11° CONGRESSO NAZIONALE

CAMPUS Cuore

Quello che le Linee Guida Non Dicono

Napoli
5-6 aprile 2024

Triplice terapia con acido bempedoico e statina-ezetimibe: a chi e quando?

Giovanni Cimmino MD, PhD
Professore Associato di Cardiologia – Università Degli Studi della Campania Luigi Vanvitelli
Responsabile UOSD Cardiologia – AOU Vanvitelli

"ASCVDs are LDL-C related!"

Regression of Atherosclerotic Lesions by High Density Lipoprotein Plasma Fraction in the Cholesterol-fed Rabbit

Juan Jose Badimon, Lina Badimon, and Valentin Fuster
Division of Cardiology, The Mount Sinai Medical School of Medicine, New York 10029

J. Clin. Invest.

0021-9738/90/04/1234/08 $2.00
Volume 85, April 1990, 1234–1241

NIH National Library of Medicine
National Center for Biotechnology Information

Cimmino g, Badimon J — Search

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18 results Page 1 of 2

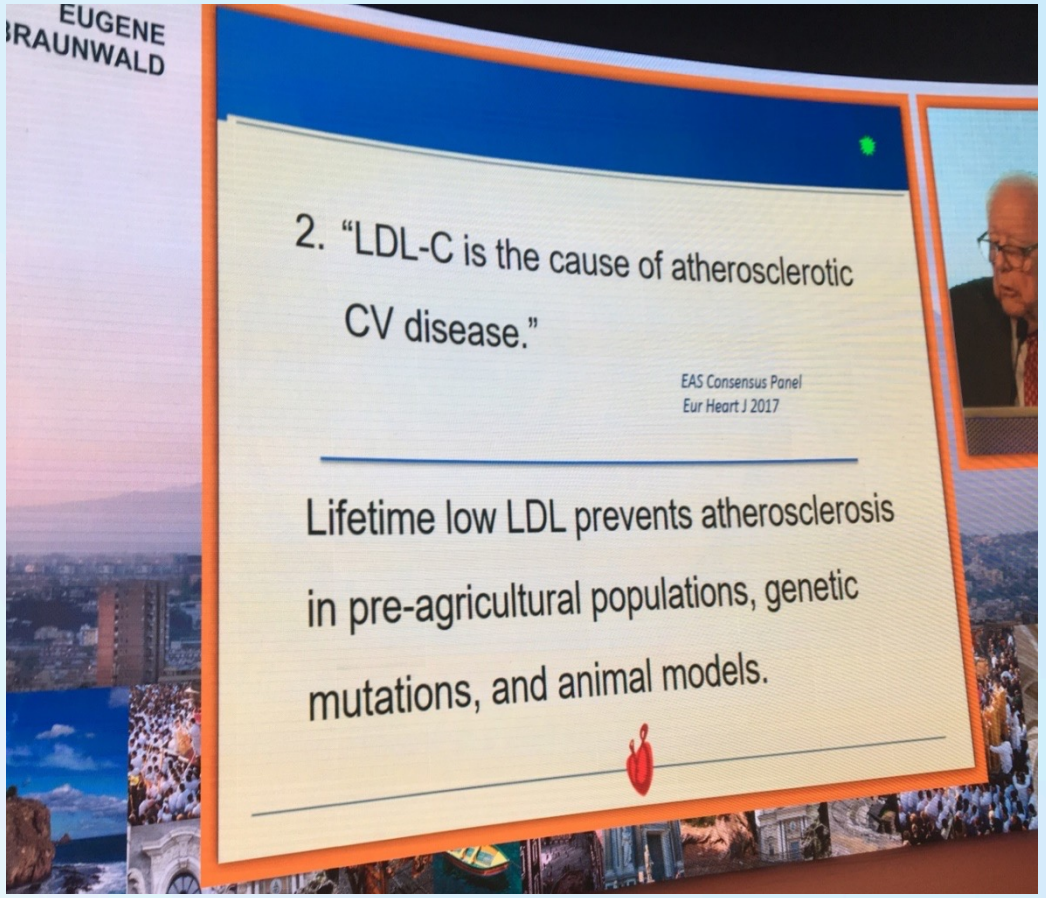
1 Cite Share
Recombinant apolipoprotein A-I Milano rapidly reverses aortic valve stenosis and decreases leaflet inflammation in an experimental rabbit model.
Speidl WS, **Cimmino G**, Ibanez B, Elmariah S, Hutter R, Garcia MJ, Fuster V, Goldman ME, **Badimon JJ.**
Eur Heart J. 2010 Aug;31(16):2049-57. doi: 10.1093/eurheartj/ehq064. Epub 2010 Mar 19.
PMID: 20304838

2 Cite Share
Atherothrombosis: role of tissue factor; link between diabetes, obesity and inflammation.
Meerarani P, Moreno PR, **Cimmino G**, **Badimon JJ.**
Indian J Exp Biol. 2007 Jan;45(1):103-10.
PMID: 17249334 Review.

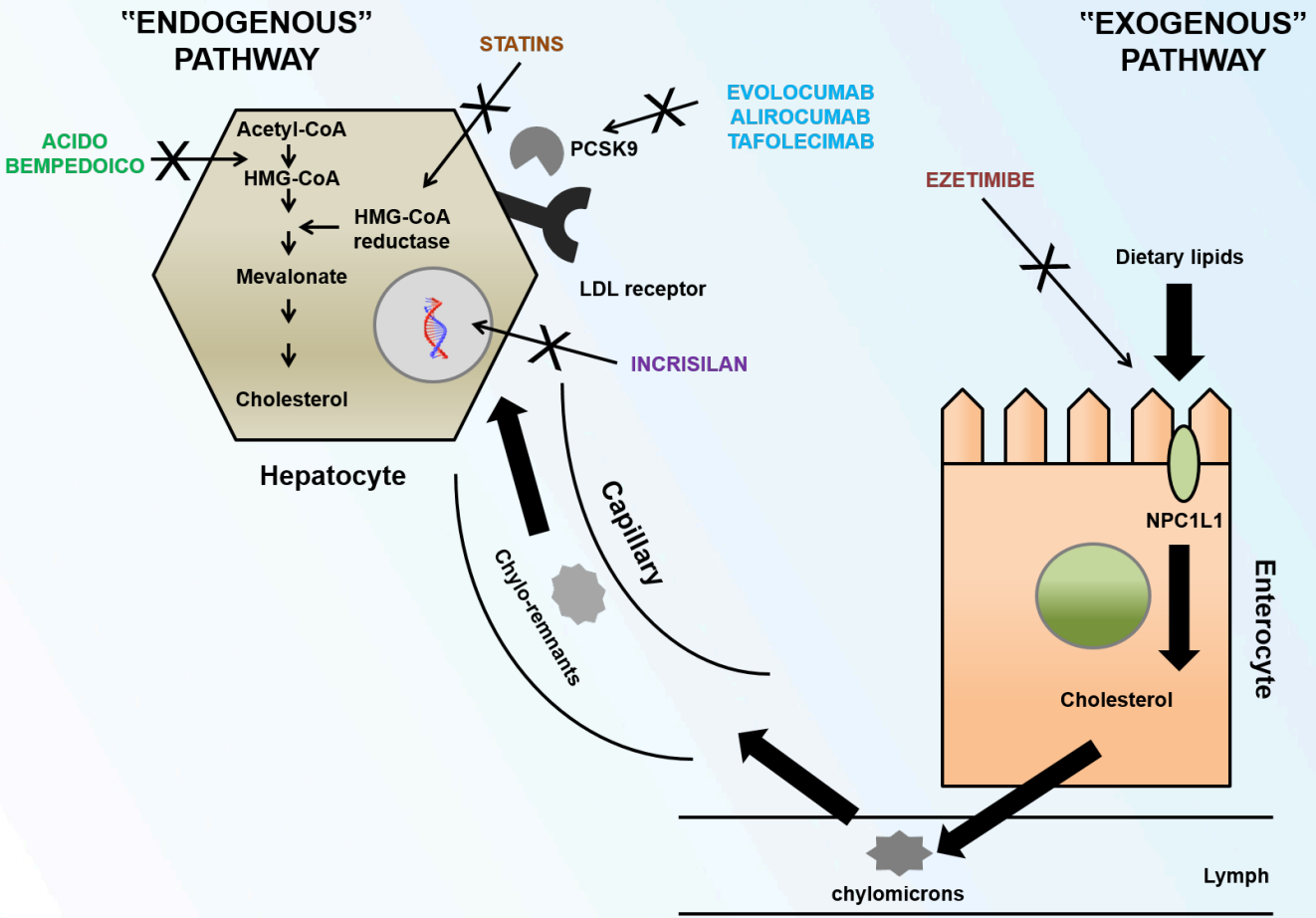
3 Cite Share
Recombinant HDL(Milano) exerts greater anti-inflammatory and plaque stabilizing properties than HDL(wild-type).
Ibanez B, Giannarelli C, **Cimmino G**, Santos-Gallego CG, Alique M, Pinero A, Vilahur G, Fuster V, Badimon L, **Badimon JJ.**
Atherosclerosis. 2012 Jan;220(1):72-7. doi: 10.1016/j.atherosclerosis.2011.10.006. Epub 2011 Oct 12.
PMID: 22030095

L'ipercolesterolemia è un fattore "causale" di malattia CV

Criterion (modified from reference[5])	Evidence grade	Summary of the evidence (references)
1. Plausibility	1	LDL and other apolipoprotein (apo) B-containing lipoproteins (very low-density lipoprotein their remnants, intermediate-density lipoprotein and lipoprotein(a)) are directly implicated in the initiation and progression of ASCVD; experimentally induced elevations in plasma LDL and other apoB-containing lipoproteins lead to atherosclerosis in all mammalian species studied.[2,5–12]
2. Strength	1	Monogenic and polygenic-mediated lifelong elevations in LDL lead to markedly higher lifetime risk.[13–20,27–31,40,43]
3. Biological gradient	1	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials uniformly demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[13–22,27–36,38–40,42–47]
4. Temporal sequence	1	Monogenic lipid disorders and Mendelian randomization studies demonstrate that exposure to elevated LDL precedes the onset of ASCVD[13–20,27–31,40,43]
5. Specificity	1	Mendelian randomization studies and randomized intervention trials both provide unconfounded randomized evidence that LDL is associated with ASCVD independent of other risk factors[28,31–33,40,43]
6. Consistency	1	Over 200 studies involving more than 2 million participants with over 20 million person-years of follow-up and more than 150 000 cardiovascular events consistently demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[13–22,27–36,38–40,42–47]
7. Coherence	1	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all show a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[15–18,21,22,28,30–32,35,36,43,44,47]
8. Reduction in risk with intervention	1	More than 30 randomized trials involving over 200 000 participants and 30 000 ASCVD events evaluating therapies specifically designed to lower LDL (including statins, ezetimibe, and PCSK9 inhibitors) consistently demonstrate that reducing LDL cholesterol (LDL-C) reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C[32–34,38,39,42,45–47]



Ference BA, et al. Eur Heart J. 2017



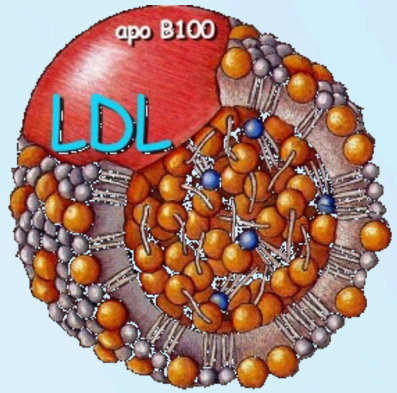
Journal of Clinical & Experimental Cardiology
Cimmino et al., J Clin Exp Cardiolog 2016, 7:10
DOI: 10.4172/2155-9880.1000468
Review Article
OMICS International

Evolving Concepts in LDL-Lowering Strategies: Are We There?

Giovanni Cimmino[1], Francesco S Loffredo[2], Giulia Arena[1] and Paolo Golino[1*]

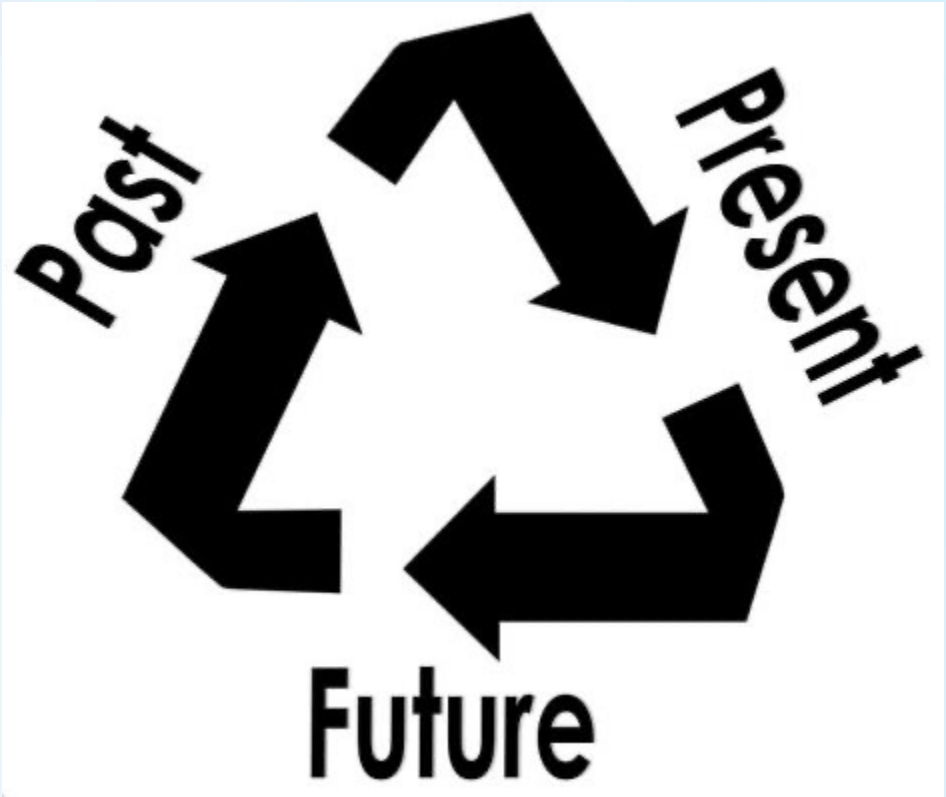
[1]*Department of Cardio-Thoracic and Respiratory Sciences, Section of Cardiology, Second University of Naples, Naples, Italy*

[2]*Molecular Cardiology, International Centre for Genetic Engineering and Biotechnology, Trieste, Cardiovascular Department, Ospedale Riuniti and University of Trieste, Trieste, Italy*



SOLIDO

STATINE



VARIEGATO

STATINE

EZETIMIBE

PCSK9i

Lopitamide

Mipomersen

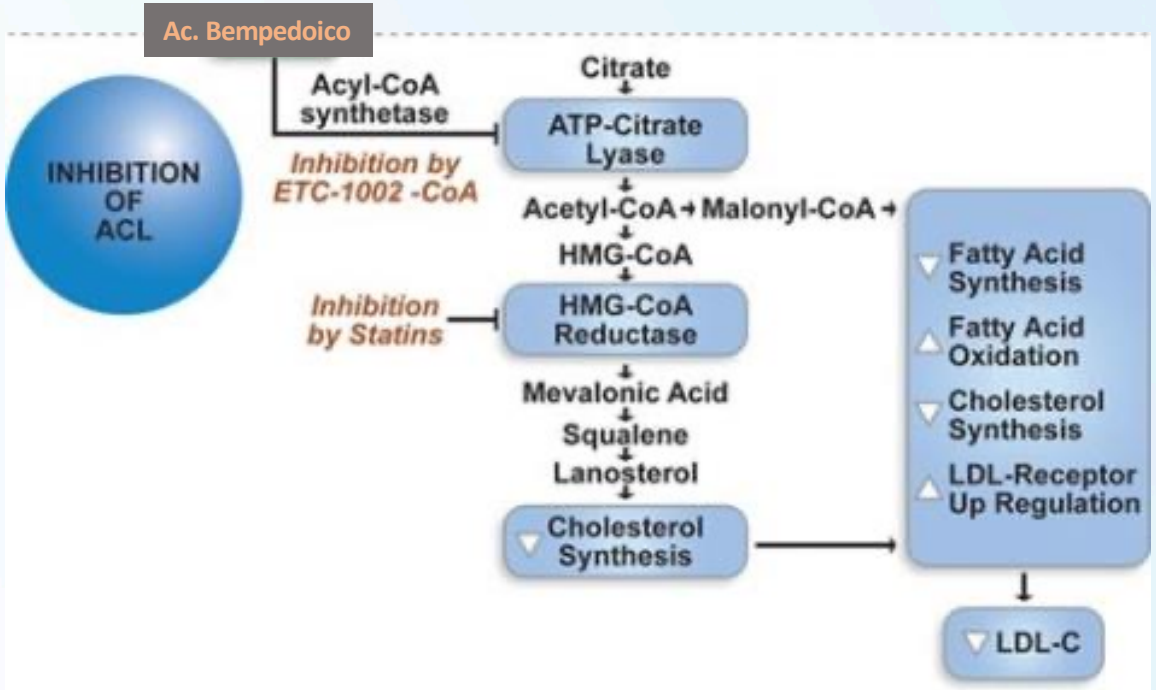
Ac. Bempedoico

INTERESSANTE

New PCSK9i

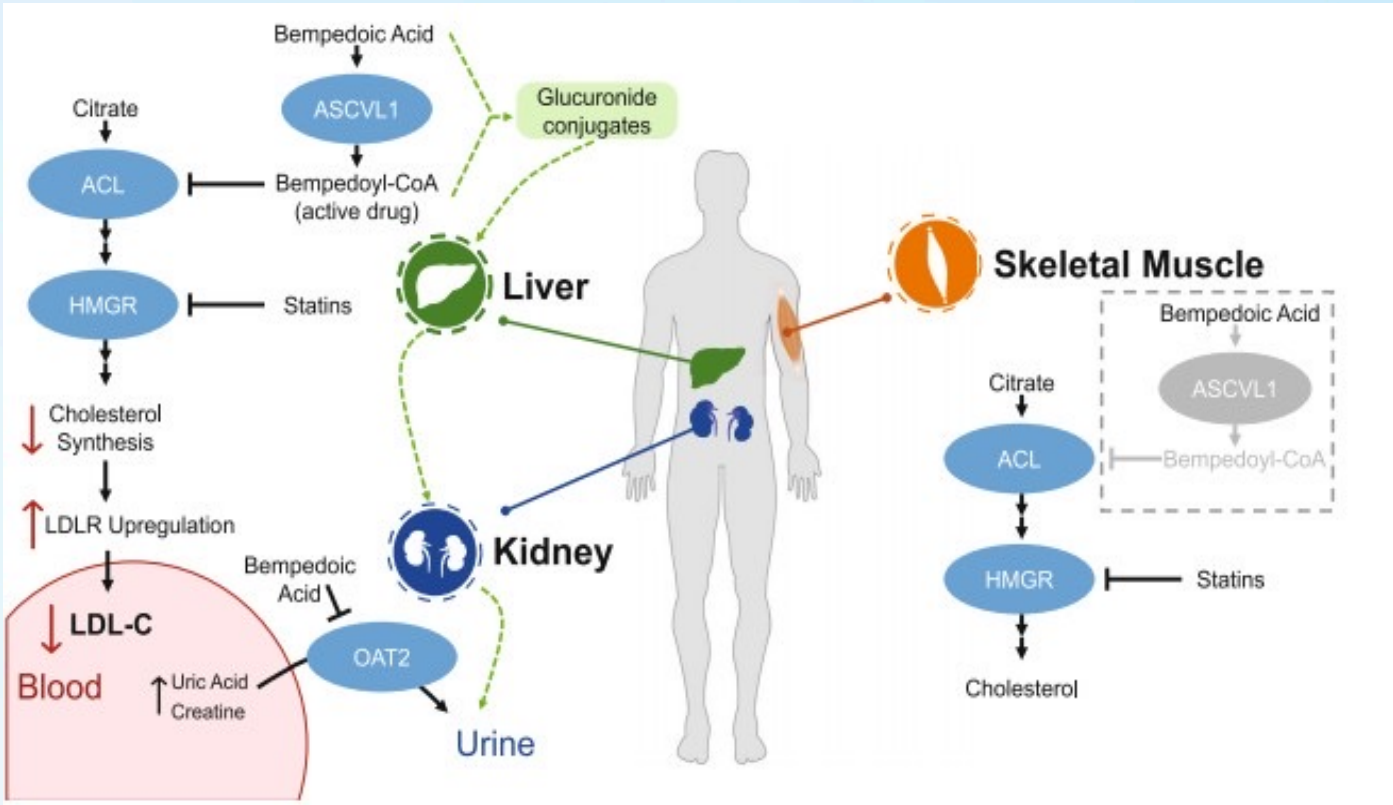
ANGPTL3i

Acido Bempedoico: Inibizione *upstream* nella cascata biologica della sintesi di colesterolo



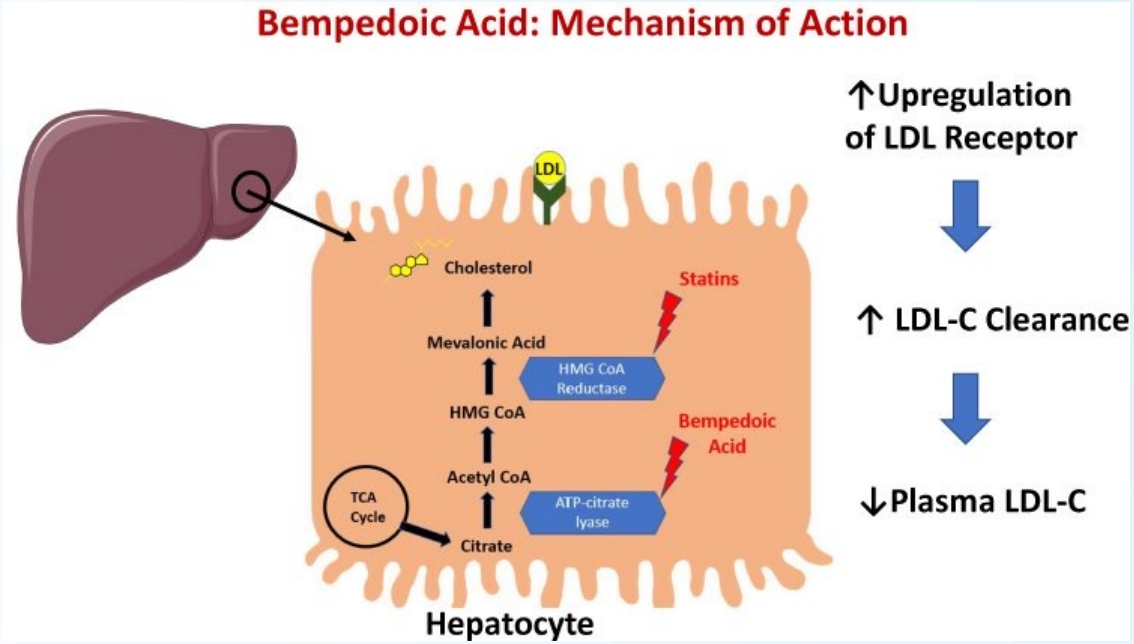
Role of Bempedoic Acid in Clinical Practice

Christie M. Ballantyne[1] · Harold Bays[2] · Alberico L. Catapano[3] · Anne Goldberg[4] · Kausik K. Ray[5] · Joseph J. Saseen[6]

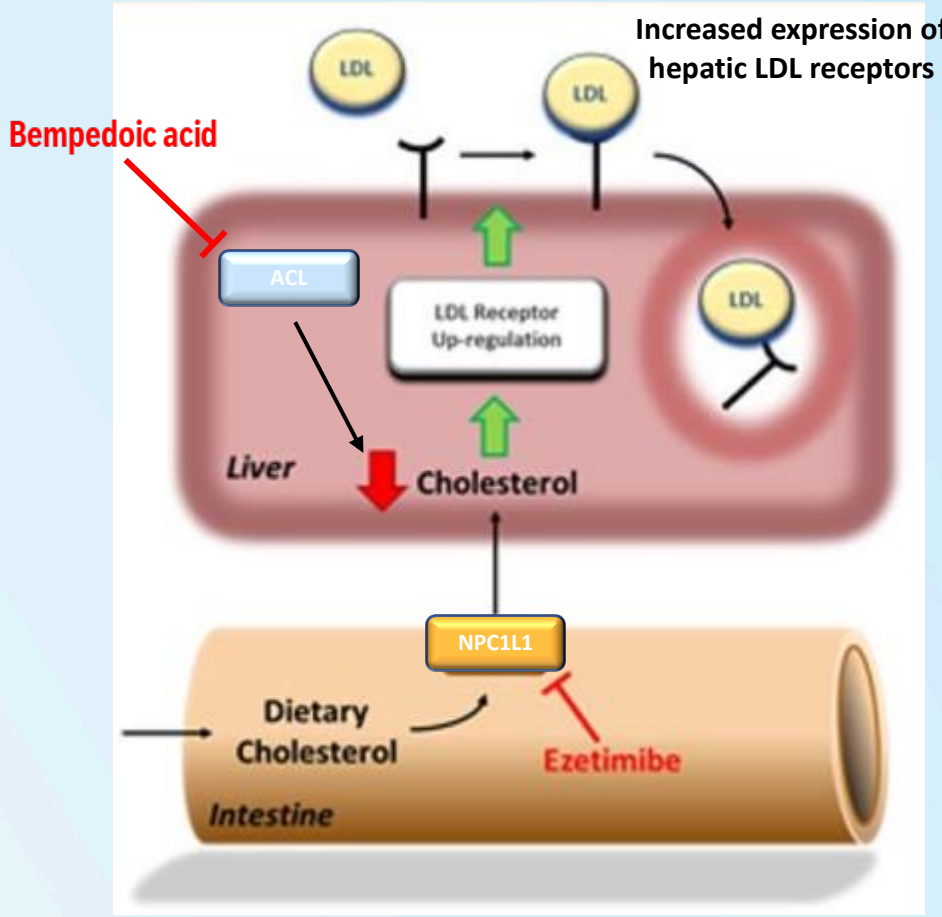


Pinkosky S et al. *Nat Commun*. 2016;7:13457. doi: 10.1038/ncomms1345

Acido Bempedoico e Statina:
"Blocco sequenziale ed azione sinergica"

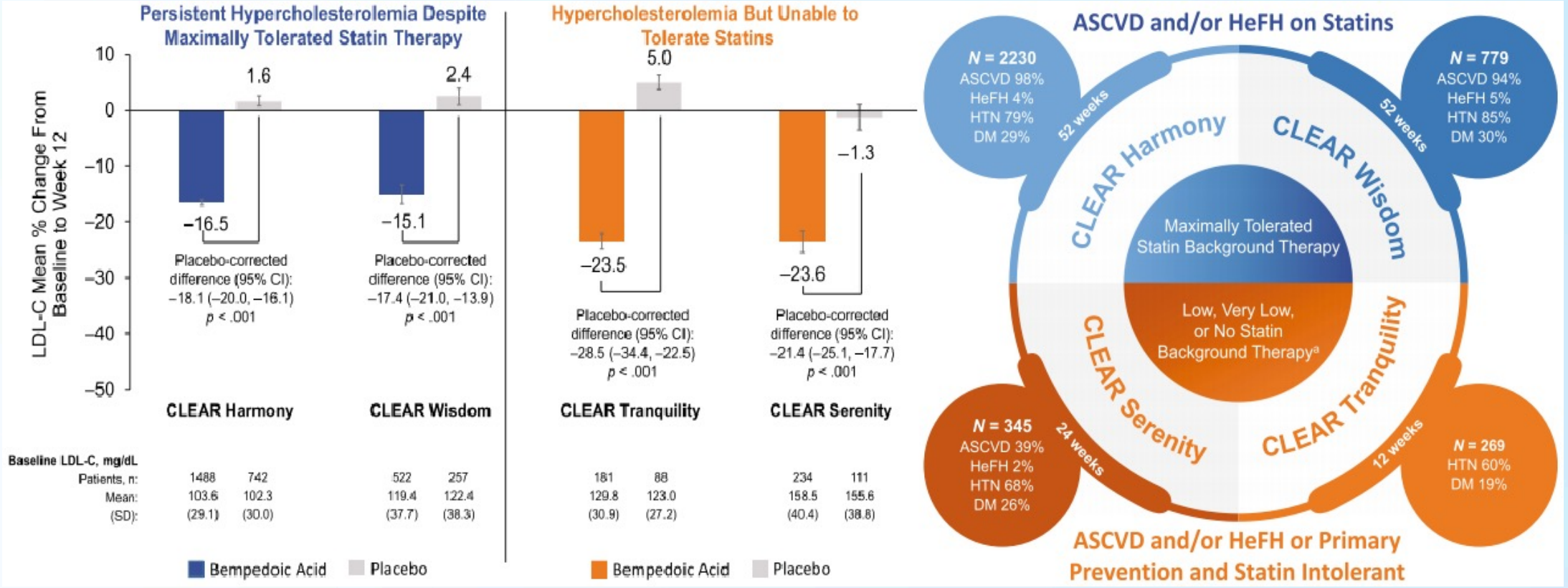


Acido Bempedoico ed Ezetimibe:
Better together



Maciej Banach, Peter E. Penson, *Atherosclerosis*, https://doi.org/10.1016/j.atherosclerosis.2021.01.009

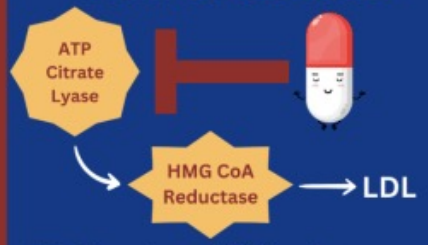
Acido Bempedoico: Solido programma di sviluppo



CLEAR Outcomes Trial

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients
Nissen et al. March 2023. NEJM.

BEMPEDOIC ACID



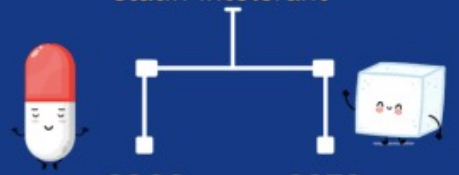
ATP Citrate Lyase inhibitor that targets cholesterol synthesis upstream of statins

QUESTION

Does bempedoic acid decrease adverse CV events in patients who require 1* or 2* prevention of CV disease but are statin-intolerant?

METHODS

Randomized, double-blinded study
Patients were 18-85 years old, with or at high risk for CVD who were statin-intolerant*



6992 6978

1:1 ratio of bempedoic acid 180mg or placebo
Median follow-up for 40.6 months
(> 90% white in both arms)

*Statin intolerance defined as inability to tolerate ≥2 statins, one at a low dose

PRIMARY ENDPOINT

Composite MACE†

11.7% 13.3%

HR 0.87, 95% CI 0.79-0.96 (p = 0.004)

†MACE: death from CV cause, nontal MI, nonfatal stroke, coronary revascularization

SECONDARY ENDPOINTS

Death from CV cause, nonfatal stroke, or nonfatal MI	8.2%	9.5%
Fatal or nonfatal MI	3.7%	4.8%
Coronary revascularization	6.2%	7.6%
	All significant	
Fatal or nonfatal stroke, death from CV cause, death from any cause	Non-significant	

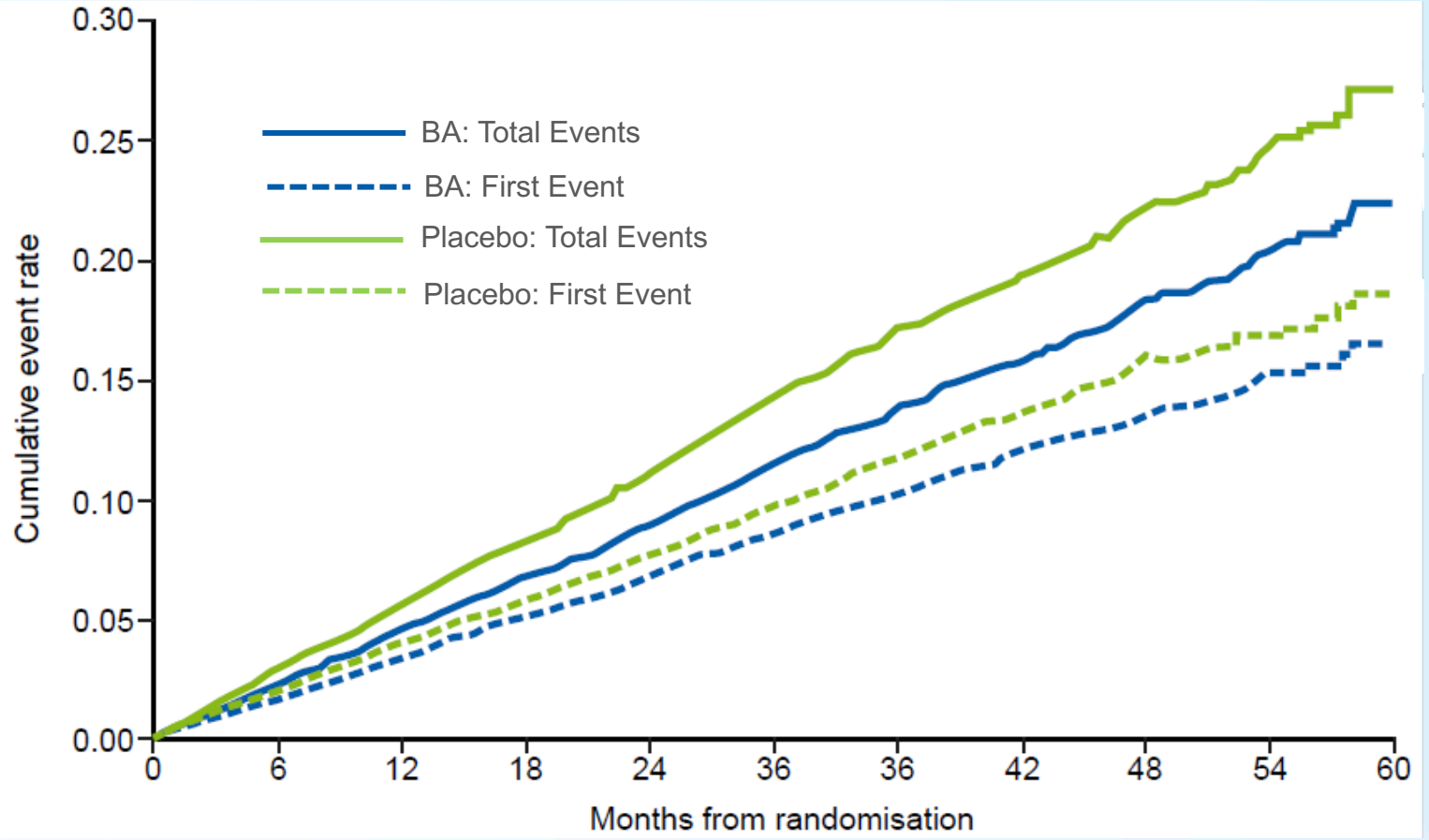
Adverse events: ↑ gout & cholelithiasis in bempedoic acid group

CONCLUSION

Use of bempedoic acid compared to placebo in patients with or at high risk for CVD resulted in a 13% relative risk reduction in composite MACE at 40 months.

Created by: @CaliRClark. Reviewed by @EuniceDuganMD, @DrAlaaDiab, @TySweeney6, @DeveshRaiMD

Effect of BA on Time to first and total incidence of 4-component MACE

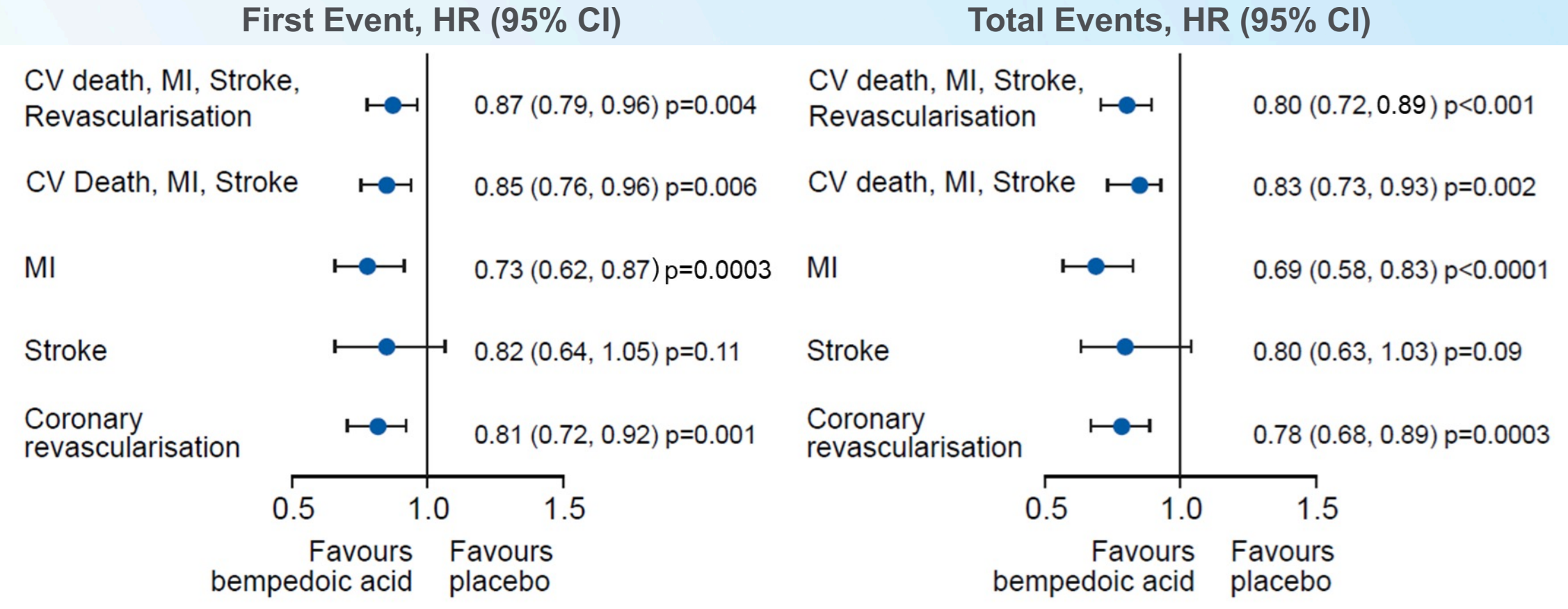


Total Events:
HR 0.80 (95% CI 0.72–0.89)

First Event:
HR 0.87 (95% CI 0.79–0.96)

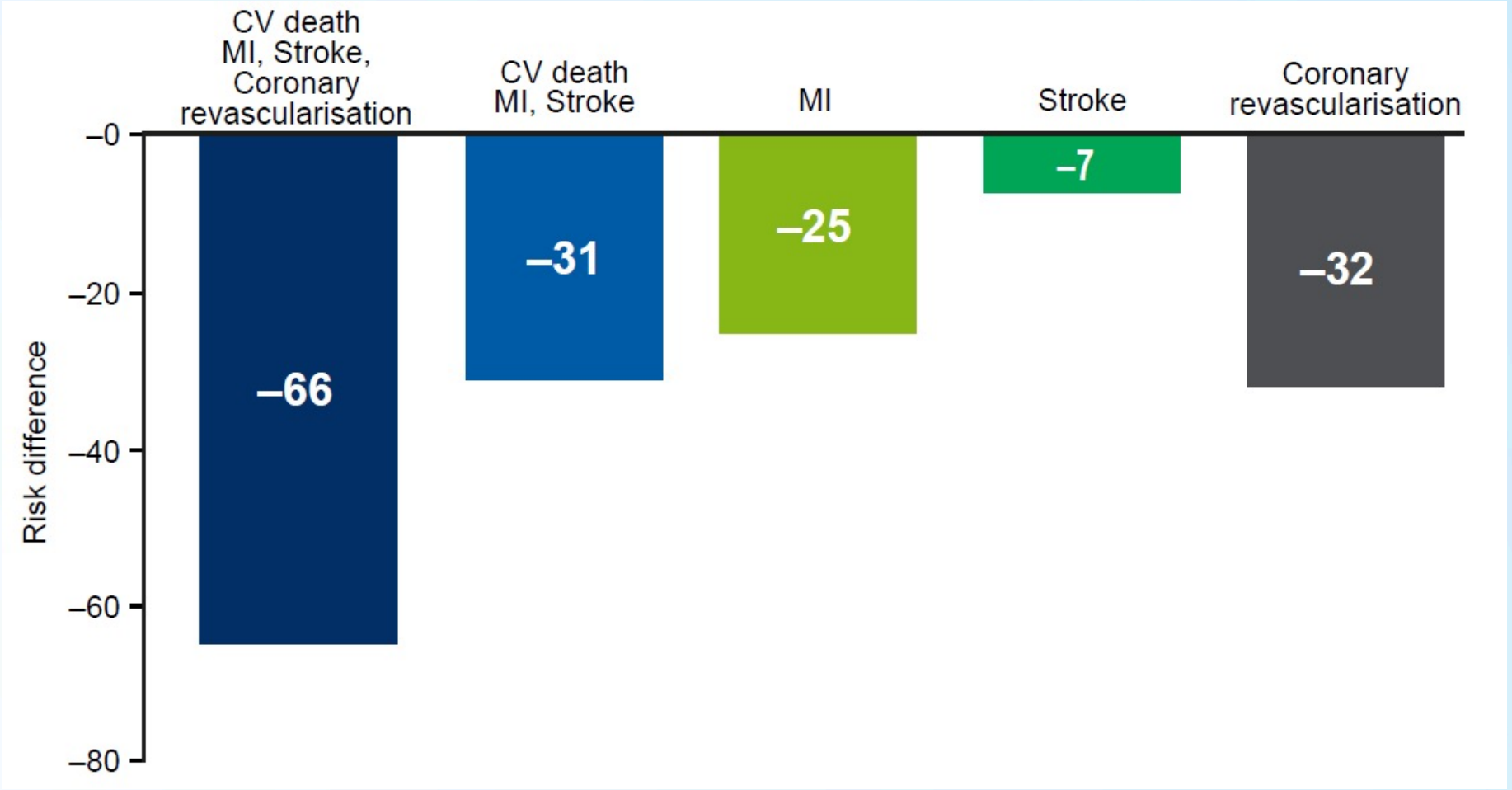
- All RRR (%) and HRs in publicly available sources have been rounded. HRs and 95% CIs are estimated based on Anderson-Gill model, using Cox regression with robust sandwich estimates of standard errors. **4-component MACE,** CV death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularisation; **BA**, bempedoic acid; **CI**, confidence interval; **CV**, cardiovascular; **HR**, hazard ratio; **MACE**, major adverse cardiovascular event; **RRR,** relative risk reduction

Effect of BA on First and Total CV Events



- All RRR (%) and HRs in publicly available sources have been rounded. HR and 95% CIs are estimated based on Anderson-Gill model, using Cox regression with robust sandwich estimates of standard errors. **BA,** bempedoic acid; **CI**, confidence interval; **CV**, cardiovascular; **HR**, hazard ratio; **MI**, myocardial infarction; **RRR,** relative risk reduction

Risk Differences per 1000 Patients Treated with BA



- **BA,** bempedoic acid; **CV,** cardiovascular; **MI,** myocardial infarction

- The CLEAR Outcomes trial included 45.6% of patients with diabetes, 41.5% with pre-diabetes, and 12.9% with normoglycaemia. In contrast, PCSK9-inhibitor and EZE outcome trials had a lower proportion of patients with diabetes (27–29%)[1-3]
- The LDL-C lowering after 6 months was similar in patients with diabetes, pre-diabetes, and normoglycaemia, with 24%, 25%, and 26% reduction, respectively[4]
- Patients with diabetes derived similar reductions in 4-component MACE with BA compared to placebo (HR 0.83, 95% CI 0.72, 0.95) as patients with pre-diabetes (HR 0.94, 95% CI 0.81, 1.09) and patients with normoglycaemia (HR 0.84, 95% CI 0.63, 1.10) (p-for-interaction non-significant)[4]
- Since the baseline risk is higher in patients with diabetes, the absolute risk reduction with BA was higher in patients with diabetes (ARR: 2.4%) compared to patients with pre-diabetes (ARR: 0.6%) and normoglycaemia (ARR: 1.9%)[4]
- There was no increase in the incidence of new-onset diabetes in patients treated with BA compared to placebo after a median follow-up of 40.6 months. The side effects of BA was similar in patients with diabetes, pre-diabetes and normoglycaemia[4]

- All RRR % and HRs in publicly available sources have been rounded. **4-component MACE,** CV death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularisation; **3-component MACE**, CV death, nonfatal myocardial infarction, or nonfatal stroke. **ARR,** absolute risk reduction; **BA,** bempedoic acid; **CI,** confidence interval; **CV,** cardiovascular; **EZE**, ezetimibe; **HR,** hazard ratio; **LDL-C,** low-density lipoprotein cholesterol; **MACE,** major cardiovascular event outcome; **PCSK9,** proprotein convertase subtilisin/kexin type 9.
- 1. Nissen SE, et al. N Engl J Med. 2023;388(15):1353-1364; 2. Schwartz GG, et al. N Engl J Med 2018; 379:2097-2107; 3. Cannon CP, et al. N Engl J Med 2015; 372:2387-2397; 4. Ray KK. Presented on 26 August as a late-breaker oral presentation at ESC 2023, Amsterdam, Netherlands.

Studio SANTORINI – dati al baseline

Nonostante le Linee Guida ESC/EAS siano il riferimento più frequente per la classificazione del rischio, i livelli di LDL-C restano più elevati degli obiettivi raccomandati.

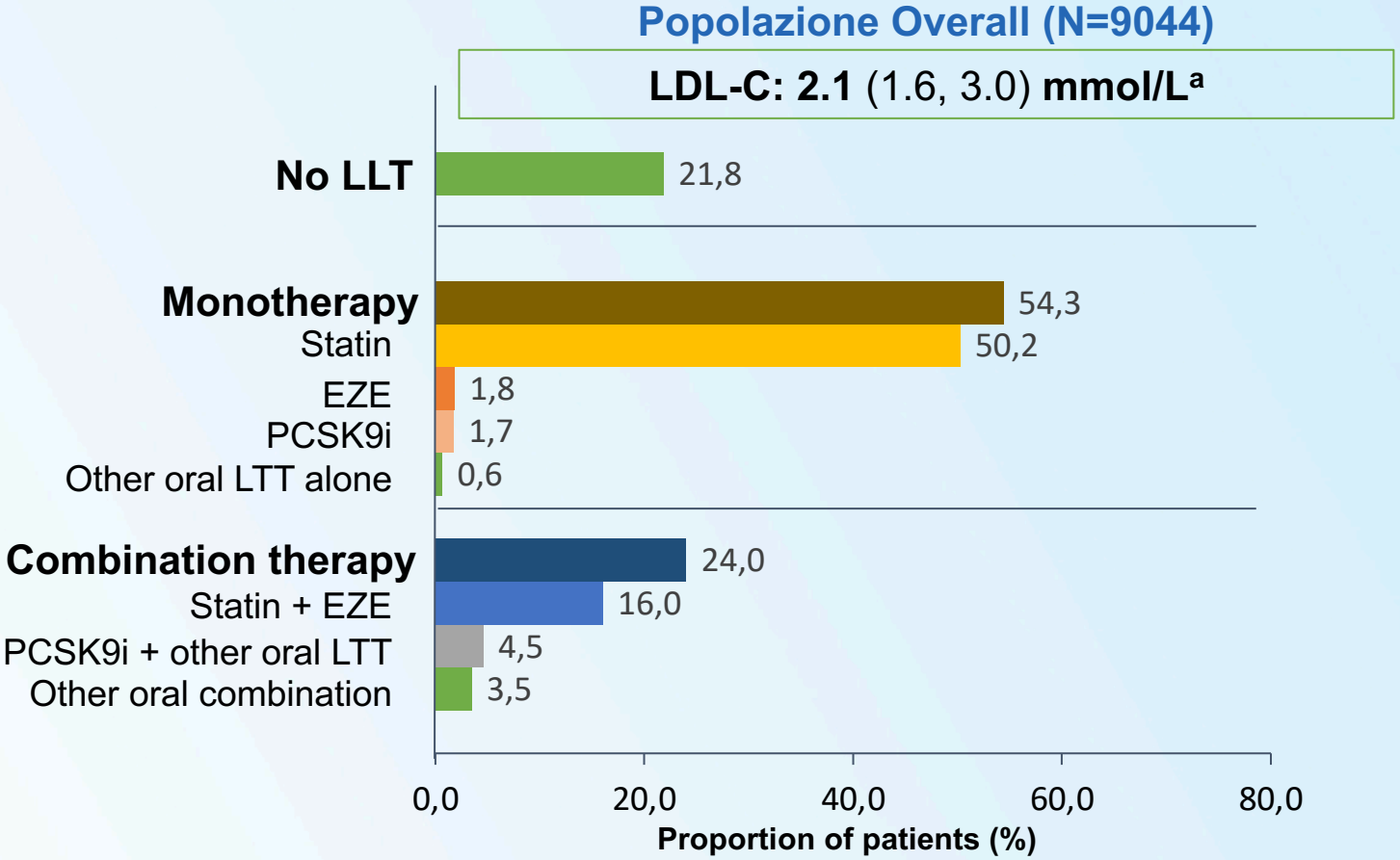
Table 1. Baseline patient characteristics

Characteristic	Overall (N=9044)	No ASCVD (N=2089)	ASCVD (N=6954)
Male, n (%)	6563 (72.6)	1218 (58.3)	5345 (76.9)
Age, years, mean (SD)	65.3 (10.9)	62.5 (12.1)	66.1 (10.4)
LDL-C, mean (SD), mmol/L	2.4 (1.21)	2.8 (1.37)	2.3 (1.13)
LDL-C, mg/dL	**93**	**108**	**89**
LDL-C at goal, n (%)	1821 (20.1)	1438 (20.7)	383 (18.3)
Hypertension, n (%)	6372 (70.5)	1346 (64.4)	5026 (72.3)
Diabetes, n (%)	3038 (33.6)	931 (44.6)	2107 (30.3)

Ray, KK et al., presented at ESC Congress 2022

Studio SANTORINI – dati al baseline

La maggior parte dei pazienti è in terapia con un solo farmaco ipolipemizzante

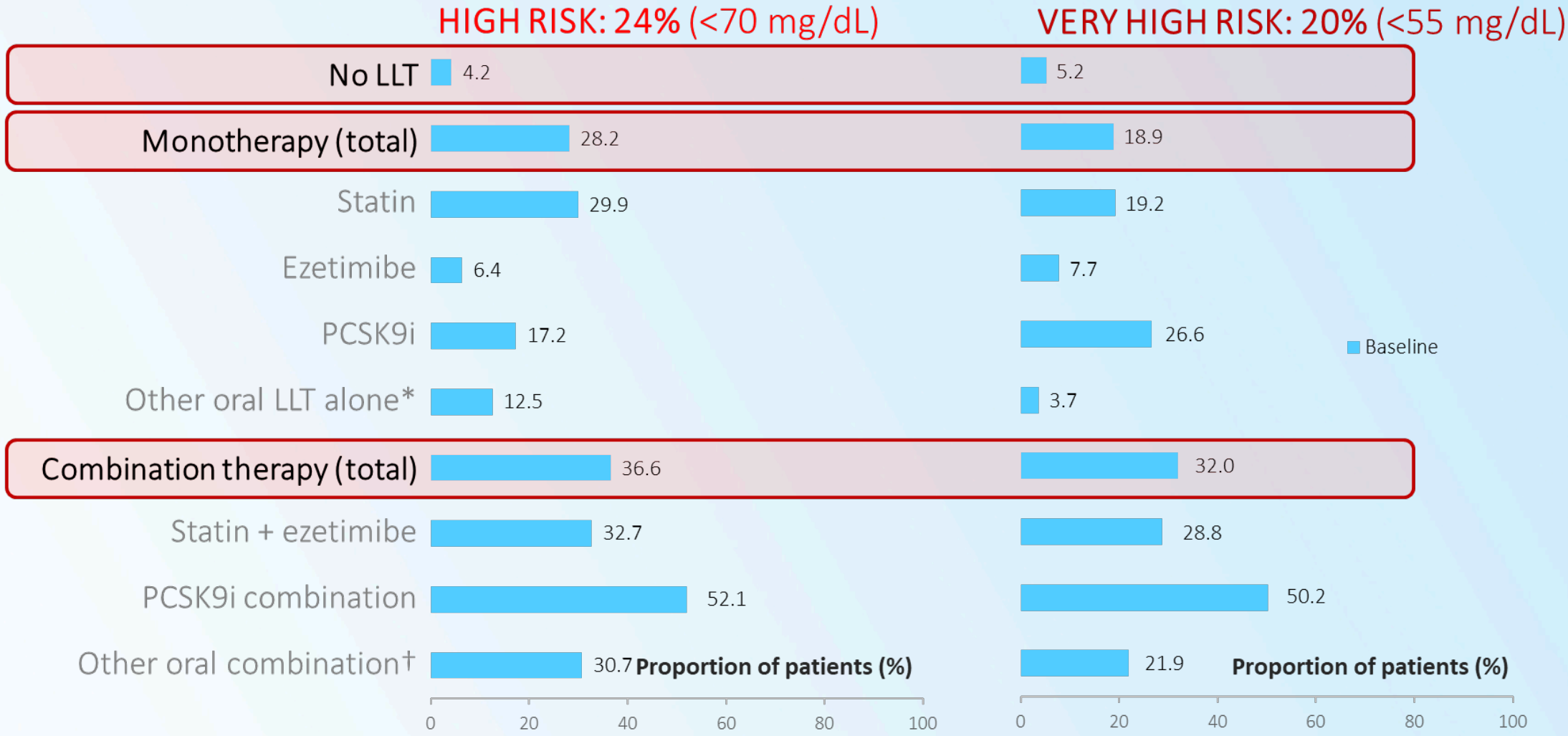


SANTORINI

- [a] Median (IQR). Missing risk, n = 6. Percentages may not add up to 100% as they are rounded and there were unknown/missing data. Statin includes: high-intensity statins (atorvastatin 40–80 mg or rosuvastatin 20–40 mg), moderate-intensity statins (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin XL 80 mg, fluvastatin 40 mg BID, or pitavastatin 2–4 mg), and low-intensity statins (simvastatin 10 mg, pravastatin 1–20 mg, lovastatin 20 mg, Fluvastatin 20–40 mg, or pitavastatin 1 mg).

Ray KK, et al. Lancet Reg. Health Eur. 2023;29:100624. https://doi.org/10.1016/j.lanepe.2023.100624

Studio SANTORINI: Raggiungimento del target di LDL-C al baseline

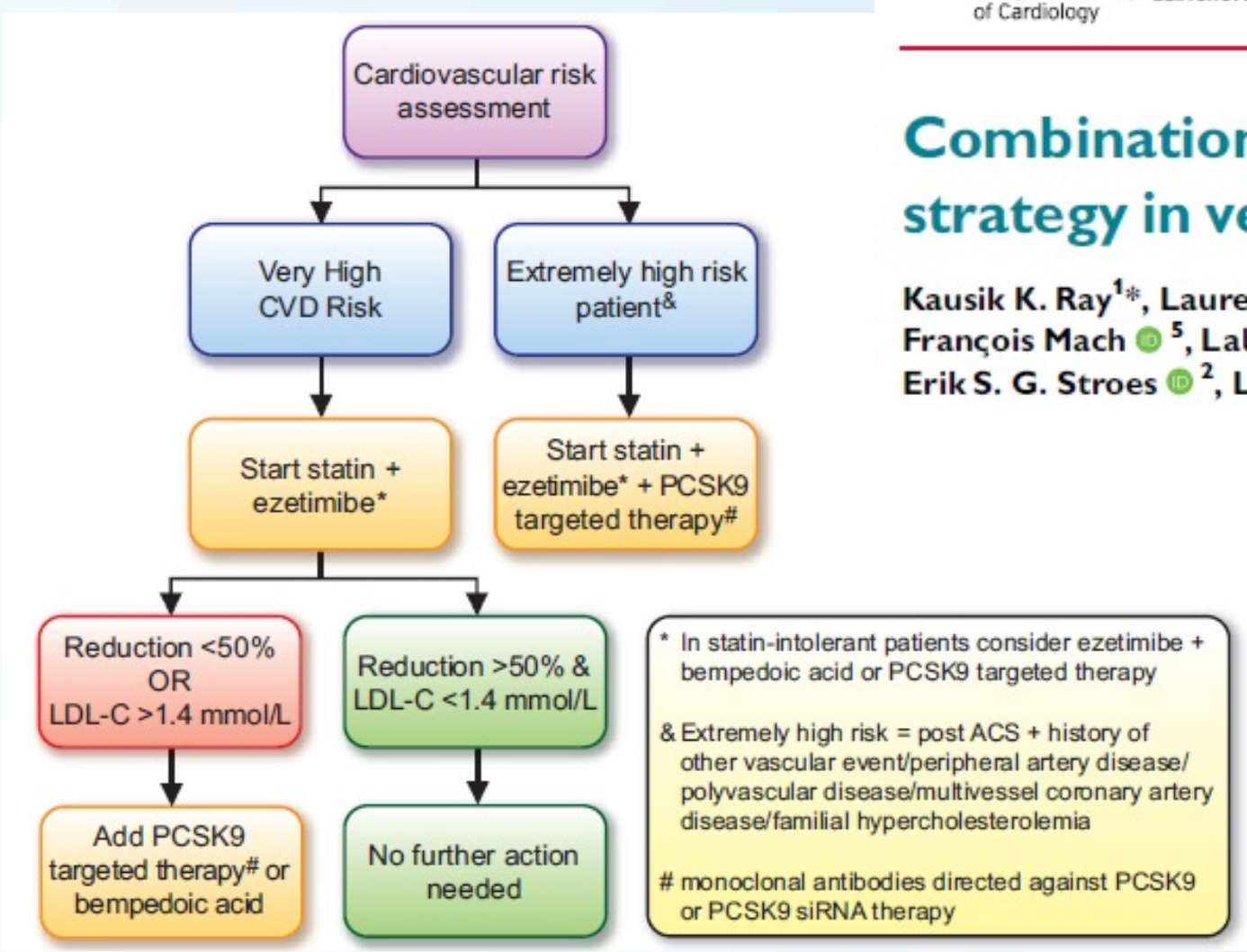


*This includes bempedoic acid monotherapy. †This includes bempedoic acid fixed dose combination with ezetimibe
LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor

Presented by Ray KK et al, at EAS Congress, May 23, 2023

Triplice Terapia con Statina + Ezetimibe + Ac. Bempedoico

A chi e quando?



ESC European Society of Cardiology

European Heart Journal (2021) 00, 1–4
doi:10.1093/eurheartj/ehab718

VIEWPOINT
Epidemiology and prevention

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

Kausik K. Ray[1]*, Laurens F. Reeskamp[2], Ulrich Laufs[3], Maciej Banach[4], François Mach[5], Lale S. Tokgözoğlu[6], Derek L. Connolly[7], Anja J. Gerrits[8], Erik S. G. Stroes[2], Luis Masana[9], and John J. P. Kastelein[2]

"If patients do not achieve the 2019 guideline-recommended LDL cholesterol goal of >50% reduction and levels <1.4 mmol/L, ***a third lipid-lowering therapy, such as bempedoic acid or PCSK9 targeted therapies should be added****."*

Progress in Cardiovascular Diseases 79 (2023) 2–11

ELSEVIER

Progres

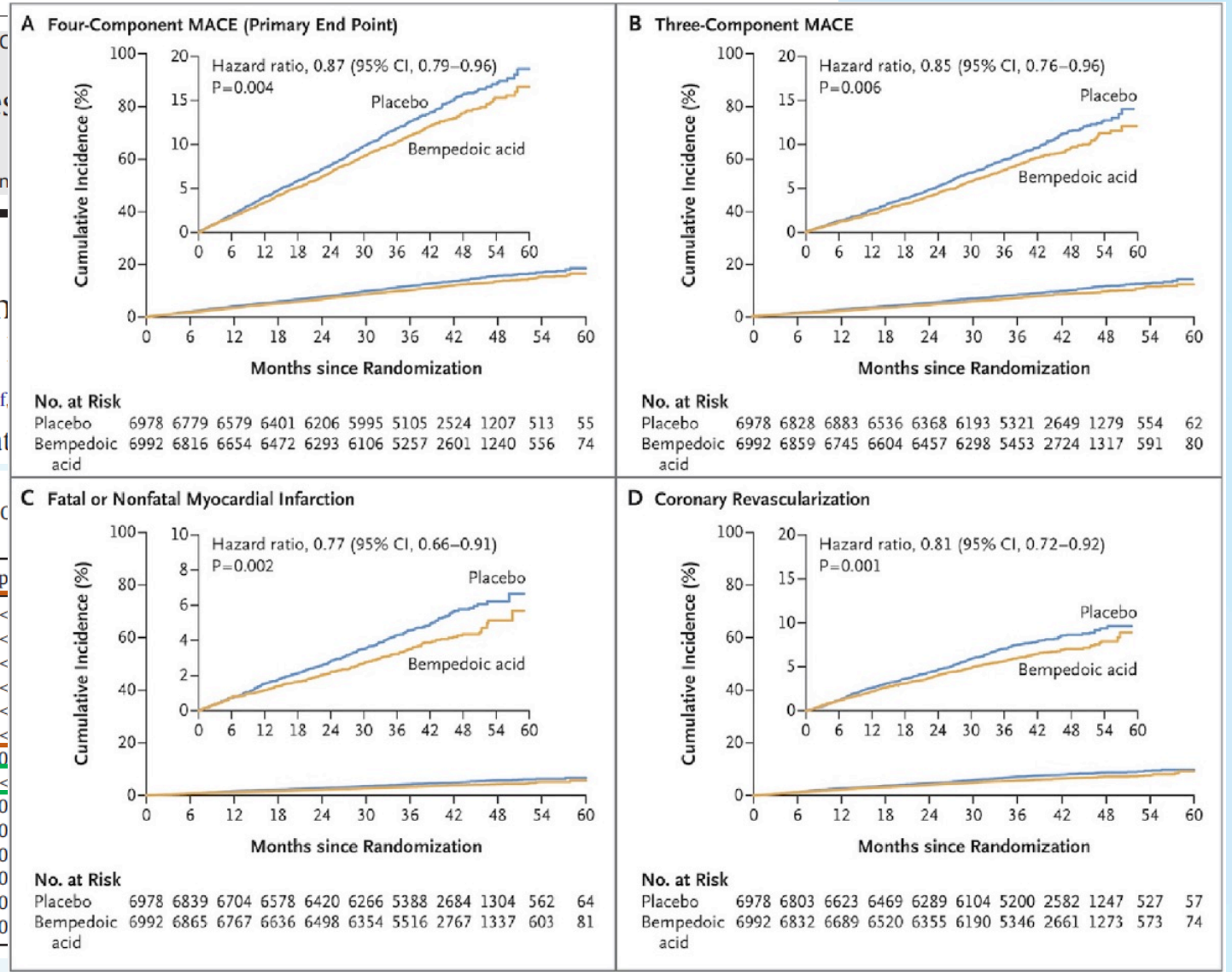
journ

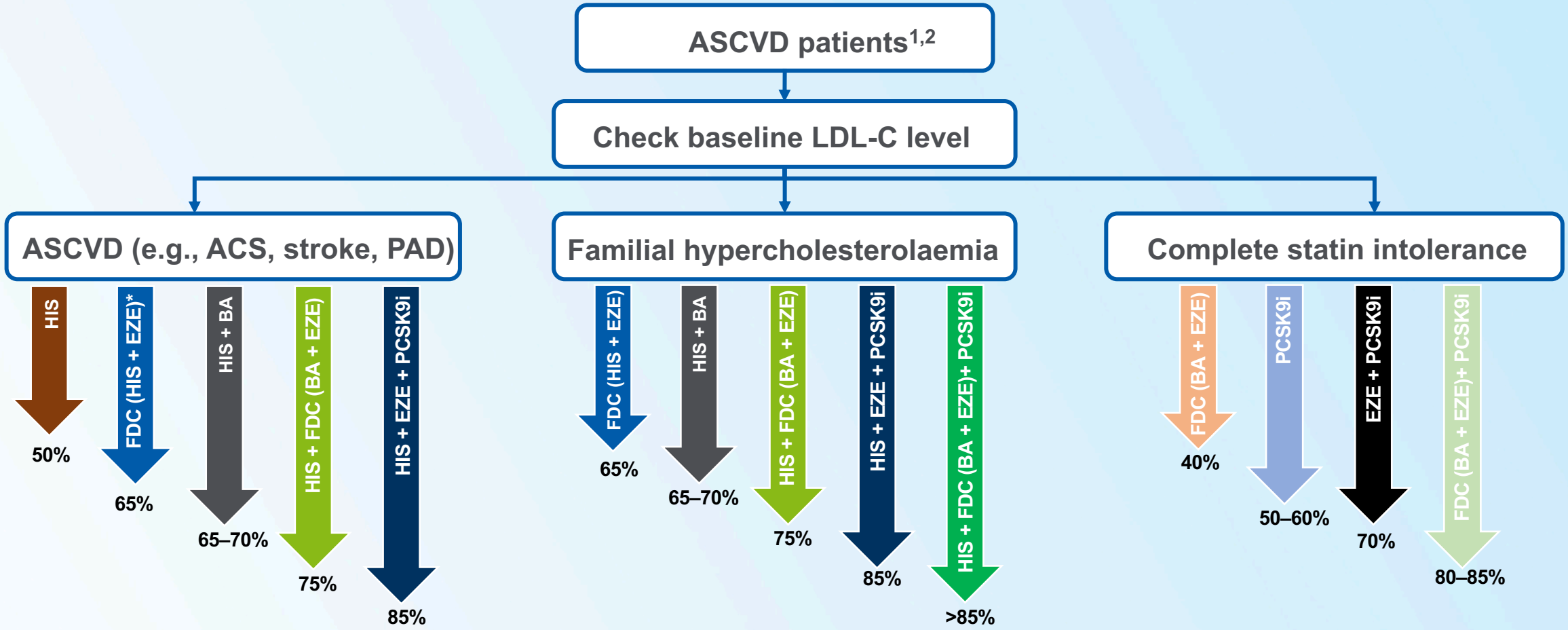
Bempedoic acid in the managem risk. 2023 position paper of the

Maciej Banach [a,b,c,d,*,1], Peter E. Penson [e,f], Francesco Paneni [m,n], Paolo Parini [o,p], Mat

Table 1
Summary of the effects of bempedoic acid (180 mg/day) versus placebo on biomarkers of cardiovascular risk. C
Ratio, MD, mean difference. Data from[17].

Parameter	Effect of bempedoic acid	p
Total cholesterol	MD −14.94%; 95% CI −17.31%, −12.57%	<
Non-high-density lipoprotein cholesterol	MD −18.17%; 95% CI −21.14%, −15.19%	<
Low-density lipoprotein cholesterol	MD −22.94%; 95% CI −26.63%, −19.25%	<
Low-density lipoprotein particle number	MD −20.67%; 95% CI −23.84%, −17.48%	<
Apolipoprotein B	MD −15.18%; 95% CI −17.41%, −12.95%	<
High-density lipoprotein cholesterol	MD −5.83%; 95% CI −6.14%, −5.52%	<
High-density lipoprotein particle number	MD −3.21%; 95% CI −6.40%, −0.02%	0
hsCRP	MD −27.03%; 95% CI −31.42%, −22.64%	<
Triglycerides	MD −1.51%; 95% CI −3.75%, 0.74%	0
Very-low-density lipoprotein particle number	MD 3.79%; 95% CI −9.81%, 17.39%	0
Apolipoprotein A-1	MD −1.83%; 95% CI −5.23%, 1.56%	0
Elevated serum uric acid	OR 3.55; 95% CI 1.03, 12.27	0
Elevated liver enzymes	OR 4.28; 95% CI 1.34, 13.71	0
Elevated creatine kinase	OR 3.79; 95% CI 1.06, 13.51	0





Recommendation	Class	Level
Bempedoic acid is recommended in combination with statins and other lipid-lowering drugs in atherosclerotic disease when the LDL-C treatment targets are not met. The initial treatment strategy should be designed considering the patient's baseline LDL-C.	I	A

Recommendation	Class	Level
In partial statin intolerance, combination therapy with bempedoic acid is recommended in combination with maximally tolerated statins and other non-statin agents to enable patients to reach therapeutic goals.	I	A

1. Banach M, et al. Arch Med Sci. 2022;18:1429–1434;
2. Banach M, et al. Prog Cardiovasc Dis. 2023:S0033–0620(23)00026–9

ILEP-Recommended Pathways on the Application of Bempedoic Acid in Different Groups of Patients

ASCVD/HeFH patients with baseline LDL-C 110–160 mg/dL* (2.8–4.1 mmol/L)

Start with upfront combination therapy of high intensity statin and EZE†

−65%

Still >55 mg/dL (1.4 mmol/L)

Start with BA

−22%

Still >55 mg/dL (1.4 mmol/L)

Start with PCSK9 targeted therapy approach if available

ASCVD/HeFH patients with baseline LDL-C >160 mg/dL (2.8–4.1 mmol/L)

Start with upfront combination therapy of high intensity statin and FDC of BA and EZE

−75%

Still >55 mg/dL(1.4 mmol/L)

Start with PCSK9 targeted therapy approach if available

Very high-risk patients with partial statin intolerance

Start with upfront combination therapy of maximally tolerated statin and EZE†

−45%

Still >55 mg/dL (1.4 mmol/L)

Start with BA

−22%

Still >55 mg/dL (1.4 mmol/L)

Start with PCSK9 targeted therapy approach if available

Very high-risk patients with complete statin intolerance

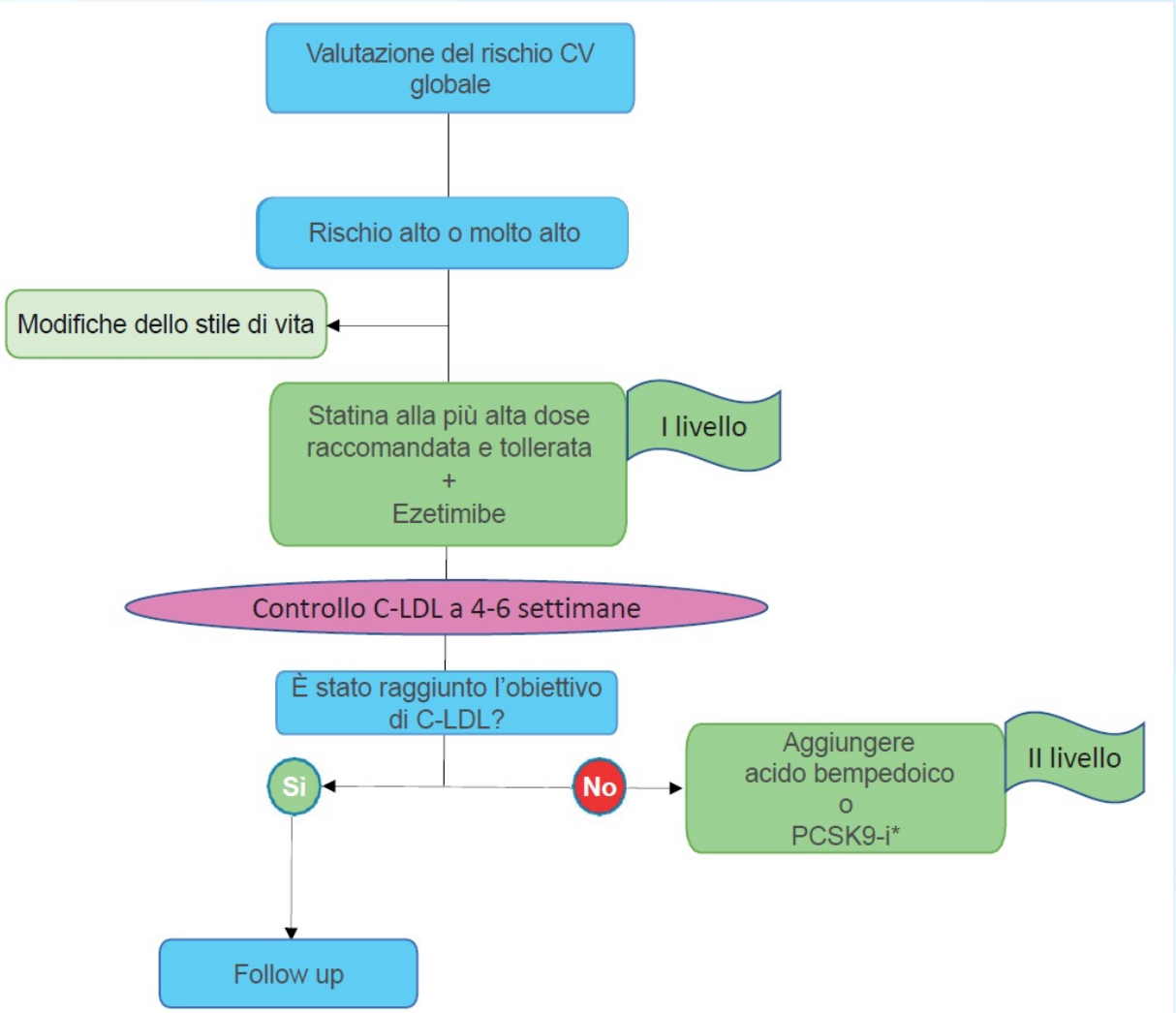
Start with upfront combination therapy of BA and EZE

−40%

Still >55 mg/dL (1.4 mmol/L)

Start with PCSK9 targeted therapy approach if available

Banach M, et al. Prog Cardiovasc Dis. 2023:S0033–0620(23)00026–9

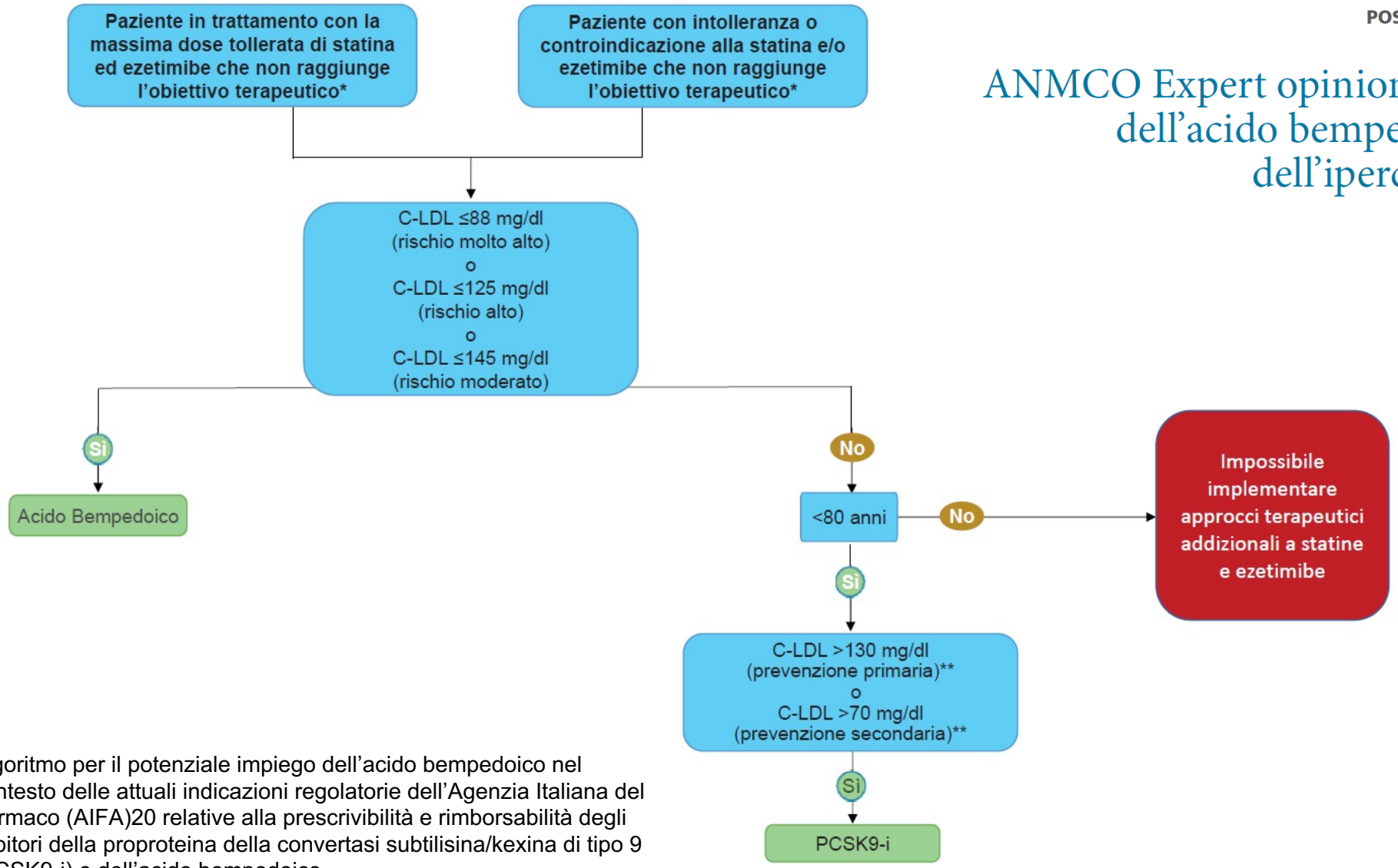


POSITION PAPER

ANMCO Expert opinion: Posizionamento terapeutico dell'acido bempedoico nel trattamento dell'ipercolesterolemia

L'acido bempedoico, da solo o in combinazione fissa con l'ezetimibe, per il **rapporto costo/efficacia più favorevole rispetto agli agenti anti-PCSK9**, rappresenta un'opzione terapeutica particolarmente utile nei pazienti che non riescono a raggiungere il target terapeutico con il trattamento statinico alla massima dose tollerata.

Di Fusco S.A et al, G Ital Cardiol 2023;24(6):490-498



Algoritmo per il potenziale impiego dell'acido bempedoico nel contesto delle attuali indicazioni regolatorie dell'Agenzia Italiana del Farmaco (AIFA)20 relative alla prescrivibilità e rimborsabilità degli inibitori della proproteina della convertasi subtilisina/kexina di tipo 9 (PCSK9-i) e dell'acido bempedoico.

POSITION PAPER

ANMCO Expert opinion: Posizionamento terapeutico dell'acido bempedoico nel trattamento dell'ipercolesterolemia

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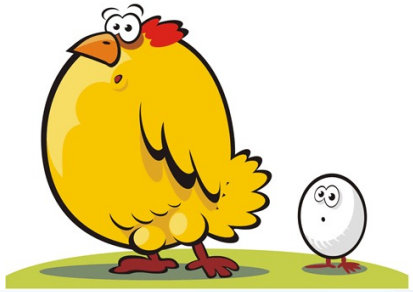
Review

Bempedoic Acid and Statins in Lipid-Lowering Strategy: Which Came First, the Egg or the Chicken?

Francesco Natale [1], Riccardo Molinari [1,2], Rosa Franzese [1,2], Noemi Mollo [1,2] and Giovanni Cimmino [2,3,*]



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6. Conclusions and Future Perspectives

In the scenario of lipid-lowering strategy, the future is full of opportunities, thanks to the ongoing research. We are now able to achieve very low target that was a dream few years ago. Unfortunately, some of these strategies remain expensive, such as the use of proprotein convertase subtilisin/kexin type 9 inhibitors, thus new agents with more affordable cost/effectiveness ratio are welcome. Bempedoic acid is an interesting new opportunity to manage the complex scenario of dyslipidemia with an intriguing biochemical profile. The fix-dose combination with ezetimibe with the opportunity to modulate statin dose according to goal to achieve might be the starting therapy for the majority of hypercholesterolemic patients. The side-effects reported in the clinical trials may be easily managed. In conclusion, in light of the existing body of evidence, bempedoic acid might have a broad utilization, even as first line therapy for LDL-C-related atherosclerotic diseases when the gap to the goal is high. Its biochemical features encourage a possible use anticipating the statin treatment. However, at the time of writing the present manuscript, no clinical data were available to support this hypothesis. Future studies are welcome to expand the use of this new molecule in the complex scenario of hypercolesterolemic disorders.

CONFRONTO COSTO ANNUO TERAPIE IPOLIPEMIZZANTI

Take home message

Acido Bempedoico in LLT: terapia efficace e sostenibile

GO LOWER

ERLIER

KEEP LONGER


THANK YOU
FOR YOUR
ATTENTION