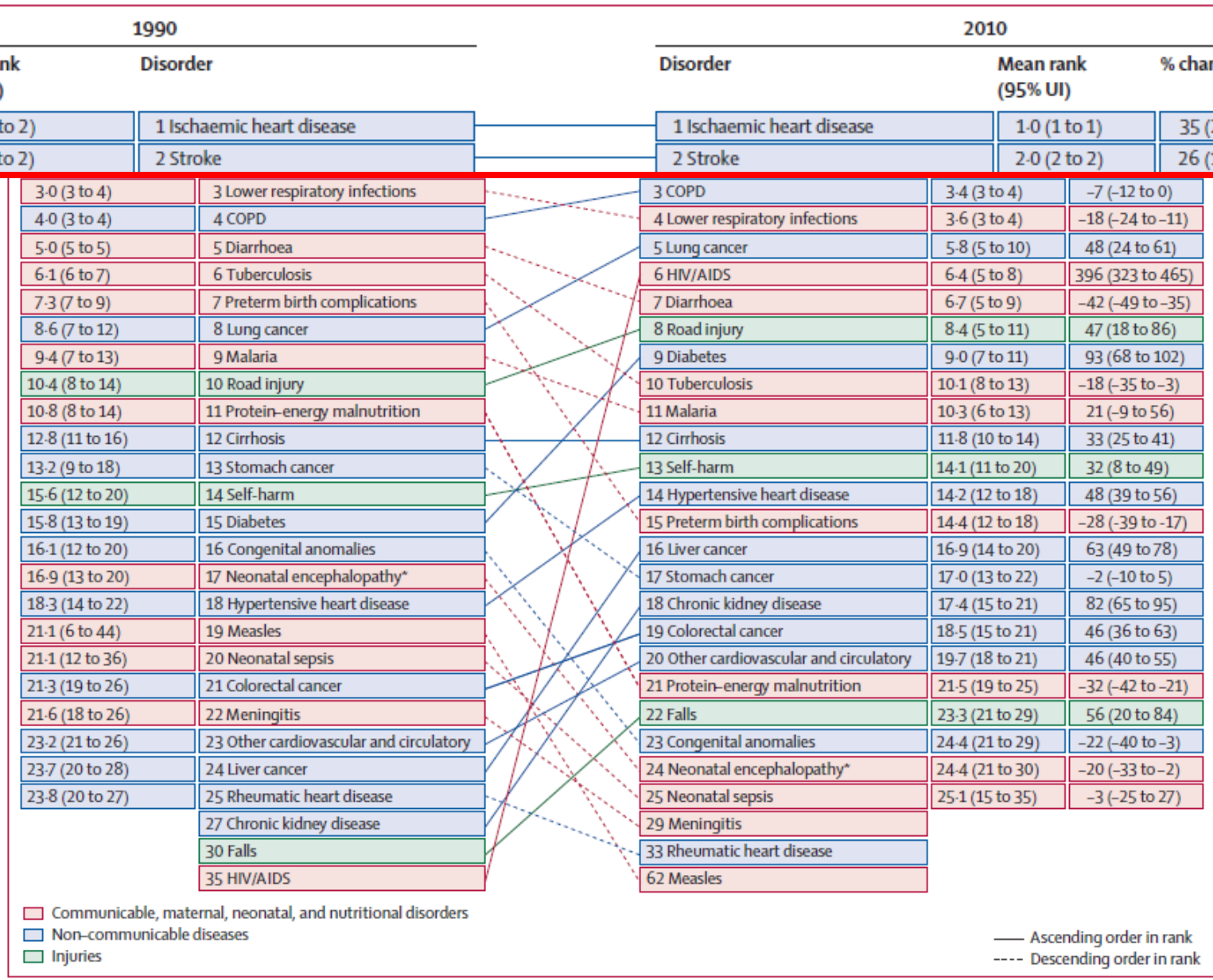
# Nuove prospettive terapeutiche nel trattamento dell'ipercolesterolemia

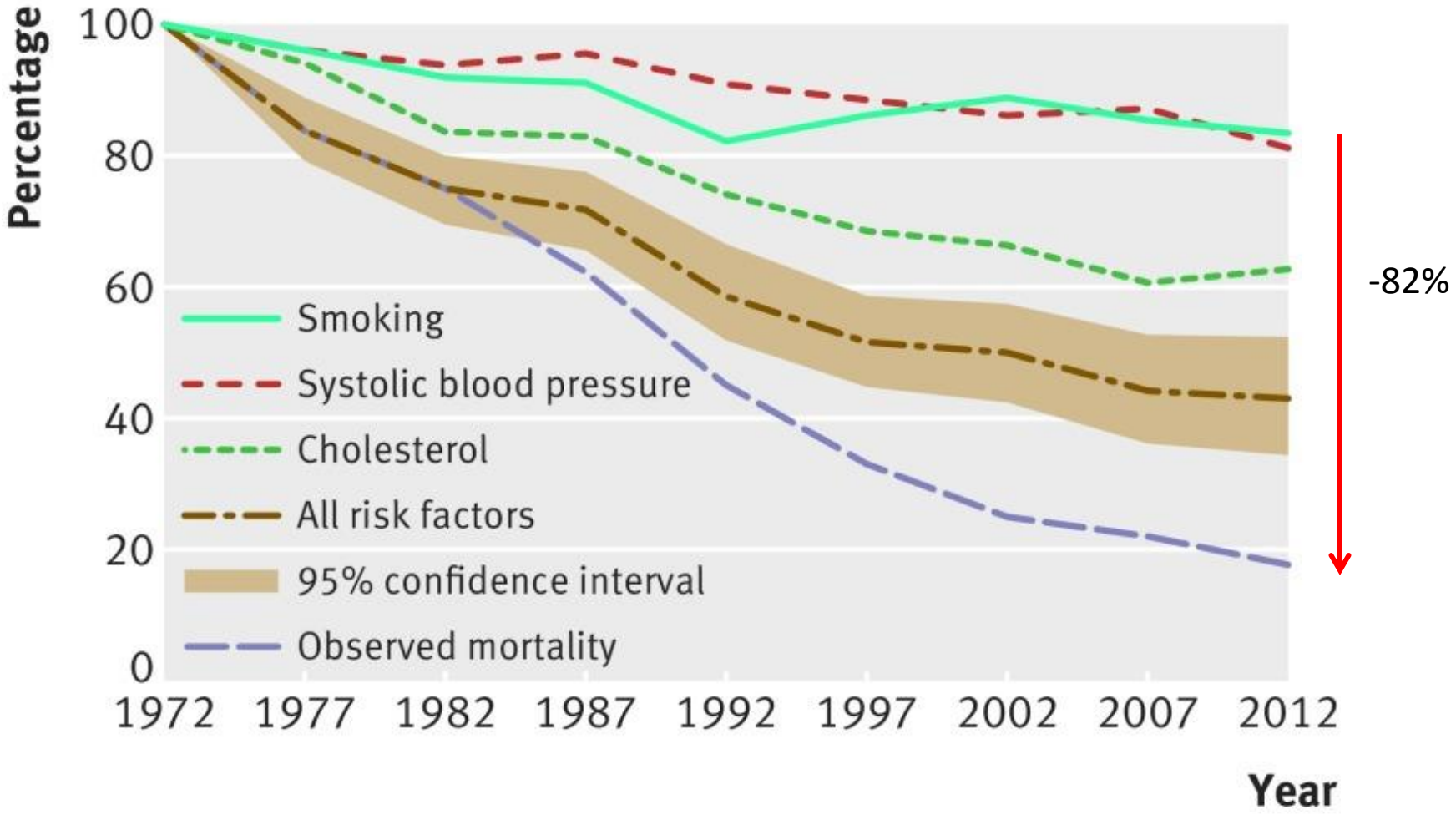
Livio Dei Cas

# Global death ranks and the percentage change between 1990 and 2010



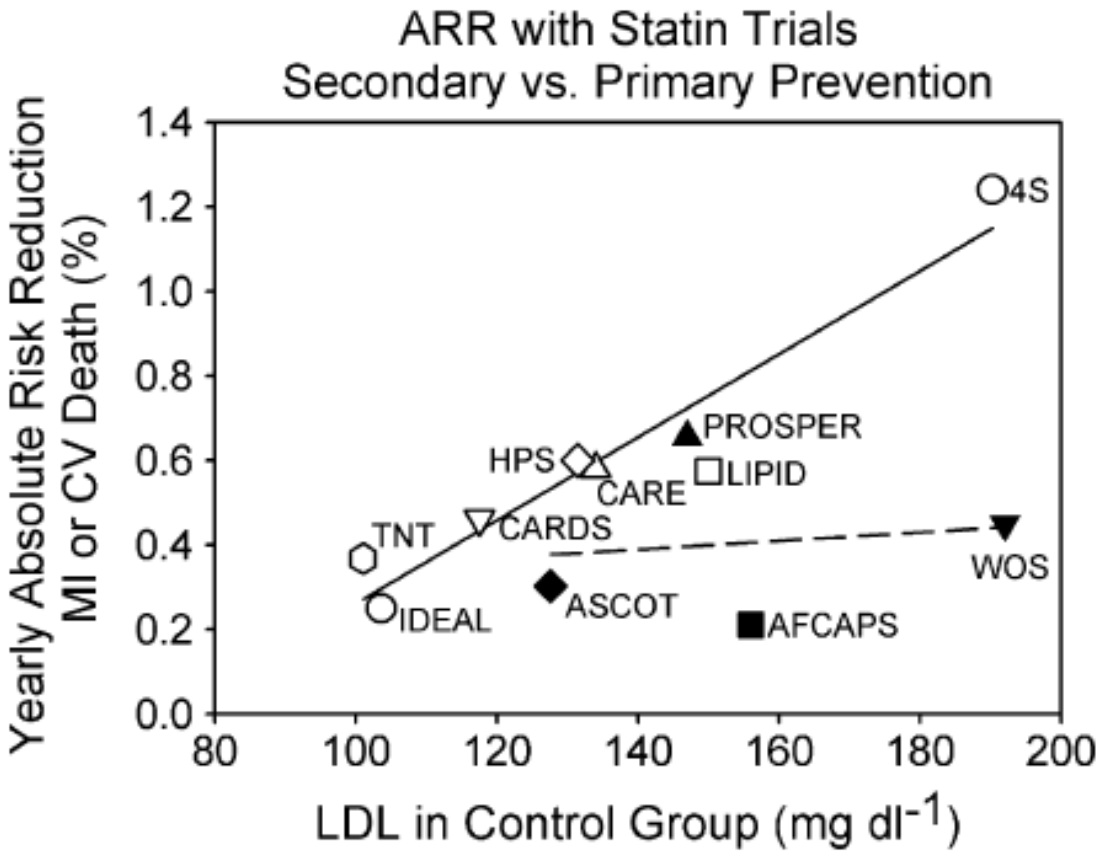

Lozano R et al. Lancet 2012

# Predicted and observed reduction (%) in coronary heart disease mortality in men aged 35-64 years, 1972-2012 (40yrs)




BMJ 2016;352:i721

# **Absolute risk reduction** in MI or CV death as a function of LDL in secondary vs primary prevention with statin therapy



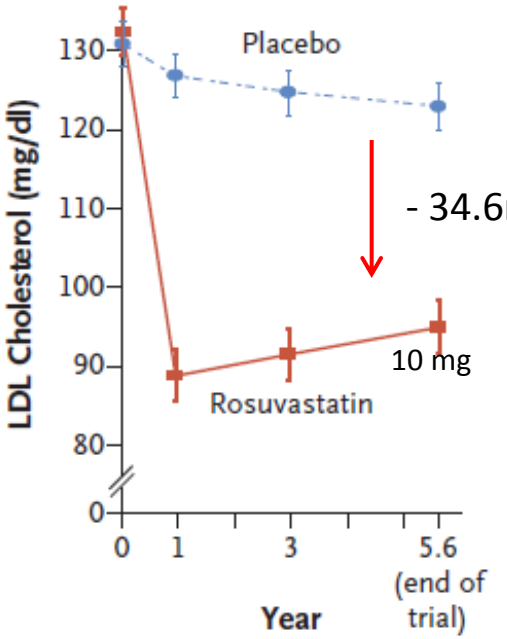

Rembold et al. Atherosclerosis 2007

# Baseline characteristics of the subjects (HOPE 3 study)

| Characteristic | Rosuvastatin Group (N=6361) | Placebo Group (N=6344) |
|---|---|---|
| Age — yr | 65.8±6.4 | 65.7±6.3 |
| Female sex — no. (%) | 2951 (46.4) | 2923 (46.1) |
| Cardiovascular risk factors — no. (%) | | |
| Elevated waist-to-hip ratio | 5540 (87.1) | 5494 (86.6) |
| Recent or current smoking | 1740 (27.4) | 1784 (28.1) |
| Low HDL cholesterol level | 2344 (36.8) | 2244 (35.4) |
| Impaired fasting glucose or impaired glucose tolerance | 809 (12.7) | 807 (12.7) |
| Early diabetes mellitus | 374 (5.9) | 357 (5.6) |
| Family history of premature coronary heart disease | 1675 (26.3) | 1660 (26.2) |
| Early renal dysfunction | 169 (2.7) | 181 (2.9) |
| Hypertension | 2403 (37.8) | 2411 (38.0) |
| Presence of 2 risk factors | 3002 (47.2) | 2924 (46.1) |
| Presence of ≥3 risk factors | 1545 (24.3) | 1523 (24.0) |

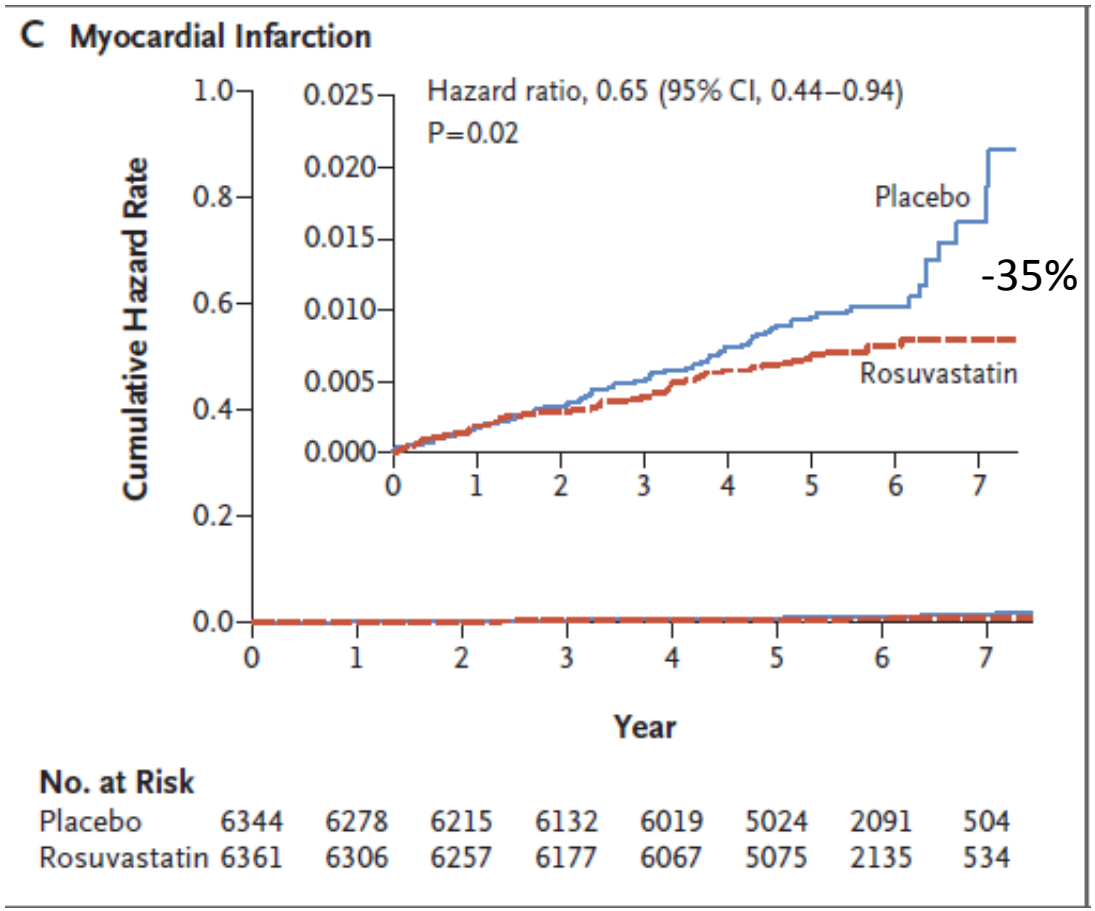
NEJM 2016; 2 Apr

# Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease (HOPE3)




**No. at Risk**

| | | | | |
|---|---|---|---|---|
| Placebo | 495 495 | 495 | 495 |
| Rosuvastatin | 480 480 | 480 | 480 |



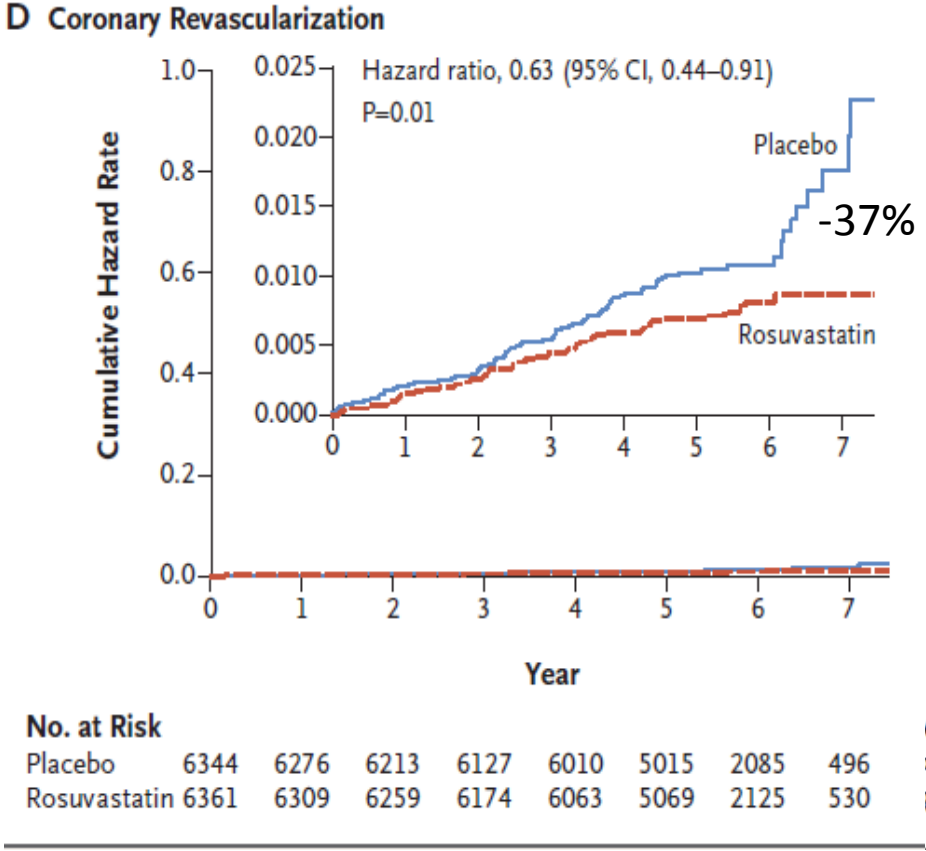

**No. at Risk**

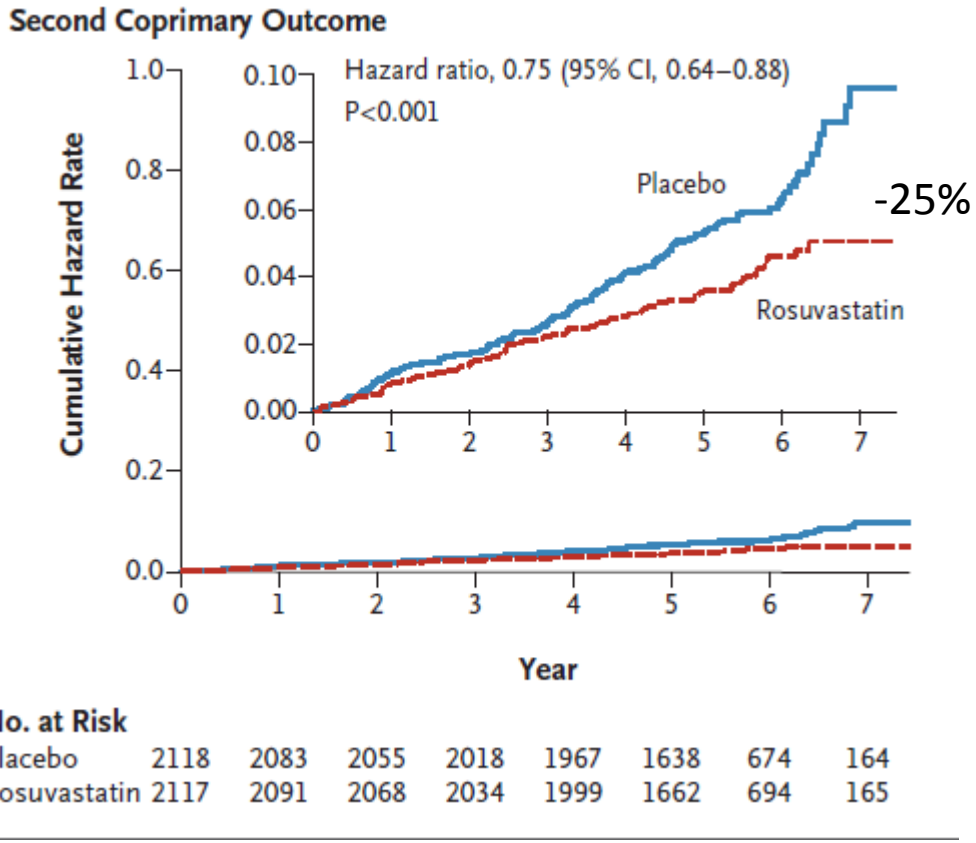
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 6344 | 6278 | 6215 | 6132 | 6019 | 5024 | 2091 | 504 |
| Rosuvastatin | 6361 | 6306 | 6257 | 6177 | 6067 | 5075 | 2135 | 534 |

NEJM 2016; 2 Apr

# Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease (HOPE3)

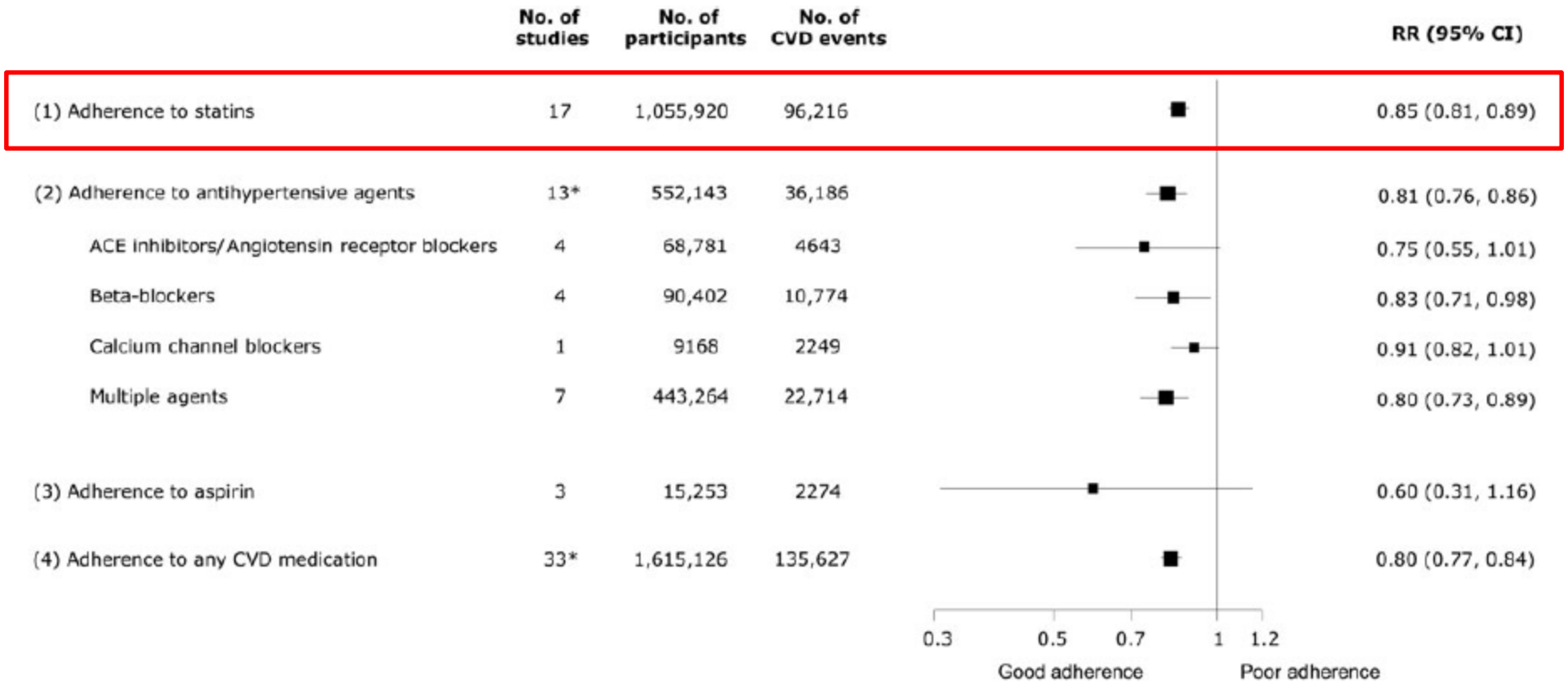
CVD, non fatal MI, stroke, HF and resuscitated cardiac arrest




NEJM 2016; 2 Apr

# Prevalence (95%CI) of adherence to CV medications among partecipants in prosepctive studies (10,308 ptz)




Chowdhury et al. European Heart Journal 2013

# Reasons cited for swiching or stopping statin use among current and former statin users

**Table 3** Reasons cited for switching or stopping statin medication use among current and former statin users who ever switched or stopped taking a statin medication

| | Total respondents (n = 10,138) | Current statin users (n = 8918) | Former statin users (n = 1220) |
|---|---|---|---|
| Mean % among patients who ever switched statin medication | | | |
| Reason for switching | (n = 4637) | (n = 3987) | (n = 650) |
| Costs (net) | 34 | 36 | 16* |
| Side effects | 33 | 28 | 65* |
| Efficacy (net) | 21 | 22 | 13* |
| Mean % among former statin users | | | |
| Reason for stopping | | | (n = 1220) |
| Costs (net) | NA | NA | 17 |
| Side effects | NA | NA | 62 |
| Efficacy (net) | NA | NA | 12 |

NA, not applicable.

*Significantly different between current and former statin users, $P < .05$.

Journal of Clinical Lipidology 2012

# Definitions of statin-associated muscle symptoms by the EAS Consensus Panel

| Symptoms | Biomarker | Comment |
|---|---|---|
| Muscle symptoms | Normal CK | Often called 'myalgia'. May be related to statin therapy. Causality is uncertain in view of the lack of evidence of an excess of muscle symptoms in blinded randomized trials comparing statin with placebo. |
| Muscle symptoms | CK >ULN <4× ULN<br>CK >4 <10× ULN | Minor elevations of CK in the context of muscle symptoms are commonly due to increased exercise or physical activity, but also may be statin-related; this may indicate an increased risk for more severe, underlying muscle problems.[19] |
| Muscle symptoms | CK >10× ULN | Often called myositis or 'myopathy' by regulatory agencies and other groups (even in the absence of a muscle biopsy or clinically demonstrated muscle weakness). Blinded trials of statin vs. placebo show an excess with usual statin doses of about 1 per 10 000 per year.[4] Pain is typically generalized and proximal and there may be muscle tenderness and weakness. May be associated with underlying muscle disease. |
| Muscle symptoms | CK >40× ULN | Also referred to as rhabdomyolysis when associated with renal impairment and/or myoglobinuria. |
| None | CK >ULN <4× ULN | Raised CK found incidentally, may be related to statin therapy. Consider checking thyroid function or may be exercise-related. |
| None | CK >4× ULN | Small excess of asymptomatic rises in CK have been observed in randomized blinded trials in which CK has been measured regularly. Needs repeating but if persistent, then clinical significance is unclear. |

CK, creatine kinase; ULN, upper limit of the normal range.

European Heart Journal 2015

# Risk factors for statin-associated muscle symptoms

**Anthropometric**

- Age >80 years old (general caution advised for age >75)
- Female
- Low body mass index
- Asian descent

**Concurrent conditions**

- Acute infection
- Hypothyroidism (untreated or undertreated)
- Impaired renal (chronic kidney disease classification 3, 4, and 5) or hepatic function
- Biliary tree obstruction
- Organ transplant recipients
- Severe trauma
- Human immunodeficiency virus
- Diabetes mellitus
- Vitamin D deficiency

**Related history**

- History of creatine kinase elevation, especially >10× the upper limit of the normal range
- History of pre-existing/unexplained muscle/joint/tendon pain
- Inflammatory or inherited metabolic, neuromuscular/muscle defects (e.g. McArdle disease, carnitine palmitoyl transferase II deficiency, myoadenylate deaminase deficiency, and malignant hyperthermia)
- Previous statin-induced myotoxicity
- History of myopathy while receiving another lipid-lowering therapy

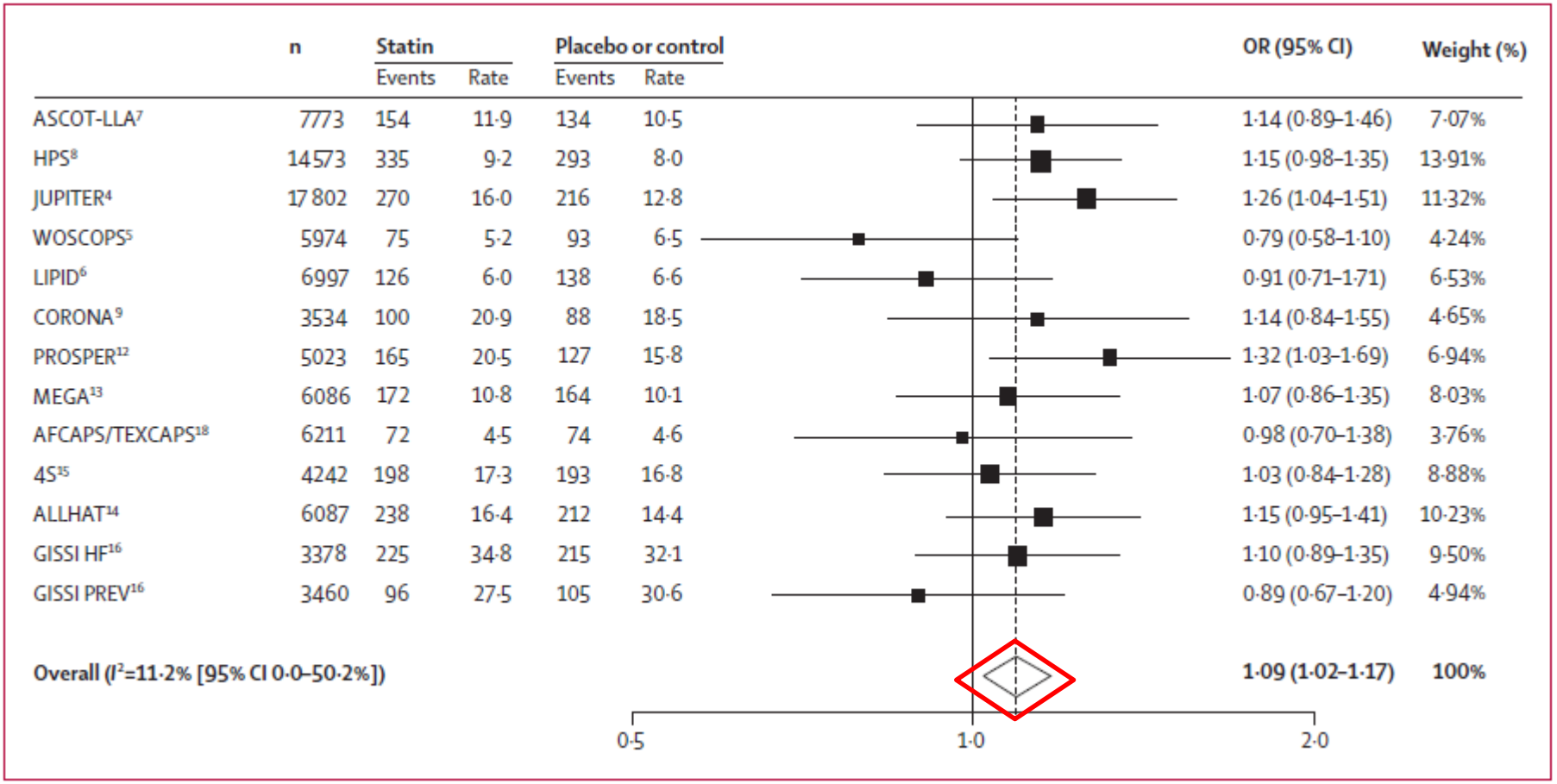
**Factors that influence the pharmacokinetics**

- High-dose statin therapy
- Polypharmacy
- Drug–drug interactions: concomitant use of certain drugs including gemfibrozil, macrolides, azole antifungal agents, protease inhibitors, and immunosuppressive drugs such as cyclosporine, and inhibitors of CYP450 isoenzymes, OATP 1B1, or P-gp, can affect the metabolism of statins, increase their circulating levels and, consequently, the risk for SAMS.

**Other risk factors**

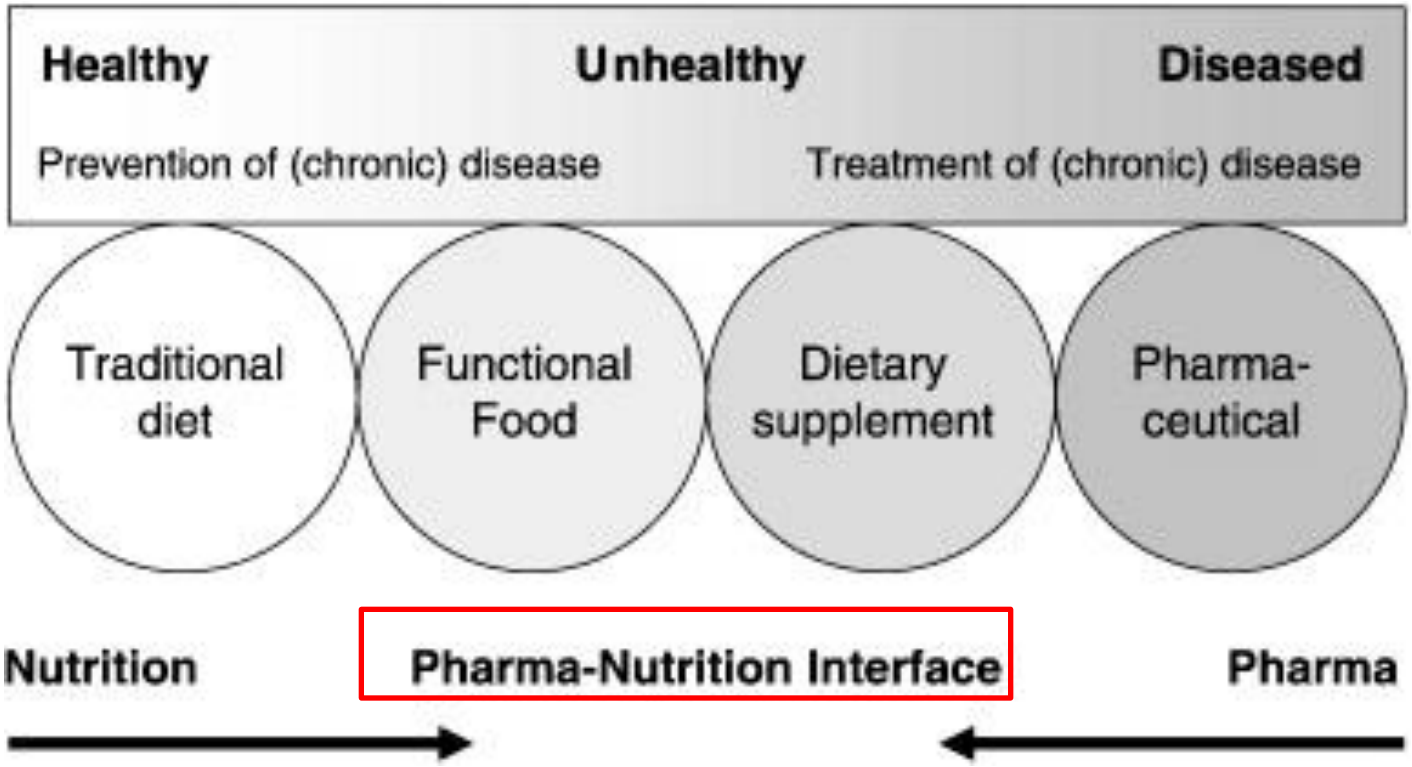
- High level of physical activity
- Dietary effects (excessive grapefruit or cranberry juice)
- Excess alcohol
- Drug abuse (cocaine, amphetamines, heroin)

# Association between therapy and incident diabetes in 13 major CV trials

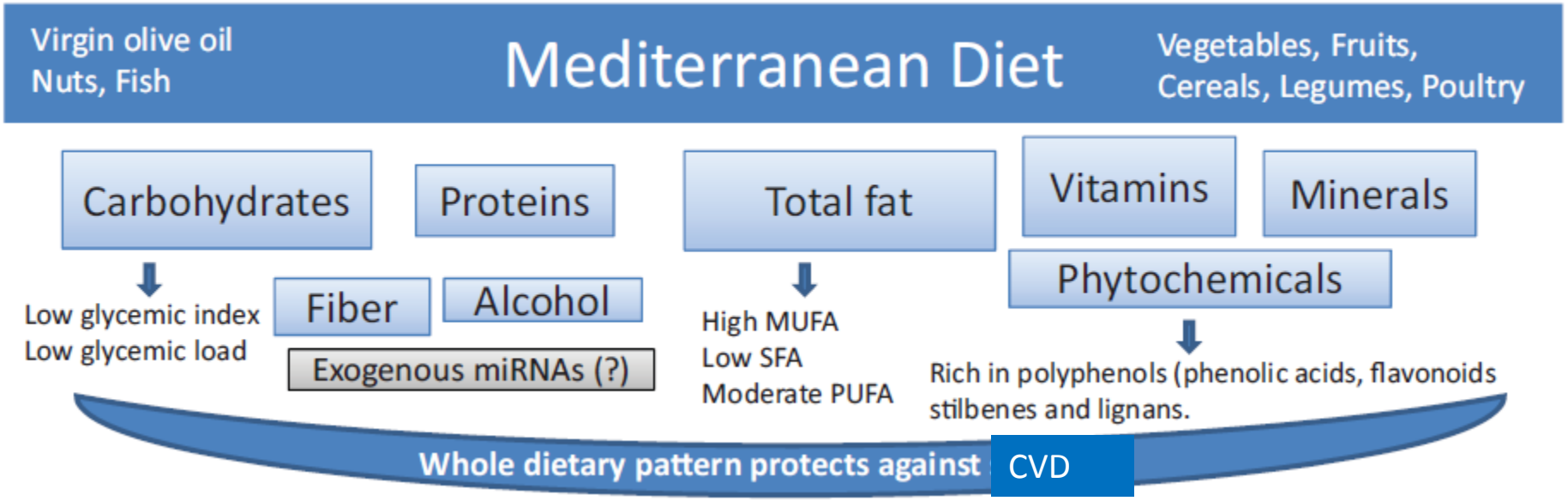



Sattar et al. Lancet 2012

# Salute-malattia

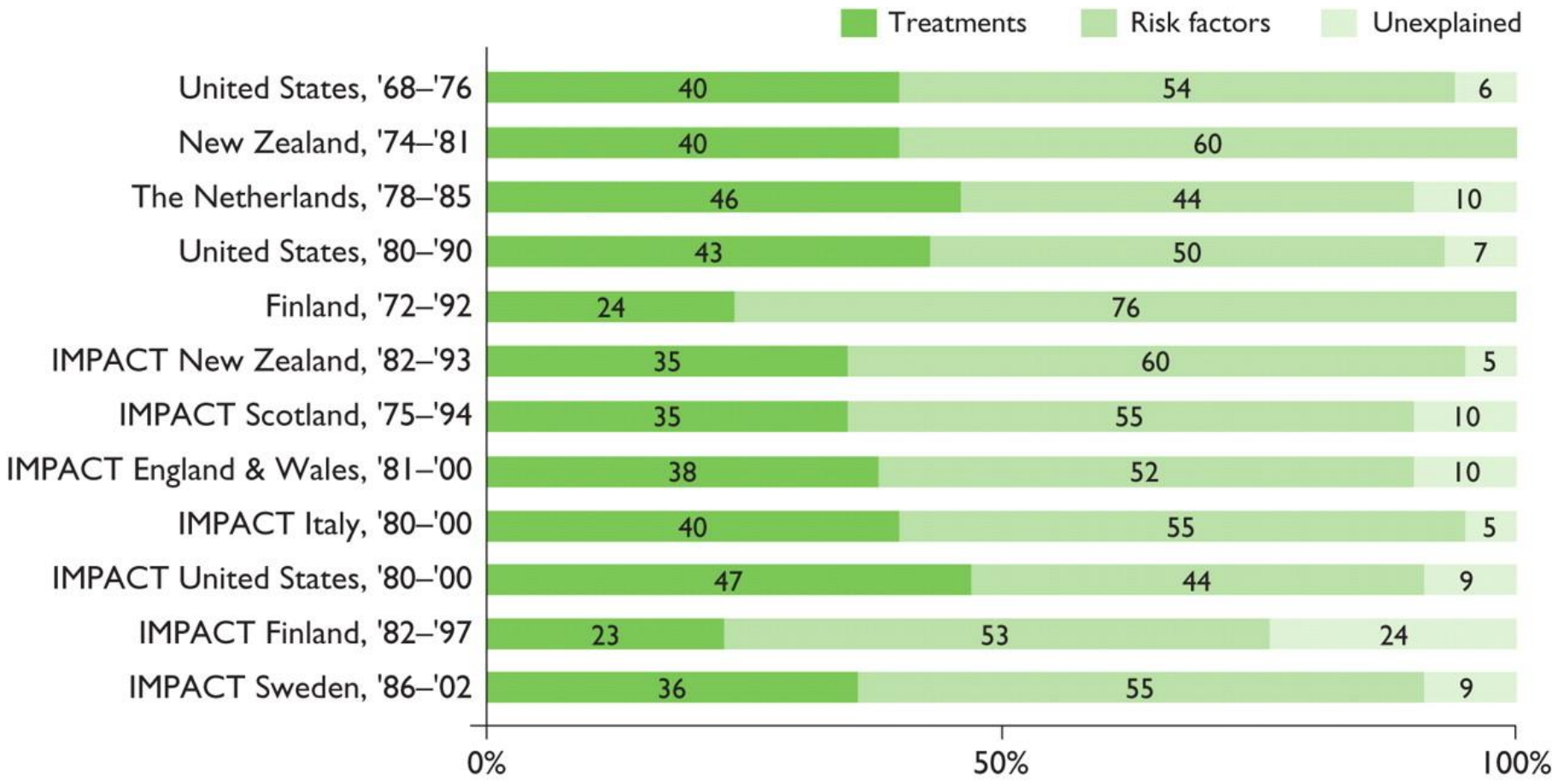


# Meccanismi tradizionali implicati negli effetti benefici della dieta mediterranea nel CVD




Corella D et la. Prospective Overviews 2014

# Percentuale della riduzione in morti per CAD imputabili all trattamento ed alle modifiche dei fattori di rischio CV in diverse popolazioni




Authors/Task Force Members: et al. Eur Heart J 2012;33:1635-1701

# Ruolo dell’intestino

**Organo nell’organo**

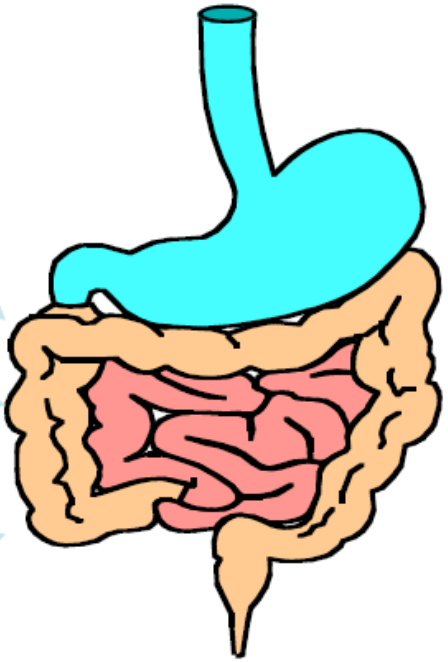
- Assorbimento dei nutrienti
- Sviluppo immunità innata ed acquisita (IgA) e modulazione immunitaria
- Azione anti-infiammatoria
- Organo endocrino (secrezione insulinica ed modulazione energetica)
- Elemento di equilibrio tra flora intestinale/nutrienti e sostanze nutritive ed enzimi

# Microbiota intestinale

Fino a 1000 specie

70%
incoltivabili

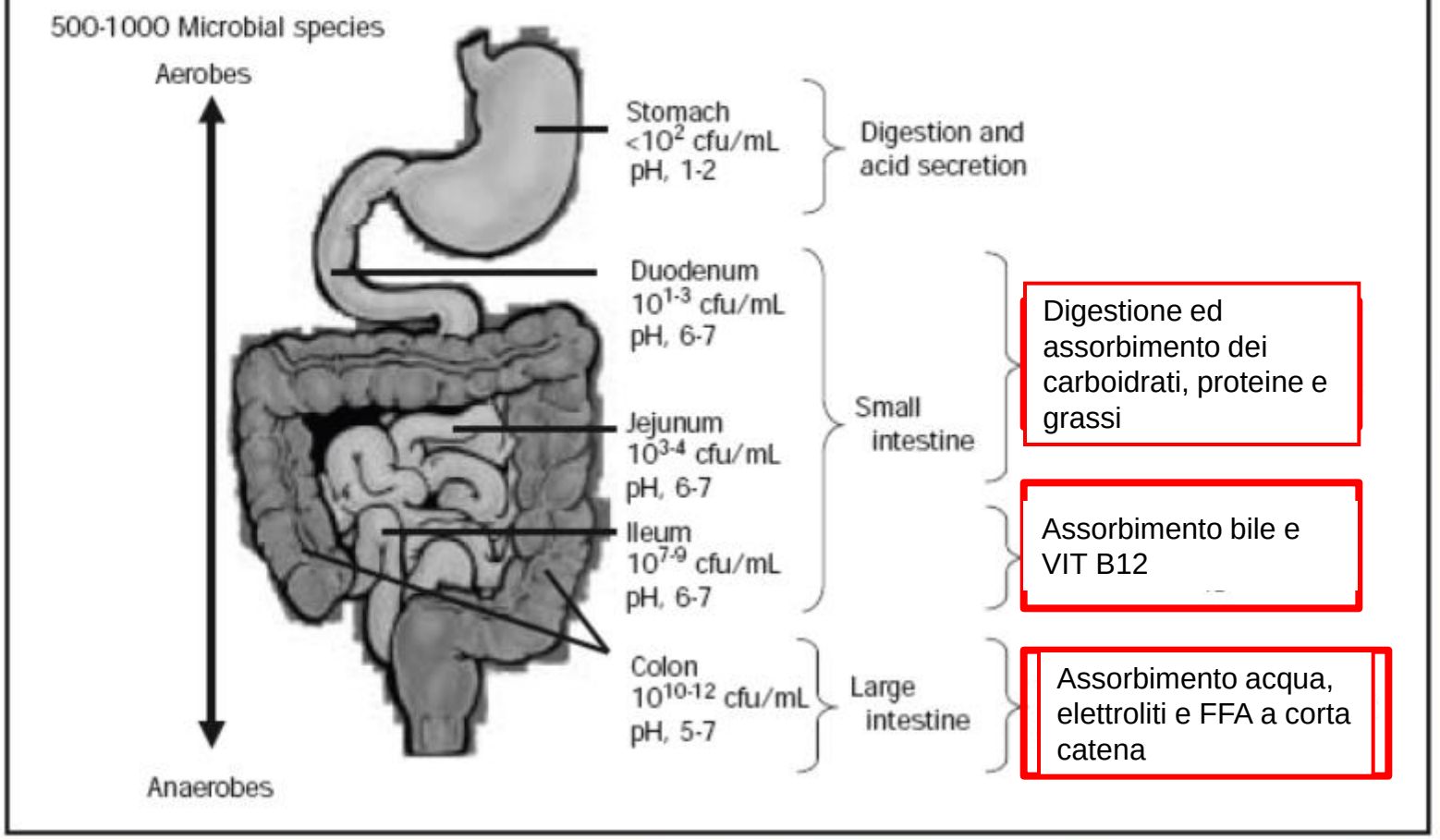
Partner microbico
strettamente co-evoluto



**Interazioni con:**

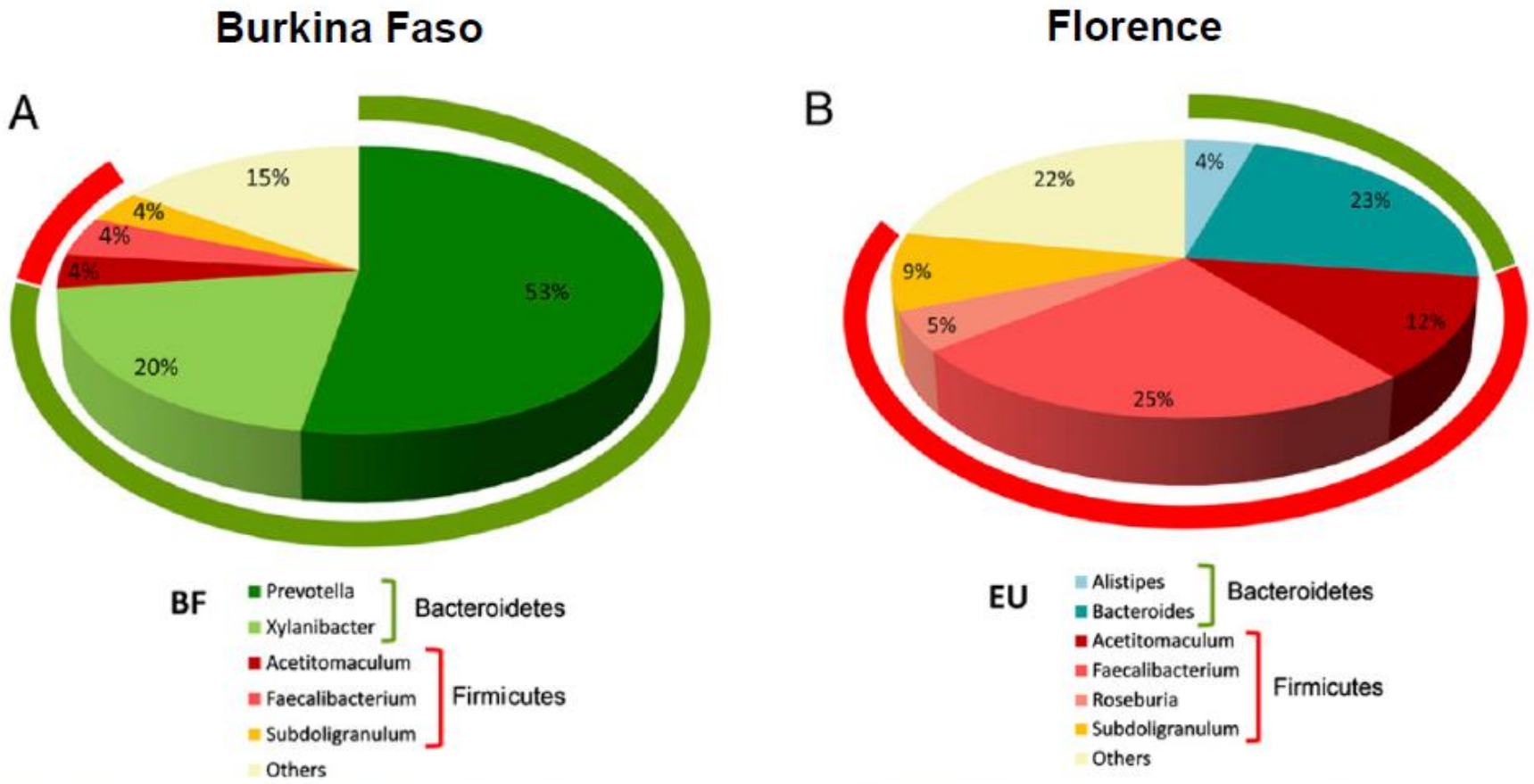
- Dieta
- Farmaci
- Sistema immunitario
- Fisiologia intestinale
- Metabolismo sistemico

# Concentrazione di batteri a vari livelli dell'apparato gastrointestinale in un individuo adulto



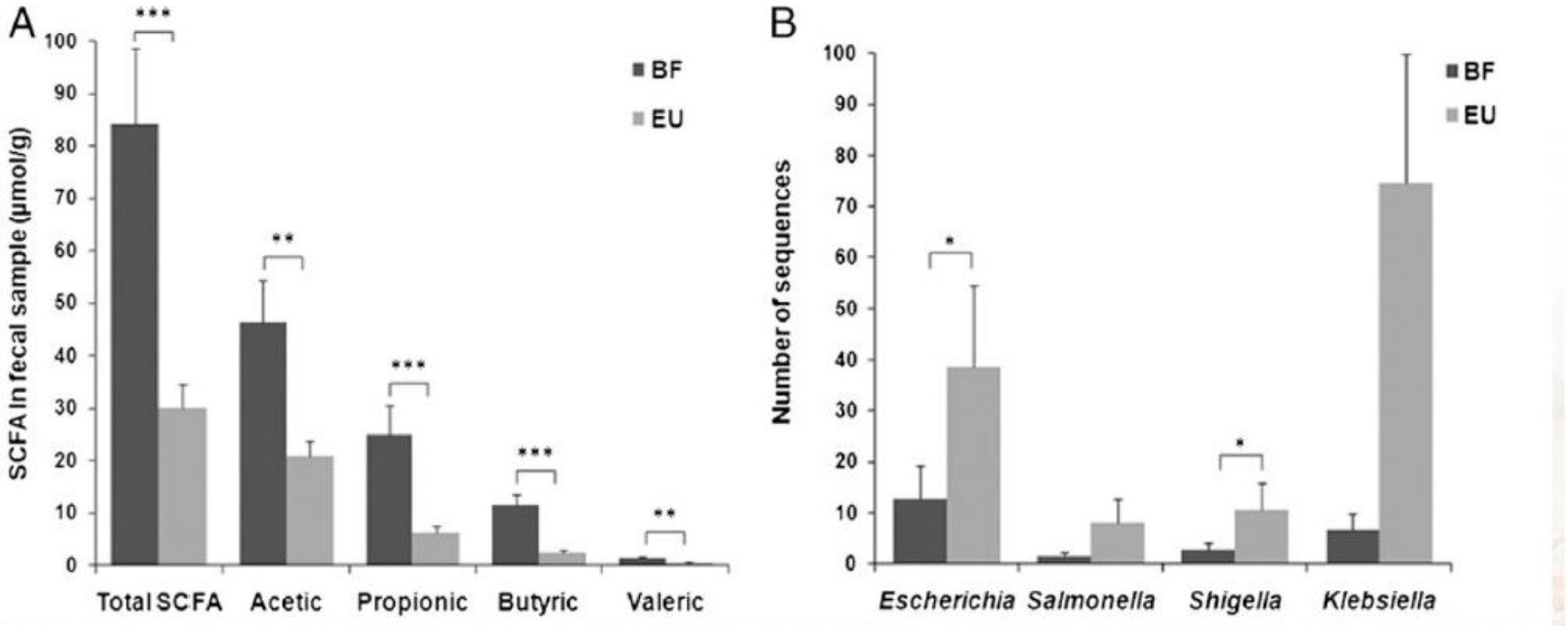

*DiBaise JK et al., Mayo Clin Proc 2008*

# Impact of diet in shaping gut microbiota in European children and children of rural African village



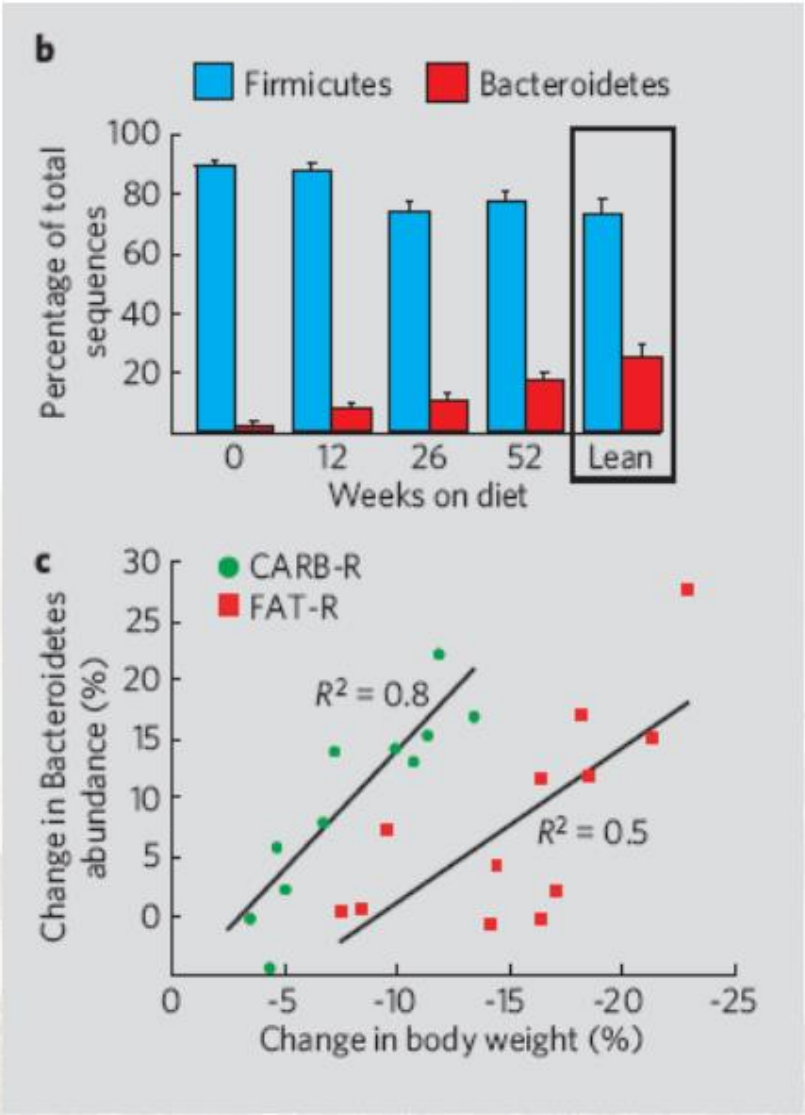

De Filippo C et al PNAS 2010

# Produzione di acidi grassi a corta catena (SCFAs) da parte del microbiota in dieta a base di vegetali




*De Filippo C et al, PNAS 2010*

# Percentuale di Firmicutes e Bacteroidetes in individui magri e in soggetti obesi prima e dopo il calo ponderale

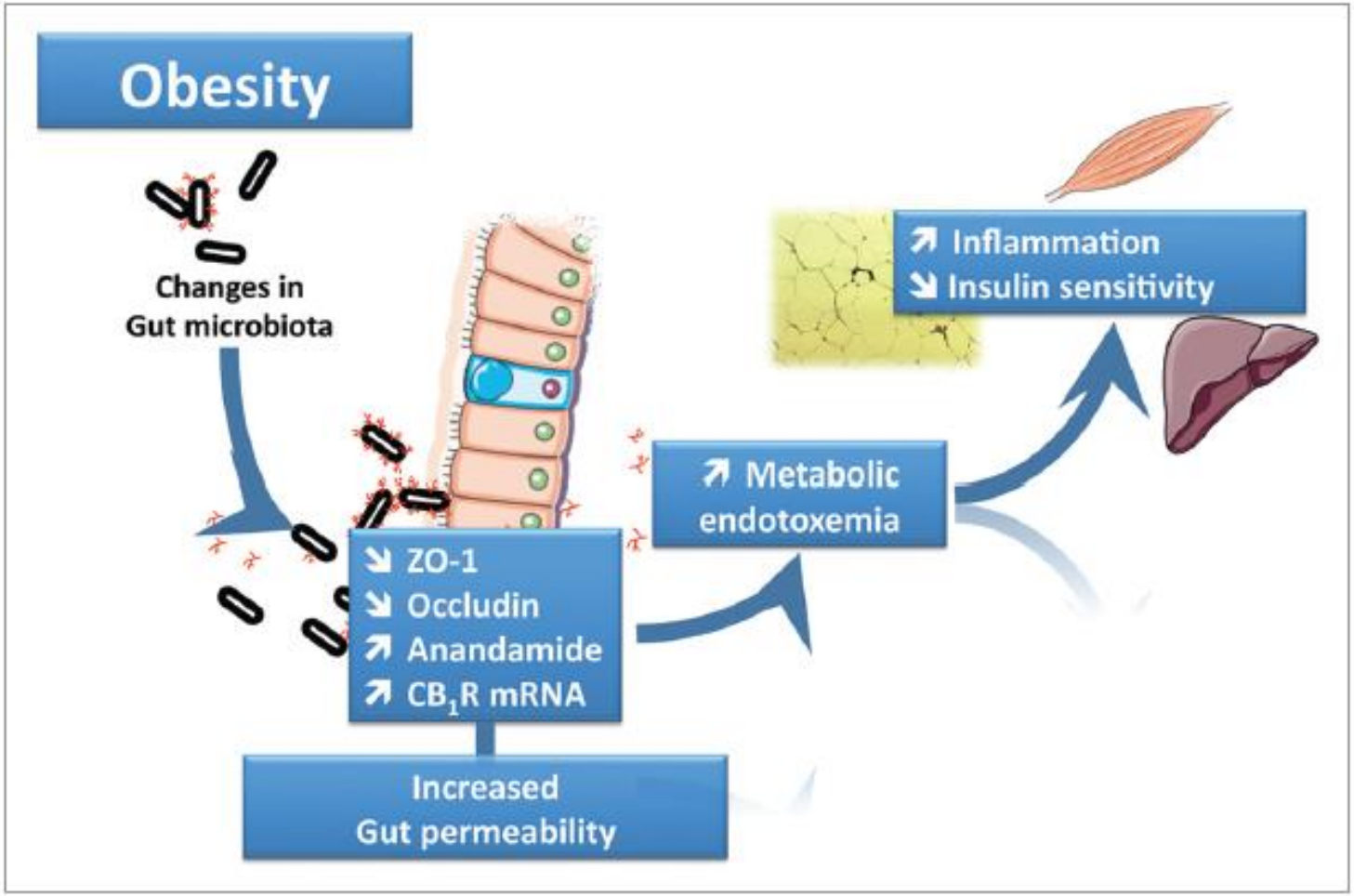



**b.** Composizione della flora batterica intestinale in soggetti normopeso ed obesi prima e dopo 52 settimane di una dieta ipocalorica ristretta in carboidrati ● CARB-R o Ristretta in Grassi ■ FAT-R .

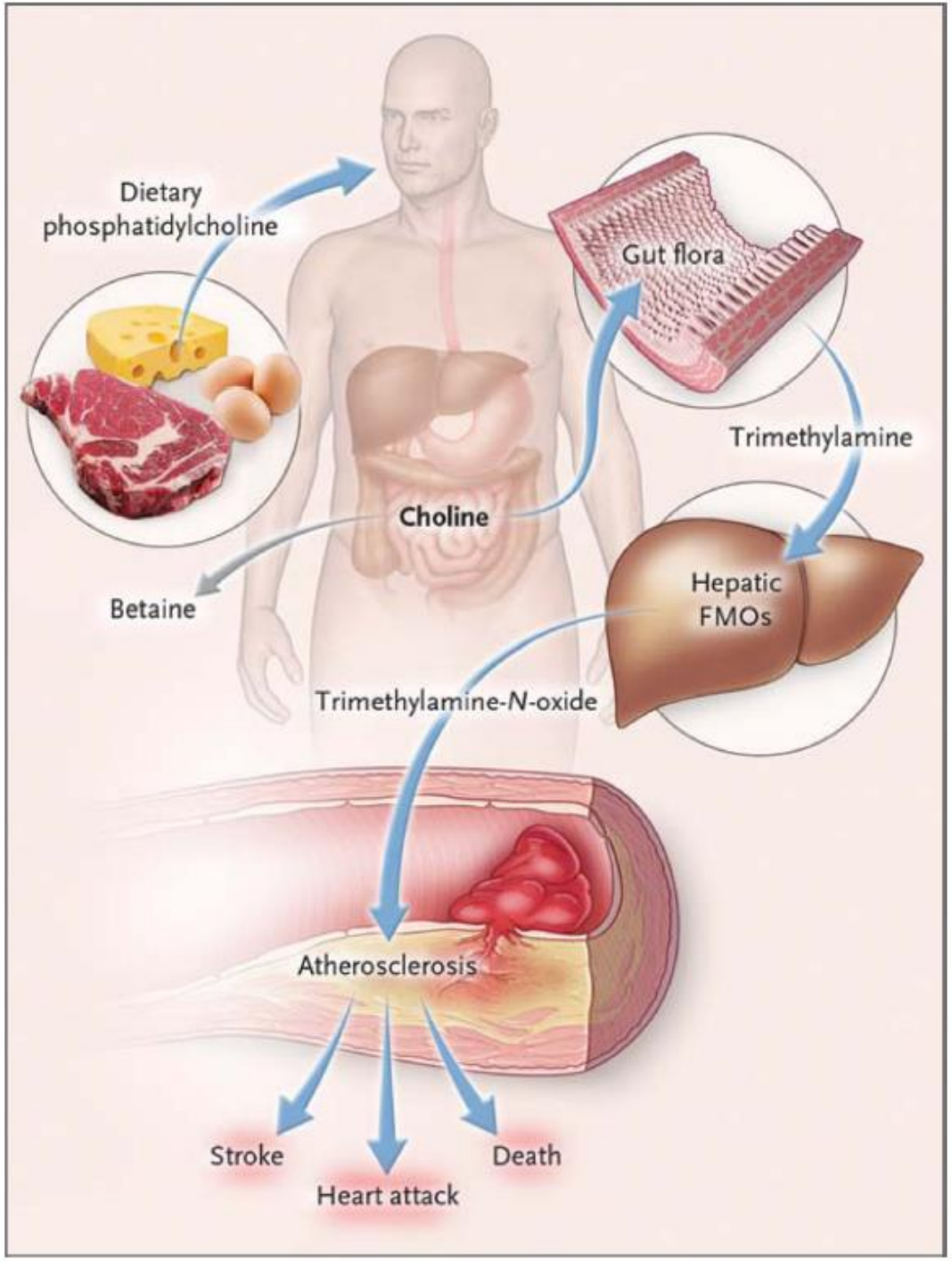
**c.** Correlazione tra l' incremento dei Bacteroidetes e la percentuale di decremento ponderale nelle due diete ipocaloriche.

*Ley RE et al., Nature 2006*

# nell'infiammazione subclinica legata all'obesità ed al diabete tipo

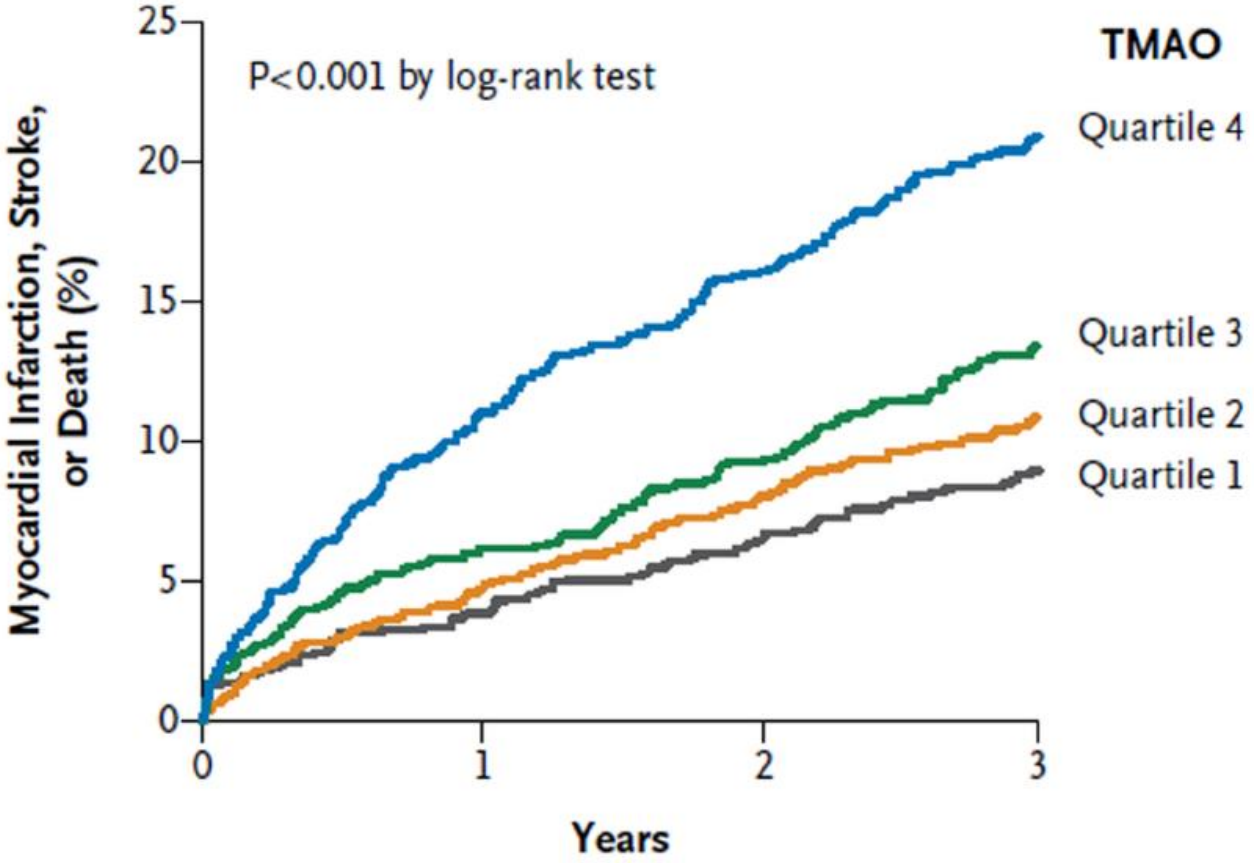



Cani PD and Gut microbiota 2012




*Wilson WH et al. NEJM 2013*

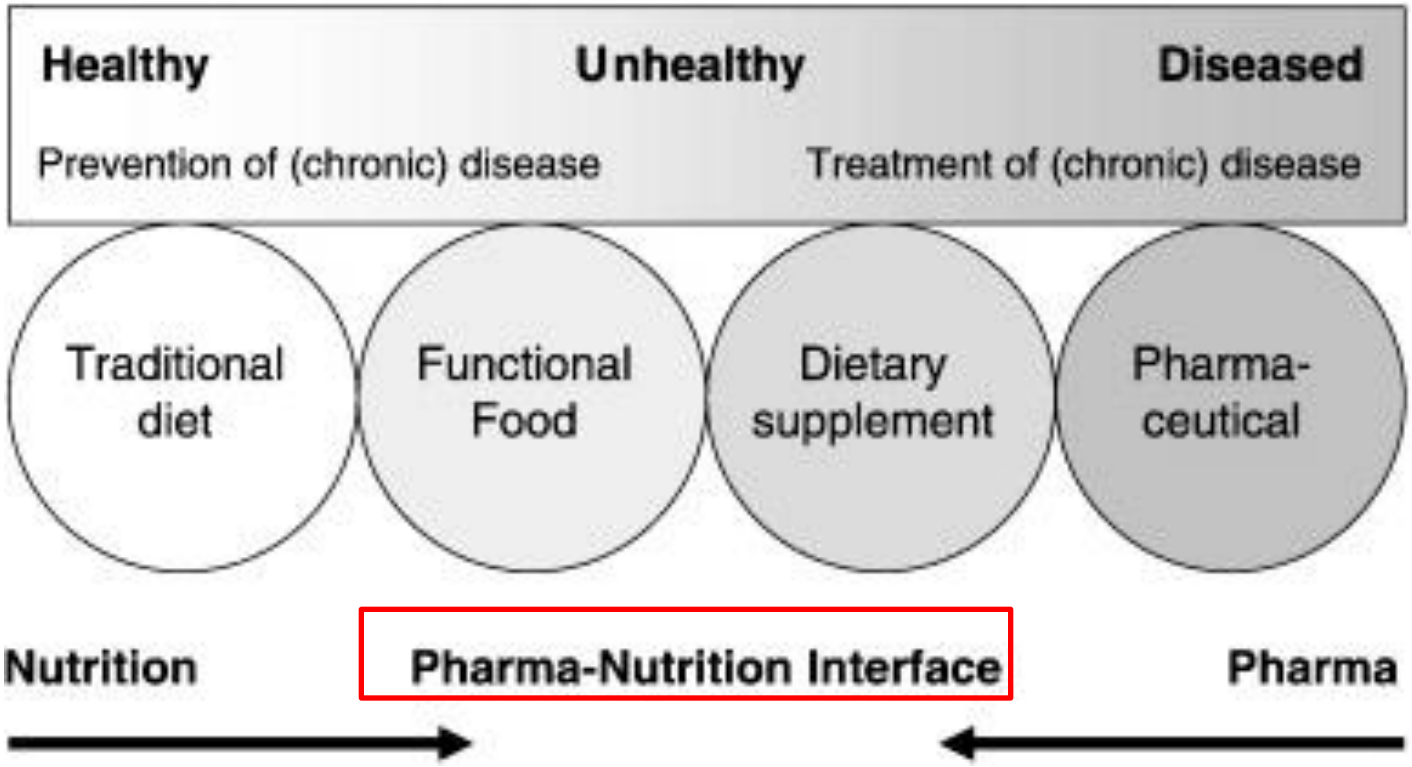
# Intestinal microbial metabolism and CV risk




| No. at Risk | | | | |
|---|---|---|---|---|
| Quartile 1 | 1001 | 933 | 869 | 827 |
| Quartile 2 | 998 | 940 | 884 | 843 |
| Quartile 3 | 1003 | 938 | 888 | 835 |
| Quartile 4 | 1005 | 913 | 849 | 791 |

*Wilson WH et al. NEJM 2013*

# Salute-malattia



# Nutraceutici, integratori ed alimenti funzionali

| CATEGORIA | DEFINIZIONE | ESEMPI |
|---|---|---|
| ***Nutraceutico*** | Estrazione naturale<br>Azioni salutistiche | Monacoline<br>Policosanoli<br>Berberina |
| ***Integratore alimentare*** | Nutrienti nella dieta<br>Da supplementare | Minerali<br>Vitamine<br>Omega-3 |
| ***Alimento funzionale*** | Cibi arricchiti di sostanze naturali salutistiche | Cibi arricchiti in: fibre, fitosteroli, omega-3 |

Cicero 2012

Nutraceutico: neologismo originato dalle parole nutrizione e farmaceutico .
Componente alimentare o principio attivo presente negli alimenti e che ha effetti positivi per il benessere e la salute, ivi inclusi la **prevenzione** e il **trattamento** delle malattie
Stephan De Felice, 1989

# FIBRE

Parti edibili non digeribili

a) **Insolubili**: crusca

b) **Solubili**: oligosaccaridi, destrina, inulina (rapidamente fermentate dal microbiota)

c) **Solubili viscose**: b-glucano, guar, pectina

(formano un gel viscoso che rallenta l'assorbimento)

d) **Solubili viscose non fermentabili**: multicellulosa riduce l'assorbimento

# FITOSTEROLI

Componenti bioattivi di natura vegetale colesterolo-simili (frutta, verdura, noci, semi, legumi, oli vegetali)

# SOIA

Rallenta l'assorbimento del colesterolo e sitosterolo

# POLICOSANOLI

Alcolici alifatici a lunga catena (cera d'api, patate, crusca di riso, canna da zucchero)

# RISO ROSSO FERMENTATO

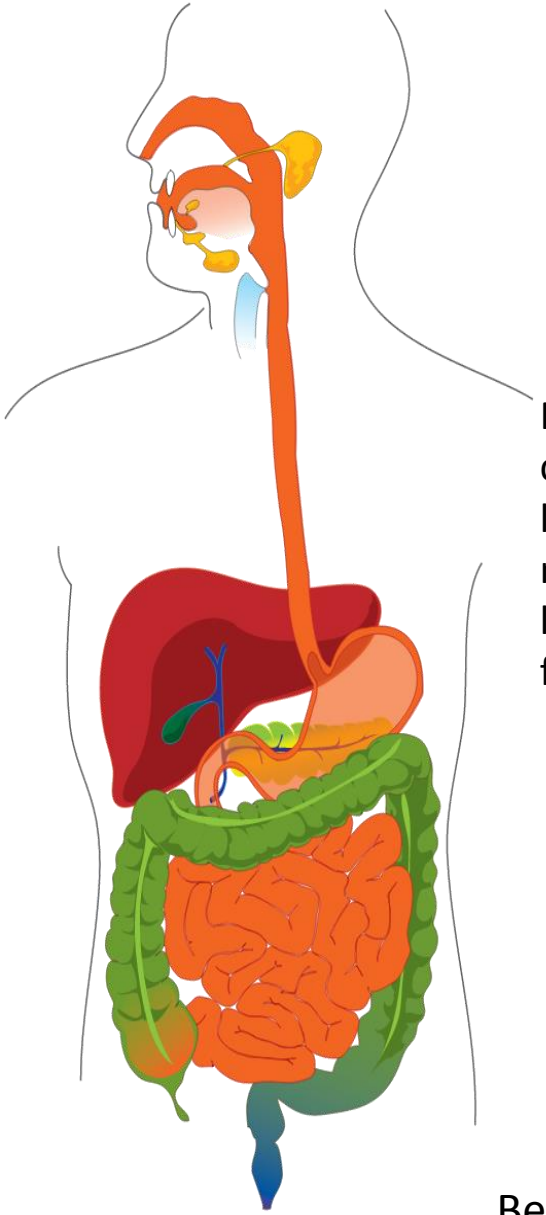
Monocolina K

# BERBERINA

Alcaloide vegetale (berberis vulgaris etc)

# NUTRACEUTICI ATTIVI SUL COLESTEROLO

Fibra alimentare: lega acidi biliari nell'intestino tenue e ne aumenta l'escrezione con le feci




Fitosteroli: hanno omologia strutturale con il colesterolo e competono a livello intestinale, sostituendolo nelle micelle. Vengono poi ritraghettati nel lume intestinale ed eliminati con le feci (assorbimento 0.5-2%)

Policosanoli: Inibitori HMGCoA reduttasi

Berberina: aumenta emivita LDLR sugli epatociti, attiva AMPK, inibendo HMGCoA reduttasi

# EFSA and FDA positions

| Nutraceutico | Dose efficace valutata nel claim | EFSA | FDA |
|---|---|---|---|
| **Fibra:** | | | |
| **β-glucano*** | ≥ 3 g/die | Riduzione del C-LDL | Riduzione del C-LDL<br>Riduzione rischio CHD |
| **Chitosano** | 3 g/die | Mantenimento di livelli normali di C-LDL | - |
| **Glucomannano** | 4 g/die | Mantenimento di livelli normali di C-LDL | - |
| **Gomma guar** | 10 g/die | Mantenimento di livelli normali di C-LDL | - |
| **HPMC** | 5 g/die | Mantenimento di livelli normali di C-LDL | - |
| **Pectine** | 6 g/die | Mantenimento di livelli normali di C-LDL | - |
| **Psyllium** | ≥ 7 g/die | - | Riduzione del C-LDL<br>Riduzione rischio CHD |
| **Fitosteroli** | 3 g/die | Riduzione del C-LDL | Riduzione del C-LDL |
| **Derivati della soia** | 25 g/die | - | Riduzione del rischio CV |
| **Policosanoli** | - | - | - |
| **Riso rosso fermentato** | 10 mg/die di monacolina K | Mantenimento di livelli normali di C-LDL | La dose di 10 mg di monacolina K è soggetta alle restrizioni vigenti per la medesima dose di lovastatina |
| **Berberina** | - | - | - |

*** da avena e orzo, CHD: malattia coronarica, C-LDL: colesterolo LDL, CV: cardiovascolare, HPMC: idrossipropilmetilcellulosa.**

# Principali evidenze di RCT nell'uomo con RRF

| Tipo di studio | Soggetti (Numero, Tipo) | Contenuto di monacolina K | Durata media (range) | Effetti osservati |
|---|---|---|---|---|
| Metanalisi di 93 RCT | n: 9625 Dislipidemia | 3-12.4 mg/die | 8 settimane (4-24 settimane) | ↓C-LDL: -28 mg/dl<br>↓TG: -36 mg/dl<br>↑C-HDL: +5.8 mg/dl |
| Metanalisi di 13 RCT | n: 804 Dislipidemia | 2-11.4 mg/die | 12 settimane (4-24 settimane) | ↓C-LDL: -34 mg/dl<br>↓TG: -20 mg/dl<br>No effetto su C-HDL |
| Metanalisi di 20 RCT | n: 2811 Dislipidemia, diabete tipo 2, CHD, ipertensione | 4.8-24 mg/die | 23 settimane 4-168 settimane | ↓C-LDL: -39 mg/dl<br>↓TG: -23 mg/dl<br>↑C-HDL: +2.7 mg/dl |
| Metanalisi di 21 RCT | n: 4558 Ipertensione | (RRF 1200-1800 mg/die) | 4-234 settimane | ↓C-LDL: -24 mg/dl<br>No effetto su TG e C-HDL |

↑: aumento, ↓: riduzione, C-HDL: colesterolo HDL, C-LDL: colesterolo LDL, CHD: malattia coronarica, RRF: riso rosso fermentato, TG: trigliceridi

-16-31%

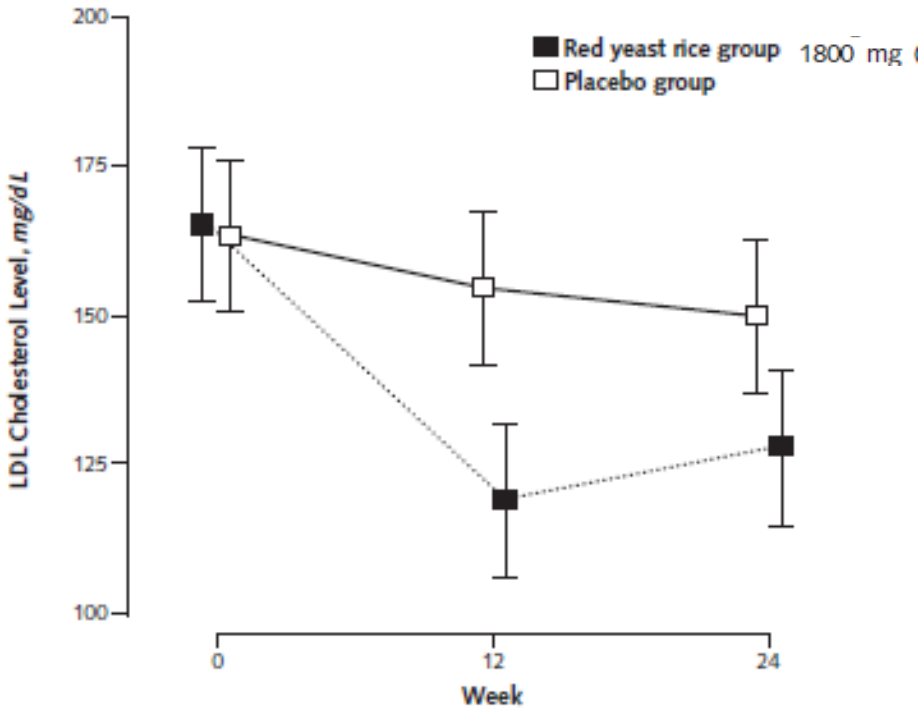
SID-SISA 2016

ARTICLE | Annals of Internal Medicine

# Red Yeast Rice for Dyslipidemia in Statin-Intolerant Patients

## A Randomized Trial

David J. Becker, MD; Ram Y. Gordon, MD; Steven C. Halbert, MD; Benjamin French, PhD; Patti B. Morris, RD; and Daniel J. Rader, MD




| Outcome Measure | Red Yeast Rice Group | | Placebo Group | |
|---|---|---|---|---|
| | Patients, *n* | Mean (SD) | Patients, *n* | Mean (SD) |
| **Weight, *kg*** | | | | |
| Baseline | 31 | 81.0 (12.8) | 31 | 81.9 (15.7) |
| Week 12 | 30 | 77.3 (12.4) | 31 | 78.3 (15.0) |
| Week 24 | 29 | 77.5 (12.5) | 29 | 78.3 (15.1) |
| Change (baseline to week 12), % | | −3.7 (2.9) | | −4.2 (3.3) |
| Change (baseline to week 24), % | | −4.0 (3.6) | | −5 (4.6) |
| **Brief Pain Inventory score*** | | | | |
| Baseline | 31 | 1.4 (1.9) | 31 | 2.6 (2.2) |
| Week 12 | 29 | 1.4 (1.6) | 33 | 1.9 (2.1) |
| Week 24 | 30 | 1.2 (1.6) | 29 | 2.0 (2.5) |
| **Creatine phosphokinase level, *U/L*** | | | | |
| Baseline | 31 | 122.4 (69.2) | 31 | 117.5 (87.5) |
| Week 12 | 29 | 135.7 (89.2) | 30 | 101.8 (40.8) |
| Week 24 | 30 | 128.3 (90.2) | 29 | 101.2 (48.1) |
| **Aspartate aminotransferase level, *U/L*** | | | | |
| Baseline | 31 | 22.9 (5.4) | 31 | 24.9 (7.5) |
| Week 12 | 29 | 24.8 (11.5) | 30 | 24.8 (11.4) |
| Week 24 | 30 | 22.5 (4.4) | 29 | 22.0 (5.6) |
| **Alanine aminotransferase level, *U/L*** | | | | |
| Baseline | 31 | 24.4 (10.2) | 31 | 26.0 (10.0) |
| Week 12 | 29 | 24.4 (14.3) | 30 | 27.5 (18.0) |
| Week 24 | 30 | 21.8 (8.9) | 29 | 20.1 (6.9) |

2009

# Marked Variability of monacolin levels in commercial red yeast rice products

**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: Total Monacolins | Monacolin K (Lovastatin) | Monacolin KA | Citrinin, ppm | Citrinin, µg/cap |
|---|---|---|---|---|---|
| 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.

Gordon R Arch Intern med 2010

# Principali evidenze di RCT nell'uomo con berberina

| Tipo di studio | Soggetti (Numero, Tipo) | Dose media (range) | Durata media (range) | Effetti osservati | Ref. |
|---|---|---|---|---|---|
| Metanalisi di 14 RCT | n: 1068<br>Diabete tipo 2 | 0.5-1.5 g/die | 12 settimane<br>(8-24 settimane) | ↓C-LDL: -13/-22 mg/dl<br>↓TG: -19/-45 mg/dl<br>↑C-HDL: +0.8/+2.7 mg/dl | (128) |
| Metanalisi di 11 RCT | n: 874<br>Dislipidemia, diabete tipo 2 | 0.5-1.5 g/die | 15 settimane<br>(8-52 settimane) | ↓C-LDL: -25 mg/dl<br>↓TG: -44 mg/dl<br>↑C-HDL: +1.9 mg/dl | (129) |
| Metanalisi di 6 RCT | n: 451<br>Dislipidemia | 0.6-1.5 g/die | 11 settimane<br>(8-17 settimane) | ↓C-LDL: -25 mg/dl<br>↓TG: -35 mg/dl<br>↑C-HDL: +2.7 mg/dl | (130) |

↑: aumento, ↓: riduzione, C-HDL: colesterolo HDL, C-LDL: colesterolo LDL, TG: trigliceridi.

-25 mg/dl

SID-SISA 2016

# Combination of simvastatin with berberine improves the lipid-lowering efficacy

Table 2
Lipid-lowering efficacies of the combination therapy using BBR and SIMVA in hypercholesterolemic patients

| Measurement (reference range) | Treatment | BBR + SIMVA (n = 23) | SIMVA (n = 16) | BBR (n = 24) |
|---|---|---|---|---|
| LDL-c | Before | 4.36 ± 0.97 | 4.28 ± 1 | 3.81 ± 0.56 |
| (<3.1 mmol/L) | After | 2.97 ± 0.93*** | 3.67 ± 0.8** | 2.9 ± 0.7*** |
| | % Change | 31.8 ± 3.6†, ‡ | 14.3 ± 4.6 | 23.8 ± 3.6 |
| TC | Before | 6.73 ± 0.98 | 6.56 ± 0.5 | 6.17 ± 0.56 |
| (<5.2 mmol/L) | After | 4.77 ± 0.82*** | 5.99 ± 0.6** | 4.82 ± 0.65*** |
| | % Change | 29.1 ± 2.4†,‡ | 9.1 ± 1.5 | 21.8 ± 1.6 |
| TG | Before | 2.72 ± 0.61 | 2.28 ± 0.9 | 1.94 ± 1.05 |
| (<1.7 mmol/L) | After | 1.66 ± 0.35*** | 2.02 ± 0.7* | 1.51 ± 0.77** |
| | % Change | 38.9 ± 6.5†,‡ | 11.4 ± 3.5 | 22.1 ± 10 |
| HDL-c | Before | 1.46 ± 0.55 | 1.15 ± 0.5 | 1.21 ± 0.34 |
| (>1.0 mmol/L) | After | 1.34 ± 0.35 | 1.18 ± 0.4 | 1.14 ± 0.3 |
| | % Change | 8.2 ± 6.8 | 2.6 ± 0.9 | 5.8 ± 1.7 |

Hypercholesterolemic patients were treated with BBR 1 g/d, SIMVA 20 mg/d, or their combination orally for 2 months. Before and after treatment, fasting blood samples were taken for the measurement of serum LDL-c, TC, TG, and HDL-c levels. Percentage changes of serum lipids from baselines to end points were calculated. Values are mean ± SEM of all of the patients in each group. For percentage changes in LDL-c, TC, and TG, $P < .01$ among groups by 1-way ANOVA.
*$P < .05$, **$P < .01$, ***$P < .001$ vs that of before treatment by paired $t$ test.
†$P < .05$ vs that of BBR alone, ‡$P < .01$ vs that of SIMVA alone by the Newman-Keuls test.

# Vantaggi e svantaggi dei nutraceutici attivi sul coletserolo

**Vantaggi**

- Possibili effetti su altri fattori di rischio CV (es berberina)
- Nessuna interazione con i farmaci ipolipemizzanti (es fitosteroli)
- Maggiore profilo di tollerabilità nel paziente intollerante a statine (es riso rosso e berberina)

**Svantaggi**

- Acquisto autonomo da parte del paziente e rischio di mancata supervisione medica
- Variabilità di composizione e purezza dei prodotti da banco

# Indicazioni cliniche

1. Pazienti con ipercolesterolemia lieve e rischio CV non elevato (TUTTI)

2. Pazienti con ipercolesterolemia lieve e sindrome metabolica (FIBRA e BERBERINA)

3. Pazienti intolleranti a più statine (FITOSTEROLI-RISO ROSSO FERMENTATO-BERBERINA)

4. In aggiunta alla terapia farmacologica per pazienti che non raggiungono livelli ottimali di C-LDL (FITOSTEROLI, BERBERINA)

# Biodisponibilita’

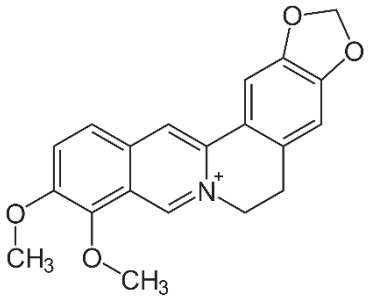
- La ***biodisponibilità*** è un termine che indica sia la quantità di farmaco che entra immodificata nel torrente circolatorio dopo la somministrazione, sia la velocità con cui lo raggiunge ed è quindi la misura con cui è disponibile nell’organismo per esercitare l’attività terapeutica ;

- (Tmax, Cmax, AUC…);

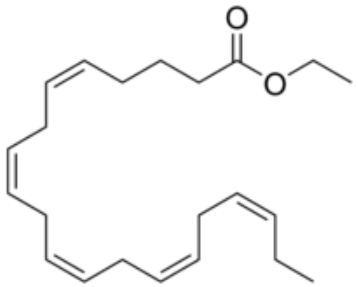
- ***<u>Tali parametri farmacologici non si devono applicare solo ai Farmaci, ma a qualsiasi preparato in grado di veicolare sostanze capaci di produrre un effetto biologico;</u>***

# Biodisponibilita’

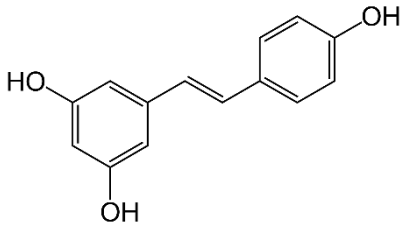
- Alcuni esempi:
  - ***BERBERINA HCl:*** molecola dal grande potenziale in ambito cardiovascolare e metabolico (sindrome metabolica, diabete) ma con scarsa biodisponibilità: necessarie tecnologie di promozione (PgP);




  - ***EPA+DHA:*** ben assorbiti grazie all’emulsionamento della bile; se somministrati in forma emulsionata, molto più biodisponibili;

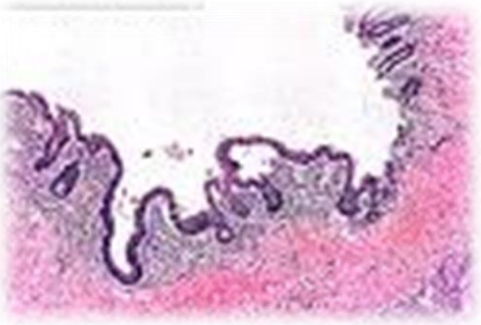



  - ***RESVERATROLO:*** biodisponibilità inferiore all’1% se assunto come molecola isolata e non dal fitocomplesso per via orale (alternativa la via sublinguale);



# I nutraceutici efficaci

- Formulazioni che nascono non solo dall'esigenza di introdurre molecole di comprovata efficacia, ma soprattutto di ***rendere i principi attivi BIODISPONIBILI;***



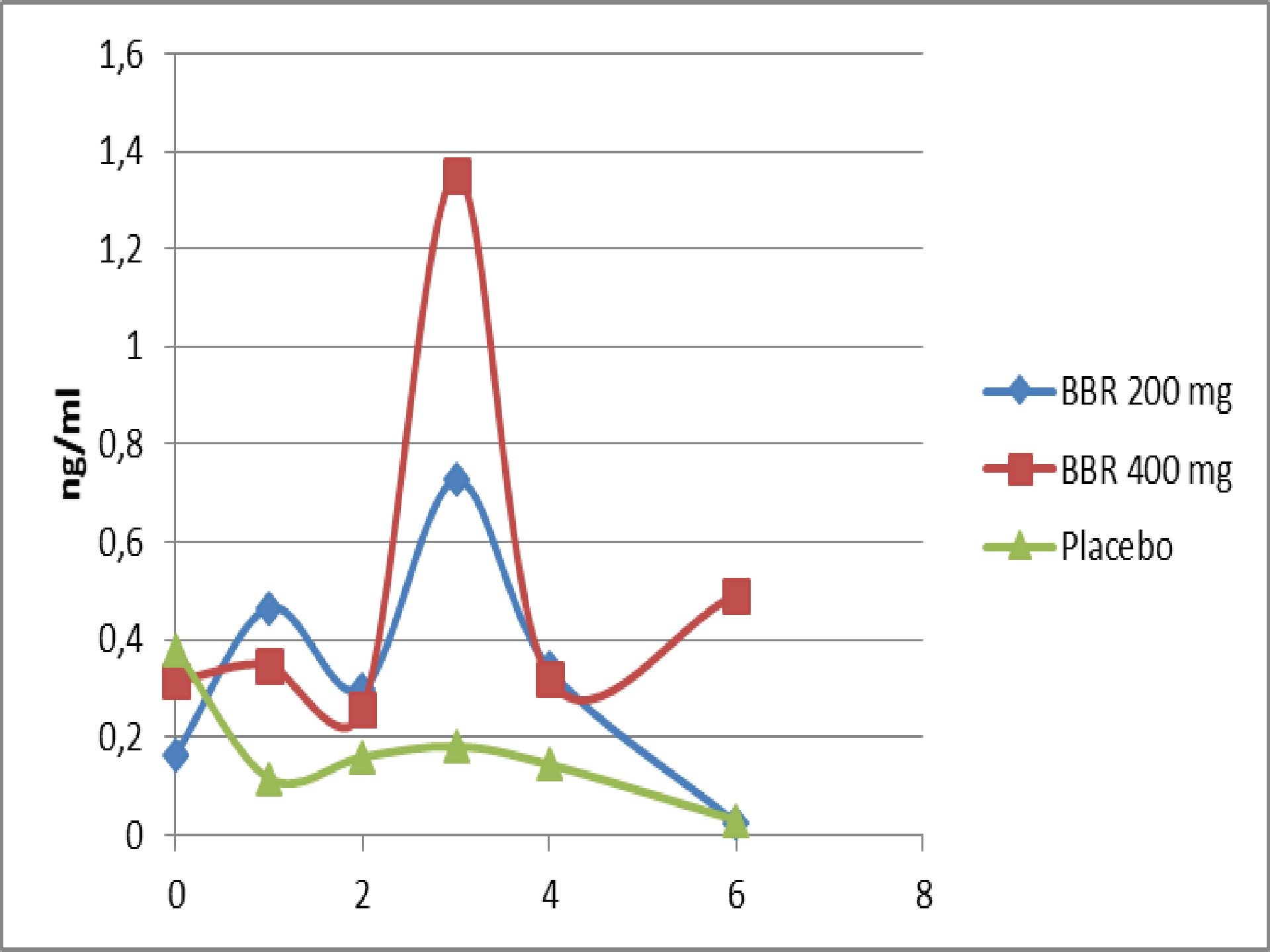
- Formulazioni nate pensando al profilo chimico-fisico delle sostanze introdotte ***e a come costruire attorno a loro una forma tecnica capace di renderle biodisponibili;***

# «COLEOSOMI™»

- Compressa/Capsula gastro-resistente;
- ***Nucleo interno con:***
  - Sale cationico di Chitosano ad attivazione enterica;

# «COLEOSOMI™»

- ***Nucleo interno con:***
  - Sale cationico di Chitosano ad attivazione enterica;
- ***Applicazioni in nutraceutiche:***
  - Aumento della biodisponibilità dei substrati della Pg-P e di quelli trattenuti dalle Tight Junctions;
  - Interazione e precipitazione dei sali biliari con effetto di riduzione dell'assorbimento enterico dei lipidi (effetto resina a scambio ionico);


1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
ng/ml
0
2
4
6
8
BBR 200 mg
BBR 400 mg
Placebo

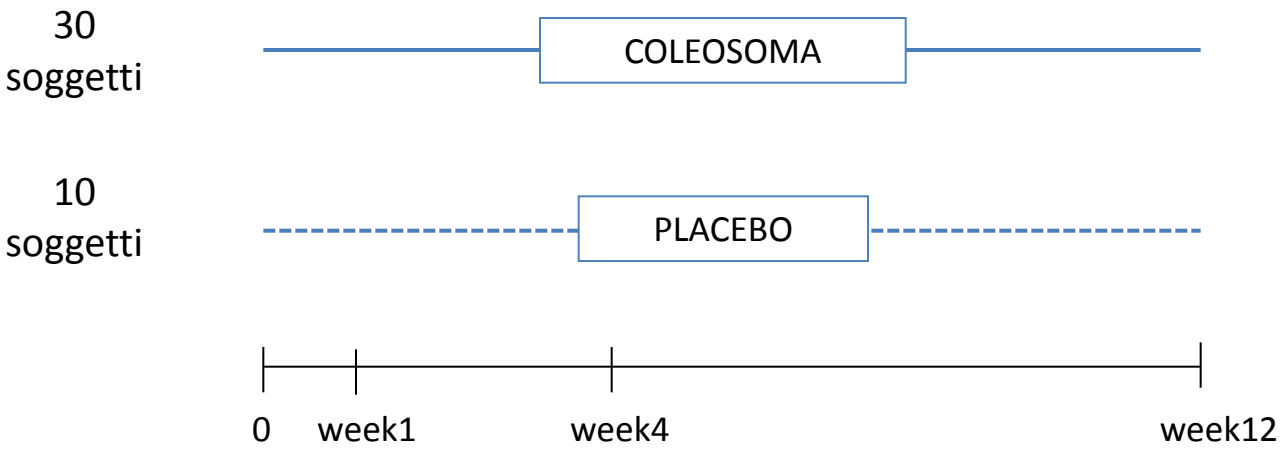
# STUDIO COLEOSOMA

(Chitosano 0.1 mg, riso rosso fermentato 3mg , berberina 200 mg e Fosfoserina)

Studio randomizzato-controllato, in doppio cieco di fase II
Randomizzazione 3:1

**Soggetti in studio**: colesterolo non-HDL≥160mg/dl e con rischio CV che non indichi utilizzo statine

**DISEGNO DELLO STUDIO**




**t0**: Consenso Informato
Anamnesi
Caratteristiche Demografiche
Criteri Inclusione/Esclusione

**w1, w4 e w12:** Parametri antropometrici
Esami Ematochimici e profilo metabolico
**Valutazione del numero delle cellule progenitrici circolanti** (solo w1 e w12)
Eventi Avversi

**END POINT:**

**END point primario: variazione assoluta o percentuale del colesterolo non-HDL dopo 12 settimane di terapia rispetto al baseline**

**END point secondari: variazioni assolute o percentuali a 4 e a 12 settimane dei seguenti parametri rispetto al baseline:**

- **colesterolo non-HDL (a 4 settimane) a 12 settimane:**
- **glicemia a digiuno**
- **BMI e circonferenza vita**
- **HbA1C**
- **Colesterolo LDL, trigliceridi e colesterolo HDL**
- **Rapporto ApoB/Apo A1**
- **Livelli di citochine infiammatorie plasmatici (IL-1, IL6, IL-10, hsPCR, TNFalpha)**
- **profilo ormonale (insulina, glucagone, GLP-1 attivo, GIP)**
- **cellule progenitrici endoteliali (EPCs)**

# Conclusioni

1. L'efficacia delle statine in prevenzione primaria è ampiamente dimostrata

2. E' importante calcolare il rischio CV individuale globale

3. L' utilizzo di statine può associarsi ad effetti indesiderati
(nei registri è dal 7-29% miopatie)

4. I nutraceutici sono in grado di ridurre i valori di col-LDL mediamente dal 10-20% e sono una valida proposta nei soggetti a basso rischio od intolleranti alle statine

5. Sono necessari ulteriori studi per valutare se la combinazione di più nutraceutici abbia un effetto additivo

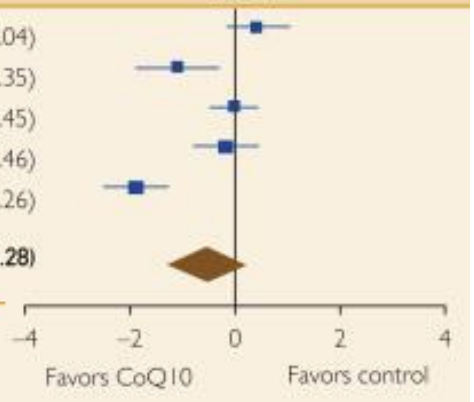
6. Studi RCT sono auspicabili anche per i nutraceutici al fine di testarne efficacia e sicurezza

# Meta-analysis

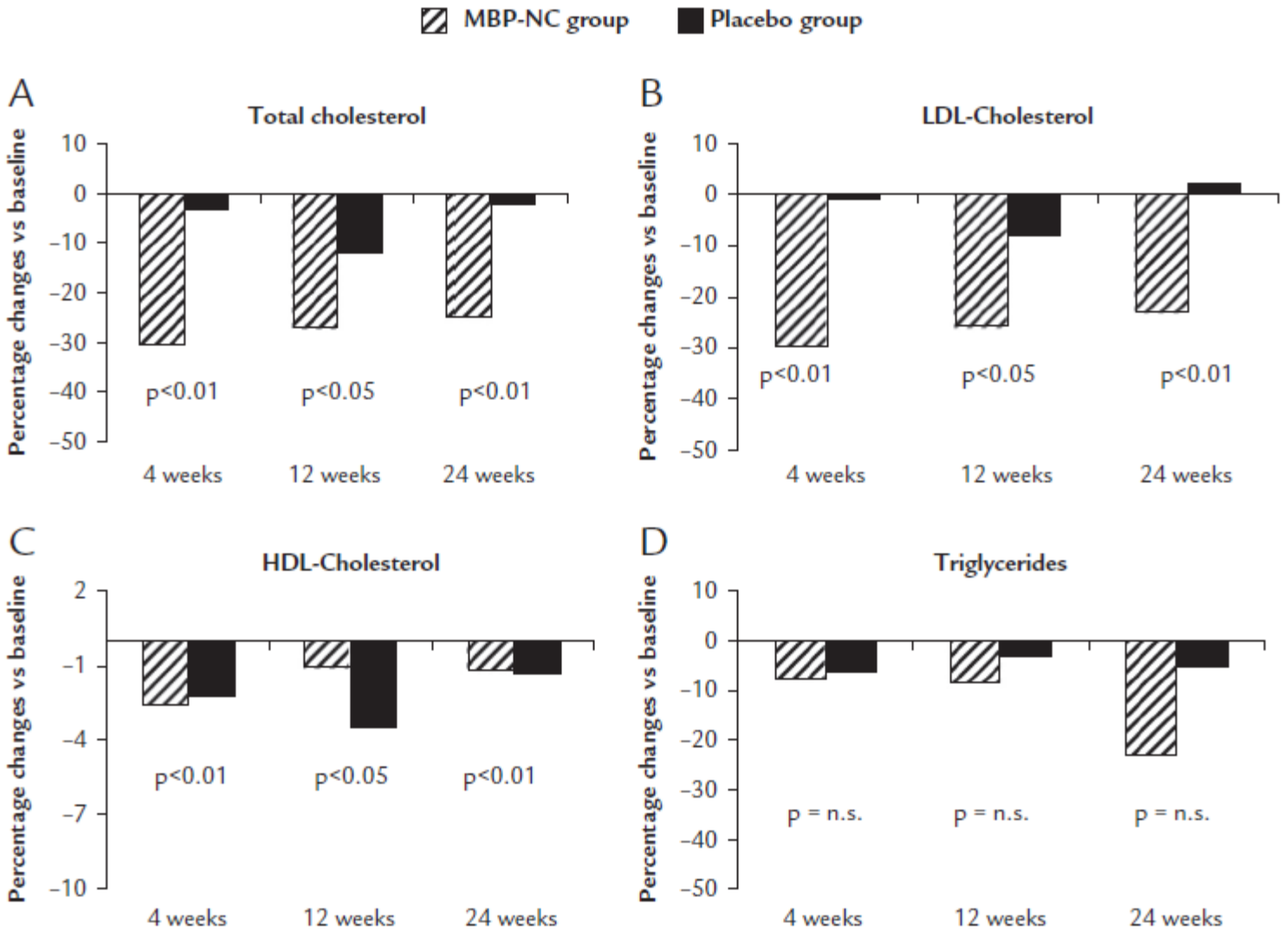
| Study or subgroup | CoQ10 Mean | CoQ10 SD | CoQ10 Total | Control Mean | Control SD | Control Total | Weight | Std. mean difference inverse variance, random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Young et al,[28] 2007 | 5.72 | 1.94 | 22 | 4.35 | 3.88 | 22 | 20.1% | 0.44 (–0.16 to 1.04) |
| Caso et al,[24] 2007 | –2.03 | 1.82 | 18 | 0.34 | 2.4 | 14 | 18.8% | –1.10 (–1.86 to –0.35) |
| Bookstaver et al,[25] 2012 | –2.8 | 2.25 | 40 | –2.8 | 2.11 | 36 | 21.1% | 0.00 (–0.45 to 0.45) |
| Bogsrud et al,[29] 2013 | –79.36 | 309.46 | 20 | –30.4 | 320.43 | 21 | 20.0% | –0.15 (–0.77 to 0.46) |
| Fedacko et al,[26] 2013 | –3.5 | 1.94 | 34 | –0.1 | 1.55 | 26 | 19.9% | –1.88 (–2.50 to –1.26) |
| **Total (95% CI)** | | | **134** | | | **119** | **100.0%** | **–0.53 (–1.33 to 0.28)** |

Heterogeneity: $Tau^2=0.74$; $\chi^2=36.63$, $df=4$ ($P<.001$); $I^2=89\%$

Test for overall effect: $Z=1.28$ ($P=.20$)



# Effetti della supplementazione combinata di nutraceutici (200mg red yeast rice extract, 500 mg berberine and 10 mg policosanols)




Current Therapeutic Research 2015

## Learning points

- Non-pharmacological treatment is the first line therapy for hypercholesterolemia. Several nutraceuticals have been shown to positively influence blood cholesterol with negligible side effects.
- Among different nutraceutical substances presented, cholesterol lowering effects of plant sterols/stanols and red yeast rice appear the most convincing.
- The use of nutraceutical products could be considered in hypercholesterolemic patients in whom statin therapy is not indicated, e.g. patients at low cardiovascular risk.
- The influence on cardiovascular endpoints, clinical safety and reliability of manufacturing processes of nutraceutical products need to be addressed by further study to define a clear indication to start a treatment with a cholesterol lowering nutraceutical.

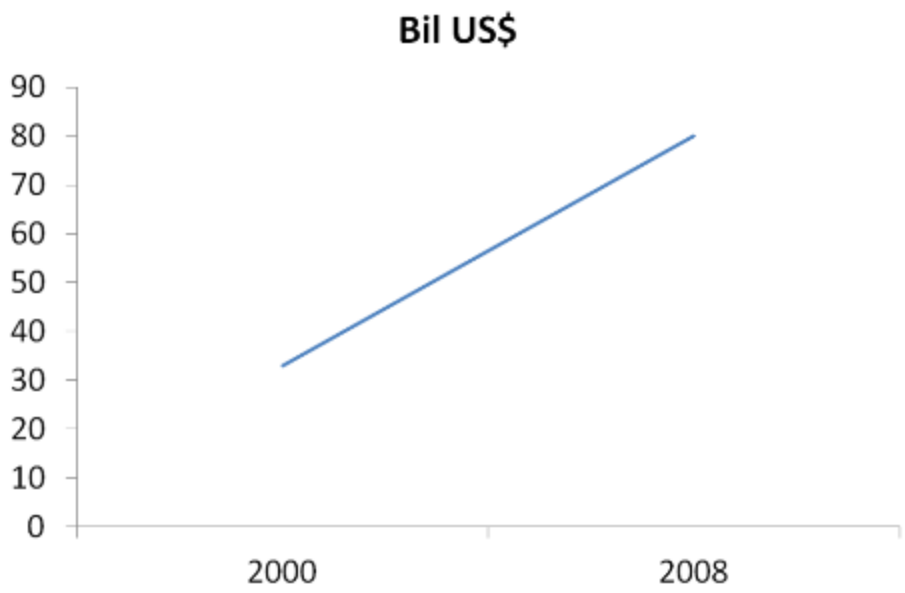
| | Vantaggi | Svantaggi | Possibili indicazioni |
|---|---|---|---|
| **Fibra** | - Riduzione **C-LDL 4-14%**<br>- Effetti su altri fattori di rischio CV<br>- Costo relativamente basso | Disconfort intestinale per dosaggi eccessivi | - Popolazione generale che non riesce ad aumentare l'apporto di fibra con la sola dieta<br>- Pazienti con ipercolesterolemia lieve e rischio CV non elevato*<br>- Pazienti con ipercolesterolemia lieve e sindrome metabolica |
| **Fitosteroli** | - Riduzione **C-LDL 8-10%**<br>- Nessuna interazione con i farmaci ipolipemizzanti | - Acquisto autonomo da parte del paziente e rischio di mancata supervisione medica<br>- Possibile iperassunzione con conseguente rischio di ridotto assorbimento delle vitamine liposolubili<br>- Costo elevato | - Pazienti con ipercolesterolemia lieve e rischio CV non elevato*<br>- Pazienti intolleranti a più statine<br>- In aggiunta alla terapia farmacologica per pazienti che non raggiungono livelli ottimali di C-LDL |
| **Derivati della soia** | -Riduzione **C-LDL 4-13%** | - Acquisto autonomo da parte del paziente<br>- Rischio allergie<br>- Costo elevato | - Popolazione generale<br>- Pazienti con ipercolesterolemia lieve e rischio CV non elevato* |
| **Riso rosso fermentato** | - **Riduzione C-LDL 16-25%**<br>- Probabile maggiore profilo di tollerabilità nel paziente intollerante a statine<br>- Riduzione del rischio CV | - Variabilità di composizione e purezza dei prodotti da banco<br>- Acquisto autonomo del paziente e rischio di mancata supervisione medica<br>- Costo superiore rispetto a statina generica<br>- Possibili effetti collaterali a dosi elevate | - Pazienti con ipercolesterolemia lieve-moderata e rischio CV non elevato**<br>- Pazienti intolleranti a più statine o che rifiutano la terapia con statine |
| **Berberina[§]** | - **Riduzione C-LDL 20%**<br>- Maggiore profilo di tollerabilità nel paziente intollerante a statine<br>- Effetto favorevole su TG, C-HDL e glicemia | - Variabilità di assorbimento intestinale<br>- Acquisto autonomo del paziente e rischio di mancata supervisione medica<br>- Costo superiore rispetto a statina generica | - Pazienti con ipercolesterolemia lieve-moderata e rischio CV non elevato***<br>- Pazienti con ipercolesterolemia lieve e sindrome metabolica[†]<br>- Pazienti intolleranti a più statine<br>- Pazienti che non raggiungono livelli ottimali di C-LDL con la terapia farmacologica |

***pazienti in cui sia richiesta una riduzione del colesterolo LDL non superiore al 10-15%, ** pazienti in cui sia richiesta una riduzione del colesterolo LDL non superiore al 20-25%, ***pazienti in cui sia richiesta una riduzione del colesterolo LDL non superiore al 20%, [§] studi effettuati pressoché esclusivamente solo nella popolazione asiatica e quindi, non facilmente trasferibili ad altre popolazioni, [†] Anche in associazione a statina in pazienti con modesto incremento della trigliceridemia e/o della glicemia, C-HDL: colesterolo HDL, C-LDL: colesterolo LDL, CV: cardiovascolare; TG: trigliceridi.**

# Effetti CV e metabolici

| Substance | Effects on cardiovascular events/mortality | Additional proposed effects |
|---|---|---|
| Soy | Soy products<br>Ischemic stroke: −34%<br>Myocardial infarction: −45% [26]<br>Isoflavones<br>Ischemic stroke: −65%<br>Myocardial infarction: −63% [26] | Isoflavones<br>↑ BMD in post-menopausal osteoporosis<br>Relieve of vasomotor symptoms of menopause<br>Prevention of breast, endometrium and prostate cancer |
| Dietary fibers | Coronary events: −14%<br>Coronary deaths: −27% [34] | ↓ Body weight<br>↓ Waist circumference<br>↓ Blood pressure<br>↓ Fasting glucose<br>(in high-risk subjects with either type 2 diabetes or at least 3 CVD risk factors) |
| Plant sterols & stanols | Unknown | Anti-inflammatory<br>Activation of cellular stress responses<br>Reduction of apoB-48 secretion from intestinal and hepatic cells<br>Reduction of cholesterol synthesis |
| Policosanol | Unknown | ↓ LDL oxidation<br>↓ Platelet aggregation<br>↓ Smooth muscle cell proliferation |
| Red yeast rice | Total mortality: −33%<br>Cardiovascular deaths: −30% [68]<br>Coronary revascularization: −33% | Suppression of adipogenesis by regulating a transcription factor in 3T3-L1 cells<br>Decreasing glycerol-3-phosphate dehydrogenase activity |
| Berberine | Unknown | Inhibition of hepatic cholesterol and TGs synthesis through the activation of AMP-activated protein kinase (AMPK) |

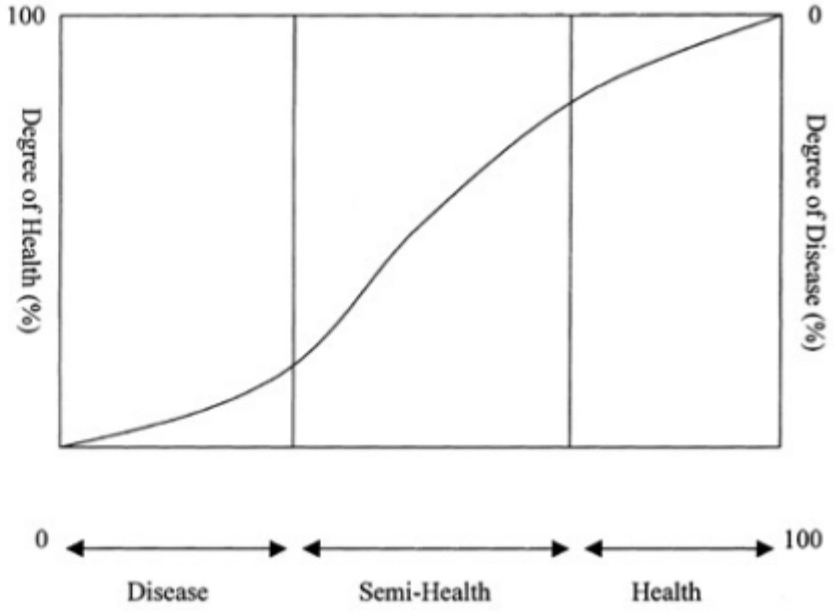
# Mercato globale



# Concetto di salute e malattia

"Salute è uno stato di completo benessere fisico, mentale e sociale e non una mera assenza di malattia o infermità."

World Health Organization




Fonte: Kwak and Juckes (2001) Food Control 12. 99-107

## 6.4 Dietary supplements and functional foods active on plasma lipid values

Innovative nutritional strategies to improve dyslipidaemias have been developed; they are based either on changing some 'risky' dietary components or on encouraging the consumption of specifically targeted 'healthy' functional foods and/or dietary supplements; these so-called 'nutriceuticals' can be used either as alternatives or in addition to lipid-lowering drugs.[69]

Nutritional evaluation of functional foods includes not only the search for the clinical evidence of beneficial effects relevant to improved health or reduction of disease risk, but also the demonstration of good tolerability and the absence of major undesirable effects. The substantiation of health claims relevant for each food should be based on results from intervention studies in humans that are consistent with the proposed claims.[88]

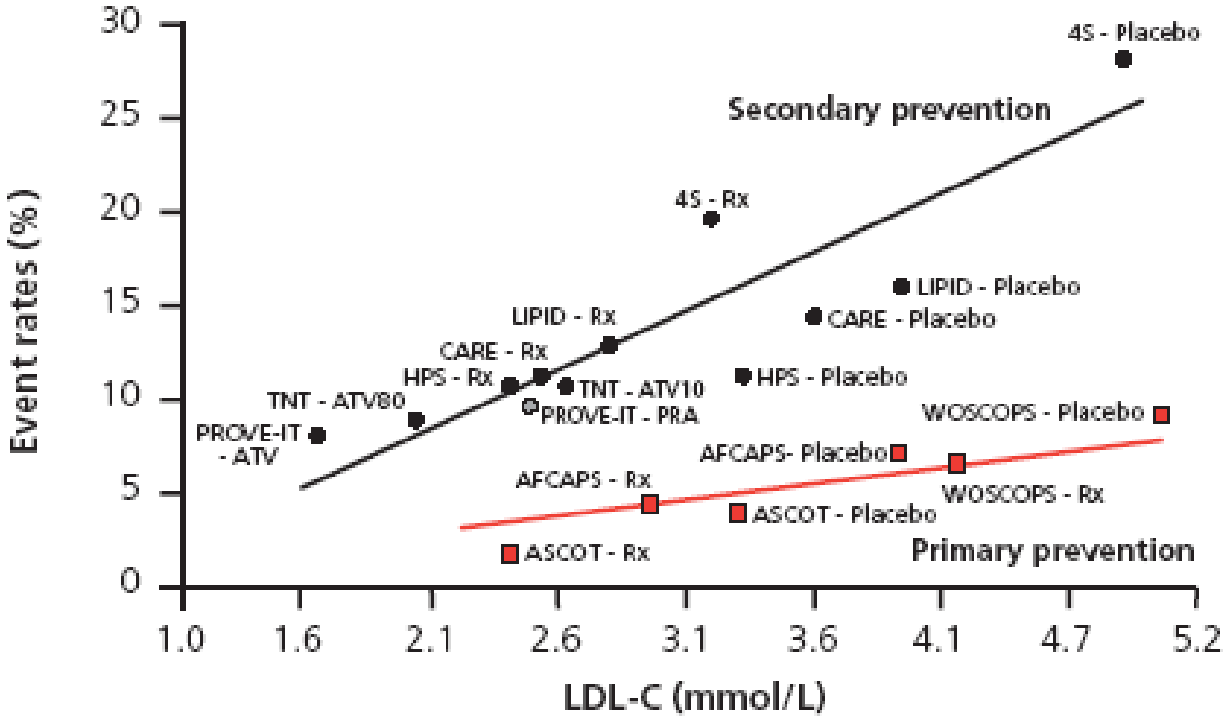
Overall, the available evidence on functional foods so far identified in this field is lacking; the major gap is the absence of diet-based intervention trials of sufficient duration to be relevant for the natural history of dyslipidaemia and CVD.

# Perché consumare nutraceutici?

## Pro e contro

| | Nutraceutici | Farmaci |
|---|---|---|
| Tossicità ed effetti collaterali | minore | maggiore |
| Possibilità di ingerimento | maggiore | minore |
| Costi | maggiori | minori |
| Efficacia d'azione | minore | maggiore |

# The lower the better




**Key:** LDL-C= low-density lipoprotein cholesterol; Rx= statin therapy; PRA = pravastatin; ATV = atorvastatin

Adapted from: Rosensen RS. *Exp Opin Emerg Drugs* 2004;9:269-79 and La Rosa JC[4]

Table 1 Proportion of patients[a] whose lipid concentrations were not at goal or abnormal, data from [16].

| | All ($n$ = 21,797) | High-risk patients ($n$ = 17,583) | Diabetes ($n$ = 4524) | CVD ($n$ = 10,587) | ESC score < 5% ($n$ = 4214) |
|---|---|---|---|---|---|
| TC not at goal (%) | 54.4 | 52.1 | 51.9 | 46.5 | 63.9 |
| LDL-C not at goal (%) | 48.5 | 46.8 | 45.3 | 41.9 | 55.8 |

CVD: cardiovascular disease; ESC: European Society of Cardiology; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.
[a] Patients were recruited from 2954 treatment centres in 11 European Union countries (Norway, Sweden, Denmark, Netherlands, Germany, Austria, Ireland, United Kingdom, France, Portugal and Spain) and Canada.

9. Available RCT evidence indicates a clear net absolute benefit of initiation of moderate-to-intensive statin therapy at a baseline estimated 10-year ASCVD risk of $\geq$7.5%.

10. Available RCT evidence indicates that when baseline ASCVD risk is 5.0% to $<$7.5%, there is still *net absolute* benefit with moderate-intensity statin therapy. However, the tradeoffs between the ASCVD risk-reduction benefit and adverse effects are less clear. Thus, a clinician-patient discussion is even more important for individuals with this range of ASCVD risk. The net benefit of high-intensity statin therapy may be marginal in such individuals.

# Intolleranza alle statine

This discrepancy can be attributed mainly to the
fact that clinical trials tend to exclude older subjects, subjects
with co-morbidities, with a history of muscle-related symptoms
or at risk for myopathy or even have a run- in period that
excludes subjects with side effects

| | Statin comparison higher vs lower | Medical condition of participants | Alanine transaminase three times upper limit of normal higher vs lower | Creatine kinase ten times upper limit of normal, or myopathy higher vs lower | Rhabdomyolysis higher vs lower | Non-vascular death higher vs lower |
|---|---|---|---|---|---|---|
| PROVE–IT (4162)[7,37] | A 80 mg vs P 40 mg | Acute coronary syndromes | 69 (3·3%) vs 23 (1·1%) | 2 (0·1%) vs 3 (0·15%) | 0 (0%) vs 0 (0%) | 17 (0·8%) vs 27 (1·3%) |
| Phase Z of the A to Z trial* (4497)[36] | S 80 mg vs S 20 mg | Acute coronary syndromes | 19 (0·9%) vs 8 (0·4%) | 9 (0·4%) vs 1 (0·04%) | 3 (0·1%) vs 0 (0%) | 21 (0·9%) vs 21 (0·9%) |
| TNT* (10 001)[5,38] | A 80 mg vs A10 mg | Stable CHD | 60 (1·2%) vs 9 (0·2%) | (0·0%) vs (0·0%) | 2 (0·04%) vs 3 (0·06%) | 158 (3·2%) vs 127 (2·5%) |
| IDEAL (8888)[6] | A 80 mg vs S 20–40 mg | Stable CHD | 43 (0·97%) vs 5 (0·11%) | 6 (0·14%) vs 11 (0·25%) | 2 (0·05%) vs 3 (0·07%) | 143 (3·2%) vs 156 (3·5%) |
| SPARCL* (4731)[39] | A 80 mg vs placebo | Post stroke or TIA (no CHD%) | 51 (2·2%) vs 11 (0·5%) | 7 (0·3%) vs 7 (0·3%) | 2 (0·1%) vs 3 (0·1%) | 117 (4·9%) vs 94 (3·9%) |

CHD=coronary heart disease. TIA=transient ischaemic attack. A=atorvastatin. P=pravastatin. S=simvastatin. *Reported as persistent elevation in alanine or aspartate transaminase.

***Table 2:*** **Safety results from large randomised trials of intensive statin therapy**

a 1.5–5 % incidence of statin-induced myopathy

*Lancet* 2007; 370: 1781–90

# Factors associated with muscle pain during high dose of statin (Primo STUDY)

| | OR | 95% CI | *P* value |
|---|---|---|---|
| History of muscle pain with another LLT | 10.12 | 8.23–12.45 | < 0.0001 |
| Unexplained cramps | 4.14 | 3.46–4.95 | <0.0001 |
| History of elevated CK | 2.04 | 1.55–2.68 | <0.0001 |
| Family history of muscular symptoms | 1.93 | 1.10–3.34 | 0.022 |
| Family history of muscular symptoms with LLT | 1.89 | 1.12–3.17 | 0.017 |
| Hypothyroidism | 1.71 | 1.10–2.65 | 0.017 |
| Duration of statin treatment | | | |
| More than 3 months | 0.28 | 0.21–0.37 | <0.0001 |
| Treatment with antidepressants | 0.51 | 0.35–0.74 | 0.0004 |
| Type of statin[a] | | | |
| Atorvastatin | 1.28 | 1.02–1.60 | 0.035 |
| Simvastatin | 1.78 | 1.39–2.29 | <0.0001 |
| Fluvastatin XL | 0.33 | 0.26–0.42 | <0.0001 |

CI, confidence interval; CK, creatine kinase; LLT, lipid-lowering therapy; OR, odds ratio; Multivariate logistic regression was performed to calculate the adjusted odds ratios with 95% confidence intervals.

[a]Odds ratios were calculated using pravastatin as the reference.

Cardiovascular Drugs and Therapy 19 403–414 2005