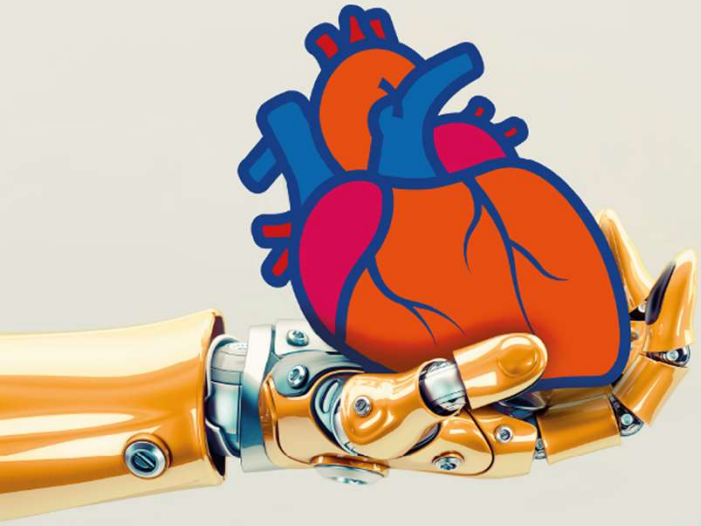


17° Meeting

CardioLucca

Heart Brings Heart 2023

Lucca, 22-24 Giugno 2023

Centro Congressi Auditorium San Francesco

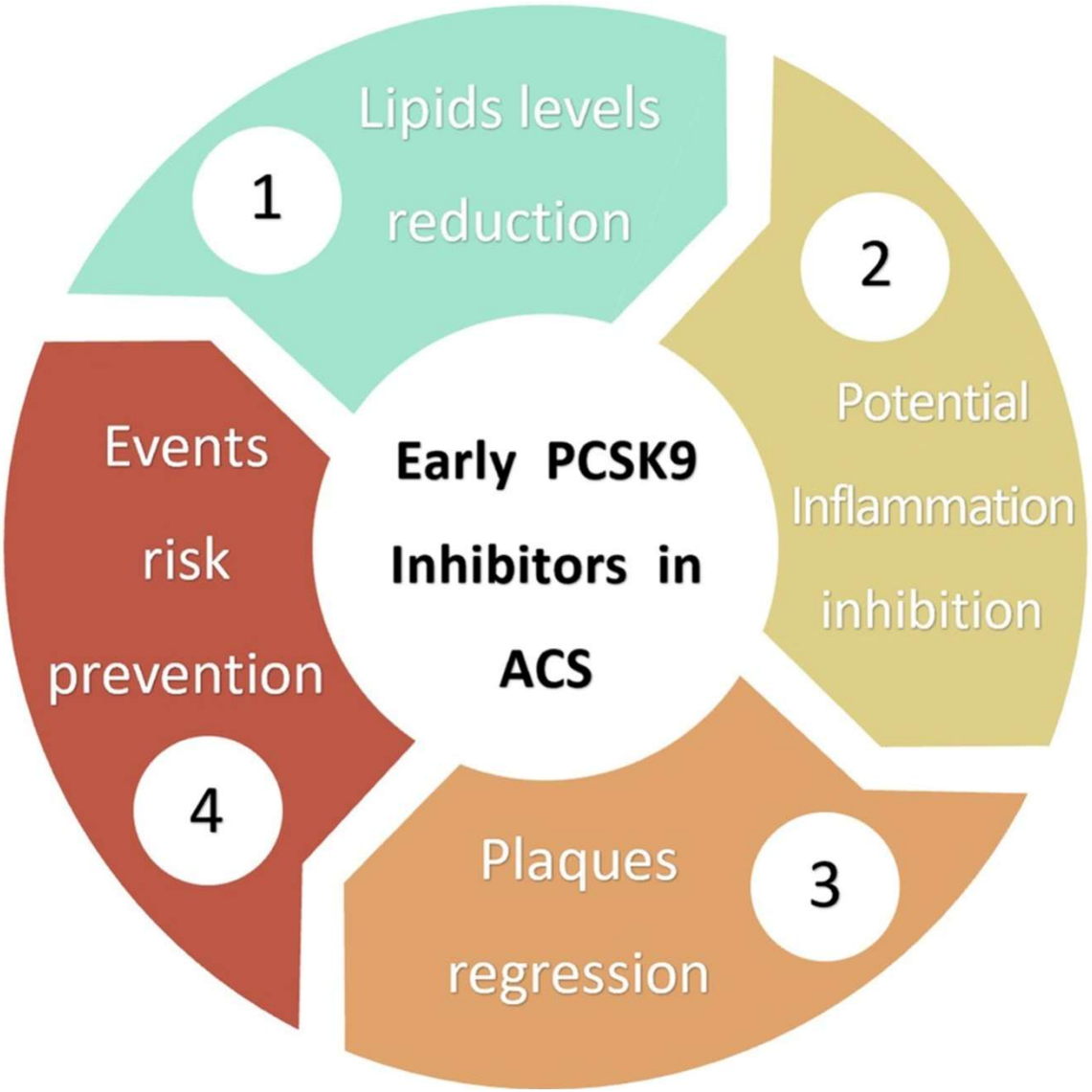
LECTURES ON DRUG THERAPY OF CARDIOVASCULAR DISEASES

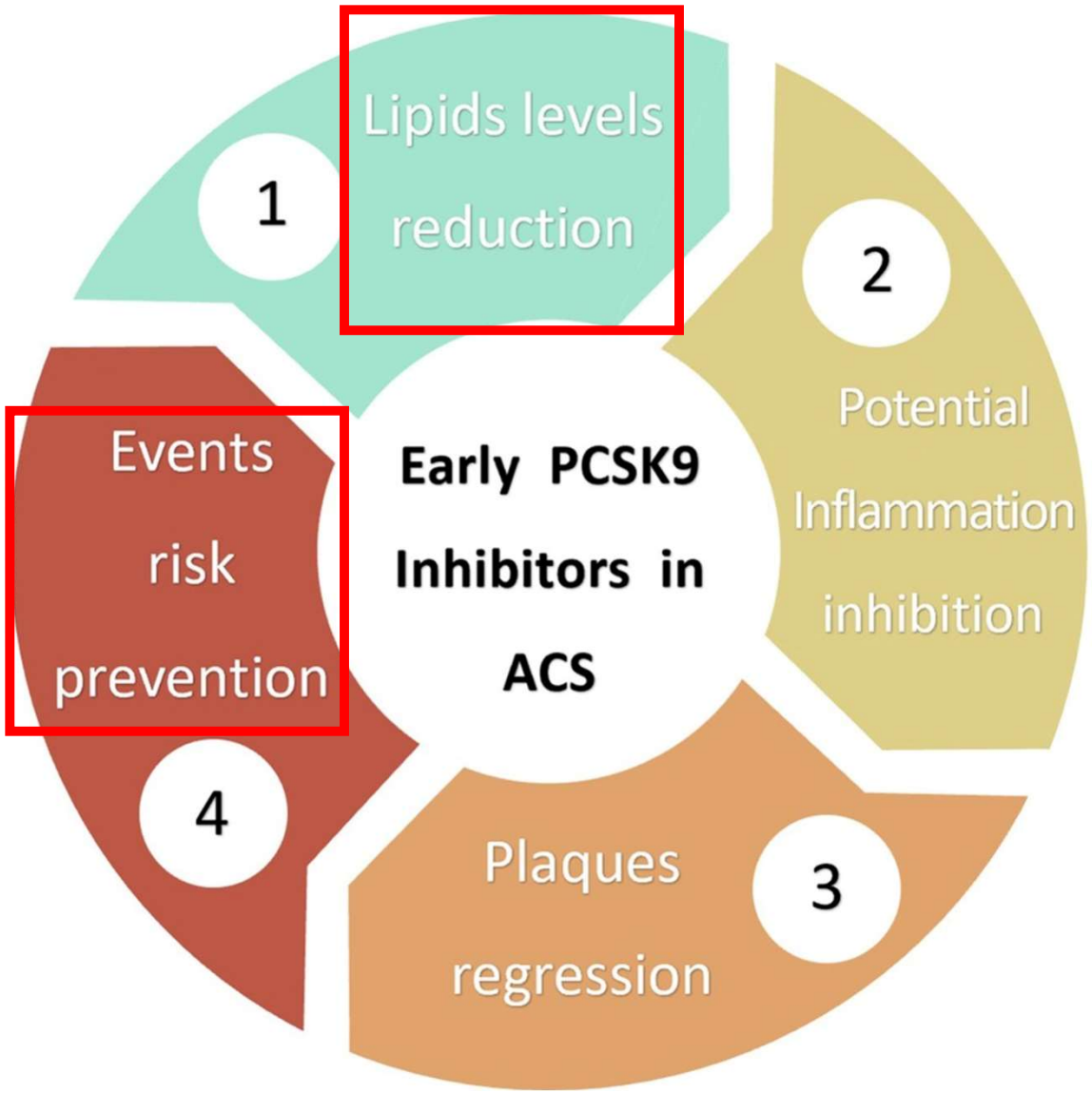
Moderatori: Giuseppe Calveri *(Varese)*, Antonio Fiscella *(Catania)*

16:15 Il trattamento precoce con PCSK9 post-SCA: opportunità o necessità?
Ferdinando Varbella *(Rivoli)*

Ferdinando Varbella MD
Head of Internal Medicine Department
Chief of Cardiology Rivoli Hospital Turin
Cath. Lab. Director
A.S.L. TO 3 Rivoli Turin
A.O.U. San Luigi Orbassano

S. Luigi Gonzaga
Orbassano (To)


Early PCSK9 Inhibitors in ACS
1
Lipids levels reduction
2
Potential Inflammation inhibition
3
Plaques regression
4
Events risk prevention


Lipids levels reduction
1
2
Potential Inflammation inhibition
Early PCSK9 Inhibitors in ACS
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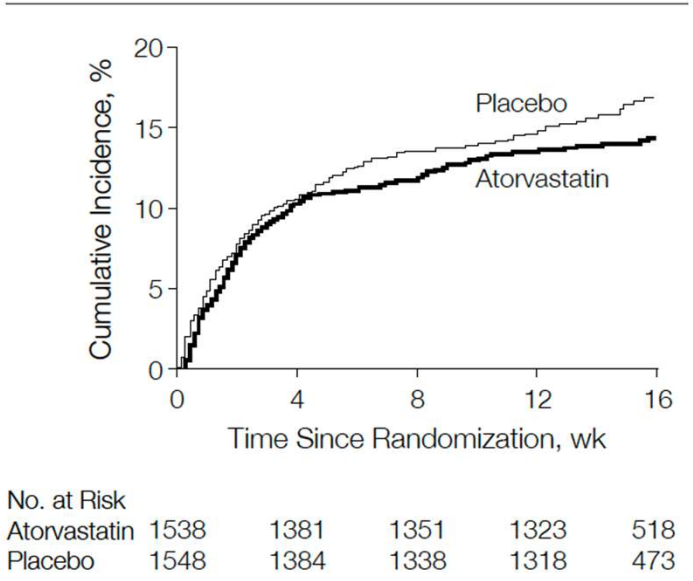
4
Plaques regression
3

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes

The MIRACL Study: A Randomized Controlled Trial

< 24-96 h ACS **death, NFMI, recurr ischemia , Resuscitated Cardiac arrest**



Scwhartz GG, Olsonn AG, Ezekowitz MD et al. J Am Med Assoc 2001

Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 46, No. 8, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.03.077

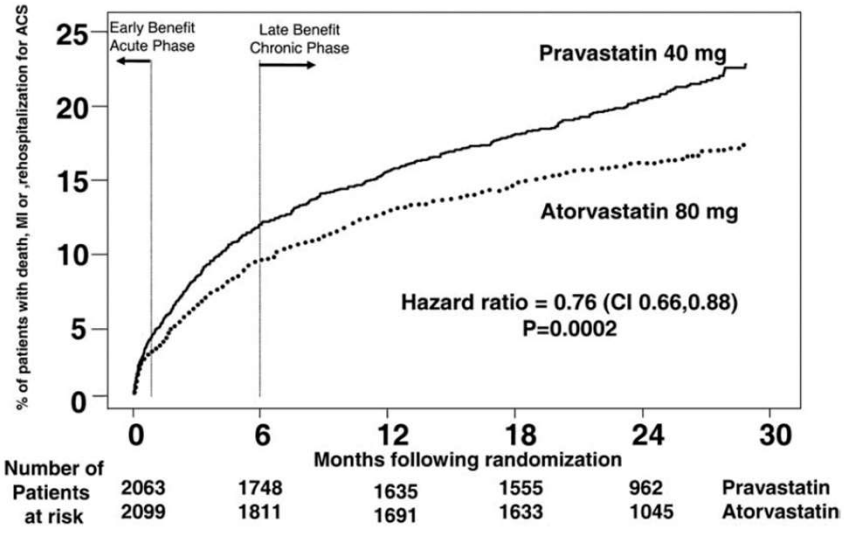
FOCUS ISSUE: PROVE IT-TIMI 22

Early and Late Benefits of High-Dose Atorvastatin in Patients With Acute Coronary Syndromes

Results From the PROVE IT-TIMI 22 Trial

Kausik K. Ray, MRCP, MD* Christopher P. Cannon, MD, FACC,* Carolyn H. McCabe, BS,*
Richard Cairns, BSc,† Andrew M. Tonkin, MD,‡ Frank M. Sacks, MD,§ Graham Jackson, MD, FRCP,‖
Eugene Braunwald, MD, MACC,* for the PROVE IT-TIMI 22 Investigators
Boston, Massachusetts; Nottingham and London, United Kingdom; and Melbourne, Australia

< 10 gg ACS **death, NFMI, recurr ACS hospitalization**

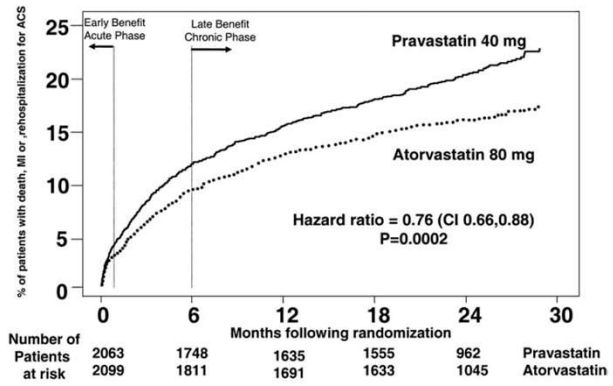


Ray KK, Cannon CP, Mc Cabe CH et al. J Am Coll Cardiol 2005

PROVE-IT TIMI 22

< 10 gg ACS

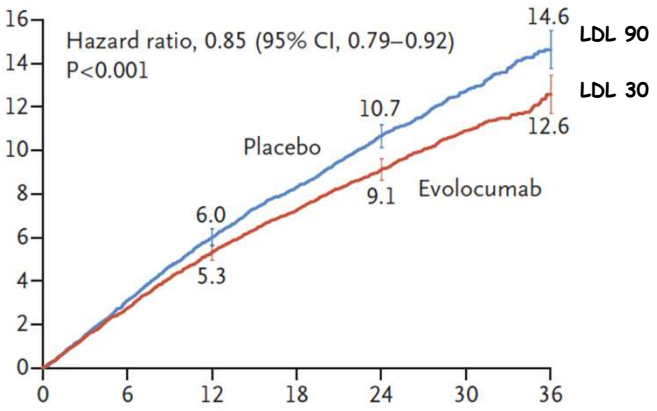
death, NFMI, recurr ACS hospitalization



Ray KK, Cannon CP, Mc Cabe CH et al. J Am Coll Cardiol 2005

FOURIER

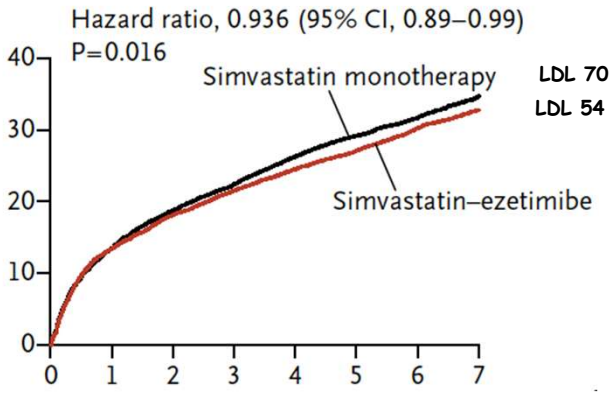
media 3.3 anni ACS



Sabatine MS, Giugliano RP et al N Engl J Med 2017

< 10 gg ACS

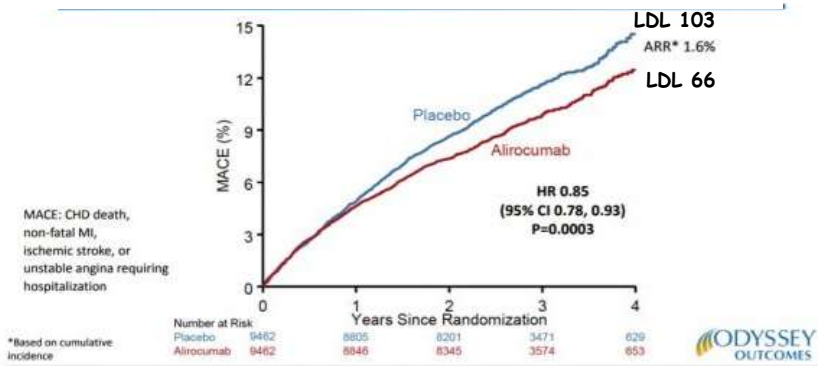
IMPROVE-IT



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

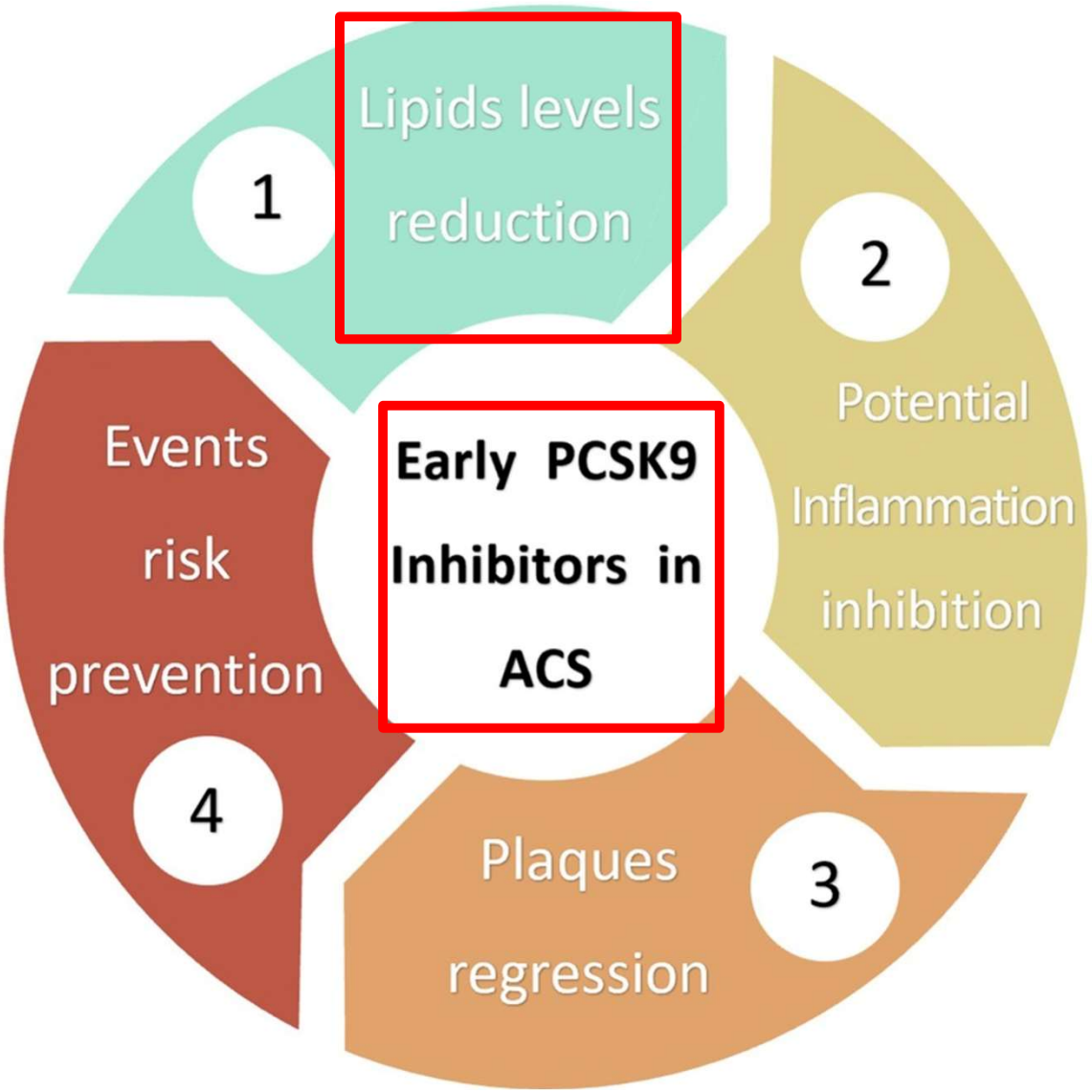
ODYSSEY OUTCOMES

media 2.6 mesi ACS



Schwartz GG, Steg PG et al. N Engl J Med 2018

USO PRECOCE PCSK9-i


Lipids levels reduction
1
2
Potential Inflammation inhibition
Early PCSK9 Inhibitors in ACS
Events risk prevention
4
Plaques regression
3

Circulation

RESEARCH LETTER

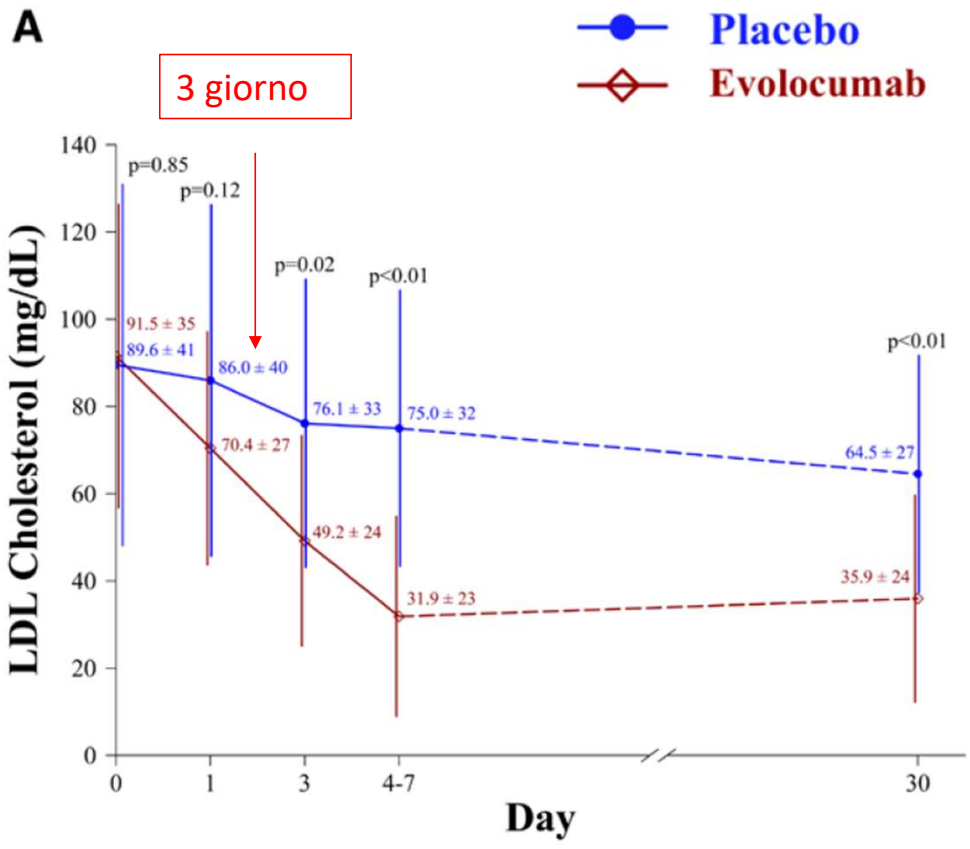
EVACS

Effect of Evolocumab on Atherogenic Lipoproteins During the Peri- and Early Postinfarction Period

A Placebo-Controlled, Randomized Trial

- **57 NSTEMI troponina I > 5ng/ml**
- **tutti con Statina alta intensità**
- **Evolocumab 420 mg sc vs placebo**
- **inizio < 24 ore**

- **prelievi basale, 3 gg, dimissione, 30 gg**



Gary Gerstenblith, MD, Johns Hopkins Hospital/Halsted 563, 600 N Wolfe Street, Baltimore, MD 21287. Email gblith@jhmi.edu

Leucker TM, Blaha M, Jones SR et al. Circulation 2020

EPIC STEMI

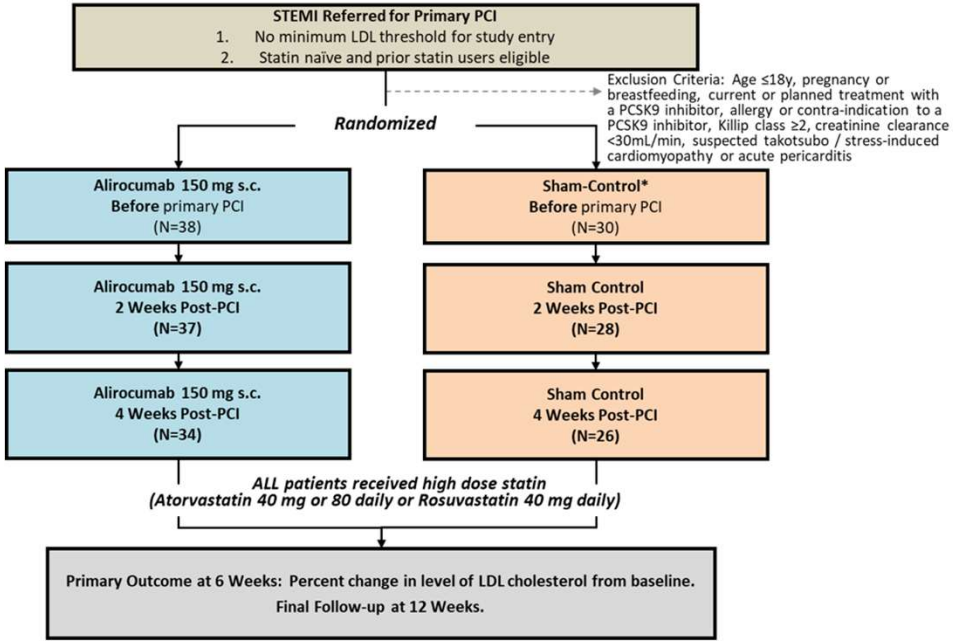
CORONARY INTERVENTIONS
CLINICAL RESEARCH

Effects of Routine Early Treatment with PCSK-9 inhibitor in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction: A randomized, double-blind, sham-controlled trial

Shamir R. Mehta[1,2,3*],MD, MSc; Guillaume Pare[1,2,3,4], MD, MSc; Eva M. Lonn[1,2,3], MD, MSc; Sanjit S. Jolly[1,2,3], MD; Madhu K. Natarajan[1,2,3], MD; Natalia Pinilla-Echeverri[1,2,3], MD, MSc; Jon-David Schwalm[1,2,3], MD, MSc; Tej Sheth[1,2,3], MD; Matthew Sibbald[2,3],MD, PhD; Michael Tsang[2,3], MD; Nicholas Valettas[2,3], MD, MASc; James L. Velianou[2,3], MD; Shun Fu Lee[1], PhD; Tahsin Ferdous[1], MSc; Sadia Nauman[3], MBBS, MSc; Helen Nguyen[1], BSc; Tara McCready[1], PhD, MBA; Matthew J. McQueen[1,2,3,4], MBChB, PhD

	Alirocumab N=38	Sham-Control N=30
Age (year)	61.37 (11.04)	63.63 (10.38)
Sex (male) - no.(%)	27 (71.05)	28 (93.33)
Statin use within 7 days of randomization no.(%)	8 (21.05)	8 (26.67)
Statin use after randomization		
Atorvastatin 40-80 mg or Rosuvastatin 40 mg daily	37 (97.37)	30 (100)
Atorvastatin 80 mg or Rosuvastatin 40 mg daily	37(97.37)	27(90.00)
Ezetimibe	2 (5.26)	1 (3.33)

68 pazienti STEMI



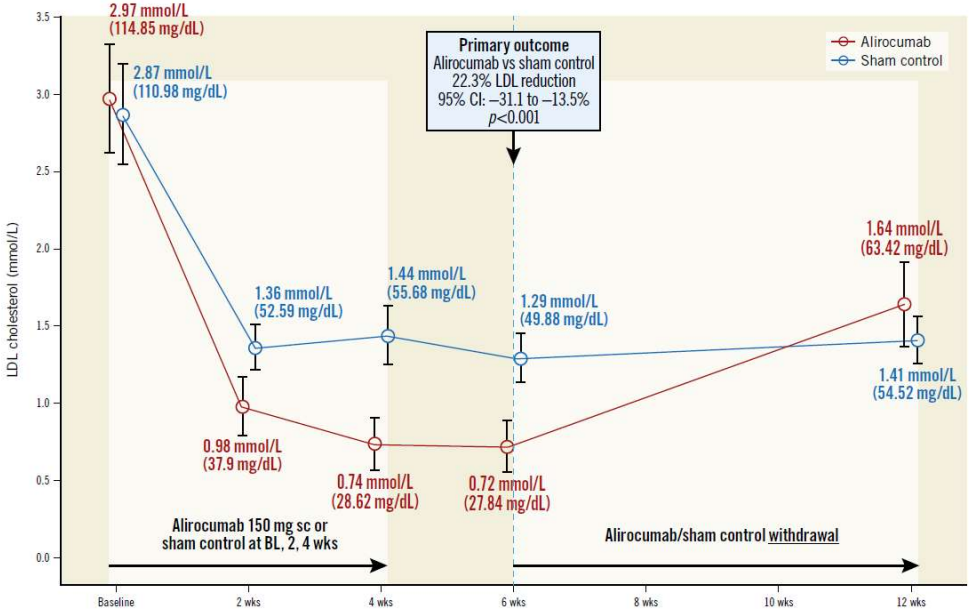
Mehta SR, Pare G, Lonn EM et al. Eurointervention 2022

EPIC STEMI

CORONARY INTERVENTIONS
CLINICAL RESEARCH

Effects of Routine Early Treatment with PCSK-9 inhibitor in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction: A randomized, double-blind, sham-controlled trial

Shamir R. Mehta[1,2,3*],MD, MSc; Guillaume Pare[1,2,3,4], MD, MSc; Eva M. Lonn[1,2,3], MD, MSc; Sanjit S. Jolly[1,2,3], MD; Madhu K. Natarajan[1,2,3], MD; Natalia Pinilla-Echeverri[1,2,3], MD, MSc; Jon-David Schwalm[1,2,3], MD, MSc; Tej Sheth[1,2,3], MD; Matthew Sibbald[2,3],MD, PhD; Michael Tsang[2,3], MD; Nicholas Valettas[2,3], MD, MASc; James L. Velianou[2,3], MD; Shun Fu Lee[1], PhD; Tahsin Ferdous[1], MSc; Sadia Nauman[3], MBBS, MSc; Helen Nguyen[1], BSc; Tara McCready[1], PhD, MBA; Matthew J. McQueen[1,2,3,4], MBChB, PhD



BL: baseline; CI: confidence interval; LDL: low-density lipoprotein; sc: subcutaneous

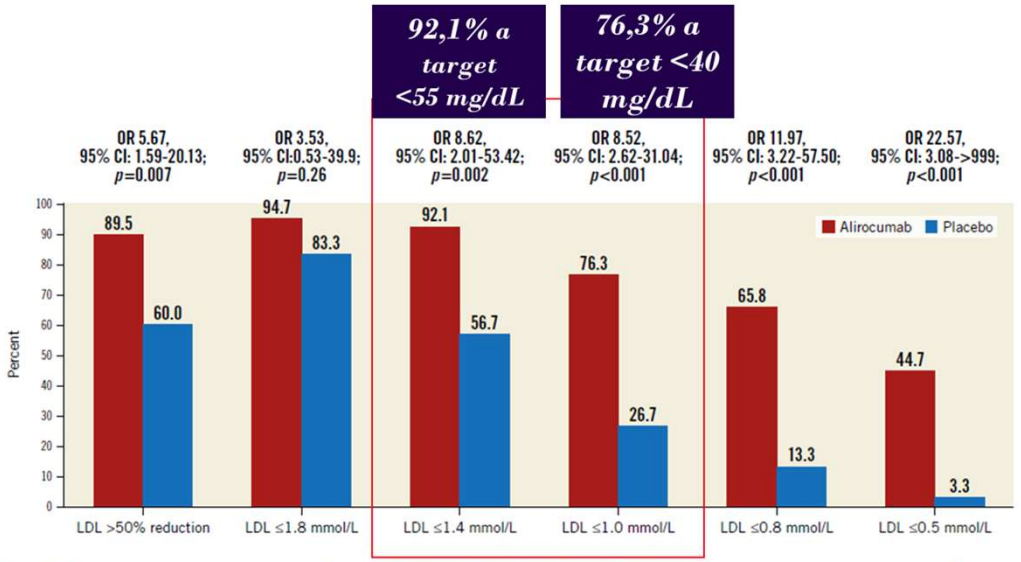
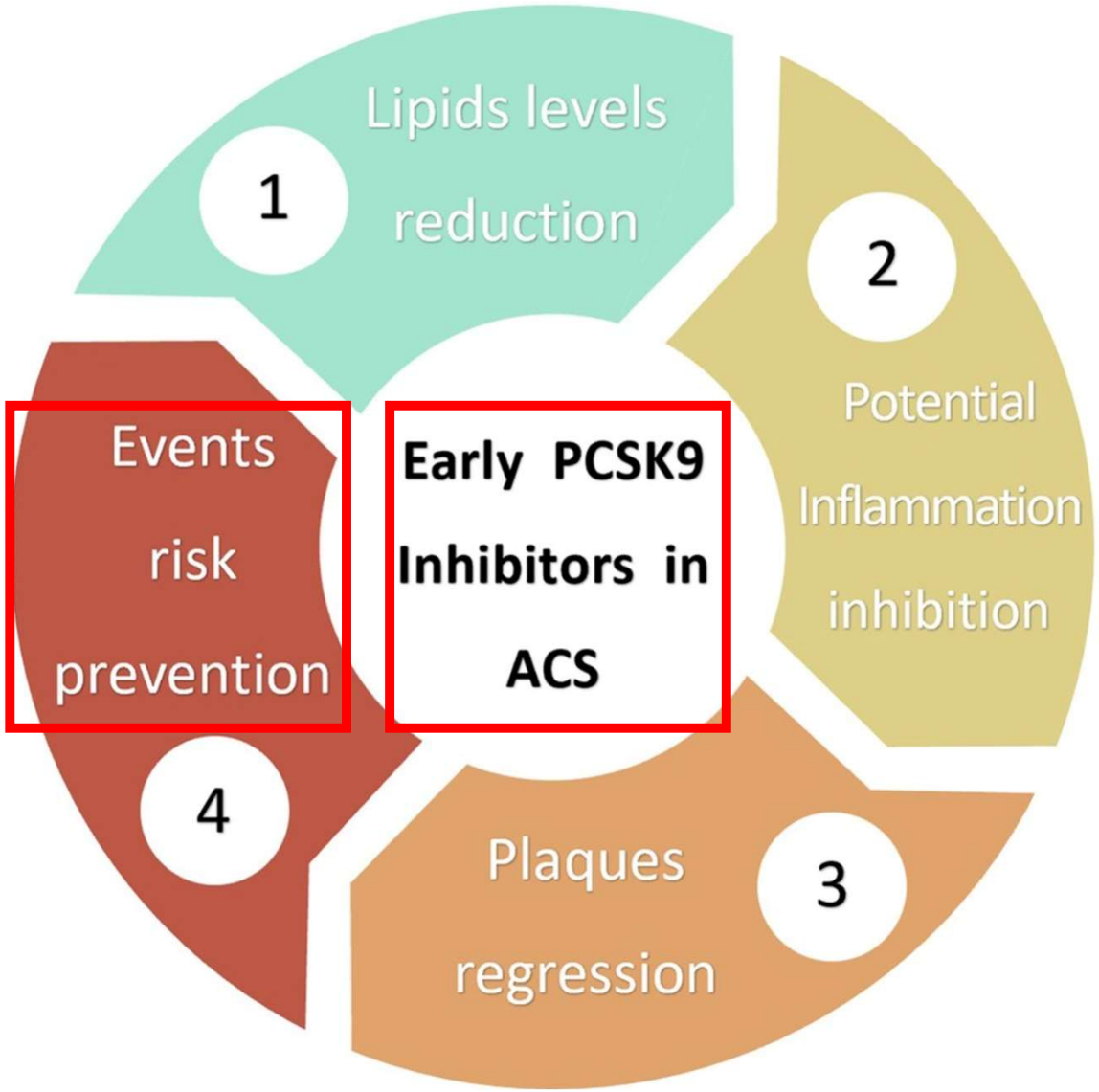


Figure 3. *Proportion in the alirocumab and sham-control groups achieving various LDL cholesterol targets at a median follow-up of 45 days. CI: confidence interval; LDL: low-density lipoprotein; OR: odds ratio*

Mehta SR, Pare G, Lonn EM et al. Eurointervention 2022

USO PRECOCE PCSK9-i
ESITI CLINICI


Lipids levels reduction
1
2
Potential Inflammation inhibition
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Events risk prevention
Early PCSK9 Inhibitors in ACS

Earlier Initiation of PCSK9i mAb therapy after index MACE is favorable

Patients:

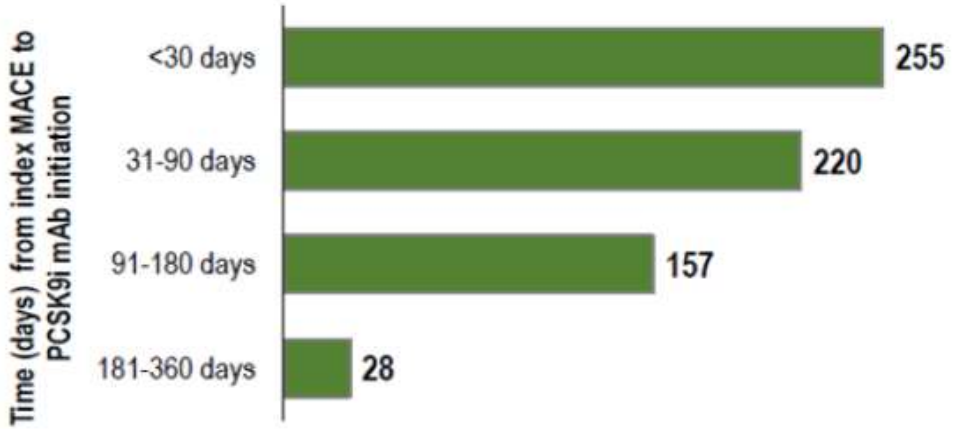
N = 58997 with PCSK9i mAb initiation on or **after index MACE**

Population: US adults (≥18 years) with ≥ 1 diagnosis or procedure code MACE (myocardial infarction, ischemic stroke, unstable angina, or coronary revascularization) during the index period*.

Outcome: To estimate rates of **subsequent MACE** based on the time to initiation of PCSK9i mAb therapy after a MACE

Data from a Retrospective, Cohort Study

Figure 3. Average time between PCSK9i mAb initiation and subsequent MACE[1]



[1]Evaluated among patients with a subsequent MACE in the post-index period.

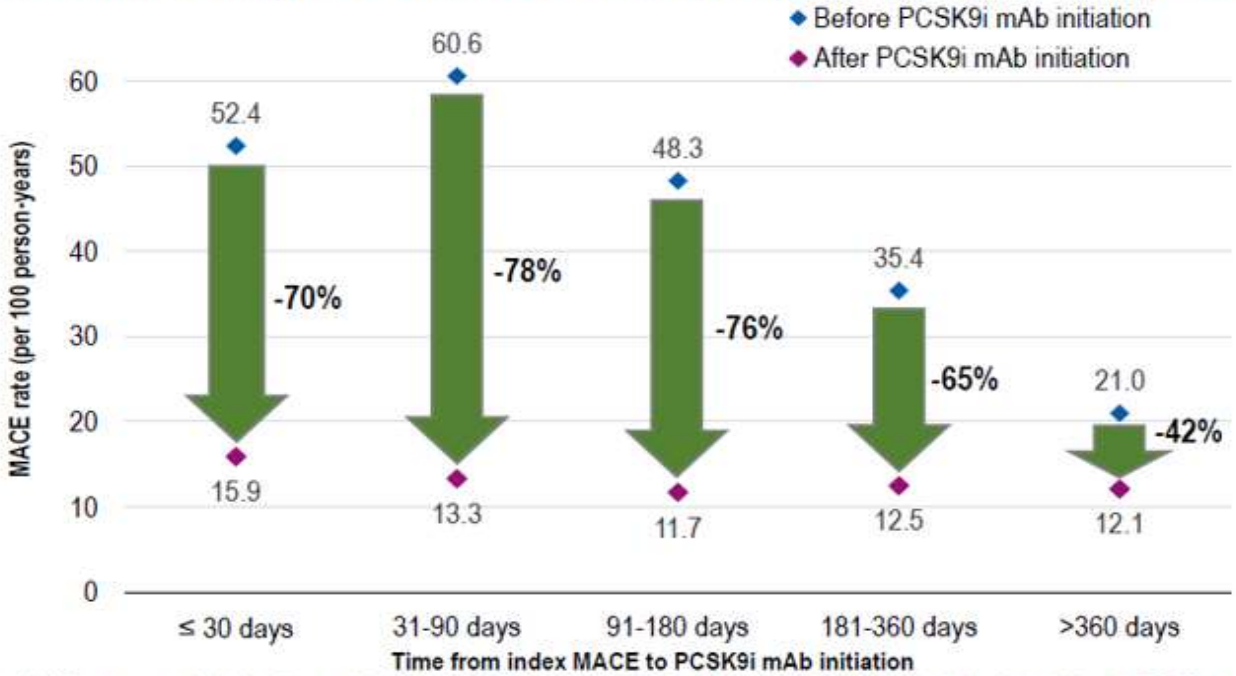
*Index period: Jan 1, 2017 – Nov 30, 2021 from IQVIA PharMetrics plus and Jan 1, 2017 – Feb 28, 2022 from open-source claim prescription (LRx) and medical (Dx) claims databases.

For patients who initiated PCSK9i mAb >360 days after the index MACE, the average time to subsequent MACE is a negative value (and is not shown in the graph) since over one-third of patients experienced ≥ 1 subsequent MACE before they received PCSK9i mAb therapy.

Martinez L, et al. Poster presented at: National Lipid Association 2023, Jun 1-4, 2023; Atlanta, GA, USA

Earlier Initiation of PCSK9i mAb therapy after index MACE is favorable

Figure 5. Relative percent change in MACE rates before and after PCSK9i mAb initiation by timing of PCSK9i mAb initiation group during the post-index period

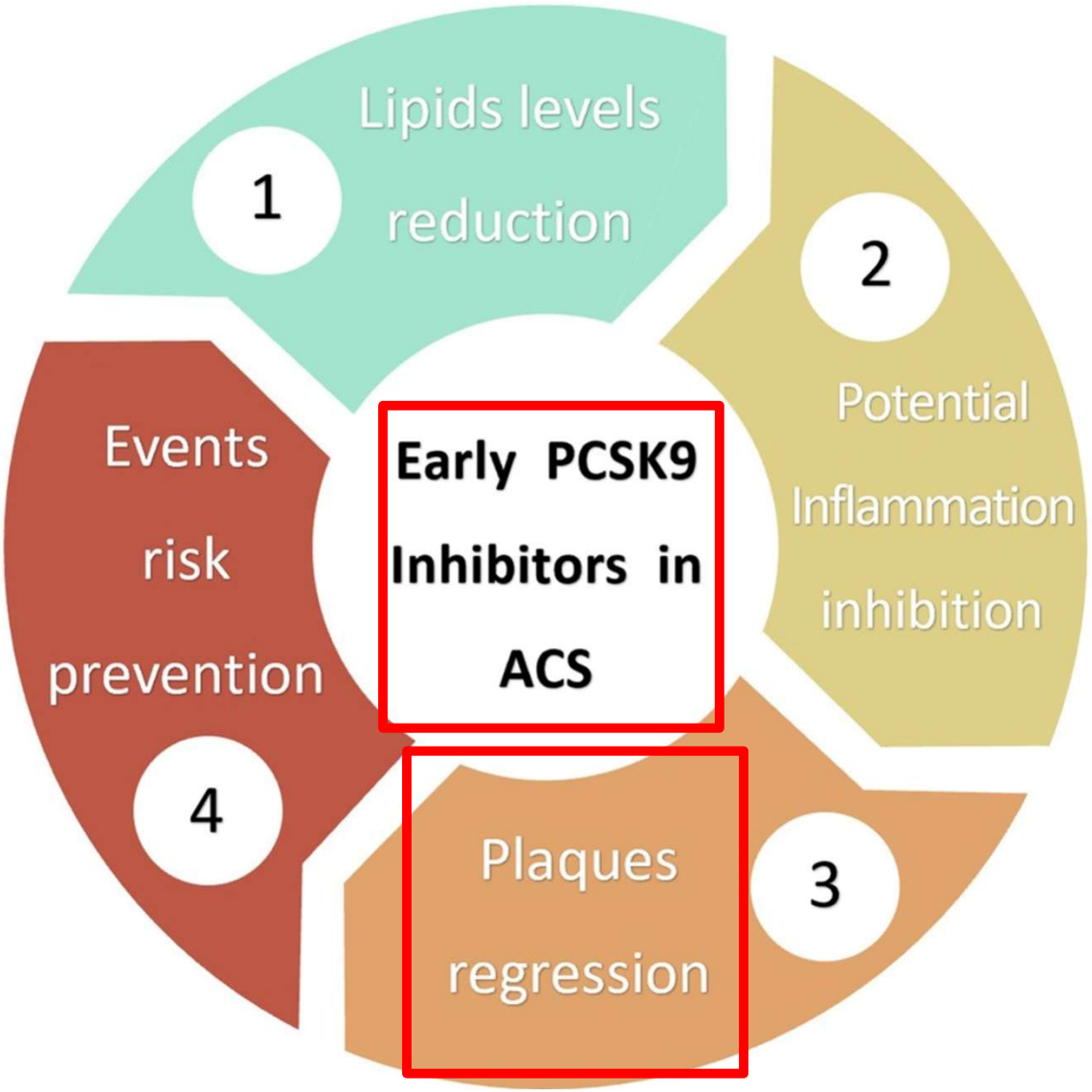


MACE rates were calculated as follows: 1) before PCSK9i mAB initiation: the total number of distinct MACE from the index date until the date PCSK9i initiation - 1 divided by total patient follow-up in years*100 in this period and 2) after PCSK9i mAB initiation: the total number of distinct MACE from the date of PCSK9i initiation until end of follow up divided by total patient follow-up in years*100 in this period

A greater reduction in the rate of subsequent MACE was observed in the groups of patients initiating PCSK9i mAb therapy early after MACE.

*Index period: Jan 1, 2017 – Nov 30, 2021 from IQVIA PharMetrics plus and Jan 1, 2017 – Feb 28, 2022 from open -source claim prescription (LRx) and medical (Dx) claims databases

Martinez L, et al. Poster presented at: National Lipid Association 2023, Jun 1-4, 2023; Atlanta, GA, USA


1
Lipids levels reduction
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Plaques regression
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Events risk prevention
Early PCSK9 Inhibitors in ACS

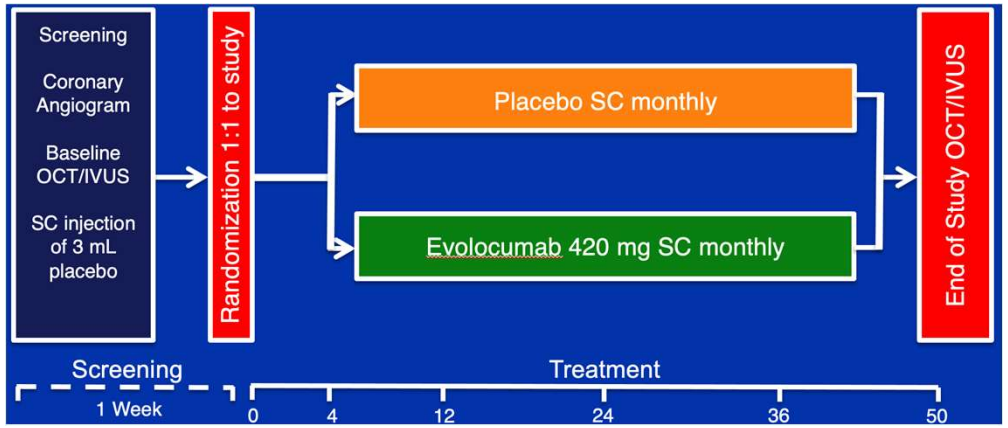
PASSIVAZIONE DELLA PLACCA

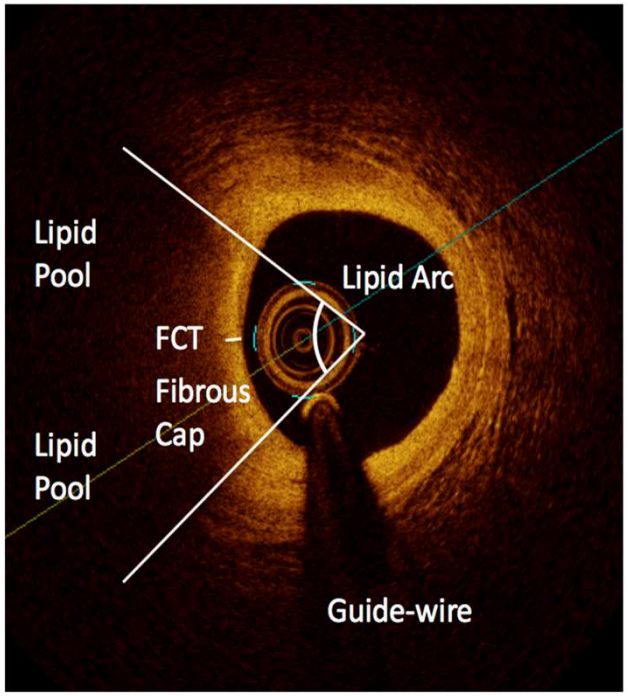
Original Article

Assessing the impact of PCSK9 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and design of the randomized, placebo-controlled HUYGENS study

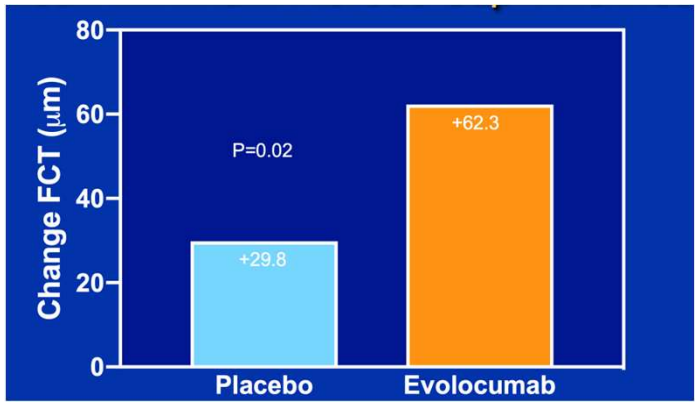
Stephen J. Nicholls, Steven E. Nissen, Francesco Prati, Stephan Windecker, Yu Kataoka, Rishi Puri, Thomas Hucko, Helina Kassahun, Jason Liao, Ransi Somaratne, Julie Butters, Giuseppe Di Giovanni, Stephen Jones, Peter J. Psaltis

160 pz
NSTEMI
LDL > 60 mg/dl
EVO 420 mg sc

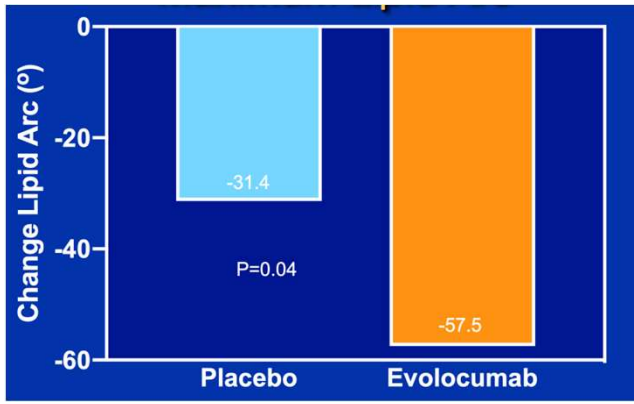




SPESSORE CAPPUCCIO FIBROSO



ARCO LIPIDICO



Nicholls SJ, Nissen SE, Prati F et al. HUYGENS Study ESC PRESENTATION 2021

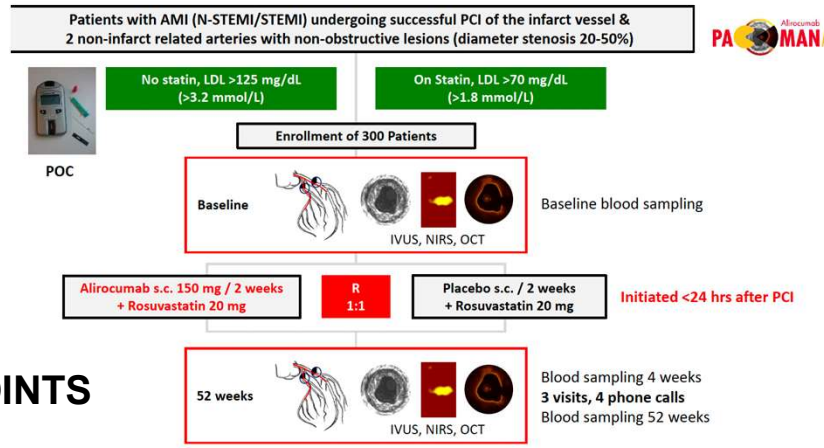
Research

JAMA | Original Investigation

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction

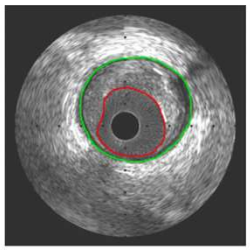
The PACMAN-AMI Randomized Clinical Trial

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

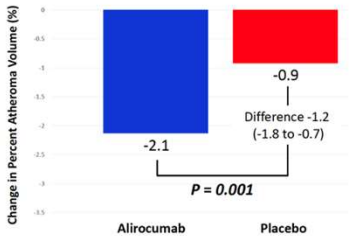


PRIMARY END POINT

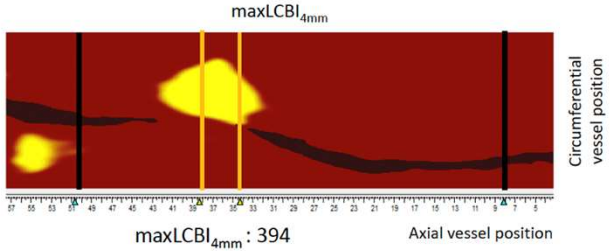
SECONDARY END POINTS



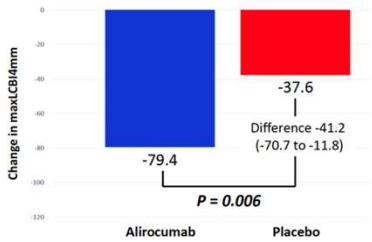
Change in **percent atheroma volume** (PAV) by **greyscale IVUS**



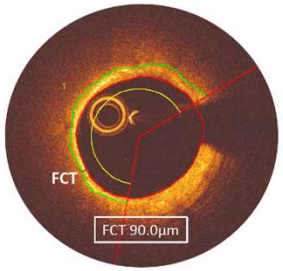
% VOLUME ATEROMA IVUS (PAV)



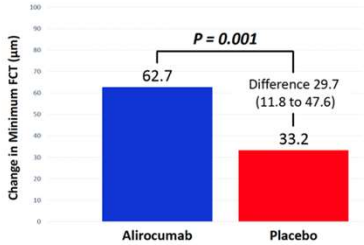
Change in **maximal lipid-core burden index** ($maxLCBI_{4mm}$) by **NIRS**



core lipidico NIRS (max LCBI $_{4mm}$)



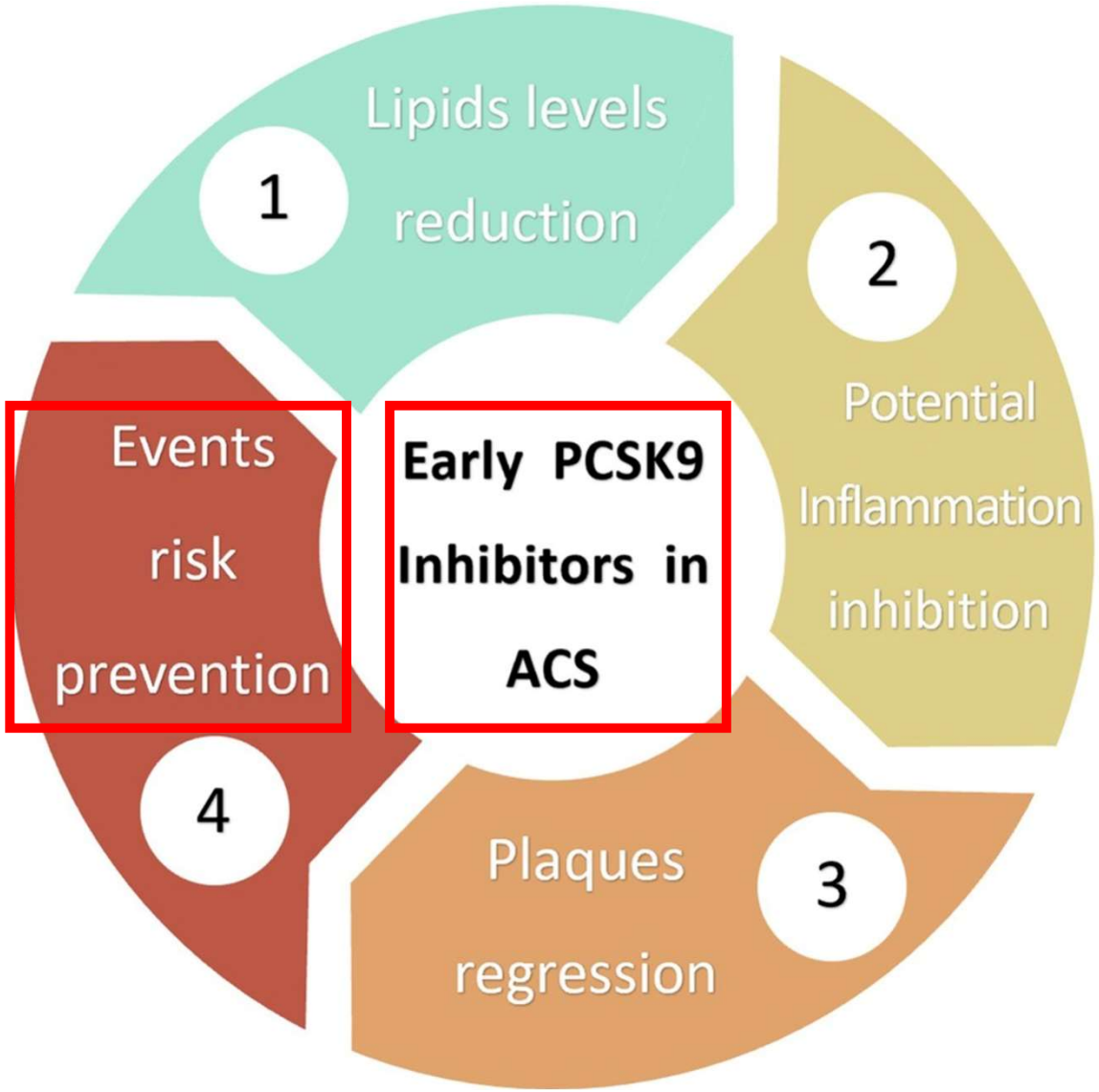
Change in **minimal fibrous cap thickness** (FCT_{min}) by **OCT**



spessore cappuccio fibroso OCT (FCT)

Raber L, Ueki Y, Otsuka T et al. J Am Med Ass 2022

END POINT PIU' AMBIZIOSO: RIDURRE LA MORTALITA'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Early PCSK9 Inhibitors in ACS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

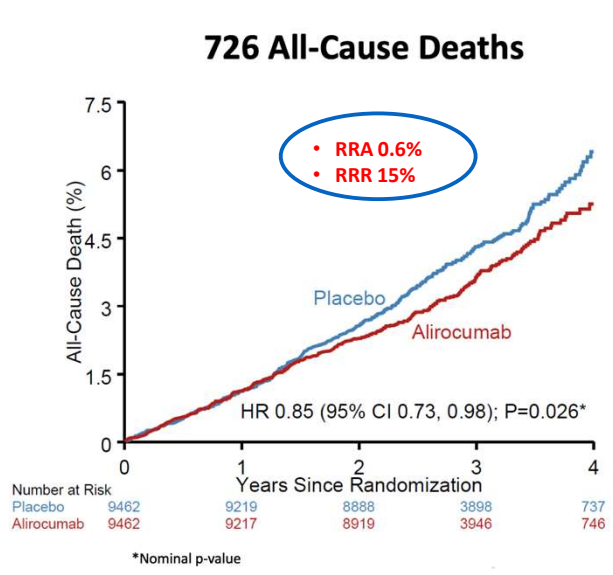
Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

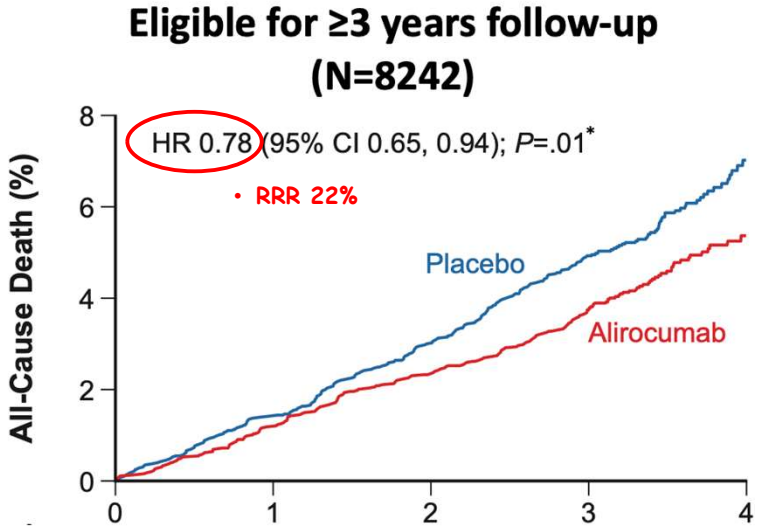
G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

ODYSSEY OUTCOMES ACC 2018

- **18924 pazienti 2012-2015 < 12 MESI ACS**
- **età media 58, donne 25%**

Death from any cause	334 (3.5)	392 (4.1)	0.85 (0.73–0.98)

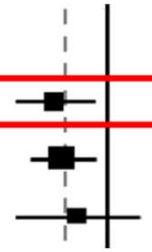




Schwartz GG, Steg PG, M Szarec et al. N Engl J Med 2018

POST ACS = PROHIBITIVE PATIENTS

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)
Index to randomization				
<2 months	6178	10.3	12.3	0.83 (0.71–0.96)
2 to <6 months	9518	9.6	11.1	0.85 (0.75–0.96)
≥6 months	3228	8.0	8.7	0.90 (0.71–1.14)



INIZIARE INIBITORE PCSK9 ALLA DIMISSIONE

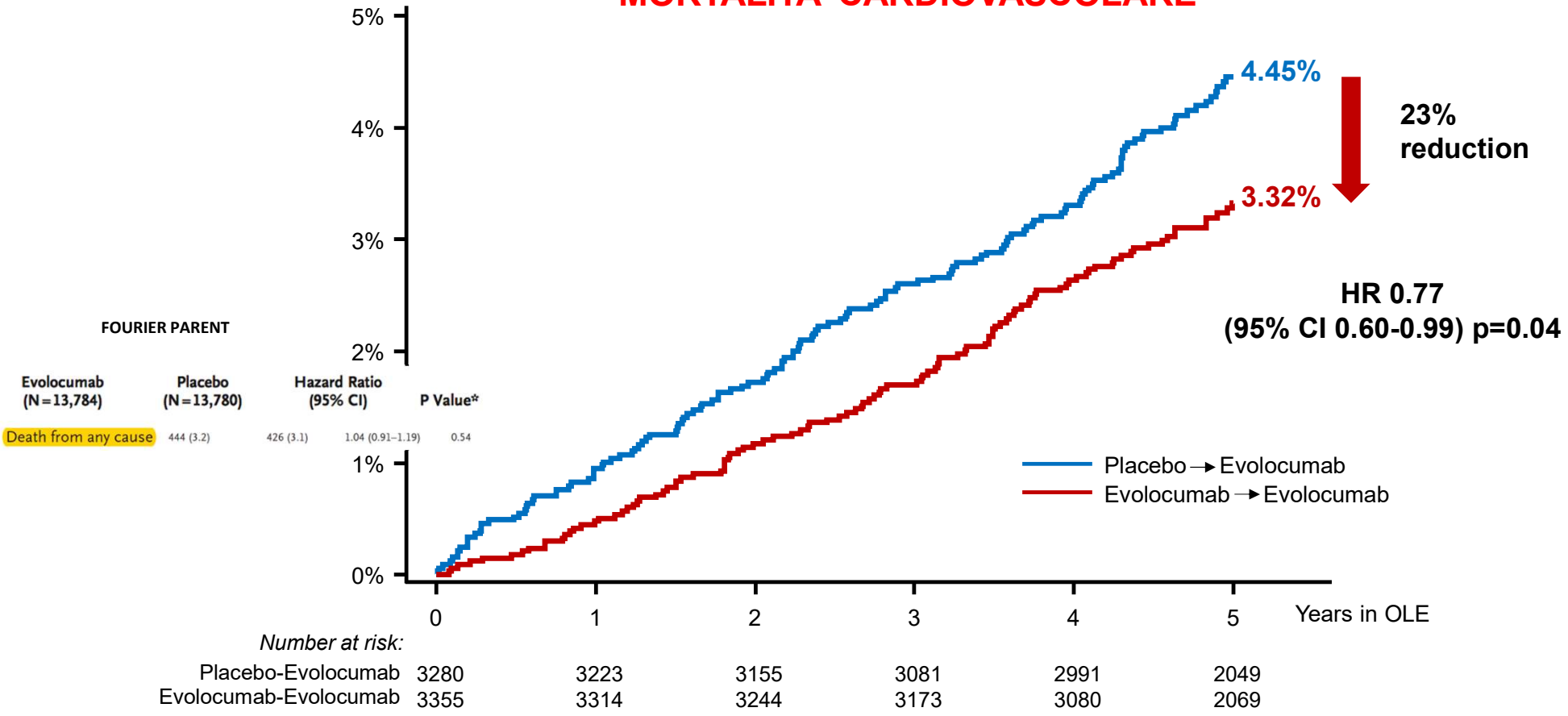
For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.	IIa	C

Mach F, Baigent C, Catapano A et al. Eur Heart J 2019
Parigi 31 Ago/4 Set 2019

Schwartz GG, Steg PG et al. N Engl J Med 2018

Efficacy During FOURIER-OLE Time Period

MORTALITA' CARDIOVASCOLARE



FOURIER PARENT

	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54

Number at risk:

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

CI, confidence interval; CV, cardiovascular; HR, hazard ratio

O'Donoghue M, Giugliano RP, Wiviott SD et al. Circulation 2022

SIAMO ANCORA MOLTO INDIETRO

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

Kausik K. Ray,[a,*] Inaam Haq,[b] Aikaterini Bilitou,[c] Marius C. Manu,[b] Annie Burden,[d] Carlos Aguiar,[e] Marcello Arca,[f] Derek L. Connolly,[g] Mats Eriksson,[h] Jean Ferrières,[i] Ulrich Laufs,[j] Jose M. Mostaza,[k] David Nanchen,[l] Ernst Rietzschel,[m] Timo Strandberg,[n,o] Hermann Toplak,[p] Frank L. J. Visseren,[q] and Alberico L. Catapano,[r,s] on behalf of the SANTORINI Study Investigators[t]

9044 pazienti LLT post 2019

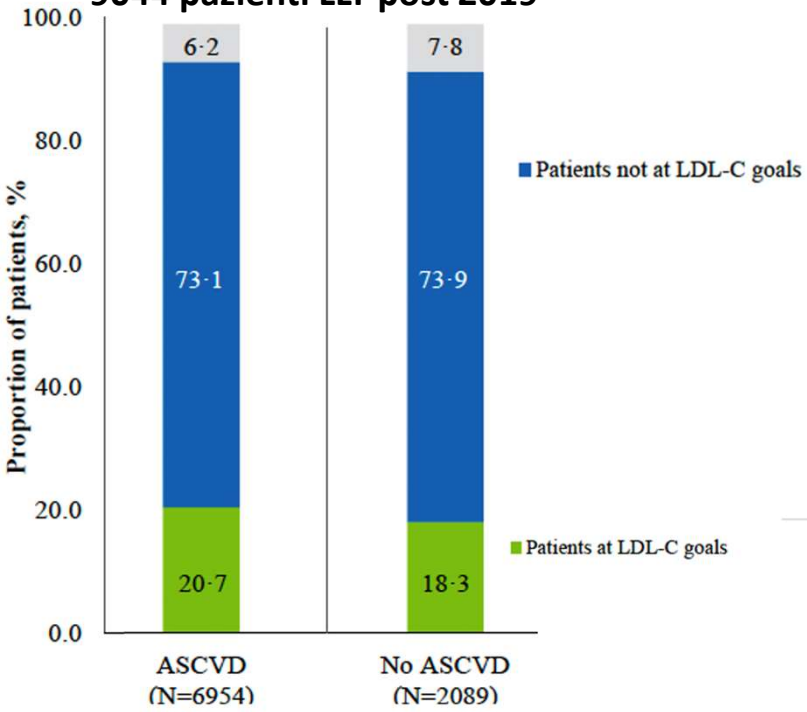


Fig. 1: LDL-C goal attainment by CV risk, ASCVD status

ESC European Society of Cardiology
European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwaa047
FULL RESEARCH PAPER

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

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

5888 pazienti LLT in 18 paesi europei post 2016

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

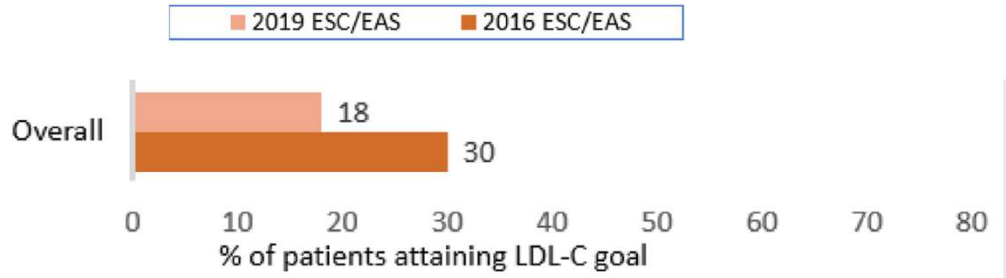


Fig. 1. LDL-C goal attainment in ASCVD patients: 2016 ESC/EAS *versus* 2019 ESC/EAS guideline goals.

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

Jane K Stock . Atherosclerosis 2020

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

JET LDL

N=1095 post SCA e post PCI (STEMI 50% NSTEMI 50%)

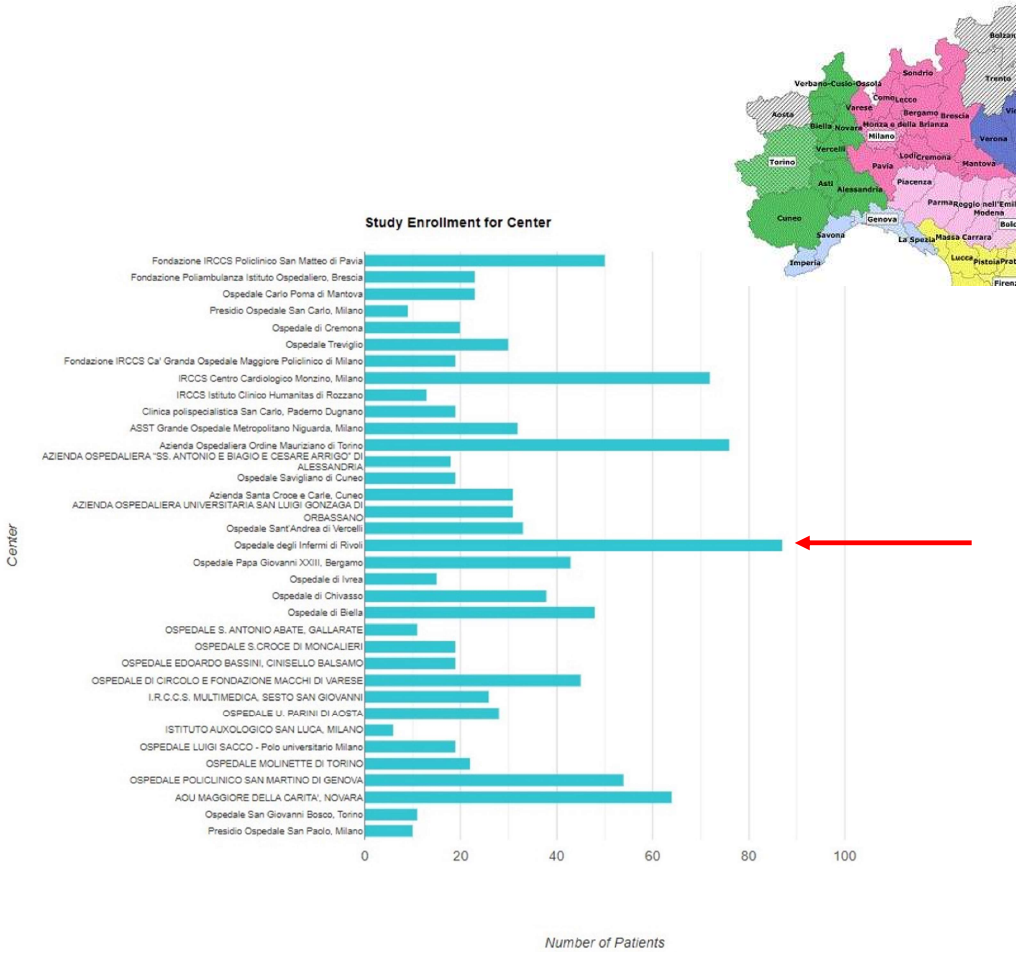
Raggiungimento di livelli target di colesterolo LDL in pazienti con sindrome coronarica acuta trattati con angioplastica coronarica percutanea: il registro JET-LDL

PI: Marco Ferlini, Luigi Oltrona Visconti, Giuseppe Musumeci

Steering Committee: Andrea Rognoni, Ferdinando Varbella, Giuseppe Patti, Battistina Castiglioni, Corrado Lettieri, Italo Porto, Alberto Menozzi

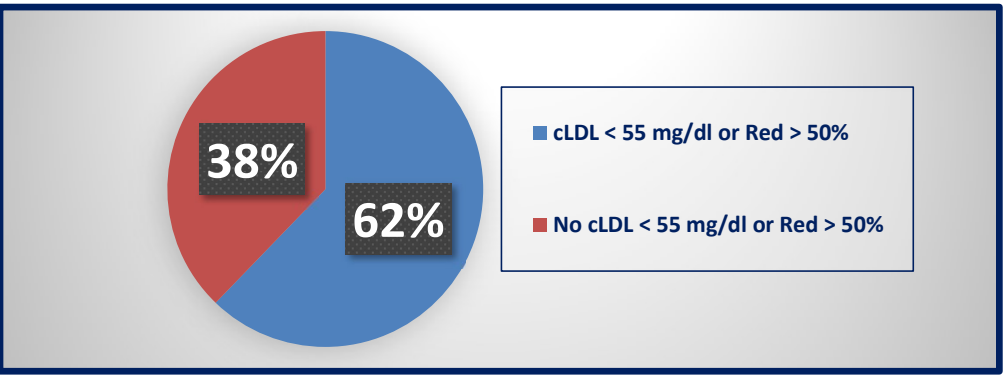
Study Coordinator: Alessia Currao

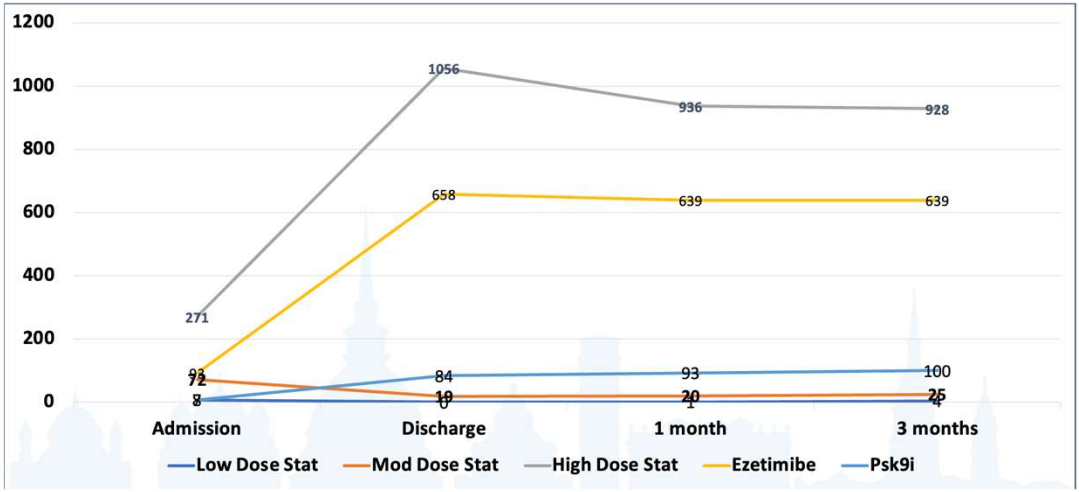
- **Scopo:** Ottimizzare il trattamento dei livelli di colesterolo (C)-LDL nei pazienti SCA trattati con PCI
- **Obiettivo:** Valutare il successo e descrivere le modalità di trattamento farmacologico del C-LDL volte al raggiungimento dei livelli raccomandati per una popolazione di pazienti con SCA trattati con PCI
- **End Pointi Primario**: Tasso di pazienti con riduzione del C-LDL di almeno il 50% rispetto al valore basale o con valori di C-LDL < 55 mg/dl a 1 mese dalla dimissione ospedaliera

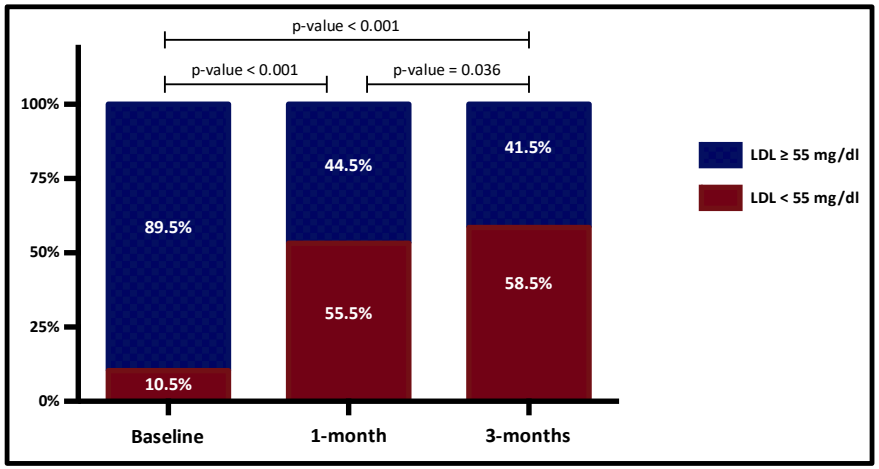


Ferlini M, Munafo' A, Varbella F et al. European Journal of Preventive Cardiology 2023

JET LDL





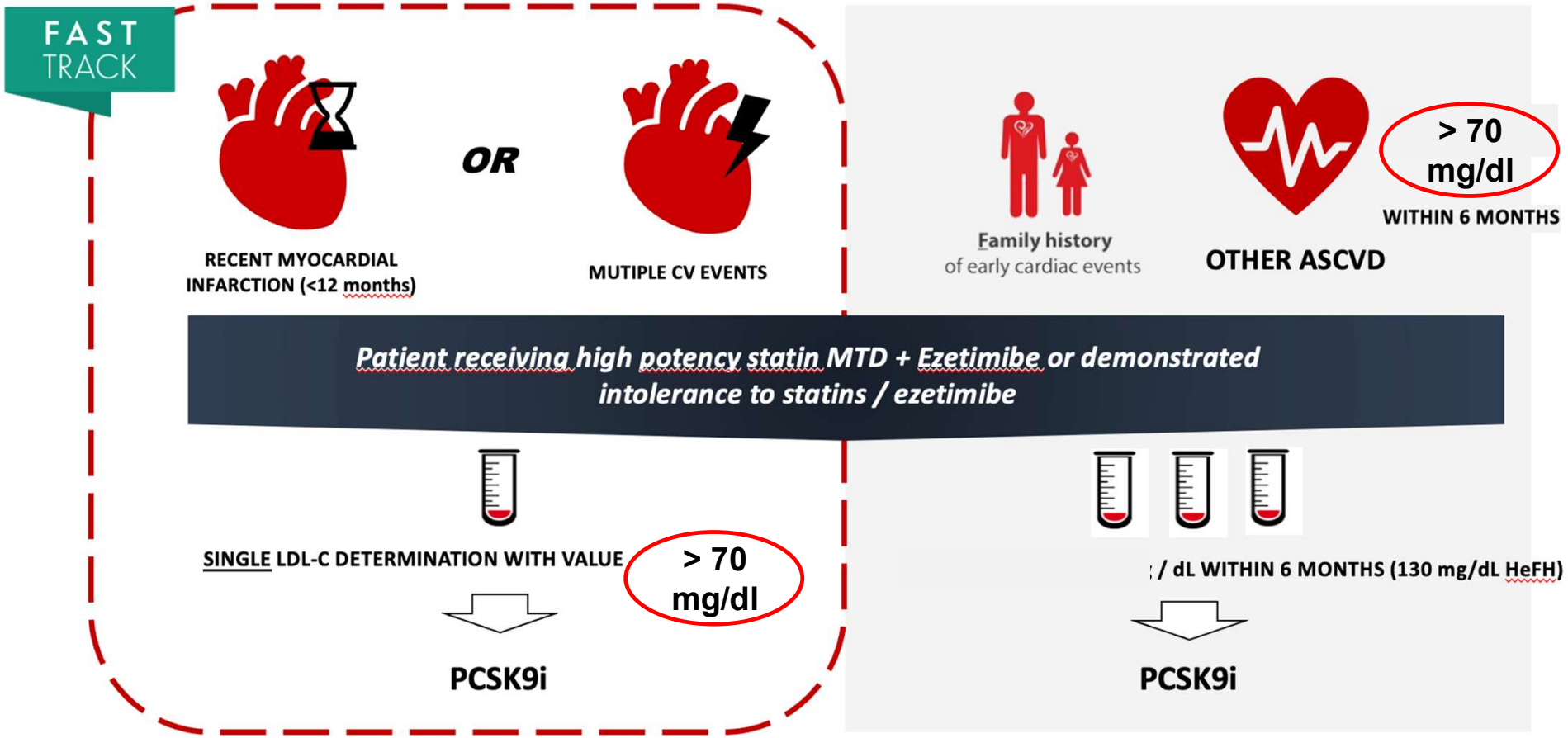


- **livelli di C-LDL a target raggiunti in circa il 60% dei casi**
- **prescrizione dei PCSK9i è stata tuttavia limitata a meno del 10% dei pazienti**
- **La terapia ipolipemizzante sembra essere ottimizzata per lo più alla dimissione ospedaliera il che suggerisce la necessità di un trattamento aggressivo precoce**

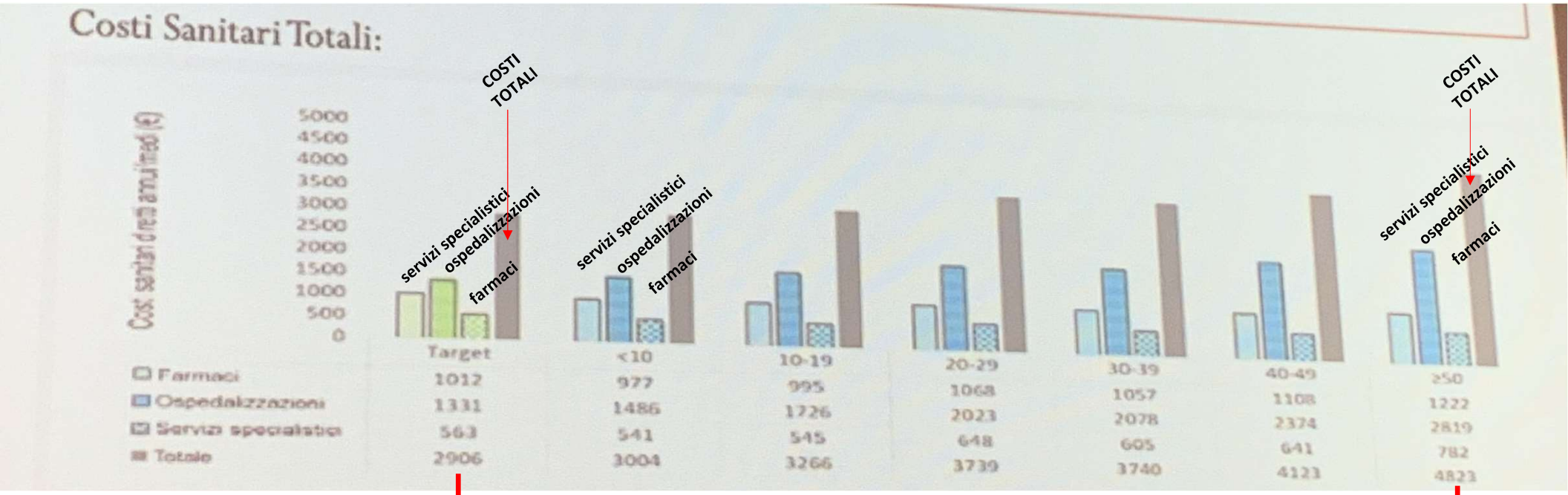
Ferlini M, Munafo' A, Varbella F et al. European Journal of Preventive Cardiology 2023

CRITERI DI RIMBORSABILITA' E SOSTENIBILITA' ECONOMICA

CRITERI DI PRESCRIVIBILITA’



COSTI SANITARI DIRETTI MEDI ANNUI PER PAZIENTE IN BASE AL RAGGIUNGIMENTO DEL TARGET

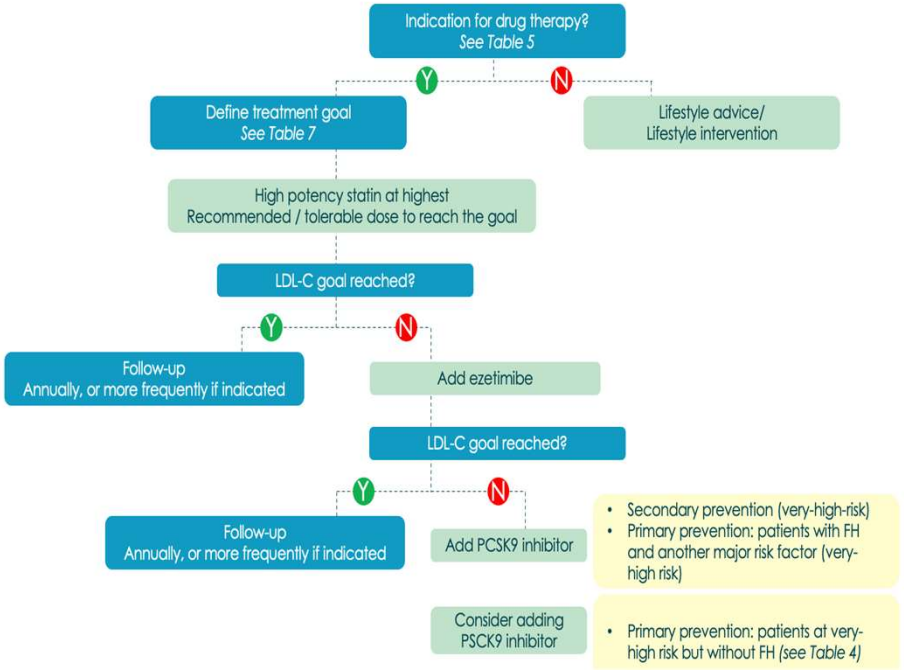


2.906 euro **vs** **4.823 euro**

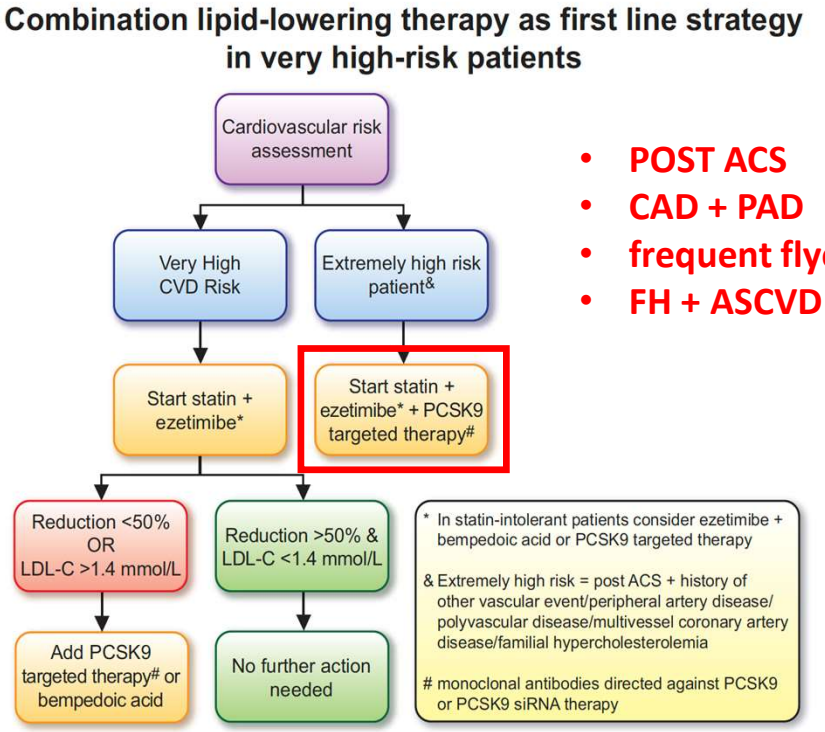
Degli Esposti L, Borghi C, Galvani M et al. Abstract 796 GIFAC 2022

CONCLUSIONI

E' IL MOMENTO DI MODIFICARE STEPWISE APPROACH ?



Mach F. et al. ESC 2019 European Heart Journal 2019/20



- **POST ACS**
- **CAD + PAD**
- **frequent flyers**
- **FH + ASCVD**

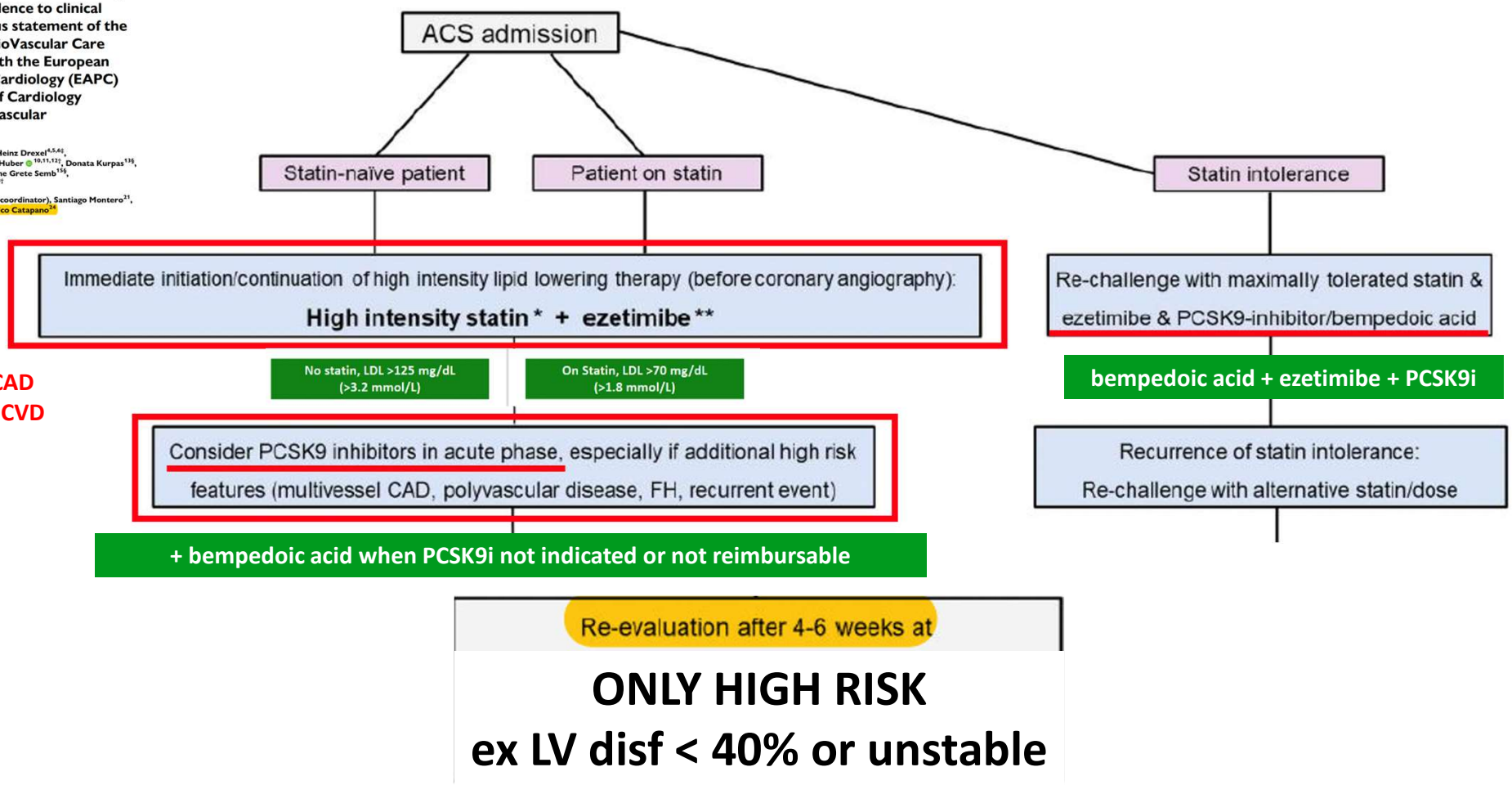
Ray KK, Reeskamp LF, Laufs U et al. Eur Heart J 2022

ESC European Society of Cardiology
European Heart Journal: Acute Cardiovascular Care (2022) 11, 939–949 https://doi.org/10.1093/ehjacc/zuac123
REVIEW
Acute Coronary Syndromes

Acute LDL-C reduction post ACS: strike early and strike strong: from evidence to clinical practice. A clinical consensus statement of the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

Konstantin A. Krychtiuk[1,2†], Ingo Ahrens[3†], Heinz Drexel[4,5,6†], Sigrun Halvorsen[7,8†], Christian Hassager[9†], Kurt Huber[10,11,12†], Donata Kurpas[13†], Alexander Niessner[14], Francesco Schiele[14†], Anne Grete Semb[15†], Alessandro Sionis[16,17†], and Marc J. Claeys[18†]

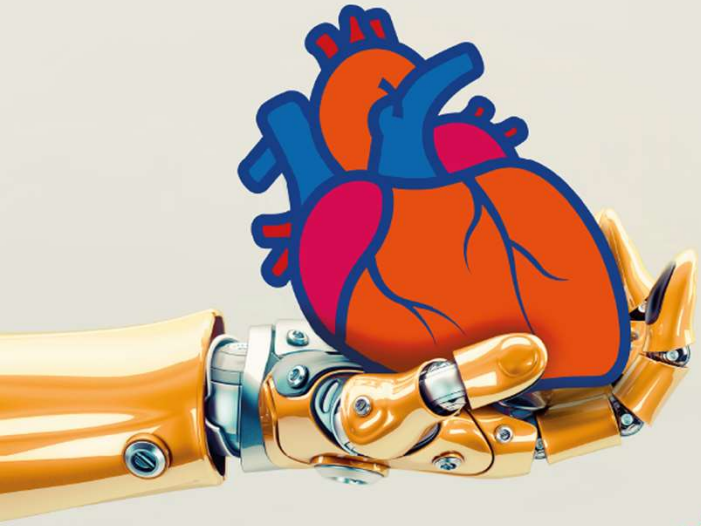
Document reviewers: José Barrabes[19,20] (review coordinator), Santiago Montero[21], Peter Sinnaeve[22], Roberto Pedretti[23], and Alberico Catapano[24]



- multivessel CAD
- CAD + PAD + CVD
- DIABETES
- RECURRENT
- ACS
- FH

ONLY HIGH RISK
ex LV disf < 40% or unstable

Krychiuk KA, Ahrens I, Drexel H et al. Eur Heart J ACC 2022



17° Meeting

CardioLucca

Heart Brings Heart 2023

Lucca, 22-24 Giugno 2023

Centro Congressi Auditorium San Francesco

GRAZIE PER L'ATTENZIONE

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Head of Internal Medicine Department
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Orbassano (To)