CAMPUS Cuore SUMMIT

Napoli, 1-2 ottobre 2021
Hotel Excelsior

Triplice terapia con acido bempedoico e statina/ezetimibe per il rischio evitabile nel paziente con malattia aterosclerotica cardiovascolare

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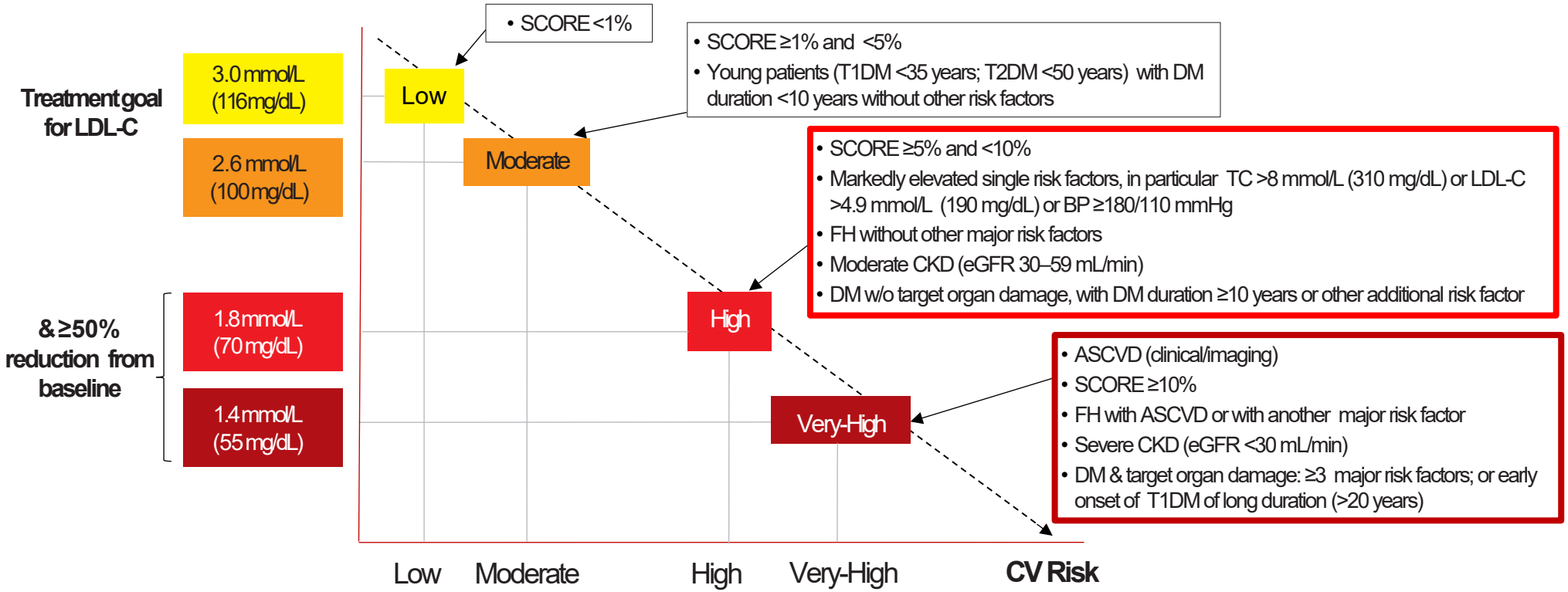
WHY DO WE NEED IT?

The ESC/EAS Guidelines Recommend to Intensively Lower LDL-C to Reduce CV Risk, Particularly in Uncontrolled Patients

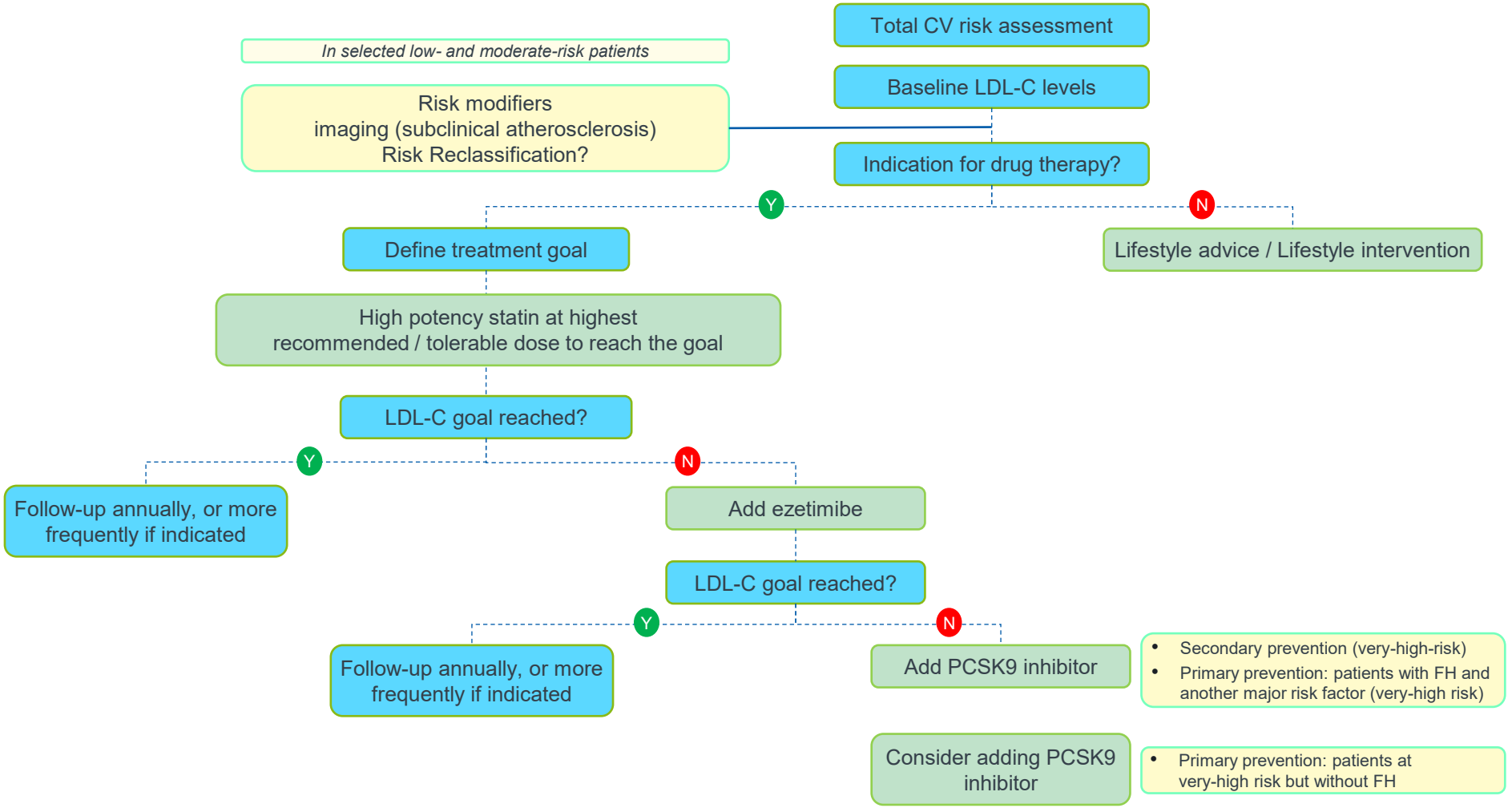
The updated ESC/EAS Guidelines recommend an LDL-C reduction of ≥50% and LDL-C goals of <70 and <55 mg/dL in high- and very high-risk patients, respectively



- **These goals are more stringent than previously because the greater the absolute LDL-C reduction, the greater the CV risk reduction**

ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J.* 2020; 41(1): 111-188

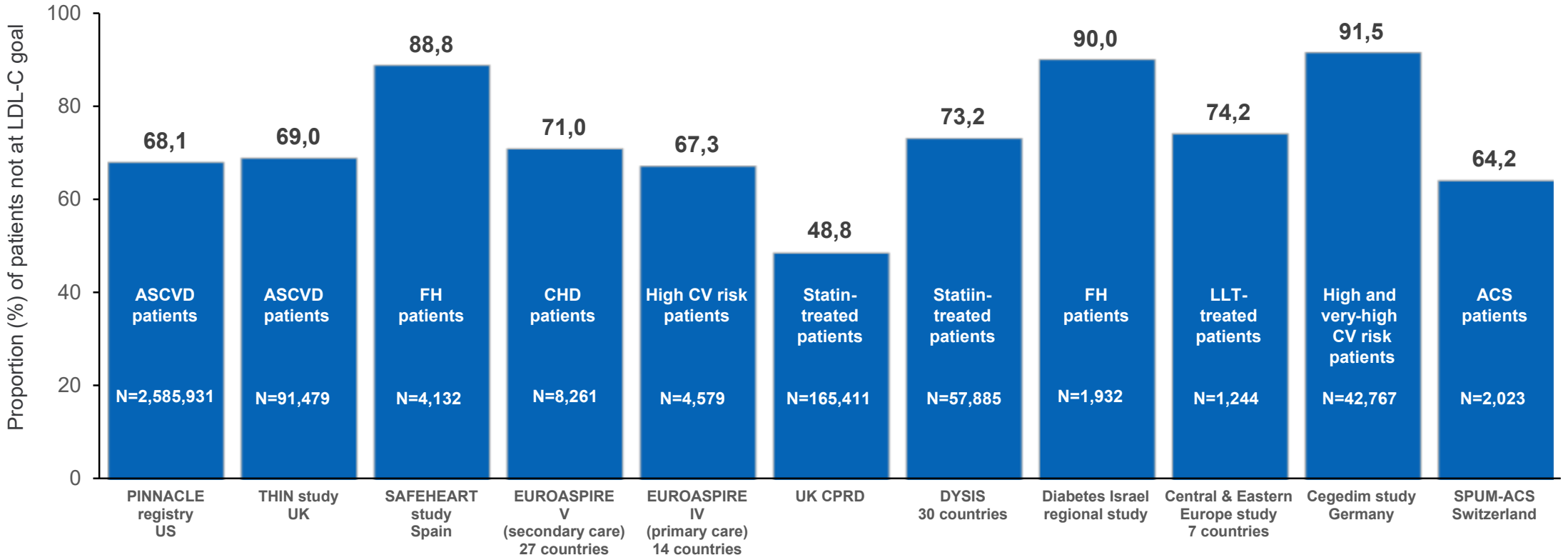
ESC/EAS Treatment algorithm for pharmacological LDL-C lowering



ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J.* 2020; 41(1): 111-188

Additional LLTs are Needed to Complement Current Therapies to Help Uncontrolled Patients Achieve Their Goals

Numerous large studies show that high and very high-risk patients are failing to achieve LDL-C goals[1–11]

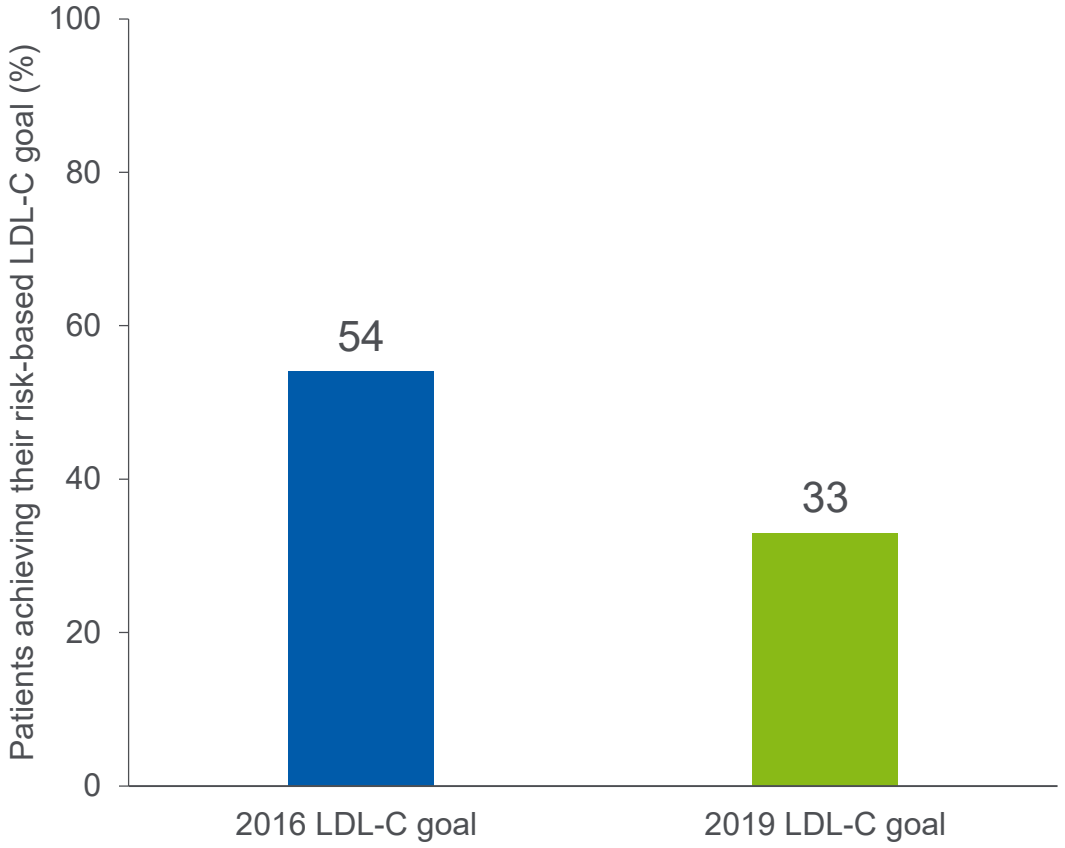


ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolmemia, LLT, lipid lowering therapy

1. Allen JA, et al. *Circulation*. 2019;140 (S1):A12904; **2**. Steen DL et al. *BMJ Open*. 2017;7:e013255; **3**.de Isla LP et al. *JACC*. 2016;67:1278–85; **4**. de Backer G et al. *Atherosclerosis*. 2019;285:135–146; **5**. Kotseva K et al. *Eur J Prev Cardiol*. 2016;23:2007–2018; **6**. Akyea RK et al. *Heart*. 2019;0:1–7; **7**. Gitt AK et al. *Atherosclerosis*. 2016;255:200-09; **8**. Zafrir B et al. *Eur J Prev Cardiol*. 2017;24:867–875; **9**. Petrov I et al. *Adv Ther*. 2019;36:608–20; **10**. März W et al. *Atherosclerosis*. 2018;268:99–107; **11**. Gencer B et al. *J Am Heart Assoc*. 2017;6:e006537.

Overall Risk-based 2016 and 2019 LDL-C Goal Attainment

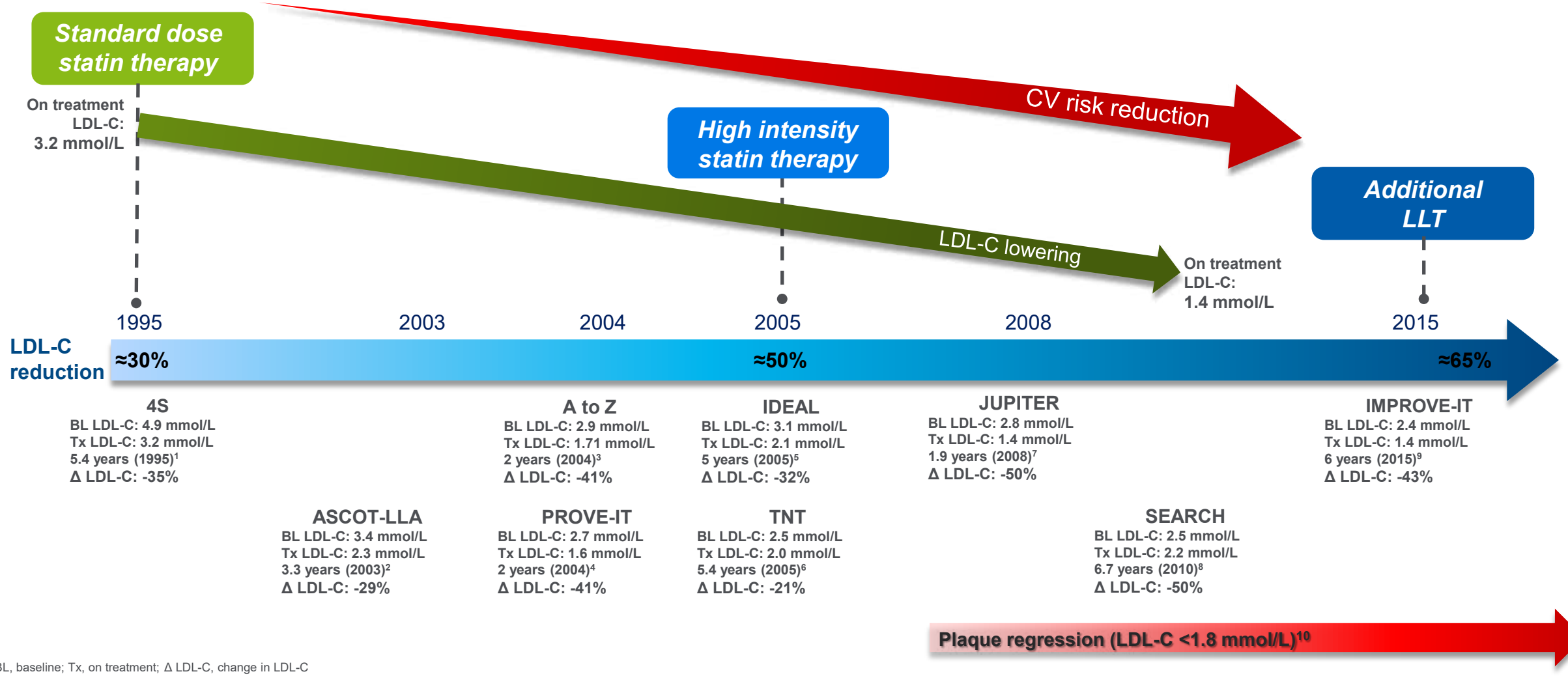
- Approximately half of all patients did not achieve their 2016 ESC/EAS risk-based LDL-C goals and two-thirds did not achieve the 2019 LDL-C goal.
- Overall, 2016 LDL-C goal attainment stratified by risk group was:
  - Low: 63% (95% CI 56–70); moderate: 75% (95% CI 73–78); high: 63% (95% CI 59–67); very-high: 39% (95% CI 37–41)
- Among patients with established ASCVD, only 39% (95% CI 37–41) achieved LDL-C levels <1.8 mmol/L.



*Stabilised LLT at time of LDL-C measurement. combo, combination; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCSK9i; proprotein convertase subtilisin/kexin type 9 inhibitor

Ray, KK et al. Eur. J. Prev. Cardiol. 2020.

Learnings from the history of lipid management: more intensive LLT results in greater CV risk reduction



BL, baseline; Tx, on treatment; Δ LDL-C, change in LDL-C

1.Pedersen TR et al. Lancet. 1994;344:1383–89; 2.Sever et al. Lancet 2003; 361:1149–58; 3.De Lemos et al. JAMA. 2004;292:1307–1316; 4.Cannon CP et al. N Engl J Med 2004;350:1495–504; 5.Pedersen TR et al. JAMA. 2005;294:2437–2445; 6.LaRosa et al. N Engl J Med 2005;352:1425–35; 7.Ridker PM et al. et al N Engl J Med 2008; 359:2195–207; 8.Armitage J et al. Lancet 2010;376:1658–69 ; 9.Cannon CP et al. et al N Engl J Med 2015;372:2387–97; 10.Nicholls SJ, et al. JAMA 2016;316:2373–2384

Treatment Of High- and Very High-risk Patients for the Prevention of Cardiovascular Events in Europe: Baseline Demographics from the Multinational Observational SANTORINI Study

Kausik K. Ray, Inaam Haq, Aikaterini Bilitou, Alberico L. Catapano; On behalf of: The SANTORINI Investigators

Presented virtually at the ESC Congress – 27–30 August 2021

Methods

- SANTORINI is a multinational, prospective, observational, non-interventional study (NCT04271280)[1]
- Patients aged ≥18 years at high and very high CV risk (as assigned by the investigators) requiring LLT were recruited from 14 European countries across primary and secondary care settings
- The primary objective is to document, in the real-world setting, the effectiveness of current treatment modalities in managing plasma levels of LDL-C in high- and very high-risk patients requiring LLT
- Patient characteristics, medical history, current LLT and any other co-medications were documented at baseline

CV, cardiovascular; **LDL-C,** low-density lipoprotein cholesterol; **LLT,** lipid-lowering therapy

Patient demographics

- Of 9606 patients recruited from March 2020 to February 2021, cleaned data on 4308 were available through to February 2021
  - 55% were from secondary care

Characteristic[a]	Overall (N=4308)	High risk (N=1320)	Very high risk (N=2987)
Female, n (%)	1199 (27.8)	522 (39.6)	677 (22.7)
Age, years, mean (SD)	64.8 (10.8)	62.4 (11.6)	65.8 (10.3)
Hypertension, n (%)	3053 (70.9)	849 (64.3)	2203 (73.8)
Diabetes, n (%)	1525 (35.4)	459 (34.8)	1066 (35.7)
Familial hypercholesterolemia, n (%)	437 (10.1)	233 (17.7)	204 (6.8)
Smoking history, n (%) Current Former Never	 710 (16.5) 1801 (41.8) 1748 (40.6)	 215 (16.3) 449 (34.0) 648 (49.1)	 495 (16.6) 1352 (45.3) 1100 (36.8)
LDL-C, mmol/L, mean (SD)	2.45 (1.21)	2.80 (1.27)	2.29 (1.14)

[a]Percentages may not add up to 100% as there were unknown/missing data.
LDL-C, low-density lipoprotein cholesterol; **SD,** standard deviation

Risk classification as reported by investigator[a]

- The majority of patients were classified as very high risk (69.3%), with 30.6% high risk
- ESC/EAS guidelines were the most common basis for risk classification

Risk classification based on

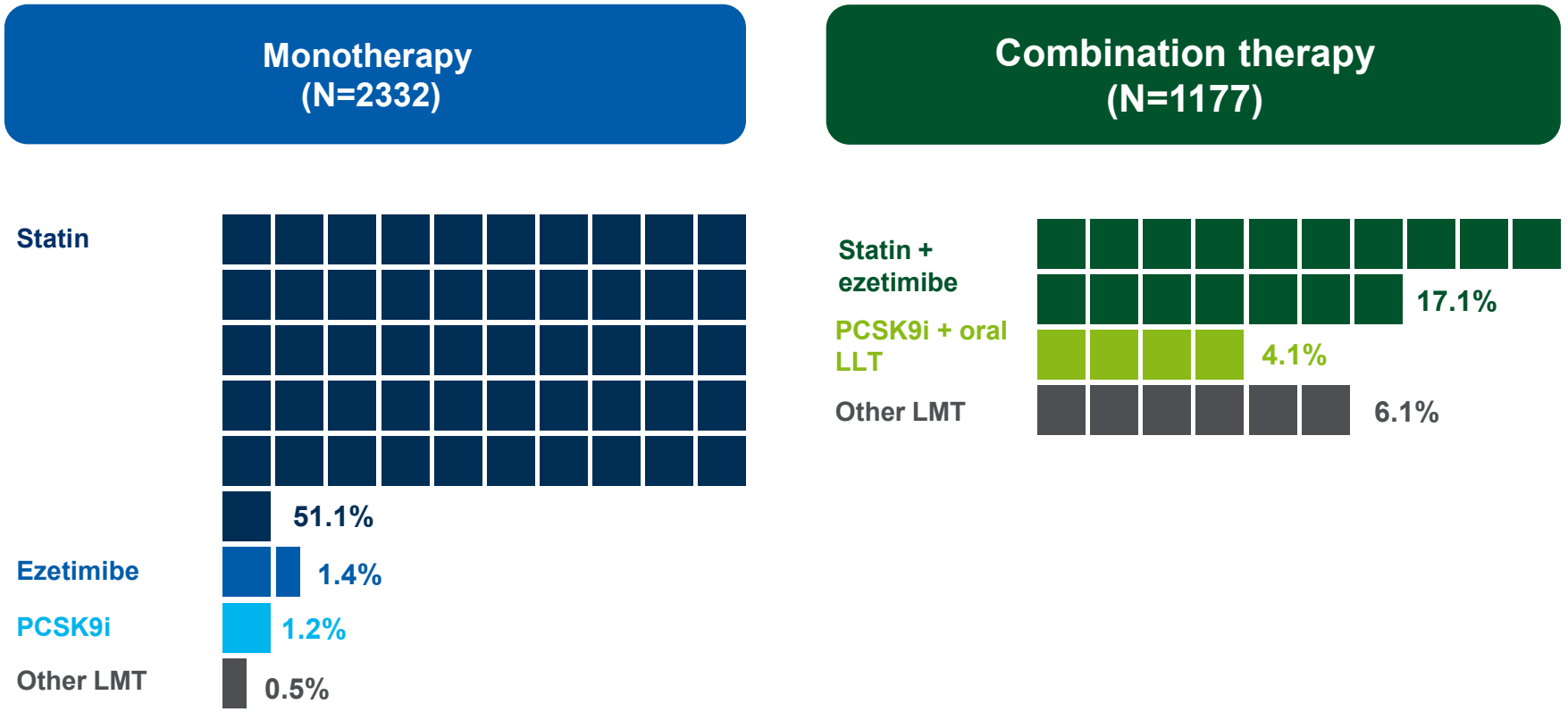
Other basis for risk classification, n (%)	
Institutional practice and/or considerations	32 (0.7)
Institutional guidelines	63 (1.5)
Regional guidelines	72 (1.7)
Other	40 (0.9)

[a]Percentages may not add up to 100% as there were unknown/missing data

EAS, European Atherosclerosis Society; **ESC,** European Society of Cardiology

Medication use at baseline – Overall population[a]

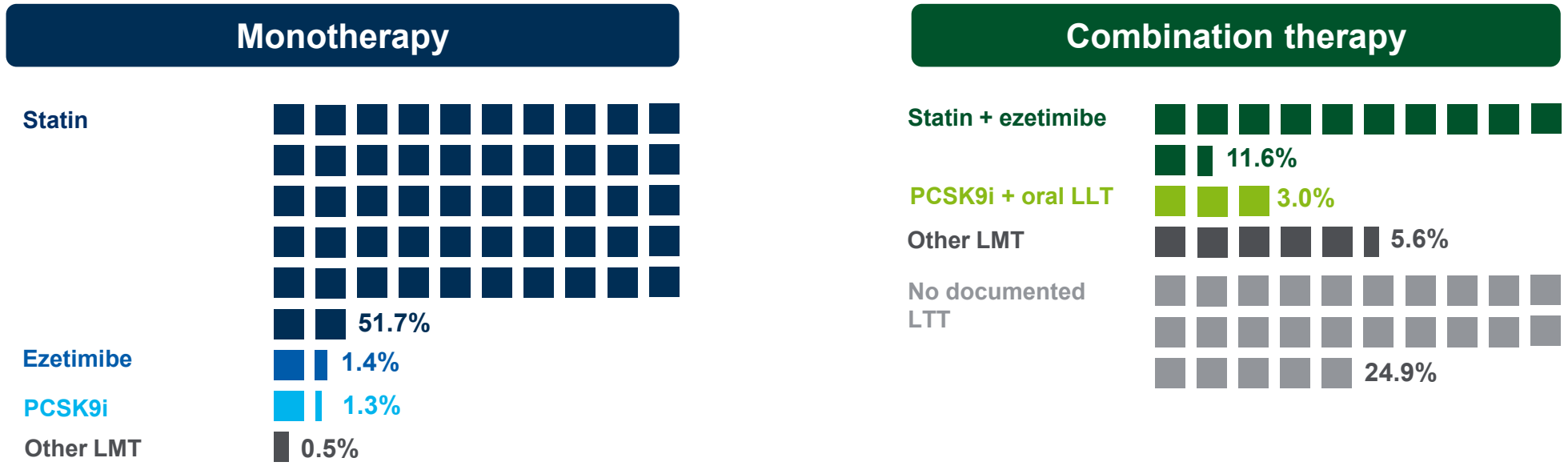
- At baseline, 18.5% of patients were not receiving any LLT. The majority of patients (54.1%) were receiving LLT monotherapy. Combination therapy was used in 27.3% of patients



[a]Percentages may not add up to 100% as there were unknown/missing data. N=4308

LLT, lipid-lowering therapy; **LMT,** lipid-modifying therapy; **PCSK9i,** proprotein convertase subtilisin kexin 9 inhibitor

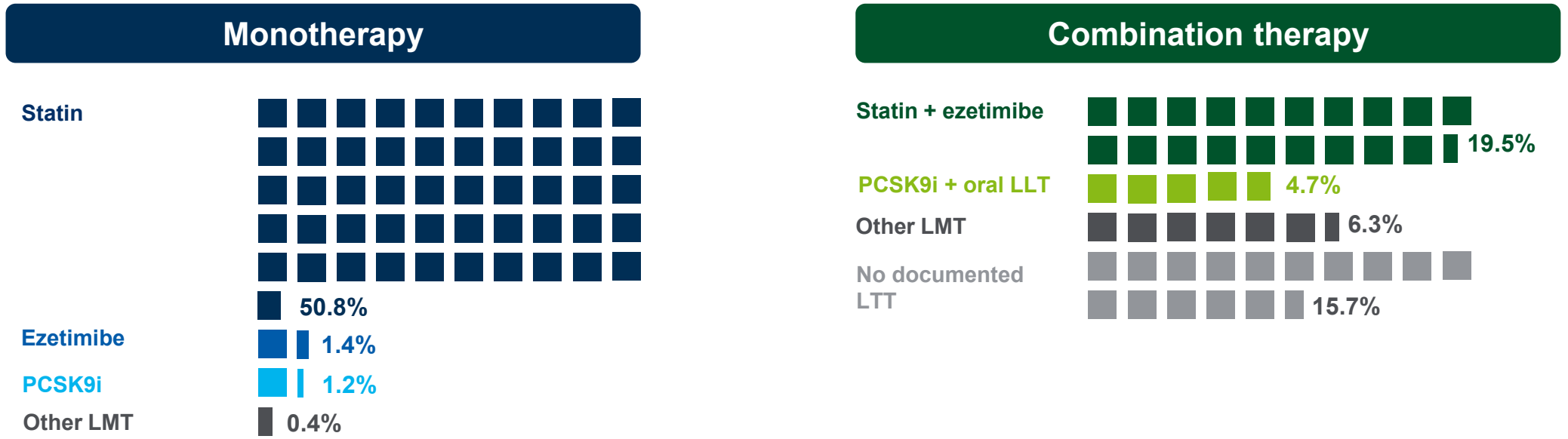
Medication use at baseline – High-risk population[a]



[a]Percentages may not add up to 100% as there were unknown/missing data. N=1320

LLT, lipid-lowering therapy; **LMT,** lipid-modifying therapy; **PCSK9i,** proprotein convertase subtilisin kexin 9 inhibitor

Medication use at baseline – Very high-risk population[a]

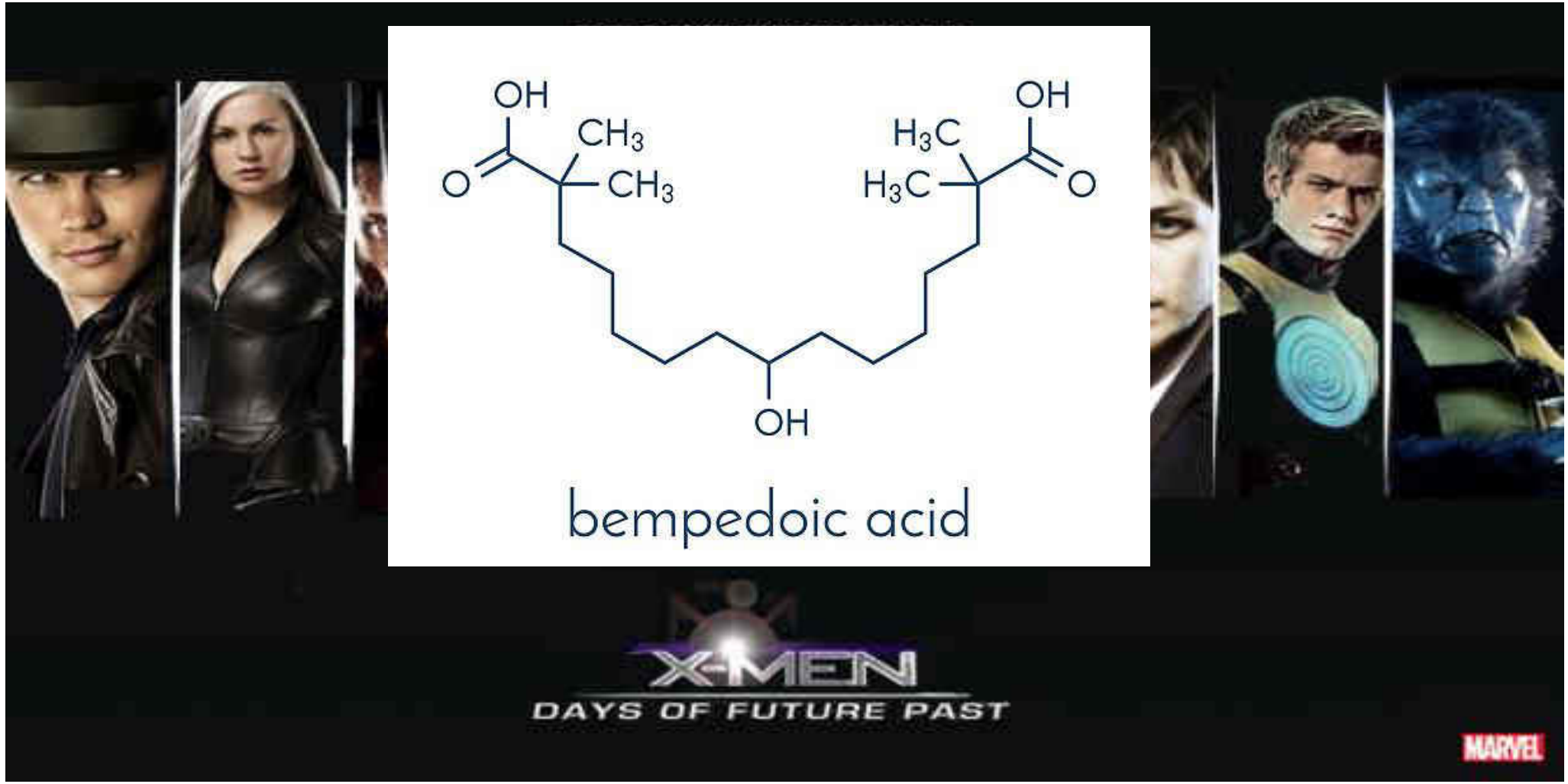


[a]Percentages may not add up to 100% as there were unknown/missing data. N=2987

LLT, lipid-lowering therapy; **LMT,** lipid-modifying therapy; **PCSK9i,** proprotein convertase subtilisin kexin 9 inhibitor

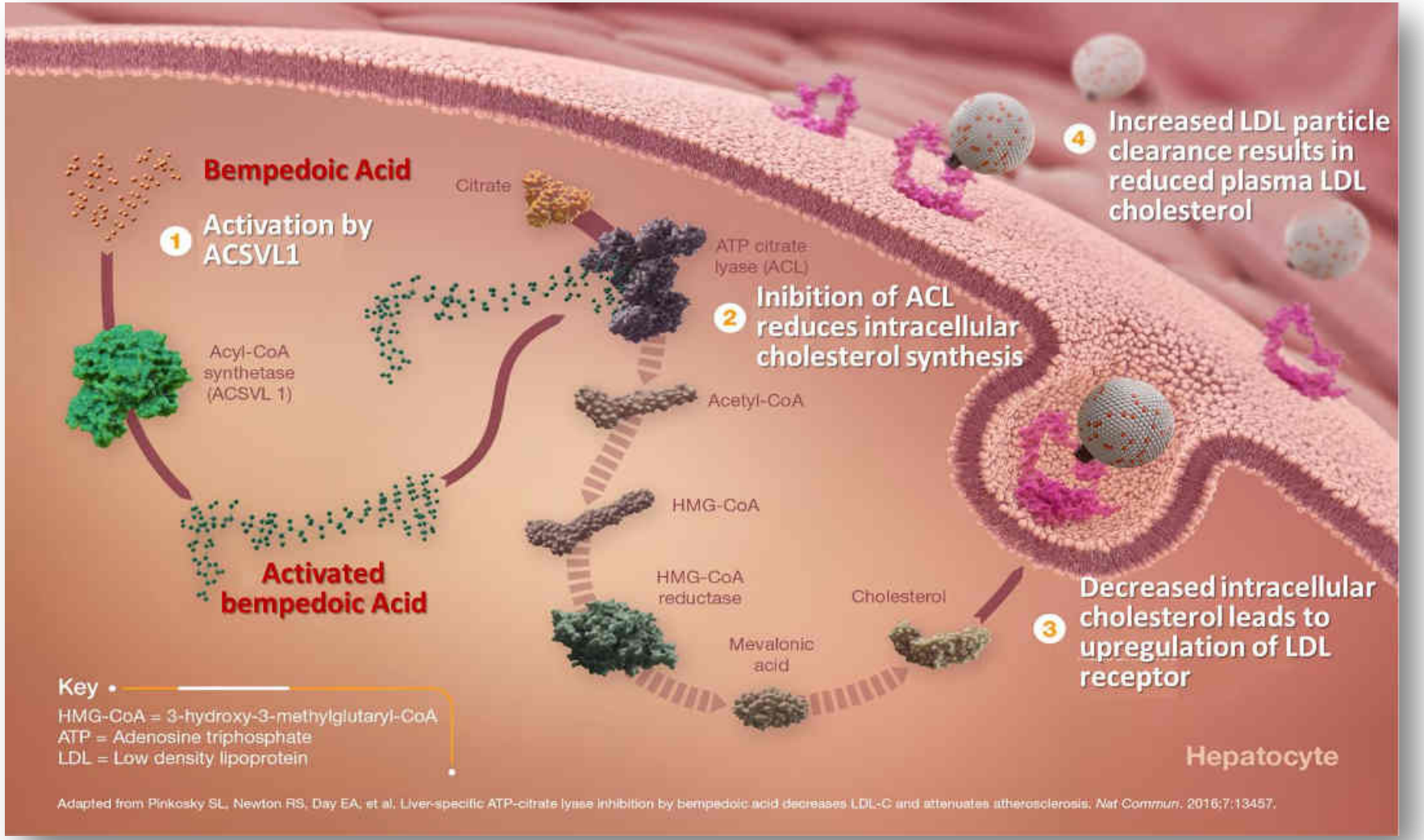
WHY DO WE NEED IT?

Bempedoic acid: old pathway, new approach



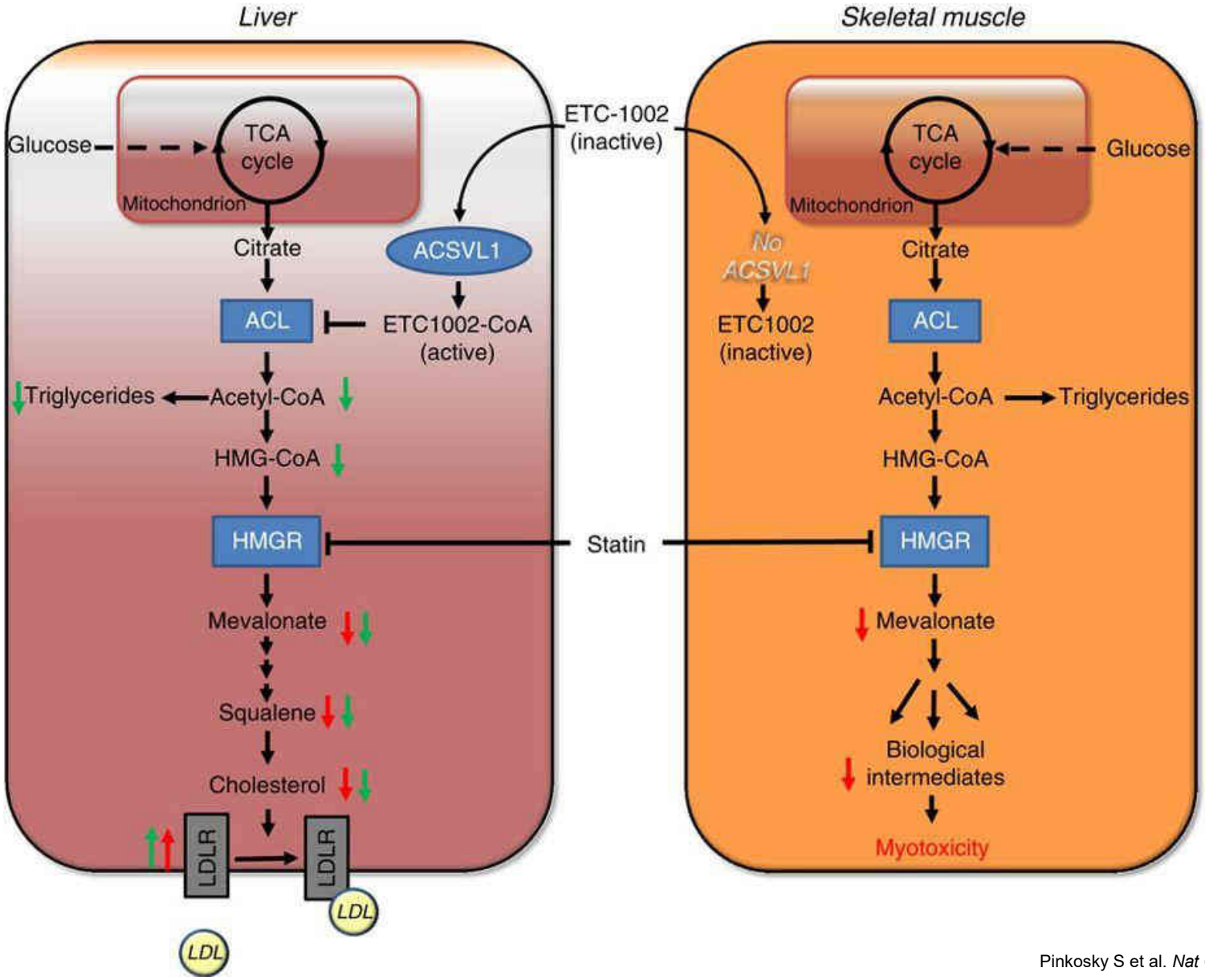
The Unique Mechanism of Action of Bempedoic Acid is Complementary, yet Distinct from Statins and Other LLTs

- Activated primarily in the liver, bempedoic acid inhibits the ACL enzyme in the well-known 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



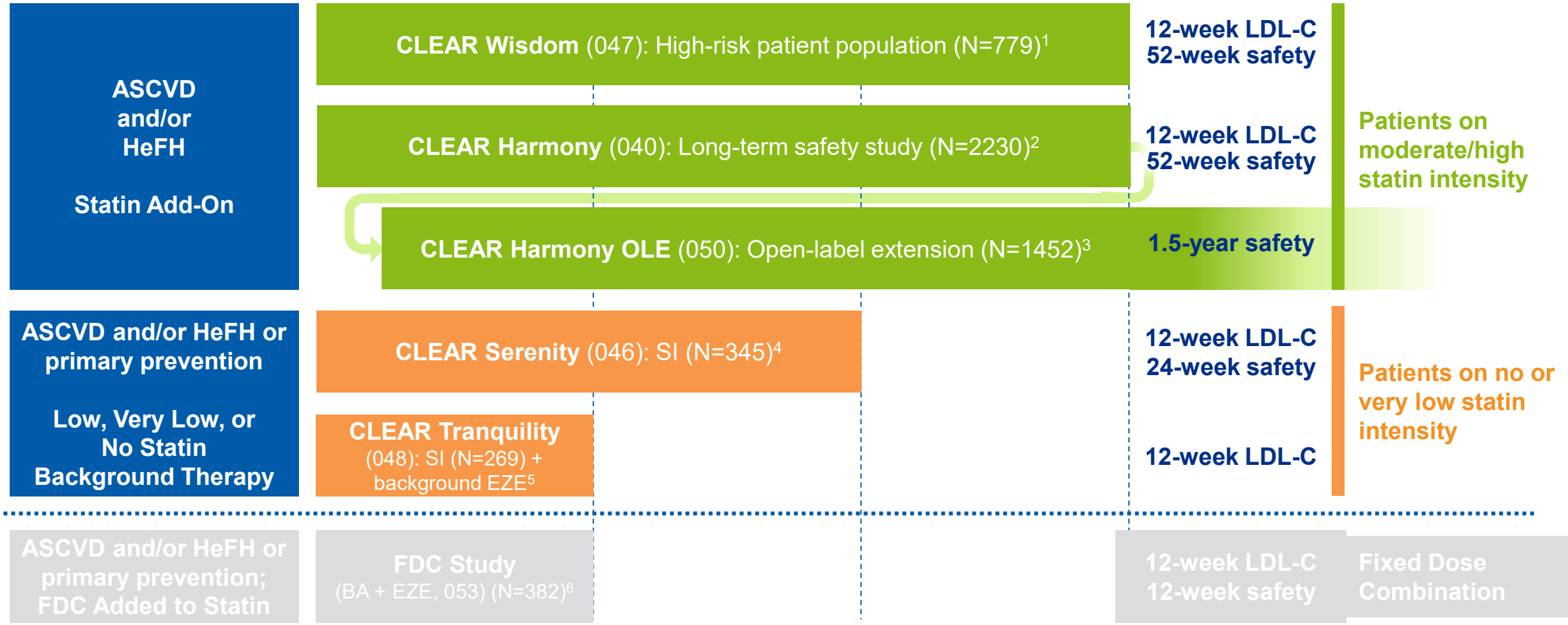
Adapted from Pinkosky et al. *Nature Communications*. 2016; 7:13457 | DOI: 10.1038/ncomms13457

Bempedoic Acid is not Activated in the Skeletal Muscle



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

Bempedoic Acid Was Evaluated in a Robust Clinical Trial Program with a Broad Range of Patients



ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; OLE = open-label extension; SI = statin intolerant

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.** ClinicalTrials.gov identifier NCT03067441; **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.

CLEAR Studies: Clinical Characteristics by Treatment Pool

Characteristic	CLEAR Harmony/CLEAR Wisdom (ASCVD/ HeFH on maximally tolerated statin therapy)		CLEAR Tranquility/ CLEAR Serenity (Patients with statin intolerance)	
	Bempedoic Acid (n =2010)	Placebo (n = 999)	Bempedoic Acid (n = 415)	Placebo (n = 199)
Age, years, mean ± SD	**65.4** (9.06)	**66.2** (8.7)	**64.6** (10.2)	**64.5** (10.2)
Male, % (n)	**71** (1427)	**69.8** (697)	**41.7** (173)	**41.2** (82)
History, % (n)				
ASCVD	**97.1** (1952)	**97.5** (974)	**NA**	**NA**
Diabetes	**28.9** (5809)	**29.3** (293)	**23.6** (98)	**21.6** (46)
Hypertension	**80.2** (1612)	**81.9** (818)	**64.8** (269)	**63.3** (126)
Background LMT, % (n)				
Statin alone	**83.9** (1687)	**83.8** (837)	**3.9** (16)	**5** (10)
Statin plus other LMT	**13.3** (268)	**13.3** (133)	**14.5** (60)	**12.6** (25)
Other LMT alone	**1.1** (23)	**1.5** (15)	**49.6** (206)	**48.2** (96)
None	**1.6** (32)	**1.4** (14)	**32** (133)	**34.2** (68)
Statin intensity, % (n)				
None	**2.7** (55)	**2.9** (29)	**81.7** (339)	**82.4** (164)
Low	**6.2** (125)	**5.9** (59)	**18.3** (76)	**17.6** (35)
Moderate	**40.3** (811)	**40.4** (404)	**NA**	**NA**
High	**50.7** (1019)	**50.8** (507)	**NA**	**NA**
Baseline ezetimibe use, % (n)	**7.5** (150)	**7.6** (76)	**51.8** (215)	**51.3** (102)
Baseline lipids, mean (SD), mg/dL				
Total cholesterol	**185.5** (38.5)	**185.4** (40.2)	**233.7** (44.7)	**226.7** (43.7)
LDL-C	**107.7** (32.3)	**107.5** (33.5)	**146.0** (39.2)	**141.2** (37.7)
Non–HDL cholesterol	**136.1** (37.3)	**135.6** (38.3)	**179.9** (43.9)	**173.4** (43.8)

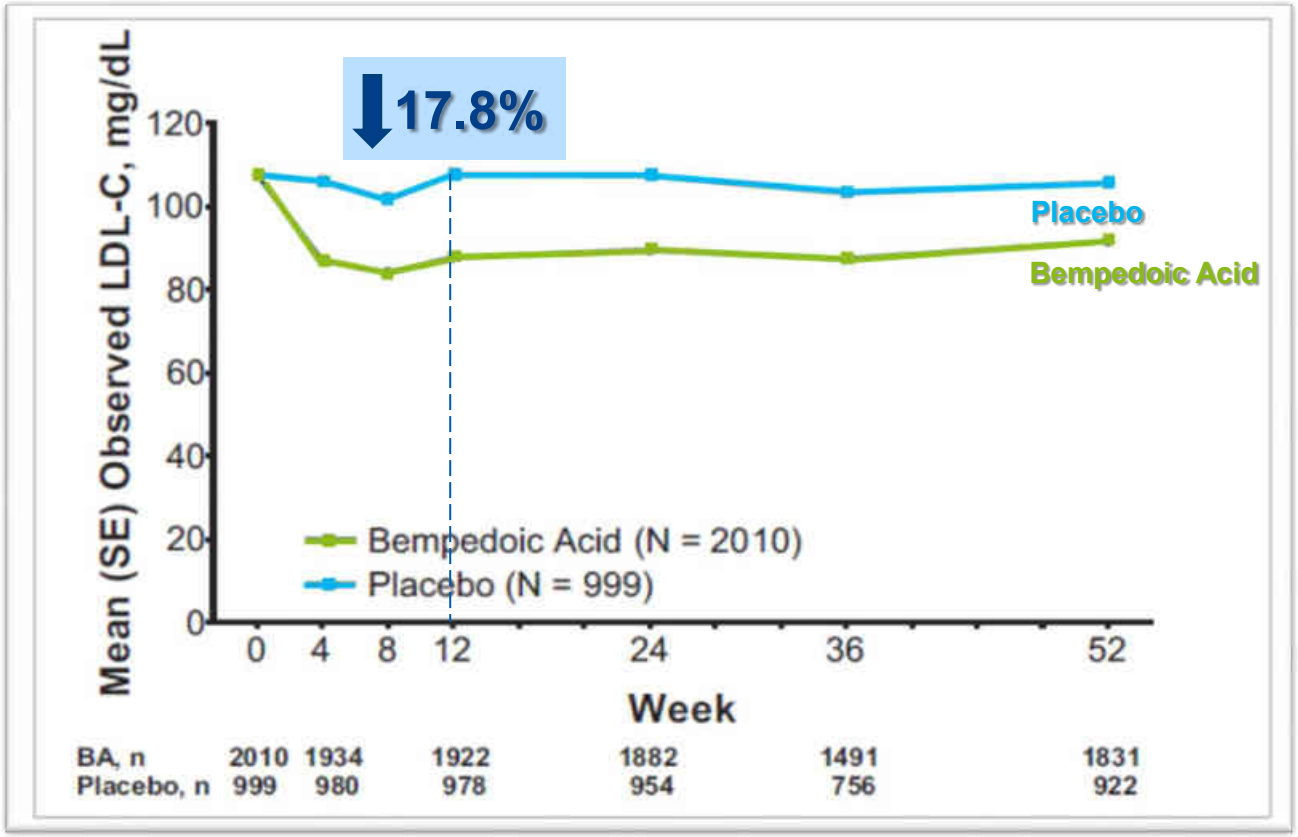
ASCVC = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; SD = standard deviation.

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

Patients on Moderate/High Statin Intensity

Pooled Analysis of CLEAR Harmony and CLEAR Wisdom

Bempedoic acid lowered LDL-C significantly more than placebo in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin



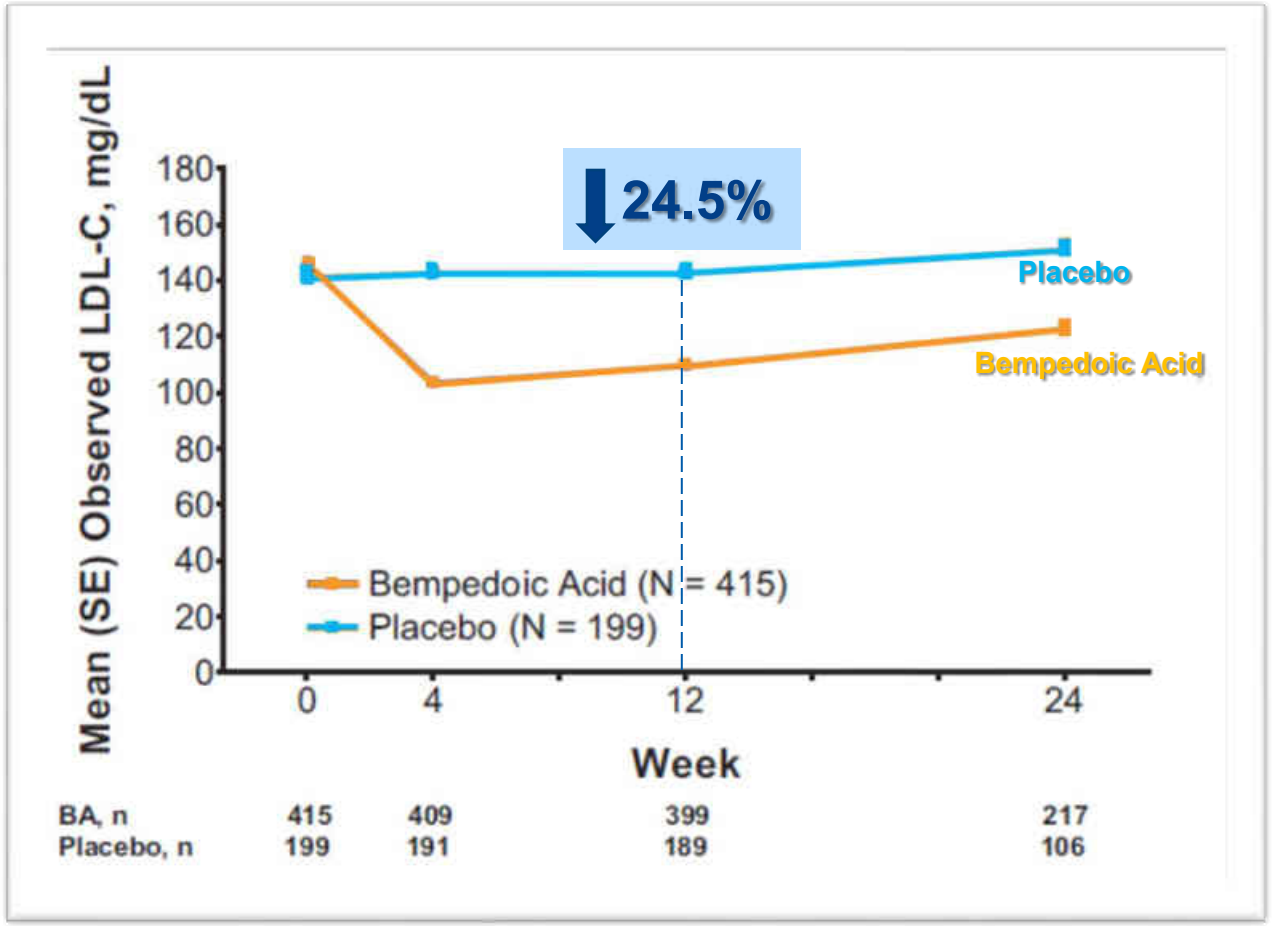
At week 12:
Mean percentage change in LDL-C:
−16.0% in the bempedoic acid group vs +1.8% in the placebo group (**−17.8**; 95% CI, −19.5 to −16.0; *P* < 0.001);
Absolute mean reduction in LDL-C:
−19.8 mg/dL in the bempedoic acid group, +0.3 mg/dL in the placebo group

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

Statin Intolerant Patients

Pooled Analysis of CLEAR Serenity and CLEAR Tranquility

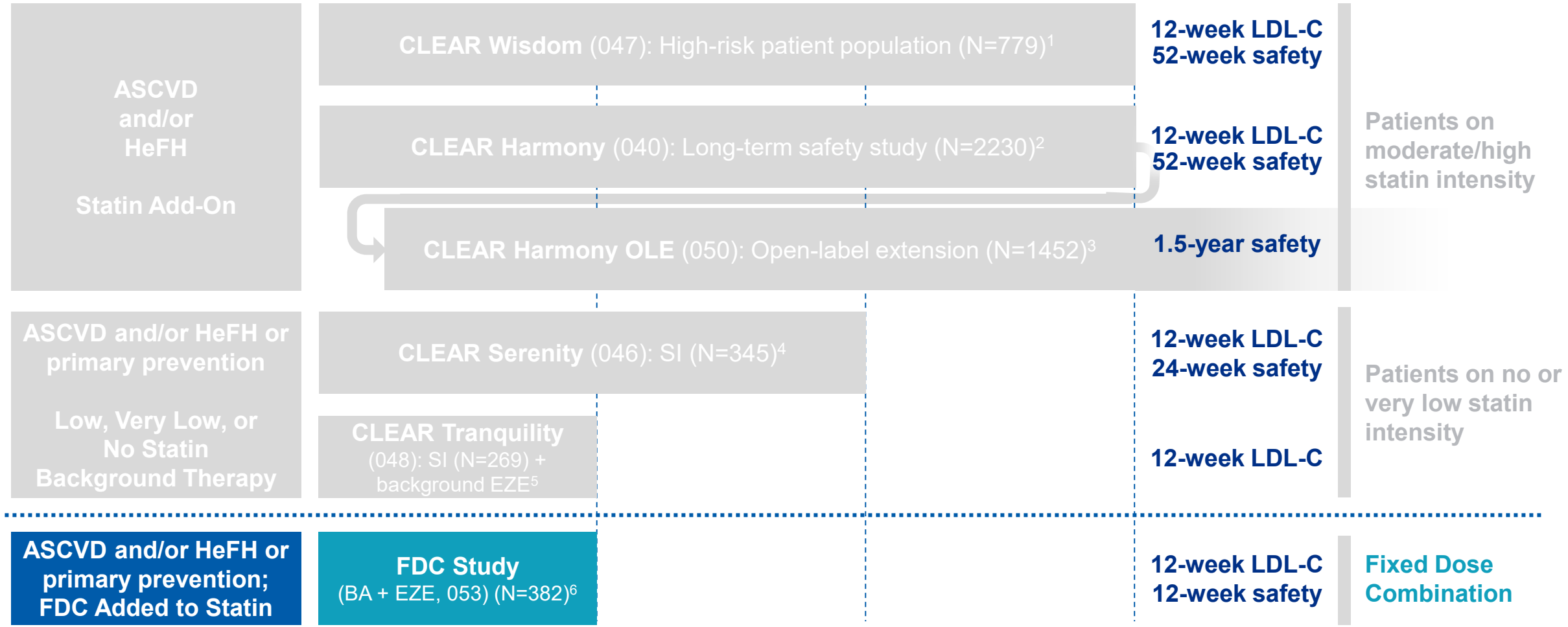
Bempedoic acid lowered LDL-C significantly more than placebo in the pool of patients with statin intolerance



At week 12:
Mean percentage change in LDL-C:
−23.0% in the bempedoic acid group vs +1.5% in the placebo group (**−24.5**; 95% CI, −27.8 to −21.1; *P* < 0.001)
Absolute mean reduction in LDL-C:
−36.5 mg/dL in the bempedoic acid group, +0.6 mg/dL in the placebo group

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

Bempedoic Acid and Ezetimibe: Fixed Dose Combination (FDC)



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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.** ClinicalTrials.gov identifier NCT03067441; **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.

Bempedoic Acid/Ezetimibe FDC

Alone we are strong, together we are stronger[1]

Complementary mechanism of action

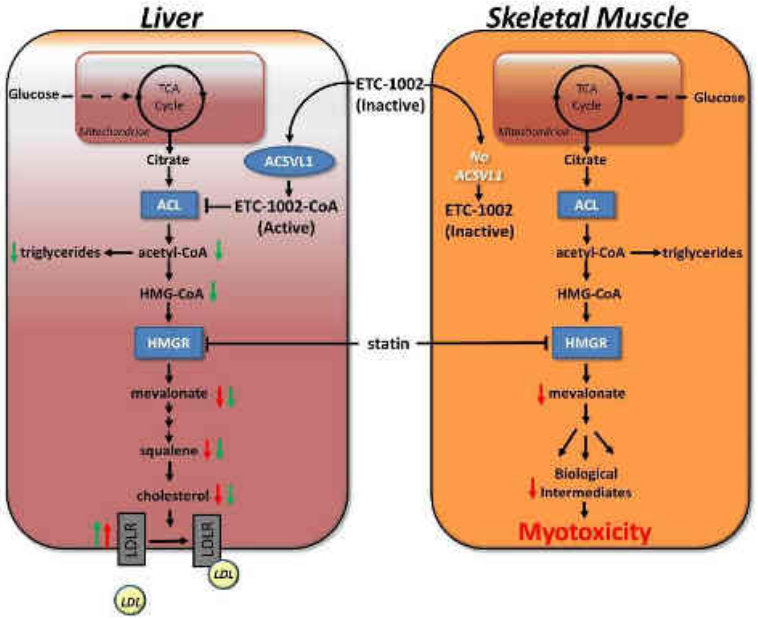
Bempedoic Acid

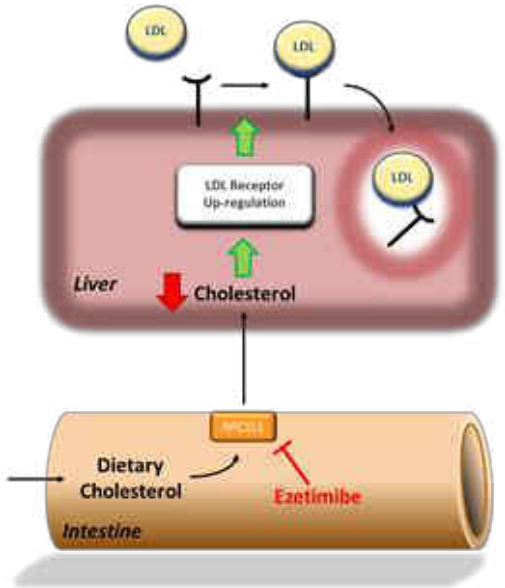
- Inhibits ATP Citrate Lyase (ACL)
  - Active in liver cells
- Acts in the same cholesterol biosynthesis pathway as statins
- **Upregulates LDL receptors**

Ezetimibe

Inhibits NPC1L1 (sterol transporter)

- Primary
  - Inhibition of gastrointestinal cholesterol absorption
- Secondary:
  - **Upregulates LDL receptors**





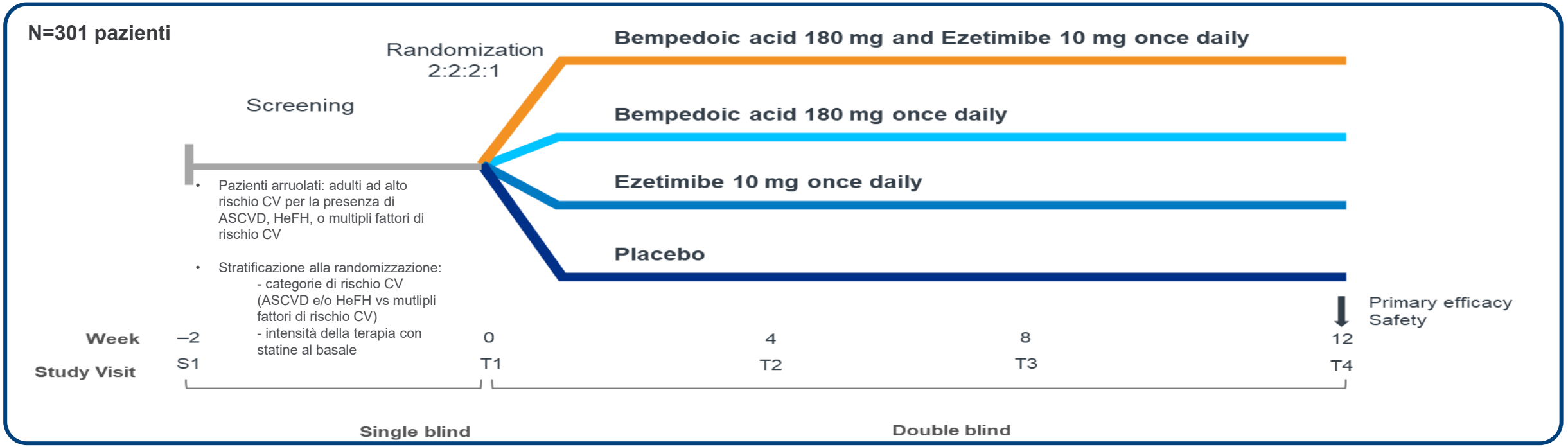
Adapted from Pinkosky et al. Nature Communications. 2016 Nov 28; DOI: 10.1038/ncomms13457; Garcia-Calvo et al. Proc Natl Acad Sci USA. 2005; 102:8132–8137; Ference et al. European Heart Journal. 2017 0, 1-14.

1. Khan S.U. et al. *Eur J Prev Cardiol.* 2020 Apr;27(6):590-592

FDC: Disegno dello studio

Studio di Fase 3, multicentrico, randomizzato, in doppio cieco, controllato con placebo

Obiettivo: Valutare efficacia e sicurezza della combinazione a dose fissa (FDC) di acido bempedoico 180 mg + ezetimibe 10 mg rispetto a placebo, ezetimibe 10 mg da solo, e acido bempedoico 180 mg da solo in pazienti ad alto rischio già in terapia con statine alla massima dose tollerata



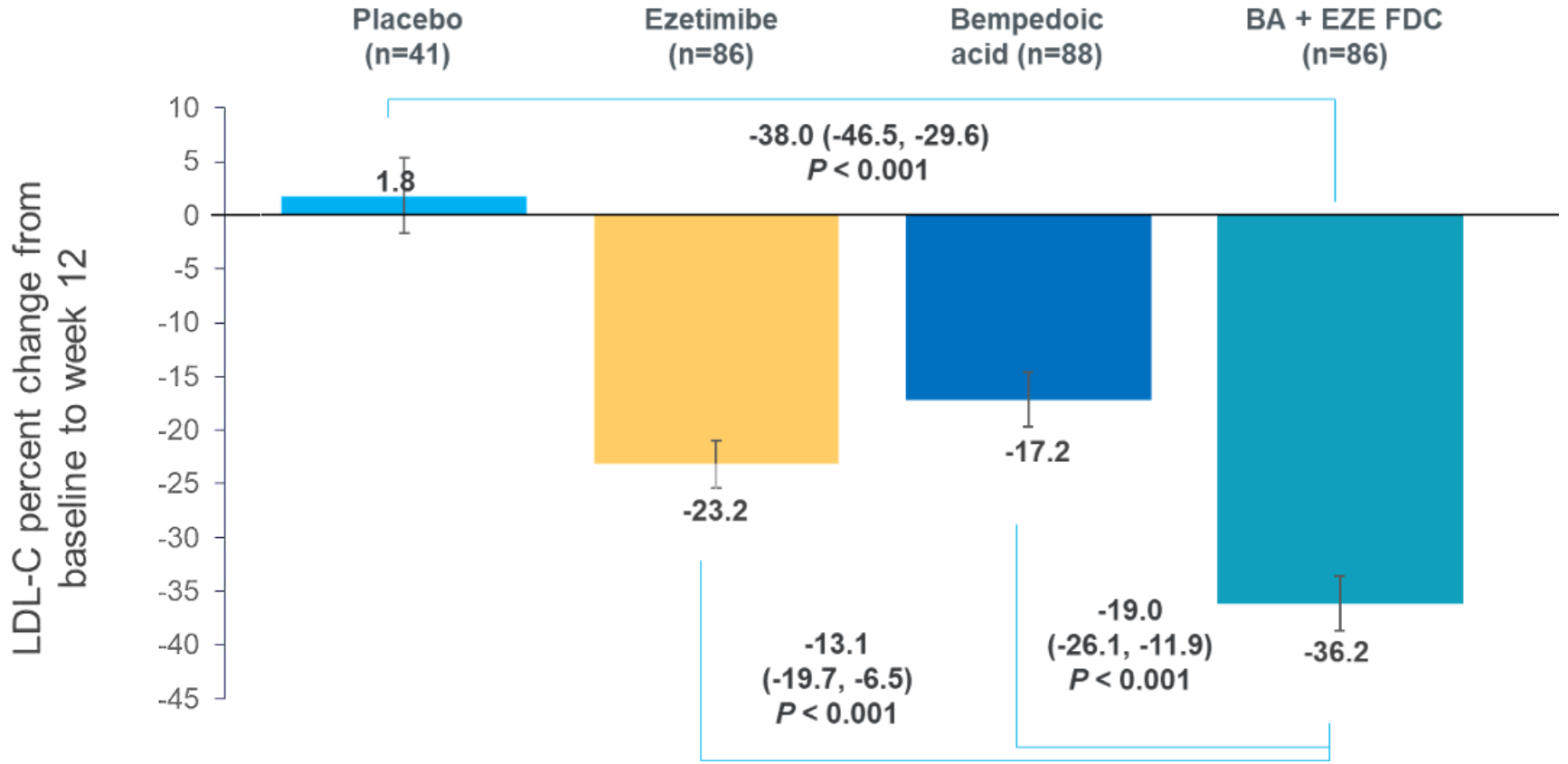
Endpoint primario: variazione percentuale di LDL-C alla settimana 12 rispetto al basale

Randomization was stratified by CVD risk category (ASCVD and/or HeFH vs. multiple CVD risk factors) and baseline statin intensity (high intensity vs. other)

Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.

Bempedoic Acid and Ezetimibe: *FDC study*

Efficacy results: change from baseline to week 12 in LDL-C



38.0% LDL-C

at week 12

- **33.7% in the FDC group had an LDL-C reduction from baseline of 50% or greater;**
- **FDC lowered LDL-C to a degree consistent across subgroups, including all intensities of background statin therapy;**

Post hoc population

BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C: low-density lipoprotein-cholesterol.

Ballantyne et al. Eur J Prev Cardiol 2019 Jul 29:2047487319864671

Bempedoic acid significantly reduces other lipid parameters and biomarkers

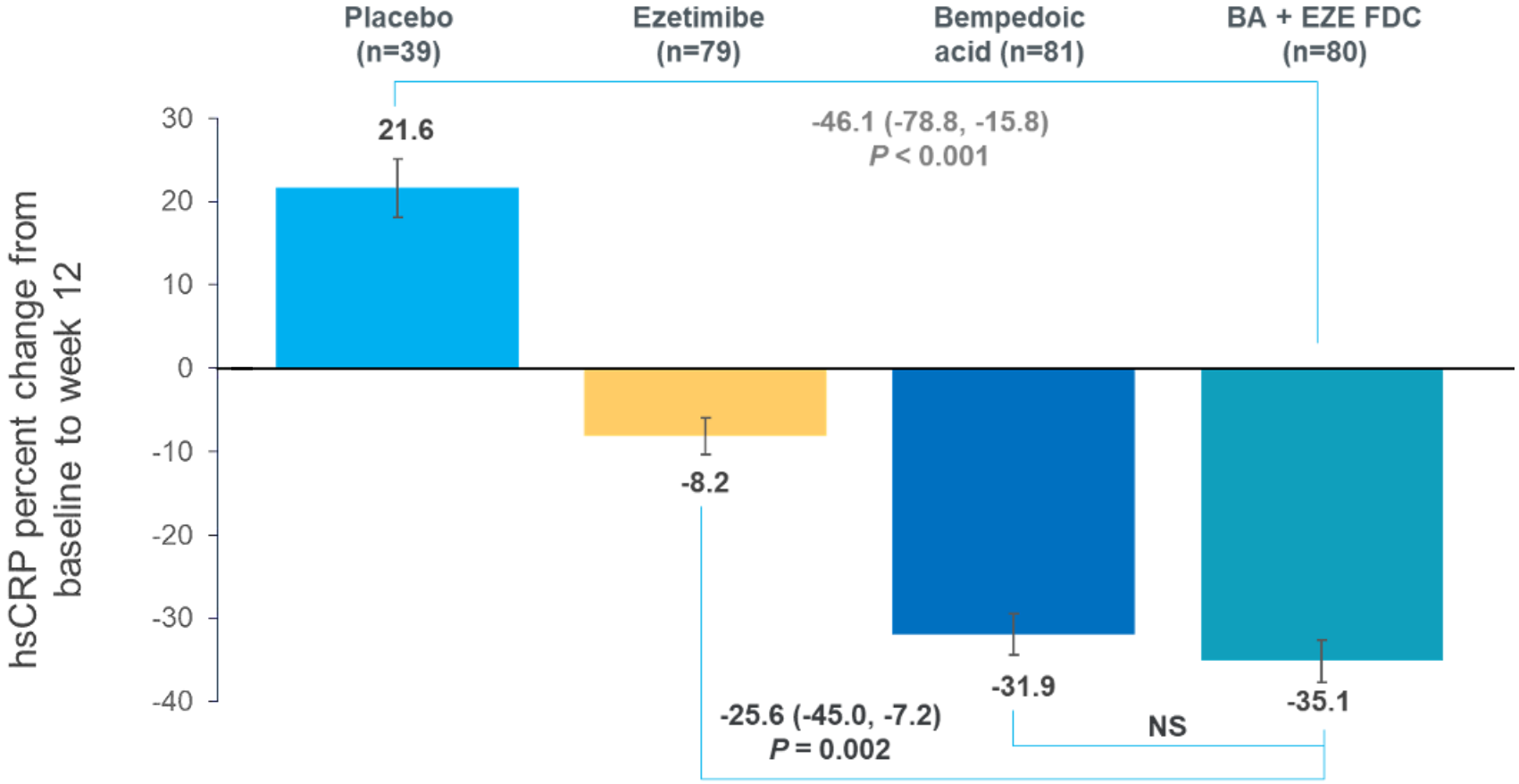
Change at Week 12 From Baseline vs. Placebo (95% CI)	CLEAR Harmony and CLEAR Wisdom Pooled analysis[3] (ASCVD/ HeFH on maximally tolerated statin therapy)	CLEAR Tranquility/ CLEAR Serenity Pooled analysis[3] (Patients with statin intolerance)
% LDL-C reduction	**−17.8** (−19.5 to −16.0) P < 0.001	**−24.5** (−27.8 to −21.1) P < 0.001
% non HDL-C reduction	**−13.1** (−14.7 to −11.6) P < 0.001	**−20.4** (−23.4 to −17.5) P < 0.001
% TC reduction	**−11.1** (−12.2 to −9.9) P < 0.001	**−16.2** (−18.4 to −13.9) P < 0.001
% apo B reduction	**−12.1** (−13.6 to −10.7); P < 0.001	**−16.9** (−19.6 to −14.2) P < 0.001
% hsCRP reduction	**−18.1** (−22.67 to −13.52) P < 0.001	**−27.4** (−36.1 to −18.5) P < 0.001

apo B = apolipoprotein B; CV = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

1. Ray KK, et al. *N Engl J Med*. 2019;380:1022-32; **2.** Anne C. Goldberg et al., *JAMA*, 2019;322(18):1780-1788. doi:10.1001/jama.2019.16585 **3** . *Banach M. et al., Efficacy of bempedoic acid: a pooled analysis of 4 pivotal phase 3 clinical trials*. resented at the American Heart Association Scientific Sessions; 17 Nov 2019. Philadelphia, USA .

Bempedoic Acid and Ezetimibe: *FDC study*

Bempedoic Acid alone as well as in FDC with ezetimibe reduces hsCRP



- **FDC reduced hsCRP by 35.1% compared with an increase of 21.6% in the placebo group (P<0.001) and a reduction of 8.2% in the ezetimibe group (P=0.002);**
- **Bempedoic acid markedly lowers hsCRP regardless of the presence or intensity of background statin therapy;**

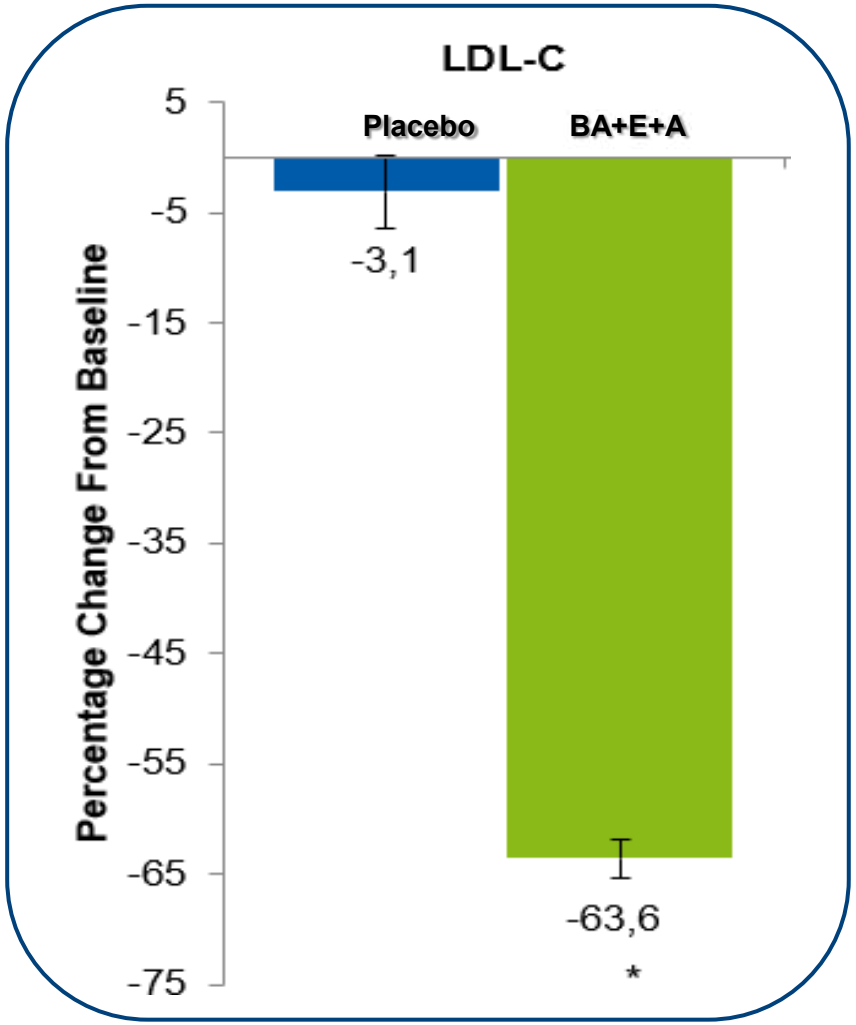
Post hoc population

BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; hsCRP, high-sensitivity C-Reactive Protein; NS, non-significant.

Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27(6):593-603.

Erik S. G. Stroes, Presented at the American College of Cardiology/World Congress of Cardiology , Chicago, March 28 2020

Combination of Bempedoic Acid, Ezetimibe, and Atorvastatin 20 mg
Efficacy of Triple Add-on Therapy



60.5%
LDL-C
at week 6

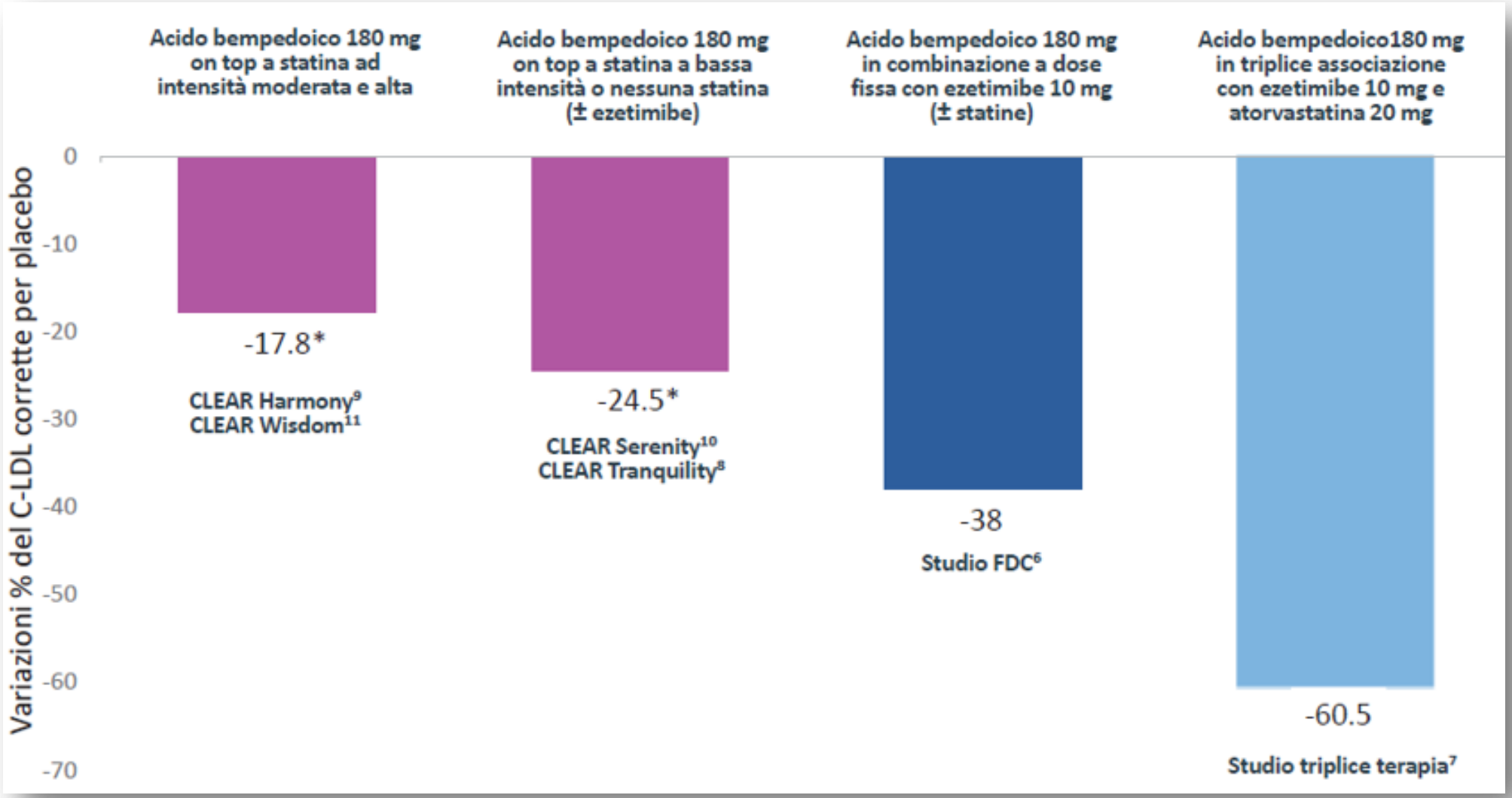
At week 6:

- **90% achieved LDL-C <70 mg/dL;**
- **95% had LDL-C lowered by ≥50%;**
- **58.5% achieved LDL-C <55 mg/dL;**

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

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

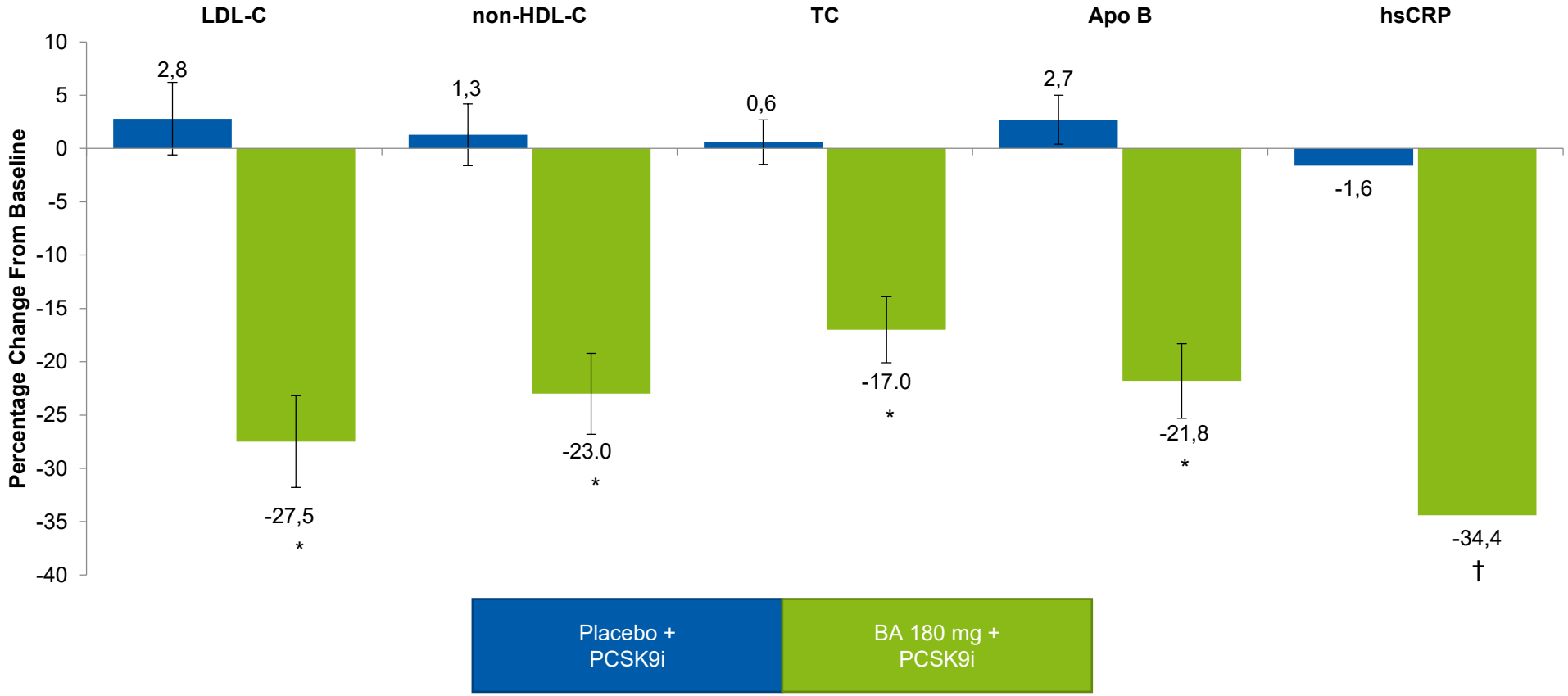
Effetti dell'acido bempedoico sulla riduzione di LDL-C



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

Lipid lowering with bempedoic acid added to a PCSK9i therapy

Lipid and Inflammation Endpoints at Week 8

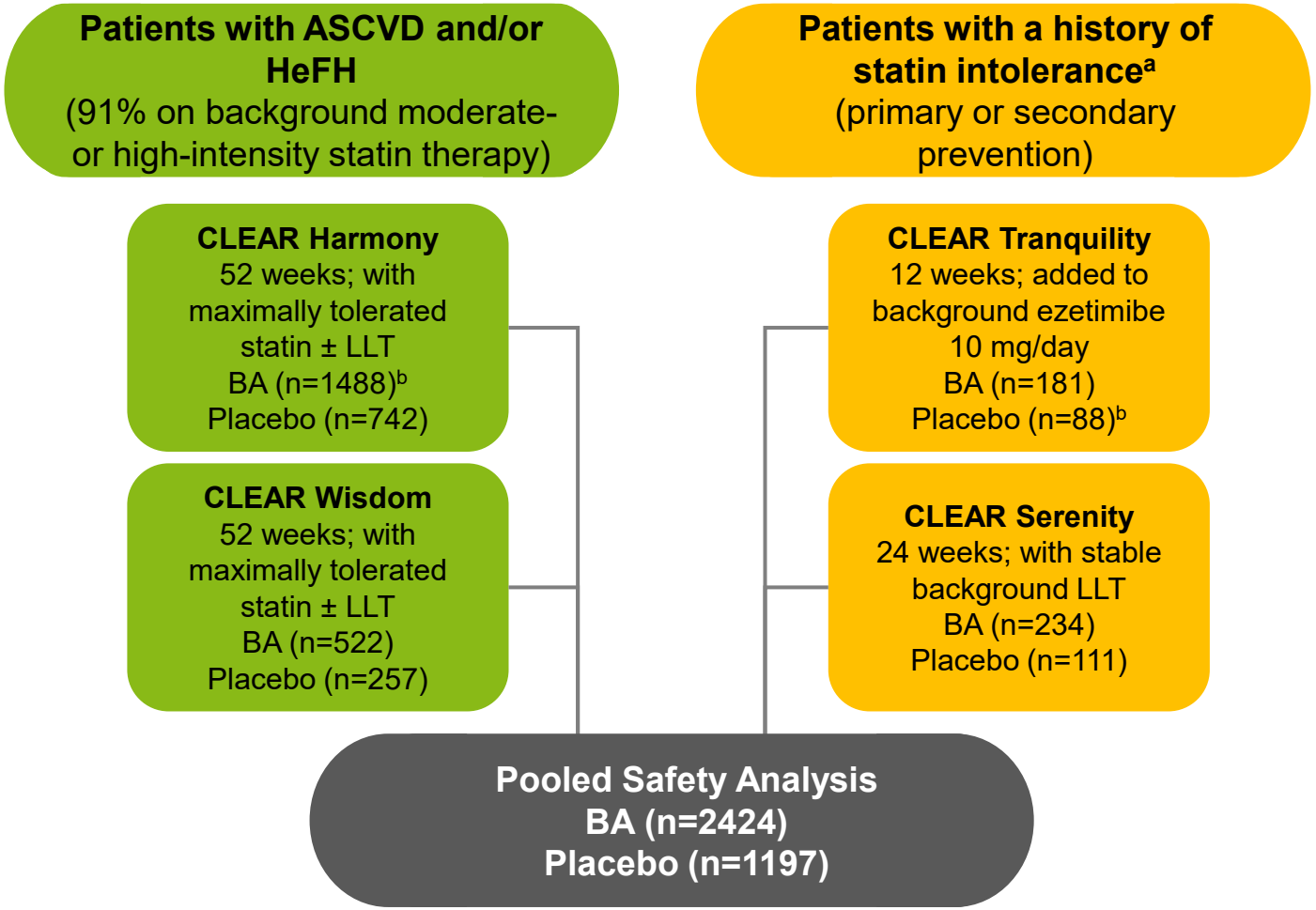


Least squares mean percentage changes from baseline to Month 2. Values are least-squares mean±SE. Data for high-sensitivity C-reactive protein (hsCRP) are medians
*$p < 0.001$; † p=0.029
LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non–high-density lipoprotein cholesterol; TC:total cholesterol;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

Rubino J et al., in preparation

A Combined Safety Analysis in More Than 3,600 Patients Confirmed that Bempedoic Acid is Well Tolerated

Studies included in the pooled analysis



HeFH, heterozygous familial hypercholesterolemia;LLT, lipid lowering therapy

[a]Patients enrolled in CLEAR Tranquility and CLEAR Serenity were permitted to be on stable background low-dose or very low-dose statin therapy.

[b]One patient did not receive any dose of study drug and was excluded from the safety analysis

Adapted from Ballantyne CM et al. Poster presentation presented at the European Society of Cardiology Congress 2019. Paris, France. 3rd September 2019

A Combined Safety Analysis in More Than 3,600 Patients Confirmed that Bempedoic Acid is Well Tolerated

Treatment-Emergent AEs	Bempedoic Acid N=2424, % (n)	Placebo N=1197, % (n)
Overview of AEs in All Patients		
Any AE	**73.1** (1771)	**72.5** (868)
Serious AEs	**14.1** (341)	**13.3** (159)
Discontinuation due to AEs	**11.3** (273)	**7.8** (93)
AE with a fatal outcome[a]	**0.9** (19)	**0.3** (4)
Fatal outcome, Cardiac Disorders SOC	**0.3** (8)	**0.2** (2)
Most common AEs leading to discontinuation		
Myalgia	**1.3** (31)	**1.8** (21)
Muscle spasm	**0.7** (18)	**0.3** (3)
Headache	**0.5** (11)	**0.3** (3)
Diarrhea	**0.5** (11)	**<0.1** (1)
Most common AEs		
Nasopharyngitis	**7.4** (180)	**8.9** (106)
Myalgia	**4.9** (118)	**5.3** (63)
Urinary tract infection	**4.5** (110)	**5.5** (66)
Arthralgia	**4.1** (100)	**4.8** (57)

Additional treatment with bempedoic acid does not lead to an overall increase of side effects vs placebo on top of those associated with existing LLTs

- Total numbers of serious adverse events were similar between treatment groups
- All fatal AEs were judged by the investigator as unrelated to study treatment

AE – adverse event; LLTs = lipid lowering therapies; SOC = system organ class.

1. Adapted from Ballantyne CM et al. Poster presentation presented at the European Society of Cardiology Congress 2019. Paris, France. 3rd September 2019, **2**. Banach M. et al., JAMA Cardiology, published online July 1, 2020. doi:10.1001/jamacardio.2020.2314

Patients on Moderate/High Statin Intensity

CLEAR Harmony Open-label Extension (OLE): Long-term safety results

Parameter	Patients, % (N)		
		Treatment during CLEAR Harmony	
	Overall OLE study (N=1462)	Bempedoic acid (N=970)	Placebo (N=492)
Overview of TEAEs			
Any TEAE	78.2 (1143)	78.1 (758)	78.3 (385)
Serious TEAE	20.5 (299)	20.8 (202)	19.7 (97)
TEAE leading to discontinuation	7.8 (114)	7.1 (69)	9.1 (45)
TEAE with fatal outcome	0.9 (13)	1.0 (10)	0.6 (3)
Most common TEAEs (>4% in any group)			
Nasopharyngitis	8.1 (119)	8.9 (86)	6.7 (33)
Urinary tract infection	6.1 (89)	5.1 (49)	8.1 (40)
Arthralgia	4.9 (71)	4.1 (40)	6.3 (31)
Upper respiratory tract infection	4.6 (67)	5.1 (49)	3.7 (18)
Back pain	3.9 (57)	4.1 (40)	3.5 (17)
Anaemia	3.4 (50)	2.9 (28)	4.5 (22)
Diarrhoea	3.4 (50)	3.1 (30)	4.1 (20)

AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA), version 20.1. TEAEs are defined as AEs that began or worsened in severity after the first dose of IMP until 30 days after last dose in the OLE study. Patients were counted only once for highest severity, once for most extreme outcome, once for most extreme action taken regarding IMP, and once for strongest relationship to investigational drug product. IMP, investigational medicinal product; OLE, open-label extension.

Ballantyne et al. Poster presented virtually at the European Society of Cardiology Congress, 29 August – 1 September 2020.

A Combined Safety Analysis in More Than 3,600 Patients Confirmed that Bempedoic Acid is Well Tolerated

Treatment-Emergent AEs	Bempedoic Acid N=2424, % (n)	Placebo N=1197, % (n)	*p*
Muscular weakness	0.5 (13)	0.6 (7)	0.82
New-onset diabetes/hyperglycemia	4.0 (96)	5.6 (67)	0.03
Blood uric acid increased	2.1 (51)	0.5 (6)	< 0.001
Hyperuricemia	1.7 (40)	0.6 (7)	0.007
Gout	1.4 (33)	0.4 (5)	0.008
Blood creatinine increased	0.8 (19)	0.3 (4)	0.12
Glomerular filtration rate decreased	0.7 (16)	<0.1 (1)	0.02
Hepatic enzyme elevation	2.8 (67)	1.3 (15)	0.004
> 3 times the upper reference limit	0.7 (18)	0.3 (3)	0.10
> 5 times the upper reference limit	0.2 (6)	0.2 (2)	> 0.99
Neurocognitive disorderse	0.7 (16)	0.8 (9)	0.83

Adverse events of special interest

- The incidences of myalgia and muscle weakness were similar between treatment groups in patients receiving background high-intensity statin therapy
- Modest changes in creatine, uric acid and occurred early, were stable, and were reversible after drug discontinuation
- Gout occurred more frequently with bempedoic acid compared with placebo, although the incidence was low in both treatment groups and events occurred primarily in patients with a prior diagnosis of gout

AE – adverse event; LLTs = lipid lowering therapies.

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

Incidence of Gout by Baseline Uric Acid Levels and by Medical History of Gout

- The rate of gout per 100 person-years was 1.6 with bempedoic acid and 0.5 with placebo.
- The incidence of gout was greater in patients who had a medical history of gout vs those with no medical history of gout (bempedoic acid, 11.0% vs 0.8%; placebo, 2.9% vs 0.3%).
- Among the **patients with a history of gout**, those with elevated uric acid levels at baseline had a greater incidence of gout vs those with uric acid levels within normal limits (bempedoic acid, 23.1% vs 5.7%; placebo, 9.5% vs 0%).
- **For those patients with no history of gout and normal uric acid levels at baseline, gout incidence was similar in the bempedoic acid arm compared with placebo (0.3% vs 0.2%, respectively)**

Parameter	TEAE of Gout		No TEAE of Gout	
	Bempedoic Acid	Placebo	Bempedoic Acid	Placebo
Patients with medical history of gout, % (n/total)	**11.0 (14/127)**	**2.9 (2/69)**	**89.0 (113/127)**	**97.1 (67/69)**
Uric acid levels at baseline, %[a] (n)				
≤ ULN	5.7 (5)	0	94.3 (83)	100 (48)
> ULN	23.1 (9)	9.5 (2)	76.9 (30)	90.5 (19)
Patients without medical history of gout, % (n/total)	**0.8 (19/2297)**	**0.3 (3/1128)**	**99.2 (2278/2297)**	**99.7 (1125/1128)**
Uric acid levels at baseline, %[a] (n)				
≤ ULN	0.3 (5)	0.2 (2)	99.7 (1841)	99.8 (899)
> ULN	3.1 (14)	0.4 (1)	96.9 (437)	99.6 (226)

[a]Percentages are calculated based on the total number of patients with or without medical history of gout in each treatment group. TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Bays HE et al. J Clin Lipidol. Published 1 September 2020. Article in press.

Rationale and design of the CLEAR-outcomes trial: Evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance

Nicholls SJ, Lincoff AM, Bays HE, Cho L, Grobbee DE, Kastelein JJP, Libby P, Moriarty PM, Plutzky J, Ray KK, Thompson PD, Sasiela W, Mason D, McCluskey J, Davey D, Wolski K, Nissen SE

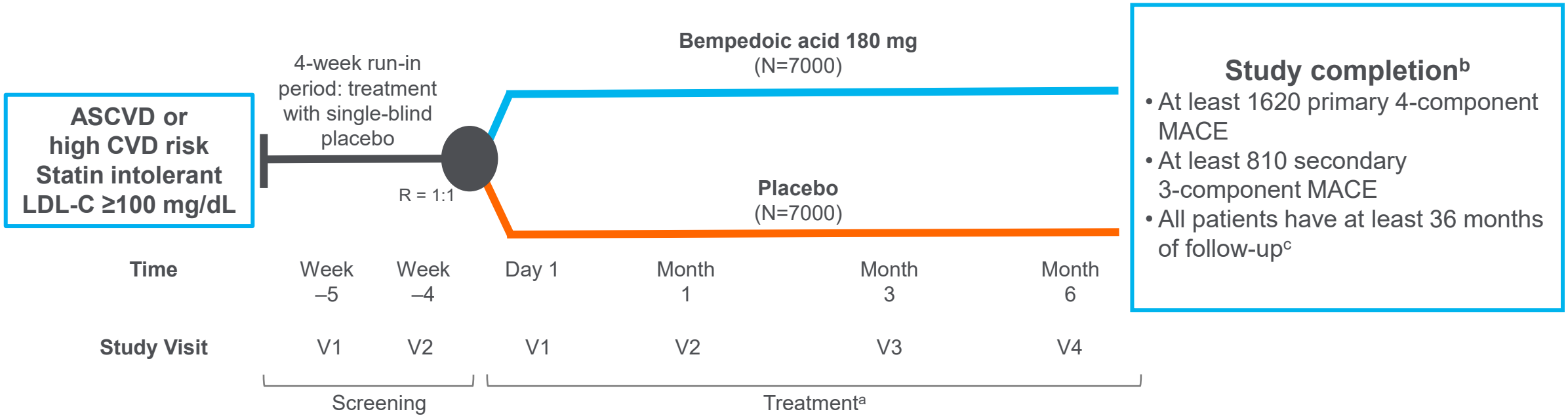
American Heart Journal, 2020; accepted for publication; https://doi.org/10.1016/j.ahj.2020.10.060

clinicaltrials.gov NCT02993406

The CLEAR Outcomes Trial: evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance

Study Design

A randomized, double-blind, placebo-controlled, event-driven trial



Primary efficacy endpoint: Time to first occurrence of any component of the major adverse cardiovascular event (MACE), including cardiovascular death, nonfatal MI, nonfatal stroke, or coronary revascularization

[a]Alternating phone contact and clinic visits every 3 months thereafter. [b] An independent, central clinical events committee, blinded to treatment status, will adjudicate all reported clinical events. [c]Follow-up every 6 months until the end of study. MACE, major adverse cardiovascular event.

Nicholls et al. Am Heart J, 2020.

The CLEAR Outcomes Trial: evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance

Patients Characteristics

Parameter	Cohort (N=14014)
Age, years	65.5 ± 9.0
Females, %	48.2
Caucasian, %	91.2
Body mass index, kg/m²	29.9 ± 5.2
Diabetes, %	42.8
Hypertension, %	84.2
Primary prevention	
Reynolds risk score >30% or SCORE >7.5%	12.9
Coronary calcium >400 Agatston units, %	1.0
Diabetes aged >65 years (women) or >60 years (men), %	17.1
Secondary prevention	
Coronary artery disease, %	50.7
Peripheral artery disease, %	11.6
Atherosclerotic cerebrovascular disease, %	14.5

Results expressed as either Mean ± standard deviation or median (interquartile range) for continuous parameter and percentage for categorical parameters.

Nicholls et al. Am Heart J. 2020.

The CLEAR Outcomes Trial: evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance

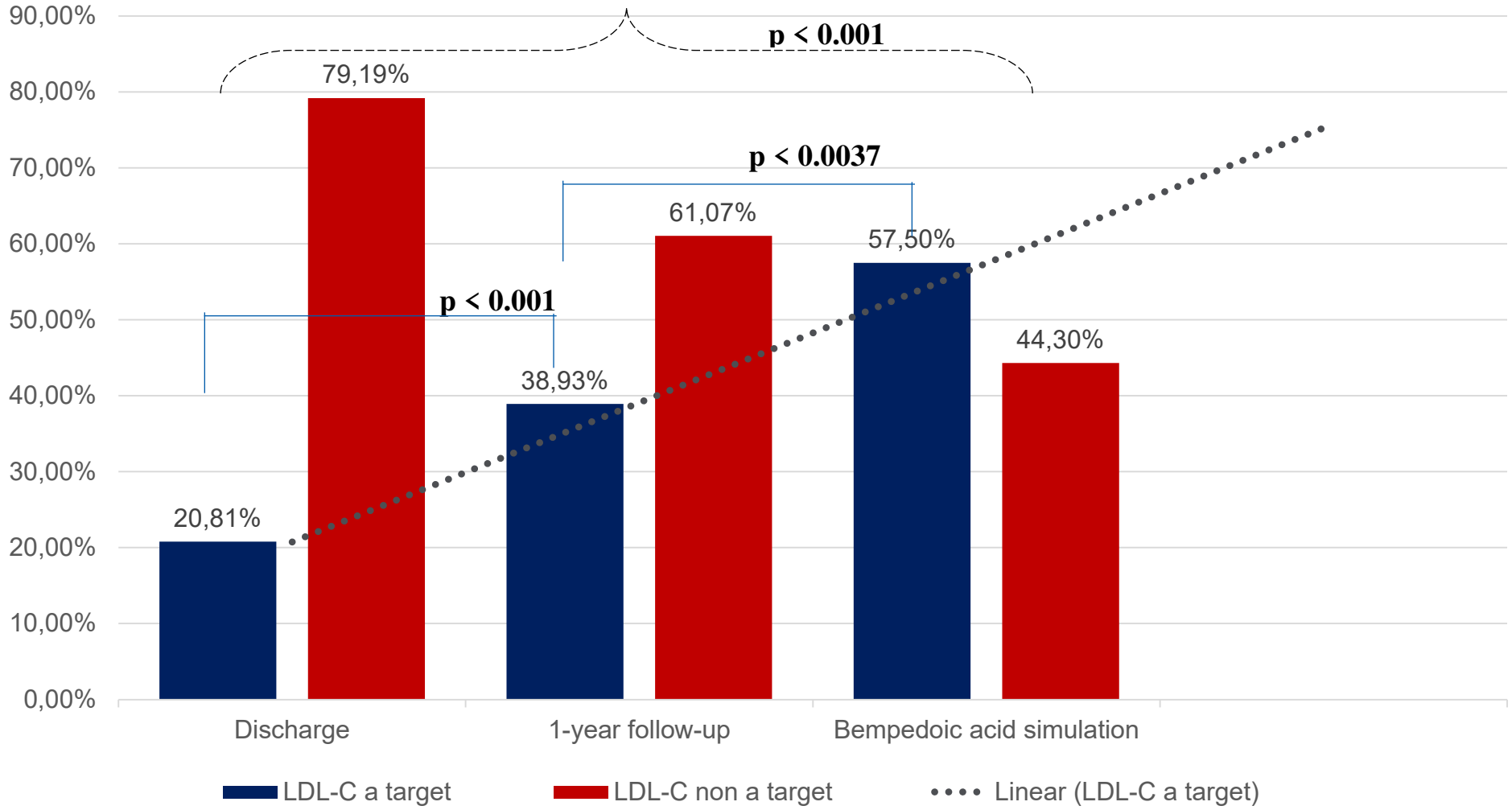
Patients Characteristics

Parameter	Cohort (N=14014)
Lipid lowering therapy use	
Very low dose statin, %	22.4
Ezetimibe, %	11.8
PCSK9 inhibitor, %	0.6
Total cholesterol, mg/dL	223.4 ± 40.9
LDL cholesterol, mg/dL	139.0 ± 35.1
<130 mg/dL, %	44.1
130 - 160 mg/dL, %	31.9
≥160 mg/dL	24.0
HDL cholesterol, mg/dL	49.6 ± 13.3
Triglycerides, mg/dL	159.0 (118.0, 215.5)
hsCRP, mg/L	2.3 (1.2, 4.5)

Results expressed as either Mean ± standard deviation or median (interquartile range) for continuous parameter and percentage for categorical parameters.

HDL, high-density lipoprotein; hsCRP, highsensitivity; C-reactive protein; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9.
Nicholls et al. Am Heart J, 2020.

Effect of simulation with BEMPEDOIC ACID on LDL-C target achievement in high risk population



Cesaro A, Calabro P - unpublished data - confidential

Acido bempedoico rappresenta una nuova opzione terapeutica per i pazienti a rischio alto o molto alto con valori non controllati di LDL-C

r ate

Dal 17 al 28%
LDL-C con acid

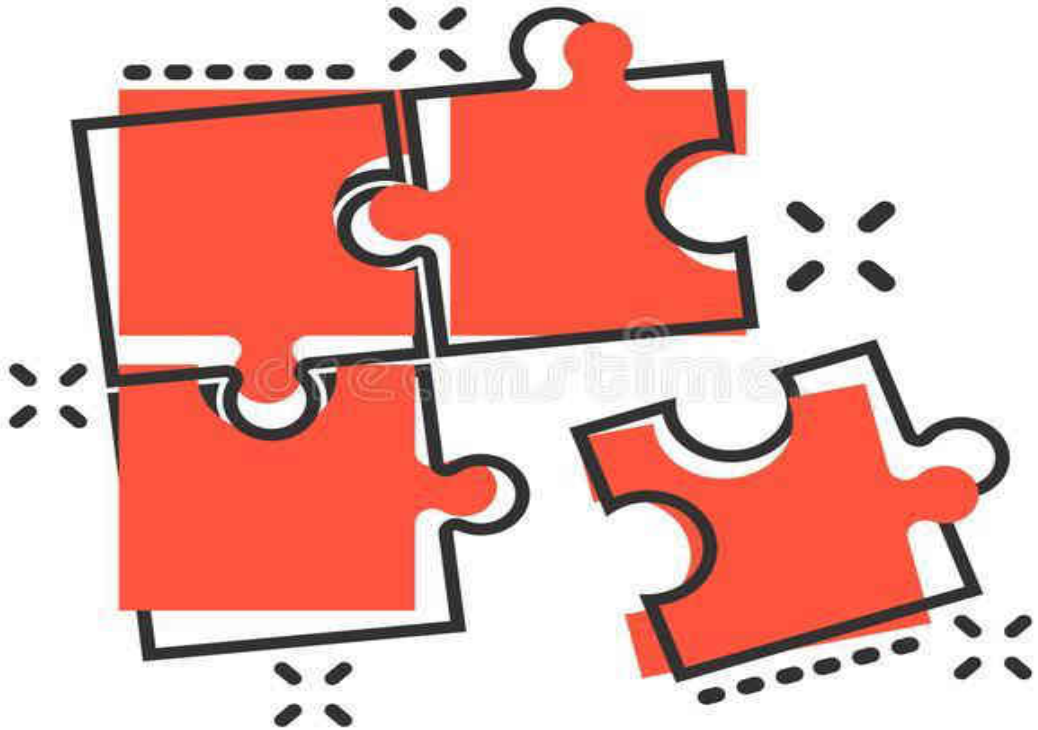
ggiuntivo con acido
on top alle terapie
sottostanti non porta
o generale di effetti
ali vs placebo

Riduzioni signific
placebo in aggiu
dosi tollerate c
ipolipemiz

urezza combinata
3.600 pazienti

38% di riduzi
con la combinazio
bempedoic

empedoico e la
binazione
doico/ezetimibe
ben tollerati



Grazie…

arturo.cesaro@unicampania.it