criterios

Criteria for the use of lipid-lowering drugs for the treatment and control of dyslipidemia as a cardiovascular risk factor

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Los autores y revisores del documento han realizado la declaración de intereses aprobada por el Grupo de Recomendaciones en Farmacoterapia de la Comunidad de Madrid. Se ha solicitado la declaración de conflicto de intereses a los autores, revisores y coordinadores del documento.

Acronyms used in the text	
95% CI	95% Confidence Interval
ACS	Acute Coronary Syndrome
AE	Adverse Effects
AMI	Acute Myocardial Infarction
ARR	Absolute Risk Reduction
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CM	Comunidad de Madrid
CPG	Clinical Practice Guidelines
CV	Cardiovascular Disease
CVR	Cardiovascular Risk
CVRF	Cardiovascular Risk Factor
DDD	Defined daily dose
HDL-C	Cholesterol HDL
HF	Heart Failure
LDL-C	Cholesterol LDL
NNH	Number of patients who need to be treated for a certain time with medication to cause an adverse event
NNT	Number of patients who need to be treated for a certain time with medication to obtain a beneficial effect or prevent an event
PAD	Peripheral Artery Disease
RCT	Randomized Clinical Trial
RR	Relative Risk
TOD	Target Organ Damage
Type 1 DM	Type 1 Diabetes Mellitus
Type 2 DM	Type 2 Diabetes Mellitus

summary

Dyslipidemia is a cardiovascular risk factor which, along with others, is involved in the development of an atherosclerotic event. So, it is recommended to look and treat all cardiovascular risk factors in people with dyslipidemia and to educate them properly about the benefits of a balanced diet, daily exercise, controlling hypertension and abandonment of cigarette smoking.

The aim of a lipid-lowering therapy is to reduce the risk of future cardiovascular events, so the decision to start a treatment will depend on the individual estimation of the risk of cardiovascular events in the coming years.

Patients at high or very high cardiovascular risk, in whom risk stratification is not necessary and require active management of cardiovascular risk factors, are:

- Patients with cardiovascular disease (coronary or non-cardioembolic ischemic stroke) have a very high risk of further events.
- Patients with dyslipidemia without prior events that have a high risk of future events: type 1 diabetes patients, type 2 diabetes patients with other greater cardiovascular risk factor or target organ damage, patients with severe hyperlipidemia, intermittent claudication of atherosclerotic origin and CKD patients at stages G3b to G5 (GFR less than 45 ml/min/ 1.73m^2).

The rest of the people should be risk-stratified to determine the purpose and intensity of the treatment based on the individual risk previously estimated.

Primary prevention

Selection of people at risk

Except for the patients at high and very high cardiovascular risk mentioned above, it is necessary to identify, using risk tables, those people with dyslipidemia without prior events that may have an increased risk of a first cardiovascular event in coming years:

- With non-diabetic people under 65 years, it is recommended to calculate the cardiovascular risk with SCORE 2011 chart for low-risk European countries.
- With people between 65 and 74 years and with type 2 diabetic patients without cardiovascular risk factors or target organ damage, it is recommended to stratify the cardiovascular risk with REGICOR chart.
- There is not a risk table to use with people over 80 years. The decision to treat them should always be individualized and will be based on comorbidity, functional status, polymedication, life expectancy and the patients' opinion.

Tables should be used according to the judgment and knowledge of the physician, assessing local conditions. It should be noted that as the entire population with high cardiovascular risk will be treated, many healthy subjects with risk factors that will not develop the disease will also be treated. Thus, lipid-lowering treatment will be given to many people who will not obtain a benefit.

Cholesterol control objective

The primary prevention trials that showed that statins reduced cardiovascular events were performed using fixed statin doses and without establishing LDL objectives. Thus, there is no evidence that the reduced cardiovascular morbidity and mortality achieved in these trials was based on reaching or not reaching LDL cholesterol target levels.

It is not recommended for those people receiving a pharmacological therapy to achieve specific LDL cholesterol values or certain objectives.

Treatment indication

Changes in lifestyle are still the mainstay of treatment for hypercholesterolemia. In people with dyslipidemia without previous events and with low or moderate risk, these changes should be considered before starting drug treatment as hygienic-dietary measures have proved sufficient to reduce the probability of a cardiovascular event. In high-risk patients, in whom the benefits of treatment with diet and exercise are more marked, the lifestyle changes will be associated with the pharmacological treatment.

Any pharmacological treatment must be supported by the demonstration of clear clinical benefits and a clear safety profile:

- In Primary Prevention, statins have been proven to reduce the risk of a first coronary event. They have also been shown to reduce the risk of stroke but in a lesser extent than in coronary events. The results are contradictory in terms of reduction of coronary or total mortality.
- These results come from clinical trials with people at high risk coming from countries with a high incidence of ischemic heart disease and with 2-3 additional cardiovascular risk factors.
- The number of events that are reduced and therefore the absolute benefit depends on the patients' baseline risk.

Considering the above, for the **general population** without a previous event:

- With high **cardiovascular risk** (SCORE > 5% or REGICOR > 10%), it is recommended starting statin therapy when hygienic-dietary measures or the control of other factors do not reduce the risk. Drug therapy is initiated at the dose required to achieve an LDL cholesterol percentage reduction of 30-40% without the need to achieve specific values or certain objectives.
- With moderate **risk,** the decision to start treatment will take into account other factors that may increase the risk and are not included in the valuation tables (very high cholesterol levels, microalbuminuria, family history of premature coronary heart disease and subclinical atherosclerotic disease).

- With **low risk** (SCORE <1% or REGICOR <5%), the overuse of drugs by inappropriate extrapolation of the results of tests conducted with high-risk males may be present; so, in the absence of evidence **the use of lipid-lowering drugs is not recommended**.
- In **older people** without previous events, with high cholesterol and without other cardiovascular risk factors, the initiation of statin therapy is not recommended unless there are other specific indications. However, there is no age limit for treatment already established if the indication was correct, except poor prognosis.

In dyslipidemic patients with **diabetes**:

- In dyslipidemic patients with type 1 diabetes or type 2 diabetes and with other greater cardiovascular risk factor or target organ damage, it is recommended starting treatment at the necessary dose to achieve reductions of 40-50%, which could amount to a decrease in LDL below 100 mg/dl.
- In patients with type 2 diabetes without any other greater cardiovascular risk factor or target organ damage but REGICOR> 10%, statin treatment is recommended at the necessary dose to achieve an LDL cholesterol percentage reduction of 30- 40%.

In patients with **severe hyperlipidaemia**:

- Once the secondary hyperlipidaemia causes have been corrected, family hyperlipidemia has been discarded, and healthy lifestyles have been established, patients with **persistently LDL cholesterol higher than 190 mg / dl** must be treated with statins.
- Patients with **isolated hypertriglyceridemia with levels higher than 500 mg / dl** are candidates for treatment with gemfibrozil once secondary hypertriglyceridemia causes have been discarded.
- In mixed hyperlipidaemia, statin therapy for the control of LDL cholesterol **should** always be prioritized because of its importance for cardiovascular prevention.

Pharmacological treatment indication in patients with dyslipidemia and associated vascular pathology without previous cardiovascular events

These are patients without previous events with a pathology that increases the cardiovascular risk in comparison with the healthy population but they have neither coronary nor cerebrovascular event rates comparable to those found in patients who have had a greater ischemic event.

Statins have shown an unquestionable benefit in coronary prevention in patients with other vascular pathologies, as the diseases we will discuss later. Results found in coronary patients should not be extrapolated due to the different relevance that cholesterol has in the development of events.

Peripheral Artery Disease

- Most of the Clinical Practice Guidelines make a weak recommendation regarding the use of drugs for this disease based on the high risk inherent in this condition. However, until new studies specifically targeting these patients are published, the treatment decision will include an exhaustive tobacco control. The use of statins in patients with symptomatic peripheral artery disease will be considered individually.
- Patients with intermittent claudication of atherothrombotic origin or revascularization are considered directly high-risk patients indicating lipid-lowering therapy with statins. The use of simvastatin 40 mg daily is recommended.
- In patients with moderate cardiovascular risk, measurement of ankle-brachial index is recommended to reassess the risk and consider indication statin therapy.

Heart failure

- Statins have not been shown to reduce cardiovascular morbidity and mortality in patients with heart failure, therefore its use is not recommended unless there is another indication.

Chronic kidney disease (CKD)

- Patients with chronic kidney disease have an increased absolute risk of cardiovascular events, mainly in patients with reduced glomerular filtration rate of 45 ml / min / 1.73 m2 (CKD stages G3b to G5); however, the risk is not comparable to that of patients with coronary event. The risk of cardiovascular events also increases with proteinuria, and does so independently of the decrease in glomerular filtration.
- In dyslipidemic patients without previous cardiovascular events in chronic kidney disease stage G1 to G3a (glomerular filtration greater than 45 ml / min / 1.73 m^2) the use of statins is recommended in patients at high risk following an individualized assessment of CVR, considering that in the moderate CVR patients the presence of microalbuminuria is a modulator of risk.
- In dyslipidemic patients without previous cardiovascular events in chronic kidney disease stage G3b to G5 (lower glomerular filtrate 45 ml / min / 1.73 m^2) lipid lowering therapy would be indicated for primary prevention without first assessing the cardiovascular risk. Simvastatin/ezetimibe at a fixed dose of 20 mg/10 mg is the best available evidence, although statins in monotherapy could be an alternative.
- In patients on dialysis or kidney transplant it is not recommended initiating lipid-lowering therapy. If the patient is already receiving treatment before entering dialysis, the suspension is not advised.

summary

Secondary prevention

All those subjects who have already suffered a cardiovascular event, and thus suffering the disease, are included: however, secondary prevention is not comparable to primary prevention in people at high cardiovascular risk or with associated vascular pathology.

We must assess and strictly control the various cardiovascular risk factors, including cholesterol. These patients are the ones who obtain most benefit from treatment.

Cholesterol control objective

No clinical trials have demonstrated effective LDL cholesterol reductions below specific thresholds. Clinical trials show that intensive treatments with statins (high doses or moderate doses with ezetimibe) at fixed doses without reaching specific LDL levels reduce the risk of new cardiovascular events comparing with treatments at moderate - low doses.

There is an open discussion about what should be the target LDL-C reduction. Some guidelines support specific LDL-C levels while others do not mention a specific value but recommend a reduction of approximately 50% in relation to the baseline.

The treatment with high doses of statins present a higher risk of severe adverse effects and treatment abandonment due to general adverse effects. So, regarding the recommendations in this document, patients at high risk for adverse effects are those whose characteristics were exclusion criteria for clinical trials. These are:

- Patients with multiple or serious comorbidities, including changes in renal, liver, thyroid or immunosuppression functions.
- History of muscle pathology or haemorrhagic stroke.
- History of statin pathology.
- Transaminases increase greater than 3 times the upper limit of normal.
- Use of concomitant medications that affect the metabolism of statins.
- People aged over 75 years.

Indication of pharmacological treatment by type of cardiovascular disease

Stable coronary disease

- The use of atorvastatin 80 mg is recommended in patients with stable coronary disease who do not present characteristics that predispose to adverse effects from statins or risks of interactions
- Statins at moderate doses, alone or in combination with ezetimibe, are recommended for: patients who meet characteristics that predispose to adverse effects from statins, patients who cannot tolerate high doses of statins and for those with whom the use of high doses is considered not appropriate.
- The use of omega 3 supplements or statin with ezetimibe is not recommended in patients with coronary disease because it does not reduce the risk of new cardiovascular events or mortality.

Acute coronary syndrome

- Early initiation of treatment with 80 mg atorvastatin is recommended except in patients with characteristics that predispose to adverse effects from statins or risk of interactions.
- In patients with adverse effects due to high doses of statins, a dose reduction or a moderate dose combined with ezetimibe could be considered. Simvastatin 40 mg and ezetimibe 10 mg combination could has the best evidence.

Non-cardioembolic ischemic stroke

In patients with a history of non-cardioembolic ischemic stroke and LDL cholesterol > 100 mg/dl is recommended to start treatment with atorvastatin 80 mg provided they do not exhibit characteristics that predispose to adverse effects from statins.

Characteristics of the available treatments

Statins

The statins are the treatment of choice in most people with treatment indication.

There are no direct comparisons of different statins at equivalent doses in the reduction of cardiovascular morbidity and mortality. There are no clinical data to suggest the superiority of any statin above the rest in reducing cardiovascular events at equipotent doses.

They are safe and well tolerated drugs. The **adverse reactions** are more likely when they are used at high doses or in combination with other drugs that interfere with their metabolism.

In case of potential **interactions** with other drugs taken by patients, pravastatin or rosuvastatin are recommended as alternatives.

Fibrates

These drugs are not used as first-line treatment except in patients with isolated severe hypertriglyceridemia or in patients who cannot take statins.

Ezetimibe

In monotherapy, unlike statins and fibrates, **has not been shown to reduce cardiovascular morbidity and mortality** and its clinical.

Resins

These are not drugs used in first-line treatment. They have mild but common gastrointestinal side effects that make them difficult to tolerate and may interfere with the absorption of some drugs and raise triglycerides.

summary

Treatment with combinations of lipid lowering drugs

- The combination of a **fibrate with a statin** obtains a more complete control of lipid profile. However, the strictest control of diabetic dyslipidemia combining a fibrate with a statin did not provide greater benefit in reducing cardiovascular morbidity and mortality than simvastatin in monotherapy.

  The combination increases the risk of muscle toxicity. Gemfibrozil should not be combined with statins due to high risk of severe myopathy.
- Clinical trials demonstrated that the **combination of ezetimibe with a statin** benefit the reduction of cardiovascular events in patients with chronic kidney disease stage G3b to G5 and in patients with acute coronary syndrome.
- Clinical trials with supplementation of omega 3 fatty acids in patients with a history of myocardial infarction **have not shown to reduce the risk of mortality and new cardiovascular events**

Recommendations for the use of lipid lowering drugs in Comunidad de Madrid

- Simvastatin 20 mg daily will be used as first choice **for primary prevention in patients without diabetes and type 2 diabetes patients with no other greater CVRF or target organ damage** when their level of CVR is appropriate according to recommended tables

  If reductions do not reached the recommended percentage **once non adherence to drug therapy** and hygienic-dietary measures have been discarded, the dose of simvastatin will be doubled or treatment with atorvastatin 20 mg will be initiated.
- In **type 1 or type 2 diabetic patients with other greater CVRF or target organ damage** simvastatin 40mg or atorvastatin 20 mg is recommended as initial treatment.

  If reductions do not reached the recommended percentage **once non adherence to drug therapy** and hygienic-dietary measures have been discarded, the dose of atorvastatin will be doubled.
- In patients with **severe non-genetic hyperlipidemia** initial treatment with simvastatin 40 mg is recommended.

  If reductions do not reached the recommended percentage **once non adherence to drug therapy** and hygienic-dietary measures have been discarded, treatment with atorvastatin 40 mg will be initiated.
- In patients with **CKD stage G3b to G5** simvastatin / ezetimibe at a fixed dose of 20 mg / 10 mg is recommended and atorvastatin 20 mg as an alternative.
- In patients with **intermittent claudication of atherothrombotic origin** simvastatin 40 mg is recommended as initial treatment.
- Initial treatment with atorvastatin 80 mg is recommended for secondary prevention, coronary or cerebrovascular. However, atorvastatin 40 mg, simvastatin 40 mg or rosuvastatin 20 mg will be the initial treatment for those patients with higher probability of side effects or interaction risks. In this case, the initial treatment will be atorvastatin 40 mg, simvastatin 40 mg or rosuvastatin 20 mg. Alternatively in coronary patients, treatment with statins at moderate doses in combination with ezetimibe will be considered. The combination of simvastatin 40 mg and ezetimibe 10 mg has the best evidence.

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INTRODUCTION AND ANALYSIS OF THE SITUATION IN THE COMUNIDAD DE MADRID

Cardiovascular diseases (CVDs) are the most common causes of death in Spain[1]. In 2012, ischemic heart disease was the leading cause of death among men (19,973 deaths, a rate of 87 per 100,000 inhabitants); while cerebrovascular diseases were the leading cause among women (17,084 deaths, rate 72 per 100,000 inhabitants). However, in both cases there was a decrease from previous years. In the Comunidad de Madrid, ischemic heart disease remains the leading cause of death in both sexes, with a gross mortality rate per 100,000 inhabitants lower than the national average (74 / 100,000 vs. 48 / 100,000). Spain, compared to other European countries, is still one of the countries with lower cardiovascular and coronary mortality rates adjusted for age as reflected in a recent report[2,3] collecting statistics of cardiovascular disease in Europe.

However, high rates of classic cardiovascular risk factors (CVRF) coexist with relatively low rates of cardiovascular morbidity and mortality. The objective of the study DARIOS[4], which included 28,887 participants, was to analyse the prevalence of cardiovascular risk factors (CVRF) in people aged 35-74 years of age in 10 regions and determine the degree of geographical variability in the distribution of CVRF. This study showed a prevalence of dyslipidemia (total cholesterol 250 mg/dl) of 41% and over 75% of the population moved away from the cut off points of total cholesterol <190 mg/dl or LDL-C <115 mg/dl proposed by the guides. As it is mentioned in the discussion of the study, these data contrast with the low incidence of coronary heart disease in our country and the high life expectancy at birth of the Spanish population. It also indicates that the mechanisms involved in the development of coronary disease have peculiarities that should be studied thoroughly and a simplistic translation of international data to our population should not be made.

In the Comunidad de Madrid, statins are one of the treatment groups leading pharmaceutical expenditure per dispensed prescription. Figure 1 represents evolution in consumption (dose per thousand inhabitants per day, DHD) that all groups of lipid-lowering drugs have had in recent years. **Since 2008, there has been an overall increase in statin use of 59% and both the number of individuals treated as the dose used per person have increased.** In 2013, about 90% of people who were treated with lipid lowering drugs took a statin, 5% with fibrate and 5% with ezetimibe (associated with a statin). Compared with the total national consumption in 2012[5], the DHD of statin in monotherapy or in combination was 13% lower in the CM (DHD, 91.65 vs 79.83).

Regarding the selection of statins by active ingredient, in Figure 2 it can be seen that in 2013, more than half of the packaging prescriptions were mainly simvastatin, dose of 20 mg, followed by atorvastatin, which was a 34% of the total prescriptions.

Figure 1: Evolution of the consumption of lipid lowering drugs in the last 8 years measured in DHD (DDD per 1,000 inhabitants per day) Source: FARMADRID

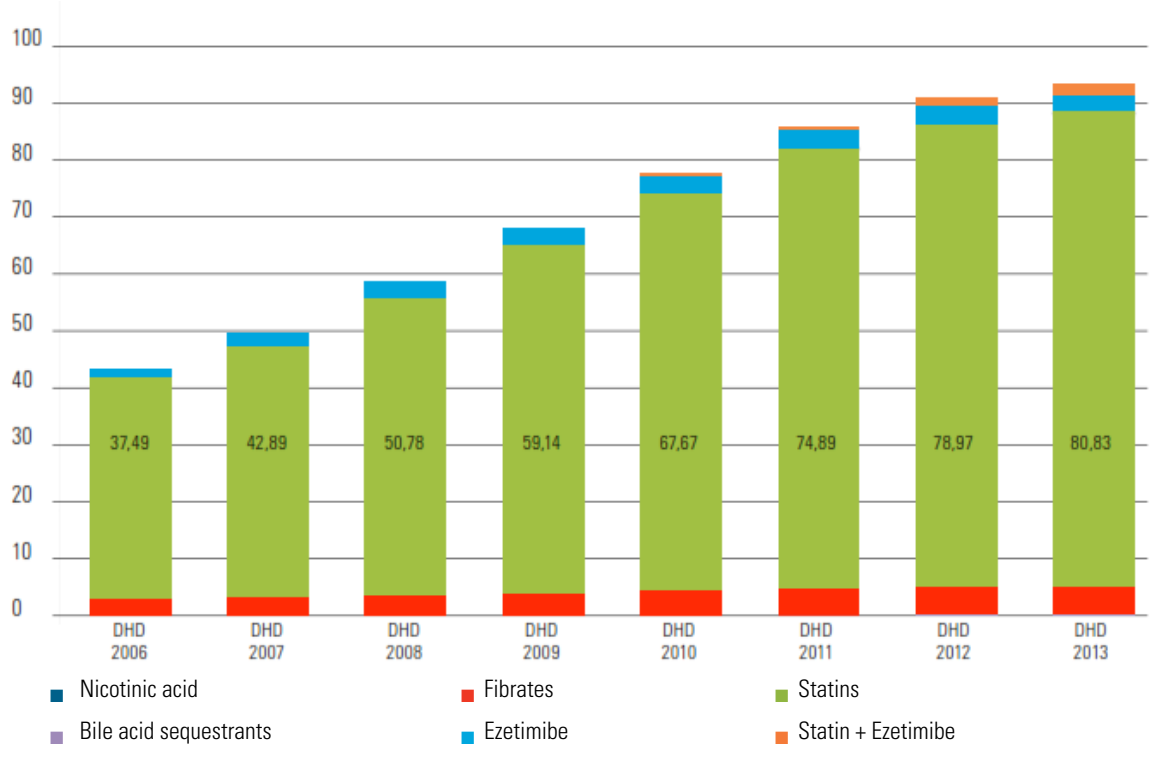
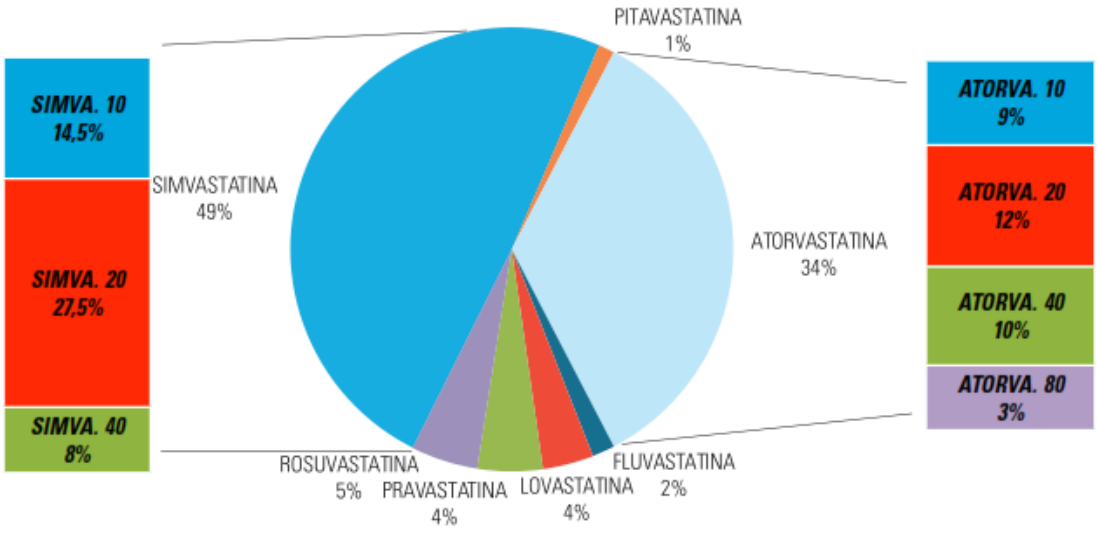


Figure 2: Consumption of items statin by active substance and dose in 2013



SCOPE AND OBJECTIVES

Numerous clinical practice guidelines (CPG) on the treatment of dyslipidemia have been published; all of them were developed by scientific societies and institutions in order to help the professional group they are addressed to with treatment decisions. These CPG have a high degree of agreement in situations where evidence is solid; however, there are major controversies in cases in which evidence is not conclusive due to either inconsistent studies or because they are not designed to answer some specific questions.

The purpose of this document is not to make a new GPC, but set criteria to identify the place of lipid-lowering drugs in adults' therapy to reduce cardiovascular events. It has been agreed by different groups of professionals from different health care settings and medical specialties, adapting the best available scientific evidence to the Comunidad de Madrid.

With this purpose in mind, it has been evaluated the efficacy of lipid-lowering drugs in different population groups according to their cardiovascular risk (CVR) and the various indications / situations in which they are used as well as their safety and efficiency in adult patients diagnosed with primary dyslipidemia. Although discussed briefly, serious genetic hyperlipidaemias are not the objective of this paper.

INITIAL APPROACH FOR PEOPLE WITH DYSLIPIDAEMIA

When approaching patients with hypercholesterolemia, we should always:

- Study the causes of hypercholesterolemia to classify the patient in primary or secondary dyslipidemia.
- Identify patients with cardiovascular events in order to recognize patients in secondary prevention.
- Patients with established CHD, non-cardioembolic ischemic stroke, intermittent claudication of atherosclerotic origin, type 1 diabetes, type 2 diabetes with other greater cardiovascular risk factor or target organ damage, patients with severe hyperlipidaemia and patients with chronic kidney disease stages G3b to G5 already have a high risk without calculating the risk stratification with the tables and require active management of cardiovascular risk factors.
- The rest of people should be risk-stratified to determine the purpose and intensity of treatment based on individual cardiovascular risk found.

PRIMARY PREVENTION

1. Primary Prevention of cardiovascular disease. Selection criteria for people at risk of events for indication of drug treatment.

The decision to start treatment to reduce plasma cholesterol levels in a person in primary prevention will depend on the estimated risk of a cardiovascular event in the next años[6,7].

The CVR refers to the probability that a person has of presenting a first cardiovascular event over a period of 5-10 years[7]. Different models have been developed to assess the CVR in subjects in primary prevention. The tables should be used according to the judgment and knowledge of the physician, assessing local conditions. It is important to keep in mind that the CVR may be overestimated in countries with low rates of mortality, as it happens in Spain.

As it is mentioned in the guide for dyslipidemia by Osakidetza[7], when identifying subjects at high cardiovascular risk, for example with 20% coronary risk according to the Framingham table, we must be aware that although some of these people will develop cardiovascular disease (CVD), many will not do so (80 of 100). Inevitably, if the entire population with high cardiovascular risk will be approached, many healthy subjects with risk factors but who will not develop the disease will be included. This is s situation somehow equivalent to false positives for a diagnostic tool. Therefore, the decision on the cutoff level (CVR level) at which drug therapy should be started is crucial, assuming that a lipid lowering treatment will be given to many people who are not going to benefit from it.

In this document the decision on the selection of subjects eligible for pharmacological treatment is taken according to the following criteria:

- subjects with high CVR should benefit from treatment,
- the benefits of the lipid-lowering treatment should exceed the risks associated with it,
- the treatment should be sustainable for the health system.

Patients with established coronary heart disease (CHD), non-cardioembolic ischemic stroke, intermittent claudication of atherosclerotic origin, type 1 diabetes mellitus, type 2 diabetes mellitus with other greater CVRF or target organ damage (TOD), people with severe hyperlipidemia (total cholesterol at or above 300 mg / dl or LDL> 190 mg / dl) and patients with chronic kidney disease (CKD) stages G3b to G5, **presented per se a high risk** without having to calculate the CVR with tables of risk stratification.

Currently, in Madrid[8], the 2011 SCORE system for low risk countries[9] is recommended for people with dyslipidemia who have not had previous events.

However, the SCORE system has a number of limitations to consider[10]:

1. **It can only be applied to people aged 40-65 years.**
2. It measures the risk of cardiovascular death regardless of morbidity which is the primary objective of large randomized clinical trials (RCTs) with medication.
3. It is not appropriate to calculate the CVR in diabetic patients**.**
4. It assumes the cardiovascular mortality risk ≥5% is equivalent to CVR without justification ≥ 20%.
5. There are CVR modifications that can refine the assessment in subjects with moderate cardiovascular risk, as for example: very high cholesterol levels, microalbuminuria, family history of premature coronary heart disease and evidence of subclinical atherosclerotic disease.

For these reasons and to facilitate the risk stratification of subjects, in this paper we have differentiated the following groups:

- General population.
- People over 65 years.
- Diabetic patients.

1.1. General population

For people under the age of 65 without previous cardiovascular events and who are not diabetic, it is recommended to calculate the cardiovascular risk with the SCORE Chart for low cardiovascular risk European countries updated in 2011.

It is recommended to risk-stratify men younger than 65 years old with the SCORE Table for European countries with low cardiovascular risk. This table classifies people according to their **risk of cardiovascular mortality at 10 years** considering at high risk all those people who have an equal or greater risk of 5%. There are electronic versions of the table available at www.heartscore.org Madrid and in the primary care programme. These electronic versions incorporate the value of HDL cholesterol to estimate the CVR.

1.2. Type 2 diabetic patients without cardiovascular risk factors or target organ damage.

In type 2 diabetic patients without cardiovascular risk factors or target organ damage is recommended to stratify cardiovascular risk with REGICOR tables.

Although it has been said that a person with diabetes is at similar risk to that of a patient with ischemic heart disease, this equivalence is questioned by differences in the studies. However, it is considered that diabetes brings an excess risk compared to other cardiovascular risk factors. A systematic review of epidemiological studies published in 2009[11] provided figures of cardiovascular risk events in diabetic and coronary patients, but showed no evidence that diabetes can be considered an equivalent of coronary heart disease. In our country, a large study compared the risk of coronary heart disease and cardiovascular mortality among diabetic patients without coronary disease in GEDAPS (n = 2260) and non-diabetic infarcted patients in REGICOR study (n = 2150). In all cases, the CVR was significantly lower in diabetic patients, although somewhat higher after 8 years of evolution of diabetes, patients with HbA1c ≥7% and in patients treated with insulina[12]. Subsequent studies[13] conclude that the benefit / risk balance of the aggressive treatment of the CVRF in diabetic patients depends on the underlying CVR; therefore, it is recommended to evaluate the risk individually before prescribing a pharmacological treatment.

The tables used in the stratification of cardiovascular risk in diabetic patients vary greatly in sensitivity, specificity and positive and negative predictive values, so those that include variables associated with diabetes[14] are more accurate. However, and since the SCORE table does not evaluate the risk in people with diabetes and specific tables for DM are not based on the Spanish population, it is recommended to stratify the CVR with the calibration for Spain in the Framingham table by categories of total coronary events with the data in the REGICOR study[15]. This table allows CVR stratification in diabetic patients and the validity of this adaptation at 5 and 10 years[16,17] has been confirmed

REGICOR allows the estimation of the risk of a coronary event (angina, acute myocardial infarction (AMI) with or without symptoms, fatal or not) to 10 years and classifies patients as at low coronary risk (<5% chance of having an episode in 10 years), at moderate (5-9%), high (10-14.9%) or at very high risk (> 15%).

1.3 Advanced age

For the elderly without previous cardiovascular events, the Framingham table calibrated for Spain by the cohort REGICOR is recommended for risk stratification.

In the first congress of Prevention and Health Promotion in Clinical Practice in Spain[18] held in June 2007, it was recognized that more than half of the incident cases are concentrated in the age group 65-70 and approximately 50% of them have clinical or subclinical disease and in the case of older patients and diabetic patients, the percentage can reach 80%.

In people over 65 years **is not possible to calculate the CVR using SCORE**[19] so the tables based on the Framingham cohort tables are recommended as they are calibrated for Spain by the REGICOR study that includes people up to 74 years old. The data on cholesterol cardiovascular risk for octogenarians and nonagenarians are weak, and there are no trials with people over 82 years. CVR stratification in this population has a number of limitations:

- Older women: the tables are usually restricted to coronary risk; however, in elderly women stroke is more prevalent. Cerebrovascular disease is best associated with low cholesterol HDL20 (at higher level, lower risk) than the high levels of LDL cholesterol (LDL-C) and the total cholesterol[21].
- The tables estimate the risk at 10 years and stop at 74 years old, but there seems to be no causal relationship between total and LDL cholesterol for people older than this age[22].

There are no risk tables for people over 80 years and the decision to treat them should always be individualized based on comorbidity, functional status, concomitant medication, life expectancy and patients' opinion.

2. Cholesterol control objectives. Criteria for the indication of pharmacological and non-pharmacological treatment.

Dyslipidemia is a cardiovascular risk factor which, along with others, is involved in the development of atherosclerotic event, so for people with dyslipidemia it is recommended seeking and managing all cardiovascular risk factors and educating patients properly about the benefits of diet, exercise, control of hypertension and abandonment of cigarette smoking.

2.1. Cholesterol control objectives

The RCTs done so far demonstrating a reduction in events have been carried out using fixed doses of statins rather than titrating dose to achieve a total or LDL cholesterol objective. No RCTs have been conducted in primary prevention to evaluate the benefit of reducing plasma cholesterol levels to reach target LDL values which may result in an event reduction. Similarly, no studies have been conducted to compare management strategies at fixed statin dose versus titrating dose to achieve an LDL-C objective. However, some RCTs have been performed comparing statins at high doses with moderate-low doses to check whether intensive treatment results in greater clinical benefit than the standard treatment, but these studies have only been conducted in patients with stable coronary artery disease[23-25] or with acute coronary syndrome (ACS)[26].

However, some guidelines[9,27] recommend treating people without previous events with statins until reaching an objective based on extrapolations from evidence. Nevertheless, other guidelines, such as NICE[28], Osakidetza lipid guideline[7] or the 2013 ACC / AHA[29], have chosen not to recommend target values for LDL-C in primary prevention but just using the standard doses used in the clinical trials.

Therefore, target LDL-C levels for cardiovascular events in primary prevention cannot be established according to available evidence. If it is necessary, **it is recommended using drugs at the necessary doses to achieve a reduction of approximately 30-40%, which is the average decrease in LDL-C achieved in RCTs with statins in primary prevention, without pursuing total or LDL-C treatment goals.**

In patients with dyslipidemia, it is recommended seeking and managing all cardiovascular risk factors and educating them properly about the benefits of diet, exercise and abandonment of cigarette smoking.

In primary prevention pharmacological treatments must be supported by the demonstration of clear clinical benefits and a clear safety profile.

The primary prevention trials that showed that statins reduced cardiovascular events were performed using fixed statin doses without established LDL goals. There is no evidence that the reduction in cardiovascular morbidity and mortality achieved in these RCTs were based on reaching target values for LDL-C; the benefit obtained was due to the use of fixed-dose statins. So, in patients in whom a drug therapy is indicated, it is not recommended reaching specific LDL-C values or certain objectives.

2.2. Hygienic-dietary measures

The first step in any treatment plan for any person with hipercolesterolemia[30] is the modification of their lifestyle, which rests on three pillars: changing dietary habits[31,32], doing exercise[33] and abandonment of harmful habits. The abandonment of smoking is probably the most effective measure for the prevention of cardiovascular and non-cardiovascular[34] diseases.

It is estimated that the change from a diet rich in saturated fat and cholesterol to a Mediterranean diet low in saturated fat (<9%) and cholesterol (<300 mg / day), can reduce LDL-C in 10-15%[36-38]. The RCT PREDIMED showed that a Mediterranean diet supplemented with olive oil or nuts reduces the incidence of cardiovascular events at 5 years in patients with cardiovascular risk factors[32].

In healthy people, increased physical activity is associated with lower overall mortality and a decrease in coronary events[38,39]. Aerobic exercise is recommended at least 45 minutes 2-3 times a week[40]. However, this should be adapted to each particular situation and exercise should be progressive and consistent[41].

In obese adults[42], a loss of about 4-6 kg is associated with a decrease in total cholesterol of 5 to 8% and HDL-C increases 0.35 mg/dl for each kilogram of weight lost[43]. The benefit of diet on cholesterol is also seen in the elderly.

The lifestyle modifications remain the mainstay of treatment of hypercholesterolemia. Dyslipidemia in people with no previous events with low or moderate risk, should be considered before starting drug treatment because dietary hygienic measures have shown to be sufficient to reduce the likelihood of a cardiovascular event. In high-risk patients, in whom the benefits of treatment with diet and exercise are more marked, they will be considered associated with drug treatment.

2.3. Use of lipid-lowering drugs in general population with hypercholesterolemia and without previous cardiovascular events.

Statins

The effectiveness of statins in patients with ischemic heart disease is well established, they have been shown to reduce the total coronary mortality and cardiovascular morbidity. However, available data on reduction of morbidity and mortality in people without previous events are not as strong.

The evidence about the efficacy of statins in primary prevention comes from clinical trials conducted versus placebo in which, initially, subjects without previous events or with moderate to high baseline cholesterol levels were included[44,45]. Subsequently, RCTs[46-48] has included individuals with moderate cholesterol levels but with 2 or 3 added CVRF or with previous events. **Therefore, the people included in the trials were at high risk because they were from countries with a high incidence of ischemic heart disease and with 2-3 additional cardiovascular risk factors**

The Jupiter RCT[49] with rosuvastatin, included a population with no history of clinical CVD, with LDL-C levels below 130 mg/dl, and elevated ultrasensitive C-reactive protein (hsCRP). The mean age of subjects was 66 years and 60% of participants had two or more risk factors of those considered in the NCEP ATP III guidelines[50]. It was therefore a higher risk population than the general population in primary prevention

with the same LDL-C levels. The study ended prematurely after an average follow-up of approximately two years when a reduction in the risk of cardiovascular events was noted (ARR 1.22% (0.79 to 1.65)).

There are two important aspects to consider when interpreting this RCT. First, the applicability of the results to the general population with dyslipidemia since hsCRP is not measured routinely in primary prevention because there are serious doubts about the predictive factor of the clinical CVR[52]. An example of this was that **80% of the preselected subjects could not be included in the study because they had high LDL levels or low hsCRP levels**. Second, it has been seen that clinical trials that are discontinued earlier than planned overestimate the beneficial effect of treatment, especially when the number of events is small, and stopping rules established a priori in RCTs, do not reduce this effect[52,53].

The use of statins in primary prevention reduces the risk of a first coronary event, as has been observed consistently in different RCTs[44-49] and meta-analyses[54-58]; it also reduces the risk of stroke, although less than coronary events.

However, the results are contradictory regarding the reduction in coronary or total mortality, depending on which trials are included in the meta-analyses and if patients with previous events are excluded from RCTs considered as primary prevention.

In general, the relative benefit obtained when treating a person who has not had a previous event with statins is similar to that obtained in a patient who has had one. Statins reduce the risk of a new coronary event by approximately 30%, about 20% the risk of stroke and could, although not shown in all studies, reduce the risk of death by almost 10%[54-57,59].

However, **the number of events that are reduced and therefore the absolute benefit will depend on the baseline risk of the subject.**

Thus, taking into account the data from RCTs conducted in primary and secondary prevention, it can be seen that for every 1,000 patients treated for 5-6 years, 2-7 serious cardiovascular events in primary prevention are avoided; while in patients with previous events, the number of events that are avoided can reach 16-22[28].

In 2012 the Cholesterol Treatment Trialists Collaboration (CTT) published the results of a meta-analysis[59] at patient level including 27 RCTs both in primary and secondary prevention. The objective was to identify the benefit of statin therapy in relation to patients' CVR and, particularly, in patients with low CVR. Patients were classified according to the risk of having, in five years, a serious vascular event, such as: first nonfatal myocardial infarction, coronary mortality, stroke or coronary revascularization; the latter representing approximately 50% of events included in risk stratification. The authors considered low risk subjects those with less than 10% of major cardiovascular events in five years; **however, this risk stratification is not comparable to any of the recommended CVR tables and the cutoff points are not equivalent to the ones in SCORE.** In fact, 17% of the patients included in this subgroup had a history of cardiovascular disease and the group of less than 5% risk included 96% of patients in primary prevention.

Despite attempts to know the benefits of statin therapy in primary prevention with people at low risk, so far, RCTs have not been conducted with this population. Published data[55,59] grouped data from subsets of patients from the clinical trials mentioned above.

Author, year	Definition of primary prevention by the author	N of trials (N)	Serious coronary events1. RR (95%CI)	Ictus RR 95%CI)
Cochrane[58], 2013	≤ 10% of participants with CVD background	19 (56.934)	14 RCT 0.73 (0.67-0.8)	10 RCT 0.78 (0.68-0.89)
Tonelli[56], 2011	MI risk at 10 years < 20%	29 (80.711)	13 RCT 0.63 (0.5 -0.79)	14 RCT 0.83 (0.74-0.93)
Brugts[55], 2009	≥ 80% of participants without established CVD	10 (70.388)	8 RCT 0.7 (0.61-0.81)*	9 RCT 0.81 (0.71-0.93)*
Mills[59], 2008	> 50% of participants without CHD background	20 (65.261)	17 RCT 0.85 (0.77-0.95)	18 RCT 0.88 (0.78-1.00)

1 Includes coronary death and nonfatal MI.
* Results are presented as odds ratio.

A very important aspect to consider is the adherence and persistence to treatment because poor adherence is a barrier for patients to obtain the maximum benefit from treatment[60,61]. Different studies have shown that about 50% of patients stop taking statins in the first 2 years. In secondary prevention, 27% of patients stop taking the medication after a year and 63% after 2 years. In primary prevention up to 77% of patients stop taking medication properly in the second year of treatment[60]

Fibrates

In Helsinki Heart Study[62] the effectiveness of gemfibrozil versus placebo was compared in men between 40 and 55 years, with dyslipidemia and without previous cardiovascular events. After 5 years of follow-up fibrate therapy was shown to reduce the incidence of the composite endpoint of cardiac death and fatal or nonfatal AMI (NNT 71 95% CI [40-344]), but found no differences in total mortality or mortality due to other causes.

Resins

The main RCT[63] that was conducted with a resin in subjects in primary prevention was with 24g cholestyramine, in men between 35 and 59 years with LDL-C ≥ 190 mg / dL. After 7.4 years of follow up, the **cholestyramine has been shown to reduce, compared to placebo, the incidence of the composite endpoint of coronary death and nonfatal MI** without showing any differences in the reduction of total mortality. .

Ezetimibe

There are no clinical trials published in primary prevention with ezetimibe in monotherapy or in combination with statin to evaluate its effectiveness in reducing cardiovascular morbidity and mortality.

Taking into account the results on event reduction of RTCs SHARP[64] and IMPROVE-IT[65], although done in a population different from patients without event, the combination of statins at low doses with ezetimibe may be considered in patients with demonstrated intolerance to statins at moderate doses.

A patient is considered to be statin intolerant[66] when, after eliminating other causes, the patient is unable to tolerate (for adverse effects or significant laboratory abnormalities) at least two different statins, one at the lowest recommended starting dose and the other at any dose. The symptoms or laboratory abnormalities are resolved or improved significantly after a dose reduction or discontinuation of statin therapy.

In the general population with dyslipidemia without prior events and **high cardiovascular risk** (SCORE >5% or REGICOR >10%) it is recommended to initiate statin therapy when dietary and hygienic measures or the control of other factors do not reduce the risk. Drug treatment should be started with the required dose to achieve a percentage reduction of 30-40% of LDL cholesterol without the need to achieve specific levels or certain objectives.

In **low-risk** patients, there is a possibility of overusing drugs by inappropriate extrapolation of the results of tests conducted in high-risk males, so in the absence of evidence, **the use of lipid-lowering drugs is not recommended.**

In people **with moderate risk**, the decision to treat is based on an individualized assessment taking into account other factors that may increase the risk and are not covered by risk assessment tables (especially high levels of cholesterol, microalbuminuria, family history of early ischemic heart disease and subclinical atherosclerotic disease).

The use of fibrates and resins in primary prevention of cardiovascular risk remains controversial. Gemfibrozil is the alternative to statins if they were contraindicated. In the case of documented intolerance to statins, low doses in combination with ezetimibe could be considered. Cholestyramine could be an alternative but has a poor tolerance and a high potential for interactions.

There are no efficacy data on the reduction of morbidity and mortality with ezetimibe in monotherapy or associated with statins. Therefore, considering that there is controversy about whether to recommend reaching target levels of C-LDL or simply reduction percentages, there seems to be no indication for the use of the combination of statin and ezetimibe in most people in primary prevention.

2.4. Use of lipid-lowering drugs in women

Statins and other lipid-lowering drugs

In 2004 a meta-analysis was published[67] in which, among others, the effectiveness of primary prevention in women with high cholesterol was valued. There were not significant differences compared to placebo in total mortality or cardiovascular mortality or myocardial infarction, or cardiovascular events. In 2006 the MEGA study[68] was published; it involved 69% of Japanese women with low coronary risk treated with pravastatin versus placebo and no significant difference in reducing coronary events was found. Similarly, two subsequent meta-analyses[54,69] failed to show benefits of the pharmacological treatment with statins or other lipid-lowering drugs in primary prevention in women.

However, the Canadian Task Force IV[70] and 2011 Guidelines for preventing cardiovascular disease in women of the American Heart Association[71] recommend the use of the tables and the indication of pharmacological treatment according to the CVR calculated, as it is done in the general population.

Given the lower coronary mortality and low representation of women in RCTs, the benefit of treatment in reducing morbidity and mortality in primary prevention has not been demonstrated. However, women should not be excluded from lipid-lowering treatment, provided they have increased CVR calculated with the recommended tables. In any case, **this decision must be based on the estimation of CVR and the detailed analysis of other treatment possibilities to reduce the risk.**

There is no data from clinical trials with women to support the use of statins in primary prevention of cardiovascular disease; however, the statin indication for primary prevention is recommended in women at high cardiovascular risk following the recommendations of the general population.

Lipid-lowering drugs should not be administered during pregnancy or while breastfeeding.

2.5. Use of lipid-lowering drugs in the elderly

Statins and other lipid-lowering drugs

So far, in the prospective studies conducted with people older than 65 years, the association between cholesterol and cardiovascular event has not been conclusive, i.e., it cannot be affirmed that cholesterol is a FRCV in this population[72,73]. Although there might be other fractions that could be better predictors of the risk of ischemic heart disease in the elderly[74], these have not been included as control objectives in RCTs.

The PROSPER study[20] is the only RCT designed specifically for individuals between 70 and 82 years with high CVR or previous vascular disease. If the results obtained in primary prevention are analysed, there are no significant differences in major coronary events, cardiovascular events or stroke between the group treated with statins and placebo groups. There was no difference in preventing cognitive impairment, although there was a difference of 25% in cancer rates, which were significantly increased in the pravastatin group[75]. In 2012 the FDA[76] warned of the possibility of usually not serious and reversible cognitive side effects (memory loss, confusion) after cessation of treatment, with no relationship between the people' age, statin type, dose or use of concomitant drugs.

In view of these observational studies and clinical trials and meta-analyses conducted to evaluate the efficacy of this treatment in older people, there is no evidence to recommend the use of statins in people over 70 years in primary prevention with high cholesterol and no other CVRF, unless there are other specific indications. There is no evidence of benefit of pharmacotherapy in people over 80 years.

There are no benefit studies with other lipid-lowering drugs but there are some observational studies[78] that show a clinically significant deterioration in renal function with the use of fibrates, which are not recommended in this population.

Initiation of statin therapy is not recommended in older people with high cholesterol without other cardiovascular risk factor unless there are other specific indications. However, there is no age limit for treatment already established if the indication was correct, except poor prognosis.

2.6. Use of lipid-lowering drugs in type 2 diabetic patients with hypercholesterolemia

Statins

The CARDS[78] study, which ended prematurely, included exclusively diabetic patients between 40 and 75 years without previous events, but with at least one risk factor (hypertension, retinopathy, smoking or micro/ macroalbuminuria) treated with atorvastatin 10 mg or placebo. In the statin-treated group, there was absolute reduction in the risk of serious cardiovascular events of 1.9%, i.e., it could be expected that treatment with atorvastatin 10 mg will avoid at least 37 major vascular events per 1000 patients with similar characteristics if treated for 4 years. However, the ASPEN[79] study, which included type 2 diabetic patients with and without previous coronary events, demonstrated no benefit from treatment with atorvastatin 10 mg neither in primary nor secondary prevention, with a variable outcome that included serious cardiovascular events and a number of other cardiovascular events.

Similarly, the diabetic patients included in the ALLHAT-LLT study[47] and in the ASCOT-LLA study[46] showed significant differences in the rate of events compared to placebo. Only the group of diabetic patients included in a sub-study of the HPS study[80] (which included approximately the same proportion of subjects with and without prior vascular disease) showed a reduction in the CVR of 22% with 40 mg of simvastatin. But it should be remembered that these are sub-studies, therefore the strength of this evidence is low and the indication that generates is controversial.

A meta-analysis[81] that included data from patients with diabetes from RCTs in both primary and secondary prevention (data from ASPEN RCT were not included) showed a reduction in coronary events and stroke which, in relative terms, is similar to that achieved in non-diabetic patients, but not in cardiovascular or total mortality.

Fibrates

In the FIELD study[82], involving nearly 10,000 diabetic patients, fenofibrate showed no cardiovascular benefit but other serious side effects and metabolic and renal control deterioration in the treatment group.

Statin + fibrate

The ACCORD study[83] objective was to assess whether, in the context of good glycaemic control, the more aggressive management of dyslipidemia combining a fibrate (fenofibrate 160 mg / day) with simvastatin (20 mg in primary prevention and secondary prevention 40 mg) gave a greater benefit in the reduction of major cardiovascular events (cardiovascular death, myocardial infarction, or nonfatal stroke) than simvastatin in monotherapy. 5,518 type 2 diabetic patients at high risk were included, either because they had a previous cardiovascular event or at least two associated cardiovascular risk factors. After a follow-up of nearly five years it was noted that adding fenofibrate to simvastatin did not reduce cardiovascular events more than simvastatin in monotherapy.

A pre-specified subgroup analysis performed based on baseline levels of TG and HDL-C suggests that patients with low HDL-C and high triglycerides (TG≥ 204 mg / dl and HDL-C ≤ 34 mg/dl) may benefit from treatment with the combination as a reduced risk of cardiovascular events close to 30% was found (0.69; 95% CI: 0.49 to 0.97). by contrast, heterogeneity between sexes was observed and the combination proved harmful to women.

Ezetimibe

There are no published clinical trials with diabetic patients with this drug in monotherapy or in combination with statin to evaluate its effectiveness in reducing cardiovascular morbidity and mortality.

Taking into account the results on event reduction of RCTs SHARP[64] and IMPROVE-IT[65], although done in a population different from patients without event, the combination of statins at low doses with ezetimibe may be considered in patients with demonstrated intolerance to statins at moderate doses.

A patient is considered to be statin intolerant[66] when, after eliminating other causes, the patient is unable to tolerate (for adverse effects or significant laboratory abnormalities) at least two different statins, one at the lowest recommended starting dose and the other at any dose. The symptoms or laboratory abnormalities are resolved or improved significantly after a dose reduction or discontinuation of statin therapy.

In dyslipidemic patients with **type 1 diabetes or type 2 diabetes and with other greater cardiovascular risk factor or target organ damage** it is recommended to start treatment with the needed dose to achieve reductions of 40-50% which could amount to a decrease in LDL below 100 mg / dl.

The **type 2 diabetic patients with no other greater cardiovascular risk factor or target organ damage** will benefit from statin therapy based on their cardiovascular risk as recommended for the diabetic population tables. For patients with a high risk (greater than 10% in REGICOR) statin use is recommended at the required dose to achieve a percentage reduction of 30-40%.

Fibrates are not first-line therapy and would be recommended only as an alternative in patients with contraindication to statins. In the case of documented intolerance to statins, low doses in combination with ezetimibe could be considered.

A combination of statin and fibrate is not advisable to use for most of diabetic patients. In those patients at high cardiovascular risk with elevated triglycerides levels, other causes of hypertriglyceridemia should be discarded and / or modify before adding a fibrate, such as: lack of fasting before extraction, poor glycaemic control, obesity, renal failure, alcohol intake or certain medicines.

2.7. Use of lipid-lowering drugs in patients with severe hyperlipidemia

Hyperlipidemia is considered severe due to its high potential of atherosclerotic complications or other life-threatening complications and it occurs with the following plasma levels[9,29]:

- Total cholesterol higher than 300 mg/dl or LDL 190 mg/dl and in general when the determination of total cholesterol or LDL is above the 95th percentile for age and sex.
- HDL-C deficit and especially levels below 25 mg/dl.
- Levels of triglycerides above 900 mg/dl represent high risk of acute pancreatitis

In all these patients, the initial attitude should be to diagnose and treat the causes of secondary hyperlipidemia, as already stated in other sections of this document. Among them, hypothyroidism, alcohol intake or uncontrolled glycaemia stand out for their frequency and also certain pharmacological treatments (among them, protease inhibitors or anabolic steroids).

It should also be suspected any genetic primary lipid disorder, especially if the patient has a family history of premature cardiovascular disease (men younger than 55 years of age and women younger than 65 years of age).

After correcting the causes of secondary hyperlipidemia and discarding family hyperlipidemia (see next section), patients with LDL-C persistently greater than 190 mg / dl despite the establishment of healthy lifestyles should be considered for treatment with statins[9,29] These patients are not shown in the usual risk tables and they have an early high risk for cardiovascular events.

Similarly, once the causes of secondary hypertriglyceridemia have been discarded, patients with isolated hypertriglyceridemia higher than 500 mg/dl may be considered for treatment with gemfibrozil[84]. In mixed hyperlipidemia, statin therapy directed at the control of LDL cholesterol should be always prioritized because of its importance in cardiovascular prevention.

2.8. Use of lipid-lowering drugs in patients with severe genetic hypercholesterolemia

Monogenic Heterozygous Familial Hypercholesterolemia (HFH) present with severe hypercholesterolemia by a defective clearance of LDL particles. Its transmission is autosomal dominant with an estimated prevalence of 1 case every 400 to 500 people in the general population.

Familial Combined Hyperlipidemia (FCH) can present with elevated levels of LDL cholesterol, of triglycerides or both. It has a phenotypic presentation with great inter- and intra-individual variability: there may be variation in serum lipid levels in the same individual and in their family over time. A population prevalence of 1-2%[85] is estimated.

Both conditions are accompanied by a premature increased risk of cardiovascular disease, so this should not be calculated using prediction tables. **These patients are considered high-risk patients** and an early and indefinite treatment with lipid-lowering drugs should be implemented once the diagnosis has been confirmed[29,86].

HFH patients have obtained a reduction in the contribution (10%) with treatment with statins and ezetimibe. The diagnosis and a report by a NHS specialist is mandatory for the approval of the prescriptions[87].

The criteria for the diagnostic and therapeutic management of patients and families affected by severe genetic hypercholesterolemia are beyond the scope and objectives of this document which is aimed at the general population with polygenic hypercholesterolemia.

Patients with severe genetic hypercholesterolemia are patients at high cardiovascular risk. The prediction tables should not be used and they should be treated with drugs. These patients benefit from statin treatment as the contribution is reduced. Prescriptions are approved after the presentation of diagnosis and report by NHS specialist.

3. Indication of pharmacological treatment in patients with associated vascular pathology but with no previous cardiovascular events

This section refers to the indications of pharmacological treatment for dyslipidemia in patients without previous cardiovascular events and with a pathology that may increase the cardiovascular risk in comparison with the healthy population. However, these patients do not present rates of coronary and cerebrovascular events comparable to rates found in subjects who have had a previous major ischemic event. Another factor to consider is that, although these clinical conditions confer a high risk of future events, the predictive value of cholesterol[88,89] or its reduction[63] in the event development or prevention is less consistent than in patients who have had a previous event.

Patients with different risk of cardiovascular events are included in this section, such as, those with chronic kidney disease (CKD) in its different stages, peripheral arterial disease (PAD) or heart failure (HF) and, as mentioned above, these patients differ from secondary prevention patients. Secondary prevention patients are those with ischemic heart disease or cerebrovascular disease. These two CVDs cause a great number of cardiovascular deaths and high rates of new ischemic event (50%, in the case of AMI and 30% in the stroke)[90,91]. 60% of total cardiovascular mortality is estimated to occur in these patients: 31% of coronary heart disease (higher in men, with 39%, than in women, with 25%) and 29% for stroke (higher in women, with 31%, than men, with 27%).

Statins have shown an unquestionable benefit in cardiovascular prevention in patients with previous coronary disease. However, due to the different weight that the cholesterol has in the development of events, results found in coronary patients should not be extrapolated to patients without previous cardiovascular event. Conclusions should be drawn from clinical trials with lipid lowering drugs in patients with CKD, PAD or HF, designed to evaluate the reduction in the incidence of a first clinical episode due to coronary heart disease or ischemic stroke and prevent the progression and deterioration of the disease (CKD, PAD or HF). Consequently, conclusions can be used to improve the prevention of disability and premature death.

3.1. Use of lipid-lowering drugs in patients with intermittent claudication of atherosclerotic origin

Peripheral arterial disease is a manifestation of systemic atherosclerosis and is caused by an obstruction in the arterial blood flow of the lower limbs. The simplest diagnostic test is the measurement of ankle-brachial index. Under normal conditions, the value is equal to or greater than 1, values

between 0.41 and 0.90 suggest mild or moderate obstruction and 0.40 or less, severe obstruction. Values greater than 1.30 indicate a calcification of vessels, as may occur in patients with diabetes or renal failure patients. However, a low ABI is a diagnostic test with low sensitivity and high specificity which means, it cannot be used as a general screening tool. However, it is used with subjects with moderate CVR in order to classify them at high CVR when ABI is less than 0.9[92].

Intermittent claudication correlates with an increase in major cardiovascular disease, stroke and coronary artery disease as, in a 5 year period, approximately 20% of patients with intermittent claudication will suffer a non-fatal cardiovascular event[93]. That is, people suffering of intermittent claudication are patients with high cardiovascular risk, especially if they have a history of coronary event or they are smokers or diabetic.

Statins

There are no clinical trials specifically designed to evaluate the efficacy of statins in variables of mortality and morbidity in patients with clinical or subclinical PAD, therefore, the benefits of this treatment are ignored. The information we have about the effectiveness of statins comes from the analysis of patients with peripheral arterial disease (PAD) included in clinical trials on efficacy in secondary prevention and high-risk patients.

A Cochrane review[94] found no association between lipid-lowering therapy and decrease in total mortality in patients with PAD. But it found differences in the reduction of cardiovascular events due to a sub-analysis of HPS trial, in which one of the inclusion criterion was patients with intermittent claudication or patients who had undergone peripheral arterial revascularization procedures, amputation or aneurysm repair. In this study[95], treatment with simvastatin 40 mg daily reduced the incidence of serious vascular events (myocardial infarction, coronary mortality, stroke, revascularization) by 19% with an NNT of 16 over 5 years (NNT 16 95% CI [12-24]) and major coronary events (AMI or coronary death) by 21% (NNT 34 95% CI [22-74]). In this analysis, the majority of patients had associated comorbidities (diabetes, ischemic heart disease, and stroke). The benefit of statins was higher in patients with a history of coronary heart disease, stroke or history of DM (NNT 15 to 17) than in patients without any of these precedents in which the reduction was not significant.

Fibrates

In one RCT[96] which used bezafibrate 400 mg / day showed no association with a reduction in coronary events and stroke that made up the primary endpoint. This study was conducted in 1,568 men with peripheral arterial disease of the lower limbs (24% had also angina, 21% previous myocardial infarction, 12% history of stroke) who were followed for almost five years. No differences were found in comparison with placebo in terms of the events that made up the main variable, but an association was found with a reduction in non-fatal coronary events.

The lack of studies specifically aimed at this group of patients, raises serious doubts about the recommendation of pharmacological treatment with statins. Most of the CPG[97,98], based on the high risk inherent in this condition and subgroup analyses, make a weak recommendation for the use of drugs in this indication.

Patients with intermittent claudication of atherothrombotic origin or revascularization are directly considered high-risk patients, so lipid-lowering therapy with statins and exhaustive tobacco control are indicated. Simvastatin 40mg daily is recommended for patients with a history of coronary heart disease, stroke or diabetes mellitus.

In patients with moderate RCV, ABI measurement is recommended to reassess the RCV and consider the indication for statin.

3.2. Use of lipid-lowering drugs in patients with heart failure

Statins

The role of statins in heart failure is controversial; first, observational studies, small clinical trials and post-hoc analyses of large RCTs showed that statins have beneficial effects in patients with heart failure[99-101]. On the other hand, two large clinical trials[102,103] conducted in different types of patients with HF and in which a statin was added to the usual therapy, did not reduce mortality or morbidity despite lowering LDL cholesterol.

Both clinical trials were conducted in patients with HF who were adequately treated with medication that reduced morbidity and mortality, to which rosuvastatin 10 mg daily or placebo were added. In the CORONA RCT[102] patients with symptomatic heart failure of ischemic origin with reduced ejection fraction were recruited, while in the GISSI-HF[103] no Heart Faillure or left ventricular systolic function restrictions were included. Besides, patients included in the CORONA study were older and more symptomatic than those in GISSI-HF. But in none of the trials differences between rosuvastatin and placebo were found regarding reduction in mortality, myocardial infarction or stroke in one trial[102] or total mortality or admissions for cardiovascular reasons in the other[103].

Two meta-analyses[104,105], from RCTs of statins versus placebo in patients with HF and reduced ejection fraction, showed that the use of statins does not increase survival and the related

complications. Moreover, there are differences between the two meta-analyses in the admission results due to HF worsening. Most of the patients included in this meta-analysis were from the CORONA and GISSI-HF studies.

Statins have not been shown to reduce cardiovascular morbidity and mortality in patients with heart failure, therefore its use is not recommended unless there is another indication.

3.3. Use of lipid-lowering drugs in patients without previous cardiovascular event and with chronic kidney disease

Patients with CKD have an increased absolute risk of cardiovascular events, particularly patients with glomerular filtration rate less than 45 ml / min / 1.73 m^2 (CKD stages G3b-G5)[106-109]. However, this risk is not comparable to that of patients with prior coronary event, as shown in a recent epidemiological study[110] involving a population cohort of more than one million subjects followed up for two years. In this study, subjects with CKD had a rate of AMI of 6.9 per thousand inhabitants, 95% CI [6.6-7.2], slightly higher than that of the diabetic population (5400 inhabitants / year. 95% CI [5.2-5.7]) but much lower than the rate of AMI in patients with previous AMI, which was 18.5 per thousand inhabitants / year, 95% CI [17.4-19.8]. Even in the group of patients with reduced glomerular filtration rate of 45 ml / min / 1.73 m^2, the event rate (below 10 per 1,000 people / year) did not reach the rate of the patients with previous AMI.

The risk of cardiovascular events also increases with proteinuria, and does so independently of the decrease in glomerular filtration. In a recent meta-analysis, the association of albuminuria above 30 mg/g (albumin/creatinine index measured in urine sample) with an increased risk of total mortality, cardiovascular mortality, acute renal failure and CKD progression was demonstrated[108]. Therefore, at any stage of CKD, proteinuria, mainly above 300 mg/g, the CVR increases dramatically.

Lipid-lowering treatment in the reduction of proteinuria or in the renal disease progression

Statins

The hyperlipidemia role in the development of kidney disease[111] is controversial and, at present, it is not known if hyperlipidemia is merely a marker of more serious underlying disease rather than a progression mediator.

Evidence of the effect of statins on the loss of glomerular filtration in human studies is rather weak[114,115]. The NICE CPG[109] for patients with chronic kidney disease concludes that there is insufficient evidence to support the role of statins in reducing proteinuria or the renal disease progression.

Lipid-lowering treatment in the reduction of cardiovascular events in patients with isolated proteinuria

Statins

The only published RCT of statins in patients with microalbuminuria without hypercholesterolemia, hypertension and reduced glomerular filtration is the PREVEND IT[114] (category G1-G2). In this study, 864 patients with microalbuminuria were randomized to receive pravastatin 40 mg or placebo. Subjects were followed up for four years. Pravastatin did not reduce cardiovascular morbidity and mortality significantly, although the main limitation of this study was the small number of cardiovascular events than patients in the study had.

There are no available RCTs in patients with isolated macroalbuminuria that evaluate the benefit of statins in reducing cardiovascular events.

Fibrates

There are no published clinical trials with these drugs in patients with proteinuria that assess their effectiveness in reducing cardiovascular morbidity and mortality.

Ezetimibe

There are no published clinical trials with this drug, or its association with statin, in patients with proteinuria that assess its effectiveness in reducing cardiovascular morbidity and mortality.

Lipid-lowering treatment in the reduction of cardiovascular events in patients with chronic kidney disease without dialysis or transplants

Statins

Three published systematic reviews[115-117] compiling the results of subgroups of patients at high cardiovascular risk and renal disease included in the RCTs of statins efficacy showed that these could reduce all-cause mortality (RR 0.81, 95% CI [0. 74 to 0.88]), cardiovascular mortality (RR, 0.78 [95% CI, [0.68 to 0.89]) and cardiovascular events (RR 0.76, 95% CI [0.73 to 0.80]). These results are mainly based on the benefit found in patients with CKD stage G3 (creatinine clearance below 60 mg/dl). In addition, these reviews have an important limitation when extrapolating the data to the global CKD patients since the results were obtained in patients at high cardiovascular risk (inclusion criterion for the trial).

Due to the high potential side effects with high doses of statins, and lack of knowledge about the safety of these drugs, the KDIGO CPG[118] recommends for patients with CKD stage 3

or greater using statins that have been used in randomized trials in this population.

Statin + ezetimibe

The main RCT in patients with CKD is SHARP[64], in which 9,270 patients of mean age 62 years were included, without known history of myocardial infarction or coronary revascularization. Patients were randomized to ezetimibe and simvastatin 20 mg or placebo for 5 years. 96% of the population included in the trial had an estimated GFR lower than 45 ml / min / 1.73 m_2, so the results can be extrapolated in a CKD population G3b to G5[119]. **The study found no difference in total mortality, although it showed a reduction in major cardiovascular events** (nonfatal MI or coronary death, non-haemorrhagic stroke or arterial revascularization) RR 0.83 (95% CI [0.74 to 0.94]), AAR 2.1% and NNT of 50. However, the lack of a group with simvastatin in monotherapy does not reveal whether adding ezetimibe to simvastatin has an advantage in efficacy or safety versus simvastatin.

Fibrates

There are no published clinical trials with these drugs in patients with kidney disease that assess its effectiveness in reducing cardiovascular morbidity and mortality.

Lipid-lowering drugs in the reduction of cardiovascular events in patients with chronic kidney disease with dialysis or transplants

Statins

The RCTs published, 4D[120] and AURORA[121], with **haemodialysis patients showed no benefit** in reducing cardiovascular events. The 4D RCT was conducted in type 2 diabetic patients on haemodialysis and efficacy of atorvastatin 20 mg versus placebo in reducing events that comprised the primary endpoint (coronary death, MI, and fatal or nonfatal stroke) was compared. The second RCT was designed to determine the efficacy of 10 mg of rosuvastatin versus placebo in CVD patients with renal insufficiency on haemodialysis and not amenable to transplant. This study failed to demonstrate the benefit of treatment in cardiovascular death, nonfatal MI or nonfatal stroke, despite a 43% reduction in LDL cholesterol and 11% of C-reactive protein in patients in the rosuvastatin group.

The ALERT study[122] with **transplant patients** treated with fluvastatin failed to significantly reduce CV events.

Statin + ezetimibe

In the SHARP study[121] ezetimibe associated with statin showed no benefit in reducing cardiovascular morbidity and mortality in patients already on dialysis, but there was a benefit in the patients who previously received medication and went on dialysis during the study.

Fibrates

There are no published clinical trials with these drugs in patients with CKD on dialysis or transplanted patients that assess their effectiveness in reducing cardiovascular morbidity and mortality. The FIELD study with diabetic patients showed an elevated plasma creatinine, so, these drugs should be used with caution in patients with CKD because they are not dialyzable.

In patients with CKD stage G1 to G3a (glomerular filtration greater than 45 ml / min / 1.73m^2) and without previous cardiovascular events, the use of statins is recommended in patients considered at high risk after an individualized assessment of CVR, taking into account that in patients with moderate CVR the presence of microalbuminuria is a modulator of risk.

In dyslipidemic patients without previous cardiovascular events and with CKD stage G3b to G5 (lower glomerular filtration of 45 ml / min / 1.73m2) the use of lipid-lowering drugs for primary prevention would be indicated without first assessing the RCV. There is good evidence to recommend simvastatin / ezetimibe at fixed doses of 20 mg / 10 mg, although statins in monotherapy could be an alternative.

In patients with isolated microalbuminuria (less than 300 mg/g), statins do not reduce cardiovascular morbidity and the outcome for patients with proteinuria greater than 300 mg/g is unknown, so the indication for statins in these patients will depend on the associated cardiovascular risk.

In patients on dialysis or with kidney transplant, the lipid-lowering therapy is not recommended. If the patient was receiving treatment before entering dialysis, treatment suspension is not advised.

SECONDARY PREVENTION

4. Secondary prevention of cardiovascular disease. Selection criteria for patients for pharmacological treatment indication. Cholesterol control objectives.

Secondary prevention includes all those people who have already suffered a coronary or cerebrovascular event and, therefore, suffer a disease, being this concept not comparable to the concept of primary prevention in people at high cardiovascular risk.

Although ischemic CVD affects the entire vascular bed, it is

also true that it does affect in the same way all the areas (heart, brain, kidney and peripheral arterial system), so it is not convenient to equalize benefits found by the different drugs in different vascular territories.

Patients aged 80 and older are not included in most RCTs that provide an indication of drug treatment; therefore, in secondary prevention decision to treat should be always individualized based on comorbidity, functional status, poly-medication and life expectancy. There is no age limit for treatment already established if the indication was correct, and treatment should not be excluded, except in the case of poor prognosis.

Coronary heart disease is the paradigm of vascular disease related to cholesterol, while stroke is the one related to high blood pressure (hypertension). Thus, it has been shown that the relative risk (RR) of hypertension in stroke is greater than in ischemic heart disease. Therefore, benefits found in reducing the coronary risk with lipid-lowering drugs are not as significant in reducing ischemic disease in other vascular beds.

Said this, it must be emphasized the need to assess and strictly control the different cardiovascular risk factors, including cholesterol, because it is in these patients where the treatment benefits are more cost-effective.

4.1 Cholesterol control objectives

Clinical trials in patients with stable coronary disease[23-25] were conducted comparing statins given in high doses or in moderate-low doses. Less than half of patients in the intensive treatment group managed to reach the target level of 70 mg/dl but they started with low LDL-C levels (85-120 mg/dl). The Treatment to New Targets (TNT) RCT[25] recruited subjects with established CHD and LDL cholesterol levels slightly elevated (up to 130 mg/dl). This trial was specifically designed to assess whether the reduction of LDL cholesterol to 70 mg/dl with atorvastatin 80 mg/day was associated with a greater reduction in cardiovascular events compared with treatment goals of less than 100 mg/dl achieved with a fixed dose of atorvastatin 10 mg/day. Prior to randomization, all patients received atorvastatin 10 mg which reduced LDL levels from an average of 135 to 98 mg/dl. Subsequently, patients were randomized to receive high doses of atorvastatin or to continue with atorvastatin 10 mg. The average levels of LDL of the patients assigned in the high-dose group were 77 mg/dl.

The generalization of the target of 70 mg / dl has two important aspects to consider. The first one is safety because as high doses of statins were used in these trials, those patients at most risk of serious adverse effects were excluded. The second aspect to consider is: if in the context of an RCT a high percentage of patients does not reach the target, in practice, this means that in many cases high doses of statins or statin in combination with other drugs would need to be used. The problem with this second point is that there are no RCTs that support their effectiveness in reducing events or their long-term safety.

Consequently, there is an open debate on what should be the target LDL-C reduction. Some guidelines support specific LDL-C levels[9,27] – and even discussed whether they should be lower than the ones currently recommended - while others[28,29] do not mention a specific value and recommend reduction percentages depending on the baseline cardiovascular risk of patients.

Next, each of the ischemic diseases from the point of view of the benefits of lipid-lowering therapies will be addressed.

In secondary prevention, as well as in primary prevention, pharmacological treatments must be supported by the demonstration of clear clinical benefits and a clear safety profile

4.2. Use of lipid-lowering drugs in patients with stable coronary disease

Statins

The evidence of the benefit of statins is based on results from clinical trials in patients with stable coronary disease. In the late 80s, the 4S[123], CARE[124] and LIPID[125] clinical trials established the fundamental place of statins in the therapy of patients with a history of myocardial infarction and / or angina. These large and long RCTs, duration between 5 and 6 years, compared statins versus placebo and showed that simvastatin and pravastatin at standard doses decreased total mortality (NNT = 31, 95% CI [20-64]. Data from 4S), coronary mortality and cardiovascular morbidity, being this reduction more important when the patient cholesterol level and the re-infarction risk associated to the patient were higher. Since then, several meta-analyses have been published versus placebo confirming that standard-dose statin treatment reduces the risk of total mortality (RR 0.79, 95% CI [0.70 to 0.9]), cardiovascular mortality (RR 0.75, 95% CI [0.68 to 0.83]), coronary mortality (RR 0.72, 95% CI [0.64 to 0.80]) as well as fatal myocardial infarction, nonfatal stroke, coronary revascularization[28,126] in patients with coronary disease.

What dose of statin is the most appropriate in patients with stable coronary disease?

After reviewing the evidence supporting the use of statins in secondary prevention of coronary event, the different clinical trials in which high doses of statins are compared with standard doses in reducing cardiovascular morbidity and mortality need to be reviewed.

The objective of these studies is to check whether the greater reduction in LDL cholesterol, obtained by the use of high doses of statins compared with moderate-low doses, would result in

a significant reduction in cardiovascular events. These clinical trials lasted between 5 and 7 years and included patients with previous myocardial infarction or established coronary disease that were on statin therapy at standard doses and with adequate levels of LDL at baseline randomization (98-121 mg / dl). In two of the trials[23,25] atorvastatin 80 mg was used for intensive therapy and in the third one[24], the therapy with simvastatin 80 mg was compared with atorvastatin 10 mg or simvastatin 20 mg.

Aggregated data from the three trials showed that intensive therapy reduced the risk of nonfatal events, mainly myocardial infarction (RR 0.80, 95% CI [0.73 to 0.87]), AAR 1.25% (95% CI [0.72-1.77]) and to a lesser extent stroke (RR 0.85, 95% CI [0.76 to 0.97]), AAR 0.58%; 95% CI [0.17-0.98]). In terms of mortality, the data available so far has not showed that high doses of statins compared to moderate doses reduce total or cardiovascular mortality.

There are no trials directly comparing the reduction of cardiovascular events with different high doses of statins. Similarly, the additional benefit that could be obtained with high doses of statins versus simvastatin 40 mg or atorvastatin 40 mg is unknown.

On the contrary, in these trials **the intensive therapy** was associated with a higher percentage of treatment abandonment due to **adverse events**[128] (RR 1.45, 95% CI [1.34-1.58]), NNH 40 (95% CI [52-33]). It should be kept in mind that most of the patients included in RCTs were selected patients who had previously shown tolerance to standard doses of statins and good treatment compliance; patients at high risk of adverse effects were excluded.

Therefore, taking into account the benefit demonstrated by the standard dose, the added benefit obtained by using intensive doses and the potential risk of using high dose statin, the use of high doses could be assessed in patients with stable coronary disease as long as they do not present characteristics that predispose to an adverse effect by statin[29]:

- Patients with multiple or serious comorbidities, including changes in renal, liver, thyroid or immunosuppression function.
- History of muscle pathology or haemorrhagic stroke.
- History of intolerance to statins (Appendix 1 Interactions).
- Elevations in levels of transaminases greater than 3 times the upper limit of normal.
- Use of concomitant medications that affect the metabolism of statins.
- Patients aged over 75 years.

Fibrates

The main RCTs conducted with fibrates, VA-HIT[129] and BIP[130], were designed with the aim of studying whether a therapy aimed at increasing HDL levels and reducing triglycerides levels may reduce the incidence of coronary events. To do this, patients with coronary disease and low levels of HDL and low or slightly elevated levels of LDL cholesterol were included. However, the results of RCTs were contradictory; whereas gemfibrozil[129] 1200 mg/day showed that reduced fatal and non-fatal AMI versus placebo after 5 years of treatment, (RR 0.8, 95% CI [0.64 to 0.94]; NNT 23, 95% CI [13-77]), the BIP[130] RCT showed a significant reduction in events with bezafibrate 400 mg/day.

Omega-3 polyunsaturated fatty acids

The first large RCT[131] in which ethyl esters of omega-3 fatty acids were added to standard therapy in patients with coronary disease showed beneficial results in reducing CV events. This trial has serious limitations that hinder extrapolation to current clinical practice. The main one is that at baseline, the percentage of patients receiving statins for secondary prevention of MI was very small (less than 5%) and was growing along the 3.5 years that the RCT lasted, but this increase was not adjusted in the analysis, which may overestimate the absolute benefit of the drug. Subsequently, other RCTs were published including patients with a history of AMI and with standard drug treatment to which omega-3 fatty acids were added at different doses. The results of all of them were published as grouped outcomes in a meta-analysis[135] including a total of 14 double-blind clinical trials performed versus placebo with 20,485 patients. The conclusion was that supplementation with **omega 3 fatty acids does not reduce the risk of new cardiovascular events or mortality risk.**

Ezetimibe

There are no published clinical trials with this drug, or its association with statin, in patients with previous coronary events to evaluate its effectiveness in reducing cardiovascular morbidity and mortality.

The use of 80 mg of atorvastatin instead of atorvastatin 10 mg or simvastatin 20 mg showed a reduction in the risk of non-fatal re-infarction, and stroke; however, it presented an increased risk of serious adverse effects and treatment abandonment for adverse reactions in general. The use of atorvastatin 80 mg is recommended in patients with stable coronary disease who do not present characteristics that predispose to adverse effects from statins or risk of interactions.

It was demonstrated the efficacy and safety of moderate doses of statins and they are the first-line treatment, alone or in combination with ezetimibe, for patients who present characteristics that predispose to adverse effects from statins, for patients who do not tolerate high doses of statins and for those with whom the use of high doses is considered inappropriate.

In patients who are intolerant to statins, other lipid-lowering treatments will be considered individually and following advice of professionals with special knowledge and interest in the treatment of dyslipidemia.

Gemfibrozil showed a reduction in the risk of stroke in patients with coronary disease and low or slightly elevated levels of LDL cholesterol. Fibrates should not be considered first-line drugs in the lipid-lowering therapy for patients with previous coronary disease.

The use of omega-3 is not recommended in the lipid-lowering treatment for patients with coronary disease

4.3. Use of lipid-lowering drugs in patients with acute coronary syndrome

The immediate period after acute coronary syndrome (ACS) represents a critical stage of the coronary heart disease with a high risk of recurrent events and death due to occlusion of the vessel of vulnerable coronary plaques. In vitro experimental data indicate that in these patients, statins, in addition to reducing the levels of LDL, could have immediate beneficial effects by improving endothelial function of arteries, stabilizing plaques, decreasing platelet aggregation and thrombus formation and reducing vascular inflammation.

The question that arises with these patients is whether the early intensive statin therapy brings benefits in reducing cardiovascular morbidity and mortality. Among the studies aimed at answering this question, the most relevant are MIRACL[136] RCT, A to Z[137], PROVE-IT[26], IMPROVE-IT[65] and a Cochrane systematic review[138]:

- The MIRACL[136] trial was designed to test the hypothesis that treatment with atorvastatin 80 mg daily, started shortly after the onset of symptoms of unstable angina or non-Q wave AMI, reduces recurrent ischemic events and mortality in the phase immediately after the onset of symptoms. 3,086 patients were included and after 16 weeks of follow-up atorvastatin reduced the composite primary endpoint (death, nonfatal MI, cardiac arrest with resuscitation, recurrent symptomatic myocardial ischemia requiring re-hospitalization) compared to placebo, but in the limit significance (RR 0.84, 95% CI [0.7-1.00], p = 0.048). The reduction is mainly due to the decreased risk of recurrent angina requiring hospitalization and is not conclusive because the confidence interval includes the one.
- Similarly, A to Z study[137] aimed to evaluate the efficacy of early treatment therapy with simvastatin 40 mg daily for one month followed by simvastatin 80 mg versus placebo for 4 months followed by simvastatin 20 mg. 4,497 patients were included aged between 21 and 80 years, with ACS with or without ST elevation and without previous statin therapy. The primary endpoint was the composite of cardiovascular death, nonfatal MI, stroke, or readmission for ACS. After two years of follow-up, the early and intensive statin therapy showed no greater benefit than the less intense treatment (0.89 95% CI [0.77 to 1.04]).
- A Cochrane systematic review[138] was done including 18 trials and 14,303 patients with ACS comparing early statin therapy versus placebo or usual treatment in order to evaluate the benefits and risks of the statin therapy at 3-6 months and a year. The results of the meta-analysis showed a statistically significant reduction of events (death, myocardial infarction or stroke) in patients treated early with statin at a month, at 4 months and at a year. The only significant reductions were in the risks of stable angina at 4 months and revascularization at 12 months.
- The PROVE-IT[26] trial was designed to verify whether early treatment with moderate doses of statin (pravastatin 40 mg) was not clinically inferior to a more intensive statin therapy (atorvastatin 80 mg) in the prevention of mortality and major cardiovascular events in patients with ACS. After two years of follow-up, treatment with atorvastatin 80 mg reduced the incidence of events in the composite primary endpoint (all-cause death, myocardial infarction, unstable angina requiring re-hospitalization, revascularization procedures) mainly due to the reduction of recurrent angina and revascularization. This difference was significant after 6 months of treatment.
- The IMPROVE-IT[65] aimed to study the extra benefit provided by adding ezetimibe to simvastatin 40 mg treatment in patients with high-risk ACS with baseline levels of LDL-cholesterol below 100 mg/dl. After an average of 6 years follow-up, the combined treatment showed, compared to monotherapy with simvastatin 40 mg, a modest benefit (32.7% vs 34.7%; HR 0.94, 95% CI [0.89-0.99]) in the reduction of events, which was the main combined variable (cardiovascular mortality, myocardial infarction, hospitalization for unstable angina, coronary revascularization or stroke).

For ACS, early initiation of treatment with high-dose statin reduces the risk of recurrent ischemia and may reduce revascularization procedures, but does not confer benefit in the reduction of AMI or stroke. Regarding mortality, intensive statin therapy has not demonstrated a decrease in the short term and could be beneficial in long-term treatment (2 years).

High doses of statins increase liver and muscle adverse effects and treatment abandonment due to adverse effects. It should be kept in mind that most of the patients included in RCTs were selected patients since patients at high risk of adverse effects or drug interactions were excluded.

Therefore, taking into account the added benefit of using intensive doses, as well as the potential risk of statin use at high doses, the use of high doses in patients with ACS is

recommended provided patients do not present characteristics that predispose an adverse effect for statins[29]:

- Patients with multiple or serious comorbidities, including changes in renal, liver, thyroid or immunosuppression function.
- History of muscle pathology or haemorrhagic stroke.
- History of statin intolerance.
- Elevated levels of transaminases greater than 3 times the upper limit of normal.
- Use of concomitant medications that affect the metabolism of statins (Appendix 1 Interactions).
- People aged over 75 years.

In patients with acute coronary syndrome, early initiation of treatment with atorvastatin 80 mg is recommended except for patients with characteristics that predispose to adverse effects for statins or risk of interactions.

In patients with adverse effects associated with high doses of statin, a dose reduction or the use of statins at moderate doses associated with ezetimibe could be considered. The combination of simvastatin 40 mg and ezetimibe 10 mg has the best available evidence.

4.4. Use of lipid-lowering drugs for patients with non-cardioembolic ischemic stroke

Statins

Although there were doubts whether cholesterol is a risk factor for stroke (especially in patients over 60 years) and if the levels of plasma lipids can predict stroke[124,139] several meta-analyses showed the positive effect of statins in the primary prevention of stroke in patients who previously had coronary disease[140-142].

So far, the SPARCL[143] has been the only RCT designed to determine the efficacy of statin therapy in patients with recent stroke but no history of coronary disease. High doses of atorvastatin (80 mg daily) were used with a total of 4,731 patients, mean age 63 years, with stroke or transient ischemic attack in the preceding 6 months, without evidence of coronary artery disease and LDL-C > 100 mg / dl (mean LDL cholesterol of 132 mg/dl). Patients with suspected cardioembolic stroke were excluded, and also those with atrial fibrillation, patients with subarachnoid haemorrhage and those with characteristics that predispose to adverse effects with statins. After nearly five years of follow-up, the results showed that, **compared with placebo**, **atorvastatin 80 mg / day decreased the incidence of stroke by 1.9% in absolute terms** (NNT 52 95% CI [26-1303]) **and by 22% in relative terms** (HR 0.84, 95% CI [0.71 to 0.99]). **Major cardiovascular events were also reduced, but not total or cardiovascular mortality, all secondary endpoints of the study. On the contrary, there was an increase of 0.9% in absolute terms of brain haemorrhage** (HR 1.6, 95% CI [1.09-2.55]) in patients treated with intensive therapy and elevated transaminases, despite being a group of highly selected patients.

Later, **three meta-analyses**[144-146] were published that included, besides SPARCL data, data of subgroups of patients with stroke and / or previous **TIA** from clinical trials in patients with coronary heart disease or high CVR. **The results are in line with those obtained in the SPARCL, there was a reduction in the recurrence of ischemic stroke (0.88, 95% CI [0.78-0.99]) and cardiovascular events, but not in total mortality. This effect was partially counteracted by an increase in haemorrhagic stroke (1.73, 95% CI [1.19 to 2.50]).**

Moreover, the use of high doses of statins is associated with a higher incidence of serious adverse events and a higher percentage of treatment abandonment due to adverse effects. It should be kept in mind that most of the patients included in RCTs were selected patients and patients at high risk of adverse effects were excluded.

Therefore, taking into account the added benefit of using intensive doses, as well as the potential risk of using high dose statin, the use of high doses is recommended in patients with atherothrombotic ischemic stroke as long as patients do not present characteristics that predispose an adverse effect of statin[29]:

- Patients with multiple serious comorbidities or comorbidities, including changes in renal, liver, thyroid or immunosuppression function.
- History of muscle pathology or haemorrhagic stroke.
- History of intolerance to statins.
- Elevated levels of transaminase elevations greater than 3 times the upper limit of normal.
- Use of concomitant medications that affect the metabolism of statins (Appendix 1 Interactions).
- Patients aged over 75 years.

Fibrates

There is little information about the efficacy of fibrates in the secondary prevention of stroke and it is based mainly on **two small clinical trials with clofibrate compared to placebo.** Both trials are included in a Cochrane[146] review in which it was observed that there was no reduction in the risk of a new cerebrovascular event (1.48, 95% CI [0.94 to 2.30]).

In patients with a history of non-cardioembolic ischemic stroke and LDL cholesterol > 100 mg / dl, atorvastatin 80 mg showed to reduce the recurrence of ischemic stroke and the risk of cardiovascular events. In these patients we recommend starting treatment with high-dose statin (atorvastatin 80 mg) provided they do not exhibit characteristics that predispose to adverse effects from statins.

There is no evidence of the benefits of using statins in patients older than 80 years, or in patients with low levels of LDL, or with lower doses of statin.

The use of fibrates on lipid-lowering therapy for secondary prevention of stroke is not recommended.

CHARACTERISTICS OF THE AVAILABLE TREATMENTS

1. Hydroxymethylglutaryl CoA reductase inhibitors (statins)

Statins inhibit the enzyme hydroxymethylglutaryl CoA reductase involved in endogenous cholesterol synthesis which results in a decrease in plasma LDL-C levels. Statins are the most effective drugs at reducing the levels of LDL-C[147], between 20% and 60%. They modestly raise HDL-C (5-10%) and their action on this is not dose dependent and does not correlate with baseline levels. Statins cause a moderate decrease in triglycerides (10-35%).

Many pleiotropic effects of the statins have been described (besides the decrease in LDL-C): on endothelial function, antioxidants, stabilizers of arterial plaque and anti-inflammatory among others. In a meta-regression analysis[148] including studies with different pharmacological and non-pharmacological treatments, the regression lines with or without statins were similar. They demonstrated a relationship between a reduction in LDL cholesterol and cardiovascular events. Pleiotropic effects may not contribute a clinically significant additional effect to the reduction of cholesterol.

There are no direct comparisons of equivalent doses of the different types of statins regarding the reduction in cardiovascular morbidity and mortality in patients without previous events. The indirect comparisons regarding the reduction in events suggest no significant difference between the most and the least potent statins[55]. **Fluvastatin and pitavastatin are not included in these analyses because there are no published RCTs on morbidity and mortality.**

As for the reduction in cholesterol levels, the results of clinical studies and meta-analyses[149-151] showed that per milligram, rosuvastatin is the statin that reduces the highest percentage of LDL cholesterol at the authorized doses. This is referred to the average population, since the response to statins has a large inter-individual variability. In general, statins administered at therapeutically equivalent doses achieve similar reductions in cholesterol; the reduction in LDL-C is higher when the statin dose increases, but doubling statin dose results in a further reduction in LDL between 5 and 7%. Higher levels of HDL-C and reduced triglyceride levels are similar at an equivalent dose of the active principles.

Statins should be administered at night in single doses as high cholesterol synthesis is at night and their highest clinical efficacy has been proven[152]. Once clinically effective and well tolerated doses have been achieved, treatment should not be suspended.

Pravastatin or rosuvastatin are an alternative for those patients who can anticipate interactions with other drugs metabolized by cytochrome P450 (Appendix 1 Interactions).

Regarding potency, in terms of percentage reduction in LDL-C achieved with different statins and different doses, not all scientific literature is unanimous. Probably due to the significant inter-individual variability observed in clinical trials. The results of the different meta-analyses and RCTs included in the CPG, are therefore, a mean estimate and do not coincide with each other.

Safety

Statins are safe and generally well tolerated drugs. The adverse reactions are more likely to occur when they are used at high doses or concomitantly with certain medications[153] that may interfere with the metabolism and increase plasma levels.

The use of high doses of statins has been associated with an increased incidence of adverse effects that result in treatment abandonment (NNH 47, 95% CI [35-69]) compared with lower doses[154,155]. If patients do not tolerate high doses of statins, they should be treated with the maximum tolerated dose as any dose of statin reduces the CVR.

- **Muscle Toxicity,** is an adverse effect of statin. Myalgias are relatively common, 5-10% of patients in statin treatment, although it is possible that many of them are unrelated to the use of statins, at least when these are used at average doses. However, the incidence of severe reactions, such as myopathy / myositis and rhabdomyolysis are rare at standard doses. This risk is increased when high doses are used in patients with risk factors and when statins are used in combination with other drugs that interact with statins or lead to myotoxicity effects. Special caution should be taken in patients with predisposing factors for rhabdomyolysis:
  - People aged > 80 years.
  - Renal insufficiency. .
  - Uncontrolled hypothyroidism.

– Personal or family history of hereditary muscular disorders.

– Previous history of muscular toxicity with a statin or fibrate.

– Alcoholism.

In a published analysis[156] of reports of suspected muscle side effects related to the use of statins (period 2005-2011, about 150,000) to FDA Safety Information and Adverse Event Reporting Program, it was observed that in general, the higher the potency of the statin the higher the risk of muscle side effects. The statin associated with increased risk of muscle side effects was rosuvastatin; atorvastatin and simvastatin showed an intermediate risk, while pravastatin and lovastatin had the lowest rates of risk. The exception was fluvastatin which, being the least potent statin was associated with an increased risk of muscle side effects, only surpassed by the risk associated with rosuvastatin.

Recently the FDA[157] and MHRA[158] have limited the indications of simvastatin 80 mg to selected patients. These alerts have been motivated by the discovery found in SEARCH[24] trial in which there was a higher incidence of myopathy, mainly in the first year of treatment, in patients treated with simvastatin 80 mg compared with those who were treated with simvastatin 20 mg (0.9% vs 0.03%). While the FDA recommends not starting new treatment with simvastatin 80 mg, the English admit that the dose of 80 mg can be used in patients at high cardiovascular risk by monitoring the safety of treatment.

If muscle side effects appear associated with statin therapy and phospho creatine kinase increases 5-10 times the normal value, statin therapy should be discontinued. If the alterations disappear, and after reconsidering the indication, the statin therapy may be reintroduced at a lower dose or the statin may be changed to another one with less risk of side effects. In the case of persistent elevations in transaminases levels 3 times above the normal value and if the relationship of this elevation with the statin is confirmed, the statin therapy should not be reintroduced.

- **Hepatic adverse effects**. Moderate elevations (less than 3 times the upper limit of normal) in serum transaminases usually appear shortly after starting treatment. They are usually transient, not usually accompanied by other symptoms and treatment discontinuation may not be necessary.

  Treatment with intensive therapy compared with moderate doses of statins has been associated with an increased risk of transaminase elevations, but it has not been associated with an increase in liver disease. Elevations greater than 3 times the upper limit of normal may be found in 1% of patients at low or intermediate doses, and in 2-3% of those with high doses.

  All statins are contraindicated in active liver disease, including unexplained or persistent elevations of serum transaminases when the level is 3 times above the upper limit of normal.

  In the case of persistent elevations in transaminases 3 times above the normal value, if the relationship with the statin is confirmed, the statin therapy should not be reintroduced.

- **Risk of haemorrhagic stroke**: In a post-hoc analysis[143,159] of stroke subtypes performed from SPARCL RCT, whose aim was to study the effectiveness of intensive statin therapy in secondary prevention of stroke, an increase in haemorrhagic stroke was found (HR 1.6, 95% CI [1.08-2.55]) in patients treated with atorvastatin 80 mg compared to placebo. This increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at the time of inclusion in the study. For patients with prior haemorrhagic stroke or lacunar infarct, the benefit-risk balance of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic stroke should have to be carefully considered before starting treatment. The meta-analyses[144-146], along with the SPARCL, which include data of subgroups of patients with stroke and / or prior TIA from clinical trials in patients with coronary heart disease or high CVR (primarily HPS), found an increase in haemorrhagic stroke in line with those obtained in the SPARCL.

  By contrast, some meta-analyses[161] recently published did not show that statin therapy is associated with an increased risk of haemorrhagic stroke, regardless of the statin dose or indication.

- Increase in the **risk of diabetes**. Statins may increase the risk of diabetes mellitus in patients at risk of developing the disease, so these patients need to be monitored. However, the benefit-risk balance of statins remains clearly favourable: a new case of DM per 225 patients, exceeded by the benefit of preventing 5.4 cardiovascular events per 225 patients[162].

  After the publication of a meta-analysis[162] which found that statin therapy was associated with a slight increase in the occurrence of diabetes, the European Medicines Agency conducted an assessment of this risk based on all available data. After the analysis[163], the conclusion was that there is sufficient evidence to support the causal relationship between statin use and the onset of diabetes. However, this increased risk seems to be confined mainly to patients at risk of developing diabetes (increased fasting glucose before starting treatment, history of hypertension, increased triglycerides or high BMI) and therefore, control of these patients is recommended. Although it was found that the risk of developing diabetes is increased in susceptible patients, available studies clearly show that the statin use reduces major cardiovascular events in these patients.

  An analysis[164] of combined data from five trials showed that high-dose statin was associated with an increased risk of diabetes compared with moderate doses.

2. Fibrates

Monotherapy

Fibrates activate PPAR-alpha which results in a noticeable decline in VLDL production and an increase in the removal of VLDL. Last generation fibrates also inhibit the enzyme hydroxymethylglutaryl CoA reductase with less intensity than statins.

Fibrates cause a 10% decrease in total cholesterol and 10-20% of LDL. They lower triglycerides by 20%-60% and raise HDL by about 15%.

A meta-analysis[165] of 18 RCTs versus placebo designed to assess morbidity showed that in all patients, both in primary and secondary prevention, treatment with fibrates may reduce the risk of cardiovascular events. This decrease is mainly due to the reduction in coronary events, but it is lower than that achieved with statins. As the European Medicines Agency recommended in an evaluation of the risk-benefit ratio of these drugs[166], **fibrates are not used as first-line treatment, except in patients with severe hypertriglyceridemia or primary prevention patients who cannot use statins.**

Statins + fenofibrate or bezafibrate:

The combination of a fibrate with a statin obtain a more complete lipid profile control because besides reducing the levels of LDL-cholesterol, it lowers triglycerides and raises HDL cholesterol. However, as shown in the ACCORD RCT[85], a tight control of diabetic dyslipidemia combining a fibrate with a statin did not result in a greater benefit in reducing cardiovascular morbidity compared to control of LDL levels obtained with a statin.

Safety

The most common adverse effects associated with the use of fibrates are gastrointestinal (abdominal pain, nausea, vomiting, diarrhoea, flatulence), they increase the risk of cholelithiasis, so caution should be taken in patients who already have it. Similarly to statins, moderate transaminase elevations (less than 3 times the upper limit of normal) may occur. Muscle toxicity cases may occur while the incidence of more severe reactions myopathy / myositis and rhabdomyolysis is rare

The combination of fibrate and statin increases the risk of muscle toxicity. Gemfibrozil should not be combined with statin due to high risk of severe myopathy. The use of the combination of statin and fenofibrate or bezafibrate requires observing certain precautions and analytical monitoring of CPK at baseline and after the subsequent introduction of any medicine. The combination should be avoided in patients with kidney or thyroid disease, maximum dose of statin should not be reached and administration of each drug should be separated at least at 8-12 hours.

3. Ezetimibe

This drug selectively inhibits the transporter involved in intestinal cholesterol absorption from the diet and hepatic synthesis as well as from vegetable cholesterol esters. It has no effects on the absorption of triglycerides, fatty acids, bile acids or fat-soluble vitamins[167]. It is administered in a single daily dose of 10 mg. **Higher doses do not increase its effectiveness**.

Monotherapy

It has been shown in short-term clinical trials versus placebo that this drug reduces LDL cholesterol by 18.6% (95% CI [19.7% to 17.4%])[168]. This decrease causes an increase in the activity of HMG-CoA synthase and reductase, so its effect is greater when administered with a statin.

In **monotherapy** and as an adjunct to diet, it is only authorized in homozygous sitosterolemia or in patients with primary hypercholesterolemia in which a statin is considered inappropriate or not tolerated. Unlike statins and fibrates, **it has not been shown to reduce cardiovascular morbidity and mortality in monotherapy** and its clinical impact on CVD is unknown.

Combination with statins

In **combination with statins** produce an additional decrease in cholesterol of 13.9% (95% CI [14.9-13]) to the one obtained with statins[168].

The combination with statin is indicated in patients who have not reached the desired reduction in LDL-C despite having reached the maximum tolerated dose of statins. However, **there are no clinical trials that demonstrate the benefit of the combination in the reduction of clinically relevant cardiovascular events, except in patients with chronic kidney disease stages G3b a G5[169, 170] and in patients with SCA[65].**

Furthermore, in an attempt to find new indications for statins, some clinical trials have been conducted to study the effect of the combination of ezetimibe with statins versus placebo in reducing cardiovascular morbidity in situations where the effectiveness of statins was not clearly demonstrated. This is the case of SEAS RCT[171] conducted in patients with mild to moderate aortic stenosis without indication for lipid-lowering therapy. After more than 4 years of follow-up, no benefit of the combination therapy versus placebo was found in reducing cardiovascular events in the composite primary endpoint (valvular illness and atherosclerotic disease related events) or on the progression of stenosis.

Safety

Ezetimibe is generally well tolerated. The most common side effects include headache, abdominal pain and diarrhoea. When used as monotherapy, myalgia and rarely rhabdomyolysis have been reported.

In combination with statins has a side effect profile similar to that of statins

4. Resins as bile acid sequestrants

Efficacy

These drugs act as bile acid sequestrants preventing bile acids from binding to cholesterol and thereby avoiding cholesterol intestinal absorption.

They produce an average decrease of 18% in total cholesterol and 24% in LDL. They increase HDL by 6%-8% but with the disadvantage of increasing triglycerides by 10%.

Safety

Resins are particularly safe because their systemic absorption is less than 1%, but **they have gastrointestinal side effects (constipation, bowel sounds, and fullness), generally mild but frequent, making them difficult to tolerate.**

They should be taken with liquid before meals and **may interfere with the absorption of some drugs,** so they should be administered separately from other drugs at least 4 hours.

Resins are not drugs **of first-line treatment and, as fibrates, their use is recommended in primary prevention for patients who cannot use statins.**

5. Omega-3 polyunsaturated fatty acids

Efficacy

The ethyl esters of omega-3 fatty acids, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) are essential fatty acids present in different types of fish. In the short term, they are known to reduce triglyceride levels, which can increase levels of LDL-cholesterol in some patients with hypertriglyceridemia and produce small HDL- cholesterol increases, significantly lower than those observed after administration of fibrates[172].

Drug administration has been associated with the elevation of nitric oxide synthesis, improvement in endothelial function and reduction of the progression of atheromatous plaque which is stabilized. It is also associated with a reduction of platelet aggregation, increase in fibrolysis and thromboxane A2 decrease (causing an increase in bleeding time).

The official indications[172] for the drug marketed in Spain are:

- Endogenous Hypertriglyceridemia as a supplement to the diet when dietary measures alone are insufficient to produce an adequate response: type IV in monotherapy, IIb/III types added to statins when control of triglycerides is insufficient.
- In secondary prevention of myocardial infarction, as adjunctive therapy in combination with other drugs of reference.

This latter indication for the drug is not funded by the NHS.

As discussed in the section on secondary prevention, so far, available evidence shows that supplementation with omega 3 fatty acids in patients with a history of myocardial infarction has not been shown to reduce the risk of mortality and new cardiovascular events[135].

Safety

The most common side effects are gastrointestinal discomfort with reflux and belching with taste and smell of fish, nausea and abdominal bloating. They may also cause acne and skin eczema. The administration of 4 g of EPA / DHA has been associated with a moderate increase in bleeding.

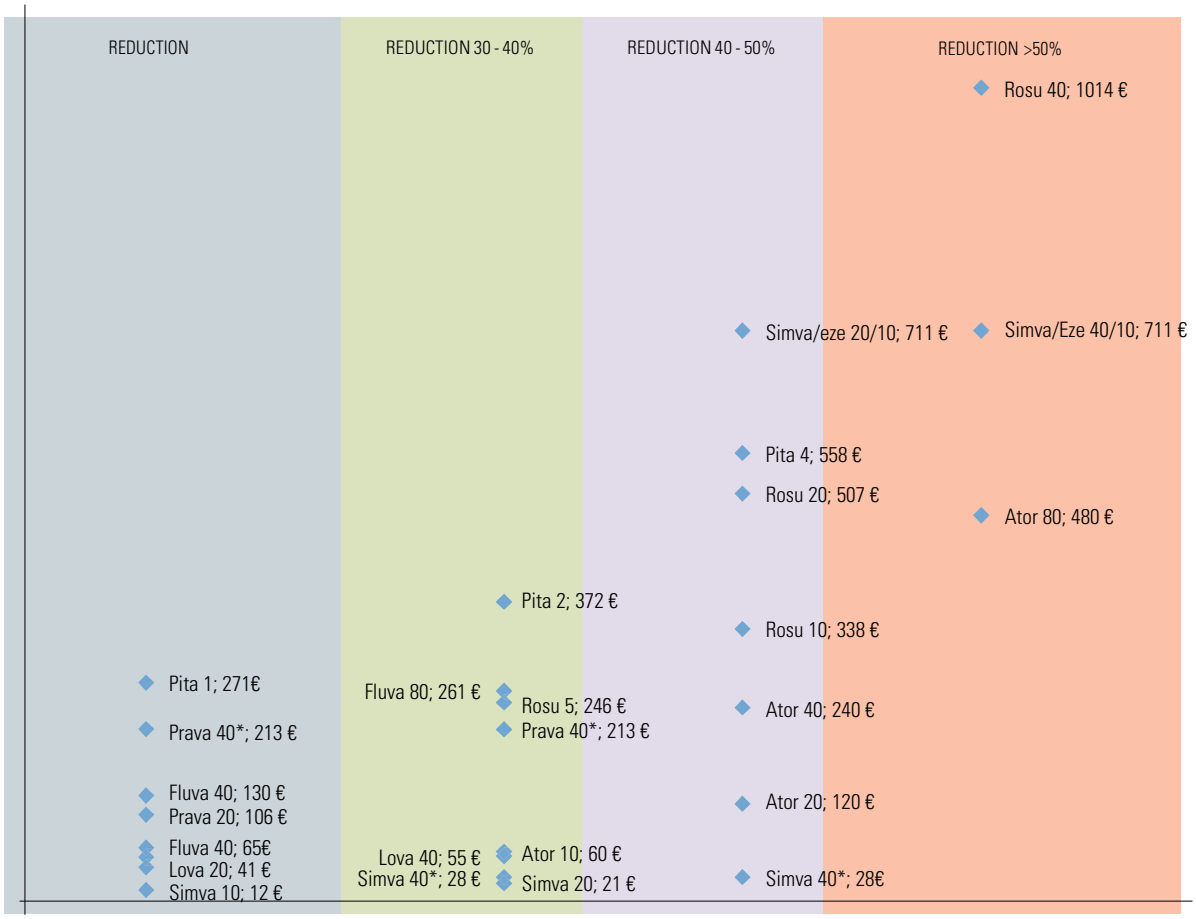
After administration, INR needs to be monitored and also transaminase if high doses of the drug are used. It should not be administered in patients with exogenous hypertriglyceridemia, children, pregnant or lactating women.

COST ANALYSIS

There are no clinical trials in primary prevention comparing statins at equipotent doses in reducing cardiovascular events or in terms of safety. Only in secondary prevention, trials have been published comparing high-dose statin (simvastatin 80 mg, atorvastatin 80 mg) versus statins at low to moderate doses (20 mg simvastatin, atorvastatin 10 mg).

There is no scientific evidence to support, either for reduction in events or for safety, the selection of a particular active ingredient. So, the annual cost of different statins is shown in terms of LDL reduction intervals extracted from the different meta-analyses and clinical trial data[29,149-151]. To calculate the average cost, the prices of the various specialties to March 2014 have been used

In his graph, it can be easily visualized the molecules with the lowest annual cost at the same percentage reduction in LDL.



* Data from scientific literature do not coincide.

RECOMMENDATIONS FOR THE USE OF LIPID-LOWERING DRUGS IN THE COMUNIDAD DE MADRID

Statins **are considered the drugs of choice** for the treatment of dyslipidemia. These recommendations are based on (a) the clinical efficacy demonstrated in RCTs in the reduction of cardiovascular events and mortality in populations of high CVR, (b) existing safety analyses based on patient characteristics and (c) cost analysis.

These are the first-line treatments to be considered:

- **In primary prevention patients without diabetes, type 2 diabetes patients with no other greater CVRF or target organ damage** and when their level of CVR is calculated according to the recommended tables, simvastatin 20 mg daily will be used as first choice.

  If the reductions do not reach the recommended percentage once non-adherence to drug treatment and to hygienic-dietary measures have been discarded, simvastatin dose will be doubled or treatment with atorvastatin 20 mg will be initiated.

- **In patients with type 1 DM or type 2 DM with other greater CVRF or target organ damage**, atorvastatin 20 mg or simvastatin 40 mg. is recommended as initial therapy

  If reductions do not reach the recommended percentage once non-adherence to drug treatment and to hygienic-dietary measures have been discarded, the dose of atorvastatin will be doubled.

- In **patients with severe non-genetic hyperlipidemia** simvastatin 40 mg is recommended as initial treatment.

  If reductions do not reach the recommended percentage once non-adherence to drug treatment and to hygienic-dietary measures have been discarded, atorvastatin 40 mg is recommended as initial treatment.

- In patients **with CKD stage G3b to G5**, simvastatin / ezetimibe is recommended at fixed dose of 20 mg / 10 mg and atorvastatin 20 mg as an alternative.

- In patients **with intermittent claudication of atherothrombotic origin** simvastatin 40 mg is recommended as initial treatment

- In patients in secondary, coronary or cerebrovascular prevention, early treatment with atorvastatin 80 mg will be initiated, except in those patients with higher probability of risk of side effects or interactions. In these ones, treatment will be initiated with atorvastatin 40 mg, simvastatin 40 mg or rosuvastatin 20 mg.

BIBLIOGRAPHY

1. INE. Defunciones según la causa de muerte. Año 2012, www.ine.es/prensa/np830.pdf.

2. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M. European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis, 2012.

3. Nichols M, Townsend N, Scarborough P, et al. Cardiovascular disease in Europe: epidemiological update. Eur Heart J 2013; 34: 3028–3034.

4. Grau M, Elosua R, Cabrera de León A, et al. Factores de riesgo cardiovascular en España en la primera década del siglo XXI : análisis agrupado con datos individuales de 11 estudios de base poblacional, estudio DARIOS. Rev Esp Cardiol 2011; 64: 295–304.

5. Utilización de medicamentos hipolipemiantes en España durante el periodo 2000-2012. Agencia Española del Medicamento, http://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/hipolipemiantes-2000-2012.pdf (accessed 6 February 2014).

6. Brotons Cuixart C, Mauricio D, Rodríguez Artalejo F, et al. Adaptación española de la guía europea de prevención cardiovascular. Rev Esp Salud Pública 2004; 78: 435–438.

7. San Vicente Blanco R, Perez Irazusta I, Ibarra Amarica J, et al. Guía de práctica clínica sobre el manejo de los lípidos como factor de riesgo cardiovascular, www.guiasalud.es/GPC/GPC_433_Lipidos_compl_cast.pdf.

8. Dirección General de Salud Pública y Alimentación. Plan de Salud Cardiovascular de la Comunidad de Madrid. Comunidad de Madrid, 2007.

9. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011; 32: 1769–1818.

10. Simón BB, Sánchez IP, Buitrago F, et al. Comparación entre la tabla del SCORE y la función de Framingham-REGICOR en la estimación del riesgo cardiovascular en una población urbana seguida durante 10 años. Med Clin Barc 2006; 127: 368–73.

11. Bulugahapitiya U, Siyambalapitiya S, Sithole J, et al. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med J Br Diabet Assoc 2009; 26: 142–148.

12. Cano JF, Baena-Diez JM, Franch J, et al. Long-term cardiovascular risk in type 2 diabetic compared with nondiabetic first acute myocardial infarction patients: a population-based cohort study in southern Europe. Diabetes Care 2010; 33: 2004–2009.

13. Timbie JW, Hayward RA, Vijan S. Variation in the net benefit of aggressive cardiovascular risk factor control across the US population of patients with diabetes mellitus. Arch Intern Med 2010; 170: 1037–1044.

14. Chamnan P, Simmons RK, Sharp SJ, et al. Cardiovascular risk assessment scores for people with diabetes: a systematic review. Diabetologia 2009; 52: 2001–2014.

15. Marrugat J, Solanas P, D'Agostino R, et al. Estimación del riesgo coronario en España mediante la ecuación de Framingham calibrada. Rev Esp Cardiol 2003; 56: 253–261.

16. Marrugat J, Subirana I, Comín E, et al. Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA Study. J Epidemiol Community Health 2007; 61: 40–47.

17. Marrugat J, Vila J, Baena-Díez JM, et al. Validez relativa de la estimación del riesgo cardiovascular a 10 años en una cohorte poblacional del estudio REGICOR. Rev Esp Cardiol 2011; 64: 385–394.

18. Guijarro Herraiz C; Brotons Cuixart C; Camarelles Guillen F; Medrano Albero M.J.; Moreno Gonzalez J.L. Del Río Ligorit A; Pintó Sala X; Rodriguez Mañas L; Suárez Fernández C; Villar Alvarez F. Primera Conferencia Española de Prevención y Promoción de la Salud en la Práctica Clínica. Prevención cardiovascular. Madrid: Ministerio de Sanidad y Consumo, http://www.msc.es/profesionales/saludPublica/prevPromocion/conferenciaPPS/conferencia.htm (2007).

19. Lobos-Bejarano JM, Royo-Bordonada MA, Brotons-Cuixart C. Uso de tablas de riesgo cardiovascular en personas mayores. Med Clínica 2005; 125: 438; author reply 438–439.

20. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623–1630.

21. Aronow WS, Ahn C. Risk factors for new coronary events in a large cohort of very elderly patients with and without coronary artery disease. Am J Cardiol 1996; 77: 864–866.

22. Krumholz HM, Seeman TE, Merrill SS, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. JAMA J Am Med Assoc 1994; 272: 1335–1340.

23. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA J Am Med Assoc 2005; 294: 2437–2445.

24. Armitage J, Bowman L, Wallendszus K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010; 376: 1658–1669.

25. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425–1435.

26. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495–1504.

27. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143–3421.

28. NICE. CG 181. Lipid modification Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Full Clinical guideline Methods, evidence and recommendations. London: Royal College of General Practitioners (UK), http://www.nice.org.uk/guidanceNBK55501/ (2014, accessed 5 August 2014).

29. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013.

30. Knoops KTB, Groot de LC, Fidanza F, et al. Comparison of three different dietary scores in relation to 10-year mortality in elderly European subjects: the HALE project. Eur J Clin Nutr 2006; 60: 746–755.

31. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013; 368: 1279–1290.

32. Rees K, Dyakova M, Wilson N, et al. Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev 2013; 12: CD002128.

33. Williams PT, Thompson PD. Walking Versus Running for Hypertension, Cholesterol, and Diabetes Mellitus Risk Reduction. Arterioscler Thromb Vasc Biol 2013; 33: 1085–1091.

34. Banegas JR, Díez Gañán L, González Enríquez J, et al. La mortalidad atribuible al tabaquismo comienza a descender en España. Med Clínica 2005; 124: 769–771.

35. Gomez-jerique J, Fuentes, J. A.G, de la Camara, A.G. Dieta y riesgo cardiovascular en Espana (DRECE II). Descripcion de la evolucion del perfil cardiovascular. Med Clínica 2000; 115: 726–729.

36. Mantilla T, Álvarez A, Blasco M, et al. Dislipemias: manejo de las dislipemias en atención primaria, http://www.elmedicointeractivo.com/ap1/emiold/documentos/anuarioap2001/106-114.pdf (2007).

37. Alfonso F, Segovia J, Heras M, et al. Prevención cardiovascular: ¿siempre demasiado tarde? Rev Esp Cardiol 2008; 61: 291–298.

38. Powell KE, Thompson PD, Caspersen CJ, et al. Physical activity and the incidence of coronary heart disease. Annu Rev Public Health 1987; 8: 253–287.

39. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. Am J Epidemiol 1990; 132: 612–628.

40. Stensel D. Primary prevention of CVD: physical activity. Clin Evid 2007; pii:0218.

41. Manson JE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med 2002; 347: 716–725.

42. Douketis JD, Macie C, Thabane L, et al. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. Int J Obes 2005 2005; 29: 1153–1167.

43. Jenkins DJ, Kendall CW, Vuksan V. Viscous fibers, health claims, and strategies to reduce cardiovascular disease risk. Am J Clin Nutr 2000; 71: 401–402.

44. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333: 1301–1307.

45. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA J Am Med Assoc 1998; 279: 1615–1622.

46. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361: 1149–1158.

47. ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA J Am Med Assoc 2002; 288: 2998–3007.

48. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7–22.

49. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359: 2195–2207.

50. Center for Drug Evaluation and Research. FDA U.S. Food and Drug Administration. Crestor. Medical Review(s)., http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (2010).

51. Kaul S, Morrissey RP, Diamond GA. By Jove! What is a clinician to make of JUPITER? Arch Intern Med 2010; 170: 1073–1077.

52. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 2011; 64: 407–415.

53. Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 2010; 303: 1180–1187.

54. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 2009; 338: b2376.

55. Tonelli M, Lloyd A, Clement F, et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. CMAJ Can Med Assoc J J Assoc Medicale Can 2011; 183: E1189–1202.

56. Ray KK, Seshasai SRK, Erqou S, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med 2010; 170: 1024–1031.

57. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev Online 2013; 1: CD004816.

58. Mills EJ, Rachlis B, Wu P, et al. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol 2008; 52: 1769–1781.

59. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380:

581–590.

60. Hinchliffe A. SEWC. South East Wales Cardiac Network - Patient adherence to treatment with Statins for the prevention of cardiovascular disease, http://www.wales.nhs.uk/sites3/docmetadata.cfm?orgid=490&id=170387 (accessed 9 August 2012).

61. NICE. CG76 Medicines adherence: full guideline. NICE, http://www.nice.org.uk/ (accessed 9 August 2012).

62. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987; 317: 1237–1245.

63. The Lipid Research Clinics Coronary Primary Prevention Trial results. Reduction in incidence of coronary heart disease. JAMA J Am Med Assoc 1984; 251: 351–364.

64. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181–2192.

65. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372: 2387–2397.

66. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci AMS 2015; 11: 1–23.

67. Walsh JME, Pignone M. Drug treatment of hyperlipidemia in women. JAMA J Am Med Assoc 2004; 291: 2243–2252.

68. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006; 368: 1155–1163.

69. Petretta M, Costanzo P, Perrone-Filardi P, et al. Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis. Int J Cardiol 2010; 138: 25–31.

70. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol 2009; 25: 567–579.

71. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. Circulation 2011; 123: 1243–1262.

72. Psaty BM, Koepsell TD, Manolio TA, et al. Risk ratios and risk differences in estimating the effect of risk factors for cardiovascular disease in the elderly. J Clin Epidemiol 1990; 43: 961–970.

73. Schatz IJ, Masaki K, Yano K, et al. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. Lancet 2001; 358: 351–355.

74. Clarke R, Emberson JR, Parish S, et al. Cholesterol fractions and apolipoproteins as risk factors for heart disease mortality in older men. Arch Intern Med 2007; 167: 1373–1378.

75. Packard CJ, Ford I, Robertson M, et al. Plasma lipoproteins and apolipoproteins as predictors of cardiovascular risk and treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Circulation 2005; 112: 3058–3065.

76. FDA. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. U.S. Food and Drug Administration, http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm (2012, accessed 27 March 2007).

77. Zhao YY, Weir MA, Manno M, et al. New fibrate use and acute renal outcomes in elderly adults: a population-based study. Ann Intern Med 2012; 156: 560–569.

78. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685–696.

79. Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care 2006; 29: 1478–1485.

80. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; 361: 2005–2016.

81. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371: 117–125.

82. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366: 1849–1861.

83. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010; 362: 1563–1574.

84. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011; 123: 2292–2333.

85. Mantilla Morató T, Alonso R, Mata P. Diagnóstico y tratamiento de las hiperlipemias familiares. Atencion Primaria Soc Esp Med Fam Comunitaria 2004; 34: 557–564.

86. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012; 33: 1635–1701.

87. Real Decreto 1348/2003, de 31 de octubre, Boletín Oficial del Estado número 264, del 4 de noviembre de 2003.

88. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA J Am Med Assoc 1987; 257: 2176–2180.

89. Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med 1979; 90: 85–91.

90. Gil M, Martí H, Elosúa R, et al. Análisis de la tendencia en la letalidad, incidencia y mortalidad porinfarto de miocardio en Girona entre 1990 y 1999. Rev Esp Cardiol 2007; 60: 349–356.

91. Marrugat J, Arboix A, García-Eroles L, et al. Estimación de la incidencia poblacional y la mortalidad de la enfermedad cerebrovascular establecida isquémica y hemorrágica en 2002. Rev Esp Cardiol 2007; 60: 573–580.

92. Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. Arterioscler Thromb Vasc Biol 2005; 25: 1463–1469.

93. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992; 326: 381–386.

94. Aung PP, Maxwell HG, Jepson RG, et al. Reducción del nivel de lípidos para la enfermedad arterial periférica de los miembros inferiores (Revisión Cochrane traducida). Cochrane Database Syst Rev Online 2007; CD000123.

95. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg 2007; 45: 645–654

96. Meade T, Zuhrie R, Cook C, et al. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. BMJ 2002; 325: 1139.

97. Grupo de Trabajo de Diagnóstico y Tratamiento de las Enfermedades Arteriales Periféricas, de la Sociedad Europea de Cardiología (ESC). Guía de práctica clínica de la ESC sobre diagnóstico y tratamiento de las enfermedades arteriales periféricas. Rev Esp Cardiol; 65: 172.e1–e57.

98. Rooke TW, Hirsch AT, Misra S, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J

Am Coll Cardiol 2013; 61: 1555–1570.

99. Xu M, Yuan G, Wei F. Effect of atorvastatin in patients with chronic heart failure – insights from randomized clinical trials. Arch Med Sci 2010; 6: 866–873.

100. Dobre D, Rossignol P, Murin J, et al. Statin therapy and clinical outcomes in myocardial infarction patients complicated by acute heart failure: insights from the EPHESUS trial. Eur J Heart Fail 2013; 15: 221–227.

101. Gastelurrutia P, Lupón J, de Antonio M, et al. Statins in heart failure: the paradox between large randomized clinical trials and real life. Mayo Clin Proc Mayo Clin 2012; 87: 555–560.

102. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007; 357: 2248–2261.

103. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372: 1231–1239.

104. Lipinski MJ, Cauthen CA, Biondi-Zoccai GGL, et al. Meta-analysis of randomized controlled trials of statins versus placebo in patients with heart failure. Am J Cardiol 2009; 104: 1708–1716.

105. Zhang S, Zhang L, Sun A, et al. Efficacy of statin therapy in chronic systolic cardiac insufficiency: a meta-analysis. Eur J Intern Med 2011; 22: 478–484.

106. Go AS, Bansal N, Chandra M, et al. Chronic Kidney Disease and Risk of Presenting with Acute Myocardial Infarction versus Stable Exertional Angina in Adults with Coronary Heart Disease. J Am Coll Cardiol 2011; 58: 1600–1607.

107. NICE. CG 182: Chronic kidney disease (partial update). Early identification and management of chronic kidney disease in adults in primary and secondary care. Methods, evidence and recommendations. London: Royal College of Physicians, http://www.nice.org.uk/ (2014).

108. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375: 2073–2081.

109. Wen CP, Cheng TYD, Tsai MK, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. Lancet 2008; 371: 2173–2182.

110. Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012; 380: 807–814.

111. Appel GB, Radhakrishnan J, Avram MM, et al. Analysis of metabolic parameters as predictors of risk in the RENAAL study. Diabetes Care 2003; 26: 1402–1407.

112. Strippoli GFM, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ 2008; 336: 645–651.

113. Sandhu S, Wiebe N, Fried LF, et al. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol JASN 2006; 17: 2006–2016.

114. Asselbergs FW, Diercks GFH, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004; 110: 2809–2816.

115. Palmer SC, Craig JC, Navaneethan SD, et al. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012; 157: 263–275.

116. Upadhyay A, Earley A, Lamont JL, et al. Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012; 157: 251–262.

117. Hou W, Lv J, Perkovic V, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Eur Heart J 2013; 34: 1807–1817.

118. The Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD. Kidney Int Suppl 2014; 3.

119. Center for Drug Evaluation and Research, Food and Drug Administration. New Drug Application 21-687/S-039: VYTORIN ® (ezetimibe/simvastatin), www.fda.gov.

120. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005; 353: 238–248.

121. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009; 360: 1395–1407.

122. Holdaas H, Fellström B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet 2003; 361: 2024–2031.

123. 4S Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–1389.

124. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996; 335: 1001–1009.

125. LIPID Study Group T. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998; 339: 1349–1357.

126. A systematic review and economic evaluation of statins for the prevention of coronary events - NIHR Health Technology Assessment programme: Executive Summaries - NCBI Bookshelf, http://www.ncbi.nlm.nih.gov/books/NBK62291/ (accessed 17 April 2012).

127. Spector R, Snapinn SM. Statins for secondary prevention of cardiovascular disease: the right dose. Pharmacology 2011; 87: 63–69.

128. High dose versus standard dose statins in stable coronary heart disease. Ther Initiat Evid Based Drug Ther, http://ti.ubc.ca/TherapeuticsLetter (2012).

129. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999; 341: 410–418.

130. The Bezafibrate Infarction Prevention (BIP) study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. Circulation 2000; 102: 21–27.

131. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999; 354: 447–455.

132. Galan P, Kesse-Guyot E, Czernichow S, et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ 2010; 341: c6273.

133. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010; 363: 2015–2026.

134. Rauch B, Schiele R, Schneider S, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation 2010; 122: 2152–2159.

135. Kwak SM, Myung S-K, Lee YJ, et al. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med 2012; 172: 686–694.

136. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA J Am Med Assoc 2001; 285: 1711–1718.

137. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA J Am Med Assoc 2004; 292: 1307–1316.

138. Vale N, Nordmann AJ, Schwartz GG, et al. Statins for acute coronary syndrome. Cochrane Database Syst Rev Online 2011; CD006870.

139. Patel A, Woodward M, Campbell DJ, et al. Plasma lipids predict myocardial infarction, but not stroke, in patients with established

cerebrovascular disease. Eur Heart J 2005; 26: 1910–1915.

140. O'Regan C, Wu P, Arora P, et al. Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am J Med 2008; 121: 24–33.

141. Henyan NN, Riche DM, East HE, et al. Impact of statins on risk of stroke: a meta-analysis. Ann Pharmacother 2007; 41: 1937–1945.

142. Atkins D, Psaty BM, Koepsell TD, et al. Cholesterol reduction and the risk for stroke in men. A meta-analysis of randomized, controlled trials. Ann Intern Med 1993; 119: 136–145.

143. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006; 355: 549–559.

144. Vergouwen MDI, de Haan RJ, Vermeulen M, et al. Statin treatment and the occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease. Stroke J Cereb Circ 2008; 39: 497–502.

145. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol 2009; 8: 453–463.

146. Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev Online 2009; CD002091.

147. Miguel García F, García Ortiz A, Montero Alonso MJ. Prevención primaria con estatinas, consensos y tablas de riesgo. Atencion Primaria Soc Esp Med Fam Comunitaria 2005; 36: 31–38.

148. Robinson JG, Smith B, Maheshwari N, et al. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol 2005; 46: 1855–1862.

149. Weng T-C, Yang Y-HK, Lin S-J, et al. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther 2010; 35: 139–151.

150. Smith MBMEB, Lee NJNJ, Haney EE, et al. Drug Class Review: HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin: Final Report Update 5. Portland (OR): Oregon Health & Science University, http://www.ncbi.nlm.nih.gov/pubmed/21089253 (2009, accessed 4 March 2012).

151. Nicholls SJ, Brandrup-Wognsen G, Palmer M, et al. Meta-analysis of comparative efficacy of increasing dose of Atorvastatin versus Rosuvastatin versus Simvastatin on lowering levels of atherogenic lipids (from VOYAGER). Am J Cardiol 2010; 105: 69–76.

152. Wallace A, Chinn D, Rubin G. Taking simvastatin in the morning compared with in the evening: randomised controlled trial. BMJ 2003; 327: 788.

153. Drugs for lipids. Treat Guidel Med Lett 2008; 6: 9–16.

154. Silva M, Matthews ML, Jarvis C, et al. Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther 2007; 29: 253–260.

155. Mills EJ, O'Regan C, Eyawo O, et al. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. Eur Heart J 2011; 32: 1409–1415.

156. Hoffman KB, Kraus C, Dimbil M, et al. A survey of the FDA's AERS database regarding muscle and tendon adverse events linked to the statin drug class. PloS One 2012; 7: e42866.

157. FDA. Drug Safety and Availability - FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury, http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm (accessed 17 September 2012).

158. Medicines and Healthcare products Regulatory Agency (MHRA) www mhra gov uk. Simvastatin: increased risk of myopathy at high dose (80 mg), http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085169 (accessed 17 September 2012).

159. Goldstein MR, Mascitelli L, Pezzetta F. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology 2009; 72: 1448; author reply 1448–1449.

160. McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. Stroke J Cereb Circ 2012; 43: 2149–2156.

161. Hackam DG, Woodward M, Newby LK, et al. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. Circulation 2011; 124: 2233–2242.

162. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. The Lancet 2010; 375: 735–742.

163. Pharmacovigilance Working Party, European Medicines Agency. HMG-CoA reductase inhibitors – Risk of new onset diabetes, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/01/WC500120115.pdf (2012).

164. Preiss D, Seshasai SRK, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA J Am Med Assoc 2011; 305: 2556–2564.

165. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet 2010; 375: 1875–1884.

166. Press release. European Medicines Agency recommends use of fibrates as second-line treatment. European Medicines Agency, http://www.ema.europa.eu (2010).

167. Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002; 90: 1092–1097.

168. NICE. TA132 Hypercholesterolaemia - ezetimibe: guidance, http://publications.nice.org.uk/ezetimibe-for-the-treatment-of-primary-heterozygous-familial-and-non-familial-ta132 (accessed 9 October 2012).

169. Gudzune KA, Monroe AK, Sharma R, et al. Effectiveness of Combination Therapy With Statin and Another Lipid-Modifying Agent Compared With Intensified Statin Monotherapy: A Systematic Review. Ann Intern Med 2014.

170. Monroe AK, Gudzune KA, Sharma R, et al. Combination Therapy Versus Intensification of Statin Monotherapy: An Update. Rockville (MD): Agency for Healthcare Research and Quality (US), http://www.ncbi.nlm.nih.gov/books/NBK189822/ (2014, accessed 27 March 2014).

171. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008; 359: 1343–1356.

172. Agencia Española de Medicamentos y PS. Ficha técnica Omacor. Lab. Pronova Biopharma Norge As, https://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm&version=new (2010).

APPENDIX 1 INTERACTIONS

Statins have high affinity for HMCoA reductase without acting on other enzymes or receptors so they will not affect the activity of other drugs. However, when co-administered with other drugs, their activity may be affected. This occurs mainly when their metabolism is affected, so if their metabolism is reduced, their plasma concentrations increase and toxicity problems may occur, usually muscle toxicity. Not all statins will interact with the same drugs, or to the same extent, nor all patients will be affected in the same way. In general:

- The pharmacological activity of simvastatin and lovastatin are going to be affected by drugs that inhibit or induce their metabolism by cytochrome P-450, mostly 3A4 (CYP3A4). The levels of atorvastatin will also be affected by these drugs but in a lesser extent than with simvastatin.
- Fluvastatin is going to be affected by drugs that inhibit or induce the activity of CYP2C9.
- Pravastatin, rosuvastatin and pitavastatin do not seem to be affected by inducers or inhibitors of cytochrome P450 activity, but by inducers or inhibitors of membrane transporter OATP1B1, which facilitates the entry of statin in the hepatocyte.

Drug	Mechanism	Affected statin	Recommendation	Effect
Gemfibrozil		All	Avoid gemfibrozil	Increase in the risk of adverse effects (myopathy)
Macrolide Azole antifungals Danazol	potent CYP3A4 inhibitors	Simvastatin Lovastatin	contraindicated during treatment with the inhibitor drug	
		Atorvastatin	Avoid co-administration. If not possible, reduce doses of atorvastatin.	
Amiodarone Calcium antagonists	moderate CYP3A4 inhibitors	Simvastatin Lovastatin	With diltiazem: maximum dose simvastatin 40 mg	
			With amiodarone, amlodipine or verapamil: maximum doses simvastatin 20 mg, lovastatin 40 mg	
		Atorvastatin	Precaution	
Grapefruit juice Cilostazol	CYP3A4 Inhibitor	Simvastatin, atorvastatin, lovastatin	Grapefruit juice contraindicated	
			Precaution when co-administered with cilostazol	
Cyclosporine	CYP3A4, OATP1B1 Inhibitor	All	Rosuvastatin and Pitavastatin: Contraindicated	
			Lovastatin: maximum dose 20 mg	
			Simvastatin and atorvastatin: maximum dose 10 mg	
			Pravastatin and fluvastatin: precaution	
Erythromycin		Pitavastatin	Avoid co-administration	
		Pravastatin	Precaution	
Dronedarone	CYP3A4, OATP1B1 Inhibitor	All	Precaution. Reduce statin dose.	
Fluconazole	CYP2C9 Inhibitors	Fluvastatin	Precaution	
Colchicine	Competition CYP3A4 and Pgp	Simvastatin, lovastatin, atorvastatin and fluvastatin	Precaution	
Rifampicin, carbamazepine barbiturates	CYP3A4 Inductors	Simvastatin, atorvastatin, lovastatin	Statin dose may need to be adjusted	May reduce statin efficacy
Resins	Absorption reduction	All	Separate lipid-lowering drug administration	
Dicoumarins		All	Monitor INR	INR alterations
Digoxin		Atorvastatin (mainly at high doses)	Monitor digoxin	↑Digoxin toxicity

Macrolides: Erythromycin, clarithromycin, telithromycin.
Azole antifungal: fluconazole, itraconazole, ketoconazole, posaconazole Precaution with voriconazole
Calcium antagonists: amlodipine, verapamil, diltiazem.

Interactions between statins and protease inhibitors for the treatment of HIV and hepatitis C virus

The co-administration of statins and protease inhibitors used for the treatment of HIV or hepatitis C virus may lead to an increase in the risk of statin toxicity, mainly muscle adverse reactions.

Estatina	IP/ AAD	Recomendación estatinas
Simvastatin and lovastatin	HIV protease inhibitors Boceprevir Telaprevir Ombitasvir/paritaprevir/ritonavir with or without dasabuvir	Contraindicated
	Simeprevir Daclatasvir Sofosbuvir/ledipasvir	Precaution
Atorvastatin	Tipranavir + ritonavir Telaprevir Ombitasvir/paritaprevir/ritonavir with or without dasabuvir	Precaution
	Lopinavir + ritonavir	Do not exceed 20 mg of atorvastatin daily
	Darunavir + ritonavir Fosamprenavir Fosamprenavir + ritonavir Saquinavir + ritonavir Nelfinavir Boceprevir	Do not exceed 40 mg of atorvastatin daily
	Simeprevir Daclatasvir Sofosbuvir/ledipasvir	Precaution
Pravastatin	Boceprevir Telaprevir Simeprevir Daclatasvir Sofosbuvir/ledipasvir	Precaution
	Ombitasvir/paritaprevir/ritonavir con o sin dasabuvir	Reduce pravastatin dose at 50%
Fluvastatin	Telaprevir Simeprevir Daclatasvir Sofosbuvir/ledipasvir	Precaution
	Ombitasvir/paritaprevir/ritonavir with or without dasabuvir	Not recommended
Rosuvastatin	Sofosbuvir/ledipasvir	Contraindicated
	Atazanavir ± ritonavir Lopinavir + ritonavir Ombitasvir/paritaprevir/ritonavir	Do not exceed 10 mg of rosuvastatin daily
	Ombitasvir/paritaprevir/ritonavir with dasabuvir	Do not exceed 5 mg of rosuvastatin daily
	Darunavir + ritonavir Tipranavir + ritonavir Telaprevir Simeprevir Daclatasvir	Precaution
Pitavastatin	Telaprevir Simeprevir Daclatasvir	Precaution
	Ombitasvir/paritaprevir/ritonavir with or without dasabuvir	Not recommended

- FDA drug safety communication: interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. U.S. Food and Drug Administration Web site. http://www.fda.gov/Drugs/DrugSafety/ucm295591.htm Accessed Abril, 2014
- Data Sheets of the active ingredients of statins, telaprevir and boceprevir, simeprevir, daclatasvir, Harvoni®, Viekirax®, Exviera.

The present document addresses the treatment of dyslipidemia as a risk factor involved, along with others, in the onset of cardiovascular events. To do this, we review the evaluation of the risk that a patient has to undergo a cardiovascular event in the coming years. The decision to start treatment with statins and the intensity of the treatment will depend on the individual cardiovascular risk of the person. All this without forgetting the importance of treating other possible risk factors, hygienic-dietary measures as part of the treatment and ensuring that the patient complies adequately with the prescribed medication.