PREDICTION OF UNCONTROLLED DYSLIPIDEMIA OF CARDIAC OUTPATIENTS AND THE ADVERSE EFFECT OF PHARMACEUTICAL EXCIPIENTS

By

HADEER AKRAM ABDULRAZZAQ

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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 nephew Ahmed, and nieces Sara and Aya. To all my faith friends.

Thanks for love, inspiration and doa.

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&	and
ABN	abnormal
ACE-I	Angiotensin-Converting Enzyme Inhibitors Type I
ADR	Adverse Drug Reactions
AIHW	Australian Institute of Health and Welfare
ARB	Angiotensin receptor blocker
B-BK	Beta Blockers
BCRP	Breast cancer resistance protein
BHT	Butylated hydroxytoluene
Ca Ch Bk	Calcium Channel Blockers
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Diseases
CADRMP	Canadian Adverse Reaction Monitoring Program
CDER	Center for Drug Evaluation and Research
CEPHEUS SA	CEntralised Pan-South African survey on tHE Under-treatment of hypercholeSterolaemia
CFCs	Chlorofluorocarbon
CHD	Coronary Heart Diseases
CI	Confidence Interval
CI	Contraindication
CNS	Central Nervous System
COAD	Coronary Obstructive Artery Disease
CVS	Cardiovascular Diseases
CYP	Cytochrome P450
D-D	Drug- drug interaction
DIC	Drug Information Centre
dl	Deciliter

DM	Diabetes Mellitus
DMSO	Dimethyl sulfoxide
e.g.	example
EECH	Europe Economics Chancery House
EFFECTUS	The Evaluation of Final Feasible Effect of Ultra Control Training and Sensitization
FD & C	Food, Drug and Cosmetic
FDA	Food And Drug Administration
GIT	Gastrointestinal tract
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HMGCoA	Hydroxymethyl Glutaryl-Coenzyme A
HP-β-CD	2-Hydroxypropyl-beta-cyclodextrin
Hypothyr.	Hypothyroidism
i.e	it est.
IC_{50}	The half maximal inhibitory concentration
IHD	Ischemic Heart Disease
IPEC	International Pharmaceutical Excipients Council
LDL	Low Density Lipoprotein
mg	Milligram
MI	Myocardial Infarction
ml	Milliliter
mM	Millimeter
mmol	Millimole
mo.	month
MRP2	Multidrug Resistance-Associated Protein 2
NCEP	National Cholesterol Education Program
no.	number
OMPN	Outpatients medical progress notes
OR	Odd ratio

OTC	Over the counter
PEG	Poly ethylene glycol
P-gp	Plasma glycoprotein
PVAP	Polyvinyl acetate phthalate
PVD	Peripheral Vascular Disease
PVP	Polyvinylpyrrolidon
ref.	Reference
SD	Standard Deviation
SPSS	Statistical Package For Social Sciences Software
TC	Total Cholesterol
STATT	The Simvastatin Treats Asians to Target
TG	Triglyceride
UK	United Kingdom
US	United State
USM	Universiti Sains Malaysia
USP	United States Pharmacopeia
v/v	Volume per volume
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization
yr.	year

PERAMALAN DISLIPIDEMIA TIDAK TERKAWAL DALAM KALANGAN PESAKIT JANTUNG YANG MENERIMA RAWATAN SEBAGAI PESAKIT LUAR DAN KESAN ADVERS TERHADAP EKSIPIEN FARMASEUTIKAL

ABSTRAK

Dislipidemia tidak terkawal masih merupakan masalah yang sukar ditangani semasa rawatan pesakit jantung. Beberapa penulis menyatakan terdapat sumbangan kepatuhan pesakit, amalan pakar perubatan dan bahan aktif untuk mencapai matlamat kawalan dislipidemia, akan tetapi tiada pernyataan yang menyebut tentang sumbangan gabungan semua sebab-sebab ini. Malangnya, hanya sedikit kajian membincangkan kesan-kesan eksipien farmaseutikal dalam amalan klinikal dan terutamanya dislipidemia. Objektif kajian ini adalah untuk menentukan prediktor-prediktor bagi dislipidemia tidak terkawal, profil lipid yang lemah, kesan advers ubat-ubatan (ADRs), dan kesan-kesan eksipien farmaseutikal. Yang kedua adalah pelaksanaan satu kaedah intervensi untuk menambah baik pengetahuan profesional kesihatan berkaitan eksipien farmaseutikal. Objektif pertama telah dijalankan di Klinik Kardiologi, Hospital Pulau Pinang di Malaysia, manakala yang kedua telah dilaksanakan di Hospital Pulau Pinang (Malaysia) dan Hospital Pengajaran Al-Kadhimiya (Iraq). Kawalan dislipidemia dan profil lipid telah dinilai berdasarkan garis panduan Program Pendidikan Kolesterol Kebangsaan (National Cholestrol Education Program-NCEP). Soal selidik yang disahkan telah dijawab oleh pesakit untuk menentukan kepatuhan mereka dan kesan advers (ADRs) yang biasa berlaku semasa rawatan. Profesional kesihatan telah menjawab soal selidik yang telah disahkan; satu adalah untuk pakar perubatan bagi menentukan amalan mereka berkaitan kawalan dislipidemia, dan satu lagi adalah untuk menilai pengetahuan mereka mengenai eksipien farmaseutikal. Lain-lain maklumat seperti ciri-ciri pesakit,

ubat-ubatan yang diambil bersama, penyakit-penyakit, dan profil lipid diperolehi daripada fail kemajuan pesakit. Maklumat mengenai eksipien farmaseutikal didapati daripada risalah ubat-ubatan, syarikat pengilang dan Unit Maklumat Ubat hospital berkenaan. Pakej Statistik untuk Sains Sosial (Statistical Package for the Social Sciences - SPSS) versi 18 digunakan dengan ujian khi-kuasa dua (chi-square), regresi logistik berganda (multiple logistic regression) dan laporan nisbah ganjil (odd ratio - OR), Mann-Whitney, Wilcoxon *signed ranks test,* dan regresi ordinal (ordinal regression). Keputusan dengan nilai p kurang daripada 0.05 dianggap sebagai penting. Seramai 504 orang pesakit jantung warganegara Malaysia yang menerima rawatan sebagai pesakit luar didaftarkan dalam kajian ini, kebanyakan mereka adalah lelaki (76.4%) dan Melayu (40.5%) dengan umur purata 58 ± 49 tahun. Peratus pesakit yang mencapai sasaran kawalan dislipidemia adalah 47.2% dan 45.4% untuk LDL dan bukan-HDL masing-masing. Peratus penilaian profil lipid yang optimal, normal dan diingini adalah 37.5%, 50.1%, 61.7% dan 57% untuk LDL, HDL, TC dan TG masing-masing. Kejadian tertinggi ADRs yang diperhatikan dalam sakit sendi (50.6%), manakala ADR yang ringan, sederhana dan teruk yang biasa dilaporkan adalah batuk (37.3%), kerap membuang air kecil (18.2%), dan kekebasan (5.4%) masing-masing. Terdapat 10 eksipien sahaja dan 15 eksipien dengan bahan aktif yang menghasilkan polifarmasi. ADRs sederhana dan teruk ditemui apabila bilangan bahan-bahan melebihi 11 dan 15 masing-masing. Terdapat peningkatan yang ketara selepas intervensi dilakukan kepada profesional kesihatan dengan penambahbaikan yang boleh diterima dalam aspek pengetahuan am, ADRs, kontraindikasi dan interaksi eksipien. Kesimpulannya, kurang daripada separuh pesakit jantung berada di bawah kawalan dislipidemia yang dipengaruhi oleh pengkhususan dan pengalaman pakar perubatan, kepatuhan pesakit, bahan aktif ubat-

ubatan dan eksipien. Pelaporan kendiri pesakit adalah alat yang sesuai untuk mengumpulkan ADRs yang dipengaruhi oleh ciri-ciri pesakit, penyakit lain yang dihidapi, dan bahan aktif ubat-ubatan serta eksipien. Polifarmasi eksipien mesti diambil kira apabila menjalankan kajian klinikal. Selain itu, program intervensi diperlukan untuk menambahbaik pengetahuan profesional kesihatan berkaitan eksipien farmaseutikal.

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ABSTRACT

Uncontrolled dyslipidemia is still a difficult problem to be achieved during therapy of cardiac patients. Several authors stated contribution of patients' adherence, physicians' practice and active ingredients to attain goals of dyslipidemia control, but none combined all these causes. Unfortunately few studies discussed the effects of pharmaceutical excipients in clinical practice and especially dyslipidemia. Objectives of this study were to determine predictors of uncontrolled dyslipidemia, poor lipid profile, adverse drug reactions (ADRs), and effects of pharmaceutical excipients. Second is implementation of an intervention tool to improve the knowledge of healthcare professionals about pharmaceutical excipients. First objective was carried out at Cardiac Clinic of Hospital Pulau Pinang in Malaysia, while the second was conducted at Hospital Pulau Pinang (Malaysia) and Al-Kadhimiya Teaching Hospital (Iraq). Dyslipidemia control and lipid profile were evaluated depending on the National Cholesterol Education Program (NCEP) guideline. Validated questionnaires were filled by patients to determine their adherence and common ADRs during therapy. Healthcare professionals answered validated questionnaires; one for physicians to determine their practice for dyslipidemia control, and another to assess their knowledge about pharmaceutical excipients. Other information like patients' characteristics, concurrent medications, diseases, and lipid profile were collected from patients' progress files. Information of pharmaceutical excipients was obtained from medications' leaflets, manufactured companies and Drug Information Center (DIC) of the Hospital. Statistical Package for the Social Sciences (SPSS) version 18 was used with chi-square, multiple logistic regression and reporting odd ratio (OR),

Mann-Whitney, Wilcoxon signed ranks test, and ordinal regression. Results with *p* value less than 0.05 considered as significant. There were 504 Malaysian cardiac outpatients enrolled in current study, majority of them were males (76.4%) and Malays (40.5%) with mean age 58 ± 49 years. Percentage of patients who achieved the targets of dyslipidemia control was 47.2% and 45.4% for LDL and non-HDL respectively. Percentages of optimal, normal or desired lipid profile evaluation were 37.5%, 50.1%, 61.7% and 57% for LDL, HDL, TC and TG, respectively. Highest incidence of ADRs observed in joint pain (50.6%), while the common reported mild, moderate and severe ADR was cough (37.3%), frequent urination (18.2%) and numbness (5.4%), respectively. The polypharmacy of pharmaceutical excipients was 10 (alone) or 15 (with active ingredients). Moderate and severe ADRs found when number of ingredients exceeded 11 and 15 respectively. There was significant enhancement found after intervention done to healthcare professionals with acceptable improvements in general knowledge, ADRs, contraindications and interactions of excipients. In conclusion, less than half of cardiac patients were under dyslipidemia control which influenced by physicians' specialty and experience, patients' adherence, medications' active ingredients and excipients. Patients' self-reporting was the appropriate tool for collecting the ADRs that was influenced by patients' characteristics, concurrent diseases, and medications' active ingredients and excipients. Polypharmacy of excipients must be taken in the consideration when conducting the clinical studies. Also, interventional programs are needed to improve healthcare professionals' knowledge about pharmaceutical excipients.

CHAPTER 1

INTRODUCTION

1. Background

1.1 Dyslipidemia

Dyslipidemia means the abnormal changes for one or more of lipids in the blood (NCEP, 2001). It is considered as strong predictor and pathogenic factor for common cardiovascular problems. There is significant relationship between blood cholesterol level and incidence of cardiac diseases, reduction of 1% cholesterol level decreases 1% incidence of cardiac diseases (Neaton *et al.*, 1992; 4S study, 1994 Grundy *et al.*, 2004).

1.2 Types of dyslipidemia

Two types of dyslipidemia mentioned by the literatures, these are primary and secondary. These types characterized by differences in levels of lipoproteins and cholesterol.

1.2.1 Primary dyslipidemia

It is caused by either single or multiple genetic changes induced overproduction and/or defects in the clearance of cholesterol, triglyceride (TG), low density lipoprotein (LDL), or due to higher clearance of high density lipoprotein (HDL). This type of dyslipidemia was discovered by Fredrickson and Friedewald (Friedewald *et al.*, 1972; NCEP, 2001; American Diabetes Association, 2006), and classified into subtypes 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

This type of dyslipidemia caused either by diseases like diabetes mellitus, hypothyroidism, hepatic diseases, renal insufficiency, pregnancy and systemic lupus, or chronic use of alcohol, estrogen, or therapy with antihypertensives like beta blockers and thiazides (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	
	Cyclosporine	Increased	Unchanged	Unchanged	Increased	Unchanged	Unchanged	

* Increased only in third trimester, SCr = Serum creatinine, TSH = Thyroid stimulating hormone

1.3 Dyslipidemia control

Reports of National Cholesterol Education Program (NCEP) in US found that elevation of cholesterol is the main cause for cardiac diseases like stroke, myocardial infarction…etc. The main parameters that needed to be controlled according to the Adult Treatment Panel (ATP) III report of NCEP are LDL and non-HDL (refers to total cholesterol excluding HDL) (Ballantyne *et al.*, 2001; NCEP, 2001).

Lipid profile is usually determined by calculating LDL, which can be measured by using the Friedewald equation (equation 1.1). Very low density lipoprotein (VLDL) is equal to TG/2.2 (the equation is considered invalid when the amount of TG more than 4.5 mmol/l). The non-HDL can be calculated directly from the equation no 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 Targets of dyslipidemia control

The control of dyslipidemia depended mainly on two parameters, LDL and non-HDL as reported by the NCEP ATP report III (NCEP, 2001). The goal of therapy to achieve these goals depended on the patient's health risks. These risks are classified into primary and secondary preventions.

Secondary prevention means the patients under the existed risks because of cardiac diseases or equivalent, which includes:

1- Clinical CHD myocardial ischemia, MI, coronary bypass graft and prior unstable angina.
2- Carotid artery diseases: stroke history, transient ischemia attack.

3- Peripheral arterial diseases.

4- Abdominal aortic aneurysm.

5- Diabetes mellitus.

Primary prevention means the expected risk of the patient in the future which depended on several parameters like gender, age, family history of CHD, hypertension, total cholesterol, HDL, and smoking (LaCroix *et al.*, 1991; Stamler *et al.*, 1993; Wilson, 1998; van den Hoogen *et al.*, 2000).

NCEP instructed the goals of therapy needed to control the dyslipidemia and prevent the cardiovascular diseases, for both LDL and non-HDL as shown in Table 1.3.

Table 1.3 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

Secondary dyslipidemia showed higher importance depending on the recommendations and results of the previous reports and studies because the relationship is significant between the targets and diseases. LDL elevation more than 100 mg/dl was correlated with the incidence of cardiovascular diseases (4S, 1994; Sacks *et al.*, 1996; LIPID, 1998). Therefore goal of therapy for patients with secondary prevention must be less than 100mg/dl (2.6 mmol/l) (Nissen *et al.* 2004),

while risk of patients with primary prevention reduced when LDL level was less than 129 mg/dl (3.4 mmol/l) (NCEP, 2001; Pearson *et al.*, 2003).

1.5 Assessment of lipid profile

According to NCEP reports, the lipid profile can be assessed to optimal, desirable, borderline high, high and very high depending on the levels of lipids as shown in the Table 1.4

Table 1.4 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

1.6 Antihyperlipidemics

Many antihyperlipidemics are used to achieve the control of dyslipidemia. Therefore, these medications are used either as single or in combination therapy. These medications are statins, niacin, ezetimibe, resin, fibrates, and fish oil. Among all these medications, statins are the more common use for cardiac patients because the highest efficacy according NCEP ATP reports (NCEP, 2001).

1.6.1 Statins

Statins are considered as the drug of choice for treatment of dyslipidemia and as prophylaxis against many cardiovascular diseases. Statins are inhibitors of 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) reductase which involved in the cholesterol synthesis (Goldstein and Brown, 1990; Grundy *et al.*, 1997; NCEP, 2001; Vaughan and Gotto, 2004).

1.6.2 Types of statins

Statins include atorvastatin, simvastatin, rosuvastatin, lovastatin, pravastatin, fluvastatin, and cerivastatin. The last type of statin was banned from the market because serious adverse drug reactions (ADRs). Eventhough, these types of statin are different in their efficacy due to the difference in the pharmacokinetic properties like bioavailability, lipophilicity, half life, and excretion (Jones *et al.*, 1998; Peter, 2003).

1.7 Uncontrolled dyslipidemia during therapy

Several reasons are correlated to inability to achieve dyslipidemia control during therapy; however few studies were focused on physicians' practice, patients' adherence and treatment adverse metabolic effects.

1.7.1 Physician's knowledge and practice

One of the reasons for failure of dyslipidemia therapy is the knowledge and awareness of physicians, because lacking in updated information resources such as reports and studies in assessing the patient properly and prescribing the optimal therapy (Sager *et al.*, 2010). Therefore physicians were needed for specific updated guidelines, based on the previous studies, about the significant required changes in the medications and regimens toward complications during therapy. The benefit of guidelines is improving the knowledge and decisions making of physicians after assessing and evaluating the patient's health status and the ways of managing the expected risks faced particularly in cardiovascular field. This is because cardiovascular diseases are considered number one cause of death for patients in many countries (Davidson, 2002; Pearson *et al.*, 2002; Davidson *et al.*, 2005; Asch *et al.*, 2006; Doroodchi, 2008)

NCEP recommendations to control of dyslipidemia obligated the physicians to determine the risks and how to prescribe the specific medications for this type of risk (Sheridan, 2003). Physicians' knowledge and awareness toward dyslipidemia guidelines are contributed to achieve the targets of control in health care system, where proportional relationship between physicians' knowledge and the improved patients' health status (Foley *et al.*, 2003; Heidrich *et al.*, 2005). Recent programs are

used nowadays in order to achieve the goals of therapy. Invented educational programs and management algorithms were implemented to obtain optimal assessment of control. The effective program depended on development of the old dyslipidemia guidelines of control like physicians' knowledge about the primary and secondary prevention, and programs of lifestyle changes such as nutrition and exercises (Goldberg *et al.*, 2007).

Different guidelines are followed in different countries, but the knowledge is the main tool to get the optimal result and improve the health status of patients. Some systems depended on computer to calculate the risk and the intervention needed to attain the goals of therapy, while other on physicians' performance to calculate these risks. Recently many inventions and programs were introduced in developed countries to facilitate and provide accurate evaluations, assessments, and treatment. The main reason was belonged to the practice and knowledge of physicians toward control of dyslipidemia and prophylaxis against the cardiovascular diseases (Hetlevik *et al.*, 2000; Murray *et al.*, 2004; Davidson *et al.*, 2005). Thus physicians' awareness in developed countries is significant to achieve the targets of dyslipidemia control (Erhardt and Hobbs, 2007; Cacoub *et al.*, 2008), while low control found in undeveloped countries was due to poor or average of physicians' knowledge toward the goals of therapy (Al-Omran, 2007).

Many physicians did not follow the instructions recommended by NCEP reports, allowing themselves prescribing the dosage regimens depending on their own experience which later cause fluctuation in control of dyslipidemia. To give an example, not all physicians believed that LDL is the main risk of cardiovascular

diseases if compared to total cholesterol (Goldberg *et al.*, 2007). Most of family physicians have differences in their knowledge towards the requirements to control dyslipidemia and other cardiovascular diseases (Eaton *et al.*, 2004). Previous studies showed poor knowledge of physicians in assessing the expected risks and medications regimens required to avoid the morbidities and mortalities, as well as, the evaluation of patients' health status and adherence (Mosca *et al.*, 2005).

Many international studies showed failure of achieving the goals of therapy, even patients were on the ideal guidelines and with good adherence to therapy. This is because most of physicians were motivated to prescribe higher doses of statin to attain the goals of therapy. Inversely, the patients' acceptance and confusion to use higher doses may reflect on their adherence to the prescribed medications, causing lower percentage of dyslipidemia control (EUROASPIRE II Study Group, 2001). On another view, physicians believed that higher dose of statin will achieve the predicted reduction of cholesterol to be in the healthy range, without determining the main reasons for the elevations of cholesterol (Schwandt and Brady, 2004; Van Ganse *et al.*, 2005)

Physicians are knowledgeable towards the adverse effects of common medicines like elevation of liver enzymes or renal disorders, but not to adverse effects of other medications like statins (Davidson *et al.*, 2005; Erhardt and Hobbs, 2007; Guan *et al.*, 2010). Studies reported that many physicians claimed that patient is the main cause of uncontrolled dyslipidemia either by not following their instructions like restricted diet and changing of life style, or due to the high cost of medications which affected on their adherence (Eaton *et al.*, 2006). Other studies

stated patients' related complaints for adverse effects of medications with higher doses and chronic therapy which triggered them either stopping usage or asking for changing of these medications (Pasternak *et al.*, 2004). As a result for the physicians' and patients' factors, new barrier observes is the responsiveness and efficacy of medications (Mosca *et al.*, 2005; Christian, 2006). The main objective of all previous studies was to eliminate the barriers and obstacles toward attaining the ideal result of dyslipidemia control sharing that with other healthcare professionals like pharmacists and nurses (Goldberg *et al.*, 2007). A gap found between physicians' knowledge and control of dyslipidemia; very low incidence of patient with CHD risks or risk equivalent found under control, while physicians claimed that most of their patients were controlled during the first years (Pearson, 2000; Mosca *et al.*, 2005). Depending on previous studies of dyslipidemia control, the patients with uncontrolled were correlated with the physicians who failed in estimation of the correct goal of therapy and prescribing of medications (Montgomery, 2000; Hirsch *et al.*, 2001; Hajjar and Kotchen, 2003; Pignone, 2003; Sheridan, 2003; Saydah *et al.*, 2004).

Second reason which believed to be contributed in the elevations of cholesterol and failure of treatment is insufficient number of recommended lipid profile tests performed to the cardiac patients which is considered as another commitment to the physicians toward their patients. Several reports and studies recommended increasing the number of lipid profile tests for patients per year and depending on the patients' health stability (Gold, 2004). There is responsibility of physicians for advising their patients about lifestyle and dietary therapy to control the dyslipidemia and cardiovascular diseases, because some habits like eating, smoking and consuming of alcohol may change the goals of therapy and aggravate the cardiovascular risks.

However, many physicians are not performing their non-pharmacological therapy, for example no difference between the physicians' dietary therapy and common smoking advices (Mukherjee *et al.*, 2002; Olson *et al.*, 2005; Doroodchi *et al.*, 2008; Sheridan and Crespo, 2008). Some of physicians' characteristics play role in enhancement of patients' health status such as years of experience, age, gender, and location of work. Some studies proved that old physicians had good experience in administration of therapy, but they are in lower adherence to the updated researches. Also, the awareness of the rural physicians is lower than urban which affects on the medical improvement of the patient (Doroodchi *et al.*, 2008).

1.7.2 Patients' adherence to dyslipidemia therapy

World Health Organization (WHO) defined the patients' adherence for long term as "the extent to which a person's behavior taking a medicine, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider". Patients' adherence means the compliance to their physicians' orders related to strategy of therapy (Rigby, 2007). It is considered one of serious problems related to achieve the goals of therapy to avoid the relapse or failure of therapy (Natarajan *et al.*, 2007). Failure of therapy was mostly happened in elderly patients who used multiple medications for very long time (Senior *et al.*, 2004). Many studies highlighted the common reasons of discontinuation of therapy because adverse drug reactions, cost of medications, psychological acceptance and many others (Vermeire *et al.*, 2001). Several methods were used in evaluation of patients' adherence either by direct effect of drug on blood drug concentration or indirect by questionnaires, pill count, refill rates, counseling, follow-up reminders and physiological parameters like cholesterol level (Osterberg and Blaschke, 2005).

Therefore tools were invented to assess the adherence of patients toward their therapy. The most useful and efficient scale was that of Morisky scale which used by many studies related to therapy of diabetes, hypertension and dyslipidemia (Morisky, 1986).

Several authors stated the relationship between patients' adherence and achieving the goals of therapy of dyslipidemia and maintain patients' life against cardiovascular risks (Kiortsis *et al.*, 2000). The number of patients were taken statin properly and regularly found with fewer incidences of cardiovascular risks and mortality (Heart Protection Study Collaborative Group, 2002). Kiortsis and colleagues declared that good hypercholesterolemia therapy adherents were old, none or seldom smoking patients, complained fewer adverse reactions, and those were regularly attended their appointments with doctors and used proper dosage regimens (Kiotrsis *et al.*, 2000).

Shalev V *et al.* found that patients with suboptimal adherence to statin therapy had got suboptimal LDL control (Shalev *et al.*, 2009). The discontinuation of statin therapy was also differently reported from study to another, but according to previous studies the rate of discontinuation ranged between 30-70% (Sokol *et al.*, 2005; Penning-van Beest *et al.*, 2007; Perreault 2008; Shalev *et al.*, 2009). However all these studies stated significant positive correlation between the duration of therapy and incidence of patients stopped taking their therapy (Benner *et al.*, 2002). To give some examples, Insull W. stated that incidence of patients discontinued statin therapy ranged 6-30% after five years (Insull, 1997). Australian Institute of Health and Welfare (AIHW) reported the incidence of patients discontinued their

therapy after six months was 10-28% which was raised to be 21-47% after 24 months (Rigby, 2007). While other studies stated unexpectedly low adherence with unexpected range of discontinuation; adherence to statin therapy was 50-85% after the first year and 45-50% after the fifth year (Newby *et al.*, 2006; Kulik *et al.*, 2011). Latry *et al.* believed that patients' poor adherence to lipid lowering agents was mainly affected by their characteristics such as gender, concurrent medication and diseases, but very few studies discussed the other cofactors related to adherence (Latry *et al.*, 2011). Another reason was related to physicians, Schedlbauer A *et al.* correlated between the physicians' performance and their patients' adherence to lipid lowering agents, where improvement of patients' adherence was seen after intervention given for physicians (Schedlbauer *et al.*, 2004). Another important cause for rate of discontinuation of statin is the cost factor. Several studies highlighted the relationship between the cost of medication and adherence rate. Interestingly the good adherence reduced the overall cost due to significant improvement of health patients' status and might be lower admissions or re-prescribing of new medications (Corrao *et al.*, 2011).

1.7.3 Common cardiac active ingredients and dyslipidemia

There were active ingredients that induced abnormal changes of lipid profile which were classified as secondary type of dyslipidemia (Stone *et al.*, 2008). All active ingredients were different in percentage of lipid profile changes; some increase, decrease or others unchanged, i.e. some may increase LDL while unchanged to HDL and so on. Many antihypertensives interact with lipid metabolism caused alterations in lipid profile like LDL, HDL, TG and TC, which they worsened patients' cardiac risks within the first year of therapy and minimizing the beneficial

effect of lipid lowering agents (Krone *et al.*, 1983; Rohlfing and Brunzell, 1986; Weidmann *et al.*, 1988; Grimm, 1990; Rabkin, 1993; Madu, 1996; Patel and Jackson, 2010). Ballantyne believed that long-term of thiazide diuretics was associated to higher incidence of atherosclerosis because observed elevation in LDL and dropping in HDL level (Ballantyne, 1990). Moreover, authors stated uncontrolled dyslipidemia within long duration of diuretic therapy, because the adverse metabolic indirect effect of these medication to patients' lipid profile (Ames, 1987; Ames, 1988; Lardinois and Neuman, 1988). Others found association between incidence of mortality and long term using high doses of thiazides and beta blockers, because affecting the insulin resistance, release of glucose and elevation of LDL cholesterol (Teuscher and Weidmann, 1997; Sarafidis and Bakris, 2006).

Lijnen and colleagues stated the mechanisms for the worst antihypertensive type, the thiazides, which induced biochemical changes by inhibiting phosphor-diesterase enzyme and inducing lipolysis (Lijnen *et al.*, 1989). Weir and Moser revealed other mechanisms of diuretics; first by decreasing the insulin sensitivity causing higher production of cholesterol, and second by lowering the potassium level during thiazide therapy (Weir and Moser, 2000). However the adverse metabolic effect of thiazides was more predictable for patients following therapy up to 4 years (ALLHAT Collaborative Research Group, 2002). Calcium channel and beta blockers were also correlated to change of lipid profile by different mechanisms such as affecting cellular lipid metabolism, lipase dysfunction, and LDL receptors (Krone W *et al.*, 1987; Wolinsky, 1987; Lijnen *et al.*, 1989). A stimulation of alpha adrenergic receptors as result of blocking beta receptors caused reducing the activity of lipase enzyme and catabolism of TG, VLDL, and then reduced the HDL level (Weir and

Moser, 2000). Also it noticed there is no relationship between abnormality of lipid profile and selectivity type of beta blockers, both selected and non-selected drugs increased TG and reduced HDL levels (Lehtonen, 1985; Hunninghake, 1991). Sharp *et al.* explored the adverse metabolic effects of antihypertensives in twelve studies concluded changes of lipid profile induced by carvidolol comparing with selective beta blockers. So they recommended for choosing the appropriate antihypertensive type because it also attributed for therapy failure of dyslipidemia, hypertension and congestive heart failure (Sharp *et al.*, 2008). Cooper-DeHoff found significant increase in patients' body weight and triglyceride during therapy of beta blockers and hydrochlorthiazide (Cooper-DeHoff *et al.*, 2010). As well as, these antihypertensives were different in increments of certain lipid (Rouffy *et al.*, 1984). To give example spironololactone is the lowest adverse lipid elevator when compared to other types of diuretics (Ames, 1988). Some authors believed that changes of lipid profile were mostly attributed to the dose of administrated antihypertensive medications (Weirand Moser, 2000).

Inversely some studies found antihypertensive medications, such as alpha blockers, reduced the total cholesterol and improved HDL level by stimulating carbohydrate and lipid metabolism, reducing glucose, LDL, VLDL and improving HDL (Waite, 1991). Ashida found Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) have neutral effect toward cholesterol (Ashida, 2001). Other studies predicted the neutrality and positive lowering effect of some antihypertensives compared to lipid elevating medications, a reduction and better control of cholesterol during administration of calcium channel blockers, ARBs and ACE-Is (Brook, 2000; Papademetriou, 2007; Nouri-Majalan *et al.*, 2009).

Recent studies insisted about the possible interactions of antihypertensive medications with lipid profile changes. Diltiazem inhibited the activity of CYP3A causing better efficacy of statin and more reduction in LDL level (You *et al.*, 2010). Therefore selectivity of antihypertensives must be considered during prescribing the ideal medication to control hypertension with lowest adverse metabolic effects (Salvetti A and Ghiadoni, 2006).

1.8 Definition of the excipient

There are several definitions of excipients mentioned by many previous reports. According to the common definition mentioned by the National Formulary Admission Policy that "Excipients are any component other than the active substance(s) intentionally added to the formulation of a dosage form" (USP, 1992). Another definition in term of pharmaceutical manufacturing by Steinberg, "any material used in the preparation or formulation of a finished drug dosage form, other than the active pharmacological agent", and the new excipient is "a compound which has not been previously used or permitted for use in a pharmaceutical preparation" (Steinberg *et al.*, 1996). There is another definition in point of view of the safety and toxicity by International Pharmaceutical Excipients Council (IPEC) of America for the excipient, which is defined as "Any substance other than the active drug or prodrug which has been appropriately evaluated for safety and is included in a drug delivery system" (Steinberg *et al.*, 1996).

1.8.1 Benefits of excipients

All medications must have excipients that perform a function inside the dosage form to enable the medications to work properly inside the human body. Number of active ingredients in each dosage form is lower if compared with number of excipients The main sources of excipients are either naturally or synthetically, and different in their nature i.e. organic or inorganic (Bhattacharyya *et al.*, 2006). IPEC determined the functions and requirements for using of excipients in manufacturing of medications (Steinberg *et al.*, 1996), these are: (1) support the system of manufacturing, (2) enhance or improve the palatability, stability, solubility and bioavailability, (3) support the identification of medication, and (4) supply the evidences of its safety and efficacy. The main functions of excipients are to advance the properties of the dosage form and bioavailability. The excipients are used for a function inside the formulation to make its performance better and targeted, these materials are; (1) fillers or diluents, (2) binders, (3) disintegrants or super disintegrants, (4) lubricants, (5) antiadherents, (6) glidants, (7) wetting and surface active agents, (8) colors and pigments, and (9) flavors, sweeteners, and taste maskers (Chowan, 1998; Wheatley, 2000; Bhattacharyya, 2006). Some excipients have been used to a specific function in its dosage form, work as antimicrobial which react with oxygen to inhibit the contamination of medication or food such as sulfites (Bush *et al.*, 1986), or to improve the acceptability by patients in term of palatability or color. Some excipients used to activate the active ingredient, for example polyethylene glycol (PEG) added to enhance the activity and bioavailability of calcium channel blockers or benzodiazepines (Hjortkjaer *et al.*, 1999; Rahman and Lau-Cam, 1999).

Excipient were also classified in to three classes based on their common use; established (approved), new (novel), and essentially new excipients (from other industries). The first class referred to the known excipients which had been used for long time in pharmaceutical preparations. The first twelve common excipients among 800 substances used in US are; water, magnesium stearate, starch, lactose, microcrystalline cellulose, stearic acid, sucrose, talc, silicon dioxide, gelatin, acacia, dibasic calcium phosphate, and sugar free excipients. Approvals of new excipients depended on preclinical studies which are different from country to another. For example some new excipients are not found in US (CDER) or Japan but use in Europe (Brown, 1983; Shangraw, 1986; Center for Drug Evaluation and Research, 1987; DeGeorge *et al.*, 1997; Japanese Technical Requirements for New Drug Registration, 1997; Baldrick, 2000; Bhattacharyya, 2006).

Based on previous reports for manufacturing of medications, changes of excipients in dosage forms cause changes in results of their standardization, which make companies to look for new excipients for new formulations as new products. Furthermore, the companies need to prepare the clinical trial studies about the safety of new pharmaceutical excipients, and appropriateness to the other ingredients in dosage form (Pifferi *et al.*, 1999). Although significant developments in manufacturing of medications, many of excipients still cause fatal problems such as bladder tumor and adrenal/testes problems due to saccharine and polyols respectively, and some derivatives of cyclodextranes may cause renal dysfunctions (Herbert, 1998; Thompson, 1997; Mosher and Thompson, 2000).

1.8.2 Safety of excipients

Everything related to manufacturing of medications must be supervised by a main organization to control the using of excipients, called The International Pharmaceutical Excipients Council (IPEC). This organization approves the memberships of the companies, manufacturing, and use of chemicals and excipients. It has also many branches over the world, such as in US, Europe and Asia. Therefore, the new excipients must be approved by the IPEC to ensure the safety and toxicity of the new products. The safety committee of the IPEC is responsible to conduct the studies related to toxicity of the excipients, especially the animal studies and human with chronic exposure to excipients (Steinberg *et al.*, 1996). In the world, including developed countries, there are no regulations of registration for the excipients as a separate entity, neglecting the activity and safety of the excipients. FDA started to test all the medications in US for both active ingredients and excipients of formulations, for getting the full details of their safety and efficacy (Brown, 1983).

Most of the toxicities and adverse drug reactions correlated mainly with the pharmacokinetic of all excipients, and some with pharmacodynamic for few excipients. The studies search the pharmacokinetic of active ingredients and excipients called Toxicokinetics, which related with the absorption, distribution, metabolism, and excretion of these chemicals. Excipients are similar to active ingredients in their pharmacokinetics but there is difference in percentages of absorption, distribution... etc. This difference allow some excipients to exert their adverse effects and other parameters of toxicity, for example, some of excipients may pass the blood brain barrier, placenta, testis barrier, which likelihood cause some adverse reactions in the related areas. The absorption of the excipients is

varying depending on the physicochemical properties of these excipients. To give example, high molecular weight compounds lack to the absorption property, so they are without systemic effect, but it may cause gastrointestinal adverse effects. There is another factor related with pharmacokinetics is the age of the user, which refers to the pharmacokinetic and physiological changes of elderly persons, and their effects on absorption of both active ingredients and excipients. However, these parameters of toxicokinetics are different among the animal species if compared to humans (Frank *et al.*, 2000).

There are types of experiments that must be done to approve the safety of the excipients after manufacturing, however the human studies depended mostly on the single dose treatment. The safety must cover the carcinogenicity and mutagenicity like fertility and embryo fatality, as well as, the chronic use must be applied for 3 months as maximum and must be done on animals only (U.S. Federal Food, Drug, and Cosmetic Act, 1990; Steinberg, 1996). Most of excipients used in the formulations are safe in terms of teratogenicity and carcinogenicity, but there are exceptions about some excipients which can not considered as safe materials like narrow safety margins' materials (Golightly *et al.*, 1988). These types of preclinical studies that must be applied before use of excipients are; 14 days therapy or less, infrequent use, repeated dose toxicity and this must be applied on two mammalians for one month (Davis, 2006). The IPEC and the FDA are responsible to determine the strategy of preclinical studies, depending on the duration and strength of seriousness (Osterberg and See, 2003). Most of excipients previously tested to be safe for teratogenicity and carcinogenicity or with minimal toxicity when tested in animals. Eventhough, some excipients induced severe adverse reactions like nasal

toxicity due to ethylene glycols, maternal toxicity by corn oil, renal and liver toxicity in rats by cyclodextrines, renal dysfunction with proteinuria by dibasic sodium phosphate, increase in triglycerides and cholesterol by Poloxamer (P-407), and maternal and embryo toxicity by propylene glycol. Polyvinyl acetate phthalate (PVAP) cause gastrointestinal tract irritations. Tartaric acid caused diarrhea, emesis, and fall of blood pressure in dogs and nephrotoxicity in monkeys. Also pharmaceutical excipients of parenteral formulations caused hemolytic changes. Regrettably the preclinical studies are given the minimal evidence about the safety of excipients and other medications (Baldrick, 2006;Robert, 2006).

Most of healthcare professionals believed that testing in animals is safe to be used by human. Although many studies applied on animals to show the safety of excipients but the results found in animals are different with humans. In other word, it is not possible to generalize these results of these healthy animals to elderly human patients (Napke, 1994). Moreover, there are differences in species between human and other animals in metabolism, which affect on the activities of excipients and then safety and ADRs. Thus there was inadequate information about the metabolism of excipients in human if compared to animals. Some of excipients and active ingredients are good absorbed in human and poor in animals which later affect on the safety and ADRs, and vice versa. For example, cyclamate is metabolized in human's intestine forming toxic substance cyclohexylamine which not formed in animals, therefore its toxicity disappeared due to differences in the metabolism occurred in bowel (Bopp *et al.*, 1986; Frank, 2000).

The development in manufacturing of new dosage forms was followed by many changes in the old excipients, which later changed in their activity and safety and needed to be retested again. Most of new invented excipients had got new properties like enhancing the function of excipients or by having multiple functions in same time, but not focused on the new adverse reactions and toxicities (Pifferi *et al.*, 1999). As well as, there was difference in incidence of toxicity induced by excipients depending on type of dosage form (oral, parenteral, transdermal …etc). For the most popular dosage form, oral forms, it required some tests to approve the excipients like; acute oral toxicity, 28 days toxicity, teratogenicity and chronic use in animals, chromosomal damages and mutations, and skin problems. There is challenge about excipients and their safety in human, because first it is impossible to perform studies in human using new excipients. Second the safety and activity of excipients are different from dosage form to another, therefore it is not possible to say that this excipient is safe in all dosage forms. As example, some authors recommended for changing of human serum albumin to polysorbate 80 because it influenced on immunogenicity of the proteins medications (Sharma, 2007).

Some new excipients without full reports about their safety and toxicity are added in the manufacturing of medications to do a function in the dosage form. For example, some excipients used in the prodrug formulation, or to enhance the efficacy of medications like chitosan, or in monoclonal antibodies that considered as new dosage forms. There are many other factors influence and motivate the toxicities in human body, like the impurities of excipients used or due to the excipients interactions (Nema *et al.*, 2002). Many of the excipients used by the food manufacturing are used in pharmaceutical medications too which helped the

manufacturers to consider these excipients as safe, but some differences found like the period of exposure and then safety. This is because most of excipients tested for not more than 6 weeks to show safety and not all excipients are taken by people continuously and for long duration concurrently with diseases. Second, the food's excipients are used by oral route only which excluded pharmaceutical excipients of other routes. Third, standardizations of pharmaceutical excipients in dosage forms are higher than food one, because food excipients are not standards with less purity (Ja¨kel and Keck, 2000). In Japan, all the excipients used in manufacturing of food considered as new excipients in manufacturing of pharmaceutical products (Uchiyama, 1999).

Manufacturers believed that pharmaceutical excipients are safe and harmless to human body, because most of their serious adverse reactions were not predicted yet. Also, the multiple numbers of excipients taken by patients had showed inability to diagnose the problems caused by excipients in clinical trial studies (Napke, 1994). To give a good example about unsafe excipient, lactose is commonly found in food and pharmaceutical preparations, and its incidence of intolerance or sensitivity of white patients was 5% to 15%, while for other races was 60% - 90%. Lactose also contributed for high incidence of abdominal distension and diarrhea after lactose ingestion (Toskes, 1992). So, how many studies involved animals ingested with lactose as placebo or patients used lactose dosage forms, and what its effects on the studies' outcomes (Napke, 1994).

Even the small doses of excipients presented in dosage forms and taken by patient, but always there is minimal adverse reactions were predicted, as found

during use of benzalkonium chloride that not showed ADRs in the first dose (Rafferty *et al.*, 1988; O'Driscoll *et al.*, 1989). However, the toxicity for some excipients was independent to the concentration especially those with multiple functions. For example, benzyl alcohol used as preservative and solubilizer, and decomposed into hydrogen peroxide and benzaldehyde but adverse reactions are different than main compound (Ja¨kel and Keck, 2000).

Governments and health organizations obligated manufacturing companies in developed countries to disclose the full details of their products to the patients and healthcare professionals to avoid problems found during therapy (Napke, 1994). Previous study showed evidence of adverse drug reactions of excipients; patients with Addison disease were more comfortable to one brand and complained new ADRs after changing to another brand. Main reasons are either direct by the excipients themselves or indirect because changeable parameters of bioavailability of the active ingredient (Whittet, 1971). Thus conducting of clinical studies is required, focusing on the long duration of therapy especially the new excipients found in medications' dosage forms (Spire *et al.*, 2003). Trial studies are burdens for the manufacturers because of reliable results of equivalence and safety, but in case of multiple doses with multiple medications in chronic use by ill patients, this opinion shows some limitations (Castle *et al.*, 1969). Edward Napke believed there is deficiency in reported information of ADRs in hospitals, and need for development of ADR surveillance system, especially related to excipients and their ADRs because the system information is only related to active ingredients (Napke, 1994; Anderson *et al.*, 2006).