CLINICAL PRACTICE GUIDELINE
On the Management of Lipids
as a Vascular Risk Factor

Clinical Practice Guideline
On the Management of Lipids as a Cardiovascular Risk Factor

Osakidetza

EUSKO JAURLARITZA
GOBIERNO VASCO

FUNDING: This CPG is financed by Osakidetza and the Basque government's Ministry of Health. In 2004, the CPG was allocated a grant for commissioned research on the assessment of new health technologies, managed by Osteba.

CONFLICTS OF INTEREST: Itziar Pérez, Javier Urraca, Fernando Uribe, Ricardo Samper, Iñaki Berraondo and Ramón Ugarte have stated the absence of a conflict of interest. Ricardo San Vicentre has received funds from Pfizer and Novartis to attend conferences; Josu Ibarra received funds from Belmac and Almiral to attend conferences and meetings; Fátima Almagro received funds from MSD and Pfizer to attend conferences and meetings; Javier Andrés received funds from MSD, Pfizer, Schering and Novartis to attend conferences and meetings.

TO CITE THIS DOCUMENT:
San Vicente Blanco R., Pérez Irazusta I., Ibarra Amarica J., Berraondo Zabalegui I., Uribe Oyarbide.F., Urraca Garcia de Madinabeitia J., Samper Otxotorena.R., Aizpurua Imaz I., Almagro Mugica F., Andrés Novales J., Ugarte Libano R. Guía de Práctica Clínica sobre el manejo de los lípidos como factor de riesgo cardiovascular. Osakidetza. Vitoria-Gasteiz.

Edition: 2008
Print run: 500

http://www.osakidetza.euskadi.net
Published by: Osakidetza
C/Álava, 45
01006 VITORIA-GASTEIZ
ISBN: 978-84-691-2434-5
Copyright deposit: BI-2701-08

Contents

Presentation by the Basque minister

This is the new set of clinical practice guidelines prepared by and for Osakidetza professionals, with systematically developed recommendations based on the best scientific evidence available.

In this case, the health problem described is **lipid management as a cardiovascular risk factor.** As you will see, the title indicates a different approach to health problems: lipid levels are viewed as a predictive factor for cardiovascular risk rather than a management issue. This new approach is highly important.

Primary prevention of cardiovascular problems is a first-order activity in Primary Care surgeries, primarily, but it is also a priority in Specialized Care. That is why we need to adjust our practices to a context of low cardiovascular risk, where we stress the importance of a *Mediterranean lifestyle* as a key preventive factor. These guidelines adapt to our actual practice by focusing on the situation for patients in our context.

It also addresses the issue of secondary prevention in cardiovascular disease and enhanced survival, particularly in patients with ischaemic heart disease. The guidelines also pay special attention to risk vs. benefit assessment in drug therapy in order to adjust drugs and dosages to the highest possible advantage for patients at minimum risk.

My acknowledgement to the professionals who made these guidelines possible. I am aware of the hours they devoted to reviewing scientific evidence, sharing knowledge and arriving at a consensus. They have proved once again the importance of joint work cutting across several professional categories. My thanks to them all.

I am certain that all of the issues addressed in this guideline will be highly useful for family doctors and primary care nurses, as well as cardiologists, internal medicine physicians, endocrine specialists and other specialist physicians, aiding them in their medical decision-making and serving as an aid to improving the health of every citizen in the Basque autonomous region.

Vitoria-Gasteiz, September 2008
Gabriel Mª Inclán Iribar
BASQUE MINISTER OF HEALTH

Guideline authorship and review

Coordinator
Ricardo San Vicente Blanco. Family doctor. CS Ezkio-Itsaso. Guipuzcoa Mendebalde region.

Authors
Ricardo San Vicente Blanco. Family doctor. C. S. Ezkio-Itsaso. Gipuzkoa Mendebalde region.
Iciar Pérez Irazusta. Family doctor. Unidad Docente de MFyC de Gipuzkoa.
Josu Ibarra Amarica. Family doctor. C.S. Zaramaga. Comarca Araba.
Iñaki Berraondo Zabalegui. Family doctor. Managing Director of Bidasoa Hospital
Fernando Uribe Oyarbide. Family doctor. C.S. Desierto. Comarca Araba.
Javier Urraca García de Madinabeitia. Family doctor. C. S. Txagorritxu-Gazalbide. Araba region
Ricardo Samper Otxotorena. Pharmacist. Primary Care Department. Vitoria-Gasteiz.
Iñigo Aizpurua Imaz. Pharmacist. Basque Drug Information Centre (CEVIME). Vitoria-Gasteiz.
Javier Andrés Novales. Cardiologist. Hospital San Eloy. Barakaldo. Bizkaia.
Fátima Almagro Mugica. Internal Medicine. Lipids Unit. Donostia Hospital. Donostia.
Ramón Ugarte Libano. Paediatrics. C.S. Aranbizkarra.Araba region.

External Reviewers:
Idoia Alcorta Michelena. Family doctor. C.S. Renteria. Gipuzkoa Ekialde region.
Javier Andrés Novales. Cardiologist. Hospital San Eloy. Barakaldo. Bizkaia.
Jesús Mª de la Viuda Unzueta. Internal Medicine. Hospital Galdakao. Galdakao.
Roberto Elosúa Llanos. Vascular and genetic epidemiology. Lipids Unit. Donostia Hospital. Instituto Municipal de Investigación Médica. Barcelona.
Rosa Esquisabel Martínez. Family doctor. C. S. Txagorritxu-Gazalbide. Araba region
Félix Miguel García. Family doctor. Health Expert. Primary Care Management. SACYL.Valladolid Oeste.
María Miguez Vazquez. Nurse. C.S. Zaldibia. Comarca Gipuzkoa Mendebalde.
Rafael Rotaeche del Campo. Family doctor. C.S. Alza. Comarca Gipuzkoa Ekialde.
Adalberto Serrano Cumplido. Family doctor. C.S. Repelega. Comarca Ezkerraldea-Enkarterri.
Osatzen cardiovascular group. Basque Family and Community Society.

Structured summary

BACKGROUND: Cardiovascular diseases are the primary cause of death in the Autonomous Community of the Basque Country in women and second in the case of men, after tumours. Cardiovascular diseases accounted for almost 32% of deaths in 2001 and their importance in clinical practice are reflected, among other aspects, in the high volumeof prescriptions for hypolipidaemic drugs.

AIMS: The aim of this guideline is to improve the health care of these patients by offering them alternative, more beneficial treatments based on the best tests and evidence available in the scientific literature and to reduce the variability in clinical practice observed in the treatment and management of lipids as a cardiovascular risk factor.

METHODOLOGY: A combined method for the adaptation-preparation of Clinical Practice Guidelines has been selected. Evidence has been classified and recommendations graded as recommended by the Institute of Clinical Excellence (NICE), which uses the Scottish Intercollegiate Guidelines SIGN method for studies of treatment and prognosis, and of the Centre for Evidence-Based Medicine of Oxford for diagnostics studies.

SEARCH STRATEGY: At an international level, Cochrane and CPG reviews have been used as initial material. When the questions needed to be updated partially or totally or drafted from scratch, the methodology proposed by NICE in its guidelines manual was adopted. Searches have been made in Cochrane Library, Medline-Pubmed, DARE, Evidece Based Review and EMBASE. These searches covered the period September 2007-January 2008 in accordance with the question.

INCLUSION CRITERIA: High-quality CPGs have been included, selected on the basis of the AGREE assessment tool and published as of 2002, and articles published before January 2008 were evaluated according to the critical reading templates of SIGN for two evaluators.

QUESTIONS AND RECOMMENDATIONS PROPOSED IN THE GUIDELINES:
Relating to the prognosis and treatment of lipids as a cardiovascular risk factor.

Questions to answer

1. Which CVR score chart is the most appropriate for use in the general population in our environment? What should the cut-off point be after which therapeutic intervention is to be recommended?

2. Is coronary risk screening effective in the general population in order to reduce cardiovascular morbidity and mortality?

3. What are the screening age limits and how often should this be carried out in order to reduce cardiovascular morbidity and mortality?

4. What is the contribution of the ankle/arm index in the assessment of coronary risk?

5. What are the target figures for LDL-c: in primary prevention, secondary prevention and in patients with diabetes?

6. Should patients with low HDL-c and normal LDL-c be treated with hypolipidaemic drugs?

7. Under what conditions should analytical tests be used?

8. What parameters define familial hypercholesterolaemia?

9. When do we suspect a case of familial hypercholesterolaemia (FH)?

10. What parameters define hypertriglyceridaemia?

11. What tests must be included in the initial study of a patient to assess his/her coronary risk?

12. What is the attitude with regard to lipids in monitoring a patient in accordance with his/her coronary risk?

13. What patients should be referred from primary care to specialised care?

14. As of what age is the treatment with hypolipidaemic drugs not justified in adults?

15. Are the changes in lifestyle that affect the lipid profile effective in reducing cardiovascular morbidity and mortality in primary and secondary prevention?

16. What are the most efficient strategies to secure a change in lifestyle?

17. How long must we wait after securing changes in lifestyle before beginning lipid-lowering treatment?

18. When must we begin lipid-lowering treatment in primary prevention in Southern Europe?

19. What is the most effective lipid-lowering treatment in primary prevention?

20. When is it necessary to begin lipid-lowering treatment in secondary prevention?

21. What is the most effective lipid-lowering treatment in secondary prevention?

22. When is it necessary to begin lipid-lowering treatment in secondary prevention?

23. What should the therapeutic approach be to hypertriglyceridaemia?

24. How should combined hyerlipidaemia be treated?

25. What are the conditions for combined lipid-lowering treatment?

26. Are functional foods, vitamin supplements and dietary complements efficient in reducing cardiovascular morbidity and mortality in patients with lipid disorder?

27. Are medicinal plants effective in reducing cardiovascular morbidity and mortality in patients with lipid disorder?

28. When should the lipid profile be requested in the case of children?

29. What are the target levels and figures in children?

30. What therapeutic measures can be adapted in children with familial hypercholesterolaemia?

Summary of recommendations

Cardiovascular risk assessment

B Use tables adapted and validated for the population of the Spanish State.

C Use REGICOR charts to calculate coronary risk in patients with no cardiovascular disease.

✓ Do not use REGICOR charts to calculate coronary risk in patients of over age 74, in the presence of known vascular disease, familial hypercholesterolaemia, genetic dyslipidaemia, and in situations in which the total cholesterol level is >320 mg/dl or LDL-c > 240 mg/dl.

✓ Avoid reference to the results of clinical analyses, desirable cholesterol figures and normal lipid ranges, because their relevance will depend on the individual situations of patients, such as the presence of cardiovascular disease, familial hypercholesterolaemia, combined familial hyerlipidaemia, previous case histories of disease in the family or premature cardiovascular mortality or, in their absence, of the patient's coronary risk.

✓ Further research is required to establish the nature of the association between triglycerides and coronary disease.

✓ The recommended age for lipid screening to calculate coronary risk in the general population is age 40 in men and age 45 in women.

✓ Use the REGICOR chart to assess coronary risk initially, and every four years after that in patients who were at a low risk.

D There is no evidence to support the calculation of coronary risk in patients over age 75.

✓ Lipid profiles of patients with previous family case histories of premature vascular disease, familial dyslipidaemia or obesity should be made on an individual basis.

D In patients with hypertension or diabetes, a lipid profile should be part of the initial assessment of the individual and it should be repeated annually.

C Determining total colesterol and HDL-c as lipid variables is sufficient to estimate coronary risk.

D A full 12-hour fasting lipid profile is required before making a decision to begin lipid-lowering therapy.

D A minimum of two lipid profile determinations is recommended before taking decisions concerning lipid-lowering treatment.

D Lipid determinations are not recommended until 12 weeks have elapsed after acute myocardial infarction and until after 8 weeks following traumatism, surgery, bacterial or viral infection, or birth

D A patient should be seated for at least five minutes prior to blood extraction. Avoid prolonged venal occlusion. If this cannot be done, loosen the tourniquet one minute after tying it and try and extract blood from the other arm, or wait a few minutes before attempting to puncture again.

✓ Consider an ankle/arm index when drug therapy is proposed for patients at a coronary risk of 10% to 19% according to the REGICOR chart.

✓ Target LDL-c levels in primary prevention cannot be established based on the available evidence.

✓Suspect familial hypercholesterolaemia in:

1. Patients with previous cases of familial hypercholesterolaemia in first-degree relatives.

2. In individuals who have no familial hypercholesterolaemia, early cardiovascular disease and highly cholesterol levels.

3. Individuals > 40 years of age with total cholesterol levels higher than 360 mg/dl or levels of LDL-c>260 mg/dl and in individuals of between 30- 39 years of age with levels of TC>340 or LDL>240 mg/d.

✓ Total cholesterol determinations in all first-degree relatives of patients with familial hypercholesterolaemia starting at age 10 are recommended.

✓ Individuals suspected of familial hypercholesterolaemia should be given the MedPed test and referred to specialist care.

Non drug therapy

C-B* Advise the population in general and to individuals who have suffered a coronary event (*) to follow the Mediterranean dietary model (diet and physical activity). This advice should be given primarily at infirmaries.

B Efforts should be made to promote the daily consumption of fruit and vegetables.

C The general population and patients who have suffered cardiovascular disease should be advised to continue to drink alcoholic beverages if their previous alcohol consumption pattern was low or moderate.

C The recommendable alcohol consumption level should not exceed 2 units/day of alcohol in males and 1 unit/day in women.

✓ Give a clear explanation of what one unit of alcohol represents and the damaging effects of heavy drinking when providing information on the benefits of drinking.

B Aerobic intensity exercise such as walking, running, swimming with a moderate intensity for at least 30 minutes, five days a week, or a high-intensity activity for at least 20 minutes, three days a week, are recommended.

C Overweight and obese individuals are recommended to reduce calorie intake and to increase physical activity.

D Eating fish as a source of omega-3 acids and non saturated fats as part of the Mediterranean diet is recommended.

A The use of medicinal plants to reduce coronary risk is not recommended.

Drug therapy in primary prevention

D Dieting and physical activity for six months before beginning lipid-lowering therapy is recommended.

A Primary preventive measures with low to mild statin doses should be established for patients between the ages of 40 and 75 whose coronary risk is >20% according to the REGICOR chart. Give recommendations on lifestyles for a healthy heart before and/or when prescribing drug therapy.

B Give low to mild dose statin therapy to patients at a 10% to 19% coronary risk according to the REGICOR chart after they were treated for other cardiovascular risk factors (obesity, HBP, smoking).

B Consider low to mild dose statin therapy for patients at a 10% to 19% coronary risk according to the REGICOR chart and with other unavoidable cardiovascular risk factors (family case histories of premature coronary death, previous cases of familial hypercholesterolaemia, preclinical evidence of arteriosclerosis).

✓ Low to mild dose statin therapy should be started in patients with isolated total cholesterol levels over 320 mg/dl and/or 240 mg/dl of LDL-c.

✓/ B(*)/ D(**) Insist upon non-drug therapy and lower dose statin or changing to a different statin for patients under statin therapy in primary prevention who report an intolerance to statin. If the intolerance continues, the recommedation is to begin treatment with fibrates*. Other options might be resins*, and/or ezetimibe**.

✓In primary prevention, a 10% to 19% coronary risk in women of ages 40 to 75 according to the REGICOR chart should be given priority over other cardiovascular risk factors before beginning the lipid-lowering drug therapy.

C In women of ages 40 to 75 at a coronary risk >20%, treatment should begin with low to mild dose statin.

D Estimations of the risk of coronary disease based on cholesterol levels is not recommended in patients over age 75.

✓ A decision to begin lipid-lowering statin therapy in primary prevention in patients of over age 75 should be taken on an individual basis after the risks have been assessed, because the risk may exceed potential benefits for which there is no evidence.

✓ In primary prevention, the life expectancy and quality of life of the patients over age 80 should be considered when weighing the advisability of continuing statin therapy.

C Estimate the coronary risk of diabetic patients with no cardiovascular disease before deciding on a lipid-lowering treatment. The REGICOR coronary risk chart is recommended to estimate coronary risk in diabetic patients at the primary prevention level.

B Low to mild dose statin therapy is recommended for patients of ages 40 to 75 with a coronary risk >10% according to the REGICOR chart.

✓In diabetics over age 75, an individual assessment of cardiovascular risk is reocmmended.

B Consider fibrate therapy for type 2 diabetic patients with a cardiovascular risk >10% in the REGICOR chart, who do not tolerate statins or for whom statins are contraindicated.

C In long-term diabetics of >15 years, consider low to mild dose statin therapy irrespective of coronary risk.

Drug therapy in secondary prevention

A Begin treatment with mild statin doseses irrespective of baseline LDL-c in patients with ischaemic heart disease.

B(*)/ D(**) The recommendion for patients with ischaemic heart disease on statin therapy and those who report an intolerance to statins is to lower the doses or change to another statin. If intolerance continues, begin treatment with fibrates*. Other options include nicotinic acid**, resins** and/or ezetimibe**.

✓ In patients with ischaemic heart disease for whom LDL-c levels of less than 100 mg/dl have not been obtained, consider the benefit and risks of treatment before increasing the statin dose.

A Irrespective of the total cholesterol and baseline LDL-c, mild dose statin therapy is recommended for individuals who are released from hospital after an acute coronary syndrome.

B In patients with ischaemic ictus of aterothrombotic origin and with no ischaemic cardiopathy in wich c-LDL levels of less than 100 mg/dl have not been obtained, the statin dosage may be increased after considering the benefit and risks of treatment.

✓ In patients with previous ictus in treatment with statines in wich c-LDL levels of less than 100 mg/dl have not been obtained, the statin dosage may be increased after considering the benefit and risks of treatment.

B In individuals with peripheral arterial disease and associated comorbility, moderate dosages of statines are recommended.

Hypertriglyceridemia therapy

D When triglyceride levels are under 500 mg/dl, clinical decisions must consider the overall cardiovascular risk status of the patient.

- In patients with triglyceride levels of over 200 mg/dl, as a first step it is recommended to get the patient to lose weight, decrease fat intake, increase physical activity and reduce or eliminate alcohol consumption.

D Treatment with fibrates is recommended when triglyceride levels remain above 500 mg/dl in spite of lifestyle changes.

D Omega-3 fatty acids can be used to treat hypertriglyceridemia as a contributory measure to treatment with fibrates.

Treatment of patients with isolated drop in c-HDL

A In order to increase c-HDL levels, regular aerobic exercise is recommended, as well as reducing weight in the case of obese patients and stopping smoking in the case of smokers.

✓ It is recommended not to begin pharmacological treatment in the case of isolated levels of c-HDL without taking into consideration the coronary risk according to the REGICOR function.

Mixed hyperlipidaemia

✓ Due to the greater risk of premature coronary disease from the hereditary forms of mixed hyperlipidemia, before beginning treatment, case histories must be drawn up of previous cases of premature cardiovascular disease and lipid disorders in the family. Should these be positive, these patients can be considered to be of high cardiovascular risk.

✓ In primary prevention, in the case of a patient with mixed hyperlipidemia with no previous cases in the family, the coronary risk must be calculated in accordance with the REGICOR equation. The main aim of the treatment must be to reduce the coronary risk.

Combined treatment, adverse effects of hypolipemiants

✓ In those patients in which a combination of two drugs is required, statines can be associated with ionic exchange resins in low dosages and in the case of any intolerance to these, ezetimibe.

D When a combination of statines and fibrates is required, the use of fenofibrate is recommended.

✓ Combined treatment will be assessed in:

• Family hypercholesterolemies in which adequate controls are not achieved with a drug.

• Circumstantially in patients with mixed hyperlipidemias of family origin.

D Suspending treatment with fibrates must be assessed if there is a sustained increase in creatinine.

D In patients with renal insufficiency requiring treatment with fibrates, gemfibrozil is the first choice.

D Resins must be avoided in patients who suffer from constipation or intestinal disorders.

D If another accompanying medication is taken with ionic exchange resins, these must be administered one hour before or four hours after the resins are administered.

Assessment and monitoring of patients undergoing pharmacological treatment

D Before starting the pharmacological treatment, it is recommended to make two determinations of the lipid profile. Following pharmacological treatment, it is recommended to make the first control within 8-12 weeks and after that on an annual basis with an annual coronary risk assessment in primary prevention. In secondary prevention, once the adequate control has been achieved, a yearly analysis is recommended.

D Before beginning treatment with statines or fibrates, AST/ALT values must be determined. If these values are high, it is recommended that the cause be investigated before beginning treatment.

B CPK determinations are not required before beginning treatment with statins or fibrates in asymptomatic patients.

D Consider a CPK determination before starting statin or fibrate therapy on patients who report explicable muscle symptoms and those who have a high risk of muscle toxicity (elderly persons, hepatic dysfunction and in the case of potentially myotoxic pharmacological combinations).

D Do not begin statin therapy if a patient's CPK level is greater than five times the upper limit of normal.

D Determine AST, ALT and creatinine levels and evaluate the presence of cholelithiasis before beginning fibrate therapy.

D Determine the presence of transaminases 8-12 weeks after statin therapy started.

D Determine the presence of transaminase in patients on statin therapy annually. Lower the statin dose if transaminase levels rise above three times the upper limit of normal. If the rise persists, consider discontinuing therapy.

D Patients should be informed of potential muscle symptoms associated to therapy and of the need to request medical advice should this occur.

D Request a creatine kinase determination at the onset of muscle symptoms. If CPK rises above 10 times the upper limit of normal, discontinue statin therapy.

D Determinatons of AST and ALT values are recommended 8-12 weeks after beginning fibrate therapy and at annual intervals thereafter.

D AST and ALT determinations are not required during routine monitoring of plasma creatinine.

D A plasma creatinine determination is recommended for patients on fibrate therapy who take other drugs such as metformin and statins. Discontinue fibrate therapy if plasma creatinine rises (above 1.5 mg/dl in men and 1.4 mg/dl in women).

D Patients should be informed of potential muscle symptoms associated with the treatment and of the need to request medical advice should this occur. Discontinue fibrate therapy if CPK rises above 10 times the upper limit of normal.

Referral criteria

✓It is recommended to refer the patient to a lipids unit or a second level specialist in the case of:
• Suspected familial hypercholesterolaemia
• Serious genetic hyperlipidaemias (TC> 400 or LDL-c >260 mg/dl or Triglycerides > 1000 mg/dl)
• The need to add a third drug.
• The appearance of adverse effects that require specialist intervention.

Hypercholesterolaemia in children

A Population screening for cholesterol is not recommended in infants and adolescents.

✓Cholesterol screening is recommended in children as of 10 years of age in the case of a first-degree relative with monogenic familial hypercholesterolaemia.

D In the case of children with hypercholesterolaemia without a family history of monogenic dyslipidaemias, patients are advised to follow a Mediterranean diet, do physical activities and maintain adequate weight levels.

1. Introduction

1.1 Justification

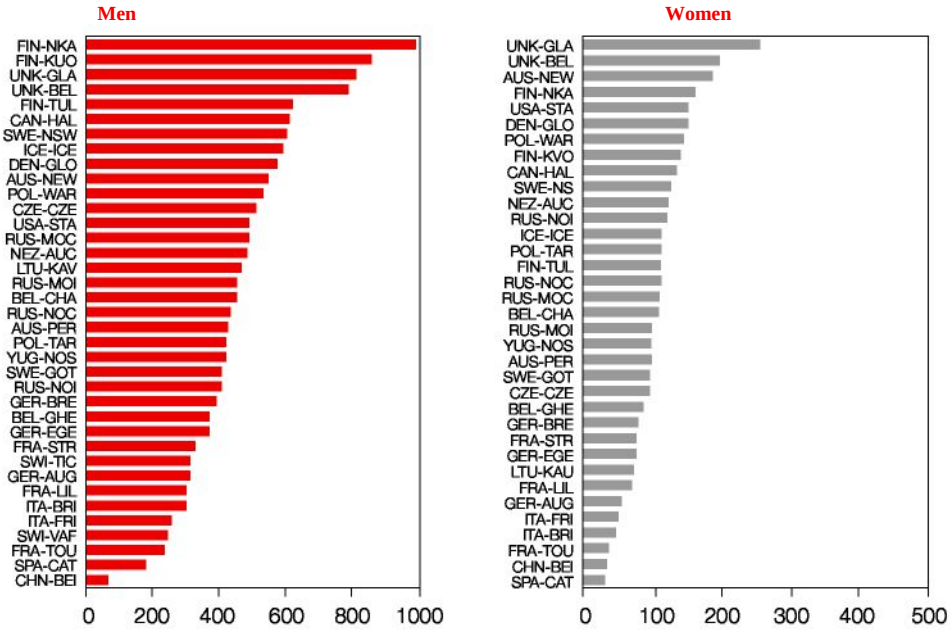
Cardiovascular diseases are the primary cause of death in most industrialized countries. In the Basque Autonomous Region (CAPV), they are the primary cause of deaths in women and the second in men, after tumours, causing close to 32% of all deaths in 2001. This is why an intervention in this health problem is one of the priority items in the Health Plan (1).

As in other countries in our area, the mortality rate in diseases of the circulatory system is generally positive for both sexes, particularly with regard to the mortality rate attributable to ischaemic heart disease in patients of ages 25-74 (Table 1). In fact, in 1992-2001 the mortality rate among patients with ischaemic heart disease mortality diminished almost 2% in both men and women. This progress may be related to interventions in cardiovascular (CV) prevention in primary and secondary care (2; 3), among other factors.

Table 1. **Evolution in CAPV Health Plan indicators. Basque Health Plan. 2006 Report (2)**

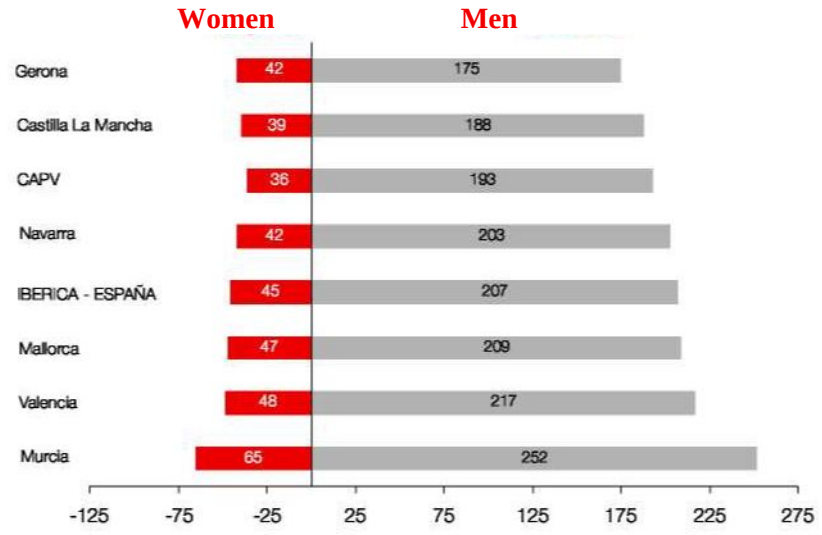
Health Plan Indicators	Initial context	2002	2003	2004	2005
Mortality rate attributable to diseases of the circulatory system in men under 65	57.1	49.7	49.0	52.26	51.2
Mortality rate attributable to diseases of the circulatory system in women under 65	6.1	13.8	15.0	11.4	14.7
Mortality rate attributable to cerebro-vascular diseases in men under 75	23.0	21.3	17.1	19.7	16.7
Mortality rate attributable to cerebro-vascular diseases in women under 85	25.5	21.0	20.2	17.0	17.7
Mortality rate attributable to ischaemic heart disease in men (ages 25-74)	83.1	65.2	61.0	55.5	55.5
Mortality rate attributable to ischaemic heart disease in women (ages 25-74)	17.2	11.2	13.0	11.2	9.4

Figure 1. **Annual coronary event index per 100,000. MONICA Project (5)**



The IBERICA study data show that acute myocardial infarction (AMI) is highly lethal (35% at 28 days after infarction). AMI rates in the CAPV occupy an intermediate position in relation to the Spain as a whole (Figure 2) (7).

Figure 2. **Standardized AMI incidence rates ages 25-74. (6)**



The importance of cardiovascular diseases in clinical practice is shown by the high volume of lipid-lowering drugs prescribed (Tables 2 and 3), among other aspects. As the tables show, statin ingestion has experienced excess growth in relation to the epidemiological situation of cardiovascular diseases in the CAPV. The increase is probably attributable to more prescriptions for lipid-lowering drugs in primary prevention, whereas patients who have already suffered a cardiovascular event still go without drug therapy. 25% of those who have experienced a coronary event are still not being treated with a statin (CAPV data for December 2007).

Table 2. **Evolution in statin ingestion in the CAPV (DDD No.)**
2002-2007 DDD INGESTION PER STATIN

	Atorvastin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
2002	11,379,760	900,438	2,063,011	5,074,258	9,120,442
2003	14,675,276	2,488,528	2,050,654	5,678,918	11,299,269
2004	18,897,732	3,453,576	1,931,674	6,053,138	13,307,425
2005	23,544,136	4,927,874	1,903,989	6,510,826	15,920,336
2006	26,543,552	5,966,128	1,789,791	6,619,830	18,361,299
2007	30,324,868	6,922,986	1,699,949	6,703,088	21,070,094

Table 3. **Evolution in statin ingestion in the CAPV (DDD No.)**
INTER-ANNUAL INCREMENTS

	Atorvastin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
2002-2003	29.0%	176.4%	-0.6%	11.9%	23.9%
2003-2004	28.8%	38.8%	-5.8%	6.6%	17.8%
2004-2005	24.6%	42.7%	-1.4%	7.6%	19.6%
2005-2006	12.7%	21.1%	-6.0%	1.7%	15.3%
2006-2007	14.2%	16.0%	-5.0%	1.3%	14.8%

Nonetheless, cardiovascular risk (CVR) and, consequently, coronary event rates in the CAPV are much lower than in most other industrialized countries (Figures 1 and 2). The risk that can be attributed to coronary events at the population's cholesterol level is lower than in other risk factors, such as

overweight and smoking (4). It is fundamental to consider other aspects when weighing intervention decisions. It should be stressed that practically all clinical trials (RCT) in primary prevention are made in groups of patients with a higher CVR than other people in the CAPV. As a result, the benefits that could be expected from an intervention in the CAPV are lower than the ones found in benchmark studies. Therefore, the number of patients who need to be treated to prevent a cardiovascular event (NNT) would be higher in the CAPV than the number calculated in the countries where the prevention studies were conducted and where the CVR is higher, as pointed out earlier.

The recommendations in the Clinical Practice Guidelines (CPG) on hypercholesterolaemia, which were prepared by groups of experts from other countries, are not uniform. Moreover, they were written in countries whose epidemiological contexts are very different to those in Mediterranean countries. In many cases, they are based on the use of CVR tables that have not been validated in our context (8-11).

Therefore, the Basque Government's Ministry of Health and the Osakidetza Health Care Board saw a need to develop a CPG that would respond to the questions posed by medical staff in the treatment of lipids. The guidelines would also need to take CVR factors into consideration, and current morbidity and mortality in the CAPV caused by cardiovascular diseases. The clinical reflections provided in this guideline would not have been possible without the funding from Osteba and the boost provided by the Osakidetza Primary Care Department.

1.2. Purpose of the Guidelines

The mission of the guideline is to formulate recommendations that will decision-making on lipid management as a CVR factor in the CAPV. Thus, the guideline is intended to:

♦ Improve health care for CVR patients by suggesting options that are more beneficial to them, based on focusing attention on the best tests and evidence available in scientific literature on lipids as a factor in CVR.

♦ Diminish the differences observed in the treatment and management of lipids as a CVR factor in clinical practice, and to bring the best evidence closer to clinical decision-making.

This guideline does not address:

♦ The management of individuals with familial hypercholesterolaemia (FH) and other genetic dyslipidaemias.

♦ Other cardiovascular risk factors such as smoking, high blood pressure (HBP) and diabetes.

1.3. Method of Preparation

To prepare the guidelines, a multi-disciplinary working group was formed. Their first task was to select the questions that health professionals usually raise about lipid management in primary and secondary preventive care. The selected questions were sent to a list of 10 external reviewers. 27 questions referring to adults and 3 questions on the special issue of addressing hypercholesterolaemia in children were selected by consensus (Table 4).

The clinical questions were structured as shown in the chart:

Patient	intervention/comparison	result/outcome
The most appropriate type of study.		

This is how, after much thought, we arrived at the questions that are answered in this guideline:

The answers to the questions obey a two-step strategy.

1. Do existing CPG and/or Cochrane reviews provide a consistent answer to the question? If yes: Can the recommendations be extrapolated to our epidemiological context?
If no:

2. What does the available evidence have to say on the matter? Search evidence to find out.
Therefore, the CPG is based on a combined strategy (12).

The first step consisted in locating and selecting CPGs drawn up according to acceptably strict standards, by conducting

Table 4. **Selected questions**

Screening

1. Which CVR score chart is the most appropriate one to use for the general population in our context?
Which cut-off point should we use to decide when we should recommend treatment?
2. How effective is coronary risk screening in the general population in lowering the risk of cardiovascular morbidity and mortality?
3. Which are the age limits for screening and how regularly does it need to be done to lower cardiovascular morbidity and mortality?

Prognostic

4. What does the ankle/arm rate contribute to coronary risk assessment?
5. Which are the target figures for LDL-c: in primary prevention, secondary prevention and in patients with diabetes?
6. Do people with low HDL-c and normal LDL-c need lipid-lowering drug therapy?

Diagnostic

7. Under what conditions should analytical tests be made?
8. What parameters define familial hypercholesterolaemia?
9. When do we suspect familial hypercholesterolaemia?
10. What parameters define hypertriglyceridaemia?
11. Which tests should be included in a preliminary study of patients to assess their coronary risk?

Follow-up

12. Which should be the attitude towards lipids in patient follow-up based on their coronary risk?
13. Which patients should be referred from primary care to specialized care?

Treatment

14. At what age is treatment with lipid-lowering agents no longer justified in adults?
15. Are the changes in lifestyles that have an impact on lipid profiles effective in reducing cardiovascular morbidity and mortality in primary and secondary prevention?
16. What are the most efficient strategies to secure a change in lifestyle?
17. How long must we wait after securing changes in lifestyle before beginning lipid-lowering treatment?
18. When must we begin lipid-lowering treatment in primary prevention in Southern Europe?
19. What is the most effective lipid-lowering treatment in primary prevention?
20. When is it necessary to begin lipid-lowering treatment in secondary prevention?
21. What is the most effective lipid-lowering treatment in secondary prevention?
22. When is it necessary to begin lipid-lowering treatment in patients with diabetes?
23. What should the therapeutic approach be to hypertriglyceridaemia?
24. How should combined hyperlipidaemia be treated?
25. What are the conditions for combined lipid-lowering treatment?
26. Are functional foods, vitamin supplements and dietary complements effective in reducing cardiovascular morbidity and mortality in patients with lipid disorder?
27. Are medicinal plants effective in reducing cardiovascular morbidity and mortality in patients with lipid disorder?

Children

28. When should a lipid profile be requested?
29. What are the target levels and figures?
30. What therapeutic measures should be adopted?

an exhaustive bibliographic search and a subsequent methodological assessment of the selected guidelines using the AGREE instrument (13).

10 CPGs were found and assessed, of which four were selected because they met high enough quality criteria to be included and had been published or updated after 2003:

♦ The Assessment and Management of Cardiovascular Risk. New Zealand Guidelines Group (NZGG) (10).

♦ Lipid Management in Adults. Institute for Clinical Systems Improvement (ICSI) (11).

♦ Risk estimation and the prevention of cardiovascular disease. A national clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN) (9).

♦ The Third report of the National Cholesterol Education Program (NECP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). National Heart, Lung, and Blood Institute National Institute of Health, US Department of Health and Human Services (8).

Five criteria were used to assess whether the reviews and/or CPGs answered each of the questions adequately and, consequently, to study whether a question raised in the guidelines and/or reviews could be adapted. The criteria were:

♦A recommendation's consistency across the guidelines

♦The need to update

♦The degree of recommendation: Recommendation based on solid evidence or expert opinions

♦ Clarity in the recommendation

♦ Whether the recommendation could be applied in our context

If it was found that a question had not been answered adequately and, as a result, an *ad hoc* bibliographic search and synthesis of evidence was needed, the method used was the one suggested by the National Institute of Clinical Excellence (NICE) in their guidelines manual (14):

♦ Evidence search: Cochrane Library, Medline-PubMed, DARE, Evidence Based Review, EMBASE. The search period was extended until December 2007, depending on the question.

♦ Evidence assessment by two evaluators, based on the critical reading templates provided by the Scottish Intercollegiate Guidelines Network (SIGN). The features and outcomes of the main studies included are shown in the evidence tables.

A "formal assessment" or reasoned judgement was used to formulate the recommendations. The working group resolved and wrote the recommendations by consensus.

The recommendations of NICE, which use the SIGN method for treatment and prognosis studies and Oxford's Centre for Evidence-Based Medicine for the diagnostic studies (Tables 5 and 6), were used. Any aspects that the authors of the guideline considered worth highlighting as an area in which conclusive evidence was lacking, or because it addressed particularly relevant clinical aspects were marked with a ✓ and were given the consideration of an opinion reached by consensus.

Table 5. SIGN levels of evidence and grades of recommendation for intervention studies

LEVELS OF EVIDENCE

1++ High quality meta-analyses, systematic reviews of controlled clinical trials or high quality clinical trials with a very low risk of bias.
1+ Well conducted meta-analyses, systematic reviews of clinical trials or well conducted clinical trials with a very low risk of bias.
1- Meta-analyses, systematic reviews of clinical trials or clinical trials with a high risk of bias.
2++ High quality systematic reviews of cohort and case-control studies.
Cohort and case-control studies with a very low risk of bias and with a high probability of establishing a causal relationship.
2+ Well-conducted cohort and case-control studies with a low risk of bias and a moderate probability of establishing a causal relationship.
2- Cohort and case-control studies with a high risk of bias and with a significant risk of establishing a non-causal relationship.
3 Non-analytic studies, e.g. case reports and series of cases.
4 Expert opinion.

DEGREES OF RECOMMENDATION

A At least one meta-analysis, systematic review or clinical trial rated as 1++, directly applicable to the guideline's target population; or a body of evidence consisting of studies rated as 1+ and showing considerable consistency with each other.
B A body of evidence including studies rated as 2++, directly applicable to the guideline's target population, and showing considerable consistency with each other; or evidence extrapolated from studies rated as 1++ or 1+.
C A body of evidence including studies rated as 2+, directly applicable to the guideline's target population, and showing considerable consistency with each other; or evidence extrapolated from studies rated as 21++.
D Evidence level 3 or 4, or evidence extrapolated from studies rated as 2+.
✓ Consensus of the editorial team.

Table 6. **Levels of evidence and grades of recommendation for diagnostic studies**
Adapted from *The Oxford Centre for Evidence-based Medicine Levels of Evidence* and the Centre for Reviews and Dissemination *Report Number 4* (2001)

LEVELS OF EVIDENCE	TYPE OF EVIDENCE
Ia	Systematic review (with uniformity) of Level 1[a] studies
Ib	Level 1[b] studies
II	Level 2[c] studies Systematic reviews of Level 2 studies
III	Level 3[d] studies Systematic reviews of Level 3 studies
IV	Consensus, expert reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or "first principles".

[a] Uniformity means that there is little or no variation in the directions and degrees of results between the individual studies included in the systematic review.

[b] Level 1 studies:
• Studies that compare the test blindly with a certified benchmark (gold standard) and in which a sample of patients reflects the population on whom the test would be applied.

[c] Level 2 studies:
• Studies that deal with a small number of people (the patient sample does not represent the population on whom the test would be applied)
• Studies that use a poor benchmark standard (where "test" is included in the "benchmark", or where the "tests" have an impact on the "benchmark")
• The comparison between the test and the benchmark is not blind
• Case-control studies

[d] Level 3 studies: Studies that present at least two or three of the features included in Level 2

DEGREES OF RECOMMENDATION

A Level of evidence Ia or Ib studies

B Level of evidence II studies

C Level of evidence III studies

D Level of evidence IV studies

2. Cardiovascular risk assessment

Questions to answer

♦ **Which CVR score chart is the most appropriate one to use in our context?**

♦ **What parameters define hypertriglyceridaemia?**

2.1. Calculation of cardiovascular risk: A preliminary issue

Estimating CVR has become the accepted method of primary prevention decision-making for patients with no cardiovascular disease. After several years of using the original Framingham study score charts to calculate coronary risk (CR) in our context, score charts adapted to the Spanish population appeared amidst a certain amount of controversy as to whether the original Framingham scores should be used, or the SCORE or REGICOR projects' scores (Framingham score charts adapted to the Spanish population) (Annex 1).

One of the questions we proposed to answer in this guideline refers to this issue: **Which CVR score chart is the most appropriate one to use in primary prevention in our context? After selecting the score that provides the best risk estimate, where should we establish the cut-off point for recommending therapeutic intervention?**

In the opinion of the working group, selecting the most appropriate method for estimating CVR in the CAPV's population was a primary concern to be dealt with before the other questions in the guideline could be posed. This approach to measuring CVR responds to the related issue of defining hypercholesterolaemia as an estimation of abnormally high cholesterol levels. In other words: **What parameters define hypercholesterolaemia?**

A number of studies show a continuous and linear relationship between total cholesterol (TC) and a coronary disease event, and no defined TC threshold

to separate a higher or lower risk (15). Moreover, the reduction in relative risk linked to an absolute reduction in LDL-c is similar all along the logarithmic scale. Assuming that CVR is a continuum linked to cholesterol levels, among other factors, it would appear to be more practical to establish too high a level of risk rather than define hypercholesterolaemia on its own, apart from other risk factors. This is the approach found in the more relevant CPGs (8-11).

Therefore, this guideline avoids outlining the parameters that define hypercholesterolaemia, for it is considered that intervention decision-making for a patient should take into consideration all the patient's CVR factors. Isolated estimates of lipid profiles are not recommended, with the exception of familial hypercholesterolaemia, established vascular disease, and in situations where the TC level is higher than 320 mg/dl or the LDL-c level is higher than 240 mg/dl (16).

The discussion should focus, therefore, on the most appropriate risk estimate score for the CAPV's epidemiological context, in keeping with the recommendations in the selected guidelines, which suggest using CVR scores adapted to the epidemiological patterns in each country. A recent systematic review (SR) (17) showed that the Framingham score charts overestimate CVR in populations with a low CVR, whereas the contrary occurs in population sub-groups at higher levels of risk. Therefore, the Framingham score charts should not be used in countries such as Spain where the morbidity and mortality rate is much lower and, consequently, so is CVR (5).

The REGICOR project considered that the Framingham score charts overestimate CVR in Spain, and provides an interesting alternative to the problem by adapting and validating them to Spain's epidemiological reality (18; 19). The SCORE project scores, however, have not been validated for the Spanish population. They may lead to an overestimation of the number of patients over age 65 who are candidates for treatment, while estimating the probability of cardiovascular death only in part (20-22).

Whether a CVR score is able to estimate the risk of a specific population is highly important. If the risk is overestimated, many patients may be treated unnecessarily, particularly if the NNT in primary care to prevent a CV event is taken into consideration, for it will be higher than the number given in the original primary prevention studies.

However, there is no evidence to demonstrate the efficacy of using CVR scores as a strategy for lowering CV morbidity and

mortality (17). From the point of view of clinical decision-making, the score provides a comprehensive view of the main factors of risk in an individual. Therefore, they help clinicians to estimate the impact of each factor on a patient's global risk, and provide a guideline for prioritizing prevention interventions.

For all the above reasons, the REGICOR project's coronary risk scores were used as tools to aid decision-making.

As occurs in other guidelines, whether a risk is considered high, average, low or very low is a subjective estimate of a risk ratio that is considered too high. In this guideline, the consideration is:

- High risk: 20%
- Average risk: 10% to 9%
- Low risk: 5% to 9%
- Very low risk: less than 5%

At this point, the idea of risk as the probability of developing a CV disease should be considered. Risk should not be used as a diagnostic tool to separate those patients who will develop CV disease from those who will not. Rather, it should be used to ensure that resources target those who are at a higher CR.

Some patients who are at a high CR (e.g., a CR of 20%) will develop a cardiovascular disease but many others will not (80 out of 100). Inevitably, interventions conducted on all patients at a high CR will include many patients who are not going to develop the disease, in a way similar to the false positives in a diagnostic tool.

Therefore, it is essential to decide the cut-off point (CR level) after which drug therapy should commence, assuming that lipid-lowering treatment will be given to many people who will not profit from it. In this guideline, the cut-off point was based on three criteria:

- That people with a high CR would not be prevented from benefiting from the treatment (20)
- That the benefits of lipid-lowering drug therapy would be higher than the risks (23)
- That it would be sustainable for the health care system (24).

Using 10% as a cut-off point, the sensitivity and specificity of the REGICOR project score are 37% and 88%, respectively. If the cut-off point is 15%, the sensitivity is 16% and the specificity is 96%. Taking the latter cut-off point, the number of patients treated unnecessarily diminishes, but the number of people who will have an undetected coronary event increases. Therefore, the cut-off point for interventions to reduce CV events in these patients was set at 10%. Individuals with a 20% coronary risk in the REGICOR score are candidates for drug therapy. Individuals with an average 10% to 9% risk require an individual decision-making. In other words, a patient's global context should be considered before therapy, including lipid-lowering therapy, is used as a risk- based primary prevention measure (20; 25).

The factors of risk to consider in average risk patients include:

- Family histories of early heart disease (<55 in men and <65 in women) (26-29).
- Obesity (30).

Risk charts should not be used in:

- Ischaemic heart disease
- Cerebrovascular disease
- Peripheral arterial disease
- Familial hypercholesterolaemia and other genetic dyslipidaemias
- Extreme levels of total cholesterol (>320 mg/dl) and LDL-c (>240 mg/dl)
- Elderly individuals over age 74.

The target levels of cholesterol to be attained in (average to high-risk) patients is another issue Some guidelines recommend certain target LDL-c levels , but no basis for making such recommendations has been found to date. Therefore, this guideline does not recommend target LDL-c levels in primary prevention.

Evidence summary

2++	Applying recommendations on charts based on the population of other countries may overestimate the risk. The use of charts that are not adapted to our context overestimates CR (17).
2++	There is no evidence on the efficacy of using CVR charts to diminish cardiovascular morbidity and mortality rates (17).
2++	Although the prevalence of CVR is similar to or higher in Spain than in other countries, our cardiovascular morbidity and mortality rates are lower (5).
2 +	The REGICOR project charts were adapted to the nature of the risk and the prevalence of risk factors in Spain's population. The validity of the REGICOR charts allows coronary risk to be estimated more specifically (18; 19).

Recommendation

B	Use tables adapted and validated for Spain's population.
C	Use the REGICOR charts to calculate coronary risk in patients who have no coronary disease.
✓	Do not use the REGICOR charts to calculate coronary risk in patients over age 74, in cases of known vascular disease, familial hypercholesterolaemia, genetic dyslipidaemias and in situations where the total cholesterol level is >320 mg/dl or LDL-x > 240 mg/dl.
✓	Avoid reference to desirable cholesterol levels and normal lipid ranges in the results of clinical analyses, since their relevance will depend on the patients' particular circumstances, such as previous cardiovascular disease, familial hypercholesterolaemia, combined familial hyperlipidaemia, family histories of early cardiovascular death and, in the absence of these, on the patients' coronary risk.

2.2. Definition of dyslipidaemia

QUESTIONS TO ANSWER

- **What parameters define hypercholesterolaemia?**
- **What parameters define hypertriglyceridaemia?**
- **Are triglycerides a cardiovascular risk factor?**

2.2.1. Hypercholesterolaemia

As mentioned earlier, despite the strong temptation to define the total cholesterol level after which a patient may be considered hypercholesterolemic, the working group decided to recommend basing intervention decision-making on the estimation of CR, while considering the patient's risk factors. Deciding the level at which a patient should be considered to have hypercholesterolaemia may seem attractive for demonstrating the role of cholesterol levels as a CVR factor, but it has the inconvenience of distracting attention from what is really important: to estimate CR instead of decision-making based on hypercholesterolaemia. Therefore, this guideline does not refer to explicit levels that define hypercholesterolaemia, since their relevance will depend on the patients' particular circumstances: whether or not there is a family history of cardiovascular disease or hypercholesterolaemia, previous case histories of disease in the family and early cardiovascular death. If no such family history exists, it will depend on other risk factors and, finally, on the patients' individual coronary risk.

2.2.2. Hypertriglyceridaemia

There is a long-standing debate on the importance of triglycerides (TG) as a CVR-increasing factor. The controversy arises from contradictory outcomes and the fact that positive studies show a modest extent of the effect.

An association between TG and cardiovascular disease was found in several meta-analyses (31; 32).

In fact, a recent meta-analysis of 29 prospective studies found an increase in the risk of coronary disease in the patients with the highest TG [OR 1.72 (95% CI: 1.56 to 1.90)]. Nonetheless, the outcome should be accepted with caution due to the heterogeneous nature of the

studies (31). This meta-analysis analyses the data from two nested case-control studies (33; 34) in which individuals with higher levels of TG were at a higher risk of coronary disease, with an Odds Ratio (OR) of 1.76(95% CI: 1.39 to 2.21) (33) and OR 1.57(95% CI: 1.10 to 2.24) (34). In one of the studies, however, no data adjusted for HDL-c is available, a factor that weakens the link between TG and coronary disease (33). In any event, the outcomes of the study indicate that the impact of TGs on coronary risk would be similar in men and women. Another meta-analysis of 17 prospective studies also found a higher risk of cardiovascular disease events in subjects with high TG levels. Relative risk (RR) was 1.14 (95% CI: 1.05 to 1.28) in men and of 1.37 (95% CI: 1.13 to 1.66) in women, even after adjusting other risk factors such as HDL-c. In this study, however, the analysis was not adjusted to the glucose levels, another factor that could lower the effect of TG as a CVR factor (32).

On the other hand, this association between high TG levels and a higher risk of coronary disease was not found in a secondary analysis of the data from 3 RCTs that included over 15,000 subjects (35). In this study, the adjustment for other coronary risk factors mitigated the extent of the association, which lost meaning, although the univariant analysis does show a significant association between TG levels and coronary disease. The above data suggests that measuring TG levels does not add information on the risk of coronary disease beyond the data obtained by measuring sub-fraction cholesterol levels.

Subsequently, two cohort studies have been published which establish an association between postprandial TG (as opposed to previous studies referring to baseline TG) and coronary disease [Hazard Ratio (HR):1.98 (95% CI: 1.21 to 3.25)] with TG> 171 mg/dl (36; 37).

The conclusion is that the available information is not enough to establish that TG are a CVR factor on their own. Further research is required to establish a link between triglycerides and coronary disease. Nonetheless, although the link may not be very clear, CVR increases with high TG levels combined with cardiovascular risk lipid profiles (low HDL-c and high LDL-c), and the existence of small, dense LDL-c particles. In such a context, lowering TG would help to reduce cardiovascular events (8; 38; 39).

Table 7. **Values that define hypertriglyceridaemia**

Normal TG	<150 mg/dl
Borderline high TG	150 – 199 mg/dl
High TG	200 mg/dl
Very high TG	500 mg/dl

To be operational, this guideline adopts the NCEP (ATP III) levels to define hypertriglyceridaemia (8).

Evidence summary

2+	It cannot be established that TG are an independent cardiovascular risk factor (31; 32; 35-37)

Recommendation

✓	Further research is needed to help to establish the nature of the association between triglycerides and coronary disease

2.3. Screening for dyslipidaemia

QUESTIONS TO ANSWER

♦ **How effective is screening for coronary risk in the general population in lowering the risk of cardiovascular morbidity and mortality?**

♦ **What would be the ideal regularity and age limit for screening?**

The selected guidelines recommend basing cholesterol screening on circumstantial evidence (8-11). Firstly, the guidelines attribute the studies' lower morbidity and mortality rates to secondary prevention for patients with a cardiovascular disease. Furthermore, given the linear relationship found between cholesterol and CVR, and the possibility of predicting CVR, the studies assumed that the benefits observed in the secondary prevention trials could be extrapolated to the general population. According to this hypothesis, morbidity and mortality could be lowered by screening the general population to detect patients with high cholesterol levels and an average to high coronary risk, and then treating them. The US Task Force on preventive care takes a similar stance (40).

A number of studies have shown that a continuous and linear relationship exists between total cholesterol (TC) and a coronary disease event, with no defined TC threshold to separate a higher or a lower risk (15).

In the absence of studies that assess the efficacy of screening in lowering cardiovascular morbidity and mortality rates, however, recommendations should be based on the outcomes of primary prevention trials in the various subgroups of risk in the general population. The trials were conducted on populations over age 40 and, in general, on patients at an average to high risk. In general, over 50 patients were to be treated in the primary prevention trials to lower cardiovascular events, a fact that should also be taken into consideration. There is no evidence that lipid-lowering agents modify coronary morbidity and mortality in women with no coronary disease. To these considerations we could add the fact that mean study follow-up was 4.3 years, within a range of 3.2 to 5.2 years, and that the mean age of the trial participants varied between 55.1 and 75.4 (41).

Apart from the above evidence based on the outcomes from studies on primary prevention, any decision to recommend the screening of a specific population should also take into consideration the baseline risk of coronary disease, since low risk tends to provide fewer benefits than expected (42).

Likewise, any decision as to which is the best age to start screening should take into account how effective interventions based on a high CVR may be. However, as mentioned above, no evidence exists on the benefits of using lipid-lowering therapy in women at risk in primary care. Nonetheless, surprisingly enough, all of the CPGs studied recommended screening.

Furthermore, the potential benefits of lipid screening should be compared to the adverse effects of lipid-lowering treatments. Labelling individuals as being "at risk" and, therefore, as candidates for drug therapy, may lead to a situation where they are submitted to a series of medical checkups over many years although they will probably never develop the disease. Moreover, the cost-opportunity of carrying out the intervention to the detriment of more beneficial alternatives should be added to the cost of screening and the subsequent intervention.

For all the above reasons, this CPG takes a conservative approach in line with the available evidence, and recommends beginning screening at age 40 in men and age 45 in women. In line with the cardiovascular

screening agreed for the general population in the Basque autonomous region, coronary risk (including blood pressure, glycaemia, total cholesterol and HDL) should be calculated every four years after the recommended ages.

Despite the lack of evidence for recommending lipid screening in women, this guideline recommends a CR calculation to detect women at a higher risk who require intervention for one or more existing risk factors.

This recommendation for the general population does not apply to situations in which a lipid profile is required at any age and for men and women in order to quantify cardiovascular risk.

♦ Obesity is a CVR factor that is separate from HBP and related lipid disorders [RR 1.49 (95% CI: 1.32 to 1,67)] (30).

♦ A history of early coronary disease in first-degree relatives (<55 in men and <65 in women) increases CR [OR 5.0 (95% CI: 2.8 to 8.7)] (26-29).

♦ Early ischaemic heart disease is present in 50.3% of men and 49.5% of women whose first and second-degree relatives have FH.

♦ Hereditary familiar hyperlipidaemia implies a higher risk of early coronary disease and cardiovascular mortality [RR 1.7 (95% CI: 1.1 to 2.7)] (44; 45).

♦ Diabetics have a higher CVR than individuals who are not diabetic (46). In this sense, it is worth noting that several studies compare the CVR of diabetics with the CVR of individuals who have had an acute myocardial infarction (AMI), but the study outcomes are inconsistent with each other. Nonetheless, diabetic women and individuals who have had diabetes for more than 15 years are at a higher CVR (47-54).

♦ The CAPV's CPG on HBP recommends annual lipid profile checkups for patients with a diagnosis of HBP (55).

Evidence summary

2+	Observational studies show a linear relationship between total cholesterol values and CVR (15).
1 ++	Lipid-lowering therapy diminishes coronary events in 40-70 year olds at an average or high CVR (56-60).
1 +	Lipid-lowering therapy has not proved to diminish cardiovascular events in women with no cardiovascular disease (41).
2+ 3(*)	Family histories of early coronary death, obesity, diabetes, HBP, familial hypercholesterolaemia (*), and combined familial hyperlipidaemia (*) are separate CVR factors (26; 27; 30; 43-45; 47-54).

Recommendation

✓	Screen the general population for a lipid profile at age 40 in men and age 45 in women to prevent coronary risk.
✓	Repeat the calculation of coronary risk every four years using the REGICOR chart after age 40 in individuals who are at low risk in the first evaluation.
D	There is no evidence to support the assessment of coronary risk in patients over age 75.
✓	Assess individual lipid profile in patients with a family history of early vascular disease, familial dyslipidaemia or obesity.
D	An annual lipid profile should be part of the preliminary assessment of patients with high blood pressure or diabetes.

2.4. Preliminary Assessment

QUESTIONS TO ANSWER

♦ **Which tests should be included in a preliminary study of patients to assess their coronary risk?**

♦ **Under what conditions should analytical tests be made?**

♦ **Is an ankle-brachial test advisable to discard subclinical arteriosclerosis in patients at an average cardiovascular risk?**

♦ **Which are the target figures for LDL-c?**

♦ **When do we suspect familial hypercholesterolaemia?**

2.4.1 Preliminary Assessment of Coronary Risk

Apart from the data required to calculate CR according to the REGICOR project – age, diastolic and systolic blood pressure, baseline glycaemia, TC, HDL-c and smoking habits, a detailed anamnesis on a patient's personal and family history is essential to discard situations that put a patient at a higher CR than the general population.

Anamnesis:

♦ Personal and family record of cardiovascular disease.

♦ Patients should be questioned on the onset of cardiovascular events in first-degree relatives <55 in men and <65 in women.

♦ Family histories of lipid disorders in first-degree relatives to discard congenital atherogenic hyperlipidaemia (FH, combined familial hyperlipidaemia and dysbetalipoproteinaemia).

Physical activity:

♦ Weight and height. Body Mass Index (BMI)

♦ Consider an ankle-brachial test (ABT) in individuals at average risk.

The CPGs and SR consulted did not include the need for further tests, such as an ECG, which would depend on the existence of other cardiovascular risk factors or an associated pathology (8-11; 61-66).

2.4.2. Conditions for Laboratory Tests

Fasting samples are not needed to determine TC and HDL-c levels, although a fasting HDL-c measurement in this situation underestimates HDL-c levels by 5% to 0% (9). Intervention decision-making based on an average-high CR, however, requires tLDL-c testing, and therefore a complete fasting lipid profile (TC, HDL-c and TG) is needed. A 12-hour fasting period is required to obtain reliable levels, which poses practical problems. In any event, fasting should not exceed 9 hours, and even then, an individual's LDL-c levels may be underestimated by 2%-4% (9; 67).

Given physiological and analytical variability in LDL-c, HDL-c and TG measurements, a single determination is not sufficient for diagnostic decision-making, and even less so for treatment and follow-ups. Allow at least one week to elapse between measurements (67).

To keep variations in HDL-c levels to a minimum, recommend patients to continue their normal diet and to not lose weight over the two weeks prior to testing. Do not perform tests during the 12 weeks following an AMI and during 8 weeks after surgery, a bacterial or viral infection, or childbirth; because such processes lower HDL-c levels and raise TG levels (67).

Ask patients to remain seated for at least 5 minutes prior to taking a blood sample. Avoid prolonged venal occlusion. If no blood sample is obtained, release the tourniquet one minute after tying it and try the other arm, or wait for a few minutes before attempting to take a sample again (67).

Take variations in LDL-c levels into consideration when interpreting the results of a test. LDL-c levels should not vary more than 25%, and TG levels should not vary more than 50%. If the variations are any higher, a third test is required, in which case the baseline level will be the mean result of all three tests (67).

Evidence summary

3	LDL-c, HDL-c and TG levels between individuals vary due to biological fluctuations and variations in methods of measurement (67).
3	Reliable tests require a 12 hour fasting period, and even then they may underestimate LDL-c levels by 2%-%.
3	AMI, pregnancy, bacterial and viral infections and traumas requiring surgery lower HDL-c levels and raise TG levels (67).

Recommendation

C	To determine lipid variables such as total cholesterol and Hal-c is sufficient to estimate coronary risk.
D	Decision-making at the beginning lipid-lowering intervention requires a complete lipid profile obtained after 12-hour fasting.
D	At least two lipid profiles are required before a decision to begin a lipid-lowering intervention.
D	Lipid profile determinations should not be made until 12 weeks after acute myocardial infarction and up to 8 weeks after a trauma, surgery, a bacterial or viral infection, and childbirth.
D	Ask patients to remain seated for 5 minutes prior to taking a blood sample. Avoid prolonged venal occlusion. If this is not possible, release the tourniquet one minute after tying it and try the other arm, or wait a few minutes before attempting to extract a sample again.

2.4.3. Ankle-Brachial index test

The guidelines selected did not address the issue of ankle-brachial index tests, so a documentary search designed specifically to answer this question was made. The search found 2 meta-analyses of cohort studies that studied the relationship between the ankle-brachial index and the total risk of mortality, cardiovascular mortality, coronary disease and acute cardiovascular event (ACVE) (68; 69).

The analysis of the community-based cohort studies showed very low sensitivity in predicting coronary disease and ACVE (16%) and mortality (31.2%) (95% CI: 27.8 to 34.6). In contrast, the test's specificity is close to 90%. Sensitivity in the subgroup of patients at high cardiovascular risk is around 85% (95% CI: 82.1 to 87.5) for cardiovascular mortality and 38% specificity. Unfortunately, the study does not provide data on the validity of the ABI test in individuals with an average risk in whom a pathology test could orientate towards changes in therapy (68).

Another meta-analysis that includes 11 cohort studies (44,590 individuals) shows an increase in the total mortality risk [RR 1.60 (95% CI: 1.32 to 1.95], cardiovascular mortality [RR 1.96 (95% CI: 1.46 to 2.64)], coronary disease [RR 1.45 (95% CI: 1.08 to 1.93)], and of y de ACVE [RR 1.35 (95% CI: 1.10 to 1.65)], in individuals with an ABI of less than 0.9. The ABI acts as an independent marker for predicting future coronary events in individuals in primary care and can help to indentify individuals in the general population at a higher risk of having cardiovascular events (69).

Other cohort studies published after the above meta-analyses showed an increase in the risk of coronary events and mortality in patients with an ABI< 0.9 (70-72).

In their 5th conference on prevention, the American Heart Association (AHA) describes ABI as an independent risk factor for cardiovascular mortality and recommends using it to detect sub-clinical disease in the prevention of cardiovascular risk. The AHA considers ABI tests useful for assessing CVR in selected populations, particularly in individuals >50 and those who have an average or high CVR (68).

Finally, the outcomes of certain cross-cutting studies, such as VITAMIN (73) and MERITO (74), on Spain's population, indicate that hidden or asymptomatic peripheral arterial disease exists in populations with a high ABI.

Evidence summary

2++	ABI levels >0.9 are associated with a higher risk of cardiovascular disease, cardiovascular mortality and total mortality (68; 69).
II (ED)	The ABI test has low sensitivity and high specificity in the general population. However, sensitivity increases (85%) and specificity declines (38%) in the CVR population (68). There is no evidence of the diagnostic value of ABI in the intermediate CVR population.

Recommendation

C	When considering drug therapy, the ankle/arm index should be performed on patients with a 10% to 9% coronary risk in the REGICOR chart.

2.4.4 Target Figures for LDL-c

Currently there is no evidence to support an objective target level in primary and secondary prevention.

1. The ATP III (8) recommendations on an objective LDL-c target level of <100 mg/dl comes from epidemiological studies that associate decreases in coronary morbidity and mortality with decreases in cholesterol levels. They are also based on post-hoc ABI tests which were not designed for that purpose (75-77). The recommendations do not take into consideration that other ABI do not confirm the association (78; 79). Moreover, to support the recommendation of attaining target levels of <70 mg/dl, in the 2004 update (80) the ATP III is based on ecological conglomerates in which confusion factors are sometimes hard to control (81). It is also based on the above-mentioned post-hoc studies: Herat Protection Study (HPS) (76) and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT-TIMI 22) (77).

2. Several SRs study the association between a decrease in LDL-c levels and the clinical benefits of statins. They show that for every mmol/L (39 mg/dL) that decreases LDL-c, a relative risk reduction (RRR) occurs in 25% of coronary events (fatal and non-fatal AMI) (82; 83). The reviews include RCTs performed with low and mild dose statin. The more LDL-c is lowered,

the more coronary events are reduced, to the extent that a decrease of 69 mg/dL in LDL-c can bring about a 51% reduction in coronary events after 2-3 years of therapy. The extent of the reduction is lower in the first two years of treatment (82; 84). Although RRR remains constant independently of LDL-c levels, the benefit in absolute terms is greater in individuals with high LDL-c levels and in those who have a high baseline risk (81).

3. There are no RCTs that compare the standard for administering fixed dose statin to the standards that use progressive doses until target LDL-c levels are attained. The existing evidence comes from RCTs where high dose statin (80 mg of Atorvastatin) were used in very selected patients with average levels of low LDL-c [98 mg/dl (85) and of 121 mg/dl (86)] before being randomized to include them in the studies. It is worth mentioning that a high percentage of the individuals in these studies showed adverse effects or abandoned the treatment.

4. Of the patients at a high CVR included in the studies (77; 58-87), at least half of the patients who received high dose statin managed to attain target LDL-c levels of 70 mg/dl. To attain these levels in clinical practice would often require the use of other drugs, such as ezetimibe, whose long-term safety has not been well-established (88). Ultimately, although it has been shown that decreased LDL-c levels are linked to a decreased risk of coronary events –and mainly in secondary prevention– there is no evidence that allows a target level to be set for patients with ischaemic heart disease.

Evidence summary

1++	A drop in LDL-c levels is associated with a decline in the risk of coronary events (82; 83). No RCTs compare fixed statin doses with raising doses to attain target levels. There is no evidence to support an objective target level in primary and secondary prevention.

Recommendation

✓	Target LDL-c levels in primary prevention cannot be based on the existing evidence.

2.4.5. Suspected cases of familial hypercholesterolaemia

FH is a hereditary autosomal dominant disorder with a penetration of 100%, caused by LDL-c receptor mutations. Progress is marked by lipoprotein metabolism disorders, characterized by very high LDL-c concentrations in blood plasma, a family history of hypercholesterolaemia, tendon xanthomata, and an increased risk of early coronary disease.

In a study of 819 individuals in Spain with FH, the mean TC concentration was 407 (SD: 83 mg/dl), LDL-c levels were 312 (SD: 79 mg/dl) and HDL-c levels were 53 (SD: 15 mg/dl). 22.5% of the study subjects had tendon xanthomata and 45.5% had an arcus corneae. Moreover, 190 individuals (23.2%) had a record of cardiovascular disease, with early onset in 178 cases. Early cardiovascular disease frequency in first and second-degree family members was 50.3% in men and 49.5% in women. The clinical features of FH are similar to the ones described in other countries, with a very high cardiovascular disease frequency in relation to the general population in both men and women (43).

How can familial hypercholesterolaemia be diagnosed?

Early detection of FH patients is essential to establish an appropriate treatment. Several diagnostic tests have been used to detect FH, with varying degrees of validity dependent on the existence or non-existence of a family history of hFH.

1. Biochemical diagnosis

LDL-c levels in FH nearly double general population levels, varying between 190-400 mg/dl, whereas TG levels tend to be average (89). Cholesterol levels on their own are not sufficient to ratify a diagnosis of FH, however, for they come within a range that overlaps non-hereditary polygenic hypercholesterolaemia levels, with 8% and 18% of false positives and false negatives (90), respectively.

The U.S. MedPed study proposes TC and LDL-c levels for establishing a diagnosis of suspected FH by age and family histories of FH (Table 8) (91).

The US MedPed Program criteria have a sensitivity of 87% and a specificity of 98% in the case of first-degree relatives of patients with FH. The criteria are not valid as a diagnostic tool in the general population, however, due to their low sensitivity (91; 92).

Table 8. **Total cholesterol levels (LDL-c) as a diagnostic criterion for potential hFH**

Age	First degree	Second degree	Third degree	General population
> 18	220 (155)	230 (165)	240 (170)	270 (200)
20-29	240 (170)	250 (180)	260 (185)	290 (220)
30-39	270 (190)	280 (200)	290 (210)	340 (240)
≥40 a	290 (205)	300 (215)	310 (225)	360 (260)

2. Clinical diagnosis

In any event, TC and LDL-c levels are not sufficient to establish a diagnosis for these patients. Therefore, a series of prediction rules have been developed to take other clinical characteristics into considerations (92). These are:

♦ **Simon Broume Register Group (SBR):** Assess cholesterol levels, clinical characteristics, the molecular diagnosis and family history. A final diagnosis is reached if the patient has high TC levels and xanthomata, or if the patient has a mutation of the LDL-r gene or the apolipoprotein B-10 gene.

♦ **Dutch Lipid Clinic Network (DLC) or Dutch MedPed:** Similar to the previous one. Scores are assigned according to the family history of hyperlipidaemia or heart disease, according to clinical characteristics and, finally, according to LDL-c levels. A score higher than or equal to 8 is considered definitive (Annex 6).

There is little evidence as to the sensitivity and specificity of each one of the rules for FH diagnosis. In a study (93) made on a Danish population with suspected FH, the validity of the diagnostic tests (SBR, US MedPed and DLC) for diagnosing FH was compared to a benchmark routine molecular genetic analysis. The individuals included in the study had to meet 2 out of 3 characteristics:

♦ Total cholesterol > 310 mmol/L, LDL-c > 232 mmol/L and TG < 220 mmol/l.

♦ Tendon xanthomata

♦ A history of coronary disease before age 60 in the patient and/or first-degree relatives.

As Table 9 shows, the molecular diagnosis showed very little difference in sensitivity and specificity between the SBR and the Dutch MedPed.

Table 9. **Sensitivity and specificity in several criteria standards for diagnosis of FH**

Clinical criteria		% Sensitivity	% Specificity
Simon Broome Register	Definitive FH	34.1 (95% CI:26.1-42-7)	89.4 (95% CI:85.1-92.8)
US MEDPED	TC	63.4 (95% CI:54.5-71.6)	73.4 (95% CI:67.8-78.6)
Dutch Lipid Clinic or Dutch MedPed	Definitive	41.5 (95% CI:33.1-50.3)	87.9 (95% CI:83.4-91.5)

Finally, although none of the above standards is valid in our context, the International Panel on Management of Familial Hypercholesterolaemia recommends using the Dutch MedPed clinical criteria (Annex 6) (89).

3. Genetic diagnosis

FH can be caused by different types of mutations that vary according to geographic locations. The most frequent disorder is familial hypercholesterolaemia caused by mutations in the LDL-r gene. It is worth mentioning that mutations in the LDL-r gene often go undetected, even when a positive genetic diagnosis is conclusive (89).

Who should be suspected of having familiar hypercholesterolaemia?

1. All first-degree relatives of individuals with a diagnosis of familial hypercholesterolaemia should be screened. This involves testing for LDL-c. One of the criteria below needs to be met before a clinical diagnosis of FH is made (89):

- Tendon xanthomata
- Arcus corneae before age 45 with LDL-c > 190 mg/dl.
- LDL-c > 250 mg/dl in individuals over age 18, or >190 mg/dl if the individual is <18 years of age.
- LDL-c between 190 and 249 mg/dl on at least 2 occasions

2. In individuals with early cardiovascular disease and high TC levels (43).

3. In individuals >40 in whom TC levels are higher than 360 mg/dl or levels of LDL-c >260 mg/dl and in individuals age 30-39 with levels of TC >340 or LDL >240 mg/dl (89; 91).

Evidence summary

4	The U.S. MEDPED study proposes TC and LDL-c levels for establishing a diagnosis of suspected FH by age and family histories of FH. These TC and LDL-c levels present 98% specificity for a diagnosis of FH (91).

Recommendation

✓	Familial hypercholesterolaemia should be suspected in: 1. Patients with previous cases of familial hypercholesterolaemia in first-degree relatives. 2. In individuals with no previous cases of familial hypercholesterolaemia, with early cardiovascular disease and high cholesterol levels. 3. Individuals >40 with total cholesterol levels above 360 mg/dl or LDL-c levels of >260 mg/dl, and in individuals 30-39 years old with TC levels of >340 or LDL>240 mg/dl.
✓	The recommendation is to determine total cholesterol in all first-degree relatives of patients with familial hypercholesterolaemia, starting at age 10.
✓	Individuals suspected of familial hypercholesterolaemia should undergo the MedPed test and be referred to specialist care.

3. Non pharmacological measures

3.1. Lifestyles

QUESTIONS TO ANSWER

♦ Are the changes in lifestyles that have an impact on lipid profiles effective in reducing cardiovascular morbidity and mortality in primary and secondary prevention?

♦ What are the most efficient strategies to secure a change in lifestyle?

♦ How long must we wait after securing changes in lifestyle before beginning lipid-lowering treatment?

3.1.1. Diet

We have to start with the assumption that changes in diet may have beneficial effects on a broad range of factors that increase the risk of cardiovascular disease. Replacing saturated fats in a diet with carbohydrates, polyunsaturated fats and monounsaturated fats, for instance, has an impact on an individual's lipid profile and oxidation status. Therefore, searching for evidence on different diets poses important operational issues.

Despite the difficulties, however, the selected guidelines are consistent in recommending diets that are low in saturated fats and rich in fibre. However, we must not forget that the guidelines are of Anglo-Saxon origin, and therefore they do not mention the Mediterranean diet explicitly (8-11).

The Mediterranean diet

Discussions on the benefits of a Mediterranean diet started with the seven countries study (94). The diet refers to the dietary patterns of the Mediterranean countries towards the end of the 50s and beginning of the 60s (Annex 7). It

is important to highlight that the Mediterranean diet should be considered a lifestyle that includes other healthy habits such as physical activity and a simple dietary pattern.

Although diets vary between regions, the key features of a Mediterranean diet are:

- A high ingestion of grains, pulses, fruit, vegetables, nuts and dried fruit
- Olive oil as the primary source of fat
- Moderate chicken, fish, milk and diary product consumption (in the shape of cheese and yoghourt)
- A low consumption of meat
- A moderate consumption of wine
- A high degree of physical activity

Certain authors suggest that the Mediterranean diet may be linked to a reduction in CVR and cancer because it contains substances such as selenium and glutathion, as well as a positive omega-6/omega-3 ratio, large quantities of fibre, antioxidants (the resveratrol content of wine and the polyphenols in olive oil), and vitamins E and C (95).

In fact, Mediterranean countries have higher survival rates than northern European countries and, at the same time, lower ischaemic heart disease levels (5; 94) despite a high prevalence of CVR factors. This has led to the assumption that certain lifestyles, such as diet and physical activity, may be associated to this epidemiological scenario.

All the observational studies are along the same lines, including a SR that assessed the heart protection effect of a Mediterranean diet in primary prevention, with a reduction in the risk of coronary events with RR varying between 0.55 and 0.92 (96).

Another review, which included experimental studies, showed positive effects in lipid profiles, insulin resistance, antioxidant capacity, cardiovascular mortality and cancer incidence in obese individuals and those who have had an ischaemic heart disease (97).

One RCT was found to assess the efficacy of the Mediterranean diet in secondary prevention: The Lyon Diet Heart Study (98). The study included individuals with AMI, and compared the Mediterranean diet with the medical advice normally given to AMI patients. The 46.7-month follow-up showed a reduction in

coronary mortality and non-fatal AMI [RR 0.28 (95% CI: 0.15 to 0.53)]. However, the study showed methodological limitations –notably that the intervention group was administered a margarine rich in linolenic acid– which made it difficult to generalize the outcomes. Another study on the Mediterranean diet, the Indo-Mediterranean Diet Heart Study (99), also had important methodological limitations.

Therefore, further experimental studies are needed to assess the role of the Mediterranean diet in primary prevention. One trial, called the PREDIMED study, is currently being developed in individuals with at a high CVR and the intermediate outcomes have already been published. The study compares the effect of two Mediterranean diets, one with a supplement of virgin olive oil (1 litre per week) and the other with walnuts (30 gr daily), with a low-fat diet. When compared to the low-fat diet, the Mediterranean diet (olive oil or walnuts) has a positive effect on the lipid profile, increasing HDL-c and reducing the TC/HDL-c ratio and the TG. The Mediterranean diet also improves the glycaemic profile and arterial blood pressure levels. However, no differences are to be found in the AMI of individuals who consume one diet or the other (100; 101).

Fat intake

Low-fat and modified-fat diets

In daily medical practice, a low-fat/modified-fat diet is frequently recommended to change lipid profiles and, subsequently, to prevent cardiovascular diseases. In low-fat diets, the total fat intake should be less than 30% of the diet's total calories, with less than a 10% intake of saturated fats and a limited intake of cholesterol-rich foods (less than 300 mg daily in primary prevention and less than 200 mg daily in secondary prevention).

As to whether low-fat diets are effective, one SR includes 27 RCTs comparing low-fat/modified-fat diets and/or cholesterol with a normal diet, control diet and placebo diet. In the review, the studies with a follow-up of more than 2 years showed a reduction in cardiovascular events [RR 0.76 (95% CI: 0.56 to 0.90)]. No differences in mortality were found. The differences in event ratios were similar in patients at a high and at a low CVR, aside from the methods used to modify the diet.

Another recent SR compares low-fat diets with diets low in carbohydrates and shows that the latter produce positive changes in TG and HDL-c levels.

Low-fat diets bring about higher reductions in TC and LDL-c (103).

Although the above reviews suggest that the reduction and/or modification in a diet's fats should prevent cardiovascular events, their outcomes are not conclusive. Moreover, such diets may be difficult to follow (103). In contrast, the Mediterranean diet is richer in fats; it belongs to our culture, and it has proved to be effective. Therefore, it should be easier to follow for healthy individuals and/or those who have had an episode of ischaemic heart disease.

Monosaturated and polyunsaturated fatty acids

Olive oil. Olive oil as the main source of fats is one of the key features of a Mediterranean diet. Virgin olive oil is rich in unsaturated fatty acids and polyphenol antioxidants (104). However, whereas virgin olive oil retains its original properties, these may be lost during the refining process.

As to its effects, certain case-control studies conducted in Navarre support the beneficial effects of olive oil by showing that in an olive oil (54 gr daily, on average) intake (the highest versus the lowest quintile) is associated with a reduction in the risk of AMI [OR 0.18 (95% CI: 0.06 to 0.63)] (105).

Walnuts. Walnuts are rich in monosaturated and polyunsaturated fatty acids and have beneficial effects on lipid profiles. One SR shows that an intake of 4 walnuts daily (40-84 gr per day), as compared to a control diet, lowered TC between 2% and 16% and LDL-c levels between 2% and 19% (106). In these studies, eating walnuts was part of a low-fat healthy heart diet.

Fruit and vegetable intake

Although the benefits of eating fruit and vegetables are largely assumed in western culture, all RCTs assess their efficacy in lowering cardiovascular morbidity and mortality. Nonetheless, several SR of observational studies point out that an increased intake of fruit and vegetables could be related to a reduction in CVR (107-109). The outcomes of several meta-analyses of cohort studies point in the same direction by showing a reduction in cardiovascular events associated with an increase in fruit and vegetable intake (110; 111). The intake of more than 5 portions daily reduces the risk of cardiovascular events by 17% [RR 0.83 (95% CI: 0.77 to 0.89)] (110).

How should advice on diets be given?

Several SR that assessed the efficacy of dietary advice in diminishing CV risk were detected (112; 113).

After 3-12 months of a diet intervention that included oral and written advice delivered in hand or by phone, and individually or in small groups, 5 mg/dl reductions in TC and 5.02 mg/dl reductions in LDL-c were found (112).

When a dietician assigns a diet, the reductions are higher than when the intervention is done by a doctor [-0.25 mmol/L (95% CI: -0.37 to -0.12 mmol/L)]. However, no differences are found when an intervention by a dietician is compared to an intervention by a nurse or when patients are given self-help material (written material with information on nutrition, diets, and videos) (113).

Finally, although the Mediterranean diet has proved to be effective (mainly in secondary prevention), the efficacy of the recommendation as such is not known.

Evidence summary

1+	A Mediterranean diet reduces the incidence of AMI and coronary mortality in individuals who have had AMI (98).
1+	Compared to low-fat diets, the Mediterranean improves lipid profiles (raises HDL-c and lowers the TC/HDL-c ratio and TG), glycaemic profiles and blood pressure levels in patients at a high CVR (100; 101).
1+	Apart from CVR levels, low-fat diets and fat or cholesterol-modified diets show a decline in cardiovascular events when compared to a normal diet (102).
1+	An intake of 4 walnuts daily (40-84 gr per day) lowers TC between 2% and 16% and LDL-c levels between 2% and 19% (106).
2+	A daily intake of fruit and vegetables is associated with a decline in cardiovascular events (107-111).
1+	Oral or written dietary recommendations, either face-to-face or by phone, and in small groups or individually, secures minor reductions in TC and LDL-c (112).
1+	Dietary recommendations given by nursing staff evidenced no difference in reducing cholesterol levels compared to the recommendations given by dieticians (113).

Recommendation

C-B*	It is recommended to advise the general population and individuals who have suffered a coronary event (*) to follow the Mediterranean dietary model (diet and physical activity). Essentially, this advice should be given in infirmaries.
B	Efforts should be made to promote the daily consumption of fruit and vegetables.

3.1.2. Alcohol

A moderate alcohol intake has beneficial effects on cardiovascular disease. At the same time, however, the adverse effects of alcohol when taken in excess should also be considered. Several observational studies support the foregoing statement by showing a J-shaped relationship between alcohol intake and global mortality. That is, CVR gradually diminishes with a moderate alcohol intake, after which the curve reaches a plateau and subsequently tends to become inverted with a higher vascular risk accompanying a heavy wine intake. Thus, a moderate alcohol intake has a preventive effect, whereas an heavy alcohol intake causes an increase in cancer and other fatalities (8-11).

In fact, a meta-analysis of the observational studies shows a 32% reduction in cardiovascular risk associated with wine intake [RR 0.68 (95% CI: 0.59 to 0.77)], as well as a slightly lower reduction (22%), associated to beer intake [RR 0.78 (CI 95%: 0.70 to 0.86)]. The highest preventive effect occurs with an intake of 25 g/d of alcohol (2 units/d)* in men and 10 g/d in women (1 unit/d)* (114; 115).

Another review of experimental studies, in which positive changes were found in lipid and thrombolytic profiles, estimates similar benefits accompanied by biochemical changes. Thus, the estimation is a 3.99 mg/dl increase in HDL-c levels (95% CI: 3.25 to 4.73) associated with an average daily alcohol intake of 30 gr (3 units of alcohol), in comparison to abstemious individuals (116; 117).

No guidelines recommend telling non-drinkers to take alcohol for health purposes, with the exception of the SIGN guideline that mentions the possibility of advising a moderate alcohol intake (9). Both positions were attained by a consensus between the guideline authors.

Given that a moderate alcohol intake may prevent the development of cardiovascular disease, it may be used as advice to individuals at a moderate to high risk of suffering a cardiovascular disease.

This implies that, as in other aspects addressed in this guideline, a patient's CVR should be taken into account when considering the beneficial effects of a moderate alcohol intake.

---

* 1 unit of alcohol is equal to 1 small glass of wine, 1 beer, half a glass of brandy or one coffee with brandy. 2 units of alcohol are equal to 1 glass of wine, a glass of brandy or one Rum and Coke highball or similar.

Evidence summary

2++	An association is observed between drinking wine or beer and a reduction in CVR. The highest preventive effect occurs with an intake of 25gr/d of alcohol (2 units/d) in men and 10 g/d in women (1 unit/d) (114; 115).
2++	Benefits in cardiovascular disease were only found in moderate wine ingestion. The complex relationship found between wine ingestion and CVR reflects a higher vascular risk associated with heavy drinking (114; 115).

Recomendación

C	It is recommended to advise the general population and patients who have suffered a cardiovascular disease that they should continue to consume alcohol, providing their previous alcohol consumption pattern was low or moderate.
C	The recommended level of alcohol consumption must not exceed 2 units daily of alcohol in men and 1 unit daily in women.
✓	Information on the benefits of alcohol must be accompanied by a clear explanation of what one unit of alcohol represents and the adverse effects of heavy drinking.

3.1.3. Physical activity

The 2002 Basque Health Survey (ESCAV-2002) shows less physical activity during free time, so only 23% of men and 14% of women age 16 and over can be considered active (118).

Physical activity, however, is a complex variable that is difficult to study, and therefore there are no widely accepted definitions. Physical activity has been defined as "any body movement caused by skeletal muscle contractions that increases energy expenditure" (119). Activities include walking, sports, and dancing.

Exercise, therefore, is considered a subcategory of physical activity. The International Paris Task Force defines exercise as a series of specific movements for training purposes, or to develop the body for routine practice and health-promoting training (120).

In any event, physical activity of any sort brings about changes in a lipid profile by lowering TG and TC concentrations, and raising HDL-c levels (43; 117; 121; 122).

Although cohort studies show a lower global mortality rate and fewer coronary events in individuals who are more physically active, there are no RCTs in primary prevention to assess the efficacy of physical activity in reducing cardiovascular events. Recommendations to do physical activity attains higher increases in activity levels when moderate-high intensity exercise is prescribed, and/or when the advice is accompanied by written material or phone call follow-ups (123).

A SR that compared a rehabilitation intervention program with the regular secondary prevention care dispensed to patients with ischaemic heart disease was analysed. In the studies, intervention varied from a programme of aerobic exercises twice a week for 4 weeks to interventions lasting 30 months. Heart rehabilitation managed to lower global mortality [OR 0.8 (95% CI: 0.68 to 0.93)] and heart mortality [OR 0.74 (95% CI: 0.61 to 0.96)]. The effect on global mortality was separate from the type of rehabilitation, duration, and doses of exercise (108; 123).

The NICE CPG on physical activity recommends moderate activity for 30 minutes at least 5 days per week (124).

3.1.4. Weight loss

Currently, obesity (BMI>30 kg/m^2) is an important and highly prevalent health problem. The ESCAV-2002 finds a 9.9% prevalence of obesity in the CAPV (10.4% in men and 9.5% in women). It is also one of the most important risk factors in cardiovascular disease (4).

As one SR that includes 302,296 individuals' shows, obesity is associated with a risk of coronary disease even after taking the effect of obesity on blood pressure and cholesterol levels. The review demonstrates that moderate overweight (BMI: 25-29.9 kg/m^2) with an RR of 1.17 (95% CI: 1.11 to 1.23) and, above all, obesity (BMI>30 kg/m^2) with a RR of 1.49 (95% CI: 1.32 to 1.67) are associated with a higher CR (30).

Primary prevention

One SR that assesses the efficacy of several interventions (drug therapy, exercise, behavioural techniques and a combination of all three) for weight loss in obese adults finds a 10 kg weight loss accompanied by TC reduced by 9.6 mg/dl and diastolic blood pressure reduced by 3.6 mmHg (125). Moreover, the HDL-c may increase 0.35 mg/dl per kg of weight loss (117).

These benefits are more marked in individuals with a high CVR (126). Although weight loss would have a modest effect on each individual risk factor, the benefit on global CVR may be high. Although observational studies suggest that weight loss in obese patients with associated morbidity lowers mortality, there are not RCTs that demonstrate the effect of weight loss on cardiovascular morbidity and mortality (127).

Combined treatments (diet, physical activity and behavioural techniques) reduce weight more effectively than ordinary treatments. Low-fat diets cause more weight loss after 12 months than normal diets (5.3 kg (95% CI: 4.8 to 5.9)], with the differences disappearing after 36 months. When diet is combined with exercise, weight loss is 8.22 kg after 36 months (95% CI: 1.16 to 5.27) as compared to diet alone (107). Combining exercise with diet leads to important changes in HDL-c and TG levels after 12 months of treatment (125). However, the above studies include supervised exercise programmes that are hard to put into practice because they include walking, running and biking until

a maximum heart rate of 60-80% is reached, with at least 20 minutes of exercise up to a maximum of 90 minutes 3 times per week.
Finally, there is no conclusive evidence about the effect of lifestyles (diet, physical activity and behavioural techniques) on preventing weight gain and maintaining weight (107).

Evidence summary

2+	Higher levels of physical activity by healthy people are associated with lower global mortality and fewer coronary events (123).
1+	In primary prevention, physical activity increases more when moderate-high intensity exercise is recommended, and when the advice is accompanied by written material or phone call follow-ups (123).
1++	Heart rehabilitation diminishes global mortality and cardiac mortality (123).
2++	Moderate overweight and obesity are associated with an increase in the risk of coronary disease (30).
1++	A 10 kg weight loss in obese adults is associated with a reduction in total cholesterol of 9.6 mg/dl and reductions of 3.6 mmHg in diastolic blood pressure. HDL-c increases 0.35 mg/dl per kg of weight loss. These benefits are more marked in high CVR populations (126).
1++	Combined interventions (diet, physical activity and behavioural techniques) to lose weight are more effective than isolated interventions in obese adults (107).

Recommendation

B	The general recommendation is aerobic-intensive exercise such as walking, running, moderately strenuous swimming for at least 30 minutes, five days per week; or strenuous activity for at least 20 minutes, three days per week.
C	In overweight or obese individuals, the recommendation is to reduce calorie intake and to increase physical activity.

3.2. Functional foods

QUESTIONS TO ANSWER

♦ Are functional foods, vitamin supplements and dietary complements effective in reducing cardiovascular morbidity and mortality in patients with lipid disorders?

Functional foods have been defined as foods that provide health benefits beyond their basic nutritional value. Several substances are employed as supplements and additives in foods to improve cardiovascular health, namely omega-3 fatty acids, plant sterols and soy protein (Annex 10).

3.2.1 Omega-3 fatty acids

Guidelines recommend omega-3 fatty acids from fish (eicosapentaenoic acid and docosahexaenoic acid) and vegetables (alpha-linolenic acid) as supplements and/or by fish intake (8-11; 120) (Annex 11).

A recent SR, however, which includes RCTs with follow-ups in excess of 6 months did not find that taking omega-3 fatty acids with the diet or as supplements had any effect on total mortality, cardiovascular events and cancer in the general population, in individuals at high CVR, and those who had cardiovascular diseases. Mention should be made, however, that the studies included in the RCT are not uniform (128), and heterogeneity disappeared when the study by Burr et al. was eliminated (129). This study, which includes patients with angina, found an increase in mortality in the group assigned to omega-3 [(RR 1.26 (95% CI: 1 to 1,58)]. In contrast, the GISSI-prevenzione study, which included patients with recent AMI, found that omega-3 fatty acids reduced global mortality [RR 0.86 (95% CI: 0.77 to 0.97)] (130).

Thus, although omega-3 fatty acids were not found to diminish cardiovascular events, they may benefit a subgroup of AMI patients (128).

As to the effect of omega-3 fatty acids on lipid profiles, a meta-analysis of 21 RCTs designed to assess the effect of consuming fish oil on plasma CVR markers found that fish oil intake increased LDL-c by 6 mg/dl

(95% CI: 3 to 8), increased HDL-c by 1.6 (95% CI: 0.8 to 2.3), and lowered TGs by a net 27 mg/dl (95% CI: 20 to 33), with no effect on TC (131).

3.2.2. Phytosterols

Phytosterols or plant sterols are molecules of plant origin that are similar to cholesterol in structure. Stanol esters are saturated sterols produced by the hydrogenation of plant sterol esters. The most common sterols are beta-sitosterol, campesterol and stigmasterol, and their most widely used saturated forms are sitostanol and campestanol (132).

The phytosterol mechanism occurs primarily through a competitive inhibition of cholesterol absorption at the intestinal level. Phytosterols added to margarine, yoghourt, cereal and dairy products have been proposed for hypercholesterolaemia therapy due to their effect on blood lipids.

The guidelines (8-11) consider phytosterols as a treatment option for reducing cholesterol levels, although studies made with plant sterols have short follow-up periods and only changes in lipid levels were studied as outcome variables. No RCTs that assess the effect of phytosterols in reducing mortality and cardiovascular events were found.

As mentioned above, several meta-analyses study the effect of sterol/stanol esters in blood lipids (133-136). They show a 10% decrease in blood LDL-c levels and a 7% to 1% reduction in TC. No changes in HDL-c and TG were found (133; 134). An optimal reduction in LDL-c is attained with an intake of around 2 g/day of sterol/stanol ester (135; 136) and intakes of less than 1 g/day or of more than 3 g/day are not justified (132). The effect of sterols and stanol esters remain after one year of intake (135).

These studies found no important secondary effects and the sterols and stanol ester were well tolerated. It should be mentioned, however, that the Katan meta-analysis shows a significant reduction in hydrocarbonated caretenoids (carotenes) (135). Although no alterations of vitamin A and D were detected, the effect of a decrease in betacarotene for prolonged periods in children and during pregnancy are unknown.

Therefore, the consumption of butter, yoghourt and other foodstuffs with sterol and stanol ester supplements may be considered clinically unjustified in the general population (135). This consideration is particularly important where children are concerned.

3.2.3. Soy

Although the guidelines make no clear recommendation on the use of soy (8-11) and no RCTs assess the efficacy of soy in reducing cardiovascular morbidity and mortality, soy protein has been widely used as a therapeutic option in lowering LDL-c. Therefore, the available evidence was analysed.

Soy with and without isoflavones

In two recent meta-analyses of 23 and 41 RCTs that used soy protein with isoflavones, the reduction in LDL-c and TC was very discreet (4 to 8 mg/dl and 5 to 8 mg/dl, respectively). The duration of most of the studies is limited to a few weeks of follow-up (3-6 weeks) and heterogeneity among the studies was high. The doses of soy protein were so unequal between studies (between 20-106 mg/day) that it was impossible to decide the most appropriate quantity to use. No secondary effects are reported in these two meta-analyses (137; 138).

Another meta-analysis, designed to assess the precise effect of soy isoflavones on TC, LDL-c and HDL-c found a reduction in LDL-c of 5 mg (95% CI: 2.7 to 7.7 mg/dl), associated with an intake of soy protein enriched with isoflavones in comparison to non-enriched soy protein (with no isoflavones). The difference in TC reduction was minimal [TC: 3.9 mg/dl (95% CI: 0.8 to 6.6)] between the two types of soy protein (139).

In any event, such a discreet reduction in LDL-c and TC associated with soy intake, the short duration of the studies and the lack of data on their impact in clinical variables does not allow the studies to be used as a basis for a recommendation.

Evidence summary

1++	Omega-3 fatty acids have not proved to diminish cardiovascular events reliably. However, some subgroups of AMI patients may obtain a clinical benefit from using them (128).
1++	Omega-3 fatty acids lower TGs by a net 27 mg/dl (95% CI: 20 to 33), with no effect on TC as compared to a placebo (131). No RCTs assess the effect of phytosterols in reducing mortality and cardiovascular events.
1+	2 grams of phytosterols lower LDL-c by 10%-5%. Phytosterols lower blood carotenes with no repercussions on vitamin A in the short term (135).
1+	Soy protein causes very discreet reductions in LDL-c and TC (138).

Recommendation

D	To eat fish as a source of omega-3 acids, and non-saturated fats as part of the Mediterranean diet.

3.3. Medicinal plants

QUESTION TO BE ANSWERED

♦ **Are medicinal plants effective in reducing cardiovascular morbidity and mortality in patients with high cholesterol levels?**

Several medicinal plants have been used to lower cholesterol levels, including garlic (Allium sativum), guggul (Commiphora mukul), whole grain red rice (Monascus purpureus), and artichokes (Cynara scolymus).

However, no RCTs assess the efficacy of these products in reducing cardiovascular events. The ATP III Guideline (8) does not recommend using medicinal plants to reduce CVR and warns of potential interactions between medicinal plants and drugs.

Several SR have analysed the effects of medicinal plants in lowering cholesterol (140-142).

♦ **Garlic (Allium sativum).** Published studies suggest that garlic acid is superior to placebo in reducing cholesterol levels. However, the effect is small and outcomes among the studies are inconsistent (140).

♦ **Guggul (Commiphora mukul).** The studies that assess the effects of this medicinal plant on individuals with high cholesterol levels show contradictory outcomes. Moreover, it causes intestinal disorders, skin allergies, and interactions with drugs such as propanolol and diltiazem (141; 142).

♦ **Whole grain red rice (Monascus purpureus).** Several RCTs show reductions in TC concentrations of 16% to 31%. The most frequently found adverse effects are dizziness, epigastralgia and flatulence (142).

♦ **Artichokes (Cynara scolymus).** The outcomes of 2 RCTs show contradictory conclusions (142).

In short, the conclusion would be that the efficacy of these medicinal products in lowering CVR and their safety in the long term has not been reliably established.

Evidence summary

1++	The available evidence shows inconsistent data on the efficacy of medicinal plants in lowering cholesterol levels (140-142). No RCTs assess clinical outcomes.

Recommendation

A	The use of medicinal plants to lower coronary risk is not recommended.

4. Drug therapy

4.1. Drug therapy in primary prevention

4.1.1. General population

QUESTIONS TO ANSWER

- **When must we begin lipid-lowering therapy in primary prevention in Southern Europe?**
- **What is the most effective lipid-lowering therapy in primary prevention?**
- **When is it necessary to begin lipid-lowering therapy in secondary prevention?**

As mentioned above, in Mediterranean countries the risk of cardiovascular death is lower than the risk found in northern Europe countries and America. None of the selected guidelines addresses the issue specifically, owing to their Anglo-Saxon origin. Therefore, the recommendations for intervention given in this guideline are based on a lower CR in the CAPV than cardiovascular risk in the countries were most of the studies were conducted. Thus, in the interpretation of findings in the studies that analyse the efficacy of lipid-lowering drug therapy, it is worth noting that the trials were carried out on populations whose baseline CVR was considerably higher than CVR in the CAPV (4 times higher, according to the MONICA study). This is an important limitation when it comes to applying the outcomes of the said studies to the CAPV context (5).

Moreover, the controversial aspect of lipid-lowering drug therapy in the primary prevention of cardiovascular disease is worth mentioning as a preliminary consideration. An example is the recommendations given in the guidelines used as a benchmark in the process of preparing this guideline (8-11). Whereas SIGN (9) considers that drug therapy should be begun in patients at a higher CVR than 20%, the

ATP III Report (8) establishes several treatment strategies, depending on the level of risk and the existence of other CVR factors.

On the other hand, the guidelines recommend therapy with no drugs (diet, physical activity) for 3 to 6 months prior to lipid-lowering therapy (8-11).

To answer this question, several RCTs have been published in which trials were carried out on individuals with no record of cardiovascular disease.

The findings of the review are given separately for each study outcome.

Mortality

♦ **Statins.** SRs based on studies in primary prevention do not show that statins reduce total mortality and coronary mortality. The study by Vrecer et al. shows a reduction in cardiovascular mortality of little clinical significance [RR 0.66 (95% CI: 0.49 to 0.90)], since the NNT is 229 (147; 148).

No differences in total mortality are to be found in the meta-analysis by Thavendiranathan et al. [RR 0.93 (95% CI: 0.86 to 1.01)], or in coronary mortality [RR 0.77 (95% CI: 0.56 to 1.08)] between the statin and placebo groups (149).

No reductions in global and coronary mortality were found in the primary RCTs (56; 57; 59; 60). The West of Scotland Coronary Prevention Study Group (WOSCOPS), carried out on men ages 45 to 65 at a high CVR was the only study that showed a reduction in cardiovascular mortality of little clinical significance[RR 0.68 (95% CI: 0.48 to 0.98); NNT 143] (143). Recently published data on the follow-up of this cohort of individuals show that 10 years after therapy was discontinued, the group who were initially assigned pravastatin continued to have a lower risk for the combined variable (non-fatal AMI and death attributable to coronary disease) [0.82 HR (95% CI: 0.69 to 0.96)]. No differences in mortality between the two groups were found, however (150).

♦ **Fibrates** An increase in non-cardiovascular mortality was found in two meta-analyses that included primary and secondary prevention RCTs carried out with fibrates [1.16 OR (95% CI: 1.05 to 1.29)] with an insignificant trend towards an increase in total mortality in the fibrates group in comparison to the placebo group [1.07 OR (95% CI: 0.99 to 1,15)] (151; 152). These differences are not maintained when the RCTs using clofibrates as an active therapy were excluded (145; 153). Likewise, this

difference in non-cardiovascular mortality was not found in another meta-analysis where the WHO study using clofibrate as an active therapy was excluded (154). The WHO study showed an increase in total mortality [1.28 RR (95% CI: 1.02 to 1.61)] in the treatment group related to other medical causes, namely hepatic and intestinal pathology (145).

The Helsinki Heart Study (HHS) carried out with gemfibrozil in primary prevention found no difference in global mortality and death attributable to other causes between the intervention and placebo groups (144).

♦ **Resins.** Several SRs study the efficacy of resins (cholestyramine and colestipol) without finding a decrease in global mortality. One of the studies, however, includes primary and secondary prevention studies that show a discreet decrease in coronary mortality [0.7 RR (95% CI: 0.50-0.99)] (148; 152).

♦ **Niacin (nicotinic acid).** Primary prevention efficacy studies with niacin are short lasting, conducted with a limited number of patients and for outcome variables, they only study niacin's effect on lipid profiles, not on clinical variables.

One meta-analysis that included 30 trials showed that niacin therapy is accompanied by a reduction in TC levels (-10%), TG (-20%) and LDL-c (-12%), and an increase in HDL-c (16%) (154).

A 1000 to 3000 mg/day dose was used in single-drug therapy (155; 156) and in combination with statins (157; 158). This combination produces higher reductions in LDL-c that the statins in single-drug therapy (159).

Coronary events

♦ **Statins.** The meta-analyses conducted by Vrecer et al. and Cucherat et al, which includes primary prevention patients, show a decrease in the risk of coronary events in patients undergoing treatment with statins [0.67 RR (95% CI: 0.58-0.77)] (147; 148).

A decrease in major coronary events (non-fatal AMI and coronary death) was also found, with an RR of 0.71 (95% CI: 0.60-0.83) in the meta-analysis by Thavendiranathan et al. However, the value of their conclusions is restricted by the clinical heterogeneity among the clinical trials included in the study and reflected in the variable's statistical heterogeneity (149).

Likewise, the RCTs (56; 57; 143) on primary prevention patients show that statins lower the incidence of non-fatal AMI [0.7 RR (95% CI: 0.57-0.86)]

(143) and unstable angina [0.67 RR (95% CI: 0.52-0.85)] (56). In any event, the patients who require therapy over a 5 year period to prevent a coronary event varies in number between 54 and 225, with the patients at the highest risk being the ones who will benefit the most from statin therapy.

♦ **Fibrates.** Gemfibrozil in primary prevention for patients with slightly high TG (175 mg/dl) has also proved to lower non-fatal AMI (0.63 RR (95% CI: 0.43-0.91); NNT 77] (144; 151).

Cerebrovascular event

♦ **Statins.** The meta-analysis by Vrecer et al. found no difference between the statin and placebo groups in the prevention of total ACVE (0.96 RR (95% CI: 0.32-2.88)] (147). In another meta-analysis, however, a slight decrease in major Cerebrovascular events [0.86 RR (95% CI: 0.75-0.97); NNT 280] of little clinical significance were found (149).

The Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm Study (ASCOT-LLA) (59) found a slight decrease of little clinical significance in the risk of fatal and non-fatal ACVE [0.73 RR (95% CI: 0.56-0.96); NNT 156]. However, in most of the primary prevention studies for which data on cerebral ACVE were collected, statins have not proved to prevent the onset of cerebrovascular events (56; 57; 60; 143).

♦ **Fibrates.** Only a very limited number of events are recorded in the HHS study (144).

Compounded outcome variables

The clinical trial's main outcome variable consisted in an aggregate

variable which included several combinations:

1. Non-fatal AMI or coronary death (59; 143)
2. Non-fatal and fatal AMI, and coronary death (144)
3. Non-fatal AMI, coronary death or unstable angina (56)
4. Fatal and non-fatal infarction, or coronary death, sudden death or revascularization (57).

♦ **Statin.** A reduction in the compound variable of 31% to 36% was found [0.7 RR (95% CI: 0.58 to 0.84)] in the two studies conducted with patients at a major CVR

(59; 143). The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), which included unstable angina in the combined variable, also obtained a reduction in risk[0.63 RR (95% CI: 0.50 to 0.79)] in patients who took statins. In this study, more than 30% of the decrease in risk was owed to a decrease in the incidence of unstable angina (0.69 RR (95% CI: 0.50 to 0.95); NNT 123] (56).

♦ **Fibrates.** In the HHS study, the main variable (fatal AMI, non-fatal AMI, cardiac death) showed a RR of 0.66 (95% CI: 0.47 to 0.92) in favour of gemfibrozil therapy with a NNT of 72 (144).

♦ **Resins.** The largest RCT in primary prevention using cholestyramine was conducted on men ages 35-53 with primary hypercholesterolaemia during a 7.4-year follow-up and with a daily dosage of 24 gr. The study showed a reduction in the primary variable (coronary death and non-fatal AMI) of 19% (95% CI: 3 to 2), [0.81 RR (90% CI: 0.68 to 0.97)], with no differences found in global mortality (146).

♦ **Ezetimibe.** Currently there are not RCTs that assess clinical outcome variables using ezetimibe.

None of the RCTs conducted in primary prevention show an increase in survival with the use of statins at low to mild dosages, although a decrease in non-fatal coronary events in high-risk patients was found.

All commercial statins lower TC and LDL-c levels and raise HDL-c levels. On the other hand, statins have a non-linear dose-response curve, so their effect does not increase proportionately with the doses. Their pharmacological effect is dose-dependent, and all statins have similar efficacy and adverse effects when administered in equally strong doses.

Evidence summary

1++	In primary prevention, statins do not lower total mortality and coronary mortality (56; 57; 60; 147; 148).
1+	Clofibrate therapy in primary prevention increases total mortality, compared to placebo. No evidence exists that mortality will increase with other fibrates (145; 154).
1++	In primary prevention, statins at low to mild doses do not lower total mortality and coronary mortality (56; 57; 143; 144; 147).
1+	Gemfibrozil in primary prevention in patients with moderately high TG have proved to lower non-fatal AMI (144).
1+	In primary prevention, cholestyramine has proved to reduce acute events without lowering total mortality (146; 148; 152).
1++	No differences exist between statins and placebo in the primary prevention of fatal and non-fatal ACVE (59; 60; 130; 143; 147).
1+	In high blood pressure patients with a high CVR, ACVE was lowered in patients undergoing statin therapy, compared to placebo patients (59). There are no RCT to assess clinical outcome variables for ezetimibe.
1+	Niacin is associated to a reduction in TC, TG and LDL-c levels and an increase in HDL-c. There are no studies to assess clinical outcomes (154).

Recommendation

D	6 months of dieting and physical activity is recommended prior to beginning the lipid-lowering treatment.
A	Primary preventive measures with low to mild dose statin are recommended in patients of ages 40-75 with >20% coronary risk levels according to the REGICOR equation. Recommendations for a cardio-healthy lifestyle should be given before and/or during pharmacological treatment.
B	Treatment with low to mild statin doses in patients with coronary risks of between 10% and 19%, determined by means of the REGICOR project equation, must be made after treating other cardiovascular risk factors (obesity, HBP, smoking).

(Continues below)

(Continuation)

B	In patients with coronary risks of between 10% and 19%, determined by means of the REGICOR project equation and the presence of other non modifiable cardiovascular risk factors (family case histories of premature coronary death, previous cases of family hypercholesterolaemia, preclinical evidence of arteriosclerosis), starting treatment with low to mild statin doses should be considered.
✓	Therapy should begin with low to mild dose statin in patients with isolated levels of total cholesterol higher than 320 mg/dl and/or LDL-c levels of 240 mg/dl.
✓ **B(*)** **D(**)**	The recommendation for patients with a prescription for statin therapy in primary prevention and intolerance to statins is to insist on non-drug therapy and to lower the dose or change to another statin. If intolerance persists, the recommendation is to begin fibrate therapy*. Other options may be resins* and/or ezetimibe**.

4.1.2. Women

As in other sections of this guideline, a systematic bibliographic search was conducted to respond to the efficacy of drug therapy in primary prevention for women. The outcomes draw attention owing to the limited number of RCTs that allow the matter to be addressed. Only one SR collects the outcomes of 5 RCTs with statins and one with colestipol to analyse statin in the prevention of coronary mortality in women. The review, which included outcomes found in 11,435 women with no cardiovascular disease, did not find evidence of a beneficial effect of statins in primary prevention for women. It should be mentioned that the review found few primary prevention studies in this population group, some of which would not allow a gender-disaggregated analysis. Nonetheless, the available outcomes based on this one review do not allow beneficial outcomes to be expected in women undergoing statin therapy. An RR for CV mortality of 1.07 (95% CI: 0.4 to 2.4) is found in women treated with statins (41).

Two more RCTs were published after this review. One of them, the ASCOTLLA, conducted with Atorvastatin, includes women with a high CVR (high blood pressure with two or more risk factors), among other patients. In the trial's subgroup of women, no decrease in coronary death and AMI [1.10 RR (95% CI: 0.57 to 2.12)] was found in women treated with Atorvastatin (59). Likewise, the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study conducted in a Japanese population with a low CVR also failed to find benefits for coronary disease with pravastatin [0.71 RR (95% CI: 0.44 to 1.14)] (57).

Currently available evidence does not show that statins are effective as a primary prevention method in the case of women. Therefore, it should be stressed that the available evidence is based on only a few studies that include a relatively low number of women.

At this point, consideration should be given to CR in women in the CAPV. As mentioned above, apart from the MEGA study, the risk is considerably lower than in women from the countries were the benchmark studies were conducted (57).

Therefore, in the absence of evidence of the efficacy of statin therapy in women, and taking women's low CR in the CAPV into consideration, caution should apply before beginning drug therapy in primary prevention. In any event, the decision should be based on an estimate of CR and a detailed analysis of other therapy options to lower CR by intervening on other risk factors.

Evidence summary

1+	In primary prevention, statins have not proved effective in lowering coronary morbidity and mortality (41; 57; 59).
3	The CVR in women in the CAPV is lower than in women from Anglo-Saxon countries, where the studies that provided the available evidence were conducted (160).

Recommendation

✓	In primary prevention, women of ages 40 to 75 at a 10% to 9% coronary risk according to the REGICOR equation should be intervened with preference over other CVR factors before they begin lipid-lowering drug therapy.
C	Women of ages 40 to 75 at a risk of coronary disease >20% should begin statin therapy a low to mild doses.

4.1.3. The elderly

Surprisingly, the selected guidelines do not address the subject of the elderly with sufficient arguments (8-11). Thus, the New Zealand guideline recommends treating patients over age 75 in the same manner as younger patients, with no bibliography whatever to support the recommendation (10). SIGN (9) indicates that age is not a contraindication for beginning the therapy and recommends basing the decision for statin therapy on an estimation of CVR in 10 years, on life expectancy and quality of life, and refers to the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (58). However, the majority of individuals included in this study, on which SIGN bases the recommendation, are patients in secondary prevention.

The instruments for estimating absolute risk of cardiovascular disease in the elderly are less reliable than for middle-aged individuals (8). Moreover, there are no validated instruments in our context with which to estimate CR in patients over age 75 (18; 19).

In such a climate of uncertainty, the results of one SR that recovers 33 cohort studies in the elderly over age 65 is particularly relevant, despite its methodological limitations. In the review, an inverse relationship is found between cholesterol levels and global mortality in the subgroup of patients over age 80.

It is also found that TC levels in men over age 65 are accompanied by a higher incidence of cardiovascular events, and in women, cholesterol levels greater than 260 mg/dl are not accompanied by a higher risk of cardiovascular mortality (161). These outcomes match those of the Honolulu Herat Program, in which, if men ages 71 to 93 are adjusted by age and other CVR factors, global mortality is lower in the subgroup with cholesterol figures greater than 210 mg/dl, with an RR of 0.72 (95% CI: 0.60 to 0.87) when compared, for instance, with mortality for the subgroup with cholesterol levels between 175 to 210 mg/dl (162).

Another recently published cohort study adds even more controversy to the role played by LDL-c and TC in the estimation of CVR in the elderly. In the study, conducted on a Mediterranean population, it is found that the risk of global mortality in women is curved, with a non-linear lowering of risk with the LDL-c level. Global mortality in men and cardiovascular mortality in both sexes shows a J shaped association with LDL-c levels (163).

Finally, a recent meta-analysis of 61 prospective studies indicates that the TC level accompanied by cardiac mortality in all ages includes the elderly, although the association is lower for the elderly over age 70 (0.83 HR (95% CI: 0.81 to 0.85)]. However,

No relationship was found between mortality caused by ACVE and TC in the elderly and in individuals with high arterial blood pressure (164).

It is important to point out that there is only one RCT with lipid-lowering agents conducted specifically in the elderly population. The PROSPER trial included 5.804 patients of ages 70 to 82 with a high CVR or vascular disease. Although beneficial effects for pravastatin was found for the study's main variable (coronary death, non-fatal AMI, fatal and non-fatal ACVE) in a mixed primary and secondary prevention population, the outcomes were modest, with an HR of 0.85 (95% CI: 0.74 to 0.97) and an NNT of 48 patients to be treated over 3 years. In this study, and in keeping with the available information based on the above-mentioned observational studies, the baseline LDL-C levels showed no association with a higher risk of cardiovascular events. Likewise, changes in the LDL-c levels in the group treated with pravastatin were not associated with a lowering of major events. In the subgroup of patients treated in primary prevention, pravastatin did not provide significant benefits for any of the principal study variables (58).

Finally, in an analysis of the subgroup of most elderly patients included in the AFCAPS study, no evidence of the benefits of lovastatin in the prevention of coronary death, non-fatal AMI and unstable angor in patients at a moderate risk (56).

Evidence summary

1++	In the elderly over age 70, pravastatin in primary prevention does not diminish fatal and non-fatal AMI or fatal and non-fatal ACVE (58).
1+	In the elderly with a moderate CVR estimation, lovastatin has no beneficial effects on cardiovascular morbidity and mortality (56).
2+	In the Mediterranean population, cardiovascular mortality showed a J-shaped association with LDL-c levels. For women, a non-linear lowering of global mortality was found with LDL-c levels (163).
2++	A recent meta-analysis of 61 prospective studies indicates that the TC level accompanied by cardiac mortality in all ages includes the elderly, although the association is lower for the elderly over age 70 [0.83 HR (95% CI: 0.81-0.85)] However, no relationship was found between mortality caused by an ACVE and TC in the elderly (164).

Recommendation

D	Estimating the risk of coronary disease with the information afforded by cholesterol levels is not recommended in patients over age 75.
✓	In primary prevention, the decision to begin lipid-lowering therapy with statins in patients over age 75 should be made individually and only after assessing the risks, which may be higher than the benefits for which there is no evidence.
✓	In primary prevention, patients over age 80 previously undergoing treatment with statins, the recommendation is to assess the convenience of interrupting statin therapy on the basis of the patient's life expectancy and quality of life.

4.1.4. Diabetes

QUESTIONS TO ANSWER

- **Are type 2 diabetics at the same cardiovascular risk as individuals who have suffered a coronary event?**
- **When is it necessary to begin lipid-lowering treatment in patients with diabetes?**
- **Should lipid-lowering agents be given to all diabetics?**

4.1.4.1. Cardiovascular risk in diabetes

Risk tables for the diabetic population

This issue is highly important, considering the high prevalence of diabetes mellitus in our context. The estimated prevalence of type 2 diabetes among the general population in the CAPV is 4.6%, and can affect 12.6% of the population of ages 65 to 74 (165).

On the other hand, diabetes is associated with a higher risk of cardiovascular disease. In fact, certain guidelines recommend considering the diabetic population as on the same level for indicating lipid-lowering therapy as patients who have already had a cardiovascular disease (8-11).

Undoubtedly, diabetics are at a higher CVR than individuals who are not diabetic. The risk is 50% higher in women than in men (46). However, the diabetic population is very heterogeneous, with varying levels of CVR. A number of studies compare CVR in diabetics with patients who have had AMI and do not show consistent outcomes between them. However, a higher CVR is found in diabetic women and in patients who have had diabetes for more than 15 years (47-54).

Therefore, tools such as the CVR tables should be used to select the diabetics who will begin treatment with lipid-lowering agents. As in the general population, the recommendation is to use the REGICOR project's risk tables, for which 941 diabetics were included in the validation study. No significant differences were found between the expected events rate based on the REGICOR equation and the events found in the cohort follow-up (19). It is worth mentioning that, aside from the REGICOR equation, one table of risk that only includes the diabetic population exists, designed in the context of the United Kingdom Prospective Diabetes Study (UKPDS). Apart from major risk factors, the study takes the duration

of the diabetes and the levels of glycosylated haemoglobin (HbA1C) into consideration. However, the latter risk tables have not been validated in our context (166).

4.1.4.2. Lipid-lowering therapy in diabetes

The above reasons call for an assessment of the efficacy of lipid-lowering therapy in diabetics with no cardiovascular disease in preventing cardiovascular morbidity and mortality. Several meta-analyses and RCTs that assess the efficacy of drug therapy in diabetics can be found (167-173) (Annex 14).

♦ **Statins.** The two meta-analyses include diabetic patient subgroups from the large RCTs conducted in primary prevention (56; 59; 60; 144) and mixed populations (58; 76). Trials with statins are included, except for the HHS conducted with gemfibrozil. Another SR was recently published with data on 18,686 diabetics from an RCT on primary and secondary prevention (174). The reviews conclude that lipid-lowering therapy (statins, in particular) lower the risk of cardiovascular events but do not increase survival. However, the heterogeneity of the diabetic population makes it impossible to define the type of diabetics to whom the benefits of therapy could be extrapolated (169; 172; 174).

The Collaborative Atorvastatin Diabetes Study (CARDS) is the first study conducted on a diabetic population alone. It includes diabetics of ages 40 to 75, with no previous cardiovascular disease, moderate levels of LDL-c and with at least one of the following risk factors: HBP, retinopathy, a smoking habit and micro-macro albuminuria. In the study, 10 mg atorvastatin therapy was accompanied by a 37% reduction in the incidence of major cardiovascular events (coronary disease, ACVE and revascularization), with a NNT of 31 patients over a 4 year period. No differences in mortality were found between the two groups, however [0.68 HR (95% CI: 0.73 to 1.01)]. However, the study outcomes cannot be extrapolated to countries with a low risk of coronary disease, in which the NNT to prevent a cardiovascular event would be much higher. Diabetic populations with not very high cholesterol levels (TC 187 mg/dl) are included, however, in which 85% have high blood pressure. The situation is very similar to ours, although it poses the issue of which would be the baseline risk for diabetics in our context.

Moreover, the CARDS study shows reductions in cardiovascular events at set and low statin doses. This implies that no study to date has demonstrated a positive balance between the benefits and risks of using high doses and of combining drugs to attain target LDL-c levels in primary prevention (168).

The data from the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoint in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) were recently published. The study was conducted on type 2 diabetics in whom 10 mg of atorvastatin were compared to a placebo. The study had certain methodological limitations, since it was designed for diabetics who had suffered AMI or revascularization, although subsequently the protocol was changed to include diabetics in primary prevention. Thus, although no positive outcomes for atorvastatin therapy were found, no conclusions can be drawn from the study (170).

♦ **Fibrates.** Diabetes is accompanied by disorders in the lipid metabolism of complex origin and a variable phenotypic expression. However, in general, these are very ordinary characteristics of high TG and decreased levels of HDL-c. Therefore, considering the efficacy of lipid-lowering therapies, these patients receive fibrate therapy rather frequently. One SR that includes primary and secondary prevention studies shows a reduction in coronary events with the use of fibrates as compared to placebo [0.84 RR (95% CI: 0.74-0.96)], with no differences in mortality, AMI and an ACVE. Although the authors of the SR point out that fibrates are also beneficial in primary prevention, the assertion is difficult to confirm with the data given in the study (167).

Actually, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study included in the said SR is the only RCT conducted with fenofibrates in a type 2 diabetic population with low HDL-c levels (38.5 mg/dl) and slightly high TG (170 mg/dl), and also included 22% of patients with a prior CVD. In this study, fenofibrate manages to lower global cardiovascular events (coronary mortality, AMI, ACVE, revascularization) and non-fatal AMI in diabetics with no record of cardiovascular disease, with no difference between coronary and cardiovascular mortality.

However, it should be mentioned that 19.2% of the patients who took fenofibrate and 36% of the control group began to take statins (173).

Evidence summary

1++	Atorvastatin is effective in lowering cardiovascular events, although in primary prevention it does not increase survival of diabetic patients of age 40 to 75 at a mild-high CR (168). There is no evidence to show benefits that surpass the risks of statin therapy in diabetic patients over the age of 75.
1+	In type 2 diabetics with low HDL-c levels and slightly high TG, 200 mg/day of fenofibrate decreases cardiovascular events, although it does not show an increase in survival (173).

Recommendation

C	In diabetic patients with no cardiovascular disease, the coronary risk should be estimated to make decisions on lipid-lowering intervention. When estimating coronary risk in diabetic patients liable for primary prevention, the recommendation is to use the REGICOR project tables for coronary risk.
B	In type 2 diabetic patients age 40 to 75 with a CR of >10% according to the REGICOR project's tables, the recommendation is to begin statin therapy with low to mild doses.
✓	In diabetic patients over age 75, the recommendation should be made on an individual basis according to the patient's cardiovascular risk factors.
B	The administration of fibrates may be considered in type 2 diabetic patients with a cardiovascular risk of >10% in the REGICOR project table, who do not tolerate statins or for whom statins are contraindicated.
C	In long-term diabetics of > 15 years, assess treatment with statins at low to mild dosages, irrespective of coronary risk.

4.1.5. Adverse effects

See sections 7 and 8.

4.2. Drug therapy in secondary prevention

QUESTIONS TO ANSWER

♦ When should lipid-lowering therapy begin in individuals who have had a coronary event or ischaemic heart disease?

♦ What is the lipid-lowering therapy of choice and at what dosage?

♦ What is the most effective lipid-lowering therapy in individuals who have had an ACVE? What dosage?

♦ What is the most effective lipid-lowering therapy in individuals who have a peripheral arteriopathy? What dosage?

4.2.1. Ischaemic heart disease

ISCHAEMIC HEART DISEASE

The guidelines studied to prepare this document recommend statin therapy in any patient with coronary disease or a coronary equivalent (non-coronary arteriosclerosis, aortic aneurism) (8-11). In certain cases, it even points out that treatment should begin regardless of LDL-c levels and that the purpose should be to attain LDL-c levels below 100 mg/dl in high-risk patients (8) and 70 mg/dl in very high-risk patients (80). It should be mentioned that certain authors consider that patients should be informed of the risks and benefits of therapy before the treatment commences (9).

This recommendation is based on evidence from many SRs that have assessed the efficacy of lipid-lowering agents, and statins in patients with ischaemic heart disease, in particular (82-84; 147; 148; 169; 175-180). All the reviews include 3 broad RCTs conducted in secondary prevention, using low to moderate dose statin, which showed the efficacy of the lowering of cardiovascular morbidity and mortality in secondary prevention (75; 78; 79); and the two highly influential RCTs conducted with fibrates (181; 182). The past few years have also seen the publication of the outcomes of two other RCTs (85; 86) where the efficacy of intensive therapy in these patients compared to mild doses. Certain guidelines recommend high dose statin in high-risk patients based on these studies (8). The studies give an aggregate variable as the main outcome variable, according to which a sample size was calculated. Therefore, individual analyses of other outcome variables may show no significant outcomes owing to the lack of statistical strength (Annex 13).

Mortality

♦ Statins.

Standard doses vs. placebo. The SR that include mortality as an outcome variable show that statins increase survival in individuals with ischaemic heart disease, with an RR that ranges between 0.77 to 0.79 (82; 147; 148; 152; 180). The decrease in mortality is caused by a decrease in coronary mortality, with no increase in non-vascular deaths to be found. In the review by Baigent et al., which includes individual data on 90,056 patients from 14 RCTs shows that the 12% decrease in global mortality in the group treated with statins is mainly due to a proportional 19% reduction in coronary mortality (0.81 RR (95% CI: 0.76-0.85) per mmol/L of lowered LDL-c. No differences were found in mortality caused by an ACVE [0.91 RR (95% CI: 0.74 to 1.11)], or in vascular diseases [0.95 RR (95% CI: 0.90 to 1,01)]. The data refer to a population that includes patients in primary and secondary prevention and lead to the conclusion that a 19% reduction in mortality attributable to coronary events implies 14 (95% CI: 9 to 19) deaths prevented per 1,000 individuals in secondary prevention with statins at moderately low doses during a 5-year period (82).

High doses vs. standard doses. The latest RCTs published (85; 86), where high dose statin were administered, do not show an increase in survival. Thus, the Treating to New Targets (TNT), where 80 mg of atorvastatin are compared to 10 mg of atorvastatin in 1,001 patients with ischaemic heart disease and baseline LDL-c levels of 98 mg/dl, show a 1.01 RR of death (95% CI: 0.85 to 1.19) after 4.9 years of follow-up. Deaths unrelated to cardiovascular events are not higher in the 80 mg [1.25 HR (95% CI: 0.99 to 1.57)] atorvastatin group (85). The Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study of 8,888 patients in secondary prevention compares 20 mg of simvastatin to 80 mg of atorvastatin. The study also shows no increase in survival with high doses of statin [0.98 RR (95% CI: 0.85 to 1.13)] (86). No significant reductions in coronary deaths are to be found in the two studies.

♦ **Fibrates.** One meta-analyses that includes 9 RCTs conducted with fibrates does not show differences in survival between the treatment group and the control group [0.96 RR (95% CI: 0.86 to 1.08)]. To the contrary, an increase in non-cardiovascular death is found when studies of primary and secondary prevention are analysed together [1.13 RR (95% CI: 1.01 to 1.27)] (152). Mention should be made that in this review, the two most influential studies are the Veterans Affaire High-Density Lipoprotein Intervention Trial (VA-HIT) (182) conducted with gemfibrozil, and the Bezafibrate Infarction Prevention (BIP) with bezafibrate (181). The two studies included patients with coronary disease and low HDL-c levels (<40 and <45 mg/dl), respectively.

♦ **Resins and nicotinic acid.** One meta-analysis shows a RR of death for resins of 0.56 (95% CI: 0.82 to 1.82)], and of 0.96 (95% CI: 0.86 to 1.08) for nicotinic acid (152).

Coronary events and non-fatal infarction

♦ **Statins.**
Standard doses vs. placebo. The SRs use several outcome variables to assess coronary events: non-fatal AMI, revascularization, heart failure and fatal AMI. All the SR show the beneficial effects of statins at low to mild doses (82; 147; 148; 169). Thus, the Baigent et al. SR shows a 25% reduction in non-fatal AMI and fatal AMI per mmol/L (39 mg/dl) of reduction in LDL-c, accompanied by 30 (95% CI: 24 to 37) events avoided per 1,000 patients treated over a 5-year period (82).

High doses vs. standard doses of statin. In the RCTs conducted with high doses of statin, the TNT (85) and the IDEAL (86) studies, it could be asserted that the reduction in coronary events is attributable to the reduction in non-fatal AMI.

♦ **Fibrates.** The outcomes for fibrates are controversial. Whereas 600 mg/dl of gemfibrozil (86) in patients with ischaemic heart disease and with HDL-c levels <40 mg/dl and LDL-c <140 mg/dl show a reduction in fatal and non-fatal AMI [0.80 RR (95% CI: 0.68 to 0.94); NNT 23], bezafibrate at doses of 400 mg/d shows no significant reduction in coronary events (181).

Cerebrovascular event

The role of cholesterol and LDL-c as an ACVE risk factor is controversial (164; 183; 184). Several SR have addressed the issue by assessing the efficacy of lipid-lowering agents in the secondary prevention of ACVE. However, it should be mentioned that in all of the RCTs included in the reviews, ACVE are a secondary variable or part of the main aggregated variable (82; 147; 169; 176; 179; 185).

♦ **Statins.**
Standard doses vs. placebo. Although the outcomes are consistent in showing the efficacy of statins in lowering global cerebrovascular events (fatal and non-fatal) in patients with a prior coronary event [0.75 RR (95% CI: 0.65 to 0.87)] (185), no reduction in the incidence of fatal ACVE was found [0.94 OR (95% CI: 0.78 to 1.13)], or in the incidence of haemorrhagic ACVE [0.90 OR (95% CI: 0.65 to 1.26)] (176).

High doses vs. standard doses. Although the IDEAL study outcomes are not statistically significant, the high dose statin (80 mg of atorvastatin) show a tendency to lower fatal and non-fatal ACVE (86).

♦ **Fibrates.** With regard to fibrate, no significant differences were found between the active treatment and the placebo in the VA-HIT study, where 1,200 mg/dl of gemfibrozil were used in individuals with ischaemic heart disease and low LDL-c and HDL-c levels, or in the BIP study, where bezafibrate was used (181).

Compounded outcome variables

♦ Statins.

High doses vs. standard doses. The main outcome variable in the last two RCTs conducted with high doses consisted in an aggregate variable. The two studies showed the higher efficacy of intensive statin therapy (85; 86). However, the adverse effect ratio (8.1% vs. 5.8%) and of abandons (7.2% vs. 5.3%) was higher with the higher statin doses (85). These data match the IDEAL study data, where the dose was reduced by half for 13% of the people who took 80 mg of atorvastatin and where the remaining 14% of patients abandoned treatment (86).

Evidence summary

1++	Mild dose statin have proved to increase survival in patients with unstable ischaemic heart disease at the expense of lowering coronary death, without increasing non-vascular death (82; 147; 148; 152; 180).
1+	High dose statin (80 mg of atorvastatin) manage to decrease coronary events compared to placebo. However, intensive therapy has not proved to be an additional benefit in the survival of individuals with stable ischaemic heart disease (85; 86; 175).
1++	Statins cause a reduction in incidences of non-fatal AMI in individuals with ischaemic heart disease (85; 86; 147).
1++	Statins reduce fatal and non-fatal ACVE in patients who have ischaemic heart disease (82; 85; 86; 169; 176; 179; 185).
1++	Fibrates, resins and nicotinic acid derivatives do not increase survival in patients with ischaemic heart disease (152).
1+	1,200 mg/dl of gemfibrozil reduces coronary events (fatal and non-fatal AMI) and fatal and non-fatal ACVE in patients with ischaemic heart disease, HDL-c levels <40 mg/dl and LDL-c <140 mg/dl.

Recommendation

A	In patients with ischaemic heart disease, the recommendation is to begin treatment with mild statin doses, regardless of baseline LDL-c.
B(*) **D(**)**	In patients with ischaemic heart disease and intolerance to statin, the recommendation is to lower the doses or change to a different statin. If the intolerance persists, begin treatment with fibrates*. Other options may be nicotinic acid**, resins**, and/or ezetimibe**.
✓	After informing the patient of the benefits and risks of treatment, the statin dosage may be increased in patients with ischaemic heart disease in whom LDL-c levels of less than 100 mg/dl have not been attained.

ACUTE CORONARY SYNDROME

The selected guidelines recommend early treatment with lipid-lowering agents in individuals with acute coronary syndrome. Subsequently, the dose may be adjusted, if necessary. This recommendation is reinforced by the fact that beginning treatment during the hospital stay improves adherence to therapeutic patterns in the long term (10).

To assess the efficacy of this recommendation, mention must be made of four recently published SR that assess the efficacy of beginning statin therapy during the first 15 days following the acute coronary syndrome and, moreover, the use of high doses as opposed to normal or placebo therapy (175; 177; 186; 187). Two studies in the reviews are noteworthy for the number of patients and the duration of the follow-ups. We are referring to the PROVE IT-TIMI 22 (77) and A to Z (87) studies.

The outcomes of the two reviews vary according to the variable under study.

The outcomes come from the two trials mentioned above (PROVE IT-TIMI 22 and A to Z) (77; 87) are different to each other, and so are the patients included in them.

Thus, in the A to Z study, the participants had more risk factors and inclusion in the study was earlier. Likewise, they received fewer definitive therapies (surgery and revascularization), and therefore the probability of events is higher. The study compares early onset in the first 5 days with 40 mg simvastatin for one month, followed by 80 mg simvastatin, compared to placebo up to the fourth month and maintenance with 20 mg/dl simvastatin until the end of the study. Although a tendency for events to diminish is detected, no differences between the two groups were found in the main combined variable (cardiovascular death, AMI, re-admittance for acute coronary syndrome and ACVE), or 4 months and 2 years later with a RR of 0.89 (95% CI: 0.76 to 1.04) y NNT 43 (87).

In the PROVE IT-TIMI 22 study, the efficacy of 40 mg of pravastatin is compared to the efficacy of 80 mg of atorvastatin during the first 10 days of admittance for acute coronary syndrome. The combined outcome (death for any reason or a major cardiovascular event) shows an event rate after 2 years of 22.4% in the atorvastatin group and of 26.3% in the pravastatin group, with 0.8 HR (95% CI: 0.74 to 0.95), and a NNT of 28. This difference becomes apparent after day 30 and continues for up to 2 years (87).

Although the outcomes of the two studies appear to differ, when variables with similar outcomes are analysed, the reduction in events is likewise similar. This occurs despite the fact that reductions in LDL-c are higher in the PROVE IT-TIMI 22 study and reductions in HDL-c are higher in patients treated with high doses of simvastatin than the outcomes obtained with high doses of atorvastatin.

Combined variable of outcomes

In this combined variable of results, which includes death, AMI and ACVE, no differences are found in an early and intensive beginning with statins and the usual practice 4 months after follow-up [0.93 RR (95% CI: 0.81 to 1.07)] (177; 186). In the long-term, the reviews analysed show consistent outcomes, with no differences found in favour of intensive therapy (175; 186).

Mortality

Intensive therapy brings about a reduction in all causes of mortality [0.75 HR (95% CI: 0.61 to 0.93], and cardiovascular mortality [0.76 RR (95% CI: 0.60 to 0.98)] after 2 years of follow-up (175; 187).

Myocardial infarction

No differences in the incidence of AMI were found between the two groups.

Evidence summary

1++	Intensive statin therapy in patients with acute coronary syndrome did not diminish coronary events after 4 months (177; 186) or after 2 years of follow-up (175; 186).
1++	Intensive therapy brings about a reduction in all causes of cardiovascular morbidity and mortality after 2 years of therapy (175; 187).

Recommendation

A	Treatment should begin with mild statin doses in individuals discharged from hospital after acute coronary syndromes, regardless of their total cholesterol and LDL-c base levels.

4.2.2. Cerebrovascular event

Statins lower the incidence of ACVE in individuals with ischaemic heart disease, although none of the studies that assessed ACVE as an outcome measure were designed for that specific purpose (82; 147; 169; 176; 179). Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) is the only RCT that assesses statin efficacy in patients with a prior record of an ACVE or transitory ischaemic event (TIS), of atherothrombotic origin and no ischaemic heart disease, and where the main outcome are ACVEs. In this study, 4731 patients were randomized, with LDL-c levels of 100-190 mg/dl, at 80 mg atorvastin vs. placebo and a mean 4.9-year follow-up (188).

Previously, the outcomes of a subgroup of patients by the Heart Protection Study (HPS) were published (76). The subgroup included 3,280 individuals with a prior ACVE, of whom 1,820 had no heart disease (189).

Recently, a review of 61 observational studies was published, in which no association was found between cholesterol and ACVE mortality, particularly among the elderly individuals with high blood pressure levels (164).

Fatal and non-fatal ACVE

In the SPARCL study, a 16% reduction in recurrent ACVE was found after 4.9 years of follow-up [0.84 HR (95% CI: 0.71 to 0.99)], as well as lower fatal ACVEs [0.57 HR (95% CI: 0.35 to 0.95)] (188). The analysis of the study established that the reduction occurred in ischaemic ACVE, while an increase in haemorrhagic ACVE was found in patients treated with high doses of atorvastatin [0.66 HR (95% CI: 1.08 to 2.55)]. The trend towards an increase in haemorrhagic ACVE was also found in the analysis of the HPS subgroups, where the incidence of haemorrhagic ACVE was higher in the 40 mg simvastatin group (21 events vs. 11), while no differences were found in the number of ACVE in the two groups (10.4% vs. 10.5%) (189; 190).

Cardiovascular events

The information provided by the SPARCL study suggests that 80 mg atorvastatin provides higher benefits in lowering major cardiovascular events (coronary death, non-fatal AMI and reanimation after heart failure) than the reduction in ACVE. Thus, 29 patients (95% CI: 18 to 75) would have to be treated over a 5-year period to prevent a coronary event, whereas 46 patients would have to be treated to avoid an ACVE (95% CI: 24 to 243) (188).

Mortality

No differences were found in global mortality nor in the specific causes of death analysed (cancer, infection, cardiovascular, accidental and violent) between the 80 mg atorvastatin group and the placebo group (188).

Should target levels be established?

The only available data come from the SPARCL study, which manages to lower LDL-c levels to 73 mg/dl in the 80 mg atorvastatin group. On the other hand, one meta-analysis quantifies the reduction in ACVE risk at 22% per mmol/L (39 mg/dl) in LDL-c levels (82).

Thus, in patients with ACVE of atherothrombotic origin and with no ischaemic heart disease, 80 mg atorvastatin produces a higher cardiovascular than neurological benefit compared to placebo, with an increase in haemorrhagic ACVE. Therefore, further clinical analyses with much lower statin doses are needed to asses the efficacy and safety of statins in these patients. No clinical trials examine dosified lipid therapy targeting LDL-c levels, and therefore the studies cannot be used to establish objective LDL-c levels.

Evidence summary

1+	In patients with ACVE and no ischaemic heart disease, 80 mg atorvastatin provides higher benefits in lowering major cardiovascular events (coronary death, non-fatal AMI and reanimation after heart failure) than the reduction in ACVE.
1++	80 mg atorvastatin lowers recurrent ischaemic ACVE and increases haemorrhagic ACVEs in patients with atherothrombotic ACVEs and no ischaemic heart disease (188; 189).

Recommendation

B	In patients with ischaemic ictus of atherothrombotic origin and no ischaemic heart disease, treatment should begin with mild statin doses and recommendations on lifestyle. Begin treatment with statins regardless of baseline LDL-c.
✓	In patients with a prior ictus in whom LDL-c levels of less than 100 mg/dl have not been attained, the statin dose may be increased after informing the patient of the benefits and risks of treatment.

4.2.3. Peripheral arterial disease

Peripheral arterial disease (PAD) is a frequent pathology affecting more than 20% of the population over 65 years of age.

The ATP III guideline (8) considers PAD to be an equivalent of coronary disease and suggests using the same approach and targets with these patients as in patients with ischaemic heart disease.

The evidence that supports the recommendation includes a recently published analysis of subgroups by HPS (76; 192), which included 6,748 individuals with peripheral arterial disease and compared 40 mg atorvastatin with placebo. The patients included in the study had a highly developed CVR. 33% had undergone peripheral artery surgery or angioplasty, and in 2% a limb was amputated. 60% had an ischaemic heart disease, 8% had a cerebrovascular disease, and 23% were diabetic. In the analysis, 40 mg simvastatin reduced major cardiovascular events (non-fatal AMI and coronary deaths) [0.78 RR (95% CI: 0.71 to 0.85)] and peripheral revascularization procedures (carotid endarterectomy, non-coronary angioplasty). These outcomes are apart from baseline TC and LDL-c levels. Simvastatin's benefits in reducing major cardiovascular events, however, are not significant in patients with non-diabetic PAD, ischaemic heart disease and ACVE [0.86 RR (95% CI: 0.72 to 1.03)].

Prior to this study, an RCT was published in which 400 mg bezafibrate was compared to placebo in people with peripheral arteriopathy. No differences were found in the incidence of ischaemic heart disease and cerebrovascular disease (193).

Evidence summary

1+	40 mg simvastatin lowers non-fatal AMI and coronary deaths in individuals with symptomatic peripheral arterial disease and related comorbidity (diabetes, ischaemic heart disease, ACVE). The benefit obtained is not significant in patients with peripheral arterial disease and no related pathology (192).

Recommendation

B	Mild dose statin is recommended in patients with peripheral arterial disease and related comorbidity.

4.2.3.4. Adverse effects

See sections 8 and 9.

4.3. Statins of choice

The choice of statins and the recommended doses should be based on the availability of studies with outcomes on cardiovascular morbidity and mortality, reduction in LDL-c levels, safety and cost. Currently, there are studies on simvastatin, lovastatin, pravastatin and atorvastatin. At low to moderate doses, adverse effect tolerance and incidence is similar for all statins.

Not all statins secure the same reductions in LDL-c levels, an effect that also depends on the dosage. One review of 164 RCTs estimates reductions in LDL-c levels based on a mean pre-therapy LDL-c concentration of 186 mg/dl. The reductions are higher in patients who had higher concentrations prior to treatment. Thus, this meta-analysis shows that mild dose statin can achieve a 61.87 mg/dl reduction in LDL-c, which lowers the risk of coronary by half after 2 years of treatment (84) (See Tables 10 and 11).

Table 10. **Absolute reductions in mg/dl, and relative concentrations of LDL-c**

Amended from Law et al. (84)

Statin	**10mg**	**40mg**	**80mg**
Atorvastatin	69.2 (62.6-76) 37%	91.2 (82-100.1) 49%	102.1 (89.3-114.5) 55%
Fluvastatin	28.6 (21.3-36) 15%	50.3 (46-54.5) 27%	61.1 (54.1-68.1) 33%
Lovastatin	39.4 (27.4-51.8) 21%	68.4 (61.9-75) 37%	83.1 (71.9-94) 45%
Pravastatin	36.7 (32.1-41.4) 20%	53.4 (50.7-56.4) 29%	61.9 (56.5-67.3) 33%
Rosuvastatin	80.4 (76.6-84.3) 43%	99 (93.6-104.4) 53%	108.3 (101.7-114.8) 58%
Simvastatin	50.7 (47.2-54.1) 27%	68.8 (64.2-73.5) 37%	77.7 (70.4-84.7) 42%

In other words, 10 mg atorvastatin, 40 mg lovastatin and 40 mg simvastatin per day cause 35% reductions in cholesterol levels (84).

At this point, it is worth pointing out that the purchase cost should be taken into consideration when selecting statins. Simvastatin costs less than other statins.

Table 11. **Cost per packet of statin at equally strong doses**

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Dose (mg)	10	40/80*	40	40	40
Price (euros)	27.01	22.10/34.78	12.00	29.89	11.58

* The cost of the 80 mg dose of fluvastatin is for the extended-release formula.

In line with this reasoning, the SIGN guideline recommends simvastatin where statins are required. In the specific case of patients undergoing therapy with drugs metabolized by cytochrome P450, pravastatin could be used to prevent interactions (9).

In the trials included in RCT by Law et al., atorvastatin and rosuvastatin were prescribed in the morning, while the other statins were taken in the evening. It is worth mentioning that 4 RCTs that compared morning and evening statin administrations found LDL-c lowered by 0.22 mmol/L (8.5 mg/dl), which was higher than the reduction attained with the evening administration. This may be attributable to the peak in cholesterol synthesis at night and to the fact that the average life of statins is lower, with the exception of rosuvastatin and atorvastatin (84).

Thus, mild doses of 40 mg simvastatin, 10-20 mg atorvastatin, 40 mg pravastatin, and 40-80 mg fluvastatin are suggested, taking into account the statin doses used in the primary and secondary RCTs (Annexes 12, 13, and 14) and the reductions attained in LDL-c levels.

5. Therapy for hypertriglyceridaemia

QUESTION TO BE ANSWERED

♦ **What should be the therapeutic approach to hypertriglyceridaemia?**

Typically, fibrates and nicotinic acid have been used in HTG therapy. Nicotinic acid is only available as a special prescription but it may become commercially available in a few months' time. That is probably why fibrates are the drug most frequently used against hypertriglyceridaemia, apart from their efficacy in lowering TG levels.

♦ **Fibrates.** In one meta-analysis of studies conducted with fibrates and nicotinic acid, fibrates showed a mean reduction in TG of 36% [-70.5 mg/dl (95% CI: -79.7 to 61.22)]. The percentage of TG reduction with the different fibrates was 48% with gemfibrozil, 45% with ciprofibrate, 40% with fenofibrate, and 31% with bezafibrate (154). Fibrates have proved effective in lowering coronary morbidity and mortality in primary and secondary prevention. Their indication is based on several studies:

In the HHS, a primary prevention study conducted with gemfibrozil in patients with high cholesterol (TC 289) and low TG (175 + 118 TG) found no difference in coronary death and total mortality between the placebo group and the therapy group. However, non-fatal AMI was lowered by 37% [0.63 RR (95% CI: 0.43 to 0.91); NNT 77] in the group on gemfibrozil therapy (144). In this study, the most important effect of gemfibrozil on the lipid profile was a reduction in TG (34%), and a discreet rise in HDL-c (8%) which went from 47.1 to 51.2 mg/dl. One post-hoc analysis found that the subgroup that showed the best response to treatment with gemfibrozil had high TG levels (>204 mg/dl) (194).

The VA-HIT study conducted on patients with an established coronary disease, 16.+68 mg/dl TG, low HDL-c (32+5 mg/dl), and LDL-c lower than 140 mg(dl (112+23 LDL) found that gemfibrozil therapy lowered

coronary events by 22% [0.8 RR (95% CI: 0.68 to 0.94); NNT 23].

The reduction was at the expense of non-fatal AMI (lowered by 22%), with an insignificant reduction in coronary death and total mortality. In this study, TG was lowered by 31%, and HDL-c increased by 6%, with no changes found in LDL-c (182).

Finally, in a BIP study conducted with bezafibrate in a predominantly male population with a record of coronary disease, HDL-c <45 mg/dl and moderately high TC and TG, with a 6.2-year follow-up, the intervention group showed no benefits compared to the placebo group in the main variable (fatal and non-fatal AMI and coronary death), or in the secondary variable (hospital admittance for unstable angina, angioplasty, coronary bypass). The sole benefit in the main variable was found in the subgroup of patients with high baseline TG (>200 mg/dl). In this study, bezafibrate reduced TG levels by 21% and raised HDL-c by 18% (181).

♦ **Omega-3 fatty acids.** Omega-3 fatty acids are another optional therapy for HTG. One recent meta-analysis, which included 52 RCTs, referred a net reduction in TG of 27 mg/dl (95% CI: 20 to 33) in the group of patients who took omega-3, compared to the levels found in the placebo group. The doses of omega-3 varied between 0.045 and 5.9 gr/day. A 6 mg/dl (95% CI: 3 to 8) rise in LDL-c was also found, apart from the reduced TG. It is worth mentioning, however, that the studies included in the meta-analysis showed heterogeneous outcomes, with the range of net effects varying between a 6% to 60% improvement and a 6% to 14% worsening of the lipid profile (131).

In short, although high TG as a factor in individual CVR has not been established, HTG behaves as an additional CVR factor when an increase in TG coincides with TC/HLD-c>5 (195; 196). In fact, this group of patients was the one that benefited the most from a reduction in coronary events attributable to fibrate therapy (144; 181; 194).

Thus, the approach to HTG therapy will depend on aetiology, degree of high TG, and coronary risk. Secondary causes of HTG –obesity, heavy drinking, diabetes mellitus, hypothyroidism, kidney and liver disease, drug therapy (diuretics, beta blockers, corticoids and tamoxifene) (197)– and genetic disorders (FH, dysbetalipoproteinaemia) (198) should be not be considered initially.

Apart from the risk of pancreatitis, which implies high TG, the correct approach to HTG has not been precisely established. The approaches given in guidelines and documents by experts vary. Taking

the recommendations in the guidelines and the above considerations into account, the recommended therapeutic pattern is the one given below (Annex 4).

1. When TG levels are higher than 500 mg/dl, treatment should begin with changes in lifestyle: weight loss, moderate exercise, stop drinking and smoking, and low-fat diet. Typically, changes in lifestyle treatments lower TG significantly (199). A daily intake of 2-3 gr of omega-3 may help to lower TG levels (131; 200). If changes in lifestyle fail to work, start fibrate therapy to lower the risk of pancreatitis (201).

TG levels in excess of 1,000 mg/dl increase the risk of pancreatitis significantly, and the risk becomes very high with levels of more than 1,700 to 1,800 mg/dl (202). Plasma chylomicrons are largely responsible for this situation (203).

A low-fat diet is required when TG levels exceed 1,000 mg/dl. Reduce eating to 10%-5% of the total energy intake, increase physical activity, and begin fibrate therapy (198; 201). Avoid drugs that could increase TG (estrogens, furosemide, isotertionine, tamoxifene, and beta-blockers).

Apart from restricting fats (10%-5%), give medium chain triglycerides (MCTs) as a calorie supplement in the shape of fats in the case of severe HTG in patients with familial hyperchelomicronaemia owing to a deficit of lipase lipoprotein or ApoC-II (204).

When triglyceride levels fall below 500 mg/dl, clinical decision-making should consider the patient's global risk of cardiovascular disease.

2. When TG levels are between 200 and 499 mg/dl with a coronary risk of less than 10%, changes in lifestyle are required: Weight loss and more activity that is physical, no smoking, no drinking or reduce intake to 30 gr daily, less fewer saturated fats and replace them with monosaturated or polyunsaturated fats. There is no evidence that, in the absence of other risk factors, therapy for isolated HTG can prevent the risk of coronary events (39).

3. However, **when TG levels fall below 200-499 mg/dl and are accompanied by a CR>20%,** decision-making should consider that the patients will have related risk factors that require intervention: Low HDL-c, HBP, diabetes, obesity, or a smoking habit. In this scenario, statin therapy is recommended to lower coronary risk.

4. Insist in lifestyle changes and assess the need for drug therapy after 3 months **when TG levels are 200-499 mg/dl and CR is 10-20%**. In diabetic patients, start statin therapy.

5. Statins are the therapy of choice for patients with **coronary disease and TG levels of 200-499 mg/dl**. Consider increasing statin doses or adding a fibrate if lifestyle changes fail to reduce triglyceride levels.

Finally, suspect genetic dyslipidaemia (combined familial hyperlipidaemia, dysbetalipoproteinaemia) in HTG patients with a family history of dyslipidaemia or early coronary disease (before age 55 in men and age 65 in women).

Evidence summary

2++	There is no evidence to consider hypertriglyceridaemia as an isolated factor of cardiovascular risk (35; 39).
2+	Associated high triglycerides and low HDL-c increases CVR (195; 196).
2++	There is no evidence to support that assumption that, in the absence of other risk factors, therapy for isolated HTG can prevent cardiovascular morbidity and mortality (39).
1+	A daily intake of 2-3 gr of omega-3 lowers TG levels by 27 mg/dl in patients with hypertriglyceridaemia (95% CI: 95%: 20 to 3) (200; 203).

Recommendation

D	When triglyceride levels fall below 500 mg/dl, clinical decision-making should consider the patient's global risk of cardiovascular disease.
D	The first measures to recommend in patients whose triglyceride levels exceed 200 mg/dl are to lose weight, eat fewer fats, increase physical activity and drink less alcohol or stop altogether.
D	Treatment with fibrates is recommended when triglycerides levels remain higher than 500 mg/dl despite changes in lifestyle.
D	Omega-3 fatty acids may be used as a treatment for hypertriglyceridaemia, in conjunction with fibrates.

6. Treatment in patients with isolated low HDL-c

QUESTION TO BE ANSWERED

♦ Do patients with isolated low HDL-c need to be treated with lipid-lowering agents?

Population studies show that HDL-c is a reverse predictor of coronary disease (205; 206). However, the risk of dying from a cardiovascular disease is relatively small [4.9 per 10,000 men/year, 1.38 RR (95% CI: 1.06 to 1.78)] in patients with low HDL-c and normal TC, compared to the risk of patients with high HDL-c and normal TC. Moreover, no differences were found in the total mortality of the two groups of patients (207).

The New Zealand guideline recommends combined therapy or fibrate therapy in patients with low HDL-c who have suffered a coronary event. Likewise, it recommends intensive intervention on lifestyle, and probably fibrate therapy, in patients with low HDL-c, high TG and at a CVR of 15% or higher (10). Other guidelines also recommend an assessment of patients with HDL-c (<40 mg/dl), although they stress that therapy should target LDL-c levels primarily.

There are no studies in scientific literature on therapy for patients with isolated low HDL-c. RCTs conducted with drugs that raise HDL-c levels were carried out on populations that had other lipid disorders, making it difficult to assume that the benefit of a reduction in CVR is attributable to isolated low levels of HDL-c.

Similarly, no positive outcomes in morbidity and mortality were found in RCTs conducted with cholesteryl ester transfer protein (CETP) (torcetrapib, anacetrapib), which cause relevant increases in HDL-c and a reduction in LDL-c.

One recently published RCT conducted on patients of age 45-75 with a record of cardiovascular disease or type 2 diabetes compared torcetrapib (CETP) + atorvastatin to atorvastatin in single-drug therapy. An increase in the risk of

total mortality was found [1.58 RR (95% CI: (1.14 to 2.09)] and cardiovascular events [1.25 RR (95% CI: 1.09 to 1.44)] in the torcetrapib/atorvastatin group, compared to atorvastatin alone. A 72.1% increase in HDL-c and a 24.9% reduction in LDL-c was attained (208).

In previous studies, torcetrapib did not manage to lower the development of atherosclerosis in carotids (209) and coronary arteries (210).

On the other hand, one SR of 31 RCTs, designed to assess the effect of HDL-c with clinical events, found no evidence that an HDL-c increase reduces the incidence of major cardiovascular events (117).

Aerobic exercise, stop smoking, weight loss and moderate drinking (30 gr/day) have been shown to raise HLD-c levels. Likewise, substituting saturated fat with mono and polyunsaturated fats reduce the LDL-c/HLD-c ratio. Changes in HDL-c levels are attained with several types of lipid-lowering therapies.

Evidence summary

1+	There are no RCTs conducted in patients with isolated low HDL-c. Aerobic exercise, stop smoking, weight loss and moderate drinking (30 gr/day) and a diet low in saturated fats raise HDL-c levels.

Recommendation

A	Aerobic exercise on a regular basis, weight loss if obesity exists, and to quit smoking are recommended to increase HDL-c levels.
✓	Drug therapy for isolated HDL-c levels is not recommended without taking coronary risk according to the REGICOR chart into account.

7. Combined hyperlipidaemia

QUESTION TO BE ANSWERED

♦ **How should mixed hyperlipidaemia be treated?**

Mixed hyperlipidaemia includes high TC and TG levels, occasionally linked to low HDL-c. Although other disorders accompanied by mixed hyperlipidaemia can be reasonably discarded, the possible causes include hereditary combined familial hyperlipidaemia (CFH), one of the lipoprotein disorders found most frequently in patients with early coronary cardiopathy (44; 45).

Hereditary lipid disorders predispose to early coronary disease and put first-degree relatives at a higher risk of cardiovascular mortality. Therefore, make a record of the family history of early cardiovascular disease and/or lipid disorders before beginning therapy. If such cases exist, the patients should be considered as a high cardiovascular risk (44).

There are no RCTs conducted with statins and fibrates on a population with mixed hyperlipidaemia that assess mortality and cardiovascular event outcomes. In one RCT on patients with mixed hyperlipidaemia that compared the efficacy of 10 mg atorvastatin with fenofibrate, it was found that atorvastatin causes higher reductions in LDL-c levels, although fenofibrate lowered TG and raised HDL-c (211). In any event, statins have proved effective in lowering cardiovascular events in other high-risk populations (see primary and secondary prevention).

Several recently published RCTs on patients with mixed hyperlipidaemia in which statins and fibrates were combined to lower LDL-c and TG levels, and to raise HDL-c levels. Study follow-ups were short, however, and did not assess outcomes such as mortality and coronary events. Moreover, the combined statin-fibrate had a higher number of adverse effects, particularly when a statin with combined with gemfibrozil.

Evidence summary

2+	Hereditary familiar hyperlipidaemia implies a higher risk of early coronary disease and cardiovascular mortality [RR 1.7 (95% CI: 1.1-2.7)] (44; 45).

Recommendation

✓	The risk of early coronary disease is higher in hereditary forms of mixed hyperlipidaemia. Therefore, a family history of early cardiovascular disease and lipid disorders should be made before beginning treatment. If such cases exist, the patients should be considered as a high cardiovascular risk.
✓	In primary care, the coronary risk in patients with mixed hyperlipidaemia and no family history should be calculated according to the REGICOR equation. The main purpose of treatment should be to lower coronary risk.

8. Combined drug therapy indications

QUESTION TO BE ANSWERED

♦ **What are the conditions for combined lipid-lowering treatment?**

8.1 Combined statin and fibrate therapy

No RCTs have assessed the effect of combined statin-fibrate therapy in lowering cardiovascular events, so their effect in these clinical variables is unknown.

Several trials have found that a combination of statins and fibrates improves lipid profiles compared to therapies using the two drugs in single-drug therapy (211-214).

The risk of rhabdomyolisis associated with combined statin + fibrate therapy is higher than the risk involved when the two drugs are administered separately (215). Although no cases of rhabdomyolisis or kidney failure were found in the analysis of combined data from 36 RCTs using a statin + gemfibrozil, studies of series of cases report a higher incidence of rhabdomyolisis associated to statin + gemfibrozil than in treatment with a statin alone (61; 216; 217).

Myopathy is defined as myalgia with creatine phosphokinase (CPK) levels 10 times higher than the upper limit of normal. In this group of patients, who developed myalgia and other muscle symptoms, it was 0.12%. CPK elevations greater than 10 times the upper limit of normal was found in 2.1% of patients and increases transaminase over 3 times the upper limit of normal in 3.2% of patients.

In case reports, a higher incidence of rhabdomyolisis was found with statin + gemfibrozil than with statin + fenofibrate. This incidence was 15 times higher with gemfibrozil than with fenofibrate (215; 218).

8.2. Combined statin and ezetimibe therapy

Ezetimibe is a recently introduced molecule that inhibits cholesterol absorption in the intestines. In the selected guidelines, it is considered a medication because, when accompanied by statins, it helps to lower LDL-c in patients where an adequate reduction with high dose statin is difficult and in patients with intolerance to high statin doses. They also consider using it in treating severe genetic hyperlipidaemia.

A number of RCTs have assessed the use of ezetimibe in combination with statins to achieve a higher reduction in LDL-c levels in patients with hypercholesterolaemia and/or coronary disease. As the studies show, combined ezetimibe and statins lowers LDL-c levels considerably (88; 157; 219-232). Ezetimibe in single-drug therapy is estimated to attain reductions of 18% in LDL-c levels. The additional reduction attained when ezetimibe is added to statin varies between 13% and 25%, depending on the studies. The studies are short-term, however (6-12 weeks), and have not assessed clinical outcome variables.

Although combined ezetimibe + statin has been well tolerated, certain studies found that an increase in GTP is more frequent compared to statin alone and placebo. These elevations are generally slight and therapy does not need to be discontinued. It is worth mentioning, however, that in most of the studies, ezetimibe-statin therapy did not last more than 12 weeks.

One 48-week trial was redesigned to assess safety and tolerance of the ezetimibe combination. It was found that 19% and 17% of patients in the ezetimibe + simvastatin group and the placebo + simvastatin group, respectively, had therapy-related adverse side effects. The most frequent adverse reactions were gastrointestinal, with no disorders found in the biochemical parameters (GOT, GPT, CPK) in the two groups during follow-up. There were no cases of rhabdomyolisis (233).

It should be stressed, however, that such short-term studies do not allow the safety profile of an ezetimibe + statin combination to be known in the long term.

8.3. Combined statin and fibrate therapy

An ezetimibe + fibrate combination has also been used in patients with mixed hyperlipidaemia. The addiction of 10mg ezetimibe to 160mg fenofibrate causes a further

reduction in LDL-c of 14%-5% [a 22% (20.3 to 23.7)] reduction in LDL-c and a 12%-4% reduction in non-HDL (230).

In the McKenney et al. study (230), 160mg fenofibrate was compared to 160mg fenofibrate + 10mg ezetimibe over a 48-week follow-up. There were no cases of myopathy or CPK elevations greater than 10 times the upper limit of normal in either of the two groups. The increase in GOT and GPT values was similar in the two groups. Finally, the total number of therapy-related adverse effects was 16.1% fenofibrate group and 13.8% in the fenofibrate + ezetimibe group, with an increase in creatinine greater than 1.5 mg/dl in around 10% of the two groups.

8.4. Combined statin and resin therapy

None of the studies that compare combined therapy to single-drug therapy assesses morbidity and mortality variables.

A number of studies analyse changes in lipid profiles attributable to such combinations. Thus, adding colestipol or cholestyramine to a statin reduces LDL-c by 7%-20% (234; 235). A combination of low doses of resins (bile acid sequestrants) and statins may be less or equally effective in lowering LDL-c as high doses of either drug in single-drug therapy (236; 237).

Combined cholestyramine + fluvastatin therapy lowers LDL-c by up to 44% (+15) (235). Adding colesevelam to atorvastatin causes an additional reduction of 10% (38% with 10 mg atorvastatin and 48% with 10 mg atorvastatin + 3.8 gr colesevelam) (234).

The studies do not reach the same conclusions on the tolerance to treatment with resins combined with statins. One 24-month RCT which used pravastatin with cholestyramine obtained a 45% incidence of adverse gastrointestinal effects and 47% abandoned therapy (237), whereas other studies found no adverse effects worth mentioning (238; 239).

Evidence summary

1+	A combination of statins and fibrates improves lipid profiles compared to therapies using the two drugs separately (211-214).
2++	Statin + fibrate carry a higher risk of rhabdomyolisis compared to statins in single-drug therapy (61; 216).
1+	Low statin and resin doses cause the same reduction in LDL-c as high doses of each drug on its own (237; 237).
1+	Combined statin and ezetimibe lowers LDL-c by 13-25%. Maximum study follow-up was 12 weeks (157; 219-227; 229; 231; 232).
1+	The safety profile of statin + ezetimibe in the long term is not known. No important adverse effects were found in the only study made after 48 weeks (233).
1+	In short-term studies (12 weeks), combined fibrate and ezetimibe lowered LDL-c by an additional 14%-5% and non-HDL by 12%-4% compared to fenofibrate in single-drug therapy (230).
1+	The safety profile of ezetimibe + fibrate in the long term is not known. In one study made after 48 weeks, the adverse effects in the fenofibrate and fenofibrate + ezetimibe groups were 16.1% and 13.8%, respectively (230).
3	Fenofibrate combined with statins is associated with a lower risk of rhabdomyolisis than gemfibrozil (217; 218).

Recommendation

✓	In patients who require a combination of two drugs, statins and low doses of ion-exchange resins may be combined, or ezetimibe can be used in the event of intolerance to the former.

D	Fenofibrates are recommended when a combination of statins and fibrates is required.
✓	Consider combined treatment in: • Familial hypercholesterolaemia where adequate control is not secured with a drug. • Circumstantially, in patients with mixed hyperlipidaemia of family origin.

9. Adverse effects of drug therapy

Statins

The guidelines analysed coincide in pointing out the low risk of secondary effects of statins in single-drug therapy, with a 1%-1.9% rise in transaminase. The risk of myopathy, with CPK >10 times higher than the upper limit of normal, is close to 1/1,000 patients in treatment with statins. The risk of rhabdomyolisis is even lower (1/10,000 per year of exposure to statins) (8-11). Certain statins (lovastatin, atorvastatin and simvastatin) metabolize via the cytochrome P450 isoenzyme CYP3A4 and the concurrent use of other powerful enzyme inhibitors (azole anti-fungal agents, protease inhibitors, macrolides, verapamil, amiodarone, diltiazem, and grapefruit juice) may raise plasma statin, thus increasing the risk of adverse effects such as rhabdomyolisis (9).

In one 18 RCT meta-analysis with 71,000 patients to collect data on the adverse effects found during the trials, it was found that statin therapy increased the risk of any adverse effect by 39% [1.4 OR (95% CI: 1.09 to 1.80); NNH197] compared to placebo. When the statins were compared to each other, a higher risk of adverse effects was found with atorvastatin and a lower risk with fluvastatin [0.28 OR (95% CI: 0.18 to 0.44)] (atorvastatin > simvastatin = pravastatin > fluvastatin). The most frequent adverse effects were myalgia, myopathy, and CPK and transaminase elevations. Most of the cases were not severe and remitted when therapy was discontinued. The authors conclude that 5 adverse effects can be expected with treating 1,000 patients with a statin (240).

In any event, it is worth noting that the participants in RCTs are selected patients who are given a minimum amount of concurrent medication that could have an impact on statin metabolism, so the frequency of adverse effects may be underestimated when the outcomes are extrapolated to the general population.

♦ **Risk of cancer:** Several meta-analyses studied the relationship between statins and the risk of cancer. The studies, which included mild dose statin, found no significant difference in cancer incidence and mortality between statins and placebo during a 2 to 5 year follow-up period [1.01 OR (95% CI:

0.93 to 1.09)] (82; 241; 242). However, carcinogenic factors are not immediate, even with a short latency period (3-4 years), so it would be difficult to detect an increase in the risk of cancer in a meta-analysis of studies with only a 5-year follow-up (243). In one recent meta-analysis of 12 RCT found that the age of the study participants changed the association significantly, although no association was found between the use of pravastatin and cancer [1.06 RR (95% CI: 0.99 to 1.13)]. Thus, the risk of cancer is higher at ages over 75 years (244). Another meta-analysis of 18 RCTs that included 31,633 patients over the age of 60 indicated that the RR of cancer in patients on statin therapy is 6% higher in the patients who took placebo [1.06 RR (95% CI: 0.95 to 1.18)], although the difference is not significant (245).

♦ **Risk of rhabdomyolisis.** The terminology used to define muscle toxicity varies considerably from one study to the next. In an effort to unify terms, myopathy has been defined as muscle pain, high sensitivity, and muscle weakness associated with abnormal CPK elevations >10 times the upper limit of normal. Rhabdomyolisis would be a more severe form of muscle disorder, with CPK 10 times higher than the upper limit of normal associated with liver disorders, although in some cases the two terms were used to refer to the same process (64). Rhabdomyolisis is a rare, potential secondary effect of statins that is similar among the various statins (61; 82; 216; 246; 247). In the cases of rhabdomyolisis associated with the use of atorvastatin, simvastatin and lovastatin, 60% of the patients were taking some other drug that blocked isoenzyme CYP3A4 metabolism of the statins (diltiazem, verapamil, protease inhibitors such as ritonavir, ciclosporine, macrolides, and azole anti-fungal agents). Fatal rhabdomyolisis is extremely rare in patients on statin therapy, with around 0.15 deaths per million prescriptions (66).

♦ **Myalgia.** Myalgia, defined as muscle pain, is a relatively frequent adverse effect associated with taking statins. Although it is rarely found in the RCTs (1% to 5%), it can be responsible for up to 25% of all statin-related adverse effects. The onset of myalgia requires a CPK determination and liver damage assessment (246).

♦ **Hepatic enzyme elevation and hepatic failure.** Statin therapy may cause an increase in hepatic enzymes of more than 3 times the upper limit of normal, in around 1% of patients (61; 62; 245; 248). Most of the studies were conducted with low to mild statin doses,

which supports the drugs' safety. The statin-related hepatic failure is a secondary effect with a very low incidence (61; 62). In fact, the risk of statin-related hepatic failure is estimated at 0.5/100,000 patients per year, an incidence no higher than the risk of hepatic failure in the general population who take no statins.

♦ **High statin doses.** Raising the statin dose also raises the frequency of muscle symptoms, and twice the maximum recommended dose (160 gr simvastatin, 80-160 mg pravastatin) causes unacceptable levels of muscle damage (66). Thus, according to one recent meta-analysis that included 4 main RCTs with intensive therapy, high dose statin increased the risk of secondary effects (1.44 OR (95% CI: 1.33 to 1.55)] compared to mild dose statin.

One adverse effect for every 30 patients undergoing therapy was found (NNH). Intensive therapy was also associated with a higher probability of adverse effects that require interrupting the therapy [1.28 OR (95% CI: 1.18 to 1.39)], [NNH: 47 (95% CI: 35 to 9)]. GOT or GPT elevation greater than three times the upper limit of normal occurred more frequently under intensive therapy than under moderate therapy [4.48 OR(95% CI: 3.27 to 6.16)]; NNH 86 (95% CI: 71 to 106)]. Likewise, CPK elevation greater than 10 times the upper limit of normal occurred more frequently in patients who received high doses compared to patients who received mild doses [9.97 OR (95% CI: 1.28 to 77.92)] [NNH 1,534 (95% CI: 890 to 5,528)], although the risk of rhabdomyolisis among the two groups did not differ significantly (249). The outcomes of the A to Z study were along the same lines, with 9 (0.4) cases of myopathy (CPK elevation greater than 10 times the upper limit of normal associated to muscle symptoms) in the group that took 80 mg statin, whereas no cases were found in the patients who received 20-40 mg simvastatin doses. This supports the use of low to mild dose statin.

Evidence summary

1++	Low to mild statin doses have proved to be safe drugs with few secondary effects and of little importance (61; 82; 240; 246; 248).
1++	High statin doses are associated with a higher number of adverse effects that cause more patients to abandon therapy, although they are not severe in most cases (249).
1++	Statin therapy is not associated with a higher incidence of cancer, although the risk may be increased in patients older than age 75 (82; 241; 242; 244).

9.2. Fibrates

Although fibrates may cause severe adverse effects, they are well tolerated in general. Thus, one meta-analysis that included 53 RCTs with fibrates found only one major incidence of gastrointestinal symptoms compared to treatment with fibrates [1.37 RR (95% CI: 1.10 to 1.70)] (154).

♦ **Fibrates and kidney function.** Elevated creatinine levels without affecting glomerular filtration have been documented (173; 250-252). Therefore, if a clinically significant increase in creatinine levels is observed in patients in fibrate therapy, other causes should be discarded, renal function values monitored, and discontinuing therapy should be considered if creatinine levels continue to rise.

Renal function should be monitored if fibrates are used in combination with drugs such as metformin that require adjusting the dose for patients with renal insufficiency. This is because renal clearance with fibrates diminishes in patients with renal insufficiency and therefore they should be used with caution in such cases (250).

Short retrospective studies have found that fenofibrate and bezafibrate raise creatinine levels more than gemfibrozil (250), although a slight increase in creatinine (252) was also found in the analysis of subgroups of patients with chronic renal insufficiency (CRI) in the VA-HIT study.

♦ **Cholelithiasis** The CDP study showed that the patients treated with clofibrate had a higher incidence of cholelithiasis than the subjects assigned to the control group (3% vs. 1.3%) respectively (153). However, no higher incidence of gall bladder disease was observed in the studies with gemfibrozil (144; 182), fenofibrate (173) and bezafibrate (181).

♦ **Myopathy.** A higher risk of myopathy has also been associated to fibrates in single-drug therapy and in combination with statins, although the problem does not appear very frequently. One retrospective cohort study (215) with over 20,000 patients in fibrate therapy (gemfibrozil and fenofibrate), the mean incidence of rhabdomyolisis was 2.82/10,000 patients per year (95% CI: 0.58-8.24). In any event, fibrates in single-drug therapy are associated with a risk of myopathy 5.5 times higher than the risk associated to statins in single-drug therapy. In one study of case reports declared to the FDA since 1969, gemfibrozil-related adverse effects were more frequent than with fenofibrate (1.24 OR (95% CI: 1.15 to 1.34)]. The gemfibrozil-related rhabdomyolisis rate

was 10 times higher than for fenofibrate, although the difference is largely attributable to the increase of risk in patients taking gemfibrozil concurrently with statins.

♦ **Mortality.** Fibrates have proved to lower non-fatal AMI, but in some studies, particularly in the ones that used clofibrate, an increase in cardiovascular and total mortality was observed (145). In the WHO (145) study conducted on 5,000 subjects with no coronary disease who underwent clofibrate therapy for 5 years, there was a 36% increase in mortality in the clofibrate group, owing to non-cardiovascular causes. The excess of deaths was attributable to an increase in gastrointestinal neoplasia, complications following cholecystectomy and pancreatitis. No significant differences were found in total mortality in other studies conducted with gemfibrozil (144; 182), fenofibrate (173) and bezafibrate (181) between the active group and the placebo group, however.

♦ **Other adverse effects.** In the FIELD study, the patients who were assigned fenofibrate had a higher risk of pancreatitis than the placebo (0.5% vs. 0.8%; p=0.031). A slight increase in the risk of fenofibrate-related pulmonary embolism 0.7% in the placebo group vs. 0.1% with fenofibrate, p=0.022, was also found (173).

Evidence summary

1+	Clofibrate is associated to an increase in non-cardiovascular mortality. It is also related to an increase in the risk of cholelithiasis and cholecystectomy (153). Fibrates are occasionally associated with moderate creatinine elevations (173; 215; 250; 251).
3	In chronic renal insufficiency, renal excretion of gemfibrozil is the one that changes the least (251).

Recommendation

D	Discontinuing treatment with fibrates should be considered if a sustained increase in creatinine levels occurs.
D	Gemfibrozil should be the first choice in patients with renal insufficiency who require treatment with fibrates.

9.3 Resins

Although resins (cholestyramine and colestipol) are not associated with systemic toxicity, they regularly cause unpleasant gastrointestinal effects such as constipation, dyspepsia, flatulence and belching (8; 236). Owing to its bad taste, 41% (95% CI: 38- 44%) abandon therapy after one year (253).

In the LRC-CPPT RCT, in which cholestyramine was administered for 7 years to patients with high cholesterol, a higher number of gastrointestinal events (constipation and pyrosis, in particular) was found during the first year in the group treated with cholestyramine (68% vs. 43%), although the difference disappeared at the end of the study. Likewise, there was more surgery done and a higher number of nervous system procedures in the cholestyramine group than in the placebo group (40 vs. 23), owing to more lumber interventions (19 vs. 9) and carpal tunnel decompressions (7 vs. 1). Moreover, operations for cholelithiasis were more frequent in the cholestyramine group (36 vs. 25), although the difference was not significant. Finally, it is worth mentioning that 27% of the men in cholestyramine therapy were taking less than 2 gr/day by the end of the study, despite the target dose of 24 gr/day (146).

Studies made with very few patients found that cholestyramine and colestipol might lower the absorption of drugs (thiazide diuretics, furosemide, spironolactone; diltiazem, tricyclic antidepressants, corticoids, digoxin, raloxifene, loperamide and vitamin K) because they bond with them at the intestinal level (254-259). Therefore, the recommendation is to take these drugs 1 hour before or 4 hours after taking ion-exchange resins (8). Finally, resins tend to increase TGs, and therefore they are contraindicated in patients with TG>400mg/dl.

Evidence summary

1+	The most frequent adverse effects of resins are gastrointestinal disorders, constipation and pyrosis in particular (146; 253).
3	Resins may interfere in the absorption of certain drugs (thiazide diuretics, furosemide, spironolactone; diltiazem, tricyclic antidepressants, corticoids, digoxin, raloxifene, loperamide and vitamin K) (253-259).

(Continues below)

(Continuation)

Recommendation

D	Avoid resins in patients with constipation or intestinal disorders.
D	If the patient is taking any other medication concurrently with ion exchange resins, administer the other medication one to four hours after administering the resins.

9.4. Niacin

Several meta-analyses study the adverse effects associated with niacin therapy (154; 260). The most frequently documented adverse effect in patients in niacin therapy and the main reason abandoning therapy is hot flushes [7 RR (95% CI: 3.98 to 2.26)]. Adverse gastrointestinal effects are also observed [1.57 RR (95% CI: 1.05 to 2.34], skin reactions [RR 2.71 (95% CI: 1.48 to 4.97], and muscle symptoms [2.87 RR (95% CI: 0.49 to 6.91)]. Liver toxicity is caused in 2.1% of the subjects who were given niacin 3.15 RR (95% CI: 1.85 to 7.85)], and increases in glycaemia [3.04 RR (95% CI: 1.28-7.21)].

Evidence summary

1++	The most frequent adverse effects of niacin are hot flushes, although it also causes gastrointestinal disorders, skin reactions and muscle symptoms (154; 260).

9.4. Ezetimibe

Ezetimibe has been used in single-drug therapy to improve the lipid profile of patients with hyperlipidaemia.

Several short-term (12 weeks) RCTs that compared 10 mg ezetimibe to placebo found an 18% reduction in LDL-c, with a slight 1% to 2% increase in HDL-c (261; 262). During therapy, a mean change for GPT and GOT values of 1 to 2 mU/ml higher with ezetimibe vs. placebo was observed, with <1% of patients with GOT or GPT>3 times the upper limit of normal (262).

No differences in CPK levels were found. However, the studies' short follow-up does not allow the long-term safety profile to be known (263; 264).

10. Initial assessment and monitoring of patients on drug therapy

QUESTIONS TO ANSWER

♦ **Which attitude should be adopted during follow-ups of patients on lipid-lowering therapy?**

♦ **Which are the criteria for referral to specialized care?**

10.1. Regular lipid profiles

To assess whether goals are being met with the drug therapy, the guidelines (ATP III, New Zealand) recommend a lipid profile control after 6-12 weeks and subsequently every 8-12 weeks until targets are met. After that, one control every 6-12 months is enough. The CPGs, systematic reviews and review articles consulted did not include the need for further tests, such as an ECG, which would depend on the existence of other cardiovascular risk factors or an associated pathology (61-66).

10.2. Preliminary analytical text assessment

Two reviews and several documents by experts were used to define the recommendations, apart from the selected guidelines (8-11; 66; 265; 266).

♦ **Statins** The documents consulted recommend determining transaminase levels before commencing treatment with statins. If any disorders in the levels of these enzymes are found, the cause should be investigated before therapy begins (63).

CPK levels should be determined before statin therapy in patients at a high risk of muscle toxicity (the

elderly, patients with hepatic dysfunction, and when statins are used in conjunction with a drug that increases myotoxicity* (8; 63; 66). This consideration is not necessary in other patients (63).

Starting treatment with statins is not recommended when the CPK level is 5 times higher than the upper limit of normal (265).

♦ **Fibrates** The various guidelines recommend determining GOT/GPT and plasma creatinine before beginning fibrate therapy (8-11). Consideration should be given to the fact that fibrates may be associated with mild elevations of creatinine, although it is rare. Therefore, they should be used with caution in patients with a renal disorder (250).

As in the case of statins, a CPK determination is recommended before fibrate therapy in patients at a high risk of muscle toxicity (the elderly, patients with a hepatic dysfunction, and when fibrates are used in conjunction with a drug that increases myotoxicity*), but it is not necessary in other patients (250).

Finally, the guidelines recommend evaluating the presence of cholelithiasis or abdominal symptoms before beginning fibrate therapy (8-11). If the patient shows symptoms of cholelithiasis, the recommendation is to investigate whether cholelithiasis exists before beginning fibrate therapy, since fibrates may raise cholesterol saturation in the bile, thereby increasing the risk of cholelithiasis. Fibrate therapy should not be considered in the case of cholelithiasis, or therapy should be discontinued if lithiasis is detected in patients who are already on fibrate therapy (250).

♦ **Resins.** Resins have low systemic toxicity, so the guidelines do not recommend preliminary analytical tests. Assessing the presence of symptoms such as constipation, flatulence, and abdominal swelling or discomfort is recommended before commencing therapy, however (8).

* Azole anti-fungal agents, marcolides, protease inhibitors, Diltiazem, Verapamil.

Recommendation

D	Two lipid profiles are recommended before beginning drug therapy. After drug therapy, one control after a 8-12 week interval is recommended, followed by annual coronary risk assessment in primary care. After adequate control is attained, an annual analysis in secondary prevention is recommended.
D	The GOT/GPT levels should be determined before beginning treatment with statins or fibrates. If the levels are high, we recommend investigating the cause before treatment commences.
B	The CPK does not need to be determined before beginning treatment with statins or fibrates in patients with no symptoms.
D	In patients who are starting treatment with statins or fibrates, CPK levels should be determined before beginning treatment in patients who refer unexplainable muscle symptoms and in patients with a high risk of muscle toxicity (patients who are elderly or have a liver disorder, and in the event of potentially miotoxic pharmacological combinations).
D	Starting treatment with statins is not recommended when the CPK level is 5 times higher than the upper limit of normality.
D	GOT, GPT and creatinine levels should be tested, and the presence of cholelithiasis assessed before starting treatment with fibrates.

10.3. Regularity of analytical tests in drug therapy follow-ups

♦ **Statins.** The selected guidelines recommend a new determination of transaminase levels 8-12 weeks after beginning statin therapy (8-11; 63). Most of the guidelines recommend subsequent annual transaminase testing if the liver function was stable in previous controls (8; 10; 11; 65).

Therapy does not need to be discontinued if elevated transaminase levels under 3 times the upper limit of normal are found in asymptomatic patients. If the transaminase levels exceed 3 times the upper limit of normal, analyses should be repeated and the existence of other pathologies need to be discarded if the levels remain high. If statin therapy is the cause, the doses may be lowered. If the elevation persists despite the reduced dose of statin, consider discontinuing therapy (63).

Although the severe adverse hepatic effects of statins are rare, special attention should be paid to patients who have jaundice, malaise, and feel tired or lethargic, because they can be indications of hepatic toxicity. Discontinue statin therapy if damage to the liver is suspected. Bilirubin fraction is the most widely recommended biochemical test for detecting damage to the liver in the absence of biliary obstruction (62; 63).

Measuring CPK levels in asymptomatic patients is not necessary during statin therapy, since clinically relevant increases in CPK are rare and elevations of the enzyme may be observed in relation to exercise and other hepatic causes. However, owing to the potential adverse muscle effects associated with statin therapy, the groups of experts recommend asking patients on statin therapy whether they have any muscle symptoms such as myalgia, muscle weakness or cramps. If any muscle symptoms exist, CPK levels should be tested to estimate whether there has been muscle damage and to facilitate decision-making on whether to continue the therapy. Discontinue treatment with the drug in cases where CPK is 10 times higher than the upper limit of normal (63; 66).

Likewise, inform and advise patients who request medical advice when starting statin therapy if they show signs of myalgia, weakness, cramps and other muscle symptoms.

The risk of rhabdomyolisis is low, and likewise with pravastatin, simvastatin and atorvastatin (82; 215).

Monitoring the kidney function or the existence of proteinuria is not considered necessary (63) (Annex 5).

Recommendation

D	A determination of transaminase 8-12 weeks after commencing treatment with statins is recommended.
D	An annual transaminase determination in patients in treatment with statins is recommended. Statins dosages should be lowered in cases where the transaminase is more than three times higher than normal, and treatment should be discontinued if the high levels persist.
D	Patients should be informed that treatment might be accompanied by muscle symptoms and of the need to request medical advice with their onset.
D	A creatine phosphokinase (CPK) determination should be requested if muscle symptoms appear. Discontinue treatment with statins in cases where CPK is 10 times higher than the upper limit of normality.

Fibrates. Some of the selected guidelines recommend a new transaminase determination 8-12 weeks after beginning fibrate therapy (8; 11).

One review of fibrate safety does not consider routine creatinine monitoring necessary, unless the patient is on metformin or statin. Therapy should be discontinued if a creatinine increase greater than 1.4 mg/dl in women and 1.5 mg/dl in men is found.

The selected guidelines recommend CPK determinations in patients at a high risk of muscle toxicity, but it is not necessary in other patients. Measuring CPK in asymptomatic patients is not considered necessary (8; 11).

As in the case of statins, patients should be asked whether they have muscle symptoms. If a patient refers to muscle symptoms during

fibrate therapy, CPK should be determined to assess whether muscle damage exists. Discontinue fibrate therapy in patients who have intolerable muscle symptoms, whether or not CPK levels are high. Discontinue therapy in those cases where CPK is 10 times higher than the upper limit of normal (250).

Finally, fibrates enhance anti-coagulant therapy, so the INR should be monitored when fibrates are administered to a patient on anti-coagulants (Annex 17).

Recommendation

D	GOT and GPT values should be determined 8-12 weeks after treatment with fibrates commences and annually thereafter.
D	Routine seric creatinine determinations are not necessary during therapy.
D	Plasma creatinine levels should be determined in patients under treatment with fibrates who take other drugs as well, such as metformin and statins. Therapy should be discontinued if a creatinine increase greater than 1.4 mg/dl in women and 1.5 mg/dl in men is found.
D	Patients should be informed that treatment might be accompanied by muscle symptoms and of the need to request medical advice with their onset. Discontinue treatment with fibrates in cases where CPK is 10 times higher than the upper limit of normality.

11. Referral criteria

The selected CPGs give no specific response to this issue. No publications that approach the issue of referral directly or indirectly were found. Therefore, the recommendation to refer patients to a lipid unit or a second-level specialist was established by consensus among group members, taking the recommendations of other working groups into consideration as well.

Recommendation

✓	Referral to a lipid unit or second-level care is recommended in the event of: - Suspected cases of familial hypercholesterolaemia - Severe genetic hyperlipidaemia with abnormally high lipid profiles (TC> 400 or LDL-c > 260 mg/dl or TG> 1000 mg/dl) - the need to add a third drug - The onset of adverse effects that require specialised intervention

12. Hypercholesterolaemia in children

QUESTIONS TO ANSWER

- **When should a lipid profile be requested?**
- **What are the target levels and figures?**
- **What therapeutic measures should be adopted?**

12.1. Screening

Screening for arteriosclerosis begins at an early age. The potential tendency to maintain childhood lipid levels within the same range or ratio in adult life makes the recommendation to screen at an early age an attractive idea.

Most of the guidelines are based on recommendations agreed by consensus. They recommend making a cholesterol determination in children age 2 and above, with a family history of early cardiovascular disease (first-degree male relative with a coronary event record at age 55 or earlier, and at age 65 or earlier in women), and if the child has a parent with a TC level higher than 240 mg/dl (268; 269). The ICSI guideline recommends screening when the cholesterol level of one parent is >300 mg/dl (11).

However, selective screening (children with first-degree family records of early cardiovascular disease or one parent with cholesterol >240 mg/dl) compared to the population screening does not show important benefits for a diagnosis of dyslipidaemia (positive probability ratios (CP+) of 1.38 to detect high LDL-c levels) (270).

On the other hand, consideration should be given to several issues in order to establish the usefulness of cholesterol screening in children:

- Is screening for hypercholesterolaemia at paediatric age able to lower or delay the incidence of coronary disease in adults?

♦ Does hypercholesterolaemia therapy at paediatric age reduce the incidence of coronary disease in adults?

♦ Do children with hypercholesterolaemia continue to have high cholesterol when they reach adulthood?

♦ At what age should childhood /adolescent screening be done?

1. Is screening for hypercholesterolaemia at paediatric age able to lower or delay the incidence of coronary disease in adults?

One SR finds no studies that assess the efficacy of screening children and adolescents for dyslipidaemia in order to lower the incidence of adult coronary events or delay their onset (271).

2. Does hypercholesterolaemia therapy at paediatric age reduce the incidence of coronary disease in adults?

One SR indicates that no studies evaluate whether treating dyslipidaemia with drugs, diet or exercise during infancy or adolescence contributes to lower the incidence of dyslipidaemia or the onset of cardiovascular events when they reach adulthood (271).

3. Do children with hypercholesterolaemia continue to have high cholesterol when they reach adulthood? Cohort studies in one SR show that around 40% to 50% of children with high cholesterol continue to have high levels at 4-15 years follow-up (271).

4. At what age should childhood /adolescent screening be done?

Certain authors point out that the progression of cholesterol levels during childhood and adolescence follows a curve rather than a linear pattern, which makes it even more difficult to establish an ideal age for screening that correlates with adult cholesterol levels (272). Studies that approach the frequency and optimal age for cholesterol screening in childhood and adolescence do not exist (271).

The absence of data that associate cholesterol levels during childhood and adolescence with adult cardiovascular disease, and insufficient evidence on the efficacy and safety of treatments for hypercholesterolaemia at that age make it necessary to detect individuals with a high CVR and not just those who have hyperlipidaemia (273). However, several good quality diagnostic studies that assess family histories as a diagnostic test for hypercholesterolaemia do not demonstrate the benefits of selective screening compared to population screening (271).

Evidence summary

1++	There are no studies available on the efficacy of screening children and adolescents in order to lower the incidence of adult coronary events or delay their onset (271).
4 (ED)	Selective screening (children with first-degree family records of early cardiovascular disease or cholesterol >240 mg/dl) compared to population screening does not afford important benefits for a diagnosis of dyslipidaemia [positive probability ratios (CP+) of 1.38 to detect high LDL-c levels] (270). No studies establish the frequency and optimal age for cholesterol screening in childhood and adolescence.

Recommendation

A	Population screening for cholesterol in children and adolescents is not recommended.
✓	Cholesterol screening is recommended after the age of 10 in children with a first-degree relative with single-gene familiar hypercholesterolaemia.

12.2. Levels and target figures

Dyslipidaemia is defined by a laboratory test and statistical criteria (271). Blood cholesterol levels vary by geographical areas, so population studies for each territory would be needed in order to determine normal lipid levels in children and adolescents (268).

The current recommendations are based on the lipid levels obtained from the Lipid Research Clinics (LRC) Prevalence Study (146; 271; 268). According to these data, the 95 percentile would have 200 mg/dl total cholesterol and 130 mg/dl LDL-c. Data that is more recent provides levels in the 95 percentile of 216 mg/dl for TC and 152 mg/dl for LDL-c (274). These values vary with age, gender (girls have higher levels) and race (271).

At State level, the RICARDIN study analysed the variability of cholesterol levels in children and adolescents from several Spanish provinces. For instance, mean HDL-c in Biscay is significantly higher than in Madrid, 66.5 mg/dl (SD16) compared to 57.8 mg/dl (SD23) and, in general, they are lower than an international review (272). These differences, in conjunction with their curved upward-downward trend, make it more difficult to establish a single acceptable or high level in children, for the ratio of high cholesterol levels could be overestimated or underestimated, depending on the age chosen (275).

In one recent SR of cross-cutting studies, the TC in 22.2% (95% CI: 7.6 to 36.8) of schoolgirls and 20.5% (95% CI: 10 to 31.3) of schoolboys was higher than 200 mg/dl (276).

Evidence is lacking on the usefulness of cholesterol screening in childhood to delay the onset or to prevent coronary disease in adults; it is difficult to establish a single level that could be used to diagnose hypercholesterolaemia; and cholesterol levels vary according to geographical areas. For all these reasons, lipid determinations in childhood would only be justified in children and adolescents with first-degree relatives with an established diagnosis of FH, adopting for that purpose TC or LDL-c levels higher than the 95 percentile for the geographical area, age, gender and race.

Evidence summary

3	Total cholesterol and LDL-c levels vary between cohorts according to geographical location, age and gender (271).

12.3. Treatment

Diet treatment

♦ **Familial hypercholesterolaemia.** The USPSTF's SR, which included 5 RCTS that assessed diet therapy in children with FH or combined FH, found a reduction in TC levels (7.4% to 11%) and LDL-c (10% to 14%) (271).

In another RCT SR conducted with children and adolescents with FH, no short-term differences were found between the cholesterol-lowering diet and other diets in relation to their lipid profiles. The studies gave no long-term outcomes (277).

♦ **Non-familial hypercholesterolaemia.** Several studies with diet interventions have been conducted in the general population of children and adolescents, none of which assessed clinical outcomes such as cardiovascular events and mortality. In one RCT conducted with children ages 8 to 10 during a 3-year follow-up, very few differences in terms of a reduction in cholesterol and LDL-c were found between group put on a diet that restricted total fats, cholesterol and saturated fatty acids and the control group. The therapy group follow-up consisted in weekly sessions initially, then every two weeks and home visits during the first 6 months, and subsequently, 4-6 sessions per year until the study ended. Moreover, the difference between the two groups was not significant at 5 and 7-year follow-up (278).

The outcomes and diet studies (conducted on children and adolescents with non-familial FH) can hardly be applied to our context, which has such different eating habits (there are no studies on the Mediterranean diet). The studies also include the interventions on other factors, such as exercise.

Drug therapy

Familial hypercholesterolaemia

♦ **Statins:** All of the lipid-lowering drug therapy studies on children and adolescents were conducted with FH patients. In one SR that included 6 RCTs of 12-104 months duration of children under age 18 with a FH, TC was lowered 23% (95% CI: 19 to 23, LDL-c: 30% (95% CI: 24 to 36), and a slight HDL-c elevation of 3.64%

(95% CI: 1.33 to 5.94). Clinical variables were not assessed because the studies were restricted to no more than 2 years' duration and cardiovascular events in the population age group were unlikely. Although no differences in secondary events were found between the control and therapy groups, two studies showed a significant difference in dehydroepiandrosterone sulphate levels between the statin group and the placebo group.

The changes had no clinical repercussions, although the short follow-ups made it impossible to know the long-term effects on sexual maturation, growth, and any adverse liver and muscle effects in children on statin therapy (210).

In other non-controlled studies, statins were associated to high hepatic enzyme and CPK levels (271).

♦ **Ion-exchange resins** (cholestyramine and colestipol). The studies conducted with cholestyramine and colestipol lowered TC and LDL-c without causing changes in HDL-c and TG levels. The main problems are gastrointestinal discomfort (flatulence and constipation) and the bad taste, which led many patients to abandon therapy or to the administration of sub-optimal doses (271; 279).

♦ **Non-familial hypercholesterolaemia.** None of the studies assesses drug therapy in children with hypercholesterolaemia in the general population (271).

Non drug therapy: physical activity

♦ **Familial hypercholesterolaemia.** None of the studies assesses the role of exercise in lowering cholesterol levels in children with a FH (271).

♦ **Non-familial hypercholesterolaemia.** 6 studies assess exercise in children with high cholesterol levels. In most of cases, physical activity was part of a complex intervention (271). The studies showed no changes or only minimal changes in lipid levels compared to the control group. Only one study showed discreet improvements in TG levels in the physical activity group compared to the control group, with no difference found in other lipid markers between the two groups.

Evidence summary

1++	Statins lower total cholesterol and LDL-c in children and adolescents with familial hypercholesterolaemia (210). The long-term effects of statin treatment on growth, sexual maturation, and liver and muscle function in children are not known. There is no evidence on statin treatment in patients with non single-gene hypercholesterolaemia.
1++	The effect of a cholesterol-lowering diet on TC in children and adolescents with familial hypercholesterolaemia is not known (277).
1+	There is no evidence that diet therapy in the general population of children lowers TC and LDL-c levels (278).

Recommendation

D	A Mediterranean diet, physical activity and adequate weight control are recommended for children with hypercholesterolaemia and no family record of single-gene dyslipidaemia.

13. Dissemination and implementation

The strategy to implement this guideline consists of two stages. To deploy and implement the recommendations in this guideline, the strategy needs to consider the context in which it will be disseminated, as well as the content of the guideline as such.

Another consideration is the availability of tests on the efficacy of the implementation strategies. The literature suggests that the recommendations are more likely to be followed if multiple approach strategies are used.

The CPG on lipid management as a CVR factor will be used by Primary Care professionals and other players who approach the issue in an out-patient context. Therefore, the guideline will need:

- Adequate dissemination in two formats:
  - A condensed version: Distribution of a printed condensed version to all Primary Care professionals and other potential users of the Guideline.
  - A digital condensed version and a full version that can be downloaded from the Osakidetza/Svs intranet and the websites of the Companies that support the guidelines recommendations.

- Presentation of the guideline at health councils in the various health regions.

- Peer-to-peer discussions on the recommendations, led by the guideline's authors.

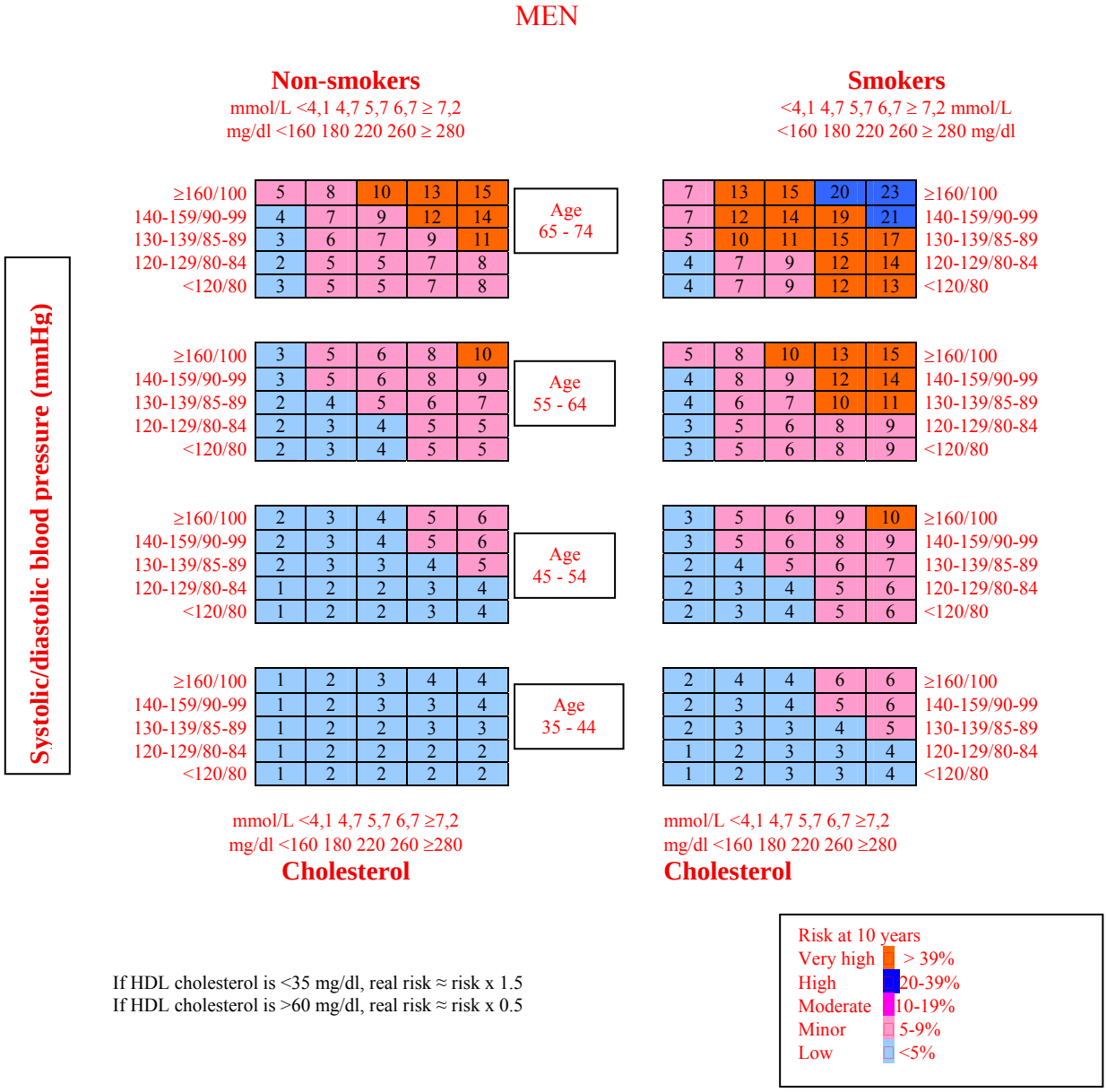
- Specific workshops on the prescription of statins according to CVR.

- Debates at scientific meetings held by scientific companies.

APPENDICES

1. REGICOR charts for calculating coronary risk

REGICOR charts for calcalculating coronary risk in men.



If HDL cholesterol is <35 mg/dl, real risk ≈ risk x 1.5
If HDL cholesterol is >60 mg/dl, real risk ≈ risk x 0.5

REGICOR charts for calculating coronary risk in women

WOMEN

Systolic/diastolic blood pressure (mmHg)

Non-smokers

mmol/L <4,1 4,7 5,7 6,7 ≥ 7,2
mg/dl <160 180 220 260 ≥ 280

≥160/100	5	6	8	8	10	Age 65 - 74
140-159/90-99	4	5	6	6	8	
130-139/85-89	3	4	5	5	6	
120-129/80-84	3	4	5	5	6	
<120/80	2	3	3	3	4	
≥160/100	5	6	8	8	10	Age 55 - 64
140-159/90-99	4	5	6	6	8	
130-139/85-89	3	4	5	5	6	
120-129/80-84	3	4	5	5	6	
<120/80	2	3	3	3	4	
≥160/100	3	4	5	5	7	Age 45 - 54
140-159/90-99	3	3	4	4	5	
130-139/85-89	2	3	3	3	4	
120-129/80-84	2	3	3	3	4	
<120/80	2	2	2	2	3	
≥160/100	2	1	2	2	3	Age 35 - 44
140-159/90-99	1	2	2	2	2	
130-139/85-89	1	1	2	2	2	
120-129/80-84	1	1	2	2	2	
<120/80	1	1	1	1	1	

mmol/L <4,1 4,7 5,7 6,7 ≥7,2
mg/dl <160 180 220 260 ≥280

Cholesterol

Smokers

<4,1 4,7 5,7 6,7 ≥ 7,2 mmol/L
<160 180 220 260 ≥ 280 mg/dl

6	8	10	10	12	≥160/100	
5	7	8	8	11	140-159/90-99	
4	5	6	7	9	130-139/85-89	
4	5	6	7	9	120-129/80-84	
3	3	4	4	5	<120/80	
6	8	10	10	13	≥160/100	
5	7	8	8	11	140-159/90-99	
4	5	6	7	9	130-139/85-89	
4	5	6	7	9	120-129/80-84	
3	3	4	4	5	<120/80	
4	5	6	7	9	≥160/100	
4	4	5	5	7	140-159/90-99	
3	4	4	4	6	130-139/85-89	
3	4	4	4	6	120-129/80-84	
2	2	3	3	4	<120/80	
2	2	2	3	3	≥160/100	
2	2	2	2	3	140-159/90-99	
1	2	2	2	2	130-139/85-89	
1	2	2	2	2	120-129/80-84	
1	1	1	1	2	<120/80	

mmol/L <4,1 4,7 5,7 6,7 ≥7,2
mg/dl <160 180 220 260 ≥280

Cholesterol

If HDL cholesterol is <35 mg/dl, real risk ≈ risk x 1.5
If HDL cholesterol is >60 mg/dl, real risk ≈ risk x 0.5

Risk at 10 years	
Very high	> 39%
High	20-39%
Moderate	10-19%
Minor	5-9%
Low	<5%

REGICOR charts for calculating coronary risk in diabetic men

DIABETIC MEN

Systolic/diastolic blood pressure (mmHg)

Non-smokers

mmol/L <4,1 4,7 5,7 6,7 ≥ 7,2
mg/dl <160 180 220 260 ≥ 280

≥160/100	7	12	14	20	21	Age 65 - 74
140-159/90-99	6	11	13	17	20	
130-139/85-89	5	9	10	14	16	
120-129/80-84	4	7	8	11	12	
<120/80	4	7	8	11	12	
≥160/100	4	8	9	12	14	Age 55 - 64
140-159/90-99	4	7	8	11	13	
130-139/85-89	3	6	7	9	10	
120-129/80-84	3	4	5	7	8	
<120/80	3	4	5	7	8	
≥160/100	3	5	6	8	9	Age 45 - 54
140-159/90-99	3	5	5	7	8	
130-139/85-89	2	4	4	6	7	
120-129/80-84	2	3	3	5	5	
<120/80	2	3	3	5	5	
≥160/100	2	3	4	5	6	Age 35 - 44
140-159/90-99	2	3	4	5	5	
130-139/85-89	2	3	3	4	4	
120-129/80-84	1	2	2	3	3	
<120/80	1	2	2	3	3	

mmol/L <4,1 4,7 5,7 6,7 ≥7,2
mg/dl <160 180 220 260 ≥280

Cholesterol

Smokers

<4,1 4,7 5,7 6,7 ≥ 7,2 mmol/L
<160 180 220 260 ≥ 280 mg/dl

11	19	22	29	33	≥160/100
10	18	21	27	31	140-159/90-99
8	14	17	22	25	130-139/85-89
6	11	13	17	20	120-129/80-84
6	11	13	17	20	<120/80
7	12	15	20	22	≥160/100
6	11	13	18	20	140-159/90-99
5	9	11	14	17	130-139/85-89
4	7	8	11	13	120-129/80-84
4	7	8	11	13	<120/80
4	8	9	13	15	≥160/100
4	7	9	12	13	140-159/90-99
3	6	7	9	11	130-139/85-89
3	5	5	7	8	120-129/80-84
3	5	5	7	8	<120/80
3	5	6	8	9	≥160/100
3	5	6	8	9	140-159/90-99
2	4	5	6	7	130-139/85-89
2	3	4	5	5	120-129/80-84
2	3	4	5	5	<120/80

mmol/L <4,1 4,7 5,7 6,7 ≥7,2
mg/dl <160 180 220 260 ≥280

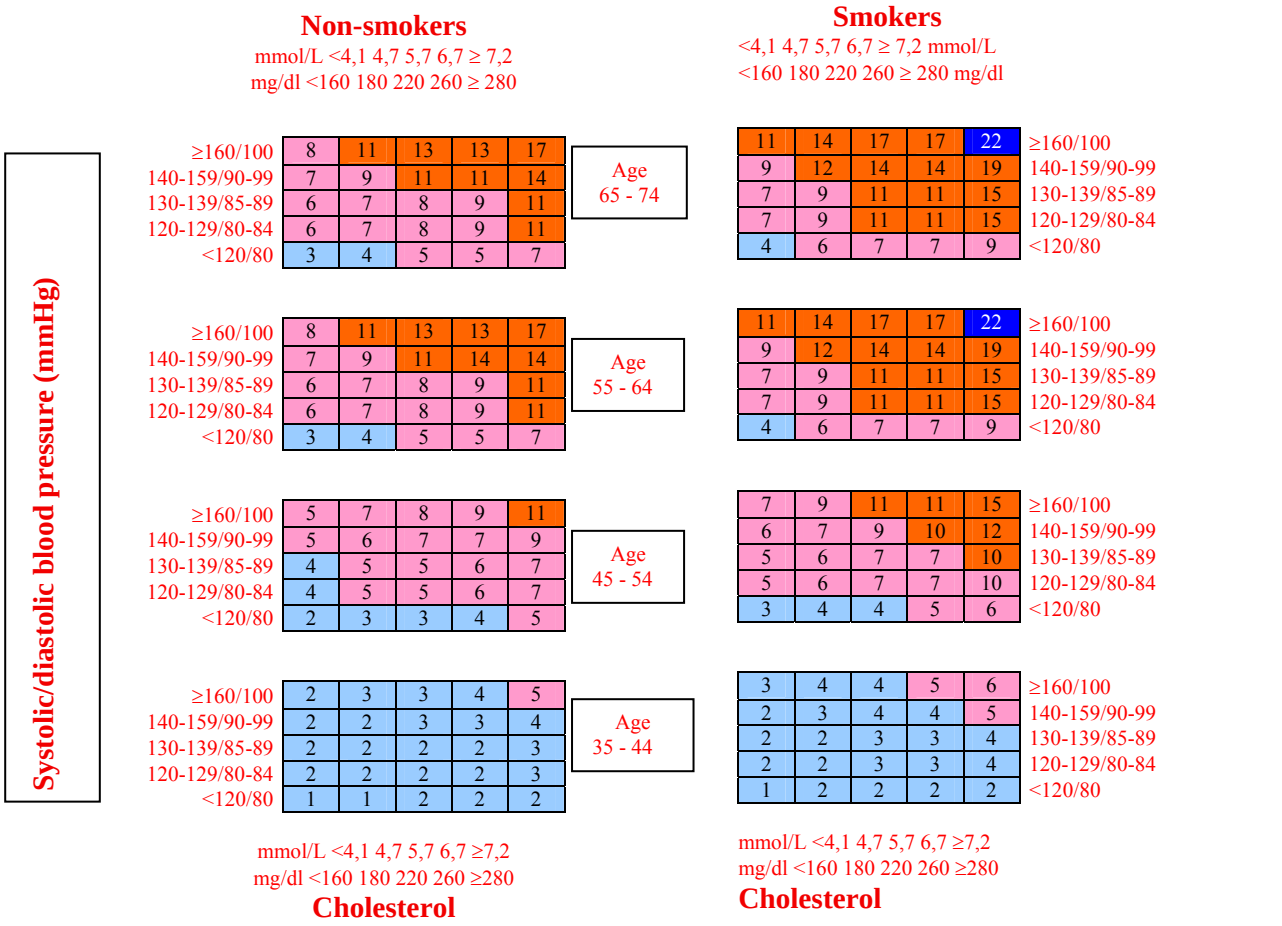
Cholesterol

If HDL cholesterol is <35 mg/dl, real risk ≈ risk x 1.5
If HDL cholesterol is >60 mg/dl, real risk ≈ risk x 0.5

Risk at 10 years	
Very high	> 39%
High	20-39%
Moderate	10-19%
Minor	5-9%
Low	<5%

REGICOR charts for calculating coronary risk in diabetic women

DIABETIC WOMEN

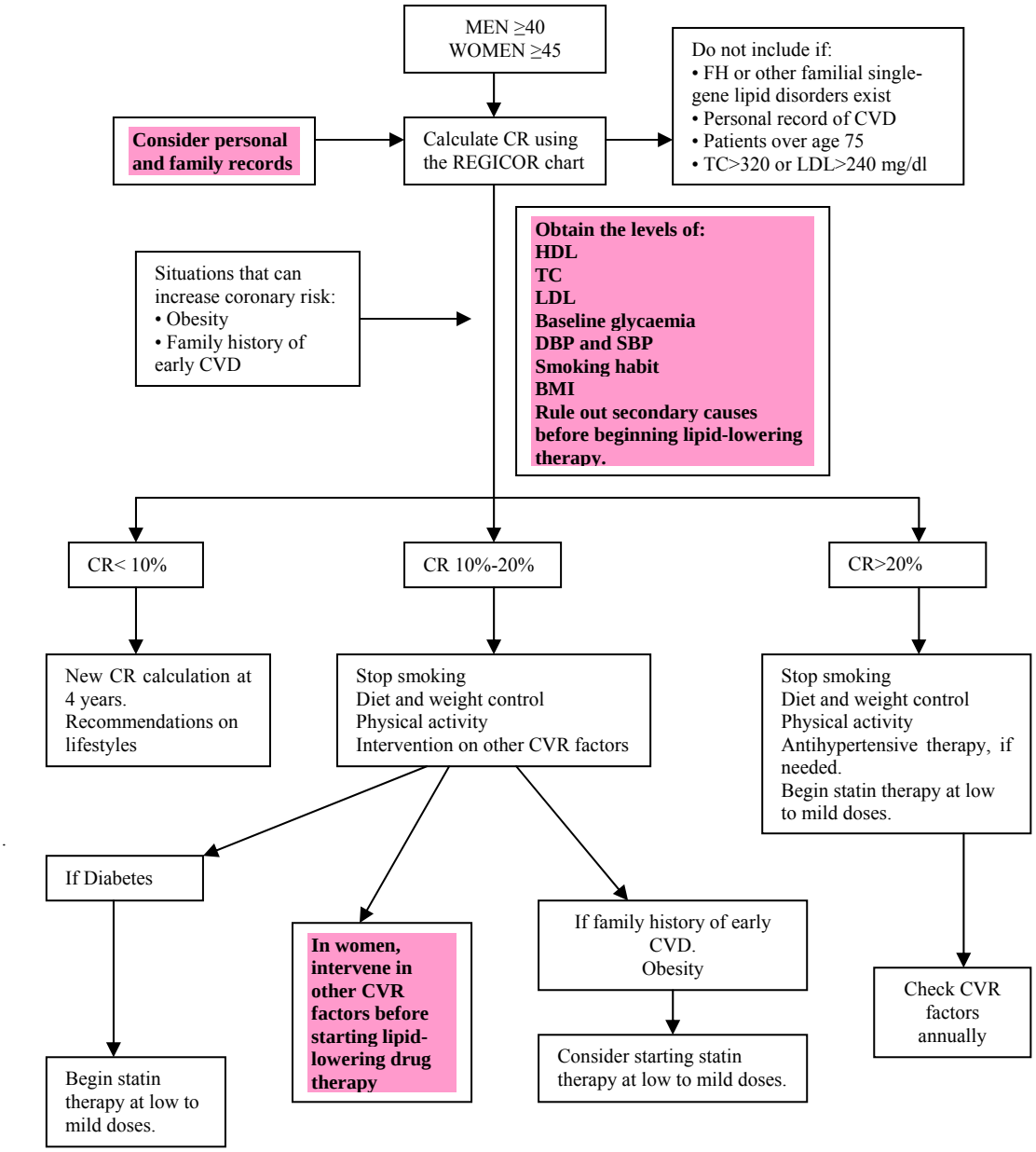


If HDL cholesterol is <35 mg/dl, real risk ≈ risk x 1.5
If HDL cholesterol is >60 mg/dl, real risk ≈ risk x 0.5

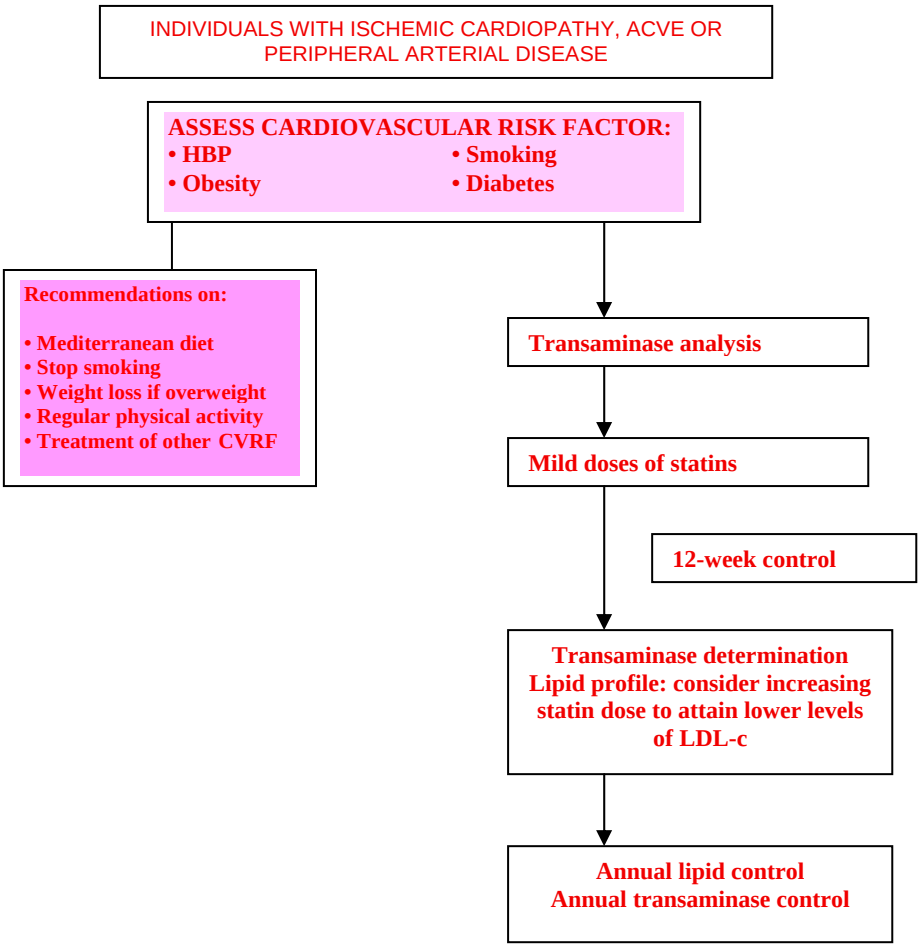
Risk at 10 years

Very high	> 39%
High	20-39%
Moderate	10-19%
Minor	5-9%
Low	<5%

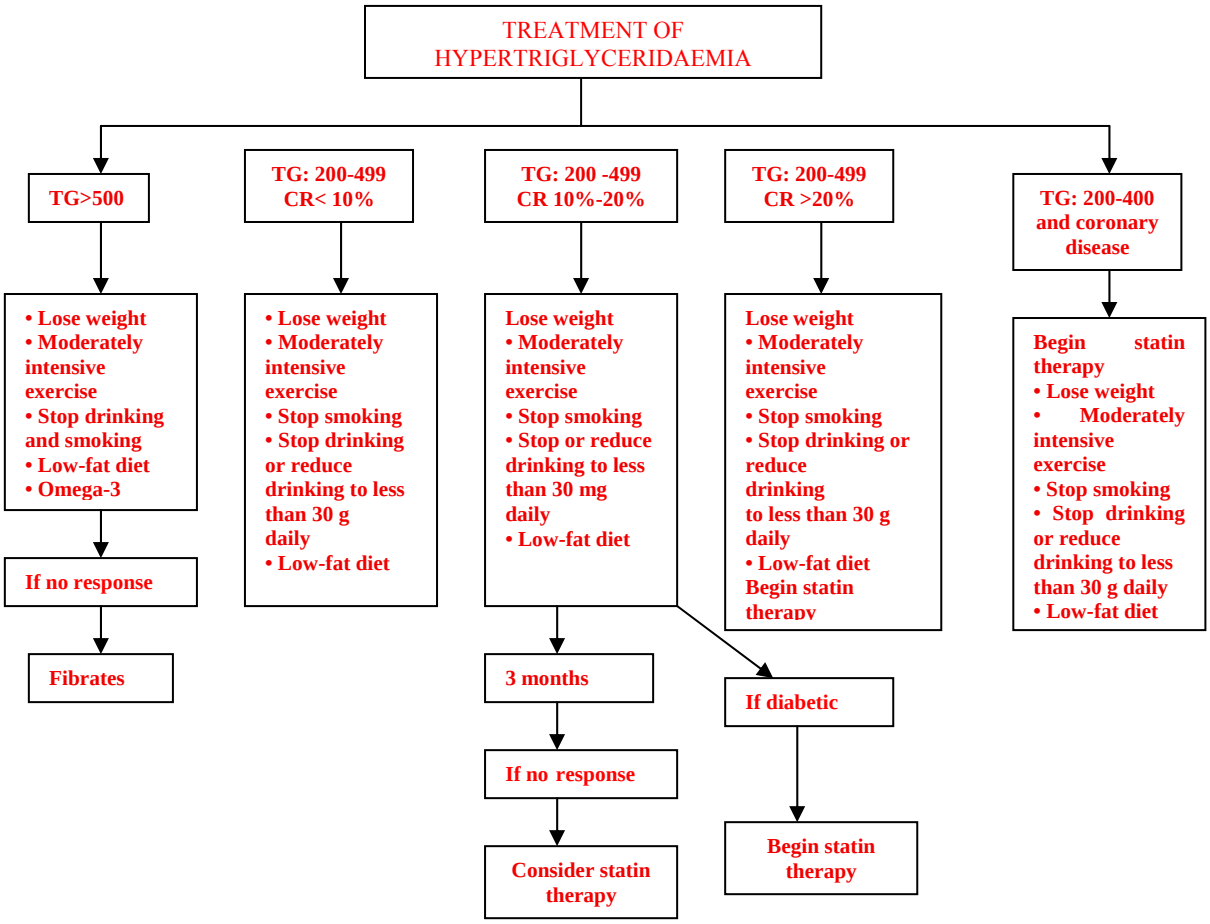
2. Algorithms for primary prevention care



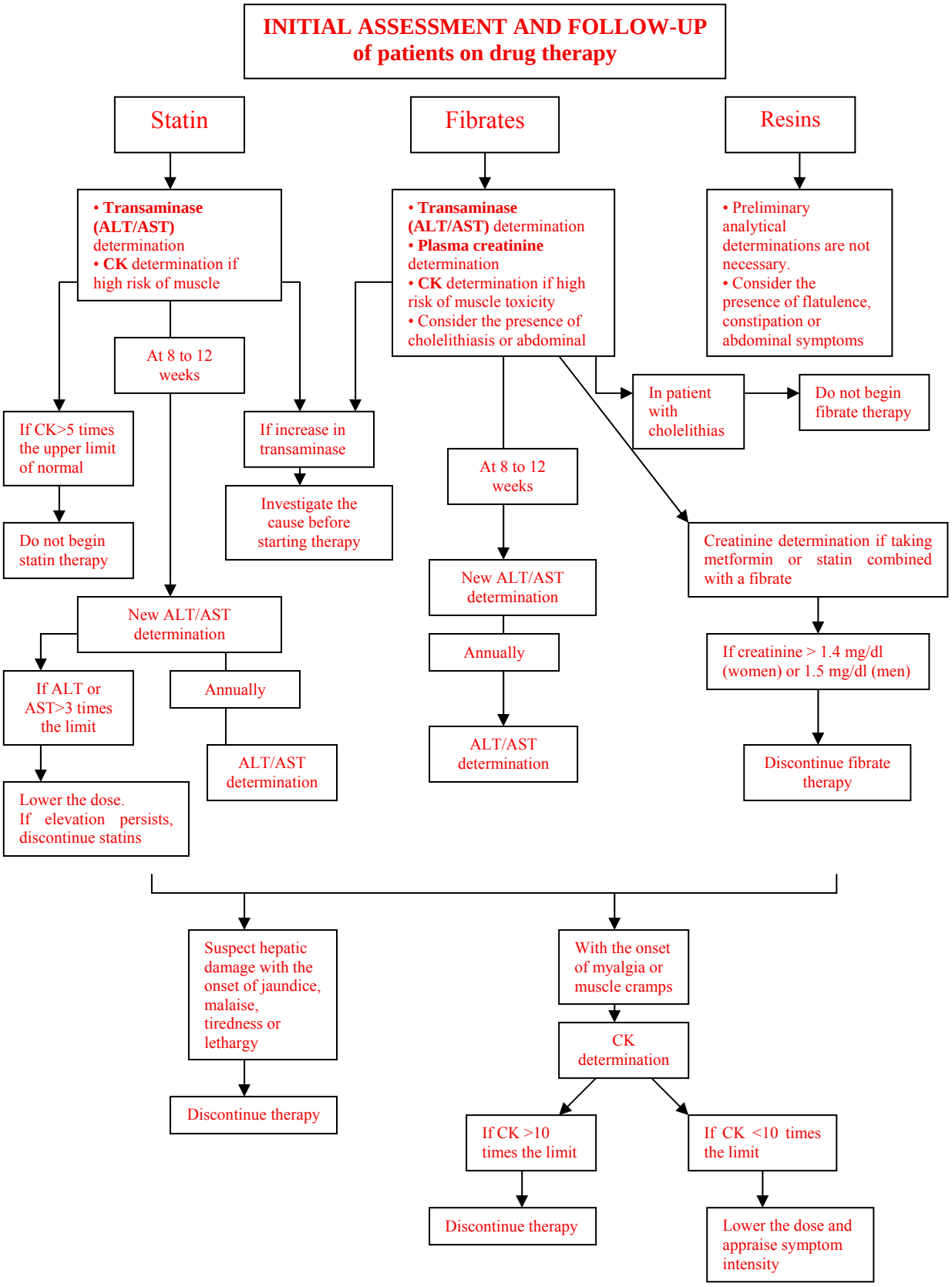
3. Algorithm for secondary prevention



4. Algorithm for hypertriglyceridaemia care



5. Algorithm for initial appraisal and monitoring of lipid-lowering treatment



6. MEDPED criteria for a medical diagnostic of familial hypercholesterolaemia*

Family History	**Score**
I. First-degree relative with early coronary and/or vascular disease	**1**
II. First-degree relative with LDL-c >= 210 mg/dl	**1**
III. First-degree relative with Xanthomata and/or Arcus Corneae	**2**
IV. Child under age 18 with LDL-c >= 150 mg/dl	**2**
Personal History	
I. Record of early coronary disease	**2**
II. Record of peripheral vascular disease or early cerebral disease (early= < age 55 in men and < age 60 in women)	**1**
Physical exploration	
I. Tendon xanthomata	**6**
II. Arcus Corneae before age 45	**4**
Fasting analysis, with triglycerides < 200 mg/dl:	
I. LDL-c >= 330 mg/dl	**8**
II. LDL-c 250-329 mg/dl	**5**
III. LDL-c 190-249 mg/dl	**3**
IV. LDL-c 155-189 mg/dl	**1**
Functional alteration of the LDLR gene	**8**

TOTAL SCORE:

Clinical diagnostic of Familial Hypercholesterolaemia:

Certain: > 8 points **Probable:** 6-7 points

* Amended, by the Thematic Network in ISCIII Research on Genetic Hyperlipidaemia in Spain of the Dutch lipid clinic network diagnosis of FH.

7. Mediterranean diet: Recommendations for patients

♦ Eat vegetables, preferably fresh, with each main meal (lunch and dinner).

♦ Eat fruit, preferably fresh, with breakfast, lunch and dinner.

♦ Eat pulses twice a week.

♦ Eat fish, 50% white (non-oily) fish (e.g. whiting, monkfish, cod, megrim, sole, perch, panga seabream, and gilthead bream) and 50% oily fish (e.g. tuna, herring, salmon, Atlantic bonito, sardines, and mackerel) Do not forget to freeze it for 48 hours beforehand.

♦ Avoid eating red meat (e.g. pork, beef, and lamb) more than once a week and preferably eat white meat (e.g. fowl, pork, and rabbit). Lean pork cuts are preferable to other red meats.

♦ Use virgin olive oil, even for frying, and unrefined, if possible.

♦ Eat grains daily, in the shape of whole-wheat bread, rice and pasta.

♦ If you drink alcohol, do so in moderate amounts (2 glasses of wine per day if you are a man and 1 if you are a woman).

♦ Take a handful of dried fruit and nuts per day.

♦ Drink two glasses of milk, preferably skimmed, or the equivalent in yoghurt or soft cheese.

♦ Try to go for a brisk 30-minute walk 3 times a week. Once a day is even better.

SAMPLE DIETS:

DAY 1

Breakfast

♦ A glass of skimmed mild with instant coffee or cocoa

♦ Toast with virgin olive oil or some corn flakes

♦ A piece of fruit

Mid-morning snack

♦ One yoghurt with 5 raw walnuts, hazelnuts or almonds

Lunch

♦ Seasonal vegetables with a boiled potato the size of a large egg, a handful of rice or pulses, dressed with chopped garlic and unrefined virgin olive oil.-{}-

♦ Baked, microwaved or grilled oily fish

♦ Dessert: A piece of fruit

♦ Half a bread roll, preferably whole-wheat

Snack

♦ Yoghurt

Dinner

♦ Tomato salad with a handful of corn, some olives and a tin of bonito.

♦ Half a bread roll, preferably whole-wheat

DAY 2

Breakfast

♦ The same

Mid-morning snack

♦ A piece of fruit

Lunch

♦ Vegetables

♦ Roast chicken or grilled pork loin or roast rabbit or an omelette made with two eggs

♦ Dessert: Yoghurt

♦ Half a bread roll, preferably whole-wheat

Snack

♦ A piece of fruit

Dinner

♦ Green salad with a handful of pasta cooked al dente and some cubes of cooked ham, soft cheese and a handful of raw nuts

♦ Dessert: Yoghurt

♦ Half a bread roll, preferably whole-wheat

8. Recommendations on losing weight: Diet and exercise

♦ Losing weight is not very complicated, but it is difficult to keep the weight over time. The main problem is a sudden change of habits which can be very drastic. We need to be realistic and plan small changes that we can add to our everyday life and that we will be able to continue in the long term.

♦ One good intention is to try to walk instead of going by car or bus. If we have to take a bus, we can try to get off one or two stops before our destination and walk the rest of the way.

♦ Another way to lose weight is to eat half of the first course and complete the other half with vegetables. If the first course is lentil stew, for instance, and we normally serve ourselves 3-4 ladles of it, we will serve 2 ladles and add a vegetable until we have completed our usual helping. We can do the same thing with rice, other pulses and pasta.

♦ If you eat out, one possibility would be to ask for two starters instead of a starter and a main dish, or ask the waiter to serve only half of the main dish. For dessert, choose the one that is the least fattening.

♦ Drinking less alcoholic beverages than usual cuts down on significant number of calories. You can do this by adding water to your wine or ask for one glass of wine and one of water.

♦ If you are able to make these small changes in your habits, you will lose one or two kilos a month. This is enough, and you will have lost a significant amount of weight after one year.

9. Recommendations for preparing fast yet healthy food

Nowadays there is not much time to cook. However, the are several healthy ways to overcome the difficulty:

♦ Cooked vegetables that are sold frozen or in glass bottles can be a substitute for a starter. Add a potato cut into pieces that only takes 10 minutes to cook. You will also find a wide choice of grilled vegetables in the frozen food department which you can use as a main dish by adding a few more shrimp, or some more ham or chicken.

♦ Fry some frozen onions and add them to vegetables sold in glass bottles. Fry them with virgin olive oil. Some of the fried onions or combined onion and courgettes sold on the market are made with virgin olive oil as well.

♦ Salads are sold already washed and cut. Add a variety of foodstuffs to make a full main course (corn or soy sprouts, cooked beets, cooked carrots and other vegetables on the market). Rinse them in plenty of water to remove some of the added salt. Tinned fish in sunflower or olive oil can also be added to ready-made salads, or cooked shrimp and surimi, either in the shape of seafood fingers or eels.

♦ Make a sandwich of tomato slices and a couple of slices of serrano-style ham (remove the fat from the edges), or cooked ham or chicken, or an omelette, or a bit of Atlantic bonito, tuna or sardines in olive oil. These are all healthy options for an occasional dinner and quick to make.

♦ A plate of spaghetti cooked al dente (they cook in 6-8 minutes, depending on their thickness) with tomato sauce made with olive oil can also be a delicious, healthy dinner.

♦ You can also buy ready-made broth and add some rice, noodles or cooked vegetables as a quick, healthy starter.

10. Food enriched with functional components

FUNCTIONAL COMPONENT	FUNCTIONAL FOOD	QUANTITY (mg)/100 g	BRAND NAME
FATTY ACIDS OMEGA 3	Oil	1350 (500) 3500 (0)	Cuida-T Plus (La Masia) Soy Plus Omega 3 (La española)
	Olives stuffed with anchovies	80 (80) 120 (120)	La Española Omega 3 El Serpis Omega 3
	Cookies	209 (156)	F Plus Cuetara
	Eggs	300 (280) 440 (280)	Brudy Omega 3 Eroski Omega 3, Matines Omega3
	Milk	30 (30) 60 (34) 60 (60) 90 (0)	Celta Omega 3 Puleva Omega 3 Eroski Omega 3; Kaiku Omega 3
	Fermented milk-yoghurt	37 (37)	Puleva Omega 3
	Milk for babies (under age 3)	26 (18) 90 (0)	Puleva Peques con Omega 3 Nestle Crecimiento 1
	Milk for babies (ages 3-12)	35 (24) 70 (0)	Puleva Max con Omega 3 Nestle 3+
	Margarine	3000 (500) 4000 (0)	Cuida-T Plus (La Masia), Tulipan Idea Flora ; Flora Oliva
	Fruit juice	30 30) 50 (50	Eroski Omega 3 Juver Omega 3
FATTY ACIDS OMEGA 3 AND PHYTOSTEROLS	Margarine	W3= 1000 (0) Fito= 8000 W3= 3000 (0) Fito= 7500	Benecoll con aceite de oliva (kaiku) Flora Pro-Activ
FATTY ACIDS OMEGA 3 AND SOY	Milk – drink	W3= 100 (0) Soja= 13000 W3= 110 (0) Soja= 6400 W3= 140 (0) Soja= 13000 W3= 140 (0) Soja= 3000 W3= 150 (0) Soja= 7200 W3= 200 (0) Soja= 14000	Sojavit (Kaiku) Alprosoja (Central Lechera Asturiana) Vive Soy (Pascual) Bon Soy (Eroski) Provamell Calcimel (Santiveri) Yosoy (Liquat Vegetais)
	Fermented milk-yoghurt	W3= 100 (0) Soja= 76100	Sojavit Yogur (kaiku)

(Continues)

Food enriched with functional components (Continuation)

FUNCTIONAL COMPONENT	FUNCTIONAL FOOD	QUANTITY (mg)/100 g	BRAND NAME
PHYTOSTEROLS	Milk	300 1000	Benecol UHT (Kaiku) Flora Pro-Active
	Fermented milk-yoghurt	900 1500 1600 2000 2800	Danacol 125g (Danone) Naturcol 100g (Central lechera Asturiana) Benecol 125g (Kaiku) Flora Pro-Active 100g Benecol liquido 70g (Kaiku)
SOY	Cookies	2000 4500 5000 8000	Gullon Diet Fontaneda digestive Soja y Fruta Marie Lu Soja Eroski Soja y Fibra
	Milk and- drinks	7200	Soja Natura (Bjorg), Provamel (Santiveri)
	Soy sauces	-	Calve, Don Simon, Heinz
	Enriched fruit juice	2700	Vive Soy

The Omega-3 products indicate the total Omega-3 content and the quantity of EPA and DHA between parentheses

11. Omega-3 content in fish and shellfish

FISH AND SHELLFISH	QUANTITY (mg/100 g)
Salmon, Atlantic, from fish farm, cooked, dry heat	1,800
Anchovy, European, preserved in oil, drained	1,700
Sardine, Pacific, preserved in tomato sauce, drained, with bones	1,400
Herring, Atlantic, salted	1,200
Mackerel, Atlantic, cooked, dry heat	1,000
Trout, rainbow, farmed, cooked, dry heat	1,000
Swordfish, cooked, dry heat	700
Tuna, white, preserved in water, bones, drained	700
Mackerel, Atlantic, cooked, dry heat	500
Flat fish (flounder, sole), cooked, dry heat	400
Halibut, Atlantic and Pacific, cooked, dry heat	400
Kingclip, cooked, dry heat	200
Cod, Atlantic, cooked, dry heat	100
Mussels, blue, cooked, steamed	700
Cupped oysters, wild, cooked, dry heat	500
Scallops, several species, cooked, dry heat	300
Carpetshells, several species, cooked, steamed	200
Shrimp, several species, cooked, steamed	300

Reference: USDA Nutrient Database for Standard Reference

12. Table of clinical trials in primary prevention

	HHS (144)	WOSCOP (143)	AFCAPS (56)
Age	Ages 40-55	Ages 45-64 Men	45 – 73 (M) 55 – 73 (W)
Drug	1200 mg Gemfibrozil	40mg pravastatin	20-40mg lovastatin
Duration (years)	5	4.8	5.2
Characteristics			
>65 years of age	0	0	21,4
HBP (%)	14	-	-
Diabetes Mellitus (%)	2.6	1	2.3
Smokers (%)	36	44	12%
TC mg/dl	270	272	221
LDL mg/dl	189	192	
Main variable	Fatal and non-fatal MI and coronary death	NFMI and coronary death	NF and FAMI, unstable angina, sudden death
RR	0.66 (0.47-0.92)	0.70 (0.58-0.84)	0.63 (0.50-0.79)
RRR	34 (8-52.7)	31 (14-43)	37 (20-49)
NNT	72	45	50
Total mortality			
RR	1.06 (0.70-1.61)	0.78 (0.60-1)	0.96 (0.71 to 1.31)
RRR	-	-	-
NNT	-	-	-
Cardiovascular mortality			
RR	0.95 (0.53-1.69)	0.68 (0.49-0.98)	0.68 (0.37 -1.26)
RRR	-	32% (3-53)	-
NNT	-	143	-
Coronary mortality			
RR	0.73 (0.37-1.45)	0.73 (0.48-1.10)	0.73 (0.34 to 1.59)
RRR	-	-	-
NNT	-	-	-
Non cardiovascular Mortality			
RR	1.20 (0.65-2.19)	0.89 (0.68-1.28)	1.21(0.84-1.74)
RRR	-	-	-
NNT	-	-	-
Major coronary events			
RR	0.66 (0.47-0.92)	0.70 (0.58-0.84)	0.63 (0.50-0.79)
RRR	34 (8-52.7)	30 (15.6-42)	37 (20.5-49)
NNT	72	45	50
Fatal and non-fatal ictus			
RR	1.48 (0.42 - 5.25)	0.90 (0.61-1.34)	-
RRR	-	-	-
NNT	-	-	-

Amended from Salcylite No. 2, 2004

	ALLHAT (60)	PROSPER (58)	ASCOT-LLAT (59)	MEGA (57)
Age	>55 years of age	Ages 70-82	Ages 40-79	Ages 40-70
Drug	40 mg pravastatin	40 mg pravastatin	10 mg atorvastatin	10-20 mg pravastatin
Duration (years)	4.8	3.2		5.3
Characteristics				
>65 years of age	55.1	100	63.9% (>60years of age)	
HBP (%)	-	-	-	42
Diabetes Mellitus (%)	35	19	24.5	21
Smokers (%)	23%	27	-	20
TC mg/dl	224	219	212	242
LDL mg/dl	146	146	131	156
Main variable	Mortality from any cause	Coronary death, NFMI, fatal and non-fatal CVA	NFMI and fatal coronary disease	Coronary death, NFMI, angina and revascularization
RR	0.99 (0.89-1.11)	0.94 (0.78 - 1.14)	0·64 (0.50-0.83)	-
RRR	-	-	35.5 (17.2-49.5)	-
NNT	-	-	95	-
Total mortality				
RR	0.99 (0.89-1.11)	-	0.87 (0.71-1.06)	0.72 (0.51-1.01)
RRR	-	-	-	-
NNT	-	-	-	-
Cardiovascular mortality				
RR	0.99 (0.84-1.16)	-	0.90 (0.66-1.23)	0.63 (0.30-1.33)
RRR	-	-	-	-
NNT	-	-	-	-
Coronary mortality				
RR	0.99 (0.80-1.24)	-	-	-
RRR	-	-	-	-
NNT	-	-	-	-
Non cardiovascular Mortality				
RR	1.01 (0.86-1.18)	-	0.85 (0.66-1.09)	0.74 (0.50-1.09)
RRR	-	-	-	-
NNT	-	-	-	-
Major coronary events				
RR	0.91(0.79-1.04)	0.91 (0.72 to 1.14)	0.71 (0.59-0.86)	0.67 (0.49-0.91)
RRR	-	-	28.4 (13.5-40.7)	33 (8.9-50.7)
NNT	-	-	74	119
Fatal and non-fatal ictus				
RR	0.91 (0.75-1.09)	1.03 (0.73 to 1.45)	0.73 (0.56-0.96)	0.83 (0.57-1.21)
RRR	-	-	26.9 (4.1-44.2)	-
NNT	-	-	158	-

13. Table of clinical trials in secondary prevention

	4S (75)	CARE (78)	LIPID (79)	HPS (76)
Age	35-70	21-75	31-75	40-80
Drug	20-40mg simvastatin	40mg pravastatin	40 mg pravastatin	40 mg simvastatin
Duration (years)	5.4	5	6.1	5
TC (mg/dl)	261	209±17	218	227
LDL-c (mg/dl)	188.3	139±15	150	131
HDL-C (mg/dl)	46	39±9	36	40.9
Triglycerides (mg/dl)	133.7	155±61	138	123.9
Ischaemic heart disease (%)	100	100	100	65
ACVE (%)	-	-	4	15.9
HBP (%)	25	43	42	-
Diabetes (%)	4	15	9	29
Smoker (%)	27	21	10	-
Main variable	Global mortality	Fatal coronary disease and symptomatic AMI	Death from cardiovascular disease	Major cardiovascular events
RR	0.7(0.59-0.85)	0.77 (0.65-0.91)	0.77 (0.66-0.89)	0.76 (0.72-0.81)
RRR	-	24 (9-36)	23.2 (11-33.8)	-
NNT	31 (20-63)	34 (21-100)	52 (34-125)	18 (15-23)
Total mortality				
RR	0.7 (0.59-0.85)	-	0.78 (0.7-0.88)	0.87 (0.81-0.94)
RRR	28.8 (14.7-40.6)	-	22 (13-31)	-
NNT	31 (20-63)	-	34 (23-59)	57 (37-124)
Cardiovascular mortality				
RR	-	-	0.76 (0.67-0.87)	0.83 (0.75-0.91)
RRR	-	-	-	-
NNT	-	-	44 (30-91)	65 (44-130)
Coronary mortality				
RR	0.58 (0.46-0.73)	0.81 (0.62-1.05)	-	-
RRR	41.2 (26.2-53.1)			
NNT	29 (20-50)			
Non cardiovascular mortality				
RR	-	-	0.83 (0.68-1.02)	0.95(0.85-1.07)
RRR	-	-	-	-
NNT	-	-	-	-
Major coronary events				
RR	0.69 (0.62-0.77)	-	0.72 (0.63-0.83)	0.73 (0.67-0.79)
RRR	30.6 (22.7-37.7)	-	27.6 (17.2-36.7)	-
NNT	12 (10-17)	-	36 (25-59)	32 (25-45)
Fatal and non-fatal ictus				
RR	0.64 (0.47-0.88)	0.69 (0.49-0.97)	0.83 (0.68-1.01)	0.75 (0.66-0.85)
RRR	35.7 (11.8-53.2)	31 (3-52)	-	-
NNT	66 (39-250)	87 (46-1000)	-	73 (51-129)

	TNT (85)	IDEAL (86)	VA-HIT (182)	BIP (181)
Age	35-75	<80	<74	45-74
Drug	80 mg atorvastatin	80mg atorvastatin	600mg per day gemfibrozil	400 mg bezafibrate
Duration (years)	4.9	4.8	5.1	6.2
TC (mg/dl)	175±24	196	175	212±17
LDL-c (mg/dl)	98±18	121.5	112	148±17
HDL-C (mg/dl)	47±11	46	32	34.6±5.5
Triglycerides (mg/dl)	151±72	149	160	145±51
Ischaemic heart disease (%)	100	100	100	100
ACVE (%)	5.2	8.5		1.1
HBP (%)	54.2	33	57%	32.4
Diabetes (%)	15	12.1	25%	10
Smoker (%)	13.4	21.2	19%	11.8
Main variable	Major CV event	Coronary death, NFMI, angina and revascularization	Fatal and non-fatal AMI	Fatal and non-fatal AMI and sudden death
RR	0.78 (0.69-0.89)	0.89 (0.78-1.01)	0.8 (0.68-0.94)	1.1 (0.93-1.31)
RRR	20.6 (10.5-29.6)		22 (7-35)	-
NNT	45 (30-91)		23 (14-77)	
Total mortality				
RR	1.01 (0.85-1.19)	0.98 (0.85-1.13)	0.9 (0.76-1.08)	1.06 (0.86-1.31)
RRR	-	-	-	-
NNT	-	-	-	-
Cardiovascular mortality				
RR	0.8 (0.61-1.03)	1.03 (0.85-1.24)	0.79 (0.61-1.02)	1.08 (0.82-1.44)
RRR	-	-	-	-
NNT	-	-	-	-
Coronary mortality				
RR	-	-	-	-
RRR				
NNT	85 (54-197)			
Non cardiovascular mortality				
RR	-	-	-	1.04 (0.74-1.45)
RRR	-	-	-	-
NNT	-	-	-	-
Major coronary events				
RR	0.8 (0.69-0.92)	0.84 (0.76-0.91)	0.8 (0.68-0.94)	-
RRR	-	-	-	-
NNT	68 (38-168)	28 (19-50)		23 (14-77)
Fatal and non-fatal ictus				
RR	0.75 (0.59-0.96)	0.87 (0.7-1.08)	0.76 (0.55-1.07)	0.94 (0.69-1.28)
RRR	-	-	-	-
NNT	-	-	-	-

14. Table of clinical trials in diabetes

	FIELD (173)	ASPEN* (170)	CARDS (168)	HPS (281)	ASCOT-LLA (171)
Age	50-75	40-75	40-75	40-80	
Drug	Fenofibrate	10 mg atorvastin	10 mg atorvastatin	40 mg simvastatin	10 mg atorvastatin
Duration (years)	**5**	4	3.9	5	3.3
TC (mg/dl)	194	195±31	206.9±31.7	220.4±39.8	204.9±31
LDL-c (mg/dl)	108	114±26	116.8±27	123.7±31.7	127.6±27
HDL-C (mg/dl)	42.5	48±14	55±13.1	41±13.9	46.4±11.6
Triglycerides (mg/dl)	153	145(99-205)	147.8±	203.5±140.7	168.1±88.4
Ischaemic heart disease (%)	17	0	0	33	-
ACVE (%)	4	4	0	18**	7.4
HBP (%)	141/82**	52	84	40	165/92.9**
Smoker (%)	9	12	23	13	20.4
Main variable	Coronary events	Cardiovascular death (Fatal AMI, fatal ACVE, sudden death, heart failure, arrhythmia), non-fatal AMI, non-fatal ACVE, revascularization, unstable angina	Coronary event, revascularization and ACVE	Major cardiovascular events****	Fatal and non-fatal AMI
RR	0.89 (0.75-1.05)	0.97 (0.75-1.26)	0.63 (0.48-0.83)	0.69 (0.48-0.9)	0.84 (0.55-1.29)
RRR			37 (15.7-50.6)	31 (10-52)	
NNT			32 (20-77)	24 (15.4-53.4)	
Total mortality					
RR	1.11 (0.95-1.29)	-	0.73 (0.52-1.01)	-	-
RRR	-	-	-	-	-
NNT	-	-	-	-	-
Cardiovascular mortality					
RR	1.11 (0.87-1.41)	1.25 (0.69-2.26)	-	-	-
RRR	-	-	-	-	-
NNT	-	-	-	-	-
Coronary mortality					
RR	1.19 (0.9-1.57)	-	-	-	-
RRR	-	-	-	-	-
NNT	-	-	-	-	-
Non cardiovascular mortality					
RR	-	0.86 (0.47-1.55)	-	-	-
RRR	-	-	-	-	-
NNT	-	-	-	-	-
Major coronary events					
RR	0.89 (0.89-0.99)	0.81 (0.5-1.33)	HR 0.69 (0.45-0.91)	-	-
RRR	10.3 (0.7-19)	-	-	-	-
NNT	70 (36-1000)	-	37 (15.7-50.6)	-	-
Fatal and non-fatal ictus					
RR	0.90 (0.73-1.12)	0.92 (0.55-1.54)	HR 0.52 (0.21-0.89)	-	-
RRR	-	-	-	-	-
NNT	-	-	-	-	-

*ASPEN: Primary prevention data
**Mean TAS/TAD figures
***ACVE and peripheral arteriopathy
****Data from 2912 diabetic patients in primary prevention

15. Lipid-lowering drugs Commercial formats

ACTIVE INGREDIENT	RANGE DAILY DOSE (mg)	DAILY INTAKES	BRAND NAMES AND FORMATS
STATINS			
Atorvastatin	10-80	1	Cardyl, Prevencor, Zarator: 10 mg 28 pills, 20 mg 28 pills, 40 mg 28 pills, 80 mg 28 pills
Fluvastatin	20-80	1	Digaril, Lescol, Liposit, Lymetel, Vaditon: 20 mg 28 caps, 40 mg 28 caps Digaril Prolib, Lescol Prolib, Liposit Prolib, Lymetel Prolib, Vaditon Prolib: 80 mg 28 pill
Lovastatin	10-80	1-2	Aterkey, Colesvir, Liposcler, Lovastatina EFG, Mevacor, Mevasterol, Nergadan: 20 mg 28 pill, 40 mg 28 pill Taucor: 20 mg 30 pill, 40 mg 30 pill
Pravastatin	10-40	1	Bristacol, Lipemol, Liplat, Prareduct, Pravastatina EFG, Pritadol: 10 mg 28 pill, 20 mg 28 pill, 40 mg 28 pill
Simvastatin	5-80	1	Alcosin, Arudel, Belmalip, Colemin, Glutasey, Histop, Lipociden, Pantok, Simvastatina EFG, Zocor: 10 mg 28 pill, 20 mg 28 pill, 40 mg 28 pill
FIBRATES			
Bezafibrate	200-600 400	1-3 1	Eulitop: 200 mg 60 pill Difaterol Retard, Eulitop Retard: 400 mg 30 pill
Fenofibrate	100-300 160 250	1-3 1 1	Liparison: 100 mg 50 cap, 100 mg 100 cap Secalip: 145 mg 30 pill, 200 mg 30 cap Secalip Supra: 160 mg 30 pill Liparison Retard, Secalip Retard: 250 mg cap
Gemfibrozil	900-1.200	1-2	Gemfibrozilo EFG, Lopid, Pilder, Trialmin: 600 mg 60 pill, 900 mg 30 pill
ANIONIC EXCHANGE RESINS			
Colestipol	5.000-30.000	1-3	Colestid: 5 g 30 sobr
Cholestyramine	12.000-36.000	1-4	Resincolestiramina: 4 g 50 sobr Efensol: 3 g 40 sobr
INTESTINAL CHOLESTEROL ABSORPTION BLOCKERS			
Ezetimibe	10	1	Ezetrol: 28 pill
OTHER LIPID AND TRIGLYCERIDE-LOWERING DRUGS			
Colextran	2.000-4.000	2	Dexide: 500 mg 50 cap
Icosapento/ doconexento	1.680-3.360	1	Omacor: 840 mg 28 cap, 840 mg 100 cap
Sulodexin	36-72 30	3 1	Aterina: 15 mg 60 cap Luzone: 6 mg 60 cap, 12 mg 60 cap Aterina: 30 mg 6 amp
Piperazine sultosilate	1.500	3	Mimedran: 500 mg 45 pill

16. Cost of statins

ACTIVE INGREDIENT	DOSAGE (MG)	FORMAT	RETAIL PRICE
Atorvastatin	10	28 pills	27.01
Atorvastatin	20	28 pills	45.74
Atorvastatin	40	28 pills	53.97
Atorvastatin	80	28 pills	53.97
Fluvastatin	20	28 capsules	15.11
Fluvastatin	40	28 capsules	22.10
Fluvastatin	80	28 pills	34.78
Lovastatin	20	28 pills	6.90
Lovastatin	20	30 pills	6.10
Lovastatin	40	28 pills	13.75
Lovastatin	40	30 pills	12,00
Pravastatin	10	28 pills	8.49
Pravastatin	20	28 pills	16.91
Pravastatin	40	28 pills	29.89
Simvastatin	10	28 pills	2.89
Simvastatin	20	28 pills	5.81
Simvastatin	40	28 pills	11.58

Source: Spanish Ministry of Health and Consumer Affairs 2008

17. Lipid-lowering drugs: precautions, counter indications, interactions and adverse reactions

DRUG	PRECAUTIONS	CONTRAINDICATIONS	INTERACTIONS	ADVERSE EFFECTS
STATINS	♦History of hepatic disease or alcohol abuse ♦ Hyperthyroidism ♦Patients at risk of myopathy or rhabdomyolisis **Fluvastatin, pravastain and simvastatin** ♦Kidney failure	Hypersensitivity ♦Active hepatic disease or persistent and unexplainable elevations of blood transaminase ♦Pregnancy ♦Breastfeeding period **Atorvastin and fluvastatin** ♦Myopathy	♦Adapt and monitor with: – *Ciclosporin*: systemic statin exposure Ezetimibe: incidence of rhabdomyolisis may – *Sirolimus*: incidence of rhabdomyolisis may ♦Monitor if associated with: – *Fibrates, niacin*: risk of muscle toxicity. Avoid associating *Lovastatin* with *gemfibrozil*. **Lovastatin, simvastatin, atorvastastin, fluvastatin** ♦Monitor if associated with: – *Oral anticoagulants*: anticoagulant effect **Lovastatin, simvastatin, atorvastastin:** ♦Avoid associating with: – Powerful CYP3A4 inhibitors: *intraconazole, ketaconazole, HIV protease inhibitors, telithromycin, erythromycin, clarithromycin, nefazodone*: plasma concentration of statin ♦Adapt and monitor with: – *Diltiazem and verapamil*: plasma concentration of statin **Pravastatin:** ♦Adapt and monitor with: Colestipol: intake combined with 40%-50% statin bioavailablity. Take statin 1 hour before. **Simvastatin:** ♦Adapt and monitor with: – *Amiodarone*: the incidence of rhabdomyolisis with high statin doses. Do not exceed 20mg daily doses of simvastatin	♦Frequent: diarrhoea, nausea, vomiting, abdominal pain, dyspepsia, transaminase, itch, rash. ♦Rare: headache, dizziness, tachycardia, palpitation, hypotension, rhinitis, breathlessness, insomnia, rash, peripheral edema, uric acid, plaque, prothrombin time, fainting spells, low tolerance to glucose, myalgia, myopathy and myasthenia. ♦Very rare: rhabdomyolisis
FIBRATES	History of hepatic disease or alcohol abuse♦Mild kidney failure	♦Hypersensitivity ♦Severe hepatic failure ♦Severe renal failure ♦Biliary lithiasis ♦ Known reactions of photosensitivity or phototoxicity while in treatment with fibrates. ♦Pregnancy ♦Breastfeeding period ♦Children	♦Adapt and monitor with: – *Sirolimus*: incidence of rhabdomyolisis may ♦Monitor if associated with: – Oral anticoagulants: prothrombine time – Statins: risk of muscle toxicity. ♦Avoid combining *lovastatin* with *gemfibrozil*. – Oral anticoagulants: anticoagulant effect **Bezafibrate** ♦Avoid combining with: ♦MAOIs or perhexiline: risk of hepatic toxicity	♦Frequent: dyspepsia, abdominal pain, diarrhoea, rash, itch, headache, weakness, dizziness, insomnia ♦Rare: Enlarged liver, cholelithiasis, cholestasis, hypoglycaemia, impotence, anaemia, risk of haemorrhage, baldness, atrial fibrillation, myositis, phototoxicity, reactions of photosensitivity.

Lipid-lowering drugs: precautions, counter indications, interactions and adverse reactions (Continuation)

DRUG	PRECAUTIONS	CONTRAINDICATIONS	INTERACTIONS	ADVERSE EFFECTS
RESINS	♦Constipation, if it can make the disease more severe (haemorrhoids, heart disease) ♦Hyperthyroidism ♦Peptic ulcer ♦Triglycerides>200 mg/dl ♦ Pregnancy ♦Breastfeeding period	♦Hypersensitivity ♦Complete biliary obstruction (non effective) ♦Familial dysbetalipoproteinaemia. ♦Triglycerides>400 mg/dl	Adapt and monitor with: – Digoxin, digitoxin, furosemide, tetracyclins, hydrocortisone, and the abosorption thereof. ♦Avoid administering concurrently with: – Thiazides: diuretic absorption. – Pravastatin 40%-50% statin bioavailability. Take statin 1 hour before.	♦Frequent: constipation ♦Infrequent: diarrhoea, gastrointestinal discomfort, nausea and vomiting. ♦Rare: breathlessness, tachycardia, palpitations, peripheral edema, headache, faeces impactation ♦Very rare: haemorrhage, acidosis, hyperchloraemia and hypercalciuria
NICOTINIC ACID (NIACIN)	♦Unstable angina, acute myocardial infarction, diabetes mellitus, record of peptic ulcer, gout. ♦Hepatic failure ♦Kidney failure ♦Pregnancy	♦Arterial haemorrhage ♦Active peptic ulcer ♦Breastfeeding period	♦Monitor if associated with: – Statins: Risk of rhabdomyolisis	♦Frequent: diarrhea, abdominal pain, nausea, vomiting, dyspepsia, rubefaction, itch. ♦Infrequent: Headache, tachycardia, palpitations, breathlessness, peripheral edema, dizziness. ♦Rare: insomnia, fainting spells, myalgia, myopathy, myasthenia. ♦Very rare: rhabdomyolisis.
INTESTINAL CHOLESTEROL ABSORPTION BLOCKERS	♦ Pregnancy	♦Hypersensitivity ♦Mild to severe hepatic failure ♦Children under age 10 ♦Breastfeeding period	Avoid combining with: – Fibrates: moderation of ezetimibe concentrations (1.5 times) and risk of gallstones. ♦Adapt and monitor with: – Statins: incidence of rhabdomyolisis may – Ciclosporin: concentration of ezetimibe (up to 3.4 times)	♦Frequent: headache, abdominal pain, diarrhoea. ♦Rare: rash, nausea, hepatitis, myalgia, transaminase, CPK ♦Very rare: angioedema, thrombocytopenia, cholecystitis, cholelithiasis, pancreatitis, myopathy, rhabdomyolisis
OMEGA 3 FATTY ACIDS	♦Patients with a high risk of haemorrhage (e.g.: after surgery or severe trauma) ♦Liver function disorder	Hypersensitivity ♦Exogenic hypertriglyceridaemia ♦Children ♦Pregnancy ♦Breastfeeding period		♦Frequent: dyspepsia, nausea. ♦Infrequent: dizziness, dysgeusia, gastroenteritis, hypersensitivity, abdominal pain, gastrointestinal disorders, gastritis, epigastric pain. ♦Rare: hyperglycaemia, headache, abdominal pain, liver disorders, acne, itchy rash. ♦Very rare: hypotension, lower intestinal haemorrhage, nasal dryness, hives.

Source: The drug's specifications and Stockley's Interaction Alerts
Comments: The adverse effects are ordered according to frequency, using the criteria below: very frequent (>1/10), frequent (>1/100, <1/10), infrequent (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated communications.

18. Total cholesterol and HDL-c levels in Spanish children

TOTAL CHOLESTEROL IN BOYS (mg/dl)

Age Mean	TC	SD	P3	P5	P10	P25	P50	P75	P90	P95
6	156	28	106	113	121	138	156	172	190	206
7	160	28	112	118	124	139	160	178	195	209
8	161	61	109	114	124	140	158	180	199	206
9	158	29	110	115	122	137	156	177	197	210
10	160	29	108	115	123	139	159	178	200	207
11	159	30	112	116	121	136	158	178	199	212
12	161	32	111	115	121	138	156	180	204	219
13	151	31	105	108	114	129	147	170	190	204
14	148	29	103	107	112	125	146	164	188	201
15	146	29	103	107	111	125	143	164	184	197
16	147	31	103	107	112	122	142	166	192	206
17	146	28	106	108	113	124	142	162	185	197
18	146	28	103	107	112	125	140	163	183	194

TOTAL CHOLESTEROL IN GIRLS (mg/dl)

Age Mean	TC	SD	P3	P5	P10	P25	P50	P75	P90	P95
6	164	33	115	117	124	142	160	183	205	217
7	162	33	111	113	124	138	158	178	202	223
8	161	29	112	116	125	142	159	177	199	210
9	160	29	112	115	124	139	157	180	197	208
10	163	33	110	115	124	139	161	181	204	217
11	161	30	112	116	12	140	157	179	203	214
12	160	30	109	112	121	137	157	179	197	215
13	154	29	107	113	119	133	152	172	191	210
14	154	31	105	111	118	134	151	172	198	208
15	162	33	109	113	123	137	160	181	207	219
16	159	32	107	111	117	136	158	177	200	213
17	157	30	108	112	119	132	155	177	198	209
18	158	32	108	112	118	136	156	173	203	218

*Factores de riesgo cardiovascular en la infancia y la adolescencia en España. Estudio RICARDIN II. Valores de referencia.
Grupo Cooperativo Español para el Estudio de los Factores de Riesgo Cardiovascular en la infancia y la Adolescencia. An
Esp Pediatr 1995; 43:11-17.

19. Glossary and Abbreviations

Glossary

Absolute Risk Reduction (ARR): The mathematical difference between the risks of developing the event in the treatment group and in the control group.

AGREE: An international initiative to facilitate the design and assessment of the quality of clinical practice guidelines.
By definition, it can be reproduced. It requires information to be identified, critically assessed and summarized according to preset criteria.

Cochrane library: A database on efficacy produced by the Cochrane collaboration project, comprising the organization's original systematic reviews.

Confidence Interval (CI): An interval –established with a preset degree of certainty or confidence– within which the actual magnitude of an effect (never known exactly) is likely to be included. One often speaks of a "95% confidence interval" (or "95% confidence limits), which means that the true value will be within that interval in 95% of the cases.

DARE: A database containing abstracts of high-quality systematic reviews on the efficacy of health interventions, prepared by the NHS Centre for Reviews and Dissemination of York.

DDD: The assumed average maintenance dose per day for a drug used for its main indication in adults.

DSM (Difference against Standard Measurement): The effect of the measurement of a result when studies measure differences on the same scale.

Embase: A European (Dutch) database created by Excerpta Medica with clinical medicine and pharmacological content.

Hazard Ratio (HR): A measure of risk that typically involves a particular group of analyses that measure the "time until an event" (e.g. the Kaplan-Meier estimator).

Likelihood Ratio: The likelihood of a positive result in patients divided by the likelihood of the same result in non-patients. The LR indicates the measure in which the result of a test supports the presence of disease (likelihood ratio higher than 1) or the absence of disease (likelihood ratio lower than 1).

Medline: A mainly clinical database compiled by the U.S. National Library of Medicine, available as a CD and freely available on the Internet (PubMed).

Meta-analysis: A statistics technique that allows the results of several related studies (e.g. diagnostic test studies, clinical tests, studies of cohorts) to be combined into a single estimator, thereby giving more weight to the studies with more assumptions and conditions.

Negative Predictive Value (NPV): The probability that a person actually has a disease when the result of a test is negative. Predictive values depend on the prevalence of a test as well as its sensibility and specificity.

NICE: An authority of the NHS (National Health Service) in England. Its role is to provide physicians, patients and the general population with the best available evidence, fundamentally in the form of clinical guidelines.

Number needed to treat (NNT/NNH): A measure used in assessing the efficacy of treatment. It is the number of people who would need to be treated (NNT) with a specific treatment to produce, or to prevent, an additional event. Conversely, the number of patients who would need to be treated to assess any undesirable effects before one of them was harmed is known as the number needed to harm (NNH). The NNT is calculated as 1/RAR.

Odds Ratio (OR): A measure used in assessing the efficacy of treatment. If it is equal to 1, the effect of the treatment is no different than the effect of the control. If the OR is higher (or lower) than 1, the effect of the treatment is higher (or lower) than the effect of the control. It should be noted that the effect that is being measured might be adverse (death, disability) or desireable (to give up smoking…).

Oxford Centre for Evidence-Based Medicine: A Centre for Evidence-Based Medicine situated in Oxford (United Kingdom) for the purpose of promoting, giving support and facilitating the resources needed to develop EBM.

Positive Predictive Value (PPV): The probability that a person actually has a disease when the result of a test is positive.

Relative Risk (RR): The ratio between the events rate in the treatment group and the control group. Its value follows the same interpretation as the OR.

Sensibility: The proportion or percentage of patients with a disease who give a positive result in a test; in other words, the proportion of true positives.

SIGN: A multi-disciplinary Scottish agency that compiles evidence-based clinical practice guidelines and methodological documents on how to design them.

Specificity: The proportion or percentage of actually healthy people who obtain a negative result in a test.

Systematic Review (SR): A review on a single issue for which an exhaustive search for information has been carried out to answer the issue being researched.

Test validity: The degree to which the results of a test correspond with the actual phenomenon being measured.

WMD (Weighted Measurement Difference): The effect of the measurement of a result when studies measure differences on different scales.

This glossary is based in part on the CASPe glossary (a critical appraisal skills programme in Spain) on http://www.redcaspe.org/homecasp.asp.

Abbreviations

ABI Ankle-Brachial index

ACCE Cerebro and cardiovascular event

AFCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study

AGREE Appraisal of Guidelines Research and Evaluation

AHA American Heart Association

AHT Arterial Hypertension

ALLHAT-LLT Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial

AMI Acute Myocardial Infarction

ASCOT-LLA Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm

ASPEN Atorvastatin Study for Prevention of Coronary Heart Disease Endpoint in Non- Insulin-Dependent Diabetes Mellitus

ATPIII Adult Treatment Panel III

BIP Bezafibrate Infarction Prevention

BMD Bone Mineral Density

BMI Body Mass Index

CAP Capsule

CAPV Comunidad Autónoma Vasca (Basque Autonomous Region)

CARDS Collaborative Atorvastatin Diabetes Study

CARE Cholesterol and Recurrent Events

CD Coronary Disease

CETP Inhibitors of cholesterol ester transfer protein

CI Confidence Interval

COMP Pill

CPG Clinical Practice Guidelines

CPK Creatine phosphokinase

CV Cardiovascular

CVD Cardiovascular Disease

CVR Cardiovascular Risk

DARE Database of Abstracts of Reviews of Effects

DDD Defined Daily Dose

DLC Duch Lipid Clinic Network

DS Diagnostic studies

ESCAV Basque Health Survey

FAMI Fatal Acute Myocardial Infarction

FH Familial hypercholesterolaemia

FIELD Fenofibrate Intervention and Event Lowering in Diabetes

GDP Gross Domestic Product

GISSI-Prevention Grupo Italiano per lo Studio Della Sopravivenza nell'Infarto Miocardico

HDL-c High Density Lipoprotein Cholesterol

HHS Helsinki Heart Study

HPS Heart Protection Study

HR Hazard Ratio

HTG Hypertriglyceridaemia

ICSI Institute for Clinical Systems Improvement

IDEAL Incremental Decrease in End Points Through Aggressive Lipid Lowering

IM Intramuscular

IV Intravenous

LDL-c Low Density Lipoprotein Cholesterol

LIPID Long-Term Intervention with Pravastatin in Ischaemic Disease

LIPS Lescol Intervention Prevention Study

LR Likelihood ratio

MEGA Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese

NECP National Cholesterol Education Program

NFAMI Non-Fatal Acute Myocardial Infarction

NICE National Institute of Clinical Excellence

NNH Number Needed to Harm

NNT Number Needed to Treat

NPC Negative Predictive Value

NZGG New Zealand Guidelines Group

OR Odds Ratio

PAD Peripheral arterial disease

PC Primary Care

PLAC Pravastatin Limitation of Atherosclerosis in the Coronary Arteries

Post-CABG Post Coronary Artery Bypass Graft

PPV Positive Predictive Value

PROSPER Prospective Study of Pravastatin in the Elderly at Risk

PROVE IT-TIMI Pravastatin or Atorvastatin Evaluation and Infection Therapy

22 -Thrombolysis in Myocardial Infarction 22 Researchers

RC Coronary Risk

RCT Randomized Clinical Trial

RR Relative Risk

RRR Relative Risk Reduction

4S Scandinavian Simvastatin Survival Study

SBR Simon Broume Register Group

SIGN Scottish Intercollegiate Guidelines Network

SPARCL Stroke Prevention by Aggressive Reduction in Cholesterol Levels

SR Systematic Review

TC Total Cholesterol

TD Temporary Disability

TG Triglycerides

TG Triglycerides

TNT Treating to New Targets

UKPDS United Kingdom Prospective Diabetes Study

VA-HIT Veterans Affaire High-Density Lipoprotein Intervention Trial

WOSCOPS West of Scotland Coronary Prevention Study

20. Indicators

Estimating the efficacy of a clinical practice guideline is a difficult task, conditioned by the limitations of current information systems. Therefore, reference should be made to the method recommended in this guideline to estimate cardiovascular risk. The fact that many of the recommendations in the guideline are based on the REGICOR equation means that, where certain indicators are concerned, an assessment of the guideline's efficacy cannot be based on a study of a chronological series. An approach of that nature can be suggested for certain other indicators, however.

TREATMENT IN PRIMARY PREVENTION:

♦ Patients between the ages of 40 and 75, with a CR of ≥20% according to the REGICOR project's tables, in low to moderate dose statin therapy.
♦ Type 2 diabetic patients between the ages of 40 and 75, with a CR of ≥10% according to the REGICOR project's tables, in low to moderate dose statin therapy. When an estimate of a specific type of risk is taken as a point of departure, the above two indicators lack prior measurements and therefore, as mentioned earlier, changes in their trend cannot be used to measure the guideline's efficacy. Monitoring them, however, may provide information on progress in the indicator's level of acceptance.
♦ Women who have no cardiovascular disease, and who are under treatment with statins with no CVR assessment. Obviously, a change in the indicator's trend should be observed, whereby the proportion of women under treatment with statins with no previous CV risk assessment should diminish as the result of the guideline's effective impact on clinical practice.

TREATMENT IN SECONDARY PREVENTION:

♦ Patients with ischaemic heart disease under treatment with moderate doses of statin.
♦ Patients with cerebrovascular disease under treatment with statins. In the case of the above two indicators, a change in trend towards a higher use of statins in patients with health problems of this nature would be predictable.

21. Areas for improvement

Despite increased publication of cardiovascular RCTs, evidence is limited in some aspects. There is a need for further studies on the efficacy of non-drug interventions, such as healthy habits and the impact of using cardiovascular risk tables on clinical outcomes such as cardiovascular events.

Moreover, despite the existence of many studies on statins, there is a need for RCTs in which the pattern of administration is dosified rather than fixed, so certain LDL-c levels could be attained. There is also a need for a study on the efficacy of lipid-lowering treatment in certain subgroups: women, the elderly, diabetics, and individuals with peripheral arteriopathy. An assessment of the safety of high statin doses is also needed.

An RCT that assesses clinical outcomes (cardiovascular disease) instead of lipid profiles is needed before widespread use of functional foods such as esterols and drugs such as ezetimibe, in order to establish the precise risk-benefit balance involved.

22. Method of Preparation

SIGN levels of evidence and grades of recommendation for intervention studies

LEVELS OF EVIDENCE

1++ High quality meta-analyses, systematic reviews of controlled clinical trials or high quality clinical trials with very low risk of bias.

1+ Well conducted meta-analyses, systematic reviews of clinical trials or well conducted clinical trials with very low risk of bias.

1- Meta-analyses, systematic reviews of clinical trials or clinical trials with a high risk of bias

2++ High quality systematic reviews of cohort and case-control studies. Cohort and case-control studies with a very low risk of bias and with a high probability of establishing a causal relationship.

2+ Well-conducted cohort and case-control studies with a low risk of bias and a moderate probability of establishing a causal relationship.

2- Cohort and case-control studies with a high risk of bias and with a significant risk of establishing a relationship that is not causal.

3 Non-analytic studies, e.g. case reports and case series.

4 Expert opinion.

DEGREES OF RECOMMENDATION

A At least one meta-analysis, systematic review or clinical trial rated as 1++, directly applicable to the guideline's target population; or a body of evidence consisting of studies rated as 1+ and showing considerable consistency with each other.

B A body of evidence including studies rated as 2++, directly applicable to the guideline's target population, and demonstrating considerable consistency with each other; or evidence extrapolated from studies rated as 1++ or 1+.

C A body of evidence including studies rated as 2+, directly applicable to the guideline's target population, and demonstrating considerable consistency with each other; or evidence extrapolated from studies rated as 21++.

D Evidence level 3 or 4; or evidence extrapolated from studies rated as 2+.

4 Consensus of the editorial team.

Levels of evidence and grades of recommendation for diagnostic studies

Adapted from *The Oxford Centre for Evidence-based Medicine Levels of Evidence* and the Centre for Reviews and Dissemination *Report Number 4* (2001)

LEVELS OF EVIDENCE TYPE OF EVIDENCE

Ia	Systematic review (with homogeneity)[a] of Level 1[b] studies
Ib	Level 1[b] studies
II	Level 2[c] studies Systematic reviews of Level 2 studies
III	Level 3[d] studies Systematic reviews of Level 3 studies
IV	Consensus, expert reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or "first principles".

a Homogeneity means that there is very little or no variation in the directions and degrees of results between the individual studies included in the systematic review.

b Level 1 studies:
• Studies that compare the test blindly with a certified benchmark (gold standard) and in which a sample of patients reflects the population on whom the test would be applied.

c Level 2 studies:
• use a poor benchmark standard (where "test" is included in the "benchmark", or where the "tests" have an impact on the "benchmark")
• the comparison between the test and the benchmark is not blind
• case-control studies

d Level 3 studies:
Studies that present at least two or three of the features included in Level 2

DEGREES OF RECOMMENDATION

A Level of evidence I[a] or I[b] studies
B Level of evidence II studies
C Level of evidence III studies
D Level of evidence IV studies

Bibliography

1) Políticas de Salud para Euskadi. Plan de Salud 2002-2010. Departamento de Sanidad Gobierno Vasco 2002 [accedido septiembre 2007]; Disponible en: www.euskadi.net

(2) Plan de Salud de Euskadi. Informe 2006. Departamento de Sanidad Gobierno Vasco 2006 [accedido septiembre 2007]; Disponible en: www.osasun.ejgv.euskadi.net

(3) El infarto de miocardio en la Comunidad Autónoma de Euskadi.1997-2000. Departamento de Sanidad Gobierno Vasco 2007 [accedido en septiembre 2007]; Disponible en: www.osasun.ejgv.euskadi.net

(4) Medrano MJ, Pastor-Barriuso R, Boix R, del Barrio JL, Damian J, Alvarez R, et al. Coronary disease risk attributable to cardiovascular risk factors in the Spanish population. Rev Esp Cardiol 2007 Dec;60(12):1250-6.

(5) Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations.
Monitoring trends and determinants in cardiovascular disease. Lancet 1999 May 8;353(9164):1547-57.

(6) Marrugat J, Elosua R, Aldasoro E, Tormo MJ, Vanaclocha H, Segura A, et al. Regional variability in population acute myocardial infarction cumulative incidence and mortality rates in Spain 1997 and 1998. Eur J Epidemiol 2004;19(9):831-9.

(7) Alvarez-Leon EE, Elosua R, Zamora A, Aldasoro E, Galcera J, Vanaclocha H, et al. Hospital resources and myocardial infarction case fatality. The IBERICA study. Rev Esp Cardiol 2004 Jun;57(6):514-23.

(8) Thrid report of the National Cholesterol Education Program (NECP) Expert Panel on Detection,Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). National Heart,Lung,and Blood Institute,national Institutes of Health,US Departament of Health and Human Services 2001 [accedido septiembre 2007]; Disponible en: www.nhlbi.nih.gov/guidelines/cholesterol/index.htm

(9) Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of cardiovascular disease.A National Clinical Guideline. Scottish Intercollegiate Guidelines Network 2007 February [accedido septiembre 2007]; Disponible en: www.sign.ac.uk.

(10) New Zealand Guidelines group (NZGG). The Assessment and Management of Cardiovascular Risk. New Zealand Guidelines group 2003 January [accedido septiembre 2007]; Disponible en: www.nzgg.org.nz

(11) Institute for Clinical Systems Improvements (ICSI). Lipid management in adults. Institute for Clinical Systems Improvements (ICSI) 2007 June [accedido septiembre 2007]; Disponible en:www.icsi.org/guidelines_and_more/guidelines__order_sets__protocols/

(12) Etxeberria A, Rotaeche R, Lekue I, Callén B, Merino M, Villar M. Descripción de la metodología de elaboración-adapatación-actualización empleada en la guía de práctica clínica sobre asma de la CAPV. Proyecto de Investigación Comisionada.Vitoria-Gasteiz. 2005. Departamento de Sanidad. Informe nº: Osteba D-05-03.

(13) The AGREE Collaboration. AGREE Instrument Spanish Version. [accedido septiembre 2007]; Disponible en: www.agreecollaboration.org.

(14) National Institute for Health and Clinical Excellence. The guidelines manual 2007. [accedido septiembre 2007];Disponible en: www.nice.org.uk/.

(15) Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ 1994
Feb 5;308(6925):367-72.

(16) Brotons C. Adapatación española de la Guia Europea de Prevencion Cardiovascular. [accedido septiembre 2007];Disponible en:www.searterioesclerosis.org.

(17) Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart 2006 Dec;92(12):1752-9.

(18) Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, Cordon F, et al. Coronary risk estimation in Spain using a calibrated Framingham function. Rev Esp Cardiol 2003 Mar;56(3):253-61.

(19) Marrugat J, Subirana I, Comin E, Cabezas C, Vila J, Elosua R, et al. Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA Study. J Epidemiol Community Health 2007 Jan;61(1):40-7.

(20) Comin E, Solanas P, Cabezas C, Subirana I, Ramos R, Gene-Badia J, et al. Estimating cardiovascular risk in Spain using different algorithms. Rev Esp Cardiol 2007 Jul;60(7):693-702.

(21) Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003 Jun;24(11):987-1003.

(22) Mostaza JM, Vicente I, Taboada M, Laguna F, Echaniz A, Garcia-Iglesias F, et al. The application of the SCORE charts to advanced age males triple the number of highrisk subjects compared to the Framingham function. Med Clin (Barc) 2005 Apr 9;124(13):487-90.

(23) Jackson PR, Wallis EJ, Haq IU, Ramsay LE. Statins for primary prevention: at what coronary risk is safety assured? Br J Clin Pharmacol 2001 Oct;52(4):439-46.

(24) Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A Systematic review and economic evaluation of statins for the prevention of coronary events. Health Technology Assessment 11 nº14 2007 [accedido noviembre 2007];
Disponible en: www.ncchta.org

(25) Miguel GF, Garcia OA, Montero Alonso MJ. Primary prevention with statins, consensus and risk tables. Aten Primaria 2005 Jun 15;36(1):31-8.

(26) Scheuner MT, Whitworth WC, McGruder H, Yoon PW, Khoury MJ. Expanding the definition of a positive family history for early-onset coronary heart disease. Genet Med 2006 Aug;8(8):491-501.

(27) Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr., Levy D, Murabito JM, Wang TJ, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. JAMA 2004 May 12;291(18):2204-11.

(28) Sesso HD, Lee IM, Gaziano JM, Rexrode KM, Glynn RJ, Buring JE. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. Circulation 2001 Jul 24;104(4):393-8.

(29) Nilsson PM, Nilsson JA, Berglund G. Family burden of cardiovascular mortality: risk implications for offspring in a national register linkage study based upon the Malmo Preventive Project. J Intern Med 2004 Feb;255(2):229-35.

(30) Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med 2007 Sep 10;167(16):1720-8.

(31) Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007 Jan 30;115(4):450-8.

(32) Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996 Apr;3(2):213-9.

(33) Jonsdottir LS, Sigfusson N, Gudnason V, Sigvaldason H, Thorgeirsson G. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. J Cardiovasc Risk 2002 Apr;9(2):67-76.

(34) Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. Br J Cancer 1999 Jul;80 Suppl 1:95-103.

(35) Avins AL, Neuhaus JM. Do triglycerides provide meaningful information about Herat disease risk? Arch Intern Med 2000 Jul 10;160(13):1937-44.

(36) Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA 2007 Jul 18;298(3):299-308.

(37) Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA 2007 Jul 18;298(3):309-16.

(38) Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol 1998 Feb 26;81(4A):7B-12B.

(39) Cucuzzella M, Smith PC, Nashelsky J, Spencer DC. Clinical inquiries. When should we treat isolated high triglycerides? J Fam Pract 2004 Feb;53(2):142-4.

(40) U.S.Preventive Service Task Force. Clinical Preventive Task Force.[accedido noviembre 2007];Disponible en: www.ahrq.gov/clinic/uspstfix.htm .

(41) Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. JAMA 2004 May 12;291(18):2243-52.

42) Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H. What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003 Feb;253(2):169-80.

(43) Alonso R, Castillo S, Civeira F, Puzo J, de la Cruz JJ, Pocovi M, et al. Heterozygous familial hypercholesterolemia in Spain. Description of 819 non related cases. Med Clin (Barc) 2002 Apr 13;118(13):487-92.

(44) Genest JJ, Jr., Martin-Munley SS, McNamara JR, Ordovas JM, Jenner J, Myers RH, et al. Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation 1992 Jun;85(6):2025-33.

(45) Austin MA, McKnight B, Edwards KL, Bradley CM, McNeely MJ, Psaty BM, et al. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: A 20-year prospective study. Circulation 2000 Jun 20;101(24):2777-82.

(46) Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006 Jan 14;332(7533):73-8.

(47) Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998 Jul 23;339(4):229-34.

(48) Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. Arch Intern Med 2001 Jan 22;161(2):242-7.

(49) Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med 2001 Jul 23;161(14):1717-23.

(50) Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001 Sep 13;345(11):790-7.

(51) Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. BMJ 2002 Apr 20;324(7343):939-42.

(52) Eberly LE, Cohen JD, Prineas R, Yang L. Impact of incident diabetes and incident nonfatal cardiovascular disease on 18-year mortality: the multiple risk factor intervention trial experience. Diabetes Care 2003 Mar;26(3):848-54.

(53) Becker A, Bos G, de VF, Kostense PJ, Dekker JM, Nijpels G, et al. Cardiovascular events in type 2 diabetes: comparison with nondiabetic individuals without and with prior cardiovascular disease. 10-year follow-up of the Hoorn Study. Eur Heart J 2003 Aug;24(15):1406-13.

(54) Hu G, Jousilahti P, Qiao Q, Peltonen M, Katoh S, Tuomilehto J. The gender-specific impact of diabetes and myocardial infarction at baseline and during follow-up on mortality from all causes and coronary heart disease. J Am Coll Cardiol 2005 May 3;45(9):1413-8.

(55) Dirección de Asistencia Sanitaria de Osakidetza-Servicio Vasco de Salud. Guía de Práctica Clínica sobre Hipertensión Arterial. Osakidetza-Servicio Vasco de Salud 2002 [accedido febrero 2008]; Disponible en: www.osanet.euskadi.net

(56) Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, 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 1998 May 27;279(20):1615-22.

(57) Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006 Sep 30;368(9542):1155-63.

(58) Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002 Nov 23;360(9346):1623-30.

(59) Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, 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 Apr 5;361(9364):1149-58.

(60) 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 2002 Dec 18;288(23):2998-3007.

(61) Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006 Apr 17;97(8A):52C-60C.

(62) Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. Am J Cardiol 2006 Apr 17;97(8A):77C-81C.

63) McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol 2006 Apr 17;97(8A):89C-94C.

(64) Pasternak RC, Smith SC, Jr., Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 2002 Aug 7;40(3):567-72.

(65) Smellie WS, Wilson D, McNulty CA, Galloway MJ, Spickett GA, Finnigan DI, et al. Best practice in primary care pathology: review 1. J Clin Pathol 2005 Oct;58(10):1016-24.

(66) Thompson PD, Clarkson PM, Rosenson RS. An assessment of statin safety by muscle experts. Am J Cardiol 2006 Apr 17;97(8A):69C-76C.

(67) NIH From the Working Group on Lipoprotein Measurement. National Colesterol education Program:Recommendations on Lipoprotein Measurement. National Institute of health.National Heart,Lung, and Blood Institute; 1995 Sep. Report No.: NIH Publication n.95-3044.

(68) 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 Jul;25(7):1463-9.

(69) Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: Systematic review. Atherosclerosis 2006 Nov;189(1):61-9.

(70) Weatherley BD, Nelson JJ, Heiss G, Chambless LE, Sharrett AR, Nieto FJ, et al. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord 2007;7:3.

(71) Cleven AH, Kester AD, Hooi JD, Knottnerus JA, van den Brandt PA, Stoffers HE. Cardiovascular outcome stratification using the ankle-brachial pressure index. Eur J Gen Pract 2005 Sep;11(3-4):107-12.

(72) Lamina C, Meisinger C, Heid IM, Lowel H, Rantner B, Koenig W, et al. Association of ankle-brachial index and plaques in the carotid and femoral arteries with cardiovascular events and total mortality in a population-based study with 13 years of follow-up. Eur Heart J 2006 Nov;27(21):2580-7.

(73) Manzano L, Garcia-Diaz JD, Gomez-Cerezo J, Mateos J, del Valle FJ, Medina- Asensio J, et al. Clinical value of the ankle-brachial index in patients at risk of cardiovascular disease but without known atherothrombotic disease: VITAMIN study. Rev Esp Cardiol 2006 Jul;59(7):662-70.

(74) Manzano L, Mostaza JM, Suarez C, Cairols M, Redondo R, Valdivielso P, et al. Value of the ankle-brachial index in cardiovascular risk stratification of patients without known atherotrombotic disease. MERITO study. Med Clin (Barc) 2007 Feb 24;128(7):241-6.

(75) Randomised trial of cholesterol lowering in 4444 patients with coronary Herat disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994 Nov 19;344(8934):1383-9.

(76) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002 Jul 6;360(9326):7-22.

(77) Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004 Apr 8;350(15):1495-504.

(78) Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, 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 Oct 3;335(14):1001-9.

(79) 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 Nov 5;339(19):1349-57.

(80) Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004 Jul 13;110(2):227-39.

(81) Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. Ann Intern Med 2006 Oct 3;145(7):520-30.

(82) Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005 Oct 8;366(9493):1267-78.

(83) Genser B, Marz W. Low density lipoprotein cholesterol, statins and cardiovascular events: a meta-analysis. Clin Res Cardiol 2006 Aug;95(8):393-404.

(84) Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003 Jun 28;326(7404):1423.

(85) Waters DD, Guyton JR, Herrington DM, McGowan MP, Wenger NK, Shear C. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? Am J Cardiol 2004 Jan 15;93(2):154-8.

(86) Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005 Nov 16;294(19):2437-45.

(87) de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, 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 2004 Sep 15;292(11):1307- 16.

(88) Pearson T, Denke M, McBride P, Battisti WP, Brady WE, Palmisano J. Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: subanalyses of data from a randomized, double-blind, placebo-controlled trial. Am J Geriatr Pharmacother 2005 Dec;3(4):218-28.

(89) Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis 2004 Mar;173(1):55-68.

90) Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis 2003 May;168(1):1-14.

(91) Williams RR, Hunt SC, Schumacher MC, Hegele RA, Leppert MF, Ludwig EH, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol 1993 Jul 15;72(2):171-6.

(92) Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol 2004 Sep 1;160(5):407-20.

(93) Damgaard D, Larsen ML, Nissen PH, Jensen JM, Jensen HK, Soerensen VR, et al. The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population. Atherosclerosis 2005 May;180(1):155- 60.

(94) Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, et al. The diet and 15-year death rate in the seven countries study. Am J Epidemiol 1986 Dec;124(6):903-15.

(95) Simopoulos AP. The Mediterranean diets: What is so special about the diet of Greece? The scientific evidence. J Nutr 2001 Nov;131(11 Suppl):3065S-73S.

(96) Panagiotakos DB, Pitsavos C, Polychronopoulos E, Chrysohoou C, Zampelas A, Trichopoulou A. Can a Mediterranean diet moderate the development and clinical progression of coronary heart disease? A systematic review. Med Sci Monit 2004 Aug;10(8):RA193-RA198.

(97) Serra-Majem L, Roman B, Estruch R. Scientific evidence of interventions using the Mediterranean diet: a systematic review. Nutr Rev 2006 Feb;64(2 Pt 2):S27-S47.

(98) de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999 Feb 16;99(6):779-85.

(99) Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet 2002 Nov 9;360(9344):1455-61.

(100) Fito M, Guxens M, Corella D, Saez G, Estruch R, de la TR, et al. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. Arch Intern Med 2007 Jun 11;167(11):1195-203.

(101) Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 2006 Jul 4;145(1):1-11.

(102) Hooper L, Summerbell CD, Higgins JPT, Thompson RL, Clements G, Capps N, et al. Reducción o modificación de las grasas en la dieta para la prevención de enfermedades cardiovasculares (Revisión Cochrane traducida).[accedido noviembre 2007];Disponible en: www.update-software.com.

(103) Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, Jr., Brehm BJ, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006 Feb 13;166(3):285-93.

(104) Perez-Jimenez F, Alvarez dC, Badimon L, Barja G, Battino M, Blanco A, et al. International conference on the healthy effect of virgin olive oil. Eur J Clin Invest 2005 Jul;35(7):421-4.

(105) Fernandez-Jarne E, Martinez-Losa E, Prado-Santamaria M, Brugarolas-Brufau C, Serrano-Martinez M, Martinez-Gonzalez MA. Risk of first non-fatal myocardial infarction negatively associated with olive oil consumption: a case-control study in Spain. Int J Epidemiol 2002 Apr;31(2):474-80.

(106) Mukuddem-Petersen J, Oosthuizen W, Jerling JC. A systematic review of the effects of nuts on blood lipid profiles in humans. J Nutr 2005 Sep;135(9):2082-9.

(107) Hooper L. Primary prevention:diet and weight loss. BMJ Publishing Group 2007 [accedido noviembre 2007];Disponible en: www.clinicalevidence.bmj.com

(108) Iestra JA, Kromhout D, van der Schouw YT, Grobbee DE, Boshuizen HC, van Staveren WA. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review. Circulation 2005 Aug 9;112(6):924-34.

(109) Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA 2002 Nov 27;288(20):2569-78.

(110) He FJ, Nowson CA, Lucas M, MacGregor GA. Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. J Hum Hypertens 2007 Sep;21(9):717-28.

(111) Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. J Nutr 2006 Oct;136(10):2588-93.

(112) Brunner EJ, Thorogood M, Rees K, Hewitt G. Intervenciones dietéticas para la reducción del riesgo cardiovascular (Revisión Cochrane traducida). La Biblioteca Cochrane Plus 2007 [accedido noviembre 2007]; Disponible en: www.updatesoftware.com.

(113) Thompson RL, Summerbell CD, Hooper L, Higgins JPT, Little PS, Talbot D, et al. Asesoramiento dietético por un dietista versus otro profesional de la salud o recursos de autoayuda para reducir el colesterol en sangre (Revisión Cochrane traducida). La Biblioteca Cochrane Plus 2007 [accedido noviembre 2007];Disponible en: www.update-software.com.

(114) Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: a meta-analysis. Addiction 2000 Oct;95(10):1505-23.

(115) Di CA, Rotondo S, Iacoviello L, Donati MB, De GG. Meta-analysis of wine and beer consumption in relation to vascular risk. Circulation 2002 Jun 18;105(24):2836-44.

(116) Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ 1999 Dec 11;319(7224):1523-8.

(117) Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA 2007 Aug 15;298(7):786-98.

(118) Encuesta de Salud de la CAPV 2002. Departamento de Sanidad 2004 [accedido noviembre 2007]; Disponible en: www.euskadi.net

(119) Howley ET. Type of activity: resistance, aerobic and leisure versus occupational physical activity. Med Sci Sports Exerc 2001 Jun;33(6 Suppl):S364-S369.

(120) Abenhaim L, Rossignol M, Valat JP, Nordin M, Avouac B, Blotman F, et al. The role of activity in the therapeutic management of back pain. Report of the International Paris Task Force on Back Pain. Spine 2000 Feb 15;25(4 Suppl):1S-33S.

(121) Kelley GA, Kelley KS, Tran ZV. Walking and Non-HDL-C in adults: a meta-analysis of randomized controlled trials. Prev Cardiol 2005;8(2):102-7.

(122) Halbert JA, Silagy CA, Finucane P, Withers RT, Hamdorf PA. Exercise training and blood lipids in hyperlipidemic and normolipidemic adults: a meta-analysis of randomized, controlled trials. Eur J Clin Nutr 1999 Jul;53(7):514-22.

(123) Stensel D. Primary prevention of CVD:physical activity. BMJ Publishing Group 2007 [accedido noviembre 2007];Disponible en: www.clinicalevidence.bmj.com

(124) National Institute for Health and Clinical Excellence. Four commonly used Methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling. NHS 2006 [accedido febrero 2008];Disponible en: http://www.nice.org.uk/nicemedia/pdf/PH002_physical_activity.pdf

(125) Avenell A, Broom J, Brown TJ, Poobalan A, Austin MA, Stearns SC, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. Health Technology Assessment vol 8:nº21 2004 [accedido noviembre 2007]; Disponible en: http://www.ncchta.org/

(126) Douketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. Int J Obes (Lond) 2005 Oct;29(10):1153-67.

(127) McTigue KM, Harris R, Hemphill B, Lux L, Sutton S, Bunton AJ, et al. Screening and interventions for obesity in adults: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2003 Dec 2;139(11):933-49.
(128) Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al.
Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer:
systematic review. BMJ 2006 Apr 1;332(7544):752-60.

(129) Burr ML, shfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr 2003 Feb;57(2):193-200.

(130) 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 Aug 7;354(9177):447-55.

(131) Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega- 3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis 2006 Nov;189(1):19-30.

(132) Thompson GR, Grundy SM. History and development of plant sterol and stanol esters for cholesterol-lowering purposes. Am J Cardiol 2005 Jul 4;96(1A):3D-9D. (133) Moruisi KG, Oosthuizen W, Opperman AM. Phytosterols/stanols lower colesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. J Am Coll Nutr 2006 Feb;25(1):41-8.

(134) Chen JT, Wesley R, Shamburek RD, Pucino F, Csako G. Meta-analysis of natural therapies for hyperlipidemia: plant sterols and stanols versus policosanol. Pharmacotherapy 2005 Feb;25(2):171-83.

(135) Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc 2003 Aug;78(8):965-78.

(136) Law M. Plant sterol and stanol margarines and health. BMJ 2000 Mar 25;320(7238):861-4.

(137) Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. Am J Clin Nutr 2005 Feb;81(2):397-408.

(138) Reynolds K, Chin A, Lees KA, Nguyen A, Bujnowski D, He J. A meta-analysis of the effect of soy protein supplementation on serum lipids. Am J Cardiol 2006 Sep 1;98(5):633-40.

(139) Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: a meta-analysis of 11 randomized controlled trials. Am J Clin Nutr 2007 Apr;85(4):1148-56.

(140) Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A metaanalysis of randomized clinical trials. Ann Intern Med 2000 Sep 19;133(6):420-9.

(141) Ulbricht C, Basch E, Szapary P, Hammerness P, Axentsev S, Boon H, et al. Guggul for hyperlipidemia: a review by the Natural Standard Research Collaboration. Complement Ther Med 2005 Dec;13(4):279-90.

(142) Thompson Coon JS, Ernst E. Herbs for serum cholesterol reduction: a Systematic view. J Fam Pract 2003 Jun;52(6):468-78.

(143) Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, 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 Nov 16;333(20):1301-7.

(144) Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Herat 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 Nov 12;317(20):1237-45.

(145) A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. Br Heart J 1978 Oct;40(10):1069-118.

(146) The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984 Jan 20;251(3):351-64.

(147) Vrecer M, Turk S, Drinovec J, Mrhar A. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. Int J Clin Pharmacol Ther 2003 Dec;41(12):567-77.

(148) Cucherat M, Lievre M, Gueyffier F. Clinical benefits of cholesterol lowering treatments. Meta-analysis of randomized therapeutic trials. Presse Med 2000 May 13;29(17):965-76.

(149) Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med 2006 Nov 27;166(21):2307-13.

(150) Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med 2007 Oct 11;357(15):1477-86.

(151) Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease—a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J 2007 Nov;154(5):943-53.

(152) Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality: a systematic review. Arch Intern Med 2005 Apr 11;165(7):725-30.

(153) Clofibrate and niacin in coronary heart disease. JAMA 1975 Jan 27;231(4):360-81.

(154) Birjmohun RS, Hutten BA, Kastelein JJ, Stroes ES. Efficacy and safety of highdensity lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. J Am Coll Cardiol 2005 Jan 18;45(2):185-97.

(155) Guyton JR, Blazing MA, Hagar J, Kashyap ML, Knopp RH, McKenney JM, et al. Extended-release niacin vs gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. Niaspan-Gemfibrozil Study Group. Arch Intern Med 2000 Apr 24;160(8):1177-84.

(156) Grundy SM, Vega GL, McGovern ME, Tulloch BR, Kendall DM, Fitz-Patrick D, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med 2002 Jul 22;162(14):1568-76.

(157) McKenney JM, Jones PH, Bays HE, Knopp RH, Kashyap ML, Ruoff GE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). Atherosclerosis 2007 Jun;192(2):432-7.

(158) Wink J, Giacoppe G, King J. Effect of very-low-dose niacin on high-density lipoprotein in patients undergoing long-term statin therapy. Am Heart J 2002 Mar;143(3):514-8.

(159) Davignon J, Roederer G, Montigny M, Hayden MR, Tan MH, Connelly PW, et al. Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia. Am J Cardiol 1994 Feb 15;73(5):339-45.

(160) Alvarez CA, Diaz GL, Lopez F, V, Prieto Diaz MA, Suarez GS. Comparison of the SCORE and Framingham models in calculating high cardiovascular risk for a sample of males within the 45-65 age range in Asturias, Spain. Rev Esp Salud Publica 2005 Jul;79(4):465-73.

(161) Anum EA, Adera T. Hypercholesterolemia and coronary heart disease in the elderly: a meta-analysis. Ann Epidemiol 2004 Oct;14(9):705-21.

(162) Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and allcause mortality in elderly people from the Honolulu Heart Program: a cohort study. Lancet 2001 Aug 4;358(9279):351-5.

(163) Tikhonoff V, Casiglia E, Mazza A, Scarpa R, Thijs L, Pessina AC, et al. Low-density lipoprotein cholesterol and mortality in older people. J Am Geriatr Soc 2005 Dec;53(12):2159-64.

(164) Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007 Dec 1;370(9602):1829-39.

(165) Arteagoitia JM, Larranaga MI, Rodriguez JL, Fernandez I, Pinies JA. Incidence, prevalence and coronary heart disease risk level in known Type 2 diabetes: a sentinel practice network study in the Basque Country, Spain. Diabetologia 2003
Jul;46(7):899-909.

(166) Stevens RJ, Kothari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001 Dec;101(6):671-9.

(167) Allemann S, Diem P, Egger M, Christ ER, Stettler C. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. Curr Med Res Opin 2006 Mar;22(3):617-23.

(168) Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, 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 Aug 21;364(9435):685-96.

(169) Costa J, Borges M, David C, Vaz CA. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ 2006 May 13;332(7550):1115-24.

(170) Knopp RH, d'Emden M, Smilde JG, Pocock SJ. 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-insulindependent diabetes mellitus (ASPEN). Diabetes Care 2006 Jul;29(7):1478-85.

(171) Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005 May;28(5):1151-7.

(172) Vijan S, Hayward RA. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. Ann Intern Med 2004 Apr 20;140(8):650-8.

(173) Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of LONGTERM fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005 Nov 26;366(9500):1849-61.

(174) Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008 Jan 12;371(9607):117-25.

(175) Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. Heart 2007 Aug;93(8):914-21.

(176) Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 2004 Dec;35(12):2902-9.

(177) Briel M, Schwartz GG, Thompson PL, de Lemos JA, Blazing MA, van Es GA, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA 2006 May 3;295(17):2046-56.

(178) Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. Br J Clin Pharmacol 2004 May;57(5):640-51.

(179) Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sanchez P, Lechat P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. Arch Intern Med 2003 Mar 24;163(6):669-76.

(180) LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a metaanalysis of randomized controlled trials. JAMA 1999 Dec 22;282(24):2340-6.

(181) Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. Circulation 2000 Jul 4;102(1):21-7.

(182) Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, 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 Aug 5;341(6):410-8.

(183) Hachinski V, Graffagnino C, Beaudry M, Bernier G, Buck C, Donner A, et al. Lipidsand stroke: a paradox resolved. Arch Neurol 1996 Apr;53(4):303-8.

(184) Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. Lancet 1995 Dec 23;346(8991-8992):1647-53.

(185) Briel M, Studer M, Glass TR, Bucher HC. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med 2004 Oct 15;117(8):596-606.

(186) Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med 2006 Sep 25;166(17):1814-21.

(187) Bavry AA, Mood GR, Kumbhani DJ, Borek PP, Askari AT, Bhatt DL. Long-term benefit of statin therapy initiated during hospitalization for an acute coronary syndrome: a systematic review of randomized trials. Am J Cardiovasc Drugs 2007;7(2):135-41.

(188) Amarenco P, Bogousslavsky J, Callahan A, III, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006 Aug 10;355(6):549-59.

(189) Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004 Mar 6;363(9411):757-67.

190) Vergouwen MD, de Haan RJ, Vermeulen M, Roos YB. Statin treatment and the occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease. Stroke 2008 Feb;39(2):497-502.

(191) Grupo de trabajo de la Guía de Práctica clínica sobre la Prevención Primaria y Secundaria del Ictus. Guía de Práctica clínica sobre la Prevención Primaria y Secundaria del Ictus. Madrid: Plan Nacional para el SNS del MSC.2008.

(192) 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 Apr;45(4):645-54.

(193) Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. BMJ 2002 Nov 16;325(7373):1139.

(194) Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL colesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. Circulation 1992 Jan;85(1):37-45.

(195) Assmann G, Schulte H. Role of triglycerides in coronary artery disease: lessons from the Prospective Cardiovascular Munster Study. Am J Cardiol 1992 Dec 14;70(19):10H-3H.

(196) Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. Circulation 2001 Dec 18;104(25):3046-51.

(197) Garg A, Simha V. Update on dyslipidemia. J Clin Endocrinol Metab 2007 May;92(5):1581-9.

(198) Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ 2007 Apr 10;176(8):1113-20.

(199) Pejic RN, Lee DT. Hypertriglyceridemia. J Am Board Fam Med 2006 May;19(3):310-6.

(200) Harris WS. n-3 fatty acids and serum lipoproteins: human studies. A m J Clin Nutr 1997 May;65(5 Suppl):1645S-54S.

(201) Brunzell JD. Clinical practice. Hypertriglyceridemia. N Engl J Med 2007 Sep 6;357(10):1009-17.

(202) Gan SI, Edwards AL, Symonds CJ, Beck PL. Hypertriglyceridemia-induced pancreatitis: A case-based review. World J Gastroenterol 2006 Nov 28;12(44):7197-202.

(203) Leaf DA. Chylomicronemia and the chylomicronemia syndrome: a practical approach to management. Am J Med 2008 Jan;121(1):10-2.

(204) Santamarina-Fojo S. The familial chylomicronemia syndrome. Endocrinol Metab Clin North Am 1998 Sep;27(3):551-67, viii.

(205) Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989 Jan;79(1):8-15.

(206) Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002 Jan 16;287(3):356-9.

(207) Goldbourt U, Yaari S, Medalie JH. Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality. A 21-year follow-up of 8000 men. Arterioscler Thromb Vasc Biol 1997 Jan;17(1):107-13.

(208) Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007 Nov 22;357(21):2109-22.

(209) Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N Engl J Med 2007 Apr 19;356(16):1620-30.

(210) Avis HJ, Vissers MN, Stein EA, Wijburg FA, Trip MD, Kastelein JJ, et al. A Systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2007 Aug;27(8):1803-10.

(211) Koh KK, Quon MJ, Han SH, Chung WJ, Ahn JY, Seo YH, et al. Additive beneficial effects of fenofibrate combined with atorvastatin in the treatment of combined hyperlipidemia. J Am Coll Cardiol 2005 May 17;45(10):1649-53.

(212) Pauciullo P, Borgnino C, Paoletti R, Mariani M, Mancini M. Efficacy and safety of a combination of fluvastatin and bezafibrate in patients with mixed hyperlipidaemia (FACT study). Atherosclerosis 2000 Jun;150(2):429-36.

(213) Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol 2005 Feb 15;95(4):462-8.

(214) Athyros VG, Papageorgiou AA, Athyrou VV, Demitriadis DS, Pehlivanidis AN, Kontopoulos AG. Atorvastatin versus four statin-fibrate combinations in patients with familial combined hyperlipidaemia. J Cardiovasc Risk 2002 Feb;9(1):33-9.

(215) Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La GL, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004 Dec 1;292(21):2585-90.

(216) Chang JT, Staffa JA, Parks M, Green L. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. Pharmacoepidemiol Drug Saf 2004 Jul;13(7):417-26.

(217) Shek A, Ferrill MJ. Statin-fibrate combination therapy. Ann Pharmacother 2001 Jul;35(7-8):908-17.

(218) Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol 2005 Jan 1;95(1):120-2.

(219) Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003 May 20;107(19):2409-15.

(220) Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. Am Heart J 2005 Mar;149(3):464-73.

(221) Ballantyne CM, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol 2007 Mar 1;99(5):673-80.

(222) Barrios V, Amabile N, Paganelli F, Chen JW, Allen C, Johnson-Levonas AO, et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. Int J Clin Pract 2005 Dec;59(12):1377-86.

(223) Catapano A, Brady WE, King TR, Palmisano J. Lipid altering-efficacy of ezetimibe co-administered with simvastatin compared with rosuvastatin: a metaanalysis of pooled data from 14 clinical trials. Curr Med Res Opin 2005 Jul;21(7):1123-30.

(224) Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002 Dec 18;40(12):2125-34.

(225) Davidson MH, Ballantyne CM, Kerzner B, Melani L, Sager PT, Lipka L, et al. Efficacy and safety of ezetimibe coadministered with statins: randomised, placebocontrolled, blinded experience in 2382 patients with primary hypercholesterolemia. Int J Clin Pract 2004 Aug;58(8):746-55.

(226) Denke M, Pearson T, McBride P, Gazzara RA, Brady WE, Tershakovec AM. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. Diab Vasc Dis Res 2006 Sep;3(2):93-102.

(227) Farnier M, Volpe M, Massaad R, Davies MJ, Allen C. Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. Int J Cardiol 2005 Jul 10;102(2):327-32.

(228) Feldman T, Koren M, Insull W, Jr., McKenney J, Schrott H, Lewin A, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol 2004 Jun 15;93(12):1481-6.

(229) Goldberg RB, Guyton JR, Mazzone T, Weinstock RS, Polis A, Edwards P, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc 2006 Dec;81(12):1579-88.

(230) McKenney JM, Farnier M, Lo KW, Bays HE, Perevozkaya I, Carlson G, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardiol 2006 Apr 18;47(8):1584-7.

(231) Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J 2003 Apr;24(8):717-28.

(232) Patel JV, Hughes EA. Efficacy, safety and LDL-C goal attainment of ezetimibe 10 mg-simvastatin 20 mg vs. placebo-simvastatin 20 mg in UK-based adults with coronary heart disease and hypercholesterolaemia. Int J Clin Pract 2006 Aug;60(8):914-21.

(233) Masana L, Mata P, Gagne C, Sirah W, Cho M, Johnson-Levonas AO, et al. LONGTERM safety and, tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. Clin Ther 2005 Feb;27(2):174-84.

(234) Saseen J, Tweed E, Crawford P. Clinical inquiries. What are effective medication combinations for dyslipidemia? J Fam Pract 2006 Jan;55(1):70-2.

(235) Bard JM, Ose L, Hagen E, Duriez P, Pfister P, Fruchart JC, et al. Changes in plasma apolipoprotein B-containing lipoparticle levels following therapy with fluvastatin and cholestyramine. European Fluvastatin Study Group. Am J Cardiol 1995 Jul 13;76(2):65A-70A.

(236) Schectman G, Hiatt J. Dose-response characteristics of cholesterol-lowering drug therapies: implications for treatment. Ann Intern Med 1996 Dec 15;125(12):990- 1000.

(237) Eriksson M, Hadell K, Holme I, Walldius G, Kjellstrom T. Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care. J Intern Med 1998 May;243(5):373-80.

(238) Jacotot B, Banga JD, Waite R, Peters TK. Long-term efficacy with fluvastatin as monotherapy and combined with cholestyramine (a 156-week multicenter study). French-Dutch Fluvastatin Study Group. Am J Cardiol 1995 Jul 13;76(2):41A-6A.

(239) McCrindle BW, Helden E, Cullen-Dean G, Conner WT. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. Pediatr Res 2002 Jun;51(6):715-21.

(240) Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. Clin Ther 2006 Jan;28(1):26-35.

(241) Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA 2006 Jan 4;295(1):74-80.

(242) Bjerre LM, LeLorier J. Do statins cause cancer? A meta-analysis of large randomized clinical trials. Am J Med 2001 Jun 15;110(9):716-23.

(243) Guallar E, Goodman SN. Statins and cancer: a case of meta-uncertainty. Am J Med 2001 Jun 15;110(9):738-40.

(244) Bonovas S, Sitaras NM. Does pravastatin promote cancer in elderly patients? A meta-analysis. CMAJ 2007 Feb 27;176(5):649-54.

(245) Roberts CG, Guallar E, Rodriguez A. Efficacy and safety of statin monotherapy in older adults: a meta-analysis. J Gerontol A Biol Sci Med Sci 2007 Aug;62(8):879-87.

(246) Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003 Apr 2;289(13):1681-90.

(247) Gaist D, Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. Epidemiology 2001 Sep;12(5):565-9.

(248) de DS, Spinler SA, Miller K, Peterson AM. Statins and liver toxicity: a meta-analysis. Pharmacotherapy 2004 May;24(5):584-91.

(249) Silva M, Matthews ML, Jarvis C, Nolan NM, Belliveau P, Malloy M, et al. Metaanalysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther 2007 Feb;29(2):253-60.

(250) Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. Am J Cardiol 2007 Mar 19;99(6A):3C-18C.

(251) Broeders N, Knoop C, Antoine M, Tielemans C, Abramowicz D. Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? Nephrol Dial Transplant 2000 Dec;15(12):1993-9.

(252) Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. Kidney Int 2004 Sep;66(3):1123-30.

(253) Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs—do rates reported in clinical trials reflect rates in primary care settings? N Engl J Med 1995 Apr 27;332(17):1125-31.

(254) Turner SW, Jungbluth GL, Knuth DW. Effect of concomitant colestipol hydrochloride administration on the bioavailability of diltiazem from immediate- and sustainedrelease formulations. Biopharm Drug Dispos 2002 Dec;23(9):369-77.

(255) al-Balla SR, el-Sayed YM, al-Meshal MA, Gouda MW. The effects of cholestyramine and colestipol on the absorption of diclofenac in man. Int J Clin Pharmacol Ther 1994 Aug;32(8):441-5.

(256) Neuvonen PJ, Kivisto K, Hirvisalo EL. Effects of resins and activated charcoal on the absorption of digoxin, carbamazepine and frusemide. Br J Clin Pharmacol 1988 Feb;25(2):229-33.

(257) Hunninghake DB, Hibbard DM. Influence of time intervals for cholestyramine dosing on the absorption of hydrochlorothiazide. Clin Pharmacol Ther 1986 Mar;39(3):329- 34.

(258) Johansson C, Adamsson U, Stierner U, Lindsten T. Interaction by cholestyramine on the uptake of hydrocortisone in the gastrointestinal tract. Acta Med Scand 1978;204(6):509-12.

(259) Jacobson TA, Armani A, McKenney JM, Guyton JR. Safety considerations with gastrointestinally active lipid-lowering drugs. Am J Cardiol 2007 Mar 19;99(6A):47C-55C.

(260) Goldberg AC. A meta-analysis of randomized controlled studies on the effects of extended-release niacin in women. Am J Cardiol 2004 Jul 1;94(1):121-4.

(261) Knopp RH, Dujovne CA, Le BA, Lipka LJ, Suresh R, Veltri EP. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia: a pooled analysis from two controlled phase III clinical studies. Int J Clin Pract 2003 Jun;57(5):363-8.

(262) Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J 2003 Apr;24(8):729-41.

(263) Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. Clin Ther 2001 Aug;23(8):1209-30.

(264) Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002 Nov 15;90(10):1092-7.

(265) Smellie WS. Testing pitfalls and summary of guidance in lipid management. BMJ 2006 Jul 8;333(7558):83-6.

(266) Kasiske B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R, Jr., et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant 2004;4 Suppl 7:13-53.

(267) Webber LS, Srinivasan SR, Wattigney WA, Berenson GS. Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study. Am J Epidemiol 1991 May 1;133(9):884-99.

(268) American Academy of Pediatrics. Committee on Nutrition. Cholesterol in childhood. Pediatrics 1998 Jan;101(1 Pt 1):141-7.

(269) National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992 Mar;89(3):495-501.

(270) O'Loughlin J, Lauzon B, Paradis G, Hanley J, Levy E, Delvin E, et al. Usefulness of the American Academy of Pediatrics recommendations for identifying youths with hypercholesterolemia. Pediatrics 2004 Jun;113(6):1723-7.

(271) Haney EM, Huffman LH, Bougatsos C, Freeman M, Steiner RD, Nelson HD. Screening and treatment for lipid disorders in children and adolescents: Systematic evidence review for the US Preventive Services Task Force. Pediatrics 2007 Jul;120(1):e189-e214.

(272) Brotons C, Gabriel Sanchez J. Patrón de la distribución de colesterol total y c-HDL en niños y adolescentes españoles:estudio RICARDIN. Med Clin (Barc) 2000 Nov 18;115(17):644-9.

(273) Friedman LA, Morrison JA, Daniels SR, McCarthy WF, Sprecher DL. Sensitivity and specificity of pediatric lipid determinations for adult lipid status: findings from the Princeton Lipid Research Clinics Prevalence Program Follow-up Study. Pediatrics 2006 Jul;118(1):165-72.

(274) Hickman TB, Briefel RR, Carroll MD, Rifkind BM, Cleeman JI, Maurer KR, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4-19 years: data from the Third National Health and Nutrition Examination Survey. Prev Med 1998 Nov;27(6):879-90.

(275) Labarthe DR, Nichaman MZ, Harrist RB, Grunbaum JA, Dai S. Development of cardiovascular risk factors from ages 8 to 18 in Project HeartBeat! Study design and patterns of change in plasma total cholesterol concentration. Circulation 1997 Jun 17;95(12):2636-42.

(276) Medrano MJ, Cerrato E, Boix R, gado-Rodriguez M. Cardiovascular risk factors in Spanish population: metaanalysis of cross-sectional studies. Med Clin (Barc) 2005 Apr 30;124(16):606-12.

(277) Poustie VJ, Rutherford P. Dietary treatment for familial hypercholesterolaemia. Cochrane Database Syst Rev 2001;(2):CD001918.

(278) Lauer RM, Obarzanek E, Hunsberger SA, Van HL, Hartmuller VW, Barton BA, et al. Efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol in children with elevated LDL cholesterol: the Dietary Intervention Study in Children. Am J Clin Nutr 2000 Nov;72(5 Suppl):1332S-42S.

(279) Tonstad S, Knudtzon J, Sivertsen M, Refsum H, Ose L. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. J Pediatr 1996 Jul;129(1):42-9.

(280) Ferguson MA, Gutin B, Le NA, Karp W, Litaker M, Humphries M, et al. Effects of exercise training and its cessation on components of the insulin resístanse syndrome in obese children. Int J Obes Relat Metab Disord 1999 Aug;23(8):889-95.

(281) Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003 Jun 14;361(9374):2005-16.