Pharmacology of Hyperlipidemia

Introductions and definitions

Types of lipoproteins in the body

:As you know, lipoproteins are divided into four categories

- Chylomicrons) are mainly composed of triglycerides; About08 to59) of them are triglycerides %
- VLDL (mainly composed of triglycerides)
- LDL is mainly composed of cholesterol; About (59) of it is cholesterol %
- HDL) "is mainly composed of proteins and phospholipids; It is called "good cholesterol (

In general, most of the body's cholesterol accumulates in chylomicrons and VLDLs .VLDL and LDL are known as bad forms and HDL .as good forms of fat in the body

Cholesterol homeostasis

In general, the body's cholesterol is supplied through the diet and to a greater extent through the endocrine system (mainly the liver. Cholesterol production in the body is a function of a circadian cycle) and most of it is at night. Destiny suffers: a) (consumed by the body, b) stored in tissues or c) excreted from .the body

Cholesterol synthesis

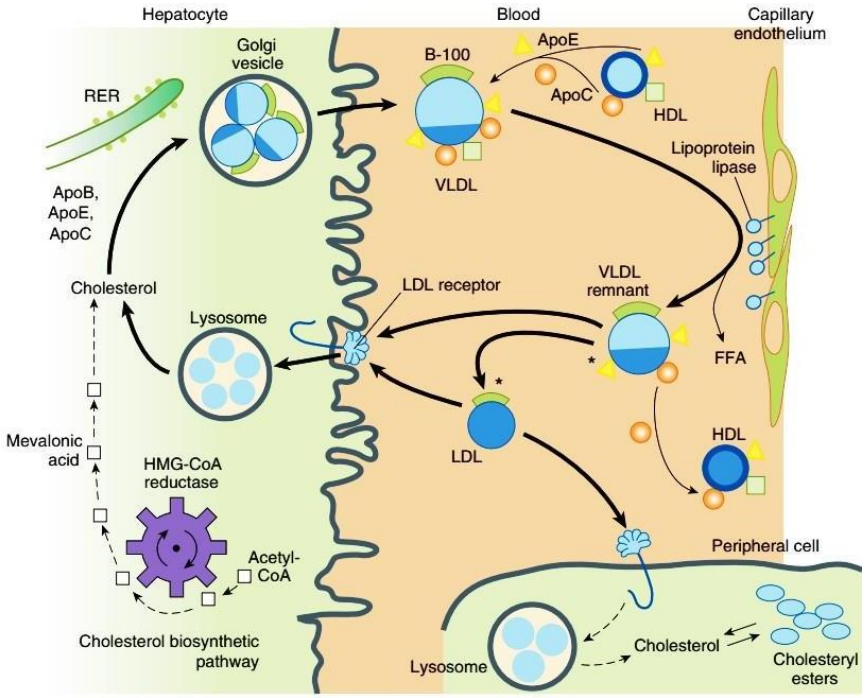
In liver cells, acetyl-CoA converted to)HMG-CoA reductase tomevalonic acid is first converted to mevalonic (acid and then, in stages, to cholesterol, then cholesterol, in combination with various apoproteins, is converted to VLDL particles .

VLDL is a rich triglyceride compound that is made by the liver and released into the bloodstream. When) this compound passes through the arteries, it is affected by the enzyme lipoprotein lipaselipo protein lipase)) which breaks down triglycerides to produce free fatty acids ,FFAs) .

VLDL shrinks with the loss of triglyceride and first converts to the remainder of the VLDL remnant (VLDL (also called IDL in some sources) and then to LDL .

, Thus LDL is made from VLDL .which is then recognized and picked up by hepatocyte receptors ,LDL can supply cholesterol to cells. Cholesterol is a component of membranes and also in the production of hormones. Steroids (such as cortisol, aldosterone, estrogen, progesterone and testosterone) and bile salts are used. Due to the physiological functions of cholesterol, the levels of this substance can not be reduced !to zero

HDL performs the task of removing unwanted cholesterol from the cell surface and is therefore called a cholesterol scavenger .High levels of this lipoprotein in the body are considered a positive factor .



HDL and LDL structure

These two lipoproteins have a spherical structure of3 .layers

- On the outer surface, there are apolipoproteinsA and B which play a role in the interactions of , .these particles with cells
- .The middle layer consists of phospholipids and cholesterol
- .The inner layer contains triglycerides and cholesterol

At the core of HDL and LDL particles are fat-soluble antioxidants such as vitamin E and beta-carotene, which protect these particles from oxidation.

HDL properties

High density lipoprotein; high density protein; HDL) HDL is the smallest, densest, and most soluble lipoprotein. HDL is made by cells in the liver and small intestine and is involved in removing cholesterol from tissues. HDL levels and the risk of cardiovascular disease have been shown to be inversely related.

Quantitative calculations related to lipids and cholesterol in the body

- Serum cholesterol levels below 288 mg / dL are considered appropriate. Cholesterol levels between 235 - 288 mg / dL in the border area and levels higher than 258 mg / dL is considered high cholesterol. It should be noted that serum cholesterol is in 3 components LDL, VLDL and HDL.
- Optimal cholesterol level in HDL-C (serum HDL between) (58-80 mg / dL

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- To calculate the LDL-C parameter, the sum of VLDL-C and HDL-C values must be subtracted from the total serum cholesterol (TC) value:

LDLC TC HDLC VLDLC - □ □ □ - □ - □

- The value of VLDL-C is obtained by dividing the amount of triglyceride by 9. However, these instructions are for triglycerides with concentrations above

LDLC TC HDLC TG - □ □ □ - □ / 5 □ . Not responsive 588 mg / dL

- Another important parameter is non-HDL-C which is obtained from the difference between HDL-C, and total cholesterol:

nonHDLC TC HDLC - - □ □ -

Risk factors for cardiovascular disease

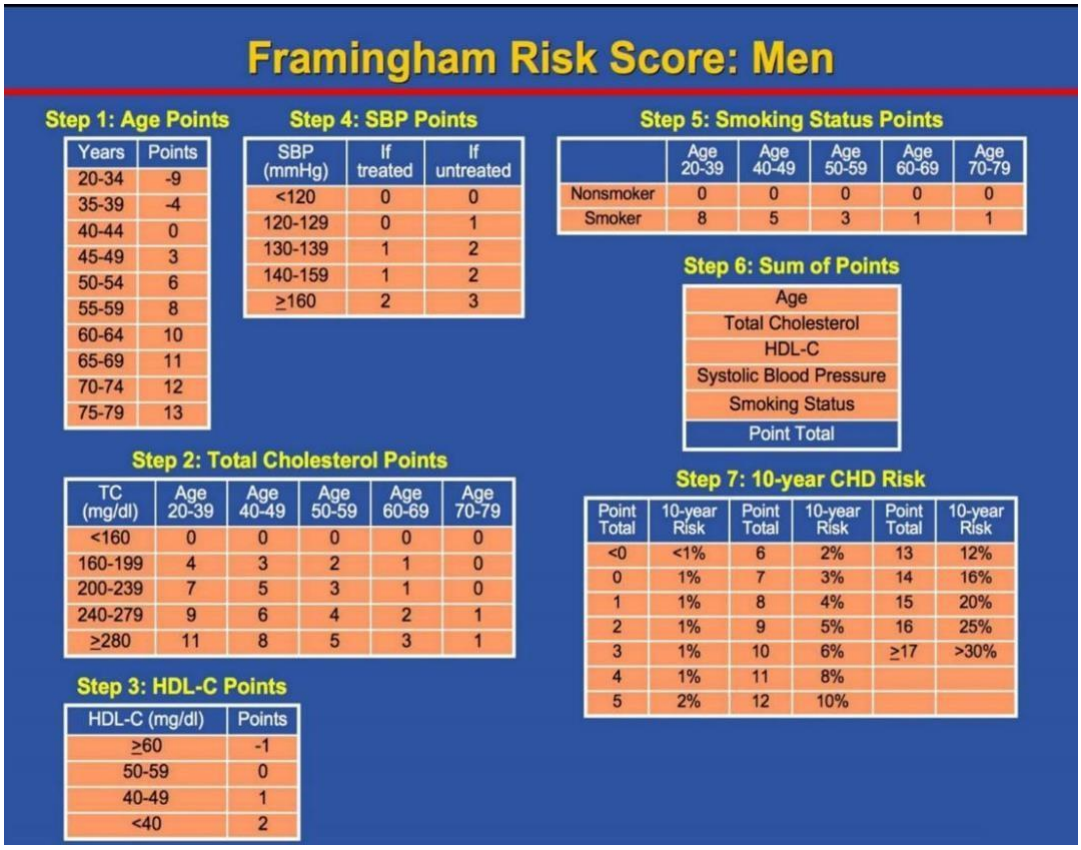
- Main risk factors: old age, high serum cholesterol levels, high non-HDL-C and LDL-C levels, low HDL-C levels, diabetes mellitus, hypertension, chronic kidney disease stages 3 and 5, smoking, family history of heart disease (Atherosclerotic vessels ASCVD)

,Other risk factors include obesity, family history of hyperlipidemia, elevated coagulation factors .elevated inflammatory markers, elevated homocysteine and uricacid levels

Calculation of vascular disease risk by Framingham method

Framingham risk score tables (to predict the probability of08 (years year risk -10 (coronary heart disease) CAD (used in the individual. In calculations of age parameters, total cholesterol) TC cholesterol in ,) HDL- C (HDL systolic blood pressure ,(SBP .and smoking history used (

As can be seen in the picture, the final score is obtained from the sum of the scores of each section, which determines the risk of contracting the person during the next08 years; For example, if a person's total score is09 his risk of developing the disease is estimated at ,28 .%



Framingham Risk Score: Men

Step 1: Age Points

Years	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Step 4: SBP Points

SBP (mmHg)	If treated	If untreated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Step 5: Smoking Status Points

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Step 6: Sum of Points

Age
Total Cholesterol
HDL-C
Systolic Blood Pressure
Smoking Status
Point Total

Step 2: Total Cholesterol Points

TC (mg/dl)	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

Step 7: 10-year CHD Risk

Point Total	10-year Risk	Point Total	10-year Risk	Point Total	10-year Risk
<0	<1%	6	2%	13	12%
0	1%	7	3%	14	16%
1	1%	8	4%	15	20%
2	1%	9	5%	16	25%
3	1%	10	6%	≥17	>30%
4	1%	11	8%		
5	2%	12	10%		

Step 3: HDL-C Points

HDL-C (mg/dl)	Points
≥60	-1
50-59	0
40-49	1
<40	2

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In addition, there are some websites such as that calculate the probability of .cardiovascular accidents by receiving data from the user

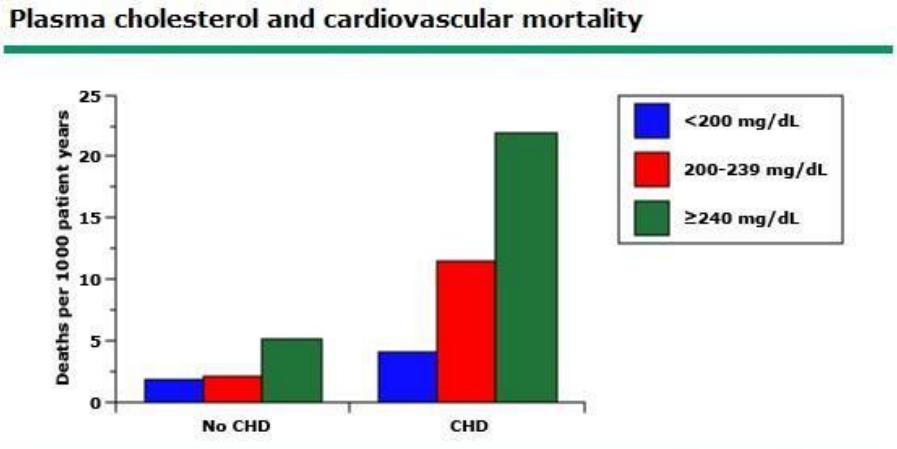
Therapeutic targeting based on01 year risk

As can be seen in the image below, after calculating the08 year risk, treatment measures should be-initiated and treatment goals set. For example, if the Framingham formula's risk is above38) %e xtreme risk), the LDL - C should be rapidly reduced belowm g / dL. 99 .reduced

10-YEAR RISK (%)	Risk Category	Risk factors/10-year risk	Treatment Goals (mg/dL)		
			LDL-C	Non-HDL-C	Apo B
>30	Extreme risk	• Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL • Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH • History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
>20	Very high risk	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% • DM or stage 3 or 4 CKD with 1 or more risk factor(s) • HeFH	<70	<100	<80
10 - 20	High risk	• ≥2 risk factors and 10-year risk 10%-20% • DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
<10	Moderate risk	• ≤2 risk factors and 10-year risk <10%	<100	<130	<90
<10	Low risk	• 0 risk factors	<130	<160	NR

Investigating the relationship between plasma cholesterol levels and mortality from cardiovascular events

As can be seen in the chart below, the presence of coronary artery disease (abbreviated as CHD in the picture) and high cholesterol levels both increase mortality among cardiovascular patients . Gives .



Relation between the baseline plasma cholesterol concentration and ten-year cardiovascular death rate in patients without and with manifestations of coronary heart disease (CHD) in the Lipid Research Council study. Cumulative death rates were increased at higher plasma cholesterol levels in both groups, but the effect was more pronounced in patients with preexisting CHD.

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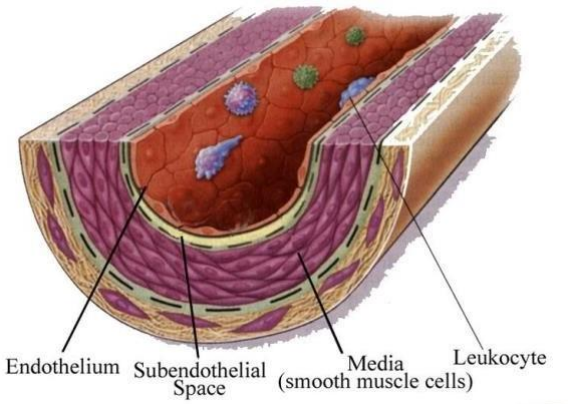
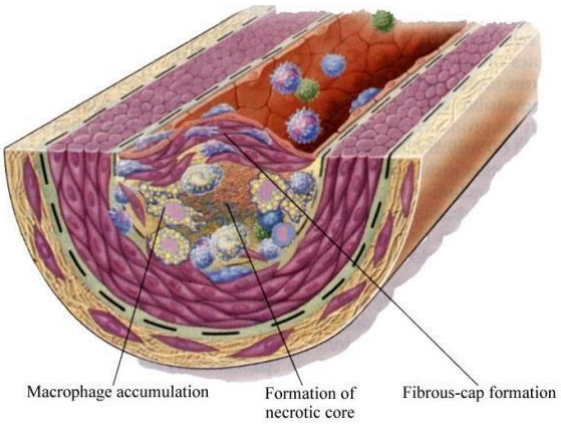
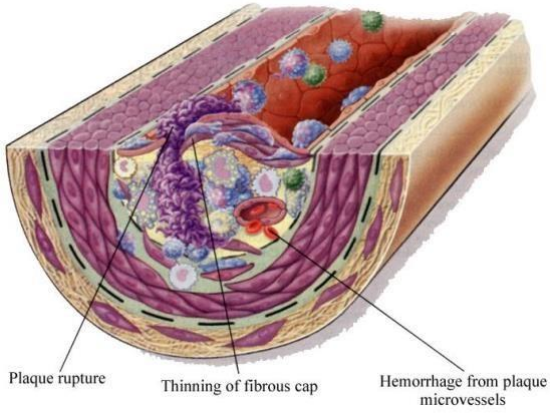
Atherosclerosis







LDL cholesterol is easily oxidized to form oxidized LDL. LDL particles, both oxidized and non-oxidized, travel to the space below the vascular endothelium due to their small size.

Subsequently, macrophages (from circulating monocytes) enter this space to swallow fats. Fatty macrophages, called foam cells play an important role in,) the formation of fatty streaks fatty streaks) and (.eventually atherosclerotic plaques

Then, due to the interaction of intima smooth muscle cells with lipoproteins, the atherosclerotic plaque becomes larger and a fibrous cap forms in the upper part.

In the event of a rupture, platelets accumulate at the site, and subsequently, platelet aggregation initiates a ;coagulation cascade, which can block the entire artery This event appears in the heart in the form of MI and in the brain as CVA.

Antiplatelet drugs

These drugs play a very important role in Avoid MI and CVA, play. These include aspirin ticlopidine, clopidogrel, and glycoprotein IIb/IIIa inhibitors such as obsiximab (abciximab) Noted.

Hyperlipidemia

Hyperlipidemia refers to an increase in the level of lipids and lipoproteins in the blood. Hyperlipidemia is a ,common disorder in the population that increases the risk of cardiovascular disease. In general ."hyperlipidemia can be divided into "primary" "inherited" and "secondary

are divided into9 categories.

Primary hyperlipidemia (classification Frederickson)

Accordingly, hereditary types of hyperlipidemia

- Type I High : chylomicron
- Top LDL : Type IIa

DL : Type IIb •

in triglycerides of IV , I and V. Cholesterol is high in type II
.

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Type III Dysbeta lipoproteinemia :

Top VLDL : Type IV Top VLDL Chylomicrons and: Type V

Secondary hyperlipidemia

,Causes of secondary hyperlipidemia include obesity, hypothyroidism, diabetes mellitus, kidney nephrotic and uremic syndrome, medications, steroids, diuretics, beta-blockers, contraceptives .alcohol. These causes are preventable and reversible

Pharmacotherapy of hyperlipidemia

To reduce the level of triglycerides and cholesterol in the body, various drugs have been prepar .produced that can be classified as follows

- HMG-CoA reductase .inhibitors / statins such as simvastatin, atorvastatin, rosuvastatin, etc
- ... Bile resins binding bile acids such as cholestyramine and
- Nicotinic acid (niacin)
- Fiberic acid derivatives such as gemfibrozil
- Cholesterol uptake inhibitors such as aztimib
- Newer drugs such as PCSK9 inhibitors

.In the following, we will examine each of these drug categories in detail

_ Statins_ _

beneficial effects_ _

- reduce LDL and increase HDL by inhibiting the enzyme HMG-CoA reductase .

,Other effects of statins include: stabilizing and preventing the progression of atherosclerotic plaque reducing inflammation at the plaque site, reducing the risk of thrombosis, reducing fibrinogen, and .reducing plasma viscosity

- Angiogenic effects (statins are stimulation of new blood vessel production) Angiogenesis (and reduction .of mortality rate) independent of cholesterol lowering
- Statins also activate AKt protein kinase which in turn has the opposite effects: increased ,NO production , .improved endothelial cell survival, ischemic tissue revascularization, and inhibition of cellular apoptosis
- In other studies, two other beneficial effects have been reported for statins: reducing dementia in people over98 .and reducing the risk of bone fractures

) names -

- Lovastatin (lovastatin) was .the first statin drug to enter the market
- Three pravastatins (pravastatin ,simvastatin , (simvastatin (and fluvastatin) were then introduced .
- Atorvastatin is one of the newer statins .that is widely used in the world and in Iran

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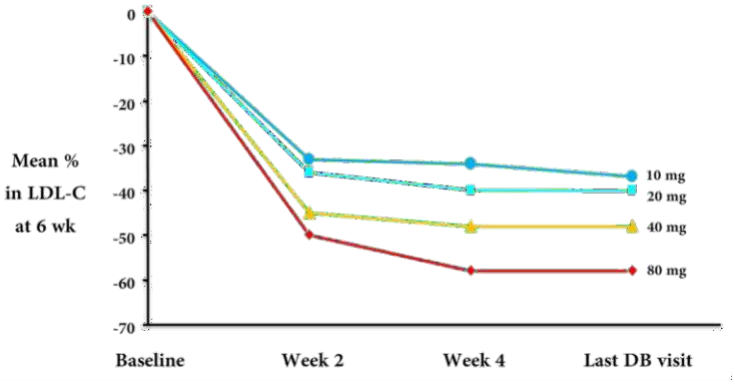
- cerivastatin .was a type of statin that was withdrawn from the market due to post-use mortality (
- rosuvastatin is a newer statin that has been dubbed suprostatin due to its more than (98 reduction in % postoperative LDL .

) comparison -

LDL reduction , daily dose and time, effect on HDL and TG levels ,etc .; For example, atorvastatin , simvastatin, and rosuvastatin, in addition to lowering LDL can increase , HDL .

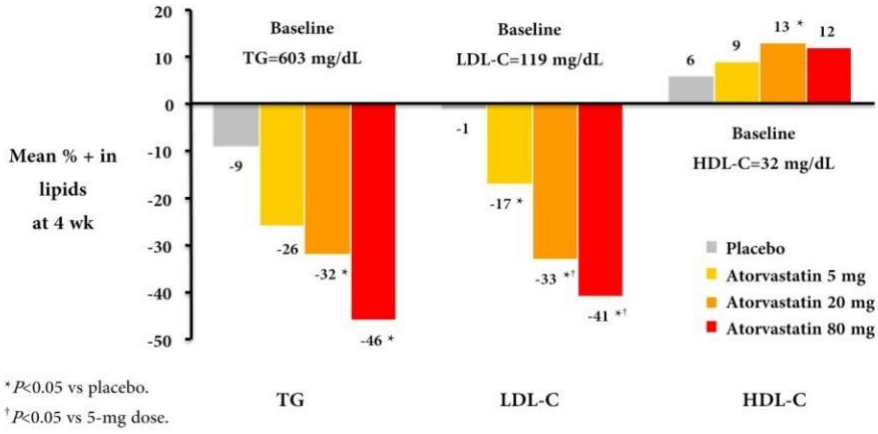
	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Brand	Lipitor	Lescol	Mevacor	Livalo	Pravachol	Crestor	Zocor
LDL ↓	38-54%	17-33%	29-48%	31-41%	19-40%	52-63%	28-48%
Dose	10-80	20-80	20-80	1-4	10-40	10-40	10-80
Time of admin.	Evening	Bedtime	With meals	Anytime	Bedtime	Anytime	Evening
HDL	*					***	**
TG	*					*	
Side effect	Lipophilic	**Less** Lipophilic	Lipophilic	Lipophilic	**Less** Hydrophilic	**Less** Hydrophilic	Lipophilic

diagrams and quantitative calculations



 As can be seen in the diagram below (atorvastatin dose-response curve), statin use in the first two weeks is associated with significant results that depend on the dose received. After5 weeks, the effects of statins peak and then .stabilize

 As can be seen in the diagram below, the reducing effects of atorvastatin on ^{TG} and $LDL-^{C}$ and its enhancing effects on $HDL-^{C}$ .increase with increasing dose



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 As can be seen in the table below, the effect of different types of statins on $LDL-^{C}$ depletion is not the ,same. For example ^{mg} 08 atorvastatin and ^{mg} Both fluvastatin reduce blood $LDL-^{C\ by}$ 30 to39 . %

 It can also be deduced from the table that atorvastatin istwice as potent as simvastatin. In the early years of the drug, its potency was estimated to befive times that of atorvastatin, but today it is generally twice as potent .

LDL-C reduction	20-25 %	26-30 %	31-35 %	36-40 %	41-50 %	51-55 %
fluvastatin	20 mg	40 mg	80 mg			
lovastatin	10 mg	20 mg	40 mg	80 mg		
simvastatin		10 mg	20 mg	40 mg	80 mg	
atorvastatin			10 mg	20 mg	40 mg	80 mg

Rosuvastatin

5mg Ros =10? or 20? mg Ator
10 mg =20? or 40? mg Ator

(pharmacokinetics) Pharmacokinetics

- .These drugs are taken orally and are well tolerated
- Statins are metabolized by the liver to cytochrome^{P450} which is why metabolism-inhibiting drugs can , increase the concentration of these drugs in the blood and, conversely, stimulants that reduce the .concentration of these drugs
- These drugs cross the^{BBB} and placenta. Due to the passage of the placenta during pregnancy, they are in the class of$^{X\ drugs}$ .and are prohibited

(side effects) side effects

;In general, statins are well tolerated by the body and have only a slight gastrointestinal side effect However, there aretwo possible :side effects of statin drugs

- Hepatotoxicity israre .
- Myopathy : Statin-induced myopathy is dose-dependent2 forms of^{myositis} and in severe cases rhabdomyolysis occurs .These disorders are described in detail below .
    - ✓ Cerivastatin ^{was}banned ! due to rhabdomyolysis
    - ✓ It is reiterated that statins are generally not allowed during pregnancy or .breastfeeding

Myopathy caused by statins

- Many patients taking statins experience pain in the muscles and joints. There may be no change in creatine kinase levels in these patients; However, if its level should increase significantly (more than08 times the normal range), statin should be discontinued. In acute conditions, the main concern is .rhabdomyolysis
- People with these characteristics are more likely to develop statin-induced myopathy: the elderly especially those over the age of)08 women, lean people, people with ,($^{multisystem\ diseases}$ patients with , Chronic renal failure due to diabetes, use of metabolic inhibitors, people with vitamin$^{D\ deficiency}$ people , .with hypothyroidism
- Due to the increased incidence of myopathy in patients who continue to use statins at the time of hospitalization and before surgery, it is recommended that statin be discontinued at the time of) hospitalization for surgeryperioperative periods . (

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Hepatotoxicity due to statins

 About8 .9 to2) of patients taking statins have an increase in transaminases %ALT and AST If .(this increase is more than3 ,times, discontinuation of the drug is recommended. If you stop taking statins .the blood concentration of transaminases decreases

 Rarely, liver failure may be due to elevated transaminases. Despite the low probability of this happening, it should be considered. It should also be noted that statins are generally dose-dependent and .are of greater concern at higher doses

drug interactions_ _

:Concomitant use of statins with these drugs can cause side effects

- Fibrates (especially gemfibrozil) Nicotinic acid - Cyclosporine -
- Azole antifungals Macrolide antibiotics - Protease inhibitors in the treatment of -HIV
-) Nefazodone) Antidepressant) Amiodarone) Antiarrhythmic Verapamil -

contraindications _ _ _

,Definitive contraindications include: active liver disease or cholestasis, pregnancy and lactation persistently high levels of transaminases

,Caution is advised in patients with a history of the following: Liver disease, history of alcohol abuse renal failure

 .Statins are not recommended for use in children

Bileacid-binding resins (bile acid-binding resins)

The therapeutic effect of these drugs is to reduce LDL levels .(they have no effect on triglycerides)3 :examples of drugs in this group are

-) Cholestyraminec holestyramine) which is available in Iran in the form of 5 gram powder packages and is .consumed after hydration by water or juice
-) Clestipolc olestipol) is available in granular or tablet form, which should be taken with water or juice in .any case
-) colesevelam (

The mechanism of action

As shown in the figure below, the liver produces bile salts, transports them to the bile, and then transports ,them to the intestine through the bile duct, where they help digest and absorb fats better. In the ileum .most of these bile salts are reabsorbed

The function of resins that bind to bile salts is to bind to bile salts in the intestines and excrete them through the feces, which is why the body is forced to make bile salts continuously in the liver. When ,cholesterol levels fall due to high production of bile salts in the liver LDL receptors on the liver surface increase, thus increasing LDL uptake .by the liver

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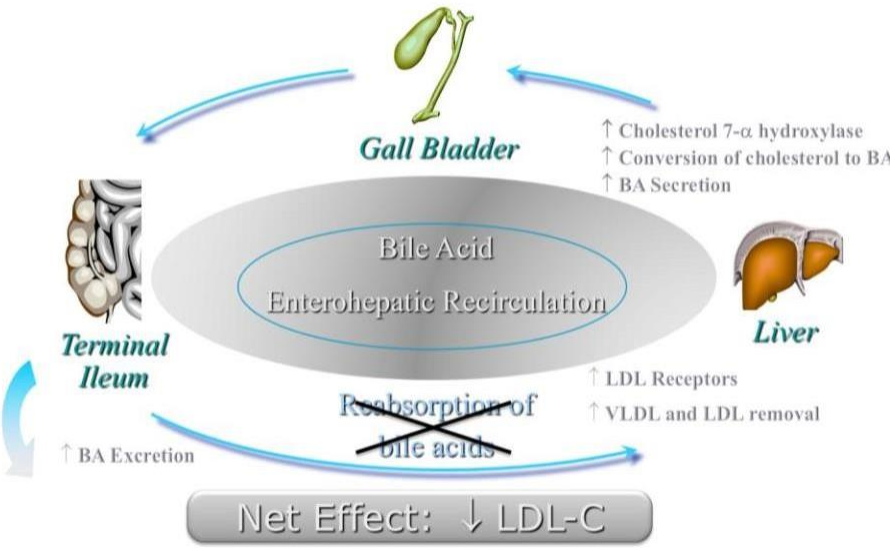


Side effects and drug interactions

- Skin effects (dry skin and itching)
- Gastrointestinal effects (constipation and bloating)

✓ .Calcolam is claimed to have fewer gastrointestinal effects

- Resins are able to bind and repel many drugs; Therefore, it is recommended to use other drugs either0 hours before using the resin or5 .hours after taking it

✓ .Again, calculolam is claimed to be less absorbent and superior to other resins

prohibited usage

□ .Resins are not definitely used

□ Relative uses include severe diverticulosis and symptomatic hemorrhoids)) .

□ It is recommended that resins be used in patients with chronic constipation or in patients who may .have constipation (such as hemorrhoids)

) Nicotinic acid / Niacin (Nicotinic acid / niacin

The therapeutic effect and the most important advantage of this drug in increasing HDL levels is more than .any other drug. However, this drug is generally less used due to its many side effects

side effects

- .Skin effects (redness and itching), possibly due to the production and release of prostaglandins

✓ It has been suggested that if a drug such as ibuprofen is taken before niacin, it .can control this complication

- Digestive problems (nausea, vomiting and diarrhea Hyperglycemia (disruption of glucose ((tolerance test
- Liver toxicity Increased blood uric acid

How to consume

,It is recommended that the drug be started at lower doses (for example088 mg) to increase the patient's tolerance and then increase the dose based on the patient's tolerance to the drug, usually0.9 g being the .minimum effective dose of the drug

Fibrates

In Iran, the drugs gemfibrozil (gemfibrozil) and fenofi brate are used. Fibrates stimulate the transcription of a number of nuclear agents called PPAR - alpha which regulate genes that control glucose metabolism. And , lipids, inflammation, and endothelial dysfunction play an important role, so fibrates are used to treat hyperlipidemia, and fibrates have a major effect in lowering triglycerides; these drugs have less effect on LDL levels (unlike statins).

- It lowers VLDL and slightly increases HDL But it has little effect on ;LDL .
- Gemfibrozil in the form of capsules098 and388 :mg) Maximum dose mg 0288 produced in Iran. Due to) the fact that this drug is a triglyceride lowering agent, it is recommended that the patient take it half an .hour before a meal
- .The most important complication of fibrates is the formation of gallstones, especially in obese women In addition, myopathy and hepatotoxicity are their possible complications. These drugs should not be .prescribed to pregnant women and children

Fenofibrate

- This drug is more suitable than gemfibrozil for concomitant use with statins, because gemfibrozil reduces the hepatic uptake of statins and competes with them to bind to the metabolizing enzyme statins (a type of glucuronosyl transferase); therefore, levels of both gemfibrin and Herman .consumption may increase

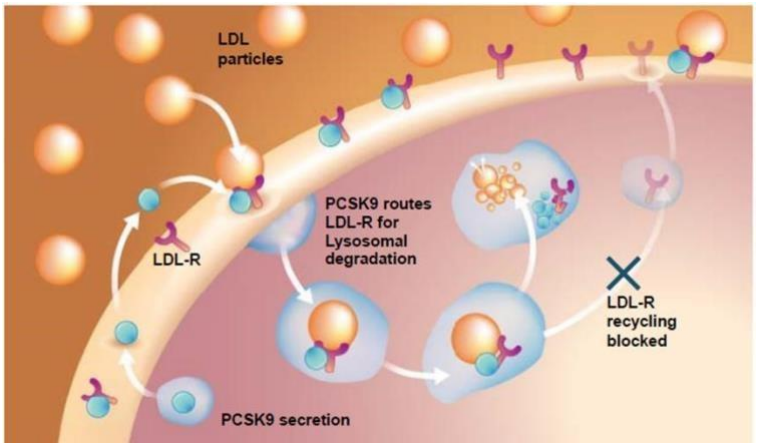
) Ezetimibe (

- This drug inhibits the gastrointestinal absorption of cholesterol and can maximize its effect with mg 08 (.with or without food (leave

- / Combination of this drug with statins (concomitant administration or combination pills such as aztimib simvastatin (further reduces LDL This synergistic effect can be explained as follows: if the production . of cholesterol in the liver is reduced) effect of statins (gastrointestinal absorption of this substance as .Compensation increases, in contrast, if the gastrointestinal absorption of cholesterol decreases
- Allergic reactions to this drug are rare, but its concomitant use with statins is not recommended during .pregnancy

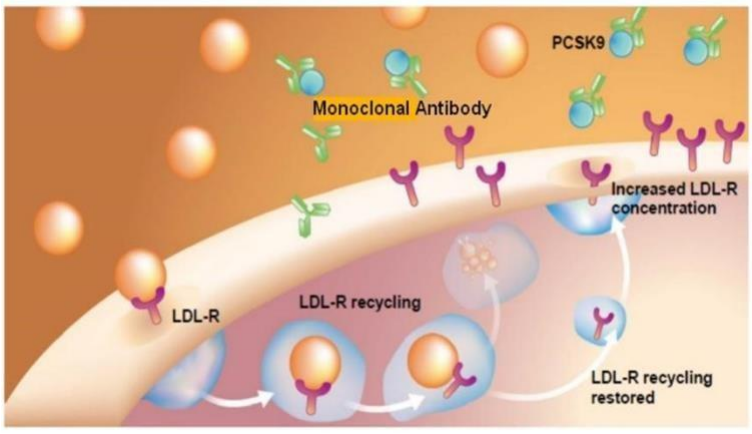
PCSK9 Inhibitors

These injectable drugs have recently found a place in the treatment of hyperlipidemia; However, they are .expensive and are used only in special circumstances



PCSK9 is made by liver cells [as well as intestinal, kidney and CNS cells] and released into the bloodstream. This substance is located next to LDL - R (LDL) receptors In the . presence of LDL all ,3 components are ,ingested into the cell. Inside the cell LDL receptors are destroyed by PCSK9 and naturally .will not be able to return to the cell surface If PCSK9 can be inactivated, the LDL receptor returns to the cell surface and removes more LDL from the blood and into the liver, which is the basis of PCSK9 inhibitors .

Monoclonal antibodies



- use of monoclonal antibodies against PCSK9 causes the LDL receptor to return to the cell surface and remove more LDLs from the .blood
- Another important drug of this kind is evolocumab under the brand name Rapata Repatha is used as an injection and is also available in Iran. This drug can be added to statins to increase their effect in lowering cholesterol and LDL .

3 fatty acids

- Omega3 .has two sources: plant and animal

- 3 ,is found mainly in walnuts , flax seeds and .echium Omega - 3 fatty acids found in plant sources are alpha-linolenicacid (ALA) .They are affordable and are widely used today .
- -3 fatty acids are found in marine oils especially fish, as well as in seaweed and , phytoplankton .

- Omega3 is mainly a triglyceride reducer and has little effect on LDL reduction The mechanisms of action . of this substance in reducing TG :are

- Decreased hepatic lipogenesis
- Increased beta-oxidation of fatty acids
- Inhibition of key enzymes in hepatic triglyceride synthesis
- Increased expression of lipoproteinlipase enzyme

3 fatty acids are also believed to have anti-arrhythmic, anticoagulant, anti-atherosclerotic and anti-inflammatory effects. In addition, omega-3s are effectivein improving endothelial function and lowering blood pressure, all of which can be used to justify beneficial effects. Cardiovascular know it. Two of these :effects are

- Decreased blood pressure (systolic and diastolic) in patients with hypertension and normal people
- Improvement of varicose veins due to increased circulation and reduced fibrin degradation due to EPA and DHA

) Based on these effects, the American Heart Association AHA) defines daily - omega3 intake for patients :with hypertriglyceridemia as follows

- Borderline subjects with serum TG concentrations between mg / dL 055 -098 Need for daily consumption8 They have .9 to0 -grams of omega3 .

- Patients with serum $^{\text{TG levels}}$ between $^{\text{mg / dL}}$ 558 -288 should consume0 to2 - grams of omega3 daily .
- Patients with serum $^{\text{TG concentrations}}$ greater than $^{\text{mg / dL}}$ 988 should consume between 2 and5 -grams of omega3 . in addition to prescription drugs