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# Review of the 2016 European dyslipidaemia guidelines

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## Summary

In 2016 the European Society of Cardiology (ESC) published guidelines on the prevention of cardiovascular disease (CVD) in clinical practice, with sections addressing global strategies to minimise the burden of CVD at population and individual levels. A few months later in August, the 2016 ESC / European Atherosclerosis Society (EAS) published guidelines for the management of dyslipidaemias, focusing on their evaluation and treatment. The release of these guidelines was a source of great interest among clinicians, as new emergent therapies, such as proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors have been approved for the treatment of dyslipidaemias. Concurrently, the ESC/EAS produced a consensus paper in order to guide clinicians in the appropriate use of PCSK9 inhibitors for patients at high risk of CVD. These papers followed on from the extremely controversial 2013 American Heart Association (AHA) guidelines on the treatment of blood cholesterol, in which the indication for statin therapy was extended to primary prevention according to the new recommended Pooled Cohort equations. Furthermore, the concept of a low-density lipoprotein cholesterol target was withdrawn, and the intensity of statin therapy defined according to CVD risk for the patients. In this review article, we will summarise the key points, as well as the novelties of the 2016 ESC/EAS guidelines for the management of dyslipidaemias and prevention of CVD.

Key words: cardiovascular prevention; lipids; guidelines; statin; PCSK9 inhibitors

In 2016 the European Society of Cardiology (ESC) published guidelines on the prevention of cardiovascular disease (CVD) in clinical practice, with sections addressing global strategies to minimise the burden of CVD at population and individual levels [1]. A few months later, the ESC / European Atherosclerosis Society (EAS) published their guidelines for the management of dyslipidaemias, focusing on disease evaluation and treatment [2]. The release of these guidelines was a source of great interest among clinicians in the light of the recent approval of new emergent therapies, such as proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors, for the treatment of dyslipidaemias [3]. Concurrently, the ESC/EAS produced a consensus

paper in order to guide clinicians in the appropriate use of PCSK9 inhibitors for patients at high risk of CVD (in press). These papers follow the extremely controversial 2013 American Heart Association guidelines on the treatment of blood cholesterol, in which the indication for statin therapy was widened to the primary prevention setting according to the new recommended Pooled Cohort equations [4]. Furthermore, the concept of a low-density lipoprotein cholesterol target was withdrawn, and the intensity of statin therapy defined according to the patient's cardiovascular risk. The purpose of this review article is to summarise the key points, as well as the innovations, in the 2016 ESC/EAS guidelines for the management of dyslipidaemias and prevention of CVD. It does not constitute an official recommendation for clinicians, but should be read as a summary selected by the authors from the official ESC documents. The AGLA/GSLA (Swiss Society of Atherosclerosis) recommendations should be used in clinical practice for Swiss patients.

## Risk assessment recommended by the 2016 ESC guidelines

The risk assessment of CVD is recommended to guide clinicians in the selection of the most appropriate treatment, especially when a pharmacological therapy is needed in addition to lifestyle counselling. The ESC guidelines continue to recommend the use of the country-adapted SCORE system to assess a patient's 10-year risk of undergoing a fatal cardiovascular event. The estimate is based on age, gender, total cholesterol (with an optional use of data relating to high-density lipoprotein cholesterol [HDL-C]), smoking status and blood pressure. Screening for CVD should be considered in asymptomatic men >40 years old and in women >50 years old. A repeat CVD risk assessment every 5 years is recommended, more frequently for individuals with risks close to the threshold requiring drug therapy. People at very high risk are by definition those with: (1) documented CVD, defined as acute coronary syndromes (ACS), coronary revascularisation,

stroke or transient ischaemic attack and peripheral artery disease; (2) type 1 or type 2 diabetes, (3) very high levels of individual risk factors, such as familial hypercholesterolaemia or severe hypertension; (4) severe chronic kidney disease (glomerular filtration rate <30 ml/min/1.73 m<sup>2</sup>); and (5) a calculated SCORE 10% for 10-year risk of fatal CVD. Additional factors that could modify the interpretation of the SCORE risks include social deprivation, obesity, physical inactivity, psychosocial stress, family history of, or premature occurrence of, CVD, inflammatory disease, atrial fibrillation or left ventricular hypertrophy.

### LDL-C targets recommended by the 2016 ESC guidelines

The targets for low-density lipoprotein cholesterol (LDL-C) levels are summarised in table 1 and are meant to help clinicians in their choice of a pharmacological lipid-lowering agent when this is needed in addition to lifestyle counselling. The LDL-C target of 1.8 mmol/l (70 mg/dl) is still widely recommended for very high-risk patients who need drug therapy, and a 50% LDL-C reduction is recommended for those patients whose baseline LDL-C ranges between 1.8 and 3.5 mmol/l. The LDL-C target of <2.6 mmol/l is recommended for high-risk patients (SCORE 5–10%), while for patients with a moderate (SCORE 1–5%) or low (SCORE <1%) risk the LDL-C target is <3.0 mmol/l. Triglyceride measurements are indicated for risk estimation (class I, level C). The risk of CVD is increased for fasting triglyceride values >1.7 mmol/l, and drug therapy should be considered when triglyceride values are >2.3 mmol/l in high risk patients (e.g., statin as first-line treatment). HDL-C is not recommended as a therapeutic target, but is a strong independent risk factor when values are <1.0 mmol/l in men and <1.2 mmol/l in women. According to the 2016 ESC dyslipidaemia guidelines, the measurement of lipoprotein(a) [Lp(a)] levels should be considered in selected cases at high risk, such as: (1) premature CVD; (2) familial hypercholesterolaemia; (3) a family history of premature CVD and/or elevated Lp(a);

(4) recurrent CVD despite optimal statin treatment; and (5) ≥5% 10-year risk of fatal CVD according to SCORE. The risk is considered significant for Lp(a) ≥50 mg/dl, but no randomised controlled trial has yet demonstrated that the reduction of Lp(a) levels is associated with a reduction of cardiovascular events.

Neither routine assessment of circulation or urinary biomarkers, nor carotid ultrasound for intima media thickness (IMT) screening are recommended for CVD risk assessment stratification [1]. A meta-analysis has suggested that the addition of IMT to the recommended clinical risk score is not relevant for the prediction of future cardiovascular events, including in patients at intermediate risk [5]. Real-practice data will be needed to evaluate whether IMT is overused by clinicians. The use of other imaging methods, such as coronary artery calcium scoring, is more controversial. Atherosclerotic plaque detection by carotid scanning and ankle-brachial index may be considered in cardiovascular risk prediction, especially in patients with an estimated cardiovascular risk between 5 and 10% [1]. However, the documentation of preclinical CVD based on imaging, such as significant plaque on coronary angiography or carotid ultrasound, classifies patients in the very high-risk category, with need of appropriate lipid-lowering therapy [1].

### Treatment strategies recommended by the ESC guidelines

#### Population-based approach

For physical activity, smoking and nutrition, recommendations for population-based approaches are characterised by multilevel actions in: (1) governmental restrictions and mandates, (2) media and education, (3) labelling and information, (4) economic incentives, (5) schools, (6) workplace and (7) community.

#### Lifestyle

Several data suggest that a so-called Mediterranean diet is effective in improving the control of cardiovascular risk factors. To control LDL-C levels, the recommended diet favours the consumption of fruit, vegetables, wholegrain cereal products, nuts, fish, poultry and low-fat dairy products. Other recommendations include limiting the consumption of sweets, sugar-sweetened drinks, red meat, dietary saturated fat and trans fats. Bodyweight reduction and physical activity have an effect on LDL-C levels, but also on other CVD risk factors. Regarding the use of functional foods, “nutraceuticals”, no recommendation is available given the absence of strong evidence. Red yeast rice contains monacolin K, the active element of lovastatin, which

**Table 1:** Recommended treatment goals for low-density lipoprotein cholesterol (LDL-C).

Risk categories	LDL-C goal
Very high risk (>10% SCORE risk)	<1.8 mmol/l or a reduction of ≥50% if baseline is between 1.8 and 3.5 mmol/l.
High risk (5–10% SCORE risk)	<2.6 mmol/l or a reduction of ≥50% if baseline is between 2.5 and 4.9 mmol/l.
Low (<1% SCORE) or moderate (1–5% SCORE) risk	<3.0 mmol/l

has a statin-like lipid-lowering mechanism. However, the long-term safety of red yeast is not documented and its impact on cardiovascular events needs to be clarified [6].

Regarding physical activity, it is recommended for healthy adults of all ages to perform at least 150 minutes a week of moderate physical intensity, or 75 minutes a week of vigorous intensity, aerobic physical activity or an equivalent combination. Regarding smoking, it is recommended to identify smokers and provide advice on aids to stopping the habit (e.g., nicotine replacement, varenicline and bupropion).

### Statins

Statins inhibit the synthesis of cholesterol in the liver. The reduction in LDL-C levels depends on the statin type and dosage, patient compliance with the treatment and, variations in genes for both cholesterol and statin metabolism. Several randomised controlled trials and meta-analyses have shown that statin is associated with a reduction of CVD morbidity and mortality [7]. In the large Cholesterol Treatment Trialist (CTT) study, for each reduction of LDL-C of 1.0 mmol/l, the relative risk reduction was 10% for all-cause mortality and 20% for CVD mortality. The predicted CVD deaths avoided from reductions in LDL-C with statin treatment differ according to risk: the higher the baseline risk, the higher the number of deaths avoided by appropriate interventions [8]. Table 2 summarises the main steps of the decision algorithm for statin therapy. The ESC guidelines emphasise the involvement of the patient for an individualised approach to risk management and treatment decisions [2]. Statins remain the first-line therapy to lower LDL-C and triglyceride levels and the most effective lipid-lowering therapy for the reduction of CVD mortality. Statins may be responsible for raising HDL-C levels (by  $\approx$ 10%). For subjects at very high- or high-risk, the recommended decrease of LDL-C should be at least 50% (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg daily) and drug combinations should be considered if the highest tolerable/tolerated

statin dose is not sufficient. Statin-associated muscle symptoms are the most frequent side effect, but in the great majority of cases the symptoms do not fulfil criteria for the potential risk of rhabdomyolysis (creatinine kinase at least 10 times higher than the upper limit of the reference range? [9].

### Ezetimibe

Ezetimibe inhibits intestinal uptake of dietary and biliary cholesterol and has the effect of lowering LDL-C levels by 20% in monotherapy or in addition to a statin. In the IMPROVE-IT trial, (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) the addition of ezetimibe to the standard treatment with simvastatin among 18 144 patients after ACS significantly reduced the occurrence of cardiovascular events after 5 years (32.7% vs 34.7%,  $p = 0.016$ ), as well as LDL-C levels (1.8 mmol/l vs 1.4 mmol/l) [10]. The findings from the IMPROVE-IT trial support the use of ezetimibe as a second-line therapy if LDL-C target levels are not reached with maximum tolerated doses of statin

### PCSK9 inhibitors

The use of monoclonal antibodies against PCSK9 has reduced LDL-C by 60% compared with standard care (e.g., maximum tolerated statin dosage) [11]. Alirocumab and evolocumab have been approved by Swissmedic for the treatment of primary hypercholesterolaemia. The guidelines recommend that for patients at very high risk and those with familial hypercholesterolaemia who did not reach the recommended LDL-C targets with maximum tolerated dosages of statin, PCSK9 inhibitors may be considered. Although post-hoc analyses suggest that PCSK9 inhibitors might be associated with a reduction in cardiovascular events, more data are needed from appropriately powered randomised controlled trials.

### Familial hypercholesterolaemia

Familial hypercholesterolaemia is the most common genetic disease (prevalence between 1/200 and 1/500) and a common form of monogenic dyslipidaemia (95% of cases are caused by mutations of the LDL receptor, and others are due to mutations of apolipoprotein B [Apo(B)] and PCSK9) [2]. Familial hypercholesterolaemia is associated with lifelong elevated LDL-C levels causing premature cardiovascular events (<55 years of age in men and <60 years in women), and an estimated 10-fold increased risk of any cardiovascular event. Earlier recognition and treatment of familial hypercholesterolaemia can improve the prognosis. The Dutch Lipid Clinic Network classified subjects into groups with pos-

**Table 2:** Recommended steps for statin management.

1. Evaluation of the subject's total CVD risk.
2. Involve the patient with decisions on CVD risk management.
3. Identify the suitable/best/appropriate LDL-C goal for the risk level.
4. Calculate the percentage reduction of LDL-C required to achieve the goal.
5. Choose a statin with an appropriate dosage.
6. Assess response to statin and the need for titration.
7. If the highest tolerable/tolerated statin dose does not reach the goal, consider drug combinations.

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol

sible, probable and definite familial hypercholesterolaemia. The score is based on family history of premature CVD or hypercholesterolaemia, and a clinical history of premature cardiovascular events. Clinical investigations include LDL-C levels and DNA analysis. The causal mutations of probable and definite familial hypercholesterolaemia are found in 60–70% of cases. Family cascade screening is recommended when an index case is diagnosed. According to the ESC guidelines, patients with familial hypercholesterolaemia are considered by definition to be at high risk.

Treatment to lower LDL-C should be started once the diagnosis is established, since cumulative LDL-C levels increase over time. High-intensity statin therapy should be initiated in combination with ezetimibe to reach the LDL-C target <2.5 mmol/l or, if CVD is present, <1.8 mmol/l. Treatment with PCSK9 inhibitors may be considered in patients with CVD or at very high risk (e.g., high Lp(a) levels). In children with familial hypercholesterolaemia, statin therapy should be considered from 8 to 10 years of age; the LDL-C goal above 10 years is <3.5 mmol/l [2].

### Special populations and conditions specified by the ESC guidelines

#### *Gender*

ESC guidelines recommend the assessment of CVD for women >50 years old or postmenopausal with no known cardiovascular risk factors, as their risk is deferred by approximately 10 years [1]. Indications for statin therapy and LDL-C are similar to those for men [2]. As safety data covering pregnancy and breastfeeding are lacking, the use of statins and/or other lipid-lowering therapies, except bile acid sequestrants, is not recommended [2].

#### *Elderly*

The absolute number of cardiovascular events is especially high in individuals older than 65 years. However, evidence for the benefit of statins for patients older than 80 to 85 years is limited and medical decisions should be individualised. Post-hoc analysis of randomised controlled trials with statin treatment did not suggest a correlation between treatment effect and age. Treatment with a statin is recommended for older adults with established CVD in the same way as for younger patients. Main concerns are related to safety and adverse effects due to comorbidities and polypharmacy. Statin dosage should be started at the lowest level and up-titrated to achieve the optimal LDL-C levels

#### *Diabetes*

Dyslipidaemia in the metabolic syndrome is characterised by a cluster of lipid abnormalities including an increase of both fasting and postprandial triglyceride, apo(B) and small dense LDL, with low HDL-C and apo(A1). Trials specifically performed in patients with diabetes or subgroup analyses have shown the benefit of statin therapy on cardiovascular events. In all patients with type 1 diabetes, and in the presence of microalbuminuria and renal disease, statin therapy is recommended to lower LDL-C by at least 30%, irrespective of basal LDL-C levels. In patients with type 2 diabetes and CVD or chronic kidney disease, or those over the age of 40 years with one or more other CVD risk factors, the recommended target for LDL-C is <1.8 mmol/l. In all patients with type 2 diabetes, the recommended target is <2.5 mmol/l.

#### *Acute coronary syndromes*

ACS patients are considered to be very high-risk subjects, and the management of dyslipidaemia should be integrated into global risk factor management and into a well-coordinated and multidisciplinary cardiac rehabilitation programme. The initiation of high doses of statin is recommended early after admission for ACS, regardless of LDL-C values [12]. If the recommended LDL-C target of 1.8 mmol/l is not reached with the highest tolerable/tolerated statin dose, ezetimibe should be considered as an add-on 4 to 6 weeks after ACS. Pre-treatment with a high-dose statin should be considered in elective percutaneous coronary intervention or in non-ST segment elevation ACS.

#### *Chronic kidney disease*

Patients with moderate chronic kidney disease (stage 3) are considered as high-risk patients, and those with severe or terminal disease (stage 4–5 or on dialysis) are regarded as very high-risk CVD subjects. The use of statins or a statin plus ezetimibe is recommended for patients with non-dialysis-dependent chronic kidney disease. In patients on dialysis, a statin or statin/ezetimibe should be continued if they were prescribed before dialysis initiation.

#### *Transplantation*

Lipid abnormalities are common in patients after solid organ transplantation, and a global cardiovascular risk management strategy is recommended. Statins are the first-line therapy and should be initiated at low doses with careful up-titration and with caution regarding interactions with ciclosporin. Ezetimibe can be considered if the control of LDL-C is suboptimal with the maximum tolerated dose of statin.

### *Human immunodeficiency virus and autoimmune diseases*

Patients with human immunodeficiency virus (HIV) can have high levels of LDL-C and triglycerides when undergoing highly active antiretroviral treatment. HIV-infected patients have a higher risk of CVD, even after adjustment for traditional risk factors [13]. Lipid-lowering therapy (mostly statin and preferably pravastatin) should be considered for HIV patients in order to achieve an LDL-C goal of <2.5 mmol/l (for high-risk subjects). However, HIV patients have been excluded from large trials and no data are available regarding the impact of statins or ezetimibe on cardiovascular events in this population.

### **Recommended performance measurement of CVD prevention**

It is important that performance measurements are established and followed in practice in order to improve the quality of care. Adherence to the following criteria defining specific groups of patients has been recommended in the guidelines:

1. Subjects identified as tobacco users who received smoking cessation intervention
2. Subjects whose sedentary habits have been recorded and who are being counselled to increase physical activity
3. Subjects whose unhealthy diet / nutritional habits have been recorded and who are being counselled to improve their diet
4. Subjects whose weight and body mass index and/or waist circumference is documented as being above normal limits and who are being counselled on weight management
5. Subjects >40 years old with at least one lipid profile performed within the past 5 years
6. Patients <60 years old with hypertension who had a recorded blood pressure reading at their most recent visit <140/90 mm Hg
7. Patients with diabetes mellitus who had a glycated haemoglobin <7.0% at the most recent visit.
8. Patients with a cardiovascular event who have been referred to a cardiac rehabilitation programme.

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