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Review article

Lifestyle interventions and nutraceuticals: Guideline-based approach to cardiovascular disease prevention

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HIGHLIGHTS

- LDL-C reduction is associated with reduce cardiovascular (CV) disease risk.
- Lifestyle interventions are the primary strategy for reducing CV risk.
- Nutraceuticals are included in EU guidelines as lifestyle interventions.
- Meta-analysis of RCTs showed that nutraceuticals improve lipid profile.
- Nutraceuticals may be considered in specific patient groups.

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ABSTRACT

Lowering low-density lipoprotein cholesterol (LDL-C) levels is associated with a well-documented reduction in cardiovascular (CV) disease (CVD) risk. Current guidelines and literature support lifestyle interventions as the primary strategy for reducing CV risk. Association of dietary modifications (such as the Mediterranean diet), physical activity and the cessation of smoking with reduced CV morbidity and mortality has been evidenced. Where lifestyle interventions are not adequate for lowering LDL-C levels and CV risk, pharmacological therapies, most commonly statins, may also be considered. The benefits of lifestyle and pharmacological interventions in the prevention of CVD are widely known, but poor adherence and persistence to these necessitate an approach that aims to improve LDL-C lowering for CVD prevention.

Nutraceuticals (targeted functional foods or dietary supplements of plant or microbial origin) are included in EU guidelines as lifestyle interventions and may provide an additional approach to controlling LDL-C levels when a pharmaceutical intervention is not (yet) indicated. However, among different nutraceuticals, the level of clinical evidence supportive of efficacy for lipid lowering needs to be considered. Meta-analyses of randomised clinical trials have demonstrated that some nutraceuticals (e.g. red yeast rice and berberine) and some nutraceutical combinations improve lipid profiles, including lowering of LDL-C, total cholesterol and triglyceride levels. Therefore, nutraceuticals may be considered in specific patient groups where there is appropriate evidence to support the efficacy and safety.

1. Introduction

Cardiovascular (CV) diseases (CVDs) are the number-one cause of death globally and remain a leading cause of morbidity [1,2]. Therefore, it is vital to assess the risk of CVDs and to understand the importance of preventing associated risk factors [2,3]. High lipid levels are a major risk factor for CVD and reductions in low-density lipoprotein cholesterol (LDL-C) are associated with significant risk reduction

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[2]. Lifestyle interventions, including dietary modifications, physical activity and smoking cessation, can reduce LDL-C levels and are the primary strategy for reducing CV risk before pharmacological intervention [2–4]. Where an alternative or adjunct to lifestyle or pharmacological interventions may be needed to lower LDL-C, nutraceuticals could provide an additional approach [5]. All of these interventions will be discussed in this review.

2. Lifestyle intervention

2.1. Dietary modifications

Modifying dietary factors, or other lifestyle interventions, may affect CV risk by influencing atherogenesis directly or through effects on plasma lipid levels, body weight, blood pressure or diabetes [2,3]. A lifetime approach to tackling CV risk is recommended and a healthy lifestyle should not only be promoted in those with an increased risk of CVD or with documented CVD, but also in healthy individuals. Treatment focuses on lowering lipids for CVD prevention, primarily LDL-C. Evidence from studies investigating the effects of lifestyle interventions, including specific dietary modifications, on plasma lipid levels are summarised in Table 1 [2].

The effects of dietary modifications and patterns on CV risk and potential CVD prevention have been investigated in observational and interventional studies [3]. For example, beneficial effects of the Mediterranean diet have been reported in many interventional studies, including the Prevención con Dieta Mediterránea (PREDIMED) trial [6–11]. The Mediterranean diet is traditionally characterised by high consumption of olive oil, fruit, vegetables, nuts, cereals and seeds; moderate consumption of fish, seafood and poultry; moderate intake of wine with meals; and low consumption of dairy products, red and processed meats, and sweets. These dietary modifications are effective in CV risk reduction for the primary and secondary prevention of CVD [2,6,8]. General dietary recommendations include consumption of wholegrain cereals, vegetables, legumes, fruit, oily fish and poultry to lower LDL-C levels and improve the lipid profile [2].

The PREDIMED trial compared the effects of the Mediterranean diet supplemented with extra virgin olive oil or nuts with a control diet in a large cohort of individuals with high CV risk. The supplemented Mediterranean diet was associated with a reduction in the incidence of a major CV event (myocardial infarction, stroke and death from CV causes). The relative risk reduction was approximately 30% when supplemented with extra virgin olive oil (hazard ratio 0.70; 95% confidence interval 0.53, 0.91; $p = 0.009$) or nuts (hazard ratio 0.70; 95% confidence interval 0.53, 0.94; $p = 0.02$) compared with the control diet (Fig. 1) [8]. The Mediterranean diet has also been associated with reversion of metabolic syndrome and reductions in the relative risk of diabetes, atrial fibrillation and malignant breast cancer [7,9–11].

2.2. Additional lifestyle interventions

Further lifestyle interventions recommended for the prevention of CVD include physical activity and cessation of smoking [2,3].

Regular physical activity reduces all-cause and CV mortality and is, therefore, an important modifiable risk factor in CVD prevention [3,12]. The Copenhagen City Heart Study followed healthy joggers over 12 years and determined an association between jogging and all-cause mortality; light and moderate joggers have lower all-cause mortality rates than sedentary non-joggers [13]. Physical activity is also important in secondary CVD prevention; lightly and moderately active patients with coronary heart disease have lower all-cause and CVD-related mortality risk compared with inactive patients [12].

Smoking is a risk factor for many diseases, including CVD. Smokers have approximately double the 10-year fatal CV risk and a 50% chance

Table 1
The effect of lifestyle interventions on lipid levels. Adapted from Catapano et al. 2016 [2].

Lifestyle intervention	Effect on lipid levels		
	Reduce TC and LDL-C	Reduce TG-rich lipoprotein	Increase HDL-C
Dietary modification			
Reduce dietary trans fat	+ + +		+ + +
Reduce dietary saturated fat or replace saturated fat with mono- or polyunsaturated fat	+ + +	+	
Increase dietary fibre	+ +		
Reduce dietary cholesterol	+		
Reduce total amount of dietary carbohydrate or replace dietary carbohydrates with unsaturated fat		+ +	+ +
Reduce intake of mono- and disaccharides		+ +	+/−
Physical activity and body weight			
Increase habitual physical activity	+	+ +	+ + +
Reduce excessive body weight	+ +	+ + +	+ +
Alcohol			
Reduce alcohol intake		+ + +	
Continue modest consumption of alcohol			+ +
Smoking			
Cease smoking			+
Nutraceuticals			
Use RYR supplements	+ +		
Use functional food enriched with phytosterols	+ +		
Use soy protein products	+/−		
Use n-3 polyunsaturated fat supplements		+ +	

Magnitude of effect	
Marked effect	+ + +
Less pronounced effect	+ +
Small effect	+
No effect	–
Level of evidence	
Multiple RCTs or meta-analyses	
Single RCT or large non-randomised studies	
Consensus of opinion of experts or small studies	

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; RCT: randomised controlled trial; RYR: red yeast rice; TC: total cholesterol; TG: triglyceride.

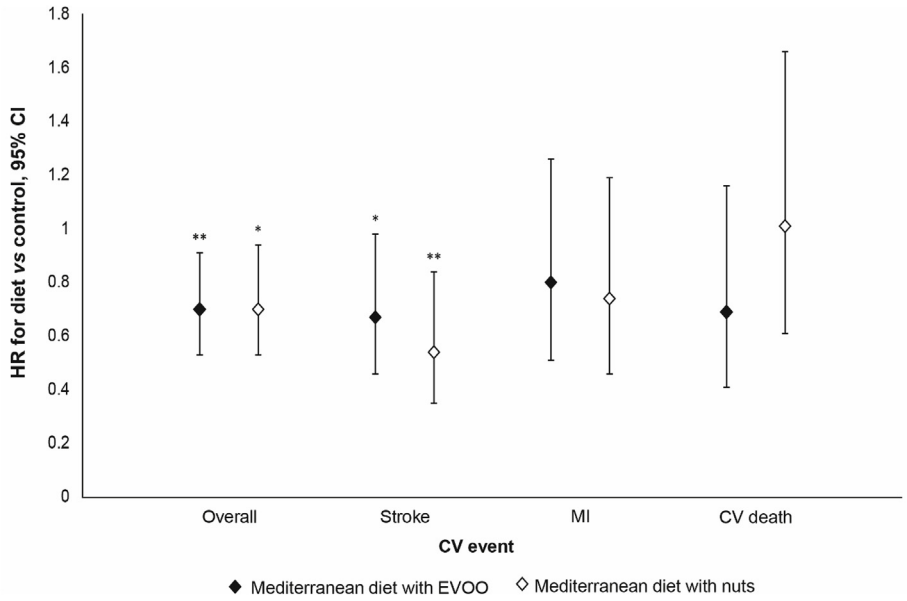

Fig. 1. The effect of a Mediterranean diet with EVOO or nuts *versus* control diet on the risk reduction of major CV events in high-risk individuals. Adapted from Estruch et al. (2013) [8].
*p < 0.05; **p < 0.01 for Mediterranean diet *versus* control diet.
CI: confidence interval; CV: cardiovascular; EVOO: extra virgin olive oil; HR: hazard ratio; MI: myocardial infarction.

of smoking-related death [3]. Cessation of smoking has well-established benefits, with a clear reduction in overall CV risk, and is the most cost-effective strategy for CVD prevention [2,3]. In patients with coronary heart disease, cessation of smoking was associated with a 36% reduction in total mortality risk [14].

Reflecting the benefits of these lifestyle interventions, 2016 European guidelines on CVD prevention in clinical practice recommend at least 150 min of moderate- or 75 min of vigorous-intensity physical activity, or equivalent, per week for healthy adults of all ages. They also recommend identifying smokers and advising smoking cessation and interventions to include professional support, nicotine replacement therapy and pharmacological therapy [3].

3. Nutraceuticals

3.1. Rationale for nutraceutical use

LDL-C is the primary treatment target for reducing CV risk [2]. A healthy lifestyle is recommended for all individuals and for high-risk patients. Where LDL-C levels are not controlled by lifestyle interventions alone, pharmacological intervention may also be considered for CVD prevention. Statins are one of the most studied pharmacological therapies for lowering LDL-C, and a wide body of evidence supports the substantial reduction in CV morbidity and mortality associated with their use [2]. Despite the known benefits of a healthy lifestyle and statin therapy, adherence remains a challenge. Poor adherence to lifestyle interventions is common and, reportedly, up to 77% of patients treated for primary prevention of CVD discontinue the use of statins within 2 years [2,4]. Increasing benefits in CVD prevention are observed with higher levels of adherence and longer persistence to LDL-C-lowering therapies [15]. This highlights the need for an attempt to improve the LDL-C-lowering approach for CVD prevention. Furthermore, mild lipid elevations are often found among subjects without a history of CVD, which fail to be controlled by lifestyle interventions but may not necessarily require the use of LDL-C-lowering therapies [3]. In these circumstances, latency in the implementation of LDL-C-lowering interventions is quite common, thus contributing to long-term exposure to mild lipid elevations and an increased lifetime CVD risk.

Nutraceuticals are targeted functional foods or dietary supplements of plant or microbial origin that can be used as an adjunctive to lifestyle interventions and pharmacological therapies to lower LDL-C levels [2,4,5,16]. Some nutraceuticals have demonstrated lipid-lowering effects; therefore, they provide a potential additional approach for CVD prevention [4]. In addition, persistence to nutraceutical therapy has been observed, possibly due to a high perceived safety for this therapeutic approach [15].

4. Nutraceuticals for hypercholesterolaemia

Nutraceuticals have been described as having benefits on the lipid profile and CV risk; the level of clinical evidence for this should be considered and Table 1 summarises some of the key nutraceuticals and their effects on the levels of specific lipids [2,5,17].

Two of the most popular nutraceuticals, red yeast rice (RYR) and berberine (BBR), have demonstrated lipid-lowering activity [4]. For centuries, RYR has been used in China as a food colouring, a flavour enhancer and in herbal medicine. In a large meta-analysis of randomised controlled trials, RYR was effective in reducing LDL-C, total cholesterol and triglyceride (TG) in patients with dyslipidaemia (Fig. 2) [4,18]. Several clinical trials have also reported the lipid-lowering effects of RYR, with reductions in LDL-C ranging from 22% to 32% [4]. One mechanism by which RYR reduces LDL-C is through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is related to the LDL-C-lowering mechanism of statins [2,4,18,19]. An isoquinoline alkaloid extracted from plants, BBR, has reported LDL-C reductions of 25% [4,5]. Meta-analyses of clinical trials demonstrated the effects of BBR on total cholesterol, TGs and high density lipoprotein cholesterol (HDL-C), as well as on LDL-C, with effects in patients for both primary and secondary prevention [17]. The LDL-C-lowering effect is achieved through different mechanisms, including increasing the expression of the LDL receptor and inhibiting proprotein convertase subtilisin/kexin type 9 [4,17].

The possible risks associated with nutraceuticals, including adverse events and patients replacing their normal medications without consulting a physician, should be considered. The long-term safety of nutraceuticals is not fully known, although RYR is generally reported to have a good safety profile. In clinical studies, adverse events associated with BBR were mostly gastrointestinal and were mainly observed at higher doses [4].

4.1. Nutraceutical combinations

Combination therapies containing multiple nutraceuticals aim to complement the lipid-lowering effects of each nutraceutical and reduce dose to ensure or improve tolerability [4]. RYR and BBR combinations are bioavailable and, in clinical studies, improved surrogate markers of

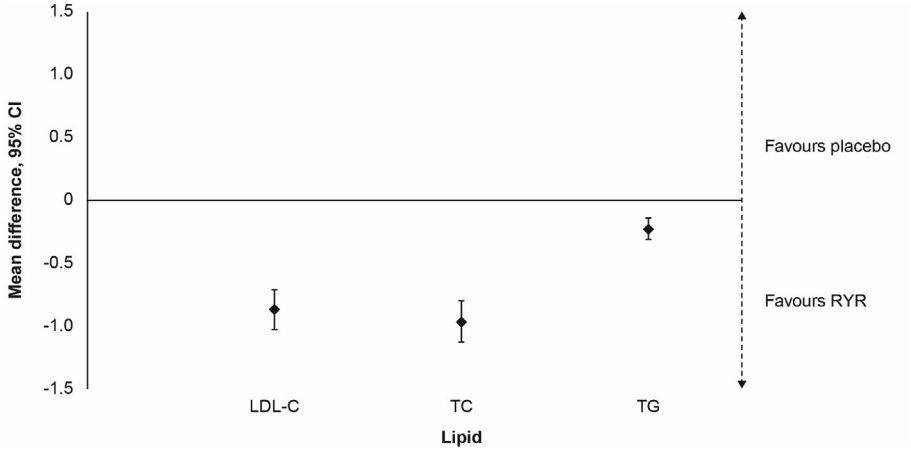

Fig. 2. The lipid-lowering effect of RYR compared with placebo. Adapted from Li et al. (2014) [18].
CI: confidence interval; LDL-C: low-density lipoprotein cholesterol; RYR: red yeast rice; TC: total cholesterol; TG: triglyceride.

CV risk and lipid profiles [19]. Furthermore, a meta-analysis of randomised controlled trials investigating a RYR, BBR, policosanol, astaxanthin, coenzyme Q10 and folic acid combination identified an overall improvement in lipid profile, with effects on total cholesterol, LDL-C, HDL-C and TGs, indicating this may be an effective potential approach [20]. Since the author's workshop, an International Lipid Expert Panel has recently recommended considering the use of nutraceuticals in some patients; in particular the nutraceutical combination of RYR, BBR and policosanol is the most evidence-based among the other clinically-investigated nutraceuticals and has proven long-term efficacy [21].

5. Conclusion

Reducing CV risk is important for CVD prevention. Lifestyle interventions and pharmacological therapies are effective approaches for reducing CV risk through effects including LDL-C lowering [2,3]. Adherence to lifestyle interventions (often dietary modifications and physical activity) can be disappointing in the long-term, particularly in view of the low persistence and modest reduction (0.16 mmol/L) of LDL-C that can be achieved [2,22]. The 2016 European guidelines take a broad approach to the concept of lifestyle interventions and include considering use of some nutraceuticals in specific patient groups. Adherence to overall lifestyle interventions may be significantly improved when an effective nutraceutical is also included [2]. In light of the overall safety and lipid-lowering efficacy of some nutraceuticals and nutraceutical combinations, along with their ability to improve some markers of vascular function, they may be considered as an additional approach for CVD prevention in specific patient groups [21]. Despite the promising evidence from clinical studies and meta-analyses, it must be highlighted that the use of nutraceuticals is not aimed at replacing more effective therapies for which current guidelines have expressed clear recommendations, and should only be considered when there is appropriate supporting scientific evidence for their efficacy and safety [2,4,5,17].

Conflicts of interest

ALC has received grants from Pfizer, Sanofi, Regeneron, Merck, Mediolanum, non-financial support from SigmaTau, Menarini, Kowa, Recordati, Eli Lilly, personal fees from Astrazeneca, Genzyme, Bayer, SigmaTau, Menarini, Kowa, Eli Lilly, Recordati, Pfizer, Sanofi, Mediolanum, Merck, Aegerion, Amgen.

VB has received fees for lectures or scientific consulting as a member of advisory boards from Amgen, AstraZeneca, MSD, Mylan, Pfizer, Recordati and Sanofi.

AFGC has received scientific consultancy fees from Meda SpA, Menarini International SpA and Pentagroup SpA.

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