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Hypercholesterolemia — Statin Therapy — Indications, Side Effects, Common Mistakes in Handling, Last Evidence and Recommendations in Current Clinical Practice

Lucía Cid-Conde and José López-Castro

Additional information is available at the end of the chapter

1. Introduction

1.1. Pharmacology of statin

It is known as statins a group of drugs used to lower cholesterol in patients suffering from hypercholesterolemia and who have therefore increased risk of developing atherosclerosis and have episodes cardiovascular disease. From the pharmacological point of view, fall within the HMG-CoA reductase. Enzyme inhibition is precisely this which justifies the reduction of certain fractions of cholesterol in the body and explains its importance: their positive intervention on cardiovascular risk factors, leading to numerous cardiovascular diseases, which are the leading cause of death in the developed world [1,2]. Despite its short history (less than forty years) are many studies that have been done on statins and hundreds of thousands of patients who have taken these drugs. This has given rise to an extensive knowledge of the characteristics of these drugs has led to the synthesis of new substances that improve the properties of the above statins; in this line part of pharmaceutical research is still moving. However, it has also given rise to broadly meet the real toxicological profile for each substance. The phase IV studies have revealed the risks of using these substances for long periods or in certain basal conditions, which has led, among other things, the withdrawal of any member of the family due to their increased incidence of severe adverse reactions. Because of the variability in origin, the pharmacokinetics of statins differ greatly, however, its pharmacodynamic similarities allowed their joint study group them because, in terms of mechanism of action and effects of statins, and especially, regarding the clinical consequences of its use, there

is an important congruence group, which has been widely studied (Table 1). All developed statins are used orally and absorbed by this route on a variable range from 30% of lovastatin to 35% of pravastatin, decreasing its absorption in the presence of food in the stomach. However, the changes in peak concentrations or the respective curves of assimilation have no impact on the final results in the modification of cholesterol levels, so it is generally advisable to take them at any time of day and in most cases with or without food. Also, there appears to be accumulation due to multiple doses, which is general consensus decision single dose. The recommendations do not drink grapefruit juice while being treated with statins is due to interference with the metabolism, not altered absorption. Generally, the bioavailability of the statins is low, ranging from 5% of lovastatin and 17% of pravastatin. Binding to plasma proteins is variable, but in general very high lines. Except 50% of pravastatin, all have a 95% binding to proteins. The tissue distribution is broad, crossing the blood-brain and placental barriers, even going to milk in lactating women. Liver specificity of these drugs is determined by its degree of lipophilicity and by the presence of some organic anion transporter proteins that allow more hydrophilic statins such as pravastatin and rosuvastatin, entering the hepatocyte [3]. Moreover, some statins may inhibit P-glycoprotein (multidrug resistance protein), a carrier protein of many drugs in the cell, which could predispose to drug interactions. [4]

PHARMACOLOGICAL CHARACTERISTICS OF STATIN						
	Sinvastatin	Pravastatin	Lovastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Pitavastatin
Prodrugs	YES	NO	YES	NO	NO	NO	NO
Food and absorption	No influence	↓	↑	↓	↓	No influence	
Bioavailability	≤5%	17%	≤5%	24%	14%	20%	≥30%
Binding to plasma proteins	94%	50%	>95%	98%	98%	88%	-
Crosses blood-brain barrier	YES	NO	YES	NO	NO	NO	YES
Metabolism	CYP3A4	sulphation	CYP3A4	CYP2C9	CYP3A4	CYP2C9	CYP2C9 CYP2C8
Biliary excretion	60%	70%	83%	95%	-	90%	-
Urinary excretion	13%	20%	10%	5%	<2%	30%	3%
Elimination half-life	2-3h	0.8h	1-4h	2.5h	20h	20h	-

Table 1. Pharmacological characteristics of statin

The metabolism of statins is liver, undergoing first pass metabolism. In most, there are differences in the metabolism regarding sex and age, but not enough to change the doses in the absence of other pathologies. It seems clear that are substrates of CYP450: lovastatin, simvastatin and atorvastatin are metabolized exclusively by CYP3A4, and fluvastatin does exclusively by 2C9. For rosuvastatin, only 10% use the CYP2C9 and 2C19. Pitavastatin has a

low affinity for CYP2C9, so not a major metabolic pathway. Pravastatin is not metabolised by the cytochrome, but does so by enzymes present in the cytoplasm of hepatocytes. The metabolites may be hydroxylated derivatives, omega or beta-oxidized methylated glucuronide. The pharmacological activity of the same is very variable. Thus, the range is wide, from lovastatin, simvastatin, which are really a pharmacologically inactive lactones and performing their pharmacological activity through its metabolites, to fluvastatin, which has virtually inactive metabolites. For the most part, excretion in feces is due to its poor absorption. According to each type of statins, renal excretion ranges from 2% to 20%.

Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a key metabolite in the biosynthesis of cholesterol. Blocking occurs due to the high structural resemblance with these drugs exhibit HMG-CoA. The affinity of the enzyme by statins is 1.000 to 10.000 times that of the natural substrate (Figure 1).
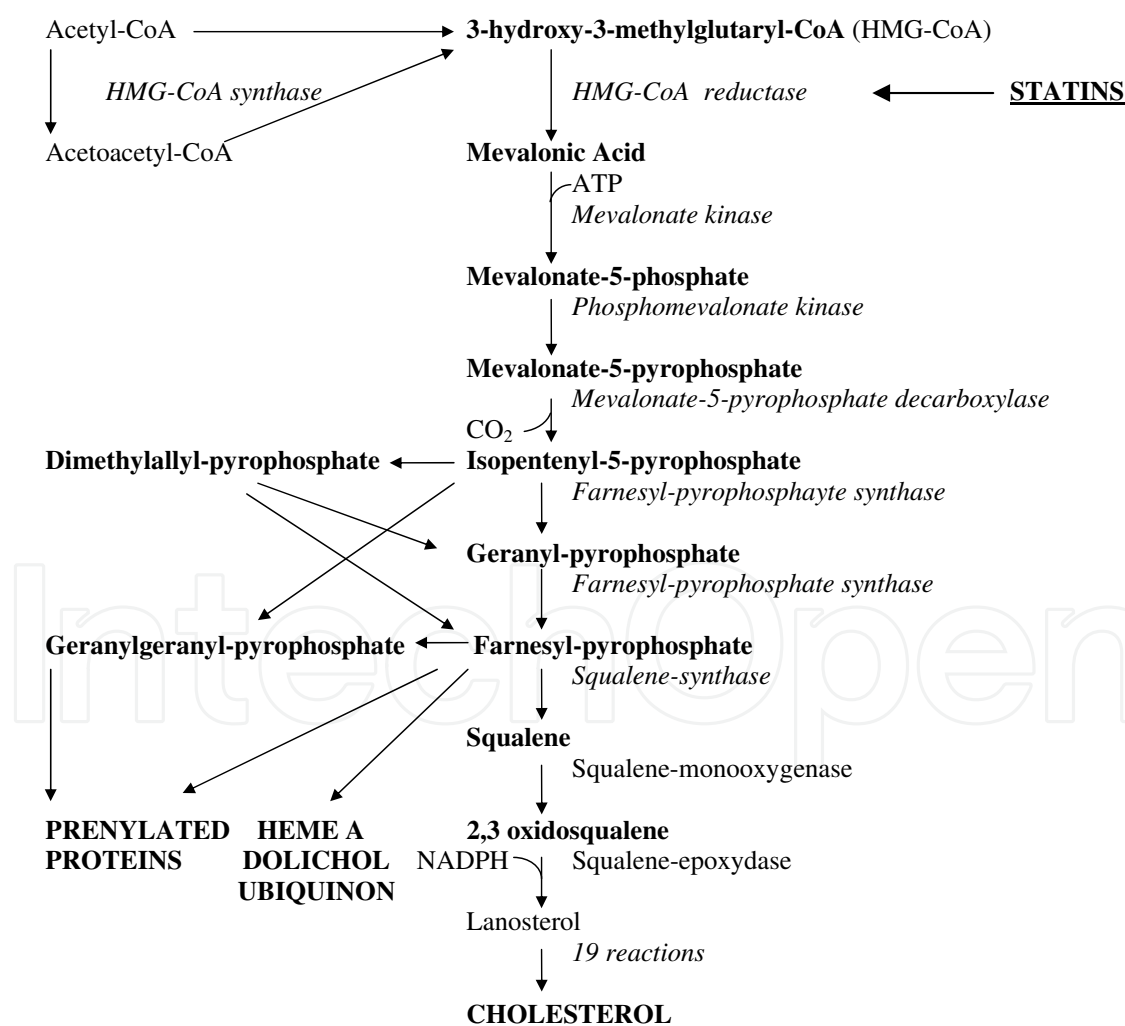

Figure 1. Biosynthesis of cholesterol

The blockade of hepatic cholesterol synthesis causes an activation of the regulatory proteins SREBP (sterol regulatory elements-binding proteins), which activate transcription of protein and thus result in higher expression of the LDL receptor gene and increased the number of functional receptors on hepatocytes [5]. Moreover, it has been shown that statins also produced inhibition associated antigen-1 with the function of lymphocytes (LFA-1: lymphocyte function-associated antigen-1) [6]. The LFA-1 is a glycoprotein integrin family expressed on the surface of leukocytes. When the LFA-1 is activated by certain receptors, binds to the intracellular molecule-1 adhesion (ICAM-1 or CD-54) and stimulates the extravasation of leukocytes and activation of T lymphocytes. This means that the LFA-1 is a proinflammatory agent and its inhibition is beneficial in conditions such as rheumatoid arthritis and rejection of homograft. It was shown that statins and particularly, lovastatin, bind to a site of LFA-1 domain, lovastatin currently designated site. This is the molecular mechanism by which lovastatin, simvastatin and other statin lesser extent inhibit the LFA-1 [7]. This would be one of the anti-inflammatory mechanisms and hence possessing antiatherogenic statins.

2. Effects of statins

The consequences of the inhibition of HMG-CoA may be grouped into two groups:

a. **Derivatives of interaction on cholesterol metabolism**: Lower levels of total cholesterol and LDL, substances closely related to atherosclerosis and increased cardiovascular risk. Density decreases LDL particles, increasing the size of these, leading to decreased atherogenesis [8]. Apolipoprotein B also falls substantially during treatment with statins. In addition, some statins modestly increase cHDL and reduces plasma triglycerides. As a result of these changes, the ratio of total cholesterol to HDL cholesterol and the ratio of LDL and HDL cholesterol are reduced. We have considered the combination of fibrate and enhancer preventing cardiac of statins, especially having no competitive metabolism pathways.

b. **Pleiotropic effects:** In addition to its effects on the lipid profile, statins have other beneficial cardiovascular effects, especially on the arterial wall, known as pleiotropic effects which explain the additional benefit not attributable to the reduction in cLDL observed in many studies intervention [9].

By inhibiting HMG-CoA reductase inhibitors, statins interfere with the formation of isoprenoids from mevalonate. [10] Isoprenoids are molecules such as farnesyl pyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), derived from the metabolism of mevalonate, which serve as lipid-tags for the posttranslational modification of a variety of proteins, including the gamma subunit of G proteins and small GTP unidoras proteins. As a result, the prenylation of the G proteins (Rho, Rac, Ras and Rab Rac1) is reduced. Prenylation of these molecules is necessary for anchoring to the cell membrane and thus to exercise their mechanism of action related to migration, differentiation and cell proliferation. Generally, stimulate and inhibit proinflammatory pathways useful mechanisms for endothelial homeostasis. Through these potential effects on cellular proteins, statins may have a number of antiather-

osclerotic and antithrombotic properties, such as inhibiting the growth of smooth muscle cells, cell adhesion, platelet activation and secretion of C-reactive protein among other. The mevalonic acid, may also act directly by inhibiting the synthesis of nitric oxide (NO) in a process dependent transferase inhibiting genilgeranil. NO is an essential molecule for proper function and vasodilatation of endothelium. To this should be added the effects resulting from inhibition of LFA-1, which in turn significantly impacting on endothelial function in blood vessels. These pleiotropic effects are constant source of research, since they can extend the usage profile of statins. Moreover, these drugs maintain and improve endothelial function to increase the bioavailability of NO, which is synthesized by the enzyme NO synthase (eNOS). NO is the principal regulator of the homeostasis of the arteries and endothelium-dependent vasodilation. The functions are, among others, inhibiting proinflammatory mechanisms and act as an antioxidant on lipoproteins [12].

Statins preserve and increase the bioavailability of NO in several ways:

1. Inhibition of Rho protein increases the expression of the enzyme nitric oxide synthase.

2. Increasing the half-life of the messenger RNA of the enzyme nitric oxide synthase.

3. Reduce excess caveolin molecule that acts as an inhibitor of nitric oxide synthase enzyme.

4. Inhibit the production of superoxide.

5. To protect the NO statins decrease platelet aggregation and reducing thromboxane A2 by platelets and thus limit the formation of unstable plaque.

6. Increasing the expression of tissue plasminogen activator and inhibit the expression of endothelin-1, a potent vasoconstrictor with mitogenic action [12].

The hypolipidemic action itself inherently reduces oxidative stress. However, of statins have their own antioxidant mechanisms that inhibit the production of superoxide anion radical. Superoxide is synthesized by NADPH oxidase, an enzyme which can be activated by the action of membrane receptor of angiotensin II, type I (R-1) receptors. Statins block the R-AT1 and also inhibit the phosphorylation of the NADPH oxidase, inactivating it [13].

Statins also block RhoA, one of the mediators of smooth muscle proliferation. The smooth muscle proliferation is a central phenomenon in the pathogenesis of vascular lesions, including post-angioplasty restenosis, transplant atherosclerosis and occlusion of the coronary vein grafts [14].

Atherosclerosis is a strong inflammatory component characterized by the presence of monocytes, macrophages and T cells in the plate. This process is induced by proinflammatory cytokines, free radicals and NO deficiency. Statins increase the bioavailability of NO and inhibit several proinflammatory cytokines [1].

A marker of inflammation and predictor of coronary heart disease risk is C-reactive protein (PCR). It is considered that PCR is also proinflammatory as joining the cLDL of the atheromatous, activates complement plate and induces the expression of inhibitor-1, plasminogen activator (PAI-1), reduces the expression of eNOS and increases the expression of adhesion

molecules [15]. Therefore, it is valid to assume that the decrease in plasma CRP levels might be beneficial. Large studies with statins, as the AFCAPS/TexCAPS showed reduced blood PCR. For its anti-inflammatory action, statins increase the stability of the atheromatous plaque, and much of the reduction in coronary events attributable to the mechanism. Preclinical studies demonstrated that statins reduce the accumulation of macrophages in the atheromatous plaque and inhibit metalloproteinase production by activated macrophages. Metalloproteinases are capable of degrading proteins support and are therefore partly responsible for the accident plaque with thrombus formation [16].

Clinically the effects of statins lead to a reduction in cardiovascular risk, through the following mechanisms:

1.   Directly decreasing cholesterol levels.

2.   Improving endothelial function and inflammatory response.

3.   Stabilizing atherosclerotic plaque.

4.   Preventing thrombus formation.

Then offer recommendations for clinical practice for the treatment of hypercholesterolemia in adults and reduce the risk of atherosclerotic cardiovascular disease, which includes coronary heart disease, cerebrovascular disease, peripheral artery disease and other atherosclerotic probable origin.

3. Indications of statin in clinical practice

Statins are indicated as an adjunct to diet to reduce elevated total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides; and to increase HDL cholesterol in patients with:

1.   Primary hypercholesterolaemia.

2.   Mixed dyslipidemia.

3.   Homozygous familial hypercholesterolemia.

Also present clear indication in cardiovascular prevention [17]:

Primary prevention of coronary events: in hypercholesterolemic patients without clinical evidence of coronary heart disease.

1.   Reduce the risk of myocardial infarction.

2.   Reduce the risk of myocardial revascularization procedures.

3.   Reduce the risk of cardiovascular mortality with no increase in death from non-cardiovascular causes.

Secondary prevention of cardiovascular events: in patients with clinical evidence of cardiovascular disease.

1. Reduce the risk of total mortality by reducing coronary death.

2. Reduce the risk of myocardial infarction.

3. Reduce the risk of myocardial revascularization procedures.

4. Reduce the risk of stroke and transient ischemic attacks (TIA).

5. Slow the progression of coronary atherosclerosis.

The latest evidence recommends an individualized approach (tailored treatment approach) identified four risk groups associated with therapeutic strategy (Figure 2). Groups that benefit from the use of statin therapy in moderate intensity: LDL reduction of 30-49% or high intensity, LDL reduction of >49% both demonstrate reduction cardiovascular risk (RCV) [17].

1. *Group 1*: Patients with clinical cardiovascular disease (secondary prevention): high intensity treatment with statins (<75 years) or moderate intensity (>75 years).

2. *Group 2:* Patients with LDL > 190 mg/dL: high intensity treatment.

3. *Group 3:* Diabetic patients between 40-75 years, LDL 70-189 mg/dL without cardiovascular disease: treatment of at least moderate intensity and high intensity probably if cardiovascular estimated 10-year risk ≥7.5%.

4. *Group 4:* Patients without diabetes and without clinical cardiovascular disease, with LDL between 70-189 mg / dl but with estimated 10-year risk> 7.5%: treatment of moderate to high intensity.

3.1. Types of statin therapy

The main therapeutic strategies are (Table 2),

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily doses lowers LDL on average >50%	Daily dose lowers LDL on average 30-50%	Daily dose lowers LDL on average 30%
Atorvastatin 40-80 mg *Rosuvastatin 20 -40 mg*	*Atorvastatin 10-20 mg* *Rosuvastatin 5-10 mg* *Simvastatin 20-40 mg* *Pravastatin 40-80 mg* *Lovastatin 40 mg* *Fluvastatin XL 80 mg* *Fluvastatin 40 mg BID* *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* *Pravastatin 10-20 mg* *Lovastatin 20 mg* *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

Table 2. Low, moderate and high-intensity statin therapy categories in treating patients with varying risks.

Statin therapy of high, moderate and low intensity according to studies is classified:

1. *Statin therapy in high-intensity studies*: Atorvastatin 40-80 mg or rosuvastatin 20-40 mg.

2. *Statin therapy in moderate intensity*: Atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvas-tatin 20-40 mg (higher doses are not recommended by the incidence of adverse effects), pravastatin 40-80 mg, lovastatin 40mg, fluvastatin XL 80 mg, *Fluvastatin 40 mg bid and pitavastatin 2 to 4 mg.*

3. *Statin therapy in low-intensity*: Simvastatin 10 mg, * Pravastatin 10 mg-20 mg, lovastatin 20 mg, fluvastatin 20-40 mg and *Pitavastatin 1 mg.

* FDA approved but not tested in randomized controlled trials.

3.2. Specific risks

1. Primary prevention with LDL ≥ 160 mg/dL.

2. Genetic testing hyperlipidemias.

3. Family history of premature cardiovascular disease with onset <55years in a male first-degree relative or <65 years female.

4. C-reactive protein levels of high sensitivity (hs-CPR) >2 mg /L,

5. Coronary artery calcium (CAC) score ≥300 Agatston units or ≥ 75th percentile for age, sex and ethnicity.

6. Ankle-brachial index <0.9.

3.3. Treatment strategies

1. *Treat for goals*: It is the strategy most used in the past 15 years, but with 3 problems: Current randomized clinical trials do not specify what the best goal. The magnitude of the further reduction of the atherosclerotic cardiovascular disease than is obtained with a lower cholesterol goal another is unknown. Does not account the possible adverse effects of polypharmacy, which may be necessary to achieve a specific goal.

2. *"Lower is better"*: This approach does not take into account the possible adverse effects of polypharmacy with an unknown magnitude reduction in atherosclerotic cardiovascular disease.

3. *Dealing with the level of atherosclerotic cardiovascular disease* (currently preferred): Consider both benefits in reducing cardiovascular risk and adverse effects of statin therapy. Hence the 4 groups that benefit, as previously mentioned, with the exception of use in individuals undergoing hemodialysis or heart failure with NYHA functional class III-IV out. This strategy is advocated today.

4. *Risk throughout life*: Are yet tracking data on >15 years, safety, reduction of atherosclerotic cardiovascular disease when statins are used for periods >10 years and treatment in individuals <40 years.
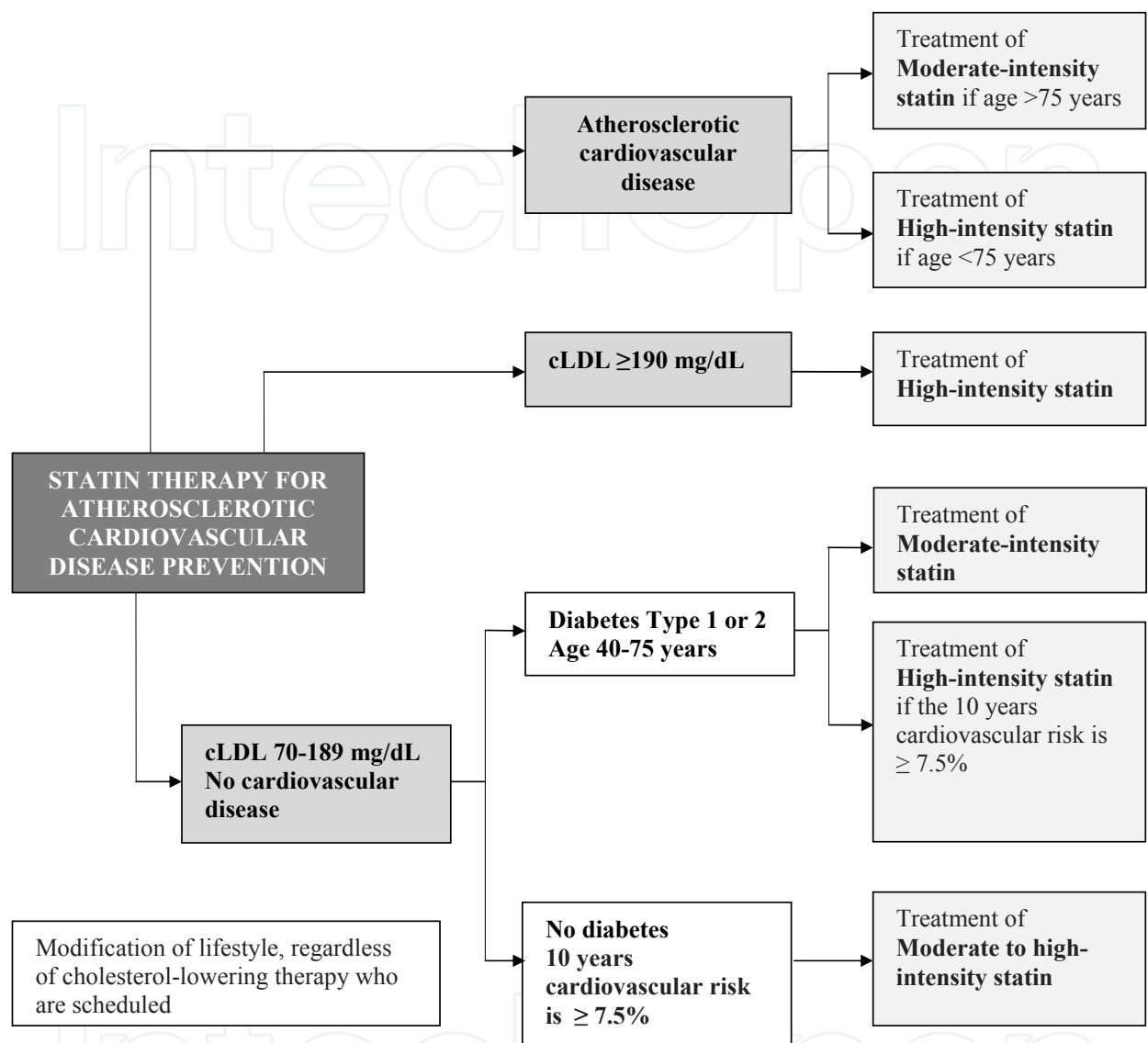
Figure 2. Statin therapy for atherosclerotic cardiovascular disease prevention

4. Side effects of statin and clinical management

4.1. Adverse effects of statins

In general, statins are well tolerated and the dropout rate in clinical trials as a result of any adverse effect is <10%, similar to that of patients taking placebo, and less than 1% are serious side effects (Table 3).

DIFFERENCES IN ADVERSE EFFECTS BETWEEN STATINS				
Adverse effects	Incidence versus placebo	Dose-response relationship	Differences (favor/ against)	Statistically significant overall difference against
Abandonment adverse impact	6%	yes	Simvastatin/atorvastatin Pravastatin/atorvastatin Pravastatin/rosuvastatin	-
Significantly relevant myalgia	2%	-	-	-
Relevant significantly increased transaminases	1%	yes	Simvastatin/atorvastatin Simvastatin/fluvastatin Pravastatin/atorvastatin Pravastatin/fluvastatin Rosuvastatin/atorvastatin Rosuvastatin/fluvastatin	Atorvastatin Fluvastatin
Relevant significantly increased CPK	0.6%	yes	Fluvastatin/others	Pitavastatin
Diabetes	9%	-	-	-

Table 3. Differences in adverse effects between statins

1. *Myotoxicity*: The most serious adverse effect associated with the muscular condition, which can range from myalgia (proximal muscle pain and/or weakness with a value of creatine kinase (CK) normal or slightly increased) to more severe forms, such as myopathy (pain and/or weakness over the presence of very high CK, usually >10 times normal) or rhabdomyolysis (serious muscle condition, with muscle weakness and pain, the presence of very high CK, myoglobinuria and renal failure) [18]. In general, the most common disorder is myalgia without elevated CK. Special mention should be cerivastatin withdrawal from the market, since it is the statin showed higher number of severe myopathy. The rate of fatal rhabdomyolysis associated with cerivastatin use at least 15 times higher than that produced by other statins, and was associated with the use of high doses of the drug (0.8 mg/day) or when coadministered with gemfibrozil [19].

The drugs and clinical conditions that increase the risk of myopathy are,

a. Chronic diseases (renal failure and diabetes).

b. Multiple drugs.

c. Surgical interventions.

d. High doses of statins.

    e. Statins in combination with:

- Fibrates.
- Nicotinic acid (not clearly stated)
- Cyclosporine.
- Antifungal azoles.
- Macrolide antibiotics
- Inhibitors of HIV protease.
- Verapamil.
- Amiodarone.
- Abuse of alcohol.
- Grapefruit juice (> 1/4 liter daily)

2. Hepatotoxicity: active hepatopathy or unexplained persistent elevations of serum transaminases (hypertransaminasemia). An elevation of three times the upper limit of normal transaminases in patients treated with statins occurs between 0.5% to 2% of cases and is directly related to the dose [20]. Hypertransaminasemia is reversible with drug discontinuation and progression to liver failure rarely occurs.

3. Hypersensitivity to any statin or any of the excipients of commercial presentations.

4. Dyspepsia.

5. Less common: sleep disturbances and memory, depression,....

4.2. Absolute contraindications to statins

1. Pregnancy and lactation.

2. Concomitant administration of potent inhibitors of CYP3A4 (itraconazole, ketoconazole, protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) or CYP2C9 (relative contraindication not dependent on CYP450 statins).

4.3. Relative contraindications to statins (but you can take a special medical supervision is required)

1. Elderly (age >70 years).

2. Renal failure.

3. Uncontrolled hypothyroidism.

4. Personal or family history of hereditary muscular disorders.

5. History of muscular toxicity with a statin or fibrate.

6.   Alcoholism.

7.   Concomitant weak inhibitors of CYP3A4 (Table 4)

OTHER DRUG THAT INTERACT WITH STATIN	
antacids	↓ absorption of statins
anticoagulants	↑ the anticoagulant effectiveness
Ion exchange resins	↓ absorption of statins
colchicine	↑ toxicity of colchicine
glibenclamide	↑ plasma levels of glibenclamide
oral contraceptives	↑ up to 30% in blood hormone levels

Table 4. Other drug that interact with statin

4.4. Recommendations to prevent adverse effects with statin use

Select the dose and type of statin, according to the type of patient cardiovascular risk and potential adverse effects.

Use moderate intensity therapy if the patient has renal or hepatic dysfunction including unexplained persistent transaminase elevations, history of muscular disorders or intolerance to statin use, ALT elevations >3 times the upper limit, concurrent use of medication known interactions with statin, age greater than 75 years, history of hemorrhagic stroke event, asian ancestry. This behavior can substantially reduce adverse events with statin use. The use of simvastatin is not recommended at doses of 80 mg/day because of the risk of toxicity. Liver function tests should be performed before starting statin therapy, with dose changes with the change of drug. During treatment should be monitored signs and symptoms of muscle toxicity.

Whenever a statin prescribing or replaced by another is important to analyze the other co-administered drugs due to the risk of clinically relevant interactions. In the absence of abnormal liver function and potential interactions with coadministered drugs, statins are all interchangeable. In the presence of inducing drugs or inhibitors of CYP3A4, fluvastatin, pravastatin and rosuvastatin are interchangeable. In the presence of inducers or inhibitors of CYP2C9 drugs, statins are all interchangeable, except fluvastatin. In the presence of drugs inducing activad or inhibitors of P-gp, fluvastatin and rosuvastatin are interchangeable. In the presence of inducers or inhibitors of OATP1B1 drugs, is not recommended therapeutic interchange of pravastatin and rosuvastatin. For all other statins, the exchange must be made with caution.

4.5. Analytical monitoring

Monitoring of CK at baseline in patients with or without a history of myopathy, have no solid evidence. It could only be recommended if the patient has muscle symptoms, weakness or fatigue. The only test that is fully justified, prior to initiating statin is the measurement of ALT. The liver function should be measured if the patient is suspected of hepatotoxicity statin use. With the same level of evidence is regular monitoring of blood glucose, the onset of diabetes mellitus associated with treatment [21].

4.6. Attitude pain, muscle stiffness, weakness or muscle fatigue statin taker

Clarify if the symptoms actually developed or intensified therapy. If there is a causal relationship apparent, and muscle symptoms are intolerable, discontinue medication. If rhabdomyolysis is suspected, measure CK-creatinine and urinalysis. If muscular symptoms are mild or moderate statin should be discontinued to reassess symptoms and assess whether the patient has conditions that increase risk of muscle symptoms (hypothyroidism, renal or hepatic dysfunction, polymyalgia rheumatica, steroid myopathy, vitamin D or primary) myopathies. If symptoms are resolved and there are no contraindications, restart the same statin at a lower dose. If symptoms relapse: start another statin at a lower dose and increase slowly. If after 2 months, the symptoms do not improve or CK levels do not decrease, consider alternative etiologies. If muscle symptoms persist after stopping statin or other clinical condition correspond to restart therapy [21].

In summary, the adverse events associated with statin therapy are uncommon. Statins are not associated with cancer risk, but on the contrary there is a greater chance of diabetes. Simvastatin and pravastatin appear to be safer and better tolerated than other statins [22]. It has not been able to show that there are real differences between the effects generic statin drug and reference mark to the modification of the lipid profile, nor in adverse reactions, assessed according to the elevation of transaminases and CPK [23,24].

5. Conclusions

Atherosclerotic cardiovascular disease is one of the most important public health problems of our time, both in Europe and in the rest of the world. Consistency of clinical care, incorporating new evidence and synthesis of recommendations from current practice is common task in various committees for clinical practice worldwide (Europe-ESC, American-AHA / ACC, British-NICE, Australian, Canadian…). This has generated discrepancies with the publication of the latest guidelines of the 2013 AHA/ACC compared to its European namesake 2011 ESC/EAS. The innovation of greatest impact of the latest guidelines, has been the abandonment of the therapeutic strategy based on the target values LDL. The individualized strategy (tailored treatment approach) is recommended identifying four risk groups associated with therapeutic strategy. Are advised to use statins as well as healthy habits and lifestyle changes for all patients. The CK should not be measured routinely in patients on statins and there is no reason to monitor LDL levels.

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