Ministry of higher education and scientific research
University of Babylon
College of pharmacy

GRADUATION PROJECT

Statistical study of antihyperlipidemic drugs

A graduation project submitted to the college of pharmacy / Babylon University as partial fulfillment of the requirement of the BSc degree in pharmacy

prepared by

Mays Murtadha Khalaf

Noor AlHuda Jassim

Dalal Hassoun Gganim

Supervised by

Prof.Dr Fakhir Maktof

Assistant lecturer Ahmed Hassan

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بسم اله
الرحمان
الرحيم

(قَالَ لَهُ مُوسَىٰ
هَلْ أَتَّبِعُكَ عَلَىٰ
أَنْ تُعَلِّمَنِ مِمَّا
عُلِّمْتَ رُشْدًا)

سورة الكهف أية (٦٦)

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Abstract

Hyperlipidemia: is a condition that incorporates various genetic and acquired disorders that describe elevated lipid levels within the human body. Hyperlipidemia is extremely common throughout the world and is a major risk factor for cardiovascular diseases, and there are many medication used to treat high level of lipids (such as cholesterol and triglycerides) in the blood like HMG-CoA reductase inhibitors (Statins): Lovastatin, Simvastatin, Pravastatin, Atorvastin,Rosuvastin. Bile acid sequestrants (Resins): Cholestyramineand, Colestipol. Activate lipoprotein lipase (Fibric acid derivatives): Clofibrate, gemfibrozil, benzafibrate and fenofibrate. Inhibit lipolysis and triglyceride synthesis: Nicotinic acid.Others: Ezetimibe, Gugulipid. Hyperlipidemia accure more in women than men. The age of patients that included (15 _70), and hyperlipidemia accure more in age between (50_59). Rusavastatin from company astrazenica is most drug that used in treatment of hyperlipidemia according to our study.

Statistical study of antihyperlipidemic drugs

1- INTRODUCTION:

Hyperlipidemia:

is an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters and phospholipids and or plasma lipoproteins including very low density lipoprotein and low-density lipoprotein, and reduced high-density lipoprotein levels[1,2].
Lipids are fats in the blood stream, commonly divided into cholesterol and triglycerides. Cholesterol circulates in the bloodstream and is involved in the structure and function of cells. Triglycerides (TG) are best viewed as energy that is either used immediately or stored in fat cells. TG is manufactured in the liver from the foods or by being absorbed from the intestine.

The most common type of hyperlipidemia is high cholesterol. Other forms of hyperlipidemia include hypertriglyceridemia and mixed hyperlipidemia, (in which both cholesterol and triglyceride levels are high.

Hyperlipidemia is very common, especially in modern developed countries. It's also increasing around the world.

Hyperlipidemia (high cholesterol) that's not treated can allow plaque to collect inside of your body's blood vessels (atherosclerosis). This can bring on hyperlipidemia complications that include :

Heart attack, Stroke, Coronary heart disease. Carotid artery disease carotid-artery-disease-carotid-artery-stenosis). Sudden cardiac arrest, Peripheral artery disease ,Microvascular disease[1,2].

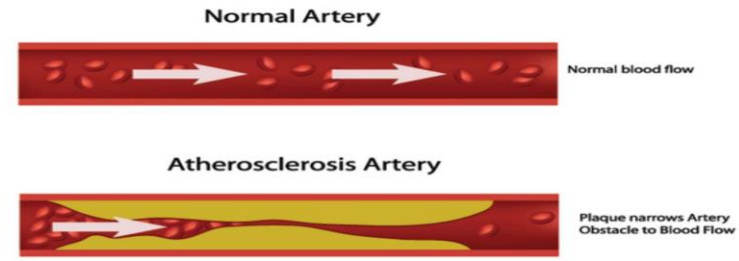


Figure 1: effect of high lipid levels on blood flow

Fieger 1

1-2 HYPERLIPIDEMIA CLASSIFICATION:

Hyperlipidemia in general can be classified to:

1/ Primary is also called familial due to a genetic defect,i.e., mutation within receptor protein, it may be monogenic: a single gene defect or polygenic: multiple gene defects. This type may occur as a result of change in dietary and lack of proper physical activities. See table below for summaries the various classes of primary hyperlipidemia [5] Fieger 2 [6].

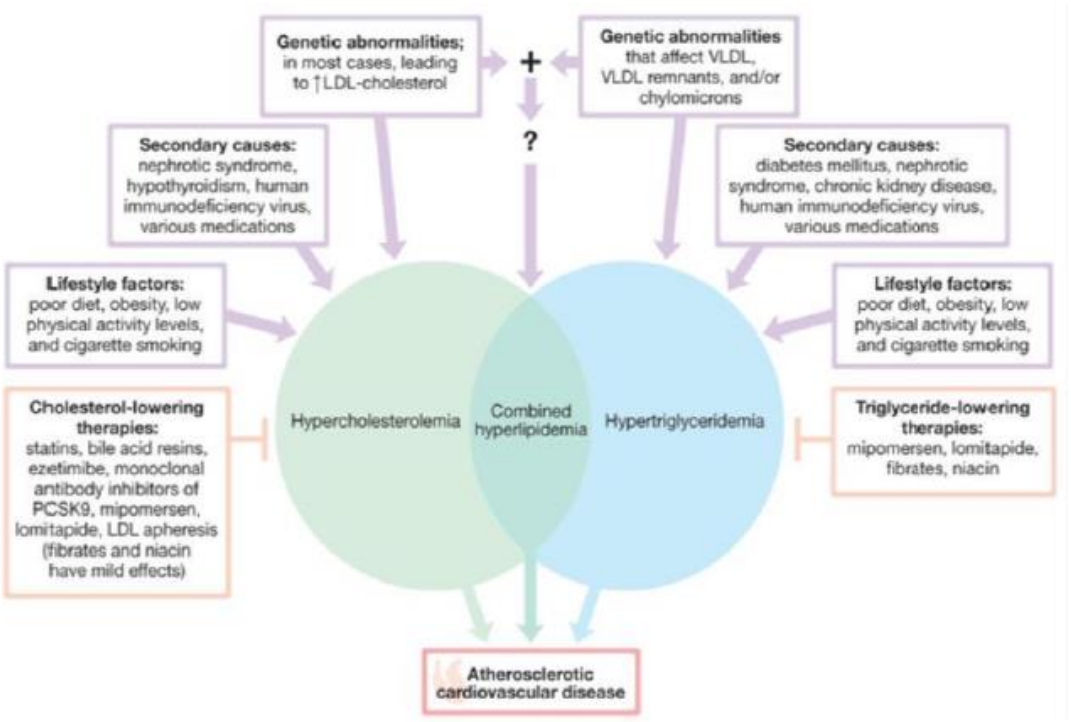
Fredrickson classification of primary hyperlipidemia

Type	Disorder	Cause	Occurrence	Elevated plasma lipoprotein
I	Familial hyperchylomicronemia Or Primary hyperlipoproteinemia	Lipoprotein lipase deficiency or Altered ApoC2	Very rare	Chylomicrons
IIa	Familial hypercholesterolemia Or Polygenic hypercholesterolemia	LDL receptor deficiency	Less common	LDL
IIb	Familial combined hyperlipidemia	Decreased LDL receptor and increased ApoB	Commonest	LDL and VLDL
III	Familial dysbetalipoprotenemia	Defect in Apo E- 2 synthesis	Rare	IDL
IV	Familial hypertriglyceridemia	Increased VLDL production and decreased excretion	common	LDL
V	Endogenous hypertriglyceridemia	Increased VLDL production and decreased LPL	Less common	VLDL and chylomicrons

2/ Secondary hyperlipidemia it is acquired because it is caused by another disorder like diabetes, nephritic syndrome, chronic alcoholism, hypothyroidism and with use of drugs like corticosteroids, beta blockers and oral contraceptives [4,5].

The main cause of hyperlipidemia includes changes in lifestyle habits in which risk factor is mainly poor diet in which fat intake form saturated fat and cholesterol exceeds 40 percent of the total calories uptake [8].

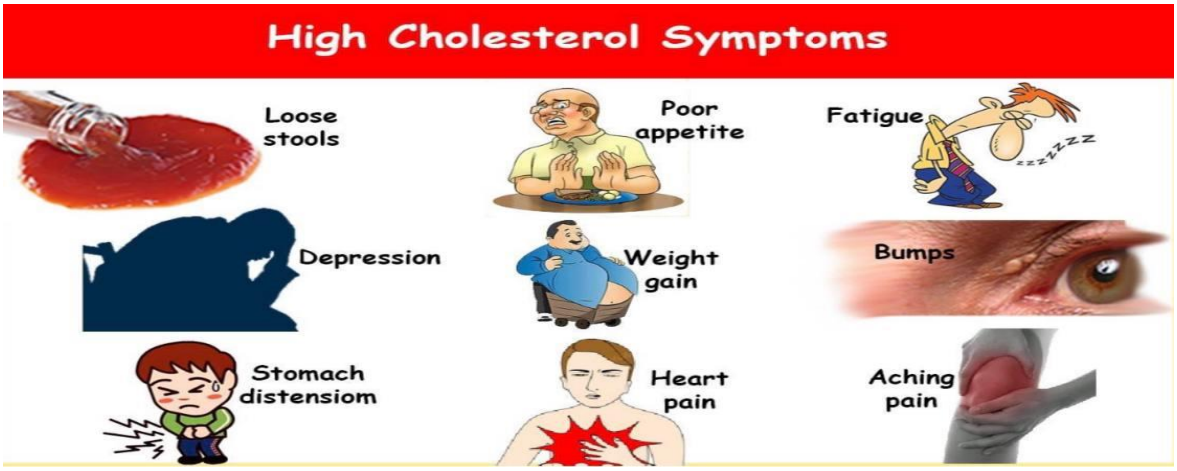
Causes of hyperlipidemia [9,10].



Fieger 3.

1-3 SYMPTOMS OF HYPERLIPIDEMIA

Generally, hyperlipidemia does not have any obvious symptoms but they are usually discovered during routine examination or until it reaches the danger stage of a stroke or heart attack.
Patients with high blood cholesterol level or patients with the familial forms of the disorder can develop
xanthomas which are deposits of cholesterol may form under the skin, especially under the eyes. At the same time, patients with elevated levels of triglycerides may develop numerous pimple-like lesions at different sites in their body [11].



Fieger 4

1-4 THE PROBLEM STATEMENT

The objective of this study is to conduct a statistical analysis to assess the effectiveness and safety of antihyperlipidemic drugs in the treatment of hyperlipidemia, with the aim of providing evidence-based recommendations for their use in clinical practice.

This problem statement highlights the need to examine the statistical data and evidence regarding antihyperlipidemic drugs to evaluate their efficacy and safety in managing hyperlipidemia. The study seeks to address gaps in knowledge by utilizing statistical methods to analyze the available data, ultimately aiming to inform healthcare professionals and decision-makers about the use of these drugs in treating hyperlipidemia.

1-5 TREATMENT OF HYPERLIPIDEMIA:

Non pharmacological therapy :

The objectives of dietary therapy are to decrease the intake of total fat, saturated fatty acids (i.e., saturated fat), and cholesterol progressively and to achieve a desirable body weight (1). This involves:

1. Reduced saturated fat intake to 7 percent of daily calories.

2. Reduced total fat intake to 25 to 35 percent of daily calories.

3. Limited dietary cholesterol to less than 200 mg per day.

4. Eating 20 to 30 g a day of soluble fiber, which is found in oats, peas, beans, and certain fruits; and

5. Increased intake of plant stanols or sterols, substances found in nuts, vegetable oils, corn and rice, to 2 to 3 g daily. Other foods that can help control cholesterol include cold-water fish, such as mackerel, sardines, and salmon. These fish contain omega-3 fatty acids that may lower triglycerides. Soybeans found in tofu and soy nuts and many meat substitutes contain a powerful antioxidant that can lower LDL [13].

Pharmacological therapy:

This involves mainly the use of drugs. The major drug involves in the treatment of hyperlipidemia is known as statin. Generally, the drugs involve in the treatment of hyperlipidemia are classified as follows;

ϖ HMG-CoA reductase inhibitors (Statins): Lovastatin, Simvastatin, Pravastatin, Atorvastin, Rosuvastin [13].

ϖ Bile acid sequestrants (Resins): Cholestyramine, Colestipol.

ϖ Activate lipoprotein lipase (Fibric acid derivatives): Clofibrate, Gemfibrozil,Benzafibrate and Fenofibrate.

ϖ Inhibit lipolysis and triglyceride synthesis: Nicotinic acid.

ϖ Others: Ezetimibe, Gugulipid.

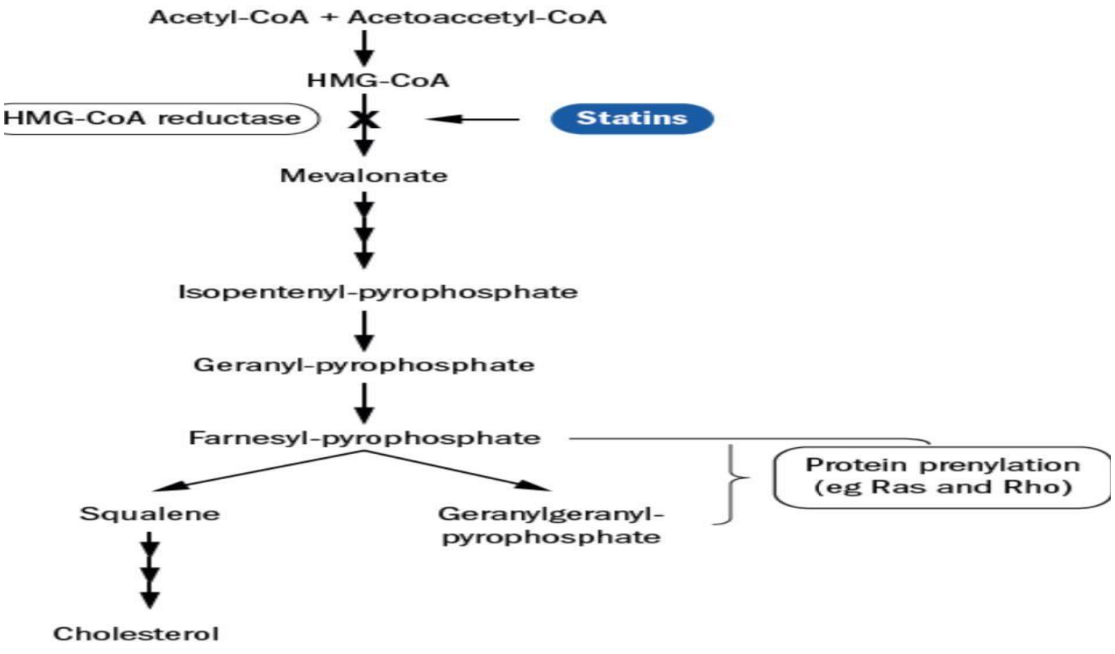
➢ **3-Hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductaseinhibitors (statins)**.

This class includes (Lovastatin ,Simvastatin, Pravastatin, Fluvastatin, Atorvastatin and Rosuvastatin). Statins are broadly prescribed in the treatment of hypercholesterolemia, can
achieve 20%–50% reductions in cholesterol levels and have been linked to the reduced incidence of coronary morbidity and mortality in high-risk adults [14].

Mechanism of action:

These drugs are structural analogues of HMG-coenzyme A reductase. They act by inhibiting the rate limiting enzyme (HMG-coenzyme A reductase) in the biosynthesis of cholesterol in the liver. By inhibiting this enzyme, statins significantly reduce plasma levels of total cholesterol (TC), LDL and ApoB. Meanwhile, statins also cause a modest decrease in plasma triglycerides and a small increase in plasma level of HDL [15].

Other HMG-CoA reductase inhibitors include the diallyldisulfide (DADS) and diallylthiosulfinate. DADS, is an organosulfur compound derived from garlic, has been shown to reduce cholesterol synthesis by 10–25% at low concentrations. Diallylthiosulfinate,a metabolite of allicin, block the formation of 7-dehydrocholesteroland reduced the production of cholesterol. Bis-(3-(4-nitrophenyl) prop-2-ene) disulfide, anew derivatives of diallyl disulfide, is effective in reducing plasma total cholesterol [16]. Fieger 4 [29]



5: Statins and the cholesterol synthesis pathway – the mevalonate pathway

Side effects:

Statins are frequently well tolerated with the most common adverse effects being transient gastrointestinal symptoms, headache, myalgia and dizziness. These symptoms are more common with higher doses and may solve if a different statin is used [17].

Statins also cause myopathy, rhabdomyolsis and an increase serum transaminase. These substances are harmful to the kidney and often cause kidney damage. Additionally statins may cause cardiomyopathy [18].

Recent clinical trials showed that statin use has
been linked to an increase in type 2 diabetes [19].

➢ Fibrates (cholestyramine, colestipol, colesevelam):

1. The primary action of bile acid resins (BARs) is to bind bile acids in the intestinal lumen, with a concurrent interruption of enterohepatic circulation of bile acids, which decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in an increase in cholesterol biosynthesis and an increase in the number of LDL receptors on the hepatocyte membrane, which stimulates an enhanced rate of catabolism from plasma and lowers LDL levels. The increase in hepatic cholesterol biosynthesis may be paralleled by increased hepatic VLDL production and, consequently, BARs may aggravate hypertriglyceridemia in patients with combined hyperlipidemia [20].

2. BARs are useful in treating primary hypercholesterolemia (familial hyper-cholesterolemia, amilial combined hyperlipidemia, type IIa hyperlipoproteinemia).

Adverse effects:

Gastrointestinal complaints of constipation, bloating, epigastric fullness, nausea, and flatulence are most commonly reported. These adverse effects can be managed by increasing fluid intake, modifying the diet to increase bulk, and using stool softeners. The gritty texture and bulk may be minimized by mixing the powder with orange drink or juice. Colestipol may have better palatability than cholestyramine because it is odourless and tasteless. Tablet forms should help improve adherence with this form of therapy. Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; hypernatremia and

hyperchloremia; gastrointestinal obstruction; and reduced bioavailability of acidic drugs such as warfarin, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron. Drug interactions may be avoided by alternating administration times with an interval of 6 hours or greater between the BAR and other drugs [20].

➢ Fibric acid derivatives(Fibrates)

Fibrates include (clofibrate, gemfibrozil, fenofibrate, and bezafibrate) are widely used class of antihyperlipidemic agents, results in a significant reduction in plasma triglycerides and a modest reduction in LDL cholesterol. HDL cholesterol level increases moderately. Angiographictrials results showed that fibrates play an important role in slowing the progression of coronary atherosclerosis and decrease the incidence of coronary artery disease.

Mechanism of action:

Data from studies in rodents and in humans imply four main mechanisms of fibrates:

Stimulation of lipoprotein lipolysis:

Fibrates function primarily as ligands for the nuclear transcription receptor, PPAR. They increased the expression of lipoprotein lipase, apo, and down-regulate apo C-III, an inhibitor of lipolysis. Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI andapo AII [21].

Increase hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production:

Fibrates enhance the production of fatty acid transport protein and acyl-CoA synthetase, which contribute to the increase uptake of fatty acid by the liver and as a result in a lower availability of fatty acids for triglyceride production [22].

Increase removal of LDL particles:

Fibrate, appears to enhance LDL catabolism via the receptor-mediated pathway; LDL particles became larger and more lipid rich and therefore had more affinity for receptors. Fibrates also inhibits the formation of slowly metabolized, potentially atherogenic LDL particles [23,24].

Side effects:

Generally, fibrates are considered to be well tolerated. Side effects may include gastrointestinal symptoms, myopathy, arrhythmia, skin rashes and gallstones. Fibrates should be avoided in patients with liver and renal dysfunction [25].

Niacin:

1. Niacin (nicotinic acid) reduces the hepatic synthesis of VLDL, which in turn leads toa reduction in the synthesis of LDL. Niacin also increases HDL by reducing its catabolism.

2. The principal use of niacin is for mixed hyperlipidemia or as a second-line agent in combination therapy for hypercholesterolemia. It is a first-line agent or alternative for the treatment of hypertriglyceridemia and diabetic dyslipidemia.

Mechanism of action:

Niacin performs a number of functions in the body and so has many mechanisms, not all of which have been fully described. Niacin can decrease lipids and apolipoprotein B (apo B)-containing lipoproteins by modulating triglyceride synthesis in the liver, which degrades apo B, or by modulating lipolysis in adipose tissue.

Niacin inhibits hepatocyte diacylglycerol acyltransferase-2. This action prevents the final step of triglyceride synthesis in hepatocytes, limiting available triglycerides for very low density lipoproteins (VLDL). This activity also leads to intracellular degradation of apo B and decreased production of low density lipoproteins, the catabolic product of VLDL.

Niacin also inhibits a high density lipoprotein (HDL) catabolism receptor, which increases the levels and half life of HDL.[30]

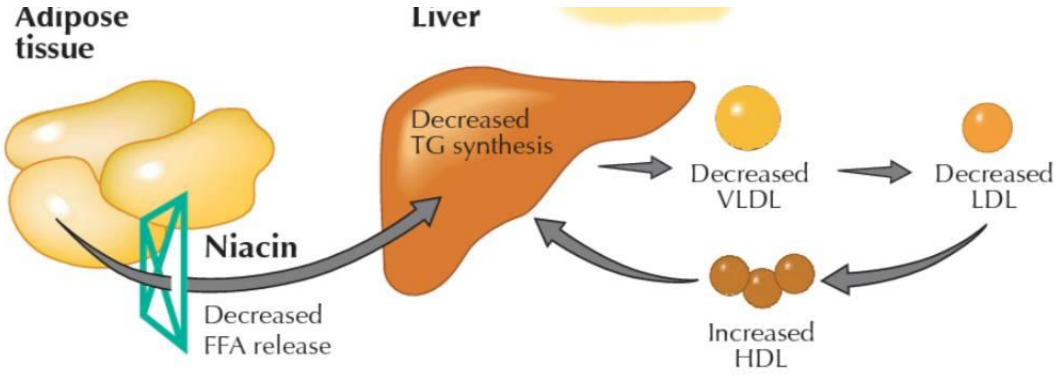
Niacin has many common adverse drug reactions:

most of the symptoms and biochemical abnormalities seen do not require discontinuation of therapy. Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by taking aspirin 325 mg shortly before niacin ingestion.

Taking the niacin dose with meals and slowly titrating the dose upward may minimize these effects. Concomitant alcohol and hot drinks may magnify the flushing and pruritus from niacin, and they should be avoided at the time of ingestion. Gastrointestinal intolerance is also a common problem.

Potentially important laboratory abnormalities occurring with niacin therapy include elevated liver function tests, hyperuricemia, and hyperglycemia. Niacin-associated hepatitis is more common with sustained-release preparations, and their use should be restricted to patients intolerant of regular-release Hyperlipidemia: etiology and possible control. Niacin is contraindicated in patients with active liver disease, and it may exacerbate preexisting gout and diabetes [13].

Nicotinamide should not be used in the treatment of hyperlipidemia because it does not effectively lower cholesterol or triglyceride levels.



Fieger 5: Effect of niacin on blood lipids [30].

➢ Selective cholesterol absorption inhibitor (Ezetimibe)

The discovery and development of ezetimibe, the first member of a group of drugs that inhibit intestinal absorption of phytosterols and cholesterol, has improved the treatment of hypercholesterolemia. It inhibits the absorption of cholesterol from the small intestine without any effect on the plasma concentrations of the fatsoluble vitamins [26], A combination

of statins and ezetimibe can achieve a reduction in LDL cholesterol levels by25%.

Mechanism of action:

Ezetimibe selectively inhibits absorption of cholesterol in the small lintestine, leading to a decrease in the delivery of intestinal cholesterol to the liver by blocking the Niemann–Pick C1-like 1 protein (NPC1L1), a human sterol transport protein. This causes an increase in the clearance of cholesterol from the blood [24].

Side effects:

Ezetimibeis usually well tolerated; the most common side effects include headache, abdominal pain and diarrhea. Ezetimibe appears to cause elevations in liver function tests include elevations in alanine transaminase and aspartate Transaminase [29].

Method:

the Data was collected at two pharmacies and one laboratory fro 10th of November to 2th of march according to table below:

Result:

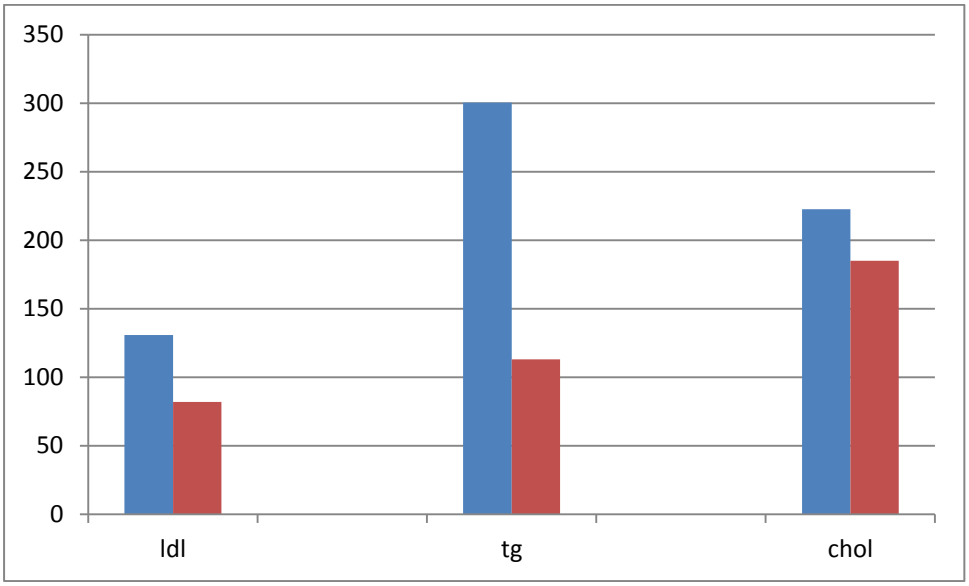


Figure 1: Levels of low density lipoproteins, triglycerides, and cholesterol (mg/dl) in patients (blue color)compare with normal persons (red color).

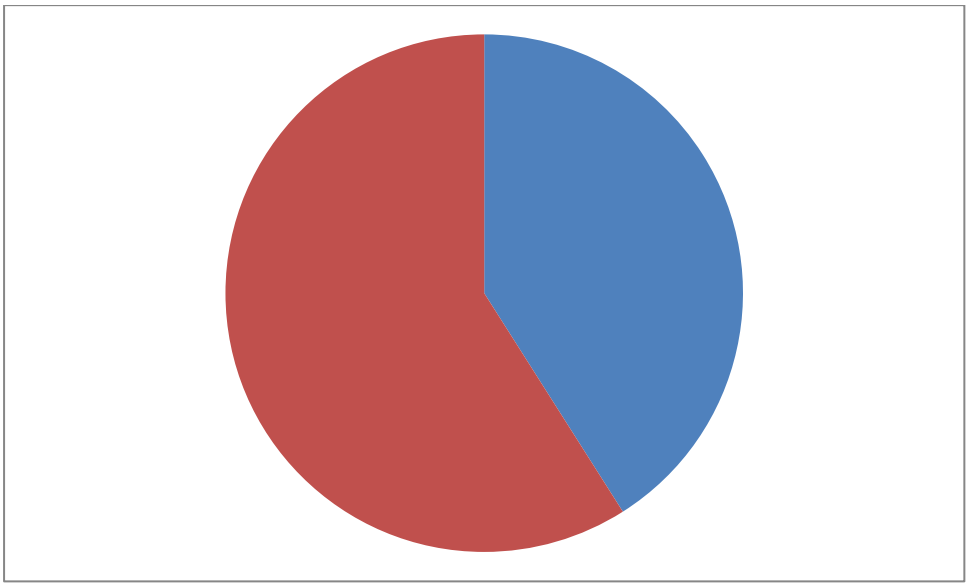


Figure 2: Distribution of hyperlipidemia according to gender (female patients: 59% with red color, male patients: 41% with blue color).

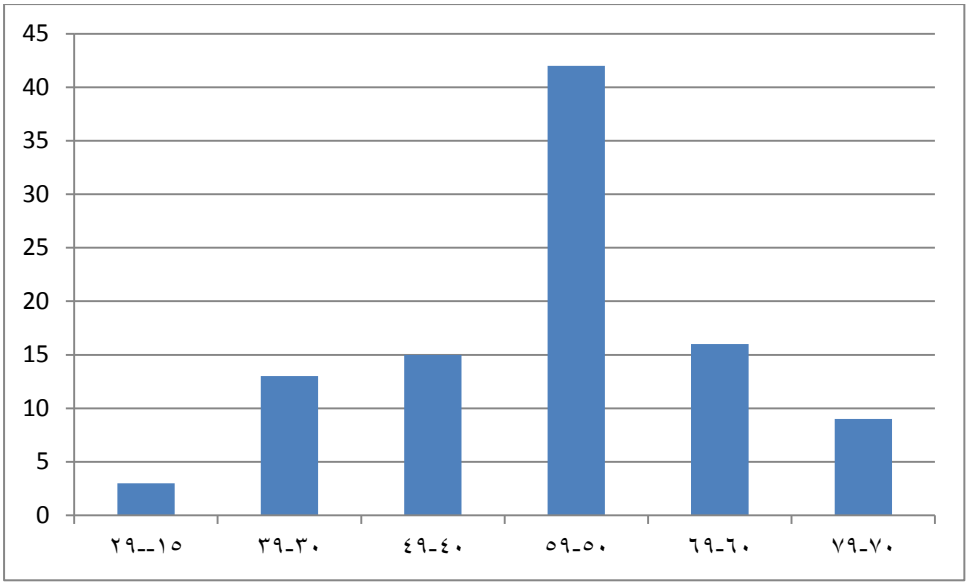


Figure 3: Distribution of hyperlipidemia according to age.

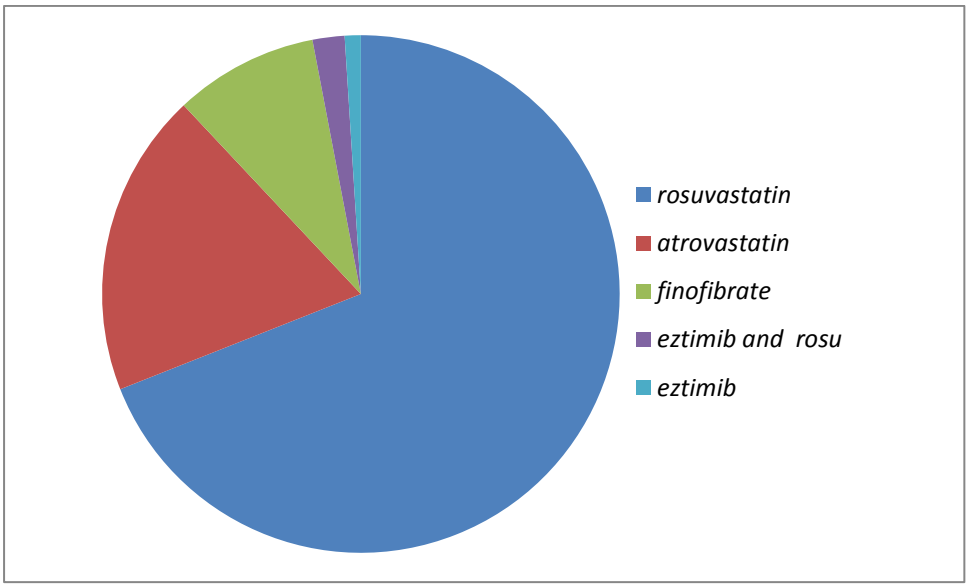


Figure 4: Percentage of the drugs used for the treatment of hyperlipidemia.

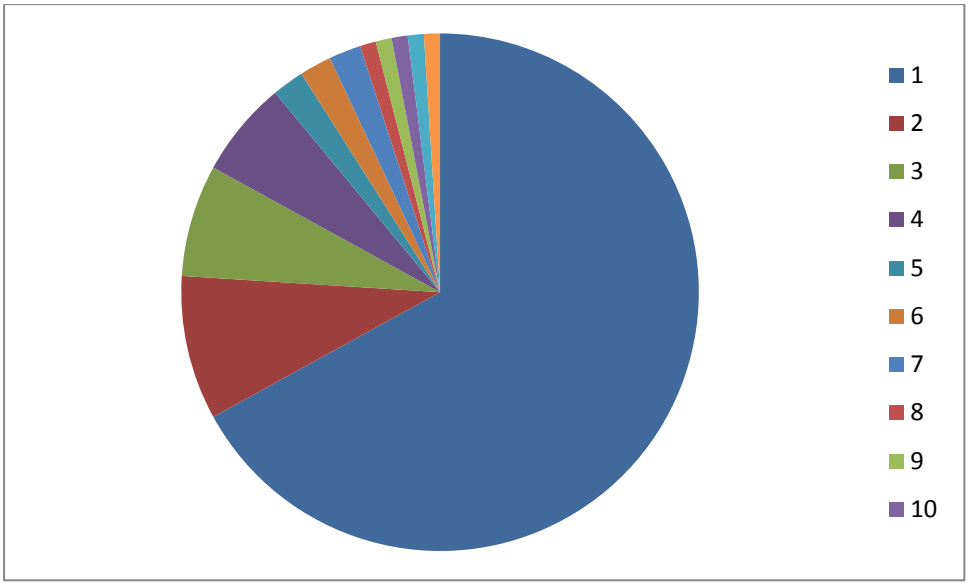


Figure 5: Drug companies of the current research

divator3000	flamingo35000	micro2000	accord9000	abboot22000	astrazen 13000	tabac21000	jazeera2500	bilim2500	neutec 14000	atmed9000	zada5000
1	1	1	1	1	2	2	2	6	7	9	67

Discussion

Based on the data we've been collected and analyzed, we found that triglycerides (more than 300 mg\dl , normal value : less than 150 mg\dl) Higher more than the plasma lipids (cholesterol more than 220 mg\dl normal value less than 200 mg\dl , LDL more than 120 mg\ dl , normal value : less than 100 mg\ dl) may be because of life style of patients , side effect of some drugs .

Hyperlipidemia accure more in women (59%) than men (41%), because Women experience a number of hormonal changes throughout their lifetime, including those changes associated with puberty, menarche, pregnancy, and menopause. Each of these hormonal perturbations can alter serum lipoprotein levels [28,29].

The age of patients that included (15 _70) (60_69) 16 patients, (70_79) 9 patients, (4_49) 15 patients, (30_39) 13 patients, (15_29) 4 patients, and hyperlipidemia accrue more in age between (50_59) (42 of 100 patient), because elder patients have a lot of disease may aggravate hyperlipidemia, Adult patients with an unhealthy lifestyle are unable to do exercise, and hyperlipidemia may have occurred due to an unhealthy lifestyle other than lack of exercise.

Rusavastatin from company astrazenica is most drug that used in treatment of hyperlipidemia according to our stady (65%) of data and that is may be because:

1) the cost: rusavastatin (astrazencia) consider medium in cost there are a lot of drugs highest than (atorvastatin avas 2000 ID) and lowest in cost than (lepanrhil 22000 ID).

2) the effectiveness: perhaps, the physician found that is rusavastatin more effective than other drugs.

3) illness condition: statins more effective in decrease cholesterol plasma, statins also cause a modest decrease in plasma triglycerides and a small increase in plasma level of HDL, this possibility is less true because the most patient in our study have highest tgd.

4) the company: AstraZeneca is one of most famous companies
, specializing in the pharmaceutical and biopharmaceutical industry.

Atorvastatin the most second drug that used in treatment of hyperlipidemia according to our study is one of statin group drugs but It came in second place, perhaps because it is less effective than the first drug, but it remains more used compared to other drugs, (with the exception of rusavastatin).

In third place is fenofibrate, and in last place is eztimib.

However, it is important to note that our study has some limitations, such as The patients are not having the same lipid profile so we choose three plasma lipids that lighest more than the other (cholesterol, triglyseide, LDL). Changing the some aims of graduation research due to the lack of sufficient data on the study, such as: Patients do not know the lipid profile before treatment, after treatment, or the current lipid profile, and they do not contact us to inform us of the duration of treatment.

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