Papel de Ezetimiba en Cardiología

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ESC/EAS GUIDELINES

ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation†

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Keywords Dyslipidaemia • Cholesterol • Triglycerides • Treatment • Cardiovascular diseases • Guidelines

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Abbreviations and acronyms

4D	Die Deutsche Diabetes Dialyse Studie
4S	Scandinavian Simvastatin Survival Study
ABC-1	ATP-binding cassette transporter 1
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACS	acute coronary syndrome
AIM-HIGH	Atherothrombosis Intervention in Metabolic syndrome with Low HDL-C/High Triglyceride and Impact on Global Health Outcomes
ALT	alanine aminotransferase
apo (a)	apolipoprotein (a)
apo A1	apolipoprotein A1
apo B	apolipoprotein B
apo E	apolipoprotein E
apo C	apolipoprotein C
ARBITER-6	Arterial Biology for the Investigation of the
HALTS	Treatment Effects of Reducing Cholesterol 6 HDL and LDL Treatment Strategies in Atherosclerosis
ARMYDA	Atorvastatin for Reduction of Myocardial Damage During Angioplasty
ASSIGN	CV risk estimation model from the Scottish Intercollegiate Guidelines Network
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events
BIP	Bezafibrate Infarction Prevention
BMI	body mass index
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARE	Cholesterol and Recurrent Events
CETP	cholesterylester transfer protein
CI	confidence interval
CIMT	carotid intima–media thickness
CK	creatine phospholkinase
CKD	chronic kidney disease
CORONA	COntrolled ROsuvastatin multiNAtional study in heart failure
CPG	ESC Committee for Practice Guidelines
CTT	Cholesterol Treatment Trialists' Collaboration
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450 isoenzyme
Dal-OUTCOMES	Dalcetrapib Outcomes trial
DALYs	disability-adjusted life years
DHA	docosahexaenoic acid
DGAT-2	diacylglycerol acyltransferase-2
EAS	European Atherosclerosis Society
EMEA	European Medicines Agency
EPA	eicosapentaenoic acid
ER	extended release form
ESC	European Society of Cardiology
ESRD	end-stage renal disease
FATS	Familial Atherosclerosis Treatment Study
FCH	familial combined hyperlipidaemia
FDA	Food and Drug Administration
FH	familial hypercholesterolaemia
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
GFR	glomerular filtration rate
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Effect of rosuvastatin in patients with chronic Heart Failure
GISSI-P	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione
GP	general practitioner
GPR	G protein-coupled receptor
HAART	highly active antiretroviral treatment
HATS	HDL-Atherosclerosis Treatment Study
Hb_{A1c}	glycated haemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
HeFH	heterozygous familial hypercholesterolaemia
HF	heart failure
HHS	Helsinki Heart Study
HIV	human immunodeficiency virus
HMG-CoA	hydroxymethylglutaryl coenzyme A
HoFH	homozygous familial hypercholesterolaemia
HPS	Heart Protection Study
HPS2-THRIVE	Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events
hs-CRP	high sensitivity C-reactive protein
HTG	hypertriglyceridaemia
ICD	International Classification of Diseases
IDL	intermediate-density lipoprotein
ILLUMINATE	Investigation of Lipid Levels Management to Understand its Impact in Atherosclerotic Events
JUPITER	Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin Study
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LDL-C	low-density lipoprotein-cholesterol
Lp(a)	lipoprotein(a)
LPL	lipoprotein lipase
MetS	metabolic syndrome
MI	myocardial infarction
MTP	microsomal transfer protein
MUFA	monounsaturated fatty acid
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
Non-HDL-C	non-HDL-cholesterol
NYHA	New York Heart Association
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/Kexin 9

PPAR	peroxisome proliferator-activated receptor
PPP	Pravastatin Pooling Project
PROCAM	Prospective Cardiovascular Munster study
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PUFA	polyunsaturated fatty acid
RAAS system	renin–angiotensin–aldosterone system
RCT	randomized controlled trial
REVEAL	Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification
RRR	relative risk reduction
RYR	red yeast rice
SCORE	Systematic Coronary Risk Estimation
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis
SFA	saturated fatty acids
SHARP	Study of Heart And Renal Protection
SLE	systemic lupus erythematosus
TC	total cholesterol
TG	triglyceride
TIA	transient ischaemic attack
TNT	Treating to New Targets Trial
TRL	triglyceride-rich lipoprotein
ULN	upper limit of normal
USF 1	upstream transcription factor 1
VA-HIT	Veterans Affairs High-density lipoprotein Intervention Trial
VLDL	very low density lipoprotein
VLDL-C	very low density lipoprotein-cholesterol
WHO	World Health Organization

Conversion factors

mg/dL cholesterol = mmol/L × 38.6
mg/dL triglycerides = mmol/L × 88.5
mg/dL glucose = mmol/L × 18

1. Preamble

Guidelines summarize and evaluate all available evidence at the time of the writing process on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient, with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes but are complements for textbooks and cover the ESC Core Curriculum topics. Guidelines and recommendations should help physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

A large number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

therapies. The evidence showing that reducing TC and LDL-C can prevent CVD is strong and compelling, based on results from multiple randomized controlled trials (RCTs). TC and LDL-C levels continue therefore to constitute the primary targets of therapy.

Besides an elevation of TC and LDL-C levels, several other types of dyslipidaemias appear to predispose to premature CVD. A particular pattern, termed the atherogenic lipid triad, is more common than others, and consists of the co-existence of increased very low density lipoprotein (VLDL) remnants manifested as mildly elevated triglycerides (TG), increased small dense low-density lipoprotein (LDL) particles, and reduced high-density lipoprotein-cholesterol (HDL-C) levels. However, clinical trial evidence is limited on the effectiveness and safety of intervening in this pattern to reduce CVD risk; therefore, this pattern or its components must be regarded as optional targets of CVD prevention.

Dyslipidaemias may also have a different meaning in certain subgroups of patients which may relate to genetic predisposition and/or co-morbidities. This requires particular attention complementary to the management of the total CV risk.

3. Total cardiovasular risk

3.1 Total cardiovascular risk estimation

CV risk in the context of these guidelines means the likelihood of a person developing an atherosclerotic CV event over a defined period of time.

Rationale for total cardiovascular disease risk

All current guidelines on the prevention of CVD in clinical practice recommend the assessment of total CAD or CV risk because, in most people, atherosclerotic CVD is the product of a number of risk factors. Many risk assessment systems are available, and have been comprehensively reviewed, including Framingham, SCORE (Systemic Coronary Risk Estimation), ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network), QRisk, PROCAM (Prospective Cardiovascular Munster Study), and the WHO (World Health Organization).[4,7]

Most guidelines use risk estimation systems based on either the Framingham or the SCORE projects.[8,9]

In practice, most risk estimation systems perform rather similarly when applied to populations recognizably similar to that from which the risk estimation system was derived,[4,7] and can be re-calibrated for use in different populations.[4] The current joint European Guidelines on CVD prevention in clinical practice[5] recommend the use of the SCORE system because it is based on large, representative European cohort data sets.

Risk charts such as SCORE are intended to facilitate risk estimation in apparently healthy persons with no signs of clinical or pre-clinical disease. Patients who have had a clinical event such as an acute coronary syndrome (ACS) or stroke are at high risk of a further event and automatically qualify for intensive risk factor evaluation and management.

Thus, although refined later in this chapter, very simple principles of risk assessment can be defined as follows[5]:

(1) **Those with**
- **known CVD**
- **type 2 diabetes or type 1 diabetes with microalbuminuria**
- **very high levels of individual risk factors**
- **chronic kidney disease (CKD)**

are automatically at VERY HIGH or HIGH TOTAL CARDIOVASCULAR RISK and need active management of all risk factors.

(2) **For all other people, the use of a risk estimation system such as SCORE is recommended to estimate total CV risk because many people have several risk factors which, in combination, may result in unexpectedly high levels of total CV risk.**

SCORE differs from earlier risk estimation systems in several important ways, and has been modified somewhat for the present guidelines.

The SCORE system estimates the 10 year risk of a first fatal

(1) Those with
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(2) For all other people, the use of a risk estimation system such as SCORE is recommended to estimate total CV risk because many people have several risk factors which, in combination, may result in unexpectedly high levels of total CV risk.

the vast majority, especially of men, will have estimated CV death

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El riesgo puede ser más alto de lo indicado en las gráficas en los siguientes casos:

- Individuos socialmente desvalidos; la precariedad social conlleva muchos otros factores de riesgo.
- Sujetos sedentarios y sujetos con obesidad central; estas características determinan muchos de los aspectos relativos al riesgo que se detallan más adelante.
- Individuos con diabetes mellitus: los nuevos análisis de los datos del SCORE indican que los individuos con diabetes conocida tienen un riesgo mucho mayor (5 veces más alto en mujeres y 3 veces más alto en varones).
- Individuos con títulos bajos de cHDL o apolipoproteína A1 (apoA1), aumento de los títulos de TG, fibrinógenos, homocisteína, apolipoproteína B (apoB) y lipoproteína (a) [Lp(a)], hipercolesterolemia familiar (HF) o aumento de la hs-CRP. Estos factores indican un mayor nivel de riesgo en ambos sexos, todos los grupos de edad y todos los niveles de riesgo. Como ya se ha mencionado, las gráficas complementarias que se incluyen en el anexo 1 ilustran el impacto adicional del cHDL en la estimación del riesgo.
- Individuos asintomáticos con evidencia preclínica de aterosclerosis; por ejemplo, la presencia de placas o un aumento del grosor de la íntima-media (GIM) carotídeo detectado por ultrasonografía carotídea.
- Individuos con función renal afectada.
- Individuos con historia familiar de ECV prematura; se considera que este factor aumenta 1,7 veces el riesgo en mujeres y 2 veces en varones.
- Por el contrario, el riesgo podría ser más bajo de lo que aparece indicado en personas con títulos elevados de cHDL o con historia familiar de longevidad.

Table 3 Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

*In patients with MI, statin therapy should be considered irrespective of LDL-C levels.[13,14]

[a]Class of recommendation

[b]Level of evidence. References to level A: 15–41.

CV = cardiovascular; LDL-C = low-density lipoprotein-cholesterol; MI = myocardial infarction.

Recommendations	Class[a]	Level[b]	Ref[c]
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.	I	A	15, 32, 33
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.	IIa	A	15, 16, 17
In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	IIa	C	-

Table Percentage reduction of LDL-C requested to achieve goals as a function of the starting value

STARTING LDL-C		% REDUCTION TO REACH LDL-C		
mmol/L	~mg/dL	<1.8 mmol/L (~70 mg/dL)	<2.5 mmol/ (~100 mg/dL)	<3 mmol/L (~115 mg/dL)
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	–
1.8–2.3	70–90	<22	–	–

Table Percentage reduction of LDL-C requested to achieve goals as a function of the starting value

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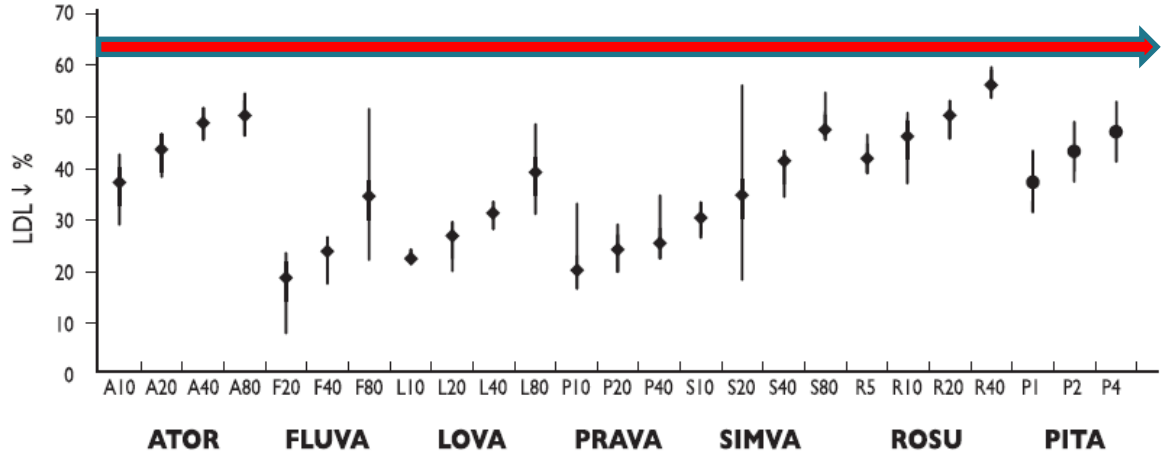
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	–
1.8–2.3	70–90	<22	–	–



Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151
Mukhtar RY, *et Al. Int J Clin Pract* . 2005;59(2):239-252

Figure A systematic review and meta-analysis on the therapeutic equivalence of statins.

Recommendations	Class[a]	Level[b]	Ref[c]
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In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	IIa	C	-

Table 4 Recommendations for lipid profiling in order to assess total CV risk

Condition	Class[a]	Level[b]
Lipid profiling is indicated in subjects with: Type 2 diabetes mellitus	I	C
Established CVD	I	C
Hypertension	I	C
Smoking	I	C
BMI >30 kg/m^2 or waist circumference >94 cm (90 cm[c]) for men, >80 cm for women	I	C
Family history of premature CVD	I	C
Chronic inflammatory disease	I	C
Chronic kidney disease	I	C
Family history of familial dyslipidaemia	I	C
Lipid profiling may be considered in men >40 and women >50 years of age	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
[c]For Asian males.
BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease.

needed for the calculation of LDL-C with the Friedewald formula. TC, apo B, apo A1, and HDL-C can be determined in non-fasting samples.[42] Fasting state is also essential if blood glucose is measured in screening programmes.

Intraindividual variation

There is considerable intraindividual variation in plasma lipids. For TC, a variation of 5–10% and for TG >20% has been reported, particularly in those with hypertriglyceridaemia (HTG). This variation is to some extent due to analytical variation, but is also due to environmental factors such as diet and physical activity and a seasonal variation, with higher levels of TC and HDL-C during the winter.

Lipid and lipoprotein analysis

Throughout this section it should be noted that most risk estimation systems and virtually all drug trials are based on TC and LDL-C, and that clinical benefit from using other measures including apo B, non-HDL-C, and various ratios, while sometimes logical, has not been proven. While their role is being established, traditional measures of risk such as TC and LDL-C remain robust and supported by a major evidence base. Furthermore, multiple clinical trials have established beyond all reasonable doubt that, at least in high risk subjects, reduction of TC or LDL-C is associated with a statistically and clinically significant reduction in cardiovascular mortality. Therefore, TC and LDL-C remain the primary targets recommended in these guidelines.

Total cholesterol

In screening programmes, TC is recommended to be used to estimate total CV risk by means of the SCORE system. In the individual case, however, TC may be misleading. This is especially so in women who often have high HDL-C levels and in subjects with diabetes or the metabolic syndrome (MetS) who often have low HDL-C levels. For an adequate risk analysis, at least HDL-C and LDL-C should be analysed. Note that assessment of total risk does not include patients with familial hyperlipidaemia (including FH and FCH) or those with TC >8.0 mmol/L (~310 mg/dL). These patients are always at high risk and should receive special attention.

Low-density lipoprotein-cholesterol

In most clinical studies LDL-C has been calculated using Friedewald's formula (unless TG are elevated >4.5 mmol/L or more than ~400 mg/dL).

The calculated value of LDL-C is based on a number of assumptions:

- Methodological errors may accumulate since the formula necessitates three separate analyses of TC, TG, and HDL-C.
- A constant cholesterol/TG ratio in VLDL is assumed. With high TG values (>4.5 mmol/L or more than ~400 mg/dL), the formula cannot be used.
- The use of Friedewald's formula is not indicated when blood is obtained under non-fasting conditions (class III C). Under these conditions, non-HDL-C may be determined.

Despite its limitations, the calculated LDL-C is still widely used. However, direct methods for determining LDL-C should be used whenever available.

A number of commercially available methods for direct determination of LDL-C have appeared. The modern generation of these methods have good reproducibility and specificity, and have the advantage that the analysis is made in one step and they are not sensitive to variations in TG levels to the same extent. Comparisons between calculated LDL-C and direct LDL-C show good agreement; considering the limitations of calculated LDL-C, direct LDL-C is recommended, although most trials have been performed with calculated LDL-C.

A large amount of data is the basis for the current recommendations, and internationally there is a good agreement between different target levels. Non-HDL-C or apo B may give a better estimate of the concentration of atherogenic particles, especially in high risk patients with diabetes or MetS.

Non-high-density lipoprotein-cholesterol

Non-HDL-C is used as an estimation of the total number of atherogenic particles in plasma [VLDL + intermediate-density lipoprotein (IDL) + LDL] and relates well to apo B levels. Non-HDL-C is easily calculated from TC minus HDL-C.

Non-HDL-C can provide a better risk estimation compared with LDL-C, in particular in HTG combined with diabetes, the MetS, or CKD. This is supported by a recent meta-analysis including 14 statin trials, seven fibrate trials, and six nicotinic acid trials.[44]

High-density lipoprotein-cholesterol

Most available assays are of high quality, but the method used should be evaluated against the available reference methods and controlled in international quality programmes.

Triglycerides

TG are determined by accurate and cheap enzymatic techniques. A very rare error is seen in patients with hyperglycerolaemia where falsely very high values for TG are obtained.

High TG are often associated with low HDL-C and high levels of small dense LDL particles.

Recently studies have been published suggesting that non-fasting TG may carry information regarding remnant lipoproteins associated with increased risk.[12,45] How this should be used in clinical practice is still debated.

Apolipoproteins

From a technical point of view there are advantages in the determination of apo B and apo A1. Good immunochemical methods are available and easily run in conventional autoanalysers. The analytical performance is good. The assay does not require fasting conditions and is not sensitive to moderately high TG levels.

Apolipoprotein B. Apo B is the major apolipoprotein of the atherogenic lipoprotein families VLDL, IDL, and LDL. The concentration of apo B is a good estimate of the number of these particles in plasma. This might be of special importance in the case of high concentrations of small dense LDL. Apo B has been shown in several prospective studies to be equal to LDL-C in risk prediction. Apo B has not been evaluated as a primary treatment target in statin trials, but several post-hoc analyses of statin trials suggest that apo B may be not only a risk marker but also a better treatment target than LDL-C.[46] The major disadvantages of apo B are that it is not included in algorithms for calculation of global risk, and it has not been a pre-defined treatment target in controlled trials. Recent data from a meta-analysis by the Emerging Risk Factor Collaboration[42] indicate that apo B does not provide any benefit beyond non-HDL-C or traditional lipid ratios. Likewise, apo B provided no benefit beyond traditional lipid markers in people with diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.[47] In contrast, in another meta-analysis of LDL-C, non-HDL-C, and apo B, the latter was superior as a marker of CV risk.[48]

Apolipoprotein A1. Apo A1 is the major protein of HDL and provides a good estimate of HDL concentration. Each HDL particle may carry several apo A1 molecules. Plasma apo A1 of < 120 mg/dL for men and < 140 mg/dL for women approximately correspond to what is considered as low for HDL-C.

Apolipoprotein B/apolipoprotein A1 ratio, total cholesterol/high-density lipoprotein-cholesterol ratio, and non-high-density lipoprotein-cholesterol/high-density lipoprotein-cholesterol ratio

The different ratios give similar information. The ratio between apo B and apo A1 has been used in large prospective studies as an indicator of risk. Ratios between atherogenic lipoproteins and HDL-C (TC/HDL-C, non-HDL-C/HDL-C, apo B/apo A1) are useful for risk estimation, but for diagnosis and as treatment targets the components of the ratio have to be considered separately.

Lipoprotein(a)

Lp(a) has been found in several studies to be an additional risk marker.[49] Lp(a) has properties in common with LDL but contains a unique protein, apolipoprotein (a) [apo(a)], which is structurally different from other apolipoproteins. The plasma level of Lp(a) is to a major extent genetically determined. Several methods for determination of Lp(a) are available, but standardization between assays is needed as well as use of size-insensitive assays. Lp(a) is generally expressed as total Lp(a) mass; however, it is recommended to express it as mmol/L (or mg/dL) of Lp(a) protein.[50] Plasma Lp(a) is not recommended for risk screening in the general population; however, Lp(a) measurement should be considered in people with high CVD risk or a strong family history of premature atherothrombotic disease.[51]

Table 5 lists the recommendations for lipid analyses for screening for CVD risk and *Table 6* the recommendations for lipid analyses for characterization of dyslipidaemias; *Table 7* gives the

Table 5 Recommendations for lipid analyses for screening for CVD risk

Recommendations	Class[a]	Level[b]
TC is recommended to be used for the estimation of total CV risk by means of the SCORE system.	I	C
LDL-C is recommended to be used as the primary lipid analysis for screening and risk estimation.	I	C
TG adds information on risk and is indicated for risk estimation.	I	C
HDL-C is a strong risk factor and is recommended to be used for risk estimation.	I	C
Non-HDL-C should be considered as an alternative risk marker, especially in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	C
Lp(a) should be recommended in selected cases at high risk and in subjects with a family history of premature CVD.	IIa	C
Apo B should be considered as an alternative risk marker, especially in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	C
The ratio apo B/apo A1 combines the risk information of apo B and apo A1 and may be recommended as an alternative analysis for risk screening.	IIb	C
The ratio non-HDL-C/HDL-C may be recommended as an alternative analysis for risk screening.	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; MetS = metabolic syndrome; TC = total cholesterol; TG = triglyceride.

Table 6 Recommendations for lipid analyses for characterization of dyslipidaemias before treatment

Recommendations	Class[a]	Level[b]
LDL-C is recommended to be used as the primary lipid analysis.	I	C
TG adds information to risk and is indicated for diagnosis and choice of treatment.	I	C
HDL-C is recommended to be analysed before initiation of treatment.	I	C
Non-HDL-C should be recommended for further characterization of combined hyperlipidaemias and dyslipidaemia in diabetes, the MetS or CKD.	IIa	C
Apo B should be recommended for further characterization of combined hyperlipidaemias and dyslipidaemia in diabetes, the MetS or CKD.	IIa	C
Lp(a) should be recommended in selected cases at high risk and in subjects with a family history of premature CVD.	IIa	C
TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment.	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; MetS = metabolic syndrome; TC = total cholesterol; TG = triglyceride.

Table 7 Recommendations for lipid analyses as treatment target in the prevention of CVD

Recommendations	Class[a]	Level[b]	Ref[c]
LDL-C is recommended as target for treatment.	I	A	15, 16, 17
TC should be considered as treatment target if other analyses are not available.	IIa	A	5, 15
TG should be analysed during the treatment of dyslipidaemias with high TG levels.	IIa	B	52
Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	B	48
Apo B should be considered as a secondary treatment target.	IIa	B	48, 53
HDL-C is not recommended as a target for treatment.	III	C	-
The ratios apo B/apo A1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; MetS = metabolic syndrome; TC = total cholesterol; TG = triglyceride.

recommendations for lipid analyses as treatment target in the prevention of CVD.

Lipoprotein particle size

Lipoproteins are heterogeneous classes of particles, and a lot of evidence suggests that the different subclasses of LDL and HDL may bear different risks for atherosclerosis.[54]

Determination of small dense LDL may be regarded as an emerging risk factor that may be used in the future[54] but is not currently recommended for risk estimation.[55]

Genotyping

Several genes have been associated with CVD. At present the use of genotyping for risk estimation is not recommended. However, studies suggest that in the future a panel of genotypes may be used for identification of high risk subjects.[56]

For the diagnosis of specific genetic hyperlipidaemias, genotyping of apolipoprotein E (apo E) and of genes associated with FH may be considered.

Apo E is present in three isoforms (apo E2, apo E3, and apo E4). Apo E genotyping is primarily used for the diagnosis of dysbetalipoproteinaemia (apo E2 homozygosity) and is indicated in cases with severe combined hyperlipidaemia.

Tools for genetic screening in families with FH are now available and should be used in specialized clinics.[57]

5. Treatment targets

Treatment targets of dyslipidaemia are primarily based on results from clinical trials. In nearly all lipid-lowering trials the LDL-C level has been used as an indicator of response to therapy. Therefore, LDL-C remains the primary target of therapy in most strategies of dyslipidaemia management.

The most recent Cholesterol Treatment Trialists' Collaboration (CTT) meta-analysis of several trials involving >170 000 patients confirmed the dose-dependent reduction in CVD with LDL-C lowering.[15]

The overall guidelines on CVD prevention in clinical practice strongly recommend modulating the intensity of the preventive intervention according to the level of the total CV risk. Therefore, the targets should be less demanding when the total CV risk decreases from very high to high or moderate.

Table 11 Dietary recommendations to lower TC and LDL-C

	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cereals	Whole grains	Refined bread, rice and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables		Vegetables prepared in butter or cream
Legumes	All (including soy and soy protein)		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, fructose, glucose, chocolate, candies	Cakes, ice creams
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skimmed milk and yogurt, egg white	Low fat milk, low fat cheese and other milk products	Regular cheese, cream, egg yolk, whole milk and yoghurt
Cooking fat and dressings	Vinegar, ketchup, mustard, fat-free dressings	Vegetable oils, soft margarines, salad dressing, mayonnaise	Butter, solid margarines, trans fats, palm and coconut oils; lard, bacon fat, dressings made with egg yolks
Nuts			
Cooki			

LDL-C = L

7. Drugs for treatment of hypercholesterolaemia

At least ommende CVD, to sources of prevention rated fat sively fro or pharm intake sho amount of salt used for food seasoning but also by reducing the consumption of foods preserved by the addition of salt; this recommendation should be more stringent in people with hypertension or MetS.[5] Dietary recommendations to lower TC and LDL-C are summarized in *Table 11*. *Table 12* summarizes lifestyle measures and healthy food choices for managing total CV risk.

All individuals should be advised on lifestyles associated with a lower CVD risk. High risk subjects, in particular those with dyslipidaemia, should receive specialist dietary advice, if feasible.

7. Drugs for treatment of hypercholesterolaemia

Cholesterol levels are determined by multiple genetic factors as well as environmental factors, primarily dietary habits. Hypercholesterolaemia can also be secondary to other medical conditions.

Secondary dyslipidaemia can have different causes; the possibility of secondary hypercholesterolaemia (*Table 13*) should be

- Consumption of fruit, vegetables, legumes, nuts, wholegrain cereals and bread, fish (especially oily) should be encouraged.
- Saturated fat should be replaced with the above foods and with monounsaturated and polyunsaturated fats from vegetable sources, in order to reduce energy intake from total fat to <35% of energy, saturated fat to <7% of total energy, trans fats to <1% of total energy, and dietary cholesterol to <300 mg/day.
- Salt intake should be reduced below 5 g/day by avoiding table salt and limiting salt in cooking, and by choosing fresh or frozen unsalted foods; many processed and convenience foods, including bread, are high in salt.
- For those who drink alcoholic beverages, moderation should be advised (<10–20 g/day for women and <20–30 g/day for men) and patients with hypertriglyceridaemia (HTG) should abstain.
- The intake of beverages and foods with added sugars, particularly soft drinks, should be limited, particularly for patients with HTG.
- Physical activity should be encouraged, aiming at regular physical exercise for at least 30 minutes/day every day.
- Use and exposure to tobacco products should be avoided.

Table 13 Examples of causes of secondary hypercholesterolaemia

• Hypothyroidism
• Nephrotic syndrome
• Pregnancy
• Cushing syndrome
• Anorexia nervosa
• Immunosuppressant agents
• Corticosteroids

meta-analysis[14,17,41] addressed the issue of primary prevention, with results regarding efficacy and safety that are, in general, consistent with the conclusions from the CTT.[15] Regarding cost-effectiveness and quality of life, caution is still needed in prescribing statins for primary prevention among people at low total CV risk.[41]

At maximal recommended doses the different statins differ in their LDL-C-lowering capacity.

Current available evidence suggests that the clinical benefit is largely independent of the type of statin but depends on the extent of LDL-C lowering; therefore, the type of statin used should reflect the degree of LDL-C reduction that is required to reach the target LDL-C in a given patient.[15,100] More details on this are provided in Addendum II to these guidelines.

The following scheme is proposed:

- Evaluate the total CV risk of the subject
- Involve the patient with decisions on CV risk management
- Since the response to statin treatment is variable, up-titration to reach target is mandatory
- If the statin cannot reach the goal, consider drug combinations.

Of course these will be only general criteria for the choice of drug. The clinical conditions of the subjects, concomitant treatments, and drug tolerability will play a major role in determining the final choice of drug and dose.

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- If the statin cannot reach the goal, consider drug combinations.

7.1 Statins

Mechanism of action

Statins reduce synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity. The reduction in intracellular cholesterol concentration induces low-density lipoprotein receptor (LDLR) expression on the hepatocyte cell surface, which results in increased extraction of LDL-C from the blood and a decreased concentration of circulating LDL-C and other apo B-containing lipoproteins including TG-rich particles.

7.1 Statins

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Meta-analyses

In the CTT meta-analyses of individual participant data from >170 000 participants in 26 randomized trials of statins,[15] a 10% proportional reduction in all-cause mortality and 20% proportional reduction in CAD death per 1.0 mmol/L (~40 mg/dL) LDL-C reduction is reported. The risk for major coronary events was reduced by 23% and the risk for stroke was reduced by 17% per mmol/L (40 mg/dL) LDL-C reduction. The proportional reductions in major CV event rates per mmol/L (mg/dL) LDL-C reduction were very similar in all of the subgroups examined. The benefits were significant within the first year, but were greater in subsequent years. There was no increased risk for any specific non-CV cause of death, including cancer, in those receiving statins. The excess risk of rhabdomyolysis with statins was small and not significant. Information on episodes of increased liver enzymes was not examined in this meta-analysis. Other therapy, as well as in the incidence of adverse effects.

Muscle

Statins are generally well tolerated, and serious adverse events are rare. Over 129 000 patients have been systematically studied in controlled trials with blinded randomized assignment to statin vs. placebo treatment groups.[15] Factors such as advanced age, small body size, female gender, renal and hepatic dysfunction, perioperative periods, hypothyroidism, multisystem disease, and alcohol abuse increase the likelihood of side effects with statins.

The most serious adverse effect associated with statin therapy is myopathy, which may progress to rhabdomyolysis, and that, in turn, can lead to renal failure and death. Creatine phosphokinase (CK) elevation has become the primary marker for ongoing muscle cell death and destruction. The myoglobin release from these cells can directly damage the kidneys. An elevation of CK is the best indicator, although not unequivocal, of statin-induced

COMBINACIÓN

Side effects and interactions

Gastrointestinal adverse effects (most commonly flatulence, constipation, dyspepsia and nausea) are often present with these drugs even at low doses, which limit their practical use. These side effects can be attenuated by beginning treatment at low doses and ingesting ample fluid with the drug. The dose should be increased gradually. Reduced absorption of fat-soluble vitamins has been reported. Furthermore, these drugs may increase TG in certain patients.

Bile acid sequestrants have important drug interactions with many commonly prescribed drugs and should therefore be administered either 4 h before or 1 h after other drugs. Colesevelam represents a newer formulation of the bile acid sequestrant, which may be better tolerated than cholestyramine. The drug reduces LDL-C and also improves glycated haemoglobin (HbA_{1c}) in patients with type 2 diabetes.[109,110] Colesevelam has fewer interactions with other drugs and can be taken together with statins. For other drugs, however, the same general rules for administration as for other sequestrants should be applied.

7.3 Cholesterol absorption inhibitors

Mechanism of action

Ezetimibe is the first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption at the level of the brush border of the intestine (most probably by interacting with the NPC1L1 protein), ezetimibe reduces the amount of lipoprotein cholesterol circulated to the liver. In response to reduced cholesterol delivery, the liver reacts by up-regulating LDLR, which in turn leads to increased clearance of LDL from the blood.

Efficacy in clinical studies

In clinical studies ezetimibe in monotherapy reduces LDL-C hypercholesterolaemic patients by 15–22%. Combined therapy with ezetimibe and a statin provides an incremental reduction LDL-C levels of 15–20%. The efficacy of ezetimibe in associati with simvastatin has been addressed in subjects with aortic steno in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study and in patients with CKD in the Study of Heart and Renal Protection (SHARP) (see Sections 7.5.2 and 10.9). In the SHARP study reduction of 17% in CV events was demonstrated in the simvastatin–ezetimibe arm vs. placebo.[111]

Ezetimibe can be used as second-line therapy in association w statins when the therapeutic target is not achieved at maxim tolerated statin dose or in patients intolerant of statins or w contraindications to these drugs.

Side effects and interactions

Ezetimibe is rapidly absorbed and extensively metabolized the pharmacologically active ezetimibe glucuronide. The r ommended dose of ezetimibe of 10 mg/day can be administer in the morning or evening without regard to food intake. There are no clinically significant effects of age, sex, or race on ezetimibe pharmacokinetics, and no dosage adjustment is necessary in patients with mild hepatic impairment or mild to severe renal insufficiency. Ezetimibe can be co-administered with any dose of any statin. No major side effects have been reported; the most frequent side effects are moderate elevations of liver enzymes and muscle pain.

7.4 Nicotinic

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7.5 Drug com

Although the target le apy in many patients, with very high LDL-C also patients who are higher statin doses. be considered.[112]

7.5.1 Statins and bile acid sequestrants

Combination of a statin and cholestyramine, colestipol, or colesevelam could be useful in achieving LDL-C goals. On average the addition of a bile acid sequestrant to a statin reduces LDL-C further by 10–20%. However, there are no published clinical outcome trials with either conventional bile acid sequestrants or colesevelam in combination with other drugs. The combination has been found to reduce atherosclerosis, as evaluated by coron-

triple therapy (bile acid sequestrant, statin, and ezetimibe or nicotinic acid) will further reduce LDL-C. Clinical outcome studies with these combinations have not been performed.

Functional food containing phytosterols as well as plant sterol-containing tablets additionally reduce LDL-C levels by up to

- Ezetimiba reduce el cLDL 15-22%
- Ezetimiba + estatina = reduccion adicional del cLDL del 15-20%.
- Estudio SEAS
- Estudio SHARP: se demostro una reduccion del 17% en la tasa de eventos CV en el grupo de tratamiento con simvastatina + ezetimiba respecto al grupo control

- Ezetimiba puede ser utilizada como tratamiento de segunda línea asociado a estatinas cuando el objetivo terapéutico no se alcance con las dosis máximas toleradas de estatinas o en pacientes con intolerancia o contraindicaciones a estas

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7.4 Nicotinic acid

Nicotinic acid has broad lipid-modulating action, raising HDL-C in a dose-dependent manner by ~25%, and reducing both LDL-C by 15–18% and TG by 20–40% at the 2 g/day dose. Nicotinic acid is unique in lowering Lp(a) levels by up to 30% at this dose. It is therefore primarily used in subjects with low HDL-C levels as

- Independiente de la ingestión de comida
- No efectos clínicamente significativos asociados a edad, sexo o raza
- No es preciso ajustar la dosis en pacientes con afección hepática leve o insuficiencia renal de leve a grave
- Se puede administrar en combinación con cualquier dosis de cualquier estatina
- No se han comunicado efectos secundarios graves

... tomatic aortic stenosis showed that ezetimibe and simvastatin applied concomitantly reduce the incidence of ischaemic CVD events (up to 16% in the patients with less severe aortic stenosis) but not events related to aortic valve stenosis.[28] Recently the data of the SHARP trial were presented with positive results in CKD patients (see Section 10.9).[111]

7.5.3 Other combinations

In high risk patients such as those with FH, or in cases of statin intolerance, other combinations may be considered. Co-administration of ezetimibe and bile acid sequestrants (colesevelam, colestipol, or cholestyramine) resulted in an additional reduction of LDL-C levels without any additional adverse effects when compared with the stable bile acid sequestrant regimen alone. Adding ezetimibe to nicotinic acid further reduces LDL-C and does not affect nicotinic acid-induced HDL-C increase. Also triple therapy (bile acid sequestrant, statin, and ezetimibe or nicotinic acid) will further reduce LDL-C. Clinical outcome studies with these combinations have not been performed.

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with very high LDL-C levels need additional treatment. There are also patients who are statin intolerant or are not able to tolerate higher statin doses. In these cases combination therapy should be considered.[112]

7.5 Drug combinations

7.5.2 Statins and cholesterol absorption inhibitors

- Estudio SEAS: ezetimiba + simvastatina redujo la incidencia de eventos CV isquemicos … pero no los eventos relacionados con la estenosis aortica

7.5.2 Statins and cholesterol absorption inhibitors

Combining ezetimibe with a statin reduces LDL-C by an additional 15–20%.[114] The results of the SEAS study in patients with asymptomatic aortic stenosis showed that ezetimibe and simvastatin applied concomitantly reduce the incidence of ischaemic CVD events (up to 46% in the patients with less severe aortic stenosis) but not events related to aortic valve stenosis.[28] Recently the data of the SHARP trial were presented with positive results in CKD patients (see Section 10.9).[111]

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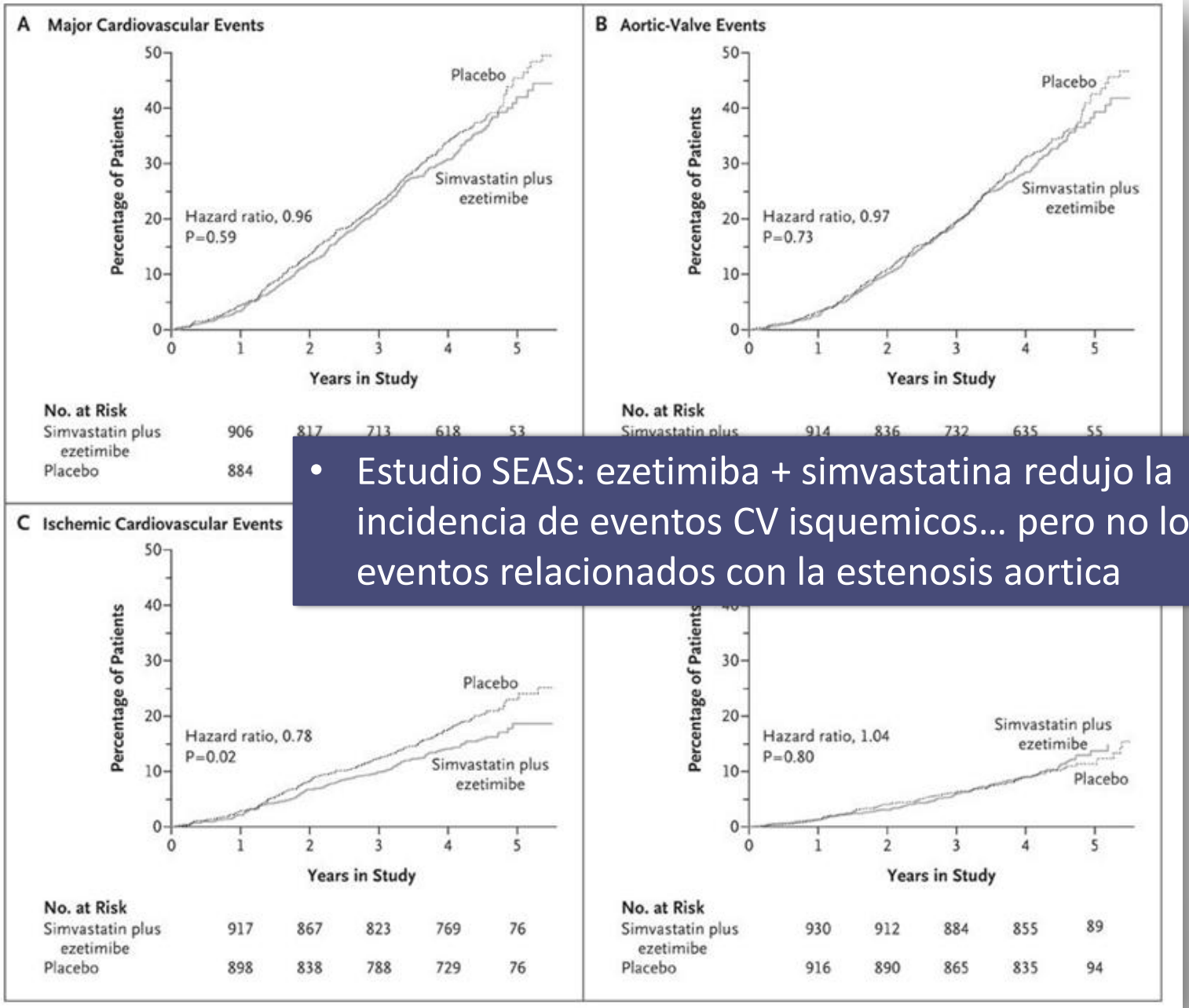

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Ezetimibe is the first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption at the level of the brush border of the intestine (most probably by interacting with the NPC1L1 protein), ezetimibe reduces the amount of lipoprotein cholesterol circulated to the liver. In response to reduced cholesterol delivery, the liver reacts by up-regulating LDLR, which in turn leads to increased clearance of LDL from the blood.

Efficacy in clinical studies

In clinical studies ezetimibe in monotherapy reduces LDL-C hypercholesterolaemic patients by 15–22%. Combined therap with ezetimibe and a statin provides an incremental reduction LDL-C levels of 15–20%. The efficacy of ezetimibe in associati with simvastatin has been addressed in subjects with aortic steno in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study and in patients with CKD in the Study of Heart and Renal Prote tion (SHARP) (see Sections 7.5.2 and 10.9). In the SHARP study reduction of 17% in CV events was demonstrated in the simvast tin–ezetimibe arm vs. placebo.[111]

Ezetimibe can be used as second-line therapy in association wi statins when the therapeutic target is not achieved at maxim tolerated statin dose or in patients intolerant of statins or wi contraindications to these drugs.

Side effects and interactions

Ezetimibe is rapidly absorbed and extensively metabolized the pharmacologically active ezetimibe glucuronide. The rec ommended dose of ezetimibe of 10 mg/day can be administered in the morning or evening without regard to food intake. There are no clinically significant effects of age, sex, or race on ezetimibe pharmacokinetics, and no dosage adjustment is necessary in patients with mild hepatic impairment or mild to severe renal insufficiency. Ezetimibe can be co-administered with any dose of any statin. No major side effects have been reported; the most frequent side effects are moderate elevations of liver enzymes and muscle pain.

7.4 Nicotinic acid

Nicotinic acid has broad lipid-modulating action, raising HDL-C in a dose-dependent manner by ~25%, and reducing both LDL-C by 15–18% and TG by 20–40% at the 2 g/day dose. Nicotinic acid is unique in lowering Lp(a) levels by up to 30% at this dose. It is

7.5.3 Other combinations

7.5 Drug combinations

Although the target levels of LDL-C are reached with monotherapy in many patients, a proportion of high risk subjects or patients with very high LDL-C levels need additional treatment. There are also patients who are statin intolerant or are not able to tolerate higher statin doses. In these cases combination therapy should be considered.[112]

7.5.1 Statins and bile acid sequestrants

Combination of a statin and cholestyramine, colestipol, or colesevelam could be useful in achieving LDL-C goals. On average the addition of a bile acid sequestrant to a statin reduces LDL-C further by 10–20%. However, there are no published clinical outcome trials with either conventional bile acid sequestrants or colesevelam in combination with other drugs. The combination has been found to reduce atherosclerosis, as evaluated by coronary angiography.[113–115]

- Ezetimiba + secuestrador ácidos biliares reduce cLDL sin aumento de los efectos adversos
- Ezetimiba + acido nicotínico reduce el cLDL sin afectar al aumento del cHDL
- Secuestrador ácidos biliares + estatina + ezetimiba o acido nicotínico reduce cLDL

alone. Adding ezetimibe to nicotinic acid further reduces LDL-C and does not affect nicotinic acid-induced HDL-C increase. Also triple therapy (bile acid sequestrant, statin, and ezetimibe or nicotinic acid) will further reduce LDL-C. Clinical outcome studies with these combinations have not been performed.

Functional food containing phytosterols as well as plant sterol-containing tablets additionally reduce LDL-C levels by up to

Abbreviations and acronyms

4D	Die Deutsche Diabetes Dialyse Studie
4S	Scandinavian Simvastatin Survival Study
ABC-1	ATP-binding cassette transporter 1
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACS	acute coronary syndrome
AIM-HIGH	Atherothrombosis Intervention in Metabolic syndrome with Low HDL-C/High Triglyceride and Impact on Global Health Outcomes
ALT	alanine aminotransferase
apo (a)	apolipoprotein (a)
apo A1	apolipoprotein A1
apo B	apolipoprotein B
apo E	apolipoprotein E
apo C	apolipoprotein C
ARBITER-6	Arterial Biology for the Investigation of the
HALTS	Treatment Effects of Reducing Cholesterol 6 HDL and LDL Treatment Strategies in Atherosclerosis
ARMYDA	Atorvastatin for Reduction of Myocardial Damage During Angioplasty
ASSIGN	CV risk estimation model from the Scottish Intercollegiate Guidelines Network
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events
BIP	Bezafibrate Infarction Prevention
BMI	body mass index
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARE	Cholesterol and Recurrent Events
CETP	cholesterylester transfer protein
CI	confidence interval
CIMT	carotid intima–media thickness
CK	creatine phospholkinase
CKD	chronic kidney disease
CORONA	COntrolled ROsuvastatin multiNAtional study in heart failure
CPG	ESC Committee for Practice Guidelines
CTT	Cholesterol Treatment Trialists' Collaboration
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450 isoenzyme
Dal-OUTCOMES	Dalcetrapib Outcomes trial
DALYs	disability-adjusted life years
DHA	docosahexaenoic acid
DGAT-2	diacylglycerol acyltransferase-2
EAS	European Atherosclerosis Society
EMEA	European Medicines Agency
EPA	eicosapentaenoic acid
ER	extended release form
ESC	European Society of Cardiology
ESRD	end-stage renal disease
FATS	Familial Atherosclerosis Treatment Study
FCH	familial combined hyperlipidaemia
FDA	Food and Drug Administration
FH	familial hypercholesterolaemia
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
GFR	glomerular filtration rate
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Effect of rosuvastatin in patients with chronic Heart Failure
GISSI-P	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione
GP	general practitioner
GPR	G protein-coupled receptor
HAART	highly active antiretroviral treatment
HATS	HDL-Atherosclerosis Treatment Study
Hb_{A1c}	glycated haemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
HeFH	heterozygous familial hypercholesterolaemia
HF	heart failure
HHS	Helsinki Heart Study
HIV	human immunodeficiency virus
HMG-CoA	hydroxymethylglutaryl coenzyme A
HoFH	homozygous familial hypercholesterolaemia
HPS	Heart Protection Study
HPS2-THRIVE	Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events
hs-CRP	high sensitivity C-reactive protein
HTG	hypertriglyceridaemia
ICD	International Classification of Diseases
IDL	intermediate-density lipoprotein
ILLUMINATE	Investigation of Lipid Levels Management to Understand its Impact in Atherosclerotic Events
JUPITER	Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin Study
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LDL-C	low-density lipoprotein-cholesterol
Lp(a)	lipoprotein(a)
LPL	lipoprotein lipase
MetS	metabolic syndrome
MI	myocardial infarction
MTP	microsomal transfer protein
MUFA	monounsaturated fatty acid
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
Non-HDL-C	non-HDL-cholesterol
NYHA	New York Heart Association
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/Kexin 9

PPAR	peroxisome proliferator-activated receptor
PPP	Pravastatin Pooling Project
PROCAM	Prospective Cardiovascular Munster study
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PUFA	polyunsaturated fatty acid
RAAS system	renin–angiotensin–aldosterone system
RCT	randomized controlled trial
REVEAL	Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification
RRR	relative risk reduction
RYR	red yeast rice
SCORE	Systematic Coronary Risk Estimation
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis
SFA	saturated fatty acids
SHARP	Study of Heart And Renal Protection
SLE	systemic lupus erythematosus
TC	total cholesterol
TG	triglyceride
TIA	transient ischaemic attack
TNT	Treating to New Targets Trial
TRL	triglyceride-rich lipoprotein
ULN	upper limit of normal
USF 1	upstream transcription factor 1
VA-HIT	Veterans Affairs High-density lipoprotein Intervention Trial
VLDL	very low density lipoprotein
VLDL-C	very low density lipoprotein-cholesterol
WHO	World Health Organization

Conversion factors

mg/dL cholesterol = mmol/L × 38.6
mg/dL triglycerides = mmol/L × 88.5
mg/dL glucose = mmol/L × 18

1. Preamble

Guidelines summarize and evaluate all available evidence at the time of the writing process on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient, with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes but are complements for textbooks and cover the ESC Core Curriculum topics. Guidelines and recommendations should help physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

A large number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 26 Recommendations for treatment of dyslipidaemia in HF or valvular disease

Recommendations	Class[a]	Level[b]	Ref[c]
n-3 PUFAs 1 g/day may be considered to be added to optimal treatment in patients with HF (NYHA classification II–IV).	IIb	B	164
Cholesterol-lowering therapy with statins is not indicated in patients with moderate to severe HF (NYHA classification III–IV).	III	A	34,39
Lipid-lowering treatment is not indicated in patients with valvular disease without CAD.	III	B	38

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CAD = coronary heart disease; HF = heart failure; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid.

Table 27 Recommendations for treatment of dyslipidaemia in autoimmune diseases

Recommendations	Class[a]	Level[b]
As yet there is no indication for the preventive use of lipid-lowering drugs only on the basis of the presence of autoimmune diseases.	III	C

[a]Class of recommendation.
[b]Level of evidence.

Table 27 lists the recommendations for the treatment of dyslipidaemia in autoimmune diseases.

10.9 Renal disease

The prevalence of CKD, in particular mild to moderate CKD, is rapidly increasing worldwide. A decreasing GFR is associated with CVD independently of other risk factors.[189] In a recent survey in Europe the standardized CV mortality rate was 38 per 1000 person years (95% CI 37.2–39.0) higher in patients starting dialysis than in the general population.[190]

Lipoprotein profile in chronic kidney disease

The lipid profile shows both quantitative and qualitative abnormalities that worsen with declining GFR, being most pronounced in subjects with end-stage renal disease (ESRD). Dyslipidaemia comprises typically elevations of TG and lowering of HDL-C, whereas the changes of TC and LDL-C are less marked in stage 1–2 CKD. The elevation of TG is caused by both increased production and impaired removal of TRLs due to changes in regulatory enzymes and proteins. Consequently non-HDL-C and apo B levels are clearly increased. LDL subclasses display a shift to excess of small dense LDL particles. In patients with ESRD the catabolic rate of LDL is markedly prolonged, resulting in clear elevation of both TC and LDL-C levels. Plasma Lp(a) levels also start to increase early due to the prolonged residence times of these particles in the circulation. Altogether, most patients with stage 3–5 CKD have mixed dyslipidaemia and the lipid profile is highly atherogenic with adverse changes in all lipoproteins.

Evidence for lipid management in patients with chronic kidney disease

Available data from post-hoc analyses of statin trials provide evidence for the beneficial effects of statin therapy on CVD outcomes in patients with stages 2 and 3 CKD. The Pravastatin Pooling Project (PPP) included 19 737 subjects with a median follow-up of 64 months.[191] The benefit was most marked in subjects with both CKD and diabetes. Notably there was also a significant reduction in the risk of all-cause mortality (relative risk 0.81, 95% CI 0.73–0.89). In the Heart Protection Study (HPS) the absolute risk reduction was 1.1% in a subgroup of subjects with mild CKD as compared with 5.4% in the total cohort.[192]

The results from patients with more advanced CKD (stage 4–5) and on dialysis are less clear. Two observational studies have reported benefits of
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trial[61] in a cohort of 1
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point of CVD. The res
Use of Rosuvastatin
Assessment of survival
patients on haemodi
LDL-C as expected but had no significant effect on the composite CVD endpoint. These negative results question the benefits of statins in these very high risk patients with poor outcomes. SHARP reported results in ~9500 high risk subjects with CKD. Major atherosclerotic events were reduced by 17% ($P = 0.0022$) and major vascular events by 15.3% ($P = 0.0012$) in patients on ezetimibe plus simvastatin as compared with placebo.[111] Importantly, although no significant heterogeneity existed between non-dialysis and dialysis subjects, this was also true for placebo vs. dialysis subjects.

Therapeutic targets for patients with chronic kidney disease

CKD is acknowledged as a CAD risk equivalent. This has set the LDL-C reductions as the primary target of therapy. Non-HDL-C should be the second objective in the management of mixed dyslipidaemia. The treatment algorithm should be based on GFR. Drugs eliminated mainly by the hepatic route should be preferred (fluvastatin, atorvastatin, pitavastatin, and ezetimibe). Statins metabolized via CYP3A4 may result in adverse effects due to drug–drug interactions, and special caution is required.

Table 28 lists the recommendations for lipid-lowering drugs in patients with moderate to severe CKD.

10.9 Renal disease

Table 26 Recommendations for treatment of dyslipidaemia in HF or valvular disease

Recommendations	Class[a]	Level[b]	Ref[c]
n-3 PUFAs 1 g/day may be considered to be added to optimal treatment in patients with HF (NYHA classification II–IV).	IIb	B	184
Cholesterol-lowering therapy with statins is not indicated in patients with moderate to severe HF (NYHA classification III–IV).	III	A	36,39
Lipid-lowering treatment is not indicated in patients with valvular disease without CAD.	III	B	38

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CAD = coronary heart disease; HF = heart failure; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid.

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Recommendations	C
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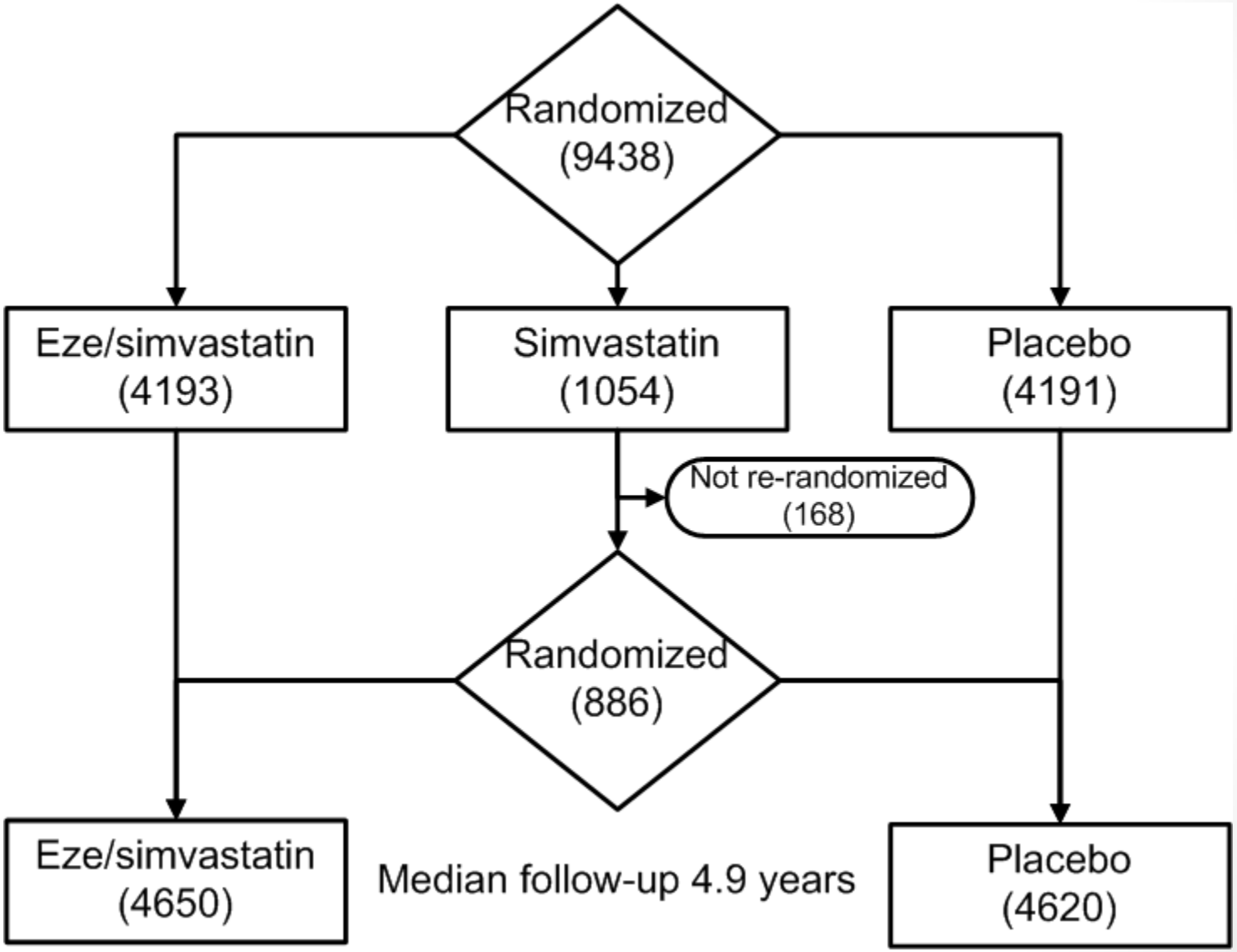
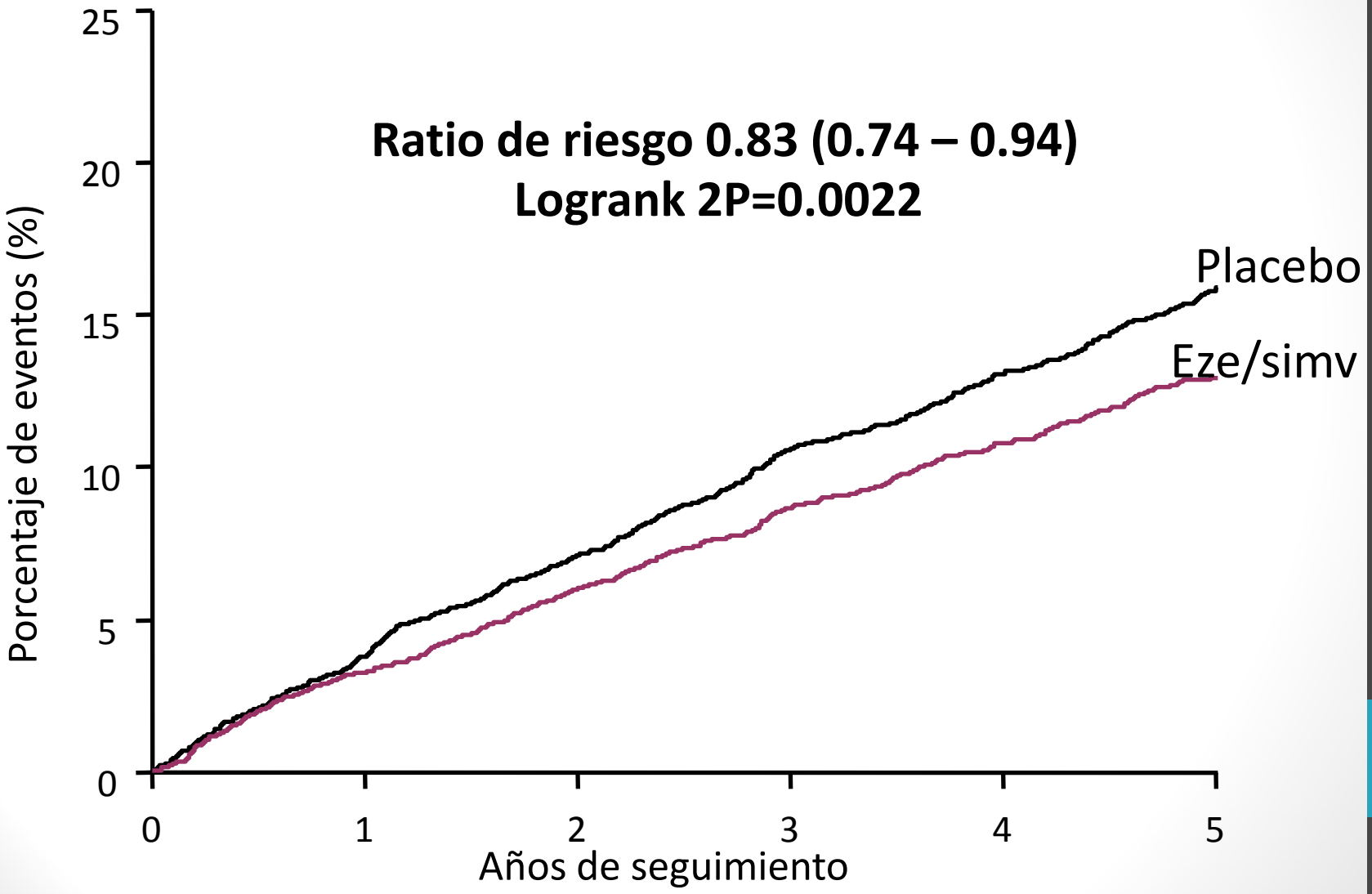
SHARP: Criterios de Inclusión

- Pacientes con enfermedad renal crónica
  - No dializados: creatinina elevada en 2 ocasiones
    - Hombres: ≥1.7 mg/dL (150 µmol/L)
    - Mujeres: ≥1.5 mg/dL (130 µmol/L)
  - En diálisis: hemodiálisis o diálisis peritoneal.
- Edad ≥40 años
- Sin historia de IAM o revascularización

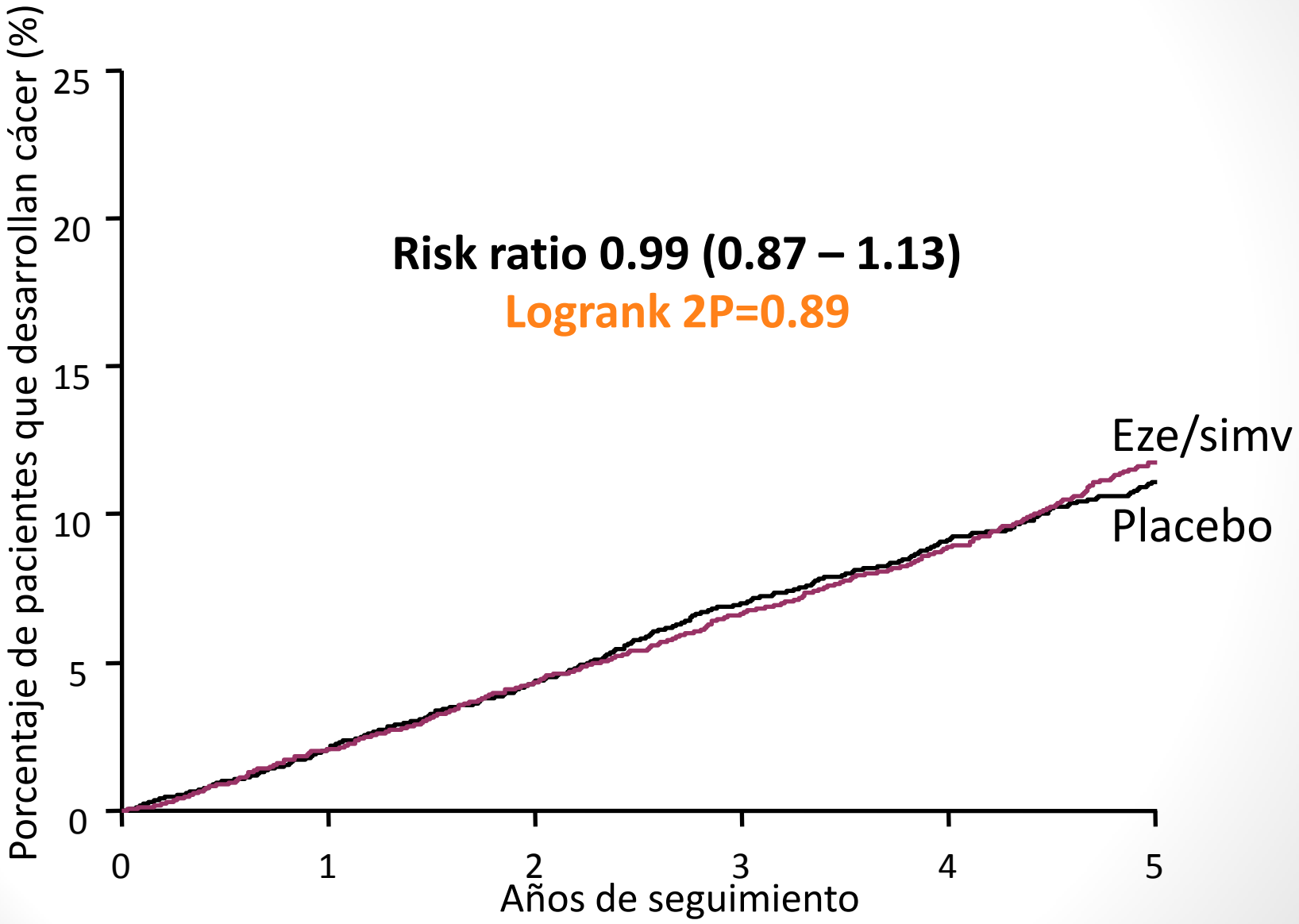
SHARP: Diseño



SHARP: Principales eventos isquémicos



SHARP: Incidencia de Cáncer

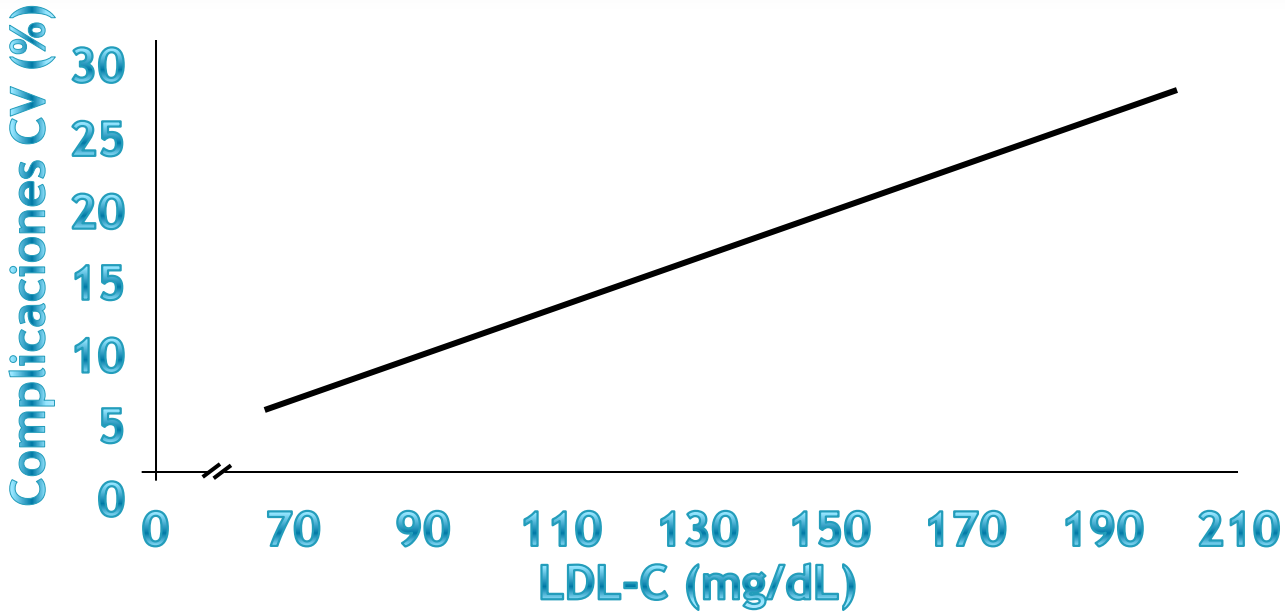


SHARP: Resumen

- **Reducción de eventos isquémicos: RR 17%, p<0.0022 con un 66% de cumplimiento**
- **Reducción de eventos CV: RR 15%, p=0.0012**
- **Reducciones de eventos similares en dializados y no dializados**
- **Perfil de seguridad semejante en ambas ramas de estudio**
- **No aumento de incidencia de cáncer o de mortalidad por cáncer**
- **El efecto clínico obtenido con la combinación ezetimiba/simvastatina fue consistente con la relación entre la disminución de LDL y la reducción del riesgo cardiovascular del CTT**

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**



Interpretation Further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1·0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2–3 mmol/L would reduce risk by about 40–50%.

Table 28 Recommendations for lipid lowering drugs in patients with moderate to severe CKD (stages 2–4, GFR 15–89 mL/min/1.73 m^2)

Recommendations	Class[a]	Level[b]	Ref[c]
CKD is acknowledged as a CAD risk equivalent; in these patients LDL-C reduction is recommended as the primary target of therapy.	I	A	189, 190
LDL-C lowering reduces CVD risk in CKD subjects and should be considered.	IIa	B	111, 193
Statins should be considered to slow the rate of kidney function loss modestly and thus protect against the development of ESRD requiring dialysis.	IIa	C	-
Since statins have a beneficial effect on pathological proteinuria (>300 mg/day) they should be considered in patients with stage 2–4 CKD.	IIa	B	194
In moderate to severe CKD statins as monotherapy or in combination with other drugs should be considered to achieve LDL-C <1.8 mmol/L (less than ~70 mg/dL).	IIa	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CAD = coronary artery disease; CKD = chronic kidney disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein-cholesterol.

INTOLERANCIA ESTATINAS

Follow-up safety assessments

Where statins are used, safety blood tests are advised by regulators, including ALT and CK at baseline to identify the limited number of patients where treatment is contraindicated. CK should at least be checked in patients with high risk for myopathy such as the very elderly with co-morbidities, patients with earlier muscle symptoms, or patients on interacting drugs. Follow-up is advised at 6 or 12 monthly intervals to monitor potential toxic side effects, but such assessments have a limited scientific basis. A systematic review[218] found that the incidence of drug-induced hepatotoxicity in patients taking lipid-lowering drugs is unknown, with few cases occurring in large-scale randomized trials. Recent reviews[219] are encouraging about the safety of long-term lipid-lowering therapy.

There is no predictive value of routine repeat CK testing for rhabdomyolysis since the test can rise with muscle injury or excess muscular exercise. However, CK must be assessed immediately in patients, especially the elderly, presenting with muscle pains and weakness, and treatment stopped if >5 times the ULN. In patients whose liver function tests rise above three times the ULN, explanations such as alcohol ingestion or non-alcoholic fatty liver disease should be sought and the levels monitored. If levels remain elevated, then statins should be stopped but may be cautiously re-introduced under monitoring after levels have returned to normal. There is limited evidence to suggest that some statins have more likelihood of being associated with muscle symptoms (but not CK change), or liver enzyme changes.

Table 33 summarizes the recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy.

12. How to improve adherence to lifestyle changes and compliance with drug therapy

No smoking, healthy eating, and being physically active are the foundations of preventive cardiology. These lifestyles are most effectively achieved through formal programmes of preventive care; such programmes are also more appropriate for initiating and up-titrating drug therapies, achieving the treatment goals, and adherence over the long-term which in turn improves event-free survival.[220] However, in everyday care, statins are usually prescribed at the lowest dose and often not up-titrated to achieve goals. In addition, adherence over the long term is poor, with up to a third of patients or more stopping their statin treatment within a year. Not up-titrating the dose of statin, and poor adherence to this therapy, are the main reasons why over half of all coronary patients, and four out of five of all high risk patients, are not achieving the lipid goals and, as a consequence, are not achieving the maximum benefits of these preventive strategies.[221]

So, the challenges for clinical practice are to initiate treatment in both vascular patients and those at high risk of developing CVD, up-titrate the dose to achieve the lipid goals wherever feasible, and achieve adherence.

Most of the problems related to adherence to lifestyles are currently assumed to be similar to those related to compliance with lipid-lowering drug therapy. Two of the most important factors

Table 34 Hints to help adherence to lifestyle changes

• Develop a good alliance with the patient.
• Make sure that the patient understands how lifestyles affect cardiovascular disease and use this to gain commitment to the change in behaviour.
• Explore potential barriers to the change.
• Design with the patient a lifestyle change plan that is realistic and encouraging.
• Reinforce the patient's efforts to change.
• Involve other experts wherever needed and possible.
• Arrange a schedule of follow-up visits.

Table 35 Tips to help compliance with multiple drug therapies

• Simplify the dosing regimen if possible by reducing daily doses and concomitant medications.
• Choose cheaper alternatives.
• Provide clear written and oral instructions.
• Undertake a dialogue with the patient regarding adherence.
• Tailor the regimen to the patient's lifestyle and needs.
• Involve the patient as partner in the treatment.
• Use behavioural strategies (reminder systems, cues, self-monitoring, feedback, reinforcement)

contributing to poor adhere
and lifelong nature of the di
adherence may be related t

- demographic factors suc
- the patient's understandi
- the healthcare provider's
- the relationships betwee
- influences from the healt
- complex chronic drug re

Poor socioeconomic statu
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In *Table 34* some hints a
adherence to lifestyle changes.

The responsibility for adherence must be shared between the healthcare provider, the patient, and the healthcare system.

GRACIAS !!!!