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The analysis of pharmacotherapy in patients suffering from hyperlipidemia

(Diploma Thesis)

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ABSTRACT ENGLISH

The analysis of pharmacotherapy in patients suffering from hyperlipidemia
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Introduction: Hyperlipidemia is a serious condition whereby the blood levels of lipids, cholesterol and triglycerides are abnormally elevated. This condition is generally asymptomatic but may lead to atherosclerotic heart disease and other types of cardiovascular pathology if not treated effectively. Various risk factors can affect the onset and severity of hyperlipidemia and those include genetic predisposition, hypertension, diabetes mellitus, obesity, poor diet, lack of regular exercise, smoking etc. Measurement and monitoring of blood levels of triglycerides, cholesterol and lipoproteins can be used as prevention method for assessing the risk for an individual to develop hyperlipidemia. Once a patient is diagnosed with the condition several approaches exist for the treatment. The main goal of the treatment is to reduce the risk of atherosclerosis-based disease, to reduce another complication of hyperlipidemia – namely. pancreatitis, by lowering the levels of LDL-C, triglycerides and cholesterol in the blood and to lower the influence of other risk factors. Medication is usually prescribed to reduce lipid levels. The main type pf pharmacotherapy involves the use of statins either as a monotherapy or in combination with other medication such as fibrates or ezetimide. In addition, lifestyle changes are considered to enable the decrease of lipid levels and enhance the effectiveness of the pharmacotherapy.

Aim: The aim of the practical part of this project was to analyse, in a pilot pharmacotherapy study, hyperlipidemia in Greece.

Methods and results: We used information obtained from selected patients diagnosed with hyperlipidemia (sample of 78 patients in a Greek village) and understand the background of the disease onset and severity. In addition, the pharmacotherapy approaches followed to treat the patients were analysed along with an evaluation of the effectiveness of the medication. The information was obtained with the aid of a questionnaire filled by the patients, providing the appropriate information on their medication scheme and their views on the treatment. Statins were uses as a more frequent pharmacotherapy and majority patient´s belief to the effect of medicine is high.

ABSTRACT CZECH

Analýza farmakoterapie u nemocných trpících dyslipidémií
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Úvod: Hyperlipidémie je závažný stav, při kterém jsou abnormálně zvýšeny krevní lipidy: cholesterol a triglyceridy. Tento stav je obvykle asymptomatický, a pokud není efektivně léčen, může vést k aterosklerotickým změnám cév a pak k poškození myokardu nebo jiných na kyslíku významně závislých orgánů. Různé rizikové faktory (např. genetická predispozice, arteriální hypertenze, obezita, nevhodné stravovací návyky, nedostatek pohybu, kouření) mohou ovlivnit začátek a závažnost hyperlipidémie. Monitorování triglyceridů, cholesterolu a lipoproteinů je jednou z preventivních metod určení rizika individuálního rozvoje hyperlipidémie. Jsou různé strategie léčby, jejichž cílem je redukovat rizika vývoje nemocí na základě atherosklerózy a i komplikace přímého vlivu lipidů na jednotlivé orgány – jako je např. pankreatitida. Cíle léčby dyslipidémie je dosahováno snížením lipidů v plazmě a snižování dalších rizikových faktorů související s atherosklerózou. Lékem volby ve většině případů jsou statiny v monoterapii nebo v kombinaci s ezetimidem a důležitou roli vždy hrají i režimová opatření a potravní návyky.

Cíl: Cílem praktické části bylo v pilotní studii analyzovat farmakoterapii u řecké populace.

Metoda a výsledky: Použili jsme dotazníkovou metodu u návštěvníků lékárny s diagnózou dyslipidíémie. Také jsme u nich sbírali údaje informace o této nemoci, způsobu kontroly, komorbiditách a farmakoterapii. Nejčastěji byly používány statiny a u většiny nemocných byla i vysoká důvěra v předepsanou farmakoterapii.

Table of Contents

1. INTRODUCTION

Hyperlipidemia or dyslipidemia refers to the disorder of lipoprotein metabolism. The condition is characterized by elevated levels of lipids, triglycerides and cholesterol in the blood. Hyperlipidemia is implicated in the development of cardiovascular disorders such as atherosclerosis, coronary heart disease (CHD), peripheral vascular disease and it may lead to heart failure and myocardial infraction (MI) as well as stroke [1]. Hyperlipidemia is typically associated with elevated serum lipoprotein levels which result in increased total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), while the high-density lipoprotein-cholesterol (HDL-C) levels are decreased [2].

Hyperlipidemia is an asymptomatic disease [3] that if is left untreated or undiagnosed could lead to decline of cardiac function and eventually to heart disease. The elevated lipid levels in blood can induce atherosclerosis (hardening of the arteries) causing a plaque formation in the walls of the arteries. The plaque is composed of the lipids circulating in the blood. As a result, arteries are getting narrower and the blood flow is reduced, thus increasing the risk of heart and vascular disease and/or stroke [4].

Diagnosis of the condition is carried out by measuring the lipid levels in blood. Prevention of the disease is based on the healthy diet and regular exercise and most importantly on the understanding of the strong genetic background of the disorder [4].

It is advised that individuals are regularly monitoring their blood levels of lipids, blood pressure (hypertension), maintain a healthy diet, take regular exercise and generally follow a healthy lifestyle. In diagnosed cases of hyperlipidemia, medication is usually prescribed. The aim of medication for the treatment of hyperlipidemia is to reduce the risk of developing atherosclerotic heart disease by lowering the levels of LDL-cholesterol, triglycerides and increase the HDL-cholesterol levels [4].

Collaboration between the physician and pharmacist is required to provide all the required information to the patient. The best prevention comes through knowledge and understanding of the pathophysiology and risks that may lead to hyperlipidemia and subsequently to heart disease.

2. HYPERLIPIDEMIA

2.1 Epidemiology

Occurrence of hyperlipidemia varies among populations in different countries and it seems it is related to the diet people follow. For example, populations that follow Western type diets (rich-in saturated fatty acids) generally have higher TC, TG and LDL-C levels than countries where people consume small amounts of saturated fats (trans fatty acids, etc). It's important to mention that theoretically there is no ideal serum lipid concentration and it could vary among different people through different countries of Europe. Just for practical purposes we use to consider work with some values as present the target levels of lipids for the patients who are under pharmacotherapy for secondary prevention of CVD. These target levels are listed below in Table 1. Even though we reach a 50% reduction in death rate caused by CVD the last 25 years, this disease still remains one of the main causes of premature death and morbidity, according to the British Heart Foundation. Figure 1 demonstrates the significantly higher risk of low and middle income individuals to develop CVD compared to other serious disorders such as cancer, respiratory or infectious diseases. There is a greater risk for developing CVD for each person when the level of TC is high. Until now, at individual level, there is no evidence that a further reduction in TC and LDL-C could reduce the risk of CVD. Males have a threefold greater risk of death caused by CVD than females, but due to the fact that women have higher life expectancy than men, and they are at higher risk of brain stroke after the age of 75, their life time risk for that disease is higher according to information provided by the British National Institute of Health and Clinical Excellence [5]. An example among populations' specificities is that in British men aged 45-64 years the TC levels tend to increase over the years reaching a level that exceeds 5 mmol/L while the population average is 5.6 mmol/L. On the contrary, in agrarian Japan and China areas, the average level of peoples' TC is 4 mmol/L. [5]

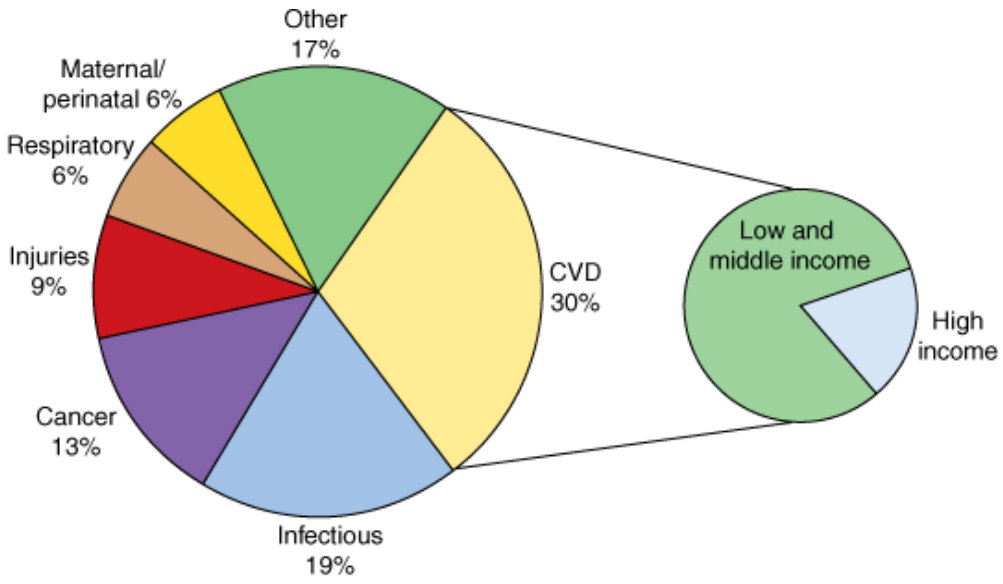
Table 1: Optimal serum lipid profile [5]

Biomolecule	**Target level**
Total cholesterol (TC)	< 4 mmol/L
LDL cholesterol (LDL-C)	< 2 mmol/L
Triglycerides (TG)	< 1.7 mmol/L
HDL cholesterol (HDL-C)	> 1 mmol/L in men > 1.2 mmol/L in women

(LPL: lipoprotein lipase; HDL: High Density Lipoprotein Cholesterol; CHD: Coronary heart disease).

According to current worldwide surveys, about 85% of the world's population live in low and middle-income countries, we have expected information about deaths caused by CVD. In the year 2001 have been estimated 3 million deaths in developed countries and in the rest of the world just 13 million [6]. The aforementioned fact proves of how great importance is the life style and diet for individuals. In developed countries where people mostly have a sedentary and stressful life due to many obligations and the nature of their jobs of the type of diet they follow, which is mostly processed food, make the risk of CVD to be much higher.

See also the chapter "5.3 - Risk factors".



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Figure 1: Cardiovascular Disease (CVD) data compared with other causes of death. [6]

2.2 Pathophysiology

There are several types of lipids in human organism. Those with clinical importance in the development of dyslipidemia are the non-esterified and esterified cholesterol and triglycerides; which are not soluble in blood serum and thus get incorporated into lipoproteins rendering miscible.

Six main classes of lipoproteins have been identified and these include: **i)** High-density lipoproteins (HDL-C), **ii)** Low-density lipoproteins (LDL-C), **iii)** Intermediate-density lipoproteins (IDL-C), **iv)** Very low-density lipoproteins (VLDL-C), **v)** Chylomicron remnants and **vi)** Chylomicrons**.**
Lipoproteins consist of the lipid and protein part. Protein components are known as apoproteins (apo). The most important apoproteins are A-1, B, C and E. Apoprotein B (apoB) exists in two forms: B-48 (found in chylomicrons and contributes to the transportation of ingested lipids) and B-100 (present in endogenous VLDL-C contributing to the transportation of lipids from the liver).

After digestion TG and cholesterol are transported to intestinal lymphatics from intestine as chylomicrons. Triglycerides normally constitute 80% of the chylomicrons' lipid core. An enzyme known as lipoprotein lipase which is located in adipose and skeletal muscle tissues is activated by apoC-II located at the surface of chylomicrons. This enzyme is responsible for the breakdown of TG from chylomicrons to glycerol and free fatty acids and then they can enter the adipose, muscle and cardiac tissue for further metabolic pathways. After that step, the chylomicron remnants distribute the cholesterol to the liver by binding to receptors at the surface of hepatocytes, for their clearance via the blood circulation. The transportation of TG from the liver to the peripheral tissues is carried out by endogenously secreted VLDL-C with the same manner like chylomicrons, and IDL-C are formed.

An enzyme called lecithin-cholesterol acyltransferase (LCAT) converts cholesterol to a more hydrophobic molecule, the cholesterol ester. Cholesterol esters constitute approximately the 50% of the lipid core of IDL-C particles and TG in the same percentage, respectively. IDL-C particles loose about 50% of their body mass after their clearance in the liver and the rest is further hydrolysed and thus apoE-I and LDL-C particles are formed. LDL-C is of great importance because it is the major transporter of

cholesterol in the blood serum. It has the ability to provide the cholesterol molecules to cells that require it in order to build up their membranes as well to create bile acids and steroid hormones. LDL-C is also strongly associated with atherogenesis, a harmful process for vascular bed. It is of great importance to mention that LDL-C implicated to atherogenesis only when it is oxidized by free radicals inside the arterial endothelium [7].

Monocytes migrate into the permeable endothelium and there under the M-CSF influence they are differentiated into macrophages. Macrophages finally engulf the oxidized LDL-C particles forming the foam cells. LDL-C and VLDL-C are considered as the harmful lipoproteins for the development of atherosclerosis, whilst, the HDL-C is known as the "good" lipoprotein which works towards preventing atherogenesis. It is also known as the antiatherogenic lipoprotein. LDL-C carries out approximately 65% of TC while HDL about 25% [8, 9]. It may be mentioned that HDL-C has a key role in preventing atherosclerosis via a metabolic pathway known as reverse cholesterol transport. This is the pathway through which lipoprotein and cholesterol return to the liver in order to be excreted. HDL-C major structural protein is the apoA-I. It consists of unesterified cholesterol and phospholipids which have been removed from the proteins rich in TG and other peripheral tissues.

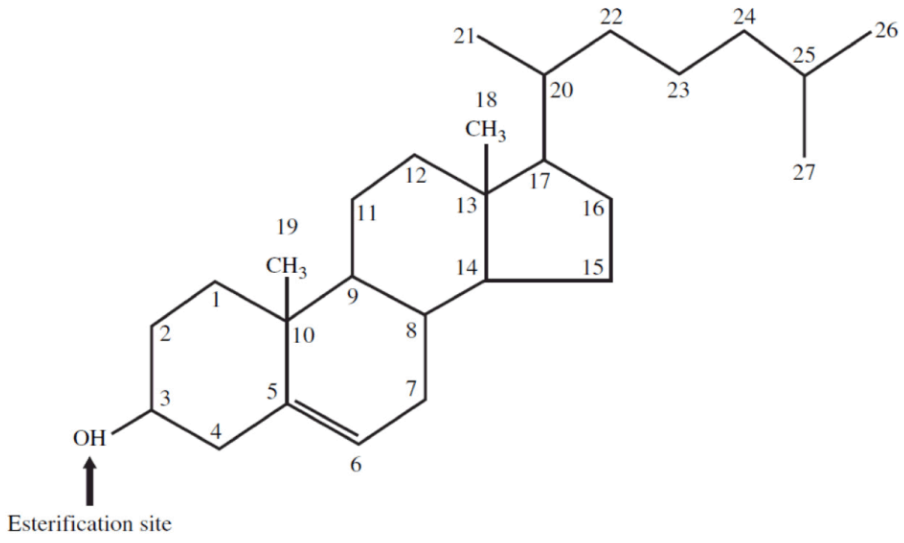


Figure 2: Cholesterol, the chemical structure of cholesterol [13]

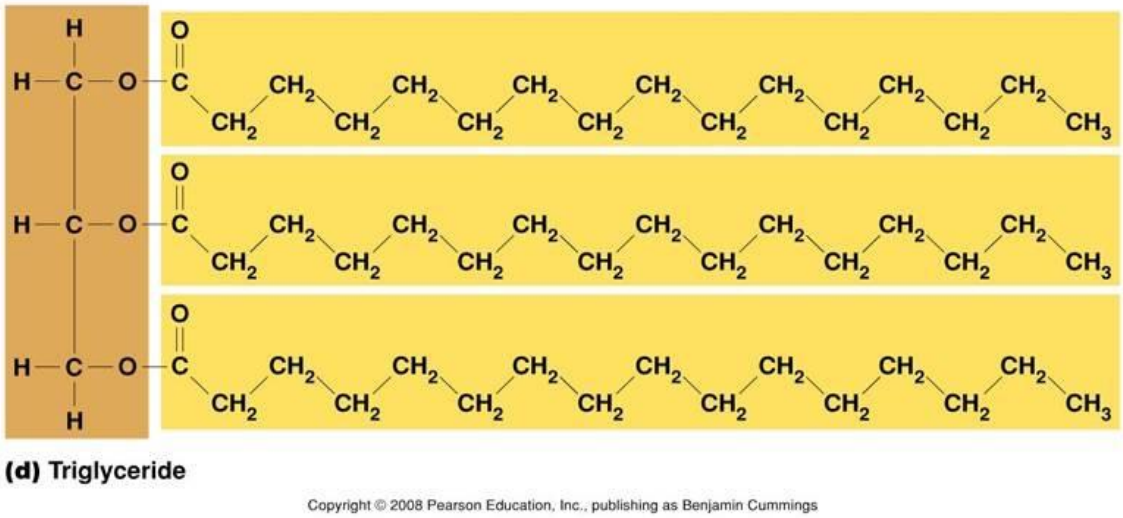


Figure 3: Triglycerides, the chemical structure of triglycerides [14]

The abnormalities of the lipid metabolism can be caused due to the combination of genetic and environmental factors. Hyperlipidemia can be classified into primary and secondary. Primary hyperlipidemia is usually a result of genetic defects. Secondary hyperlipidemia on the other hand, is associated with other conditions such as obesity, type 2 diabetes, low levels of HDL-cholesterol, high levels of triglycerides and increased blood pressure (hypertension), all of which are directly linked to heart disease [2, 10, 11].

Some disorders may be associated with dyslipidemia, but they are not the causal factors for it. An example is hyperuricemia and hypertriglyceridemia which co-exist in about 50% of men. In this case the treatment of one disorder cannot resolve the other. The following tables (Tables 2 and 3) show the categories of the primary hyperlipoproteinemias caused by known single gene mutations and the number of disorders which negatively affect the lipid profile, in the cases of secondary dyslipidemias.

Table 2: Primary hyperlipoproteinemias caused by single gene mutations

Genetic Disorder	Protein (gene) defect	Lipoproteins elevated	Clinical findings	Genetic transmission	Estimated incidence
Lipoprotein lipase deficiency	LPL	Chylomicrons	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
Familial apolipoprotein C-II deficiency	ApoC-II (APOC2)	Chylomicrons	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
ApoA-V deficiency	ApoA-V (APOA5)	Chylomicrons and VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AD	<1/1,000,000
GPIHBP1 deficiency	GIDIHBP1	Chylomicrons	Eruptive xanthomas, pancreatitis	AD	<1/1,000,000
Familial hepatic lipase deficiency	Hepatic lipase (LIPC)	VLDL remnants	Pancreatitis, CHD	AR	<1/1,000,000
Familial dysbetalipoproteinemia	ApoE (APOE)	Chylomicron and VLDL remnants	Palmar and tuberoeruptive xanthomas, CHD, PVD	AR or AD	1/10,000

Familial hypercholesterolemia	LDL receptor (LDLR)	LDL	Tendon xanthomas, CHD	AD	1/500
Familial defective apoB-100	ApoB-100 (APOB)	LDL	Tendon xanthomas, CHD	AD	<1/1,000
Autosomal dominant hypercholesterolemia	PCSK9 (PCSK9)	LDL	Tendon xanthomas, CHD	AD	<1/1,000,000
Autosomal recessive hypercholesterolemia	LDLRAP	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000
Sitosterolemia	ABCG5 or ABCG8	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000

Resource: HARRISON'S PRINCIPLE OF INTERNAL MEDICINE, VOLUME 2, 18th Edition, page 3149. (LPL: lipoprotein lipase; ApoA-V: apolipoprotein A5; ApoB-100: apolipoprotein B-100; ApoC-II: apolipoprotein C2; ApoE: apolipoprotein E; VLDL: very low density lipoprotein; GIDIHBP1: glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1; LIPC: hepatic lipase; CHD: coronary heart disease; PVD: peripheral vascular disease; LDLR: low density lipoprotein receptor; PCSK9: proprotein convertase subtilisin/kexin type 9; LDLRAP: low density lipoprotein receptor adapter protein; ABCG 5 or 8: ATP-binding cassette, subfamily G, member 5 or 8, respectively).

Table 3: Secondary forms of Hyperlipidemia

LDL elevated	LDL reduced	HDL elevated	HDL reduced	VLDL elevated	IDL elevated	Chylomicrons elevated	Lp(a) elevated
Hypothyroidism	Severe Liver Disease	Alcohol	Smoking	Obesity	Multiple myeloma	Autoimmune disease	Renal insufficiency
Nephrotic syndrome	Malabsorption	Exercise	DM 2	DM2	Monoclonal gammopathy	DM 2	Inflammation
Cholestasis	Malnutrition	Exposure to chlorinated hydrocarbon	Obesity	Glycogen storage disease	Autoimmune disease		Menopause
Acute intermittent porphyria	Gaucher's disease		Malnutrition	Hepatitis	Hypothyroidism		Orchidectomy
Anorexia nervosa	Chronic infectious disease		Gaucher's disease	Alcohol			Hypothyroidism
Hepatoma	Hyperthyroidism			Renal failure			Acromegaly
				Sepsis			Necrosis
				Stress			
				Cushing's syndrome			

				Pregnancy			
				Acromegaly			
				Lipodystrophy			

Resource: HARRISON'S PRINCIPLE OF INTERNAL MEDICINE, VOLUME 2, 18th Edition, page 3152 (LPL: lipoprotein lipase; HDL: High Density Lipoprotein Cholesterol; VLDL: very low density lipoprotein; IDL: Intermediate lipoprotein cholesterol; Lp(a): Lipoprotein a).

The different types of hyperlipidemia are listed and discussed below:

1) Familial hypercholesterolemia.

This type of hyperlipidemia is divided in two subtypes. Heterozygous familial hypercholesterolemia that affects about one over 500 individuals, caused by a variety of genes mutations affecting negatively the metabolic pathway of clearance of LDL-C and influencing the function of LDL receptors, and homozygous type of hypercholesterolemia which is very rare and the organism is fully unable to create LDL receptors hence it is impossible to clear the LDL-C. In the case of familial hypercholesterolemia, treatment quite often requires liver transplantation. Patients with heterozygous FH, suffer from CVD approximately 20 years earlier than other individuals and patients with homozygous type suffer of MI even at the age of 1.5-3 years. Sudden deaths have been reported even before the age of 20 years. [10]

2) Familial combined hyperlipidemia.

In this type of hyperlipidemia, patients suffer from excessive VLDL-C synthesis and have also high levels of LDL-C and TG. The levels of apoB and small dense LDL particles are also elevated. Patients suffering from combined hyperlipidemia have an increased risk for CHD, before reaching the age of 60. [11]

3) Familial type III hyperlipoproteinemia.

In this type of hyperlipidemia, VLDL and chylomicron levels in blood serum are increased through the failure of their clearance by hepatic receptors. It happens due to the fact that polymorphic forms of apoE are less active than in normal individuals. The levels of TG and TC are also elevated. This disorder is accompanied with premature atherosclerosis. [12]

2.3 Risk Factors

While the major cause of CVD is atherosclerosis, the management of risk factors is of great importance, because it can reduce the progression of atherosclerotic complications.
For practical purpose we could divide risk factors into two categories:

Treatable Risk Factors and Untreatable Risk Factors. [15, 16]

Treatable Risk Factors:

1. Hypelipidemia
2. Low HDL-C[a]
3. Hypertension
4. Smoking
5. Diabetes mellitus
6. Sedentary life
7. Obesity[b]

Untreatable risk factors:

1. Age[c]
2. Sex[d]
3. Genetic disposition
4. Family history of premature CHD[e]

[a] *<40 mg/dL for men and <50 mg/dL for women*

[b] *Body mass index (BMI) >25 kg/m2*

[c] *Male >45 years of age and Female >55 years of age*

[d] *Men have higher incidence for CVD than women*

[e] *A first-degree relative (male <55 year old or female <65 year old when the first CHD event occurs)*

Another cluster of CHD risk factors is the metabolic syndrome. It is associated with five CHD risk factors, the following: Abdominal obesity, Hypertriglyceridemia, Low HDL-C levels, Hypertension and Hyperglycemia.

According the NCEP guidelines, if an individual presents three or more of the aforementioned risk factors, then we define the metabolic syndrome. Concerning clinical identification of metabolic syndrome, the waist circumference for men should be higher than 102 cm and for women higher than 88 cm. TG levels higher or equal to 150 mg/dL, HDL-C for men lower than 40 mg/dL and for women lower than 50 mg/dL. The systolic blood pressure higher or equal with 130/85 mm Hg and the fasting glucose higher than 100 mg/dL[9,15,16].

2.4 Risk assessment

Concerning primary prevention, in patients with no evidence of cardiovascular or other atherosclerotic diseases, we can use the following tables, for the 10-year risk prediction of CVD events and then decide to treat or not the individual according the goals of lipid levels. It's is recommended from Joint British Societies that all people over 40 years old, even with no CVD or diabetes mellitus history and even they are not under pharmacotherapy for high blood pressure or dyslipidemia, should receive every five years an opportunistic screening.

Adults over the age of 75, as well as people with a pre-existing cardiovascular event, do not require risk assessment because their 10-year risk prediction is at least 20%. [16]

Table 4: Assessing 10-year risk of cardiovascular disease events (MEN) [5]

RISK FACTORS AND CVD POINTS

Points	**Age**	**HDL-C (mg/dL)**	**Total Cholesterol (mg/dL)**	**SBP not treated (mm Hg)**	**SBP treated (mm Hg)**	**Smoker**	**Diabetic**
-2		60+		<120			
-1		50-59					
0	30-34	45-49	<160	120-129	<120	No	No
1		35-44	160-199	130-139			
2	35-39	<35	200-239	140-159	120-129		
3			240-279	160+	130-139		Yes
4			280+		140-159	Yes	
5	40-44				160+		
6	45-49						
7							
8	50-54						
9							
10	55-59						
11	60-64						
12	65-69						
13							
14	70-74						
15	75+						

Estimated CVD risk

Points	**Risk**	**Points**	**Risk**	**Points**	**Risk**
≤ -3	**< 1%**	**5**	**3.9%**	**13**	**15.6%**
-2	**1.1%**	**6**	**4.7%**	**14**	**18.4%**
-1	**1.4%**	**7**	**5.6%**	**15**	**21.6%**
0	**1.6%**	**8**	**6.7%**	**16**	**25.3%**
1	**1.9%**	**9**	**7.9%**	**17**	**29.4%**
2	**2.3%**	**10**	**9.4%**	**18+**	**>30%**
3	**2.8%**	**11**	**11.2%**		
4	**3.3%**	**12**	**13.2%**		

Table 5 – Assessing 10-year risk of cardiovascular disease events (WOMEN) [5]

RISK FACTORS AND CVD POINTS

Points	Age	HDL-C (mg/dL)	Total Cholesterol (mg/dL)	SBP not treated (mm Hg)	SBP treated (mm Hg)	Smoker	Diabetic
≤ -3				<120			
-2		60+					
-1		50-59			<120		
0	30-34	45-49	<160	120-129		No	No
1		35-44	160-199	130-139			
2	35-39	<35		140-149	120-129		
3			200-239		130-139	Yes	
4	40-44		240-279	150-159			Yes
5	45-49		280+	160+	140-149		
6					150-159		
7	50-54				160+		
8	55-59						
9	60-64						
10	65-69						
11	70-74						
12	75+						

Estimated CVD risk

Points	Risk	Points	Risk	Points	Risk
≤ -2	**< 1%**	**6**	**3.3%**	**14**	**11.7%**
-1	**1.0%**	**7**	**3.9%**	**15**	**13.7%**
0	**1.2%**	**8**	**4.5%**	**16**	**15.9%**
1	**1.5%**	**9**	**5.3%**	**17**	**18.5%**
2	**1.7%**	**10**	**6.3%**	**18**	**21.5%**
3	**2.0%**	**11**	**7.3%**	**19**	**24.8%**
4	**2.4%**	**12**	**8.6%**	**20**	**28.5%**
5	**2.8%**	**13**	**10.0%**	**21+**	**>30%**

2.5 Diagnosis-tests

The main aim of the treatment for hyperlipidemia is to reduce LDL-C and TC concentrations in blood serum and thus to reduce the risk of atherosclerotic heart disease.

The target lipid for treatment of hyperlipidemia, according ATP III guidelines, is the LDL-C and Non-HDL-C. We should keep in mind that non-HDL-C derives from the following calculation:

Non-HDL-C = TC – HDL-C

Table 6 shows the classification of the clinically important lipids for the assessment carried out by clinicians, according to the necessity of treatment in patients with suspected hyperlipidemia. Table 7 one provides the goal levels of LDL-C and non-HDL-C as well as the LDL-C levels at which drug therapy is recommended according the risk category of individuals.

Table 6: Classification of plasma lipid levels (mg/dL)[a]

Total cholesterol:	
<200	Desirable
200 – 239	Borderline high
≥240	High
HDL-C	
<40	Low (consider <50 mg/dL as low for women)
>60	High
LDL-C	
<70	Optimal for very high risk (minimal goal for CHD equivalent patients)
<100	Optimal
100 – 129	Near optimal
130 – 159	Borderline high
160 – 189	High
≥190	Very high

Triglycerides	
<150	Normal
150 – 199	Borderline high
200 – 499	High
≥500	Very high

[a]2001 National Cholesterol Education Program guidelines. From the expert panel, 2002. *Goodman & Gilman's, The Pharmacological Basis of Therapeutics 12th edition, page 887. (LPL: lipoprotein lipase; HDL: High Density Lipoprotein Cholesterol; CHD: Coronary heart disease).*

Table 7: Treatment based on LDL-C levels (2004 Revision of NCEP adult treatment panel III Guidelines)

Risk Category	**LDL-C goal (mg/dl)**	**Non-HDL-C goal (mg/dl)**	**Therapeutic life style change**	**Threshold for drug therapy (mg/dl)**
Very high risk Atherosclerosis-induced CHD plus one of: • Multiple risk factors • Diabetes mellitus • A poorly controlled single factor • Acute coronary syndrome • Metabolic syndrome	<70[a]	<100	No threshold (initiate change)	No threshold (initiate therapy)
High risk CHD or CHD equivalent	<100[a]	<130	No threshold	No threshold

Moderately high risk □ 2+ risk factors □ 10-year risk <10%	<130 (optional <100)	<160	No threshold	≥130 (100 – 129)[b]
Moderate risk □ 2+ risk factors □ 10-year risk <10%	<130	<160	No threshold	>160
0-1 risk factor	<160	<160	No threshold	≥190 (optional: 160 – 189)[c]

[a] *If pretreatment LDL-C is near or below goal value, then a statin dose sufficient to lower LDL-C by 30-40% should be prescribed.*

[b] *Patients in this category include those with a 10-year risk of 10-20% and one of the following: age >60 years, three or more risk factors, a severe risk factor, triglycerides >200 mg/dL, metabolic syndrome, highly sensitive C-reactive protein (CRP) >3 mg/dL, and coronary calcium score (age/gender adjusted) >75thpercentile.*

[c] *Patients include those with any severe single risk factor, multiple major risk factors, 10-year risk >8%*

(LPL: lipoprotein lipase; HDL: High Density Lipoprotein Cholesterol; CHD: Coronary heart disease).

After attaining the LDL-C goal, additional therapy may be necessary to reach the non-HDL-C goal. CHD equivalent are peripheral vascular disease, abdominal aortic aneurism, symptomatic carotid artery disease, >20% 10-year CHD risk or diabetes mellitus *(NCEP, National Cholesterol Education Program).*

The first step in the diagnosis of hyperlipidemia is to identify its origin and determine the type of the condition. Many patients suffering from hyperlipidemia have a genetic or primary cause for the disorder, but there are also cases in which the causal factor is secondary. A patient's medical and family anamnesis in that case is very helpful, because the obtained information can lead to a clearer viewpoint about an individual case.

For the identification we can measure certain biomolecules to make the diagnosis. These tests are the following:

- Fasting blood glucose[1]
- Urine protein and serum creatinine[2]
- Liver function test[3]
- Thyroid function test[4]
- TC
- LDL-C
- HDL-C
- TG

[1] This test should take place after ten to twelve hours of fasting period.

[2] This test is used to eliminate the possibility of the existence renal insufficiency and nephrotic syndrome.

[3] This test is used to exclude the possibility of hepatitis and/or cholestasis, by measuring γ-GT, ALT, AST, ALP, bilirubin.

[4] This test is used to eliminate the possibility of hypothyroidism existence by measuring TSH, T-3, T-4.

2.6 Treatment of hyperlipidemia

The strategy which is followed for the treatment of individual patients depends on the phase and severity of the disease. The first step in order to make the decision to treat dyslipidemia is the determination of individual's lipid profile, measuring serum total cholesterol, triglycerides and HDL-C.

During the course of a lipid-lowering therapy certain risk factors are being considered, such as smoking, obesity, high alcohol consumption, lack of exercise, or the existence of some underlying disorders such as hypertension or diabetes mellitus. Lifestyle and other conditions that may contribute to the onset of hyperlipidemia and drug-drug interactions are also taken into consideration. Concerning life style changes to reduce the risk of heart disease it is usually suggested to the patient to follow dietary and lifestyle guidelines that work towards decreasing the risk for CVD, such as maintenance of a normal body weight which matches a BMI from 20 to 25 kg/m^2, healthy diet, poor-in trans fats and dietary salt and rich-in omega-3 fatty acids, plant sterols and antioxidants. Aerobic exercise and stress management in combination with the previous suggestions can contribute to decrease atherosclerotic complications [17].

The strategy of managing dyslipidemias is divided in two classes: Primary and secondary prevention. The first one includes the identification and management of the risk factors exist in patients and contributes to prevent the first-ever CHD event. But in the case of secondary prevention the strategy is differentiated and is focused mostly on the prevention of risk factors progression than treating already identified ones. Concerning primary prevention it's appropriate to advise patient to follow a 3 to 6 months life style and dietary changes. Generally, these changes cannot provide the desirable effects on lipids, although this must not be a reason for the individual to quit a healthier way of living.

The treatment in primary prevention should not only focus in management of dyslipidemia but also in optimization of use of other agents such as antihypertensive or cardio-protective and also appropriate control of blood glucose levels.

Therapy in patients with no evidence of arterial diseases, therapy should be started when the risk of patient for CVD is more than 20% over the next 10 years and normally includes:

a) a lipid-lowering agents such as simvastatin 40mg/day(or alternative) but no treatment targets are set
b) Personalized suggestions on modifiable risk factors
c) Control of diabetes
d) Smoking cessation
e) Maintenance of blood pressure below 140 mm Hg systolic and 90 mm Hg diastolic.

On the other hand, treatment in secondary prevention for patients with cardiovascular or other major atherosclerotic diseases should include:

a) a lipid-lowering agent to decrease TC < 4mmol/L and LDL-C < 2mmol/L

b) Advise for smoking cessation

c) Personalized suggestions on modifiable risk factors

d) Treatment of blood pressure to achieve below at least 140 mm Hg systolic and 90 mm Hg diastolic.

e) Tight control of blood pressure and glucose levels in diabetics

f) Low-dose aspirin (75 mg per day)

g) ACE inhibitors

h) β-blockers for patients in post-MI state or with CHF

i) Anticoagulants or low-dose aspirin for patients suffering from atrial fibrillation or have additional risk factors for stroke. [25]

3. ANALYSIS OF DRUG RELATED PROBLEMS (HYPOLIPIDEMICS)

3.1 Introduction

Five main categories of drugs are used for the treatment of dyslipidemias.

These are: Statins, Fibrates, Bile acid binding agents, Cholesterol absorption inhibitors and Nicotinic acid and its derivatives. The type of dyslipidemia is the crucial factor on deciding which of these agents or which combination of them should be used.

Statins still remain the 1st choice drugs for the majority of patients suffering from dyslipidemia, while there is strong evidence in reducing CVD events with these agents [17].

3.2 Statins

Statins are drugs that inhibit competitively the enzyme called HMG-CoA reductase which is responsible for the rate-limiting step of cholesterol biosynthesis. Thus they reduce the conversion of HMG-CoA reductase to mevalonate in hepatocytes and the cholesterol levels in blood decreases. Statins have also

the ability to enhance the LDL receptors transcription through a feedback of transcription factors on the LDL receptor gene. The LDL receptors degradation is decreased, too [18]. Whilst, the number of them gets higher at the hepatocyte cell surface, the clearance of LDL particles from the blood is enhanced and the LDL-C is reduced. Potent statins such as rosuvastatin, atorvastatin and simvastatin, when administered in high doses can also reduce TG levels caused by elevated VLDL. Some statins have the ability to increase HDL-C levels, but until now this property is under investigation. Evidence for the safety as well effectiveness of simvastatin, atorvastatin, rosuvastatin, pravastatin and lovastatin came from multiple clinical trials where the reduction of fatal and non-fatal cardiovascular events, brain strokes and total mortality are documented.

About historical issues we should mention that the first statin studied in humans was mevastatin, isolated from a *Penicillium citrinum* mold, in 1976 by Endo and his colleagues.

Simvastatin, mevastatin, pravastatin and lovastatin are all fungal metabolites with small differences in chemical structures as mentioned in the following picture. On the contrary, rosuvastatin, pitavastatin, fluvastatin and atorvastatin are synthetic compounds. It's very important to mention that statins also reduce triglycerides in the blood serum. The reduction of TG levels achieved by statins in percentage is close to that of LDL-C. [19]

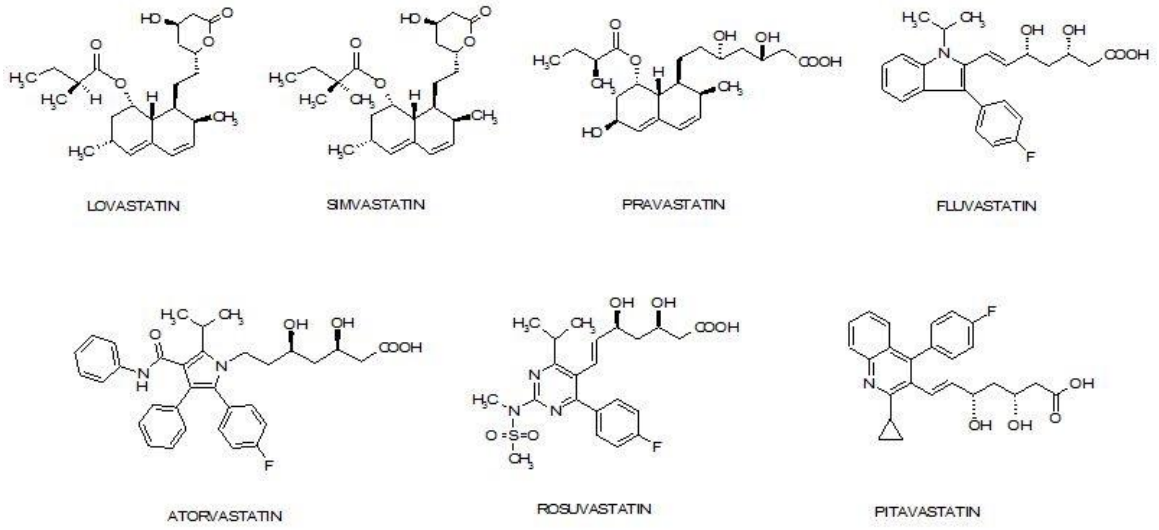


Figure 4: Chemical structure of statins. [20]

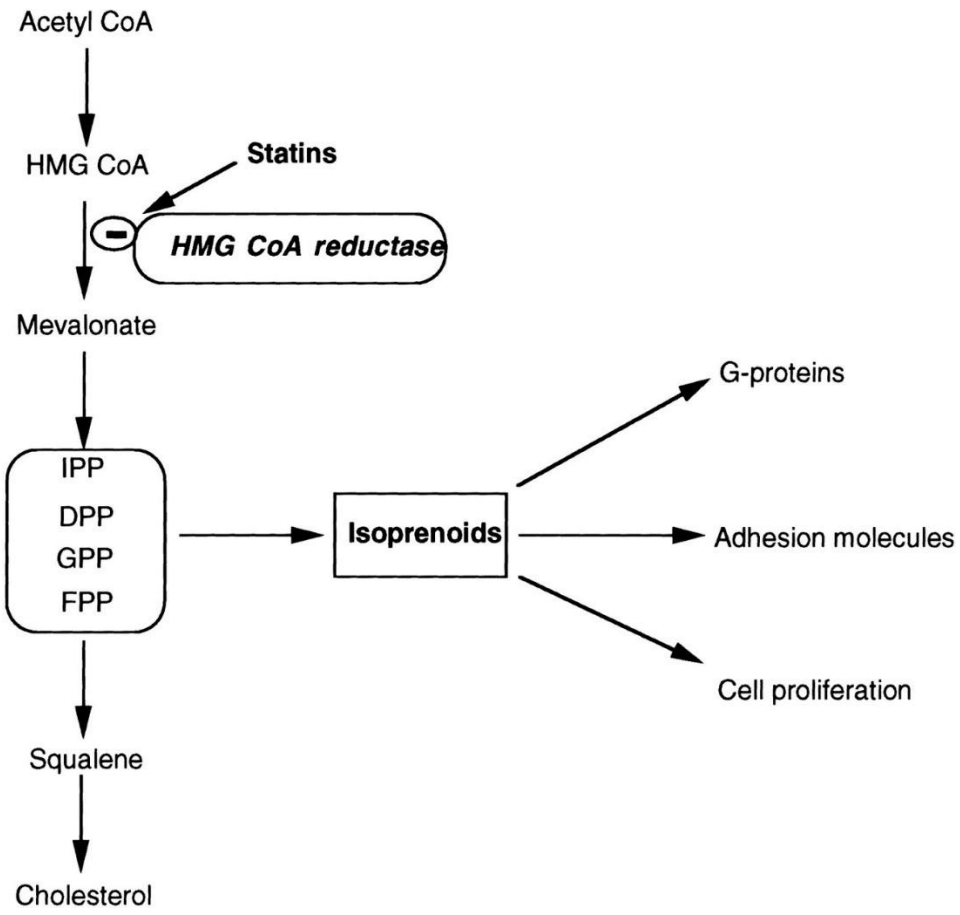


Figure 5: Statins mechanism of action. [21]

Crucial parameter for the benefit outcomes of statins is their pleiotropic properties contribution in potential cardioprotective effects other than LDL-C reduction. These effects include stabilization of atheromatic plaque, reduction in venous thromboembolic events, reduction in lipoprotein oxidation, increased release of vasodilator nitric oxide by endothelial cells while they have also an anti-inflammatory role. [21]

Statins are metabolized by the cytochrome CYP 450. Simvastatin, atorvastatin and lovastatin are metabolized by the isoenzyme CYP 3A4. Simvastatin is an extensive metabolizer of CYP3A4 and this is a factor that increases the intensity of interactions with other drugs as shown in the following table. Another isoenzyme, the CYP2C9 is responsible for the metabolism of fluvastatin, while both rosuvastatin and pravastatin are metabolized in a lesser extent by CYP450 and they follow other metabolic pathways.

Instead, caution is required during co-administration of ciclosporin with pravastatin because a 5 to 23-fold increase of its bioavailability has been reported. Some advises have been published for the prevention of interactions of simvastatin and atorvastatin with CYP3A4 inhibitors. [24, 25]

Table 8: Drug-drug interaction among statins and the CYP450 enzyme pathway. [5]

(CYP: Cytochrome)

CYP450 isoenzyme	Inducers	Inhibitors
CYP3A4 Simvastatin Atorvastatin Lovastatin	 Phenytoin Barbiturate Rifampicin Dexamethasone Cyclosporine Carbamazepine Omeprazole	 Ketoconazole Itraconazole Fluconazole Erythromycin Clarithromycin Tricyclic antidepressants Nefazodone Venlafaxine Fluoxetine Sertraline Ciclosporin Tacrolimus Diltiazem Verapamil Protease inhibitors Midazolam Corticosteroids Grape fruit juice Tamoxifen Amiodarone
CYP2C9 Fluvastatin	 Rifampicin Phebarbitone Phenytoin	 Ketoconazole Fluconazole Sulfaphenazole

Table 9: Advice for prescribing simvastatin and atorvastatin with CYP3A4 inhibitors. [5]

Avoid co-administration of simvastatin with potent inhibitors of CYP3A4	HIV protease inhibitor, azole antifungals, erythromycin, clarithromycin, telithromycin
Do not exceed the following doses	Simvastatin 10 mg daily with ciclosporin, gemfibrozil or niacin (>1g/day). Simvastatin 20 mg daily with verapamil or amiodarone. Simvastatin 40 mg daily with diltiazem.
Avoid grapefruit juice when taking simvastatin	
Atorvastatin to be used cautiously with CYP3A4 inhibitors	Additional care required at high doses of atorvastatin. Avoid drinking large quantities of grapefruit juice.

Statins have side effects that are usually mild and evanescent. The most common adverse effects are GIT discomfort, liver function alteration as well as muscle pain. In some cases some side effects have been reported but are not common enough. These are increased levels of hepatic transaminases up to 3 times higher than the upper normal limits, hepatitis, rash, headache, insomnia, nightmares and difficulties on focusing.

Another very serious but rare repercussion is myopathy. Myopathy caused by rhabdomyolysis and leading to myoglobinuria can occur at any dose of statins. Some situations are responsible for increased risk of myopathy.

These include:

i) Family history of muscle disorders, underlying muscle disorder, renal impairment, current hypothyroidism, alcoholic patient, female sex or patient over 65 year old.
ii) Co-prescription of statins with fibrates or niacin
iii) History of myopathy caused by statins or another hypolipidemic agent.
iv) Co-prescription of simvastatin or atorvastatin with potent inhibitors of cytochrome 3A4.

Therapy with statins is contraindicated during pregnancy because their safety has not been established. For nursing mothers the recommendation is also to avoid therapy with statins.
Statins reduce LDL cholesterol and triglyceride levels in blood while they increase HDL cholesterol. Concerning triglycerides, statins reduce their levels essentially to a similar percentage as they affect LDL-C, when the TG levels are above >250 mg/dL. In hypertriglyceridemic patients who are under pharmacotherapy with the highest dose of most potent statins, have a reduction in TG fasting levels of 35-45%.
Another effect of statins is their ability to increase HDL-C. Patients suffering from hypercholesterolemia and have normal levels of HDL-C appropriate to their gender, an elevation 5-10% of serum HDL-C levels has been observed irrespectively the statin dose. Nevertheless, on patients with low HDL-C levels <35 mg/dL, effect of statins differs regarding their ability to increase them. Simvastatin at a dose of 80 mg daily provides higher increase of HDL-C and apoA-I in a comparable dose of atorvastatin. Preliminary studies with hypertriglyceridemic patients with low HDL-C shown that rosuvastatin increases high density lipoprotein levels at about 15-20%.

The effectiveness of statins on LDL-C levels varies among different members of the drug group. They can lower the LDL-C levels from 20 to 55%. Large trials provided information of different statins efficacy in certain pharmacological doses, according decrease LDL-C levels, as shown in the following table. An exception on statin effectiveness is patients who suffer from homozygous familiar hypercholesterolemia where statins provide little response due to dysfunction of LDL hepatic receptors. [19]

Table 10: Dose (mg) of statins required to achieve various reductions in LDL. [19]

	20-25%	26-30%	31-35%	36-40%	41-50%	51-55%
Atorvastatin	-	-	10	20	40	80
Fluvastatin	20	40	80	-	-	-
Lovastatin	10	20	40	80	-	-
Pitavastatin		1	2	4	-	-
Pravastatin	10	20	40	-	-	-
Rosuvastatin	-	-	-	5	10	20, 40
Simvastatin	-	10	20	40	80	-

3.3 Fibrates

Fibrates are derivatives of fibric acid. Clofibrate, bezafibrate, fenofibrate, gemfibrozil and ciprofibrate are members of this group of drugs. All of them bind to peroxisome proliferator-activated receptor α (PPAR-α) on the liver cells and in this way change the expression of responsible for lipoprotein metabolism genes. Fibrates reduce TG levels and to a lesser expanse LDL-C levels [22]. They also increase the "good cholesterol" HDL-C in blood plasma. Their optimum effect is measurable after a month of daily administration.

Other effects of fibrates include a possible antithrombotic mechanism and improvement of glucose tolerance. Must keep in mind that fenofibrate has also some uricosuric effects when administered chronically and it provides an advantage for those patients who are hyperlipidemic and suffer also from gout or hyperuricemia.

There is a possibility to administer a statin with a fibrate with caution in patients with mixed hyperlipidemia, except gemfibrozil, which is the only fibrate which should not be used concomitantly with statins.

In any case, fibrates are not first-line agents for treatment of hyperlipidemia either in primary or secondary prevention. Only in cases of severe isolated hypertriglyceridemia we can use fibrates as first-line agents. [5][8]

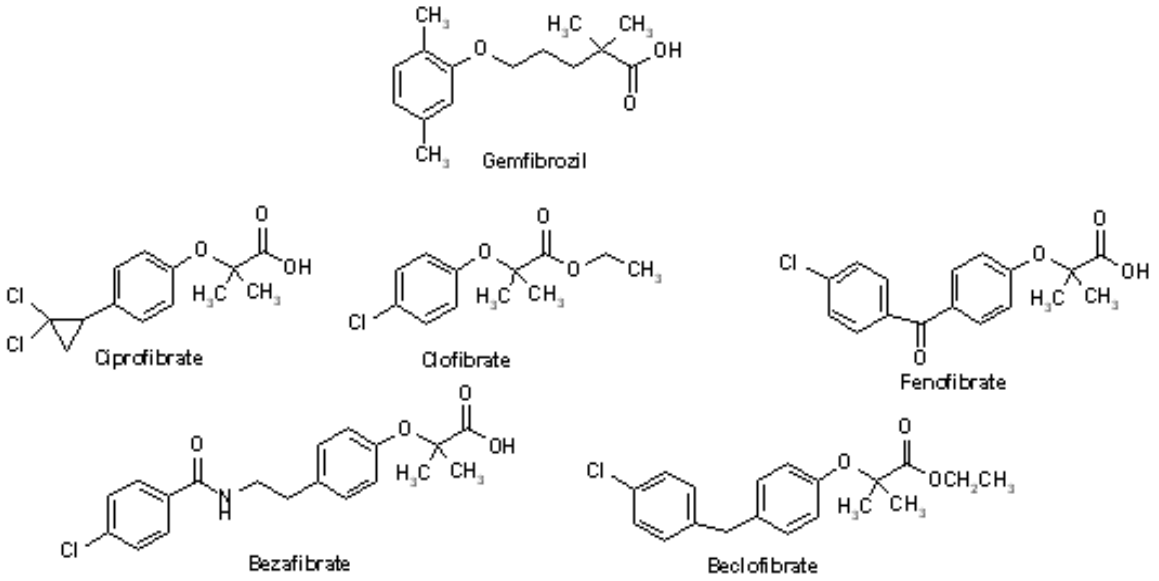


Figure 6: Chemical structure of fibrates [5]

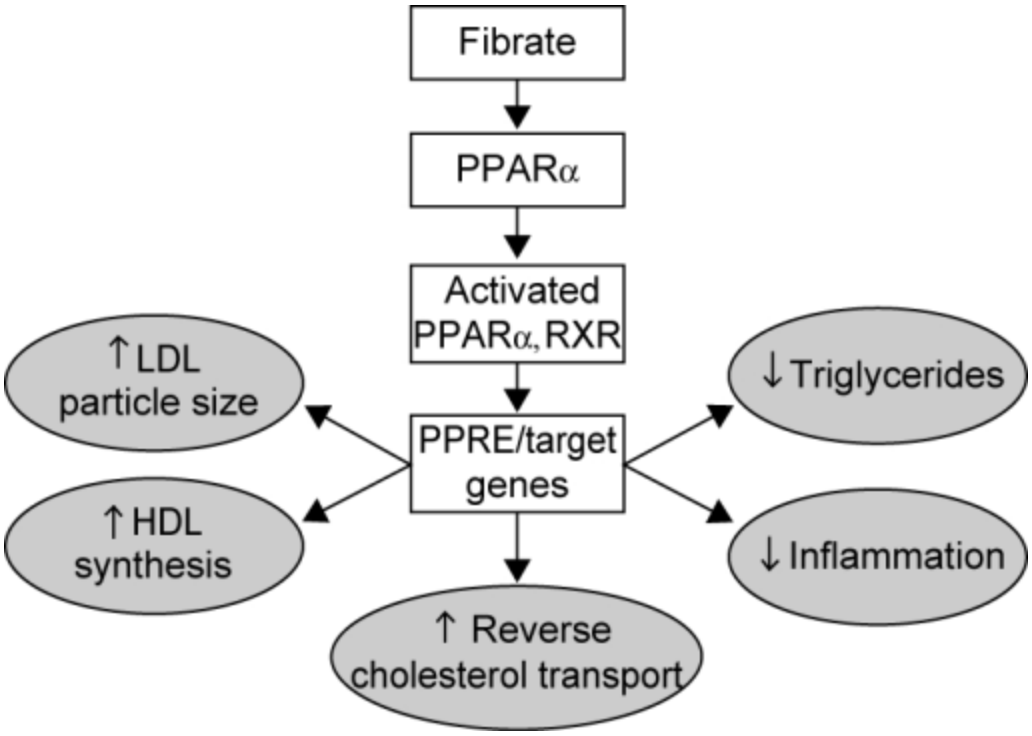


Figure 7: Fibrates mechanism of action. [23]

All these agents are implicated in drug interactions with certain drugs. The most serious of them involve anticoagulants and statins. In the first case there is a significant increase on anticoagulant effects, while in the second one, the risk for myopathy is high. It has been noted that cerivastatin and gemfibrozil when administered together, cause rabdomyolysis and this was the reason why cerivastatin was excluded from clinical use. [23]

Table 11: Drug interaction of fibrates with other agents. [24]

Drug group	Interacting drug	Comments
Fibrates	Antidiabetic agents	Improvement in glucose tolerance
	Ciclosporin	Increased risk of renal impairment
	Colestyramine/colestipol	Reduced bioavailability of fibrate
	Statin	Increased risk of myopathy
	Warfarin	Increased anticoagulant effect

Mild side effects have been reported for fibrates. Different side effects occur among members of this pharmacodynamics group. The most common include GIT discomfort, nausea, diarrhea and abdominal pain but all of them are transient and can be resolved after a couple of days of therapy with these agents. Myositis has also been reported in some individuals either when fibrates are co-administered with statins or alone. In the second case the mechanism remains unknown but probably there is a direct toxic effect on muscle cells.

A relative contraindication for the use of fibrates is renal failure. Hepatic dysfunction and use by children or pregnant women is also not recommended while both are situations that contraindicated. Fibrates are most effective on patients suffering from type III hyperlipoproteinemia. Two complications of this type of hyperlipidemia, palmar and tuberoeruptive xanthomas are possible to regress completely. There is also great improvement of angina pectoris, intermitted claudication and TG and cholesterol levels are both reduced very much.

In patients with TG levels <400 mg/dl, mild hypertriglyceridemia, fibrates increase HDL-C about 15% and reduce TG levels up to 50% while LDL-C either remains unchanged or increases slightly. Fibrates of second generation, fenofibrate, ciprofibrate and bezafibrate, reduce VLDL particles in a similar manner as gemfibrozil do, but also reduce LDL by 15-20%.

On the other hand, in patients with more serious hypertriglyceridemia, with TG levels for instance from 400 to 1000 mg/dL, reduction of triglycerides seems similar but LDL levels increase more, about 10-30%.

A 5-year study with hyperlipidemic patients treated with gemfibrozil gave the following results as reported here:

Reduction in total cholesterol: 10%

Reduction in LDL-C: 11%

Increase in HDL-C: 11%

Reduction in triglycerides: 35%

Decrease in the sum of fatal and non-fatal CV events: 34%

No effects on total mortality were observed.

3.4 Bile acid binding agents

Three drugs belong to this pharmacodynamic group of hypolipidemic agent, which are in current use. These are colestyramine, colestipol and colesevelam. In the past, colestipol and colestyramine were the first-line agents for the therapy of familiar hypercholesterolemia. Today, all of these three drugs have very limited use.

After oral administration, these drugs are not absorbed from the GIT, but they bound to the bile acids inside the intestine forming an insoluble complex, which blocks their re-absorption. After that, they excreted in faeces. This mechanism stimulates the production of bile acids by cholesterol in the liver caused by upregulation of the enzyme called 7-α-hydroxylase.

By this way the activity of LDL receptors increases and LDL-C removed from the blood. On the other hand, bile acid binding agents increase the VLDL synthesis in the liver and this is a consequence that explains why these drugs when administered increase the TG levels. [25]

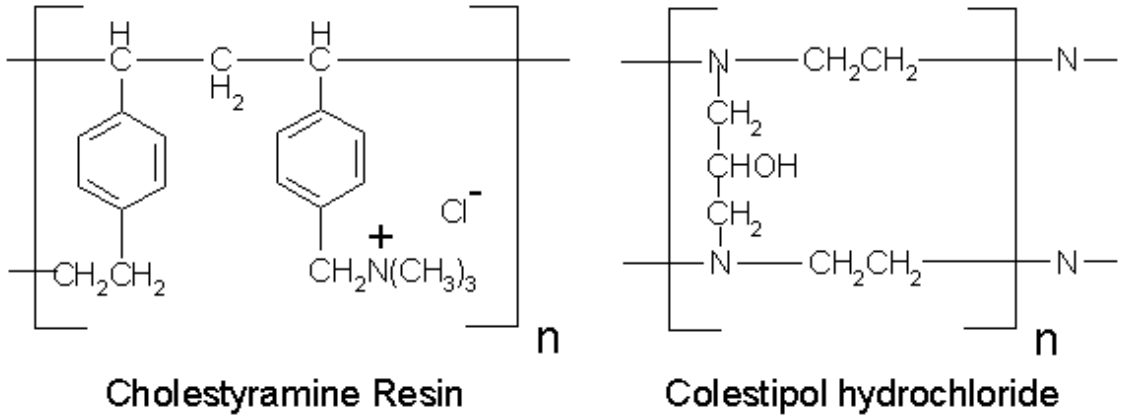


Figure 8: Cholestyramine & Colestipol, Chemical structure of cholestyramine & colestipol [25]

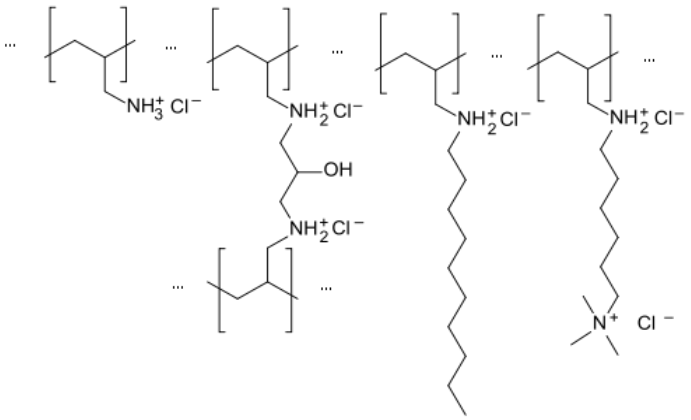


Figure 9: Colesevelam, Chemical formula of colesevelam [26]

Bile acid sequestrates interact with a variety of drugs mainly by interfering with their absorption. It's important to mention that bile acid sequestrates when used for long-term may cause alterations in absorption of fat-soluble vitamins. In order to prevent avitaminosis, supplementation with vitamins A,D and K is recommended. [5]

Table 12: Interactions of bile acid binding agents with other drugs. [5]

Drug group	Interacting drug	Comment
Colestyramine, Colestipol		All medications should be taken 1 hour before or at least 4 hours after colestyramine or colestipol in order to reduce absorption caused by binding in the gut.
	Acarbose	Absorption reduced
	Digoxin	Absorption reduced
	Diuretics	Absorption reduced
	Levothyroxine	Absorption reduced
	Mycophenolate mofetil	Absorption reduced
	Paracetamol	
	Raloxifene	
	Valproate	Absorption reduced
	Statins	Absorption reduced
	Vancomycin	Absorption reduced
		Absorption reduced
	Warfarin	Effect of oral vancomycin antagonized by colestryramine. Increased anticoagulant effect due to depletion of vitamin K or reduced anticoagulant effect due to binding of warfarin in gut.

Colesevelam	Ciclosporin Digoxin Glyburide Levothyroxine Oral contraceptive Statins Valproate Warfarin	All medications should be taken at least 4 hours before or 4 hours after coleselevam in order to reduce absorption caused by binding in the gut. Absorption reduced Absorption uncharged Absorption reduced Absorption reduced Absorption reduced Absorption uncharged Absorption uncharged Absorption uncharged. Increased anticoagulant effect possible due to depletion of vitamin K.

Side effects of this group of drugs occur more often in patients over 60 year old and when these agents are taken in high doses. Common ones include flatulence, heartburn, bloating and constipation. The last one, constipation is the major adverse effect of fibrates and it may be severe in some cases. [5]

Bile acid sequestrates are contraindicated in patients suffering from hypertriglyceridemia. [27]

Effectiveness of resin in reducing LDL-C is dose dependent. Reduction of LDL-C has been observed with cholestyramine 8 to 12g or colestipol 10-15g by 12-18%. Highest doses of both drugs, 24 and 30 grams respectively can reduce LDL-C not more than 25% while HDL-C increases by 4-5%. Note that in such doses, resins cause GIT problems and are difficulty tolerated. Colesevelam when administered in doses of 3 to 3.75 grams reduces levels of LDL-C by 9-19%.

Concerning triglycerides, patients with normal levels may experience a slight increase but after a period of time their levels return to baseline. [19]

3.5 Cholesterol absorption inhibitors

Ezetimibe is the only agent belongs to this pharmacodynamic group. It's a 2-azetidinone derivative and inhibits the cholesterol re-absorption from the intestine though interacting with the intestinal cholesterol transporter. A reduction about 15-20% in LDL-C levels, small reduction on triglycerides as well as small increase in HDL-C have been reported. This drug can be concomitantly administered with a statin for further LDL-C and TG reduction, or with a fibrate or nicotinic acid derivative.

Until now, there is no evidence that use of ezetimibe provides a further reduction in CV morbidity and mortality. [28]

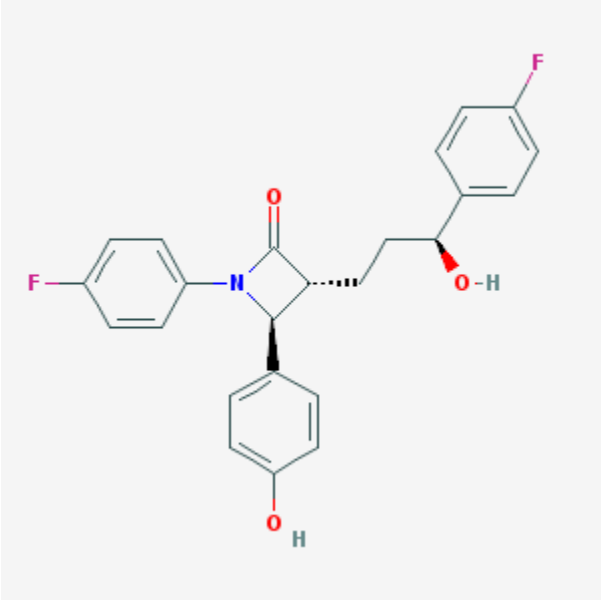


Figure 10: Chemical formula of Ezetimibe [28]

No drug interactions have been mentioned with ezetimibe. Crucial advice for women who are under pharmacotherapy with medicines combine and statin and ezetimibe, is to avoid these drugs in

childbearing years in the absence of contraception, since statins are contraindicated in pregnancy and nursing women. [19]

Side effects of ezetimibe have not been reported. Only very rare allergic reactions can occur in some patients. It's important to mention that ezetimibe in very high doses, 10 to 150 higher than the therapeutic dose of 10 mg in human, have caused fetal abnormalities in animal experiments with rabbits and rats. [5]

The use of ezetimibe during pregnancy has not been established [19].

Ezetimibe alone, without a combination with a statin, when administered can reduce LDL-C level by 15 to 20%. It also slightly increase HDL-C levels while reduces also triglycerides.

A combination of ezetimibe with simvastatin, 10 mg and 80 mg respectively, provides a reduction of LDL-C by 60%. This percentage of reduction of LDL-C is higher than a patient can attains by maximum dose of any statin as monotherapy.

3.6 Nicotinic acid and derivatives

Niacin when administered in therapeutic doses from 1.5 to 6 grams, decreases LDL-C, TG, VLDL-C, apoB, TC and Lp(a) while increases HDL-C levels in blood serum. It has approval for the treatment of dyslipidemias in combination with a statin or as monotherapy when patient is statin-intolerant or statins are contraindicated. A chemical compound called acipimox has similar structure to this of nicotinic acid and also similar pharmacological effects on lipid profile but it appears to be less potent. [5]

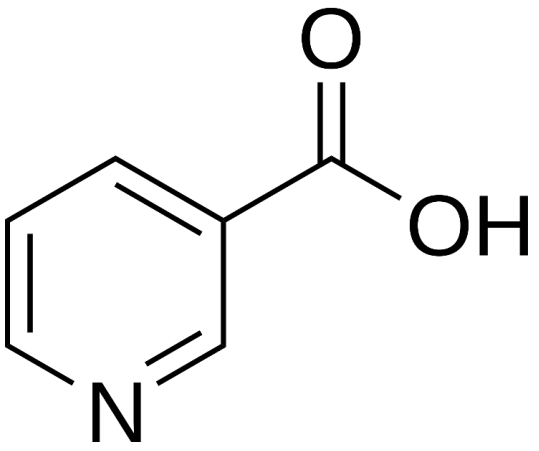


Figure 11: Chemical structure of niacin. [29]

Niacin may have some potential interactions with certain drugs. These drugs include acetylsalicylic acid in high doses, uricosuric agents such as sulfapyrazone and alcohol. [30]

Side effects of niacin include flushing, mainly on the head, neck and upper part of the body. These effects occur in a high percentage of patients, usually over 90% and this is the main reason for therapy discontinuation up to 25-40% of the cases. For the management of this problem many strategies exist. Some of them come from pharmaceutical technology which provides extended-release tablets of niacin, administration of the drug with meals or at bedtime, avoidance of alcohol consumption and patient education for avoiding hot beverages, hot showers and spicy foods close to the time of drug administration or after it.

Some other adverse reaction but less common include diarrhea, hepatic dysfunction, and exacerbation of peptic ulcers, gout and hyperglycemia. [5]

Contraindications for the use of niacin include a history of gout and pregnancy while birth defects have been reported. [19]

Niacin in pharmacological doses of 2 to 6 grams per day can reduce levels of triglycerides by 35 to 50% and this reduction can be obtained within a week. Doses of niacin 4.5 to 6 grams per day bring reduction of LDL-C levels up to 25%, while this maximal effect obtained after 3-6 weeks.

4. EXPERIMENTAL PART

4.1 Methods

The experimental part of this thesis was carried out in a pharmacy in a village of Greece. The aim of this project was to recruit a number of patients diagnosed with hyperlipidemia and assess the pharmacotherapeutic approach used to treat the condition, at the time. The choice of the sample was based on patients diagnosed with hyperlipidemia that came for their prescription dispensation. As a result, 78 prescriptions were collected and information was obtained about the disorders patients suffer from and their pharmacotherapy. The information was collected after the patients consented and filled in a questionnaire that was produced for the scope of this thesis. This questionnaire was constructed in order to allow the collection of information on the pharmacotherapy methods followed to treat the patients, based on the prescription and diagnosis of the disease. Other factors concerning the weight, age, social and psychosocial factors were taken into consideration as well as additional conditions that patients suffered from. Information on the effectiveness of the therapeutic approach followed was solely based on the patients' provided information about lipid reduction but not on actual data from blood tests measuring past and present lipid levels in blood. Therefore, no quantitative conclusions can be reached on the efficacy and effectiveness of the therapeutic approaches for the patients that took part in the study.

The data obtained was used in order to analyse and understand the current pharmacotherapeutic approaches followed to treat hyperlipidemia and to gain insight into the effectiveness of the treatments as well as the patient's views on the medication and treating of the specific condition.

Questionnaire patients completed:

YOUR VIEWS ABOUT

MEDICINES PRESCRIBED FOR YOU

(BMQ SPECIFIC)

- We would like to ask you about your personal views about medicines prescribed for you.
- These are statements other people have made about their medicines.
- Please show how much you agree or disagree with them by ticking the appropriate box.

There is no right or wrong answer.

We are interested in your personal views

Views about MEDICINES PRESCRIBED FOR YOU:	**Scale Structure**
My health, at present, depends on my medicines N	N= Specific Necessity
Having to take medicines worries me C	C= Specific Concerns
My life would be impossible without my medicines N	
I sometimes worry about long-term effects of my medicines C	
Without my medicines I would be very ill N	
My medicines are a mystery to me C	
My health in the future will depend on my medicines N	
My medicines disrupt my life C	
I sometimes worry about becoming too dependent on my medicines C	
My medicines protect me from becoming worse N	
These medicine give me unpleasant side effects C	

All items scored: 5= strongly agree, 4= agree, 3= uncertain, 2= disagree, 1= strongly disagree

YOUR VIEWS ABOUT
MEDICINES IN GENERAL
(BMQ GENERAL)

- These are statements that other people have made about medicines in general.
- Please show how much you agree or disagree with them by ticking the appropriate box.

Views about MEDICINES IN GENERAL	**Strongly Agree**	**Agree**	**Uncertain**	**Disagree**	**Strongly Disagree**
Doctors use too many medicines	5	4	3	2	1
People who take medicines should stop their treatment for a while every now and again	5	4	3	2	1
Most medicines are addictive	5	4	3	2	1
Natural remedies are safer than medicines	5	4	3	2	1
All medicines are poisons	5	4	3	2	1
Medicines do more harm than good	5	4	3	2	1
Doctors place too much trust on medicines	5	4	3	2	1
If doctors had more time with patients they would prescribe fewer medicines	5	4	3	2	1
Medicines help many people to live better lives	5	4	3	2	1
In most cases the benefits of medicines outweigh the risks	5	4	3	2	1

All items scored: 5= strongly agree 4= agree, 3= uncertain, 2= disagree, 1= strongly disagree

4.2 Results and Evaluation

In this project 78 patients (n=78), that were previously diagnosed with hyperlipidemia, were asked to fill in a questionnaire and the data obtained was analyzed. A key finding included the identification of the different types of hyperlipidemia amongst the sample population. The vast majority of the patients was diagnosed with pure hypercholesterolemia (76.9%), while 21.8% of the patients was diagnosed with combined hyperlipidemia and only a small percentage of the sample (1.3%) was diagnosed with pure hypertriglyceridemia (Figure 12 and Table 13). This suggests that the main cause of the condition in the population sample was elevated counts of cholesterol in blood.

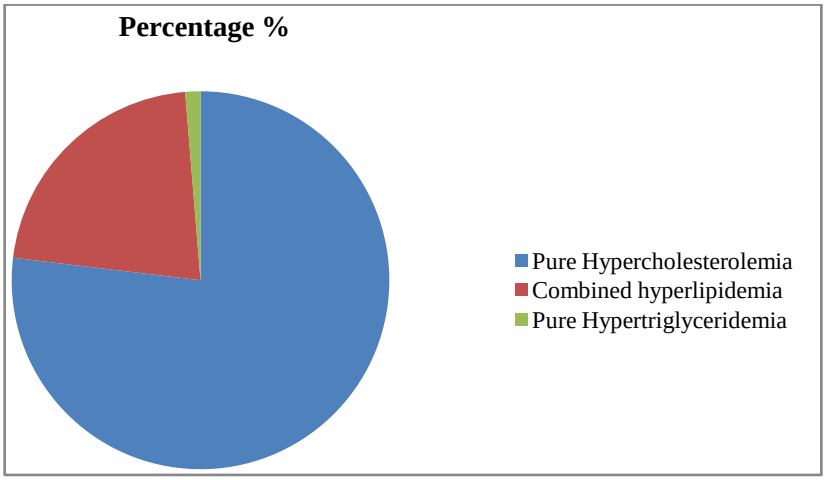


Figure 12: Types of hyperlipidemia in the patient sample. The majority of patients were diagnosed with pure hypercholesterolemia (where 100% = 78, n=78).

Table 13: Different types of hyperlipidemia amongst the sample of patients (n=78).

Type of dyslipidemia	**Number of patients**	**Percentage %**
Pure Hypercholesterolemia	60	76.9
Combined hyperlipidemia	17	21.8
Pure Hypertriglyceridemia	1	1.3

An important observation was the occurrence of certain additional conditions that patients suffered from, according to doctor's diagnosis. The most prevalent condition that seemed to co-exist alongside hyperlipidemic patients was found to suffer from hypertension (51.3%) followed by type 2 diabetes (15.4%) and ischemic heart disease (15.4%). This observation confirms the strong link between hypertension and hyperlipidemia and of course supports the implication of hyperlipidemia in heart disease. Other conditions that were observed in the sample of patients included hyperuricemia (10.3%) and interestingly, depression (10.3%). A number of other conditions were also met in the population sample and these are all summarised in the diagram in Figure 13 and Table 14.

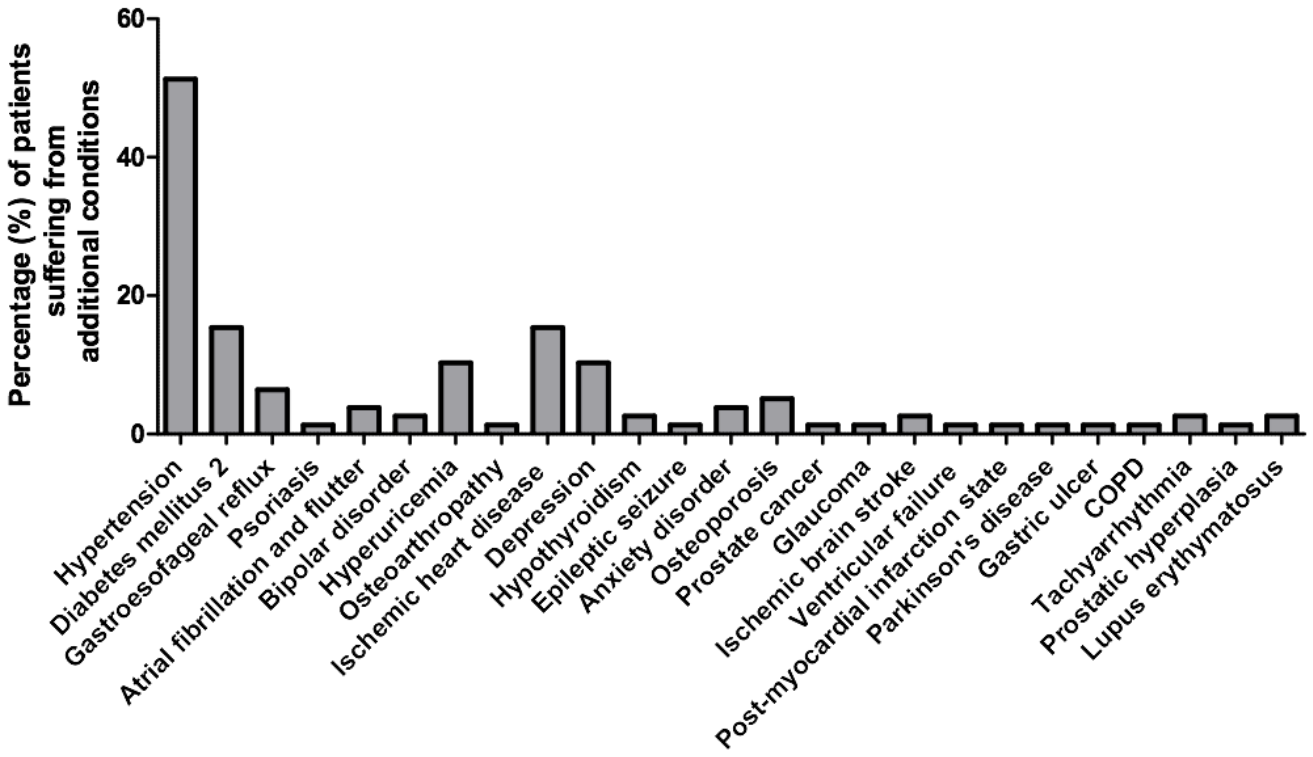


Figure 13: The majority of patients with hyperlipidemia were diagnosed with hypertension (where 100% = 78, n=78).

Table 14: Other disorders that were diagnosed for the patients with hyperlipidemia (where 100% =78, n=78).

Medical disorder	Number of patients	Percentage %
Hypertension	40	51.3
Diabetes mellitus 2	12	15.4
Gastroesofageal reflux	5	6.4
Psoriasis	1	1.3
Atrial fibrillation and flutter	3	3.8
Bipolar disorder	2	2.6
Hyperuricemia	8	10.3
Osteoarthropathy	1	1.3
Ischemic heart disease	12	15.4
Depression	8	10.3
Hypothyroidism	2	2.6
Epileptic seizure	1	1.3
Anxiety disorder	3	3.8
Osteoporosis	4	5.1
Prostate cancer	1	1.3
Glaucoma	1	1.3
Ischemic brain stroke	2	2.6
Ventricular failure	1	1.3
Post-myocardial infarction state	1	1.3

Parkinson's disease	1	1.3
Gastric ulcer	1	1.3
COPD	1	1.3
Tachyarrhythmia	2	2.6
Prostatic hyperplasia	1	1.3
Lupus erythymatosus	2	2.6

A summary of the risk factors that could have contributed to the onset and/or the severity of the disease were taken into consideration. A very important risk factor that is often associated with cardiovascular disorders and conditions that may lead to heart disease (e.g. hyperlipidemia) is cigarette smoking. Surprisingly, only a small percentage of the sample patients were smokers (14.1%), while the majority (85.9%) were non-smokers (Table 15). Unfortunately, no information was gathered about the possible smoking habits of the non-smokers in the past, and whether they advised to stop smoking because of the diagnosed hyperlipidemia. As a result, we may not directly conclude any relation between cigarette smoking and the onset of hyperlipidemia in the selected patients.

Table 15: Smoker and non-smoker patients (where 100% =78, n=78).

	Number of patients	**Percentage %**
Smokers	11	14.1
Non-smokers	67	85.9

Table 16: Risk factors (excluding hyperlipidemia), where 100% =78, n=78.

Number of risk factors	Number of patients	Percentage %
1	23	29.5
2	32	41.0
3	22	28.2
4 or more	1	1.3

Obesity is a risk factor that considered to be associated with hyperlipidemia and consequently with heart disease. Therefore, the selected patients were asked to provide information about their body weight and results are presented as Basal Metabolic Index (BMI) values (Kg/m^2), in order to determine the association of obesity to hyperlipidemia. It was therefore not surprising that the majority of the patients (61.5%) were obese and the 30.8% was overweight (Figure 14 and Table 16). The relation of poor diet or diet of low nutrition and rich in fat have a direct link to obesity and this may result in hyperlipidemia.

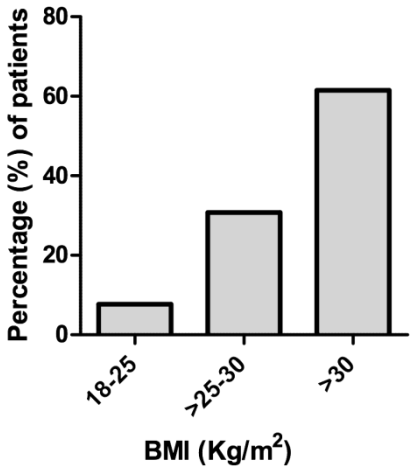


Figure 14: Link of obesity to hyperlipidemia (where 100% =78, n=78).

Table 16: BMI (basal metabolic index) of patients (where 100% =78, n=78).

BMI (kg/m^2)	Patients number	Percentage %
18-25	6	7.7
>25 – 30	24	30.8
>30	48	61.5

Sex is also considered a risk factor for developing hyperlipidemia, with men being at higher risk than women [1, 23]. The sample population that was recruited for this study was did not show a large difference in terms of percentage between men and women (Figure 15 and Table 17). This observation suggested that sex is not a definitive risk factor for developing hyperlipidemia, at least for the selected patient population. On the other hand, age was shown to be a very important risk factor for developing hyperlipidemia. The outcome of the study demonstrated that the risk for developing the condition was increased with age (Figure 16 and Table 18). The patients at the age range between 36-45, 46-55 and 56-65 demonstrated an increased incidence of hyperlipidemia which showed a peak in patients of the 66-75 age range group. The hyperlipidemia incidence dropped in the groups of patients in the age groups 75-85 to 96-100, but so did the number of patients.

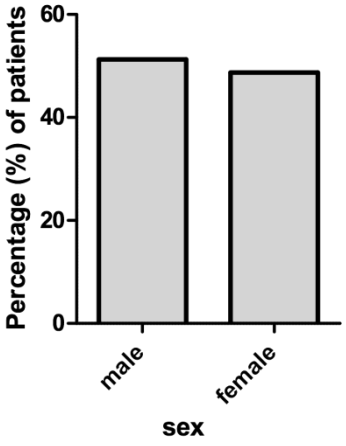


Figure 15: Sex did not seem to affect the diagnosis of the condition (where 100% = 78, n=78).

Table 17: Number of patients according to sex (where 100% = 78, n=78).

Sex	Patients number	Percentage %
Male	40	51.3
Female	38	48.7

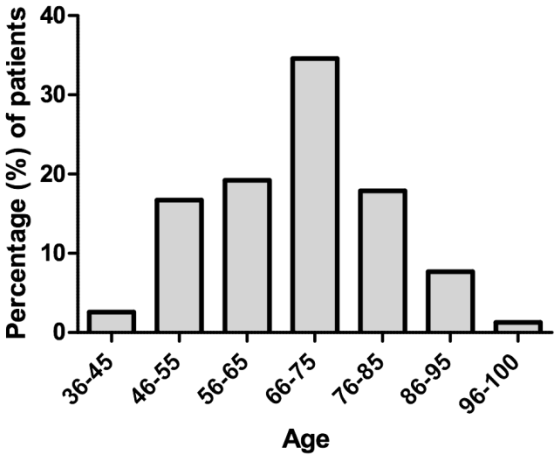


Figure 16: Relation of patient age to the diagnosis of hyperlipidemia (where 100% = 78, n=78).

Table 18: Hyperlipidemic patients according to age (where 100% = 78, n=78).

Age group (years)	Patients number	Percentage %
36-45	2	2.6
46-55	13	16.7
56-65	15	19.2

66-75	27	34.6
76-85	14	17.9
86-95	6	7.7
96-100	1	1.3

The characterization and analysis of the background of the selected patients for the hyperlipidemia study was an important and useful task in terms of understanding the risk factors in the onset and severity of the condition. Moreover, the next important task involved the analysis of the prescribed medication for treating these patients. According to the data obtained from the prescriptions for the 78 patients four different pharmacotherapeutic approaches were documented. The vast majority of patients (85.9%) were treated with statins. The second type of treatment was a combination of statins with Ezetimide used to treat 8.9% of the patients. Another combination of statins and fibrates was used to treat 2.6% of the patients and finally the remaining 2.6% of the patients was treated with fibrates alone (Figure 17 A). The choice of statin based therapy or statin combination therapy was probably based on the severity of the conditions in the different patients. When focusing on the statin treated patients (n=67) it was observed that different types of statins were used for different patients (Figure 17 B). Atorvastatin seemed to be the most popular choice according to the prescriptions received, since 47.8% of the statin-based treated patients were treated with it. Simvastatin was the second choice of statin (37.3% of patients), followed by rosuvastatin (11.9% of patients), pravastatin (1.5% of patients) and lovastatin (1.5% of patients). Different doses of the statin types were used to treat the patients. The selection of the dose was probably based on the severity of the disease in the different patients but could have also been due to the combination treatments with fibrates or Ezetimide (Table 19).

A. **B.**

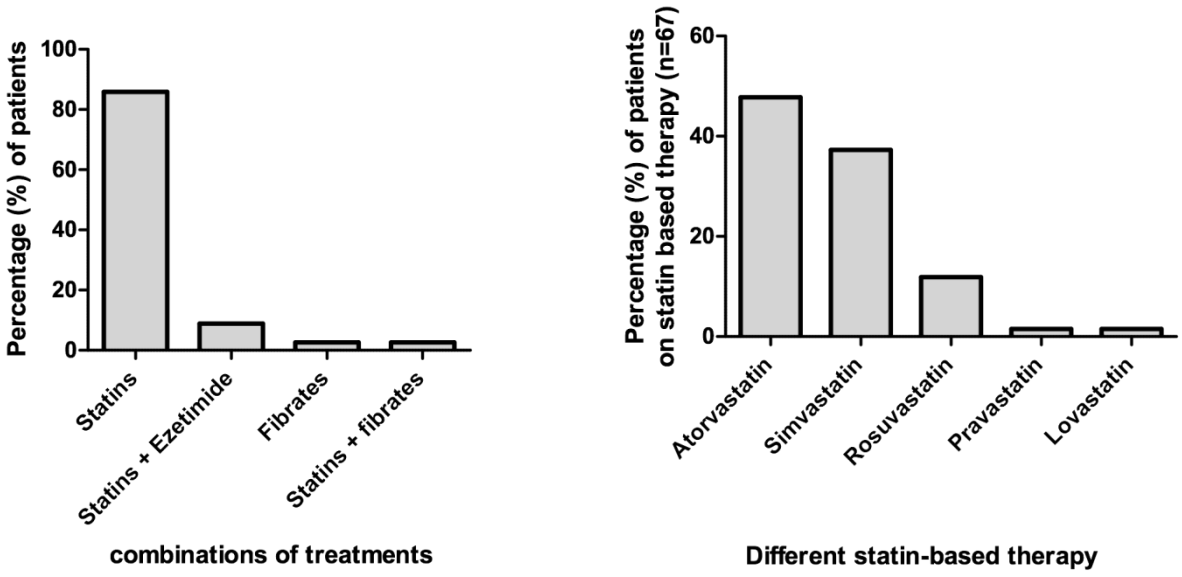


Figure 17: Therapeutic approaches used to treat the patient population. (A) All the different therapeutic approaches used to treat the total patient population (n=76). **(B)** The statin based approach used alone (not in combination with other medication) used to treat a number of the patients (n=67).

Table 19: Patients under pharmacotherapy on different types of statins (where 100% =67, n=67).

Drug group		**Number of patients**	**Percentage %**
Atorvastatin		32	47.8
Atorvastatin:	10mg	5	7.5
	20mg	21	31.3
	40mg	6	9.0
Simvastatin		25	37.3
Simvastatin:	20mg	7	10.4
	40mg	18	26.9

Rosuvastatin		8	11.9
Rosuvastatin:	5mg	1	1.5
	10mg	6	9.0
	20mg	1	1.5
Pravastatin	20mg	1	1.5
Lovastatin	20mg	1	1.5

Table 20: Patients under pharmacotherapy with statin plus ezetimibe (where 100% =7, n=7).

Drug combination		**Number of patients**	**Percentage %**
Ezetimibe		7	100
Ezetimibe + Simvastatin:	10+10mg	2	28.6
	10+20mg	2	28.6
	10+40mg	2	28.6
Ezetimibe + Atorvastatin:	10+40mg	1	14.3

Table 21: Patients under pharmacotherapy with fibrates (where 100% =2, n=2).

Drug		**Number of patients**	**Percentage %**
Gemfibrozil	600mg	1	50.0
Fenofibrate	145mg	1	50.0

Table 22: Patients under pharmacotherapy with fibrates plus a statin (where 100% =2, n=2).

Drug combination	Number of patients	Percentage %
Fenofibrate + Simvastatin: 145+40mg	1	50.0
Fenofibrate + Rosuvastatin: 145+20mg	1	50.0

Subsequently, the efficacy of the treatments was assessed in order to gain more insight into the effectiveness of the different pharmacotherapeutic methods used. Patients under different medication were asked about the reduction of the lipid levels in blood following their current treatments. The 76 patients on statin or statin combination therapy were showed various reduction ranges in terms of percentage in their lipid levels in blood (Figure 18). The majority of patients (56.6%) demonstrated a reduction of 36-40% in their lipid levels, while 18.4% of the patients showed a 31-35% decrease and the 17.1% of patients showed a 41-50% decrease in the lipid levels. These results demonstrate the effectiveness of statin based therapy, either in the form of monotherapy of in combination in lowering the LDL-C levels. Unfortunately, information on actual lipid counts and blood tests was restricted and thus the information obtained was solely from the patients' statements. The lack of previous lipid level measurements from the patients may not allow for a precise evaluation of the effectiveness of the therapeutic approaches.

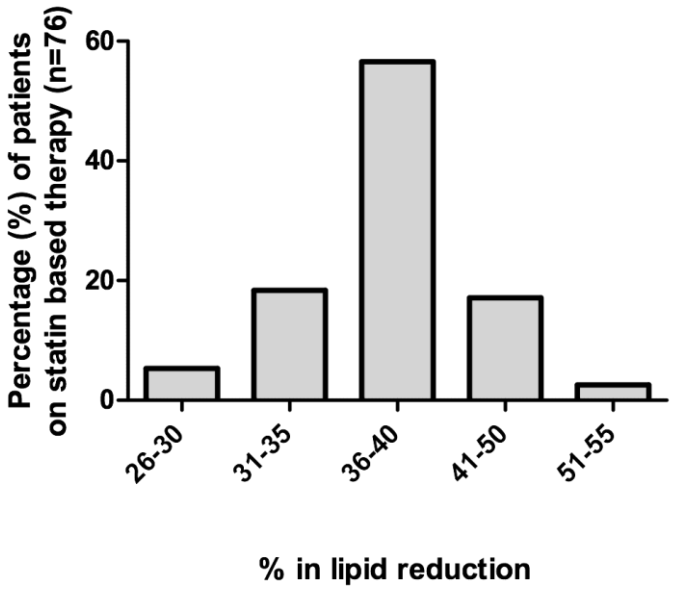


Figure 18: Efficacy of statin-based therapy (only statin and combination) in reducing the lipid levels in blood of hyperlipidemic patients (where 100% = 67, n=67).

Table 23: Patients under different statin but in equivalent potency due to dose (where 100% = 76, n=76).

Statin in equipotency		**Number of patients**	**Percentage %**
Lipid reduction by 26 – 30 %		4	5.3
Lovastatin	20mg	1	1.3
Pravastatin	20mg	1	1.3
Simvastatin	10mg	2	2.6
Lipid reduction by 31 – 35 %		14	18.4
Atorvastatin	10mg	5	6.6

Simvastatin 20mg	9	11.8
Lipid reduction by 36 – 40 %	43	56.6
Atorvastatin 20mg	21	27.6
Rosuvastatin 5mg	1	1.3
Simvastatin 40mg	21	27.6
Lipid reduction by 41 – 50 %	13	17.1
Atorvastatin 40mg	7	9.2
Rosuvastatin 10mg	6	7.9
Lipid reduction by 51 – 55 %	2	2.6
Atorvastatin 80mg	0	0
Rosuvastatin 20mg	2	2.6

Table 24: Number of patients taking generics or prototype drugs (where 100% = 78, n=78).

Drug	**Number of patients**	**Percentage %**
Patent drug	**21**	**26.9**
Generic	**57**	**73.1**

Table 25: Patients under pharmacotherapy with prototypes or generics (where 100% = 78, n=78).

Drug & Strength		Prototype	Generic
Atorvastatin:	10mg	1	4
	20mg	1	20
	40 mg	1	6
Lovastatin	20 mg	0	1
Pravastatin	20 mg	0	1
Rosuvastatin:	5mg	1	0
	10mg	6	0
	20mg	2	0
Simvastatin:	10mg	0	2
	20mg	0	9
	40mg	0	21

Table 26: List of patients' beliefs according to answers of questionnaire (where 100% = 78, n=78).

Views about medicines prescribed for you:	**Strongly agree (%)**	**Agree (%)**	**Uncertain (%)**	**Disagree (%)**	**Strongly disagree (%)**
My health, at present, depends on my medicines	34(43.6)	32(41.0)	2(2.6)	8(10.3)	2(2.6)
Having to take medicines worries me	13(16.7)	21(26.9)	2(2.6)	27(34.6)	15(19.2)
My life would be impossible without my medicines	23(29.5)	27(34.6)	11(14.1)	11(14.1)	6(7.7)
I sometimes worry about long-term effects of my medicines	19(24.4)	19(24.4)	6(7.7)	28(35.9)	6(7.7)
Without my medicines I would be very ill	22(28.2)	30(38.5)	11(14.1)	11(14.1)	4(5.1)
My medicines are a mystery to me	8(10.3)	8(10.3)	8(10.3)	43(55.1)	11(14.1)
My health in the future will depend on my medicines	28(35.9)	36(46.2)	4(5.1)	8(10.3)	2(2.6)
My medicines disrupt my life	6(7.7)	17(21.8)	6(7.7)	34(43.6)	15(19.2)
I sometimes worry about becoming too dependent on my medicines	11(14.1)	12(15.4)	8(10.3)	36(46.2)	11(14.1)
My medicines protect me from becoming worse	42(53.8)	34(43.6)	0(0)	0(0)	2(2.6)
These medicine give me unpleasant side effects	2(2.6)	6(7.7)	6(7.7)	30(38.5)	34(43.6)

Views about medicines in general	**Strongly Agree**	**Agree**	**Uncertain**	**Disagree**	**Strongly Disagree**
Doctors use too many medicines	18(23.1)	13(16.7)	9(11.5)	29(37.2)	9(11.5)
People who take medicines should stop their treatment for a while every now and again	9(11.5)	9(11.5)	16(20.5)	28(35.9)	16(20.5)
Most medicines are addictive	2(2.6)	18(23.1)	13(16.7)	41(52.6)	4(5.1)
Natural remedies are safer than medicines	9(11.5)	20(25.6)	20(25.6)	16(20.5)	13(16.7)
All medicines are poisons	7(9.0)	12(15.4)	22(28.2)	33(42.3)	4(5.1)
Medicines do more harm than good	2(2.6)	13(16.7)	9(11.5)	36(46.2)	18(23.1)
Doctors place too much trust on medicines	14(17.9)	36(46.2)	13(16.7)	13(16.7)	2(2.6)
If doctors had more time with patients they would prescribe fewer medicines	13(16.7)	18(23.1)	18(23.1)	25(32.1)	4(5.1)
Medicines help many people to live better lives	50(64.1)	24(30.8)	2(2.6)	2(2.6)	0(0)
In most cases the benefits of medicines outweigh the risks	34(43.6)	31(39.7)	9(11.5)	4(5.1)	0(0)

From the conducted questionnaire it may be suggested that a lot of patients feel that their well-being depends on their prescribed medication and some do worry about the dependency on it as well as their future health status.

The majority of patients seem to trust their physicians and their prescribed medication and they generally believe that the therapeutic approaches followed are improving the quality of their lives and alleviate their condition. A number of patients expressed that they worry about side effects arising from their medication but they generally feel that the benefits of the treatments outweigh the risks.

5. Discussion

Cardiovascular disease (CVD) is the leading cause of death worldwide. The direct link of CVD with hyperlipidemia, as discussed in the introductory part of the thesis, is very strong. Therefore, it is of outmost importance to understand the onset of hyperlipidemia and the best possible approaches to either prevent it or treat it. The main focus of this thesis was to shed light on to various different pharmacotherapeutic methods used to treat patients that were diagnosed with hyperlipidemia and discuss the effectiveness of these treatments.

The key outcome of the research conducted in the form of questionnaire revealed important information about the background of hyperlipidemia [12, 14]. The most common type of hyperlipidemia was pure hypercholesterolemia (76.9% of patients), followed by combined hyperlipidemia and pure hypertriglyceridemia, as shown in Figure 12. A number of the selected patients were also diagnosed with at least one other type of condition. The most prevalent conditions in the hyperlipidemic patients were hypertension (with 51.3% occurrence), type 2 diabetes (15.4%) and ischemic heart disease (15.4%) as shown in Figure 13. In addition, the majority of the diagnosed patients were obese. This fact confirms the direct link of obesity (due to bad dietary habits) to hyperlipidemia (Figure 14). Sex of the selected patients did not seem to be an important factor in terms of disease occurrence (Figure 15). On the other hand, age was an important factor in terms of hyperlipidemia occurrence. Most of the patients diagnosed with the condition were in the range of 66-75 years old (Figure 16).

Statin based therapy was shown to be the most popular therapeutic approach to treat hyperlipidemia as it has demonstrated the strongest evidence for lowering the LDL-C levels [18]. In addition, combinations

of statins with other medication such as fibrates or ezetimide were used for the treatment of hyperlipidemic patients (Figure 17). Atorvastatin was the mostly prescribed statin, followed by simvastatin (Figure 17 B). The choice of atorvastatin as a statin based medication was due to its increased efficacy in reducing the levels of LDL-C compared to other members of the statin group of prescribed drugs. The severity of hyperlipidemia defines the choice of prescribed medication, and thus severe cases of hyperlipidemia require a more potent statin such as atorvastatin [21, 23]. The reason why atorvastatin is the preferred statin is possibly due to the fact that higher dose of atorvastatin can more potently and efficiently reduce the LDL levels in comparison to simvastatin treatment. Hence, we could assume that the severity of hyperlipidemia in the majority of patients cannot be managed in a proper way with simvastatin and administration of more potent statins is required. Additionally, the only patient who was treated with gemfibrozil was the one diagnosed with familial type III hyperlipoproteinemia i.e. hypertriglyceridemia. Three of the patients diagnosed with familial combined hyperlipidemia (total number n=17), were treated with fenofibrate as monotherapy or in combination with a statin. Finally, as regards ezetimibe 7 patients use a medicine that combines ezetimibe with a statin.

Another important limitation of the questionnaire approach followed includes the lack of information on the genetic background of the patients. Hyperlipidemia is characterized by a strong genetic profile that was not taken into account in this project. An interesting addition in the questionnaire could be questions concerning the patients' family history on hyperlipidemia and/or cardiovascular disease in general to gain a more thorough insight in the genetic background and prevalence of the disorder. Further on, information on the general lifestyle of the selected patients was not gathered. The lifestyle is one of the main risk factors for heart disease [17]. The one particular lifestyle piece of information that was obtained concerned the smoking habit of the patients (Table 15). But, more information about the past smoking habits and maybe information on exercise and other crucial lifestyle habits could be advantageous in understanding the background and the patients' profiles. The dietary scheme of the patients was completely neglected in this particular study. A combination of questions about medication and diet followed to treat the disease could also provide some more insight about the role of diet in the onset of hyperlipidemia.

The lack of lipid level measurements from blood tests did not allow for the precise evaluation of the pharmacotherapy followed. Past and present lipid level values could have enabled reaching a better defined conclusion on the effectiveness of the pharmacotherapy followed.

The sample number was relatively small to provide with a broad picture on the population in Greece in terms of hyperlipidemia. But, the sample selected combined different types of the disorder and different pharmacotherapeutic approaches to allow for some insight into the medication used and the effectiveness of the different combinatorial approaches. Finally, the outcomes of the questionnaire in terms of the patients' beliefs and views regarding their medication regime are summarized. The majority of patients believe that their health greatly depends on their prescribed medications (Table 26) and they have stated that their life would be impossible without the medicines. Approximately 50% of the patients either strongly agree (24.4%) or agree (24.4%) with the existence of long term effects of their medication. But, they stated that they would feel very ill without the treatment and suggested that their future health greatly depends on the drug regime and that it is the medication that protects them from worsening of their condition (53.8% strongly agree and 43.6% agree). The majority of patients have not experienced or suffered from unpleasant side effects due to the treatment. The view about medicines in general was also asked in the questionnaire. Only 23.1% of the patients think that doctors prescribe too many drugs. A large percentage of the patients (46.2% agree and 17.9% strongly agree) think that doctors place too much trust in the use of medication to treat disease. The majority of the patients do not think that medicines are addictive and they believe in the therapeutic efficiency of their prescribed medicines, suggesting that medication may enhance the quality of people's lives and alleviate symptoms of disease.

6. ABBREVIATIONS

ABCG5 - ATP-binding cassette sub-family G member 5

ABCG8 - ATP-binding cassette sub-family G member 8

ACE - Angiotensin converting enzyme

AD - Autosomal dominant

ALP - Alkaline phosphatase

ALT - Alanine transaminase

Apo - Apoprotein

AR - Autosomal recessive

AST - Aspartate transaminase

ATP - Adenosine triphosphate

ATP III - Adult treatment panel III

BMI - Basal metabolic index

CHD - Coronary heart disease

CoA - Coenzyme A

CRP - C-reactive protein

CV - Cardiovascular

CVD - Cardiovascular disease

CYP - Cytochrome

DPP - Dimethylallyl pyrophosphate

FPP - Farnesyl pyrophosphate

γ-GT - Gamma-glutamyl transferase

GIT - Gastrointestinal tract

GPIHBP - Glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1

GPP - Geranyl pyrophosphate

HDL-C - High-density lipoprotein cholesterol

HMG-CoA - 3-hydroxy-3-methylglutaryl coenzyme

IDL-C - Intermediate-density lipoprotein cholesterol

IPP - Isopentenyl pyrophosphate

JBS2 - Joint British Societies' guidelines

LCAT - Lecithin acyltransferase

LDLR - Low-density lipoprotein receptor

LDLRAP - Low density lipoprotein receptor adaptor protein

LDL-C - Low-density lipoprotein cholesterol

LIPC - Hepatic lipase gene

Lp(a) - Lipoprotein a

M-CSF - Macrophage colony-stimulating factor

mm Hg - Millimeter of mercury

mmol/L - millimole per litre

NCEP - National Cholesterol Education Program

OTC - Over the counter

PCSK9 - Proprotein convertase subtilisin/kexin type 9

PPAR-a - Peroxisome proliferator-activated receptor alpha

PPRE - Peroxisome proliferator response element

PVD - Peripheral vascular disease

PXR - Pregnane X receptor

T-3 - Triiodothyronine

T-4 - Thyroxine

TC - Total cholesterol

TG - Triglycerides

TSH - Thyroid-stimulating hormone

VLDL-C - Very-low density lipoprotein

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