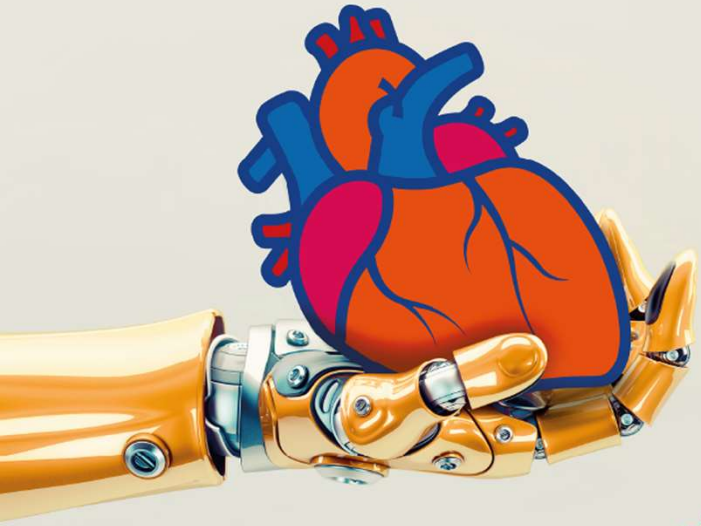


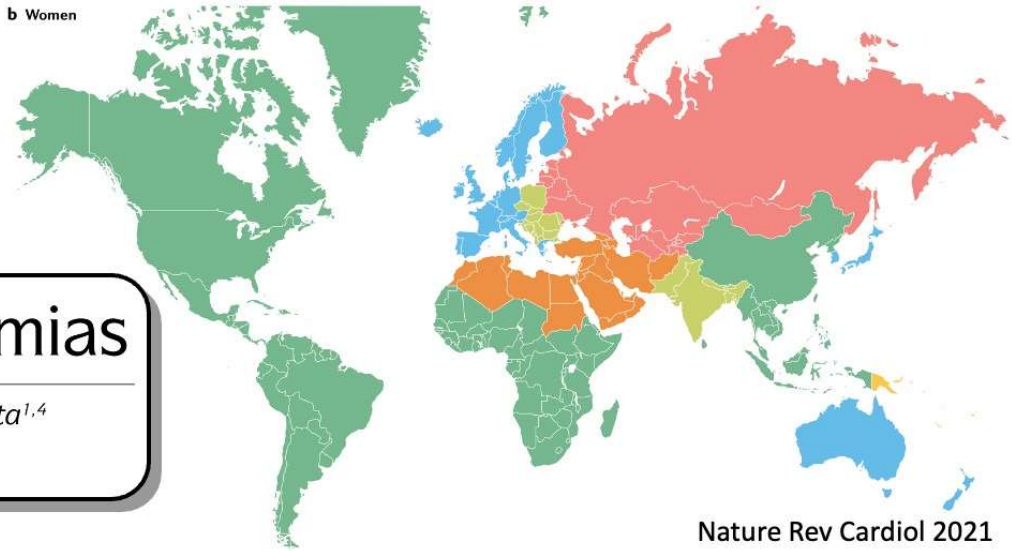
17° Meeting
CardioLucca
Heart Brings Heart 2023
Lucca, 22-24 Giugno 2023
Centro Congressi Auditorium San Francesco

Giovambattista Desideri
UO Geriatria e Lungodegenza
Dipartimento MESVA
Università degli Studi di L'Aquila

Strategie di prevenzione primaria dell'intolleranza alle statine

Age- standardized death rates per 100,000 of the general population

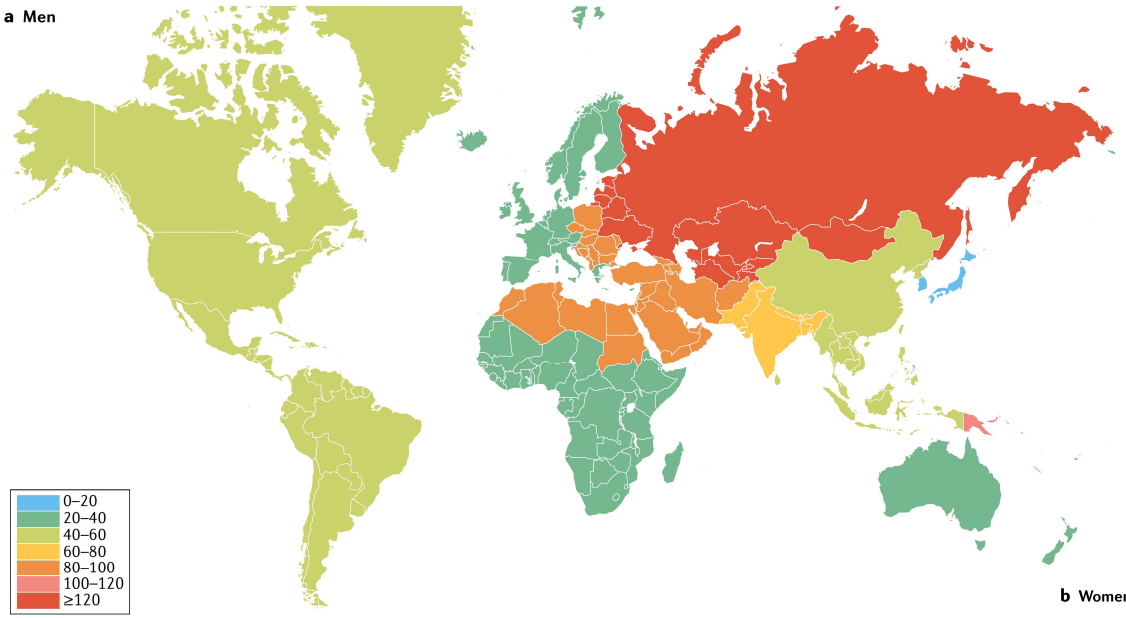
Global death rates from Ischaemic Heart Disease attributable to dyslipidaemia



Global epidemiology of dyslipidaemias

Angela Pirillo[1,2], *Manuela Casula*[2,3], *Elena Olmastroni*[3], *Giuseppe D. Norata*[1,4] *and Alberico L. Catapano*[2,4]✉

Nature Rev Cardiol 2021



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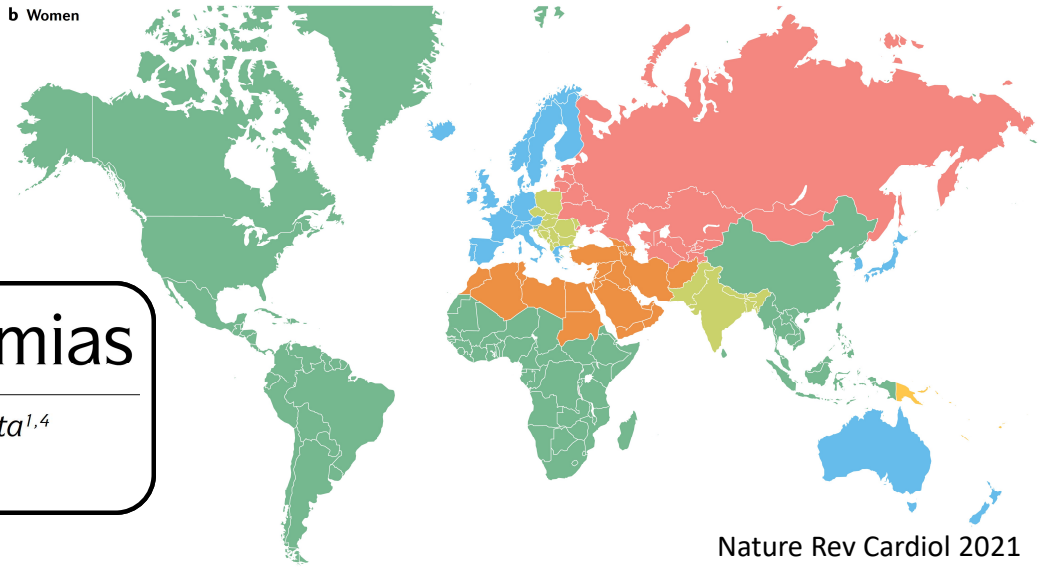

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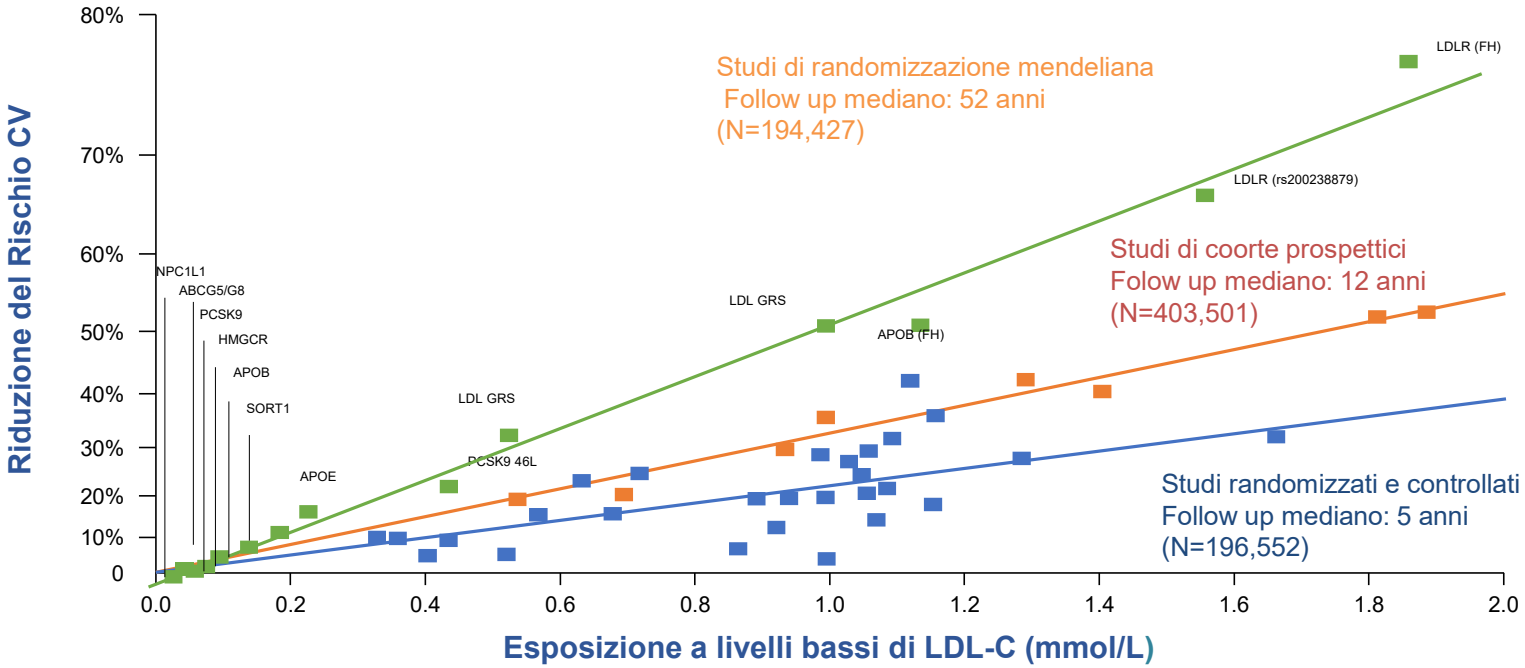
Nature Rev Cardiol 2021

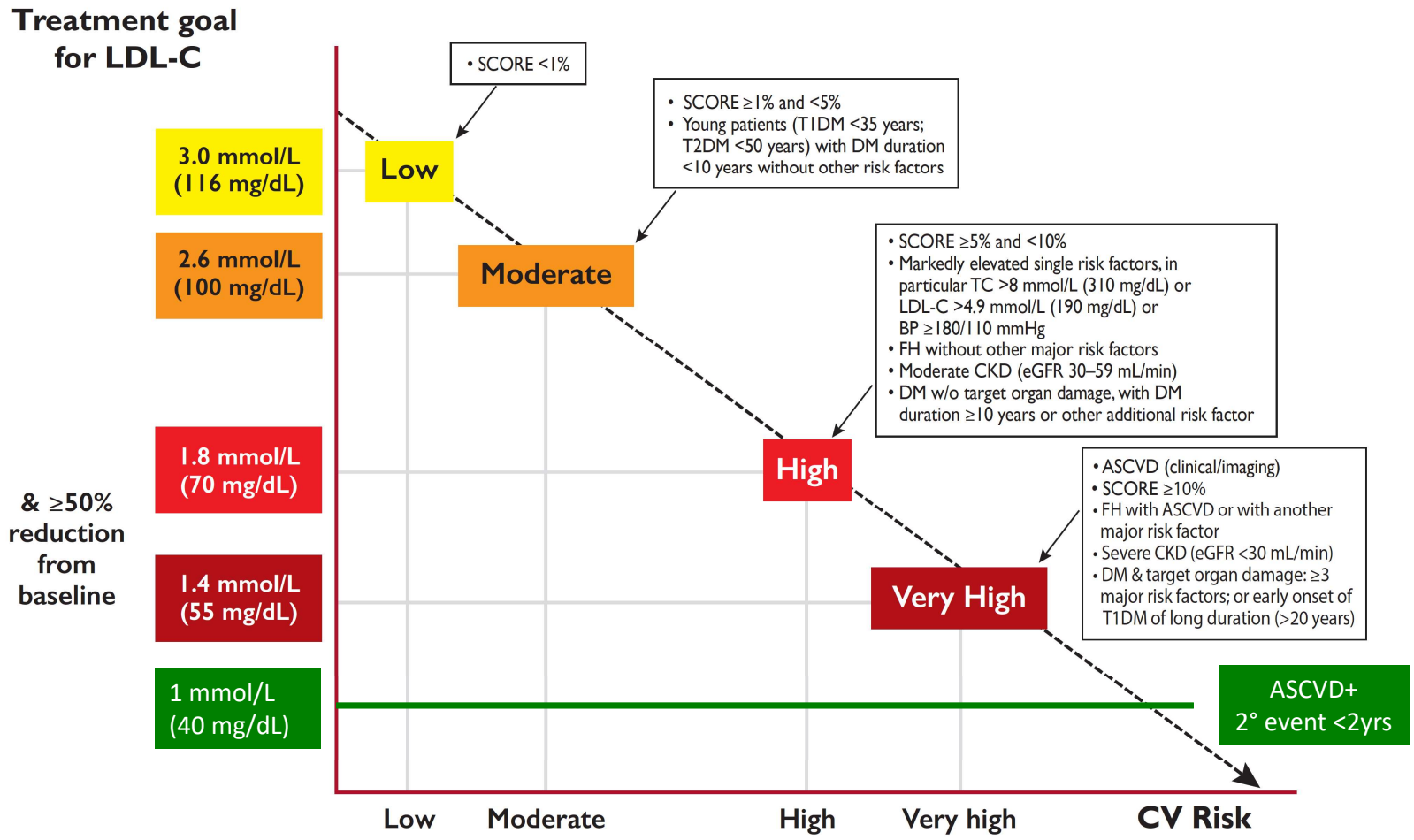
Associazione dei livelli LDL con il rischio CV



THE LOWER, THE EARLIER, THE LONGER

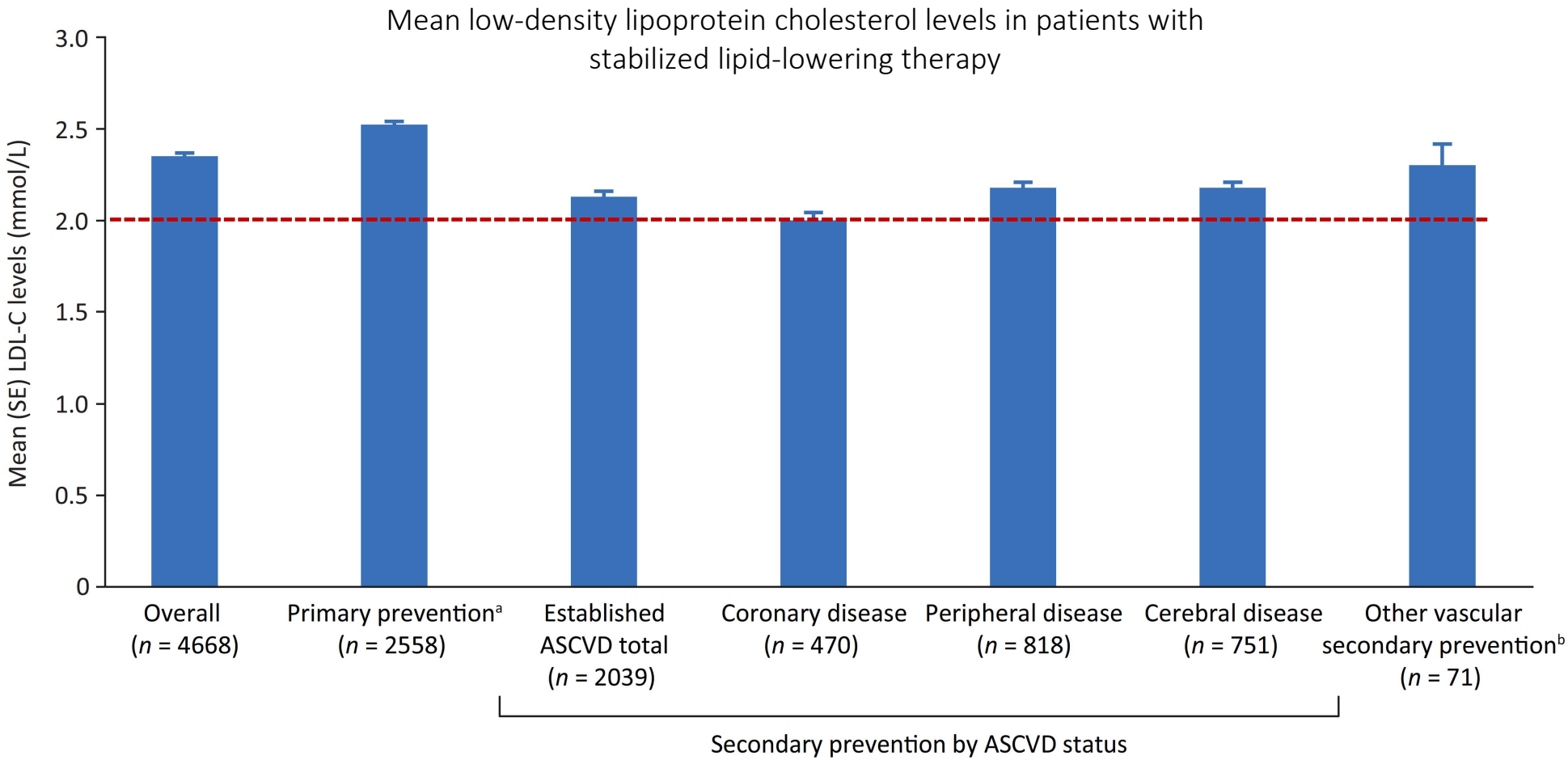
Ference BA et al. Eur Heart J. 2017.

Treatment goals for low-density lipoprotein cholesterol across categories of total cardiovascular disease risk.



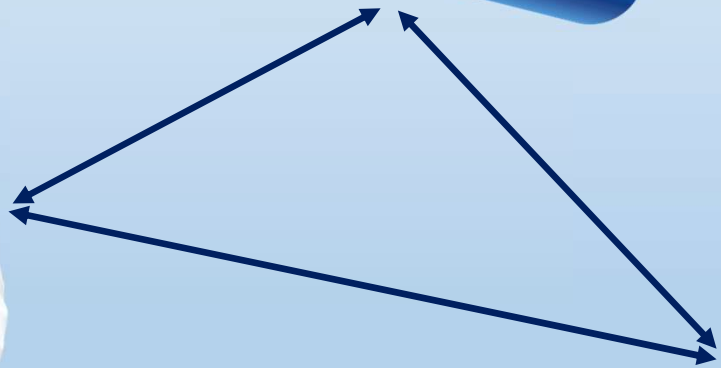
Mach F et al. European Heart Journal (2020) 41, 111188

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DAVINCI study



Ray KK et al. Eur J Prev Cardiol 2021

Gestione del paziente con ipercolesterolemia : vecchi problemi e nuove soluzioni terapeutiche



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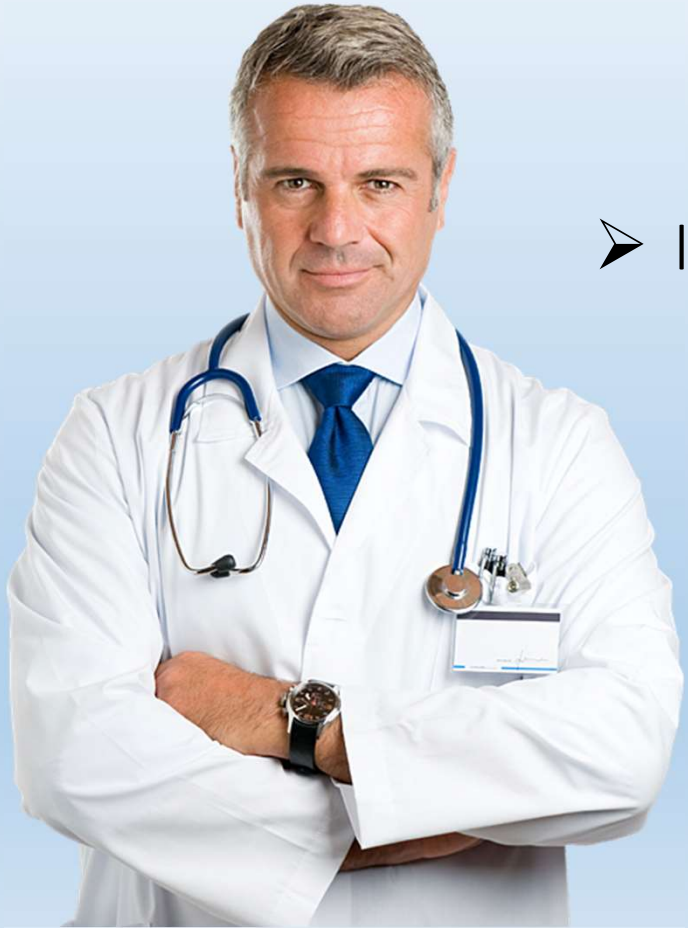
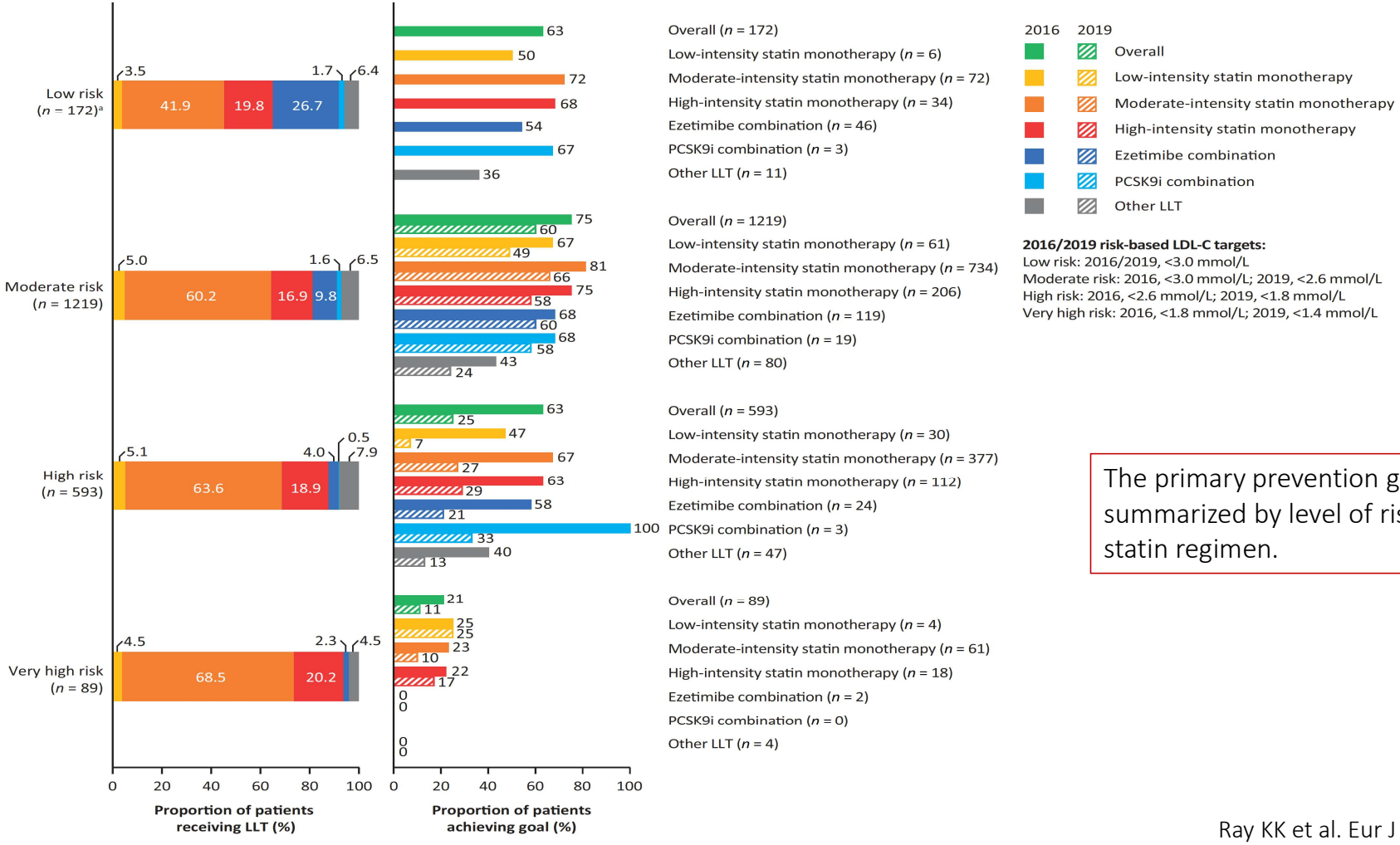


- Inerzia terapeutica da parte del medico nel perseguire il raggiungimento dei target terapeutici

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DAVINCI study



The primary prevention group summarized by level of risk and statin regimen.

Ray KK et al. Eur J Prev Cardiol 2021

Gestione del paziente con ipercolesterolemia : **vecchi problemi** e nuove soluzioni terapeutiche

- Inadeguata aderenza da parte del paziente alle prescrizioni terapeutiche

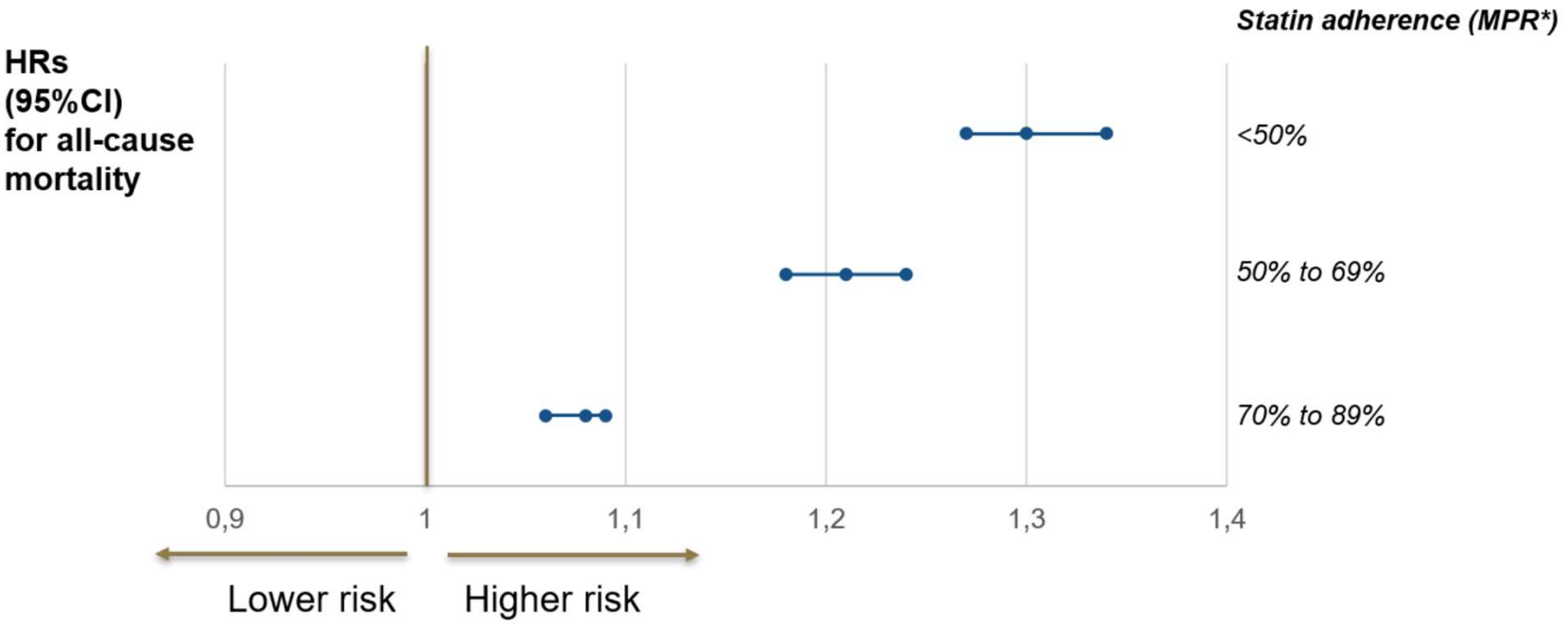
Aderenza e persistenza al trattamento con farmaci ipolipemizzanti

	Totale N=209.595	Nord N=85.084	Centro N=42.365	Sud N=82.146
Bassa aderenza al trattamento con ipolipemizzanti (%)*†				
45-54 anni	15,0	12,6	14,5	17,2
55-64 anni	14,8	12,4	14,6	17,2
65-74 anni	15,9	14,2	15,6	17,9
75-84 anni	16,9	15,4	16,6	19,0
≥ 85 anni	18,0	16,4	18,0	19,8
Donne	17,8	15,8	17,8	19,8
Uomini	13,5	11,9	13,0	15,5
Totale	**15,8**	**13,9**	**15,6**	**17,9**
Alta aderenza al trattamento con ipolipemizzanti (%)*†				
45-54 anni	41,2	43,8	43,0	38,2
55-64 anni	42,2	45,3	43,2	38,9
65-74 anni	41,0	43,2	41,9	38,4
75-84 anni	41,3	43,5	41,6	38,3
≥ 85 anni	41,9	43,9	43,5	38,5
Donne	36,3	38,6	37,1	33,6
Uomini	47,3	49,5	48,5	44,3
Totale	**41,5**	**43,9**	**42,4**	**38,5**

Persistenza (%)	3 mesi	6 mesi	12 mesi
Uomini	71.3	55.0	43.1
Donne	75.9	61.7	51.5

Long term statin adherence inversely associated with all-cause mortality in n Patients With Atherosclerotic Cardiovascular Disease

A retrospective cohort study using data from the **VA Health System** (N=347.104)

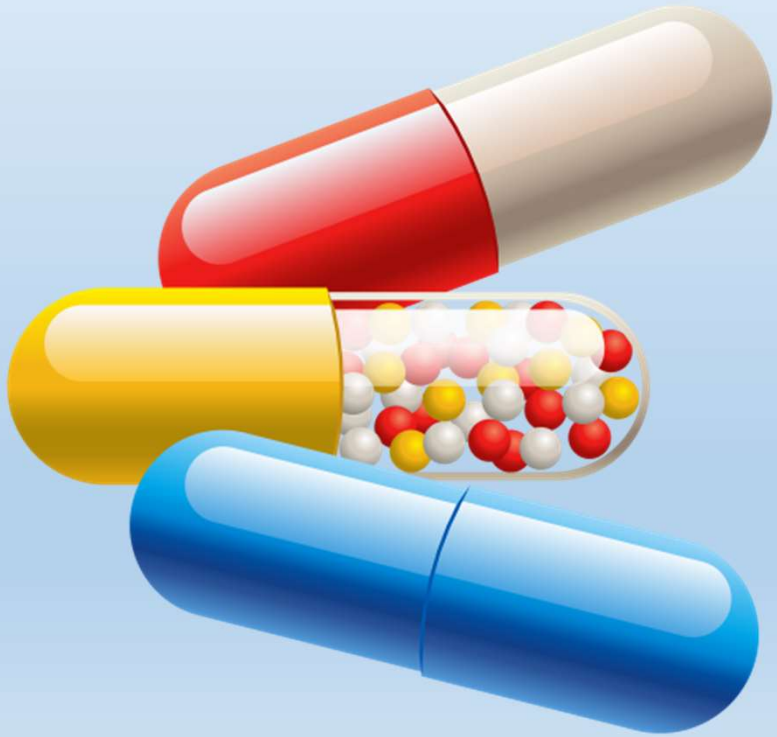


ASCVD: atherosclerotic cardiovascular disease
**MPR (medication possession rate): The number of days of outpatient statin supplied during a 12-month period divided by the number of days that the patient was not hospitalized and alive during the 12-month period*

Rodriguez F et al. JAMA Cardiol. 2019 Mar; 4(3): 206–213.

Gestione del paziente con ipercolesterolemia : **vecchi problemi** e nuove soluzioni terapeutiche

- Strategie terapeutiche non completamente adeguate (potenza, tollerabilità, semplicità)



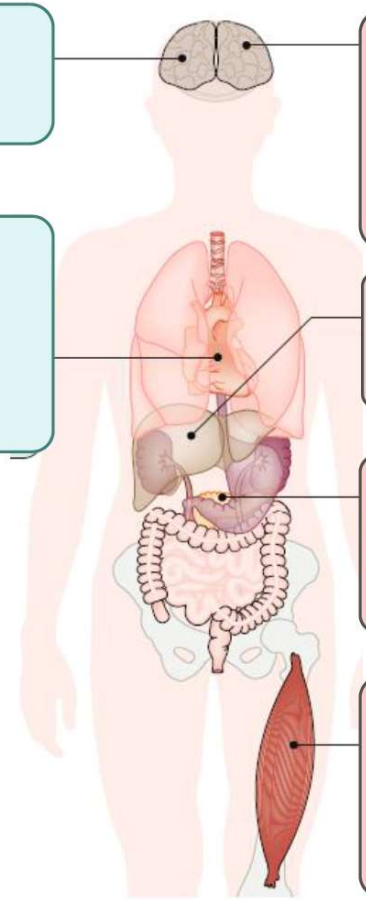
Benefits vs Risks of Statin Therapy

Benefits

Risk of stroke
- ↓ 16% for total stroke
- ↓ 21% for ischaemic stroke

Risk of major coronary events
- ↓ 27% for non-fatal MI
- ↓ 20% for CHD death

Risk of revascularisation procedures
- ↓ 25%



Adverse effects

Cognitive dysfunction
- No evidence

Risk of haemorrhagic stroke
- Small increase in individuals with prior haemorrhagic stroke in one study*

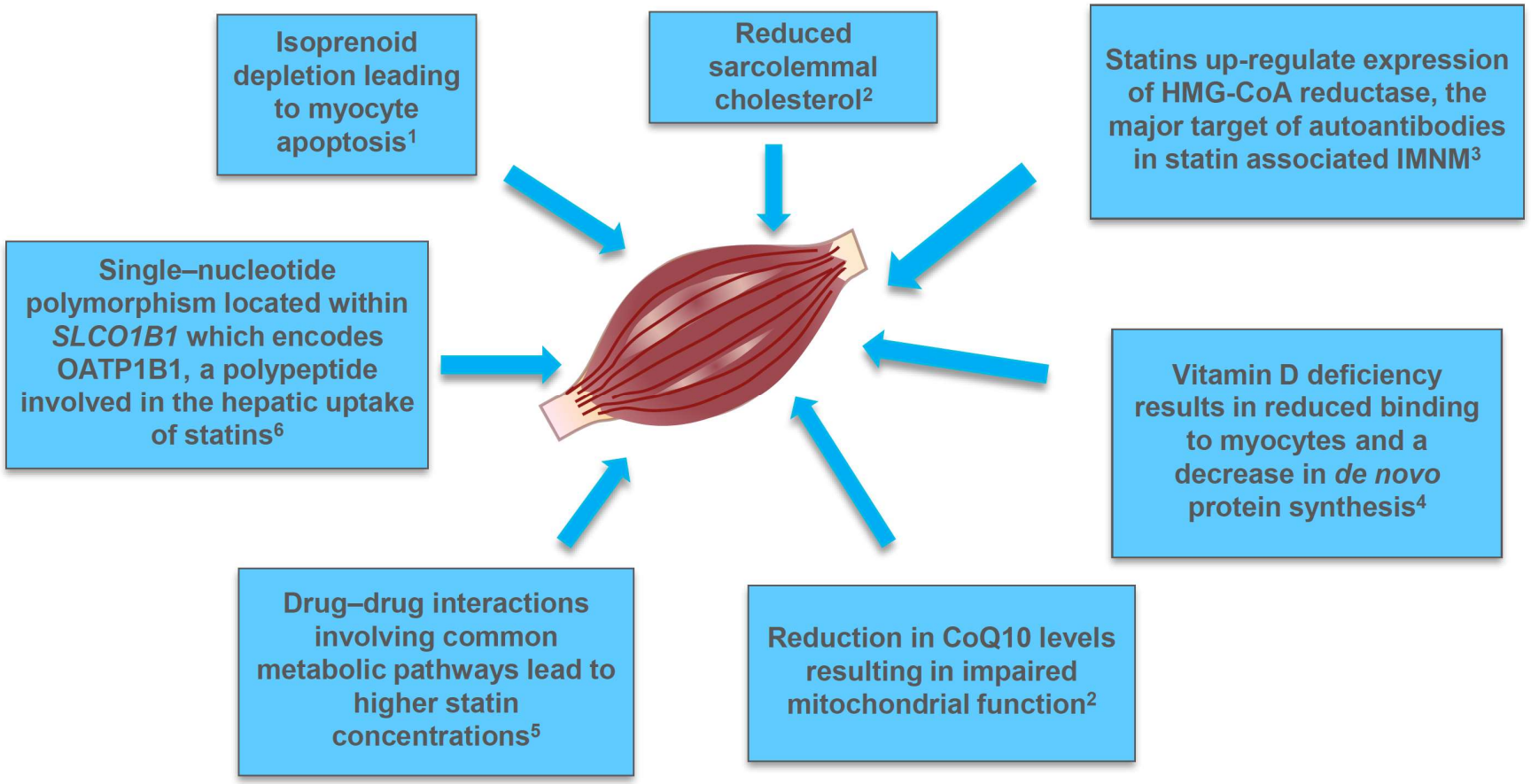
Liver symptoms/diseases
- Clinically insignificant liver enzyme elevations
- Incidence of liver failure: 1/100,000

Incidence of new-onset diabetes mellitus
- Moderate-intensity statin therapy: 0.1% per year
- High-intensity statin therapy: 0.2% per year

Incidence of muscle symptoms/diseases
- SAMS: 10-29% in observational studies and 1-2% in RCTs
- Myopathy: 1/1000
- Rhabdomyolysis: 1/10,000

**Not confirmed by any other studies.*
CHD, coronaryheartdisease; MI, myocardialinfarction;
RCT, randomisedcontrolledtrial; SAMS, statin-associatedmuscle symptoms.
Adaptedfrom AdhyaruBB, Jacobson TA. NatRevCardiol2018;15(12):757-69.

Possible Mechanisms of Statin-Associated Myopathy



**This leads to higher statin concentrations in muscle cells. CoQ10, coenzymeQ10 (ubiquinone); OATP1B1; organicanion-transportingpolypeptide1B1; SLCO1B1, solute carrier organicaniontransporterfamily member1B1; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; IMNM, immune-mediated necrotizing myopathy 1. Arca M and Pigna G. DiabetesMetabSyndrObes. 2011:4;155–166; 2. Di Stasi et al. PhysTher. 2010:90;1530–1542; 3. MammenAL et al. ArthritisRheum. 2011;63:713–721; 4. Goldstein MR et al. QJM. 2009;102:890–891; 5. Ballantyne CM et al. Arch InternMed. 2003;163:553–564; 6. SEARCH Collaborative Group. N Eng J Med. 2008;359:789–799;*

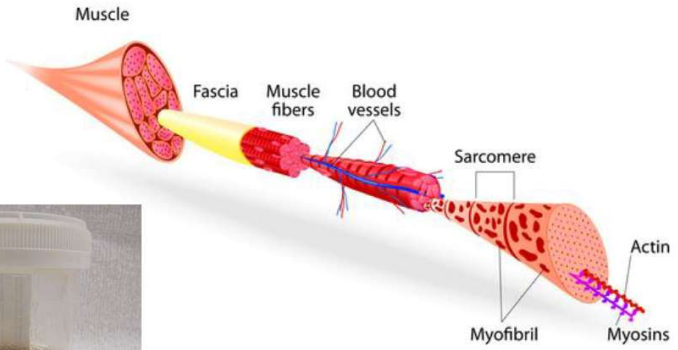
Muslce Adverse Event Terminology

SAMS
Muscle symptoms reported during statin therapy but not necessarily caused by the statin

Myalgia
Muscle pain or aches

Myopathy
Unexplained muscle pain or weakness accompanied by CK concentration > 10 x ULN

Rhabdomyolysis
Severe form of myopathy, with CK typically > 40 ULN, which can cause myoglobinuria and acute renal failure



CK, creatinine kinase; SAMS, statin-associatedmuscle symptoms; ULN, upperlimitof normal.
Newman CB, et al. ArteriosclerThrombVascBiol2019;39:e38-e81.

There is currently no consensus regarding the definition of statin intolerance (SI)

Proposed definitions:

EMA:[1] 'Unable to tolerate ≥2 statins at the lowest approved daily dose due to skeletal muscle related symptoms, e.g., pain, aches, weakness, or cramping that began or increased during statin therapy and stopped when statin therapy was discontinued'

NLA definition:[2] 'Adverse symptoms, signs or laboratory abnormalities attributed by the patient (or provider) to the statin and in most cases perceived by the patient to interfere unacceptably with activities of daily living leading to a decision to stop or reduce statin therapy'

Canadian Working Group Consensus:[3] A broad description of side-effects including nonspecific, mild symptoms or transient side effects such as gastrointestinal discomfort, fatigue and skin involvement, in addition to more statin-specific symptoms including elevated liver enzymes and adverse muscle effects such as aches, myalgia, weakness, stiffness, and cramps. These muscle-related side effects may or may not be associated with elevations in serum CK levels. Skeletal muscle-related adverse effects range from myalgias to rhabdomyolysis.

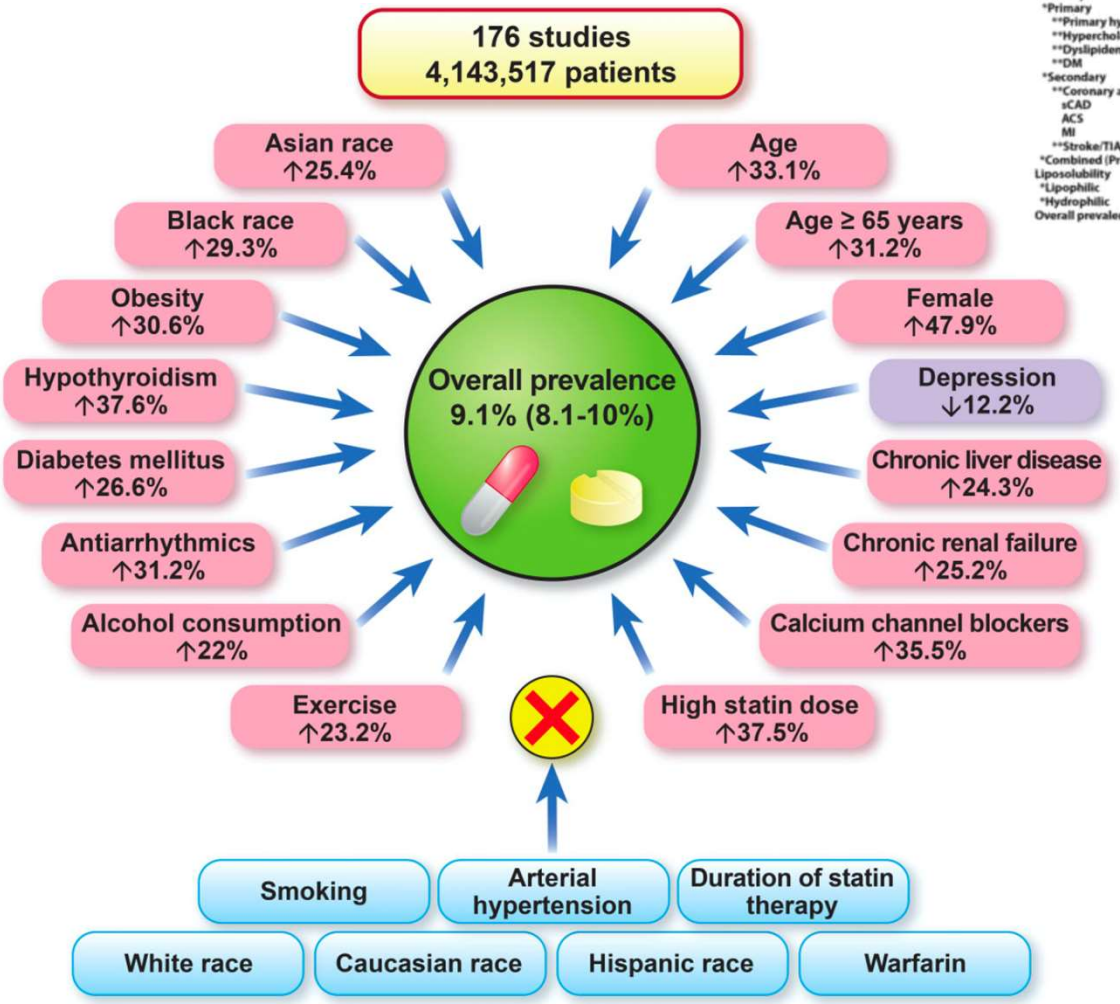
SI, statin intolerance; EMA, European Medicines Agency; NLA, National Lipid Association; CK, creatine kinase

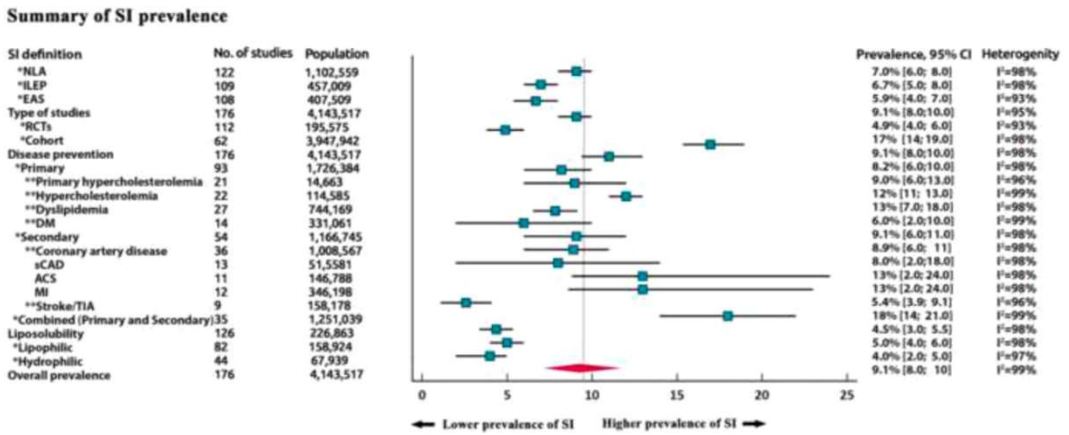
1. Guideline on clinical investigation of medicinal products in the treatment of lipid disorders, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/01/WC500159540.pdf, accessed 16 october 2014; 2. Guyton JR et al. J Clin Lipidol. 2014;8:S72–S81; 3. Mancini GB et al. Can J Cardiol. 2011;27:635–662

Statin Intolerance – NLA Definition and Recommendations for ASCVD Risk Management

Recommendation	Class of Recommendation (Strength)	Level of Evidence
Statin intolerance is defined as one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of a statin, or partial intolerance, with inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.		
For patients demonstrating non-adherence, or lack of persistence with statin therapy, statin intolerance should be evaluated as a potential contributing factor.	**I**	**B-R**
For patients with suspected statin intolerance, clinicians should attempt multiple strategies to identify a tolerable statin regimen (e.g., lower dose, switching statins, non-daily dosing), because complete statin intolerance is uncommon (<5% of patients).	**I**	**B-R**
When non-statin therapies are used, those with data from randomized trials showing reduced cardiovascular event risk should be favored.	**I**	**A**
For patients with known or suspected statin intolerance who are at high- or very-high ASCVD risk, non-statin therapy should be considered while additional attempts are made to identify a tolerable statin regimen to avoid excessive delay in lowering atherogenic lipoproteins.	**IIa**	**B-R**
For patients with statin intolerance, it is reasonable to consider the nocebo effect as a possible cause; however, this does not make such symptoms less clinically relevant and ASCVD risk related to elevated atherogenic lipoproteins should be addressed.	**IIa**	**A**
For patients with complete or partial statin intolerance, it is reasonable to consider non-statin therapy to assist in lowering atherogenic lipoproteins.	**IIa**	**A**

J Clin Lipid 2022;16:361





Summary of SI prevalence

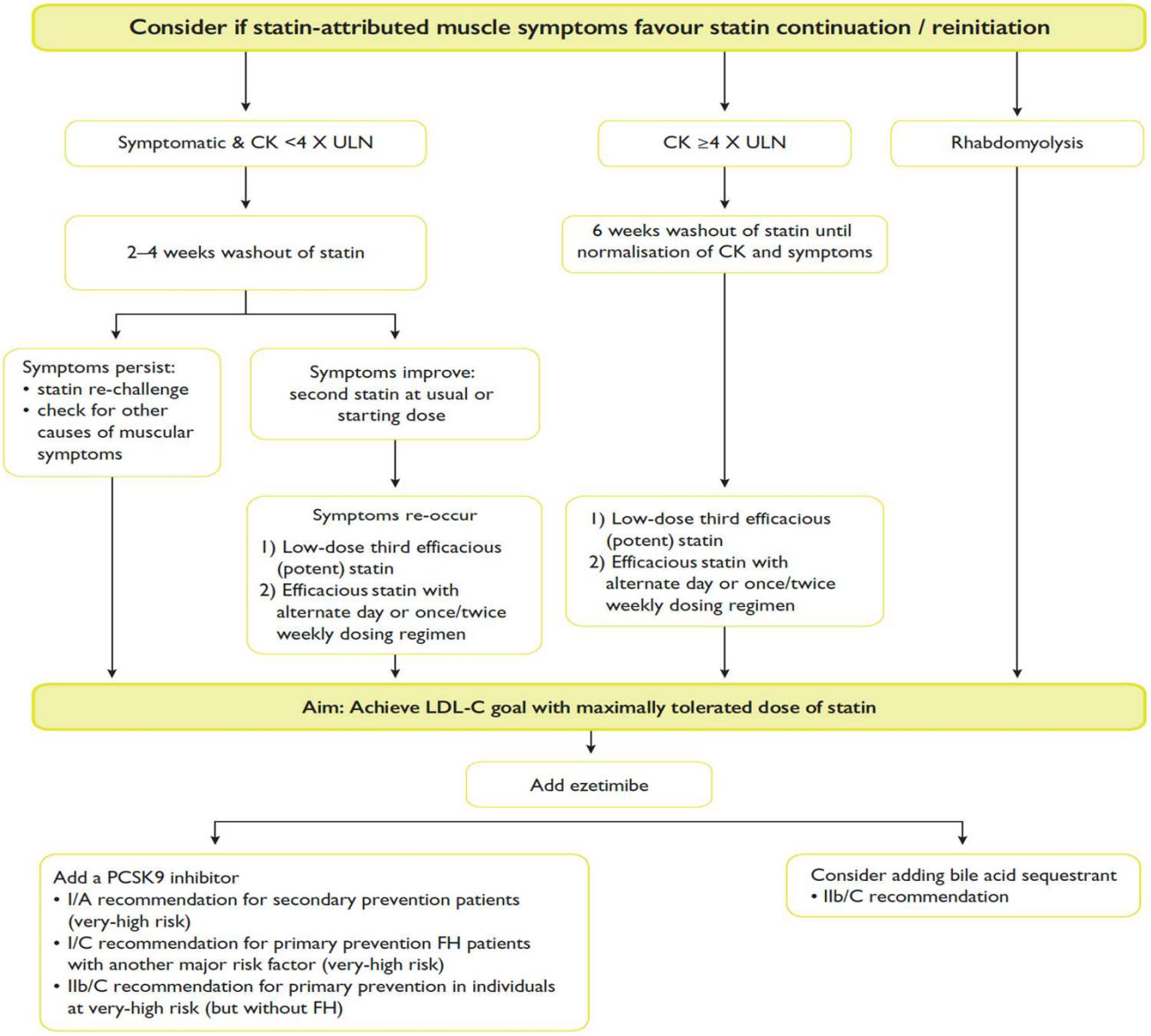
SI definition	No. of studies	Population	Prevalence, 95% CI	Heterogenity
*NLA	122	1,102,559	7.0% [6.0; 8.0]	I²=98%
*ILEP	109	457,009	6.7% [5.0; 8.0]	I²=98%
*EAS	108	407,509	5.9% [4.0; 7.0]	I²=93%
Type of studies	176	4,143,517	9.1% [8.0;10.0]	I²=95%
*RCTs	112	195,575	4.9% [4.0; 6.0]	I²=93%
*Cohort	62	3,947,942	17% [14; 19.0]	I²=98%
Disease prevention	176	4,143,517	9.1% [8.0;10.0]	I²=98%
*Primary	93	1,726,384	8.2% [6.0;10.0]	I²=98%
**Primary hypercholesterolemia	21	14,663	9.0% [6.0;13.0]	I²=96%
**Hypercholesterolemia	22	114,585	12% [11; 13.0]	I²=99%
**Dyslipidemia	27	744,169	13% [7.0; 18.0]	I²=98%
**DM	14	331,061	6.0% [2.0;10.0]	I²=99%
*Secondary	54	1,166,745	9.1% [6.0;11.0]	I²=98%
**Coronary artery disease	36	1,008,567	8.9% [6.0; 11]	I²=98%
sCAD	13	51,5581	8.0% [2.0;18.0]	I²=98%
ACS	11	146,788	13% [2.0; 24.0]	I²=98%
MI	12	346,198	13% [2.0; 24.0]	I²=98%
**Stroke/TIA	9	158,178	5.4% [3.9; 9.1]	I²=96%
*Combined (Primary and Secondary)	35	1,251,039	18% [14; 21.0]	I²=99%
Liposolubility	126	226,863	4.5% [3.0; 5.5]	I²=98%
*Lipophilic	82	158,924	5.0% [4.0; 6.0]	I²=98%
*Hydrophilic	44	67,939	4.0% [2.0; 5.0]	I²=97%
Overall prevalence	176	4,143,517	9.1% [8.0; 10]	I²=99%

0 5 10 15 20 25

Lower prevalence of SI — Higher prevalence of SI

Prevalence of statin intolerance: a meta-analysis

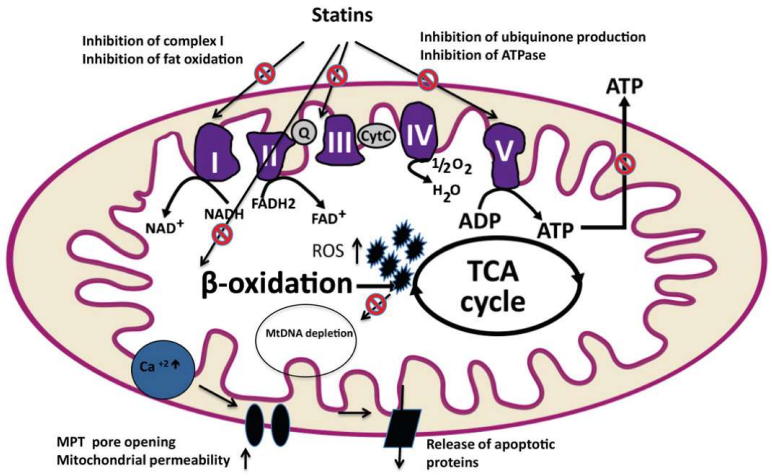
Bytyçi I et al. Eur Heart J (2022) 43, 3213–3223



ESC European Society of Cardiology
European Heart Journal (2020) 41, 111–188
doi:10.1093/eurheartj/ehz455
ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)



Mach F et al. European Heart Journal (2020) 41, 111188
Stroes FS et al. European Heart Journal (2015) 36, 1012–1022

Alternative Treatment Options for SI Patients (Before PCSK9-i and bempedoic acid)

Ezetimibe[1]

- Ezetimibe 10 mg/day was administered to 56 SI patients followed by addition of atorvastatin 10 mg/twice weekly[1]
  - 9% of patients achieved LDL-C goal on monotherapy
  - 84% of patients achieved LDL-C goal on combination therapy

Fibrates

- Fenofibrate[2]
  - ↓ TC by 12–30%
  - ↓ LDL-C by 13–35%
  - ↓ TG by 15–43%
  - ↑ HDL-C by 1–34%
- Similar side-effect profile to statins[3]
- Combining statins with fibrates may enhance risk for myopathy[4]

Bile acid sequestrants

- Colesevelam monotherapy can reduce LDL-C by close to 20%[5]

Niacin[5]

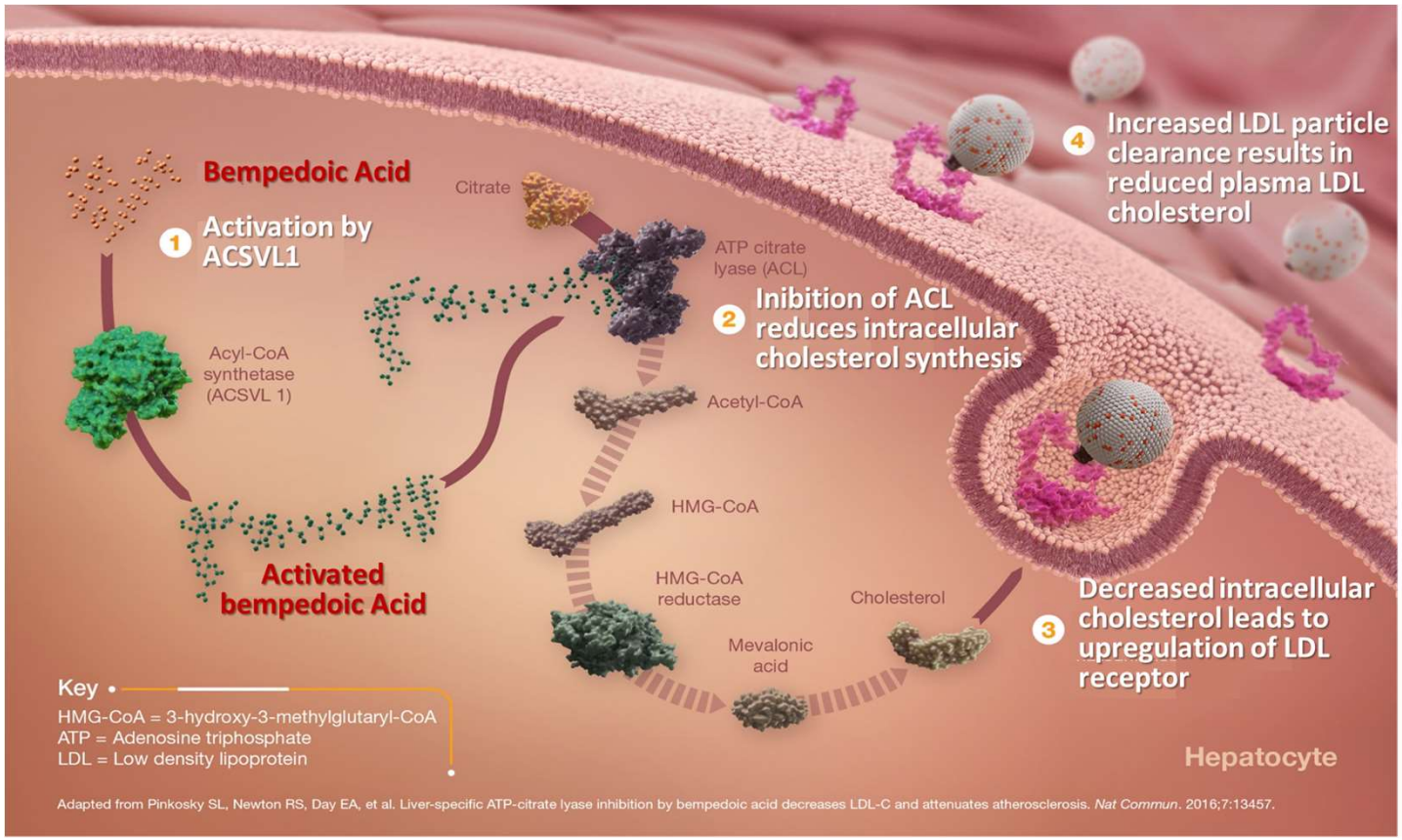
- Niacin failed to reduce CV events in AIM-HIGH and HPS2-THRIVE
- It remains an option for patients who are unable to achieve adequate reduction with other therapies

SI, statinintolerant; TC, total cholesterol; LDL-C, lowdensitylipoproteincholesterol; HDL-C, high densitylipoproteincholesterol; TG, triglycerides; EMA, EuropeanMedicinesAgency; CV, cardiovascular

1. AthyrosVG et al. Am J Cardiol. 2008;101:483–485; 2. Keating GM and OrmrodD. Drugs. 2002;62:1909-1944; 3. FenofibrateSmPC, Zentiva, availableat: http://www.medicines.org.uk/emc/print-document?documentId=22425, accessedOctober2014; 4. Reiner Z et al. EurHeartJ. 2011;32:1796–1818; 5. TompkinsR et al. Nat Rev. 2014;96:74–80

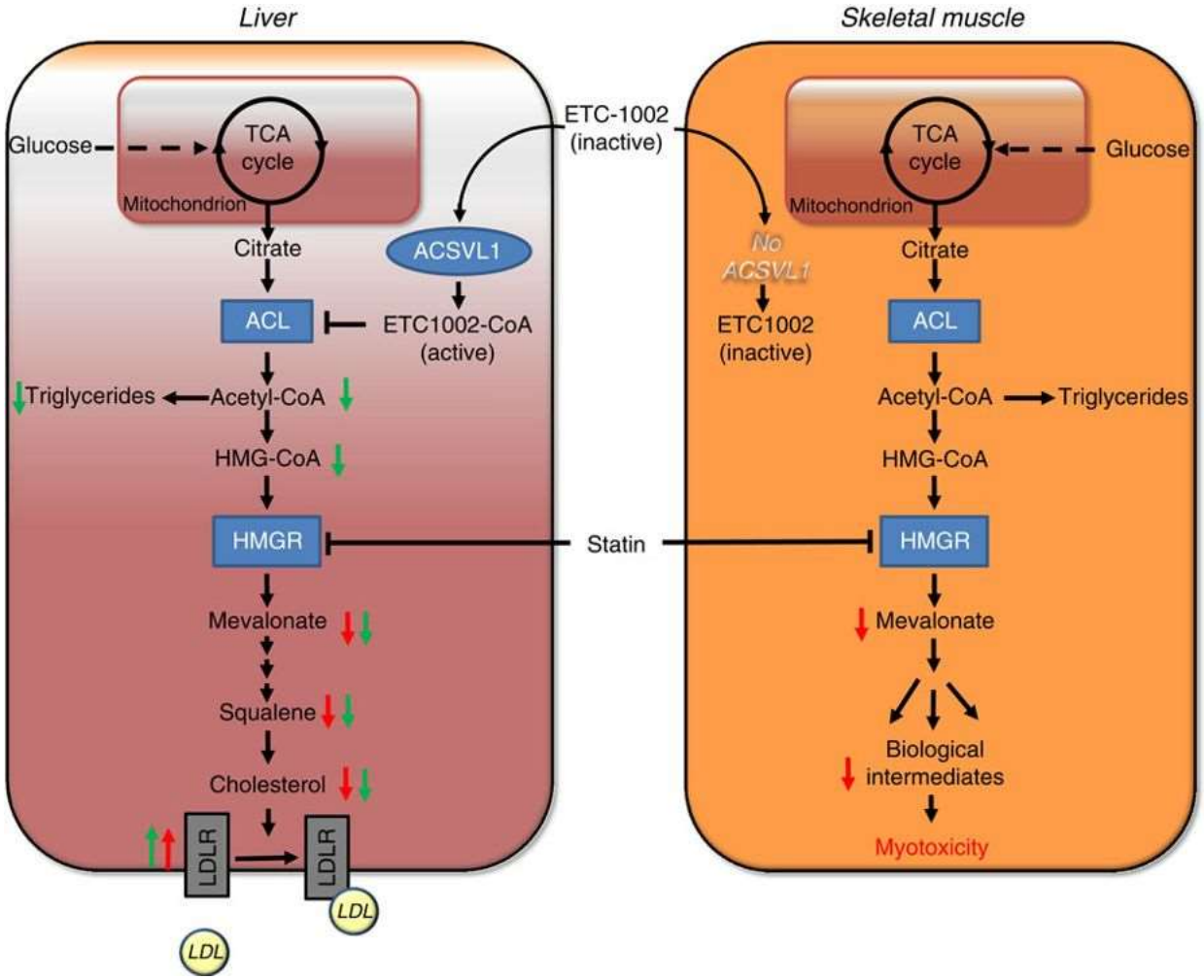
The Unique Mechanism of Action of Bempedoic Acid is Complementary, yet Distinct from Statins and Other LLTs

- **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**



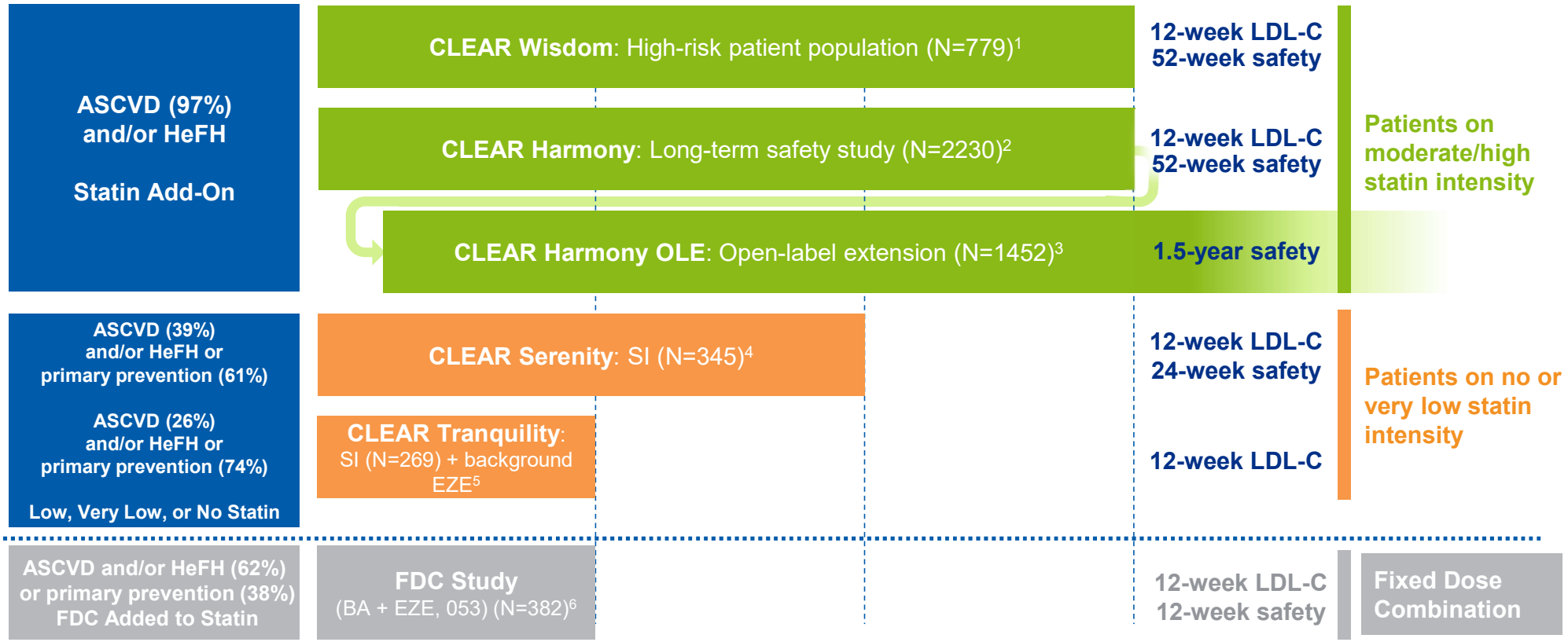
Adapted from Pinkosky et al. Nature Communications. 2016; 7:13457 | DOI: 10.1038/ncomms13457

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

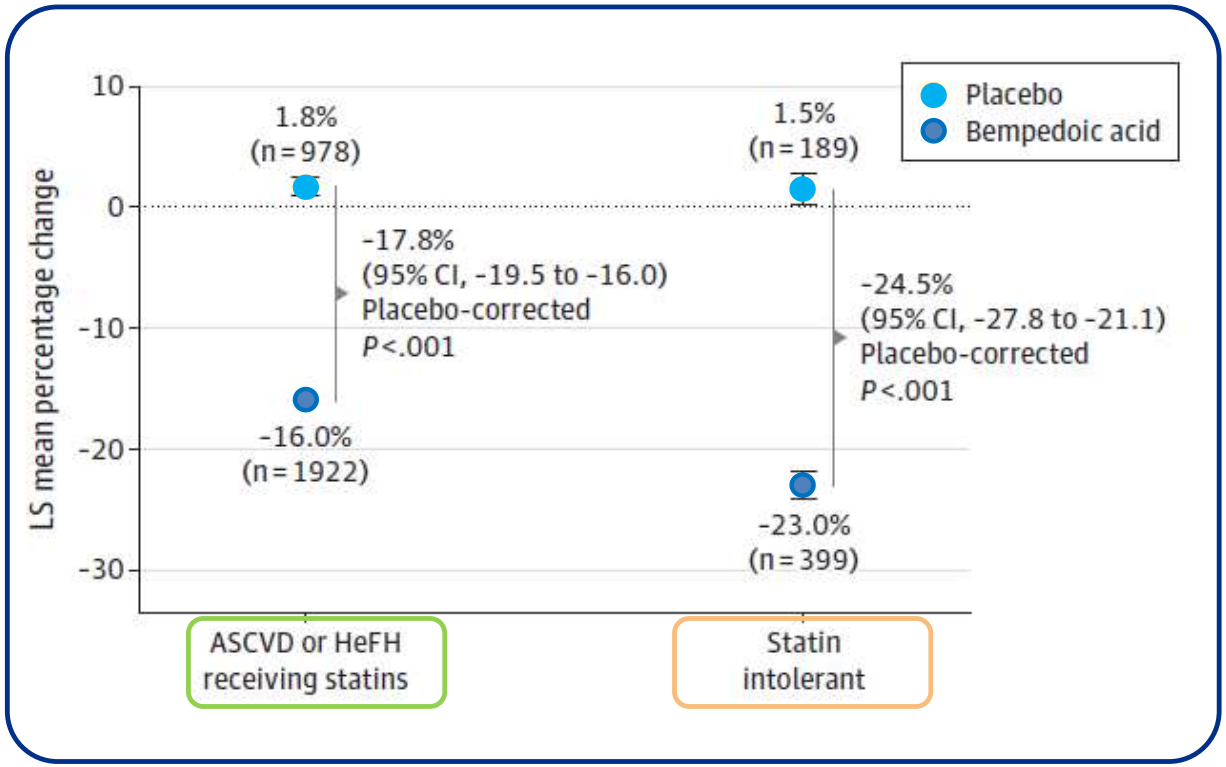


ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; OLE = open-label extension; SI = statin intolerant

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.

L'Acido Bempedoico ha determinato una significativa riduzione dei livelli di LDL-C vs Placebo in aggiunta alla massima dose tollerata di statina, con o senza altre terapie ipolipemizzanti

At week 12



La riduzione media assoluta dei livelli di LDL-C associata con la somministrazione di acido bempedoico era **19.8 mg/dL** nei pazienti con ASCVD e/o HeFH in trattamento con statine alla massima dose tollerata e **36.5 mg/dL** nei pazienti intolleranti alle statine.

Con l'utilizzo di acido bempedoico possiamo attendere una riduzione del rischio di eventi a 5 anni dell'11% e 21% rispettivamente nelle due popolazioni studiate.

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

Bempedoic Acid/Ezetimibe FDC

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

Complementary mechanism of action

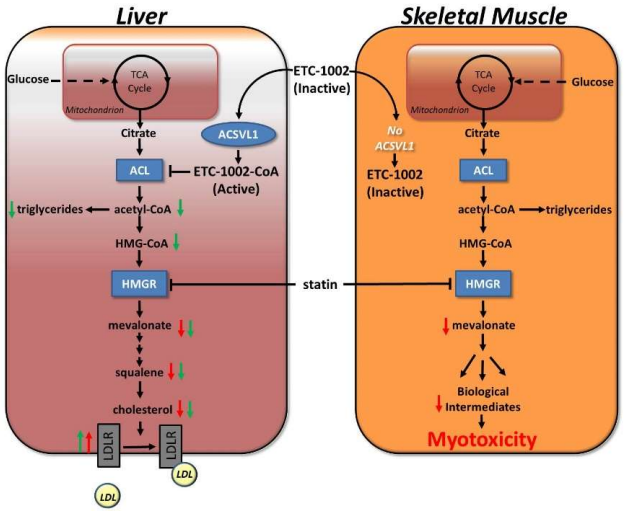
Bempedoic Acid

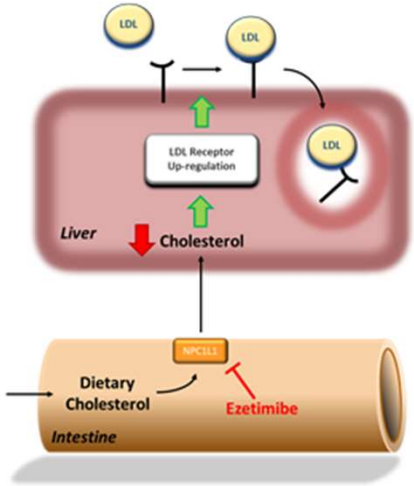
- Inhibits ATP Citrate Lyase (ACL)
  - Active in liver cells
- Acts in the same cholesterol biosynthesis pathway as statins
- **Upregulates LDL receptors**

Ezetimibe

Inhibits NPC1L1 (sterol transporter)

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



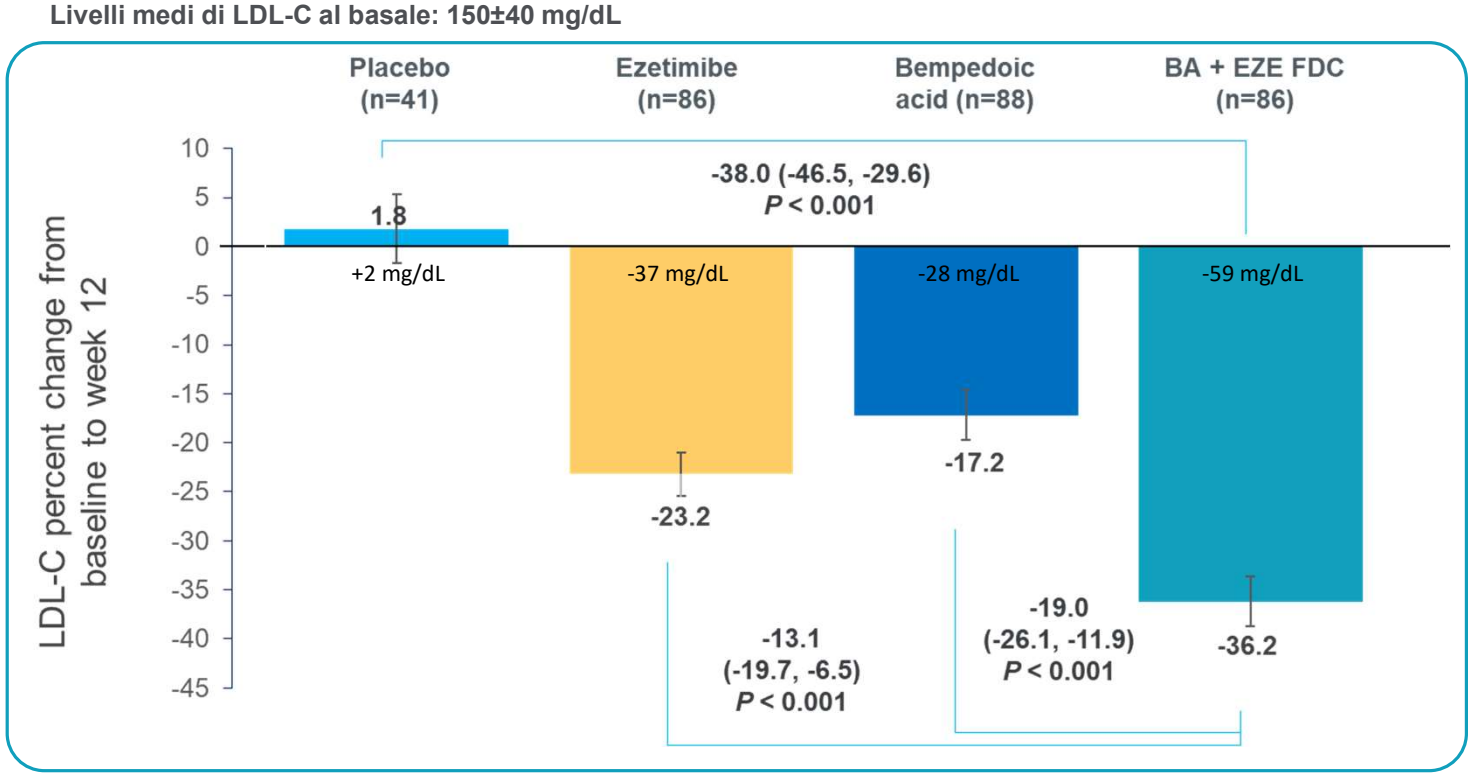


Adapted from Pinkosky et al. Nature Communications. 2016 Nov 28; DOI: 10.1038/ncomms13457;
Garcia-Calvo et al. Proc Natl Acad Sci USA. 2005; 102:8132–8137; Ference et al. European Heart Journal. 2017 0, 1-14.

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

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 consistently across subgroups, including all intensities of background statin therapy**

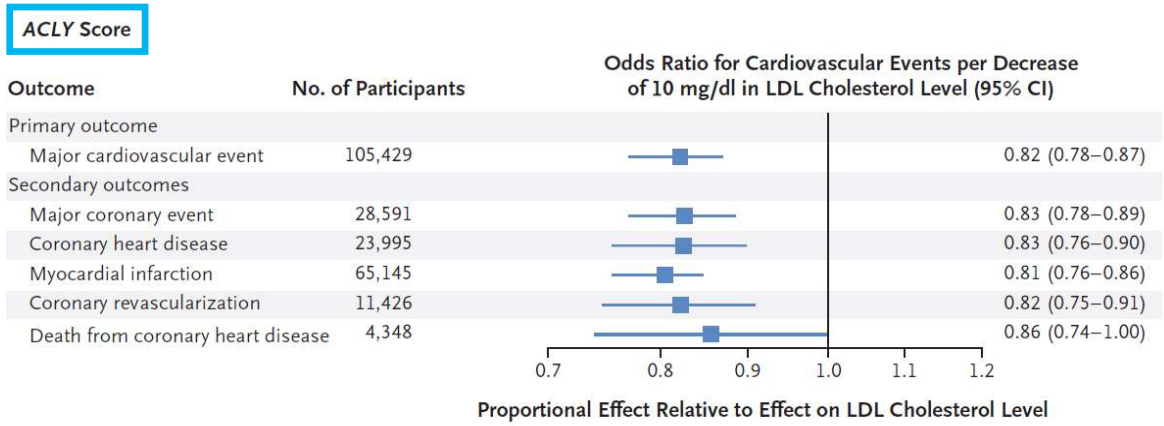
Post hoc population

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

ACLY gene variants are associated with lower LDL-C levels and reductions in CV risk

- **For people with ACLY gene variants, a 10 mg/dL decrease in LDL-C levels is associated with:**
  - A 17.7% reduction in major CV event risk
  - A 19.4% reduction in the risk of MI
- **The effect of lifelong exposure to low LDL-C levels produced by ACLY and HMGCR gene variants are similar**



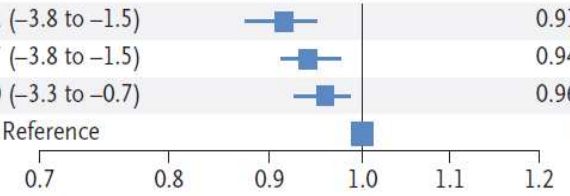
Ference BA, et al, N Engl J Med. 2019;380:1033–1042

ACLY gene variants are associated with lower LDL-C levels and reductions in CV risk

- Combined exposure to variants in the ACLY+HMGCR genes and ACLY+NPC1L1* genes produced **additive decreases** in LDL-C levels and corresponding additive decreases in the risk of major CV events
- The effects of bempedoic acid on LDL-C levels and CV risk **should be additive** when combined with statins or ezetimibe

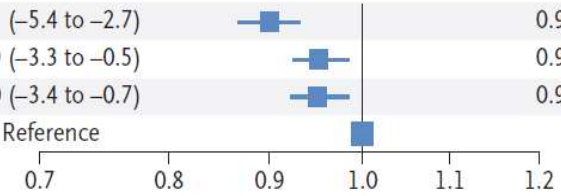
Combined Effect of *ACLY* and *HMGCR* Scores

2×2 Analysis	No. of Participants	Change in LDL Cholesterol Level (95% CI)	Change in Apolipoprotein B Level (95% CI)	Odds Ratio for Major Cardiovascular Events (95% CI)
		mg/dl		
Both scores >median	101,623	−5.3 (−6.6 to −3.9)	−4.2 (−3.8 to −1.5)	0.91 (0.88 to 0.94)
HMGCR score >median	124,206	−3.3 (−4.6 to −2.0)	−2.7 (−3.8 to −1.5)	0.94 (0.91 to 0.98)
ACLY score >median	110,092	−2.4 (−3.9 to −0.8)	−2.0 (−3.3 to −0.7)	0.96 (0.93 to 0.99)
Both scores ≤median	134,557	Reference	Reference	Reference



Combined Effect of *ACLY* and *NPC1L1* Scores

2×2 Analysis	No. of Participants	Change in LDL Cholesterol Level (95% CI)	Change in Apolipoprotein B Level (95% CI)	Odds Ratio for Major Cardiovascular Events (95% CI)
		mg/dl		
Both scores >median	105,011	−5.2 (−7.2 to −3.2)	−4.1 (−5.4 to −2.7)	0.90 (0.87 to 0.93)
NPC1L1 score >median	128,346	−2.5 (−4.2 to −0.8)	−1.9 (−3.3 to −0.5)	0.96 (0.92 to 0.99)
ACLY score >median	106,705	−2.5 (−4.0 to −0.9)	−2.0 (−3.4 to −0.7)	0.95 (0.92 to 0.99)
Both scores ≤median	130,416	Reference	Reference	Reference



Ference BA, et al, N Engl J Med. 2019;380:1033–1042

ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

CLEAR Outcomes
Objective & Design

A total of 13,970 patients underwent randomization; 6992 were assigned to the bempedoic acid group and 6978 to the placebo group.

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
Baseline Characteristics

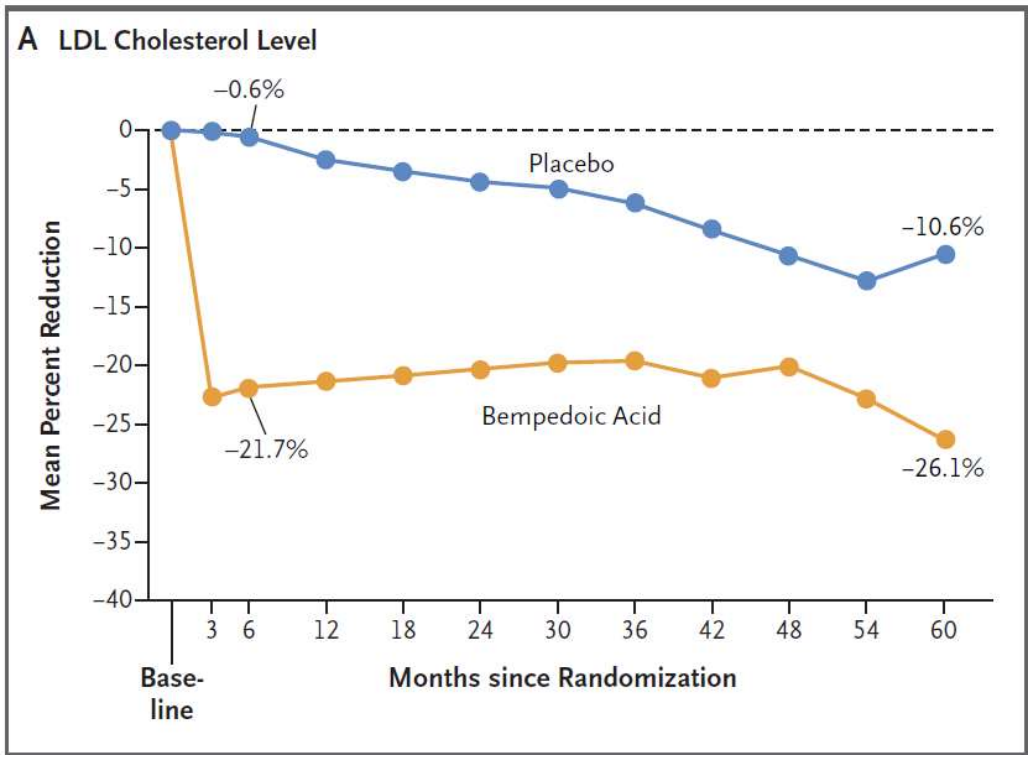
	Bempedoic Acid N=6.992	Placebo N=6.978
Mean Age (years)	65.5	65.5
Female Sex	48.1%	48.4%
LDL-C (mg/dL)	139.0	139.0
hsCRP (mg/L)	2.3	2.3
High Risk Primary Prevention*	30.0 %	30.2%
Secondary Prevention**	70.0%	69.8%
Diabetes	45.0%	46.3%
Baseline statin use	22.9%	22.5%
Ezetimibe use	11.5%	11.6%

***High Risk Primary Prevention:**
- Reynolds risk score >30% or SCORE risk score >7.5% over 10 years, coronary artery calcium score >400 agatston units or type 1 or type 2 diabetes aged >65 years in women and >60 years in men.

****Secondary Prevention:**
- Coronary artery disease, defind by prior myocardial infarction, prior coronary revascularization or presence of a stenosis ≥ 50% in at least one major coronary artery on invasive or computed tomography angiography.
- Symptomatic peripheral arterial disease, defined by claudication or resting limb ischemia with an ankle-brachial index < 0,9 or angiogram showing ≥ 50% stenosis, prior peripheral revascularization, abdominal aortic aneurysm or lower extremity amputation.
- Atherosclerotic cerebrovascular disease, defined by ischemic stroke or carotid endarcterectomy, stenting or presence of >70% stenosis on imaging.

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

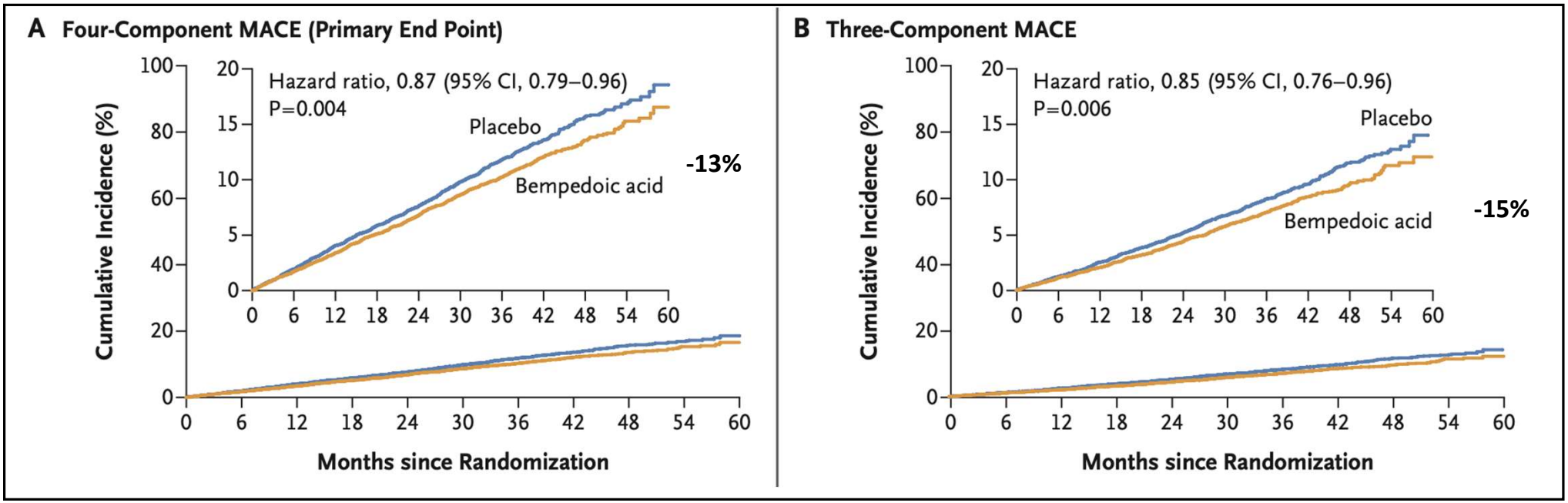
CLEAR Outcomes
LDL-C reduction over time



- At 6 months, the observed difference in LDL-C was 21.1% in favor of bempedoic acid (95% confidence interval [CI], 20.3 to 21.9).
- Among the patients in the placebo group, 15.6% received additional lipid-lowering therapy, as compared with 9.4% of the patients in the bempedoic acid group.
- Median duration of follow-up was 40.6 months

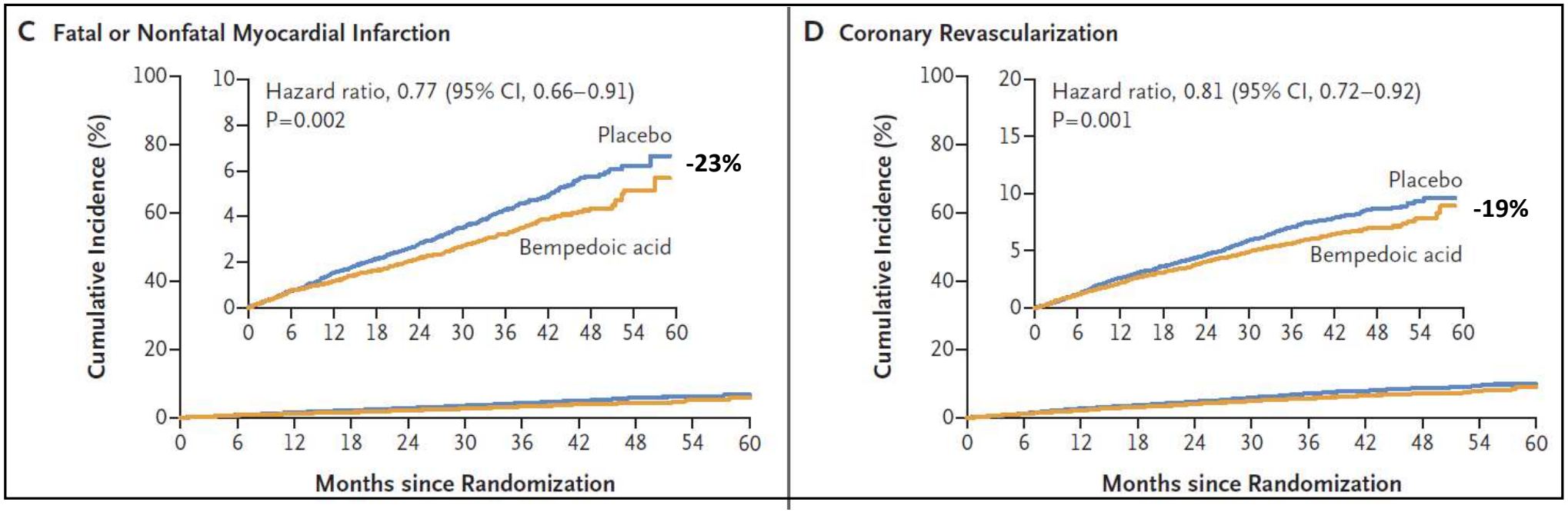
Nissen S E et al N Engl J Med 2023; DOI: 10.1056/NEJMoa2215024

CLEAR Outcomes
Primary CV Endpoints



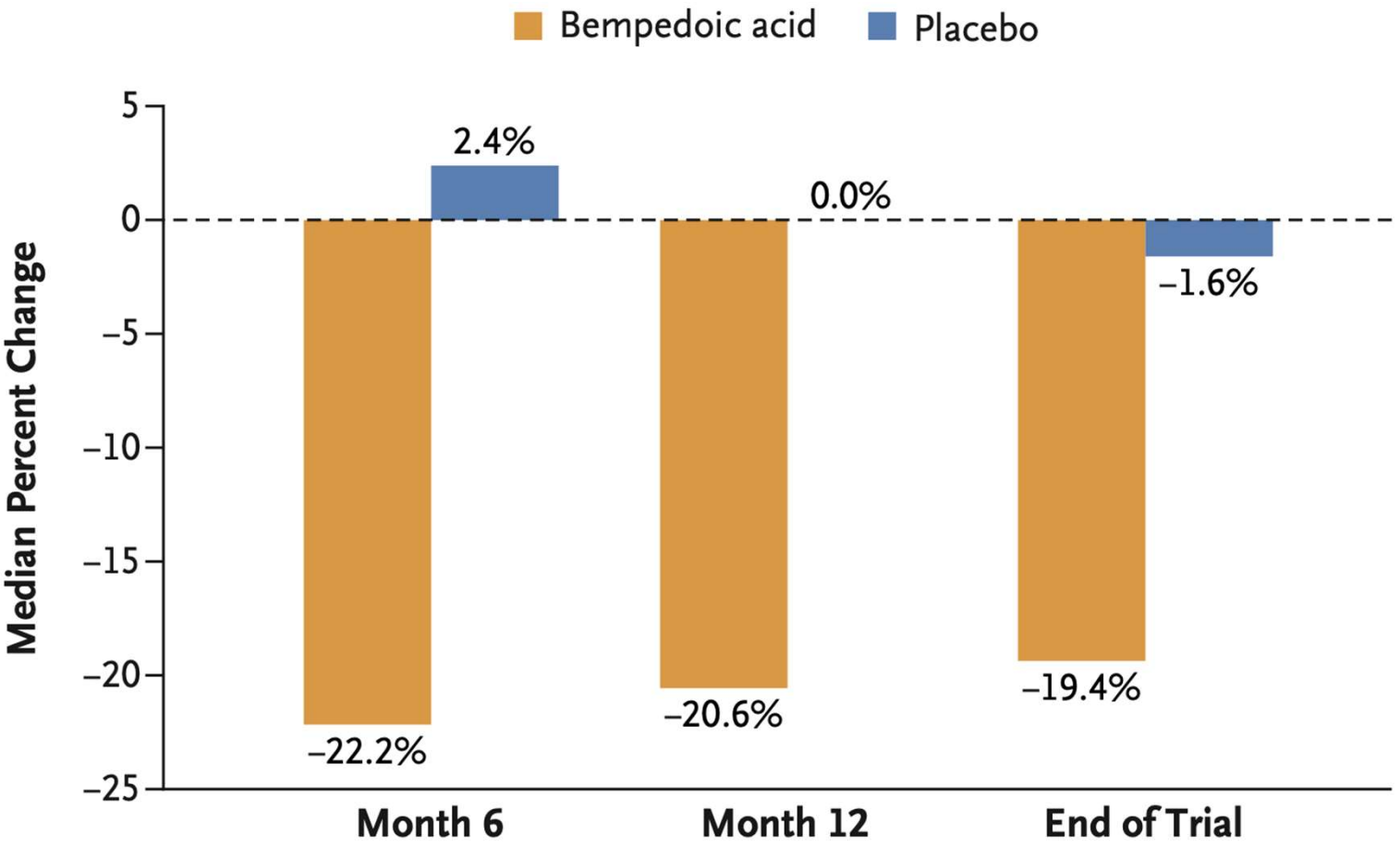
Nissen S E et al N Engl J Med 2023; DOI: 10.1056/NEJMoa2215024

CLEAR Outcomes
Key Secondary CV Endpoints



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

CLEAR Outcomes
High-Sensitivity CRP Level



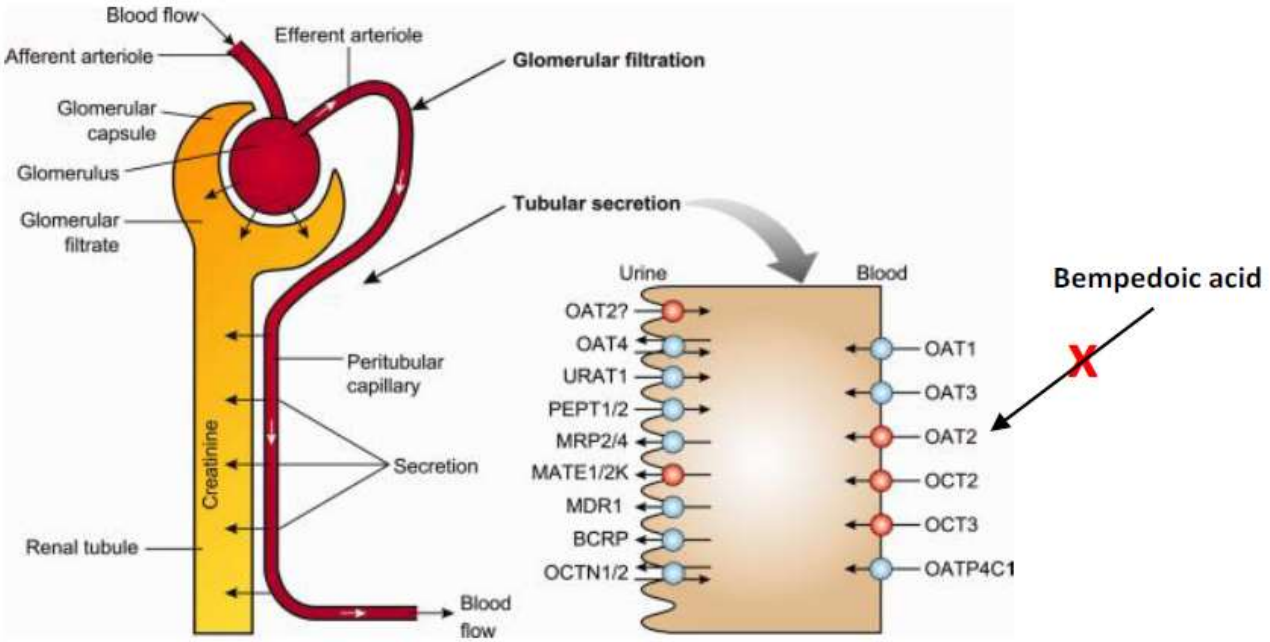
Nissen S E et al N Engl J Med 2023; DOI: 10.1056/NEJMoa2215024

CLEAR Outcomes
Investigator reported adverse effects

	Bempedoic Acid N=7.001	Placebo N=6.964
Serious Treatment Emergent Adverse event	25.2%	24.9%
Adverse event leading to drug discontinuation	10.8%	10.4%
Any muscolar disorder	15.0%	15.4%
New onset of diabetes	16.1%	17.1%
Elevated hepatic enzymes	4.5 %	3.0%
Renal impairment	11.5%	8.6%
Hyperuricemia	10.9%	5.6%
Gout	3.1%	2.1%
Cholelithiasis	2.2%	1.2%
Laboratory results after 6 mo — mg/dL		
Change from baseline in uric acid level	0.76 ± 1.2	−0.03 ± 1.0
Change from baseline in creatinine level	0.05 ± 0.2	0.01 ± 0.2

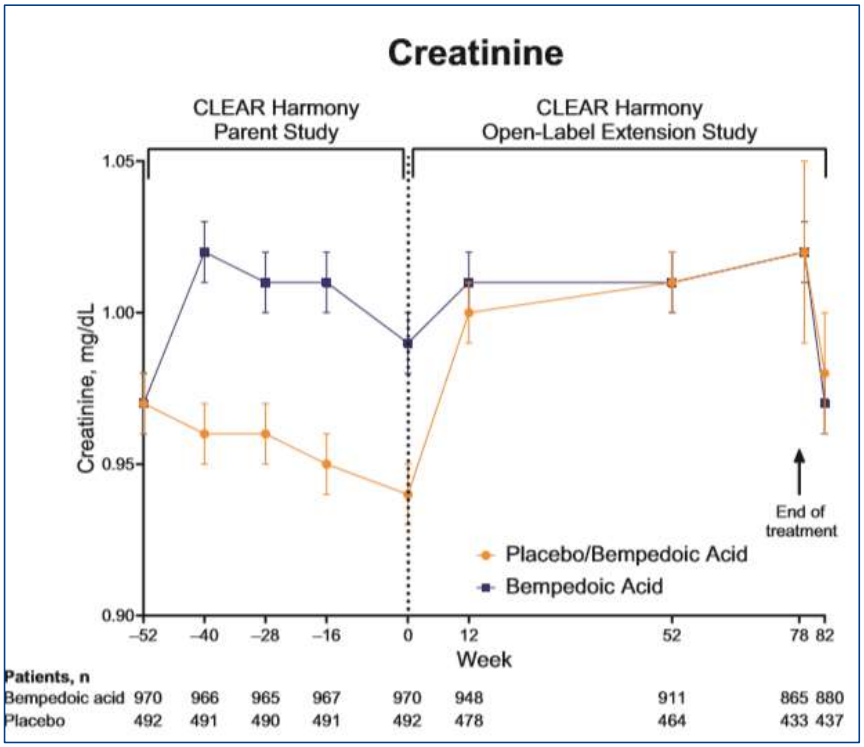
Nissen S E et al N Engl J Med 2023; DOI: 10.1056/NEJMoa2215024

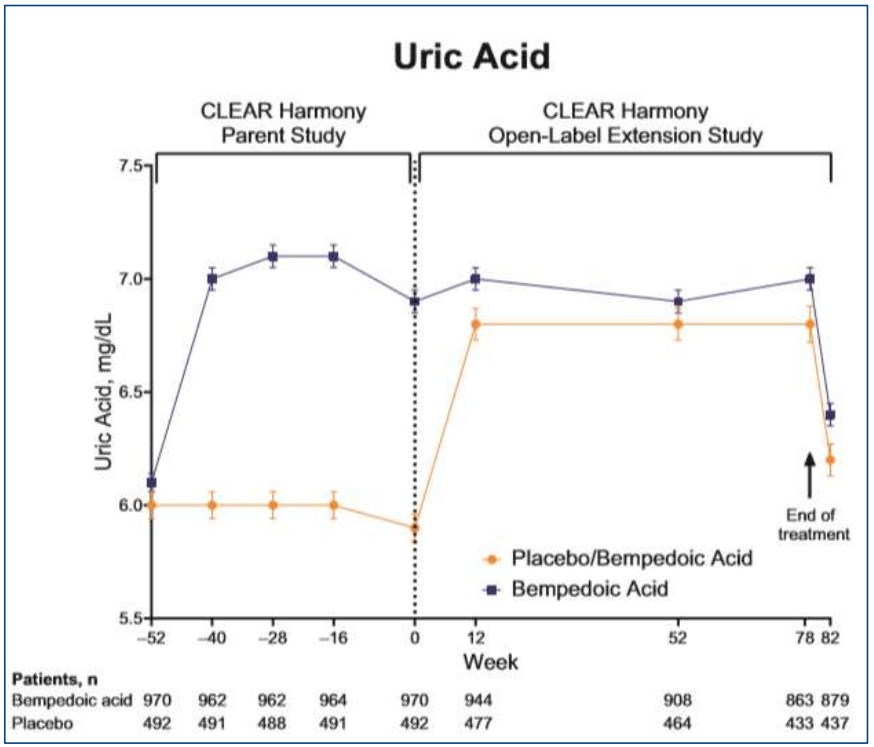
Bempedoic Acid
One potential mechanism for uric acid and creatinine changes



- OAT2 is one renal transporter involved in the excretion of both uric acid and creatinine
- Nonclinical studies have demonstrated that bempedoic acid is a **weak inhibitor of OAT2**
- Additional nonclinical and clinical evidence needed to establish the mechanism(s)

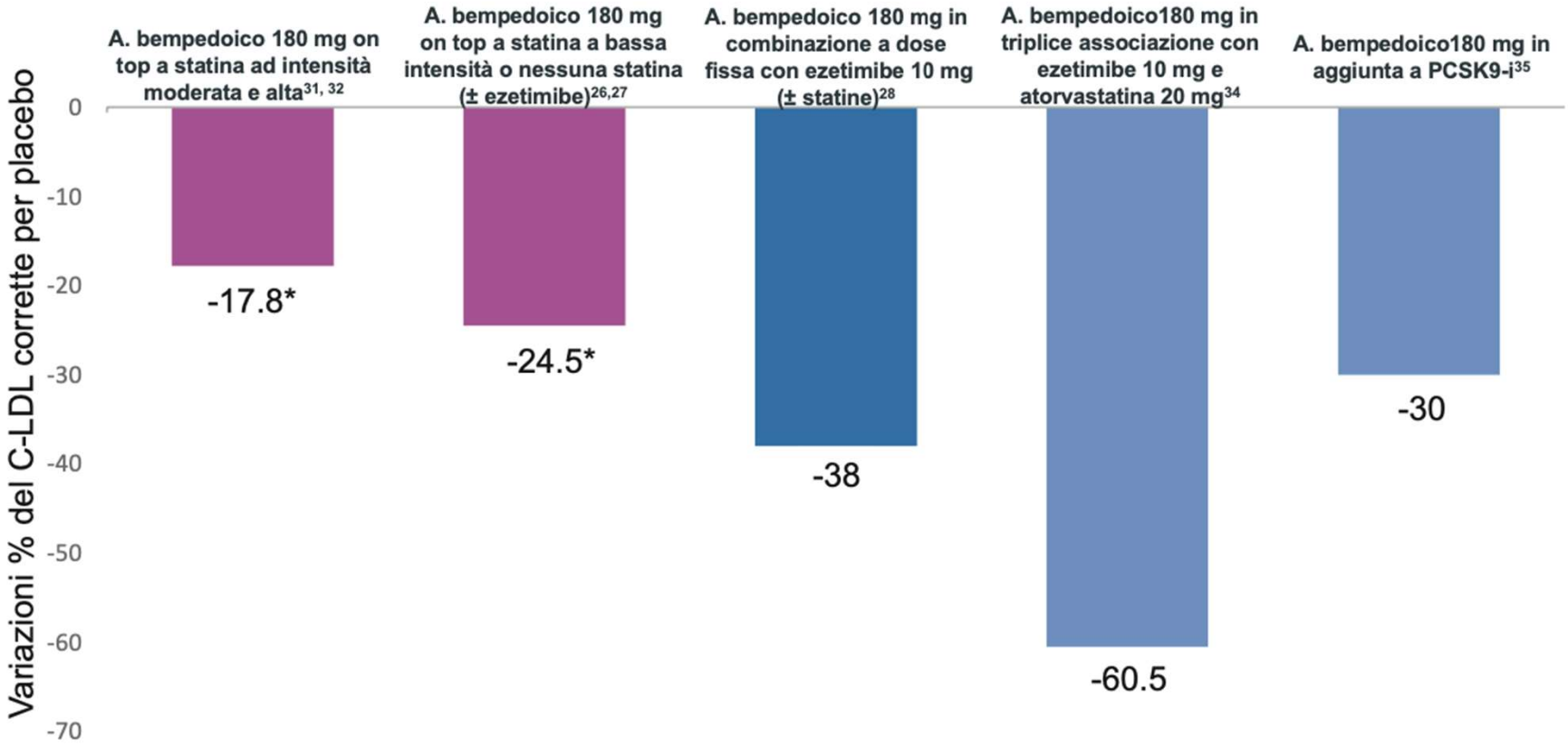
Modest changes in creatine, uric acid and occurred early, were stable, and were reversible after drug discontinuation



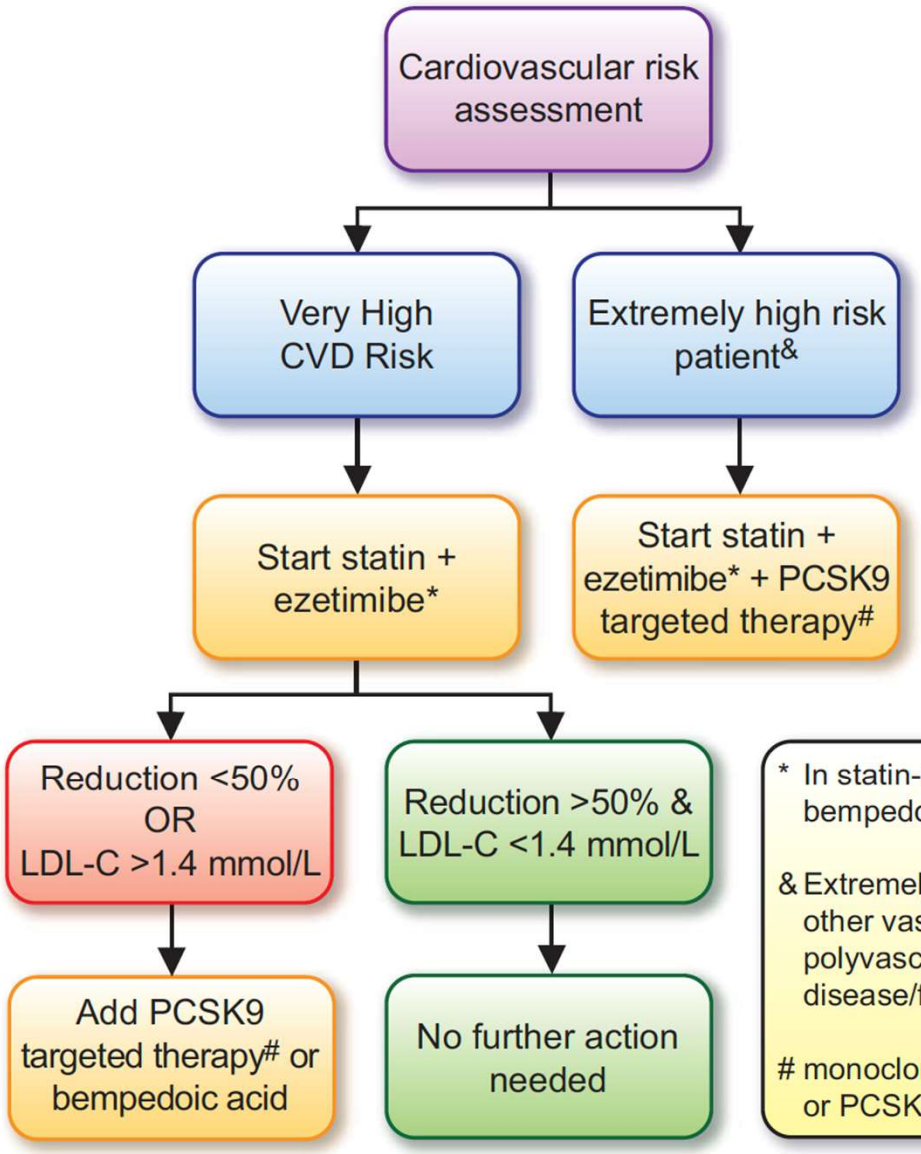


Ballantyne et al. Poster presented virtually at the European Society of Cardiology Congress, 29 August – 1 September 2020.

Riduzione dei valori di colesterolo legato alle lipoproteine a bassa densità (C-LDL) ottenuta con l'impiego dell'acido bempedoico in aggiunta a differenti terapie ipolipemizzanti.



Di Fusco S.A et al, G Ital Cardiol 2023;24



* In statin-intolerant patients consider ezetimibe + bempedoic acid or PCSK9 targeted therapy

& Extremely high risk = post ACS + history of other vascular event/peripheral artery disease/ polyvascular disease/multivessel coronary artery disease/familial hypercholesterolemia

monoclonal antibodies directed against PCSK9 or PCSK9 siRNA therapy

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 <1.4mmol/L, ***a third lipid-lowering therapy, such as bempedoic acid or PCSK9 targeted therapies should be added****."*

Conclusions

- Treatment with bempedoic acid **reduces LDL-C by 17–25%** vs placebo (depending on statin background therapy);
- Significant LDL-C reductions is **maintained** throughout the treatment period, and is **consistent** across different patient subgroups (LLT background therapy; primary vs secondary prevention; other comorbidities);
- The **safety profile** is consistent across patient subgroups; bempedoic acid do not increase myalgia and muscle weakness to a clinically meaningful degree,
- No overall difference in safety and efficacy is observable between **elderly** and the **younger** population.
- Significant improvements is also eveident in total cholesterol, non–HDL-C, apoB, and hsCRP levels;
- The reduction of LDL-C with bempedoic acid is associated with the expected reduction of cardiovascular events

Bempedoic acid represents a new, useful opportunity to improve lipid profile and reduce the CV risk burden in dyslipidemic subjects (not only in those are intolerant to statin….)