



La nutraceutica a supporto del calo ponderale e per la gestione dei fattori di rischio cardiovascolari del paziente obeso



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The cardiovascular disease paradox

- The leading cause of mortality in Western countries
- We know the most part of risk factors
- Life-style improvement has proven to decrease the CV disease risk
- However, we fail to improve CV risk profile of general population
- Why ???

Lancet. 2016;387(10033):2145-54.

Responsabilities of a world-wide failure

General population

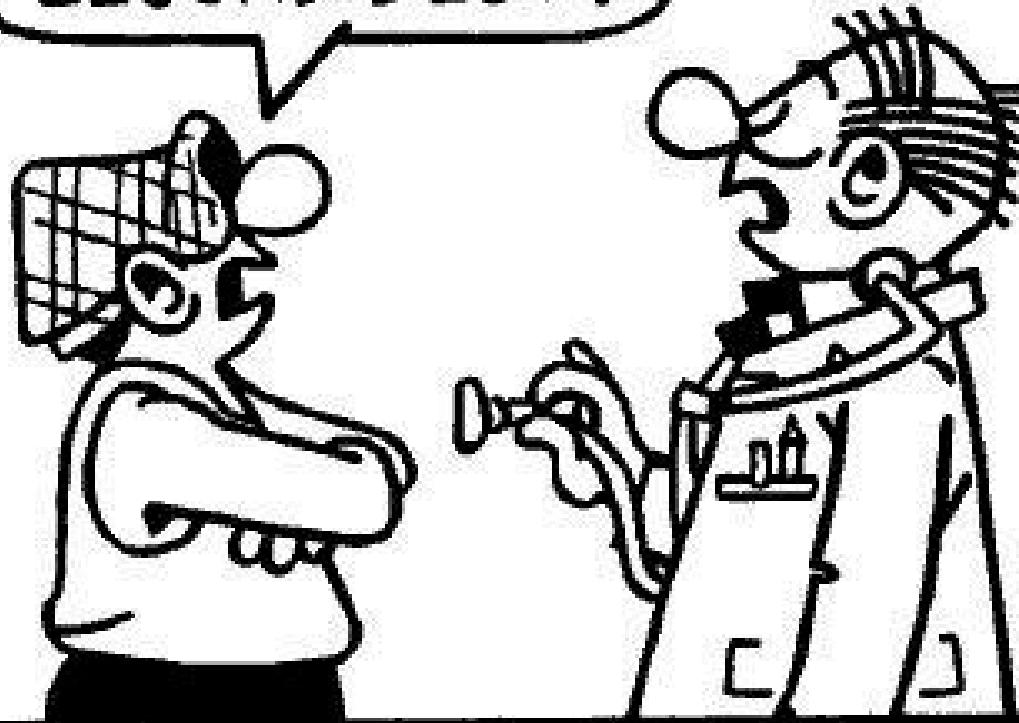
- Wrong perception of risk factors
- Lack of will/difficulty to change life-style
- Lack of knowledge on how to change life-style
- Lack on confidence on the efficacy of life-style improvement

Experts

- Wrong perception of risk factors
- Lack of knowledge on what is really efficacious
- Lack of confidence in general population will to change
- Scientific messages often far from practical application

THE BEST THING YOU CAN
DO IS GIVE UP SMOKING,
DRINKING AND FRIED FOOD

WHAT'S THE
SECOND BEST?





Recommendation for cost-effective prevention of cardiovascular disease

Recommendation	Class ^a	Level ^b
Measures aimed at promoting healthy lifestyles at the population level should be considered.	IIa	B

ROBERT

Before



After



In only 2 weeks
Robert lost his glasses

The «healthy diet»

Box 1 Milestones of a Healthy Diet

- Total energy intake proportional to physical activity
 - Low salt intake
 - Carbohydrates with low glycemic index as the main source of energy
 - Very low intake of simple sugars
 - Large intake of water, fresh vegetables, legumes, and berries
 - Fish and nuts and moderate amount of nonprocessed meat
 - Moderate doses of dairy products (preferably fermented, rich in probiotics, and low-fat)
 - Coffee, high-quality dark chocolate, and low quantity of alcohol (from either wine or beer) not forbidden
-

CV risk related to the most common risk factors (%): data from the EURIKA survey

Hypertension	32.7 (32.0-33.4)
Dyslipidemia	15.1 (14.8-15.4)
Smoking	10.4 (9.9-11.0)
Diabetes	16.4 (15.6-17.2)
All risk factors	57.7 (57.0-58.4)

Gyakkar et al., *BMC Public Health* 2011;
11:704

Nutraceuticals for Metabolic Syndrome Management: From Laboratory to Benchside

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¹*Atherosclerosis and Metabolic Diseases Research Center, Medicine & Surgery Dept., Alma Mater Studiorum University of Bologna, Bologna- Italy;* ²*Turkish Ministry of Health, Şanlıurfa Education and Research Hospital, Department of Endocrinology and Metabolic Diseases, Şanlıurfa- Turkey*

Nutraceutici in supporto alla dieta

Meccanismi diretti:

- Induzione meccanica di sazietà (Fibre)
- Rallentamento digestione di carboidrati e/o lipidi (Fibre, Faseolamina)
- Rallentamento assorbimento di carboidrati e/o lipidi (Fibre, Faseolamina)
- Stimolazione del metabolismo (EGCG, Acido clorogenico)
- Insulino-sensibilizzanti (Berberina, Banaba, Cannella, Curcumina)

Meccanismi indiretti:

- Eubiosi intestinale (Probiotici)
- Riduzione ansia/insonnia/depressione correlati alla fame
- Integrazione di vitamine/sali minerali/aminoacidi essenziali in corso di diete fortemente ipocaloriche

Effetti su parametri correlati

- Insulino-resistenza, Glicemia, Glicemia post-prandiale, Emoglobina glicata
- Trigliceridemia, Trigliceridemia post-prandiale
- Infiammazione vascolare e sistemica

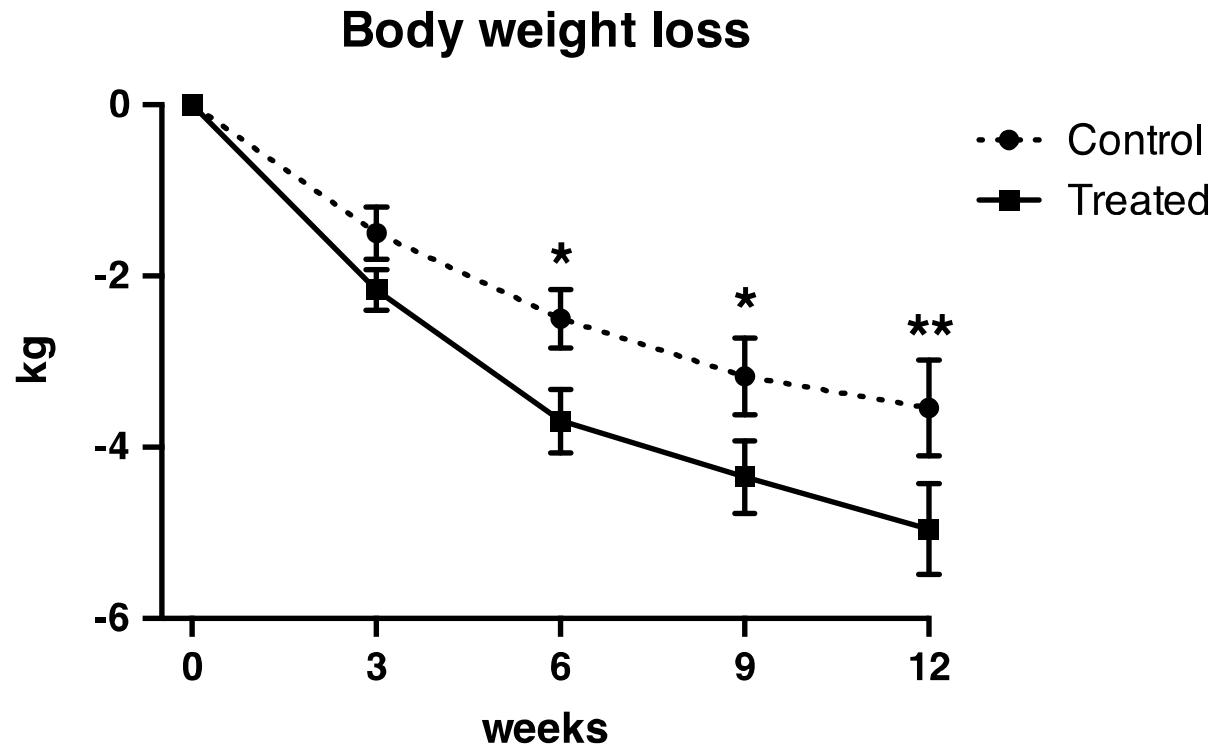


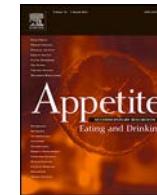
Research report

Body weight loss, reduced urge for palatable food and increased release of GLP-1 through daily supplementation with green-plant membranes for three months in overweight women [☆]



Caroline Montelius, Daniel Erlandsson, Egzona Vitija, Eva-Lena Stenblom, Emil Egecioglu,
Charlotte Erlanson-Albertsson *



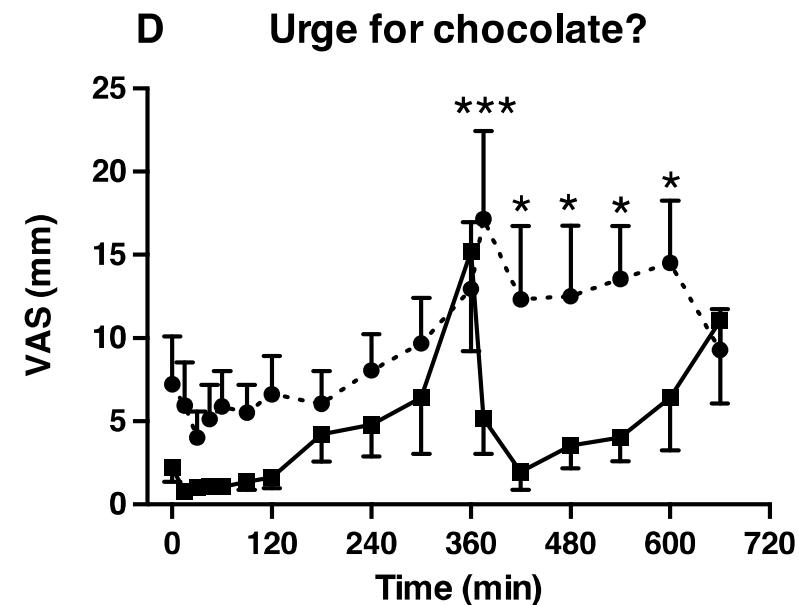
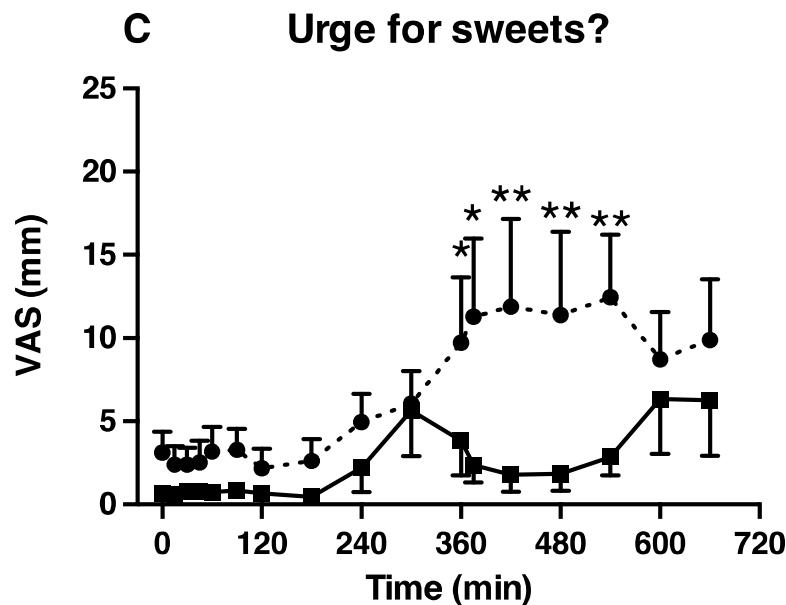


Research report

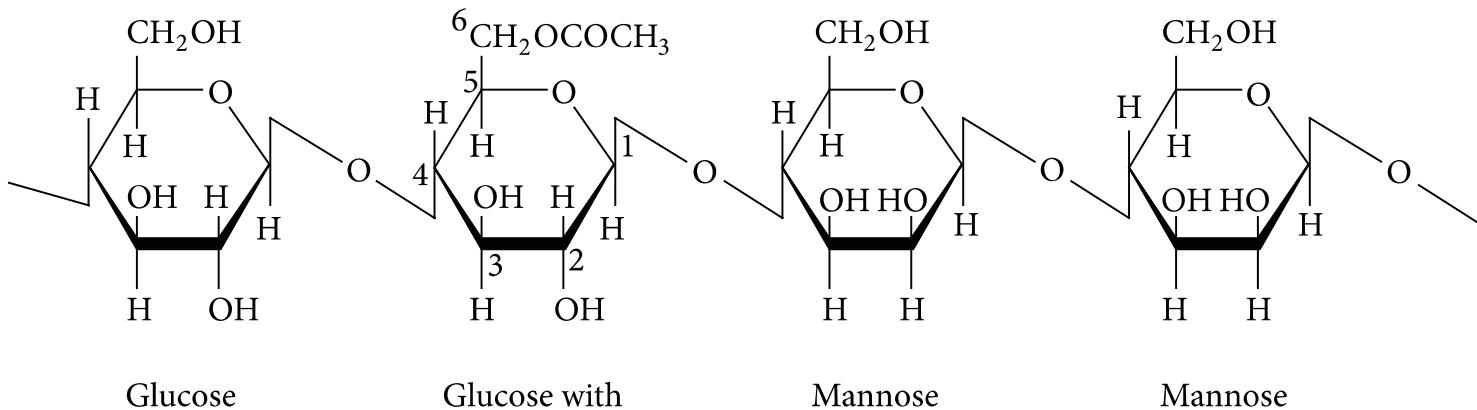
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Charlotte Erlanson-Albertsson *



• - - Control
■ - Treated



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Journal of Obesity

Volume 2013, Article ID 610908, 7 pages

<http://dx.doi.org/10.1155/2013/610908>

Clinical Study

Safety and Efficacy of Glucomannan for Weight Loss in Overweight and Moderately Obese Adults

Joyce K. Keithley,¹ Barbara Swanson,¹ Susan L. Mikolaitis,² Mark DeMeo,³ Janice M. Zeller,⁴ Lou Fogg,⁵ and Jehan Adamji⁶

1.33 gr t.i.d. (!!!): no effetti su calo ponderale e parametri antropometrici

Hindawi Publishing Corporation
Journal of Obesity
Volume 2013, Article ID 610908, 7 pages
<http://dx.doi.org/10.1155/2013/610908>

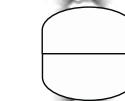
Clinical Study

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Meccanismi d'azione su cui intervenire per contrastare l'insulino- resistenza

- Rallentamento/Riduzione assorbimento carboidrati
-> Fibra, Faseolamina
- Stimolazione metabolismo -> Acido clorogenico
- Stimolazione diretta insulino-sensibilità ->
Berberina, Banaba, Cannella, Cissus/Iringia
- Riduzione dei livelli di cortisolemia -> Curcumina,
Fosfatidilserina



Hindawi Publishing Corporation
ISRN Nutrition
Volume 2014, Article ID 650264, 7 pages
<http://dx.doi.org/10.1155/2014/650264>

Review Article

Effects of Commercially Available Dietary Supplements on Resting Energy Expenditure: A Brief Report

Roger A. Vaughan,^{1,2,3} Carole A. Conn,³ and Christine M. Mermier¹

*"Numerosi studi prospettici e due meta-analisi che indicano che il consumo moderato e regolare di caffè **riduce il rischio di diabete mellito di tipo 2**, e che l'associazione non dipende da distribuzione geografica e genere".*

Natella e Scaccini 2012. Nutrition Reviews® Vol. 70 (4): 207–217.

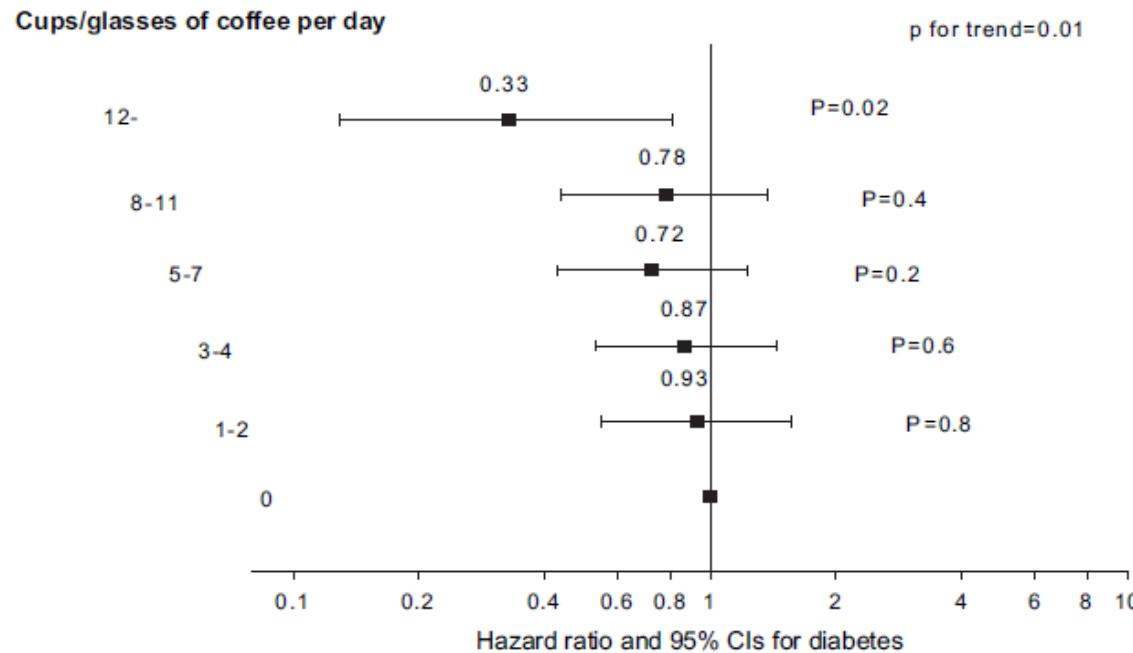


Figure 2 Hazard ratios (and 95% CIs) for incident diabetes by daily coffee consumption categories adjusted for age, gender, smoking, alcohol use, family history of diabetes, physical activity, body mass index.

Zhang 2011 Nutrition, Metabolism & Cardiovascular Diseases 21, 418-423.

SHORT COMMUNICATION

Caffeine intake is related to successful weight loss maintenance

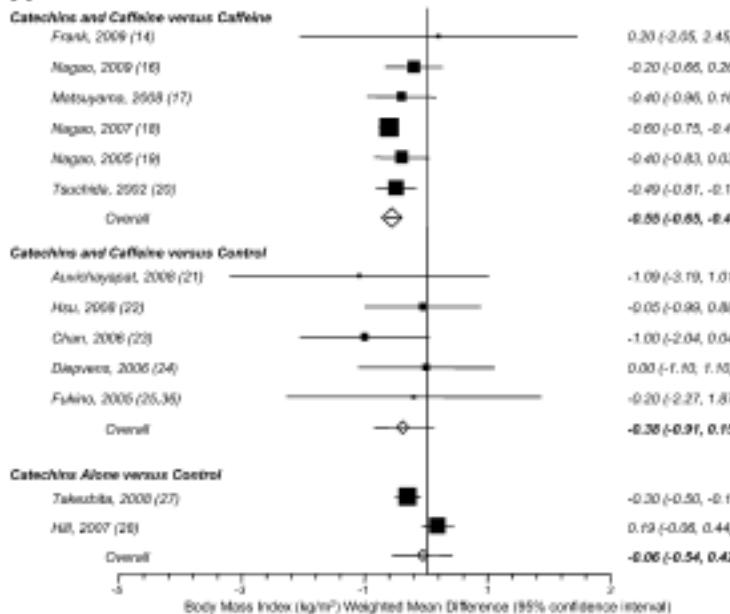
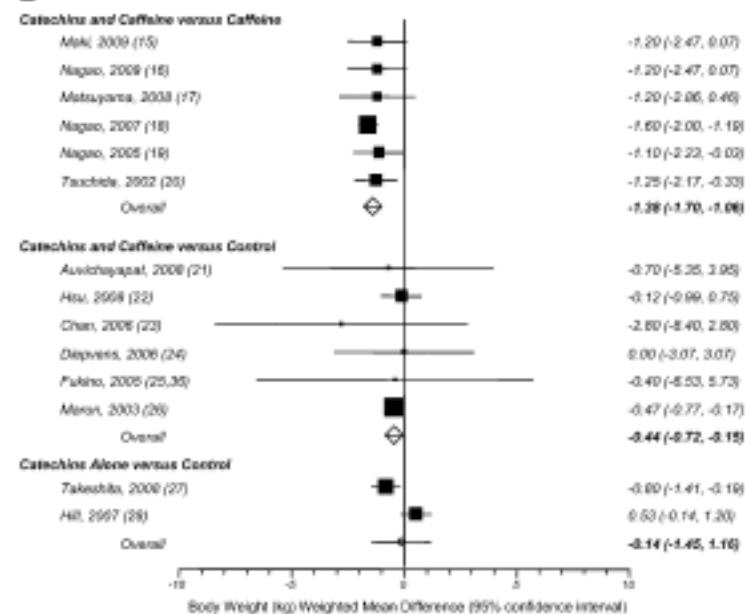
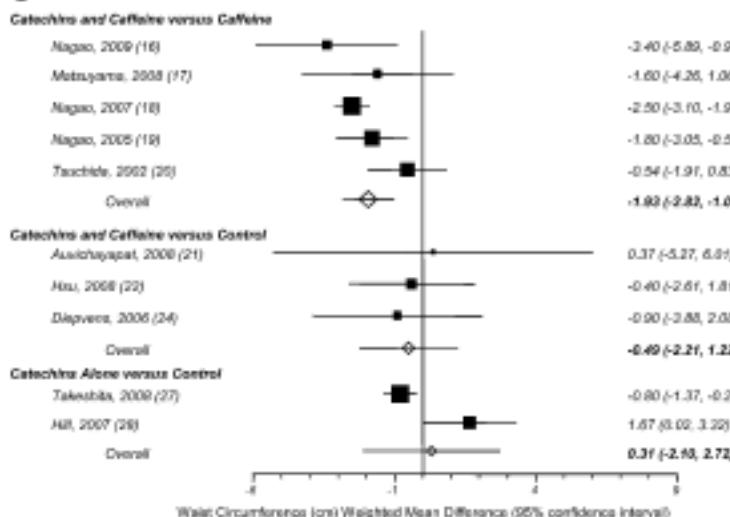
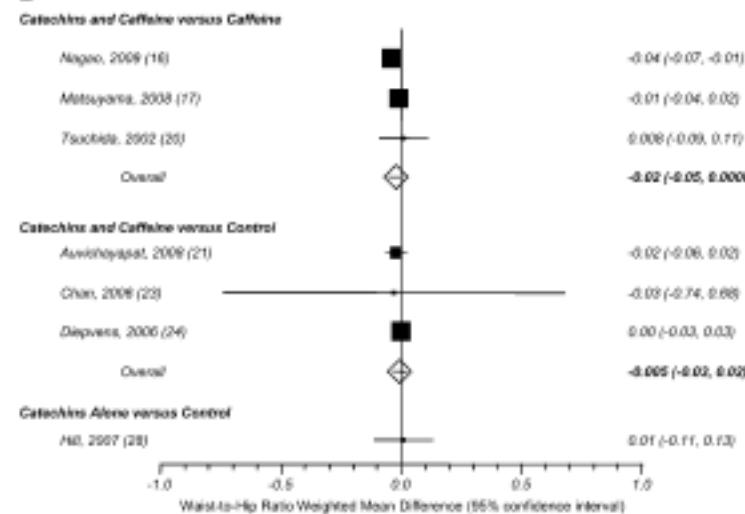
D Icken¹, S Feller², S Engeli³, A Mayr⁴, A Müller¹, A Hilbert⁵ and M de Zwaan¹

494 weight loss maintainers and 2129 individuals from the general population

Table 2. Logistic regressions model comparing weight loss maintainers of the German Weight Control Registry and a representative German population sample

	<i>Regression coefficient</i>	<i>s.e.</i>	<i>Wald</i>	<i>df</i>	<i>P-value</i>	<i>Odds ratio</i>	<i>95% confidence interval</i>
Sex	-0.538	0.113	22.843	1	<0.001	0.584	0.468
Age	0.007	0.005	2.166	1	0.141	1.007	0.998
Academic degree	-0.807	0.110	53.715	1	<0.001	0.446	0.360
Employment	-0.138	0.129	1.142	1	0.285	0.871	0.676
Partnership	-0.816	0.134	36.934	1	<0.001	0.442	0.340
Current BMI	0.000	0.012	0.001	1	0.980	1.000	0.976
IPAQ inactive			3.373	2	0.185		
IPAQ minimally active	-0.335	0.188	3.156	1	0.076	0.716	0.495
IPAQ HEPA active	-0.099	0.123	0.650	1	0.420	0.906	0.712
Coffee and caffeinated beverages	0.164	0.033	24.257	1	<0.001	1.179	1.104
							1.258

Abbreviations: BMI, body mass index; HEPA, health-enhancing physical activity; IPAQ, International Physical Activity Questionnaire.

A**B****C****D**

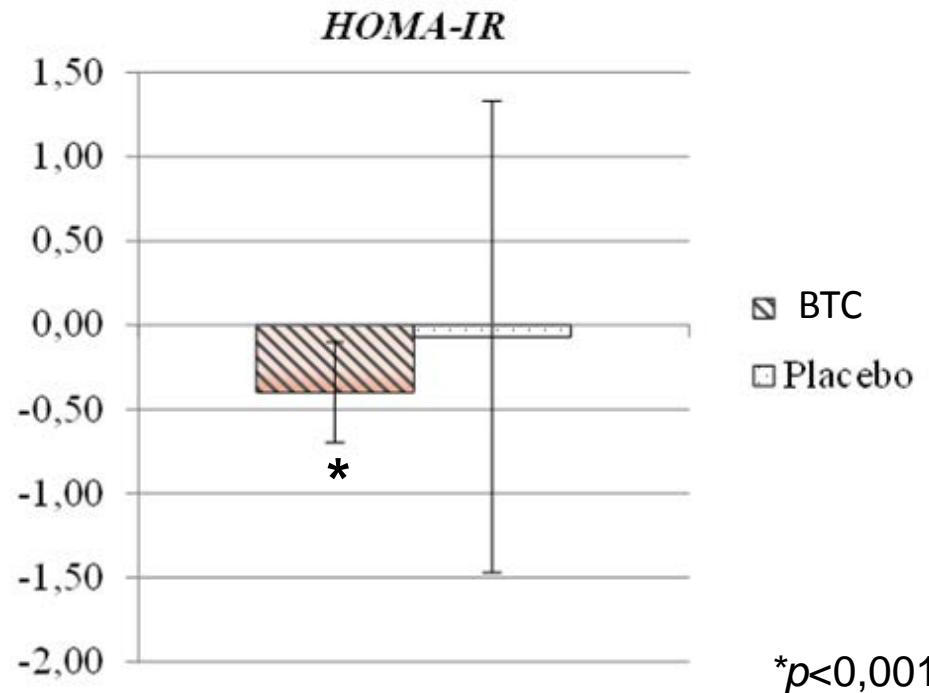
RESEARCH

Open Access

Short-term effects of a combined nutraceutical of insulin-sensitivity, lipid level and indexes of liver steatosis: a double-blind, randomized, cross-over clinical trial

Arrigo FG Cicero^{1,2*}, Martina Rosticci¹, Angelo Parini¹, Martino Morbini¹, Riccardo Urso¹, Elisa Grandi¹ and Claudio Borghi¹

Effetti sull'insulino-resistenza



HOMA Index =

FPG(mg/dl) X Insulina a digiuno (mUI/l)

The 11- β -Hydroxysteroid Dehydrogenase Type 1 Inhibitor INCB13739 Improves Hyperglycemia in Patients With Type 2 Diabetes Inadequately Controlled by Metformin Monotherapy

JULIO ROSENSTOCK, MD¹

SALOMON BANARER, MD¹

VIVIAN A. FONSECA, MD²

SILVIO E. INZUCCHI, MD³

WILLIAM SUN, PhD⁴

WENQING YAO, PhD⁴

GREGORY HOLLIS, PhD⁴

ROBERT FLORES, BSN⁴

RICHARD LEVY, MD⁴

WILLIAM V. WILLIAMS, MD⁴

JONATHAN R. SECKL, MD³

REID HUBER, PhD⁴

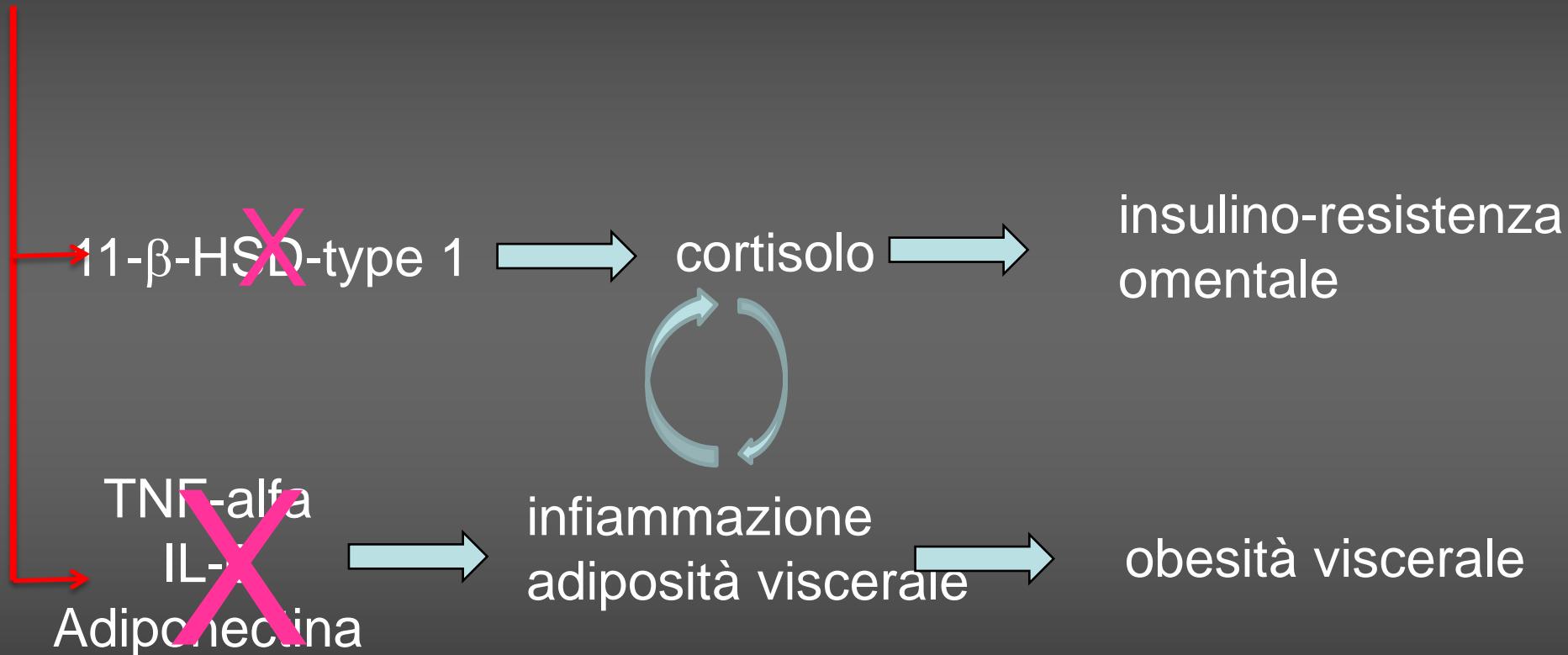
FOR THE INCB13739-202 PRINCIPAL
INVESTIGATORS*

The phenotypic similarities between obesity, type 2 diabetes, and Cushing's syndrome have sparked considerable interest in the plausible role for endogenous glucocorticoids in the pathogenesis of type 2 diabetes. 11 β HSD1 is an 11 β -reductase that catalyzes the intracellular conversion of inactive cortisone into active cortisol (1). 11 β HSD1 is expressed in specific tissues, most notably in liver, adipose, vasculature, brain, and macrophages (2,3), where it increases intracellular cortisol levels but does not participate in adrenal cortisol biosynthesis from chole-

OBJECTIVE— 11- β -hydroxysteroid dehydrogenase type 1 (11 β HSD1) converts inactive cortisone into active cortisol, thereby amplifying intracellular glucocorticoid action. The efficacy and safety of the 11 β HSD1 inhibitor INCB13739 were assessed when added to ongoing metformin monotherapy in patients with type 2 diabetes exhibiting inadequate glycemic control (A1C 7–11%).



Curcumina



Curcumin Extract for Prevention of Type 2 Diabetes

SOMLAK CHUENGSAMARN, MD^{1,2}
SUTHEE RATTANAMONGKOLGUL,⁴ MD³
RATAYA LUECHAPUDIPORN, PHD

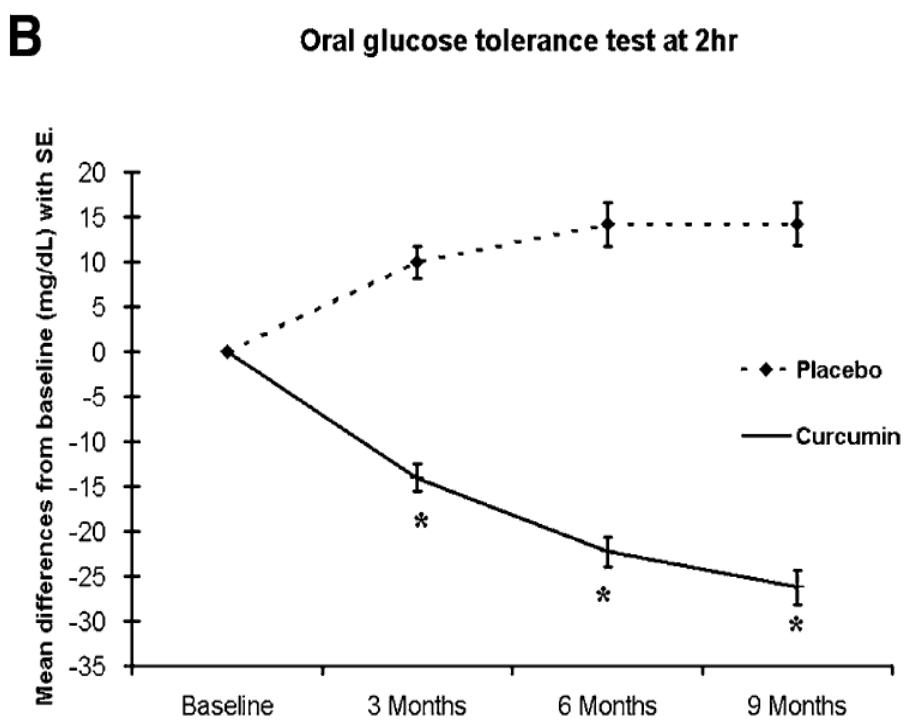
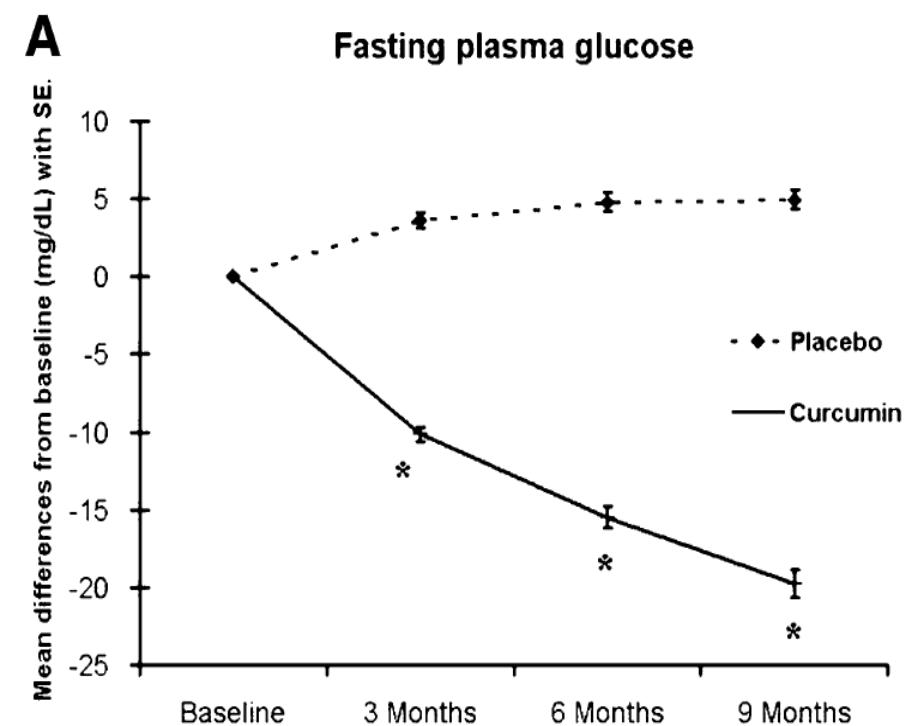
CHADA PHISALAPHONG, PHD⁵
SIWANON JIRAWATNOTAI, PHD^{6,7}

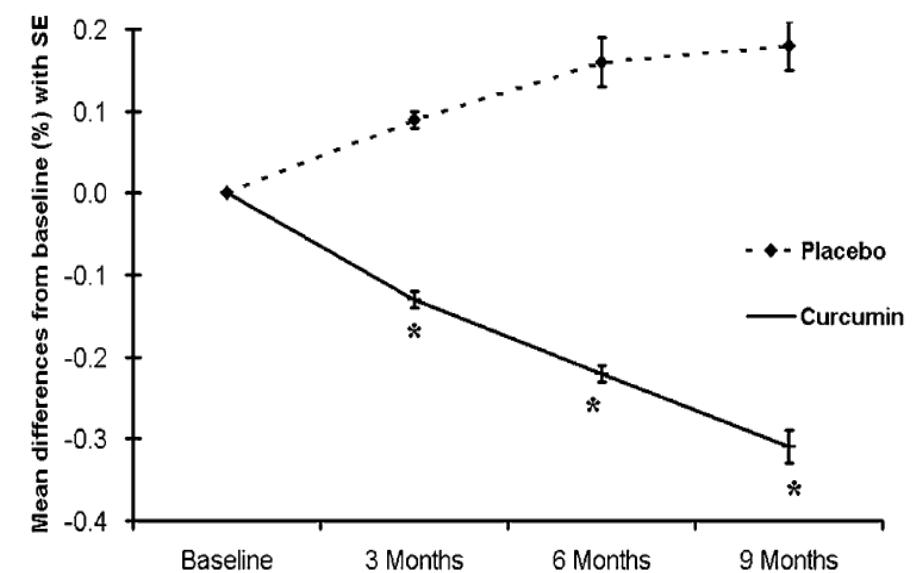
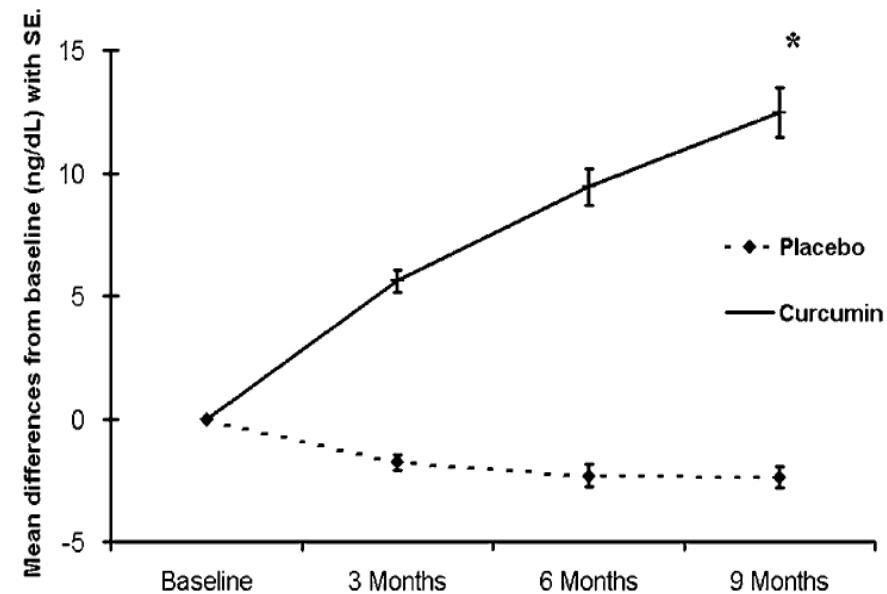
OBJECTIVE—To assess the efficacy of curcumin in delaying development of type 2 diabetes mellitus (T2DM) in the prediabetes population.

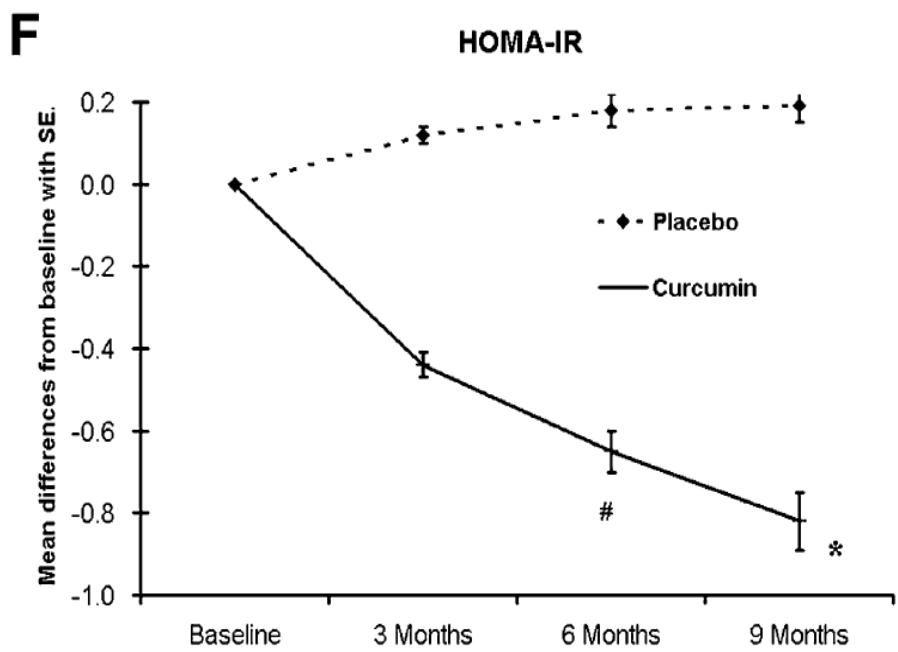
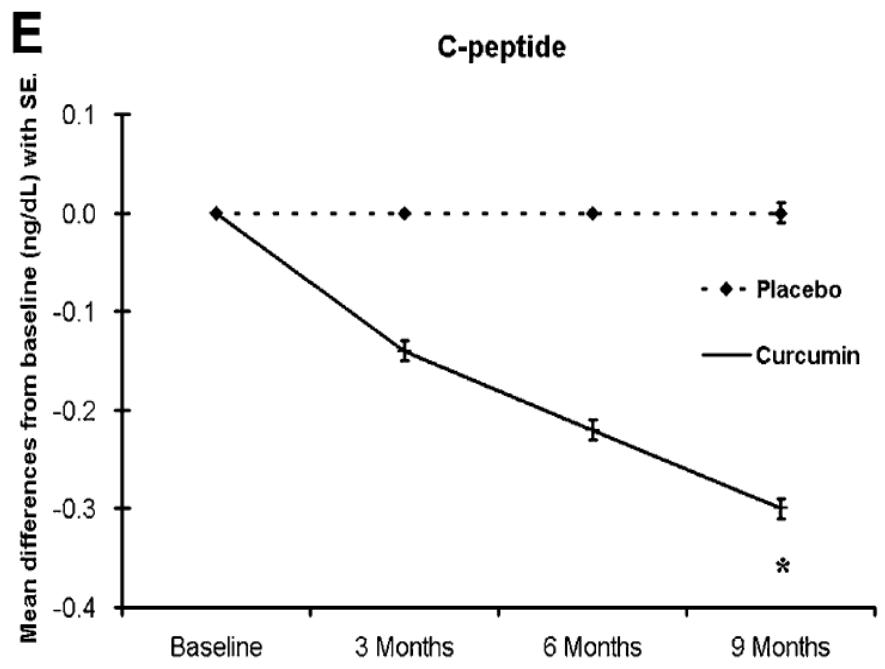
RESEARCH DESIGN AND METHODS—This randomized, double-blinded, placebo-controlled trial included subjects ($n = 240$) with criteria of prediabetes. All subjects were randomly assigned to receive either curcumin or placebo capsules for 9 months. To assess the T2DM progression after curcumin treatments and to determine the number of subjects progressing to T2DM, changes in β -cell functions (homeostasis model assessment [HOMA]- β , C-peptide, and proinsulin/insulin), insulin resistance (HOMA-IR), anti-inflammatory cytokine (adiponectin), and other parameters were monitored at the baseline and at 3-, 6-, and 9-month visits during the course of intervention.

RESULTS—After 9 months of treatment, 16.4% of subjects in the placebo group were diagnosed with T2DM, whereas none were diagnosed with T2DM in the curcumin-treated group. In addition, the curcumin-treated group showed a better overall function of β -cells, with higher HOMA- β (61.58 vs. 48.72; $P < 0.01$) and lower C-peptide (1.7 vs. 2.17; $P < 0.05$). The curcumin-treated group showed a lower level of HOMA-IR (3.22 vs. 4.04; $P < 0.001$) and higher adiponectin (22.46 vs. 18.45; $P < 0.05$) when compared with the placebo group.

CONCLUSIONS—A 9-month curcumin intervention of a prediabetes population significantly lowered the number of prediabetic individuals who eventually developed T2DM. In addition, the curcumin treatment appeared to improve overall function of β -cells, with very minor adverse effects. Therefore, this study demonstrated that the curcumin intervention in a prediabetes population may be beneficial.



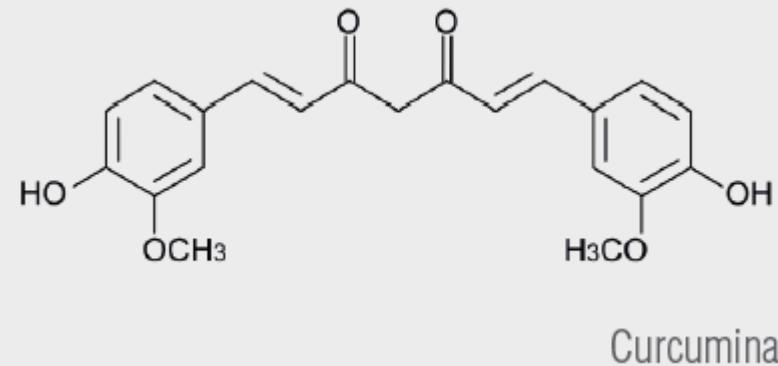
C**HbA1C****D****HOMA- β** 



The intervention

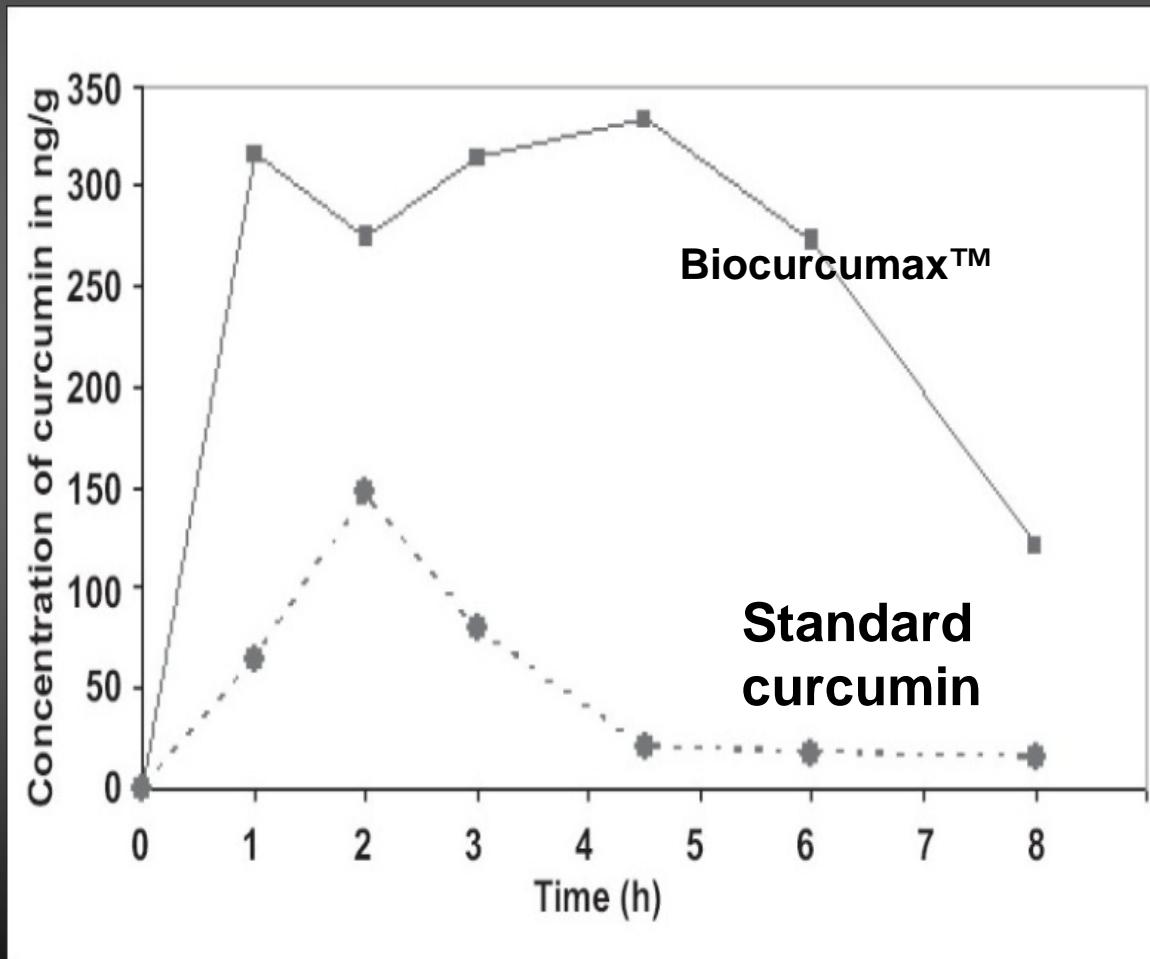
All participants were instructed to take three capsules with blinded labels of either curcumin or placebo twice a day (total of six capsules per day) for 9 months continuously. Each curcumin capsule has curcuminoid content of 250 mg. Curcumin and identical placebo cap-

**1500 mg/die per 9 mesi (6 compresse/die!)
Al giusto dosaggio...può funzionare!**



Nanoparticelle	Biodisponibilità
	Piperina Somministrazione affiancata da estratto di curcumina x 20 - 40
	Quercetina Somministrazione affiancata da estratto di curcumina x 1,8-2
	Betacyclodestrine Curcumina unita a complessi molecolari x 1,8-2
	Liposomi Miscrosfera lipidica che incapsula la curcumina x 2 - 3
	Fitosomi Microsfera lipidica con fosfolipidi uniti alla curcumina x 3 - 29
	Nanoparticelle solide lipidiche Curcumina in una matrice di particelle solide lipidiche: SLN x 65

Not all curcumins have same bioavailability: the role of sesquiterpenoids



*Indian J
Pharm Sci.*
2008;70(4):
445–449.

Research

Open Access

The use of a *Cissus quadrangularis/Irvingia gabonensis* combination in the management of weight loss: a double-blind placebo-controlled study

	Body weight (mean kg)				Weight change (%)		
	Initial	4 weeks	8 weeks	10 weeks	4 Weeks-Initial	8 Weeks-Initial	10 Weeks-Initial
Placebo	98.05 ± 12.30	98.76 ± 8.20	96.74 ± 10.60	95.99 ± 15.20	0.72	-1.33	-2.10
CQ	98.92 ± 10.60	95.77 ± 12.32 ^a	91.47 ± 8.69 ^a	90.19 ± 7.60 ^b	-3.19	-7.53 [†]	-9.82 [†]
CQ-IG	99.79 ± 13.50	95.77 ± 7.40	90.91 ± 5.72 ^{b,*}	87.95 ± 3.17 ^{c,***}	-4.02 [†]	-8.90 [†]	-11.86 [†]

	Body fat (mean %)				Fat reduction (%)		
	Initial	4 weeks	8 weeks	10 weeks	4 Weeks-Initial	8 Weeks-Initial	10 Weeks-Initial
Placebo	33.32 ± 7.60	32.37 ± 12.86	32.31 ± 10.91	32.00 ± 14.63	-2.85	-3.33	-3.97
CQ	33.07 ± 10.26	30.81 ± 5.92	29.42 ± 5.49	28.23 ± 6.12 ^a	-6.83	-11.05 [†]	-14.63 [†]
CQ-IG	35.66 ± 12.27	32.41 ± 7.91	29.53 ± 5.15	28.51 ± 4.17 ^{a,*}	-9.11 [†]	-17.19 [†]	-20.06 [†]

Research

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The use of a *Cissus quadrangularis/Irvingia gabonensis* combination in the management of weight loss: a double-blind placebo-controlled study

	Waist (mean cm)				Waist Change (%)		
	Initial	4 weeks	8 weeks	10 weeks	4 Weeks-Initial	8 Weeks-Initial	10 Weeks-Initial
Placebo	102.40 ± 16.26	101.82 ± 12.21	101.76 ± 13.30	101.37 ± 16.55	-0.56	-0.63	-1.00
CQ	99.83 ± 13.38	97.10 ± 18.57	93.81 ± 10.70 ^a	91.20 ± 7.6 ^b	-2.73	-6.03 [†]	-8.64 [†]
CQ-IG	104.30 ± 23.10	98.28 ± 17.41	96.00 ± 12.20 ^{b**}	82.42 ± 3.88 ^{c***}	-5.77 [†]	-7.96 [†]	-20.98 [†]

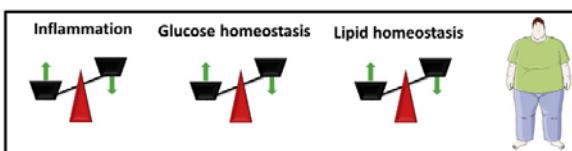
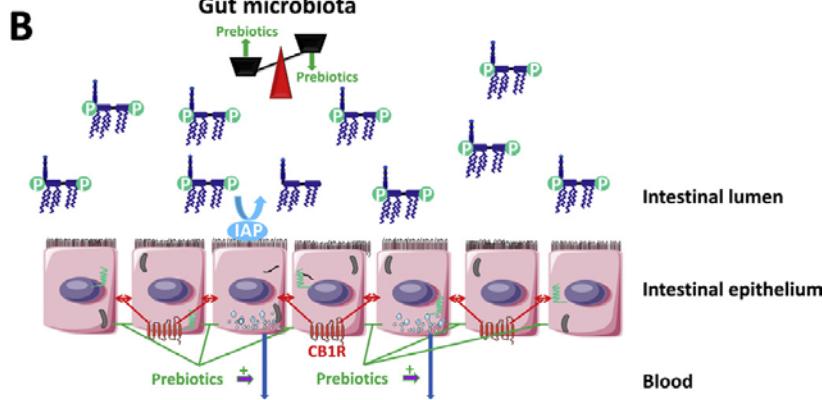
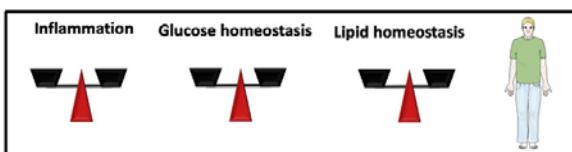
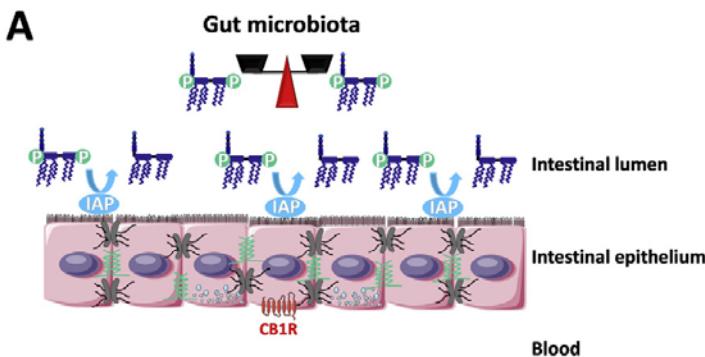
	Blood glucose (mean mg/dL)				Change (%)		
	Initial	4 weeks	8 weeks	10 weeks	4 Weeks-Initial	8 Weeks-Initial	10 Weeks-Initial
Placebo	79.43 ± 11.63	78.34 ± 10.41	76.53 ± 10.42	77.32 ± 8.90	-1.37	-3.67	-2.65
CQ	80.32 ± 8.45	71.56 ± 5.28 ^a	70.30 ± 9.40 ^a	68.38 ± 7.78 ^b	-10.90 [†]	-12.47 [†]	-14.85 [†]
CQ-IG	87.68 ± 6.32	68.32 ± 11.11 ^{b*}	65.47 ± 8.31 ^{b**}	60.11 ± 4.31 ^{b***}	-22.07 [†]	-25.32 [†]	-31.44 [†]

& Research Clinical Gastroenterology 27 (2013) 73–83

7

Diabetes, obesity and gut microbiota

Amandine Everard, M.Sc., Pharm,
Patrice D. Cani, PhD, Professor *



Enterocytes
 L cell
 Lipopolysaccharides phosphorylated
 IAP Intestinal Alkaline Phosphatase
 Claudin 3
 Zonula occludens 1
 Occludin
 Effects of prebiotic treatment
 Lipopolysaccharides dephosphorylated

Practice points

- Gut microbiota composition is directly dependent on nutrient intake (e.g., fat, digestibility of carbohydrates)
- Metabolic endotoxaemia and gut barrier dysfunction are involved in the onset of metabolic diseases associated with obesity
- Prebiotic-induced changes in the gut microbiota improve glucose, lipid and inflammation homeostasis

Research agenda

- The exact taxonomic composition of the gut microbiota or associated metabolic functions needs to be defined to design novel targeted approaches
- Detailed studies are necessary to study gut permeability and related gut barrier dysfunctions in obese and type 2 diabetic patients
- The role of 'novel' beneficial microbes (e.g., *F. prausnitzii* and *A. muciniphila*) as therapeutic tools warrants controlled human studies

reserved.

TOPIC HIGHLIGHT

Table 3 Studies conducted on humans showing effects of probiotics on metabolic disorders

teine levels

Table 5 Studies conducted on humans showing effects of prebiotics on metabolic disorders

Research

Open Access

The use of a *Cissus quadrangularis/Irvingia gabonensis* combination in the management of weight loss: a double-blind placebo-controlled study

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CQ-IG	99.79 ± 13.50	95.77 ± 7.40	90.91 ± 5.72 ^{b,*}	87.95 ± 3.17 ^{c,***}	-4.02 [†]	-8.90 [†]	-11.86 [†]

	Body fat (mean %)				Fat reduction (%)		
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Placebo	33.32 ± 7.60	32.37 ± 12.86	32.31 ± 10.91	32.00 ± 14.63	-2.85	-3.33	-3.97
CQ	33.07 ± 10.26	30.81 ± 5.92	29.42 ± 5.49	28.23 ± 6.12 ^a	-6.83	-11.05 [†]	-14.63 [†]
CQ-IG	35.66 ± 12.27	32.41 ± 7.91	29.53 ± 5.15	28.51 ± 4.17 ^{a,*}	-9.11 [†]	-17.19 [†]	-20.06 [†]

Research

Open Access

The use of a *Cissus quadrangularis/Irvingia gabonensis* combination in the management of weight loss: a double-blind placebo-controlled study

	Waist (mean cm)				Waist Change (%)		
	Initial	4 weeks	8 weeks	10 weeks	4 Weeks-Initial	8 Weeks-Initial	10 Weeks-Initial
Placebo	102.40 ± 16.26	101.82 ± 12.21	101.76 ± 13.30	101.37 ± 16.55	-0.56	-0.63	-1.00
CQ	99.83 ± 13.38	97.10 ± 18.57	93.81 ± 10.70 ^a	91.20 ± 7.6 ^b	-2.73	-6.03 [†]	-8.64 [†]
CQ-IG	104.30 ± 23.10	98.28 ± 17.41	96.00 ± 12.20 ^{b**}	82.42 ± 3.88 ^{c***}	-5.77 [†]	-7.96 [†]	-20.98 [†]

	Blood glucose (mean mg/dL)				Change (%)		
	Initial	4 weeks	8 weeks	10 weeks	4 Weeks-Initial	8 Weeks-Initial	10 Weeks-Initial
Placebo	79.43 ± 11.63	78.34 ± 10.41	76.53 ± 10.42	77.32 ± 8.90	-1.37	-3.67	-2.65
CQ	80.32 ± 8.45	71.56 ± 5.28 ^a	70.30 ± 9.40 ^a	68.38 ± 7.78 ^b	-10.90 [†]	-12.47 [†]	-14.85 [†]
CQ-IG	87.68 ± 6.32	68.32 ± 11.11 ^{b*}	65.47 ± 8.31 ^{b**}	60.11 ± 4.31 ^{b***}	-22.07 [†]	-25.32 [†]	-31.44 [†]

Rari casi di epatotossicità da *Garcinia cambogia* (acido idrossicitrico)

Weight loss supplement	N	Clinical features	Predominant pattern of injury	Underwent transplantation
Hydroxycut				
Stevens <i>et al.</i>	2	Fatigue, jaundice	Hepatocellular and cholestatic	0
Fong <i>et al.</i>	8	Nausea, vomiting, abdominal pain	Hepatocellular	3
Jones	1	Nausea, vomiting, and jaundice	Hepatocellular	0
Shim	1	Fatigue, jaundice	Hepatocellular	0
Laczek	3	Malaise, jaundice	Hepatocellular	0
Dara	2	Nausea, vomiting, fatigue, abdominal pain	Hepatocellular	0
Kaswala	1	Nausea, vomiting, abdominal pain, jaundice	Hepatocellular	0
OxyElite Pro				
Roitman <i>et al.</i>	8	Nausea, fatigue, abdominal pain, jaundice	Hepatocellular	2
Foley <i>et al.</i>	7	Nausea, vomiting, jaundice, abdominal pain	Hepatocellular	1

Esempi negativi

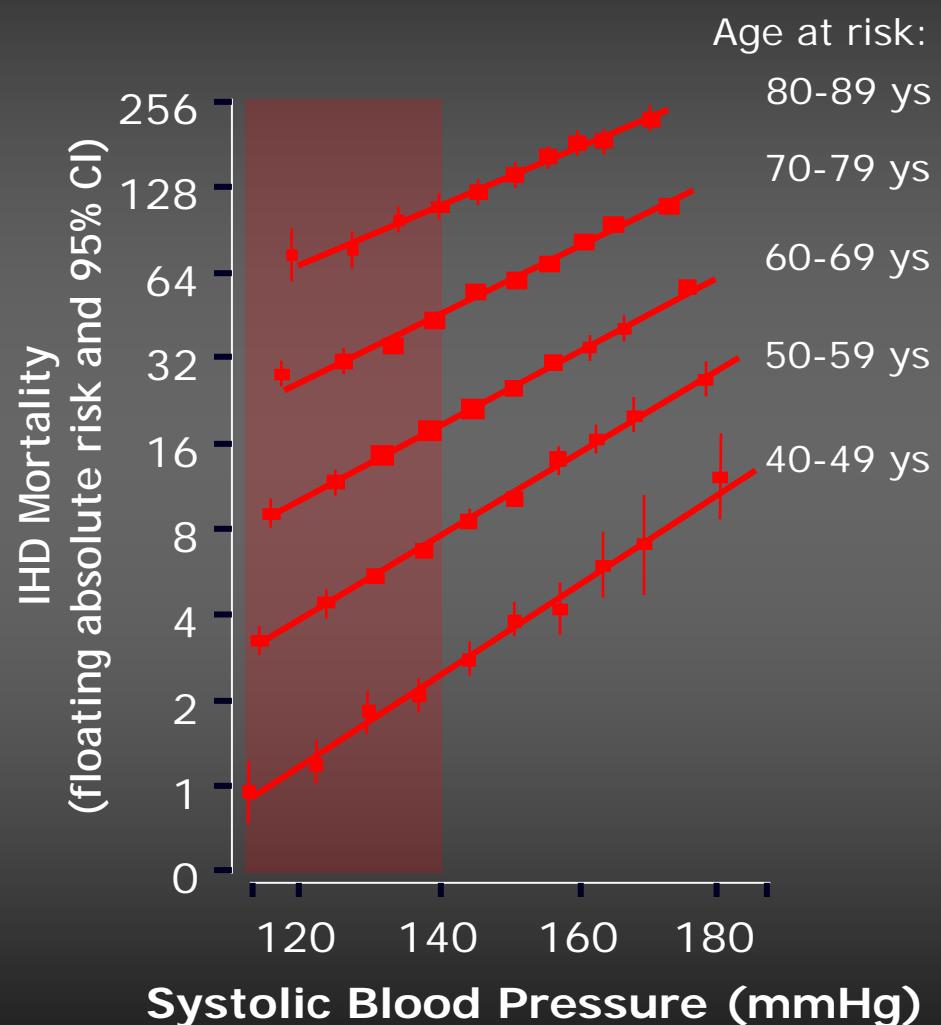
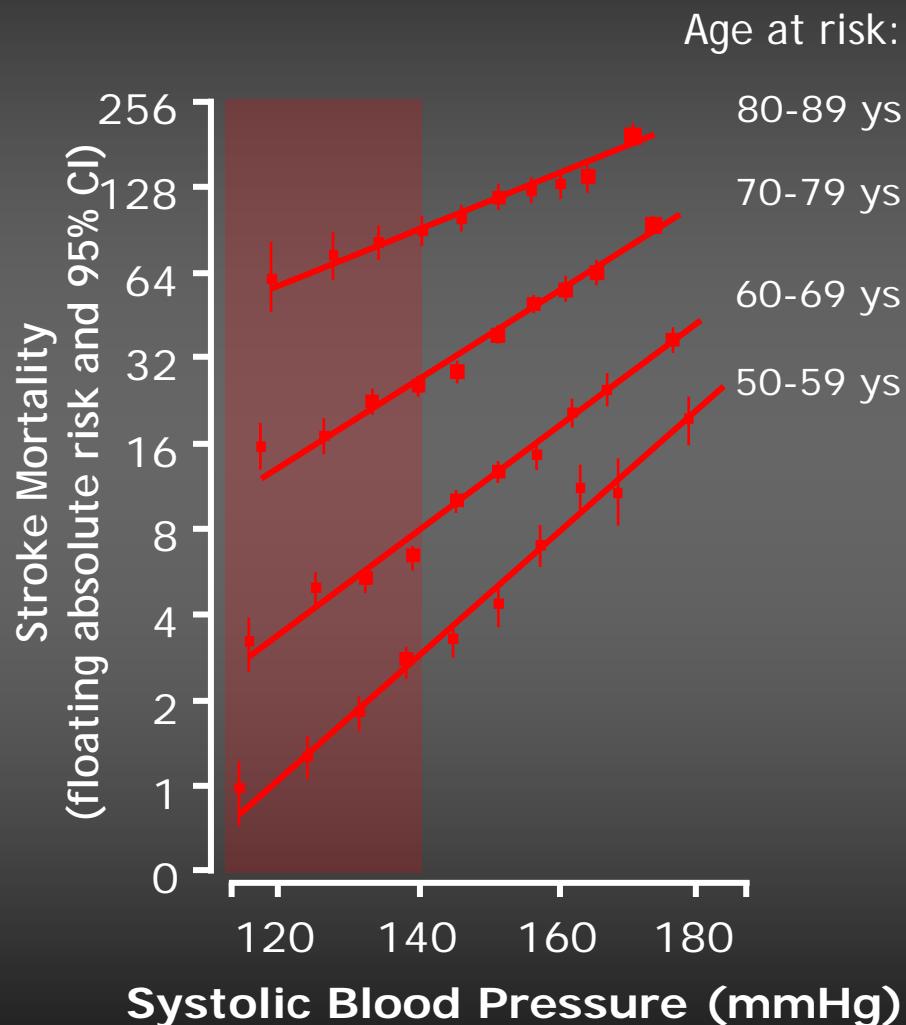
- Lassativi
- Diuretici (“Drenanti”)
- Prodotti contenenti iodio
 (“stimolanti della
 tiroide”)/Estratti di tiroide

Iipertensione e nutraceutica: Nessuno ci lavora ma ...

- L'ipertensione è fortemente prevalente: 30% degli ultracinquantenni, 50% degli ultrasessantenni, 80% degli ultrasettantenni
- Si riconosce con test economico e non invasivo
- Piccole modificazioni di PA coincidono con importanti vantaggi preventivi
- Esiste tanta letteratura sui nutraceutici



CHD and Stroke mortality vs BP by age



BP lowering nutraceuticals

Dietary supplement/Nutraceuticals	Level of evidence
• Polyunsaturated fatty acids (high dosages)	Meta-analysis of RCTs
• Isoflavones	Meta-analysis of RCTs
• Lactotripeptides	Meta-analysis of RCTs
• Fish peptides	Different small RCTs
• L-Arginine (high dosages)	Meta-analysis of RCTs
• Potassium	Different RCTs
• Chelated magnesium	Meta-analysis of RCTs
• Calcium (in pregnancy)	Meta-analysis of RCTs
• Vitamin C	Meta-analysis of RCTs
• Cocoa flavonoids	Meta-analysis of RCTs
• Hibiscus sabdariffa teas	Meta-analysis of RCTs
• Coenzyme Q10 (high dosage in hypertensives)	Meta-analysis of RCTs
• Lycopene	Meta-analysis of RCTs
• CR melatonin (night hypertension)	Meta-analysis of RCTs
• Aged garlic extract	Meta-analysis of RCTs

Nutraceutica ed ipertensione

- Punti di forza
 - Ottima conoscenza dei meccanismi d' azione
 - Numerosa e forte letteratura clinica
-
- Punti di debolezza
 - Grande variabilità di tipologie di paziente iperteso
 - Pochi trials su outcomes «importanti»

BP lowering nutraceuticals supported by meta-analyses of RCTs

- Polyunsaturated fatty acids
- Isoflavones
- Lactotripeptides
- Resveratrol
- L-Arginine
- Potassium
- Chelated magnesium
- Calcium
- Vitamin C
- Cocoa flavonoids
- Beet juice
- Hibiscus sabdariffa teas
- Coenzyme Q10
- Lycopene
- CR melatonin
- Aged garlic extract

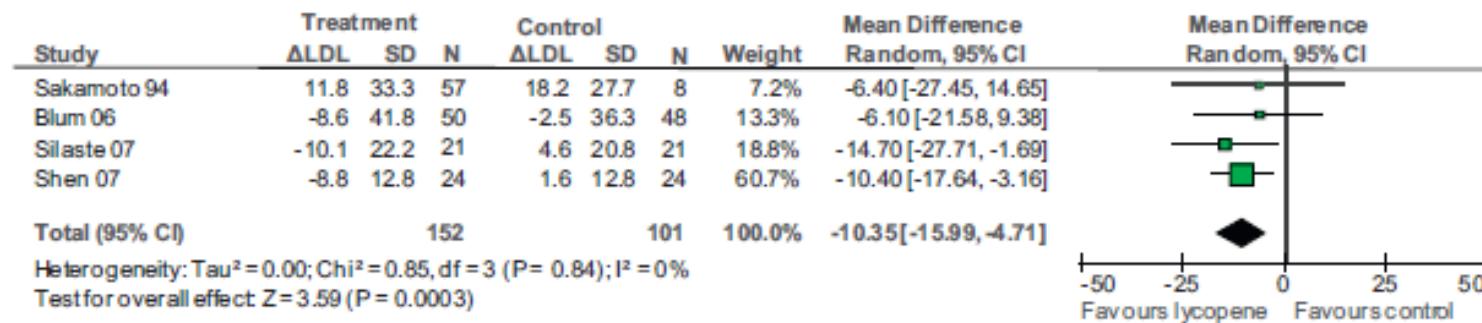
Problems with BP lowering

nutraceuticals

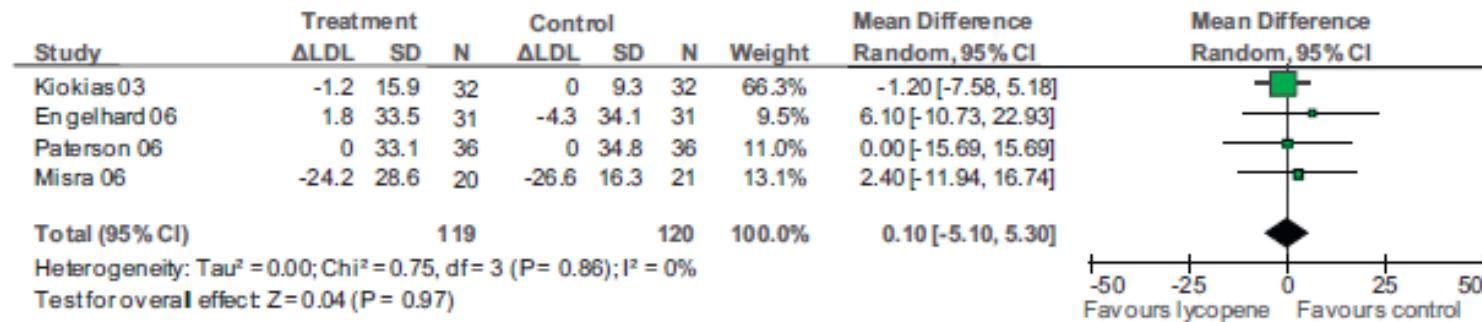
• Polyunsaturated fatty acids	High dosage, high costs, ADRs
• Isoflavones	Limited to peri-menopausal women
• Lactotripeptides	Limited to Asians, high cost
• Resveratrol	High dosage, high costs
• L-Arginine	High dosages, ADRs
• Potassium	Risk in CKD
• Chelated magnesium	Risk in CKD
• Calcium	Limited to pregnancy
• Vitamin C	High variability of available formulation
• Cocoa flavonoids	High cost, low palatability
• Beet juice	Low palatability, high dosages
• Hibiscus sabdariffa teas	Trials not replicated outside Middle-East
• Coenzyme Q10	Limited to hypertensives, high dosages
• Lycopene	High dosages, high costs
• CR melatonin	Legal problems, Limited to night hypertension
• Aged garlic extract	ADRs

LYCOPENE, LDL-C and BP: a meta-analysis of RCTs

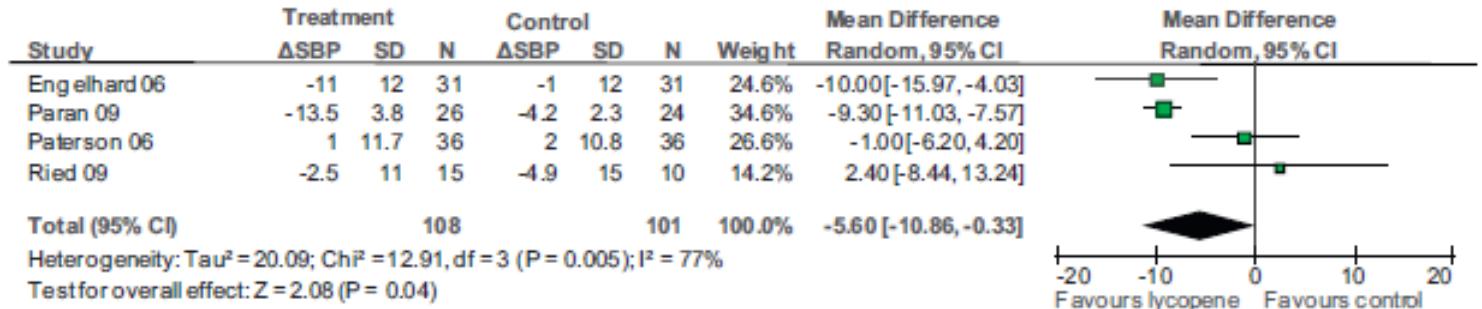
C LDL cholesterol, high dose lycopene



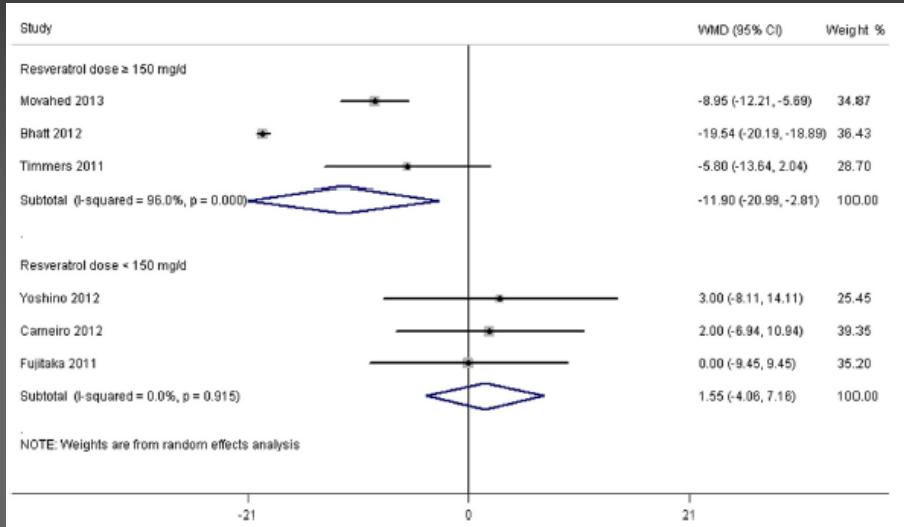
D LDL cholesterol, low dose lycopene



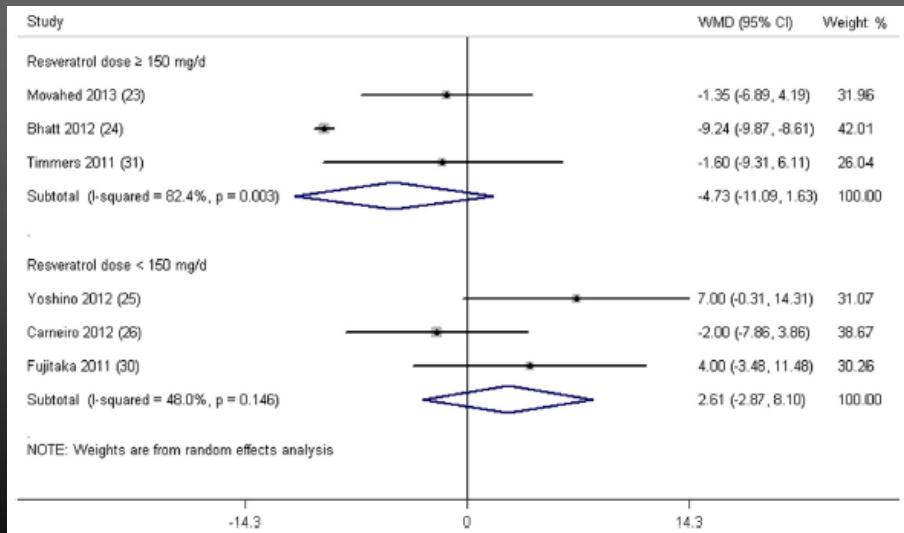
A SBP all studies



Resveratolo e pressione



$\rightarrow -12 \text{ mmHg}$

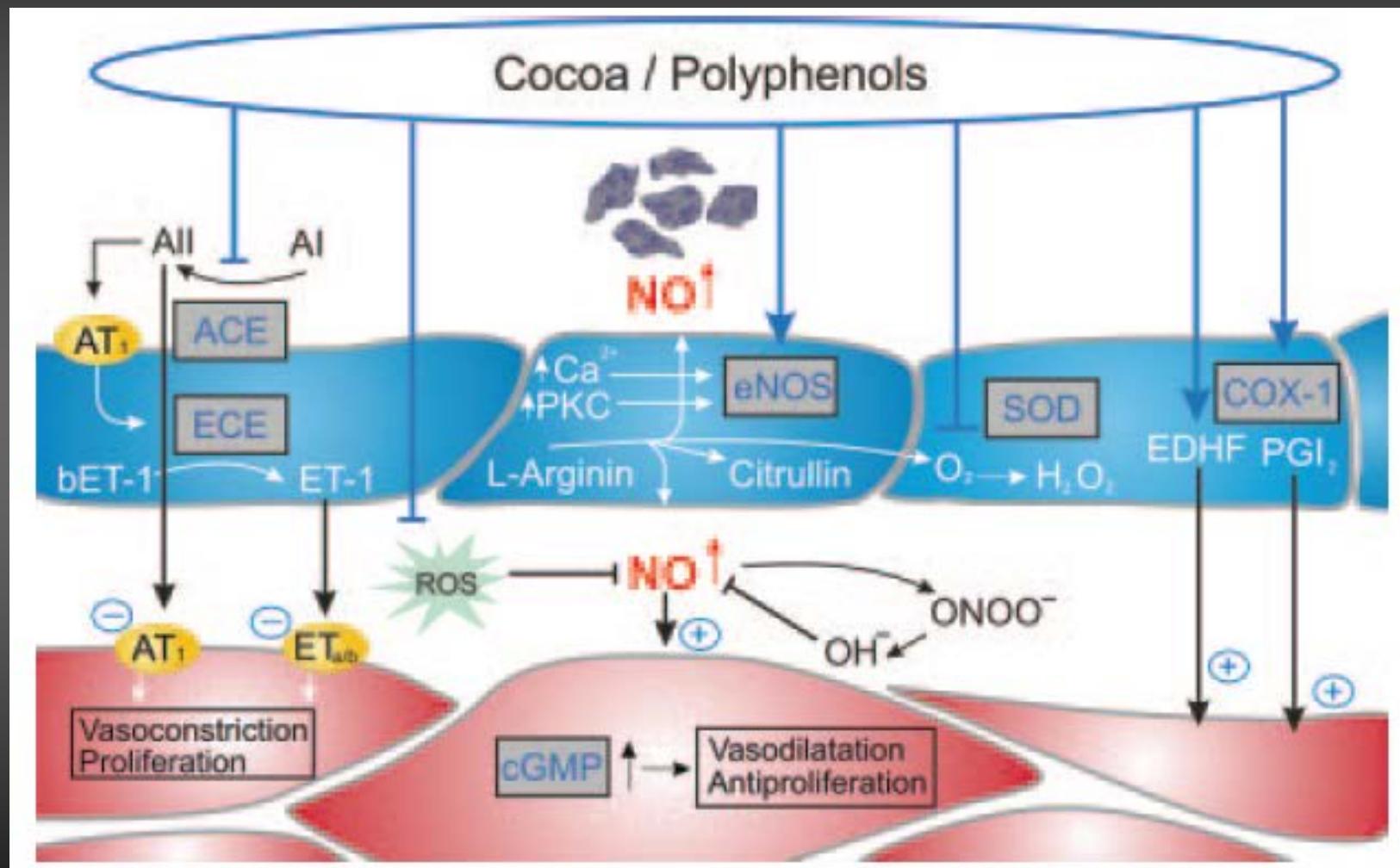


$\rightarrow -5 \text{ mmHg}$

nibo 2007

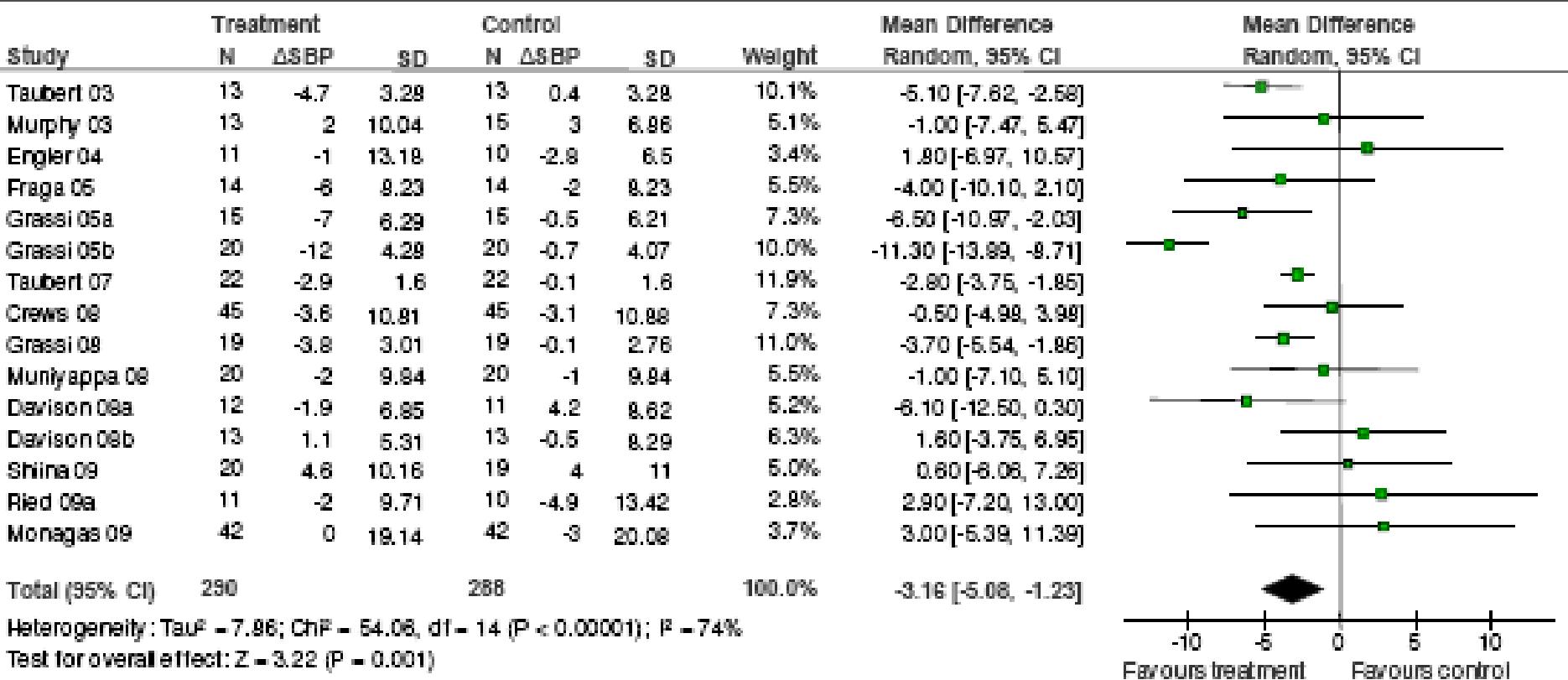
Clin Nutr. 2015;
34(1):27-34.

Effetti endotelio dipendenti dei polifenoli del cioccolato

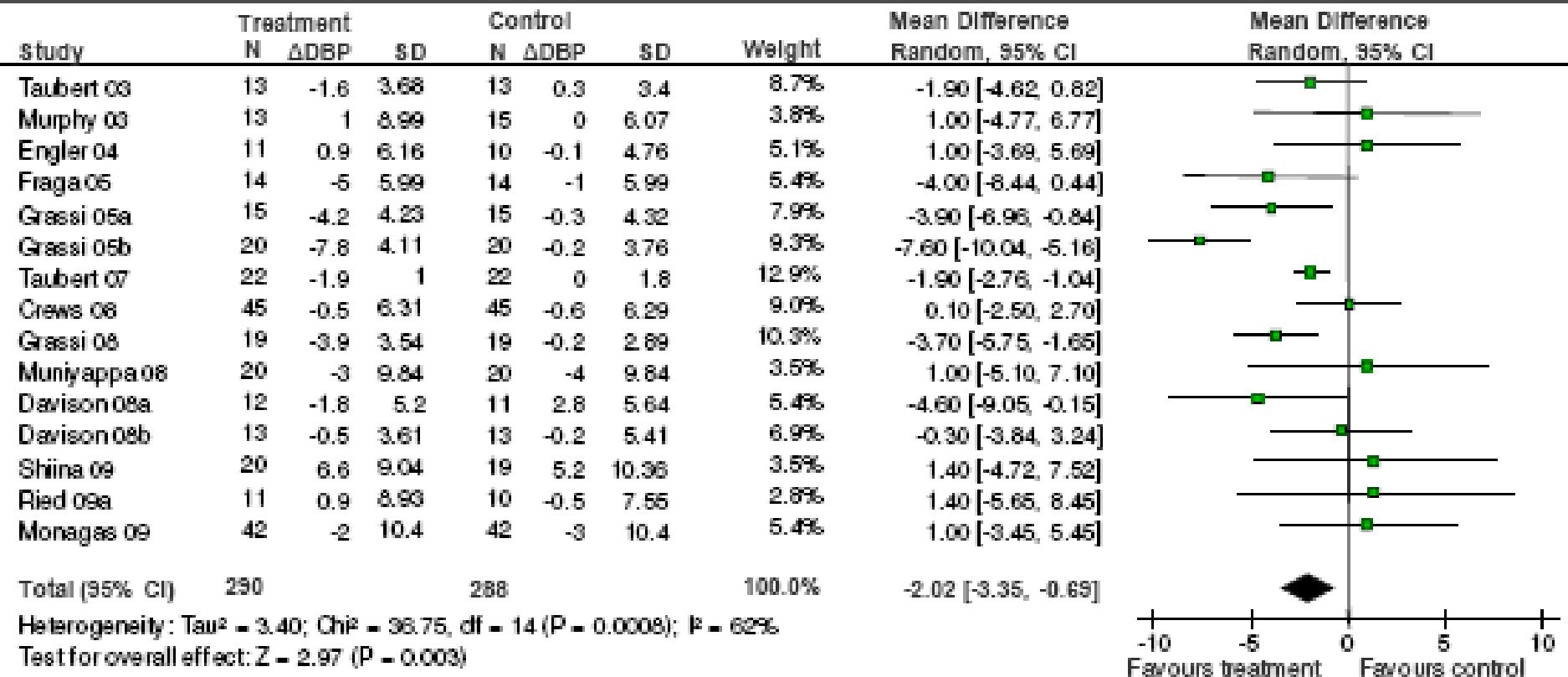


Corti R et al. Circulation. 2009;119:1433-41

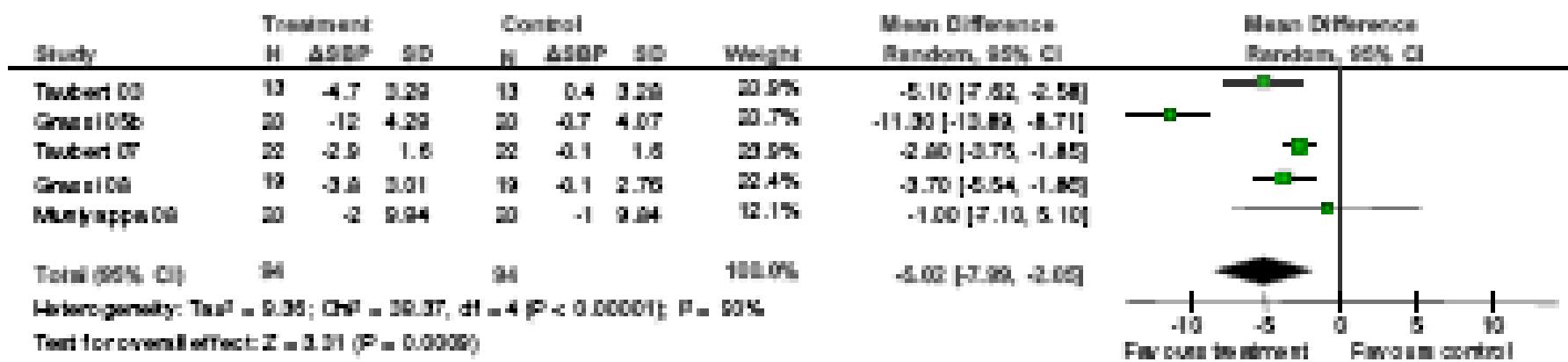
Cioccolato e pressione sistolica



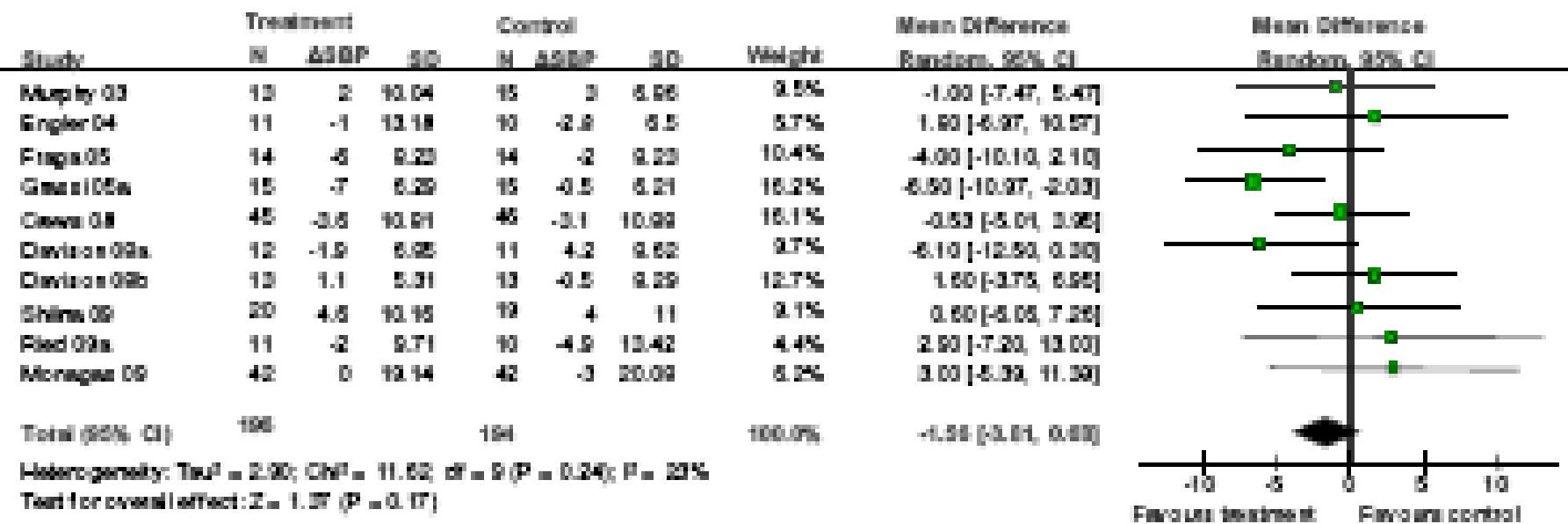
Cioccolato e pressione diastolica



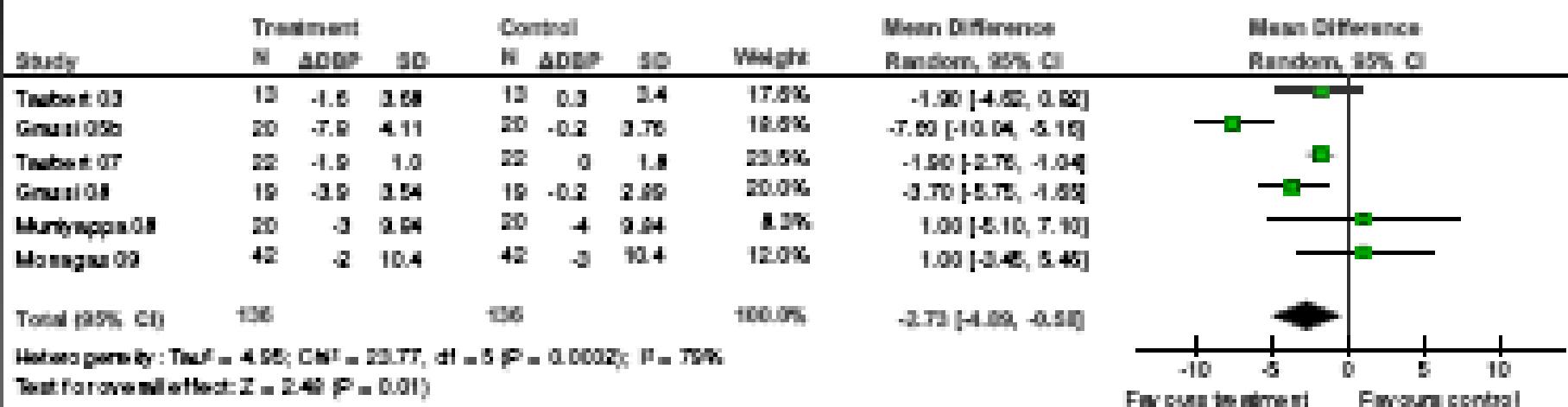
A) SBP hypertensive subgroup (≥ 140 mm Hg)



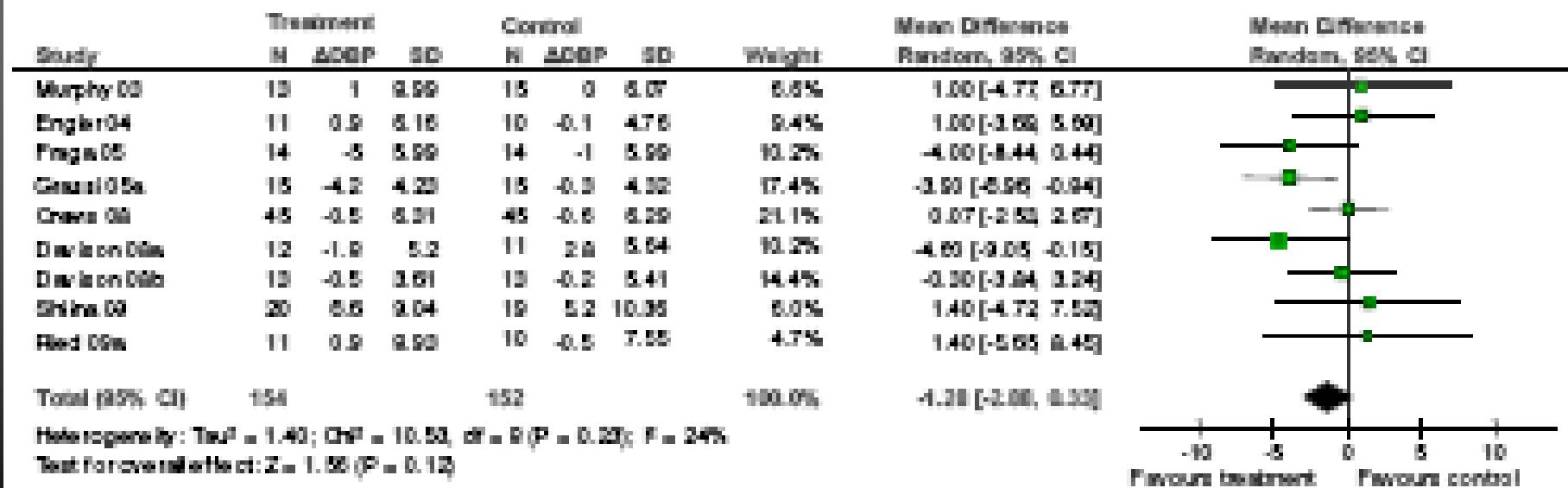
B) SBP nonhypertensive subgroup (< 140 mm Hg)



C) DBP (pre-) hypertensives subgroup (≥ 80 mm Hg)



D) DBP normotensives subgroup (< 80 mm Hg)





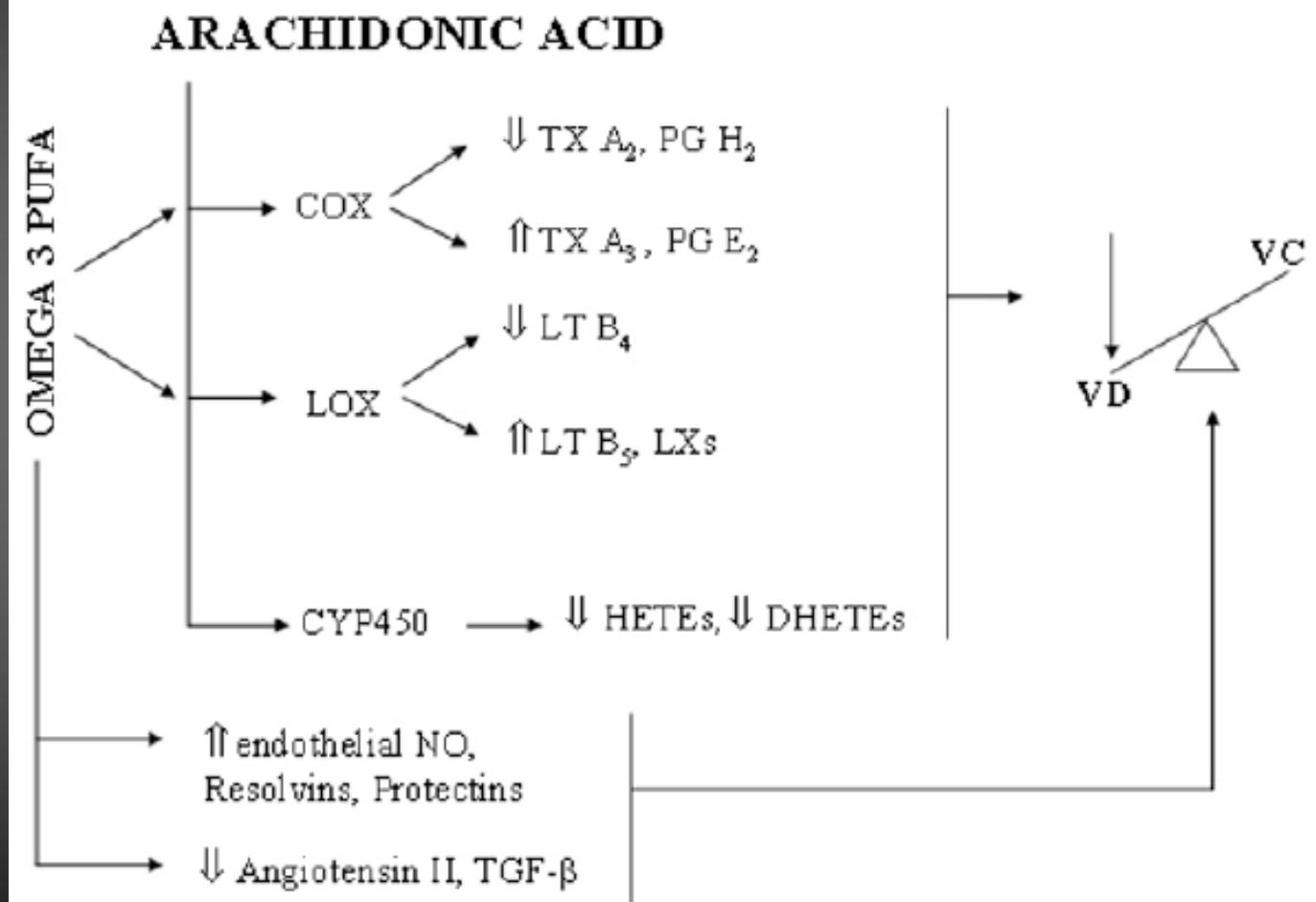
The effect depends on age !

THE COCHRANE
COLLABORATION®

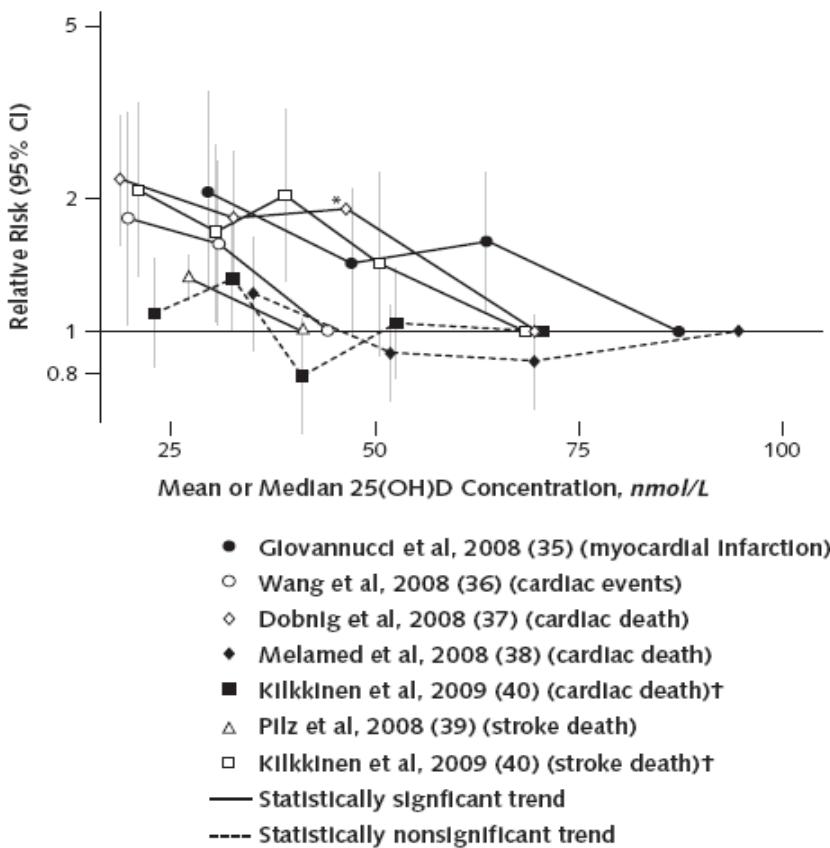
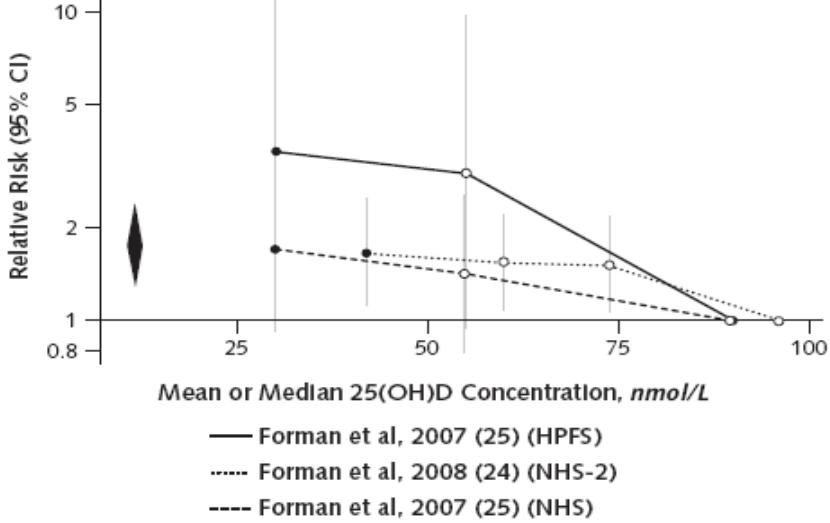
	< 50yrs	> 50yrs
Mean difference SBP (95% CI)	-4.57 (7.41, -1.73) mm Hg, p=0.002, n=10	-0.96 (-3.44, 1.52) mm Hg, p=0.45, n=10
Mean difference DBP (95% CI)	-3.85 (-5.45, -2.26) mm Hg, p<0.001, n=9	-0.89 (-1.80, 0.01) mm Hg, p=0.05, n=10

*Cochrane Database of Systematic
Reviews 2012, Issue 8. Art. No.: CD008893.*

Omega 3 PUFAs and BP



-3 mmHg
SBP
- 2.5
mmHg
DBP



Concentrazione sierica di Vitamina D ed incidenza di ipertensione e malattia cardiovascolare in studi epidemiologici

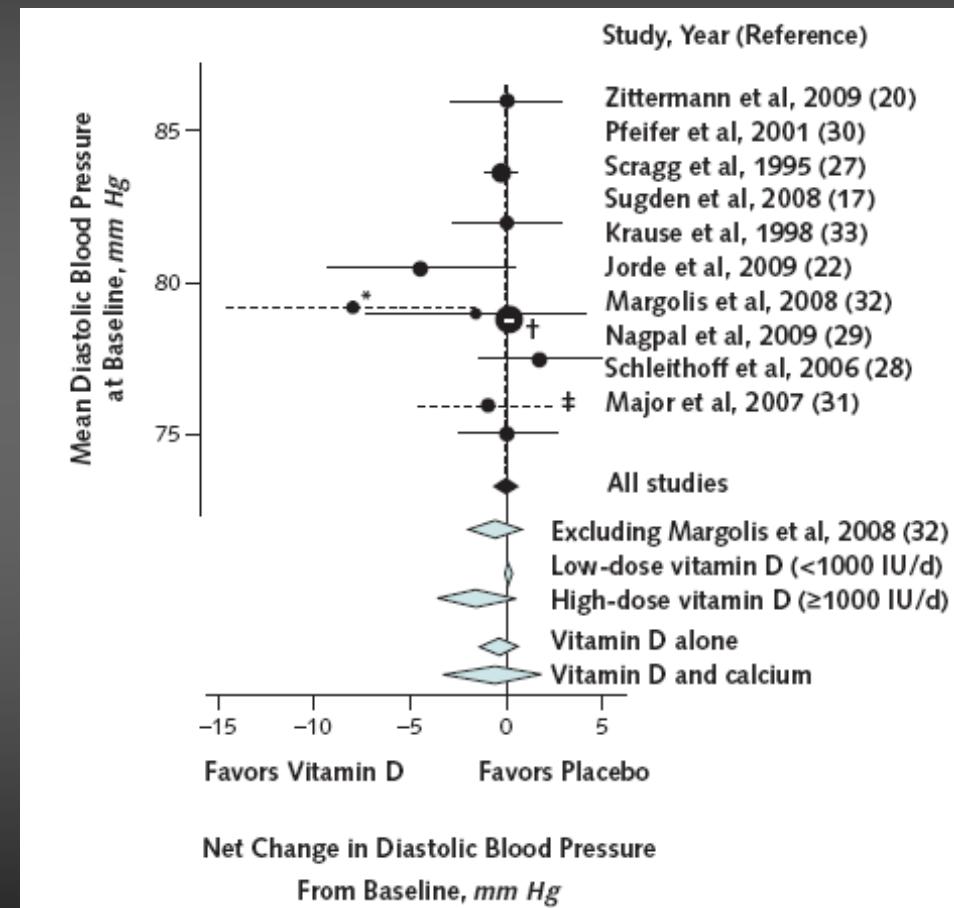
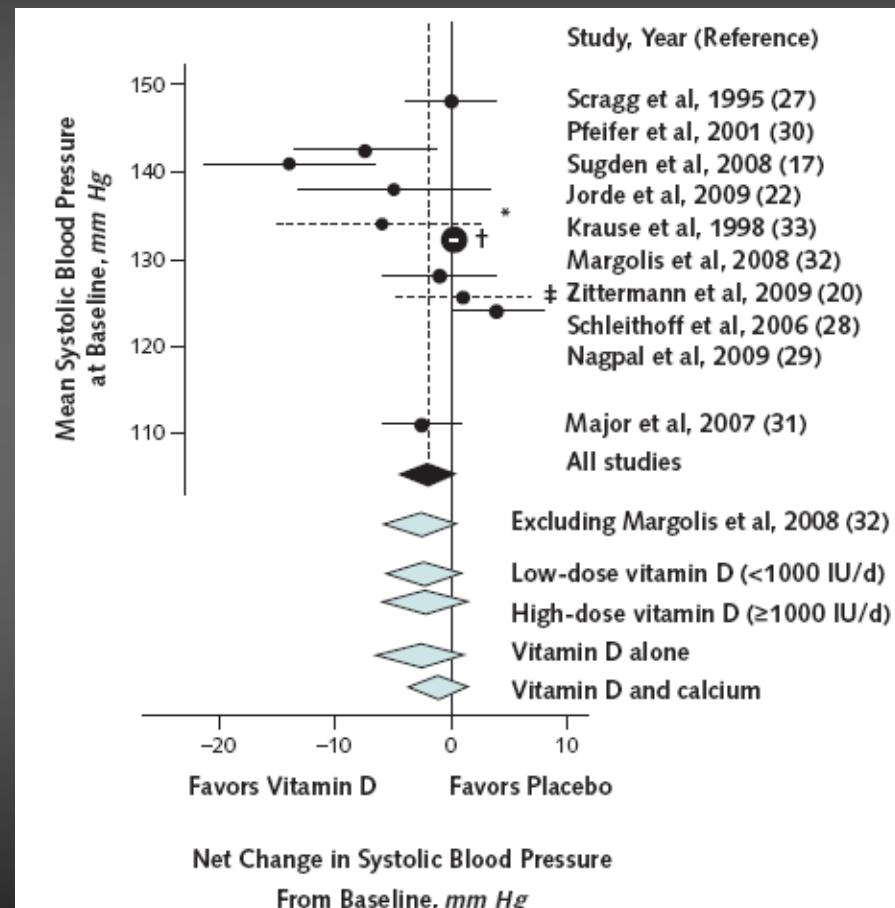
Pittas et al. Ann Intern Med.
2010;152:307-314

Vitamin D and Vascular Disease: The Current and Future Status of Vitamin D Therapy in Hypertension and Kidney Disease

Anand Vaidya · John P. Forman

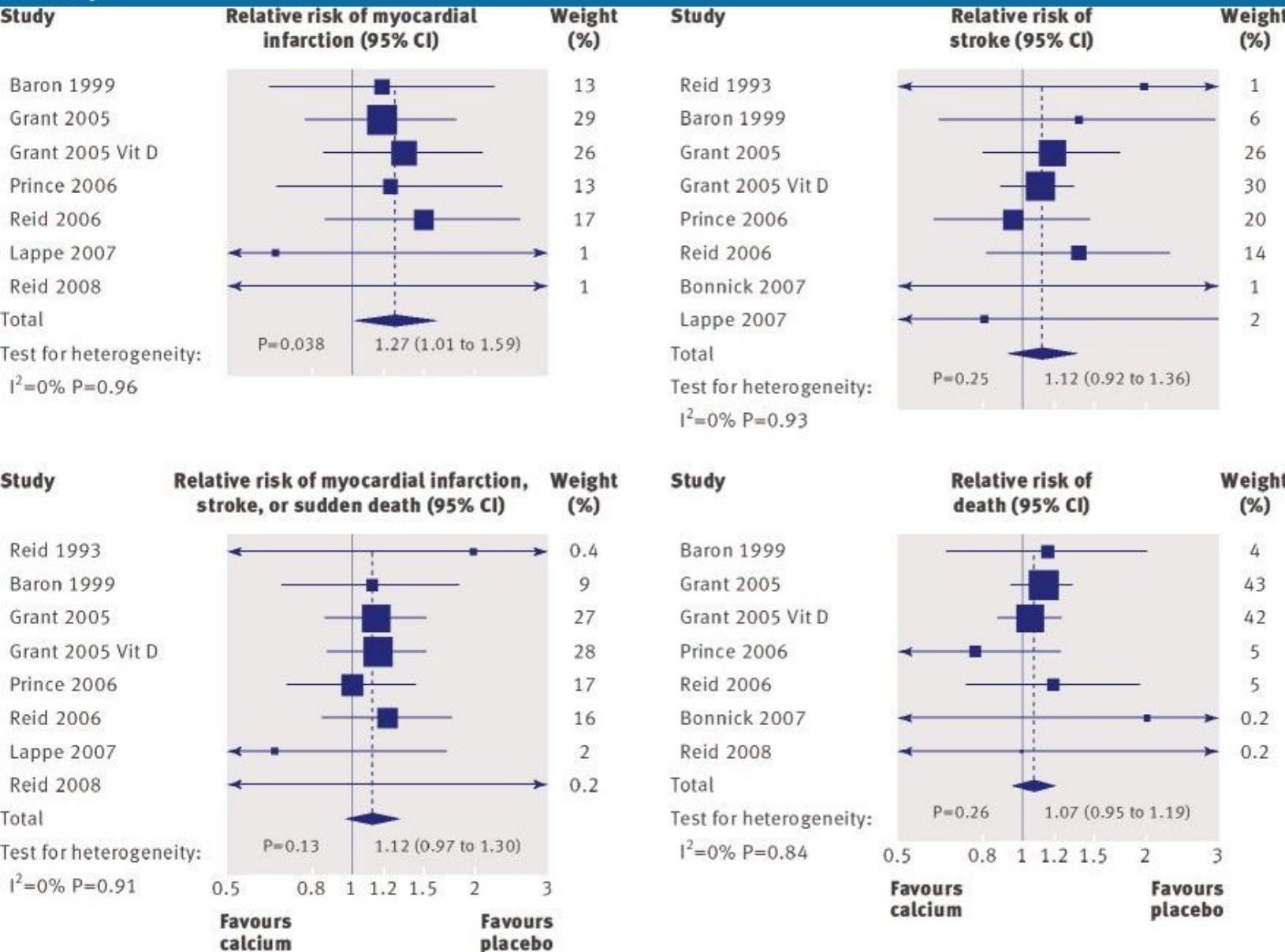
Study	Year	N	Intervention	Duration	Significant decrease in proteinuria
Agarwal et al. [84]	2008	220 (CKD stages 3–4)	Paricalcitol	≤6 months	Yes
Alborzi et al. [85]	2008	24 (CKD stages 2–3)	Paricalcitol	1 month	Yes
Szeto et al. [86]	2008	10 (IgA nephropathy)	Calcitriol	12 weeks	Yes
Fishbane et al. [87]	2009	61 (CKD stages 2–4)	Paricalcitol	6 months	Yes
de Zeeuw et al. [88•]	2010	281 (CKD stages 2–4)	Paricalcitol	6 months	Yes

Metanalisi degli studi di intervento



Il calcio da solo ...

Medscape

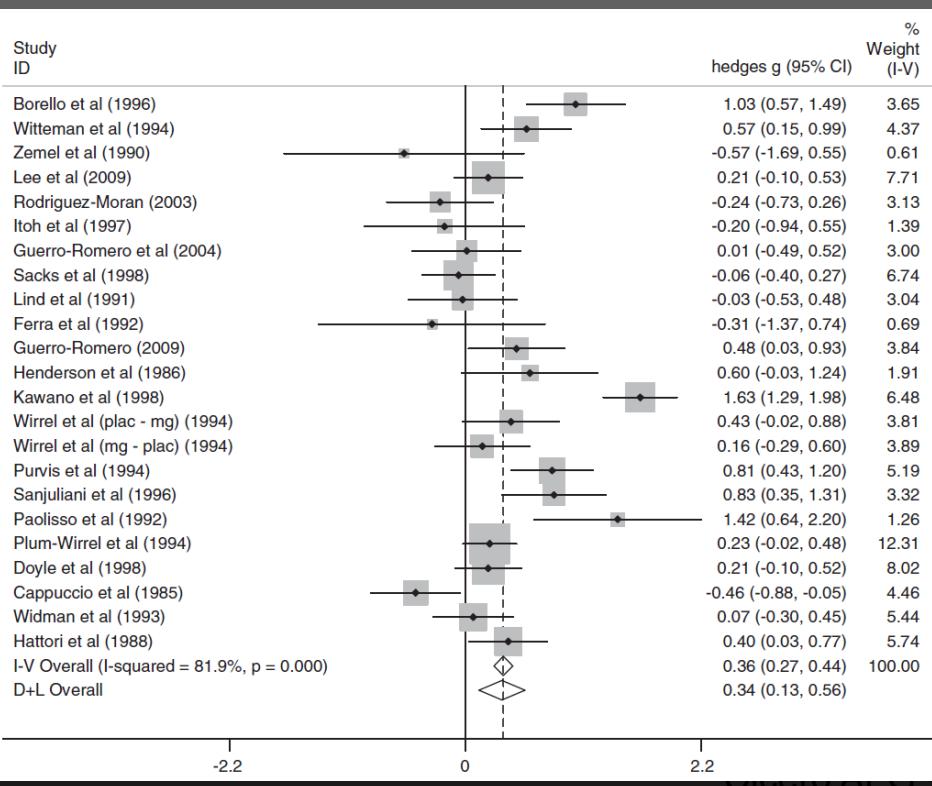


Bolland MJ
et al. BMJ
2010;
341:c3691

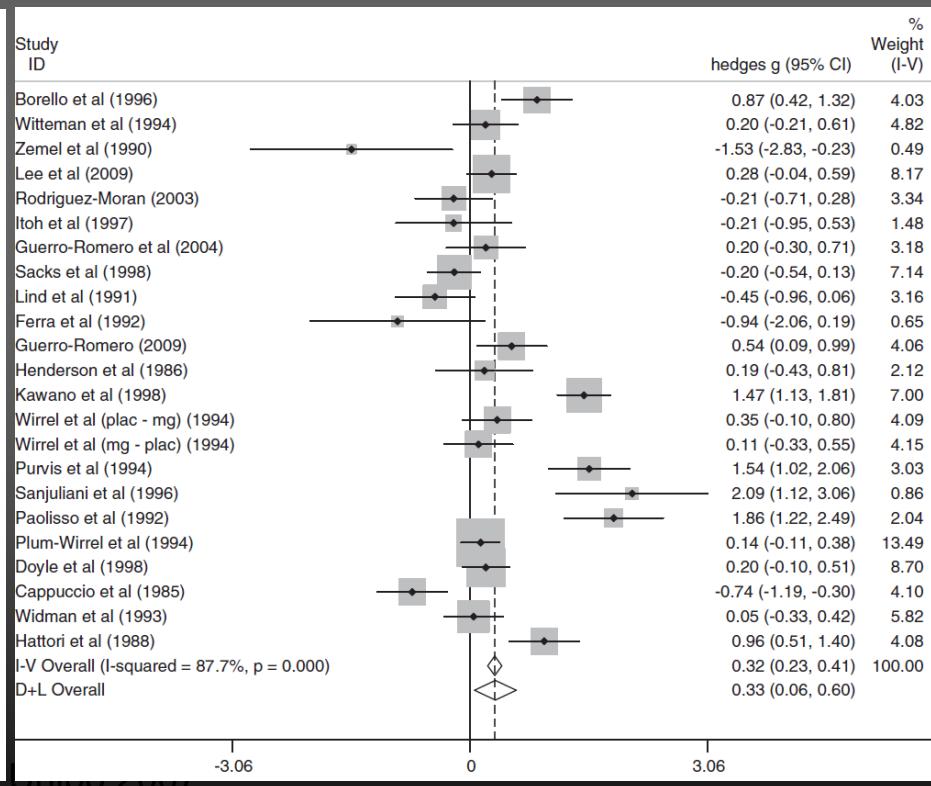
SYSTEMATIC REVIEW

Effect of magnesium supplementation on blood pressure: a meta-analysis

L Kass¹, J Weekes¹ and L Carpenter²



SBP



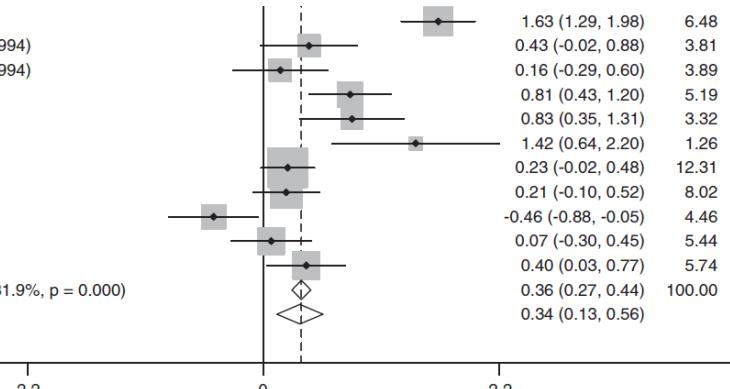
DBP

SYSTEMATIC REVIEW

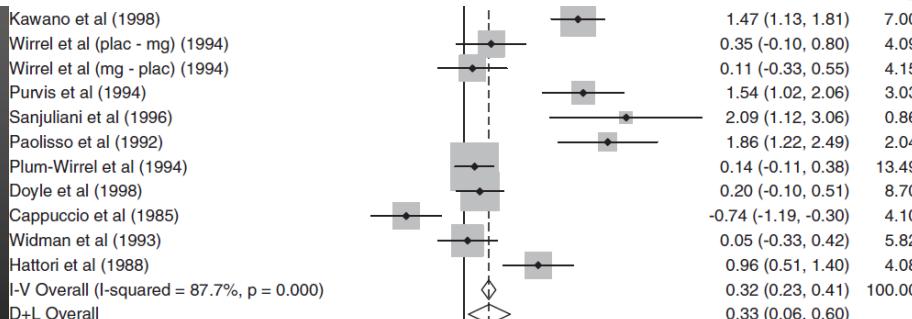
Effect of magnesium supplementation on blood pressure: a meta-analysis

Combining all trials did show a decrease in SBP of 3-4mmHg and DBP of 2-3mmHg,
which further increased with crossover
designed trials and intake >370 mg/day

Kawano et al (1998)
Wirrel et al (plac - mg) (1994)
Wirrel et al (mg - plac) (1994)
Purvis et al (1994)
Sanjuliani et al (1996)
Paolisso et al (1992)
Plum-Wirrel et al (1994)
Doyle et al (1998)
Cappuccio et al (1985)
Widman et al (1993)
Hattori et al (1988)
I-V Overall (I-squared = 81.9%, p = 0.000)
D+L Overall



SBP

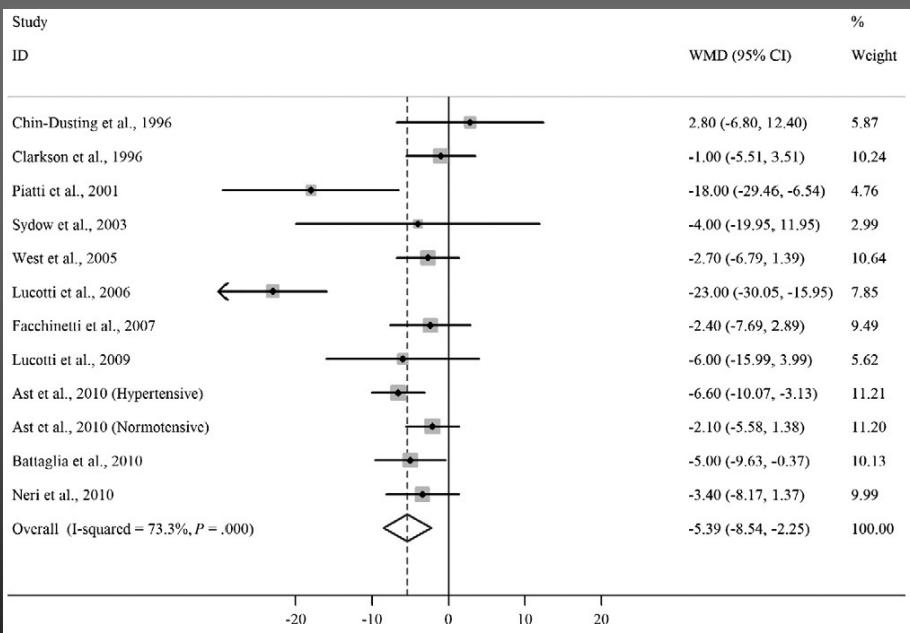


DBP

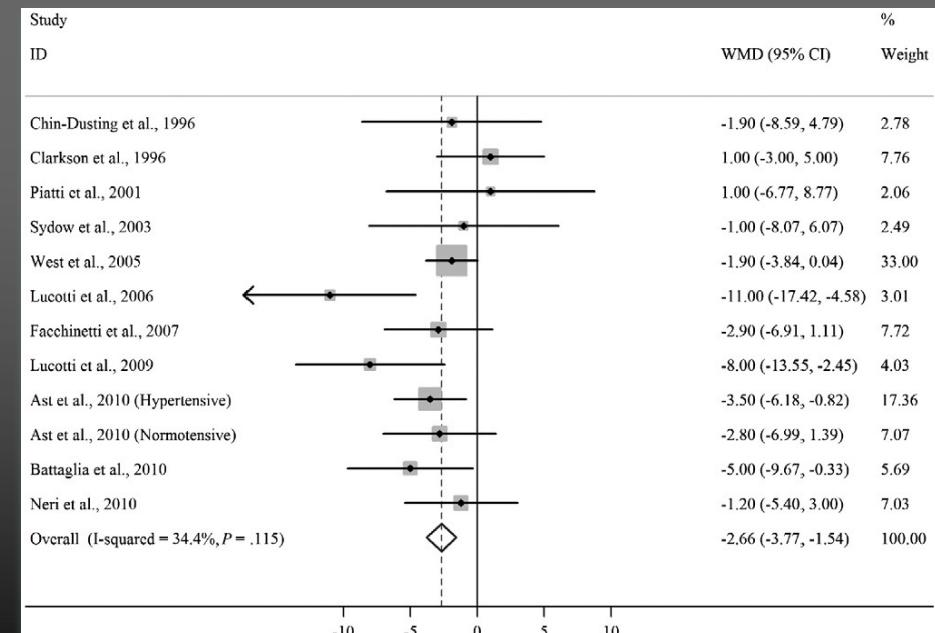
Effect of oral L-arginine supplementation on blood pressure: A meta-analysis of randomized, double-blind, placebo-controlled trials

Dong et al. Am Heart J 2011;162:959-65

Dose ranging from 4 to 24 gr/day

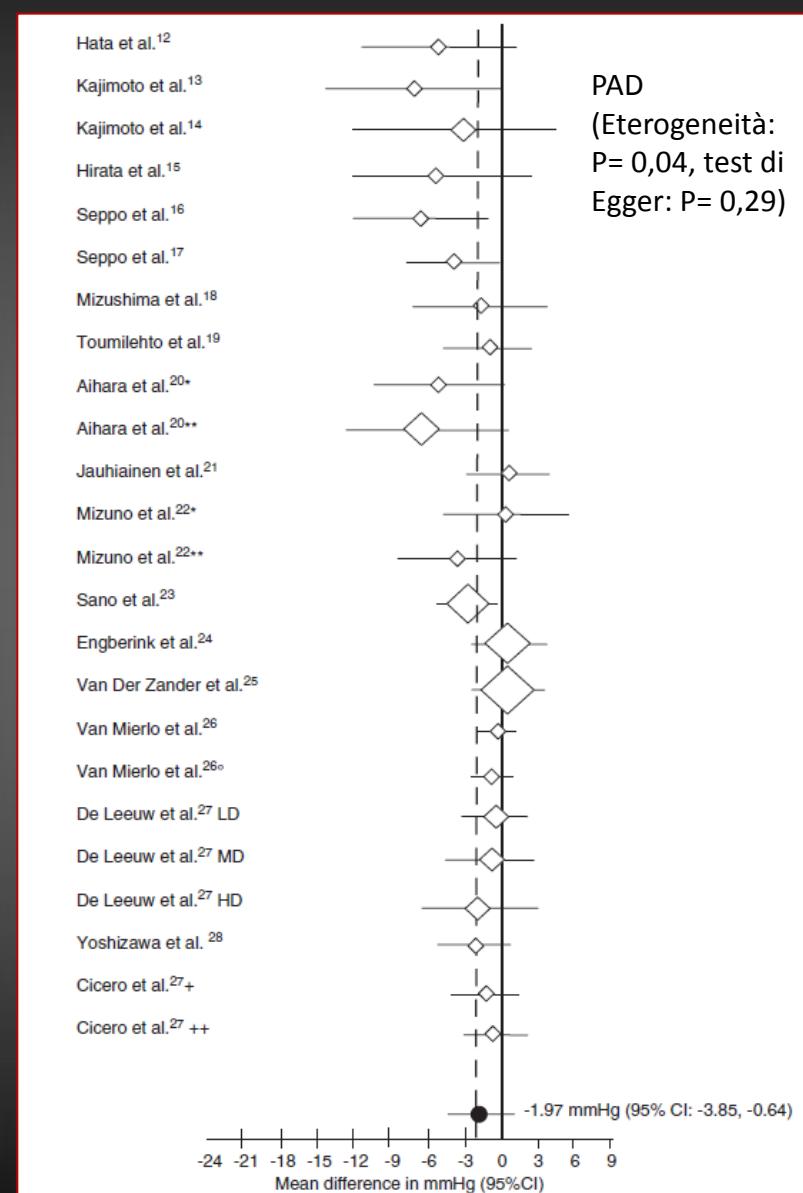
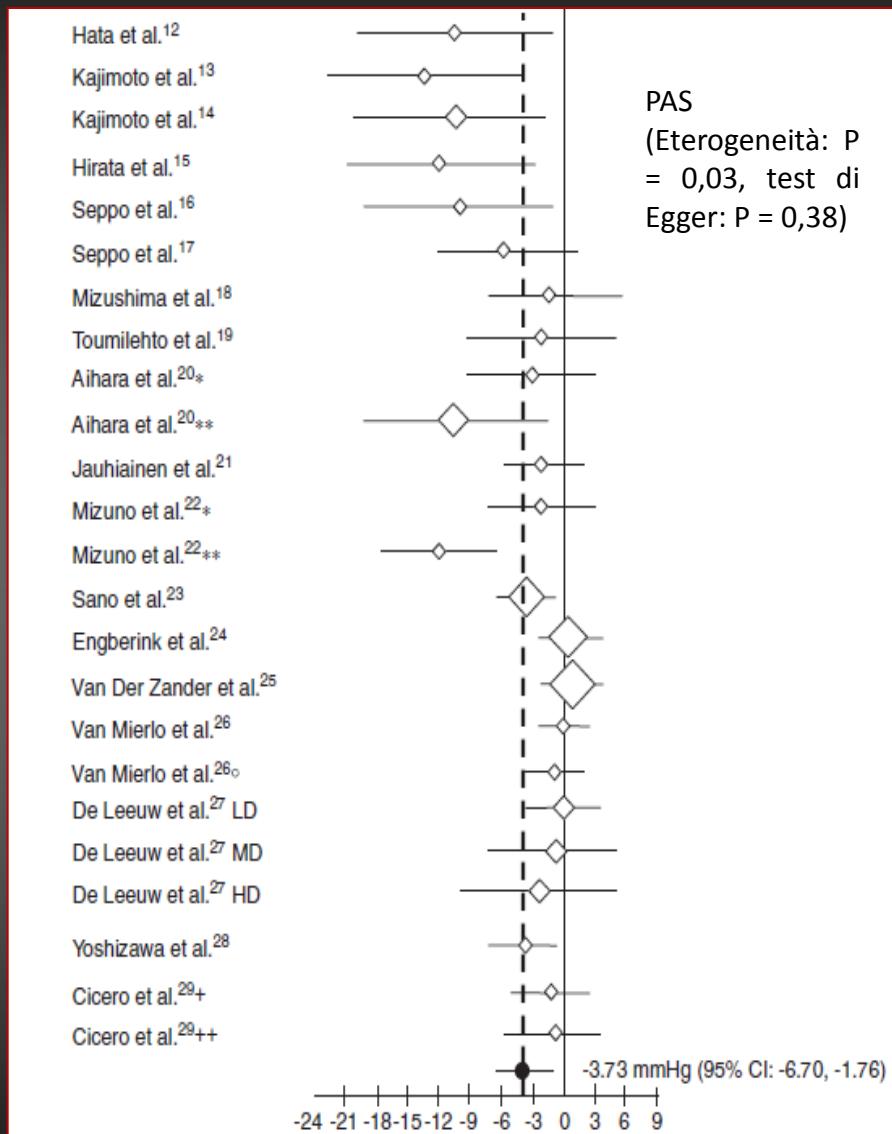


SBP



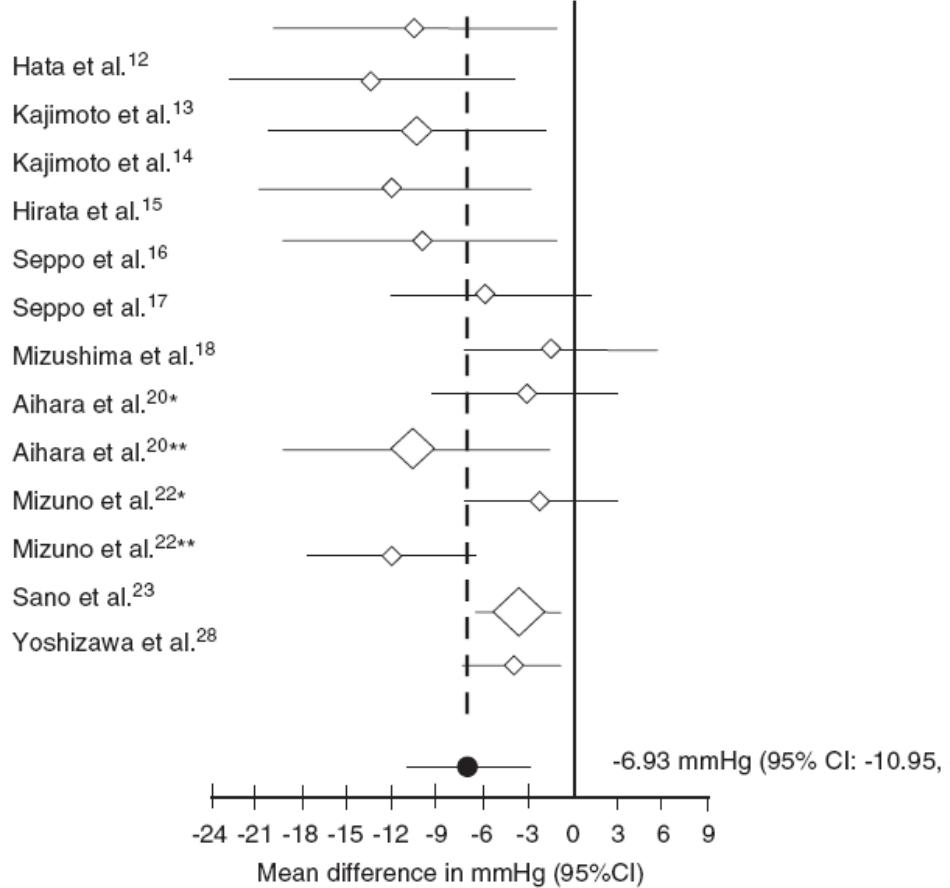
DBP

Meta-analysis of RCTs on LTPs and Blood Pressure

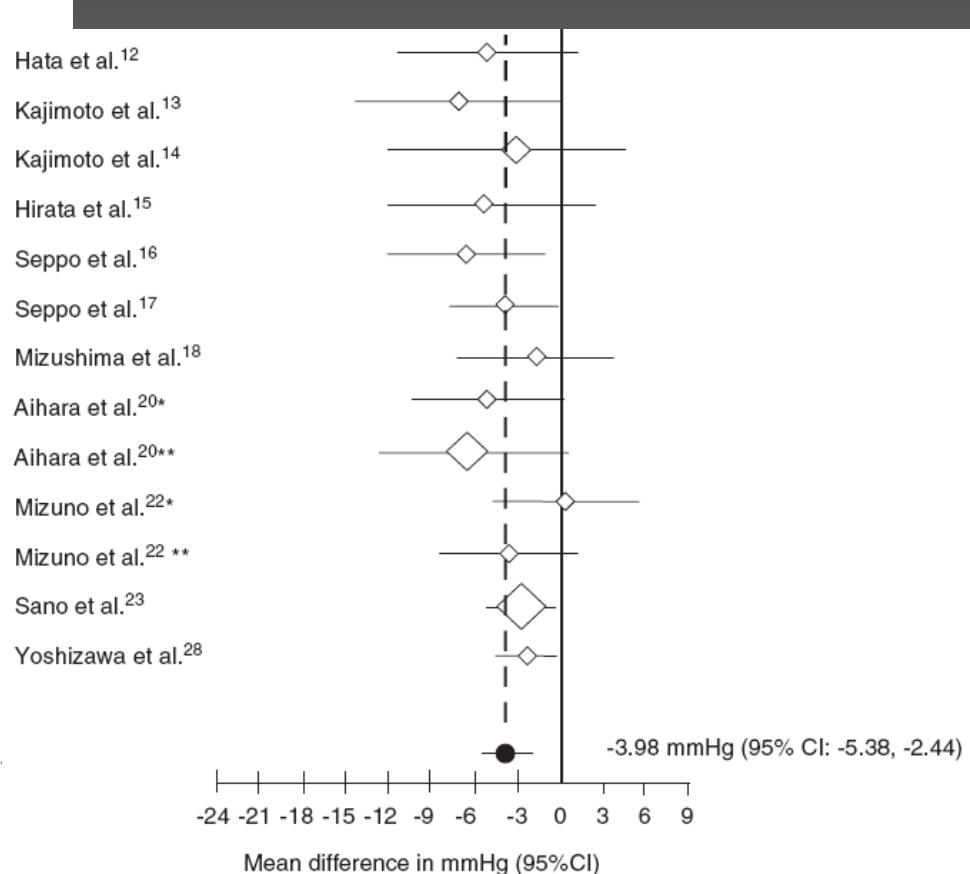


Is the effect significantly higher in Asian subjects?

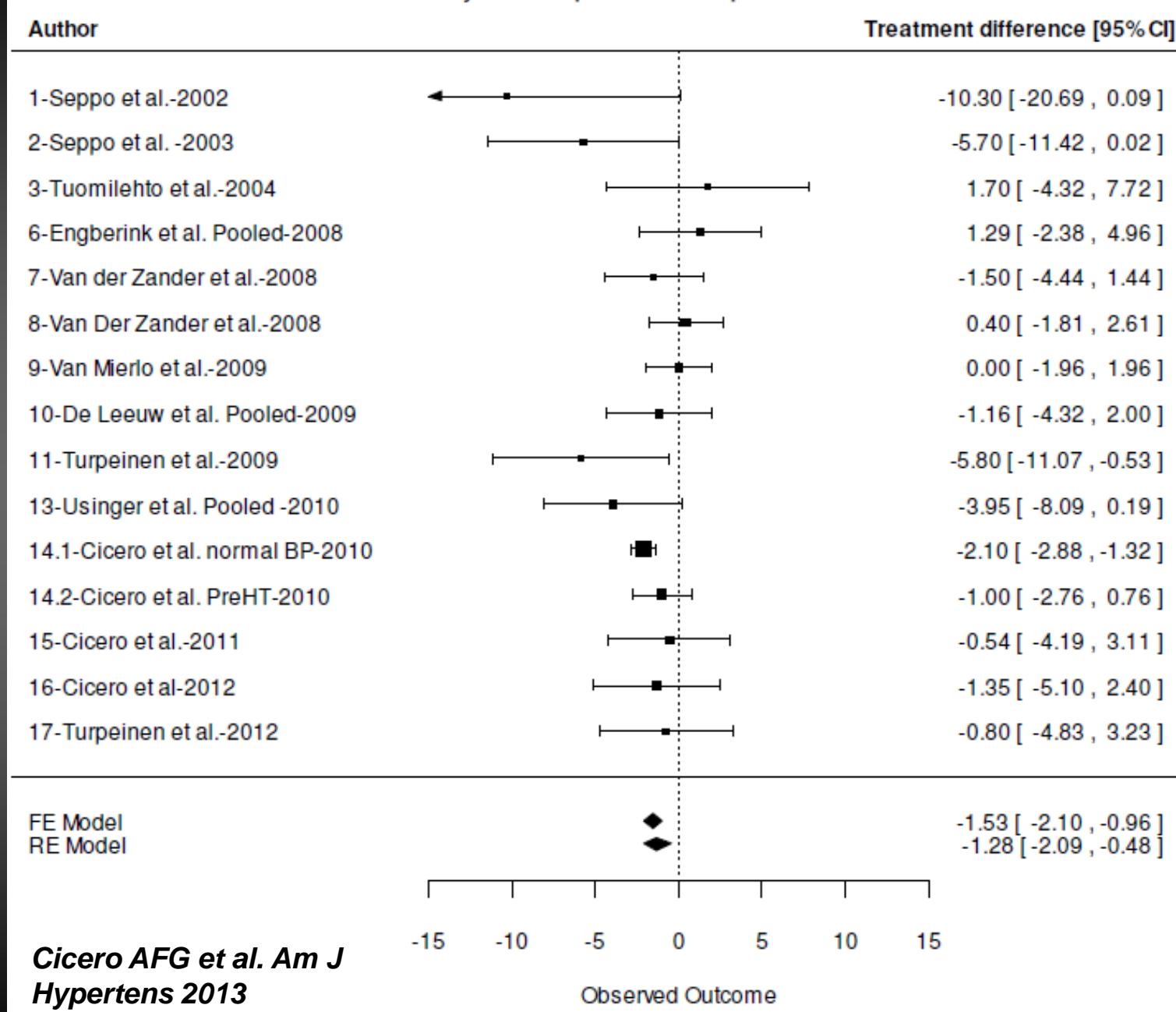
- 7 mmHg



- 4 mmHg



Meta-analysis on 14 published European studies

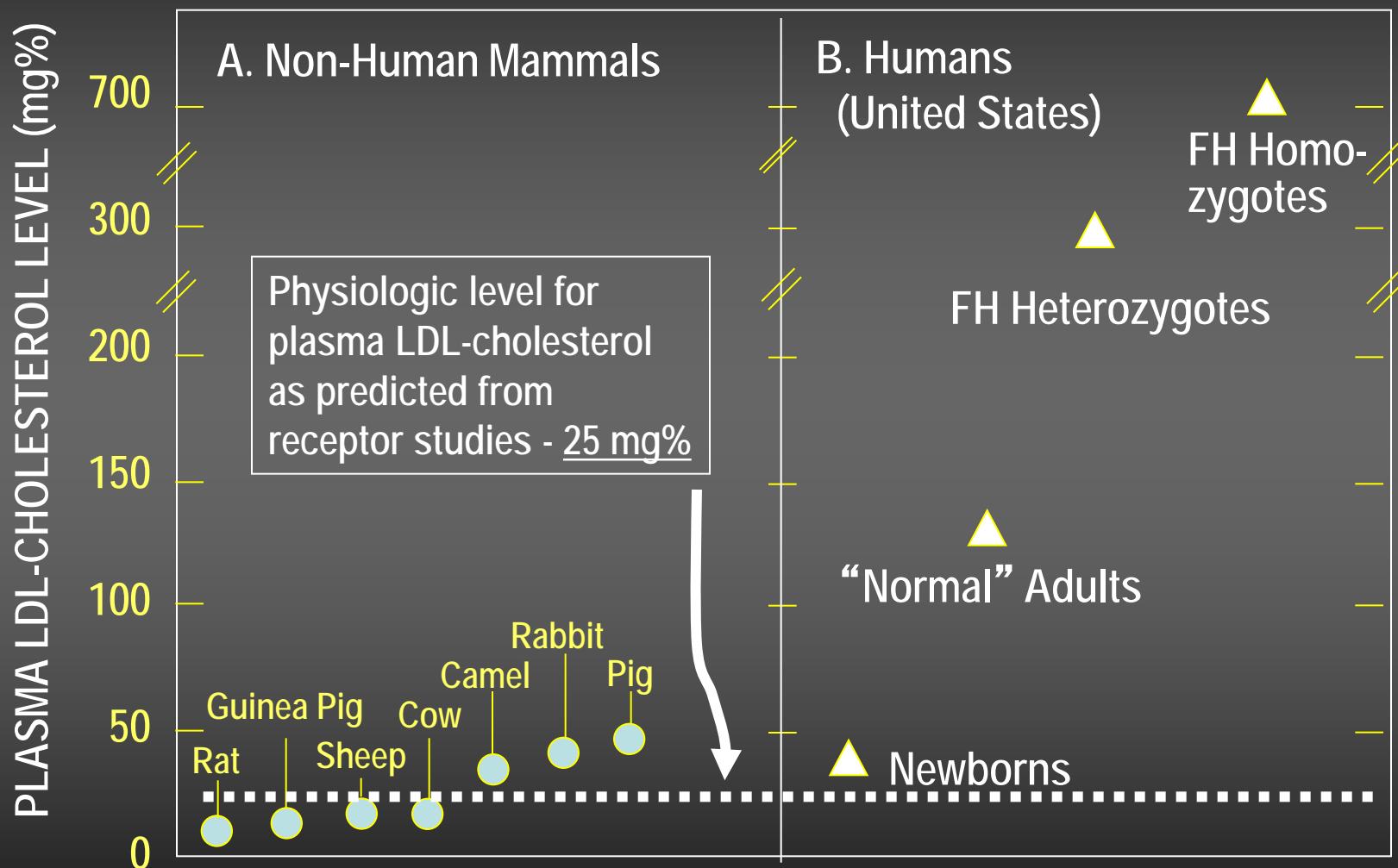


Nutraceutici ed ipercolesterolemia: il razionale scientifico

The 5 «why»

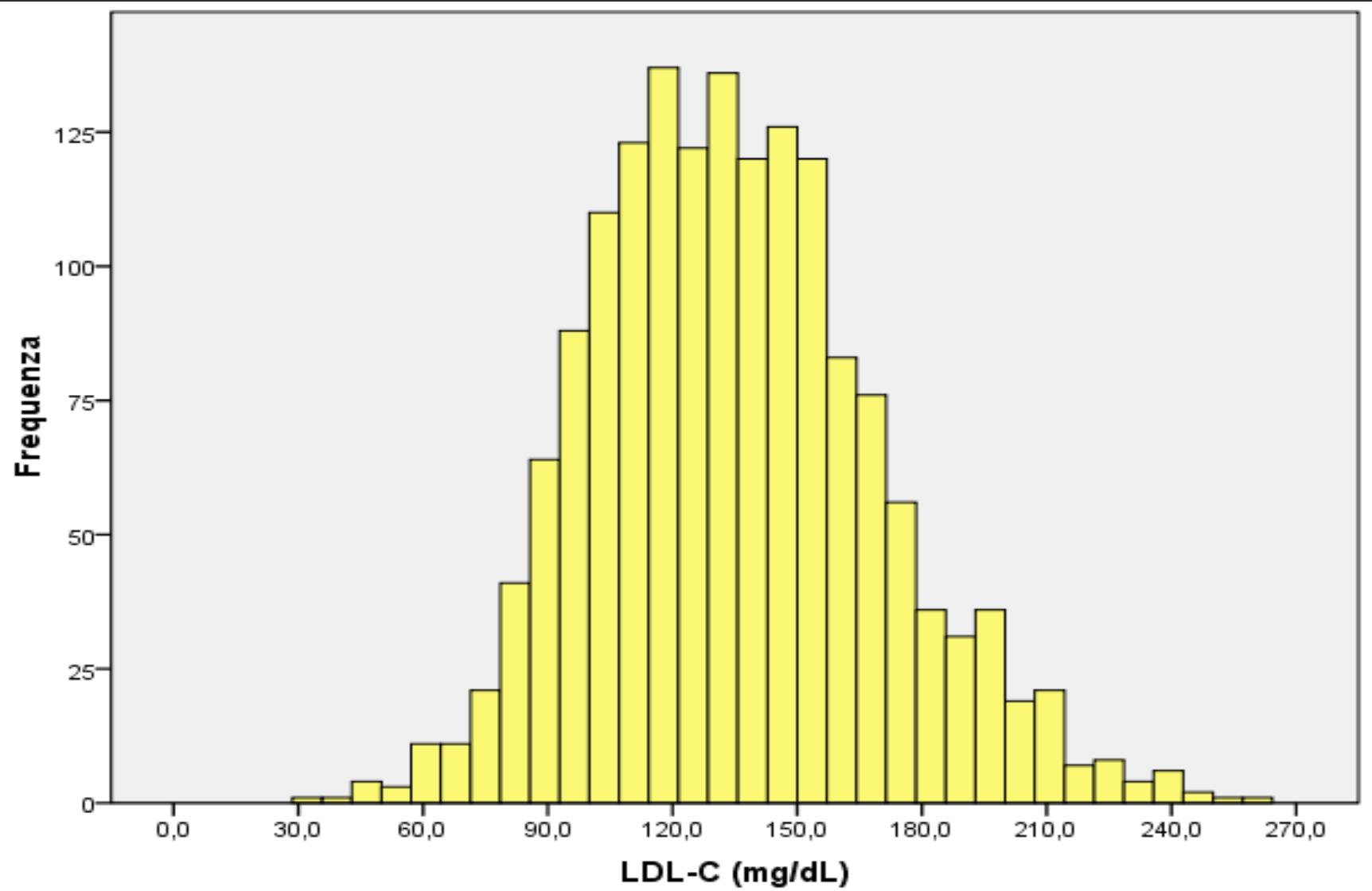
- 1) Because we need it: hypercholesterolemia is strongly prevalent!**
- 2) Because diet and physical activity have a limited impact on cholesterol control**
- 3) Because the international guidelines suggest to use lipid-lowering nutraceuticals**
- 4) Because the patients use them**
- 5) Because (some of them) are effective !**

LDL-C LEVELS IN HUMANS AND NON-HUMAN MAMMALS

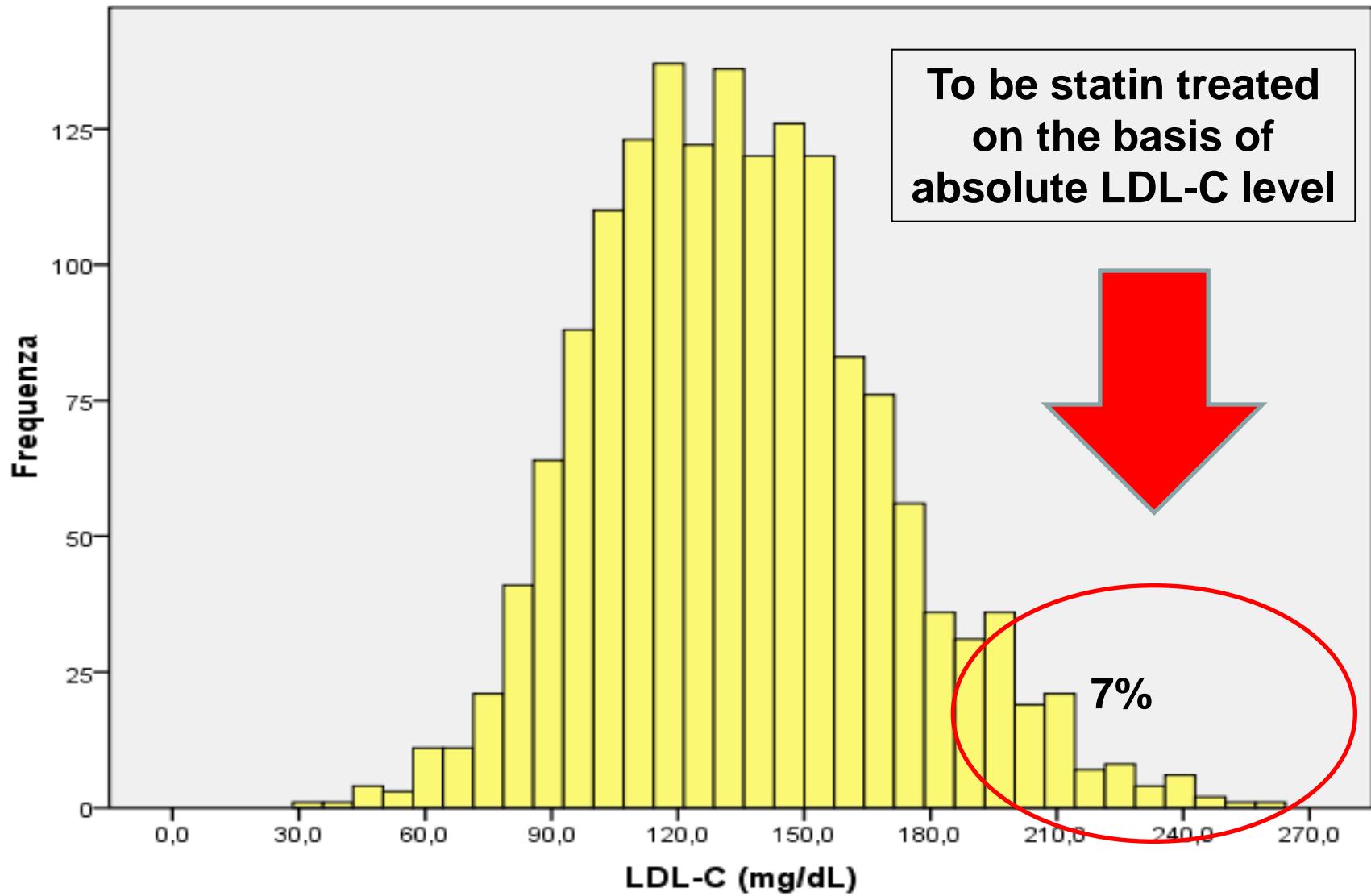


Goldstein J.L., 1982

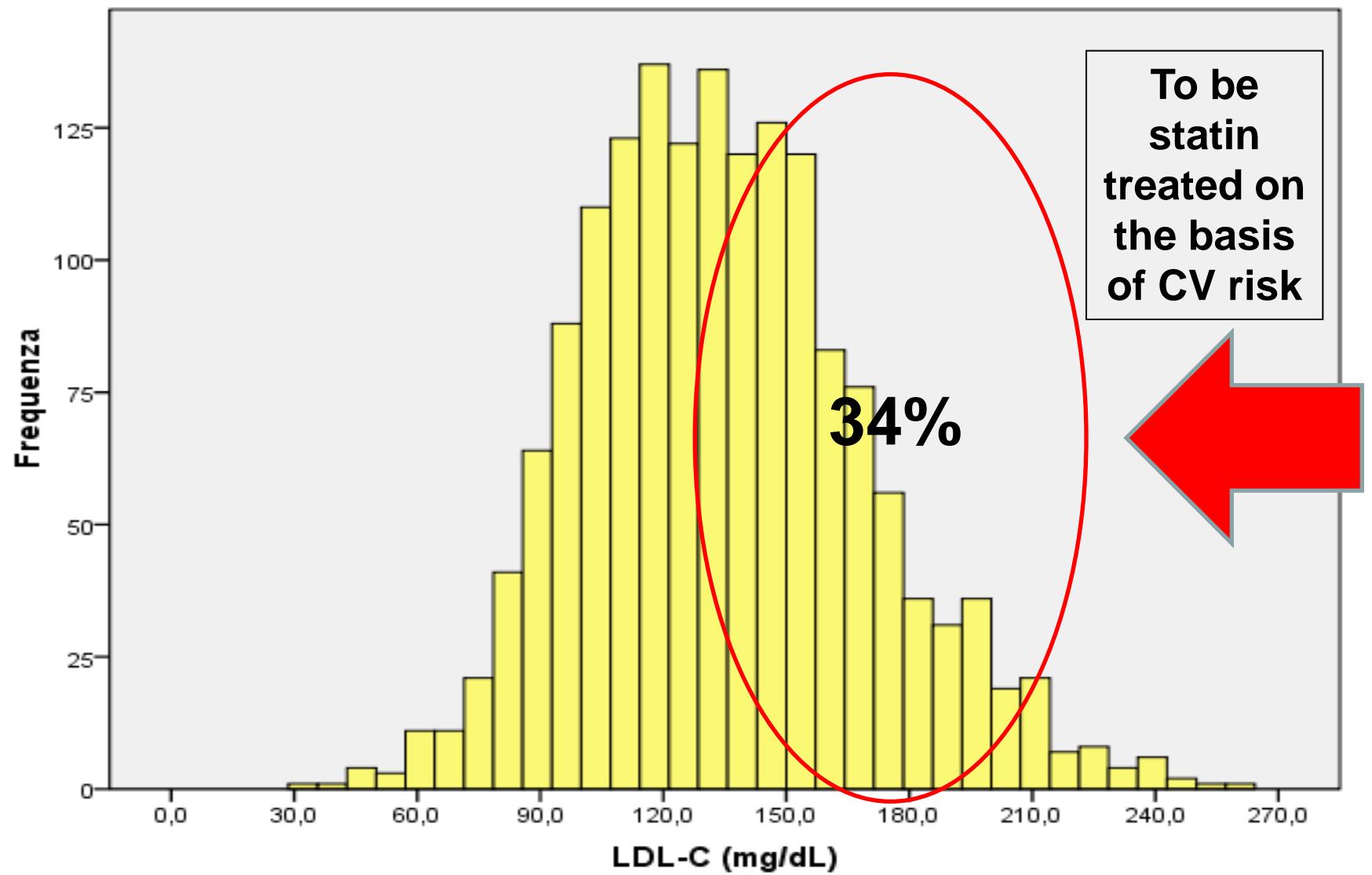
Data from 1624 non-statin treated subjects



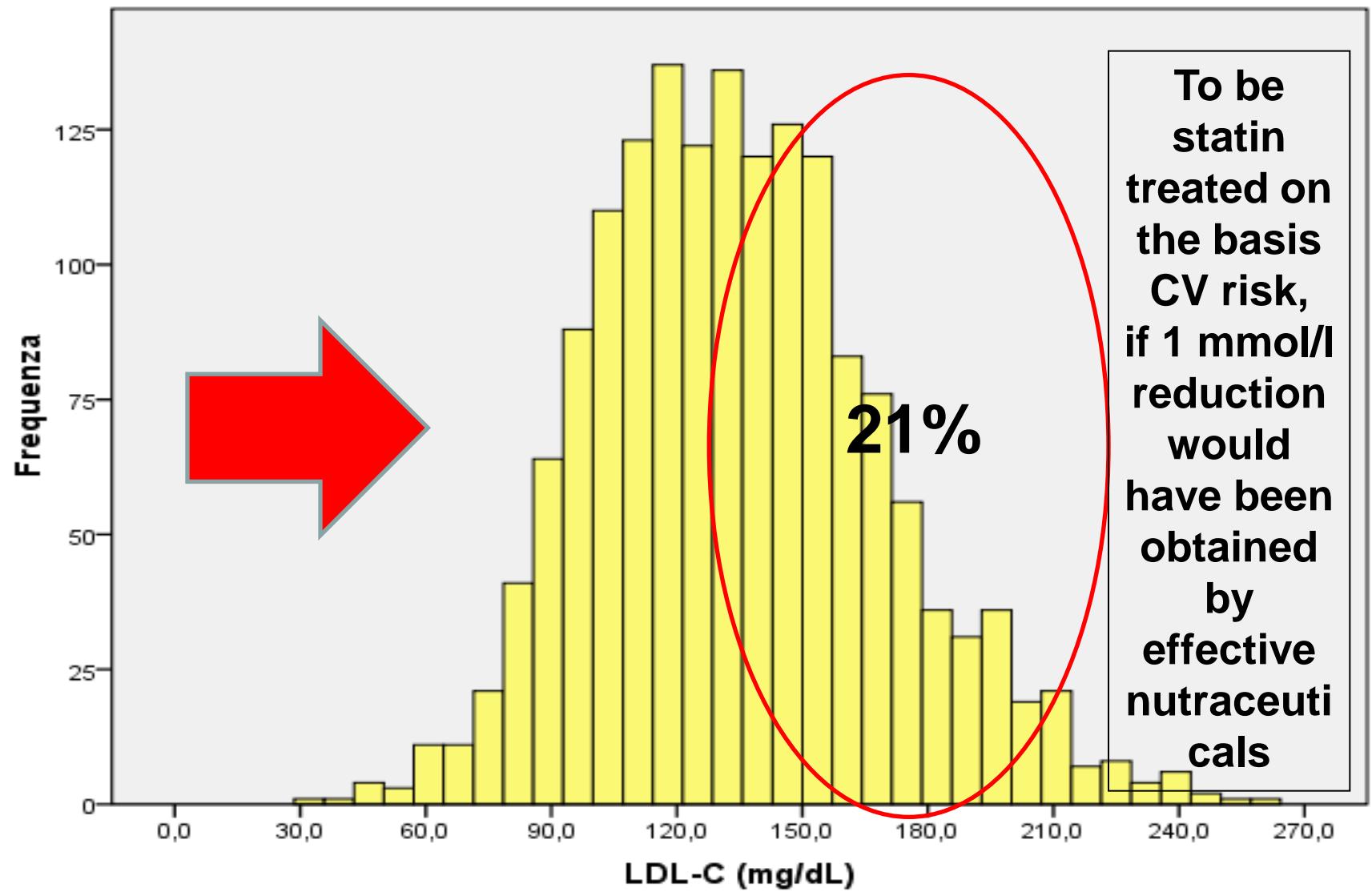
Data from 1624 non-statin treated subjects



Data from 1624 non-statin treated subjects



Data from 1624 non-statin treated subjects

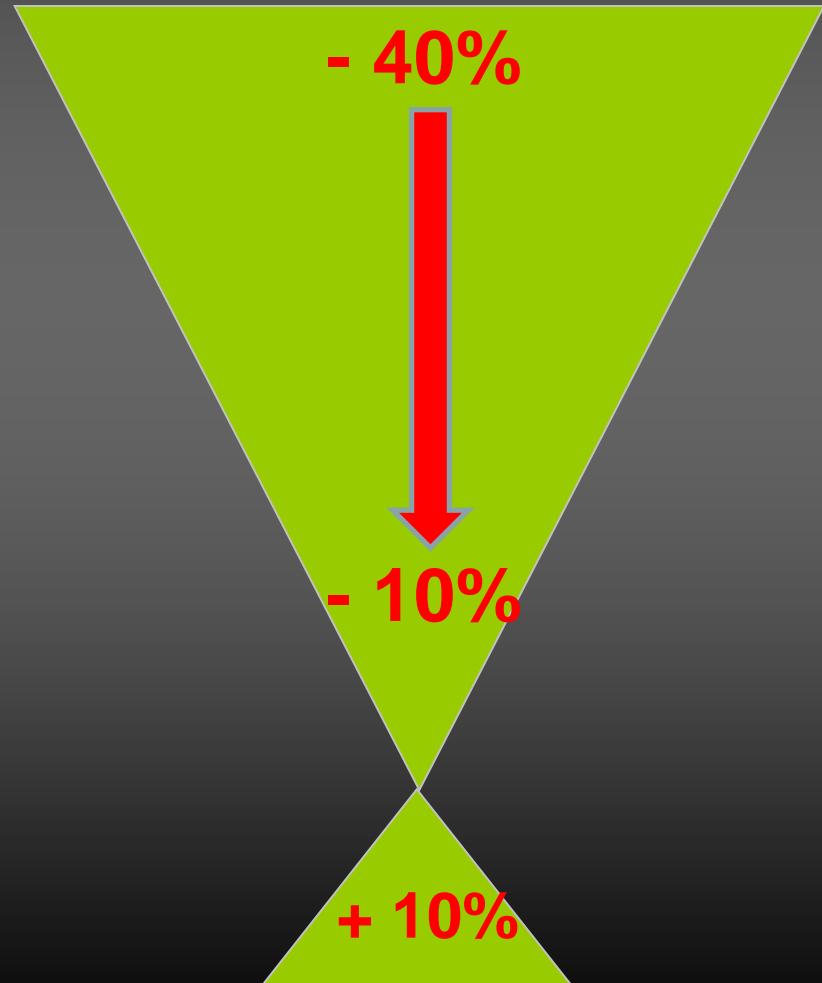


The 5 «why»

- 1) Because we need it: hypercholesterolemia is strongly prevalent!**
- 2) Because diet and physical activity have a limited impact on cholesterolemia control**
- 3) Because the international guidelines suggest to use lipid-lowering nutraceuticals**
- 4) Because the patients use them**
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Relative efficacy of life-style change in improving different CV risk factors

- Triglyceridemia
- Glycemia
- Blood Pressure
- Microinflammation
- LDL-C
- Lp(a)
- HDL-C



Is diet efficacious?

- Diet combined with aerobic exercise, but not diet or exercise alone, may reduce non-HDL-C among adults in some settings

(*Cholesterol.* 2012;2012:840935)

- A small but potentially important reduction in CV risk on modification of dietary fat, but not reduction of total fat, in longer trials. Lifestyle advice to all those at risk of CV disease and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturates. The ideal type of unsaturated fat is unclear

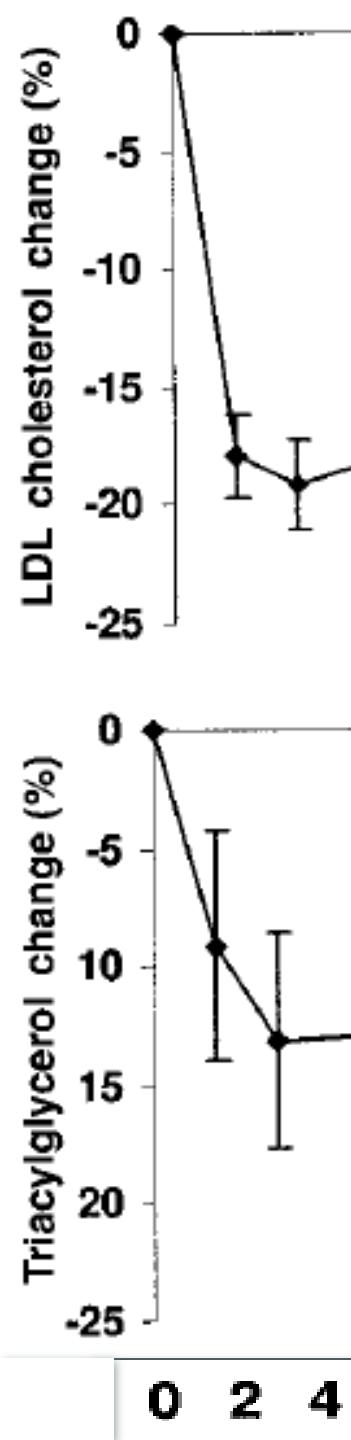
(*Cochrane Database Syst Rev.* 2012;5:CD002137)

Short-term Jenkins Diet

- 20%

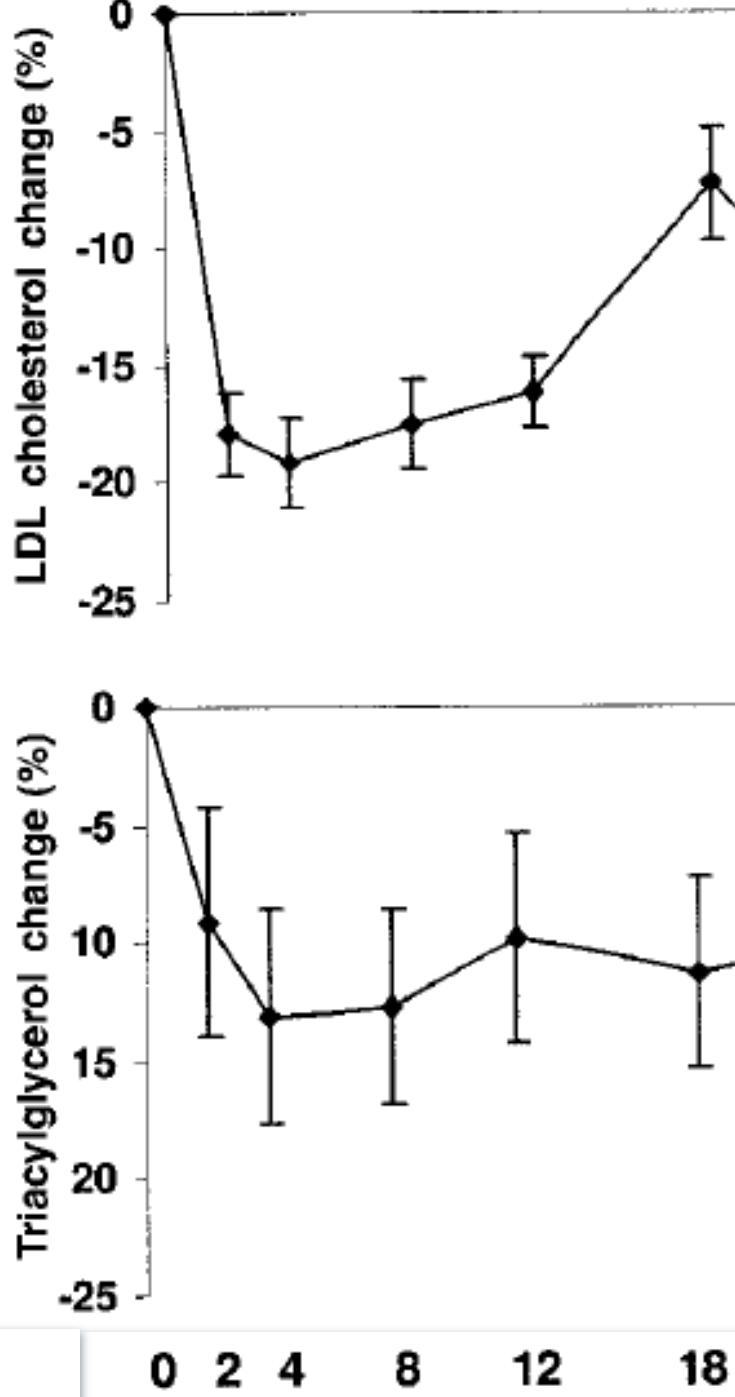
Jenkins DJA et al. Am J Clin Nutr 2006;83:582–91.

- 15%



Middle-term Jenkins diet

*Jenkins DJA et al.
Am J Clin Nutr
2006;83:582–91.*



The 5 «why»

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NCEP ATP III 2001:

role of nutraceuticals and functional foods in dyslipidemia management

- Life-style improvement (TLS)
- Life-style + Functional foods/Nutraceuticals
- Life-style improvement (TL + Drugs)
- Life-style + Drugs + Functional foods/Nutraceuticals

ESC/EAS Guidelines for the management of dyslipidaemias

- Life-style improvement (TLS)
- Life-style + Functional foods/Nutraceuticals
- Life-style improvement (TL + Drugs)
- Life-style + Drugs + Functional foods/Nutraceuticals

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

- Therapeutic life-style (TLS)
- TLS + Functional foods/Nutraceuticals
- TLS improvement (TL + Drugs)
- TLS + Drugs + Functional foods/Nutraceuticals

Lipid lowering nutraceuticals in clinical practice: an evidence-based consensus of a large number of Italian scientific societies

Con l'endorsement di Federazione delle Associazioni Dei Dirigenti Ospedalieri Internisti (FADOI), Società Italiana di Tossicologia (SITOX), Società Italiana Nutrizione Sport e Benessere (SINSEB), Società Italiana Ipertensione Arteriosa (SIIA), Fondazione Società Italiana Ipertensione Arteriosa), Associazione Medici Endocrinologi (AME), Società Italiana dell'Obesità (SIO), Gruppo di Studio Nutraceutica dell'Associazione Italiana di dietetica e nutrizione clinica (ADI), Operatori Sanitari di Diabetologia Italiani (OSDI), Associazione Italiana Dietisti (ANDID), Società Italiana Medicina Funzionale (SIMF), Società Italiana di Nutrigenomica ed Epigenetica (SINE), Federazione dei produttori di supplementi dietetici (FEDERSALUS) e *Lipid and Blood Pressure Meta-analysis Collaboration* (LBPMC) Group

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

Arrigo F.G. Cicero^{1*}, Alessandro Colletti¹, Gani Bajraktari², Olivier Descamps³, Dragan M. Djuric⁴, Marat Ezhov⁵, Zlatko Fras⁶, Niki Katsiki⁷, Michel Langlois⁸, Gustavs Latkovskis⁹, Demosthenes B. Panagiotakos¹⁰, Gyorgy Paragh¹¹, Dimitri P. Mikhailidis¹², Olena Mitchenko¹³, Bernhard Paulweber¹⁴, Daniel Pella¹⁵, Christos Pitsavos¹⁶, Željko Reiner¹⁷, Kausik K. Ray¹⁸, Manfredi Rizzo¹⁹, Amirhossein Sahebkar²⁰, Maria-Corina Serban²¹, Laurence S. Sperling²², Peter P. Toth²³, Dragos Vinereanu²⁴, Michal Vrablík²⁵, Nathan D. Wong²⁶, Maciej Banach^{27*} on behalf of the International Lipid Expert Panel (ILEP)

With the official endorsement of:

Austrian Atherosclerosis Society (AAS)

Baltic Atherosclerosis Society

Belgian Atherosclerosis Society

Croatian Atherosclerosis Society

Czech Atherosclerosis Society

Hellenic Atherosclerosis Society

Hungarian Atherosclerosis Society

Italian Society of Nutraceuticals (SINut)

Kosovo Society of Cardiology

Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group

Polish Lipid Association (PoLA)

Romanian Society of Cardiology

Russian National Atherosclerosis Society

Serbian Association for Arteriosclerosis, Thrombosis and Vascular Biology Research

Slovak Association of Atherosclerosis

Slovenian Society of Cardiology

Ukrainian Atherosclerosis Society

**Arch Med Sci. 2017;
13(5):965-1005.**

Ethical prescription of cholesterol-lowering nutraceuticals

- «Resistance» to the therapeutic life-style changes
- Psychological need of quick results (as a support to the diet)
- Low level of added global CVD risk
- “Resistance” to conventional treatments
- “Intollerance” to conventional treatments
- Need to improve the efficacy of conventional treatments without increasing dosages or number of administrations
- Scarce confidence and/or fear against conventional therapies

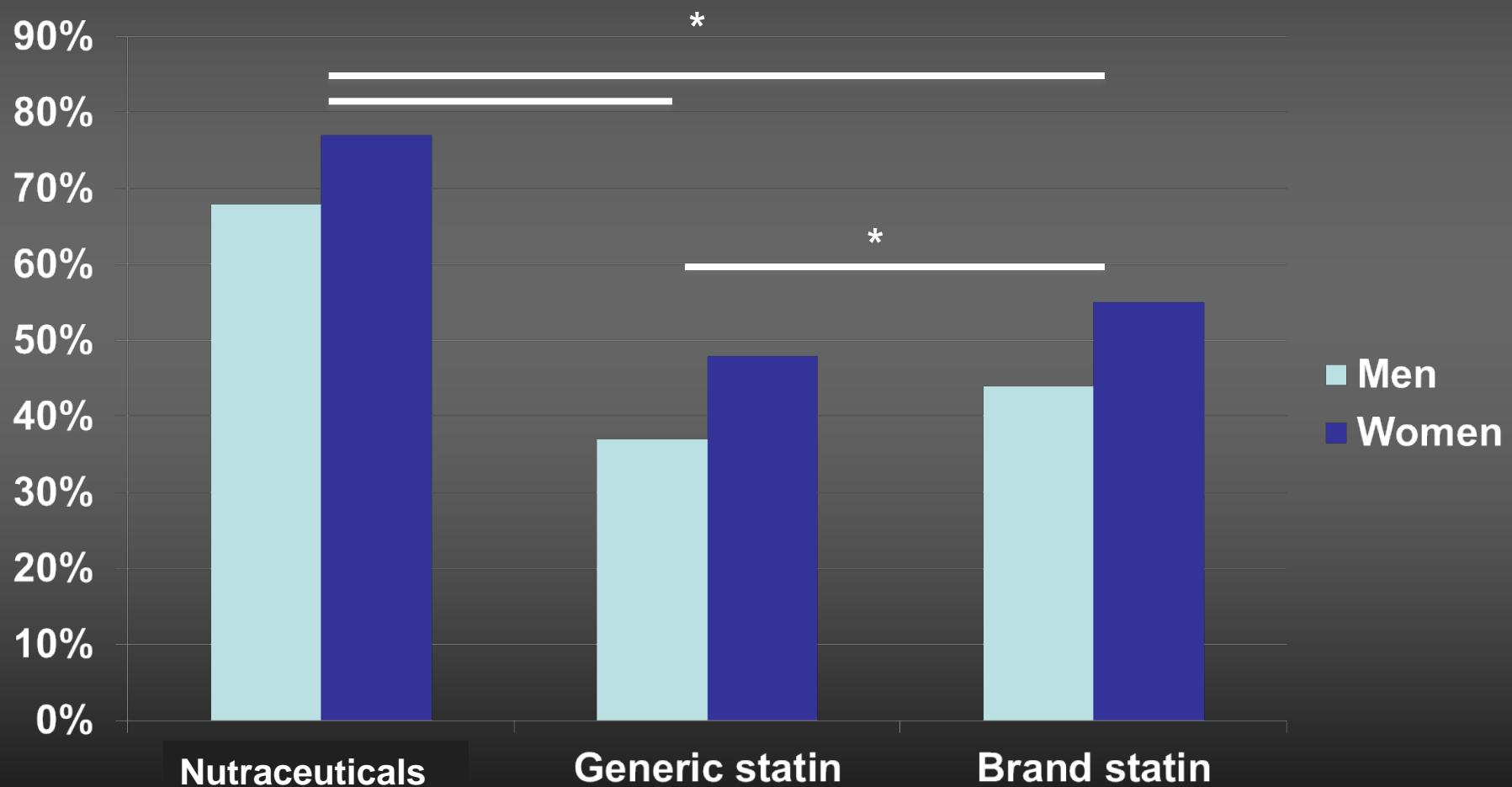
Ethical prescription of cholesterol-lowering nutraceuticals

All those patients with LDL-C above the desired one and for which a statin treatment is not advisable

The 5 «why»

- 1) Because we need it: hypercholesterolemia is strongly prevalent!
- 2) Because diet and physical activity have a limited impact on cholesterol control
- 3) Because the international guidelines suggest to use lipid-lowering nutraceuticals
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2-years persistence in paid LDL-lowering treatment



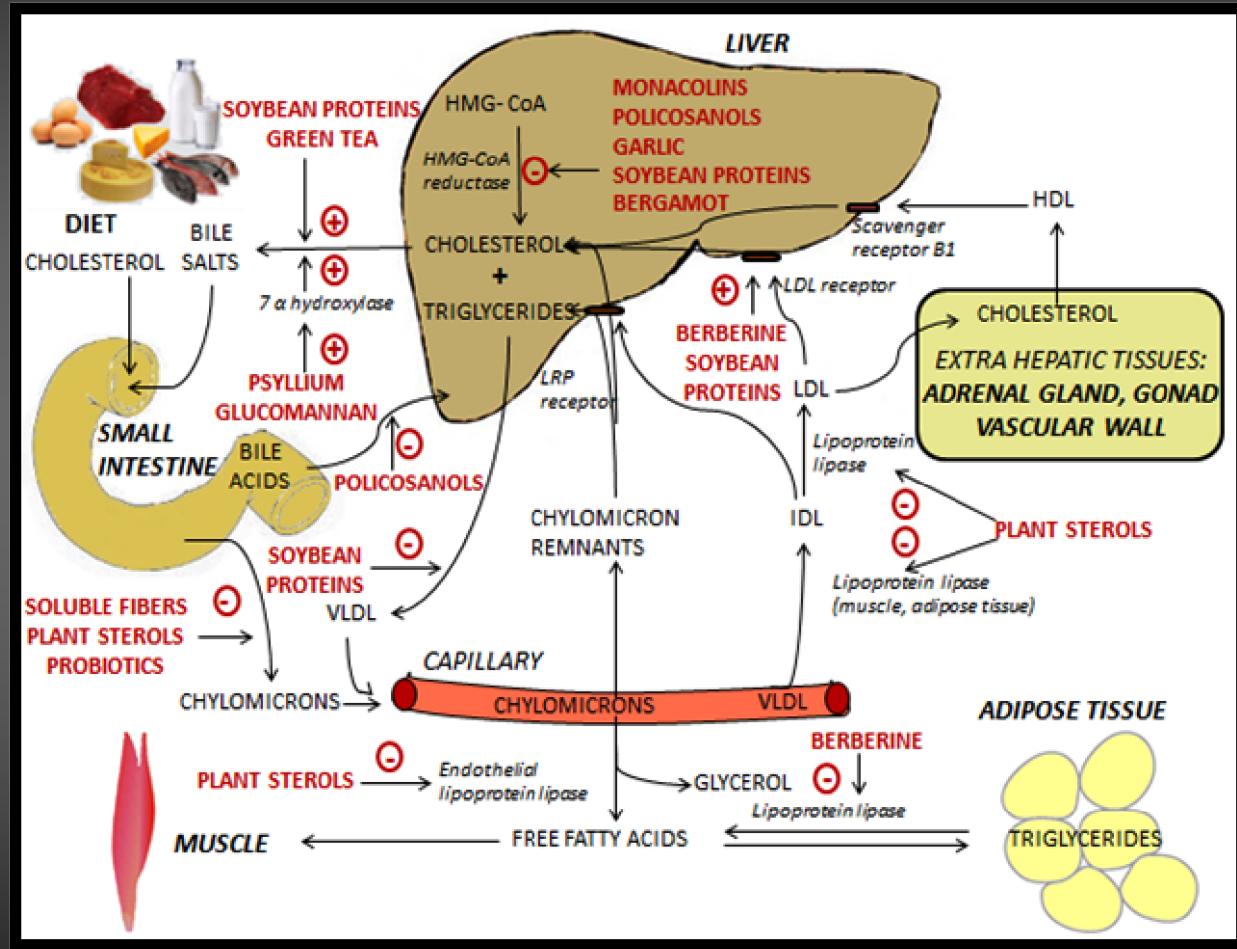
The 5 «why»

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- 3) Because the international guidelines suggest to use lipid-lowering nutraceuticals**
- 4) Because the patients use them**
- 5) Because (some of them) are effective !**

Active principles with lipid-lowering activity

- 1284 in vitro
- 238 in vivo
- 52 in humans
- 13 confirmed in repeated RCTs
- 126 dietary supplements registered in the Italian market
- 15 supported by «a kind» of clinical test
- 7 supported by RCTs published on peer-reviewed international journals

Lipid-lowering nutraceuticals: sites of action

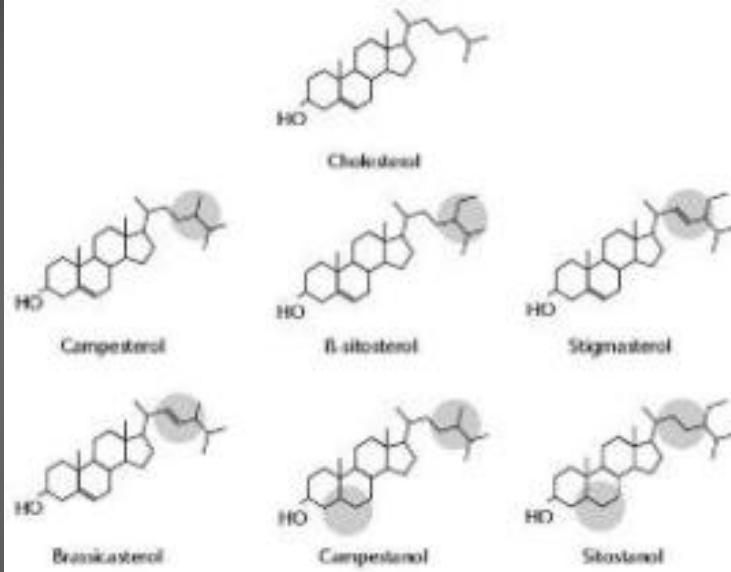


Cicero AFG, Colletti A. In: Combined therapy in dyslipidemia. Springer-Verlag. 2015

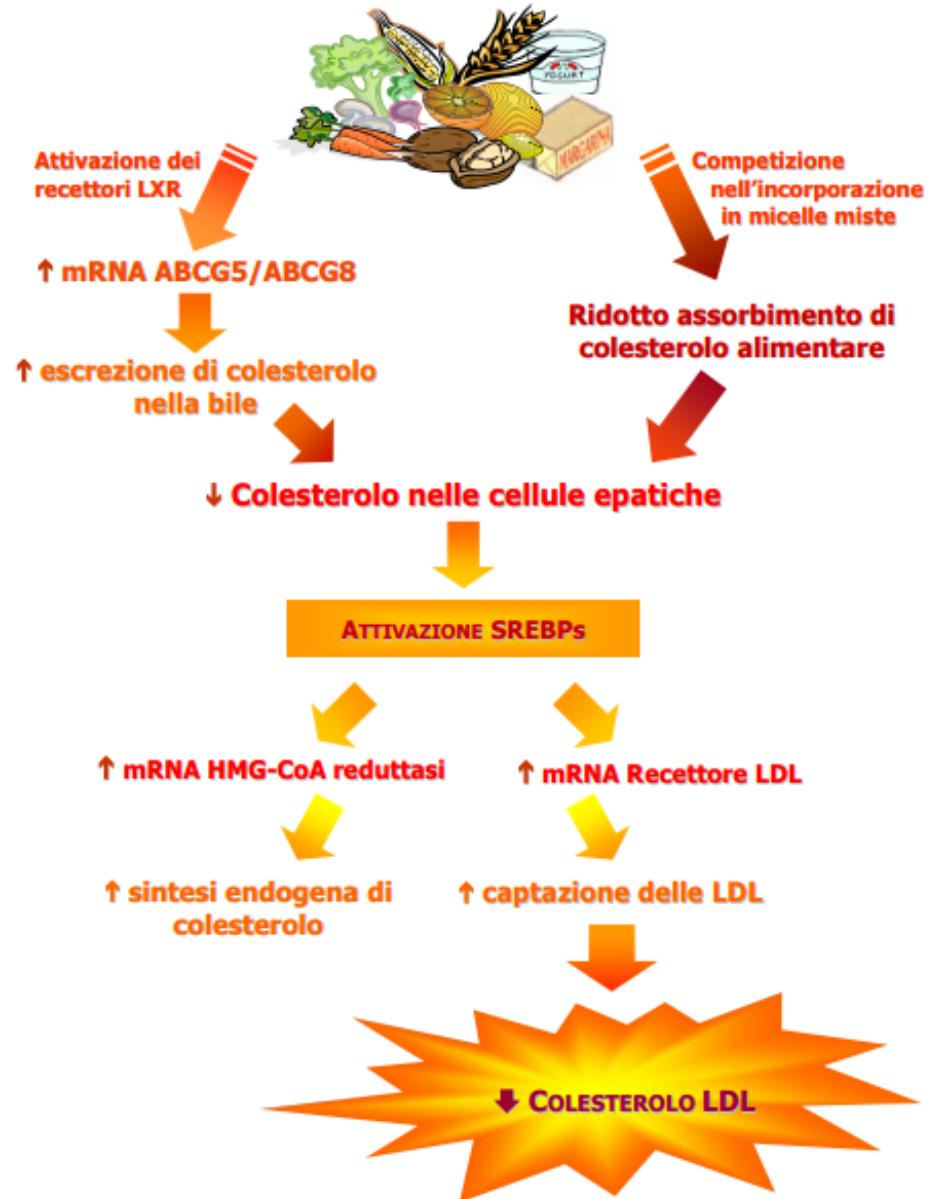
Evidence/Efficacy

	Clinical evidence	Clinical efficacy
Red Yeast Rice	+++	+++
Berberine	++	++
Soluble Fibers	+++	+
Phytosterols	+++	+
Garlic	++	+
Policosanols	++	+/-
Vegetal proteins	++	+
Tocotrienols	+	+
Panthetine	+	+
Probiotics	+	+

Fitosteroli

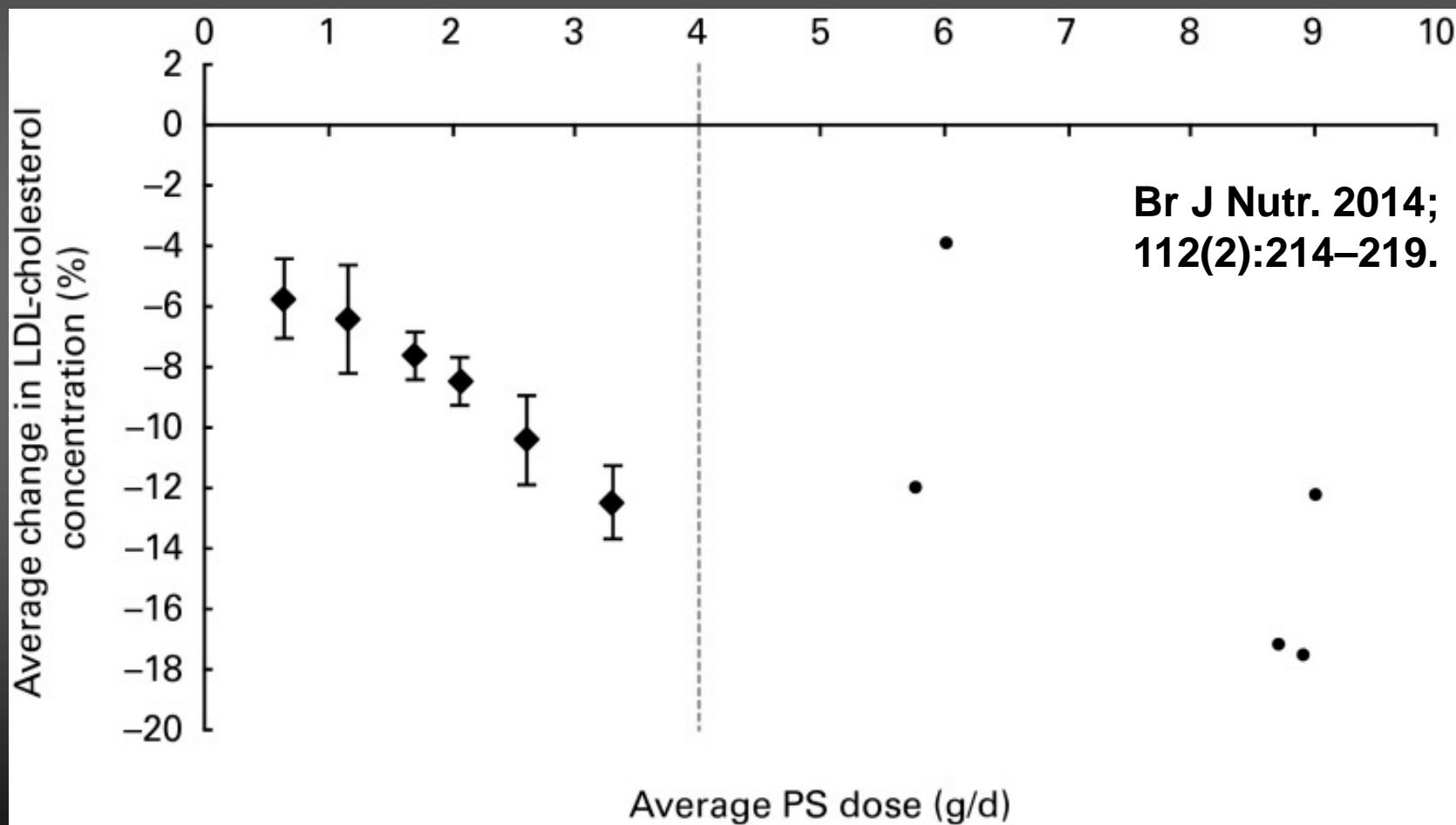


Assunzione di fitosteroli



Cicero AF et al. Food Funct. 2017 May 25.
[Epub ahead of print]

Average effects on LDL-C concentration for different dose ranges of phytosterols



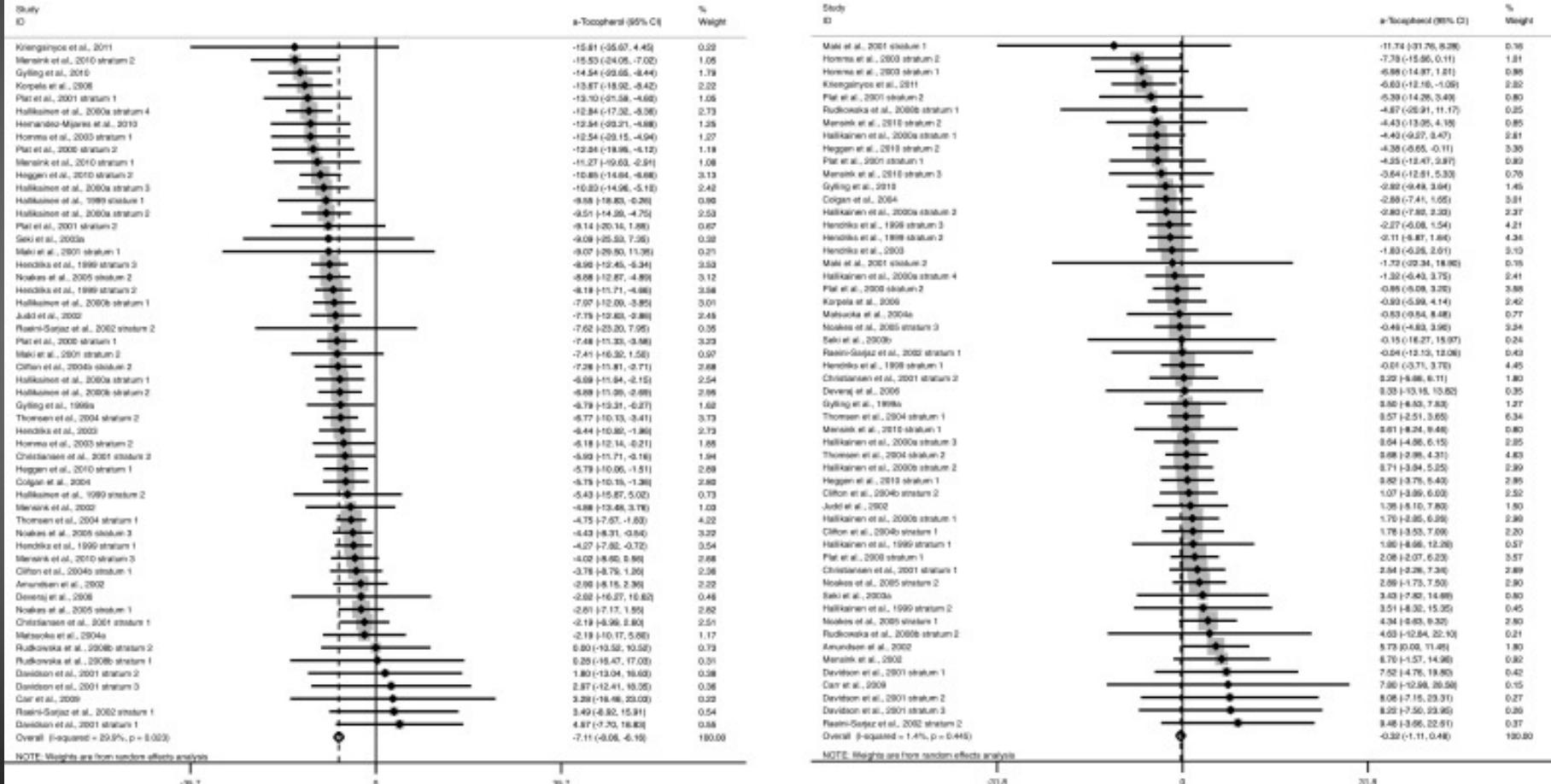
Vantaggi dei fitosteroli

- Virtualmente privi di effetti collaterali
- Virtualmente privi di interazioni farmacologiche
- Non assorbiti (= utilizzabili anche in gravidanza ed età pediatrica)
-

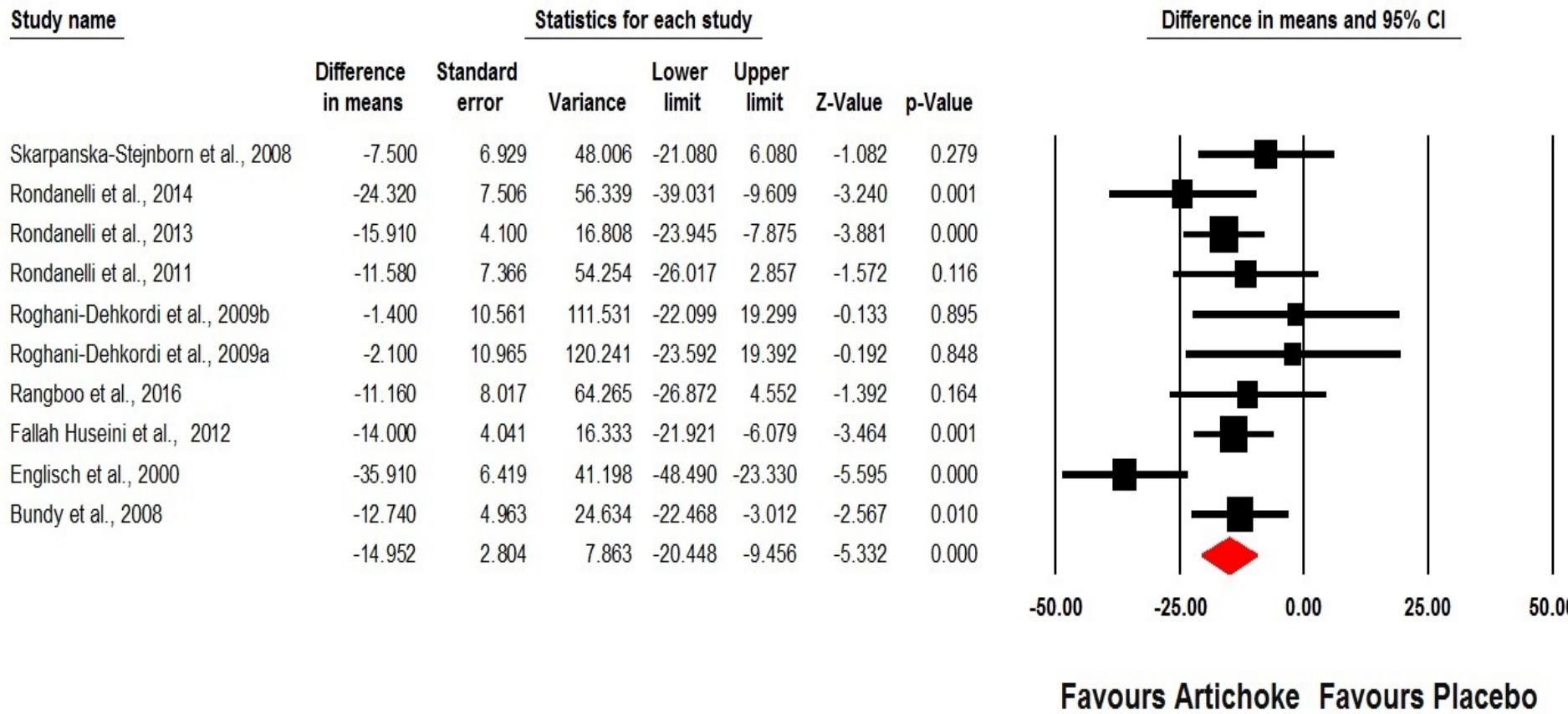
Dubbi:

- Beta-sitostolemia
- Assorbimento carotenoidi (?)

Relative change in non-standardized (left) and TC-standardized (right) plasma α -tocopherol concentrations

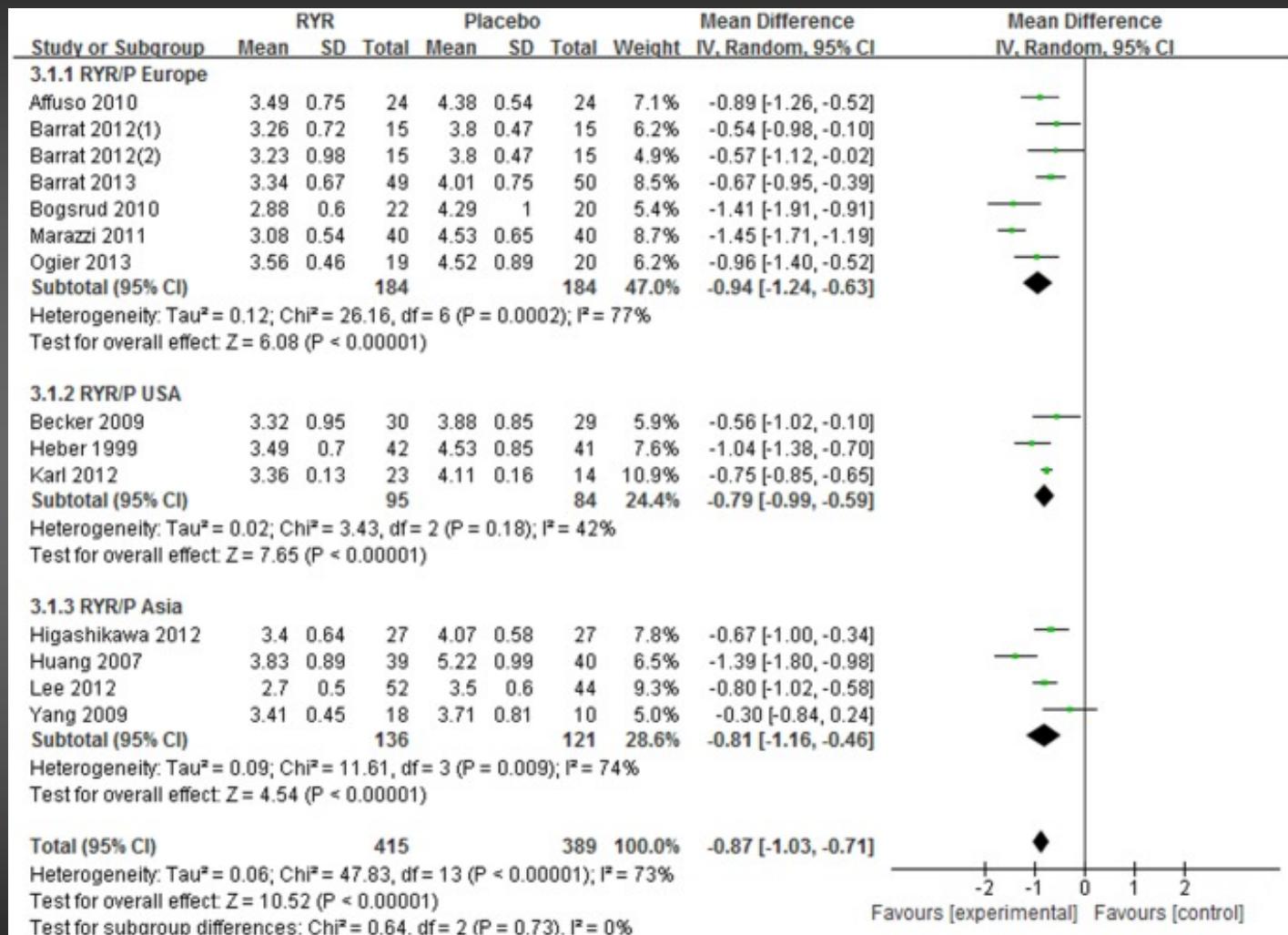


Effect of Artichoke extracts on LDL-C (mg/dL) level in RCTs



Cicero et al. Curr Res Food Sci Nutr 2017

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



EFFECTS ON LDL-C

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

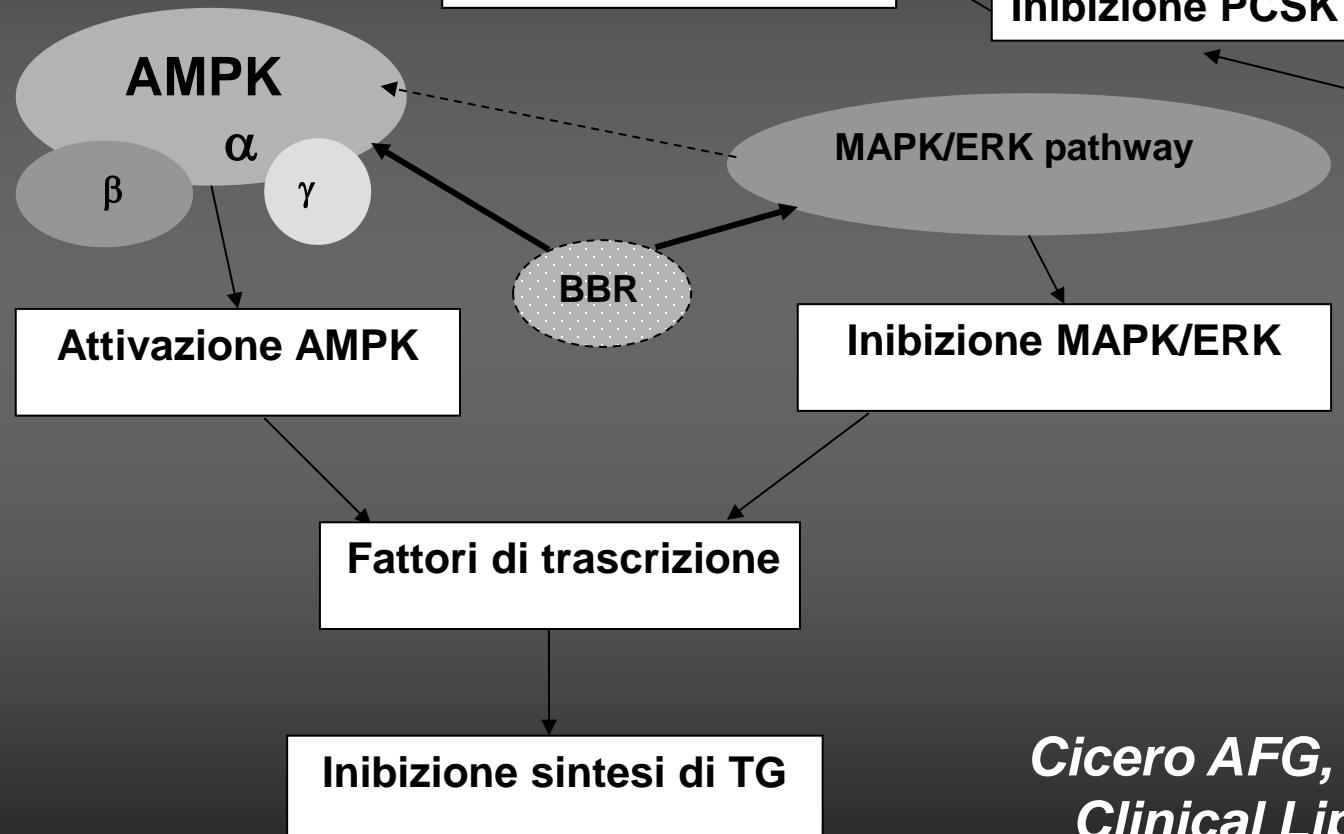
BERBERINE

LDL



LDLR up-regulation

Inibizione PCSK 9



Cicero AFG, Ertek S.
Clinical Lipidology
2009

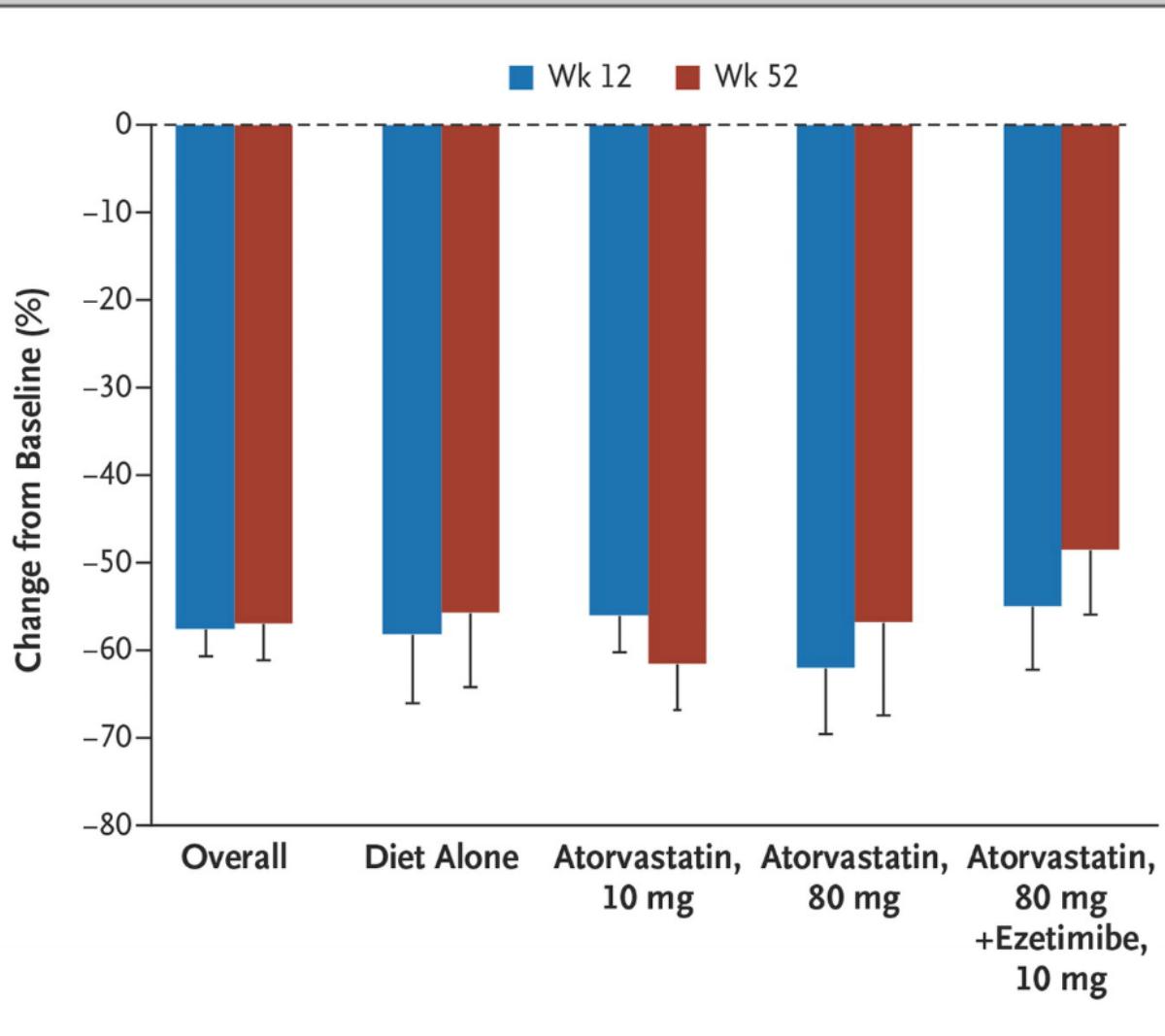


Figure 2. Percent Reduction from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels in the Evolocumab Group, as Compared with the Placebo Group, at Weeks 12 and 52, According to Background Lipid-Lowering Therapy.

Values are means with lower 95% confidence limits (as indicated by T bars) in the active-treatment groups after taking into account the values in the placebo group. LDL cholesterol was measured by means of ultracentrifugation separation.

Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins

Weijia Kong^{1,5}, Jing Wei^{2,5}, Parveen Abidi^{3,5}, Meihong Lin³, Satoru Inaba³, Cong Li³, Yanling Wang⁴, Zizheng Wang², Shuyi Si¹, Huaining Pan², Shukui Wang², Jingdan Wu², Yue Wang⁴, Zhuorong Li¹, Jingwen Liu³ & Jian-Dong Jiang^{1,4}

Endocrine Care

Treatment of Type 2 Diabetes and Dyslipidemia with the Natural Plant Alkaloid Berberine

Yifei Zhang,* Xiaoying Li,* Dajin Zou, Wei Liu, Jialin Yang, Na Zhu, Li Huo, Peihong Wu, Guoguang Ren, and Guang Ning

Journal of Ethnopharmacology 161 (2015) 69–81

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

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



ELSEVIER

Review

Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipidemia and hypertension

The Effects of Berberine on Blood Lipids: A Systemic Review and Meta-Analysis of Randomized Controlled Trials

Authors

Hui Dong^{1*}, Yan Zhao², Li Zhao^{1*}, Fuer Lu¹

¹ Institute of Integrated Traditional Chinese and Western Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P.R. China

² Department of Integrated Traditional Chinese and Western Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P.R. China



CrossMark

Original Papers

437

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

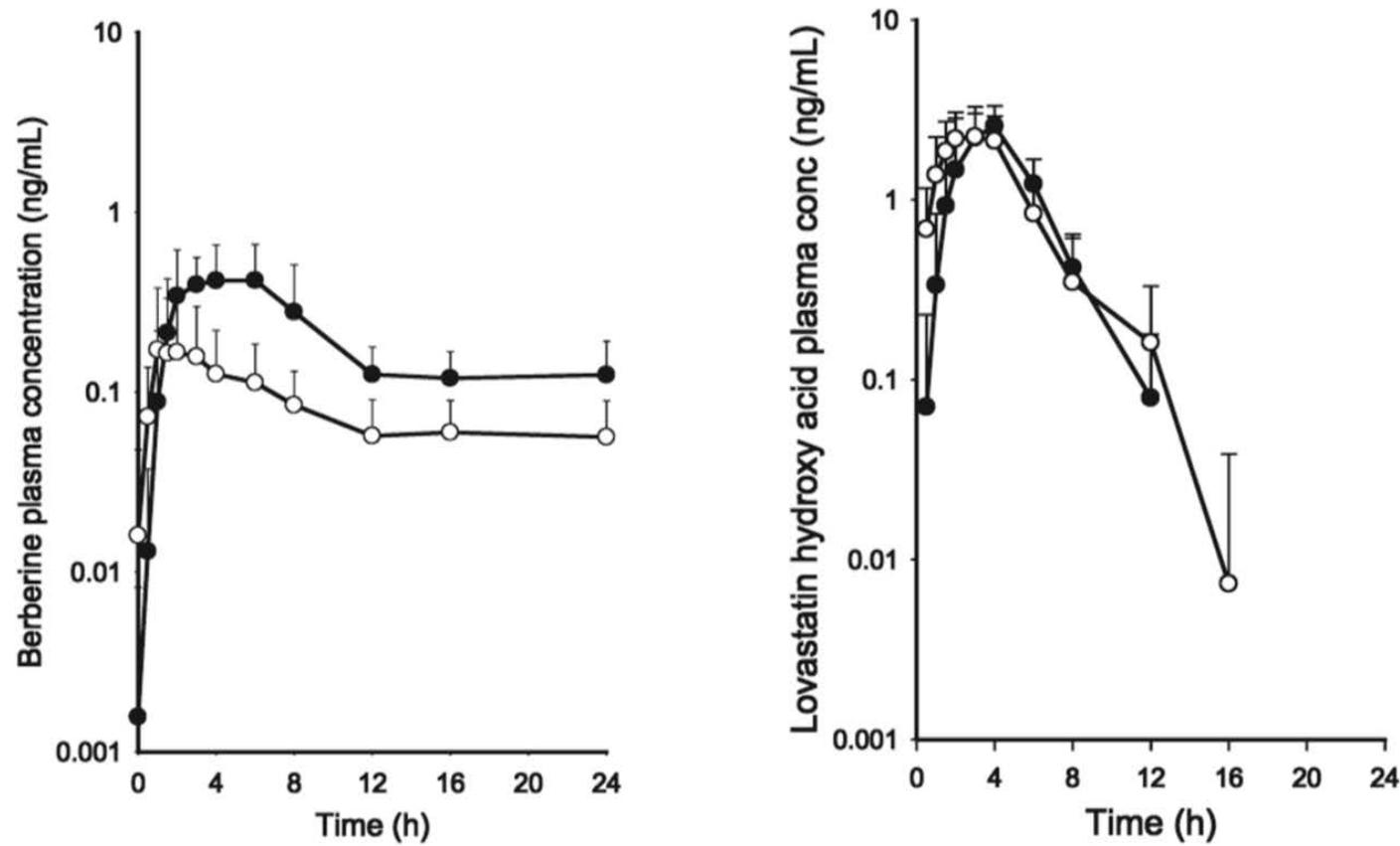
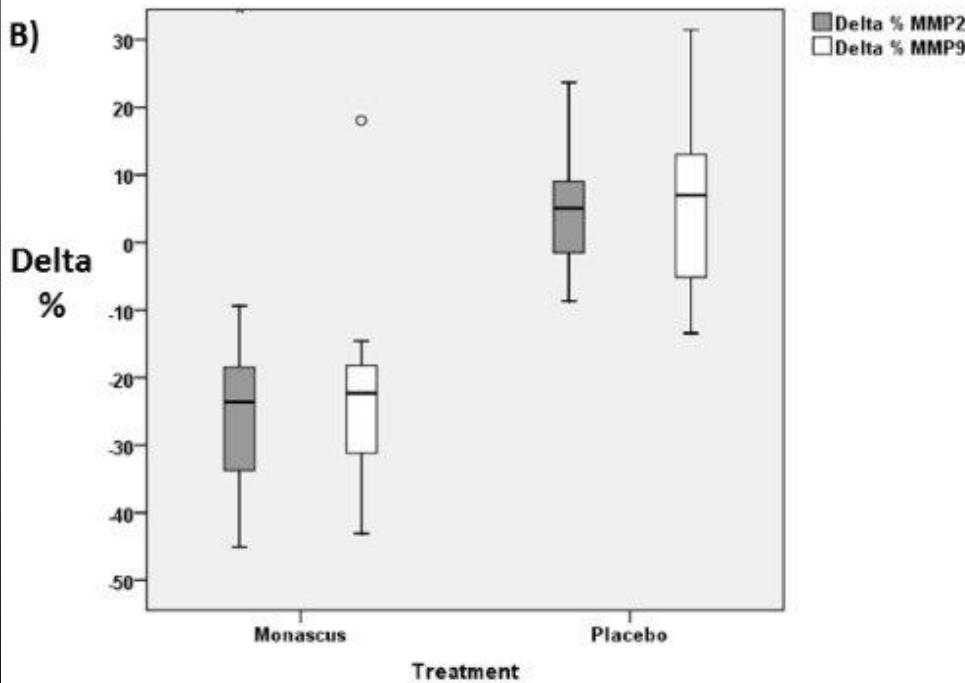
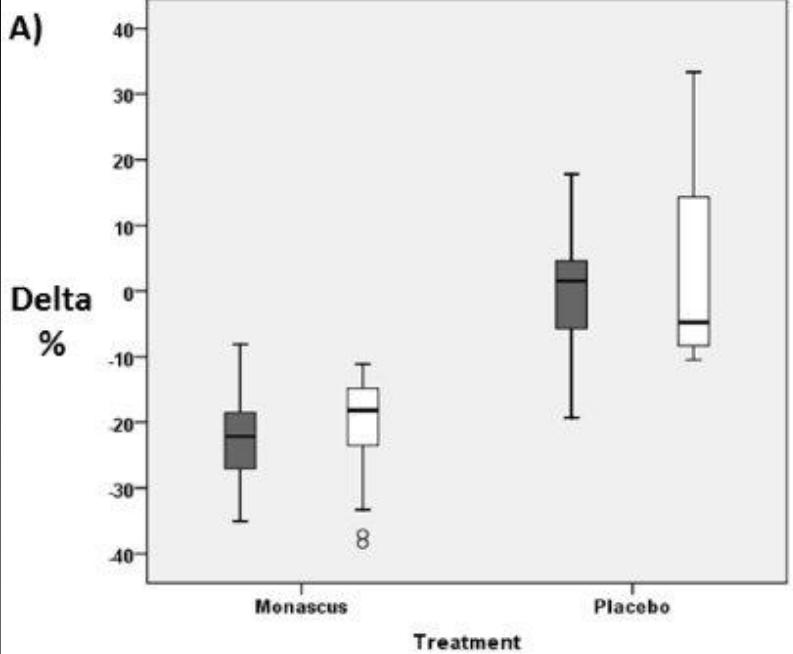


Fig. 1 Mean (\pm SD) plasma concentration-time profile of berberine and lovastatin hydroxy acid in fed condition (●) and fasted condition (○) in healthy subjects.

The efficacy of a nutraceutical emerges when its pharmacological power overwhelms the spontaneous variance of the studied parameters.

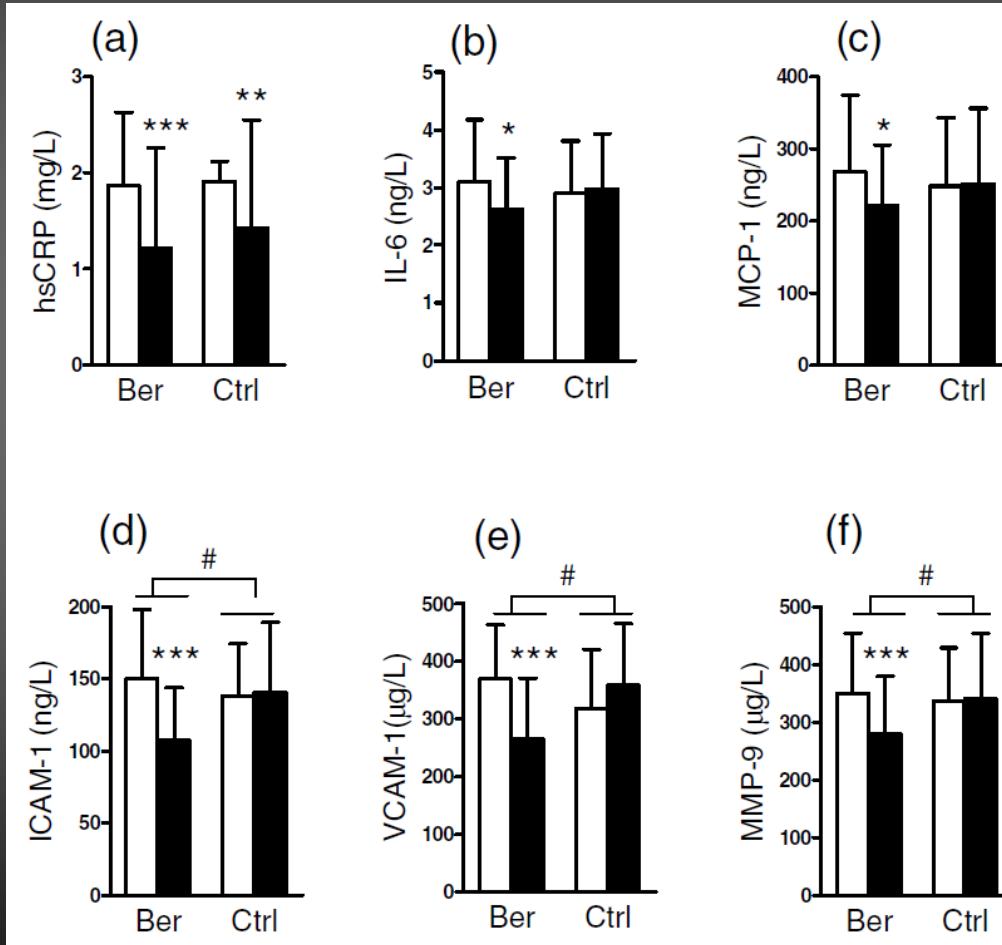
**Do exist clinical evidence of
nutraceutical efficacy on
«intermediate/hard» outcomes ???**

Red Yeast Rice, hsCRP and MMPs: a cross-over, RCT



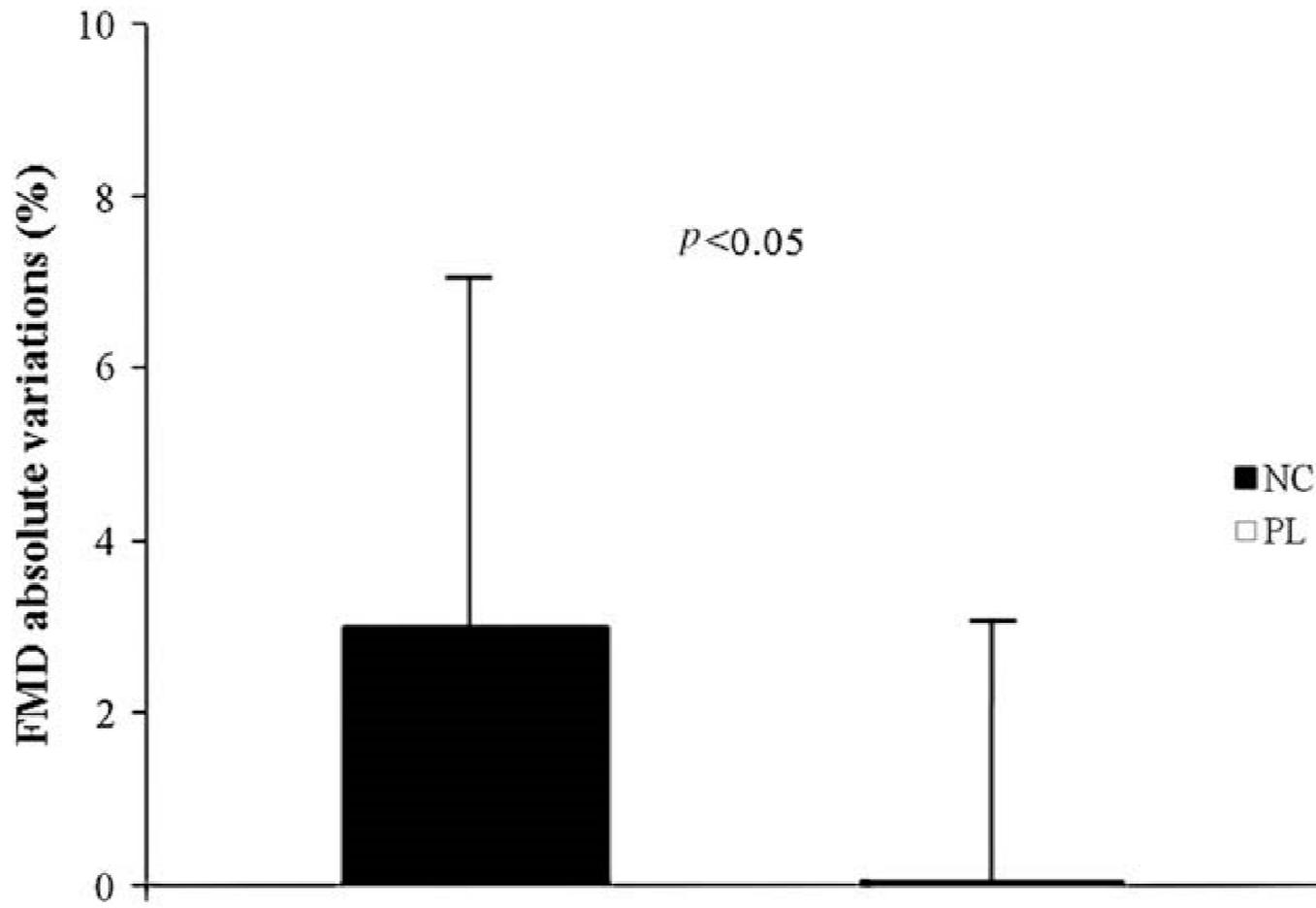
Cicero et al. 2013; Nutr Res
33(8):622-8.

Berberine ameliorates inflammation in patients with ACS following percutaneous coronary intervention

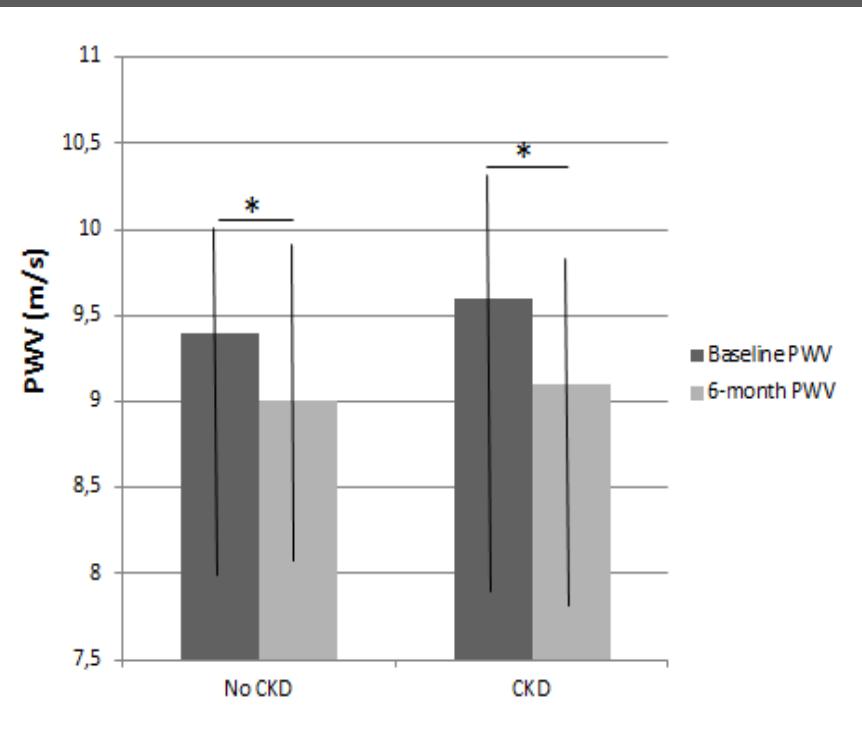
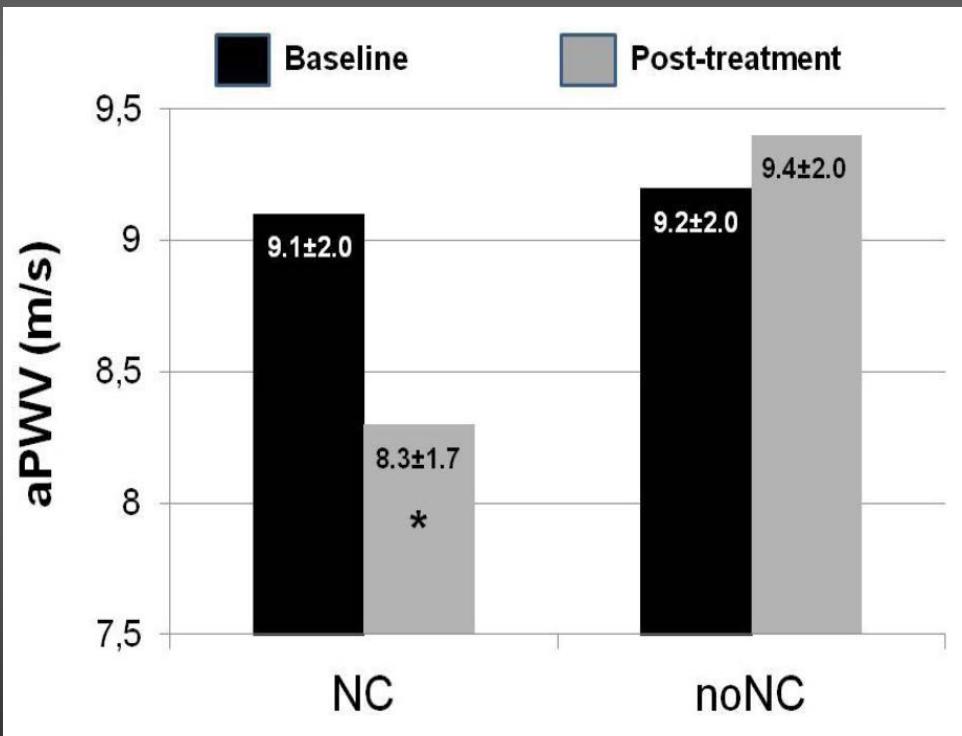


Clin Exp
Pharmacol
Physiol
2012;39(5):
406-11.

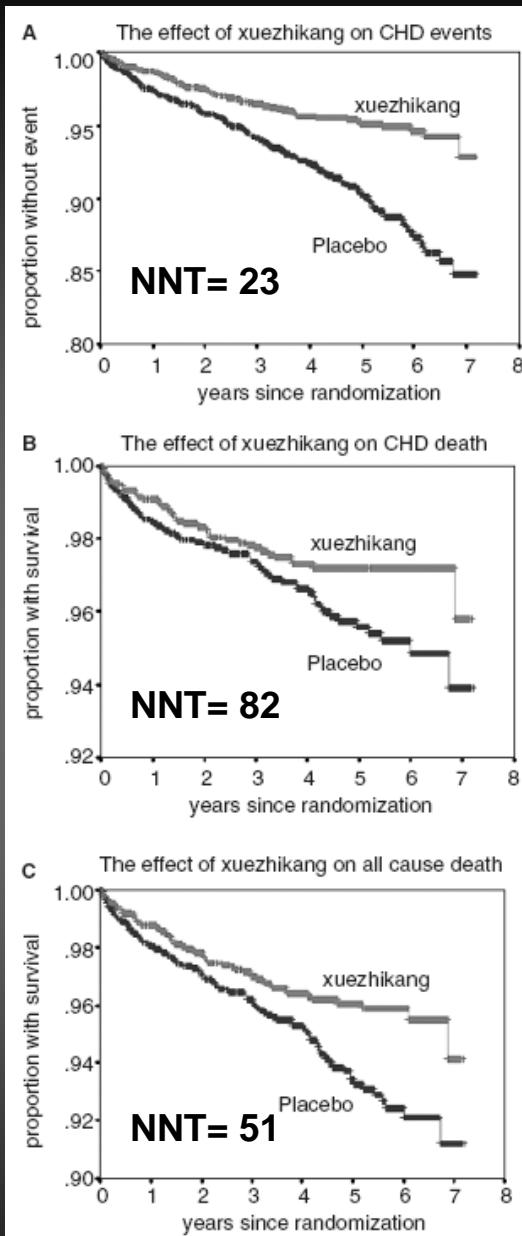
RYR-BRB effect on FMD



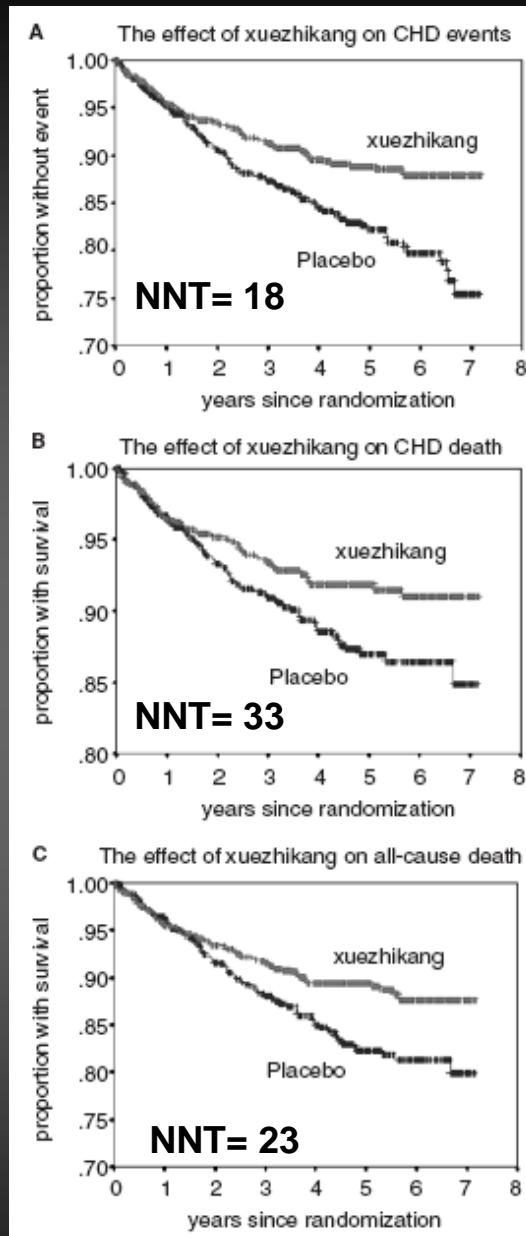
RYR-BRB effects on carotid-femoral PWV



China Coronary Secondary Prevention Study



Adult patients



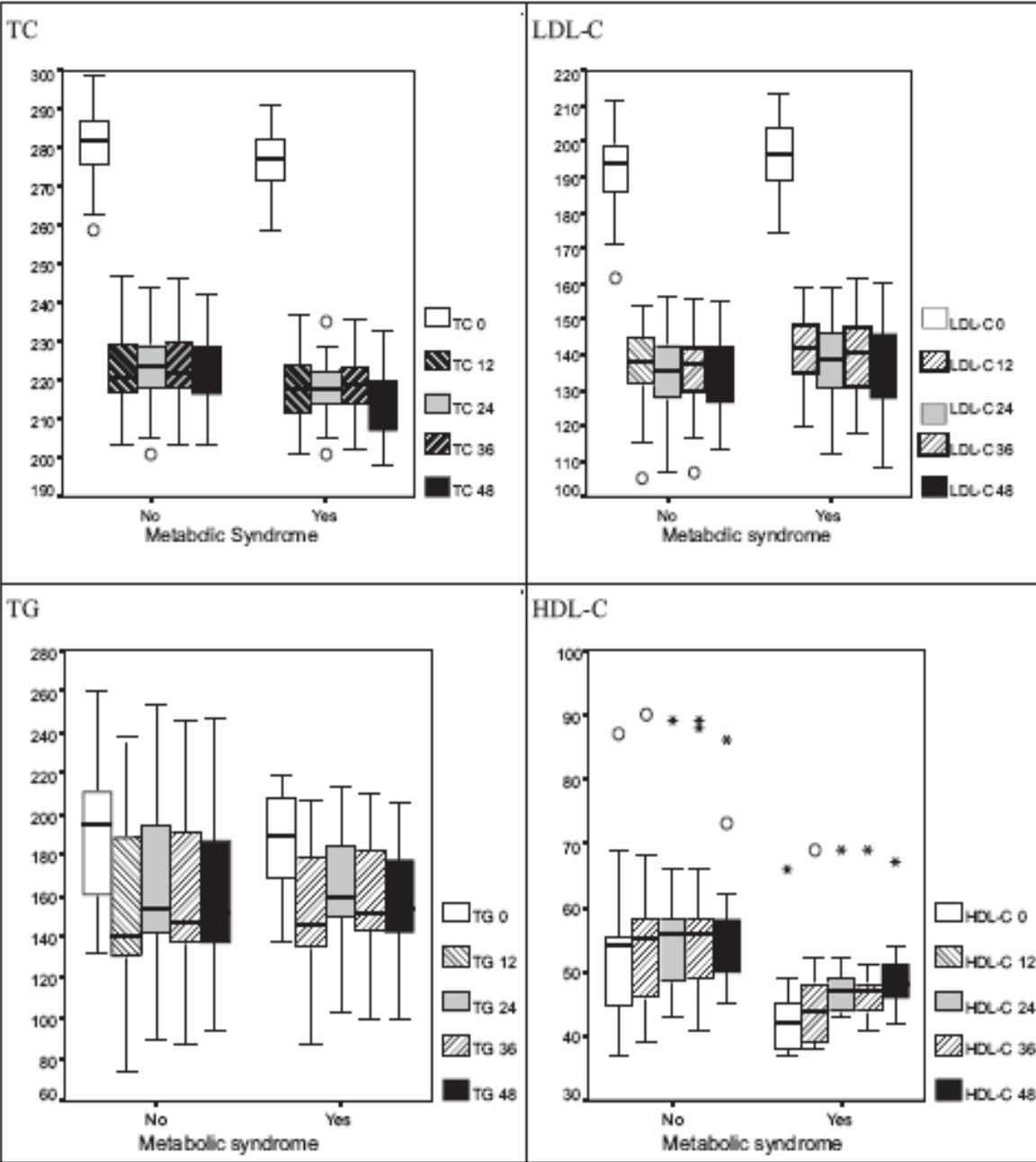
Elderly patients

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

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

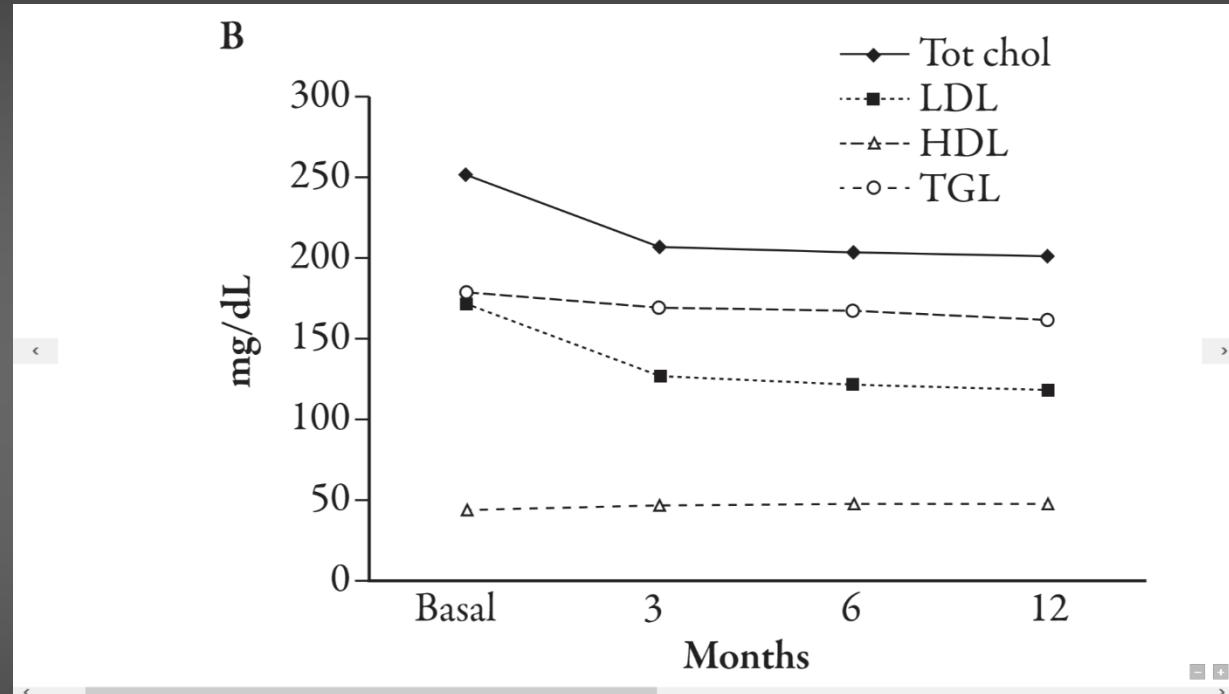
Long-term effectiveness and safety of an Armolipid Plus based approach to reduce cholesterololemia in statin intolerant subjects with and without metabolic syndrome

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



RYR-BRB tolerability in elderly (>75) statin intolerant patients (N. 80): a single-blind, placebo-controlled RCT

Marazzi G et al. Adv Ther 2011;28(12):105-13.



	NCP group		Placebo group	
	Basal	End	Basal	End
AST (U/L)	23±5	24±5	22±4	22±4
ALT (U/L)	25±6	28±5	26±4	26±4
CK (mU/mL)	113±25 ^F	119±18 ^G	116±20	117±25

No PK interaction with common drugs

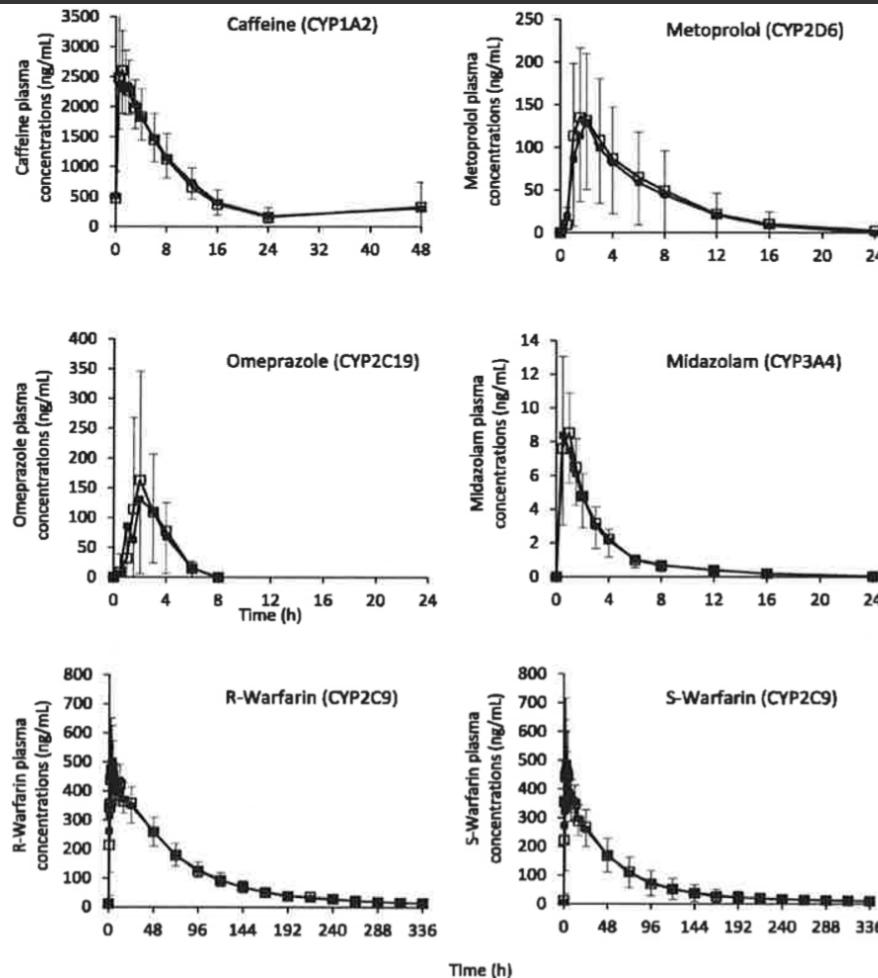


Fig. 1 Mean plasma concentrations for each probe administered as cocktail alone (reference treatment, open symbols) or with the combination of berberine and monacolin (test treatment, close symbol).

N = 12, SD are shown by positive vertical bar for the reference treatment and by negative vertical bar for the test treatment.

La controparte lipidica del colesterolo LDL...

- Trigliceridi
- Colesterolo HDL
- Colesterolo non-HDL
- Dislipidemia aterogena
- Sindrome Metabolica
- ...

Biological effects of n-3 FAs

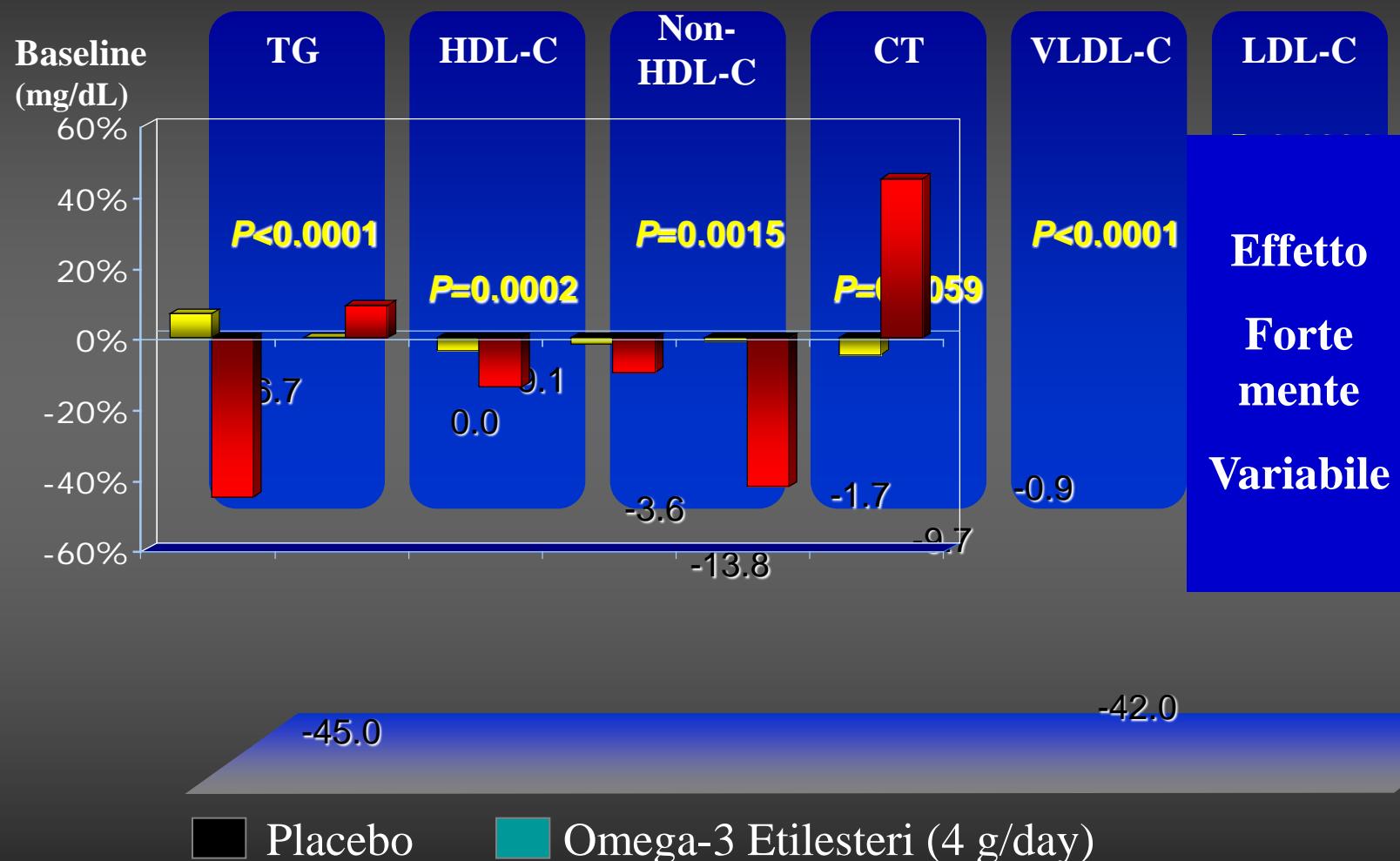
- * Interaction with omega-6 fatty acids
 - Production of inactive leucotrienes and thromboxanes
- * Decrease in biological mediators
 - IL-1, IL-2, TNF, PDGF
- * Effect on blood lipoprotein levels
 - Decrease in plasma VLDL and triglyceride levels
- * Hypotensive effect
 - Changes in eicosanoids, in blood viscosity, in hormonal-cellular response, in renin secretion, decreased response to vasopressors
- * Decrease in plasma viscosity
 - Decreased plasma fibrinogen
- * Effects on coagulation
 - Prolonged bleeding time, decrease in fibrinogen, factor VII, von Willebrand factor, increased fibrinolysis
- * Increased arterial compliance
 - Increased production of nitric oxide
- * Effects on adhesion molecules
 - Decreased ICAM-1, VCAM-1, E-selectin levels.
- * Effects on vascular smooth muscle cells
 - Modulation of proliferation, migration and apoptosis and improved vasoreactivity by interaction with intracellular calcium dynamics.

Scientific evidences

- Children development – B
- Hypertension – A
- Hypertriglyceridemia – A
- Primary CV prevention – B
- Secundary CV prevention – A
- Age-related macular degeneration – B
- Stroke prevention – C
- Dementia – C
- Cancer prevention – C
- Obesity - C
- Systemic inflammatory diseases – C
- Psychiatric disorders – C
- IgA Nephropathy - C

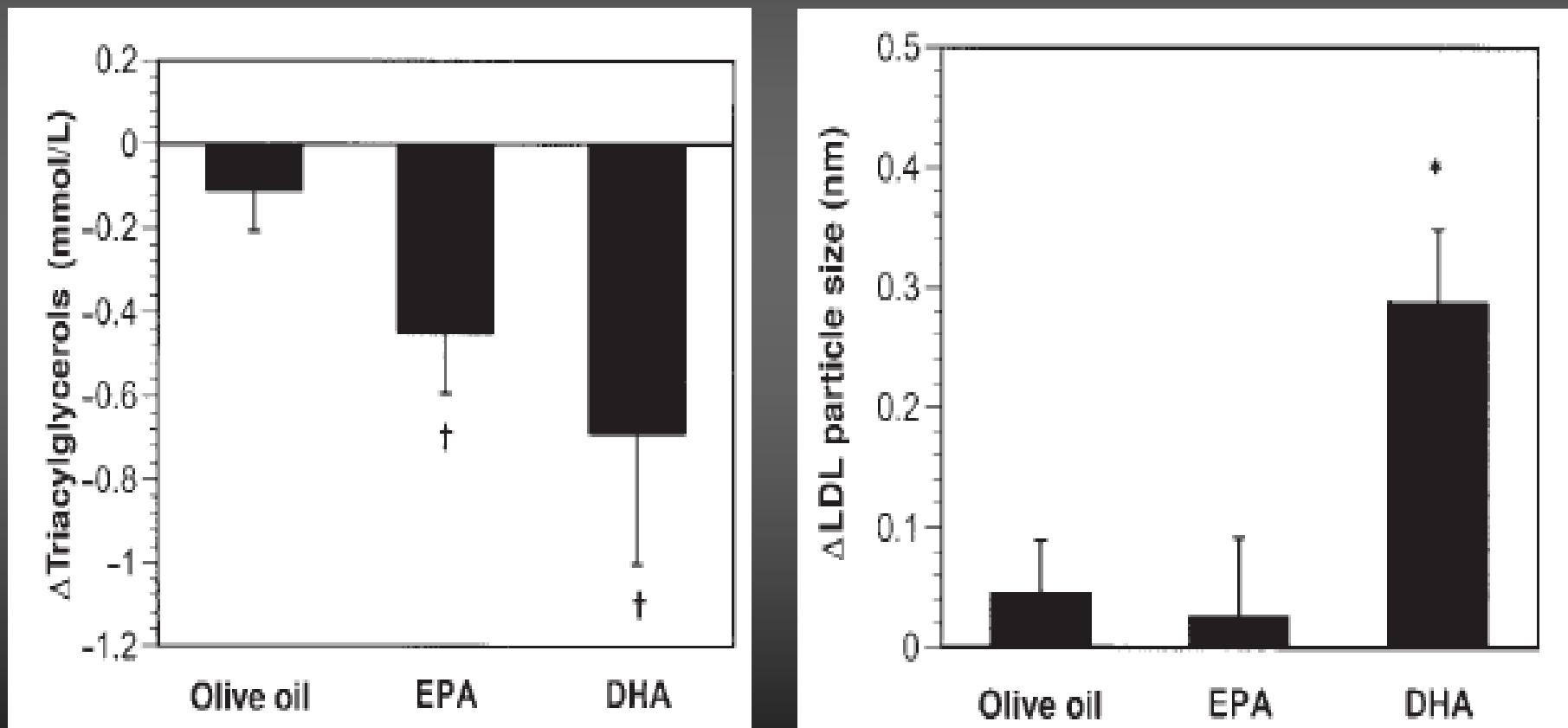


Omega-3 etilesteri e lipidi plasmatici in pazienti con TG >500 mg/dL



Pooled analysis: Harris WS et al. J Cardiovasc Risk 1997;4:385-391. Pownall HJ et al. Atherosclerosis 1999;143:285-297.

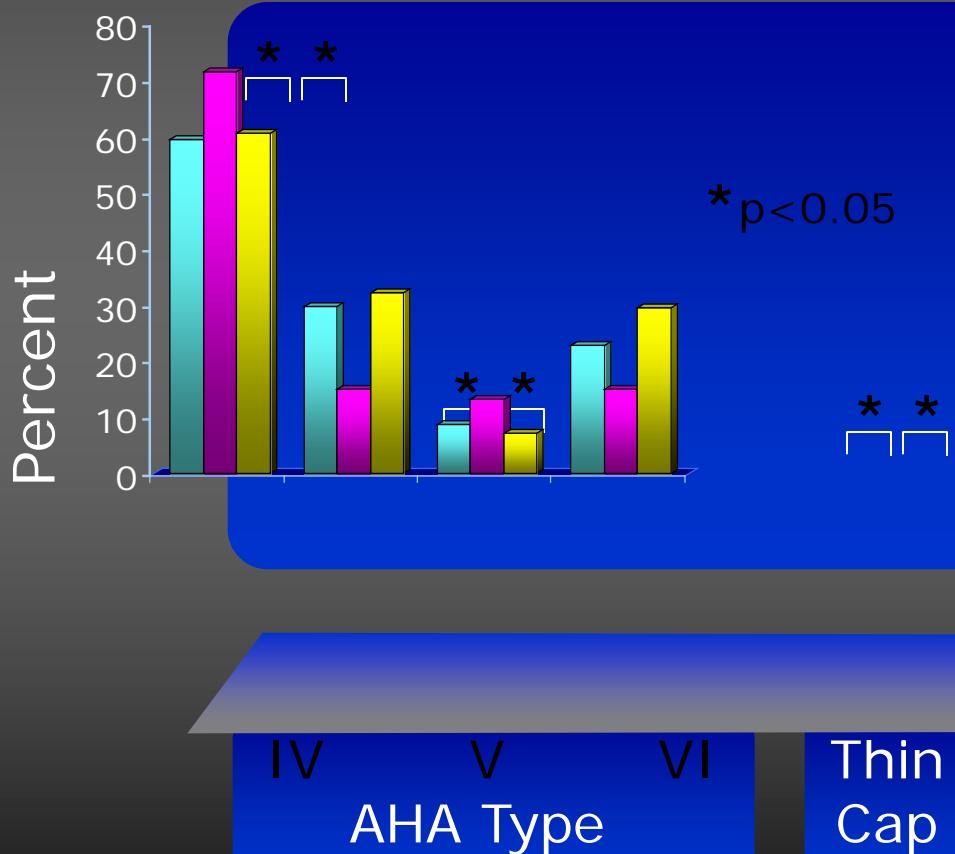
Purified EPA and DHA have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men



Mori et al. *Am J Clin Nutr* 2000;71:1085–94

Omega-3 FA and Plaque Stability: *Plaque Characteristics*

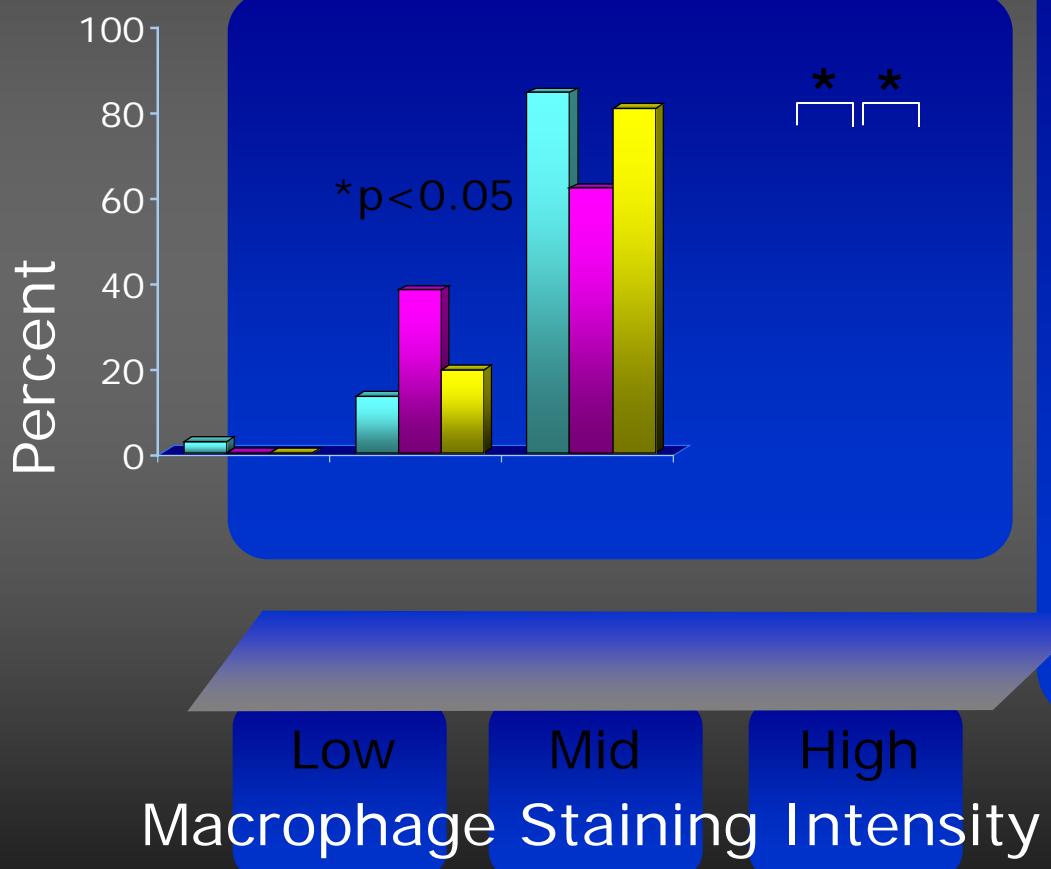
■ Control ■ Omega-3 ■ Omega-6



- Patients awaiting carotid endarterectomy ($n=188$) were randomized to control, fish oil (omega-3), or sunflower oil (omega-6) supplementation for median 34, 46, and 43 days preprocedure
- Plaques in omega-3 patients appeared to be more stable

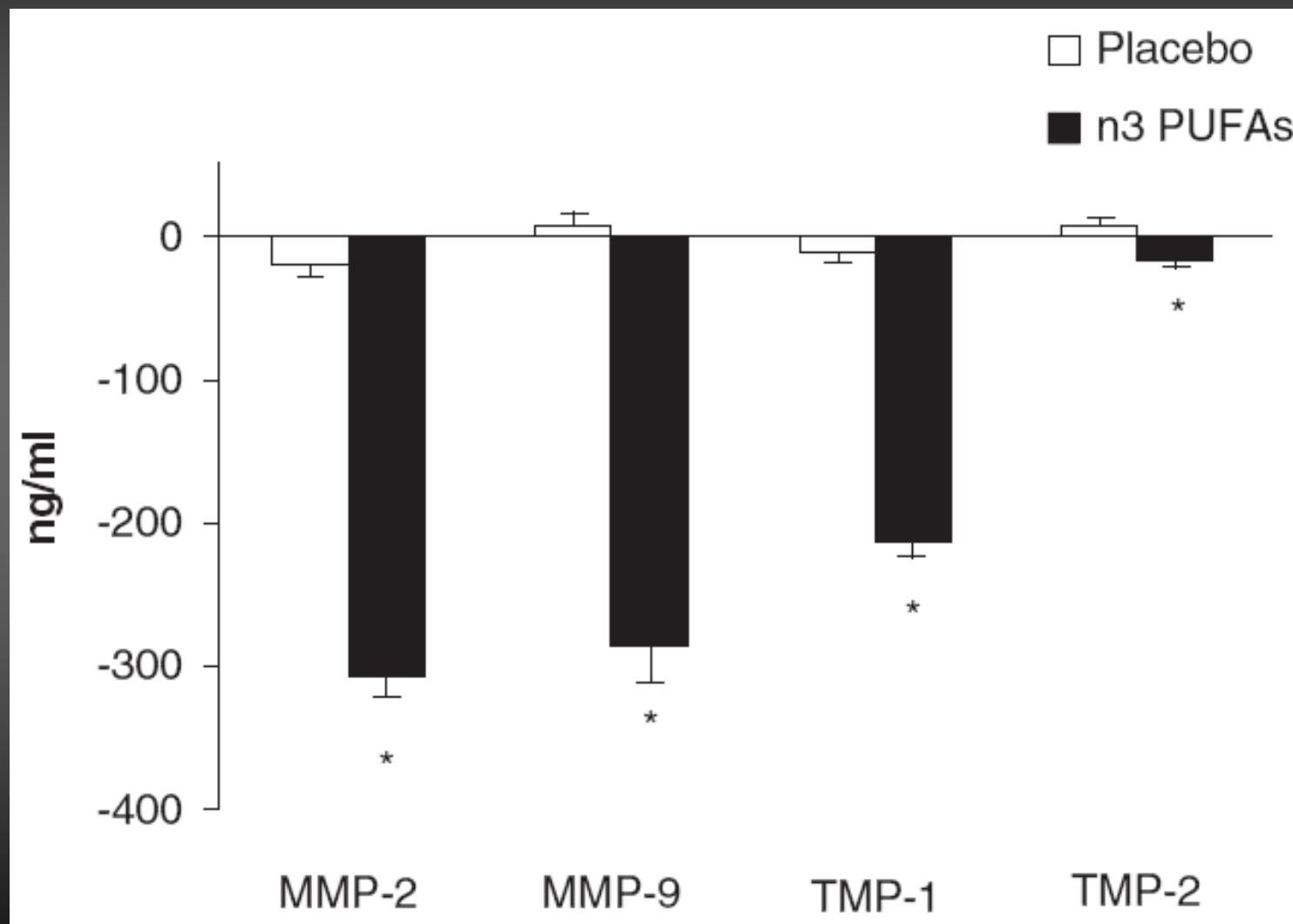
Omega-3 FA and Plaque Stability: *Macrophage Staining Intensity*

■ Control ■ Omega-3 ■ Omega-6

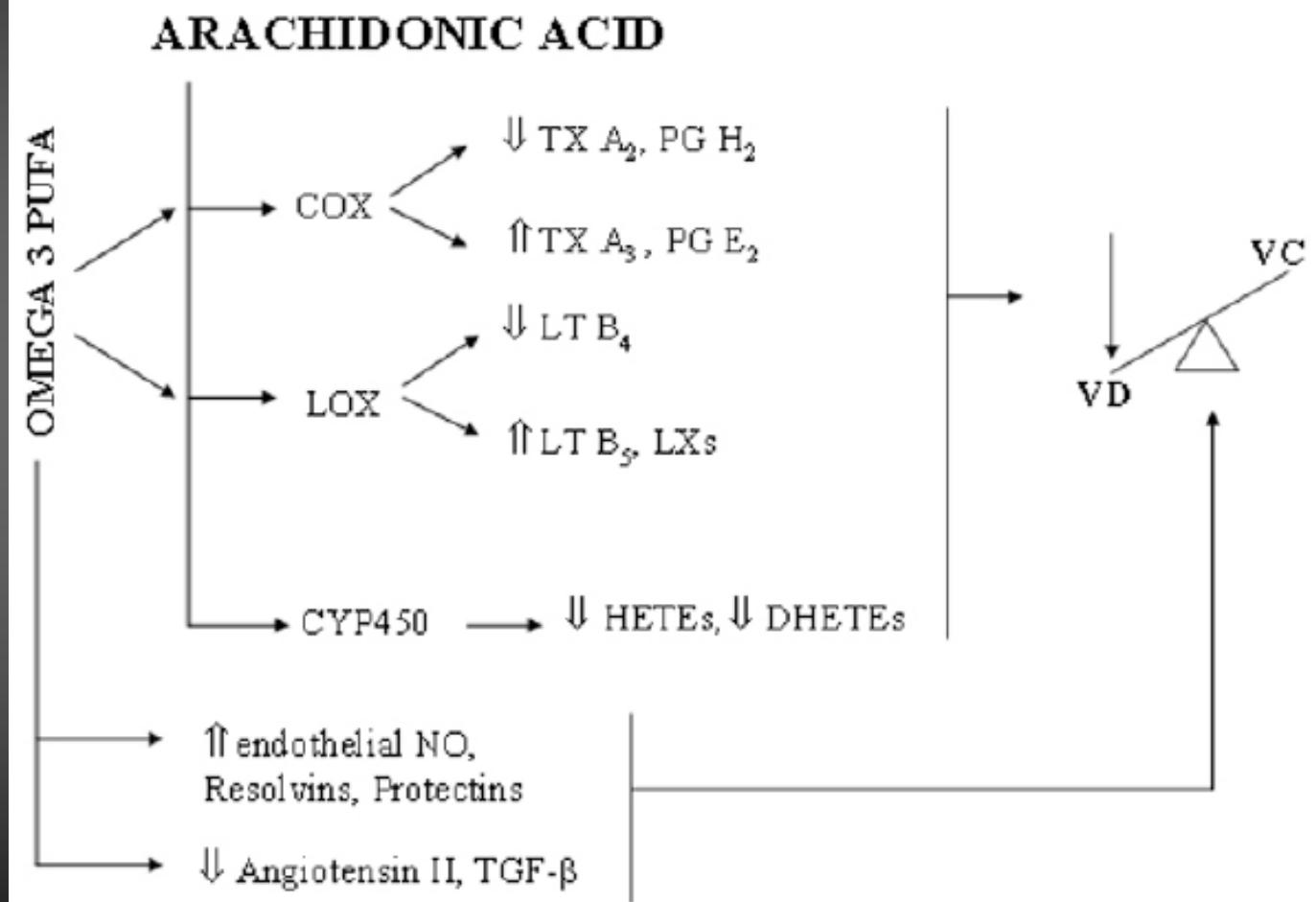


- Plaque burden of macrophages (CD68) and T cells (CD3) was examined by immuno-histochemistry
- There was less macrophage staining in the omega-3 group

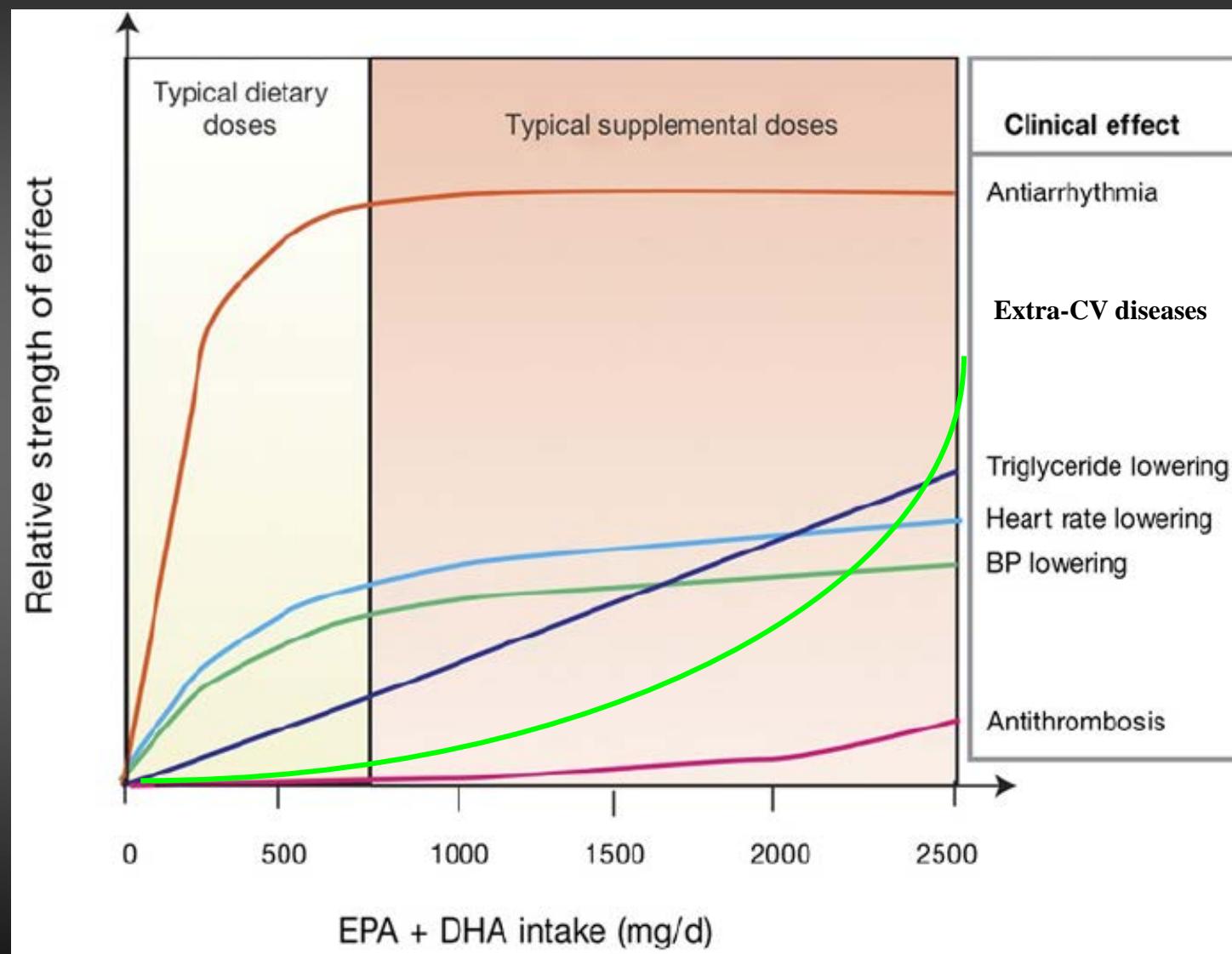
Effect of 3gr/day EPA/DHA on MMP and TIMP plasma level



Omega 3 PUFAs and BP



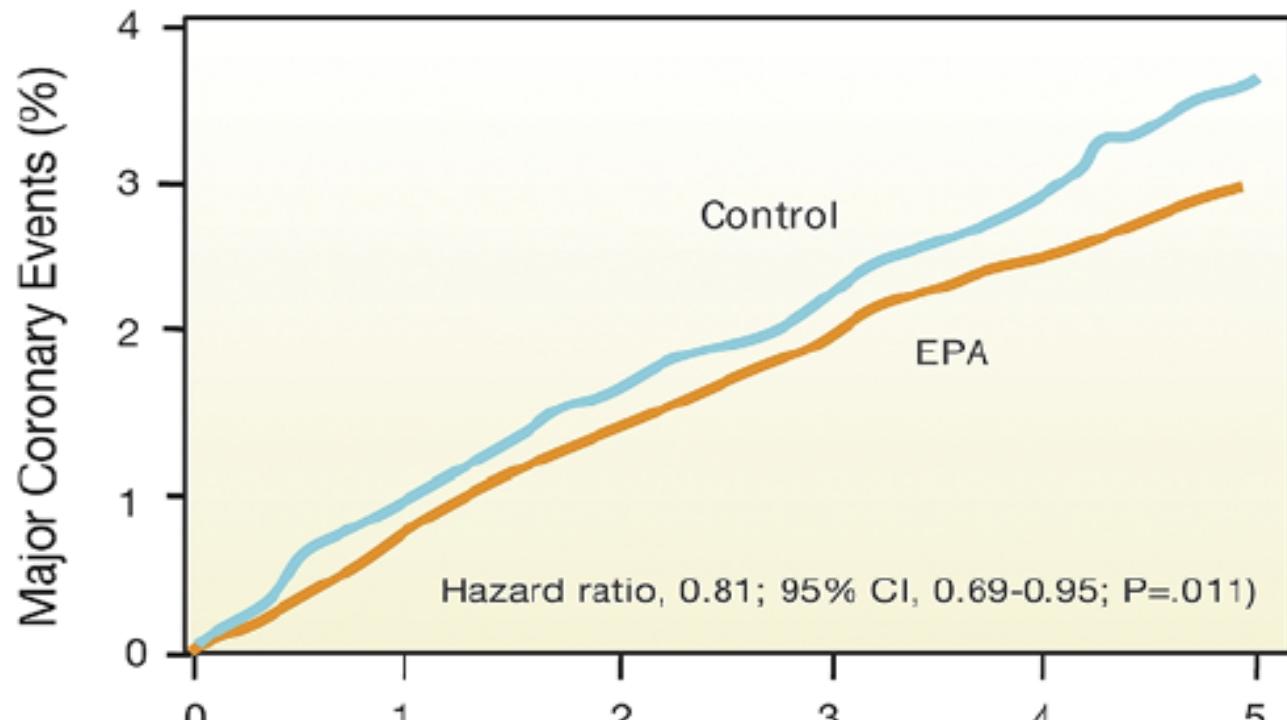
EPA/DHA dosing and CV effects



PUFAs in primary prevention: the JELIS study

Control =
Prava
20/Simva
5 mg

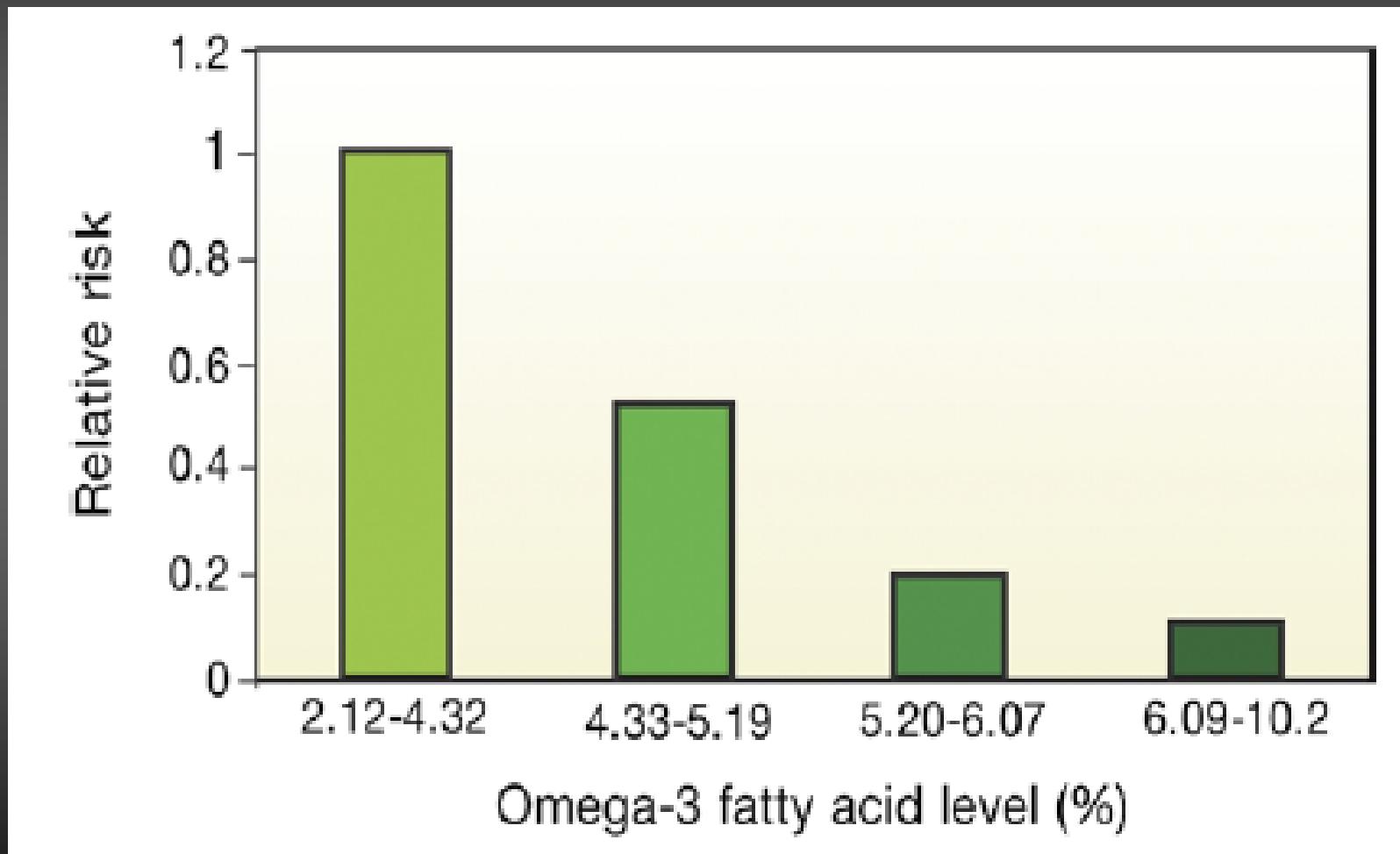
EPA=
Idem +
EPA 1800
mg



No. of patients at risk

Control group	9319	8931	8671	8433	8192	7958
Treatment group	9326	8929	8658	8389	8153	7924

Plasma PUFA level and CVD mortality risk in secondary prevention



Albert CM et al. N Engl J Med 2002;346:1113– 8.

Relationships Between On-Treatment EPA, AA, and EPA/AA Ratio, and Adjusted Risk of Coronary Events

Endpoint	Major coronary events			Sudden cardiac death or fatal/nonfatal MI		
	Low	Intermediate	High	Low	Intermediate	High
EPA (mol%)	0–2.59	2.60–4.79	≥4.80	0–2.59	2.60–4.79	≥4.80
No. of patients	1,047	1,125	1,089	1,047	1,125	1,089
HR (95%CI)	1.00	1.02 (0.78–1.35)	0.82 (0.62–1.09)	1.00	0.74 (0.45–1.24)	0.65 (0.38–1.10)
P value (vs Low)		0.854	0.172		0.258	0.107
AA (mol%)	0–4.24	4.25–4.99	≥5.00	0–4.24	4.25–4.99	≥5.00
No. of patients	1,050	1,032	1,179	1,050	1,032	1,179
HR (95%CI)	1.00	0.99 (0.75–1.31)	1.18 (0.91–1.55)	1.00	1.43 (0.82–2.51)	1.78 (1.04–3.02)
P value (vs Low)		0.927	0.212		0.209	0.035
EPA/AA ratio	0–0.55	0.56–1.05	≥1.06	0–0.55	0.56–1.05	≥1.06
No. of patients	1,064	1,108	1,089	1,064	1,108	1,089
HR (95%CI)	1.00	0.96 (0.73–1.26)	0.80 (0.61–1.06)	1.00	0.62 (0.37–1.04)	0.58 (0.34–0.97)
P value (vs Low)		0.759	0.113		0.069	0.038

CHOLINE

PHOSPHATE

GLYCEROL

1 FATTY ACID

2 FATTY ACID

DHA and EPA

KRILL



SERINE

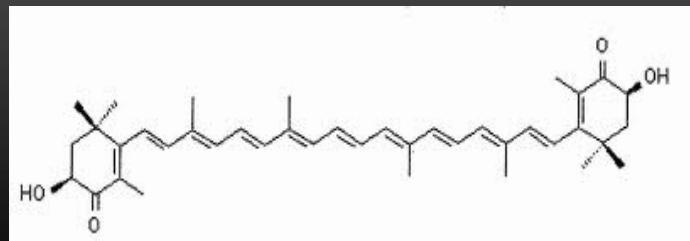
PHOSPHATE

GLYCEROL

1 FATTY ACID

2 FATTY ACID

DHA and EPA



Plasma phospholipid EPA, DHA, and total n-3 FA levels 72 h after ingestion of supplements

		rTAG	EE	Krill oil	<i>p</i> *
AUC [%*h]	EPA	37.05 ± 15.97	38.68 ± 18.60	53.62 ± 17.31	0.057
	DHA	22.73 ± 26.23	8.85 ± 22.57	26.41 ± 29.54	0.246
	EPA+DHA	59.78 ± 36.75	47.53 ± 38.42	80.03 ± 34.71	0.119
	total n-3 FA	66.35 ± 37.53	49.49 ± 46.88	88.40 ± 42.81	0.134
C _{max} [%]	EPA	0.98 ± 0.26	0.79 ± 0.51	1.18 ± 0.45	0.095
	DHA	0.42 ± 0.48	0.21 ± 0.18	0.40 ± 0.41	0.323
	EPA+DHA	1.12 ± 0.66	0.72 ± 0.76	1.51 ± 0.69	0.039
	total n-3 FA	1.44 ± 1.06	0.73 ± 0.76	1.44 ± 0.89	0.110
t _{max} [h]	EPA	11.5 ± 7.6	10.2 ± 8.6	7.8 ± 5.8	0.500
	DHA	5.0 ± 6.2	9.8 ± 20.6	4.2 ± 6.6	0.538
	EPA+DHA	10.5 ± 10.2	9.0 ± 9.2	7.1 ± 6.0	0.649
	total n-3 FA	16.2 ± 20.2	9.0 ± 9.2	8.0 ± 8.2	0.307

Enhanced increase of omega-3 index in healthy individuals with response to 4-week supplementation from krill vs. fish/corn oil

Parameter	Treatment	Baseline		End-Point		Change	
		Mean ± STD	P. value ¹	Mean ± STD	P. value ¹	Mean ± STD	P. value ¹
EPA	Krill oil	0.82 ± 0.23	0.8825	1.48 ± 0.38 ^{*#}	<0.0001	0.66 ± 0.29 ^{*#}	<0.0001
	Fish oil	0.80 ± 0.23		1.10 ± 0.25 [*]		0.30 ± 0.26 [*]	
	Corn oil	0.80 ± 0.21		0.74 ± 0.22		-0.05 ± 0.16	
DPA	Krill oil	2.24 ± 0.27	0.7470	2.42 ± 0.21 ^{*#}	0.0421	0.18 ± 0.23	0.0787
	Fish oil	2.29 ± 0.28		2.28 ± 0.24		-0.01 ± 0.29	
	Corn oil	2.25 ± 0.34		2.26 ± 0.27		0.00 ± 0.31	
DHA	Krill oil	4.12 ± 0.83	0.2140	4.50 ± 0.75 [*]	0.0039	0.38 ± 0.44 ^{*#}	0.0002
	Fish oil	4.16 ± 0.73		4.34 ± 0.83		0.17 ± 0.64	
	Corn oil	4.21 ± 0.89		4.12 ± 0.72		-0.09 ± 0.56	
Total n-3 PUFA	Krill oil	7.52 ± 1.03	0.4531	8.74 ± 1.08 ^{*#}	<0.0001	1.22 ± 0.77 ^{*#}	<0.0001
	Fish oil	7.59 ± 0.86		8.04 ± 1.00 [*]		0.45 ± 1.00 [*]	
	Corn oil	7.59 ± 1.22		7.47 ± 0.95		-0.11 ± 0.90	
EPA + DHA	Krill oil	4.94 ± 0.97	0.6873	5.97 ± 1.03 ^{*#}	<0.0001	1.04 ± 0.59 ^{*#}	<0.0001
	Fish oil	4.96 ± 0.79		5.43 ± 0.97 [*]		0.47 ± 0.77 [*]	
	Corn oil	5.00 ± 1.02		4.86 ± 0.80		-0.14 ± 0.61	

Lipid-lowering and anti-inflammatory effects of ω-3 ethyl esters and krill oil: a randomized, cross-over, clinical trial

Inclusion criteria: age between 18 and 70 years, and fasting plasma TG level between 150 and 500 mg/dL, confirmed at least in 2 sequential blood samples before signing the consent form.

Treatments: omega 3 ethyl ester PUFAs 1000 mg twice a day vs. krill oil 500 mg twice a day to be taken once a day, at evening before the meal

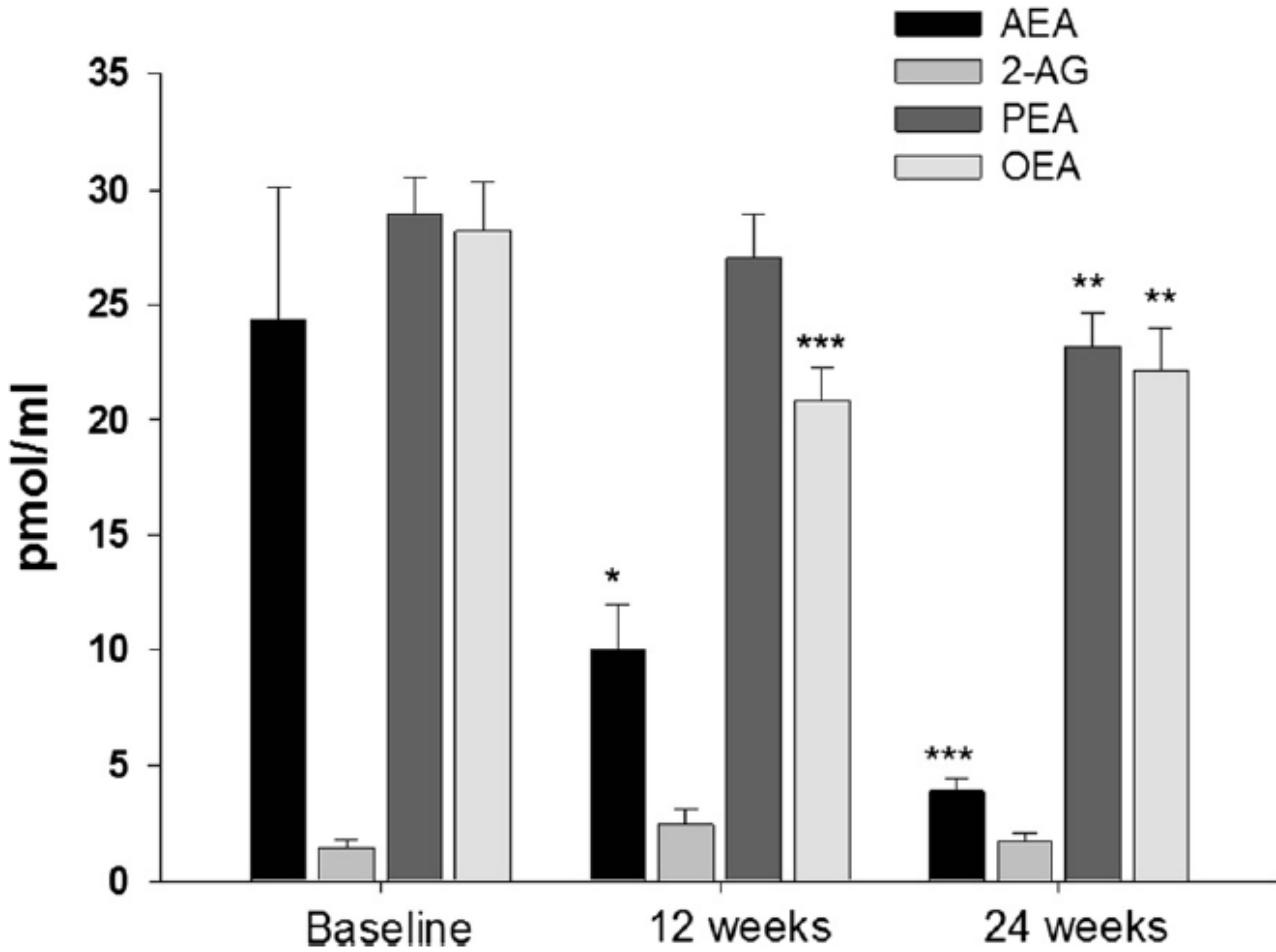
Lipid-lowering and anti-inflammatory effects of ω-3 ethyl esters and krill oil: a randomized, cross-over, clinical trial

	Esterified Omega 3 PUFAS (n. 25)			Krill Oil (n. 25)		
Δ (T1-T0)	Mean	SD	P vs Baseline	Mean	SD	P vs Baseline
Δ TC (mg/dL)	-2.1	3.4	0.397	-3.8	4.1	0.078
Δ HDL-C (mg/dL)	+1.4	4.9	0.156	+4.5*	2.1	0.039
Δ LDL-C (mg/dL)	-1.9	3.8	0.462	-3.7	3.9	0.111
Δ TG (mg/dL)	-72.8	28.9	0.001	-55.7*	18.3	0.003
Δ Non HDL-C (mg/dL)	-3.1	3.8	0.069	-8.1*	4.7	0.009
Δ ApoAI (mg/dL)	+11.1	20.9	0.060	+19.4	15.1	0.049
Δ ApoB (mg/dL)	-2.8	8.8	0.958	-2.6	5.45	0.529
Δ FPG (mg/dL)	+1.9	8.5	0.665	+2.2	11.4	0.758
Δ Creatinine (mg/dL)	-0.07	0.21	0.087	-0.03	0.14	0.317
Δ CPK (U/L)	+6.8	34.35	0.569	+4.4	44.3	0.668
Δ AST (U/L)	+4.5	11.7	0.363	+2.2	4.8	0.133
Δ ALT (U/L)	+5.4	14.7	0.360	+1.1	10.0	0.581
Δ hs-CRP (mg/L)	-0.14	0.07	0.030	-0.35*	0.12	<0.001

Lipid-lowering and anti-inflammatory effects of ω-3 ethyl esters and krill oil: a randomized, cross-over, clinical trial

	Esterified Omega 3 PUFAS (n. 25)			Krill Oil (n. 25)		
Δ (T1-T0)	Mean	SD	P vs Baseline	Mean	SD	P vs Baseline
Δ HDL-C (mg/dL)	+1.4	4.9	0.156	+4.5*	2.1	0.039
Δ TG (mg/dL)	-72.8	28.9	0.001	-55.7*	18.3	0.003
Δ Non HDL-C (mg/dL)	-3.1	3.8	0.069	-8.1*	4.7	0.009
Δ ApoAI (mg/dL)	+11.1	20.9	0.060	+19.4	15.1	0.049
Δ hs-CRP (mg/L)	-0.14	0.07	0.030	-0.35*	0.12	<0.001

Krill powder reduces plasma TG and anandamide levels in mildly obese men



Parameter	Baseline	Week 12	Week 24
Cholesterol (mg/dL)	210.3 ± 27.7	203.0 ± 39.5	206.3 ± 40.8
HDL (mg/dL)	45.1 ± 9.5	43.2 ± 10.5	43.6 ± 9.8
LDL (mg/dL)	139.1 ± 24.2	133.0 ± 28.6	137.9 ± 33.6
Triglycerides (mg/dL)	192.6 ± 96.3	149.3 ± 70.5	$152.8 \pm 96.2 *$

Berge et al. Lipids in Health and Disease 2013, 12:78

Effects of Krill Oil Premenstrual Syndrome and Dysmenorrhea

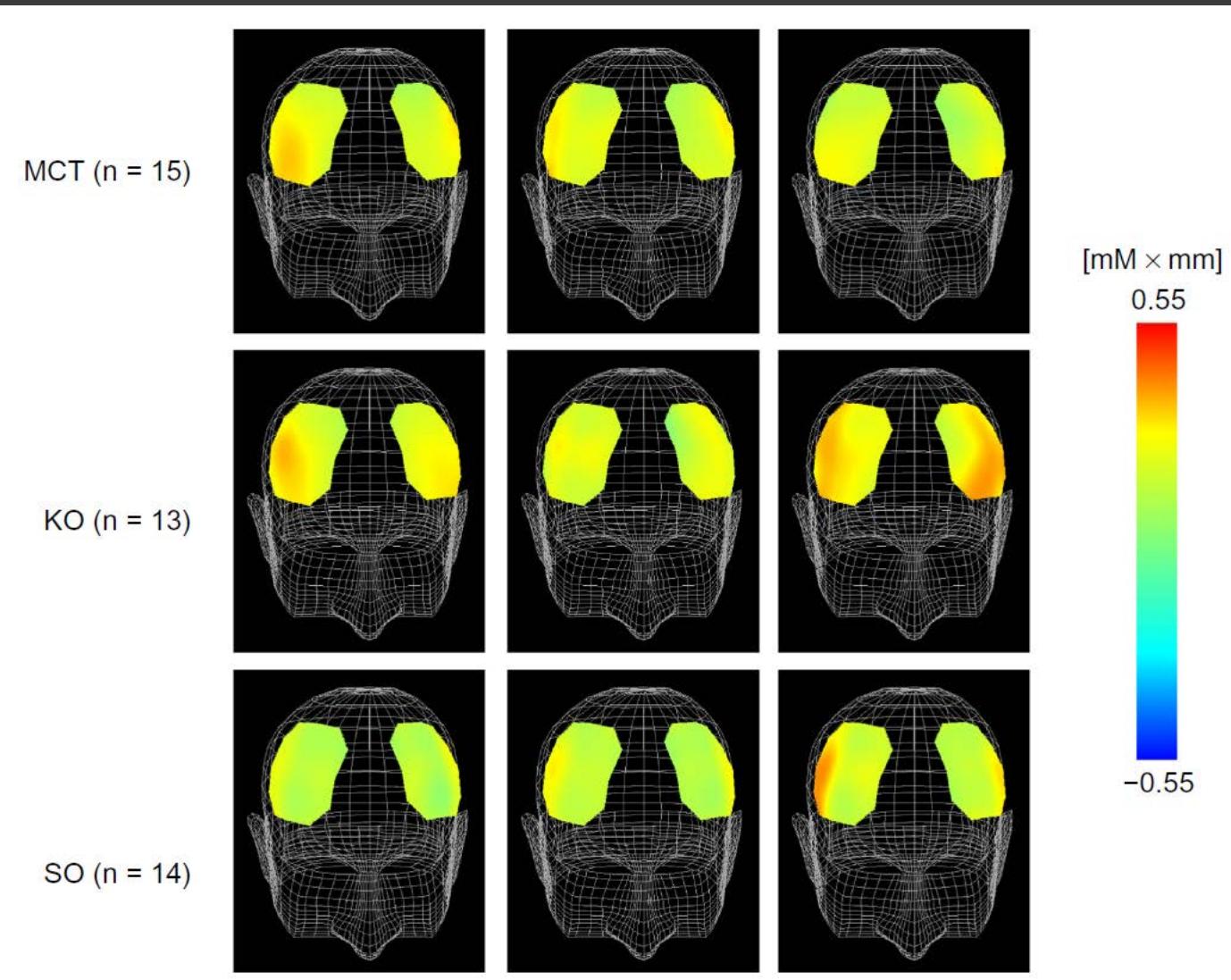
Symptom	Krill Oil						Control					
	Base-line*	45 days		90 days		Mean diff.**	Base-line*	45 days		90 days		Mean diff.**
		Score (SD)	P-value	Score (SD)	P-value			Score (SD)	P-value	Score (SD)	P-value	
Breast Tenderness	6.9	5.7(2)	<0.001	4.0(2)	<0.001	0.3	5.9	4.9(2)	=0.38	5.0(2)	=0.38	0.2
Overwhelmed	6.7	5.2(2)	<0.001	3.9 (2)	<0.001	0.3	7.0	5.9(1)	=0.06	6.7(2)	=0.40	0.1
Stress	7.2	5.7(2)	<0.001	4.5(3)	<0.001	0.2	6.9	5.4(2)	=0.07	6.1(2)	=0.07	0.1
Irritable	6.0	5.1(2)	<0.001	3.2(2)	<0.001	0.3	5.8	4.9(2)	=0.13	5.2(2)	=0.13	0.1
Depression	6.9	5.4(2)	<0.001	4.2(2)	<0.001	0.2	7.2	5.4(3)	=0.27	6.3(2)	=0.27	0.1
Joint Pain	5.8	4.7(2)	<0.001	2.1(2)	<0.001	0.5	5.2	3.7(3)	=0.18	4.0(2)	=0.18	0.2
Weight Gain	7.5	5.8(2)	<0.001	5.3(3)	<0.001	0.2	8.0	4.7(3)	=0.04	6.8(1)	<0.01	0.2
Abdominal Pain	7.4	5.6(2)	<0.001	4.9(2)	<0.001	0.2	7.0	4.9(4)	=0.04	5.6(3)	<0.001	0.2
Swelling	7.6	5.6(2)	<0.001	4.8(2)	<0.001	0.2	6.9	4.7(3)	=0.07	5.2(2)	<0.001	0.2
Bloating	7.6	6.1(2)	<0.001	6(2)	<0.001	0.1	7.1	6.0(3)	=0.08	6.4(2)	=0.08	0.1

Range:0-10

* Higher scores indicate more severe symptoms.

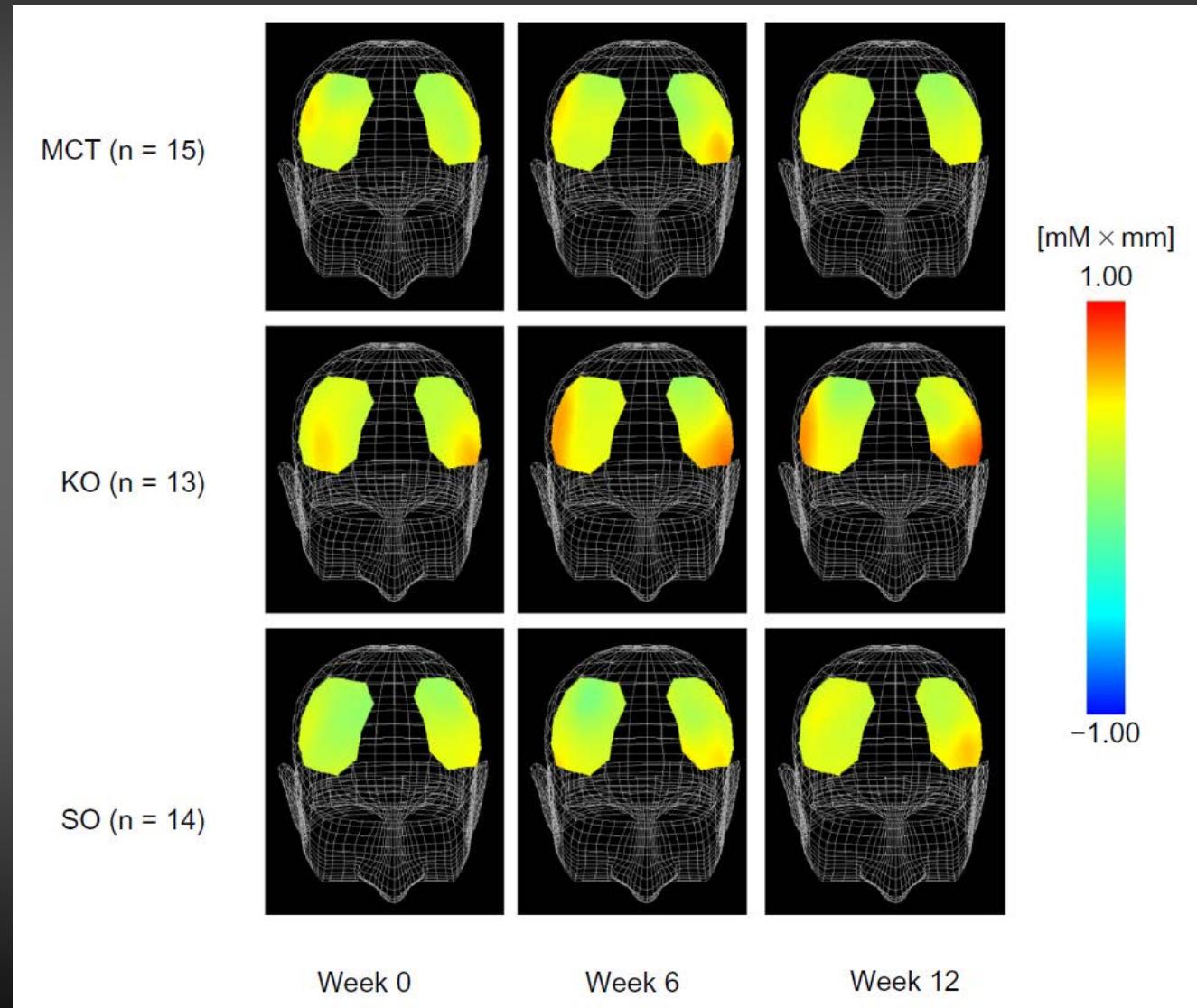
**Mean difference refers to the mean difference observed between baseline and 90 days of treatment.

Topographic maps of changes in oxy-hb concentration at 225.0 seconds during working memory task



Clin Interv
Aging 2013:8
1247–1257

Topographic maps of changes in oxy-hb concentration at 150.0 seconds during the calculation task



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1247–1257

«Esercizio e nutraceutici e i trigliceridi non calano mai!!!»

