PRESENT AND FUTURE APPROACHES TO THE CONTROL OF DYSLIPIDAEMIAS

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Lifestyle interventions and the role of nutraceuticals

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Disclosure of potential conflicts of interest

Maciej Banach Department of Hypertension, Medical University of Lodz, Poland

EMPLOYEMENT	-
RESEARCH GRANT / RESEARCH SUPPORT	Amgen, Mylan, Sanofi, Valleant,
SPEAKER BUREAU	Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, KRKA, Mylan, Novartis, Novo-Nordisk, Polpharma, Polfarmex, Sanofi-Aventis, and Servier; Grants from Amgen, Mylan, Sanofi and Valeant
HONORARIA	-
EXPERT WITNESS	-
OWNERSHIP INTEREST	
CONSULTANT/ ADVISORY BOARD	Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, Novartis, Novo-Nordisk, Polfarmex, Sanofi-Aventis
OTHER	-

Da Vinci Study – Why we so ineffective?

ESC European Society of Cardiology
European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwaa047

FULL RESEARCH PAPER

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study

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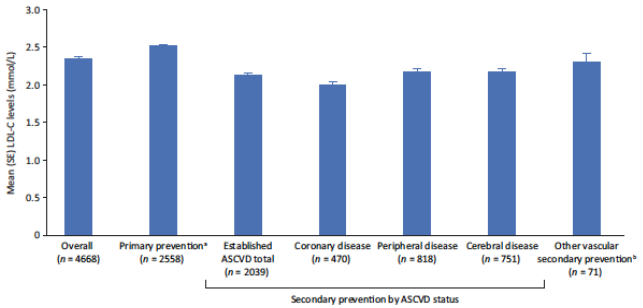

Figure 3 Mean low-density lipoprotein cholesterol levels in patients with stabilized lipid-lowering therapy. *n*, the number of patients in the category on stabilized lipid-lowering therapy and with non-missing low-density lipoprotein cholesterol goal data. [a]Primary prevention: at low-density lipoprotein cholesterol measurement, 142 patients enrolled as secondary prevention, whose first atherosclerotic cardiovascular disease event occurred after the date low-density lipoprotein cholesterol levels were stabilized, are included in the primary prevention group. [b]Patients with other evidence of atherosclerosis or other manifestation of vascular disease at enrolment. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; SE, standard error.

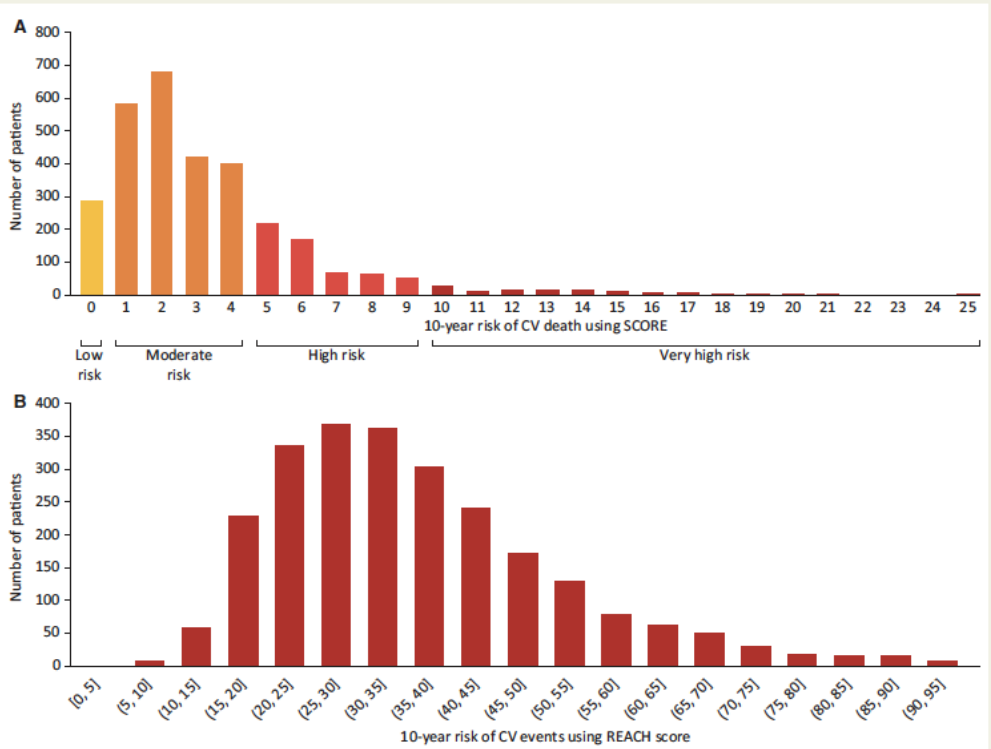

Figure 1 Estimated 10-year cardiovascular risk at low-density lipoprotein cholesterol measurement in primary prevention group[a] (*A*) and estimated 10-year risk of fatal and non-fatal cardiovascular events at low-density lipoprotein cholesterol measurement in established atherosclerotic cardiovascular disease group[b] (*B*). [a]Data shown are for all patients considered primary prevention at low-density lipoprotein cholesterol measurement (*n* = 3142); of these, 2073 were on stabilized lipid-lowering therapy at low-density lipoprotein cholesterol measurement and had data available to calculate systematic coronary risk evaluation and glomerular filtration rate risk. [b]Data shown are for all patients considered having established atherosclerotic cardiovascular disease at low-density lipoprotein cholesterol measurement (*n* = 2659); of these, 2039 were on stabilized lipid-lowering therapy at low-density lipoprotein cholesterol measurement. CV, cardiovascular; REACH, Reduction of Atherothrombosis for Continued Health; SCORE, systematic coronary risk evaluation.

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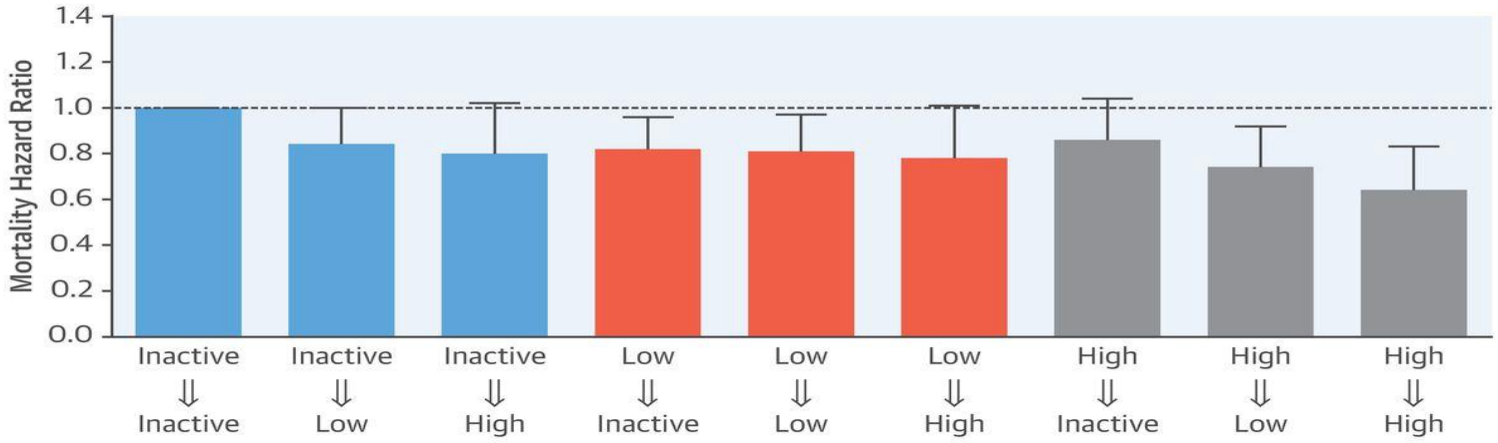
Ray KK, Banach M, et al., DA VINCI study. European Journal of Preventive Cardiology 2020; DOI: 10.1093/eurjpc/zwaa047

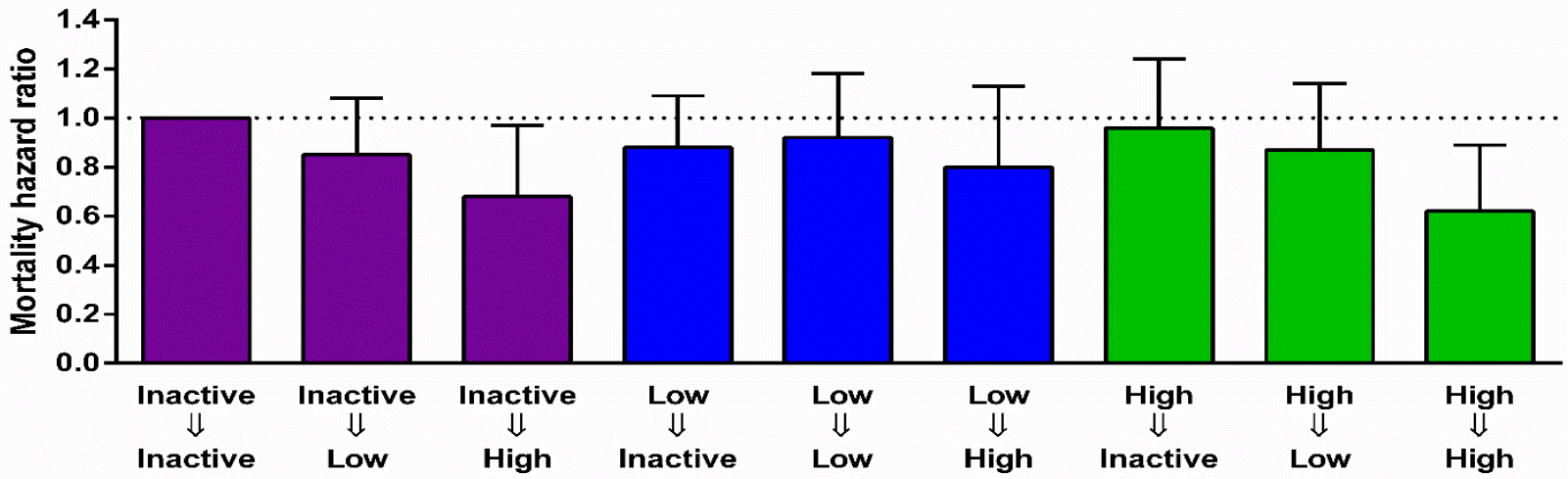
Ray KK, Banach M, et al., DA VINCI study. European Journal of Preventive Cardiology 2020; DOI: 10.1093/eurjpc/zwaa047

Lifestyle changes: exercise and all-cause and CHD mortality

CENTRAL ILLUSTRATION: Change in Physical Activity Level and Mortality Risk



Moholdt, T. et al. J Am Coll Cardiol. 2018;71(10):1094–101.



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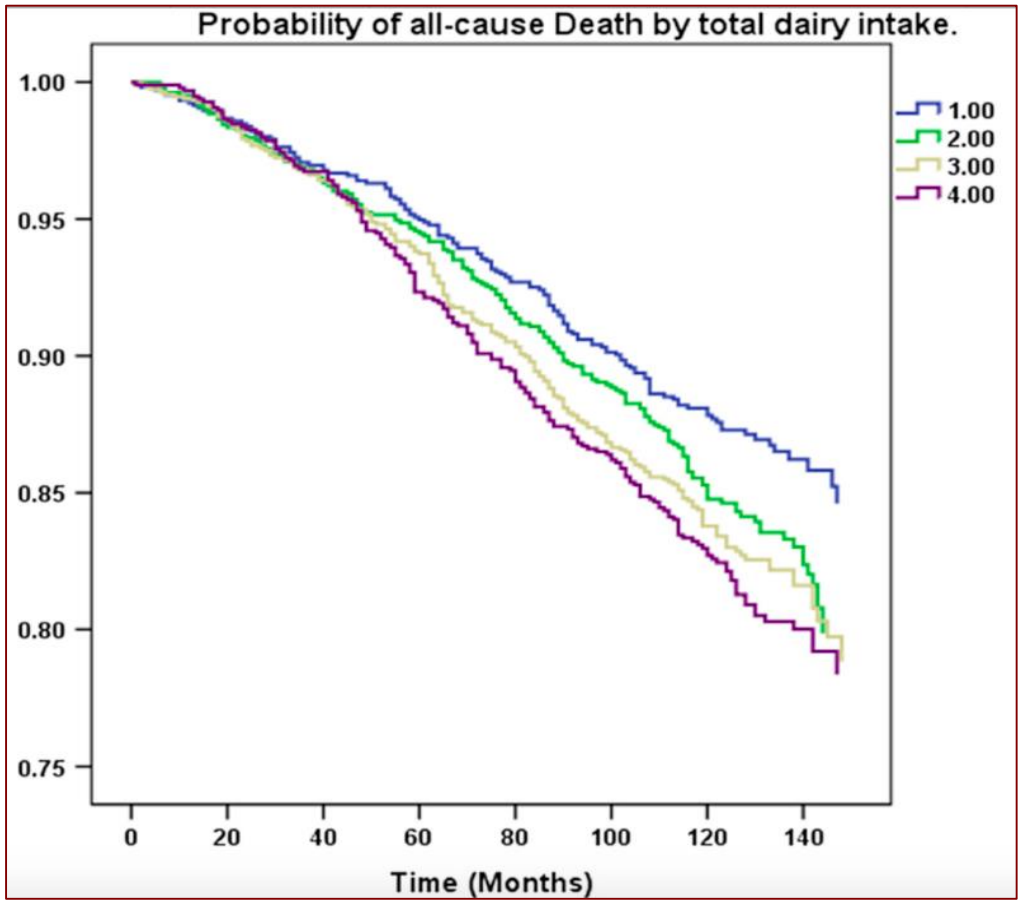
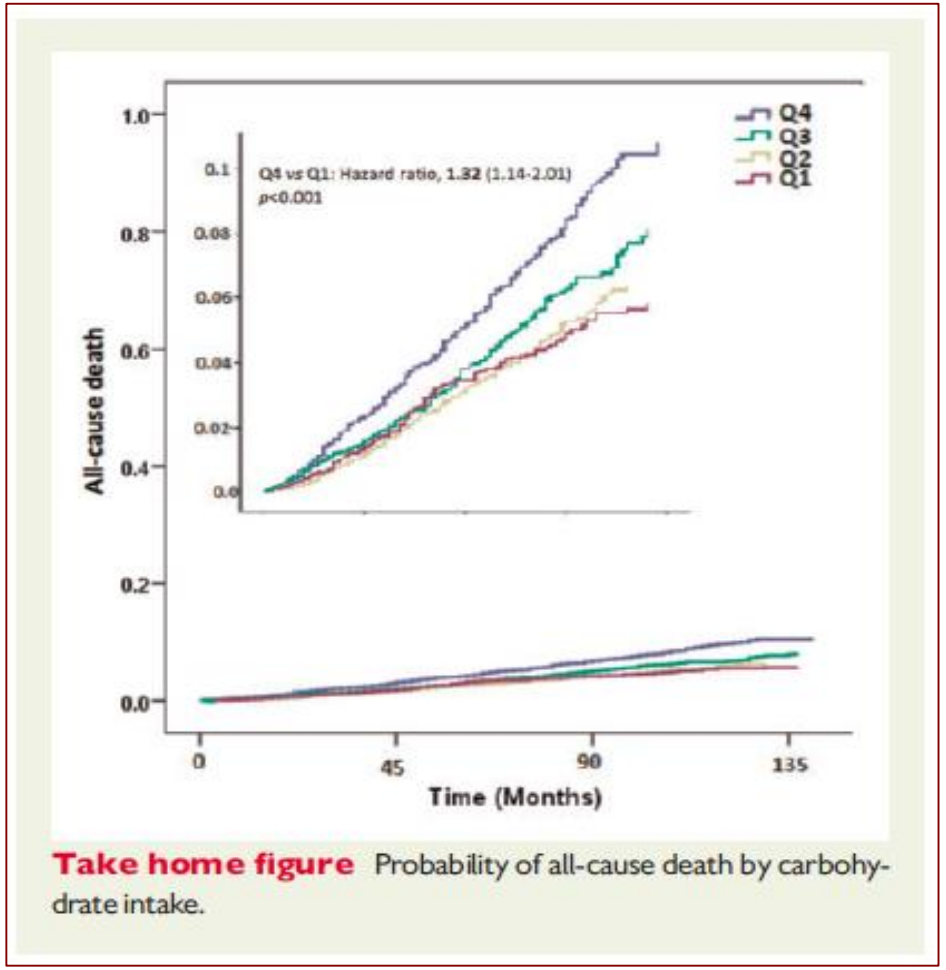
Role of diet and diet's components and mortality

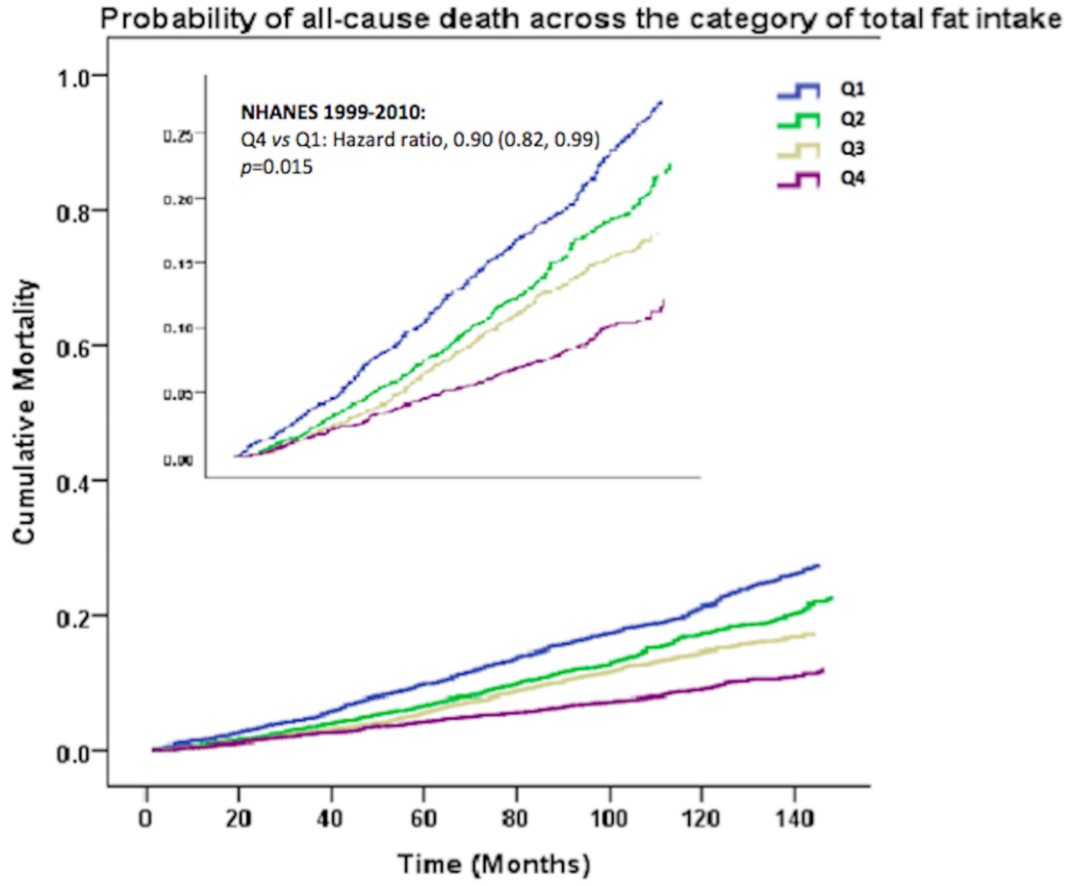


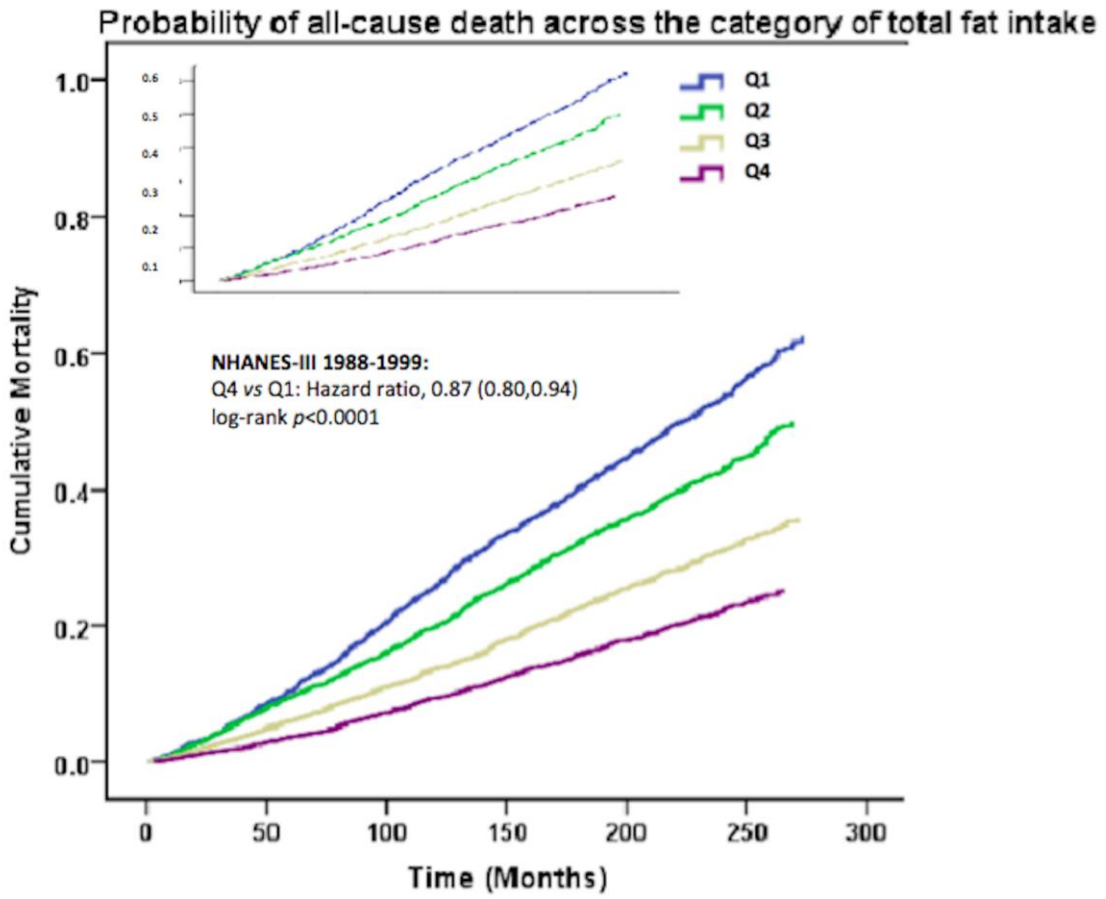


Take home figure Probability of all-cause death by carbohydrate intake.

(1) Mazidi M, Banach M, et al. LBPMC Group. Clin Nutr 2018; doi: 10.1016/j.clnu.2018.12.015.
(2) Mazidi M, Banach M et al. LBPMC Group & ILEP. Eur Heart J 2019; doi: 10.1093/eurheartj/ehz174

Probability of all-cause death across the category of total fat intake in NHANES 1999-2010 (1A) and NHANES 1988-1999 (1B).





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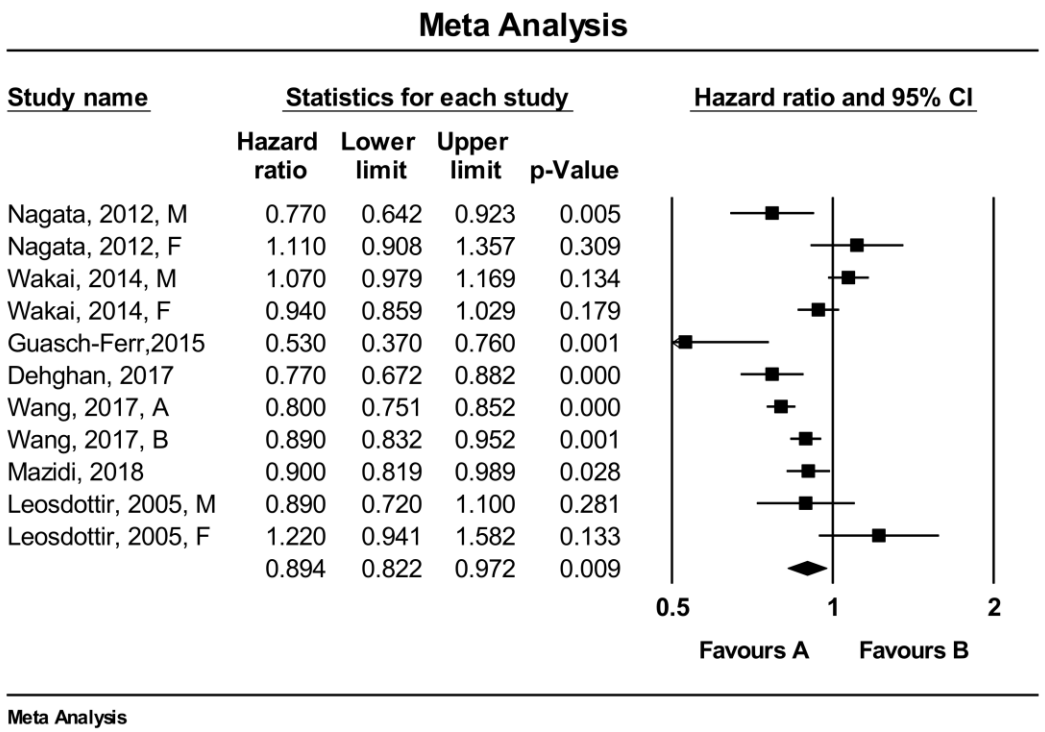
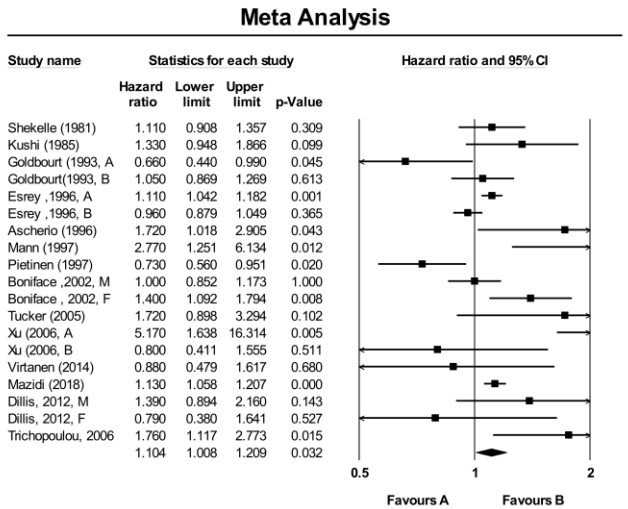
Mazidi M, Banach M, et al.; International Lipid Expert Panel (ILEP) & Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Clin Nutr. 2020 Dec;39(12):3677-3686.

Dietary fats – quantity or quality?

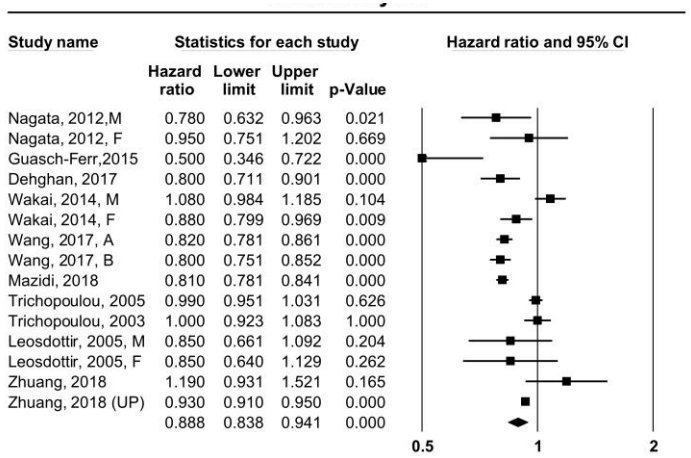
Forest plot of total fat consumption and all-cause mortality.



We found a negative and significant association between total fat consumption and all-cause mortality (HR: 0.89, 95%CI: 0.82-0.97, *p*=0.009, n=11 studies, I^2: 27%). There was no significant association between total fat with both CVD and CHD mortality (HR: 0.92, 95%CI: 0.79-1.08, *p*=0.340, n=8 studies, I^2: 46%, and HR: 1.03, 95%CI: 0.99-1.09, *p*=0.115, n=7 studies, I^2: 42%, respectively).



We observed a positive but non-significant association between SFA and all-cause mortality; no association was also showed between SFA intake and CVD mortality, **while we found a significant and positive association with CHD mortality (HR: 1.10, 95%CI: 1.01-1.20, *p*<0.001, n=19 studies, I^2: 52%)**. No association was observed between SFA and stroke mortality.



There was a reverse link between PUFA consumption and risk of all-cause mortality (HR: 0.88, 95%CI: 0.83-0.94, *p*<0.001), while no significant association between PUFA intake and CVD and CHD mortality was observed. **There was a negative significant effect of PUFA consumption on the risk of stroke mortality (HR: 0.84, 95%CI: 0.80-0.90, *p*<0.001**).

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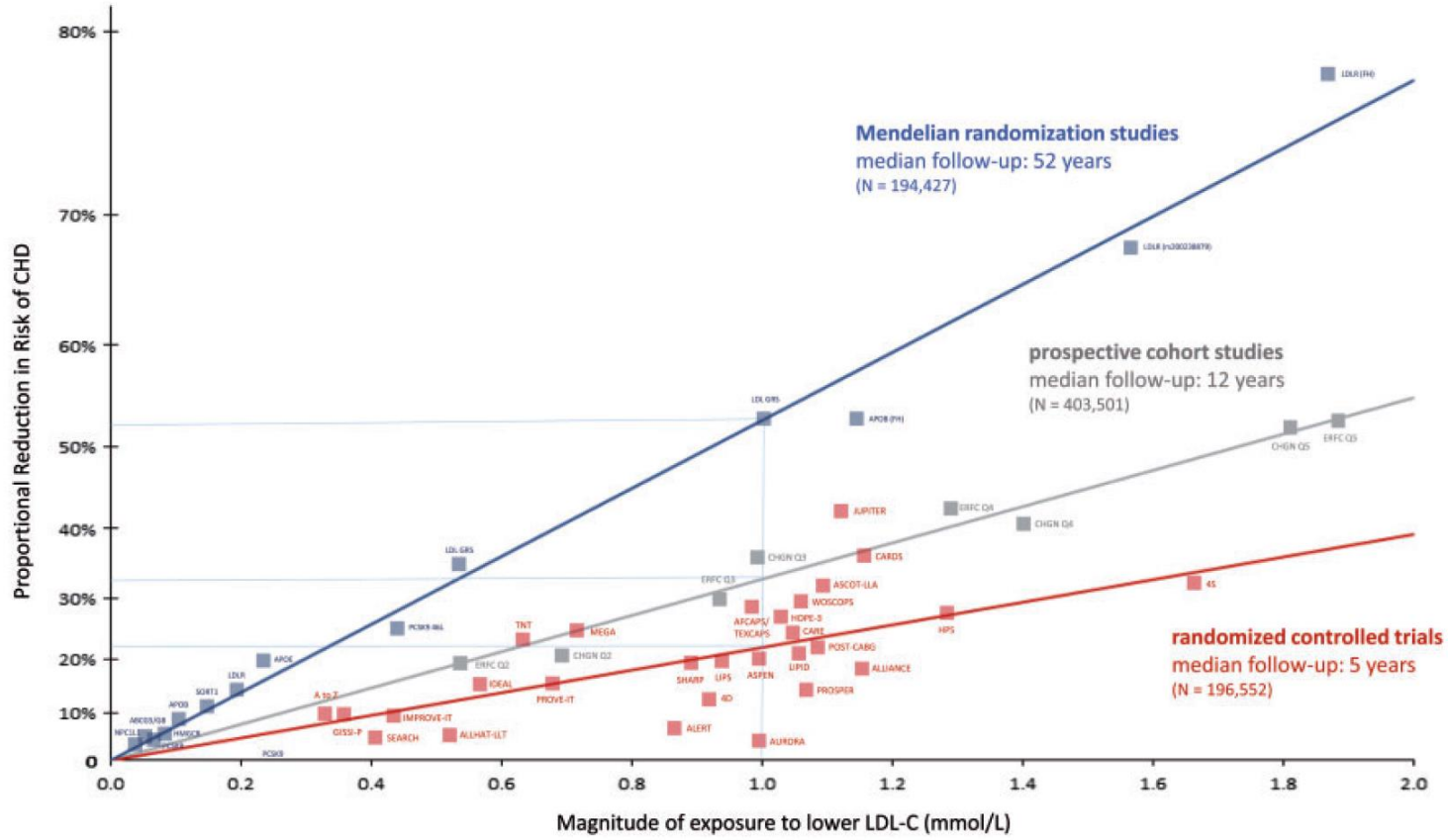
The effect of duration of LDL-C-reducing therapy on CV risk has been assessed in a Mendelian randomisation study



5 years
of LDL-c-reducing therapy

~20–25%
ASCVD risk reduction per mmol/L reduction in LDL-c

40 years
of LDL-c-reducing therapy

~50–55%
ASCVD risk reduction per mmol/L reduction in LDL-c

Early intervention to reduce LDL-c levels could reduce and/or delay the risk of ASCVD

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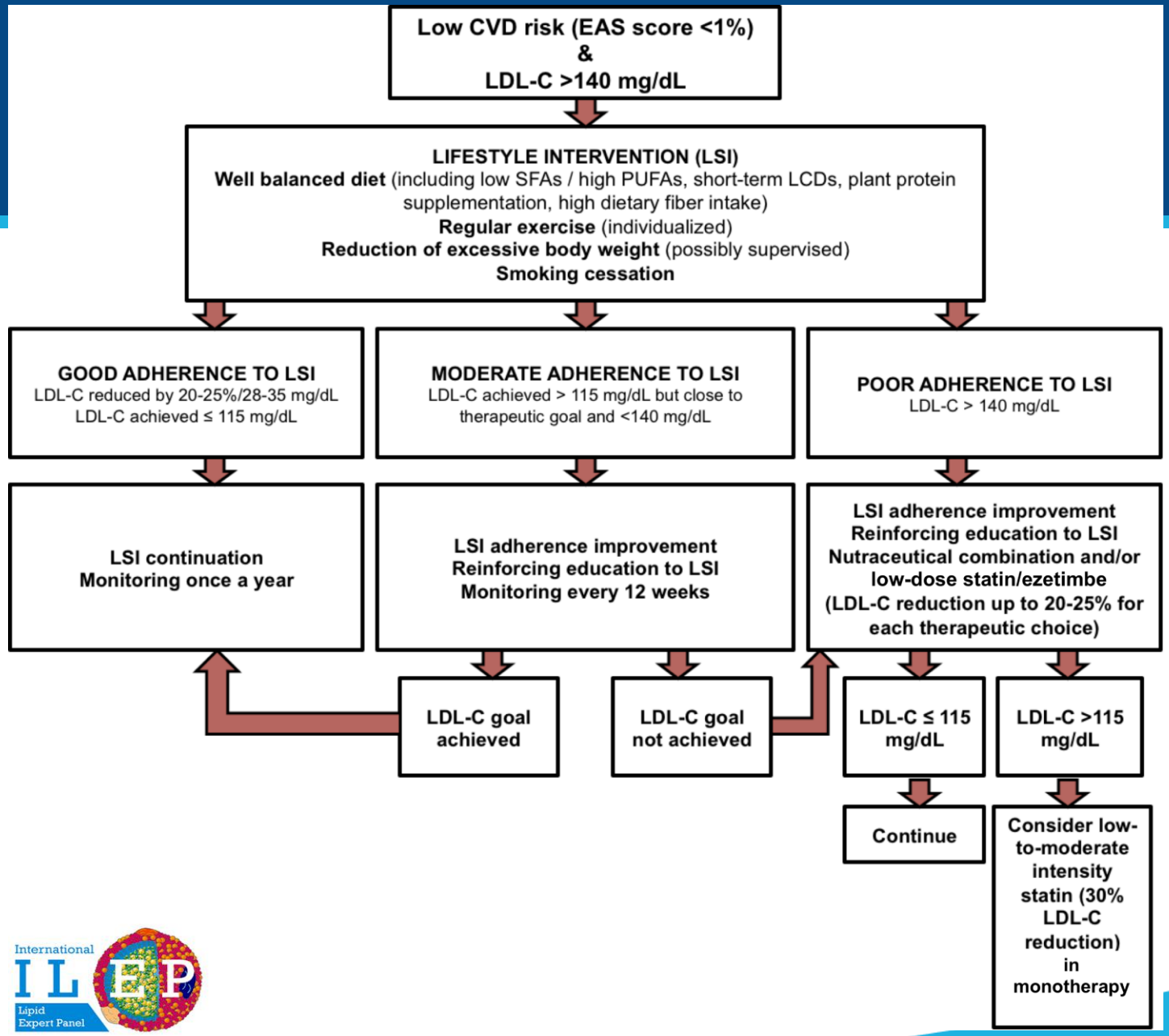
Ference BA, et al. Eur Heart J 2017;38(32):2459–2472
Penson P, Pirro M, Banach M. BMC Med 2020;18(1):320

ILEP Recommendations on how to manage with low-risk patients with persistently elevated LDL-C



Penson P, Pirro M, Banach M, on behalf of ILEP. BMC Med 2020;18(1):320.

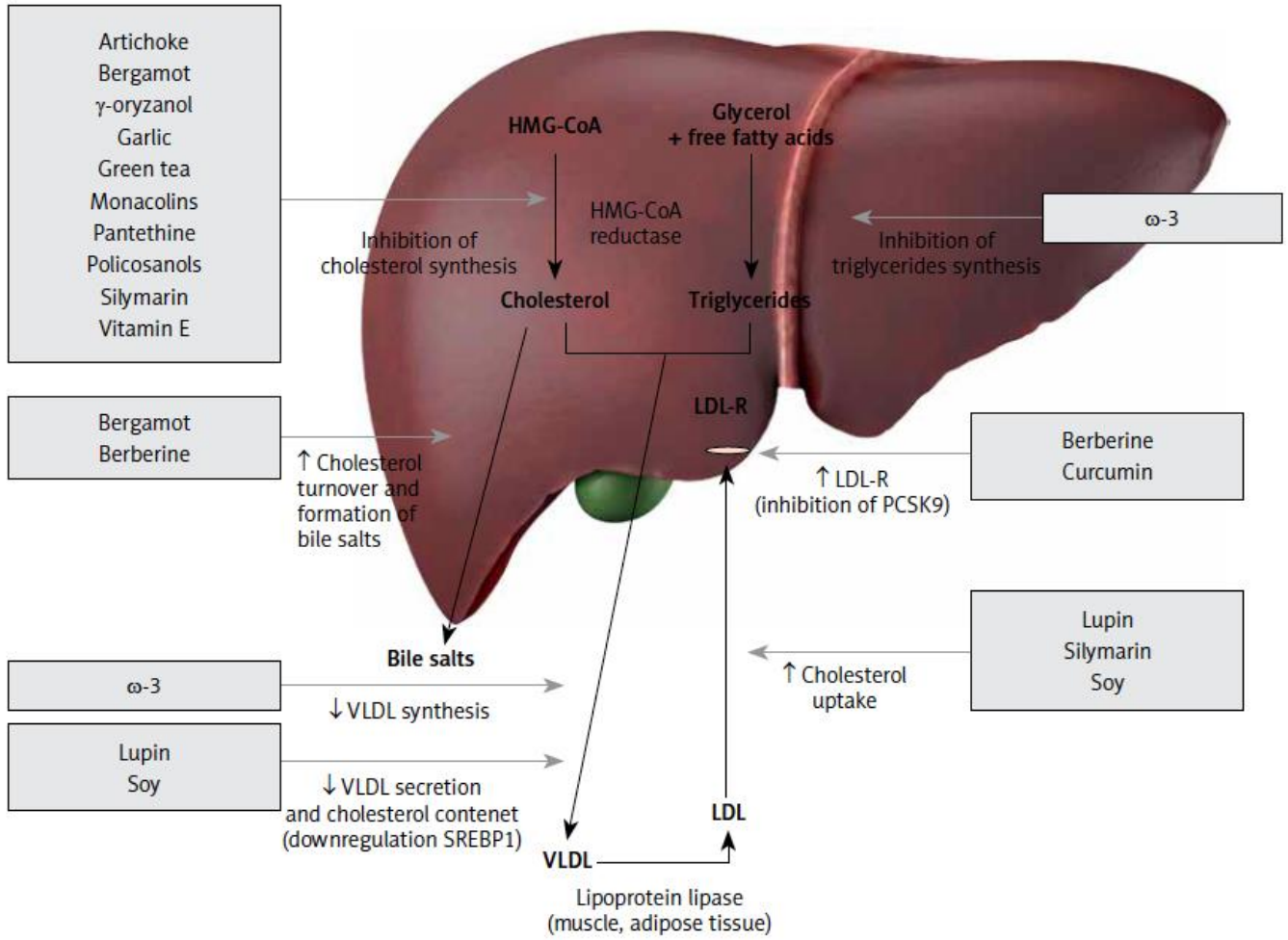


Figure 1. Nutraceuticals acting as inhibitors of liver cholesterol synthesis

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.

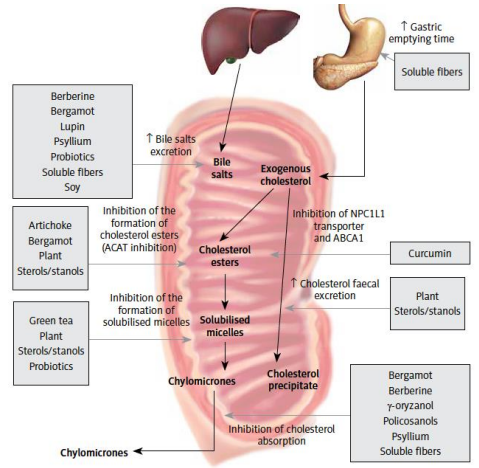


Figure 2. Nutraceuticals acting as inhibitors of intestinal cholesterol absorption and enhancers of cholesterol excretion

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

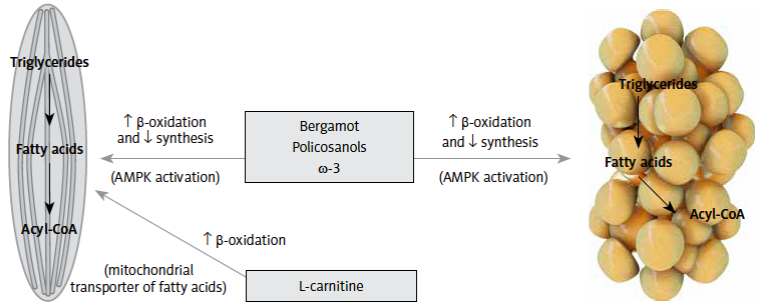


Figure 3. Nutraceuticals acting on fatty acids

AMPK – AMP-activated protein kinase.

Cicero AFG, Banach M, et al.; International Lipid Expert Panel. Nutr Rev. 2017;75(9):731-767.

Lipid-lowering or pleiotropic effects of nutraceuticals?

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

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

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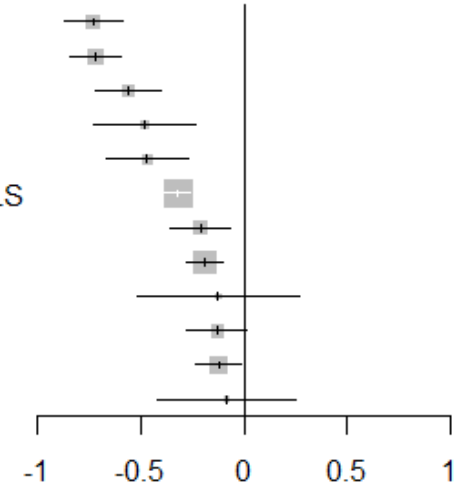
Cicero AFG, Banach M, et al.; International Lipid Expert Panel. Nutr Rev. 2017;75(9):731-767.

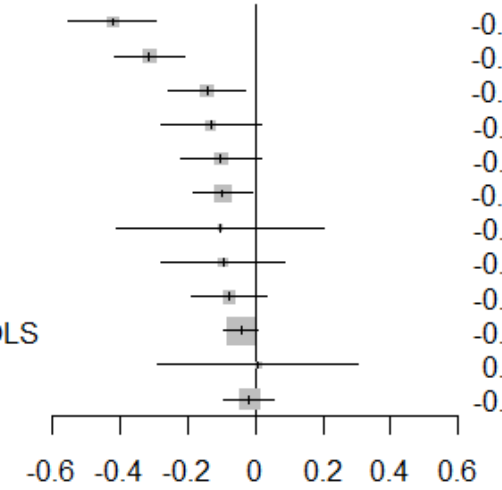
Comparative effects of nutraceuticals on LDL-C

Nutraceutical group	MD (95% CI)	P-score
POLICOSANOLS	-0.73 [-0.87; -0.59]	0.95
RED YEAST RICE	-0.72 [-0.84; -0.60]	0.94
BERBERINE	-0.56 [-0.72; -0.40]	0.79
SPIRULINA	-0.48 [-0.73; -0.24]	0.72
ARTICHOKE	-0.47 [-0.67; -0.28]	0.71
PLANT STEROLS/STANOLS	-0.32 [-0.39; -0.26]	0.57
GREEN TEA EXTRACT	-0.21 [-0.36; -0.06]	0.39
SOLUBLE FIBERS	-0.19 [-0.28; -0.11]	0.36
SILYMARIN	-0.13 [-0.52; 0.27]	0.28
GARLIC	-0.13 [-0.28; 0.01]	0.26
SOYBEAN	-0.13 [-0.24; -0.01]	0.24
LUPIN	-0.09 [-0.42; 0.25]	0.22



Comparative effects of nutraceuticals on TGs

Nutraceutical group	MD (95% CI)	P-score
BERBERINE	-0.42 [-0.55; -0.29]	0.99
RED YEAST RICE	-0.31 [-0.42; -0.21]	0.91
POLICOSANOLS	-0.14 [-0.26; -0.03]	0.65
ARTICHOKE	-0.13 [-0.28; 0.02]	0.60
GREEN TEA EXTRACT	-0.10 [-0.22; 0.02]	0.52
SOYBEAN	-0.10 [-0.19; -0.01]	0.51
SILYMARIN	-0.10 [-0.41; 0.20]	0.49
SPIRULINA	-0.10 [-0.28; 0.09]	0.49
GARLIC	-0.08 [-0.19; 0.03]	0.44
PLANT STEROLS/STANOLS	-0.04 [-0.09; 0.01]	0.31
LUPIN	0.01 [-0.29; 0.30]	0.26
SOLUBLE FIBERS	-0.02 [-0.09; 0.05]	0.22



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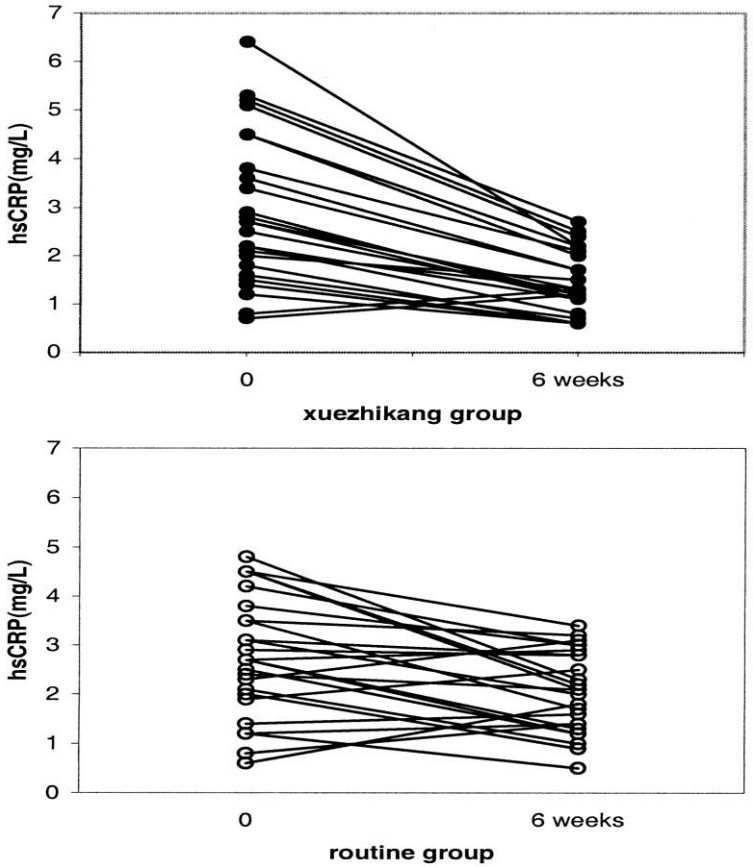
Morze J, Banach M, et al. Circulation. 2019;140:A13360

Pleiotropic effects of nutraceuticals?



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

	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.

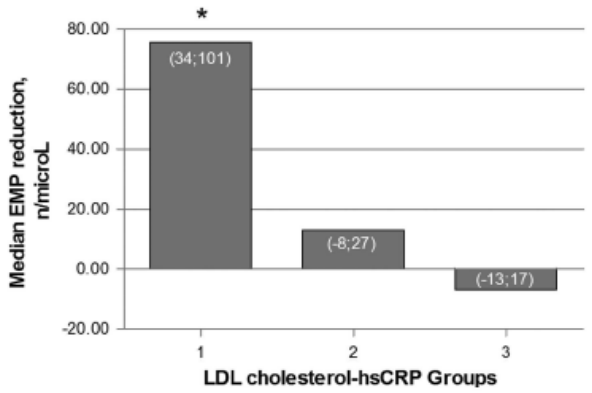
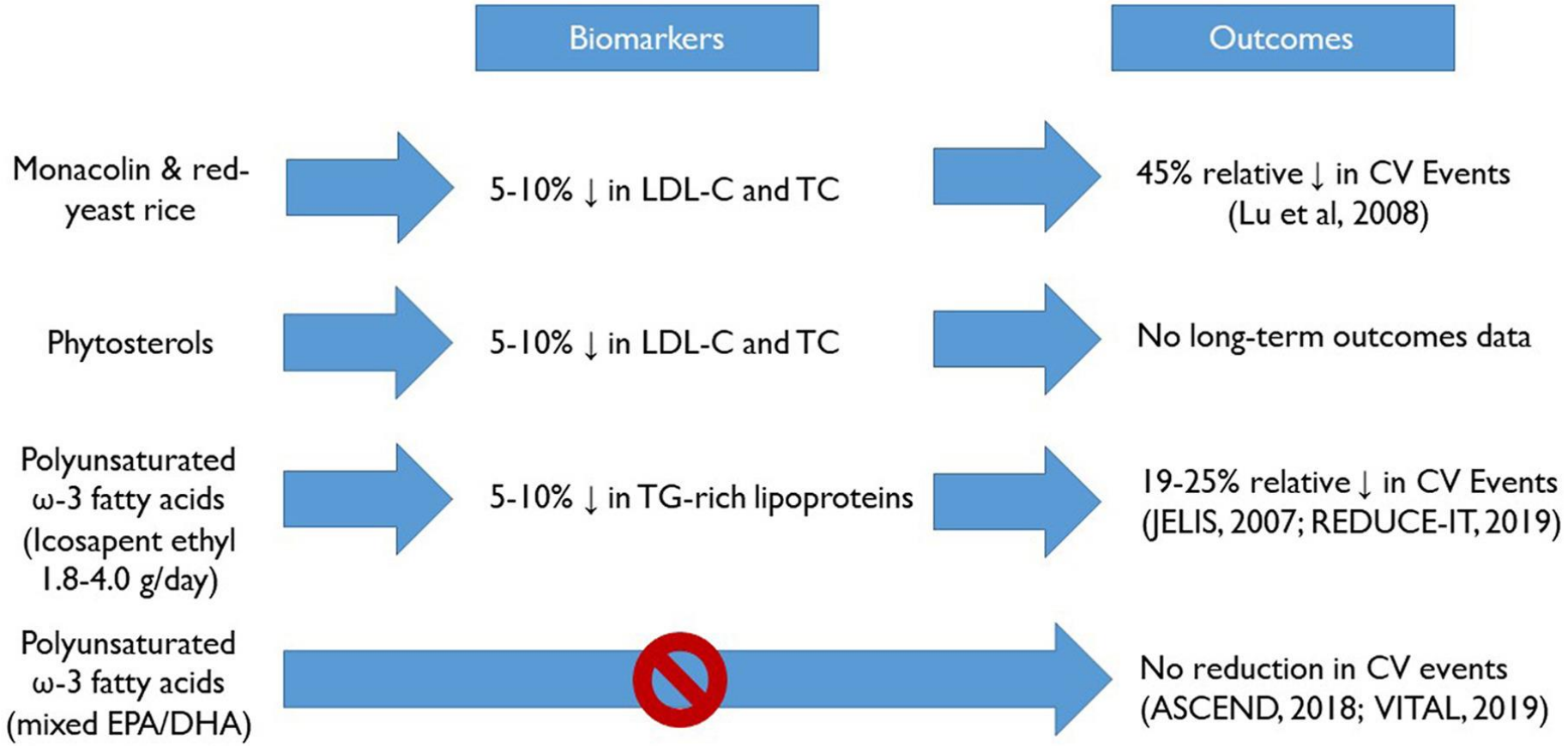


Figure 1. Post-intervention median EMP reduction according to the degree of LDL cholesterol and hsCRP changes. Group 1 includes patients with both LDL cholesterol and hsCRP reductions. Group 2 includes patients with either a LDL cholesterol or hsCRP reduction. Group 3 includes patients without evidence 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.

Endothelial microparticle (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

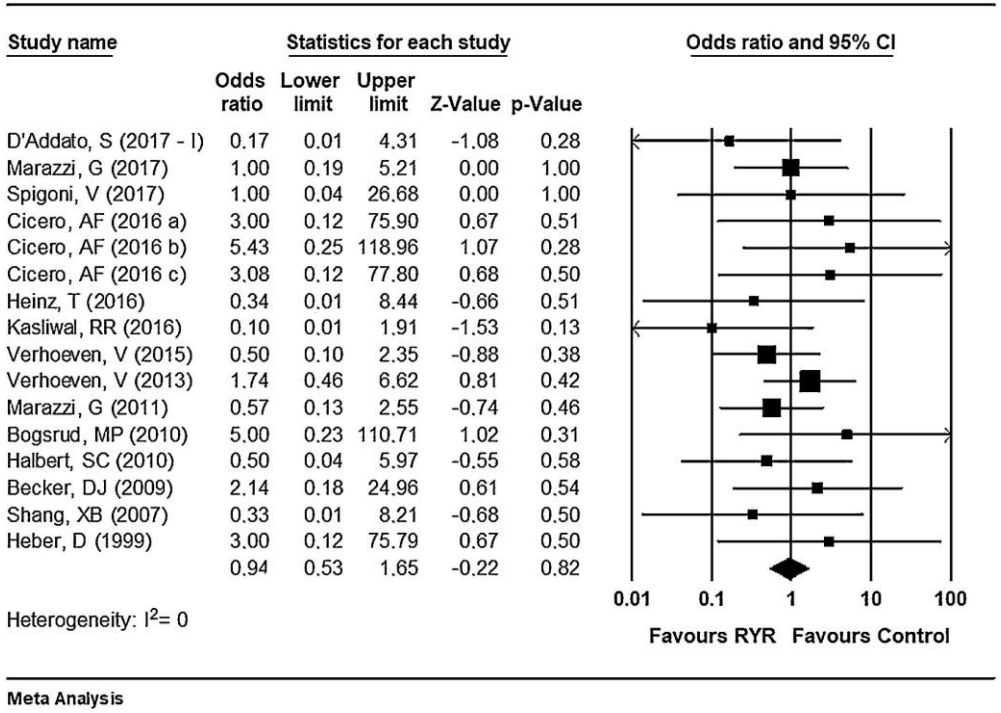
Shui Ping Zhao et al. Circulation. 2004;110:915-920.
Pirro M, et al. Sci Rep 2016;6:23587.

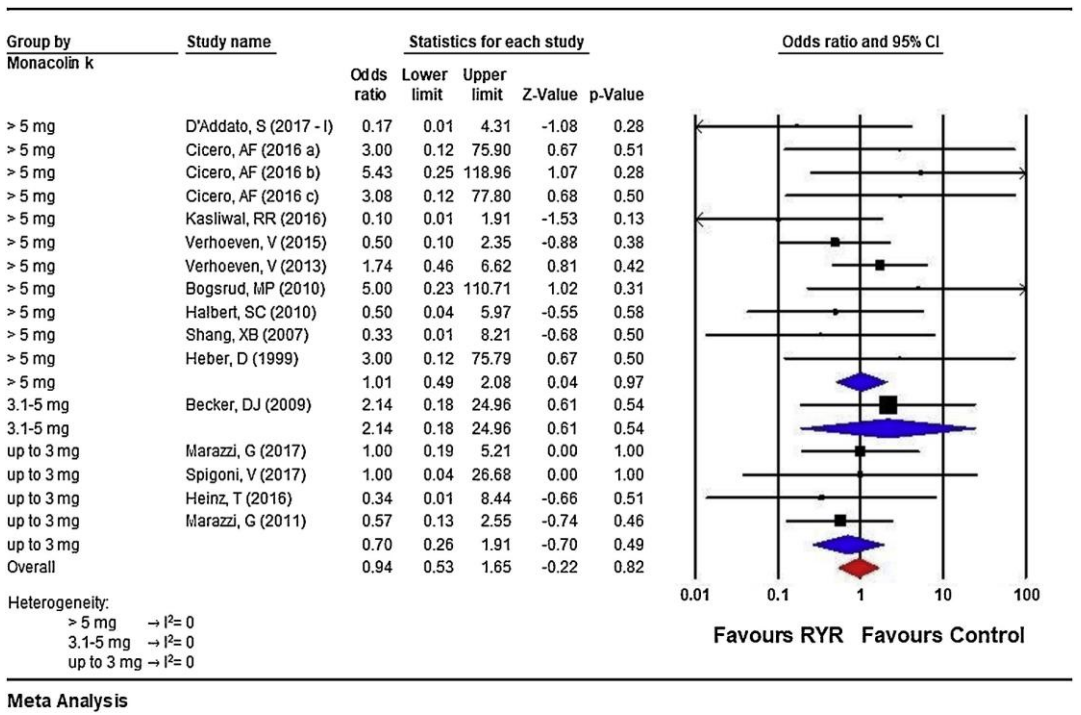
We should not expect CVOT trials with nutraceuticals!



Penson PE, Banach M, et al. Atherosclerosis 2020; 10.1016/j.atherosclerosis.2020.11.015

RYR and musculoskeletal disorders



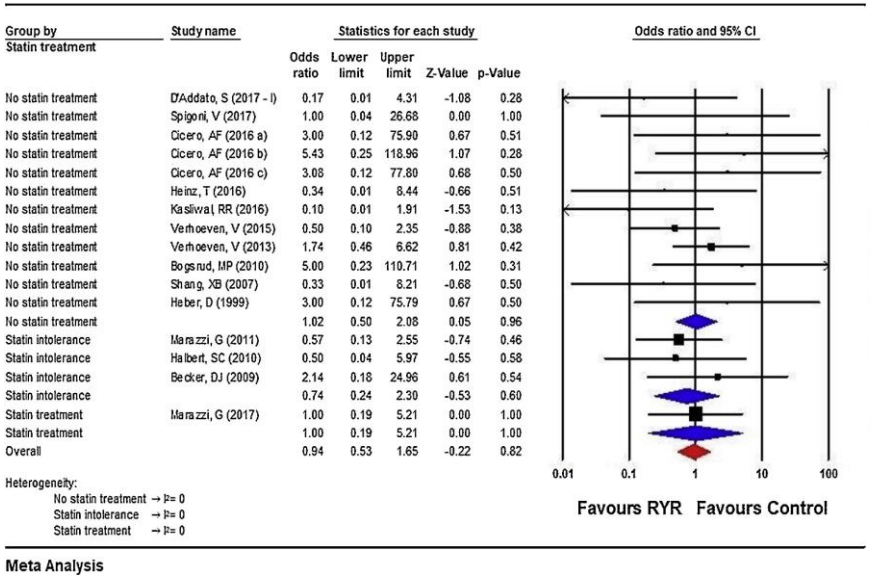


No MuD was experienced by subjects enrolled in 37 studies among those selected for the meta-analysis. In the others, monacolin K administration was neither associated with increased risk of MuD in the entire sample (**OR = 0.94, 95%CI 0.53,1.65**; *Fig. 1*) nor in subsets of studies categorized according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

Data were pooled from **53 RCTs comprising **112 treatment arms, which included 8535 subjects***

Fogacci F, Banach M, Mikhailidis DP, et al. Pharmacol Res. 2019;143:1-16.

RYR and musculoskeletal, SAEs & non-MuD disorders

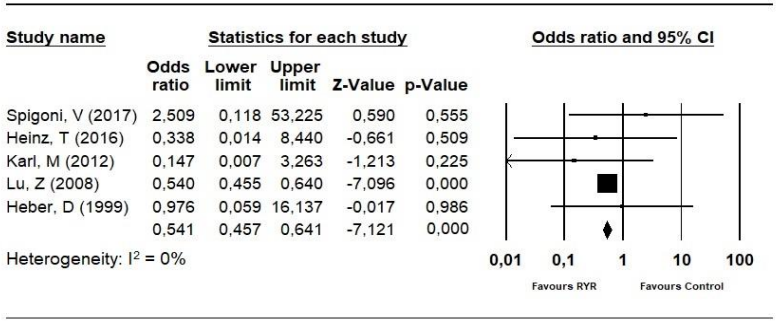


Group by Statin treatment	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
No statin treatment	D'Addato, S (2017 - I)	0.17	0.01	4.31	-1.08	0.28
No statin treatment	Spigoni, V (2017)	1.00	0.04	26.68	0.00	1.00
No statin treatment	Cicero, AF (2016 a)	3.00	0.12	75.90	0.67	0.51
No statin treatment	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

Heterogeneity:
No statin treatment → I²= 0
Statin intolerance → I²= 0
Statin treatment → I²= 0

Meta Analysis

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.

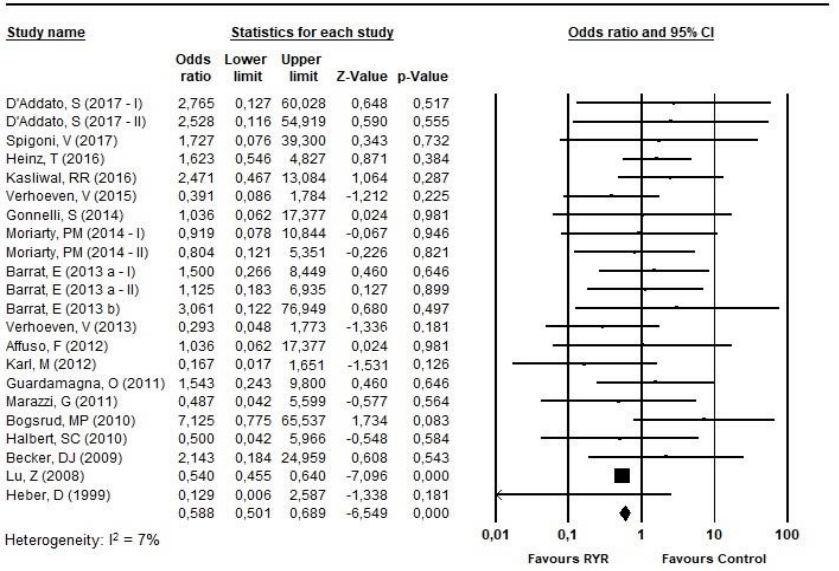


Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Spigoni, V (2017)	2,509	0,118	53,225	0,590	0,555
Heinz, T (2016)	0,338	0,014	8,440	-0,661	0,509
Karl, M (2012)	0,147	0,007	3,263	-1,213	0,225
Lu, Z (2008)	0,540	0,455	0,640	-7,096	0,000
Heber, D (1999)	0,976	0,059	16,137	-0,017	0,986
	0,541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



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

Forest plot comparing the RYR associated risk of non-MuD. We showed reduced risk of Non-MuD vs. control (**OR 0.59, 95%CI 0.50,0.69**). Meta-regression analyses did not suggest an increased risk for RYR associated Non-MuD depending on age and dose.

Fogacci F, Banach M, Mikhailidis DP, et al. Pharmacol Res. 2019;143:1-16.

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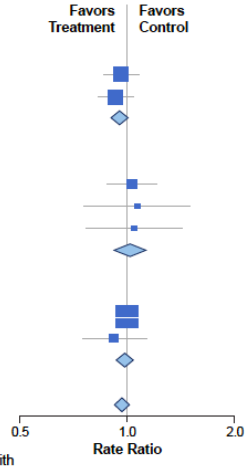
Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

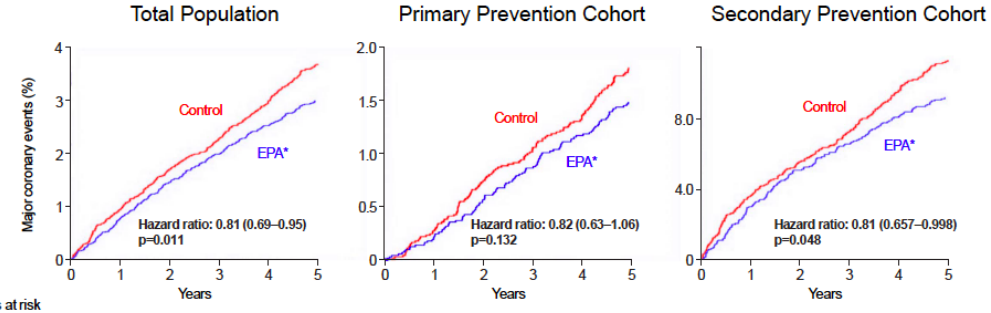
Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93–1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=.10



Adapted with permission* from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol.* 2018;3:225-234. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients

Kaplan-Meier Estimates of Incidence of Coronary Events



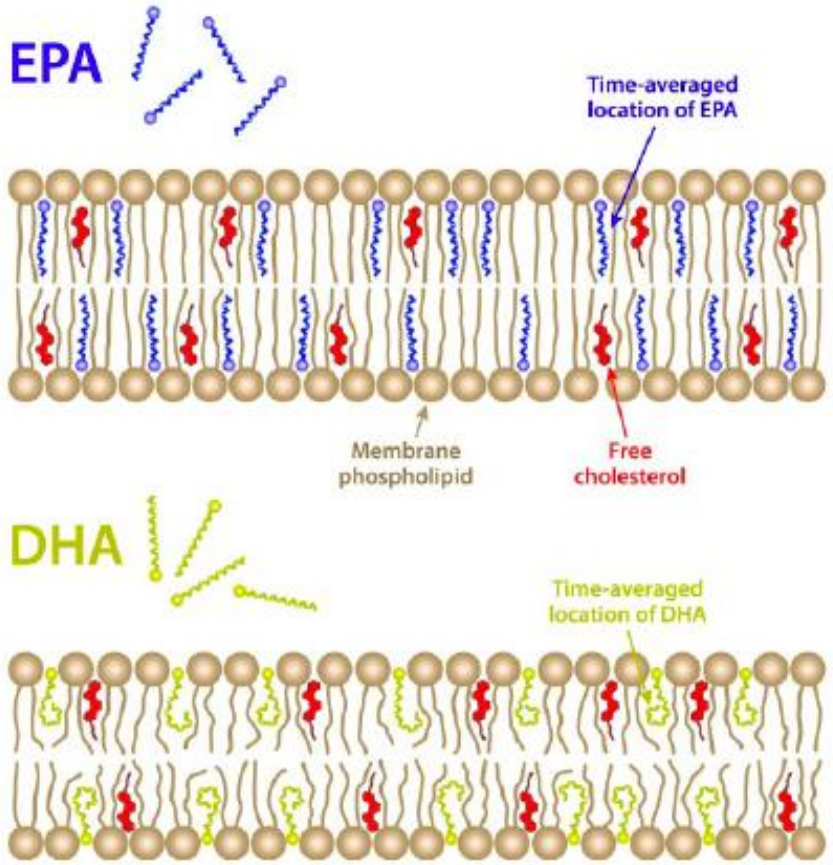
Numbers at risk																		
Control group	9319	8931	8671	8433	8192	7958	7478	7204	7103	6841	6678	6508	1841	1727	1658	1592	1514	1450
Treatment group	9326	8929	8658	8389	8153	7924	7503	7210	7020	6823	6649	6482	1823	1719	1638	1566	1504	1442

*1.8 g/day

Adapted with permission from Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

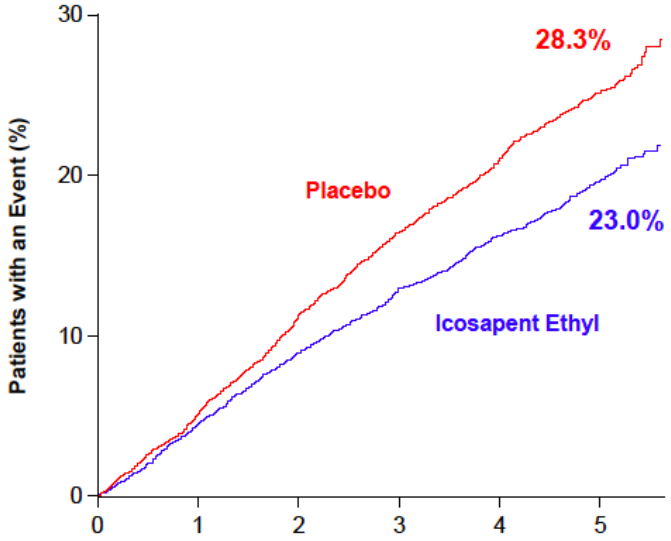
EPA and DHA Have Differing Effects on Cellular Membranes

reduce-it



Reprinted with permission* from Sherratt SCR, Mason RP. Eicosapentaenoic acid and docosahexaenoic acid have distinct membrane locations and lipid interactions as determined by X-ray diffraction. *Chem Phys Lipids*. 2018;212:73-79. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

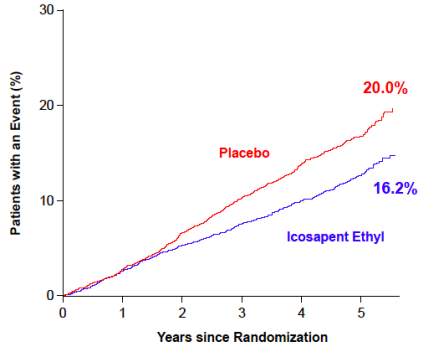
Effects on Biomarkers from Baseline to Year 1

	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point:
CV Death, MI, Stroke

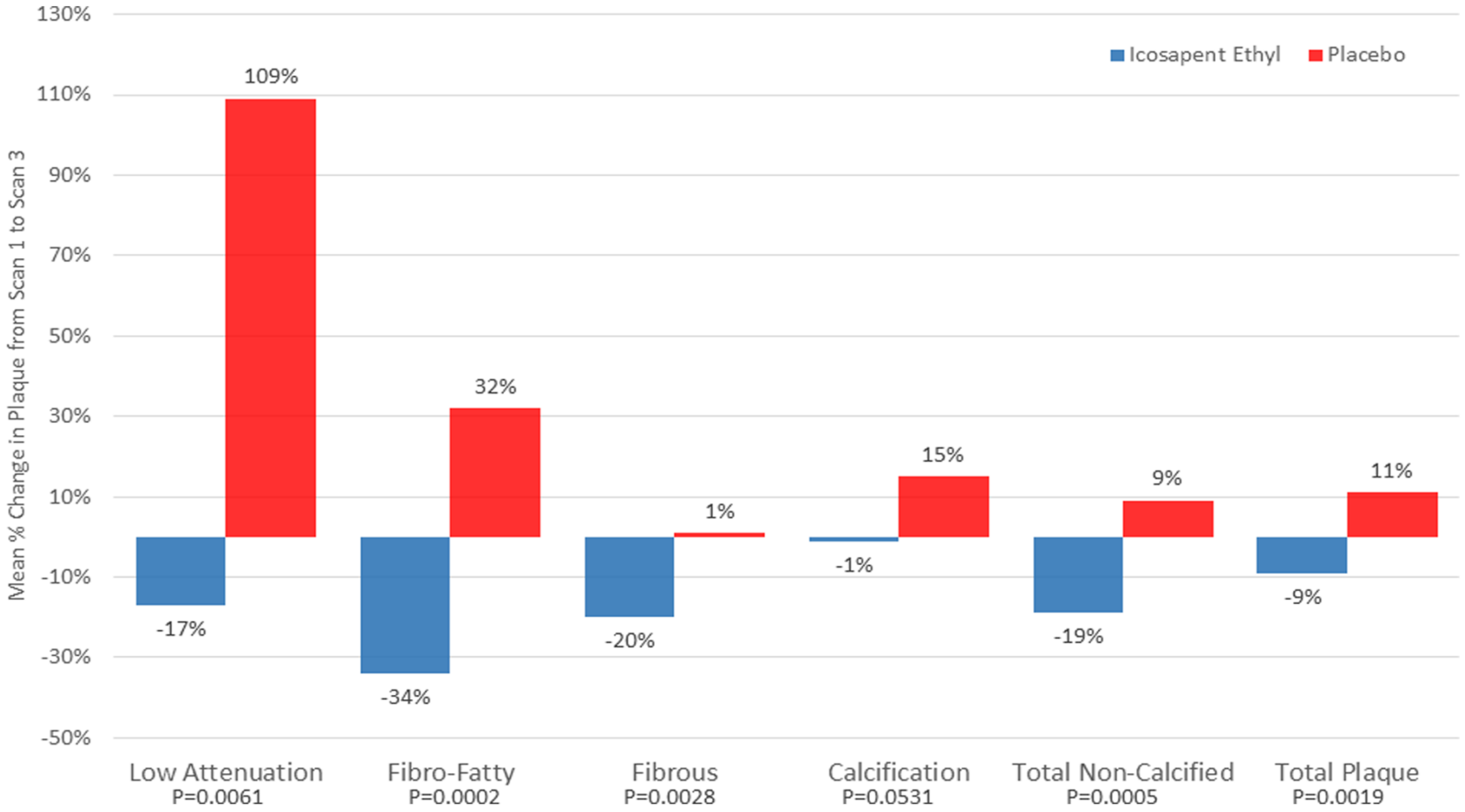


Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

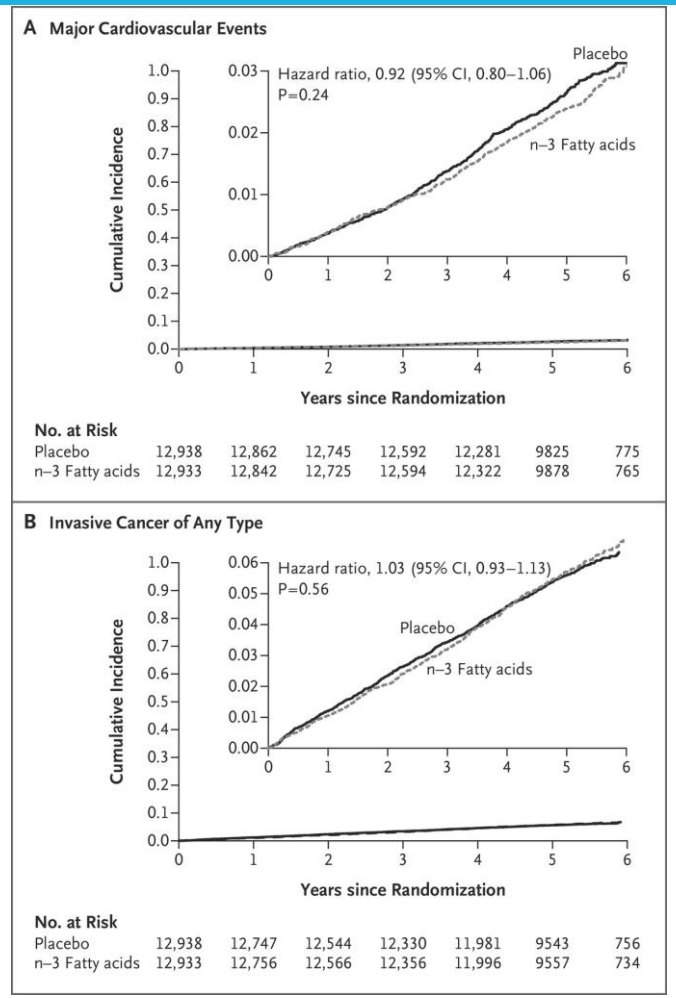
EVAPORATE Trial:

Mean plaque progression for each type of plaque composition measured on CV CT for the icosapent ethyl and placebo groups after multivariable adjustment

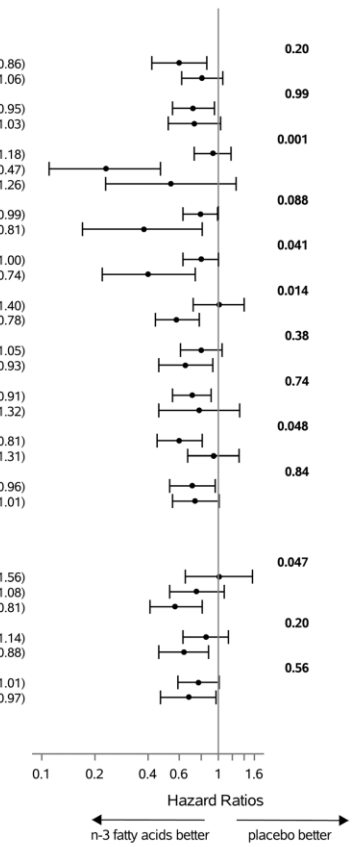


Eur Heart J, Volume 41, Issue 40, 21 October 2020, Pages 3925–3932, https://doi.org/10.1093/eurheartj/ehaa652

Vital Study with mixed EPA/DHA fatty acids



Subgroups	Total	No Events (n-3)	No Events (Placebo)	HR (95% CI)	Inter-action P-value
Pre-specified:					
Age (years)	**25871**				**0.20**
<median (66.7)	12859	49	81	0.60 (0.42-0.86)	
≥median (66.7)	13012	96	119	0.81 (0.62-1.06)	
Sex	**25871**				**0.99**
Male	12786	89	123	0.72 (0.55-0.95)	
Female	13085	56	77	0.73 (0.52-1.03)	
Race	**25304**				**0.001**
Non-Hispanic White	18046	126	135	0.93 (0.73-1.18)	
African American	5106	9	39	0.23 (0.11-0.47)	
Other	2152	8	16	0.54 (0.23-1.26)	
Current Smoker	**25485**				**0.088**
No	23649	136	172	0.79 (0.63-0.99)	
Yes	1836	9	24	0.38 (0.17-0.81)	
Diabetes (medication-treated)	**25860**				**0.041**
No	23132	130	163	0.80 (0.63-1.00)	
Yes	2728	15	37	0.40 (0.22-0.74)	
Hypertension (medication-treated)	**25698**				**0.014**
No	12907	71	69	1.01 (0.72-1.40)	
Yes	12791	74	129	0.58 (0.44-0.78)	
Cholesterol Medication	**25428**				**0.38**
No	15904	94	118	0.80 (0.61-1.05)	
Yes	9524	50	76	0.65 (0.46-0.93)	
Parental History of MI *	**22915**				**0.74**
No	19262	101	143	0.71 (0.55-0.91)	
Yes	3653	25	31	0.78 (0.46-1.32)	
Fish consumption (servings/wk)	**25435**				**0.048**
<median (1.5 servings/wk)	13514	74	121	0.60 (0.45-0.81)	
≥median (1.5 servings/wk)	11921	67	72	0.94 (0.67-1.31)	
Vitamin D randomization	**25871**				**0.84**
Placebo	12944	73	103	0.71 (0.53-0.96)	
Active	12927	72	97	0.74 (0.55-1.01)	
Other Subgroup Analyses:					
# of Cardiovascular Risk Factors **	**25871**				**0.047**
No Risk Factors	7802	41	40	1.01 (0.65-1.56)	
1 Risk Factor	8948	53	70	0.75 (0.53-1.08)	
2 or More Risk Factors	9121	51	90	0.57 (0.41-0.81)	
Baseline Aspirin Use	**25497**				**0.20**
No	13927	82	96	0.85 (0.63-1.14)	
Yes	11570	62	98	0.64 (0.46-0.88)	
Baseline Statin Use	**25447**				**0.56**
No	16557	95	123	0.77 (0.59-1.01)	
Yes	8890	49	72	0.68 (0.47-0.97)	

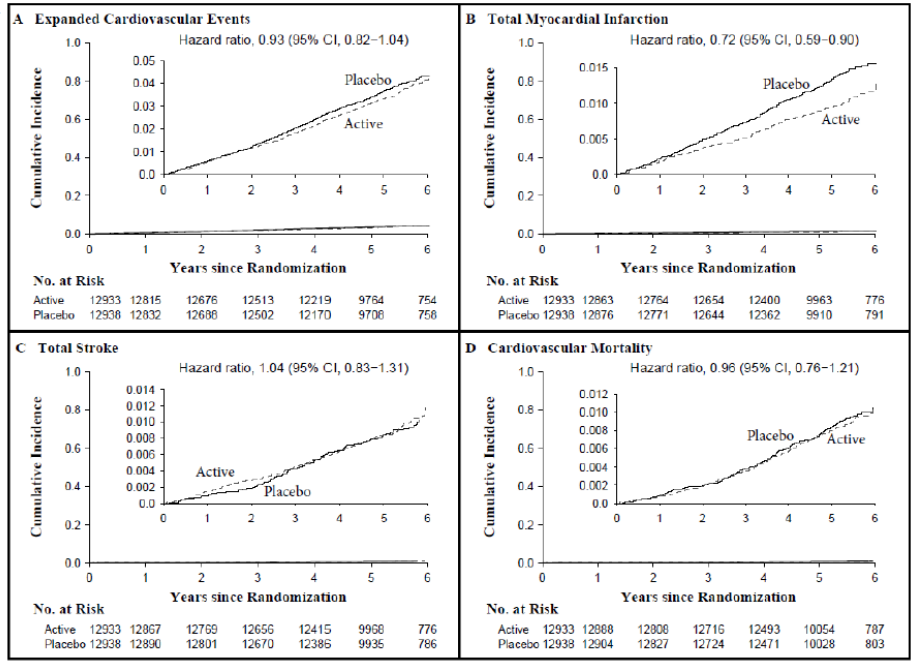


HR = hazard ratio; CI = confidence interval; MI = myocardial infarction

* Premature MI in a parent (before age 60 in father and before 65 in mother)

** Number of traditional cardiovascular disease risk factors (smoking, diabetes, hypertension high cholesterol, parental history of premature MI)

Figure S2. Cumulative Incidence Rates of A) Expanded Cardiovascular Events, B) Total Myocardial Infarction, C) Total Stroke, and D) Cardiovascular Mortality, By Year of Follow-up. From Cox regression models controlling for age, sex, and vitamin D randomization group (intention-to-treat analyses). The insets show the data on an enlarged y axis.



Consuming the right amount of omega-3 fatty acids reduces the risk of a heart attack, especially in **smokers, diabetics, consuming less than 1.5 portions of fish per week**

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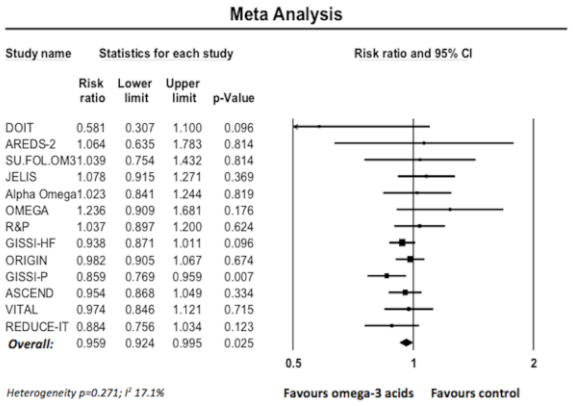
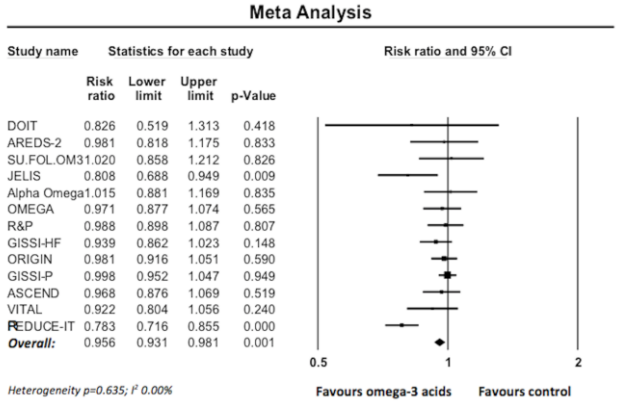
Manson JE et al., Circ Res 2020 Jan 3;126(1):112-128.

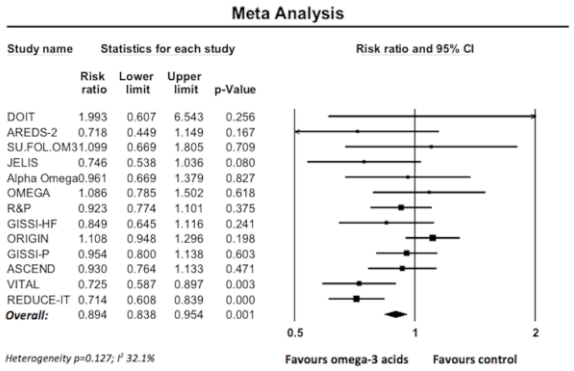
The role of omega-3 acids on all-cause and cause-specific mortality: A meta-analysis of 13 studies with 127,447 participants and MR Study.



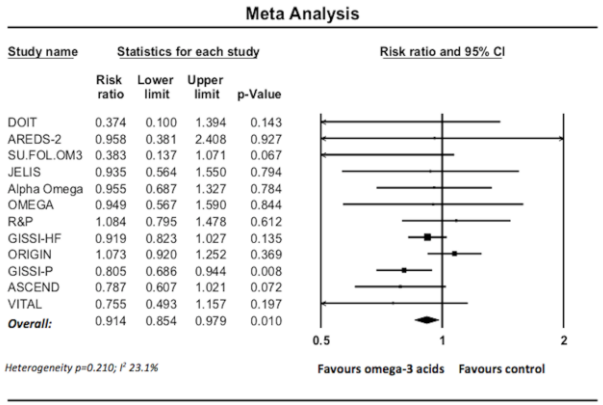
The pooled estimate (risk ratio [RR]) of the effect of omega-3 fatty acid supplementation on major vascular events.



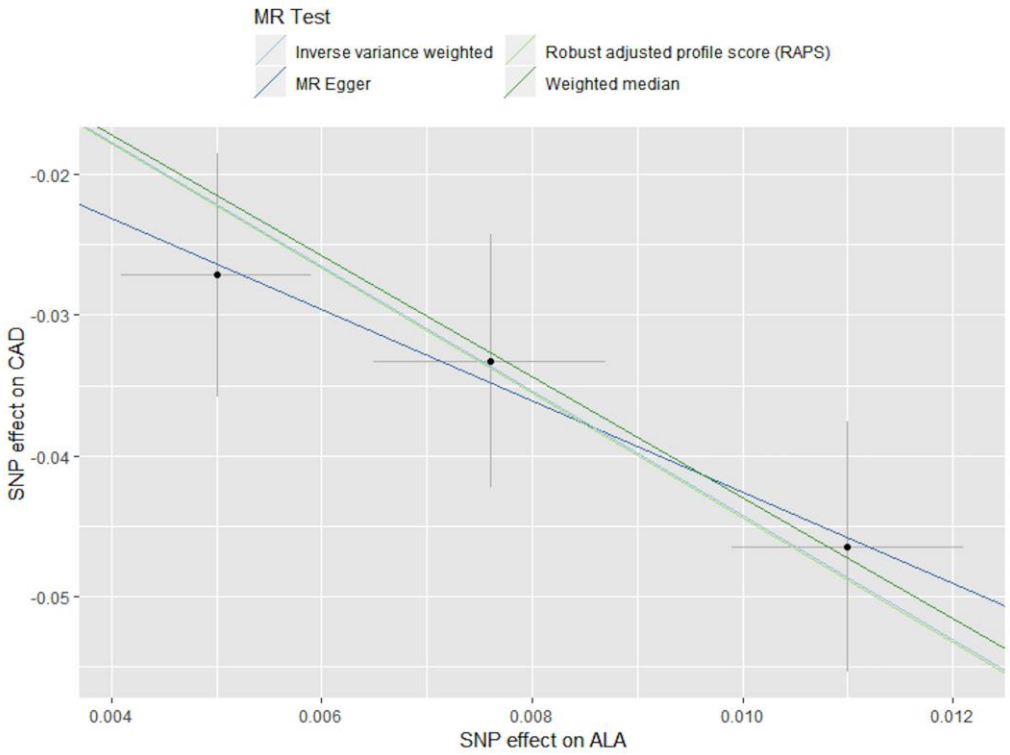
The pooled estimate (risk ratio [RR]) of the effect of omega-3 fatty acid supplementation on all-cause mortality.



The Pooled Estimate (Risk Ratio [RR]) Of The Effect Of Omega-3 Fatty Acid supplementation on non-fatal myocardial infraction.



The pooled estimate (risk ratio [RR]) of the effect of omega-3 fatty acid supplementation on coronary heart disease death.



Scatter plots of genetic associations with serum alpha-linolenic acid (ALA) against genetic associations with coronary heart disease. The slopes of each line represent causal associations for each method

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Mazidi M, Mikhailidis DP, Banach M. Circulation 2019;140:e965–e1011

ALA Metabolic Cascade (pathway): Summary of health effects

TABLE 1 Summary of the physiological roles and potential health benefits of very long-chain (n-3) fatty acids

Physiological role of very long-chain (n-3) fatty acids	Potential health benefit	Disease target
Regulation of blood pressure	Decreased blood pressure	Hypertension, CVD[1]
Regulation of platelet function	Decreased likelihood of thrombosis	Thrombosis, CVD
Regulation of blood coagulation	Decreased likelihood of thrombosis	Thrombosis, CVD
Regulation of plasma TG concentrations	Decreased plasma TG concentrations	Hypertriglyceridemia, CVD
Regulation of vascular function	Improved vascular reactivity	CVD
Regulation of cardiac rhythm	Decreased cardiac arrhythmias	CVD
Regulation of heart rate	Increased heart rate variability	CVD
Regulation of inflammation	Decreased inflammation	Inflammatory diseases (arthritis, inflammatory bowel diseases, psoriasis, lupus, asthma, cystic fibrosis, dermatitis, neurodegeneration, etc.), CVD
Regulation of immune function	Improved immune function	Compromised immunity
Regulation of fatty acid and TG metabolism	Decreased TG synthesis and storage	Weight gain, weight loss, obesity
Regulation of bone turnover	Maintained bone mass	Osteoporosis
Regulation of insulin sensitivity	Improved insulin sensitivity	Type-2 diabetes
Regulation of tumor cell growth	Decreased tumor cell growth and survival	Some cancers
Regulation of visual signaling (via rhodopsin)	Optimized visual signaling	Poor infant visual development (especially preterm)
Structural component of brain and central nervous system	Optimized brain development leading to better cognitive and learning processes	Poor infant and childhood cognitive processes, learning, and behavior

[1] CVD, cardiovascular disease. Reproduced with permission of (1).

In patients at least high risk with TG ≥1.7 mmol/L (≥150 mg/dL) despite statin treatment, the use of icosapent ethyl (2 x 2 g/day) in combination with a statin should be considered.	IIa	C
In high-risk patients with TG ≥2.3 mmol/L (≥200 mg/dL) despite statin treatment, omega-3 fatty acids (PUFA 2 to 4 g / day) may be considered in combination with a statin.	IIb	C

Román GC, et al. Rev Neurol (Paris). 2019 Dec;175(10):724-741.

JACC STATE-OF-THE-ART REVIEW

The Role of Nutraceuticals in Statin Intolerant Patients

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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.

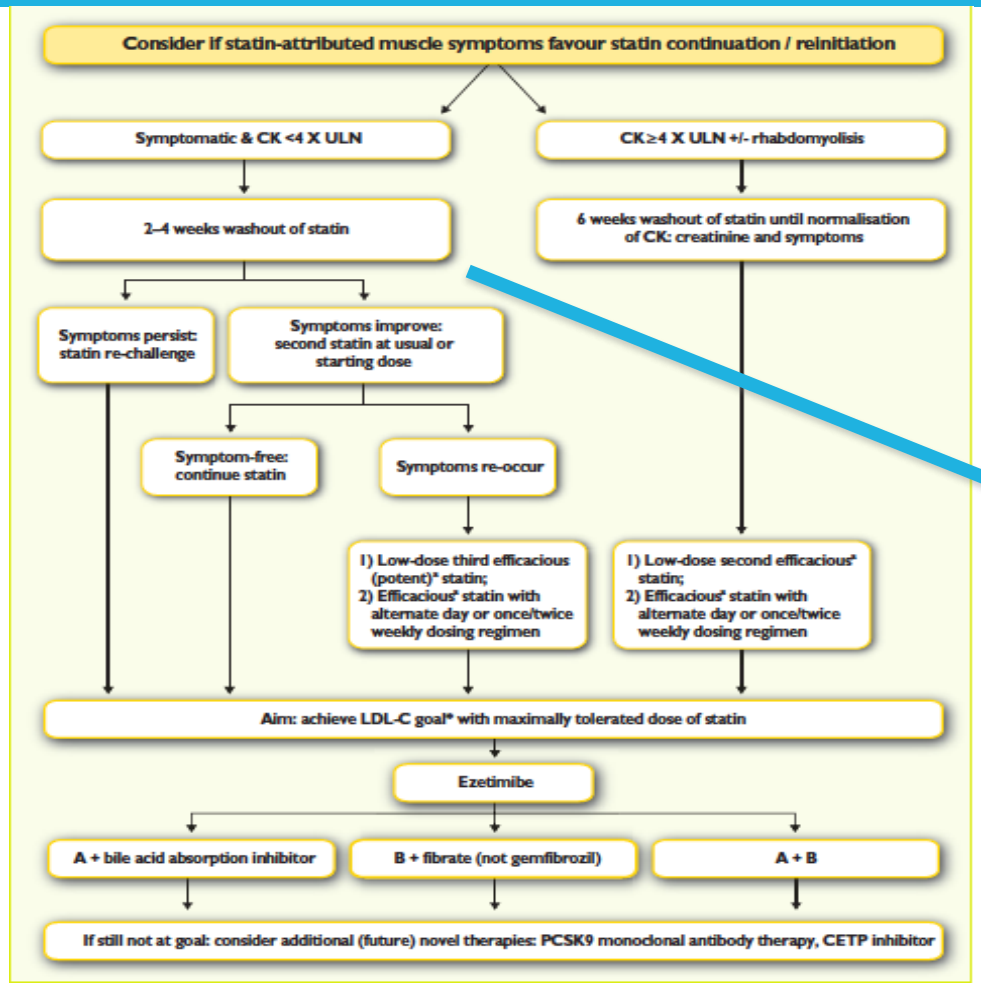
TABLE 10 Polyunsaturated Omega-3 Fatty Acids

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.

Banach M, Patti AM, Giglio RV, et al..; International Lipid Expert Panel (ILEP). J Am Coll Cardiol. 2018;72(1):96-118.

The potential role of nutraceuticals in statin intolerant patients



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

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Banach M, Penson PE. Cardiovasc Res. 2019 Mar 1;115(3):e26-e31; Stroes ES, et al. Eur Heart J. 2015 May 1;36(17):1012-22; Penson PE, Banach M, et al. Eur Heart J 2019;40(Suppl._1); doi: 10.1093/eurheartj/ehz747.0310; Banach M, et al. J Am Coll Cardiol. 2018 Jul 3;72(1):96-118.

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)

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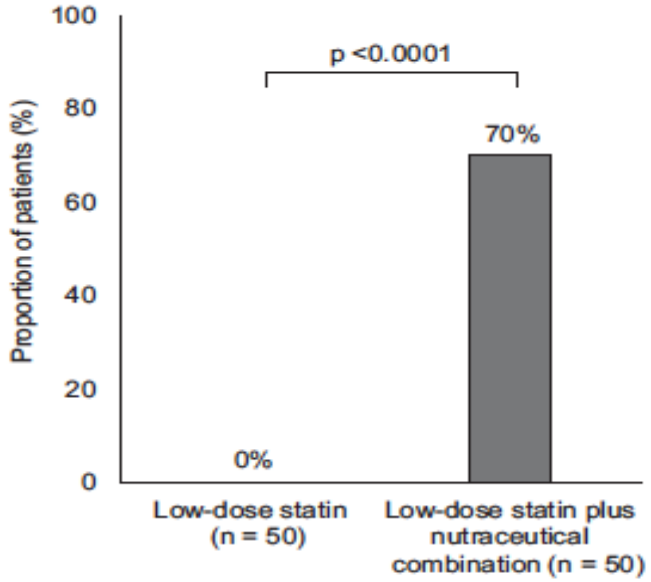


Figure 1. Proportion of patients who achieved the primary outcome of a reduction in low-density lipoprotein cholesterol (LDL-C) to the therapeutic target (<70 mg/dl) after 3 months of treatment.

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.

Marazzi G, et al. Am J Cardiol. 2017 Sep 15;120(6):893-897.

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]

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

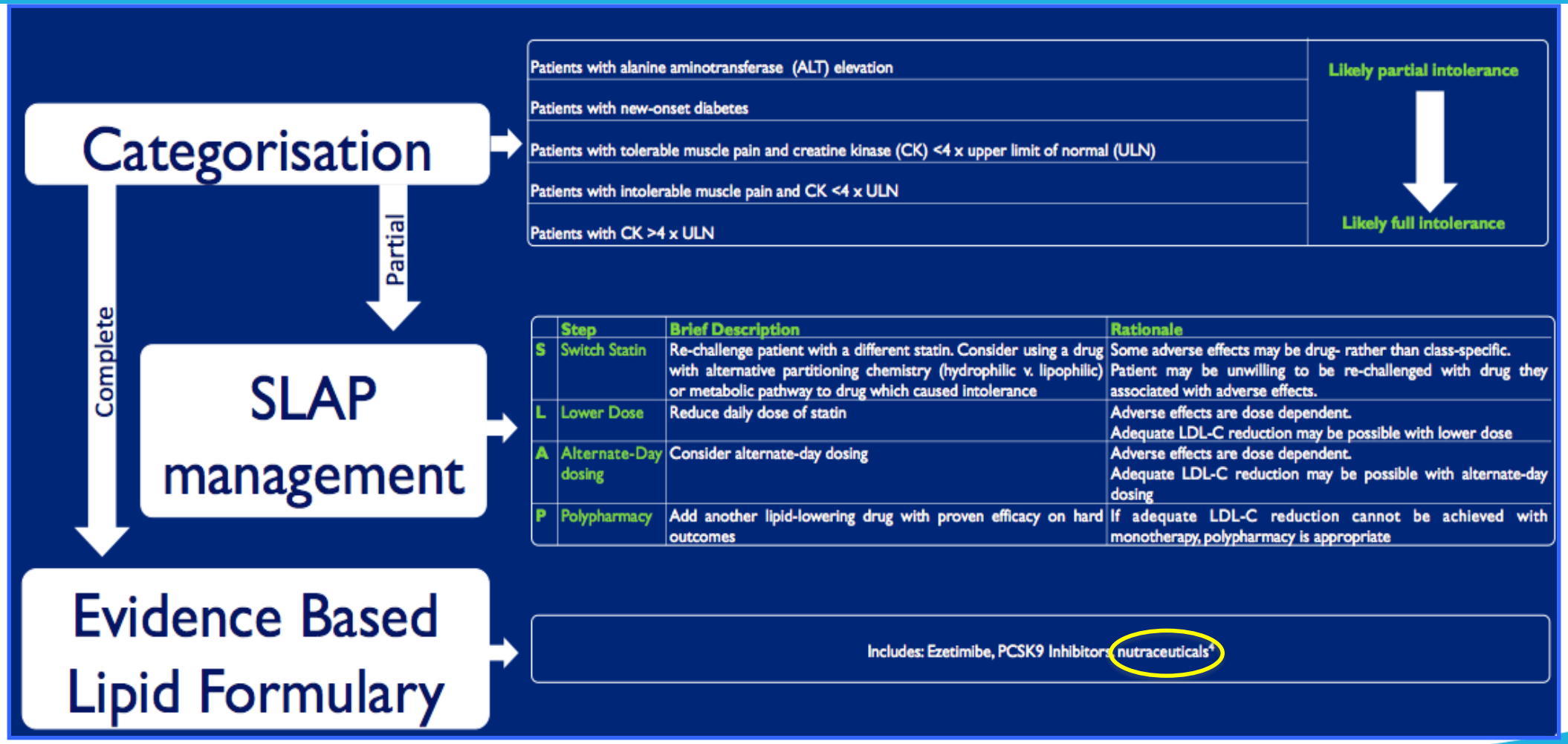
Variable	Nutraceutical combination (n=14)			p-value	Emetizibe plus Nutraceuticals (n=86)			p-value
	Base-line	3 months	12 months		Base-line	3 months	12 months	
Total cholesterol (mg/dl)	205±11	165±7	163±7	<0.0001	189±15	166±12	164±13	<0.0001
Low-density lipoprotein cholesterol (mg/dl)	136±6	98±3	95±3	<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

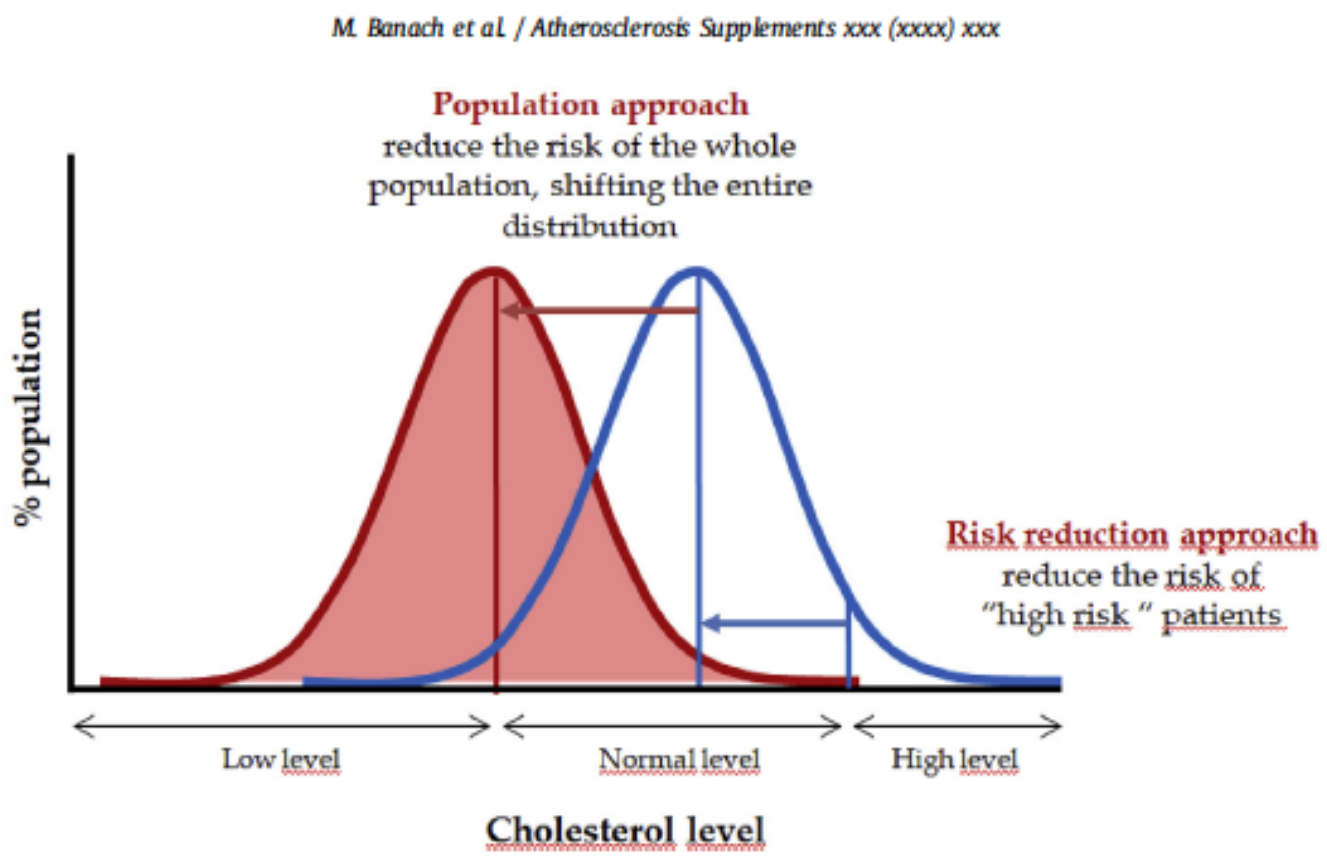
Marazzi G, Pelliccia F, Campolongo G, et al. Am J Cardiol. 2015;116(12):1798-801.

Step-by-Step Diagnosis and Management of Statin Intolerance:
A Recommendation Paper 2020 from an *International Lipid Expert Panel*



Penson PE, Banach M, et al. on behalf of ILEP. Eur Heart J 2019;40(Suppl._1); doi: 10.1093/eurheartj/ehz747.0310

Population risk reduction with nutraceuticals' applications



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).*

Banach M, Bruckert E, Descamps OS, et al. Atheroscler Suppl. 2019 Dec;39:e1-e8..