FARMACI 2018. Una risorsa a disposizione di ogni cardiologo che ottiene risultati che dobbiamo valorizzare

TERAPIA MEDICA DELLA CARDIOPATIA ISCHEMICA CRONICA

Ruolo della terapia ipolipemizzante nella terapia primaria e secondaria

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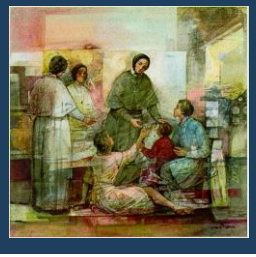
Ospedale Valduce – Como (IT)

H. Valduce 1879



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CONFLITTI DI INTERESSE: NESSUNO

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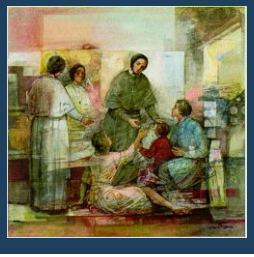
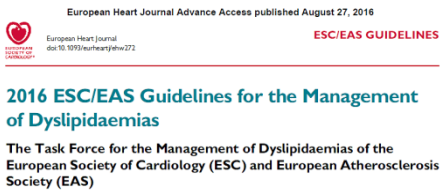
H. Valduce 1879



BACKGROUND

- CVD kills > 4 million people in Europe/yr
- It kills more ♀ (55%) than ♂ (45%), although CV deaths < 65 yrs are more common in ♂
- More pts are surviving their first CVD event and are at high risk of recurrences. In addition, the prevalence of some risk factors, notably diabetes and obesity, is increasing.
- In 2009, healthcare costs related to CVD in Europe amounted to €106 billion, representing ~9% of the total healthcare expenditure across the European Union (EU). In the USA, direct annual costs of CVD are projected to triple between 2010 and 2030

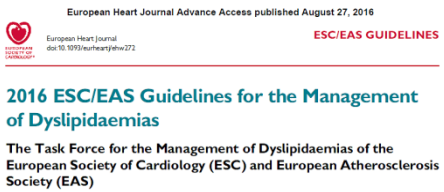


BACKGROUND

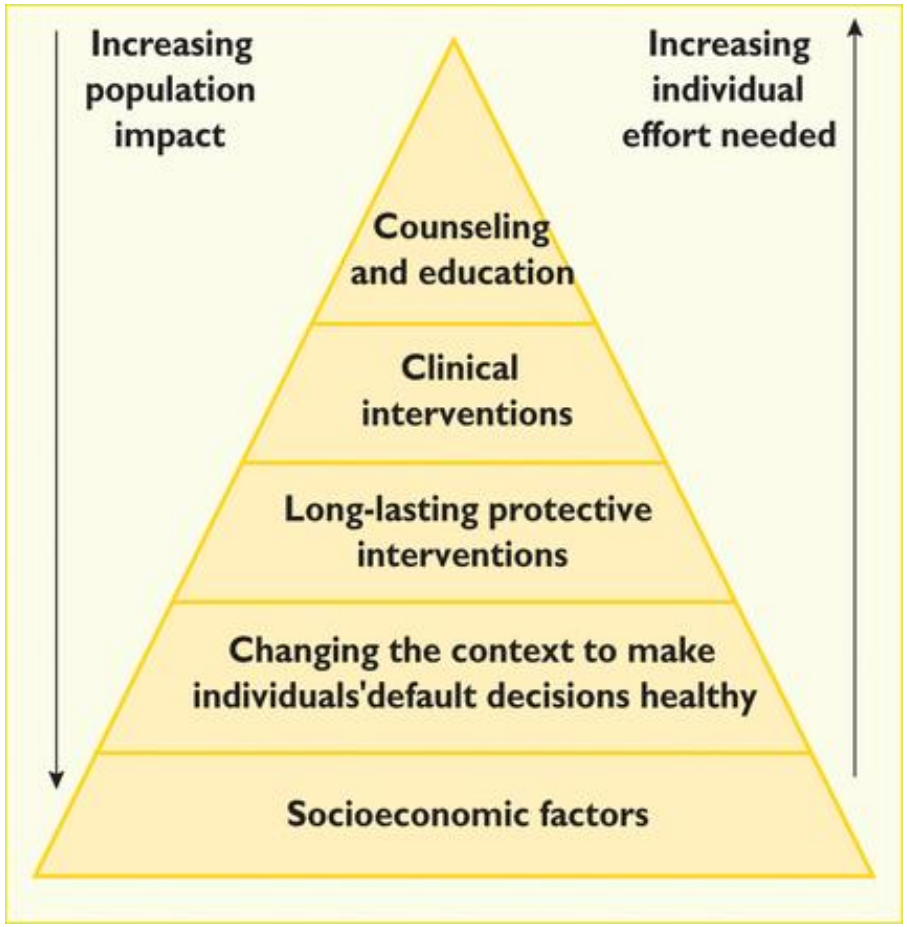
The importance of CVD prevention remains undisputed and should be delivered at different levels:

- **in the general population by promoting healthy lifestyle behaviour**
- **at the individual level, in those at moderate to high risk of CVD or patients with established CVD, by tackling an unhealthy and by reducing increased levels of CV risk factors.**

According to the WHO, policy and environmental changes could reduce CVD in all countries for <US$1 per person per year, while interventions at the individual level are considerably more expensive.



BACKGROUND



Recommendation	Class [a]	Level [b]
Measures aimed at implementing healthy lifestyles are more cost-effective than drug interventions at the population level.	IIa	B

European Heart Journal Advance Access published August 27, 2016
European Heart Journal
doi:10.1093/eurheartj/ehw272
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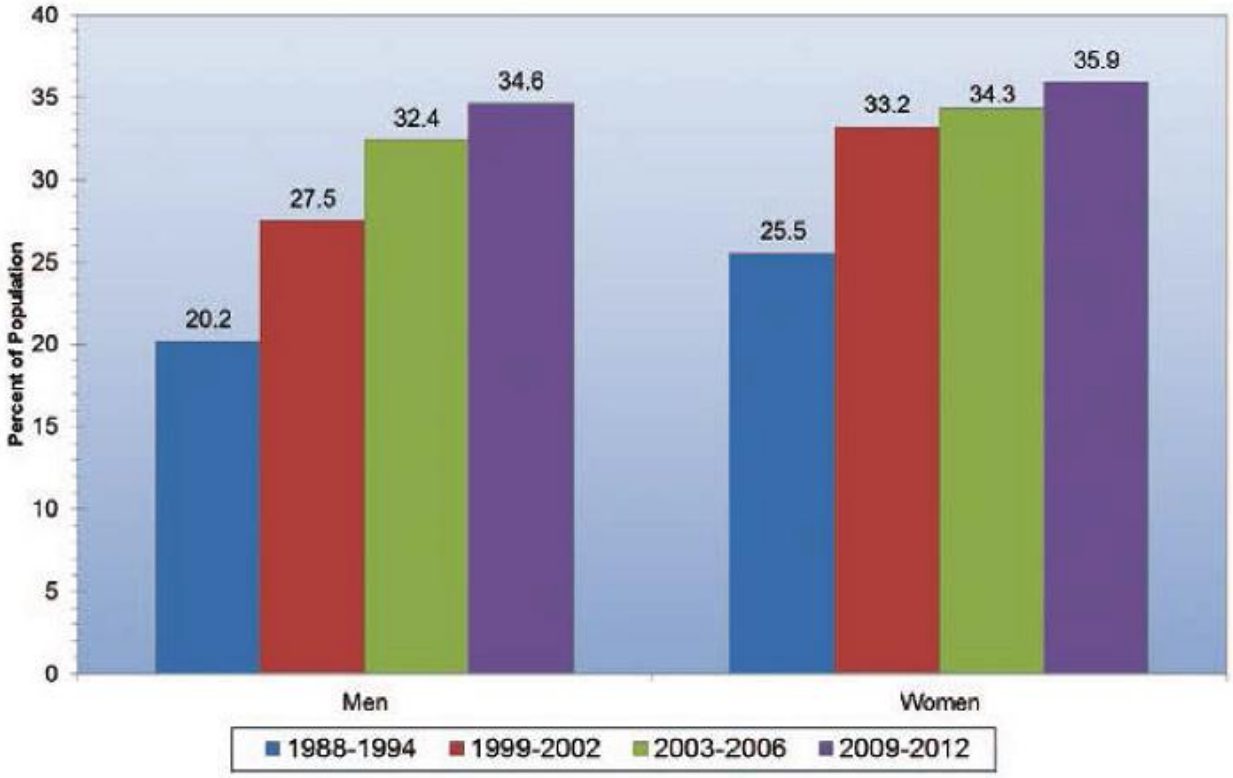
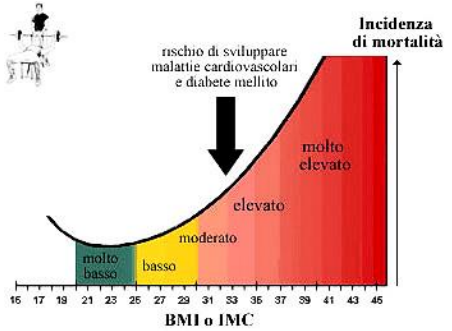
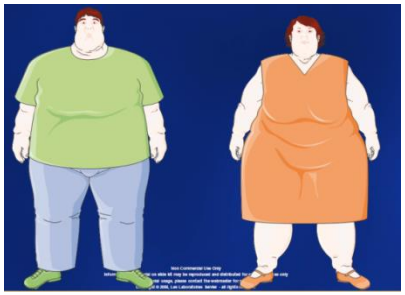
SOVRAPPESO/OBESITA’

Age-adjusted prevalence of obesity in adults 20–74 years of age





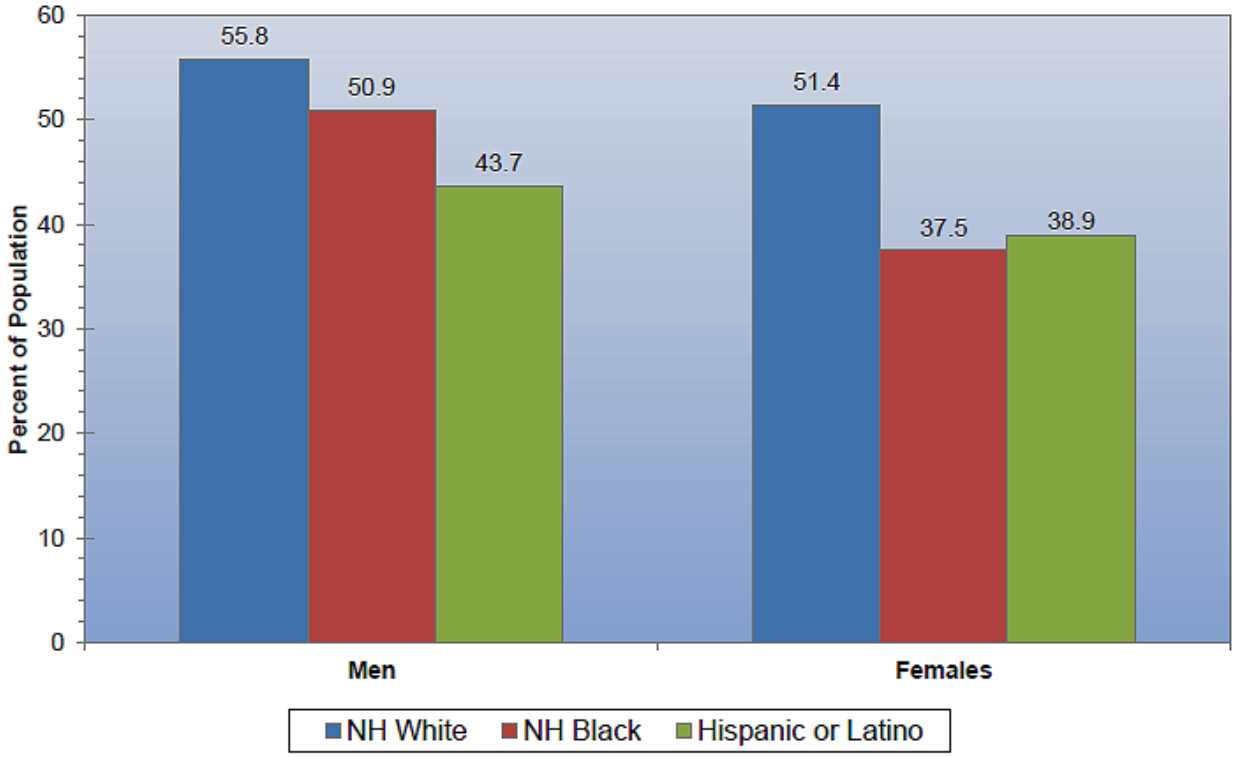


Data derived from *Health, United States, 2014.*

Mozaffarian D et al. Published online in *Circulation* Dec. 16, 2015

SEDENTARIETA’

Prevalence of meeting the aerobic physical activity guidelines among adults ≥18 years of age
(NHIS 2014)



NH indicates non-Hispanic. Percents are age-adjusted. Meeting the 2008 Federal PA Guidelines is defined as engaging in moderate leisure-time physical activity for at least 150 minutes per week or vigorous activity at last 75 minutes per week or an equivalent combination.

Mozaffarian D et al. Published online in *Circulation* Dec. 16, 2015

LA SFIDA DEL MONDO REALE

Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries

*Kornelia Kotseva, David Wood, Guy De Backer, Dirk De Bacquer, Kalevi Pyörälä, Ulrich Keil, for the EUROASPIRE Study Group**

Summary

Background The first and second EUROASPIRE surveys showed high rates of modifiable cardiovascular risk factors in patients with coronary heart disease. The third EUROASPIRE survey was done in 2006–07 in 22 countries to see whether preventive cardiology had improved and if the Joint European Societies' recommendations on cardiovascular disease prevention are being followed in clinical practice.

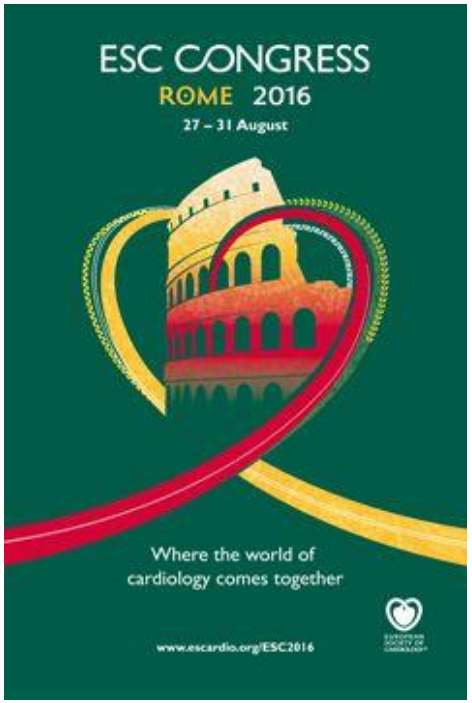
Methods EUROASPIRE I, II, and III were designed as cross-sectional studies and included the same selected geographical areas and hospitals in the Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, and Slovenia. Consecutive patients (men and women ≤70 years) were identified after coronary artery bypass graft or percutaneous coronary intervention, or a hospital admission with acute myocardial infarction or ischaemia, and were interviewed at least 6 months later.

Findings 3180 patients were interviewed in the first survey, 2975 in the second, and 2392 in the third. Overall, the proportion of patients who smoke has remained nearly the same (20·3% in EUROASPIRE I, 21·2% in II, and 18·2% in III; comparison of all surveys p=0·64), but the proportion of women smokers aged less than 50 years has increased. The frequency of obesity (body-mass index ≥30 kg/m²) increased from 25·0% in EUROASPIRE I, to 32·6% in II, and 38·0% in III (p=0·0006). The proportion of patients with raised blood pressure (≥140/90 mm Hg in patients without diabetes or ≥130/80 mm Hg in patients with diabetes) was similar (58·1% in EUROASPIRE I, 58·3% in II, and 60·9% in III; p=0·49), whereas the proportion with raised total cholesterol (≥4·5 mmol/L) decreased, from 94·5% in EUROASPIRE I to 76·7% in II, and 46·2% in III (p<0·0001). The frequency of self-reported diabetes mellitus increased, from 17·4%, to 20·1%, and 28·0% (p=0·004).

Interpretation These time trends show a compelling need for more effective lifestyle management of patients with coronary heart disease. Despite a substantial increase in antihypertensive and lipid-lowering drugs, blood pressure management remained unchanged, and almost half of all patients remain above the recommended lipid targets. To salvage the acutely ischaemic myocardium without addressing the underlying causes of the disease is futile; we need to invest in prevention.

Funding European Society of Cardiology through grants from Merck Sharp & Dohme (EUROASPIRE I); AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Pfizer (EUROASPIRE II); and AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Sanofi-Aventis, Servier, Merck/Schering-Plough, and Novartis (EUROASPIRE III).

ANCHE PRESSO I CARDIOLOGI…



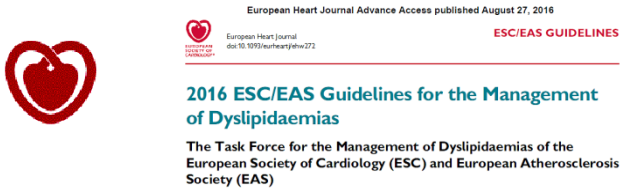
CALCOLO DEL RISCHIO

Simple principles of risk assessment, developed in these guidelines, can be defined as follows. Persons with

- **documented CVD**
- **type 1 or type 2 diabetes**
- **very high levels of individual risk factors**
- **chronic kidney disease (CKD)**

are automatically at very high or high total CV risk. No risk estimation models are needed for them; they all need active management of all risk factors.

For all other people, the use of a risk estimation system such as SCORE is recommended to estimate total CV risk since many people have several risk factors that, in combination, may result in unexpectedly high levels of total CV risk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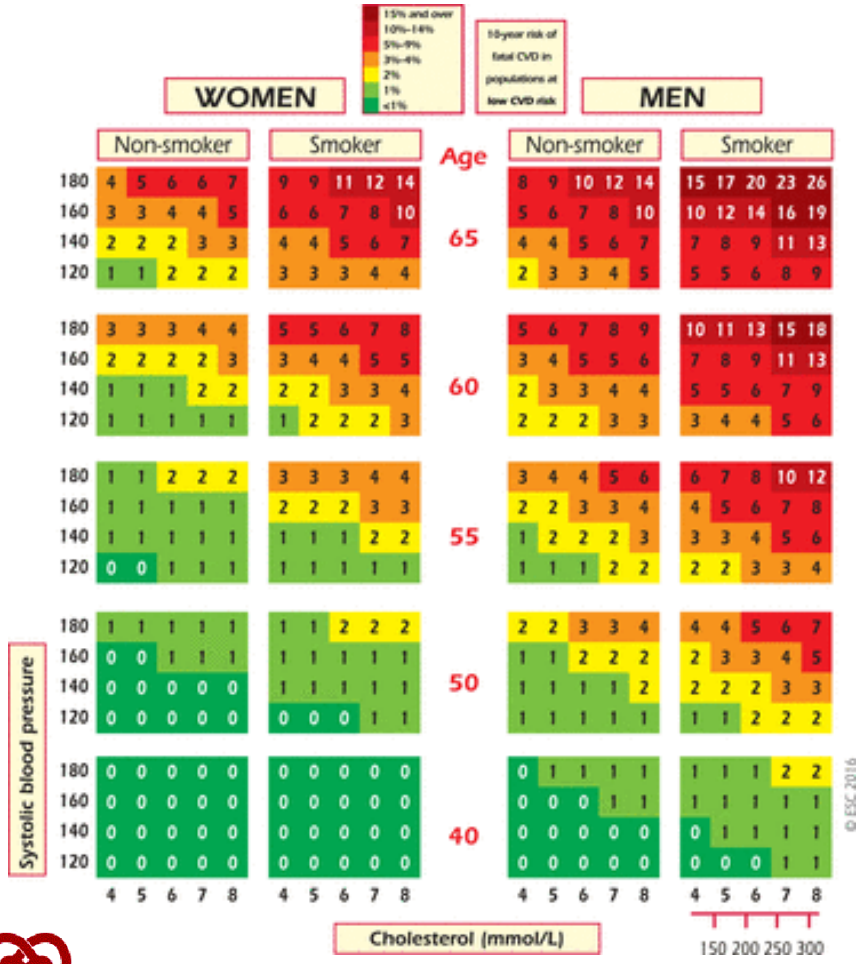
STIMA DEL RISCHIO



10-year risk of fatal CVD in populations at low CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol.

To convert the risk of fatal CVD to risk of total (fatal + non-fatal) hard CVD multiply by 3 in men and 4 in women, and slightly less in old people.

STIMA DEL RISCHIO

Very high-risk	Subjects with any of the following: • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	SCORE <1% for 10-year risk of fatal CVD.

Recommendations	Class [a]	Level [b]
Total risk estimation using a risk estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD or familial hypercholesterolaemia.	I	C
High and very high-risk individuals can be detected on the basis of documented CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, familial hypercholesterolaemia or a high SCORE risk and are a high priority for intensive advice with regard to all risk factors.	I	C

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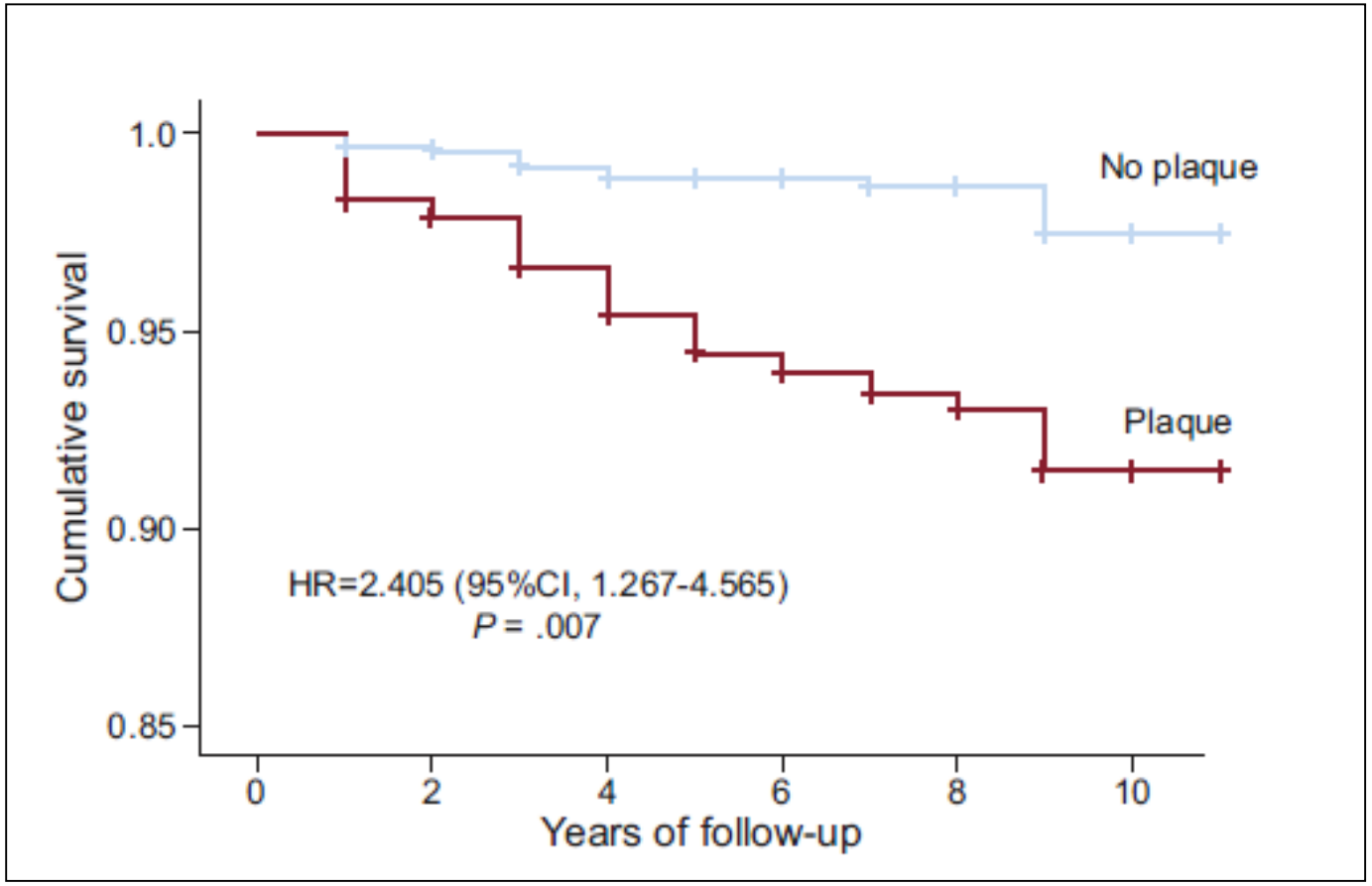
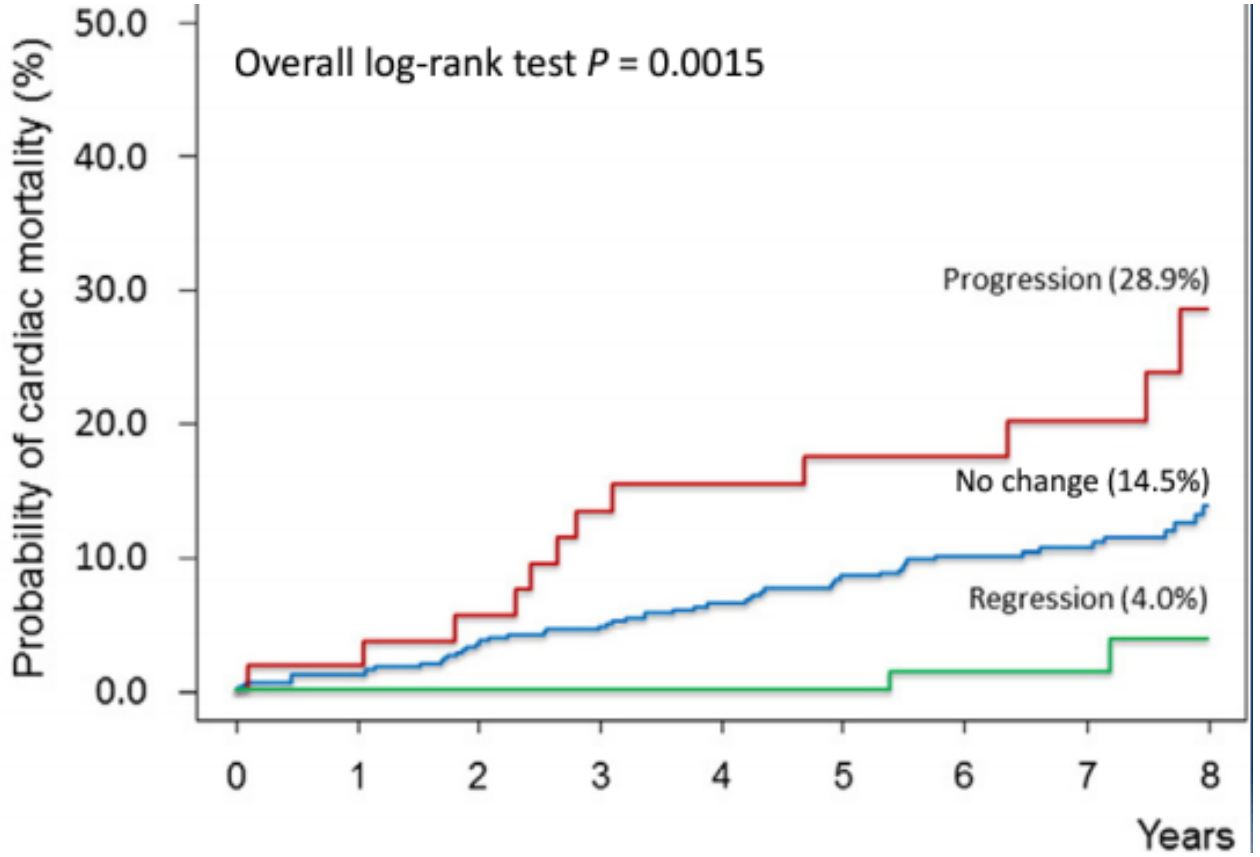
ATHEROSCLEROTIC PLAQUE AND SURVIVAL



A.M. Bea et al. Rev Esp Cardiol. 2017

ATHEROSCLEROSIS PROGRESSION AND CORONARY DEATH



Ndrepepa G et al. Am Heart J 2016;177:9–16.

STIMA DEL RISCHIO

Social deprivation–the origin of many of the causes of CVD.
Obesity and central obesity as measured by the body mass index and waist circumference, respectively.
Physical inactivity.
Psychosocial stress including vital exhaustion.
Family history of premature CVD (men: <55 years; women: <60 years).
Autoimmune and other inflammatory disorders.
Major psychiatric disorders.
Treatment for human immunodeficiency virus (HIV) infection.
Atrial fibrillation.
Left ventricular hypertrophy.
Chronic kidney disease.
Obstructive sleep apnoea syndrome.

Factors modifying SCORE risks

European Heart Journal Advance Access published August 27, 2016

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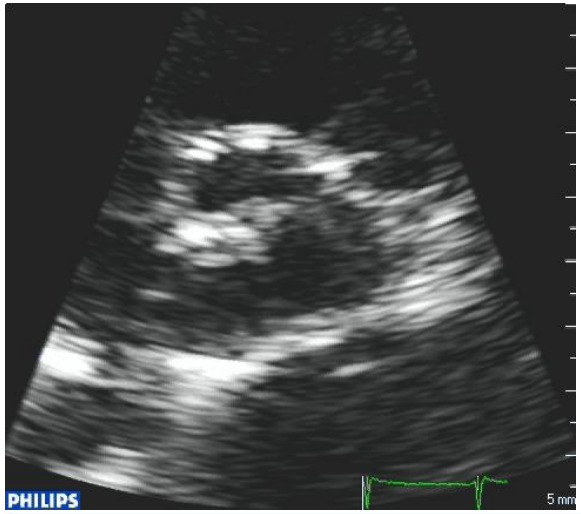
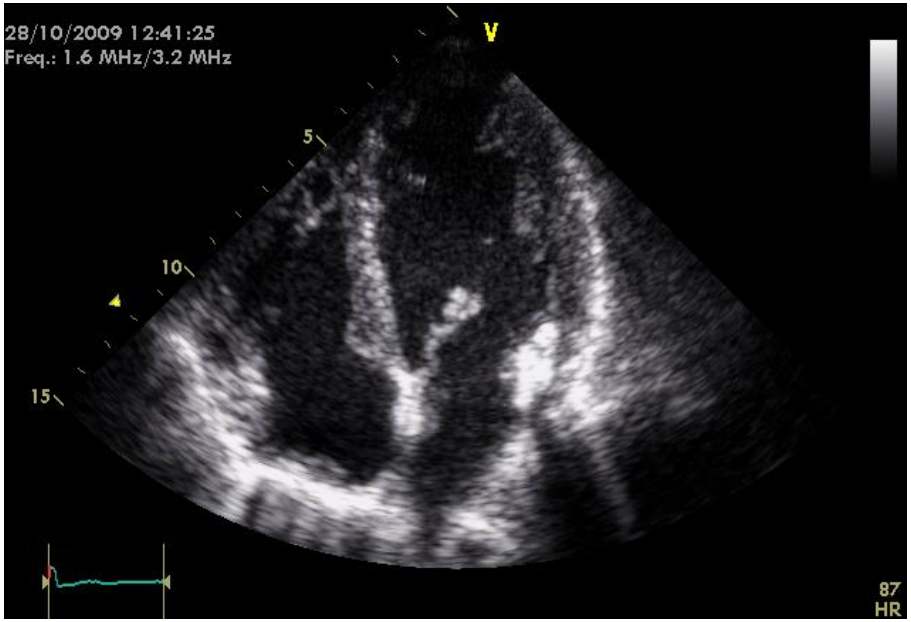
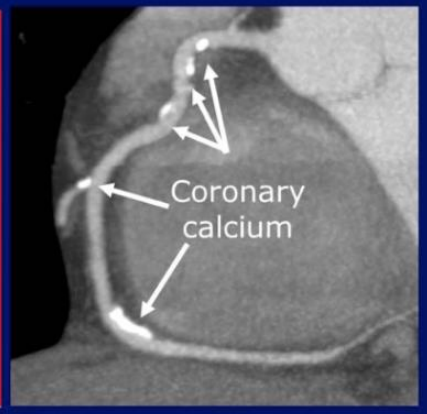
LOW-COST CALCIUM SCORE



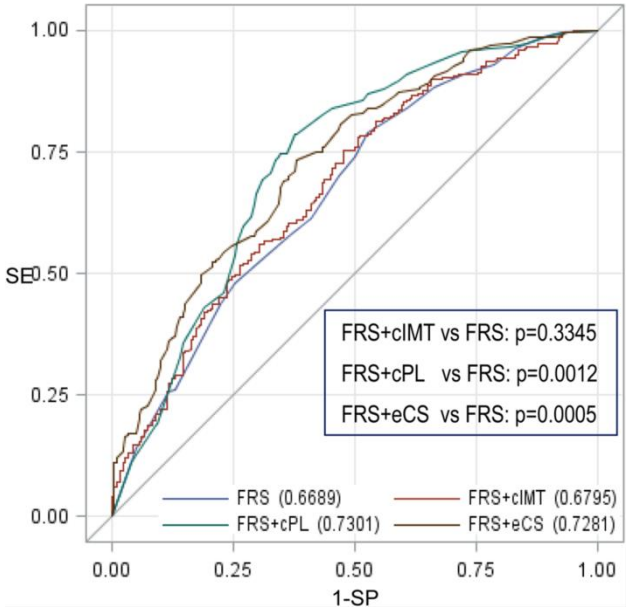


Early detection of calcified cholesterol plaques in the coronary arteries allows timely initiation of preventive medical therapies that stop the disease on its track.



Coronary Calcium score = 600

ECHOCARDIOGRAPHIC CALCIUM SCORE



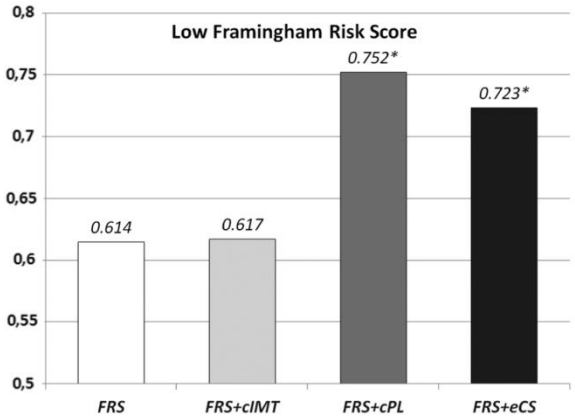
European Heart Journal – Cardiovascular Imaging (2016) 17, 991–1000
doi:10.1093/ehjci/jev222

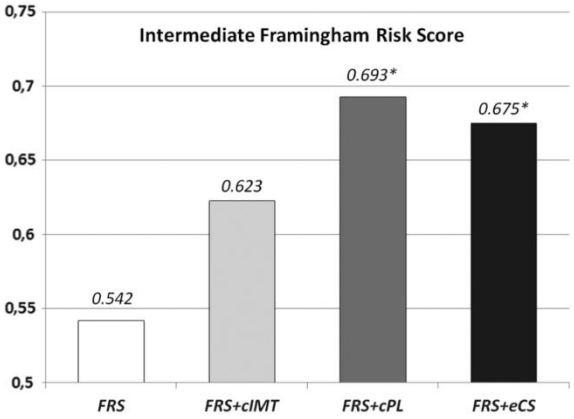
Differential incremental value of ultrasound carotid intima–media thickness, carotid plaque, and cardiac calcium to predict angiographic coronary artery disease across Framingham risk score strata in the APRES multicentre study

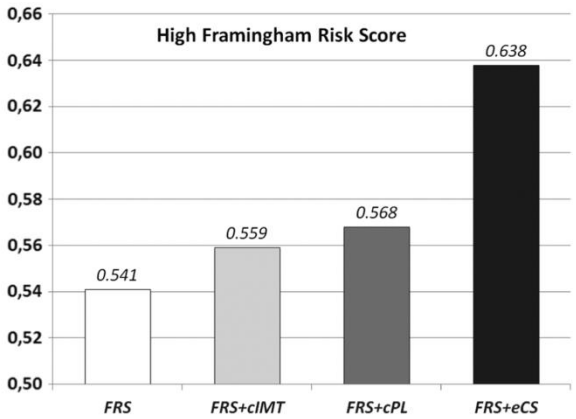
Nicola Gaibazzi[1]*, Fausto Rigo[2], Rita Facchetti[3], Scipione Carerj[4], Cristina Giannattasio[3], Antonella Moreo[5], Gian Francesco Mureddu[5], Massimo Salvetti[6], Elisabetta Grolla[2], Giacomo Faden[7], Francesca Cesana[3], and Pompilio Faggiano[7]

Received 1 July 2015; accepted after revision 10 August 2015; online publish-ahead-of-print 10 September 2015

Conclusions Ultrasound eCS and cPL assessments were significant predictors of angiographic CAD in patients without prior CAD but with signs or symptoms suspect for CAD, independently and incrementally to FRS, across all pre-test risk probability strata, although in high-risk subjects, only eCS maintained an incremental value. The use of cIMT was not significantly incrementally useful in any FRS risk category.



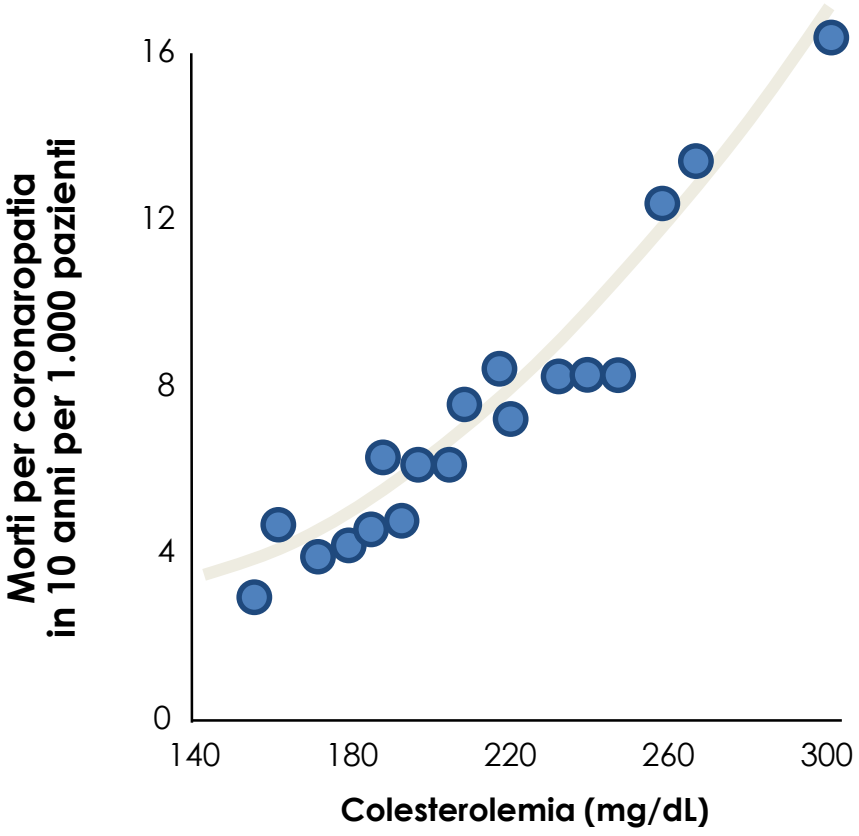




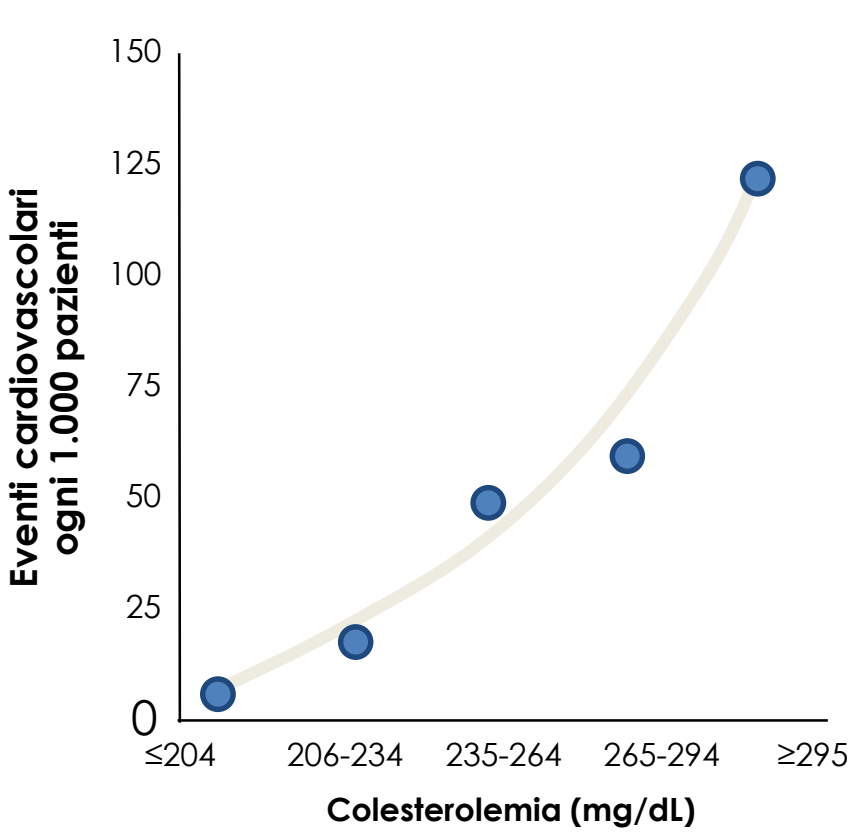
*Indicates Models with AUC p<0.05 compared with baseline FRS model.

LIVELLI DI COLESTEROLO SIERICO E RISCHIO CORONARICO

Multiple Risk Factor Intervention Trial (MRFIT) (n=356.222)

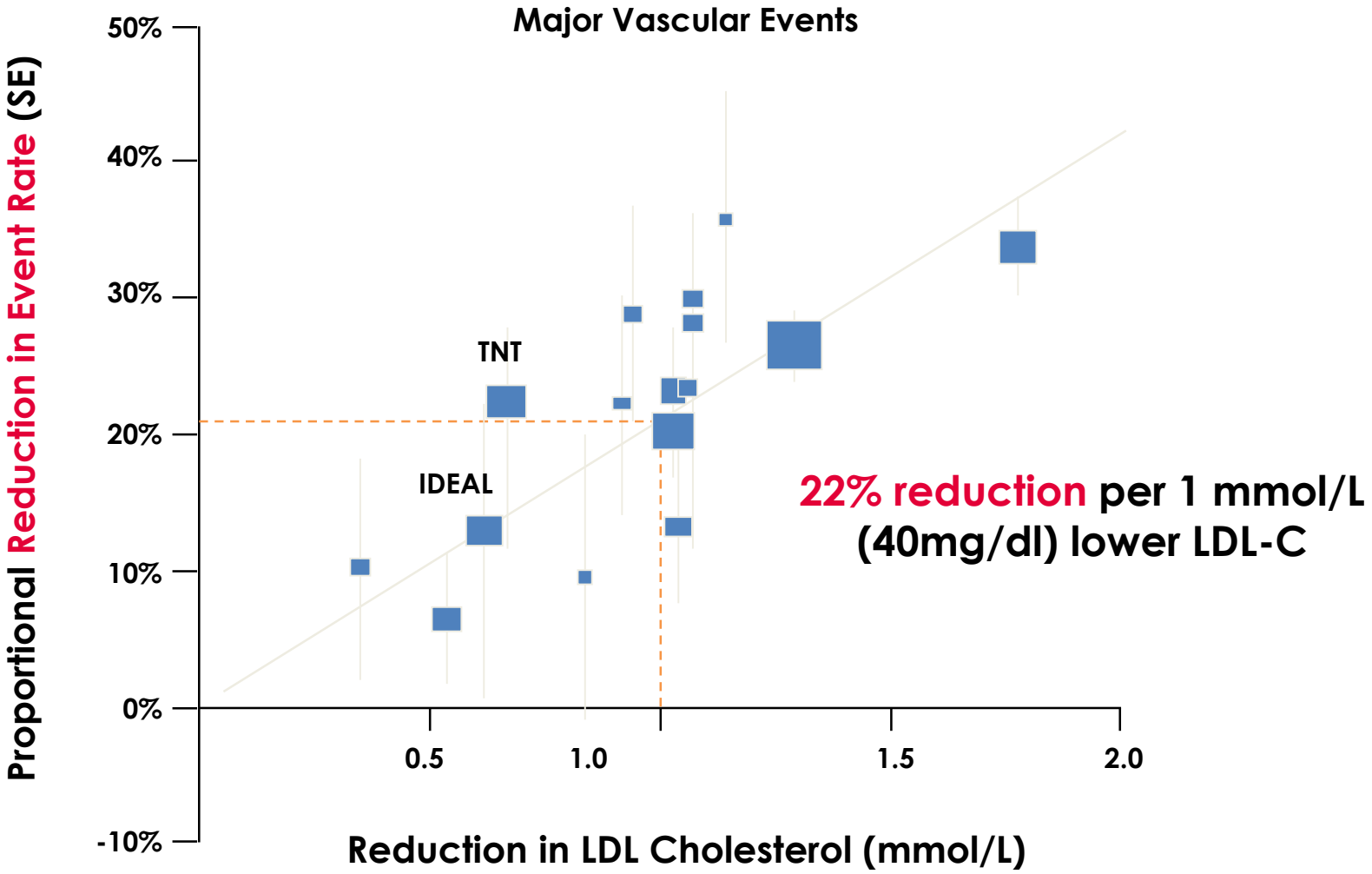


Studio di Framingham (n=5.209)



Stamler J et al. JAMA 1986;256:2823-2828
Castelli WP et al. JAMA 1986;256:2835-2838

CHOLESTEROL TRIALIST COLLABORATION META-ANALYSIS OF DYSLIPIDEMIA TRIALS

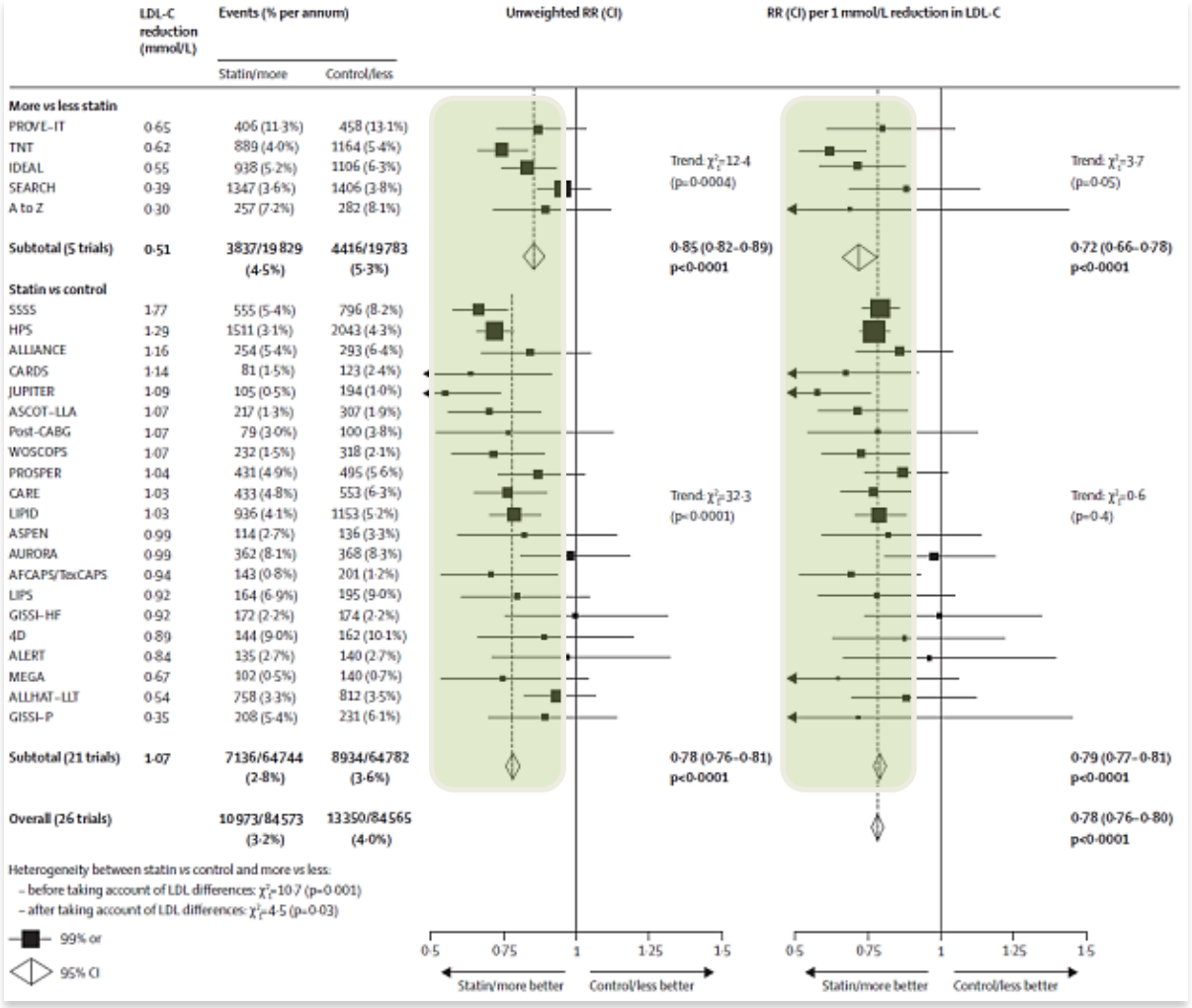


Adapted from CTT Collaborators. Lancet. 2005; 366:1267-78

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**

26 trial per un totale di 170 000 pazienti



Lancet 2010; 376:1670–81

DYSLIPIDEMIA TREATMENT

Recommendations	Class [a]	Level [b]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

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Recommendations	Class [a]	Level [b]
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

FARMACI: STATINE

- **A number of large-scale trials have demonstrated that statins substantially reduce CV morbidity and mortality in both primary and secondary prevention, in both genders and in all age groups. Statins have also been shown to slow the progression or even promote regression of coronary atherosclerosis.**

Starting LDL-C		Reduction to reach LDL-C goal, %		
mmol/L	~mg/dL	<1.8 mmol/L (~70 mg/dL)	<2.6 mmol/L (~100 mg/dL)	<3 mmol/L (~115 mg/dL)
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	–
1.8–2.3	70–90	<22	–	–

Percentage reduction of low-density lipoprotein cholesterol (LDL-C) requested to achieve goals as a function of the starting value.

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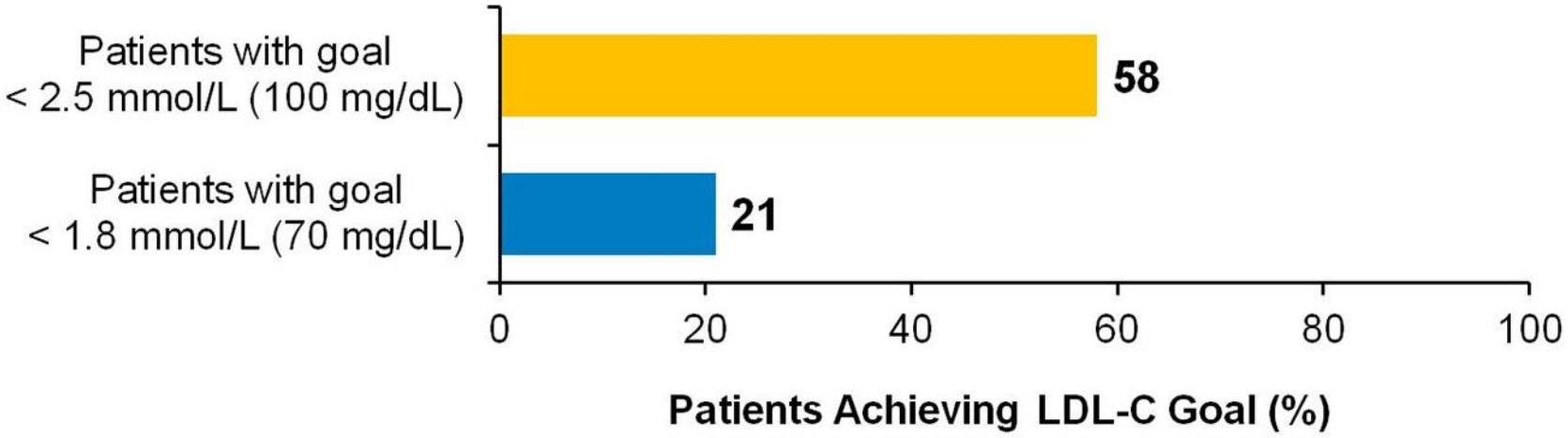
ANZIANI

Recommendations	Class [a]	Level [b]
Treatment with statins is recommended for older adults with established CVD in the same way as for younger patients.	I	A
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.	IIa	C
Statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia.	IIa	B

Recommendations for the treatment of dyslipidaemia in older adults

EUROASPIRE IV

- There is a clear need to treat high-risk patients[1]
- The majority (87%) of secondary-prevention patients now receive a statin[2]
- Issues remain in bringing patients to LDL-C goals[1,2]



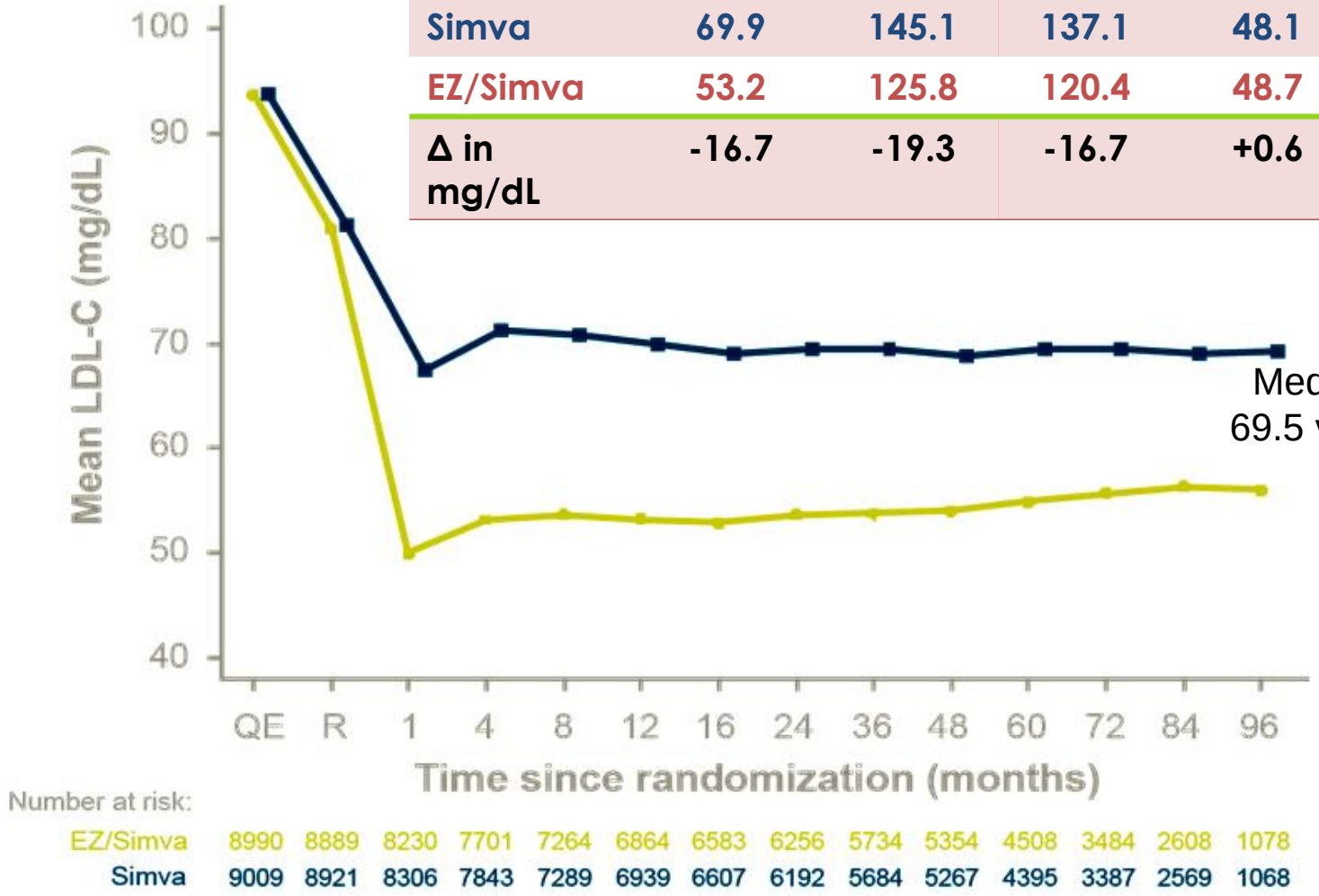
IMPROVE-IT: GOALS

- **IMPROVE-IT**: First large trial evaluating clinical efficacy of combination **EZ/Simva vs. simvastatin** (i.e., the addition of ezetimibe to statin therapy):
  - Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?
  - "Is (Even) Lower (Even) Better?" (estimated mean LDL-C ~50 vs. 65mg/dL)
  - Safety of ezetimibe

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

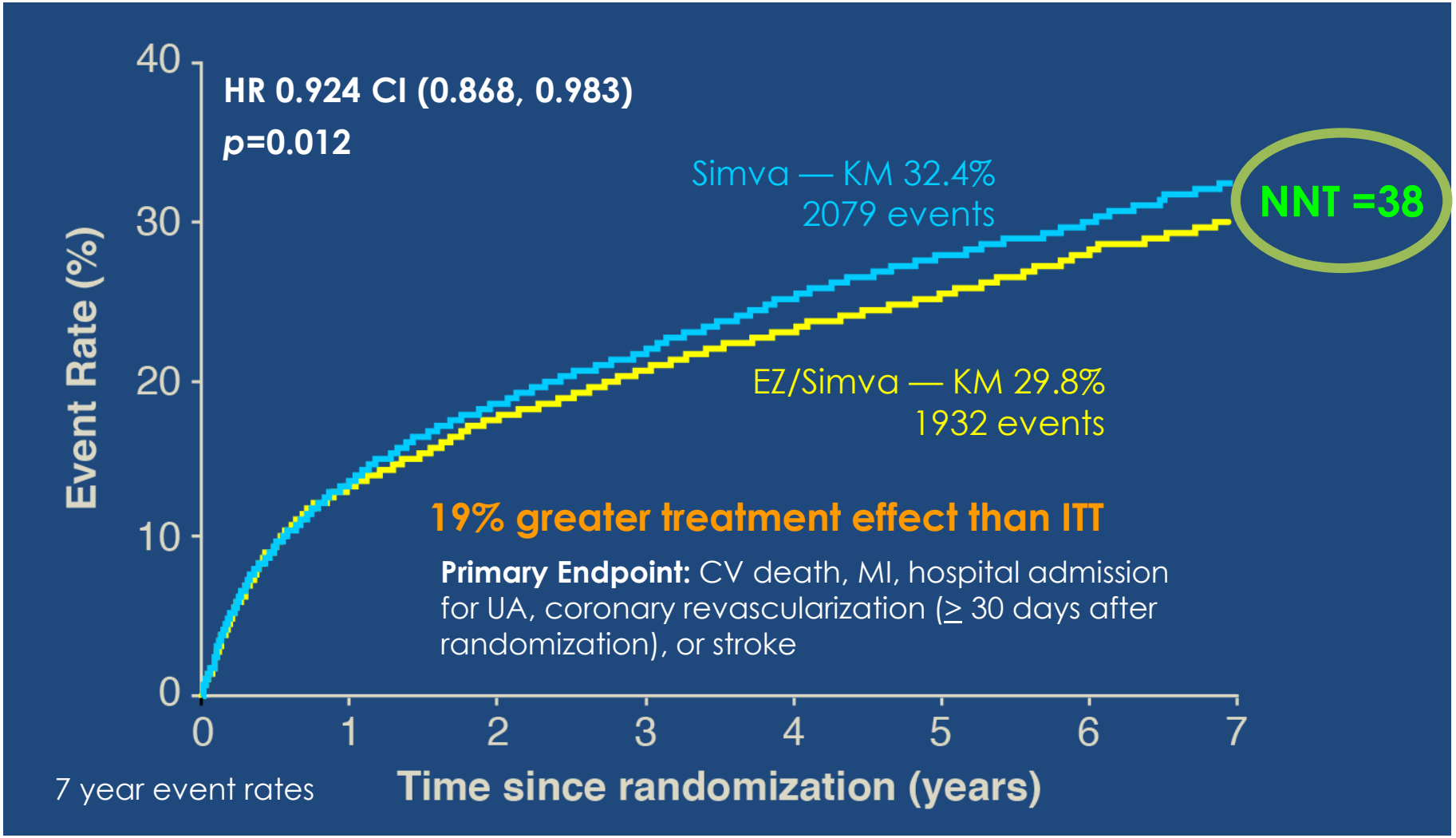
LDL-C AND LIPID CHANGES

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

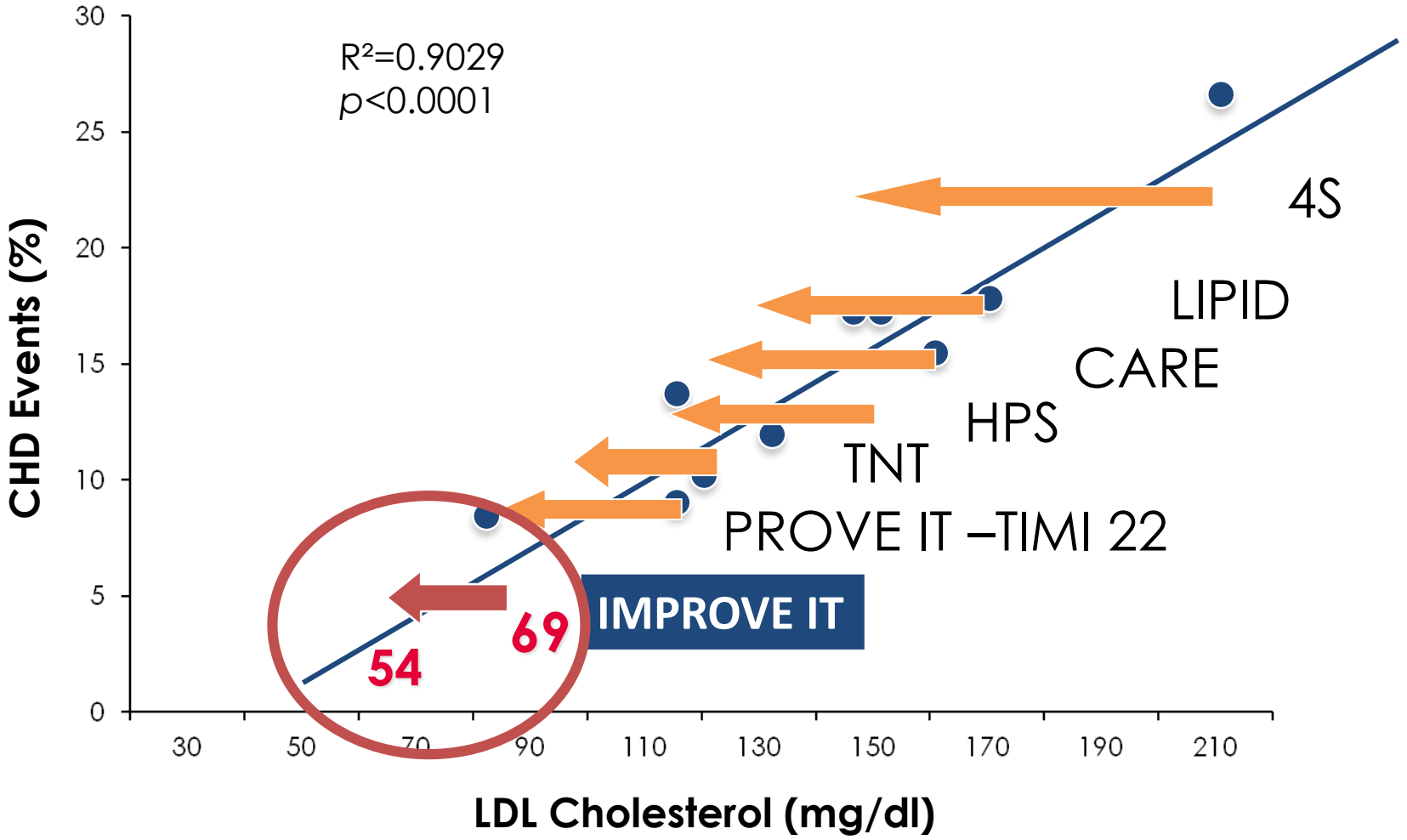


Median Time avg
69.5 vs. 53.7 mg/dL

PRIMARY ENDPOINT ON TREATMENT

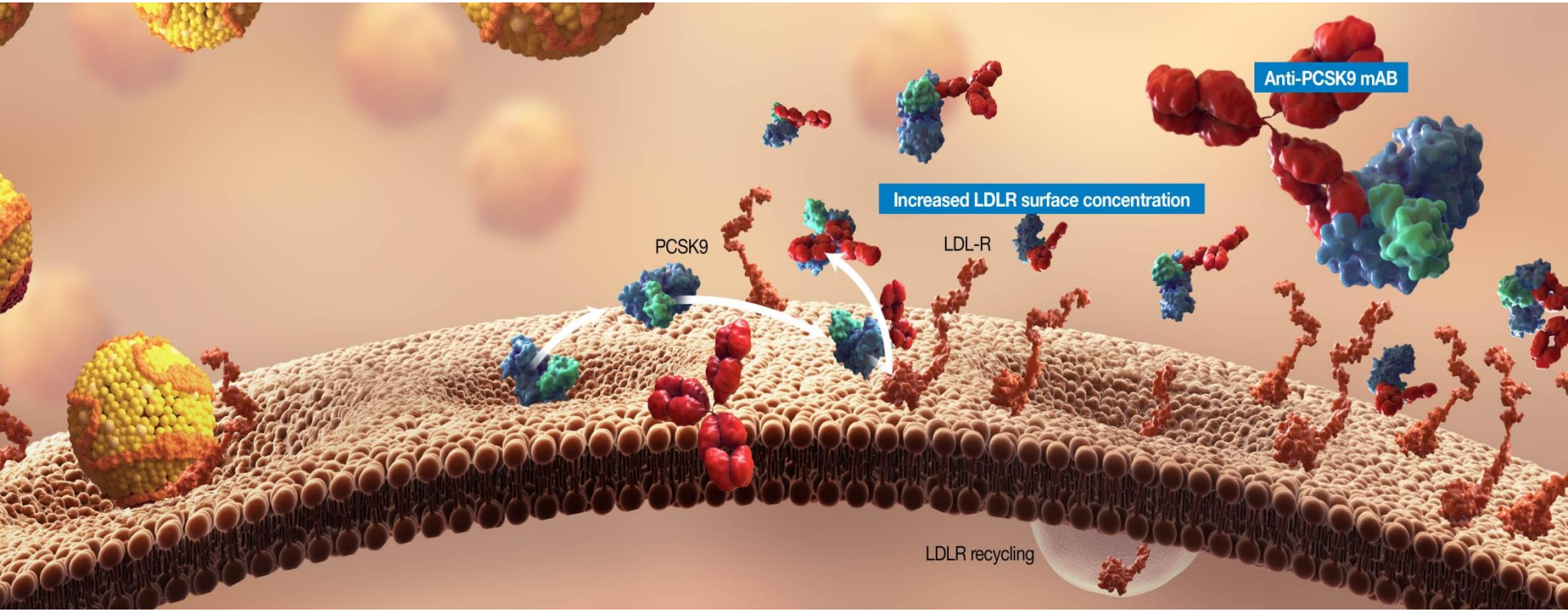


THE STATIN DECADE: FOR LDL: "LOWER IS BETTER"



Adapted and Updated from O'Keefe, J. et al, J Am Coll Cardiol 2004;43:2142-6.

BLOCKADE OF PCSK9/LDLR INTERACTION MAY LOWER LDL LEVELS



Elaborated from 1. Chan JC, et al. *Proc Natl Acad Sci U S A.* 2009;106:9820-9825.

Journal of the American College of Cardiology

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EDITORIAL COMMENT

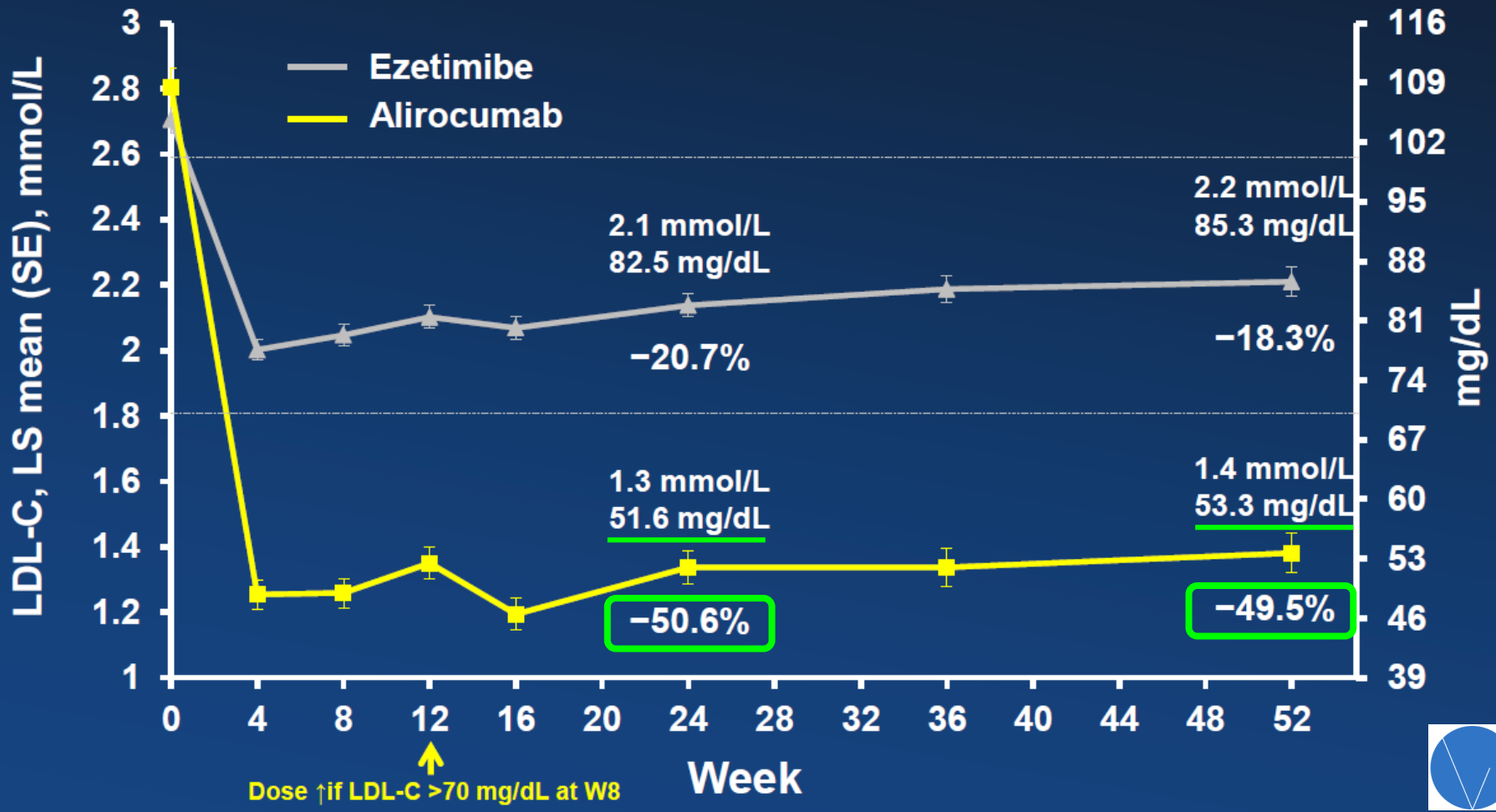
PCSK9 Inhibition

The Next Statin?*

Robert A. Vogel, MD
Denver, Colorado

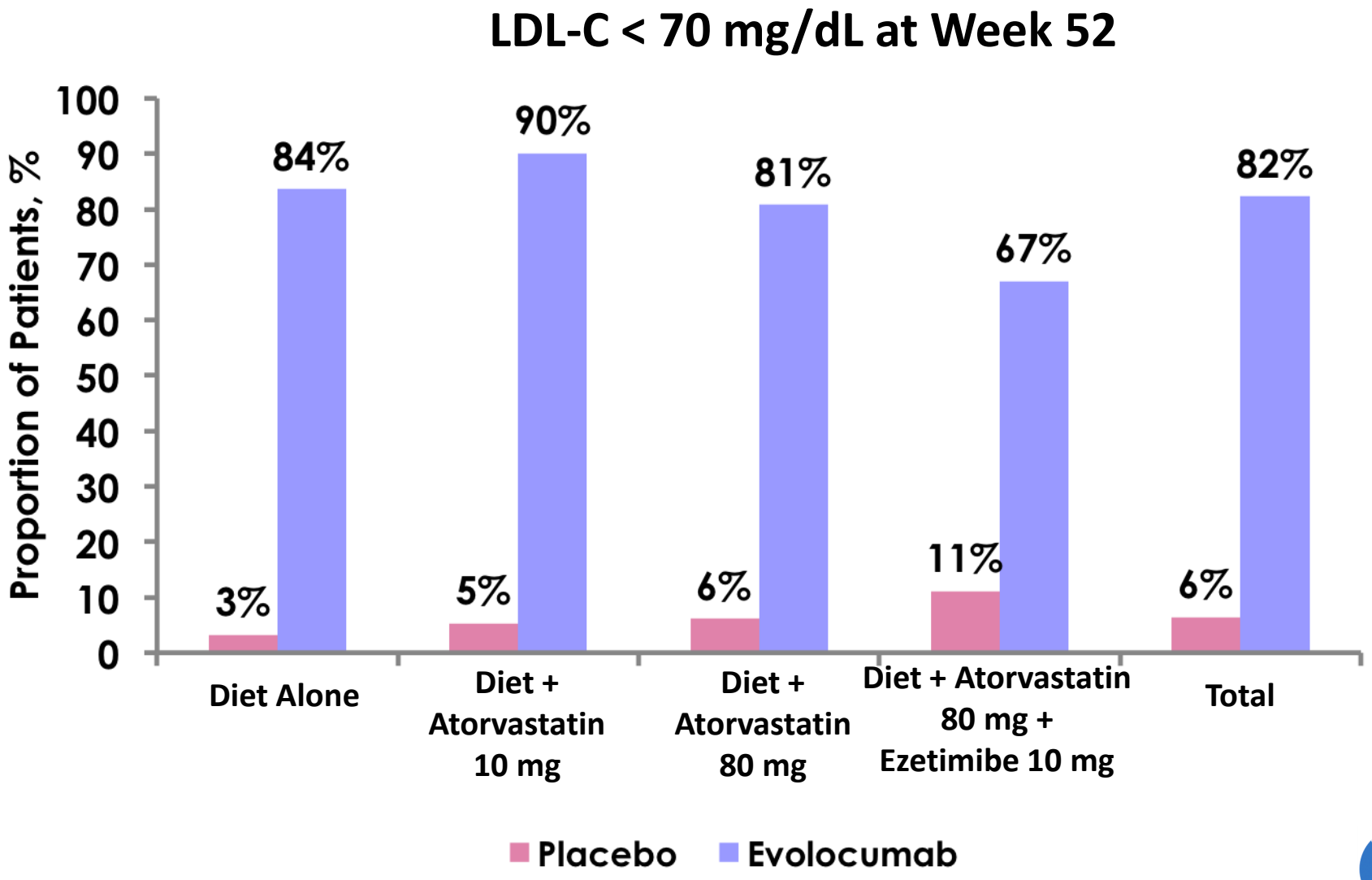
Alirocumab Maintained Consistent LDL-C Reductions over 52 Weeks

Achieved LDL-C Over Time on Background of Maximally-Tolerated Statin



Intent-to-treat (ITT) analysis

DESCARTES: UC LDL-C GOAL ACHIEVEMENT



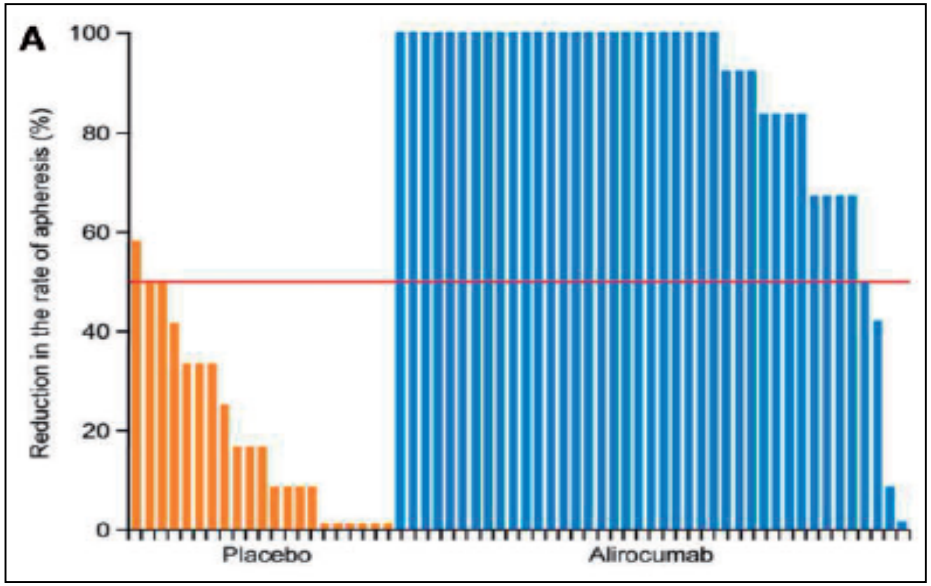
European Heart Journal Advance Access published August 29, 2016

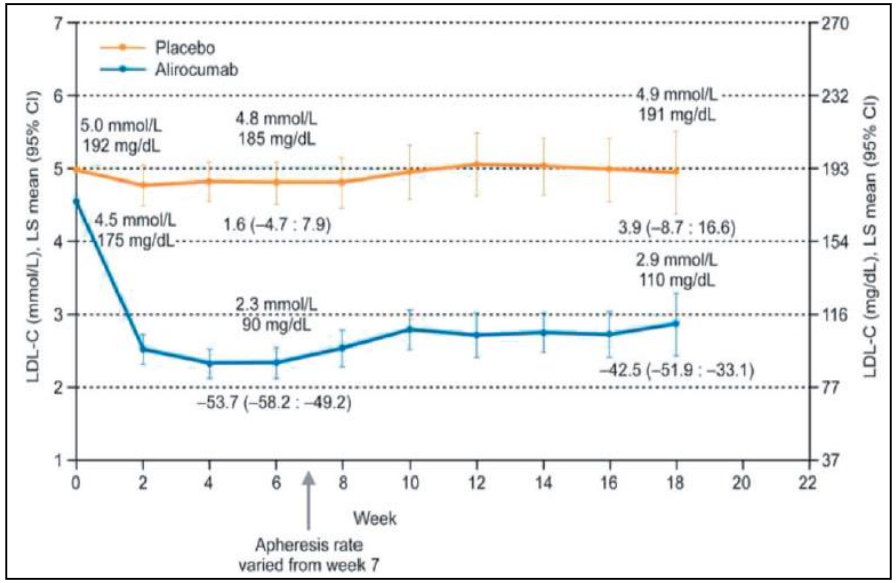
European Heart Journal (2016) **0**, 1–8
doi:10.1093/eurheartj/ehw388

ESC FASTTRACK
ESC Hot Line

Lipids

Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial





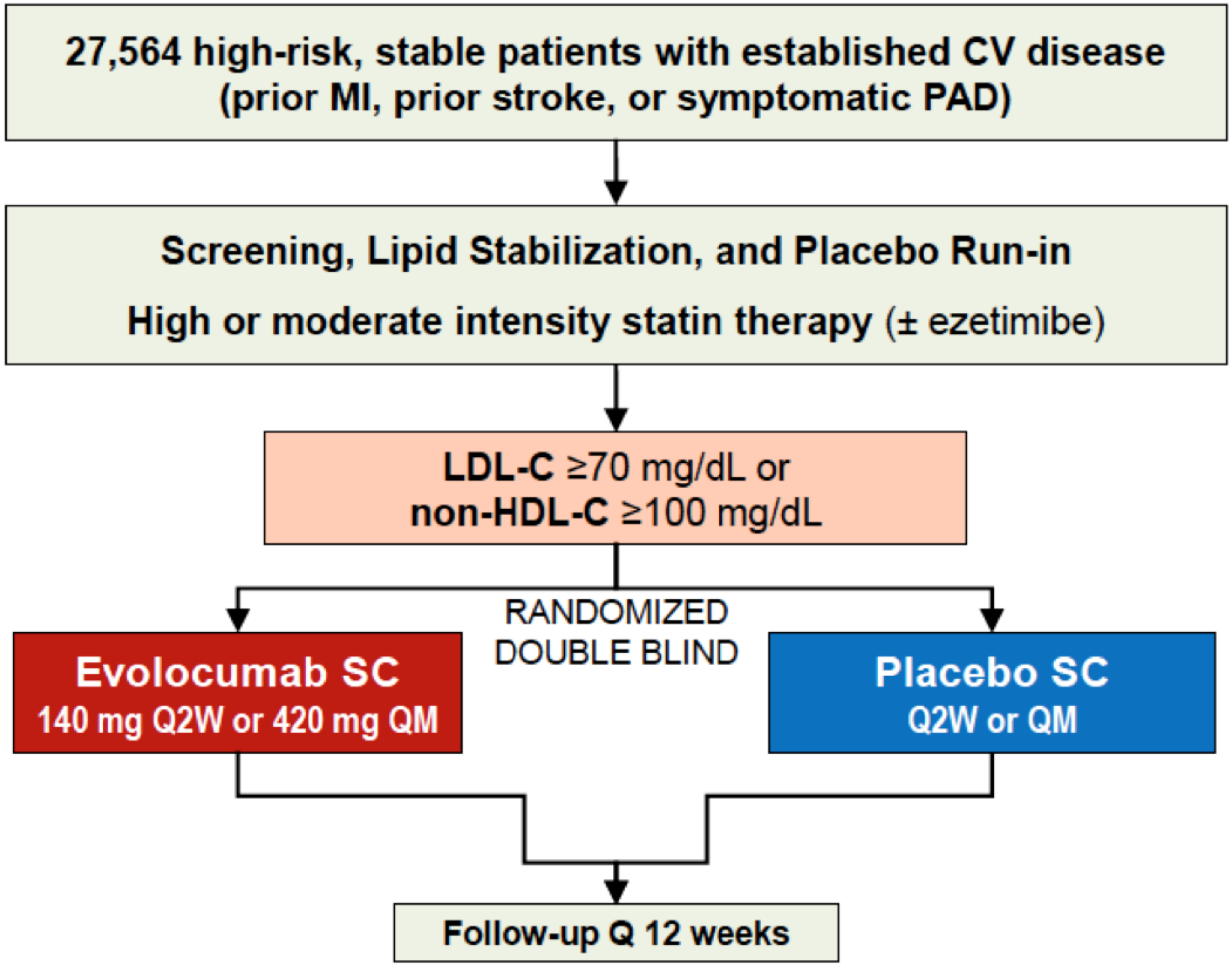
Conclusions Lipoprotein apheresis was discontinued in 63.4% of patients on alirocumab who were previously undergoing regular apheresis, and the rate was at least halved in 92.7% of patients. Alirocumab was generally safe and well tolerated.

FOURIER STUDY

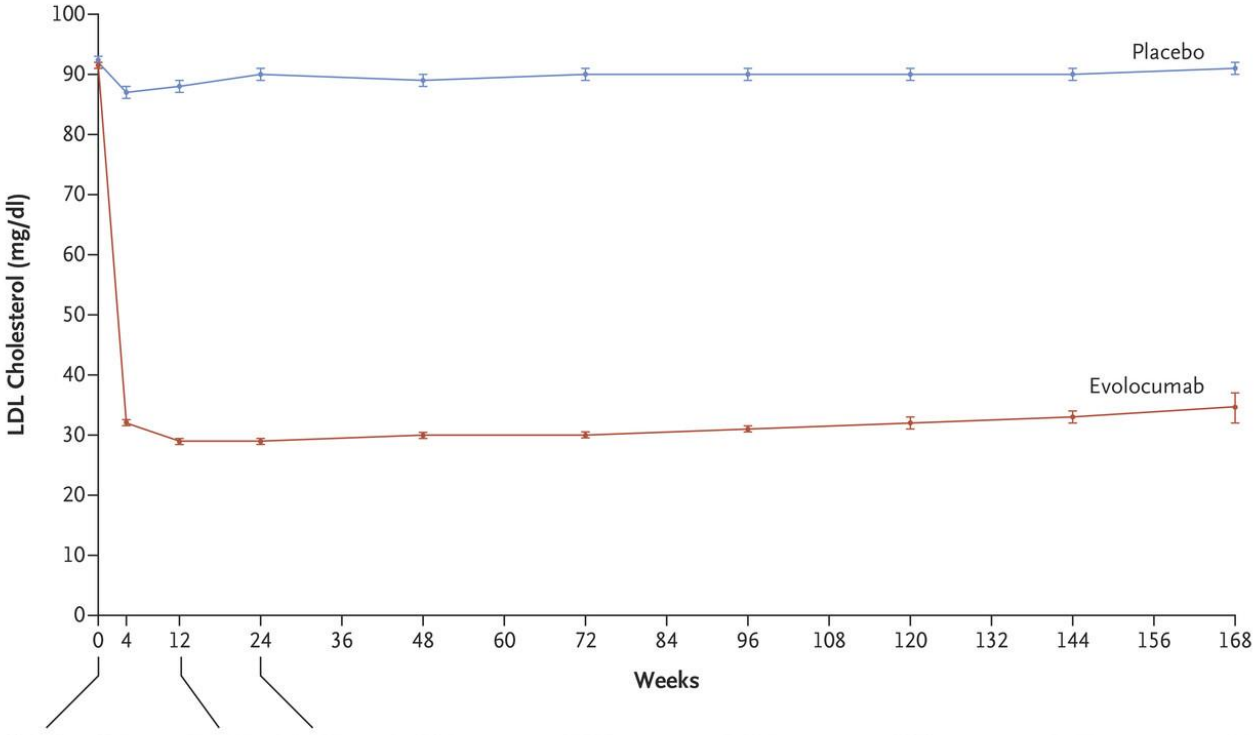
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*



LDL LEVELS OVER TIME



No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Sabatine MS et al. N Engl J Med 2017;376:1713-1722.

The NEW ENGLAND JOURNAL of MEDICINE

PRIMARY AND SECONDARY END POINTS

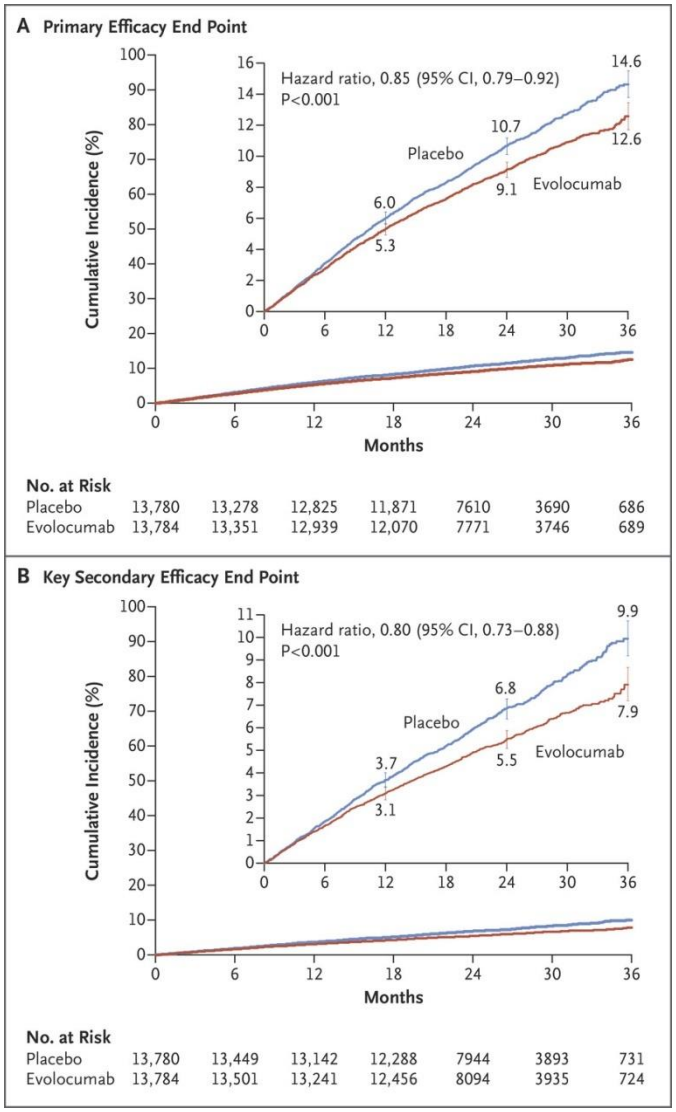


Table 2. Primary and Secondary End Points.

Outcome	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

* Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary end points should be considered significant, whereas all other P values should be considered exploratory.

† The Cholesterol Treatment Trialists Collaboration (CTTC) composite end point consists of coronary heart death, nonfatal myocardial infarction, stroke, or coronary revascularization.

Sabatine MS et al. N Engl J Med 2017;376:1713-1722.

The NEW ENGLAND JOURNAL of MEDICINE

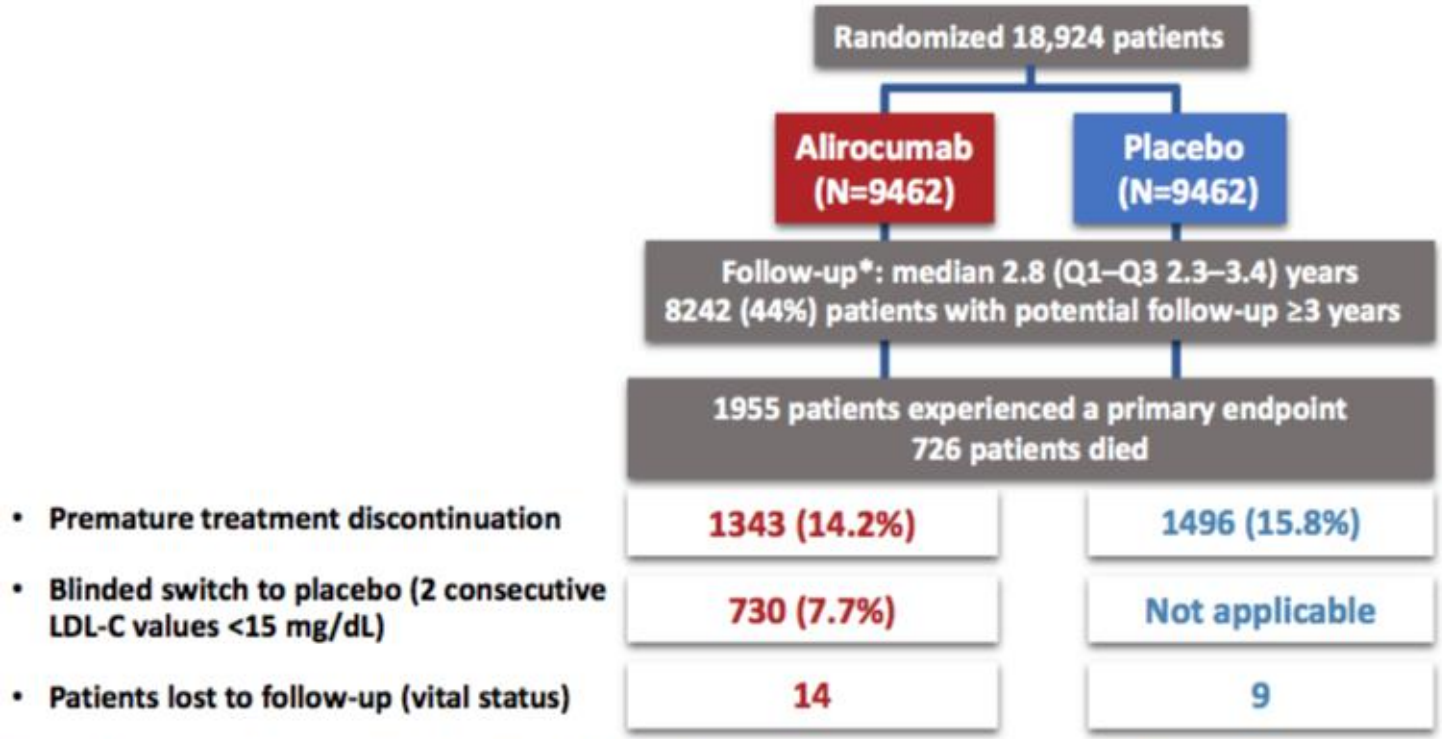
ODYSSEY OUTCOMES

The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher, **Ph. Gabriel Steg**
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

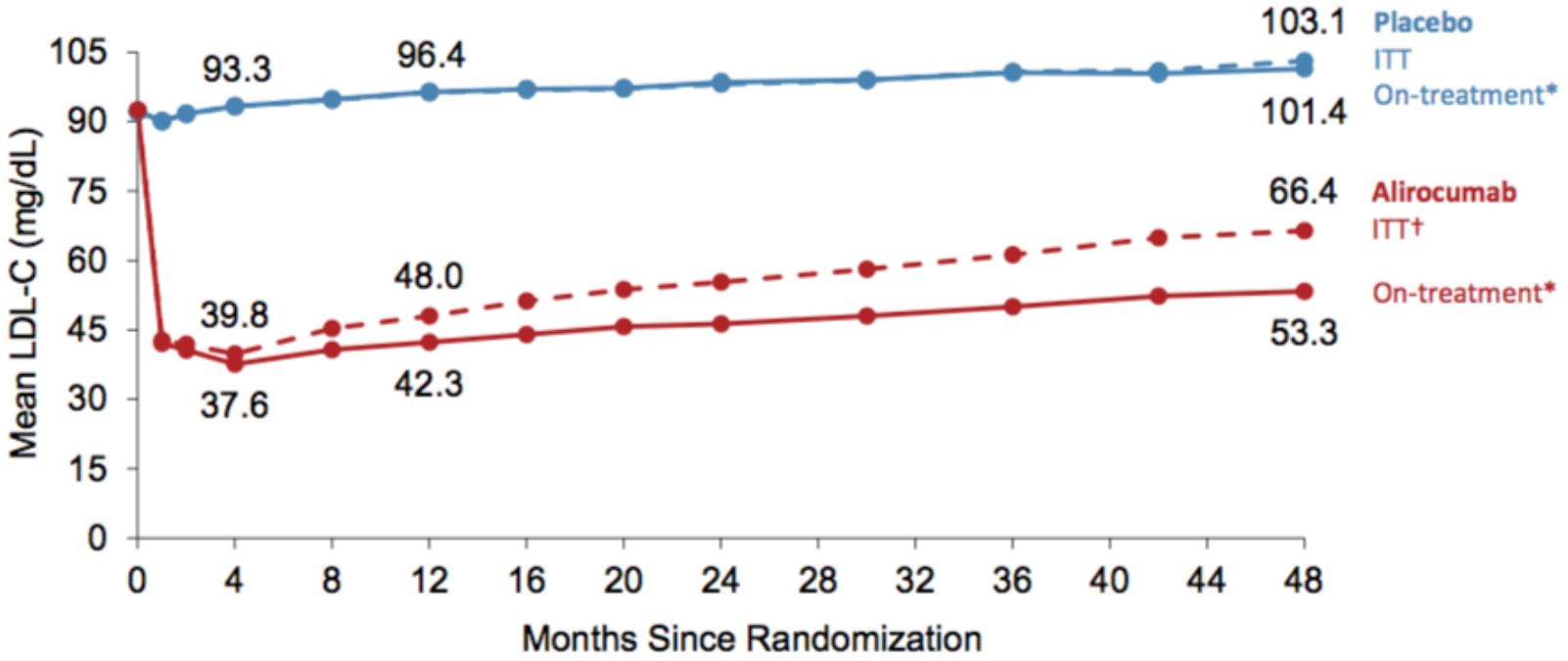


*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

ODYSSEY OUTCOMES

ODYSSEY OUTCOMES

LDL-C: ITT and On-Treatment Analyses

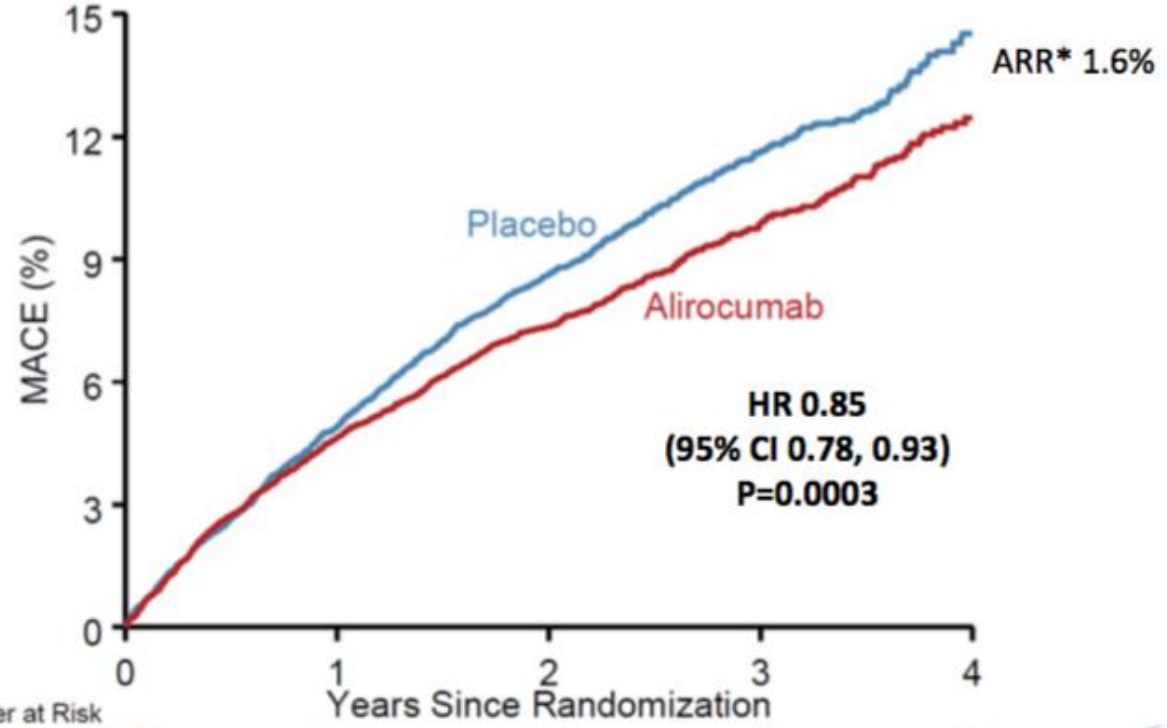


*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

ODYSSEY OUTCOMES

ODYSSEY OUTCOMES

Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

ODYSSEY OUTCOMES

ODYSSEY OUTCOMES

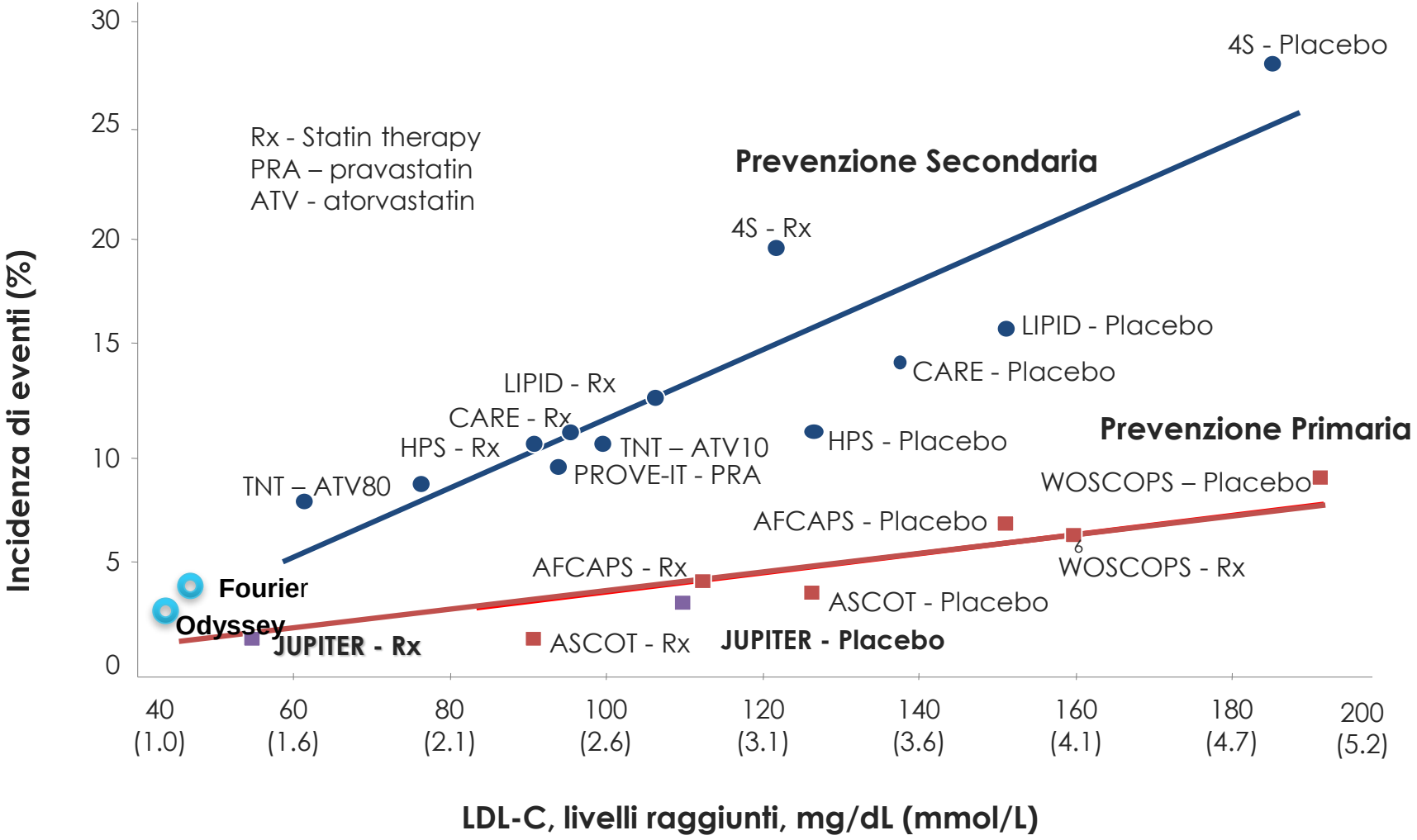
Clinical Perspective

- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions
- Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo
  - ➢These are the patients who may benefit most from treatment

ARR, absolute risk reduction

ODYSSEY OUTCOMES

INCIDENZA DI EVENTI IN FUNZIONE DEI LIVELLI DI LDL-C RAGGIUNTI NEI TRIAL CON STATINE



LOWER IS BETTER

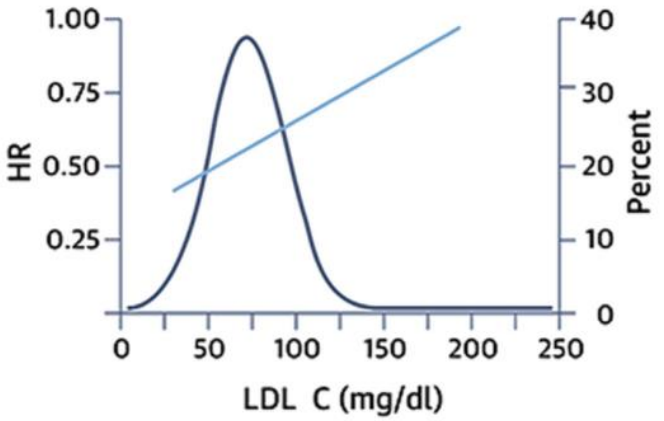
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 5, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.02.615

Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events

A Meta-Analysis of Statin Trials

S. Matthijs Boekholdt, MD, PhD,* G. Kees Hovingh, MD, PhD,† Samia Mora, MD, MHS,‡ Benoit J. Arsenault, PhD,† Pierre Amarenco, MD,§ Terje R. Pedersen, MD, PhD,‖ John C. LaRosa, MD,¶ David D. Waters, MD,# David A. DeMicco, DPharm,** R. John Simes, MD,†† Antony C. Keech, MBBS, MSc,†† David Colquhoun, MD,‡‡ Graham A. Hitman, MD,§§ D. John Betteridge, MD,‖‖ Michael B. Clearfield, DO,¶¶ John R. Downs, MD,##*** Helen M. Colhoun, MD,††† Antonio M. Gotto, Jr, MD, DPhil,‡‡‡ Paul M. Ridker, MD, MPH,‡ Scott M. Grundy, MD, PhD,§§§ John J.P. Kastelein, MD, PhD†



CENTRAL ILLUSTRATION **On-Statin LDL-C Levels and Risk for Major Cardiovascular Events**

Distribution of achieved on-statin LDL-C levels (**dark blue curve**; right *y*-axis) and the risk of major cardiovascular events (**light blue line**; left *y*-axis). The *x*-axis represents achieved on-statin LDL-C levels. LDL C = low-density lipoprotein cholesterol; HR = hazard ratio.

CONCLUSIONS The reductions of LDL-C, non-HDL-C, and apoB levels achieved with statin therapy displayed large interindividual variation. Among trial participants treated with high-dose statin therapy, >40% did not reach an LDL-C target <70 mg/dl. Patients who achieve very low LDL-C levels have a lower risk for major cardiovascular events than do those achieving moderately low levels. (J Am Coll Cardiol 2014;64:485–94) © 2014 by the American College of Cardiology Foundation.

COSTI

RESEARCH LETTER

Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial

Table 2. Clinical and Economic Outcomes of Treatment Strategies in ASCVD[a]

	Statin + Ezetimibe Relative to Statin Alone, Difference (80% Uncertainty Interval)	Statin + PCSK9 Inhibitor Relative to Statin + Ezetimibe, Difference (80% Uncertainty Interval)
Total MACE averted[b]	2 164 000 (1 305 300 to 2 913 100)	2 893 500 (1 647 600 to 4 295 800)
NNT, No. (80% uncertainty interval)[c]	41 (30 to 67)	37 (25 to 65)[d]
Life-years gained	4 849 000 (2 924 100 to 6 491 900)	6 087 500 (3 390 400 to 9 081 200)
QALYs gained	4 423 700 (2 661 900 to 5 938 100)	5 558 400 (3 085 600 to 8 333 700)
Incremental costs, $ millions[e]		
Drugs	870 084 (866 573 to 873 118)	2 485 684 (2 470 148 to 2 501 282)
Cardiovascular care	−85 540 (−115 905 to −51 262)	−109 478 (−162 994 to −60 892)
Noncardiovascular care[f]	97 002 (58 462 to 129 960)	123 415 (69 214 to 184 453)
Incremental cost-effectiveness ratio		
Per life-year gained	182 000 (137 000 to 299 000)	411 000 (277 000 to 721 000)
Per QALY gained (primary outcome)	199 000 (150 000 to 328 000)	450 000 (301 000-787 000)[g]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular events; NNT, number needed to treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life-year.

[a] The model assumed the health system perspective and a lifetime analytic horizon, and discounted future costs and QALYs at 3% a year. To reflect the precision of the model, MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and incremental cost-effectiveness ratios to the 1000s. This analysis included patients with a history of ASCVD and low-density lipoprotein cholesterol of 70 mg/dL or more taking statin therapy (n = 8 947 000 in 2015).

[b] MACE was defined as a composite of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes.

[c] No. of patients that would need to be treated for 5 years to avert 1 MACE.

[d] This is the number of patients that would have to be treated for 5 years with statin + PCSK9 inhibitor compared with statin + ezetimibe to avoid 1 MACE. For context, 20 patients would have to be treated for 5 years with statin + PCSK9 inhibitor compared with statin alone to avoid 1 MACE.

[e] All costs are reported in 2017 US dollars.

[f] Noncardiovascular costs include age-specific background health care costs (ie, health care costs unrelated to management of cardiovascular disease).

[g] For reference purposes, the incremental cost-effectiveness ratio of the statins + PCSK9 inhibitor group relative to statin therapy was $339 000/QALY (80% uncertainty interval, $284 000 to $430 000).

JAMA August 22/29, 2017 Volume 318, Number 8

Although computer simulations that synthesize data from observational studies and clinical trials may not precisely reflect clinical effectiveness that may be observed in practice over time, these updated results continue to demonstrate that reducing the price of PCSK9 inhibitors remains the best approach to delivering the potential health benefits of PCSK9 inhibitors therapy at an acceptable cost

IL PT AIFA

Note

Qualora i dati inseriti e loro modifiche non fossero corrispondenti alle disposizioni regolatorie e/o alla reale condizione clinica del paziente, la responsabilità dell'uso improprio del registro sarà interamente a carico dell'utente (medico e/o farmacista) che ha effettuato l'inserimento e/o la modifica. Si ricorda che tutte le attività degli utenti dei registri AIFA sono tracciate nel sistema e, in caso di modifica dati, altresì notificate al direttore sanitario della struttura sanitaria di appartenenza.

Indicazioni

Indicazioni autorizzate e rimborsate SSN (decisione CTS):
- pazienti di età <=80 aa con ipercolesterolemia familiare omozigote
- in prevenzione primaria in pazienti di età <=80 aa con ipercolesterolemia familiare eterozigote e livelli di LDL-C >=130 mg/dL nonostante terapia da almeno 6 mesi con statina ad alta potenza alla massima dose tollerata + ezetimibe oppure con dimostrata intolleranza alle statine (vedere successivamente la definizione di intolleranza);
- in prevenzione secondaria in pazienti di età <=80 aa con ipercolesterolemia familiare eterozigote o ipercolesterolemia non familiare o dislipidemia mista con livelli di LDL-C >=100 mg/dL nonostante terapia da almeno 6 mesi con statina ad alta potenza alla massima dose tollerata + ezetimibe oppure con dimostrata intolleranza alle statine (vedere successivamente la definizione di intolleranza)

Per il calcolo del Dutch Lipid Score fare riferimento a Dutch Lipid Clinic Network diagnostic criteria for Familial Hypercholesterolemia
http://nlaresourcecenter.lipidjournal.com/Content/PDFs/Tables/4.pdf

Per la gestione terapeutica di pz che hanno presentato una "Sintomatologia Muscolare Associata alle Statine" (SAMS) si prega di fare riferimento alla Consensus SAMS 2015 dell'EAS European Atherosclerosis Society, https://www.eas-society.org/?page=sams_consensus

(E)	Diagnosi *:	Ipercolesterolemia non familiare (noFH)
	Anno della diagnosi (aaaa) *:	1980
(E)	Sono state escluse cause secondarie di ipercolesterolemia (es. patologie come ipotiroidismo, sindrome nefrosica o da farmaci come immunosoppressori, antiretrovirali e inibitori delle aromatasi)? *:	Si
(E)	Abitudine al fumo *:	Pregressa
(E)	Eventuali comorbilità associate *:	☐ Nessuna ☑ Diabete mellito ☐ Ipertensione arteriosa ☐ Iperuricemia ☑ Malattia cardiovascolare (cardiopatia ischemica, IMA, bypass aortocoronarico, angioplastica, procedura di rivascolarizzazione coronarica, coronaropatia) ☐ Malattia cerebrovascolare (pregresso ictus o TIA, rivascolarizzazione carotidea) ☐ Arteriopatia periferica
(E)	Il diabete presenta complicanze croniche (es. nefropatia anche incipiente, retinopatia, etc.) *:	No
	Funzione renale *:	Compromessa
(E)	Grado di insufficienza renale (GFR) *:	Moderato (GFR 59-30 mL/min)
	Funzione epatica *:	Normale
(E)	Paziente in trattamento con statine secondo le indicazioni incluse nella Nota 13 AIFA? *:	Si
(E)	Indicare la statina attualmente assunta dal paziente *:	Rosuvastatina

(E)	Indicare la posologia della statina *:	40 mg/die
(E)	Altre terapie ipolipemizzanti associate *:	☐ Nessuna ☑ Ezetimibe ☐ PUFA-N3 ☐ Fibrati ☐ Lomitapide ☐ Resine sequestranti acidi biliari ☐ Aferesi lipoproteine
(E)	Il Medico prescrittore certifica che il paziente è in trattamento con la statina selezionata (± altra terapia ipolipemizzante) in maniera regolare e continuativa da almeno 6 mesi *:	Si

Profilo lipidico
Si riferisce a controlli effettuati precedentemente all'inizio del trattamento con Repatha.
Il trattamento di almeno sei mesi con statina ad alta potenza al massimo della dose tollerata è una delle condizioni obbligatorie ai fini dell'eleggibilità con questo medicinale.

E' necessario inserire 3 determinazioni, eseguite in momenti diversi, del profilo lipidico.
Ai fini dell'eleggibilità, il sistema considera che tutti e tre i valori di colesterolo LDL siano al di sopra del target specifico

	Data prelievo 1a determinazione *:	19/05/2010
	Colesterolo totale 1a determinazione *:	189 mg/dL
	Colesterolo HDL 1a determinazione *:	41 mg/dL
	Trigliceridi 1a determinazione *:	120 mg/dL
(E)	Colesterolo LDL 1a determinazione *:	104 mg/dL
	Data prelievo 2a determinazione *:	15/06/2017
	Colesterolo totale 2a determinazione *:	183 mg/dL
	Colesterolo HDL 2a determinazione *:	47 mg/dL
	Trigliceridi 2a determinazione *:	140 mg/dL
(E)	Colesterolo LDL 2a determinazione *:	108 mg/dL
	Data prelievo 3a determinazione *:	02/10/2017
	Colesterolo totale 3a determinazione *:	174 mg/dL
	Colesterolo HDL 3a determinazione *:	46 mg/dL
	Trigliceridi 3a determinazione *:	98 mg/dL
(E)	Colesterolo LDL 3a determinazione *:	108 mg/dL
	Altri parametri lipidici disponibili *:	☑ Nessuno ☐ Lp(a) ☐ ApoB ☐ ApoA1 ☐ Altro
	Paziente già in trattamento con Repatha secondo le indicazioni della scheda di monitoraggio AIFA? *:	No

Data Valutazione 30/10/2017

Nuova Prescrizione | Nuova Rivalutazione | Indietro | Visualizza storico trattamento

TRIGLICERIDI

Genetic predisposition
Obesity
Type 2 diabetes
Alcohol consumption
Diet high in simple carbohydrates
Renal disease
Hypothyroidism
Pregnancy (physiological triglyceride concentrations double during the third trimester)
Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus
Multiple medications including: • Corticosteroids • Oestrogens, especially those taken orally • Tamoxifen • Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides • Isotretinoin • Bile acid-binding resins • Ciclosporin • Antiretroviral regimens (protease inhibitors) • Psychotropic medications: phenothiazines, second generation antipsychotics

Possible causes of hypertriglyceridaemia

Recommendations	Class [a]	Level [b]
Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL).	IIa	B
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	IIb	B
In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins.	IIb	C

Recommendations for drug treatments of hypertriglyceridaemia

European Heart Journal Advance Access published August 27, 2016
ESC/EAS GUIDELINES
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TRIGLICERIDI

A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.
If TG are not controlled by statins or fibrates, prescription of n-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.

Summary of the efficacy of drug combinations for the management of mixed dyslipidaemias

Recommendations	Class [a]	Level [b]
Statins and fibrates raise HDL-C with a similar magnitude and these drugs may be considered.	IIb	B
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	IIb	B

Recommendations if drug treatment of low high-density lipoprotein cholesterol is considered

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CONCLUSIONI

- **L'ipercolesterolemia è associata ad aumento di CAD, CVD e morte prematura**
  - **necessari diagnosi precoce, stili di vita corretti e trattamento con statine**
  - **Tuttavia molti pazienti falliscono il raggiungimento del target di LDL-C con le sole statine**
- **Bisogna garantire ogni sforzo per ridurre e mantenere il target lipidico di LDL-C adeguato (ezetimibe, anti-PCSK)**
- **I costi e le barriere prescrittive costituiscono allo stato attuale un limite ad un utilizzo più estensivo degli anti-PCSK**

FARMACI 2018. Una risorsa a disposizione di ogni cardiologo che ottiene risultati che dobbiamo valorizzare

GRAZIE PER LA VOSTRA ATTENZIONE

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