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CHOLESTEROL GUIDELINES: CAUSE FOR CONCERN? EUROPEAN AND AMERICAN GUIDELINES DIFFERENCES AND SIMILARITIES NICA, ADA, ESC, WHO, AHA, ATP III and ATP IV

Kliti Hoti[1], Edite Sadiku[2], Bashkim Resuli[2]

[1]Faculty of Public Health, University of Medicine,Tirana (UMT), Albania
[2]Faculty of Medicine, University of Medicine, Tirana (UMT), Albania

Introduction

Cardiovascular disease (CVD) is the leading cause of death in Developed Countries 1

Forever CVD predominantly affects people older than 50 and age is the main determinant of risk. Apart from age and sex, three modifiable risk factors – smoking raised blood pressure and raised cholesterol – make a major contribution to CVD risk, particularly in combination. These account for 80% of all cases of premature coronary heart disease (CHD)[2].

CVD event can be calculated from these risk factors and people at highest risk can be identified. There are also major identifiable population groups at particular risk. CVD is strongly associated with low income and social deprivation, the lifetime burden is greater in women because of their longevity and their increased risk of stroke over the age of 75[3].

Blood cholesterol has a log–linear relationship to the risk of CHD and is a key modifiable risk factor. It is estimated that in high-income countries blood cholesterol levels in excess of 150mg/dl are responsible for more than 50% of CVD events[4]. Blood cholesterol can be reduced by dietary change, more likely to develop CVD at a younger age. Family history of premature CHD identifies an important group that contains people with a genetic predisposition.

Throughout the World Health Organization (WHO) European Region cardiovascular disease is estimated to be the leading cause of death, accounting for more than 5 million deaths as well as almost one-quarter of the region's disease burden. CVD is forecast to remain the leading cause of disability in developed countries up until 20205. Risk factors such as smoking, physical inactivity, obesity, high blood pressure, lipids (raised total cholesterol and LDL cholesterol, low HDL cholesterol and raised triglycerides), raised glucose levels and family history of premature coronary disease are responsible for a sizeable proportion of the total burden of cardiovascular disease in the region. The WHO attributes 8.7% of the total burden of disease in the region to high blood cholesterol6, and comments that existing knowledge on disease detection; treatment and rehabilitation should be "better and more equitably applied, so that all stand to share in the benefits"7

Two main forms of cholesterol are generated in the human body. The most relevant to this article is low-density-lipoprotein cholesterol (LDL-C). This is often known as "bad" cholesterol because it can build up in the artery walls, causing them to narrow. The World Health Organization (WHO) believes that 60% of coronary heart disease and 40% of strokes are due to elevated cholesterol levels 8.

Reducing LDL-C has long been the primary target of cholesterol policy and this remains the case today.

The second form of cholesterol is high-density lipoprotein (HDL-C), known as "good" cholesterol due to its role in taking excess cholesterol away from the arteries.
The cholesterol threat to health has grown out of dietary changes in developed countries, with increasing consumption of saturated fats, to which the human body has been unable to fully adapt 9. Steps to reduce bad cholesterol, firstly through dietary and lifestyle changes, and subsequently through drug therapy, are proven to be effective in tackling the increasing burden of cardiovascular disease (CVD), particularly coronary heart disease (CHD)10. The annual financial cost of CVD in the European Union has been calculated to exceed •169 billion, the majority of which consists of the cost of treatment; primarily the cost of hospitalisation11,

ISSN: 2304-2354
Number 4, Volume 44, 2013

plus the economic costs from CVD as a leading cause of disability12.

The rising European challenge of cholesterol as a risk factor for CVD is clear, yet the variations in practice have no obvious clinical explanation. The variations in local guidance give particular cause for concern in the context of consistent failures to achieve cholesterol targets. The EUROASPIRE II study, for example, found that only 51% of patients on lipid lowering therapy were achieving the treatment goals of the European guidelines 13.

Cardiovascular disease (CVD) and its cardiometabolic risk factors (hypertension, obesity, smoking, dyslipidemia, and diabetes mellitus) are common in the United States. More than 82 million Americans have CVD, including 16.3 million who have coronary heart disease (CHD), 7.9 million with myocardial infarction (MI), 7.0 million with stroke, and 5.7 million with heart failure.[3] More than 33 million Americans have hyperlipidemia as defined by the American Heart Association (AHA) as a total cholesterol concentration of 240mg/dL or higher. However, many other people have dyslipidemia (an umbrella term that encompasses a variety of lipid disorders in addition to elevated total cholesterol levels) that increases their risk for CVD without meeting the AHA criterion. Analysis of epidemiologic data revealed that 71 million Americans had elevated levels of low-density lipoprotein (LDL) cholesterol between 2005 and 2008.[14] The percentage of patients with dyslipidemia who received treatment (48%) and achieved control (33%) had increased since 1999-2002, but room for improvement remains. Managing dyslipidemia can minimize the burden of CVD.

The pace of new research findings in patients with dyslipidemia is rapid, and evidence-based guidelines for the management of dyslipidemia quickly become out of date. The ATP III guidelines were published in 2001 and updated in 2004.[15] An updated guideline for secondary prevention and risk reduction in patients with CHD and other atherosclerotic vascular disease from AHA and the American College of Cardiology (ACC) was released in November 2011.[16] A 2012 version of the American Diabetes Association (ADA) standards of medical care in diabetes that addresses dyslipidemia in this patient population also is available. The release of new NCEP guidelines (ATP IV) has been delayed several times since 2009 and is now expected sometime this year.

What are likely to be some of the main differences between the recommendations in ATP IV and those in ATP III, and what evidence is the basis for these changes?

The primary target in treating dyslipidemia has been and will likely continue to be LDL cholesterol because it is the most atherogenic lipoprotein and it correlates more closely than other lipids with CHD. Statin therapy will likely continue to be emphasized because statins are the most effective lipid- lowering agents for reducing LDL cholesterol concentrations, and their efficacy for lowering the risk for cardiovascular events has been proven.[17]

The goal LDL cholesterol levels in ATP III (Table 1) depend on the presence of atherosclerotic vascular disease (e.g., CHD, ischemic stroke, peripheral arterial disease, abdominal aortic aneurysm), diabetes, and major cardiovascular risk factors (age e"45 years for men or e"55 years for women, hypertension, smoking, family history of premature CHD, and high-density lipoprotein [HDL] cholesterol <40 mg/dL). In ATP III, an optional LDL cholesterol goal of less than 70 mg/ dL applies only to individuals who are at very high risk for cardiovascular events. Very high risk is defined as the presence of established CVD plus multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), multiple metabolic syndrome risk factors (especially triglycerides e"200 mg/dL plus non-HDL-cholesterol e"130 mg/dL with HDL cholesterol <40 mg/dL), or acute coronary syndrome (ACS).

The ATP IV recommendations should reflect the results of recent clinical trials evaluating the impact of aggressive LDL cholesterol reduction on cardiovascular events. The benefit of intensive LDL cholesterol reduction using atorvastatin 80 mg/day instead of atorvastatin 10 mg/day (the control group) for 5 years was demonstrated in a subgroup analysis of 1501 patients with CHD and diabetes participating in the randomized, double-blind .

Table 1. ATP III LDL Cholesterol Goals in Patients with Dyslipidemia

Risk Category	LDL Cholesterol Goal (mg/dL)
High risk: CHD or CHD risk equivalents[a] (10-year risk >20%)	<100 (optional <70)
Moderately high risk: ≥2 risk factors[b] (10-year risk 10% to 20%)	<130 (optional <100)
Moderate risk: ≥2 risk factors[b] (10-year risk <10%)	<130
Lower risk: 0 or 1 risk factor[b]	<160

ATP = adult treatment panel; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein

ISSN: 2304-2354
Number 4, Volume 44, 2013

Although 70 mg/dL or lower is considered an optional LDL cholesterol goal that applies only to patients at very high risk for cardiovascular events in current ATP III guidelines, new ATP IV guidelines are likely to recommend this goal for all patients with coronary heart disease, regardless of the presence of other comorbidities.

The ATP IV recommendations for patients with diabetes and dyslipidemia probably will reflect the results of several note- worthy clinical trials. The effectiveness of aggressive LDL cholesterol reduction using atorvastatin 10 mg/day for primary prevention of major cardiovascular events in patients with type 2 diabetes without high baseline concentrations of LDL cholesterol was demonstrated in a randomized, double-blind, placebo-controlled study.[18] After a median follow up of 3.9 years, there was a 37% lower incidence of major cardiovascu- lar events in the atorvastatin group compared with the placebo group, a difference that is significant. At the end of the study/

In a 2008 consensus statement for lipoprotein management in patients with cardiometabolic risk, ADA and ACC recommend a goal LDL cholesterol less than 70 mg/dL for patients at the highest risk for cardiovascular events, which they define as:

- Patients with known CVD

- Patients with diabetes plus at least one major risk factor for CVD other than dyslipidemia (e.g., cigarette smoking, hypertension, and family history of premature coronary artery disease)

A goal LDL cholesterol less than 100 mg/dL is recommended in the ADA/ACC consensus statement for patients at high risk for cardiovascular events:

- Patients without CVD or diabetes but with two or more other major risk factors

- Patients with diabetes and no other major risk factors

The most recent (2012) ADA standards of medical care in diabetes call for the addition of statin therapy to lifestyle therapy, regardless of baseline lipid levels, for patients with overt CVD.[6] This therapeutic approach also is recommended by ADA for patients without CVD if they are more than 40 years of age and have at least one other CVD risk factor. The goal LDL cholesterol is less than 70 mg/dL for patients with overt CVD and less than 100 mg/dL in patients without overt CVD, according to ADA.

The new ATP IV guidelines are likely to recommend statin-based therapy for all patients with diabetes who are more than 40 years of age, regardless of their baseline LDL cholesterol value. These patients stand to benefit based on the results of the Heart Protection Study.[19] The new ATP IV guidelines probably also will recommend a goal LDL cholesterol less than 70 mg/dL for patients with CVD (regardless of the presence of diabetes) and a goal less than 100 mg/dL for patients without CVD but with multiple major risk factors (including diabetes). These goals are optional in ATP III but evidence supports their use in patients who meet these criteria, so there is an evidence-based argument to make the formerly optional goals standard goals in ATP IV.

What recommendations do you expect to see in ATP IV for the use of fibrates or nicotinic acid in combination with statins?

According to ATP III, combining a fibrate or nicotinic acid with LDL-lowering therapy should be considered for patients with high triglycerides or low HDL cholesterol values once LDL cholesterol is addressed.[20] However, the results of recent studies have raised concerns about the usefulness of this treatment approach.

Fibrates and nicotinic acid primarily for patients with severe hypertriglyceridemia (triglycerides e"500 mg/dL), an undisputed role for these agents in the management of dyslipidemia, may be suggested in ATP IV.

Current ADA standards of medical care in diabetes acknowledge that if lipid goals are not achieved using the maximum tolerated statin dosage, adding other lipid-lowering agents may be considered.[21] However, the ADA standards include the caveat that the safety and impact of these combinations on cardiovascular outcomes have not been evaluated in outcome studies.

Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

Recommendations for the Management of Dyslipidemia

* **New Recommendation**

Prevention

People with type 1 or type 2 diabetes should be encouraged to adopt a healthy lifestyle to lower their

ISSN: 2304-2354
Number 4, Volume 44, 2013

risk of CVD. This entails adopting healthy eating habits, achieving and maintaining a healthy weight, engaging in regular physical activity, and smoking cessation.

Risk Assessment

Most people with type 1 or type 2 diabetes should be considered at high risk for vascular disease. The exceptions are younger people with type 1 or type 2 diabetes with shorter duration of disease and without complications of diabetes (including established CVD) and without other CVD risk factors. A computerized risk engine (e.g. UKPDS risk engine, Cardiovascular Life Expectancy Model) can be used to estimate vascular risk.

Screening

Fasting lipid levels (TC, HDL-C,TG and calculated LDL-C) should be measured at the time of diagnosis of diabetes and then every 1 to 3 years as clinically indicated. More frequent testing should be per- formed if treatment for dyslipidemia is initiated.

Targets

The primary target of therapy is the LDL-C; the secondary target is the TC/HDL-C ratio.

If the TC/HDL-C ratio is e"4.0, consider strategies to achieve a TC/HDL-C ratio <4.0, such as improved glycemic control, intensi- fication of lifestyle (weight loss, physical activity, smoking cessa- tion) and, if necessary, pharmacologic interventions.

Plasma apo B can be measured, at the physician's discretion, in addi- tion to LDL-C and TC/HDL-C, to monitor adequacy of lipid-lowering therapy in the high-risk patient. Target apo B should be <0.9 g/L.

Treatment

Patients at high risk of a vascular event should be treated with a statin to achieve an LDL-C d"80mg/ L. Clinical judgment should be used as to whether additional LDL-C lowering is required for patients with an on-treatment LDL-C of 90 to 100 mg/L. In patients with serum TG >10.0 mmol/L, despite best efforts at optimal glycemic control and other lifestyle interventions, a fibrate should be prescribed to reduce the risk of pancreatitis. For those with moderate hyper-TG (4.5-10.0 mmol/L), either a statin or a fibrate can be attempted as first-line therapy, with the addition of a second lipid-lowering agent of a different class if target lipid levels are not achieved after 4 to 6 months on monotherapy.

For patients not at target(s), despite optimally dosed first-line therapy as described above, combination therapy can be considered. Although there are as yet no completed trials demonstrating clinical outcomes in patients receiving combination therapy, pharmacologic treatment options include (listed in alphabetical order):

- Statin plus ezetimibe
- Statin plus fibrate
- Statin plus niacin

- Adapted from Canadian Diabetes Association Clinical Practice Guidelines

Evaluation of Total Cardiovascular Risk Using the SCORE Scale

The new guidelines recommend stratifying total risk using the SCORE risk table. According to this scale, patients can be classified as having very high, high, moderate, or low cardiovascular risk.

The preference for the SCORE system over other risk scales is based on the fact that it was designed and evaluated using representative European cohorts. The SCORE scale allows for estimating the 10-year risk of the first lethal atherosclerotic complication based on the following risk factors: age, sex, tobacco use, systolic blood pressure, and total cholesterol. Different tables are available for high and low risk areas of Europe as well as for each sex. Based on the patient's background and current risk factors, the recommended risk classification system in these European protocols is more simple and practical than in others: patients with a documented background of cardiovascular disease, type 2 diabetes mellitus (DM) or type 1 with organ damage (e.g., microalbuminuria), moderate or advanced chronic renal failure, and those with a SCORE risk calculation >10% are automatically

Recommendations from the European Guidelines for the Management of Dyslipidemias, Organized by the Class of the Recommendation and Level of Evidence Given

Target Cholesterol Control Values for Low-Density Lipoproteins According to the European Guidelines for the Management of Dyslipidemias.

ISSN: 2304-2354
Number 4, Volume 44, 2013

Table 2

Type of patient	Target	Recommendation	Supporting studies
Very high risk	< 70 mg/dl (1,8 mmol/l)	I (A)	Refs. 12, 13 and 14
High risk	< 100 mg/dl (2,5 mmol/l)	IIa (A)	Refs. 12, 15 and 16
Moderate risk	< 115 mg/dl (3,0 mmol/l)	IIa (C)	?
Low risk	?	?	?

The terms "very high risk," "high risk," "moderate risk," and "low risk" are derived from the SCORE scale and are explained in the text.

Classified as having very high cardiovascular risk. In all other cases, the SCORE scale is recommended d for es timating the risk of cardiovascular death (high, 5%-10%; moderate, 1%-5%; and low, <1%) (Table2). Another element to highlight is the inclusion of high-density lipoprotein cholesterol (HDLc) measurements in the SCORE calculation of risk, which recognizes the role these molecules play in the biopathology of cardiovascular disease (CVD).[23]

Treatment Objectives

The new guidelines continue to recognize that elevated levels of total cholesterol and LDLc are the most important dyslipidemia in terms of prognosis as well as quantity of available epidemiologic, pathologic, and therapeutic data exist. Other dyslipidemias are also discussed, however briefly, that predispose the patient to premature coronary disease, such as the atherogenic lipid triad, in which very low density lipoproteins are elevated and which is expressed by a moderate elevation of plasma levels of triglycerides and LDLc, with reduced levels of HDLc. An extrapolation of the available data shows that an absolute reduction in LDLc to values <70 mg/dl, or a relative reduction of 50% from initial values, provides a greater benefit in terms of CVD prevention. As such, this is the target in patients with very high risk and it is not considered optional, as it was in the NCEP- ATP III protocols.[24] Stricter LDLc targets have also been developed for high-risk (<10 0 mg/dl) and moderate-risk (<115 mg/dl) patients, although these recommendations are base d solely on expert consensus. The guidelines no longer differentiate between threshold concentrations for starting nonpharmacological or pharmacological treatment, as well as recommended and special target concentrations. Both HDLc and apolipoprotein B (ApoB) can be considered as possible treatment targets, especially in patients with type 2 DM, metabolic syndrome, or combined dyslipidemia.

Table 2 summarizes these recommendations and the evidence used to support them. Clear evidence exists for the recommendations given in the case of patients with high or very high risk, but not for the moderate-risk group, with no explanation in the text. With the target of <115 mg/dl, it is possible that some patients may be prescribed statins when lifestyle changes would be sufficient. Additionally, low-risk patients have no recommendations for treatment goals.

On the other hand, it may surprise that the guidelines do not excessively state target cholesterol levels, nor have they delved seriously into markers other than the traditionally used LDLc, HDLc, triglycerides, and total cholesterol. However, this is justified since not all analytical laboratories in Europe (which is the natural scope of the guidelines) possess the necessary technology for making PCRas, ApoB, ApoA-I, direct LDLc, and other complex analytical measurements on a regular basis. Additionally, the majority of these laboratory analyses have a significantly lower evidence level than the commonly used metrics. The therapeutic targets for LDLc differ from those in other guidelines.

The ATP III sets different targets for patients at different risk levels: high, <100 mg/dl (optional, 70 mg/dl); moderate- high, <130 mg/dl; moderate, <160 mg/dl; and low, <160 mg/dl.

Another arguable aspect is that the guidelines recommend, above all and in a very specific manner, interventions in patients with clinical CVD or high risk, which equates to indicating lipid-lowering drugs in patients with advance d vascular damag e, and ye t interventions are minimized over the long term. The guidelines should put greater emphasis on the treatment of moderate- and low- risk patients, since preventing the development of atheromatous plaques is far simpler than preventing their return.

ISSN: 2304-2354
Number 4, Volume 44, 2013

The Importance of Nonpharmacological Treatment

The guidelines place a great amount of emphasis on the effects of lifestyle changes such as diet, physical activity, and other habits of healthy living on the different plasma lipids associated with the atherosclerotic process. The recommendations related to lifestyle modifications aimed at reducing general cardiovascular risk, and dyslipidemias in particular, are presented in great detail, including which foods are more or less advisable according to their beneficial or deleterious effects on cardiovascular risk, physical activity, and smoking cessation, which is essential in all cases.

In addition, and for the first time in guidelines of this sort, some thought is given to the results and possible indications for the controversial nutraceuticals. Of the many functional foods and diet supplements that are promoted as being beneficial for people with dyslipidemia and in the re duction of cardiovascular risk , the guidelines only recommend foods enriche d with phytosterols (1-2 g/day) for people with elevated total cholesterol and LDLc levels in which the total cardiovascular risk level does not justify the use of statins.

Although these recommendations are clear and indisputable, it is interesting that no specific mention is made of the Mediterranean diet, nor do we find an explicit recommendation for the length of attempts to treat solely with lifestyle changes before starting pharmacological treatment, in contrast to the 3 months recommended by the ATP III.

Choice of Lipid-lowering Drugs: Emphasis on Statins

The discussion of the pharmacological properties and practical aspects of use for all available lipid-lowering drugs is well-developed and appropriate. The emphasis on statins as the essential treatment for cardiovascular prevention is logical, given the large number of studies that have demonstrated their efficacy in prevention.[25] The guidelines recommend wide prescription of statins, even the highest allowable or tolerable doses, in order to reach the previously mentioned LDLc goals. For patients with statin intolerance, the recommendation is for bile acid chelating agents or niacin, although this was published before the AIM-HIGH[19] study was prematurely terminated due to lack of effectiveness of this treatment (the HPS2-THRIVE study, however, is ongoing). Absorption inhibitors are not recommended with much zeal, although they are mentioned in possible association with low doses of statins in patients whose poor tolerance impedes prescribing adequate statin levels, or with bile acid chelating agents or niacin (a combination virtually unexplored in our country). It is also logical that the guidelines assign only a marginal role to fibrates, since new studies point towards issues in their safety, which is questionable at the least, as well as the absence of any effect on mortality and long-term cardiovascular complications. It is interesting to point out that the guidelines extensively discuss combinations of drug treatments, establishing indications for combined lipid-lowering drug treatment and its adverse reactions.

Niacin (nicotinic acid) is the drug of choice for treating low LDLc

levels.

With regard to safety, the primary document mentions that the majority of statins, with the exception of pravastatin, rosuvastatin, and pitavastatin, are significantly metabolized by cytochrome P450, which could provide an advantage in terms of safety. Additionally, statins should be used in patients with renal failure, since these compounds are preferentially eliminate d through the hepatic pathway (fluvostatin, atorvastatin, and pitavastatin). Recently, the Food and Drug Administration *(FDA) released an alert regarding the increased risk of myopathy and rhabdomyolysis with 80mg doses of simvastatin. The guidelines also recommend that doses not exceed 10mg/day of simvastatin in patients taking amiodarone, verapamil, or diltiazem, and not exceed 20mg/day of simvastatin when taken together with amlodipine.*

Although the guidelines have been very exhaustive and clear on several aspects of the management of patients with dyslipidemia, there is a lack of definition of which specific statins may be preferable in each situation. For example, are all statins capable of reaching a target LDLc<70 mg/dl? The table with supplementary material that shows the % reduction in LDLc necessary to reach target goals derived from baseline values could be completed by including the type of statin and the dosage used.

important to stress that a multifactorial approach that addresses all risk factors yields most benefit. This is because the effect of modifying several risk factors is multiplicative.

ISSN: 2304-2354
Number 4, Volume 44, 2013

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

In February 2010 NICE Guidance Executive agreed to withdraw the recommendation that the Framingham risk equation should be the equation of choice for assessment of CVD risk, but agreed that it should be considered as one of the possible equations to use. Recommendations relating specifically

to the use and modification of the Framingham risk equation have been moved to appendix D. Consider these recommendations when using the Framingham risk equation for assessment of CVD risk.

NICE clinical guideline 67 – Lipid modification

Treatment and care should take into account patients' needs and preferences. People at high risk of CVD or with established CVD should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals.

Primary prevention of CVD

- For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people ***aged 40–74*** who are likely to be at high risk.
- People should be prioritized on the basis of an estimate of their CVD risk before a full formal risk assessment. Their CVD risk should be estimated using CVD risk factors already recorded in primary care electronic medical records.
- Risk equations should be used to assess CVD risk.
- People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention ***over a 10-year period***. This information should be in a form that:

- presents individualized risk and benefit scenarios
- presents the absolute risk of events numerically
- uses appropriate diagrams and text. (See www.npci.org.uk)

- Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimized if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidemia should be treated. Assessment should include:

- smoking status
- alcohol consumption
- blood pressure (see 'Hypertension', NICE clinical guideline 34)
- body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)
- fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)
- fasting blood glucose
- renal function
- liver function (transaminases)
- thyroid-stimulating hormone (TSH) if dyslipidemia is present.

- Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available or appropriate (for example, older people, people with diabetes or people in high-risk ethnic groups).
- Treatment for the primary prevention of CVD should be initiated with statins(Fluvastatine – Lescol 40mg)

Secondary prevention of CVD

- For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors. Blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

- smoking status
- alcohol consumption

ISSN: 2304-2354
Number 4, Volume 44, 2013

- blood pressure (see 'Hypertension', NICE clinical guideline 34)

- body mass index or other measure of obesity (see 'Obesity', NICE

clinical guideline 43)

- fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)

- fasting blood glucose

- renal function

- liver function (transaminases)

- thyroid-stimulating hormone (TSH) if dyslipidaemia is present.

This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094NICE clinical guideline 67 – Lipid modification

- Statin therapy is recommended for adults with clinical evidence of CVD.
- People with acute coronary syndrome should be treated with a higher intensity statin. Any decision to offer a higher intensity statin should take
- In people taking statins for secondary prevention, consider increasing to statins if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity statin should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.

NCEP-ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

1-Determine lipoprotein levels–obtain complete lipoprotein profile after 9- to 12-hour fast.

LDL Cholesterol – Primary Target of Therapy

<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high

Total Cholesterol

<200	Desirable
200-239	Borderline high
≥240	High

HDL Cholesterol

<40	Low
≥60	High

2-Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

3-Determine presence of major risk factors (other than LDL):

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

Cigarette smoking

Hypertension (BP >140/90 mmHg or on antihypertensive medication) Low HDL cholesterol (<40 mg/dL)*

Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)

Age (men >45 years; women >55 years)

* HDL cholesterol >60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

4-If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess

10-year (short-term) CHD risk (see Framingham tables).

ISSN: 2304-2354
Number 4, Volume 44, 2013

Three levels of 10-year risk:

- >20% — CHD risk equivalent
- 10-20%
- <10%

5-Determine risk category:

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cut points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.

Risk Category	LDL Goal	Lifestyle Changes (TLC)	Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
			10-year risk 10-20%: ≥130 mg/dL
			10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

** Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

6-Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.

TLC Features

- TLC Diet:

— Saturated fat <7% of calories, cholesterol <200 mg/day

— Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols

(2g/day) as therapeutic options to enhance LDL lowering

- Weight management
- Increased physical activity.

7-Consider adding drug therapy if LDL exceeds levels shown in Step 5 table:

- Consider drug simultaneously with TLC for CHD and CHD equivalents
- Consider adding drug to TLC after 3 months for other risk categories.

Drugs Affecting Lipoprotein Metabolism

HMG CoA reductase inhibitors(STATINAT) exp. Fluvastatine 40-80 mg, Simvastatine20-80mg, Pravastatine20-40 mg.

Nicotinic Acid exp. Cholestyramine4-16g

Fibric Acid exp.Gembrozil 600mgBID), Fenofibrate 200mg Clofibrate 1000mgBID

8-Identify metabolic syndrome and treat, if present, after 3 months of TLC.

Clinical Identification of the Metabolic Syndrome – Any 3 of the Following:

ISSN: 2304-2354
Number 4, Volume 44, 2013

Risk Factor	Defining Level
Abdominal obesity*	Waist circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* Overweight and obesity are associated with insulin resistance and the metabolic syndrome.

Treatment of the metabolic syndrome

• Treat underlying causes (overweight/obesity and physical inactivity):

– Intensify weight management

– Increase physical activity.

• Treat lipid and non-lipid risk factors if they persist despite these lifestyle therapies:

– Treat hypertension

– Use aspirin for CHD patients to reduce prothrombotic state

– Treat elevated triglycerides and/or low HDL (as shown in Step 9).

9-Treat elevated triglycerides.

ATP III Classification of Serum Triglycerides (mg/dL)

<150	Normal
150-199	Borderline high
200-499	High
<500	Very high

Treatment of elevated triglycerides (?150 mg/dL)

- Primary aim of therapy is to reach LDL goal
- Intensify weight management
- Increase physical activity

• If triglycerides are ≥200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total – HDL)

30 mg/dL higher than LDL goal.

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Table 3

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD Risk Equivalent(10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130	<160
0-1 Risk Factor	<160	<190

If triglycerides 200-499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal:

- intensify therapy with LDL-lowering drug, or
- add nicotinic acid or fibrate to further lower VLDL.

If triglycerides ≥500 mg/dL, first lower triglycerides to prevent pancreatitis:

- very low-fat diet (≤15% of calories from fat)
- weight management and physical activity
- fibrate or nicotinic acid

ISSN: 2304-2354
Number 4, Volume 44, 2013

- when triglycerides <500 mg/dL, turn to LDL-lowering therapy.

Treatment of low HDL cholesterol (<40 mg/dL)

- First reach LDL goal, then:
- Intensify weight management and increase physical activity
- If triglycerides 200-499 mg/dL, achieve non-HDL goal
- If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent consider nicotinic acid or fibrate.

Table 4

Optimal/Near-Optimal, Borderline, and High-Risk Serum Lipid Concentrations

Lipid serum	Optimal/near-optimal concentration	Borderline serum concentration	High-risk/very high-risk serum concentration
TC, mg/dL	<200	200-239	≥240
HDL-C, mg/dL	≥60 (negative risk factor) 50-59 (women)	40-59 (men) <50 women[b]	<40 men
LDL-C, mg/dL (100-129 near-optimal)	<100 optimal	130-159	160-189 high ≥190 very high
TG[a], mg/dL	<150	150-199	200-499 high ≥500 very high
Apo B, mg/dL	<90 (patients at risk of CAD, including those with diabetes) <80 (patients with established CAD or diabetes plus ≥1 additional risk factor)		

Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

[a] Both borderline and high-risk values may signify familial combined dyslipidemia or dyslipidemia of diabetes; values >1000 indicate high risk for pancreatitis.

[b] Moderate reductions of high-density lipoprotein cholesterol in women may indicate insulin resistance syndrome.

Table 5

Lipid Goals for Patients at Risk for Coronary Artery Disease
(20 [EL 4], 37 [EL 1], 38 [EL 1], 39 [EL 1], 40 [EL1], 41 [EL 4])

Lipid Parameter	Goal	EL
TC, mg/dL	<200	
LDL-C, mg/dL	<100; <70 (all very high risk patients)	
HDL-C, mg/dL	As high as possible, but at least >40 in both men and in women	
Non–HDL-C, mg/dL	30 above LDL-C goal	
TG, mg/dL	<150	
Apo B, mg/dL	<90 (patients at risk of CAD, including those with diabetes) <80 (patients with established CAD or diabetes plus ≥1 additional risk factor)	

Abbreviations: apo, apolipoprotein; EL, evidence level; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

ISSN: 2304-2354
Number 4, Volume 44, 2013

Table 6. Classification of Elevated Triglyceride Levels

Table 6 Classification of Elevated Triglyceride Levels		
Triglyceride category	**Triglyceride concentration, mg/dL**	**Goal**
Normal	<150	<150 mg/dL
Borderline-high	150-199	
High	200-499	
Very high	≥500	

Recommendations

The direction of travel is clear. Clinical trial evidence is widening the scope of cholesterol management in the prevention and treatment of CVD, particularly in the inclusion of most or all people with diabetes. It is also leading to increasingly aggressive targets for those at most risk.

Whilst improvements in diet and lifestyle remain the first option for cholesterol reduction, assisted by developments in plant sterolenhanced foods, the focus of guidelines remain on reducing LDL-C with lipid lowering drugs as the first line of therapy when this proves necessary in the achievement of cholesterol targets. There is a clear and significant time lag between the incorporation of clinical trial evidence into pan-European standards of best practice, widely endorsed by lipid experts and their national associations, and their incorporation into national and local practice across Europe. Thus CVD remains a leading cause of avoidable death and Disability.

REFERENCE:

1.Murray CJL, Lopez AD Alternative projections of mortality and disability by cause 1990-2020: Global burden of disease study Lancet; 349; May 24 1997, pp1498-1504.
2.World Health Organization: Gaining Health: The European Strategy for the Prevention and Control of non-communicable diseases. WHO Regional Committee for Europe www.euro.whu.int/Document/ RC56/edoc08.pdf (Accessed 18 May 2007).
1.Sources: World Health Organisation, December 2004 www.who.int/healthinfo/statistics/ bodgbddeathdalyestimates. (Accessed 18 May 2007), and World Bank.
2. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al; the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2011;32:1769- 818.
3.National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143- 421.
4.Grundy SM, Cleeman JI, Merz CN, Brewer HB, Clark LT, Hunninghake DB, et al; Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol. 2004;44:720-32.
5.Lobos JM, Royo-Bordonada MA, Brotons CA, Alvarez-Sala L, Armario P, Maiques A, et al. Guía europea de prevención cardiovascular en la práctica clínica. Adaptación española del CEIPC 2008. Rev Esp Salud Pública. 2008;82:581-616.
6.Working Group of the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS). Guías de la ESC/EAS sobre el manejo de las dislipemias. Rev Esp Cardiol,

ISSN: 2304-2354
Number 4, Volume 44, 2013

2011;64:1168.e1-e60. doi: 10.1016/j.recesp.2011.09.014.
7.European Society of Cardiology. HeartScore: cardiovascular disease (CVD) risk assessment and management. Disponible en: www.heartscore.org
8. Cooney MT, Cooney HC, Dudina A, Graham IM. Total cardiovascular disease risk assessment: a review. Curr Opin Cardiol. 2011 Aug 4 [Epub ahead of print].
9.Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007
10.Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the Eur opean Socie ty of Car diology (ESC). J Hypert ens. 2007;25:1105-87.
11.Barrios V, Escobar C, Murga N, De Pablo C, Bertomeu V, Calderón A, et al. Clinical profile and management of hypertensive patients with chronic ischemic heart disease and renal dysfunction attended by cardiologists in daily clinical practice. J Hypertens. 2008;26:2230-5.
12.Buitrago F, Cañón-Barroso L, Díaz-Herrera N, Cruces-Muro E, Escobar-Fernández M, Serrano-Arias JM. Comparación de las tablas REGICOR y SCORE para la clasificación del riesgo cardiovascular y la identificación de pacientes candidatos a tratamiento hipolipemiante o antihipertensivo. Rev Esp Cardiol. 2007;60:139-47.
13.Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376:1670-81.
14. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005;294:2437-45.
15.LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425-35.
16.Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ.2009;338:b2376.
17.Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments. A network meta- analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008;52:1769-81.
18.Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice: Fourth Joint.
19.Emberson JR, Whincup PH, Morris RW et al. (2003) Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: impact of regression dilution bias. European Heart Journal 24: 1719–26.
20.Seshadri S, Beiser A, Kelly-Hayes M et al. (2006) The lifetime risk of stroke: estimates from the Framingham Study. Stroke 37: 345–50.
21. World Health Organization (2002) The world health report 2002. Reducing risks, promoting healthy life. World Health Organisation. www.who.int/whr/2002/en
22.Task Force of the European Society of Cardiology and other societies. Eur J Cardiovasc Prev Rehabil. 2007;14 Suppl2:S1-113.
23.Genest], McPherson R, Frohlich], Anderson T, Campbell N, Carpentier A, eta!.2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult-2009 recommendations. Can] Cardia!.2009;25:567-79