DYSLIPIDEMIA CONTROL AND ADVERSE DRUG REACTIONS OF STATINS AMONG PATIENTS AT CARDIAC CLINIC OF PENANG HOSPITAL, MALAYSIA

By

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Thesis submitted in fulfillment of the
requirements for the degree of
Master of Science

June 2009

بسم الله الرحمن الرحيم
وقل اعملوا فسيرى الله عملكم ورسوله والمؤمنون
وستردون الى عالم الغيب والشهادة فينبئكم
بما كنتم تعملون
صدق الله العظيم

سورة التوبة اية ١٠٥

DEDICATION

This work is dedicated to my father (if was dead or alive), my mother, my brothers Atheer and Naseer. To my lovely nieces Sara and Aya. To all my faith friends.

Thanks for love, inspiration and doa.

ACKNOWLEDGEMENTS

First I would like to thank ALLAH for helping me in completing my study and for giving life and everything in my life.

Thanks to my supervisors Assoc.Prof. Dr. Noorizan Abdul Aziz and Prof. Dr. Yahaya Hassan for their support throughout my study and hope the best wishes in their life. Thanks to my field supervisor Dato Dr.Omar Ismail and all physicians, all nurses in cardiac clinic and thanks to all patients who particiapted in this study. Also thanks to Dr. Jamilah Baharom and the staffs in pathology laboratory. Thanks to the Director of Penang Hospital.

Thanks to Dr. Nurulain Abdullah Bayanuddin for her support. Thanks to Dr. Nooraini Ahmad from the School of Mathematic Science for her statistic advises. Thanks to my faith friend Muath and all pharmacy students in USM. Thanks for Iraq that gave me chance to get the pharmacy education and thanks to Malaysia to allow for the study in higher degree.

Thanks to all who supported me in my research.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reactions
&	and
ABN	abnormal
ACE-I	Angiotensin-Converting Enzyme Inhibitors Type I
ALT	Alanin Transaminase
ARB	Angiotensin receptor blocker
AST	Aspartate Transaminase
B-BK	Beta Blockers
BID	Twice Daily
Ca Ch Bk	Calcium Channel Blockers
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Diseases
CADRMP	Canadian Adverse Reaction Monitoring Program
CHD	Coronary Heart Diseases
CI	Confidence Interval
CK	Creatinine Kinase
COAD	Coronary Obstructive Artery Disease
CRCL	Creatinine Clearance
CVS	Cardiovascular Diseases
dl	Deciliter
DM	Diabetes Mellitus
e.g.	example
FDA	Food And Drug Administration
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HMGCoA	Hydroxymethyl Glutaryl-Coenzyme A
Hypothyr.	Hypothyroidism
i.e	it est.

IHD	Ischemic Heart Disease
IL	Interleukin
LDL	Low Density Lipoprotein
mg	Milligram
MI	Myocardial Infarction
ml	Milliliter
mmol	Millimole
mo.	month
NCEP	National Cholesterol Education Program
no.	number
PVD	Peripheral Vascular Disease
QD	Once Daily
SD	Standard Deviation
SPSS	Statistical Package For Social Sciences Software
SREBPs	Sterol Regulatory Element Binding Proteins
TC	Total Cholesterol
TG	Triglyceride
TNF	Tumor Necrosis Factor
UK	United Kingdom
ULN	Upper Limit Normal
US	United State
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization
yr.	year

Kawalan Dislipidemia dan Tindakbalas Mudarat Drug Statin di Kalangan Pesakit di Klinik Jantung Hospital Pulau Pinang, Malaysia

ABSTRAK

Ramai pesakit di Malaysia menggunakan statin untuk pencegahan masalah kardiovaskular dan kematian. Walau bagaimanapun, data tempatan tentang keberkesanan dan keselamatan terapi statin adalah sangat kurang. Oleh itu, objektif kajian ini adalah untuk menilai kawalan dislipidemia dan kesan mudarat drug (ADR) statin ke atas pesakit Malaysia. Kajian ini telah dijalankan di Klinik Kardiak, Hospital Pulau Pinang, Malaysia. Penilaian kawalan dislipidemia adalah berdasarkan kepada cadangan oleh National Cholesterol Education Program (NCEP), USA. Kesan mudarat drug minor adalah berasaskan persepsi pesakit terhadap kesan tidak diingin yang dialami semasa terapi statin. Manakala, ADR serius adalah berdasarkan kepada maklumat makmal (enzim hati, ujian fungsi ginjal dan nilai “creatinine kinase”). Program statistik SPSS versi 12, dengan ANOVA, Chi Kuasa Dua, Ujian Ketepatan Fisher, Ujian t Bebas dan Ujian Pasangan t telah digunakan mengikut kesesuaian dengan nilai $p<0.05$ adalah signifikan. Terdapat 500 pesakit terlibat, lebih separuh daripada mereka adalah lelaki (70%). Kebanyakan pesakit ini adalah berbangsa Cina (37.6%), diikuti oleh bangsa Melayu (34.4%), bangsa India (26.6%) dan lain-lain (1.4%). Purata umur mereka adalah 59.8 ± 10.3 tahun (28-91 tahun). Penilaian kawalan dislipidemia menunjukkan 44% dan 41% pesakit-pesakit ini masing-masing mempunyai LDL dan selain-LDL yang terkawal. Penurunan dislipidemia daripada setiap lawatan susulan ke klinik dibandingkan dengan lawatan pertama adalah berbeza, bergantung kepada jenis-jenis lemak (LDL, selain-HDL, TG, TC, dan HDL). Purata penurunan dislipidemia dibahagikan jumlah lawatan bagi LDL adalah 26 ± 2%, selain-HDL, 22.15 ± 2%, TC, 17.7 ± 1.2 %, dan TG, 27.25 ± 2.65%. Purata peningkatan untuk HDL dibahagikan dengan jumlah lawatan adalah 10.58 ± 7.33 %. Simptom ADR minor yang paling sering (59.4 %) dan teruk adalah kelesuan. Insiden risiko hepatoksisiti (>1.5 “upper limit normal”) masing-masing adalah 3.25% dan 3.82% berdasarkan kepada enzim hati, ALT dan AST. Risiko toksisiti otot (>1.5 “upper limit normal”) adalah 3.2%. Peratus pengurangan fungsi renal (CRCL) sebanyak 25% adalah 3%, sementara peratus pengurangan CRCL sebanyak 50% adalah 0.65%. Setengah faktor-faktor penyumbang seperti bangsa, jantina, jenis dislipidemia, ketagihan alkohol, jenis statin yang digunakan, dos, kombinasi terapi antilemak, tempoh masa terapi statin (lebih dari 5 tahun) dan ubat-ubat lain yang diambil bersama menyumbang didalam pengawalan dislipidemia dan ADR. Kesimpulannya didapati kurang separuh daripada pesakit-pesakit yang terkawal dislipidemianya dalam kajian ini. Lebih sedikit separuh daripada mereka mengalami ADR minor, manakala hanya peratusan yang kecil sahaja yang mengalami ADR serius. Dos rendah lovastatin (20mg) didapati mencukupi untuk mengawal dislipidemia dalam kebanyakkan pesakit. Dos rendah dan tempoh masa terapi statin kurang dari 5 tahun di dapati mengurangkan risiko ADR.

Dyslipidemia Control and Adverse Drug Reactions of Statins Among Patients at Cardiac Clinic of Penang Hospital, Malaysia

ABSTRACT

Many Malaysian patients use statin for prevention from cardiovascular problems and mortality. However, local data on the effectiveness and safety of statin therapy are very scanty. Thus, the objective of this study is to assess the dyslipidemia control and adverse drug reactions (ADRs) of statins for Malaysian patients. The study was carried out at Cardiac Clinic, Penang Hospital, Malaysia. The assessment of the dyslipidemia control was based on National Cholesterol Education Program (NCEP), USA recommendations. Minor ADRs, were based on the patients' perceptions on undesired effects that they had during statin therapy. While serious ADRs were based on laboratory information (liver enzymes, renal function test, and creatinine kinase values). Statistical program SPSS version 12, with ANOVA, Chi Square, Fisher Exact Test, Independent t Test and Paired t Test were used when appropriate with p value <0.05 as significant. There were 500 patients involved, more than half of them were male (70%). Many of these patients were Chinese (37.6%) followed by Malay (34.4%), Indian (26.6%) and others (1.4%). Their mean age was 59.8 ± 10.3 years (28-91years). Dyslipidemia control assessment showed 44% and 41% of these patients had their LDL and non-HDL under control, respectively. Lipids reduction from each clinic visit compared to the first visit were varied depending on the types of lipids (LDL, non-HDL, TG, TC and HDL). The mean lipid reduction per total visits were LDL 26 ± 2%, non-HDL, 22.15 ± 2%, TC, 17.7 ± 1.2%, and TG, 27.25 ± 2.65%, respectively. The mean increment for HDL divided by total visits was 10.58 ± 7.33%. The most common (59.4%) and severe symptom of minor ADRs was fatigue. The incidence risk of hepatotoxicity (>1.5 upper limit normal) were 3.25%

and 3.82% based on liver enzymes, ALT and AST, respectively. The risk of muscle toxicity (>1.5 upper limit normal) was 3.2%. The percentage of reduction in renal function (CRCL) by 25% was 3%, while the percentage of reduction by 50% was 0.65%. Some of the contributing factors such as race, gender, type of dyslipidemia, alcohol consumption, type of statins used, dose, combination of antidyslipidemic therapy, duration of statin use (more than 5 years) and concurrent medications used contributed towards dyslipidemia control and ADRs. In conclusion, it was found less than half of the patients in this study had dyslipidemia under control. Slightly more than half (59.4%) had minor ADRs, while only a small percentage developed serious ADRs. Low dose of lovastatin (20mg) was found sufficient to achieve dyslipidemia control in the majority of these patients. Low dose and duration of statin therapy of less than 5 years decreased the risk of ADRs.

CHAPTER 1

INTRODUCTION

1. Background

1.1 Dyslipidemia

Dyslipidemia is defined as an abnormality in one or more type of lipids in the blood (NCEP, 2001), Dyslipidemia is a strong predictor and pathogenic factor for cardiovascular diseases (CVD) and contributes to the development of coronary graft atherosclerosis occlusion (Campeau et al, 1984). There is a real relationship between lowering the blood cholesterol level and the incidence of CVD. For example, if the cholesterol level is decreased by 1% then the incidence of CVD decreases by 1%, and, over a five-year period, there is an approximate reduction in CVD of 30%. (Neaton et al, 1992; Grundy et al, 2004; 4S study, 1994).

1.2 Types and etiology of dyslipidemia

There are two types of dyslipidemia, primary and secondary dyslipidemia. The type of dyslipidemia depends on the etiology and the diseases that lead to the increase in the lipid level.

1.2.1 Primary dyslipidemia

Primary dyslipidemia is typically due to either a single or multiple genetic alterations that may lead to either overproduction or a defective mechanism in the clearance of cholesterol, triglycerides (TG), very low density lipoprotein (VLDL), low-density lipoprotein (LDL) or an excess clearance of high-density lipoprotein (HDL). According to the Fredrickson classification, primary dyslipidemia can be subdivided into different types depending on the level of elevation of lipids and lipoproteins (Friedewald et al, 1972; American Diabetes Association, 2006; NCEP, 2001), as shown in Table 1.1.

Table 1.1 Types and properties of primary dyslipidemia (Friedewald et al, 1972)

Type	Elevated lipoproteins	Elevated lipids
I Primary hyperlipoproteinemia or Familial hyperchylomicronemia	Chylomicron	TGs
IIa Polygenic hypercholesterolemia or Familial hypercholesterolemia	LDL	Cholesterol
IIb Combined hyperlipidemia	LDL and VLDL	TGs and cholesterol
III Familial dysbetalipoproteinemia	VLDL (VLDL:TG ratio > 0.3) and Chylomicron	TGs and cholesterol
IV Endogenous hyperlipidemia	VLDL	TGs
V Familial hypertriglyceridemia	Chylomicron and VLDL	TGs and cholesterol

TG= Triglyceride, HDL=High density lipoprotein, LDL=low density lipoprotein, VLDL= very low density lipoprotein

1.2.2 Secondary dyslipidemia

Secondary dyslipidemia may occur at an advanced age, especially when an elevation in lipids levels is initiated and accompanied by several diseases, including diabetes, hypothyroidism, hepatic diseases, renal insufficiency, pregnancy and systemic lupus or chronic usage of drugs (such as estrogen, thiazide, beta blockers and others) and alcohol use. These above-mentioned contributing factors may be more prevalent in developed countries because of their different lifestyle (NCEP, 2001; Stone et al, 2008), as shown in Table 1.2.

Table 1.2 Types and properties of secondary dyslipidemia (Stone et al, 2008)

Disorder		Cholesterol	TG	HDL	LDL	VLDL	Chylomicron	Other tests
Renal failure		Unchanged	Increased	Decreased	Unchanged	Increased	Unchanged	SCr
Nephrotic syndrome		Increased	Unchanged	Unchanged	Increased	Unchanged	Unchanged	
Hypothyroidism		Increased	Increased	Unchanged	Increased	Unchanged	Increased	TSH
Type 2 diabetes		Increased	Increased	Decreased	Increased	Increased	Increased	Glucose
Obstructive liver disease		Increased	Unchanged	Unchanged	Increased	Unchanged	Unchanged	Liver function
Ethanol use		Unchanged	Increased	Unchanged	Unchanged	Increased	Unchanged	
Pregnancy		Increased	Increased*	Unchanged	Increased	Increased	Unchanged	
Systemic lupus		Unchanged	Increased	Unchanged	Unchanged	Unchanged	Increased	
Drug use	Diuretic	Increased	Unchanged	Unchanged	Increased	Unchanged	Unchanged	
	B-BK	Unchanged	Increased	Decreased	Unchanged	Increased	Unchanged	
	Estrogen	Unchanged	Increased	Unchanged	Unchanged	Increased	Unchanged	
	Cyclosporin	Increased	Unchanged	Unchanged	Increased	Unchanged	Unchanged	

* increased only in third trimester, SCr = Serium creatinine, TSH = Thyroid stimulating hormon

1.3. Dyslipidemia therapy targets

All the adult treatment panel (ATP) reports from the National Cholesterol Education Program (NCEP) in US found a strong relationship between the LDL levels and coronary artery diseases, myocardial infarction (MI), strokes, and other CVDs. LDL is considered to be the major risk factor among the different types of lipids. Another target is non-HDL, which represents all the types of lipoproteins except for HDL (NCEP, 2001; Ballantyne et al, 2001). Both HDL and TG have a significant relationship with cardiovascular diseases; in which a 1% decrease in the level of HDL correlates with a 2-3% increase in the risk of cardiovascular diseases (Gordon et al, 1989; American Diabetes Association, 2002). Thus, it is possible to consider both HDL and TG as independent risk factors (Austin et al, 1998; Assmann et al, 1998; Gordon et al, 1989) and lipid level monitoring that is based on both factors is necessary to give satisfactory results. The HDL level is not the ideal goal for therapy, since some studies have proven that when the LDL level is lower, there is a significantly decrease in the incidence of cardiovascular attacks despite a low HDL level (HPS, 2002; Downs et al, 1998). The HDL value may also be affected by some drugs. Nicotinic acid and fibrates may increase the HDL level in some patients, but not in all patients, since some patients experience a rise in the level as an adverse reaction to these drugs (Grundy et al, 2004). Interestingly, the TG value is easily influenced by laboratory variability, smoking and alcohol. Therefore, to avoid an incorrect assessment of atherogenicity, the patient must fast for 24 hours so that the TG atherogenicity will only be present in the TG-rich lipoproteins, especially in cases of hypertriglyceridemia (3rd Clinical Practice Guideline on management of dyslipidemia, Malaysia, 2003)

It is easy to identify dyslipidemia by determining the lipid profile and the amount of LDL using the Friedewald equation, such that the VLDL is equal to TG/2.2 (when the TG amount is more than 4.5 mmol/L, the equation is invalid). Therefore, the VLDL can be calculated directly from equation 1.1 (Friedewald et al, 1972). The non-HDL levels can be calculated by subtracting the HDL level from the total cholesterol, which represents all the types of lipoproteins except for HDL (equation 1.2).

LDL (mmol/l) = TC – HDL-C +TG/2.2 …... (1.1) (adapted from Bernard et al, 2002)

non-HDL = TC – HDL ………..(1.2) (adapted from Koda-Kmble, 2005)

1.4. Dyslipidemia control

The control of dyslipidemia is based on the established recommended goals for a particular type of lipid profile.

1.4.1. Categorization of dyslipidemia assessment

Depending on the lipids profile, NCEP has classified the recommendation goals into low, optimal, desirable, borderline, high and very high, which allows for the evaluation for each patient's case (NCEP, 2001).

Table 1.3 Type of dyslipidemia and assessment categorization (NCEP, 2001)

lipoproteins	Level (mg/dl)	Level (mmol/l)	Categories
TC	< 200	< 5.2	**Desirable**
	200–239	5.2-6.2	**Borderline high**
	≥ 240	> 6.2	**High**
LDL	< 100	< 2.6	**Optimal**
	100–129	2.6-3.36	**Near optimal/above optimal**
	130–159	3.37-4.11	**Borderline high**
	160–189	4.12-4.91	**High**
	≥ 190	> 4.92	**Very high**
HDL	< 40	<1.05	**Low***
	≥ 60	>1.6	**High****
TG	< 150	<1.7	**Desirable**
	150–199	1.7-2.3	**Borderline high**
	200–499	2.31-5.6	**High**
	≥ 500	>5.7	**Very high**

Note :** HDL > 1.6 is a negative risk factor

* HDL < 1.05 is a positive risk factor

1.4.2 Established recommended goals

The recommendations of the NCEP for dyslipidemia control are aimed at decreasing or preventing cardiovascular disease attacks. In coronary heart disease (CHD) or in equivalent diseases, the target lipid levels are less than 100 mg/dl (2.6 mmol/l), which is called secondary prevention (NCEP, 2002). Patients with clinical CHD and the equivalent diseases have the following characteristics:

1. Clinical CHD: myocardial ischemia (angina), MI, coronary angioplasty, and/or stent placement, coronary bypass graft and prior unstable angina.
2. Carotid artery disease: stroke history, transient ischemic attack history, carotid stenosis > 50%.
3. Peripheral arterial disease : claudiation, ankle :brachial index (ABI) > 0.9
4. Abdominal aortic aneurysm.
5. Diabetes mellitus.

If the patient does not have any of the above coronary heart diseases or equivalents, then he or she must be considered for primary prevention. This prevention is influenced by total cholesterol and HDL, age, gender (Wilson, 1998), hypertension (Stamler et al, 1993; van den Hoogen et al, 2000), family history of CHD (Barrett–Connor and Khaw, 1984), smoking (LaCroix et al, 1991), etc. All of these are considered as risk factors for cardiovascular diseases.

In an effort to prevent cardiovascular diseases, NCEP target some goals (Grundy et al, 2004; NCEP, 2001), which are based on the two main lipid factors, LDL and non-HDL.

1.4.2. (a) Low density lipoprotein (LDL) goals

1- Patients with coronary heart disease (CHD) and CHD equivalents, including diabetes (representing the secondary prevention): LDL < 100 mg/dl (<2.6 mmol/l)

2- Patients with multiple risk factors ≥ 2, e.g., smoking, hypertension, family history of CHD, etc. : LDL <130 mg/dl (<3.4 mmol/l)

3- Patients with zero to one risk factor and non-CHD: LDL < 160 mg/dl (<4.16 mmol/l)

The second and third goals represent the primary prevention as referred to in Table 1.4

1.4.2. (b) Non-high density lipoprotein (non-HDL) goals

1- Patients with coronary heart disease (CHD) and CHD risk equivalents: < 130 mg/dl (< 3.4 mmol/l)

2- Patients with multiple risks factors ≥ 2: < 160 mg/dl (< 4.16 mmol/l)

3- Patients with zero to one risk factor and non-CHD: < 190 mg/dl (< 4.94 mmol/l)

The goal for non-HDL

Table 1.4 Targets of dyslipidemia control according to the NCEP reports (NCEP, 2001)

Prevention	LDL goals		non-HDL goals	
	mg/dl	mmol/l	mg/dl	mmol/l
Primary	<130	<3.4	< 160	< 4.16
Secondary	<100	<2.6	<130	<3.4

Since there is definite relationship between the lowering of the blood cholesterol level and the incidence of cardiovascular diseases, such that a 1% decrease in the cholesterol levels decreases the incidence of cardiovascular diseases by 1% (Neaton et al, 1992). According to the epidemiology data in previous studies (Law et al, 1994) and NCEP ATP III publication reports, secondary prevention is very important for the patients who are suffering from cardiovascular diseases. This is because dyslipidemia has a strong relationship, especially with LDL, and has a log linear relationship with cardiovascular diseases. The goal recommended for LDL is less than 100 mg/dl. This is the level that is referred to as the beginning of coronary heart diseases (Sacks et al, 1996; LIPID, 1998; 4S, 1994) and this value is also considered to be the minimum point that is required to increase the incidence of cardiac attacks. HPS (Heart Protection Study) and PROVE-IT trial studies advise individuals to reduce their LDL to less than 100 mg/dl to achieve a more pronounced reduction or prevention of atherosclerotic lesions (Nissen et al 2004). This is because the HPS study found about a 20%-30% and the PROVE-IT study found a 16% reduction in the risks of cardiovascular diseases after reaching this goal (Chris and Harvey, 2004).

For primary prevention, the NCEP recommended that the goal must be less than 129 mg/dl to reduce the risk of cardiovascular diseases by 30%-40% (Pearson et al, 2003; NCEP, 2001).

The use of less effective lowering agents can lead to difficulties in controlling the lipid levels, which will lead to an increase in the dose or the need for a combination therapy in an effort to achieve the recommended goals (EUROASPIRE II Study Group, 2001).

1.5. Statins

There are many drugs that are used for the treatment of dyslipidemia, including the statins. Statins, which are inhibitors of 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) reductase, are considered as one of the most important drugs and the drug of choice for reducing an abnormal cholesterol level. Statins are normally used to decrease the risk of congestive heart death and non fatal MI, revascularization procedures, strokes and other cardiovascular mortality (NCEP, 2001, Grundy et al, 1997; Vaughan and Gotto, 2004). This is because it can reduce the level of LDL and triglycerides, as well as increase the level of HDL (NCEP, 2001).

1.5.1. Mechanism of action

Statins have the ability to catalyze the conversion of hydroxymethyl glutaryl-Coenzyme A (HMGCoA) to mevalonate leading to prevention of cholesterol synthesis (Goldstein and Brown, 1990) (Figure1).

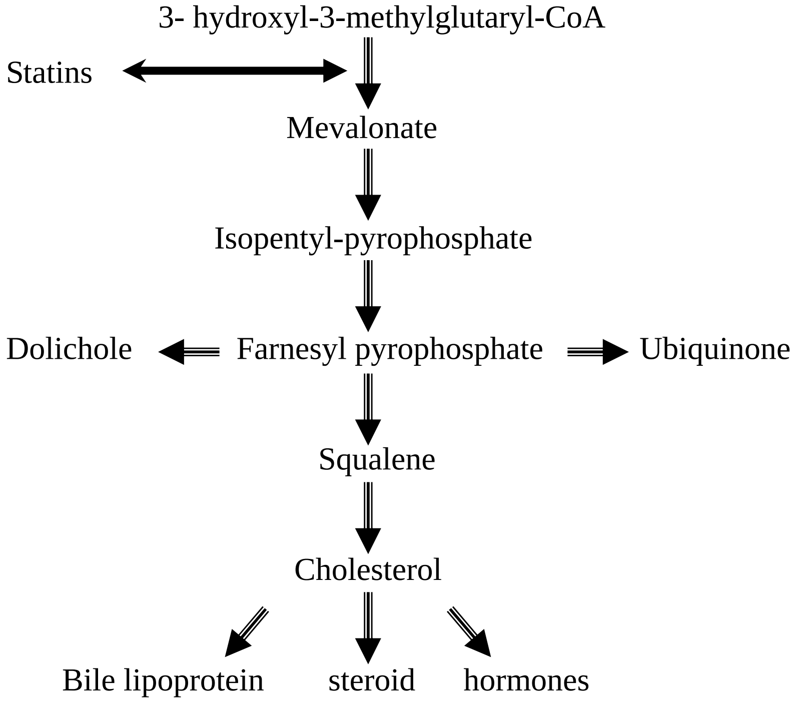
3- hydroxyl-3-methylglutaryl-CoA
Statins
Mevalonate
Isopentyl-pyrophosphate
Dolichole
Farnesyl pyrophosphate
Ubiquinone
Squalene
Cholesterol
Bile lipoprotein
steroid
hormones

Figure 1.1 Statin effect on the cholesterol synthesis (Rosanoff, 2004)

The secondary mechanism is accomplished by reducing or inhibiting the hepatic synthesis of apolipoprotein B100 and then decreasing the secretion of triglyceride-lipoprotein (Ginsberg at al, 1987; Grundy et al, 1997) and also through an inhibition of the isoperinoid compound that is produced from mevalonate, which exhibits pleiotropic properties (Liao, 2002; Corsini et al, 1999). The inhibition of cholesterol synthesis causes a stimulation of the sterol regulatory element binding proteins (SREBPs). SREBPs are factors that have the ability to activate a signaling cascade that is responsible for the regulation of the LDL-receptor gene expression. After these factors are activated, they begin to cross the nuclear membrane where they can bind to the sterol response element leading to the regulation of the LDL-receptors in the hepatocellular membrane. An increase in the receptors expression causes an increase in the cellular uptake of LDL, which leads to a decreased blood circulating LDL (William, 2007). Accumulation of mevalonate will lead to an increase in HDL, which leads to the inhibition of the cholesterol ester transfer protein (Rosenson and Tangney, 1998).

Accumulation of LDL and VLDL particles in the intimal space leads to the development of an atherosclerotic plaque, which contains a lipid core, thin fibrous cap and macrophage cells covering the lesions (Vogel et al, 1997). A statin drug changes the size of the lesions from big to small and it also softens a hard lesion so that it is less easily ruptured. The pleiotropic effects of statins improve the endothelial dilatation function and inhibit cell migration and proliferation (Nissen et al, 2004; Liao, 2002; Shishehboret al, 2003; Treasure et al, 1995; Baller et al, 1999; O'Driscoll et al, 1997). A reduction in the cholesterol level also means there is a decrease in the inflammation that normally accompanies atherosclerosis. This process involves the activity of monocytes, which have the ability to engulf LDL particles, cause ruptures and release other mediators (cytokines, chemokines, and growth factors release). Inhibiting this process by statins will also lead to a decreased formation of clots (Libby et al, 2002; Libby, 2001, Henderson et al, 1999; Ridker, 1998).

1.5.2. Types of Statins

Statin drugs include atorvastatin, simvastatin, rosuvastatin, lovastatin, pravastatin, fluvastatin and cerivastatin (the last statin was withdrawn from the market). Lovastatin was the first discovered as a naturally-occurring substance from fungi in 1987, and simvastatin was produced from a semisynthetic derivative of lovastatin in 1991. The other types, including fluvastatin, cerivastatin, rosuvastatin and atorvastatin, are synthetic enantiomer types (McTaggart et al, 2001; Blumenthal, 2000).

1.5.3. Pharmacokinetics:

The statins differ in terms of their physiochemical properties. Some of them are lipophilic, while others are hydrophilic. Some statins have metabolites and some are not metabolized. Both simvastatin and lovastatin are prodrugs that are converted in the liver so that the lacton ring is opened. While in the other above-mentioned types, the ring is already opened (Istvan and Deisenhofer, 2001). Their pharmacokinetic properties also differ in terms of their absorption, maximum concentration, maximum time, metabolism, protein binding, excretion and bioavailability (Jones et.al, 1998; Corsini et al, 2002). The differences in the pharmacokinetics lead to differences in the activity and the adverse reactions (Peter, 2003).

Table 1.5 Pharmacokinetics of statins (Corsini et al, 2005)

Parameter	Atorvastatin	Simvastatin	Lovastatin	Rosuvastatin	Pravastatin	Fluvastatin
Absorption %	30	60-80	35	20	34	98
T_{max} (h)	2-3	1.3-2.4	2-4	3	0.9-1.6	0.5-1
C_{max} (ng/ml)	27-66	10-34	10-20	37	45-55	448
Bioavailability%	12-14	5	5	20	17-18	19-29
Lipophilicity	Yes	Yes	Yes	No	No	No
Protein binding%	80-98	94-98	>95	88	43-55	>95
Metabolism	CYP3A4	CYP3A4	CYP3A4	CYP2C9, 2C19 (minor)	Sulfation	CYP2C9
Metabolites	Active	Active	Active	Active (minor)	Inactive	Inactive
Transporter protein substrate	Yes	Yes	Yes	Yes	Yes/No	No
$T_{1/2}$ (h)	14-30	2-3	2.9-4	19-20.8	1.3-2.8	0.5-2.3
Urinary excretion %	2	13	10	10	20	6
Fecal excretion %	70	58-60	83	90	70-71	90

1.5.4. Dosage forms (Jones et al, 1998)

Simvastatin:	Tablets 5, 10, 20, 40 or 80 mg
Rosuvastatin:	Tablets 5, 10, 20, 40 mg
Pravastatin:	Tablets 10, 20, 40 mg
Lovastatin:	Tablets 10, 20, 40 mg
Fluvastatin:	Tablets 20, 40 mg (capsules); 80 (XL tablets)
Atorvastatin:	Tablets 10, 20, 40, 80 mg

1.5.5. Daily dose

The doses are given here as the defined daily dose and they are supported by many studies (Jones et al, 1998; Moon, 2006; Andrews et al, 2001; Jones et al, 2003). The normal daily dose of statin is represented in Table 1.6

Table 1.6 Statins dosage regimen

Statin type	**Dosage regimen**
Atorvastatin	10-40 mg QD and the maximum dose is 80 mg QD at any time
Simvastatin	20-40 mg Q pm and the maximum dose is 80 mg Q pm with food
Fluvastatin	20-40 mg Q at bed time and the maximum dose is 40 mg BID or 80 mg XL QD
Lovastatin	20-40 mg with dinner and the maximum dose is 40 mg BID
Pravastatin	10-40 mg QD and the maximum dose is 40 mg QD
Rosuvastatin	10-20 mg QD and the maximum dose is 40 mg QD

QD = once daily   BID= twice daily

1.5.6. Other antihyperlipidemics

To reach the goal of treatment, sometimes there is a need to give combination therapies with another antihyperlipidemic, such as niacin, ezetimibe, resin, fibrates and fish oil.

1.5.7. Statins use prevalence

Of all the approved antihyperlipidemics, statins are the most frequently used. It has been reported that statin use ranges from 62.5% to 91.7% of dyslipidemic patients. Additionally, it has been reported that the rate of statins use by cardiac patients is between 0.5% to 6.7% (Avorn et al, 1998). In Malaysia, about 90% of coronary heart patients use statins (National Cardiovascular Disease Malaysia, 2006).

There is an increasing trend in statins use since 2003 especially in European countries. Ireland and Norway are two countries will a high rate of statins use, while Italy is the least-frequent user of statins. It has been reported that the increment of statins usage are between 274% and 56% (from 2000 to 2003) for Ireland and France, respectively. Some countries prefer to use lovastatin and simvastatin, while the other countries prefer rosuvastatin, atorvastatin or simvastatin. Regardless, the median of the rate of usage increase in Europe is 25.6% per year from the period 1999 to 2003 (Walley et al, 2004).

In the UK, it has been found that most patients who use statins are older than 35 years old and that 56% of the users are men. The most frequently-used type is simvastatin 20 mg (DeWilde et al, 2003). In Canada, about 90% of the utilized lipid lowering agents were statins at 2000. While in the US, at least one third of all patients use statins (NCEP, 2002). About 60% of statins users were patients older than 60 years old in Canada (Farahani et al, 2005) and statins users have increased about (1.28% - 6.59%) from the 1996 to 2004. The age of the population who uses statins has increased with age range. It has been reported that 0.1% - 0.56% of the users were between the ages of 20-45, 1.82%-7.45% of 45-65, 4.25%-20.92% of 65-85, and 0.45%-8.11% were older than 85 year. While the most common type of statin used in US is atorvastatin followed by simvastatin, pravastatin, fluvastatin, lovastatin and rosuvastatin. Cerivastatin use has declined since 2003, because of the adverse drug reactions problems. The most common diseases in which statins were used are ischemic heart disease (35.17%), diabetes (30.02%), peripheral vascular disease (3.5%), cerbrovascular disease (7.36%) and atherosclerosis (3.91%) for total number of patients in Colombia, US from 1999-2004 (Colette et al, 2007). The rate of usage in male patient is 2.62%, which is slightly more than women (2.49%), (Savoie et al, 2002). In New Zealand, simvastatin was used for the first time in 1986 (Chris and Harvey, 2006). Due to the beneficial effects of statins in lowering cholesterol and the incidence of cardiovascular diseases, clinicians have encouraged the use of statins (French et al, 1990). In Australia, about 85% of the cardiovascular patients used atorvastatin and simvastatin from 1992–2003 (Oberg, 1999).

1.5.8. Clinical benefits of statins

For the last 50 years, many US patients have suffered from coronary artery diseases and in 2002, about 500,000 patients died as a result of cardiovascular diseases, like ischemic heart disease (IHD), atherosclerosis, cerbrovascular disease or peripheral vascular disease (PVD) (American Heart Association, 2005). Statins can be used in both primary and secondary prevention (Wood et al, 1998; NCEP, 2001). The major benefits of statins for the secondary prevention patients are more significant than for the primary prevention patients; there is more need for statins in the secondary than in primary dyslipidemia (NICE, 2005; Wilt et al, 2004). Thus, most cardiovascular patients use statins. However, the chronic use of statins may cause several problems. Patients who do not benefit from statins use should avoid this drug to prevent the adverse drug reactions and unnecessary cost. (Svoie, 2002).

These drugs have significantly decreased the incidence of cardiac attacks, especially those related to heart failure, and have improved the survivor state of mortality cases. It has been reported that there is a direct impact on diastolic heart failure with an observed beneficial effect of statins in left ventricle hypertrophy patients, since it also exerts antihypertensive effects (Borghi, 2002; Glorioso et al, 1999) and arterial distensibility (Ferrier et al, 2002). It also improves the endothelial function that prevents atherosclerosis (Corti et al, 2002). The prevention effect of hypertrophy on the left ventricle (O'Rourke, 2001; Kass et al, 2004), and the increased distensibility will reduce mortality and MI cases. Other benefits of statins are the anti-inflammatory and antioxidant (Davignon, 2004) effects, which inhibit the inflammatory effect and myocardial stress that is caused by an increase in oxygen free radicals, which may affect heart failure development (Givertz and Colucci, 1998). Statins have been documented to prevent strokes, vascular diseases, and coronary heart diseases as well as decrease the mortality, morbidity and death associated with dyslipidemia (Byington et al, 2001; Sirol et al, 2001). These benefits have also been presented in many other studies (Castelli et al, 1991; Levy et al, 1990; 4S, 1994; WOSCOPS Study Group, 1998). With regard to renal system, statins participate to improve kidney function and the GFR (Bays et al, 2005).

Many previous studies showed a difference in clinical benefits depending on type of statin used. This difference are due to the pharmacokinetic and type of the statin used. Based on the Frederickson classifications, all types of statins are indicated for type I patients, it is preferred that type IIa and type IIb patients use any of the statins except lovastatin, type III patients should preferentially use atorvastatin, pravastatin and simvastatin, and type IV patients have been indicated to use all the types of statins except fluvastatin and lovastatin (Amin, 2004). Rosuvastatin is considered to have more of an effect on the reduction of LDL and an improvement of the lipid profile of patients (McKenney et al, 2003). Atorvastatin is considered to be the most active statin because of its anti-inflammatory (Taylor et al, 2002; Wiklund et al, 2002) and antioxidant effects. These effects are due to the active metabolites that are found with atorvastatin more than other types of statins (Shishehbor et al, 2003). Simvastatin significantly reduces the mortality associated with coronary heart disease (Therapeutics Initiative committee, 1999), while pravastatin significantly reduces the incidence of MI in men (Shepherd and Wenger, 1995). Many studies have proven that there is a great benefit and effect of statins use in the reduction of cardiovascular events.

The 4S study is considered to be the first study to show that simvastatin has the ability to reduce the cholesterol level and then reduce the incidence of cardiovascular diseases (Scandinavian Simvastatin Survival Study Group, 1994). The HPS (heart protection study) was carried out on 1,000,000 patients in the UK ranging in age from 40 to 80 years old who had a high risk of cardiovascular diseases. After simvastatin use, a 24% reduction in cardiovascular events and a 27% reduction in strokes and a significant reduction (13%) in mortality were observed. The rates of coronary death were decreased by 27%, major cardiovascular events were reduced by 24%, nonfatal MI were decreased by 25% and there was a 7-10% decrease in the risk of diabetes (Serruys et al, 2002; Heart protection study, 2002). The Lescol Intervention Prevention (LIP) study found that in patients ranging in age from 18 to 80 years old, fluvastatin use reduced the risk of cardiovascular events by about 22% and the risk of diabetes by 47% (Serruys et al, 2002). The AVERT study proved that use of atorvastatin at 80 mg for 1.5 years has the ability to decrease (13%) the revascularization procedure that is needed for ischemic patients (Pitt et al, 1999). The ASCOT-LLA study, which used atorvastatin at 10 mg for 3.3 years, observed a 36% reduction in both non fatal MI and fatal coronary heart diseases, a 27% reduction in risk of stroke and a 29% reduction in risk for total coronary events (Sever et al, 2003). The CARDS study, which used atorvastatin at 10 mg for 4 years for primary prevention patients, found a 37% reduction in cardiovascular events, a 36% reduction in acute coronary events, a 31% reduction in the risk of coronary revascularization, a 48% reduction in the risk of strokes and a 27% reduction in the rate of death (Colhoun et al, 2002). The CARE study, which used pravastatin at 40 mg in patients with secondary prevention for 5 years, found that there was a 24% decrease in the risk of death from CHD or nonfatal MI, a 23% reduction in the risk of nonfatal MI and a 31% reduction in the risk of stroke (Sacks et al, 1996). The LIPID study, which used pravastatin at 40 mg for 6.1 years, found that there was a 24% reduction in the risk of death from CHD, a 25% reduction in death (due to cardiovascular diseases), a 22% reduction in the risk of death due to CHD or nonfatal MI , a 29% reduction in the MI risk and a 19% reduction in the risk of stroke (The Long-term Intervention with Pravastatin in Ischemic Disease, 1998). The PROSPER study, which used pravastatin at 40 mg that was randomized for 3.2 years, found that there was a 15% reduction in risks of death from CHD, nonfatal MI, fatal or non fatal strokes, and a 24% reduction in the risk of CHD death.(Shepherd et al, 2002). The PACT study, which used pravastatin at 20-40 mg, found that there was a reduction in deaths and acute cardiovascular events by 6.4%. (Thompson et al, 2004). The PREVEND–IT study, which used pravastatin at 40 mg for 4 years, found that there was a 13% reduction in the risk of cardiovascular diseases (Asselbergs et al, 2004). The IDEAL study, which used atorvastatin (80 mg) and simvastatin (20-40 mg) during the follow up of patients who had a MI, found that there was a reduction in the cardiovascular risk after 1 year by 21%, while after 2 years there was a 14% reduction and after 5 years, there was a 34% reduction (Pedersen et al, 2006).

1.6. Adverse drug reactions

According to the World Health Organization (WHO), an adverse drug reaction is defined as any response in which there is a noxious and unintended effect that occurs at the normal doses used in man for prophylaxis, diagnosis and therapy of disease (Bruce Hawkins, 1995). According to the adverse reactions dictionary, the intensity of the adverse event's severity can be categorized into mild, moderate and severe (Connie et al, 2003).

1.6.1. Mechanism of adverse drug reactions of Statins

Inhibition of cholesterol synthesis prevents the formation of all of the precursors in the cholesterol synthesis pathway and in this process, there are two important compounds whose synthesis is inhibited. The inhibition of these two compounds leads to adverse drug reactions (ADRs). The operation of their functions are explained below. Inhibiting synthesis of these compounds would indirectly affect their normal function (Figure 1.1):

1) Ubiquinone or Co-Enzyme Q10 plays an important role in mitochondria to produce ATP, cell membrane activity, formation of collagen and elastin fibers, nerve conduction (Goldstein and Brown, 1990; Ely JTA and Krone, 2000).
2) Dolichole plays a role in glycoprotein manufacture.

Reducing lipid compounds prevents the production of many important compounds, such as bile, hormones, lipoprotein and cytokines (which consists of glycoprotein modulators of cellular functions, including interferon, interleukins and growth stimulating factors) (Kwak et al, 2000). Lipid reducing compounds also suppress helper T-cells and interferon, which stimulate macrophages (Nissen et al, 2005, Hakamada et al, 2003). Additionally, they suppress IL-6, IL-8 and tumor necrosis factor (TNF). (Ikeda and Shimada, 1999; Rezaie et al, 1999; Libby, 2003).

The reduction in the plasmatic and intracellular levels of cholesterol may reduce the cholesterol membrane wall leading to physical changes and a decrease in cell proliferation. Such changes could affect the function of the Na/K pump with irreversible damage to the cell. (Ucar, 2000)

1.6.2. Adverse drug reactions (ADRs) of statins

Many adverse reactions have been reported with statins use. These ADRs are categorized into two categories, minor and serious ADRs.

1.6.2 (a) Minor Adverse drug reactions

The minor ADRs include abdominal cramps, diarrhea or constipation, flatulence, dyspepsia, back pain, muscle pain, dizziness, chest pain, headache, pharyngitis, flu syndrome, nausea and vomiting, sleep disturbances, sexual dysfunction, fatigue, a sense of detachment, shortness of breath, vision problems, changes in body temperature and blood sugar, dry skin, rashes, blood pressure changes, nausea, upset stomach, bleeding, limbs tingling (during sleep), dry cough and phlegm, (Fallon, 2003; Shepherd et al, 2001; Amin,, 2004; AHFS, 2007).

Muscle damage is usually accompanied by an increase in serum creatine kinase (CK). This enzyme is mainly produced by skeletal muscle and myocardium (Baker and Tarnopolsky, 2001). Myalgia is one of the most common muscle disorders that may be caused by statins. It is characterized by diffuse muscle pain, tenderness, cramps and/or muscle weakness. The symptoms of myalgia are common complaints by patients who are on statin therapy (Thompson et al, 2003). The symptoms are associated with an increase the CK value. It was found that 2-7% of the patients who used statins had an increased CK value. These symptoms are also considered to be early symptoms of polyneuropathy, myopathy, or extrapyramidal disorders if they are not treated (Shetty et al, 1998).

1.6.3. Serious adverse drug reactions

The serious adverse reactions of statins include myositis, myopathy, rhabdomyolysis, polyneuropathy, cancer, liver disease and renal toxicity. These serious ADRs rarely occur during statin therapy.

1.6.3(a) Myositis: Muscle symptoms with or without increased CK levels, which are characterized by muscle weakness, and a biopsy indicates muscle damage with muscle fiber necrosis and inflammatory cell infiltration (Ucar et al, 2000), and the incidence is reported to be about 0.1-0.5% of patients who use statins (Pasternak et al, 2002)

1.6.3(b) Myopathy: The symptoms are defined as muscle pain, tenderness and /or muscle weakness, accompanied by an abnormal elevation in CK. (Ucar et al, 2000). The symptoms occur in 0.04-0.2% of the patients who are on statins (Hamilton, 2003; Pasternak et al, 2002; Maron et al, 2000)

1.6.3(c) Rhabdomyolysis: It is an acute muscle damage in which all the cell contents, such as myoglobin, enzymes and electrolytes are released into the circulation. The myoglobin and the intracellular components are toxic, especially for the kidney. When the urine pH is less than 5.6, myoglobin is converted to ferriheme, which is considered a toxin. The precipitation of this product may cause an obstruction of the renal tubules and lead to renal vasoconstriction The CK can rise between 10 and more than 100 fold above the baseline or upper limit normal (ULN) (Lewin et al, 2002). These symptoms occur in 0.05% of the statin patients. They are accompanied by severe muscle pain, stiffness, weakness, fever, malaise and dark urine (Thompson et al, 2003) and may suffer from renal failure (Hayward et al,2006).

1.6.3(d) Polyneuropathy: Known as peripheral neuropathy (irreversible damage), which is characterized by weakness, tingling sensations in the limbs, hand and foot pain and walking difficulty. These symptoms only occur in patients that use statins for 2 or more years (Gaist et al, 2002).

1.6.3(e) Cancer: May occur with use for longer durations. It has been found that skin cancer is associated with the use of statins in 243 patients (Sacks et al, 1996; Heart Protection Study, 2002). It has also been found that there is a significant increase in the risk of breast cancer in women who have had CHD and are treated with pravastatin (Pfeffer et al, 2002).

1.6.3(f) Liver diseases: Statins can cause liver diseases. They induce hepatotoxicity that mimics the symptoms of any type of hepatobiliary disease (from acute and chronic) (Kinnman, 2001). An abnormality in the liver function will start if both liver enzymes (ALT and AST) increase by more than 1.5 ULN (Pfeffer et al, 2002). The clinical effect of statins is associated with an elevation in the liver transaminase levels by more than 3 ULN. These effects have been found in about 300 cases per 100,000 cases either due to statin drug interactions, comorbidities or a high dose of statin (Maron et al, 2000). ALT and AST may increase with the use of statin at a rate of more than 1% with the lower and intermediate doses of statin. This rate may increase to between 2% to 3% in the patients who are taking the 80 mg dose of statin for an average duration of 3 years (Cohen et al, 2006). According to the 2006 report from the Alabama Medicaid Agency of Pharmac therapeutic committee meeting, an elevation in liver enzymes begin after 12 weeks of statin therapy (McEvoy,2004).

1.6.3(g) Renal toxicity: It is rare, but may occur due to proteinurea, if a high dose of statins is used (Alsheikh-Ali et al, 2005; Hayward et al, 2006).

1.7. Contributing factors in dyslipidemia control and adverse drug reactions

There are many contributing factors that influence the dyslipidemia control and ADRs, such as statin types, dose, combination therapy, age, gender, race, alcohol use, smoking and duration of therapy.

1.7.1. Statin types

The pharmacokinetic properties (Table 1.5) of statin play a role in dyslipidemia control and the adverse drug reactions severity.. Fluvastatin and rosuvastatin have lower adverse effects on the CNS, such as headache, dizziness and asthenia (Plosker and Wagstaff, 1996; Campbell et al, 2005). Lipophilic statins are metabolized to more hydrophilic compounds for excretion, while the hydrophilic statins are excreted unchanged, which therefore have a lower drug interactions incidence (Hamelin and Turgeon, 1998). Protein binding may be one of the contributing factors for drug interactions. The statin types that have a high protein binding (>95%) are more prone to interactions by another protein binding agent, which leads to an increase in free active drug (Bottorf and Hansten, 2000). The statins (simvastatin, lovastatin and atorvastatin) that are metabolized by CYP3A4 are considered to be more toxic to muscle cells. More than half of the reported cases of muscle pain were related to simvastatin use than other types of statins (Thompson et al, 2003; Ballantyne et al, 2003). While pravastatin and fluvastatin are not metabolized by the same liver enzyme, there is no competition between the metabolic enzymes and therefore their concentration will be lower. Since statins as many other drugs are metabolized by cytochrome enzymes, a drug-drug interaction can lead to an increase in the plasma level of statin (Muscari et al, 2002; NCEP, 2001). Therefore, an adverse drug-drug interaction may cause a significant increase in CK and lead to myalgia, myopathy, and rhabdomyolysis (Rosenberg et al, 1995; Veerkamp et al, 1996). Some drug-drug interactions that can cause rhabdomyolysis due to an increase in the concentration of statins in the blood include itraconazole (Segaert et al, 1996), erythromycin (Herman, 1999), cyclosporin (Meier et al, 1995), and diltiazem (Bottorf and Hansten, 1999). The above-mentioned drugs are considered to be moderate CYP3A4 inhibitors when used with lovastatin and pravastatin. These drugs may also cause a drug interaction that may lead to the prolonging of the actions of statins because of the increase in their C_{max} (for example, the lovastatin C_{max} increases from 6 ng/ml to 26.9 ng/ml) (Spach et al, 1991). The incidence of these adverse drug-drug interactions is about 300 cases per 100,000 cases. The patients have an elevation in the ALT and AST of more than 3 ULN when the dose is fixed and unrelated to a reduction in the LDL level (Bays, 2006; Law and Rudnicka, 2006). An increased pharmacokinetic rate could be contributed by statin interactions or comorbidities or a high statin dose (James, 2006). Thousands of New Zealand patients have suffered from a loss of dyslipidemia control because their medications were frequently changed from atorvastatin to pravastatin or simvastatin (Chris and Harvey, 2006). PHARMAC found that fluvastatin is the weakest type of statin in controlling lipid levels among all the types, because there is no mortality prevention or improvement of the patients' clinical states. Therefore, fluvastatin is not recommended in patients with secondary prevention (Chris and Harvey, 2006). Atorvastatin is more frequently used in European countries and is considered to be the best and strongest type of statin when compared to equivalent strengths of the other statins (Illingworth et al, 1994; Athyros et al, 2004; Schwartz et al, 2002; Sever et al, 2003).

The incidence of ADRs (both minor and serious adverse reactions) for pravastatin is 69% followed by simvastatin (63%), rosuvastatin (55%) and atorvastatin (46%) (Alsheikh-Ali et al, 2005). Studies have proven that there is no significant difference among the statins in terms of their safety or ADRs (Pasternak et al, 2002). Cerivastatin was withdrawn from the market, because according to the WHO database, it was associated with 52 cases of death (Wooltorton, 2001; Weber, 2001). There were 546 reports of cases of rhabdomyolysis resulting from statin use, which were more frequently related to cerivastatin than other types of statins. While the FDA received 6498 cases of cerivastatin use that was associated with rhabdomyolysis, some of these cases were fatal rhabdomyolysis (Furberg and Pitt, 2001). The incidence of rhabdomyolysis for cerivastatin is 3.16 per million, followed by lovastatin at 0.19 per million, simvastatin at 0.12 per million, pravastatin at 0.04 per million, atorvastatin at 0.04 per million, and fluvastatin at 0 per million. Statins can also cause liver injury and proteinuria (EMEA, 2002), the incidence of these ADRs also depends on the type of statin used, such that for atorvastatin the incidence is 0.7% and for rosuvastatin 0.4%. Rosuvastatin causes a minimal effect on liver injury (1.9%).

The incidence of myalgia was higher with fluvastatin (5%) and atorvastatin (3.2%) compared to the other types of statins, but the incidence of myalgia is 1.2% for simvastatin and 2.6% for lovastatin. The incidence of myopathy is the highest with rosuvastatin (0.1%) and pravastatin (0.1%), followed by lovastatin (0.08%) and atorvastatin (0%) (Davidson, 2005). The rate of muscle disorders is not significantly different among the types of statins (Gotto, 2003). In the UK the EXCEL study, which included a large number of patients who used lovastatin, found that cases of myopathy ranged from 0.1% to 0.2% of the study population, while pravastatin and simvastatin had incidences of myopathy from 0.01% to 0.4%. Cerivastatin users experienced myopathy in about 1.55% of the study population, which was the highest compared to the other types of statins (Michael, 2005).