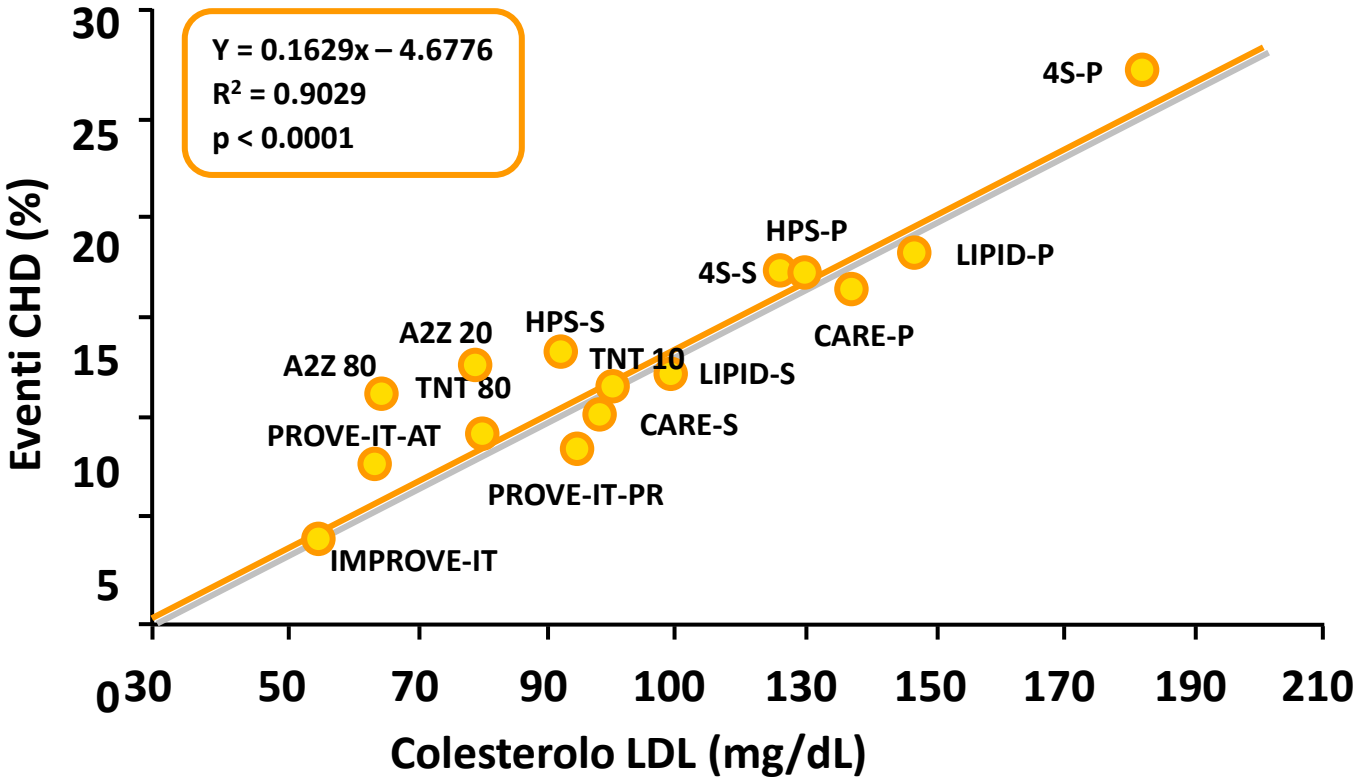
“Lower is the best”: trattamento con PCSK9-I

Giuseppe Musumeci
SC Cardiologia
AO Ordine Mauriziano, Torino

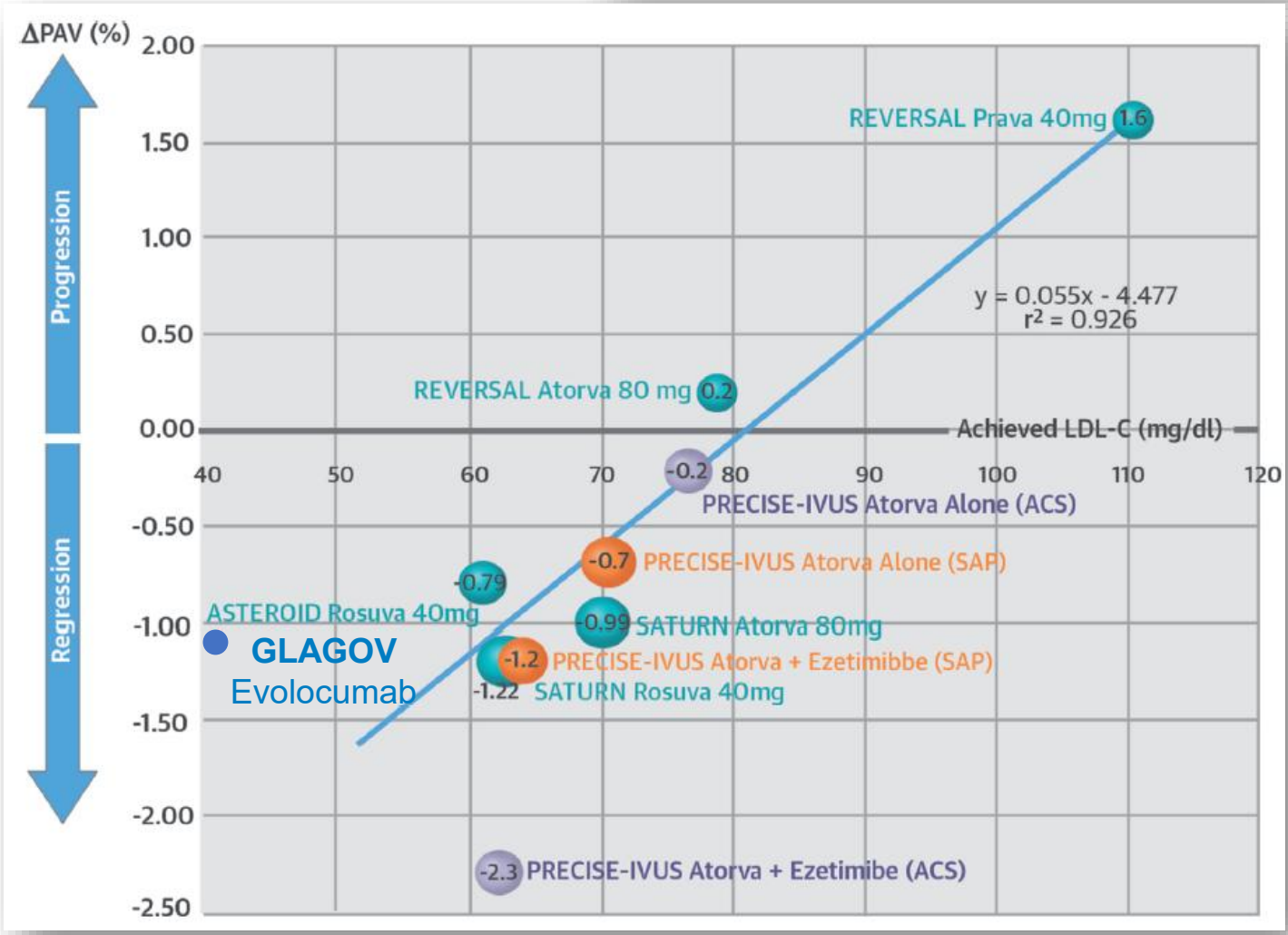
Studi con statine in prevenzione secondaria: riduzione eventi e C-LDL “on trial”



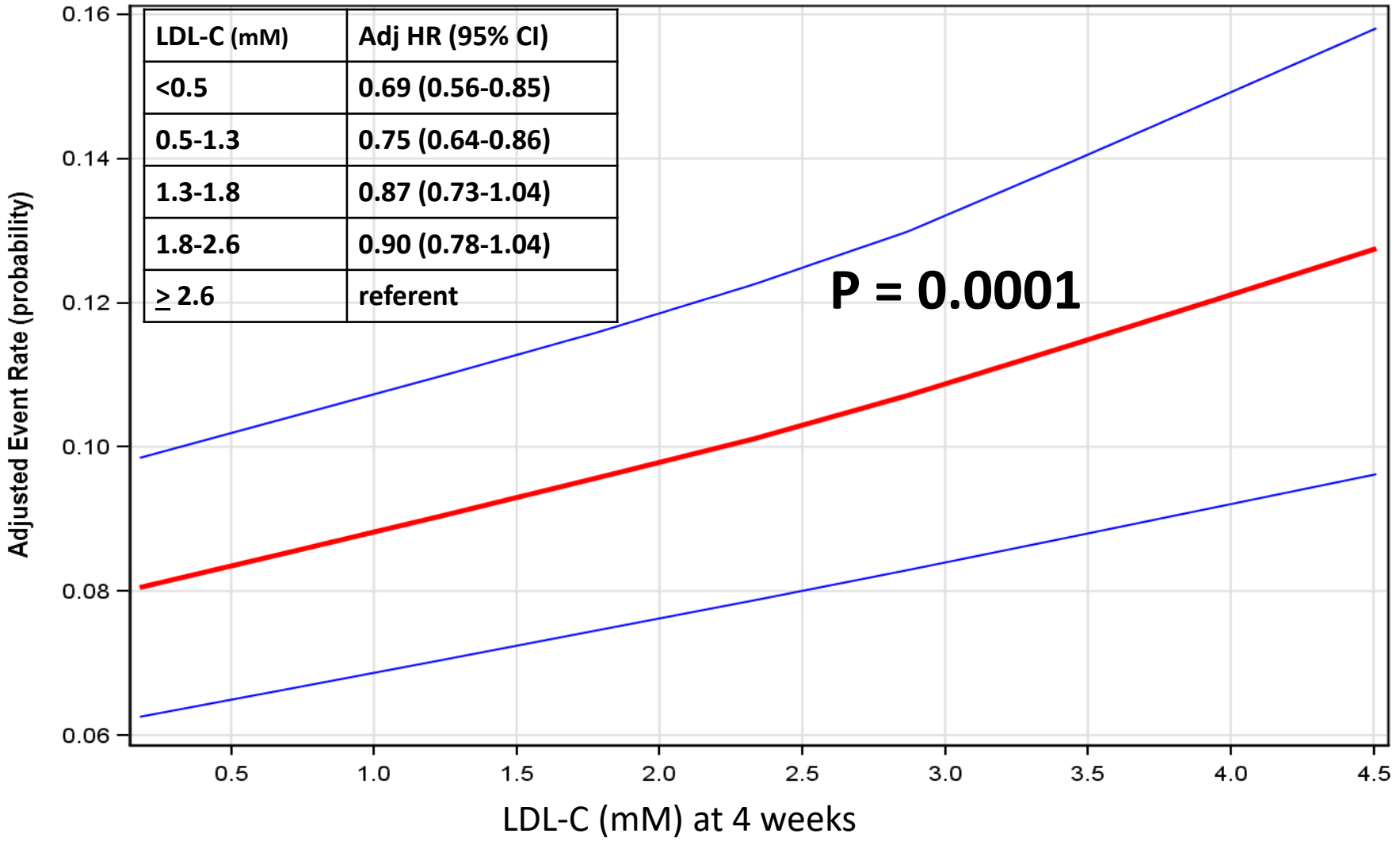
O’Keefe et al, JACC, 2004.

Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention

The Multicenter Randomized Controlled PRECISE-IVUS Trial

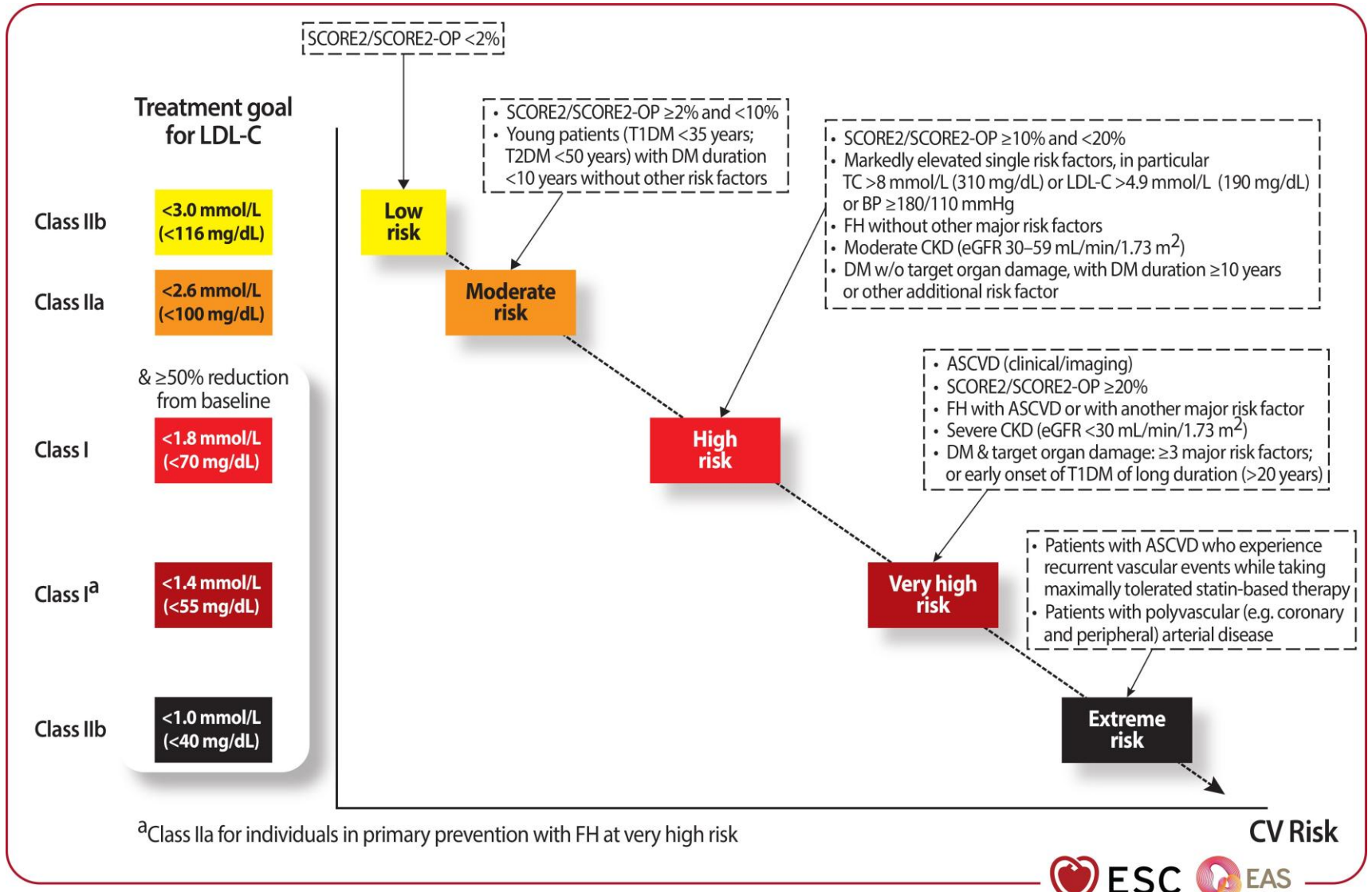


FOURIER: CV Death, MI, or Stroke



Giugliano RP et al, Lancet 2017 (on line Aug 28, 2017)

Treatment goals for LDL-C across categories of total cardiovascular ESC guidelines 2025



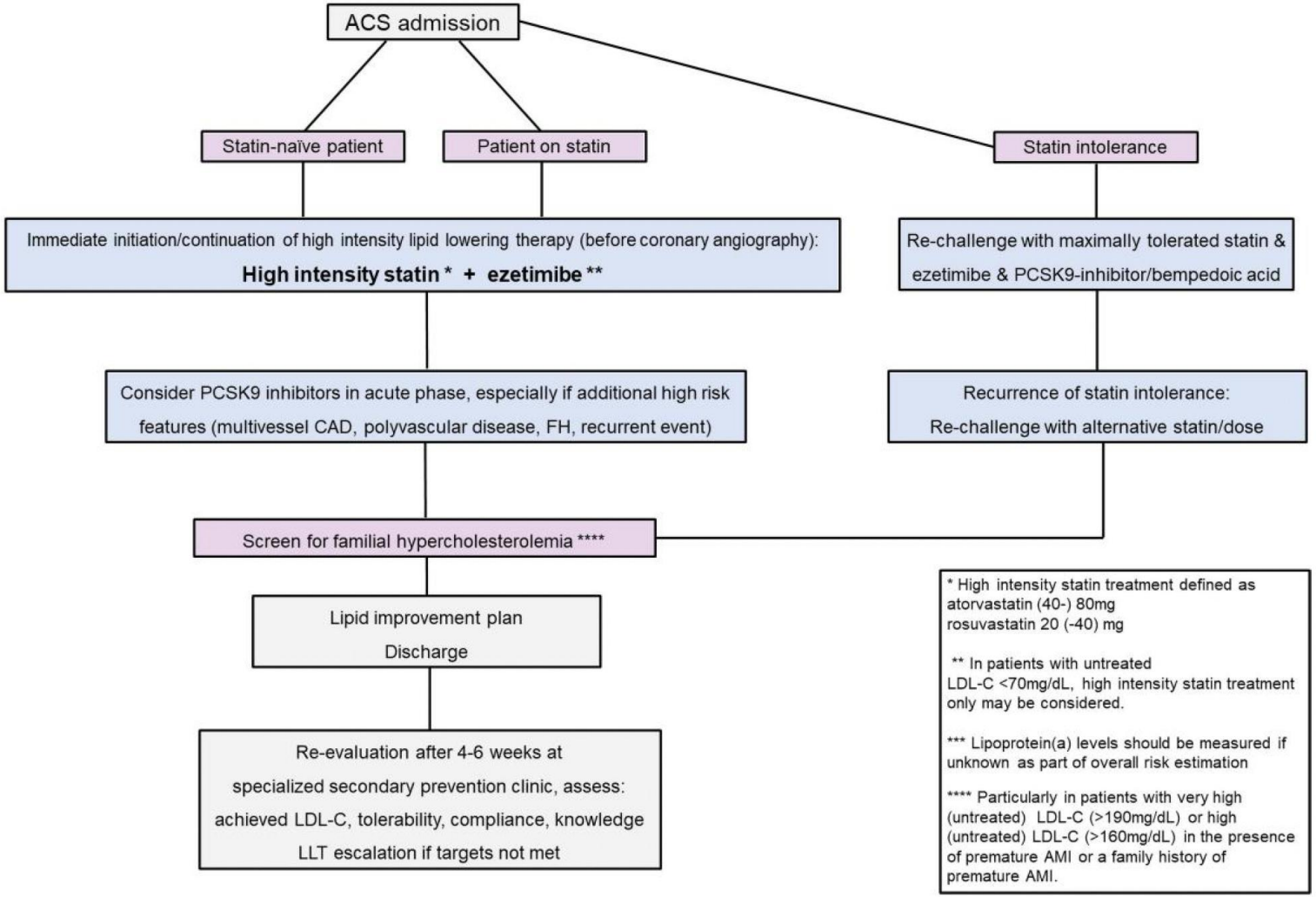
Eur Heart J, ehaf190, https://doi.org/10.1093/eurheartj/ehaf190

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[1] Alexander Niessner[1‡], Francois 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[2] Peter Sinnaeve[22], Roberto Pedretti[23], and Alberico Catapano[24]



FAST TRACK PER IMA <12 MESI E EVENTI CV MULTIPLI

Profilo lipidico

Si riferisce a controlli effettuati precedentemente all'inizio del trattamento con Repatha.

Il trattamento di almeno sei mesi con statina ad alta potenza al massimo della dose tollerata è una delle condizioni obbligatorie ai fini dell'eleggibilità con questo medicinale.

E' necessario inserire 3 determinazioni, eseguite in momenti diversi, del profilo lipidico.

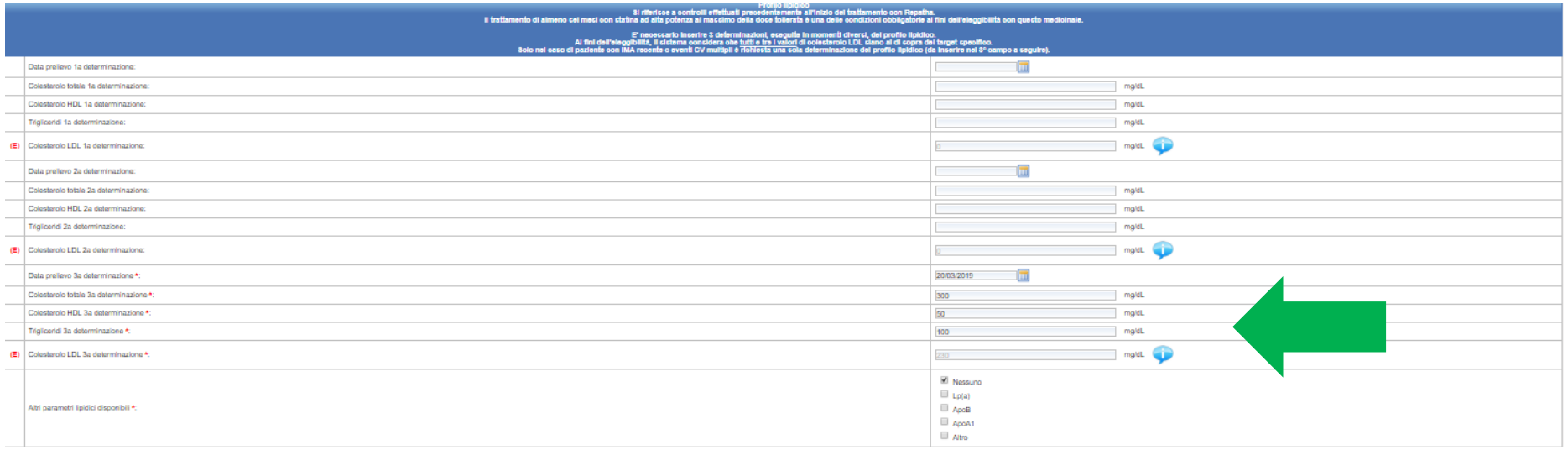
Ai fini dell'eleggibilità, il sistema considera che tutti e tre i valori di colesterolo LDL siano al di sopra del target specifico.

Solo nel caso di paziente con IMA recente o eventi CV multipli è richiesta una sola determinazione del profilo lipidico (da inserire nel 3° campo a seguire).

E' NECESSARIO 1 SOLO PROFILO LIPIDICO CON LDL-C>100

Entro 30 gg dalla data di valutazione

1 SOLO CAMPO DA COMPILARE PER IL PROFILO LIPIDICO



PER COMPLETARE CORRETTAMENTE L'ELEGGIBILITA' DEL *PAZIENTE POST-MI* <12 M O DEL *PAZIENTE CON EVENTI CV MULTIPLI* OCCORRE:

- **COMPILARE ESCLUSIVAMENTE IL TERZO CAMPO** («**COLESTEROLO LDL 3° DETERMINAZIONE**») del PROFILO LIPIDICO

- Paziente con SCA in terapia con Statine ed Ezetimibe ed LDL > 100 mg/dl

Aggiunge I-PCSK9 alla dimissione

- Paziente con SCA in terapia con Statine ed LDL > 100 mg/dl

Aggiunge Ezetimibe ed I-PCSK9 alla dimissione

- Paziente con SCA naive da Statine con LDL > 55 mg/dl ed < 140 mg/dl

Aggiunge combinazione Statine ed Ezetimibe alla dimissione e controllo a un mese per valutare I-PCSK9

- Paziente con SCA naive da Statine con LDL > 140 mg/dl

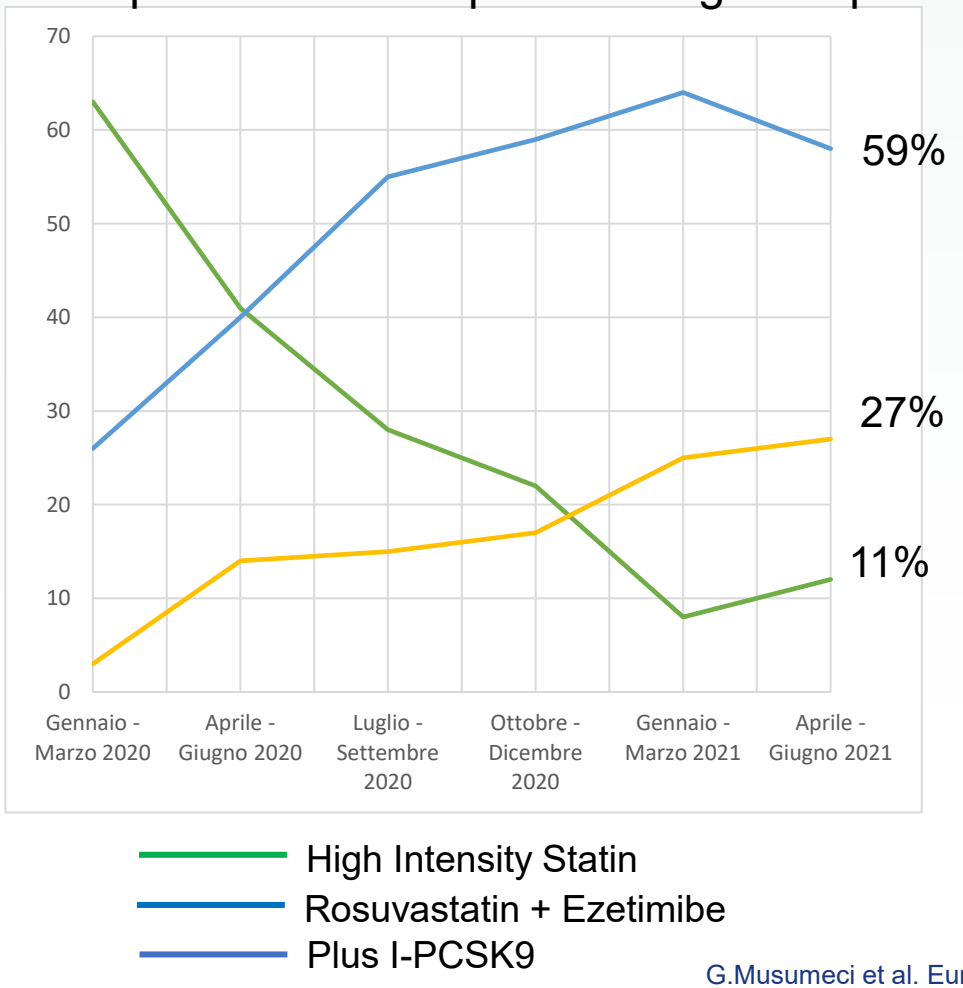
Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

Early, Effective and Established strategies for LDL-C management Translating clinical evidence into real world effectiveness:

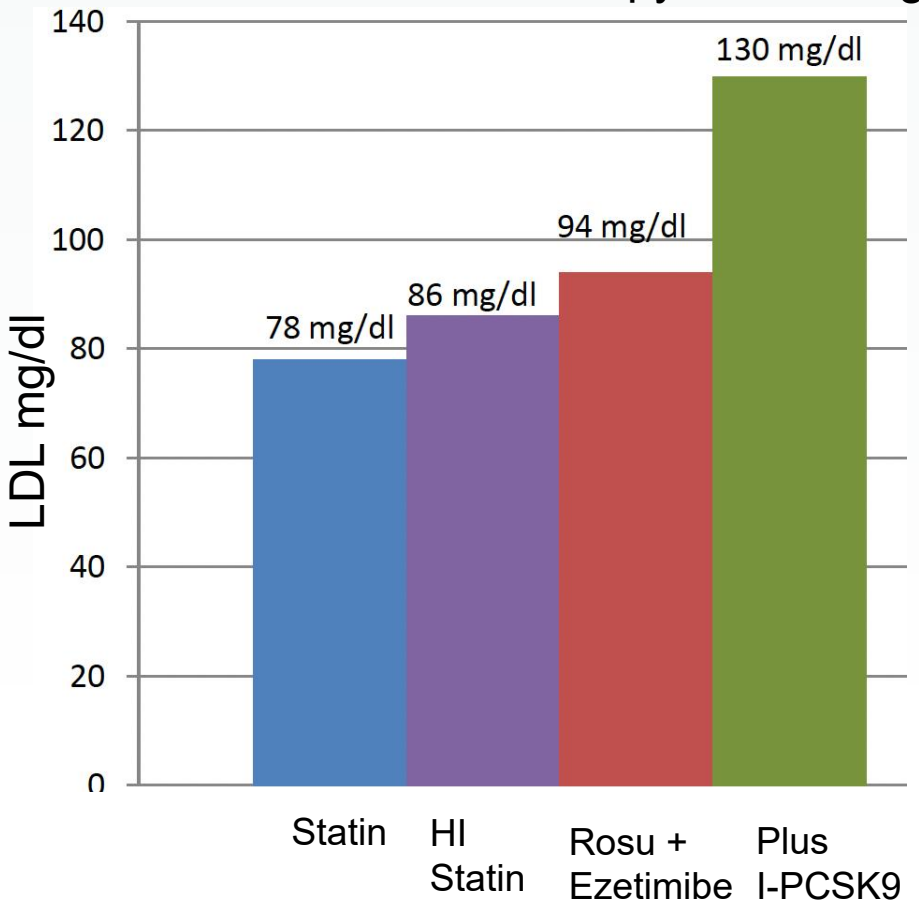
Ospedale Mauriziano Torino experience

Overall, 496 consecutive ACS patients hospitalized between April 2020 and June 2021 were enrolled; 104 of whom were discharged with I-PCSK9 (21%)

Prescription trends of lipid-lowering therapies



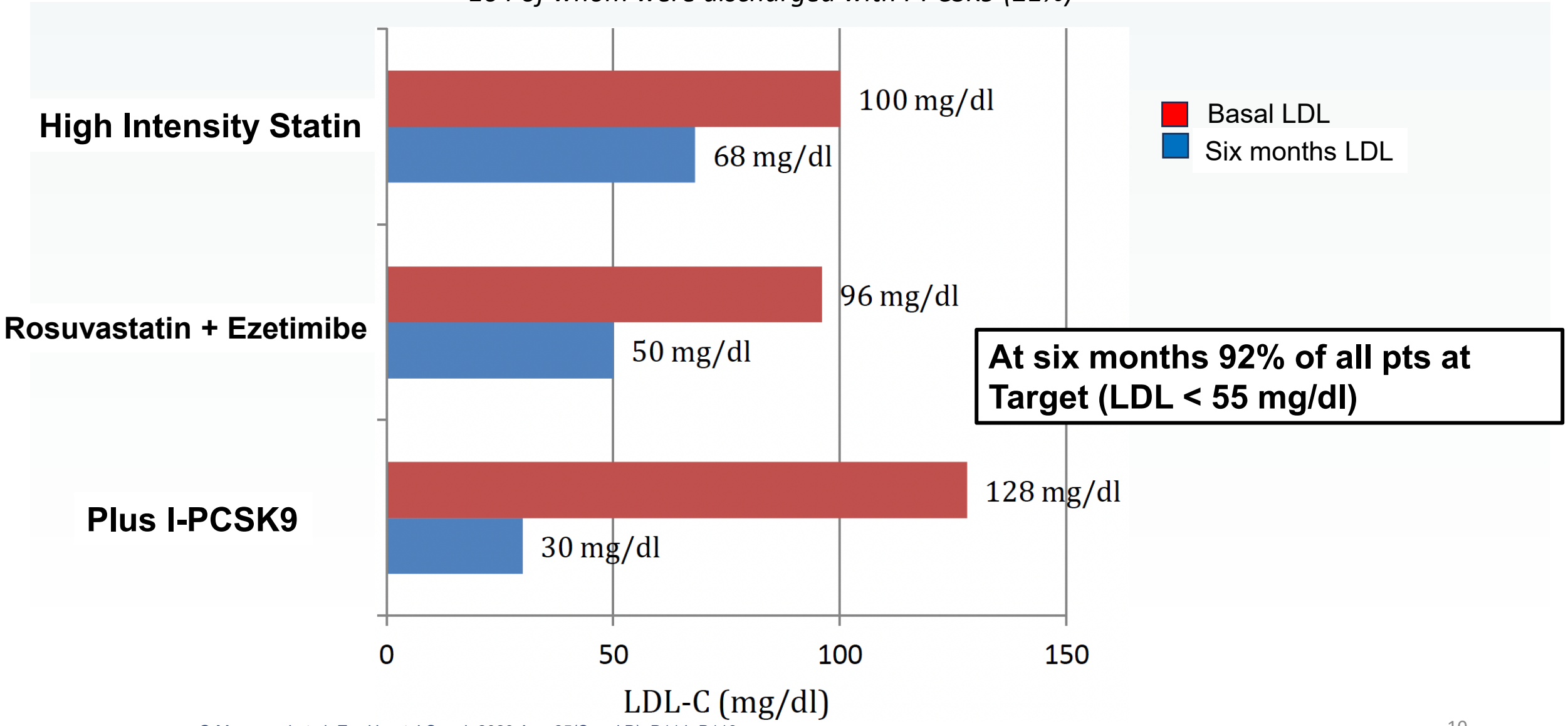
Baseline LDL and therapy at discharge



G.Musumeci et al. Eur Heart J Suppl. 2023 Apr; 25(Suppl B): B114–B118

Ospedale Mauriziano Torino experience

Overall, 496 consecutive ACS patients hospitalized between April 2020 and June 2021 were enrolled; 104 of whom were discharged with I-PCSK9 (21%)



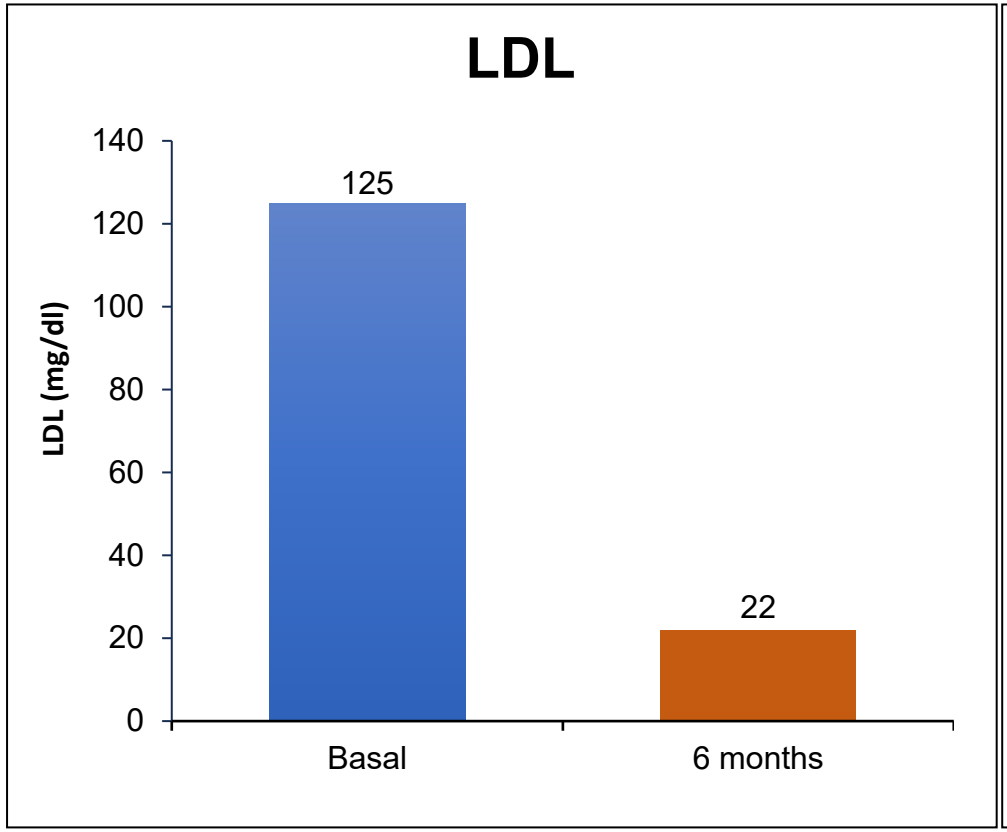
At six months 92% of all pts at Target (LDL < 55 mg/dl)

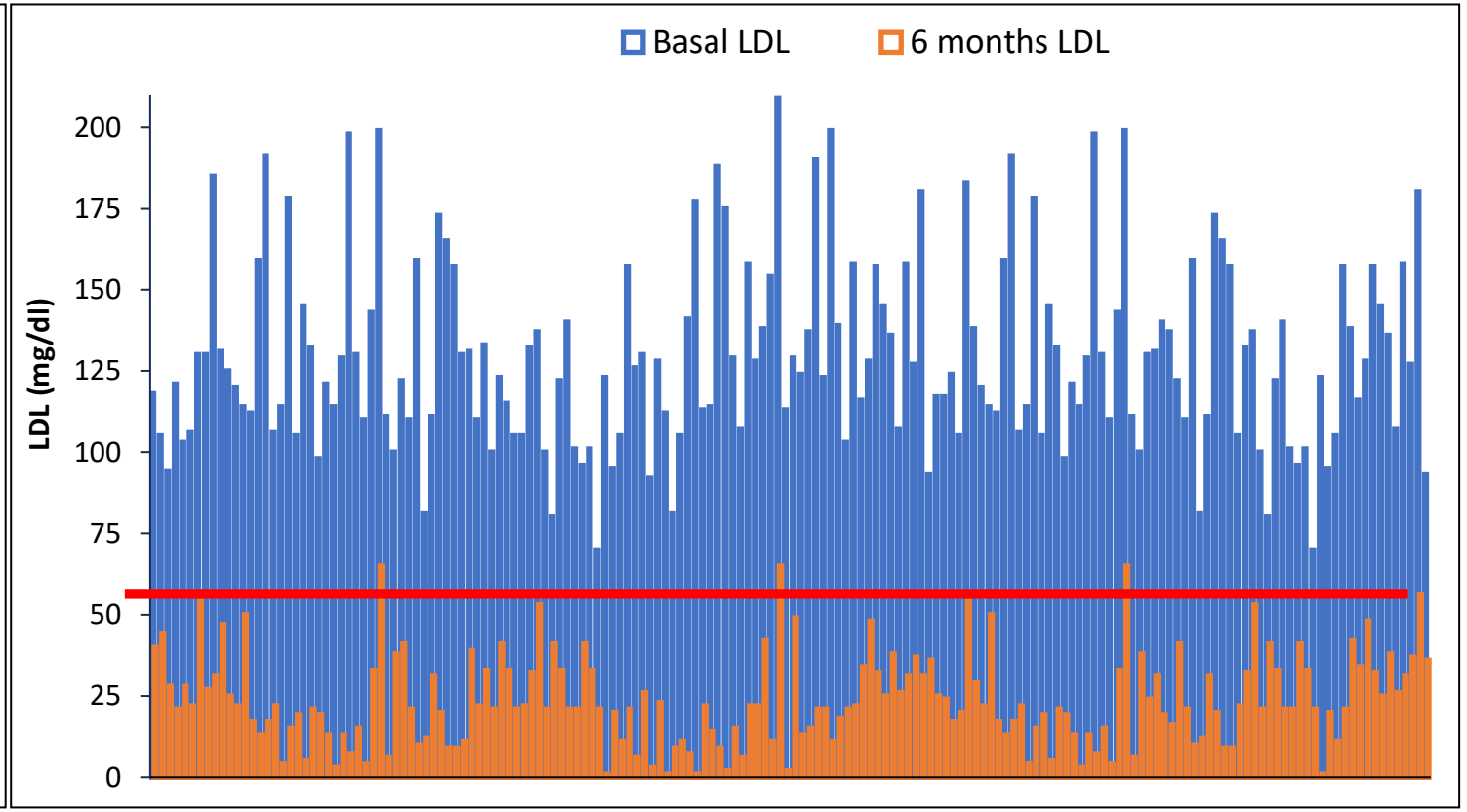
G.Musumeci et al. Eur Heart J Suppl. 2023 Apr; 25(Suppl B): B114–B118

LDL levels in ACS patients on PCSK9-I at discharge

1067 consecutive ACS patients hospitalized between April 2020 and March 2023 256 patients (24%) were discharged with PCSK9-I
6-month follow-up in 248 patients (97%)

PCSK9-I 6 months post-discharge: 244 reached <55 mg/dl (98%)





ACS, acute coronary syndrome; LDL, low density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9

F. Delnevo et al. Abstract 1564 EAS 2023 Atherosclerosis journal August 2023

Dal 16 Giugno 2022 nuova soglia di rimborsabilità per Evolocumab ed Alirocumab a LDL > 70 mg/dl

SERIE GENERALE

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zienti di eta' ≤ 80 aa con
gote o ipercolesterolemia non
livelli di LDL-C ≥ 70 mg/dL

- Paziente con SCA in terapia con Statine ed Ezetimibe ed LDL ≥ **70** mg/dl

Aggiunge I-PCSK9 alla dimissione

- Paziente con SCA in terapia con Statine ed LDL ≥ **70** mg/dl

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- Paziente con SCA naive da Statine con LDL ≥ 55 mg/dl ed < 140 mg/dl

Aggiunge combinazione Statine ed Ezetimibe alla dimissione e controllo a un mese per valutare I-PCSK9

- Paziente con SCA naive da Statine con LDL ≥ 140 mg/dl o > 70 e PAD o DM o MV

Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

FOURIER trial: NNT for the primary endpoint with evolocumab vs placebo in high-risk settings at 3 years

	NNT[c]
Overall population[1]	50
Diabetes mellitus[2]	37
PAD[3]	29
Multi-vesssel CAD[4]	29
Multiple MIs[5a]	27
Recent MI[b]	27
High genetic score[6]	25

[a] ≥2 prior MIs; [b] Within 2 years of most recent MI; [c] NNT = 1/ARR; CAD; coronary artery disease; MI; myocardial infraction; NNT, number needed to treat; PAD, peripheral artery disease

1. Sabatine MS et al. NEJM 2017;376:1713-22; 2. Sabatine MS, et al. *Lancet Diabetes Endocrinol*. 2017;5:941-950; 3. Bonaca MP, et al. *Circulation*. 2018;137:338-350; 4. Sabatine MS, et al. *Circulation*. 2018;138:756-766; 5. Gencer B, et al. *JAMA Cardiol*. 2020;5:952-95; 6. Marston NA, et al. *Circulation.* 2020;141:616-623

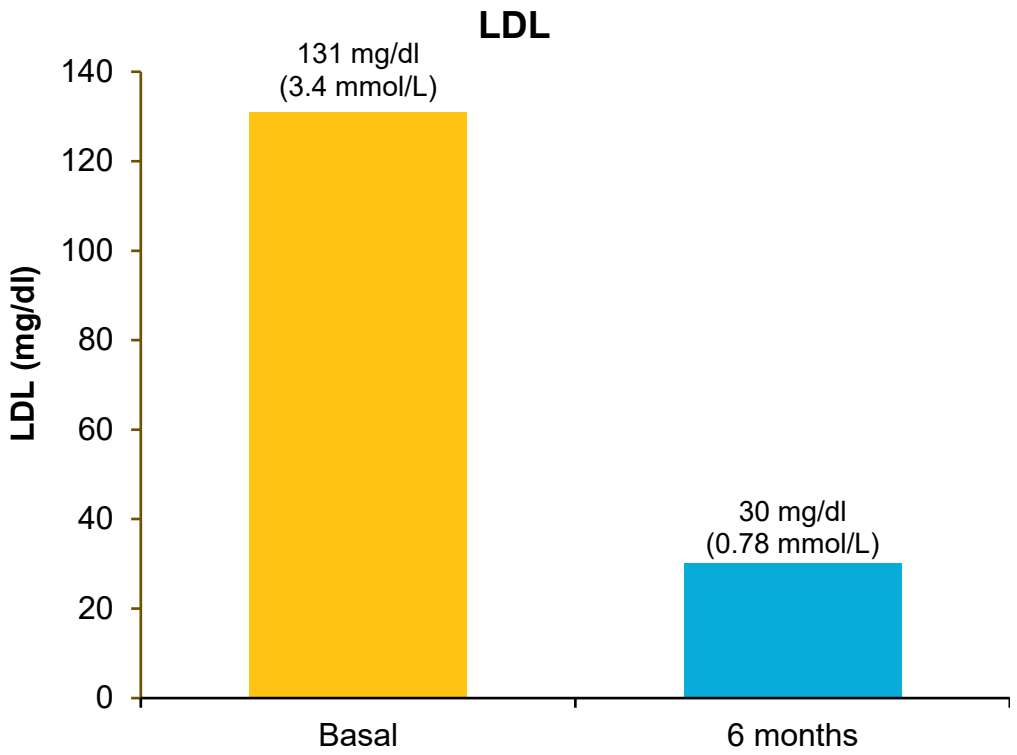
Experience at Ospedale Mauriziano and Maria Vittoria Hospital, Turin, Italy

Overall, 264 consecutive ACS patients hospitalised between July 2023 and November 2023 were enrolled; 77 of whom were discharged with PCSK9i (29%)

Therapy at discharge

ACS in patient on statin + ezetimibe therapy and LDL >100 mg/dL[a]	Added PCSK9i
ACS in patient on statin therapy and LDL >100 mg/dL[b]	Addition of ezetimibe and PCSK9i
ACS in naïve patient with LDL >100 mg/dL[a] but <140 mg/dl[b]	Introduction of statin + ezetimibe
ACS in naïve patient with LDL >140 mg/dL[b]	Introduction of statin + ezetimibe + PCSK9i
ACS in naïve patient with LDL >70 mg/dL[c] and Diabetes/MVD/PAD	Introduction of statin + ezetimibe + PCSK9i

Patients on triple therapy



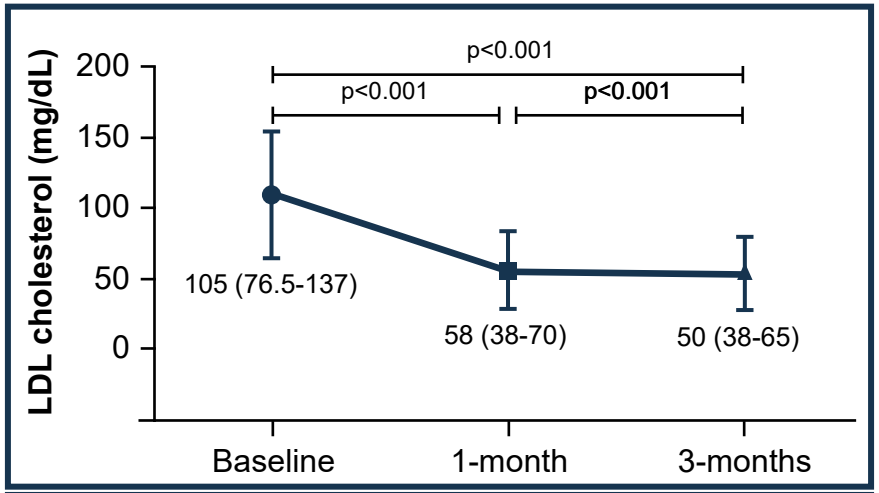
[a]>2.6 mmol/L; [b] >3.6 mmol/L; [c]>1.8 mmol/L

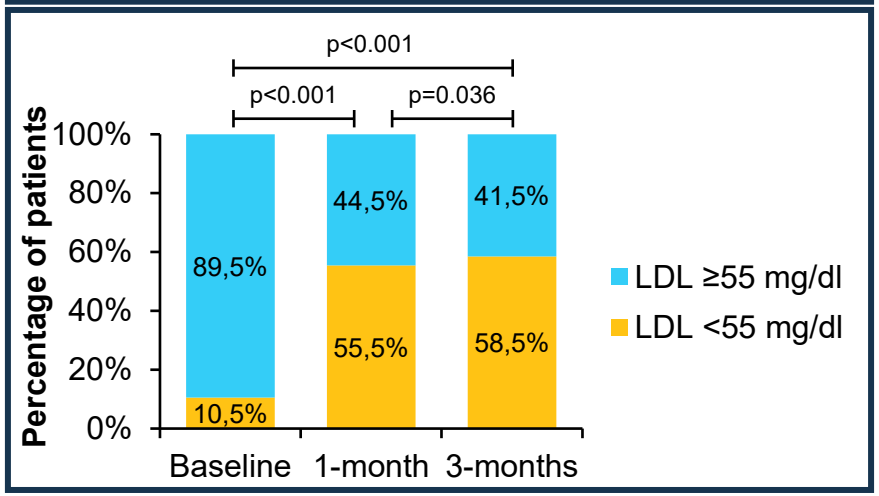
ACS, acute coronary syndrome; LDL, low density lipoprotein; MVD, multivessel disease; PAD, peripheral arterial disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor

Delnevo F, et al. Atherosclerosis. 2024 (in press). Presented at the European Atherosclerosis Society (EAS) congress 2024. Abstract 1263

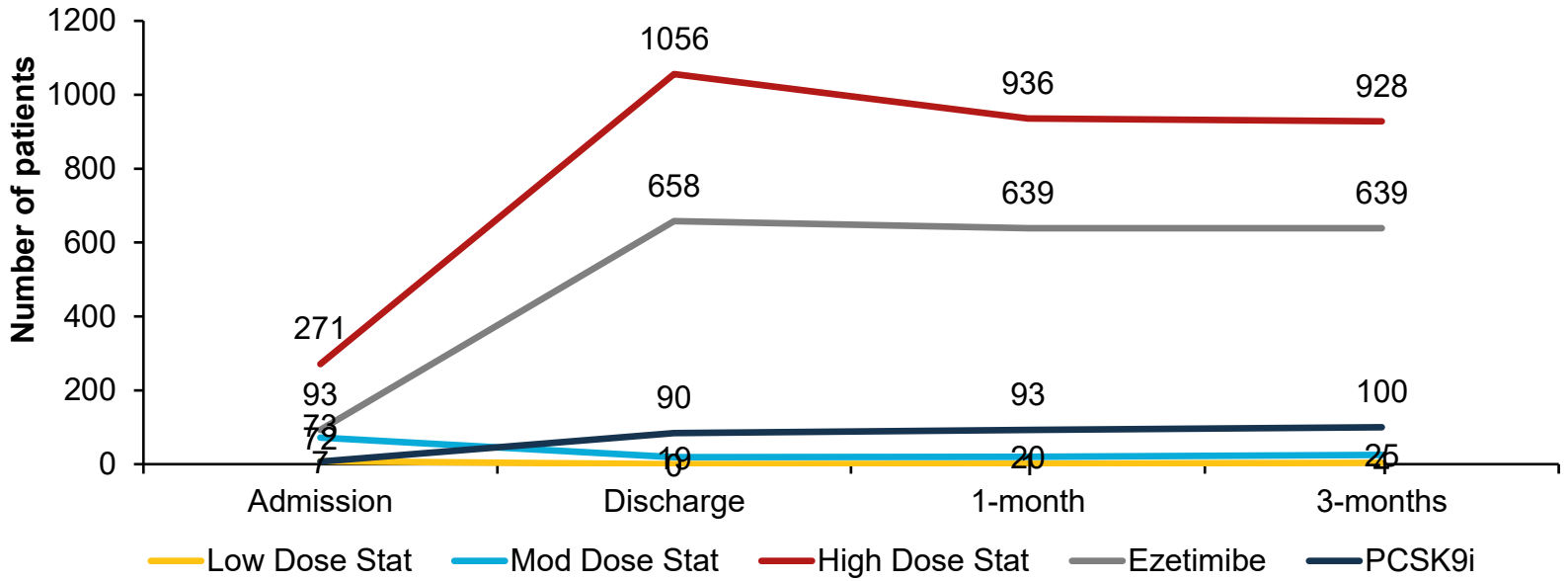
Target LDL cholesterol level in patients with ACS undergoing PCI: The JET-LDL REGISTRY

A multicenter, prospective, real-world data collection carried out during a 3-month (2022) period including consecutive ACS pts undergoing PCI at 35 Italian hospitals





- A total of 1095 patients were included
- At hospital discharge, 442 patients (40%) received statin monotherapy, 547 (50%) statin plus ezetimibe and 90 a PCSK9i (8.5%)
- At 1 month, LDL-C was at recommended target levels in 55.5% of patients, but PCSK9i prescription was not significantly increased



LDL 55 mg/dl = 1.4 mmol/L

ACS, acute coronary syndrome; LDL(-C), low density lipoprotein (cholesterol); PCI, percutaneous coronary intervention; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor

Ferlini M, et al. and G. Musumeci Int J Cardiol. 2024;397:131659

International Journal of Cardiology
Available online 21 January 2024, 131803
In Press, Journal Pre-proof What's this?

Editorial

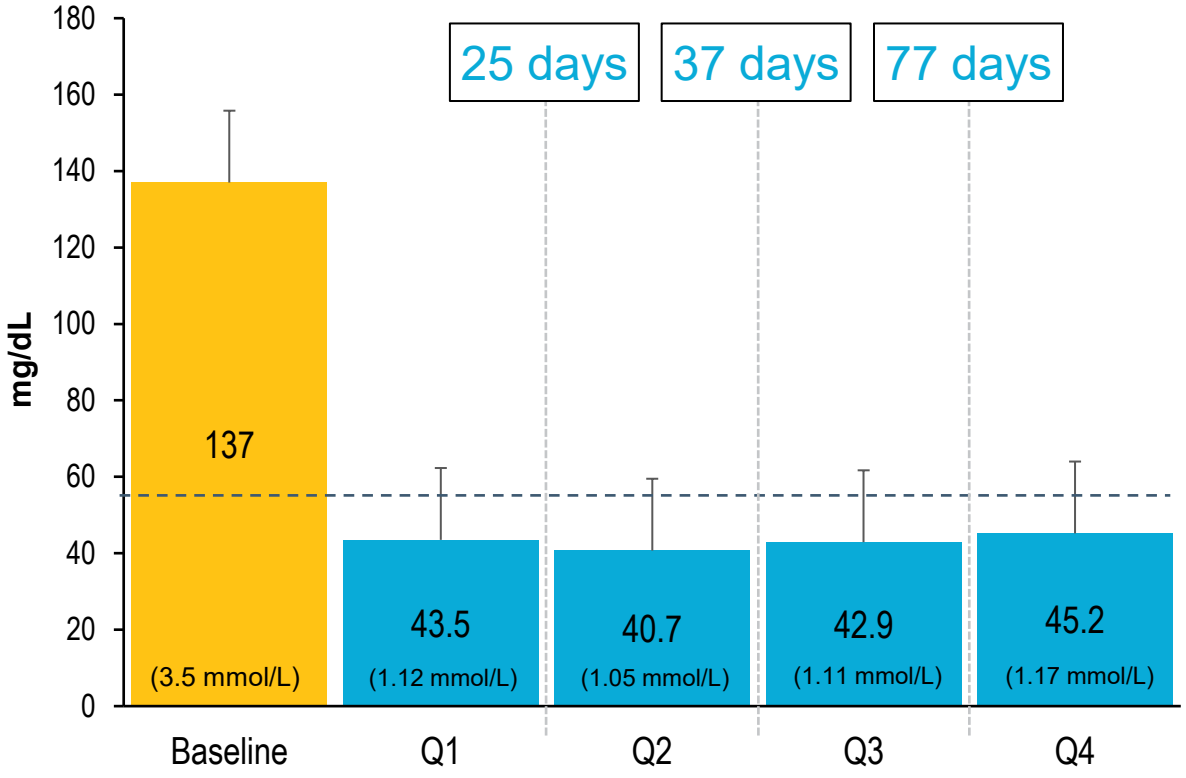
Optimizing LDL-cholesterol management in ACS patients: Breaking inertia and implementing intensified therapies

Luis Ortega-Paz [a], Marc Bonaca [b], Dominick J. Angiolillo [a]

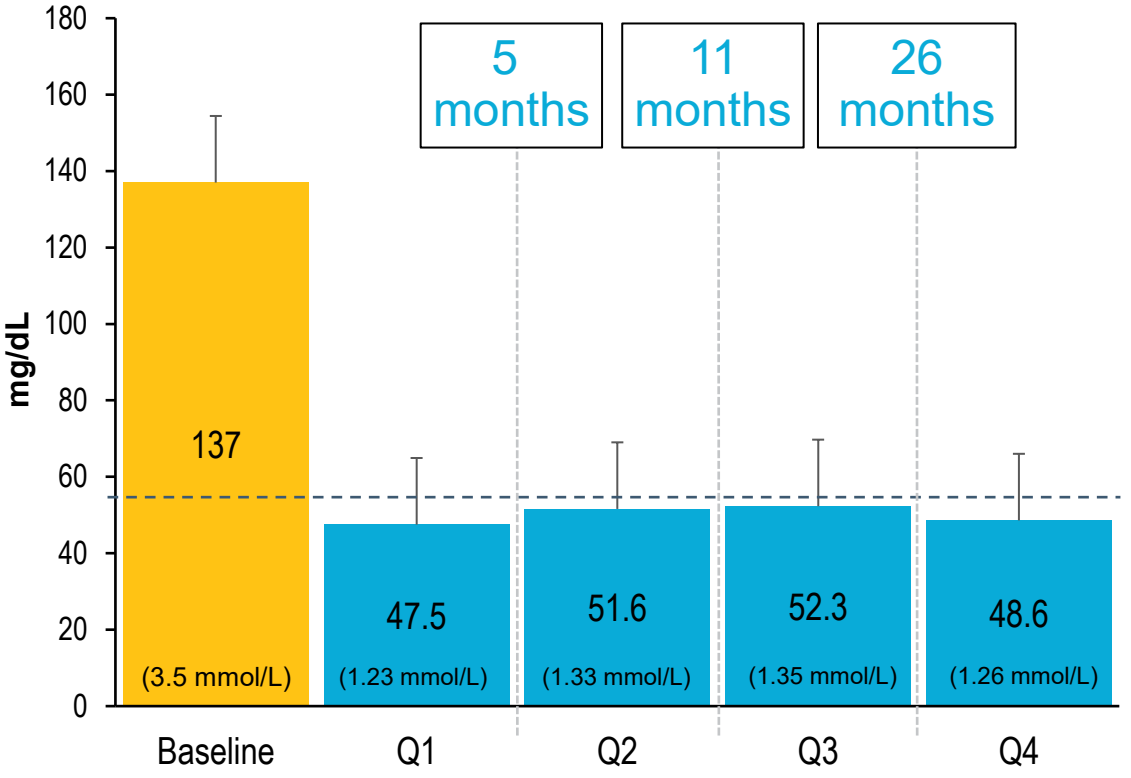
The extensive body of evidence revealing the low compliance with current recommendations for LDL-C optimization in patients with ACS should serve as a call to action. The cardiovascular community, healthcare administrators, and policymakers must rise to the occasion and promptly offer specific solutions to known barriers. A key takeaway for practitioners is to break the therapeutic inertia and implement early intensified lipid-lowering therapy early (i.e., during the inpatient recovery phase). Given the consistent data showing that lower LDL levels correlate with better outcomes, it is reasonable to consider the immediate initiation of PCSK9 inhibition following a myocardial infarction (MI). This approach is being investigated in the EVOLVE MI trial (NCT05284747). As coined by several ESC associations: Strike early and strike strong!

Effects of the strike early-strike strong lipid lowering strategy with PCSK9i in patients with ACS. A real-world evidence from the AT-TARGET-IT registry

771 ACS patients treated with PCSK9i prescription during hospitalization or at discharge in 22 Italian centres



Quartiles of follow-up	Q1	Q2	Q3	Q4
Percentage of LDL-C reduction at the first lipid control	68.2 (55.5, 86.7)	70.3 (60.1, 88.0)	68.7 (53.3, 78.9)	67.0 (54.9, 76.6)



Quartiles of follow-up	Q1	Q2	Q3	Q4
Percentage of LDL-C reduction at the last lipid control	65.2 (58.2, 81.6)	62.6 (55.9, 81.3)	61.7 (56.7, 80.1)	64.4 (52.6, 83.8)

ACS, acute coronary syndrome; LDL(-C), low density lipoprotein (cholesterol); PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Q, quartile

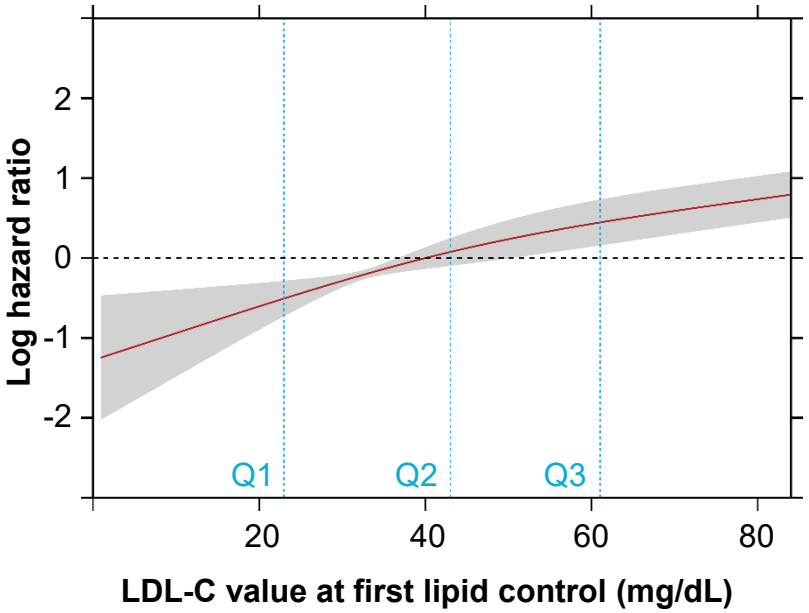
P. Gargiulo, G. Musumeci, P. Fillardi et al. Eur J Prev Cardiol. 2024 May 24:zwae170

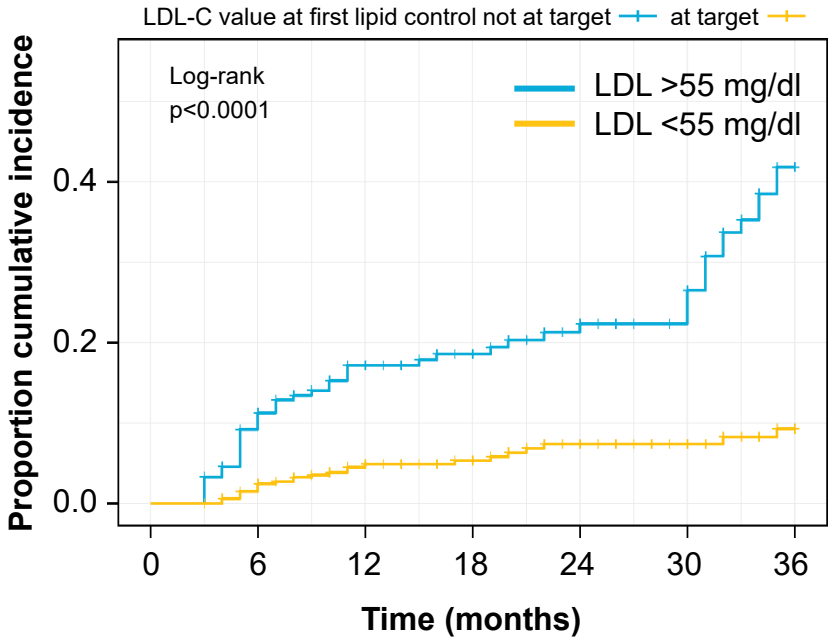
Effects of the strike early-strike strong lipid lowering strategy with PCSK9i in patients with ACS. A real-world evidence from the AT-TARGET-IT registry

771 ACS patients treated with PCSK9i prescription during hospitalization or at discharge in 22 Italian centres

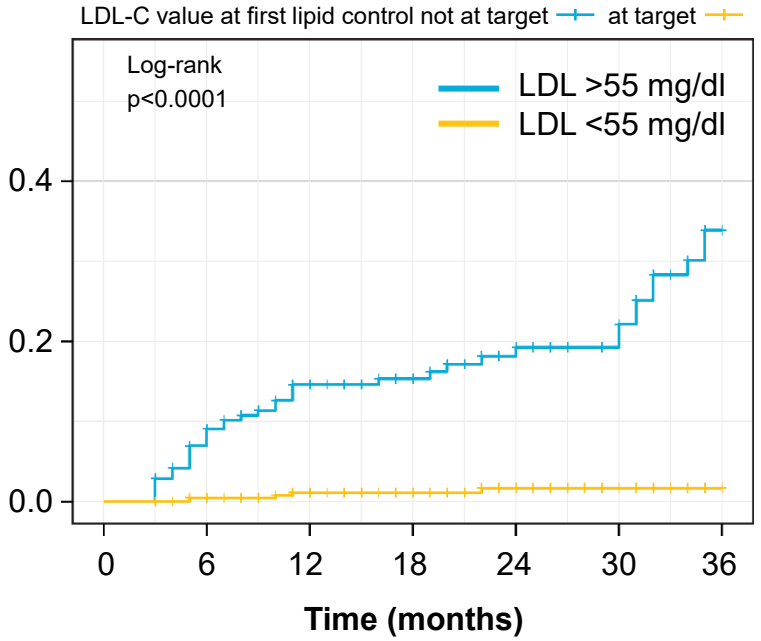
Better prognosis in patients at target

3P-MACE: Death, non-fatal MI and Stroke





All-cause mortality



LDL 55 mg/dl = 1.4 mmol/L

3-P, 3-parameter; ACS, acute coronary syndrome; LDL(-C), low density lipoprotein (cholesterol); MACE, major adverse cardiovascular event; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Q, quartile

P. Gargiulo, G. Musumeci, P. Fillardi et al. Eur J Prev Cardiol. 2024 May 24:zwae170. doi: 10.1093/eurjpc/zwae170. Online ahead of print

Impact of personalized, SES LL approach vs conventional strategies on LDL-c levels and CV outcomes

Period A (N=198; January-June 2019): LDL-C goal <70 mg/dL

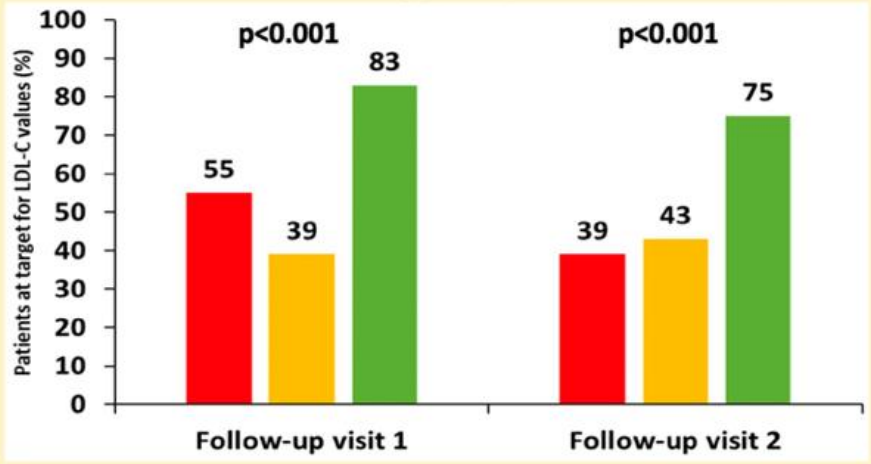
Period B (N=180; January-June 2021): LDL-C goal <55 mg/dL and stepwise approach

Period C (N=122; January-June 2023): LDL-C goal <55 mg/dL and personalized, SES lipid-lowering strategy

Patients on chronic statin treatment and LDL-C < 100 mg/dl	Increase statin dose or change to more potent statin and/or add ezetimibe
Patients on chronic statin treatment and LDL-C ≥ 100 mg/dl	«Fast track strategy» with ezetimibe plus PCSK9 inhibitor
Patients without chronic statin treatment and LDL-C < 150 mg/dl	Potent statin at high dose ± ezetimibe
Patients without chronic statin treatment and LDL-C ≥ 150 mg/dl	«Fast track strategy» with potent statin + ezetimibe + PCSK9 inhibitor

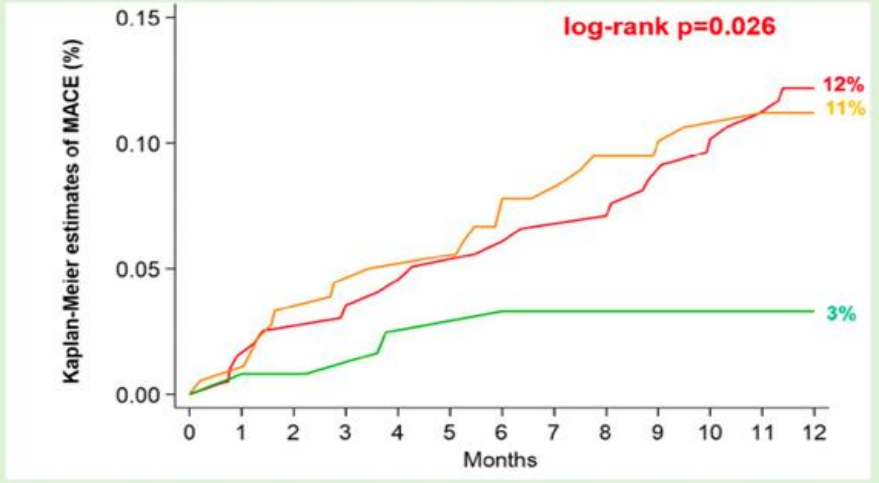
Primary Laboratory Endpoint

Prevalence of patients who achieved LDL-C goal in at least one visit during follow-up



Primary Clinical Endpoint

Kaplan-Meier curves for the incidence of MACE at one year in the three periods



G. Patti et al. European Heart Journal - Cardiovascular Pharmacotherapy, Published: 24 January 2025

ESC European Society of Cardiology
European Heart Journal (2025) 00, 1–20
https://doi.org/10.1093/eurheartj/ehaf190

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias

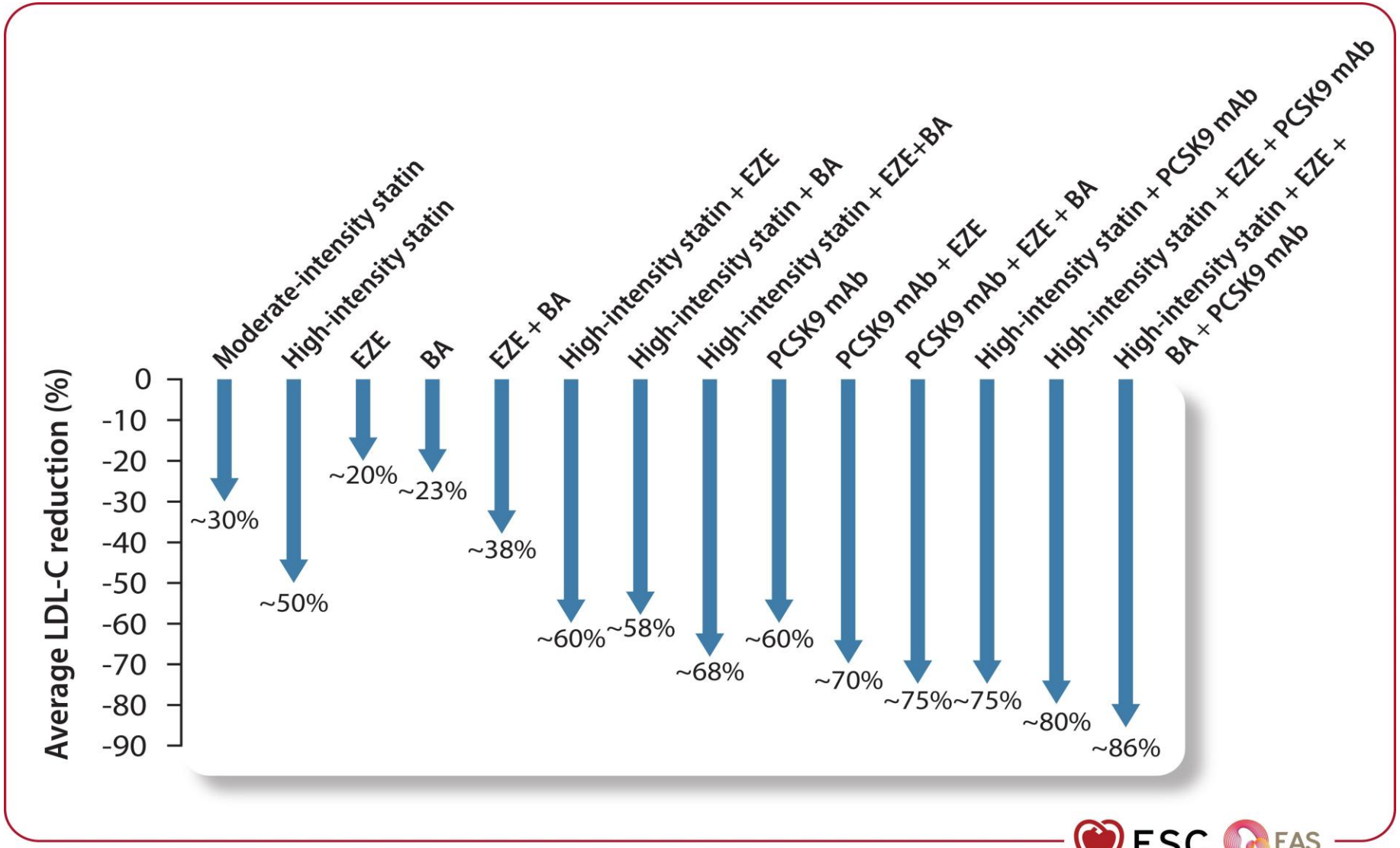
Developed by the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

Recommendation Table 3 — Recommendations for lipid-lowering therapy in patients with acute coronary syndromes (see also Supplementary data online, Evidence Table 3)

Recommendations	Class[a]	Level[b]
Intensification of lipid-lowering therapy during the index ACS hospitalization is recommended for patients who were on any lipid-lowering therapy before admission in order to further lower LDL-C levels.	I	C
Initiating combination therapy with high-intensity statin plus ezetimibe during index hospitalization for ACS should be considered in patients who were treatment-naïve and are not expected to achieve the LDL-C goal with statin therapy alone.[66]	IIa	B

As the extent of LDL-C reduction in response to pharmacological interventions is predictable based on baseline LDL-C levels, it is reasonable to assume that a significant proportion of ACS patients will not achieve their target goal with high-intensity statin treatment alone, prescribed at discharge.[77] Therefore, and in line with the current 2023 ESC Guidelines for the management of patients with ACS,[58] this Task Force proposes a strategy of early, intensive LDL-C lowering to be considered in all patients with ACS, with immediate initiation of statin therapy and combination treatment with one or more classes of non-statin therapy with proven CV benefit as needed, depending on each patient's lipid-lowering therapy prior to the ACS event. The choice of drug for combination therapy should be based on the magnitude of additional LDL-C lowering required. Several drugs and drug combinations with various efficacies and onsets of action are available to enable such a 'strike early and strong' approach (*Figure 2*). *Recommendation Table 3* includes two new recommendations for this clinical setting, for patients who present either with or without pre-existing lipid-lowering therapy at the time of the ACS event.

ESC Guidelines 2025: Average reduction in LDL-C levels with different pharmacological therapies



ESC EAS

Eur Heart J, ehaf190, https://doi.org/10.1093/eurheartj/ehaf190.

CLEAR PATH

il trattamento del paziente displipidemico al CENTRO

27 febbraio 2025
Torino

CLEAR PATH 2.0

il trattamento del paziente displipidemico al CENTRO

28-29 maggio 2025
Hotel San Rocco - Orta San Giulio

STUDIO OSSERVAZIONALE

Clear Pathway: ruolo dell'acido bempedoico nelle strategie ipolipemizzanti. Il parere dei cardiologi del Piemonte e della Valle d'Aosta

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[17]S.C. Cardiologia, Ospedale Civile, Chivasso (TO)
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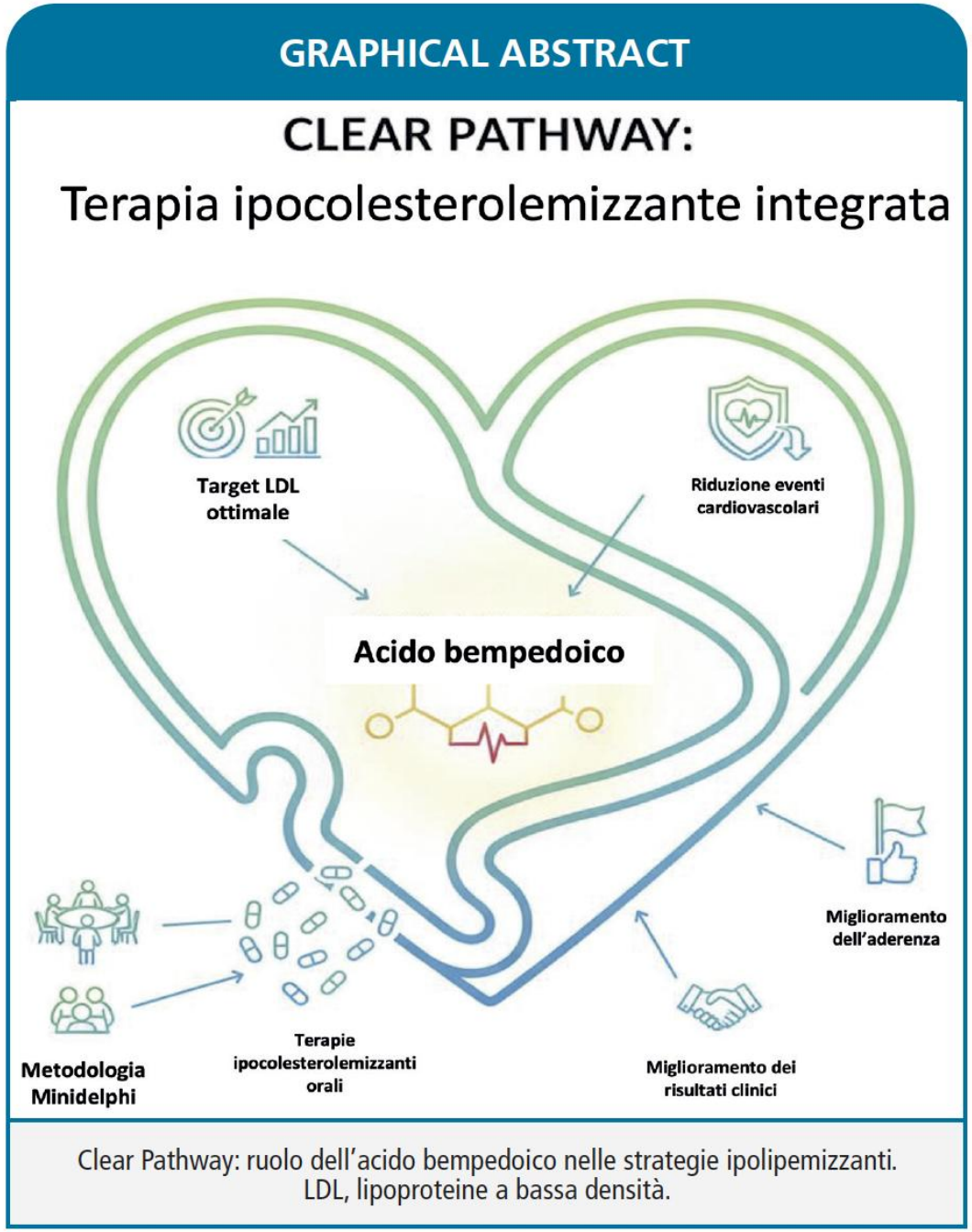
GRAPHICAL ABSTRACT



Clear Pathway: ruolo dell'acido bempedoico nelle strategie ipolipemizzanti. LDL, lipoproteine a bassa densità.

DISTANZA DAL TARGET		
n	Statement	Media voto
6	La distanza dal target LDL deve essere il criterio primario per stabilire la combinazione terapeutica più indicata per il raggiungimento del target LDL stesso	4.5
7	Nel paziente post-SCA non in trattamento con terapia ipolipemizzante e con livelli di colesterolo LDL inferiori a 140 mg/dl, potrebbe essere opportuno avviare precocemente con un percorso fast-track una terapia orale combinata composta da statina alta intensità, ezetimibe e acido bempedoico	3.7
7 rif	Nel paziente post-SCA non in trattamento con terapia ipolipemizzante e con livelli di colesterolo LDL inferiori a 140 mg/dl senza fattori di rischio aggiuntivo (malattia multivaso, diabete mellito e PAD), potrebbe essere opportuno avviare precocemente con un percorso fast-track una terapia orale combinata composta da statina alta intensità, ezetimibe e acido bempedoico	4.6
8	I pazienti post-SCA con una distanza significativa dal target LDL (ad esempio, colesterolo LDL > 140 mg/dl) sono candidati prioritari per una terapia di combinazione con statina, ezetimibe e PCSK9-I, tramite un percorso fast-track	4.9
9	I pazienti a rischio proibitivo non a target con statine, ezetimibe ed PCSK9-I potrebbero essere candidati ad una terapia di combinazione con statina, ezetimibe, PCSK9-I ed acido bempedoico	4.9

Raccomandazioni dei Panelists per l'uso di Acido Bempedoico nella Pratica Clinica

- Paziente intollerante alla terapia con statine
- Paziente a rischio cardiovascolare Moderato, Alto e Molto Alto, senza storia di eventi CV
- Paziente Diabetico
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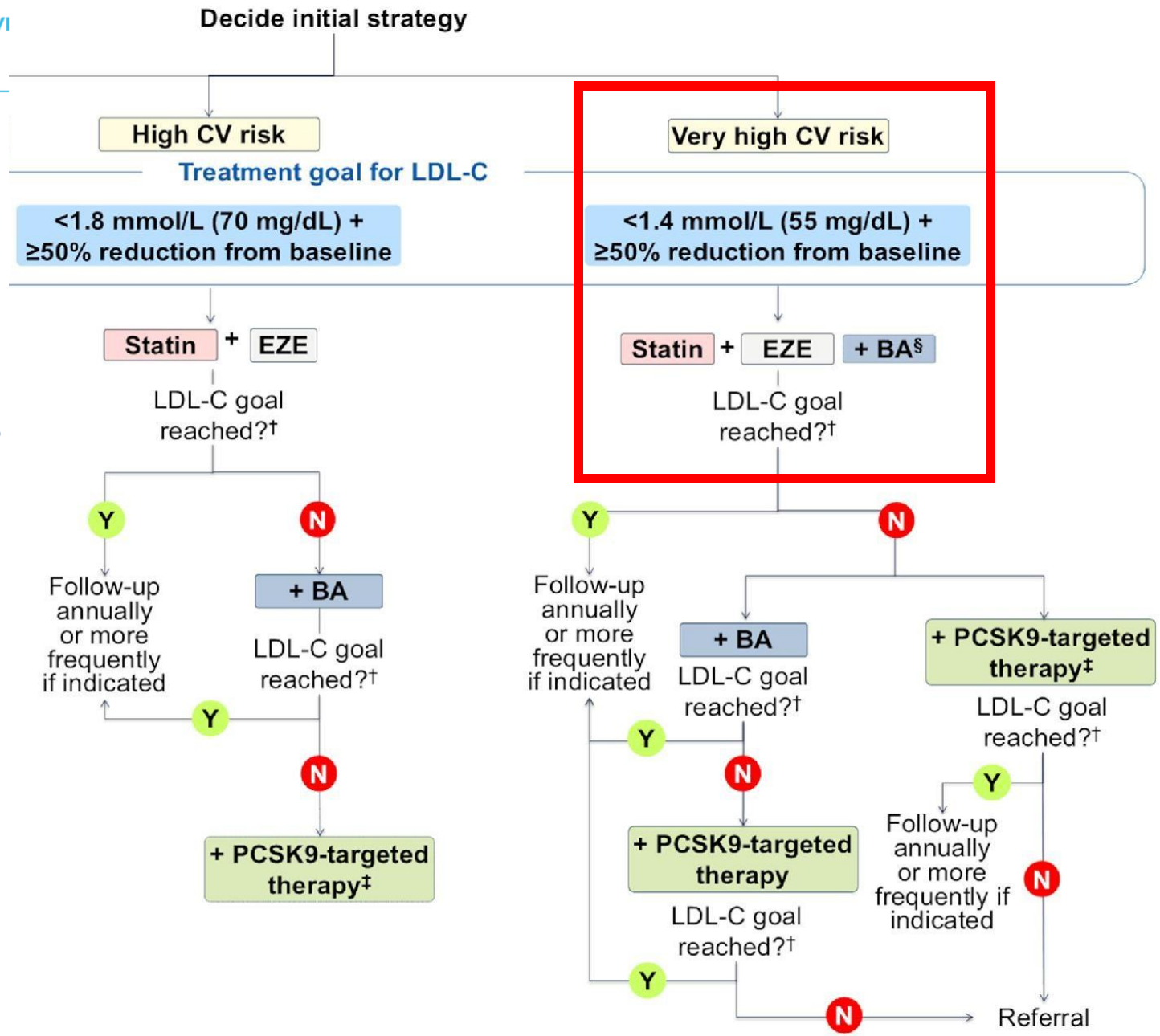
- Paziente con Arteriopatia Periferica

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2025) **0**, 1–13
https://doi.org/10.1093/ehjcvp/pvaf007

Expert opinion on the integration of combination therapy into the treatment algorithm for the management of dyslipidaemia: the integration of ezetimibe and bempedoic acid may enhance goal attainment

Klaus G. Parhofer[1,*], Carlos Aguiar[2], Maciej Banach[3,4,5,6], Heinz Drexel[7], Ioanna Gouni-Berthold[8], Leopoldo Pérez de Isla[9], Ernst Rietzschel[10], Alberto Zambon[11], and Kausik K. Ray[12]



Eur Heart J Cardiovasc Pharmacother, pvaf007, https://doi.org/10.1093/ehjcvp/pvaf007

ESC Working Group Cardiovascular Pharmacotherapy

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- Paziente con SCA in terapia con Statine ed Ezetimibe ed LDL ≥ **70** mg/dl

Aggiunge Acido Bempedoico ed I-PCSK9 alla dimissione

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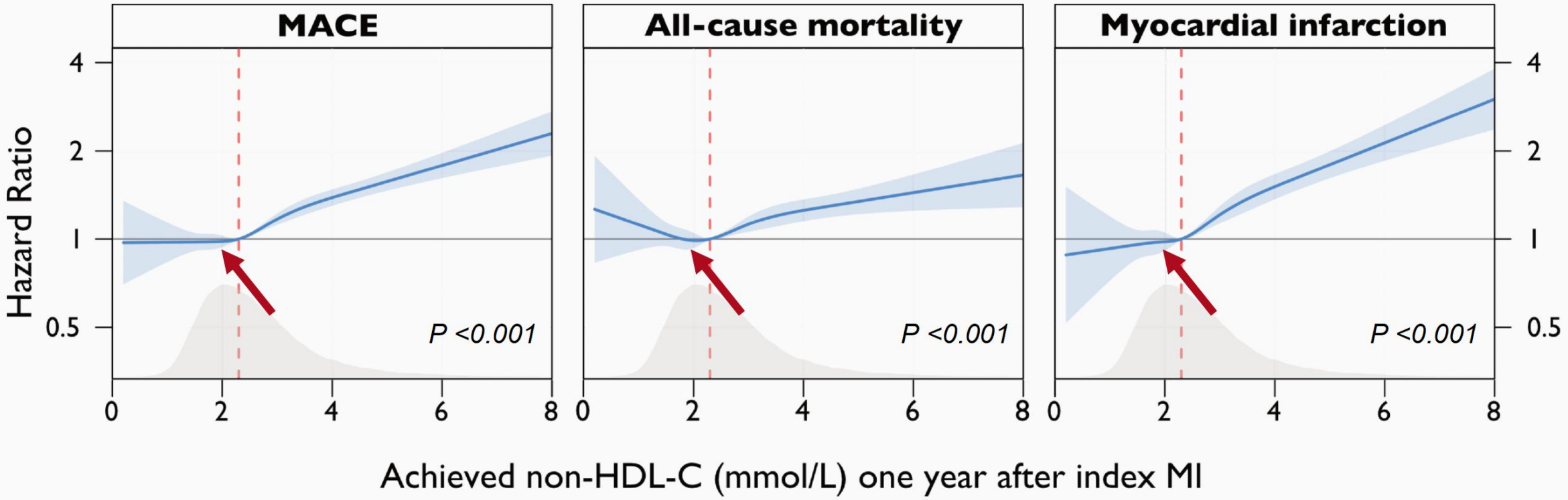
- Paziente con SCA naive da Statine con LDL ≥ 140 mg/dl o > 70 e PAD o DM o MV

Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

Conclusioni

- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ L'aggiunta degli I-PCSK9 determina un'ulteriore riduzione dei livelli di LDL e un conseguente miglioramento della prognosi ed è raccomandata in Classe I
- ✓ **L'aggiunta degli I-PCSK9 in fast-track (in-H/dimissione) è raccomandata nei pazienti ACS o eventi CV multipli già in terapia con statine e LDL $\geq$ 70 mg/dl e nei pazienti ACS naive da statine ed LDL $\geq$ 140 mg/dl in particolare se a rischio proibitivo (DM, MV, PAD, recidivanti)**
- ✓ Il progetto CLEAR-PATH in Piemonte potrebbe ottimizzare ulteriormente il trattamento garantendo non solo il raggiungimento del target nella totalità dei pazienti con ulteriore riduzione degli eventi avversi CV

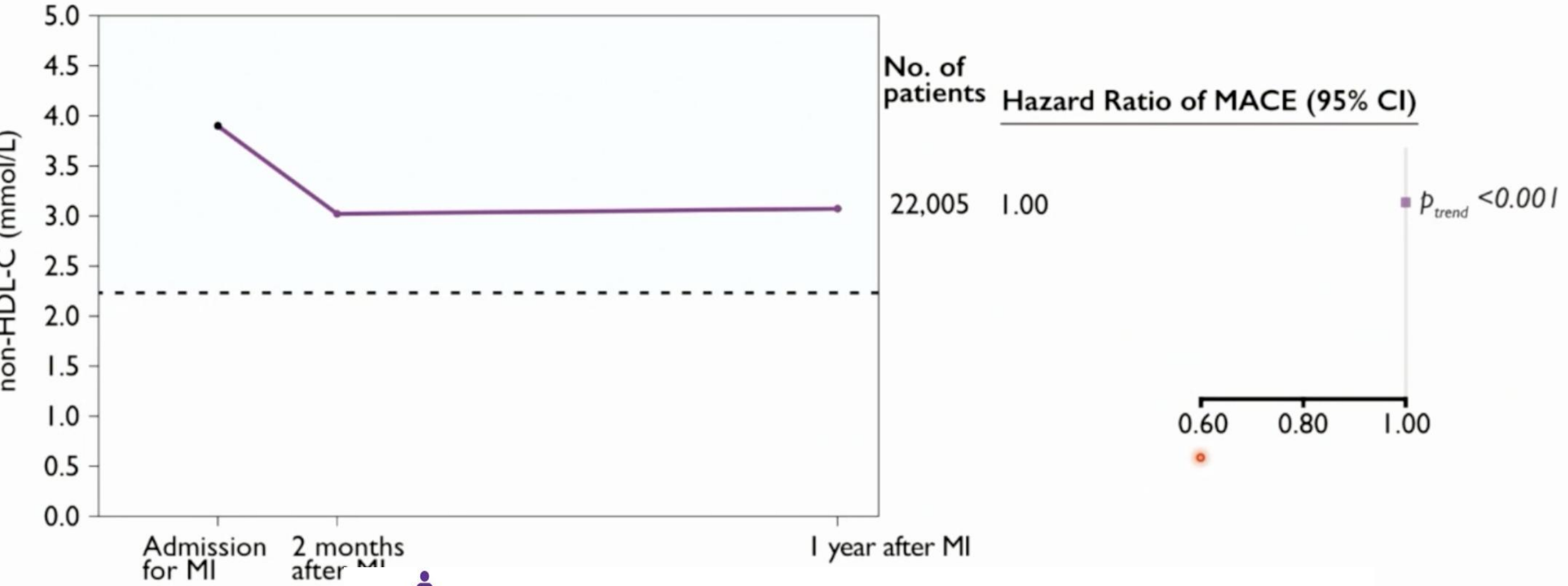
Risk of outcomes by achieved non-HDL-C



Cox regression modelled in restricted cubic spline, adjusting for age at follow-up, statin intensity at admission, systolic blood pressure at 1-year follow-up, smoking at 1-year follow-up, sex, statin intensity at 1-year follow-up, body mass index at 1-year follow-up, history of diabetes, creatinine at admission, non−HDL-C at admission, and left ventricular ejection fraction at admission.

J. Schubert et al Eur Heart J, 2024 ehae576, https://doi.org/10.1093/eurheartj/ehae576

Sometimes speed really maters- Post MI- Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained lowering vs all other approaches **the SWEDEHEART registry**



46 518 patients with MI and 7407 MACE (all-cause mortality, MI, or stroke)

Schubert J et al, EHJ 10.1093/eurheartj/ehae576

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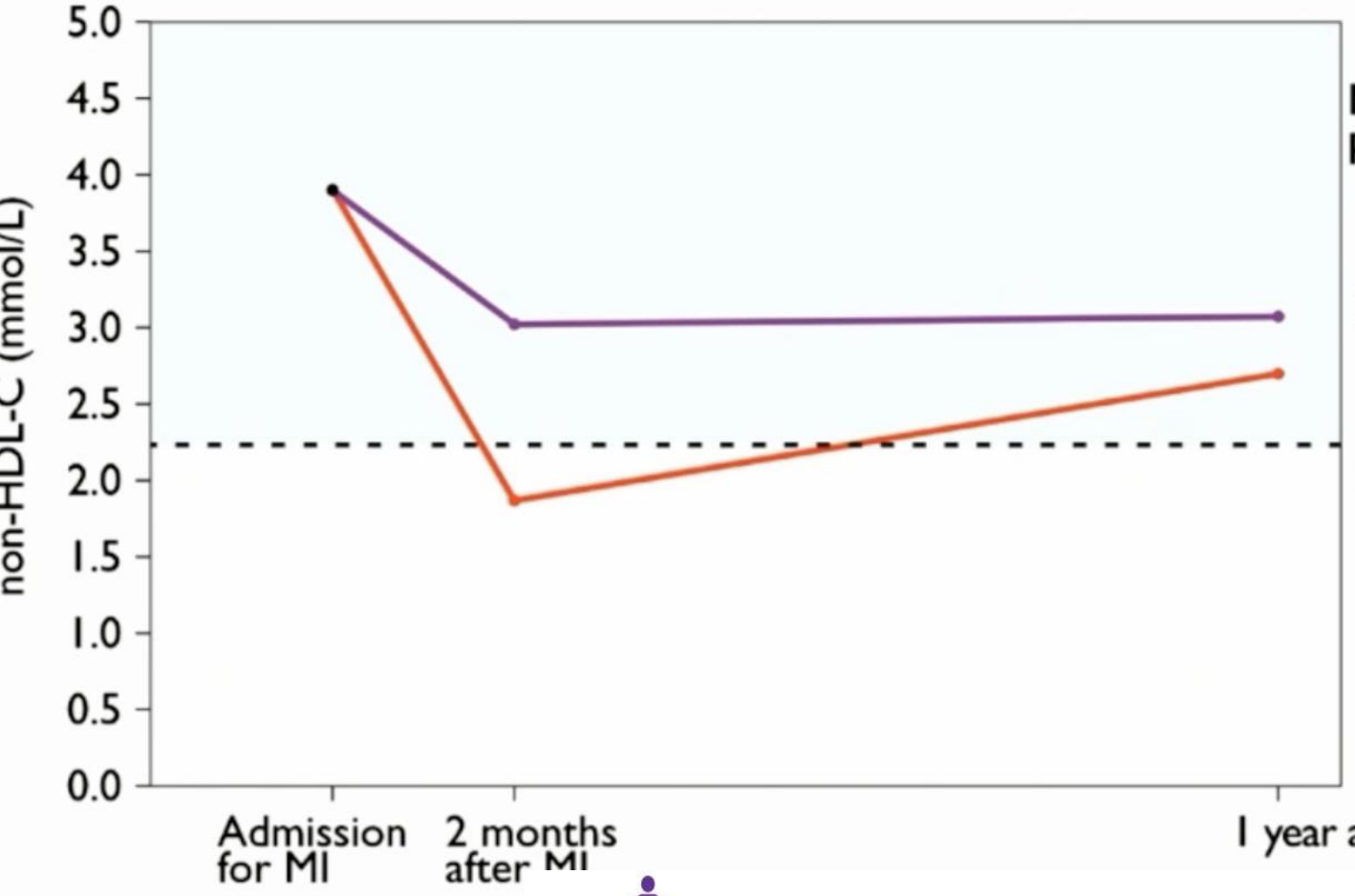

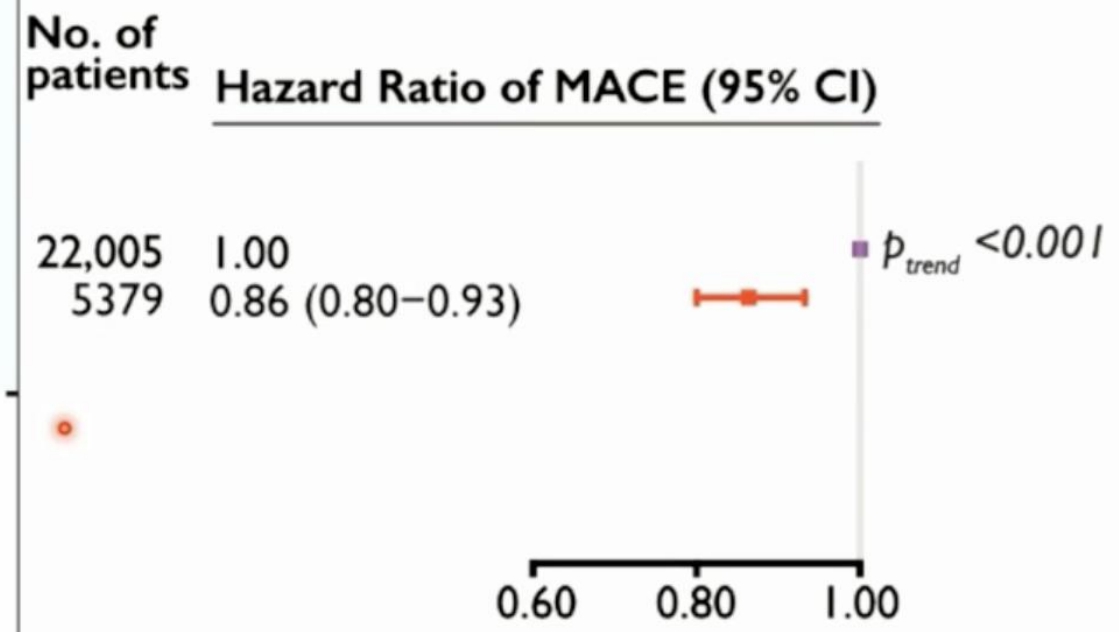

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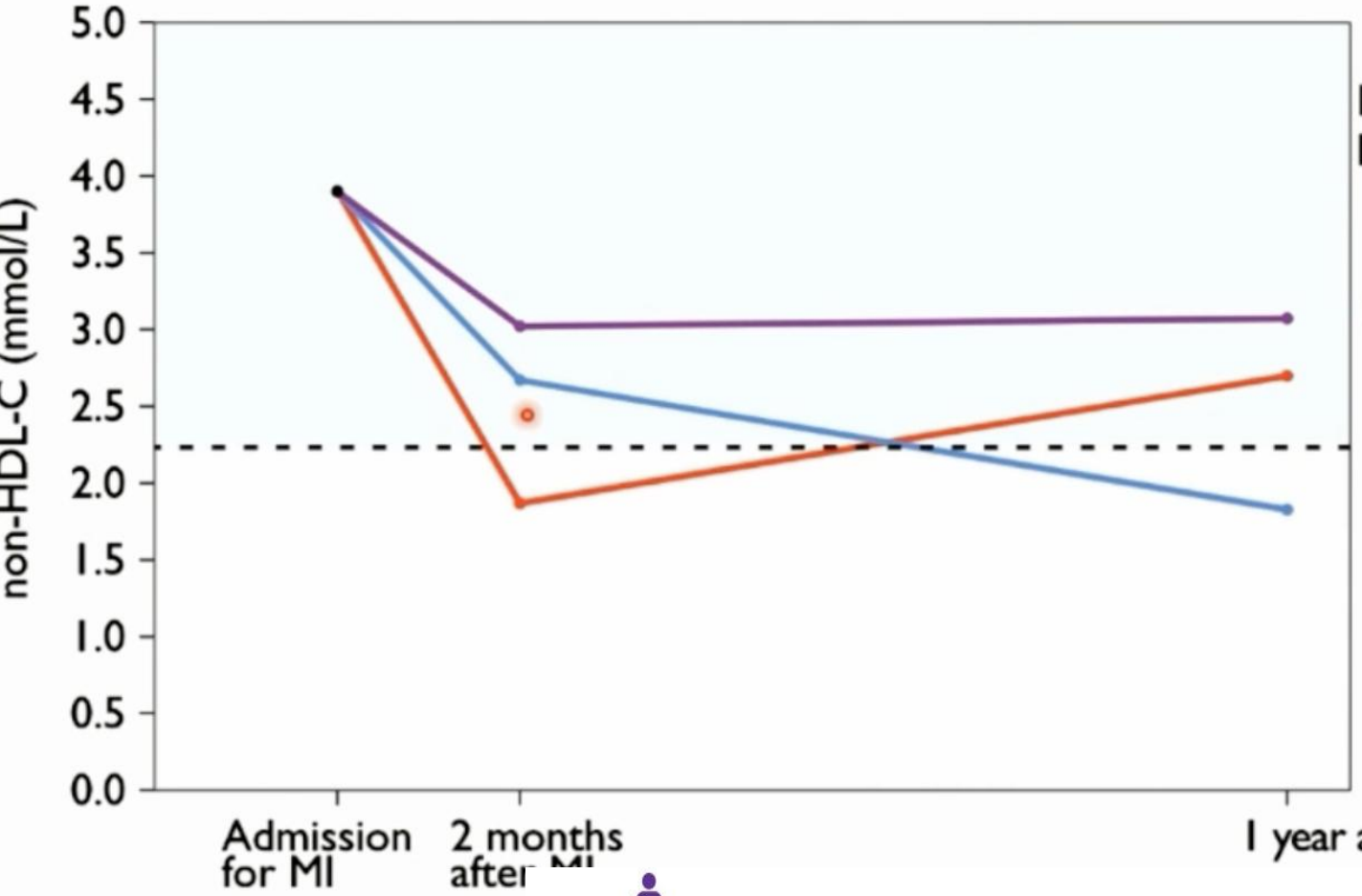

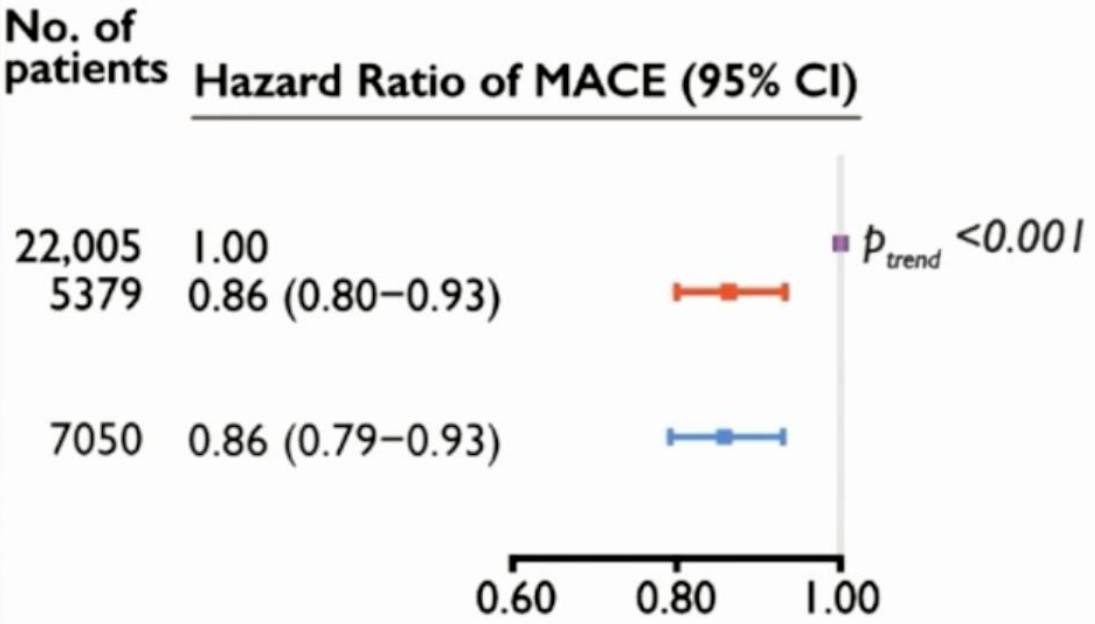

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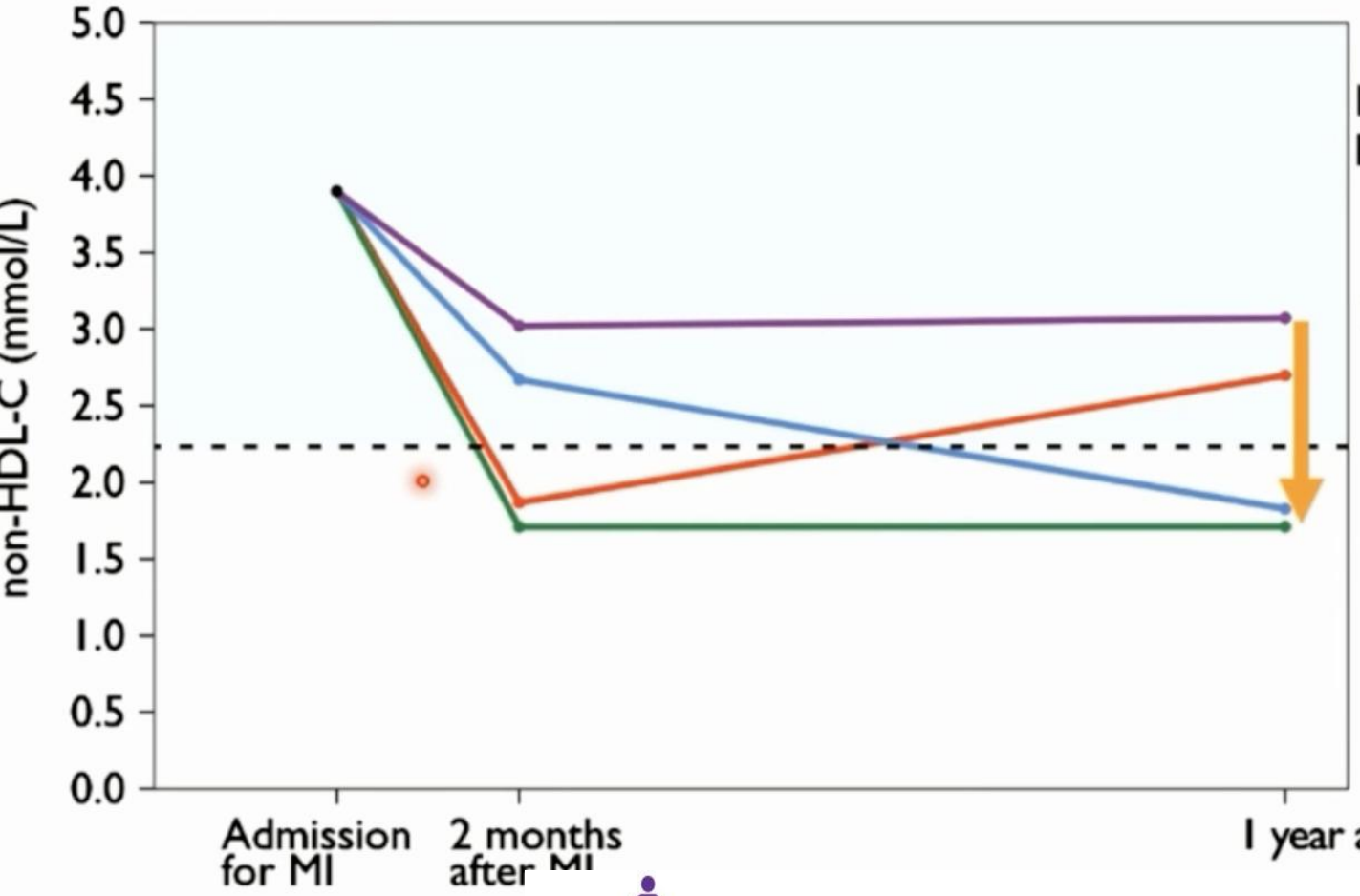
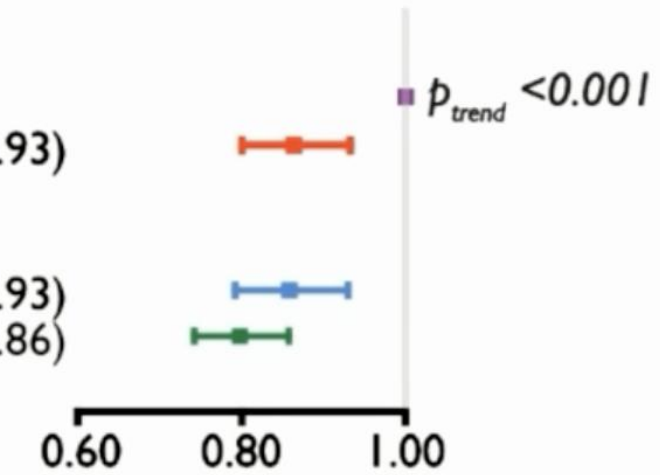


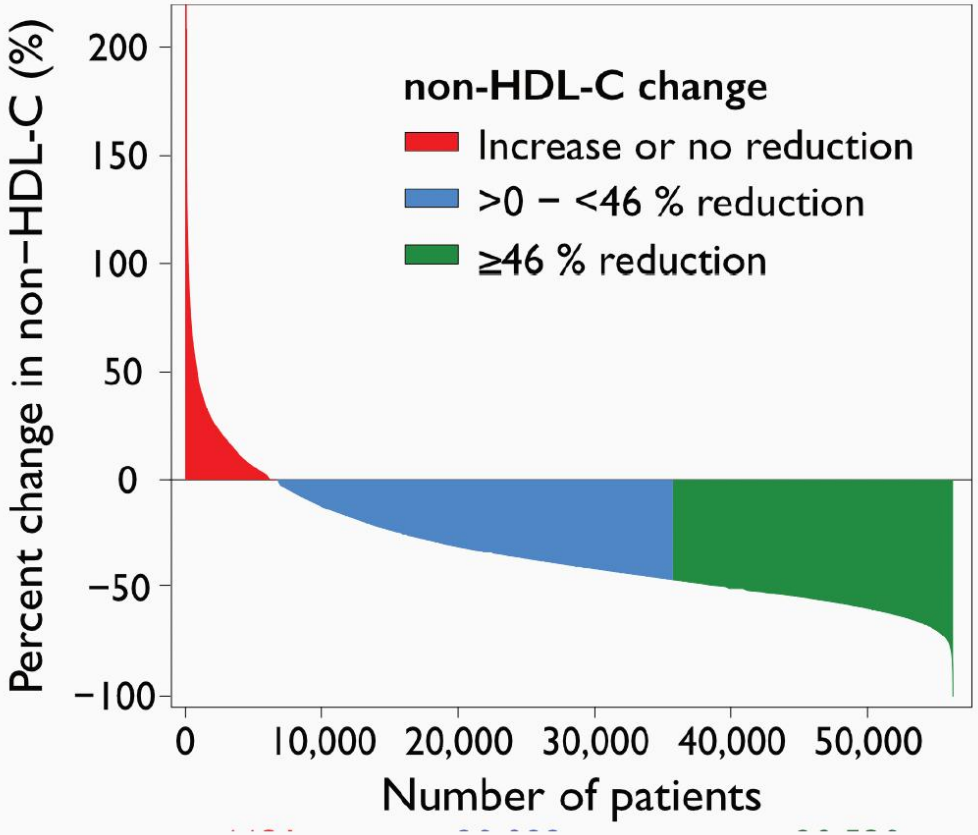
No. of patients	Hazard Ratio of MACE (95% CI)
22,005	1.00
5379	0.86 (0.80–0.93)
7050	0.86 (0.79–0.93)
12,084	0.80 (0.74–0.86)

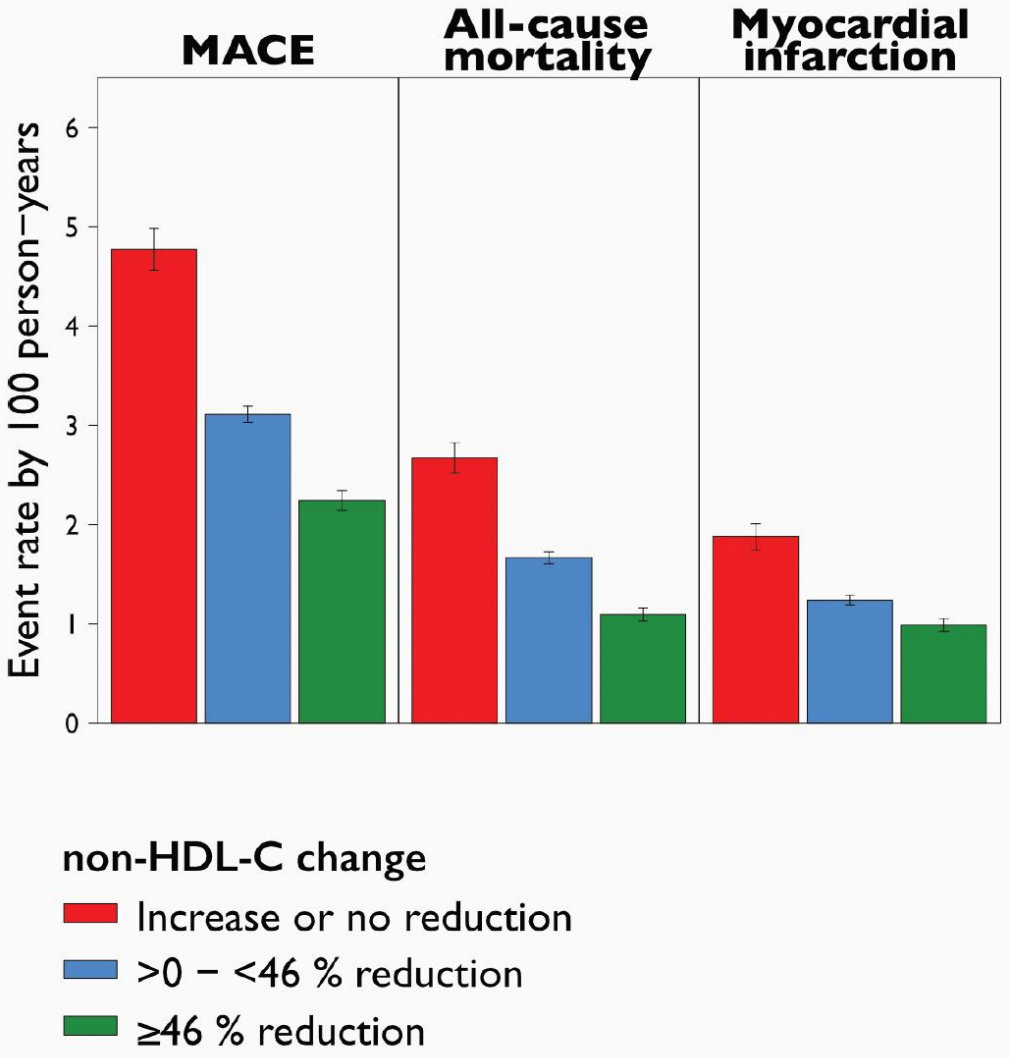


46 518 patients with MI and 7407 MACE (all-cause mortality, MI, or stroke)

Schubert J et al, EHJ 10.1093/eurheartj/ehae576

Reduction, how to aichieve it and association with outcomes





The current step-wise lipid lowering strategy might lead to delayed target achievement and risk of harm

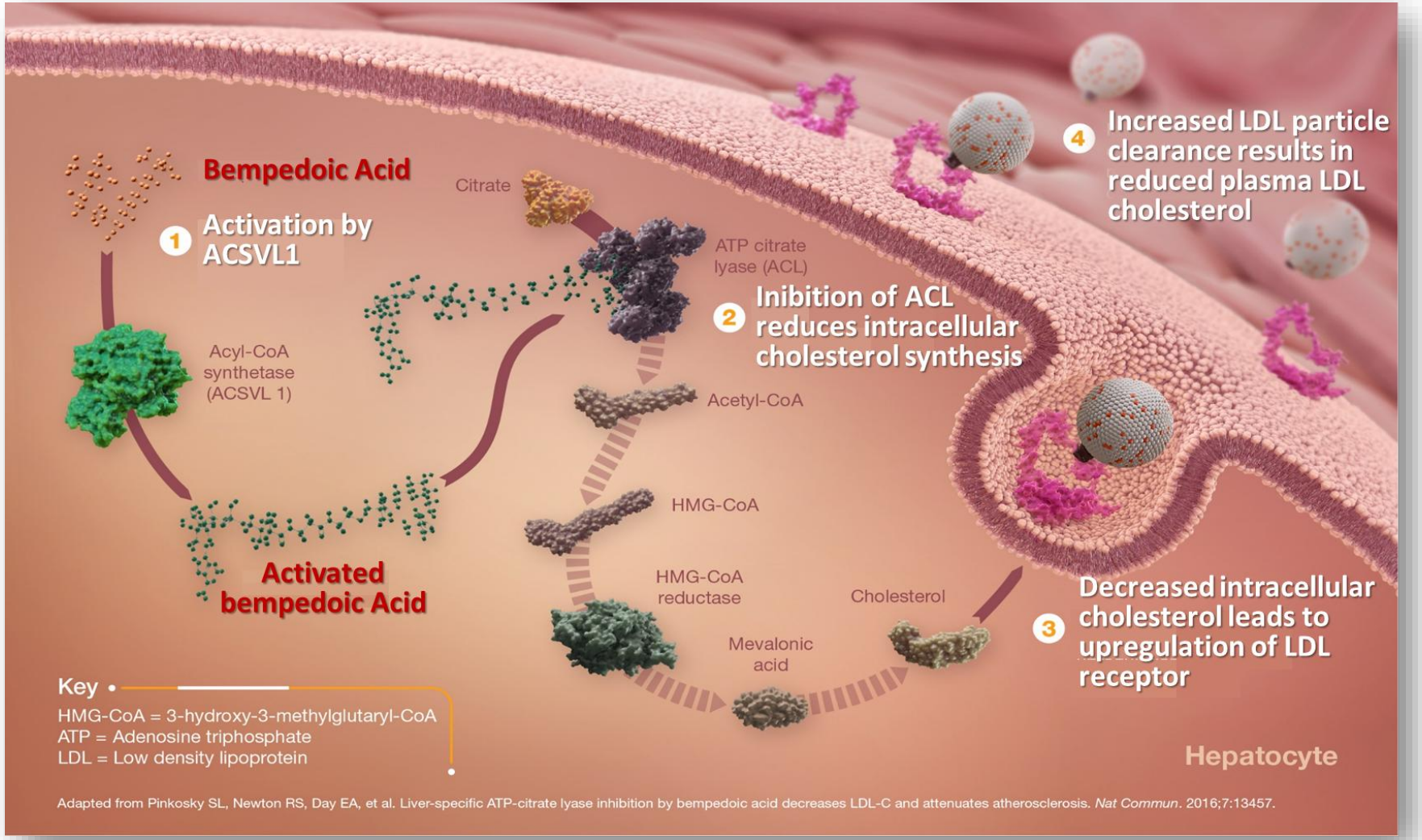
J. Schubert et al Eur Heart J, 2024 ehae576, https://doi.org/10.1093/eurheartj/ehae576

Conclusioni

- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ L'aggiunta degli I-PCSK9 in fast-track (in-H/dimissione) è raccomandata nei pazienti ACS o eventi CV multipli già in statine e LDL $\geq$ 70 mg/dl e nei pazienti ACS naive da statine ed LDL $\geq$ 140 mg/dl e garantisce raggiungimento del target e prognosi migliore
- ✓ L'acido bempedoico si è dimostrato in grado di ridurre in maniera significativa i livelli di C-LDL, sia in aggiunta alla massima dose di statina tollerata sia in pazienti con intolleranza alle statine, con un effetto ancora maggiore quando utilizzato in combinazione con l'ezetimibe.
- ✓ Inclisiran con le sue caratteristiche di somministrazione, efficacia e sicurezza potrebbe essere ideale nel paziente elettivo garantendo il raggiungimento del target e l'aderenza terapeutica

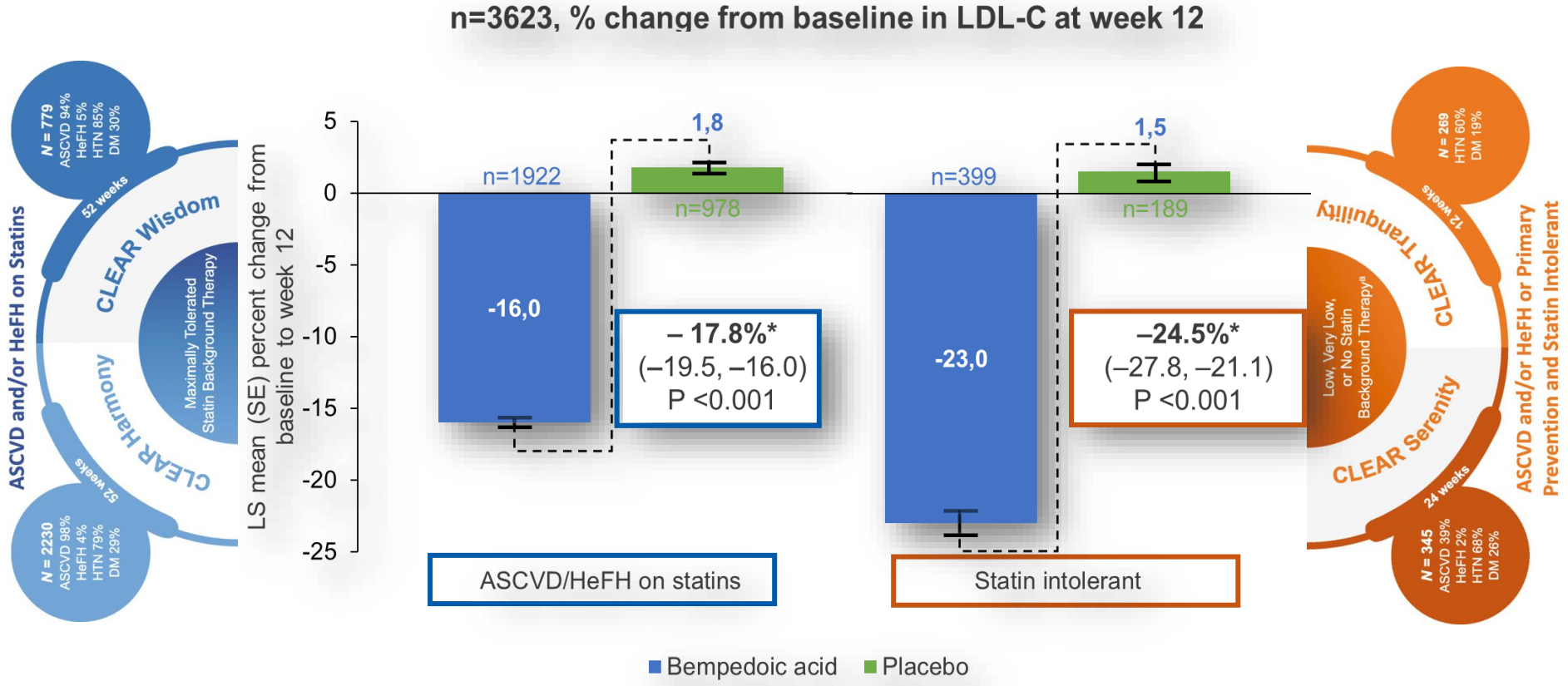
Il meccanismo d'azione unico dell'acido bempedoico è complementare ma distinto da quello delle statine e delle altre LLT

- Attivato principalmente a livello epatico, l'acido bempedoico inibisce l'enzima ATP citrato liasi (ACL) nella ben nota via di sintesi del colesterolo, a monte rispetto al target delle statine
- La conseguente sovra-regolazione dei recettori per le LDL determina un'aumentata captazione di LDL da parte delle cellule epatiche con relativa riduzione dei livelli plasmatici di C-LDL



Adapted from Pinkosky et al. *Nature Communications*. 2016; 7:13457 | DOI: 10.1038/ncomms13457

L’Acido Bempedoico ha dimostrato di ridurre LDL in un ampio spettro di pazienti



Banach M. et al., JAMA Cardiology, published online July 1, 2020. doi:10.1001/jamacardio.2020.2314

Paziente intollerante alla terapia con statine

In CLEAR Outcomes, 13,970 patients at high or very high risk, primary and secondary prevention, unwilling or unable to take a statin were randomised to bempedoic acid or placebo

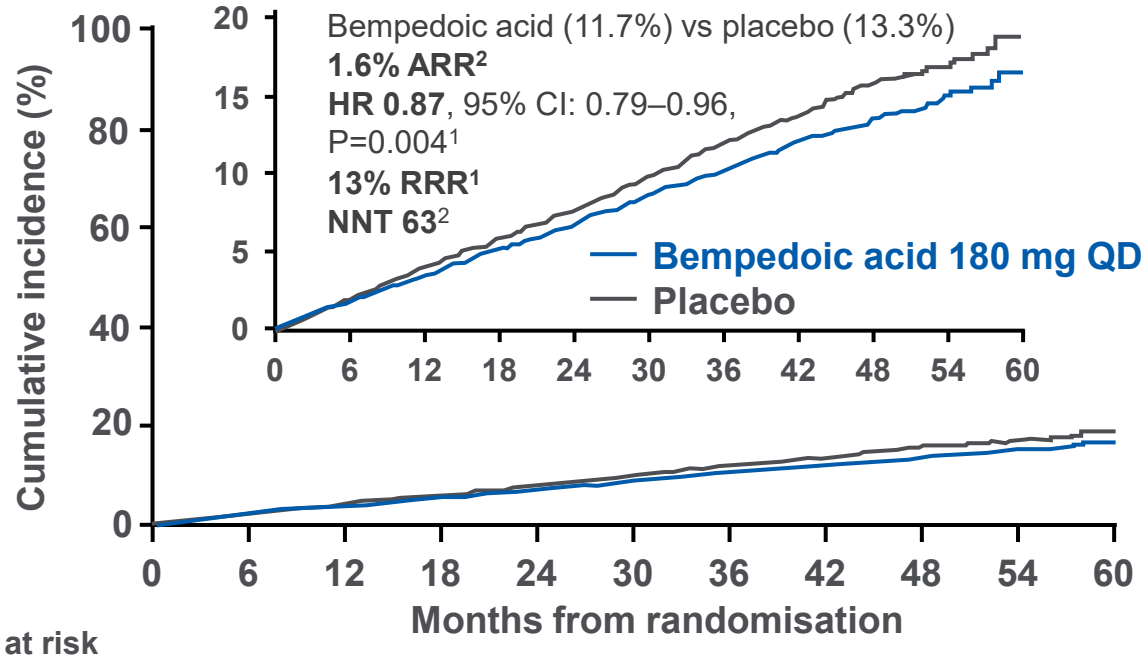
At 6 months, bempedoic acid reduced LDL-C from a baseline of 139.0 mg/dL by a mean of 29.2 mg/dL (21.1%), compared with placebo

Treatment with bempedoic acid reduced 4-component MACE, 3-component MACE, (non)-fatal MI, and coronary revascularisation compared with placebo

Bempedoic acid was well tolerated, with similar overall rates of adverse events, serious adverse events, or adverse events leading to drug discontinuation, compared with placebo

CLEAR Outcomes

4-component MACE*



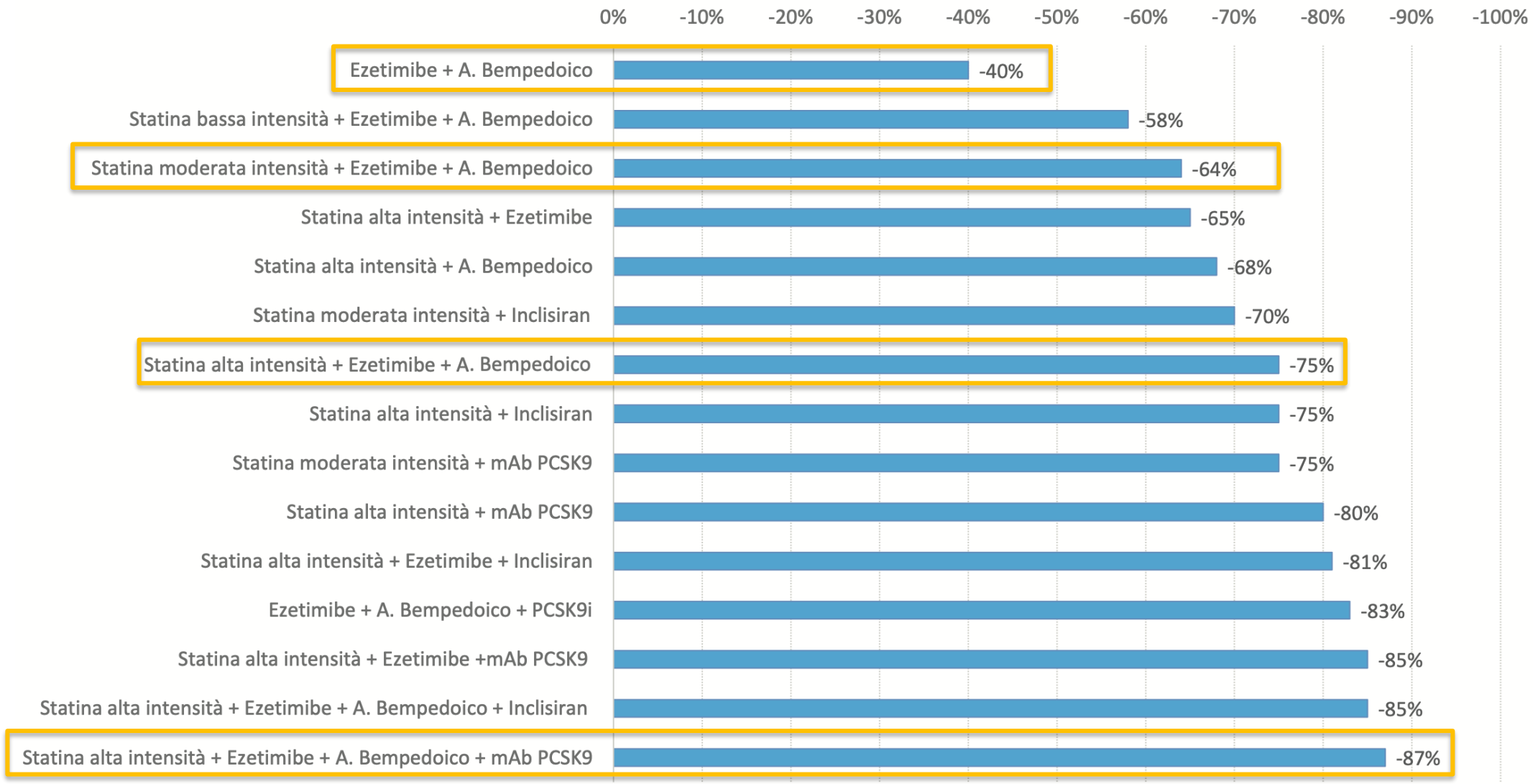
No. at risk											
Placebo	6978	6779	6579	6401	6206	5995	5105	2524	1207	513	55
Bempedoic acid	6992	6816	6654	6472	6293	6106	5257	2601	1240	556	74

*The primary efficacy endpoint is the time to first occurrence of an adjudicated event of 4-component MACE. **4-component MACE**, CV death, nonfatal MI, nonfatal stroke, or coronary revascularisation;

3-component MACE, CV death, nonfatal MI, or nonfatal stroke. **ARR**, absolute risk reduction; **CI**, confidence interval; **HR**, hazards ratio; **LDL-C**, low-density lipoprotein cholesterol; **MACE**, major adverse cardiovascular events; **MI**, myocardial infarction; **NNT**, number needed to treat; **RRR**, relative risk reduction; **QD**, once daily

1. Nissen SE, et al. N Engl J Med. 2023;388:1353–1364; 2. Banach M, et al. Prog Cardiovasc Dis. 2023;S0033-0620(23)00026-9

Riduzioni di C-LDL attese con le diverse combinazioni delle terapie ipolipemizzanti



Raccomandazioni per l'uso di Acido Bempedoico nella Pratica Clinica in Piemonte: il progetto Clear Path

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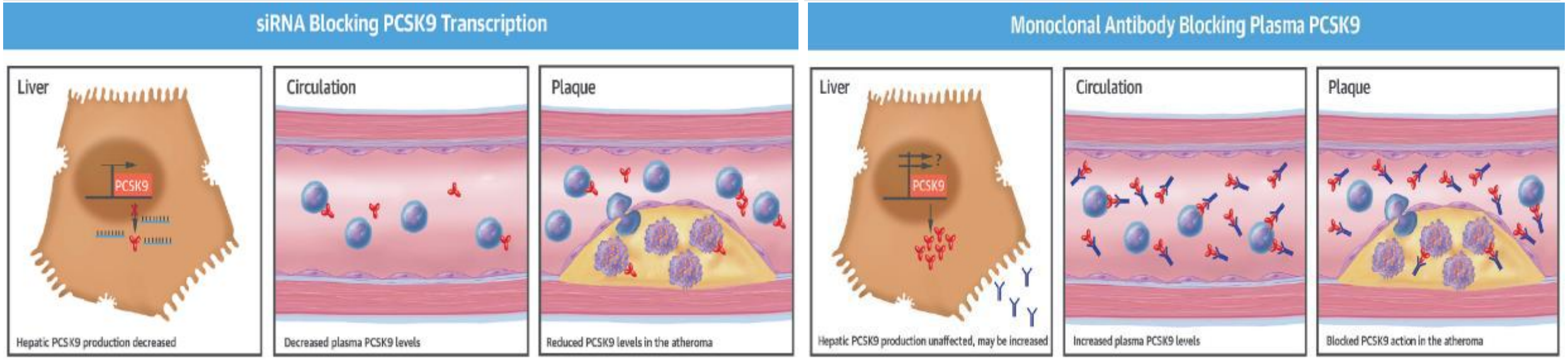
JACC STATE-OF-THE-ART REVIEW

The Evolving Future of PCSK9 Inhibitors

Robert S. Rosenson, MD,[a] Robert A. Hegele, MD,[b] Sergio Fazio, MD, PhD,[c]
Christopher P. Cannon, MD[d]

Inclisiran previene la sintesi dei PCSK9 a livello epatico

I mAbs bloccano La PCSK9 a livello plasmatico



Inclisiran cliva l'mRNA del PCSK9 nel fegato, prevenendone la produzione

I livelli di PCSK9 in circolo e a livello dell'ateroma vengono ridotti

I mAbs anti PCSK9 non alterano la produzione epatica della proteina ma agiscono inibendone la funzione

I mAbs anti PCSK9 legano la proteina a livello circolatorio e dell'ateroma. I livelli di PCSK9 in circolo aumentano

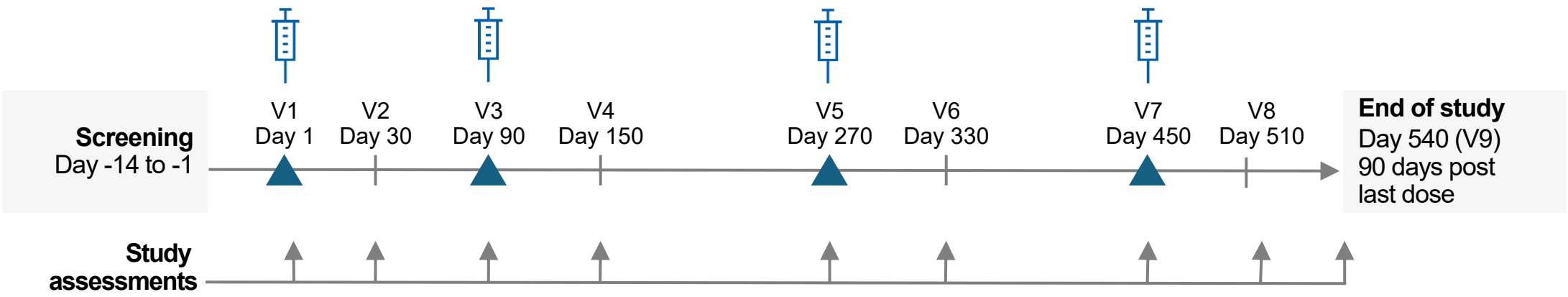
PCSK9i= proprotein convertase subtilisin/kexin type 9 inhibition.

1. Rosenson RS et al. *J Am Coll Cardiol.* 2018;72(3):314-329.
2. Khvorova A. *N Engl J Med*. 2017;376(1):4-7.

ORION 9, 10, 11: Study design and endpoints [1-4]

18-month, double-blind, randomized, placebo-controlled

Randomized 1:1 inclisiran 300 mg* vs placebo—on top of maximally tolerated statin dose



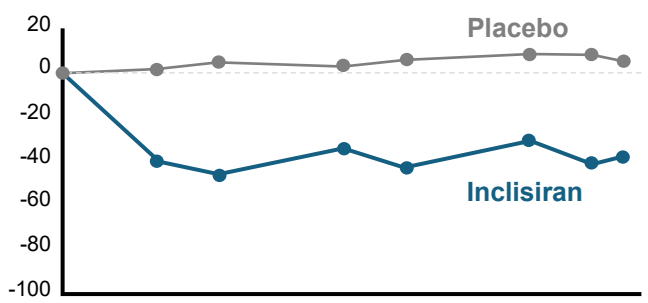
**300 mg inclisiran sodium salt, equivalent to 284 mg of inclisiran.*

__1__. Raal FJ, et al. N Engl J Med. 2020;382(16):1520-1530. __2__. Raal FJ, et al. [supplementary appendix] N Engl J Med. 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805. __3__. Ray KK, et al. N Engl J Med. 2020;382(16):1507-1519. __4__. Ray KK, et al. [supplementary appendix] N Engl J Med. doi: 10.1056/NEJMoa1912387.

ORION 9-10-11: extended reduction of LDL-C for 18 months.

LDL-C Percent change from baseline

ORION[1,3] 9

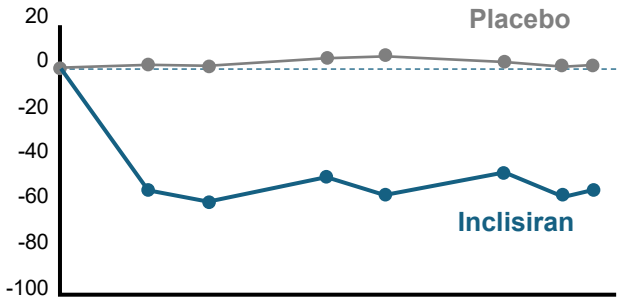


Between group difference

-47,9%

(P<0,001)

ORION[2,4] 10

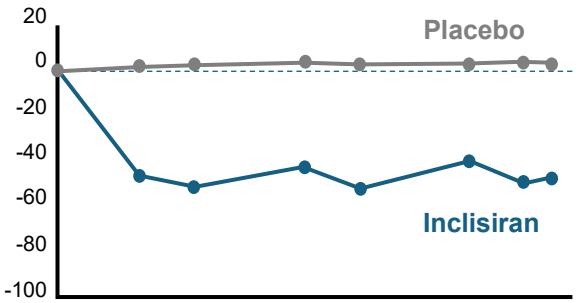


Between group difference

-52,3%

(P<0,001)

ORION[2,4] 11



Between group difference

-49,9%

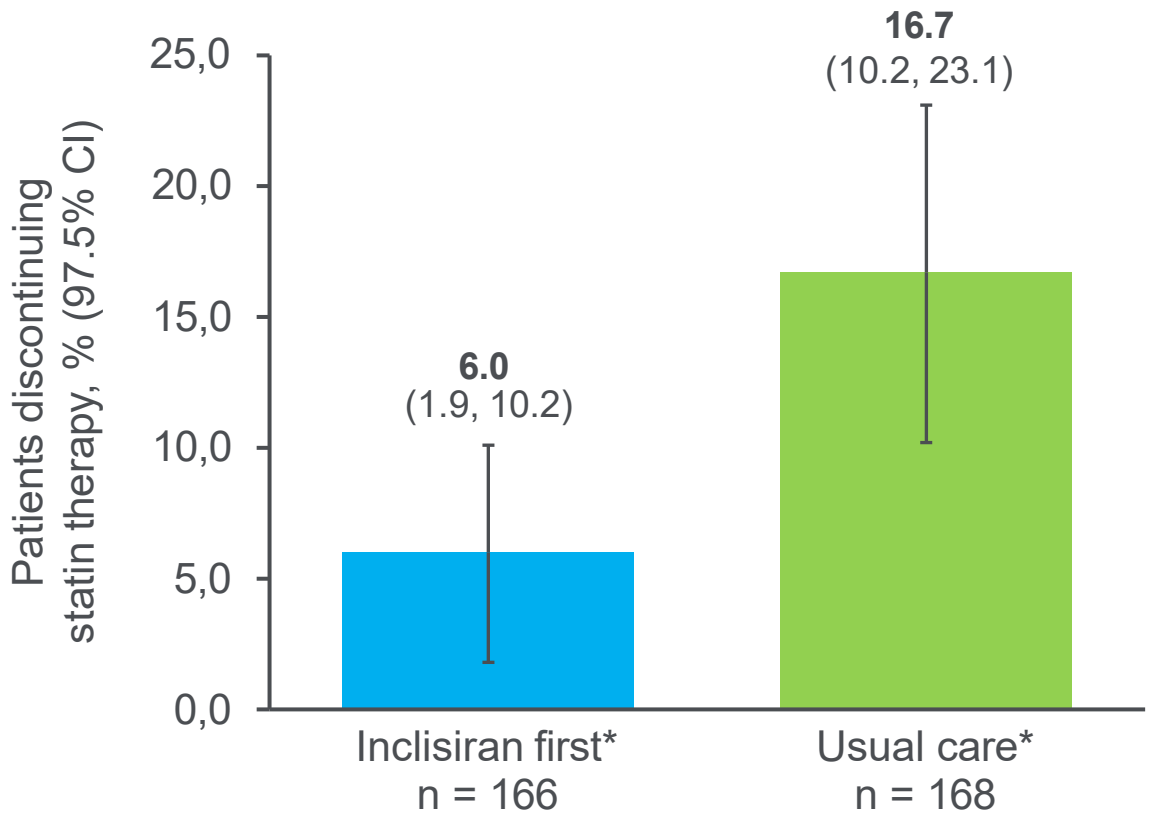
(P<0,001)

1. Raal FJ, et al. N Engl J Med. 2020;382(16):1520-1530. *2.* Ray KK, et al. N Engl J Med. 2020;382(16):1507-1519.
3. Raal FJ, et al. [supplementary appendix]. N Engl J Med. 2020;382:1520-1530. doi: 10.1056/NEJMoa1913805.
4. Ray KK, et al. [supplementary appendix]. N Engl J Med. doi: 10.1056/NEJMoa1912387

VICTORION-INITIATE Randomized Trial

Co-primary endpoint: statin discontinuation

The non-inferiority margin (15%) met comparing “inclisiran first” and usual care (−10.6% [97.5% CI: −18.3%, −3.0%])



*Only patients without a history of statin intolerance.
CI, confidence interval.

Michael J. Koren et al J Am Coll Cardiol. 2024; 83 (20): 1939-1952

Linee Guida ESC/EAS 2019: Pazienti con SCA, PAD, CAD, ICTUS sono classificati come pazienti a **rischio cardiovascolare molto alto**

RISCHIO CV MOLTO ALTO

ASCVD DOCUMENTATA CLINICAMENTE O TRAMITE IMAGING

- **SCA**
- **RIVASCOLARIZZAZIONE CORONARICA**
- **ICTUS O TIA**
- **PAD**

ASCVD DOCUMENTATA TRAMITE IMAGING

- **PLACCA RILEVANTE ALL'ANGIOGRAFIA CORONARICA, O ALLA TAC** (MALATTIA CORONARICA MULTIVASALE, CON DUE ARTERIE EPICARDICHE PRINCIPALI CON STENOSI >50%) O ALL'ULTRASONOGRAFIA CAROTIDEA.

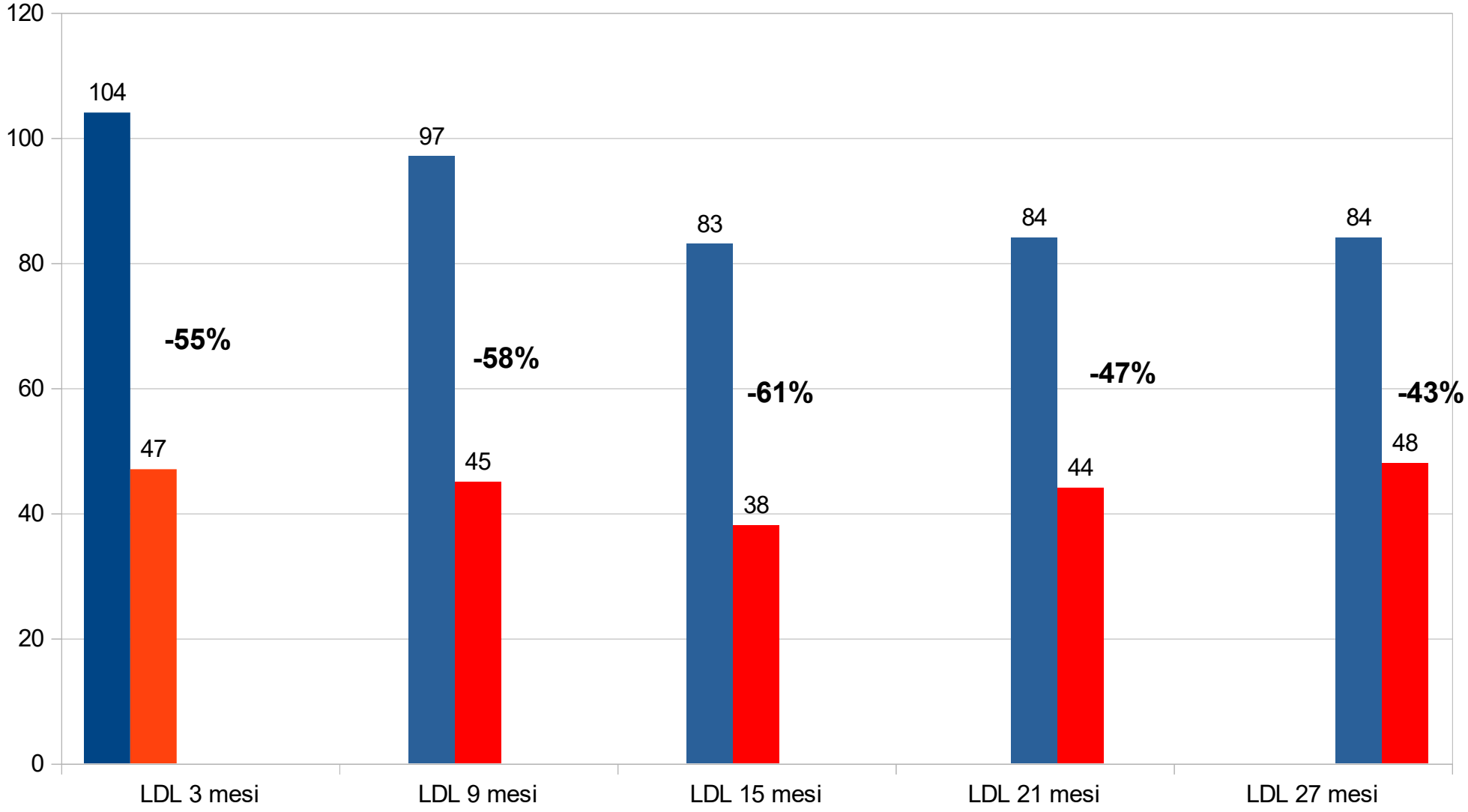
- **DIABETE MELLITO (DM) CON DANNO D'ORGANO (MICROALBUMINURIA, RETINOPATIA, NEUROPATIA) O ALMENO 3 FATTORI DI RISCHIO CV, O DM DI TIPO 1 COMPARSO PRECOCEMENTE E PRESENTE**

- **SCORE ≥10% PER IL RISCHIO A 10 ANNI DI CVD FATALE**
- **IPERCOLESTEROLEMIA FAMILIARE CON ASCVD O UN ALTRO FATTORE DI RISCHIO CV**

2019 ESC/EAS 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. European Heart Journal, 2020.

Inclisiran Cardiologia Mauriziano

Pazienti Totali	71
Maschi	65%
Morte per cause non CV	2 (2,8%)
Fallimento Terapeutico (LDL non a target)	4 (5,6%)
Drop Out	4 (5,6%)
Terapia ipolipemizzante di associazione	
Statina + ezetimibe + acido bempedoico	7 (9%)
Statina + ezetimibe	38 (54%)
Statina + acido bempedoico	1 (1%)
Acido bempedoico + ezetimibe	8 (12%)
Solo ezetimibe	5 (7%)
Nessuna terapia ipolipemizzante	12 (17%)


120
100
80
60
40
20
0
104
47
-55%
97
45
-58%
83
38
-61%
84
44
-47%
84
48
-43%
LDL 3 mesi
LDL 9 mesi
LDL 15 mesi
LDL 21 mesi
LDL 27 mesi

- Paziente con SCA o PCI elettiva in terapia con Statine ed Ezetimibe ed LDL ≥ **70** mg/dl

Aggiunge I-PCSK9 alla dimissione

- Paziente con SCA o PCI elettiva in terapia con Statine ed LDL ≥ **70** mg/dl

Aggiunge Ezetimibe, Acido Bempedoico ed I-PCSK9 alla dimissione

- Paziente con SCA o PCI elettiva naive da Statine con LDL ≥ 55 mg/dl ed < 140 mg/dl

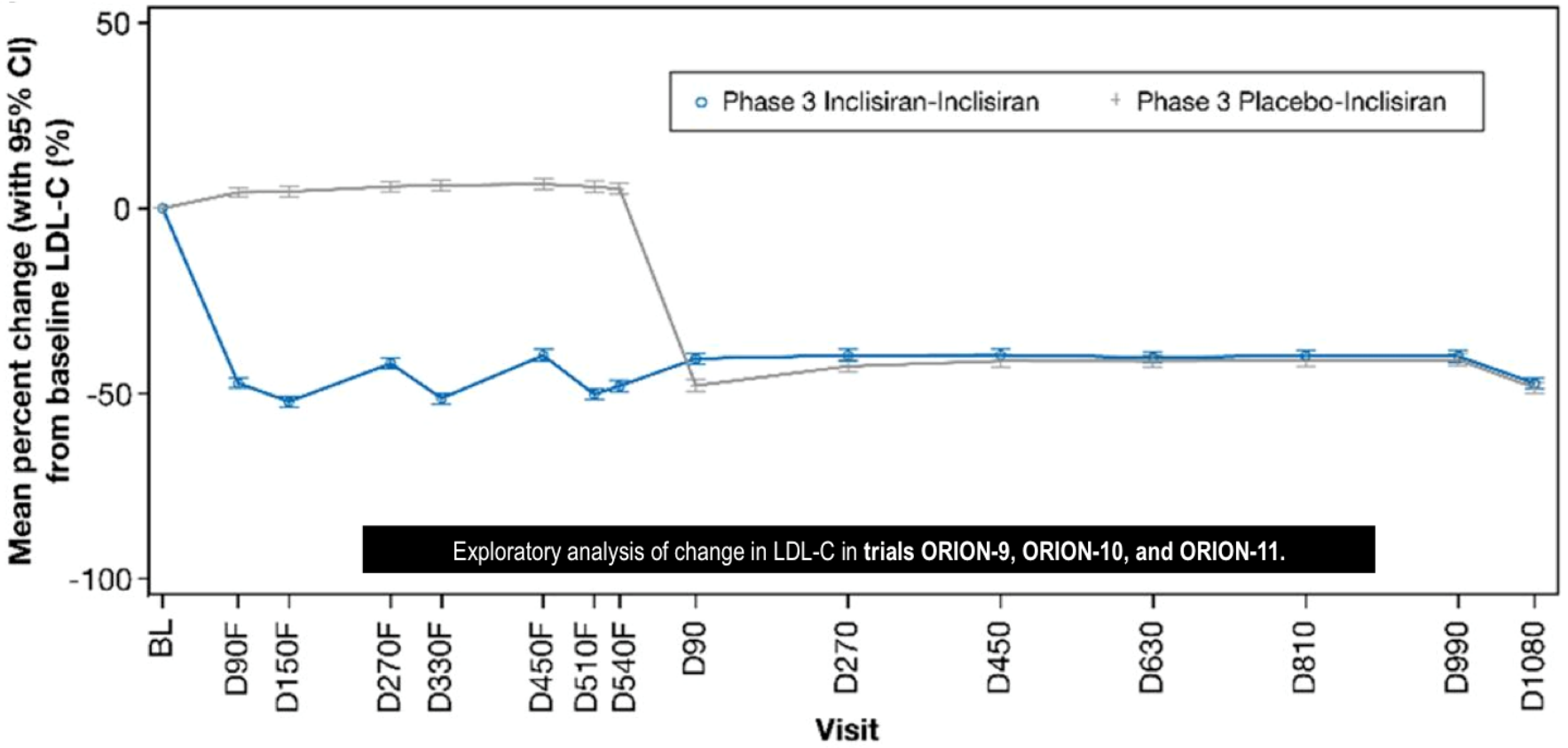
Aggiunge combinazione Statine ed Ezetimibe ed Acido Bempedoico alla dimissione e controllo a un mese per valutare I-PCSK9

- Paziente con SCA o PCI elettiva naive da Statine con LDL ≥ 140 mg/dl o > 70 e PAD o DM o MV

Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

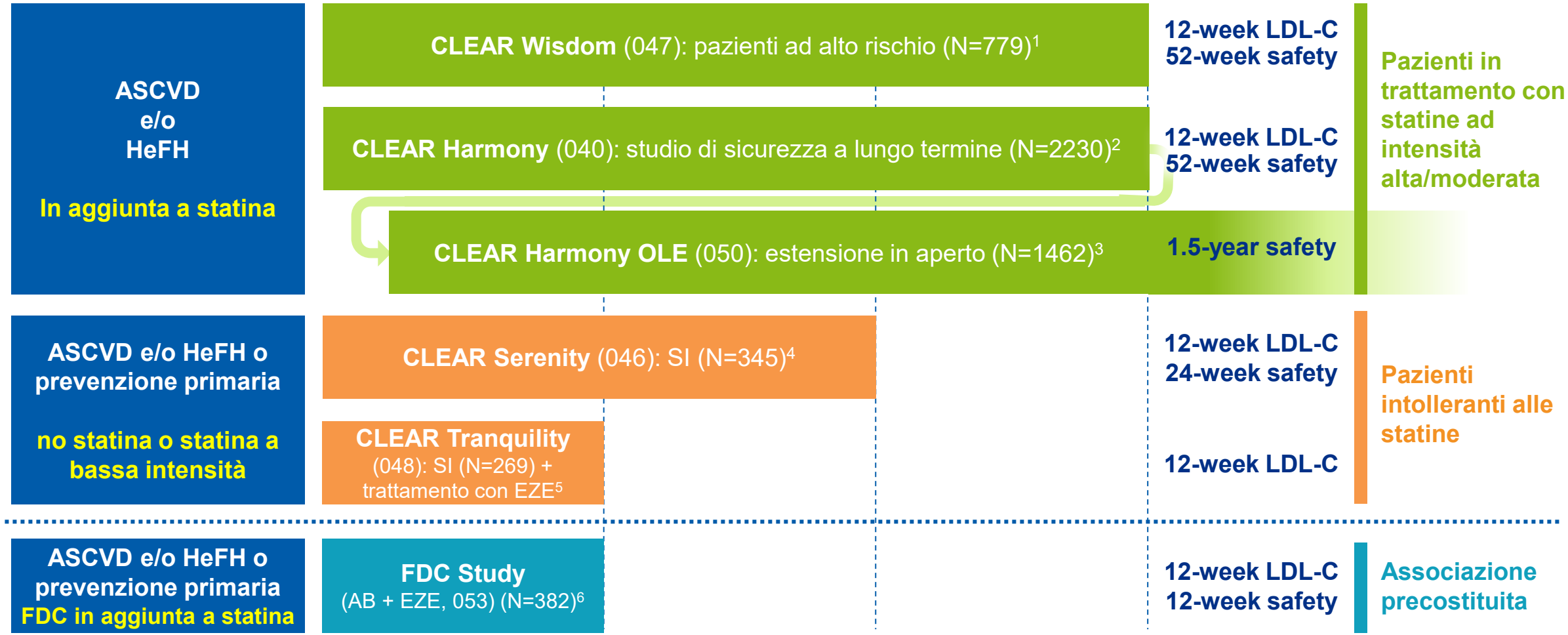
ORION 8: long term efficacy

Cardiovascular Research (2024) **120**, 1400–1410



Wright R.S. et al.; Cardiovasc Res 2024; 120 (12): 1400-1410

L'Acido Bempedoico è stato valutato in un solido programma clinico che ha incluso un ampio spettro di pazienti

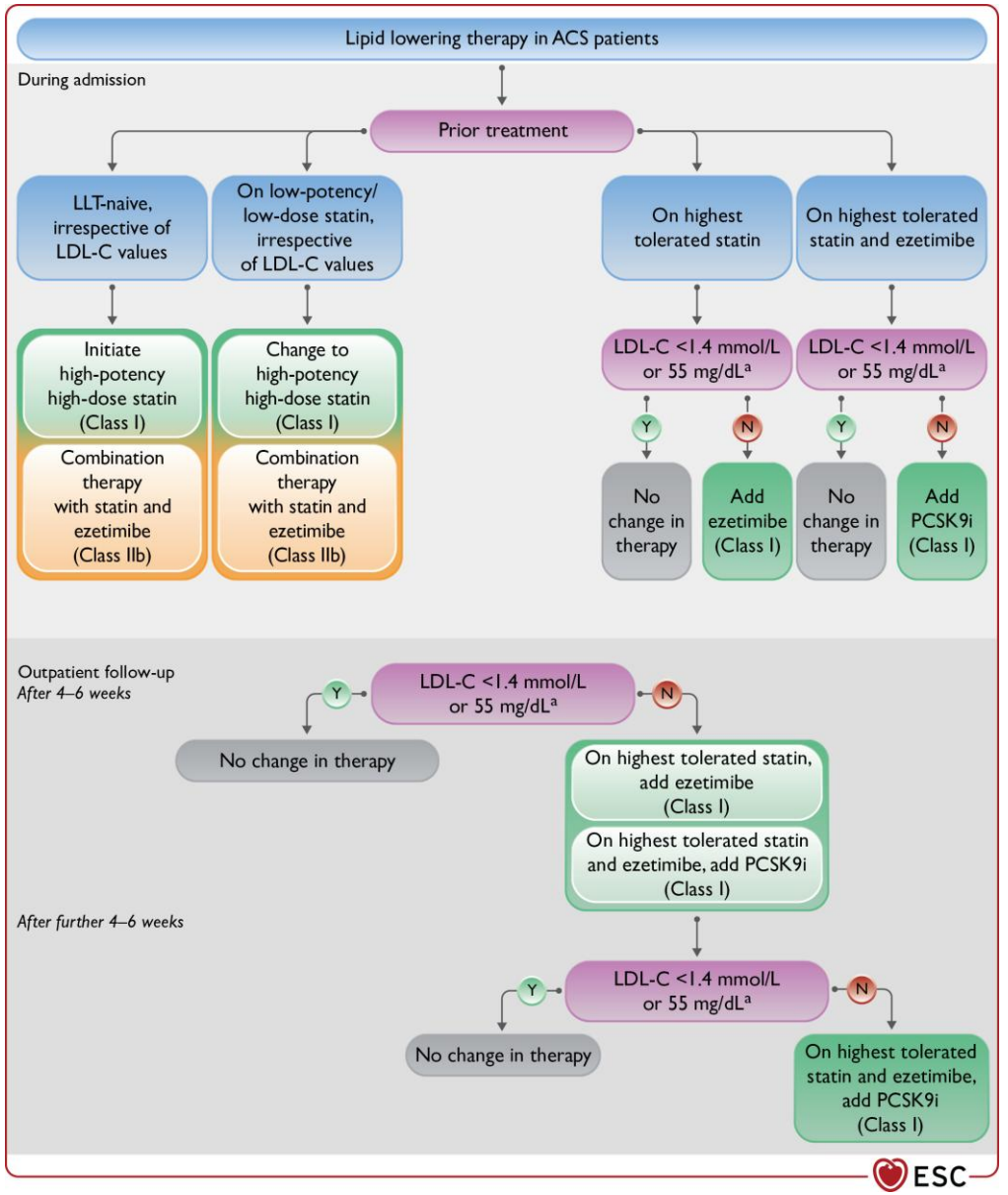


ASCVD = malattia cardiovascolare su base aterosclerotica; AB = acido bempedoico; EZE = ezetimibe; HeFH = iperholesterolemia familare eterozigote; LDL-C Colesterolo LDL; OLE = open-label extension; SI = statino-intolleranti

1.Goldberg AC et al. JAMA. 2019;322(18):1780-1788. doi:10.1001/jama.2019.16585; **2.** Ray KK, et al. *N Engl J Med*. 2019;380:1022-32; **3.** Ballantyne et al. Am J Cardiol 2022 https://doi.org/10.1016/j.amjcard.2022.03.020; **4.** Laufs U, et al. *J Am Heart Assoc*. 2019;8:e011662; **5.** Ballantyne CM, et al. *Atherosclerosis*. 2018;277:195-2036. **6.** Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.

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)

Vascular Pharmacology 148 (2023) 107141

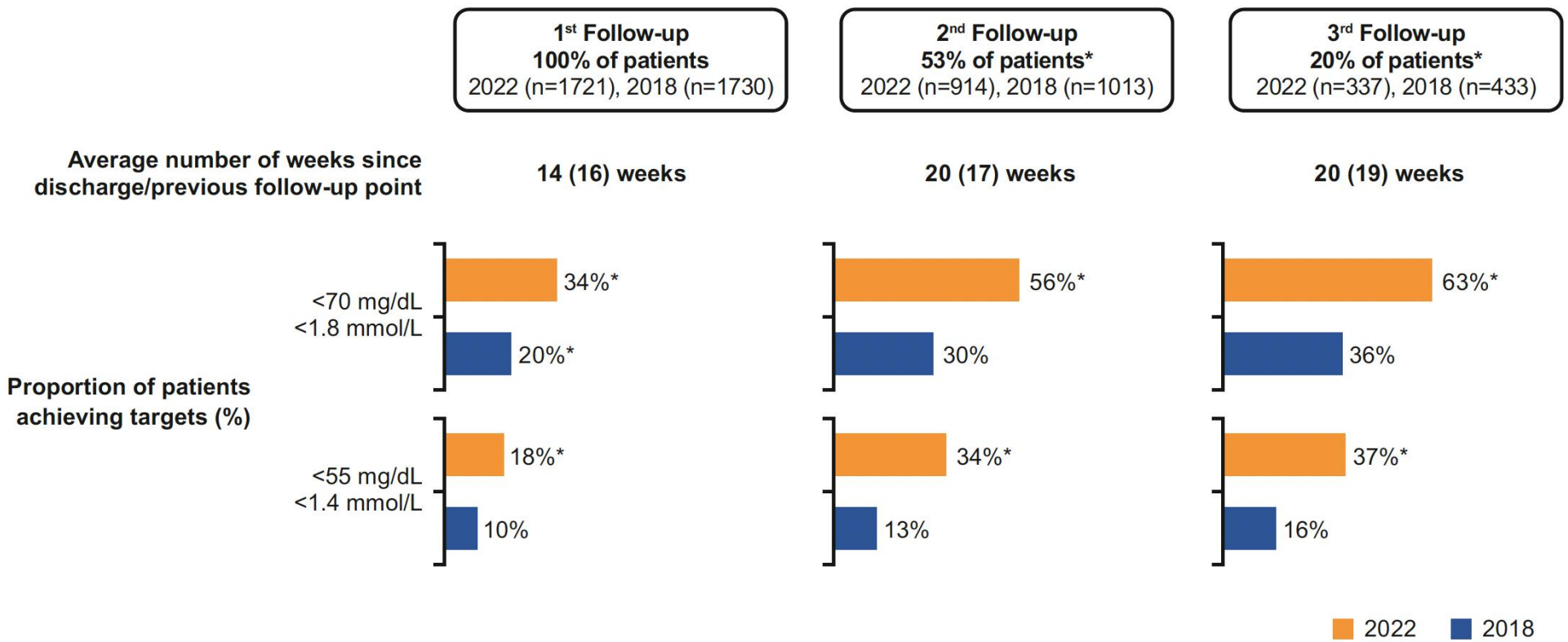
Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

The effect of the 2019 ESC/EAS dyslipidaemia guidelines on low-density lipoprotein cholesterol goal achievement in patients with acute coronary syndromes: The ACS EuroPath IV project

Ulrich Laufs [a], Alberico Luigi Catapano [b,c], Raffaele De Caterina [d,*], François Schiele [e,f], Alessandro Sionis [g,h], Azfar Zaman [i], J. Wouter Jukema [j,k]



Conclusioni

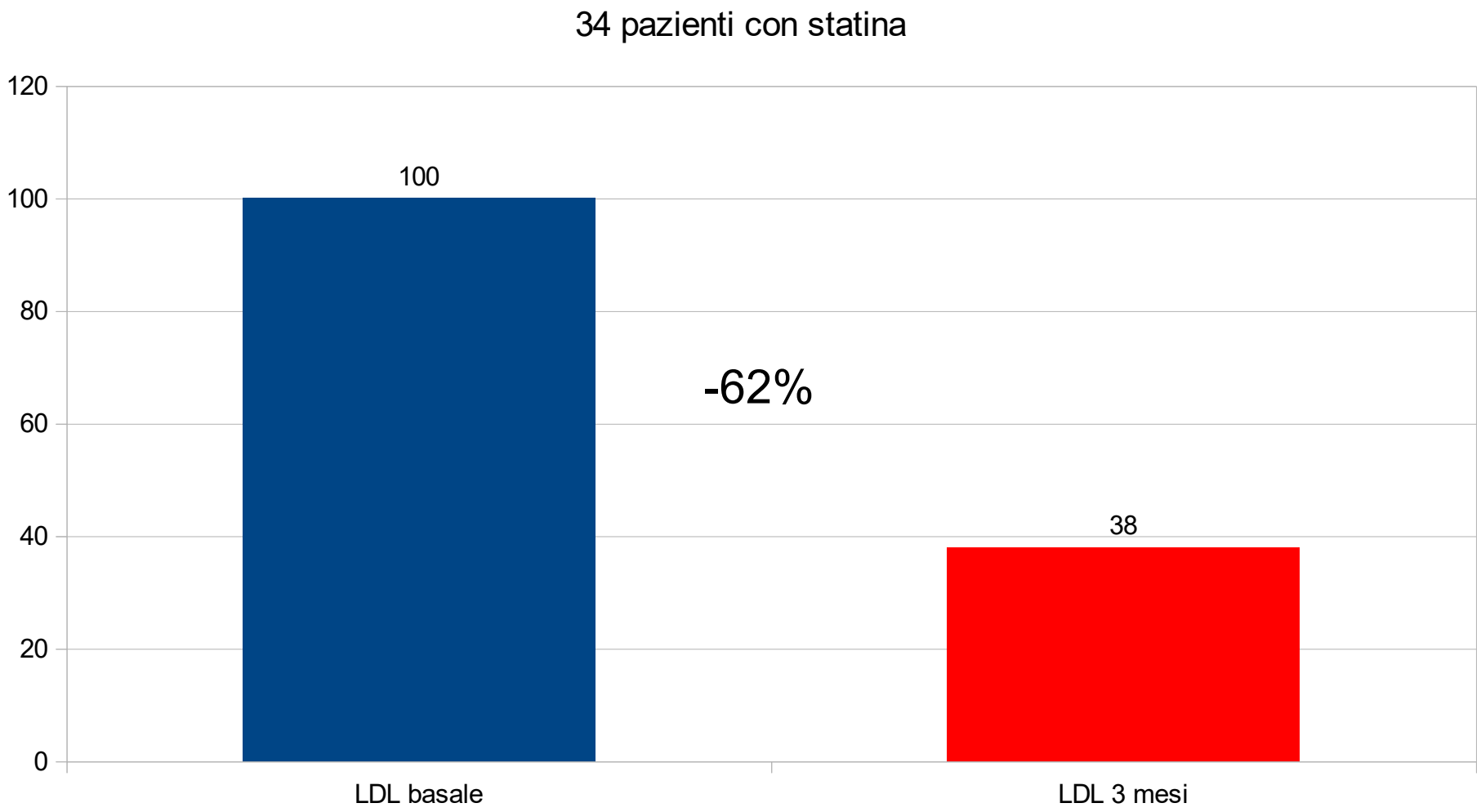
- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ L'aggiunta degli I-PCSK9 determina un'ulteriore riduzione dei livelli di LDL e un conseguente miglioramento della prognosi ed è raccomandata in Classe I
- ✓ **L'aggiunta degli I-PCSK9 in fast-track (in-H/dimissione) è raccomandata nei pazienti ACS o eventi CV multipli già in terapia con statine e LDL ≥ 70 mg/dl e nei pazienti ACS naive da statine ed LDL ≥ 140 mg/dl in particolare se a rischio proibitivo (DM, MV, PAD, recidivanti)**
- ✓ **Applicando linee guida e fast track circa il 25% dei pazienti con ACS dovrebbero ricevere I-PCSK9 alla dimissione ma purtroppo attualmente i pazienti sono sottotrattati**

Conclusioni

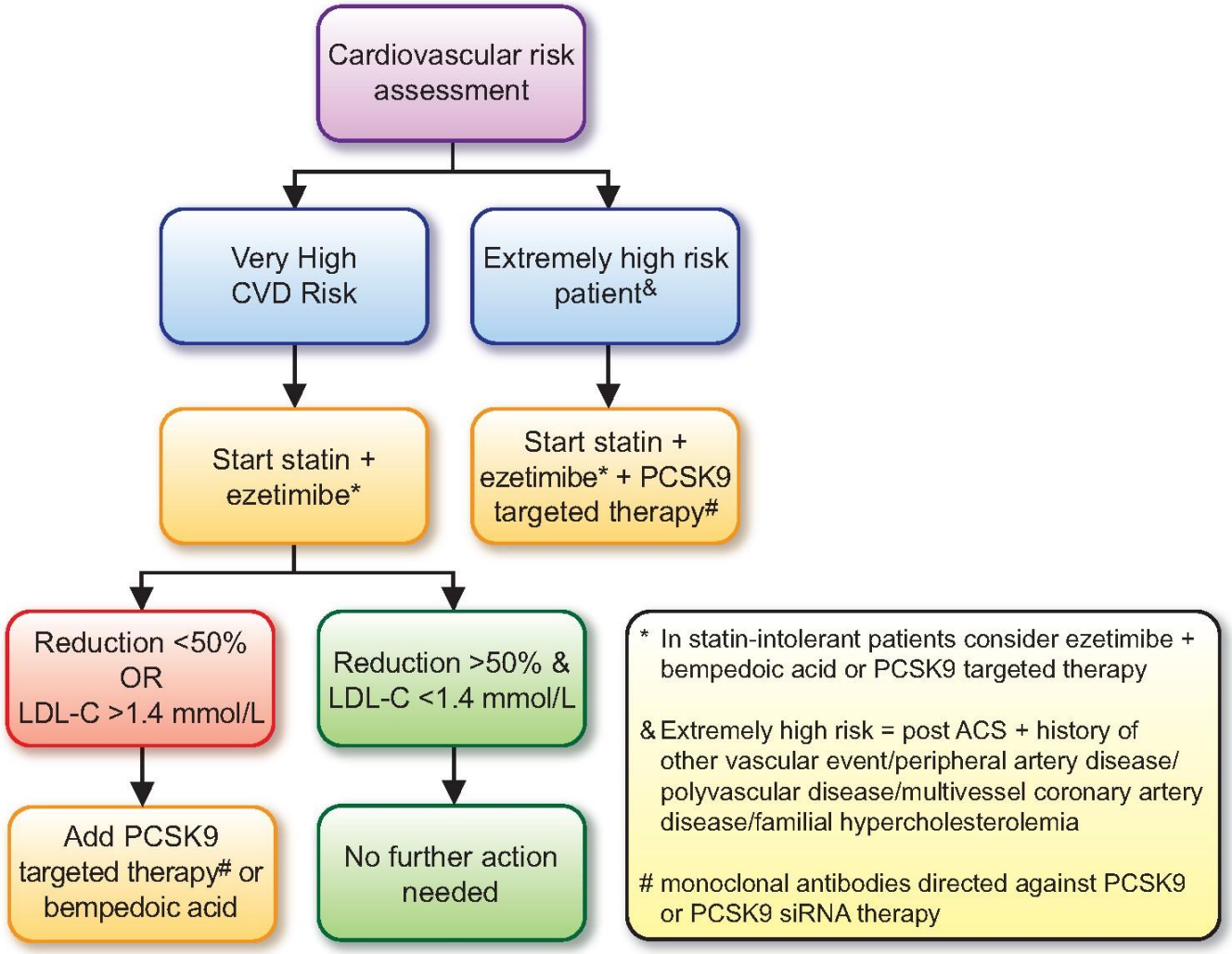
- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ Il paziente trattato con angioplastica elettiva è un paziente very high risk
- ✓ Ridurre il colesterolo LDL nel paziente very high risk ci permette di arrestare la progressione della placca e prevenire gli eventi avversi cardiovascolari acuti
- ✓ L'aggiunta degli inibitori del PCSK9 determina un'ulteriore riduzione dei livelli di LDL e un conseguente miglioramento della prognosi ed è raccomandata in Classe I
- ✓ **Inclisiran con le sue caratteristiche di somministrazione, efficacia e sicurezza potrebbe essere ideale nel paziente elettivo garantendo il raggiungimento del target e l'aderenza terapeutica**

Conclusioni

- ✓ La riduzione dei livelli di LDL si correla in modo lineare con la regressione della placca e il miglioramento della prognosi
- ✓ L'acido bempedoico si è dimostrato in grado di ridurre in maniera significativa i livelli di C-LDL, sia in aggiunta alla massima dose di statina tollerata sia in pazienti con intolleranza alle statine, con un effetto ancora maggiore quando utilizzato in combinazione con l'ezetimibe.
- ✓ **L'acido bempedoico ha un meccanismo d'azione complementare rispetto all'ezetimibe. L'associazione di acido bempedoico ed ezetimibe ha il vantaggio di ridurre significativamente i livelli di C-LDL senza aumentare il rischio di eventi avversi.**
- ✓ L'acido bempedoico in triplice terapia con ezetimibe e atorvastatina 20mg ha permesso di ottenere i valori di C-LDL raccomandati dalle linee guida in più del 90% dei pazienti arruolati, con oltre il 95% dei pazienti che ottiene una riduzione dei livelli di C-LDL >50%


34 pazienti con statina
120
100
80
60
40
20
0
100
38
-62%
LDL basale
LDL 3 mesi

Combination lipid-lowering therapy as first line strategy in very high-risk patients



Eur Heart J, ehab718, https://doi.org/10.1093/eurheartj/ehab718

Cardiovascular risk categories: clinical assessment

EAS ESC European Society of Cardiology

Very-high-risk

People with any of the following:

- Documented ASCVD, either clinical or unequivocal on imaging.
  - Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound.
- DM with target organ damage, ≥3 major risk factors or early onset of T1DM of long duration (>20 years).
- Severe CKD (eGFR <30 mL/min/1.73 m^2).
- FH with ASCVD or with another major risk factor.
- *A calculated SCORE ≥10% for 10-year risk of fatal CVD.*

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

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% ↓**

Changes in recommendations (3)

EAS ESC European Society of Cardiology

2016	2019
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
In patients at very-high risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
	For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

- Paziente con SCA in terapia con Statine ed Ezetimibe ed LDL ≥ **70** mg/dl

Aggiunge I-PCSK9 alla dimissione

- Paziente con SCA in terapia con Statine ed LDL ≥ **70** mg/dl

Aggiunge Ezetimibe ed I-PCSK9 alla dimissione

- Paziente con SCA naive da Statine con LDL ≥ **70** mg/dl ed < 140 mg/dl

Aggiunge combinazione Statine ed Ezetimibe alla dimissione e controllo a un mese per valutare I-PCSK9

- Paziente con SCA naive da Statine con LDL ≥ 140 mg/dl o > 70 e PAD o DM o MV

Aggiunge combinazione Statine ed Ezetimibe e I-PCSK9 alla dimissione

VICTORION-INITIATE Randomized Trial

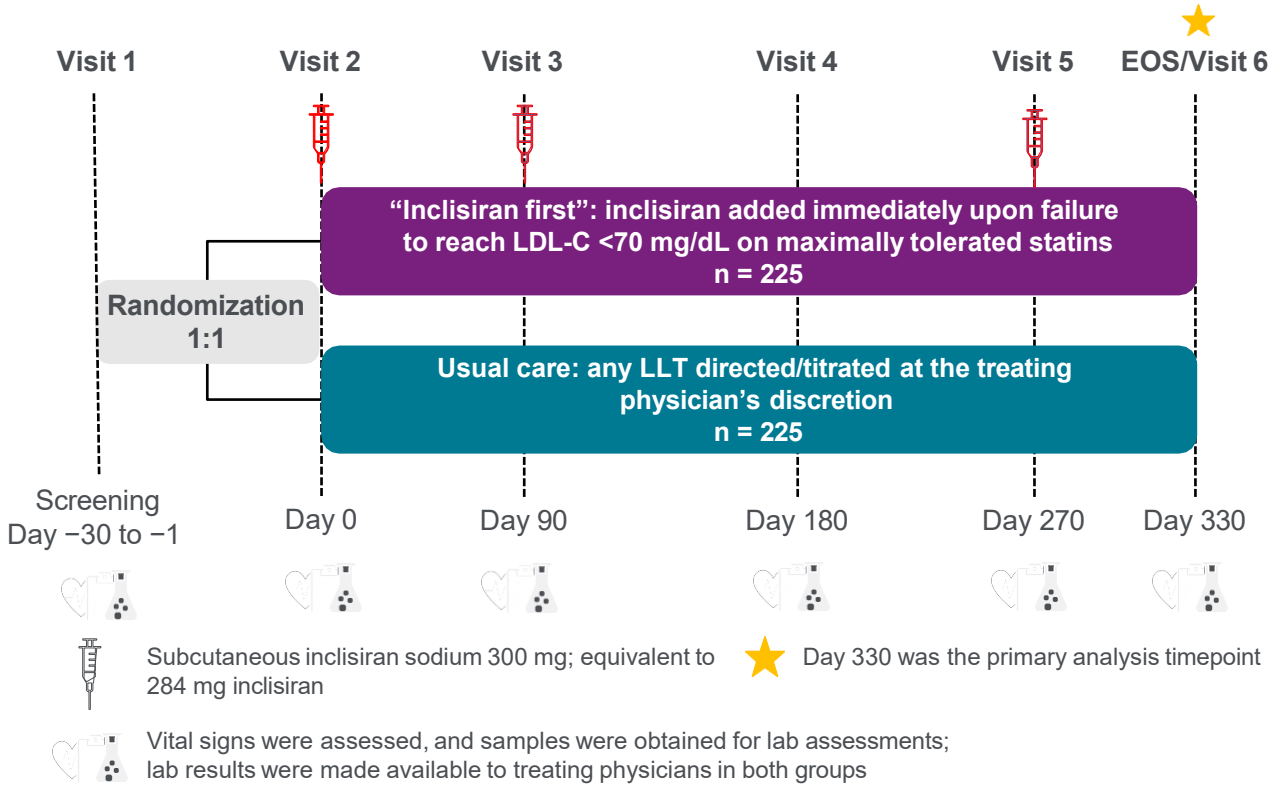
VICTORION-INITIATE (NCT04929249): prospective, randomized, open-label, Phase 3b trial that evaluated an "inclisiran first"
(i.e. adding inclisiran immediately if patients fail to reach LDL-C <70 mg/dL on maximally tolerated doses of statins)
implementation strategy compared with usual care in patients with ASCVD in representative US clinical settings

Population

- Adults ≥18 years of age with a history of ASCVD*
- LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL and fasting triglycerides <500 mg/dL
- Receiving maximally tolerated statin therapy† or had documented statin intolerance‡

Setting and procedures

- 45 sites selected from diverse settings
- Stratification by baseline health insurance status
- Study physician oversight without interference in lipid management beyond "inclisiran first" administration
- Managing physicians were provided lipid results and encouraged to follow AHA/ACC/Multisociety guidelines[1] and add therapies at their discretion



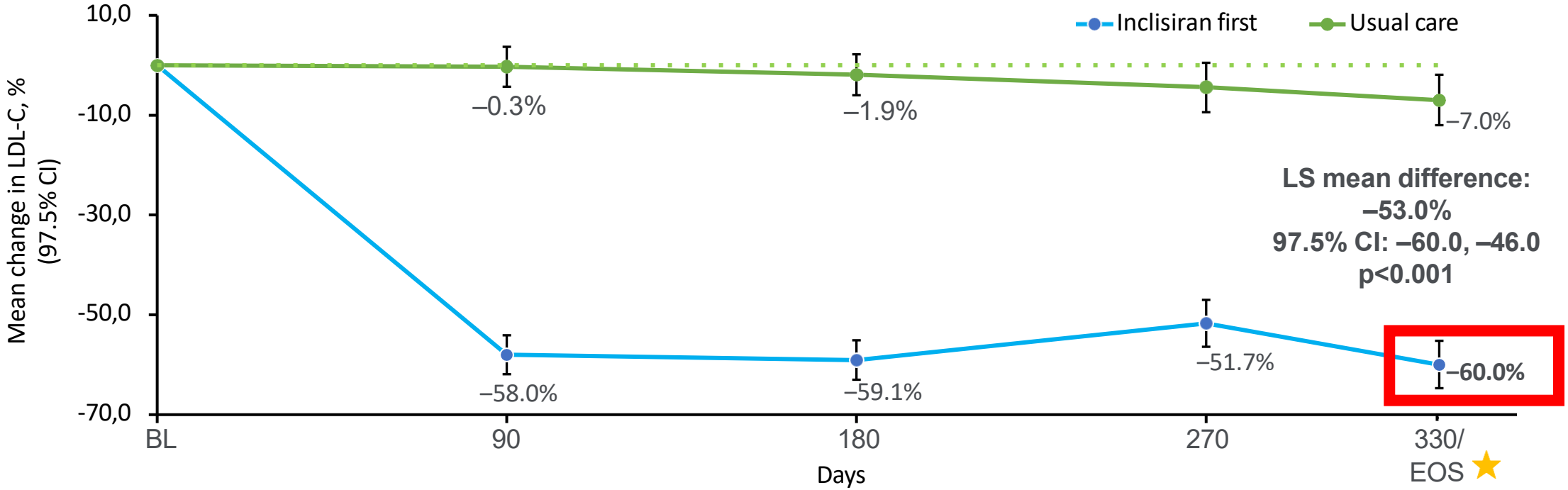
*Coronary heart disease, cerebrovascular disease, or peripheral artery disease. †Maximally tolerated statin therapy was determined by the investigator; no immediate plans to modify LLT were permitted.
‡Documented side effects on ≥2 different statins, including one at the lowest standard dose.
ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; EOS, end of study;
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; US, United States.

1. Grundy SM, et al. Circulation. 2018;139;e1082–1143.

Michael J. Koren et al J Am Coll Cardiol. 2024; 83 (20): 1939-1952

Co-primary endpoint: percent change in LDL-C

At Day 330/EOS the mean percent change in LDL-C from baseline was –60.0% (97.5% CI: –64.7, –55.2) with “inclisiran first” and –7.0% (97.5% CI: –12.0, –1.9) with usual care



	BL	90	180	270	330/EOS
Inclisiran first, n		213	207	203	205
Usual care, n		201	191	178	174

★ Day 330 is the primary analysis timepoint. The dotted line represents baseline LDL-C.
BL, baseline; CI, confidence interval; EOS, end-of-study; LDL-C, low-density lipoprotein cholesterol; LS, least squares.

Michael J. Koren et al J Am Coll Cardiol. 2024; 83 (20): 1939-1952

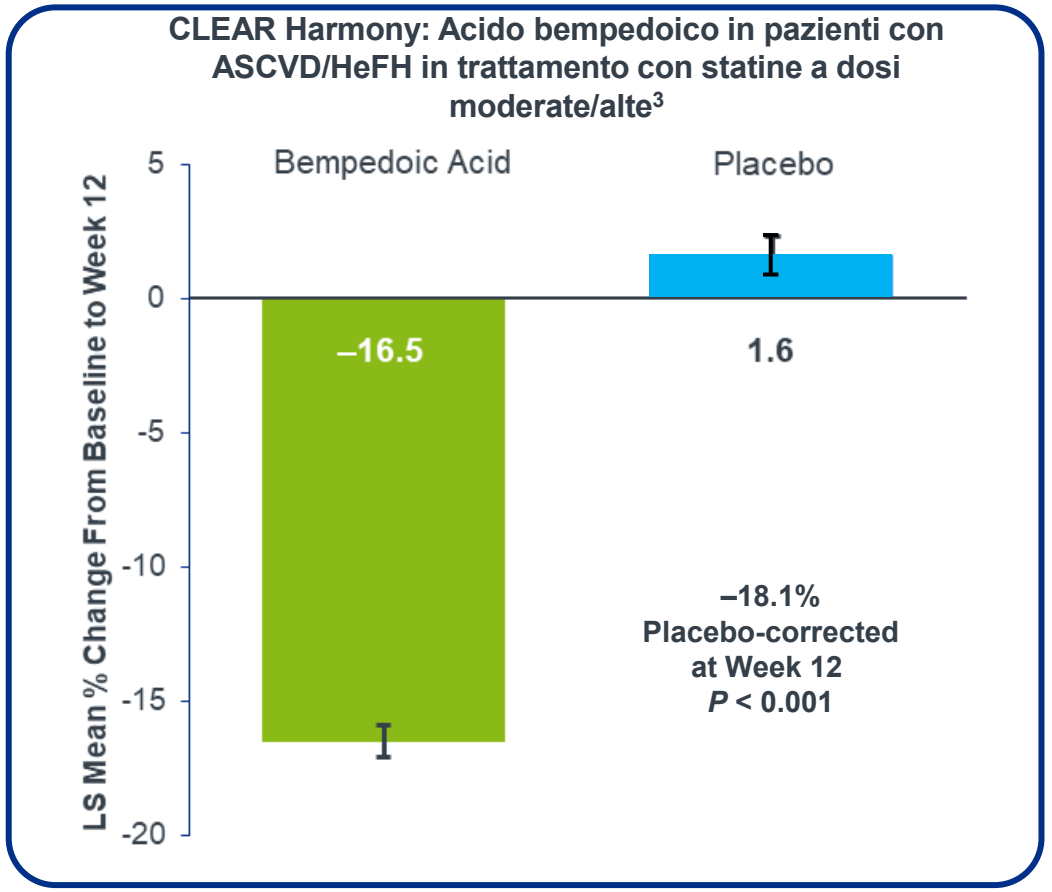
Pazienti in trattamento con statine ad intensità alta/moderata

CLEAR Harmony: acido bempedoico riduce i livelli di LDL-C in maniera significativa

- **Una percentuale di pazienti significativamente maggiore nel gruppo acido bempedoico ha raggiunto valori di LDL-C < 70 mg/dL alla settimana 12 rispetto al gruppo placebo (32.4% vs 9.0%; p < 0.001)**

- **L'efficacia dell'acido bempedoico non è risultata influenzata dal tipo né dall'intensità delle LLT sottostanti** (-20% nei pazienti in trattamento con statine a bassa-moderata intensità vs -17.5% nei pazienti in trattamento con statine ad elevata intensità; p di interazione 0.18) **ed era simile nei principali sottogruppi.**

Riduzione di LDL-C del 18.1%

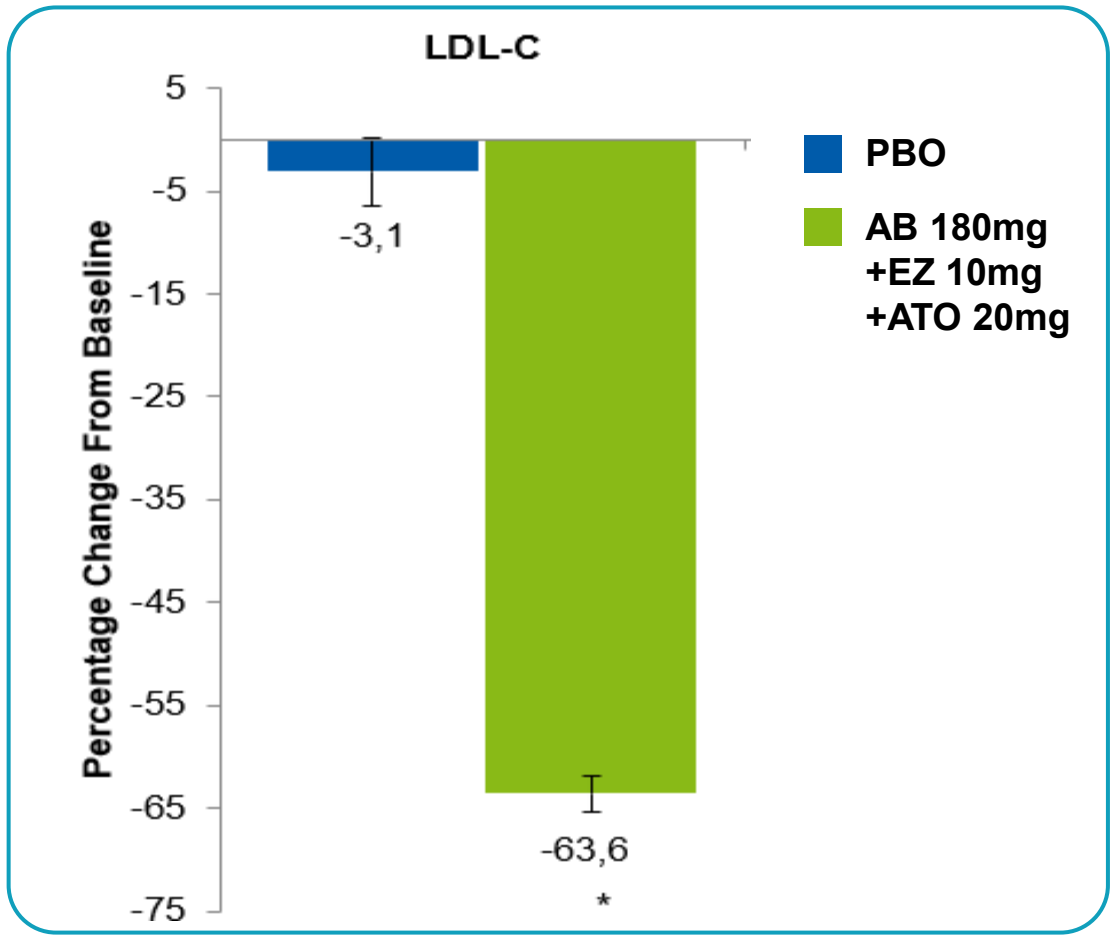


LLT = terapie ipolipemizzanti (lipid-lowering therapies)

Ray KK, et al. *N Engl J Med*. 2019;380:1022-32.

Triple Add-on: Acido Bempedoico, Ezetimibe e Atorvastatina 20 mg

In questo studio di fase 2 la terapia di *add-on* riduce i valori di LDL-C di oltre il 60%



Alla settimana 6:

- **Nel 95% dei pazienti è stata raggiunta una riduzione di LDL-C ≥50% rispetto al basale**
- **Il 90% dei pazienti ha raggiunto LDL-C <70 mg/dL**
- **Il 58.5% dei pazienti ha raggiunto LDL-C <55 mg/dL**

Triplice terapia

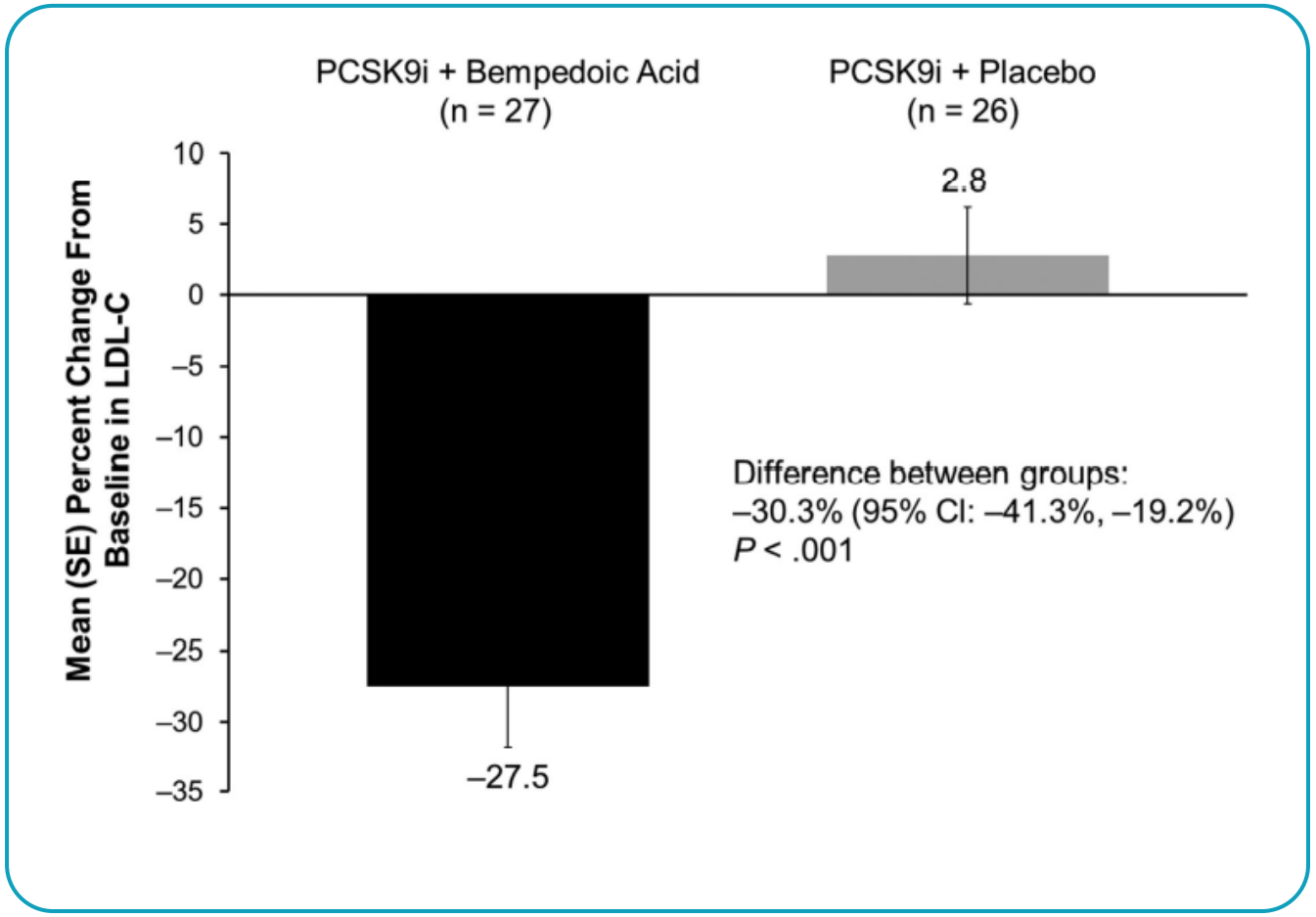
Una potenziale strategia di combinazione per un efficace riduzione dei livelli ldi colesterolo in pazienti ad alto rischio CV che non riescono a raggiungere gli obiettivi di trattamento con le terapie convenzionali.

Least squares mean percentage changes from baseline to Week 6. Values are least-squares mean±SE
*p < .001 for the comparison of triple therapy vs placebo

Rubino J. et al., Atherosclerosis, 2020, https://doi.org/10.1016/j.atherosclerosis.2020.12.023

Acido bempedoico in pazienti trattati con PCSK9i
Riduzione LDL-C

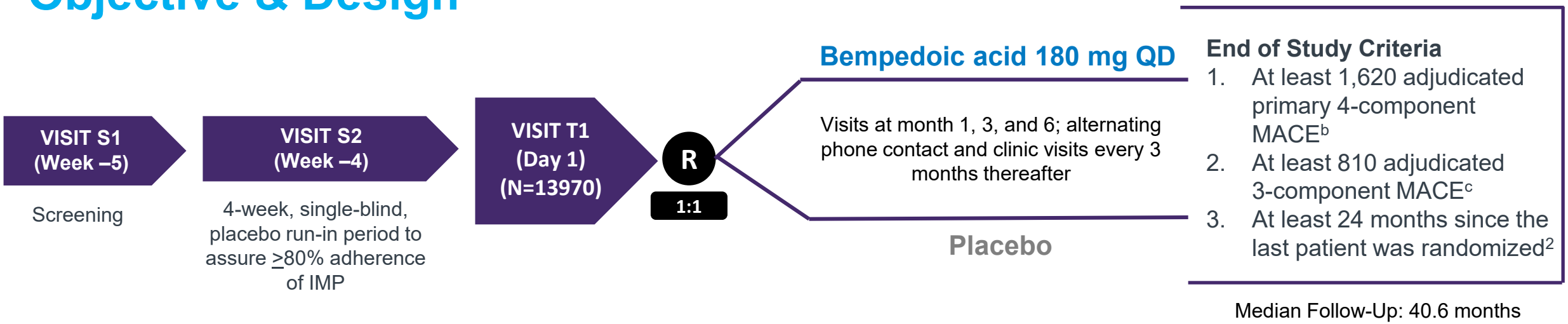
Dati di Fase II
a 8 settimane



Least squares mean percentage changes from baseline to Month 2. Values are least-squares mean±SE. Data for high-sensitivity C-reactive protein (hsCRP) are medians
*$p < 0.001$; † p=0.029
LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non–high-density lipoprotein cholesterol; TC:total cholesterol; apoB: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein.

Rubino J. et al . J Clin Lipid 2021 :https://doi.org/10.1016/j.jacl.2021.05.002

CLEAR Outcomes
Objective & Design



Median Follow-Up: 40.6 months

Objective[2]

To evaluate whether long-term treatment with bempedoic acid versus placebo reduces the risk of MACE-4 in patients with, or at high risk for, CVD who are statin intolerant.

Composite Primary Efficacy Endpoint:

Time to first occurrence of MACE (composite of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization)

Key Secondary Endpoints:

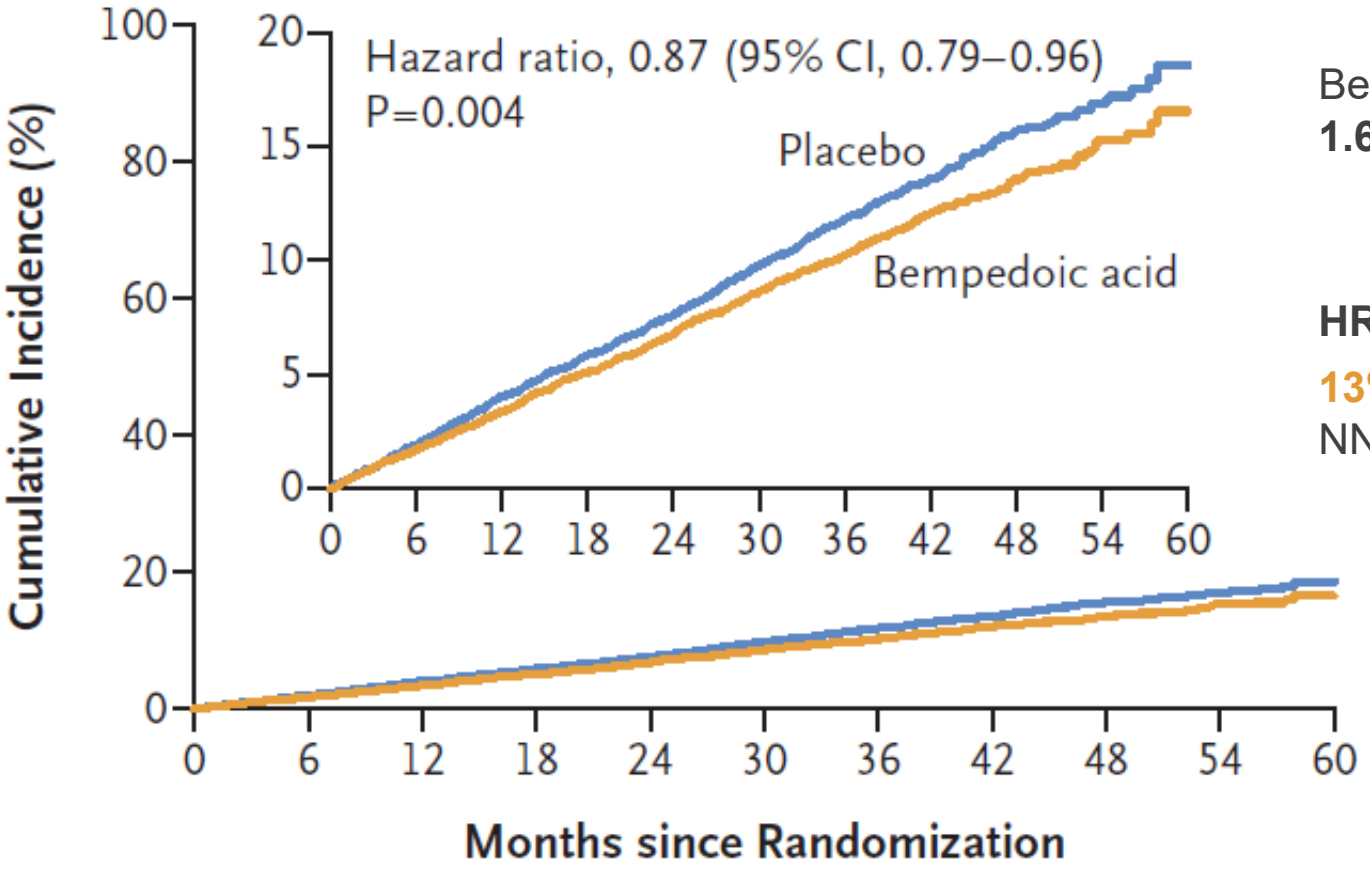
Time to first occurrence of:
- The composite of CV death, nonfatal MI, nonfatal stroke (MACE-3)
- Fatal + nonfatal MI
- Coronary revascularization
- Fatal + nonfatal stroke

Time to:
- CV death
- All-cause mortality

[a]Enrollment of high-risk patients without a history of atherosclerotic CVD was capped at 30%.
[b]Including CV death, nonfatal MI, nonfatal stroke, or coronary revascularization.
[c]Including CV death, nonfatal MI, or nonfatal stroke.
CVD=cardiovascular disease; LDL-C=low-density lipoprotein cholesterol; QD=once daily; MACE=major adverse cardiovascular event; MI=myocardial infarction, HbA1c=hemoglobin A1c; IMP=investigational medicinal product

Nissen SE et al. Epub ahead of print, March 4 2023. *N Engl J Med*. DOI: 10.1056/NEJMoa2215024. Supplement.

CLEAR Outcomes
Primary CV Endpoint: MACE-4



Bempedoic acid (11.7%) vs. placebo (13.3%)[1]
1.6% ARR

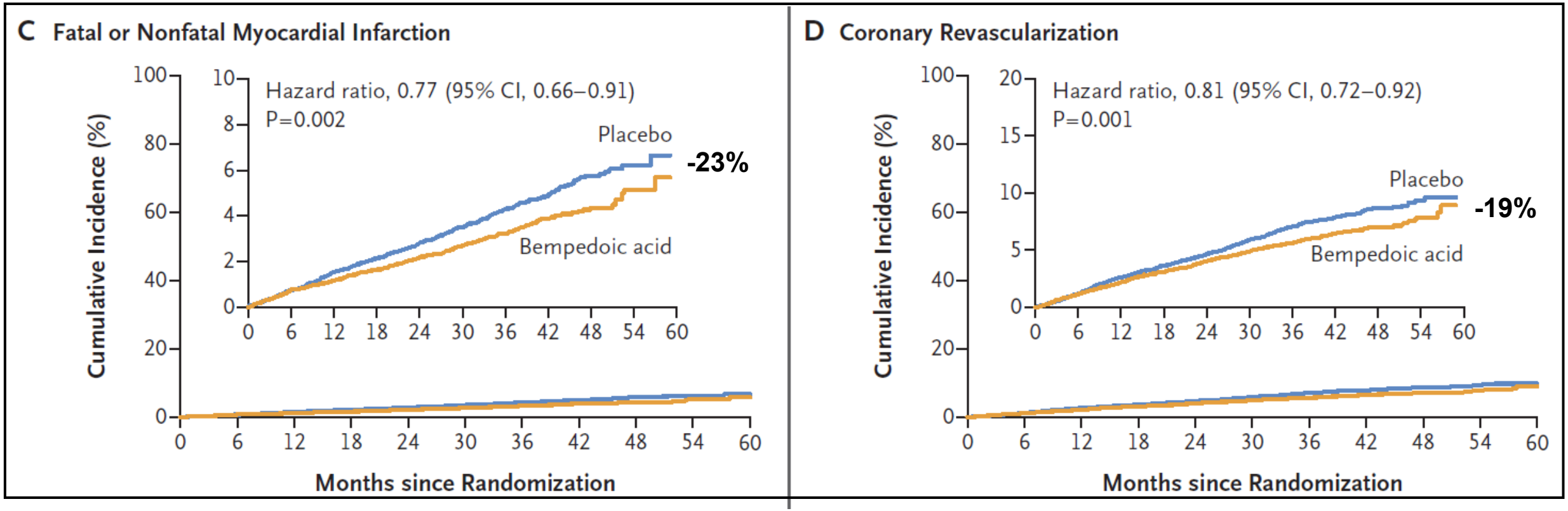
HR 0.87, 95% CI: 0.79–0.96, P=0.004[1]

13% RRR[1]
NNT 63[2]

- The primary efficacy endpoint (MACE-4) is the time to first occurrence of an adjudicated event for a composite that includes **death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularisation**.
- **All RRR % and hazard ratios (HR) in publicly available sources have been rounded**;
- **ARR**, absolute risk reduction; **CI**, confidence interval; **HR**, hazard ratio; **MACE**, major adverse cardiovascular events; **NNT**, number needed to treat; **RRR**, relative risk reduction;

1. Nissen SE, et al. N Engl J Med. 2023; 388:1353–1364 DOI: 10.1056/NEJMoa2215024.
2. Banach M, et al. Prog Cardiovasc Dis. 2023;S0033-0620(23)00026-9. doi: 10.1016/j.pcad.2023.03.001

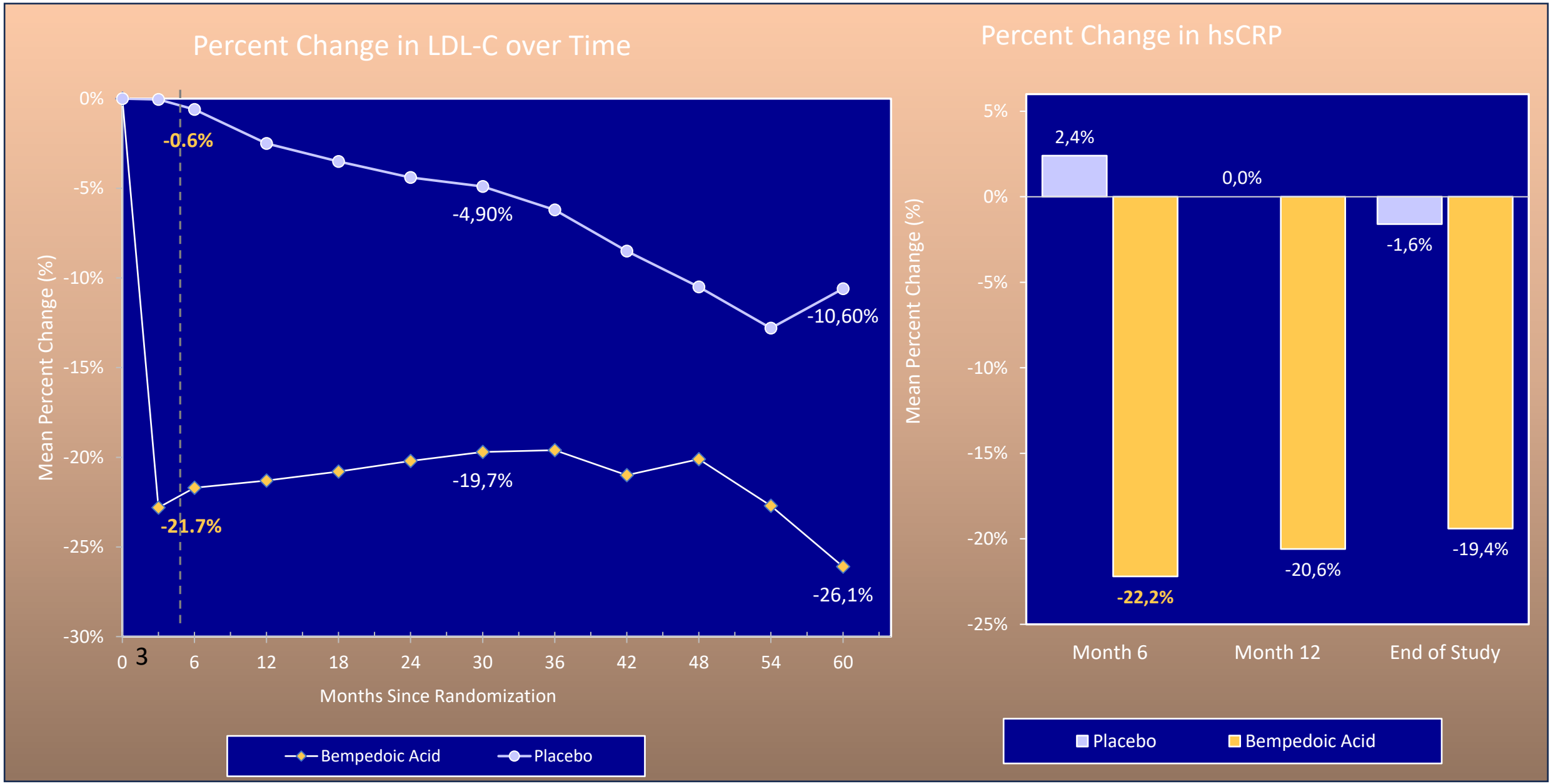
CLEAR Outcomes
Key Secondary CV Endpoints



- **All RRR % and hazard ratios (HR) in publicly available sources have been rounded**;
- **CI**, confidence interval; **MACE**, major adverse cardiovascular events; **RRR**, relative risk reduction;

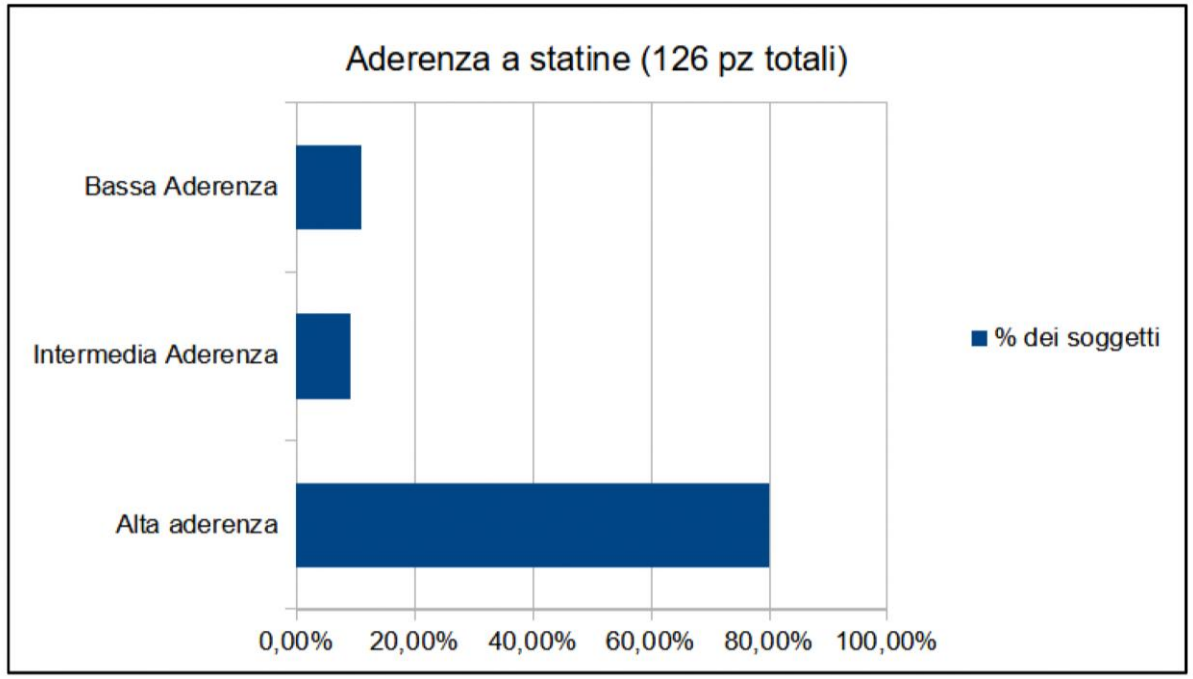
Nissen S E et al N Engl J Med 2023; 388:1353–1364 DOI: 10.1056/NEJMoa2215024

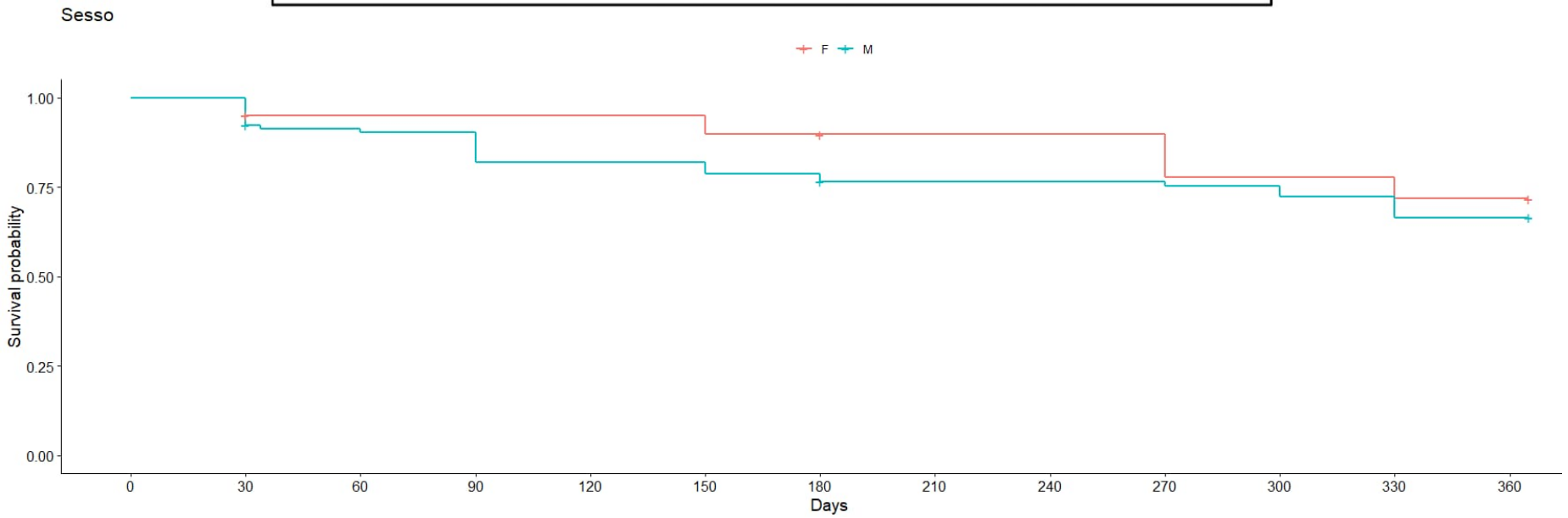
Effect of Trial Regimens on LDL-C and hsCRP



High Statin Adherence in patients treated with PCSK9-I

Ospedale Mauriziano and ASL Città di Torino

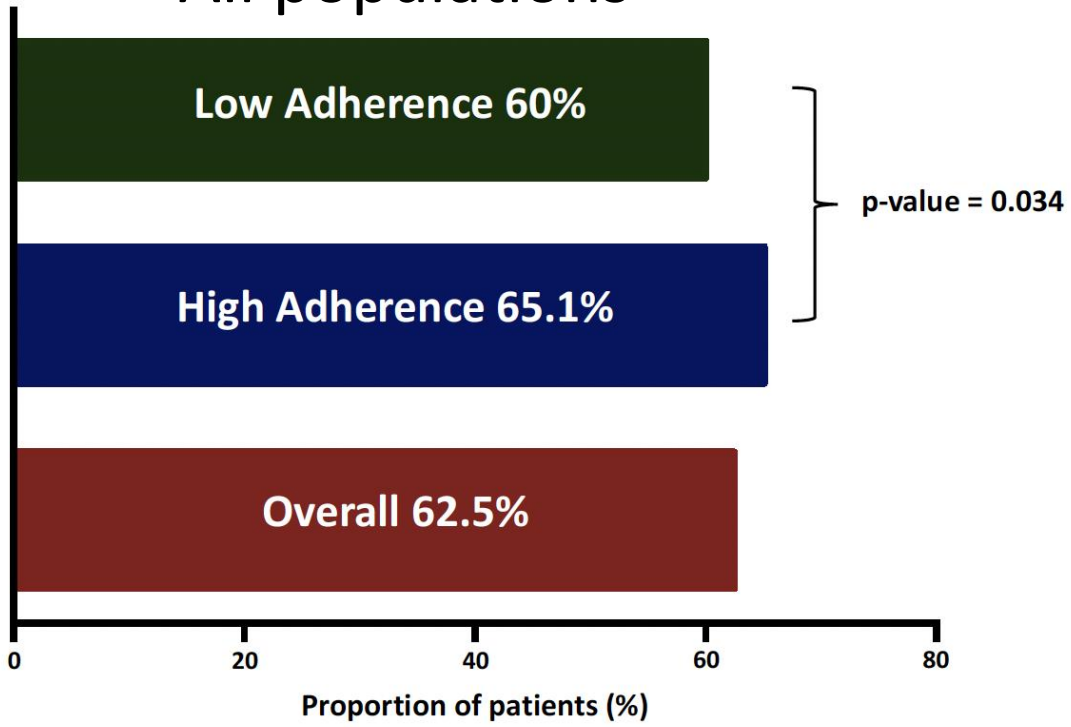




The high and sustained effect of PCSK9-I on LDL-C goal achievement was not influenced by adherence

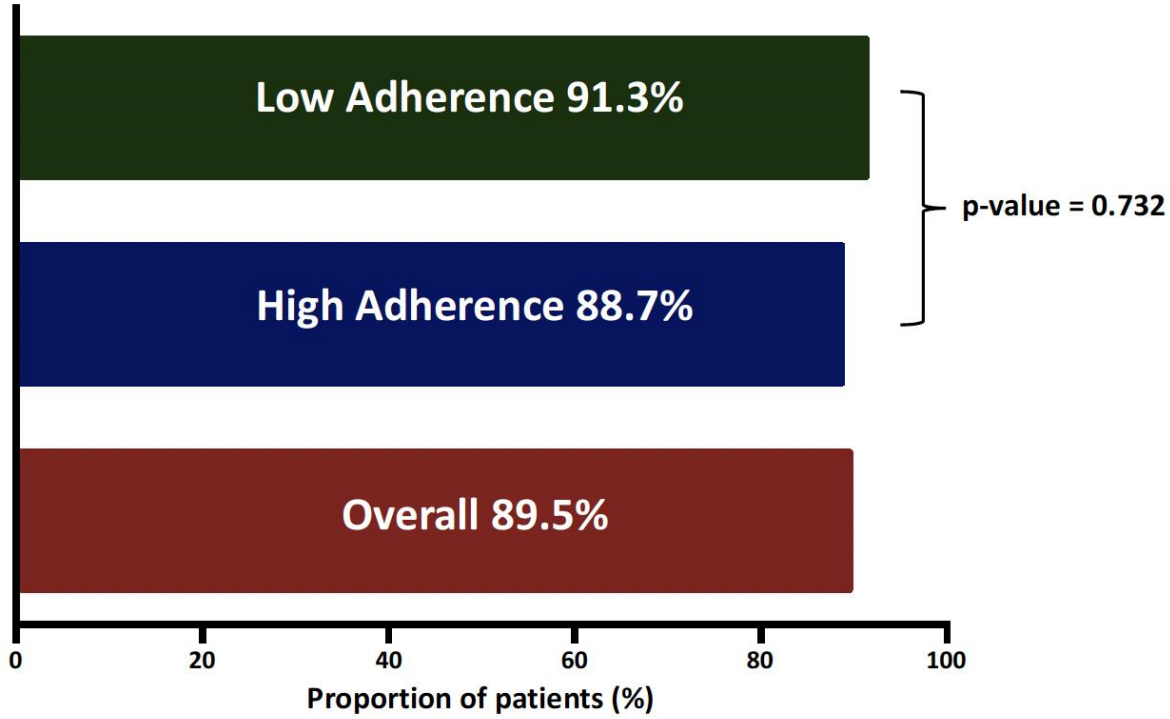
Primary analysis

All populations



Sensitivity analysis

I-PCSK9

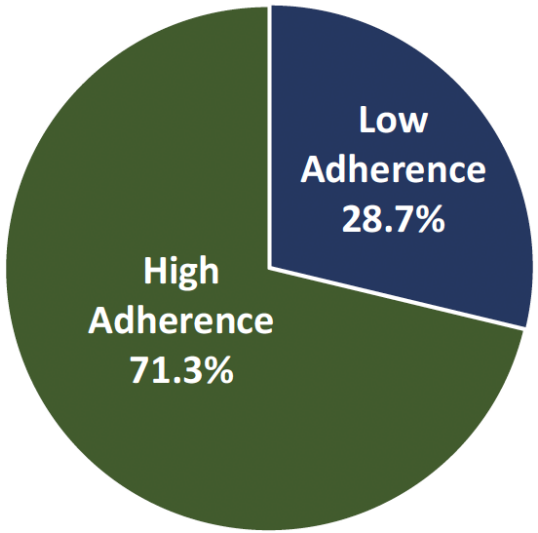


At hospital discharge, the rate of patients treated with stain and/or ezetimibe (mainly as triple therapy in combination with PCSK9-i) was lower in the LA than in the HA group. The same trend in LLT use was observed at 1- and 3-months FU

A. Munafò, M Ferlini et al. and G. Musumeci Am J Cardiol. In press

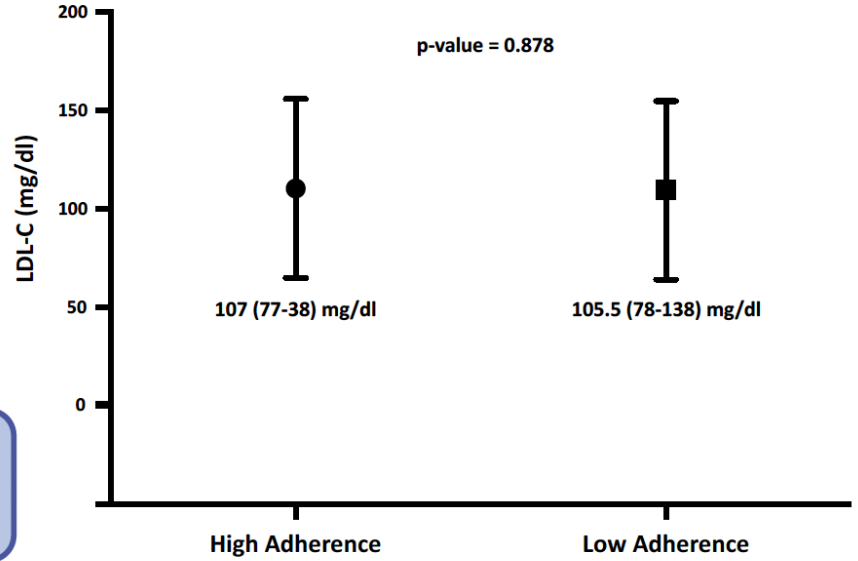
Jet-LDL registry: 1095 patients with ACS treated with LLT according to current European guidelines

For **963 patients**: availability of 3-months self-reported adherence to LLT assessed usign **the MMAS**



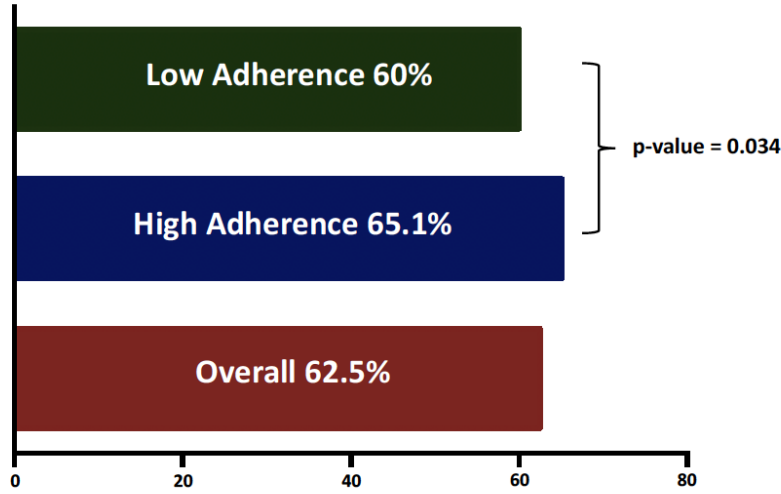
- MMAS score ≥6: high adherence
- MMAS score <6: low adherence

Baseline LDL-C levels



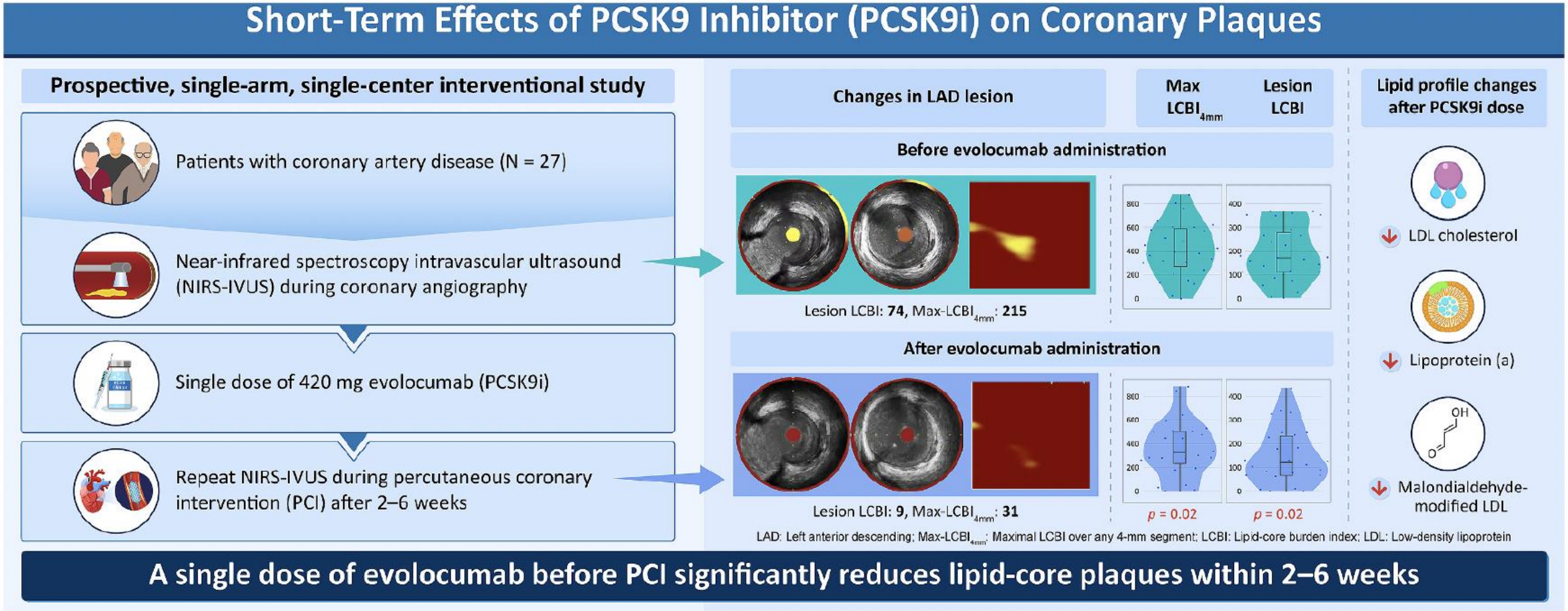
Primary endpoint

(LDL-C reduction >50% from baseline or level <55 mg/dl at 1-month)



A. Munafò, M Ferlini et al. and G. Musumeci Am J Cardiol. In press

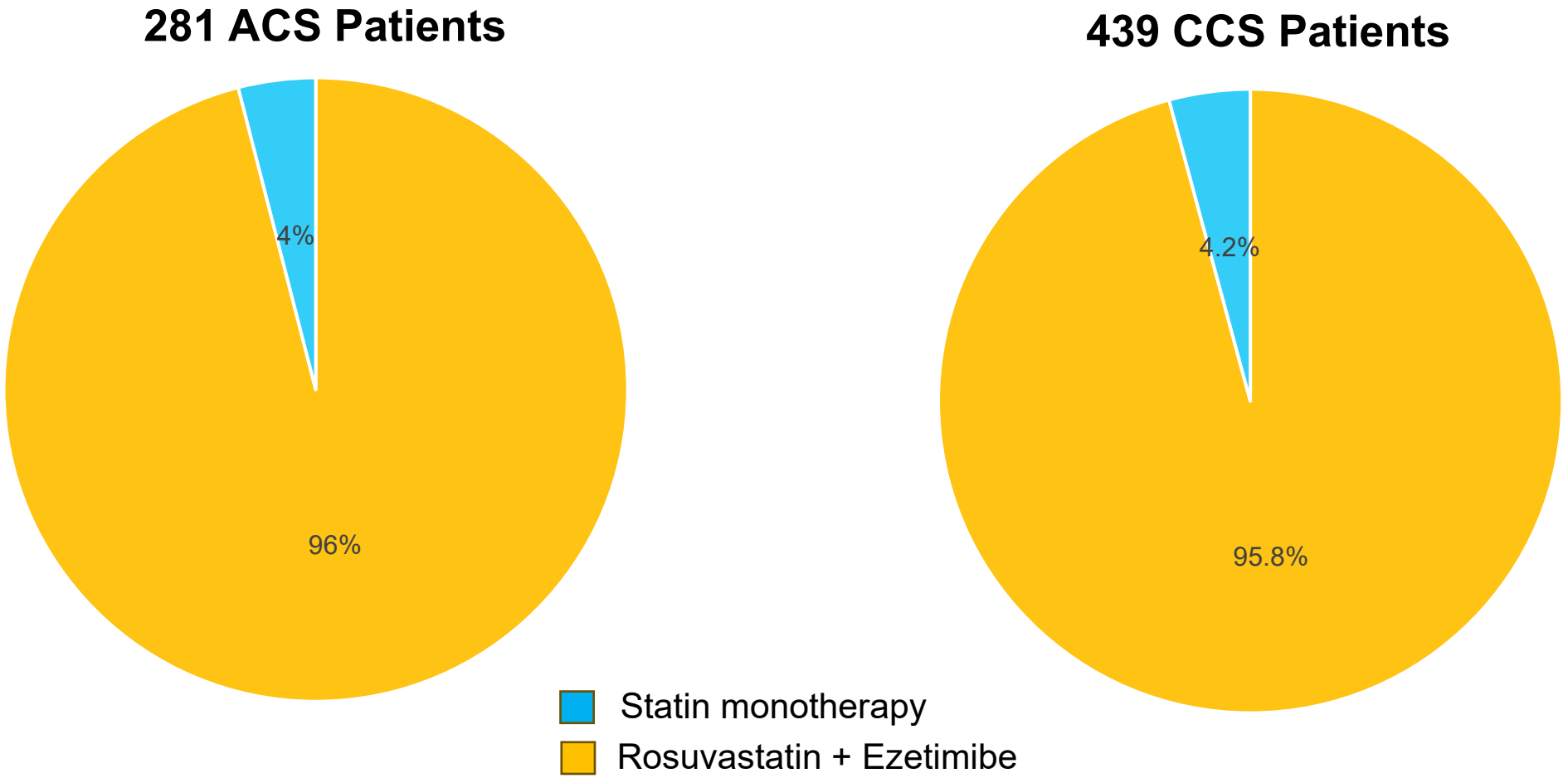
Very short-term effects of a single dose of a PCSK9 inhibitor before PCI



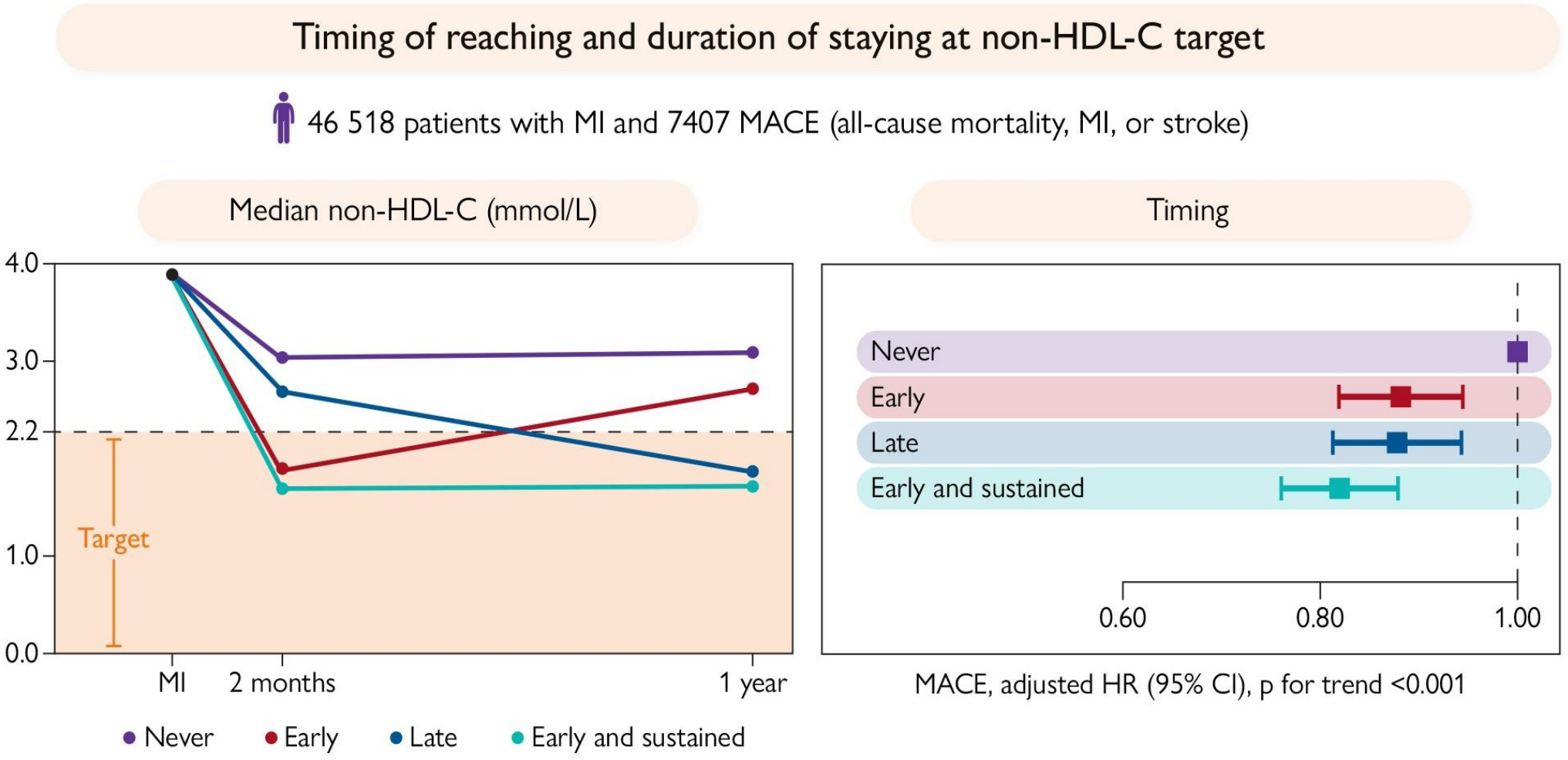
T. Kataoka et al. Atherosclerosis 2024 in press

Ospedale Mauriziano Torino experience in 2023

Overall, 720 consecutive CAD patients hospitalized between January and Decembre 2023 were enrolled; 691 of whom were discharged with combination Rosuvastatin/Ezetimibe (96%)

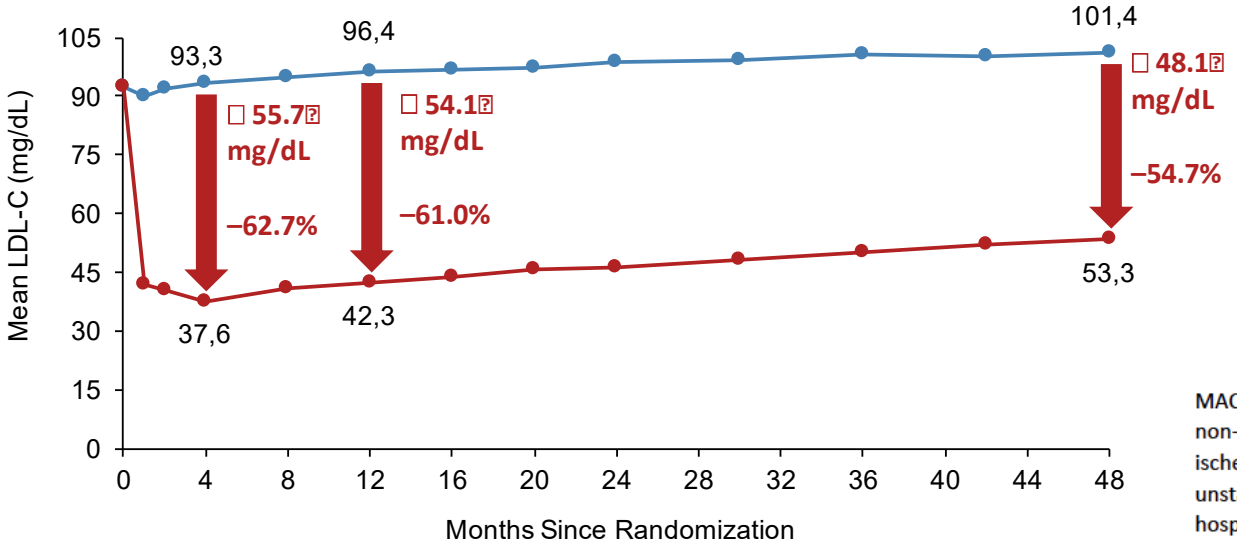


Intensive early and sustained lowering of non-high-density lipoprotein cholesterol after 1 myocardial infarction and prognosis: the SWEDEHEART registry



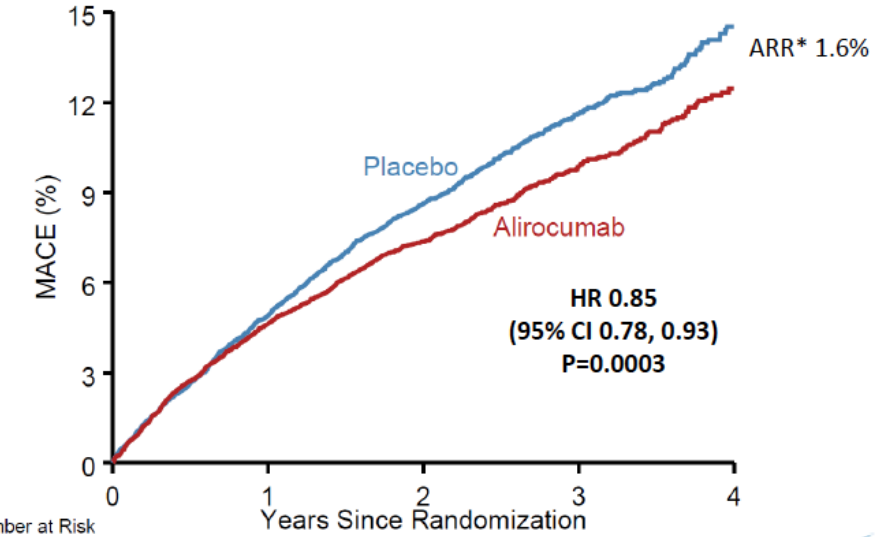
J. Schubert et al Eur Heart J, 2024 ehae576, https://doi.org/10.1093/eurheartj/ehae576

ODYSSEY OUTCOMES *Alirocumab*



Primary Efficacy Endpoint: MACE

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



Number at Risk

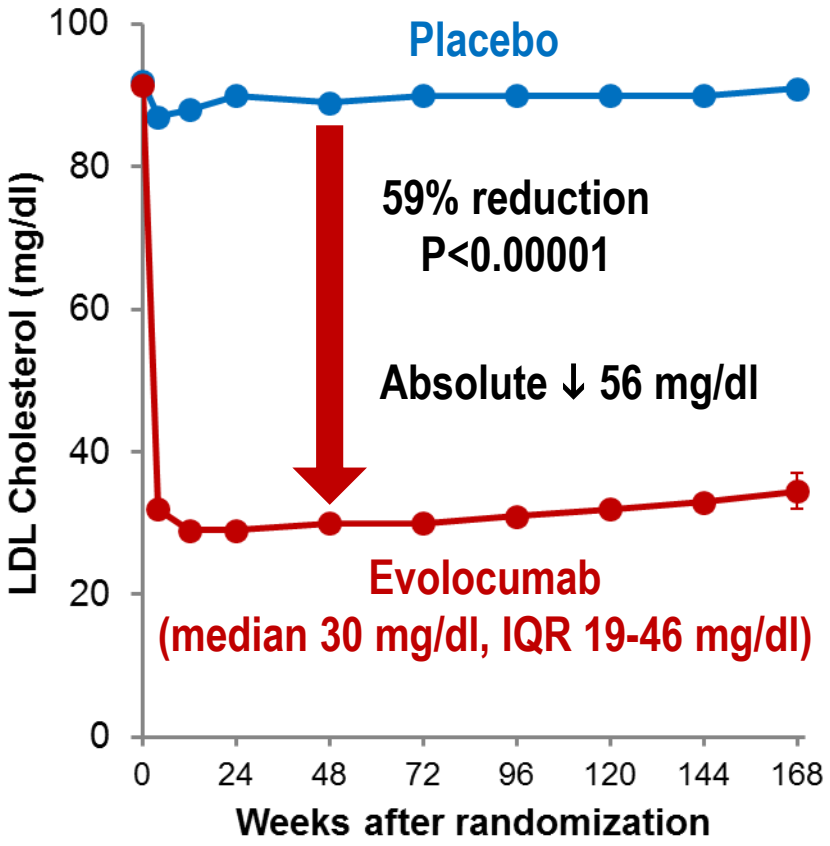
Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

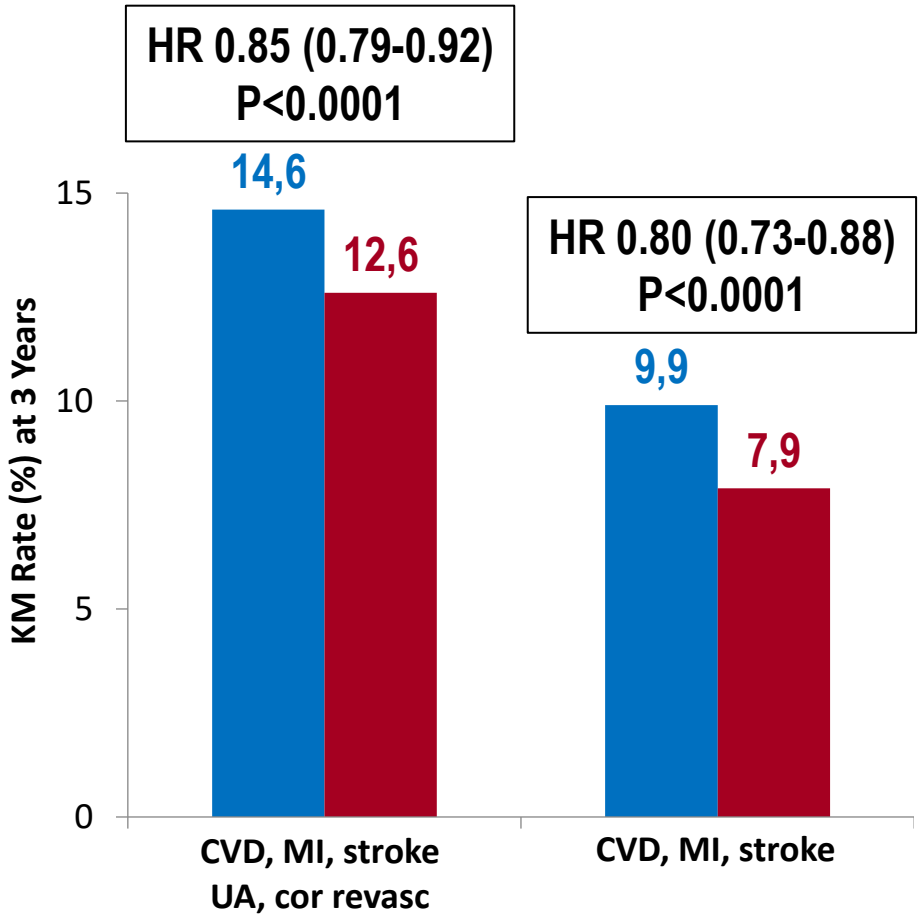
*Based on cumulative incidence

ODYSSEY OUTCOMES

FOURIER Trial *Evolocumab*

- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated

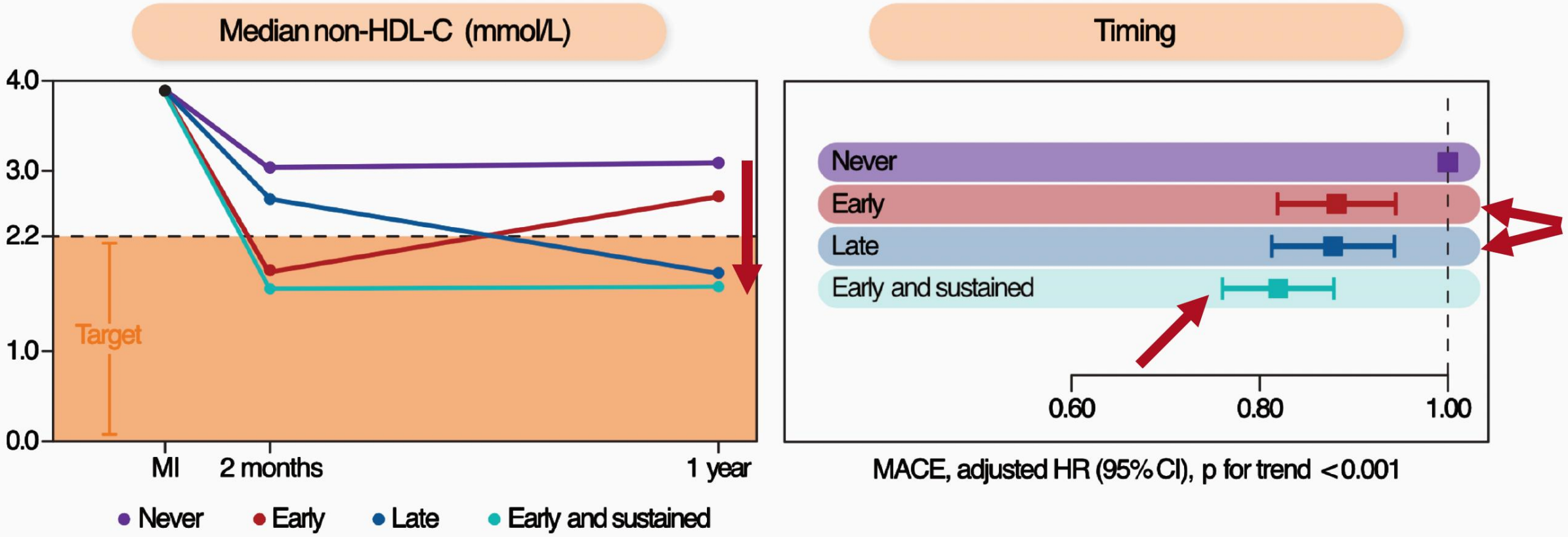




Sabatine MS et al. *NEJM* 2017;376:1713-22

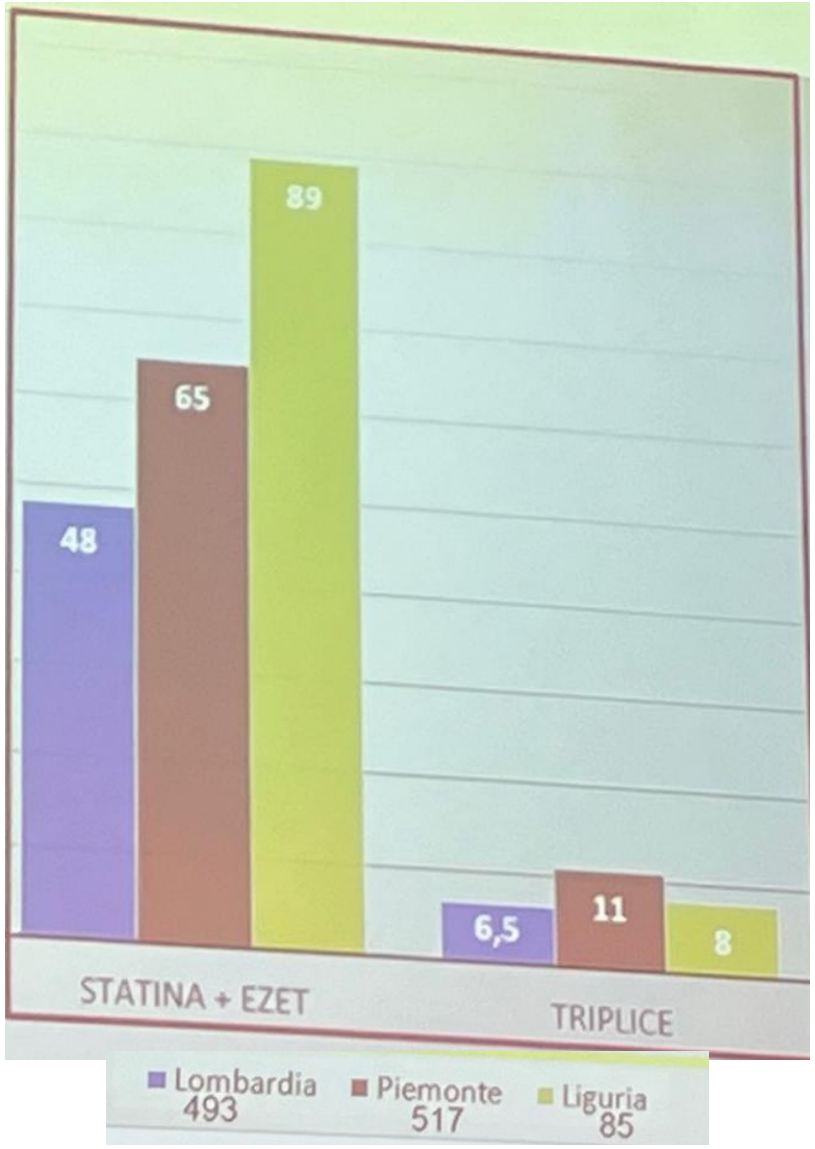
Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained

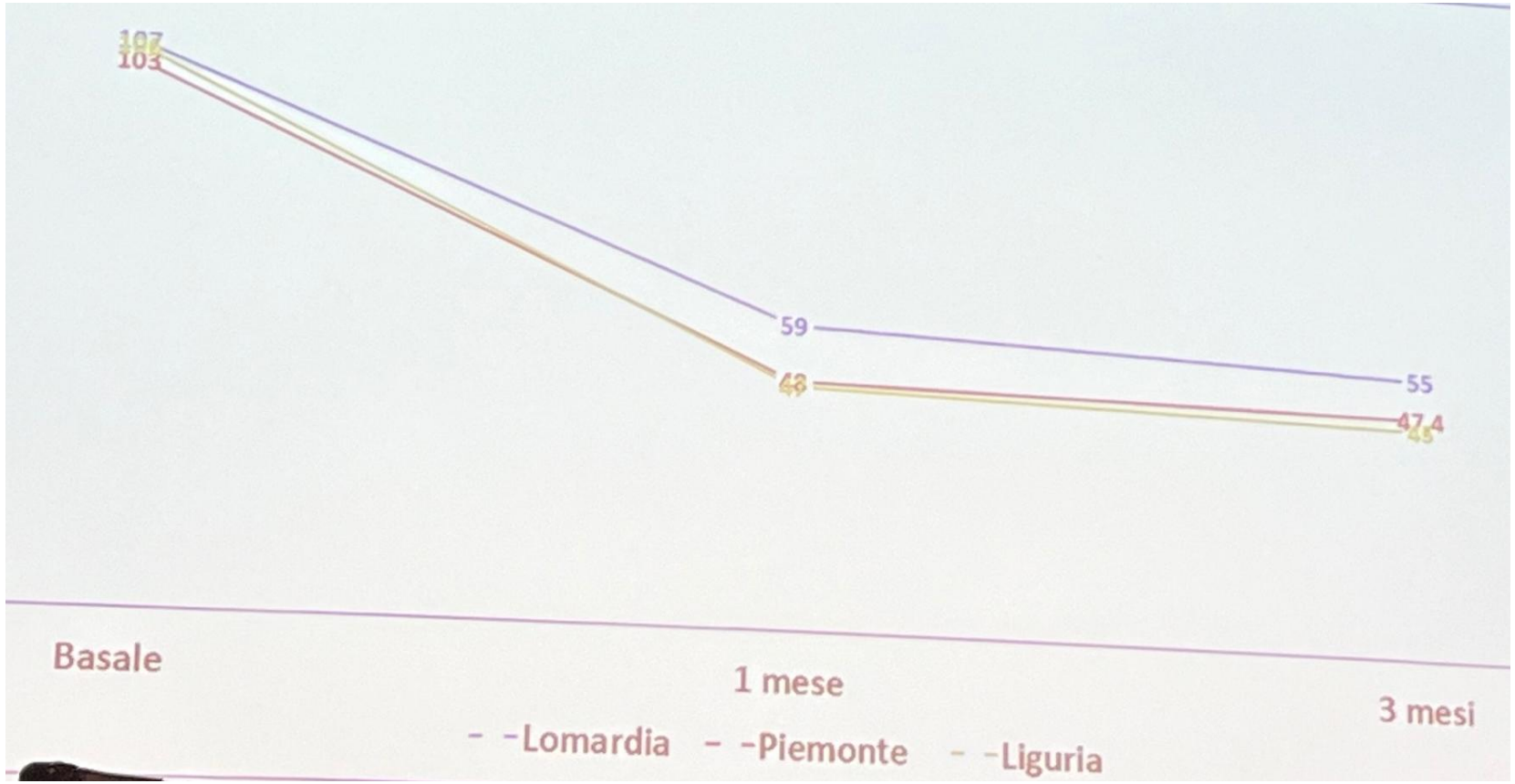
46 518 patients with MI and 7407 MACE events (all-cause mortality, MI, or stroke)



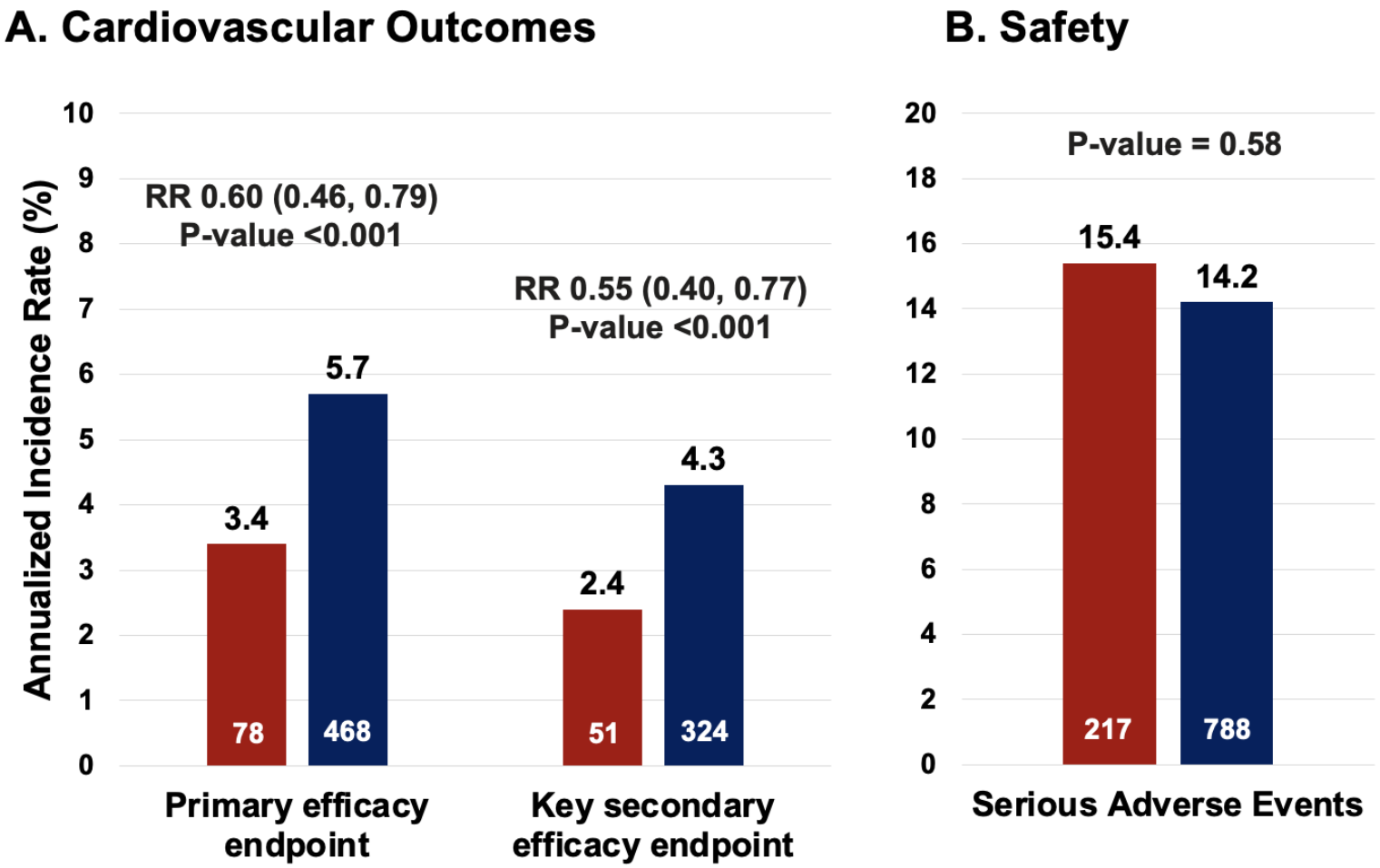
J. Schubert et al Eur Heart J, 2024 ehae576, https://doi.org/10.1093/eurheartj/ehae576

JET-LDL Registry: Lombardia vs Piemonte vs Liguria





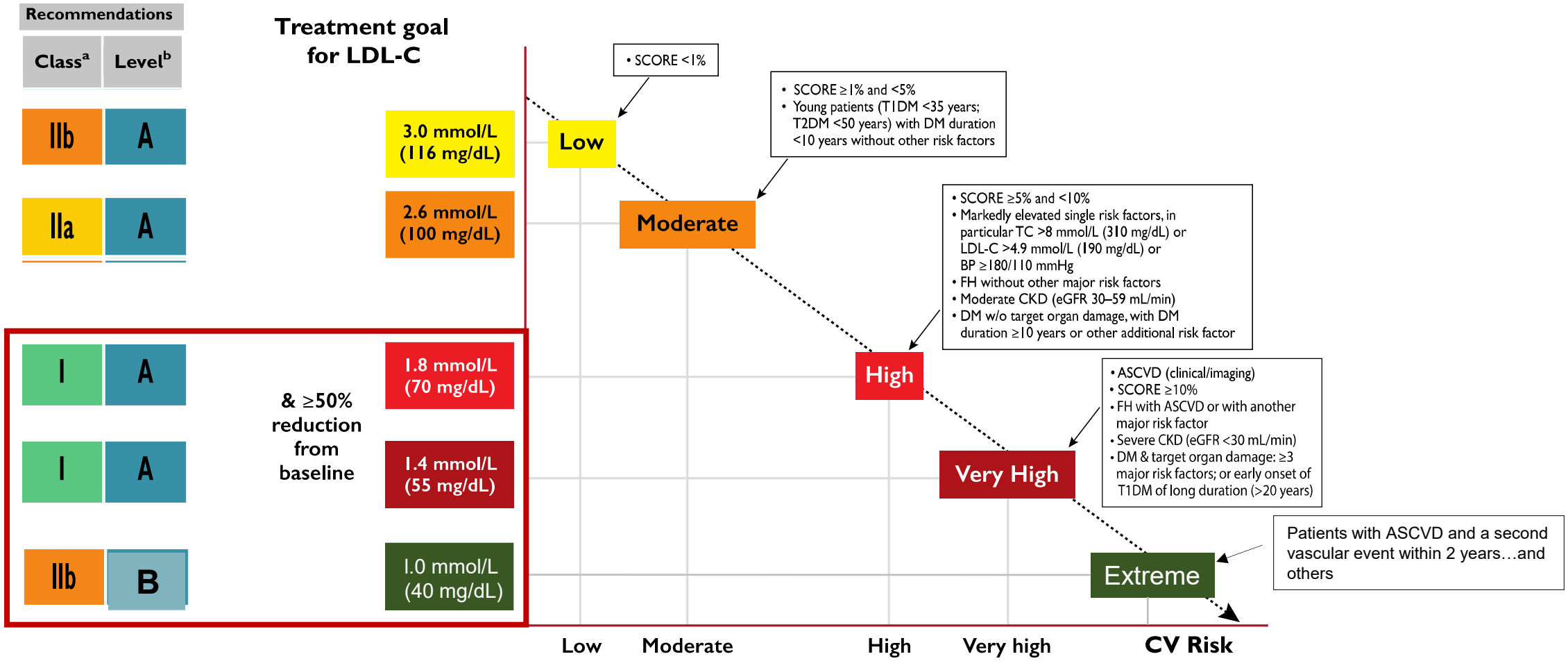
MACE & Safety w/ LDL-C <10 vs ≥100 mg/dL



LDL-C <10 mg/dL LDL-C ≥100 mg/dL

Gaba et al. Circulation 2023

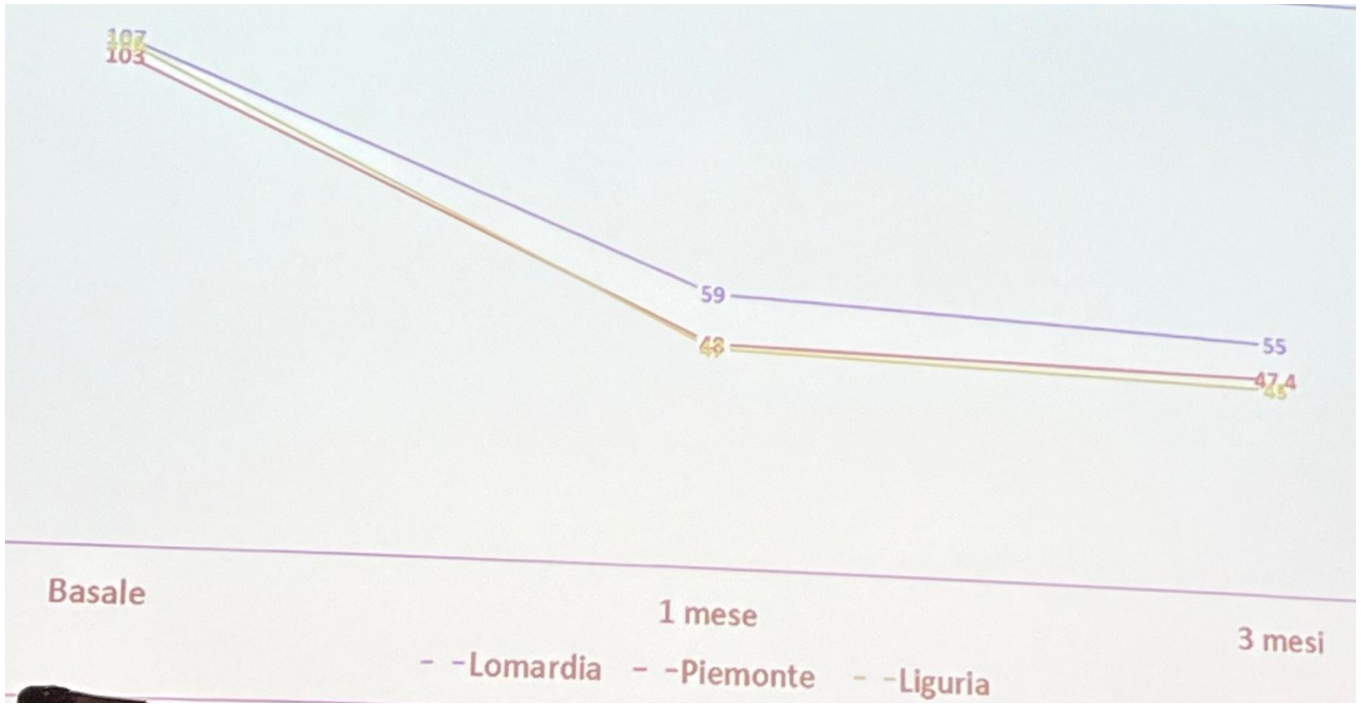
Le Linee Guida ESC/EAS 2019 per la gestione delle dislipidemie hanno stratificato i pazienti in **5 categorie di rischio** definendo target di C-LDL per ciascuna categoria di rischio



- 2019 ESC/EAS 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. European Heart Journal, 2020.

JET-LDL Registry: Lombardia vs Piemonte vs Liguria

JET-LDL Registry: Lombardia vs Piemonte vs Liguria

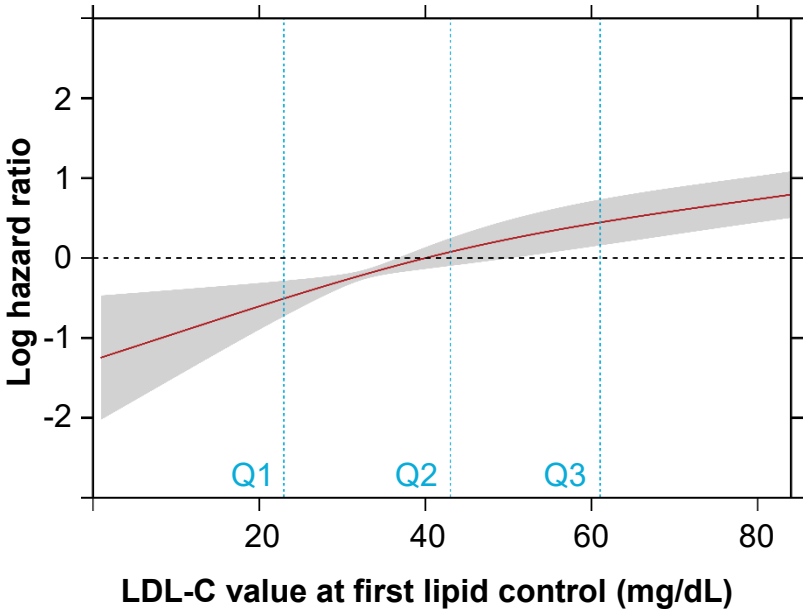


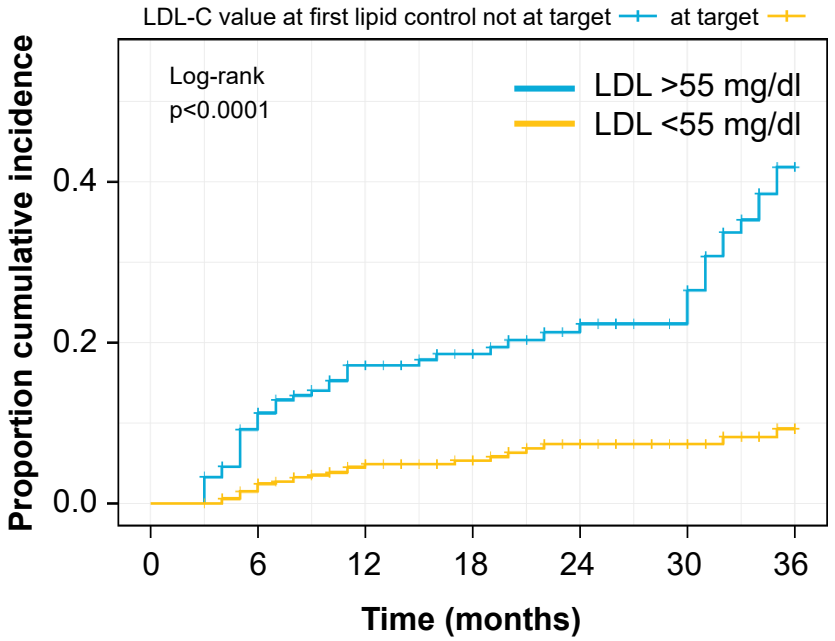
Effects of the strike early-strike strong lipid lowering strategy with PCSK9i in patients with ACS. A real-world evidence from the AT-TARGET-IT registry

771 ACS patients treated with PCSK9i prescription during hospitalization or at discharge in 22 Italian centres

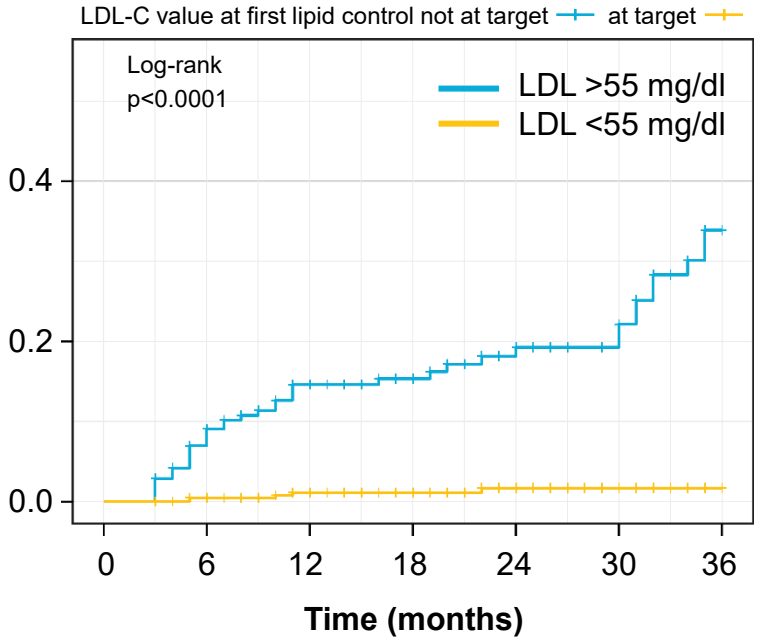
Better prognosis in patients at target

3P-MACE: Death, non-fatal MI and Stroke





All-cause mortality



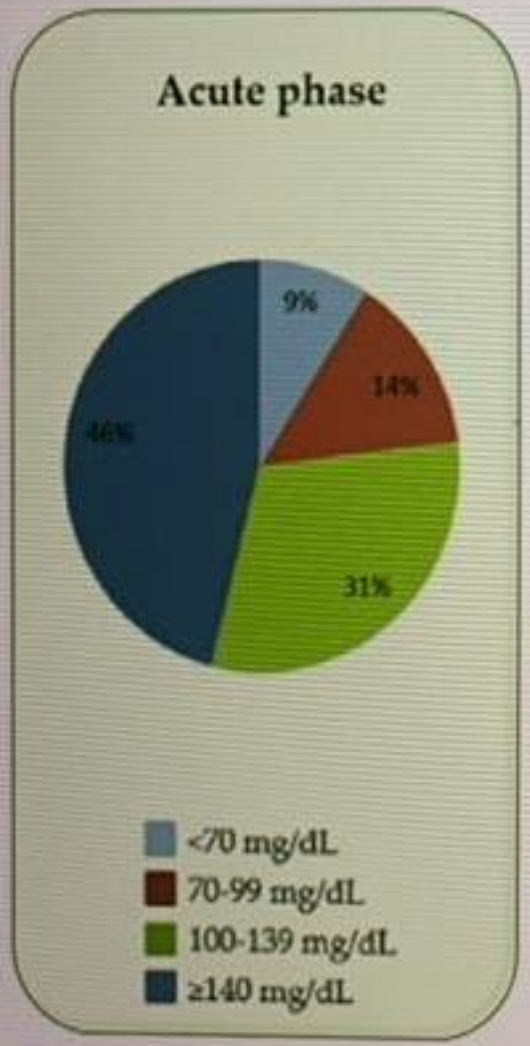
LDL 55 mg/dl = 1.4 mmol/L

3-P, 3-parameter; ACS, acute coronary syndrome; LDL(-C), low density lipoprotein (cholesterol); MACE, major adverse cardiovascular event; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Q, quartile

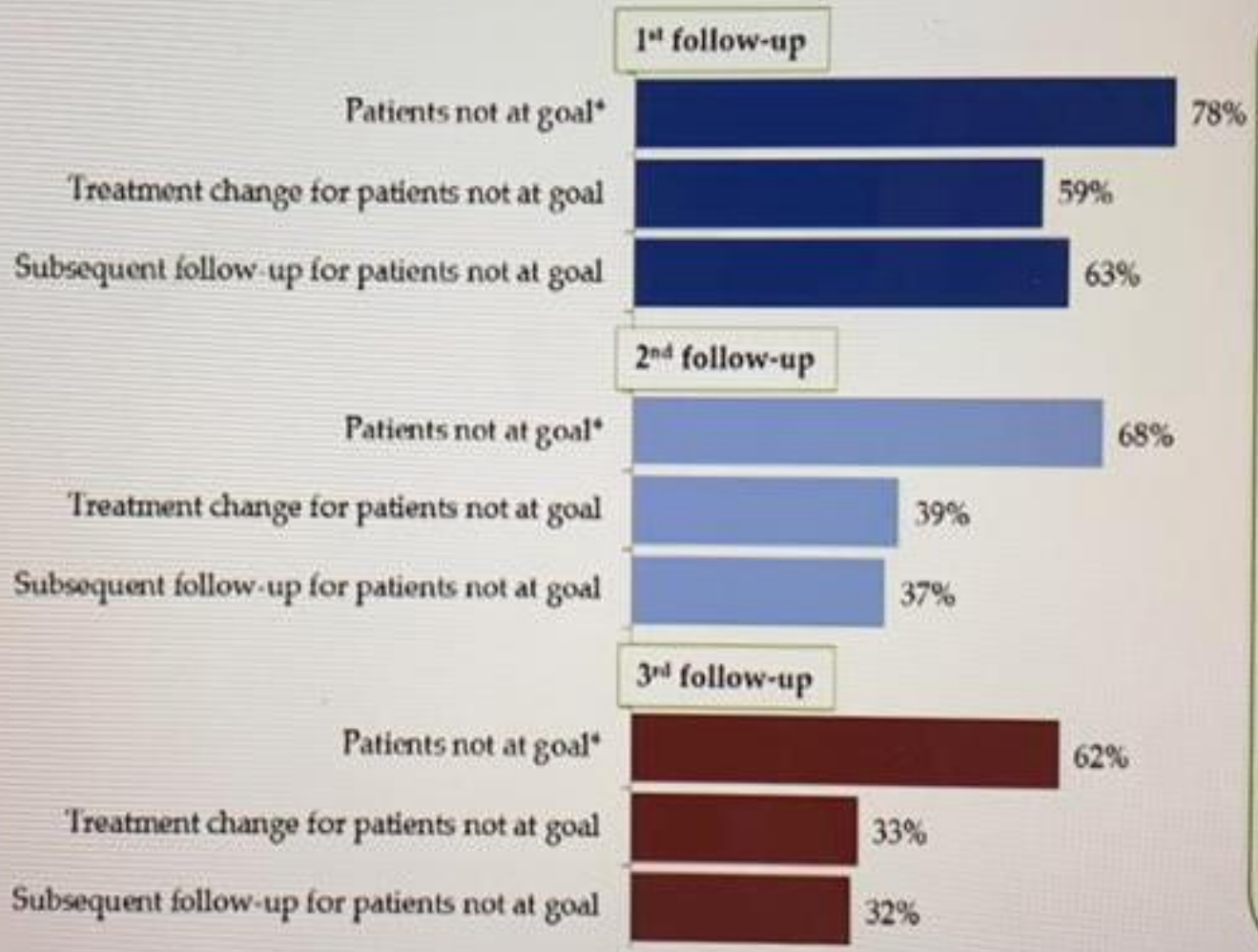
P. Gargiulo, G. Musumeci, P. Fillardi et al. Eur J Prev Cardiol. 2024 May 24:zwae170. doi: 10.1093/eurjpc/zwae170. Online ahead of print

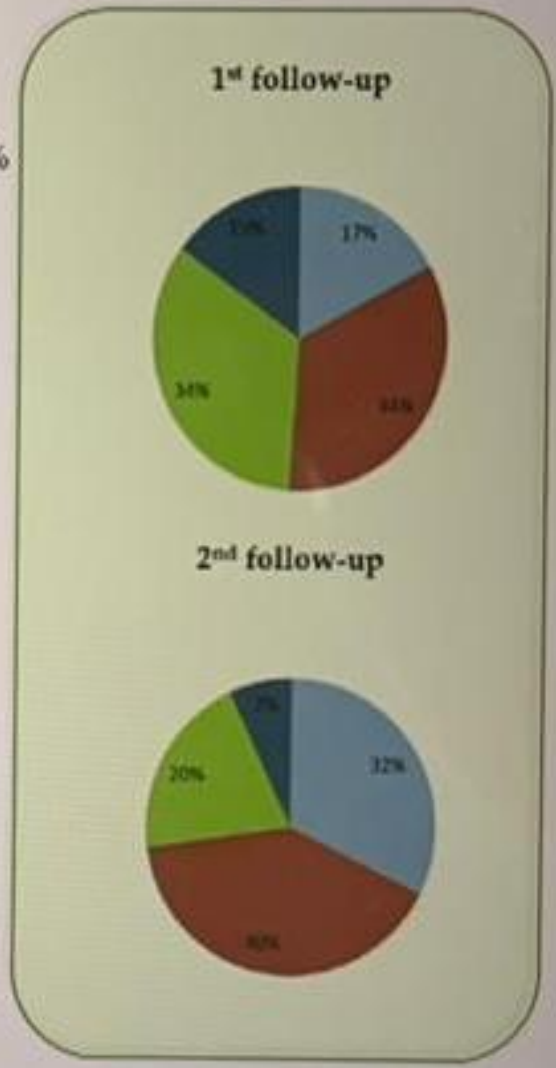
Patients not at goal, treatment changes and follow-up planning during three follow-up visits

The ACS patient pathway project



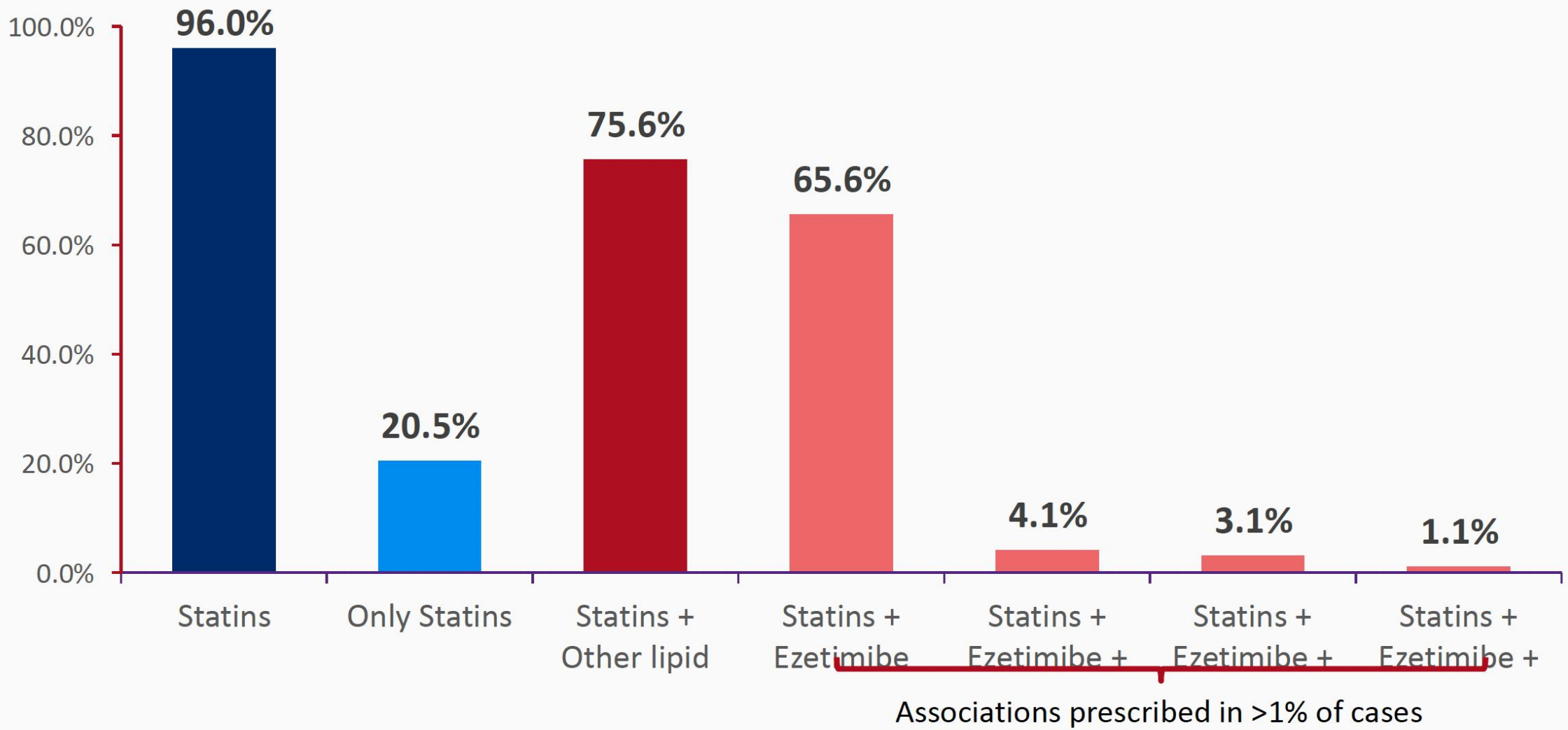
93% received LLT
66% Hi Statin



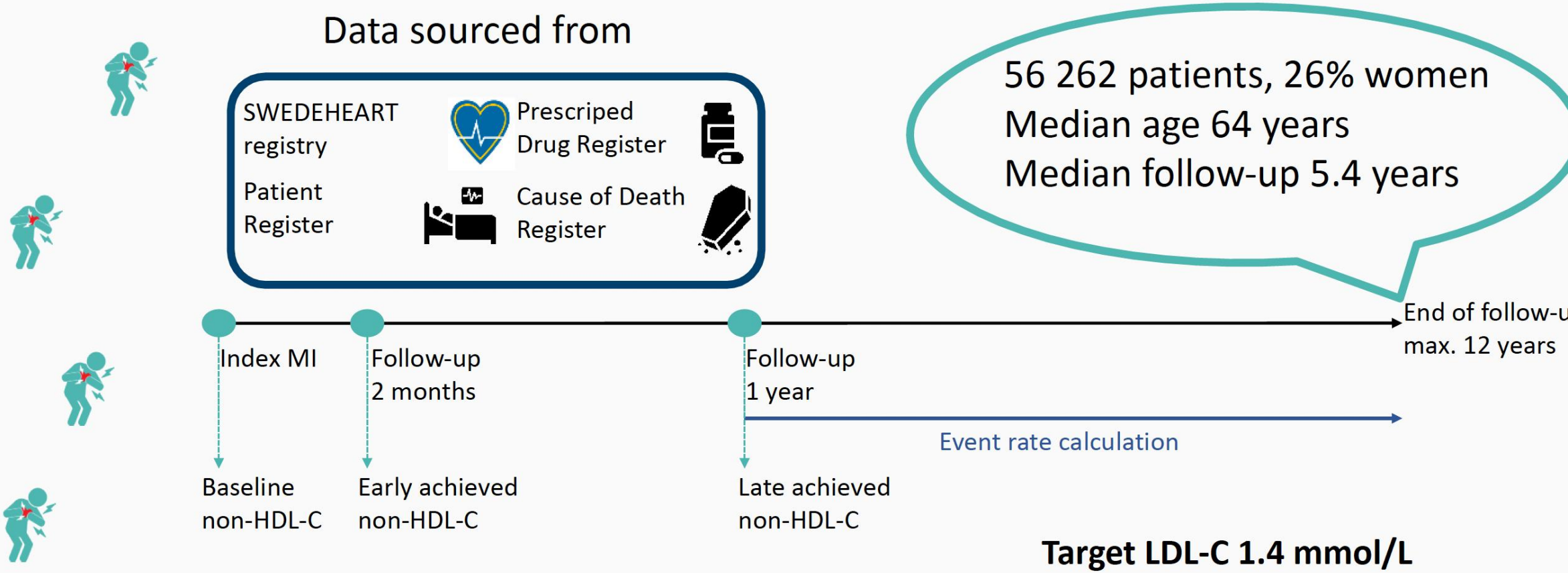


Landmesser U et al. Atherosclerosis Supplements 42 (2020) e49e58

Lipid Lowering Therapy prescribed (4790 pts)



A nationwide longitudinal registry of MI patients in Sweden

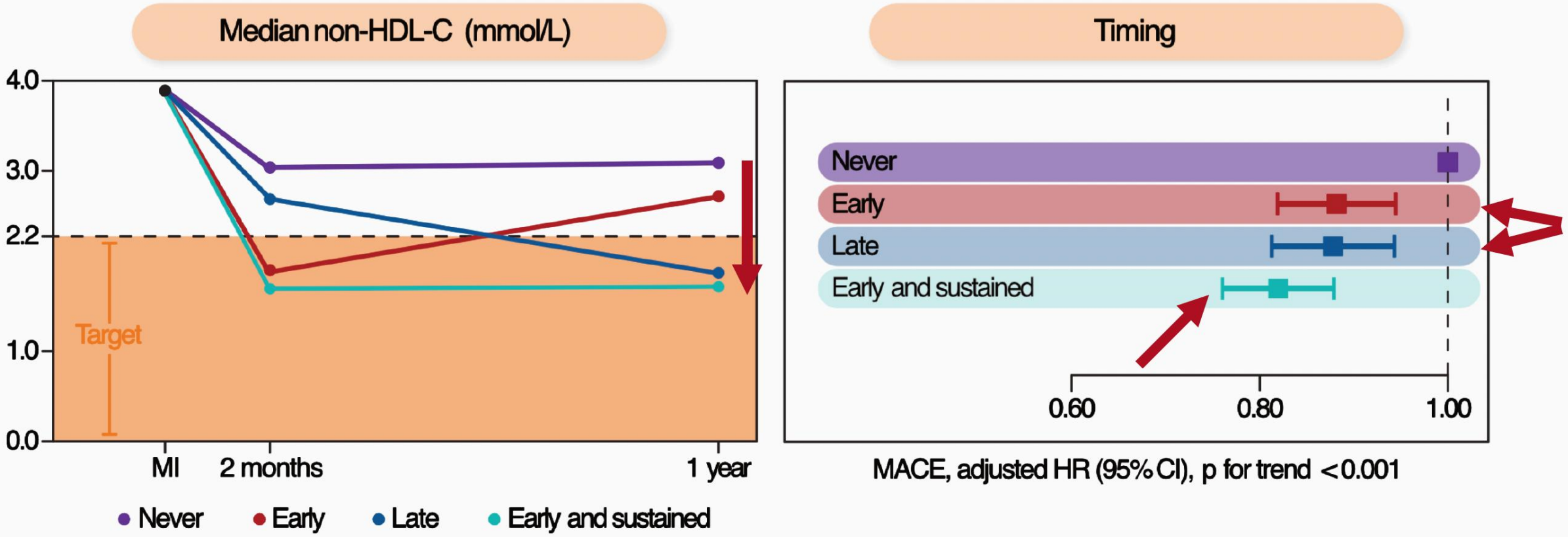


Target LDL-C 1.4 mmol/L corresponds to non-HDL-C < 2.2 mmol/L

J. Schubert et al Eur Heart J, 2024 ehae576, https://doi.org/10.1093/eurheartj/ehae576

Timing of achieved Non-HDL-C targets and outcomes after 1 year: intensive, early and sustained

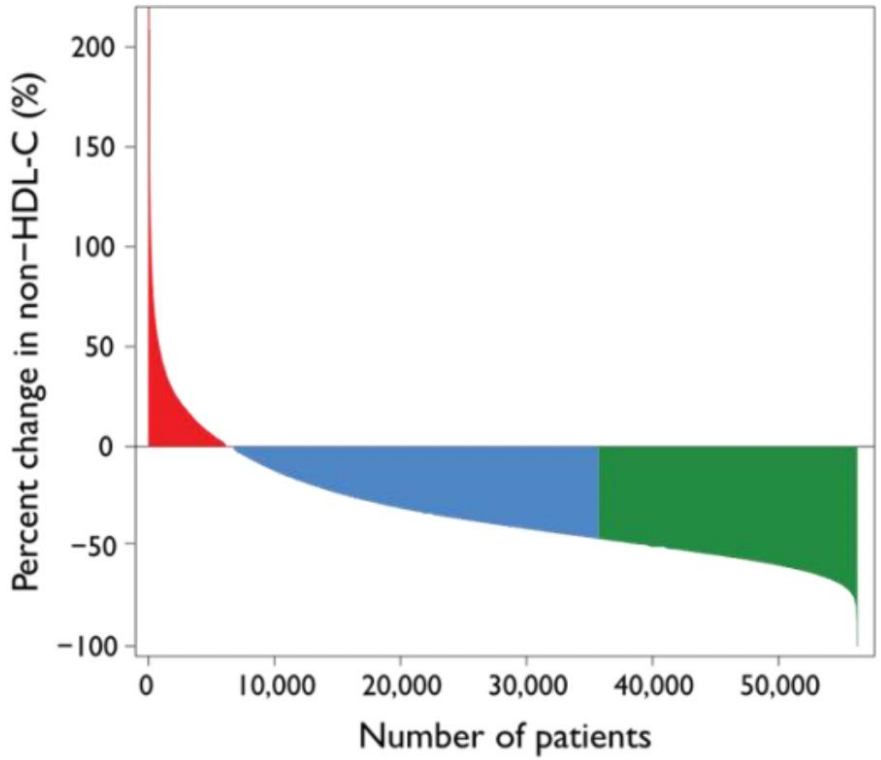
46 518 patients with MI and 7407 MACE events (all-cause mortality, MI, or stroke)

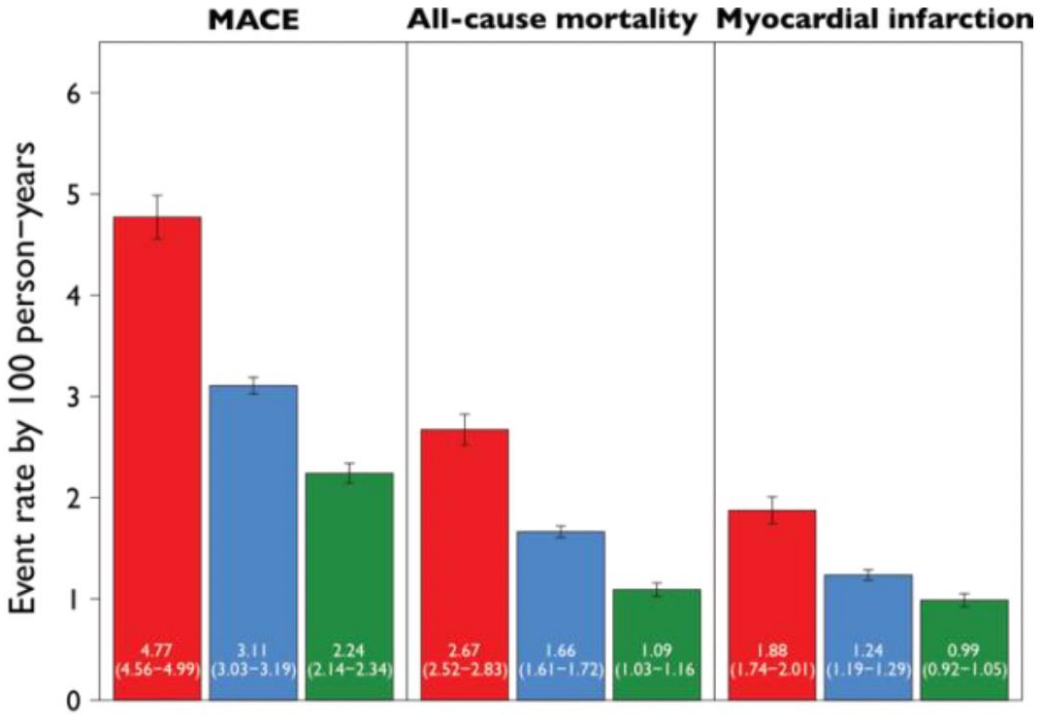


J. Schubert et al Eur Heart J, 2024 ehae576, https://doi.org/10.1093/eurheartj/ehae576

Reduction, how to aichieve it and association with outcomes

Figure S8. 46% reduction in non-HDL-C at 1 year





	n = 6631	n = 29,092	n = 20,539
No statin:	20 %	4 %	2 %
Ezetimibe mono therapy:	4 %	1 %	1 %
Low/moderate intensity statin:	37 %	35 %	12 %
Low/moderate intensity statin + ezetimibe:	3 %	2 %	2 %
High intensity statin:	31 %	46 %	53 %
High intensity statin + ezetimibe:	6 %	12 %	30 %

non-HDL-C change

- Increase or no reduction
- > 0 − < 46 % reduction
- ≥ 46 % reduction

J. Schubert et al Eur Heart J, 2024 ehae576, https://doi.org/10.1093/eurheartj/ehae576