Journal of Cardiology and Therapy

Online Submissions: http://www.ghrnet.org/index./jct/
doi:10.17554/j.issn.2309-6861.2018.05.141

Journal of Cardiol Ther 2018 February; 5(1): 701-706
ISSN 2309-6861(print), ISSN 2312-122X(online)

ORIGINAL ARTICLE

Clinical Efficacy of A Nutraceutical Approach for the Management of Dyslipidemia in Metabolic Disorders: A One-Year Treatment With Armolipid Plus

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Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: November 21, 2017
Revised: December 22, 2017
Accepted: December 25, 2017
Published online: February 31, 2018

ABSTRACT

AIM: Dyslipidemia plays a crucial role in the development of cardiovascular diseases. A correct lifestyle behaviour based on a balanced diet and moderate physical exercise is the first-line approach, however drug treatment (chiefly statins and/or ezetimibe) may be often needed. Among dietary supplements, so-called "nutraceuticals" are nowadays continuously proposed and frequently employed. In this paper we report our experience with a nutraceutical product largely utilized in Italy (as well as in Mediterranean area) (ARMOLIPID PLUS), based on red yeast rice, berberine, policosanol and some antioxidants, for the treatment of dyslipidemic people.

MATERIAL AND METHODS: In this open-label trial we treated with this nutraceutical 37 dyslipidemic nondiabetics and 15 dyslipidemic type 2 diabetics for 12 months, monitoring serum lipids, fasting glucose, glycated hemoglobin, blood pressure, and performing also anthropometric measurements including skinfold thickness.

RESULTS: Both in dyslipidemic and diabetic patients we observed a great (about 80-100 mg/dL) parallel decrease of total- and non-HDL Cholesterol, not justified by LDL-Ch decrease (about 37 mg/dL). Furthermore, while body weight and body mass index were not affected significantly by treatment, suprailiac skinfolds (around 6 cm) and total skinfold sum (10 cm) were heavily reduced by the nutraceutical in both groups of patients.

CONCLUSION: The present paper confirms that this nutraceutical, due to the synergistic complementary interaction between berberine and red yeast rice, is a reliable option for effective management of dyslipidemia in metabolic disorders with glucolipidic abnormalities.

Key words: Dyslipidemia; Nutraceutical; Diabetes mellitus; Red yeast rice; Berberine

Giampietro O, Masoni MC, Matteucci E, Giampietro C, Giordani S, Consani C, De Negri F. Clinical Efficacy of A Nutraceutical Approach for the Management of Dyslipidemia in Metabolic Disorders: A One-Year Treatment With Armolipid Plus. *Journal of Cardiology and Therapy* 2018; **5(1)**: 701-706 Available from: URL: http: //www.ghrnet.org/index.php/jct/article/view/2269

INTRODUCTION

Cardiovascular diseases are the leading cause of morbidity and mortality in Western countries[1-3]. Lipid abnormalities play a crucial role in the development of atherosclerosis, thus favouring the "cardiovascular pandemia"[4-6]. The incidence of coronary artery disease [CHD] is directly associated with total (T-Ch) and LDL-Cholesterol (LDL-Ch) levels, inversely with HDL-cholesterol

(HDL-Ch)[7]. LDL-Ch reduction, both in primary or secondary prevention, allows a significant lowering of cardiovascular events[8]. Indeed, recent trials[9] confirm that a greater LDL decrease obtained by pharmacological treatment (statins and/or ezetimibe) provides a more significant decrease of the cardiovascular risk[10]. The first-line strategy to modify lipid abnormalities requires the introduction of appropriate lifestyle changes[11]. A high-calorie diet, weight excess and physical inactivity significantly enhance the onset of dyslipidemia[12]. A balanced diet, including low saturated fats and cholesterol, enriched of alimentary fibers, as well as a correct program of physical exercise, is needed[3]. If lifestyle changes fail to succeed, in the presence of a high cardiovascular risk, a pharmacological intervention on lipid abnormalities is requested[13]. Among several drugs recently developed to lower cholesterol, statins are the most used worldwide, due to their action as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase[4]. Often, to achieve a further reduction of LDL-cholesterol, ezetimibe in association to statins may be administered[4]. A reduction of cardiovascular events, however, can be obtained only if lipid correction is prolonged in time, thus requiring a chronic therapy[14]. In addition, the efficacy of treatment in hypercholesterolemic patients depends also on its precocity and duration[14]. Although they reduce cholesterol effectively, statins may have side effects such as muscle pain, fatigue, weakness, as well as creatine phosphokinase (CPK) and liver enzyme increases, thus inducing drug withdrawal in a significant percentage (up to 10-15 %) of people[3,15]. Consequently, in primary prevention in patients with borderline lipids or in people with low cardiovascular risk, as well as in subjects intolerant to statins, an option may be the use of dietary supplements. Among them, increasing interest have gained the so-called "nutraceuticals". By definition, a nutraceutical is a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease[16]. More in details, nutraceuticals are nutrients and/or bioactive compounds present sometimes in some foods, often of botanic origin, which may be assumed also as integrators (capsules, tablets, etc)[17]. In recent years, among nutraceutical ingredients, marketed in Europe as self-medication products for a safe health improvement, mainly due to their "natural" origin[18], several substances have been employed to manage lipid and/or glucose control in metabolic disturbances[18].

Here we report our experience on the correction of glycolipidic abnormalities in non-diabetic hyperlipidemic people and, of relevance, in a group of dyslipidemic type 2 diabetics with ARMOLIPID PLUS, a nutraceutical combination of Red Yeast (fermented rice with Monascus purpureus), Berberine and Policosanol to interfere with the synthesis of cholesterol and triglycerides. The red yeast rice is a remedy belonging to traditional Chinese Medicine, largely used in Western countries as hypocholesterolemic medication because of the presence of Monacolins produced during rice fermentation. Berberine is an herbal alkaloid which, among several therapeutic properties (antimicrobic, immunomodulator, etc) has been reported to present significant plurimetabolic actions, including those on lipids and glucose profile[19]. The formulation is completed with a pool of antioxidants (Coenzyme Q10 and Astaxanthin) to counteract the oxidative processes and finally with folic acid to control homocysteine levels, aiming to reduce the cardiovascular burden.

METHODS

Aim of the present study was to evaluate the effect of Armolipid Plus on Total-Ch, LDL, HDL, non-HDL Cholesterol (non-HDL-Ch), TG, fasting plasma glucose (FPG), Systolic (SBP) and Diastolic (DBP) Blood Pressure, body weight and Body-Mass Index (BMI), as well as anthropometric features in overweight dyslipidemic non-diabetic subjects and in overweight dyslipidemic type 2 diabetic patients; in diabetic subjects glycated hemoglobin was also measured.

Subjects

The study involved 37 consecutive dyslipidemic patients (4 males, 33 females, mean age 58.7 ± 11.5 yrs, BMI 28.8 ± 5.9 kg/m^2) and 15 consecutive dyslipidemic type 2 diabetic patients (4 males, 11 females, mean age 57.6 ± 8.8 yrs, BMI 29.1±5.4 kg/m^2, HbA1c 6.9 ± 0.4 %), attending to the Diet and Metabolic Unit of Internal Medicine Department of Pisa University. Each participant had been requested to be treated with a statin or a nutraceutical, all chosing the last one. Exclusion criteria included pregnancy, serum creatinine >2 mg/dL and presence of cancer. All individuals were requested not to change their diet, to maintain a mild physical activity during the study (at least thirty min of simple walking every day). Each subject assumed one capsule of Armolipid Plus in the evening for at least 12 months.

Except the trial of Marazzi *et al*[20] performed in a particular subset of pts (all >75 yrs and intolerant to statins), to our knowledge the present is the first study of a so-long follow-up for this nutraceutical in dyslipidemics as well as in type 2 diabetics.

Experimental procedures

Total-cholesterol, LDL-cholesterol, HDL, non-HDL cholesterol, triglycerides, fasting plasma glucose, systolic and diastolic pressure, and anthropometric parameters were assessed at baseline and every 30 days in all pts, HbA1c every three months in diabetics only. In the morning (before 8 a.m., after an overnight fast of at least 12 hours), we checked weight and Body Mass Index (kg/m^2). Other anthropometric measurements included skinfold thickness (biceps, triceps, subscapular and suprailiac skinfolds) and circumferences at waist, hip, wrist, and mid-upper arm)[21].

A skilled dietician measured each anthropometric site with a graded skinfold calliper and a cloth tape measure. Fasting venous blood samples were collected into EDTA- (6% ethylenediaminetetracetic acid, 100 µl for 5 ml of blood)-treated tubes and immediately centrifuged at 4°C for 15 min. Plasma was divided into aliquots and stored at -70°C until assay. The measurement of plasma glucose and lipids was performed by standard enzymatic colorimetric methods (COBAS 6000 analyzer, Roche Diagnostics)[21]. HbA1c was evaluated by ion-exchange chromatography on HPLC-723 G7 analyzer (TOSOH Bioscience)[21]. Non HDL-Ch was calculated by the formula (T-Ch) - (HDL-Ch)[22]. The Blood Pressure was measured according to the ESH-ESC guidelines with two BP measurements made at a distance of 3 min from one another, adopting the average of the two results.

Statistical analysis

For statistics, paired t test for comparison of data before and after Armolipid Plus was employed, with a $p<0.05$ of significance threshold.

RESULTS

Both in dyslipidemic and diabetic subjects (Table 1) we observed, after twelve months of treatment with Armolipid Plus, a highly significant decrease of all lipid parameters except HDL-Ch, which was slightly increased. In particular, total-Ch ($p < 0.0001$) and non-

HDL Cholesterol ($p < 0.0001$) showed a parallel decrease both in dyslipidemic (-103 and -105 mg/dL, respectively) and in diabetic patients (-88 and -90 mg/dL, respectively) (Figure 1), while LDL-Ch reduction ($p < 0.0001$) was about 37 mg/dL in both groups. Fasting plasma glucose ($p < 0.009$) and glycated hemoglobin ($p < 0.001$) significantly decreased in diabetic individuals, as did fasting plasma glucose in dyslipidemic patients ($p < 0.016$). Both body weight (about 4 kg) and BMI decreased in a not significant manner during treatment. Focusing on the anthropometric measurements, biceps and triceps thicknesses were unaffected in both group of patients, whereas subscapular (only in diabetics significantly, 4 cm) ($p < 0.024$) and suprailiac (around 6 cm) ($p < 0.0009$ in dyslipidemics, $p < 0.0003$ in diabetics) skinfold thickness were strongly reduced at the end of treatment. The skinfold thickness sum showed a highly significant decrease in both groups ($p < 0.02$ in dyslipidemics, 10 cm; $p < 0.03$ in diabetics, 10.6 cm).

The waist circumference lowering was not significant in both groups of patients, the hip circumference decrease reached the significance only in dyslipidemic subjects ($p < 0.023$). Finally, systolic BP was unaffected by Armolipid in dyslipidemics, but decreased significantly in diabetics ($p < 0.02$); diastolic BP was significantly reduced in diabetics ($p < 0.01$), only borderline in dyslipidemics ($p < 0.055$).

DISCUSSION

Armolipid Plus is a nutraceutical combination largely marketed in Europe[23] and most frequently employed in Italy[18] for management of dyslipidemic patients[24]. The recommended dose is one tablet/day. Each tablet contains red yeast extract (200 mg, corresponding to 3 mg of monacolin), policosanol (10 mg), berberine (500 mg), folic acid (0.2 mg), astaxanthin (0.5 mg), coenzyme Q10 (2 mg). Several papers have been published on the effects of this nutraceutical in different types of patients, especially dyslipidemic, or with metabolic syndrome, infrequently in diabetic people[19,20,25-28]. In the last months two interesting reviews have concerned the role of Armolipid Plus in the treatment of dyslipidemia and prevention of the cardiovascular burden[23-24]. Treatment protocols with this nutraceutical are clearly heterogeneous for type of patients, sample size, duration of treatment (ranging from six weeks to, for one study only, one year) [20],control group etc.[23-24].

The therapeutic effects of Armolipid Plus in different patients from variable types of trials ("randomized double-blind" studies are relatively few in comparison with the majority of "open-label" studies which represent the real life) was evaluated in more than 3000 subjects, and the addition of this nutraceutical to a low-fat diet has been reported to allow significant reductions of total cholesterol (ranging 11-21%) and LDL-Ch (15-31%), along with improvement in HDL and triglycerides[23-24]. Furthermore, Armolipid Plus treatment has been reported to be useful in patients with chronic renal disease[24], to reduce vascular stiffness[24], to improve insulin resistance[24], chiefly in the metabolic syndrome[24], with high tolerability and good compliance by patients[24]. Few adverse effects (only 36 in total, 2.2%) have been reported in the literature[18,24]; in

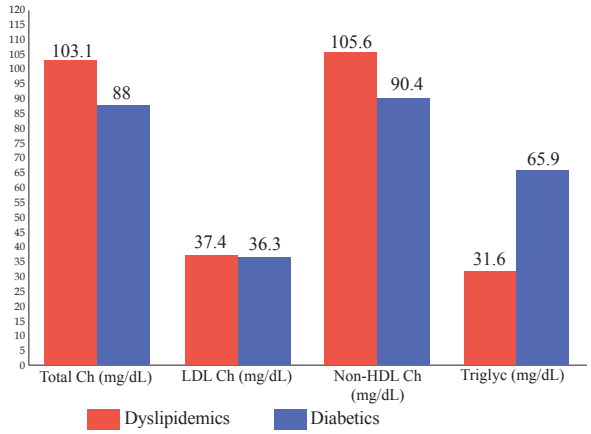

Figure 1 Decrease of Total cholesterol, LDL cholesterol, non-HDL cholesterol and Triglycerides in dyslipidemic and diabetic patients after Armolipid Plus treatment.

Table 1 Analytical data before and after treatment with Armolipid Plus.

	Dyslipidemic patients (n = 37; M 5, F 32)						Diabetic patients (n = 15; M 4, F 11)					
	Before	SD	After	SD	Differ.	P	Before	SD	After	SD	Differ.	P
Total Ch (mg/dl)	249.4	30.8	146.3	13	103.1	0.000	243.5	31.1	155.5	13.9	88	0.000
LDL Ch (mg/dl)	162.2	25.8	124.8	17.7	37.4	0.000	158.4	22.7	122.1	8.6	36.3	0.000
HDL Ch (mg/dl)	57.1	11.8	59.5	9.4	2.4	NS	50.9	14.1	53.2	7.7	2.3	NS
Non-HDL (mg/dl)	192.3	29.6	86.7	17.7	105.6	0.000	192.7	32.6	102.3	13.6	90.4	0.000
Triglyc (mg/dl)	141.6	83.8	110	18.6	31.6	0.017	189.3	104.1	123.4	6.8	65.9	0.014
FPG (mg/dl)	92.4	8.3	89	4	3.4	0.016	151.1	82.3	91.4	3.1	59.7	0.009
HbA1c (%)							6.91	0.9	6.23	0.4	0.68	0.001
Body wgt (Kg)	73.4	15.5	69.8	12.1	3.6	NS	75.8	15.6	71.2	12.3	4.6	NS
BMI (Kg/m2)	28.8	6	27.5	4.6	1.3	NS	29.1	5.4	27.3	4.2	1.7	NS
Biceps (cm)	20.8	6.6	20.6	5	0.2	NS	20.8	4.5	21.3	4.5	0.5	NS
Triceps (cm)	26	6.2	24.7	4.5	1.3	NS	26.1	6.4	24.3	5.6	1.8	NS
Subscap (cm)	30.3	8.6	27.9	6.5	2.4	NS	40	5	36.4	4.5	3.6	0.024
Suprailiac (cm)	36.4	9.2	30.3	6.8	6.1	0.001	42.9	4.6	37.3	3	5.6	0.000
Skinfold sum (cm)	113.5	23.4	103.5	17.1	10	0.02	129.9	16.4	119.3	12.5	10.6	0.03
Waist (cm)	96.2	13.1	92.1	10.1	4.1	NS (.066)	92.5	11.5	87.4	8.8	5.1	NS
Hip (cm)	104.4	9.8	100.4	8.1	4	0.023	97.9	8.1	94.6	6.4	3.3	NS
SBP (mmHg)	133.5	15	133.2	8.8	0.3	NS	140	12.5	131.2	9.6	8.8	0.02
DBP (mmHg)	81.7	8.8	79.1	3.5	2.6	NS (.055)	85	7.3	79.5	4.5	5.5	0.01

Before: before treatment (basal values). After: after 12 months of treatment. Ch: cholesterol. Triglyc: triglycerides. FPG: fasting plasma glucose. Wgt: weight. Biceps: bicipital folder thickness. Triceps: tricipital folder thickness. Subscap: subscapular folder thickness. Suprailiac: suprailiac folder thickness. Skinfold sum: folder thickness sum (bicipital + tricipital + subscapular + suprailiac). SBP: systolic blood pressure. DBP: diastolic blood pressure.

Italy a recent review has documented 29 cases (55% of all those related to products containing red yeast rice) between April 2002 and September 2015, mostly of musculoskeletal type (CPK increase, myalgia, muscle spasm), less frequently gastrointestinal/hepatobiliary or cutaneous involvement[18].

In our study we registered more significant results than those reported with other protocols and extremely intriguing for the use of Armolipid Plus in metabolic people. Indeed, both in dyslipidemic (41%) as well in diabetic (36%) individuals we observed a dramatic decrease of total-Ch with a significant milder LDL-Ch lowering in both groups (around 23%). Furthermore, while HDL-Ch was scarcely raised by the nutraceutical (0.04% in both types of patients), non-HDL Ch (our paper is the first measuring this analyte) was about halved (55% in dyslipidemics, 47% in diabetics) by Armolipid Plus; we also obtained a significant decrease (22.3% in dyslipidemics, 34.8 in diabetics) of triglyceride levels.

How to explain these quite unexpected results? In particular, how to explain that 1) LDL-Ch reduction does not completely account for the clearly higher lowering of total-Ch and 2) the decrease of non-HDL Ch is parallel to that of total-Cholesterol?

Historically, LDL has been considered the major atherogenic lipoprotein[22], becoming the first target of the lipid-lowering therapy[29]. In the last years, strong evidence is growing to suggest that very-low density (VLDL) concurs with LDL to promote atherosclerosis[22,30]. The sum of LDL- and VLDL-cholesterol includes all atherogenic cholesterol lipoproteins and has been termed non-HDL cholesterol or "atherogenic cholesterol"[22]. Besides LDL-cholesterol, non-HDL cholesterol (calculated as total-Ch minus HDL-Ch) includes the partially degraded atherogenic cholesterol-rich VLDL lipoproteins, commonly called "remnants"[22,30], and in recent statin trials it has been considered a target as relevant as LDL cholesterol, possibly replacing it in future guidelines[22]. In our patients, both dyslipidemics and diabetics, Armolipid Plus administration for 12 months induced not only a significant decrease of cholesterol carried by LDL particles and triglycerides carried by VLDL (not a novelty, as widely reported in the literature[23-24]), but the nutraceutical conceivably even inhibited the whole "atherogenic cholesterol" vehiculated both by LDL and VLDL themselves, as strongly suggested by the dramatic parallel reduction of total-Ch and non-HDL cholesterol. These findings have been documented so far for the first time and promote some considerations. Analyzing accurately the various components of the Armolipid Plus, we need to explain in detail the mode of action of each single component of this nutraceutical. Indeed, we are speaking of a "combination" of nutraceuticals. The chief components are: monacolin K, derived by the "red yeast rice" which, together with a "red " pigment, is a product of fermentation of the fungus Monascus purpureus grown on rice; and berberine, a natural plant extract, an alkaloid of the clinical practice in Traditional Chinese Medicine[17,24]. The nutraceutical composition includes also policosanol, a mixture of long-chain aliphatic alcohols present in the beewax, potatoes, rice bran and sugar cane[17,24]. Furthermore, in Armolipid Plus are present, as reported before, antioxidants, namely astaxanthin, a red carotenoid derived from an unicellular microalga (Haematococcus pluvialis) [24] and, finally, Coenzyme Q10, a physiological defense of the human body with a critical role in all redox reactions. Monacolin K (which in effect includes 15 monacolins)[31] reduces total- and LDL-cholesterol by inhibition of HMG-CoA reductase, the key enzyme in the production of the mevalonate, precursor of the cholesterol synthesis[17,24]. Monacolin K acts with a statin-like mechanism, and is considered structurally and functionally analogous to lovastatin[17,24]. Berberine reduces circulating cholesterol by more than a mechanism, i.e. via an upregulation of LDL receptor (LDLR) on the hepatocyte surface, an action different from that of statins[17,24,32-33]. Moreover, berberine decreases PCSK9 expression on hepatocytes, thus inhibiting LDL receptor degradation[34]. Finally, by stimulation of AMPK (AMP-activated protein kinase) it inactivates the production of malonyl CoA, a key step for fatty acid synthesis, hence reducing also circulating triglycerides (up to 30-35 %)[35]. For policosanol, it has been suggested a mild inhibition of the HMG-CoA reductase, but this action has not been confirmed[24]. Returning to explain the unforeseen exciting results of our study, it appears likely that while monacolin K with its statin-like mechanism has induced a reduction of total-Ch (and well of non-HDL Ch) around 10-20% at the most, as widely reported in other papers[24-25] as well as in our experience with other nutraceuticals[21]; remains to be understood how and why we have reached a so great decrease of total -CH in comparison with other trials, not justified by the lower LDL-Ch decrease and the contemporary parallel decrease of non-HDL Ch.

Obviously our attention is focused on berberine. The effects of berberine on lipid and glucose metabolism[17,23-24,35-39] have been reported for many decades by Chinese medicine; furthermore, the synergistic effect derived from the interaction between monacolin and berberine on cholesterol reduction is a defined assumption so far[17,23-24]. Conceivably, the complementary action of berberine and monacolin has very likely determined the concurrent heavy decrease of total- and non- HDL cholesterol in our patients by removing lipids (chiefly cholesterol) vehicolated by LDL as well VLDL lipoproteins[21].

Anyway, no trial with Armolipid Plus has documented so strong results as in ours[23-24]. A possible explanation may be due to the long (12 months) duration of the present protocol. Indeed, in most of studies this nutraceutical was administered for 6-8 up to 24 weeks, except a single paper of one year of duration concerning aged people intolerant to statins[20].

A further comment concerns the anthropometric data of this study. While during Armolipid Plus treatment we registered a moderate not significant lowering of patient body weight and BMI, confirmed by the small decrease of waist circumference, very intriguing appears the highly significant reduction, in both groups of patients, of suprailiac skinfold as well the severe (about 10 cm!) reduction of skinfold sum. How to possibly explain these unequivocal anthropometric data, so far never reported, and which component of the nutraceutical could be in charge of this effect? After excluding monacolin and policosanol, since both of them operate on the HMG-CoA reductase to lower cholesterol synthesis, very likely the property to induce the skinfold effect is of berberine. Indeed, berberine in diabetic patients significantly decreases fasting and postprandial glucose levels and glycated hemoglobin by increasing the expression and sensitivity of insulin receptors[35-39], thus regulating glucose homeostasis and reducing insulin resistance. Hence, may be hypothesized a significant improvement of insulin resistance by berberine at the level of visceral abdominal adipose tissue, surely subtended also by suprailiac skinfolds[35]. Lastly, may be of interest to point out the lowering effect of Armolipid Plus on systolic and diastolic values, very significant in diabetic patients, conceivably due to improvement of endothelial function by berberine[24,40].

In conclusion, our results confirm that Armolipid Plus might represent a good approach to improve glycolipidic abnormalities in people affected by metabolic syndrome, dyslipidemia and type 2 diabetes, especially if the treatment is administered for at least 12 months, as in our study.

REFERENCES

1 World Health Organization. WHO Media center. Cardiovascular diseases (CVDs). Fact sheet N°317. Geneva: World Health Organization [May 2017]. Available from: http: //www.who.int/mediacentre/factsheets/fs317/en/

2 Germano G, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Vrints C. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; **33**: 1635-1701. [DOI: 10.1093/eurheartj/ehs092]; [PMID: 22555213]

3 Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; **253**: 281-344. [DOI: 10.1016/j.atherosclerosis.2016.08.018]; [PMID: 27594540]

4 Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman M, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis* 2011; **217**: 3-46. [DOI: 10.1016/j.atherosclerosis.2011.06.028]; [PMID: 21882396]

5 Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; **256**: 2823-8. [DOI: 10.1001/jama.1986.03380200061022]; [PMID: 3773199]

6 Castelli WP. Cholesterol and lipids in the risk of coronary artery disease--the Framingham Heart Study. *Can J Cardiol* 1988; **4 Suppl A**: 5A-10A]; [PMID: 3179802]

7 Assmann G, Schulte H. Identification of individuals at high risk for myocardial infarction. Atherosclerosis 1994; **110 Suppl**: S11-21. [DOI: 10.1016/0021-9150(94)05386-W]; [PMID: 7857378]

8 Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. *Eur J Prev Cardiol* 2013; **20**: 641-57. [DOI: 10.1177/2047487313480435]; [PMID: 23447425]

9 Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015; **385**: 1397-405. [DOI: 10.1016/S0140-6736(14)61368-4]; [PMID: 25579834]

10 Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015; **372**: 2387-97. [DOI: 10.1056/NEJMoa1410489]; [PMID: 26039521]

11 Aude YW, Mego P, Mehta JL. Metabolic syndrome: dietary interventions. *Curr Opin Cardiol* 2004; **19**: 473-9. [DOI: 10.1097/01.hco.0000134610.68815.05]; [PMID: 15316456]

12 Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008; **337**: a1344. [DOI: 10.1136/bmj.a1344]; [PMID: 18786971]

13 Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen mL, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgözoglu L, Wiklund O, Zampelas A; European Society of Cardiology (ESC); European Association for Cardiovascular Prevention and Rehabilitation (EACPR); Council on Cardiovascular Nursing; European Association for Study of Diabetes (EASD); International Diabetes Federation Europe (IDF-Europe); European Stroke Initiative (EUSI); Society of Behavioural Medicine (ISBM); European Society of Hypertension (ESH); WONCA Europe (European Society of General Practice/Family Medicine); European Heart Network (EHN); European Atherosclerosis Society (EAS). European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007; **14 Suppl 2**: S1-113. [DOI: 10.1097/01.hjr.0000277983.23934.c9]; [PMID: 17726407]

14 Smith CS, Cannon CP, McCabe CH, Murphy SA, Bentley J, Braunwald E. Early initiation of lipid-lowering therapy for acute coronary syndromes improves compliance with guideline recommendations: observations from the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS-TIMI 16) trial. *Am Heart J* 2005; **149**: 444-50. [DOI: 10.1016/j.ahj.2004.06.033]; [PMID: 15864232]

15 Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, Krumholz HM. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; **114**: 2788-97. [DOI: 10.1161/CIRCULATIONAHA.106.624890]; [PMID: 17159064]

16 Poli A, Marangoni F, Paoletti R, Mannarino E, Lupattelli G, Notarbartolo A, Aureli P, Bernini F, Cicero A, Gaddi A, Catapano A, Cricelli C, Gattone M, Marrocco W, Porrini M, Stella R, Vanotti A, Volpe M, Volpe R, Cannella C, Pinto A, Del Toma E, La Vecchia C, Tavani A, Manzato E, Riccardi G, Sirtori C, Zambon A; Nutrition Foundation of Italy. Non-pharmacological control of plasma cholesterol levels. *Nutr Metab Cardiovasc Dis* 2008; **18**: S1-16. [DOI: 10.1016/j.numecd.2007.10.004]; [PMID: 18258418]

17 Pirro M, Vetrani C, Bianchi C, Mannarino MR, Bernini F, Rivellese AA. Joint position statement on "Nutraceuticals for the treatment of hypercholesterolemia" of the Italian Society of Diabetology (SID) and of the Italian Society for the Study of Arteriosclerosis (SISA). *Nutr Metab Cardiovasc Dis* 2017; **27**: 2-17. [DOI: 10.1016/j.numecd.2016.11.122]; [PMID: 27956024]

18 Mazzanti G, Moro PA, Raschi E, Da Cas R, Menniti-Ippolito F. Adverse reactions to dietary supplements containing red yeast rice: assessment of cases from the Italian surveillance system. *Br J Clin Pharmacol* 2017; **83**: 894-908. [DOI: 10.1111/bcp.13171]; [PMID: 28093797]

19 Cicero AF, Rovati LC, Setnikar I. Eulipidemic effects of berberine administered alone or in combination with other natural cholesterol-lowering agents. A single-blind clinical investigation. *Arzneimittelforschung* 2007; **57**: 26-30. [DOI: 10.1055/s-0031-1296582]; [PMID: 17341006]

20 Marazzi G, Cacciotti L, Pelliccia F, Iaia L, Volterrani M, Caminiti G, Sposato B, Massaro R, Grieco F, Rosano G. Long-term effects of nutraceuticals (berberine, red yeast rice, policosanol) in elderly hypercholesterolemic patients. *Adv Ther* 2011; **28**: 1105-13. [DOI: 10.1007/s12325-011-0082-5]; [PMID: 22113535]

21 Masoni MC, Matteucci E, Giampietro C, Giampietro O. The Effect of Low-dose Orlistat (60 mg Twice Daily) on Weight-loss and Markers of Metabolic Disease in Obese Subjects: A Preliminary Report. *J Sci Res Reports* 2015; **4**: 198-202. [DOI: 10.9734/JSRR/2015/11168];

22 Expert Panel on Dyslipidemia. An International Atherosclerosis Society position paper: global recommendations for the management of dyslipidemia: executive summary. *Atherosclerosis* 2014; **232**: 410-3. [DOI: 10.1016/j.atherosclerosis.2013.11.031]; [PMID: 24468156]

23 Millán J, Cicero AF, Torres F, Anguera A. Effects of a nutraceutical combination containing berberine (BRB), policosanol, and red yeast rice (RYR), on lipid profile in hypercholesterolemic patients: A meta-analysis of randomised controlled trials. *Clin Investig Arterioscler* 2016; **28**: 178-87. [DOI: 10.1016/j.arteri.2016.03.002]; [PMID: 27131395]

24 Barrios V, Escobar C, Cicero AF, Burke D, Fasching P, Banach M, Bruckert E. A nutraceutical approach (Armolipid Plus) to reduce total and LDL cholesterol in individuals with mild to moderate dyslipidemia: Review of the clinical evidence. *Atheroscler Suppl* 2017; **24**: 1-15. [DOI: 10.1016/j.atherosclerosissup.2016.10.003]; [PMID: 27998714]

25 Affuso F, Ruvolo A, Micillo F, Saccà L, Fazio S. Effects of a nutraceutical combination (berberine, red yeast rice and policosanols) on lipid levels and endothelial function randomized, double-blind, placebo-controlled study. *Nutr Metab Cardiovasc Dis* 2010; **20**: 656-61. [DOI: 10.1016/j.numecd.2009.05.017]; [PMID: 19699071]

26 Trimarco B, Benvenuti C, Rozza F, Cimmino CS, Giudice R, Crispo S. Clinical evidence of efficacy of red yeast rice and berberine in a large controlled study versus diet. *Med J Nutrition Metab* 2011; **4**: 133-139. [DOI: 10.1007/s12349-010-0043-6]; [PMID: 21909461.

27 Cicero AFG, De Sando V, Benedetto D, Cevenini M, Grandi E, Borghi C. Long-term efficacy and tolerability of a multicomponent lipid-lowering nutraceutical in overweight and normoweight patients. *Nutrafoods* 2012; **11**: 55-61. [DOI: 10.1007/s13749-012-0018-y]

28 Gonnelli S, Caffarelli C, Stolakis K, Cuda C, Giordano N, Nuti R. Efficacy and Tolerability of a Nutraceutical Combination (Red Yeast Rice, Policosanols, and Berberine) in Patients with Low-Moderate Risk Hypercholesterolemia: A Double-Blind, Placebo-Controlled Study. *Curr Ther Res Clin Exp* 2014; **77**: 1-6. [DOI: 10.1016/j.curtheres.2014.07.003]; [PMID: 26649075]

29 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109: 433-8. [DOI: 10.1161/01.ATV.0000111245.75752.C6]; [PMID: 14766739]

30 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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). *JAMA* 2001; **285**: 2486-97. [DOI: 10.1001/jama.285.19.2486]; [PMID: 11368702]

31 Nannoni G, Alì A, Di Pierro F. Development of a new highly standardized and granulated extract from *Monascus purpureus* with a high content of monacolin K and KA and free of inactive secondary monacolins and citrinin. *Nutrafoods* 2015; **14**: 197-205. [DOI: 10.1007/s13749-015-0047-4]

32 Kong W, Wei J, Abidi P, Lin M, Inaba S, Li C, Wang Y, Wang Z, Si S, Pan H, Wang S, Wu J, Wang Y, Li Z, Liu J, Jiang JD. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nat Med* 2004; **10**: 1344-51. [DOI: 10.1038/nm1135]; [PMID: 15531889]

33 Doggrell SA. Berberine--a novel approach to cholesterol lowering. *Expert Opin Investig Drugs* 2005; **14**: 683-5. [DOI: 10.1517/13543784.14.5.683]; [PMID: 15926873]

34 Cameron J, Ranheim T, Kulseth MA, Leren TP, Berge KE. Berberine decreases PCSK9 expression in HepG2 cells. *Atherosclerosis* 2008; **201**: 266-73. [DOI: 10.1016/j.atherosclerosis.2008.02.004]; [PMID: 18355829]

35 Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y, Ye JM, Lee CH, Oh WK, Kim CT, Hohnen-Behrens C, Gosby A, Kraegen EW, James DE, Kim JB. Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. *Diabetes* 2006; **55**: 2256-64. [DOI: 10.2337/db06-0006]; [PMID: 16873688]

36 Huang C, Zhang Y, Gong Z, Sheng X, Li Z, Zhang W, Qin Y. Berberine inhibits 3T3-L1 adipocyte differentiation through the PPARgamma pathway. *Biochem Biophys Res Commun* 2006; **348**: 571-8. [DOI: 10.1016/j.bbrc.2006.07.095]; [PMID: 16890192]

37 Kim SH, Shin EJ, Kim ED, Bayaraa T, Frost SC, Hyun CK. Berberine activates GLUT1-mediated glucose uptake in 3T3-L1 adipocytes. *Biol Pharm Bull* 2007; **30**: 2120-5. [DOI: 10.1248/bpb.30.2120]; [PMID: 17978486]

38 Zhou L, Yang Y, Wang X, Liu S, Shang W, Yuan G, Li F, Tang J, Chen M, Chen J. Berberine stimulates glucose transport through a mechanism distinct from insulin. *Metabolism* 2007; **56**: 405-12. [DOI: 10.1016/j.metabol.2006.10.025]; [PMID: 17292731]

39 Zhang H, Wei J, Xue R, Wu JD, Zhao W, Wang ZZ, Wang SK, Zhou ZX, Song DQ, Wang YM, Pan HN, Kong WJ, Jiang JD. Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. *Metabolism* 2010; **59**: 285-92. [DOI: 10.1016/j.metabol.2009.07.029]; [PMID: 19800084]

40 Pirro M, Lupattelli G, Del Giorno R, Schillaci G, Berisha S, Mannarino MR, Bagaglia F, Melis F, Mannarino E. Nutraceutical combination (red yeast rice, berberine and policosanols) improves aortic stiffness in low-moderate risk hypercholesterolemic patients. *PharmaNutrition* 2013; **1**: 73-77. [DOI: 10.1016/j.phanu.2013.02.003]

Peer Reviewer: Pietro Scicchitano