Roma, 8-11 novembre 2018

16° Congresso Nazionale AME
Joint Meeting with AACE Italian Chapter
Update in Endocrinologia Clinica

ITALIAN CHAPTER

Rimedi nutraceutici per le dislipidemie

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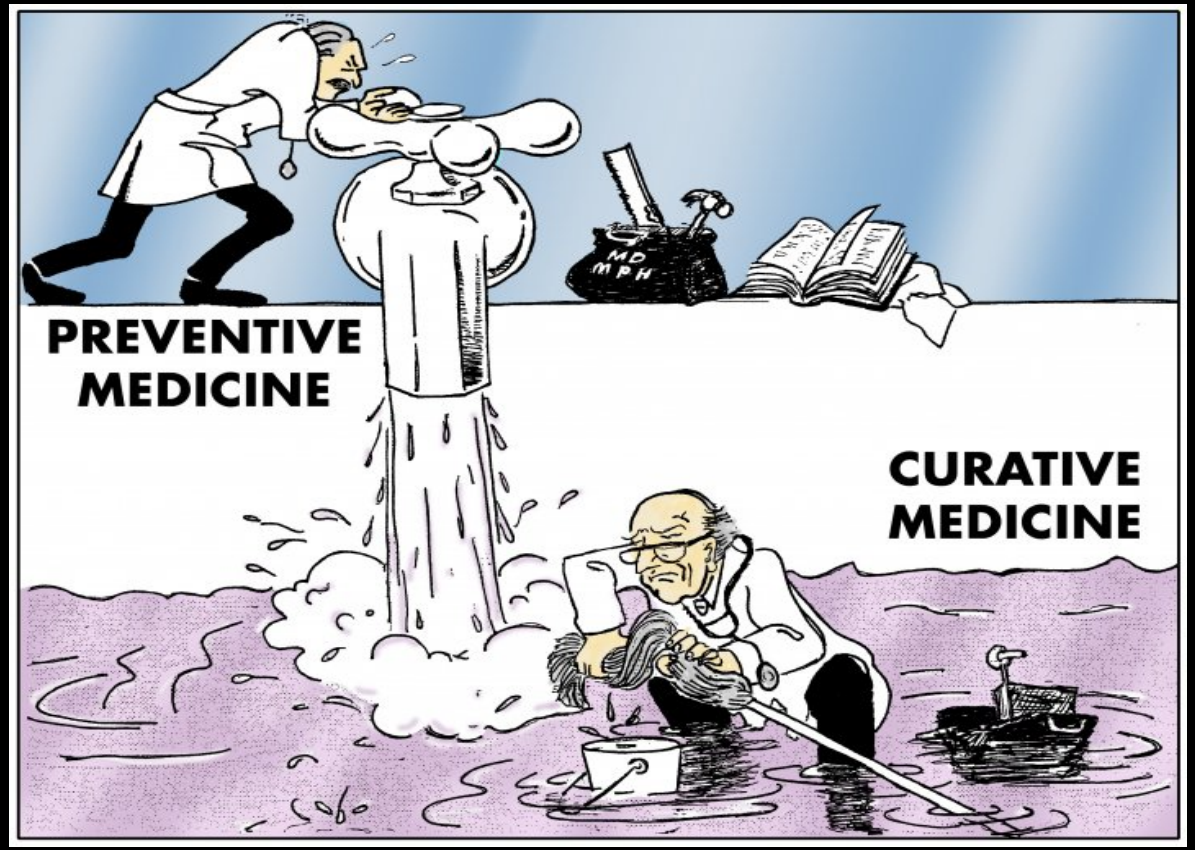
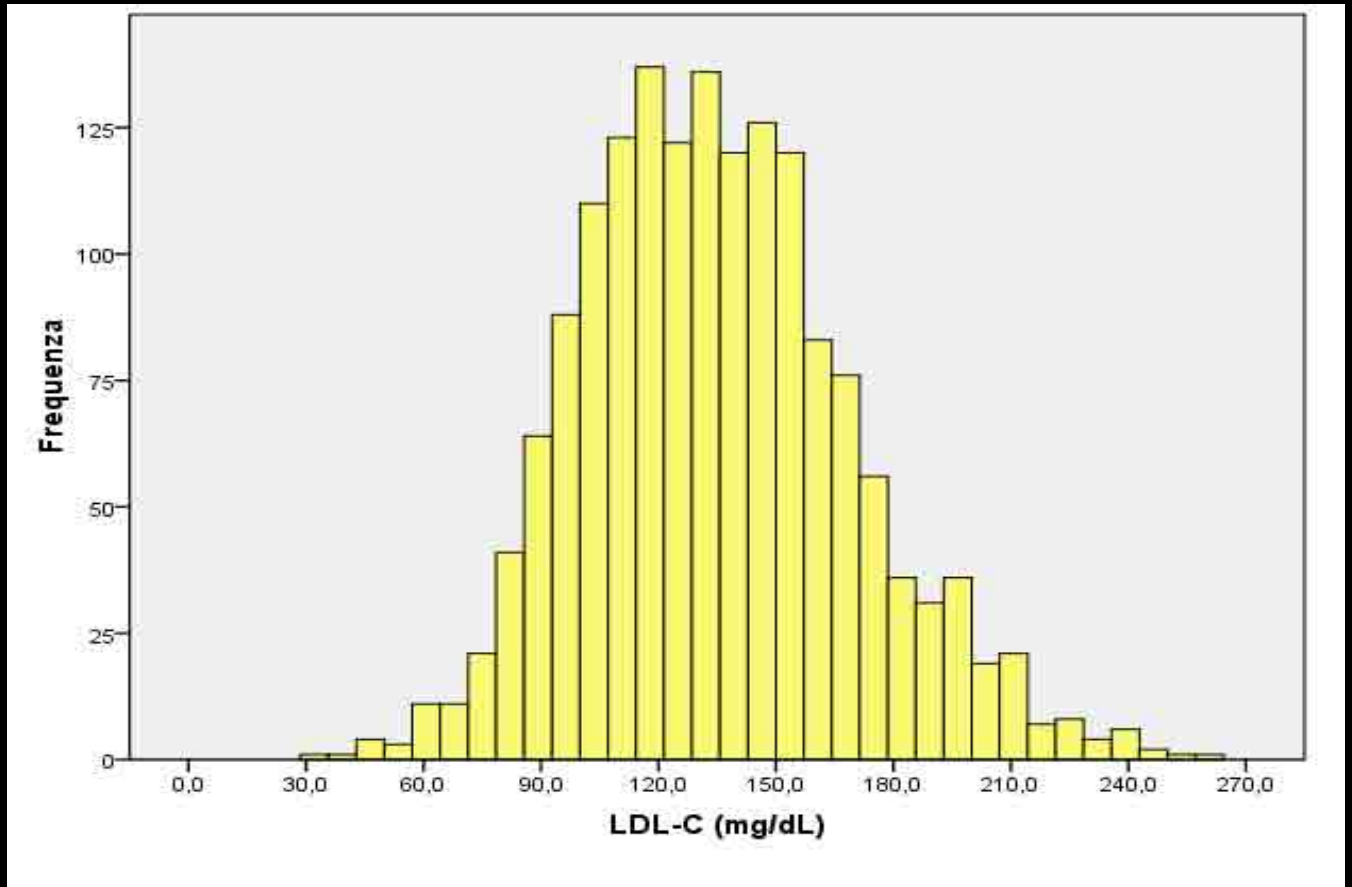
Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- HealthyVis srl


MD
MPH
PREVENTIVE
MEDICINE
CURATIVE
MEDICINE

Data from 1624 non-statin treated Brisighella volunteers



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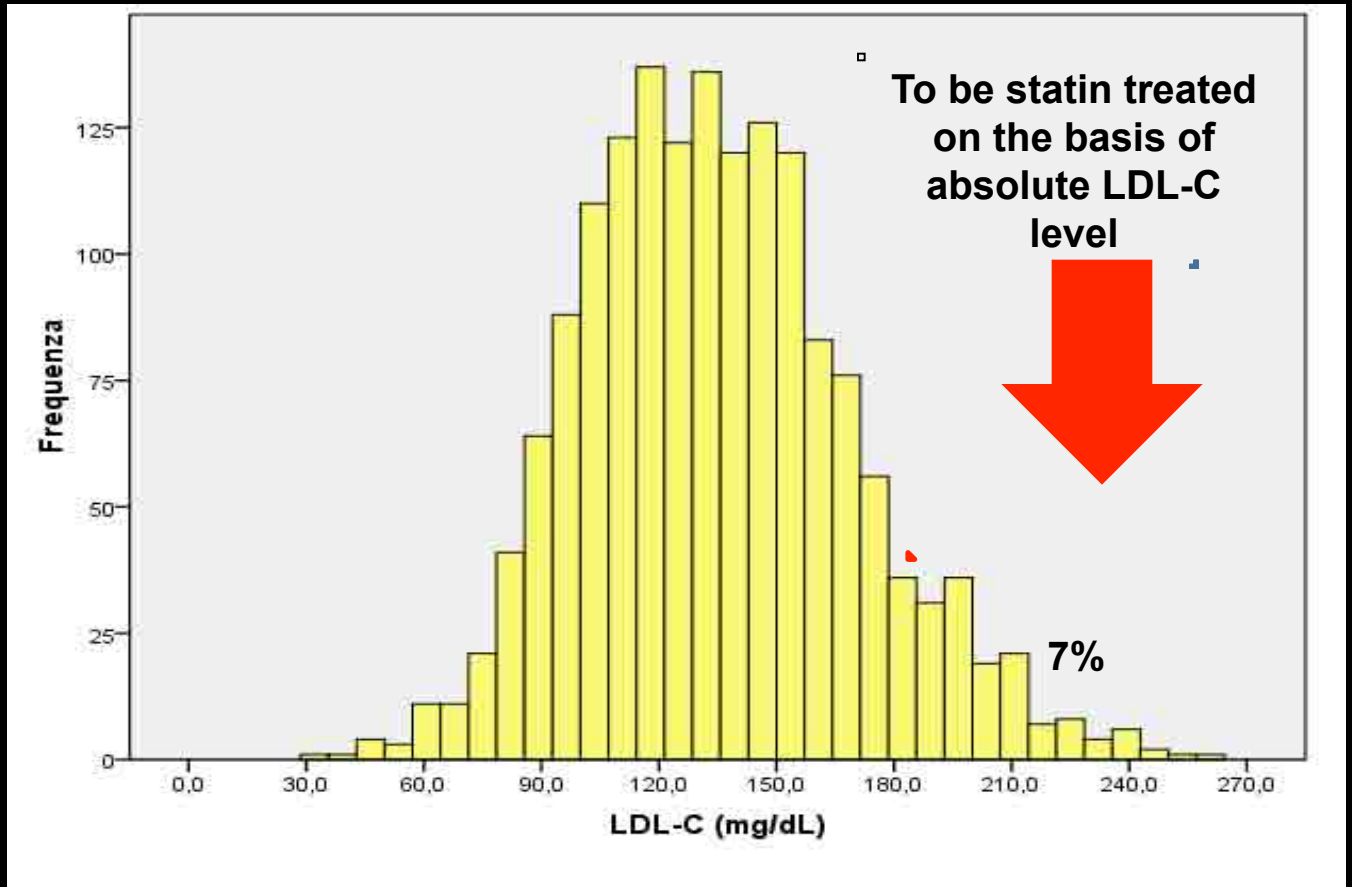
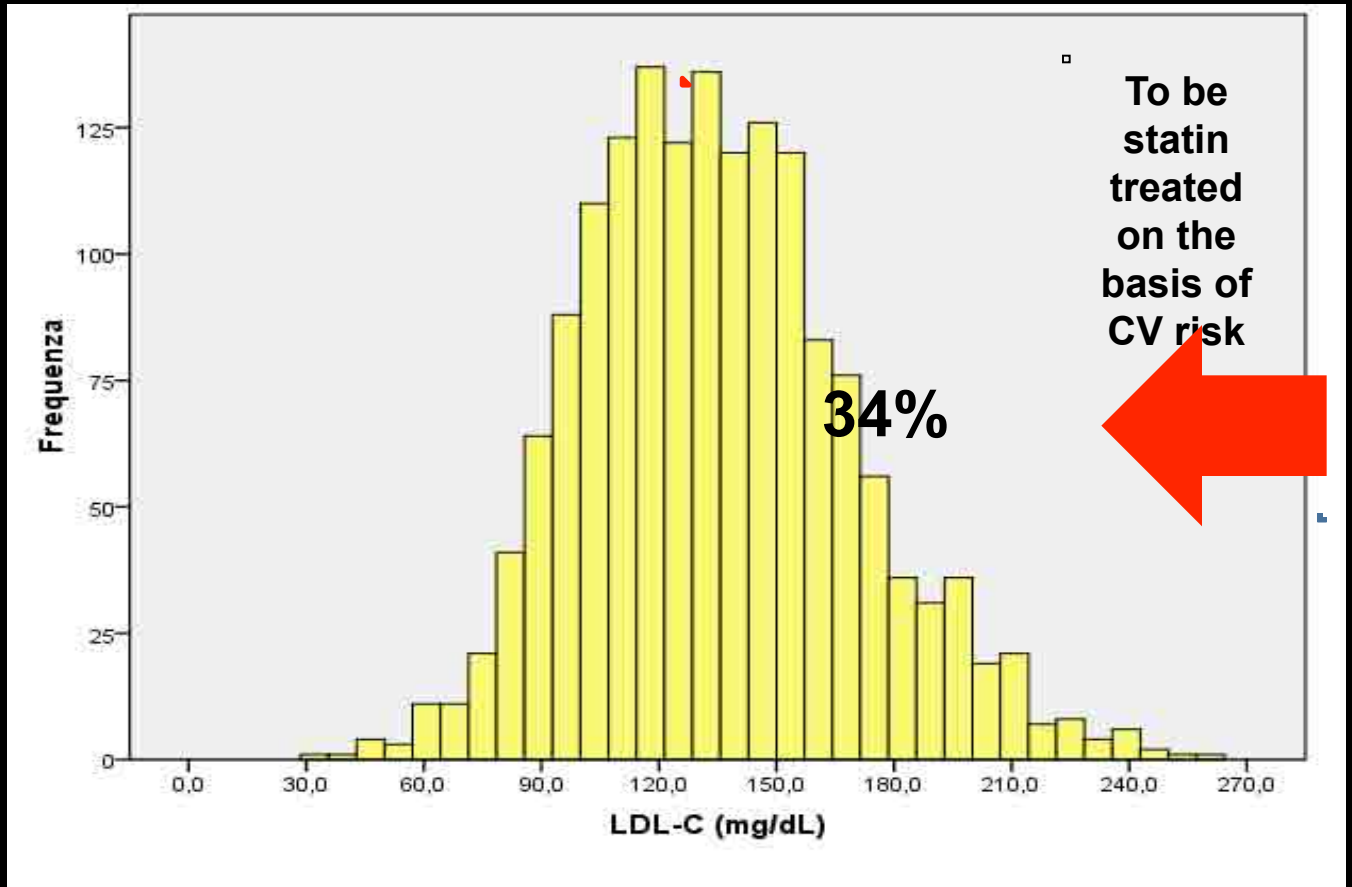
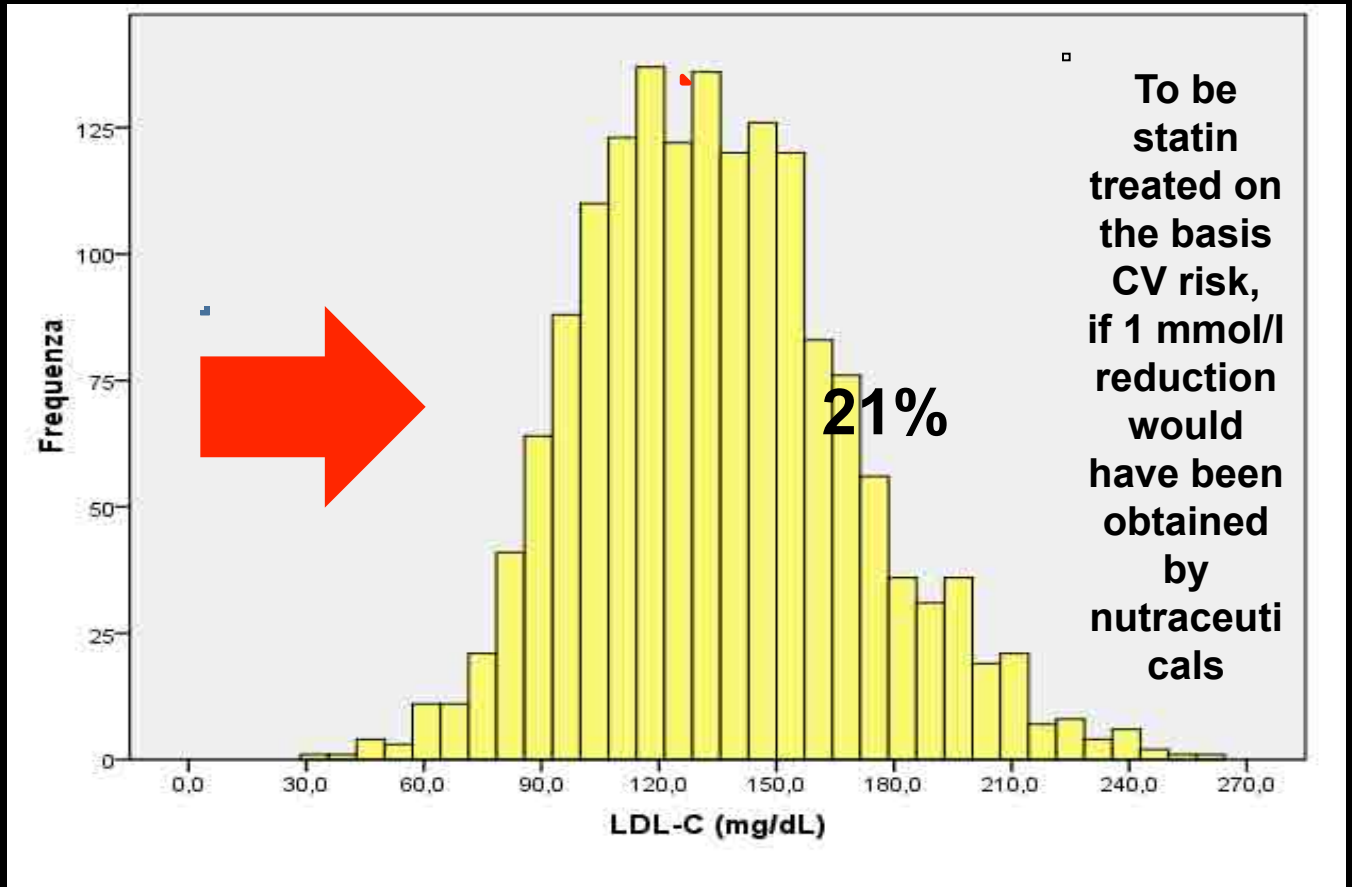


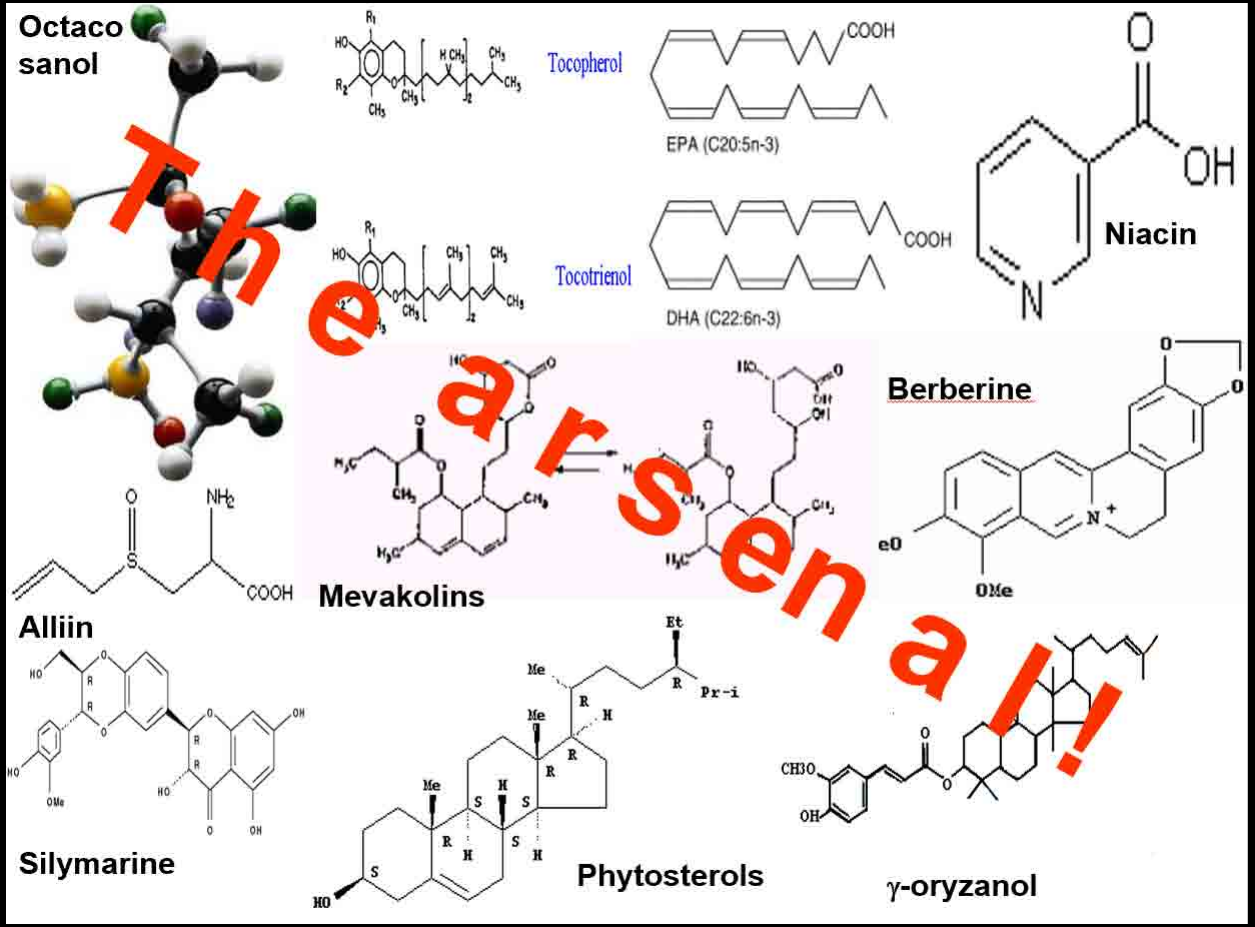
Data from 1624 non-statin treated Brisighella volunteers



Data from 1624 non-statin treated Brisighella volunteers



The arsenal!


Octaco sanol
Tocopherol
EPA (C20:5n-3)
Tocotrienol
DHA (C22:6n-3)
Niacin
Berberine
Mevakolins
Alliin
Silymarine
Phytosterols
γ-oryzanol

The consensus

Nutr Rev. 2017 Sep 1;75(9):731-767. doi: 10.1093/nutrit/nux047.

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

Cicero AFG[1], Colletti A[1], Bajraktari G[2], Descamps O[3], Djuric DM[4], Ezhov M[5], Fras Z[6], Katsiki N[7], Langlois M[8], Latkovskis G[9], Panagiotakos DB[10], Paragh G[11], Mikhailidis DP[12], Mitchenko O[13], Paulweber B[14], Pella D[15], Pitsavos C[16], Reiner Ž[17], Ray KK[18], Rizzo M[19], Sahebkar A[20], Serban MC[21], Sperling LS[22], Toth PP[23], Vinereanu D[24], Vrablík M[25], Wong ND[26], Banach M[27].

Author information

Abstract

In recent years, there has been growing interest in the possible use of nutraceuticals to improve and optimize dyslipidemia control and therapy. Based on the data from available studies, nutraceuticals might help patients obtain theraputic lipid goals and reduce cardiovascular residual risk. Some nutraceuticals have essential lipid-lowering properties confirmed in studies; some might also have possible positive effects on nonlipid cardiovascular risk factors and have been shown to improve early markers of vascular health such as endothelial function and pulse wave velocity. However, the clinical evidence supporting the use of a single lipid-lowering nutraceutical or a combination of them is largely variable and, for many of the nutraceuticals, the evidence is very limited and, therefore, often debatable. The purpose of this position paper is to provide consensus-based recommendations for the optimal use of lipid-lowering nutraceuticals to manage dyslipidemia in patients who are still not on statin therapy, patients who are on statin or combination therapy but have not achieved lipid goals, and patients with statin intolerance. This statement is intended for physicians and other healthcare professionals engaged in the diagnosis and management of patients with lipid disorders, especially in the primary care setting.

The consensus

Class of recommendation	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/Is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/ opinion is in favour of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful	Is not recommended (no efficacy on lipid profile)

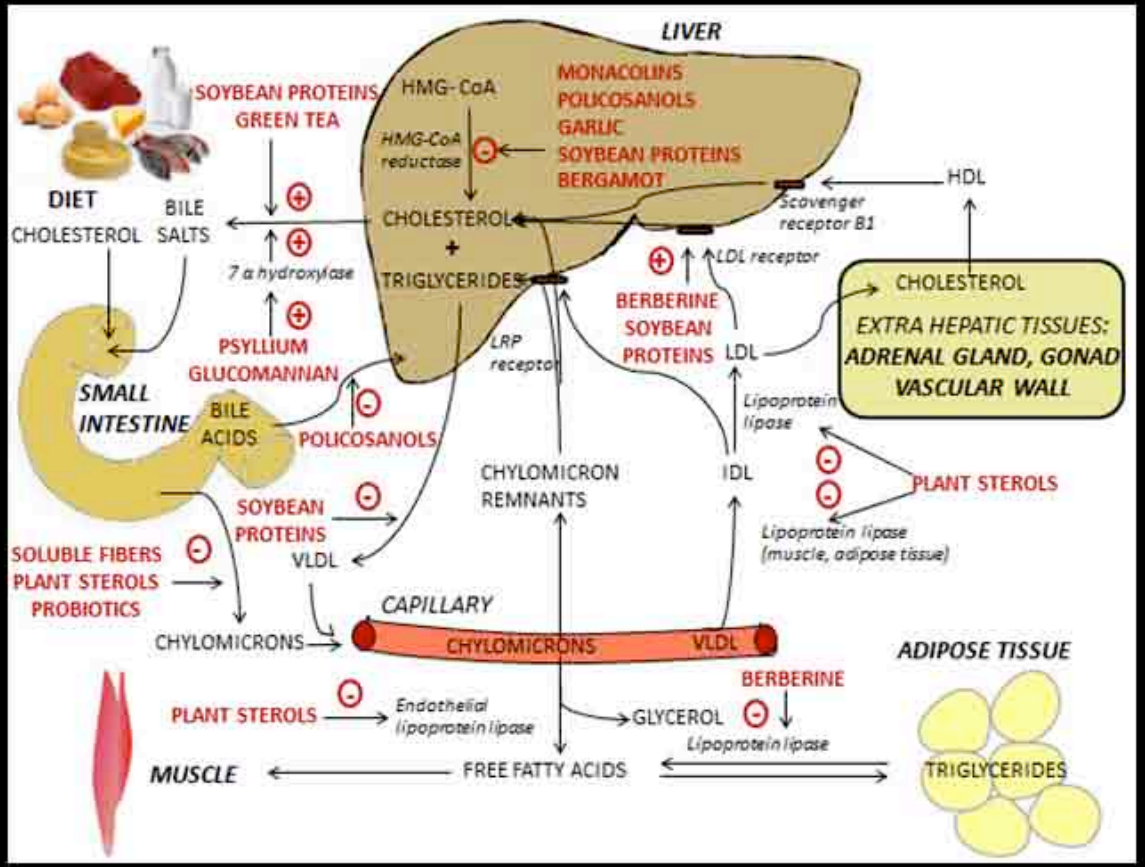
The consensus

Level of evidence	Definition
Level A	Data derived from multiple methodologically correct randomized clinical trials or their meta-analysis
Level B	Data derived from a single randomized clinical trial or large non-randomized clinical studies
Level C	Consensus or opinion of the experts and/or small studies, retrospectives studies, registries

Cosa dobbiamo conoscere

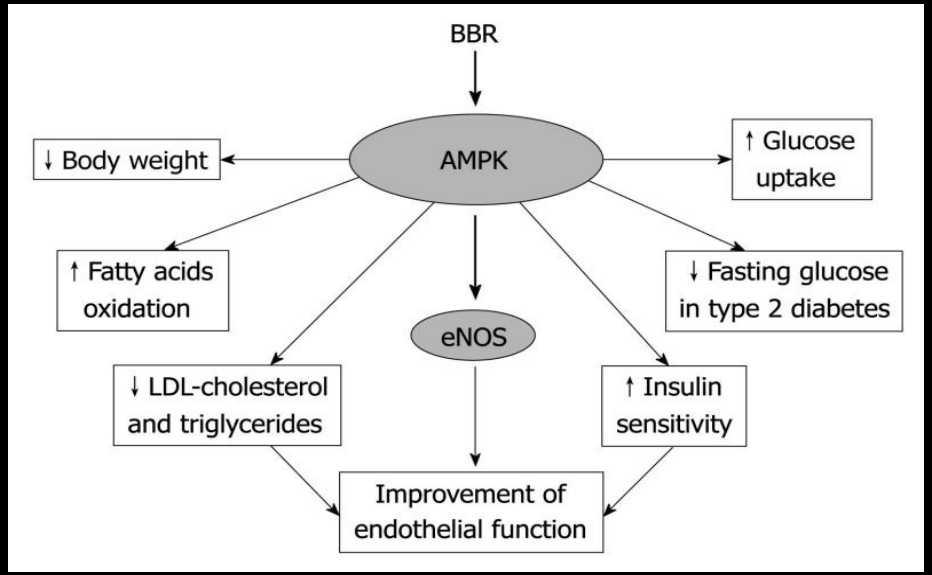
- Meccanismo d'azione
- Biodisponibilità/Biofarmaceutica
- Farmacocinetica
- Efficacia sull'assetto lipidico
- Efficacia su marcatori di salute vascolare
- Sicurezza assoluta ed in relazione a coterapie

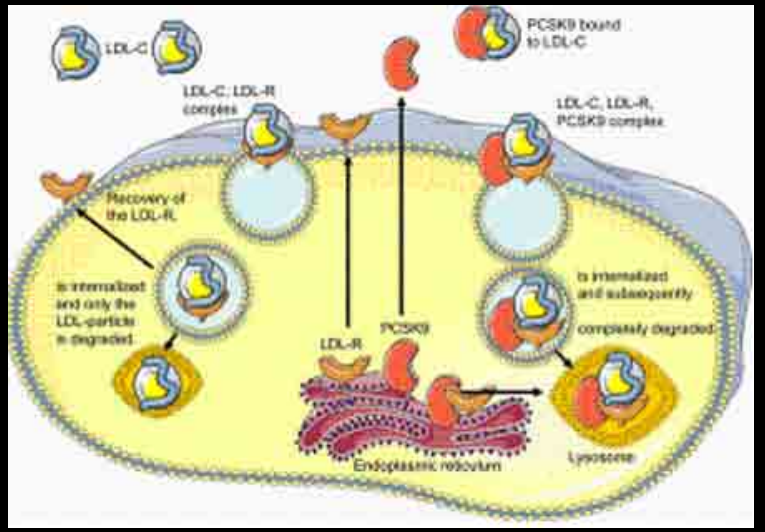
Lipid-lowering nutraceuticals: sites of action



Cicero AFG, Colletti A. In: Combined therapy in dyslipidemia. Springer-Verlag. 2015

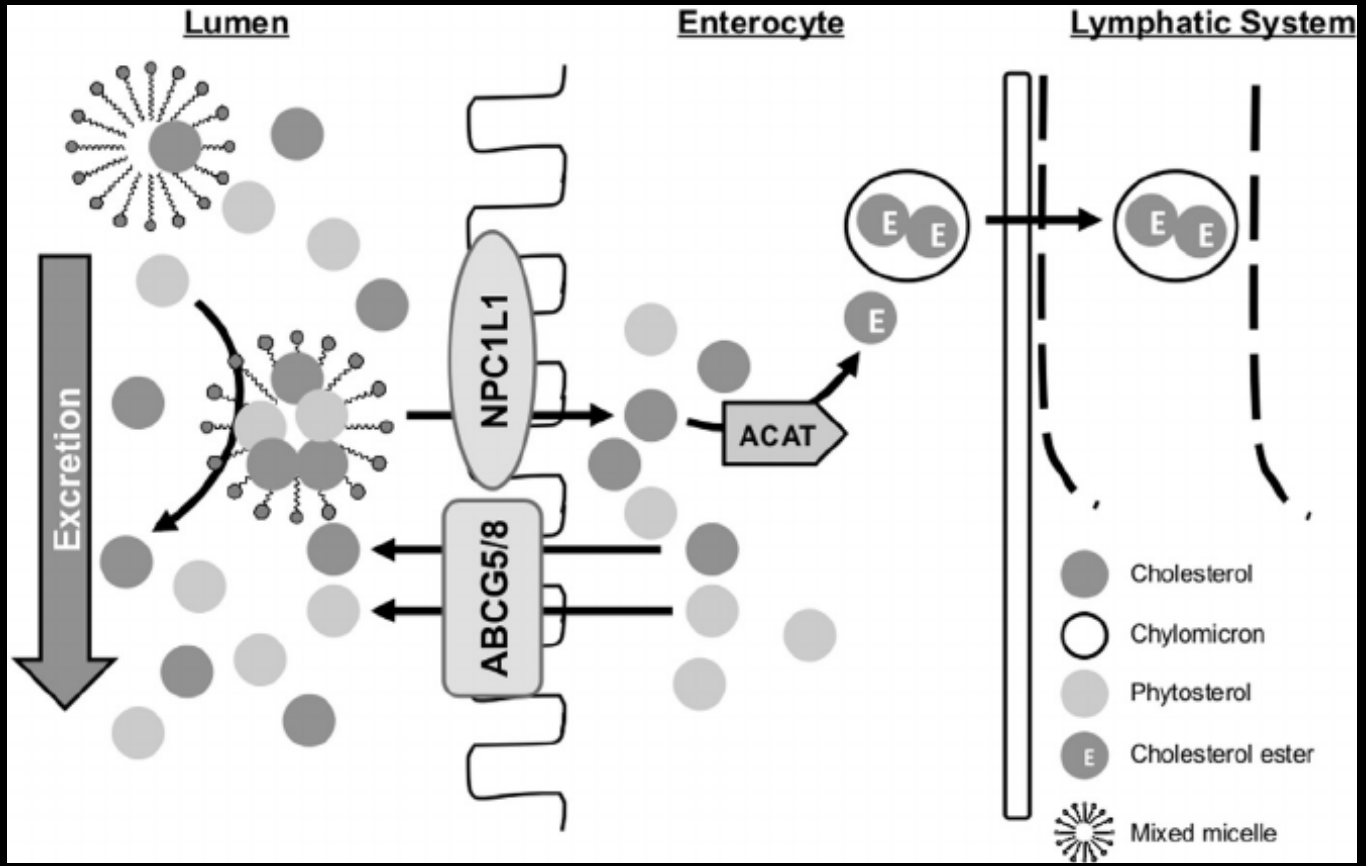
Berberine: mechanisms of action





Affuso F et al. World J Cardiol. 2010

Plant sterols: mechanisms of action



Can J Cardiol. 2014;30(10):1225-32. doi: 10.1016/j.cjca.2014.04.022.

Cosa dobbiamo conoscere

- Meccanismo d'azione
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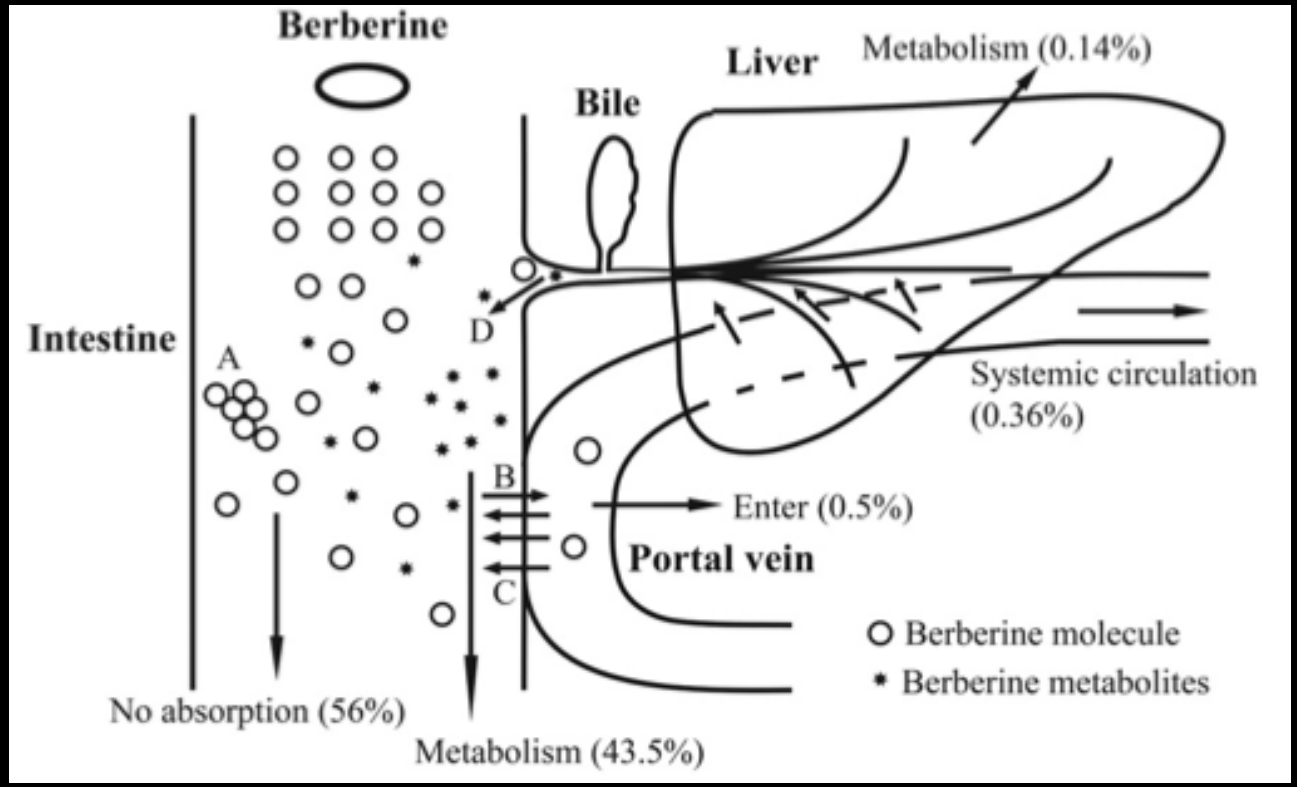
- Efficacia su marcatori di salute vascolare
- Sicurezza assoluta ed in relazione a coterapie

Berberine bioavailability



BCS CLASS III (High solubility, Poor permeability)

Chang-Shun Liu et al. Fitoterapia 109 (2016) 274–282

Nutraceuticals in fed or fasted state?

Effect of Food on the Oral Bioavailability of Berberine and Monacolin Administered in Combination in Healthy Male Volunteers

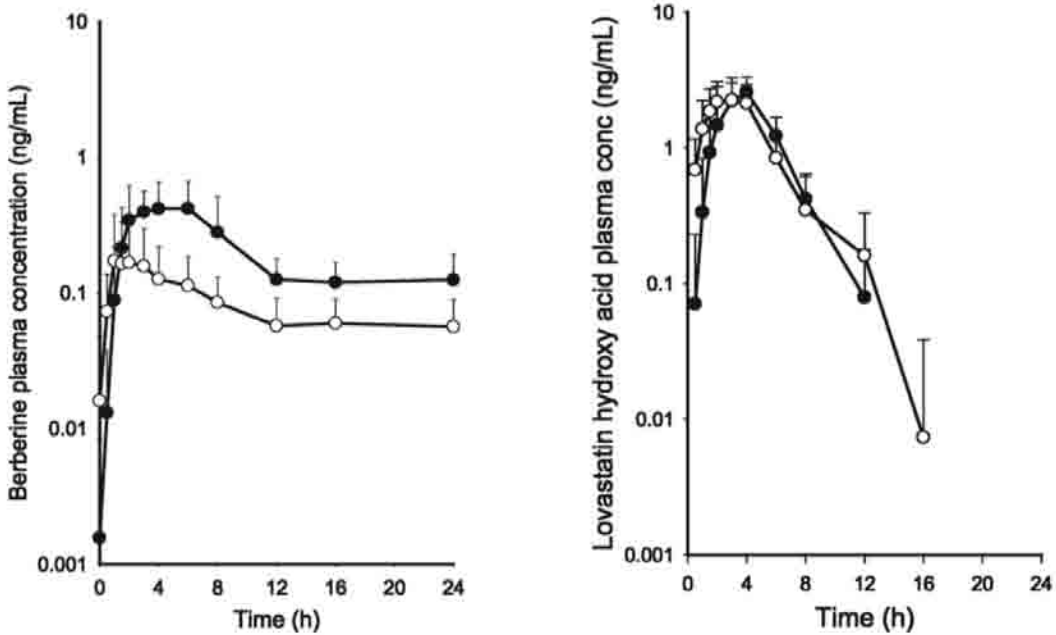
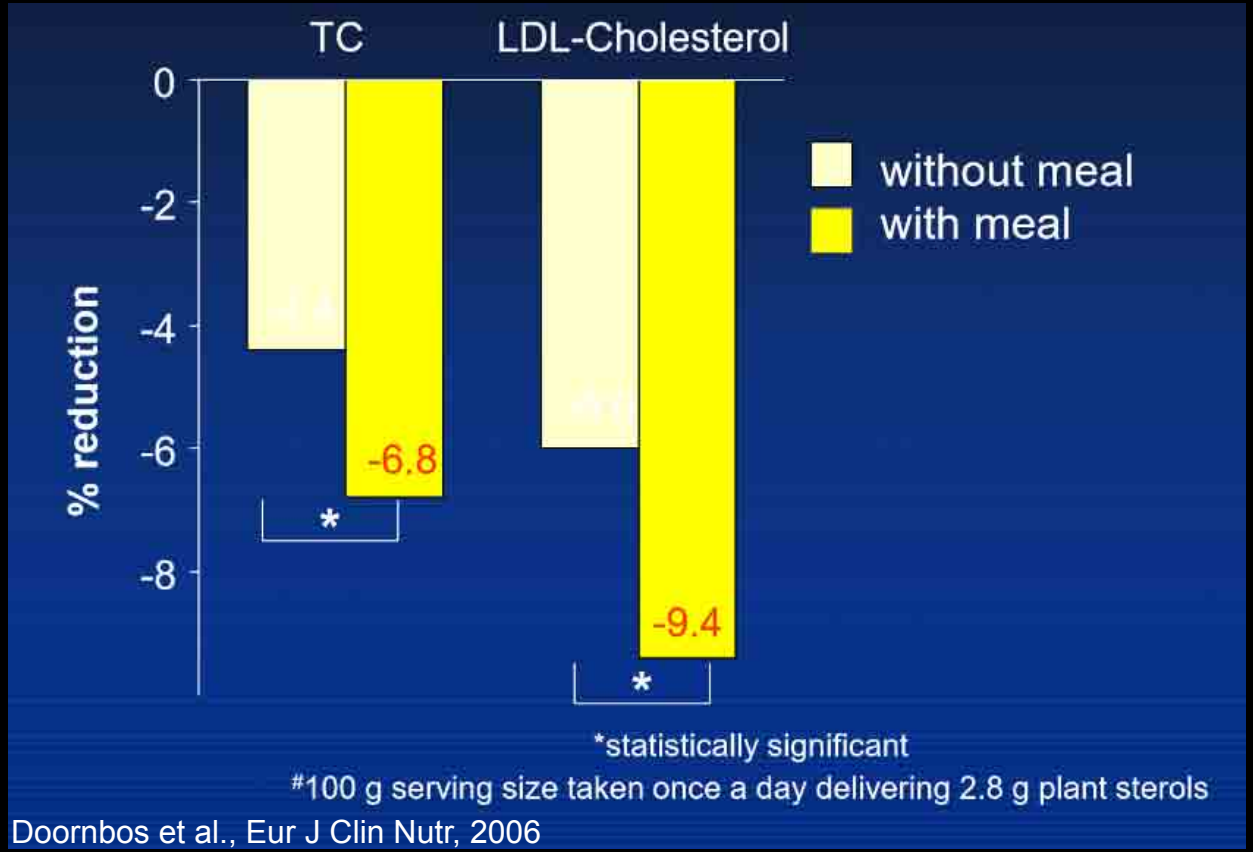


Fig. 1 Mean (±SD) plasma concentration-time profile of berberine and lovastatin hydroxy acid in fed condition (•) and fasted condition (○) in healthy subjects.

Persiani S et al. J Pharm Pharmacol 2014;2:703-712.

Nutraceuticals in fed or fasted state?



Doornbos et al., Eur J Clin Nutr, 2006

Cosa dobbiamo conoscere

- Meccanismo d'azione
- Biodisponibilità/Biofarmaceutica
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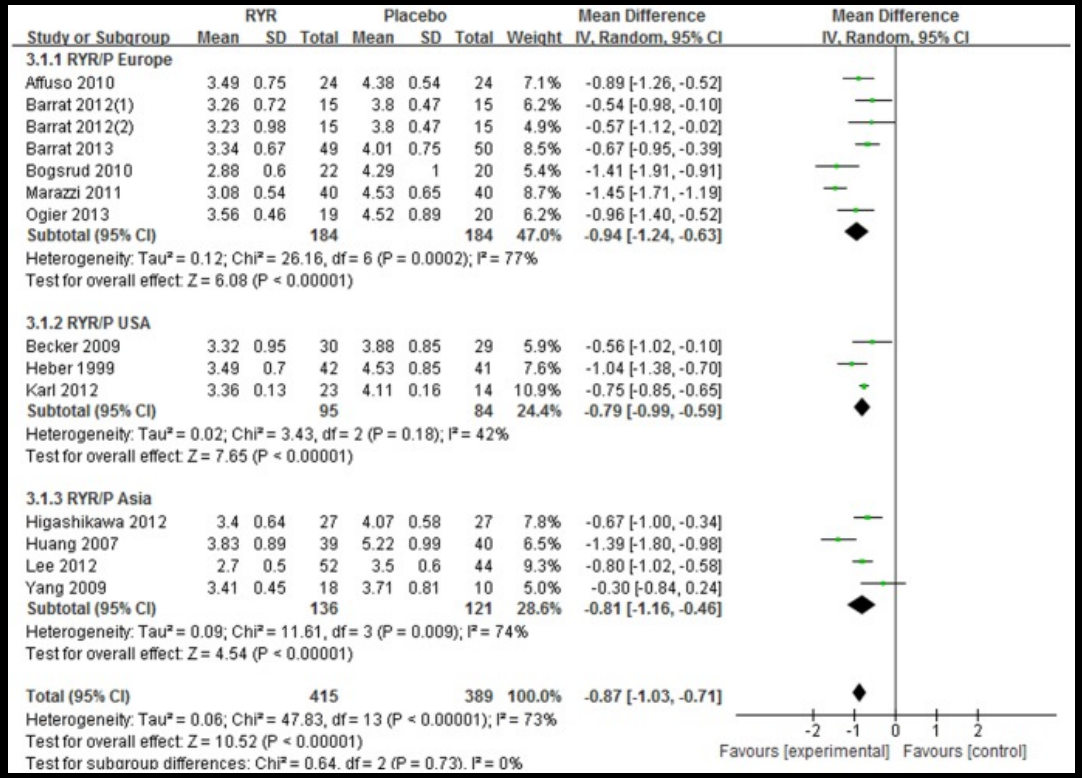
- Efficacia sull'assetto lipidico
- Efficacia su marcatori di salute vascolare
- Sicurezza assoluta ed in relazione a coterapie

Roma, 8-11 novembre 2018

A Meta-Analysis of Red Yeast Rice: An Effective and Relatively Safe Alternative Approach for Dyslipidemia

ITALIAN CHAPTER



Study or Subgroup	RYR Mean	RYR SD	RYR Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 RYR/P Europe								
Affuso 2010	3.49	0.75	24	4.38	0.54	24	7.1%	-0.89 [-1.26, -0.52]
Barrat 2012(1)	3.26	0.72	15	3.8	0.47	15	6.2%	-0.54 [-0.98, -0.10]
Barrat 2012(2)	3.23	0.98	15	3.8	0.47	15	4.9%	-0.57 [-1.12, -0.02]
Barrat 2013	3.34	0.67	49	4.01	0.75	50	8.5%	-0.67 [-0.95, -0.39]
Bogsrud 2010	2.88	0.6	22	4.29	1	20	5.4%	-1.41 [-1.91, -0.91]
Marazzi 2011	3.08	0.54	40	4.53	0.65	40	8.7%	-1.45 [-1.71, -1.19]
Ogier 2013	3.56	0.46	19	4.52	0.89	20	6.2%	-0.96 [-1.40, -0.52]
Subtotal (95% CI)			**184**			**184**	**47.0%**	**-0.94 [-1.24, -0.63]**
Heterogeneity: Tau² = 0.12; Chi² = 26.16, df = 6 (P = 0.0002); I² = 77%								
Test for overall effect: Z = 6.08 (P < 0.00001)								
3.1.2 RYR/P USA								
Becker 2009	3.32	0.95	30	3.88	0.85	29	5.9%	-0.56 [-1.02, -0.10]
Heber 1999	3.49	0.7	42	4.53	0.85	41	7.6%	-1.04 [-1.38, -0.70]
Karl 2012	3.36	0.13	23	4.11	0.16	14	10.9%	-0.75 [-0.85, -0.65]
Subtotal (95% CI)			**95**			**84**	**24.4%**	**-0.79 [-0.99, -0.59]**
Heterogeneity: Tau² = 0.02; Chi² = 3.43, df = 2 (P = 0.18); I² = 42%								
Test for overall effect: Z = 7.65 (P < 0.00001)								
3.1.3 RYR/P Asia								
Higashikawa 2012	3.4	0.64	27	4.07	0.58	27	7.8%	-0.67 [-1.00, -0.34]
Huang 2007	3.83	0.89	39	5.22	0.99	40	6.5%	-1.39 [-1.80, -0.98]
Lee 2012	2.7	0.5	52	3.5	0.6	44	9.3%	-0.80 [-1.02, -0.58]
Yang 2009	3.41	0.45	18	3.71	0.81	10	5.0%	-0.30 [-0.84, 0.24]
Subtotal (95% CI)			**136**			**121**	**28.6%**	**-0.81 [-1.16, -0.46]**
Heterogeneity: Tau² = 0.09; Chi² = 11.61, df = 3 (P = 0.009); I² = 74%								
Test for overall effect: Z = 4.54 (P < 0.00001)								
Total (95% CI)			**415**			**389**	**100.0%**	**-0.87 [-1.03, -0.71]**
Heterogeneity: Tau² = 0.06; Chi² = 47.83, df = 13 (P < 0.00001); I² = 73%								
Test for overall effect: Z = 10.52 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.64, df = 2 (P = 0.73), I² = 0%								

Mean Difference IV, Random, 95% CI

-2 -1 0 1 2

Favours [experimental] Favours [control]

EFFECTS ON LDL-C

PLoS One. 2014; 9(6): e98611.

Contents lists available at ScienceDirect

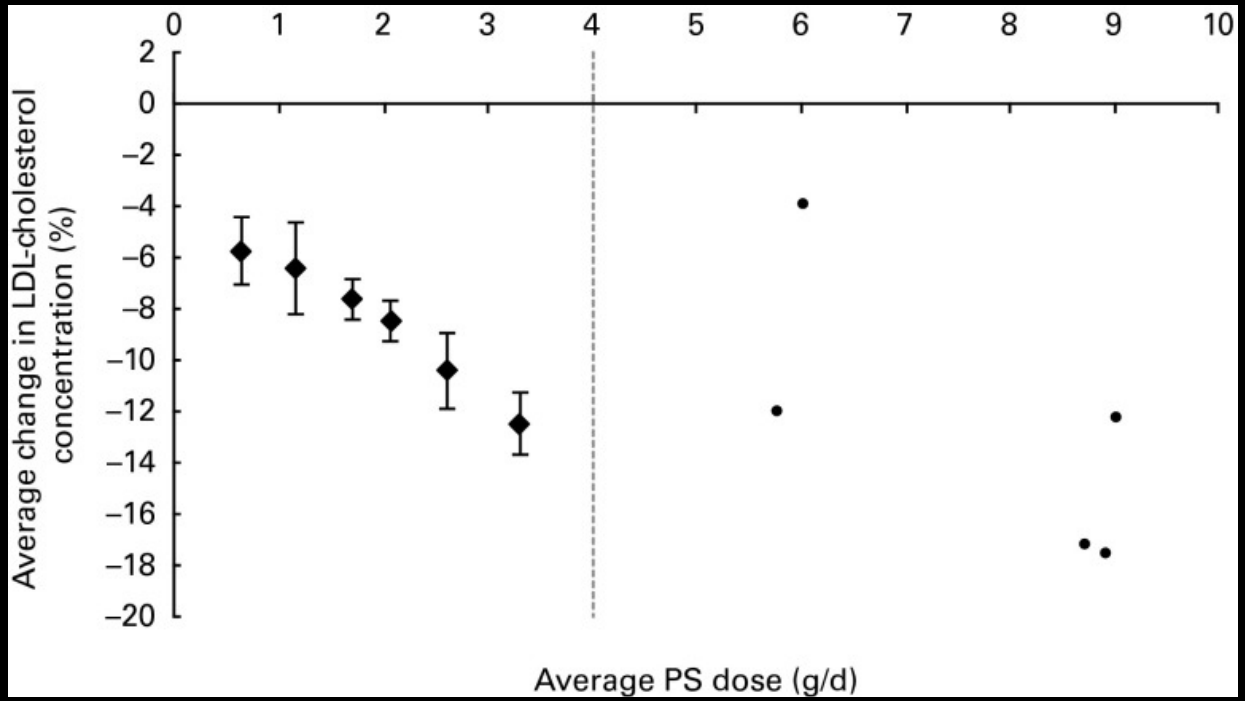
Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Consumption of plant sterol-enriched foods and effects on plasma plant sterol concentrations – A meta-analysis of randomized controlled studies

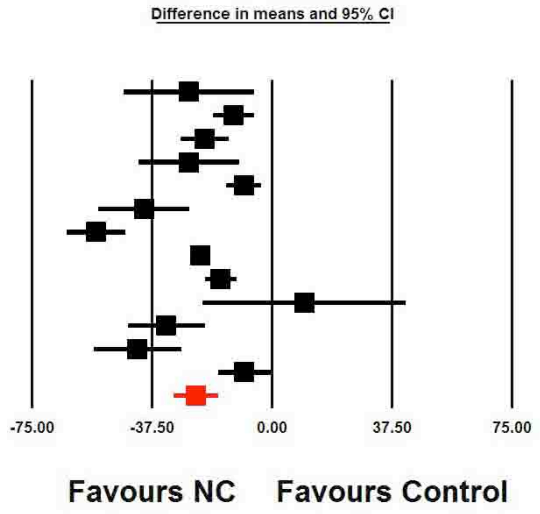
Rouyanne T. Ras*, Harry Hiemstra, Yuguang Lin, Mario A. Vermeer, Guus S.M.J.E. Duchateau, Elke A. Trautwein



Low-dosed red yeast-rice – berberine association: a meta-analysis of RCTs

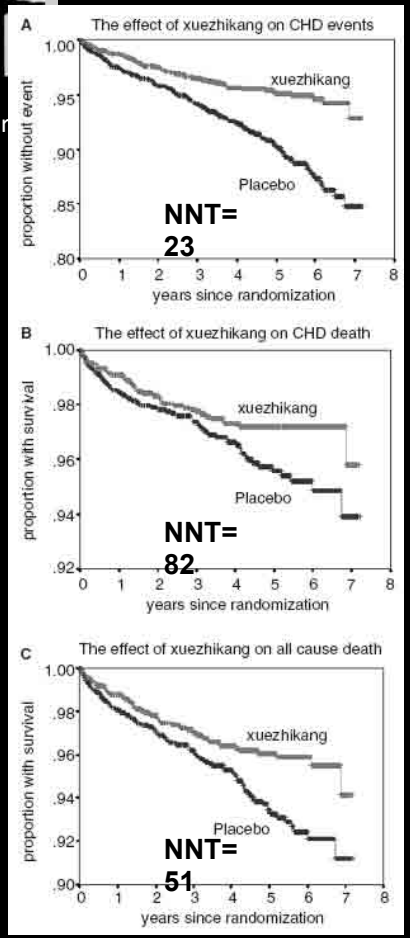
LDL-cholesterol

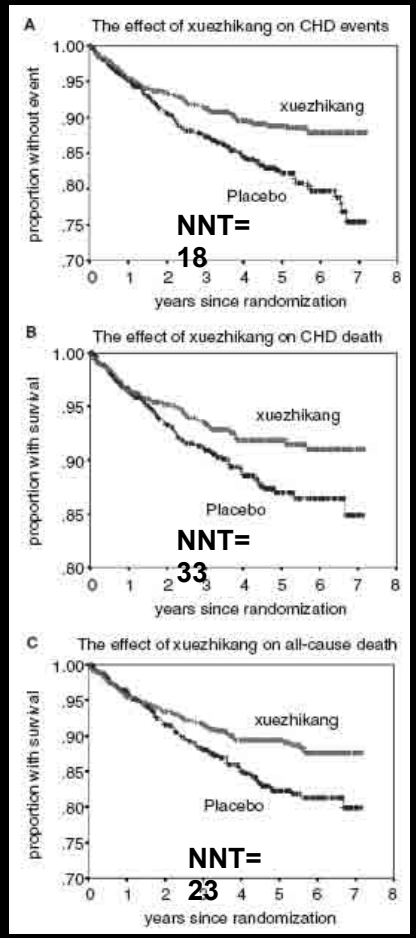
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Statistics for each study				
Ruscica et al., 2014	-26.000	10.316	106.412	-46.218	-5.782	-2.520	0.012
Pisciotta et al., 2012	-12.000	3.164	10.013	-18.202	-5.798	-3.792	0.000
Cicero et al., 2012	-21.000	3.809	14.511	-28.466	-13.534	-5.513	0.000
Affuso et al., 2012	-26.000	7.912	62.594	-41.507	-10.493	-3.286	0.001
Cicero et al., 2007	-8.800	2.732	7.465	-14.155	-3.445	-3.221	0.001
Affuso et al., 2009	-40.000	7.191	51.708	-54.094	-25.906	-5.563	0.000
Marazzi et al., 2011	-55.000	4.572	20.900	-63.960	-46.040	-12.031	0.000
Trimarco et al., 2010	-22.500	1.505	2.265	-25.450	-19.550	-14.950	0.000
Marazzi et al., 2015	-16.000	2.404	5.780	-20.712	-11.288	-6.655	0.000
Gentile et al., 2015	10.100	16.141	260.536	-21.536	41.736	0.626	0.531
Pirro et al., 2013	-33.000	6.076	36.914	-44.908	-21.092	-5.431	0.000
Gonnelli et al., 2015	-42.050	6.892	47.500	-55.558	-28.542	-6.101	0.000
Solà et al., 2014	-8.660	4.168	17.373	-16.829	-0.491	-2.078	0.038
	-23.854	3.496	12.219	-30.705	-17.003	-6.824	0.000



Pirro M et al. Pharmacol Res. 2016; http://dx.doi.org/doi:10.1016/j.phrs.2016.04.021

China Coronary Secondary Prevention Study





4780 patients in secondary prevention
1,445 aged 65 to 75
7 years follow-up

Eventi coronarici: - 36,9% (p=0.001)
Morti per malattia coronarica - 31,0% (p=0.04)
Morti per tutte le cause di mortalità -31,9% (p=0.01)

Adult patients **Elderly patients**

NNT=number needed to treat

Ye et al. J Am Geriatr Soc 2007;55:1015–1022.

Cosa dobbiamo conoscere

- Meccanismo d'azione
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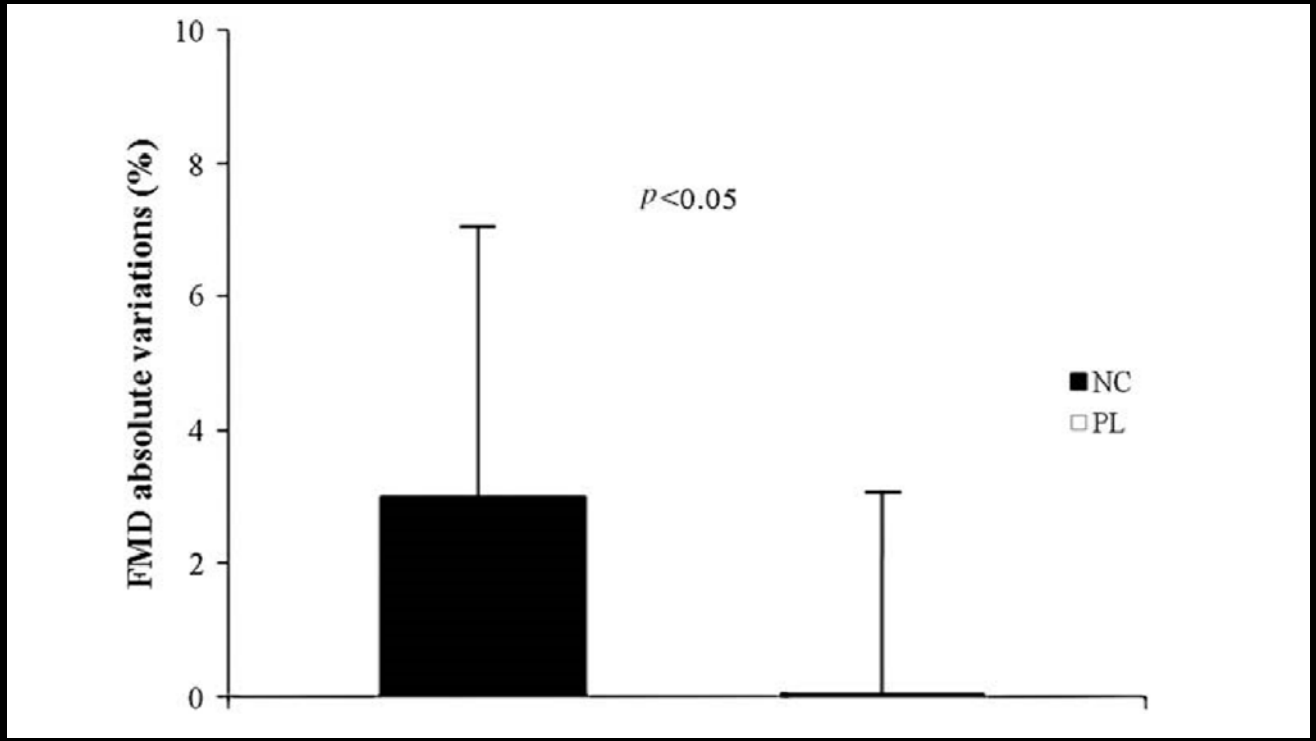
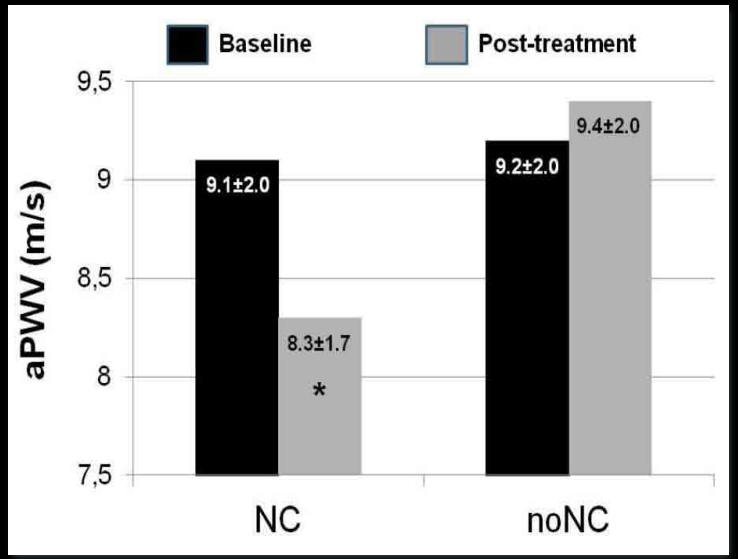
- Farmacocinetica
- Efficacia sull'assetto lipidico
- Efficacia su marcatori di salute vascolare
- Sicurezza assoluta ed in relazione a coterapie

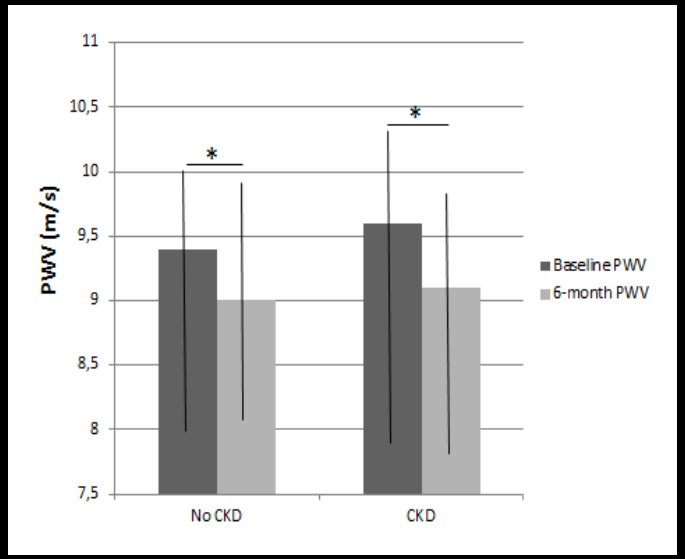
Low-dosed red yeast-rice – berberine association effect on FMD



Affuso F et al. Nutr Metab Cardiovasc Dis. 2010;20(9):656-61

Low-dosed red yeast-rice – berberine association effect on PWV

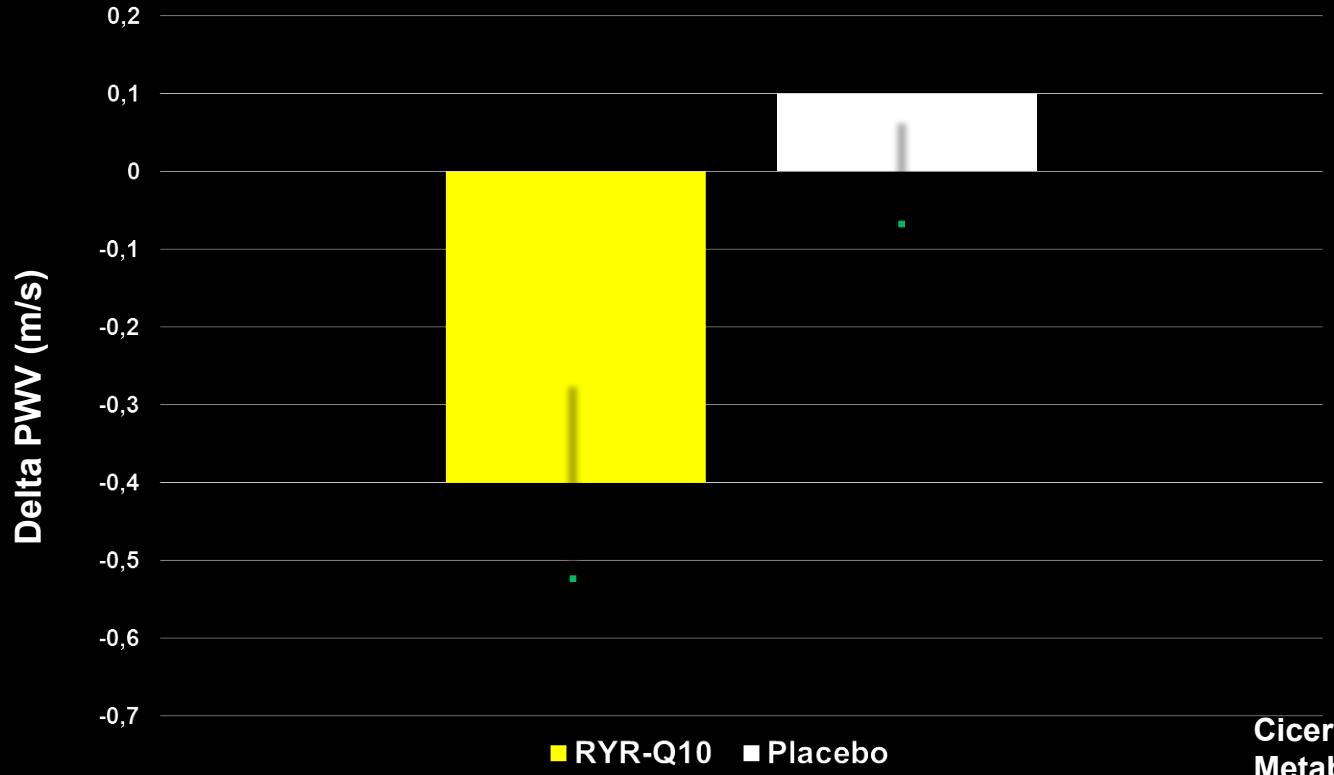




Pirro M et al. Pharmanutrition 2013

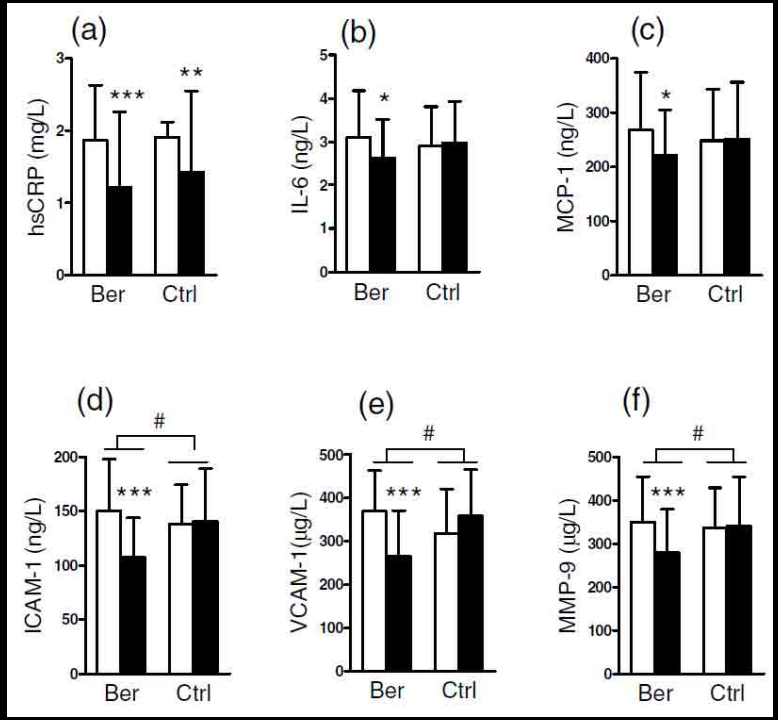
Cicero et al. The Open Hypertension J 2013

RYR-CoQ10 middle-term effect on PWV



Cicero et al. Ann Nutr Metab. 2016;68(3):213-9

Berberine ameliorates inflammation in patients with ACS following percutaneous coronary intervention



Clin Exp Pharmacol Physiol 2012;39(5): 406-11.

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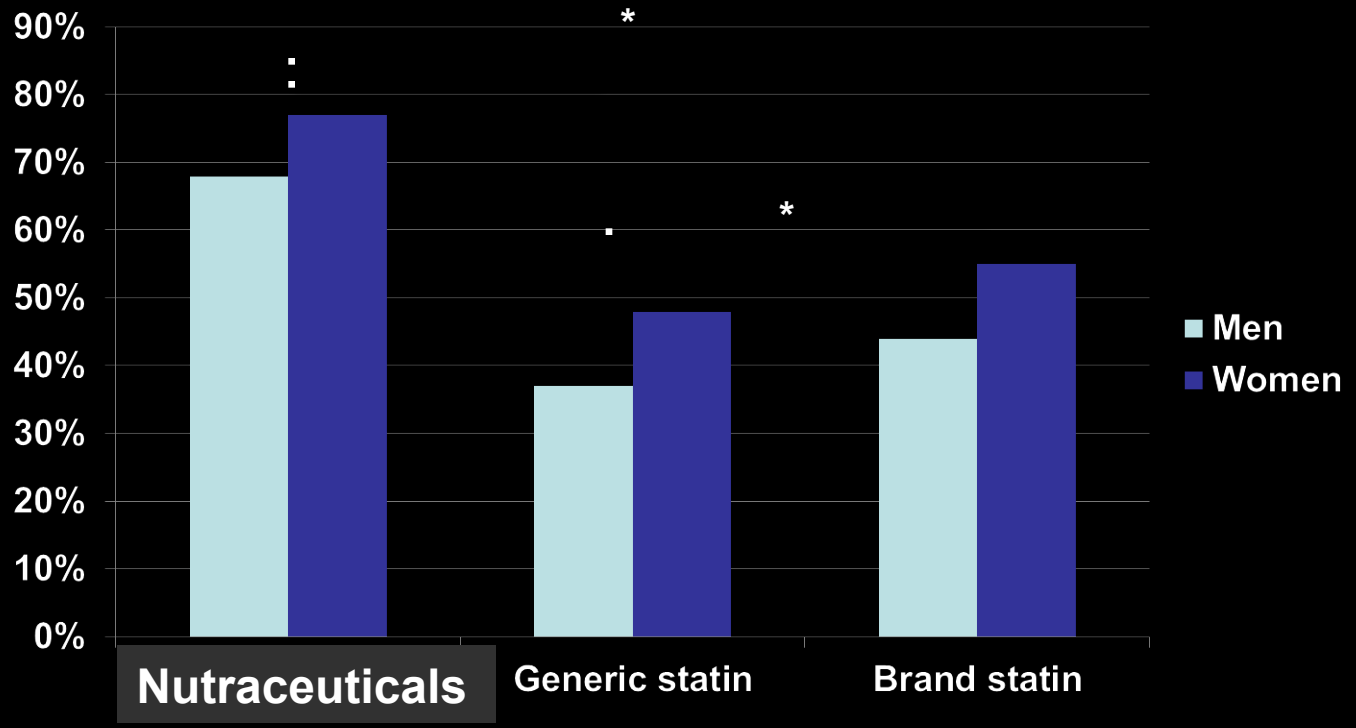
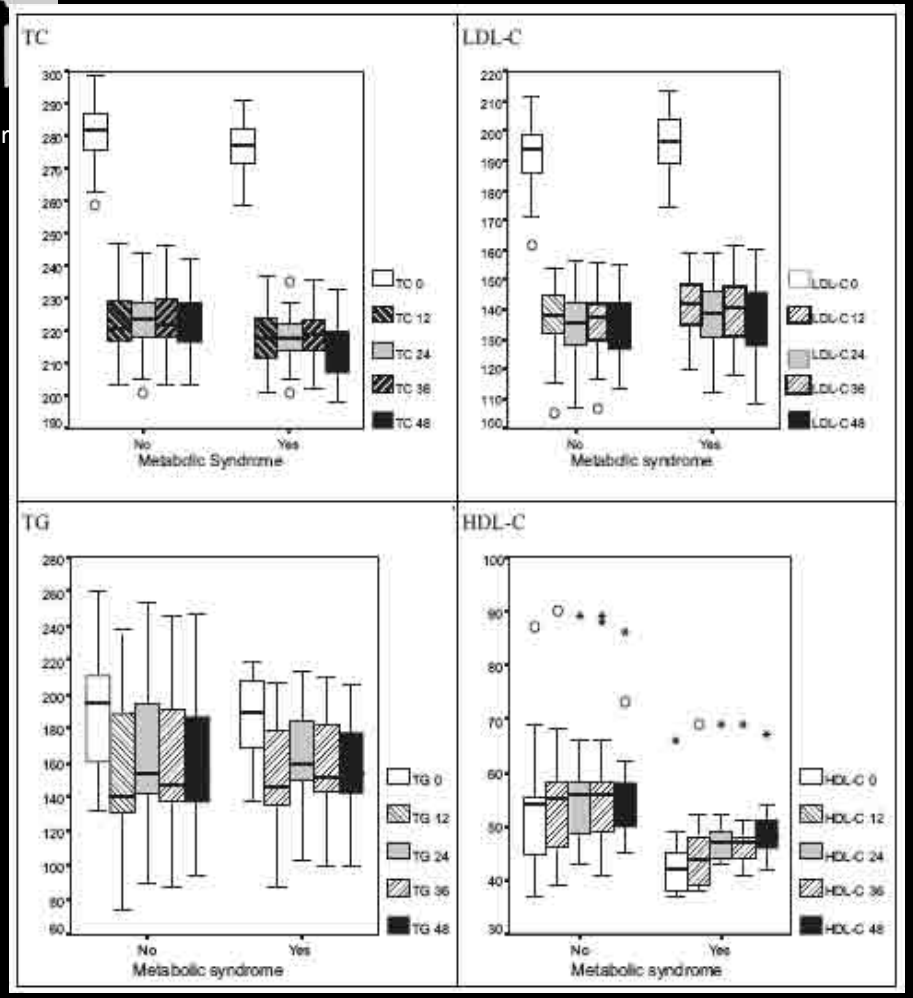
2-years persistence in paid LDL-lowering treatment



Cicero et al. Atherosclerosis 2014;235(1):81-83



Long-term effectiveness and safety of a combined nutraceutical based approach to reduce cholesterolemia in statin intolerant subjects with and without metabolic syndrome

Cicero et al. Am J Cardiol. 2010;105(10): 1504.

PS + RYR

Cicero et al. Nutrition & Metabolism (2017) 14:61
DOI 10.1186/s12986-017-0214-2

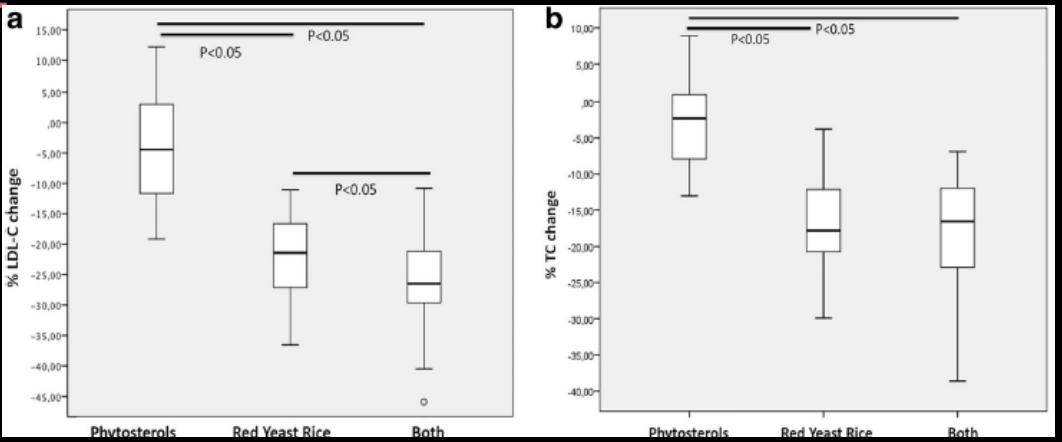
Nutrition & Metabolism

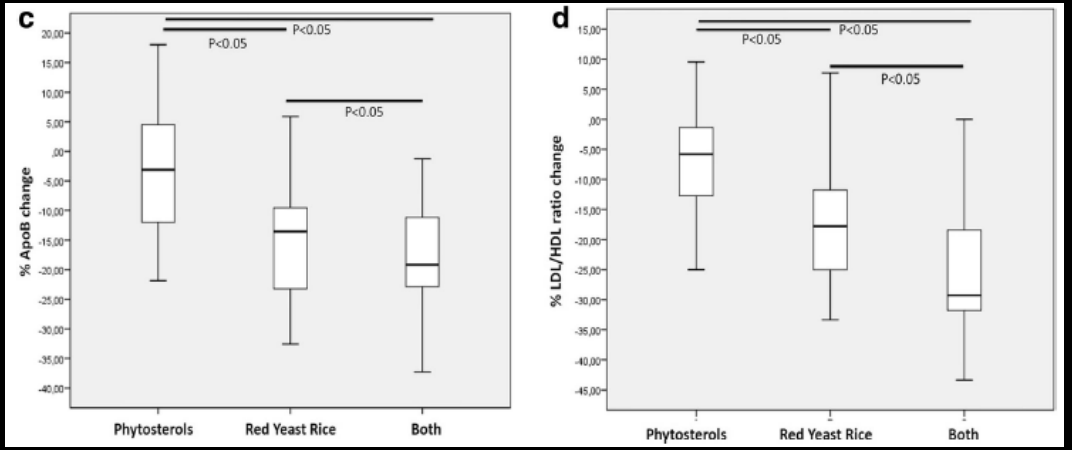
REAEARCH Open Access

Effect of a short-term dietary supplementation with phytosterols, red yeast rice or both on lipid pattern in moderately hypercholesterolemic subjects: a three-arm, double-blind, randomized clinical trial

Arrigo F.G. Cicero*, Federica Fogacci, Martina Rosticci, Angelo Parini, Marina Giovannini, Maddalena Veronesi, Sergio D'Addato and Claudio Borghi

PS + RYR

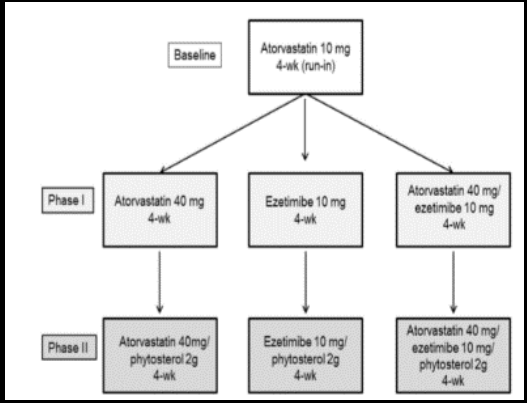




In soggetti complianti:

RYR: LDL-C −20.5% e ApoB -14.4% vs. baseline
RYR-PS: LDL-C -27% e ApoB -19% vs. baseline

PS + LLT



Additive effects of plant sterols supplementation in addition to different lipid-lowering regimens

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OBJECTIVE: Plant sterol (PS) supplementation has been widely used alone or combined with lipid-lowering therapies (LLTs) to reduce low-density lipoprotein (LDL) cholesterol. The effects of PS added to high-intensity LLT are less reported, especially regarding the effects on cholesterol synthesis and absorption.

METHODS: A prospective, randomized, open-label study, with parallel arms and blinded end points was designed to evaluate the effects of addition of PS to LLT on LDL cholesterol, markers of cholesterol synthesis, and absorption. Eighty-six patients of both genders were submitted to a 4-wk run-in period with atorvastatin 10 mg (baseline). Following, subjects received atorvastatin 40 mg, ezetimibe 10 mg, or combination of both drugs for another 4-wk period (phase I). In phase II, capsules containing 2.0 g of PSs were added to previous assigned treatments for 4 wk. Lipids, apolipoproteins, plasma campesterol, β-sitosterol, and desmosterol levels were assayed at all time points. Within and between-group analyses were performed.

RESULTS: Compared with baseline, atorvastatin 40 mg reduced total and LDL cholesterol (3% and 22%, respectively, $P < .05$), increased β-sitosterol, campesterol/cholesterol, and β-sitosterol/cholesterol ratios (39%, 47%, and 32%, respectively, $P < .05$); ezetimibe 10 mg reduced campesterol and campesterol/cholesterol ratio (67% and 70%, respectively, $P < .05$), and the combined therapy decreased total and LDL cholesterol (22% and 38%, respectively, $P < .05$), campesterol, β-sitosterol, and campesterol/cholesterol ratio (54%, 40%, and 27%, $P < .05$). Addition of PS further reduced total and LDL cholesterol by ~7.7 and 6.5%, respectively, in the atorvastatin therapy group and 5.0 and 4.0% in the combined therapy group ($P < .05$, for all), with no further effects in absorption or synthesis markers.

CONCLUSIONS: PS added to LLT can further improve lipid profile, without additional effects on intestinal sterol absorption or synthesis.

INTEGRATORI ?

DIvo 2004 e successive modifiche:
- “Si intendono per integratori alimentari i prodotti alimentari destinati ad **integrare** la comune dieta (…), aventi un **effetto nutritivo o fisiologico**”.

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