



**TERAPIA E
PREVENZIONE
CARDIOVASCOLARE
TRA NOVITÀ, CERTEZZE E DUBBI**

**10 NOVEMBRE 2018
ISEO (BS)**

**HOTEL ISEO LAGO
Via Colombera 2**

**Il trattamento delle
dislipidemie nel
paziente anziano:
statine sempre e
comunque?**

Riccardo Raddino

Quali studi a disposizione?

Quando agire?

Aggressività del trattamento

Fattori di rischio CV

- Non modificabili

- Età
- Sesso
- Razza
- Familiarità

Modificabili

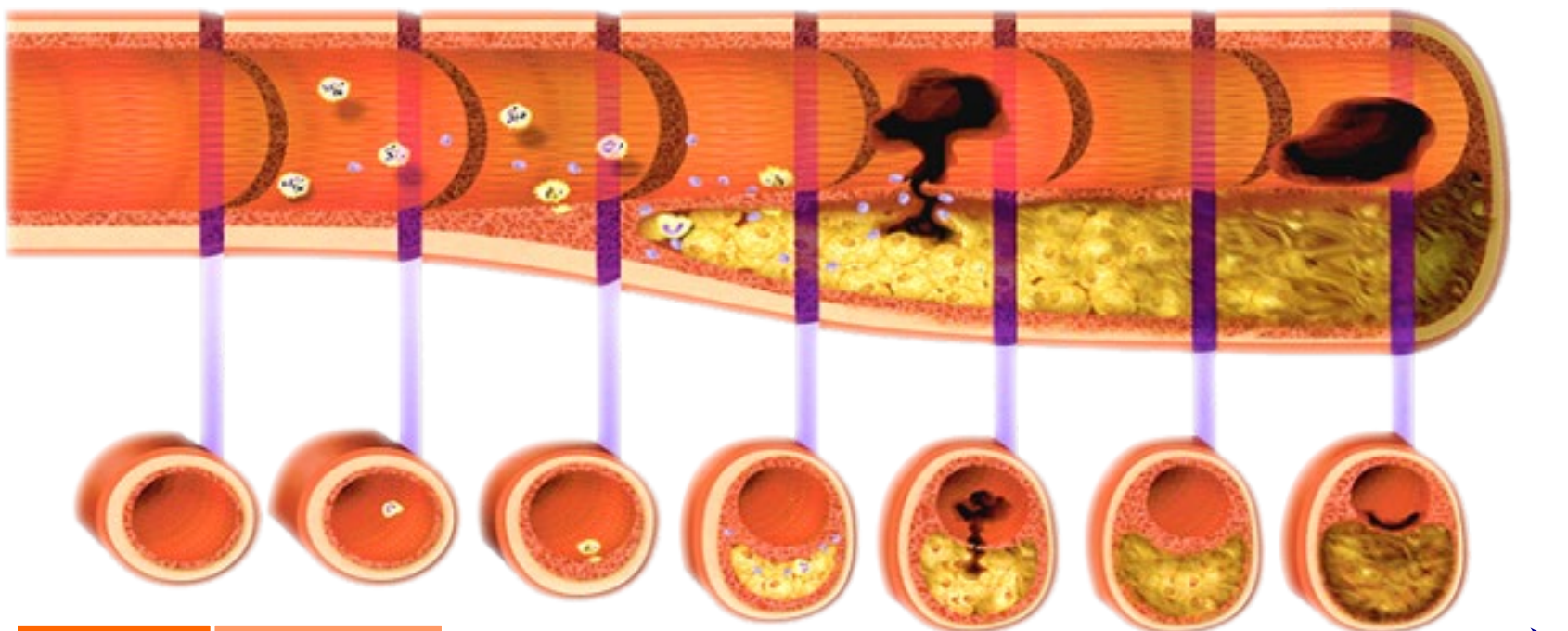
Maggiori

- Fumo
- Ipertensione arteriosa
- Iper-dislipidemia
- Diabete / iperinsulinemia / resistenza insulinica
- Obesità / sindrome metabolica
- Sedentarietà fisica

Meno documentati

- Dieta / abuso di bevande alcoliche
- Iperomocisteinemia
- Ipercoagulabilità / Infiammazione
- Contraccettivi orali / terapie ormonali

Colesterolemia e malattia aterosclerotica

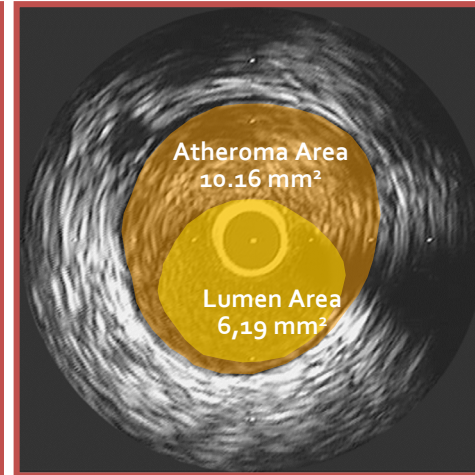
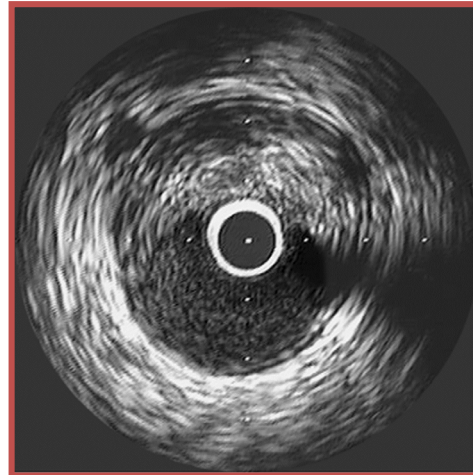


| | | | | | | |
|-----------------|-------------------------|---------------------|----------------------------|-----------------------|--------------------------|----------------------|
| arteria normale | attivazione endoteliale | | | | | |
| | | Angina stabile | Angina instabile | IMA | | |
| | | Progressione | | Complicanze | | |
| | | strie lipidiche | ateroma intramurale maturo | rottura cappa fibrosa | placca fibrosa/calcifica | erosione endoteliale |
| | | Rimodellamento | | Trombosi | Stenosi | Trombosi |

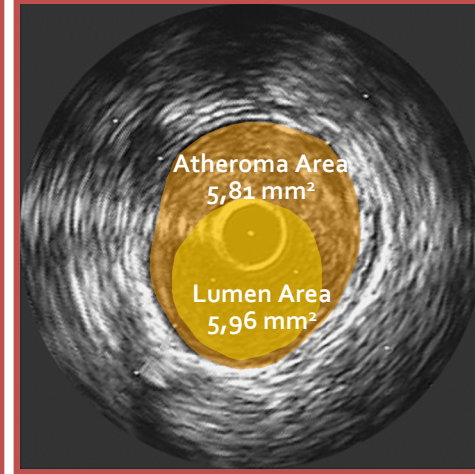
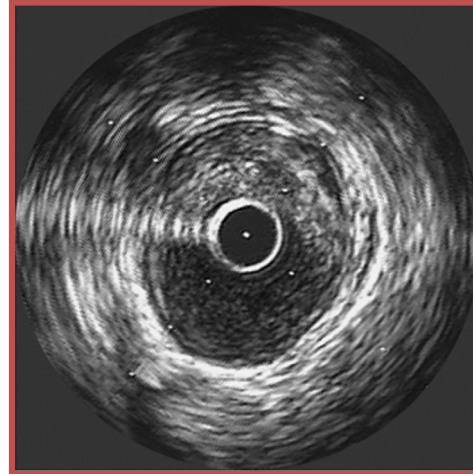
Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis

The ASTEROID Trial

IVUS
Basale



IVUS
follow-up 24 mesi
rosuvastatina
40 mg/die



Classificazione delle iperlipidemie

- Linee guida dell'*European Atherosclerosis Society* per la classificazione delle iperlipidemie

| Iperlipidemia | Concentrazione plasmatica di lipidi |
|----------------------------|--|
| Ipercolesterolemia | |
| Lieve | Colesterolo totale: 5,2-6,5 mmol/L (200-250 mg/dL) |
| Moderata | Colesterolo totale: 6,5-7,8 mmol/L (250-300 mg/dL) |
| Grave | Colesterolo totale: >7,8 mmol/L (>300 mg/dL) |
| Ipertrigliceridemia | |
| Moderata | Trigliceridi: 2,3-4,6 mmol/L (200-400 mg/dL) |
| Grave | Trigliceridi: >4,6 mmol/L (>400 mg/dL) |

- Nell'iperlipidemia mista, colesterolo totale e trigliceridi sono entrambi elevati

Farmaci ipolipemizzanti

Farmaci per l'ipercolesterolemia

- Farmaci che inibiscono il riassorbimento degli acidi biliari.
Resine a scambio ionico.
- Farmaci che inibiscono la biosintesi di colesterolo. **Statine.**

Farmaci per l'ipertrigliceridemia e l'iperlipidemia mista.

- Derivati dell'acido fenossi isobutirrico. **Fibrati.**
 - Derivati dell'**acido nicotinico.**

Riduzione delle morti per coronaropatia 1980 – 2000 negli USA

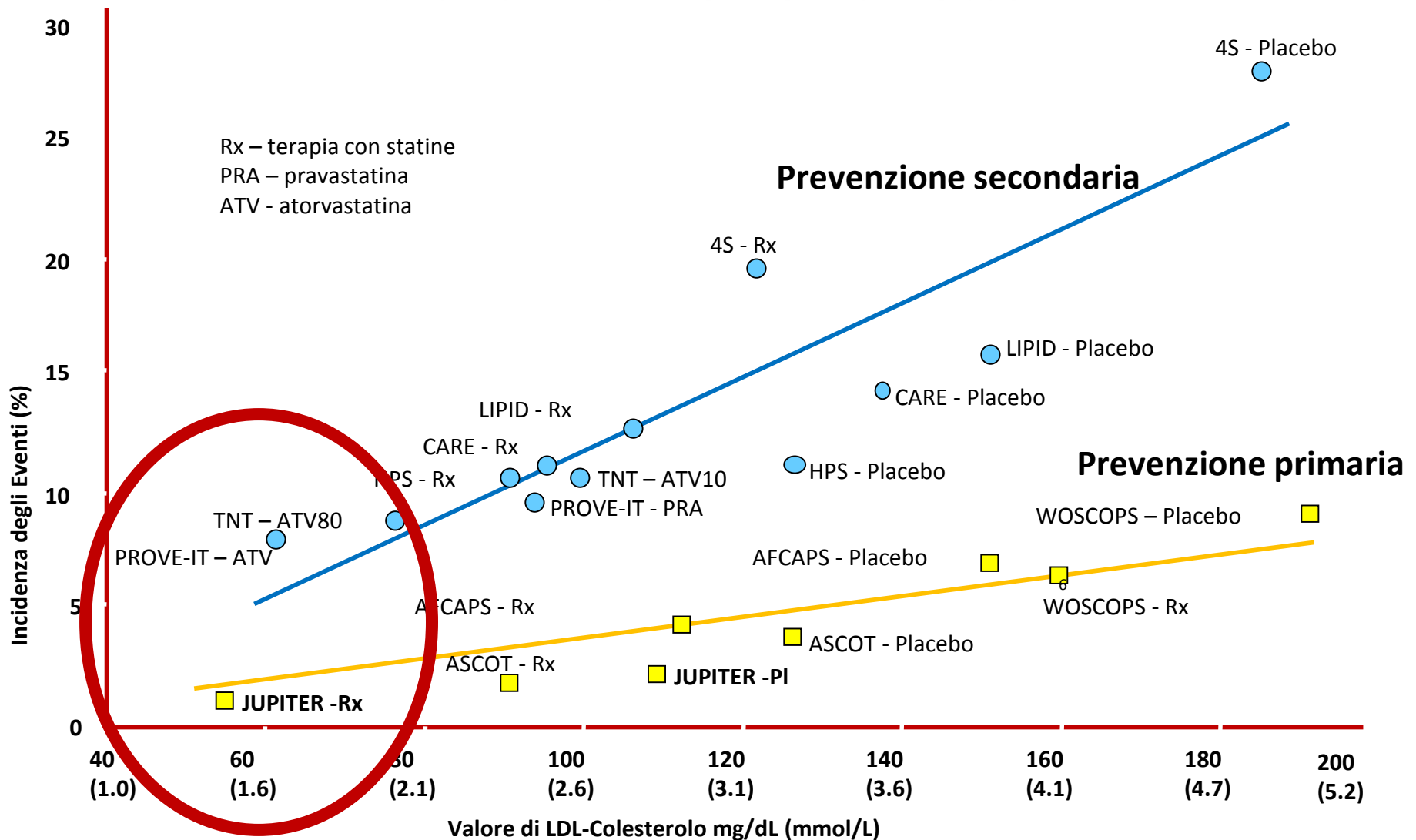
| Trattamento | % riduzione morti |
|---------------------------------------|-------------------|
| Trattamento acuto SCA | 10% |
| Trattamento cronico CAD | 11% |
| Trattamento scompenso cardiaco | 9% |
| Rivascolarizzazione su angina cronica | 5% |
| Altre terapie | 12% |
| Riduzione Colesterolo | 24% |
| Controllo della pressione arteriosa | 20% |
| Riduzione del fumo | 12% |
| Attività fisica | 5% |



Terapia
47%

Prevenzione
44%

Correlazione tra LDL e eventi cardiovascolari nei trial clinici: Lower is Better



Cardine della terapia ipolipemizzante: LE STATINE

Recommendations for the pharmacological treatment of hypercholesterolaemia

| Recommendations | Class | Level |
|--|-------|-------|
| Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level. | I | A |
| In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered. | IIa | B |
| A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance. | IIb | C |
| If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered. | IIb | C |

A photograph of an iceberg floating in the ocean. The tip of the iceberg is visible above the water surface, while the much larger submerged part is hidden below. The sky is blue with some clouds.

***L'efficacia assodata della terapia medica dimostrata da
grossi studi come il COURAGE ... è solo la punta
dell'iceberg***

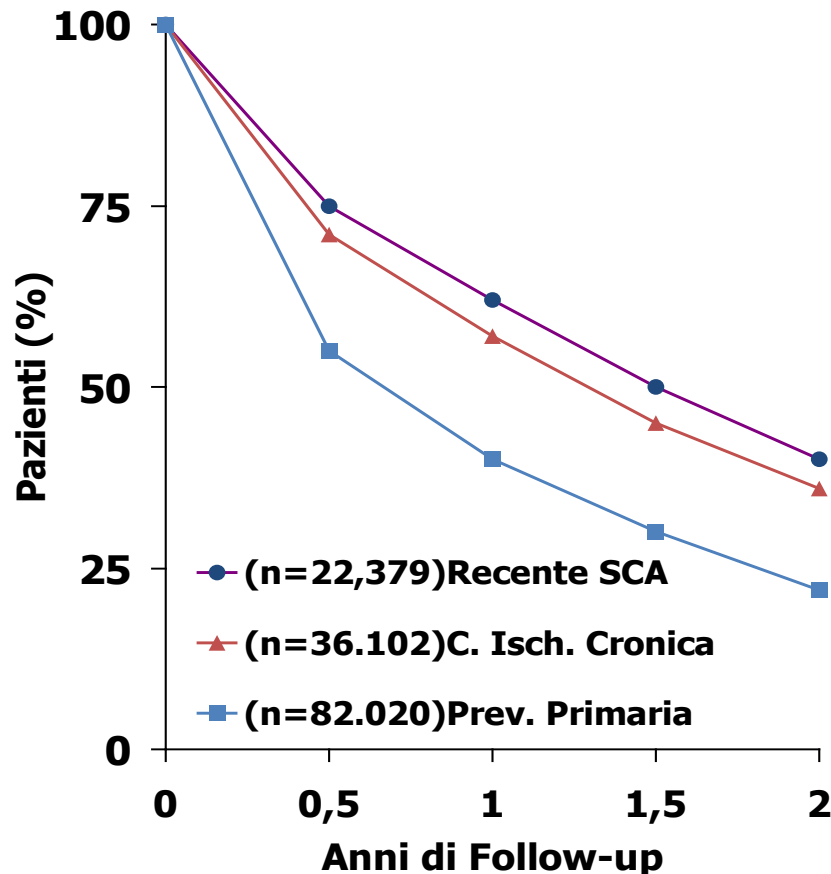
***“Drugs don't work in patients
who won't take them”
(C.Everett Koop)***

A photograph of the submerged part of an iceberg. The large, jagged mass of ice is visible below the water surface, illustrating the concept of the 'tip of the iceberg' metaphor.

***La parte nascosta dell'Iceberg comprende
aspetti non ancora noti della patologia
coronarica e aspetti legati alla realizzazione
della terapia***

Interruzione della terapia con statine nel contesto della prevenzione primaria o secondaria della Cardiopatia Ischemica

L'interruzione della terapia con statine è un fenomeno frequente nella pratica clinica corrente. In generale, il tasso di interruzione della terapia ipolipemizzante è significativamente maggiore nei pazienti in regime di prevenzione primaria.



Predittori indipendenti di interruzione della terapia con statine

- Età avanzata (≥ 75 anni)
- Basso livello socio-economico
- Depressione o demenza
- Terapia con più di 10 farmaci
- Assenza di eventi acuti con ricovero nei precedenti 12 mesi

Jackevicius CA, et al. JAMA. 2002;288:462-467.

Benner JS, et al. JAMA. 2002;288:455-461.

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

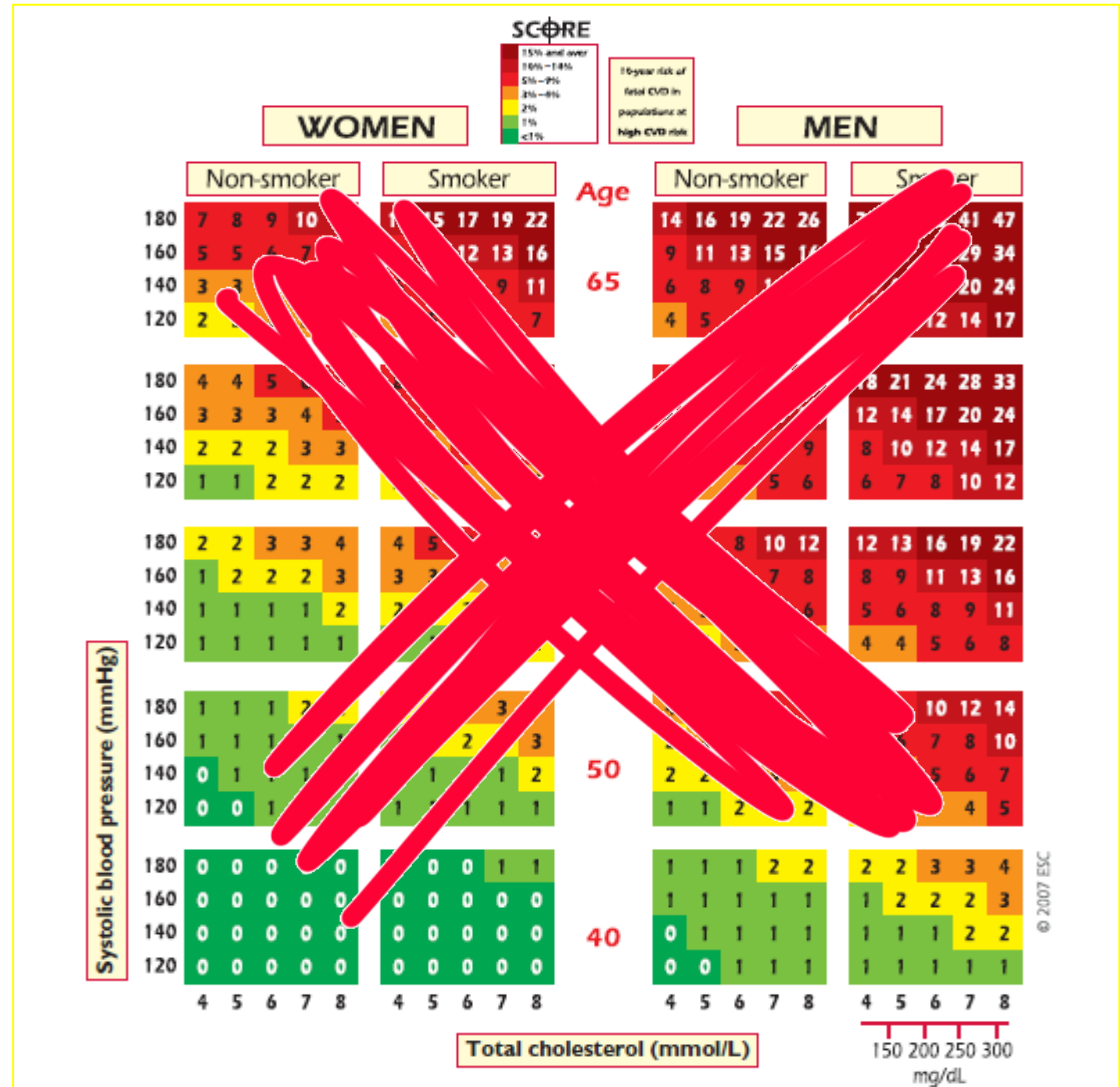
- Evaluate the total CV risk of the subject
- Involve the patient with decisions on CV risk management
- Identify the LDL-C target for that risk level
- Calculate the percentage reduction of LDL-C required to achieve that goal
- Choose a statin that, on average, can provide this reduction
- Since the response to statin treatment is variable, up-titration to reach target is mandatory
- If the statin cannot reach the goal, consider drug combinations.

Valutazione del rischio CV: tabelle SCORE

Calcolo dello SCORE: sono considerati i fattori di rischio principali quali:

- Ipertensione
- Ipercolesterolemia
- Tabagismo
- Sesso
- Età

* Le tabelle SCORE inoltre differiscono anche in base al rischio cv generale del Paese considerato



Definizione di "Anziano"

Maggior parte degli autori > 65 anni

Età compresa tra 65 e 74 anni...



...Over 75 anni



Effects of age on statin pharmacology

Ridotta capacità metabolica
(declino della funzione renale, epatica)

Ridotti livelli di albumina

Alterato rapporto massa magra/massa grassa



**Alterazione concentrazioni farmaco
(potenziale aumento degli effetti collaterali)**



**Interazioni farmacologiche
(politerapia)**



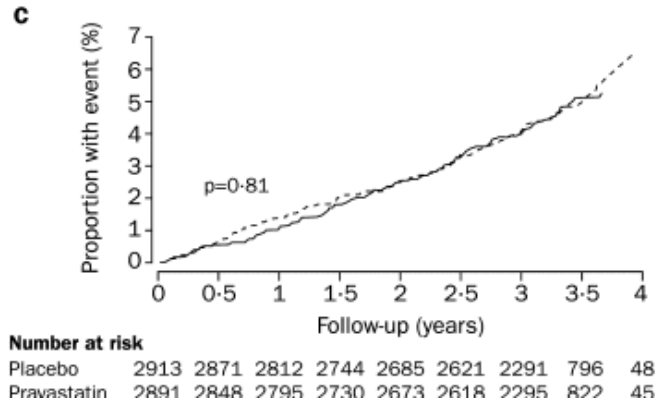
Cosa dicono le linee guida?

| ACC/AHA 2013 ^[20, 21] | Primary prevention | ESC/EAS 2016 ^[24, 25] |
|--|---|--|
| <ul style="list-style-type: none">No recommendations for primary prevention in people > 75 years of age <p>Note: "In persons with diabetes who are >75 years of age statin therapy should be individualized on the basis of considerations of ASCVD risk-reduction benefits, the potential for adverse effects and drug–drug interactions, and patient preferences"</p> | <p>Non raccomandata</p> <p>Da considerare se ad alto rischio CV</p> | <ul style="list-style-type: none">"Statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia" <p>Note: "Since older people often have co-morbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger subjects."</p> |
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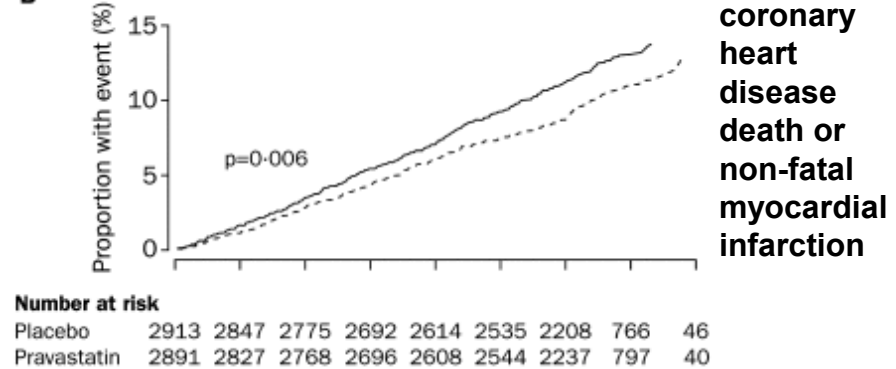
PROSPER

40 mg pravastatin VS PLACEBO

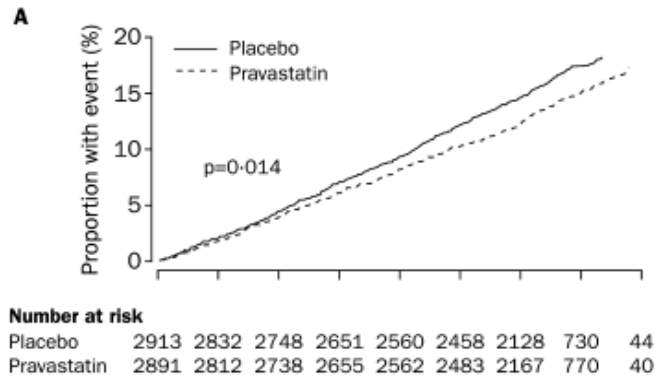
fatal or non fatal stroke



B



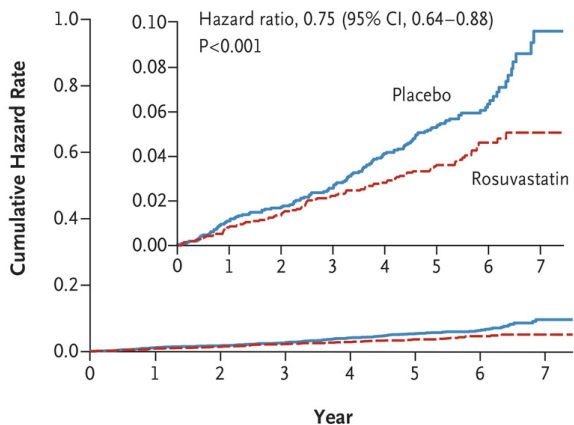
coronary heart disease death, non-fatal myocardial infarction, or fatal or non-fatal stroke



Non riduzione significativa di CHD o Stroke

HOPE-3 (Heart Outcomes Prevention Evaluation)

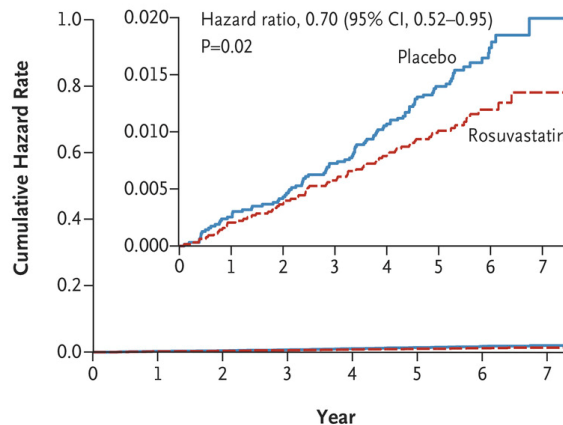
A Second Coprimary Outcome



No. at Risk

| | | | | | | | | |
|--------------|------|------|------|------|------|------|-----|-----|
| Placebo | 2118 | 2083 | 2055 | 2018 | 1967 | 1638 | 674 | 164 |
| Rosuvastatin | 2117 | 2091 | 2068 | 2034 | 1999 | 1662 | 694 | 165 |

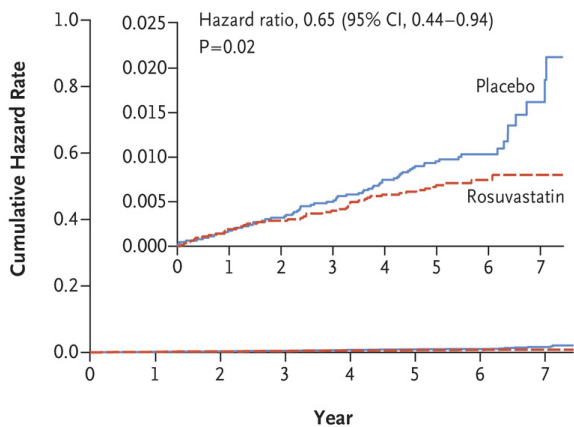
B Stroke



No. at Risk

| | | | | | | | | |
|--------------|------|------|------|------|------|------|------|-----|
| Placebo | 6344 | 6275 | 6210 | 6126 | 6010 | 5013 | 2094 | 505 |
| Rosuvastatin | 6361 | 6308 | 6259 | 6176 | 6069 | 5074 | 2132 | 534 |

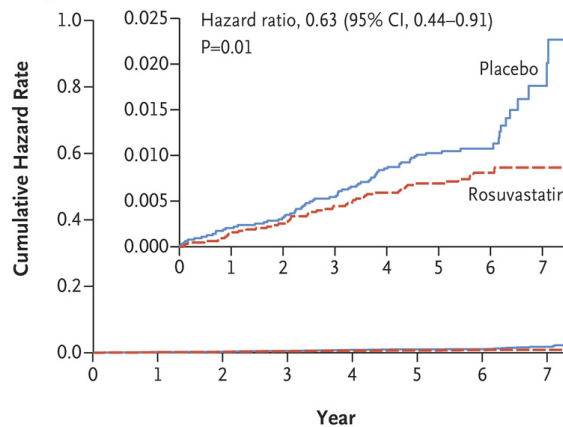
C Myocardial Infarction



No. at Risk

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

D Coronary Revascularization



No. at Risk

| | | | | | | | | |
|--------------|------|------|------|------|------|------|------|-----|
| Placebo | 6344 | 6276 | 6213 | 6127 | 6010 | 5015 | 2085 | 496 |
| Rosuvastatin | 6361 | 6309 | 6259 | 6174 | 6063 | 5069 | 2125 | 530 |

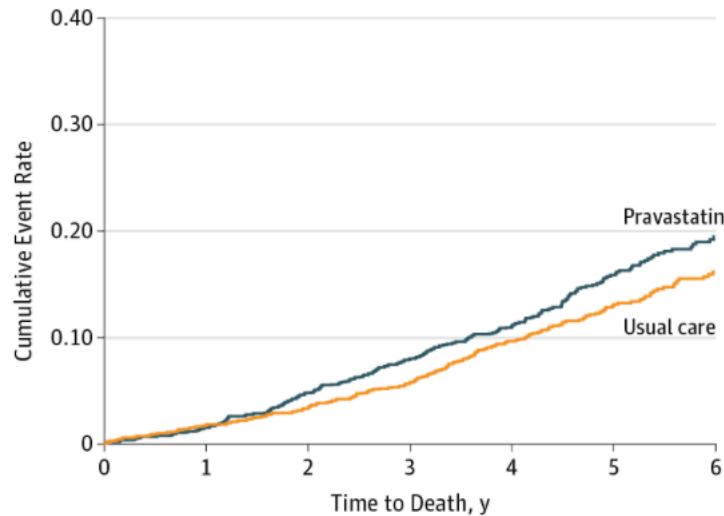
EP composito di morte CV, stroke non fatale o IMA non fatale → ridotto nel gruppo rosuvastatina (3.7% vs 4.8% p < 0.001)

Non differenze in all cause mortality (5.3% vs 5.6%)

ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to Prevent Heart Attack Trial)

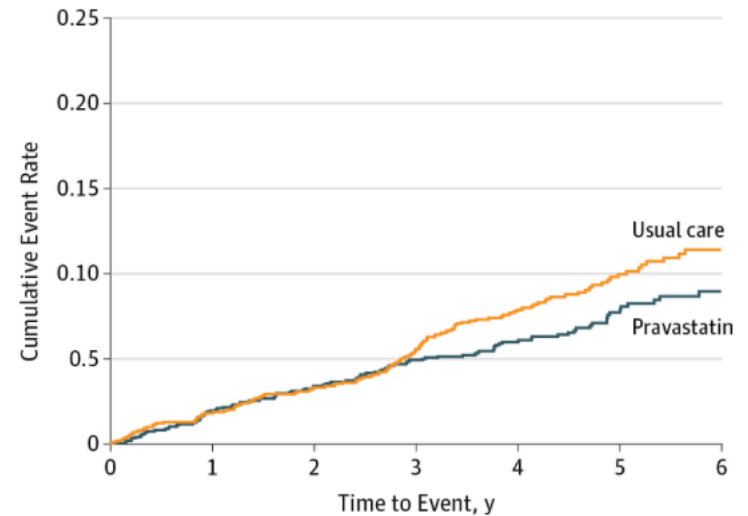
Popolazione generale

A All-cause mortality by treatment group



| No. at risk | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-------------|------|------|------|------|------|-----|-----|
| Pravastatin | 1466 | 1445 | 1395 | 1343 | 1066 | 614 | 326 |
| Usual care | 1400 | 1377 | 1351 | 1313 | 1026 | 622 | 357 |

B CHD rate by treatment group

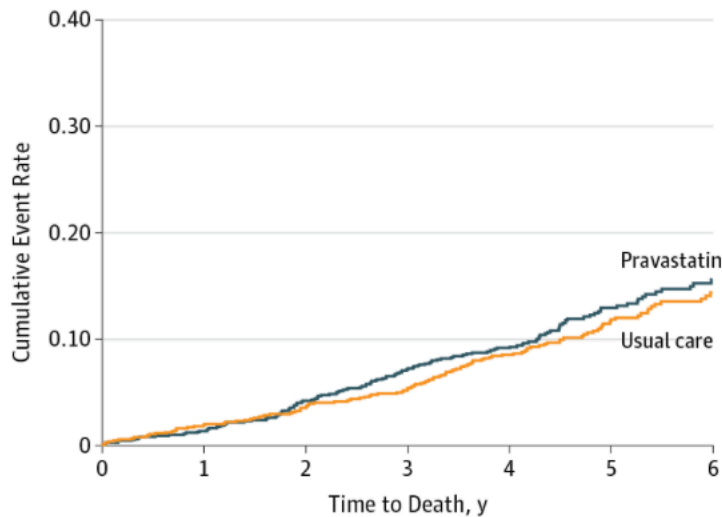


| No. at risk | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-------------|------|------|------|------|-----|-----|-----|
| Pravastatin | 1543 | 1379 | 1316 | 1254 | 986 | 556 | 283 |
| Usual care | 1387 | 1329 | 1281 | 1214 | 930 | 547 | 303 |

ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to Prevent Heart Attack Trial)

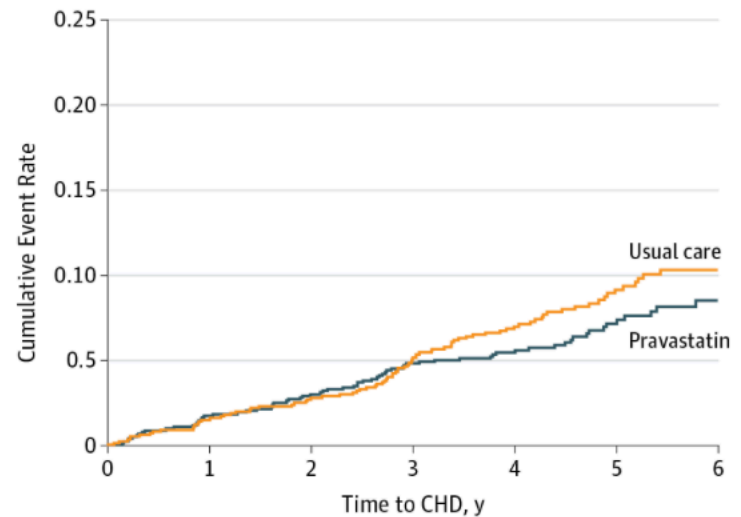
Popolazione 65 – 74 anni

C All-cause mortality by age group 65-74 y



| No. at risk | | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-------------|------|------|------|------|-----|-----|-----|---|
| Pravastatin | 1091 | 1077 | 1044 | 1007 | 810 | 478 | 263 | |
| Usual care | 1049 | 1031 | 1012 | 991 | 787 | 493 | 295 | |

D CHD rate by age group 65-74 y



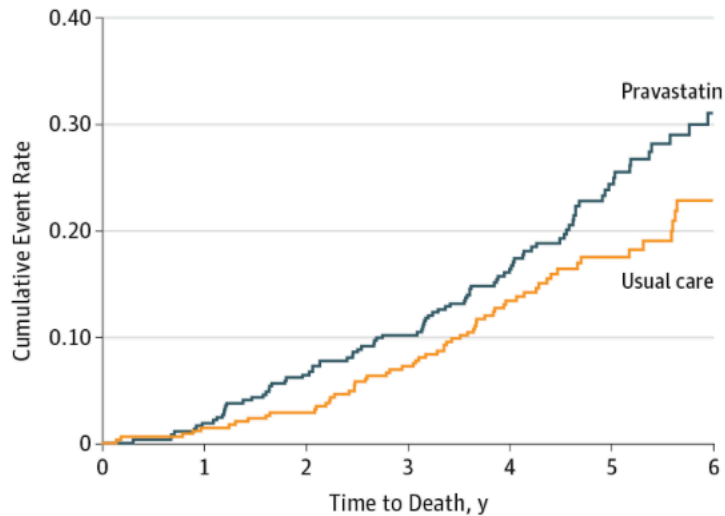
| No. at risk | | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-------------|------|------|-----|-----|-----|-----|-----|---|
| Pravastatin | 1081 | 1029 | 988 | 943 | 750 | 432 | 226 | |
| Usual care | 1042 | 1004 | 972 | 926 | 728 | 442 | 258 | |

Non riduzione della mortalità per tutte le cause o eventi CHD

ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to Prevent Heart Attack Trial)

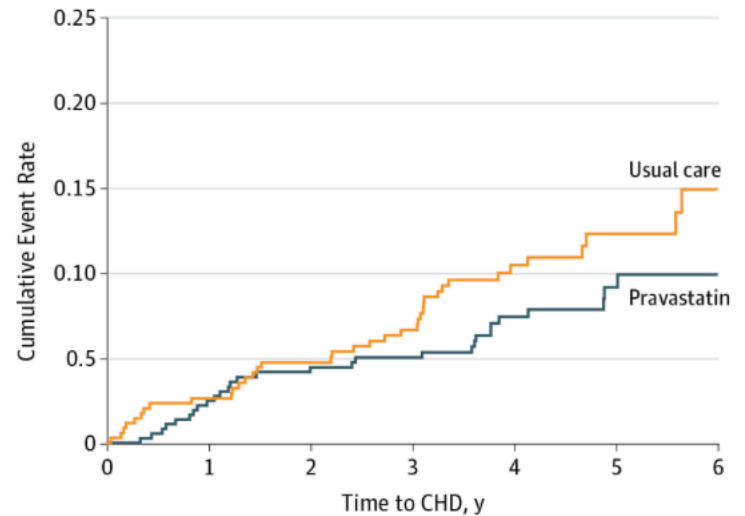
Popolazione over 75

E All-cause mortality by age group ≥ 75 y



| No. at risk | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-------------|-----|-----|-----|-----|-----|-----|----|
| Pravastatin | 375 | 368 | 351 | 336 | 256 | 136 | 63 |
| Usual care | 351 | 346 | 339 | 322 | 239 | 129 | 62 |

F CHD rate by age group ≥ 75 y



| No. at risk | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-------------|-----|-----|-----|-----|-----|-----|----|
| Pravastatin | 372 | 350 | 328 | 311 | 236 | 124 | 57 |
| Usual care | 345 | 325 | 309 | 288 | 202 | 105 | 45 |

Un lieve aumento della mortalità per tutte le cause negli over 75

Analisi post-hoc

ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm)

63% di pz over 60

Atorvastatina

Significantly reduced nonfatal MI and fatal CHD

JUPITER

5695 pz anziani (1/3 della popolazione totale dello studio)

Rosuvastatina

**A non-statistically significant difference in all cause mortality
(p = 0.09)**

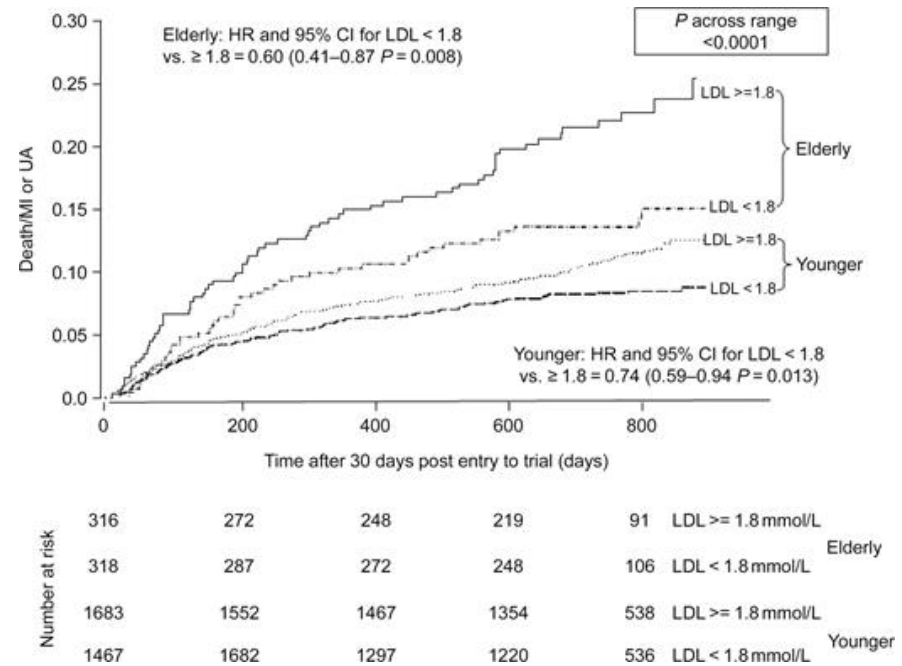
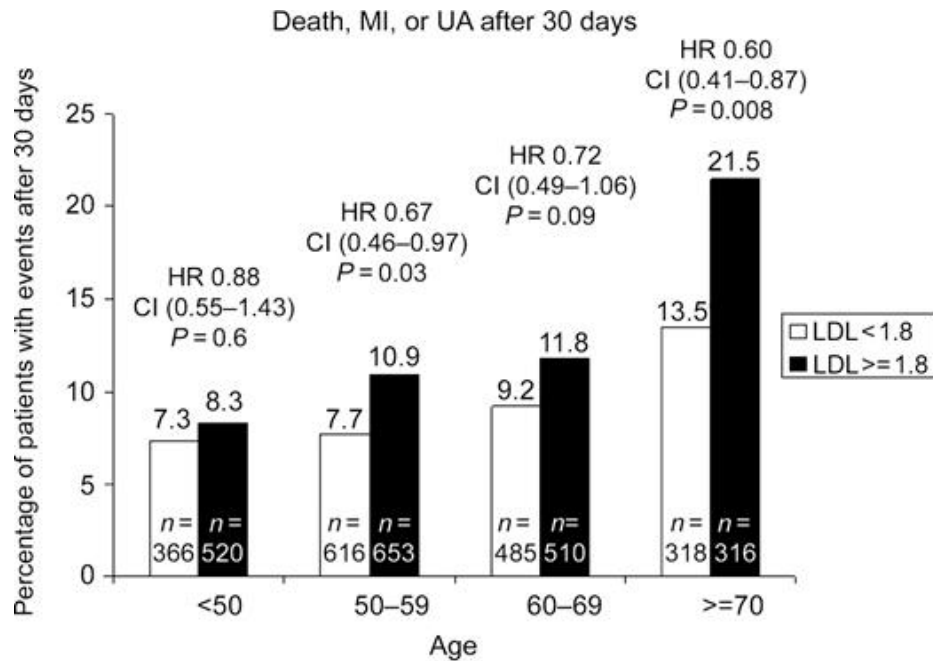
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PROVE-IT (The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction)

730 patients aged ≥ 70 years

3150 younger



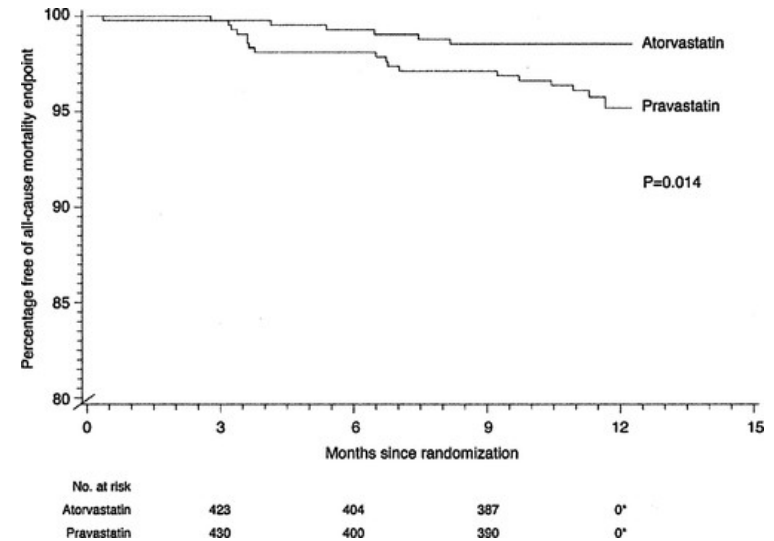
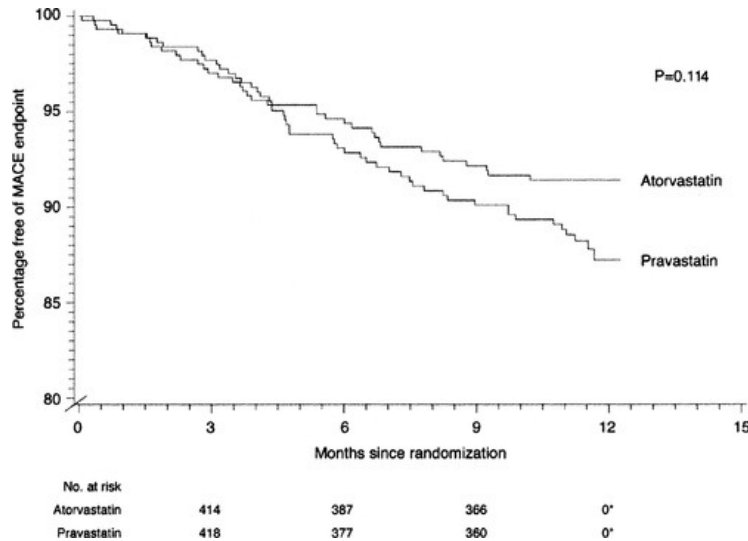
LDL-C target (< 70 mg/dl) associato a una **riduzione dell'8% del rischio assoluto e del 40% del rischio relativo di eventi** (morte, IMA o angina instabile) negli **over 70**
VS

2.3 and 26% negli **under 70**

The SAGE (Study Assessing Goals in the Elderly) trial

66–85 anni,

intensive vs moderate statin therapy (atorvastatin 80 mg vs pravastatin 40 mg/die)



- **Maggior riduzione LDL-C**
- **Trend verso riduzione di eventi CV maggiori**
- **Riduzione significativa di all-cause mortality**

SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)

Analisi post-hoc, sottogruppo di 4731 pazienti

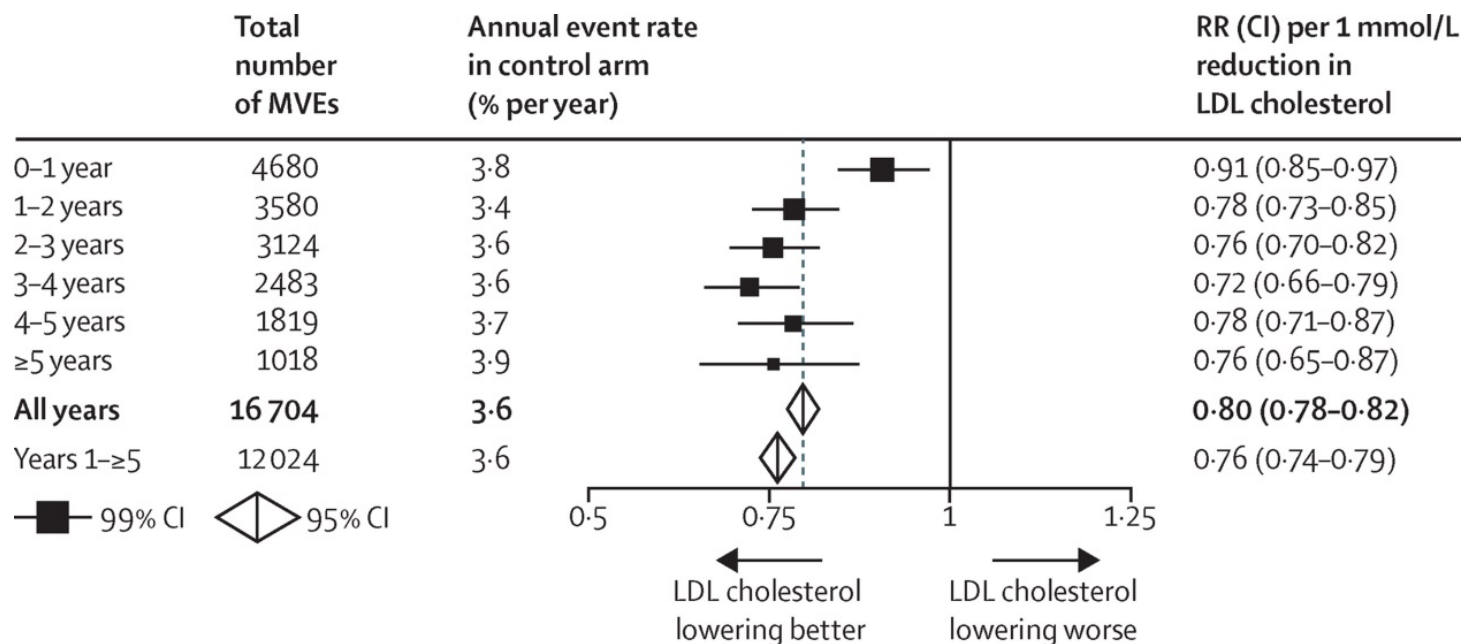
Riduzione del rischio assoluto di Stroke fatale o non fatale
(primary endpoint)

1.5% negli over 65 anni

2.6% negli under 65 anni

Higher dose statins vs control or lower

Beneficio della terapia ipolcosterolemizzante con statine...



... Ma per ogni riduzione di LDL di 1 mmol/L:

- **Over 65** → riduzione degli eventi maggiori del 13%

- **Under 65** → riduzione del 22%

Primary and secondary prevention

The HPS (Heart Protection Study) trial

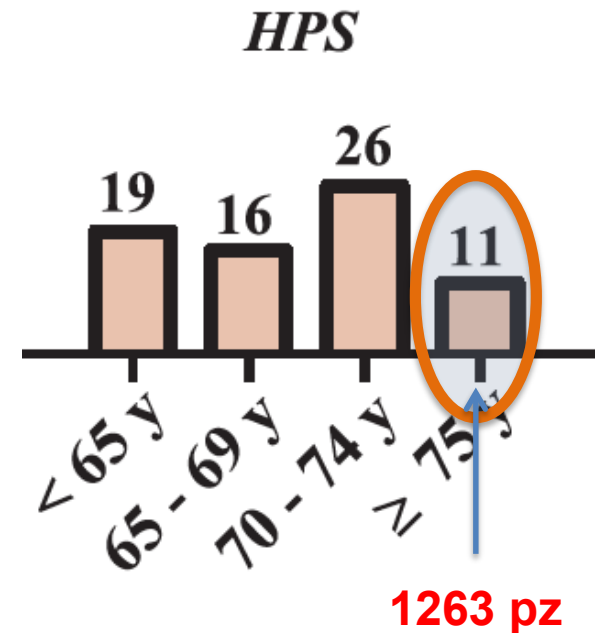
20,536 pazienti 40–80 anni ad elevato rischio CV

Simvastatina 40 mg

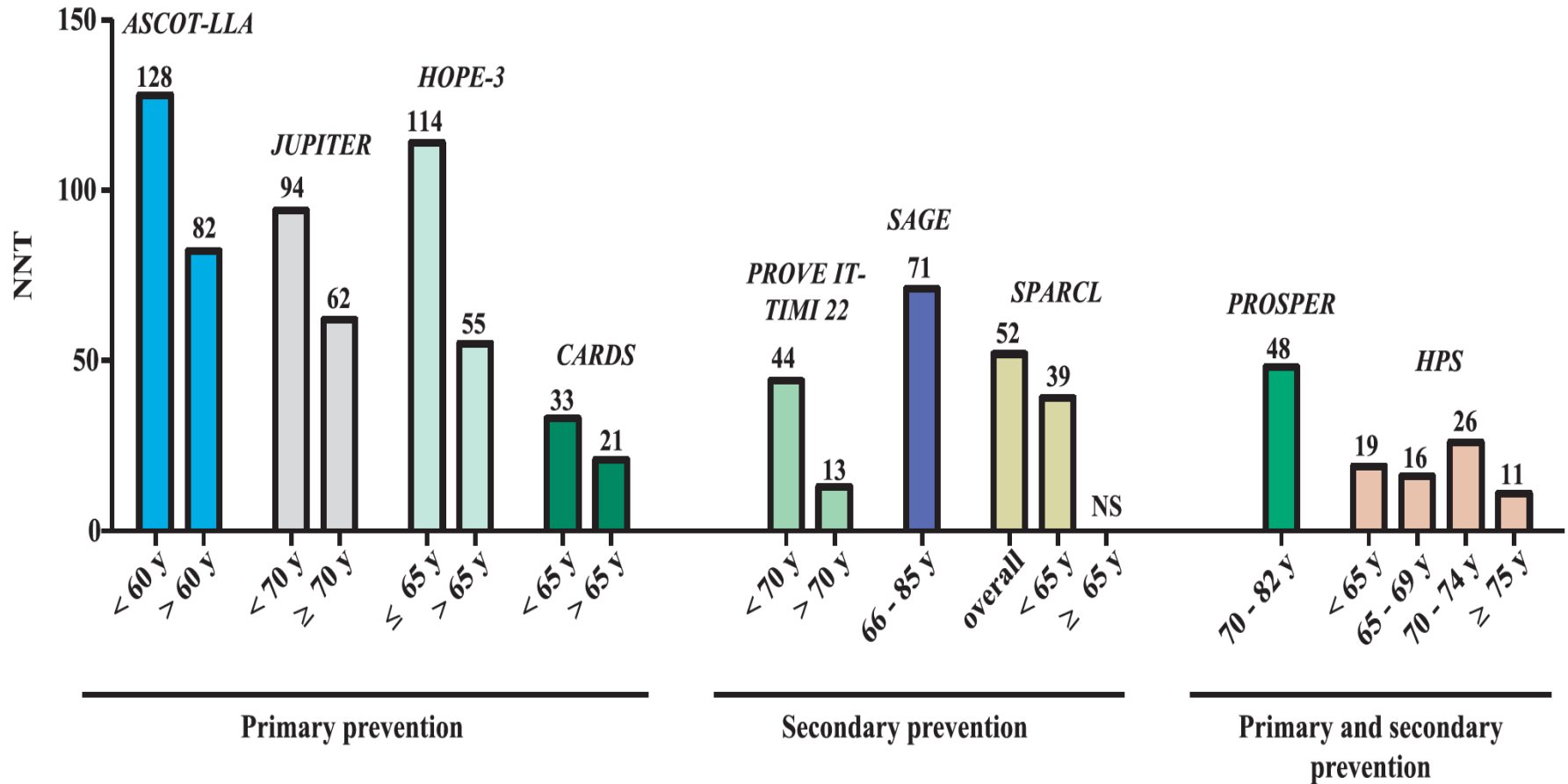
Riduzione di all-cause mortality del 13%,
maggiormente legata alla riduzione del 17%
degli eventi coronarici

5806 over 70

**Eventi CV ridotti del 23% nel gruppo
simvastatina vs 32% for placebo**



Primary and secondary prevention



RISULTATI CONTROVERSI DAI VARI TRIAL

Come comportarsi?



Meccanismi complessi e ancora non del tutto chiariti.

Alti livelli di colesterolo → marker di **“successful aging”**

- Migliore stato nutrizionale
- Minore disfunzione epatica
 - Minore fragilità

Un più alto colesterolo totale associato a un minor rischio di mortalità non cardiovascolare negli anziani.

Rachel S. Newson PhD et al. Journal of American Geriatric Society 2011

SAFETY

Potenziali interazioni farmacologiche (farmaci, vitamine, minerali, nutraceutici, rimedi erboristici o succhi di frutta, in particolare succo di pompelmo)

Mialgie dose-dipendenti negli individui anziani

Non effetti avversi delle statine sulla **capacità cognitiva**

CONCLUSIONI

Pazienti di età inferiore a 75 anni → Beneficio
(prevenzione secondaria)



Pazienti di età superiore a 85 ANNI → pochi dati,
controversi (**Non indicata**)

Tra 75 e 85 anni?



ZONA GRIGIA

valutare età biologica



Scarsa tollerabilità (evitare alti dosaggi/alta intensità)

Rapporto rischio/beneficio

Interazioni farmacologiche

Anti-PCSK9 ...

**Blocco del sistema ALFA per i
pazienti di età superiore a 80 anni**

**Ancora pochi dati nella popolazione
over 65**

Grazie per l'attenzione



Riccardo Raddino

