Il punto di vista del cardiologo:

Dal colesterolo allo screening del NT-proBNP

Dario Celentani – S.C. Cardiologia RIVOLI

Conflitto d’interessi

Il sottoscritto dichiara di aver avuto rapporti di carattere economico negli ultimi 5 anni con i seguenti portatori d’interessi in campo sanitario:

- Amgen
- Astra-Zeneca
- Aurora Biofarma
- Bayer
- Boehringer Ingelheim
- Bracco
- Daiichi Sankyo
- Firma
- Guidotti
- Lilly italia
- Lusofarmaco
- Menarini
- Neopharmed Gentili
- Novartis
- Novo Nordisk
- Pfizer
- Sandoz
- Sanofi
- Servier
- Viatris

2023 -2024

3 Cite Share

Safety and Efficacy of the Consumption of the Nutraceutical "Red Yeast Rice Extract" for the Reduction of Hypercholesterolemia in Humans: A Systematic Review and Meta-Analysis.

Trogkanis E, Karalexi MA, Sergentanis TN, Kornarou E, Vassilakou T.

Nutrients. 2024 May 11;16(10):1453. doi: 10.3390/nu16101453.

PMID: 38794691 Free PMC article. Review.

75 Cite

Zinc Supplementation in Individuals with Prediabetes and type 2 Diabetes: a GRADE-Assessed Systematic Review and Dose-Response Meta-analysis.

Nazari M, Nikbaf-Shandiz M, Pashayee-Khamene F, Bagheri R, Goudarzi K, Hosseinnia NV, Dolatshahi S,

11-023-03895-7. Epub 2023 Oct 23.

21 Cite

Efficacy of oats in **dyslipidemia**: a systematic review and meta-analysis.

Li A, Gao J, Li Y, Qi S, Meng T, Yu S, Zhang Y, He Q.

Food Funct. 2024 Apr 2;15(7):3232-3245. doi: 10.1039/d3fo04394k.

PMID: 38441173 Review.

However, no systematic reviews summarized the effect of daily consumption of oat-based products on serum lipids in patients with **dyslipidemia**. Methods: We searched eight databases and two clinical trial registries from inception to July 31, 2023. ...Conclusions: Oat-based ...

sease (CVD) risk factors, including

ributors to CVD pathogenesis. ...

15 Cite Share

Effects of Melissa officinalis (lemon balm) consumption on serum lipid profile: a meta-analysis of randomized controlled trials.

Shahsavari K, Shams Ardekani MR, Khanavi M, Jamialahmadi T, Iranshahi M, Hasanpour M.

BMC Complement Med Ther. 2024 Apr 4;24(1):146. doi: 10.1186/s12906-024-04442-0.

PMID: 38575930 Free PMC article.

Therefore, its use as a cardiovascular remedy may explain the lipid-lowering effects of lemon balm. **Dyslipidemia** can be considered as a significant preventable risk factor for atherosclerosis, coronary heart disease and type 2 diabetes. ...This study reinforces the notion ...

41 Cite Share

Meta-analysis of the intervention effects of tai chi on fasting blood glucose, blood pressure and triglyceride in middle-aged and elderly people.

Zhao W, Ju H, Zhu K.

Aging Male. 2024 Dec;27(1):2282977. doi: 10.1080/13685538.2023.2282977. Epub 2024 Jan 23.

60 Cite Share

Effect of camel milk on lipid profile among patients with diabetes: a systematic review, meta-analysis, and meta-regression of randomized controlled trials.

Khalid N, Abdelrahim DN, Hanach N, AlKurd R, Khan M, Mahrous L, Radwan H, Naja F, Madkour M, Obaideen K, Khraiwesh H, Faris M.

BMC Complement Med Ther. 2023 Dec 4;23(1):438. doi: 10.1186/s12906-023-04257-5.

PMID: 38049802 Free PMC article.

59 Cite Share

The Antiobesity Effects and Potential Mechanisms of *Theaflavins*.

Fang Y, Wang J, Cao Y, Liu W, Duan L, Hu J, Peng J.

J Med Food. 2024 Jan;27(1):1-11. doi: 10.1089/jmf.2023.K.0180. Epub 2023 Dec 7.

PMID: 38060708 Review.

In this review, the effects and molecular mechanisms of theaflavins on obesity and its comorbidities,

76 Cite Share

Effects of sumac supplementation on lipid profile: A systematic review and meta-analysis of randomized controlled trials.

Bahari H, Taheri S, Namkhah Z, Barghchi H, Arzhang P, Nattagh-Eshtivani E.

Phytother Res. 2024 Jan;38(1):241-252. doi: 10.1002/ptr.8046. Epub 2023 Oct 21.

72 Cite Share

The effect of phytosterol supplementation on lipid profile: A critical umbrella review of interventional meta-analyses.

Wang L, Feng L, Prabahar K, Hernández-Wolters B, Wang Z.

Phytother Res. 2024 Feb;38(2):507-519. doi: 10.1002/ptr.8052. Epub 2023 Oct 31.

PMID: 37905579 Review.

Despite multiple investigations assessing the impact of phytosterol supplementation on serum lipid levels, there is still a great deal of debate regarding the benefits of this intervention in the management of **dyslipidemia**. Therefore, we aimed at clarifying this dilemma by ...

77 Cite Share

Potential Value of Probiotics on Lipid Profiles in Hyperlipidemia and Healthy Participants: Systematic Review and Meta-Analysis.

Su D, Liu Y, Zhang L, Zhao S, Wang Y, Bian R, Xu B, Chen X, Xu X.

Altern Ther Health Med. 2024 Feb;30(2):84-89.

PMID: 37856800 Free article.

84 Cite Share

Effect of Alpha-Linolenic Acid Supplementation on Cardiovascular Disease Risk Profile in Individuals with Obesity or Overweight: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Yin S, Xu H, Xia J, Lu Y, Xu D, Sun J, Wang Y, Liao W, Sun G.

Adv Nutr. 2023 Nov;14(6):1644-1655. doi: 10.1016/j.advnut.2023.09.010. Epub 2023 Sep 29.

PMID: 37778442 Free PMC article. Review.

Overweight and obesity are highly prevalent worldwide and are associated with cardiovascular disease (CVD) risk factors, including systematic inflammation, **dyslipidemia**, and hypertension. Alpha-linolenic acid (ALA) is a plant-based essential polyunsaturated fatty acid asso ...

L. barbarum (Lycium barbarum L.) supplementation for lipid profiles in adults: A systematic review and meta-analysis of RCTs.

Zeng X, Zhao W, Wang S, Xiong H, Wu J, Ren J.

Medicine (Baltimore). 2023 Sep 29;102(39):e34952. doi: 10.1097/M

PMID: 37773857 Free PMC article.

BACKGROUND: **Dyslipidemia** is a global health concern with an i

97 Cite Share

The effect of cinnamon consumption on lipid profile, oxidative stress, and inflammation biomarkers in adults: An umbrella meta-analysis of randomized controlled trials.

Sarmadi B, Musazadeh V, Dehghan P, Karimi E.

Nutr Metab Cardiovasc Dis. 2023 Oct;33(10):1821-1835. doi: 10.1016/j.numecd.2023.03.010. Epub 2023 Mar 18.

PMID: 37500345

20 Efficacy of Inclisiran in Patients Having Familia
Heterozygous Compared to Homozygous Tra
analysis.
Cite
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Rai R, Devi P, Kumar K, Naeem K, Kumar H, Kumari K, Kum
G, Ali S, Maheshwari M, Jawwad M.

96 Efficacy of Pemafibrate Versus Fenofibrate Administration on Serum Lipid Levels in Patients with **Dyslipidemia**: Network Meta-Analysis and Systematic Review.
Cite
Share
Khan MS, Ghumman GM, Baqi A, Shah J, Aziz M, Mir T, Tahir A, Katragadda S, Singh H, Taleb M, Ali SS.
Am J Cardiovasc Drugs. 2023 Sep;23(5):547-558. doi: 10.1007/s40256-023-00593-6. Epub 2023 Jul 31.
PMID: 37524955
We performed the first ever network meta-analysis containing the largest ever group of patients to test
roving lipid levels compared with fenofibrate and placebo in patients
tentially relevant clinical trials ...

101 Cardiovascular events in patients treated with bempedoic acid vs. placebo: systematic review and meta-analysis.
Cite
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Mutschlechner D, Tscharre M, Huber K, Gremmel T.
Eur Heart J Cardiovasc Pharmacother. 2023 Sep 20;9(6):583-591. doi: 10.1093/ehjcvp/pvad052.
PMID: 37463824

an I, Trifan G.
):107633. doi: 10.1016/j.jstrokecerebrovasdis.2024.107633. Epub

43 After Acute Coronary Syndrome: A Meta-analysis of R

38 Safety and efficacy of bempedoic acid among patients with statin intolerance and those without: A meta-analysis and a systematic randomized controlled trial

1371/journal.pone.0297854. eCollection 2024.

117 Association Between Omega-3 Fatty Acid Intake and **Dyslipidemia**: A Continuous Dose-Response Meta-Analysis of Randomized Controlled Trials.
Cite
Share
Wang T, Zhang X, Zhou N, Shen Y, Li B, Chen BE, Li X.
J Am Heart Assoc. 2023 Jun 6;12(11):e029512. doi: 10.1161/JAHA.123.029512. Epub 2023 Jun 2.
PMID: 37264945 **Free PMC article.**

ating Adipokine Levels: A Systematic Review
linical Trials.
Cite
Share
Simental-Mendía LE, Simental-Mendía M, Sahebkar A, Atkin SL, Jamialahmadi T.
Arch Med Res. 2024 Feb;55(2):102957. doi: 10.1016/j.arcmed.2024.102957. Epub 2024 Jan 24.
PMID: 38266418
BACKGROUND: Fibrates are widely used in the treatment of **dyslipidemia** and associated metabolic abnormalities; however, their effects on adipokines are unclear. ...

MY NCBI FILTERS

RESULTS BY YEAR

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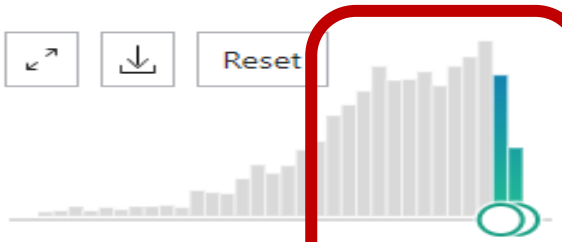

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127 results

Page 1 of 1

Filters applied: Meta-Analysis, in the last 1 year. Clear all

1 Cite Share

A Systematic Review and Meta-analysis of the Relationship between **Statin** Intake and Esophageal Cancer.

Khaghani A, Kasiri K, Heidari-Soureshjani S, Sherwin CM, Mardani-Nafchi H.

Anticancer Agents Med Chem. 2024 May 29. doi: 10.2174/0118715206292712240522043350. Online ahead of print.

PMID: 38812422

CONCLUSION: The results revealed that the odds of esophageal cancer in patients treated with **statins** decreased by 35% compared to patients not treated with **statins**. However, further well-designed prospective studies are needed to validate these findings and understa ...

2 Cite Share

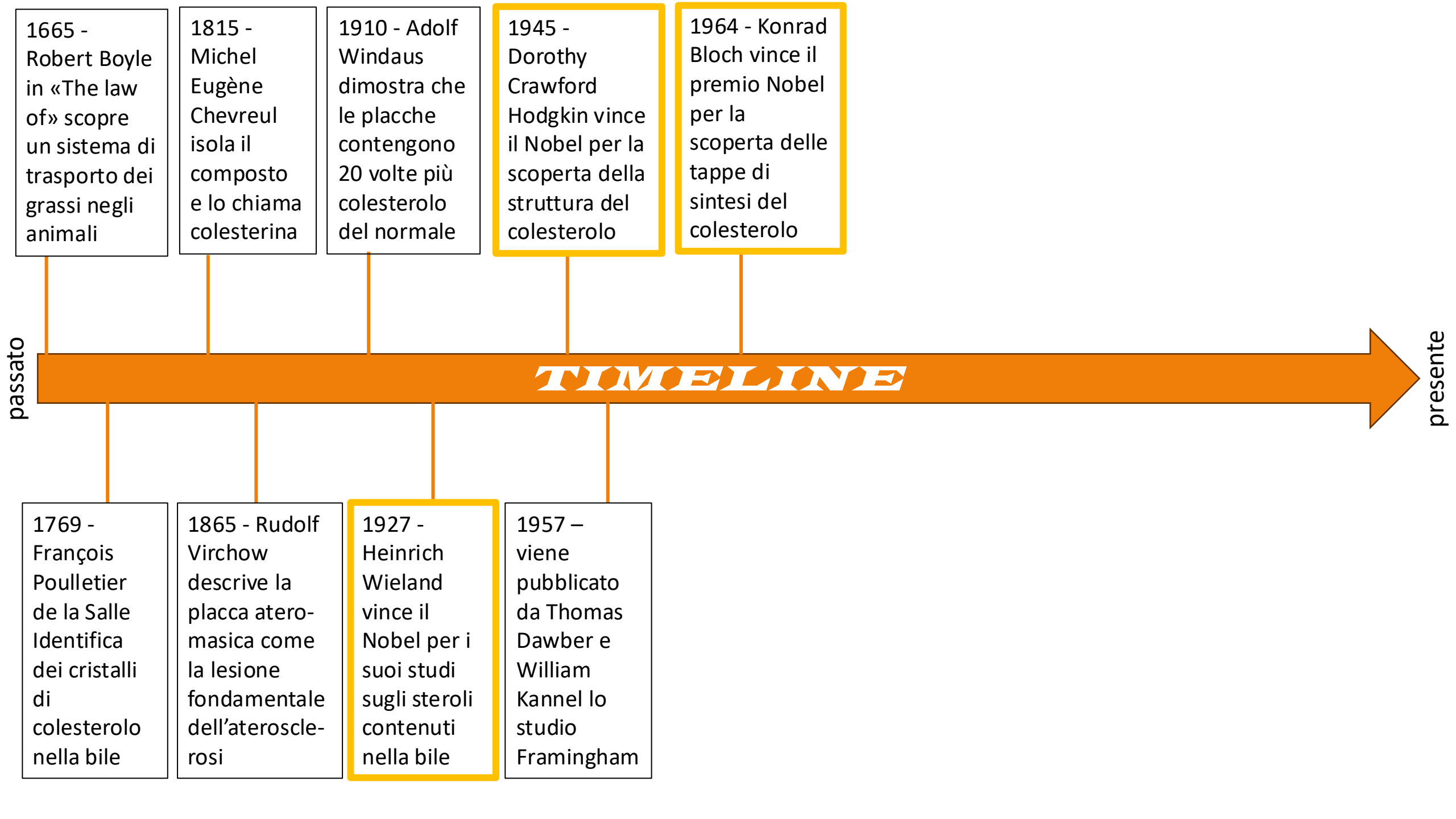
HMG-CoA **reductase** is a potential therapeutic target for migraine: a mendelian randomization study.

Qu K, Li MX, Yu P; International Headache Genetics Consortium; Wu BH, Shi M, Dong M.

Sci Rep. 2024 May 27;14(1):12094. doi: 10.1038/s41598-024-61628-9.

PMID: 38802400 Free PMC article.

Statins are thought to have positive effects on migraine but existing data are inconclusive. ...We used four types of genetic instruments as proxies for HMG-CoA **reductase** inhibition. We included the expression quantitative trait loci of the HMG-CoA **reductase** ...


1665 - Robert Boyle in «The law of» scopre un sistema di trasporto dei grassi negli animali
1815 - Michel Eugène Chevreul isola il composto e lo chiama colesterina
1910 - Adolf Windaus dimostra che le placche contengono 20 volte più colesterolo del normale
1945 - Dorothy Crawford Hodgkin vince il Nobel per la scoperta della struttura del colesterolo
1964 - Konrad Bloch vince il premio Nobel per la scoperta delle tappe di sintesi del colesterolo
passato
TIMELINE
presente
1769 - François Poulletier de la Salle Identifica dei cristalli di colesterolo nella bile
1865 - Rudolf Virchow descrive la placca atero-masica come la lesione fondamentale dell'ateroscle-rosi
1927 - Heinrich Wieland vince il Nobel per i suoi studi sugli steroli contenuti nella bile
1957 – viene pubblicato da Thomas Dawber e William Kannel lo studio Framingham

A more highly developed enzymology of the cholesterol pathway is also needed for a rational approach to the problem of metabolic regulation. This is clearly a matter of broad concern transcending purely academic curiosity. A great variety of environmental, dietary and hormonal factors have been studied and shown to influence the rate of cholesterol synthesis, but the evidence is still too scanty for specifying the point or points at which physiological control is most effectively exerted. If the principle of negative feedback operates in sterol biosynthesis as it does in so many pathways, then the first specific step of the sequence should be rate limiting and it should be sensitive to cholesterol, the end product of the biosynthetic sequence. With these considerations in mind, attention has been focused on the reduction of hydroxymethylglutaryl-CoA to mevalonic acid as a likely control site. There is experimental support for this view, particularly from the work of Bucher who has shown that the profound effects of cholesterol feeding, of X-radiation and of starvation on the rates of cholesterol synthesis appear indeed to be exerted at a stage close to or immediately before the formation of mevalonic acid[*]. This concept of a homeostatic control continues to receive attention", and it is to be hoped that the rapid progress that is being made in the elucidation of regulatory processes will lead also to a better understanding of the mechanisms that control cholesterol biosynthesis.

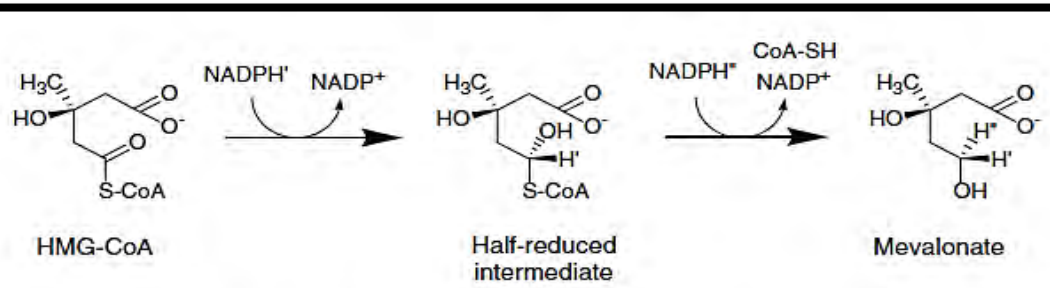
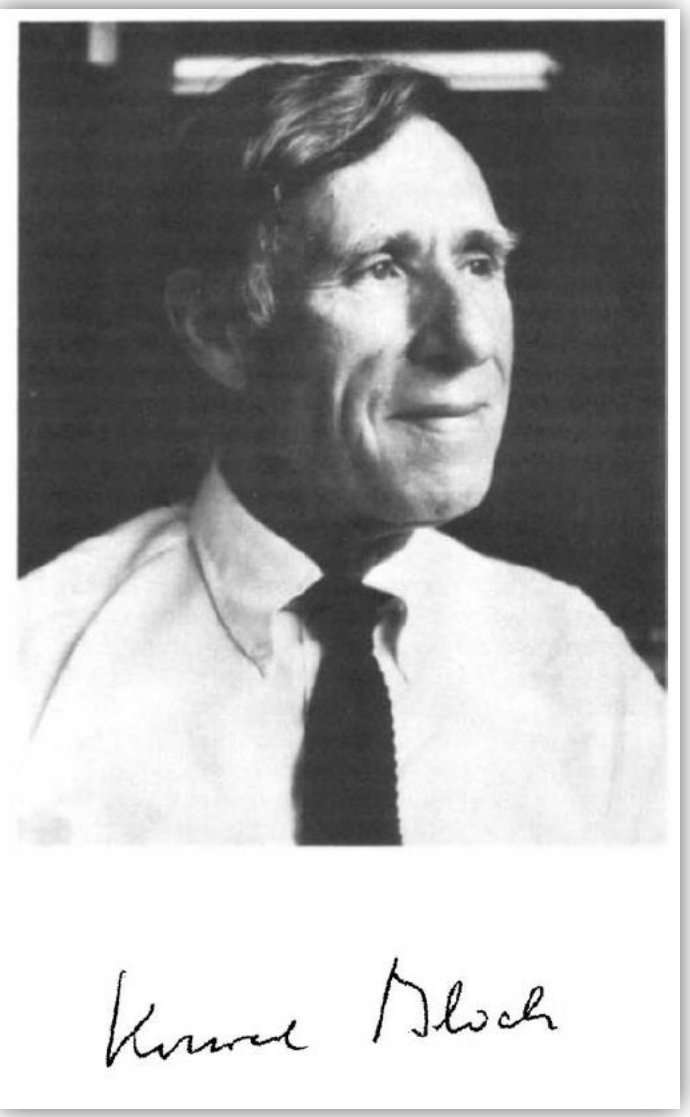


Fig. 1. HMG-CoA reductase reaction.

Along with the interest in chemical and enzymatic aspects of cholesterol biosynthesis there has been a growing appreciation of the role which sterols might play as fundamental cell constituents. The known metabolic transformations of cholesterol, the conversions to steroid hormones and bile acids, surely serve a specialized function since they take place only in vertebrate species. However, in many tissues and cells the function ofcholesterol is clearly not metabolic. In organisms which do not metabolize sterol but nevertheless produce or require it-and this is true for all but the most primitive forms of life-sterols must play some role as structural elements of the cell. Comparative biochemistry suggests what this function might be. Sterols have not been found in any bacteria or in the blue-green algae, *i.e.* in primitively organized cells which lack the various membrane-bound intracellular organelles. The elaboration of membrane-enclosed structures devoted to specialized functions is now viewed as a landmark in evolutionary diversification[78] and it would appear that the parallel development of the biosynthetic pathway to sterols is one of the biochemical expressions of these morphological events. The sterol molecule is not distributed at random inside the differentiated cell but appears to be mainly associated with the cytoplasmic membrane and its endoplasmic extensions. We do not yet know why and for what specific purpose the sterol molecule was selected during the evolution of organisms. One may speculate, however, that the rigidity, the planarity and the hydrophobic nature of the molecule provide a combination of features that is uniquely suitable for strengthening the otherwise fragile membrane of the more highly developed cell.



1912 – 2000 ; Premio Nobel per la medicina 1964

The third reaction in the first stages is the committed and rate-limiting step: reduction of HMG-CoA to mevalonate is the major point of regulation on the pathway to cholesterol (Fig. 1). The major outlines of this pathway were completed by 1960, and Bloch and Lynen were awarded the Nobel Prize in 1964.

At the Nobel Banquet in Stockholm, December 10, 1964 when Konrad Bloch and Feodor Lynen, were awarded the Nobel Prize, S. Friberg, Rector of the Caroline Institute, made the following remarks: "Your discoveries may provide us with weapons against some of mankind's gravest maladies, above all in relation to cardiovascular diseases. Achievements like yours make it not unrealistic to look forward to a time, when mankind will not only live under vastly improved conditions, but will itself be better".[20]

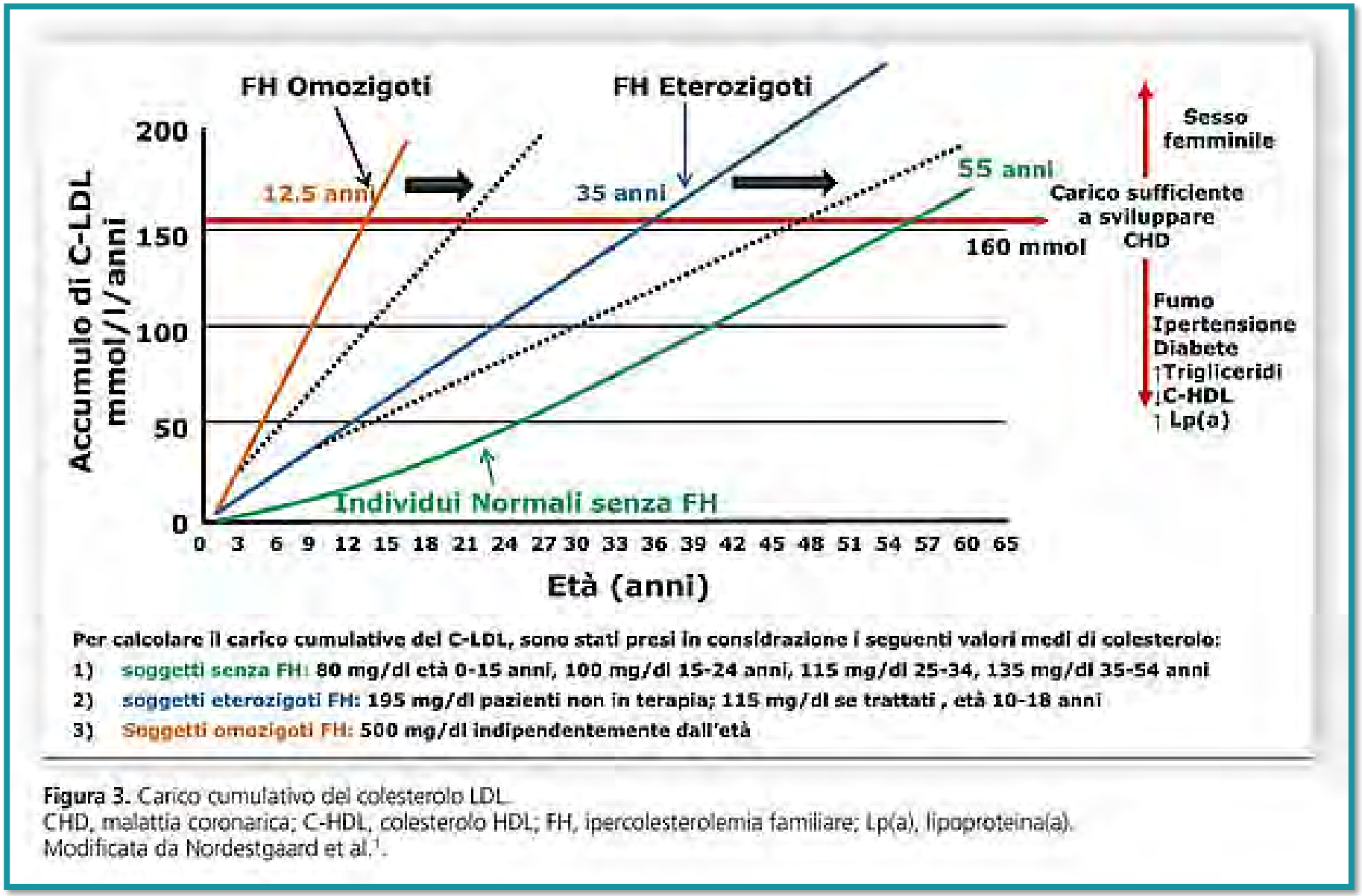
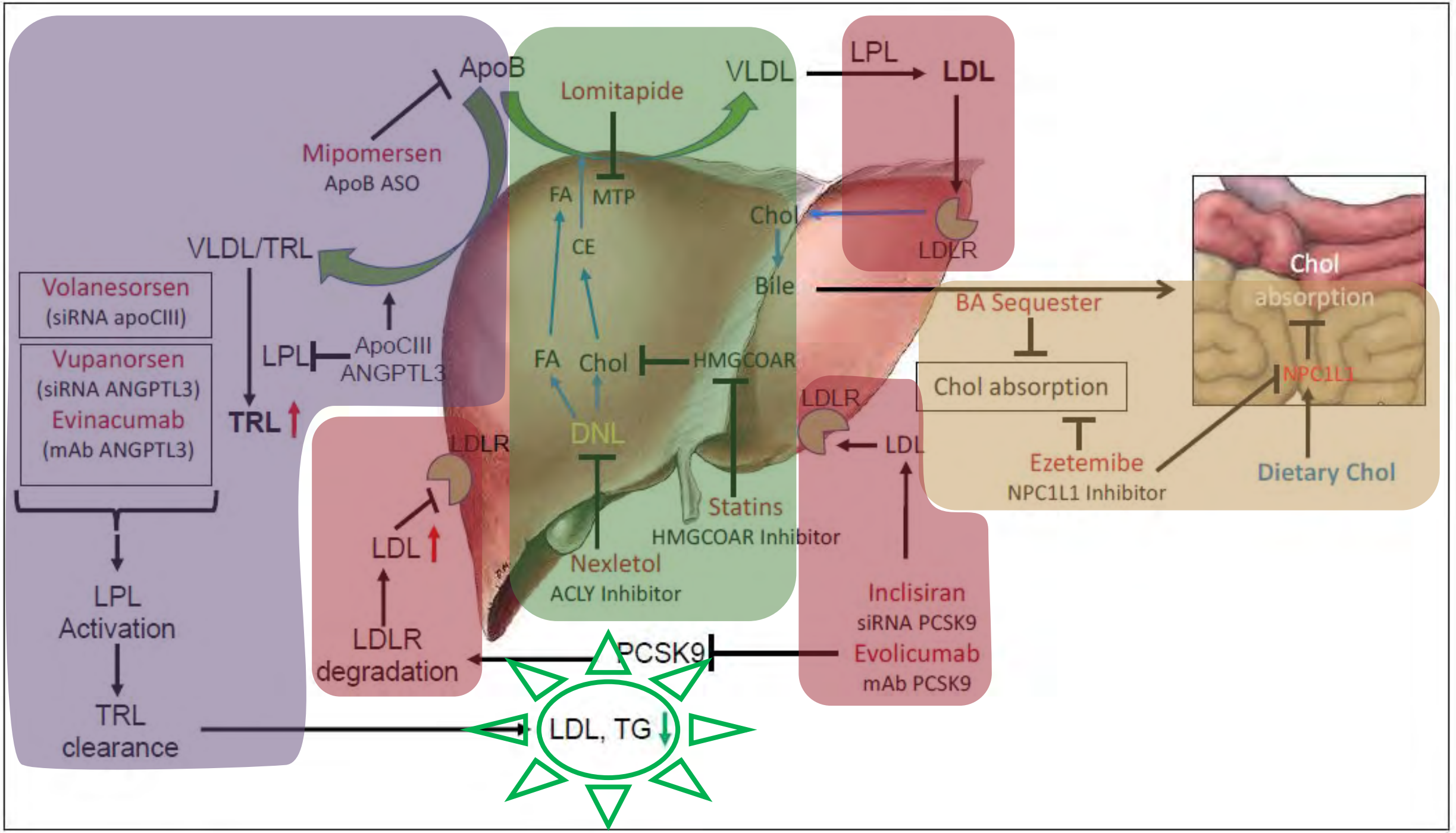
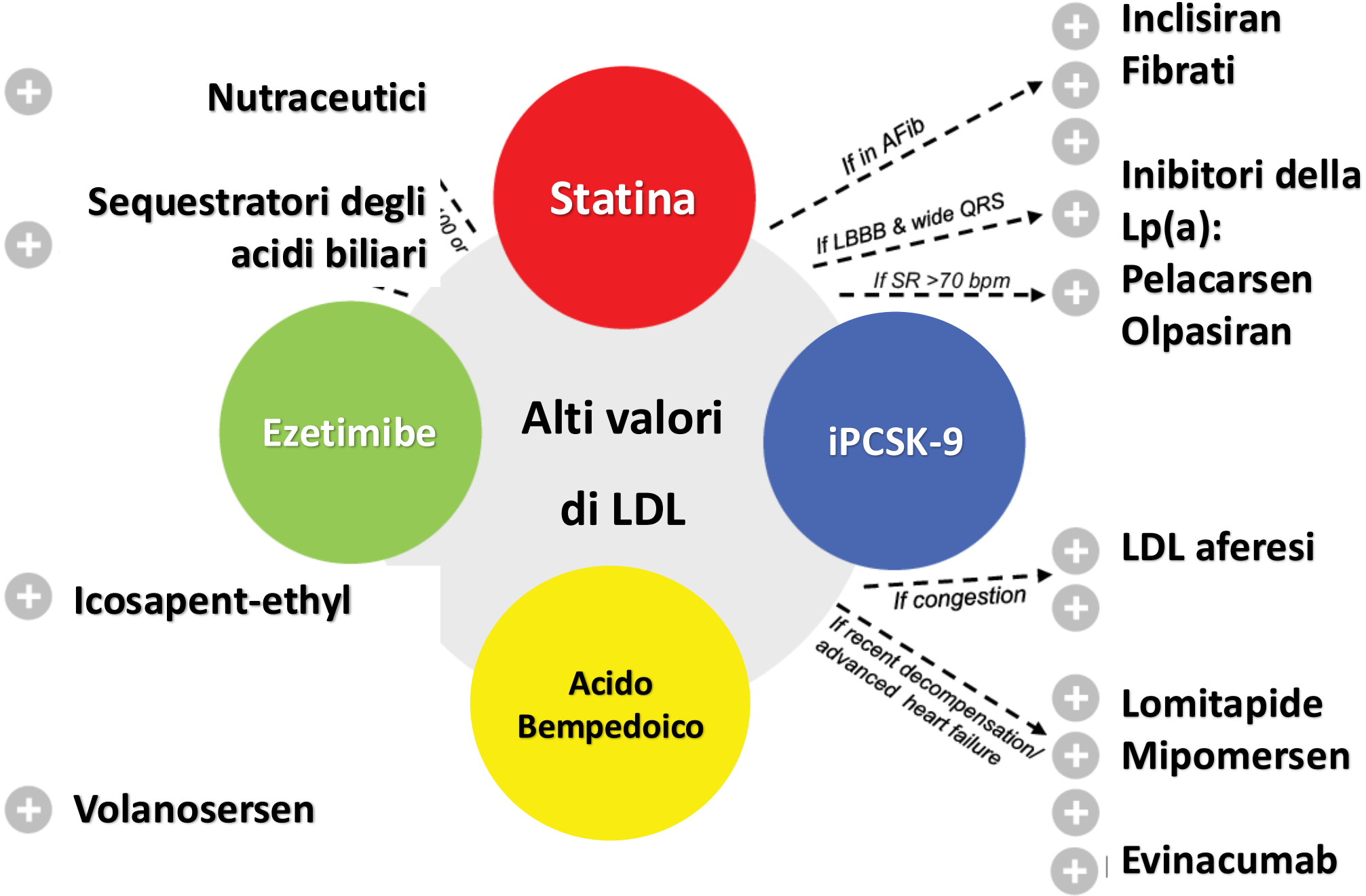


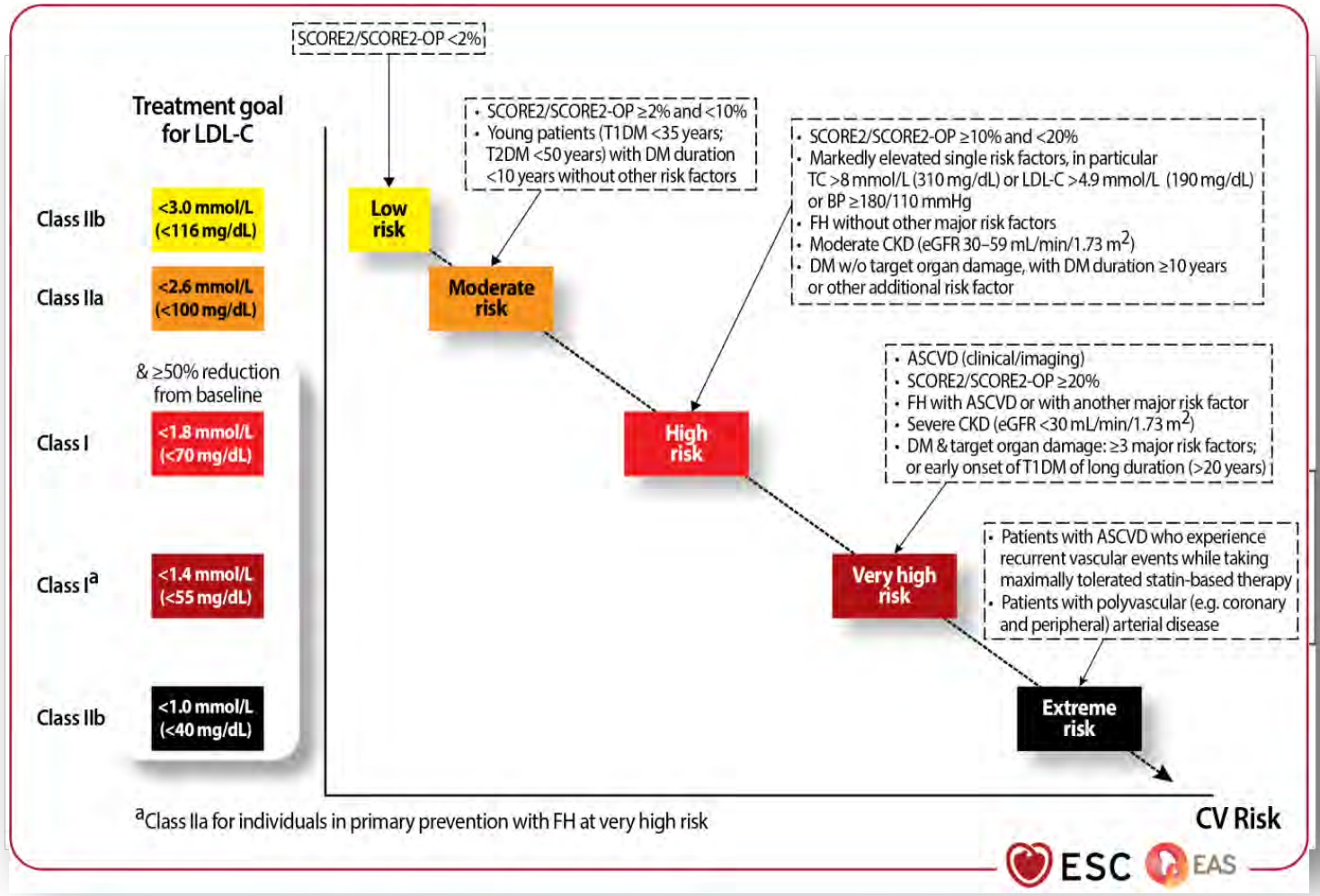
Figura 3. Carico cumulativo del colesterolo LDL.
CHD, malattia coronarica; C-HDL, colesterolo HDL; FH, ipercolesterolemia familiare; Lp(a), lipoproteina(a).
Modificata da Nordestgaard et al.[1].

Drug Name	Drug Class	Primary Endpoint	Mechanism	Refs.
Statins	LDL lowering	LDL	HMG-CoA Inhibitor	[27,28]
Cholestyramine	Bile acid sequestrants	LDL	Bile acid binding	[32,33]
Apheresis		LDL	Apheresis	[78]
Niacin	LDL lowering	TG, LDL HDL	DGAT2 Inhibitor	[34,35]
Ezetimibe	LDL Lowering	LDL	NPC1L1 inhibitor	[29,30]
Lomitapide	LDL lowering	VLDL, LDL	MTP Inhibitor	[46]
Nexletol	LDL lowering	LDL	ACLY Inhibitor	[42,44]
Mipomersen	ASO	LDL	ApoB silencing	[46,47]
Volanesorsen	siRNA	TG	ApoCIII silencing	[58,59]
ARO-ApoCIII	siRNA	TG	ApoCIII silencing	[59]
Vupanorsen	siRNA	LDL, TG	ANGPTL3 silencing	[21]
IONIS-ANGPTL3	ASO	LDL, TG	ANGPTL3 silencing	[59]
ARO-ANG3	siRNA	LDL, TG	ANGPTL3 silencing	[59]
Evinacumab	mAb	LDL, TG	ANGPTL3 silencing	[51]
Inclisiran	siRNA	LDL	PCSK9 silencing	[72,73]
Evolocumab	mAb	LDL	PCSK9 silencing	[74,75]
Alirocumab	mAb	LDL	PCSK9 silencing	[76,77]


ApoB
Mipomersen
ApoB ASO
VLDL
Lomitapide
LPL
LDL
VLDL/TRL
Volanesorsen
(siRNA apoCIII)
Vupanorsen
(siRNA ANGPTL3)
Evinacumab
(mAb ANGPTL3)
LPL
ApoCIII
ANGPTL3
TRL
FA
MTP
CE
Chol
Bile
LDLR
BA Sequester
Chol absorption
Ezetemibe
NPC1L1 Inhibitor
NPC1L1
Dietary Chol
FA
Chol
HMGCOAR
DNL
Statins
HMGCOAR Inhibitor
LDLR
LDL
LDL
LDLR
degradation
Nexletol
ACLY Inhibitor
Inclisiran
siRNA PCSK9
Evolicumab
mAb PCSK9
PCSK9
LPL
Activation
TRL
clearance
LDL, TG


Nutraceutici
Sequestratori degli acidi biliari
Statina
Ezetimibe
Alti valori di LDL
iPCSK-9
Acido Bempedoico
Icosapent-ethyl
Volanosersen
If in AFib
If LBBB & wide QRS
If SR >70 bpm
Inclisiran
Fibrati
Inibitori della Lp(a):
Pelacarsen
Olpasiran
If congestion
If recent decompensation/ advanced heart failure
LDL aferesi
Lomitapide
Mipomersen
Evinacumab

I Target definiti dalle Linee Guida



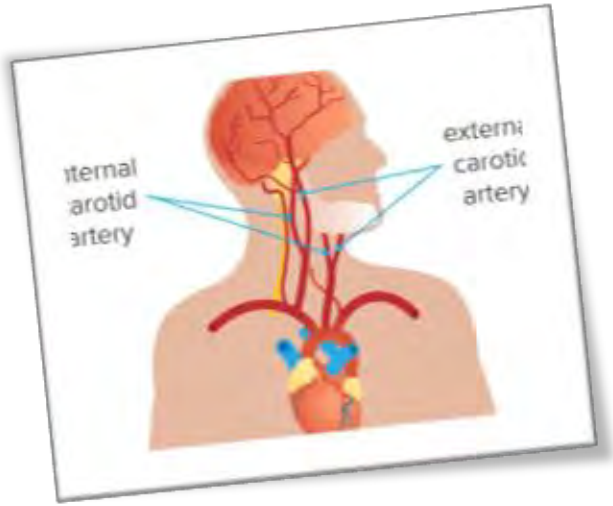
** modified from Celentani et al.*

Table 4 Cardiovascular risk categories

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ATTENZIONE:

LDL < 40 se paziente con anamnesi di plurimi eventi acuti anche a carico di due distretti arteriosi differenti !!!



Quanti pazienti a target?

ESC European Society of Cardiology

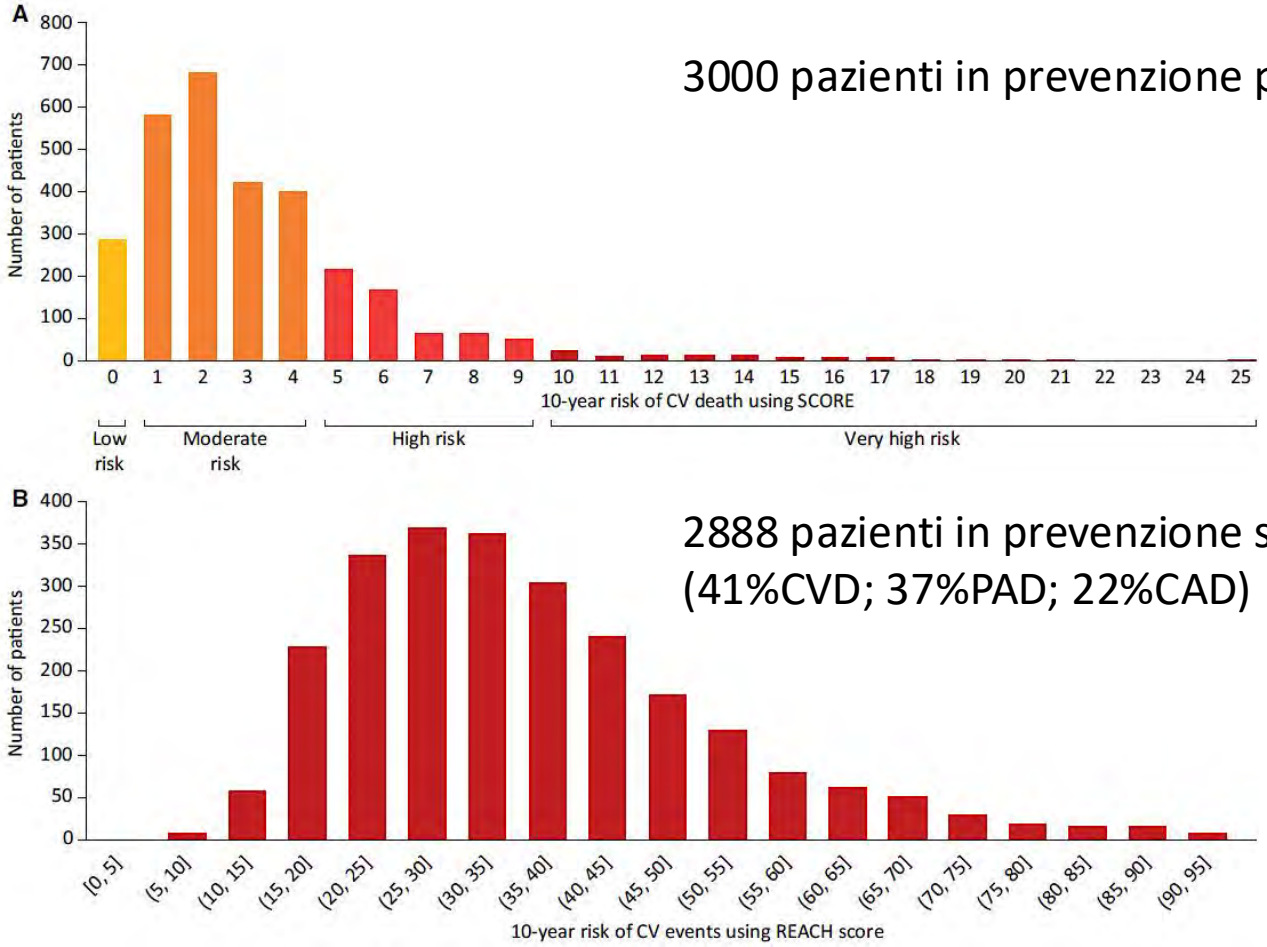
European Journal of Preventive Cardiology (2021) **28**, 1279–1289
doi:10.1093/eurjpc/zwaa047

FULL RESEARCH PAPER

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study

Kausik K. Ray[1]*, Bart Molemans[2], W. Marieke Schoonen[3], Periklis Giovas[4], Sarah Bray[5], Gaia Kiru[6], Jennifer Murphy[6], Maciej Banach[7,8,9], Stefano De Servi[10], Dan Gaita[11], Ioanna Gouni-Berthold[12], G. Kees Hovingh[13], Jacek J. Jozwiak[14], J. Wouter Jukema[15], Robert Gabor Kiss[16], Serge Kownator[17], Helle K. Iversen[18,19], Vincent Maher[20,21], Luis Masana[22], Alexander Parkhomenko[23], André Peeters[24], Piers Clifford[25], Katarina Raslova[26], Peter Siostrzonek[27], Stefano Romeo[28,29,30], Dimitrios Tousoulis[31], Charalambos Vlachopoulos[31], Michal Vrablik[32], Alberico L. Catapano[33], and Neil R. Poulter[6]; on behalf of the DA VINCI study†

Quanti pazienti a target?



3000 pazienti in prevenzione primaria

2888 pazienti in prevenzione secondaria
(41%CVD; 37%PAD; 22%CAD)

5888 pazienti arruolati in 128 centri di 18 Stati da giugno ’17 a novembre ‘18


A
Overall (n = 4112)
3.6
51.8
27.6
1.2
9.2
6.6
Low risk (n = 172)a
3.5
41.9
19.8
1.7
26.7
6.4
Moderate risk (n = 1219)
5.0
60.2
16.9
1.6
9.8
6.5
High risk (n = 593)
5.1
63.6
18.9
4.0
0.5
7.9
Very high risk (n = 2039)
2.3
43.5
37.5
1.1
9.3
6.3
0 20 40 60 80 100
Proportion of patients receiving LLT (%)
54 33 46 28 57 37 53 30 58 37 69 57 28 14
Overall (n = 4112)
Low-intensity statin monotherapy (n = 148)
Moderate-intensity statin monotherapy (n = 2131)
High-intensity statin monotherapy (n = 1134)
Ezetimibe combination (n = 380)
PCSK9i combination (n = 49)
Other LLT (n = 270)
63 50 72 68 54 67 36
Overall (n = 172)
Low-intensity statin monotherapy (n = 6)
Moderate-intensity statin monotherapy (n = 72)
High-intensity statin monotherapy (n = 34)
Ezetimibe combination (n = 46)
PCSK9i combination (n = 3)
Other LLT (n = 11)
75 60 67 49 81 66 75 58 68 60 68 58 43 24
Overall (n = 1219)
Low-intensity statin monotherapy (n = 61)
Moderate-intensity statin monotherapy (n = 734)
High-intensity statin monotherapy (n = 206)
Ezetimibe combination (n = 119)
PCSK9i combination (n = 19)
Other LLT (n = 80)
63 25 47 7 67 27 63 29 58 21 100 33 40 13
Overall (n = 593)
Low-intensity statin monotherapy (n = 30)
Moderate-intensity statin monotherapy (n = 377)
High-intensity statin monotherapy (n = 112)
Ezetimibe combination (n = 24)
PCSK9i combination (n = 3)
Other LLT (n = 47)
39 18 19 13 35 16 45 22 54 21 67 58 15 8
Overall (n = 2039)
Low-intensity statin monotherapy (n = 47)
Moderate-intensity statin monotherapy (n = 887)
High-intensity statin monotherapy (n = 764)
Ezetimibe combination (n = 189)
PCSK9i combination (n = 24)
Other LLT (n = 128)
0 20 40 60 80 100
Proportion of patients achieving goal (%)
2016 2019
Overall
Low-intensity statin monotherapy
Moderate-intensity statin monotherapy
High-intensity statin monotherapy
Ezetimibe combination
PCSK9i combination
Other LLT
2016/2019 risk-based LDL-C targets:
Low risk: 2016/2019, <3.0 mmol/L
Moderate risk: 2016, <3.0 mmol/L; 2019, <2.6 mmol/L
High risk: 2016, <2.6 mmol/L; 2019, <1.8 mmol/L
Very high risk: 2016, <1.8 mmol/L; 2019, <1.4 mmol/L

Quanti pazienti a target?

Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study

Kausik K. Ray,[1,*] Inaam Haq,[1] Aikaterini Bilitou,[1] Marius C. Manu,[1] Annie Burden,[1] Carlos Aguiar,[1] Marcello Arca,[1] Derek L. Connolly,[1] Mats Eriksson,[1] Jean Ferrières,[1] Ulrich Laufs,[1] Jose M. Mostaza,[1] David Nanchen,[1] Ernst Rietzschel,[1] Timo Strandberg,[1,2] Hermann Toplak,[1] Frank L. J. Visseren,[1] and Alberico L. Catapano,[1,3] on behalf of the SANTORINI Study Investigators

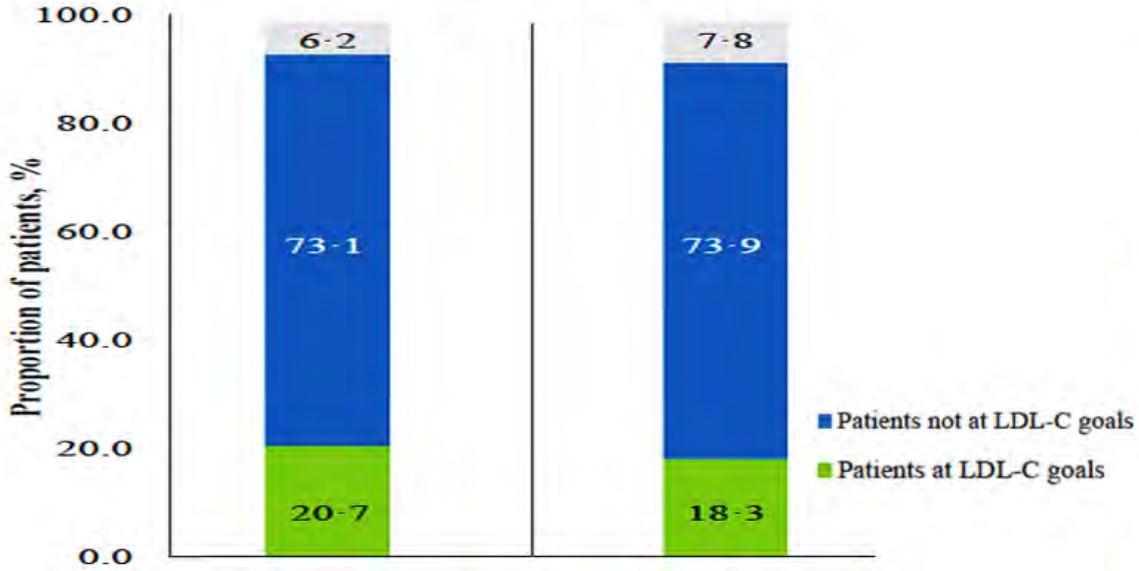
The SANTORINI Study

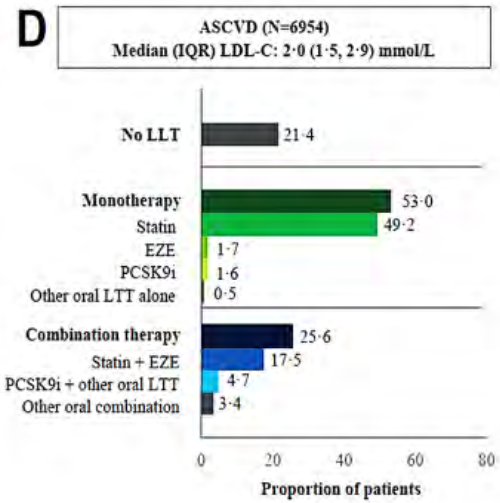
SANTORINI

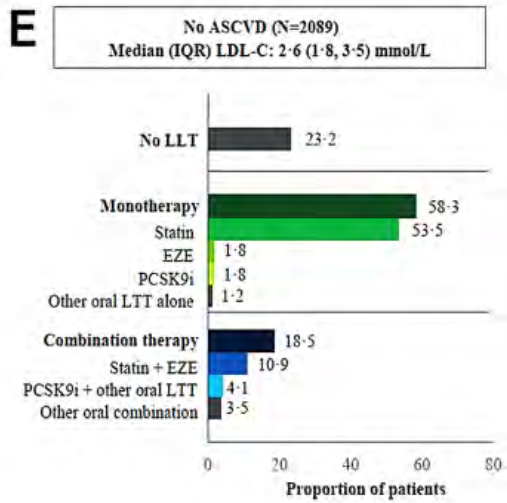
- To **describe** demographics and cardiovascular (CV) risk factors of patients with and without prior ASCVD enrolled in the SANTORINI study, as well as their CV risk as assigned
- Multinational, prospective, observational study conducted in 14 European countries
- Patients aged ≥18 years with high and very high CV risk, as assessed by the investigator, and requiring LLT were enrolled between **March 2020 and February 2021**, followed by a 12-month follow-up period per patient
- 9044 patients included in this analysis; **6954** (76.9%) had a documented **history of ASCVD**

Ray KK, Haq I, Bilitou A et al. The Lancet Regional Health 2023

SANTORINI



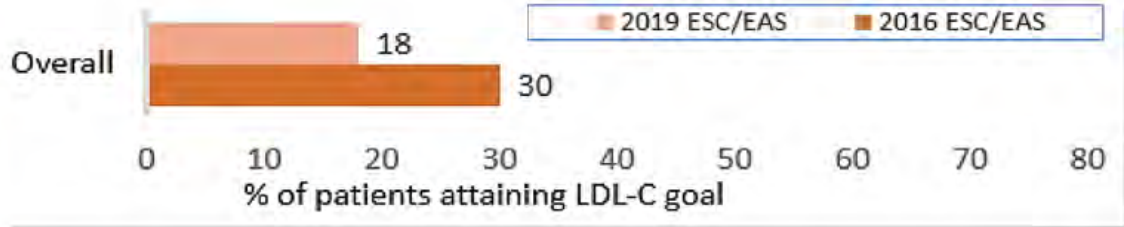


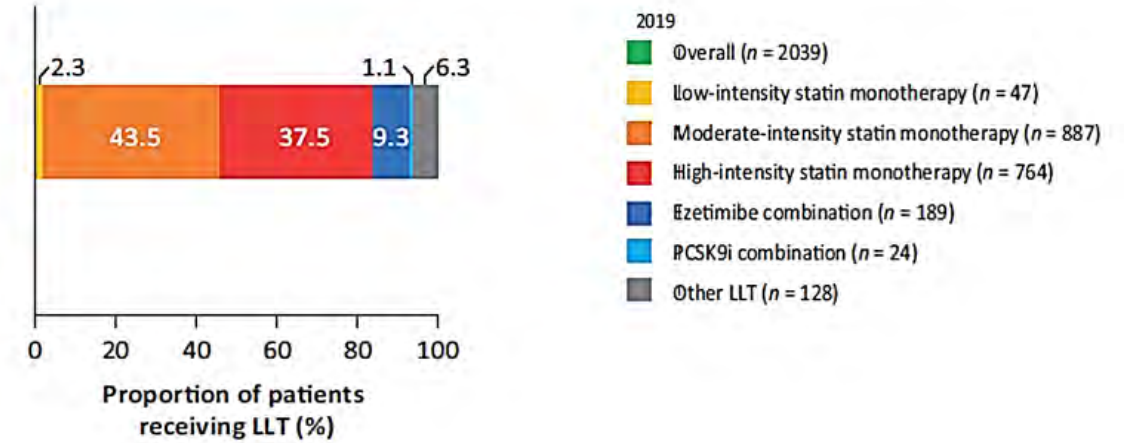


DA VINCI

5888 pazienti con prescrizione LLT in 18 paesi europei

- **3000 prevenzione primaria**
- **2888 secondaria (41%CVD; 37%PAD; 22%CAD)**

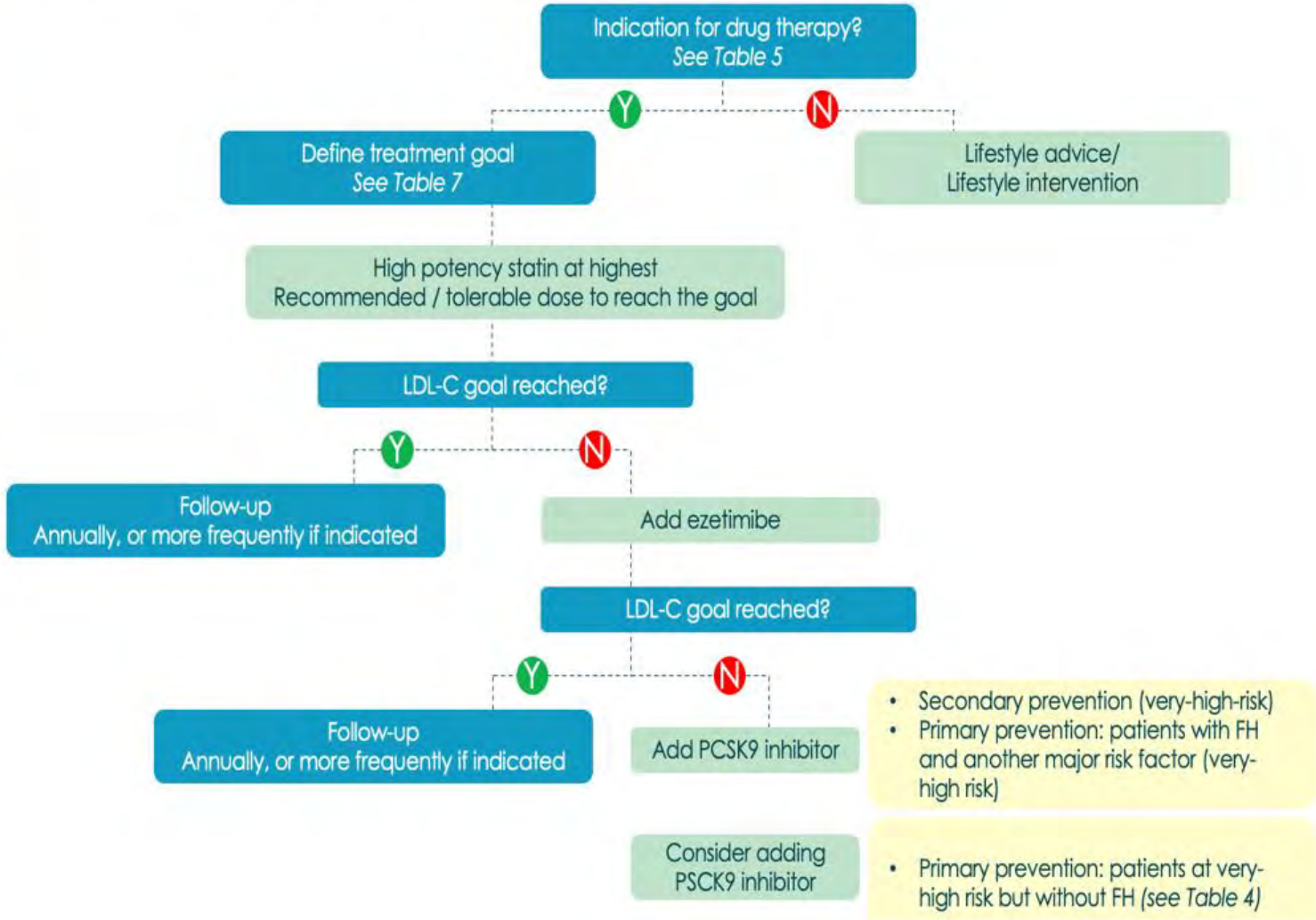




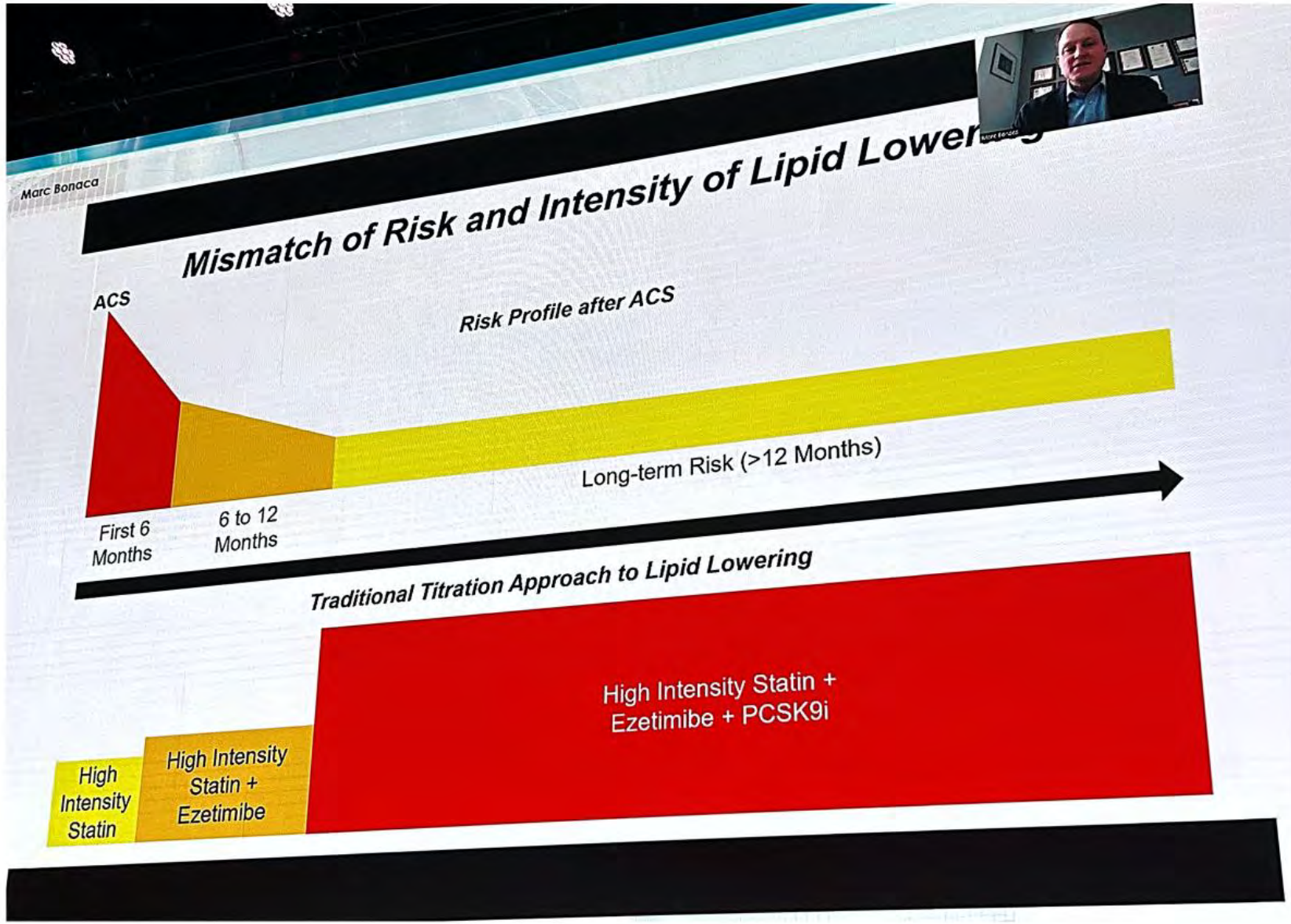
Ray KK, Molemans B, Schoonen WM et al. Eur J Prev Cardiol 2020

Jane K Stock . Atherosclerosis 2020

STEPWISE APPROACH



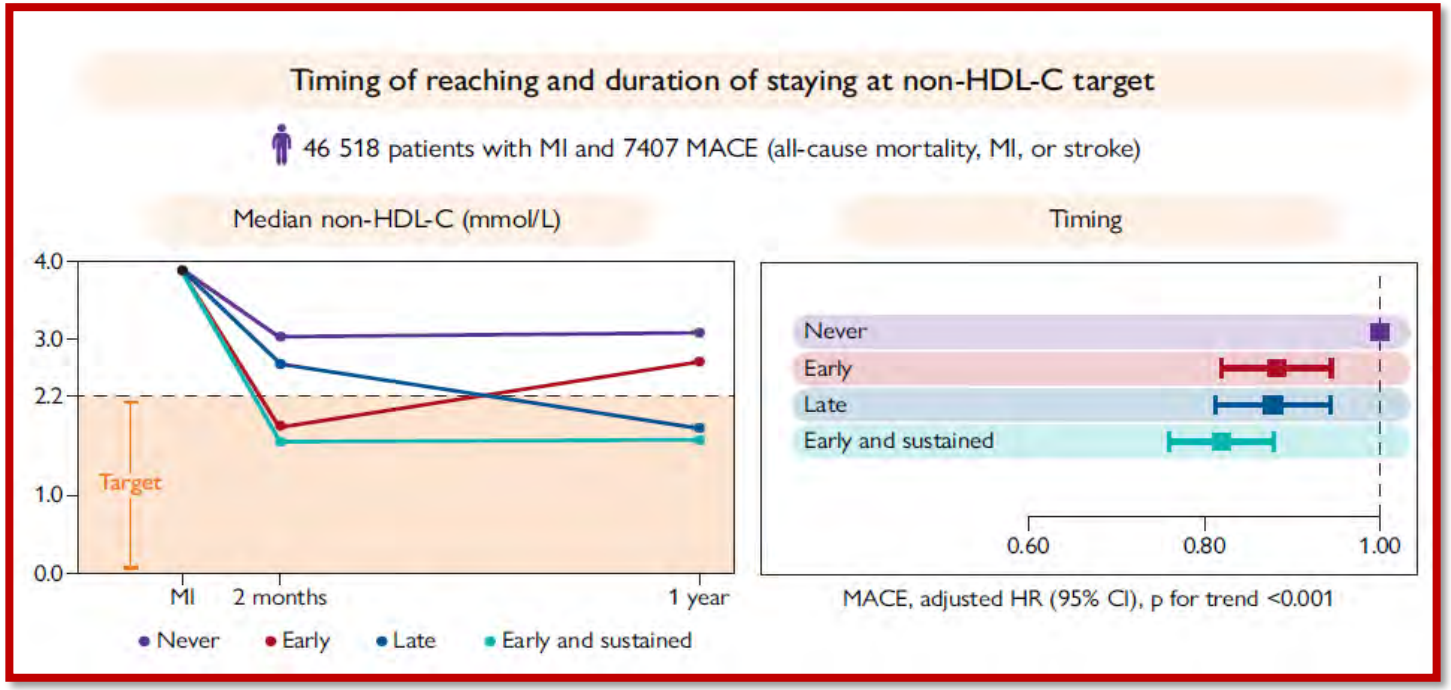
Mach F. et al Eur Heart J 2019


Marc Bonaca
Mismatch of Risk and Intensity of Lipid Lower
ACS
Risk Profile after ACS
First 6 Months
6 to 12 Months
Long-term Risk (>12 Months)
Traditional Titration Approach to Lipid Lowering
High Intensity Statin
High Intensity Statin + Ezetimibe
High Intensity Statin + Ezetimibe + PCSK9i

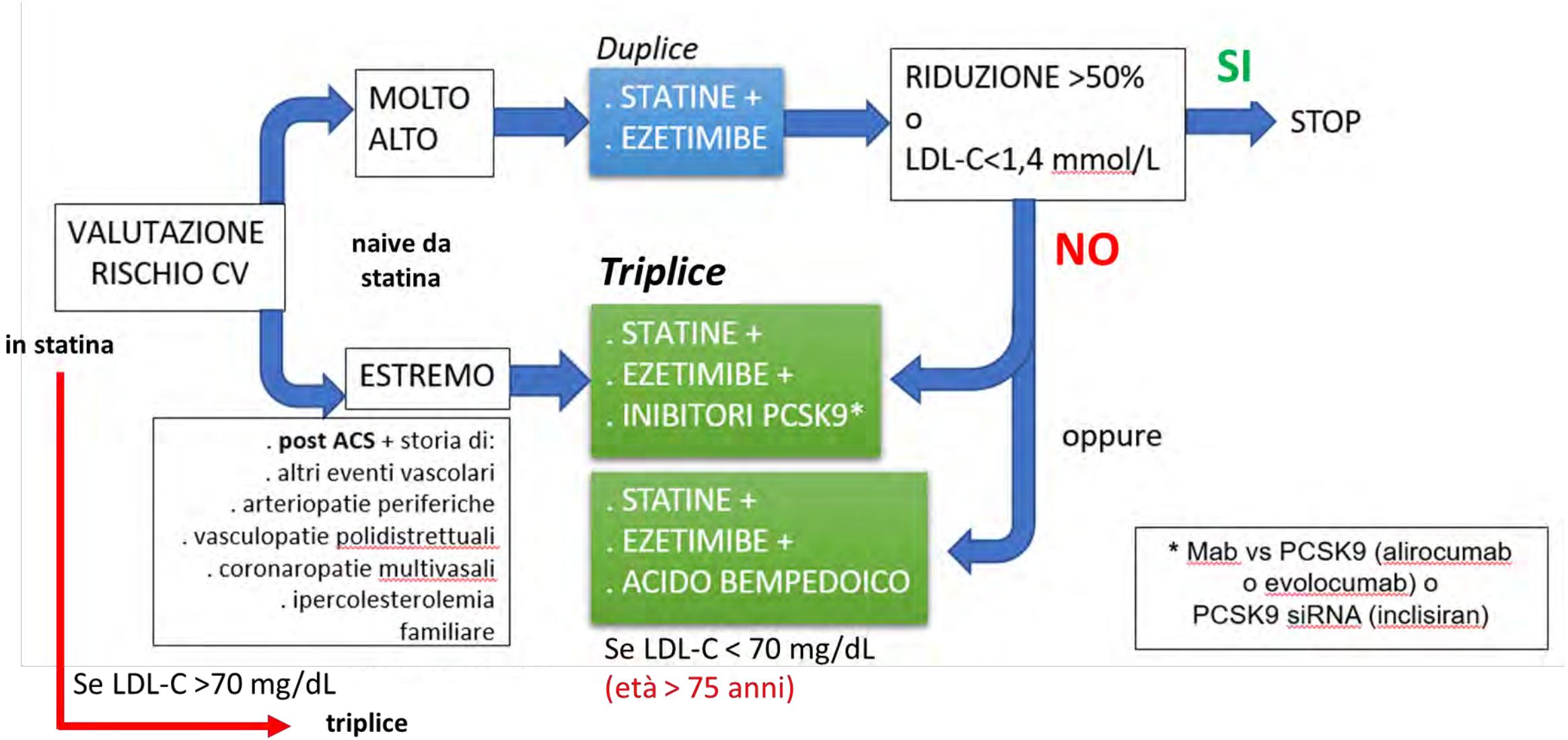
ESC European Society of Cardiology
European Heart Journal (2024) **45**, 4204–4215
https://doi.org/10.1093/eurheartj/ehae576

Intensive early and sustained lowering of non–high-density lipoprotein cholesterol after myocardial infarction and prognosis: the SWEDEHEART registry

Jessica Schubert [1]*, Margrét Leosdottir [2,3], Bertil Lindahl [1,4], Johan Westerbergh [4], Håkan Melhus [5], Angelo Modica[6], Nilo Cater [7], Jonas Brinck [8], Kausik K. Ray [9], and Emil Hagström [1,4]

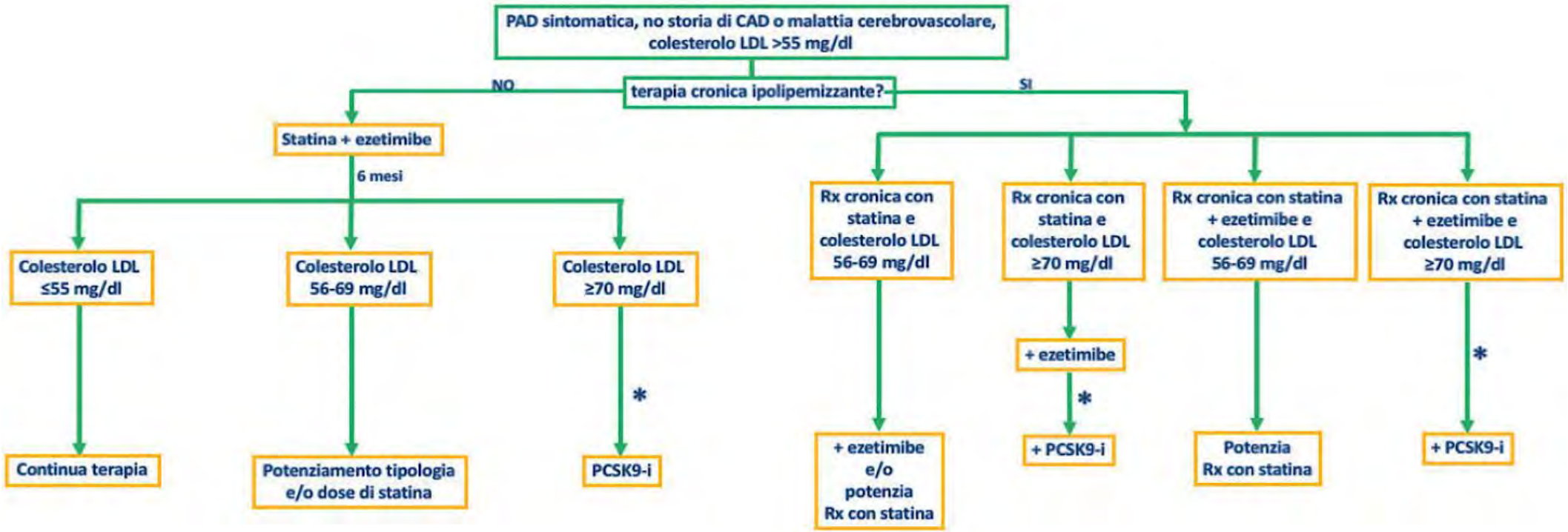


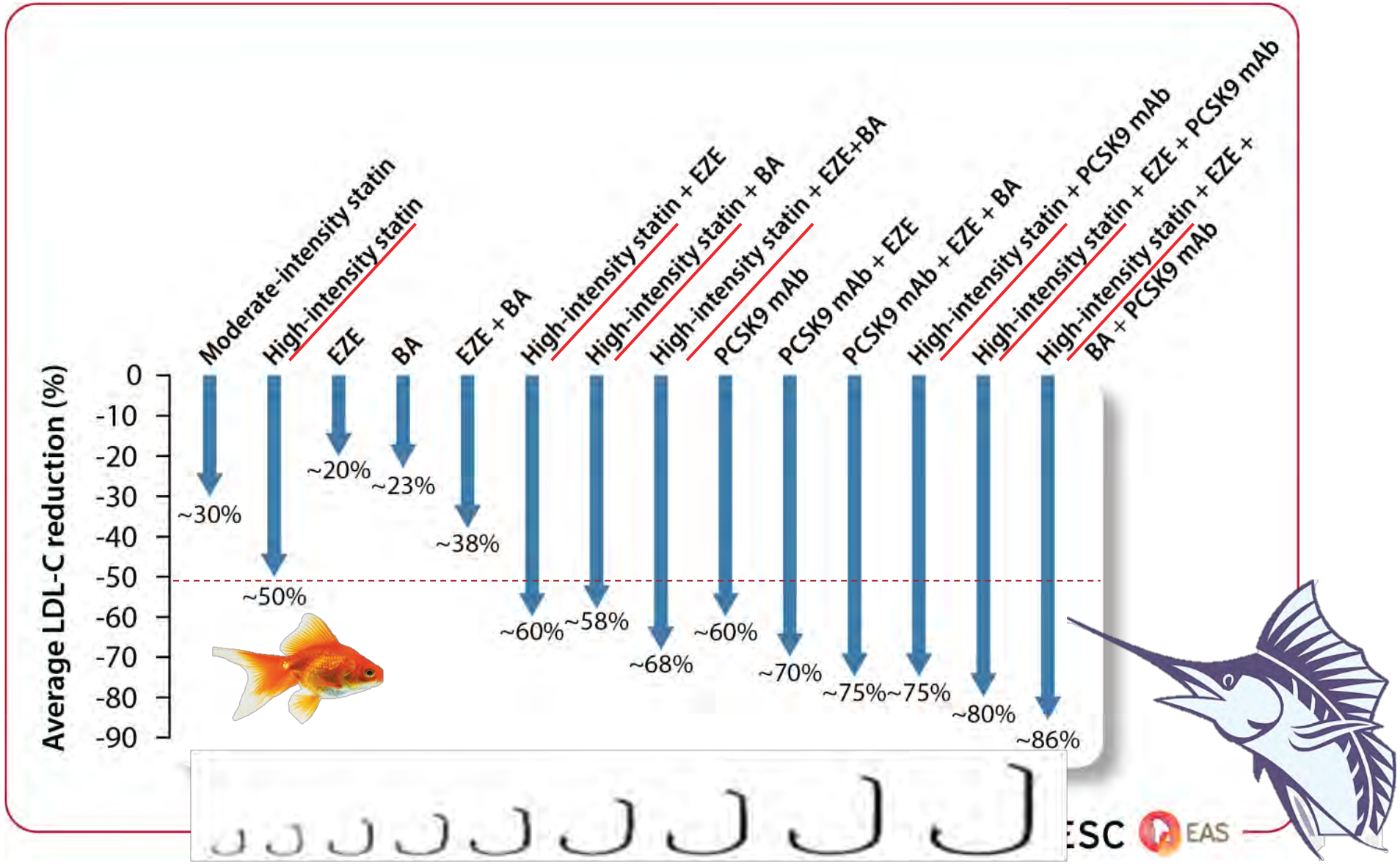
Come superare le barriere all'implementazione delle strategie di prevenzione e cura della malattia cardiovascolare aterosclerotica mediante terapia



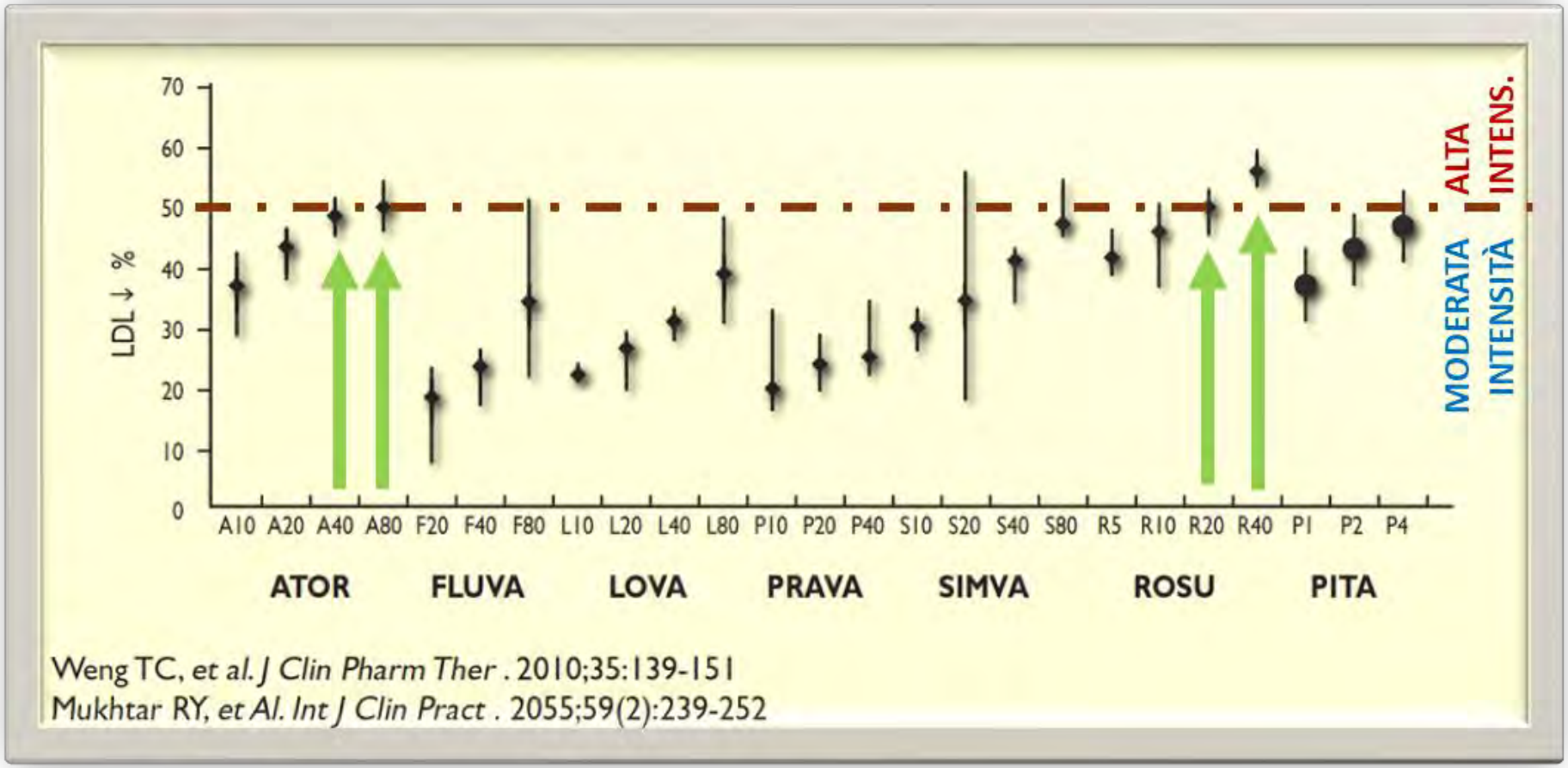
Proposta di percorso diagnostico-terapeutico assistenziale della Regione Piemonte sulla terapia ipolipemizzante ed antitrombotica in pazienti con malattia delle arterie periferiche

Giuseppe Patti[1], Ferdinando Varbella[2], Andrea Gaggiano[3], Marco Mennuni[1], Gianmarco Annibali[4], Dario Celentani[2], Fabrizio Del Nevo[4], Salvatore Piazza[3], Giuseppe Musumeci[4], a nome della Società Italiana di Cardiologia (SIC) Piemonte, dell'Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) Piemonte e della Rete delle Chirurgie Vascolari del Piemonte



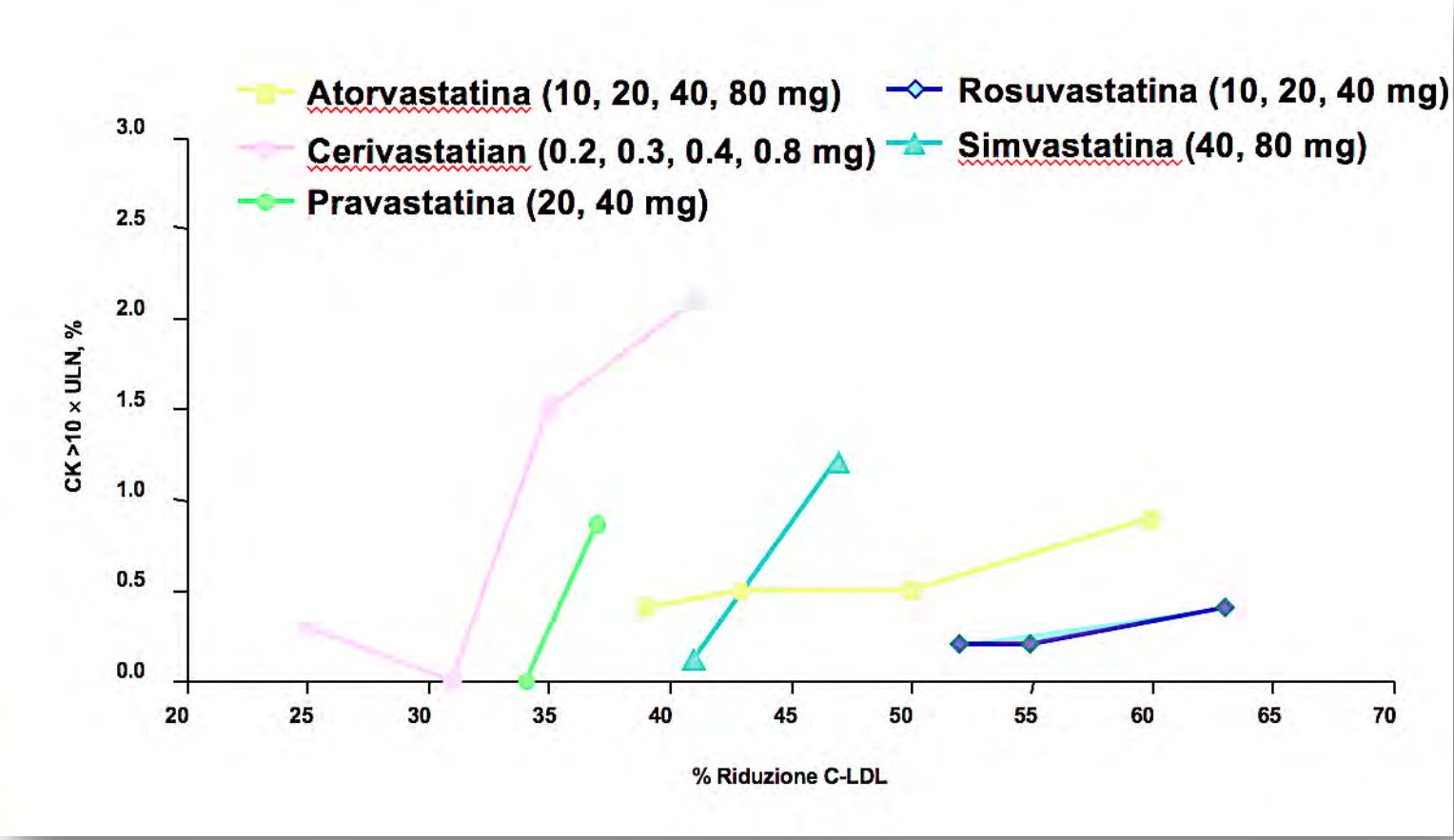

Average LDL-C reduction (%)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
Moderate-intensity statin
High-intensity statin
EZE
BA
EZE + BA
High-intensity statin + EZE
High-intensity statin + BA
High-intensity statin + EZE+BA
PCSK9 mAb
PCSK9 mAb + EZE
PCSK9 mAb + EZE + BA
High-intensity statin + PCSK9 mAb
High-intensity statin + EZE + PCSK9 mAb
High-intensity statin + EZE + BA + PCSK9 mAb
~30%
~50%
~20%
~23%
~38%
~60%
~58%
~68%
~60%
~70%
~75%
~75%
~80%
~86%
ESC
EAS

C’è statina e statina...



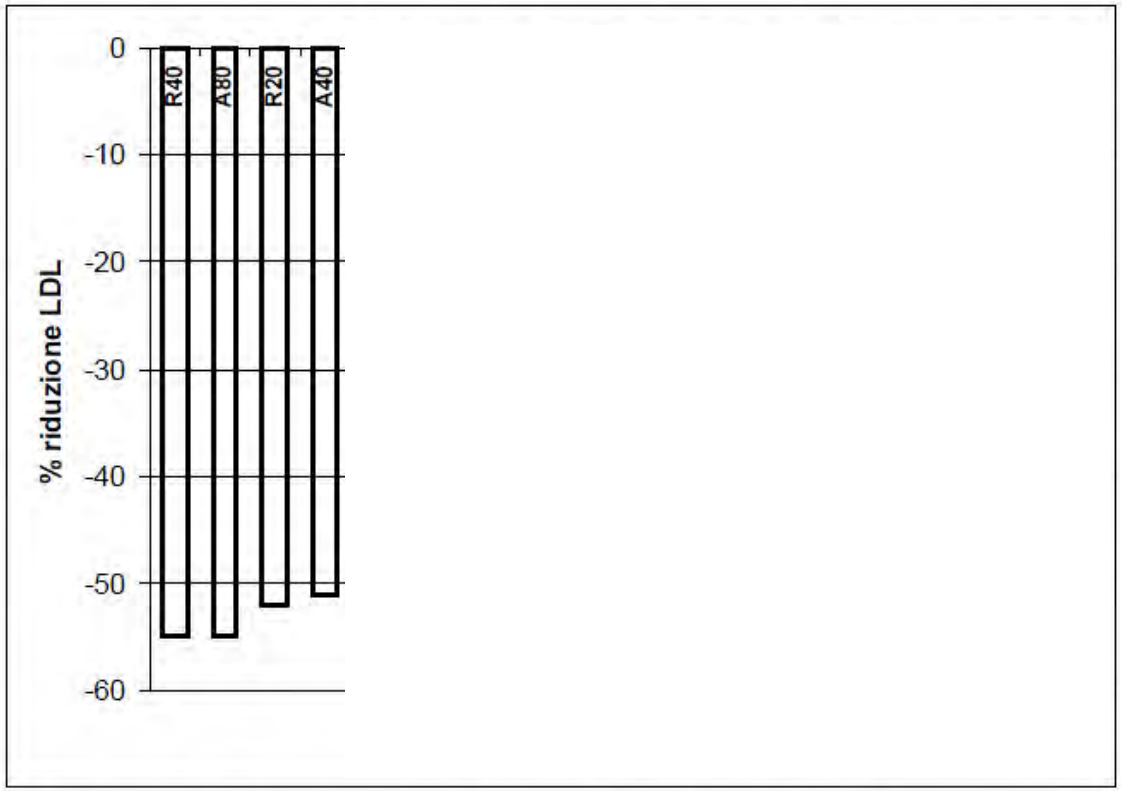
Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151
Mukhtar RY, *et Al. Int J Clin Pract* . 2055;59(2):239-252

C’è statina e statina...



La seguente figura presenta l'entità della riduzione del colesterolo LDL ottenibile con le diverse statine ai diversi dosaggi disponibili in commercio.

Grafico della riduzione percentuale del colesterolo LDL adattato dal documento del NHS Foundation Trust "*Guidelines on statin prescribing in the prevention of cardiovascular disease*" (2006).

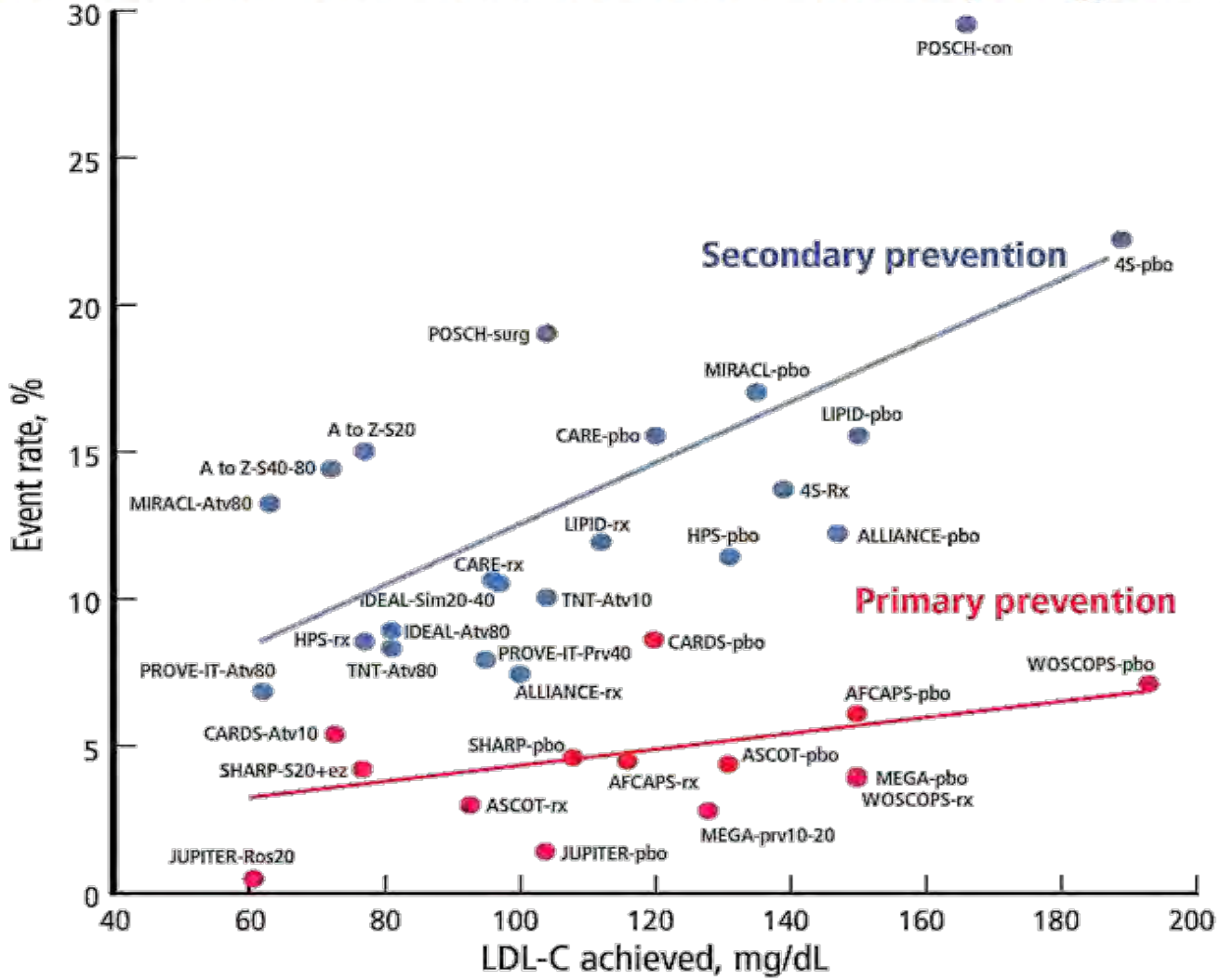


I principi attivi più efficaci sono sulla sinistra del grafico (A=atorvastatina F=fluvastatina P=pravastatina R=rosuvastatina S=simvastatina L=lovastatina. La dose è indicata dopo la lettera che indica il farmaco)

MARC S. SABATINE, MD, MPH
Chairman, TIMI Study Group; Lewis Dexter, MD, Distinguished Chair in Cardiovascular Medicine, Brigham and Women's Hospital; Professor of Medicine, Harvard Medical School, Boston, MA

CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 83 • NUMBER 3 MARCH 2016

Advances in the treatment of dyslipidemia



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

>18.000 pz a meno di 10 gg da SCA

FOLLOW UP 7 ANNI

Sim/Eze 40 + 10 mg

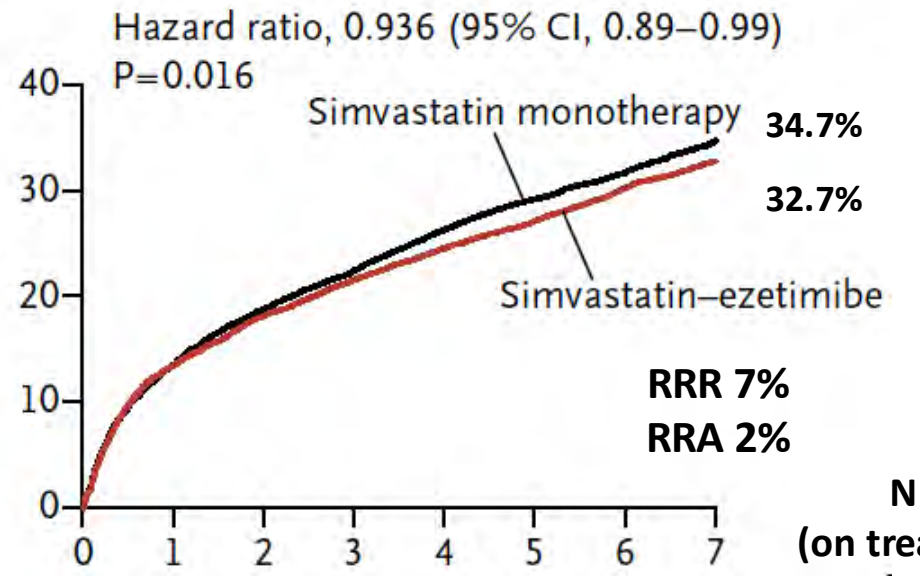
VS

Simvastatin 40 mg

(42% discontinuation)

End point composito:

- **morte cardiovasc.**
- **infarto non fatale**
- **ospedalizz. per SCA**
- **rivascolarizzazione**
- **stroke non fatale**



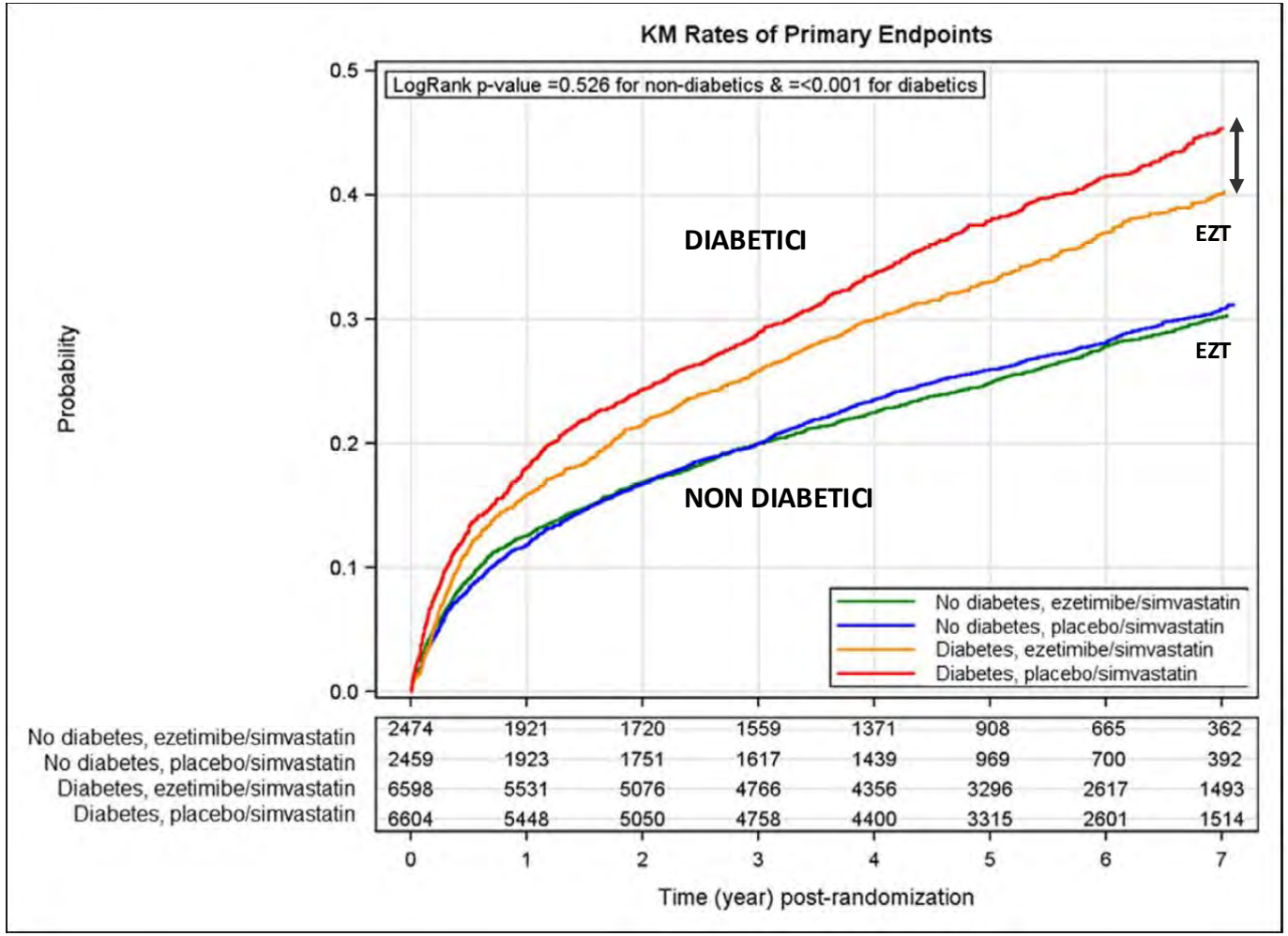
RRR 7%

RRA 2%

NNT 56

(on treatment 38)

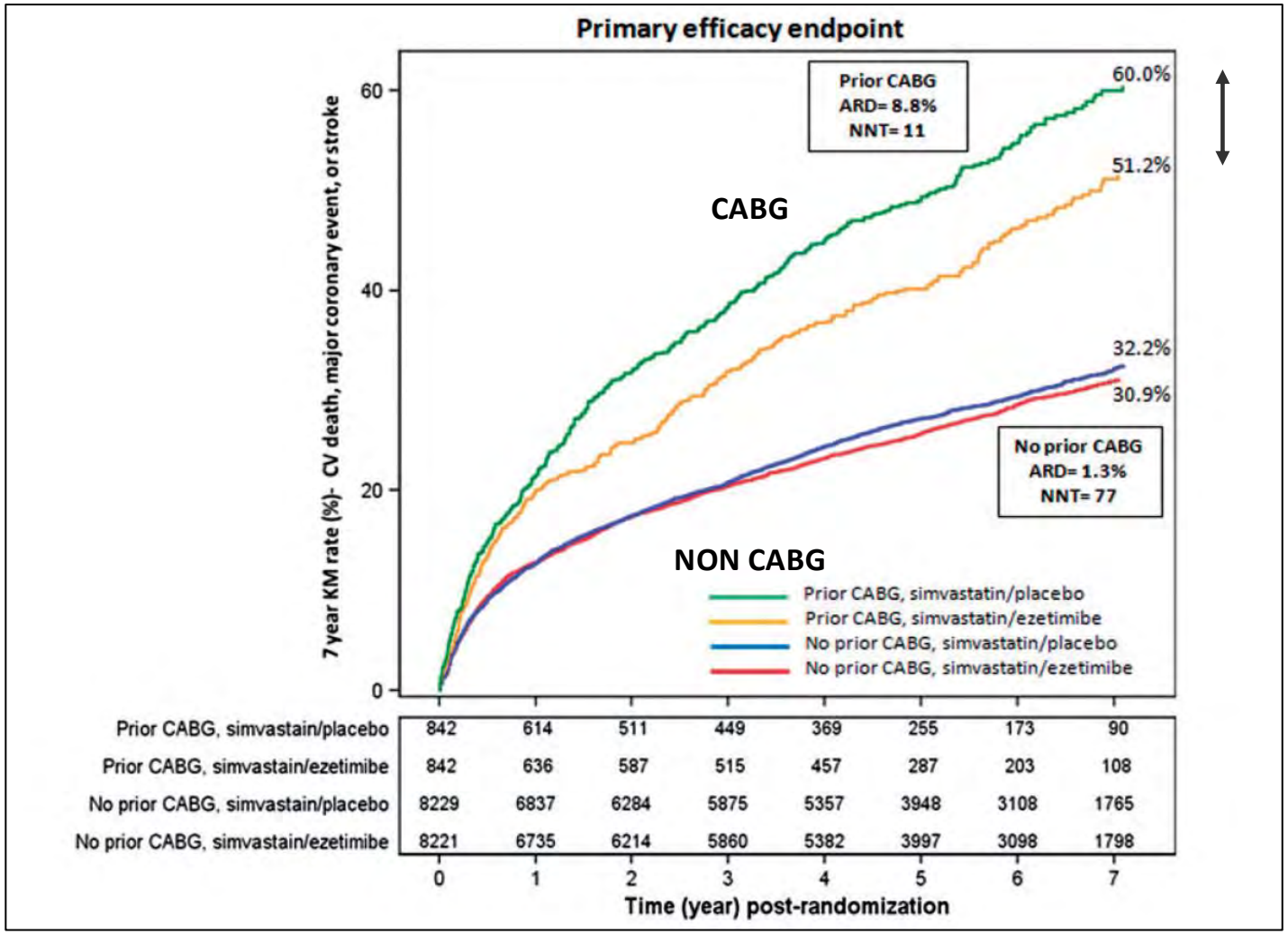
IMPROVE-IT – sottoanalisi pz. diabetici



15% RRR
NNT 20 vs 56

Cannon CP, Blazing MA, Giugliano RP et al. N Engl J Med 2015

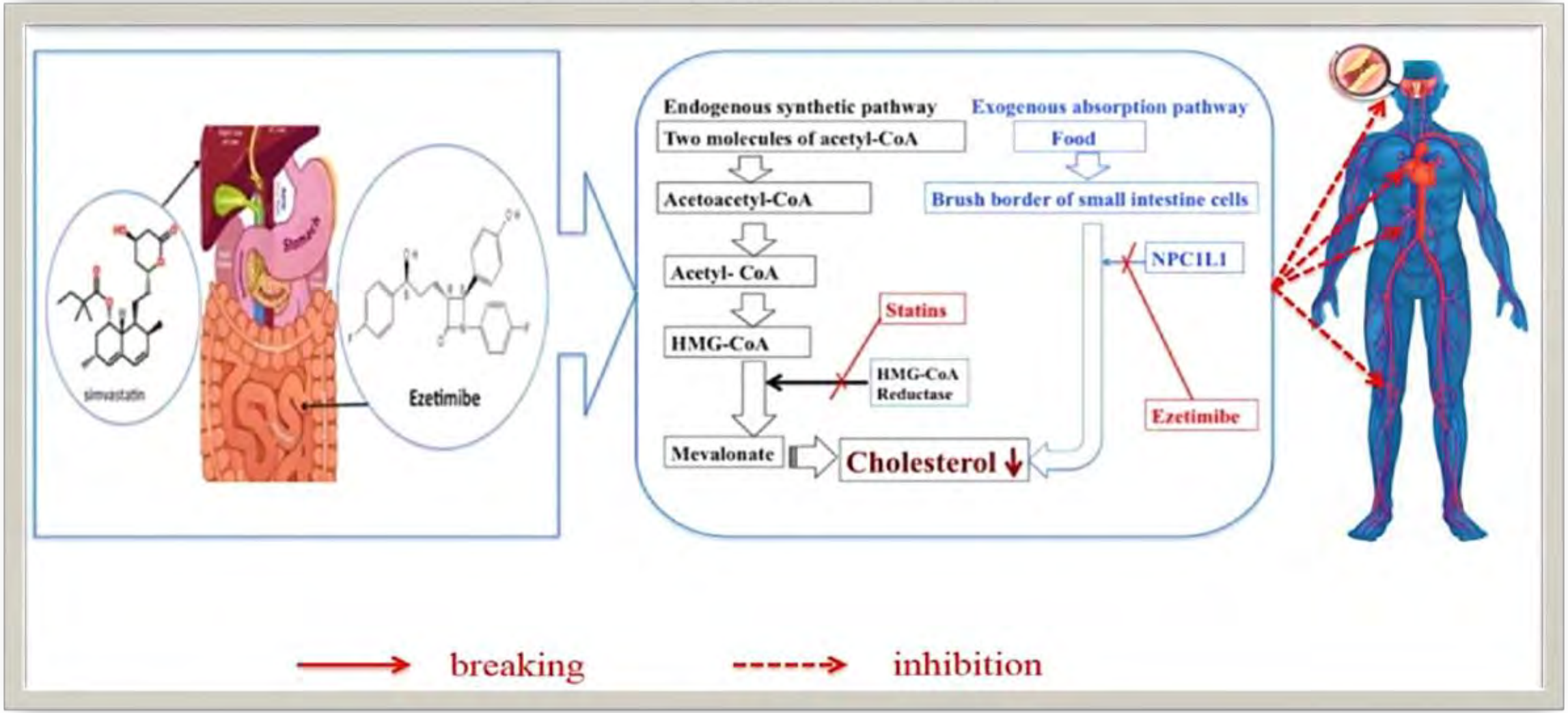
IMPROVE-IT – sottoanalisi pz. BPAC



8.8% RRA
20% RRR
NNT 11 vs 56

Cannon CP, Blazing MA, Giugliano RP et al. N Engl J Med 2015

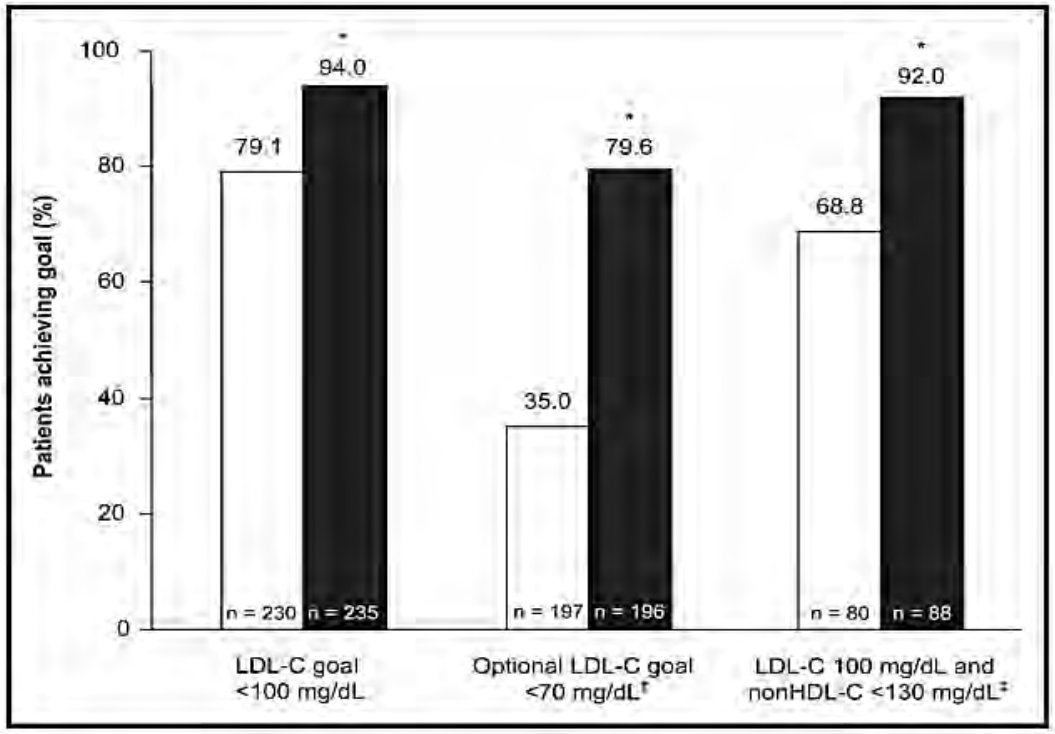
STELLAR


simvastatin
Ezetimibe
Endogenous synthetic pathway
Two molecules of acetyl-CoA
Acetoacetyl-CoA
Acetyl- CoA
HMG-CoA
Mevalonate
Statins
HMG-CoA Reductase
Exogenous absorption pathway
Food
Brush border of small intestine cells
NPC1L1
Ezetimibe
Cholesterol ↓
breaking
inhibition

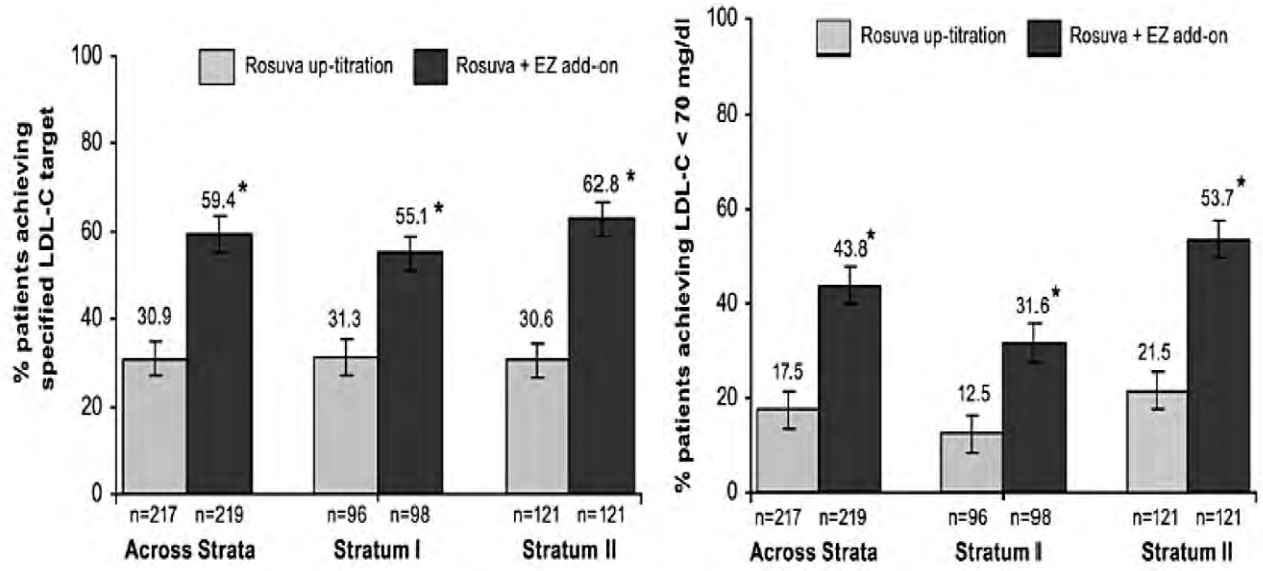
MONOTERAPIA CON ROSUVASTATINA O AGGIUNTA DI EZETIMIBE?

Efficacy and Safety of *Rosuvastatin* 40 mg Alone or in Combination With *Ezetimibe* in Patients at High Risk of Cardiovascular Disease (Results from the EXPLORER Study)

Christie M. Ballantyne, MD[a,*], Robert Weiss, MD[b], Tiziano Moccetti, MD[c], Anja Vogt, MD[d], Bernd Eber, MD[e], Froukje Sosef, MD[f], and Emma Duffield, MSc[f], for the EXPLORER Study Investigators



Safety and Efficacy of Ezetimibe Added on to Rosuvastatin 5 or 10 mg Versus Up-Titration of Rosuvastatin in Patients With Hypercholesterolemia (the ACTE Study)

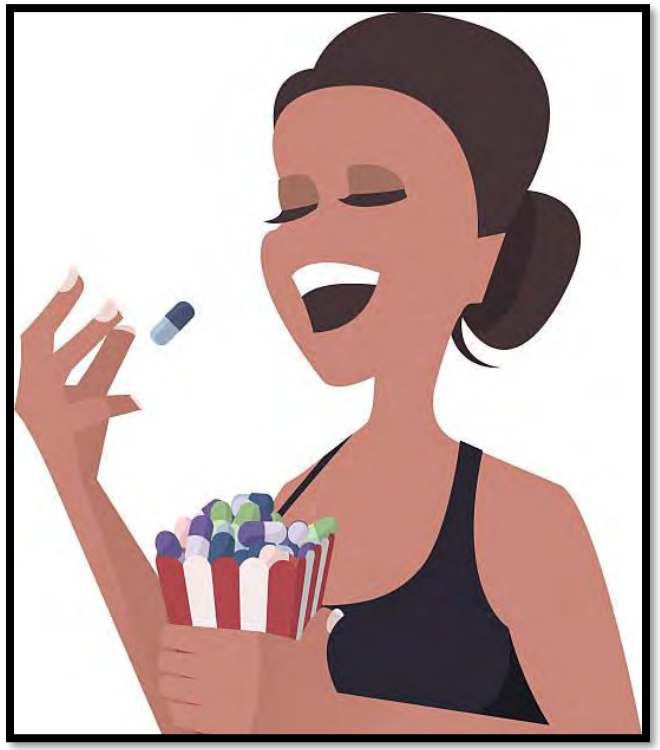


- *Across Strata all ezetimibe 10 mg add-on to rosuvastatin (5 mg, 10 mg) versus all rosuvastatin up-titration (10 mg, 20 mg);*
- *Stratum I ezetimibe 10 mg add-on to rosuvastatin 5 mg versus rosuvastatin 10 mg;*
- *Stratum II ezetimibe 10 mg add-on to rosuvastatin 10 mg versus rosuvastatin 20 mg. *p 0.001.*

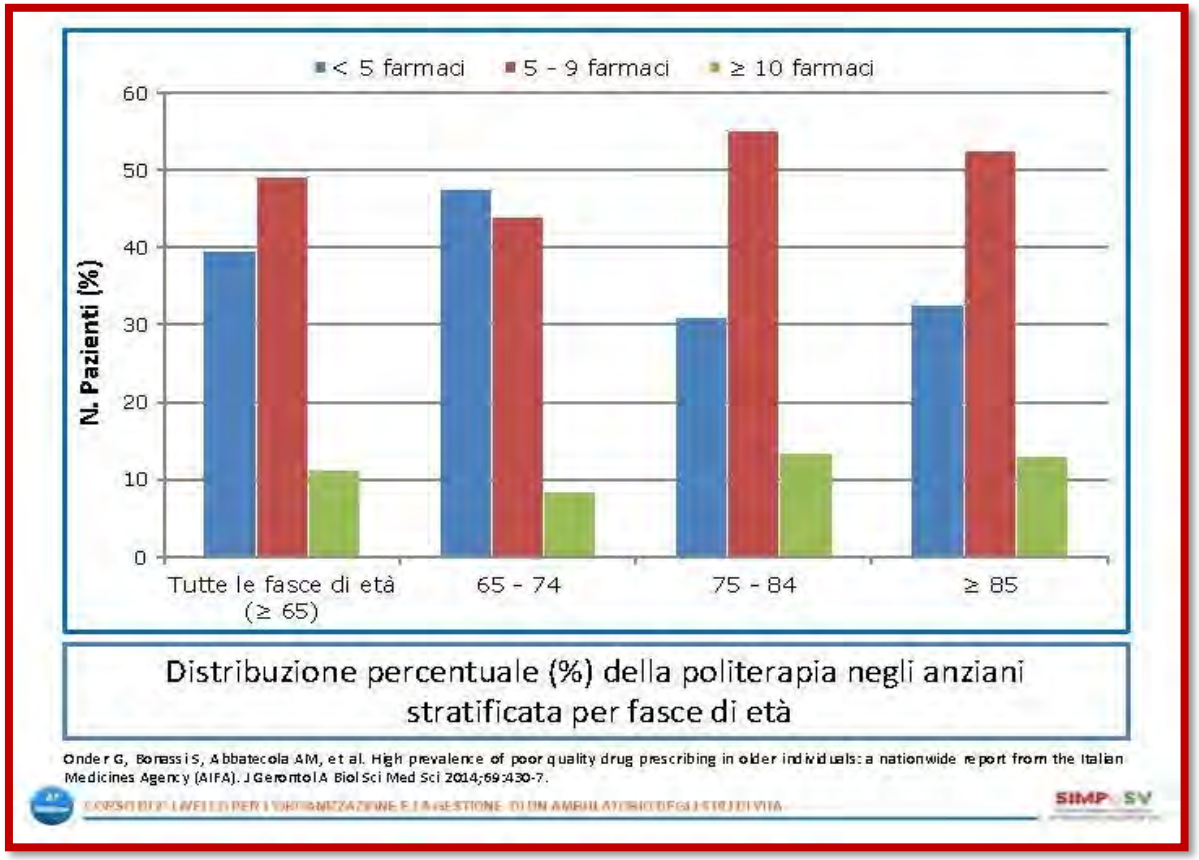
Bays HE et al. Am J Cardiol 2011


efficacia
ADERENZA
tollerabilità
semplificazione

Il problema dei tre corpi

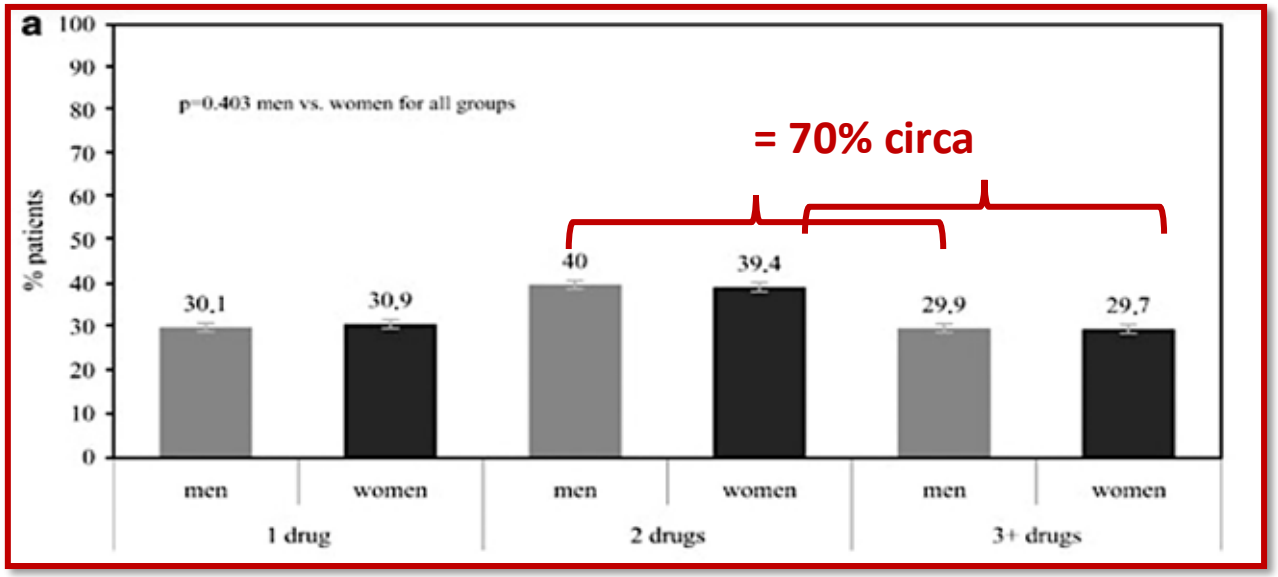


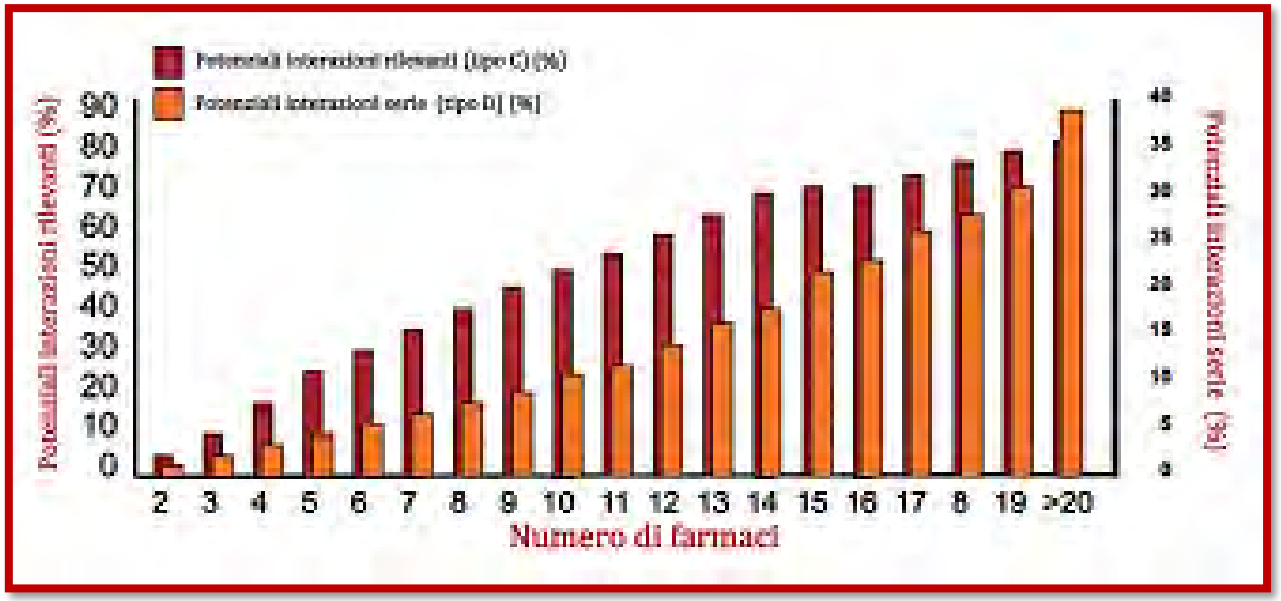
Thoenes M et al. J Hum Hypertens. 2010;24:336-344.



Distribuzione percentuale (%) della politerapia negli anziani stratificata per fasce di età

Onder G, Bonassi S, Abbatecola AM, et al. High prevalence of poor quality drug prescribing in older individuals: a nationwide report from the Italian Medicines Agency (AIFA). J Gerontol A Biol Sci Med Sci 2014;69:430-7.





Categories of Nonadherence	Examples
Health system	Poor quality of provider-patient relationship; poor communication; lack of access to healthcare; lack of continuity of care
Condition	Asymptomatic chronic disease (lack of physical cues); mental health disorders (eg, depression)
Patient	Physical impairments (eg, vision problems or impaired dexterity); cognitive impairment; psychological/behavioral; younger age; nonwhite race
Therapy	Complexity of regimen; side effects
Socioeconomic	Low literacy; higher medication costs; poor social support

Ho et al. Circulation.2009;119:3028–3035

Associazione precostituita o polipillola?

Fixed Dose Combinations refer to products containing one or more active ingredients used for a particular indication(s).

Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health & Family Welfare
Government of India

A **polypill** is a type of drug combination consisting of a single drug product in pill form (i.e., tablet or capsule) and thus *combines* multiple medications (that is, more than one active pharmaceutical ingredient). The prefix "poly" means "multiple", referring to the multiplicity of distinct drugs in a given "pill". In precise usage, a pill is a polypill if it contains at least 4 drugs (meaning that fixed-dose combinations of 2 or 3 drugs are not polypills). An occasional synonym is *combopill*. A polypill is commonly targets treatment or prevention of chronic conditions.[1]

WIKIPEDIA
The Free Encyclopedia

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PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 20, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.08.021

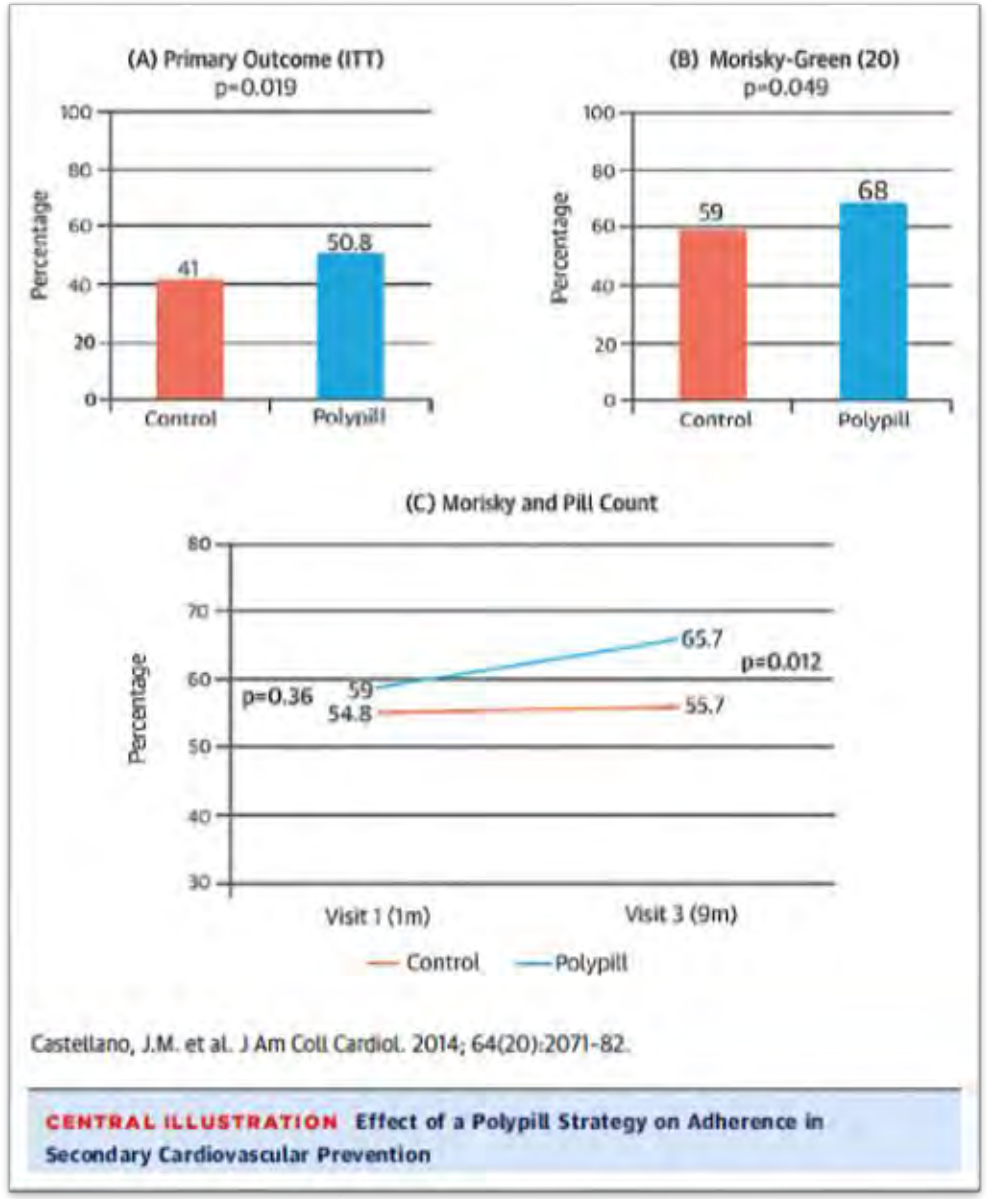
ORIGINAL INVESTIGATIONS

A Polypill Strategy to Improve Adherence

Results From the FOCUS Project

José M. Castellano, MD, PhD,*† Ginés Sanz, MD, PhD,* José L. Peñalvo, PhD,* Sameer Bansilal, MD, MS,† Antonio Fernández-Ortiz, MD, PhD,*‡ Luz Alvarez, BSc,* Luis Guzmán, MD,§ Juan Carlos Linares, MD,§ Fernando García, MD, PhD,‖ Fabiana D'Aniello, PhD,‖ Joan Albert Arnáiz, MD, PhD,¶ Sara Varea, BSc,¶ Felipe Martínez, MD,# Alberto Lorenzatti, MD,# Iñaki Imaz, MD, PhD,** Luis M. Sánchez-Gómez, MD, MSc,** Maria Carla Roncaglioni, Biol Sci Dr,†† Marta Baviera, PharmD,†† Sidney C. Smith, Jr, MD,‡‡ Kathryn Taubert, PhD,‡‡ Stuart Pocock, PhD,*§§ Carlos Brotons, MD, PhD,‖‖ Michael E. Farkouh, MD, MSc,¶¶ Valentin Fuster, MD, PhD*†

- L'associazione di più farmaci in una sola somministrazione migliora l'aderenza alla terapia.
- Studio FOCUS (associazione di aspirina + statina + antipertensivo)
- 695 pazienti randomizzati a polipillola VS singole somministrazioni
- Nessuna differenza significativa di effetti collaterali



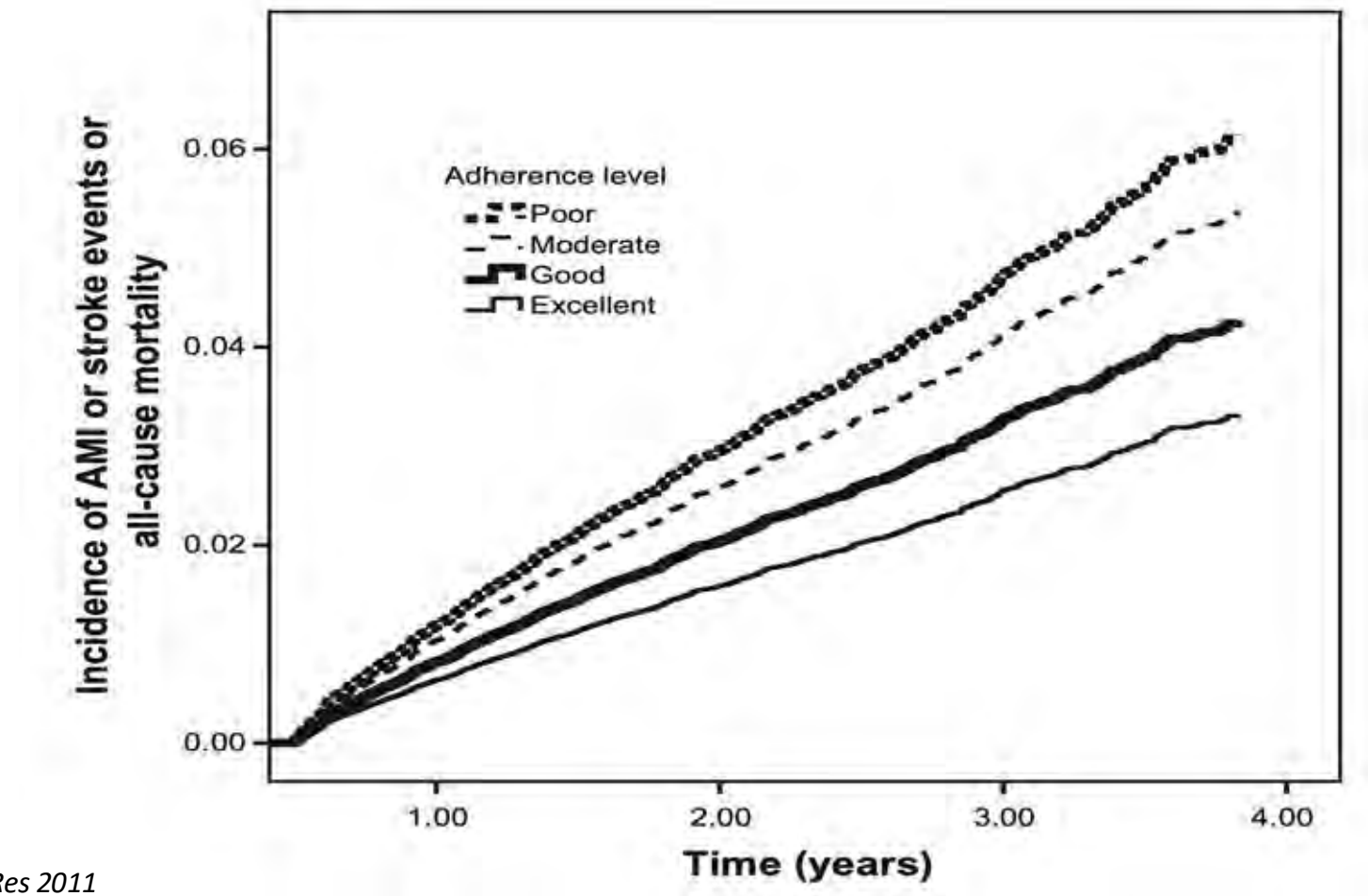
Castellano, J.M. et al. J Am Coll Cardiol. 2014; 64(20):2071-82.

CENTRAL ILLUSTRATION Effect of a Polypill Strategy on Adherence in Secondary Cardiovascular Prevention

MIGLIORE ADERENZA = MENO EVENTI

Studio retrospettivo su 31.000 pz

Follow up medio 1.9 aa

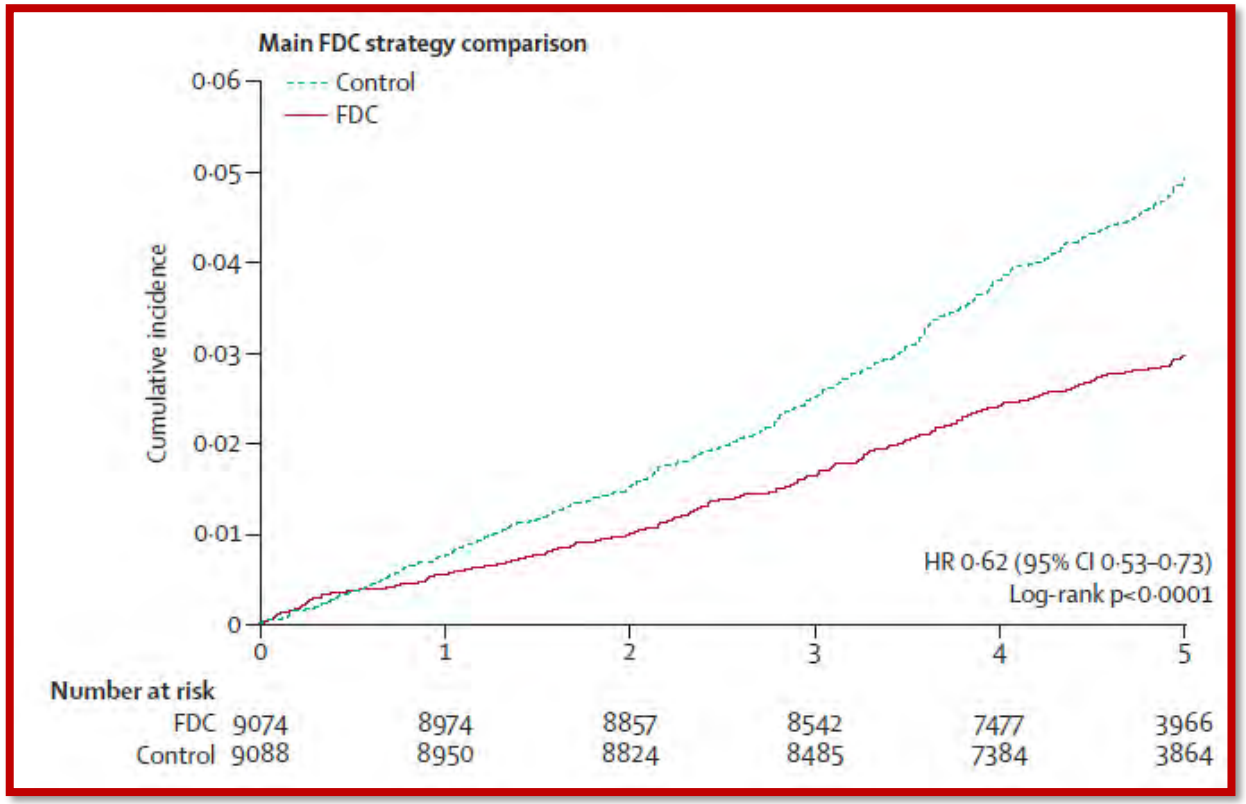


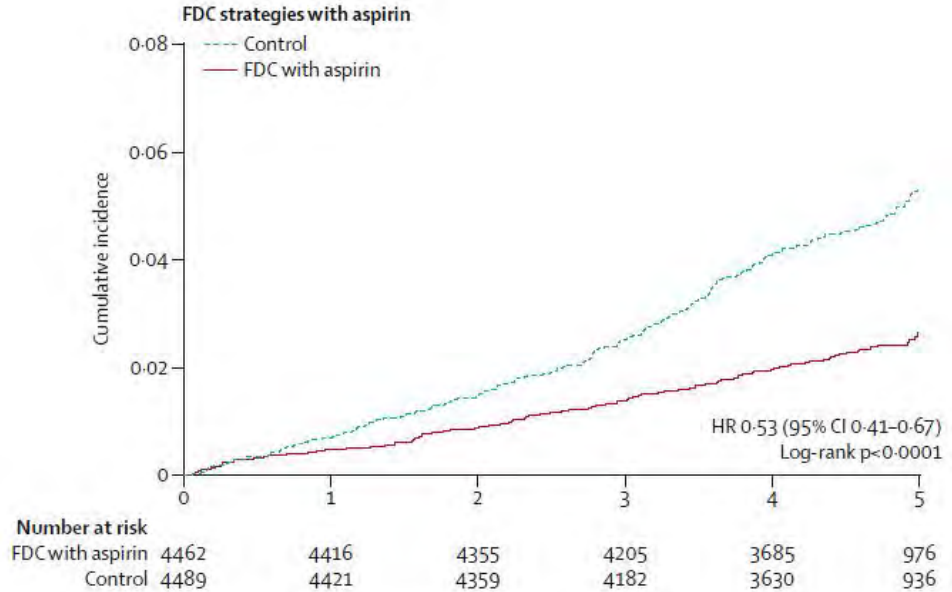
Degli Esposti et al. Clin. Outcomes Res 2011

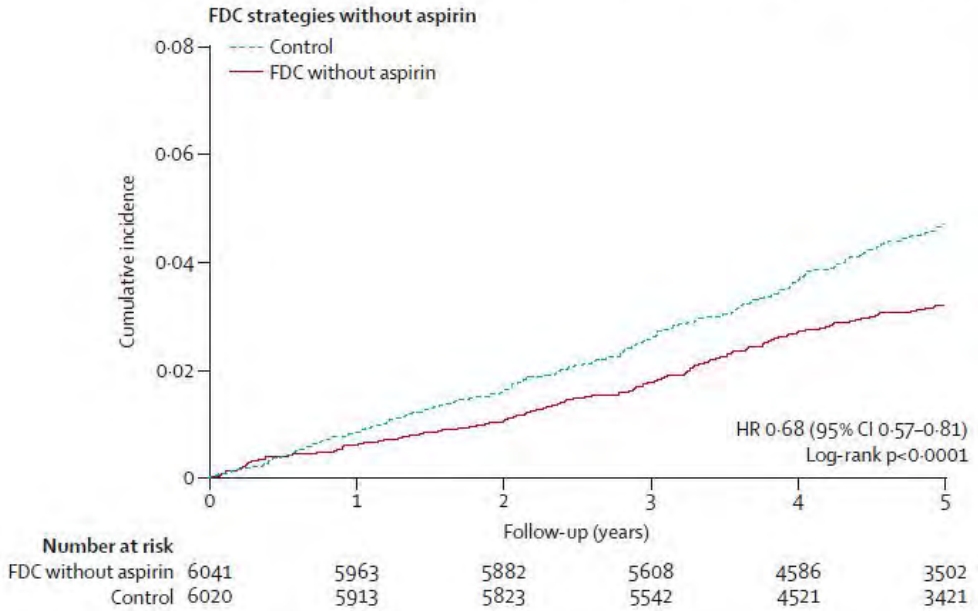
Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis

Philip Joseph, Gholamreza Roshandel, Peggy Gao, Prem Pais, Eva Lonn, Denis Xavier, Alvaro Avezum, Jun Zhu, Lisheng Liu, Karen Sliwa, Habib Gamra, Shrikant I Bangdiwala, Koon Teo, Rafael Diaz, Antonio Dans, Patricio Lopez-Jaramillo, Dorairaj Prabhakaran, Jose Maria Castellano, Valentin Fuster, Anthony Rodgers, Mark D Huffman, Jackie Bosch, Gilles R Dagenais, Reza Malekzadeh, Salim Yusuf, on behalf of the Polypill Trialists' Collaboration

	TIPS-3	HOPE-3	Polylran
Locations	Bangladesh, Canada, Colombia, India, Indonesia, Malaysia, Philippines, Tanzania, Tunisia	Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Ecuador, Hungary, India, Israel, South Korea, Malaysia, Netherlands, Philippines, Russia, Slovakia, South Africa, Sweden, UK, Ukraine	Iran
Overall trial population	5713 participants without known vascular disease but at intermediate cardiovascular disease risk*	12 705 participants without known vascular disease but at intermediate cardiovascular disease risk*	6838 participants with or without vascular disease
Population included in meta-analysis	All participants (n=5713)	Participants randomly assigned to double active group or double placebo group (polypill concept; n=6348)	Participants without a history of vascular disease (n=6101)
Study design	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Pragmatic, cluster-randomised
Intervention†	2×2×2 factorial design: daily oral polypill consisting of simvastatin 40 mg, ramipril 10 mg, atenolol 100 mg, and hydrochlorothiazide 25 mg; daily aspirin 75 mg; monthly oral vitamin D 60 000 IU	2×2 factorial design: daily oral rosuvastatin 10 mg; daily oral candesartan 16 mg and hydrochlorothiazide 12·5 mg	Daily oral polypill consisting of atorvastatin 20 mg, hydrochlorothiazide 12·5 mg, enalapril 5 mg (or valsartan 40 mg), and aspirin 81 mg
Comparator (or control)†	Matching placebos	Matching placebos	Minimal care (blood pressure measurement and risk factor counselling)


Main FDC strategy comparison
Control
FDC
Cumulative incidence
0·06
0·05
0·04
0·03
0·02
0·01
0
0
1
2
3
4
5
HR 0·62 (95% CI 0·53–0·73)
Log-rank p<0·0001
Number at risk
FDC 9074 8974 8857 8542 7477 3966
Control 9088 8950 8824 8485 7384 3864


FDC strategies with aspirin
Control
FDC with aspirin
Cumulative incidence
0·08
0·06
0·04
0·02
0
0
1
2
3
4
5
HR 0·53 (95% CI 0·41–0·67)
Log-rank p<0·0001
Number at risk
FDC with aspirin 4462 4416 4355 4205 3685 976
Control 4489 4421 4359 4182 3630 936


FDC strategies without aspirin
Control
FDC without aspirin
Cumulative incidence
0·08
0·06
0·04
0·02
0
0
1
2
3
4
5
HR 0·68 (95% CI 0·57–0·81)
Log-rank p<0·0001
Follow-up (years)
Number at risk
FDC without aspirin 6041 5963 5882 5608 4586 3502
Control 6020 5913 5823 5542 4521 3421

Circulation

PERSPECTIVE

The Polypill Revisited

Why We Still Need Population-Based Approaches in the Precision Medicine Era

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Nearly 2 decades ago, Wald and Law proposed "a strategy to reduce cardiovascular disease by more than 80%" by administering a polypill to everyone 55 years of age and older.[1] Their bold proposal had its roots in the debate surrounding risk-based versus population-based approaches to prevention, as described by Rose.[2] In risk-based approaches, preventive measures are targeted specifically at higher risk individuals, with medication therapy tailored to each patient's risk factor profile. The identification of higher risk patients typically relies on clinical and laboratory-based prediction algorithms, the traditional approach endorsed in most practice guidelines. In contrast, population-based approaches aim to shift the entire risk distribution, even modestly, with measures implemented at the population level. The latter necessitates interventions that are low in cost and have a low incidence of side effects. These are among the proposed advantages of the polypill, a fixed-dose combination of cardiovascular medications, usually including a statin and several antihypertensive drugs.

One of the objections to the Wald and Law proposal was that large numbers of low-risk individuals would end up receiving unneeded and/or unindicated drug therapy. Thus, despite randomized trials supporting the tolerability of various polypill formulations and regulatory approval in multiple countries outside the United States, momentum in the field shifted toward viewing the polypill primarily as a strategy for high-risk individuals with established cardiovascular disease. The problem is that a one-size-fits-all approach to pharmacotherapy may not be optimal for patients with established disease, for whom aggressive cholesterol and

POPOLAZIONE GENERALE

ALTO RISCHIO

Medicina di Popolazione:

BASSO RISCHIO

Medicina di Precisione:

MEDIO RISCHIO