S.I.Te.C.S.
Società Italiana di Terapia Clinica e Sperimentale

DYSLIPIDAEMIAS: PRESENT AND FUTURE APPROACHES TO PHARMACOLOGICAL INTERVENTION

November 9th-10th, Sorrento (NA) - Italy

Chairs: Alberico L. Catapano, Pasquale Perrone Filardi and Lale Tokgözoğlu

Non-pharmacological therapeutic approaches

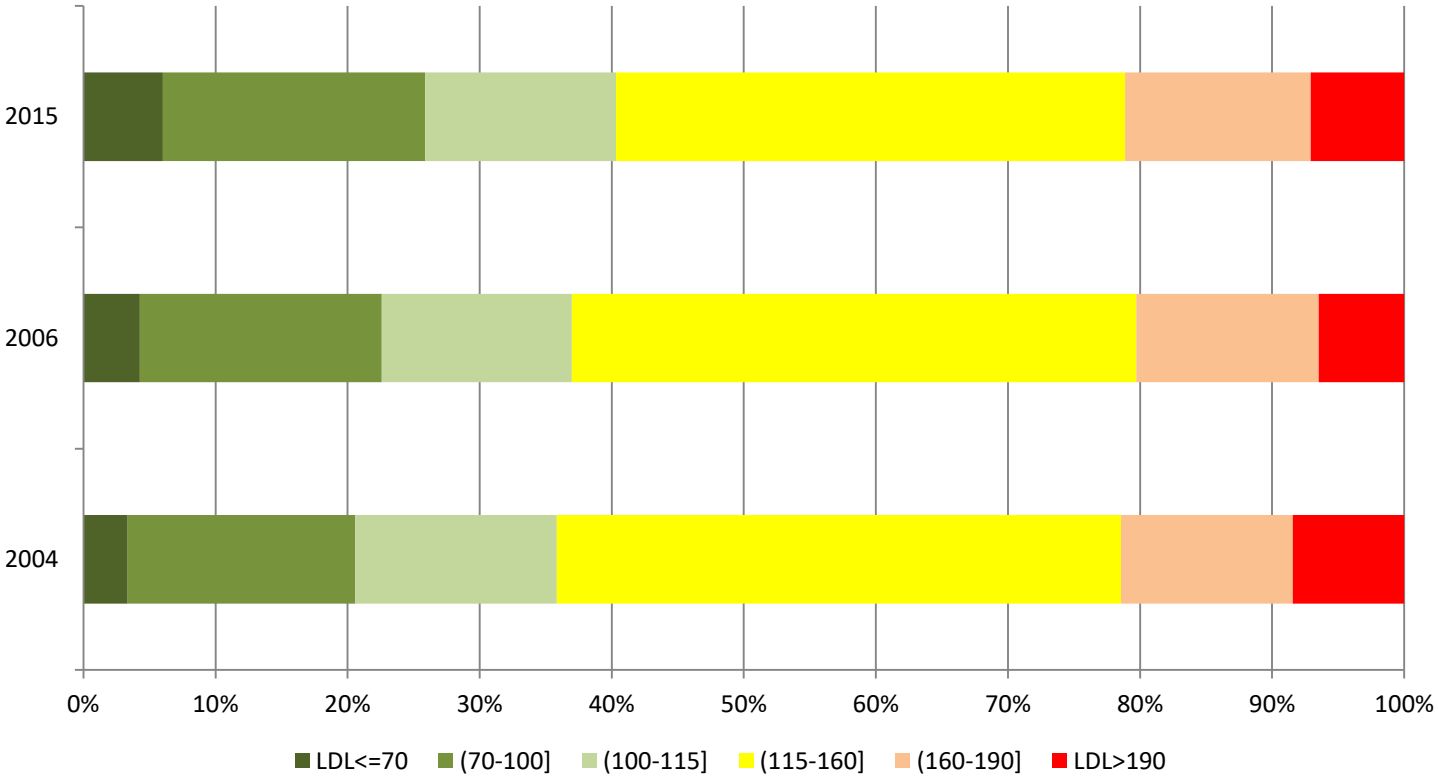
Role of Nutraceuticals

Prof. Maciej Banach (Lodz, Poland)

Disclosures

I have given talks, attended conferences and participated in studies sponsored by Abbott/Abbott Vascular, Actavis, Akcea, Biofarm, Daiichi-Sankyo, Sanofi, MSD, Mylan, Pfizer, KRKA, Valeant, Abbott Vascular, Servier, Polpharma, and Amgen. I am a member of International Advisory Board of Amgen, Lilly, Sanofi, Abbott Vascular, Esperion, Akcea, Resverlogix, Polfarmex and Daiichi-Sankyo. I have received a research grant from Valeant and Sanofi.

Changes in the proportion of individuals in different LDL-C ranges between the studies performed in 2004, 2006 and **LIPIDOGRAM2015 cohort study**



Banach M, et al. Eur Heart J 2017;38 (suppl_1):ehx493.P5306.

ESC Congress
Munich 2018

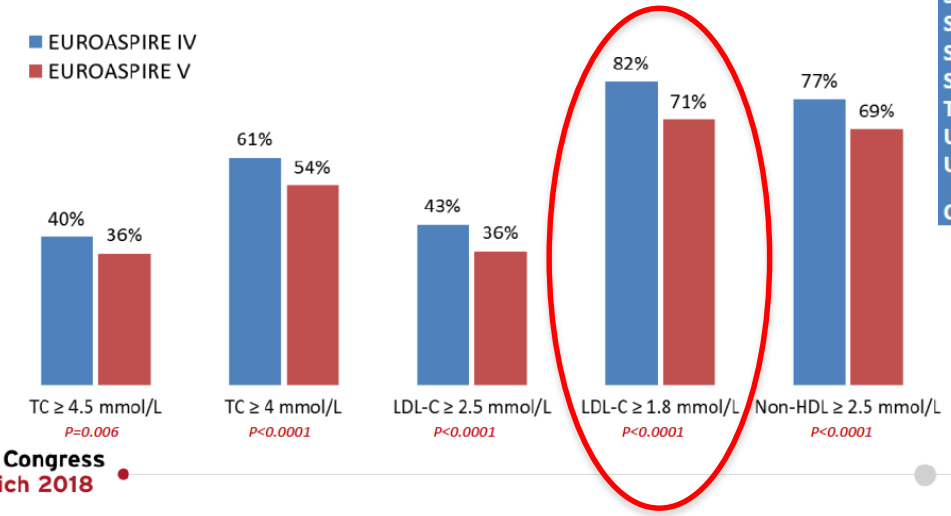
Therapeutic control of LDL cholesterol

LDL-C < 1.8 mmol/L in patients using lipid-lowering drugs

	EUROASPIRE IV	EUROASPIRE V	Change
Belgium	13%	33%	+20%
Bosnia and Herzegovina	16%	21%	+5%
Bulgaria	8%	19%	+10%
Croatia	22%	31%	+9%
Czech Republic	23%	39%	+15%
Finland	33%	50%	+17%
Germany	12%	25%	+13%
Greece	14%	25%	+12%
Latvia	30%	32%	+2%
Lithuania	5%	9%	+4%
Netherlands	21%	36%	+15%
Poland	23%	41%	+18%
Romania	21%	32%	+11%
Russian Federation	16%	29%	+13%
Serbia	12%	19%	+7%
Slovenia	34%	41%	+8%
Spain	41%	57%	+17%
Sweden	20%	41%	+21%
Turkey	10%	19%	+9%
Ukraine	15%	20%	+5%
United Kingdom	31%	42%	+11%
OVERALL	20.1%	30.6%	+10.5%

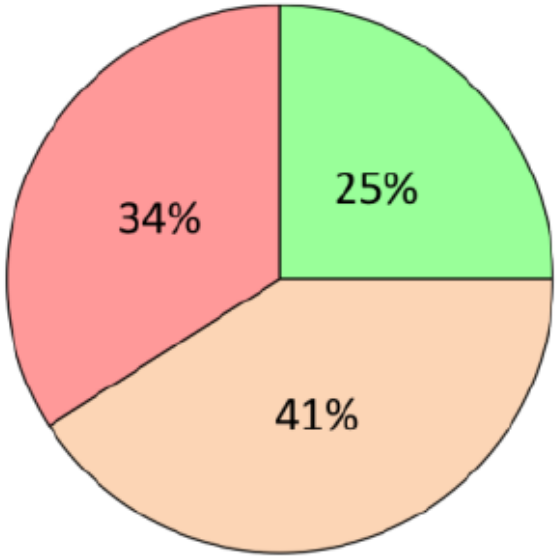
Prevalence of raised lipid levels

EUROASPIRE V vs IV



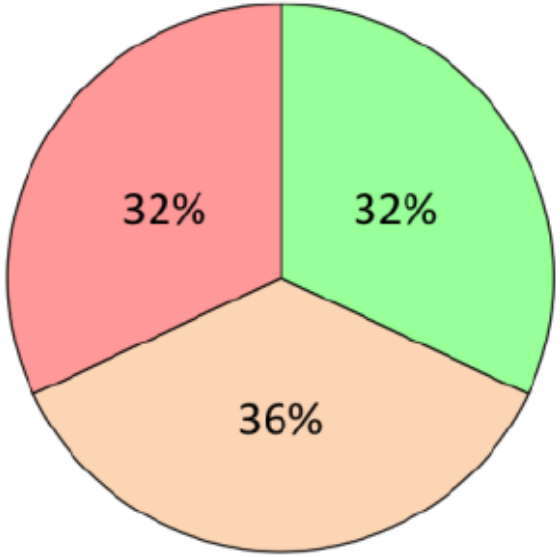
EUROASPIRE V

LDL-C in patients on high-intensity LLD therapy



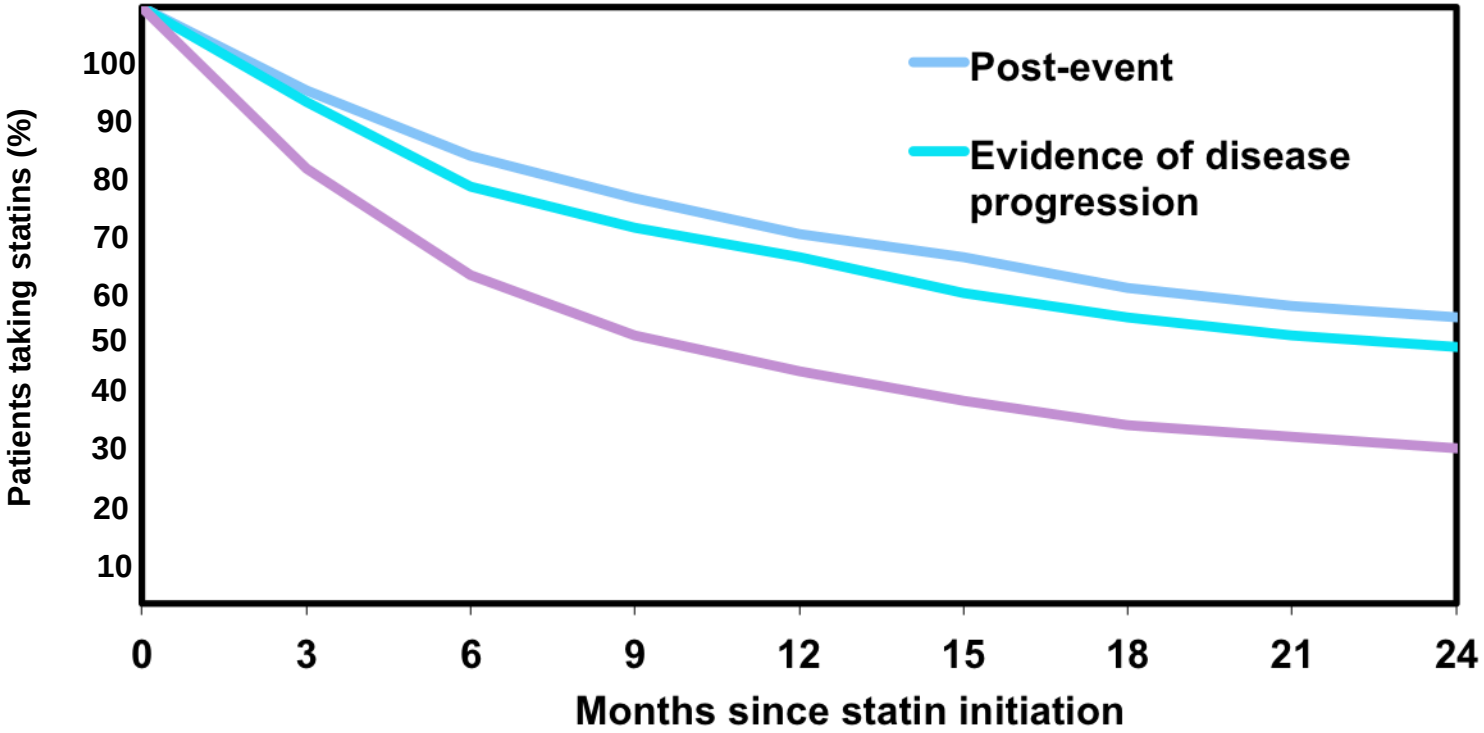
EUROASPIRE IV

- LDL-C < 1.8 mmol/L
- LDL-C 1.8-2.4 mmol/L
- LDL-C ≥ 2.5 mmol/L



EUROASPIRE V

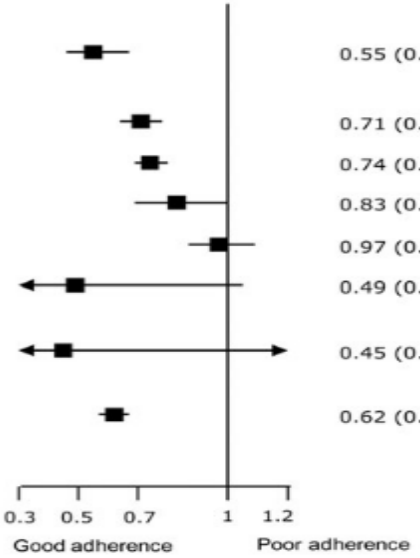
Adherence Lowest When Therapy Was Preventive



Cohort study using linked population-based administration data from Ontario, Canada (N=143,505)

Jackevicius CA et al. JAMA. 2002;288:462-467.

	No. of studies	No. of participants	No. of deaths	Proportion (95% CI)
(1) Adherence to statins	11	291,864	29,605**	0.55 (0.46, 0.67)
(2) Adherence to antihypertensive agents	11*	205,598	12,288**	0.71 (0.64, 0.78)
ACE inhibitors/Angiotensin receptor blockers	4	62,196	886**	0.74 (0.69, 0.80)
Beta-blockers	7	67,991	5,441**	0.83 (0.69, 1.00)
Calcium channel blockers	1	9168	2696	0.97 (0.87, 1.09)
Multiple agents	3	81,342	2978	0.49 (0.23, 1.05)
(3) Adherence to aspirin	3	12,980	1573	0.45 (0.16, 1.29)
(4) Adherence to any CVD medication	23*	533,381	94,126**	0.62 (0.57, 0.67)



*For individual studies reporting data for more than one medication class the results for the different categories within that study were meta-analysed (fixed effect) before use in the composite calculation; **Groups in which not all studies reported the number of deaths.

Figure 4 Relative risks for all-cause mortality in good vs. poor adherence to major cardiovascular medications.

European Heart Journal (2013) **34**, 2940–2948
doi:10.1093/eurheartj/eht295

Statin doses a year after ACS, PCI OR CABG in Poland

	Dose	LDL-C
Simvastatin	23,7±13,2	2,46±0,78
Atorvastatin	32,8±15,2	2,38±1,00
Rosuvastatin	14,6±8,1	2,21±1,07

Jankowski P i wsp. Arch Med. Sci 2015

Definition of statin intolerance

Guideline	Definition of statin intolerance
NLA 2014[13]	Characterized by the inability to tolerate **at least two statins**: one statin at the lowest starting daily **dose** AND another statin at any daily dose, due to either **objectionable symptoms (real or perceived) or abnormal lab determinations**, which **are temporally related** to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with **other known determinants being excluded.** The lowest starting statin daily dose is defined as: rosuvastatin 5mg, atorvastatin 10mg, simvastatin 10mg, lovastatin 20mg, pravastatin 40mg, fluvastatin 40mg, and pitavastatin 2mg
International Lipid Expert Panel 2015[15]	1) The inability to tolerate at least **two** different statins: one statin at the lowest starting average daily dose and the other statin at any dose 2) Intolerance associated with confirmed, **intolerable statin-related adverse effect(s) or significant biomarker abnormalities** 3) Symptom or biomarker change resolution or significant improvement upon **dose decrease or discontinuation** 4) Symptoms or biomarker changes not attributable to **established predispositions** such as **drug-drug interactions** and recognized conditions increasing the risk of statin intolerance
Canadian Consensus Working Group (2016)[16]	**Goal-inhibiting Statin Intolerance** • a clinical syndrome • characterized by significant symptoms and/or biomarker abnormalities that prevent **long-term use** of, and **adherence** to, **indicated** use of statins • **documented by challenge/de-challenge/re-challenge**, when appropriate, using at least **two statins**, including **atorvastatin and rosuvastatin** • not due to drug-drug interactions or untreated risk factors for intolerance (e.g. untreated hypothyroidism) • and leading to **failure to maintain therapeutic goals as defined by national guidelines**

Rosenson R, Baker S, Banach M, et al. JACC 2017;70(10):1290-1301.

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Statin Intolerance and Risk of Coronary Heart Events and All-Cause Mortality Following Myocardial Infarction

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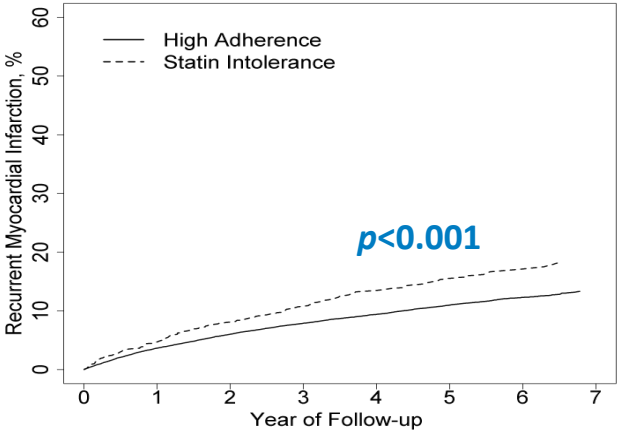
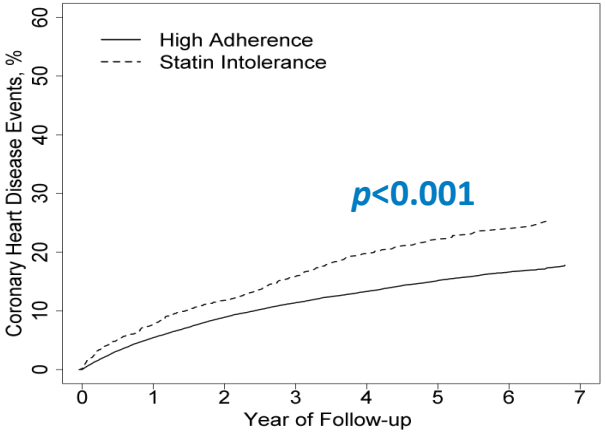
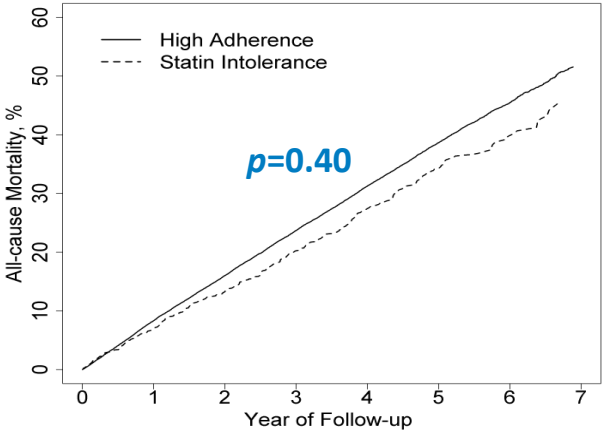
Cumulative incidence for recurrent myocardial infarction, coronary heart disease events and all-cause mortality for beneficiaries with statin intolerance and high adherence to high intensity statins.



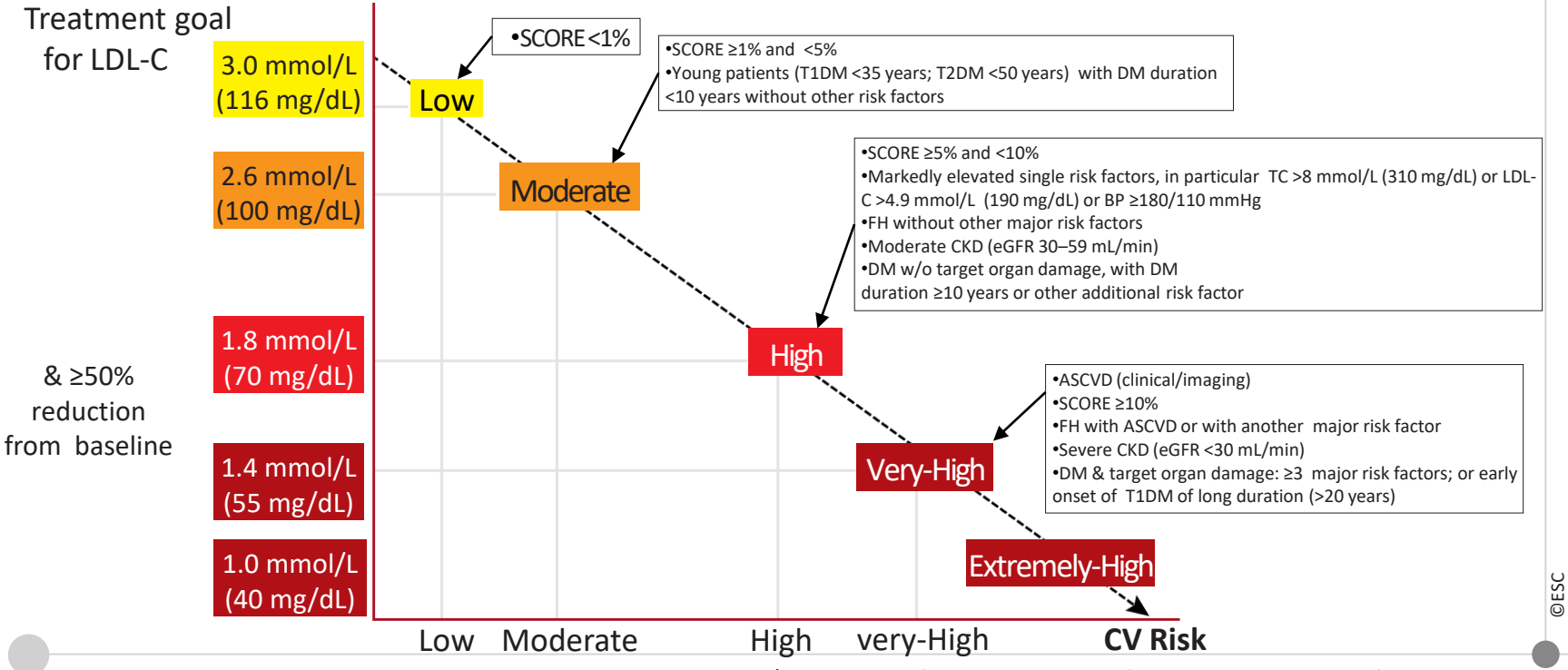




After multivariable adjustment, the hazard ratio comparing beneficiaries with statin intolerance to those with high statin adherence was 1.50 (95% CI: 1.30, 1.73) for recurrent MI, 1.49 (95% CI: 1.32, 1.68) for CHD events and 0.96 (95% CI: 0.87, 1.06) for all-cause mortality

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk

EAS ESC European Society of Cardiology



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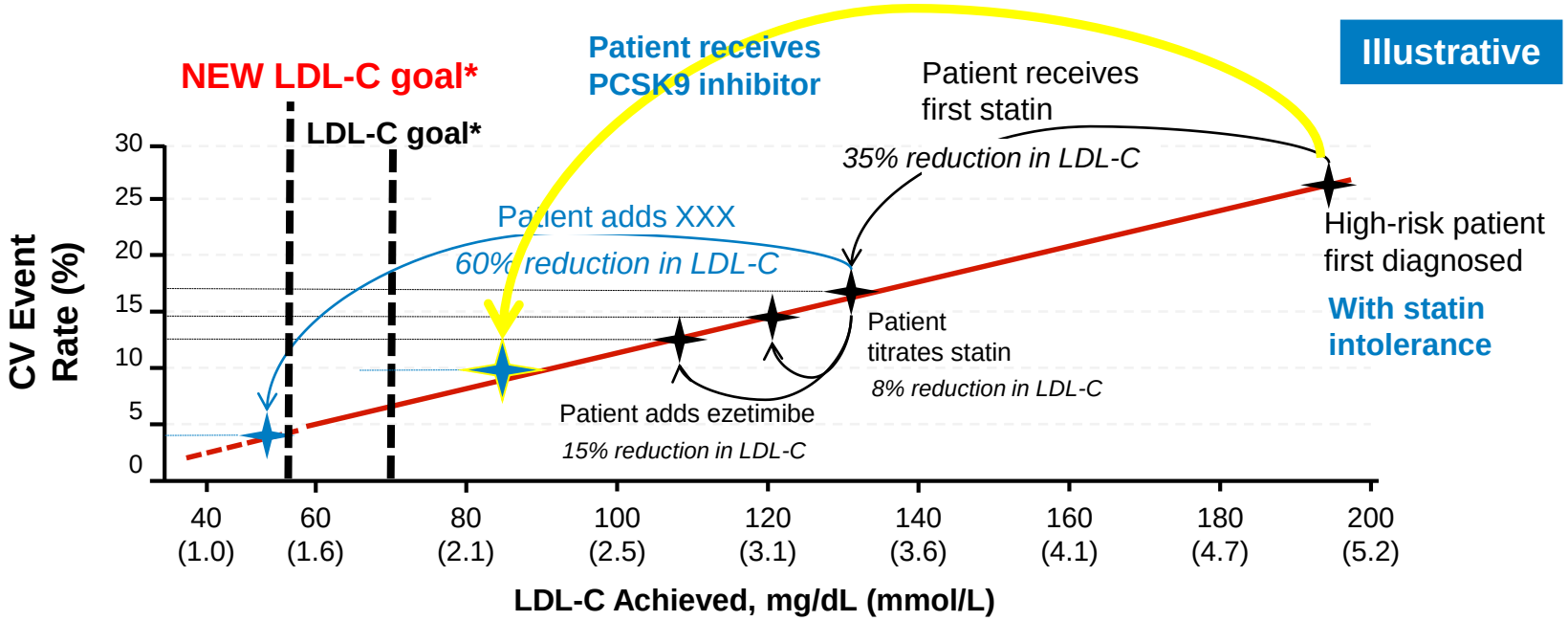
www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

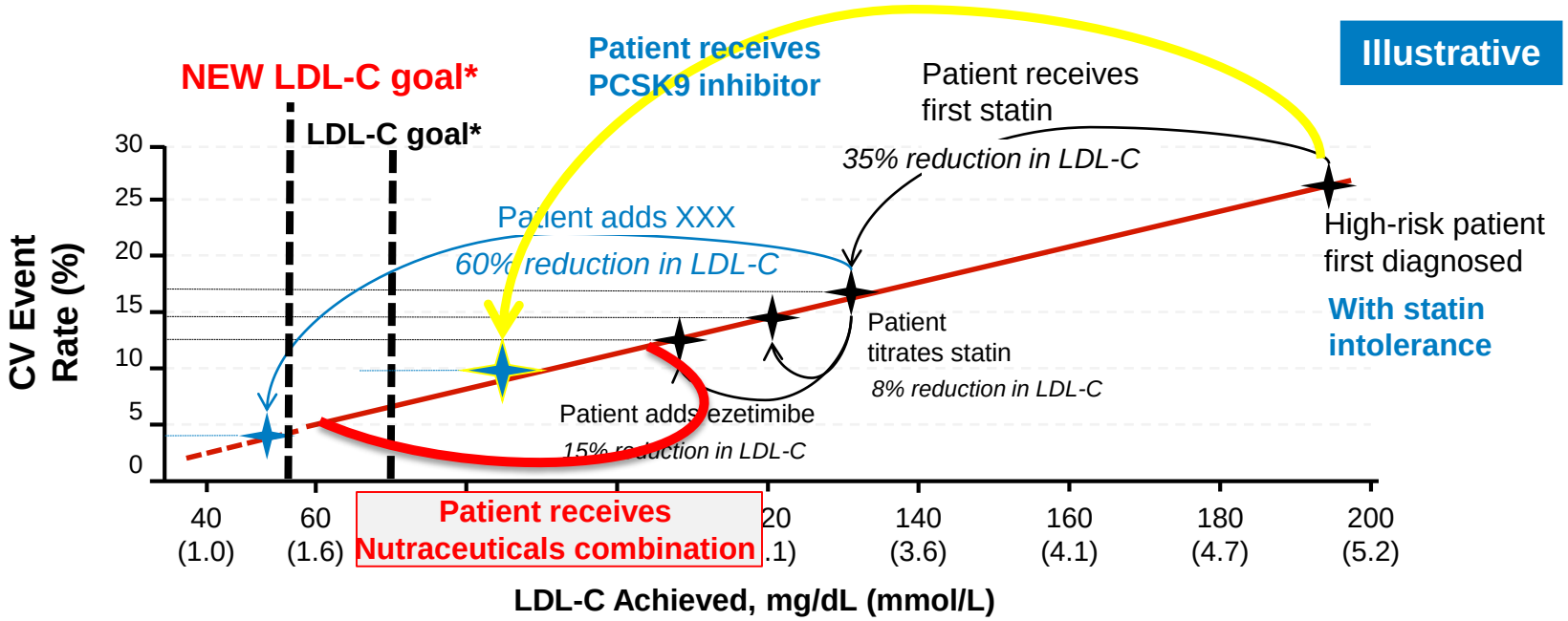
We Still Need Drugs that Helps High-risk Patients to Achieve LDL-C Goal



*LDL-C goal for high-risk and very high-risk patients as defined by ESC/EAS guidelines for the management of dyslipidemias.

Reiner Z, et al. Eur Heart J 2011;32:1769–818.

We Still Need Drugs that Helps High-risk Patients to Achieve LDL-C Goal



*LDL-C goal for high-risk and very high-risk patients as defined by ESC/EAS guidelines for the management of dyslipidemias.

Reiner Z, et al. Eur Heart J 2011;32:1769–818.

Special Article

Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel

Arrigo F.G. Cicero, Alessandro Colletti, Gani Bajraktari, Olivier Descamps, Dragan M. Djuric, Marat Ezhov, Zlatko Fras, Niki Katsiki, Michel Langlois, Gustavs Latkovskis, Demosthenes B. Panagiotakos, Gyorgy Paragh, Dimitri P. Mikhailidis, Olena Mitchenko, Bernhard Paulweber, Daniel Pella, Christos Pitsavos, Željko Reiner, Kausik K. Ray, Manfredi Rizzo, Amirhossein Sahebkar, Maria-Corina Serban, Laurence S. Sperling, Peter P. Toth, Dragos Vinereanu, Michal Vrablík, Nathan D. Wong, and Maciej Banach; on behalf of the International Lipid Expert Panel (ILEP)

Published in parallel in *Archives of Medical Science and Nutrition Reviews.*

Guidelines/recommendations

Lipid lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel#

Arrigo F.G. Cicero[1]*, Alessandro Colletti[1], Gani Bajraktari[2], Olivier Descamps[3], Dragan M. Djuric[4], Marat Ezhov[5], Zlatko Fras[6], Niki Katsiki[7], Michel Langlois[8], Gustavs Latkovskis[9], Demosthenes B. Panagiotakos[10], Gyorgy Paragh[11], Dimitri P. Mikhailidis[12], Olena Mitchenko[13], Bernhard Paulweber[14], Daniel Pella[15], Christos Pitsavos[16], Željko Reiner[17], Kausik K. Ray[18], Manfredi Rizzo[19], Amirhossein Sahebkar[20], Maria-Corina Serban[21], Laurence S. Sperling[22], Peter P. Toth[23], Dragos Vinereanu[24], Michal Vrablík[25], Nathan D. Wong[26], Maciej Banach[27]*
on behalf of the International Lipid Expert Panel (ILEP)

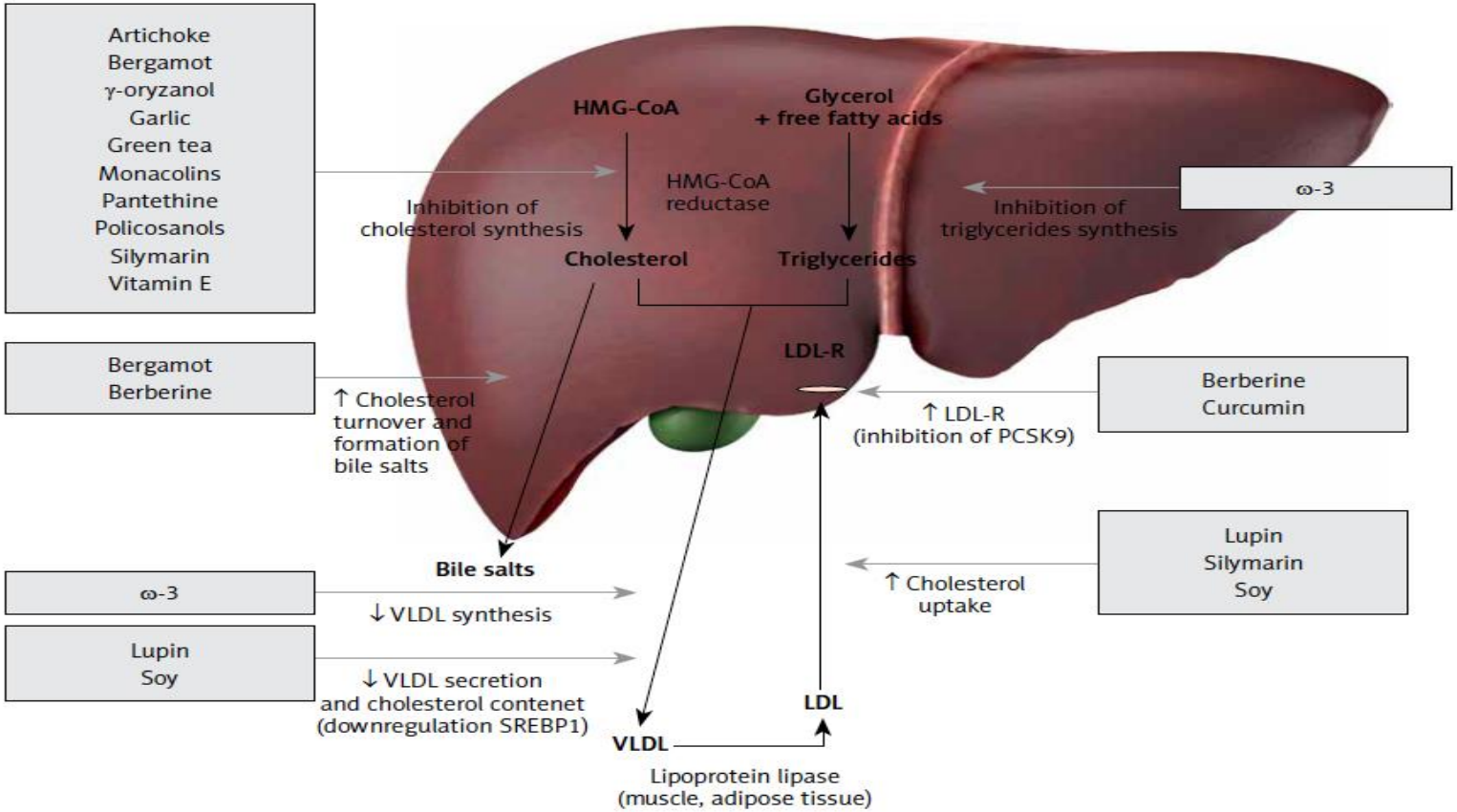


Figure 1. Nutraceuticals acting as inhibitors of liver cholesterol synthesis

HMG-CoA – 3-hydroxy-3-methylglutaryl-coenzyme A, LDL-R – low-density lipoprotein receptor, PCSK9 – proprotein convertase subtilisin/kexin type 9, SREBP1 – sterol regulatory element-binding protein 1, VLDL – very-low-density lipoprotein.

Cicero AFG, Banach M, et al. Nutr Rev. 2017;75(9):731-767.
Cicero AFG, Banach M, et al. Arch Med Sci 2017;13(5):965-1005.

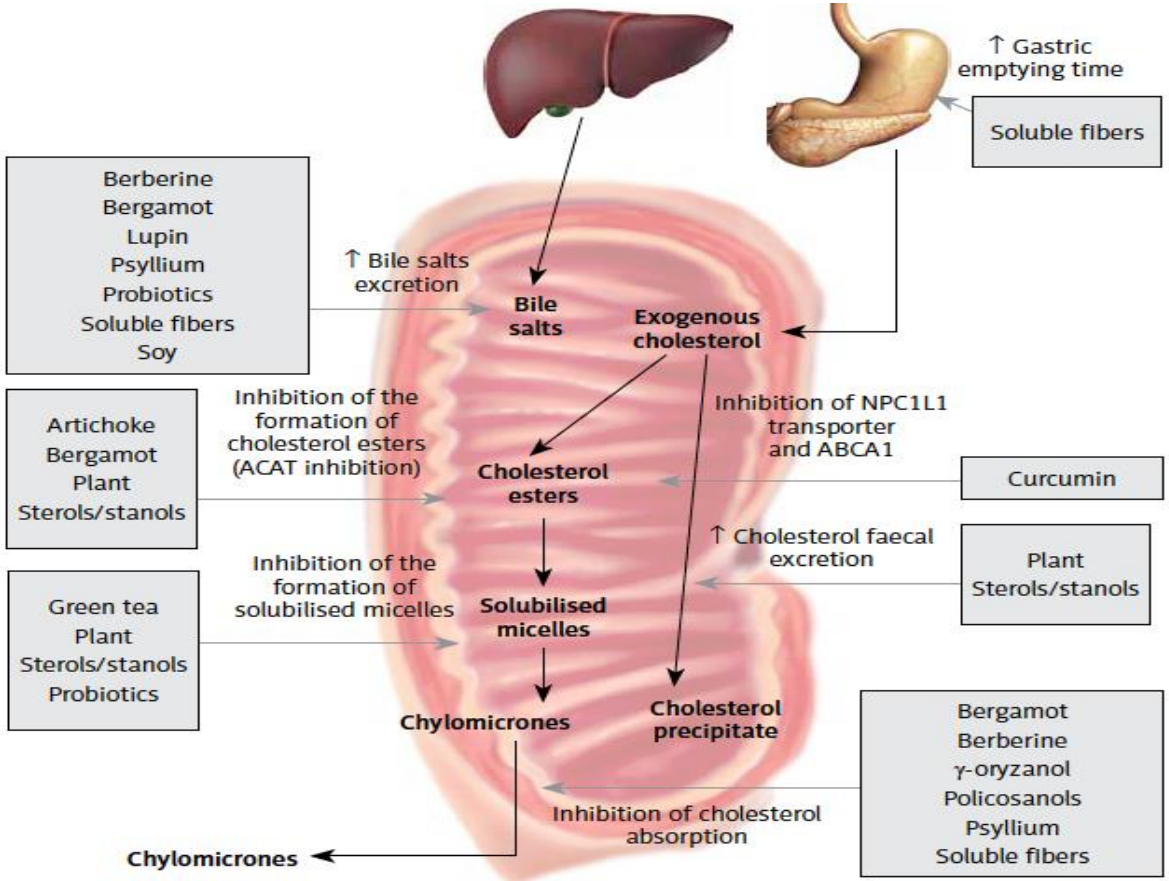


Figure 2. Nutraceuticals acting as inhibitors of intestinal cholesterol absorption and enhancers of cholesterol excretion

ABCA1 – ATP-binding cassette transporter, NPC1L1 – Niemann-Pick C1-Like 1.

Cicero AFG, Banach M, et al. Nutr Rev. 2017;75(9):731-767.
Cicero AFG, Banach M, et al. Arch Med Sci 2017;13(5):965-1005.

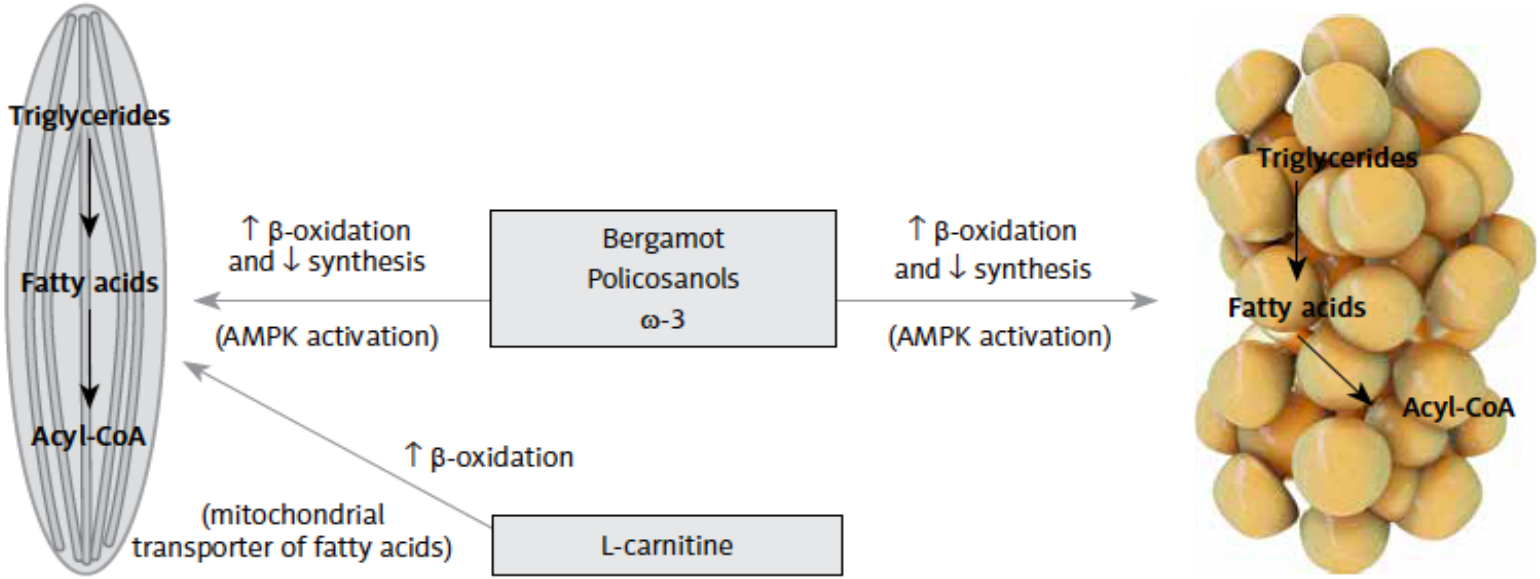


Figure 3. Nutraceuticals acting on fatty acids

AMPK – AMP-activated protein kinase.

Cicero AFG, Banach M, et al. Nutr Rev. 2017;75(9):731-767.
Cicero AFG, Banach M, et al. Arch Med Sci 2017;13(5):965-1005.

Inhibitors of intestinal cholesterol absorption

2.1. Plant sterols and stanols

Safety: In conclusion, PS produce a mean reduction of LDL-C by 8–12% in subjects with hypercholesterolemia. PS have also shown a high safety profile in the middle-term; however, data for treatment longer than 2 years are still not available [44, 50].

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	A	400–3000 mg	−8% to −12%	↓ hs-CRP	Not demonstrated

2.2. Soluble fibers

2.2.1. β-glucan

2.2.2. Psyllium

2.2.3. Glucomannan

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	A	5–15 g	−5% to −15%	↓ TG, glycemia, HOMA index, body weight	↓ CVD risk (epidemiological data on fiber-rich foods)

Inhibitors of liver cholesterol synthesis

3.1. Red yeast rice extract

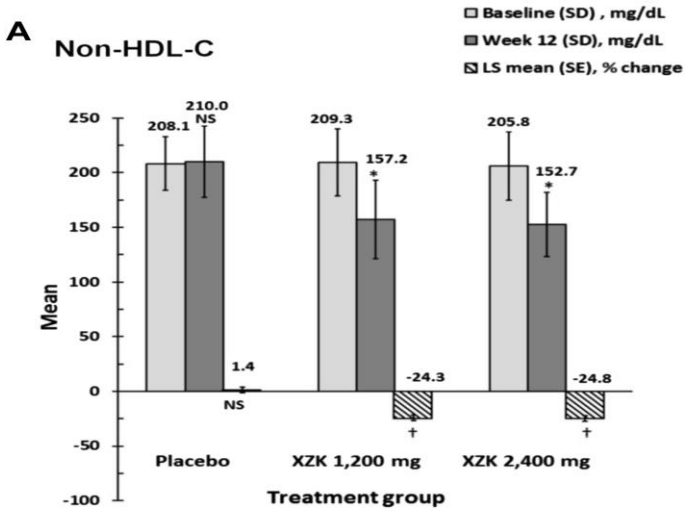
ment) [101]. However, some National Regulatory Agencies in Europe have recently suggested using lower dosages of MonK for safety purposes. Moreover, specific attention has to be given when full dosed RYR is administered in previously statin-intolerant subjects.

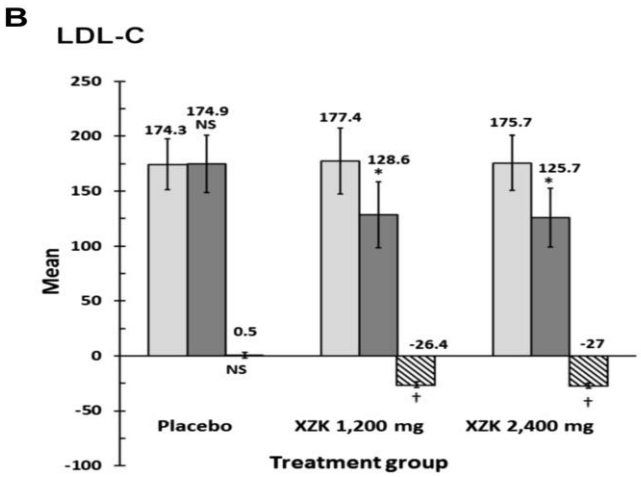
Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
I	A	3–10 mg (monacolin K)	−15% to −25%	↓ ApoB, hs-CRP, MMP-2, MMP-9	↑ FMD, ↓ PWV ↓ CV events in secondary prevention

3.2. Garlic (*Allium sativum*)

Safety: Side effects are usually minimal (mostly gastrointestinal) and the extracts are well tolerated [104].

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	A	5–6 g (extract)	−5% to −10%	↓ Blood pressure, platelet aggregation	Not demonstrated





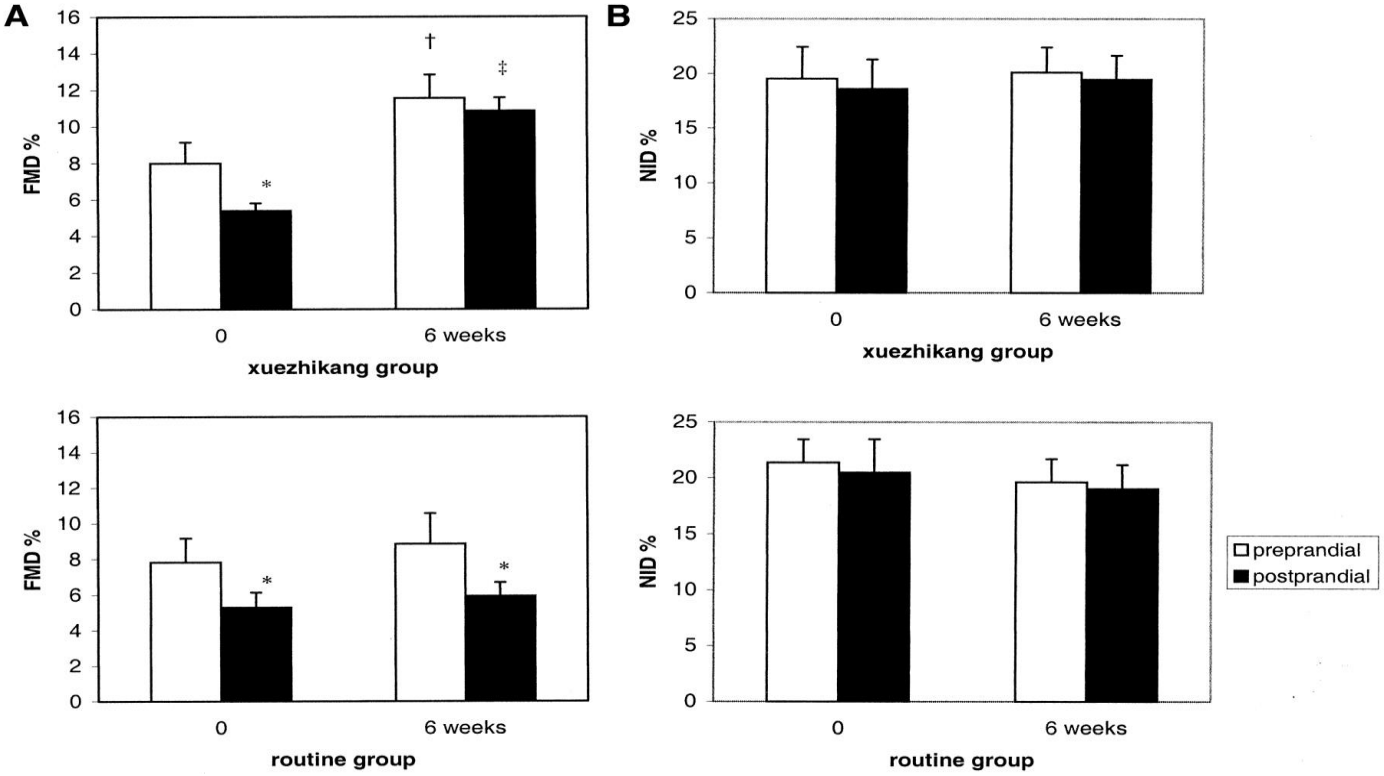
Treatment-emergent signs or symptoms	No. (%) of patients			
	Placebo (N = 37)	XZK 1200 mg (N = 36)	XZK 2400 mg (N = 42)	Total (N = 115)
All†	19 (51.4)	17 (47.2)	22 (52.4)	58 (50.4)
Gastrointestinal†	10 (27.0)	5 (13.9)	10 (23.8)	25 (21.7)
Discolored feces	5 (13.5)	0	5 (11.9)	10 (8.7)
Dyspepsia	1 (2.7)	3 (8.3)	1 (2.4)	5 (4.3)
Nausea	2 (5.4)	0	2 (4.8)	4 (3.5)
Diarrhea	1 (2.7)	2 (5.6)	0	3 (2.6)
Abdominal discomfort	2 (5.4)	0	0	2 (1.7)
Investigations/laboratory abnormalities†	5 (13.5)	2 (5.6)	1 (2.4)	8 (7.0)
Increased ALT	2 (5.4)	0	0	2 (1.7)
Increased AST	2 (5.4)	0	0	2 (1.7)
Increased blood CK	2 (5.4)	0	0	2 (1.7)
Increased leukocyte count	0	2 (5.6)	0	2 (1.7)
Infections	4 (10.8)	4 (11.1)	5 (11.9)	13 (11.3)
Upper-respiratory-tract infection	3 (8.1)	0	2 (4.8)	5 (4.3)
Nervous system disorder	3 (8.1)	1 (2.8)	3 (7.1)	7 (6.1)
Headache	2 (5.4)	1 (2.8)	2 (4.8)	5 (4.3)
Musculoskeletal and connective-tissue disorders	1 (2.7)	4 (11.1)	5 (11.9)	10 (8.7)
Muscle spasm	0	0	2 (4.8)	2 (1.7)
Myalgia	0	1 (2.8)	2 (4.8)	3 (2.6)

View Table in HTML

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; TESS, treatment-emergent signs or symptoms; XZK, Xuezhikang.

Moriarty PM, et al. Journal of Clinical Lipidology 2014 8, 568-575.
Becker DJ, et al. Ann Intern Med 2009;150:830-9.
Kasliwal RR, et al. Nutrition 2016;32:767-76.

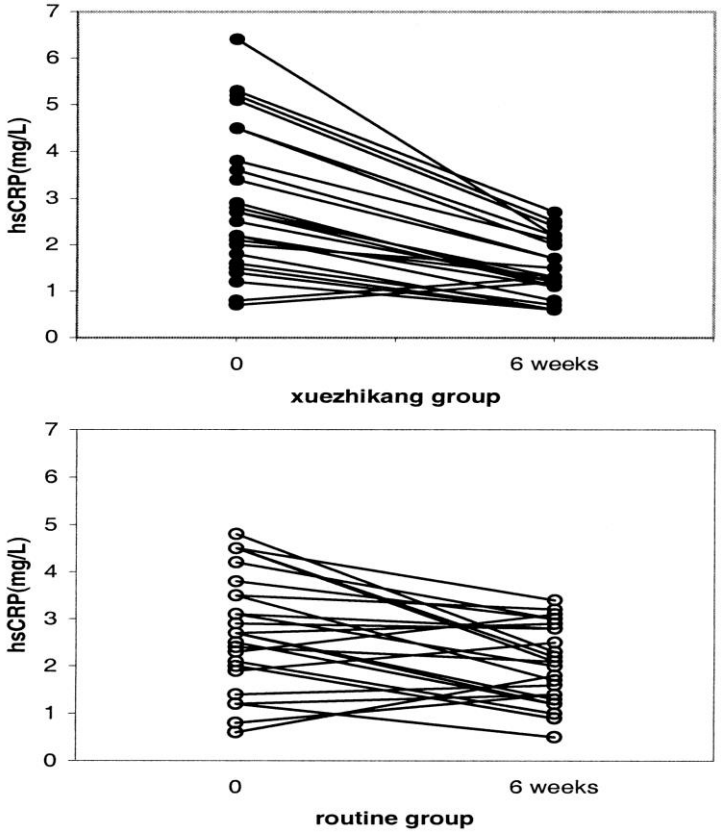
Effects of a high-fat meal on FMD and NID in CHD patients after 6 wks of RYR treatment vs placebo (routine group).



*Flow-mediated vasodilation (FMD); nitroglycerine-induced vasodilation (NID)

Shui Ping Zhao et al. Circulation. 2004;110:915-920

Changes of serum hsCRP concentrations in CHD patients after 6-week xuezhikang treatment vs placebo (routine group).



American Heart Association

Shui Ping Zhao et al. Circulation. 2004;110:915-920

SCIENTIFIC REPORTS

OPEN

Effects of a nutraceutical combination on lipids, inflammation and endothelial integrity in patients with subclinical inflammation: a randomized clinical trial

Received: 17 December 2015
Accepted: 07 March 2016
Published: 23 March 2016

Matteo Pirro[1], Massimo R. Mannarino[1], Stefano Ministrini[1], Francesca Fallarino[2], Graziana Lupattelli[1], Vanessa Bianconi[1], Francesco Bagaglia[1] & Elmo Mannarino[1]

	noNC						NC				
	Before Mean or median and SD or IQR		After Mean or median and SD or IQR		% change	p[&]	Before Mean or median and SD or IQR		After Mean or median and SD or IQR		% change
Total cholesterol, mg/dL	210	24	210	25	0.00	< 0.001	211	17	185	17	−12.32*
LDL cholesterol, mg/dL	131	16	132	18	0.76	< 0.001	134	14	105	15	−21.64*
HDL cholesterol, mg/dL	51	12	52	11	1.96	0.12	51	15	54	13	5.88
Triglycerides, mg/dL	110	72–186	103	78–154	−6.36	0.84	115	83–177	109	76–175	−5.21
Body mass index, kg/m^2	26.7	3.9	26.6	3.8	−0.37	0.99	26.5	3.4	26.3	3.6	−0.75
Waist circumference, cm	88	11	89	9	1.13	0.83	90	11	91	12	1.11
hsCRP, mg/L	2.7	2.2–4.9	3.4	1.8–5.1	25.92	0.04	3.0	2.2–4.2	2.5	1.3–3.4	−16.67*
EMPs, n/microL	401	298–514	407	278–504	1.50	< 0.001	416	302–500	353	247–438	−15.14*

Table 2. Influence of either the NC or the noNC therapy on selected variables. Values are mean ± standard deviation (SD) except for triglycerides, hsCRP and EMPs expressed as median and interquartile range (IQR). NC, nutraceutical combined therapy; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; EMPs, endothelial microparticles. *$p < 0.05$ for comparison between values at baseline and those after the NC treatment. [&]The p value is for the GLM comparison of variable variations after either NC or noNC treatment.

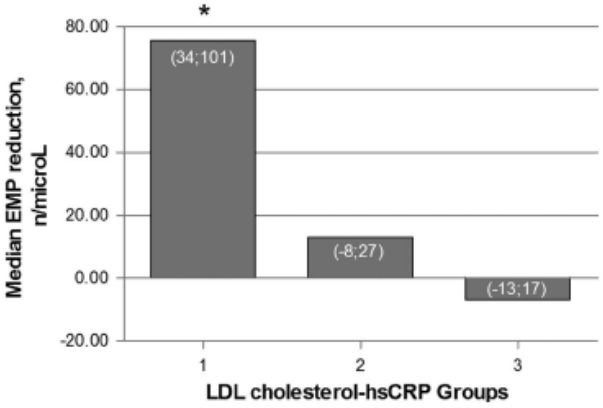
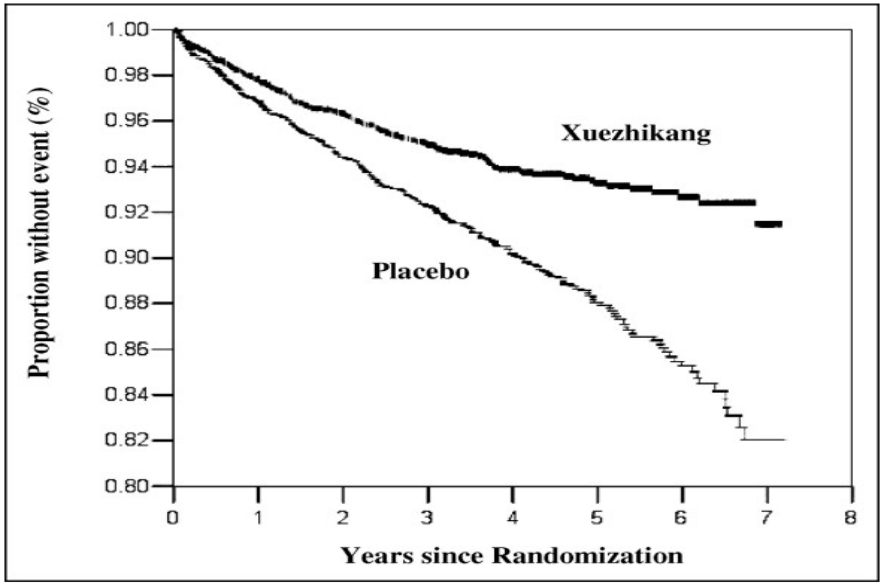


Figure 1. Post-intervention median EMP reduction according to the degree of LDL cholesterol and hsCRP changes. Group 1 includes patients with both LDL cholesterol and hsCRP reductions. Group 2 includes patients with either a LDL cholesterol or hsCRP reduction. Group 3 includes patients without evidence of LDL cholesterol and hsCRP reduction. *$p < 0.001$ for comparisons between Group 1 and Groups 2 and 3. Values inside the bars indicate the interquartile ranges.

This is a 3-month prospective randomized open-label interventional study in patients with elevated plasma hsCRP levels (>2 mg/L) and LDL-C of 100–160 mg/dL. The effect of either an oral cholesterol-lowering nutraceutical combination (NC) or no active treatment (noNC) was tested on LDL-C, hsCRP and endothelial microparticle (EMPs) levels.

**EMPs are small debris derived from endothelial cells membrane fragmentation; their release into circulation occurs in response to either endothelial activation, injury, proliferation or apoptosis*



Download full-size image

Figure 1. Kaplan-Meier curves for the proportion of patients without primary events in the XZK and placebo groups.

Table 2. Events according to study group (intention-to-treat population)

Events	Placebo		XZK		Difference Placebo-XZK (%)		p Value†
	No. of Patients	Incidence (%)	No. of Patients	Incidence (%)		Risk *Reduction With XZK (95% CI)	
Nonfatal MI	120	4.9%	47	1.9%	3%	0.38 (0.27–0.54)	<0.0001
Coronary disease mortality	134	5.5%	92	3.8%	1.7%	0.69 (0.52–0.88)	0.005
Fatal MI	28	1.2%	19	0.8%	0.4%	0.67 (0.38–1.20)	0.19
Fatal stroke	13	0.5%	12	0.5%	0.04%	0.91 (0.42–1.99)	0.85
Coronary revascularization	103	4.2%	67	2.8%	1.4%	0.64 (0.47–0.86)	0.004
CV mortality	149	6.1%	105	4.3%	1.8%	0.70 (0.54–0.89)	0.005
Cancer mortality	29	1.2%	13	0.5%	0.7%	0.44 (0.23–0.84)	0.014
Total mortality	189	7.7%	126	5.2%	2.5%	0.67 (0.52–0.82)	0.0003

*4,870 patients with a documented **previous myocardial infarction (MI)** were randomly assigned to twice-daily treatment with **XZK 600 mg** (300-mg capsule contains monacolin K at dose 2.5 to 3.2 mg/capsule) or placebo, administered orally for an **average of 4.5 years.**

No treatment-related SAEs reported, and XZK appeared to be well tolerated by patients. Total adverse experiences and discontinued participation were similar in both groups. Changes in laboratory findings did not differ between the groups. Minor occasional and transient increases in serum transaminase and CK were observed in both groups.

Lu Z, et al. Am J Cardiol. 2008;101(12):1689-93.

Inducer of LDL-cholesterol excretion

4.1. Berberine

Safety: Based on the abovementioned data, side effects are mild to moderate, mostly gastrointestinal (diarrhea, constipation, abdominal distension) and comparable to the control groups [139]. No significant differences were detected in the levels of aspartate transaminase (AST), alanine transaminase (ALT), and creatinine in comparison to the control group [140].

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
I	A	500–1500 mg	−15% to −20%	↓ ApoB, TG, hs-CRP, IL-6, MCP-1, ICAM-1, VCAM-1, MMP-9, glucose, HOMA index, blood pressure	Not demonstrated

4.2. Green tea extracts

Safety: Usually the consumption of green tea is well tolerated; however, in some cases rash, transient elevation of blood pressure and mild gastrointestinal disorders may occur. Moreover, high doses of green tea can cause a deficiency of iron and folate due to its capacity to bind and reduce their intestinal absorption. Therefore, particular attention should be given to green tea consumption during pregnancy [143].

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	A	25–100 g	−5%	↓ Blood pressure	↑ FMD, ↓ PWV (tea)

Other nutraceuticals with mixed mechanisms of action

5.1. Polyunsaturated ω-3 fatty acids

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
I	A	1–4 g	Not applicable	↓ sdLDL, TG, hs-CRP, TNF-α, ↓ adhesion molecules, ↓ blood pressure	↑ FMD, ↓ PWV, ↓ post-myocardial infarction sudden death risk

Other nutraceuticals with mixed mechanisms of action

5.3. Spirulina

Safety: Spirulina is considered to be one of the most healing and prophylactic ingredients of nutrition in the 21st century due to its nutrient profile, lack of toxicity and therapeutic effects. According to the available data it seems to be very well tolerated.

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	B	400–800 UI	−5%	↓ TG, ↑ HDL-C	Not demonstrated

5.6. Artichoke (*Cynara scolymus, Cynara cardunculus*)

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	B	1–3 g	−5% to −15%	↓ TG ↓ AST, ALT, glucose	Not demonstrated

5.4. Curcumin

Safety: Curcumin's safety profile is good and well documented. Nevertheless, a major problem is its oral bioavailability: curcumin has low solubility in water and it is a substrate of rapid metabolism. New strategies of release have been studied and tested such as phytosomal complexation with phosphatidylcholine, coadministration of piperine, using turmeric oleoresin, reducing particle size, and changing the formulation (nanoemulsion, solid lipid nanoparticle, microencapsulation); however, *in vivo* data of these new formulations are lacking [203].

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	B	1–3 g	−5%	↓ TG, Lp(a), glucose, HbA_{1c}, HOMA index, hs-CRP, TNF-α, IL-6, ↑ adiponectin, HDL-C	↑ FMD, ↓ PWV

6. Nutraceutical combinations

Red yeast rice and policosanols

Safety: Based on the data from all above-mentioned studies, no serious safety concerns have been raised.

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
I	A	Monacolin K 3–5 mg, policosanol 10 mg	−15% to −21%	Not demonstrated	Not demonstrated

Red yeast rice, policosanols and berberine

Safety: Based on the available data, no serious safety concerns have been raised.

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
I	A	Monacolin K 3 mg, policosanol 10 mg, berberine 500 mg	−20% to −25%	↓ hs-CRP, TG, glucose	↑ FMD, ↓ PWV

Red yeast rice and artichoke

Safety: Based on the available data, no serious safety concerns have been raised, but further studies with longer follow-up are necessary to conclusively confirm this.

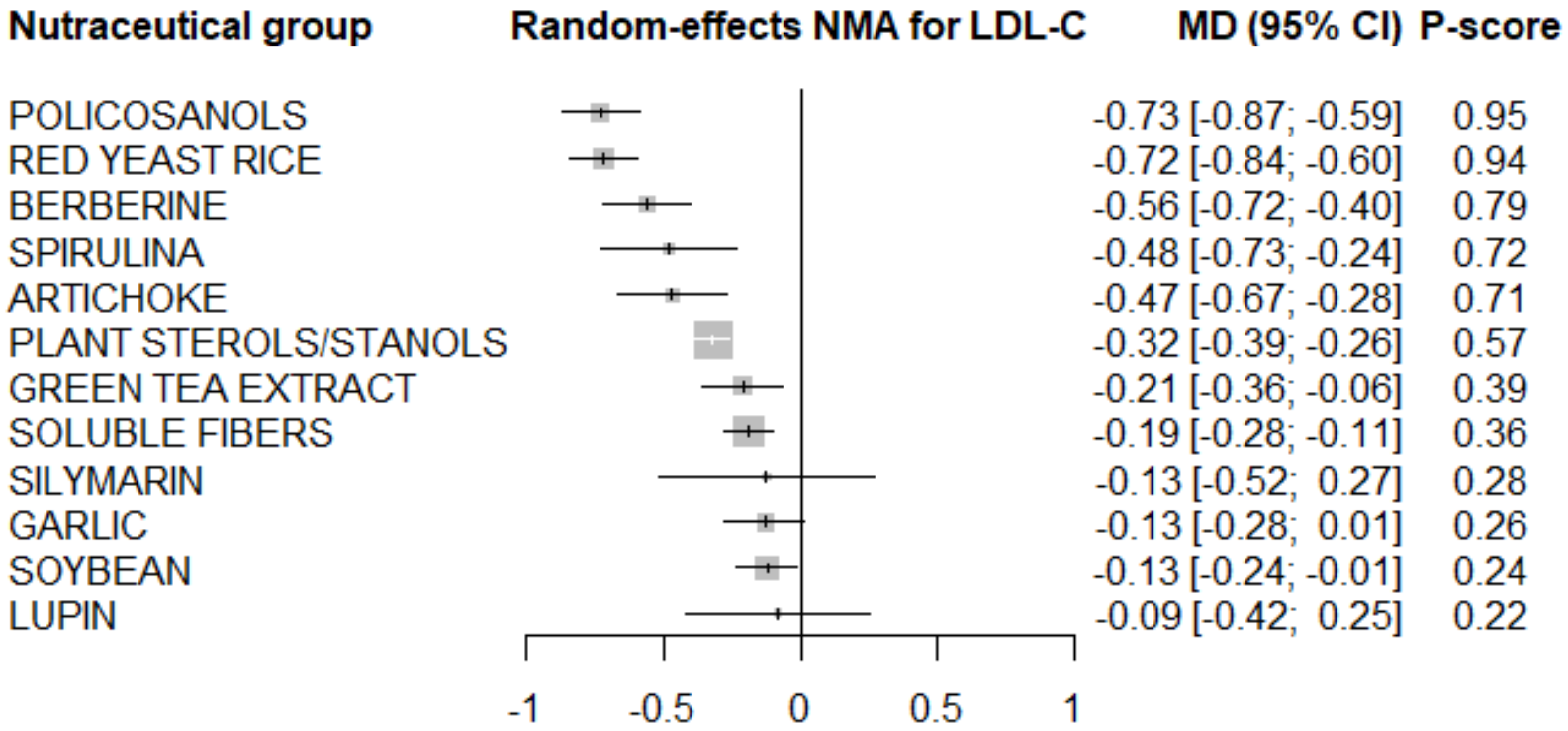
Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	B	Monacolin K 2–10 mg, artichoke extract 500–600 mg	−14% to −21%	↓ hs-CRP, TG	Not demonstrated

Red yeast rice and antioxidants

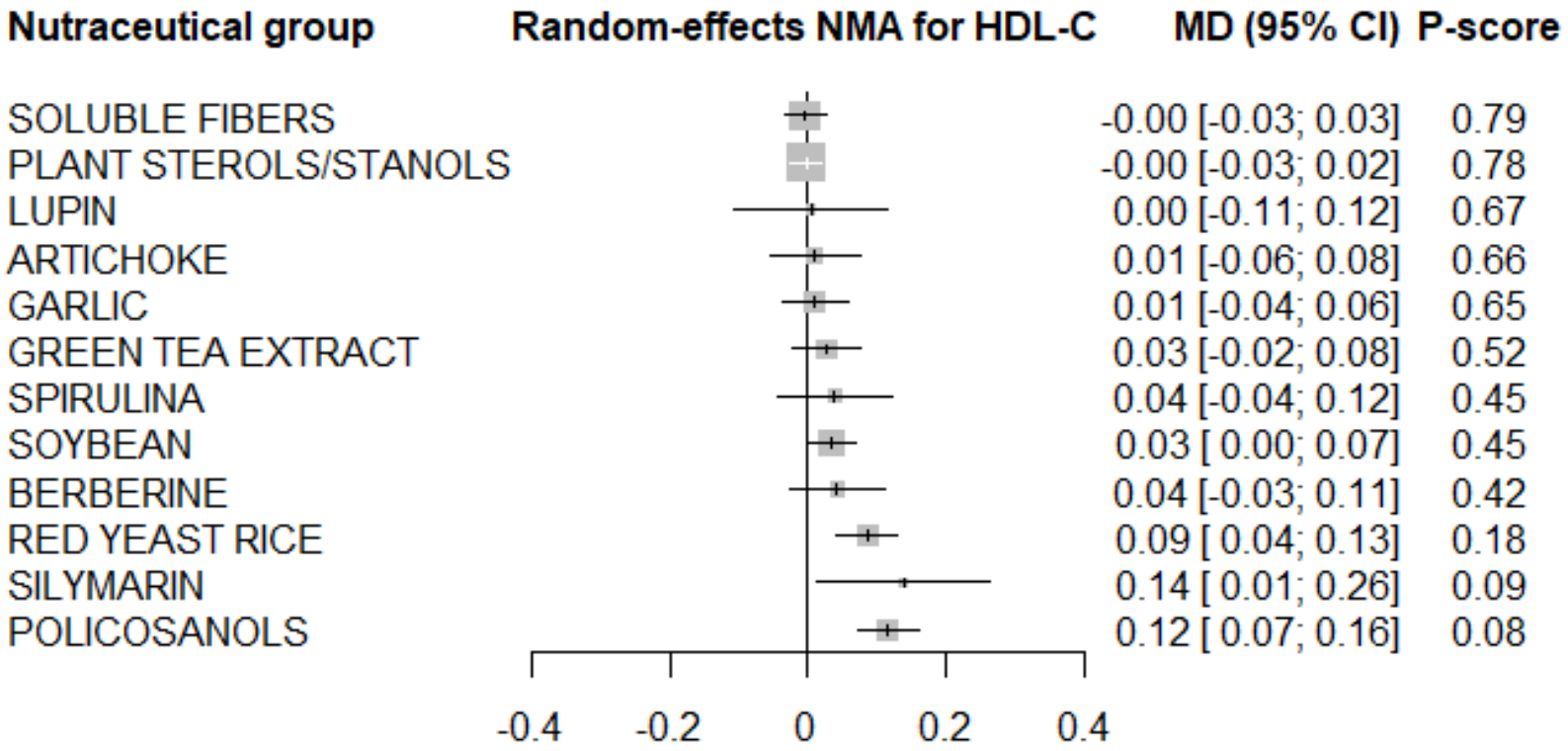
Safety: Based on the available data, no serious safety concerns have been raised.

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	B	Monacolin K 10 mg, CoQ10 or other antioxidants	−20% to −26%	↓ hs-CRP	↑ FMD, ↓ PWV

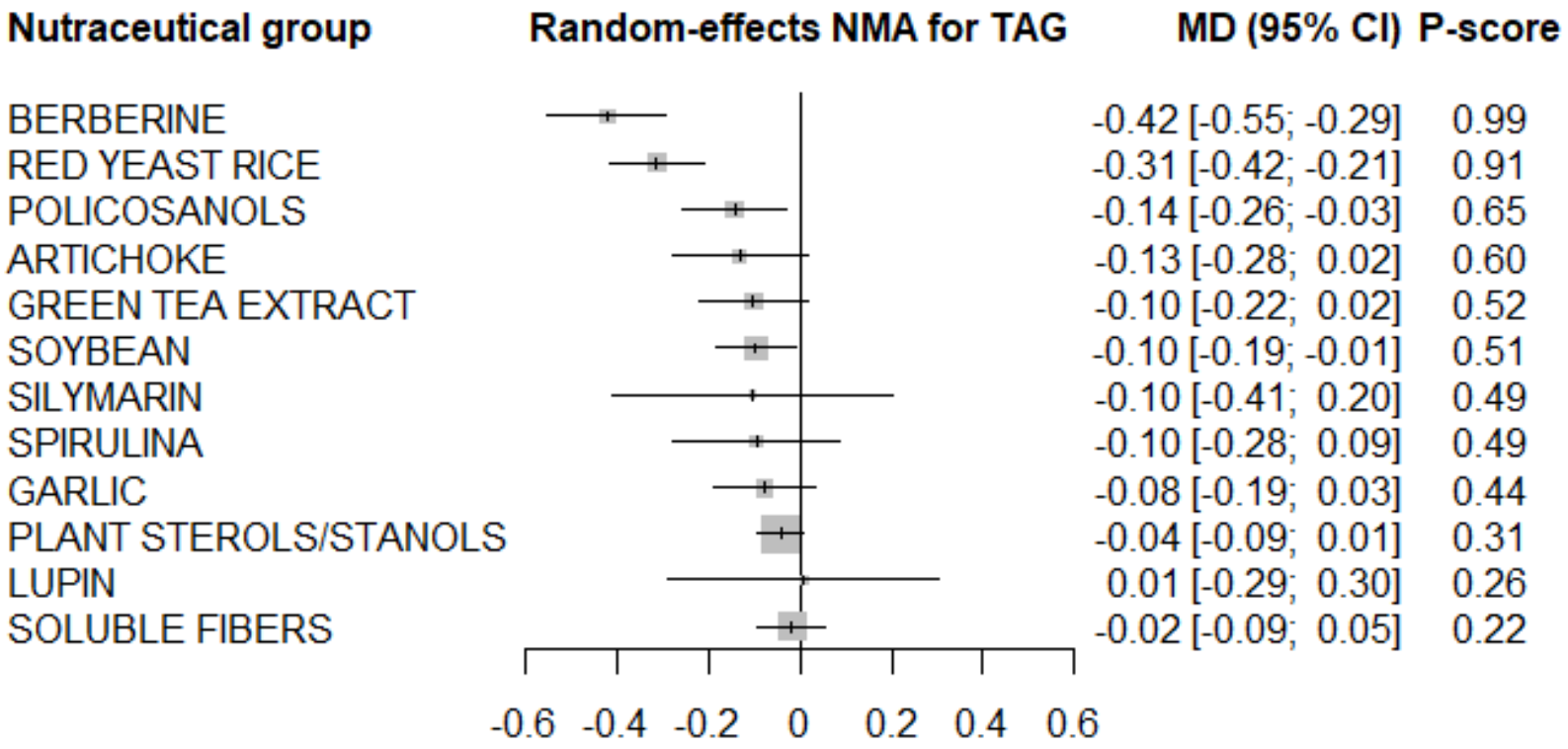
Comparative effects of nutraceuticals on LDL-C



Comparative effects of nutraceuticals on HDL-C



Comparative effects of nutraceuticals on TGs



6. Nutraceutical combinations
6.1. Red yeast rice and policosanols
6.2. Red yeast rice, policosanols and berberine
6.3. Red yeast rice and plant sterols
6.4. Red yeast rice and artichoke
6.5. Red yeast rice, policosanol, and silymarin
6.6. Red yeast rice and antioxidants
6.7. Berberine combined with bioactive lipid-lowering agents other than red yeast rice
6.8. Soy proteins and plant sterols
6.9. Different nutraceutical combinations supported by single RCTs
7. Nutraceuticals combined with pharmacological therapy
7.1. Statins and polyunsaturated fatty acids
7.2. Statins and soluble fibers
7.3. Ezetimibe, red yeast rice, policosanol and berberine
7.4. Ezetimibe or statins and berberine with silymarin
7.5. Statins/ezetimibe and plant sterols
7.6. Statins and tocotrienols
7.7. Statins and bergamot
7.8. Statins and garlic
7.9. Statins and vitamin D

Red yeast rice and plant sterols

Safety: In the available studies none of the participants reported any muscle pains and no abnormal liver function tests were observed while taking this supplement. However, further studies with longer follow-up are necessary to conclusively confirm this.

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
IIa	B	Monacolin K 5–10 mg, phytosterols 800–1250 mg	−25% to −30%	↓ ApoB	Not demonstrated

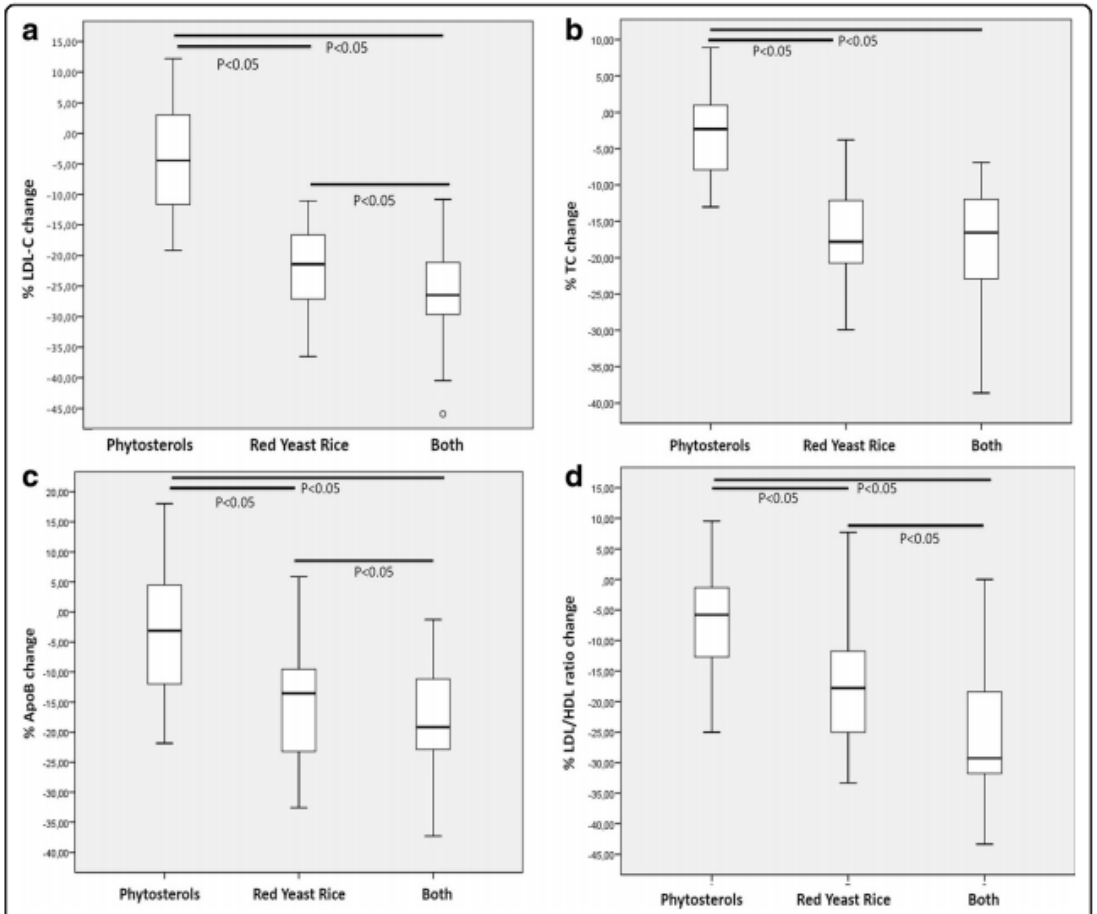
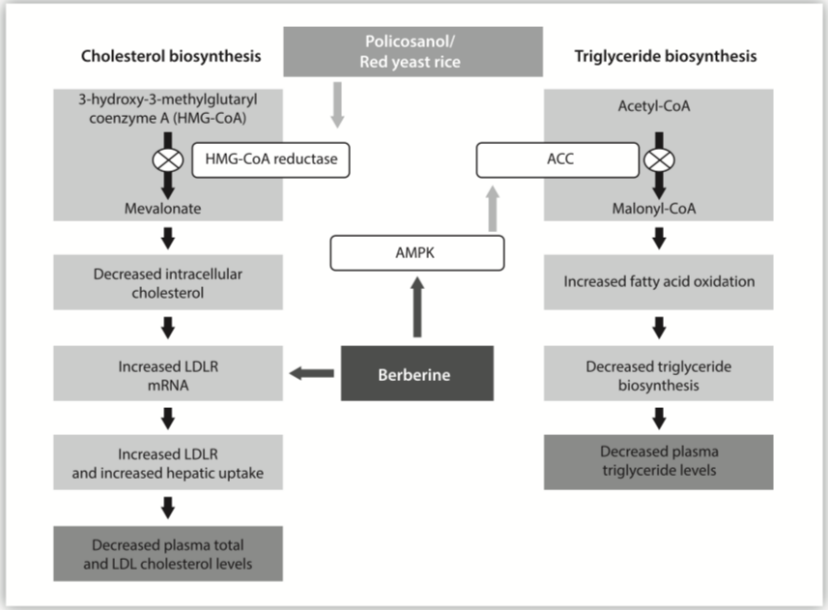


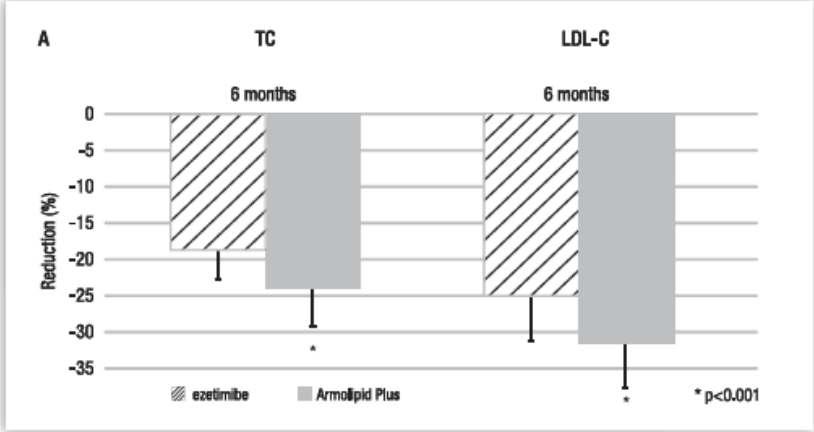
Fig. 1 Percentage change of LDL-cholesterolemia (**a**), Total Cholesterol (**b**), Apolipoprotein B (**c**) and LDL to HDL ration (**d**) in the three treatment groups versus baseline

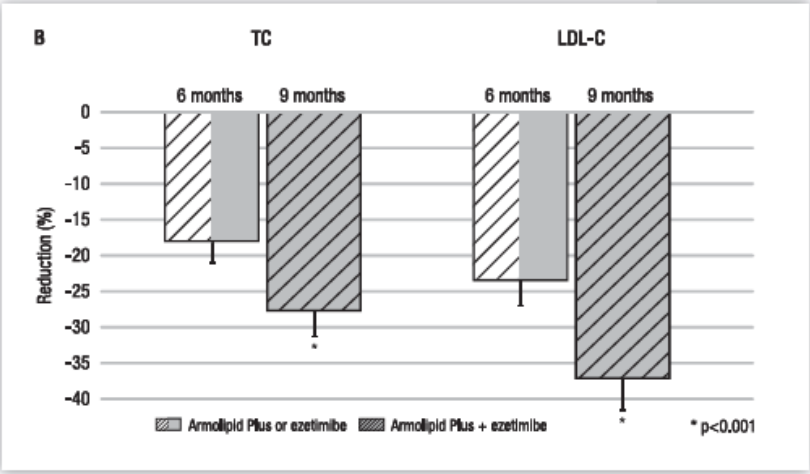
Cicero et al. Nutrition & Metabolism (2017) 14:61

Armolipid Plus®

Class	Level	Active daily doses	Expected effects on LDL-C	Safety issues
I	A	RYR 200 mg (equivalent to Monacolin K 3 mg), Policosanol 10 mg, berberine 500 mg folic acid (0.2 mg), astaxanthin (0.5 mg), and coenzyme Q10 (2 mg)	-15% to -30%	No safety concerns







Barrios V, Banach M, et al. Atheroscler Suppl. 2017 Feb;24:1-15.

ORIGINAL INVESTIGATION

Effect of Combining Psyllium Fiber With Simvastatin in Lowering Cholesterol

Abel E. Moreyra, MD; Alan C. Wilson, PhD; Ashraf Koraym, MD

Arch Intern Med. 2005;165:1161-1166

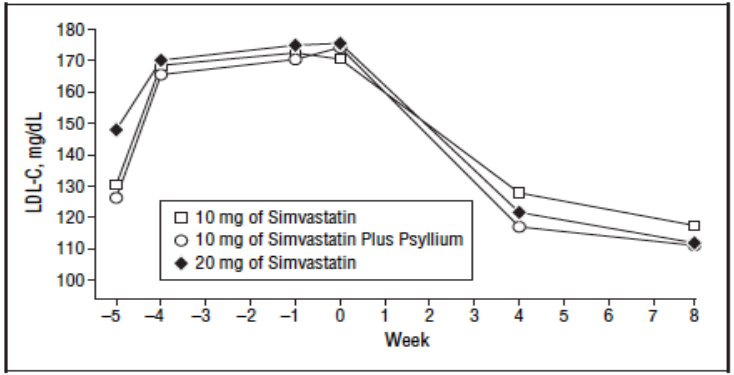


Figure 1. Plots of mean levels of low-density lipoprotein cholesterol (LDL-C) per visit, by treatment group, during the study. To convert cholesterol to millimoles per liter, multiply by 0.0259.

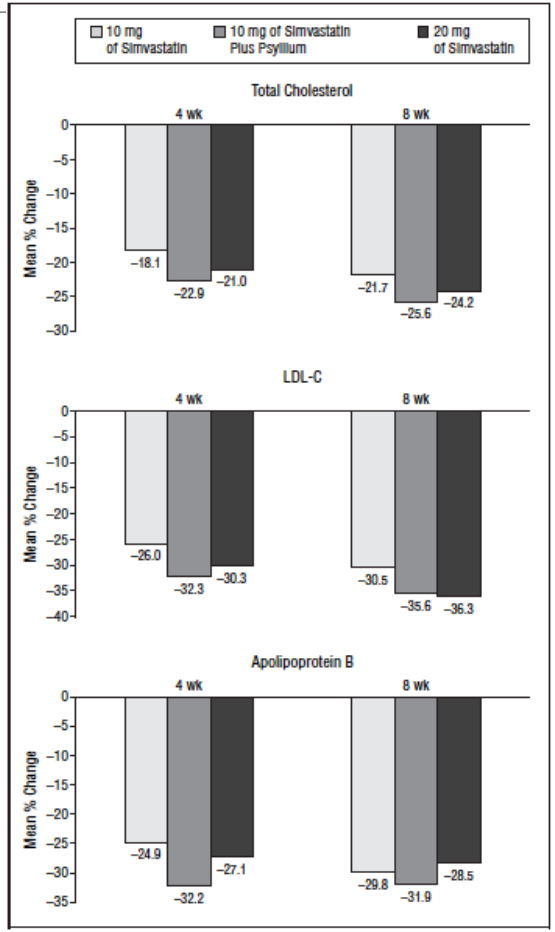


Figure 2. Charts showing mean percentage changes from baseline at 4 and 8 weeks in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B.

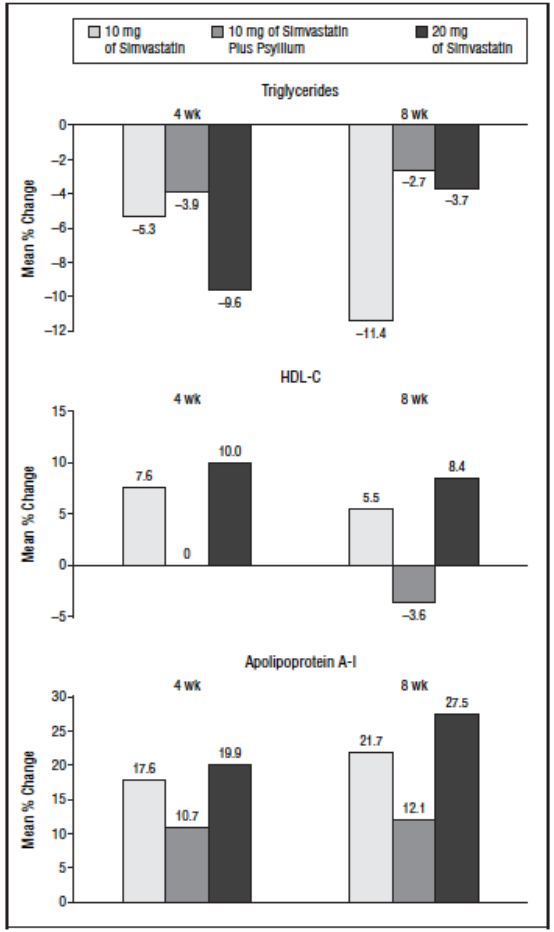


Figure 3. Charts showing mean percentage changes from baseline at 4 and 8 weeks in triglycerides, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A-I.

The Role of Nutraceuticals in Statin Intolerant Patients

Maciej Banach, MD, PhD,[a,b,*] Angelo Maria Patti, MD,[c,*] Rosaria Vincenza Giglio, BSc,[c] Arrigo F.G. Cicero, MD, PhD,[d] Atanas G. Atanasov, PhD,[e,f] Gani Bajraktari, MD, PhD,[g] Eric Bruckert, MD, PhD,[h] Olivier Descamps, MD, PhD,[i,j] Dragan M. Djuric, MD, PhD,[k] Marat Ezhov, MD, PhD,[l] Zlatko Fras, MD, PhD,[m] Stephan von Haehling, MD, PhD,[n] Niki Katsiki, MD, PhD,[o] Michel Langlois, MD, PhD,[p] Gustavs Latkovskis, MD, PhD,[q] G.B. John Mancini, MD,[r] Dimitri P. Mikhailidis, MD,[s] Olena Mitchenko, MD,[t] Patrick M. Moriarty, MD,[u] Paul Muntner, PhD,[v] Dragana Nikolic, PhD,[c] Demosthenes B. Panagiotakos, PhD,[w] Gyorgy Paragh, MD, PhD,[x] Bernhard Paulweber, MD,[y] Daniel Pella, MD, PhD,[z] Christos Pitsavos, MD, PhD,[aa] Željko Reiner, MD, PhD,[bb] Giuseppe M.C. Rosano, MD, PhD,[cc,dd] Robert S. Rosenson, MD,[ee] Jacek Rysz, MD, PhD,[a,b] Amirhossein Sahebkar, PharmD, PhD,[ff] Maria-Corina Serban, MD, PhD,[gg] Dragos Vinereanu, MD, PhD,[hh] Michal Vrablík, MD, PhD,[ii] Gerald F. Watts, DSc, PhD,[jj] Nathan D. Wong, PhD,[kk] Manfredi Rizzo, MD, PhD,[c] on behalf of the International Lipid Expert Panel (ILEP)

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

TABLE 6 Red Yeast Rice

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
I	A	1,200–4,800 mg (3-10 mg* of monacolin K)	−15% to −25%	Due to content of monacolin K some adverse effects typical for statins might appear

*Maximum recommended doses as dietary supplement recommended by the European Food Safety Authority (EFSA) (128).
LDL-C = low-density lipoprotein cholesterol.

TABLE 7 Phytosterols

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
IIa	C	Phytosterols 800–2,400 mg	−7% to −10%	Should be avoided in patients with phytosterolemia and those who are heterozygous for variants of *ABCG5* and *ABCG8* and other genes.

LDL-C = low-density lipoprotein cholesterol.

TABLE 8 Bergamot (Citrus Bergamia)

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
IIb	B	500–1,500 mg	−15% to −25%	No safety concerns

LDL-C = low-density lipoprotein cholesterol.

TABLE 9 Soy Products

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
IIb	B	25–100 g	−6% to −10%	Possible interfering with thyroid function and fertility; ↓ absorption of calcium, magnesium, copper, iron, and zinc

LDL-C = low-density lipoprotein cholesterol.

TABLE 10 Polyunsaturated Omega-3 Fatty Acids

Class	Level	Active Daily Doses	Expected Effects on LDL-C	Safety Issues
IIa	B	1–4 g	−3% to −7%	Fish oil supplementation might be proarrhythmic especially in patients at the risk of arrhythmias.

LDL-C = low-density lipoprotein cholesterol.

Armolipid Plus®

Class	Level	Active daily doses	Expected effects on LDL-C	Safety issues
I	A	RYR 200 mg (equivalent to Monacolin K 3 mg), Policosanol 10 mg, berberine 500 mg folic acid (0.2 mg), astaxanthin (0.5 mg), and coenzyme Q10 (2 mg)	-15% to -30%	No safety concerns

Usefulness of Nutraceuticals (Armolipid Plus) Versus *Ezetimibe* and Combination in Statin-Intolerant Patients With Dyslipidemia With Coronary Heart Disease

Giuseppe Marazzi, MD, PhD[a,*], Francesco Pelliccia, MD, PhD[b], Giuseppe Campolongo, MD[a], Silvia Quattrino, MD[a], Luca Cacciotti, MD[c], Maurizio Volterrani, MD, PhD[a], Carlo Gaudio, MD[b], and Giuseppe Rosano, MD, PhD[a]

Am J Cardiol 2015;116:1798–1801

Table 1
Baseline characteristics in the 2 groups

Variable	Nutraceutical Combination (n=50)	Ezetimibe (n=50)	p-value
Male	26 (52%)	28 (56%)	0.688
Age (years)	64±11	63±10	0.772
Diabetes mellitus	15 (30%)	18 (36%)	0.523
Hypertension	22 (44%)	20 (40%)	0.685
Smoker	15 (30%)	13 (26%)	0.656
Total cholesterol (mg/dl)	218± 15	219±14	0.836
Low-density lipoprotein cholesterol (mg/dl)	149±16	150±8	0.600
High-density lipoprotein cholesterol (mg/dl)	36±8	34±7	0.337
Triglycerides (mg/dl)	166±31	171±25	0.381
Ejection fraction (%)	54±8	55±11	0.815

Table 2
Comparisons between groups for lipid profile after 3 months of treatment

Variable	Nutraceutical Combination (n=50)	Ezetimibe (n=50)	p-value
Total cholesterol (mg/dl)	177±12	194±16	<0.0001
Low-density lipoprotein cholesterol (mg/dl)	109±8	126±11	<0.0001
High-density lipoprotein cholesterol (mg/dl)	39±8	36±7	0.0203
Triglycerides (mg/dl)	144±25	163±26	0.0003

Table 3
Effects of the 2 treatments on lipid profile after 12 months of treatment

Variable	Nutraceutical combination (n=14)			p-value	Emetizibe plus Nutraceuticals (n=86)			p-value
	Base-line	3 months	12 months		Base-line	3 months	12 months	
Total cholesterol (mg/dl)	205±11	165±7	163±7	<0.0001	189±15	166±12	164±13	<0.0001
Low-density lipoprotein cholesterol (mg/dl)	136±6	98±3	95±3	<0.0001	120±11	97±9	95±10	<0.0001
High-density lipoprotein cholesterol (mg/dl)	36±8	39±7	40±7	<0.0001	37±8	41±8	41±8	<0.0001
Triglycerides (mg/dl)	161±22	139±20	140±21	<0.0001	157±27	142±22	140±21	<0.0001

Table 4
Laboratory safety variables

	Nutraceutical Combination (n=14)			Ezetimibe plus Nutraceuticals (n=86)		
	Baseline	12 months	p-value	Baseline	12 months	p-value
Aspartate aminotransferase (U/L)	24±7	25±5	0.062	26±8	25±6	0.099
Alanine aminotransferase (U/L)	26±4	25±3	0.104	25±5	26±4	0.154
Creatine kinase (mU/mL)	139±34	137±23	0.074	130±28	126±31	0.073

Comparison of Low-Dose Statin Versus Low-Dose Statin + Armolipid Plus in High-Intensity Statin-Intolerant Patients With a Previous Coronary Event and Percutaneous Coronary Intervention (ADHERENCE Trial)

Giuseppe Marazzi, MD, PhD[a,*], Giuseppe Campolongo, MD[a], Francesco Pelliccia, MD, PhD[b], Silvia Quattrino, MD[a], Cristiana Vitale, MD, PhD[a], Luca Cacciotti, MD, PhD[c], Rosalba Massaro, MD[a], Maurizio Volterrani, MD, PhD[a], and Giuseppe Rosano, MD, PhD[a]

Am J Cardiol 2017;120:893–897

Table 1
Baseline characteristics in the 2 groups

Variable*	Low-dose statin (n = 50)	Low-dose statin plus nutraceutical combination (n = 50)
Men	28 (56%)	26 (52%)
Age (years), mean ±SD	67 ± 12	69 ± 10
Diabetes mellitus	20 (40%)	18 (36%)
Hypertension	34 (68%)	38 (76%)
Current smoker	3 (6%)	4 (8%)
TOT-C (mg/dl), mean ±SD	199 ± 11	198 ± 9
LDL-C (mg/dl), mean ±SD	129 ± 17	127 ± 15
HDL-C (mg/dl), mean ±SD	35 ± 4	35 ± 4
Triglycerides (mg/dl), mean ±SD	176 ± 51	177 ± 51
Left ventricular ejection fraction (% ±SD)	54 ± 3	53 ± 2
Blood creatinine (mg/dl), mean ±SD	0.8 ± 0.3	0.8 ± 0.2

* p = non-significant for all between group comparisons; SD = standard deviation.

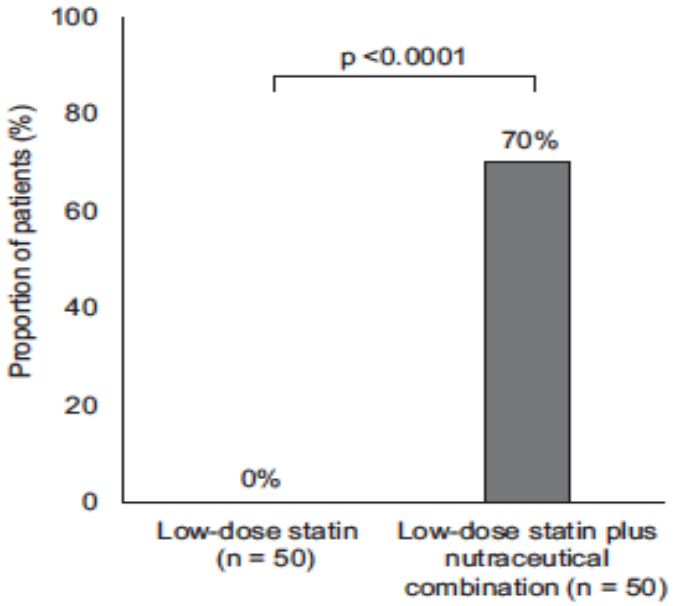
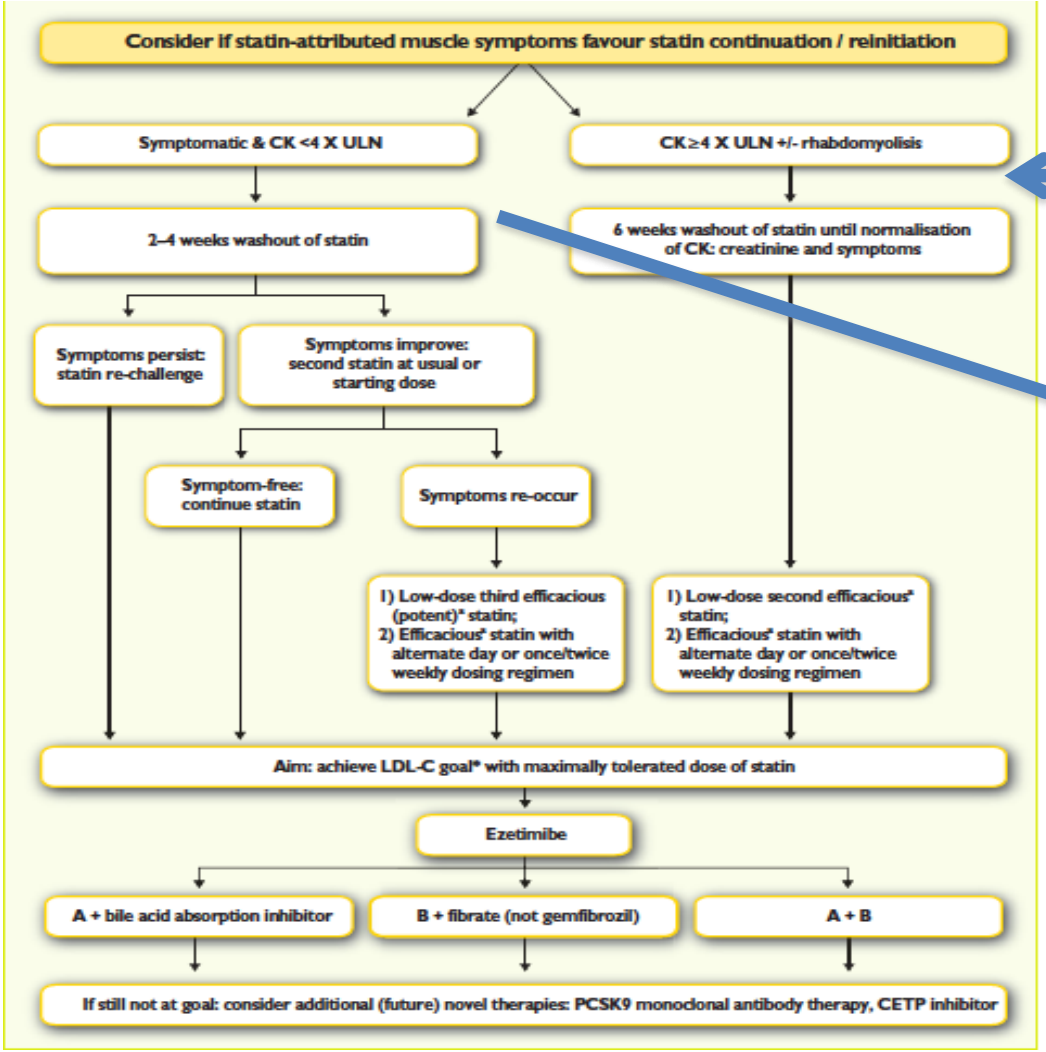


Figure 1. Proportion of patients who achieved the primary outcome of a reduction in low-density lipoprotein cholesterol (LDL-C) to the therapeutic target (<70 mg/dl) after 3 months of treatment.

Table 3
Changes in lipid concentrations from baseline to 3 months of therapy, following treatment with low-dose statin versus low-dose statin plus nutraceutical combination

Variable	Low-dose statin (n = 50)			Low-dose statin plus nutraceutical combination (n = 50)			p value*
	Baseline, mean ±SD	3 months, mean ±SD	% change	Baseline, mean ±SD	3 months, mean ±SD	% change	
TOT-C (mg/dl)	199 ± 11	192 ± 10	−3.5	198 ± 9	163 ± 8	−17.5	<0.0001
LDL-C (mg/dl)	129 ± 17	123 ± 16	−4.3	127 ± 15	93 ± 12	−26.8	<0.0001
HDL-C (mg/dl)	35 ± 4	37 ± 4	+3.7	35 ± 4	38 ± 4	+8.8	0.02
Triglycerides (mg/dl)	176 ± 51	163 ± 47	−7.9	177 ± 51	159 ± 51	−10.2	NS

* The p value is for the between group comparisons; NS = not significant; SD = standard deviation.



Selected groups of patients that might benefit most from the use of PCSK9 inhibitors based on the most recent data summarized by the ILEP[20]

Patient group	Background therapy	Biomarkers	NNT
Patients with early ACS (up to 1–12 months)	Optimal treatment	Persistent LDL ≥100 mg/dL	29
Patient with early ACS (up to 1–12 months)	Optimal treatment	Persistent LDL ≥70 mg/dL + diabetes mellitus and/or baseline Lp(a) >60 mg/dL	30
Patients with very high cardiovascular risk (after ACS)	Optimal treatment	Persistent LDL ≥70 mg/dL + diabetes and/or baseline CRP >3 mg/dL	<30
Patients with very high cardiovascular risk (after ACS)	Optimal treatment	Persistent LDL ≥70 mg/dL + with concomitant PAD	29
Patients with very high cardiovascular risk (after ACS)	Optimal treatment	Persistent LDL ≥70 mg/dL + ≥2 previous ACS and initially with diabetes/Lp(a) >60 mg/dL/CRP >3 mg/L	<30
Patients with very high cardiovascular risk (after ACS)	Optimal treatment	Persistent LDL ≥70 mg/dL + with multivessel disease	29

Ezetimibe/nutraceuticals
OR ezetimibe + nutraceuticals
OR PCSK9 inihibitors

TABLE 12 Which Nutraceuticals Can be Useful in Statin Intolerance, and for Which Patients

Recommendations	Class	Level
In high-risk or very-high-risk patients with complete statin intolerance who have not reached LDL-C targets with nonstatin therapy, nutraceuticals in monotherapy and combination should be considered.	IIa	B
In high-risk or very-high-risk patients with partial statin intolerance who have not reached LDL-C targets with tolerable statin therapy and/or nonstatin therapy, nutraceuticals in monotherapy and combination should be considered.	IIa	B
In individuals with statin intolerance and high cholesterol levels (and other risk factors) with intermediate CV risk who have not reached LDL-C targets, nutraceuticals in monotherapy and combination should be considered.	IIa	A

ELSEVIER

Pharmacological Research
Available online 4 March 2019
In Press, Accepted Manuscript

Review

SAFETY OF RED YEAST RICE SUPPLEMENTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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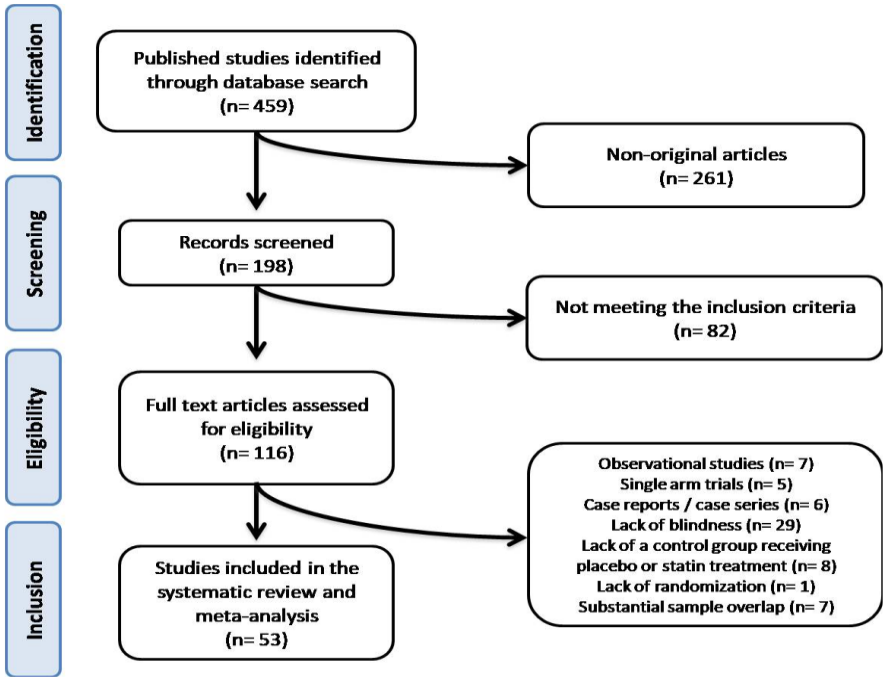
***Literature was searched from inception to Feb 27th, 2019.**

Data were pooled from **53 RCTs** comprising **112 treatment arms, which included 8535 subjects, with 4437 in the RYR arm and 4303 in the control one.** For reasons largely independent of the tested nutraceuticals (i.e. withdrawal of informed consent and personal problems), 144 subjects prematurely terminated the trials in which they were enrolled. Therefore, the meta-analysis was performed on the other subjects (**intention-to-treat (ITT) population**).

Original studies were included if they met the following criteria: (i) being a RCT with either parallel or cross-over design, (ii) testing the safety of RYR supplementation alone or in combination with other nutraceutical compounds, (iii) reporting all the adverse events, (iv) having an appropriate controlled design and (v) blinding participants to the treatment allocation.

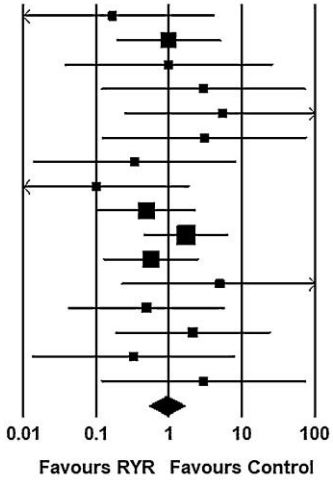


RYR and musculoskeletal disorders

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
D'Addato, S (2017 - I)	0.17	0.01	4.31	-1.08	0.28
Marazzi, G (2017)	1.00	0.19	5.21	0.00	1.00
Spigoni, V (2017)	1.00	0.04	26.68	0.00	1.00
Cicero, AF (2016 a)	3.00	0.12	75.90	0.67	0.51
Cicero, AF (2016 b)	5.43	0.25	118.96	1.07	0.28
Cicero, AF (2016 c)	3.08	0.12	77.80	0.68	0.50
Heinz, T (2016)	0.34	0.01	8.44	-0.66	0.51
Kasliwal, RR (2016)	0.10	0.01	1.91	-1.53	0.13
Verhoeven, V (2015)	0.50	0.10	2.35	-0.88	0.38
Verhoeven, V (2013)	1.74	0.46	6.62	0.81	0.42
Marazzi, G (2011)	0.57	0.13	2.55	-0.74	0.46
Bogsrud, MP (2010)	5.00	0.23	110.71	1.02	0.31
Halbert, SC (2010)	0.50	0.04	5.97	-0.55	0.58
Becker, DJ (2009)	2.14	0.18	24.96	0.61	0.54
Shang, XB (2007)	0.33	0.01	8.21	-0.68	0.50
Heber, D (1999)	3.00	0.12	75.79	0.67	0.50
	0.94	0.53	1.65	-0.22	0.82

Statistics for each study

Odds ratio and 95% CI



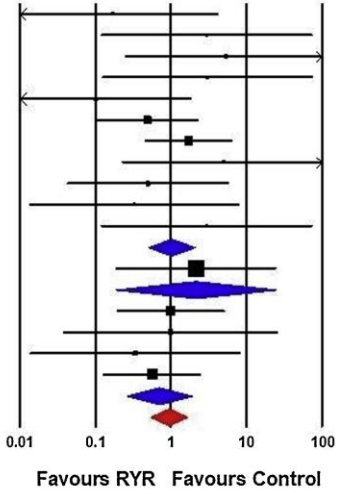
Heterogeneity: $I^2 = 0$

Meta Analysis

Group by Monacolin k	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
> 5 mg	D'Addato, S (2017 - I)	0.17	0.01	4.31	-1.08	0.28
> 5 mg	Cicero, AF (2016 a)	3.00	0.12	75.90	0.67	0.51
> 5 mg	Cicero, AF (2016 b)	5.43	0.25	118.96	1.07	0.28
> 5 mg	Cicero, AF (2016 c)	3.08	0.12	77.80	0.68	0.50
> 5 mg	Kasliwal, RR (2016)	0.10	0.01	1.91	-1.53	0.13
> 5 mg	Verhoeven, V (2015)	0.50	0.10	2.35	-0.88	0.38
> 5 mg	Verhoeven, V (2013)	1.74	0.46	6.62	0.81	0.42
> 5 mg	Bogsrud, MP (2010)	5.00	0.23	110.71	1.02	0.31
> 5 mg	Halbert, SC (2010)	0.50	0.04	5.97	-0.55	0.58
> 5 mg	Shang, XB (2007)	0.33	0.01	8.21	-0.68	0.50
> 5 mg	Heber, D (1999)	3.00	0.12	75.79	0.67	0.50
> 5 mg		1.01	0.49	2.08	0.04	0.97
3.1-5 mg	Becker, DJ (2009)	2.14	0.18	24.96	0.61	0.54
3.1-5 mg		2.14	0.18	24.96	0.61	0.54
up to 3 mg	Marazzi, G (2017)	1.00	0.19	5.21	0.00	1.00
up to 3 mg	Spigoni, V (2017)	1.00	0.04	26.68	0.00	1.00
up to 3 mg	Heinz, T (2016)	0.34	0.01	8.44	-0.66	0.51
up to 3 mg	Marazzi, G (2011)	0.57	0.13	2.55	-0.74	0.46
up to 3 mg		0.70	0.26	1.91	-0.70	0.49
Overall		0.94	0.53	1.65	-0.22	0.82

Statistics for each study

Odds ratio and 95% CI



Heterogeneity:
> 5 mg → $I^2 = 0$
3.1-5 mg → $I^2 = 0$
up to 3 mg → $I^2 = 0$

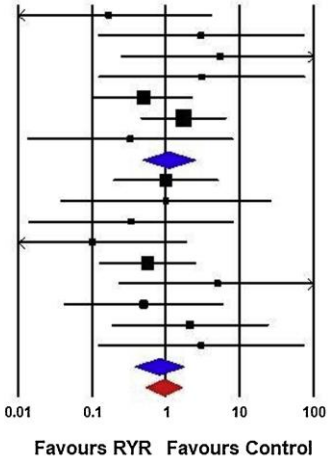
Meta Analysis

No MuD was experienced by subjects enrolled in 37 studies among those selected for the meta-analysis. In the others, monacolin K administration was neither associated with increased risk of MuD in the entire sample (**OR = 0.94, 95%CI 0.53,1.65**; *Fig. 1*) nor in subsets of studies categorized according to administrated daily dose (besides dosage ranged 3.1-5 mg/day which was based only on a single study; *Fig. 2*).

RYR and musculoskeletal disorders

Group by Follow-up	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
< 12 weeks	D'Addato, S (2017 - I)	0.17	0.01	4.31	-1.08	0.28
< 12 weeks	Cicero, AF (2016 a)	3.00	0.12	75.90	0.67	0.51
< 12 weeks	Cicero, AF (2016 b)	5.43	0.25	118.96	1.07	0.28
< 12 weeks	Cicero, AF (2016 c)	3.08	0.12	77.80	0.68	0.50
< 12 weeks	Verhoeven, V (2015)	0.50	0.10	2.35	-0.88	0.38
< 12 weeks	Verhoeven, V (2013)	1.74	0.46	6.62	0.81	0.42
< 12 weeks	Shang, XB (2007)	0.33	0.01	8.21	-0.68	0.50
< 12 weeks		1.09	0.48	2.50	0.21	0.83
at least 12 weeks	Marazzi, G (2017)	1.00	0.19	5.21	0.00	1.00
at least 12 weeks	Spigoni, V (2017)	1.00	0.04	26.68	0.00	1.00
at least 12 weeks	Heinz, T (2016)	0.34	0.01	8.44	-0.66	0.51
at least 12 weeks	Kasliwal, RR (2016)	0.10	0.01	1.91	-1.53	0.13
at least 12 weeks	Marazzi, G (2011)	0.57	0.13	2.55	-0.74	0.46
at least 12 weeks	Bogsrud, MP (2010)	5.00	0.23	110.71	1.02	0.31
at least 12 weeks	Halbert, SC (2010)	0.50	0.04	5.97	-0.55	0.58
at least 12 weeks	Becker, DJ (2009)	2.14	0.18	24.96	0.61	0.54
at least 12 weeks	Heber, D (1999)	3.00	0.12	75.79	0.67	0.50
at least 12 weeks		0.82	0.37	1.78	-0.51	0.61
Overall		0.94	0.53	1.65	-0.22	0.82

Heterogeneity:
< 12 weeks → $I^2 = 0$
at least 12 weeks → $I^2 = 0$

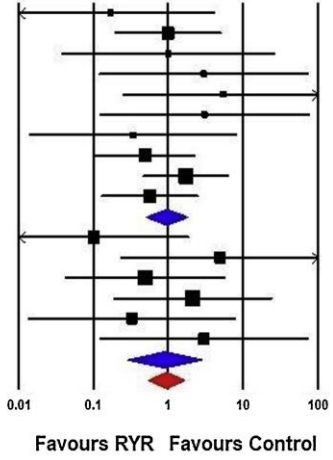


Meta Analysis

Fig. 3. Forest plot comparing the RYR associated risk of MuD. **Subgroup analysis stratified by treatment duration.** RYR: Red yeast rice, MuD: Musculoskeletal disorders.

Group by Intervention	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
NC with RYR	D'Addato, S (2017 - I)	0.17	0.01	4.31	-1.08	0.28
NC with RYR	Marazzi, G (2017)	1.00	0.19	5.21	0.00	1.00
NC with RYR	Spigoni, V (2017)	1.00	0.04	26.68	0.00	1.00
NC with RYR	Cicero, AF (2016 a)	3.00	0.12	75.90	0.67	0.51
NC with RYR	Cicero, AF (2016 b)	5.43	0.25	118.96	1.07	0.28
NC with RYR	Cicero, AF (2016 c)	3.08	0.12	77.80	0.68	0.50
NC with RYR	Heinz, T (2016)	0.34	0.01	8.44	-0.66	0.51
NC with RYR	Verhoeven, V (2015)	0.50	0.10	2.35	-0.88	0.38
NC with RYR	Verhoeven, V (2013)	1.74	0.46	6.62	0.81	0.42
NC with RYR	Marazzi, G (2011)	0.57	0.13	2.55	-0.74	0.46
NC with RYR		0.95	0.50	1.83	-0.15	0.88
RYR	Kasliwal, RR (2016)	0.10	0.01	1.91	-1.53	0.13
RYR	Bogsrud, MP (2010)	5.00	0.23	110.71	1.02	0.31
RYR	Halbert, SC (2010)	0.50	0.04	5.97	-0.55	0.58
RYR	Becker, DJ (2009)	2.14	0.18	24.96	0.61	0.54
RYR	Shang, XB (2007)	0.33	0.01	8.21	-0.68	0.50
RYR	Heber, D (1999)	3.00	0.12	75.79	0.67	0.50
RYR		0.89	0.28	2.84	-0.20	0.84
Overall		0.94	0.53	1.65	-0.22	0.82

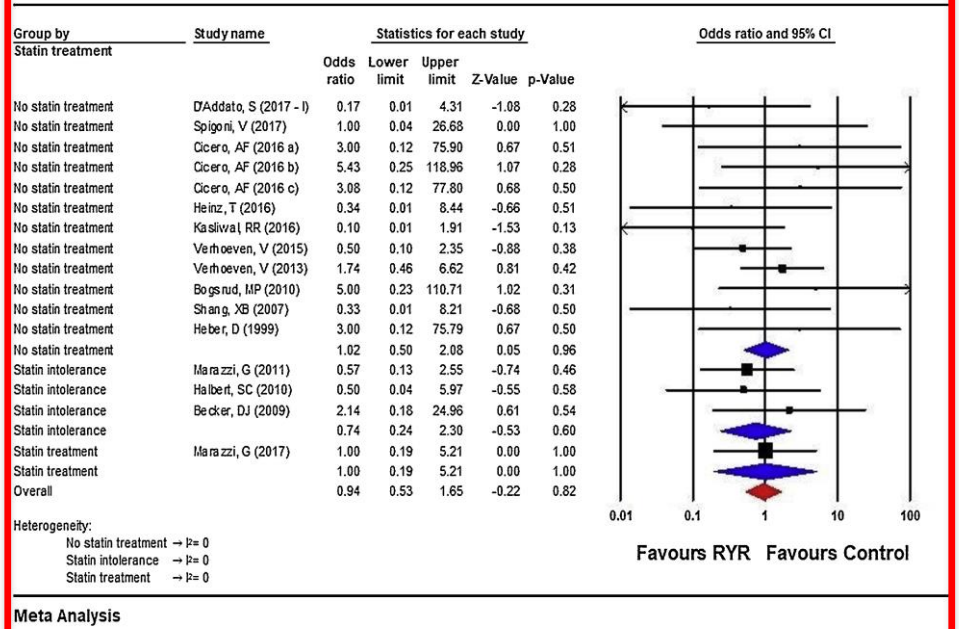
Heterogeneity:
NC with RYR → $I^2 = 0$
RYR → $I^2 = 0$



Meta Analysis

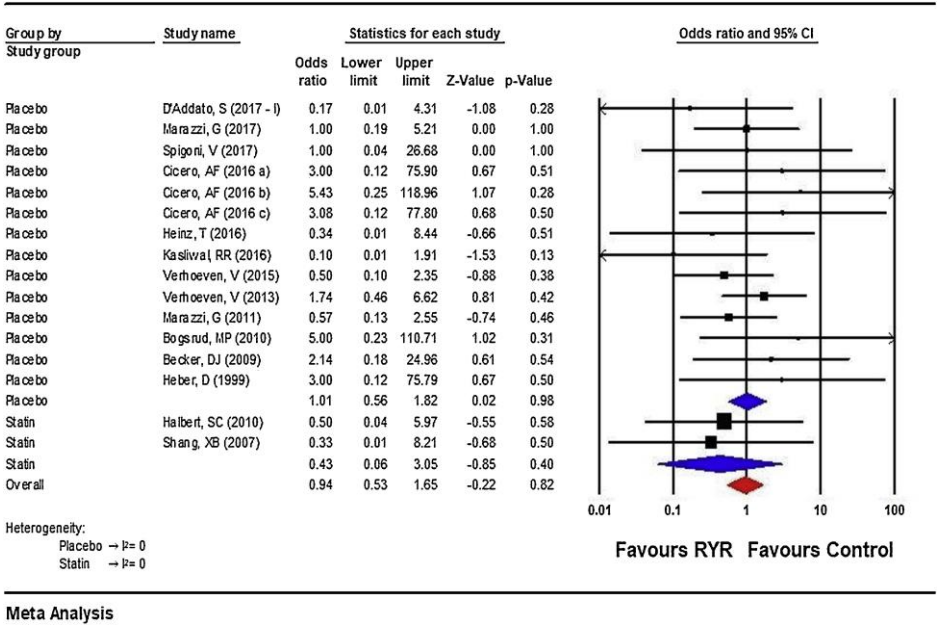
Fig. 4. Forest plot comparing the RYR associated risk of MuD. **Subgroup analysis stratified by intervention type.** NC: nutraceutical, RYR: Red yeast rice, MuD: Musculoskeletal disorders.

RYR and musculoskeletal disorders



Group by Statin treatment	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
No statin treatment	D'Addato, S (2017 - I)	0.17	0.01	4.31	-1.08	0.28
No statin treatment	Spigoni, V (2017)	1.00	0.04	26.68	0.00	1.00
No statin treatment	Cicero, AF (2016 a)	3.00	0.12	75.90	0.67	0.51
No statin treatment	Cicero, AF (2016 b)	5.43	0.25	118.96	1.07	0.28
No statin treatment	Cicero, AF (2016 c)	3.08	0.12	77.80	0.68	0.50
No statin treatment	Heinz, T (2016)	0.34	0.01	8.44	-0.66	0.51
No statin treatment	Kasliwal, RR (2016)	0.10	0.01	1.91	-1.53	0.13
No statin treatment	Verhoeven, V (2015)	0.50	0.10	2.35	-0.88	0.38
No statin treatment	Verhoeven, V (2013)	1.74	0.46	6.62	0.81	0.42
No statin treatment	Bogsrud, MP (2010)	5.00	0.23	110.71	1.02	0.31
No statin treatment	Shang, XB (2007)	0.33	0.01	8.21	-0.68	0.50
No statin treatment	Heber, D (1999)	3.00	0.12	75.79	0.67	0.50
No statin treatment		1.02	0.50	2.08	0.05	0.96
Statin intolerance	Marazzi, G (2011)	0.57	0.13	2.55	-0.74	0.46
Statin intolerance	Halbert, SC (2010)	0.50	0.04	5.97	-0.55	0.58
Statin intolerance	Becker, DJ (2009)	2.14	0.18	24.96	0.61	0.54
Statin intolerance		0.74	0.24	2.30	-0.53	0.60
Statin treatment	Marazzi, G (2017)	1.00	0.19	5.21	0.00	1.00
Statin treatment		1.00	0.19	5.21	0.00	1.00
Overall		0.94	0.53	1.65	-0.22	0.82

Fig. 5. Forest plot comparing the RYR associated risk of MuD. **Subgroup analysis stratified by presence of statin intolerance or statin therapy.** RYR: Red yeast rice, MuD: Musculoskeletal disorders.



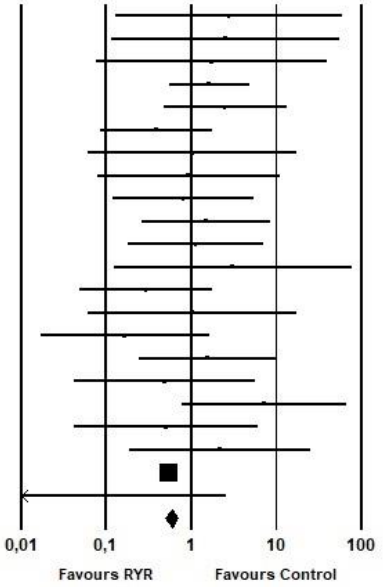
Group by Study group	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Placebo	D'Addato, S (2017 - I)	0.17	0.01	4.31	-1.08	0.28
Placebo	Marazzi, G (2017)	1.00	0.19	5.21	0.00	1.00
Placebo	Spigoni, V (2017)	1.00	0.04	26.68	0.00	1.00
Placebo	Cicero, AF (2016 a)	3.00	0.12	75.90	0.67	0.51
Placebo	Cicero, AF (2016 b)	5.43	0.25	118.96	1.07	0.28
Placebo	Cicero, AF (2016 c)	3.08	0.12	77.80	0.68	0.50
Placebo	Heinz, T (2016)	0.34	0.01	8.44	-0.66	0.51
Placebo	Kasliwal, RR (2016)	0.10	0.01	1.91	-1.53	0.13
Placebo	Verhoeven, V (2015)	0.50	0.10	2.35	-0.88	0.38
Placebo	Verhoeven, V (2013)	1.74	0.46	6.62	0.81	0.42
Placebo	Marazzi, G (2011)	0.57	0.13	2.55	-0.74	0.46
Placebo	Bogsrud, MP (2010)	5.00	0.23	110.71	1.02	0.31
Placebo	Becker, DJ (2009)	2.14	0.18	24.96	0.61	0.54
Placebo	Heber, D (1999)	3.00	0.12	75.79	0.67	0.50
Placebo		1.01	0.56	1.82	0.02	0.98
Statin	Halbert, SC (2010)	0.50	0.04	5.97	-0.55	0.58
Statin	Shang, XB (2007)	0.33	0.01	8.21	-0.68	0.50
Statin		0.43	0.06	3.05	-0.85	0.40
Overall		0.94	0.53	1.65	-0.22	0.82

Fig. 6. Forest plot comparing the RYR associated risk of MuD. **Subgroup analysis stratified by control treatment.** RYR: Red yeast rice, MuD: Musculoskeletal disorders.

RYR and non-musculoskeletal disorders

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
D'Addato, S (2017 - I)	2,765	0,127	60,028	0,648	0,517
D'Addato, S (2017 - II)	2,528	0,116	54,919	0,590	0,555
Spigoni, V (2017)	1,727	0,076	39,300	0,343	0,732
Heinz, T (2016)	1,623	0,546	4,827	0,871	0,384
Kasliwal, RR (2016)	2,471	0,467	13,084	1,064	0,287
Verhoeven, V (2015)	0,391	0,086	1,784	-1,212	0,225
Gonnelli, S (2014)	1,036	0,062	17,377	0,024	0,981
Moriarty, PM (2014 - I)	0,919	0,078	10,844	-0,067	0,946
Moriarty, PM (2014 - II)	0,804	0,121	5,351	-0,226	0,821
Barrat, E (2013 a - I)	1,500	0,266	8,449	0,460	0,646
Barrat, E (2013 a - II)	1,125	0,183	6,935	0,127	0,899
Barrat, E (2013 b)	3,061	0,122	76,949	0,680	0,497
Verhoeven, V (2013)	0,293	0,048	1,773	-1,336	0,181
Affuso, F (2012)	1,036	0,062	17,377	0,024	0,981
Karl, M (2012)	0,167	0,017	1,651	-1,531	0,126
Guardamagna, O (2011)	1,543	0,243	9,800	0,460	0,646
Marazzi, G (2011)	0,487	0,042	5,599	-0,577	0,564
Bogsrud, MP (2010)	7,125	0,775	65,537	1,734	0,083
Halbert, SC (2010)	0,500	0,042	5,966	-0,548	0,584
Becker, DJ (2009)	2,143	0,184	24,959	0,608	0,543
Lu, Z (2008)	0,540	0,455	0,640	-7,096	0,000
Heber, D (1999)	0,129	0,006	2,587	-1,338	0,181
	0,588	0,501	0,689	-6,549	0,000

Heterogeneity: $I^2 = 7\%$



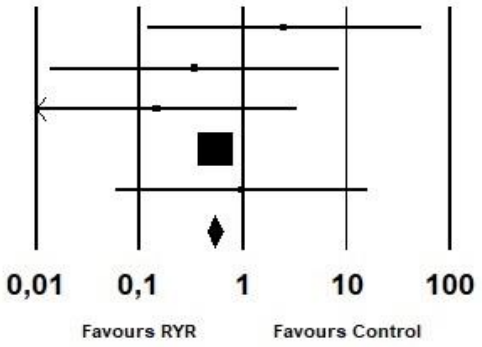
Meta Analysis

No Non-MuD was experienced by subjects enrolled in 34 studies among those selected. In the others, meta-analysis showed reduced risk of Non-MuD vs. control (**OR 0.59, 95%CI 0.50,0.69**). Subgroup analyses confirmed the high tolerability profile of monacolin K at the tested doses. Considering the entire population, meta-regression analyses did not suggest an increased risk for RYR associated Non-MuD depending on age (slope: -0.03; 95%CI: -0.06, 0.003; two-tailed $p = 0.08$). Increasing daily doses of monacolin K were negatively associated with increasing risk of Non-MuD (slope: -0.10; 95%CI: -0.17, -0.03; two-tailed $p < 0.01$).

RYR and serious adverse events (SAE)

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Spigoni, V (2017)	2,509	0,118	53,225	0,590	0,555
Heinz, T (2016)	0,338	0,014	8,440	-0,661	0,509
Karl, M (2012)	0,147	0,007	3,263	-1,213	0,225
Lu, Z (2008)	0,540	0,455	0,640	-7,096	0,000
Heber, D (1999)	0,976	0,059	16,137	-0,017	0,986
	0,541	0,457	0,641	-7,121	0,000

Heterogeneity: $I^2 = 0\%$



Meta Analysis

No SAE was experienced by subjects enrolled in 48 studies among those selected. In the others, meta-analysis showed reduced risk of SAE vs. control (**OR 0.54, 95%CI 0.46,0.64**). Considering the entire population, meta-regression analyses did not suggest an increased risk for RYR associated SAE depending on age (slope: -0.15; 95%CI: -0.49, 0.19; two-tailed $p = 0.39$) or monacolin daily dose (slope: -0.02; 95%CI: -0.24, 0.20; two-tailed $p = 0.86$).

TAKE HOME MESSAGE:

(…) *It is, however, important to once again emphasize that* ***high quality nutraceuticals cannot replace lipid-lowering therapy but might essentially help to optimize it*** *(reducing CV residual risk). Taking into account the influence of some of the presented nutraceuticals on different lipid parameters, it seems that this therapy might be especially important to consider for (1) patients with mixed dyslipidemia, especially (2) atherogenic dyslipidemia in patients with diabetes and MetS, (3) in patients with low-to-moderate hypercholesterolemia not on target, as well as (4) in all patients with statin-associated side effects, who cannot be treated with statins/suitable doses of statins and are at higher risk of CV events.*

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Atherosclerosis Supplements

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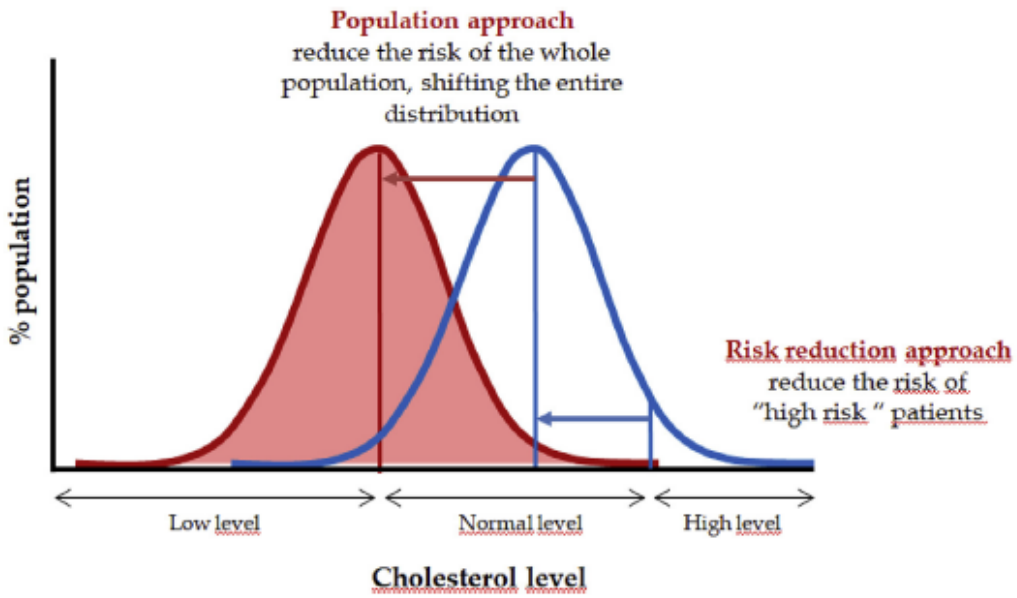
The role of red yeast rice (RYR) supplementation in plasma cholesterol control: A review and expert opinion

Maciej Banach [a, b, c], Eric Bruckert [d, e], Olivier S. Descamps [f], Lars Ellegård [g], Marat Ezhov [h], Bernhard Föger [i, j], Zlatko Fras [k], Petri T. Kovanen [l], Gustavs Latkovskis [m, n], Winfried März [o, p, q], Demosthenes B. Panagiotakos [r], György Paragh [s], Daniel Pella [t], Angela Pirillo [u, v], Andrea Poli [w], Željko Reiner [x], Günter Silbernagel [y, z], Margus Viigimaa [aa], Michal Vrablík [ab], Alberico L. Catapano [ac, ad, *]



Box 1
Recommendations to the Companies to improve the use of RYR

- *Provide clear information on the quantity of monacolin k*
- *Inform clearly on restriction of use (especially pregnant women) and risk*
- *Inform on interactions (other drugs or foods)*
- *Provide quality control data*

Box 3
Recommendations to the doctor when prescribing RYR

- *Clarify the indication of prescribing drugs or nutraceuticals containing statin in your patient. Does your patient have sufficiently high cardiovascular risk?*
- *In case of reluctance of your patient to take classical statins, clarify the exact reason: (1) adverse effect (intolerant patient), (2) specific worries about the chemical nature of a drug (the patients prefer natural medicine) or (3) worries about the statin administration in general.*
- *Based on this clarification, in cases 1 and 3, you should inform your patients on the presence of a monacolin K (= natural lovastatin) and its dose in the product.*
- *In any cases of prescription of product containing monacolin K, be careful about contraindications, advise regarding potential interactions and side effects (only if the patient accept to be informed on this), and monitor lipid reduction and biological side effects (liver and muscles).*