UTIC CLUB | ANMCO
CRITICAL CARE COMMUNITY

Ruolo della triplice terapia orale nei pazienti a rischio cardiovascolare più alto

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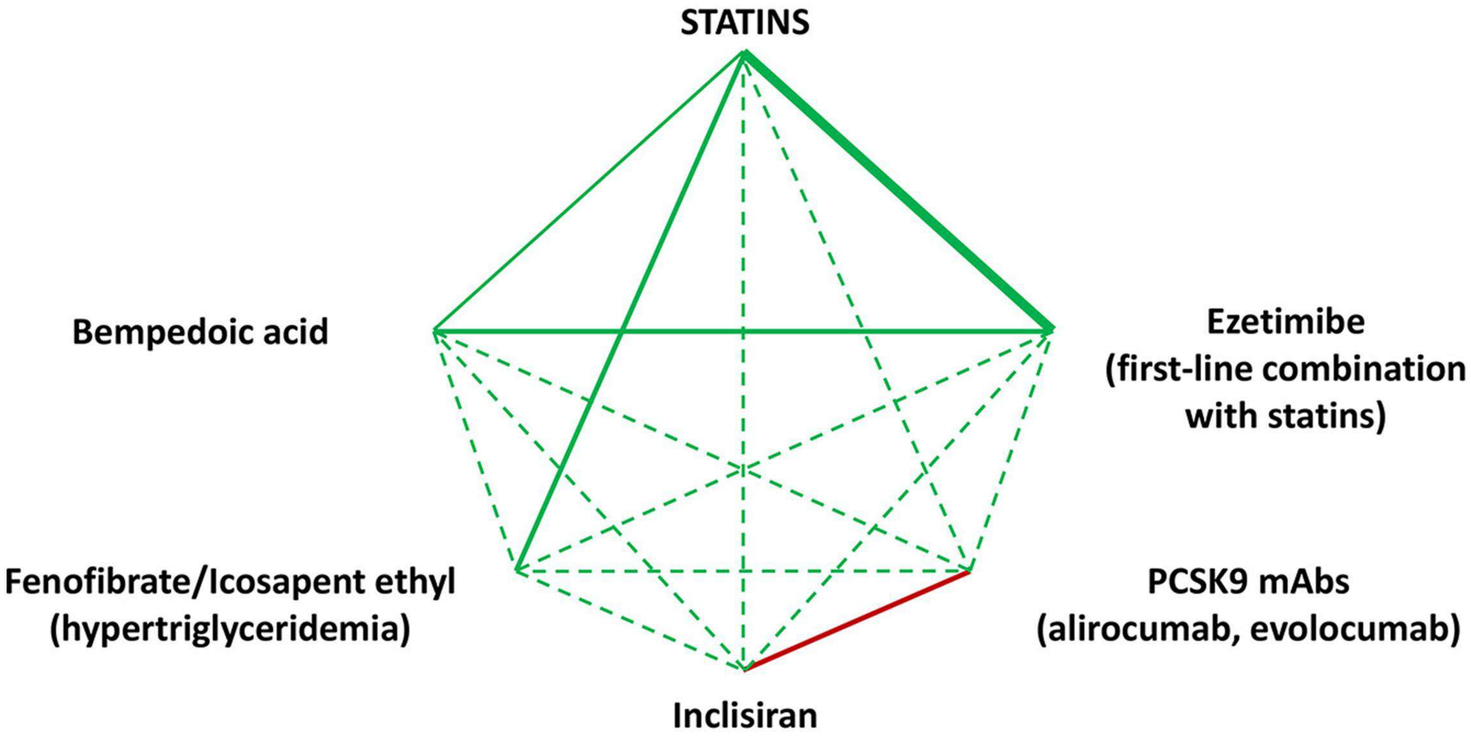
Lipid Lowering combination therapy



Recommended association (first/second line) with consolidated evidence (LDL-C lowering and cardiovascular risk reduction) [the thicker the line, the stronger the evidence]

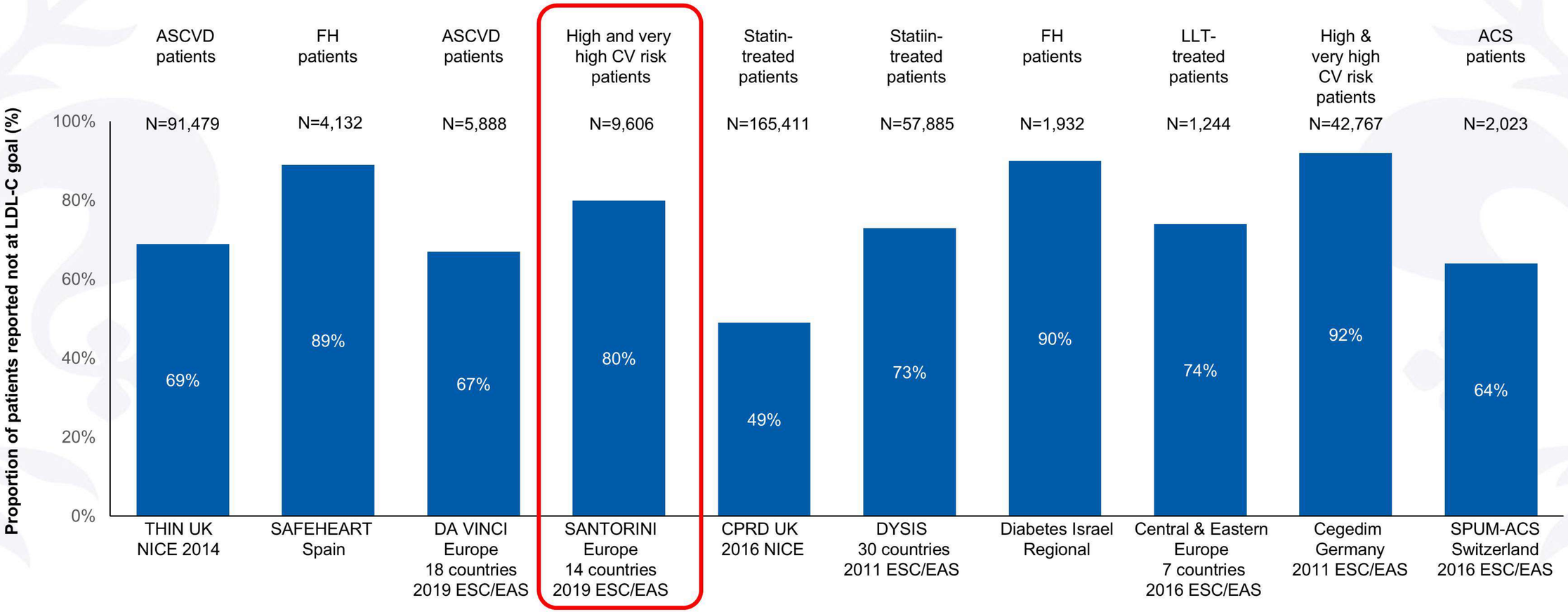
Possible association (mechanistic plausibility or preliminary evidence limited to LDL-C reduction)

No mechanistic plausibility of additional LDL-C lowering and cardiovascular risk reduction

- *C-LDL, low-density lipoprotein cholesterol. PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor. mAbs, monoclonal antibodies.*
- *Raschi et al, Pharmacol Ther. 2023 Oct:250:108507. doi: 10.1016/j.pharmthera.2023.108507.*
- *Beyond statins: New pharmacological targets to decrease LDL-cholesterol and cardiovascular events – ScienceDirect*

Unmet Needs in Hypercholesterolemia and Dyslipidemia Management

Most High- and Very High-Risk Patients Do Not Achieve LDL-C Goal



ACS, acute coronary syndrome; **ASCVD**, atherosclerotic cardiovascular disease; **CV**, cardiovascular; **FH**, familial hypercholesterolaemia; **LDL-C**, low-density lipoprotein cholesterol; **LLT**, lipid-lowering therapy

1. Steen DL, et al. BMJ Open. 2017;7:e013255. 2. de Isla LP, et al. JACC. 2016;67:1278–1285. 3. Ray KK, et al. Eur J Prev Cardiol. 2021;28:1279–1289. 4. Ray KK, et al. ESC congress 2021; poster 80441. 5. Akyea RK, et al. Heart. 2019;0:1–7. 6. Gitt AK, et al. Atherosclerosis. 2016;255:200–209. 7. Zafrir B, et al. Eur J Prev Cardiol. 2017;24:867–875. 8. Petrov I, et al. Adv Ther. 2019;36:608–20. 9. März W, et al. Atherosclerosis. 2018;268:99–107. 10. Gencer B, et al. J Am Heart Assoc. 2017;6:e006537. 11. Mach F, et al. Eur Heart J. 2019;41(1):111–188

BRING-UP Prevention

Studio osservazionale multicentrico prospettico condotto in 189 centri italiani che hanno incluso 4790 pazienti. Il 98% aveva CAD, il 6,1% CVD e il 6,9% PAD.4 Età media 67 ±11 anni, 20% donne.

Risultati

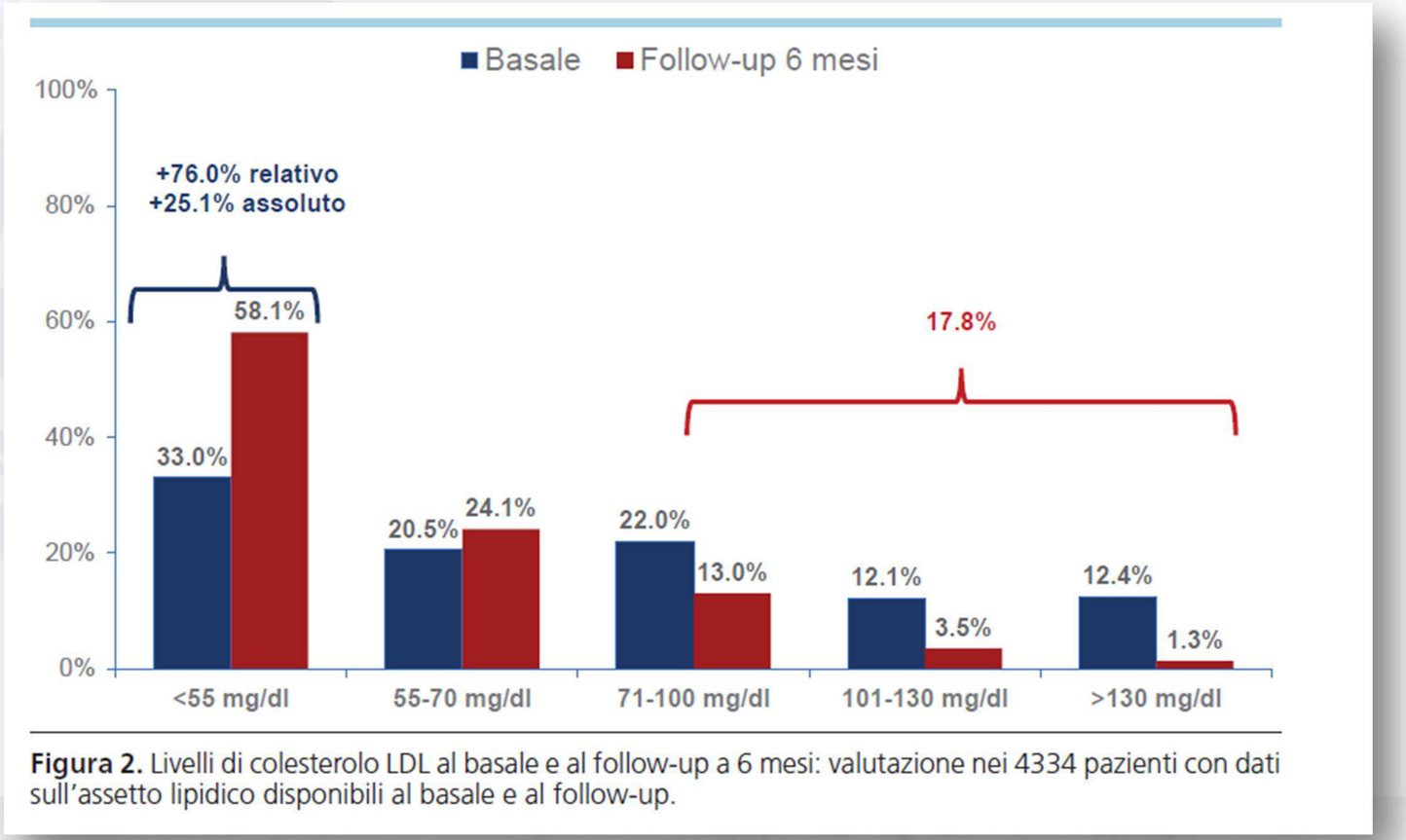


Figura 2. Livelli di colesterolo LDL al basale e al follow-up a 6 mesi: valutazione nei 4334 pazienti con dati sull'assetto lipidico disponibili al basale e al follow-up.

A 6 mesi, era stato ipotizzato un aumento relativo del 50% dei pazienti che avevano raggiunto l'obiettivo: tale obiettivo è stato raggiunto. Infatti, i risultati dei primi 6 mesi di follow-up dello studio BRING-UP Prevention hanno mostrato un aumento della percentuale di pazienti che hanno raggiunto l'obiettivo di colesterolo LDL, che è passato dal 33% al 58,1% (Figura 2), con un aumento assoluto del 25% e un aumento relativo del 76%.

Colivicchi et al. G Ital Cardiol 2025;26

BRING-UP Prevention

Studio osservazionale multicentrico prospettico condotto in 189 centri italiani

Uso di terapie non statiniche
dal basale al follow-up a 6 mesi

Tabella 1. Tasso di prescrizione dei farmaci non statinici: valutazione nei 4504 pazienti con dati sui trattamenti disponibili al basale e al follow-up.

Farmaco	Basale	Follow-up a 6 mesi	
		Pre-visita	Post-visita
Almeno un altro ipolipemizzante associato o meno a statina	3569 (79.2%)	3630 (80.6%)	3886 (86.3%)
Ezetimibe	3478 (77.2%)	3537 (78.5%)	3782 (84.0%)
Fibrati	33 (0.7%)	28 (0.6%)	32 (0.7%)
Evolocumab	141 (3.1%)	129 (2.9%)	159 (3.5%)
Alirocumab	157 (3.5%)	155 (3.4%)	187 (4.2%)
Inclisiran	68 (1.5%)	82 (1.8%)	104 (2.3%)
Acido bempedoico	194 (4.3%)	231 (5.1%)	390 (8.7%)

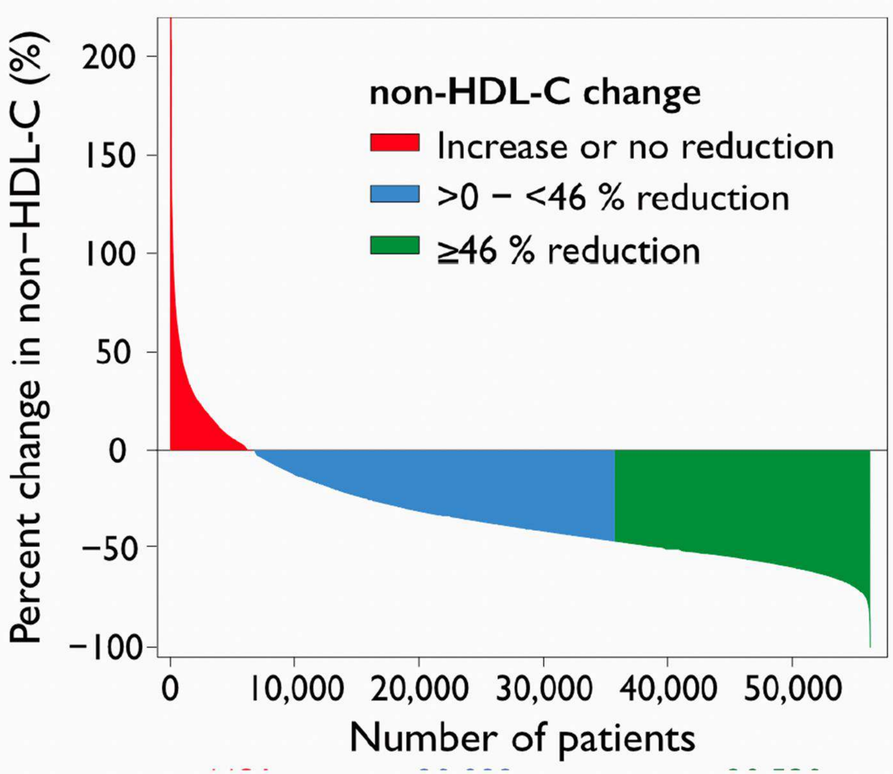
Colivicchi et al. G Ital Cardiol 2025;26

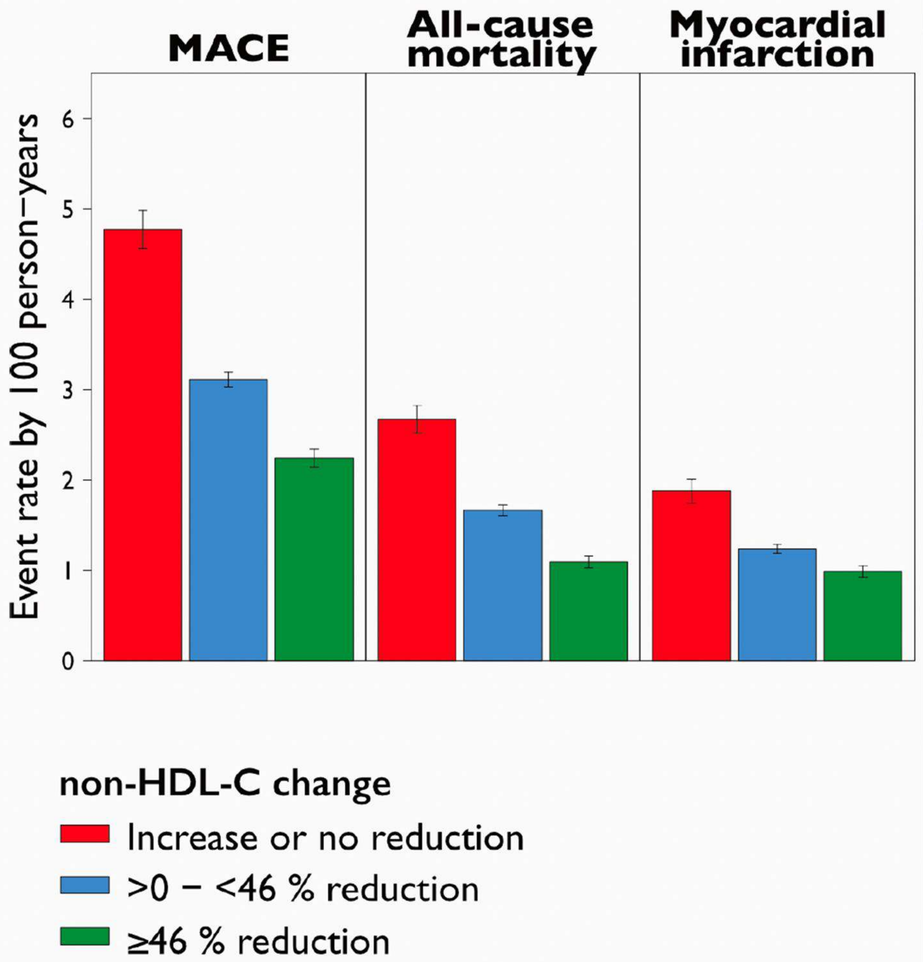
Uso di acido bempedoico

Al follow-up a 6 mesi è stato osservato un aumento della percentuale di prescrizione di acido bempedoico che potrebbe essere almeno in parte spiegato da una maggior confidenza dei clinici nell'iniziare questo farmaco, la cui autorizzazione è relativamente recente. **È stato sottolineato che l'acido bempedoico è un farmaco a relativo basso costo e con un profilo di tollerabilità estremamente favorevole che potrebbe essere utilizzato nei pazienti non molto lontani dal target con i farmaci convenzionali**

Colivicchi et al. G Ital Cardiol 2025;26

Reduction, how to aichieve it and association with outcomes



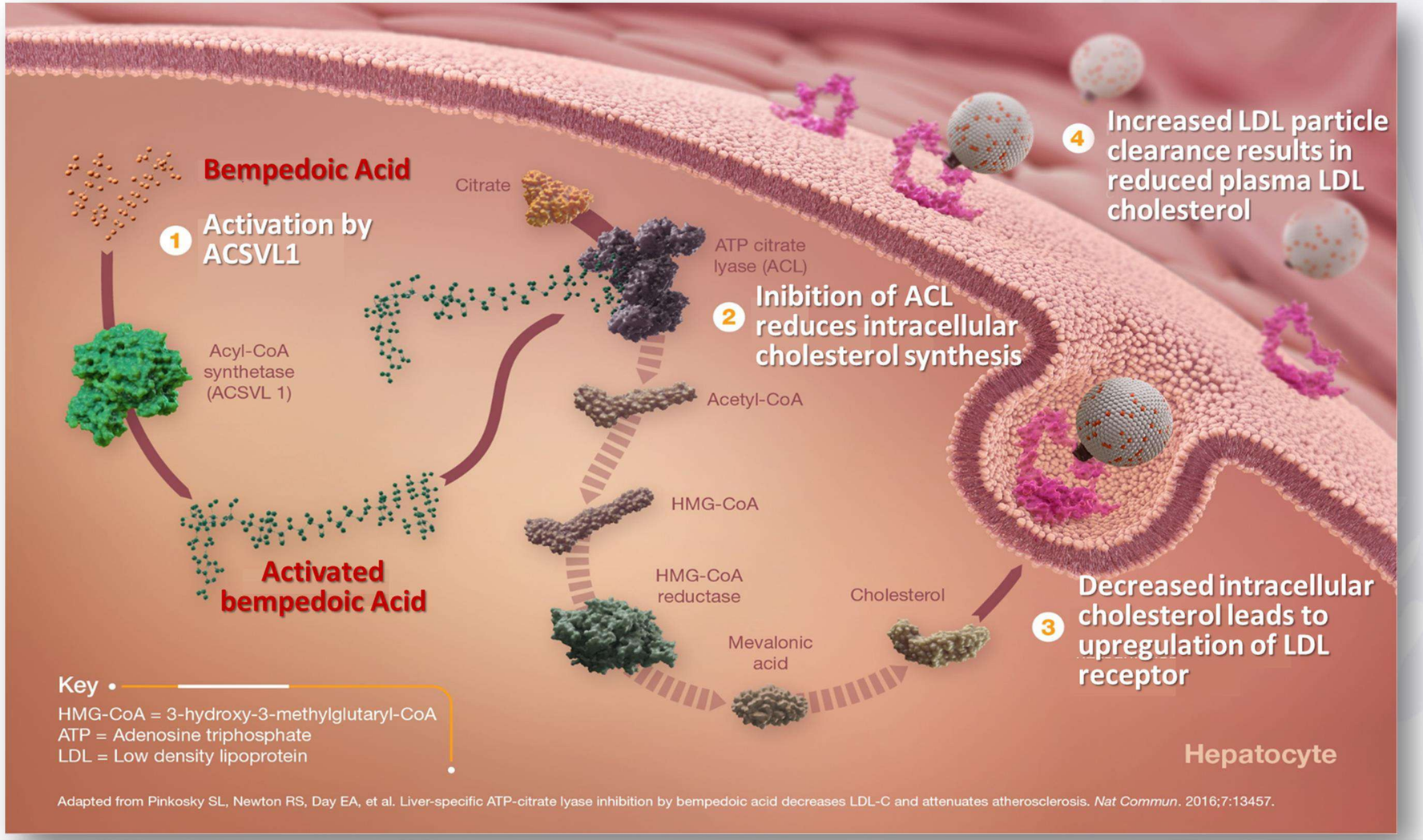


The current step-wise lipid lowering strategy might lead to delayed target achievement and risk of harm

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

Mechanism of Action of Bempedoic Acid

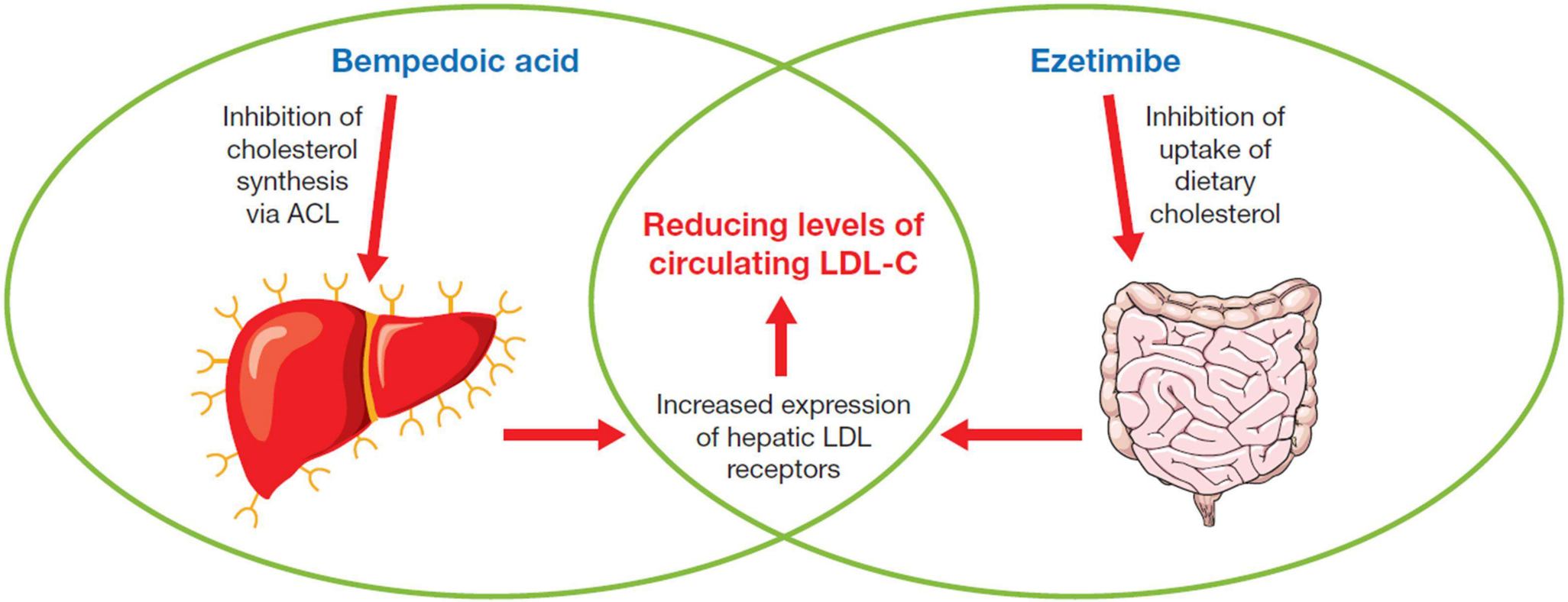
- Activated primarily in the liver, bempedoic acid inhibits the ACL enzyme in the cholesterol synthesis pathway, upstream of the statin target
- Upregulation of the LDL receptor results in an increased uptake and removal of LDL particles by the liver



ACSVL1= Acyl-CoA sythetase
ACL= ATP citrate lyase

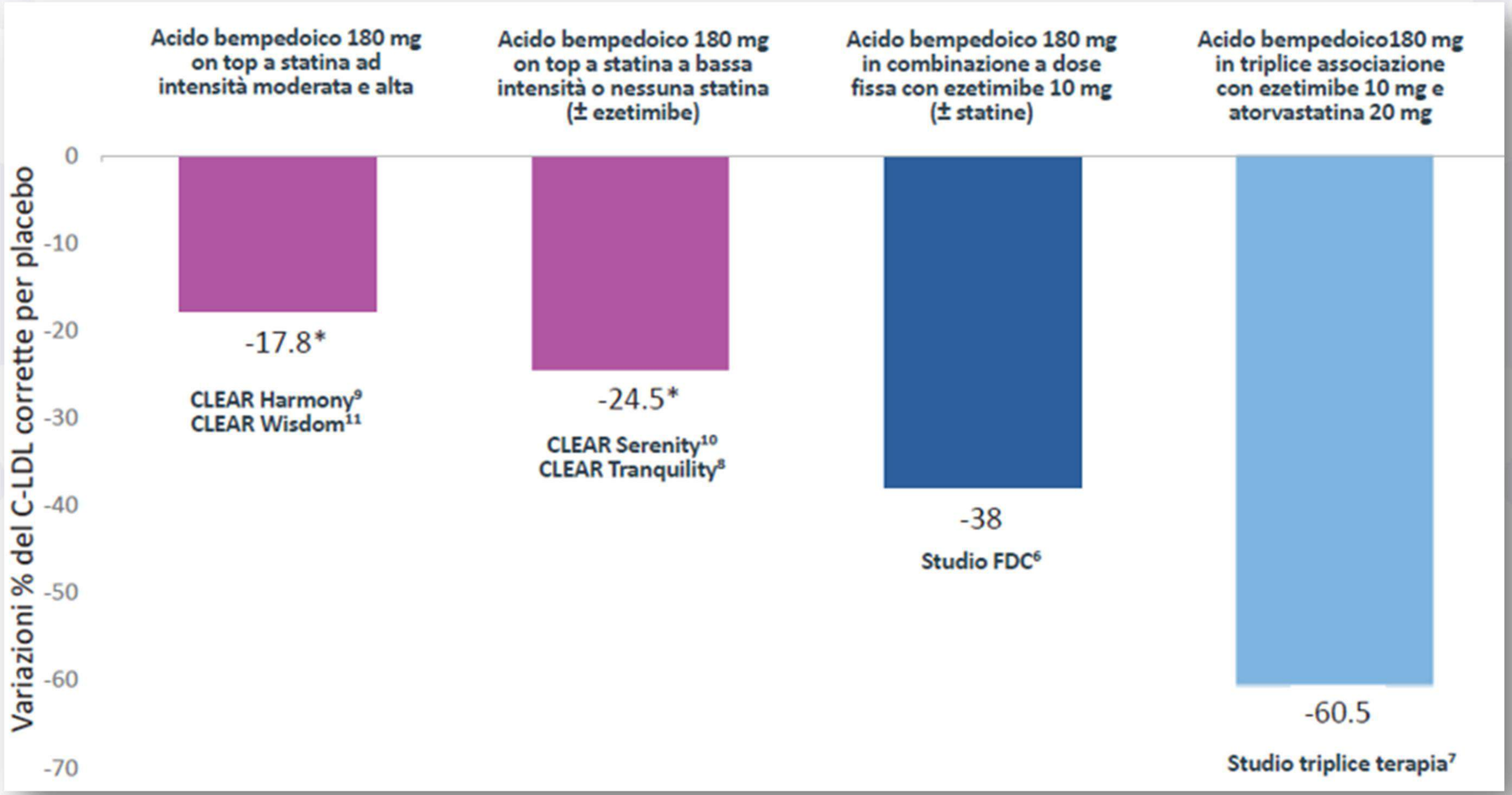
Adapted from Pinkosky S, Nature Communications 2016

Mechanism of Action: Bempedoic Acid and Bempedoic Acid/Ezetimibe FDC



ACL, adenosine triphosphate citrate lyase; **FDC**, fixed-dose combination; **LDL-C**, low-density lipoprotein cholesterol.
Ballantyne CM, et al. Eur J Prev Cardiol. 2020 Apr;27(6):593-603.

Bempedoic acid impact on lipid control



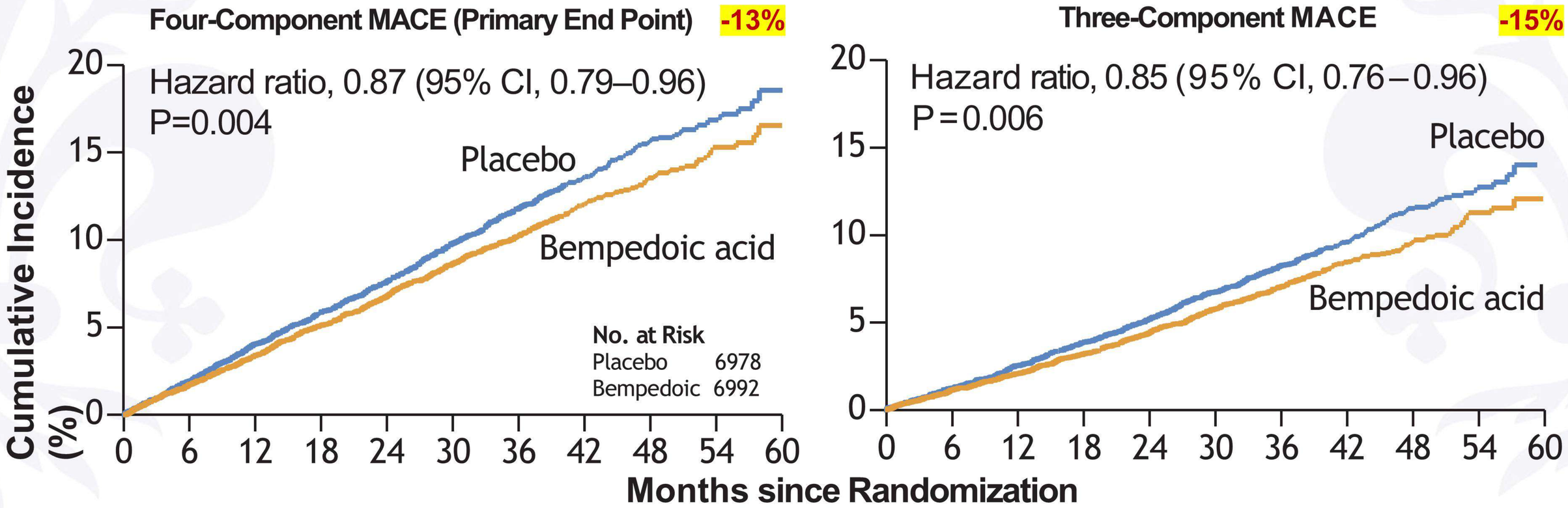
G Ital Cardiol 2021;22(4 Suppl. 1):4S | doi 10.1714/3582.35669

Bempedoic Acid and Cardiovascular Outcomes:
CLEAR Outcomes Study

Characteristic	Bempedoic Acid (N = 6992)	Placebo (N = 6978)
Age		
Mean — yr	65.5±9.0	65.5±8.9
Female sex — no. (%)	3361 (48.1)	3379 (48.4)
Body-mass index‡	29.9±5.2	30.0±5.2
LDL cholesterol		
Mean value — mg/dl	139.0±34.9	139.0±35.2
Primary prevention	2100 (30.0)	2106 (30.2)
Secondary prevention	4892 (70.0)	4872 (69.8)
Coronary artery disease	3574 (51.1)	3536 (50.7)
Peripheral arterial disease	794 (11.4)	830 (11.9)
Cerebrovascular atherosclerotic disease	1027 (14.7)	1040 (14.9)
Glycemic status — no. (%)		
Diabetes§	3144 (45.0)	3229 (46.3)
Inadequately controlled diabetes¶	1356 (19.4)	1369 (19.6)
Statin use — no. (%)	1601 (22.9)	1573 (22.5)
Ezetimibe use — no. (%)	803 (11.5)	809 (11.6)

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

Bempedoic Acid Significantly Reduced CV Events in CLEAR Outcomes

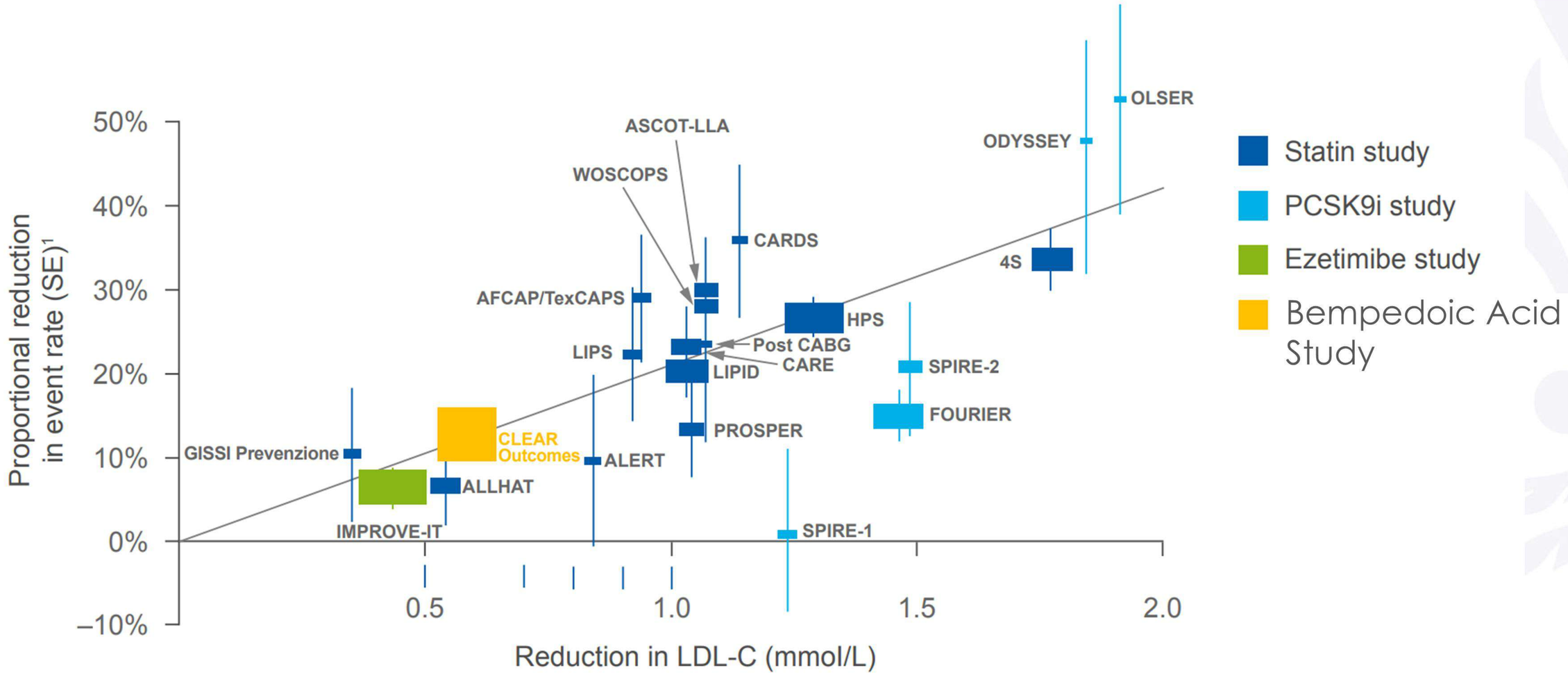


Four-component composite of major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, non fatal myocardial infarction, nonfatal stroke, or coronary revascularization.

Three-component MACE, defined as death from cardiovascular causes, non fatal myocardial infarction, or non fatal stroke (the first key secondary end point).

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

CLEAR Outcomes Provided Evidence for CV Risk Reduction



CV, cardiovascular; **LDL-C**, low-density lipoprotein cholesterol; **MACE**, major adverse cardiovascular event; **PCSK9i**, proprotein convertase subtilisin/kexin type 9 inhibitor; **SE**, standard error

1. Waters and Hsue. *Circ Res*. 2017;120(10):1537–1539;2. Nissen SE, et al. *N Engl J Med*. 2023; 388:1353–1364.

New Recommendations

Bempedoic Acid now in 2025 Focused Update of the 2019 ESC/EAS Guidelines

Recommendations	Class	Level
Recommendations for pharmacological low-density lipoprotein cholesterol lowering		
Non-statin therapies with proven cardiovascular benefit*, taken alone or in combination, are recommended for patients who are unable to take statin therapy to lower LDL-C levels and reduce the risk of CV events. The choice should be based on the magnitude of additional LDL-C lowering needed.	I	A
Bempedoic acid is recommended in patients who are unable to take statin therapy to achieve the LDL-C goal.	I	B
The addition of bempedoic acid to the maximally tolerated dose of statin with or without ezetimibe should be considered in patients at high or very high risk in order to achieve the LDL-C goal.	IIa	C

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.
This table complements the table of recommendations for pharmacological low-density lipoprotein cholesterol lowering in the 2019 ESC/EAS Guidelines and does not replace it.

*Ezetimibe, PCSK9 monoclonal antibodies, bempedoic acid.

Modified from Mach F, et al. Eur Heart J. 2025;00:1–20.

New Recommendations

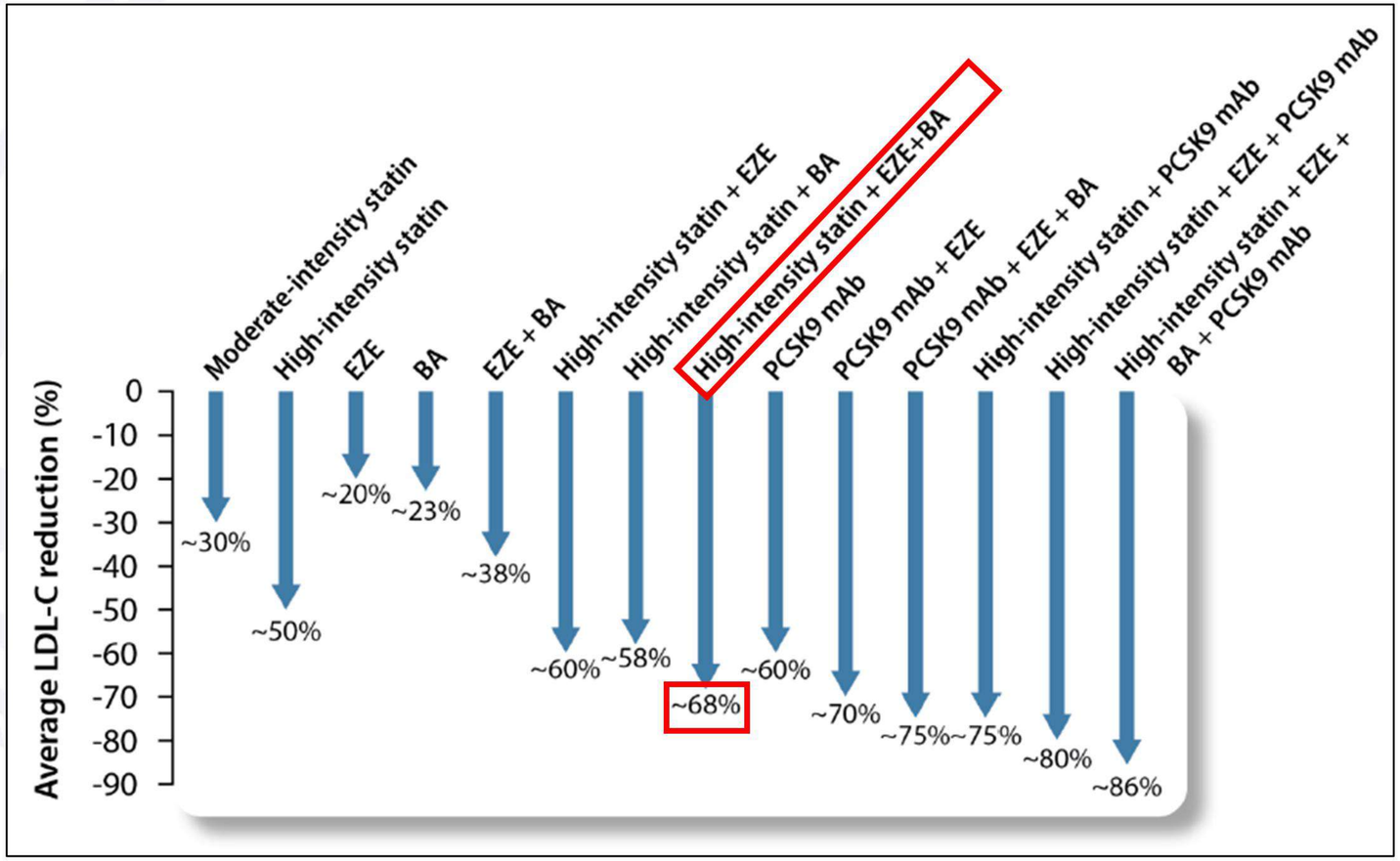
Recommendations	Class	Level
Recommendations for lipid-lowering therapy in patients with acute coronary syndromes		
Intensification of lipid-lowering therapy during the index ACS hospitalization is recommended for patients who were on any lipid-lowering therapy before admission in order to further lower 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.	**IIa**	**B**

LDL-C, low-density lipoprotein cholesterol; **ACS**, Acute Cardiovascular Syndrome
ESC, European Society of Cardiology; **CV,** Cardiovascular

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
(European Heart Journal; doi: 10.1093/eurheartj/ehaf190)

2025 Focused Update of the 2019 ESC/EAS Guidelines

Average reduction in LDL-C levels with different pharmacological therapies with proven CV benefits



- **As a general concept, this Task Force recommends to add non-statin therapies with proven cardiovascular benefit such as ezetimibe, a PCSK9 mAb, or bempedoic acid, taken alone or in combination, to lower LDL-C if the LDL-C goals are not achieved with the maximum tolerated dose of a statin**
- **The choice should be based on the magnitude of additional LDL-C lowering needed, patient preference, treatment availability, and cost.**
- **As outlined in the 2019 ESC/EAS Guidelines, LDL-C levels should be measured 4 to 6 weeks after initiation or intensification of lipid-lowering therapy.**

EZE, Ezetimibe; **BA**, Bempedoic Acid; **PCSK9 mAB,** Proprotein Convertase Subtilisin/Kexin type 9 Monoclonal Anti Body; **LDL-C,** low-density lipoprotein cholesterol
ESC, European Society of Cardiology; **EAS**, European Society of Lipidology

Mach F, et al. Eur Heart J. 2025;00:1–20..

G Ital Cardiol 2025;26

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

Federico Nardi[1], Giuseppe Patti[2], Giorgio Quadri[3], Luigi Pollarolo[1], Gianluca Alunni[4], Monica Andriani[4], Andrea Angelini[5], Marzia Bertolazzi[6], Giacomo Boccuzzi[7], Michele Capriolo[8], Alessandra Chinaglia[9], Michele De Benedictis[10], Ovidio De Filippo[4], Pierfranco Dellavesa[11], Fabrizio Delnevo[3], Sara Ferrillo[1], Massimo Giammaria[12], Antonio Lanfranchi[11], Piergiuseppe Greco Lucchina[13], Stefano Maffè[2], Marco Pavani[11], Elisa Pelloni[14], Davide Presutti[15], Maria Elena Rovere[16], Paolo Scacciatella[17], Gaetano Senatore[8], Erika Taravelli[18], Orazio Viola[19], Greca Zanda[20], Maurizio D'Amico[21], Gaetano Maria De Ferrari[4], Antonio Della Valle[22], Mauro Feola[23], Walter Grosso Marra[15], Alessandro Lupi[24], Claudio Moretti[19], Gianfranco Pistis[25], Francesco Rametta[6], Andrea Rognoni[20], Roberta Rossini[18], Marco Scaglione[5], Ferdinando Varbella[20], Giuseppe Musumeci[3]

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[21]*S.C. Cardiologia, Ospedale Santa Croce, Moncalieri (TO)*
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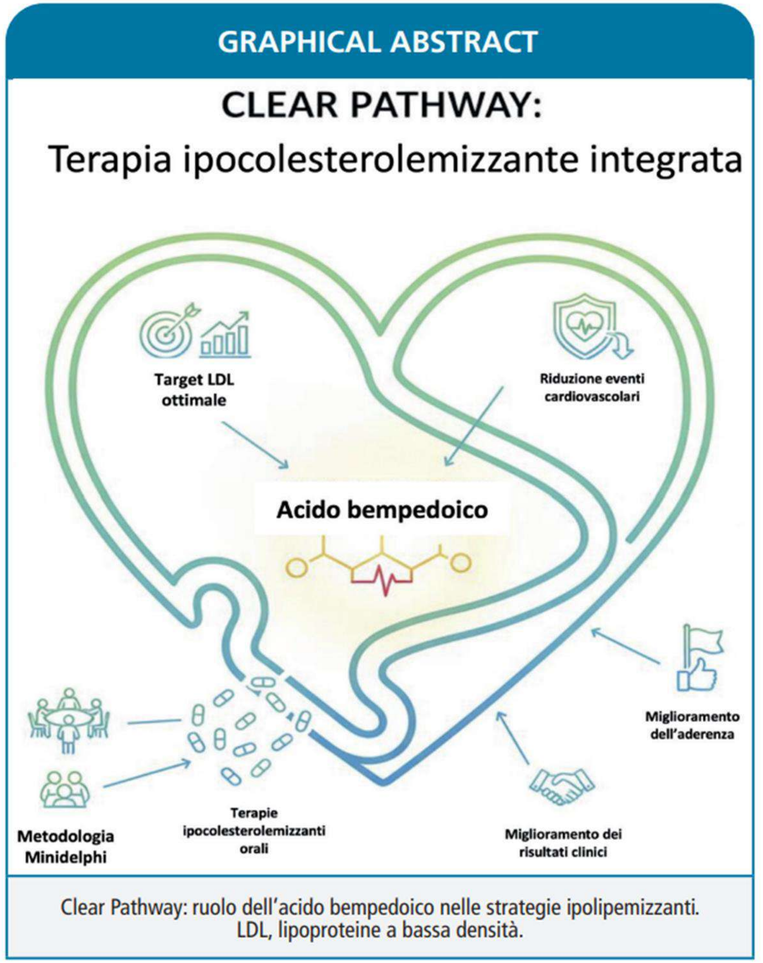
GRAPHICAL ABSTRACT



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

INTRODUZIONE

degli eventi cardiovascolari maggiori, confermando l'abbas-

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

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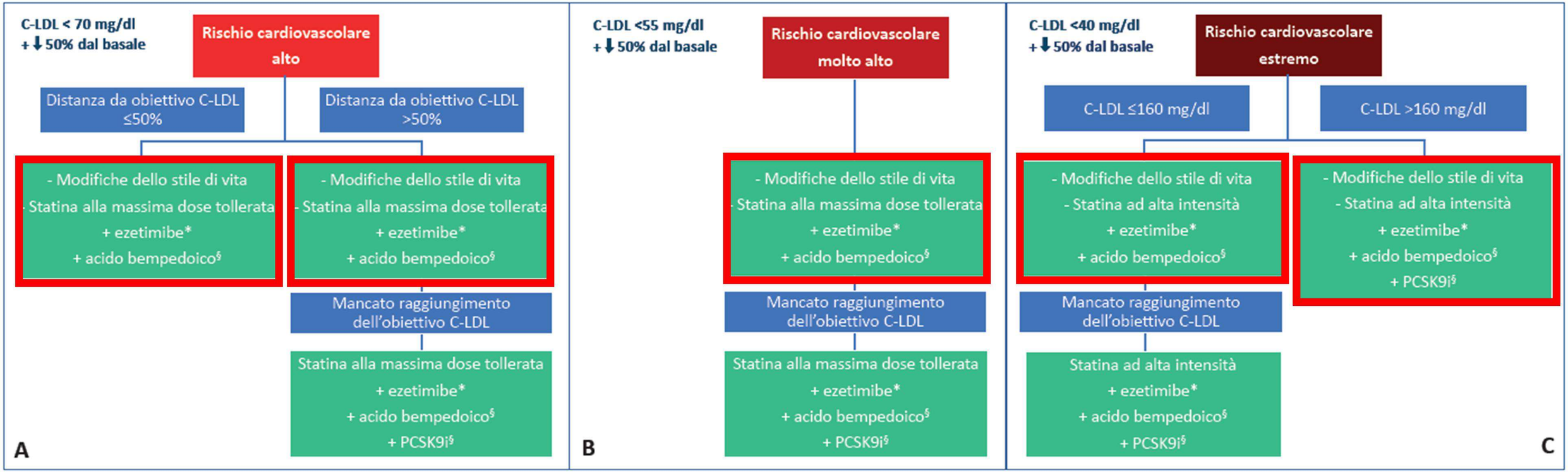
9	I pazienti a rischio proibitivo non a target con statine, ezetimibe ed PCSK9-I potrebbero essere candidati ad una terapia di combinazione con statina, ezetimibe, PCSK9-I ed acido bempedoico	4.9

STEP-RCV: Treatment algorithms for patients at high (A), very high (B), and extreme (C) cardiovascular risk

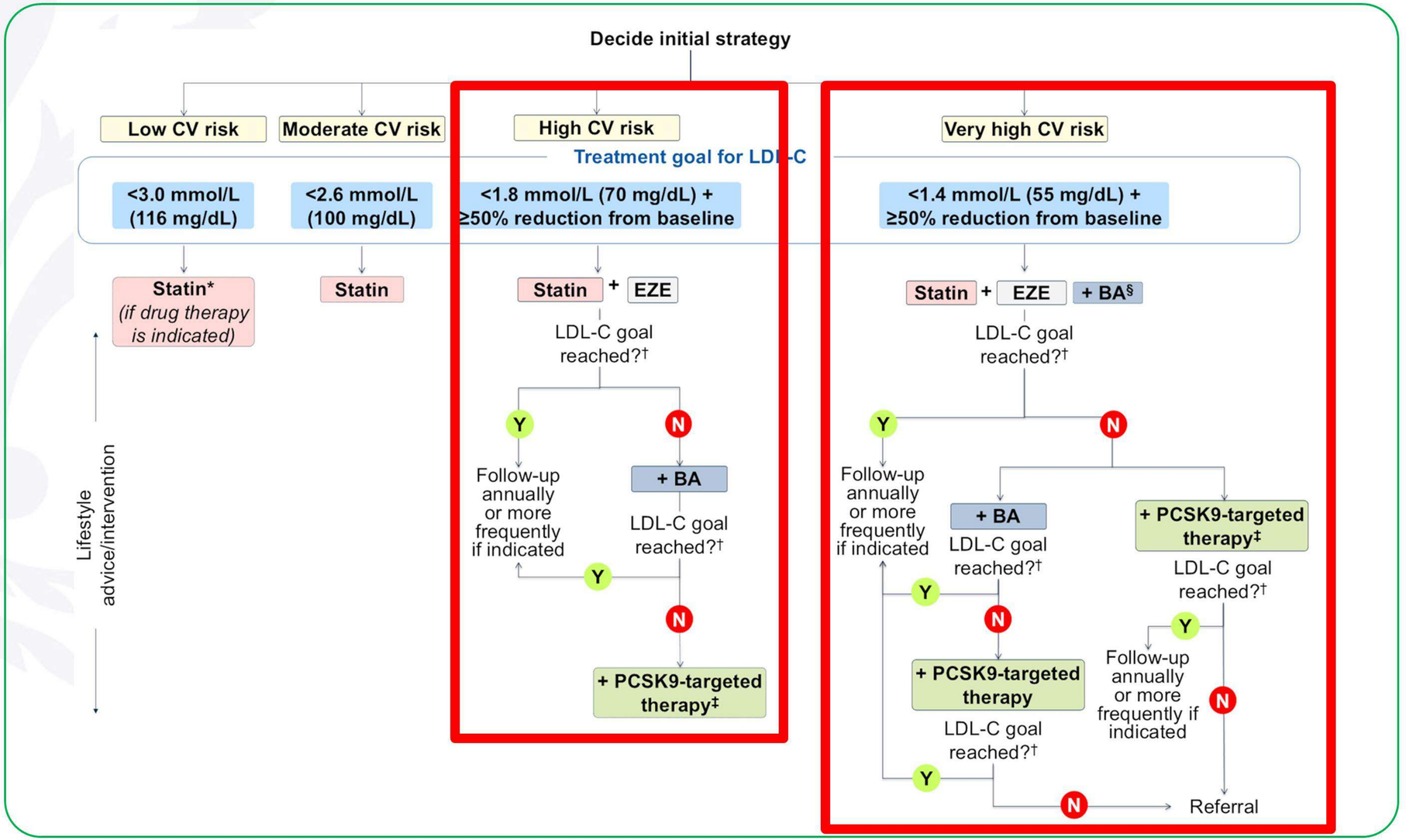


*Preferire le formulazioni con combinazioni a dose fissa di ezetimibe con statina o acido bempedoico.
§La prescrizione deve rispettare le indicazioni di rimborsabilità dell'ente regolatorio nazionale, l'Agenzia Italiana del Farmaco.

Colivicchi F.et al, G Ital Cardiol 2024;25(5):1-9

ESC Working Group on Cardiovascular Pharmacotherapy

Integration of combination therapy into the dyslipidemia treatment algorithm



Very high CV risk

«For patients with baseline LDL-C >160 mg/dL, upfront triple combination with a statin, ezetimibe and bempedoic acid may be considered, with the addition of PCSK9-targeted therapy in patients who do not reach their LDL-C goal.»

High CV risk

«The use of a moderate- to high-intensity statin in combination with ezetimibe is recommended as the first line of therapy. The subsequent addition of bempedoic acid may be considered for those who do not reach the LDL-C levels <70 mg/dL.»

Triple combination

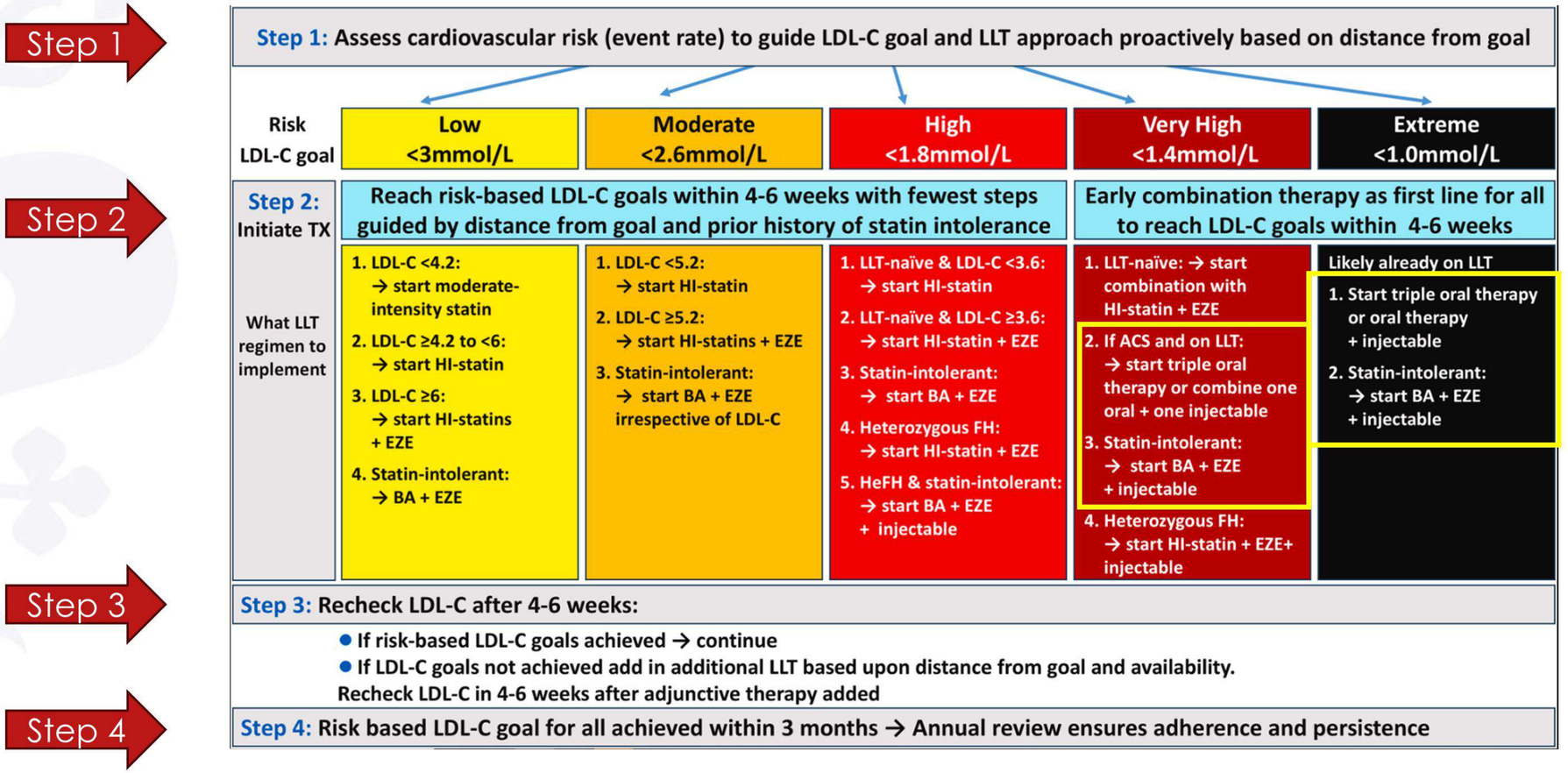
«A triple combination of maximally tolerated statin, ezetimibe and bempedoic acid may be considered as a first-line strategy in patients with very high CV risk, and it is recommended in patients with partial statin intolerance with high and very high CV risk.

*maximally tolerated statin. †monitor LDL-C at 8 ± 4 weeks (first assessment at 4–6 weeks if recent ACS). **‡PCSK9-targeted therapy may be considered depending on local restrictions**. **§triple-combination therapy may be considered in special situations**.

ACS, acute coronary syndrome; BA, bempedoic acid; CV, cardiovascular; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Parhofer KG e al. *Eur Heart J Cardiovasc Pharmacother* 2025, https://doi.org/10.1093/ehjcvp/pvaf007

Approach for lipid-lowering treatment to achieve risk-based LDL-C goals.



In patients with very high and extreme risk start with a triple oral therapy or oral therapy plus injectable

Ray et al Atherosclerosis 413 (2026) 120636

Immediate Use of Oral Triple-Combination Therapy in Patients with ACS Provided Significant and Sustained Reduction in LDL-C

To examine if LDL-C would be rapidly and safely reduced in patients with ACS, oral triple-combination therapy with rosuvastatin 40 mg, ezetimibe 10 mg and bempedoic acid 180 mg was evaluated in 122 Indian patients with ACS (after PCI) over 6 weeks

Oral triple-combination therapy showed a 57.7%, 61.7%, 61.9% and 60.6% reduction in LDL-C from baseline observed at 1, 2, 4 and 6 weeks, respectively (p<0.001). The proportion of patients achieving LDL-C ≤55 mg/dL at 4 weeks after treatment initiation was >75%

LDL-C lowering with oral triple-combination therapy was comparable to the reported efficacy of high-intensity statins in combination with PCSK9i,[1,2] and it was well tolerated generally

Reduction in LDL-C concentration and LDL-C goal attainment following oral triple-combination therapy[3]

Parameter (n=122)	Baseline	1 week	2 weeks	4 weeks	6 weeks
LDL-C (mg/dL), mean ± SD	115.6 ± 35.5	48.9 ± 18.2*	44.3 ± 17.1*	44.1 ± 16.6*	45.6 ± 16.5*
Percentage (%) reduction in LDL-C	-	57.7	61.7	61.9	60.6
Proportion (%) of patients with LDL-C <55 mg/dL† (ESC goal)[4]	2.4	72.8	79.8	78.5	73.3
Proportion (%) of patients with LDL-C <70 mg/dL (ACC goal)	8.2	90.3	92.2	92.6	86.6
Proportion (%) of patients with ApoB ≤65 mg/dL	13.1	-	-	73.9‡	-

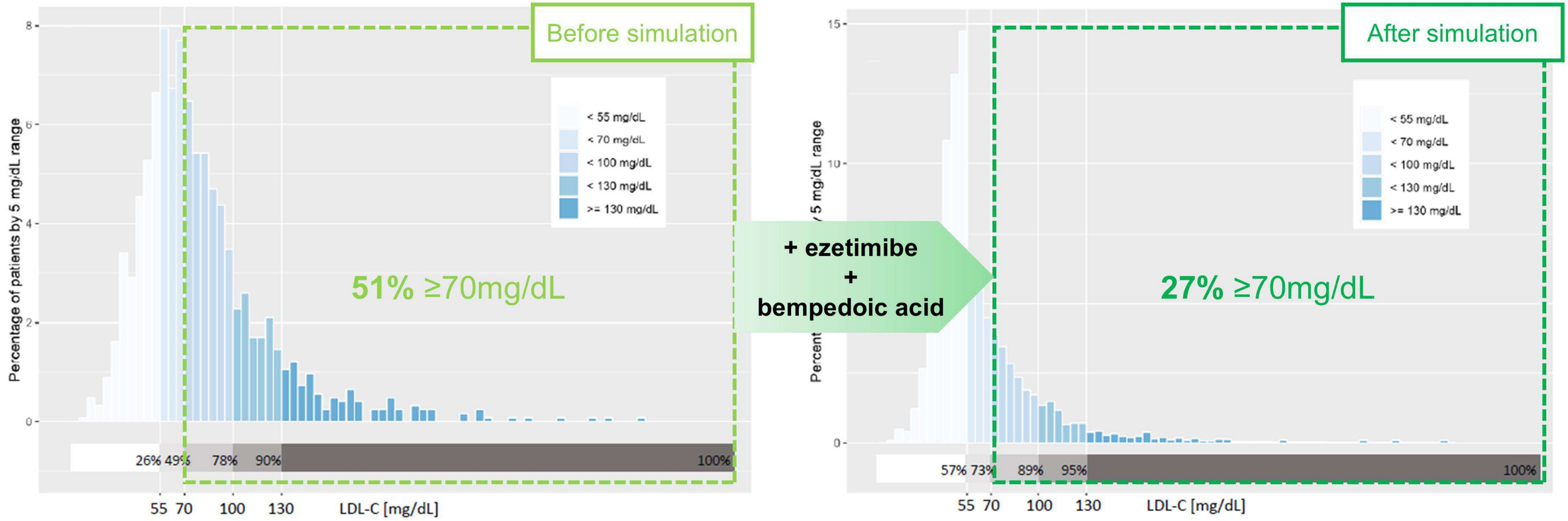
*p<0.001 compared to baseline. †ACC goal as per 2022 expert consensus for very high-risk patients.[5]
‡Apo-B measurement at 4 weeks was repeated in 87 patients only

ACC, American College of Cardiology; **ACS**, acute coronary syndrome; **ApoB**, apolipoprotein B; **ESC**, European Society of Cardiology; **HDL-C**, high-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **PCI**, percutaneous coronary intervention; **PCSK9i**, proprotein convertase subtilisin/kexin type-9 inhibitor

1. Koskinas KC, et al. J Am Coll Cardiol. 2019;74(20):2452–62; **2.** Leucker TM, et al. Circulation. 2020;142(4):419-1; **3.** Mahajan K, et al. J Clin Lipidol. 2024. Vol. 18, Issue 5. (E867-E872) **4.** Mach F, et al. Eur Heart J. 2020;41(1):111–88; **5.** Jones JE, et al. J Clin Med. 2023;12(23):7432

LDL-cholesterol goal attainment with ezetimibe and bempedoic acid in patients at high and very-high cardiovascular risk: A simulation study in the Italian cohort of the SANTORINI study

Simulation Results **Very high-risk patients** (N=1234)



1) **LDL-C goal attainment** can be **substantially increased** with **triple LLT therapy** (statin, ezetimibe, bempedoic acid).

2) With these **oral therapies**, the number of **patients requiring PCSK9i therapy** to achieve the LDL-C goals **would have been halved.**

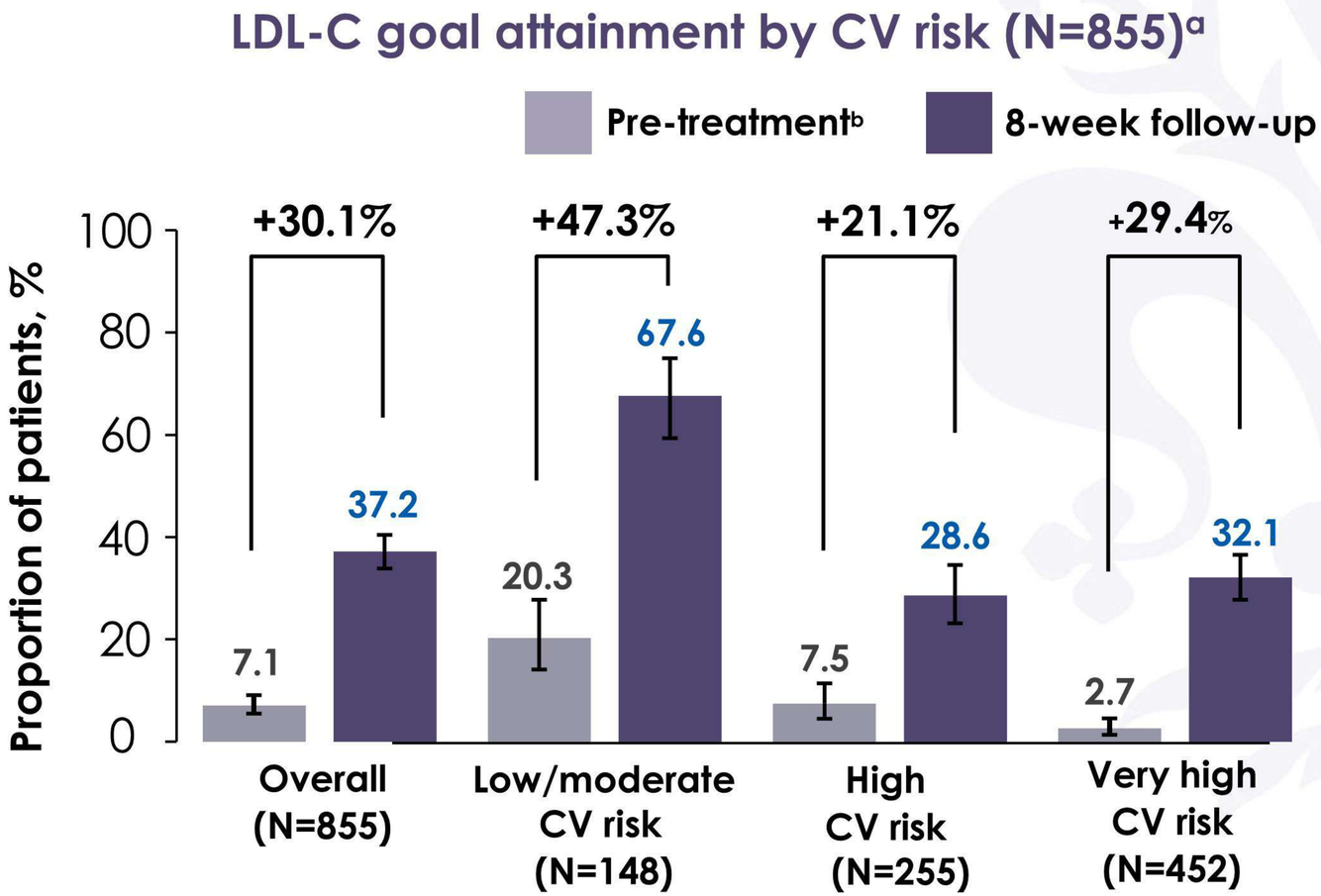
CV: cardiovascular; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; PCSK9: Proprotein Convertase Subtilisin/Kexin type 9

Arca M et al. Eur Atherosclerosis Journal 2024;3:57-66

MILOS Study
LDL-C reduction and goal attainment in 855 Italian Cohort patients

- Over an 8-week follow-up period following the initiation of BA or BA+EZE treatment, with or without background LMTs (n=627**), LDL-C levels were reduced from 2.8 mmol/L (108.5 mg/dL) prior to BA/BA+EZE treatment initiation to 2.0 mmol/L (78.4 mg/dL) at the interim 8-week timepoint**

- Overall, the proportion of patients achieving LDL-C goals increased by over 5-fold, from 7.2% (45/627) prior to BA/BA+EZE treatment initiation to 37.6% (236/627) at 8W



Error bars are 95% CIs calculated using the Clopper–Pearson method. [a]Patients with LDL-C data at both timepoints. Targeted LDL-C goal attainment was assessed based on the recommendations outlined in the 2019 ESC/EAS guidelines and CV risk assessed by investigator at baseline. [b]Most-recent LDL-C value in ≤1 year before initiation of BA or BA+EZE FDC

BA, bempedoic acid; **CI**, confidence interval; **CV**, cardiovascular; **EZE**, ezetimibe; **FDC**, fixed-dose combination; **LDL-C**, low-density lipoprotein cholesterol. **NCT04579367**. Available at https://clinicaltrials.gov/study/NCT04579367.

Poster ID SaaG099 : presented at the European Atherosclerosis Society (EAS) Congress, 4–7 May 2025

Conclusions (1)

- Combination therapy are the first choice to reduce LDL-C if the LDL-C goals are not achieved with the maximum tolerated dose of a statin[1]
- The choice should be based on the magnitude of additional LDL-C lowering needed, patient preference, treatment availability, and cost[1]
- Bempedoic acid is an add-on therapy to reach LDL-C goal and reduces cardiovascular risk, as demostrated in CLEAR Outcomes study[2]

1. Mach F. et al, European Heart Journal (2025) 00, 1–20
2. Nissen S E et al N Engl J Med 2023; DOI: 10.1056/NEJMoa2215024
3. Parhofer KG e al. *Eur Heart J Cardiovasc Pharmacother* 2025, https://doi.org/10.1093/ehjcvp/pvaf007

Conclusions (2)

- A triple combination of maximally tolerated statin, ezetimibe, and bempedoic acid may be considered as a first-line strategy in patients with very high CV risk, and it is recommended in patients with high and very high CV risk, for the reduction of CV risk, because[3]
  - Increased LDL-C goal attainment in patients at high and very high CV risk
  - Potential substantially decreased need for PCSK9 inhibitor
  - Well tolerated safety profile

- In patients with very high and extreme risk start with a triple oral therapy or oral therapy plus injectable[4]

3. Parhofer KG e al. *Eur Heart J Cardiovasc Pharmacother* 2025, https://doi.org/10.1093/ehjcvp/pvaf007
4. Ray et al Atherosclerosis 413 (2026) 120636