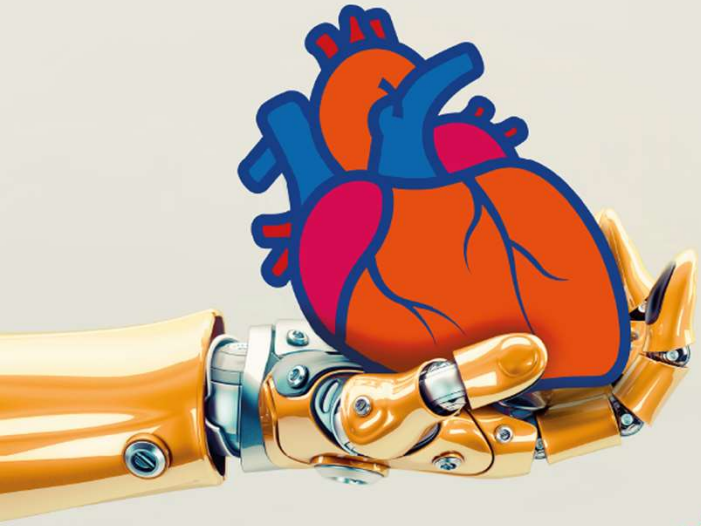


17° Meeting

CardioLucca

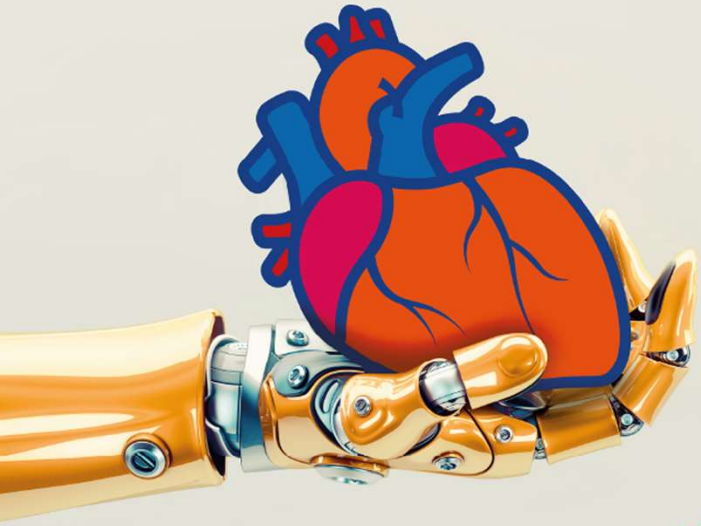
Heart Brings Heart 2023

Lucca, 22-24 Giugno 2023

Centro Congressi Auditorium San Francesco

Emilio Maria Pasanisi
UOC Cardiologia Livorno

La scelta di una terapia di combinazione precoce nella dislipidemia



17° Meeting

CardioLucca

Heart Brings Heart 2023

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Centro Congressi Auditorium San Francesco

Il sottoscritto Emilio MG Pasanisi
non presenta situazioni di CONFLITTO D' INTERESSE

(art. 53 D. lgs. N. 165/2001 come modificato dalla legge n. 190/2012)
Lucca, 24/6/23

La scelta di una terapia di combinazione precoce nella **dislipidemia**

Hypocholesterolemic Agents*

From the Cardiovascular Section, Oklahoma Medical Research Institute and the Department of Medicine, University of Oklahoma School of Medicine

ROBE
Head of

CHARLES W. ROBINSON, JR., M.D.**

Cardiovascular Research Trainee, Oklahoma Medical Research Institute

Medical Clinics of North America
Volume 45, Issue 4, July 1961, Pages 935-959

ALTHOUGH THE ROLE of the serum lipids in the genesis of human atherosclerosis is uncertain, the likelihood of an important cause-and-effect relationship is sufficiently great that research activity in the field of atherosclerosis centers on the serum lipids, their metabolism and transport.

Studies of the serum lipids have focused on cholesterol because (1) epidemiologic studies and clinical experience relate serum cholesterol levels to coronary artery disease, (2) cholesterol is the chief constituent

omes
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whose

metabolism and transport may be of more fundamental etiologic importance.

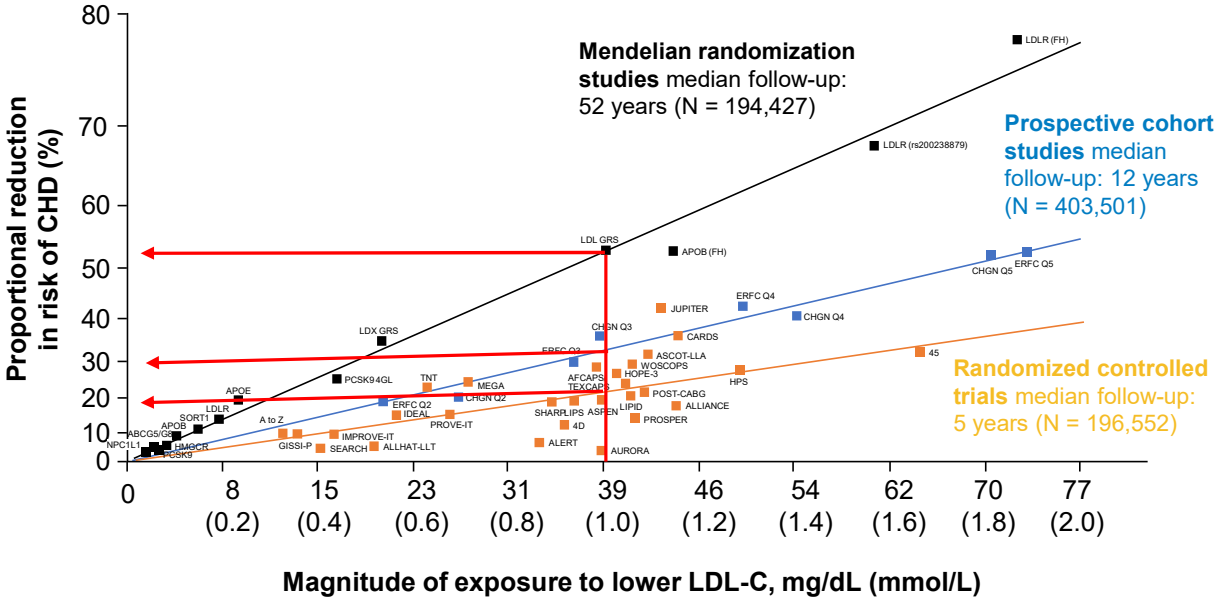
There is no question of the desirability of reducing serum lipid levels in hypercholesterolemic and "hyperlipemic" states in which early and severe atherosclerosis is the rule.

Reduction of excessive serum lipid levels increases tissue oxygen tension, myocardial blood flow and oxygen extraction.[1, 2, 3] Less well established are observations which suggest that

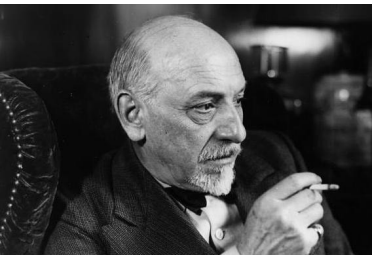
La riduzione del rischio di malattia aterosclerotica è proporzionale alla riduzione assoluta di LDL

"The remarkable consistency among these studies, in addition to biological and experimental evidence, provides compelling evidence that LDL-C is **causally associated** with the risk of ASCVD, and that **lowering LDL-C reduces the risk of ASCVD proportionally to the absolute achieved reduction in LDL-C**."
(Mach et al)

Studi di genetica e studi su terapia ipolipemizzante mostrano correlazione con la riduzione degli eventi cardiovascolari



Mach F, et al. Eur Heart J 2019.
Ference BA, et al. Eur Heart J. 2017;38:2459-2472.

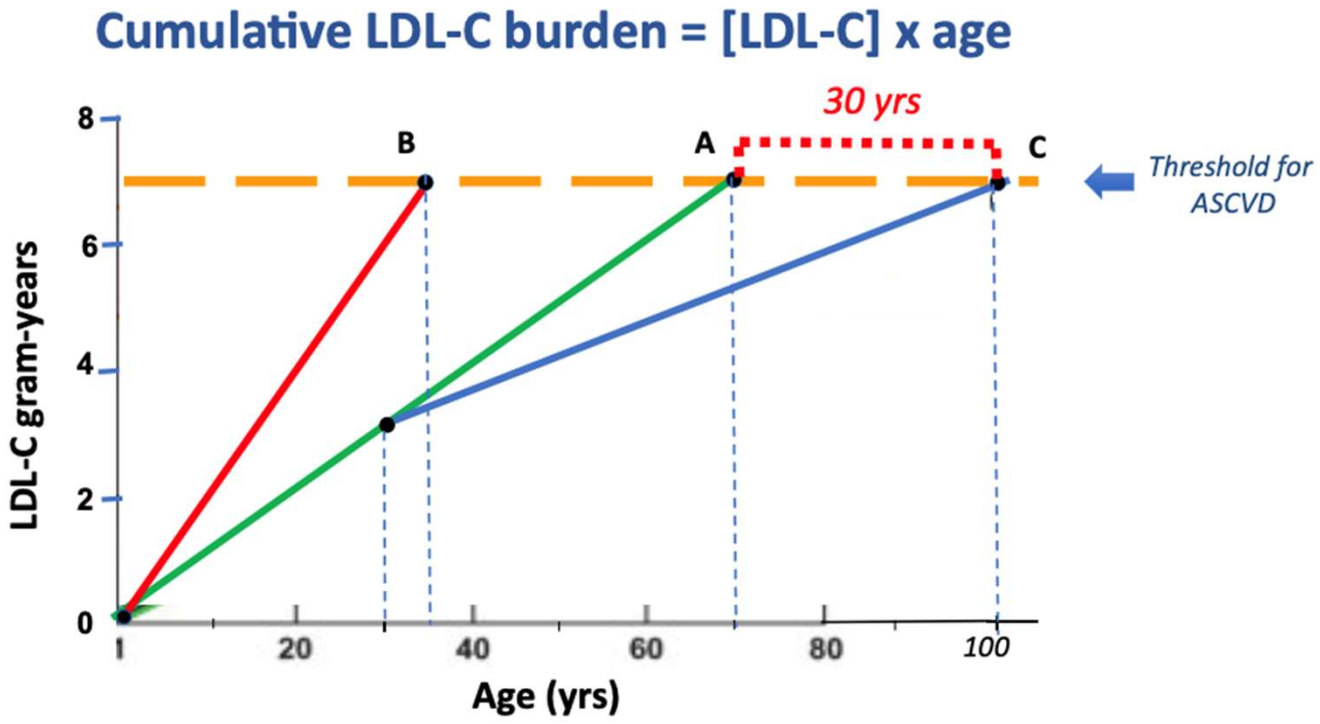


Il rischio CV è un continuum, stabilire delle categorie ben definite aiuta nella gestione terapeutica del paziente

Very high risk	High risk	Moderate risk	Low 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 PAD. 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	**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	• 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	• Calculated SCORE < 1% for 10-year risk of fatal CVD

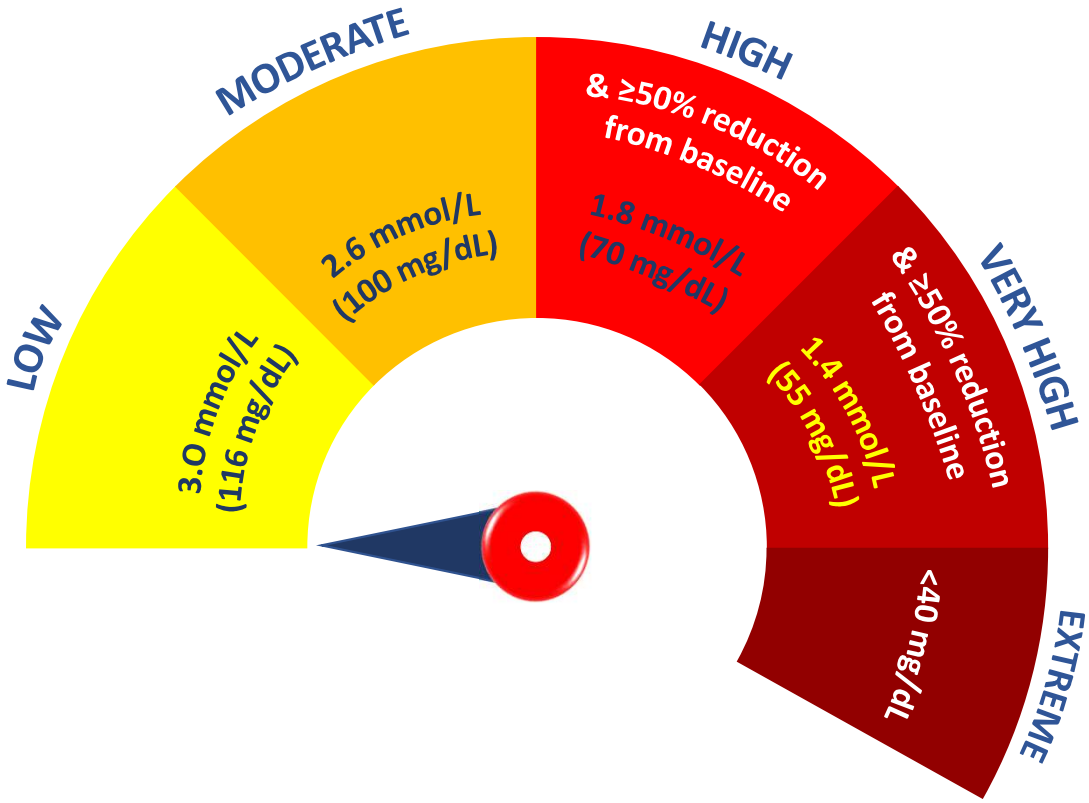
Mach F, et al. *Eur Heart J.* 2019.

Primary prevention could delay significantly the onset of clinical manifestations of ASCVD



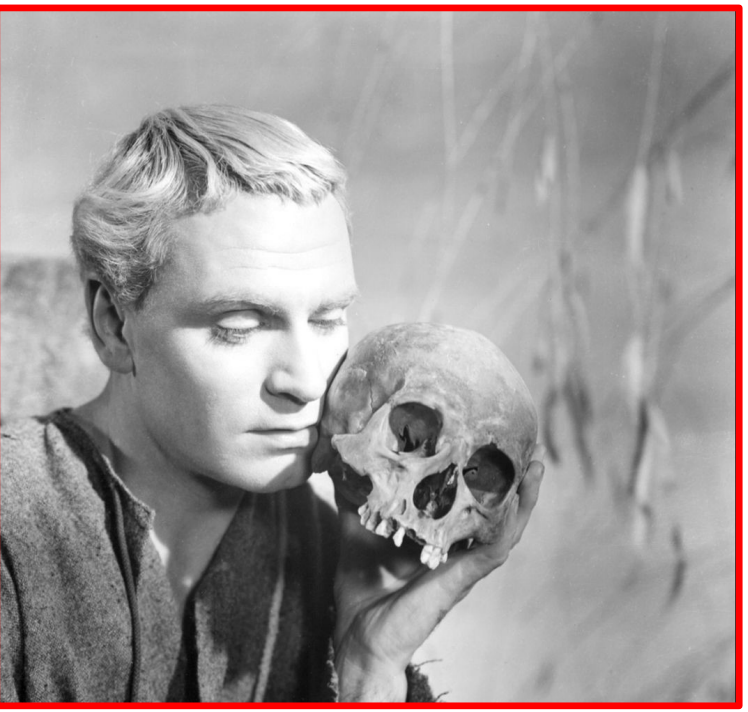
Horton JD et al . J Lipid Res 2009;50 Suppl:S172–S179.

Livelli target dalle linee guida ESC/EAS 2019 in funzione del rischio CV



Mach F et al. Eur Heart J. 2020; 41:111-88; Catapano A et al. Eur Heart J. 2016; 37(39):2999-3058

La **scelta** di una terapia di combinazione precoce nella dislipidemia



Statina o non statina….

Questa o quella per me par sono…?

Pravastatina

Lovastatina

Atorvastatina

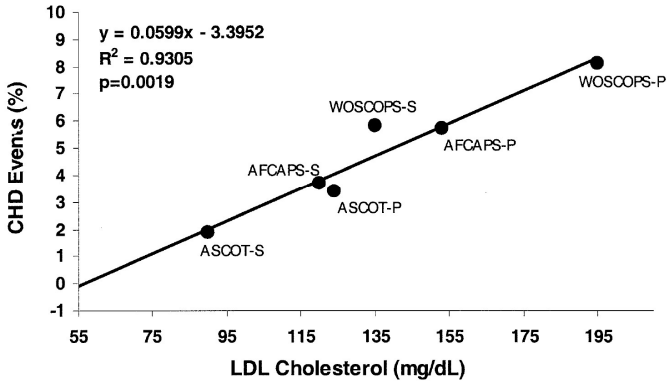
Rosuvastatina

Fluvastatina

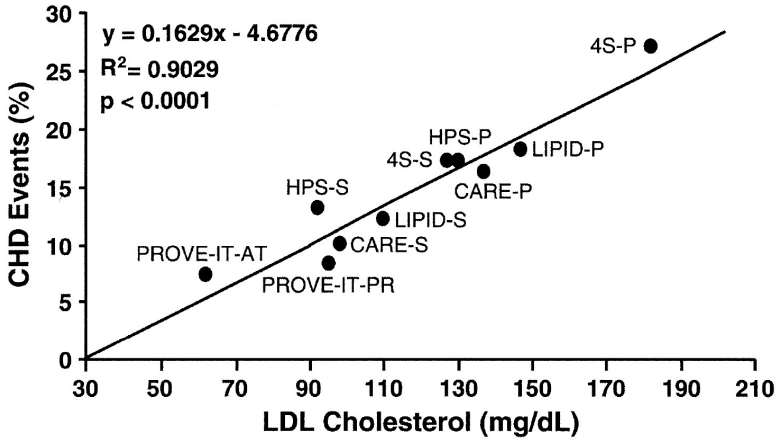
Simvastatina

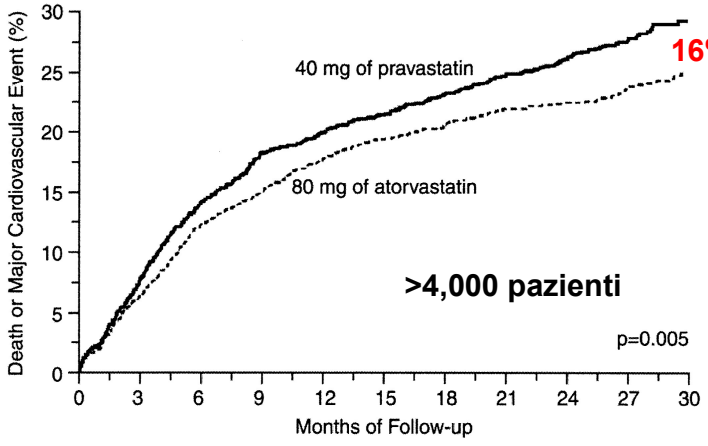
Lower is Better

Prevenzione Primaria



Prevenzione secondaria





16% di riduzione nell'end-point primario

atorvastatina (LDL 62 mg/dl)
o
pravastatina (LDL 95 mg/dl)

PROVE-IT

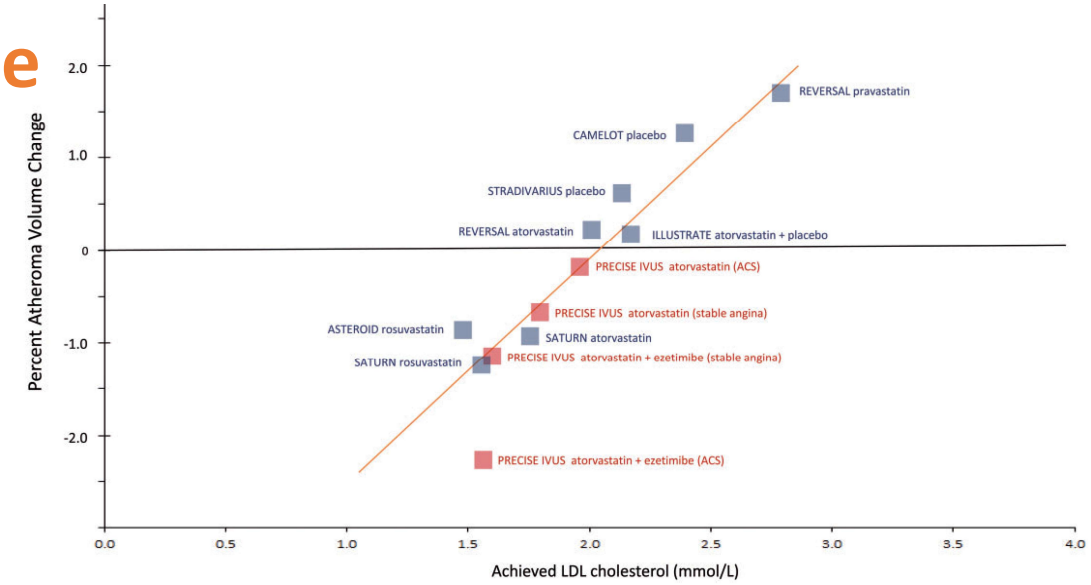
20% di riduzione del R CV ogni 38.7 mg/dl di riduzione di LDL

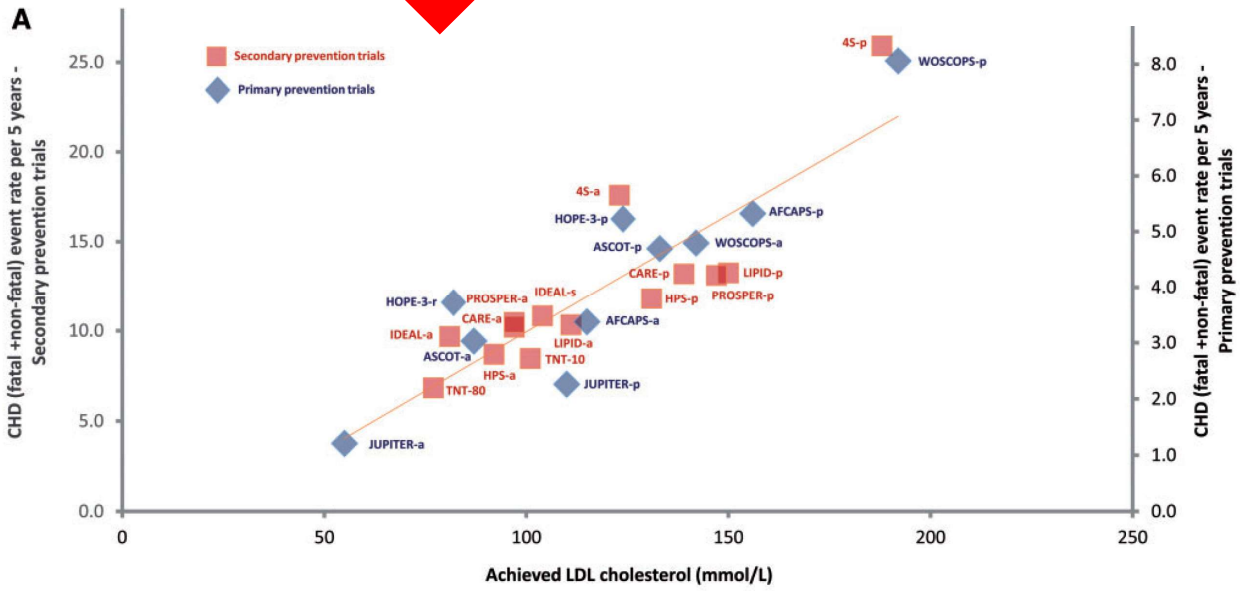
O'Keefe, Jr. et al. JACC Vol. 43, No. 11, 2004

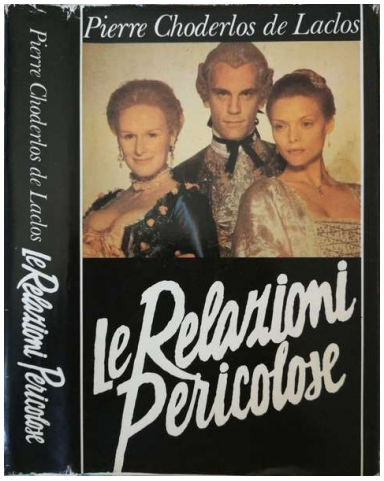
LDL e le relazioni pericolose

dalla placca

alla prognosi

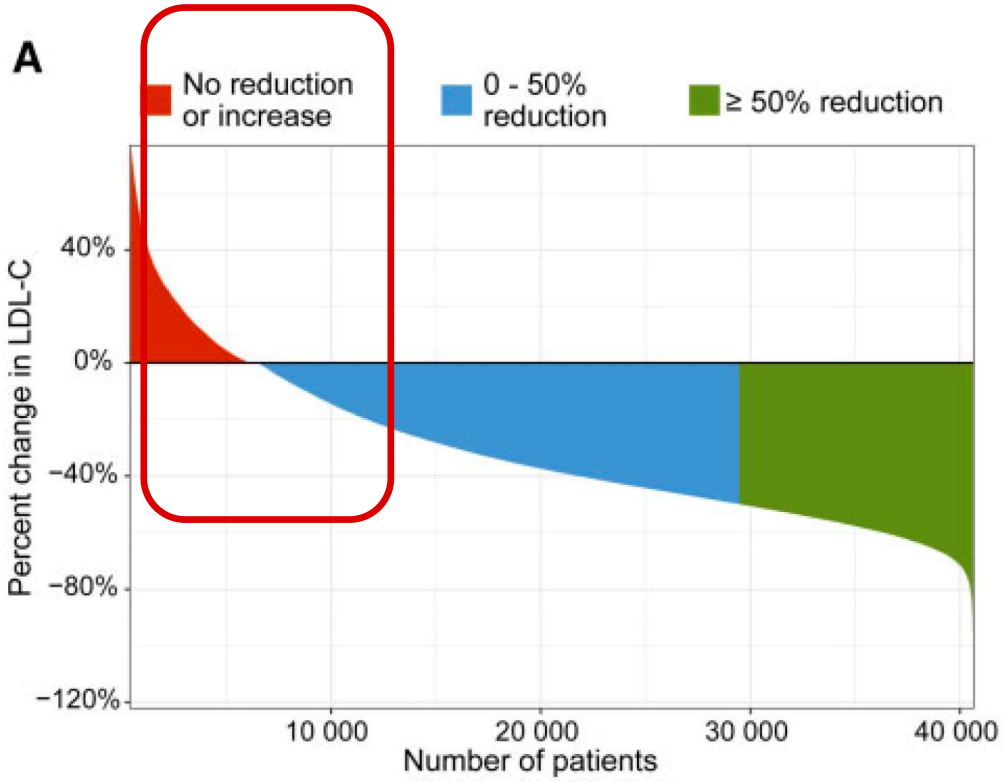


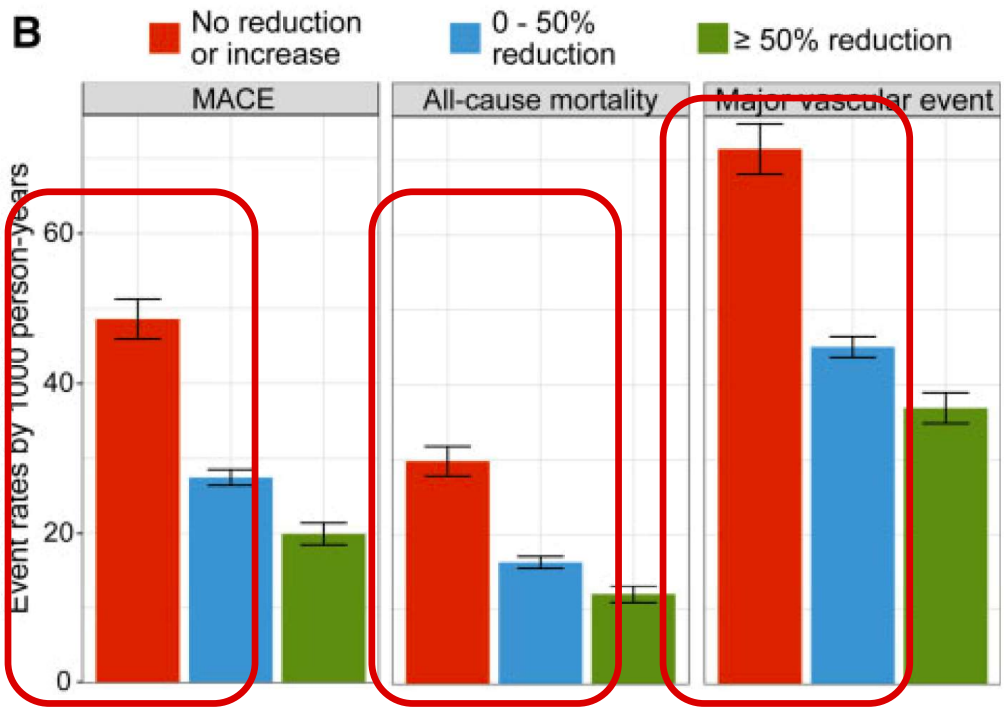




European Heart Journal (2017) 0, 1–14

Riduzione del colesterolo ed eventi

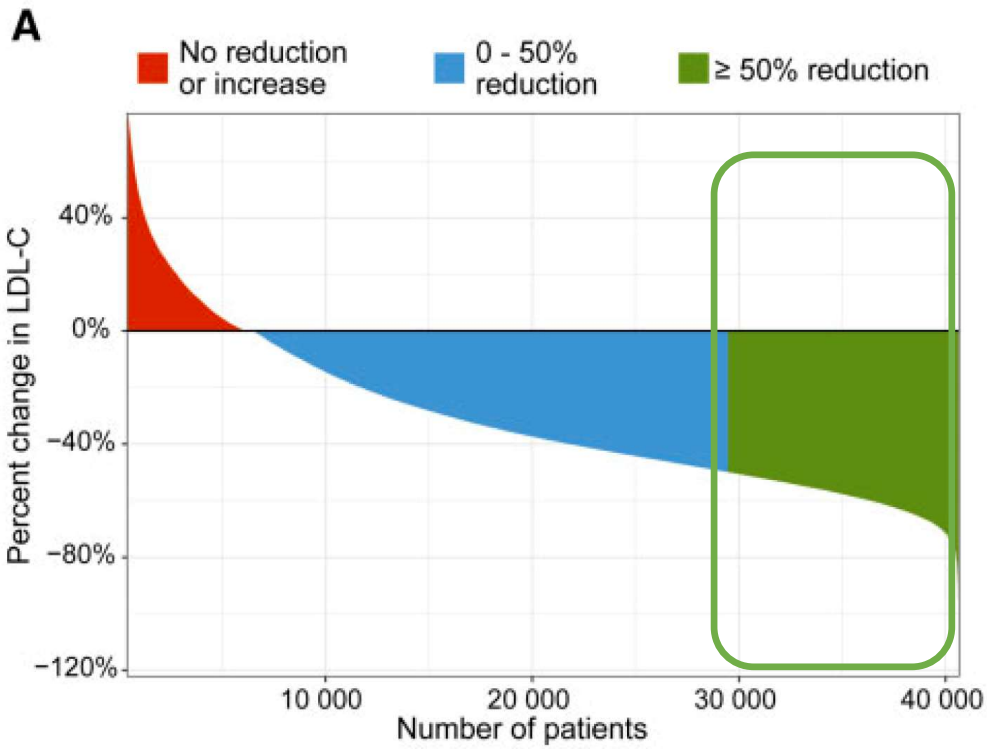


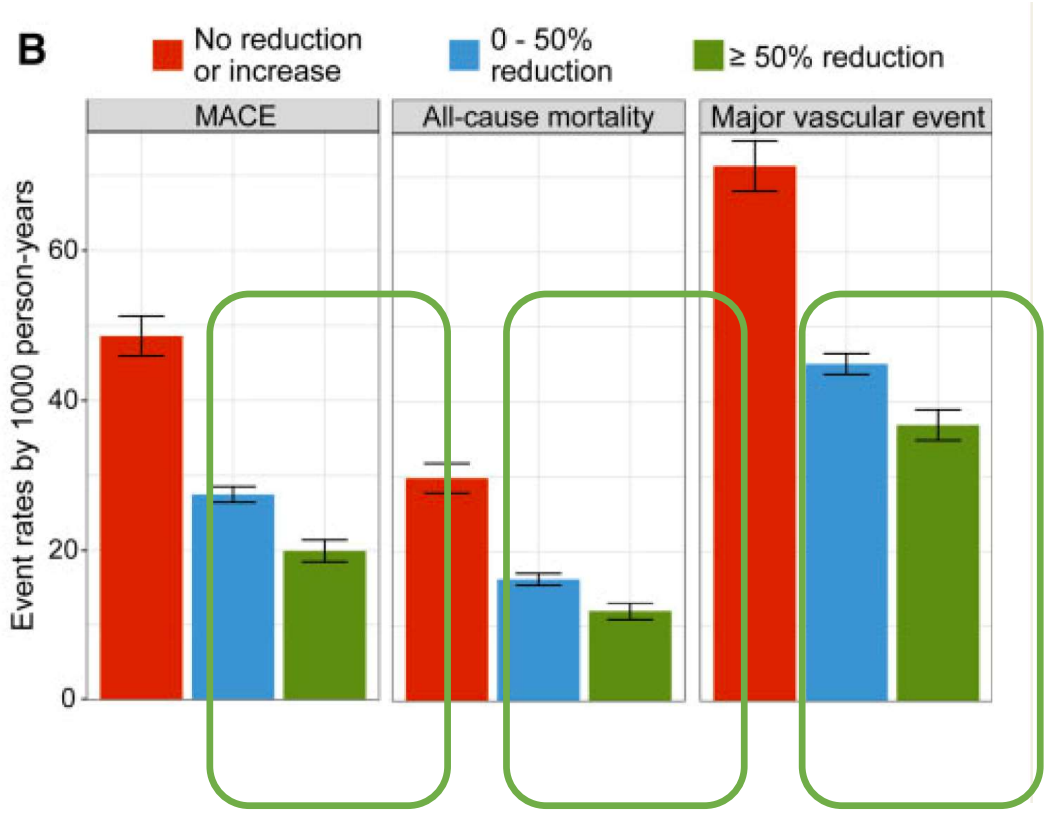


Swedish nationwide cohort study

European Heart Journal (2021) 42, 243–252

Riduzione del colesterolo ed eventi

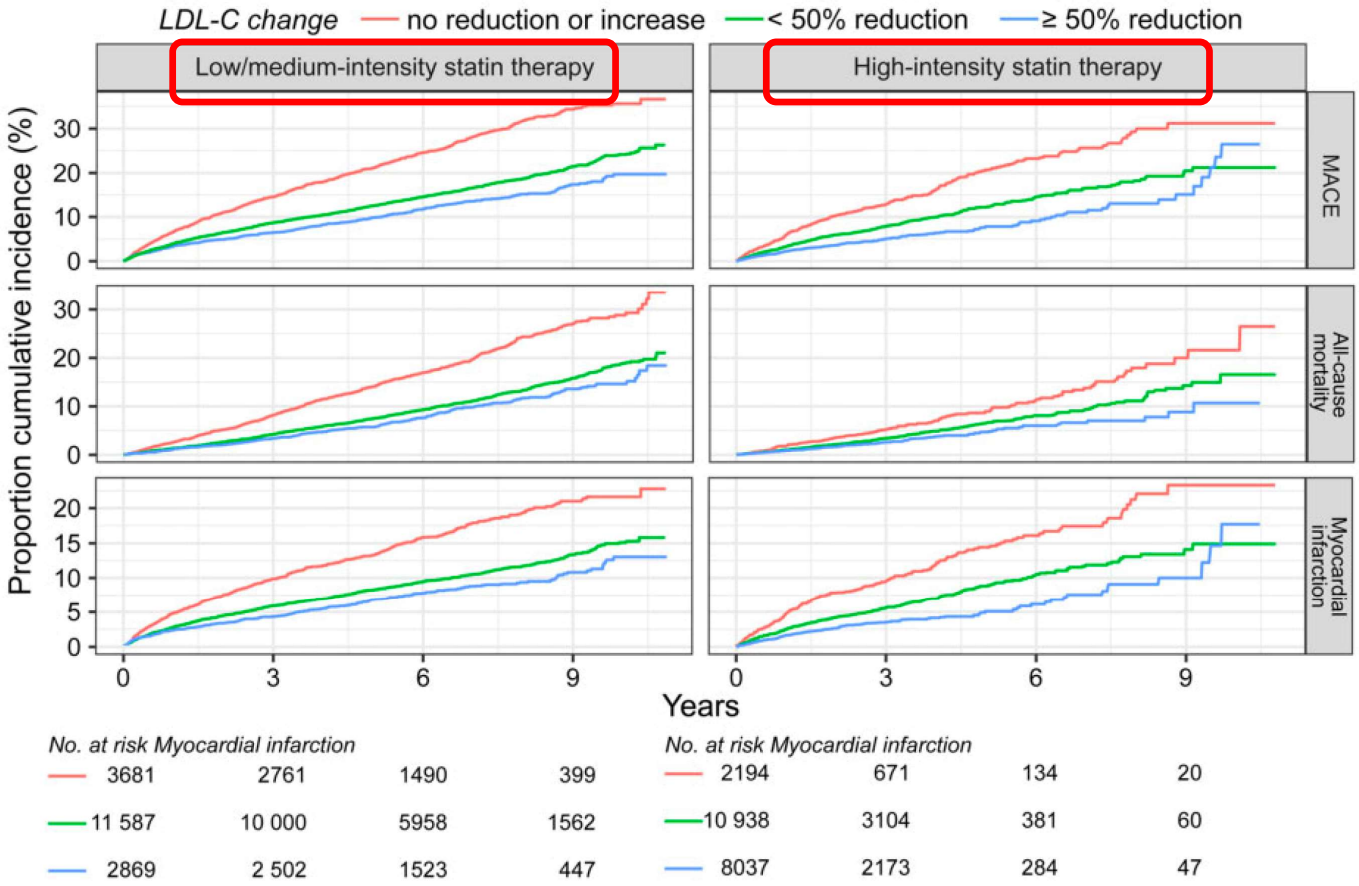




Swedish nationwide cohort study

European Heart Journal (2021) 42, 243–252

Statina a bassa-media intensità vs statina ad alta intensità e prognosi



European Heart Journal (2021) 42, 243–252

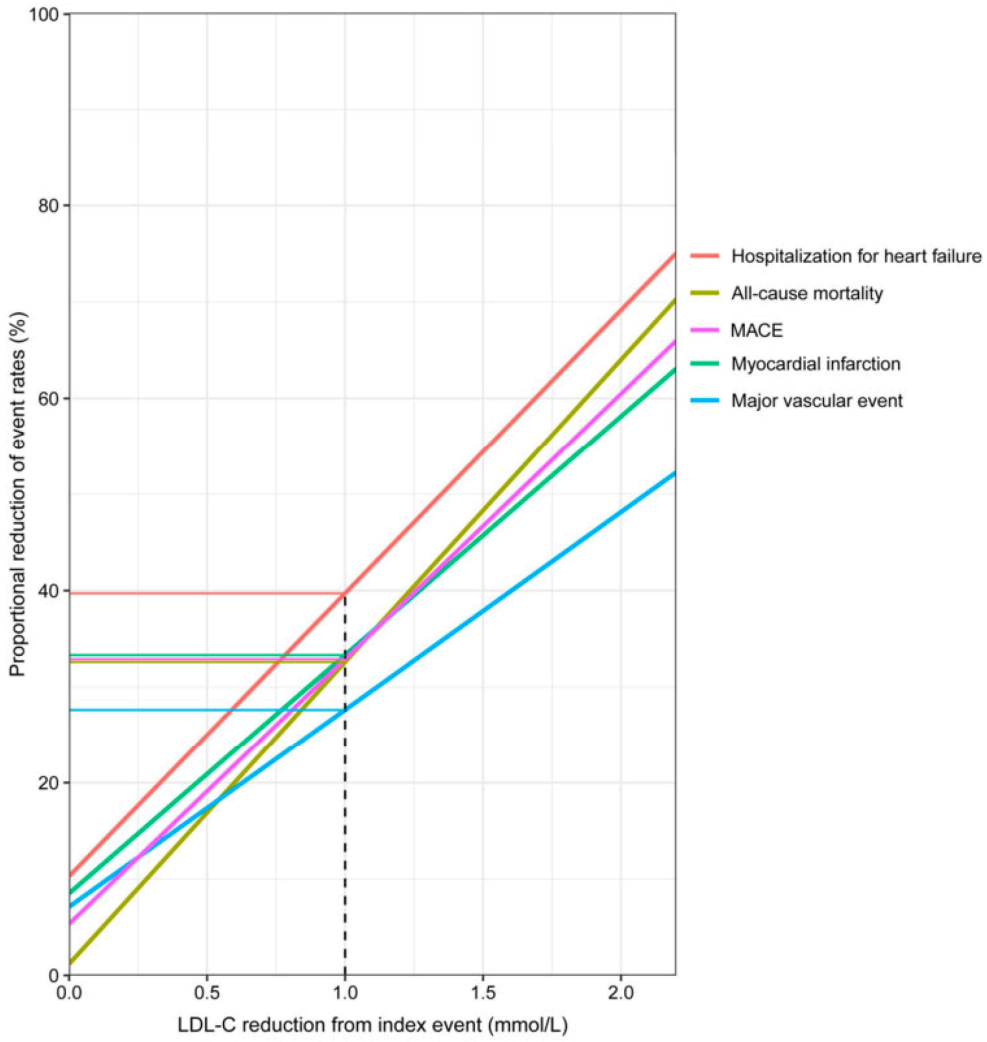
Swedish nationwide cohort study

Una riduzione aggressiva e precoce dell'LDL dopo SCA riduce gli eventi

Per la prima volta uno studio osservazionale conferma quanto visto in trial clinici

Il beneficio della riduzione dell'LDL può essere esteso a tutta i post IMA con effetti già a sei mesi

Swedish nationwide cohort study



European Heart Journal (2021) 42, 243–252

Studio SANTORINI

Solamente il 20.7% dei pazienti a rischio molto alto ha raggiunto il target di C-LDL

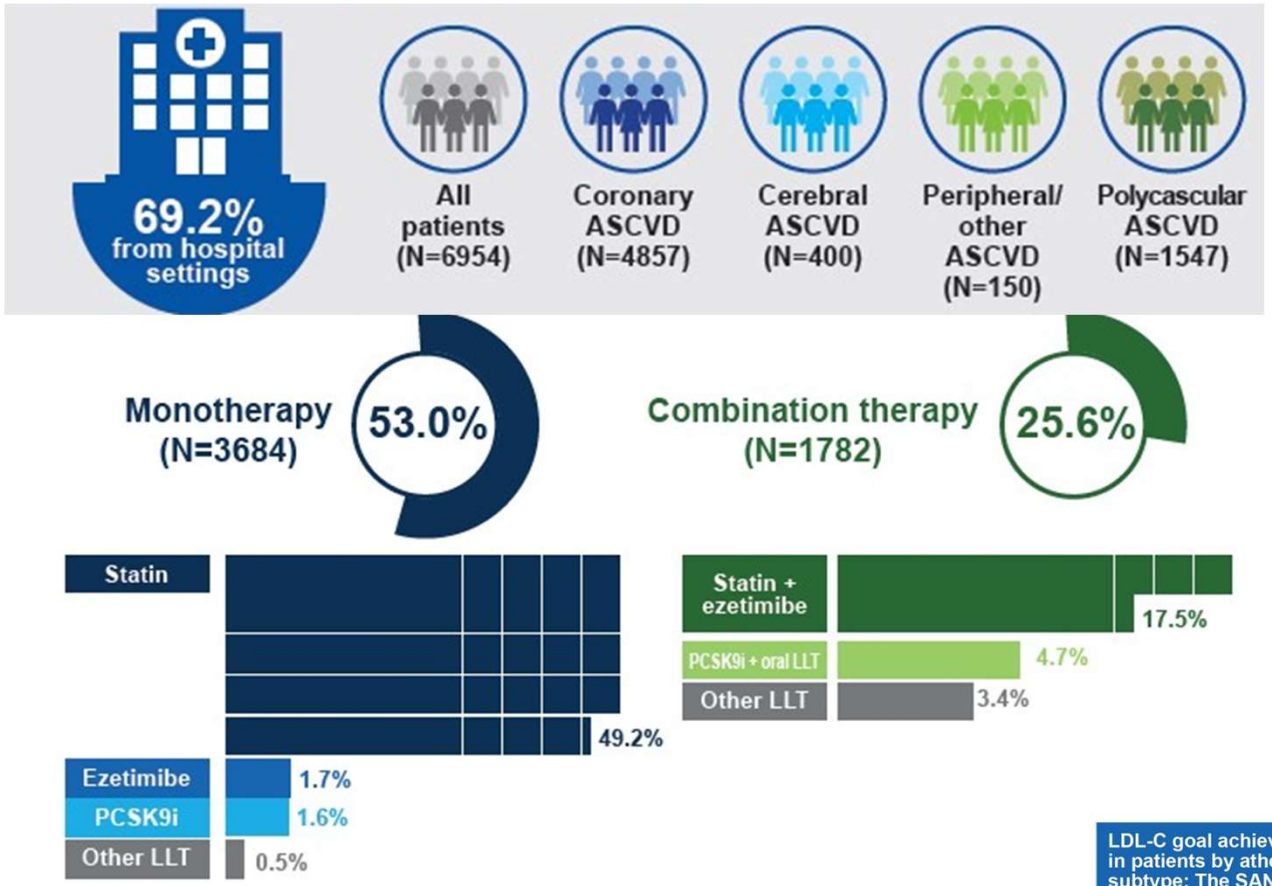
	All patients (N=6954)	Coronary ASCVD (N=4857)	Cerebral ASCVD (N=400)	Peripheral/other ASCVD (N=150)	Polyvascular ASCVD (N=1547)
Achieving LDL-C goals, n (%)	1438 (20.7)	980 (20.2)	60 (15.0)	28 (18.7)	370 (23.9)

Nel **21,4%** dei pazienti a rischio molto alto è stata documentata **una totale assenza di terapia ipolipemizzante**.

Catapano et al. ESC 2022

LDL-C goal achievement and lipid-lowering therapy in patients by atherosclerotic cardiovascular disease subtype: The SANTORINI study

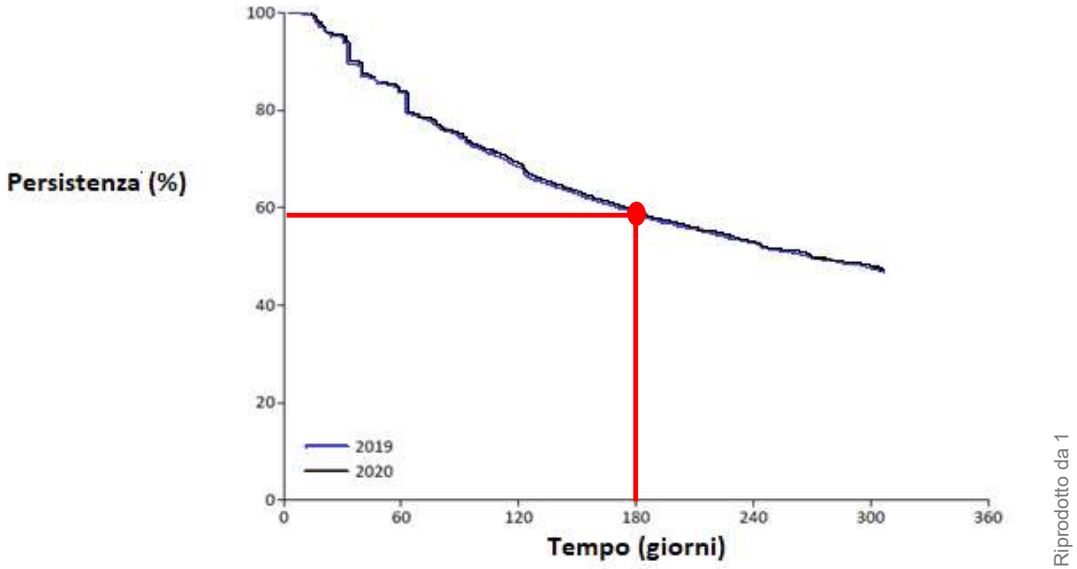
Studio SANTORINI
La maggior parte dei pazienti a rischio molto alto è in terapia con un solo farmaco ipolipemizzante



LDL-C goal achievement and lipid-lowering therapy in patients by atherosclerotic cardiovascular disease subtype: The SANTORINI study

Catapano et al. ESC 2022

La Scarsa Aderenza Alla Terapia Rimane Un Problema Irrisolto



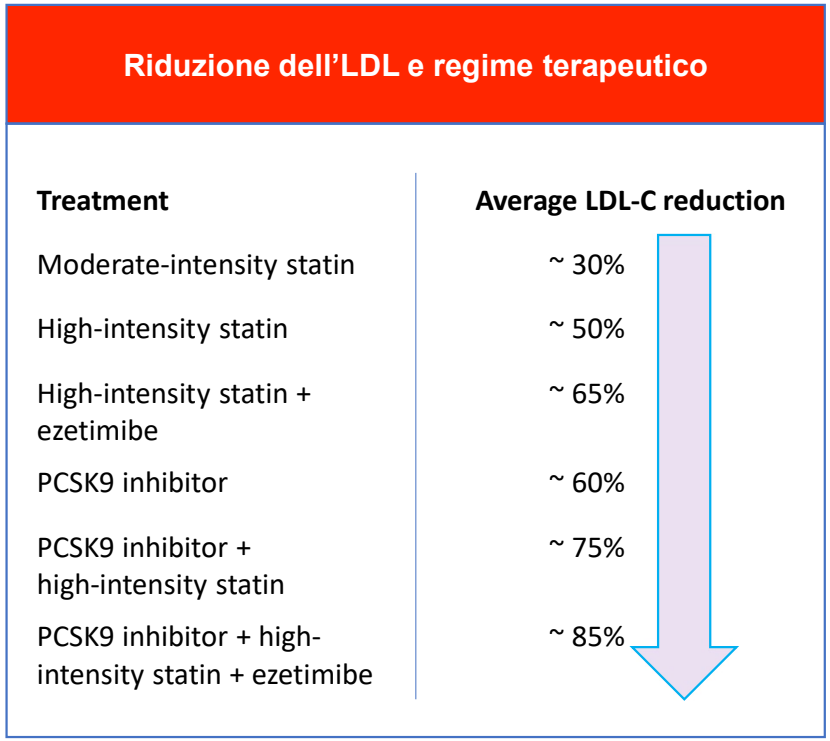
NB: un'interruzione del trattamento si verifica se il soggetto non ha una prescrizione erogata entro 60 giorni. Per questo motivo non possono osservarsi interruzioni negli ultimi 60 giorni dalla fine del follow-up (365 giorni)

Confrontando i dati di persistenza tra il 2019 e il 2020 è possibile evidenziare una sostanziale sovrapponibilità tra le due curve

1. Rapporto Nazionale OsMed 2020 sull'uso dei farmaci in Italia; https://www.aifa.gov.it/-/l-uso-dei-farmaci-in-italia-rapporto-osmed-2020

Statina, statina/ezetimibe, statina/ezetimibe/PCSK9i

- Pazienti che necessitano di ulteriore terapia sono tipicamente **pazienti alto rischio o con valori molto alti di LDL**
- In pazienti a **rischio molto elevato che rimangono ad alto rischio** **(anche se in terapia con statine ad alto dosaggio), aggiungere ezetimibe è raccomandato** (Classe I)
- Se il valore target di LDL non viene raggiunto è raccomandato aggiungere **PCSK9 i,** sia con statina che con statina+ezetimibe



Mach F, et al. *Eur Heart J.* 2019

Opzioni di strategie ipolipemizzanti

PCSK9 i + Statina +/- Ezetimibe +/- Ac Bempedoico

Inclisiran + Statina +/- Ezetimibe +/- Ac Bempedoico

Statina+Ezetimibe +/- Ac Bempedoico

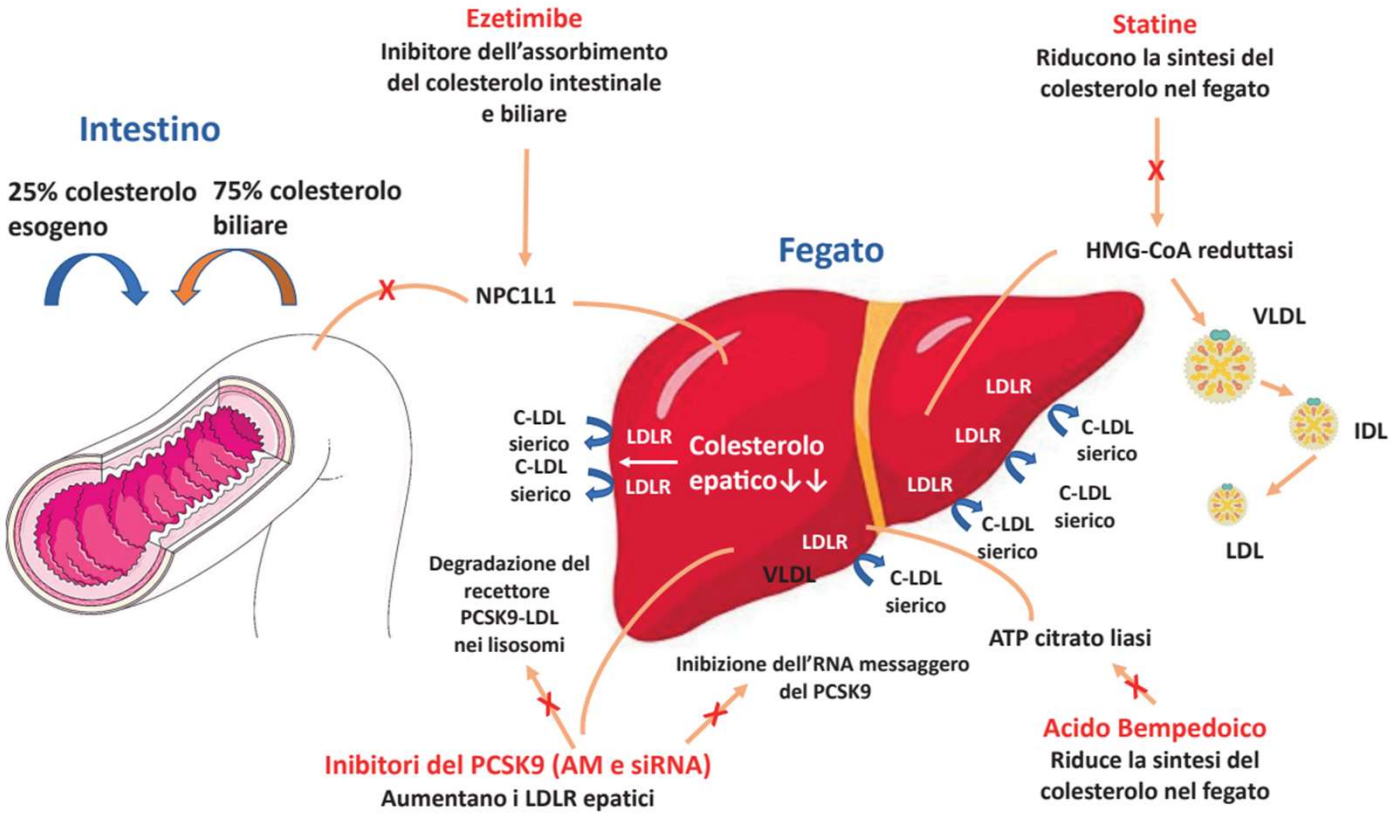
Se intollerante alle statine

Inclisiran +Ezetimibe +/- Ac Bempedoico

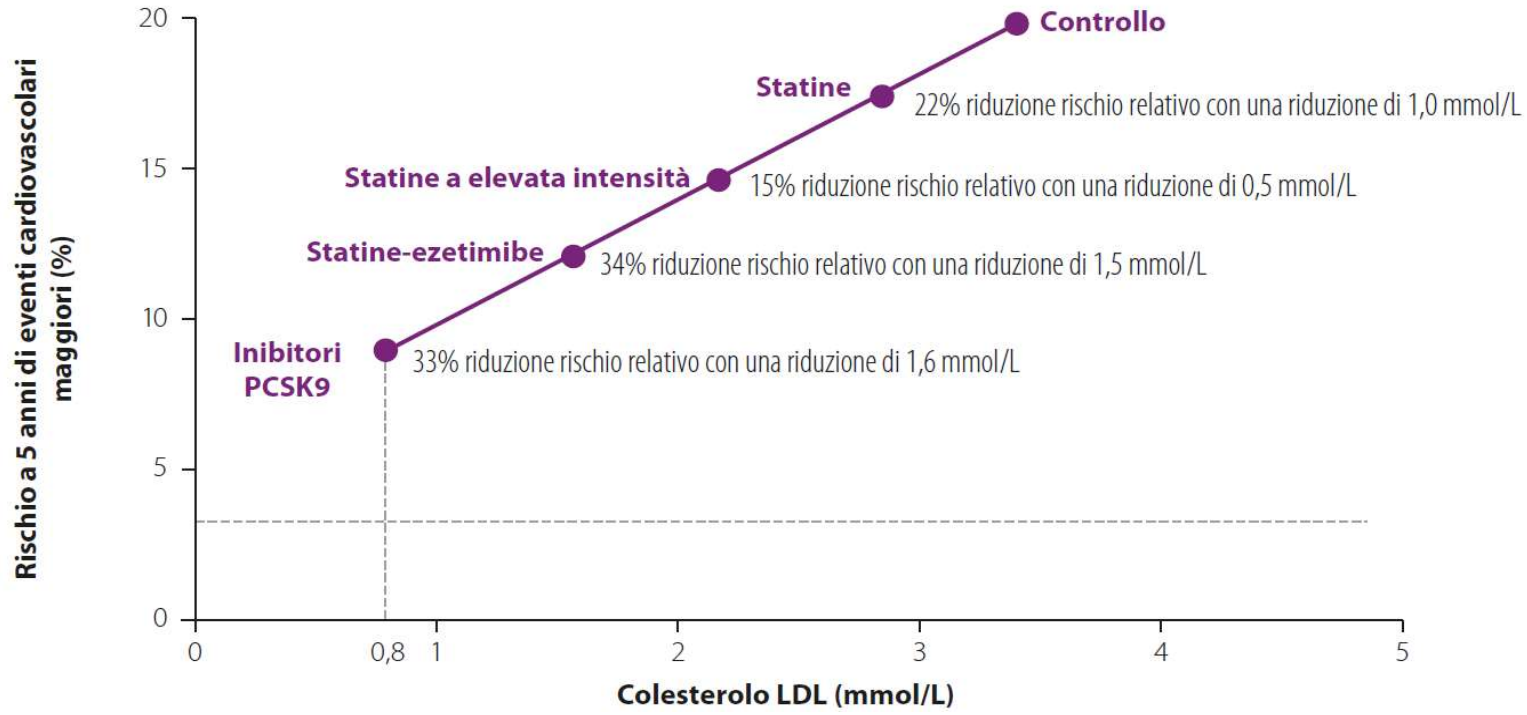
PCSK9i+Ezetimibe +/- Ac Bempedoico

Ezetimibe + Ac Bempedoico

Ipocolesterolemizzanti: meccanismo d'azione



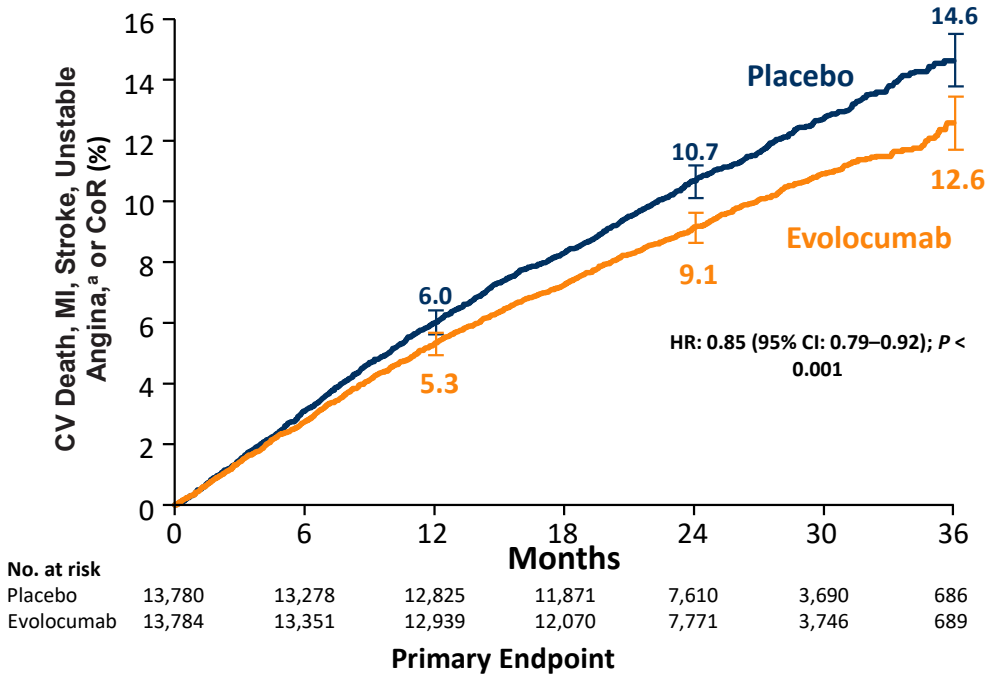
Il trattamento intensivo della ipercolesterolemia riduce gli eventi CV proporzionalmente ai valori di LDL-C raggiunti



Modificata da 1) J Am Coll Cardiol 2018;72(10):1141-1156 2) Ann Med

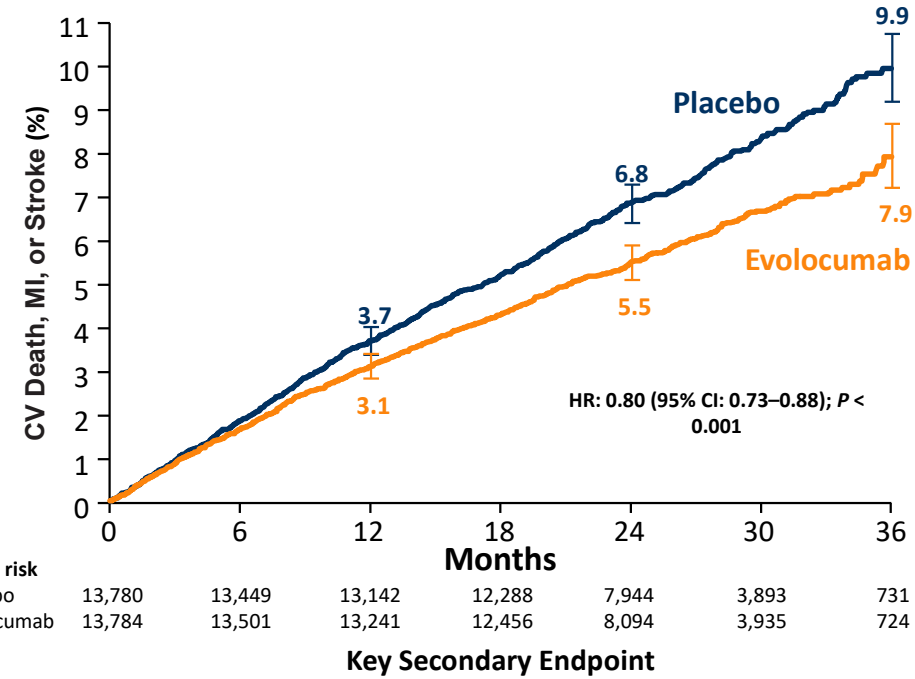
Fourier

Evolocumab e CV outcome



No. at risk							
Placebo	13,780	13,278	12,825	11,871	7,610	3,690	686
Evolocumab	13,784	13,351	12,939	12,070	7,771	3,746	689

Primary Endpoint



No. at risk							
Placebo	13,780	13,449	13,142	12,288	7,944	3,893	731
Evolocumab	13,784	13,501	13,241	12,456	8,094	3,935	724

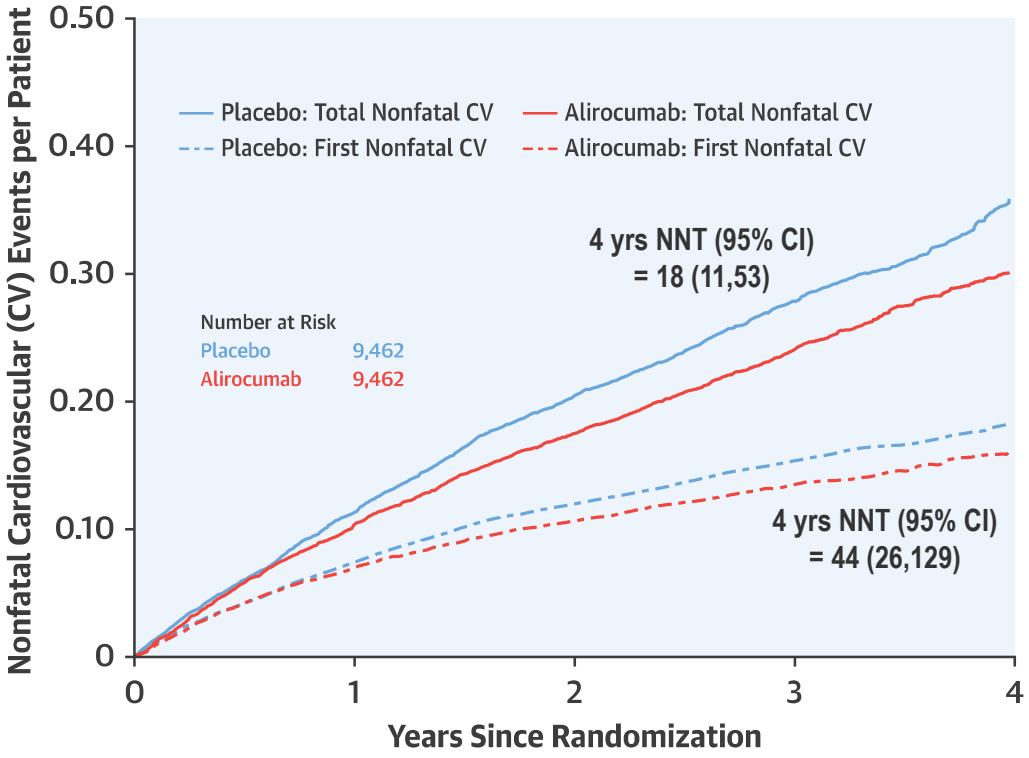
Key Secondary Endpoint

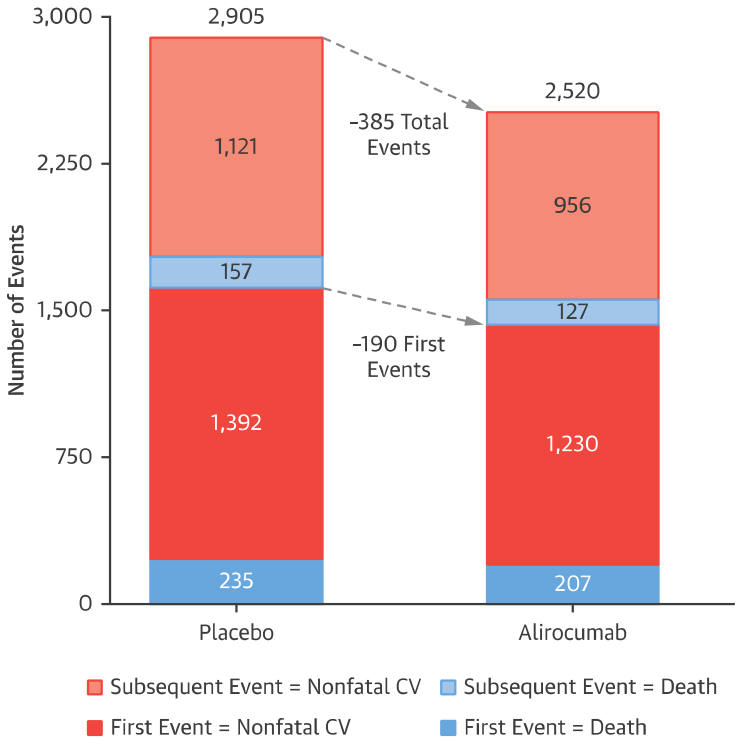
Patients receiving evolocumab experienced a 15% relative risk reduction in 5-point MACE* and 20% reduction in 3-point MACE† relative to those receiving placebo

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

Odyssey

Alirocumab riduce gli eventi non fatali e fatali



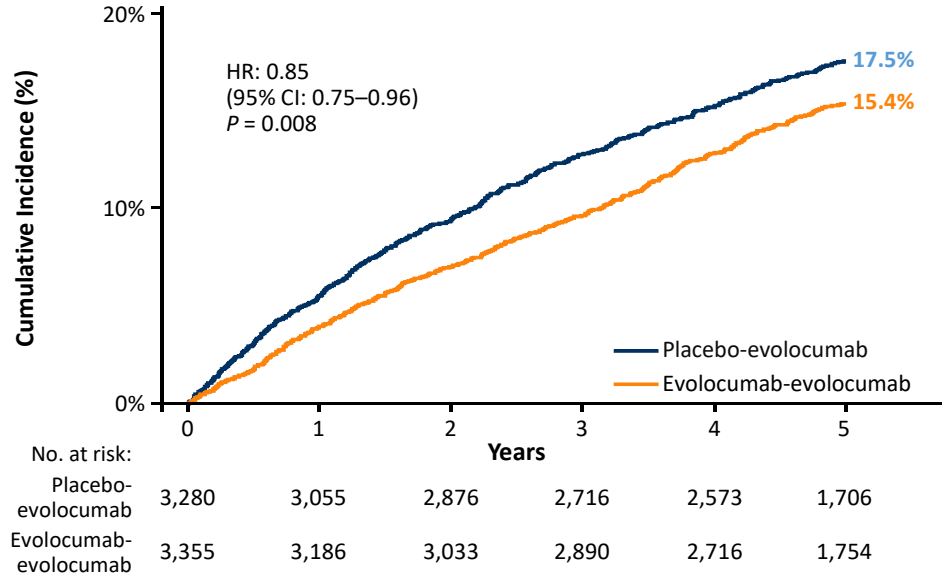


FOURIER-OLE Trial

Key Results: Major Adverse CV Events

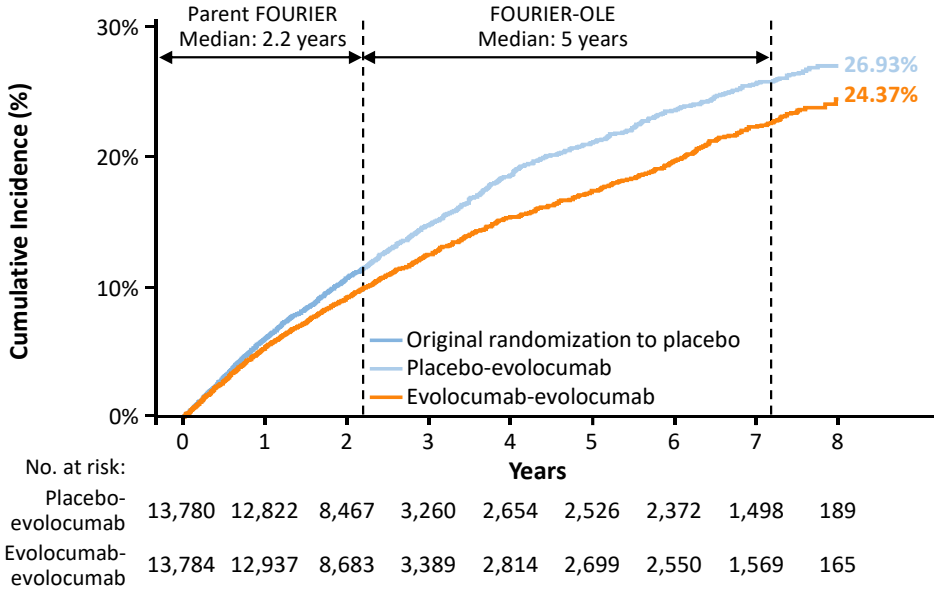
(Primary Endpoints) – CV death, MI, stroke, hospitalization for UA, or CoR*

FOURIER-OLE[1]



No. at risk:						
Placebo-evolocumab	3,280	3,055	2,876	2,716	2,573	1,706
Evolocumab-evolocumab	3,355	3,186	3,033	2,890	2,716	1,754

Parent FOURIER + FOURIER-OLE[2]



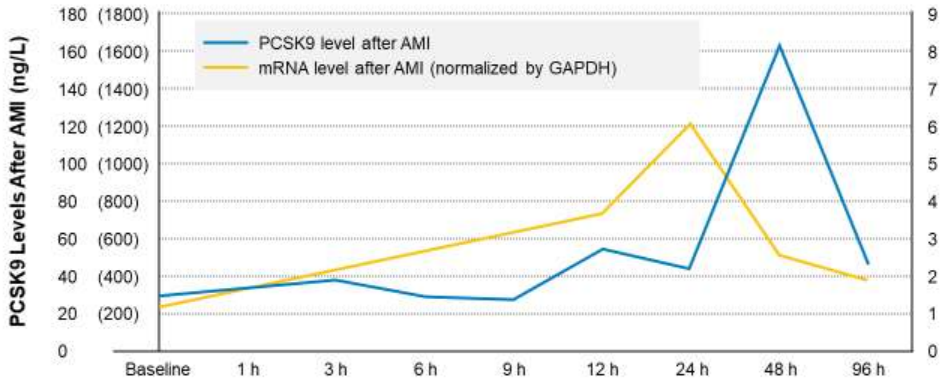
No. at risk:									
Placebo-evolocumab	13,780	12,822	8,467	3,260	2,654	2,526	2,372	1,498	189
Evolocumab-evolocumab	13,784	12,937	8,683	3,389	2,814	2,699	2,550	1,569	165

During the FOURIER-OLE trial, there was a 15% lower risk of the primary endpoint in patients originally randomized in the parent trial to evolocumab than patients originally randomized in the parent trial to placebo.

*1. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119. 2. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

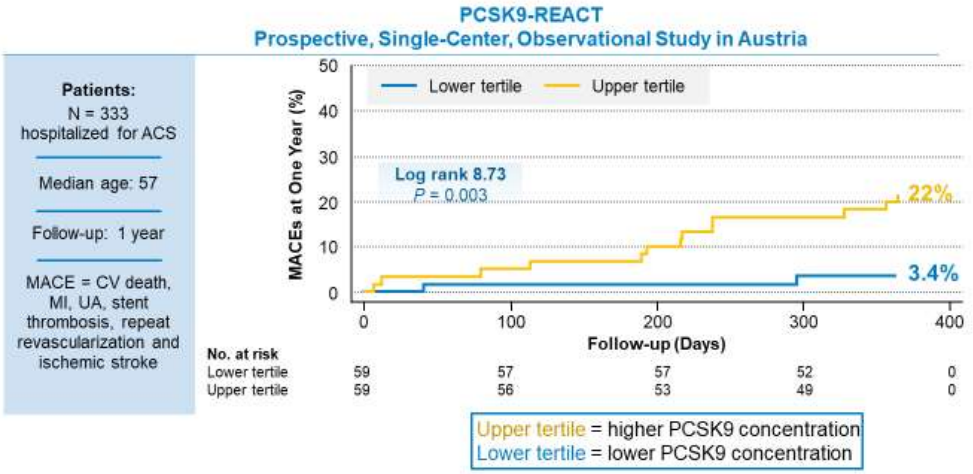
Incremento livelli PCSK9 fino a 48h post SCA

PCSK9 PEAK LEVELS RISE UP TO 48 HOURS IN ACS



Elaborato da Gencer

PCSK9 LEVELS PREDICT MACE FOLLOWING ACS



Elaborato da Navarese

- Navarese EP, et al. Int J Cardiol. 2017;227:644-649.
- Gencer B, et al. Atherosclerosis. 2018;275:368-375.

Alirocumab lega la PCSK9 *RAPIDAMENTE*…

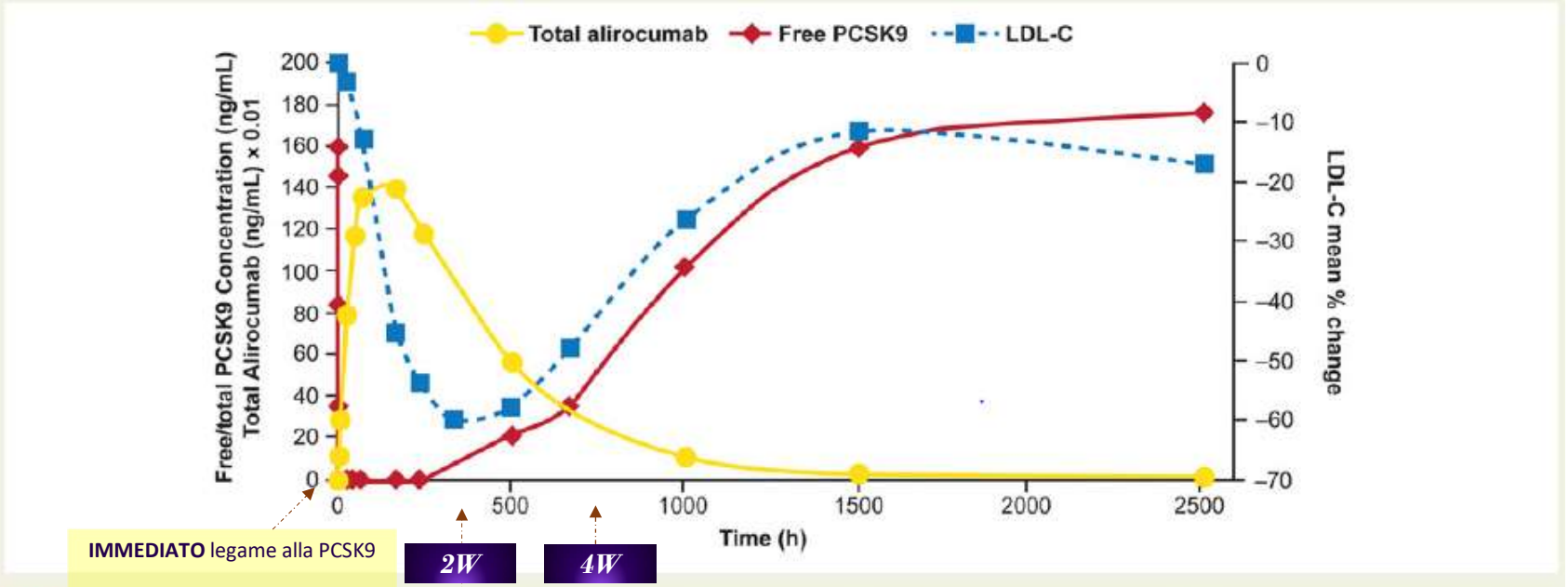
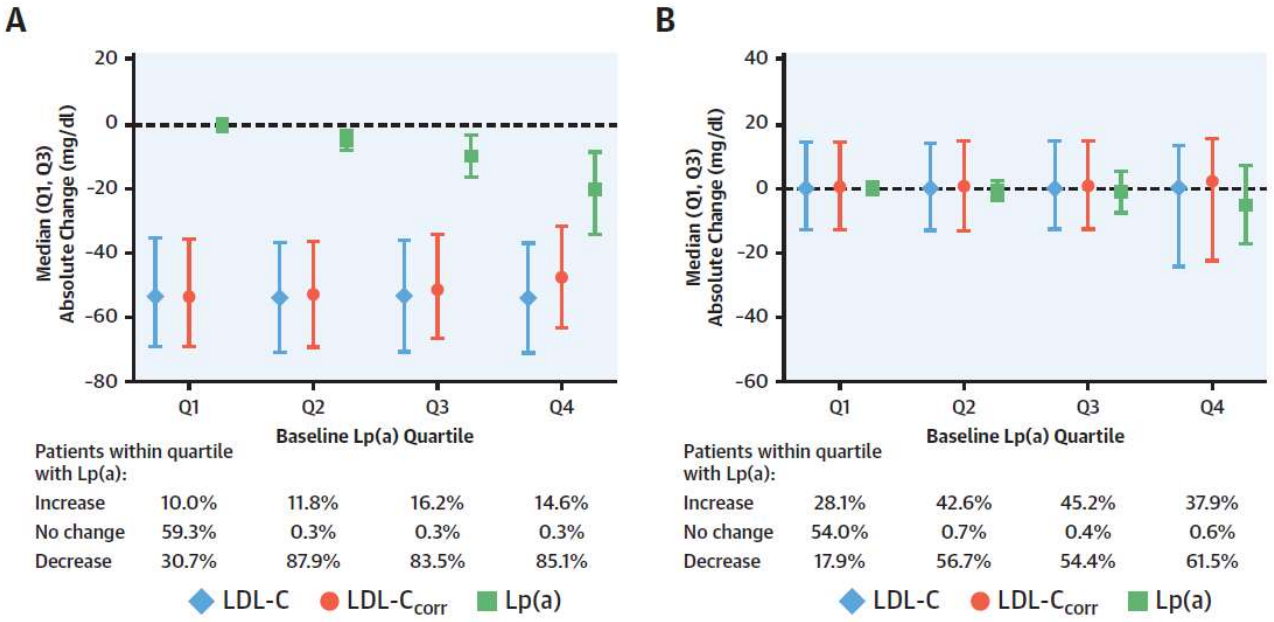


Figure 2 Relationship between anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibody, plasma free proprotein convertase subtilisin/kexin type 9, and low-density lipoprotein cholesterol concentrations (modified from Koren *et al.*[71]).

Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome

Variazioni assolute a 4 mesi del LDL-C, LDL-C corr, e **Lipoproteina(a)**

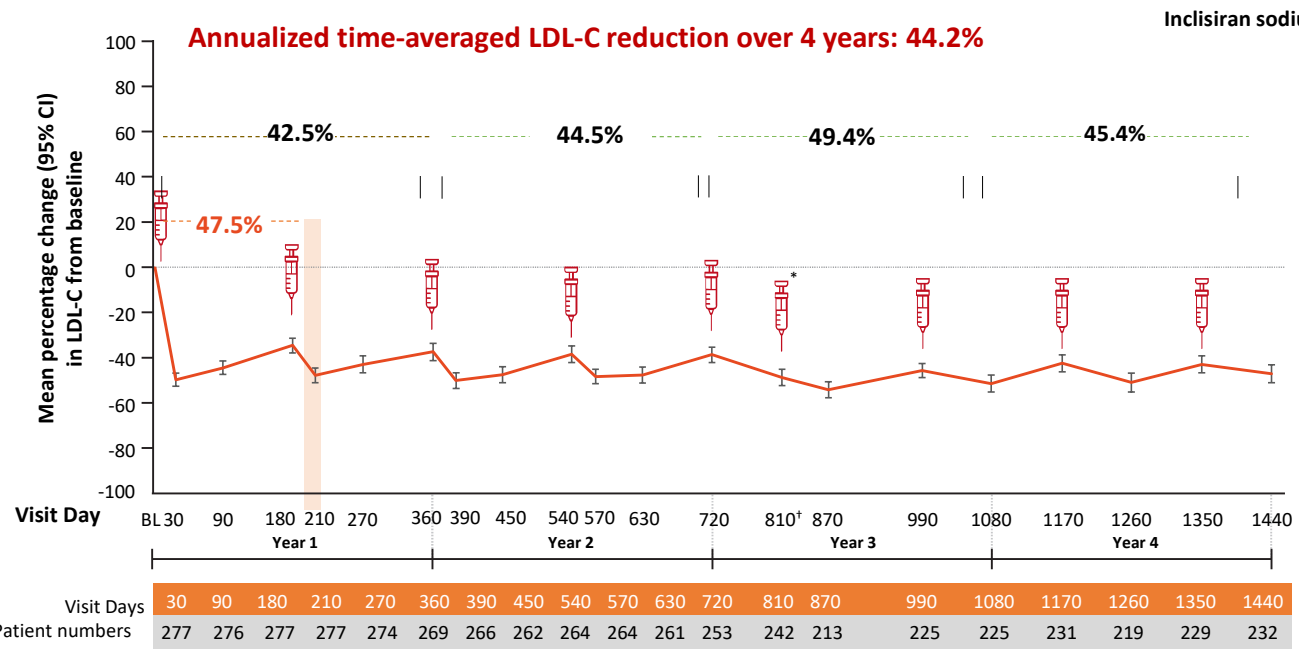


Bittner et al. J A C C V O L . 7 5 , NO . 2 , 2 0 2 0

Riduzione del LDL-C con inclisiran precoce e durevole a 4 anni

studio Orion 3

Mean percentage change in LDL-C from ORION-1 baseline to Day 1440 (4 years) of ORION-3 (inclisiran-only arm)



Primary efficacy results

–47.5‡ %

Percentage LDL-C change from baseline (Day 1 of ORION-1) to Day 210 of ORION-3

(95% CI: –50.7, –44.3; p<0.0001)

*Inclisiran-only arm. †D810 injection was administered as a one-time 90-day dosing interval as per the initial study design for exploratory purposes. ‡Without correction for placebo. The vertical rectangle denotes the primary endpoint at D210. Baseline represents the ORION-1 baseline. The analysis was carried out in the mITT population (n, 277 in the inclisiran-only arm and n, 88 in the switching arm).

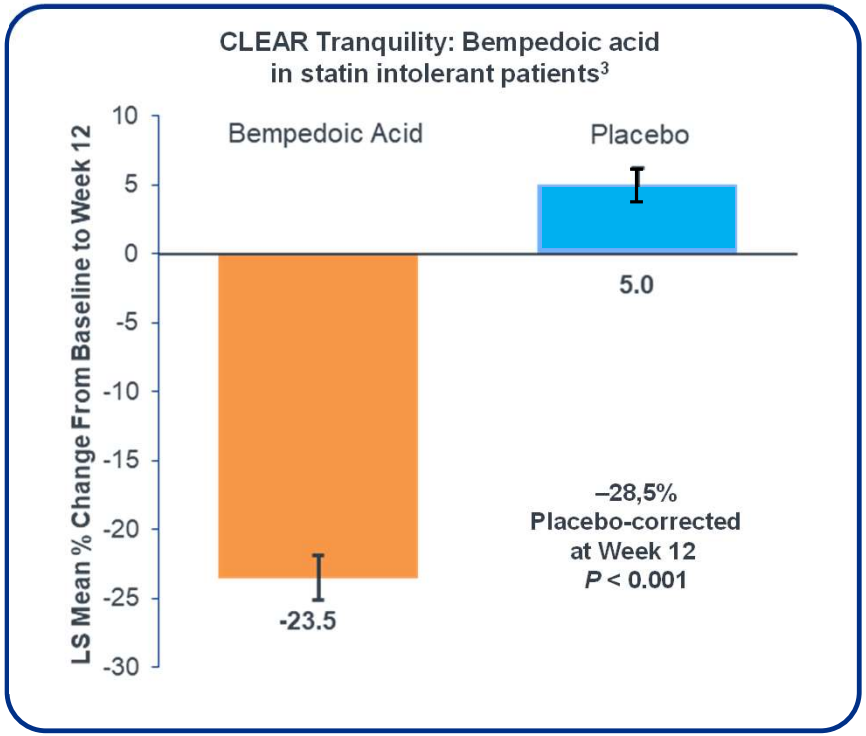
Acido bempedoico riduce i livelli di LDL-C in maniera significativa

Studio CLEAR

- **Non sono emerse differenze significative nella riduzione di LDL-C nei sottogruppi stratificati per livello di LDL-C al basale, diabete, età, razza, sesso, BMI, area geografica**

- **La riduzione di LDL-C era maggiore nei pazienti che non assumevano statina o altre terapie di base rispetto ai pazienti in trattamento con dosi basse o molto basse di statina (34.7% vs 20.5%; p di interazione= 0.032)**

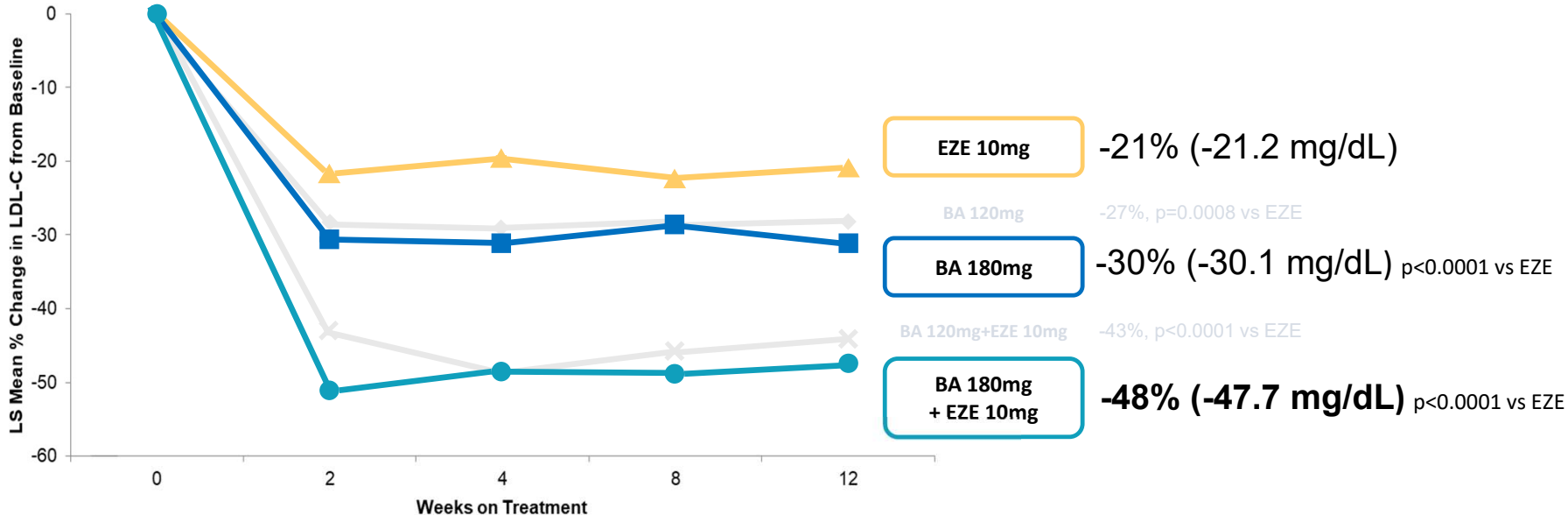
Riduzione di LDL-C del 28.5%



- Ballantyne CM, et al. *Atherosclerosis.* 2018;277:195-203..

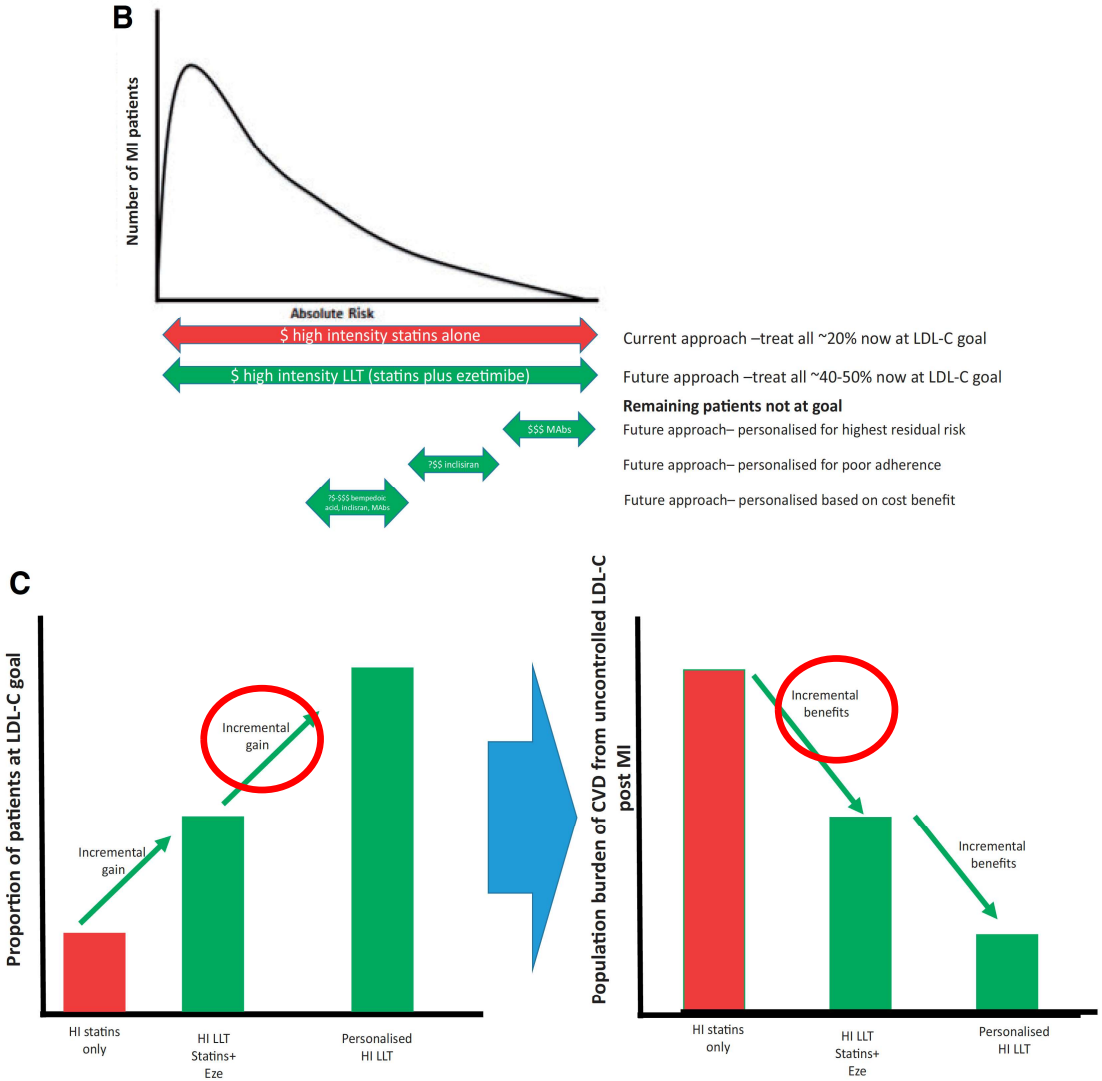
Acido Bempedoico 180 mg + Ezetimibe 10 mg

In uno studio di fase 2, la terapia di combinazione ha determinato una riduzione incrementale di LDL-C ed era ben tollerata



Thompson PD et al., J Clin Lipidol. 2016;10(3):556-67

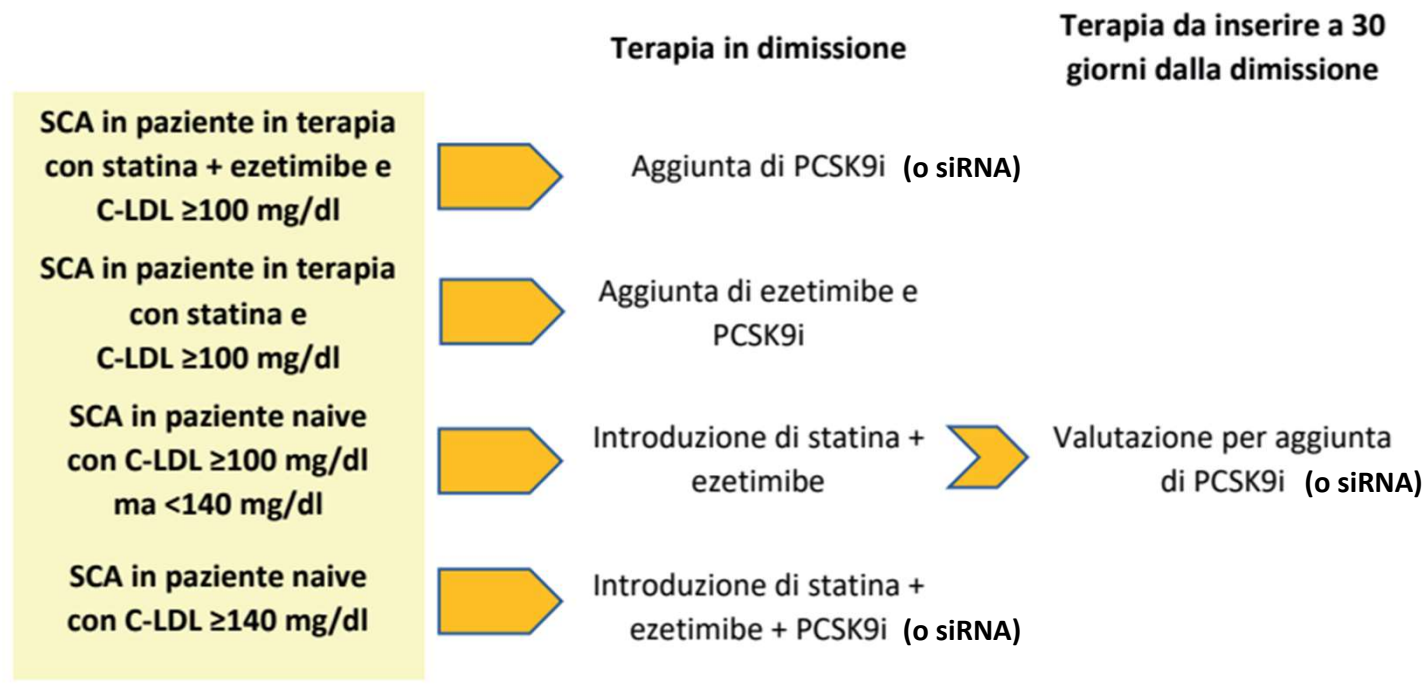
Post IMA: intensificare la cura per aumentare il beneficio



KK Ray. European Heart Journal (2021) 42, 253–256

Terapia ipolipemizzante post SCA

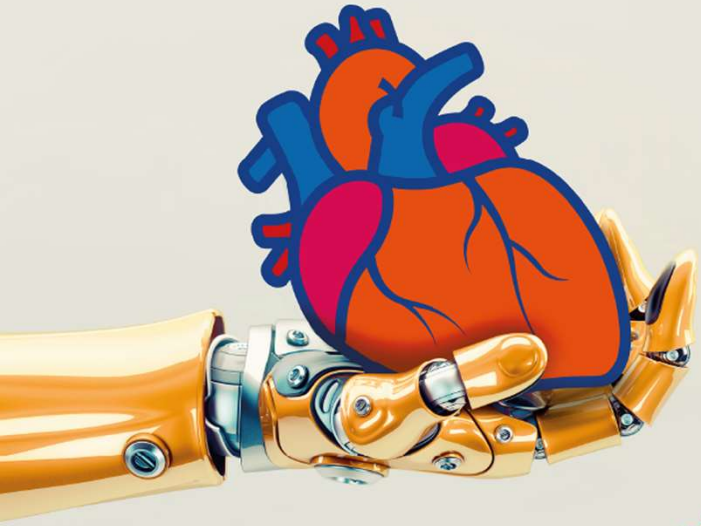
algoritmo semplificato



Modificato da Muccioli S et al G ITAL CARDIOL | VOL 23 | LUGLIO 2022

Conclusioni

- Usa **statine ad alta intensità** per raggiungere il target di LDL-C
- Usa terapia con beneficio su outcome cv come primo step (**statine, ezetimibe, PCSK9i**)
- Considera terapia di **combinazione** (**PCSK9i**) da subito se la probabilità di ottenere il target con statina ad alta intensità è bassa
- Considera **acido bempedoico** in pazienti che non raggiungono il target anche se alla dose massima di farmaci con provato beneficio prognostico
- Usa **inclisiran** in pazienti che non tollerano PCSK9i o che non possono attenersi alla terapia (in attesa di dati di prognosi)
- In pazienti con TG (> 135 mg/dL) ad alto rischio CV, considera **IPE** per ridurre il rischio residuo
- Rivaluta il paziente per verificare il raggiungimento del target terapeutico (anche mediante **telemedicina** a 4 settimane) e coinvolgi il **MMG**
- Non sono stati identificati livelli di C-LDL sotto i quali si perde il beneficio in termini di riduzione del rischio CV o si presentano problematiche di **safety**



17° Meeting

CardioLucca

Heart Brings Heart 2023

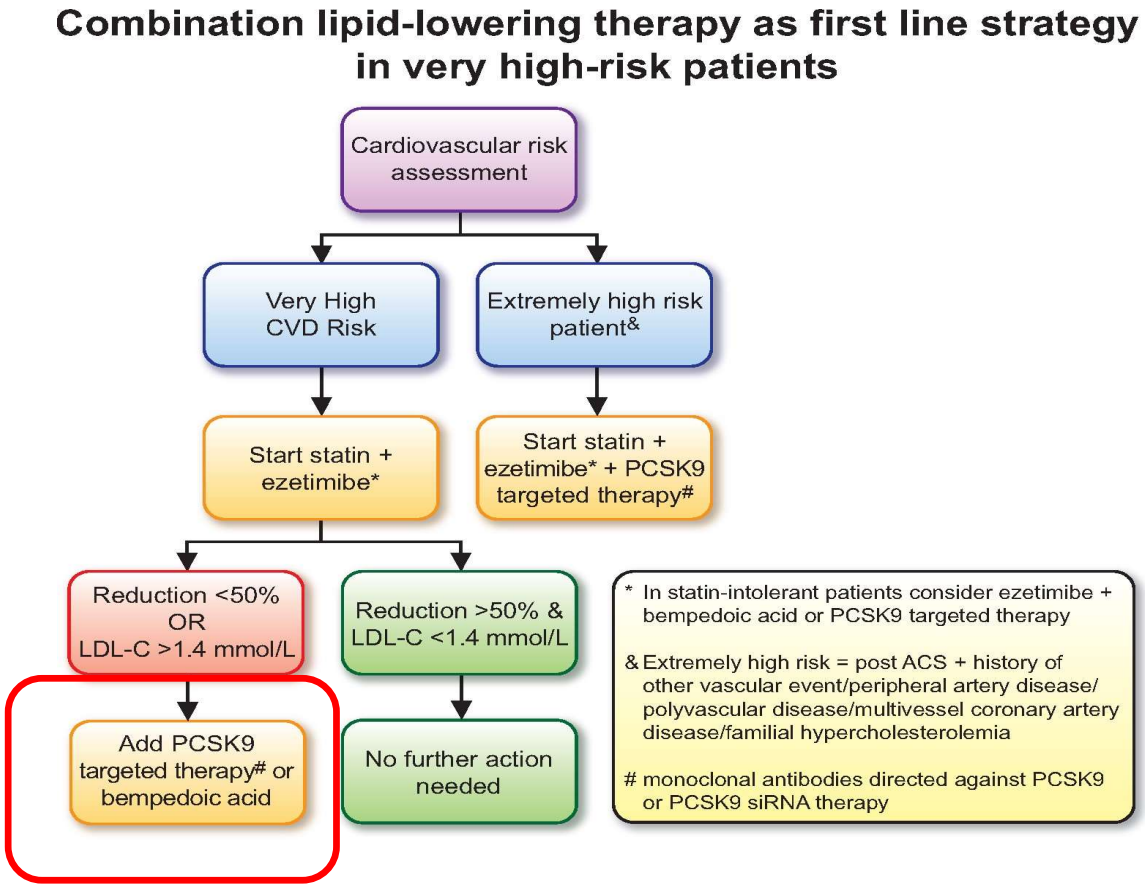
Lucca, 22-24 Giugno 2023

Centro Congressi Auditorium San Francesco

Emilio Maria Pasanisi
UOC Cardiologia Livorno

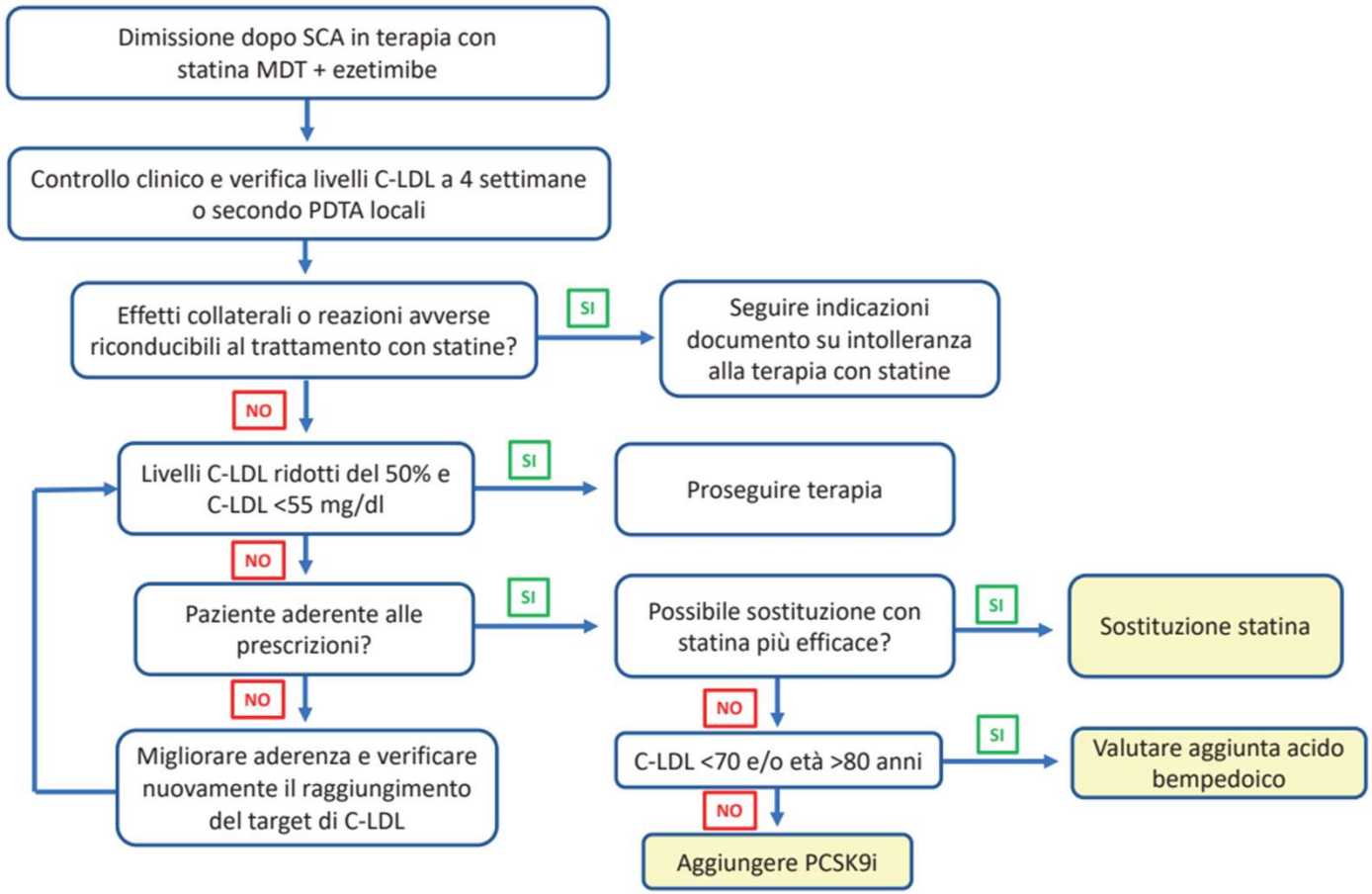
grazie

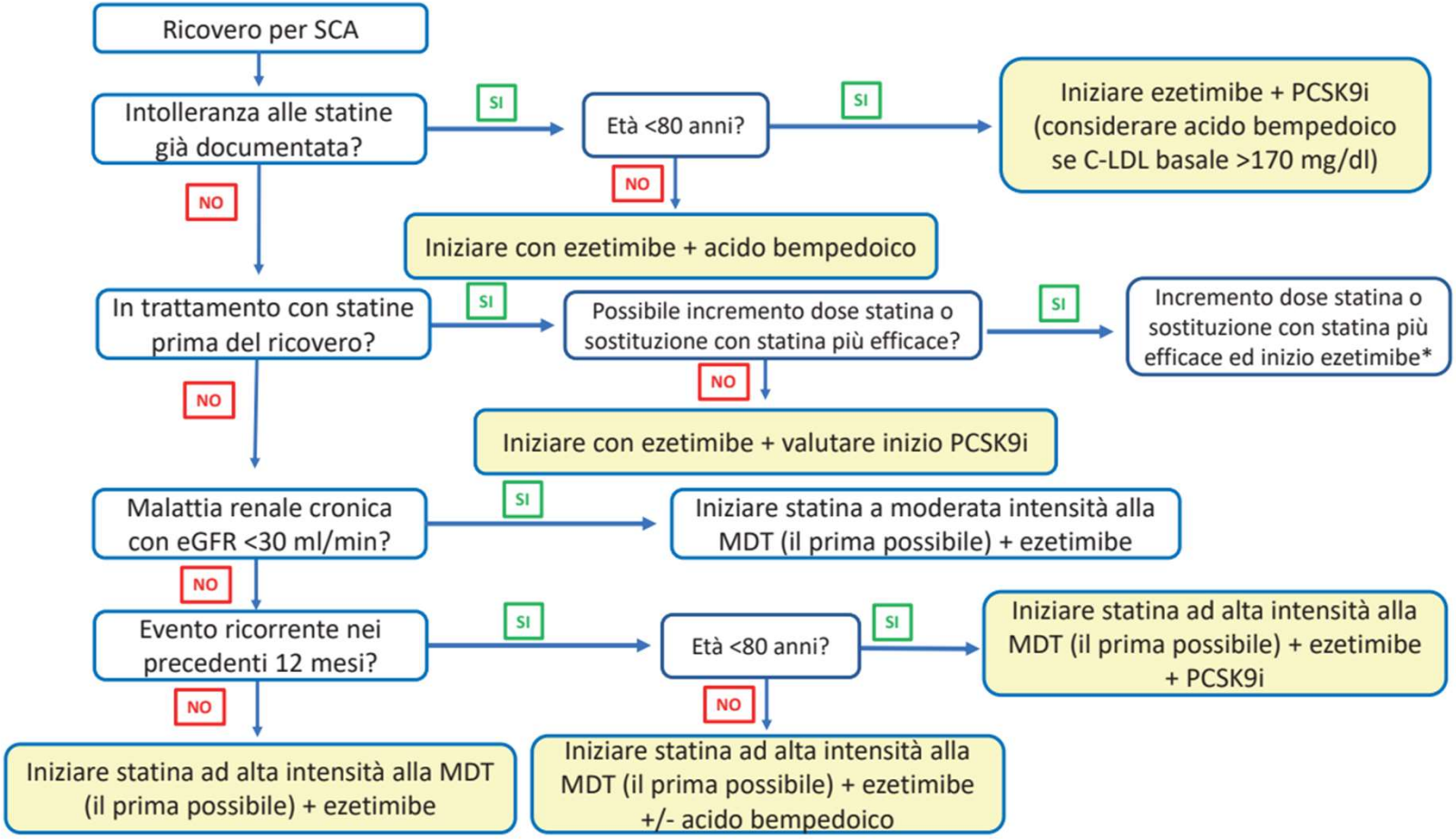
Cambiare il paradigma per la riduzione del colesterolo post-IM: dalla monoterapia con statine a regimi ipolipemizzanti intensivi e cure individualizzate

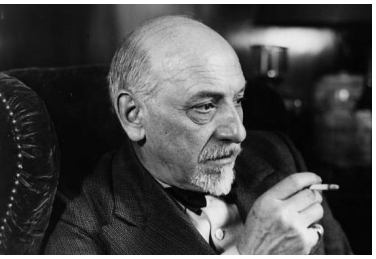


KK Ray. European Heart Journal (2021) 42, 253–256

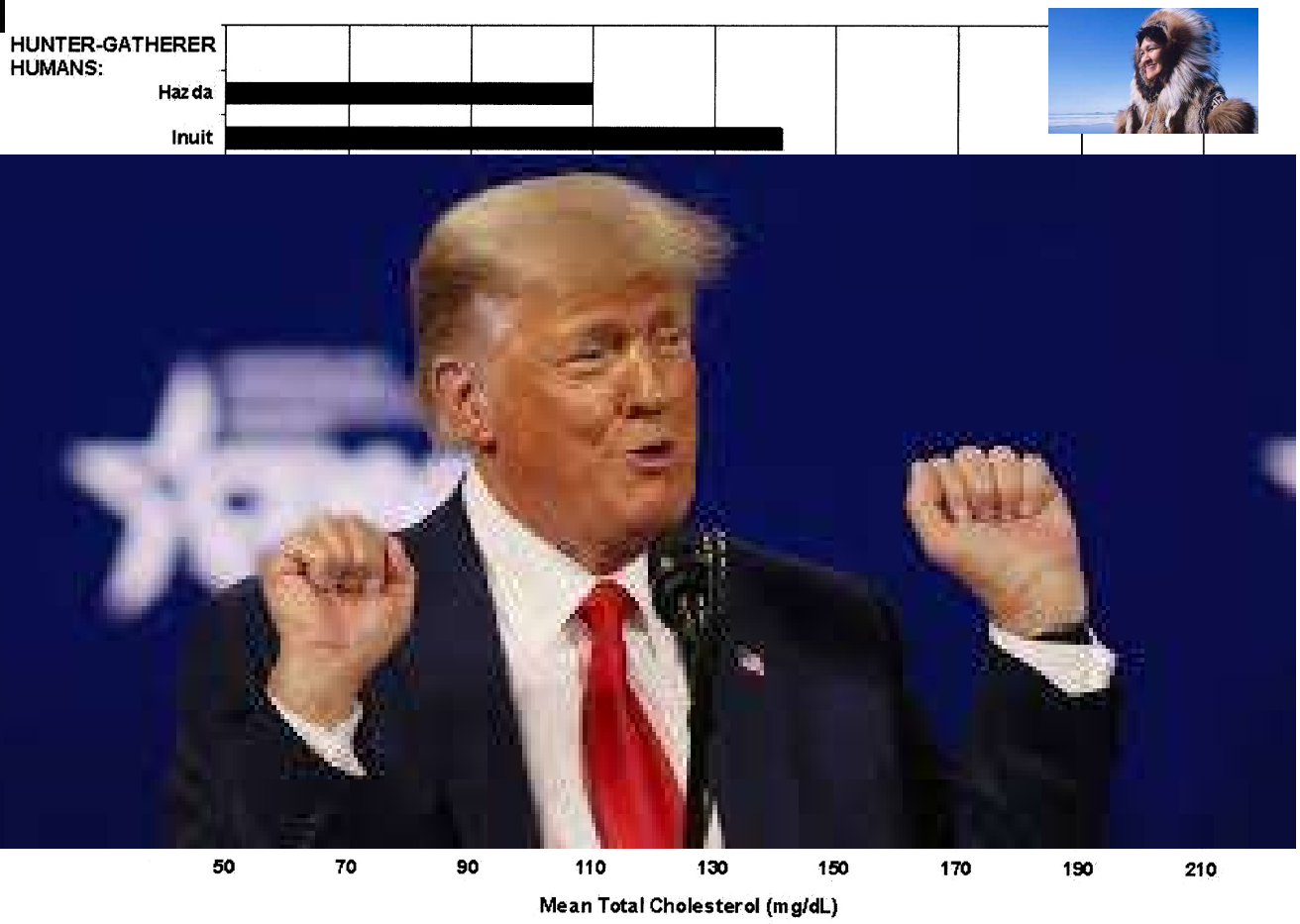
Terapia ipolipemizzante post SCA



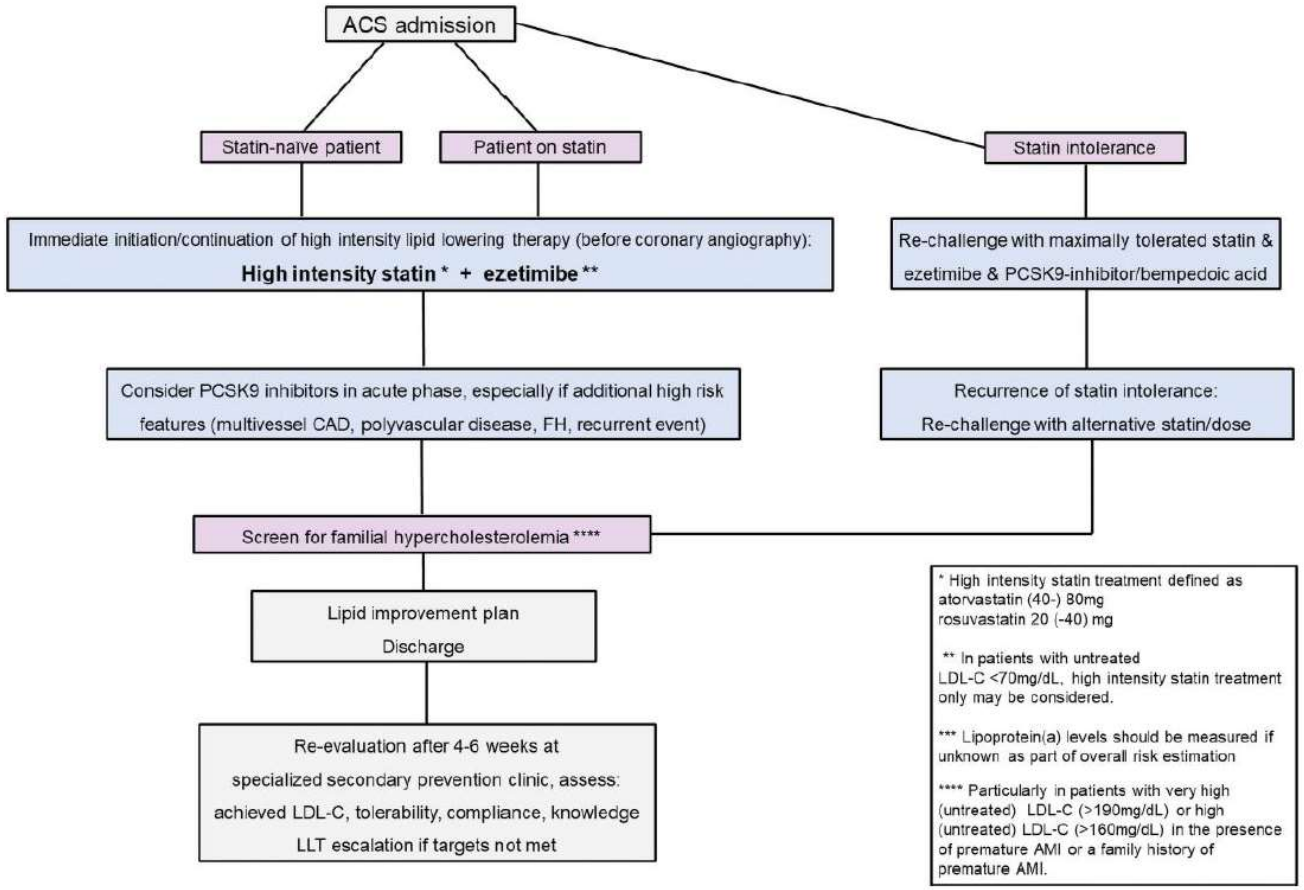

Ricovero per SCA
Intolleranza alle statine già documentata?
SI
Età <80 anni?
SI
Iniziare ezetimibe + PCSK9i (considerare acido bempedoico se C-LDL basale >170 mg/dl)
NO
NO
Iniziare con ezetimibe + acido bempedoico
In trattamento con statine prima del ricovero?
SI
Possibile incremento dose statina o sostituzione con statina più efficace?
SI
Incremento dose statina o sostituzione con statina più efficace ed inizio ezetimibe*
NO
NO
Iniziare con ezetimibe + valutare inizio PCSK9i
Malattia renale cronica con eGFR <30 ml/min?
SI
Iniziare statina a moderata intensità alla MDT (il prima possibile) + ezetimibe
NO
Evento ricorrente nei precedenti 12 mesi?
SI
Età <80 anni?
SI
Iniziare statina ad alta intensità alla MDT (il prima possibile) + ezetimibe + PCSK9i
NO
NO
Iniziare statina ad alta intensità alla MDT (il prima possibile) + ezetimibe
Iniziare statina ad alta intensità alla MDT (il prima possibile) + ezetimibe +/- acido bempedoico



Dislipidemia:
una, nessuna, centomila



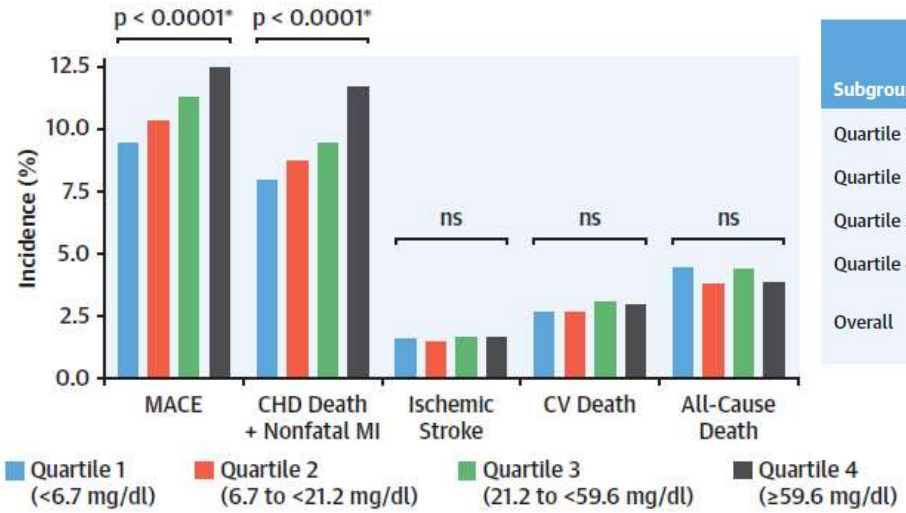
Lipid-lowering algorithm after ACS: strike early and strike strong



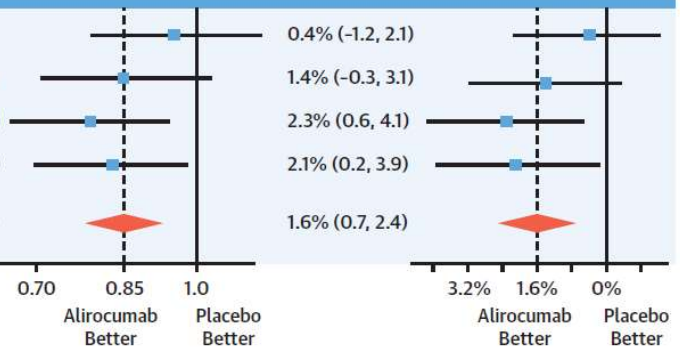
European Heart Journal: Acute Cardiovascular Care (2022) **11**, 939–949

Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome

Baseline Lipoprotein(a) Quartile as a Predictor of Events



Subgroup	MACE Incidence Alirocumab n/N (%)	Placebo n/N (%)	HR (95% CI) ($p_{interaction}$ = 0.55)	Absolute Risk Reduction (95% CI) ($p_{interaction}$ = 0.0011)
Quartile 1	211/2,327 (9.1)	228/2,403 (9.5)	0.95 (0.79, 1.15)	0.4% (-1.2, 2.1)
Quartile 2	219/2,438 (9.0)	239/2,293 (10.4)	0.85 (0.71, 1.03)	1.4% (-0.3, 3.1)
Quartile 3	212/2,356 (9.0)	269/2,373 (11.3)	0.79 (0.66, 0.94)	2.3% (0.6, 4.1)
Quartile 4	261/2,341 (11.2)	316/2,393 (13.2)	0.83 (0.70, 0.98)	2.1% (0.2, 3.9)
Overall	903/9,462 (9.5)	1,052/9,462 (11.1)	0.85 (0.78, 0.93)	1.6% (0.7, 2.4)

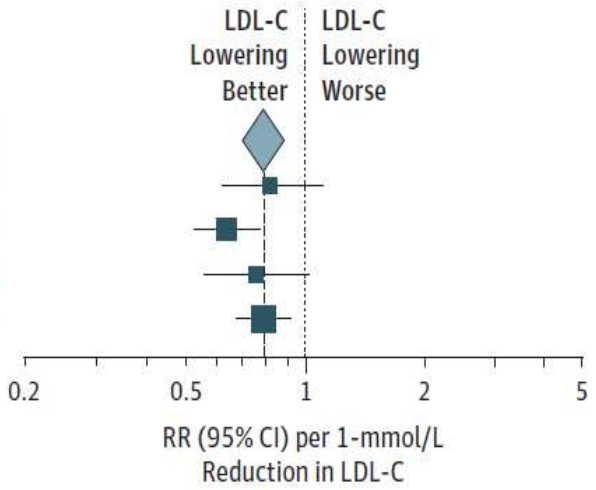


Bittner et al. J A C C V O L . 7 5 , NO . 2 , 2 0 2 0

Raggiungere livelli di C-LDL pari a 20 mg/dL determina una ulteriore riduzione del rischio cardiovascolare

Individual Efficacy Outcomes in Nonstatin Trials

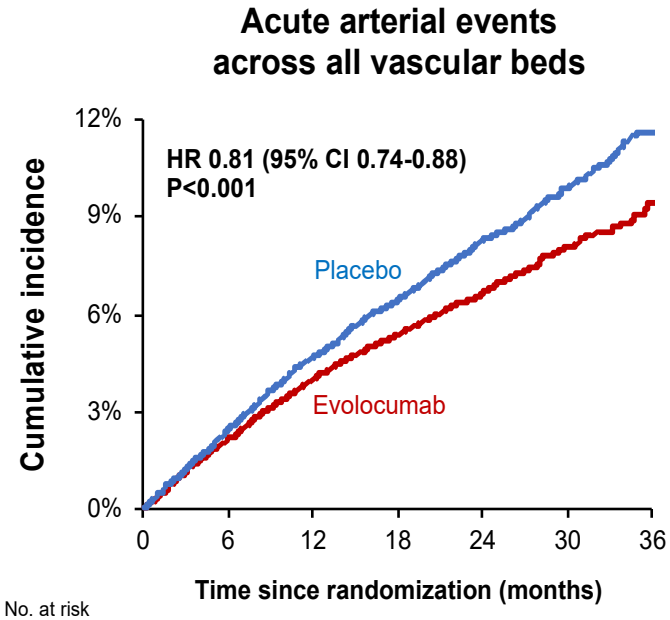
Outcome	Patients With Events, No. Experimental Arm	Control Arm	RR (95% CI)
Major vascular events	4604	4966	0.79 (0.70-0.88)
Coronary heart death	836	891	0.82 (0.62-1.10)
Myocardial infarction	1671	1930	0.64 (0.53-0.77)
Ischemic stroke	737	804	0.76 (0.56-1.02)
Coronary revascularization	3003	3228	0.79 (0.68-0.92)

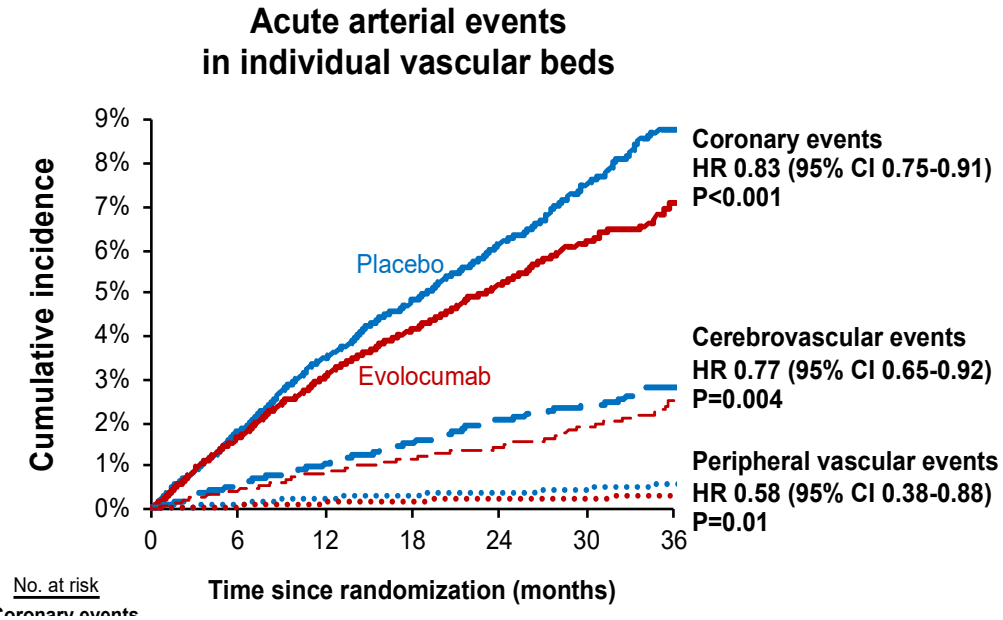


Consistent clinical benefit from further LDL-C lowering in patient populations starting as low as a median of 1.6 mmol/L (63mg/dL) and achieving levels as low as a median of 0.5 mmol/L (21 mg

Sabatine MS, et al. JAMA Cardiol. 2018;3(9):823-828.

L'impatto multidistrettuale della terapia con Evolocumab
Trattare il cuore per trattare tutto





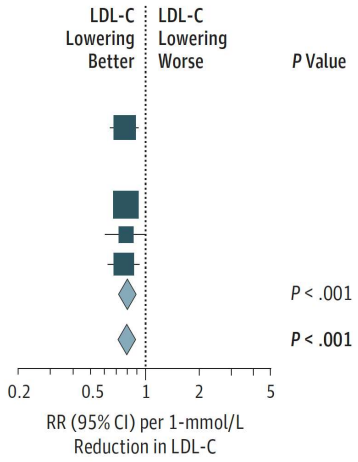
Oyama K et al European Heart Journal (2021) 00, 1–9

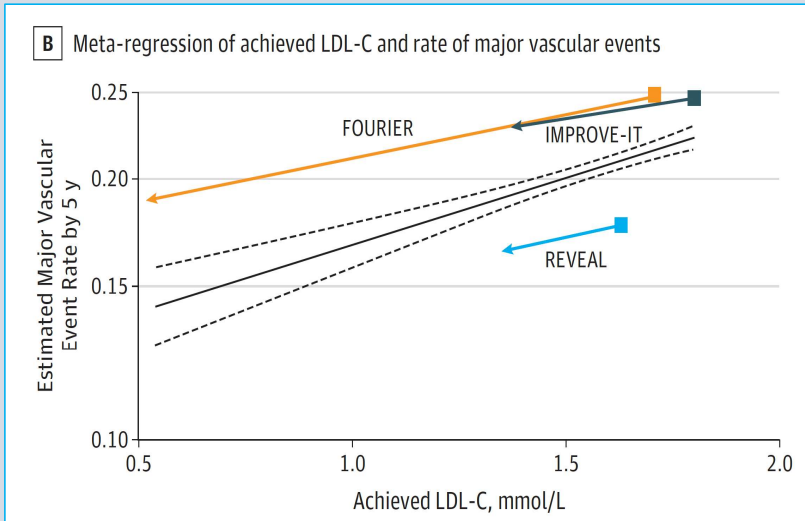
Efficacia e sicurezza della ulteriore riduzione dell'LDL in pazienti con bassi livelli di LDL: *una meta-analisi*

Partendo da 63mg/dL ottenendo valori fino a 21 mg

A Meta-analysis of effect of 1-mmol/L LDL-C lowering on the risk of major vascular events

Trial	Events, % per annum: Experimental Arm	Control Arm	RR (95% CI)	P Value
Statins				
CTTC <2 mmol/L subgroup	910 (4.1)	1012 (4.6)	0.78 (0.65-0.94)	
Nonstatin LDL-C lowering				
IMPROVE-IT	2455 (4.5)	2649 (4.9)	0.79 (0.67-0.93)	
FOURIER <1.8 mmol/L subgroup	81 (3.7)	103 (4.9)	0.80 (0.61-1.04)	
REVEAL	2068 (3.3)	2214 (3.5)	0.77 (0.63-0.96)	
Summary	4604	4966	0.79 (0.70-0.88)	P < .001
Overall summary	**5514**	**5978**	**0.79 (0.71-0.87)**	**P < .001**

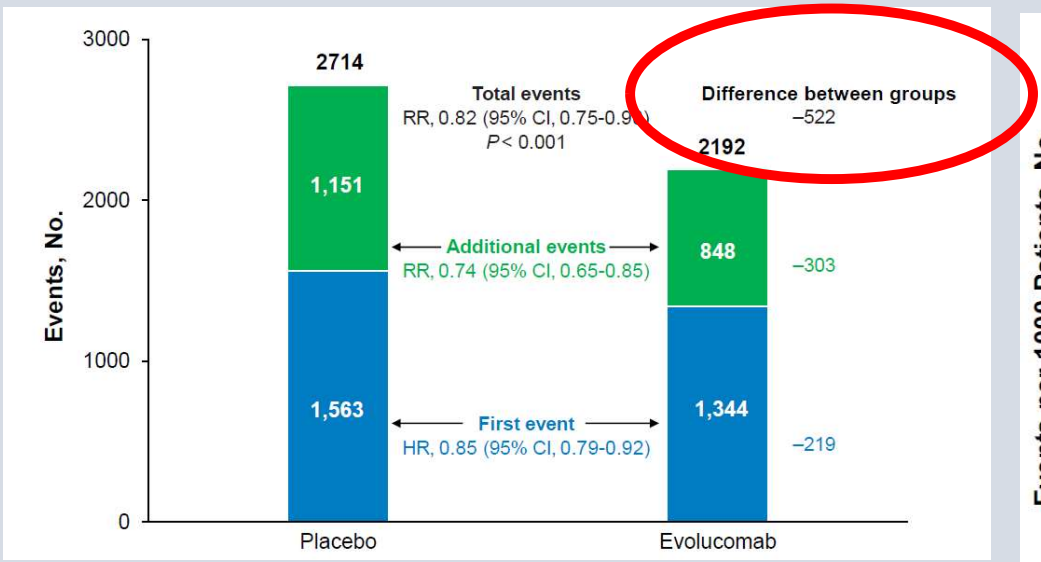




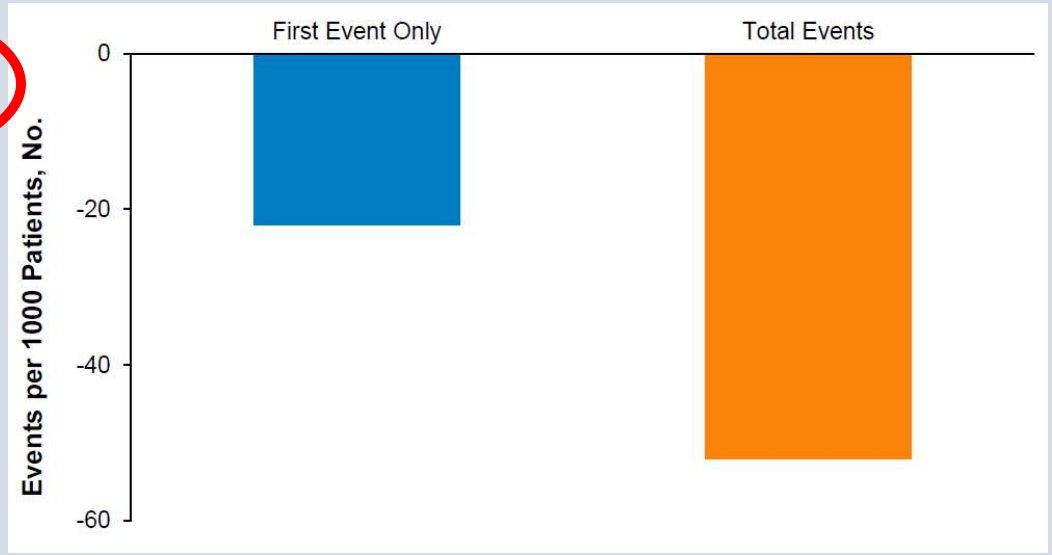
Sabatine MS, et al. JAMA Cardiol. 2018;3(9):823-828

L'aggiunta di evolocumab fornisce ulteriore prova del beneficio di una terapia ipolipemizzante aggressiva e continua per prevenire gli eventi cardiovascolari

First, Additional and Total Primary Endpoint Events During Follow-up by Randomization Group



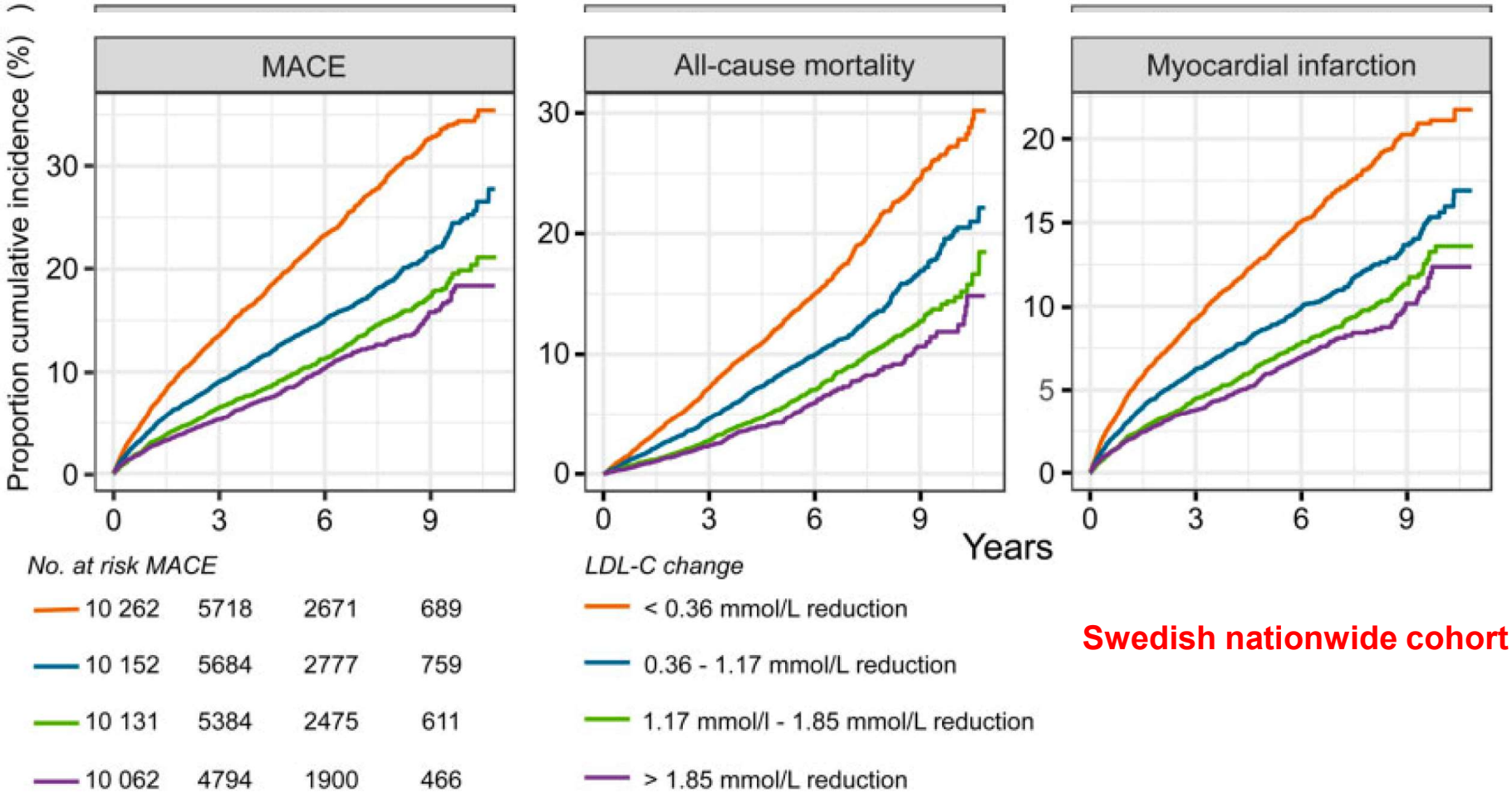
Risk Differences for 1000 Patients Treated for 3 Years With Evolocumab for the First and Total Number of the Primary Endpoint



Con Evolocumab riesco a dimezzare gli eventi rispetto al placebo

Murphy SA et a, JAMA Cardiol. 2019 May 22;4(7):613-619

Lower is better



Swedish nationwide cohort study

European Heart Journal (2021) 42, 243–252

arcelona, Spain – 29 Aug 2022: Long-term low-density lipoprotein (LDL) cholesterol lowering with evolocumab is safe and well tolerated and leads to further reductions in cardiovascular events compared with shorter treatment, according to late breaking results from the FOURIER open-label extension (OLE) study presented in a Hot Line session today at ESC Congress 2022.[1]

Principal investigator Dr. Michelle O'Donoghue of Brigham and Women's Hospital, Boston, US said: "PCSK9 inhibitors lead to marked reductions in LDL cholesterol. The major trials to date have only had median treatment durations of two to three years. However, in clinical practice lipid-lowering therapy is typically administered chronically. FOURIER-OLE was therefore conducted to better understand the long-term safety, tolerability, lipid levels, and risk of major adverse cardiovascular events in patients getting prolonged treatment with the PCSK9 inhibitor evolocumab."

In FOURIER, evolocumab reduced the risk of cardiovascular events and was safe and well-tolerated over a median follow up of 2.2 years.[2] FOURIER-OLE was conducted at select sites in Europe and the US that participated in FOURIER. The study enrolled 6,635 patients (3,355 randomised to evolocumab and 3,280 to placebo in FOURIER) who completed FOURIER. All patients in the extension study self-injected evolocumab with the choice of 140 mg every two weeks or 420 mg monthly.

Study visits were at week 12 and then every 24 weeks and included clinical assessments and fasting lipids. The primary objective was to report the long-term safety and tolerability of the drug. Major adverse cardiovascular events were reviewed by an independent clinical events committee.

The median follow-up in the extension study was 5.0 years. The maximum exposure to evolocumab in FOURIER plus FOURIER-OLE was 8.4 years. At 12 weeks in FOURIER-OLE, the median LDL cholesterol was 30 mg/dl and 63.2% of participants achieved LDL cholesterol <40 mg/dl on evolocumab. Incidences of serious adverse events, muscle-related events, new-onset diabetes, haemorrhagic stroke, and neurocognitive events with long-term evolocumab did not exceed those for placebo-treated patients during the parent study and did not increase over time.

During FOURIER-OLE, patients originally randomised in the parent trial to evolocumab versus placebo had a 15% lower risk of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation (490/3355 vs. 551/3280; hazard ratio [HR] 0.85; 95% confidence interval [CI] 0.75–0.96; p=0.008), a 20% lower risk of cardiovascular death, myocardial infarction or stroke (309 vs. 374; HR 0.80; 95% CI 0.68–0.93; p=0.003), and a 23% lower risk of cardiovascular death (107 vs. 138; HR 0.77; 95% CI 0.60–0.99; p=0.04).

Dr. O'Donoghue said: "FOURIER-OLE included patients with the longest study exposure to a PCSK9 inhibitor so far. Long-term LDL cholesterol lowering with evolocumab was safe and well tolerated for more than eight years and led to further reductions in cardiovascular events compared with delayed treatment initiation. These data provide further support to guidelines recommending lipid-lowering therapy with PCSK9 inhibitors and targeting very low levels of LDL cholesterol."

ENDS

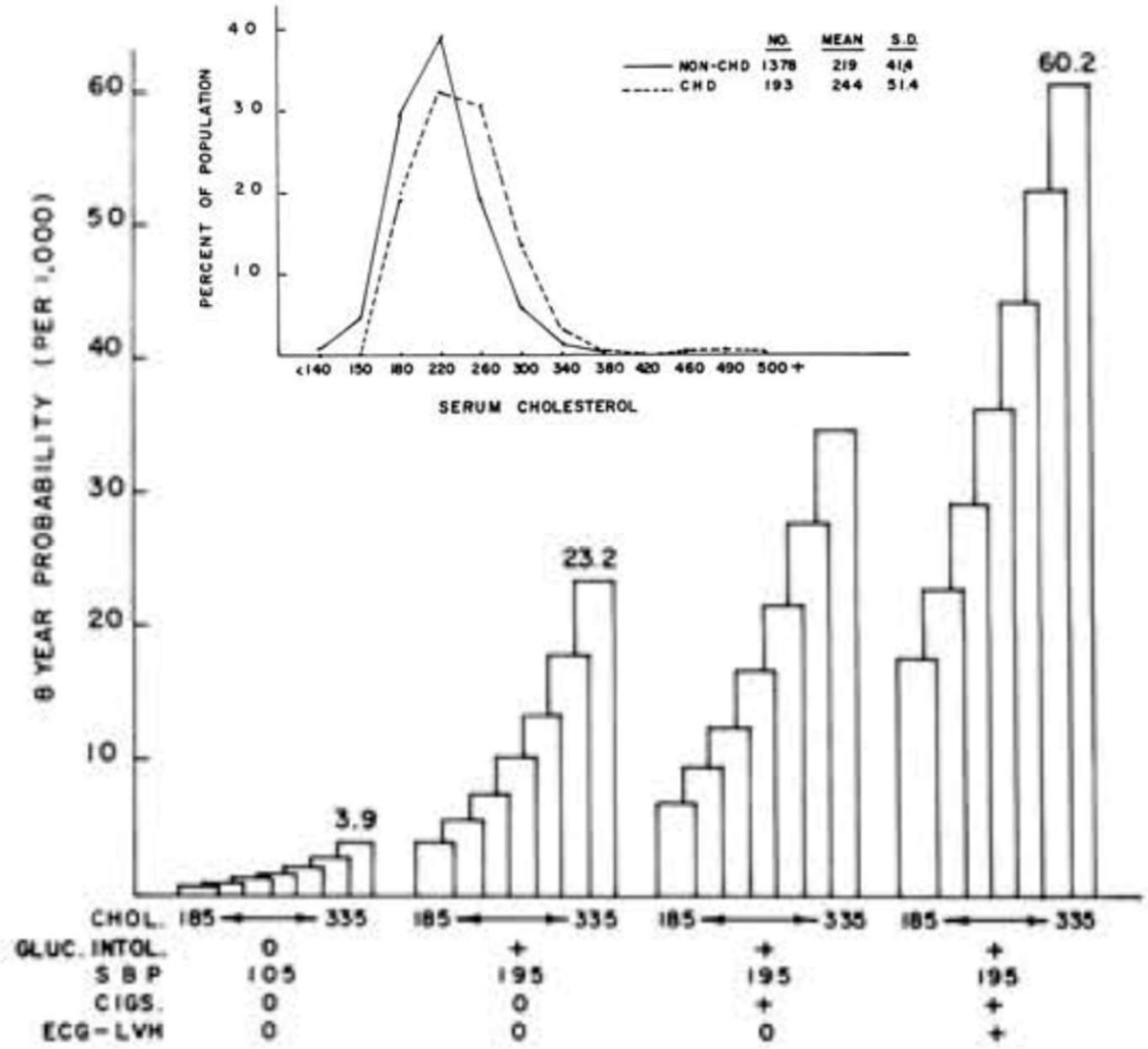
Risk of cardiovascular disease according to serum cholesterol at specified levels of other risk factors

In young victims of coronary heart disease (under age 50) in the Framingham cohort ***the average cholesterol was only 244 mg/dl.***

Within the range of values most laboratories characterize as "normal" (180 to 310 mg/dl), risk has been found to vary widely.

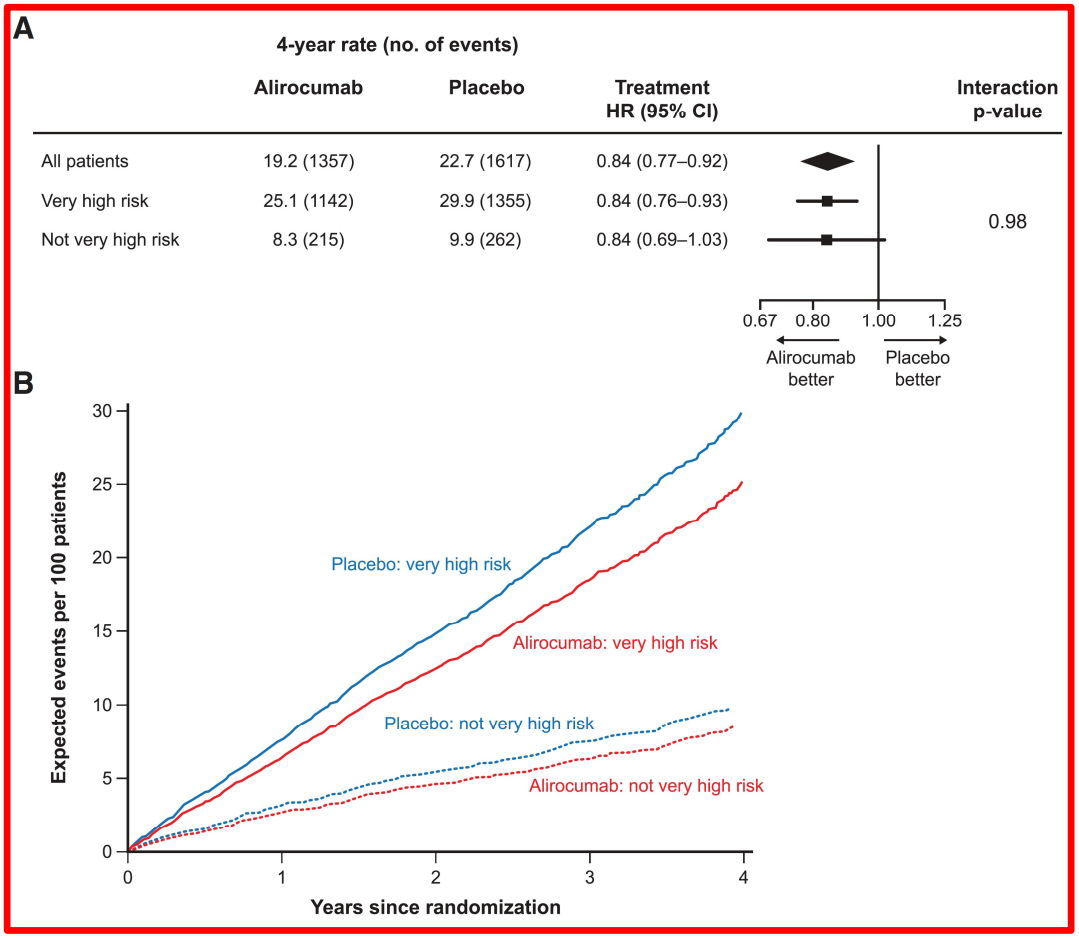
New Perspectives Based on the Framingham Study

Annals of Internal Medicine 90:85-91 , 1979



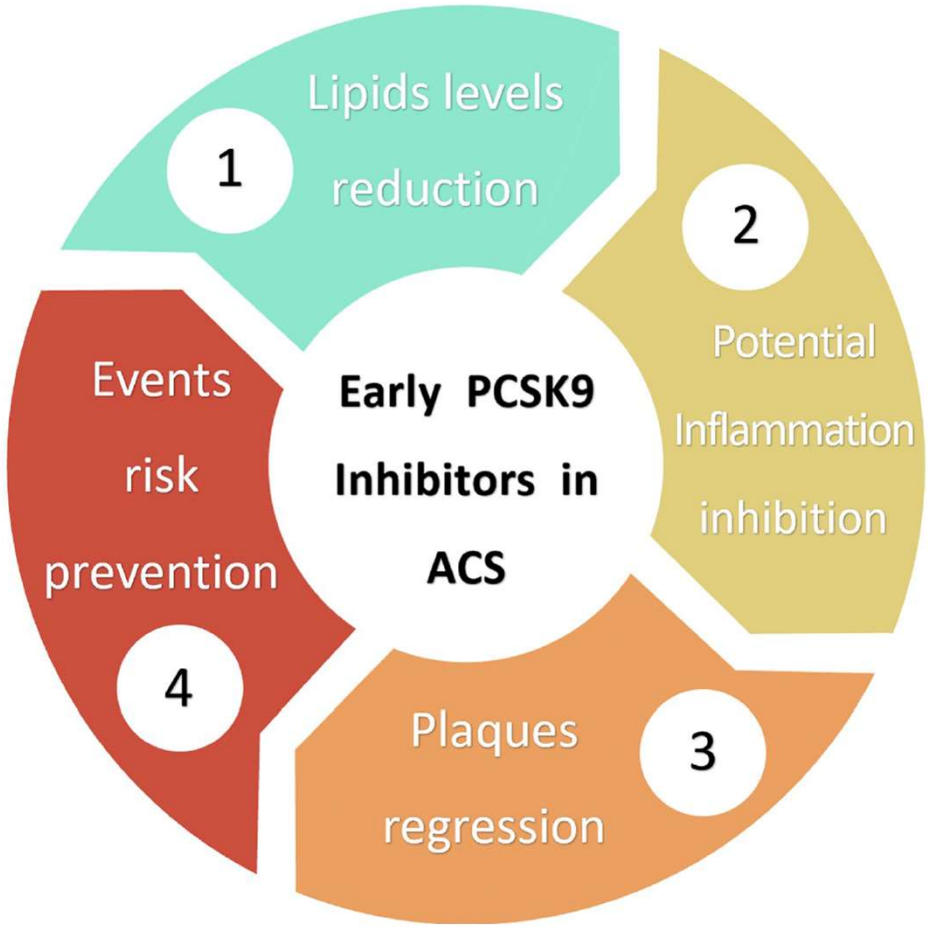
Alirocumab dopo SCA, secondo il rischio CV

NB
maggiore beneficio in paz LDL ≥100 mg/dL in tp con statina



Circulation. 2019;140:1578–1589

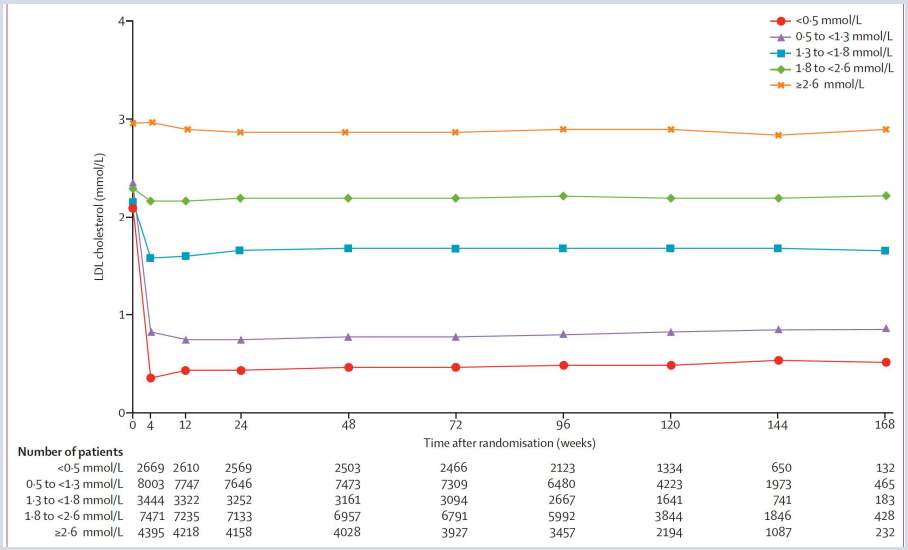
Target terapeutici ed end point

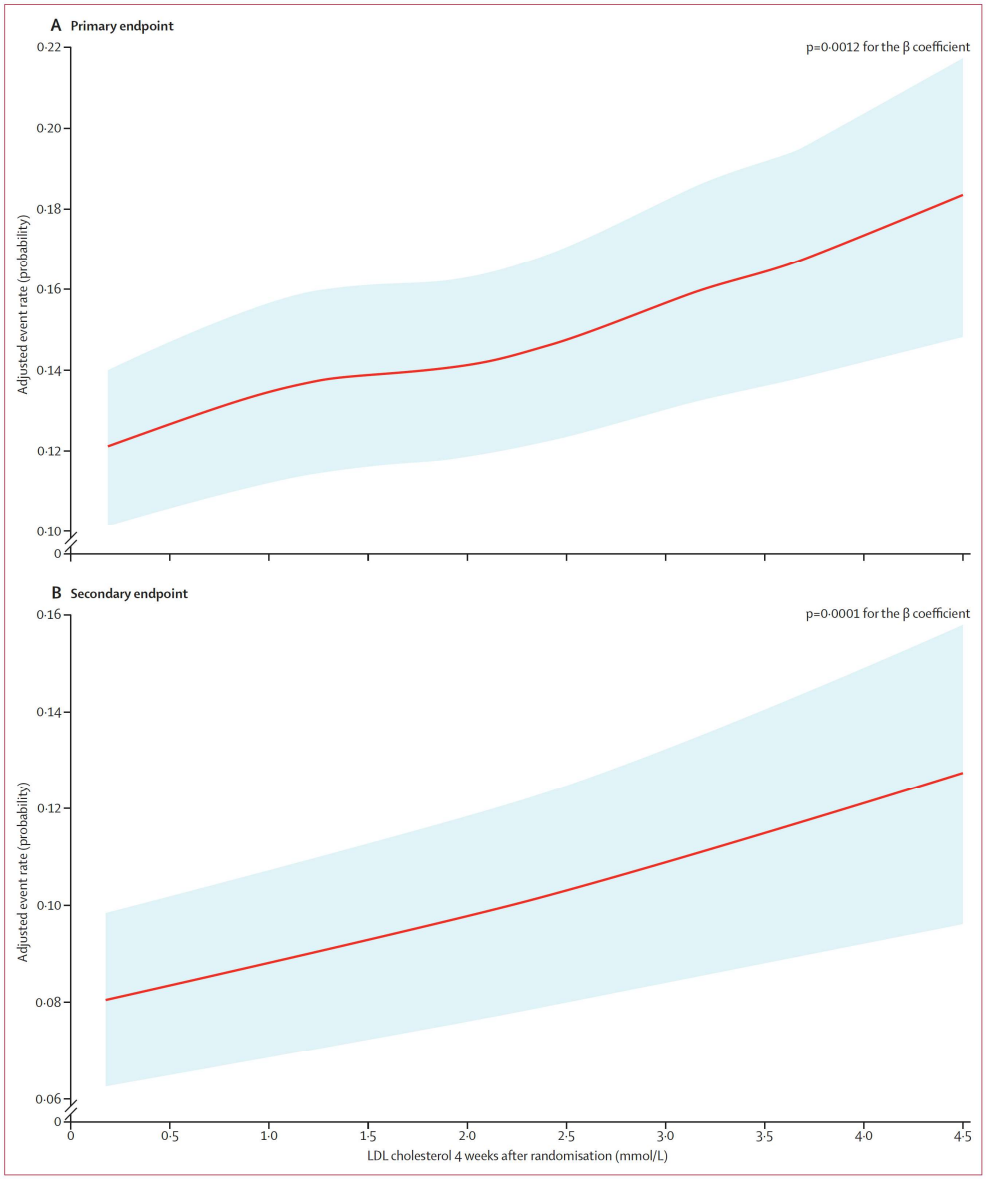


Dislipidemia e malattia cardiovascolare

- LDL-C retention and accumulation participate directly in the initiation and progression of atherosclerotic cardiovascular disease (ASCVD)
- Experimentally induced elevations in plasma LDL-C lead to atherosclerosis in animals
- Monogenically and polygenically mediated lifelong elevations in LDL-C lead to markedly higher lifetime risk of ASCVD
- Monogenic conditions, such as forms of familial hypercholesterolemia,markedly elevate LDL-C and associate with premature atherosclerosis
- Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL-C and risk of ASCVD, independent of other risk factors
- Randomized trials that have evaluated therapies specifically designed to lower LDL have consistently demonstrated that reducing LDL-C lowers the risk of ASCVD events

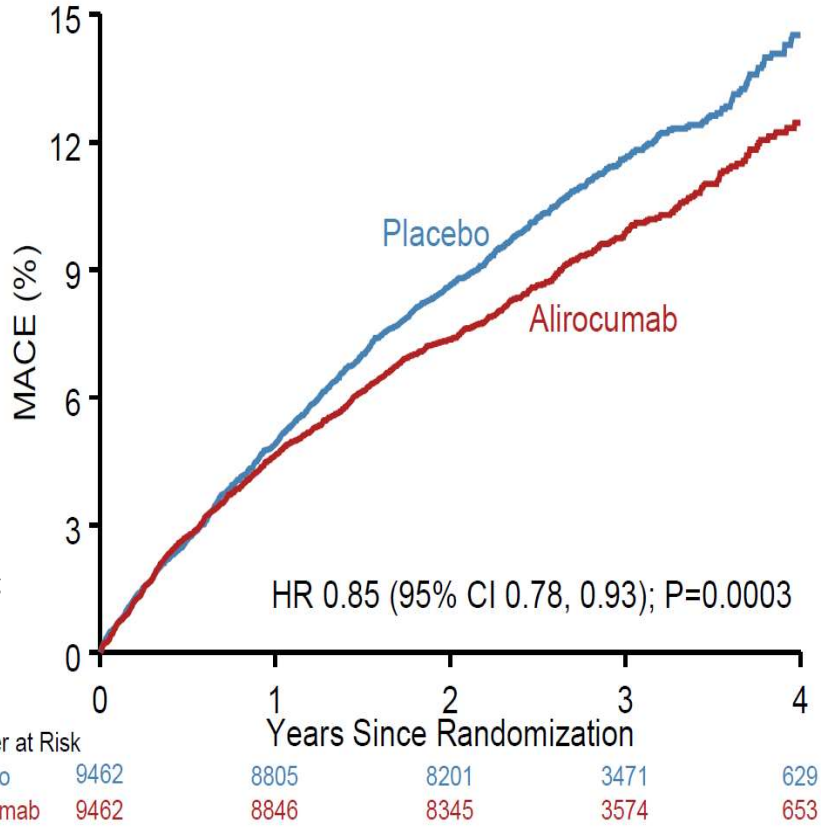
Relazione tra livelli di LDL raggiunti dopo 4 settimane di terapia con evolocumab e riduzione del rischio relativo





Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

Primary Efficacy Endpoint: MACE



ARR* 1.6%

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

*Based on cumulative incidence

•Schwartz GG et al,N Engl J Med. 2018 Nov 7.

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

Main Secondary Efficacy Endpoints:

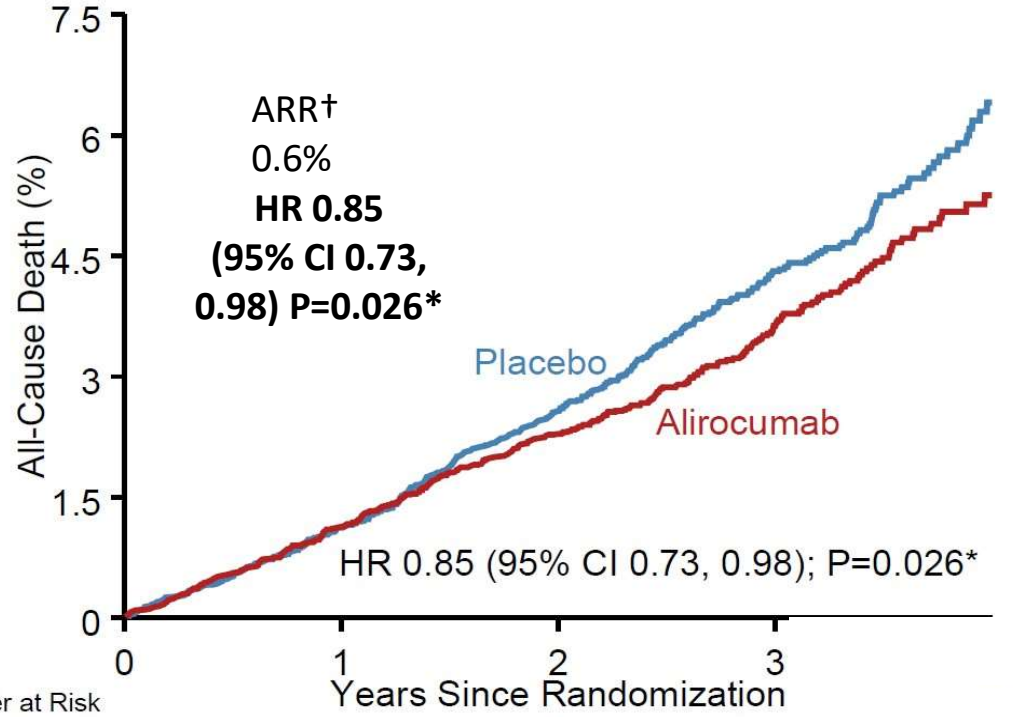
Hierarchical Testing

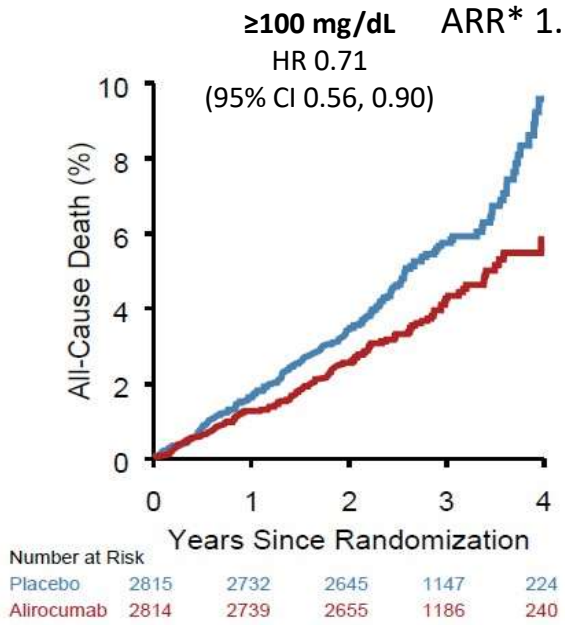
Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	**1199 (12.7)**	**1349 (14.3)**	**0.88 (0.81, 0.95)**	**0.001**
Major CHD event	**793 (8.4)**	**899 (9.5)**	**0.88 (0.80, 0.96)**	**0.006**
CV event	**1301 (13.7)**	**1474 (15.6)**	**0.87 (0.81, 0.94)**	**0.0003**
Death, MI, ischemic stroke	**973 (10.3)**	**1126 (11.9)**	**0.86 (0.79, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
CV death	**240 (2.5)**	**271 (2.9)**	0.88 (0.74, 1.05)	0.15
All-cause death	**334 (3.5)**	**392 (4.1)**	**0.85 (0.73, 0.98)**	**0.026***

*Nominal P-value

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

All-Cause Death



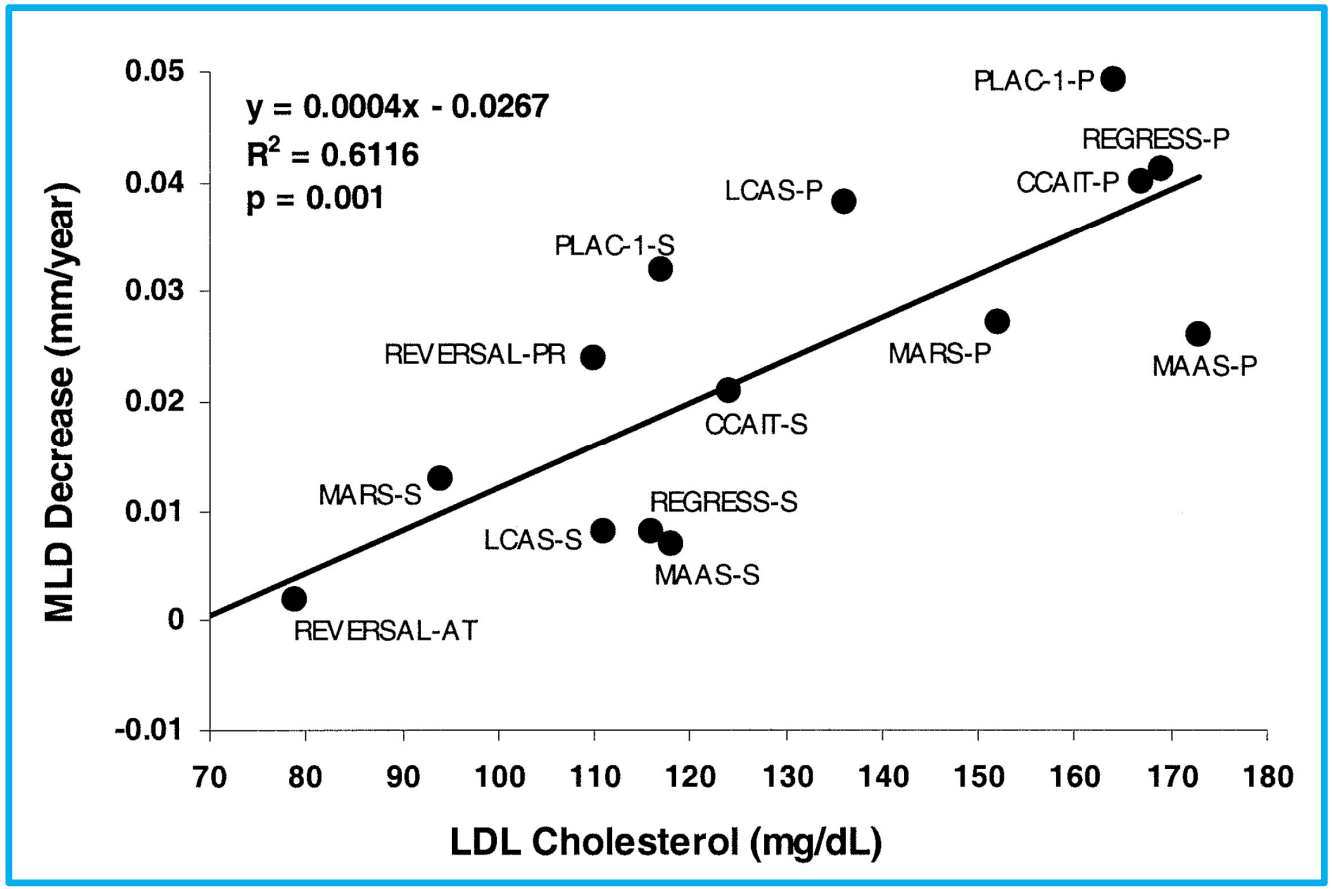


$P_{interaction}$=0.12

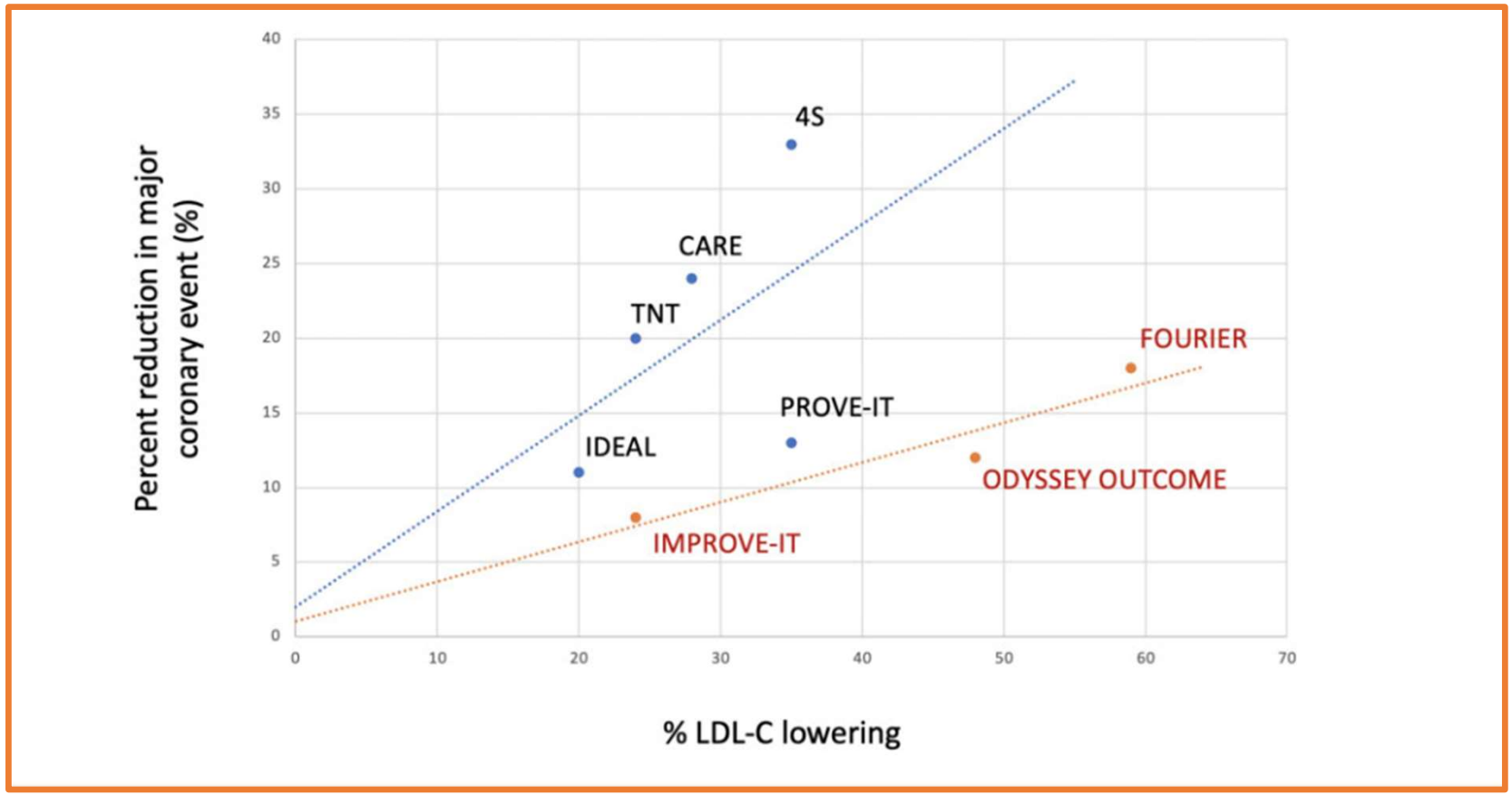
*Nominal P-value
†Based on cumulative incidence

•Schwartz GG et al,N Engl J Med. 2018 Nov 7.

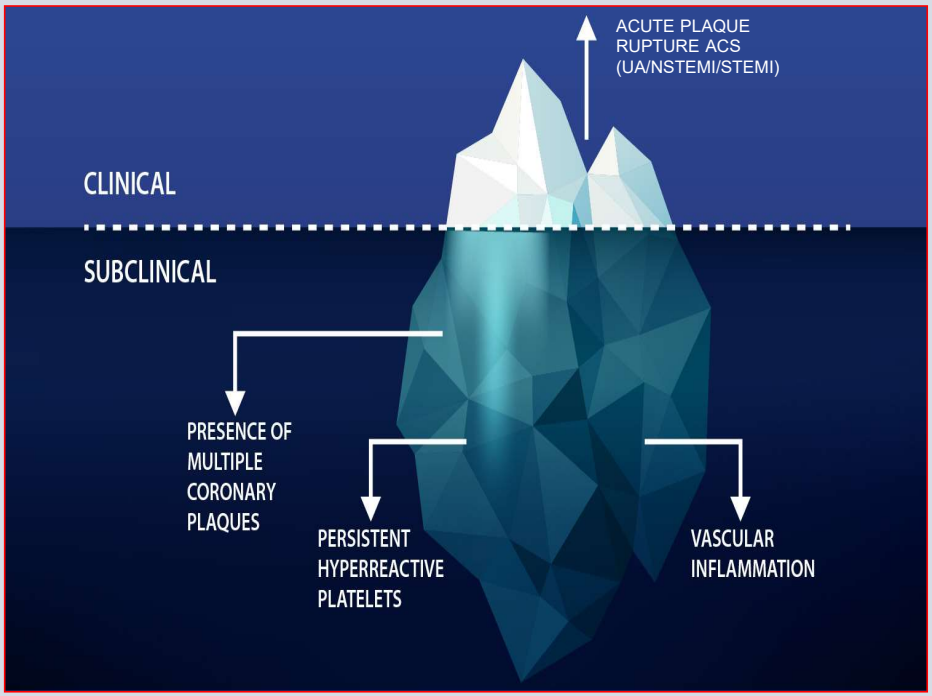
La progressione dell'aterosclerosi varia direttamente con l'LDL



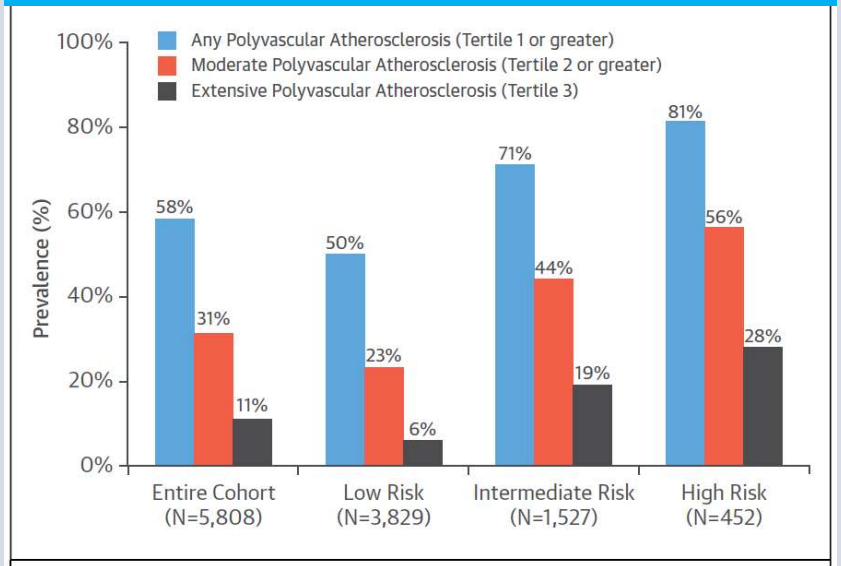
O'Keefe, Jr. et al. JACC Vol. 43, No. 11, 2004


Percent reduction in major coronary event (%)
% LDL-C lowering
0
5
10
15
20
25
30
35
40
0
10
20
30
40
50
60
70
4S
CARE
TNT
IDEAL
PROVE-IT
FOURIER
ODYSSEY OUTCOME
IMPROVE-IT

La sindrome coronarica acuta è la punta dell'iceberg dell'aterotrombosi



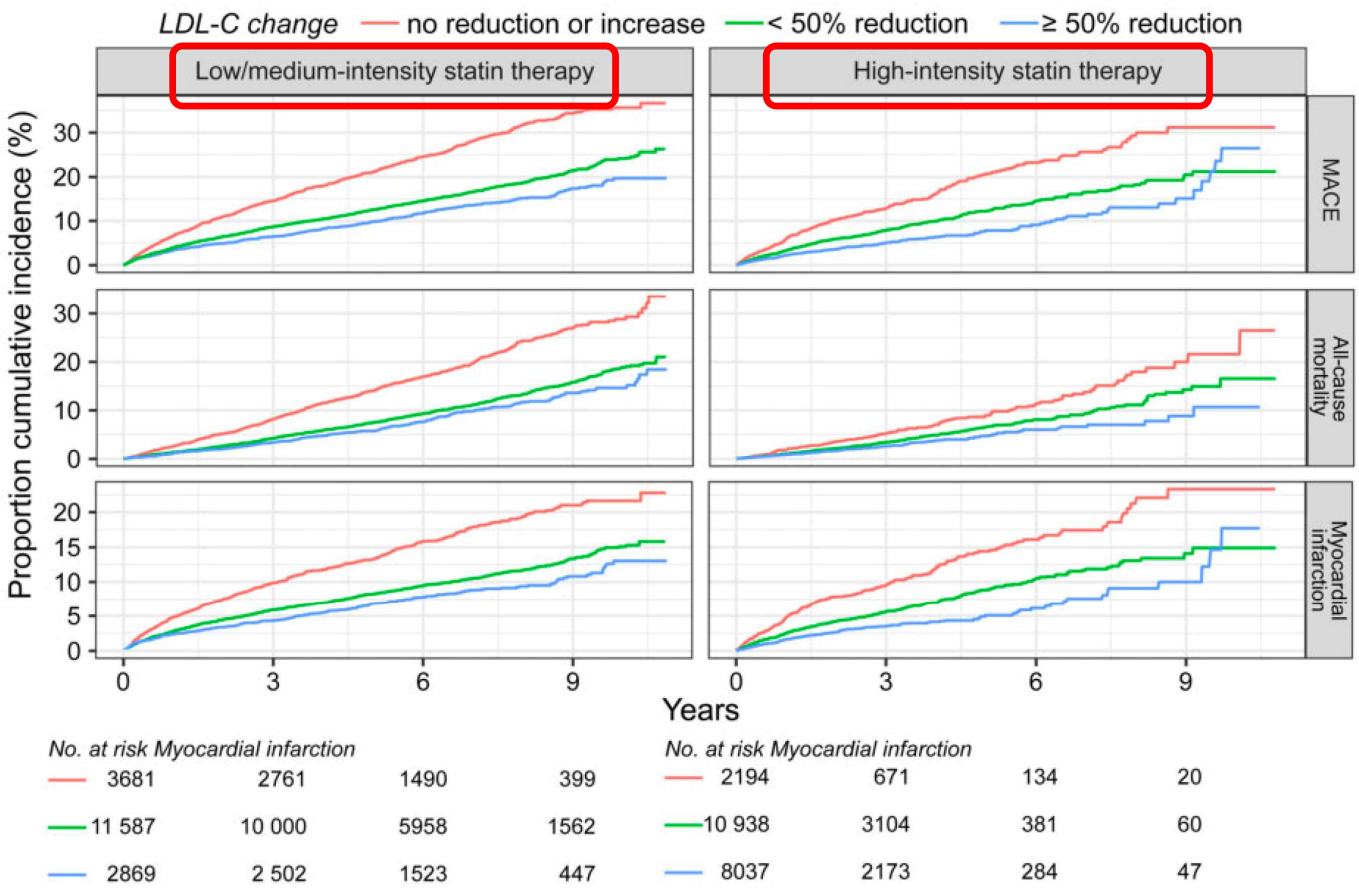
Prevalence of polivascular atherosclerosis in the overall cohort and by Framinghan risk groups



Polyvascular atherosclerosis was defined as coronary artery calcium >0 and carotid plaque burden >0. **Bar graphs** show prevalence of any (tertile 1 or greater), moderate (tertile 2 or greater), and extensive (tertile 3) polyvascular atherosclerosis.

Riprodotto da 2

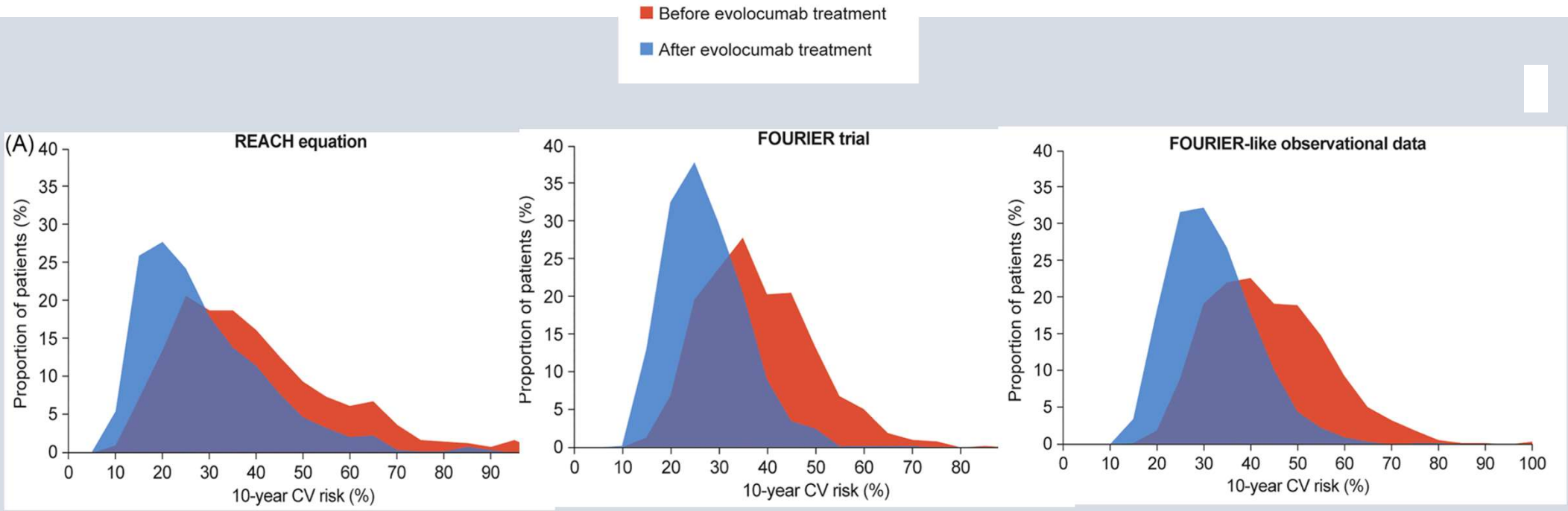
Goldstein JA. J Am Coll Cardiol 2002;39:1464–1467
Baber U et al. J Am Coll Cardiol. 2015 Mar 24;65(11):1065-74.



European Heart Journal (2021) 42, 243–252

Swedish nationwide cohort study

Applicando le LG 2019…. aggiungiamo gli PCSK9i alla terapia orale



…lessons from the HEYMANS study

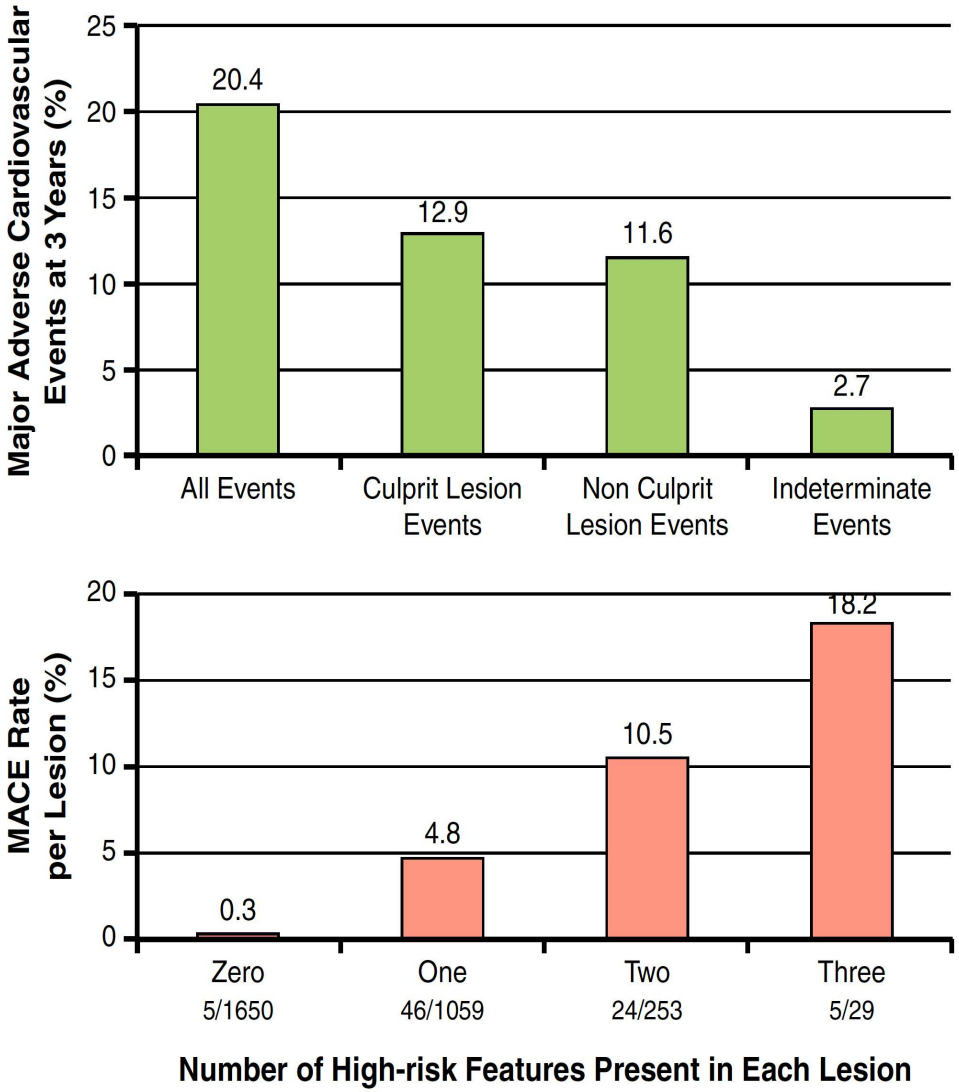
European Heart Journal - Quality of Care and Clinical Outcomes (2022) 0, 1–14

La storia naturale delle lesioni coronariche dopo una SCA: The PROSPECT Study

I predittori di MACE non legati alla culprit:

- **La placca interessa almeno il 70% del lume**
- **Spessore del cappuccio fibroso**
- **Un'area minima di 4.0 mm2**

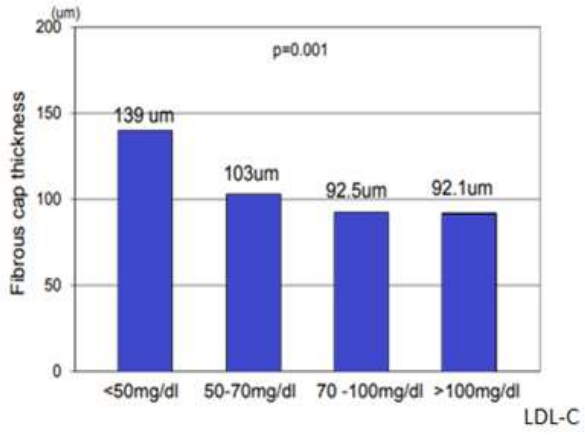
La presenza di 2 o 3 caratteristiche identifica lesioni rispettivamente con il **10% e il 18%** di probabilità di sviluppare eventi entro i successivi 3 anni



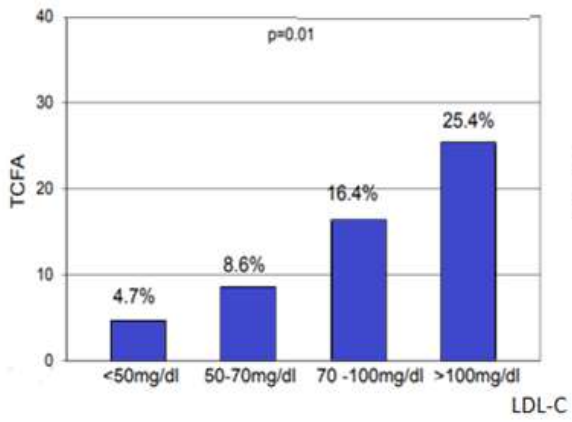
Fleg J. et al J Am Coll Cardiol Img 2012;5:941–55

Livelli di LDL più bassi sono associati ad un fenotipo di placca meno vulnerabile

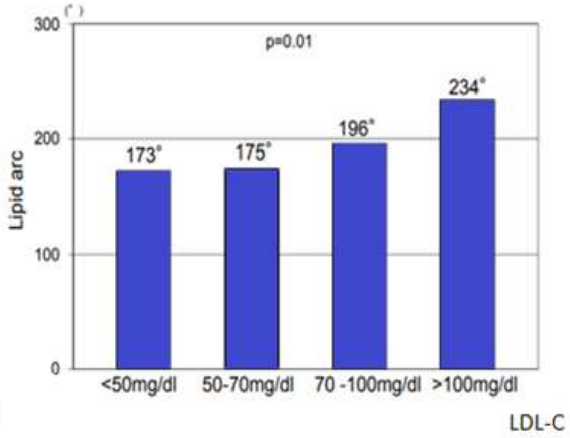
Spessore capsula fibrosa



Fibroateroma a cappuccio sottile



Arco lipidico

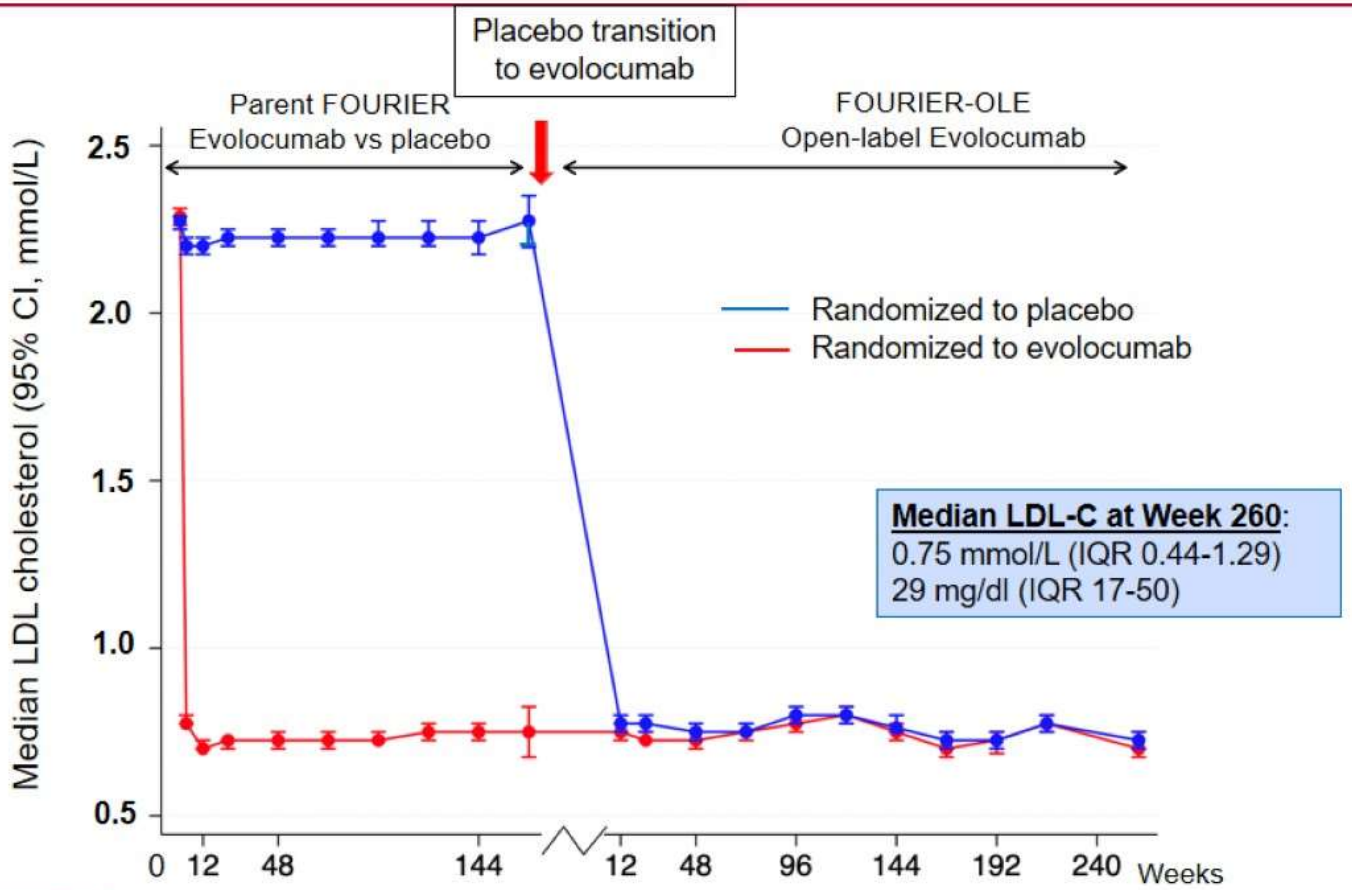


Riprodotto da Kataoka

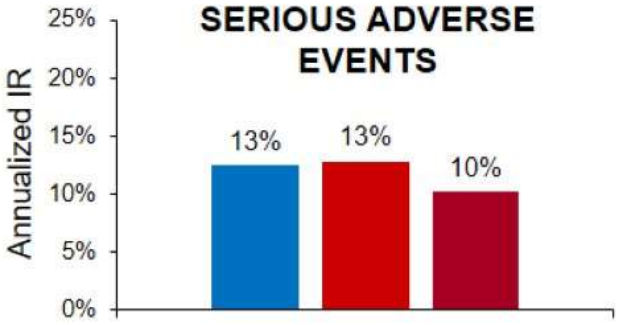
Pazienti con C-LDL ＜50 mg/dl presentano la capsula fibrosa più spessa, un arco lipidico più spesso ed una più bassa frequenza del fibroateroma a cappuccio sottile.

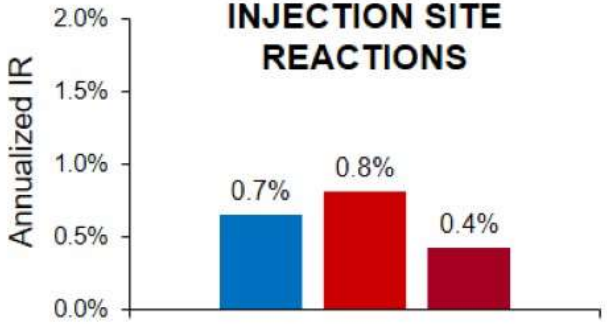
Kataoka Y, et al. Atherosclerosis, 2015; 242: 490-495; 2.
Kataoka Y et al., J Atheroscler Thromb. 2017; 24: 360-372

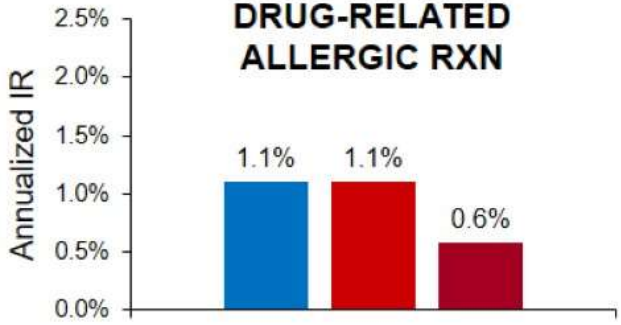
Effect on LDL-C

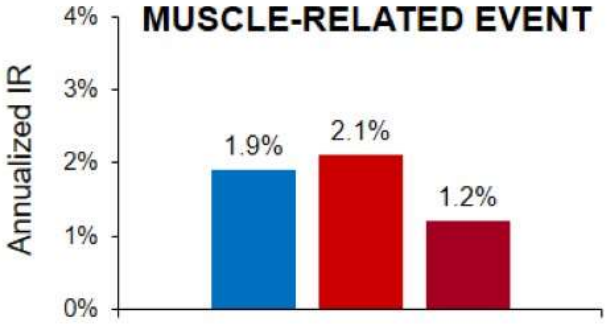


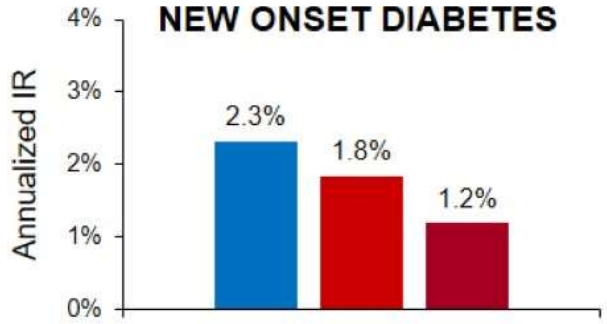
Long-Term Safety

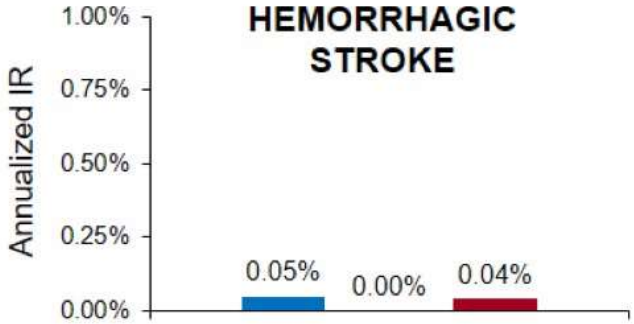








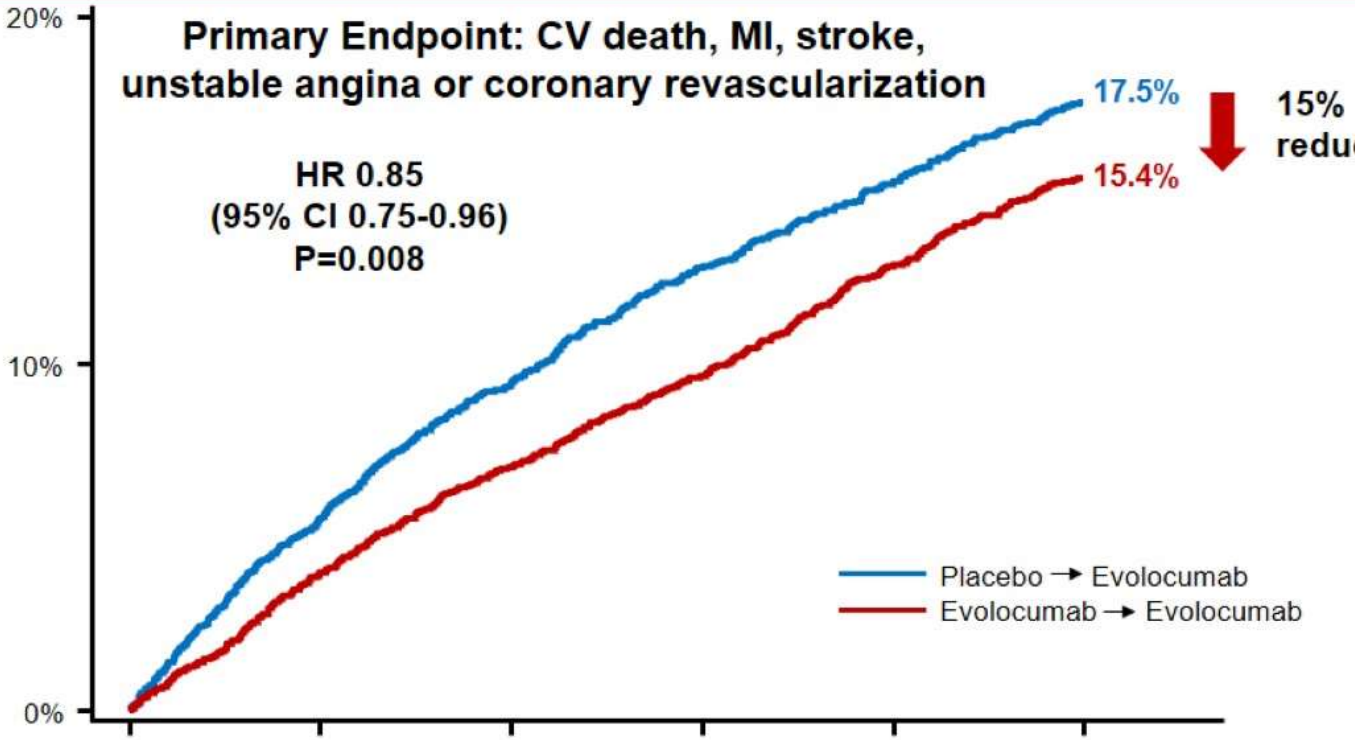




Placebo Phase FOURIER
Evolocumab Phase FOURIER
Evolocumab Phase FOURIER & OLE

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

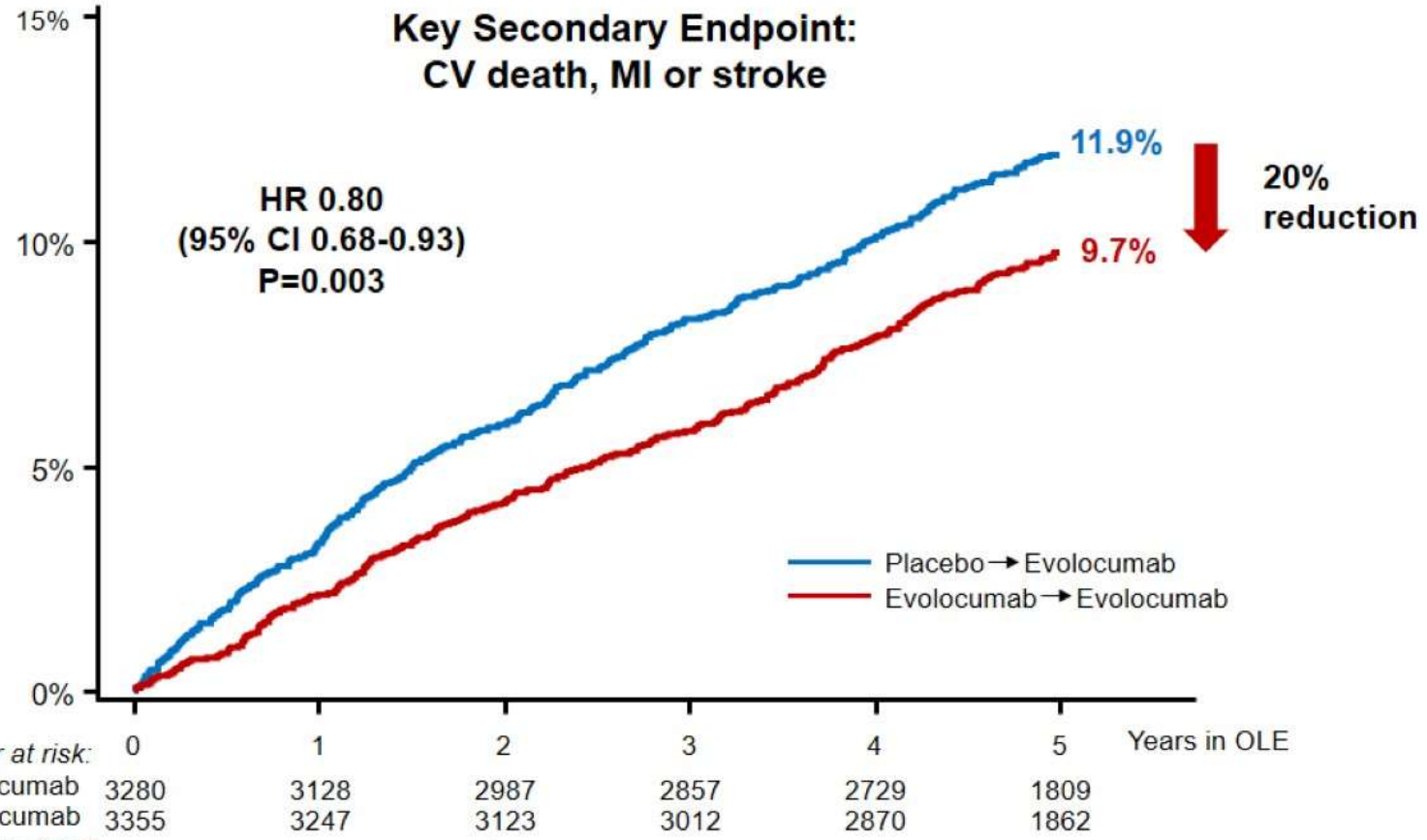
Efficacy during FOURIER-OLE



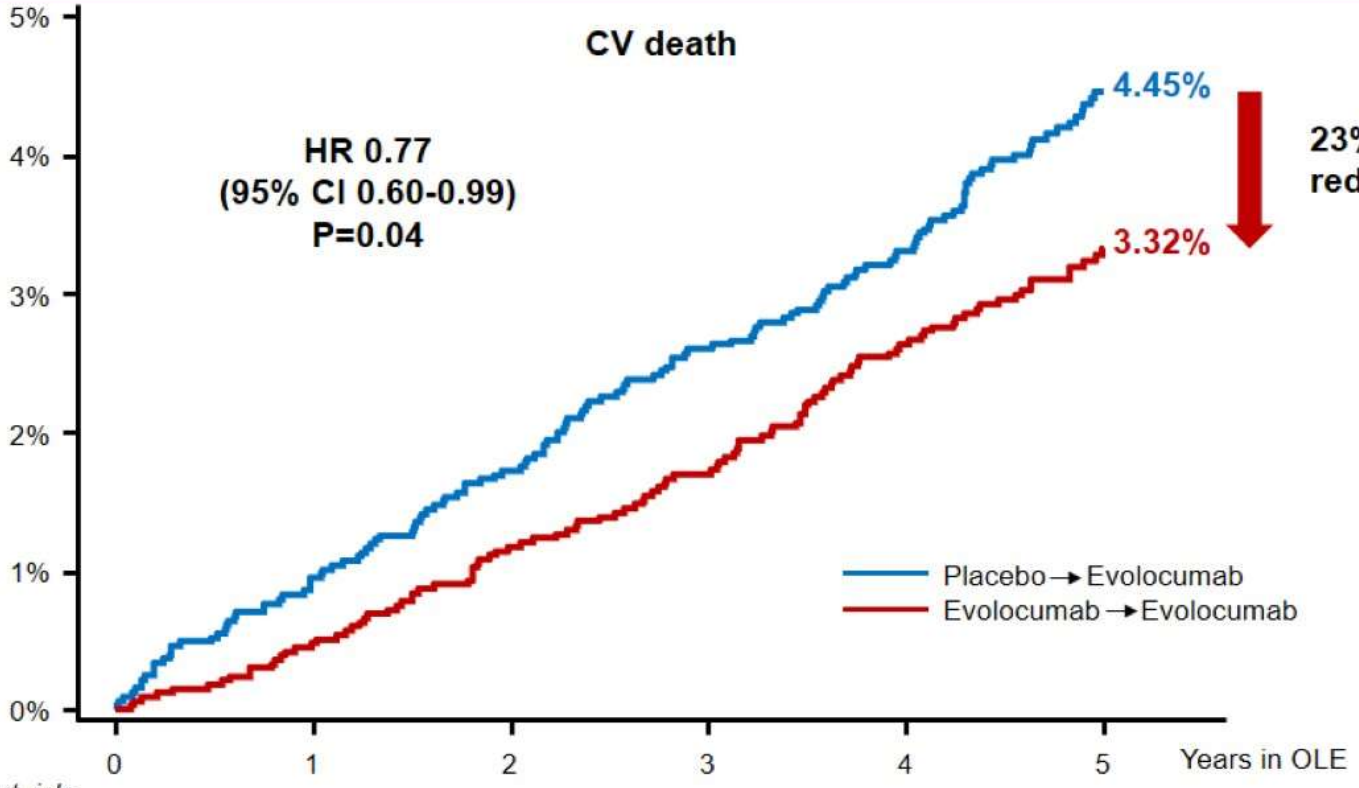
Number at risk:

Placebo-Evolocumab	3280	3055	2876	2716	2573	1706
Evolocumab-Evolocumab	3355	3186	3033	2890	2716	1754

Efficacy during FOURIER-OLE



Efficacy during FOURIER-OLE Time Period

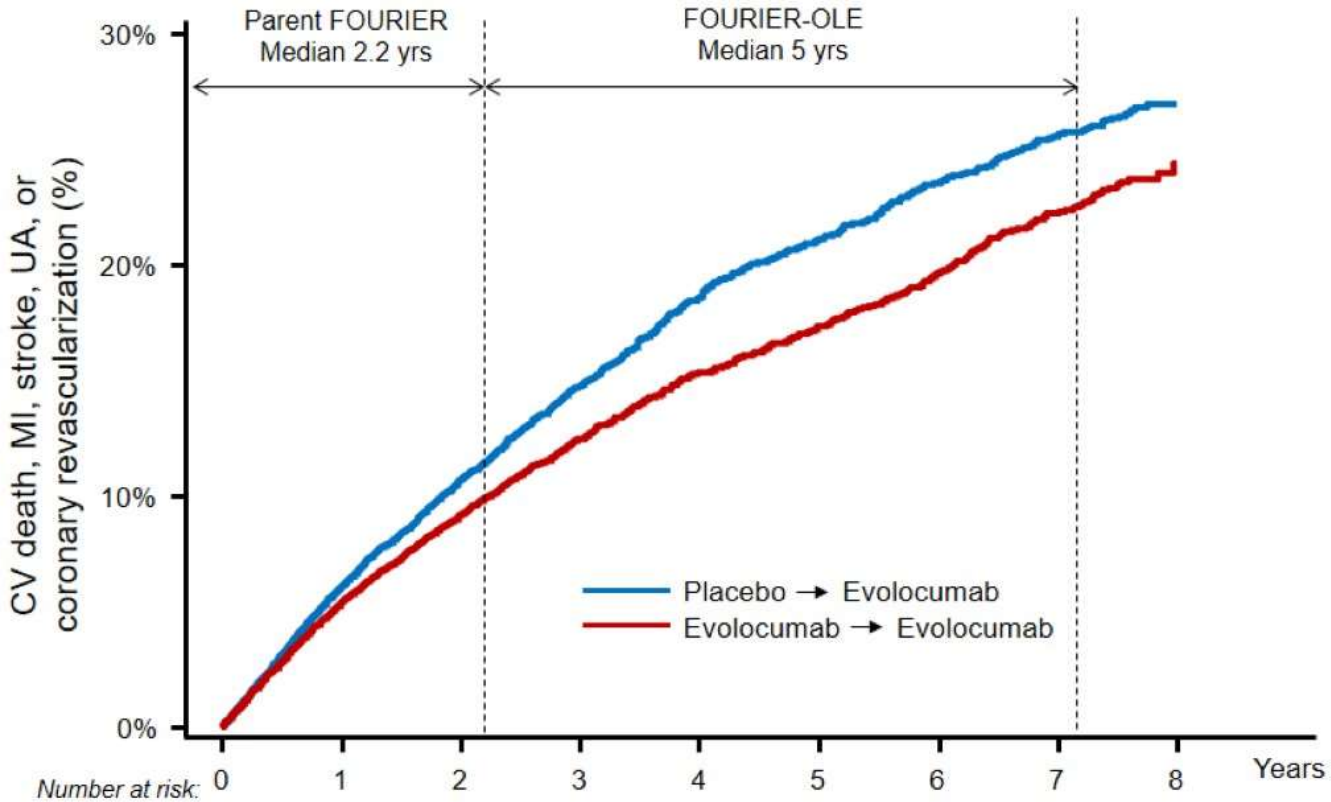


Number at risk:

Placebo-Evolocumab	3280	3223	3155	3081	2991	2049
Evolocumab-Evolocumab	3355	3314	3244	3173	3080	2069

Efficacy during FOURIER & FOURIER-OLE

FOURIER Primary Endpoint

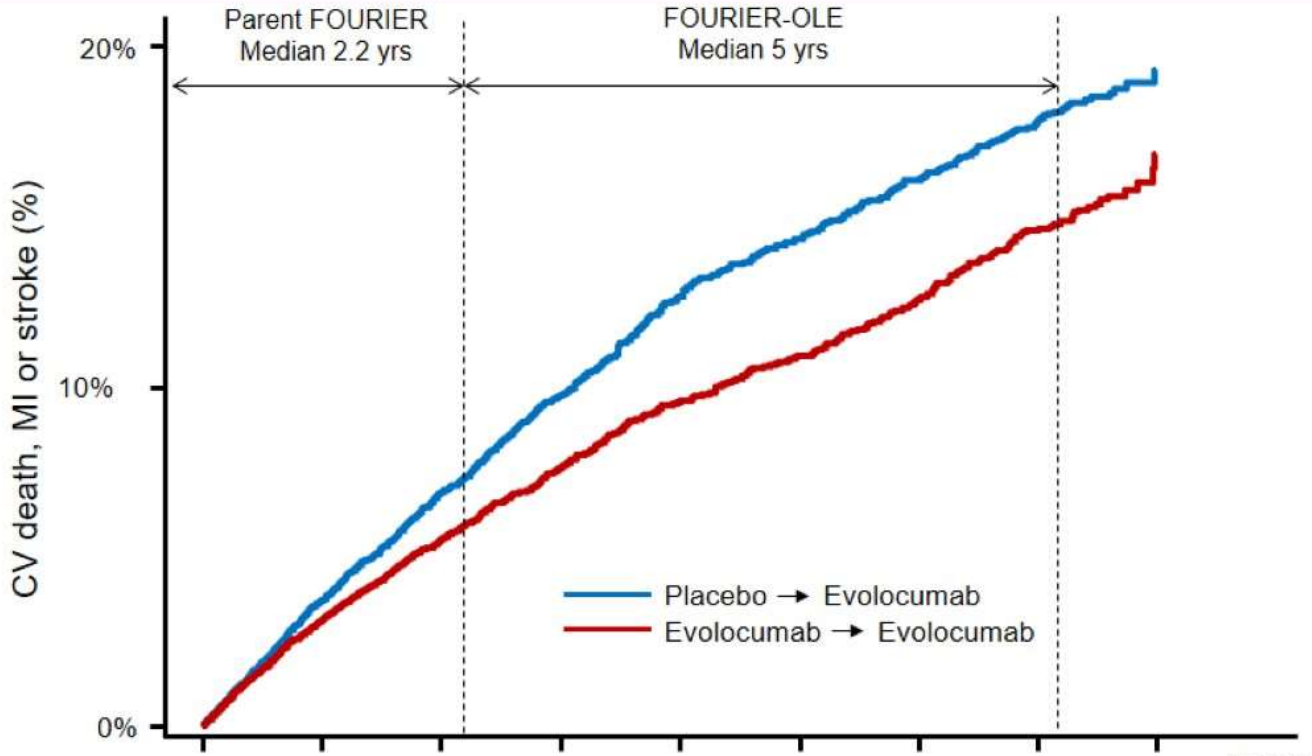


Number at risk:	0	1	2	3	4	5	6	7	8
Placebo-Evolocumab	13780	12822	8467	3260	2654	2526	2372	1498	189
Evolocumab-Evolocumab	13784	12937	8683	3389	2814	2699	2550	1569	165

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Efficacy during FOURIER & FOURIER-OLE

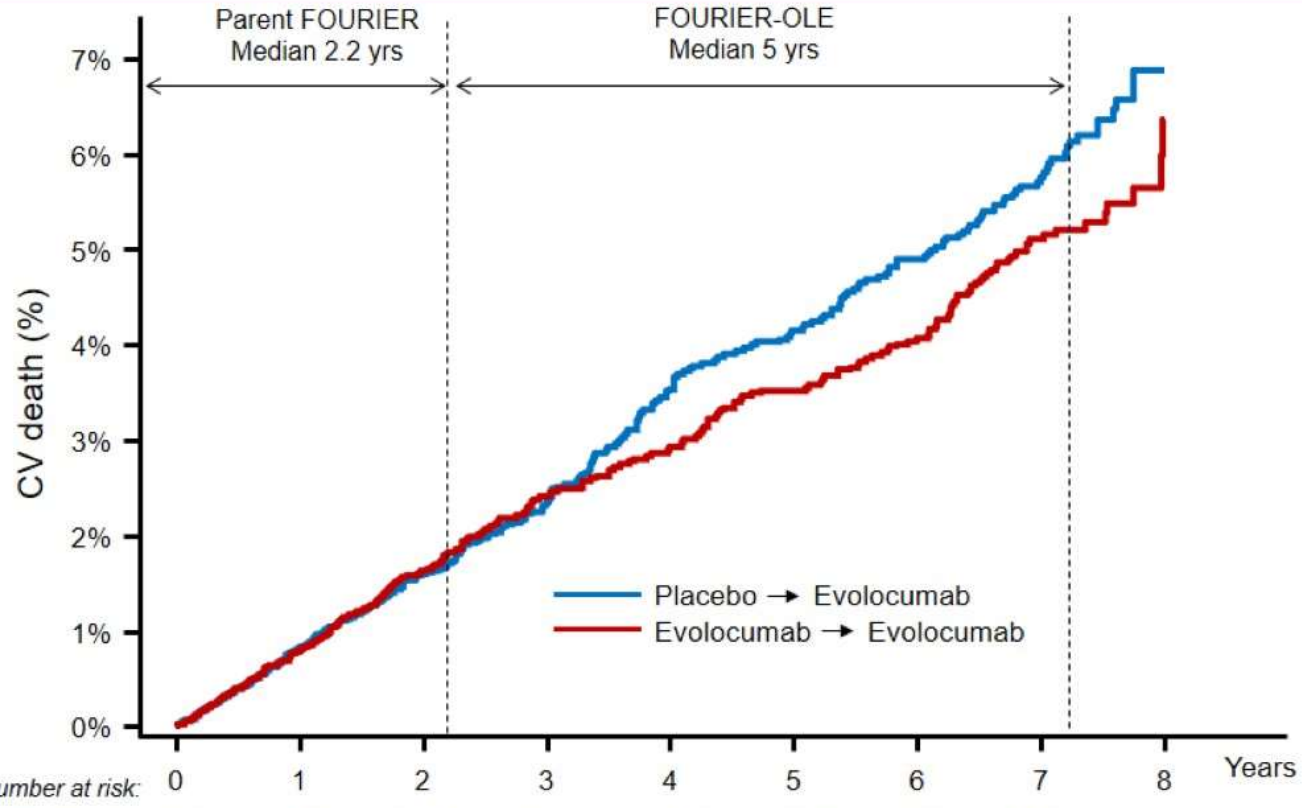
FOURIER Key Secondary Endpoint



Number at risk:	0	1	2	3	4	5	6	7	8
Placebo-Evolocumab	13780	13140	8846	3470	2861	2757	2621	1664	216
Evolocumab-Evolocumab	13784	13240	9051	3617	3046	2946	2810	1746	185

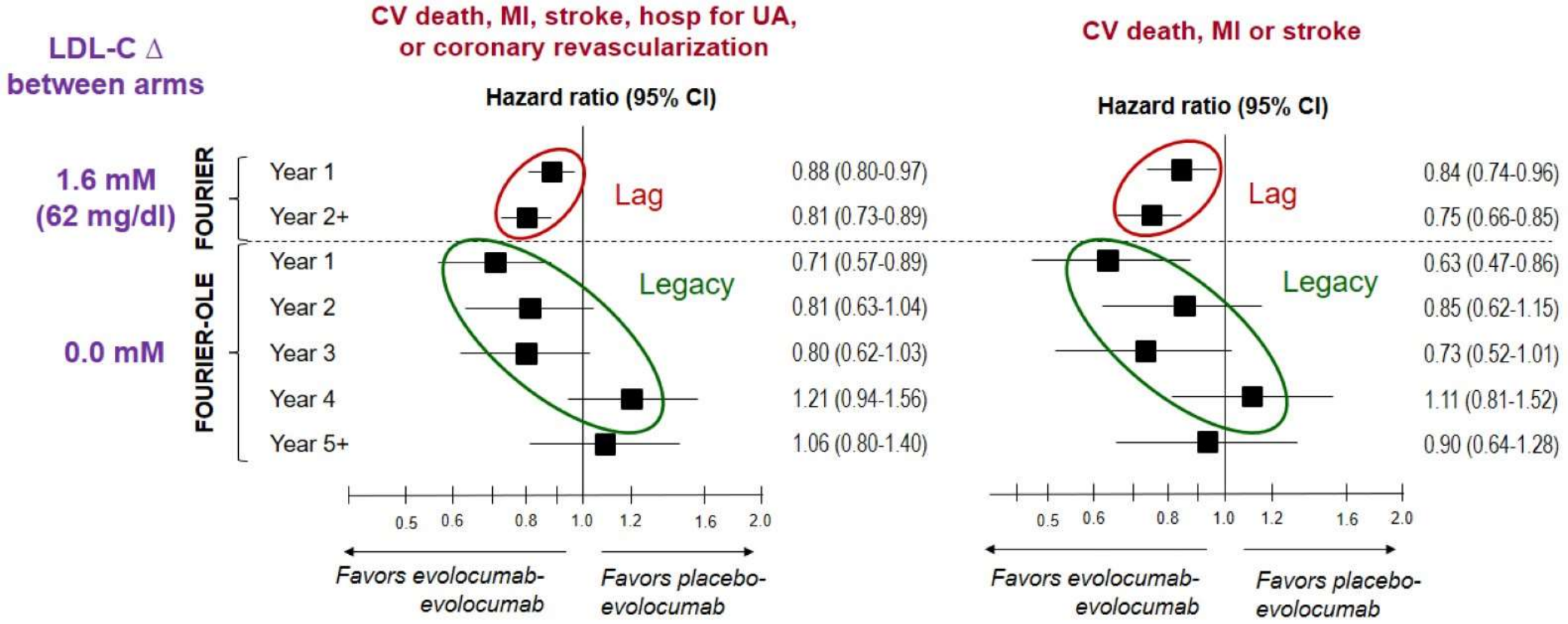
Efficacy during FOURIER & FOURIER-OLE

CV Death



Number at risk:	0	1	2	3	4	5	6	7	8
Placebo-Evolocumab	13780	13590	9399	3753	3167	3098	2996	1965	268
Evolocumab-Evolocumab	13784	13598	9464	3826	3270	3204	3109	1988	237

MACE by Year of Study



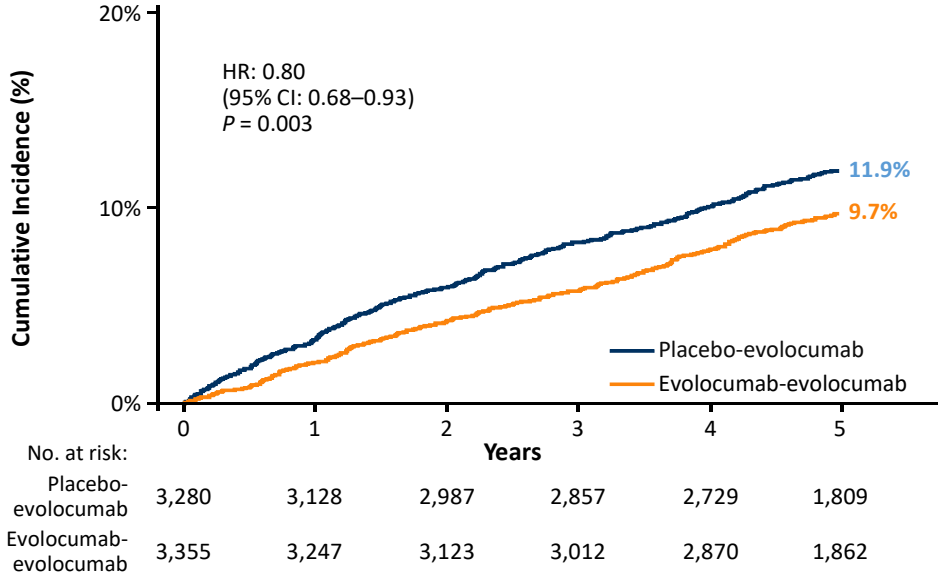
Summary

- Long-term use of evolocumab with median follow-up of more than 7 years appears both safe and well-tolerated
- Earlier initiation of evolocumab is associated with continued accrual of cardiovascular benefit, including cardiovascular mortality, over the next several years
- These findings argue for early initiation of a marked and sustained LDL-C reduction to maximize clinical benefit

FOURIER-OLE Trial

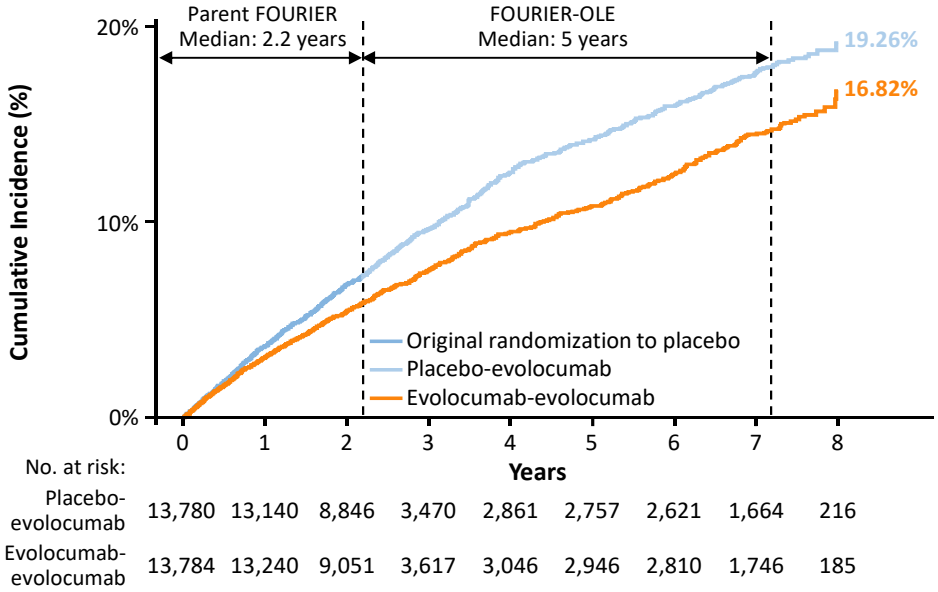
Prespecified Exploratory Analysis (Secondary Endpoints) – CV death, MI, or stroke*

FOURIER-OLE[1]



No. at risk:						
Placebo-evolocumab	3,280	3,128	2,987	2,857	2,729	1,809
Evolocumab-evolocumab	3,355	3,247	3,123	3,012	2,870	1,862

Parent FOURIER + FOURIER-OLE[2]



No. at risk:									
Placebo-evolocumab	13,780	13,140	8,846	3,470	2,861	2,757	2,621	1,664	216
Evolocumab-evolocumab	13,784	13,240	9,051	3,617	3,046	2,946	2,810	1,746	185

During the FOURIER-OLE trial, there was a 20% lower risk of the key secondary endpoint in patients originally randomized in the parent trial to evolocumab than patients originally randomized in the parent trial to placebo.

*Limitations to the FOURIER-OLE include but are not limited to: all patients in the extension program were treated with open-label evolocumab resulting in no concurrent placebo arm during this period; cardiovascular outcomes were prespecified for the current analysis, but considered exploratory; *P* values are nominal and not adjusted for multiplicity[1]

CI = confidence interval; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HR = hazard ratio; MI = myocardial infarction; OLE = open-label extension

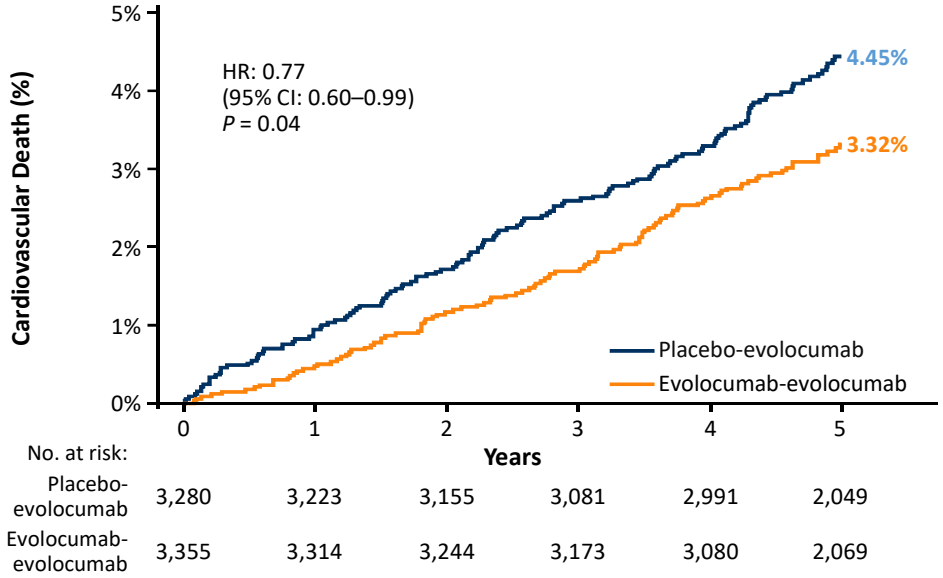
1. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119. 2. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119; supplementary material.

FOURIER-OLE Trial

Key Results: Major Adverse CV Events

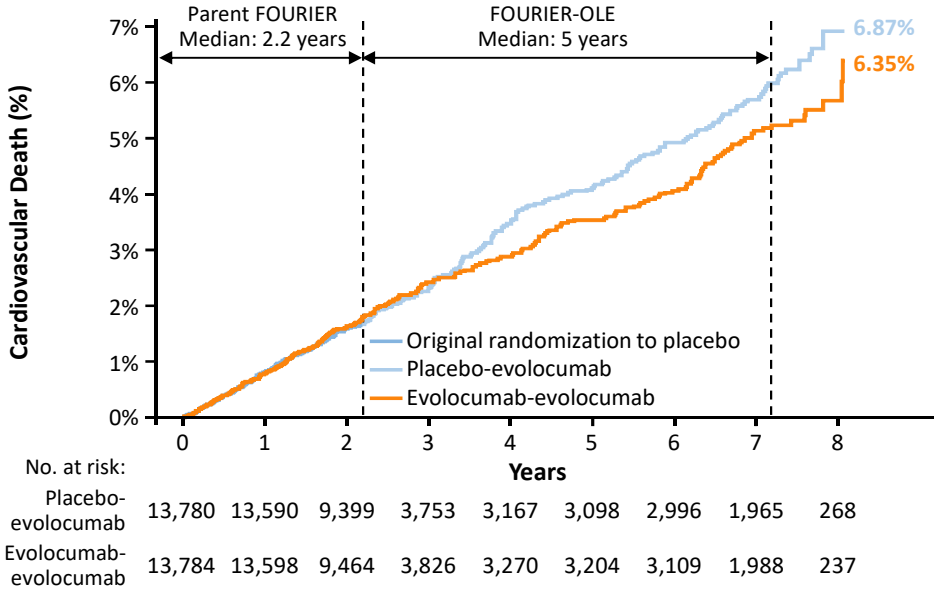
Prespecified Exploratory Analysis (CV death)*

FOURIER-OLE[1]



No. at risk:						
Placebo-evolocumab	3,280	3,223	3,155	3,081	2,991	2,049
Evolocumab-evolocumab	3,355	3,314	3,244	3,173	3,080	2,069

Parent FOURIER + FOURIER-OLE[2]



No. at risk:									
Placebo-evolocumab	13,780	13,590	9,399	3,753	3,167	3,098	2,996	1,965	268
Evolocumab-evolocumab	13,784	13,598	9,464	3,826	3,270	3,204	3,109	1,988	237

During the FOURIER-OLE trial, there a 23% lower risk of cardiovascular death in patients originally randomized in the parent trial to evolocumab than patients originally randomized in the parent trial to placebo.

*Limitations to the FOURIER-OLE include but are not limited to: all patients in the extension program were treated with open-label evolocumab resulting in no concurrent placebo arm during this period; cardiovascular outcomes were prespecified for the current analysis, but considered exploratory; *P* values are nominal and not adjusted for multiplicity[1]

CI = confidence interval; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HR = hazard ratio; OLE = open-label extension

1. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119. 2. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119; supplementary material.

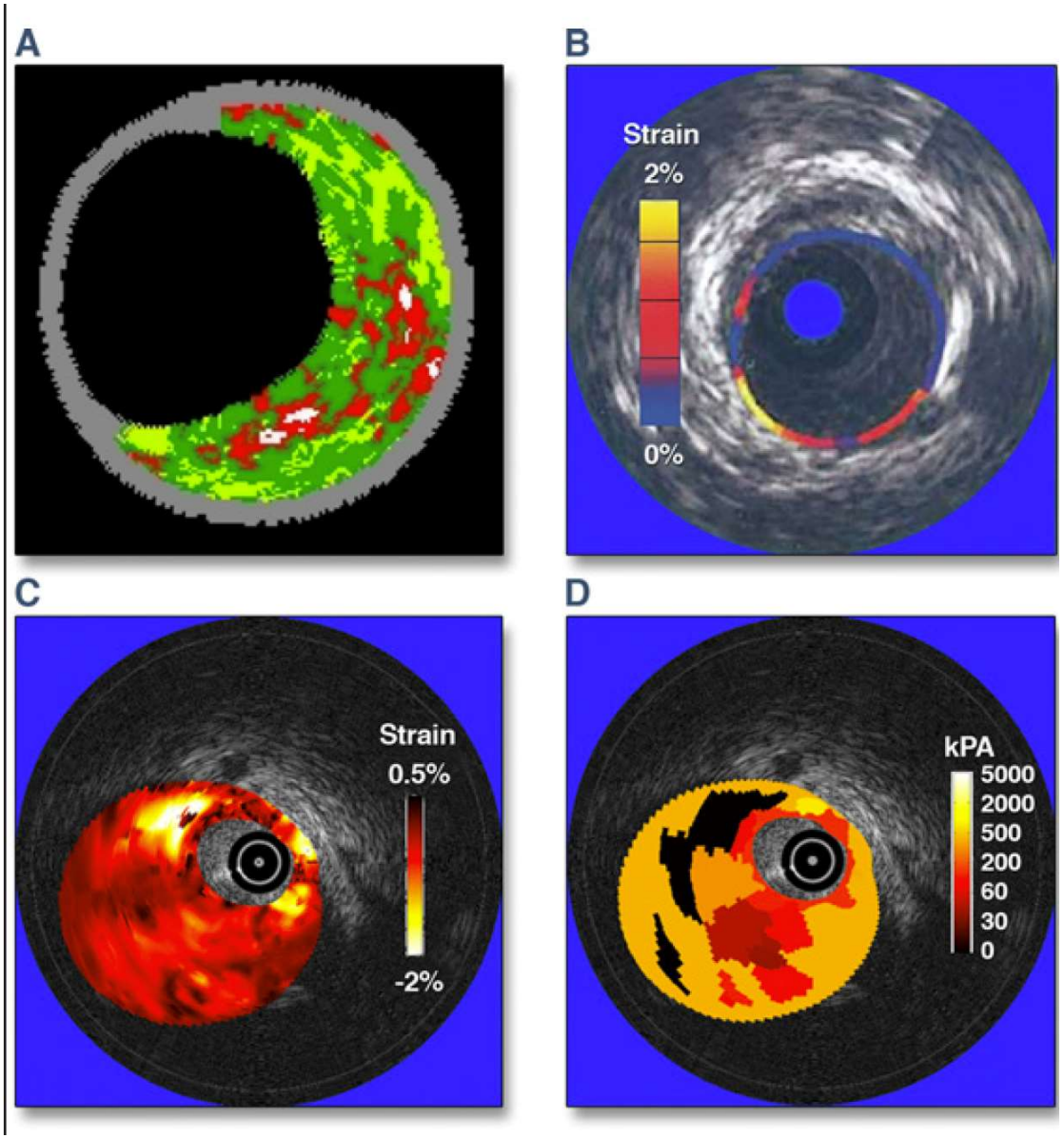
L'imaging intravascolare

(A) Istologia virtuale

(B) Palpografia

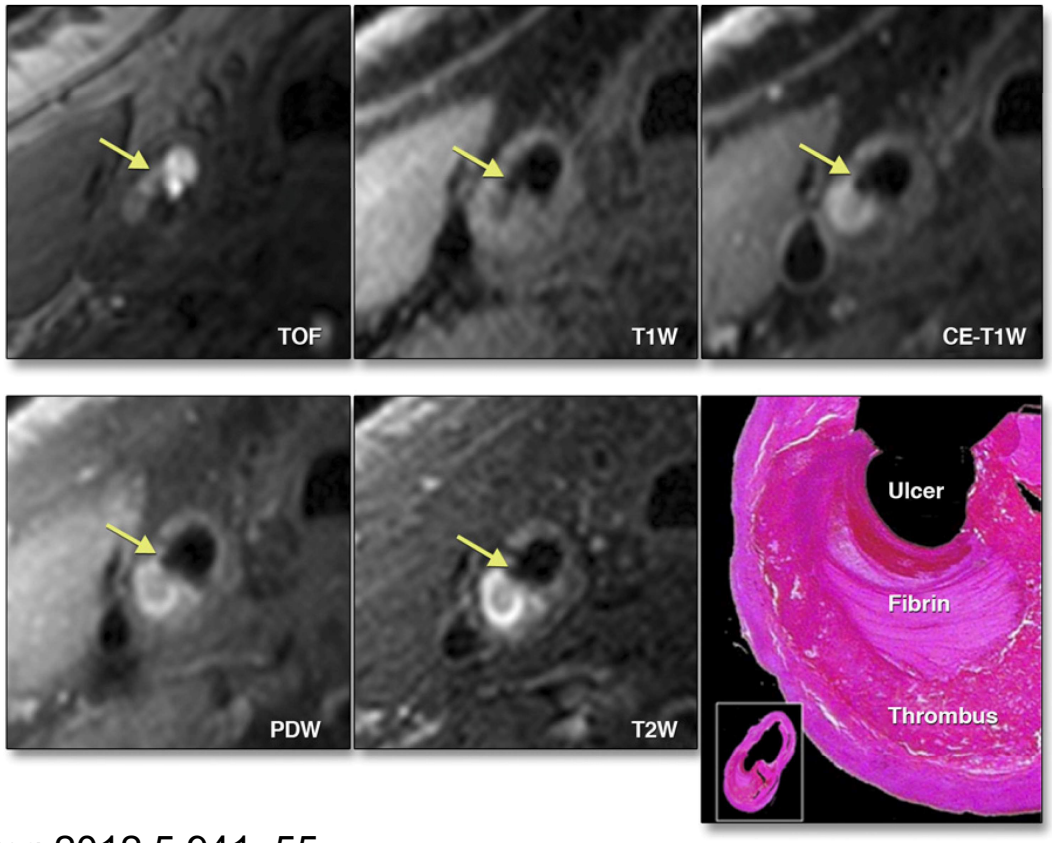
(C) Elastogramma

(D) Modulogramma



Fleg J. et al J Am Coll Cardiol Img 2012;5:941–55

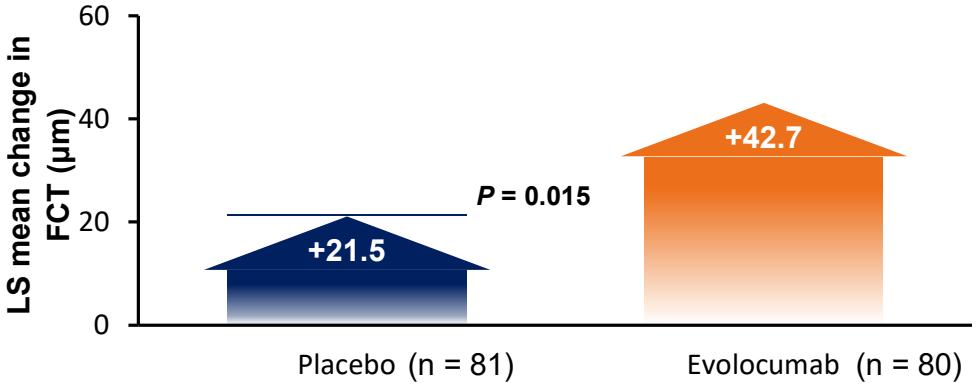
Morphological Characteristics of Carotid Atherosclerosis by MRI



Fleg J. et al J Am Coll Cardiol Img 2012;5:941–55

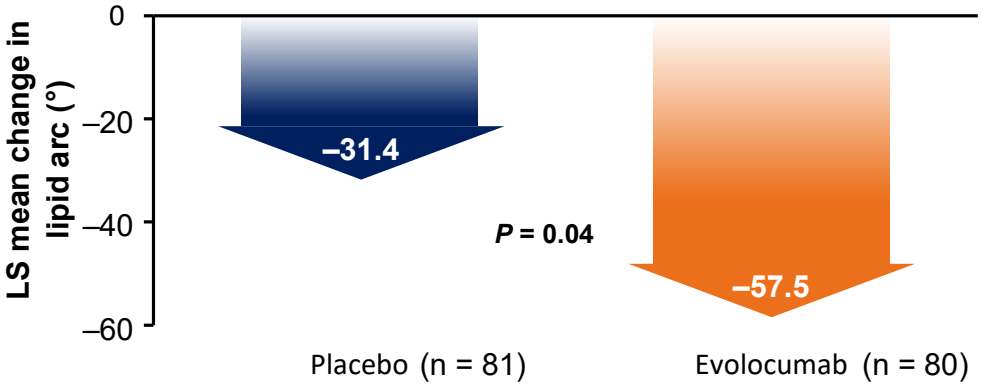
Evolocumab migliora la stabilità di placca

HUYGENS Endpoint primario: minimo FCT



Baseline FCT: **54.6 µm** **56.6 µm**

HUYGENS Endpoint secondario: Arco Lipidico



Baseline max lipid arc: **224.8°** **230.2°**

Alla fine dello studio solo il 12.5% dei pazienti in evolocumab ha minimo FCT < 65 µm, confrontato con il 30.2% del Gruppo placebo

Aggiungere evolocumab al trattamento intensivo con statine raddoppia lo spessore del cappuccio fibroso (FCT) e riduce significativamemte l'arco lipidico rispetto al gruppo in sola statina

Nicholls SJ, et al. [published online ahead of print March 16, 2022]. *JACC Cardiovasc Imaging,* Stefanidis C, et al. *J Am Heart Assoc*. 2017;6:e005543. Komukai K, et al. *J Am Coll Cardiol.* 2014;64:2207-2217. Nicholls SJ, et al. *Cardiovasc Diagn Ther*. 2021;11:120-129.

Patients with AMI (N-STEMI/STEMI) undergoing coronary angiography & successful PCI of the infarct vessel & 2 non-infarct related arteries with non-obstructive lesions

Alirocumab PACMANAMI

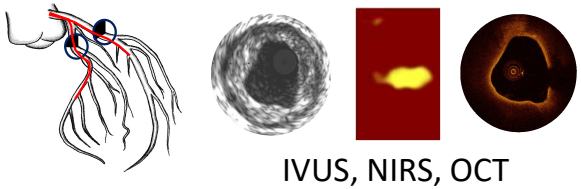
POC

No statin, LDL >125 mg/dL (>3.2 mmol/L)

On Statin, LDL >70 mg/dL (>1.8 mmol/L)

Enrollment of 300 Patients

Baseline



IVUS, NIRS, OCT

Baseline blood sampling

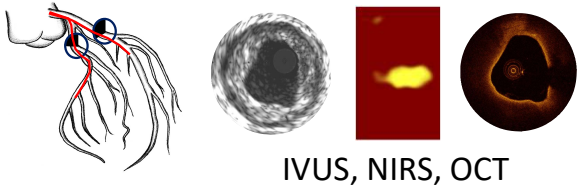
Alirocumab s.c. 150 mg / 2 weeks + Rosuvastatin 20 mg

R 1:1

Placebo s.c. / 2 weeks + Rosuvastatin 20 mg

Initiated <24 hrs after PCI

52 weeks

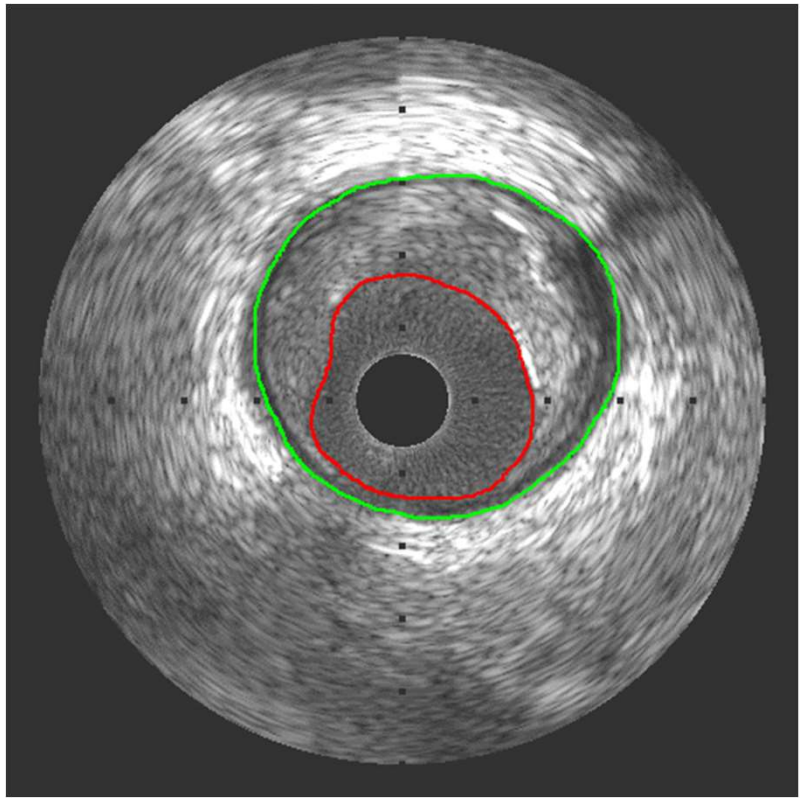


IVUS, NIRS, OCT

Blood sampling 4 weeks
3 visits, 4 phone calls
Blood sampling 52 weeks

Am Heart J 2021;238:33-44

Primary Endpoint

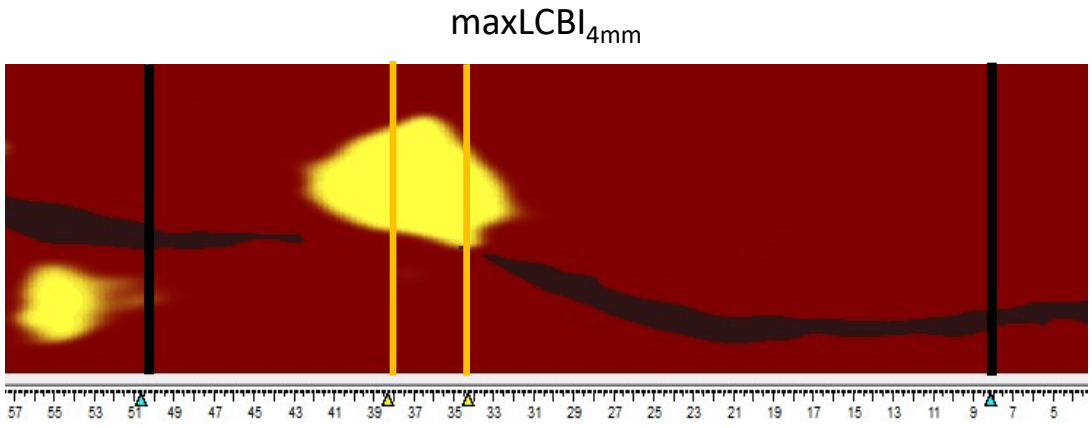


Analysis interval: 1 mm
Obtained by NIRS-IVUS catheter

$$PAV = \frac{\Sigma(EEM_{CSA} - LumenCSA)}{\Sigma EEM_{CSA}} \times 100$$

Change in **percent atheroma volume** (PAV) by **greyscale IVUS**

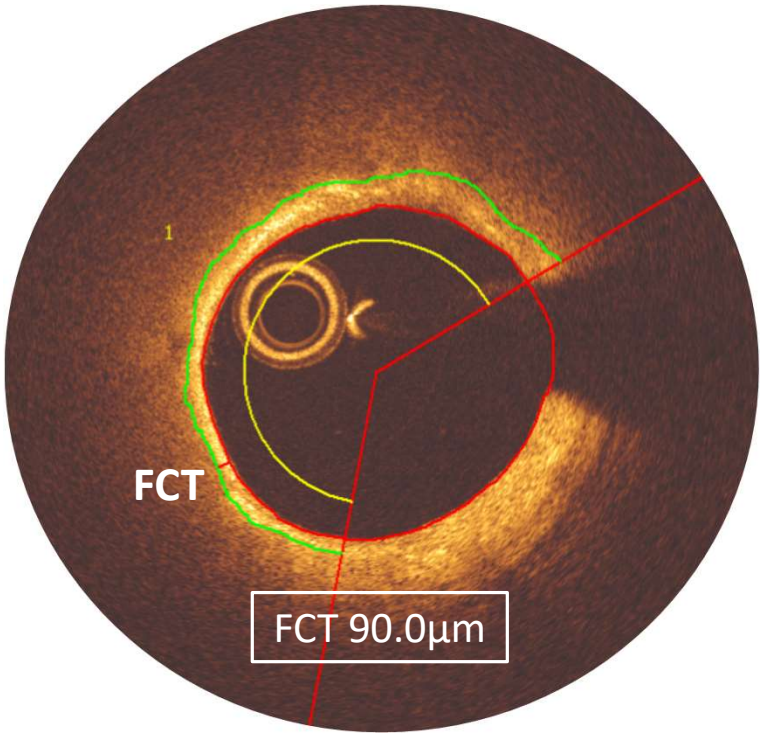
Powered Secondary Endpoint



maxLCBI$_{4mm}$=
a measure of lipid probability at the 4 mm with maximal lipid load of a vessel imaged by NIRS

Change in **maximal lipid-core burden index** (maxLCBI$_{4mm}$) by **NIRS**

Powered Secondary Endpoint



Analysis interval: 0.4 mm
Method: semiquantitative software assisted FCT tracing

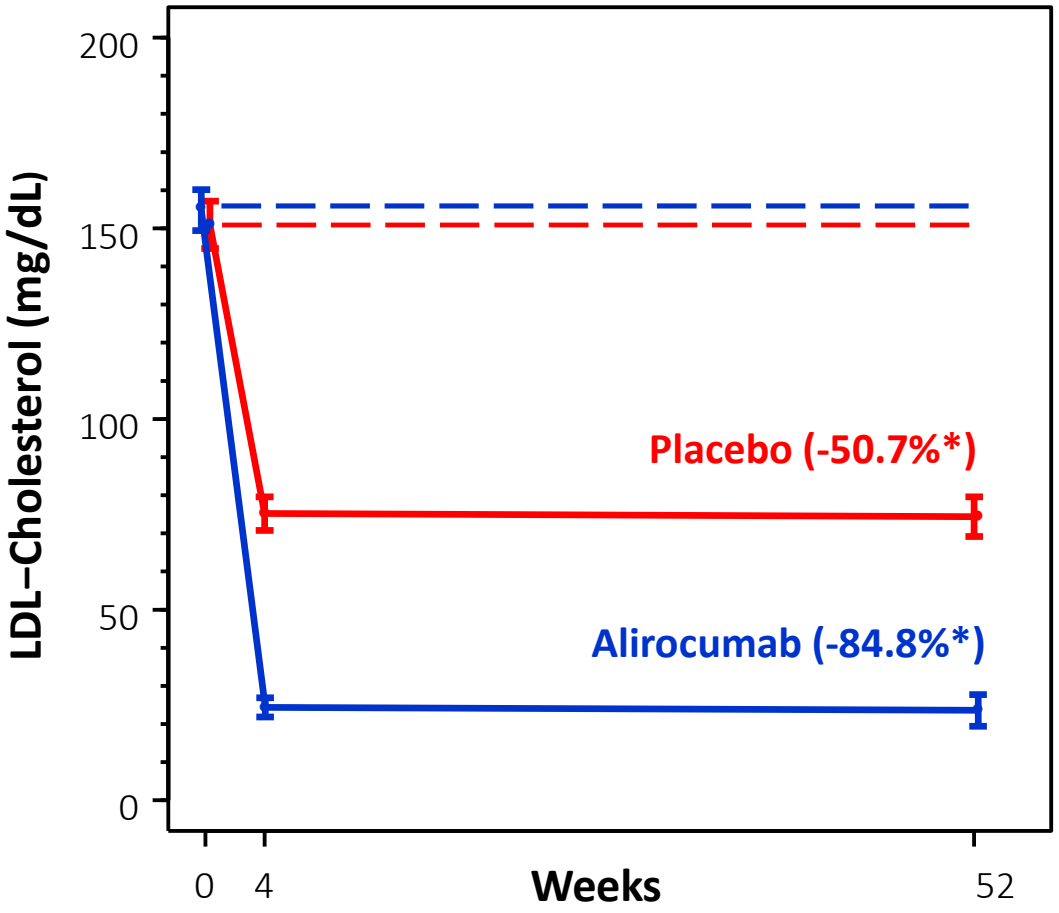
FCT_{min} = minimal fibrous cap thickness anywhere in lipid rich plaques imaged by OCT

Change in **minimal fibrous cap thickness** (FCT_{min}) by **OCT**

Riduzione dell'LDL, *media (SD)*

154.8 (31) mg/dL
4.00 (0.8) mmol/L

150.9 (36) mg/dL
3.9 (0.9) mmol/L

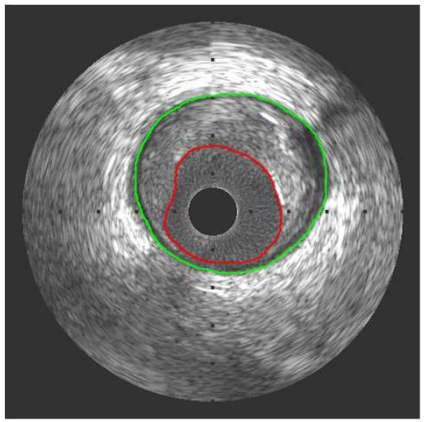


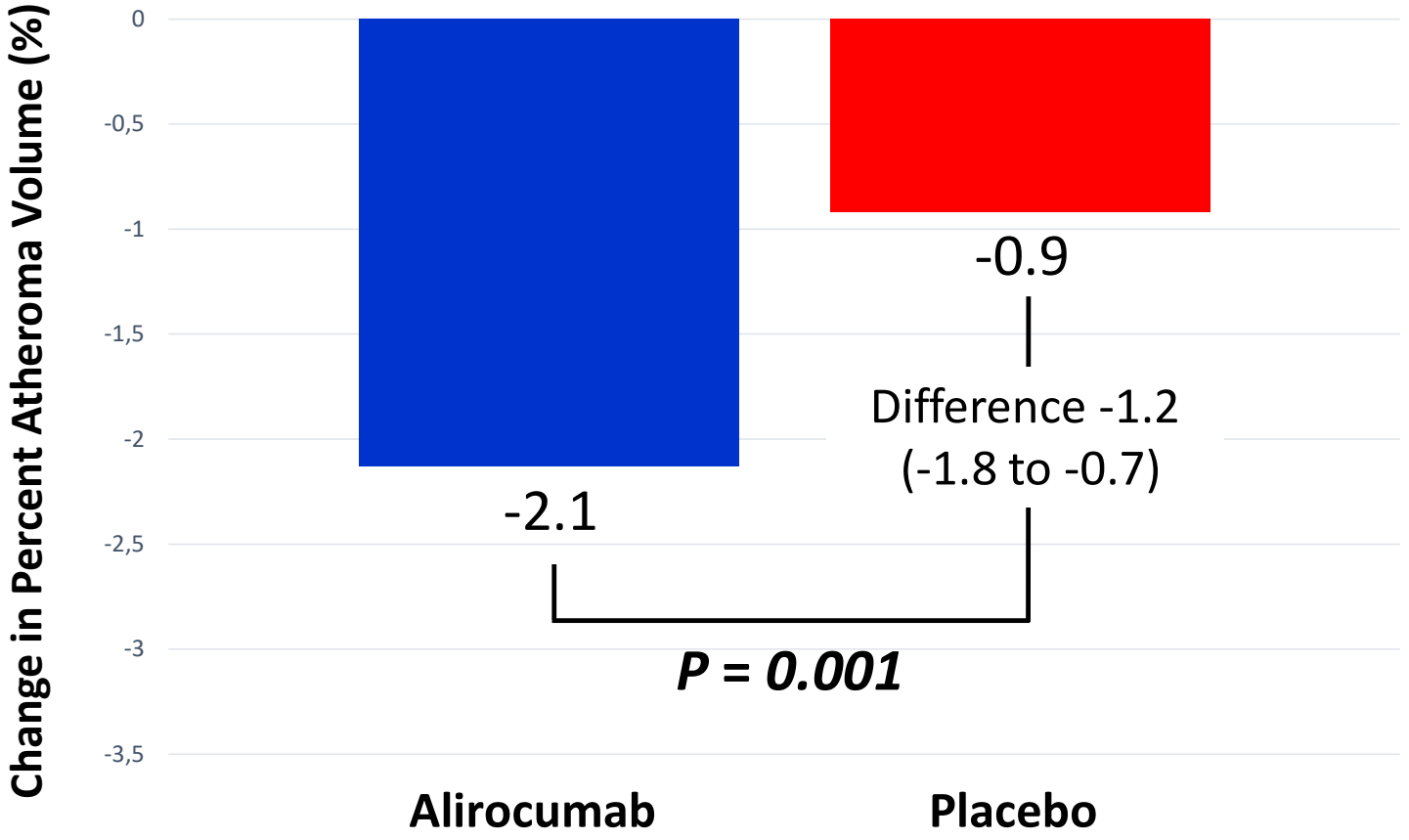
74.4 (31) mg/dL
1.9 (0.8) mmol/L

23.6 (24) mg/dL
0.6 (0.6) mmol/L

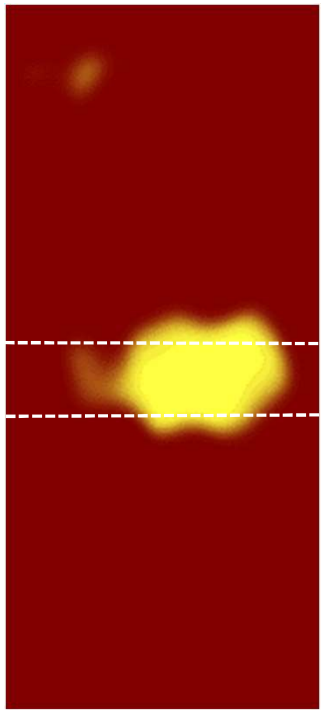
* 52 sett. vs. Baseline

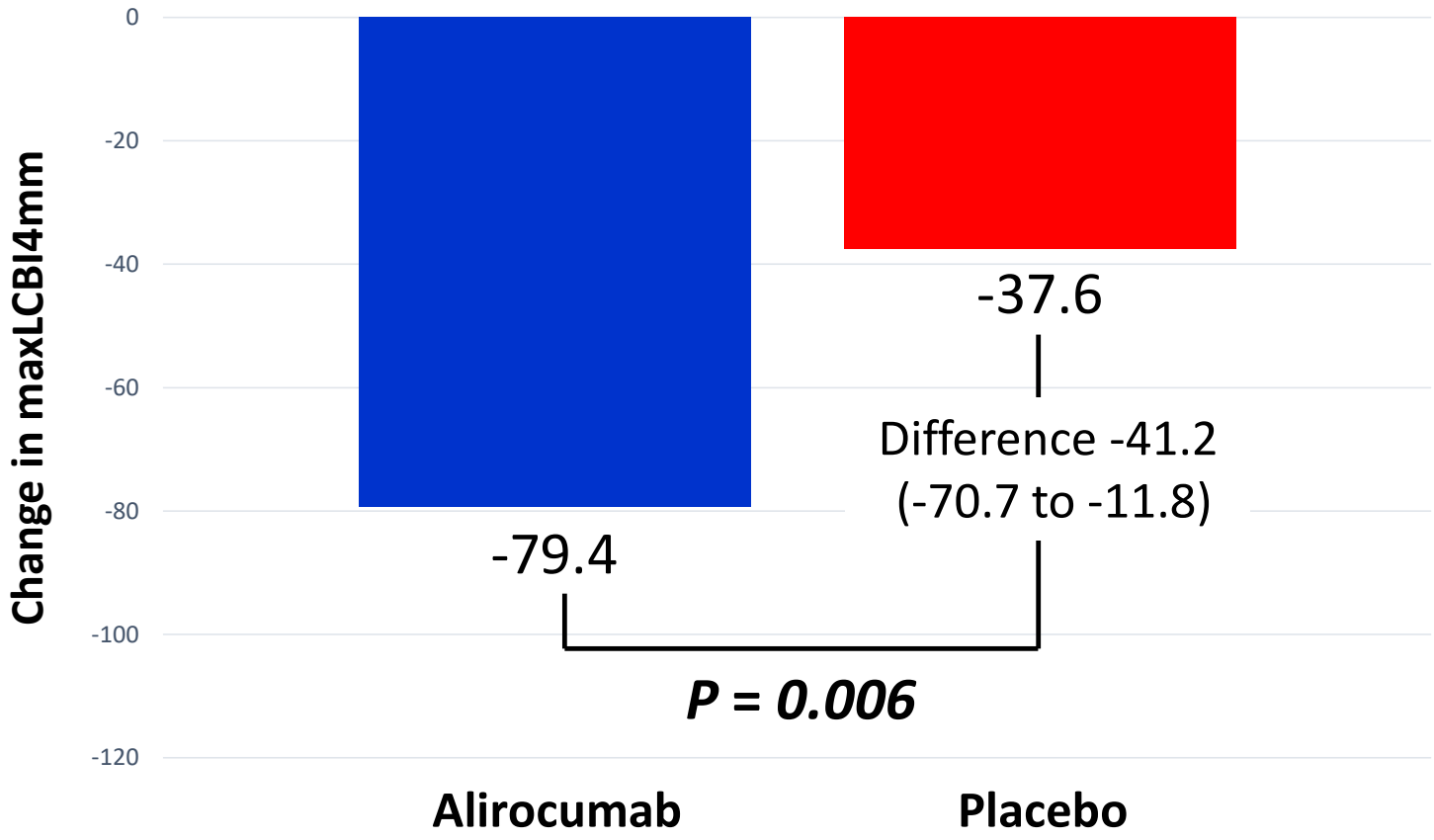
Primary EP:
riduzione del volume dell'ateroma (IVUS)



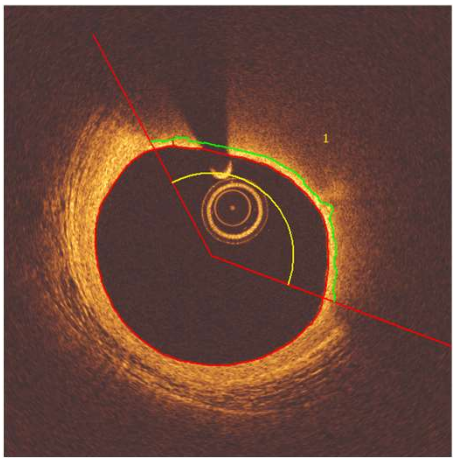


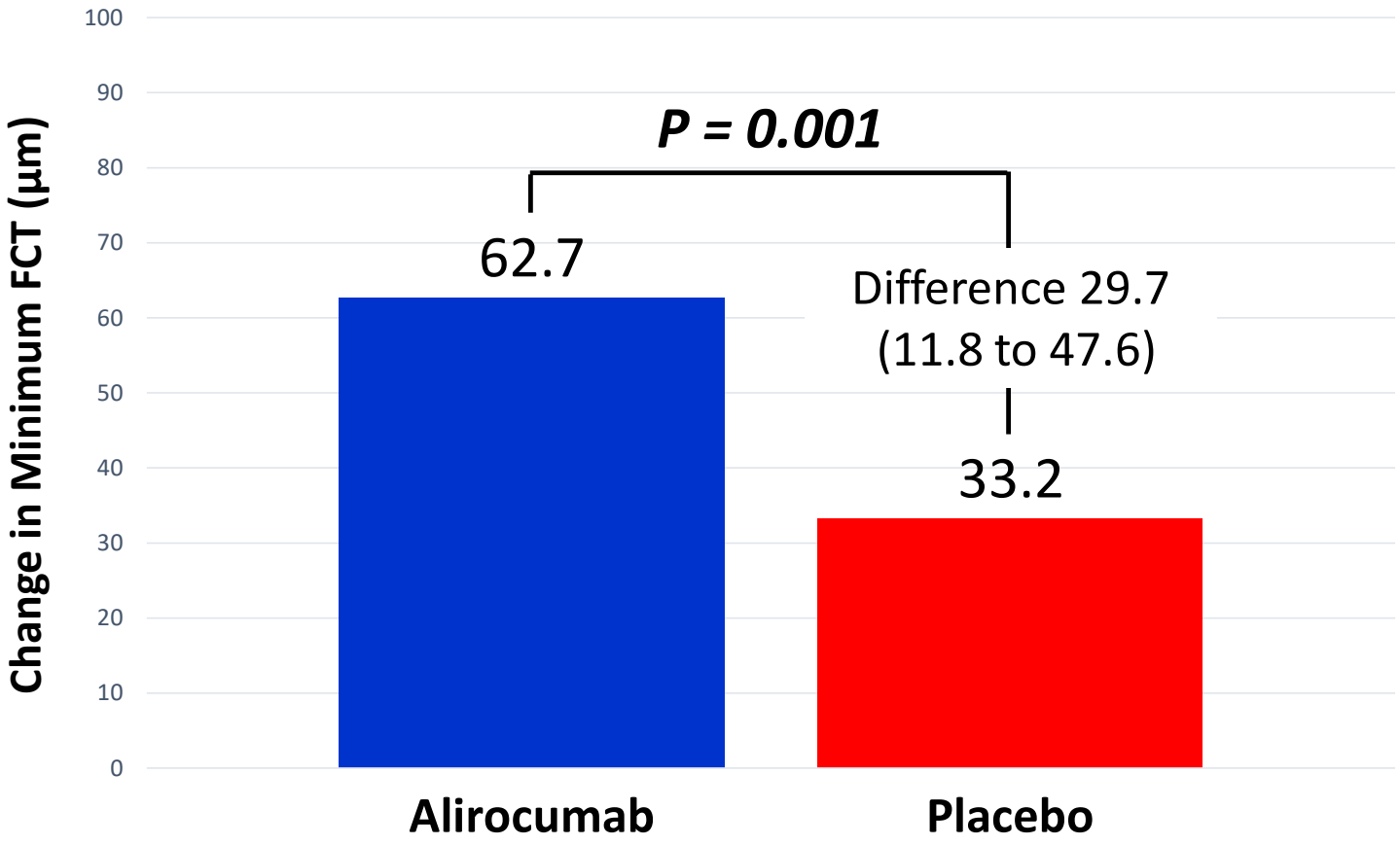
Powered Secondary EP:
Riduzione del maxLCBI$_{4mm}$ (NIRS)





Powered Secondary EP:
aumento dello spessore del cappuccio fibroso (OCT)

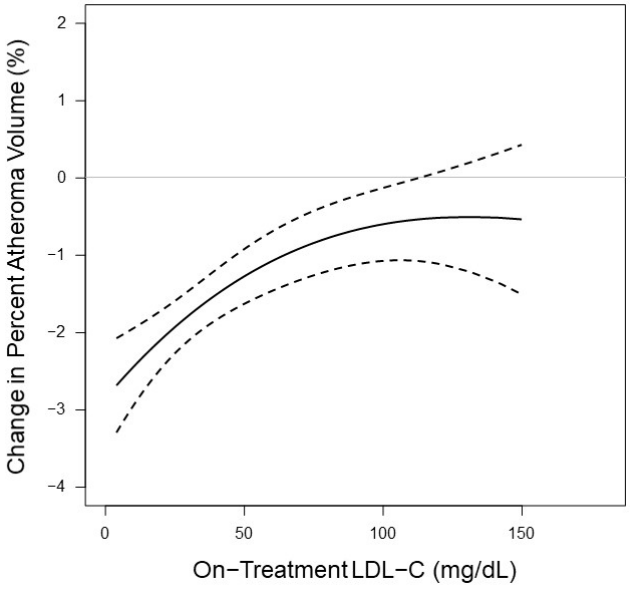




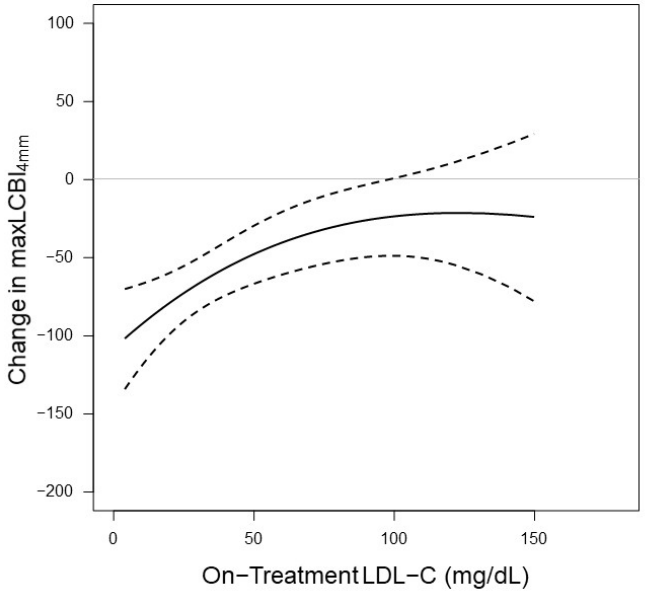
Relazione tra LDL-C e gli endpoint

Alirocumab PACMANAMI

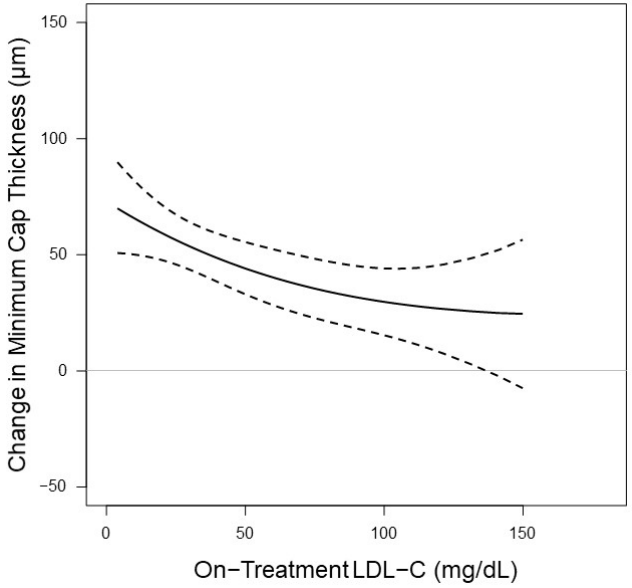
PAV



maxLCBI$_{4mm}$



FCT$_{min}$



* Non-prespecified analysis

La riduzione dei livelli di C-LDL sotto gli attuali target non è associata ad un aumentato rischio di eventi avversi

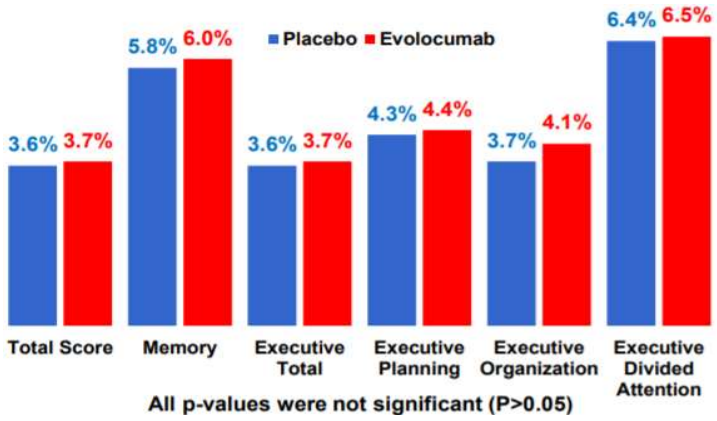
Meta-analysis of non-statin trials (FOURIER, IMPROVE-IT and REVEAL) in sub-set of patients with baseline LDL-C ~ < 70 mg/dL

Safety Outcome	Patients With Event, No.		Meta-analysis Data	
	Experimental Arm	Control Arm	Risk Ratio (95% CI)	P-value
Any serious adverse event	12,809	12,836	1.00 (0.98 – 1.02)	0.89
Myalgias or myopathy	116	135	0.85 (0.66 – 1.08)	0.19
Aminotransferase elevation	488	510	0.96 (0.85 – 1.08)	0.48
New-onset diabetes	1272	1320	0.97 (0.90 – 1.05)	0.46
Hemorrhagic stroke	132	118	1.11 (0.87 – 1.43)	0.40
Cancer	1747	1715	1.02 (0.96 – 1.09)	0.55

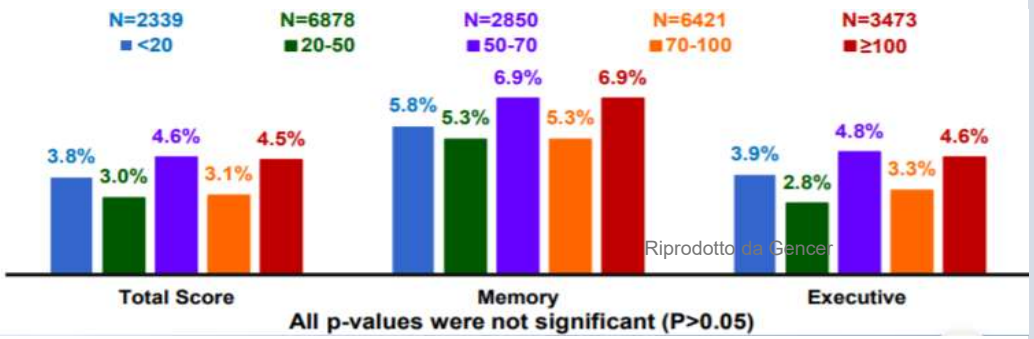
Sabatine MS, et al. JAMA Cardiol. 2018;3(9):823-828.

Il trattamento con evolocumab aggiunto alla terapia massima tollerata con statine non ha influenzato la funzionalità cognitiva anche a livelli di C-LDL molto bassi

Decline in Patient-Reported Cognition (ECog ≥2) at the End by Baseline Randomized Treatment Arm



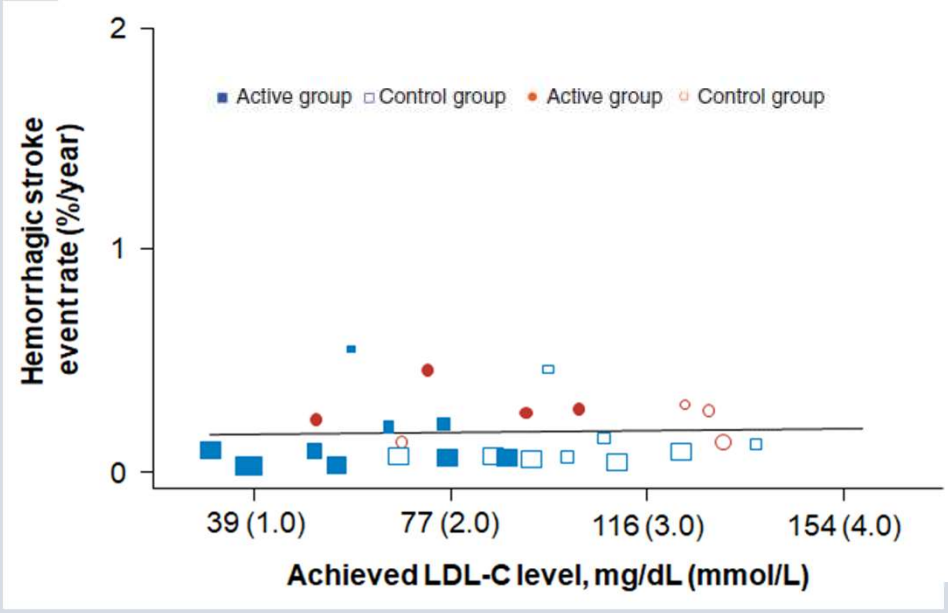
Decline in Patient-Reported Cognition (ECog ≥2) at the End by Achieved LDL-C (mg/dL) at 4 Weeks



Gencer B, et al. Poster presented at American Heart Association Scientific Sessions 2019; November 16–18, 2019, Philadelphia, PA.

La riduzione del C-LDL a < 30 mg/dL non è risultata associata ad un aumento del rischio di ictus emorragico

Associazione tra LDL ed eventi cerebrovascolari



222149 *partecipanti in 23 studi randomizzati*

Elaborato da Shin

Shin J, et al. Eur J Prev Cardiol. 2019.

Target dell'LDL raccomandati dalle Linee Guida ESC/EAS: 2019 vs 2016

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8–3.5 mmol/L (70–135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100 mg/dL) or >50% ↓ if LDL-C 2.6–5.2 mmol/L (100–200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50%↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	<2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

Elaborato da Mach e Catapano

Un secondo evento cardiovascolare in 2 anni impone la massima dose di statina tollerata e un LDL (<40 mg/dL)

Mach F, et al. Eur Heart J 2019.
Catapano AL, et al. Eur Heart J 2016;37:2999-3058.

Linee Guida 2019 ESC/EAS: raccomandazioni inerenti i C-LDL Target

Recommendations	Class*	Level†
In secondary prevention for patients at very-high risk, an LDL-C reduction of ≥50% from baselined and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended	I	A
In primary prevention for individuals at very-high risk but without FH, an LDL-C reduction of ≥50% from baselined and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered	IIb	B
In patients at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended	I	A
In individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered	IIa	A
In individuals at low risk, an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered	IIb	A

Elaborato da Mach

Mach F, et al. Eur Heart J 2019

Conclusioni

Le Linee Guida ESC/EAS 2019 sottolineano che la riduzione del rischio di malattia aterosclerotica è proporzionale alla riduzione assoluta di C-LDL

Le Linee Guida ESC/EAS 2019 hanno abbassato i target di trattamento per C-LDL rispetto alle linee-guida precedenti

Non sono stati identificati livelli di C-LDL sotto i quali si perde il beneficio in termini di riduzione del rischio CV o si presentano problematiche di safety

Livelli di C-LDL più bassi sono associati ad un fenotipo di placca meno vulnerabile

Evolocumab ha ridotto il rischio cardiovascolare in maniera inversamente proporzionale ai livelli di C-LDL raggiunti (lower is better)*

* Quando usato per ridurre i livelli di C-LDL

Scenari clinici nel contesto di pazienti con SCA

Fast Track

La rimborsabilità prevede una singola valutazione del profilo lipidico effettuata nei 30 giorni che precedono la data di valutazione dell'eleggibilità al trattamento con evolocumab.

Giugno 2022 da 100 a 70 mg/dl la soglia di prescrivibilità

Evento		Terapia da introdurre intra-ricovero	Terapia da introdurre a 4-6 settimane di follow-up	Terapia da introdurre a 8-12 settimane di follow-up
Scenario 1	I episodio di STEMI/NSTEMI in paziente naïve da statine	Statine ad alta intensità	Statine alta intensità + ezetimibe se LDL >55 mg/dl	PCSK9i se C-LDL >100 mg/dl (evolocumab rimborsabile)
				PCSK9i se C-LDL 55-99 mg/dl (decisione clinica: secondo LG europee, non rimborsabile)
		Statine ad alta intensità + ezetimibe se MVD o DM o PAD o C-LDL molto elevato	PCSK9i se C-LDL >100 mg/dl (evolocumab rimborsabile)	–
			PCSK9i se C-LDL 55-99 mg/dl (decisione clinica: secondo LG europee, non rimborsabile)	–
Scenario 2	I episodio di STEMI/NSTEMI in paziente in terapia con statine	Statine ad alta intensità + ezetimibe	PCSK9i se C-LDL >100 mg/dl (evolocumab rimborsabile)	–
			PCSK9i se C-LDL 55-99 mg/dl (decisione clinica: secondo LG europee, non rimborsabile)	–
		+ PCSK9i se MVD o DM o PAD o C-LDL molto elevato (evolocumab rimborsabile con C-LDL >100 mg/dl)	–	–
	I episodio di STEMI/NSTEMI in paziente in terapia con statine + ezetimibe	Aggiungere PCSK9i se C-LDL >100 mg/dl (evolocumab rimborsabile)		–
		+ PCSK9i se C-LDL 55-99 mg/dl (decisione clinica: secondo LG europee, non rimborsabile)		–
Scenario 3	SCA recidivante (II episodio entro 2 anni) in paziente in terapia con statine	Aggiungere ezetimibe	PCSK9i se C-LDL >100 mg/dl (evolocumab rimborsabile)	–
			PCSK9i se C-LDL 40-99 mg/dl (decisione clinica: secondo LG europee, non rimborsabile)	–
		+ PCSK9i se C-LDL >100 mg/dl e MVD o DM o PAD (evolocumab rimborsabile)	–	–
	SCA recidivante (II episodio entro 2 anni) in paziente in terapia con statine + ezetimibe	Aggiungere PCSK9i se C-LDL >100 mg/dl (evolocumab rimborsabile)		–
		+ PCSK9i se C-LDL 40-99 mg/dl (decisione clinica: secondo LG europee, non rimborsabile)		–

Centri prescrittori
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Cardiologia Lucca

Cardiologia FTGM Massa

Cardiologia Massa

Cardiologia Versilia

UOSVD Lipoaferesi FTGM Pisa

Cardiologia 1 e Diabetologia AOUP

Diabetologia Livorno

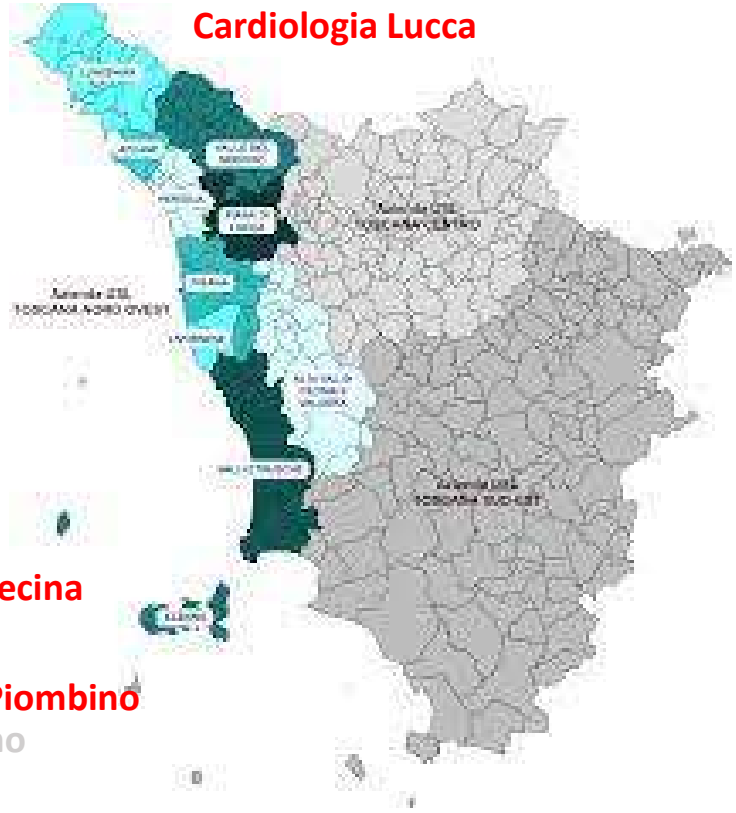
Cardiologia Livorno

Riabilitazione Cardiologica Cecina

Cardiologia Cecina

Nefrologia Cecina/Piombino

Cardiologia Piombino



Centri Hub Emodinamica

FTGM Massa e Pisa
Cardiologia 1 AOUP

Lucca
Livorno

La **scelta** di una terapia di combinazione precoce nella dislipidemia

La Babele della prescrivibilità

«The current limited use of PCSK9is reflects uncertainties among clinicians regarding reimbursement, particularly those not working in a specialized lipid setting. **Facilitating access** to PCSK9is requires less complicated local regulations than the existing criteria. Our findings suggest that a **re-evaluation** of the present reimbursement criteria for PCSK9is is required in Europe.

Lowering the LDL-C threshold for PCSK9i reimbursement could have **important benefits** for population health»

K.K. Ray et al.European Heart Journal - Quality of Care and Clinical Outcomes (2022) 0, 1–14

AIFA dixit

Con una determina pubblicata sulla GU n. 291 del 12/12/2019, l'Aifa ha reso più agevole la rimborsabilità di evolocumab garantendo una sorta di "fast track" per due tipologie di pazienti ad alto rischio cardiovascolare: i pazienti con infarto del miocardio recente (entro 12 mesi) e quelli con eventi cardiovascolari (Cv) multipli ricorrenti.

Per le popolazioni sopramenzionate, l'eggiornamento dei criteri di rimborsabilità prevede una sola valutazione del profilo lipidico (LDL-C >100 mg/dL nei 30 giorni che precedono l'inizio del trattamento con evolocumab) in linea con le indicazioni delle ultime linee guida Eas/Esc sulle dislipidemie che suggeriscono un approccio precoce ed aggressivo nei pazienti con Sca recente o eventi multipli.

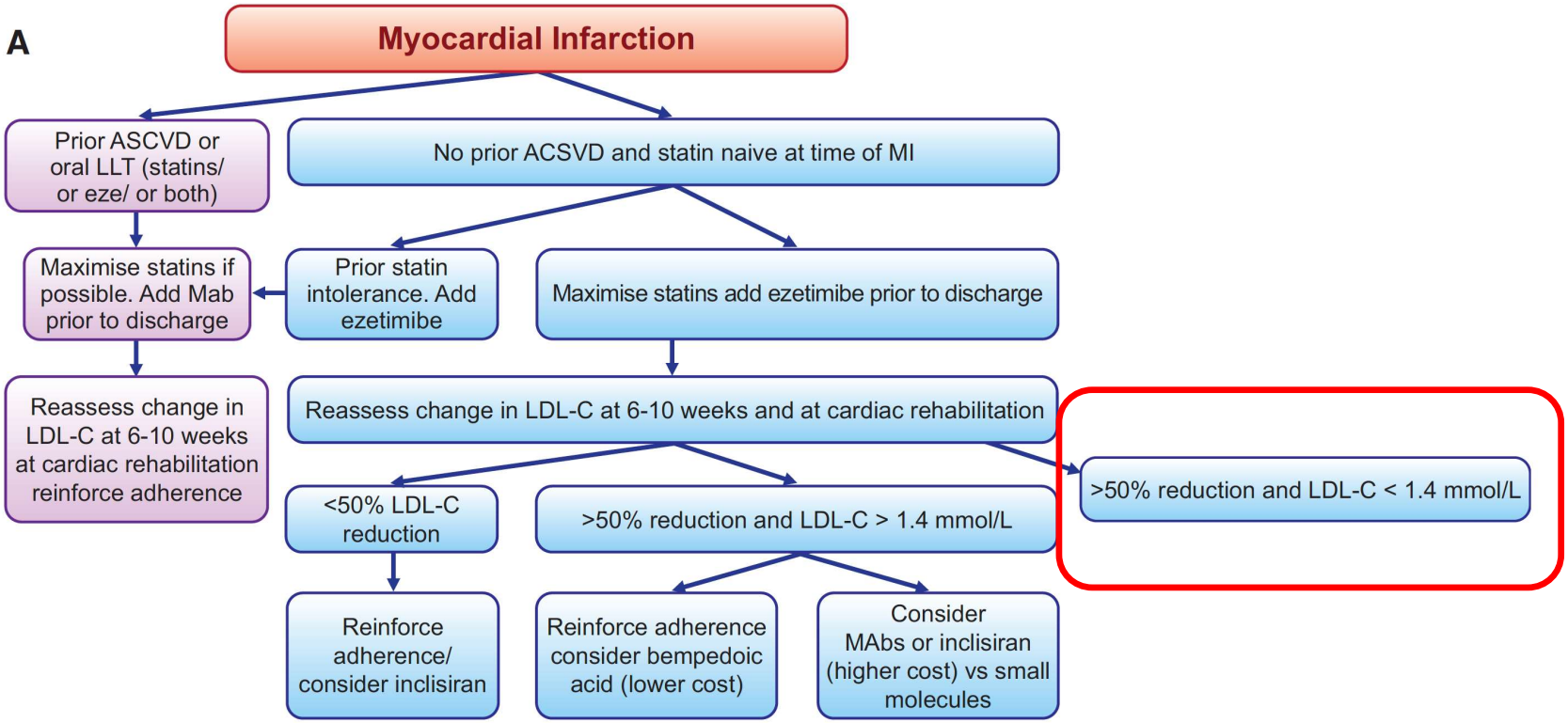
In precedenza, per poter prescrivere il farmaco in questi pazienti occorrevano 3 valutazioni effettuate nel corso di 6 mesi che confermassero la persistenza dei livelli di colesterolo LDL sopra i 100 mg/dL nonostante una terapia anticolesterolo di base ottimizzata (statina ad alta potenza alla massima dose tollerata + ezetimibe).

È stato quindi riconosciuto che questi pazienti rappresentano una popolazione a rischio cardiovascolare molto elvato, come confermato dalle recenti linee guida Eas/Esc sulla dislipidemia che stabiliscono un target di LDL-C pari a 55 mg/dL, suggerendo per i pazienti con eventi ricorrenti un target di 40mg/dL.rischio cardiovascolare. Queste due tipologie di pazienti sono infatti recepite come una popolazione a rischio CV massimo dalle recenti linee guida Eas/Esc sulla dislipidemia che stabiliscono un target di LDL-C pari a 55 mg/dL, suggerendo per i pazienti con eventi ricorrenti un target di 40mg/dL.

Infatti, nei pazienti con anamnesi di infarto del miocardio (Ima), entro l'anno dall'evento si registra il 40% di rischio di un evento successivo e il 30% di morte. Nella popolazione dello studio FOURIER, i pazienti in placebo inclusi nello studio entro l'anno dall'evento presentavano un HR pari a 1,45 verso i pazienti inclusi nello studio dopo almeno 12 mesi dall'evento

Confermando tutte le precedenti sotto-analisi dello studio FOURIER, la recente sottoanalisi presentata all'ultimo AHA di Philadelphia, in cui si è valutato l'effetto in termini di riduzione degli eventi dei pazienti con un recente Ima (entro l'anno) rispetto ai pazienti con evento meno recente (> 12 mesi), ha dimostrato che maggiore è il rischio e maggiore è anche il beneficio che si ottiene con evolocumab.
In questo setting (Ima entro 12 mesi) si è osservata una riduzione pari al 3,7% del rischio assoluto a tre anni del primary endpoint (morte CV, Ima, stroke, rivascolarizzazione e ospedalizzazione per UA), con un NNT di 27.

Cambiare il paradigma per la riduzione del colesterolo post-IM: dalla monoterapia con statine a regimi ipolipemizzanti intensivi e cure individualizzate



KK Ray. European Heart Journal (2021) 42, 253–256

Fare clic per modificare lo stile del titolo dello schema

- Modifica gli stili del testo dello schema
  - Secondo livello
    - Terzo livello
      - Quarto livello
        - Quinto livello

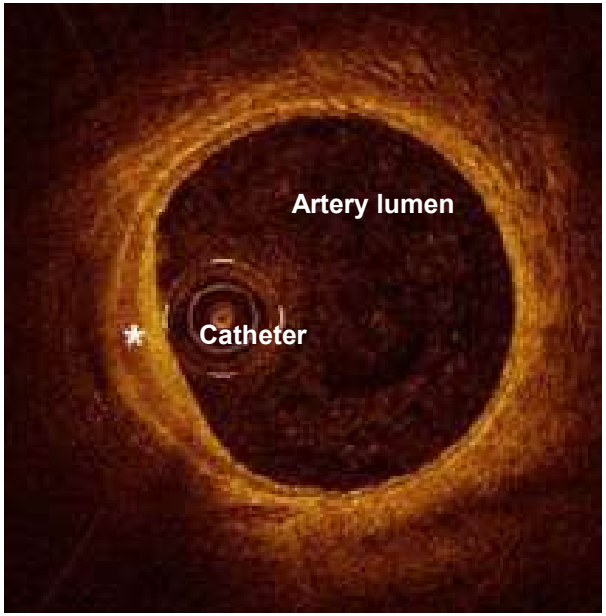
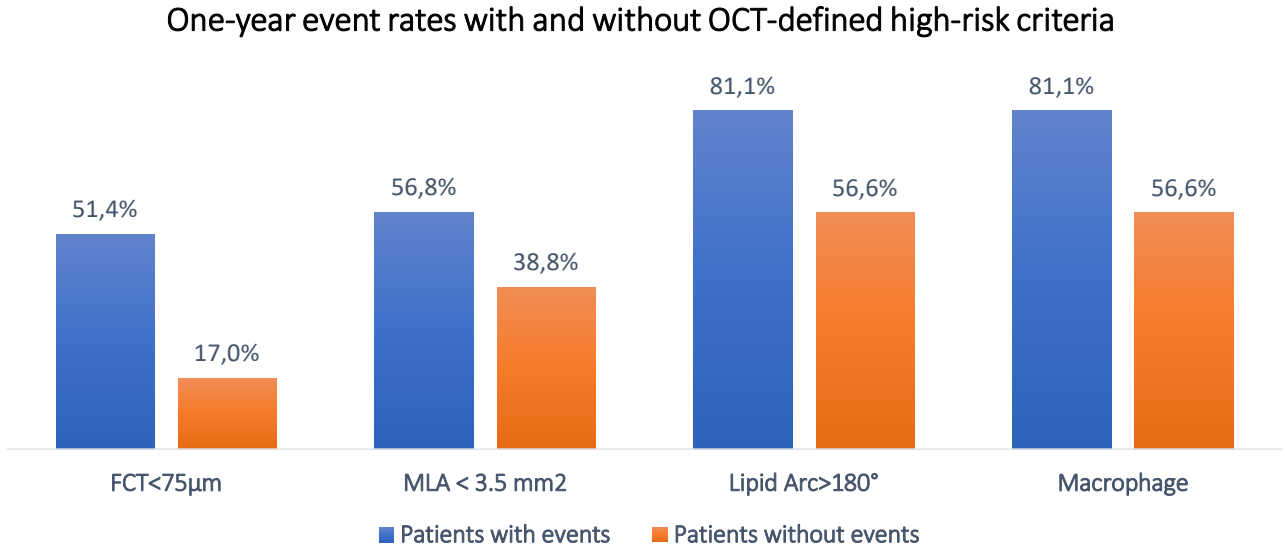


Image courtesy of van Ditzhuijzen NS, et al. *Neth Heart J.* 2011;19:442-446[2]

La presenza simultanea di 4 caratteristiche ad alto rischio della placca è associata ad un rischio più elevato di eventi coronarici maggiori

Prospective observational, multicenter registry recruiting all consecutive patients undergoing assessment of proximal LAD atherosclerosis by OCT in the context of a clinically indicated coronary angiography (n=1776 lipid plaques).



hazard ratio	4.65 (2.4 -9.0)	2.07 (1.1-4.0)	2.40 (1.2-4.8)	2.66 (1.2-6.1)
p-value	<0.001	0.032	0.13	0.021
prevalence	19.8%	39.5%	44.4%	62.4%

Elaborato da 1

La presenza di MLA <3,5 mm², FCT <75 µm, l'estensione circonferenziale dell'arco lipidico >180º e i macrofagi definiti da OCT erano tutti associati ad un aumento del rischio dell'endpoint primario.

CLIMA study. Prati F et al. Eur Heart J 2020;41(3):383-391

Fare clic per modificare lo stile de schema

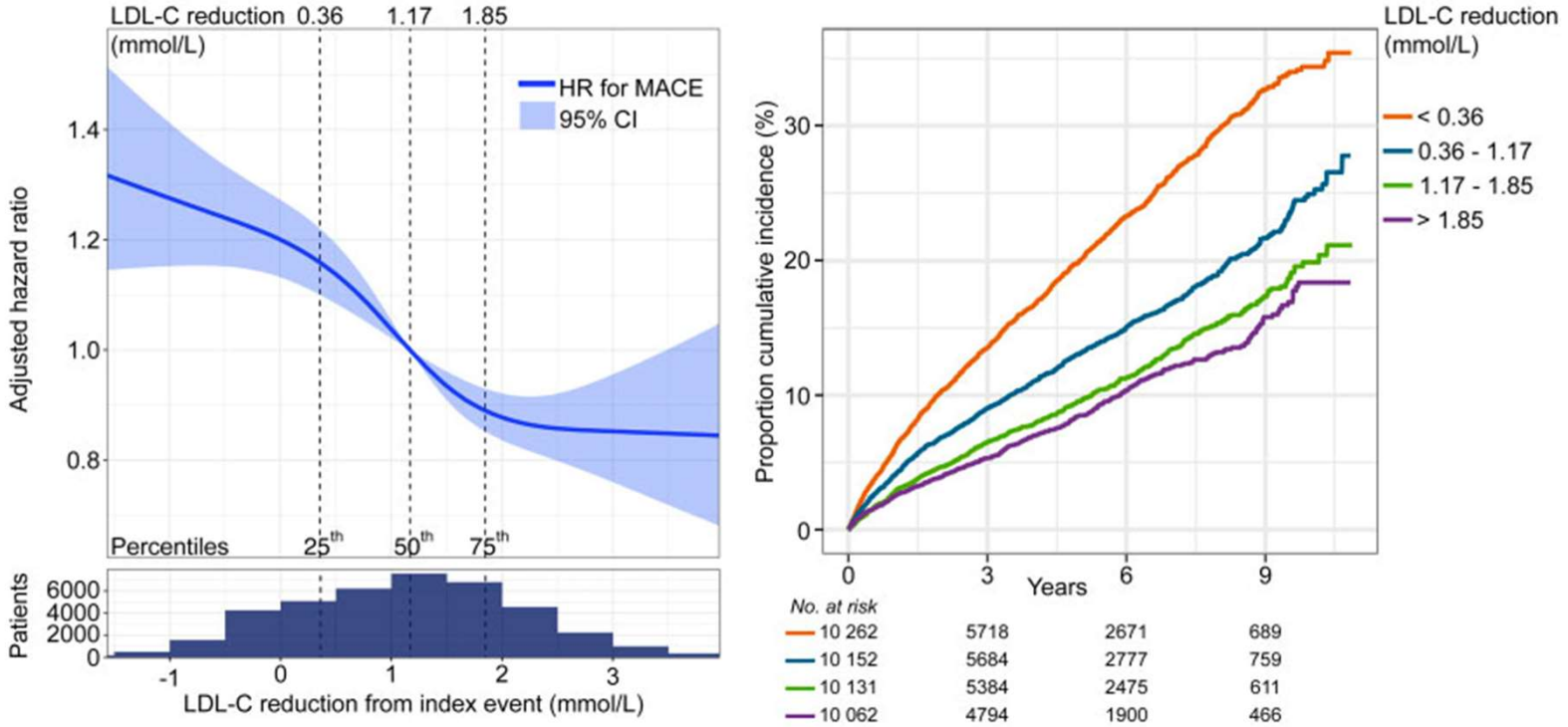
- Modifica gli stili del testo dello schema
- Secondo livello
- Terzo livello
- Quarto livello
- Quinto livello

[1]Victorian Heart Institute, Monash University, Clayton, Australia, [2]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Centre, Suita, Japan, [3]Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH, USA, [4]San Giovanni Hospital; UniCamillus "Saint Camillus International University of Health Science", Rome, Italy, [5]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Switzerland, [6]Global Development, Amgen Inc., Thousand Oaks, CA, USA, [7]Heart and Vascular Center, University of Semmelweis, Hungary, [8]Heart Center Balatonfüred, Hungary, [9]Tagore Medical Center, Balatonfüred, Hungary, [10]OLVG Oost, Amsterdam, The Netherlands, [11]Isala Hospital, Zwolle, Department of Cardiology, The Netherlands, [12]South Australian Health and Medical Research Institute, Adelaide, Australia, [13]Adelaide Medical School, University of Adelaide; Department of Cardiology, Central Adelaide Local Health Network, Adelaide, Australia.

*Contributed equally to this project

Date of Preparation: March 2022

Adjusted hazard ratio and incidence rates for major adverse cardiovascular events by change in LDL-C 6-10 weeks after myocardial infarction



HR for 1.85 vs 0.36 mmol/L LDL-C reduction: **0.77 (95% CI 0.70 - 0.84)**

European Heart Journal (2021) 42, 243–252

JAMA | Original Investigation

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
The PACMAN-AMI Randomized Clinical Trial

Lorenz Räber, MD, PhD; Yasushi Ueki, MD, PhD; Tatsuhiko Otsuka, MD; Sylvain Losdat, PhD; Jonas D. Häner, MD; Jacob Lonborg, MD; Gregor Fahrni, MD; Juan F. Iglesias, MD; Robert-Jan van Geuns, MD, PhD; Anna S. Ondracek, MSc; Maria D. Radu Juul Jensen, MD, PhD; Christian Zanchin, MD, PhD; Stefan Stortecky, MD; David Spirk, MD; George C. M. Siontis, MD, PhD; Lanja Saleh, PhD; Christian M. Matter, MD; Joost Daemen, MD, PhD; François Mach, MD; Dik Heg, PhD; Stephan Windecker, MD; Thomas Engstrøm, MD, PhD; Irene M. Lang, MD; Konstantinos C. Koskinas, MD, MSc; for the PACMAN-AMI collaborators

IMPORTANCE Coronary plaques that are prone to rupture and cause adverse cardiac events are characterized by large plaque burden, large lipid content, and thin fibrous caps. Statins can halt the progression of coronary atherosclerosis; however, the effect of the proprotein convertase subtilisin kexin type 9 inhibitor alirocumab added to statin therapy on plaque burden and composition remains largely unknown.

OBJECTIVE To determine the effects of alirocumab on coronary atherosclerosis using serial multimodality intracoronary imaging in patients with acute myocardial infarction.

DESIGN, SETTING, AND PARTICIPANTS The PACMAN-AMI double-blind, placebo-controlled, randomized clinical trial (enrollment: May 9, 2017, through October 7, 2020; final follow-up: October 13, 2021) enrolled 300 patients undergoing percutaneous coronary intervention for acute myocardial infarction at 9 academic European hospitals.

INTERVENTIONS Patients were randomized to receive biweekly subcutaneous alirocumab (150 mg; n = 148) or placebo (n = 152), initiated less than 24 hours after urgent percutaneous coronary intervention of the culprit lesion, for 52 weeks in addition to high-intensity statin therapy (rosuvastatin, 20 mg).

MAIN OUTCOMES AND MEASURES Intravascular ultrasonography (IVUS), near-infrared spectroscopy, and optical coherence tomography were serially performed in the 2 non–infarct-related coronary arteries at baseline and after 52 weeks. The primary efficacy end point was the change in IVUS-derived percent atheroma volume from baseline to week 52. Two powered secondary end points were changes in near-infrared spectroscopy–derived maximum lipid core burden index within 4 mm (higher values indicating greater lipid content) and optical coherence tomography–derived minimal fibrous cap thickness (smaller values indicating thin-capped, vulnerable plaques) from baseline to week 52.

RESULTS Among 300 randomized patients (mean [SD] age, 58.5 [9.7] years; 56 [18.7%] women; mean [SD] low-density lipoprotein cholesterol level, 152.4 [33.8] mg/dL), 265 (88.3%) underwent serial IVUS imaging in 537 arteries. At 52 weeks, mean change in percent atheroma volume was −2.13% with alirocumab vs −0.92% with placebo (difference, −1.21% [95% CI, −1.78% to −0.65%], $P < .001$). Mean change in maximum lipid core burden index within 4 mm was −79.42 with alirocumab vs −37.60 with placebo (difference, −41.24 [95% CI, −70.71 to −11.77]; $P = .006$). Mean change in minimal fibrous cap thickness was 62.67 µm with alirocumab vs 33.19 µm with placebo (difference, 29.65 µm [95% CI, 11.75-47.55]; $P = .001$). Adverse events occurred in 70.7% of patients treated with alirocumab vs 72.8% of patients receiving placebo.

CONCLUSIONS AND RELEVANCE Among patients with acute myocardial infarction, the addition of subcutaneous biweekly alirocumab, compared with placebo, to high-intensity statin therapy resulted in significantly greater coronary plaque regression in non–infarct-related arteries after 52 weeks. Further research is needed to understand whether alirocumab improves clinical outcomes in this population.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03067844

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The PACMAN-AMI collaborators are listed in Supplement 5.

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Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
The PACMAN-AMI Randomized Clinical Trial

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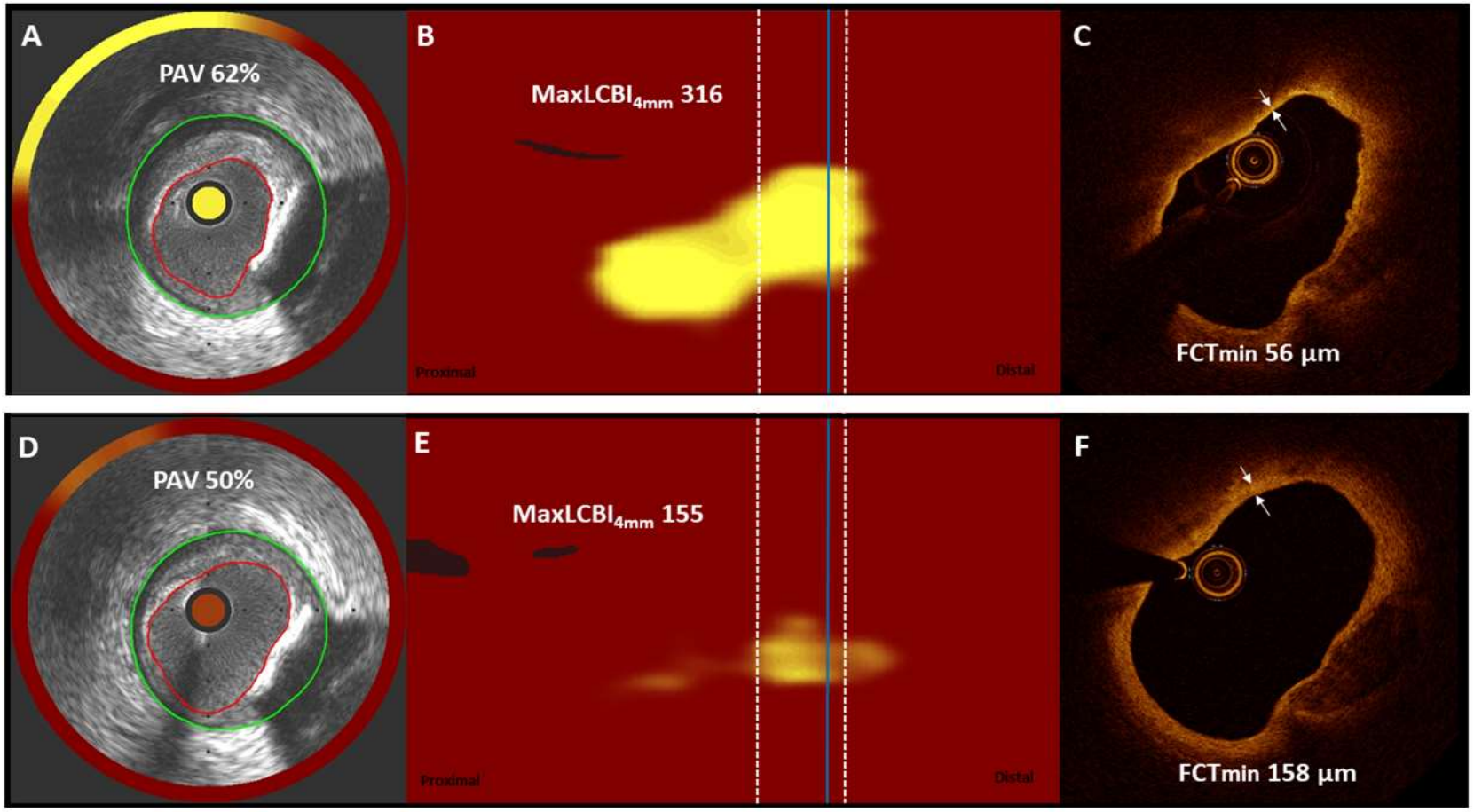
Lessons from the HEYMANS study

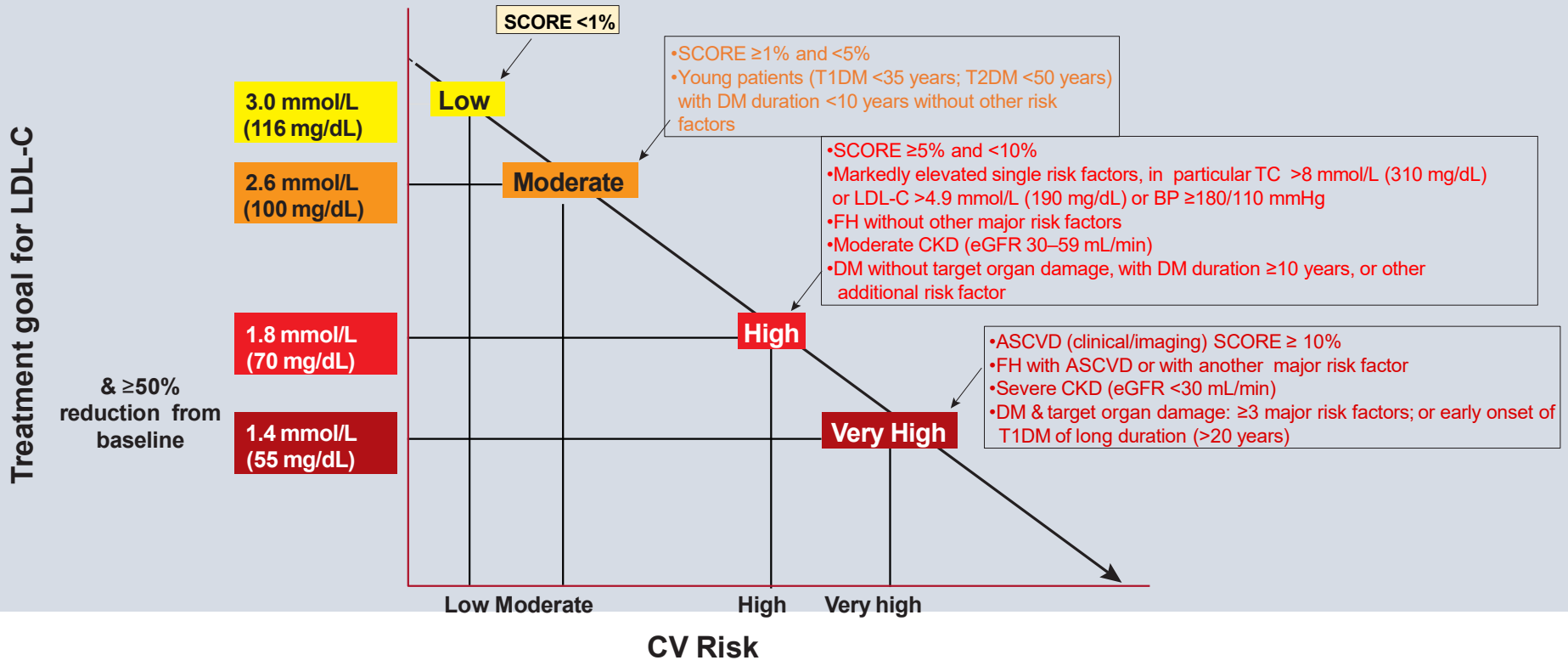
…More patients attained risk-based LDLC goals when receiving evolocumab in combination with LLT vs. those not receiving combination therapy.

Population health could be improved and LDL-C goals better attained if LDL-C thresholds for PCSK9i reimbursement were lowered, enabling more patients to receive combination therapy when needed.

Case Example Alirocumab & Statin Group



Linee Guida 2019 ESC/EAS: LDL Target in funzione delle categorie di rischio CV



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