THE CASE FOR EARLY LDL-C LOWERING IN PATIENTS AT INCREASED CV RISK WHEN SHOULD WE START

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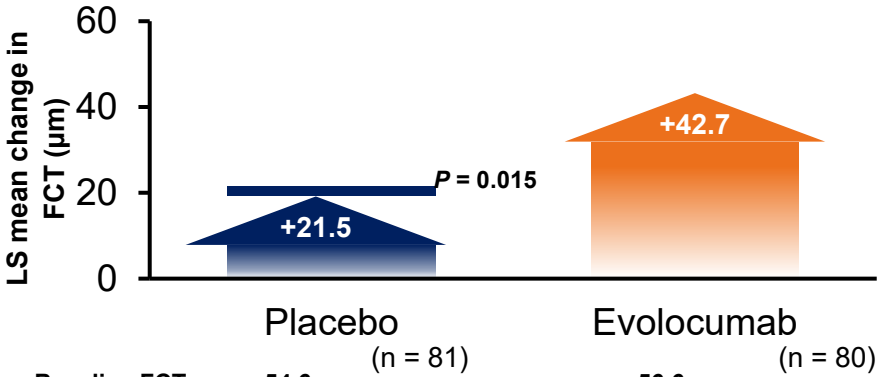
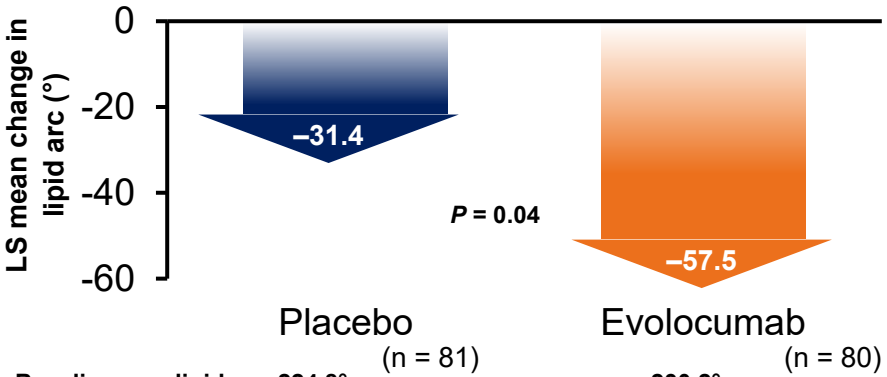
Evolocumab improved features of plaque stability compared with placebo

HUYGENS Primary Endpoint: Minimum FCT[1]



Baseline FCT: **54.6 µm** **56.6 µm**

HUYGENS Secondary Endpoint: Maximum Lipid Arc[1]



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

At the end of the study, only 12.5% of patients in the evolocumab group had at least one image with a minimum FCT < 65 µm, compared with 30.2% of patients in the placebo group; between-group difference *P* = 0.02 (exploratory endpoint).[1]

FCT is described as the signal-rich region between the lumen and signal-poor necrotic lipid core in OCT; FCT < 65 µm suggests a thin fibrous cap associated with vulnerable plaque.[2,3] Lipid arc is described as the widest arc demarcating a signal-poor region with diffuse borders in OCT. A wide lipid arc (> 90°) suggests increased lipid content.[2] The primary and secondary endpoints were analyzed using ANCOVA.[4]

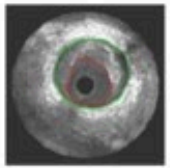
This trial was not designed to assess a correlation between changes in FCT and cardiovascular events.

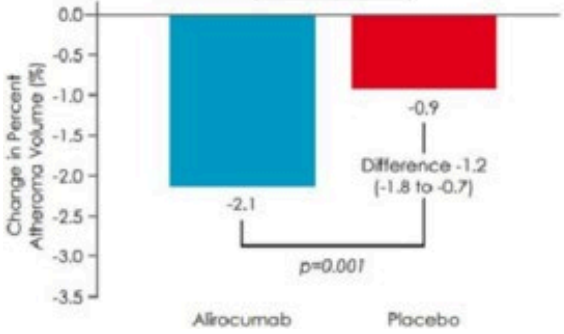
ANCOVA, analysis of covariance; FCT, fibrous cap thickness; LS, least squares; OCT, optical coherence tomography.

1. Nicholls SJ, et al. [published online ahead of print March 16, 2022]. *JACC Cardiovasc Imaging*. doi:10.1016/j.jcmg.2022.03.002. 2. Stefanidis C, et al. *J Am Heart Assoc*. 2017;6:e005543.
3. Komukai K, et al. *J Am Coll Cardiol*. 2014;64:2207-2217. 4. Nicholls SJ, et al. *Cardiovasc Diagn Ther*. 2021;11:120-129.

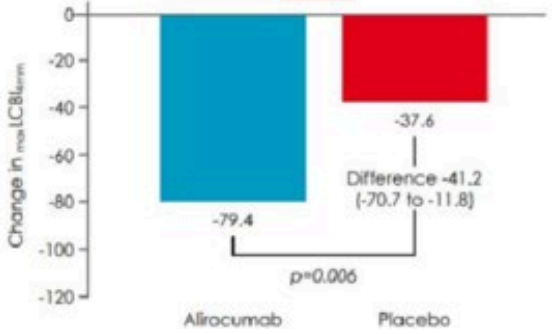
Alirocumab **reduces plaque burden** in **non-culprit** plaques

Primary EP:
Change in Percent Atheroma Volume (IVUS)

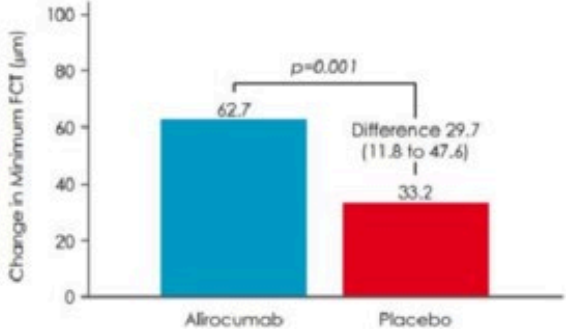




Powered Secondary EP:
Change in maxLCBI$_{4mm}$ (NIRS)

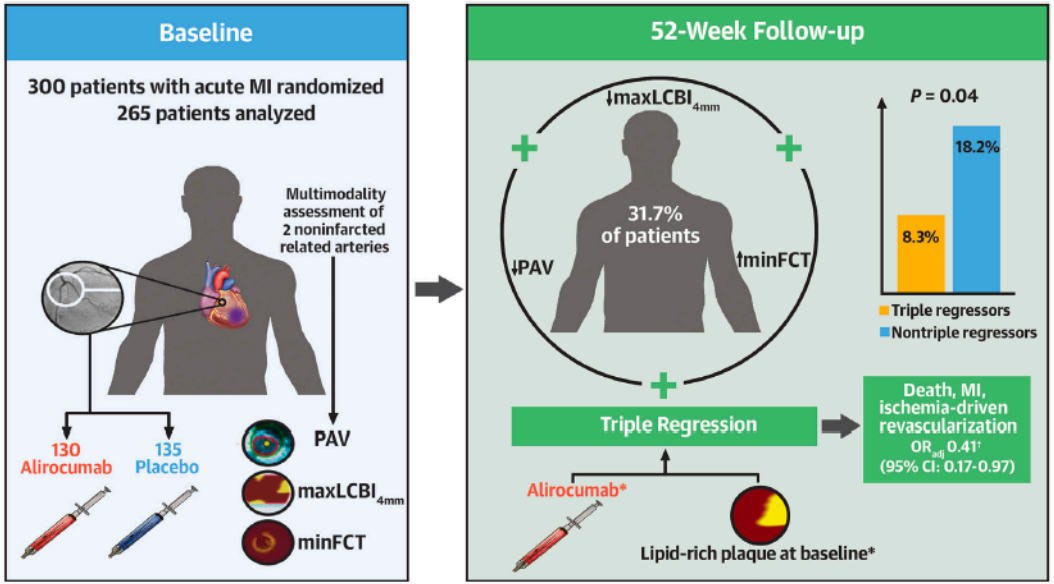


Powered Secondary EP:
Change in Minimum FCT (OCT)



De Luca & Halasz, Eur Heart J Suppl 2023;25(Suppl C):C90-C95.

CENTRAL ILLUSTRATION Triple Regression in Patients With Acute Myocardial Infarction Treated With High-Intensity Lipid-lowering Therapy



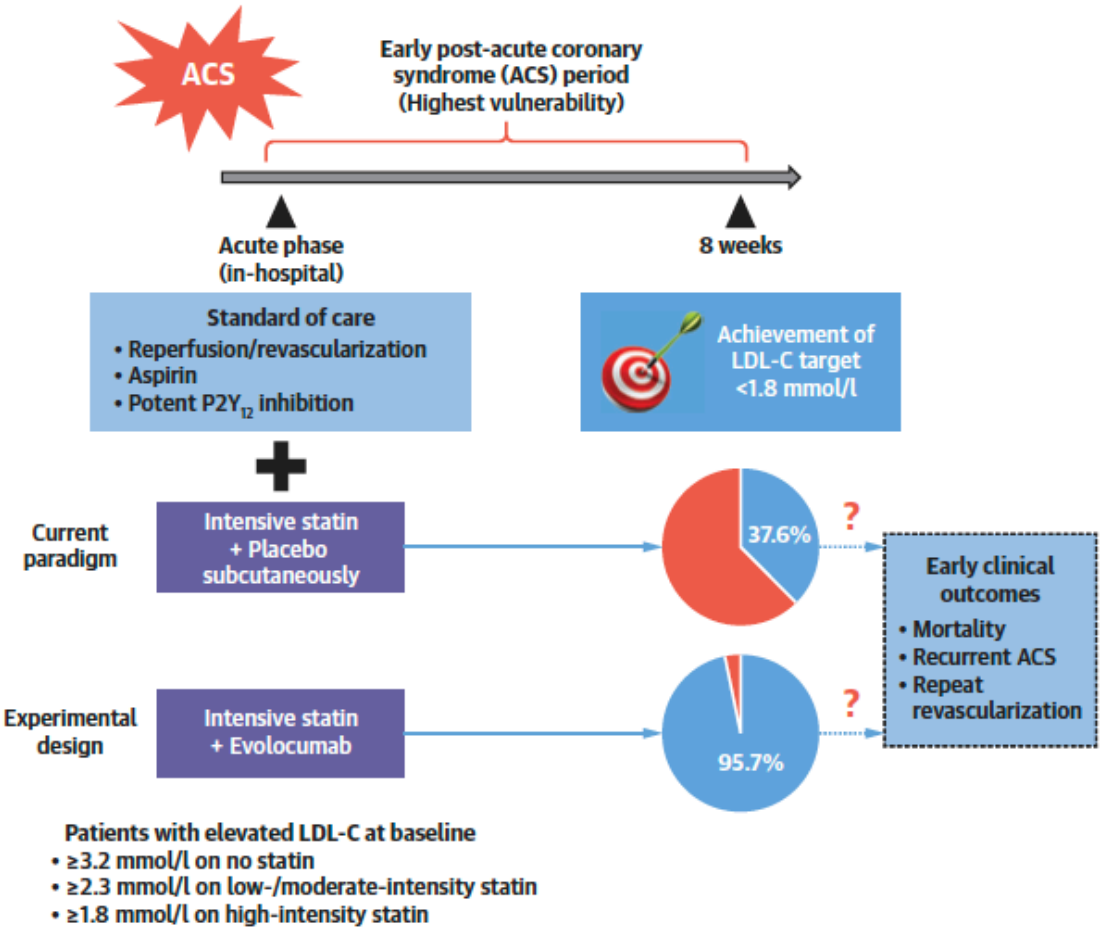
Biccirè FG, et al. J Am Coll Cardiol. 2023;82(18):1737-1747.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 74, NO. 20, 2019

PUBLISHED BY ELSEVIER

Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS)

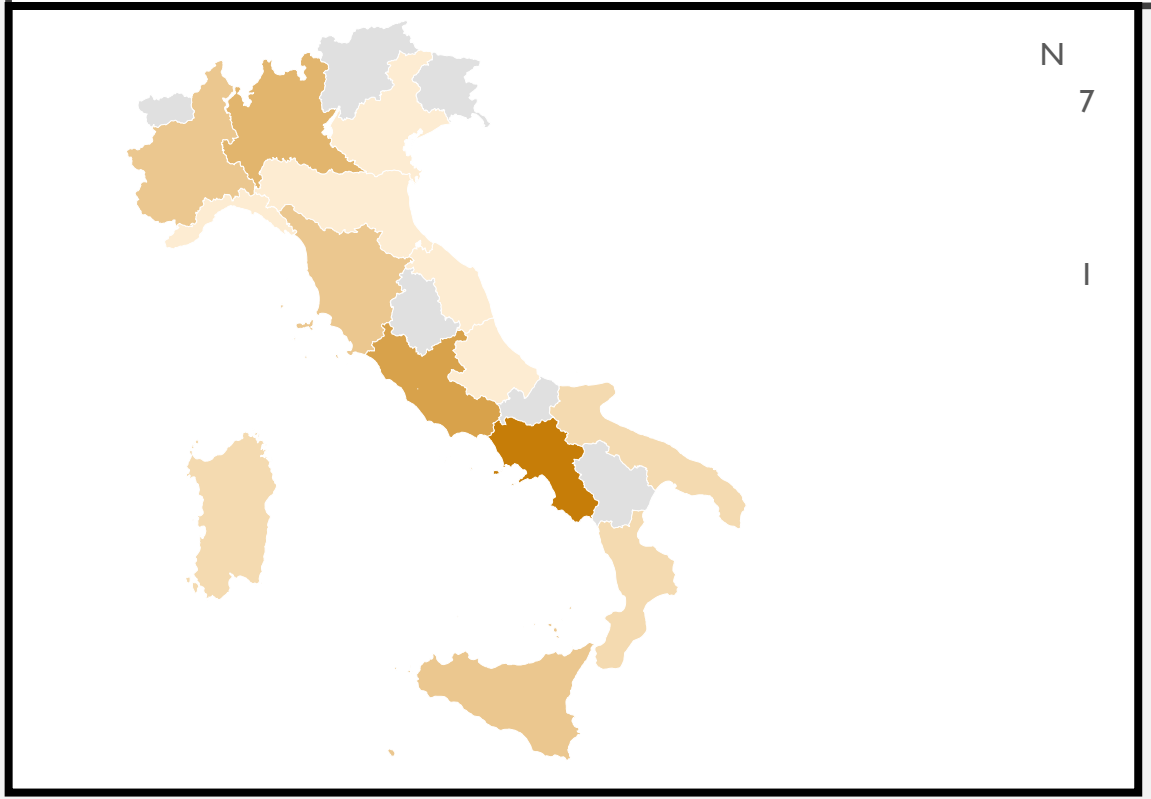
CENTRAL ILLUSTRATION Evolocumab in Patients With Acute Coronary Syndrome



Koskinas, K.C. et al. J Am Coll Cardiol. 2019;74(20):2452–62.

STRIKE EARLY-STRIKE STRONG LIPID-LOWERING STRATEGY WITH PCSK9I IN ACS PATIENTS. REAL-WORLD EVIDENCE FROM AT-TARGET-IT REGISTRY

GARGIULO P, … PERRONE FILARDI P. AT TARGET IT INVESTIGATORS. EUR J PREV CARDIOLOGY 2024



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GIAMPAOLO **NICCOLI**
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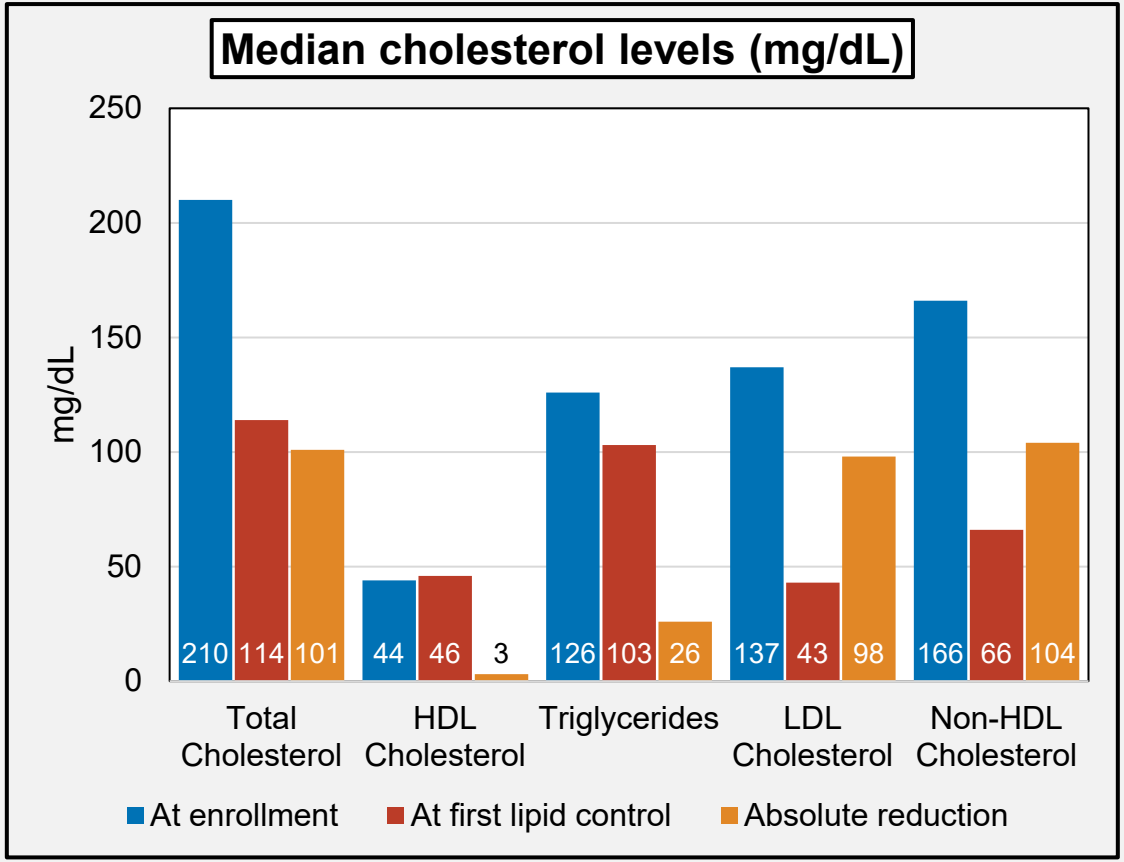
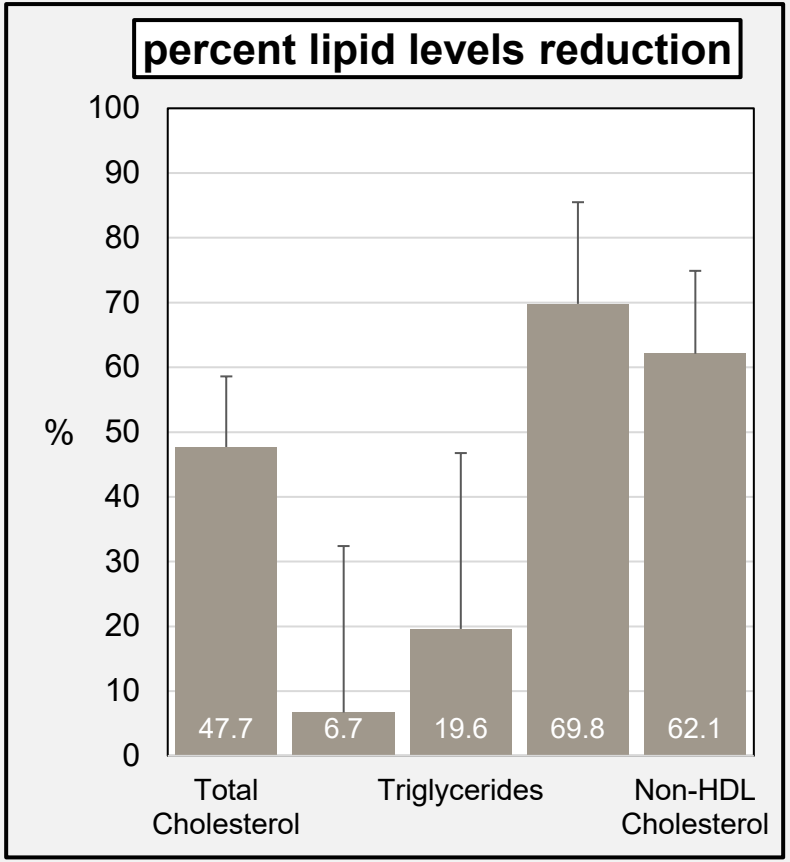
MARCO **PEPE**
ALBERTO **POLIMENI**
ITALO **PORTO**
FILIPPO MARIA **SARULLO**
ELIO **VENTURINI**

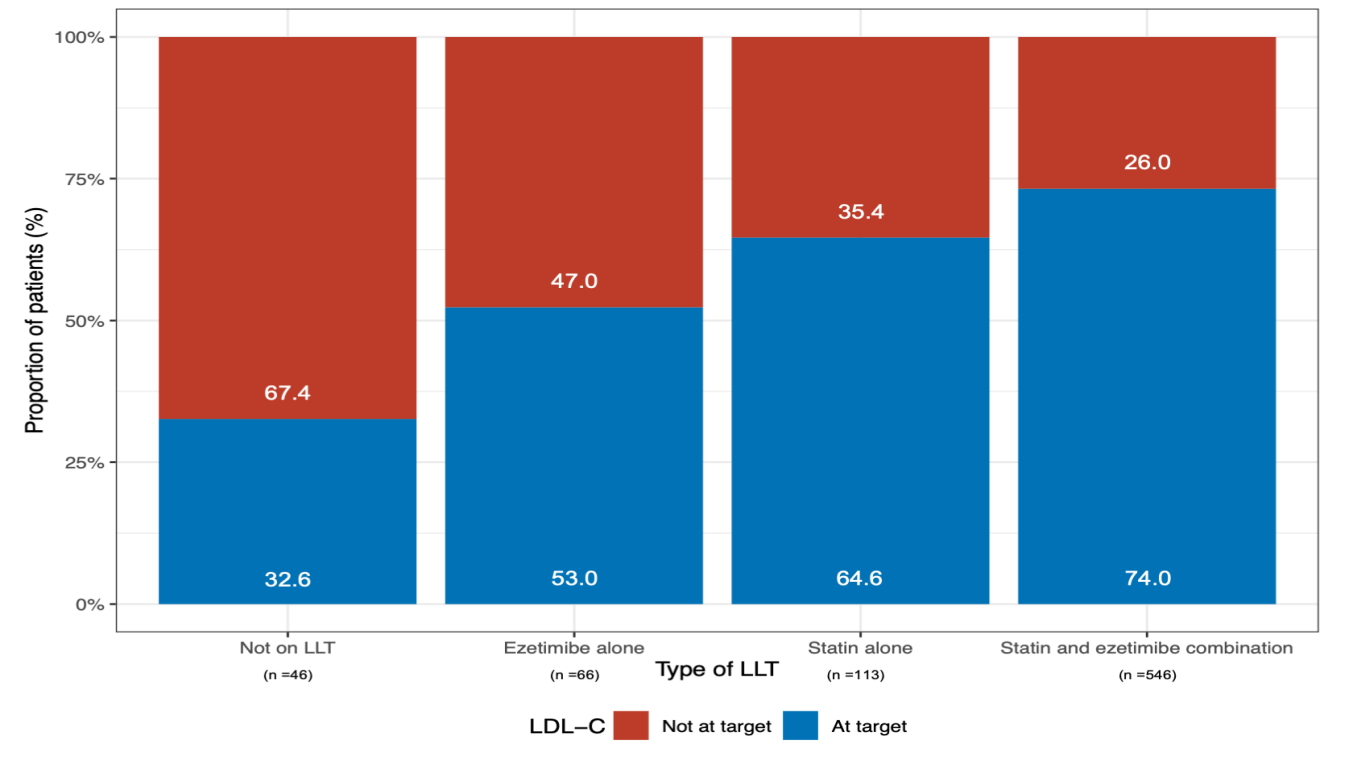
BASELINE CHARACTERISTICS OF ENROLLED PATIENTS

	Overall (N = 771)	**Alirocumab (n = 265)**	**Evolocumab (n = 506)**	**p-value**
Age (mean (SD))	62.25 (9.94)	61.53 (10.08)	62.63 (9.85)	0.145
Male sex (%)	610 (79.1)	218 (82.3)	392 (77.5)	0.144
BMI (mean (SD))	27.18 (3.57)	27.55 (3.60)	26.99 (3.55)	0.039
FH (%)	64 (8.3)	32 (12.1)	32 (6.3)	0.009
Family history of ACS (%)	336 (43.6)	132 (49.8)	204 (40.3)	0.014
Hypertension (%)	568 (73.7)	198 (74.7)	370 (73.1)	0.696
DM (%)	148 (19.2)	67 (25.3)	81 (16.0)	0.003
DM duration in months (mean (SD))	103.06 (84.83)	95.88 (86.03)	108.87 (83.94)	0.364
Smoke (%)	331 (42.9)	109 (41.1)	222 (43.9)	0.513
CCS (%)	478 (62.0)	167 (63.0)	311 (61.5)	0.730
PAD (%)	139 (18.0)	51 (19.2)	88 (17.4)	0.591
HF (%)	147 (19.1)	55 (20.8)	92 (18.2)	0.443

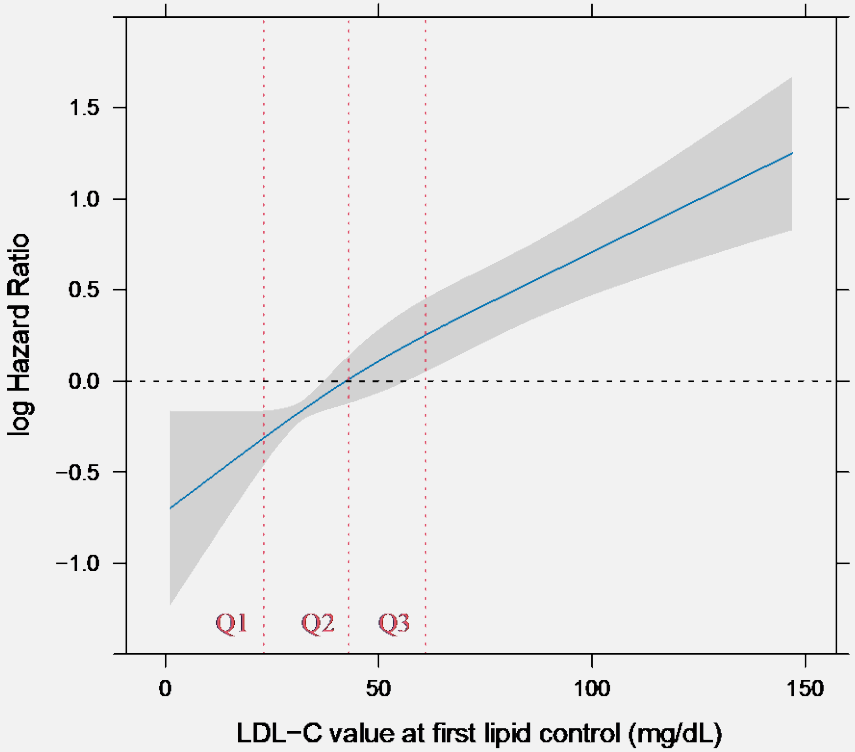

Median cholesterol levels (mg/dL)
250
200
150
100
50
0
mg/dL
210
114
101
44
46
3
126
103
26
137
43
98
166
66
104
Total Cholesterol
HDL Cholesterol
Triglycerides
LDL Cholesterol
Non-HDL Cholesterol
At enrollment
At first lipid control
Absolute reduction

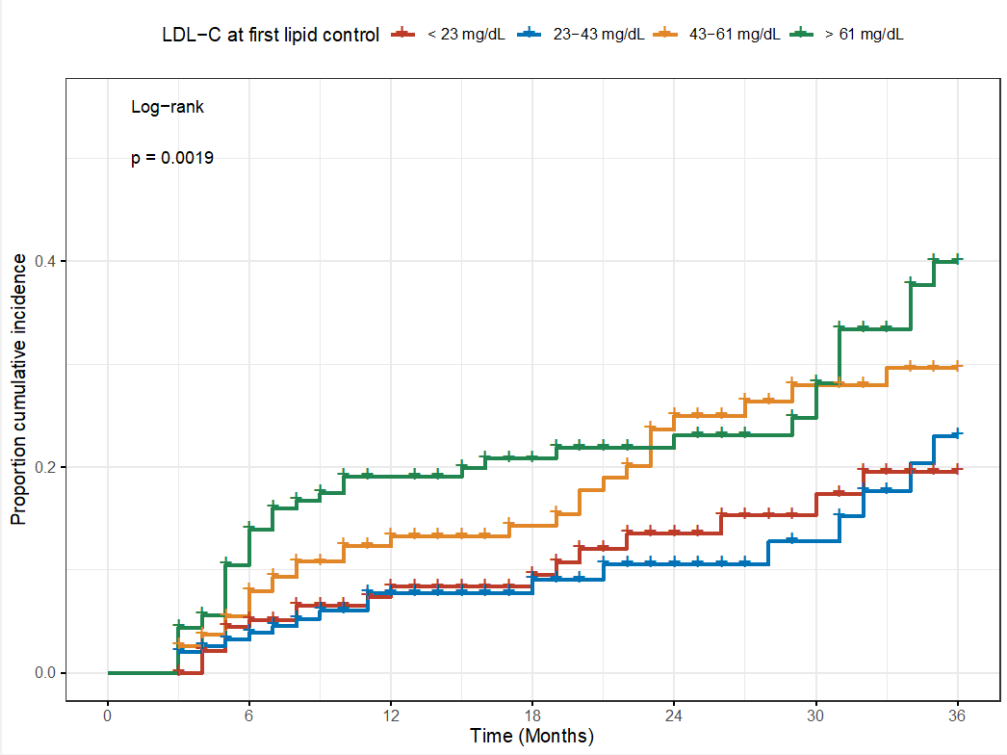

percent lipid levels reduction
100
90
80
70
60
50
40
30
20
10
0
%
47.7
6.7
19.6
69.8
62.1
Total Cholesterol
Triglycerides
Non-HDL Cholesterol

PATIENTS ACHIEVING LDL-C TARGET AT FIRST LIPID CONTROL (median 33 days from acs), STRATIFIED BY BASELINE LIPID LOWERING THERAPY

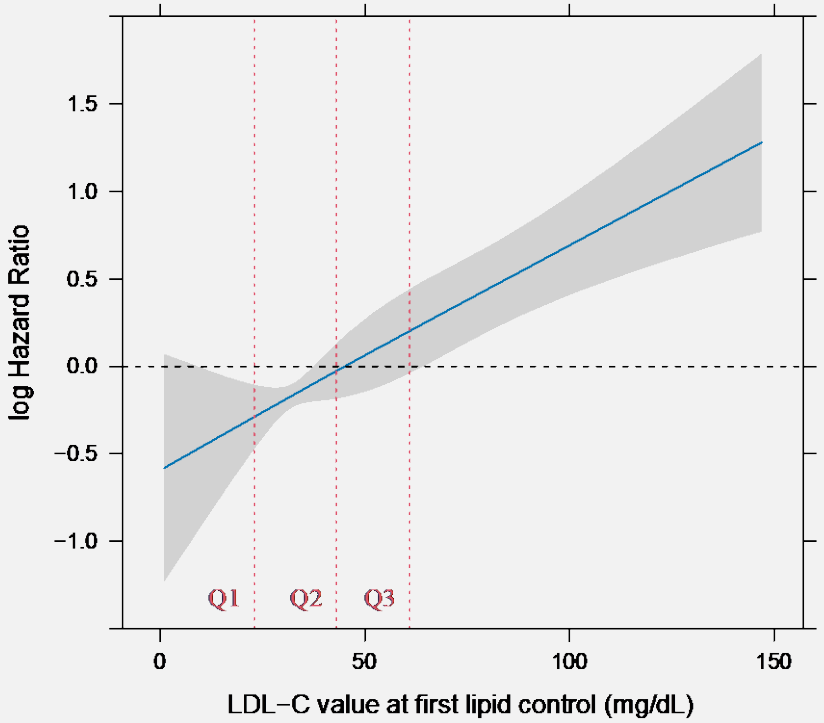


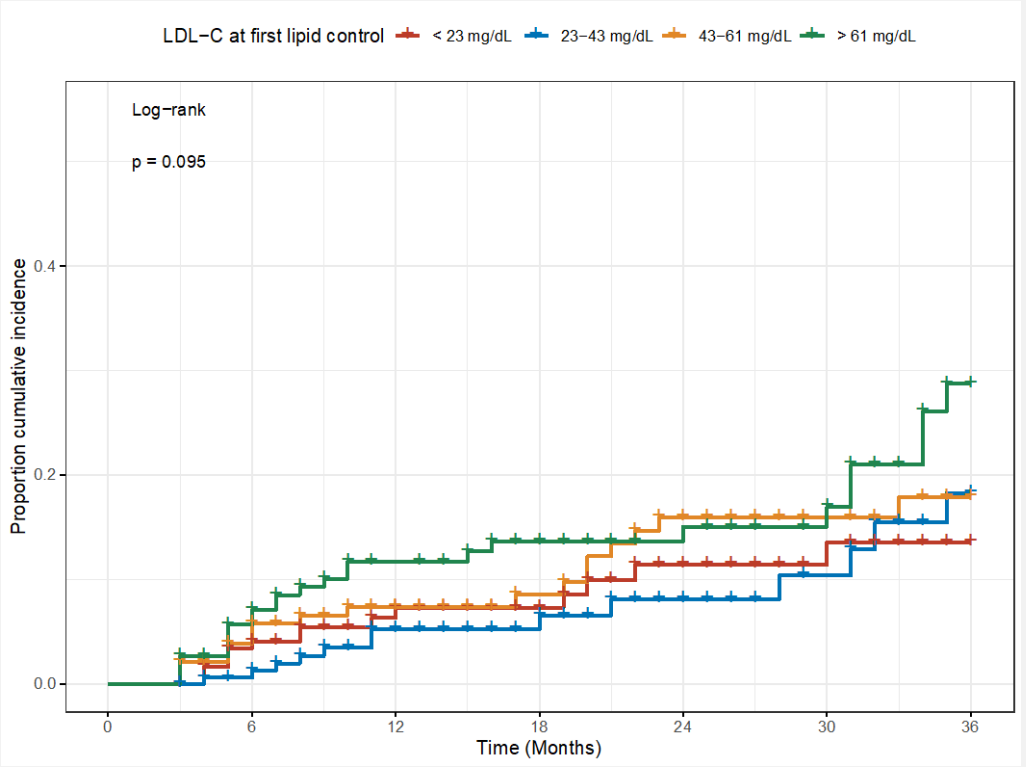
NON-FATAL MI, NON-FATAL STROKE, ISCHEMIA-DRIVEN REVASCULARIZATION AND ALL-CAUSE MORTALITY (4P-MACE)



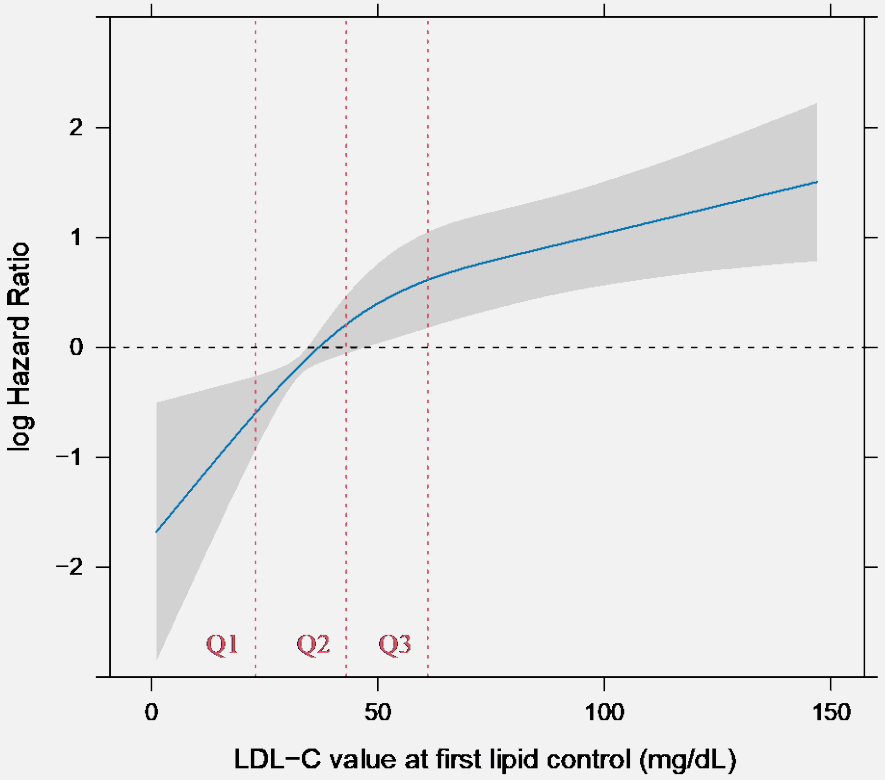


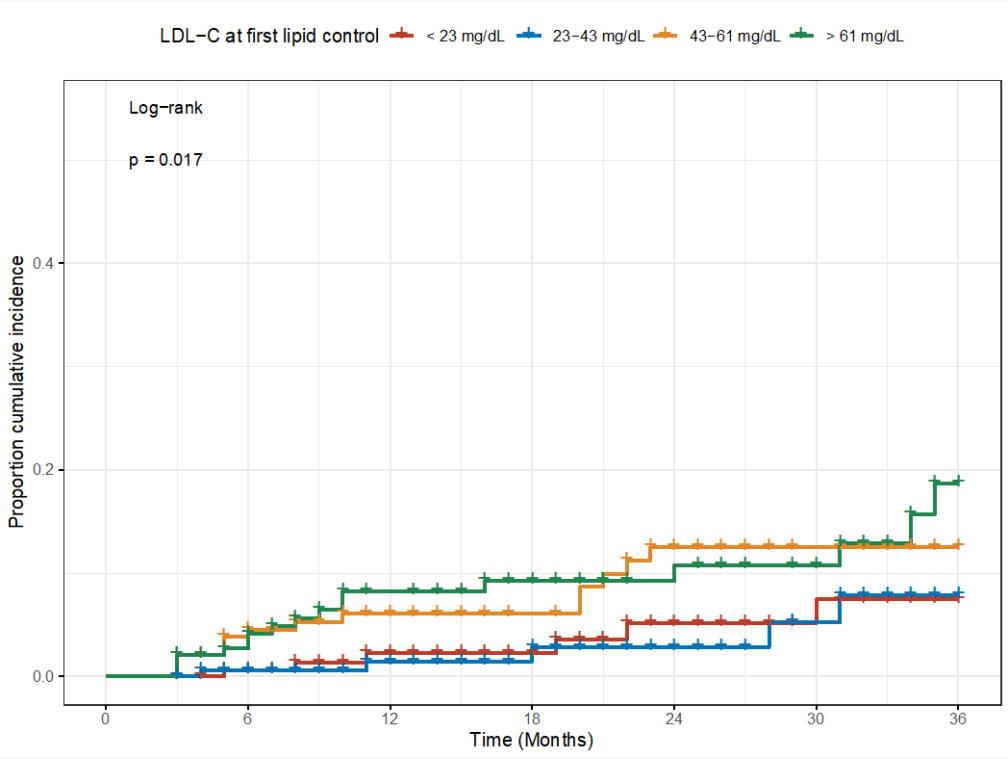
NON-FATAL MI, NON-FATAL STROKE AND ALL-CAUSE MORTALITY (3P-MACE)





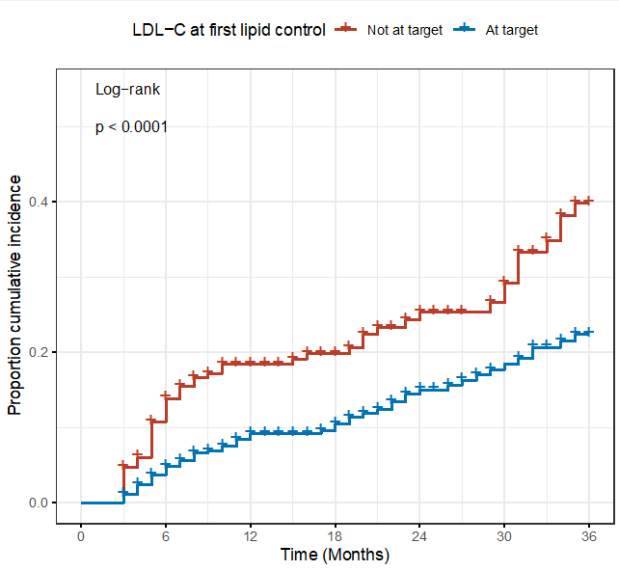
ALL-CAUSE MORTALITY



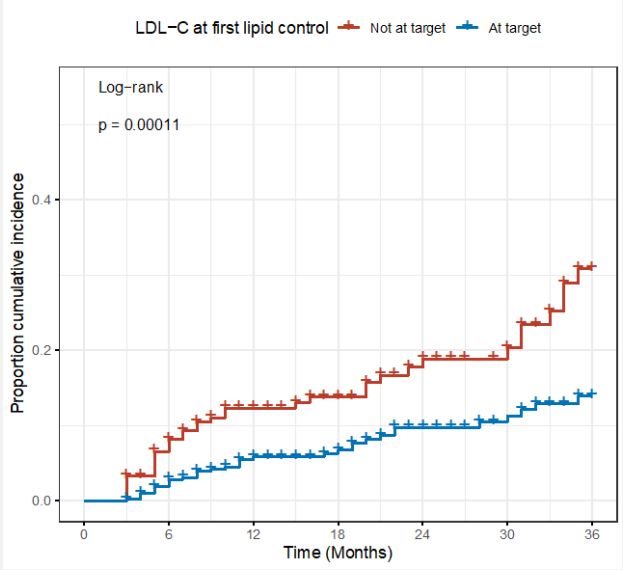


CUMULATIVE INCIDENCE RATES OF 4P-MACE, 3P-MACE AND ALL-CAUSE MORTALITY BY LDL-C TARGET STATUS AT FIRST LIPID CONTROL

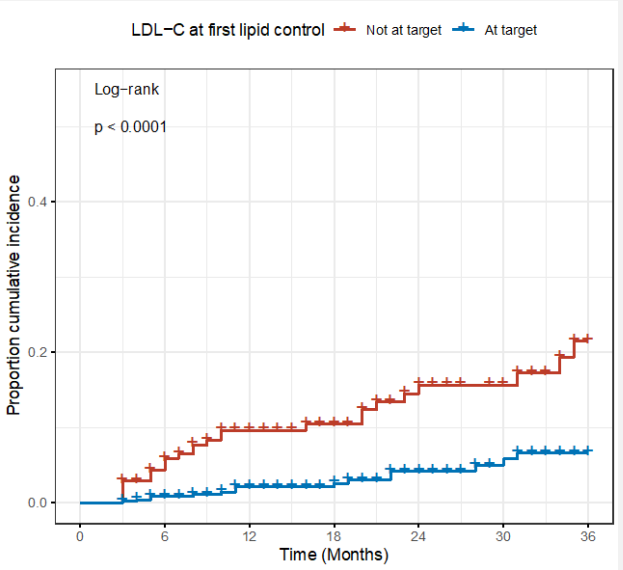
4P-MACE



3P-MACE

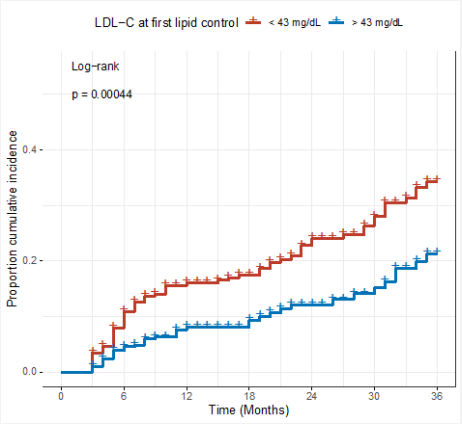


All-cause mortality

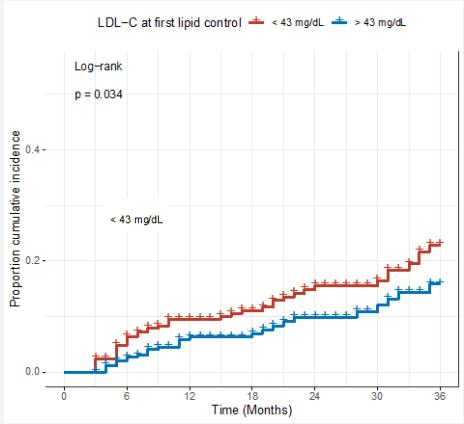


CUMULATIVE INCIDENCE RATES OF 4P-MACE, 3P-MACE, ALL-CAUSE MORTALITY, AND ISCHEMIA-DRIVEN REVASCULARIZATION, BY MEDIAN LDL-C VALUE AT FIRST LIPID CONTROL

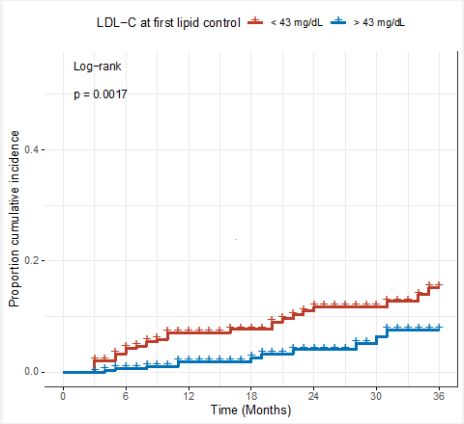
4P-MACE



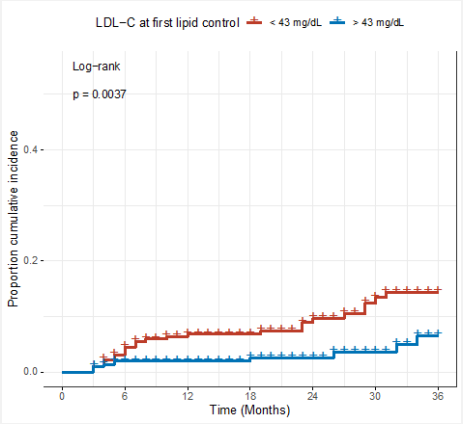
3P-MACE



All-cause mortality



Ischemia-driven revascularization



REMARKS

- PATIENTS WITH ACS SHOW HIGHEST RESIDUAL RISK IN THE EARLY PHASE AFTER DISCHARGE
- CLINICAL TRIAL SUGGEST A RELEVANT REDUCTION OF RISK IN PATIENTS REACHING VERY LOW LDL-C LEVELS
- REAL WORLD ITALIAN DATA DEMONSTRATE REDUCTION OF MACE AND OF ALL CAUSE MORTALITY IN ACS PATIENTS STARTING PCSK9i AT TIME OF HOSPITAL DISCHARGE
- OPTIMIZATION OF LIPID LOWERING THERAPY IN PATIENTS WITH ACS AS RECOMMENDED BY ESC GUIDELINES SHOULD BE IMPLEMENTED TO MITIGATE EXCESS RISK IN THESE PATIENTS

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 82, NO. 18, 2023

PUBLISHED BY ELSEVIER

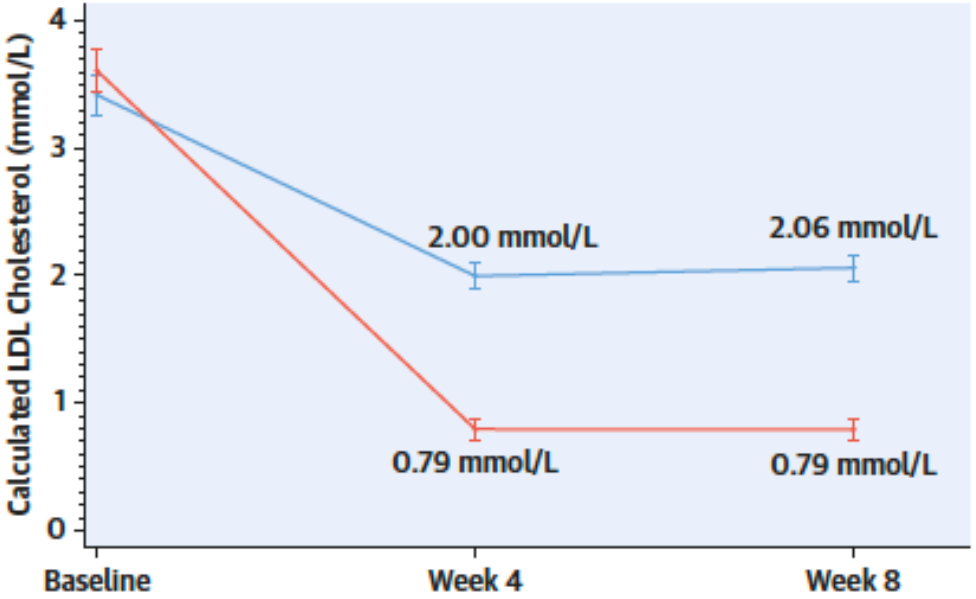
ORIGINAL INVESTIGATIONS

Concomitant Coronary Atheroma Regression and Stabilization in Response to Lipid-Lowering Therapy

Flavio G. Biccirè, MD,[a] Jonas Häner, MD,[a] Sylvain Losdat, PhD,[b] Yasushi Ueki, MD, PhD,[a] Hiroki Shibutani, MD,[a] Tatsuhiko Otsuka, MD,[a] Ryota Kakizaki, MD, PhD,[a] Thomas M. Hofbauer, MD, PhD,[c] Robert-Jan van Geuns, MD, PhD,[d] Stefan Stortecky, MD,[a] George C.M. Siontis, MD, PhD,[a] Sarah Bär, MD,[a] Jacob Lønborg, MD,[e] Dik Heg, PhD,[b] Christoph Kaiser, MD,[f] David Spirk, MD,[g,h] Joost Daemen, MD, PhD,[i] Juan F. Iglesias, MD,[j] Stephan Windecker, MD,[a] Thomas Engstrøm, MD, PhD,[e] Irene Lang, MD,[c] Konstantinos C. Koskinas, MD, MSc,[a] Lorenz Räber, MD, PhD[a]

FIGURE 2 Changes in LDL Cholesterol Levels Over Time

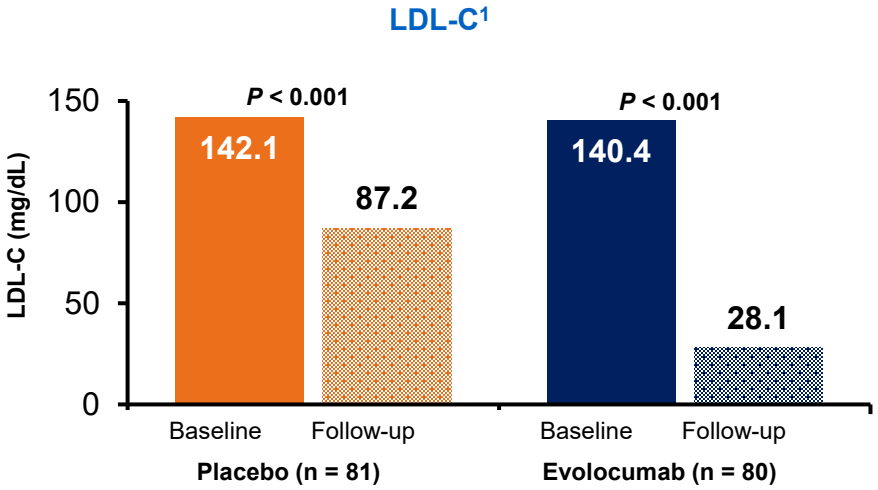
A LDL-C Levels Over Time

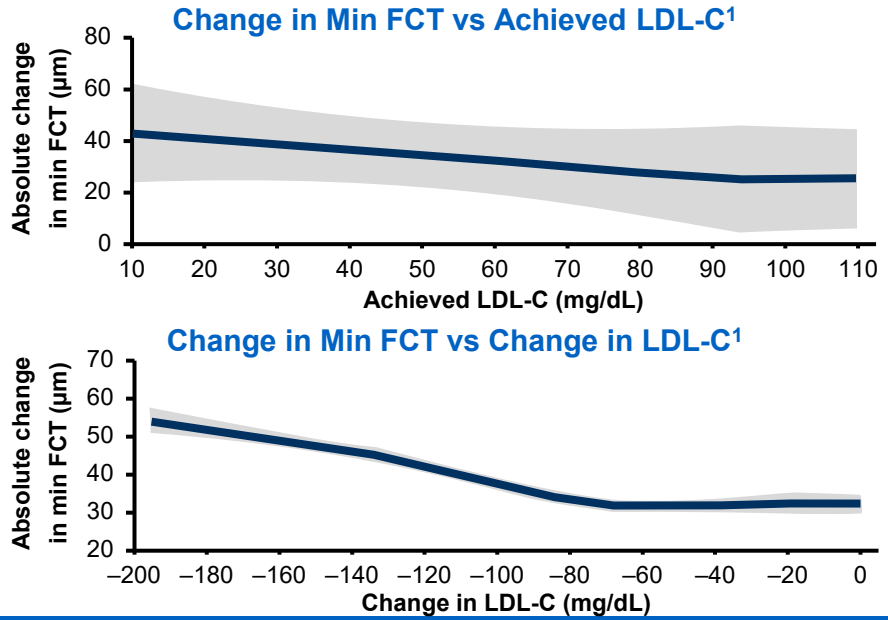


No. of Patients			
Placebo	148	144	149
Evolocumab	146	136	141
Absolute Difference (mmol/L)		1.34	1.43
Percentage Difference		38.4%	40.7%
P value		< 0.001	< 0.001

Placebo — Evolocumab

The Degree of FCT Increase Was Related to the Intensity of Lipid Lowering Observed





LDL-C was reduced by 80% in the evolocumab group, compared with 39% in patients on maximally tolerated statins alone. A correlation between achieved LDL-C and change in minimum FCT was shown.[1]

The primary and secondary endpoints were analyzed using ANCOVA.[2]

This trial was not designed to assess a correlation between changes in FCT and cardiovascular events.

ANCOVA, analysis of covariance; FCT, fibrous cap thickness; LDL-C, low-density lipoprotein cholesterol.

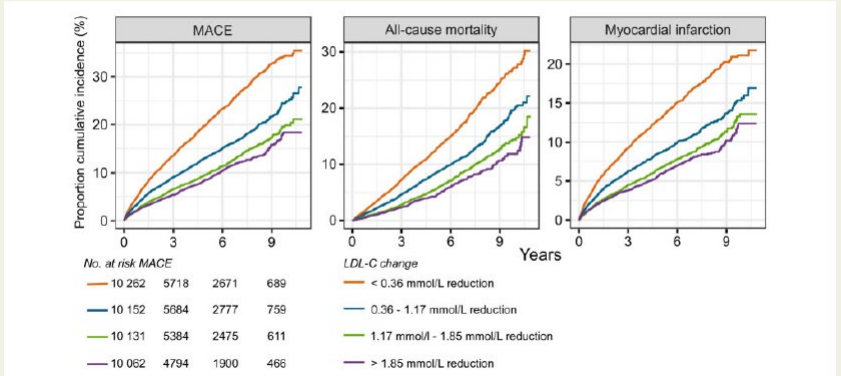
1. Nicholls SJ, et al. [published online ahead of print March 16, 2022]. *JACC Cardiovasc Imaging*. doi:10.1016/j.jcmg.2022.03.002.
2. Nicholls SJ, et al. *Cardiovasc Diagn Ther*. 2021;11:120-129.

ESC European Society of Cardiology
European Heart Journal (2020) **00**, 1–10
doi:10.1093/eurheartj/ehaa1011

CLINICAL RESEARCH

Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study

Jessica Schubert [1]*, Bertil Lindahl [1,2], Håkan Melhus [1], Henrik Renlund [2], Margrét Leosdottir [3,4], Ali Yari [5], Peter Ueda [6], Stefan James [1,2], Stephanie R. Reading [7], Paul J. Dluzniewski[7], Andrew W. Hamer[7], Tomas Jernberg [5], and Emil Hagström[1,2]



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

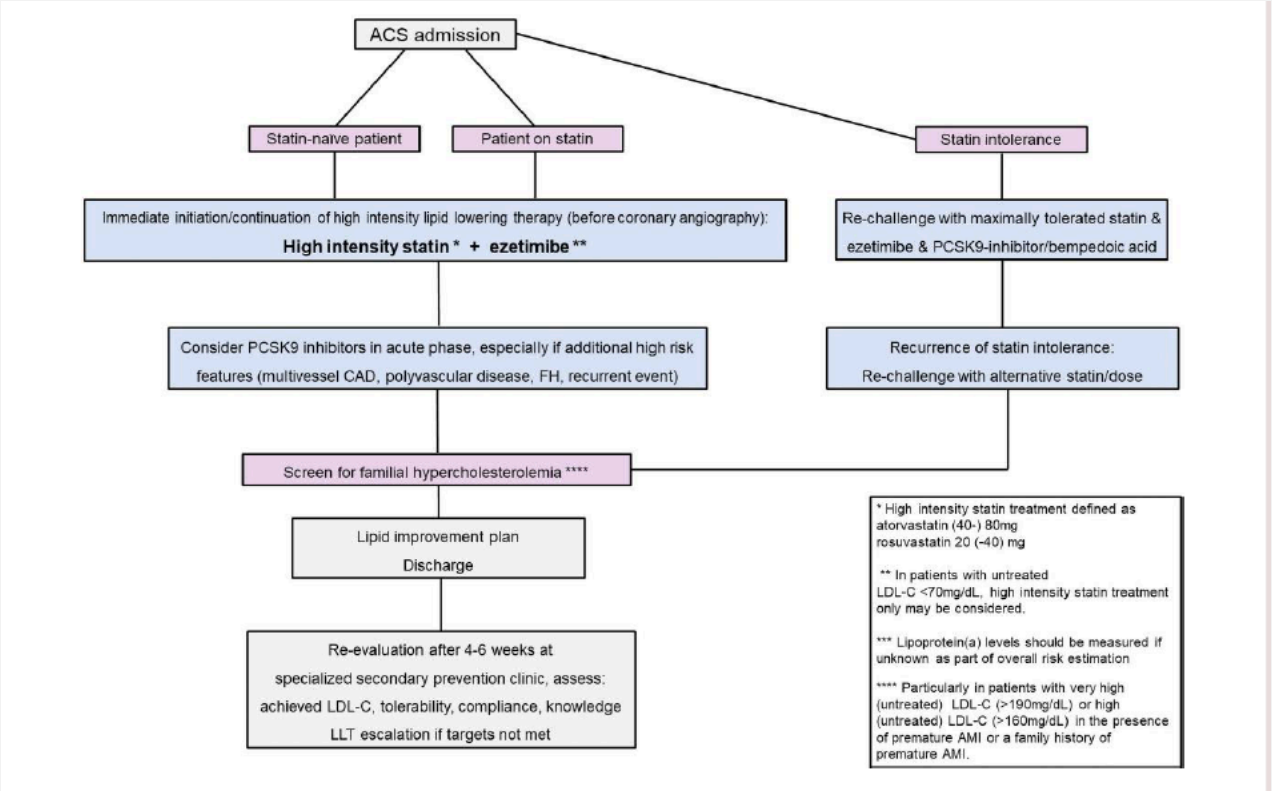
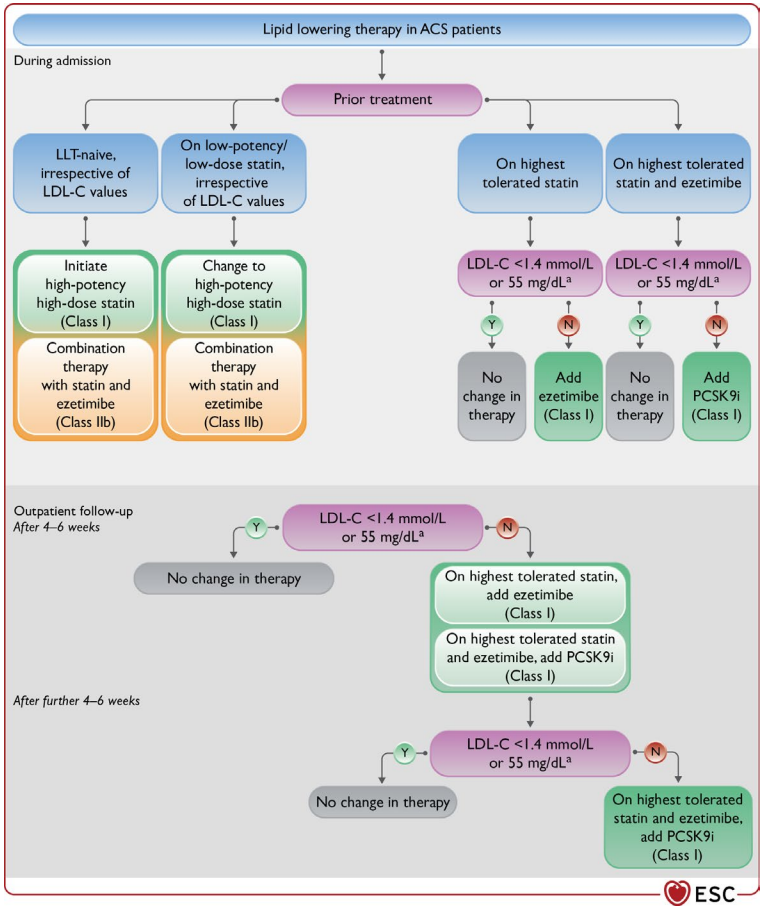

ACS admission
Statin-naive patient
Patient on statin
Statin intolerance
Immediate initiation/continuation of high intensity lipid lowering therapy (before coronary angiography):
High intensity statin * + ezetimibe **
Re-challenge with maximally tolerated statin & ezetimibe & PCSK9-inhibitor/bempedoic acid
Consider PCSK9 inhibitors in acute phase, especially if additional high risk features (multivessel CAD, polyvascular disease, FH, recurrent event)
Recurrence of statin intolerance:
Re-challenge with alternative statin/dose
Screen for familial hypercholesterolemia ****
Lipid improvement plan
Discharge
Re-evaluation after 4-6 weeks at specialized secondary prevention clinic, assess:
achieved LDL-C, tolerability, compliance, knowledge
LLT escalation if targets not met
* High intensity statin treatment defined as
atorvastatin (40-) 80mg
rosuvastatin 20 (-40) mg
** In patients with untreated LDL-C <70mg/dL, high intensity statin treatment only may be considered.
*** Lipoprotein(a) levels should be measured if unknown as part of overall risk estimation
**** Particularly in patients with very high (untreated) LDL-C (>190mg/dL) or high (untreated) LDL-C (>160mg/dL) in the presence of premature AMI or a family history of premature AMI.

Figure 18

Lipid-lowering therapy in ACS patients



2023 ESC Guidelines for the management of acute coronary syndromes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad191)