S.I.Te.C.S.
SOCIETÀ ITALIANA DI TERAPIA CLINICA E SPERIMENTALE

THE ROLE OF DYSLIPIDAEMIAS IN DETERMINING CARDIOVASCULAR RISK: FROM LIFESTYLE TO PHARMACOLOGICAL INTERVENTION

November 17-18, Naples – Italy

WHAT TO DO BEFORE INITIATING PHARMACOLOGICAL THERAPY

- The role of nutraceuticals -

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5 y Disclosures

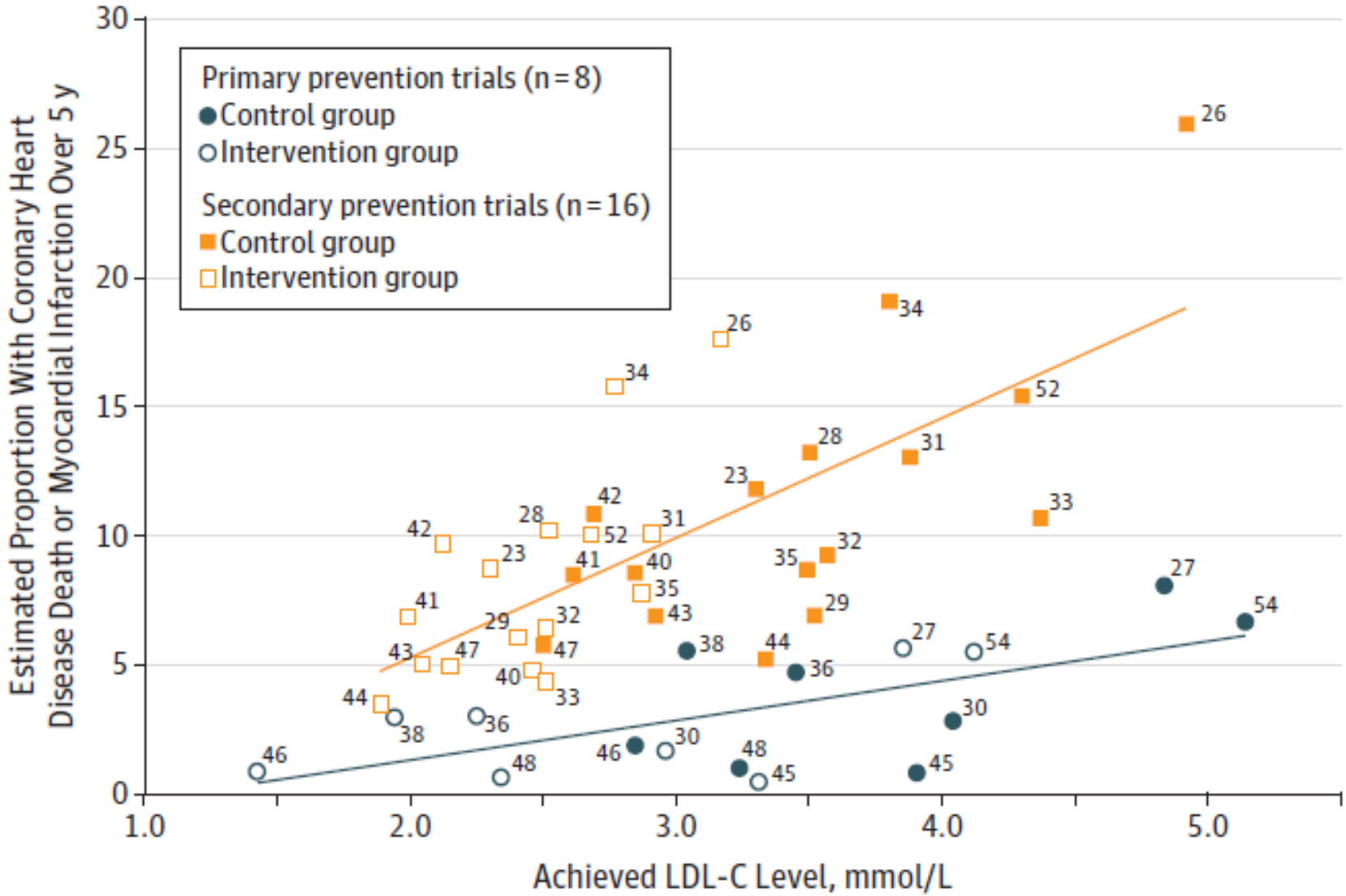
Date November 2018

- **Consulting/presentation or research contracts:** AMGEN, Ibsa, MSD, Mylan, Neopharmed-Gentili, Sanofi, Sigma-Tau
- **Employment in industry:** None
- **Stockholder of a healthcare company:** None
- **Ownership of a healthcare company:** None

The lower the better

The earlier the better

The evidence of “the lower the better”

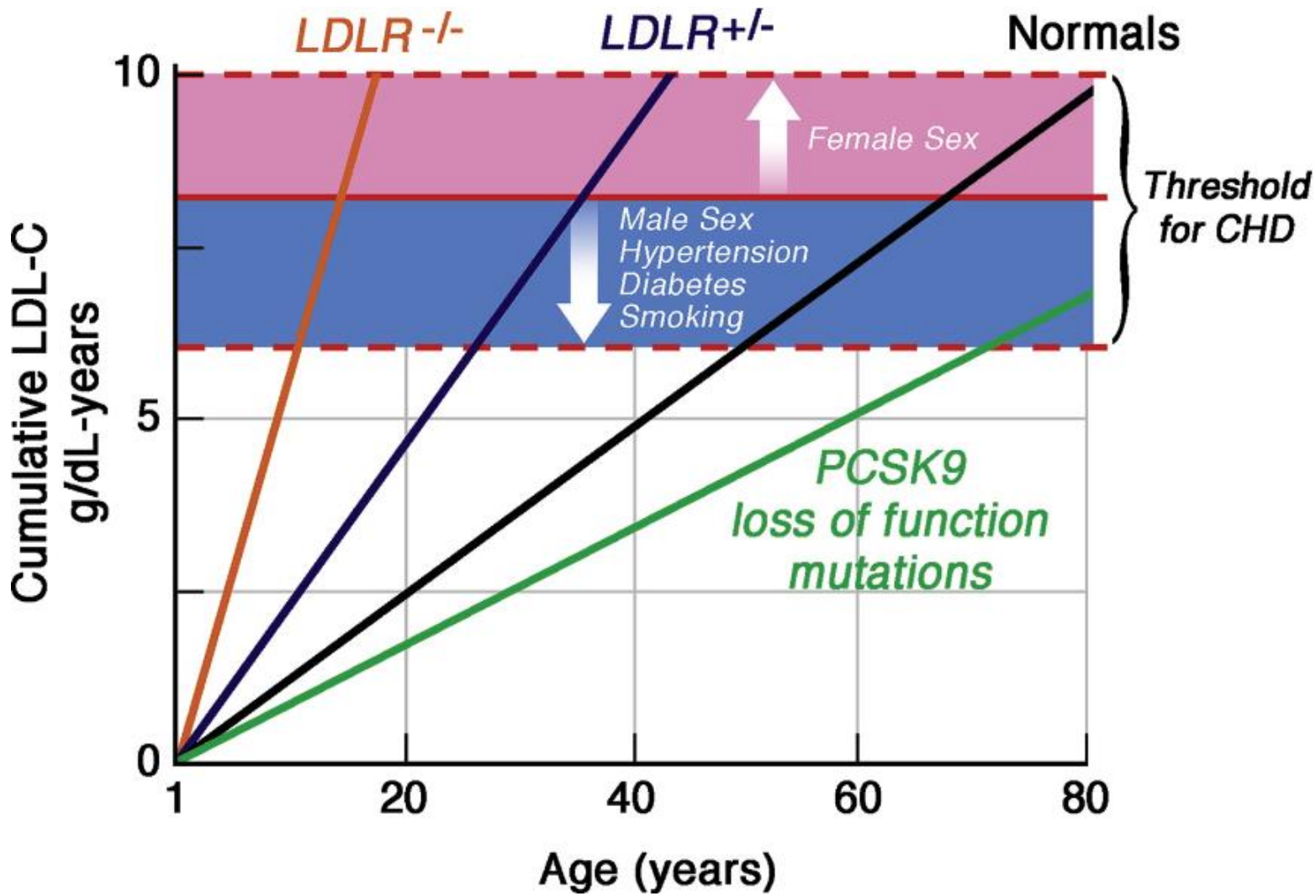


Modified from **Silverman MG, et al. JAMA. 2016 Sep 27;316(12):1289-97.**

The lower the better

The earlier the better

The evidence of “the earlier the better”



Sniderman AD et al. J Am Coll Cardiol. 2014;63(19):1935-1947.

The evidence of “the earlier the better”

About you

Age: 45

Sex: ◉ Male ○ Female

Ethnicity: White or not stated

Leave blank if unknown

Postcode:

Clinical information -- check those that apply

- Diabetic? ☐
- Had a heart attack, angina, stroke or TIA? ☐
- Angina or heart attack in a 1st degree relative < 60? ☐
- Chronic kidney disease (stage 4 or 5)? ☐
- Atrial fibrillation? ☐
- On blood pressure treatment? ☐
- Rheumatoid arthritis? ☐

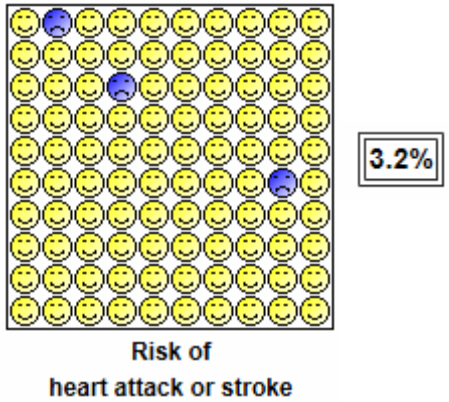
Modifiable risk factors - leave blank if unknown

	Current	What if?
Do you smoke?	Non smoker	Non smoker
Cholesterol/HDL ratio:	5.7	3.4
Systolic blood pressure (mmHg):	125	125
Height (cm):	170	
Weight (kg):	75	75

Re-calculate

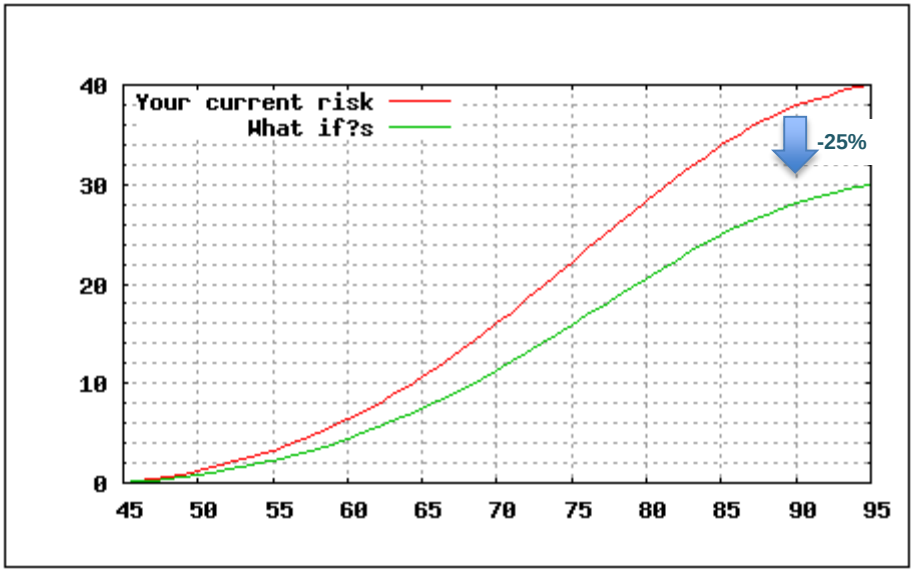
Calculate risk up to 95 years of age. Calculate

10-year CHD risk



Life-time CHD risk

Current	What if?
40%	29.9%



Treatment of hypercholesterolemia

Treatment of causes of secondary hypercholesterolemia

Lifestyle changes

Nutraceuticals (?)

Drugs

Statins

Ezetimibe

Bile Acid Sequestrants

Anti-PCSK9 mAbs

MTTP Inhibitors

Apo B ASO

Apheresis

Drug combinations…

NUTRACEUTICALS OR PHYTOCHEMICALS

“Food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease”

Stephen De Felice, founder and chairman of the Foundation for Innovation in Medicine, 1989

“A pharmaceutical-grade and standardized nutrient”

Sarris, Jerome; Murphy, Jenifer; et al, 2016

Why should we use a nutraceutical for cholesterol-lowering?

Negative prejudice on nutraceuticals should be validated as much as their efficacy/safety

We used-use drugs originally derived from natural sources

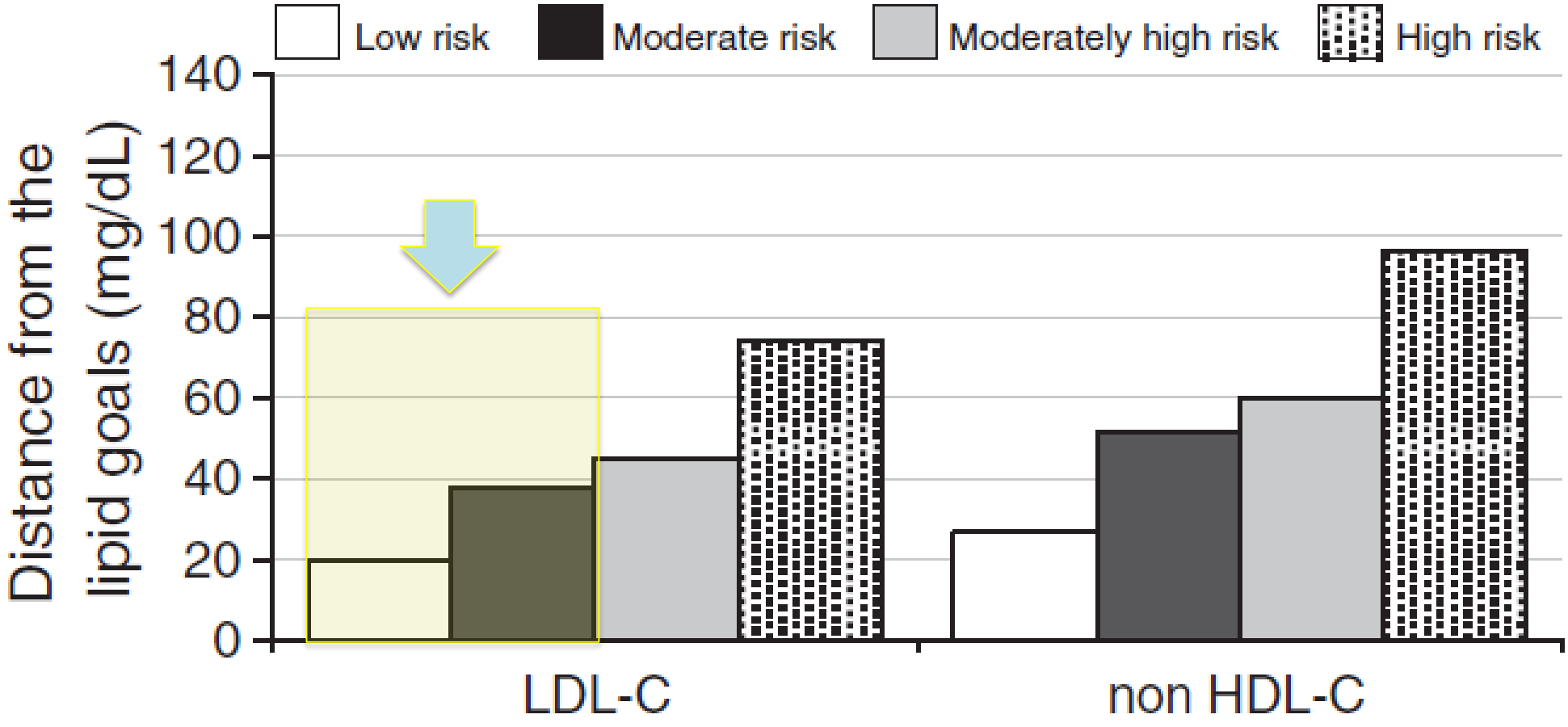
Acetylsalicylic acid (*Salicis cortex*)
Digitalis (*Digitalis purpurea*)
Morphine and Codeine (*Papaver somniferum & setigerum*)
***Streptomycin* (*Streptomyces griseus*)**
…

Why should we use a nutraceutical for cholesterol-lowering?

1) **Different degrees of hypercholesterolemia & direct association between cholesterol levels and CVD risk**
2) **Cholesterol levels are above recommended goals in a large number of subjects…look at the distance from goals**
3) Hypercholesterolemia is a modifiable CVD risk factor, which is sensitive to lifestyle changes
4) Even mild cholesterol-lowering is associated with significant CVD risk reduction

LDL-C distance from the recommended target

1264 consecutive patients not receiving cholesterol-lowering therapy, referred to our Lipid Clinic



Pirro M, et al, Eur J Intern Med. 2011 Aug;22(4):412-7.

Why should we use a nutraceutical for cholesterol-lowering?

1) Different degrees of hypercholesterolemia & direct association between cholesterol levels and CVD risk
2) Cholesterol levels are above recommended goals in a large number of subjects…look at the distance from goals
3) **Hypercholesterolemia is a modifiable CVD risk factor, which is not very sensitive to lifestyle changes**
4) Even mild cholesterol-lowering is associated with significant CVD risk reduction

Dietary advice for reducing CV risk

THE COCHRANE COLLABORATION

Advice to reduce fat intake (total and saturated fatty acids) and to increase dietary fibre, fruit and vegetable consumption

vs

No advice

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
Total cholesterol (mmol/l), change from baseline	22	3044	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.21, -0.05]
LDL cholesterol (mmol/l), change from baseline	17	1654	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.24, -0.08]
HDL cholesterol (mmol/l), change from baseline	16	1700	Mean Difference (IV, Random, 95% CI)	-6.89 [-0.02, 0.02]
Triglycerides (mmol/l), change from baseline	8	648	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.08]

Rees K, et al, Cochrane Database Syst Rev. 2013 Dec 6;(12):CD002128.

Why should we use a nutraceutical for cholesterol-lowering?

1) Different degrees of hypercholesterolemia & direct association between cholesterol levels and CVD risk
2) Cholesterol levels are above recommended goals in a large number of subjects…look at the distance from goals
3) Hypercholesterolemia is a modifiable CVD risk factor, which is sensitive to lifestyle changes
4) **Even mild cholesterol-lowering is associated with CVD risk reduction (e.g., IMPROVE-IT…↓ LDL-C -16.7 mg/dl= ↓ HR CVD risk -7%)**

Which cholesterol-lowering nutraceutical should we use?

Phytosterols	Soluble fibers	RYR
Berberine	Soy and lupin proteins	Bergamot
Chitosan	Green Tea extract	Artichoke
Garlic	Spirulina	Soy and lupin proteins
Probiotics	Anthocyanins	Curcumin
Gamma-oryzanol	Others	

Cicero AFG, et al, Arch Med Sci. 2017 Aug;13(5):965-1005

Nutr Metab Cardiovasc Dis. 2017 Jan;27(1):2-17. doi: 10.1016/j.numecd.2016.11.122. Epub 2016 Nov 22.

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).

Pirro M[1], Vetrani C[2], Bianchi C[3], Mannarino MR[1], Bernini F[4], Rivellese AA[5].

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].

J Am Coll Cardiol. 2018 Jul 3;72(1):96-118. doi: 10.1016/j.jacc.2018.04.040.

The Role of Nutraceuticals in Statin Intolerant Patients.

Banach M[1], Patti AM[2], Giglio RV[2], Cicero AFG[3], Atanasov AG[4], Bajraktari G[5], Bruckert E[6], Descamps O[7], Djuric DM[8], Ezhov M[9], Fras Z[10], von Haehling S[11], Katsiki N[12], Langlois M[13], Latkovskis G[14], Mancini GBJ[15], Mikhailidis DP[16], Mitchenko O[17], Moriarty PM[18], Muntner P[19], Nikolic D[2], Panagiotakos DB[20], Paragh G[21], Paulweber B[22], Pella D[23], Pitsavos C[24], Reiner Ž[25], Rosano GMC[26], Rosenson RS[27], Rysz J[28], Sahebkar A[29], Serban MC[30], Vinereanu D[31], Vrablík M[32], Watts GF[33], Wong ND[34], Rizzo M[2]; International Lipid Expert Panel (ILEP).

Pharmacol Res. 2018 Aug;134:51-60. doi: 10.1016/j.phrs.2018.05.015. Epub 2018 May 30.

Nutraceuticals and functional foods for the control of plasma cholesterol levels. An intersociety position paper.

Poli A[1], Barbagallo CM[2], Cicero AFG[3], Corsini A[4], Manzato E[5], Trimarco B[6], Bernini F[7], Visioli F[8], Bianchi A[9], Canzone G[10], Crescini C[11], de Kreutzenberg S[12], Ferrara N[13], Gambacciani M[14], Ghiselli A[15], Lubrano C[16], Marelli G[17], Marrocco W[18], Montemurro V[19], Parretti D[20], Pedretti R[21], Perticone F[22], Stella R[23], Marangoni F[24].

Meta-analyses of RCTs on the lipid-lowering effects of phytosterols

↓ LDL-C

-12 mg/dL

Type of study	Subjects (number, type)	Average dose (range)	Mean duration (range)	Observed effect
Meta-analysis of 49 RCT	n: >4500 Healthy subjects Hypercholesterolemia	(0.3–9 g/day)	(3–26 weeks)	↓ LDL-C: −12 mg/dl
Meta-analysis of 20 RCT	n: 1273 Healthy subjects Hypercholesterolemia	2.08 g/day (0.45–3.2 g/day)	(2–52 weeks)	↓ LDL-C: −14 mg/dl (−6/−15%) No effect on TG and HDL-C
Meta-analysis of 84 RCT	n: 6805 Healthy subjects Hypercholesterolemia	2.15 g/day (0.45–9 g/day)	(21–182 days)	↓ LDL-C: −13 mg/dl (−8.8%)
Meta-analysis of 41 RCT	n: 2084 Healthy subjects Hypercholesterolemia	1.6 g/day (0.3–3.2 g/day)	28 days (21–315 days)	↓ LDL-C: −13 mg/dl (−8.5%) No effect on HDL-C
Meta-analysis of 124 RCT	Healthy subjects Hypercholesterolemia	2.1 g/day (0.2–9 g/day)	At least 2 weeks	↓ LDL-C: −6/12%
Meta-analysis of 6 RCT[a]	n: 453 Familial hypercholesterolemia	(1.6–2 g/day)	(4–8 weeks)	↓ LDL-C: −25 mg/dl No effect on TG and HDL-C
Meta-analysis of 5 RCT	n: 148 Diabetes mellitus	(1.8–3 g/day)	(3–12 weeks)	↓ LDL-C: −12 mg/dl No effect on TG and HDL-C
Meta-analysis of 12 RCT	n: 935 Hypercholesterolemia	(0.8–4 g/day)	(3–4 weeks)	↓ TG: −11 mg/dl (−6%) No effect on HDL-C

↓ LDL-C

-25 mg/dL

Pros

LDL-C reduction by 8–10%
No interaction with lipid-lowering drugs

Cons

Possible excessive intake with the risk of reduced absorption of fat soluble vitamins

Pirro M, et al, Nutr Metab Cardiovasc Dis. 2017 Jan;27(1):2-17.

Meta-analyses of RCTs on the lipid-lowering effects of berberine

↓ LDL-C

-13 mg/dL

Type of study	Subjects (number, type)	Average dose (range)	Mean duration (range)	Observed effect
Meta-analysis of 14 RCT	n: 1068 Type 2 diabetes	0.5–1.5 g/day	12 weeks (8–24 weeks)	↓ LDL-C: −13/-22 mg/dl ↓ TG: −19/−45 mg/dl ↑ HDL-C: 0.8/2.7 mg/dl
Meta-analysis of 11 RCT	n: 874 Dyslipidemia Type 2 diabetes	0.5–1.5 g/day	15 weeks (8–52 weeks)	↓ LDL-C: −25 mg/dl ↓ TG: −44 mg/dl ↑ HDL-C: 1.9 mg/dl
Meta-analysis of 6 RCT	n: 451 Dyslipidemia	0.6–1.5 g/day	11 weeks (8–17 weeks)	↓ LDL-C: −25 mg/dl ↓ TG: −35 mg/dl ↑ HDL-C: 2.7 mg/dl

↓ LDL-C

-25 mg/dL

Pros

LDL-C reduction by 20%
Better safety profile in patients with intolerance to multiple statins
Favorable effect on TG, HDL-C and blood glucose

Cons

Variability of intestinal absorption

Pirro M, et al, Nutr Metab Cardiovasc Dis. 2017 Jan;27(1):2-17.

Meta-analyses of RCTs on the lipid-lowering effects of red yeast rice

↓ LDL-C

-24 mg/dL

Type of study	Subjects (number, type)	Content of monacolin K	Mean duration (range)	Observed effect
Meta-analysis of 93 RCT	n: 9625 Dyslipidemia	3–12.4 mg/day	8 weeks (4–24 weeks)	↓ LDL-C: −28 mg/dl ↓ TG: −36 mg/dl ↑ HDL-C: 5.8 mg/dl
Meta-analysis of 13 RCT	n: 804 Dyslipidemia	2–11.4 mg/day	12 weeks (4–24 weeks)	↓ LDL-C: −34 mg/dl ↓ TG: −20 mg/dl No effect on HDL-C
Meta-analysis of 20 RCT	n: 2811 Dyslipidemia Type 2 diabetes CHD, Hypertensive	4.8–24 mg/day	23 weeks 4–168 weeks	↓ LDL-C: −39 mg/dl ↓ TG: −23 mg/dl ↑ HDL-C: 2.7 mg/dl
Meta-analysis of 21 RCT	n: 4558 Hypertensive	(RYR 1200–1800 mg/day)	4–234 weeks	↓ LDL-C: −24 mg/dl No effect on TG and HDL-C

↓ LDL-C

-39 mg/dL

Pros

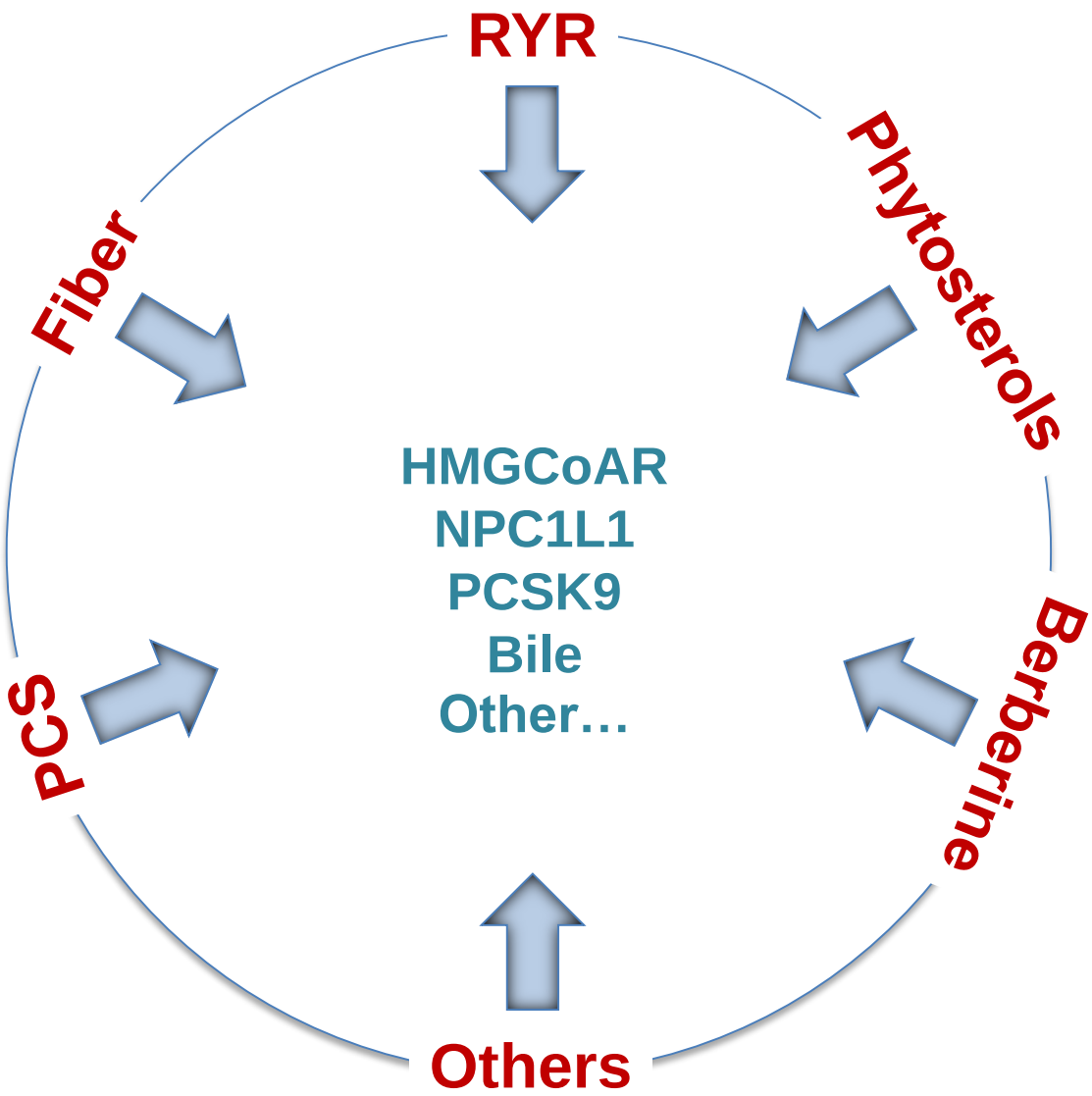
LDL-C reduction by 16–25%
Good safety profile
Reduction of cardiovascular risk

Cons

Variability of composition and purity of OTC products
Self purchasing by patients and risk of no medical supervision
Higher cost compared to generic statins
Possible side effects at high doses

Pirro M, et al, Nutr Metab Cardiovasc Dis. 2017 Jan;27(1):2-17.

What is the rationale for using nutraceutical combinations?



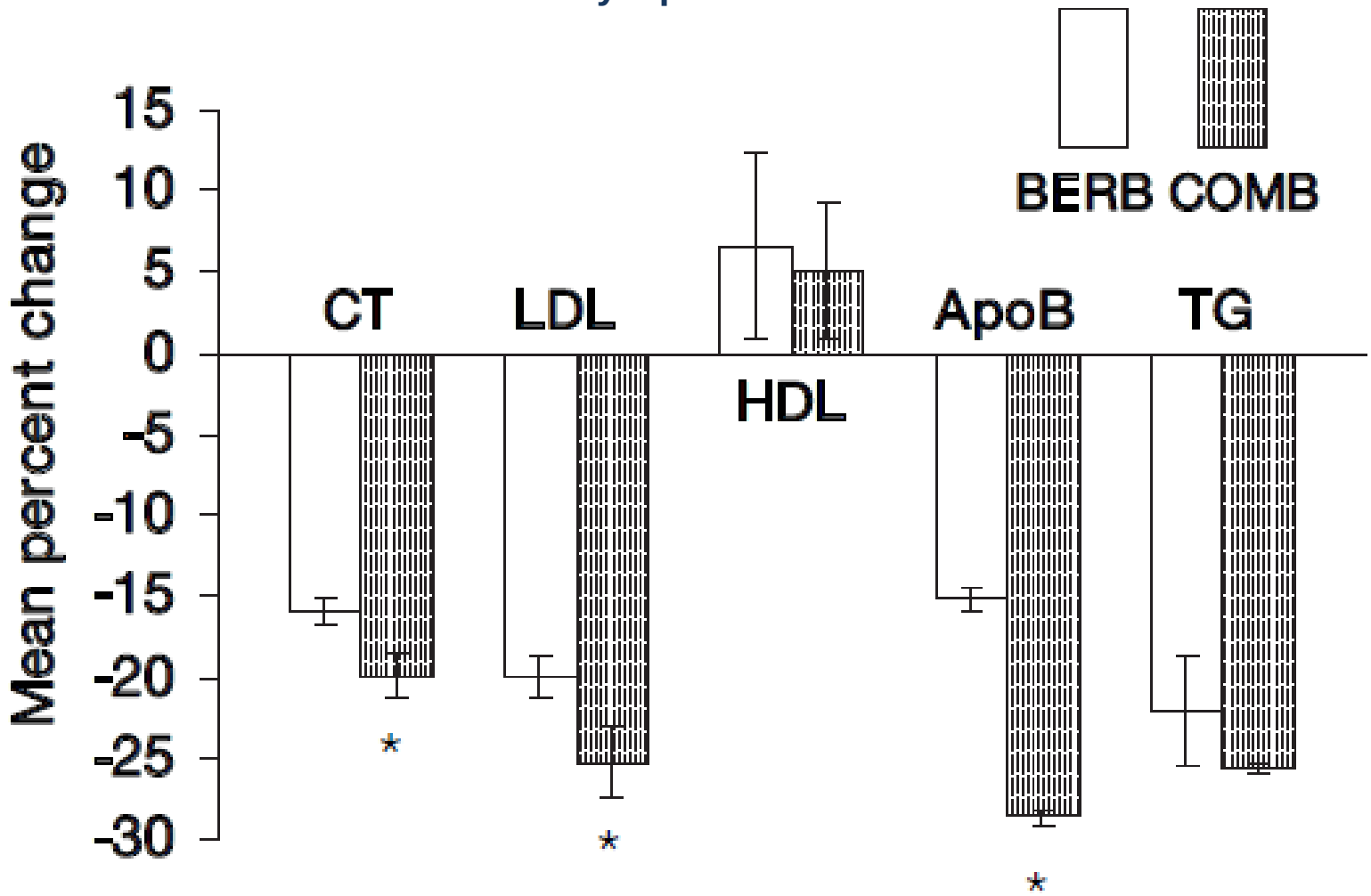
To hit multiple targets

To increase the cholesterol-lowering efficacy of each nutraceutical

To reduce the dose of each nutraceutical in order to minimize side effects

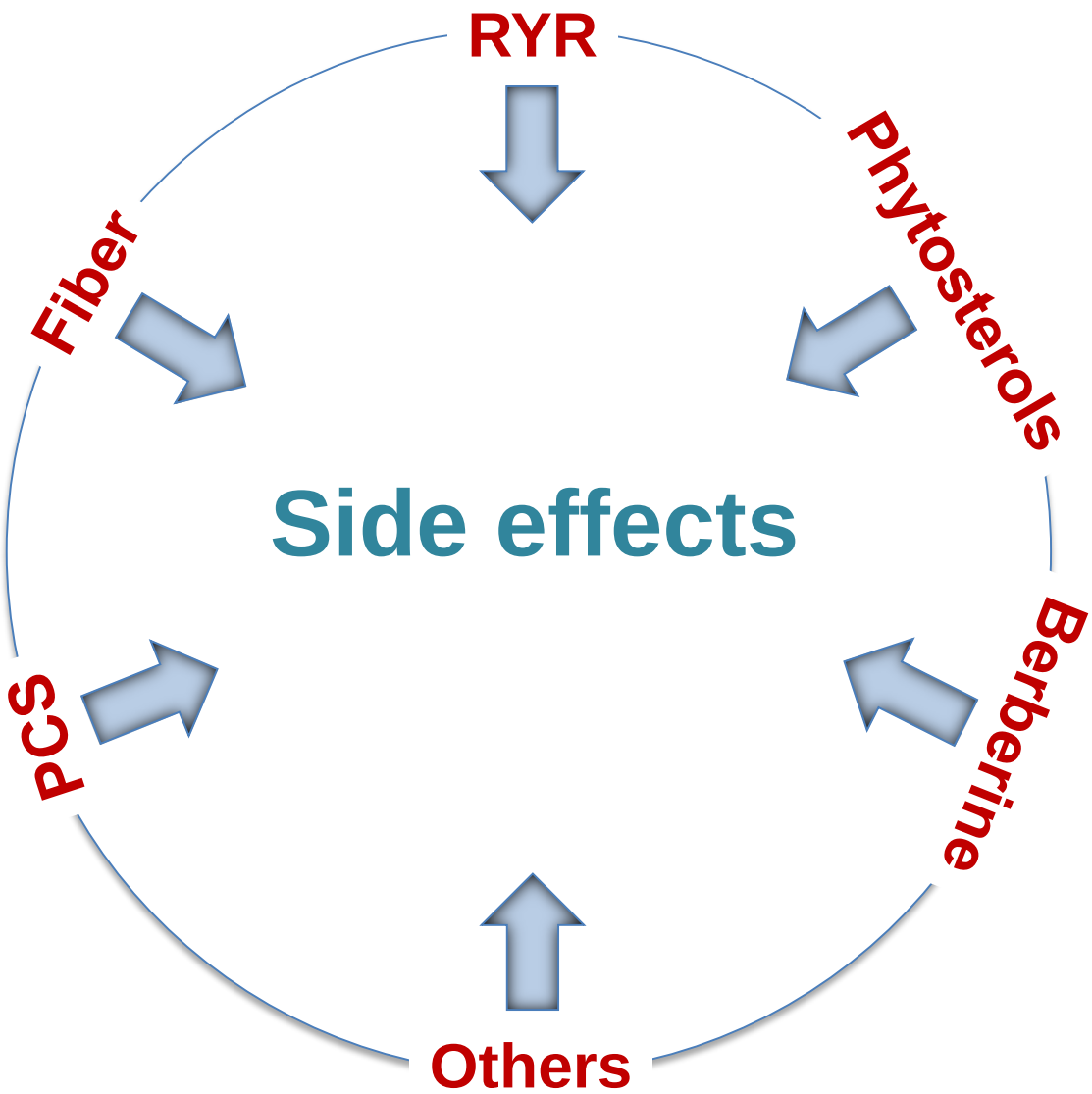
RYR+Berberine *vs* Berberine alone: effect on lipids

Percent chnge of plasma lipids after 4 weeks of treatment in 40 patients with moderate dyslipidemia



Cicero AFG et al, Arzneimittelforschung. 2007;57(1):26-30.

What is the rationale for using nutraceutical combinations?



To hit multiple targets

To increase the cholesterol-lowering efficacy of each nutraceutical

To reduce the dose of each nutraceutical in order to minimize side effects

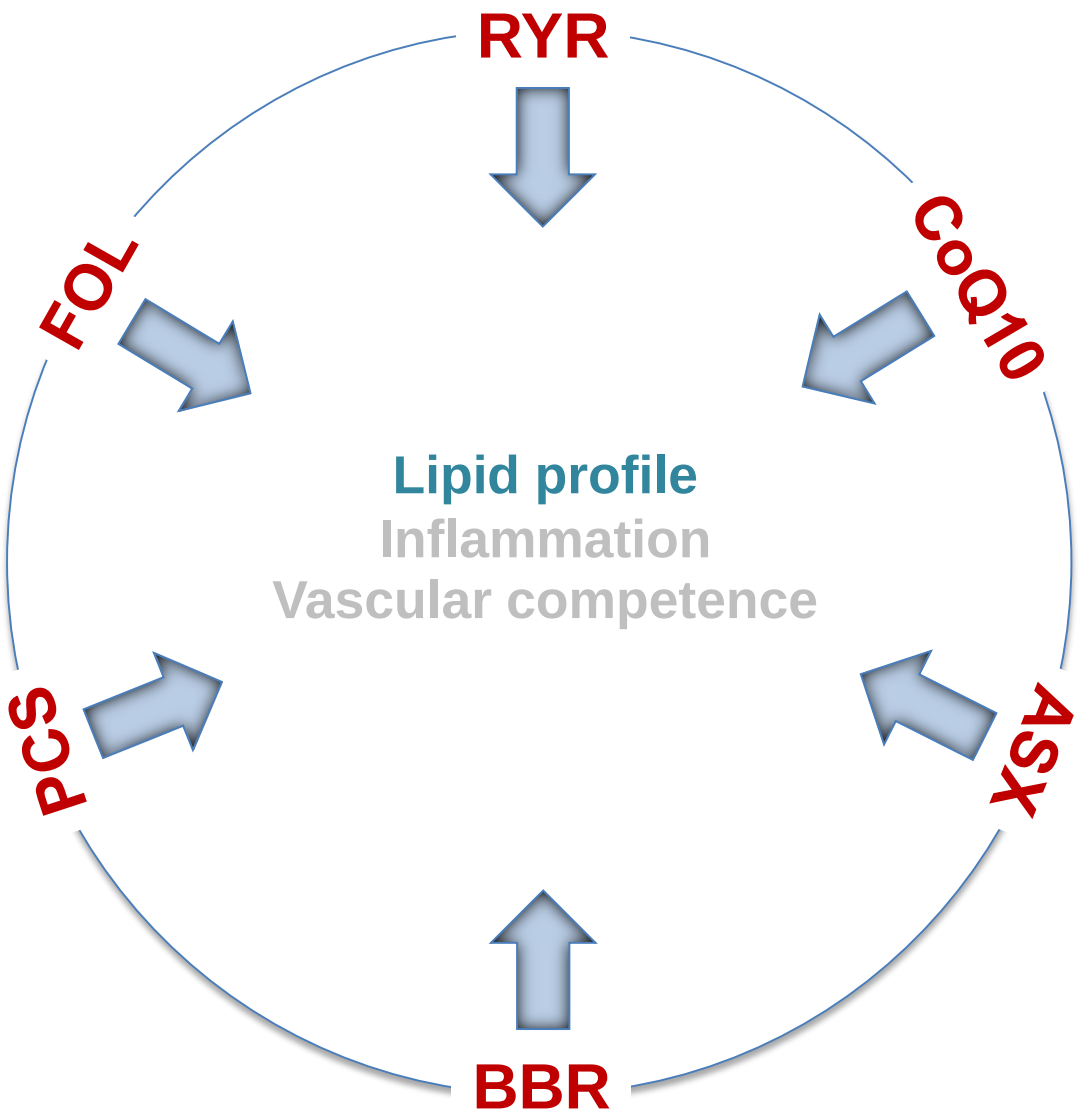
Nutraceuticals may have side effects!

Fibers……	constipation
Phytosterols……	milk related, vitamin absorption
Soy products……..	allergy
Berberine……	gastro-intestinal
Red yeast rice……	statin-like

Nutraceutical side effects are related:

- doses
- patients choiches
- production systems
- safety assessment
- other…

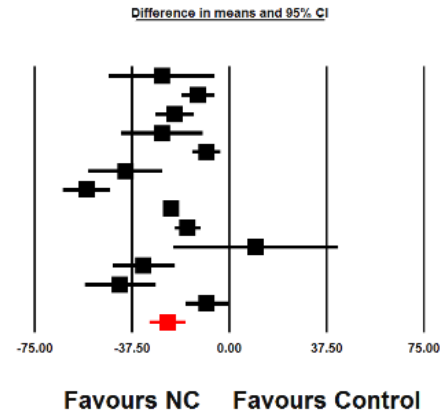
Nutraceuticals: why should we use combinations?



Effects of a NC containing RYR+Berberine on lipids: a meta-analysis of RCTs

LDL-cholesterol

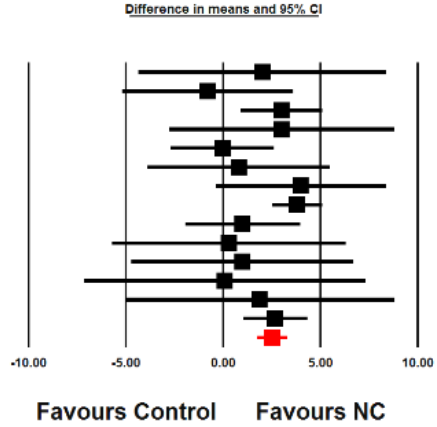
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ruscica et al., 2014	-26.000	10.316	106.412	-46.218	-5.782	-2.520	0.012
Pisciotta et al., 2012	-12.000	3.164	10.013	-18.202	-5.798	-3.792	0.000
Cicero et al., 2012	-21.000	3.809	14.511	-28.466	-13.534	-5.513	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



-23.8 mg/dL

HDL-cholesterol

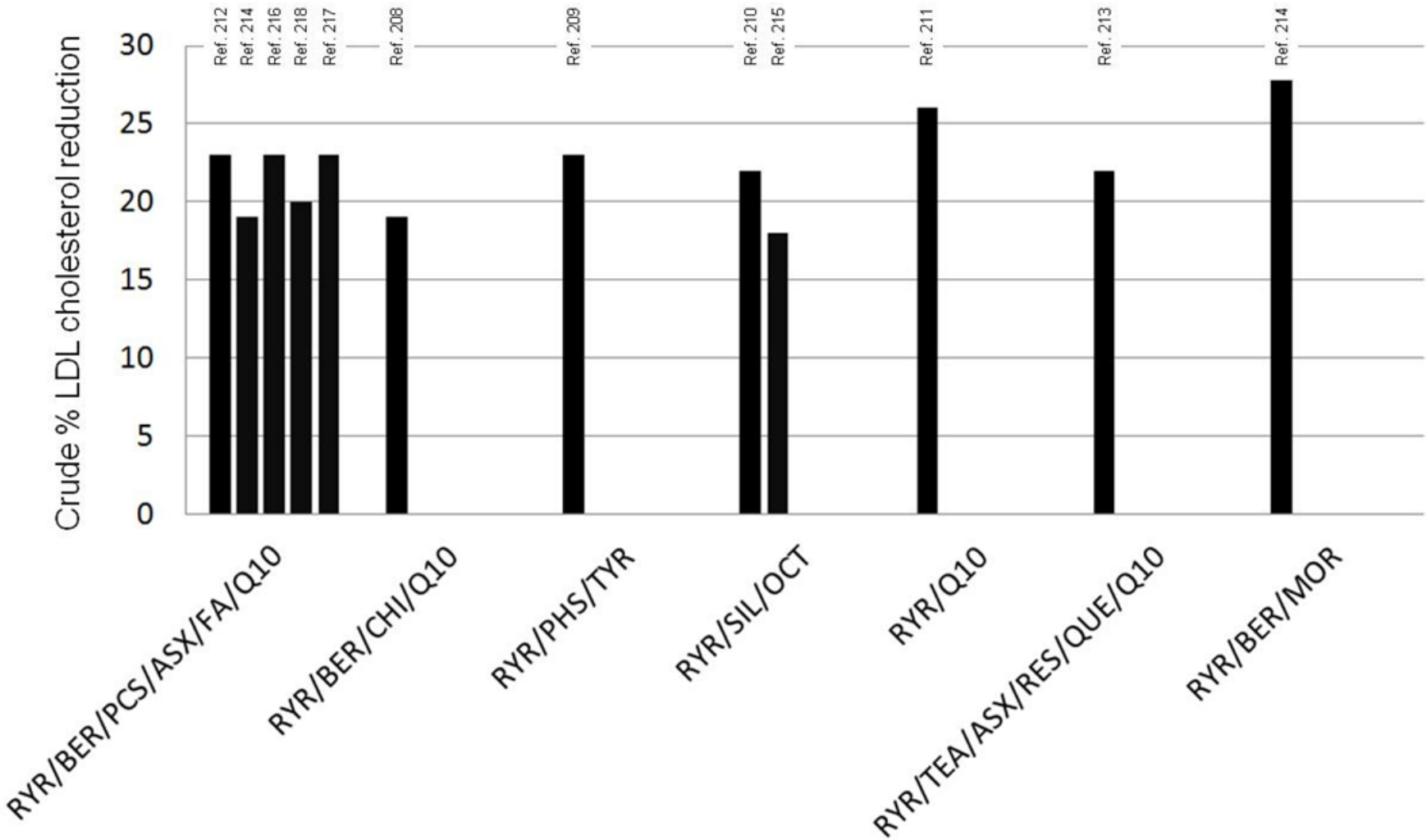
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ruscica et al., 2014	2.000	3.246	10.533	-4.361	8.361	0.616	0.538
Pisciotta et al., 2012	-0.800	2.233	4.987	-5.177	3.577	-0.358	0.720
Cicero et al., 2012	3.000	1.069	1.144	0.904	5.096	2.805	0.005
Affuso et al., 2012	3.000	2.942	8.655	-2.766	8.766	1.020	0.308
Cicero et al., 2007	-0.050	1.358	1.845	-2.712	2.612	-0.037	0.971
Affuso et al., 2009	0.800	2.380	5.667	-3.866	5.466	0.336	0.737
Marazzi et al., 2011	4.000	2.219	4.925	-0.350	8.350	1.802	0.071
Trimarco et al., 2010	3.800	0.652	0.425	2.522	5.078	5.829	0.000
Marazzi et al., 2015	1.000	1.503	2.260	-1.946	3.946	0.665	0.506
Gentile et al., 2015	0.300	3.059	9.355	-5.695	6.295	0.098	0.922
Pirro et al., 2013	1.000	2.908	8.457	-4.700	6.700	0.344	0.731
Gonnelli et al., 2015	0.090	3.677	13.518	-7.116	7.296	0.024	0.980
Solà et al., 2014	1.880	3.531	12.465	-5.040	8.800	0.532	0.594
Izzo et al., 2010	2.680	0.835	0.698	1.043	4.317	3.209	0.001
	2.533	0.391	0.153	1.766	3.300	6.473	0.000



+2.5 mg/dL

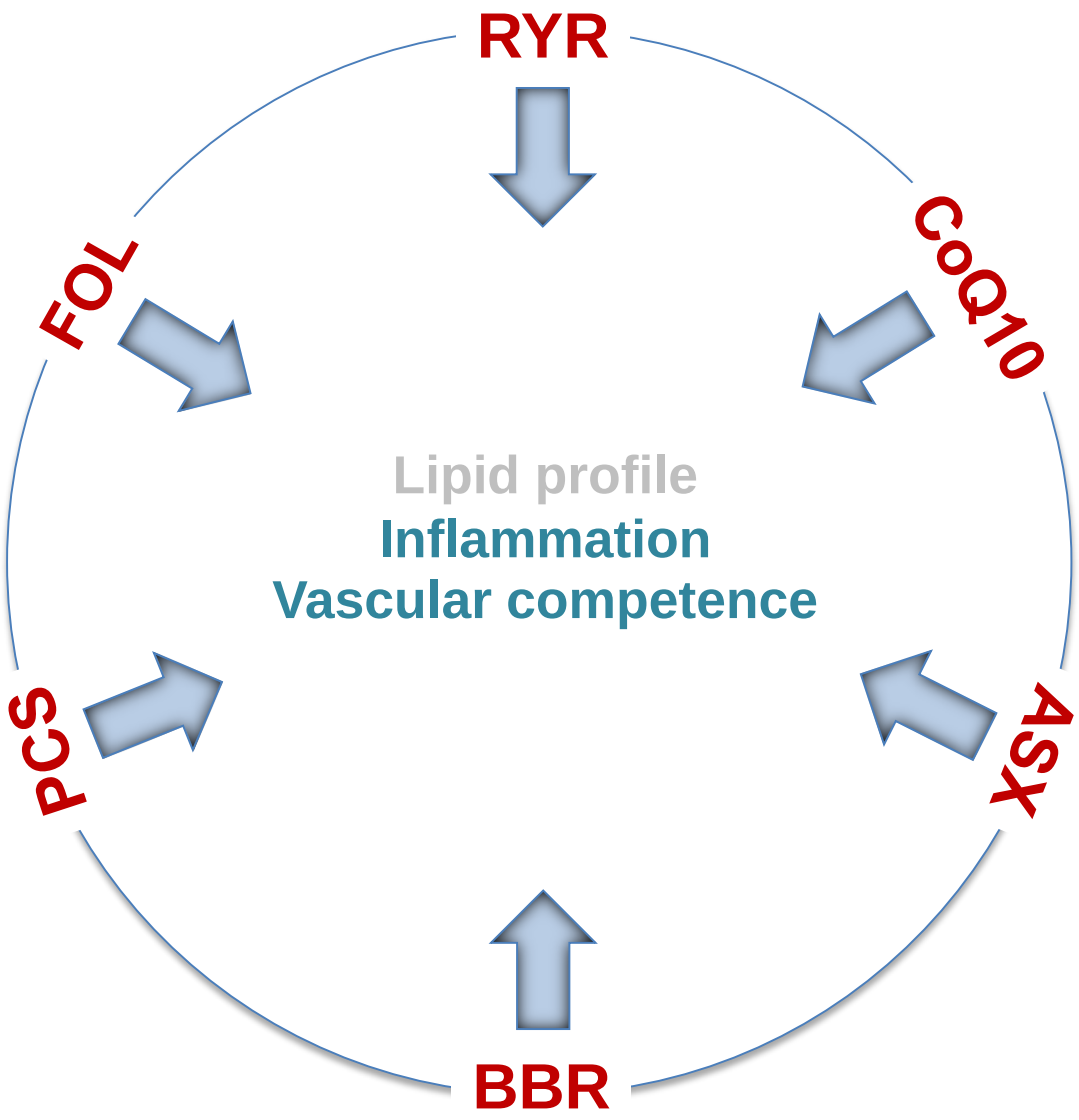
Pirro M, et al. Pharmacol Res. 2016 May 6;110:76-88.

Nutraceutical combinations: effects on LDL cholesterol



Bianconi V, Pirro M, et al. Curr Cardiol Rep 2018 (in press)

Nutraceuticals: why should we use combinations?



RYR+Berberine in patients with mild cholesterol elevation and subclinical inflammation: effects on lipids, hsCRP and EMPs

12-week prospective, single centre randomized open-label interventional study in 100 patients with low-moderate CV risk, elevated plasma high sensitivity C-reactive protein (hsCRP) levels (>2 mg/L) and LDL cholesterol of 100-160 mg/dL

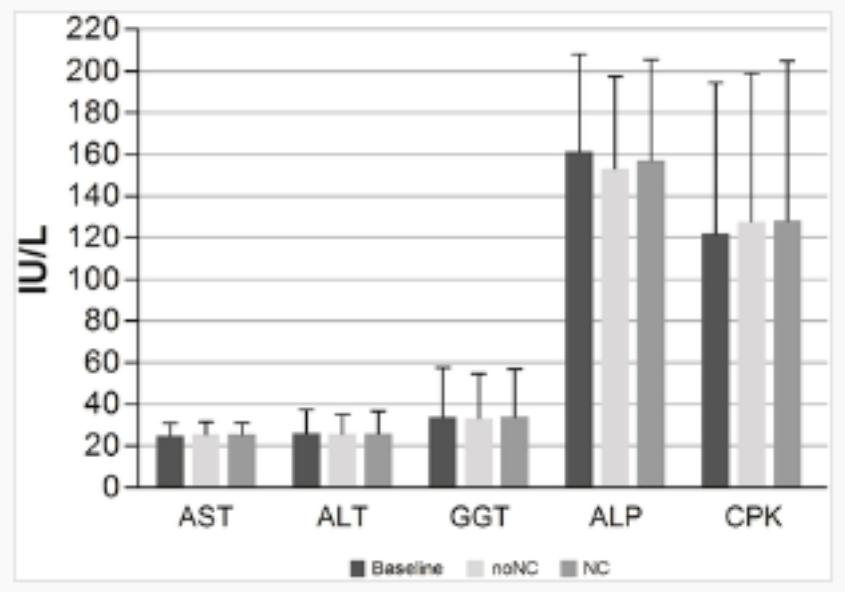
	noNC						NC				
	Before Mean or median and SD or IQR		After Mean or median and SD or IQR		% change	p[&]	Before Mean or median and SD or IQR		After Mean or median and SD or IQR		% change
Total cholesterol, mg/dL	210	24	210	25	0.00	< 0.001	211	17	185	17	−12.32*
LDL cholesterol, mg/dL	131	16	132	18	0.76	< 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*

Pirro M et al, Sci Rep. 2016 Mar 23;6:23587.

RYR+Berberine in HIV+ patients on stable ART: effects on lipids, hsCRP and aPWV

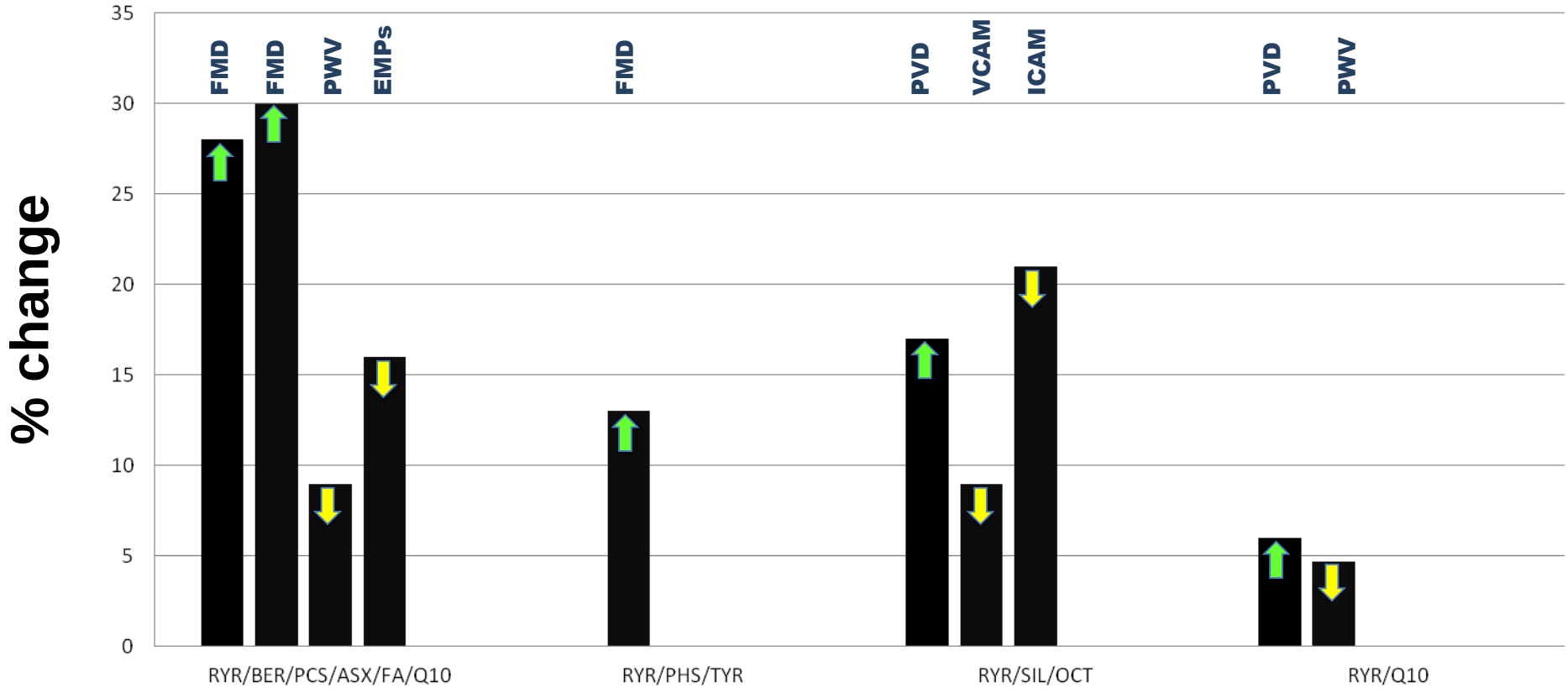
12-week prospective, single centre randomized open-label interventional study in 30 stable HIV-infected patients on ART with low-density lipoprotein cholesterol (LDL-C)>115 mg/dL, not taking lipid-lowering treatment

	Change[a], SD	*p*
Body mass index (kg/m^2)	−0.2 ± 1.6	0.39
Waist circumference (cm)	−0.8 ± 2.7	0.13
Systolic blood pressure (mmHg)	−1.9 ± 7.9	0.19
Diastolic blood pressure (mmHg)	−1.2 ± 5.3	0.22
Total cholesterol (mg/dL)	−33 ± 19	<0.001
LDL cholesterol (mg/dL)	−30 ± 14	<0.001
HDL cholesterol (mg/L)	0.6 ± 6.2	0.56
Triglycerides (mg/dL)	−19 ± 71	0.15
Glucose (mg/mL)	−1.1 ± 3.4	0.10
Lipoprotein(a) (mg/dL)	−2.4 ± 17.8	0.46
PCSK9 (ng/mL)	−30 ± 67	0.02
hs-CRP (mg/L)	−0.3 ± 0.7	0.02
Aortic PWV (m/sec)	−0.4 ± 0.7	0.005



Pirro M et al, Atherosclerosis. 2018 (in press) https://doi.org/10.1016/j.atherosclerosis.2018.11.026

Nutraceutical combinations: effects on arterial function parameters



FMD, flow-mediated dilation; **PWV**, pulse wave velocity; **EMPs**, endothelial microparticles, **PVD**, pulse volume displacement, **VCAM**, vascular cell adhesion molecule 1, **ICAM**, intercellular adhesion molecule 1

Bianconi V, Pirro M, et al. Curr Cardiol Rep. 2018 May 25;20(7):53.

Nutraceuticals: how, when and why ?

How

As an early cholesterol-lowering treatment in patients with elevated cholesterol levels or as a safe and sustainable CV prevention strategy (primordial prevention) before frank hypercholesterolemia occurs

When

When the expected beneficial effect on lipid profile allows to predict a possible achievement of the recommended therapeutic goals

Why

Because its use is supported by efficacy and safety studies, standardized production methods and strict quality controls