



Replicability issues in pharmacological and clinical research

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Agenda

- General remarks
- Gender
- Quality and composition of active pharmaceutical ingredients
- Conclusion

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Reproducibility and replicability

- *Reproducibility* is obtaining consistent results using the same input data; computational steps, methods, and code; and conditions of analysis.
 - This definition is synonymous with “computational reproducibility”.
- *Replicability* is obtaining consistent results across studies aimed at answering the same scientific question, each of which has obtained its own data.
 - Two studies may be considered to have replicated if they obtain consistent results given the level of uncertainty inherent in the system under study.

Replicability crisis in Science?

Interdisciplinary training on the crucial issues on
reliability of scientific *findings* and *predictions*

Healthy lifestyle



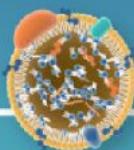
Drugs with CV outcome trials

Statins
Ezetimibe
PCSK9i MoAb*

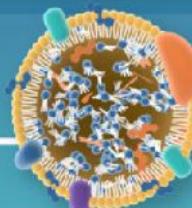
Fibrates
Icosapent ethyl

No specific therapy

*PCSK9 monoclonal antibodies



LDL-C



TGRL



Lp(a)

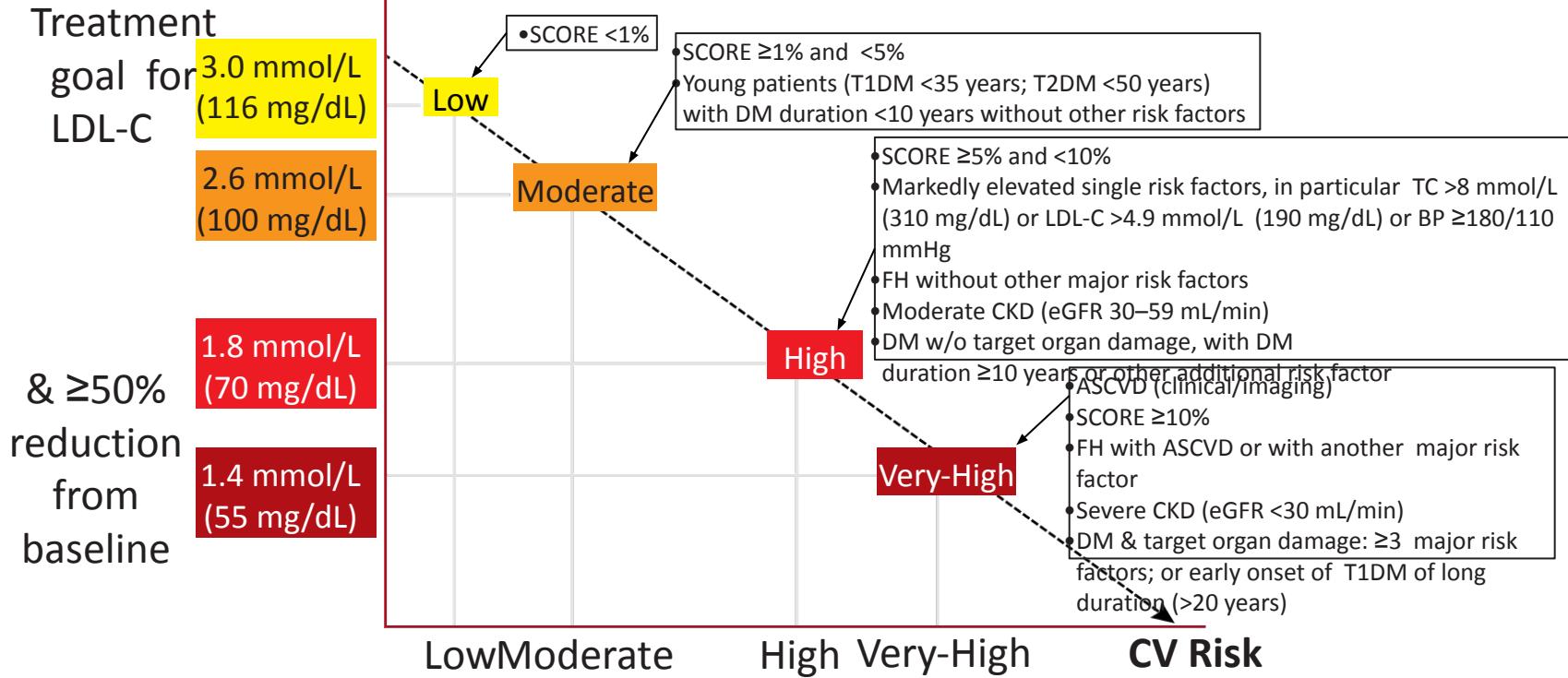
New therapies

Bempedoic acid
Inclisiran
Evinacumab
Vaccine ?
CRISPR ??

Volanesorsen
Vupanorsen
Pemafibrate
Evinacumab

Pelacarsen
Olpasiran

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



New lipid-lowering therapies

- Monoclonal antibodies inhibitors of pro-protein convertase subtilisin/kexin 9 (PCSK9): *alirocumab*, *evolocumab*

- Microsomal triglyceride transfer protein (MTP) inhibitor: *lomitapide*

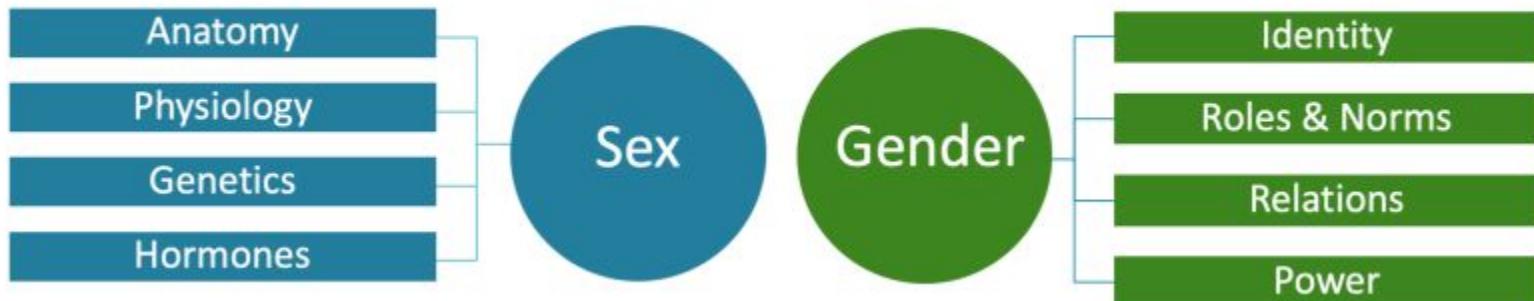
- Apolipoprotein B synthesis inhibitors antisense oligonucleotide: *mipomersen*

- ATP citrate lyase (ACL) inhibitor: *bempedoic acid*


Agenda

- General remarks
- **Gender**
- Quality and composition of active pharmaceutical ingredients
- Conclusion

Dimensions of Sex (Biological Variable) & Gender (Social and Cultural Variable)



Gender pharmacology

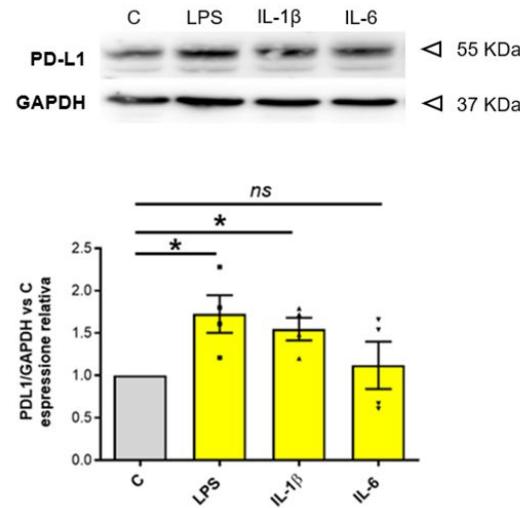


Gender-specific pharmacology

In humans, the combination of all *genetic, epigenetic, and hormonal* influences of biologic sex produces different *in vivo* environments for male and female cells

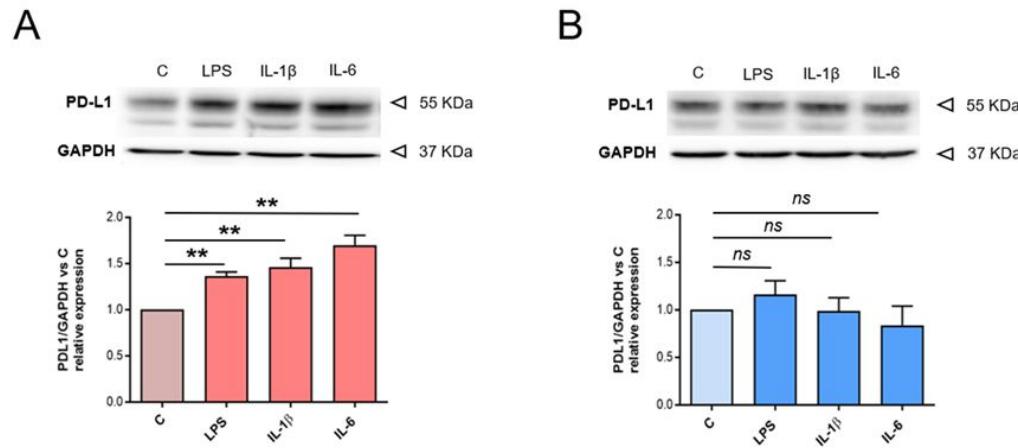


PD-L1 levels in pooled HUVECs exposed to proinflammatory stimuli



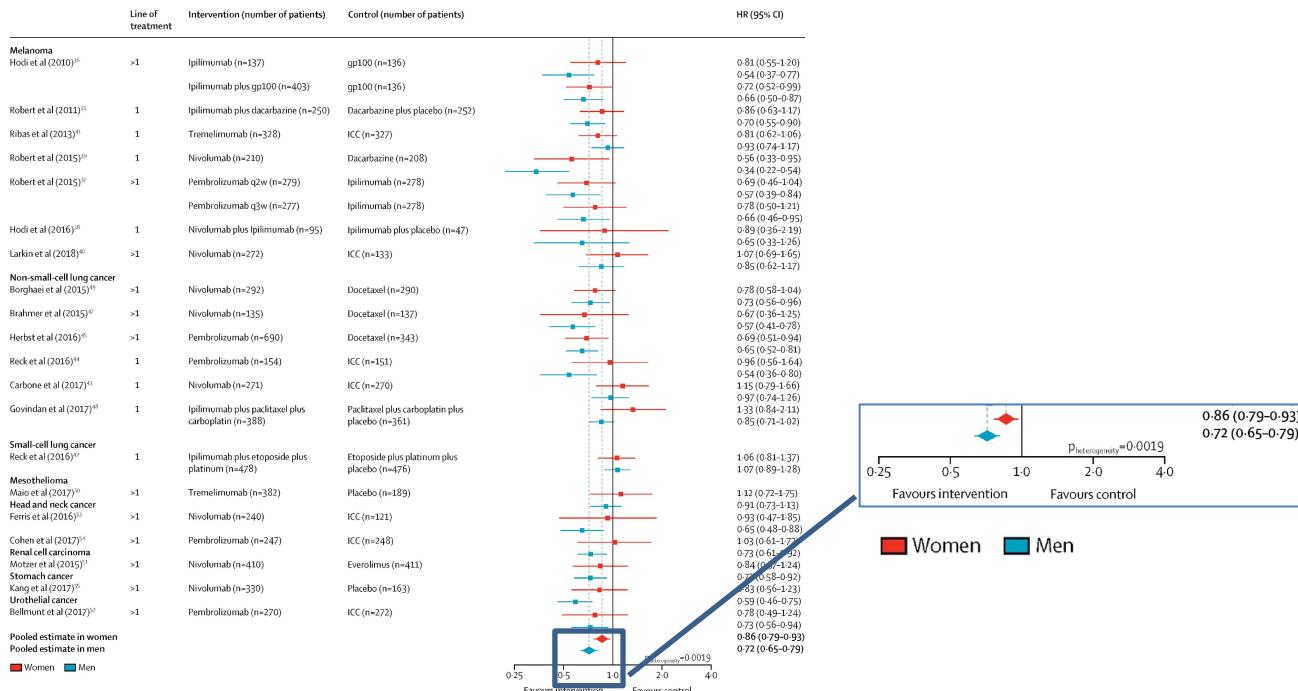
n=4 independent experiments. *p<0.05, t-test. ns, nonsignificant

PD-L1 levels in HUVECs from male and female donors exposed to proinflammatory stimuli

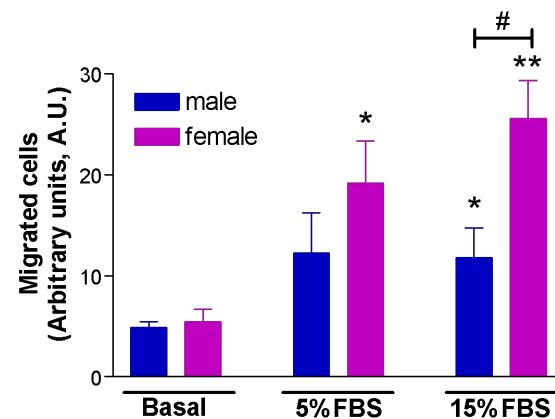
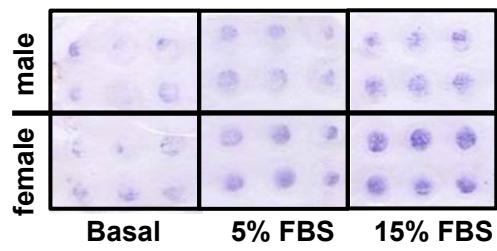


$n=3$ independent experiments. ** $p<0.01$, t -test. ns, nonsignificant

Can a patient's sex predict the efficacy of immune checkpoint inhibitors?



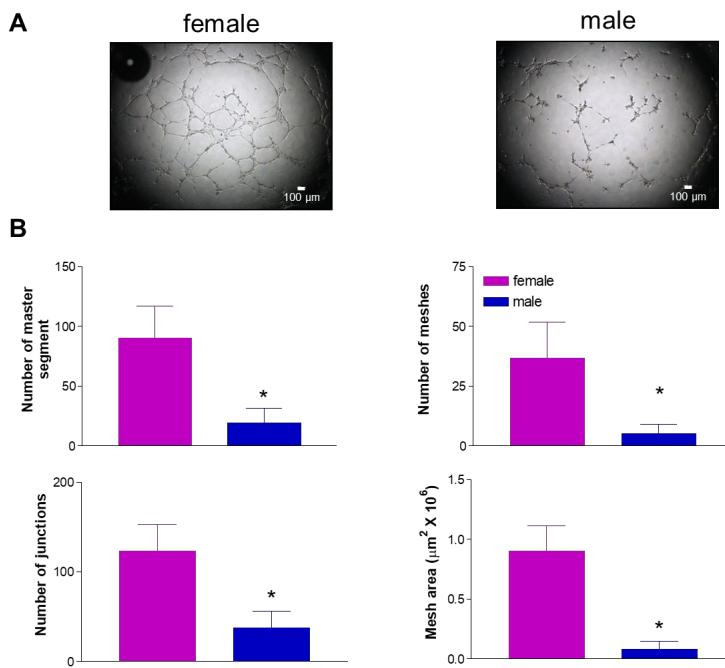
Sex-specific HUVEC migration towards 5% or 15% FBS



n = 4

p* < 0.05, *p* < 0.01 (vs. basal); # *p* < 0.05

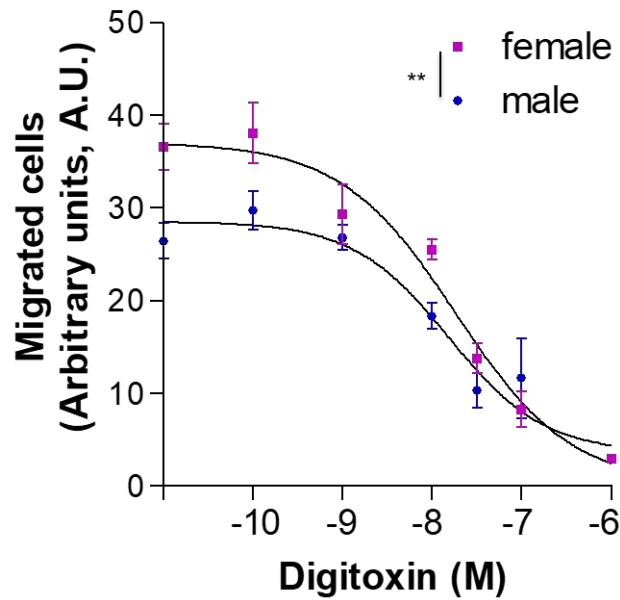
Sex-specific capillary tube-like formation



* $p < 0.05$; $n = 3$

Boscaro et al., *Front Pharmacol.* 2020; 11:587221

Sex-specific response to digitoxin treatment



$n = 5$; ** $p < 0.01$, two-way ANOVA for comparison between curves



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PERSPECTIVE | NEUROSCIENCE

Are hormones

REBECCA M. SHANSKY

SCIENCE 31 May 2019 • Vol 364, Issue 1

0

One of the most deep-seated misconceptions about the human psyche is that men are simple and women are complicated (1). Gender psychology scholars trace this belief back to at least the 19th century, when the

Outdated gender stereotypes are influencing experimental design in laboratory animals

.....More than 100 years later, this idea still shapes not just how society perceives women but also how biomedical scientists approach animal research.....

A survey of publications using primarily rodent and nonhuman primate subjects found that this imbalance was true for **physiology**, **pharmacology**, and even **endocrinology** research, but the most egregiously lopsided field was **neuroscience**, which in 2009 included male animals almost six times as often as females

A. K. Beery, I. Zucker, Neurosci. Biobehav. Rev. 35, 565 (2011)

[Biol Sex Differ.](#) 2016; 7: 34.

PMCID: PMC4962440

Published online 2016 Jul 26. doi: [10.1186/s13293-016-0087-5](https://doi.org/10.1186/s13293-016-0087-5)

PMID: [27468347](#)

Female rats are not more variable than male rats: a meta-analysis of neuroscience studies

Jill B. Becker,^{✉1,2} Brian J. Prendergast,³ and Jing W. Liang⁴

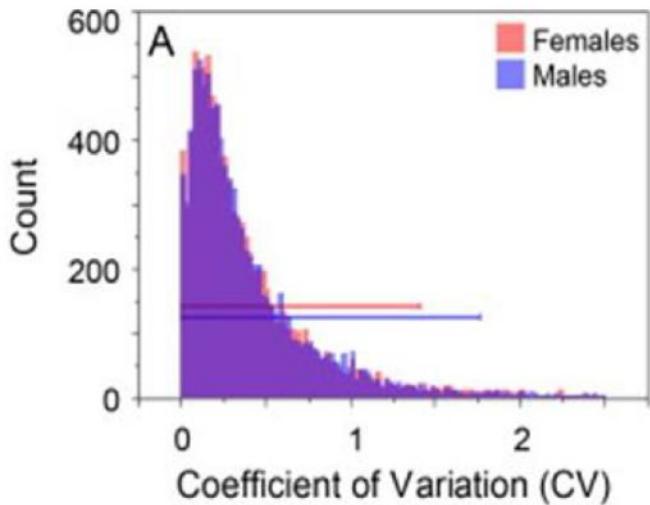
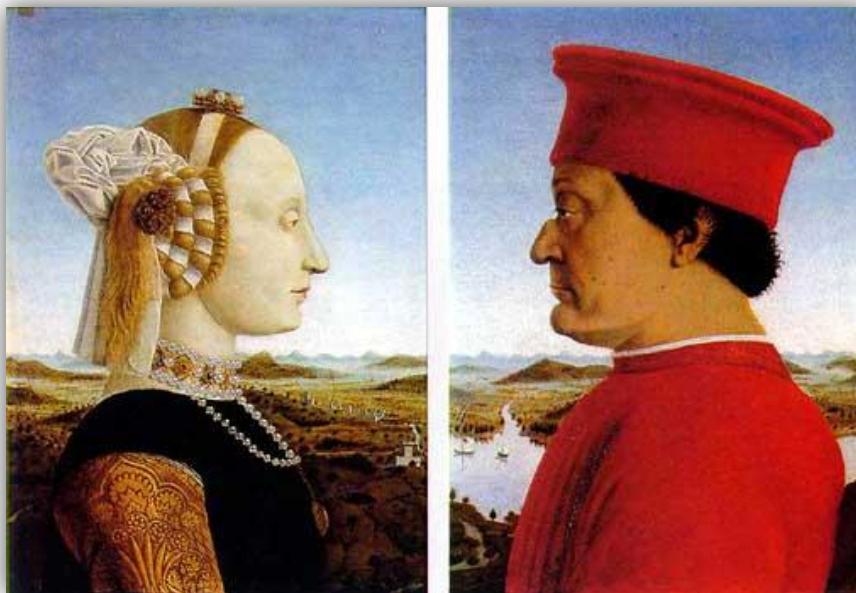


Fig. 1. Mean trait variability is no greater in female than male mice. (A) Coefficients of variation (CV; S.D./mean) for phenotypic traits ($n = 9932$) of male (blue) and female (red) wild-type mice as reported in 293 peer-reviewed articles published between 2009 and 2012.

These observations indicate that, contrary to widespread preconceptions, females are no more variable than males across diverse physiological, morphological and behavioral traits. For the average trait of interest to animal researchers, variability does not differ between **males and unstaged females**; in fact, the distribution of trait variability is significantly broader in males than in females.

Sex-Based Differences in Drug Activity

HEATHER P. WHITLEY, PharmD, *Harrison School of Pharmacy, Auburn University, Auburn, Alabama; and the Rural Health Institute for Clinical and Translational Science, The University of Alabama School of Medicine, Tuscaloosa, Alabama*
WESLEY LINDSEY, PharmD, *Harrison School of Pharmacy, Auburn University, Auburn, Alabama*



ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 120 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 120 mg of sotorasib.

4. CLINICAL PARTICULARS

4.2 Posology and method of administration

Posology

The recommended dose is 960 mg sotorasib (eight 120 mg tablets) once daily, at the same time each day.

The Seventy-Kilogram Fantasy

I was not able to locate a specific historical reference to the origin of the “70-kg man,” but it probably arises from body size data from the World War II era. That normative value continues to be perpetuated in biomedical reference sources to the present day. Yet as time wears on, the typicality of the 70-kg man fades into a fantasy world.

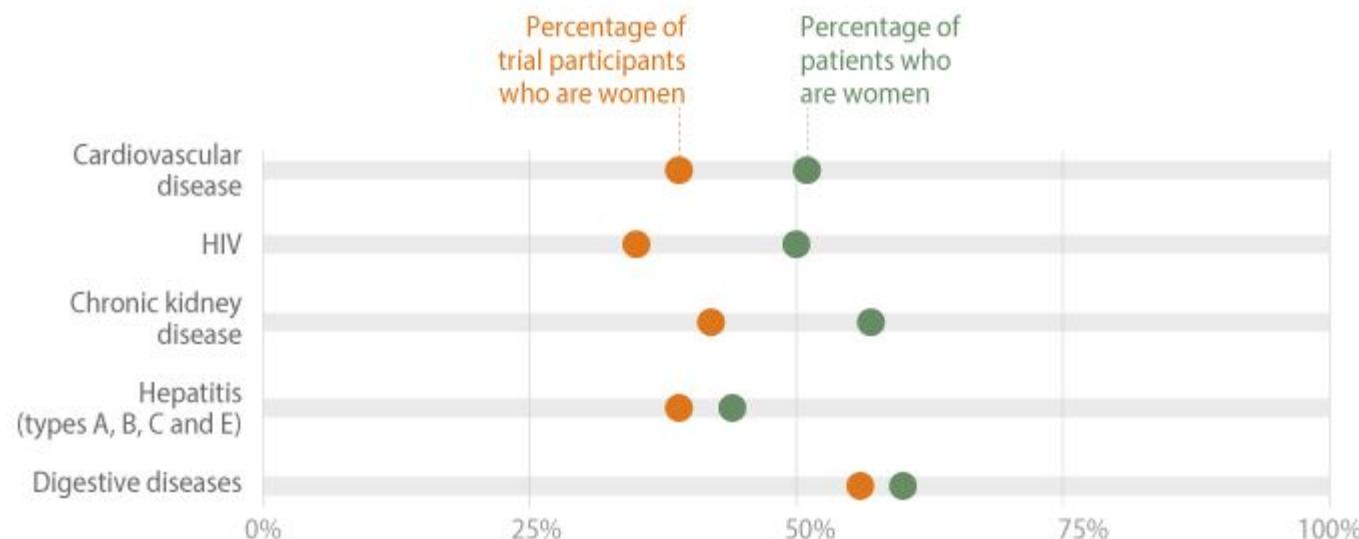
Clinical Pharmacology
in Drug Development
2(2) 101–102
© The Author(s) 2013
DOI: 10.1002/cpdd.33

The health care community has correctly expressed concern regarding the adverse health consequences of American largeness: diabetes, metabolic disorders, and cardiovascular disease. The American-based pharmaceutical industry will continue to develop medications to treat these and other disorders in large people. In drug development and clinical pharmacology, the archaic 70-kg man should be discarded in favor of weight and size indices that reflect contemporary reality. Further, we should be looking carefully at the extent to which pharmacokinetic and clinical trials data developed from other populations can be confidently extrapolated to the United States. The smaller average body sizes in Asian and African nations compared to the United States, and the possible clinical and pharmacokinetic consequences of those differences, have long been recognized. We now need to consider the consequences of substantial differences between the United States and western European nations, in which post-war height statistics may parallel or exceed those in the U. S.,¹⁶ but body weight and BMI certainly do not.

—David J. Greenblatt
Editor-in-Chief
Tufts University School of Medicine
Boston, MA, 02111

FIGURE 1

Women are underrepresented in clinical trials, including for diseases by which they are disproportionately affected



Note: Meta-analysis data regarding people of color and, specifically, the participation of women of color in clinical trials, that matched the above disease categories were not readily available; however, the literature also shows that people of color are significantly underrepresented in clinical trials for these conditions.

Sources: Katherine Ellen Foley, "25 years of women being underrepresented in medical research, in charts," Quartz, July 3, 2019, available at <https://qz.com/1657408/why-are-women-still-underrepresented-in-clinical-research/>; Terrell Jones and others, "Enrollment of Black Individuals in Cardiovascular Clinical Trials: A Meta-Analysis," *Circulation: Cardiovascular Quality and Outcomes* 12 (1) (2019), available at https://www.ahajournals.org/doi/abs/10.1161/hcq.12.suppl_1.136#:~:text=Results%3A%20We%20identified%202501%20trials,C%3A%2056.4%25%2D67%25.



← [Home](#) / [Drugs](#) / [Drug Safety and Availability](#) / [FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR](#)

FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR

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Drug Safety and Availability

This update is in follow-up to the [FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs: FDA requires lower recommended doses for certain drugs containing zolpidem \(Ambien, Ambien CR, Edluar, and Zolpimist\)](#) ↗

Content current as of:

12/11/2017

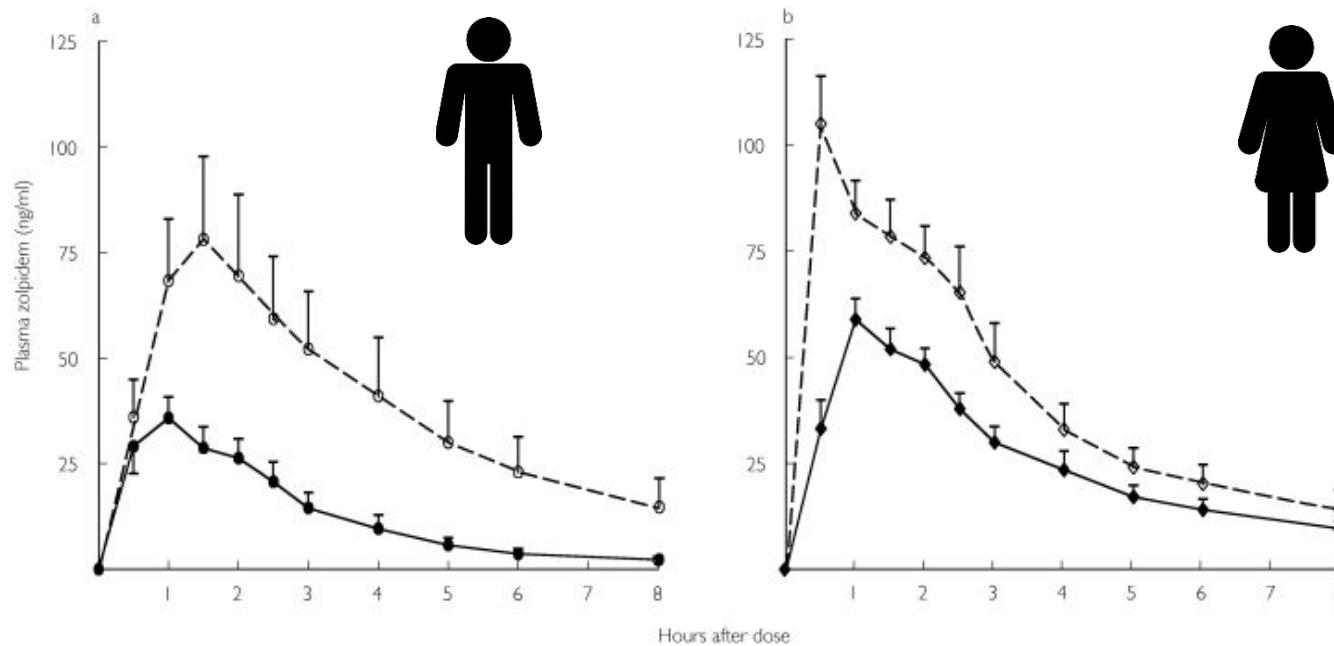
medications. FDA has approved these changes because of the known risk of next-morning impairment with these drugs.

FDA is also warning that patients who take the sleep medication zolpidem extended-release (Ambien CR)—either 6.25 mg or 12.5 mg—should not drive or engage in other activities that require complete mental alertness the day after taking the drug because zolpidem levels can remain high enough the next day to impair these activities. This new recommendation has been added to the *Warnings and Precautions* section of the physician label and to the patient Medication Guide for zolpidem extended-release (Ambien CR).

Also included in the updated label are the dosing recommendations previously stated in FDA's [January 2013 Drug Safety Communication](#):  The recommended initial dose of certain immediate-release zolpidem products (Ambien and Edluar) is 5 mg for women and either 5 mg or 10 mg for men. The recommended initial dose of zolpidem extended-release (Ambien CR) is 6.25 mg for women and either 6.25 or 12.5 mg for men. If the lower doses (5 mg for immediate-release, 6.25 mg for extended-release) are not effective, the dose can be increased to 10 mg for immediate-release products and 12.5 mg for zolpidem extended-release. However, use of the higher dose can increase the risk of next-day impairment of

Pharmacokinetic properties of zolpidem in elderly and young adults

single 5 mg oral doses of zolpidem tartrate

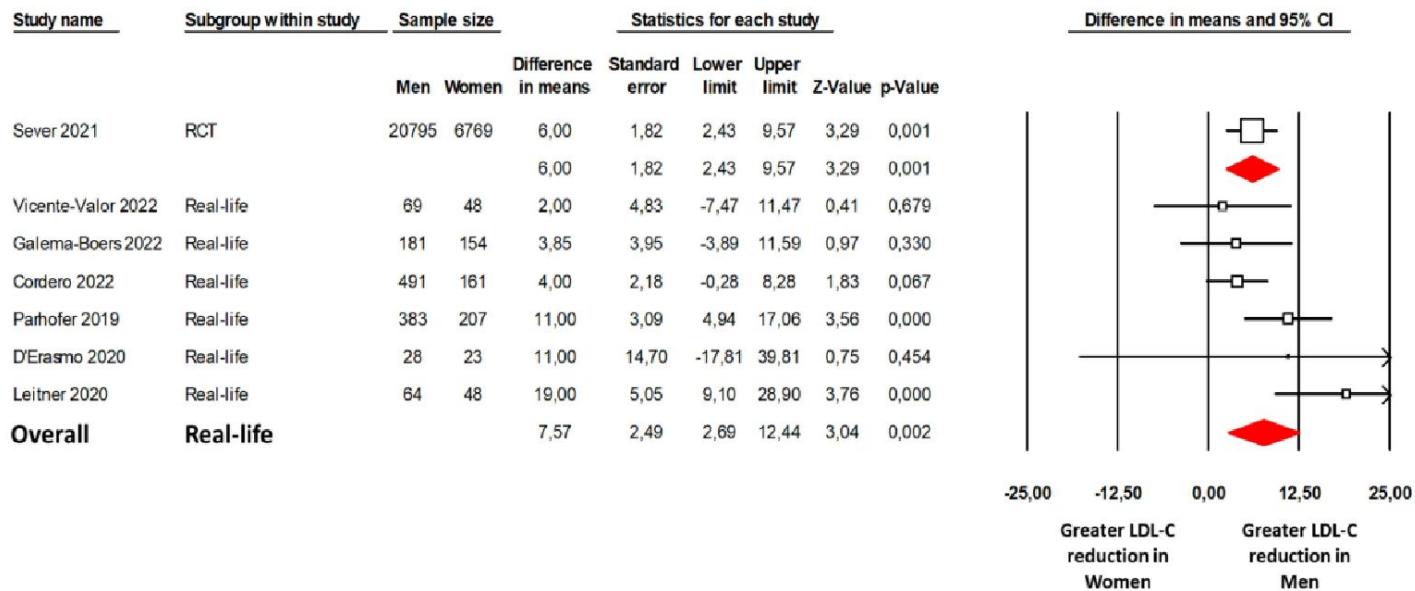


Mean (± SEM) serum zolpidem concentrations–time plots for young (•, ◆) and elderly (○, ◇) male (a) and female (b) volunteers.

Zolpidem - summary

- Women process the sleeping pill Ambien (zolpidem) more slowly than men do.
- Unfortunately, it took more than 20 years and many reports of incidents, such as women driving while almost asleep, before the FDA changed its dosing recommendations.
- Since 2013, women have been advised to take a lower dose of the drug than men.
- But for most drugs, doctors have little information about whether to prescribe differently for men and women.

Sex differences in LDL-C reduction induced by PCSK9 monoclonal antibodies in a real-life setting



Spotlight

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Regulatory

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EMA

FDA

Gender Bias in the Clinical Evaluation of Drugs

August 13, 2020

Younes Benjeaa, Yves Geysels

Applied Clinical Trials, Applied Clinical Trials-12-01-2020, Volume 29, Issue 12



Past decades have shown gender-based differences in clinical trial results are often overlooked when considering safety and effectiveness.

It is increasingly apparent that many physiological and pathological functions as well as patterns in gene expression differ between women and men and gender differences have also manifested in the outcomes of treatments.¹

Throughout the last decades, alarming evidence of gender-based differences in the safety profiles of treatments has accumulated. A study including 513,608 patients estimated that women experience a 1.5 to 1.7-time greater risk of developing adverse reactions to drugs than men.² In 2001, a report from the U.S. General Accounting Office (GAO) made the observation that 70% of drugs withdrawn from the market between 1997 and 2000 presented greater health risks for women.³ On top of that is data suggesting that women are overdosed: the dose of zolpidem, for example, was reduced by

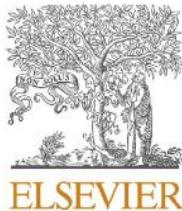
Women encounter ADRs more often than do men

Y. Zopf · C. Rabe · A. Neubert · K. G. Gaßmann ·
W. Rascher · E. G. Hahn · K. Brune · H. Dormann

Received: 30 December 2007 / Accepted: 2 April 2008 / Published online: 5 July 2008
© Springer-Verlag 2008

Table 3 Gender-specific adverse drug reactions (ADRs)

Type of ADR	Female (%)	Male (%)
Type A: Dose-related	268 (51.8)	170 (39.8)
Type B: Non-dose-related	69 (13.4)	72 (16.9)
Type C: Dose- and time-related	149 (28.8)	150 (35.1)
Type D: Time-related	30 (5.8)	34 (7.9)
Type E: Withdrawal	0	0
Type F: Unexpected failure of therapy	1 (0.2)	1 (0.2)



Contents lists available at [ScienceDirect](#)

Pharmacological Research

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



Review

Sex-tailored pharmacology and COVID-19: Next steps towards appropriateness and health equity[☆]



Andrea Spini ^{a,b,1}, Valentina Giudice ^{c,1}, Vincenzo Brancaleone ^d, Maria Grazia Morgese ^c, Silvia De Francia ^f, Amelia Filippelli ^c, Anna Ruggieri ^g, Marina Ziche ^{a,b,i}, Elena Ortona ^{g,i}, Andrea Cignarella ^{h,i}, Luigia Trabace ^{e,i,*}

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^d Department of Science, University of Basilicata, via Ateneo Lucano, 85100 Potenza, Italy

^e Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy

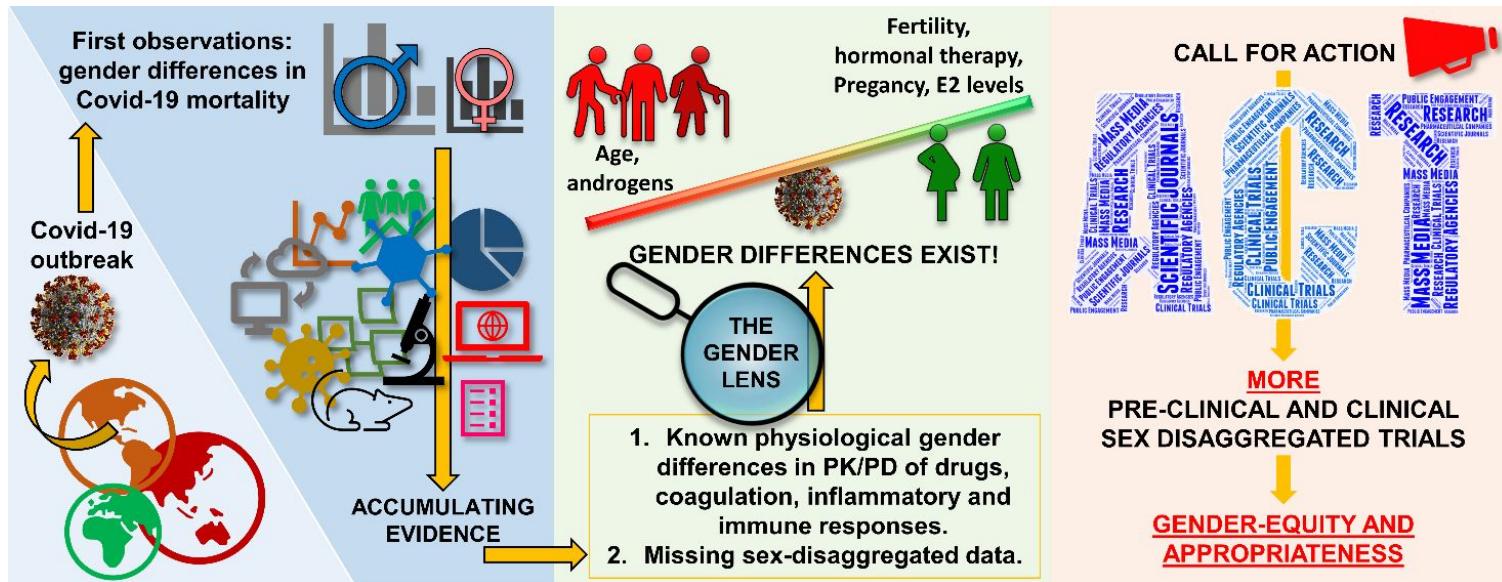
^f Department of Clinical and Biological Sciences, S. Luigi Hospital, University of Turin, Italy

^g Center for Gender Specific Medicine, Istituto Superiore di Sanità, Rome, Italy

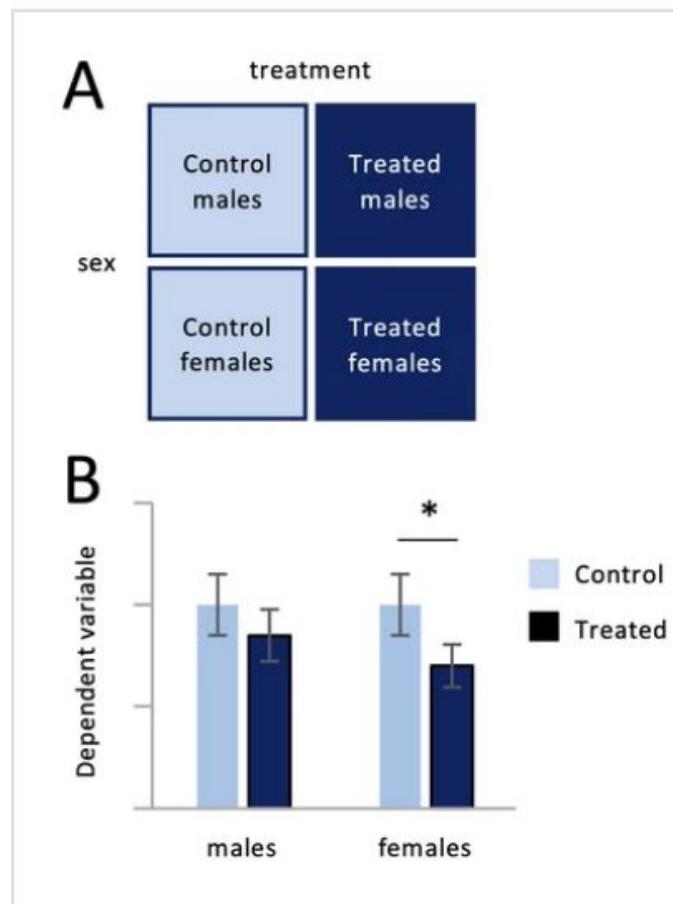
^h Department of Medicine, University of Padova, via Giustiniani 2, 35128 Padova, Italy

ⁱ Centro Studi Nazionale Salute e Medicina di Genere, Italy

Sex-tailored pharmacology and COVID-19: next steps towards appropriateness and health equity



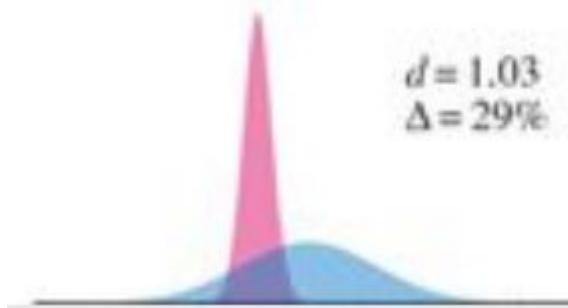
Factorial designs and sex-specific effects



Did the study have a factorial design with sex as a factor?

- This design is common when researchers are interested in testing whether the sexes respond differently to a manipulation such as a drug treatment.
- In order to draw a conclusion about whether responses to treatment differed between females and males, the effect of the treatment must be compared across sex by **testing for an interaction** between sex and treatment.
- If the interaction is significant, then a claim can be made that the sexes responded differently to the treatment.
- Disaggregating the data by sex and testing for effects of treatment separately in females and males does not test whether the magnitude of the response differs between females and males

(j) zolpidem clearance rate



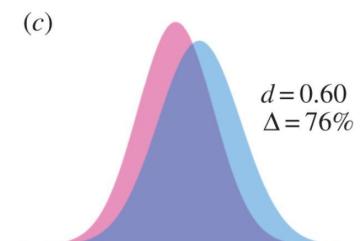
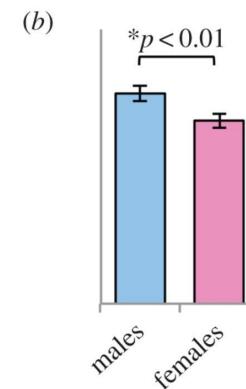
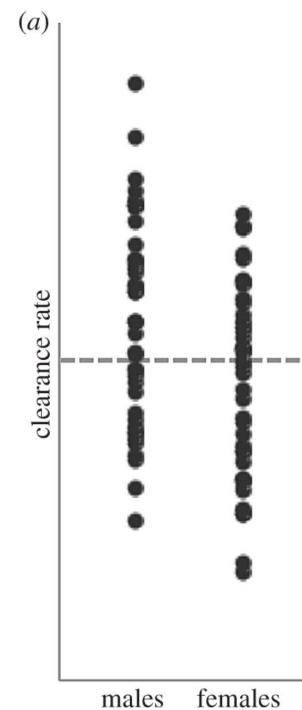
(k) driving impairment
on zolpidem



Greenblatt DJ et al. *J. Pharmacol. Exp. Ther.* 2000; 293, 435–443

Verster JC, Roth T. *Traffic Injury Prev.* 2012; 13, 286–292

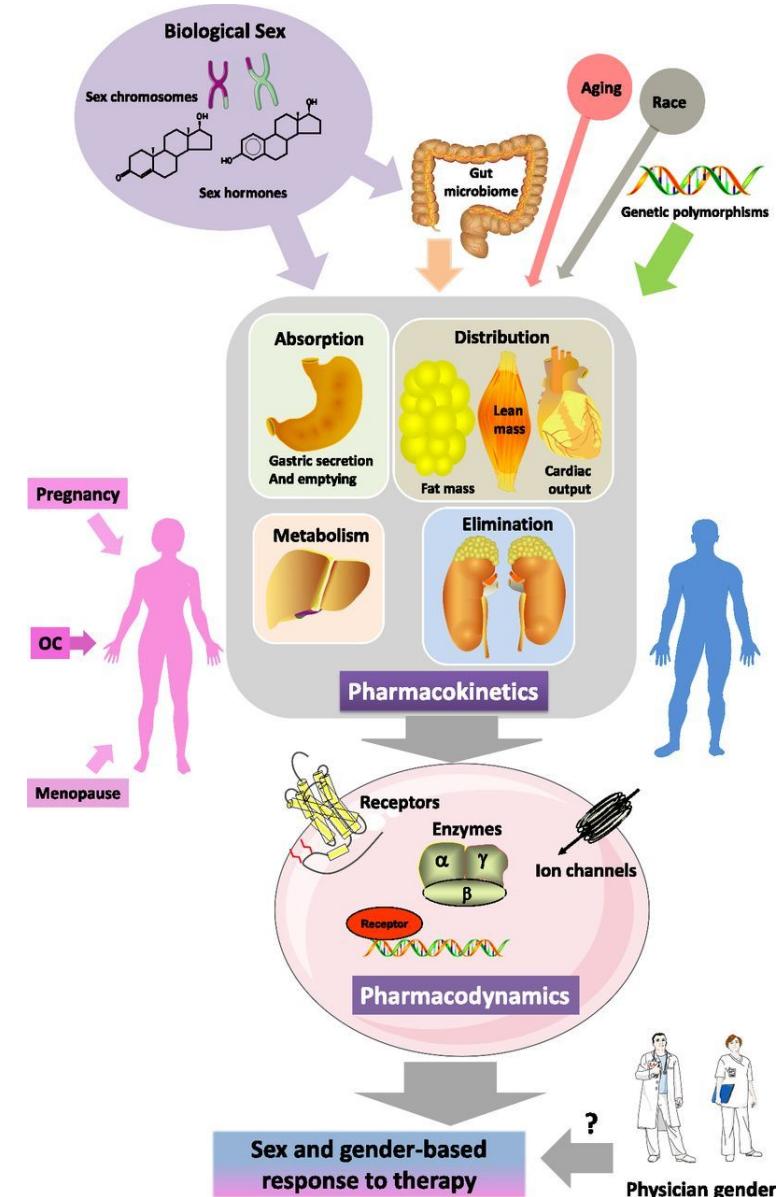
Cohen's d Effect Size



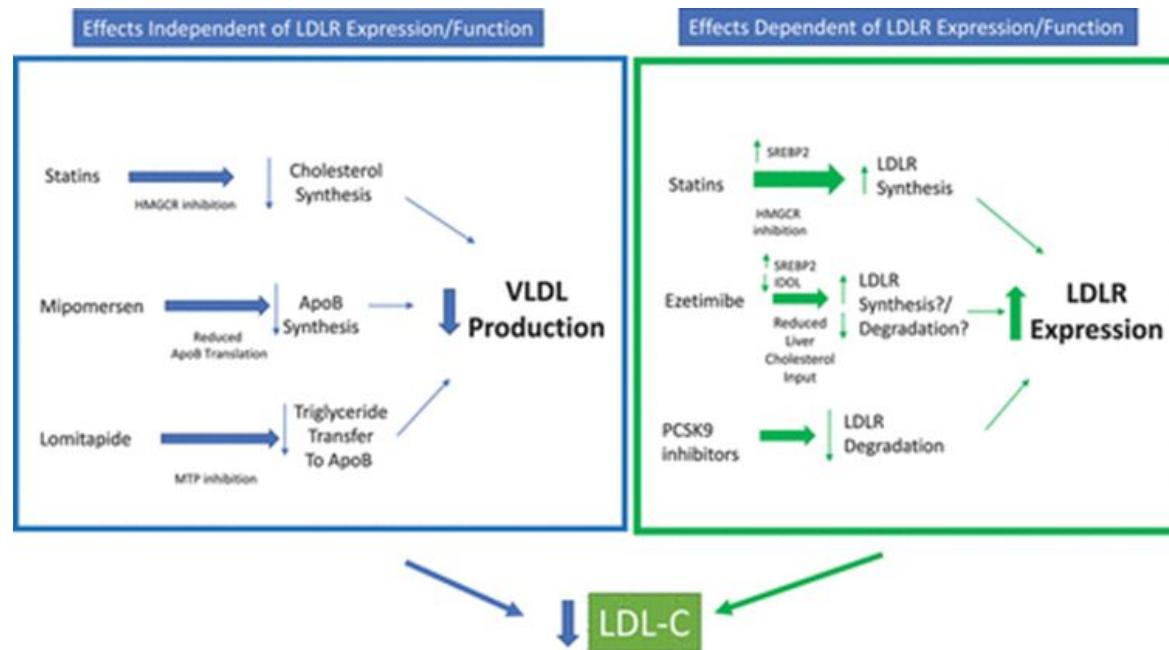
Maney DL. *Philos Trans R Soc Lond B Biol Sci.* 2016; 371(1688):20150119

Sex and gender influences on the pharmacological response to drugs

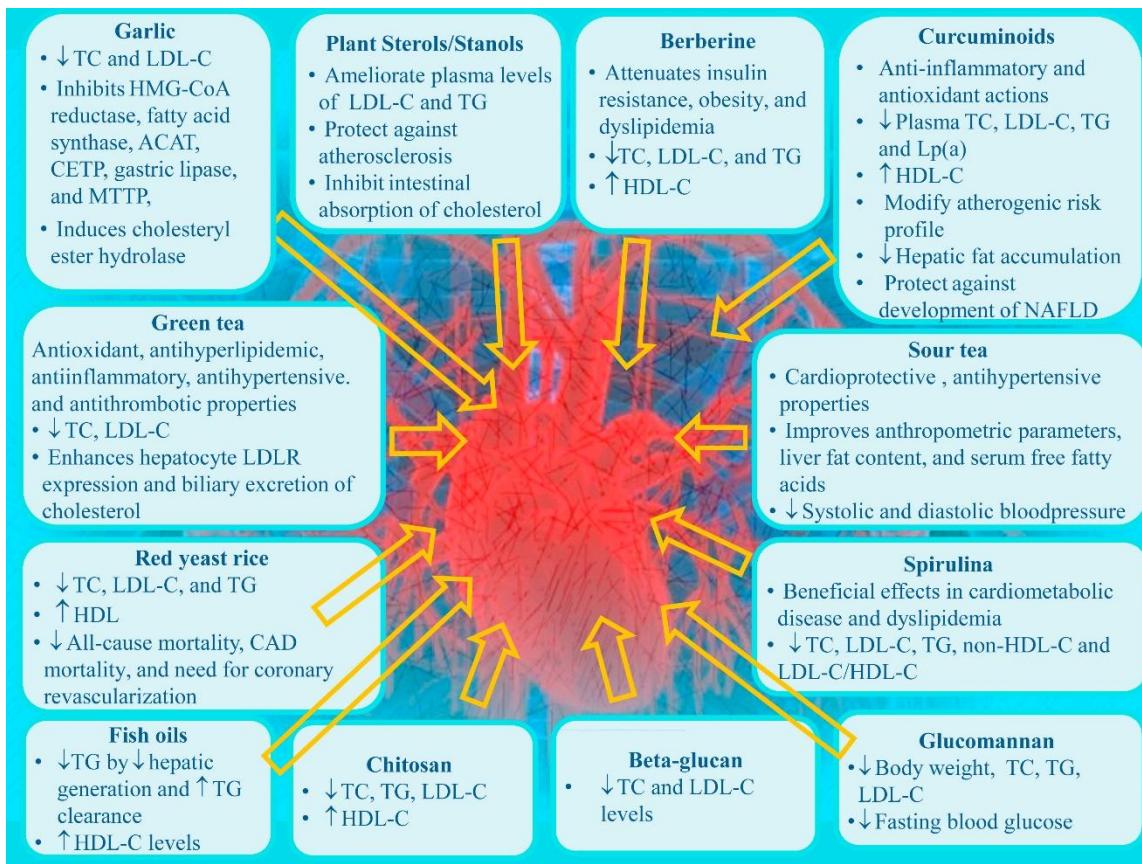
Biologic sex via sex-specific genetic and hormonal influences on cellular systems alters the transcriptome, proteome, and metabolome of all cells and organs as well as the gut microbiome and influences pharmacokinetics (e.g., absorption, distribution, metabolism, and elimination of drugs) and pharmacodynamics (e.g., the effect of drugs on receptors, ion channels, enzymes, and signaling pathways). Aging, race, and genetic polymorphism also influence pharmacokinetics and pharmacodynamics parameters in a sex-specific manner. In women, the hormonal influences of pregnancy, menopause, and the use of OCs also produce sex differences in the pharmacokinetics and pharmacodynamics of drugs. Finally, physician gender could add an additional level of difference in response to treatment.



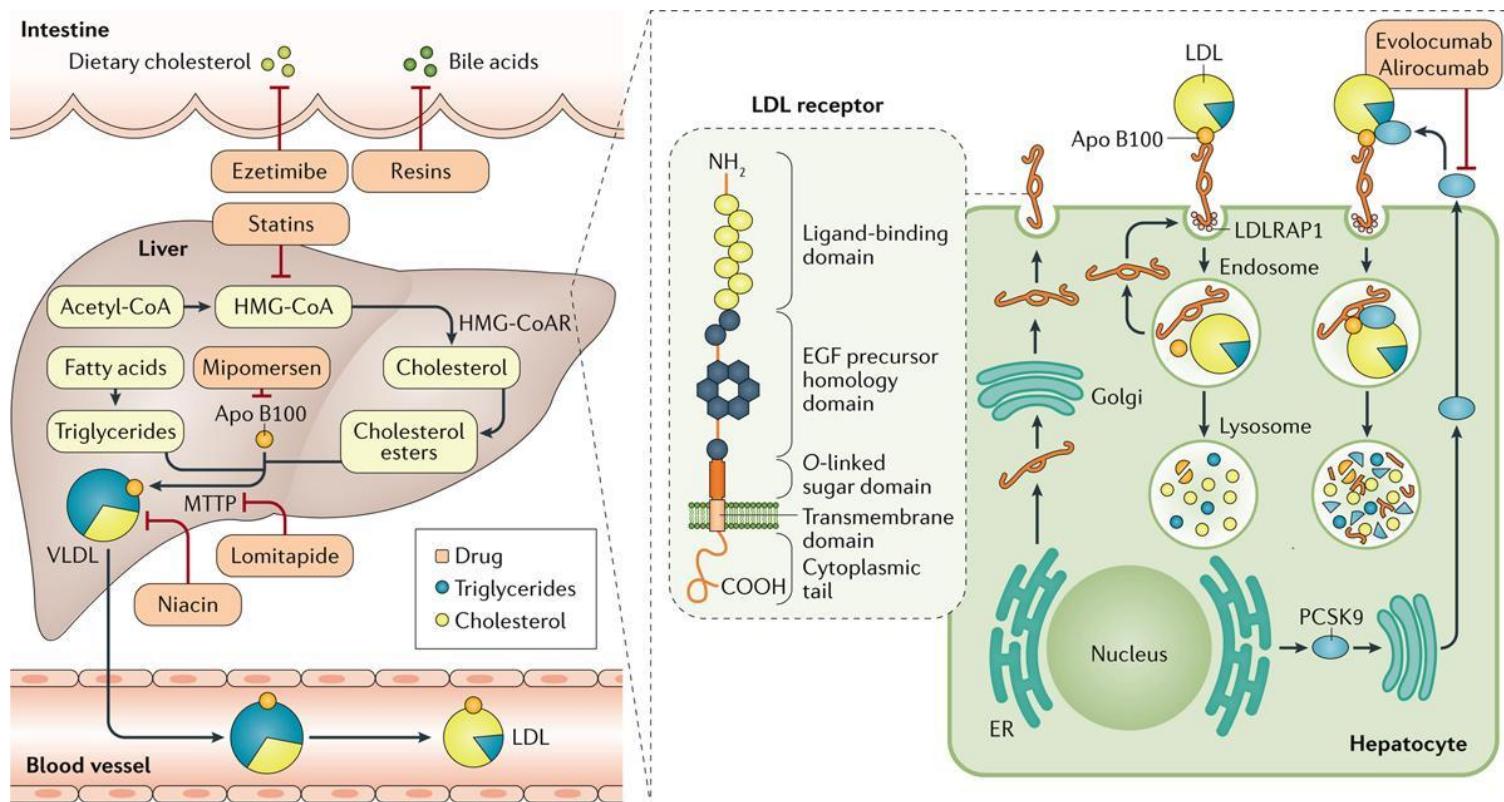
Mechanisms involved with LDL-C lowering by medications approved for homozygous familial hypercholesterolemia and their possible associations with LDL-R expression/function



Nutraceuticals used in treatment of dyslipidemia and their effects on different lipid indices

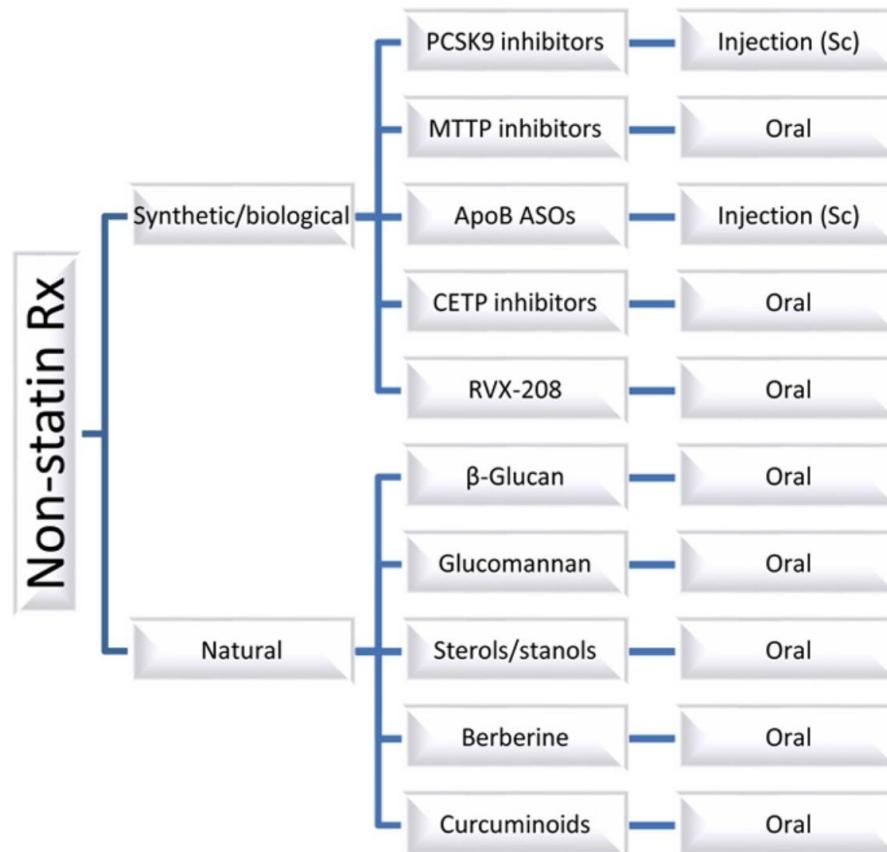


Basic pathways in LDL particle synthesis and LDLR-mediated uptake



Nature Reviews | Disease Primers

Nutraceutical and non-nutraceutical treatments for cholesterol management



Effetto sulla colesterolemia LDL di alcuni nutraceutici

Principio Attivo	Dose	Effetto sulla colesterolemia LDL
Steroli e stanoli vegetali	1,5-3,0 g/die	-9,1-18,2 mg/dL ²⁶
Riso rosso fermentato	3-10 mg/die (titolato in Monacolina K)	-33,4 mg/dL (-27,3-39,6 mg/dL) ³³
Beta-glucano	3,4 g/die	-7,3 mg/dL (-5,4-8,8 mg/dL) ⁴⁴
Policosanoli	10-80 mg/die	0,0 mg/dL (-13,8 -13,8 mg/dL) ⁶⁰
Berberina	500-1500 mg/die	-25,0 mg/dL (-20,7-29,2 mg/dL) ⁴⁵
Proteine della soia	25-50 g/die	-4,8 mg/dL (-2,3-7,3 mg/dL) ⁵²

Poli A et al. Nutraceutical and functional foods for the control of plasma cholesterol levels. An intersociety position paper. *Pharmacol Res* 2018;134:51-60.

Table 3 Advantages, disadvantages and possible indications of cholesterol-lowering nutraceuticals.

	Advantage	Disadvantages	Possible indication
Fiber	<ul style="list-style-type: none"> - LDL-C reduction by 4–14% - Effect on other CV risk factors - Relatively low-cost 	Intestinal discomfort for excessive doses	<ul style="list-style-type: none"> - General population that fails to increase fiber intake with diet alone - Patients with mild hypercholesterolemia and low to moderate cardiovascular risk^a - Patients with mild hypercholesterolemia and metabolic syndrome
Phytosterols	<ul style="list-style-type: none"> - LDL-C reduction by 8–10% - No interaction with lipid-lowering drugs 	<ul style="list-style-type: none"> - Self purchasing by patients and risk of no medical supervision - Possible excessive intake with the risk of reduced absorption of fat soluble vitamins - High cost 	<ul style="list-style-type: none"> - Patients with mild hypercholesterolemia and low to moderate cardiovascular risk^a - Patients with intolerance to multiple statins - In addition to drug therapy for patients who do not reach optimal levels of LDL-C
Soy products	- LDL-C reduction by 4–13%	<ul style="list-style-type: none"> - Self purchasing by the patient - Risk of allergies - High cost 	<ul style="list-style-type: none"> - General population - Patients with mild hypercholesterolemia and low to moderate cardiovascular risk^a
Red yeast rice	<ul style="list-style-type: none"> - LDL-C reduction by 16–25% - Good safety profile - Reduction of cardiovascular risk 	<ul style="list-style-type: none"> - Variability of composition and purity of OTC products - Self purchasing by patients and risk of no medical supervision - Higher cost compared to generic statins - Possible side effects at high doses 	<ul style="list-style-type: none"> - Patients with mild to moderate hypercholesterolemia and low to moderate cardiovascular risk^b
Berberine ^d	<ul style="list-style-type: none"> - LDL-C reduction by 20% - Better safety profile in patients with intolerance to multiple statins - Favorable effect on TG, HDL-C and blood glucose 	<ul style="list-style-type: none"> - Variability of intestinal absorption - Self purchasing by patients and risk of no medical supervision - Higher cost compared to generic statins 	<ul style="list-style-type: none"> - Patients with mild to moderate hypercholesterolemia and low to moderate CV risk^c - Patients with mild hypercholesterolemia and metabolic syndrome^e - Patients with intolerance to multiple statins - In addition to drug therapy for patients who do not reach optimal levels of LDL-C

HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, CV: cardiovascular; TG: triglycerides; OTC: over the counter.

^a Patients requiring a reduction of LDL cholesterol by up to 10–15%.^b Patients requiring a reduction of LDL cholesterol by up to 20–25%.^c Patients requiring a reduction of LDL cholesterol by up to 20%.^d Studies performed almost exclusively in Asian populations and therefore not easily transferable to other populations.^e Even in combination with a statin, in patients with modest increase in serum triglycerides and/or blood glucose.

Metabolic effects of nutraceuticals on body weight, blood pressure, blood glucose levels and plasma lipids

	Body weight	Blood pressure	Blood glucose levels	Plasma lipids		
				LDL-c	Triglycerides	HDL-c
Fiber	↓ (soluble/viscous fibers)	↓ (soluble/viscous fibers mainly in hypertensive subjects)	↓ (soluble/viscous fibers mainly β-glucan and pectin)	↓ (soluble/viscous fibers mainly oat β-glucan, psyllium, chitosan, glucomannan, guar gum, HPMC, pectin)	-	-
Polyphenols	↓/– (green tea catechins)	↓ (resveratrol, cacao flavanols, soy isoflavones mainly in hypertensive and obese subjects)	↓ (tea and cacao flavan-3-ols, soy isoflavones, olive oil phenolic compounds, resveratrol)	? (tea and cocoa flavan-3-ols) ↓ green tea catechins	↓ Anthocyanins	-
Omega-3 PUFA	?	↓ (in hypertensive subjects) – (in diabetic subjects)	– (↑ for doses > 4 g/day)	↑	↓↓	-
Phytosterol	NE	NE	NE	↓	-	-
Red yeast rice	NE	?	NE	↓↓		-
Berberine	NE	↓	↓ (in Asian population)	↓ (in Asian population)	↓ (in Asian population)	↑ (in Asian population)
Coenzyme Q 10	NE	?	NE	?	?	?
Soy protein	NE	NE	NE	–/↓ (hyperlipidemic subjects)	NE	NE

↓ Decrease, ↑ increase, – no effect, ? limited and variable data, NE not evaluated

Table 9 LDL-C reduction, levels of evidence and strength of recommendation for different cholesterol-lowering nutraceuticals.

	Degree of LDL cholesterol reduction	Level of evidence	Strength of recommendation
Fiber	+	I	A
Phytosterols	+	I	A
Soy derivatives	+/-	II	C
Policosanol	-	VI	D
Red yeast rice	++	I	A
Berberin	++	a	a

Levels of evidence and strength of recommendation according to the Italian standard of care for diabetes [153]: Levels of evidence: I: evidence obtained from multiple randomized controlled trials and/or from systematic reviews of randomized controlled trials; II: evidence obtained from one randomized trial; VI: consensus of experts. Strength of recommendation: A: strongly recommended; C: basic uncertainty; D: no recommendation.

^a The level of evidence would be I, because supported by meta-analysis of interventional studies, and strength of recommendation A; however, because these studies were conducted almost exclusively in Asian populations, the data are not easily transferable to other ethnic groups.

Strategie di prevenzione cardiovascolare

Approccio classico

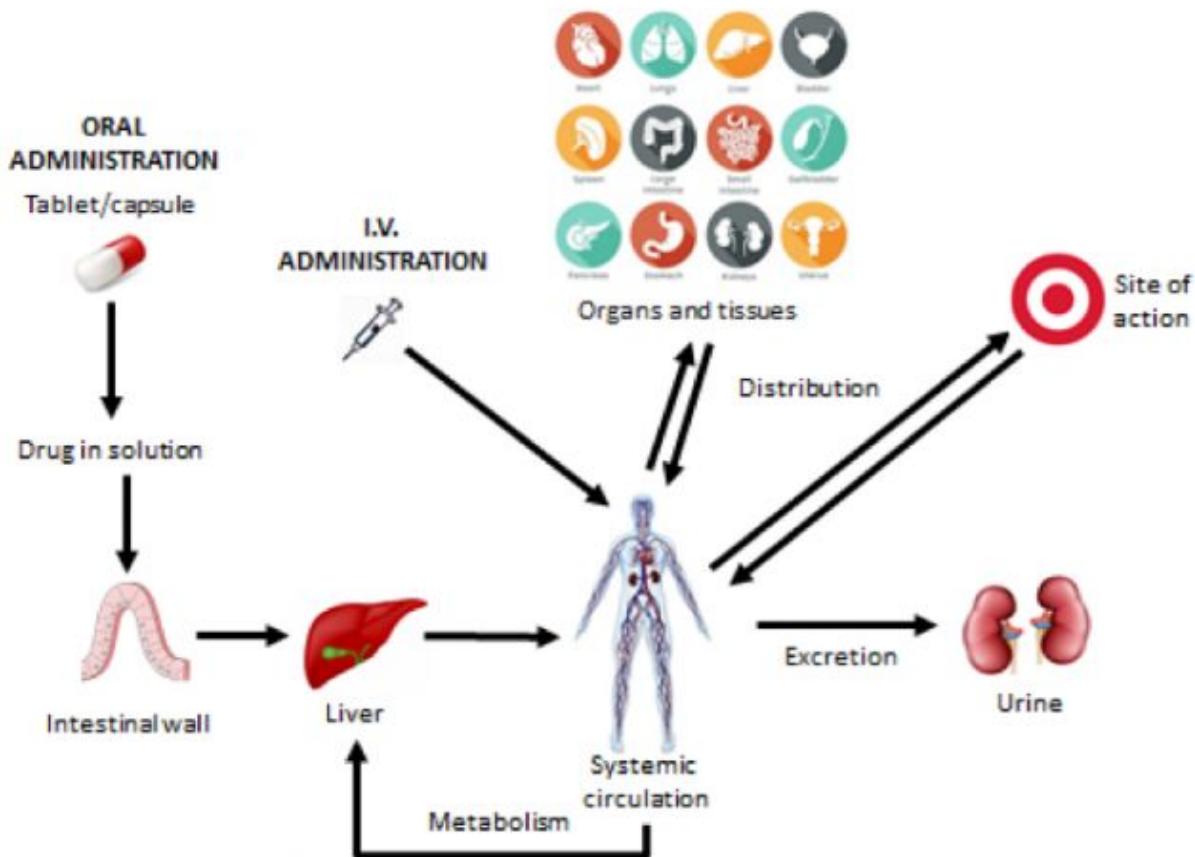


Approccio ragionato

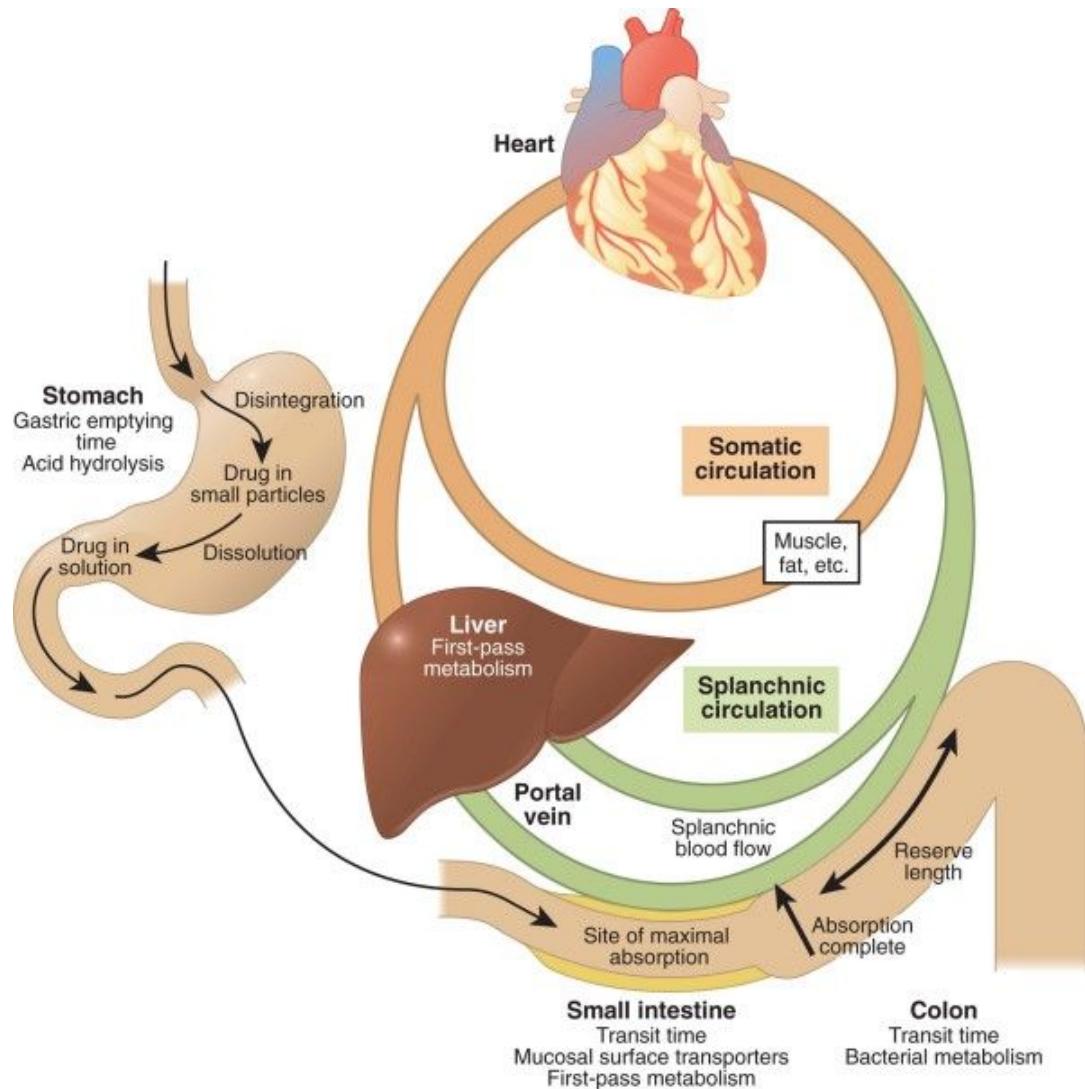


Poli A et al. Nutraceutical and functional foods for the control of plasma cholesterol levels. An intersociety position paper. *Pharmacol Res* 2018;134:51-60.

Overview of pharmacokinetics



Biopharmaceutic and physiologic processes that affect the rate and extent of absorption of an orally administered drug dose



Riso rosso fermentato

- La monacolina K contenuta nel riso rosso fermentato è chimicamente indistinguibile dalla lovastatina, un inibitore dell'HMG-CoA reduttasi
- Le monacoline contenute nell'estratto del riso rosso fermentato sono caratterizzate da una biodisponibilità sensibilmente maggiore rispetto a quella del farmaco di sintesi

Riso rosso fermentato

- La monacolina K, come la lovastatina, è metabolizzata dal citocromo P450 isoenzima 3A4: può pertanto causare interazioni di natura farmacologica potenzialmente rilevanti
- Non è raccomandata la combinazione di statine con integratori a base di riso rosso fermentato, sia per motivi farmacodinamici sia per la possibilità di indurre gli stessi effetti collaterali

CENTRAL ILLUSTRATION: Effects of Long-Term Treatment With Red Yeast Rice on Hard Outcomes and in Older Secondary Prevention Trials Carried Out With First-Generation Statins: Implication for Use in Clinical Practice

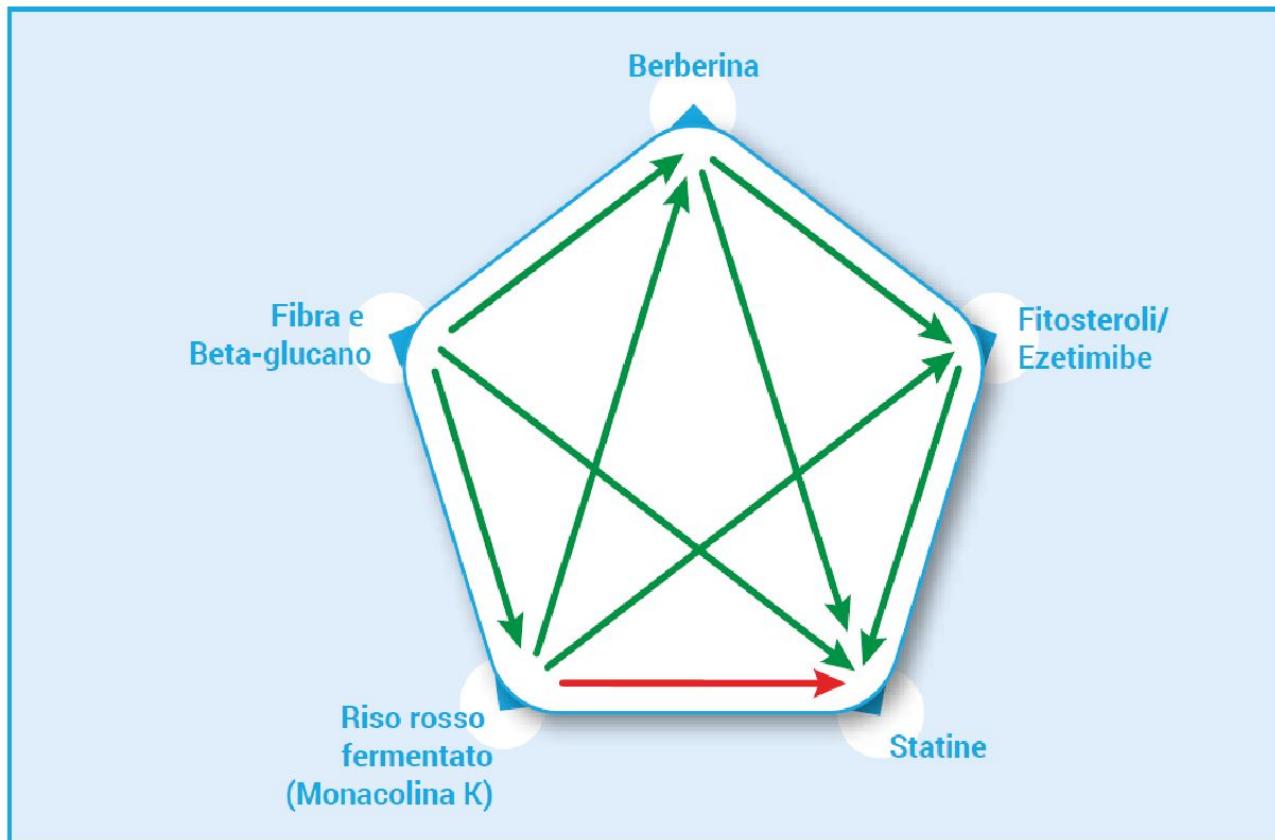
	Treatment	Patients Involved	Mean Follow-Up Duration	Endpoint	Main Effect (RRR)
Chinese Coronary Secondary Prevention Study (CCSPS)	Red Yeast Rice vs. Placebo	4,870	4.5 years	Nonfatal myocardial infarction and death from coronary heart disease (Primary)	-45%
Cholesterol and Recurrent Events trial (CARE)	Pravastatin 40 mg vs. Placebo	4,159	5 years	Nonfatal myocardial infarction and death from coronary heart disease (Primary)	-24%
Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Pravastatin 40 mg vs. Placebo	9,014	6.1 years	Nonfatal myocardial infarction and death from coronary heart disease (Secondary)	-24%
Scandinavian Simvastatin Survival Study (4S)	Simvastatin 20/40 mg vs. Placebo	4,444	5.4 years	Nonfatal myocardial infarction and death from coronary heart disease (Secondary)	-42%



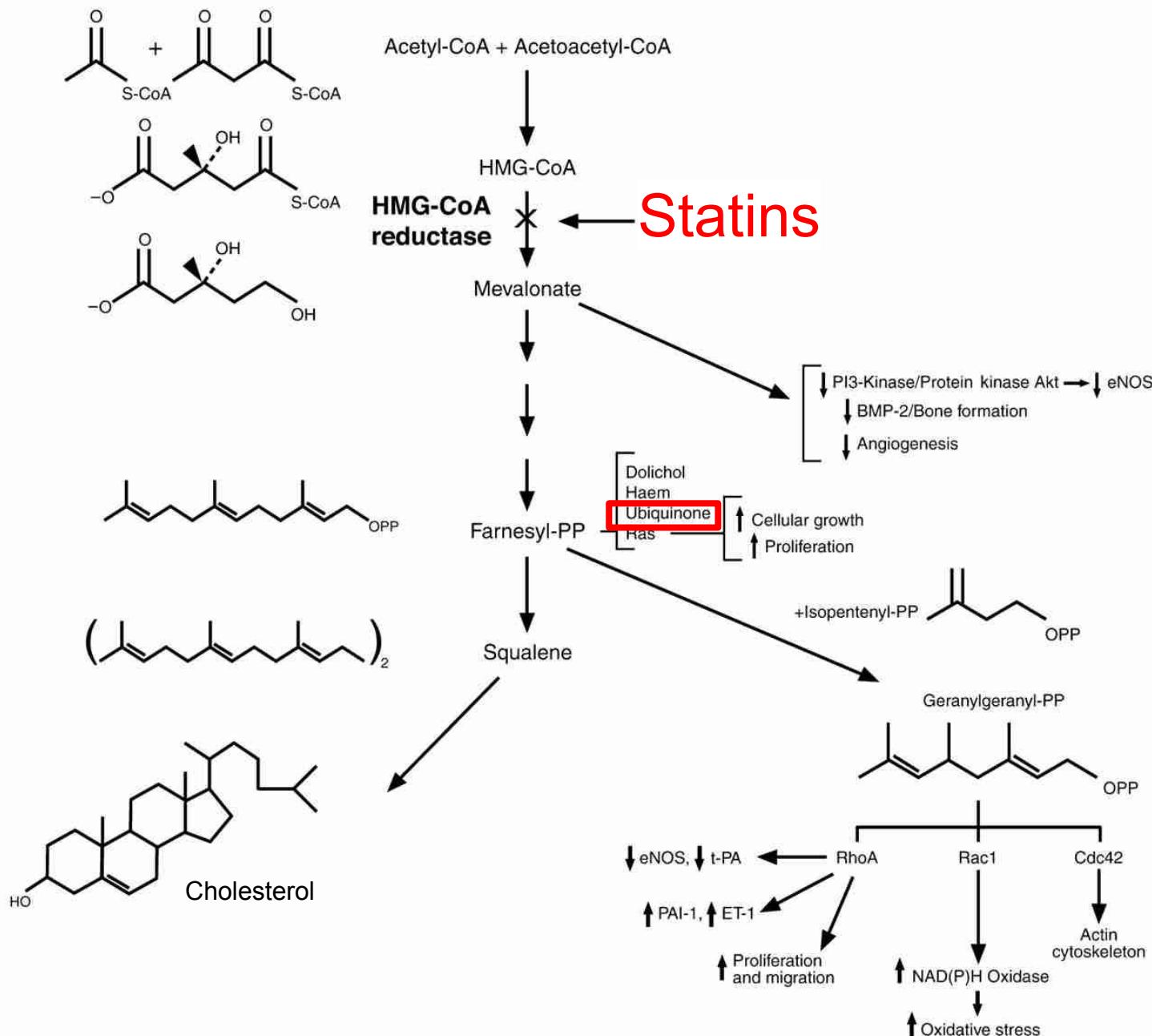
- PRO**
- Moderate but effective LDL reduction
 - Positive effects on vascular health
 - Long-term data available
 - Good safety profile
- CONS**
- Not FDA approved
 - Available to patients without mandatory medical prescription
 - Some risk of pharmacological interactions

Cicero, A.F.G. et al. J Am Coll Cardiol. 2021;77(5):620-8.

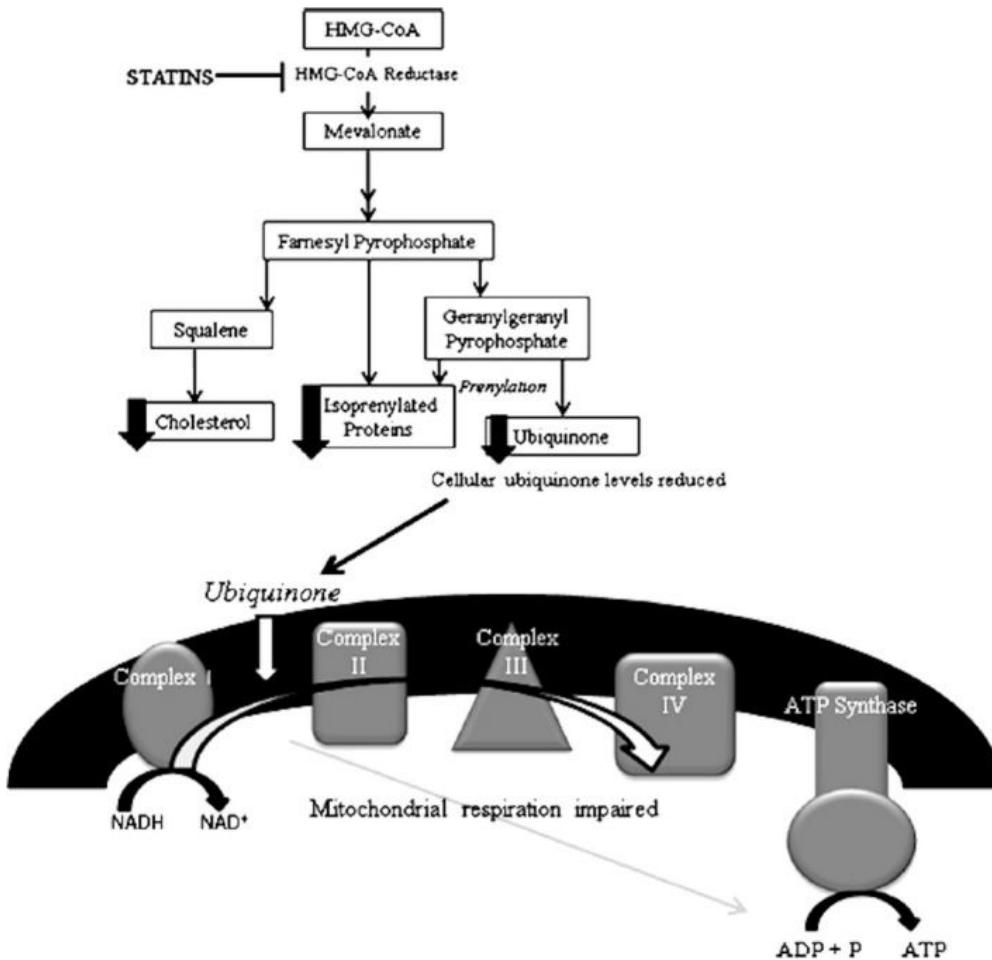
Possibili combinazioni di principi ad azione ipocoolesterolemizzante



STATINS: Mode of Action



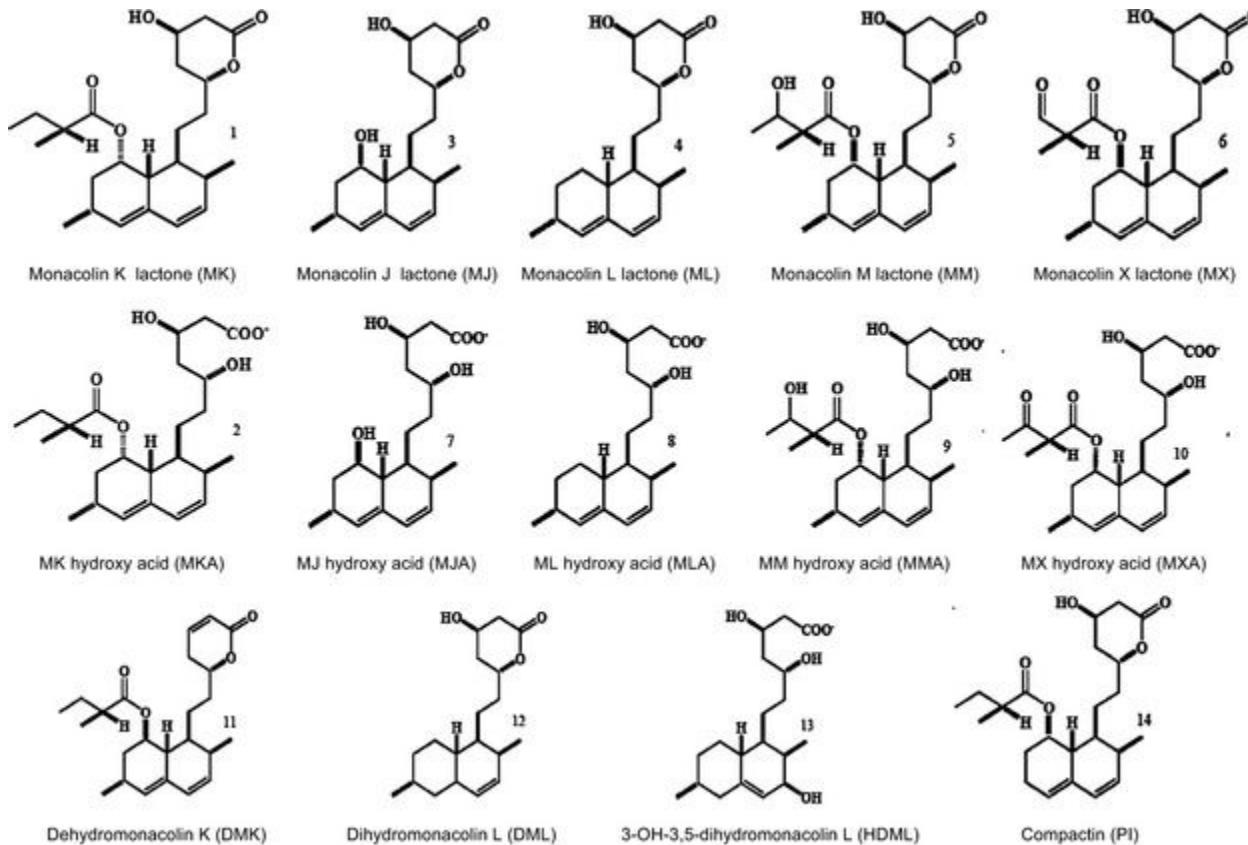
Statin myopathy as related to cellular ubiquinone depletion



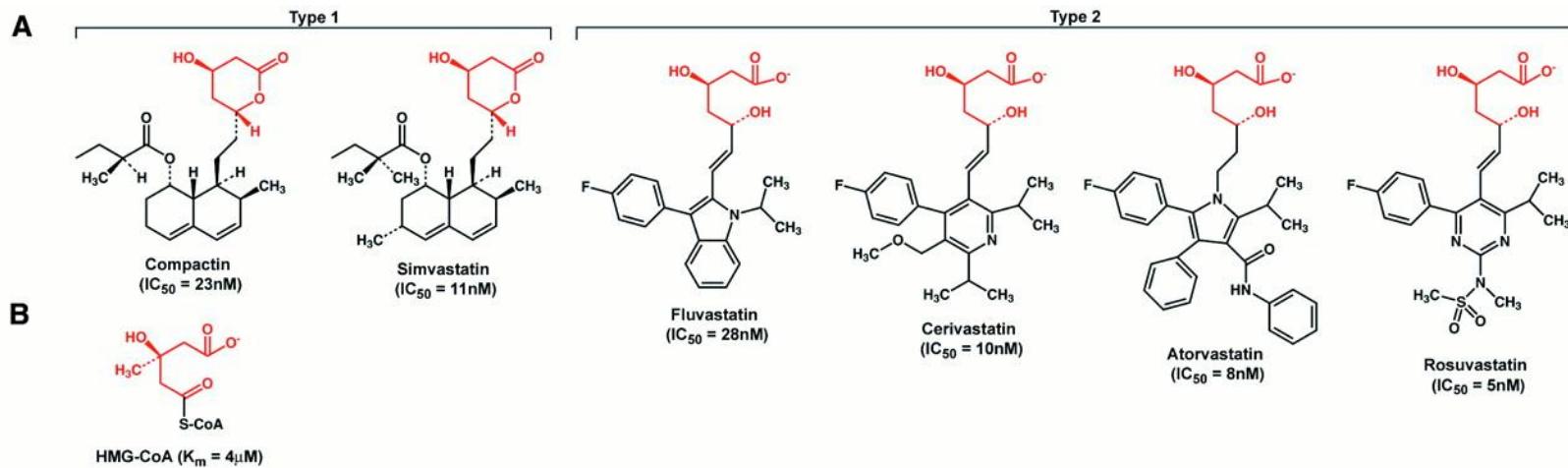
Europe: draft regulation on monacolins from red yeast rice voted by the Member States

- This regulation corresponds to
 - a ban of monacolins from red yeast rice for a daily dose greater than or equal to 3 mg/day
 - placing under restrictions (warnings) and under Union scrutiny for lower doses.
- These restrictions apply to monacolins in general (and not only monacolin K)
 - The sum of the analysed contents of monacolin K (lacton) and monacolin K (hydroxy acid) can be used to quantify the total monacolin content in preparations from red yeast rice
 - Practical methods that quantify all monacolins in red yeast rice preparations could not be identified)

List of monacolins identified in red yeast rice



Structural formulas of statin inhibitors and the enzyme substrate HMG-CoA



A) Structure of several statin inhibitors. Compactin and simvastatin are examples of type 1 statins; not shown are the other type 1 statins, lovastatin and pravastatin. Fluvastatin, cerivastatin, atorvastatin, and rosuvastatin are type 2 statins. The HMG-like moiety that is conserved in all statins is colored in red. The IC₅₀ (median inhibitory concentration) values of the statins are indicated. **(B)** Structure of HMG-CoA. The HMG-moiety is colored in red, and the K_m value of HMG-CoA is indicated.

Europe: draft regulation on monacolins from red yeast rice voted by the Member States

- Should not be consumed by pregnant or lactating women, children below 18 years old and adults above 70 years old
- Seek advice from a doctor on consumption of this product if you experience any health problems
- Should not be consumed if you are taking cholesterol-lowering medication
- Should not be consumed if you are already consuming other products containing red yeast rice

Carenza di coenzima Q10 associata all'impiego delle statine

- I sintomi muscolari associati alle statine (SAMS) sono comuni e influenzano l'aderenza al trattamento con statine
L'integrazione di CoQ10 può essere utilizzata per trattare la mialgia associata alle statine
- Le meta-analisi condotte finora sono giunte a conclusioni contraddittorie

1

STATE-OF-THE-ART PAPER

The Role of Coenzyme Q10 in Statin-Associated Myopathy

A Systematic Review

Leo Maroff, MD,* Paul D. Thompson, MD†‡

New Haven, Hartford, and Farmington, Connecticut

There are only 2 randomized trials, both in abstract form, that were designed to evaluate CoQ10 as a treatment for statin-associated myopathy

Preliminary results suggest a significant improvement in pain scores in patients treated with CoQ10, with 18 of 21 reporting improvement in symptom severity and a reduction in mean pain scores (6.2 ± 1.7 to 3.1 ± 2.2 at baseline using a 10-point scale ($p < 0.001$).

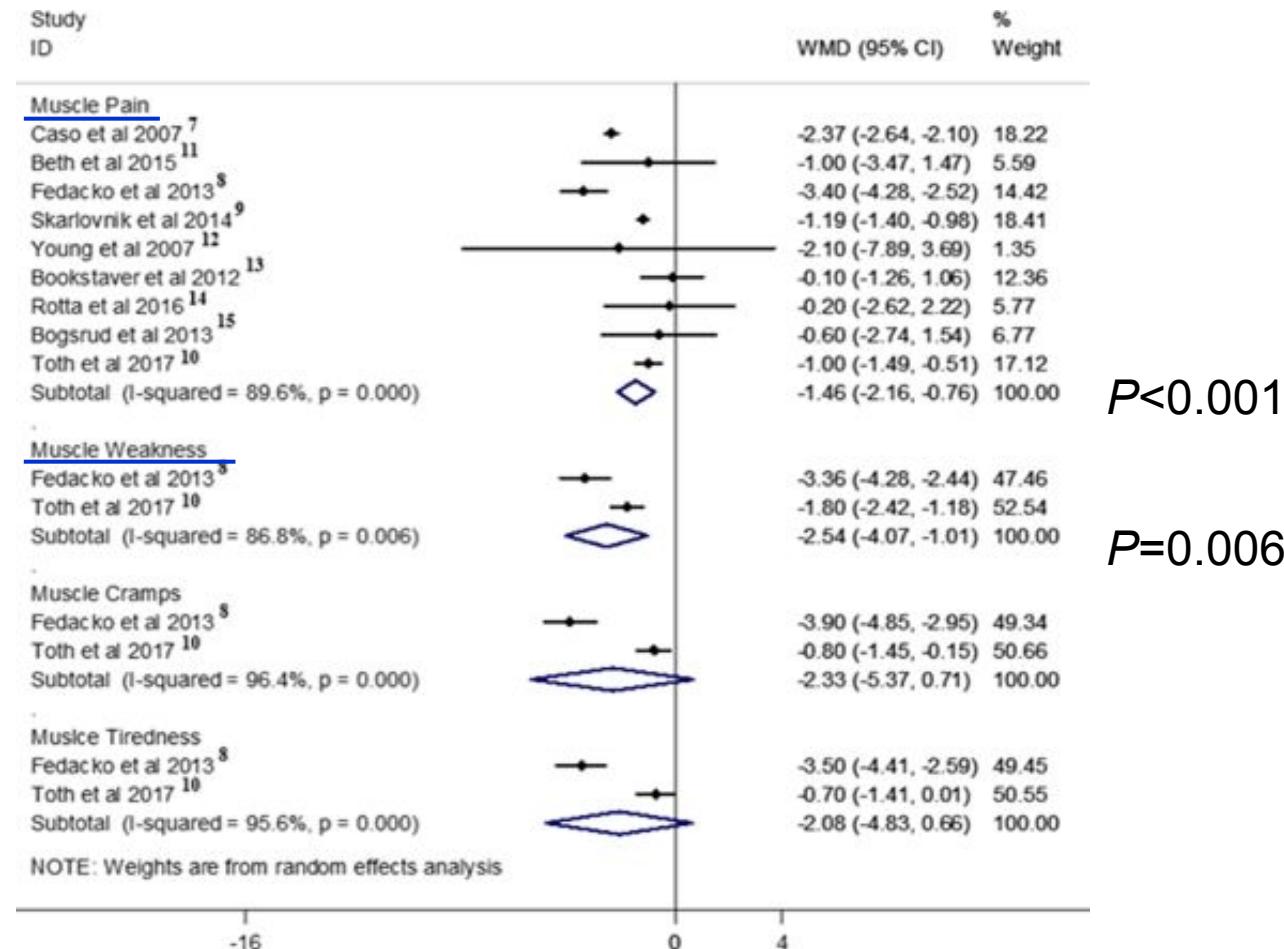
In a more recent trial that randomized 44 dyslipidemic patients with prior statin-induced myalgia to 12 weeks of treatment with escalating doses of simvastatin (10 to 40 mg/day) and CoQ10 200 mg/day or placebo, there were no differences in myalgia scores ($p = 0.63$) or in statin tolerance between the 2 treatment groups.

②

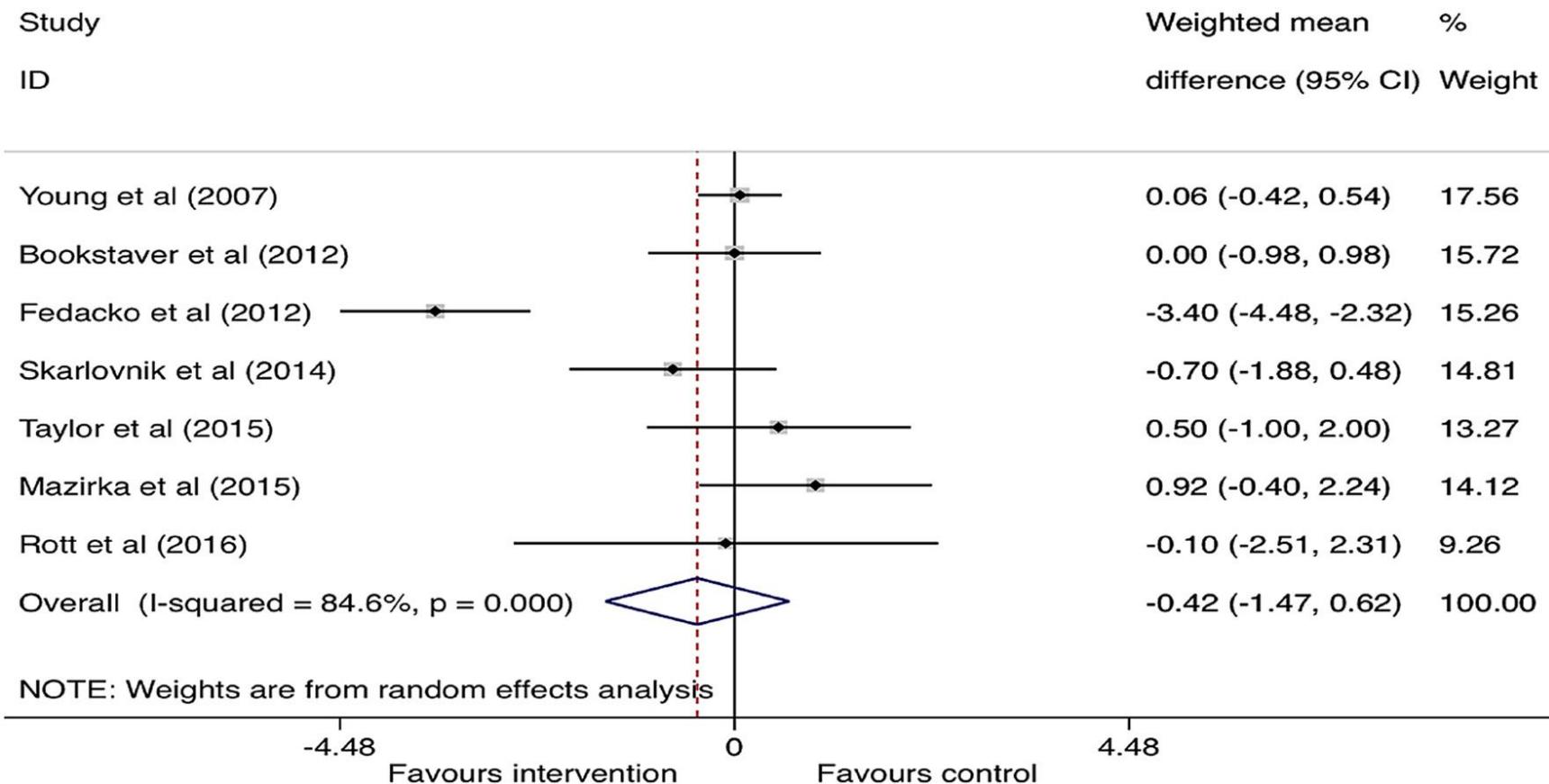
Efficacy of coenzyme Q10 (CoQ10) supplementation on statin-induced myopathy

- Compared with the control group, plasma CK activity was increased after CoQ10 supplementation, but this change was not significant (mean difference, 11.69 U/L; 95% CI, −14.25 to 37.63 U/L; $P=.38$).
- Likewise, CoQ10 supplementation had no significant effect on muscle pain despite a trend toward a decrease (standardized mean difference, −0.53; 95% CI, −1.33 to 0.28; $P=.20$).
- No dose-effect association between changes in plasma CK activity (slope, −0.001; 95% CI, −0.004 to 0.001; $P=.33$) or in the indices of muscle pain (slope, 0.002; 95% CI, −0.005 to 0.010; $P=.67$) and administered doses of CoQ10 were observed.

③ CoQ10 supplementation ameliorated muscle pain and muscle weakness



④ CoQ10 did not have significant effect on muscle pain compared to placebo



CoQ10 and Statin Intolerance – 1

- Mechanistic studies and deductive reasoning suggest that CoQ10 dysregulation could be the cause, or could at least contribute, to SAMS.
- Clinical studies, however, have not documented its effectiveness in treating SAMS.
- It is critically important to determine that subjects enrolled in a clinical trial of a certain condition, in this case SAMS, actually have the phenotype to be examined.
- CoQ10 may still be useful in some patients, perhaps through the placebo effect.

CoQ10 and Statin Intolerance – 2

- CoQ10 could have a positive impact on the management of patients more likely to develop statin-related side effects, such as those affected by fibromyalgia.
- The supplementation with CoQ10 is safe, even with chronic exposure to 900 mg/day and in frail patients, like elderly and CKD patients, without any known pharmacological interactions.

Table 2. Coenzyme Q₁₀: clinical applications in cardiovascular diseases.

	Level of Evidence	Active Daily Doses	Effects on Symptoms and/or Grade of Disease	Effects on Lab or Instrumental Parameters	Effects on Hard Outcomes
Heart Failure (HF)	Meta-analysis of RCTs	100–300 mg	↑ self-perceived quality of life and improvement in NYHA class	↑ EF (if >30%), ↑ LVEF, ↑ CO and CI, ↑ SV, ↑ EDV, ↑ exercise capacity, ↓ ventricular arrhythmias after surgery and need of inotropic drugs (after cardiac surgery), and ↓ low-grade inflammation (TNF-alpha, IL-6, and hsCRP)	↓ MACE, total mortality, and incidence of hospital stays for HF
Acute Myocardial Infarction (AMI)	RCTs	120 mg	Not investigated	Prevention of alteration of the wall thickening abnormality at the infarct site and sphericity index and ↓ wall thickness opposite the site of infarction	Not investigated
Ischemic Stroke (IS)	RCTs	300 mg	↑ NIHSS and mmSE	Reduction of oxidative stress (?)	Not investigated
Atrial Fibrillation (AF)	Meta-analysis of RCTs	100–300 mg	Improvement in NYHA class, reduction of risk to develop ventricular arrhythmias, and use of inotropic drugs after surgery	Reduction of malondialdehyde and oxidative stress	Not investigated
Cardiomyopathy	RCTs	200–300 mg	Improvement of fatigue and dyspnea	Improvement of mean interventricular septal thickness, mean posterior wall thickness, diastolic function, and mean score for the index of cardiac failure	Not investigated
Cardiotoxicity	RCTs	200–300 mg	Improvement of heart's functions (in association with L-carnitine)	Reduction of oxidative stress (nitric oxide and malondialdehyde) and ↓IL-1, TNF-α Troponin-I and Troponin-T levels (in association with L-carnitine)	Not investigated
Hypertension	Meta-analysis of RCTs	100–300 mg	Not reported	↑ Exercise capacity and arterial stiffness; ↑ NO bioavailability, and ↓ SBP and DBP (only in prehypertensive or hypertensive patients)	Not investigated
Diabetes type II, Metabolic syndrome (MetS)	RCTs	100–300 mg	Not reported	↓ Lipid peroxidation, FPC, triglycerides, and low-grade inflammation (TNF-alpha, IL-6, and hsCRP) and ↑ insulin sensitivity	Not investigated
Dyslipidemia	RCTs	100–300 mg	↑ self-perceived quality of life (reduction side effects of lipid-lowering drugs)	↑ Exercise capacity and arterial stiffness; ↓ lipid peroxidation, TC*, LDL-C*, TC*, BP*, FPG*, and low-grade inflammation (TNF-alpha, IL-6, and hsCRP); and ↑ insulin sensitivity *If >12 weeks of treatment	Not investigated
Non-Alcoholic Fatty Liver Disease (NAFLD)	Meta-analysis of RCTs	100–300 mg	Improvement in NAFLD grade	↑ Adiponectin (?) and leptin levels; ↓ AST, GGT, hsCRP, and TNF-alpha levels; and ↓ WC and lipid peroxidation	Not investigated
Chronic Kidney Disease (CKD)	Meta-analysis of RCTs	100–300 mg	Not investigated	↓ Lipid peroxidation, TC (?), LDL-C (?), Lp(a) (?), triglycerides (?), fasting plasma glucose (?), HbA1c (?), inflammation, and oxidative stress biomarkers (hsCRP (? and malondialdehyde) and ↑ insulin sensitivity	Not investigated

AST = Aspartate Aminotransferase, BP = Blood Pressure, CI = Cardiac Input, CO = Cardiac Output, DBP = Diastolic Blood Pressure, EDV = End-Diastolic Volume, EF = Ejection Fraction, FPG = Fasting Plasma Glucose, GGT = Gamma-Glutamyl Transpeptidase, HF = Heart Failure, hsCRP = high sensible C-Reactive Protein, IL-6 = Interleukin 6, LDL-C = LDL-Cholesterol, Lp(a) = Lipoprotein a, LVEF = Left Ventricular Ejection Fraction, MACE = Major Adverse Cardiac Events, mmSE = Mini Mental State Examination, NIHSS = National Institute of Health Stroke Scale, NYHA = New York Heart Association, NO = Nitric Oxide, RCTs = Randomized Clinical Trials, SBP = Systolic Blood Pressure, SV = Stroke Volume, TC = Total Cholesterol, TG = triglycerides, TNF-alpha = Tumor Necrosis Factor-alpha, WC = Waist Circumference. ↓: Worsening; ↑: Improvement; ?: Unclear.

CoQ10 and Statin Intolerance – Perspectives

- CoQ10 is a potential treatment for statin intolerance, allowing patients to continue on a statin rather than switch to expensive biological therapies, such as PCSK9 inhibitors.
- The primary outcome of future trials should be the number of patients continuing on statins when treated with CoQ10 rather than pain scores or biochemical results.



RISULTATI DELLA RICERCA



Coenzima Q 10 200
31 compresse | Farmaderbe S.r.l.



Coenzima Q10
200 complex 45 compresse | Pharmalife Research S.r.l.



Coenzima Q10
200 mg 50 capsule | Krymi Laboratori Farmaceutici S.r.l.



Coenzima Q10
24 compresse 100 mg | Erbamea S.r.l.



Coenzima Q10
30 capsule - 18 g | KOS S.r.l.



Coenzima Q10
30 capsule 13,4 g | Studio 3 Farma S.r.l.



Coenzima Q10
30 capsule 200 mg | HealthAid Italia S.r.l.



Coenzima Q10
30 capsule vegetali 9 g | Solgar Italia Multinutrient S.p.a.



Coenzima Q10
60 capsule | Zenobia S.r.l.



Coenzima Q10
coenzima q10 ubidecarenone 30 mg 60 capsule gelatinose | La Strega S.r.l.

Coenzima Q10

integratore alimentare 30 capsule | Roessler Pharma S.r.l.

Coenzima Q10 Attivo 100 mg

30 perle da 437 mg - 13,1 g | Biodue S.p.A.

Coenzima Q10 Forte

30 capsule 100 mg | KOS S.r.l.

Coenzima Q10 Forte

30 capsule 100mg 15 g | Galeno S.r.l.

Coenzima Q10 Forte

60 capsule | KOS S.r.l.

Coenzima Q10+ Resveratolo

30 pastiglie da 1000 mg- 30 g | Dr. Giorgini Ser-Vis S.r.l.

FF Formula Coenzima Q10

30 compresse 15 g | So.Farma Morra S.p.a

Maxi Coenzima Q10

30 perle softgels 12 g | Solgar Italia Multinutrient S.p.a.

Maximum Coenzima Q10

100 capsule | Naturando S.r.l.

Pure Coenzima Q10

crema viso notte 50 ml | MDS Medical Devices and Supplis S.r.l.

RISULTATI DELLA RICERCA



Q10 Coenzima
30 capsule 450 mg | Inalme S.r.l.



Ultra Coenzima Q 10
coenzima q 10 (ubiquinone) 100 mg 30 capsule gelatinose | La Strega S.r.l.

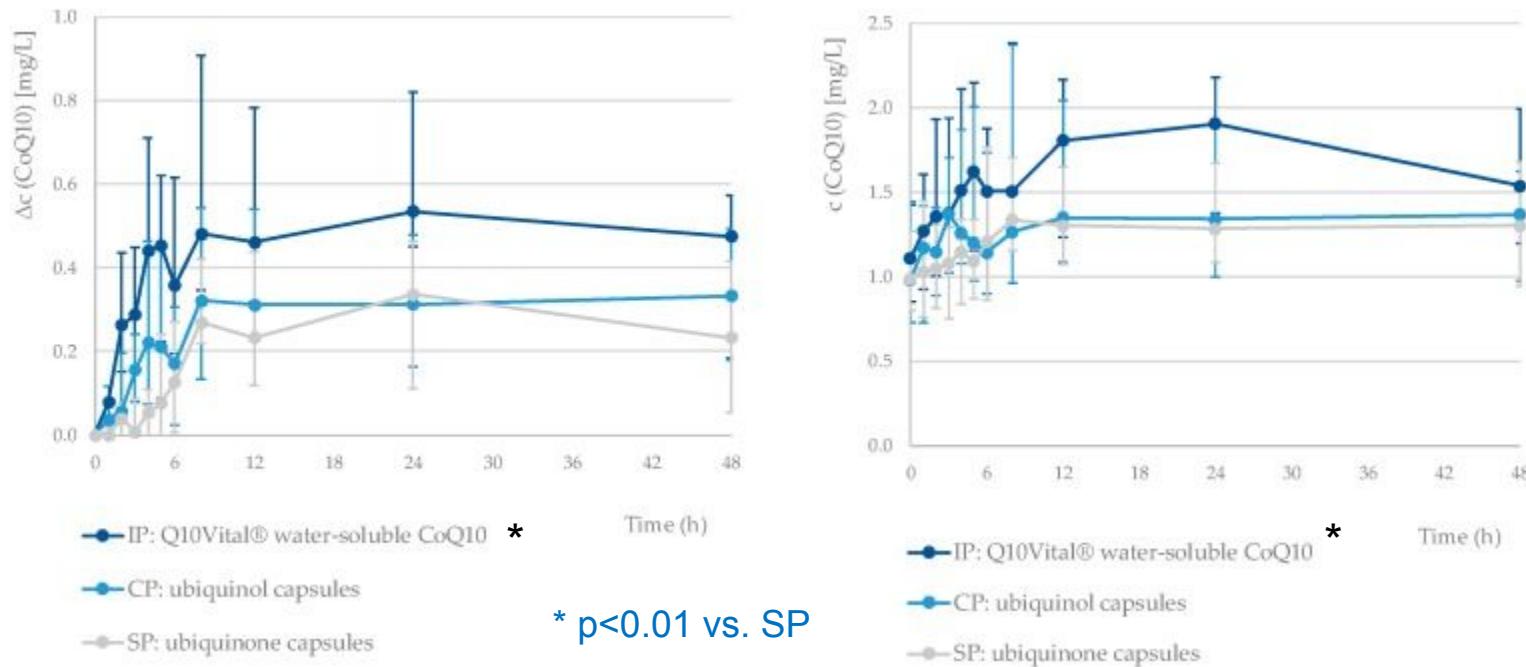


Up Coenzima Q10
60 capsule - 30 g | Up Pharma S.r.l.



Up Coenzima Q10
60 capsule - 33 g | Up Pharma S.r.l.

Pharmacokinetic profiles for three CoQ10 tested formulations in healthy elderly subjects



Median pharmacokinetic profile of Δc and c (CoQ10, total) for each tested formulation. The error bars represent the first and third quartile of the plasma concentrations ($N = 21$ for each tested formulation). Standard product (SP) means ubiquinone capsules, comparative product (CP) means ubiquinol capsules, and investigational product (IP) means Q10Vital[®] water-soluble CoQ10.

Criteri generali di uso dei nutraceutici per il controllo della colesterolemia

- Questi prodotti, secondo la normativa vigente, possono essere venduti direttamente al pubblico
- La qualità degli integratori sul mercato è molto variabile
- L'origine “naturale” dei principi non è in alcun modo garanzia di una loro “non pericolosità” e dell’assenza di interazioni farmacologiche
- Tutti i principi hanno un’azione reversibile sulla colesterolemia che si esaurisce dopo la sospensione del trattamento.

ORIGINAL INVESTIGATION

Marked Variability of Monacolin Levels in Commercial Red Yeast Rice Products

Buyer Beware!

Ram Y. Gordon, MD; Tod Cooperman, MD; William Obermeyer, PhD; David J. Becker, MD

Arch Intern Med. 2010;170(19):1722-1727

Table 2. Total Monacolin, Monacolins K and KA, and Citrinin Content per 600-mg Capsule of 12 Commercially Available Red Yeast Rice Products

Red Yeast Rice Product in 600-mg Capsules	Monacolin Level, mg/cap			Citrinin, ppm	Citrinin, µg/cap
	Total Monacolins	Monacolin K (Lovastatin)	Monacolin KA		
A	5.30	2.53	1.96	ND	0.0
B	2.16	1.02	0.61	ND	0.0
C	4.18	1.74	1.63	ND	0.0
D	1.65	1.12	0.22	24	14.3
E	6.03	3.63	1.22	ND	0.0
F	0.31	0.10	0.00	189	114.2
G	6.18	2.50	2.30	ND	0.0
H	11.15	10.09	0.52	ND	0.0
I	1.60	0.99	0.23	75.5	57.5
J	3.97	2.66	0.46	ND	0.0
K	1.36	0.97	0.19	119	70.4
L	6.13	3.12	2.07	ND	0.0
Mean (SD)	4.17 (3.00)	2.54 (2.60)	0.95 (0.84)	34.0 (62.1)	21.4 (38.2)
Median	4.08	2.12	0.57	0.00	0.00

Abbreviations: cap, capsule; ND, none detected; ppm, parts per million.

Table 1. Amounts of active ingredients, pharmaceutical forms and labelled information of food supplements containing red yeast rice as the main active ingredient. Detected MK amounts are reported as mean mg/serving \pm SD.

N.	Labelled Active Ingredient	Formulation	Recommended Servings/Day *	MK/Serving (mg) *	Detected MK/Serving (mg)	Other Active Ingredients (mg/Serving) **
1	RYR powder (100 mg, 3% MK)	Tablets	1	3	4.13 \pm 0.07	<i>Ipomea batatas</i> d.e. (160 mg); <i>Citrus reticulata</i> peels d.e. (40 mg); <i>Olea europaea</i> fruit d.e. (25 mg); Coenzyme Q10 (5 mg)
2	RYR powder (100 mg, 3% MK)	Tablets	1	3	3.07 \pm 0.03	<i>Garcinia cambogia</i> d.e. (50 mg); <i>Citrus bergamia</i> peels d.e. (50 mg); Coenzyme Q10 (20 mg)
3	RYR powder (100 mg, 3% MK)	Tablets	1	3	2.58 \pm 0.04	Coenzyme Q10 (100 mg); Policosanols (20 mg); astaxanthin (2 mg)
4	RYR powder (200 mg, 1.5% MK) RYR d.e.	Tablets	1	3	2.50 \pm 0.02	ND
5	(262.5 mg, 0.4% MK; 130 mg, 1.5% MK)	Capsules	1	3	1.51 \pm 0.09	ND
6	RYR powder (167 mg, 3% MK) RYR d.e.	Capsules	2	5	2.91 \pm 0.11	ND
7	(200 mg, 5% MK) RYR d.e.	Tablets	1	10	9.19 \pm 0.05	ND
8	(200 mg, 5% MK) RYR d.e.	Tablets	1	10	9.88 \pm 0.05	ND
9	(200 mg, 5% MK) RYR d.e.	Tablets	1	10	8.99 \pm 0.01	ND
10	RYR powder (200 mg, 5% MK)	Tablets	1	10	9.17 \pm 0.22	ND

* As reported by manufacturers. ** The amounts of active ingredients are those reported by manufacturers. RYR: red yeast rice; MK: monacolin K; d.e.: dried extract.

Range: -50 – +38%

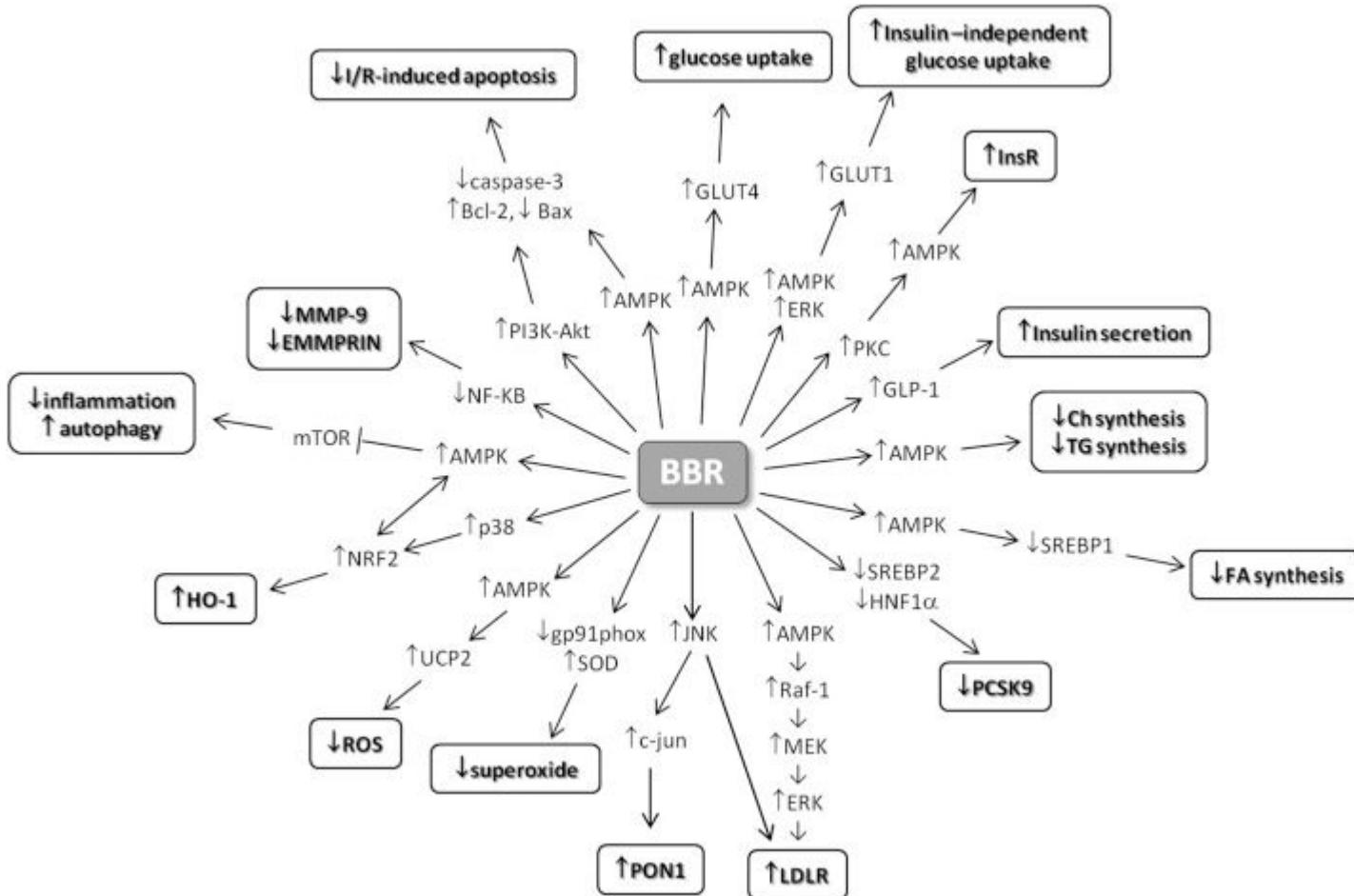
Table 3. Amounts of active ingredients, pharmaceutical forms and labelled information of food supplements containing berberine as the main active ingredient. Detected berberine amounts are reported as mean mg/serving \pm SD.

N.	Labelled Active Ingredient	Formulation	Recommended Servings/Day *	BBR/Serving (mg) *	Detected BBR/Serving (mg)	Other Active Ingredients (mg/Serving) **
11	<i>B. aristata</i> DC bark d.e. (100 mg, 97% BBR)	Tablets	2	97	97.41 \pm 0.23	Coenzyme Q10 (10 mg); Olive leaves dry extract (50 mg, 6% oleuropein); olive fruit dry extract (50 mg, 10% hydroxytirosol), <i>Silybum marianum</i> dry extract (40 mg, 2% silimaric)
12	<i>B. aristata</i> DC bark d.e. (100 mg, 97% BBR)	Tablets	2	97	97.20 \pm 0.08	ND
13	<i>B. aristata</i> DC bark d.e. (250 mg, 97% BBR)	Tablets	1 or 2	242.5	255.01 \pm 34.20	beta (1,3)-Glucan (100 mg); "Cinnamon" dry extract (100 mg, 1.6% MHCP)
14	<i>B. aristata</i> DC bark and roots d.e. (294 mg, 85% BBR)	Capsules	2	250	398.43 \pm 29.22	ND
15	<i>B. aristata</i> DC d.e. (294 mg, 85% BBR)	Tablets	2	250	280.33 \pm 21.10	ND
16	<i>B. aristata</i> DC bark d.e. (450 mg, 83.6% BBR) <i>B. aristata</i> DC d.e.	Tablets	2	376.2	514.66 \pm 11.21	ND
17	(BBR standardization unknown)	Tablets	1	500	663.17 \pm 33.01	Monacolin K (10 mg; from red yeast rice powder)
18	<i>B. aristata</i> DC bark d.e. (BBR standardization unknown)	Tablets	2	500	561.12 \pm 21.50	ND

*As reported by manufacturers. ** The amounts of active ingredients are those reported by manufacturers. BBR: berberine; d.e.: dried extract.

Range: up to +60%

Mechanism of action of berberine



Pharmacokinetics of berberine

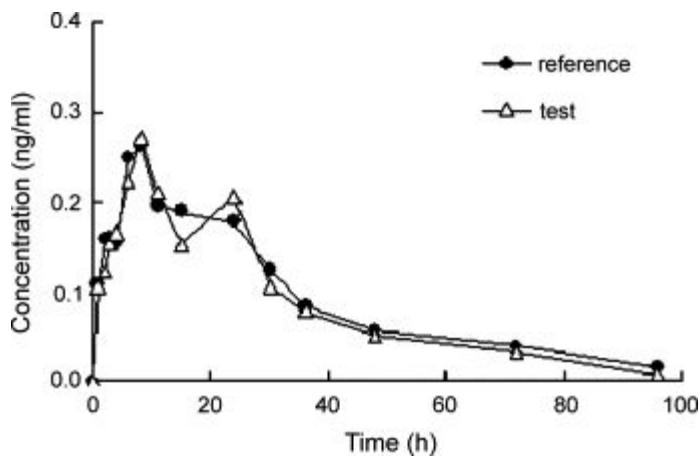


Table 5

The main pharmacokinetic parameters of berberine in 20 healthy volunteers after a single oral dose of 400 mg test and reference tablets ($n=20$)

PK parameters	Mean \pm S.D.	
	Test	Reference
C_{\max} (ng/ml)	0.4356 ± 0.4194	0.4171 ± 0.2792
$t_{1/2}$ (h)	28.6 ± 9.5	31.8 ± 12.2
t_{\max} (h)	9.8 ± 6.6	9.6 ± 5.2
AUC_{0-96} (h ng/ml)	7.835 ± 3.743	8.461 ± 4.180
$AUC_{0-\infty}$ (h ng/ml)	9.179 ± 3.767	9.803 ± 4.322

The bioavailability of berberine is lower than 1%

(Berberol®; PharmExtracta srl, Pontenure, Italy), containing 588 mg/tablet *Berberis aristata* extract (titrated in 85% berberine) plus 105 mg/tablet *Silybum marianum* extract (titrated in >60% flavanolignans).

Table 2 Effects of an oral add-on therapy, in patients with T2DM with *Berberis aristata* or Berberol®, after 120 day of treatment

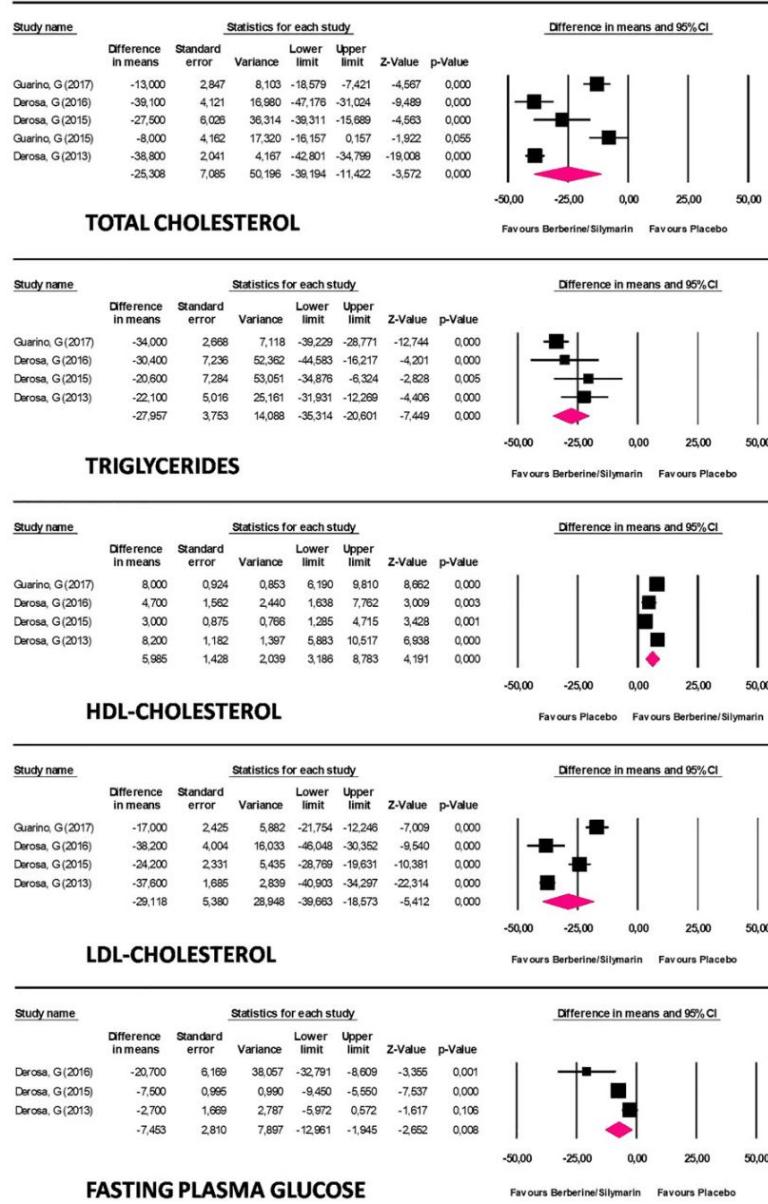
Parameter	<i>Berberis aristata</i> (A)			P	<i>Berberol</i> ® (B)			P	<i>B</i> vs <i>A</i> (after)	P
	Before	After	Variation (%)		Before	After	Variation (%)		Variation (%)	
Weight (kg)	80.55±19.38	80.84±17.65	0.36	ns	76.81±20.55	77.86±16.38	1.36	ns	-3.69	ns
BMI (Kg/m ²)	30.53±6.85	30.22±7.01	-1.07	ns	29.90±7.20	29.25±5.33	-2.18	ns	-3.21	ns
WL (cm)	100.32±17.19	95.43±31.50	-5.88	ns	98.81±14.27	96.05±11.18	-2.80	ns	0.64	ns
FG (mg/dL)	157.34±28.22	128.95±3001	-19.05	0.006	158.32±34.39	131.20±31.70	-18.13	0.007	1.74	ns
HbA _{1c} (%)	7.81±0.88	7.25±0.39	-7.18	<0.001	8.02±0.35	7.03±0.27	-12.35	<0.001	-3.04	<0.05
TC (mg/dL)	179.81±23.98	158.30±35.23	-11.97	0.007	177.54±31.65	157.93±32.05	-11.05	0.005	-0.24	ns
HDL-C (mg/dL)	50.98±13.66	49.22±14.19	-3.46	ns	51.88±12.65	50.39±14.25	-2.88	ns	2.37	ns
LDL-C (mg/dL)	96.75±27.69	85.02±28.52	-12.13	ns	94.39±29.81	78.37±28.19	-16.92	0.004	-7.83	ns
TG (mg/dL)	157.32±91.29	123.99±78.00	-21.57	0.003	155.44±71.22	120.33±65.77	-22.59	0.002	-2.96	ns
AST (U/L)	28.35±19.33	22.88±16.56	-19.30	0.032	27.34±12.86	21.66±17.34	-20.88	0.018	-5.34	ns
ALT (U/L)	32.64±22.31	28.39±17.29	-13.03	0.046	34.00±23.53	29.51±19.83	-13.21	0.040	3.94	ns

Note: All parameters are expressed as median ± standard deviation.

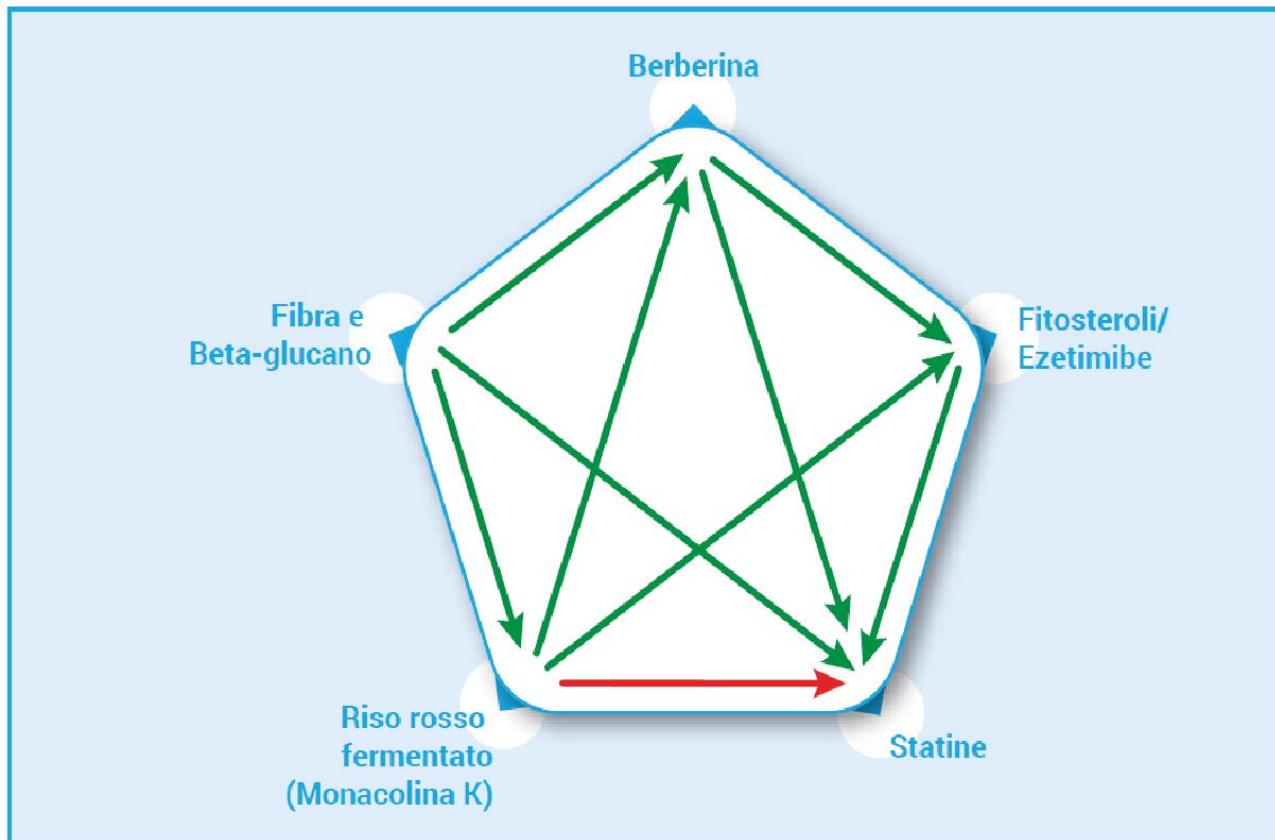
Abbreviations: ALT, alanine amino-transferase; AST, aspartate amino-transaminase; BMI, body mass index; FG, fasting glucose; HbA_{1c}, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; WL, waistline.

Lack of a control group receiving placebo

Effect of berberine and silymarin on plasma lipids and glucose concentrations

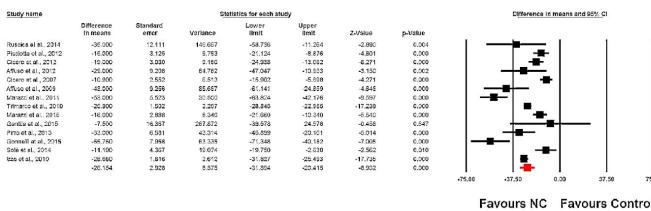


Possibili combinazioni di principi ad azione ipocoolesterolemizzante

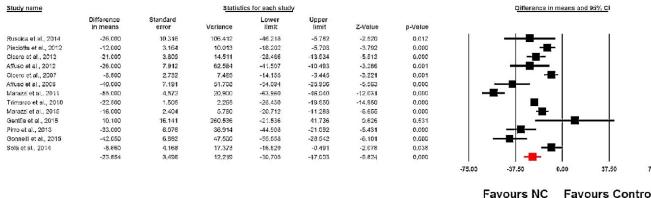


Impact of supplementation with nutraceutical combination on plasma lipid and glucose concentrations

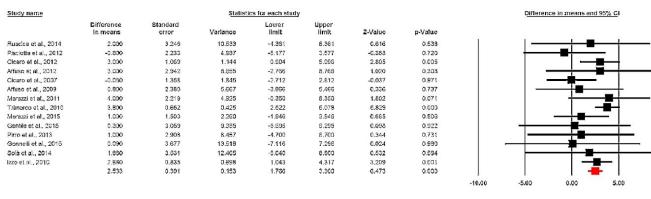
Total cholesterol



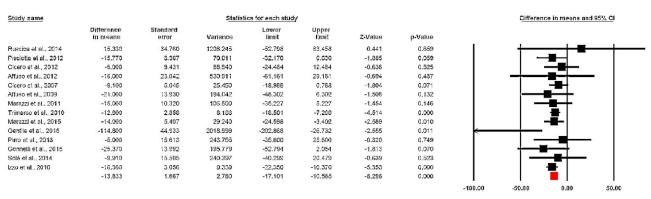
LDL-cholesterol



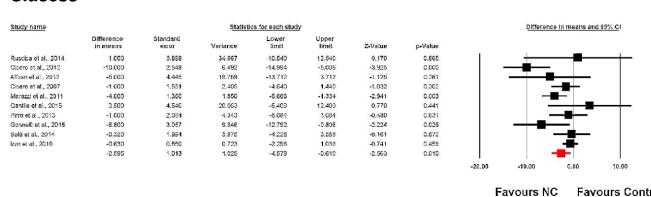
HDL-cholesterol



Triglycerides



Glucose

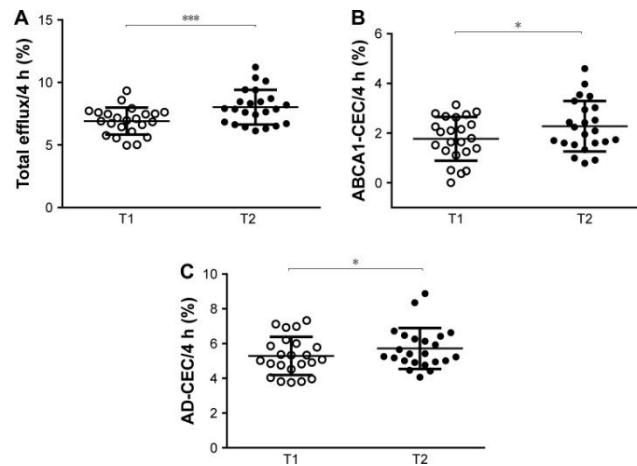


Effect of a novel nutraceutical combination on serum lipoprotein functional profile

Subjects ($n=23$) received one pill/day containing a combination of 625 mg of *Berberis aristata* cortex dry extract (corresponding to 531 mg of berberine), 220 mg of red yeast rice powder (corresponding to 3.3 mg of monacolin K) and 200 mg of *Morus alba* leaf dry extract (containing 4 mg of 1-deoxynojirimycin) for 16 weeks

Effect of NUT combination on serum lipid profile

	Baseline (n=23)	NUT combination (n=23)	Mean change %	p-value
TC (mg/dL)	218±36.2	198±31.1	-9.2	<0.001
LDL-C (mg/dL)	143±33.0	125±23.1	-12.6	<0.01
HDL-C (mg/dL)	50±10.8	49±11.1	-2	NS
TG (mg/dL)	125±62.4	116±58.5	-7.2	NS
apoA-I (mg/dL)	128.68±39.68	131.39±45.44	-2	NS



Berberine modulates expression of *mdr1* gene product and the responses of digestive tract cancer cells to paclitaxel

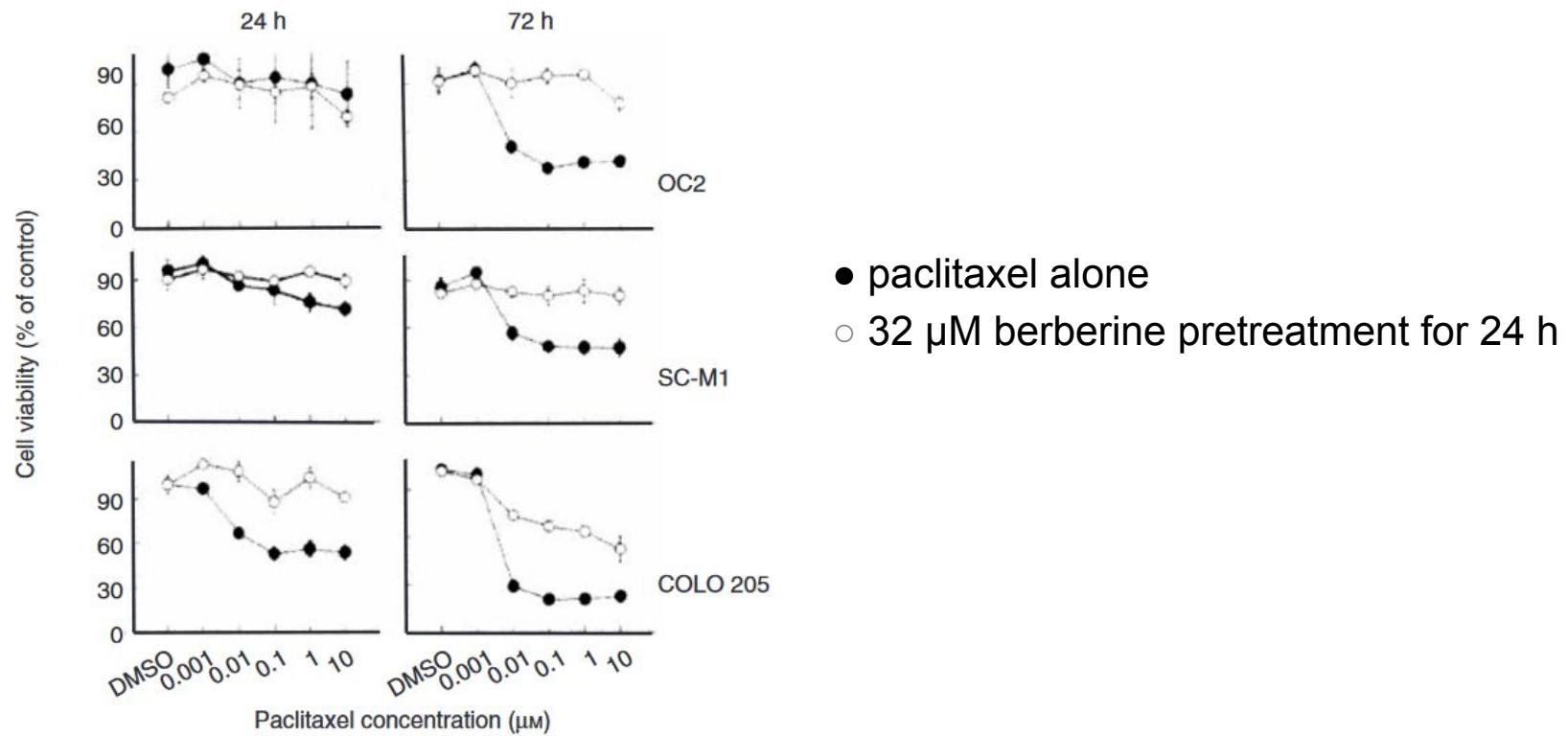


Table 1. Mechanisms of BBR-drug interactions.

Drug	CYPs/transporters involved
Metformin	OCT1/OCT2
Tacrolimus	CYP3A4
Cyclosporine A	P-gp/CYP3A4
HIV protease inhibitors	P-gp
Verapamil	P-gp
Tolbutamide	CYP2C9
Midazolam	CYP3A4
Dextromethorphan	CYP2D6
Losartan	CYP2C9
Phenacetin	CYP1A2
Digoxin	P-gp
Quinidine	OCT/P-gp

Agenda

- General remarks
- Gender
- Quality and composition of active pharmaceutical ingredients
- Conclusion

Main lipid lowering agents used clinically

- Statins: 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors
- Fibrates
- Nicotinic acid or its derivatives
- Inhibitors of cholesterol absorption
- Fish oil derivatives
- PCSK9 inhibitors

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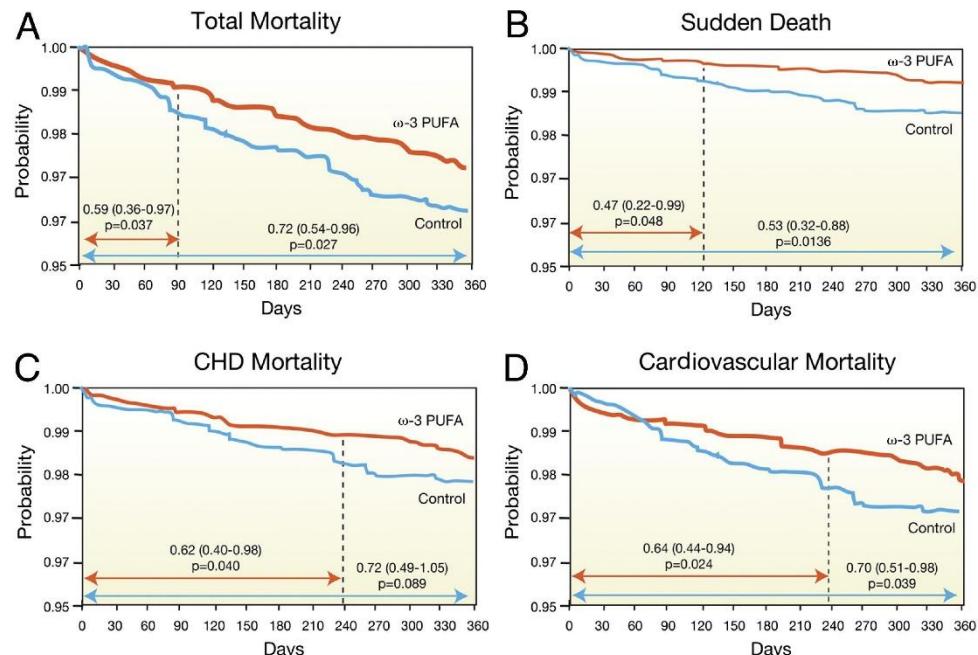
FISH OIL DERIVATIVES

- Fish oil reduce plasma triglyceride concentrations but increase LDL-cholesterol
- There is epidemiological evidence that eating fish regularly does reduce ischaemic heart disease
- Dietary supplementation with n-3 polyunsaturated fatty acids (PUFA) improves survival in patients who have recently had a myocardial infarction (*GISSI-Prevenzione*)
- The mechanism may be the potent antiarrhythmic effects of PUFA and/or inhibition of platelet function, prolongation of bleeding time, anti-inflammatory effects and reduction of plasma fibrinogen
- Omega-3-acid ethyl esters are used for prevention of recurrent events after myocardial infarction

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial

GISSI-Prevenzione Investigators* (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)

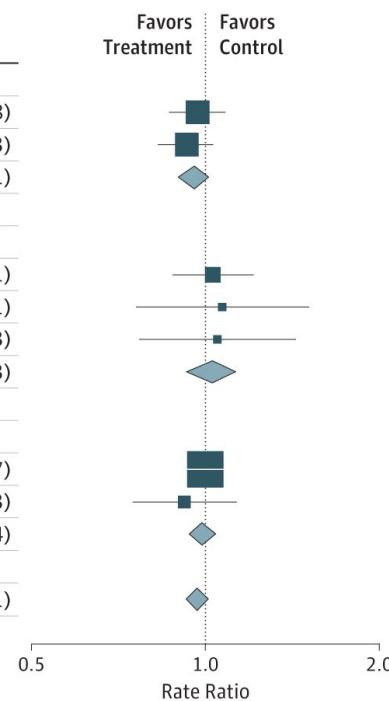
11 324 patients surviving myocardial infarction were randomly assigned supplements of n-3 PUFA 1 gelatin capsule containing 850–882 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as ethyl esters in the average ratio of EPA/DHA 1:2, vitamin E, both or neither for 3.5 years.



From: **Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals**

Associations of Omega-3 Fatty Acids With Major Vascular Events

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



Dose range: 226-1800 mg/day EPA, 0-1700 mg/day DHA

The apparent heterogeneity of treatment effect of omega-3 fatty acids preparations, which applies also to the many dietary fish oil supplements that are in widespread use as dietary supplement, is that many omega-3 fatty acids trials have used a low-dose that is likely insufficient to lower TG effectively, and hence clinical events.

Table 3

Non-prescription omega-3 fatty acid products: dietary supplements

Products	More than 300 products available
Formulations	Soft gels, liquids, powders, gummies
Sources	Fish oils, krill oils, algal oils, plant oils
Omega-3 fatty acid content and purity	Predominantly DHA + EPA in varying quantities; DHA may raise LDL-C levels May contain inconsistent DHA/EPA levels May contain saturated fat, cholesterol, oxidation products, and/or other contaminants that may have adverse health effects
Regulatory requirements	Not required to demonstrate efficacy or safety prior to marketing Should not be substituted for prescription omega-3 fatty acid products Dietary supplements are not OTC drugs; no OTC omega-3 fatty acid or fish oil products are approved or available

DHA docosahexaenoic acid, *EPA* eicosapentaenoic acid, *LDL-C* low-density lipoprotein cholesterol, *OTC* over the counter

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS



FISHing for the Miracle of Eicosapentaenoic Acid

John J.P. Kastelein, M.D., Ph.D., and Erik S.G. Stroes, M.D., Ph.D.

N Engl J Med 2019; 380:89-90

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT)

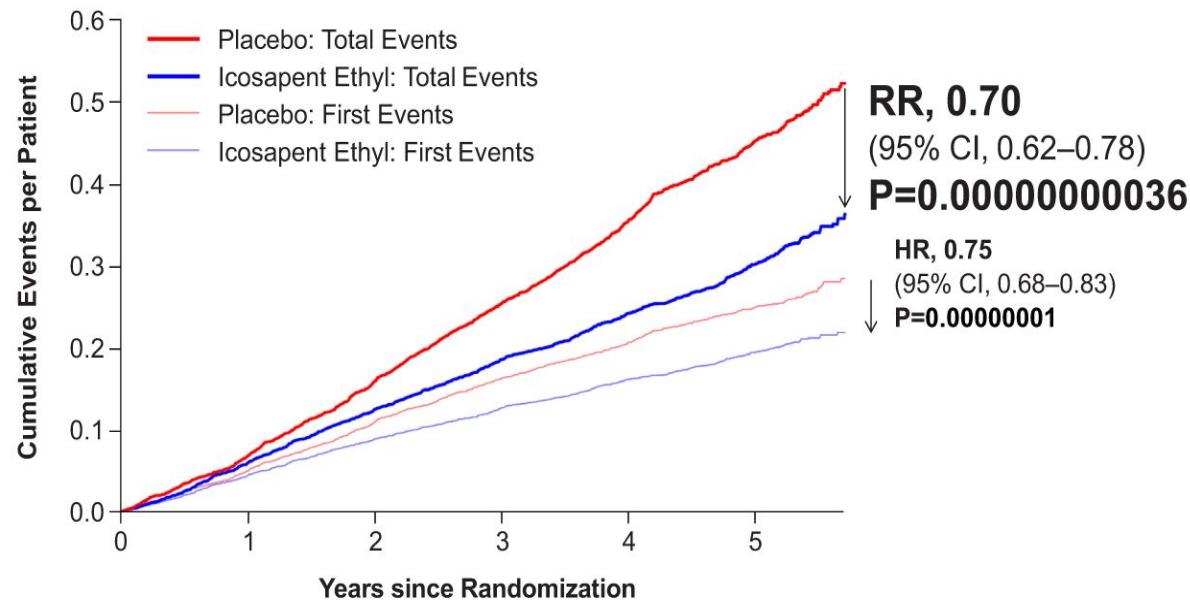
- 8179 high-risk patients who had elevated triglyceride levels and had been receiving statin therapy were randomly assigned to receive 2 g of icosapent ethyl twice daily or placebo containing mineral oil
- After a median follow-up of 4.9 years, the primary efficacy end point was reported in 22.0% of the patients in the placebo group and in 17.2% of the patients in the icosapent ethyl group — a 25% lower risk in the icosapent ethyl group.

Total (First and Subsequent) Events

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



Primary Composite Endpoint



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019;73:2791-2802.

The STRENGTH trial



JN JAMA Network®

QUESTION In statin-treated patients with high cardiovascular risk, high triglycerides, and low HDL cholesterol, does adding a carboxylic acid formulation of omega-3 fatty acids (EPA and DHA) to ongoing treatment improve cardiovascular outcomes?

CONCLUSION The findings from this randomized trial do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in patients at high cardiovascular risk.

POPULATION

8510 Men
4568 Women



Adults with high triglycerides and low HDL levels, treated with statins, and at high risk of adverse cardiovascular outcomes

Mean age: 62.5 years

LOCATIONS

675 Hospitals
in 22 countries



INTERVENTION

13 078 Patients randomized

6539

Omega-3
4 g/d of omega-3 CA (carboxylic acid) capsules containing EPA and DHA for up to 5 years



6539

Corn oil
Comparator capsules for up to 5 years



PRIMARY OUTCOME

Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization

FINDINGS

Occurrence of composite outcome events

Omega-3
785 of 6539 patients

12.0%

Corn oil
795 of 6539 patients

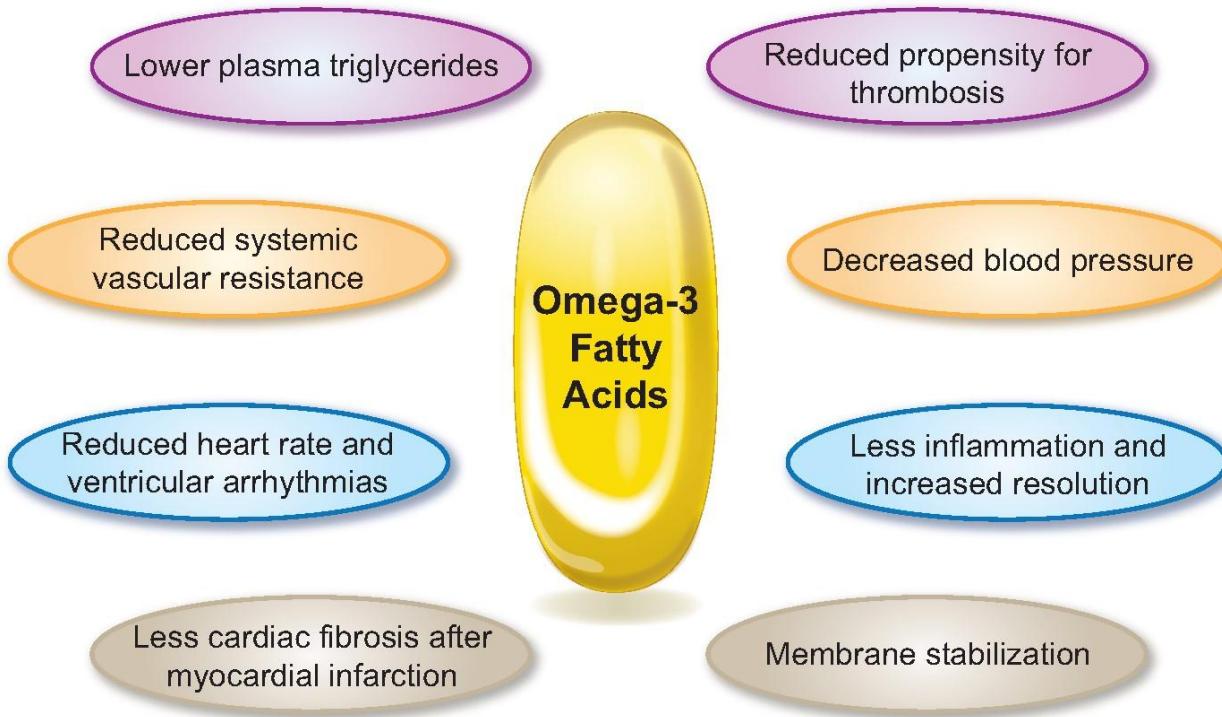
12.2%

At early trial termination, there was no significant difference between groups in the primary outcome:

HR, **0.99** (95% CI, 0.90-1.09); $P = .84$

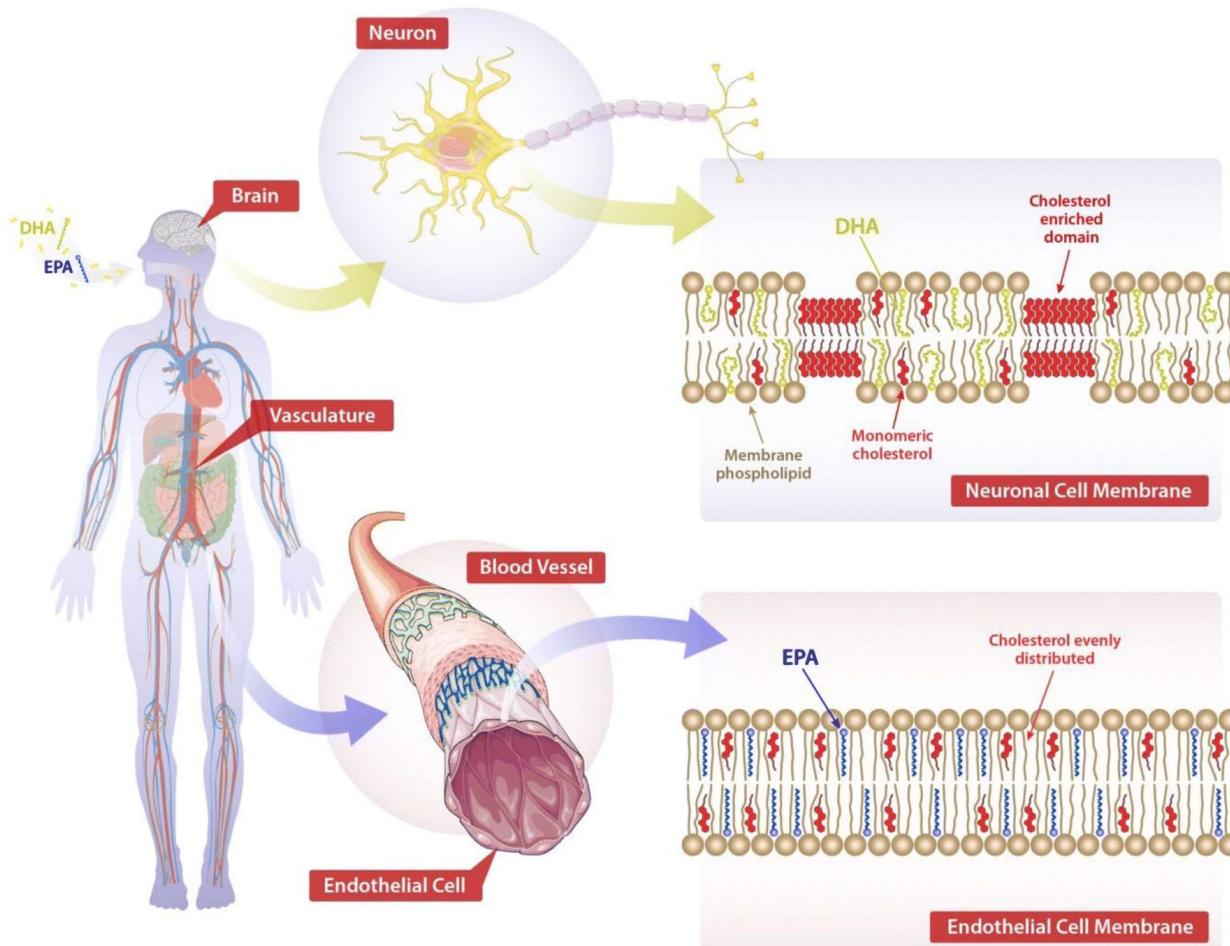
Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA. Published online November 15, 2020. doi:10.1001/jama.2020.22258

Biological effects of omega-3 fatty acids expected to favorably impact atherosclerotic cardiovascular disease



There are fundamental differences between EPA and DHA in the duration of antioxidant activity as well as effects on membrane lipid structure and function within peripheral cells

EPA and DHA have distinct tissue distributions





Vazkepa

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icosapent ethyl

Table of contents

- [Overview](#)
- [Authorisation details](#)
- [Product information](#)
- [Assessment history](#)

Overview

Vazkepa is a medicine for reducing the risk of cardiovascular events such as heart attack, stroke and other problems caused by blocked blood circulation. It is for use as add-on treatment in adults being treated with a statin medicine who have high levels of triglycerides (a type of fat) in their blood.

Vazkepa is to be used in patients either with a cardiovascular disease (a condition that affects the heart or circulation) or with diabetes and another condition that increases the risk of cardiovascular events.

Vazkepa contains the active substance icosapent ethyl.

4.2 Posology and method of administration

Posology

The recommended daily oral dose is 4 capsules taken as two 998 mg capsules twice daily.



AUTHORISED

This medicine is authorised for use in the European Union.

Agenda

- General remarks
- Gender
- Quality and composition of active pharmaceutical ingredients
- Conclusion

Conclusion

- Understanding sex and gender as variables that affect rigour, generalizability and translation of research findings is a priority.
- Women have historically been underrepresented in clinical trials across various medical conditions and treatments.
- Adequate doses and formulations of drugs and nutraceuticals are essential to improve clinical outcomes.
- Do your best to conduct and critically evaluate rigorous research.