DISLIPIDEMIA 2.0

Paolo FORNENGO

Ambulatorio Dislipidemie Genetiche e Transizione Dislipidemie familiari
AOU Città della Salute e della Scienza di Torino

Conflitto di Interessi

Il dr. Paolo Fornengo dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti

dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

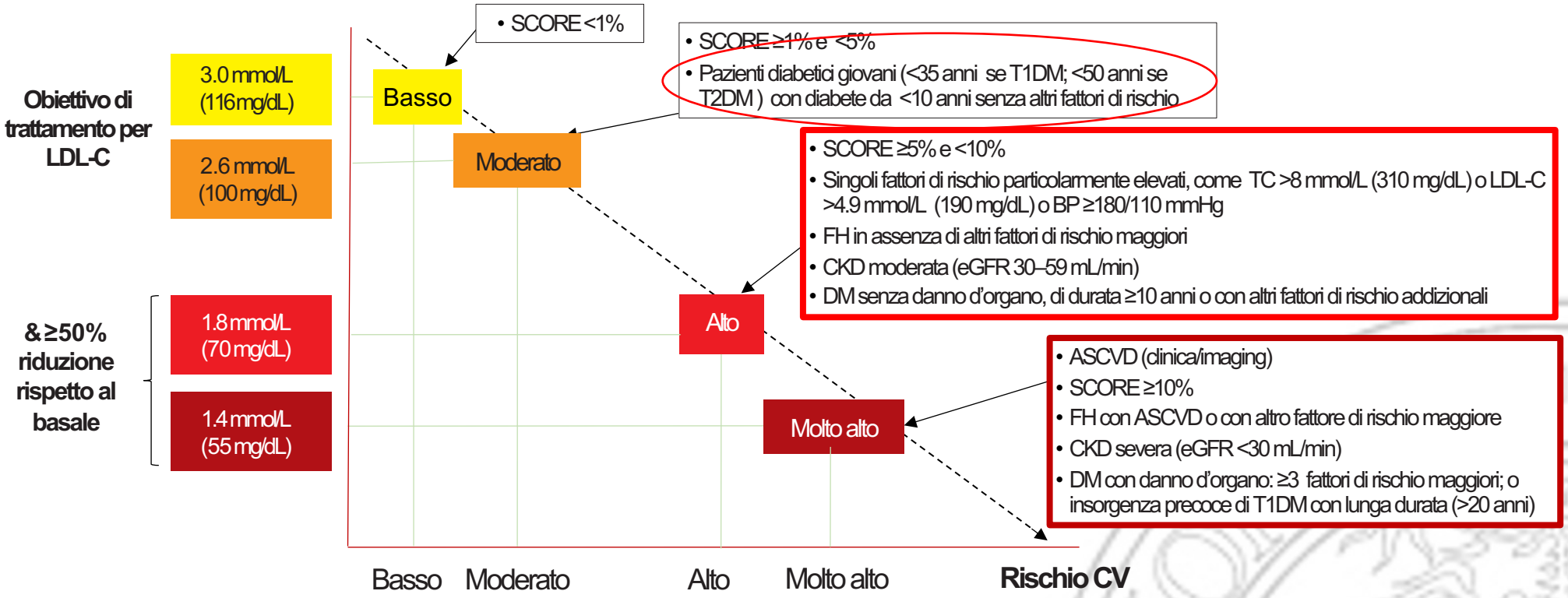
- SOBI, VIATRIS, ULTRAGENIX, AMRYT, DAIICHI SANKYO, ASTRA ZENECA

AURORA BIOPHARMA

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente aspecifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

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*



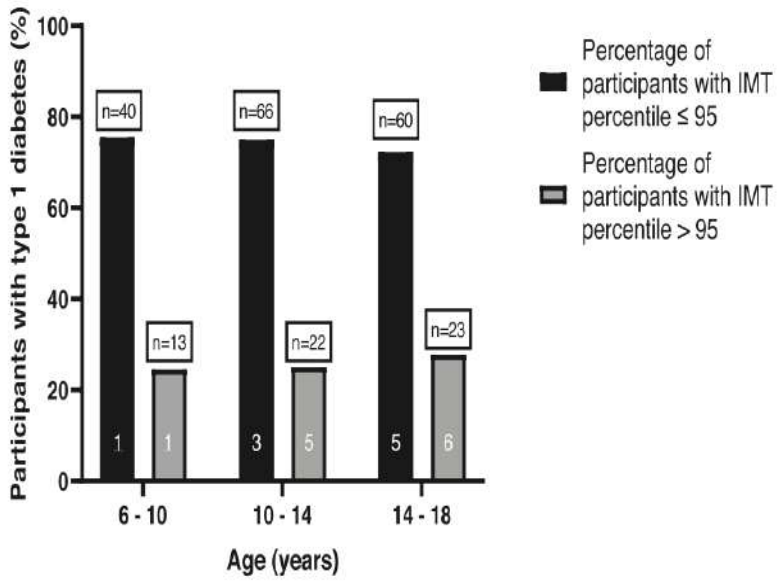
- **Questi obiettivi di trattamento sono più stringenti rispetto al passato perché maggiore è la riduzione assoluta di LDL-C, maggiore è la riduzione del rischio CV**

Prevalence of LDL-hypercholesterolemia and other cardiovascular risk factors in young people with type 1 diabetes

Journal of Clinical Lipidology (2023) 17, 483–490

Table 2 Comparison of T1D related treatment data, lipid parameters and family history of hypercholesterolemia or premature CVD in youth with and without LDL-hypercholesterolemia (LDL-C ≥ 130 mg/dL).

Parameter	LDL-hypercholesterolemia (n = 30)	No LDL-hypercholesterolemia (n = 303)	P value
TIR (%)	41.5 [38.0-59.0]	54.0 [43.7-66.0]	0.019
HbA1c (%)	7.9 [7.0-8.9]	7.3 [6.8-8.0]	0.032
Systolic blood pressure (mmHg)	117.5 [109.0-126.0]	113.0 [105.0-122.0]	0.041
Diastolic blood pressure (mmHg)	75.0 [69.7-80.0]	71.0 [65.0-75.0]	0.001
Total insulin dose (U/kg/day)	0.95 [0.79-1.09]	0.84 [0.71-1.01]	0.021
Basal insulin dose (U/kg)	0.33 [0.3-0.41]	0.30 [0,25-0.38]	0.043
Total cholesterol (mg/dl)	225.5 [210.5-234.7]	167.0 [151.0-185.0]	<0.001
HDL cholesterol (mg/dl)	56.5 [50.0-66.0]	63.0 [54.0-73.0]	0.020
Triglycerides (mg/dl)	102.5 [72.7-153.0]	71.0 [48.0-104.0]	<0.001
% with hypercholesterolemia or premature CVD in the family history	66.7	23.8	<0.001
% of smokers	13.3	2.6	0.003



Conclusion: LDL-hypercholesterolemia affected 9% of youth with T1D in this cohort and was associated with other CVRFs. A holistic therapeutic concept for these young people is essential.

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
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)

Recommendations	Class*	Level†
In secondary prevention for patients at very-high risk, an LDL-C reduction of ≥50% from baselined and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended	I	A
In primary prevention for individuals at very-high risk but without FH, an LDL-C reduction of ≥50% from baselined and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered	IIb	B
In patients at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended	I	A
In individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered	IIa	A
In individuals at low risk, an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered	IIb	A

ESC European Society of Cardiology
European Heart Journal (2023) 00, 1–98
https://doi.org/10.1093/eurheartj/ehad192

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

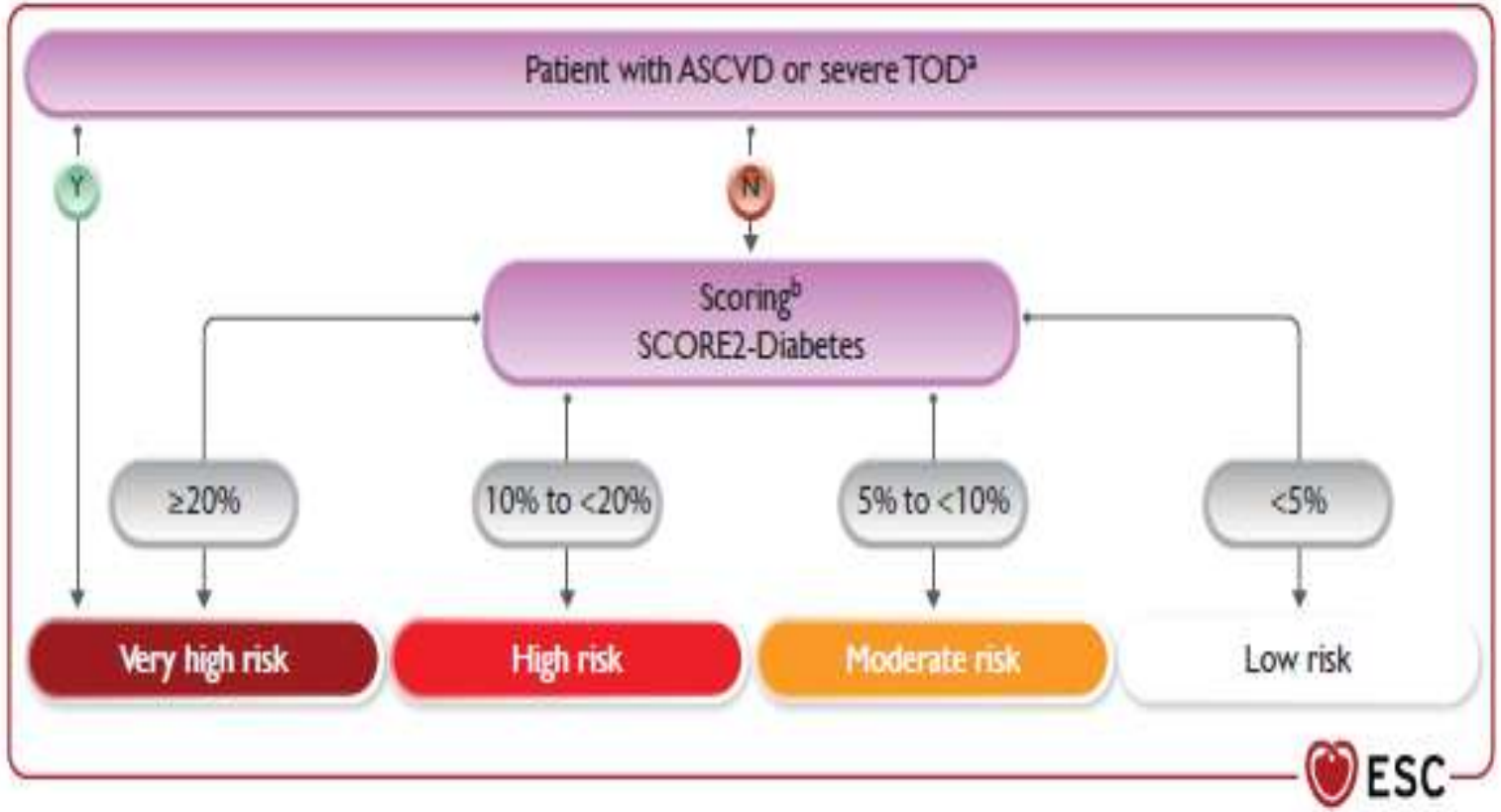
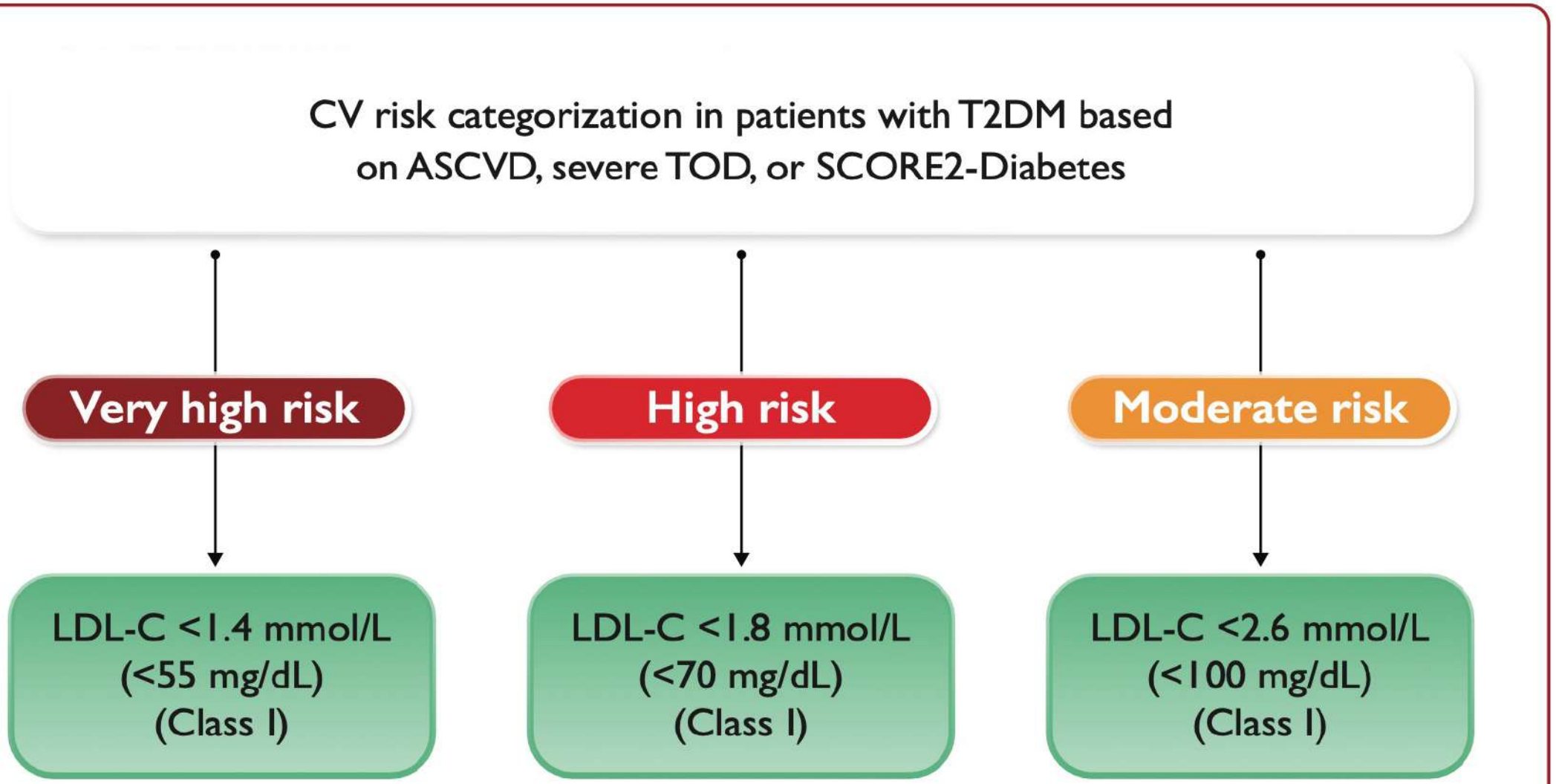
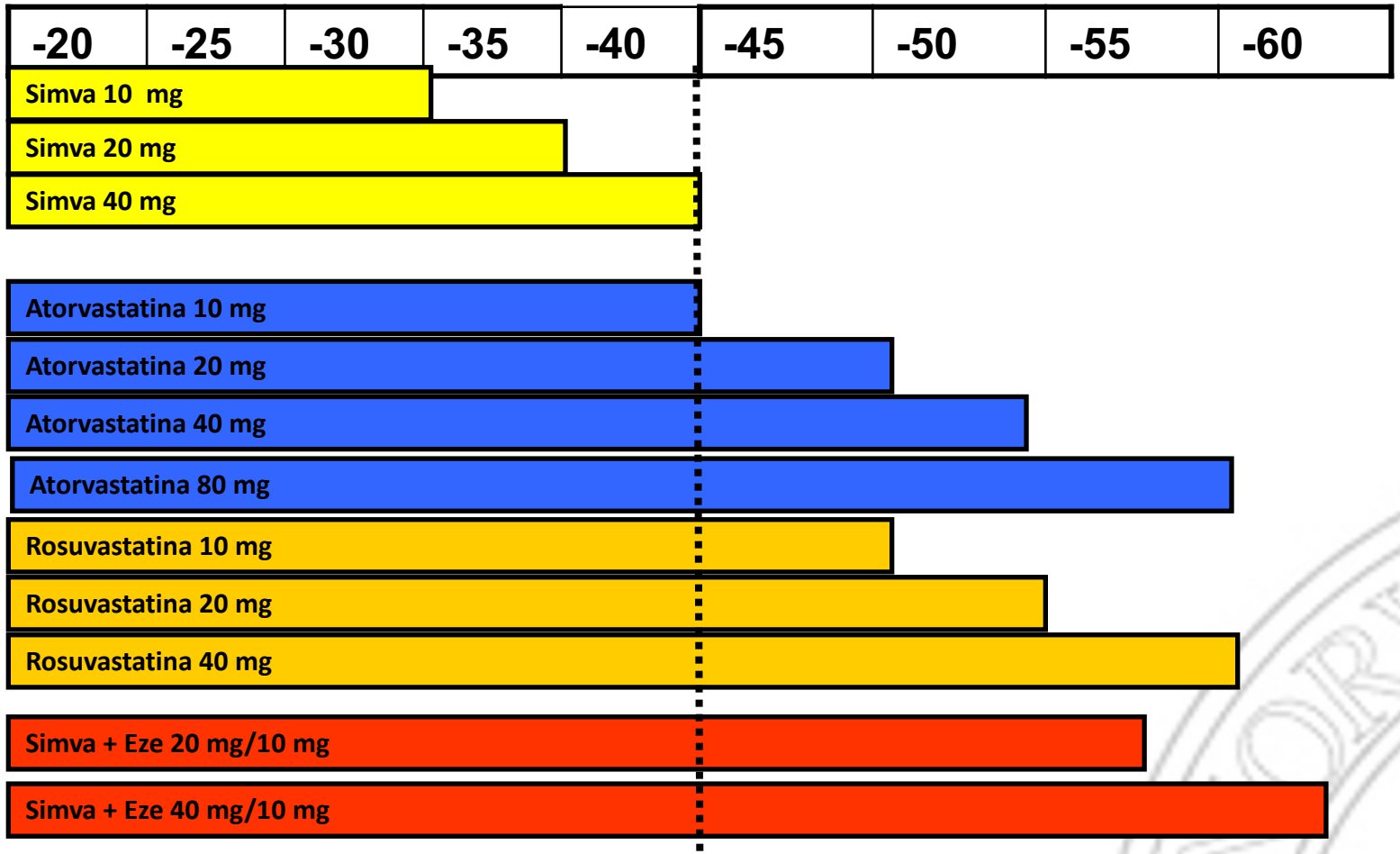


Figure 3 Cardiovascular risk categories in patients with type 2 diabetes. ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease risk; eGFR, estimated glomerular filtration rate; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio. [a]Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3), or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].[43–45] [b]The thresholds (10-year CVD risk) suggested are not definitive but rather designed to prompt joint decision-making conversations with patients about intensity of treatment, as well as additional interventions. SCORE2-Diabetes refers to patients aged ≥40 years.

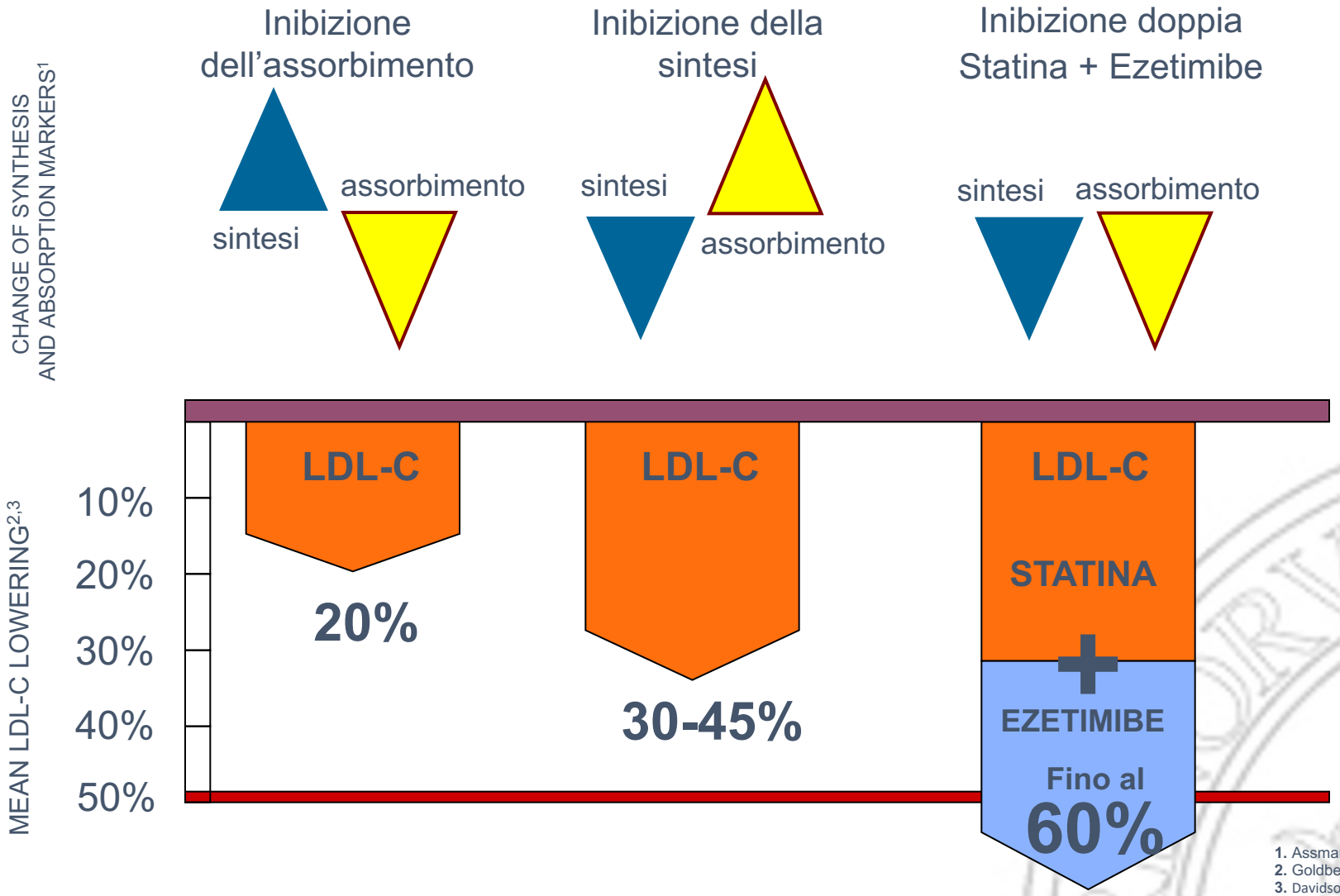

CV risk categorization in patients with T2DM based on ASCVD, severe TOD, or SCORE2-Diabetes
Very high risk
High risk
Moderate risk
LDL-C <1.4 mmol/L (<55 mg/dL) (Class I)
LDL-C <1.8 mmol/L (<70 mg/dL) (Class I)
LDL-C <2.6 mmol/L (<100 mg/dL) (Class I)

Che percentuale di riduzione del C-LDL è necessaria per raggiungere il target?



Associazioni statina + eze

Riduzione fino al 60% di LDL-C via doppia inibizione



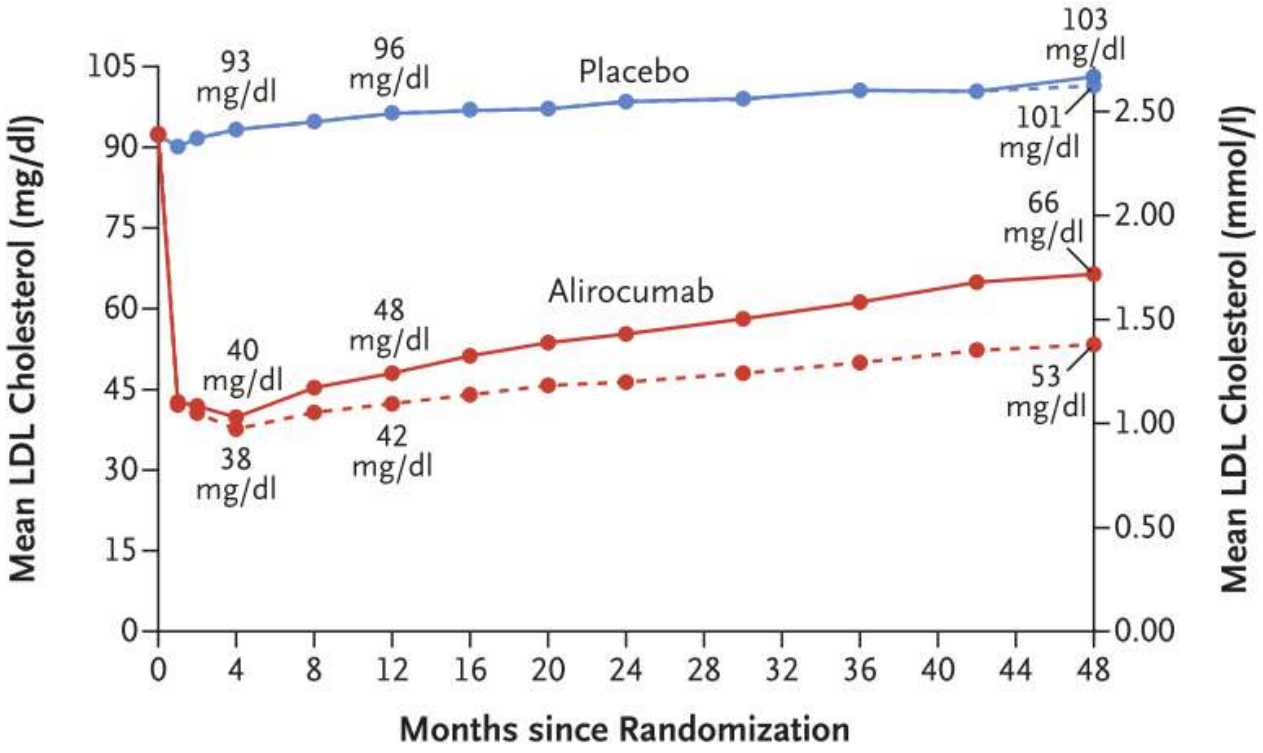
1. Assmann G, et al. *J Am Coll Cardiol* 2004;43(5, Suppl. 2):A445-A446;
2. Goldberg AC, et al. *Mayo Clin Proc.* 2004 May;79(5):620-9.;
3. Davidson M et al. J Am Coll Cardiol 2002; 40:2125-34.

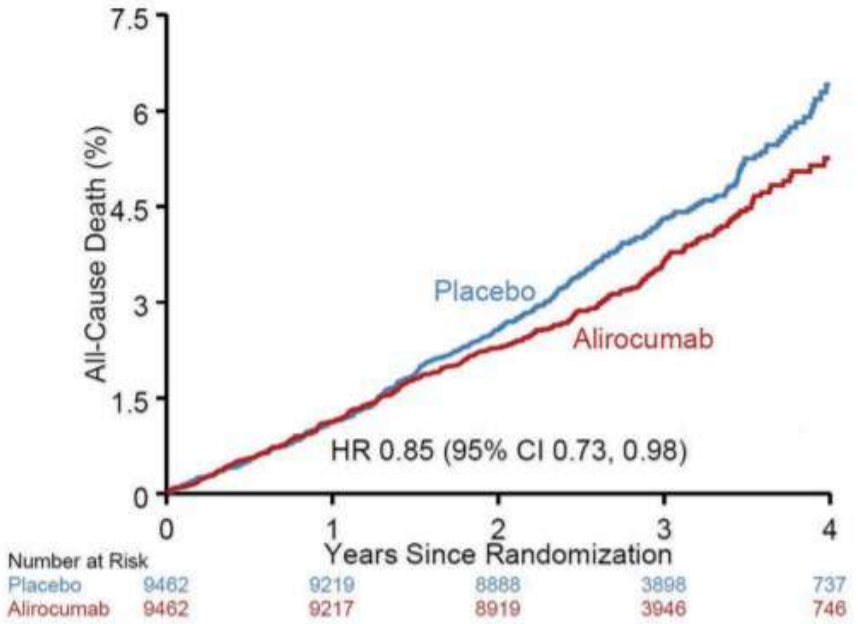
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 29, 2018 VOL. 379 NO. 22

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*





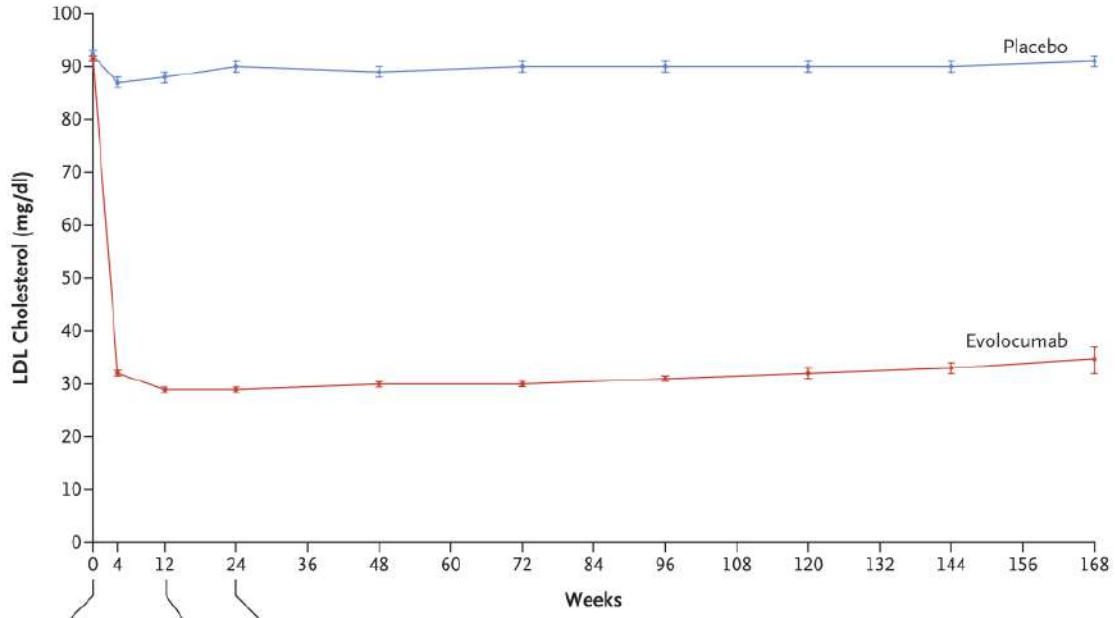
Alirocumab ha determinato una **riduzione del 15% del MACE con NNT di 49 pazienti trattati per 4 anni.** Relativamente ai soggetti con LDL > 100 mg/dl il beneficio era ancora più marcato, con un NNT di 16 pazienti trattati per 4 anni. Alirocumab ha anche determinato una **riduzione del 15% della mortalità per tutte le cause.**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

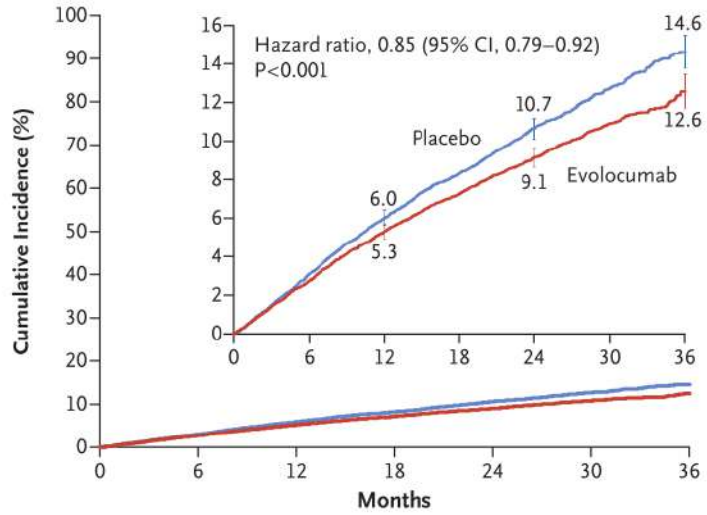
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*



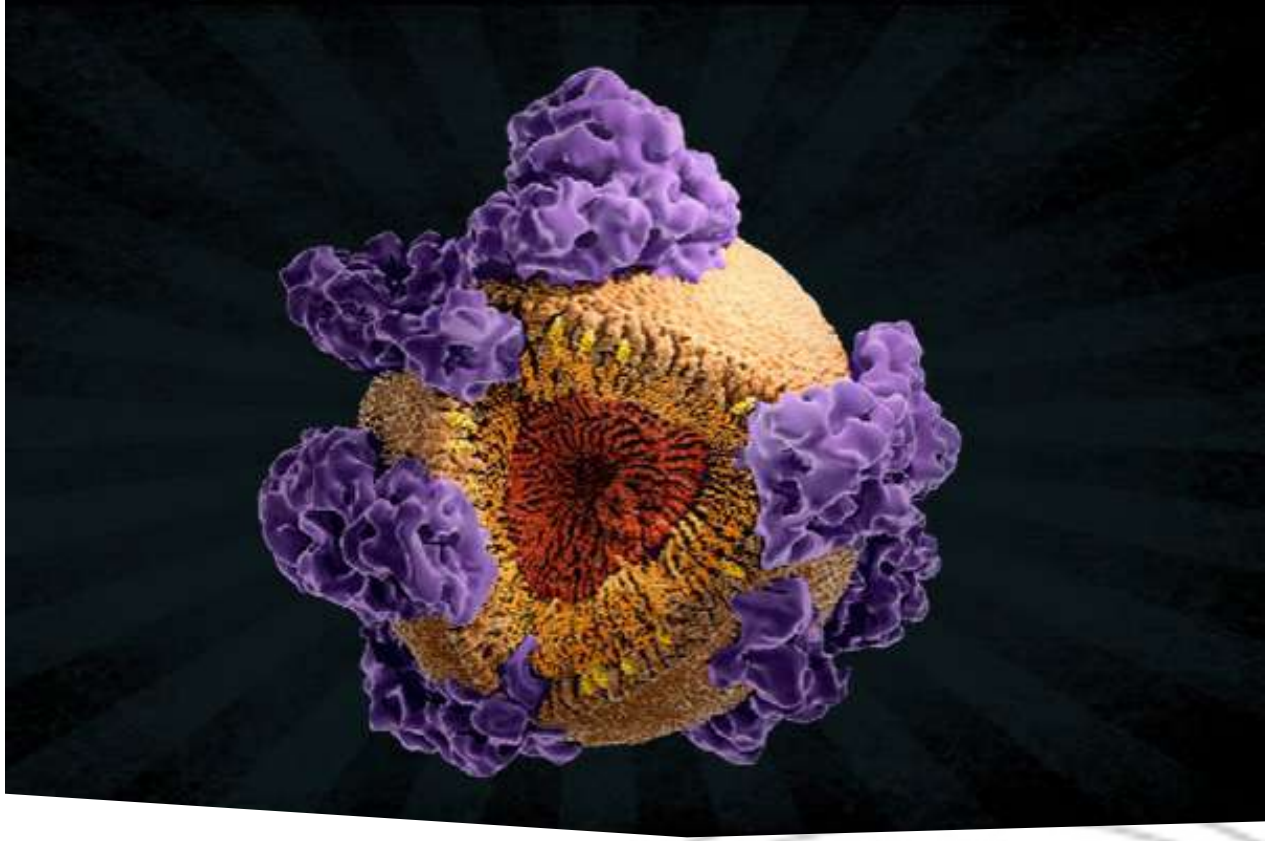
No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

A Primary Efficacy End Point



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

L'aggiunta di **evolocumab** alla terapia con statina ha determinato una **riduzione del 15% di rischio di end-point primario composito** (morte cardiovascolare, infarto, ictus ischemico, angina instabile con necessità di ricovero ospedaliero).



DISLIPIDEMIA 1.0

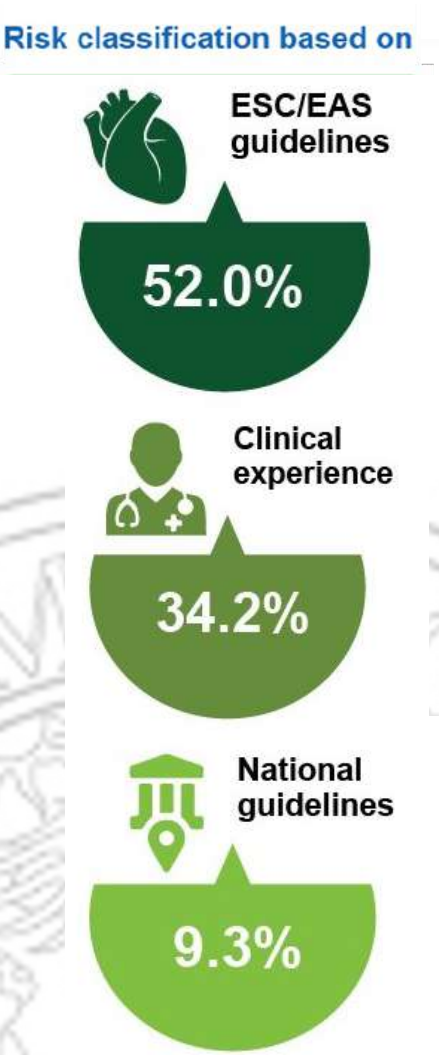
Studio SANTORINI – dati al baseline

SANTORINI

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

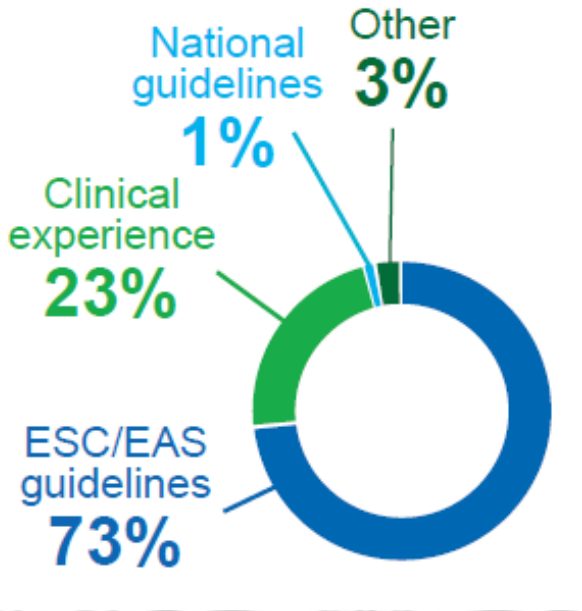
Studio SANTORINI – dati al baseline

Livelli di LDL-C molto più elevati rispetto agli obiettivi raccomandati dalle Linee Guida

SANTORINI ITALIA

Investigator reported risk categories

	Overall (N=1977)	Very High risk (N=1531)	High risk (N=446)
Patients at LDL-C goal, N (%)	**402 (20.3%)**	**305 (19.9%)**	**97 (21.8%)**
Laboratory values, Mean (SD)			
LDL-C, mg/dL	**98.4** (49.7)	**94.6** (47.3)	**111.4** (55.3)
non-HDL-C, mg/dL	**120.2** (54.4)	**116.0** (51.4)	**134.6** (61.7)
TC, mg/dL	**169.7** (57.6)	**163.3** (54.5)	**191.4** (62.4)
TG, mg/dL	**135.6** (91.9)	**134.8** (92.4)	**138.5** (90.1)
ApoB, g/L	**0.9** (0.4)	**0.9** (0.3)	**1.1** (0.4)
Lp(a)*, mg/L	**31.0** (10.0, 79.1)	**28.2** (10.0, 71.7)	**60.8** (13.0, 102.0)



- *Median (IQR)
- HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total choletsreol; TG, triglycerides.

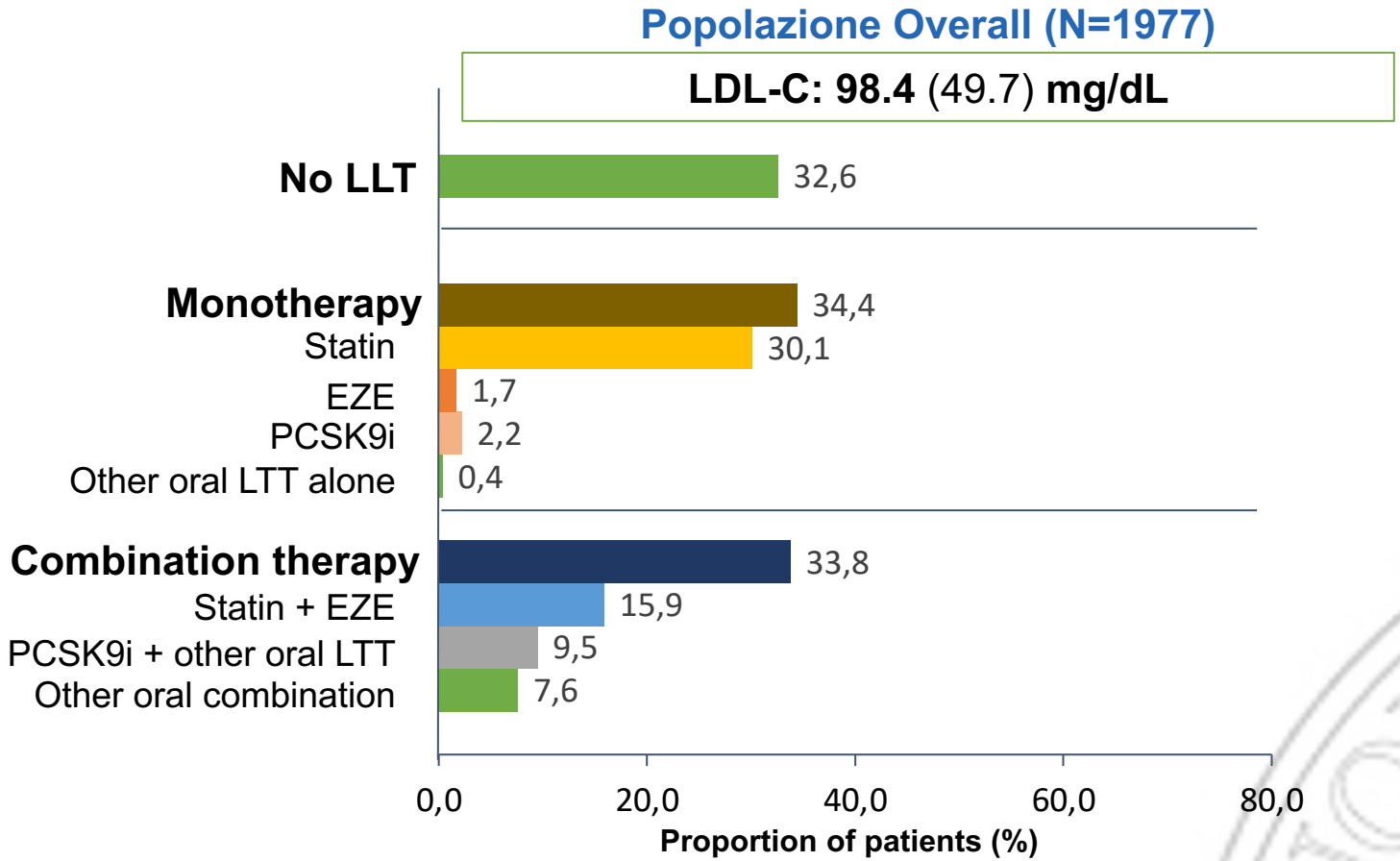
Arca M. et al, presented at SISA congress 2021

Tabella modificata da Arca M. et al. EAJ 2023;1:1-13 https://doi.org/10.56095/eaj.v2i1.26

Studio SANTORINI – dati al baseline

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

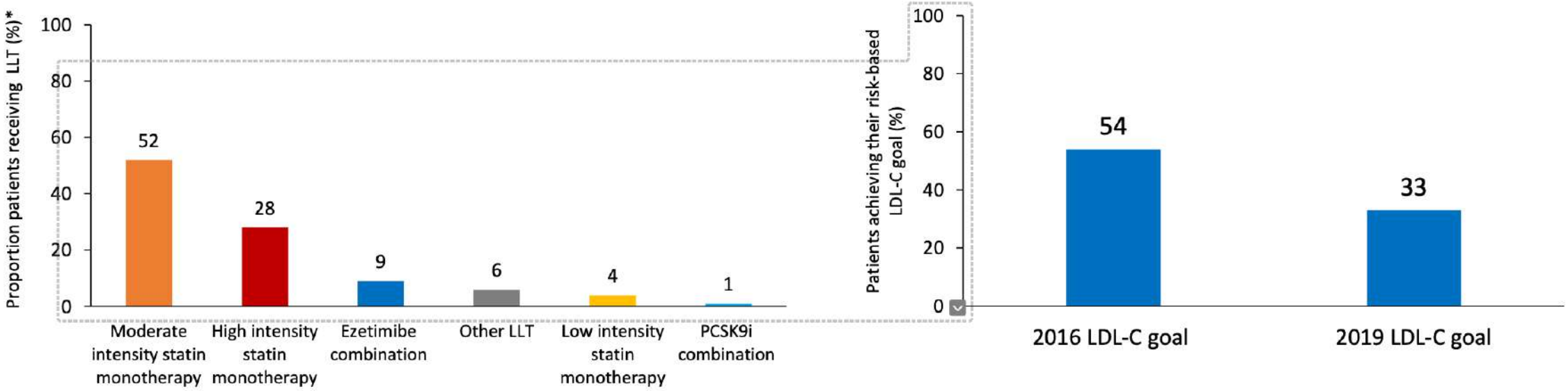
SANTORINI ITALIA



- 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).

Arca M. et al, presented at SISA congress 2021
Arca M. et al. EAJ 2023;1:1-13 https://doi.org/10.56095/eaj.v2i1.26

DA VINCI Study



- **The majority of patients were receiving moderate intensity statin monotherapy**
- **Only 28% of patients were receiving high intensity statin monotherapy**
- **Few patients (9%) were receiving ezetimibe combo**
- **A small number of patients (1%) received PCSK9i combo**

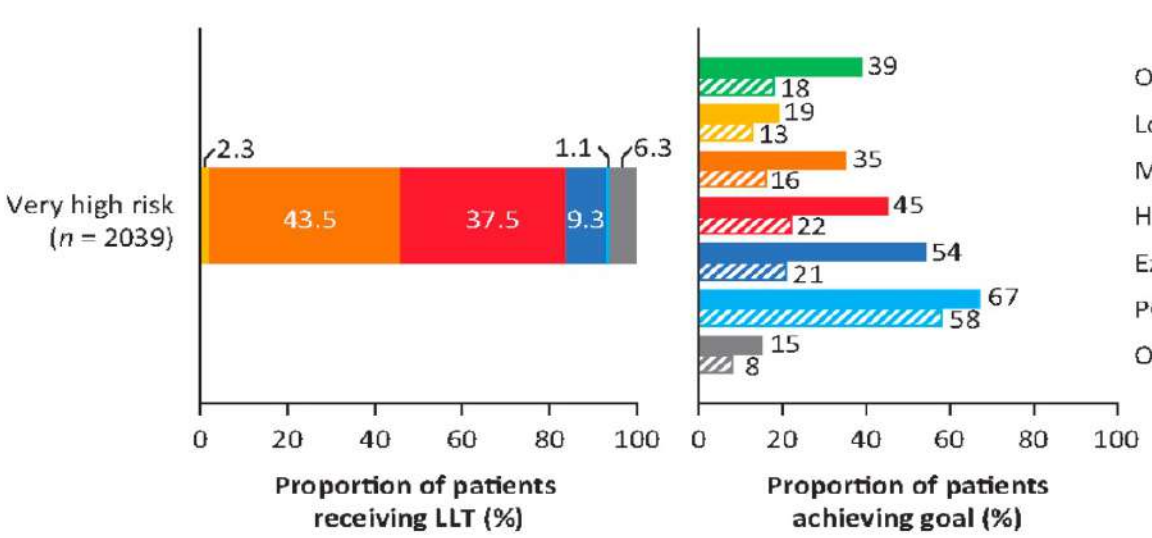
- **Approximately half of all patients did not achieve their 2016 risk-based LDL-C goal**
- **Only one-third achieved their 2019 risk-based LDL-C goal**

Ray KK EJP 2020

Real-World Data on Implementation of European Guideline Recommendations for Lipid-Lowering Therapies

18 country, cross-sectional, observational study of patients prescribed lipid lowering therapies for primary or secondary prevention in primary or secondary care across Europe

Established atherosclerotic cardiovascular disease group summarized by level of risk and statin regimen



Overall (*n* = 2039)
Low-intensity statin monotherapy (*n* = 47)
Moderate-intensity statin monotherapy (*n* = 887)
High-intensity statin monotherapy (*n* = 764)
Ezetimibe combination (*n* = 189)
PCSK9i combination (*n* = 24)
Other LLT (*n* = 128)

2016 2019
Overall
Low-intensity statin monotherapy
Moderate-intensity statin monotherapy
High-intensity statin monotherapy
Ezetimibe combination
PCSK9i combination
Other LLT

2016/2019 risk-based LDL-C targets:
Low risk: 2016/2019, <3.0 mmol/L
Moderate risk: 2016, <3.0 mmol/L; 2019, <2.6 mmol/L
High risk: 2016, <2.6 mmol/L; 2019, <1.8 mmol/L
Very high risk: 2016, <1.8 mmol/L; 2019, <1.4 mmol/L

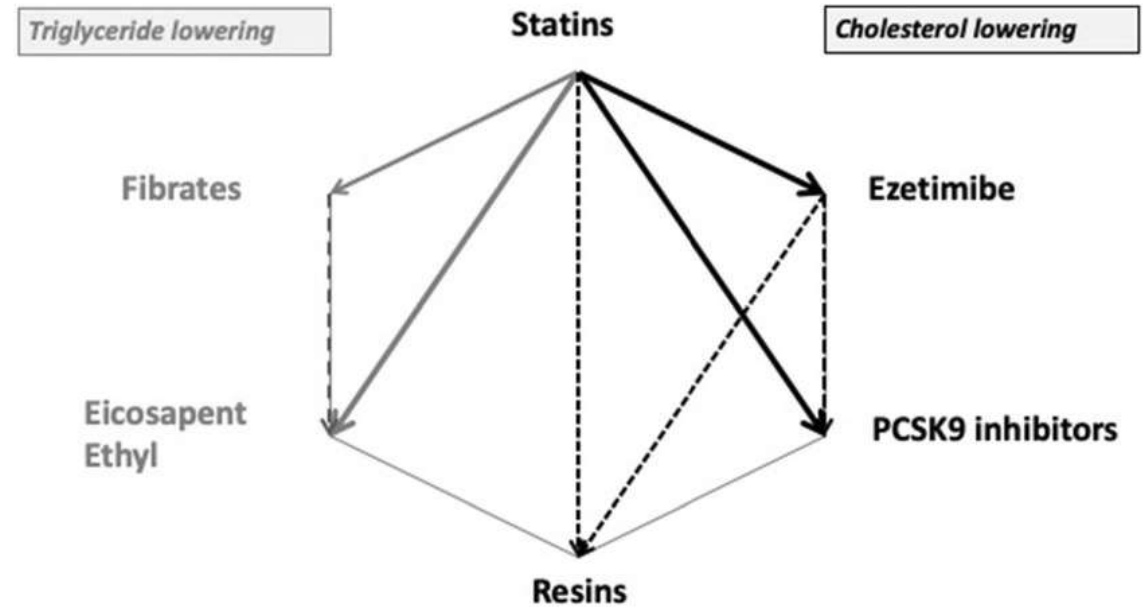
- Gaps persist between clinical guidelines and clinical practice for lipid management across Europe
- Greater utilization of non-statin therapy is likely needed to reduce these gaps for highest risk patients

Ray KK EJP 2020

DISLIPIDEMIA 2.0

Current Cardiology Reports (2020) 22: 66

a



ons Why Combination Therapy Should Be the New dard of Care to Achieve the LDL-Cholesterol Targets

owering combination therapy

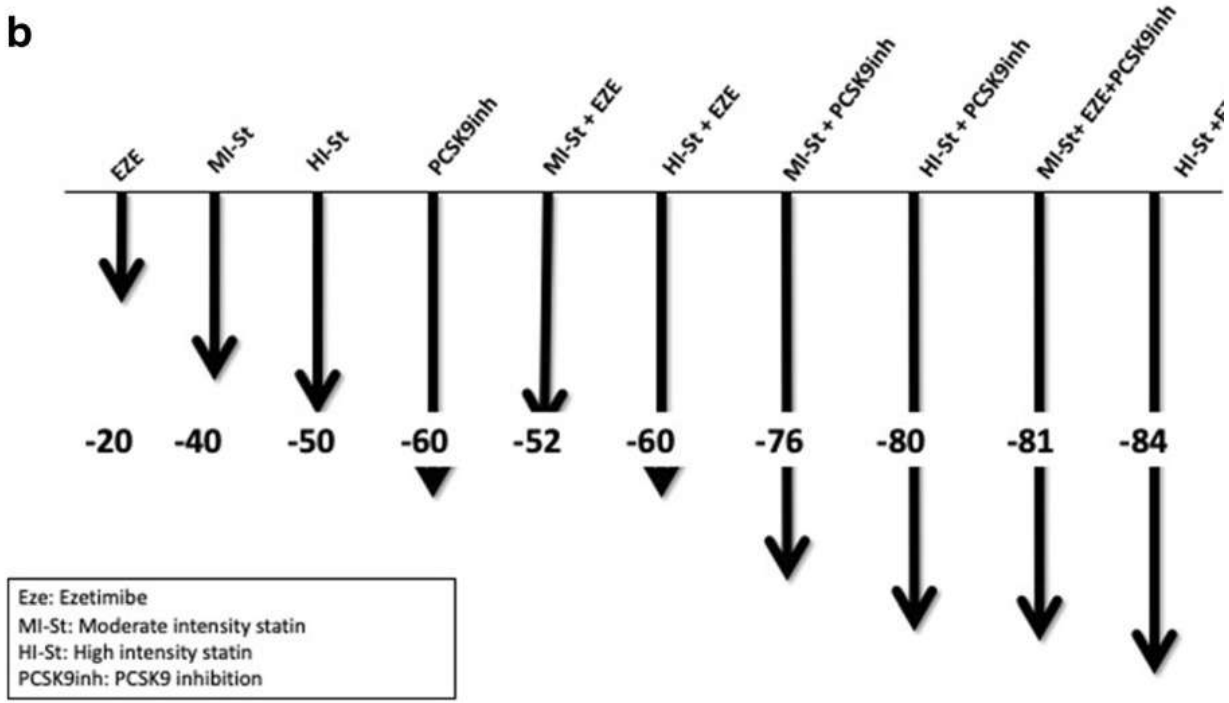
asana [1,2] · Daiana Ibarretxe [1,2] · Núria Plana [1,2]

A moderate-intensity statin plus ezetimibe is more efficient than high-intensity statin monotherapy

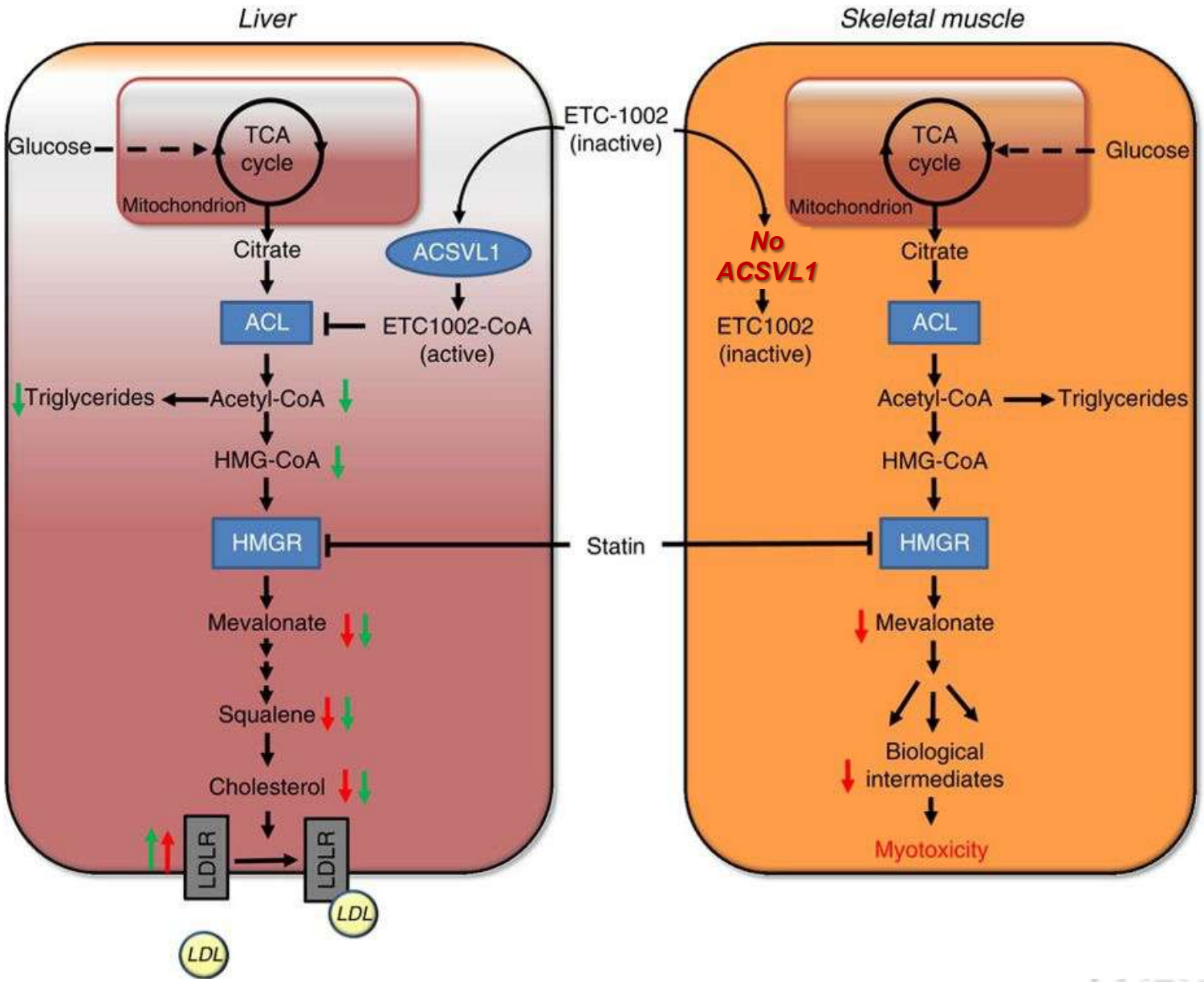
The widely implemented concept of high-intensity statin therapy must be replaced by high-intensity LDL-lowering therapy.

Combination therapies increase efficacy and reduce side effects associated with higher doses, increasing tolerability and leading to higher adherence.

b



ACIDO BEMPEDOICO

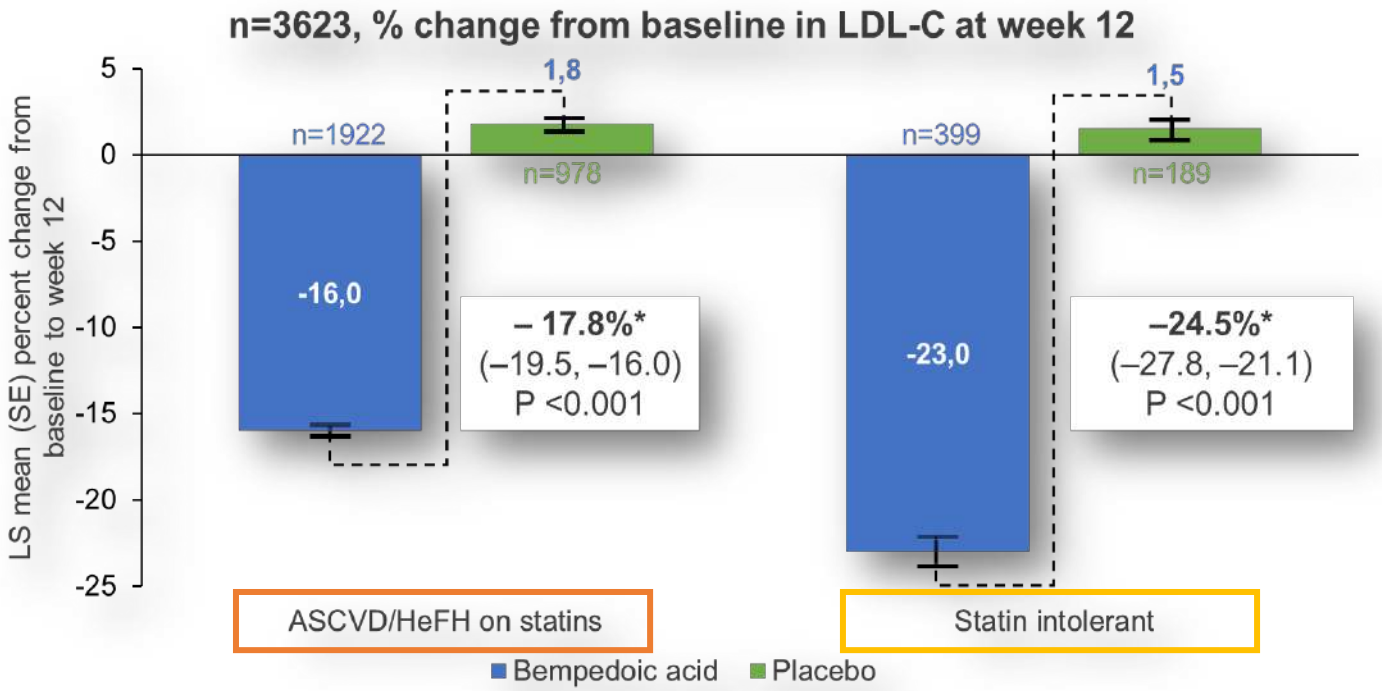


ASCVL1 is found primarily in the liver and is not detectable in skeletal muscle.

Therefore, bempedoic acid is not expected to cause muscle-related adverse effects that are associated with statins.

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

Efficacia

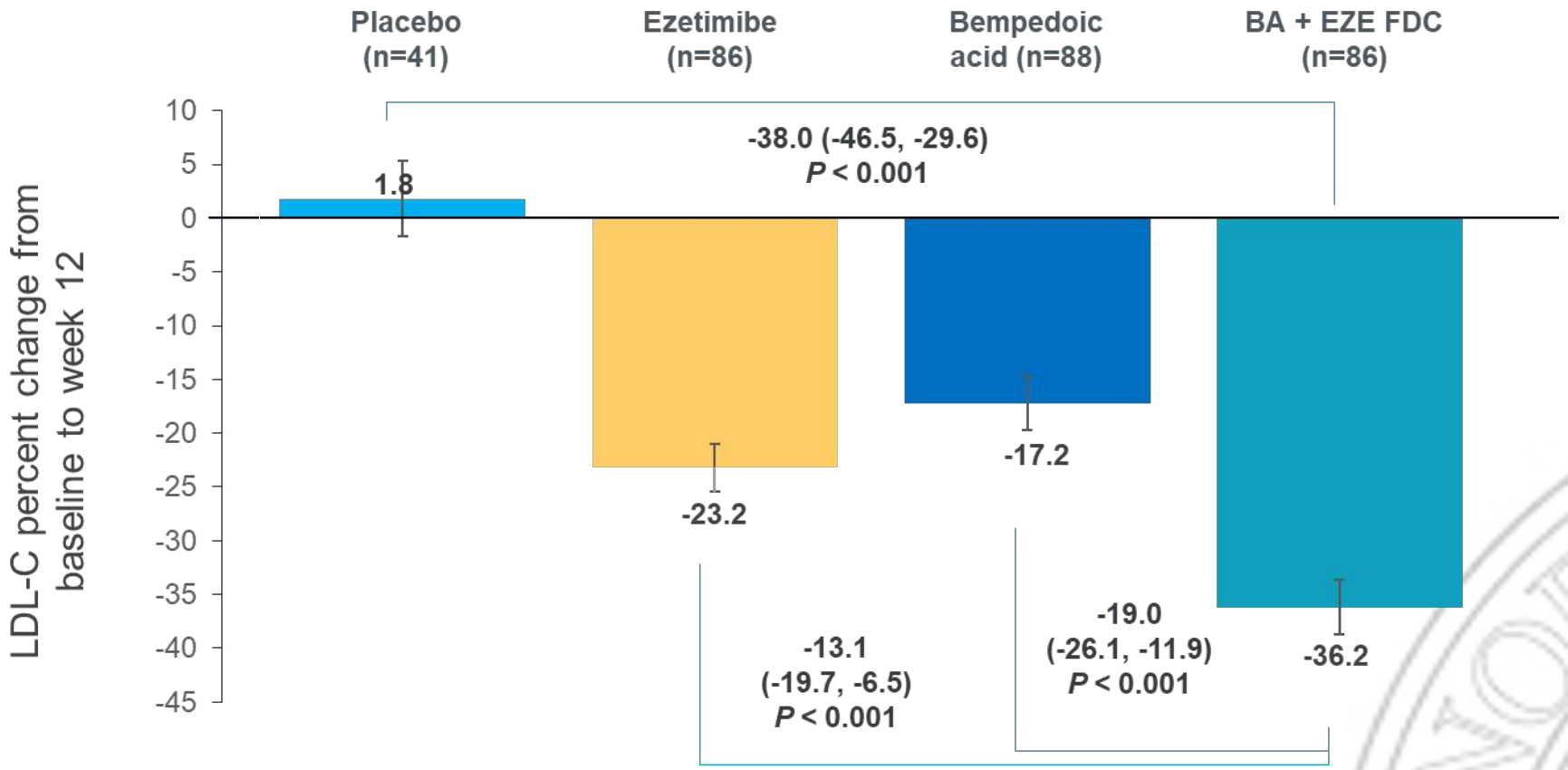


La riduzione media assoluta dei livelli di LDL-C associata con la somministrazione di acido bempedoico era **19.8 mg/dL** nei pazienti con ASCVD e/o HeFH in trattamento con statine alla massima dose tollerata e **36.5 mg/dL** nei pazienti intolleranti alle statine.

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

Acido Bempedoico + Ezetimibe FDC

Riduzione LDL-C 38%



L'associazione fissa acido bempedoico + EZE ha ridotto il colesterolo-LDL in maniera coerente nei vari sottogruppi considerati, compresi i sottogruppi trattati con terapia statinica sottostante a diversa intensità.

Il 33.7% dei pazienti nel braccio BA+Eze hanno ottenuto una riduzione di LDL-C ≥ 50% rispetto al basale

Post hoc population

BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination.

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

CLEAR OUTCOMES

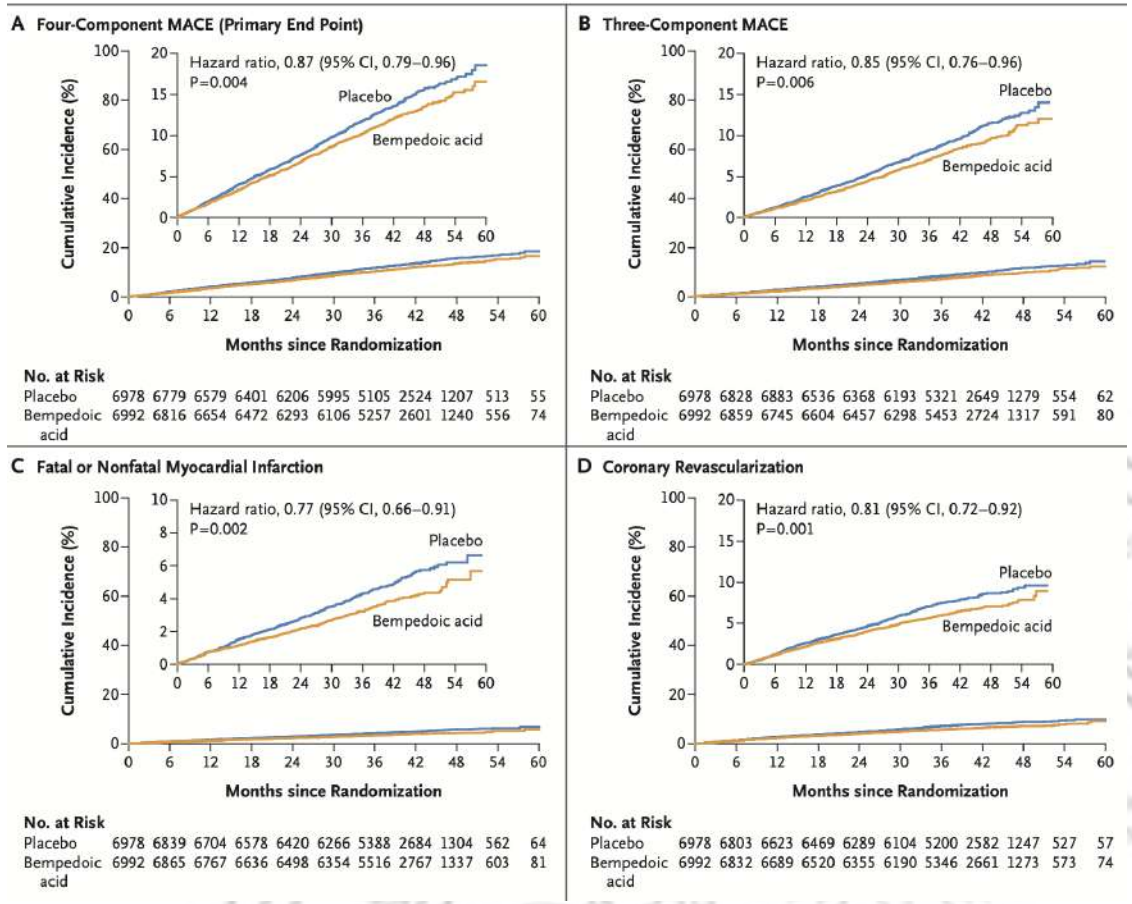
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 13, 2023 VOL. 388 NO. 15

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*

13,970 soggetti (6992 acido bempedoico; 6978 placebo) in follow-up per 40 mesi:

- **Riduzione** del **rischio** relativo (RRR) del **20%** di eventi avversi cardiovascolari maggiori (**MACE-4**)
- **Riduzione** del **rischio** di un **primo evento MACE-4 del 13**% tra i soggetti ad alto rischio di malattia cardiovascolare che non potevano o non volevano assumere statine
- **Assenza** di nuovi casi di **DM** (neutralità su glicemia e HbA1c)
- iperuricemia (10,9% vs. 5,6%), gotta (3,1% vs. 2,1%) e colelitiasi (2,2% vs. 1,2%).



Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

Un'analisi combinata di sicurezza condotta su più di 3.600 pazienti ha confermato che l'acido bempedoico è ben tollerato

Eventi avversi durante il trattamento	Acido Bempedoico N=2424, % (n)	Placebo N=1197, % (n)	*p*
Debolezza muscolare	0.5 (13)	0.6 (7)	0.82
Nuova insorgenza di diabete/iperglicemia	4.0 (96)	5.6 (67)	0.03
Aumento di acido urico nel sangue	2.1 (51)	0.5 (6)	< 0.001
Iperuricemia	1.7 (40)	0.6 (7)	0.007
Gotta	1.4 (33)	0.4 (5)	0.008
Aumento di creatinina nel sangue	0.8 (19)	0.3 (4)	0.12
Diminuzione della velocità di filtrazione glomerulare	0.7 (16)	<0.1 (1)	0.02
Aumento degli enzimi epatici	2.8 (67)	1.3 (15)	0.004
> 3 volte rispetto ai limiti superiori di riferimento	0.7 (18)	0.3 (3)	0.10
> 5 volte rispetto ai limiti superiori di riferimento	0.2 (6)	0.2 (2)	> 0.99
Disordini neurocognitivi	0.7 (16)	0.8 (9)	0.83

AE – adverse event; LLTs = lipid lowering therapies.

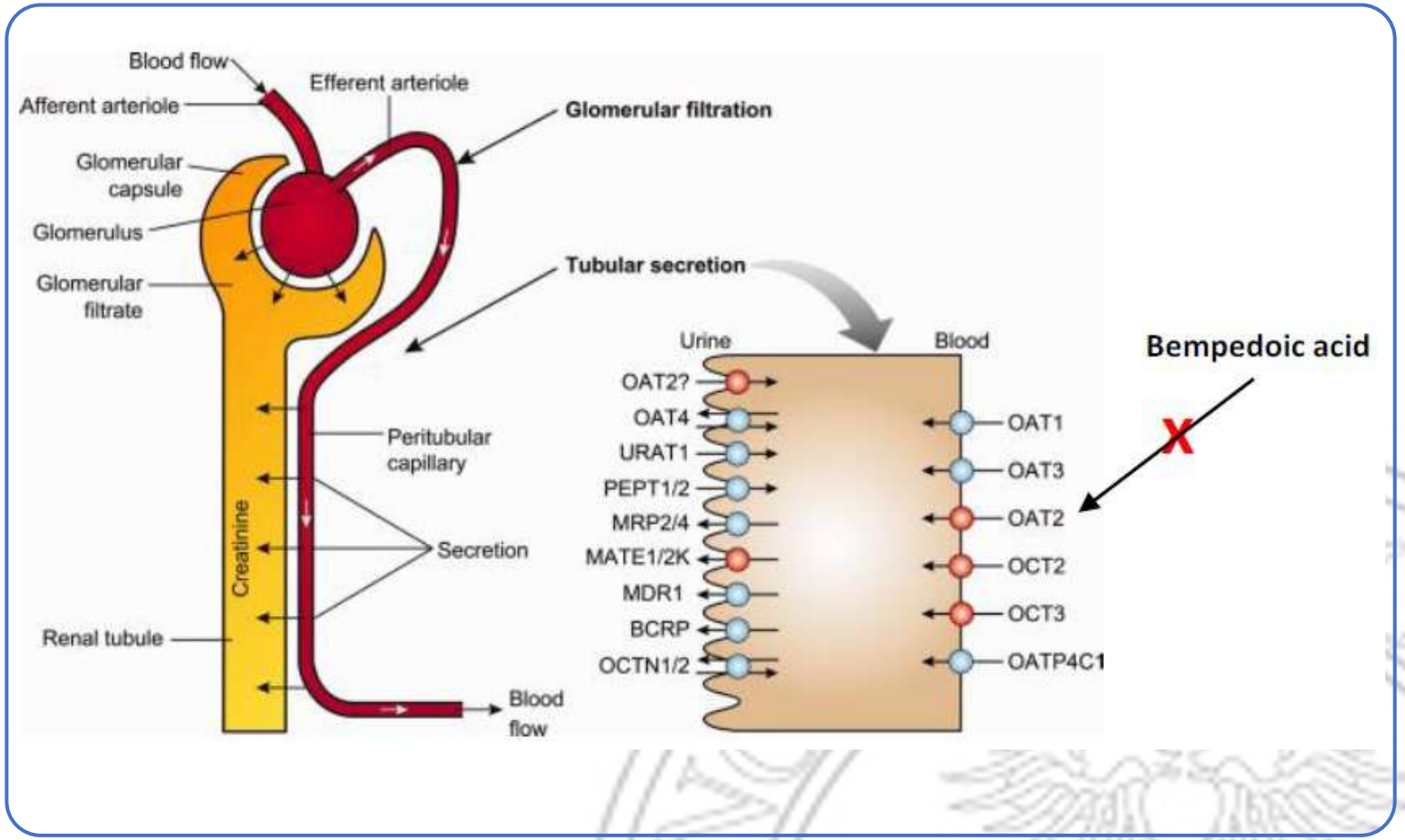
Eventi avversi di speciale interesse

- L'incidenza di mialgia e debolezza muscolare è risultata simile tra i gruppi di trattamento anche in pazienti con sottostante terapia statinica ad elevata intensità.
- **Modeste variazioni dei livelli ematici di creatinina e acido urico si sono verificate precocemente, sono risultate stabili nel tempo e reversibili dopo l'interruzione del farmaco.**
- **Episodi di gotta sono stati riportati più frequentemente nel gruppo di pazienti trattati con l'acido bempedoico rispetto al placebo, ma l'incidenza è stata comunque bassa in entrambi i gruppi di trattamento e gli eventi si sono verificati soprattutto in pazienti con una precedente diagnosi di gotta.**

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

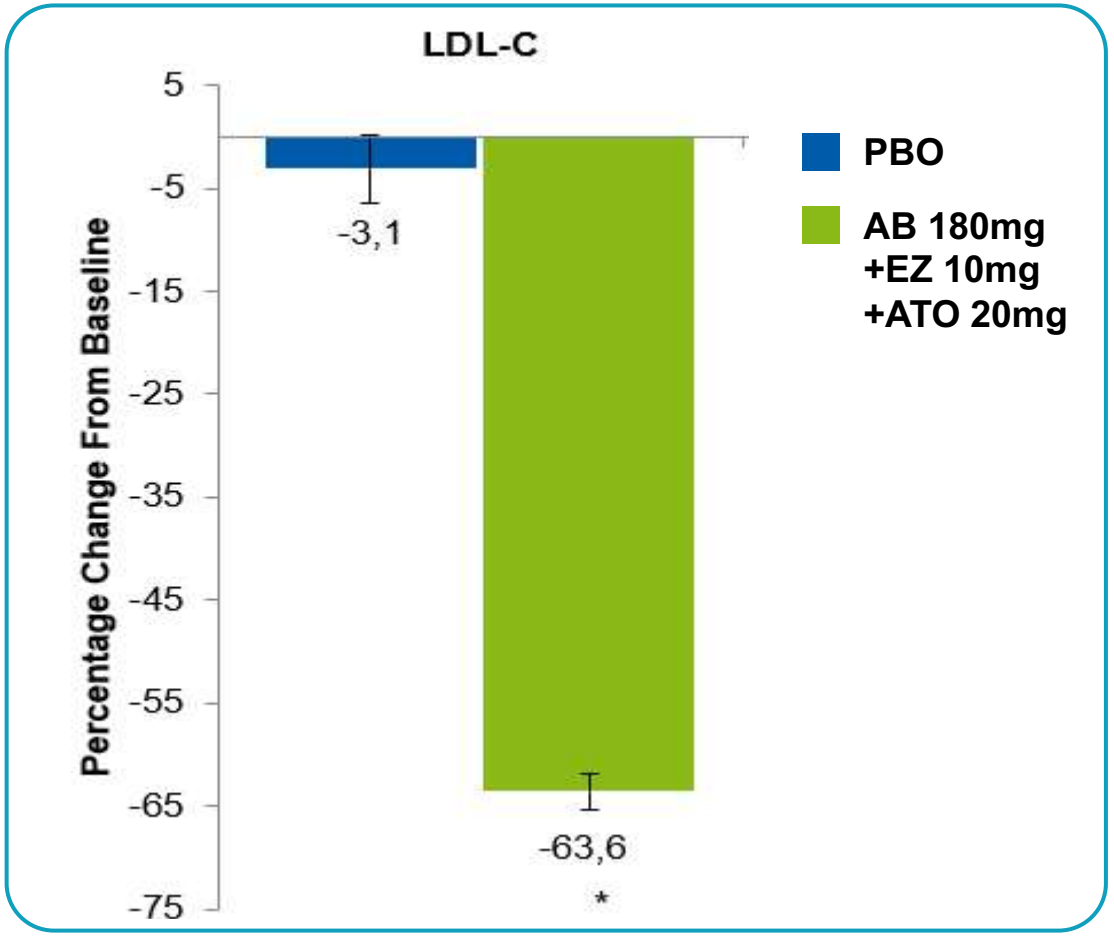
Gli aumenti di creatinina e acido urico osservati sono verosimilmente dovuti all'effetto dell'acido bempedoico sul trasportatore renale OAT2[1]

- OAT2 è un trasportatore renale coinvolto nell'escrezione sia della creatinina che dell'acido urico
- Studi pre-clinici hanno dimostrato che l'acido bempedoico è un debole inibitore dell'OAT2, con effetti specifici sulla attività di trasporto di acido urico e creatinina come substrati (dati non pubblicati)[1]
- Ulteriori evidenze pre-cliniche e cliniche sono necessarie per confermare questo meccanismo.



1. Bays HE et al., J Clin Lipidol 2020; 14:649-659.

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



Alla settimana 6:

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

Triplice terapia

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

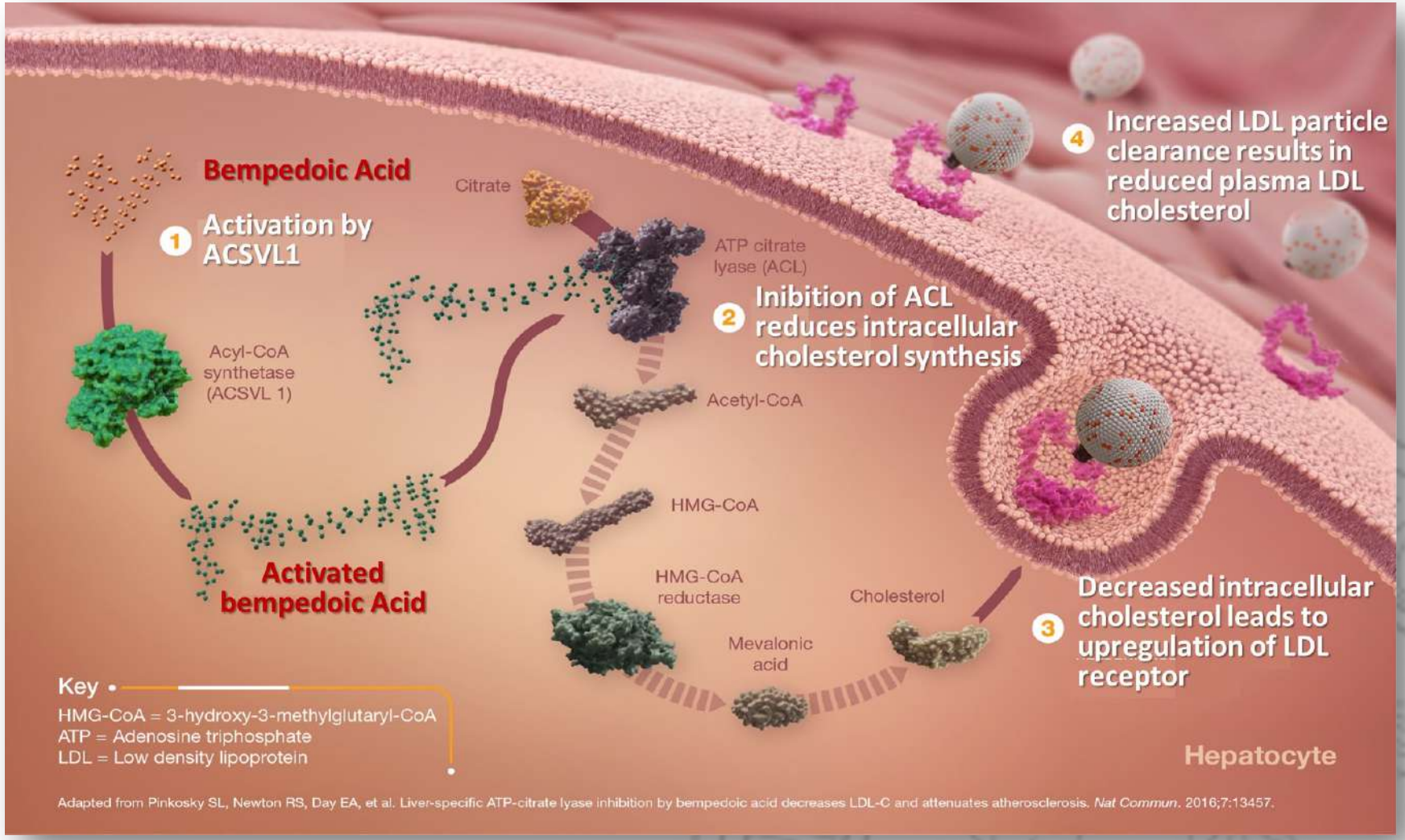
Least squares mean percentage changes from baseline to Week 6. Values are least-squares mean±SE
*p < .001 for the comparison of triple therapy vs placebo

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

ACIDO BEMPEDOICO

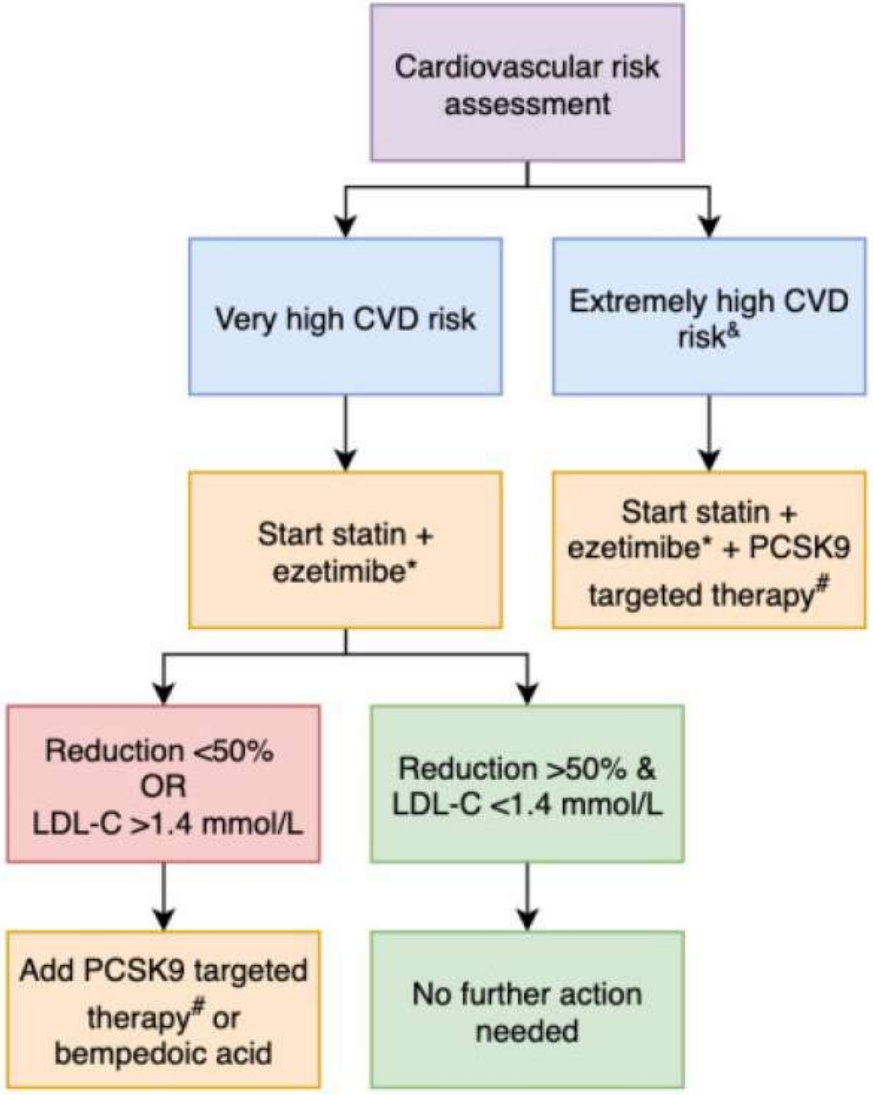
- **Attivato principalmente a livello epatico, l'acido bempedoico inibisce l'enzima ATP citrato liasi (ACL) nella ben nota via di sintesi del colesterolo, a monte rispetto al target delle statine**

- **La conseguente sovra-regolazione dei recettori per le LDL determina un'aumentata captazione di LDL da parte delle cellule epatiche con relativa riduzione dei livelli plasmatici di C-LDL**



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

Terapia di combinazione strategia di prima linea nei pazienti a rischio molto elevato

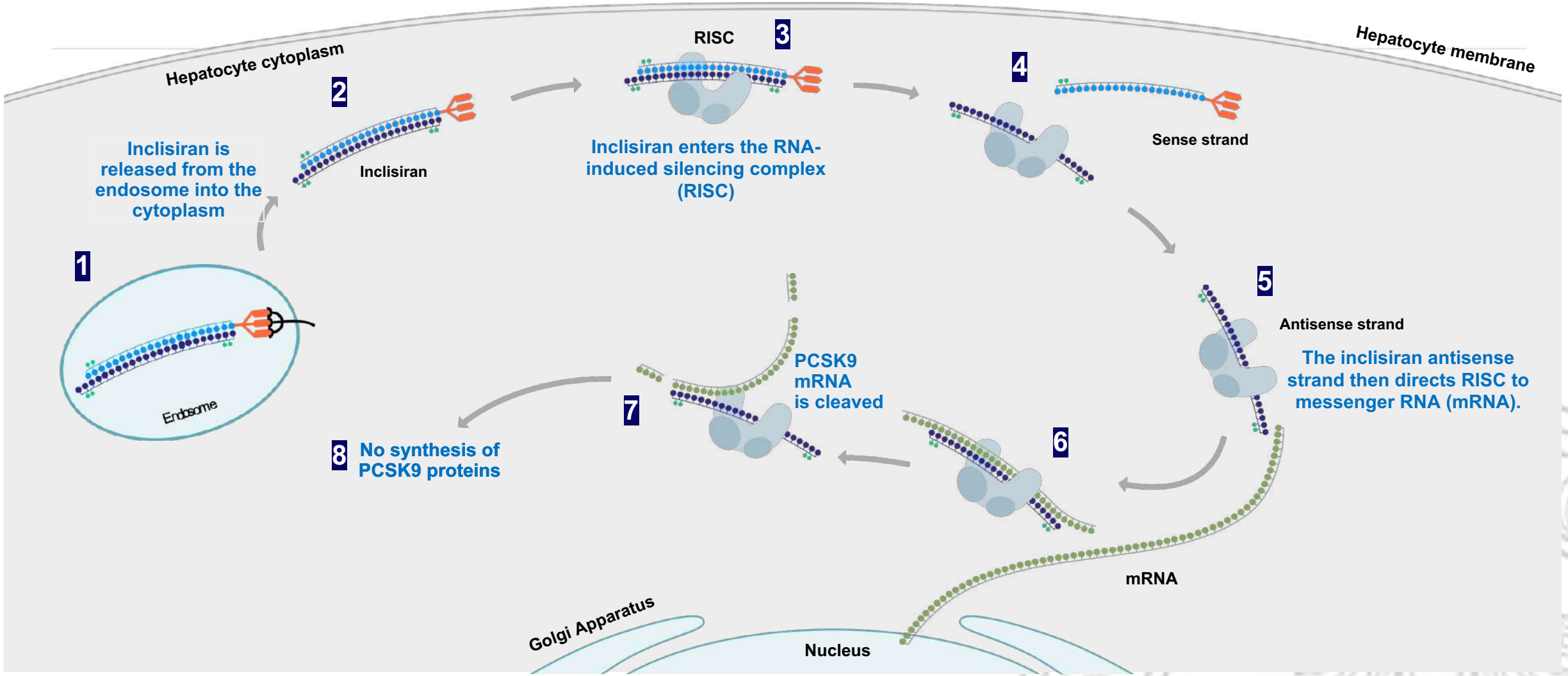


"If patients do not achieve the 2019 guideline-recommended LDL cholesterol goal of >50% reduction and levels <1.4 mmol/L (54 mg/dL), ***a third lipid-lowering therapy, such as bempedoic acid or PCSK9 targeted therapies should be added****."*

Ray K et al, *European Heart Journal* -(2021) 00, 1–4 doi:10.1093/eurheartj/ehab718

Inclisiran mechanism of action

Inclisiran promotes mRNA PCSK9 cleavage by activating RISC



A Highly Durable RNAi Therapeutic Inhibitor of PCSK9

B **Change in PCSK9 Level in Multiple-Dose Cohorts**

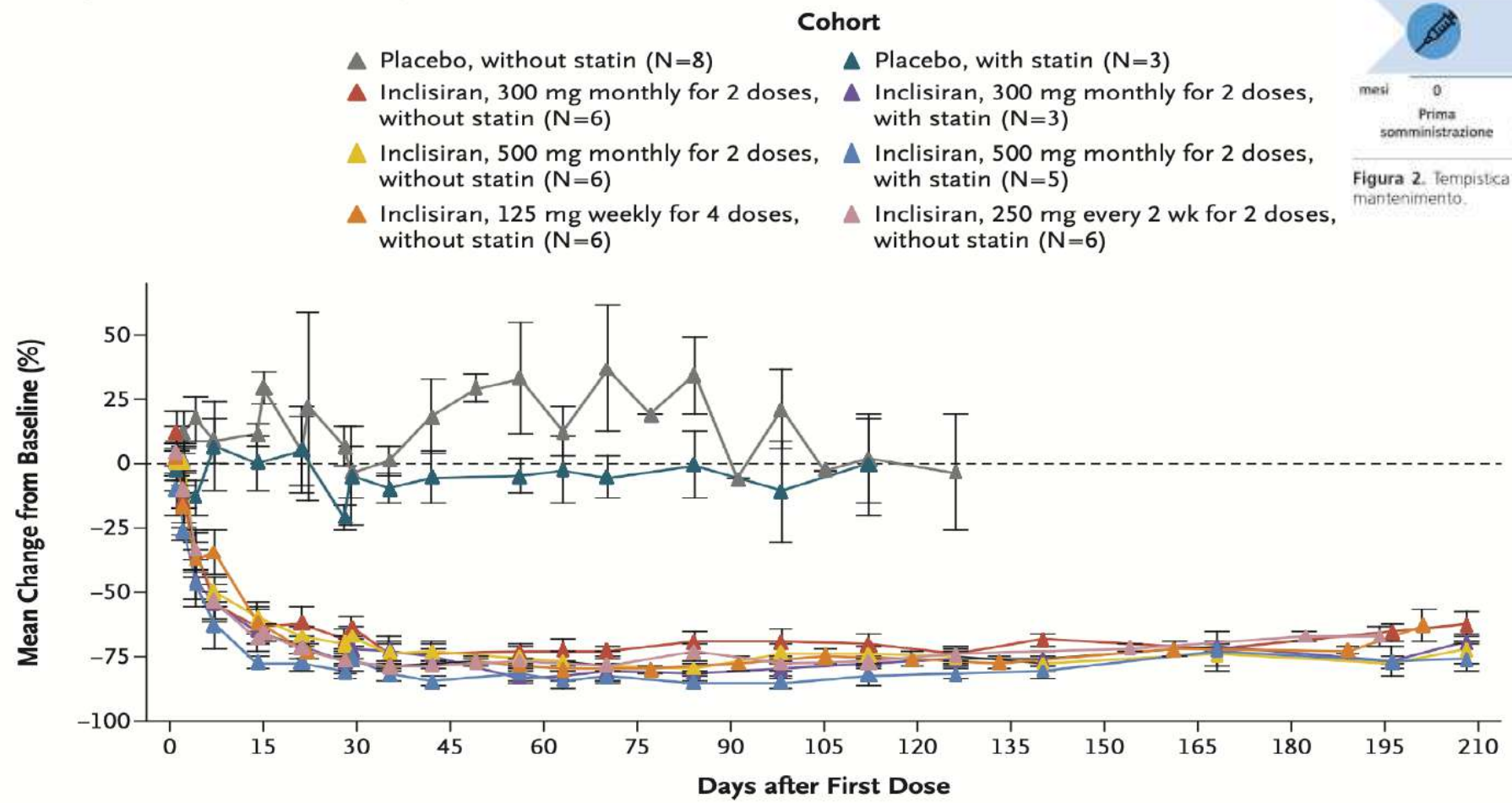


Figura 2. Tempistica di somministrazione delle dosi iniziali di inclisiran e di quelle di mantenimento.

N Engl J Med 2017;376:41-51. DOI: 10.1056/NEJMoa1609243

ESC European Society of Cardiology
European Heart Journal (2023) **44**, 129–138
https://doi.org/10.1093/eurheartj/ehac594

Inclisiran and cardiovascular events: a patient-level analysis of phase III trials

Inclisiran

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Day 1	Day 30	Day 90	Day 150	Day 270	Day 330	Day 450	Day 510	Day 540

↓ Circulating PCSK9

Liver

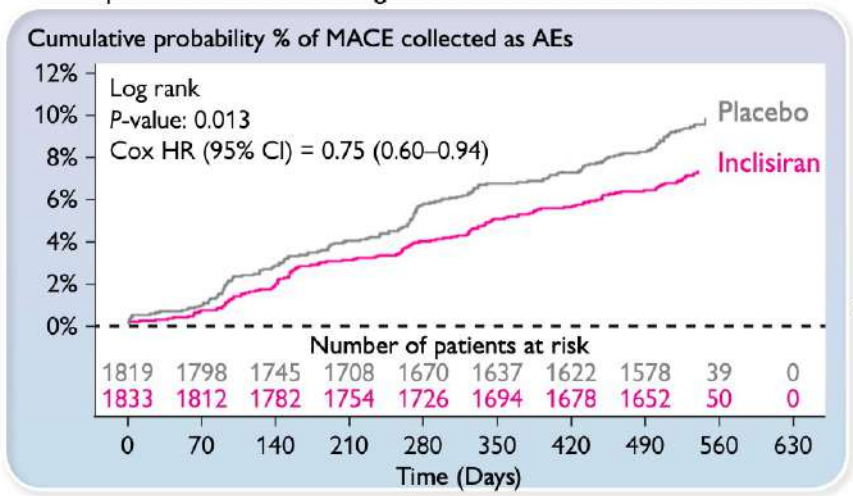
Transcription → Translation

DNA mRNA ↓ Target protein

Inclisiran (siRNA)

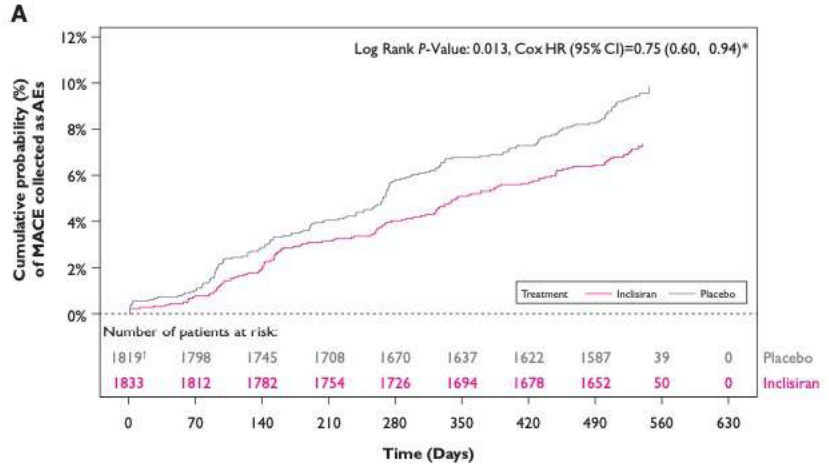
siRNAs prevent protein production by degrading unique target mRNA

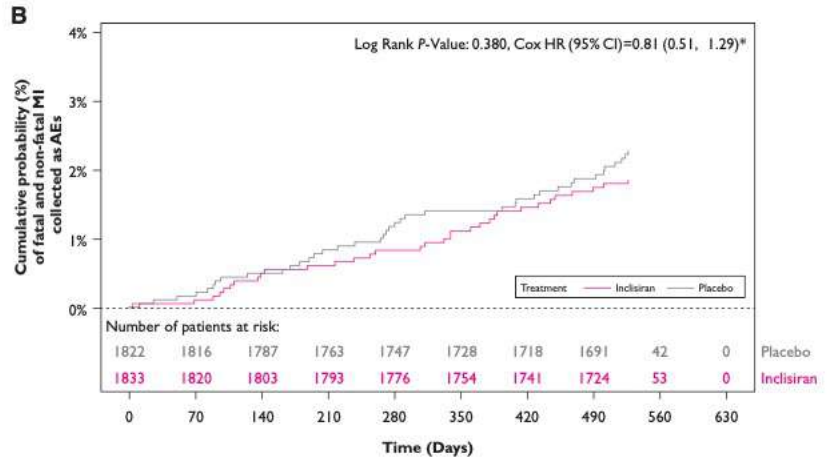
Kaplan-Meier curves showing the cumulative event rate for MACE

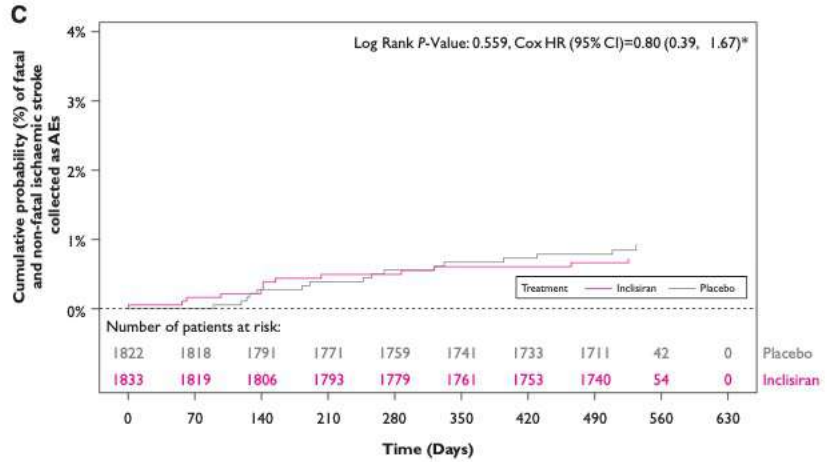


LDL-C ↓ by

Day 90	1.37 mmol/L
Day 540	1.38 mmol/L







LDL-receptor independently therapies

Evinacumab summary

- Evinacumab, showed a "remarkable" and unprecedented level of LDL-cholesterol lowering in a pivotal trial in HoFH
- Ph3 Pivotal Study: 47.1% decrease in LDL-C levels was observed in evinacumab treated patients compared with an increase of 1.9% in the placebo group at week 24
- Long-Term Study: Mean LDL-C reductions of -43.7% at week 24 were maintained at Week 48

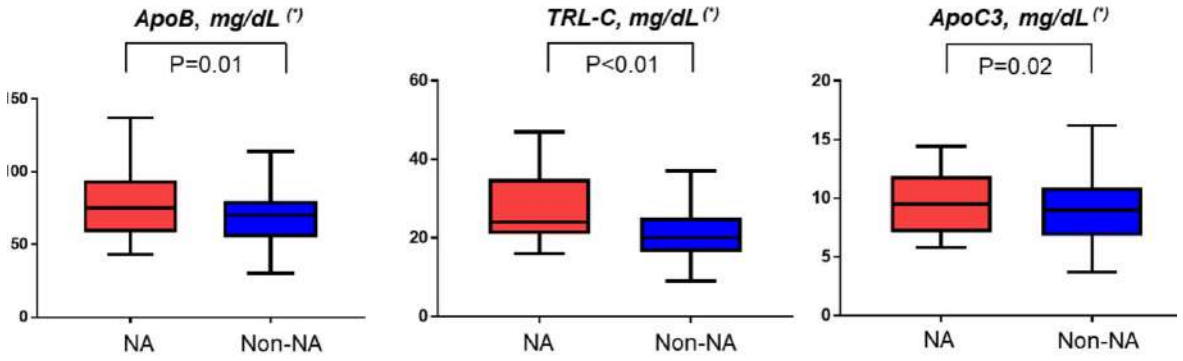
Lomitapide summary

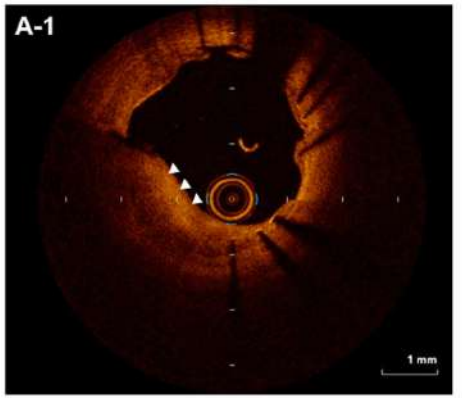
- Lomitapide has shown similar LDL-C reductions in HoFH patients to evinacumab
- 40% LDL-C reduction intent to treat (ITT) prespecified analysis – Ph3 study
- 50% LDL-C reduction and Completers Analysis – Ph3 study
- 68.2 – 76.5% LDL-C reduction – Italian real world data
- 60% LDL-C reduction – Pan-European Data

J Clin Lipidol. 2023 Mar-Apr;17(2):281-290

Impact of Triglyceride-rich lipoproteins on Early In-stent neoatherosclerosis formation in patients undergoing statin treatment

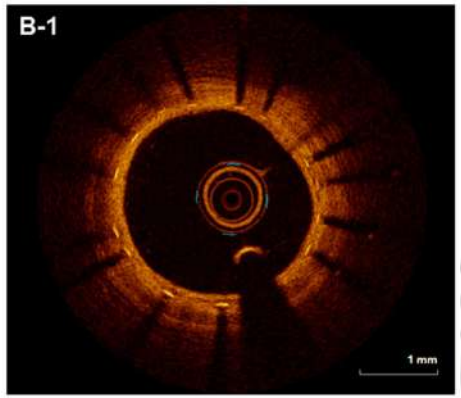
Variable	NA (n=17)	Non-NA (n=97)	P-value
TG, mg/dL	132.0 (120.0–200.0)	120.0 (75.5–147.0)	0.03
Non-HDL-C, mg/dL	100.0 (90.0–123.0)	90.0 (75.0–102.5)	0.05
HDL-C, mg/dL	42.0 (36.5–49.5)	47.0 (39.0–54.5)	0.17
LDL-C, mg/dL	77.2 ± 25.4	69.8 ± 18.7	0.15
Hs-CRP, mg/L	0.43 (0.26–1.32)	0.59 (0.24–1.85)	0.77
MDA-LDL, U/L	91.0 (64.0–98.5)	69.0 (60.0–81.0)	0.03





A-2

TG	150.0 mg/dL
LDL-C	51.0 mg/dL
HDL-C	48.0 mg/dL
Non-HDL-C	75.0 mg/dL
TRL-C	24.0 mg/dL
MDA-LDL	54.0 U/L
Apo B	51.0 mg/dL
Apo C3	9.0 mg/dL
Hs-CRP	0.40 mg/L



B-2

TG	76.0 mg/dL
LDL-C	73.0 mg/dL
HDL-C	53.0 mg/dL
Non-HDL-C	88.0 mg/dL
TRL-C	15.0 mg/dL
MDA-LDL	53.0 U/L
Apo B	65.0 mg/dL
Apo C3	5.8 mg/dL
Hs-CRP	0.49 mg/L

Fibrati

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PLOS | ONE

Variants Identified in a GWAS Meta-Analysis for Blood Lipids Are Associated with the Lipid Response to Fenofibrate

Stella Aslibekyan[1*], Mark O. Goodarzi[3,4], Alexis C. Frazier-Wood[1,2], Xiaofei Yan[4], Marguerite R. Irvin[1], Eric Kim[4], Hemant K. Tiwari[2], Xiuqing Guo[4], Robert J. Straka[5], Kent D. Taylor[4], Michael Y. Tsai[6], Paul N. Hopkins[8], Stanley G. Korenman[9], Ingrid B. Borecki[7,9], Yii-Der I. Chen[4], Jose M. Ordovas[10,11,12,9], Jerome I. Rotter[4], Donna K. Arnett[1,9]

ARTICLES

Genetic Variants in *HSD17B3*, *SMAD3*, and *IP011* Impact Circulating Lipids in Response to Fenofibrate in Individuals With Type 2 Diabetes

Daniel M. Rotroff[1,2], Sonja S. Pijut[3], Skylar W. Marvel[1], John R. Jack[1], Tammy M. Havener[4], Aurora Pujol[5,6], Agatha Schluter[5], Gregory A. Graf[3,7,8], Henry N. Ginsberg[9], Hetal S. Shah[10], He Gao[10], Mario-Luca Morieri[10], Alessandro Doria[10], Josyf C. Mychaleckyj[11], Howard L. McLeod[12], John B. Buse[13], Michael J. Wagner[4], Alison A. Motsinger-Reif[1,2] and the ACCORD/ACCORDion Investigators

A genome-wide study of lipid response to fenofibrate in Caucasians: a combined analysis of the GOLDN and ACCORD studies

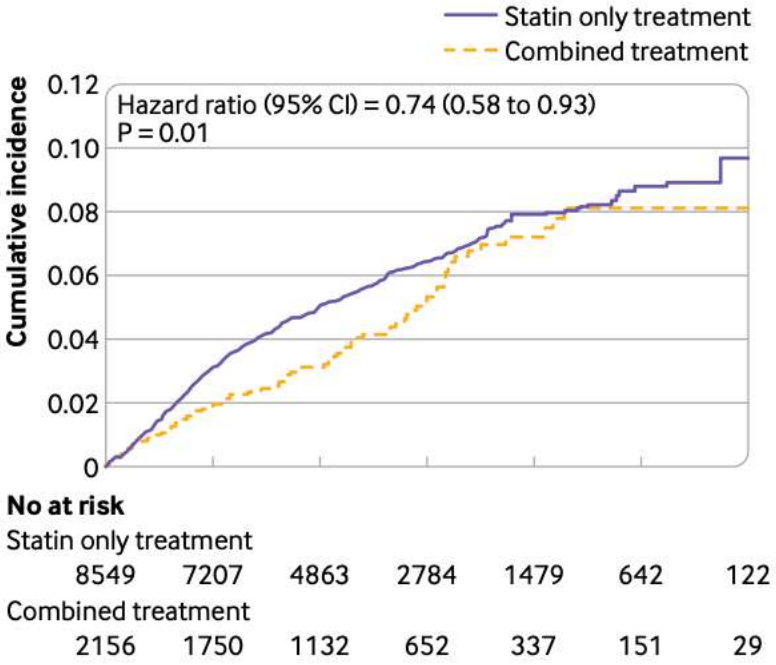
Marguerite R. Irvin[a,*], Daniel M. Rotroff[c,*], Stella Aslibekyan[a,*], Degui Zhi[b,*], Bertha Hidalgo[a], Alison Motsinger-Reif[c], Skylar Marvel[c], Vinodh Srinivasasainagendra[b], Steven A. Claas[a], John B. Buse[d], Robert J. Straka[f], Jose M. Ordovas[g], Ingrid B. Borecki[h], Xiuqing Guo[i], Ida Y.D. Chen[j], Jerome I. Rotter[k], Michael J. Wagner[e,*] and Donna K. Arnett[a,*]

Use of fenofibrate on cardiovascular outcomes in statin users with metabolic syndrome: propensity matched cohort study

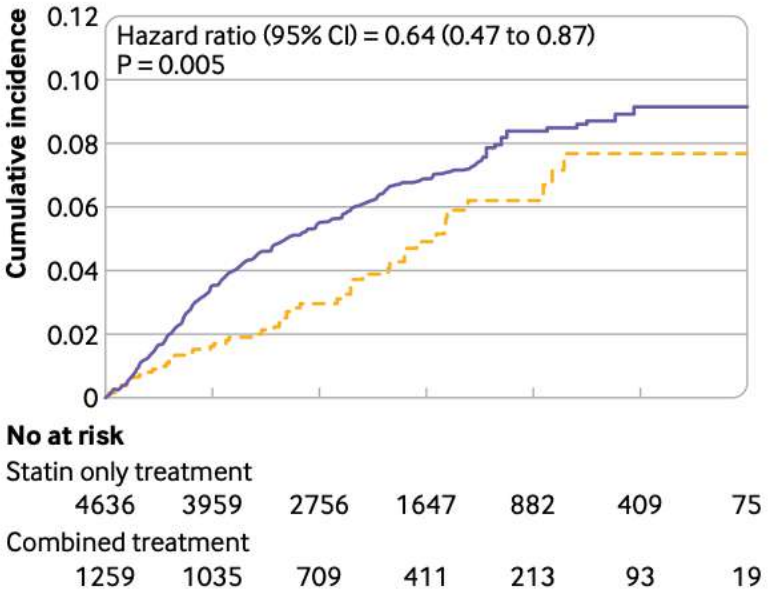
Nam Hoon Kim,[1] Ki Hoon Han,[2] Jimi Choi,[3] Juneyoung Lee,[3] Sin Gon Kim[1]

CONCLUSION

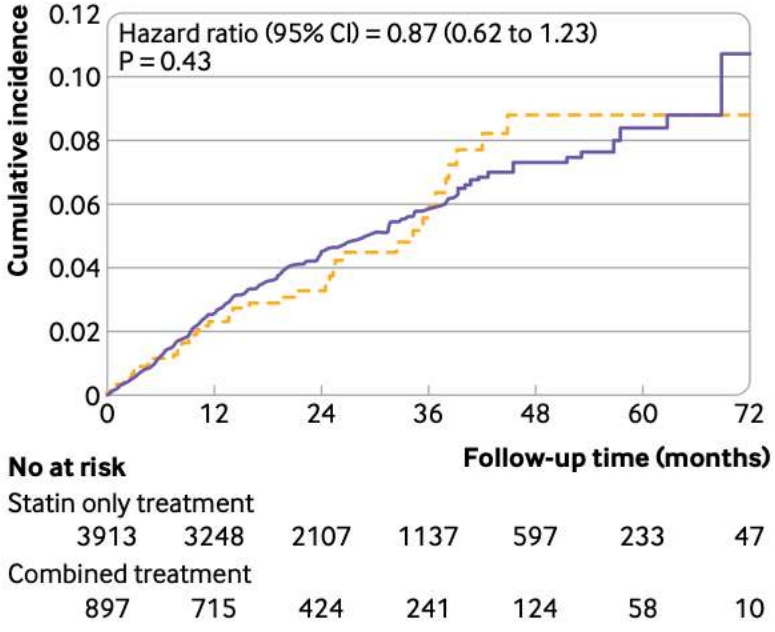
In this propensity weighted cohort study of adults with metabolic syndrome, the risk of major cardiovascular events was significantly lower with fenofibrate as add-on to statin treatment than with statin treatment alone.



All partecipants



High TGs, low HDL



Low TGs, high HDL

BMJ 2019;366:l5125

Journal of Clinical Lipidology

Efficacy and safety of pemafibrate (K-877), a selective peroxisome proliferator-activated receptor α modulator, in patients with dyslipidemia: Results from a 24-week, randomized, double blind, active-controlled, phase 3 trial

Table 2 Primary efficacy analyses on the percent change from baseline in TG

Treatment group	Baseline (mmol/L) Mean (SD)	% Change from baseline LS mean (SE)	Difference vs fenofibrate LS mean (SE) [95% CI]
Pemafibrate 0.2 mg/d	2.7 (0.6)	−46.2 (2.0)*	−6.5 (2.8) [−12.0, −1.1]†
Pemafibrate 0.4 mg/d	2.6 (0.7)	−45.9 (1.9)*	−6.2 (2.7) [−11.6, −0.8]†
Fenofibrate 106.6 mg/d	2.7 (0.8)	−39.7 (1.9)*	

ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error ; TG, triglycerides.

LS mean and 95% CI were estimated using a repeated measures ANCOVA model with the baseline as a covariate applied for the percentage changes in TG from baseline to Weeks 8, 12, 16, 20, and 24. The primary efficacy analyses were noninferiority and superiority of pemafibrate 0.2 and 0.4 mg/d to fenofibrate 106.6 mg/d. Predefined noninferiority margin was 10%. Multiplicity in the noninferiority and the superiority testings was adjusted by the closed testing procedure method to test the noninferiority before the superiority.

*$P < .001$ vs baseline.

†$P < .05$ vs fenofibrate.

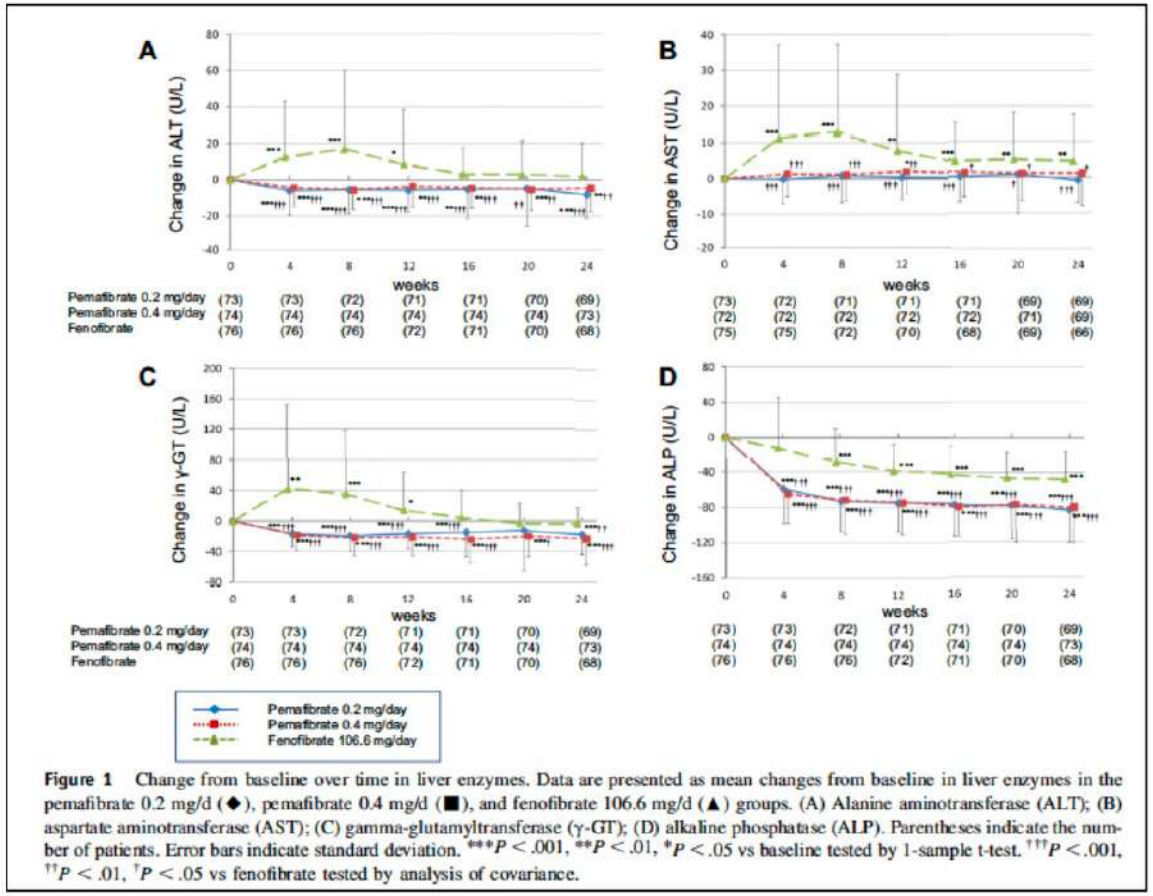


Figure 1 Change from baseline over time in liver enzymes. Data are presented as mean changes from baseline in liver enzymes in the pemafibrate 0.2 mg/d (◆), pemafibrate 0.4 mg/d (■), and fenofibrate 106.6 mg/d (▲) groups. (A) Alanine aminotransferase (ALT); (B) aspartate aminotransferase (AST); (C) gamma-glutamyltransferase (γ-GT); (D) alkaline phosphatase (ALP). Parentheses indicate the number of patients. Error bars indicate standard deviation. ***$P < .001$, **$P < .01$, *$P < .05$ vs baseline tested by 1-sample t-test. †††$P < .001$, ††$P < .01$, †$P < .05$ vs fenofibrate tested by analysis of covariance.

The NEW ENGLAND JOURNAL of MEDICINE

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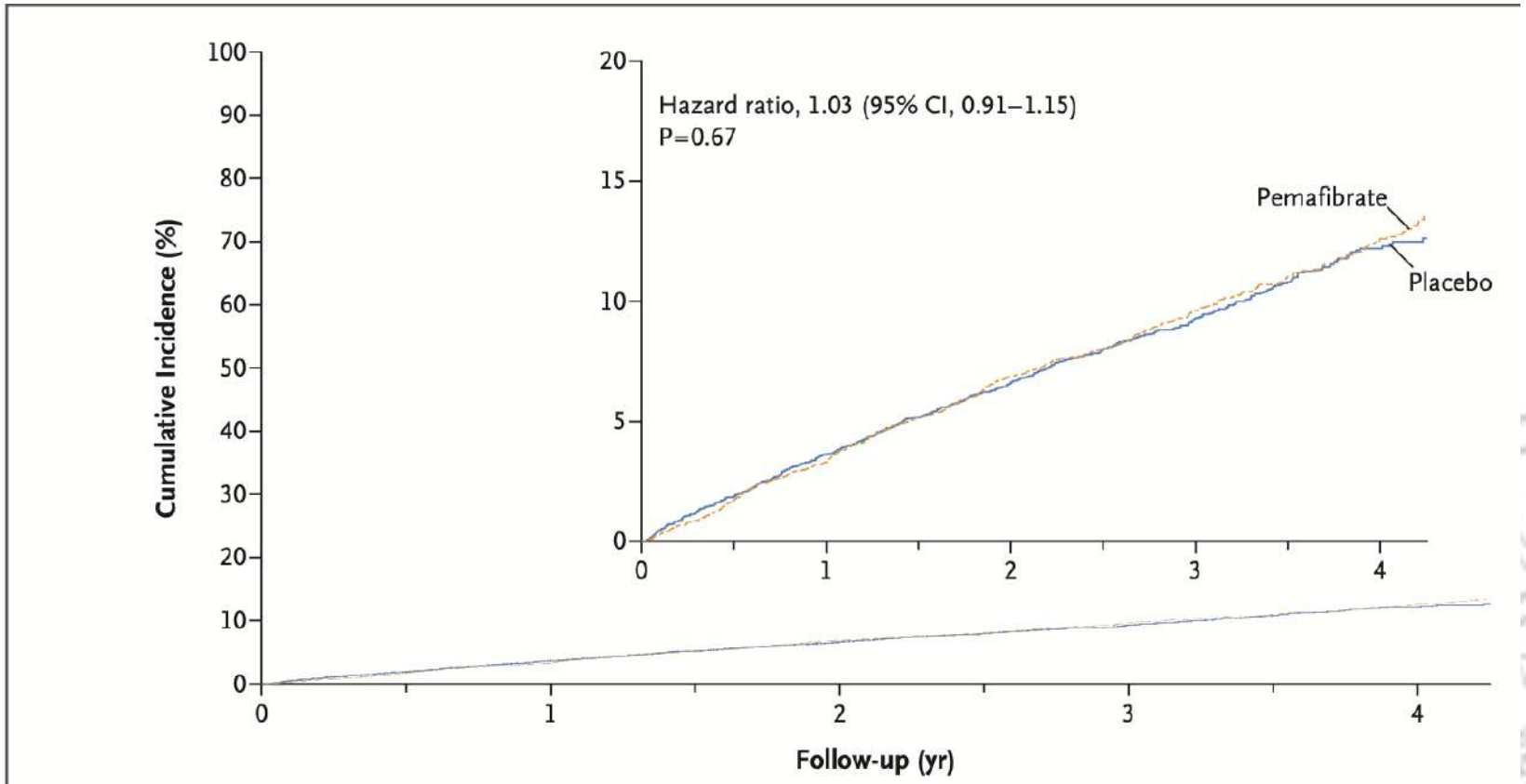
Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk



No. at Risk									
Pemafibrate	5240	5060	4901	4742	4552	3627	2820	2067	1147
Placebo	5257	5082	4925	4762	4596	3651	2838	2063	1130

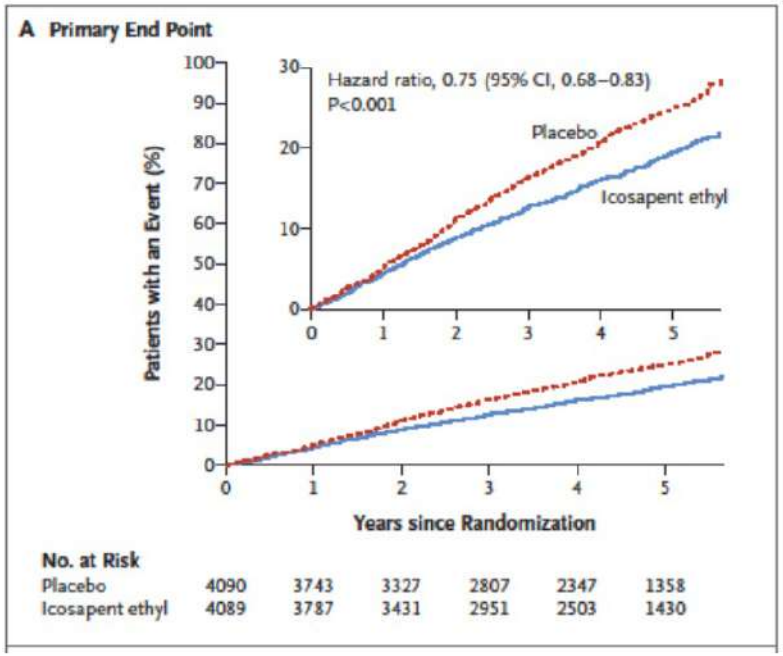
Figure 1. Cumulative Incidence of Cardiovascular Events.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*



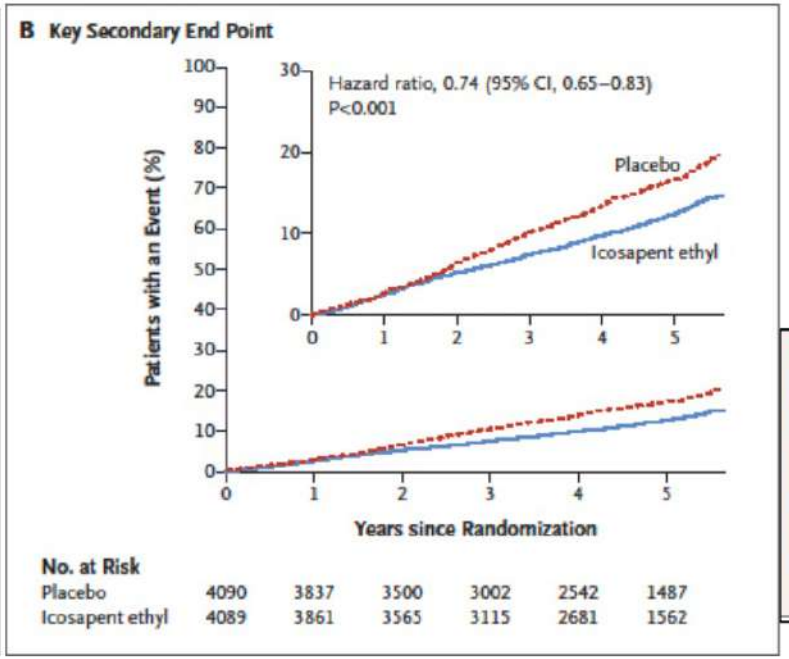


Figure 1. Cumulative Incidence of Cardiovascular Events.

Panel A shows the Kaplan–Meier event curves for the primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis. Panel B shows the Kaplan–Meier event curves for the key secondary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the two trial groups, in a time-to-event analysis. In each panel, the inset shows the same data on an expanded y axis. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Supplementary Table 3. Select Prespecified Adjudicated Tertiary Endpoints – ITT Population.

Tertiary Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)
Primary Endpoint in Patients with Diabetes at Baseline	433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68, 0.87)

Benefits of Icosapent Ethyl Across the Range of Kidney Function in Patients With Established Cardiovascular Disease or Diabetes: REDUCE-IT RENAL

Clinical Perspective

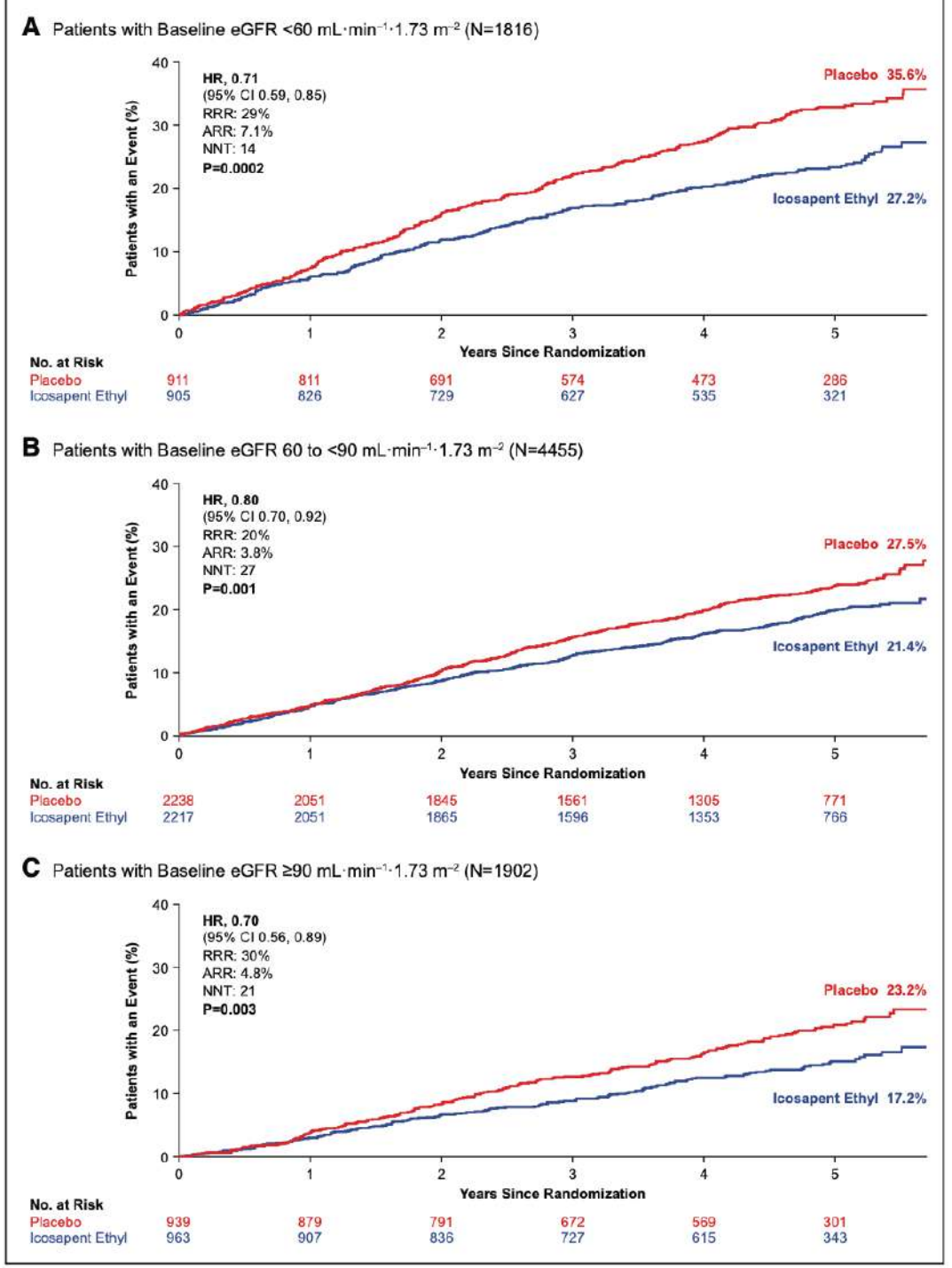
What Is New?

- Icosapent ethyl reduced cardiovascular events among patients with elevated triglycerides and well-controlled low-density lipoprotein cholesterol on statin therapy across a wide range of baseline kidney function.

What Are the Clinical Implications?

- Despite having a well-controlled low-density lipoprotein cholesterol on statin therapy, patients with elevated triglycerides have significant residual risk for coronary events.
- Treatment with icosapent ethyl has been shown to significantly reduce cardiovascular events and mortality in this patient population.
- These findings are applicable to patients with chronic kidney disease across the spectrum of baseline kidney function.

4 g/daily vs placebo



Circulation. 2021;144:1750–1759.

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–98
https://doi.org/10.1093/eurheartj/ehad192

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Lipids and diabetes—*Section 5.5*

A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.	I	A
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), a PCSK9 inhibitor added to ezetimibe should be considered.	IIa	B
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.	IIa	C
High-dose icosapent ethyl (2 g b.i.d.) may be considered in combination with a statin in patients with hypertriglyceridaemia.	IIb	B

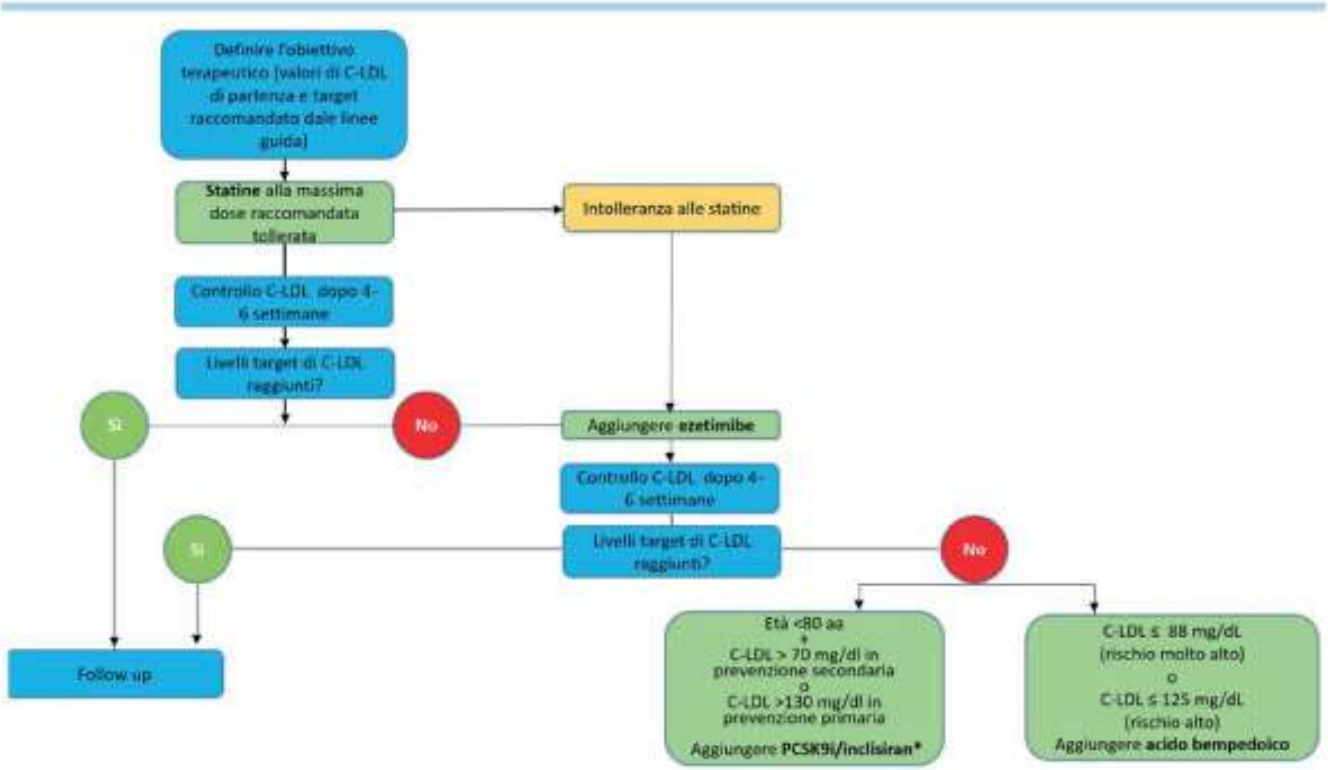
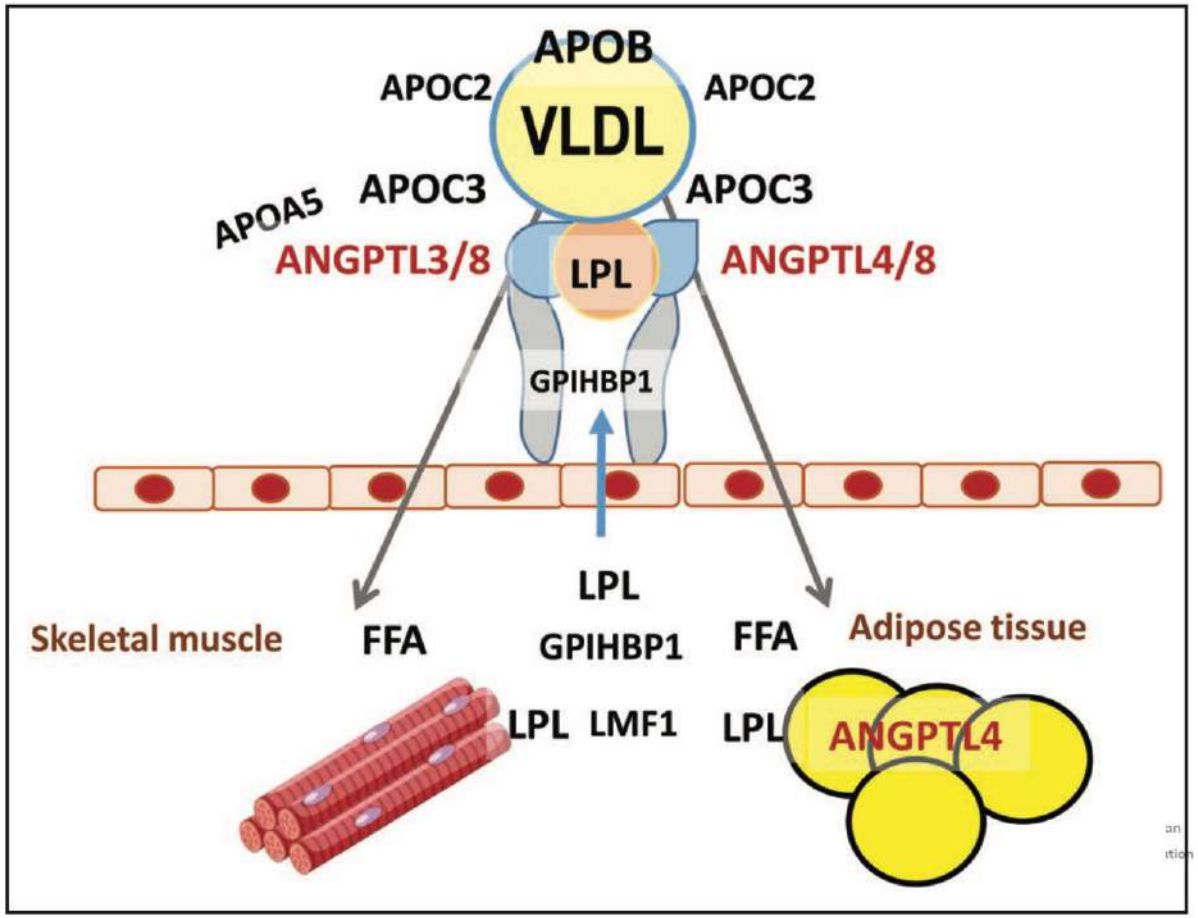
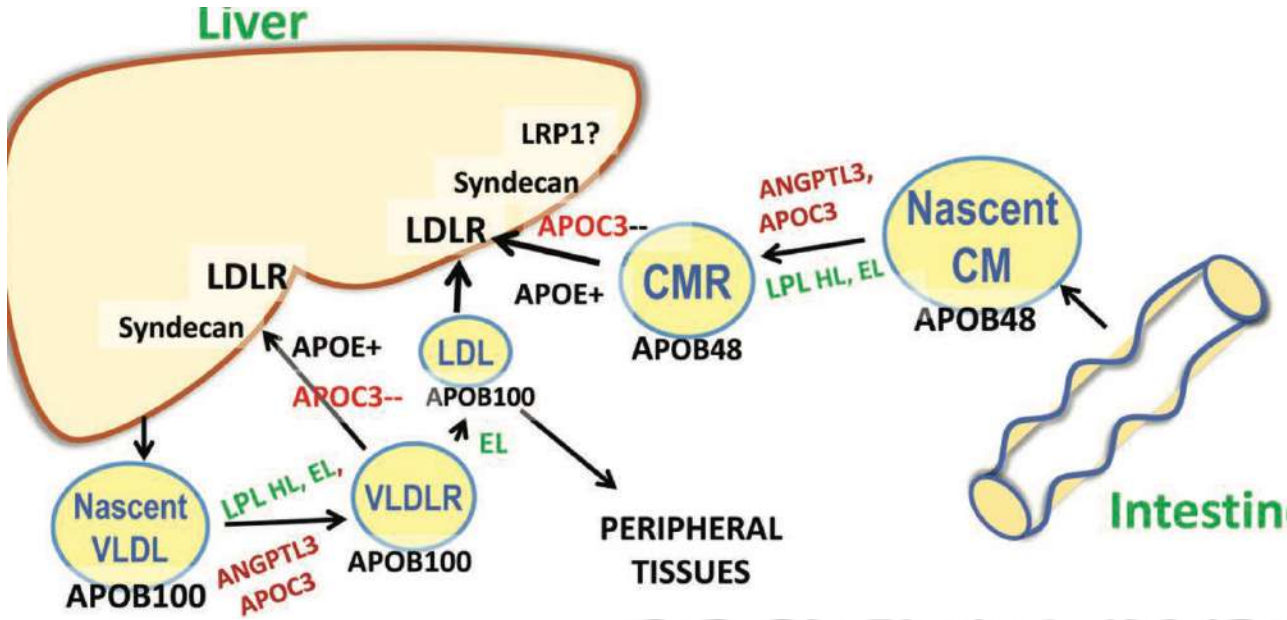


Figura 3. Algoritmo per il trattamento ipolipemizzante nel paziente a rischio cardiovascolare alto e molto alto clinicamente stabile. Per i pazienti con sindrome coronarica acuta fare riferimento al position paper ANMCO sulla gestione dell'ipercolesterolemia in questo specifico contesto clinico[41].
C-LDL, colesterolo legato alle lipoproteine a bassa densità; PCSK9i, inibitore della proproteina convertasi subtilisina/kexina tipo 9 (anticorpi monoclonali o inclisiran).
*Inclisiran da preferire in caso di potenziali problemi di aderenza e necessità di semplificazione dei percorsi clinico-assistenziali.
Adattata da Colivicchi et al.[40]



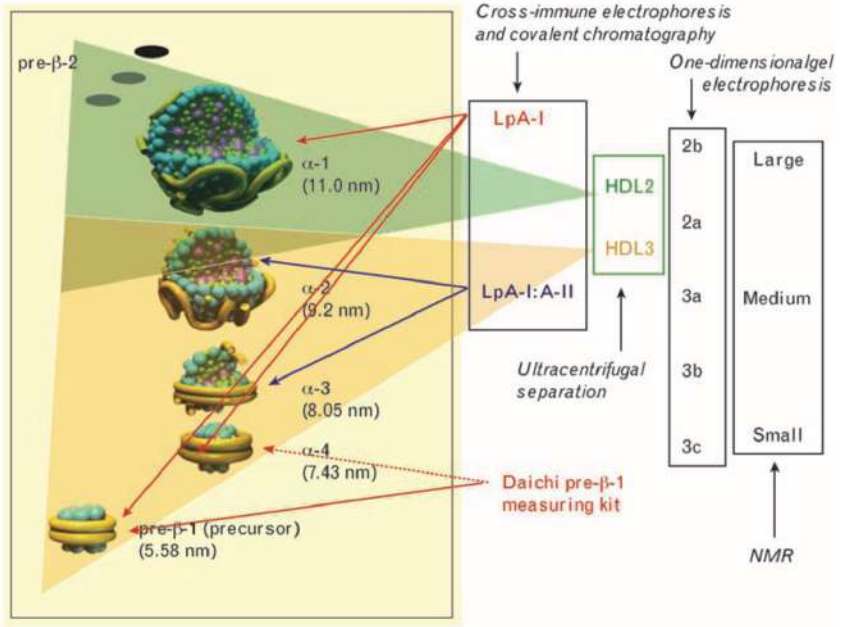


Arterioscler Thromb Vasc Biol. 2023;43:00–00. DOI: 10.1161/ATVBAHA.122.317966

LEGACY: Phase 2a Trial to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamic Effects of the Anti-EL (Endothelial Lipase) Antibody MEDI5884 in Patients With Stable Coronary Artery Disease

DRUG DEVELOPMENT

Blocking endothelial lipase with monoclonal antibody MEDI5884 durably increases high density lipoprotein in nonhuman primates and in a phase 1 trial



REVIEW

Perspective: Hepatocyte-Directed Base Editing as Novel Treatment for Human Dyslipidemia—Current Status and Remaining Challenges

Menno Hoekstra, Miranda Van Eck, Theo J.C. Van Berkel