Updates of the clinical evidences

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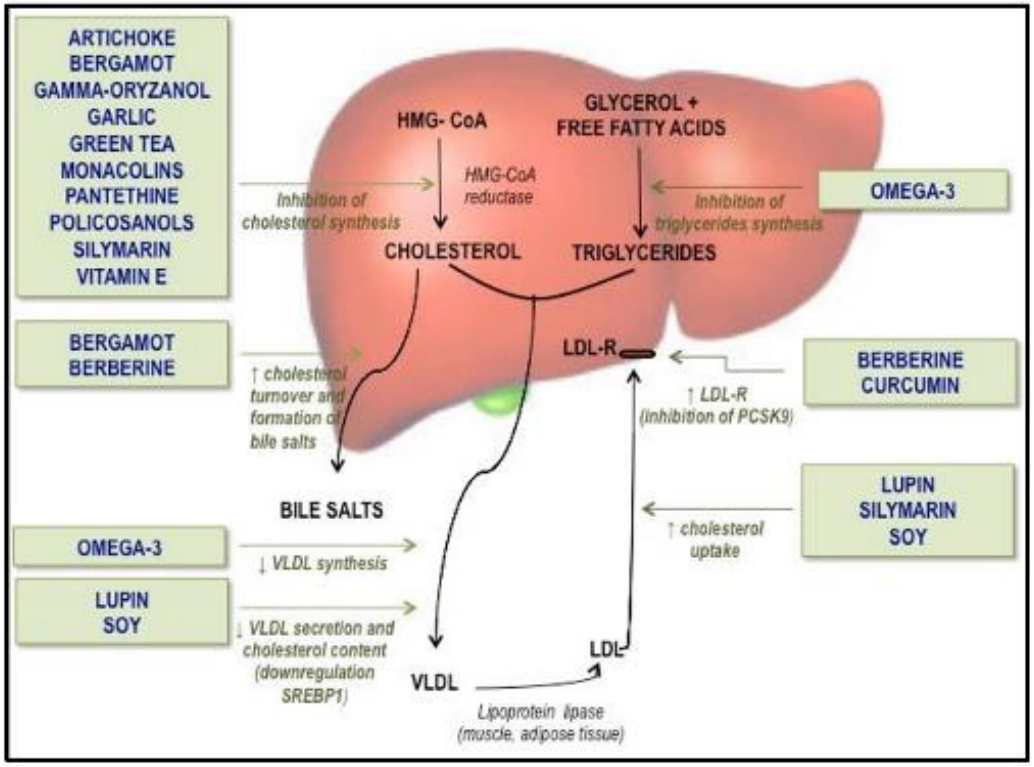
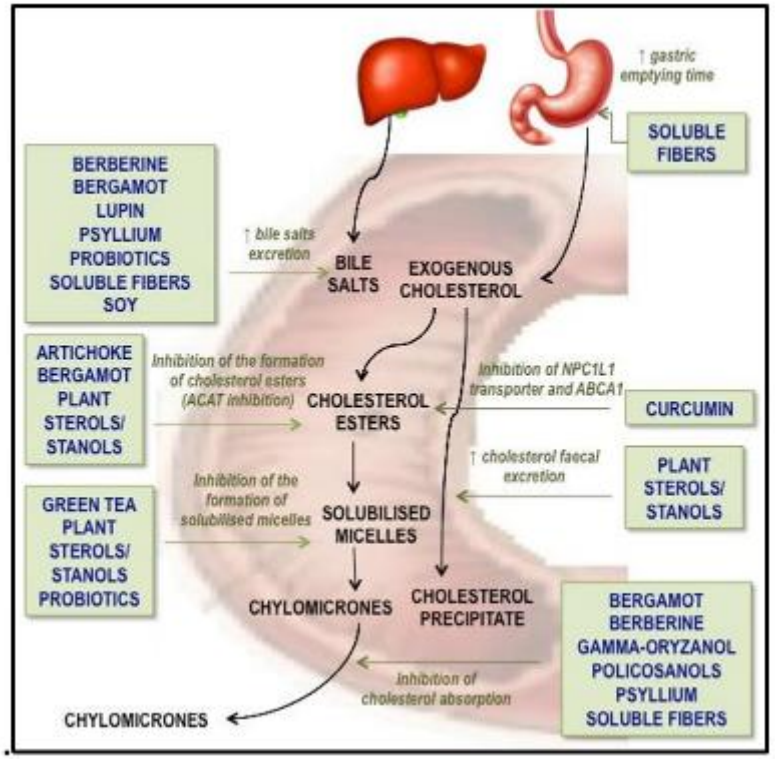
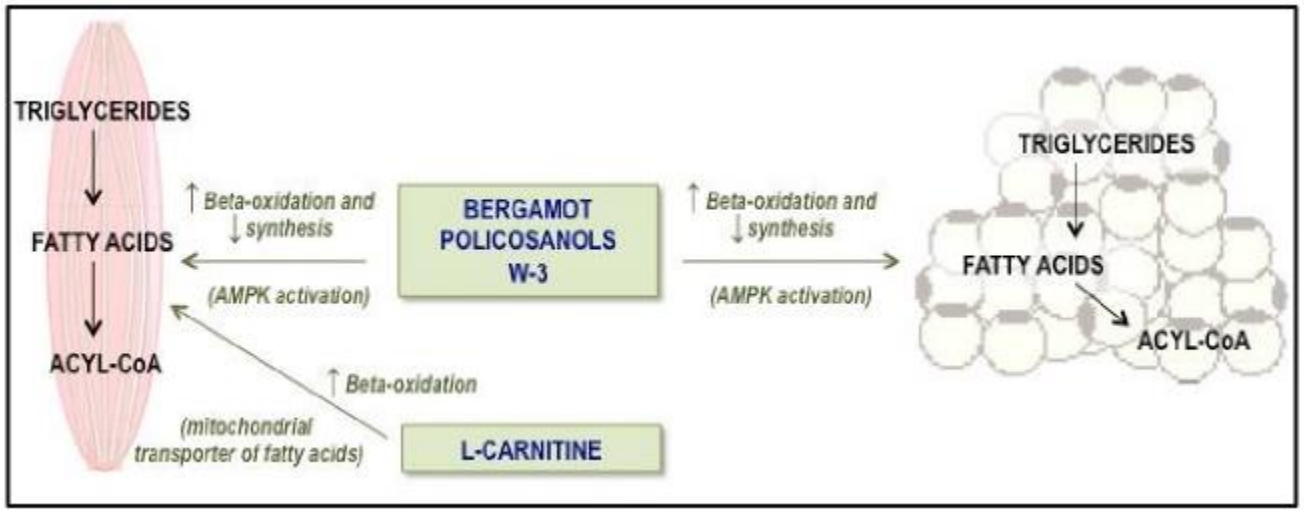






Some questions

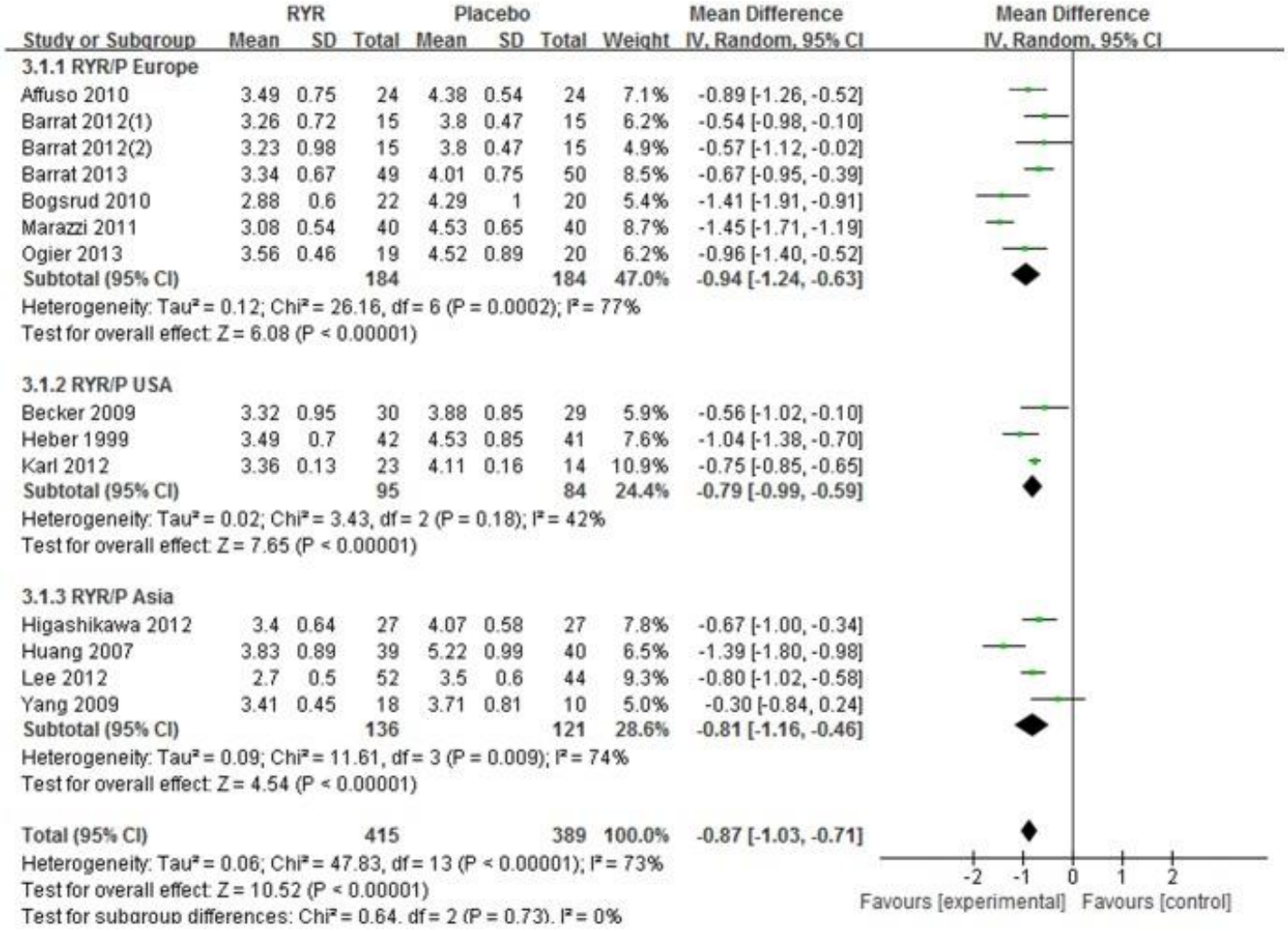
- **Do they have demonstrated significant lipid-lowering effects in humans?**
- **Are they safe?**
- **Do they have some effects on vascular health beyond «cosmetic» lipid-lowering effects?**

Evidence/Efficacy

	Clinical evidence	Clinical efficacy
Red Yeast Rice	+++	+++
Berberine	++	++
Soluble Fibers	+++	+
Phytosterols	+++	+
Garlic	++	+
Artichoke	++	++
Vegetal proteins	++	+
Policosanols	++	-
Panthetine	+	+
Guggul	+	+

Cicero AF et al. Food Funct. 2017; 8(6):2076-2088.

A Meta-Analysis of RYR: An Effective and Safe Approach for Dyslipidemia



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

EFFECTS ON LDL-C

Ad evidence-based lipid – lowering nutraceutical

Class	Level	Active daily doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects
I	A	3-10 mg (MonK)	-15 to -25%	↓ ApoB, hsCRP, MMP2, MMP9	↑ FMD, ↓ PWV. ↓ CV events in secondary prevention

Nutr Rev. 2017; 75(9):731-767.

Reccomended by:

- **International Lipid Expert Panel (ILEP)**
- **2019 ESC/EAS guidelines**

ORIGINAL CONTRIBUTION

Effect of Red Yeast Rice on Cognitive Functioning in Schizophrenia

Data From a Pilot Study

	Baseline (T0)		Week 12 (T1)		Student *t* Test T0 vs T1	
	Mean	SD	Mean	SD	*t*	*P*
WCST						
Perseverative errors	26.33	17.06	21.91	15.90	2.581	0.015
Nonperseverative errors	21.03	9.21	20.88	11.81	0.106	0.916
Total errors	47.55	22.35	43.33	23.40	2.510	0.017
Perseverative responses	29.76	20.20	25.97	20.17	1.923	0.063
Categories	3.48	2.09	3.64	2.16	−0.669	0.509
Phonemic fluency	29.55	10.69	33.15	8.80	−2.844	0.008
Semantic fluency	40.09	12.07	37.24	9.30	1.793	0.082
Stroop Test	44.24	23.25	50.42	39.28	−1.317	0.197

(*J Clin Psychopharmacol* 2019;39: 210–213)

53 RCTs
8535 Patients

Muscular AEs

Pharmacological Research 143 (2019) 1–16

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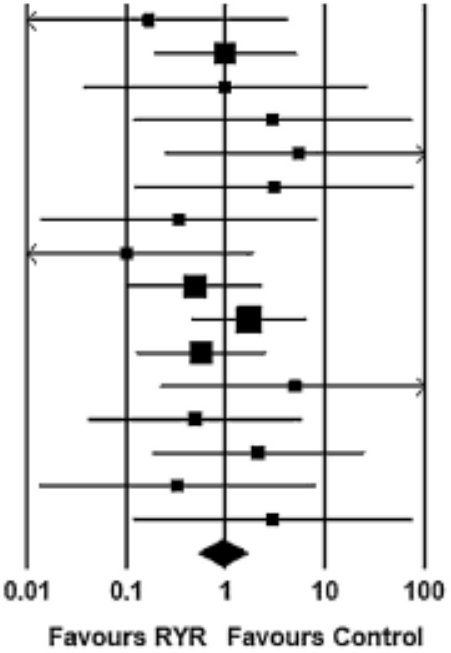
Safety of red yeast rice supplementation: A systematic review and meta-analysis of randomized controlled trials

Federica Fogacci[a,1], Maciej Banach[b,c,d,**,1], Dimitri P. Mikhailidis[e], Eric Bruckert[f], Peter P. Toth[g,h], Gerald F. Watts[i], Željko Reiner[j], John Mancini[k], Manfredi Rizzo[l], Olena Mitchenko[m], Daniel Pella[n], Zlatko Fras[o], Amirhossein Sahebkar[p,q], Michal Vrablik[r], Arrigo F.G. Cicero[a,*], on behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group, the International Lipid Expert Panel (ILEP)

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: $I^2 = 0$

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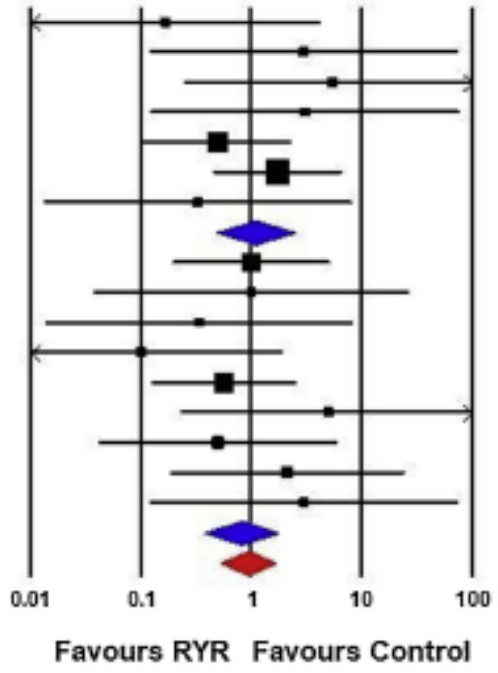
53 RCTs
8535 Patients

Muscular AEs

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	118.95	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 → $I^2 = 0$



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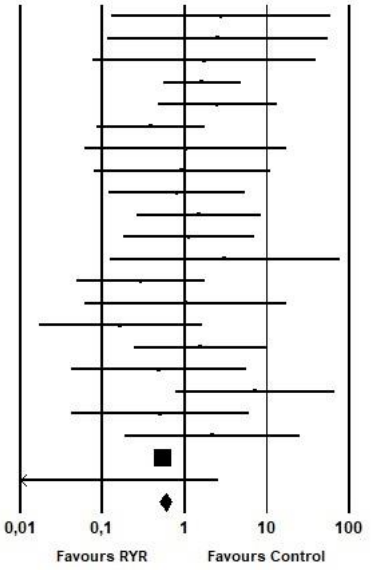
53 RCTs
8535 Patients

Non Muscular AEs

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

53 RCTs
8535 Patients

SAE rate

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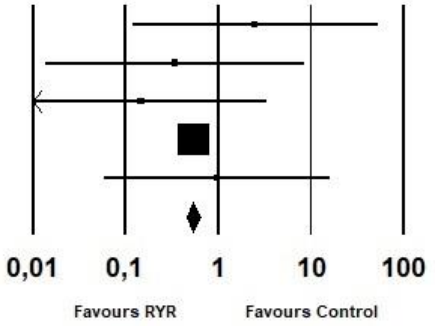
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Spigoni, V (2017)	2,509	0,118	53,225	0,590	0,555
Heinz, T (2016)	0,338	0,014	8,440	-0,661	0,509
Karl, M (2012)	0,147	0,007	3,263	-1,213	0,225
Lu, Z (2008)	0,540	0,455	0,640	-7,096	0,000
Heber, D (1999)	0,976	0,059	16,137	-0,017	0,986
	0,541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

Heterogeneity: I^2 = 0%



Meta Analysis

Phytomedicine 50 (2018) 25–34

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Phytomedicine

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

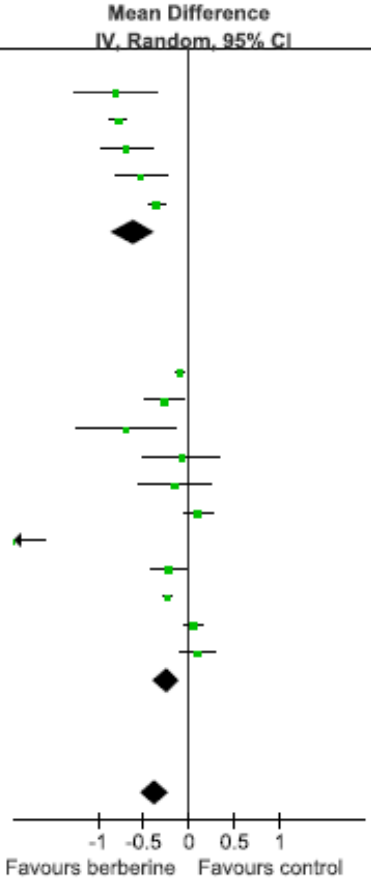
Efficacy and safety of berberine for dyslipidaemias: A systematic review and meta-analysis of randomized clinical trials

Ju Jianqing[a], Li Jingen[b], Lin Qian[c], Xu Hao[d,*]

16 RCTs, 2147 participants

Effect on LDL-C levels

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.2.1 berberine VS placebo or no drug									
Kong WJ 2004	2.8	0.8	63	3.6	1.1	28	4.6%	-0.80 [-1.25, -0.35]	2004
Ju SB 2007	4.76	0.22	45	5.54	0.21	42	7.4%	-0.78 [-0.87, -0.69]	2007
Zhang YF 2008	2.55	0.77	58	3.24	0.74	52	6.0%	-0.69 [-0.97, -0.41]	2008
Zhou YF 2011	2.72	0.64	60	3.25	0.91	60	6.1%	-0.53 [-0.81, -0.25]	2011
Wang L 2016	3.38	0.16	44	3.74	0.26	45	7.4%	-0.36 [-0.45, -0.27]	2016
Subtotal (95% CI)			**270**			**227**	**31.5%**	**-0.62 [-0.86, -0.37]**	
Heterogeneity: Tau² = 0.06; Chi² = 43.64, df = 4 (P < 0.00001); I² = 91%									
Test for overall effect: Z = 4.93 (P < 0.00001)									
1.2.2 berberine with LLD VS LLD alone									
He JJ 2007	2.8	0.08	38	2.9	0.11	40	7.6%	-0.10 [-0.14, -0.06]	2007
Yu JY 2007	2.05	0.55	50	2.32	0.56	50	6.6%	-0.27 [-0.49, -0.05]	2007
Kong WJ 2008	2.97	0.93	23	3.67	0.8	16	3.9%	-0.70 [-1.25, -0.15]	2008
Zheng BB 2009	2.37	0.92	33	2.45	0.82	33	4.8%	-0.08 [-0.50, 0.34]	2009
Su XY 2012	2.98	1.04	60	3.14	1.23	60	4.9%	-0.16 [-0.57, 0.25]	2012
Wang ZQ 2013	2.32	1.01	283	2.22	0.91	278	7.0%	0.10 [-0.06, 0.26]	2013
Zhou J 2014	4.17	0.75	33	6.12	0.8	33	5.2%	-1.95 [-2.32, -1.58]	2014
Zhu YJ 2015	1.78	0.52	50	2.01	0.47	50	6.8%	-0.23 [-0.42, -0.04]	2015
Zhan HJ 2015	2.81	0.1	40	3.05	0.14	40	7.5%	-0.24 [-0.29, -0.19]	2015
Chen N 2015	3.61	0.25	40	3.56	0.24	40	7.3%	0.05 [-0.06, 0.16]	2015
Wang ZQ 2017	2.31	1.01	180	2.22	0.9	180	6.8%	0.09 [-0.11, 0.29]	2017
Subtotal (95% CI)			**830**			**820**	**68.5%**	**-0.24 [-0.39, -0.10]**	
Heterogeneity: Tau² = 0.05; Chi² = 139.11, df = 10 (P < 0.00001); I² = 93%									
Test for overall effect: Z = 3.27 (P = 0.001)									
Total (95% CI)			**1100**			**1047**	**100.0%**	**-0.38 [-0.53, -0.22]**	
Heterogeneity: Tau² = 0.08; Chi² = 344.53, df = 15 (P < 0.00001); I² = 96%									
Test for overall effect: Z = 4.84 (P < 0.00001)									
Test for subgroup differences: Chi² = 6.49, df = 1 (P = 0.01), I² = 84.6%									



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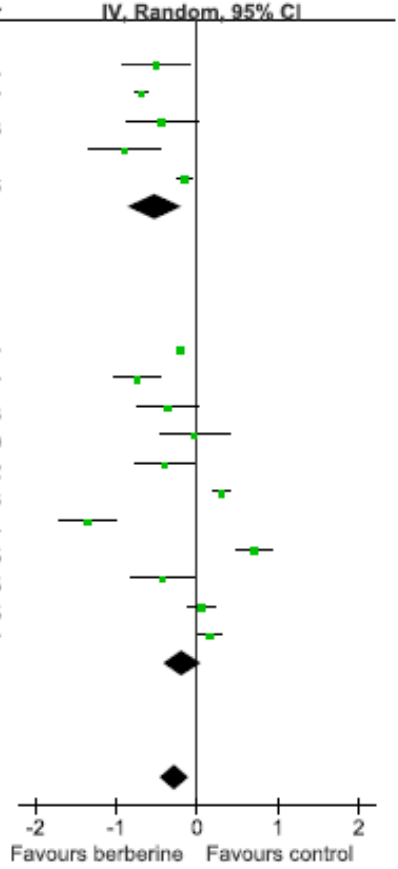
16 RCTs, 2147 participants

Effect on TG levels

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.3.1 berberine VS placebo or no drug									
Kong WJ 2004	1.5	0.8	63	2	1	28	5.3%	-0.50 [-0.92, -0.08]	2004
Ju SB 2007	1.88	0.17	45	2.57	0.21	42	7.3%	-0.69 [-0.77, -0.61]	2007
Zhang YF 2008	1.61	1.1	58	2.05	1.26	52	5.1%	-0.44 [-0.88, 0.00]	2008
Zhou YF 2011	1.75	1.01	60	2.65	1.42	60	5.2%	-0.90 [-1.34, -0.46]	2011
Wang L 2016	0.8	0.23	44	0.95	0.24	45	7.3%	-0.15 [-0.25, -0.05]	2016
Subtotal (95% CI)			**270**			**227**	**30.3%**	**-0.52 [-0.86, -0.18]**	
Heterogeneity: Tau² = 0.12; Chi² = 73.46, df = 4 (P < 0.00001); I² = 95%									
Test for overall effect: Z = 3.02 (P = 0.003)									
1.3.2 berberine with LLD VS LLD alone									
He JJ 2007	3.1	0.08	38	3.3	0.03	40	7.4%	-0.20 [-0.23, -0.17]	2007
Yu JY 2007	1.28	0.42	50	2.02	0.98	50	6.2%	-0.74 [-1.04, -0.44]	2007
Kong WJ 2008	1.66	0.35	23	2.02	0.7	16	5.7%	-0.36 [-0.73, 0.01]	2008
Zheng BB 2009	1.53	0.95	33	1.56	0.82	33	5.3%	-0.03 [-0.46, 0.40]	2009
Su XY 2012	1.83	1.02	60	2.23	0.97	60	5.8%	-0.40 [-0.76, -0.04]	2012
Wang ZQ 2013	1.91	0.8	283	1.61	0.5	278	7.2%	0.30 [0.19, 0.41]	2013
Zhou J 2014	1.65	0.8	33	3	0.69	33	5.8%	-1.35 [-1.71, -0.99]	2014
Zhan HJ 2015	2.49	0.47	40	1.78	0.5	40	6.8%	0.71 [0.50, 0.92]	2015
Zhu YJ 2015	2.56	0.97	50	2.99	1.01	50	5.6%	-0.43 [-0.82, -0.04]	2015
Chen N 2015	2.53	0.38	40	2.48	0.41	40	7.0%	0.05 [-0.12, 0.22]	2015
Wang ZQ 2017	1.78	0.82	180	1.62	0.5	180	7.1%	0.16 [0.02, 0.30]	2017
Subtotal (95% CI)			**830**			**820**	**69.7%**	**-0.18 [-0.41, 0.05]**	
Heterogeneity: Tau² = 0.13; Chi² = 226.91, df = 10 (P < 0.00001); I² = 96%									
Test for overall effect: Z = 1.53 (P = 0.13)									
Total (95% CI)			**1100**			**1047**	**100.0%**	**-0.28 [-0.46, -0.10]**	
Heterogeneity: Tau² = 0.12; Chi² = 394.09, df = 15 (P < 0.00001); I² = 96%									
Test for overall effect: Z = 3.03 (P = 0.002)									
Test for subgroup differences: Chi² = 2.67, df = 1 (P = 0.10), I² = 62.5%									



Complementary Therapies in Medicine 46 (2019) 81–86

Contents lists available at ScienceDirect

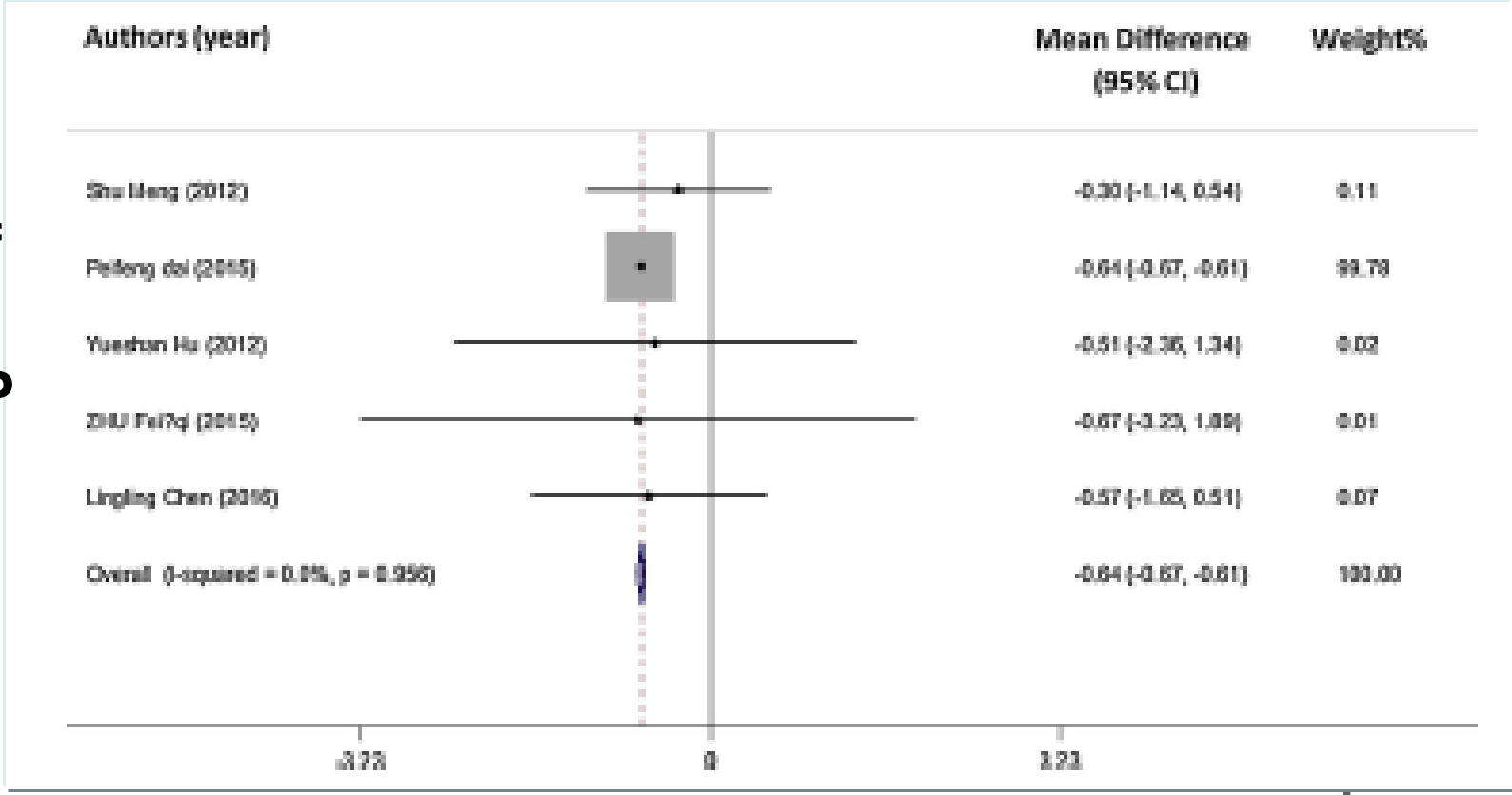
Complementary Therapies in Medicine

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

Effect of Berberine on C-reactive protein: A systematic review and meta-analysis of randomized controlled trials

Mohammad Beba[a], Kurosh Djafarian[a], Sakineh Shab-Bidar[b,*]

Effects of berberine on hsCRP level



Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2018, Article ID 2532935, 8 pages
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Review Article

The Effect of Berberine on Polycystic Ovary Syndrome Patients with Insulin Resistance (PCOS-IR): A Meta-Analysis and Systematic Review

Berberine = Metformine

TABLE 3: The result of meta-analysis regarding the effect of BBR versus MET.

Indices	SMD	95%CI	P
BMI◆1♣1◆2♣2◆3♣3	-0.158◤☆	-0.446~1.130	0.281◎
FSH	0.184◥	-0.305~0.673	0.461◎
LH◆1◆3	-0.130◥☆	-0.688~0.429	0.649◎
T◆1◆2♣2◆3	-0.516◥☆	-1.088~0.055	0.077◎
HOMA-IR◆1♣1◆2♣2◆3	-0.188◤☆	-0.476~0.100	0.201◎
TC◆1♣1◆2♣2◆3♣3	-1.233◥☆	-2.912~0.446	0.150◎
TG◆1♣1◆3♣3	0.045◤	-0.243~0.332	0.761◎
LDL-C◆1♣1◆2♣2◆3♣3	-0.701◥☆	-1.630~0.229	0.140◎
HDL-C	0.148◥	-0.984~1.280	0.798◎

Notes:

◆x: significant statistical difference (P<0.05) between final value and baseline in BBR group was reported by trial No. x.

♣x: significant statistical difference (P<0.05) between final value and baseline in MET group was reported by trial No. x.

◤:fixed effect model;◥:random effect model.

◎: P>0.05.

☆: BBR group showed a greater change than MET before and after treatment.

Berberine potentiates cyproterone acetate

TABLE 5: The result of meta-analysis regarding the effectiveness of CPA+BBR versus CPA.

Indices	SMD	95%CI	P
BMI[◆6♣6◆7♣7]	-0.235[◥☆]	-0.681~0.211	0.302[◎]
WHR[◆6♣6◆7♣7]	-0.942[◥☆]	-1.755~-0.129	0.023*
FSH	2.807[◥]	-2.688~8.301	0.317[◎]
LH[◆6]	-0.723[◤☆]	-1.111~-0.335	0.001* * *
T[◆6♣6]	-0.484[◥☆]	-1.062~0.093	0.100[◎]
FPG[◆6◆7]	-0.688[◤☆]	-0.936~-0.441	0.001* * *
FIN[◆6◆7♣7]	-0.620[◤☆]	-0.893~-0.348	0.001* * *
HOMA-IR[◆6◆7♣7]	-0.713[◤☆]	-1.026~-0.400	0.001* * *
TC[◆6◆7♣7]	-3.816[◥☆]	-6.188~-1.444	0.002**
TG[◆6◆7♣7]	-1.516[◥☆]	-2.112~-0.920	0.001* * *
LDL-C[◆6◆7]	-1.173[◥☆]	-1.661~-0.685	0.001* * *
HDL-C[◆6◆7]	1.452[◤]	1.152~1.752	0.001* * *

Notes:

[◆x]: significant statistical difference (P<0.05) between final value and baseline in CPA+BBR group was reported by trial No. x.

[♣x]: significant statistical difference (P<0.05) between final value and baseline in CPA group was reported by trial No. x.

Statistical difference between final value and baseline in each group was not reported in trial No. 8 and 9.

[◤]:fixed effect model; [◥]:random effect model.

[◎]: P>0.05; *: P<0.05; **: P<0.01; * * *: P<0.001.

[☆]: CPA+BBR group showed a greater change than CPA before and after treatment.

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Efficacy and safety of berberine for dyslipidaemias: A systematic review and meta-analysis of randomized clinical trials

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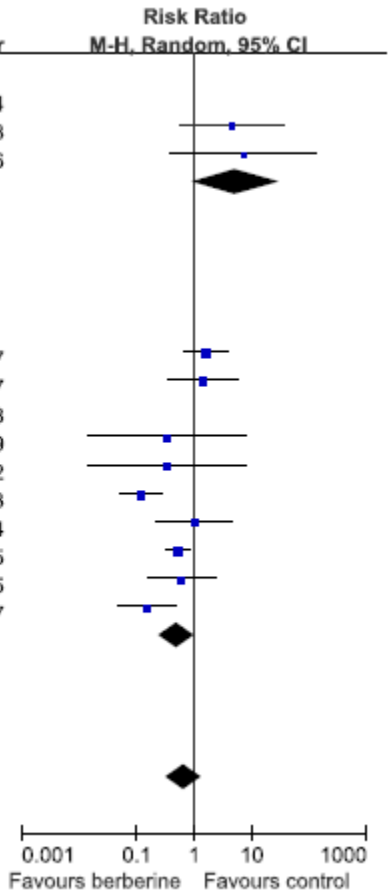
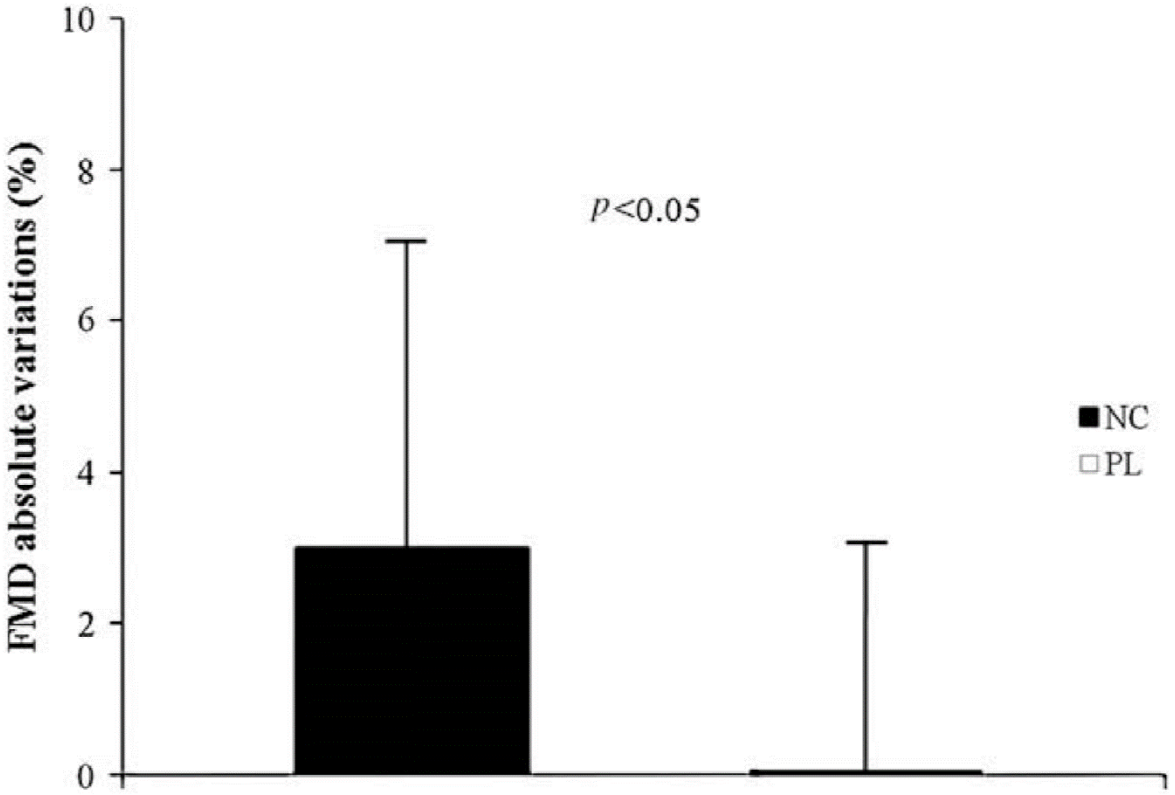
16 RCTs, 2147 participants

Adverse event rate

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.5.1 berberine VS placebo or no drug							
Kong WJ 2004	0	63	0	28		Not estimable	2004
Zhang YF 2008	5	58	1	52	6.7%	4.48 [0.54, 37.13]	2008
Wang L 2016	3	44	0	45	4.3%	7.16 [0.38, 134.62]	2016
Subtotal (95% CI)		**165**		**125**	**11.0%**	**5.26 [0.95, 29.24]**	
Total events	8		1				
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%							
Test for overall effect: Z = 1.90 (P = 0.06)							
1.5.2 berberine with LLD VS LLD alone							
Yu JY 2007	11	50	7	50	13.0%	1.57 [0.66, 3.72]	2007
He JJ 2007	4	38	3	40	9.8%	1.40 [0.34, 5.86]	2007
Kong WJ 2008	0	23	0	16		Not estimable	2008
Zheng BB 2009	0	33	1	33	3.9%	0.33 [0.01, 7.90]	2009
Su XY 2012	0	60	1	60	3.8%	0.33 [0.01, 8.02]	2012
Wang ZQ 2013	6	283	50	278	13.2%	0.12 [0.05, 0.27]	2013
Zhou J 2014	3	33	3	33	9.3%	1.00 [0.22, 4.60]	2014
Zhu YJ 2015	15	50	29	50	14.9%	0.52 [0.32, 0.84]	2015
Chen N 2015	3	40	5	40	10.1%	0.60 [0.15, 2.34]	2015
Wang ZQ 2017	3	180	20	180	11.1%	0.15 [0.05, 0.50]	2017
Subtotal (95% CI)		**790**		**780**	**89.0%**	**0.49 [0.24, 1.00]**	
Total events	45		119				
Heterogeneity: Tau² = 0.71; Chi² = 27.00, df = 8 (P = 0.0007); I² = 70%							
Test for overall effect: Z = 1.95 (P = 0.05)							
Total (95% CI)		**955**		**905**	**100.0%**	**0.64 [0.31, 1.30]**	
Total events	53		120				
Heterogeneity: Tau² = 0.83; Chi² = 33.42, df = 10 (P = 0.0002); I² = 70%							
Test for overall effect: Z = 1.23 (P = 0.22)							
Test for subgroup differences: Chi² = 6.26, df = 1 (P = 0.01), I² = 84.0%							

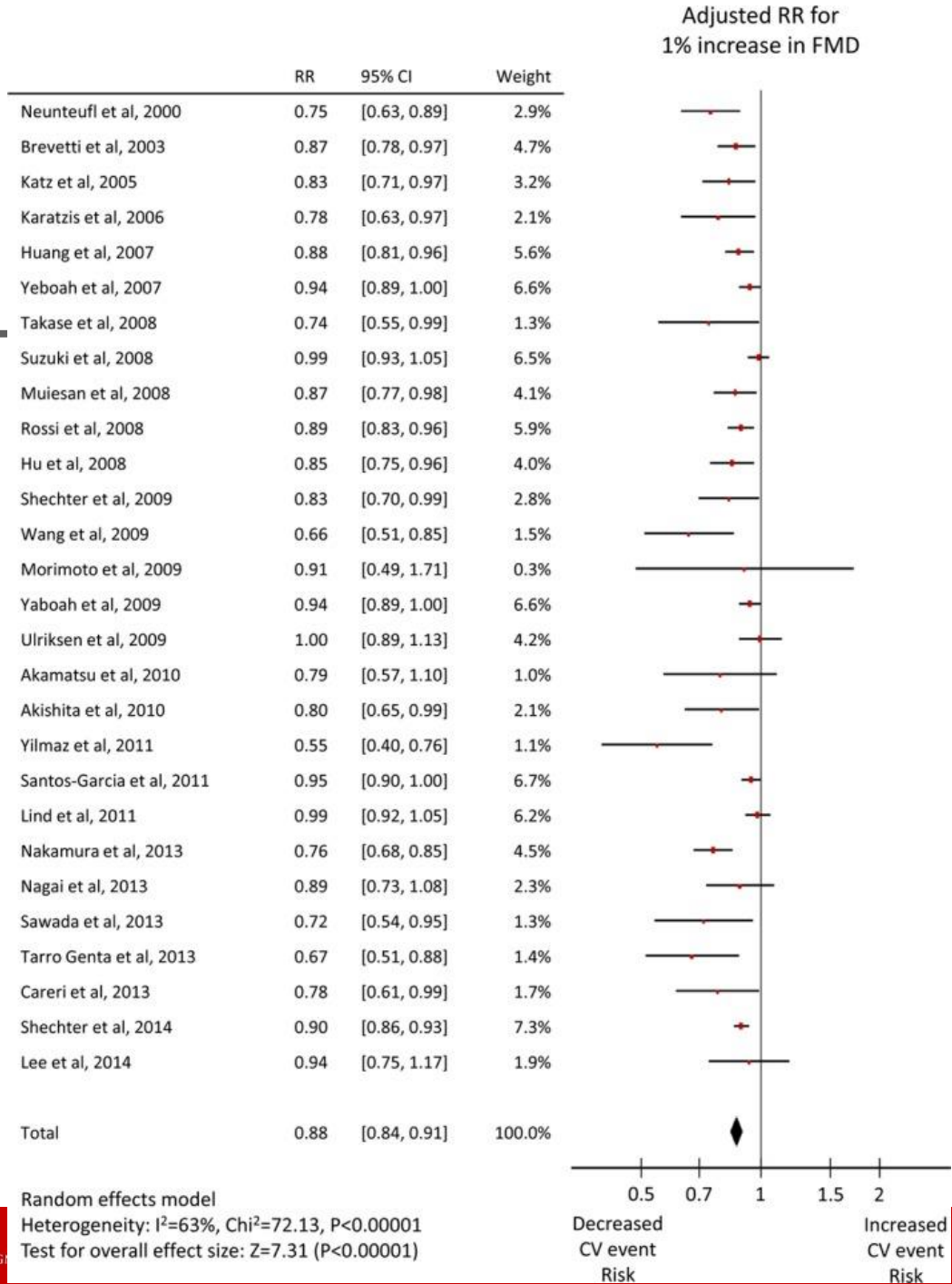


Effects of RYR-BRB on FMD



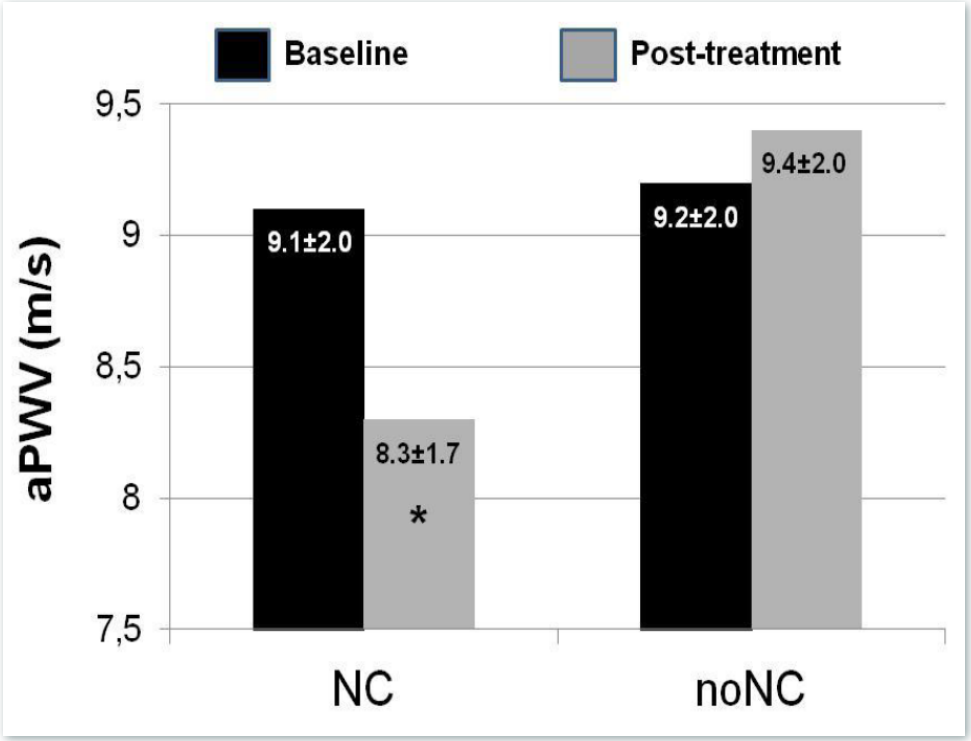
Affuso F et al. Nutr Metab Cardiovasc Dis. 2010;20(9):656-61

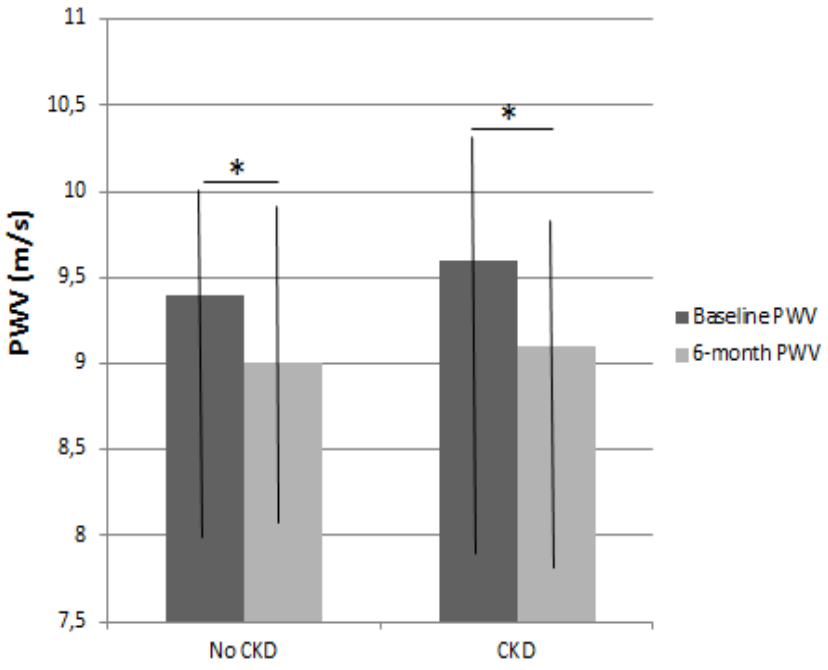
FMD and CV risk: 1% FMD increase = 12% CV risk reduction!



Matsusawa Y et al. J Am Heart Assoc. 2015;4(11): e002270.

Effects of RYR-BRB on arterial stiffness





Pirro M et al. Pharmanutrition 2013

Cicero et al. The Open Hypertension J 2013

American Heart Association.

RR 95%CI for clinical events:

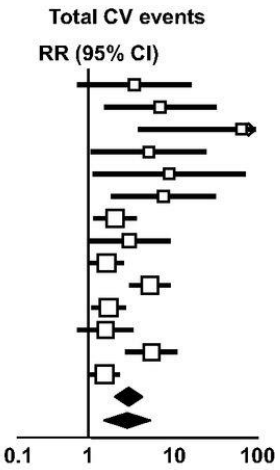
A= CV events
B= CV mortality
C= Total mortality

An increase in PWV by 1 m/s corresponds with an increase of 12%, 13%, and 6% in total CV events, CV mortality, and all-cause mortality, respectively.

Charalambos Vlachopoulos et al. Hypertension. 2012;60:556-562

A

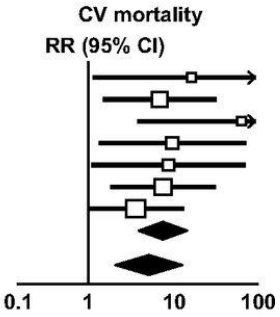
Author	Population	RR	95% CI
Kato 2012	ESRD	3.40	0.71 - 16.36
* Kitahara 2005	ESRD	7.03	1.49 - 33.12
Matsuoka 2005	GEN/ELD	68.91	3.90 - 1218.25
Meguro 2009	CVD	5.10	1.03 - 25.17
* Miyano 2010	GEN/ELD	9.01	1.08 - 75.03
Morimoto 2009	ESRD	7.67	1.81 - 32.56
Munakata 2011	ESRD	1.98	1.11 - 3.54
* Munakata 2012	HTN	2.97	0.98 - 9.06
Nakamura 2010	DM/CVD	1.57	1.00 - 2.47
Orlova 2009	CVD	5.27	3.03 - 9.18
* Sugamata 2011	CVD	1.66	1.05 - 2.62
* Tanaka 2011	ESRD	1.51	0.70 - 3.23
* Tomiyama 2005	CVD	5.47	2.69 - 11.11
Yoshida 2012	DM	1.47	0.98 - 2.19
Overall		**2.89**	**1.99 - 4.20**
Overall (High quality studies)		**2.95**	**1.63 - 5.33**



Test for heterogeneity: I^2=66.0%, P<0.001
Test for overall effect: Z=5.57, P<0.001

B

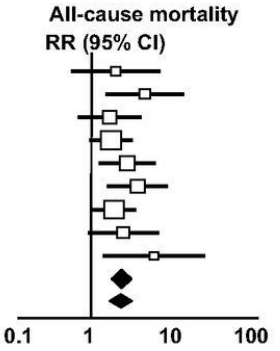
Author	Population	RR	95% CI
Kato 2012	ESRD	16.90	1.12 - 255.69
* Kitahara 2005	ESRD	7.03	1.49 - 33.12
Matsuoka 2005	GEN/ELD	68.91	3.90 - 1218.25
Meguro 2009	CVD	10.00	1.32 - 75.85
* Miyano 2010	GEN/ELD	9.01	1.08 - 75.03
Morimoto 2009	ESRD	7.67	1.81 - 32.56
* Tanaka 2011	ESRD	3.61	0.97 - 13.44
Overall		**7.68**	**3.91 - 15.07**
Overall (High quality studies)		**5.36**	**2.17 - 13.27**



Test for heterogeneity: I^2=0.0%, P=0.686
Test for overall effect: Z=5.92, P<0.001

C

Author	Population	RR	95% CI
Amemiya 2011	ESRD	2.06	0.52 - 8.11
Chen 2011	RD	5.11	1.53 - 17.08
Kato 2010	ESRD	1.70	0.64 - 4.49
* Kitahara 2005	ESRD	1.79	0.93 - 3.46
* Miyano 2010	GEN/ELD	2.97	1.25 - 7.07
Morimoto 2009	ESRD	4.09	1.61 - 10.42
Nakamura 2010	DM/CVD	1.97	1.01 - 3.84
* Tanaka 2011	ESRD	2.63	0.89 - 7.79
* Turin 2010	GEN	6.80	1.40 - 32.91
Overall		**2.48**	**1.82 - 3.37**
Overall (High quality studies)		**2.45**	**1.56 - 3.86**



Test for heterogeneity: I^2=0.0%, P=0.617
Test for overall effect: Z=5.78, P<0.001

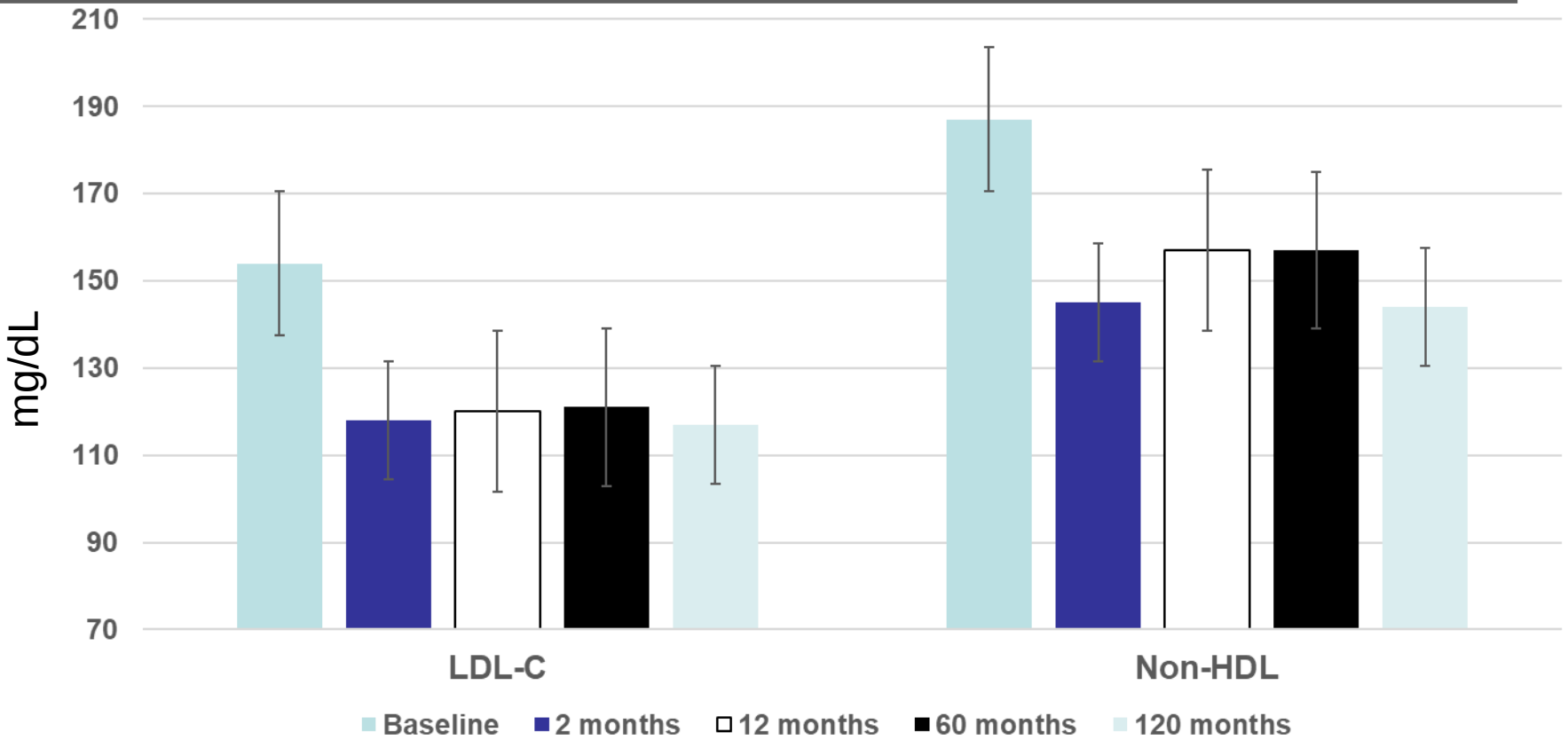
Long term effects …

- **263 never statin-treated subjects with 5 years follow-up**

- **102 never statin-treated subjects with 10 years follow-up**

Cicero AF, Mazza A, Data on file 2019

Long term effects …



Cicero AF, Mazza A, Data on file 2019

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Review

Safety of red yeast rice supplementation: A systematic review and meta-analysis of randomized controlled trials

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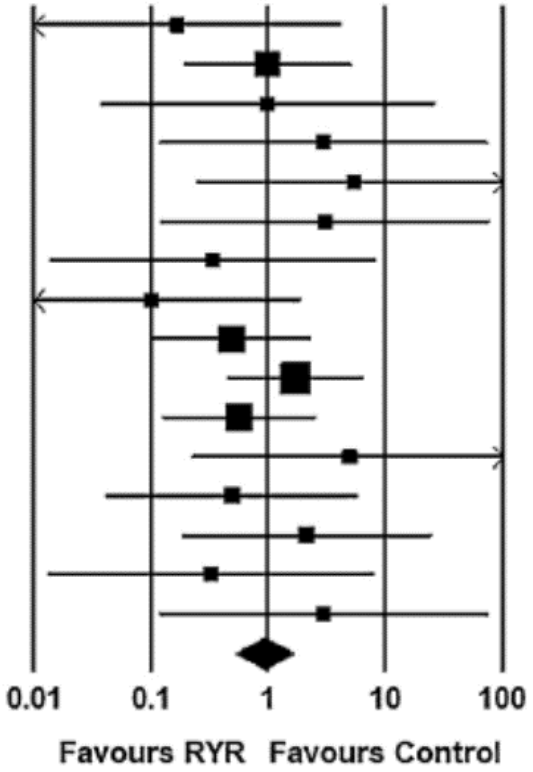
Forest plot comparing the RYR associated risk of MuD in the entire population

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

Heterogeneity: $I^2 = 0$



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 1, 2018

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JACC STATE-OF-THE-ART REVIEW

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 Vrablik, 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)

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 1, 2018

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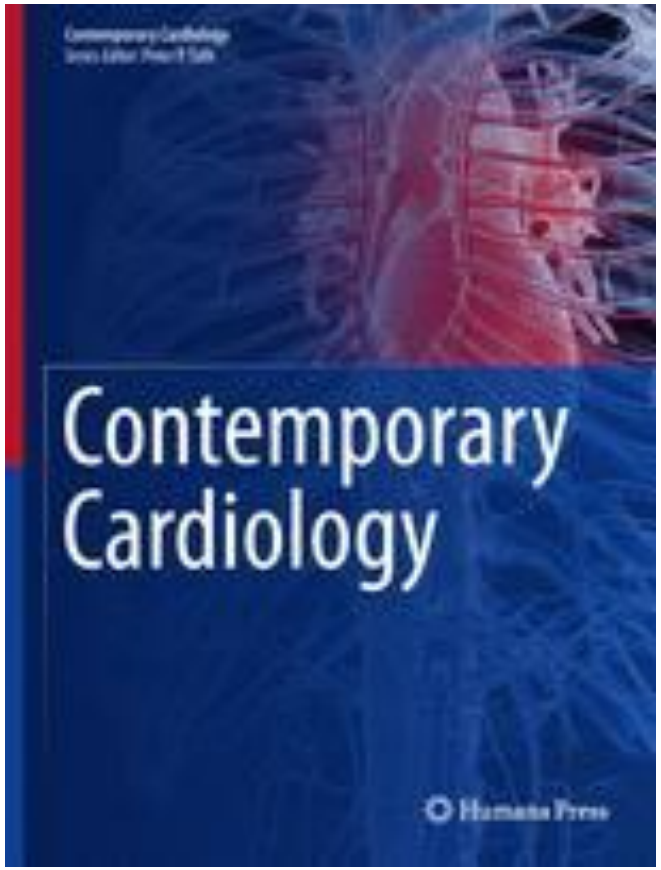
The Role of Nutraceuticals in Statin Intolerant Patients

TABLE 11 Nutraceuticals in Combination: 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



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Nutraceuticals and Cardiovascular Disease

Book Editors:
Manfredi Rizzo, MD, PhD, University of Palermo
Arrigo F.G. Cicero, MD, PhD, University of Bologna
Italian Society of Nutraceuticals (SINut)

The next step …

- **Do we need a next step ???**