)
Fibrates only	2 (9.5)	-5 (35.7)

In addition, there were no significant differences on the intensity of statin therapy expressed as “simvastatin equivalent dose”. The intensity of statin therapy is presented in Table 25, 26. At baseline, the simvastatin equivalent dose was higher in the

intervention group yet this difference did not reach statistical significance (7.5±12.2 vs 9.7±13.8 mg; p= 0.052). There were significant increase of simvastatin equivalent dose from baseline within both control and intervention groups. However, at last visit, patients in the intervention group received significantly higher dose of statin than patients in the control group (9.7±13.8 vs 13.0±14.3 mg; p = 0.014). Median simvastatin equivalent dose at baseline were 10 and 20 mg in the control and intervention groups, respectively. At last visit, the median doses were 20 mg in both groups.

Table 25. **Simvastatin equivalent dose at baseline and last visit**

Simvastatin equivalent dose	Baseline	Last visit	p value **within group**	Mean changes (mg)	p value **of mean changes between group**
Control	7.5±12.2	9.7±13.8	0.041§	2.3±11.4	0.853
Intervention	9.7±13.8	13.0±14.3	0.001§	3.2±8.2	

§Statistically significant difference within each group (Wilcoxon sign rank test; p value < 0.05)

‖Statistically significant difference between group (Mann-Whitney U test; p value < 0.05)

Table 26. Simvastatin equivalent at baseline and last visit between groups

Simvastatin equivalent dose	Baseline (mg)	Last visit (mg)
Control	7.5±12.2	9.7±13.8
Intervention	9.7±13.8	13.0±14.3
p value **between group**	0.052	0.014‖

‖Statistic significance difference between group (Mann-Whitney U test; p value < 0.05)

3.5 Subgroup analysis of patients with LDL-C ≥ 100 mg/dL at baseline

At the beginning of the study, there were 69 (69.0%) and 77 (71.3%) patients in the control and intervention groups who had LDL-C of 100 mg/dL or higher at baseline. Data analysis of this subgroup were performed and presented as follow.

3.5.1 Lipid profile

3.5.1.1 Baseline lipid profile

Baseline lipid profiles of this subgroup of patients are presented in Table 27. There were no significant differences between two groups in any lipid values. Both groups had mean LDL-C levels of over 140 mg/dL. The means TC/TG/HDL/non-HDL-C levels were 221.3±39.7/200.9±90.9/57.9±13.8/163.8±41.5 vs 217.8±35.2/ 205.1±78.1/58.5±13.5/159.3±35.2 mg/dL in the control and intervention groups, respectively.

Table 27. **Baseline lipid profiles among patients with baseline LDL-C of 100 mg/dL or higher**

Lipid profiles	Mean ± SD, mg/dL		p value **between group**
	Control group (N = 69)	Intervention group (N = 77)	
LDL-C	143.9±38.0	141.1±30.7	0.632
TC	221.3±39.7	217.8±35.2	0.574
TG	200.9±90.9	205.1±78.1	0.767
HDL-C	57.9±13.8	58.5±13.5	0.818
Non HDL-C	163.8±41.5	159.3±35.2	0.477

* Student's t test shows no statistically significant difference between the two groups (Student's *t* test; p value > 0.05)

3.5.1.2 Post-enrollment

3.5.1.2.1 Within-group comparison

Lipid parameters at last visit of the control and intervention groups are presented in Table 28. Overall, greater favorable changes in lipid parameters were observed in this subgroup of patients compared to the overall study population. In the control group, TC, TG and non-HDL-C levels were significantly decreased from baseline.

However, no significant change in LDL-C level was observed. In contrast, a significant decrease in LDL-C was seen in the intervention group while the reductions in TC, TG and non-HDL-C were observed at a greater extent than the control group. On the contrary to the overall population, no significant change in HDL-C was observed in both control and intervention groups.

3.5.1.2.2 Between-group comparison

Lipid profiles at the last follow-up visit were shown in Table 28 and depicted in Figure 14. At last visit, patients in the intervention group had significantly lower LDL-C levels than the control group (119±32 vs 134±39.6 mg/dL; p = 0.016. In addition, greater favorable changes in other lipid parameters were also observed in the intervention group compared to control group. Generally, the extent of difference was magnified in this subgroup of patients compared to the differences seen in the entire study population.

Table 28. Lipid profiles of control and intervention groups at baseline and last visit among patients with LDL-C at baseline of 100 mg/dL or higher

Lipid profile	Control			Intervention			p value **between group at last visit**
	Mean ± SD, mg/dL		p value **within group**	Mean ± SD, mg/dL		p value **within group**	
	Baseline	Last visit		Baseline	Last visit		
LDL-C	143.9±38.0	133.7±39.6	0.059	141.1±30.7	119.0±32.0	<0.001†	0.016*
TC	221.3±39.7	196.8±45.6	<0.001†	217.8±35.2	187.0±32.2	<0.001†	0.132
TG	200.9±90.9	168.2±73.9	0.003†	205.1±78.1	160.8±78.1	<0.001†	0.563
HDL-C	57.9±13.8	59.0±13.7	0.306	58.5±13.5	60.3±13.2	0.139	0.641
Non HDL-C	163.8±41.5	137.7±42.9	<0.001†	159.3±35.2	127.1±30.4	<0.001†	0.086

* Student's *t* tests showed statistically significant difference between two groups, p value < 0.05.

† Student's paired *t* tests showed statistically significant difference within each group, p value < 0.05

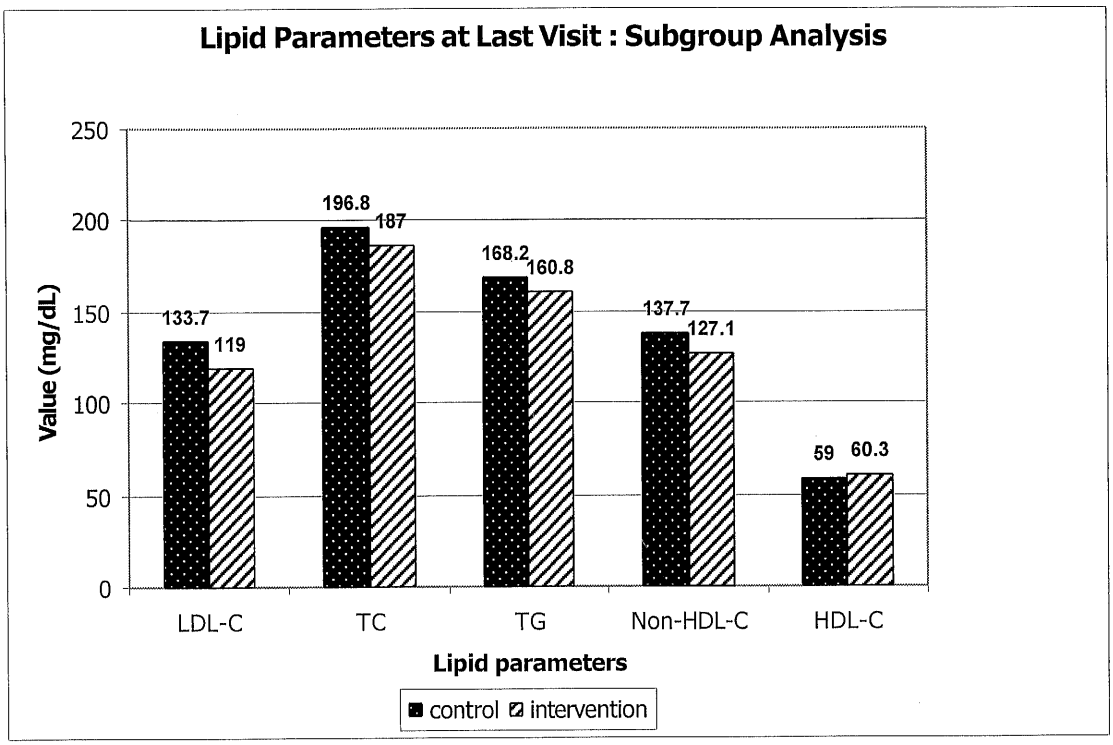

Figure 14. Lipid parameters at last visit between the intervention and control groups among patients with LDL-C of 100 mg/dL or higher

The mean changes from baseline of lipid parameters between the two groups were also compared using Student's *t* test. Data are presented in Table 29 and depicted in Figure 15. At last visit, percent mean reduction in LDL-C were almost 4 times greater in the intervention than control groups (-13.7±23.3 vs -4.2±27.6 %; p = 0.029). For other lipid parameters, greater favorable changes were seen with the intervention group but these did not reach statistical significance.

Table 29. Lipid profiles of control and intervention groups at baseline and last visit with mean changes from baseline among patients with LDL-C at baseline of 100 mg/dL or higher (N control = 69, N intervention = 77)

Lipid profiles	Mean ± SD, mg/dL		Mean changes		p value **of percent mean changes between group**
	Baseline	Last F/U	mg/dL	Δ%	
LDL-C Control intervention	 143.9±38.0 141.1±30.7	 133.7±39.6 119.0±32.0	 ↓10.2±44.2 ↓22.1±34.3	 ↓4.2±27.6 ↓13.7±23.3	0.026*
TC Control Intervention	 221.3±39.7 217.8±35.2	 196.8±45.6 187.0±32.2	 ↓24.4±48.3 ↓30.8±33.6	 ↓9.7±19.2 ↓13.2±13.9	0.221
TG Control intervention	 200.9±90.9 205.1±78.1	 168.2±73.9 160.8±78.1	 ↓32.7±89.6 ↓44.2±82.2	 ↓6.7±42.9 ↓16.4±41.1	0.165
HDL-C Control intervention	 57.9±13.8 58.5±13.5	 59.0±13.7 60.3±13.2	 ↑1.1±8.9 ↑1.8±10.7	 ↑3.3±16.3 ↑5.0±19.1	0.557
Non HDL-C Control intervention	 163.8±41.5 159.3±35.2	 137.7±42.9 127.1±30.4	 ↓26.1±47.5 ↓32.1±33.5	 ↓12.6±27.5 ↓18.5±18.2	0.132

* Student's *t* tests showed statistically significant different of percent mean changes between two groups, p value < 0.05

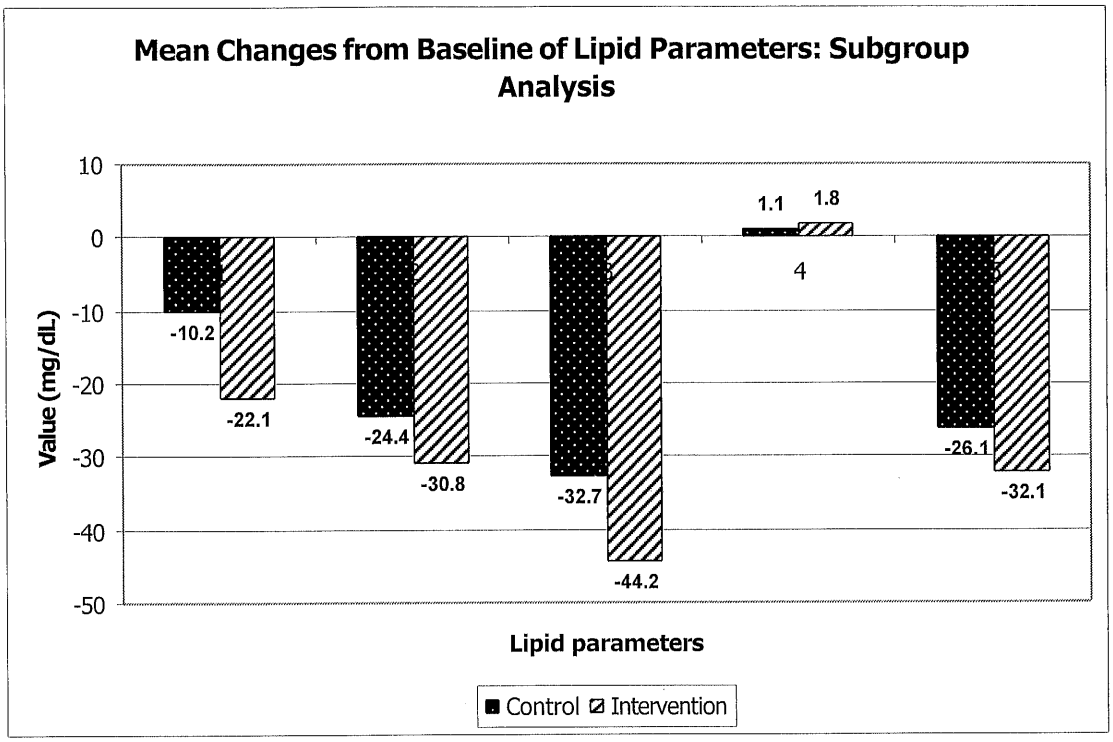

Figure 15. Mean changes from baseline of lipid parameters: subgroup analysis of patients with LDL-C at baseline of 100 mg/dL or higher (1 = LDL-C, 2 = TC, 3 = TG, 4 = non-HDL-C)

Comparison within and between groups on lipid parameters at 1st, 2nd and 3rd visits are presented in Table 30, 31 and 32, respectively. Overall, LDL-C, TC and non-HDL-C of patients in the intervention group were lower than the control group at every visit. At 1st follow-up, LDL-C, TC and non-HDL-C levels were significantly lower in the intervention group (122.3±31.9 vs 134.1±40.0; p = 0.050, 189.5±35.2 vs 203.8±44.5; p = 0.035, 128.3±31.1 vs 144.9±38.6; p = 0.005, respectively). At 2nd follow-up, TC, TG and non HDL-C were significantly lower in the intervention group (171.2±39.9 vs 191.8±34.7, p = 0.035, 149.0±60.1 vs 204.0±93.3, p = 0.008, 111.0±40.0 vs 132.6±30.9, p = 0.024, respectively). Changes in lipid profiles at each visit of both control and intervention groups are presented in Table 33.

In Table 30, comparison of lipid profiles between baseline and first visit showed that LDL-C, TC, TG and non HDL-C in the intervention group were significantly reduced (paired Student's *t* test, p value < 0.001). In contrast, only total cholesterol

and non HDL-C were significantly reduced in the control group (paired Student's *t* test, p value < 0.001). The percent mean difference in total cholesterol non-HDL-C between the two groups reaches statistical significance (Student's *t* test, p value = 0.044 and 0.012).

Table 30. Lipid profiles at baseline and 1st follow-up among patients with baseline LDL-C of 100 mg/dL or higher (N control = 69, N intervention = 77)

Lipid profiles	Mean ± SD, mg/dL		p value **within group**	Mean changes		p value **of percent mean changes between group**
	Baseline	1st F/U		mg/dL	Δ%	
LDL-C						
Control	143.5±38.2	134.1±40.0	0.073	↓9.4±42.6	↓3.9±27.6	0.060
Intervention	141.1±30.7	122.3±31.9	<0.001†	↓18.8±34.0	↓11.8±22.4	
TC						
Control	221.3±39.7	203.8±44.5	0.003†	↓17.5±47.1	↓6.4±20.3	0.044*
Intervention	217.8±35.2	189.5±35.2	<0.001†	↓28.2±36.6	↓12.4±15.3	
TG						
Control	200.9±90.9	182.7±76.7	0.092	↓18.2±88.5	↓0.9±44.4	0.097
intervention	205.1±78.1	169.6±81.2	0.001†	↓35.5±90.5	↓11.1±41.8	
HDL-C						
Control	58.0±13.9	59.6±16.2	0.198	↑1.6±10.3	↑3.6±19.7	0.266
intervention	58.5±13.5	60.7±13.7	0.081	↑2.3±11.2	↑8.5±30.7	
Non HDL-C						
Control	163.8±41.9	144.9±38.6	0.001†	↓18.9±43.0	↓7.2±32.2	0.012*
intervention	159.3±35.2	128.3±31.3	<0.001†	↓31.0±34.3	↓18.1±18.3	

* Student's *t* tests showed statistically significant different of percent mean changes between two groups, p value < 0.05

† Statistically significant difference within groups (Student's paired *t* test; p value < 0.05).

Comparison of lipid profiles between baseline and second visit is presented in Table 31. All lipid parameters except HDL-C in the intervention group were significantly lower than baseline. This was in contrast to the control group where only TC and non-HDL-C were significantly reduced. In addition, HDL-C significantly increased from baseline in the intervention group while there was no significant change of HDL-C in the control group. In the third visit, small numbers of patients in both groups limit meaningful comparisons within and between groups.

Table 31. Lipid profiles at baseline and 2nd follow-up among patients with baseline LDL-C of 100 mg/dL or higher (N control = 28, N intervention = 29)

Lipid profiles	Mean ± SD, mg/dL		p value **within group**	Mean changes		p value **of percent mean changes between group**
	Baseline	2nd F/U		mg/dL	Δ%	
LDL-C						
Control	134.4±29.4	125.0±32.2	0.142	↓12.5±43.5	↓5.5±27.5	0.316
Intervention	134.4±21.6	116.5±30.0	0.010†	↓17.9±34.6	↓12.5±25.7	
TC						
Control	218.8±36.5	191.8±34.7	0.002†	↓27.0±44.4	↓10.5±18.6	0.226
Intervention	207.5±27.2	171.2±39.9	<0.001†	↓36.3±45.1	↓10.5±19.5	
TG						
Control	215.0±85.9	204.0±93.3	0.450	↓11.0±80.2	↓0.0±39.7	0.062
intervention	196.7±72.3	149.0±60.1	0.001†	↓47.7±73.5	↓18.6±36.5	
HDL-C						
Control	58.7±17.3	60.4±19.3	0.395	↑1.7±10.2	↑3.5±21.5	0.226
intervention	62.2±15.4	62.2±15.4	0.041†	↑5.0±12.3	↑11.3±26.1	
Non HDL-C						
Control	158.1±39.9	132.6±30.9	0.001†	↓25.5±43.7	↓10.8±29.1	0.051
intervention	151.3±24.7	111.0±40.0	<0.001†	↓40.3±44.3	↓25.0±27.3	

† Statistically significant difference within groups (Student's paired *t* test; p value < 0.05)

Table 32. Lipid profiles at baseline and 3rd follow-up among patients with baseline LDL-C of 100 mg/dL or higher (N control = 14, N intervention = 6)

Lipid profiles	Mean ± SD, mg/dL		p value **within group**	Mean changes		p value **of percent mean changes between group**
	Baseline	3rd F/U		mg/dL	Δ%	
LDL-C						
Control	133.0±24.8	121.6±44.4	0.444	↓11.4±54.1	↓5.7±35.4	0.414
Intervention	129.5±18.2	103.5±39.4	0.159	↓26.0±38.5	↓19.5±28.5	
TC						
Control	225.5±32.4	184.9±47.6	0.012	↓40.5±58.9	↓16.4±22.5	0.774
Intervention	201.2±29.5	160.5±45.1	0.068	↓40.7±43.0	↓19.5±21.4	
TG						
Control	239.3±92.1	180.2±88.0	0.028	↓59.1±100.5	↓17.7±45.0	0.455
intervention	229.8±75.6	151.3±73.8	0.084	↓78.5±89.5	↓33.0±33.4	
HDL-C						
Control	58.0±21.5	61.6±19.9	0.188	↑3.5±10.3	↑10.0±28.1	0.791
intervention	51.3±10.1	53.9±10.4	0.541	↑2.6±9.6	↑6.6 19.8±	
Non HDL-C						
Control	158.3±46.6	120.0±43.4	0.008	↓38.3±56.1	↓17.7±33.2	0.767
intervention	147.3±27.1	112.2±39.0	0.065	↓35.1±41.2	↓22.0±27.9	

† Statistically significant difference within groups (Student's paired *t* test; p value < 0.05)

Table 33. Lipid profile in each visit between two groups among patients with LDL-C at baseline of 100 mg/dL or higher

Lipid profile	Mean ± SD, mg/dL				
	Baseline	1st F/U	2nd F/U	3rd F/U	Last visit
N Control	69	69	28	14	69
N Intervention	77	77	29	6	77
LDL-C					
Control	143.9±38.0	134.1±40.0	125.0±32.2	121.6±44.4	133.7±39.6
Intervention	141.1±30.7	122.3±31.9	116.5±30.0	103.5±39.4	119.0±32.0
p value	0.632	0.050*	0.307	0.401	0.015*
TC					
Control	221.3±39.7	203.8±44.5	191.8±34.7	184.9±47.6	196.8±45.6
-Intervention	217.8±35.2	189.5±35.2	171.2±39.9	160.5±45.1	187.0±32.2
p value	0.574	0.035*	0.035*	0.286	0.132
TG					
Control	200.9±90.9	182.7±76.7	204.0±93.3	180.2±88.0	168.2±73.9
Intervention	205.1±78.1	169.6±81.2	149.0±60.1	151.3±73.8	160.8±78.1
p value	0.767	0.319	0.008*	0.481	0.563
HDL-C					
Control	57.9±13.8	59.6±16.2	60.4±19.3	61.6±19.9	59.0±13.7
Intervention	58.5±13.5	60.7±13.7	62.2±15.4	53.9±10.4	60.3±13.2
p value	0.818	0.716	0.782	0.383	0.641
Non HDL-C					
Control	163.8±41.5	144.9±38.6	132.6±30.9	120.0±43.4	137.7±42.9
Intervention	159.3±35.2	128.3±31.3	111.0±40.0	112.2±39.0	127.1±30.4
p value	0.477	0.005*	0.024*	0.682	0.086

*Statistic significance between two groups (Student's *t* test p value<0.05).

3.5.2 Achievement rate of lipid goals

3.5.2.1 At baseline

Baseline achievement rates of lipid goals among patients with baseline LDL-C of 100 mg/dL or higher are presented in Table 34. At the beginning of this study, the achievement rates of lipid profiles of the two groups were not significantly different. The number of patients with LDL-C of 100-129 mg/dL were 29 (42.0%) and 30 (39.0%) in the control and intervention groups, respectively. Forty (58.0%) and 47

(61.0%) patients in the control and intervention groups had LDL-C of 130 mg/dL or higher.

Table 34. Achievement rates of lipid goals at baseline among patients with LDL-C at baseline of 100 mg/dL or higher

Lipid profile	Number (%)		p value between group
	Control (N = 69)	Intervention (N = 77)	
LDL-C			
100-129 mg/dL	29 (42.0)	30 (39.0)	0.706
≥ 130 mg/dL	40 (58.0)	47 (61.0)	0.706
TC < 200 mg/dL	29 (42.0)	38 (49.4)	0.375
TG < 150 mg/dL	25 (36.2)	23 (29.9)	0.414
HDL-C > 40 mg/dL	65 (94.2)	73 (94.8)	0.873
Non HDL-C < 130 mg/dL	11 (15.9)	10 (13.0)	0.611

Chi-square shows no statistic significance between the two groups

3.5.2.2 At last visit

At last visit, the achievement rates of lipid goals are presented in Table 35. For LDL-C, 17.4% and 28.6% of patients in the control and intervention groups attained the LDL-C goal of less than 100 mg/dL, respectively. Twenty eight (36.4%) and 20 (29.0%) patients in the control and intervention groups had LDL-C at 100-129 mg/dL, respectively. There were significantly less patients with LDL-C of 130 mg/dL or higher in the intervention than control groups (35.1% vs 53.6%; p = 0.024). For other lipid parameters, a non-significant trend in favor of the intervention group on the achievement rates of TC and Non-HDL levels is observed.

Table 35. Achievement rates of lipid goals at last visit among patients with LDL-C at baseline of 100 mg/dL or higher

Lipid profile	Number (%)		p value between group
	Control (N = 69)	Intervention (N = 77)	
LDL-C			
< 100 mg/dL	12 (17.4)	22 (28.6)	0.111
100-129 mg/dL	20 (29.0)	28 (36.4)	0.343
≥ 130 mg/dL	37 (53.6)	27 (35.1)	0.024 ‡
TC < 200 mg/dL	40 (58.0)	56 (72.7)	0.061
TG < 150 mg/dL	32 (46.4)	41 (53.2)	0.407
HDL-C ≥ 40 mg/dL	67 (97.1)	74 (96.1)	0.741
Non HDL-C < 130 mg/dL	30 (43.5)	46 (59.7)	0.050

‡ Chi-square shows statistically significant between two groups (p value < 0.05).

Changes in proportion of patients achieving lipid goals are presented in Table 36 and Figure 16. Compared to baseline, there was a 17.4% and 28.6% more patients achieved LDL-C of less than 100 mg/dL. For those with LDL-C between 100-129 mg/dL, there were 26.1% and 6.7% decrease in the control and intervention groups, respectively. For the proportion of patients with LDL-C of 130 mg/dL or higher, there were a 7.5% and 42.6% reduction in these population in the control and intervention group and reach statistic significant with p value 0.024. For other lipid parameters, both groups experienced increases in the proportion of patients achieving TC, TG, HDL-C and non-HDL-C. With the exception of HDL-C, all changes observed with the intervention group were greater than those of the control group. These differences however did not reach statistical significance.

Table 36. Difference in number of patients who achieve lipid goal between baseline and last visit among patients with LDL-C at baseline of 100 mg/dL or higher

Lipid profile	Number (% of changes)	
	Control group	Intervention group
LDL-C < 100 mg/dL	↑12 (17.4)	↑22 (28.6)
TC < 200 mg/dL	↑11 (37.9)	↑18 (47.4)
TG < 150 mg/dL	↑7 (28.0)	↑18 (78.3)
HDL-C > 40 mg/dL	↑2 (3.1)	↑1 (1.4)
Non HDL-C < 130 mg/dL	↑19 (172.7)	↑36 (360.0)

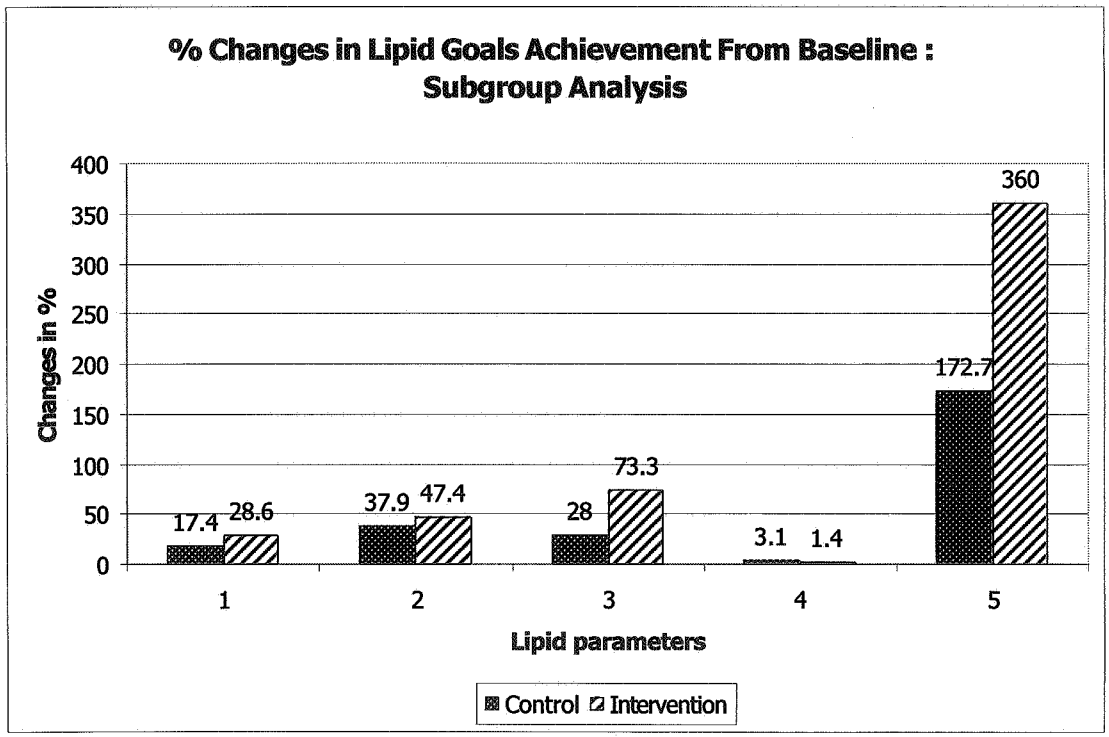

Figure 16. Changes (%) in lipid goals achievement from baseline to last visit in the control and intervention groups (1 = LDL-C, 2 = TC, 3 = TG, 4 = HDL-C, 5 = non-HDL-C)

3.5.3 Fasting blood sugar (FBS)

Data on changes in fasting blood sugar from baseline to last visit in this subgroup of patients are presented in Table 37. Similar results were found in this subgroup comparing to the overall study population. At baseline, FBS were similar in control and intervention groups (168.2±50.2 vs 171.4±55.0 mg/dL). Although FBS in the control group did not change significantly from baseline, FBS in the intervention group was significantly reduced. Despite this difference, the FBS at last visit between two groups were not significantly different.

Table 37. Fasting blood sugar of control and intervention groups at baseline and last visit among patients with LDL-C at baseline of 100 mg/dL or higher

Fasting blood sugar	Mean ± SD, mg/dL		p value **within group**	Mean change
	Baseline	Last visit		
Control	168.2±50.2	166.5±51.2	0.782	1.7±50.9
Intervention	171.4±55.0	153.3±47.1	0.001†	18.1±44.0
P value **between group**	0.670	0.107		

†Statistically significant difference within each group (Student's paired *t* test; p value < 0.05)

3.5.4 Concurrent drugs with lipid modifying properties

In this study, we collected the data on concurrent drugs that may interfere with lipid parameters including metformin, beta-blockers, thiazolidinediones, hydrochlorothiazide and alpha-blockers. The usage rates of these drugs were represented in Table 38. With the exception of beta-blockers, these drugs were used at similar rates in both groups at baseline and last visit. About 65% of patients received metformin, 20% received hydrochlorothiazide and 4-7% received alpha-blockers, respectively. More patients in the intervention group received beta-blockers compared to the control group both at baseline and last visit.

Table 38. Concurrents drugs with lipid modifying properties among patients with LDL-C at baseline of 100 mg/dL or higher

Usage rate of other medicines	Baseline (%)		p value **between group**	Last visit (%)		p value **between group**
	Control (N=69)	Intervention (N=77)		Control	Intervention	
Metformin	45 (65.2)	50 (64.9)	0.972	44 (63.8)	51 (66.2)	0.755
Thiazolidinediones	2 (2.9)	2 (2.6)	0.911	3 (4.3)	4 (5.2)	0.811
Beta-blockers	7 (10.1)	21 (27.3)	0.009‡	10 (14.5)	24 (31.2)	0.017‡
Hydrochlorothiazide	18 (26.1)	14 (18.2)	0.249	17 (24.6)	14 (18.2)	0.120
Alpha-blockers	2 (2.9)	5 (6.5)	0.310	2 (2.9)	6 (7.8)	0.195

‡Chi-square test shows statistically significant between two groups, p value <0.05.

3.5.5 Lipid lowering therapies

The usage rates of statins at baseline were depicted in Table 39. Statin monotherapy were used at a higher rate in the intervention than control groups (41.6% vs 24.6%; p = 0.031). No significant differences in the usage of other treatments were noted. Combination therapy of statin and fibrate was prescribed to 4.3% and 9.1% of patients in the control and intervention groups, respectively. Twenty five percent and 13% of patients in the control and intervention groups received monotherapy with fibrates, respectively. The usage rates of statins at last visit were presented in Table 40. Statin monotherapy were used at a higher rate in the intervention than control groups (59.7% vs 31.9%; p = 0.031). Sixteen percent and 11.7% of patients in the control and intervention groups were prescribed statin-fibrate combination. Fibrate monotherapy was used more frequently in the control than intervention groups (26.1% vs 7.8%; p = 0.003). Overall, significantly more patients in the intervention group received statin therapy while significantly more patients in the control group received fibrate therapy. Changes in the proportion of patients receiving lipid lowering therapies are presented in Table 41. Compared to baseline, there was a 29.4% and 43.8% increase in the proportion of patients receiving statin monotherapy in the intervention and control groups. There was a 4-fold increase in the proportion of patients receiving statin-fibrate combination in the control group. For the intervention group, such population increased by 28.6%. There was a 5.9% increase and 40% decrease in the proportion of

patients receiving fibrate monotherapy in the control and intervention groups, respectively.

Table 39. The usage rates of lipid lowering therapies at baseline among patients with LDL-C at baseline of 100 mg/dL or higher

Usage of lipid lowering agents	Control (%)	Intervention (%)	p value **between group**
Statin only	17 (24.6)	32 (41.6)	0.031‡
Combination statin and fibrates	3 (4.3)	7 (9.1)	0.257
Fibrates only	17 (24.6)	10 (13.0)	0.070

‡Chi-square for categorical variables shows statistically significant difference between the two groups, p value < 0.05.

Table 40. The usage rates of lipid lowering therapies at last visit among patients with LDL-C at baseline of 100 mg/dL or higher

Usage of lipid lowering agents	Control (%)	Intervention (%)	p value **between group**
Statin only	22(31.9)	46(59.7)	0.001‡
Combination statin and fibrates	11 (15.9)	9(11.7)	0.455
Fibrates only	18(26.1)	6(7.8)	0.003‡

‡chi-square for categorical variables shows statistically significant difference between the two groups, p value < 0.05.

Table 41. Difference in number of patients receiving lipid lowering therapies between baseline and last visit among patients with LDL-C at baseline of 100 mg/dL or higher

Usage of lipid lowering agents	Number (% of changes)	
	Control	Intervention
Statin only	5 (29.4)	14 (43.8)
Combination statin and fibrates	8 (267)	2 (28.6)
Fibrates only	1 (5.9)	-4 (40.0)

The intensity of statin therapy among subgroup of patients with baseline LDL-C of 100 mg/dL or higher is presented in Table 42, 43. At baseline, the simvastatin equivalent dose was significantly higher in the intervention than control groups (9.6±13.2 vs 6.4±12.6 mg; p = 0.014). There were significant increases in the intensity of statin therapy in both groups since simvastatin equivalent doses at last visit were significantly higher than baseline in both groups. At last visit, patients in the intervention group received higher dose of statin than patients in the control group (14.0±15.2 vs 10.0±15.2 mg; p = 0.010). No significant difference was noted on the mean increase in simvastatin equivalent dose between the two groups. Median simvastatin equivalent dose at baseline and last visit were 20 mg in both groups.

Table 42. Simvastatin equivalent dose and mean changes of simvastatin equivalent dose from baseline to last visit among patients with baseline LDL-C of 100 mg/dL or higher

Simvastatin equivalent dose	Baseline	Last visit	P value **within group**	Mean Changes (mg)	P value **of mean Changes**
Control	6.4±12.6	10.0±15.2	0.007§	3.7±11.2	0.429
Intervention	9.6±13.2	14.0±15.2	<0.001§	4.4±8.7	

§Statistic significance difference within each group (Wilcoxon sign rank test; p value < 0.05)

Table 43. Simvastatin equivalent dose at baseline and last visit among patients with baseline LDL-C of 100 mg/dL or higher

Simvastatin equivalent dose	Baseline	Last visit
Control	6.4±12.6	10.0±15.2
Intervention	9.6±13.2	14.0±15.2
p value **between group**	0.014‖	0.010‖

‖Statistic significance difference between group (Mann-Whitney U test; p value < 0.05)

3. Pharmacist interventions

In addition to patient education and counseling, pharmacists made 120 interventions to participating physicians with the objectives of promoting the achievement of lipid goals and monitoring of drug therapy (Table 44). Among these interventions, 39, 21 and 60 interventions were provided to initiate statin therapy, increase the dose of existing statin therapy and monitoring of lipid profile, respectively. Physicians accepted 33.3%, 38.1% and 53.3% of pharmacists' interventions, respectively.

Table 44. Number of patients received pharmacist interventions and acceptation from physicians among patients with LDL-C at baseline of 100 mg/dL or higher

Types of Intervention	Intervention Made	Acceptance (%)
Statin Interventions		
Initiation of treatment	39	13 (33.3)
Dosage increase	21	8 (38.1)
Lipid profile monitoring	60	32 (53.3)

CHAPTER V
DISCUSSION

This prospective, non-randomized, controlled study was conducted to determine the impact of physician-pharmacist collaboration on lipid management in type 2 diabetic patients compared with usual care. This study was a part of the Diabetic Care Clinic project initiated by the Bangkok Metropolitan Administration General Hospital.

Previous studies have shown that failure to achieve lipid goals especially LDL-C in diabetic patients are common, despite a large amount of evidence confirming morbidity and mortality benefits of obtaining such lipid goals (51-52, 63). Studies have shown that multidisciplinary approach with a focus on diabetes management has led to superior outcomes compared to usual care. A number of reports confirm benefits of pharmacist involvement in dyslipidemia management in general dyslipidemia population (22, 26, 54, 56-57, 59-60, 62). However, only a few reports are available for dyslipidemia in diabetic population (24, 67). Studies with some similarities with our study are studies by Cioffi et al and the subgroup analysis of the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP) which were discussed previously in the literature evaluation section. Most of these reports were originated from the United States where clinical pharmacy has been well-established for decades. Due to differences in the healthcare system and culture, it is not known whether such results will be reproducible in other regions of the world. Our study was therefore an excellent addition to the growing literature evaluating the impact of pharmacist involvement on patient outcomes, especially in the developing world.

In this study, we enrolled type 2 diabetic patients at a 450-bed hospital into the control and intervention groups. Patients in the control group received usual care from physicians while patients in the intervention group received care from physicians and clinical pharmacists. This study design was chosen to limit bias and allow comparison on the size of benefit between intervention and usual care groups.

We included only type 2 diabetic patients due to its high prevalence in the hospital compared to type 1 diabetes, a trend that is consistent with the epidemiology of diabetes in Thailand. Patients with government's universal coverage (30 baht) health plan were not included into the study since those patients were cared for by physicians outside of the Internal Medicine Department. Our study aimed to detect a 50% increase in the LDL-C achievement rate compare to the control group. From sample size calculation, we needed 168 patients in each group to detect such difference. We recruited more than 300 patients but only 208 patients had completed data on lipid profile for at least 2 visits. We could not reach target number of patients because we did not have the authority to order lipid tests. This depended on the physician's judgment. So many patients obtained only one lipid test during the 6 - month study period. Patients with incomplete lipid data were therefore excluded from our study. Second, many patients failed to present to clinic on the appointment dates. Many of these patients therefore had visited other physicians that were not participated with the DCC clinic as make-up visits. We therefore excluded these patients from our study due to mix-in effect. Finally, we had recruited only 100 and 108 patients in control and intervention groups. The subspecialties of physicians in both groups were quite similar which may help reduced the bias for certain subspecialties.

For pharmacist interventions, pharmacists provided individualized advice and education on disease complications and managements. Lifestyle modification with exercise and diet control was discussed with each patient. Educational brochures available at the hospital were used as a tool for diet education (Appendix D). Patients were encouraged to exercise at least 3 times per week. Pharmacists made inquiry regarding adverse effects of statin such as myalgia in each visit through patient interview. However, we did not see any adverse effect of statin in our patients. On average, each patient met with clinical pharmacist for 3.09 ± 1.1 visits. More than 50% of patients had more than 2 pharmacist visits. Follow-up period in the intervention group was relatively short (4.0 months). This was a result of loss to follow-up and failure of appointment system because many patients did not present to clinic at their appointment dates. Third, pharmacists were not able to meet with all patients when a large number of patients presented to clinic at the same time due to our human resource limitation.

Despite the non-randomized nature of our study, baseline characteristics of the control and intervention groups were almost identical on every aspect. Our overall study population were elderly (mean age of more than 60 years old). Approximately two thirds were female. Traditional risk factors especially hypertension was common. Glucose control based on mean fasting blood glucose was still above the target goal of 130 mg/dL recommended by the latest ADA guideline (3). End organ damage was found in about 20% of patients. We were unable to quantify the presence of metabolic syndrome in our study due to lack of information required for determination of such condition in the control group. Nevertheless, our patients had at least 3 risk factors for cardiovascular diseases including diabetes, hypertension and age. Thus, our patient population was considered as having a moderate to high risk of cardiovascular complications. Based on this information, the benefit of achieving lipid goals in this population may provide a substantial benefit of cardiac risk reduction.

Systolic and diastolic blood pressure were not significantly reduced during the evaluation period. Blood pressure reductions in diabetic patients are important since intensive blood pressure control in UKPDS significantly reduced the risks of virtually all cardiovascular and microvascular endpoints, with risk reduction ranging from 24% to 56% (68). Baseline lipid parameters in our population were consistent with “diabetic dyslipidemia” which includes borderline LDL-C and high TG levels with the exception of HDL-C. HDL-C level in our study was not as low as those commonly seen with diabetic patients. Higher proportion of female patients may partly explain higher HDL-C seen in our study. The achievement rates of lipid goals at baseline in our study were similar to previous reports with only 30% of patients were in LDL-C < 100 mg/dL category (19, 51).

At last visit, LDL-C in the intervention group was significantly lower than that of the control group. Reduction of TC, TG and non-HDL-C were twice greater than those of the control group. In addition, approximately 40% of patients in the intervention group reached the LDL-C target of less than 100 mg/dL compared to only 25% in the control group. Overall, favorable changes in lipid parameters were significantly higher in the intervention group. Comparing to previous reports, the extent of such benefits seen in our study was less than that of studies where pharmacists had pre-approved prescribing authority to initiate drug therapy. Several

reasons may explain the discrepancies between our report and others. Firstly, since clinical pharmacists in our study were not granted pre-approved prescribing authority, the decision to initiate or modify treatment was exclusively made by participating physicians. Sixty recommendations were made by clinical pharmacists to initiate statin therapy or increase the intensity of statin therapy. However, only 21 recommendations were accepted. Among patients whose statin therapy were initiated based on pharmacist's recommendation, all of them achieved LDL-C of less than 100 mg/dL. With higher acceptance rate of pharmacist intervention, the observed benefit may become larger. Secondly, our patient population had lower rate of end organ damage. Thus, the majority of treatment provided was considered as primary prevention. Physician's attitude on the aggressiveness of treatment in primary prevention setting may be less than that of secondary prevention setting. Thirdly, the follow-up time in our study was shorter than other reports. With low acceptance rate of recommendations to intensify drug therapy, one can speculate that favorable changes of lipid parameters in our study may partly come from lifestyle modification. Since diet and exercise generally may not produce rapid LDL-C reduction as seen with statin therapy, the benefit of our intervention may not be fully observed with short follow-up time. With longer follow-up period, larger differences may be noted.

In the subgroup analysis of patients with LDL-C at baseline of 100 mg/dL or higher, much larger favorable changes in lipid parameters in the intervention group were observed with the exception of HDL-C. The rate of LDL-C achievement was also higher in the intervention group. However, such difference did not reach statistical significance probably due to small sample size. However, there were significantly less patients with LDL-C of 130 mg/dL or higher in the intervention group. This suggested a shift in the LDL-C of the population closer to the target.

Comparing to similar studies by Cioffi and the diabetes subgroup analysis of the SCRIP study (Table 45), several similarities and key differences exist among studies. All studies were prospective in nature. Cioffi's and our study were conducted exclusively in diabetic patients whereas SCRIP was conducted in dyslipidemia patients with a sizable diabetes subgroup. For study design, SCRIP was the only study with randomization. While both SCRIP and our study were controlled trials, Cioffi's study lacked a control group.

The SCRIP, Cioffi's study and our study had different primary and secondary outcomes which may have significant impact on the findings of these studies. For SCRIP, the primary endpoints include composite measure of a fasting lipid profile by the primary care physician or the addition or increase in dosage of cholesterol-lowering medication. Secondary end points included the individual component of the primary end points as well as patient's satisfaction and health status. For Cioffi's study, the primary outcome of the study was changes in hemoglobin A_{1C} while secondary outcome included changes in weight, lipid parameters, blood pressure and level of microalbuminuria. For our study, the primary outcome was the achievement of lipid goals while the secondary outcomes included changes in lipid parameters, usage rates of lipid lowering agents, types of pharmacist's intervention and the acceptance rate of pharmacist's interventions. Thus, our study focused mainly on lipid management compared to other studies.

Pharmacist's interventions among these studies also varied significantly. For SCRIP, pharmacist's interventions included patient interview, measuring blood pressure and total cholesterol (commercial fingerstick test) and education on heart disease risk factors. For potential patients, pharmacists communicated their recommendations including recommendations to initiate and/or modify lipid lowering therapies to physicians by fax. Follow-up of these interventions was performed by phone. In Cioffi's study, pharmacist's intervention encompassed patient education and counseling. Interventions related to drug therapy were focused only on initiation or modification of antidiabetic agents through limited prescribing authority while no specific interventions were performed on lipid lowering therapies. Based on this information, our study shares similarity with SCRIP since intervention in both studies were focused mainly on lipid lowering therapies.

Although patients enrolled in these studies were all elderly diabetes patients with a mean age of above 60 years old, several differences in the patient population among 3 studies were noted. Patient enrollment in the SCRIP study was performed in the community pharmacy setting while Cioffi's study and our study were conducted exclusively in the hospital-based setting. Comparing patient's baseline demographics, patients in the Cioffi's study were predominantly male with less than 3% of female patients. However, female patients were a significant group of patients in the SCRIP

(43%) and our study (65%). The investigators were unable to compare the presence of co-morbidities since such information were not reported in Cioffi's and the SCRIP studies. Baseline lipid parameters among these studies varied significantly and may help explain different findings reported from these studies. Total cholesterol levels reported in these 3 studies were quite similar (195.9±37.9, 186.4±31.0 and 199.8±44.0 mg/dL in the SCRIP, Cioffi's study and our study, respectively). However, baseline LDL-C level in Cioffi's study was only 105±31.0 mg/dL which was very close to the target LDL-C of less than 100 mg/dL. On the contrary, baseline LDL-C in our study was 122.6±40 mg/dL while those of SCRIP were not reported.

For changes in lipid parameters, LDL-C, TC, TG levels in the Cioffi's study were reduced by 12.5%, 11% and 22.8%. For SCRIP, TC was reduced by 4.5%. In our study, LDL-C, TC, TG levels were reduced by 2.4%, 7.7%, 13.3% and 13.7%, 13.2%, 16.4% in the overall population and subgroup of patients with baseline LDL-C of 100 mg/dL or higher, respectively. Overall, changes in lipid parameters were quite similar between Cioffi's study and our study. For SCRIP, only TC was reported and the reduction of TC was very small.

Since there were multiple interventions in our study, it is difficult to identify the size of benefit of each intervention. However, interventions aiming to initiate statin therapy and increase the intensity of existing therapy deserve several comments. At the beginning of the study, we performed literature search and developed a guideline to make recommendation on when to start statin therapy. However, the acceptance rate of pharmacist's interventions to initiate or modify statin therapy was only 30%. Despite such limitation, however, there was a significant increase in patients receiving statin therapy in the intervention group compared to the control group. In addition, among patients receiving statin therapy, the intensity of treatment was significantly higher in the intervention group. Therefore, we believed that part of the benefits on lipid parameters seen in our study was a result of increasing rate and higher intensity of statin therapy.

Table 45. Comparison to others studies

	Cioffi study (63)	Our study	SCRIP study (23, 24)
Place	Hospital based	Hospital based	Community Pharmacy
Control	Yes	No	No
Type of study -Randomized -Prospective	 No Yes	 No Yes	 Yes Yes
Number of patients	70	208	396
Follow-up time (months)	9-12	4	4
Prescribing authority	No (Only antidiabetic drugs according to the protocol)	No	No
Inclusion criteria	Type 2 diabetes with A1C > 7%	Type 2 diabetes	Diabetes with at least 1 cardiovascular risk factor
Primary endpoint	A1C	Achievement rate of LDL-C	Improvement in cholesterol management i.e., lipid monitoring, initiation and modification of treatment
Secondary endpoint -Lipid changes	 Yes	 Yes	 No

Table 45. Comparison to others studies (continued)

	Cioffi study (63)	Our study	SCRIP study (23, 24)
Secondary endpoint			
-Usage rate of lipid-lowering agents	No	Yes	Yes
-Increase dose of lipid-lowering agents	No	Yes	Yes
-Others	-Body weight -Changes in blood pressure -Level of microalbuminuria	-Type of pharmacist intervention and acceptance	-Humanistic impact of pharmacist intervention
Pharmacist intervention	-Education and Counseling	-Education about diabetes disease, complication, goals of treatment and Counseling -Recommend the physician for starting lipid-lowering drug or increase dose through the pharmacist's note	-Interview and educate patients on cardiovascular risk factors -Measure blood pressure and total cholesterol by commercial fingerstick test -Faxing a form of pharmacist conclusion to the physician and follow 5 visits

Table 45. Comparison to others studies (continued)

	Cioffi study (63)	Our study	SCRIP study (23, 24)
Baseline lipid profile (mg/dL)			
-LDL-C	105.1±31.0	122.6±40.0	-
-TC	186.4±39.1	199.8±44.4	195.9±40.2
-TG	199.5±136.3	198.6±84.3	-
-HDL-C	41.6±11.8	56.8±12.9	-
-Non-HDL-C	-	142.7±43.0	-
Lipid changes (%)			
-LDL-C	12.5	2.4	-
-TC	11.0	7.7	4.5
-TG	22.8	13.3	-
Achievement rate of lipid parameters (%)			
-LDL < 100 mg/dL	-	39.8	-
-TC < 200 mg/dL		78.7	
-TG < 150 mg/dL		53.7	
-HDL-C > 40 mg/dL		96.3	
-Non-HDL-C < 130 mg/dL		66.7	

There were several limitations in our study. Firstly, the non-randomized nature of our study may introduce selection bias into the study. However, with almost identical baseline demographic data between two groups, we expected such bias to be at minimal level. Secondly, the follow-up time in our study was relatively short. There were only about half of patients with 2 or more of lipid values after the baseline visit. Favorable changes of lipid parameters in our study may partly come from lifestyle modification. Such interventions may require longer follow-up time for the benefit to be fully observed. Physician's reasons for rejecting pharmacists' recommendations were mostly unknown. With this information, we may be able to improve our

interventions accordingly to increase the acceptance rates. Lastly, we did not assess patient's satisfaction. The patient's response may provide us with valuable information on how patients perceived such services. Further studies that address these issues are needed to determine the long-term benefit from physician-pharmacist collaboration.

In summary, the results from this study along with previous reports suggested that physician-pharmacist collaboration can significantly improve the quality of care in diabetes patients. The model of collaboration in our study may be more applicable and feasible to be used in Thailand than models from other countries. Therefore, our model may serve as a prototype of other institution to follow.

CHAPTER VI
CONCLUSION

Despite a large number of evidence confirming benefits of lipid goals achievement, a large proportion of diabetic patients are not at these lipid goals. Studies, mostly from Western countries, suggest that multidisciplinary approach help improve the quality of care in diabetic patients including lipid management. The results of this study showed that physician-pharmacist collaboration was effective in the improvement of dyslipidemia management in diabetic patients compared to usual care. At the end of study, significantly more patients in the intervention group achieved the LDL-C goal of less than 100 mg/dL. In addition, favorable changes in most lipid parameters were observed at a greater extent in the intervention group than the control group. Overall, clinical pharmacists made 120 interventions regarding modification of lipid lowering therapy and monitoring of treatment, 53 of these were accepted by physicians.

In conclusion, physician-pharmacist collaboration can effectively increase the achievement rate of LDL-C target and favorably affect all lipid parameters in diabetic patients compared with usual care.

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APPENDIX

APPENDIX A

Statins Indication

The patient has the following conditions:	Yes	No
Coronary Artery disease such as CAD IHD, PVD	Yes	No
History of PCI, CABG	Yes	No
Stroke	Yes	No
LDL-C > 100 mg/dl after lifestyle Modification for 6 months	Yes	No

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Contraindication

The patient has at least 1 following Contraindication	Yes	No
History to myopathy form statins	Yes	No
Chronic hepatitis disease	Yes	No
Hepatitis B or C infection	Yes	No
Liver enzyme such as SGPT/SGOT More than 3 times of upper limit	Yes	No

APPENDIX B

โครงการ “ใส่ใจเพื่อนเบาหวาน”

Pharmacist Note

วันที่……

Consult.....
Objective.....
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.....
Assessment/Plan.....
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APPENDIX C

PATIENT'S PROFILE

Patient No……
Date.....

Patient Profile

Name.....Birth date.....Age.....
Sex ○ male ○ Female
HN…….. Weight.....kg. Height .....cm. IBW =..… Kg
BP ……mmHg
Doctor.....
Chief compliant.....
……..
Allergy
.....
.....

Past medical history
.....
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.....
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Present illness
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.....
.....
.....

Address.....
.....
.....
Phone.....
Contact.....

Name _____HN:_____ Code_____

Indicators for prevention and treatment of diabetes complications.

1. Blood pressure

200										
190										
180										
170										
160										
150										
140										
130										
120										
110										
100										
90										
80										
70										
60										
50										
date										
Value										

2. A1C

10										
9										
8										
7										
6										
5										
4										
Date										
Value										

Name _____HN:_____ Code _____

3. Fasting Blood Sugar (FBS)

220										
200										
180										
160										
140										
120										
100										
80										
60										
40										
Date										
Value										

4. Low density lipoprotein (LDL)

190										
180										
170										
160										
150										
140										
130										
120										
110										
100										
90										
80										
Date										
Value										

Name _____HN:_____ Code _____

5. Eye Examination

Date	Result

6. Microalbuminuria test

Date	Albumin/Creatinine ratio	Serum Creatinine (mg/dL)	CrCl mL/min

Patient No……
Name.....

Visit Date &/F/U	Data	LAB	MEDICATIONS
	Wt……kg. Ht..…...cm. BP…….. P…… …….. …… …… …… …… …… …… …… ……	FBS ……...mg/dL A1C ……mg % SCr …… mg/dl CrCl ……ml/min Hb……...mg/dL Hct……g/dL SGOT/PT ……... Lipid profile	…….. .... …… …..... ....
	Wt……kg. Ht..…...cm. BP…….. P…… …….. …… …… …… …… …… …… …… ……	FBS ……...mg/dL A1C …….. mg % SCr …… mg/dL CrCl ……ml/min Hb……...mg/dL Hct……g/dL SGOT/PT ……... Lipid profile	…….. .... …… …..... ....

Problems:

1. ……..
2. ……..
3. ……..
4. ……..
5. ……

Problem.....

Subjective:

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Objective:

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Assessment:

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Plan:

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Problem.....

Subjective:

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Objective:

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Assessment:

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Plan

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APPENDIX D

แผ่นพับแจกผู้ป่วย

อาหารเพื่อสุขภาพผู้เป็นเบาหวาน

อาหารเพื่อสุขภาพ
ของผู้เป็นเบาหวาน

อาหาร คือ ยาบำบัดรักษาสุขภาพ การควบคุม
อาหาร คือ การเรียนรู้ประเภทอาหารและ
กำหนดมื้ออาหารให้เหมาะสมต่อสุขภาพ

การเลือกประเภทอาหาร

1. อาหารที่ควรหลีกเลี่ยง

1.1

1.2

1.3

1.4

1.5


1.6
1.7
1.8
1.9
1.10
2. อาหารที่รับประทานได้
แต่จำกัดจำนวน
2.1 ประเภทน้ำนม
2.2 ผลไม้
2.3 อาหารจาก ข้าว แป้ง น้ำตาล
ข้าว
แป้ง
2.4 ไข่
2.5 ไขมัน
ปากกาฉีดอินสุลิน
โนโวเพน 3

2.6 น้ำตาล

2.7 เกลือ

2.8 อาหารสำเร็จรูป

3. อาหารที่รับประทานได้ ไม่จำกัดปริมาณ

1. ผักใบเขียวเกือบทุกชนิด และผักใบยาว

1.1 ผักกาด

1.2 ผักใบเขียว

1.3 ผักชนิดหัว

2. ผักลักษณะเป็นผล, ถั่ว

2.1 ผักตระกูลถั่ว

2.2 ผักชนิดดอก - หัว


2.3 ผักชนิดผล
2.4 ผักชนิดใบ
3. เครื่องเทศเพิ่มรสชาติอาหารต่างๆ
สมัครสมาชิก โนโวเพ็น คลับ
ปรึกษาปัญหาเบาหวาน
โทร. 0-2266-6043-5
อาหาร
เพื่อสุขภาพ
ผู้เป็นเบาหวาน
โดย มิสเตอร์ โนโวเพ็น

BIOGRAPHY

NAME Miss Ratreerat Tangjaideeborisut

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