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POSITION STATEMENT

LDL-cholesterol control in the primary prevention of cardiovascular diseases: An expert opinion for clinicians and health professionals

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Abstract *Aims:* Although adequate clinical management of patients with hypercholesterolemia without a history of known cardiovascular disease is essential for prevention, these subjects are often disregarded. Furthermore, the scientific literature on primary cardiovascular prevention is not as rich as that on secondary prevention; finally, physicians often lack adequate tools for the effective management of subjects in primary prevention and have to face some unsolved relevant

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Cardiovascular risk;
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issues. This document aims to discuss and review the evidence available on this topic and provide practical guidance.
Data synthesis: Available algorithms and risk charts represent the main tool for the assessment of cardiovascular risk in patients in primary prevention. The accuracy of such an estimate can be substantially improved considering the potential contribution of some additional risk factors (C-reactive protein, lipoprotein(a), family history of cardiovascular disease) and conditions (environmental pollution, sleep quality, socioeconomic status, educational level) whose impact on the cardiovascular risk has been better understood in recent years. The availability of non-invasive procedures to evaluate subclinical atherosclerosis may help to identify subjects needing an earlier intervention. Unveiling the presence of these conditions will improve cardiovascular risk estimation, granting a more appropriate intervention.
Conclusions: The accurate assessment of cardiovascular risk in subjects in primary prevention with the use of algorithms and risk charts together with the evaluation of additional factors will allow physicians to approach each patient with personalized strategies, which should translate into an increased adherence to therapy and, as a consequence, a reduced cardiovascular risk.

1. Introduction

The control of plasma LDL-cholesterol (LDL-C) levels is of utmost importance in both primary and secondary prevention of cardiovascular diseases (CVD) and, specifically, coronary heart disease (CHD). Therefore, physicians and all health professionals should actively manage this risk factor, either by properly identifying the patients' needs and prescribing, when appropriate, adequate therapy or by referring the patient to a specialist, e. g. a lipidologist. Interestingly, while remarkable attention is generally paid to the clinical management of LDL-C levels in patients in secondary prevention of CVD to reduce their risk of recurrent events, subjects in primary prevention are often disregarded, despite the higher absolute number of atherosclerotic cardiovascular (CV) events occurring in this much larger population [1].

On the other hand, the scientific literature on the primary prevention of CV events is not as rich as that on secondary prevention; consequently, some relevant issues are still a matter of debate, and physicians often lack adequate tools for the effective management of subjects in primary prevention.

This document aims to discuss and review the evidence available on this topic and to share with the reader the viewpoints on which consensus was found among participants of this expert panel. The document has been structured in a question-and-answer format to facilitate an agile and simple approach by clinicians and health professionals, who form its largest readership. Therefore, this paper intends to provide answers to the many issues they face in their professional activity.

Of note, heterozygous familial hypercholesterolemia (FH) will be not addressed by this document, as FH patients must be always referred to a specialized center.

2. How should I approach and evaluate a patient in primary prevention?

The approach to the patient in primary prevention must include both a detailed clinical evaluation and an estimate of his/her CV risk, to define the LDL-C goal to be reached according to published guidelines [2] and, consequently, to decide whether to start or not a specific pharmacological intervention.

A schematic summary of the anamnesis and biochemical evaluation routinely required in these patients is provided in BOX 1; the estimate of CV risk, which represents one of this document's key points, will be analyzed and discussed in detail in the following chapters.

3. How can I appraise the CV risk of my patient and use such an estimate to decide if he/she requires some LDL-cholesterol-lowering intervention and to which extent?

It is now widely accepted that estimating the individual CV risk using risk charts or algorithms is essential to properly classify patients and adopt the most appropriate therapeutic approach [2,3].

Historically, risk charts were built using a limited number of variables, i.e. the most predictive risk factors. Although limiting the accuracy of the calculation, such a decision was probably also intended to simplify and, hence, facilitate the dissemination and application of risk charts. However, this goal has not been fully reached: according to available data, risk charts use is still unsatisfactory in Europe [4]; in Italy, for example, CV risk has been estimated in less than 5% of eligible patients in the period 2014–2017 [5].

Risk charts developed within the SCORE (Systematic COronary Risk Evaluation) project represent probably the

BOX 1

Anamnesis

- Unfold the family history of hypercholesterolemia, its age of onset, concomitant pharmacological therapies or the presence of specific diseases that may impact LDL-C levels (see below), to identify any iatrogenic or secondary forms of hypercholesterolemia. Use the Dutch Lipid Clinic Network [2] score to identify individuals with a probable or possible FH, who must be referred to a specialized center.
- Investigate the presence of a family history of early coronary and/or cardiovascular events (<55y for men and <65y for women), especially in parents, children, brothers, and sisters.
- Uncover any personal or pathological conditions that may be associated with an increased cardiovascular (CV) risk, also independently from the plasma lipid profile (e.g., rheumatoid arthritis, systemic lupus erythematosus, chronic renal failure, obesity, obstructive sleep apnoea syndrome, depression, anxiety, sedentary lifestyle, social isolation, deprivation, low educational level, etc.).

Physical examination

- Assess the presence of early corneal arch and/or tendon xanthomas to identify a possible FH. Evaluate the presence of valve or vascular murmurs or weakness or absence of peripheral pulses.

Biochemical parameters determination

- Routine lipid profile includes the determination of plasma total cholesterol, triglycerides (TG), and HDL-cholesterol (HDL-C) concentrations. LDL-C can be either measured directly or estimated indirectly using the Friedewald equation (or its variants) for TG values <400 mg/dL; non-HDL-cholesterol (non-HDL-C) can be calculated as the difference between total cholesterol and HDL-C. TG need to be measured in a fasting state (for at least 12 h). ApoB plasma levels can be measured to assess the burden of all atherogenic apoB-containing particles.
- C reactive protein (CRP) should also be determined, using a high-sensitivity technique (hs-CRP), at a sufficient distance from any inflammatory or infectious disease, to improve CV risk stratification.
- As ~90% of Lipoprotein(a) [Lp(a)] levels are genetically determined and do not vary with age, it is recommended to measure the levels of Lp(a) at least once in a lifetime [2].
- To ascertain or exclude the presence of secondary forms of hypercholesterolemia, it is recommended to evaluate glycaemia and indicators of renal (creatinine and proteinuria), thyroid, and hepatic function.

best available tool, nowadays, for estimating a patient's CV risk in Europe [2]. SCORE-2 is now available as an updated algorithm tailored to European populations, which predicts 10-year risk of first-onset CVD, including either fatal or non-fatal events (in contrast with SCORE which provided CVD mortality only) [3]. On the other hand, risk charts can and should be improved [6] and rapidly increasing evidence suggests that additional factors, that are not included in current risk charts or algorithms, might improve the CV risk estimate. It is the opinion of this panel that some of these factors should now be integrated into the risk estimation process. Some candidate additional risk factors will be discussed in the next sections of the document.

4. Do HDL-C concentrations still play a role in risk estimate and the clinical management of patients at risk of CVD?

A large number of epidemiological studies reported an inverse correlation between plasma levels of HDL-C and CV risk, leading to the hypothesis that increasing HDL-C would have translated into some CV benefit [7]. Recent observational studies, however, have shown that this inverse relationship exists only up to HDL-C levels of 70–90 mg/dL and that not only higher HDL-C concentrations do not confer any additional CV protection, but, conversely, they might be associated with an increased risk of all-cause mortality, CV mortality, infections, and dementia in the general population [8–11]. In addition, randomized clinical trials with drugs aimed at substantially increasing HDL-C levels failed to show any CV benefit [12–15]. Therefore, HDL-C is not included in the secondary goals in current guidelines, which, however, recommend including HDL-C levels in the risk chart-guided CV risk estimation [2].

5. Are there additional risk factors which could be included in my patient's risk estimation?

Current guidelines recommend measuring apoB and non-HDL-C for risk assessment in people with high triglycerides (TG) levels, diabetes mellitus, obesity, metabolic syndrome, or very low LDL-C levels [2]. The assessment of apoB offers a more accurate measure of atherogenic apoB-containing lipoprotein particle number than the mere determination of LDL-C levels; non-HDL-C level, easily available at no additional costs, also provides useful information. Their contribution to risk determination, on the other hand, is similar to that provided by the determination of LDL-C, which apoB will probably soon replace. In the current guidelines' context, essentially based on the evaluation of LDL-C and its treatment, it is consequently difficult to imagine a prompt translation of the determination of apo B and non-HDL-C to clinical practice.

Additional [modifiable or non-modifiable] risk factors might improve the estimation of an individual's CV risk. Among them, available evidence suggests that the presence of a family history of premature CV events (<55y in men and <65y in women), elevated levels of lipoprotein(a)

[Lp(a)], and elevated levels of C-reactive protein may significantly enhance the accuracy of CV risk prediction.

Family history of premature CVD. A positive family history of CVD is associated with an increased CV risk [16,17]. When it involves first-degree relatives, a roughly two-fold increase in the risk for CVD is observed [18]. Positive CVD family history may also impact the relevance of specific diet-associated risk factors [19]. Nowadays, the assessment of the family history of premature CVD and its possible contribution to the patient CV risk is often left to the physician's evaluation [20].

Lipoprotein(a). Lp(a) is an LDL-like lipoprotein, in which apoB is covalently linked to apolipoprotein(a) [apo(a)] [21]. Lp(a) combines the ability of LDL to infiltrate the arterial wall, contributing to the formation of atherosclerotic plaques, with a pro-thrombotic effect attributable to the structural analogies of apo(a) with plasminogen [22]. Lp(a) levels are largely genetically determined ($\sim$90%, except in renal failure, which causes an acquired increase in Lp(a) levels) and guidelines recommend considering an Lp(a) measurement at least once in a lifetime. Lp(a) evaluation also helps identifying individuals with very high levels of Lp(a) (>180 mg/dL), who have a CV risk comparable to that conferred by FH [2]. The risk of myocardial infarction and calcific aortic valve stenosis is significantly increased for Lp(a) levels $\geq$30–50 mg/dL [23]. To date, its measurement is only aimed at better stratifying individual CV risk, but accumulating evidence suggests reducing its plasma concentrations as a secondary goal of CV prevention.

High sensitivity-C reactive protein (hs-CRP). Hs-CRP is a marker of inflammation, a process playing a crucial role in the pathogenesis of atherosclerotic CVD [24]. Although the association between hs-CRP and CVD is unlikely to be causal [25], a large body of evidence supports the use of hs-CRP in primary prevention to drive therapeutic decision-making, with values >3 mg/L indicating a significantly higher relative CV risk [16,26].

Non-conventional CV risk factors. The possible contribution of non-conventional factors (also referred to as non-metabolic risk factors) to CV risk has recently emerged; these risk factors include, among many others, high air pollution, high psychosocial stress level, low sleep quality, and low socio-economic level. Although some of them are theoretically modifiable, proof that any intervention that favourably modulates one of these factors also favourably influences the CV risk is largely missing. Furthermore, the precise quantification of their contribution to CV risk is still a matter of debate.

- *Air pollution* is a recognised risk factor for CVD, and fine particulate matter <2.5 μm diameter ($PM_{2.5}$) is the most important environmental risk factor contributing to global CV mortality and disability [27,28]. CV mortality is doubled when $PM_{2.5}$ exceeds 15 $\mu g/m^3$ according to a recent large cohort study performed in Europe [29].
- *Psychosocial stress* and *stress conditions* are independently associated with CVD in a manner that depends on the degree and duration of stress as well as the individual response to a stressor. Clinical guidelines are only now starting to recognize psychosocial stress as an independent CVD risk factor, probably because this condition is difficult to be clinically assessed and the biological mechanisms beyond this association are incompletely understood. Their role, on the other hand, is increasingly acknowledged [17,30], and the increase in CV risk associated with their presence falls within the range 1,3–2,1 according to a recent AHA statement [31].
- Several prospective studies and meta-analyses have shown that *insomnia* and *other sleep disorders* are associated with an increased risk of hypertension, myocardial infarction, heart failure, arrhythmias, and CVD risk and/or mortality [32,33]. A healthy sleep pattern is associated with a roughly one-third reduction of CV endpoints [34]. Furthermore, sleep-disordered breathing is common in people with, or at risk of, CVD, including obese individuals, or subjects having hypertension, CHD, heart failure, or atrial fibrillation [35,36].
- The contribution of social determinants of health, as best represented by *socioeconomic status* (SES), to CVD risk is incompletely understood. Low SES, on the other hand, has been linked to the development of CVD [37] and may confer a CV risk equivalent to traditional risk factors. The increased burden of CVD in people with low SES can be ascribed to several biological, behavioural, and psychosocial risk factors that are more prevalent in disadvantaged individuals [38]. Only a small part of the risk excess observed among persons with low SES, on the other hand, can be explained by lifestyle characteristics [39].

It is the opinion of this panel that information on these risk factors (presence/absence, level, intensity) should be obtained during the preliminary evaluation of the patient. This information may be used to further improve the CV risk estimate, as will be discussed later.

6. Are there genetic markers that I can use as tools to improve the CV risk estimation of my patient?

Molecular genetics and pharmacogenetics can play a key role in the diagnosis, prevention, and treatment of CVD. In the last two decades, considerable progress in this area has taken place, with new genes and their variants (often single nucleotide polymorphism) being identified as causally involved in atherogenesis and CVD development. Some of these data can already theoretically be used to improve CV risk estimation or predict the response to a drug [40,41]. The complexity of gene-gene, gene-environment, and gene-drug interactions can, on the other hand, substantially modify the impact of a gene on CV risk [19].

Molecular genetics also allowed for the identification of a large number of gene polymorphisms causally associated with the onset of CVD, which have been used to develop genetic scores representing a valuable tool for screening, diagnosis, and therapy in a single patient [42]. These

scores may play an important role also in the primary prevention of CV events [43]; their application in clinical practice is, however, still difficult, both in terms of costs and interpretation of the results.

Currently, obtaining accurate information on the family CVD history can be approximatively as informative as a risk assessment based on the best available genetic information [44]; indeed, the use of genetic scores may prove preferable to assess the CV risk in the near future.

7. Should cumulative exposure to LDL-C be considered a more reliable parameter than the current LDL-C value for the evaluation of the CV risk of my patient?

In recent times, attention has been drawn to the concept of cumulative exposure to LDL-C, i.e. the combination of LDL-C levels (but also other apoB-containing lipoproteins) and the duration of exposure, which can be roughly approximated by multiplying an individual's age by his average LDL-C level [45]. This estimate of cumulative LDL-C exposure is believed to represent a better indicator of the total extent of vascular injury caused by hypercholesterolemia rather than any single LDL-C level evaluation. The area under the LDL-C curve, thus, is likely to be also a good marker of the total plaque burden. A higher area under the curve accumulated earlier in life significantly increases the risk of experiencing CV events at a younger age and is driven by the levels of LDL-C [45].

Despite its potential relevance, this parameter is hard to be incorporated into the classic risk estimate based on LDL-C, as it requires several measurements over a significantly long time, which could be difficult to obtain in clinical practice. So far, paying attention from early in life to LDL-C levels, and their control when appropriate, is likely to be the most effective approach.

8. Can a non-invasive assessment of the arterial circulation status play a role in the assessment and management of my primary prevention patient?

Plaque progression, and possibly rupture or erosion, are modifiable steps in the evolution of atherosclerotic plaque, suggesting the importance of identifying subjects with subclinical atherosclerosis before they experience a clinical event [46]. The non-invasive assessment of subclinical atherosclerosis in individuals at intermediate CV risk may have the greatest impact since any therapeutic interventions could be started earlier when atherosclerotic vascular damage is identified.

Subclinical atherosclerosis can be detected with cost-effective procedures, such as carotid and abdominal ultrasound, but also using other diagnostic tools, including coronary artery calcium (CAC) scoring and coronary computed tomography angiography (CCTA) [47]. Several studies have shown that the presence of subclinical atherosclerosis negatively affects the clinical prognosis [46,48], and have suggested considering it as a marker of increased CV risk rather than simply local score damage [49].

The intima-media thickness (IMT) is an early indicator of carotid disease, but has a lower predictive power compared with ultrasound assessment of carotid or femoral plaque burden, as also reported in the current guidelines [2,50]. The ankle-brachial index does not offer relevant information in addition to that provided by a complete physical examination [51].

CAC is a highly accurate marker of CHD and is a powerful tool for predicting CVD in asymptomatic individuals [52,53], with subjects having any positive CAC value (particularly >100) showing a significantly increased risk of CHD. The evaluation of CAC may improve the patient classification, which may be particularly relevant for those classified as having intermediate CV risk [54]. CCTA is the method with the highest accuracy in detecting CHD and may represent an effective approach also for stratifying the risk in asymptomatic individuals [55–57]. However, its potential a large-scale use raises issues regarding the complex interplay between costs, risks, and benefits.

Based on the available evidence, current guidelines state that arterial plaque burden evaluated by ultrasonography should be considered as a risk-modifier in individuals at low or moderate risk and that CAC score assessment may be considered a risk-modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk [2].

9. Taking for granted the LDL-C goals recommended by the current ESC/EAS guidelines for each CV risk level, can I ascertain whether my patient is at a further increased CV risk and requires a more aggressive approach?

The available evidence indicates that a positive CVD family history, elevated Lp(a), elevated hs-CRP, the presence of non-conventional risk factors, and the presence of subclinical atherosclerosis should be included, as risk modifiers, in the CV risk estimate for individuals in primary prevention. Based on this, this panel advises the following:

- In the presence of at least two additional risk factors (among the following: history of premature CVD in at least two family members, Lp(a) >50 mg/dL, hs-CRP >3 mg/L) the level of CV risk calculated using SCORE algorithms is highly likely to be underestimated, and the subject should be reclassified in the next higher risk class category (with a correspondingly lower LDL-C goal).
- Physicians may consider the possibility of increasing the level of CV risk detected by the SCORE algorithms also in the presence of one or more non-conventional risk factors (among the following: pollution, stress, sleep disorders, socio-economic status) when the severity of the identified risk factor(s) is considered high, and a significant contribution to the patient's CV risk is envisaged.

The increase of the risk level identified by SCORE risk charts can take place only once, even if both the previously described criteria are met. Patients with diabetes, already at high CV risk, should not have their risk revised.

The panel also suggests that the use of vascular imaging investigations and/or CAC should be decided by the clinical evaluation of the physician, who will have to pay particular attention to "intermediate" risk subjects and consider the cost-benefit ratio (including radiation exposure for CAC determination). The detection of atheromatous plaques classifies the patient at high CV risk, as suggested by the ESC/EAS guidelines [2].

10. Does my patient require specific management of his/her CV risk if he/she belongs to specific population subgroups?

10.1. Women

Although sex-specific risk factors are associated with increased CV risk in women [58], elevated LDL-C is a causal CV risk factor in both genders [59]. Women have historically been underrepresented in clinical trials, but several meta-analyses have unequivocally shown that lipid-lowering interventions significantly reduce the CV risk in women [60–63].

Menopause is associated with a progressive increase in LDL-C, as well as changes in other lipid parameters (increase in total cholesterol, apoB, and TG, and decrease in HDL-C), with a lipid profile generally more atherogenic than in pre-menopausal women [64].

This panel recommends treating elevated LDL-C in both sexes, when the global CV risk is comparable, in a similar way.

10.2. Older people

Hypercholesterolemia is a risk factor for CVD in primary prevention at all ages; however, the relative risk of CHD associated with elevated plasma cholesterol levels, in primary prevention, declines in older patients; in some observational studies, as a consequence, elevated plasma cholesterol levels are not associated with increased risk of incident CHD in people >80 years of age in primary prevention [65,66], whereas one study showed a significant association up to 100 years of age [62]. On the other hand, the absolute CV risk increases constantly with age, supporting the concept of cumulative LDL-C burden over time even in individuals in primary prevention: the absolute benefit of cholesterol-lowering therapies, consequently, is potentially larger in the elderly.

Data from clinical trials are not conclusive: a meta-analysis of data from 28 clinical trials observed less clear evidence of benefit among patients >75 years of age without evidence of established vascular disease [67], while another meta-analysis did not observe differences in the protective effect of statin treatment in patients <75 or >75 years of age [63].

The frequent presence of co-morbidities in older people, often needing drug treatments that may increase the chance of pharmacological interactions or side effects, or that can limit the residual life expectancy, or its quality, must also be considered.

This body of evidence suggests that any intervention aimed at controlling LDL-C levels in patients >75–80 years of age should take carefully into account risks and benefits, as well as individual preferences so that the intervention can fit the needs of the specific patient who is being considered.

Elderly patients already taking a cholesterol-lowering treatment should continue the therapy.

10.3. Hypertensive patients

High blood pressure and dyslipidaemia often coexist in the same individual [68]. Hypertensive patients have a higher prevalence of dyslipidaemia than matched normotensive subjects [69]. At the same time, hypercholesterolemic patients often have higher blood pressure values than normocholesterolemic individuals [69]. Beyond the epidemiological association, each of the two conditions represents a risk factor for the development of the other.

Based on these observations, hypertensive patients (often suffering from metabolic syndrome) should be treated with drugs having a neutral effect on their lipid profile, thus preferring, whenever possible, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, and dihydropyridine calcium channel blockers rather than beta-blockers and thiazide diuretics [70].

The evidence supports an additive effect of statins and antihypertensive drugs in reducing CV risk [71]; the increasing use of combination therapies will allow for better control of several CV risk factors, and ultimately a significant reduction in major CV events.

10.4. Patients with diabetes

In diabetic patients, complex alterations of the lipid profile (hypertriglyceridemia, low HDL-C) are often recorded; nevertheless, LDL-C is the primary target of lipid-lowering therapy in these patients [2]. Achieving recommended LDL-C goals in patients with diabetes is at least as important, for CV prevention, as optimal glycaemic and blood pressure control [72]. Diabetic patients should have checked their lipid profile (total cholesterol, LDL-C, HDL-C, and TG) at least once a year, or even more frequently if the therapeutic goals are not achieved and require adjustments to their therapy.

10.5. Patients <40 years of age (excluding FH patients)

The CV risk of people under age 40 cannot be estimated through the commonly used risk charts and algorithms; this is a problem in terms of CVD prevention in young individuals, also considering that they represent a large proportion of the population. Reducing LDL-C levels earlier in life, on the other hand, can significantly reduce the cumulative LDL-C burden, slowing the progression of atherosclerosis [45].

This panel recommends that physicians decide to adopt or not interventions aimed at reducing LDL-C levels in

these subjects based on their CV risk profile, which should be estimated taking into account both the presence of factors included in the risk charts and additional risk factors discussed above.

Any intervention should be discussed with the patient to increase his/her awareness (particularly for long-term interventions) and might consider the use of nutraceuticals or functional foods as an alternative to drug use [73].

11. How can I manage LDL-C levels, once I have estimated my patient's CV risk?

All individuals should adopt healthy lifestyle habits, regardless of their LDL-C levels (see below). Any intervention with nutraceuticals, functional foods or lipid-lowering drugs, on the other hand, must be calibrated based on the individual distance from the LDL-C target, that is, on the extent of LDL-C reduction required to achieve the recommended goal.

An estimate of this parameter (the distance from the target, DfT) can be obtained by the following, simple calculation:

DfT = (basal LDL-C minus defined LDL-C target)/basal LDL-C

A diagnostic-therapeutic flow chart for individuals >40-year-old is presented in Fig. 1.

12. Dietary approach and promotion of an active lifestyle: what can I reasonably expect for my patient?

The available evidence indicates that an appropriate dietary approach has a favourable yet generally limited impact on total cholesterol and LDL-C plasma levels [74]. Usually, the achieved reduction is ~5%, and only rarely it exceeds 10%. Reducing the consumption of foods rich in saturated or *trans*-unsaturated fatty acids, and increasing the intake of dietary fibre and linoleic acid, a polyunsaturated fatty acid of the omega-6 family, are considered the most effective interventions. Reducing dietary cholesterol appears to be less relevant.

Interestingly, epidemiological studies have shown that not all dietary interventions with a cholesterol-lowering effect are associated with a reduction in CV risk; this has been observed, as an example, for the reduction of dietary saturated fatty acids, especially if derived from dairy foods [75]. An appropriate diet, on the other hand, is expected to play a cardioprotective role largely exceeding its possible effect on LDL-C levels. Increasing the consumption of plant foods rich in fibre and polyphenols (fruit, oily nuts, vegetables, and legumes), marine foods rich in polyunsaturated omega-3 fatty acids, whole cereals rich foods, and seeds likely plays an important role [76], together with reducing the consumption of foods of animal origin, such as meat and derivatives, whose contribution to diet-associated deaths is, however, rather limited. The Mediterranean

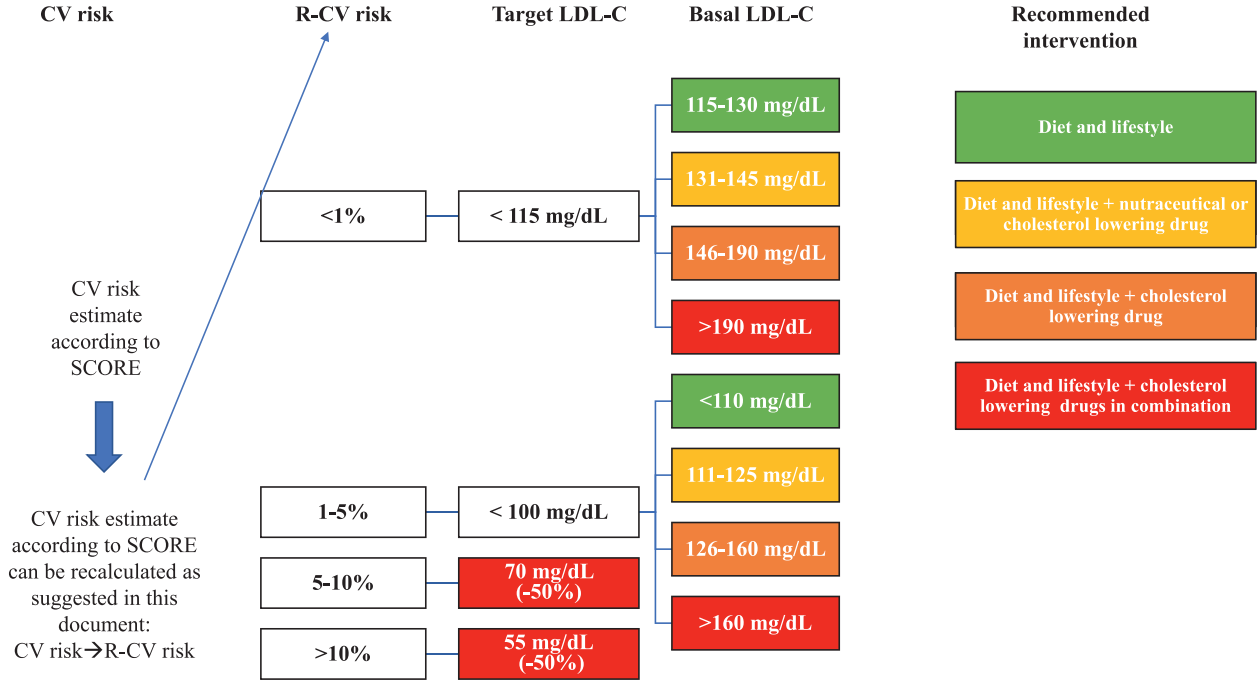

Figure 1 Suggested treatment flowchart for subjects in primary prevention >40 years of age. The target value for the subject's LDL-C can be set after calculating the cardiovascular risk based on SCORE, and modifying it based on the risk factors to be considered according to this document. Appropriate treatment to reach this target can then be selected based on the distance between the baseline LDL-C value and the defined target. The effect of the intervention should be evaluated after about eight weeks; in the presence of an unsatisfactory result, the next level of intervention can be considered.

food pattern has been associated with a significant reduction in the risk of CVD [77].

Based on these observations, this panel suggests that an appropriate diet should be advised to all patients in primary prevention; if a specific need to reduce plasma LDL-C emerges during the clinical evaluation of the patient, nutraceuticals or functional foods or drug therapy should be considered [73].

The impact of an active lifestyle on lipid profile is generally limited to a modest increase in HDL-C. No significant LDL-C reduction is usually observed. An active lifestyle, however, is associated with a reduction in coronary and CV risk, an effect likely independent of changes in lipid profile and must, therefore, be convincingly promoted [78].

13. When should I consider suggesting a nutraceutical or a functional food with cholesterol-lowering properties to my patient?

Nutraceuticals and functional foods containing active ingredients, or combinations thereof, with well-documented LDL-cholesterol-lowering efficacy, are largely available in western Europe markets. A summary of the effects of the main active ingredients of available nutraceuticals and functional foods on LDL-C levels is presented in Table 1.

It needs to be acknowledged that data showing that the use of these compounds can effectively prevent CVD events are currently limited [79]. Only one randomized placebo-controlled intervention trial conducted in China with a red yeast rice supplement reported reductions in CV event incidence and mortality from any cause in a population of patients in secondary prevention [80]. However, as the causal role of LDL-C in atherogenesis is unequivocally established, it is reasonable to anticipate a CV benefit from their use.

The use of red yeast rice-based products is now allowed in the European Union for a monacolin K (a naturally occurring statin) content <3 mg/day [81], due to a few cases of severe adverse events associated with their use [82]. These rather rare events probably occurred because these supplements can be used without any medical supervision, which is, on the opposite, of the utmost importance. Nutraceuticals and functional foods with cholesterol-lowering effects are indeed generally characterized by excellent tolerability.

Table 1 Expected LDL-C reductions with the most commonly used cholesterol-lowering nutraceuticals and functional foods.

	Expected LDL-C reduction
Red yeast rice, titrated <3 mg in monacolin K/Ka	10–20%
Phytosterols/phytostanols	8–12%
Oat fibre	8–12%
Lactobacillus *spp.*	5–8%
Berberine	10–15%
Polyphenolic fraction of bergamot	10–12%
Artichoke standardized extract	10–12%

Modified from Cicero AFG et al., 2017 [101].

The decision to suggest these products to control LDL-C levels in primary prevention patients can be made by the clinician in specific conditions [83]. These compounds can be considered for the management of mild-to-moderate hypercholesterolemia in patients with slightly increased CV risk and LDL-C levels not far from the recommended goal (in whom, in other words, reductions up to 20% are needed to achieve the LDL-C goal), who are not eligible for a cholesterol-lowering drug prescription. In subjects under age 40, in whom common algorithms and risk charts cannot be used to estimate CV risk, the use of nutraceuticals or functional foods may be a valuable tool for reducing LDL-C levels (and, thus, the cumulative LDL-C burden) when CV risk is clinically estimated to be increased. These products can also be used in statin-intolerant subjects in primary prevention, taking into account that they could experience myalgia even with supplements containing red yeast rice.

Advising the use of a red yeast rice food supplement as an alternative to statin therapy in patients unwilling to take these drugs for personal reasons may indeed help to start a treatment the clinician may consider mandatory; such approach, on the other hand, should be considered cautiously, since it is conceptually and intrinsically controversial, and is largely dependent on the relationship physician-patient.

The use of a cholesterol-lowering a nutraceutical or functional food combined with cholesterol-lowering drugs can be considered for those with a larger distance from their LDL-C therapeutic goal. Adding a red yeast rice supplement to a statin is not advised. Nutraceuticals and functional foods with LDL-cholesterol-lowering activity should never substitute drug treatment in patients with high or very high CV risk [84].

14. When should I suggest a cholesterol-lowering drug (or an association thereof) to my patient?

Statin therapy represents the most consolidated therapeutic option to reduce CV morbidity and mortality by reducing LDL-C, both in primary and secondary prevention [2,85–87]. The well-known efficacy, safety, and side effects profile of these molecules have been the subject of systematic reviews which can be referred to obtain more detailed information [88,89].

Statins reduce LDL-C by 20–40%, depending on the molecule and the dose, allowing the physician to reasonably predict the LDL-C reduction which will be obtained. Side effects often attributed to statins (especially myalgia) are much less frequent than usually perceived by the public [89].

All these molecules have long been out of patent, and their costs have consequently been reduced significantly, increasing also the economic advantages both in terms of expenditure for the national health systems and the prevention of CV events. Despite all these considerations,

lipid-lowering therapy is underutilized in patients both in primary and secondary prevention in the real world [90].

Strategies involving the use of a combination of different cholesterol-lowering drugs may represent an essential therapeutic option for reducing LDL-C when CV risk is very high. Combining statins and ezetimibe, and eventually an anti-PCSK9 monoclonal antibody, offers relevant opportunities both in terms of appropriateness and personalization of therapy. New compounds such as bempedoic acid [91] and inclisiran [92] will increase the number of possible therapeutic alternatives.

Table 2 reports the expected LDL-C reductions with all the available cholesterol-lowering therapies, either as monotherapy or combination therapy [2], even in primary prevention patients. In subjects with a distance between the baseline LDL-C values and the appropriate therapeutic goal over 50%, the achievement of the goal with a statin monotherapy is unlikely, even at full dosage; thus, it would be reasonable to initiate therapy with a statin-ezetimibe combination. Such an approach, recently supported by the results of a large randomized clinical trial [93], is unfortunately in formal disagreement with administrative guidelines in countries such as Italy [94]. For patients with high or very high CV risk, besides reaching the LDL-C goals, guidelines recommend also an at least 50% reduction in LDL-C from baseline [2], which, again, is generally achievable exclusively with combination therapies; the adoption of this strategy might avoid delay in the achievement of the recommended goals.

There is no indication for cholesterol-lowering adjustments in patients achieving very low LDL-C levels (~25 mg/dL) since no convincing evidence of harmful effects of such very low levels has been reported.

15. How can I optimize the adherence to therapy of my patient?

Therapeutic adherence and persistence are key factors for the success of all drug therapies. The benefits in terms of CV protection of cholesterol-lowering treatments depend not only on the extent of LDL-C reduction but also on compliance with the prescriptions. Medication possession ratio and proportion of days covered by therapy ≥80% are considered indicators of an optimal level of adherence.

Several studies have shown that inadequate therapy adherence and persistence increase morbidity and mortality from a wide variety of diseases and, at the same time, significantly increase health costs [95,96]. The absolute effect of good vs. bad compliance to statin therapy in terms of prevented CV events can be quite large, especially in high-risk persons [97]. So far, adherence to therapy with cholesterol-lowering drugs is still unsatisfactory [98,99]. For example, in most studies involving patients who had received a statin prescription, 25%–50% of new users discontinue therapy during the first year, with a trend worsening over time, especially among subjects in primary prevention, showing an adherence rate of only 25% after two years.

Table 2 Expected LDL-C reductions with different lipid-lowering approaches.

Treatment	Mean LDL-C reduction
Moderate-intensity statin	~30%
High intensity statin	~50%
High intensity statin + ezetimibe	~65%
PCSK9 inhibitor	~60%
PCSK9 inhibitor + high intensity statin	~75%
PCSK9 inhibitor + high intensity statin + ezetimibe	~85%

Modified from Mach F et al., 2019 [2].

Non-adherence to drug treatment is a complex phenomenon, determined by the interaction of different causes, which may depend on the patient, the doctor, and/or the organization of the health system.

Patient-dependent causes (usually the most relevant) range from simple forgetfulness to a negative attitude toward drugs, preconceived beliefs about health and drug treatments, and emotional distress [100]. Poor understanding of drug benefits and concerns about drug-related adverse events may further contribute to the lack of compliance. Hypercholesterolemic patients commonly have additional risk factors or vascular diseases, thus leading to the prescription of multiple drugs and frequent administrations per day. The complexity of the regimens and administration schedules may limit the effective management of chronic diseases, including hypercholesterolemia. Any effort to simplify therapeutic schemes by accurately indicating the importance of the various ongoing therapies can improve adherence.

The efficacy of lipid-lowering therapy significantly influences adherence to therapy: the achievement of favourable results during the first weeks of therapy may play an important role in determining long-term adherence. However, the need for several clinical checks and even more the need for many posology or drug corrections may represent an obstacle to adherence.

Indeed, there are no definite solutions to increase the patient long-term adherence to therapy. The most satisfactory solutions require cooperation between the physician and the patient (so-called concordance), by sharing the importance of treatment, establishing goals for therapy, and identifying factors that can negatively affect adherence.

Since the costs of nutraceuticals and functional foods need to be paid for by patients, and since their use will usually be long-lasting, patients must be advised of the potential financial impact of their use.

16. Conclusions

Adequate clinical management of patients with hypercholesterolemia in primary prevention is of utmost importance for CVD prevention.

Except for patients with FH (whose high or very high CV risk is established by definition), the estimate of CV risk, using the available algorithms and risk charts, is the first step of patients' evaluation in primary prevention. This panel believes that the accuracy of such an estimate can be improved, even quantitatively, by considering the potential

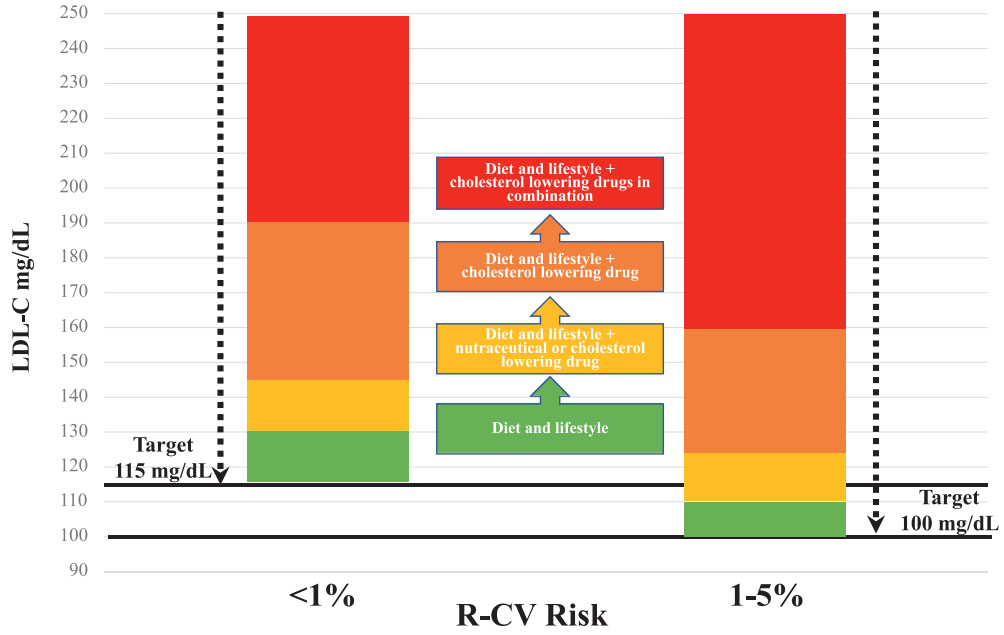

Figure 2 Graphic representation of the different cholesterol lowering interventions that can be adopted in subjects with low or moderate cardiovascular risk (calculated according to this document's proposal, R-CV Risk), depending on the basal LDL-C levels and the expected response to suggested treatments. In high risk patients (target 70 mg/dL, with a reduction from basal LDL-C level $\geq$ 50%) diet and lifestyle changes and a cholesterol lowering drugs combination are usually needed.

contribution of some modifying risk factors (hs-CRP, Lp(a), family history of CV events), as well as other conditions (environmental pollution level, sleep quality, socioeconomic status, educational level) whose impact on the CV risk has been studied in recent years. Unveiling the presence of these conditions will allow for obtaining a more accurate risk estimate, a better stratification of the individual CV risk, and a more appropriate and probably more effective intervention.

Based on the level of CV risk, the recommended LDL-C goal can be identified and the distance from that goal can be calculated, allowing the physician to adopt the most appropriate intervention, which can include a general improvement in lifestyles, the use of nutraceuticals and functional foods when indicated, or the initiation of pharmacological cholesterol-lowering therapy (Fig. 2).

Rapid achievement of therapeutic goals using the most appropriate therapeutic prescriptions can positively affect also adherence to therapy, in turn leading to the expected reduction in the incidence of CV events.

Author contributions

AP, ALC, AC, EM and JPW prepared the outline and the first draft of the document; all authors wrote parts of the document, read, reviewed, and approved the final manuscript.

Declaration of competing interest

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