Dislipidemia e rischio cardiovascolare residuo: nuove frontiere farmacologiche

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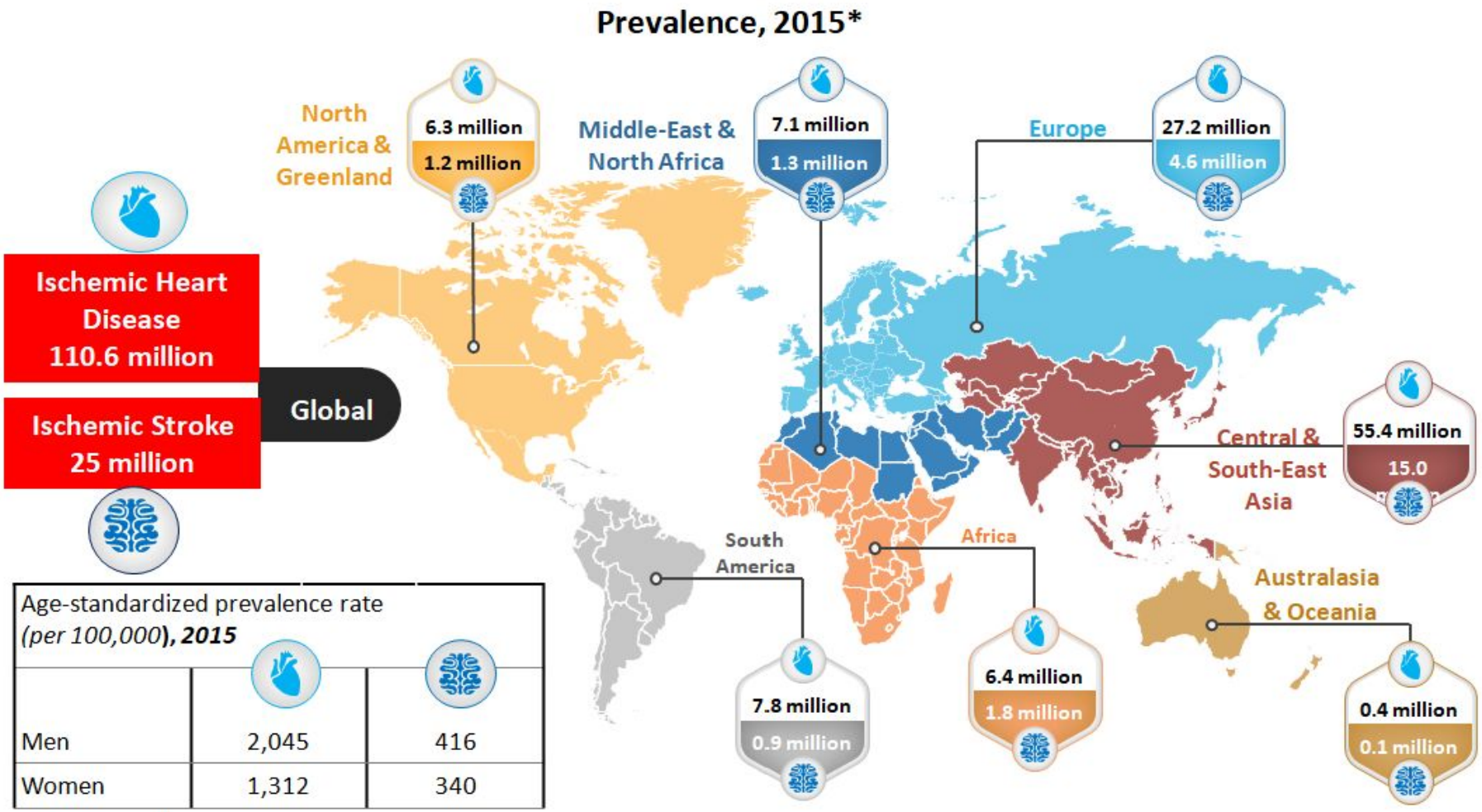
La malattia cardiovascolare aterosclerotica (ASCVD) colpisce più di 135 milioni di persone nel mondo

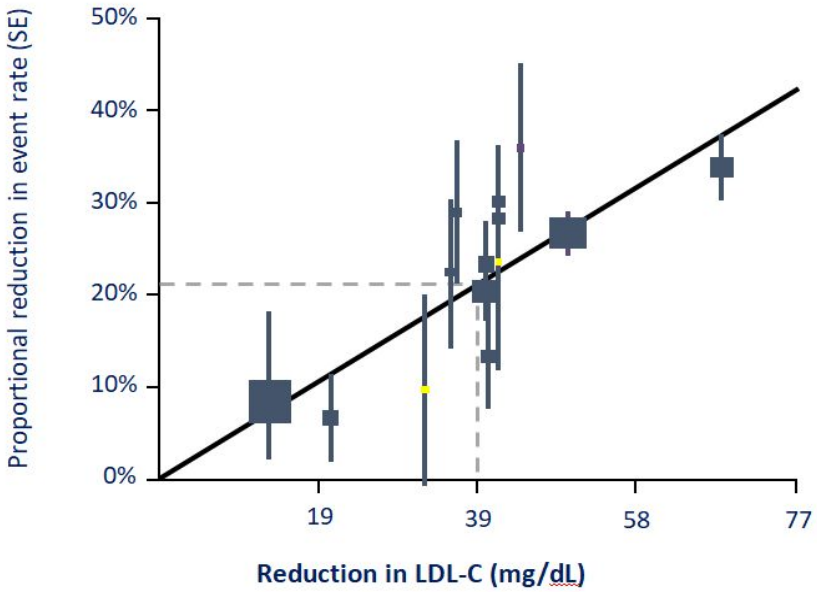


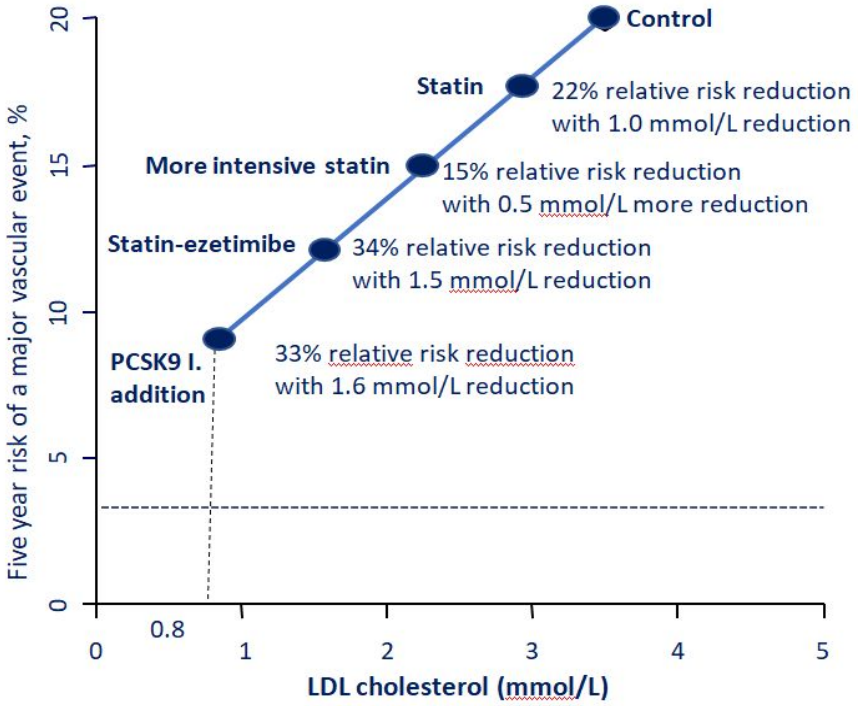
Age-standardized prevalence rate *(per 100,000)*, ***2015***		
Men	2,045	416
Women	1,312	340

**All-age prevalence*

Roth GA et al. J Am Coll Cardiol. 2017;70(1):1-25 (and supplementary)

La riduzione delle LDL-C riduce gli eventi CV senza effetto plateau o curva a J





CTTC. *Lancet*. 2005;366:1267–1278. *CTTC. Lancet*. 2010;376:1670–1681.
Cannon et al. *N Engl J Med*. 2015;372:2387 – 2397.

- Ogni **mmol/L di riduzione di LDL-C** abbassa il **rischio relativo** di eventi **ASCVD** del
  - **~10%** durante il **primo anno**
  - **16%** dopo il **secondo anno**
  - **20%** dopo **3 anni**
  - **1,5% in ogni anno successivo**

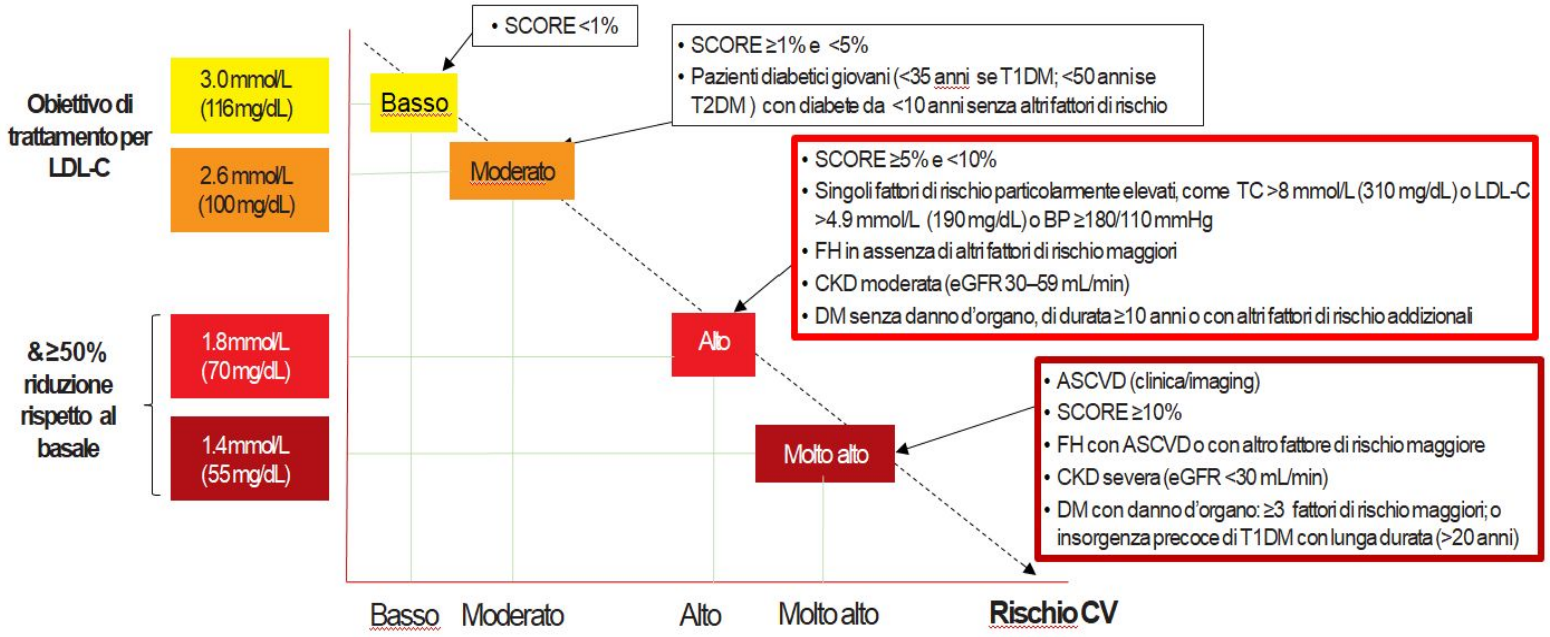
- **5 anni** di trattamento ipolipemizzante dovrebbero ridurre il rischio relativo di ASCVD del **~20–25% per ogni mmol/L di riduzione** di LDL-C
- **40 anni** di trattamento riducono gli eventi ASCVD del **~50–55% per ogni mmol/L di riduzione** di LDL-C

Ference BA et al., Eur. Heart J. 2017; 38:2459–72

Obiettivi di trattamento per il LDL-C secondo le categorie di rischio introdotti nelle LG ESC/EAS 2019

Le Linee Guida ESC/EAS raccomandano una importante riduzione dei livelli di LDL-C per ridurre il rischio CV, soprattutto nei pazienti non controllati

Le ultime Linee Guida ESC/EAS raccomandano una riduzione di LDL-C ≥50% e un obiettivo di LDL-C <70 e <55 mg/dL nei pazienti a rischio alto e molto alto rispettivamente



- 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

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

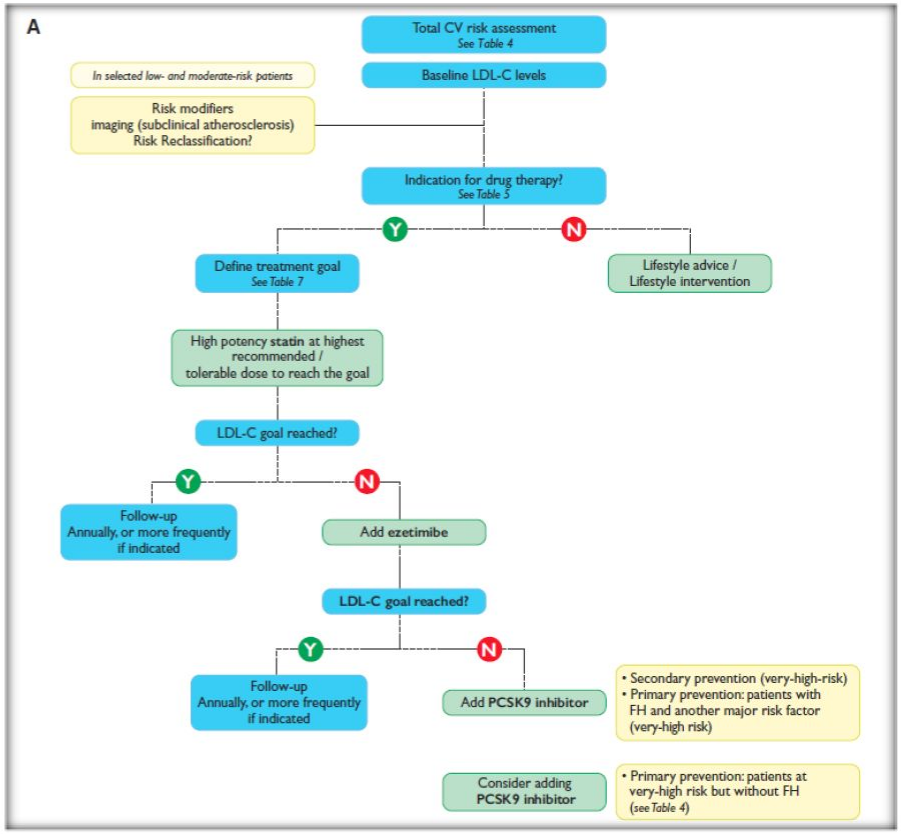
Current paradigm in dyslipidemia management

Target defined by CV risk, Statins and stepwise increase of LLT to Target

The ESC guidelines for dyslipidemia (2019) and prevention (2021) recommend :

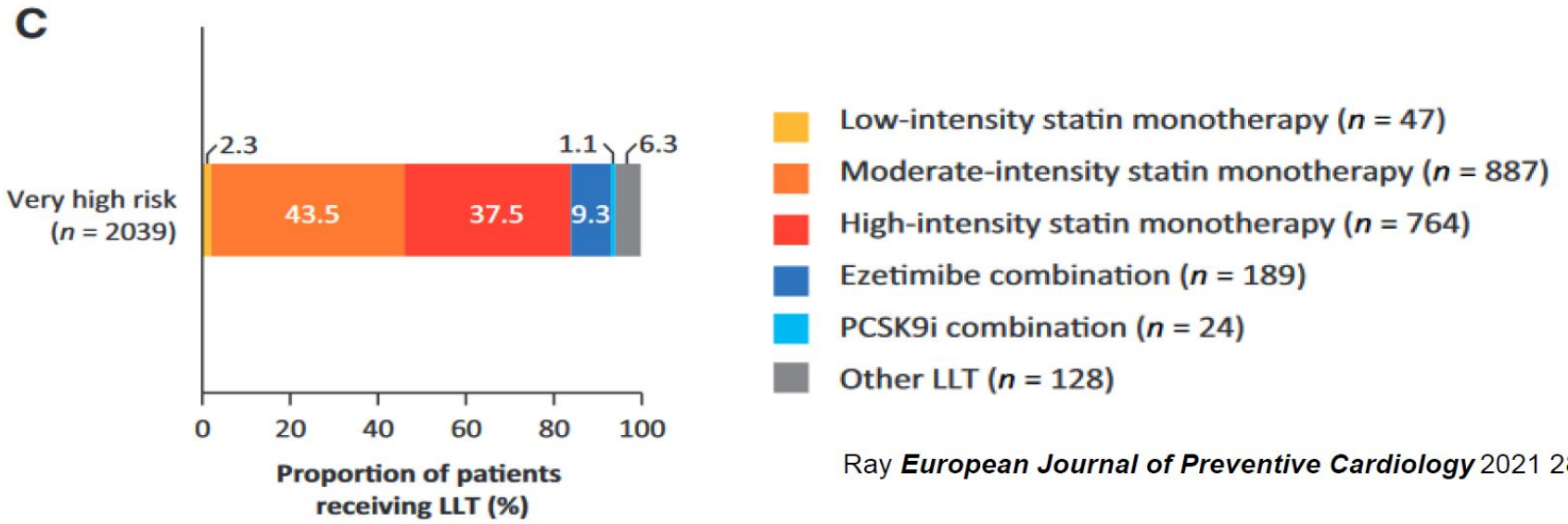
- **Decide to treat and determine the therapeutic target according to the patient's risk.**
- **Use a hierarchical order: lifestyle, statins (start with high intensity statins only in ACS patients), ezetimibe and PCSK9i.**
- **Use a strategy of stepwise intensification to reach the LDL-c target. Wait 4-6 weeks before checking if the LDL-c target is reached.**

Makes it possible to determine the lowest LLT intensity to reach the therapeutic target.
Guidelines do not explicitly recommend a time frame in which to achieve these reductions.



Mach F, et al. ***Eur Heart J.*** 2019;00:1–78

Real life with the current strategy: *initial prescription is underpowered*

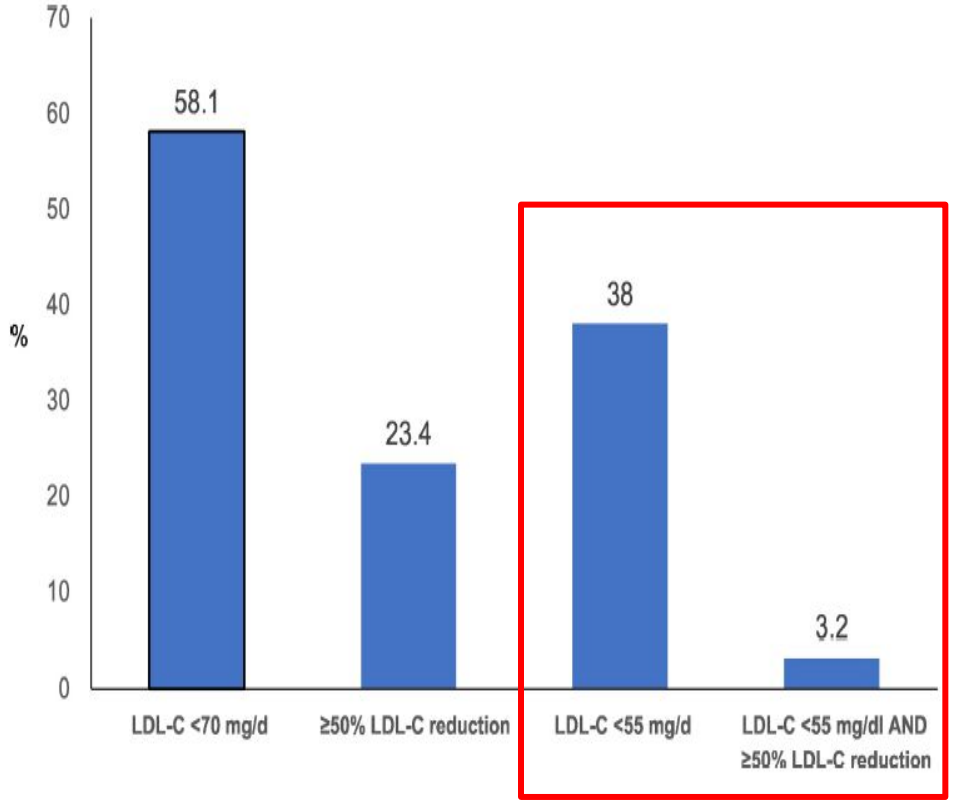


Ray ***European Journal of Preventive Cardiology*** 2021 28, 1279–1289

DA VINCI (***European Observational Study***): subset of patients at very high risk:

- 18% of the patients are at LDL-c target
- ***Statins: 37.5% at high intensity***
- Combination statin ezetimibe: 9.3%
- Combination statin PCSK9i: 1%

Registro italiano START (ANMCO): il raggiungimento dei targets di LDL è insoddisfacente



Registro nazionale italiano delle cardiologie ANMCO. 5.053 pz. con malattia cardiovascolare aterosclerotica (ASCVD) in atto.

Il 94% sono stati giudicati a rischio molto elevato di eventi secondo le carte del rischio.

Risulta evidente che il raggiungimento dei target di LDL-C rispetto alle indicazioni delle Linee Guida è largamente subottimale.

De Luca L et al Int J Cardiol 2020 Oct 1;316:229-235

Real life with the current strategy:
There is no increase in LLT during FU

A cross-sectional ESC-EORP survey (EUROASPIRE V) at 131 centers in 81 regions in 27 countries including patients with coronary artery events or interventions

Change in the LDL-C-lowering therapies from discharge to interview.

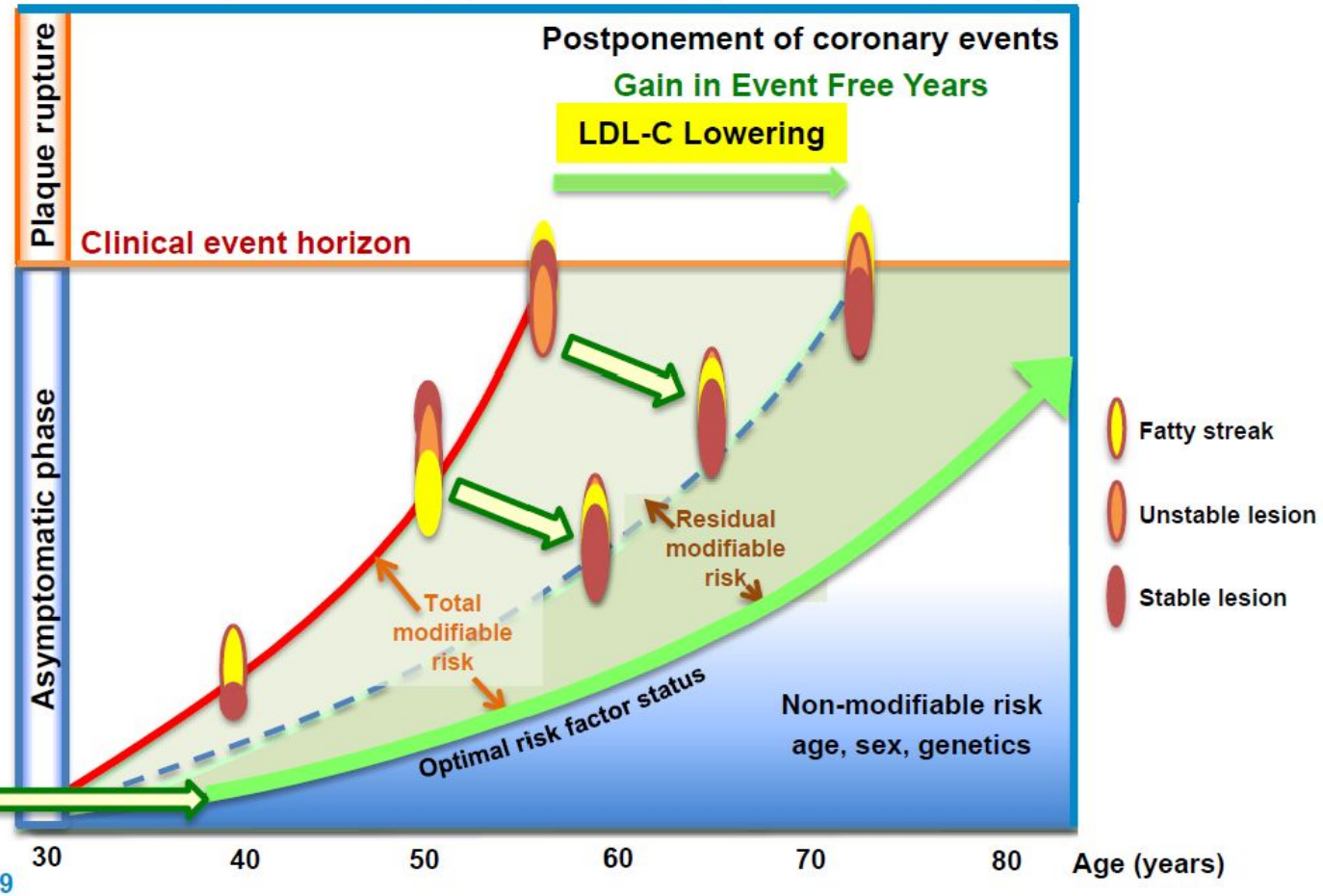
Prescribed at hospital discharge	Used at the time of interview	% (n)
No LLT	No LLT	5.0 (374/7528)
Low/Moderate intensity LLT	Low/Moderate intensity LLT	20.2 (1521/7528)
High intensity LLT	High intensity LLT	42.3 (3181/7528)
High intensity LLT	Low/Moderate intensity LLT	10.0 (755/7528)
High intensity LLT	No LLT	6.2 (463/7528)
Low/moderate intensity LLT	No LLT	4.6 (350/7528)
No LLT	Low/moderate intensity LLT	3.9 (297/7528)
No LLT	High intensity LLT	3.2 (241/7528)
Low/moderate intensity LLT	High intensity LLT	4.6 (346/7528)

- During FU: patients without high intensity statins, there is an **increase in LLT** in **11.7%**
- During FU, there is a **decrease** from high to low/moderate intensity (or no LLT) **in 20.8%**

=> Instead of an increase, there is mostly a decrease in LLT intensity during FU

De Backer, et al. ***Atherosclerosis*** . 2019;285:135–146

Pathophysiology: LDL-C lowering shifts the trajectory of plaque development, phenotype and progression



Opportunity for primordial prevention of atherogenesis

Vasc Pharmacol 2015; 71:37-9

New treatment options for LDL cholesterol

New strategies

Early combination therapy

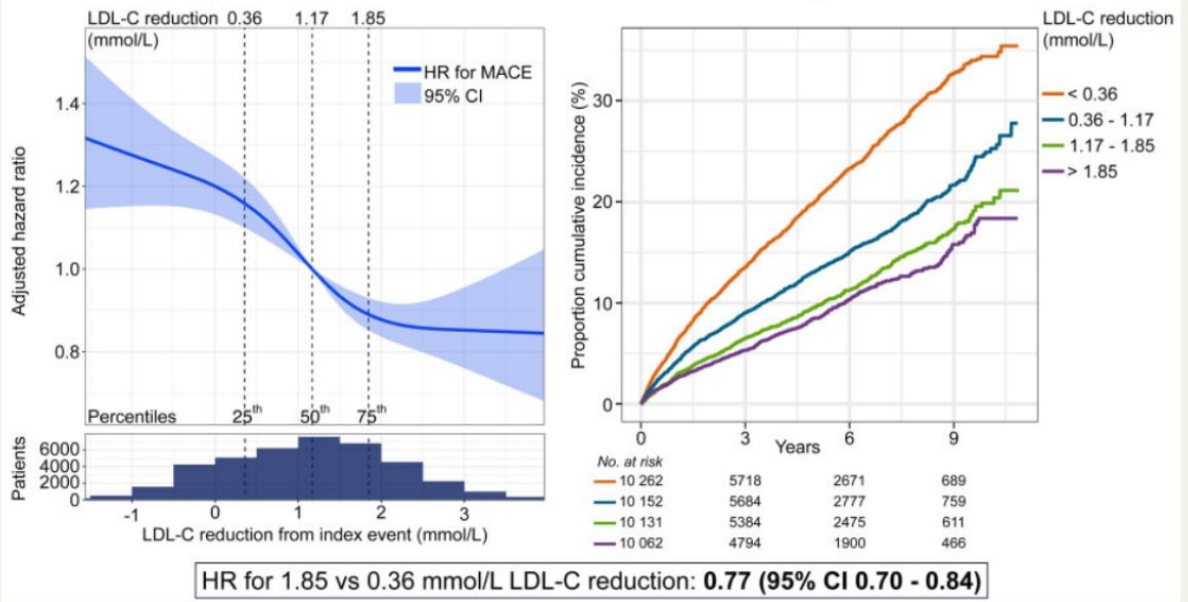
Fixed-dose combinations

Population-wide application of PCSK9-siRNA

Change in paradigm:

Lower is better , Earlier and larger % reduction is better .

40 607 patients with acute MI from SWEDEHEART registry: Larger LDL-C reduction (1.85 mmol/L, 75th percentile) ***at 6 weeks***, compared with a smaller reduction (0.36 mmol/L, 25th percentile) had lower hazard ratios (HR) for all outcomes 0.77 (0.70–0.84); all-cause mortality 0.71 (0.63–0.80); CV mortality 0.68 (0.57–0.8

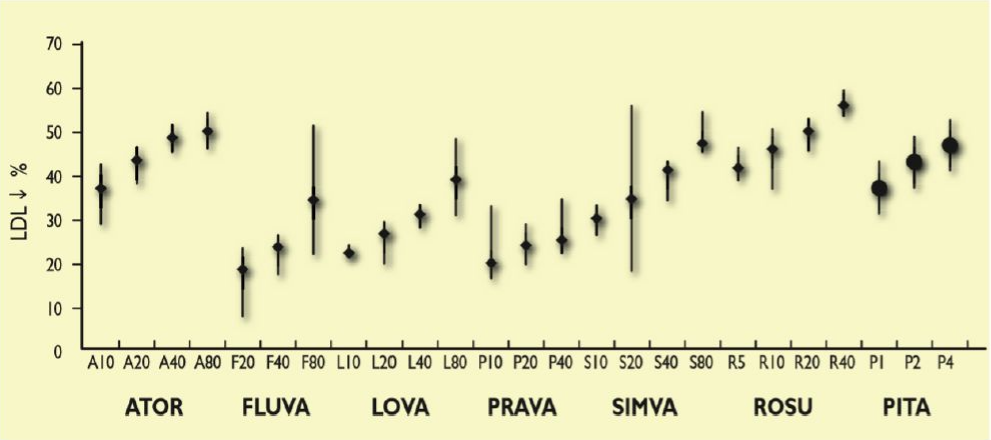


Schubert ***European Heart Journal*** (2021) 42, 243–252

Change in paradigm:

Avoid unnecessary steps

Despite individual variations, the capacity of LDL-c reduction by statins monotherapy and LLT combinations is predictable



Weng ***J Clin Pharm Ther*** 2010; 35:139-151

Intensity of lipid-lowering treatment

Treatment	Average LDL-C reduction
Moderate-intensity statin	≈30%
High-intensity statin	≈50%
High-intensity statin plus ezetimibe	≈65%
PCSK9 inhibitor	≈60%
PCSK9 inhibitor plus high-intensity statin	≈75%
PCSK9 inhibitor plus high-intensity statin plus ezetimibe	≈85%

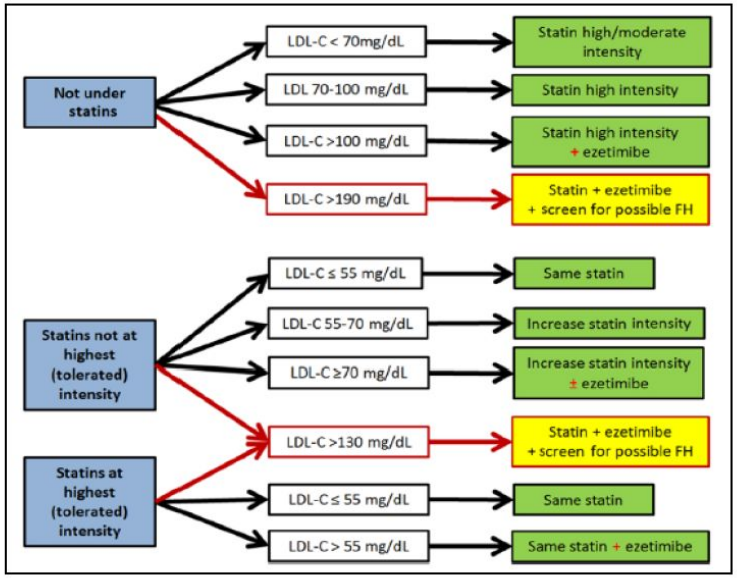
Visseren F, et al. ***Eur Heart J.*** 2021;00:1–107

"Treat to Target" = select the initial prescription likely to reach the LDL-c target.

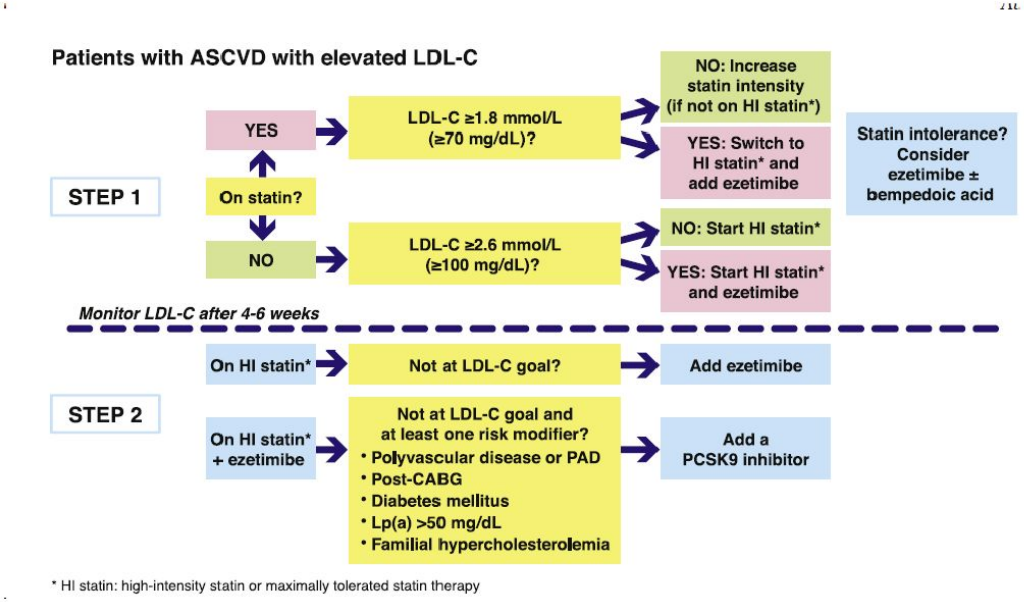
For example, to lower LDL-c <55 mg/dL, use high intensity statins + ezetimibe when baseline LDL-c is > 110mg/dL

Change in paradigm:

first line combination (with LDL-c condition)



Schiele ***EHJ-ACVC;***2018;6:532-43:



Averna EAS Task Force ***Atherosclerosis*** 325 (2021) 99–109

According to « Treat to Target », different strategies have been proposed, using a combination of HIS + ezetimibe according to baseline LDL-c (when baseline LDL-c >100 mg/dL or 110 mg/dL).

Change in paradigm: *first line combination statin + ezetimibe without condition on LDL*

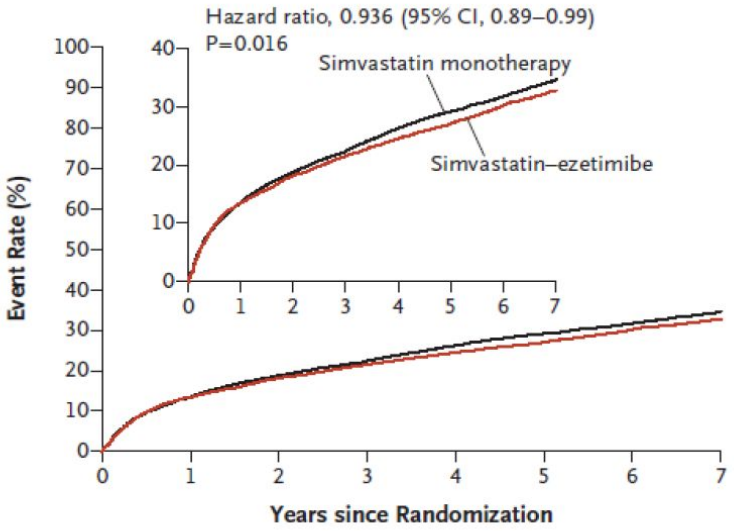
Two clinical trials with early combination of statin + ezetimibe

IMPROVE-IT:

Statin moderate intensity vs +ezetimibe

18144 pt (10 days post-ACS)

LDL-c 54 mg (simva plus ezetimibe) vs 69 mg/dL(simva)



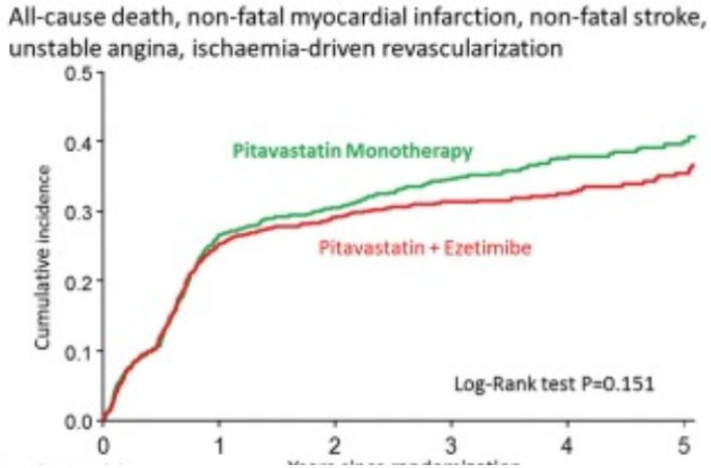
Cannon *NEJM.* 2015;372:2387–97;

HIJ-PROPER :

Pitavastatin 2mg vs + ezetimibe

1734 pts (72h post-ACS).

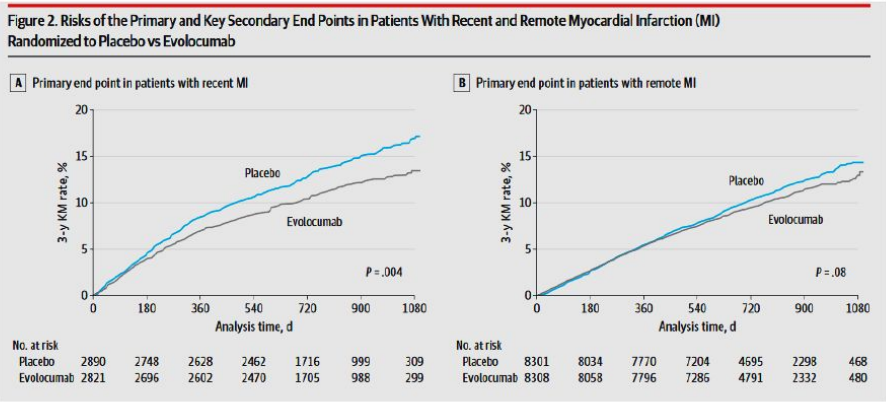
LDL-c 65.1 mg (pita plus ezetimibe) vs 84.6 mg/dL(pita)



Hagivara ***Eur Heart J*** . 2017 38:2264-2276

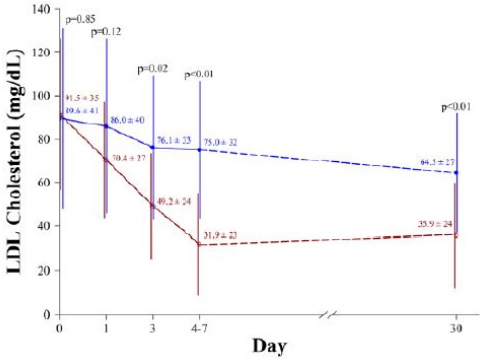
Change in paradigm: *early combination with PCSK9i ?*

Evolocumab provides higher clinical benefit when prescribed <12 months after acute MI, as compared to <12 months



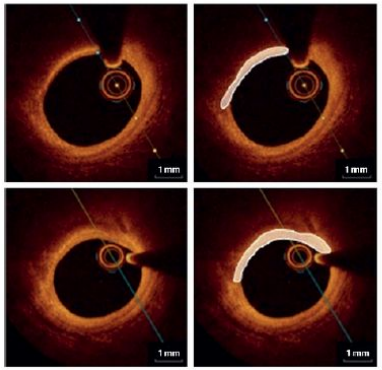
FOURIER (substudy) 16 609 patients had a remote MI and **5711 patients a recent MI**. Patients with a **recent MI were at higher risk of cardiovascular events and tended to experience greater ARRs** with evolocumab than those with more remote MIs.

Gencer ***JAMA Cardiology*** 2020; 5(8):952-957



Leucker ***Circulation*** 2020;142:419-21

EVACS: randomized study with 272 NSTEMI patients **(statins + evolocumab vs statins):** High and early reduction in atherogenic lipoproteins during peri and early postinfarction period with statins+PCSK9i



HYUGENS: randomized study with 80 patients **(statins + evolocumab vs statins).** At 52 weeks, OCT shows that statins+PCSK9i produces favorable changes in coronary atherosclerosis consistent with stabilization and regression

Nicholls ***J Am Coll Cardiol Img.*** 2022 Jul, 15 (7) 1308–1321

New treatment options for LDL cholesterol

New strategies

Early combination therapy

Fixed-dose combinations

Population-wide application of PCSK9-siRNA

Novel drugs – approved

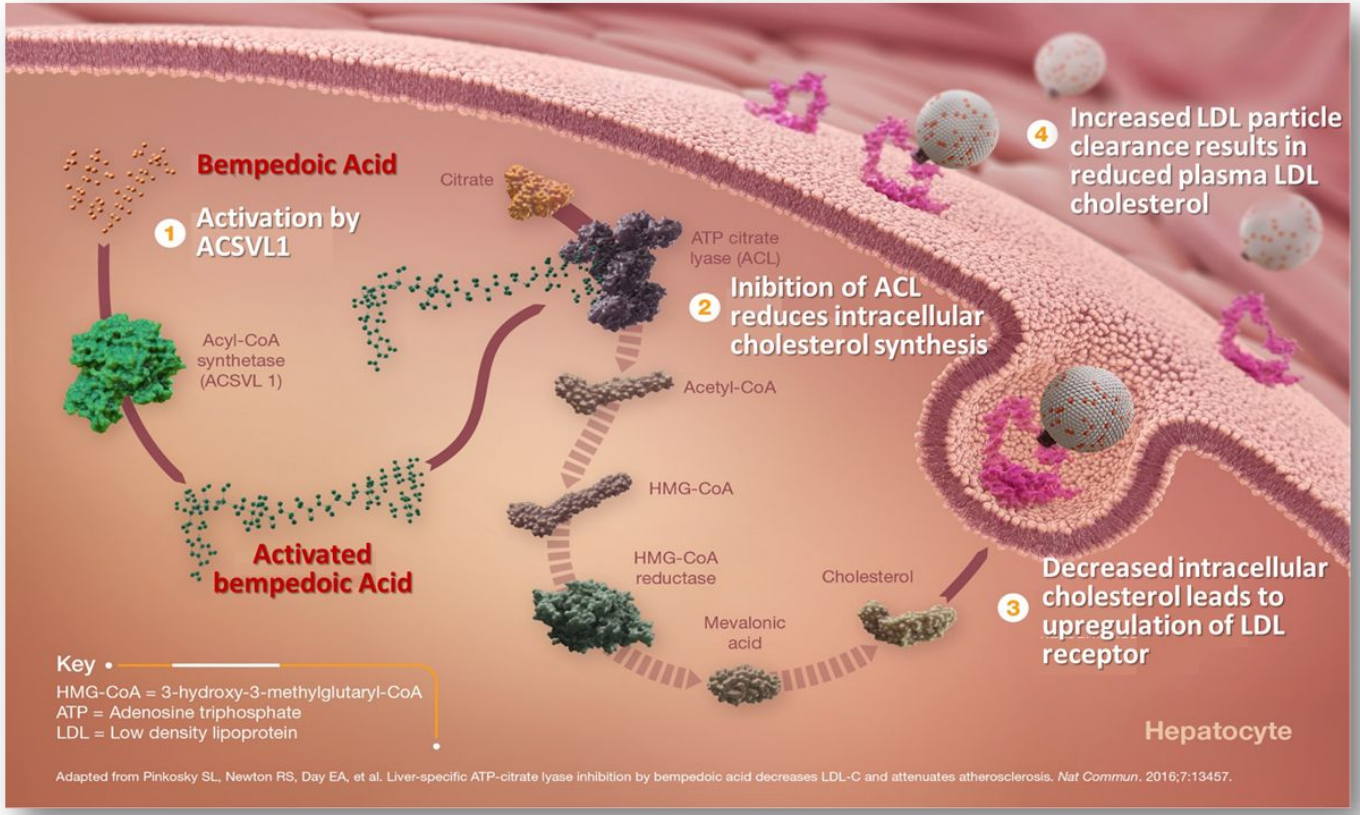
Bempedoic Acid, Inclisiran

Novel drugs - in development

AngPTLi, CETPi, oral PCSK9i, … , ?PCSK9 gene therapy

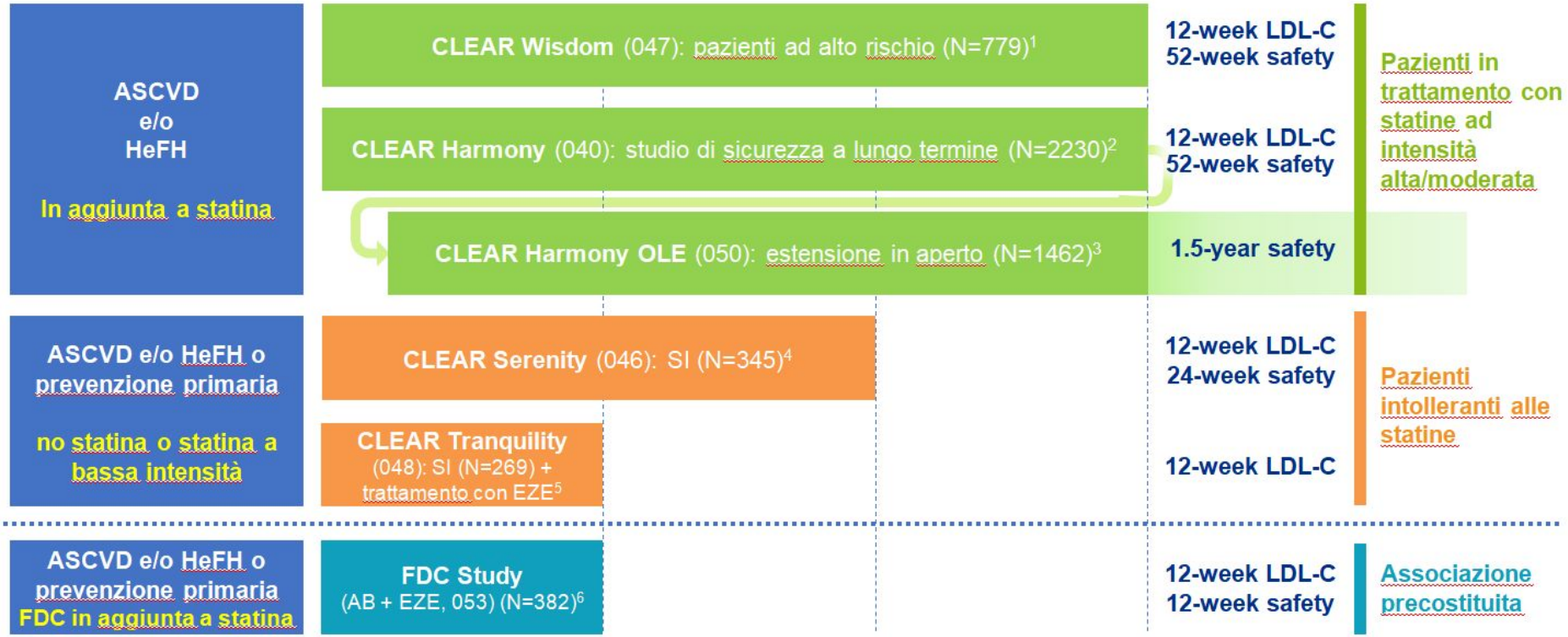
Il meccanismo d'azione unico dell'acido bempedoico è complementare ma distinto da quello delle statine e delle altre LLT

- 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

L'Acido Bempedoico è stato valutato in un solido programma clinico che ha incluso un ampio spettro di pazienti

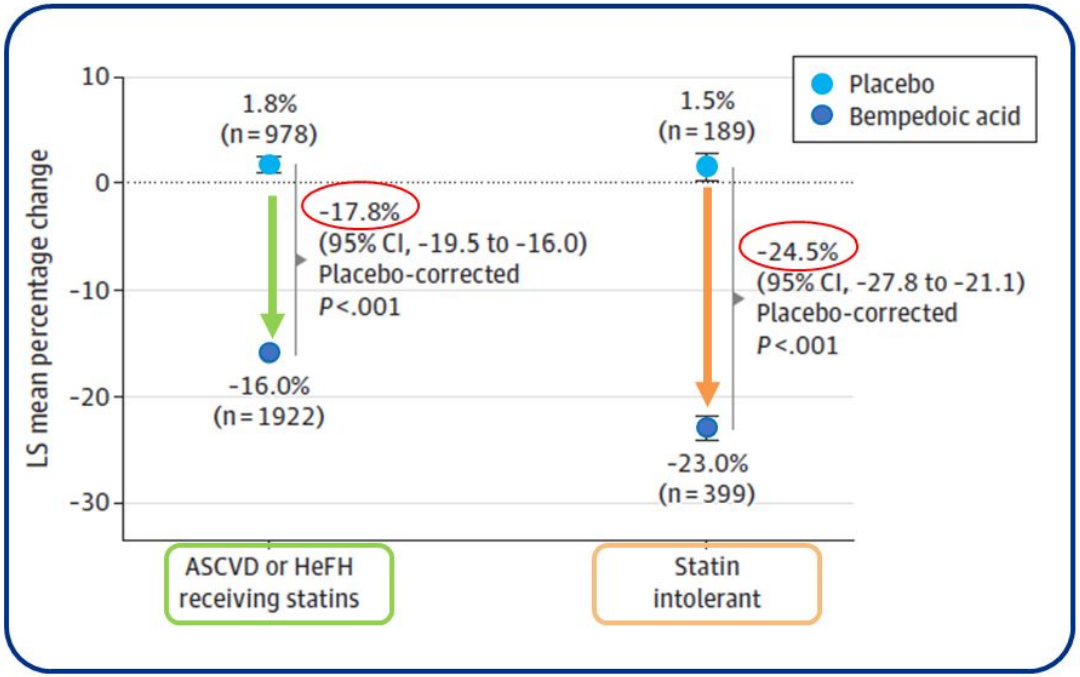


- ASCVD = malattia cardiovascolare su base aterosclerotica; AB = acido bempedoico; EZE = ezetimibe; HeFH = iperholesterolemia familare eterozigote; LDL-C Colesterolo LDL; OLE = open-label extension; SI = statino-intolleranti

- **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.** Ballantyne et al. Am J Cardiol 2022 https://doi.org/10.1016/j.amjcard.2022.03.020; **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 siginificativa riduzione dei livelli di LDL-C vs Placebo in aggiunta alla massima dose tollerata di statina, con o senza altre terapie ipolipemizanti

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

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

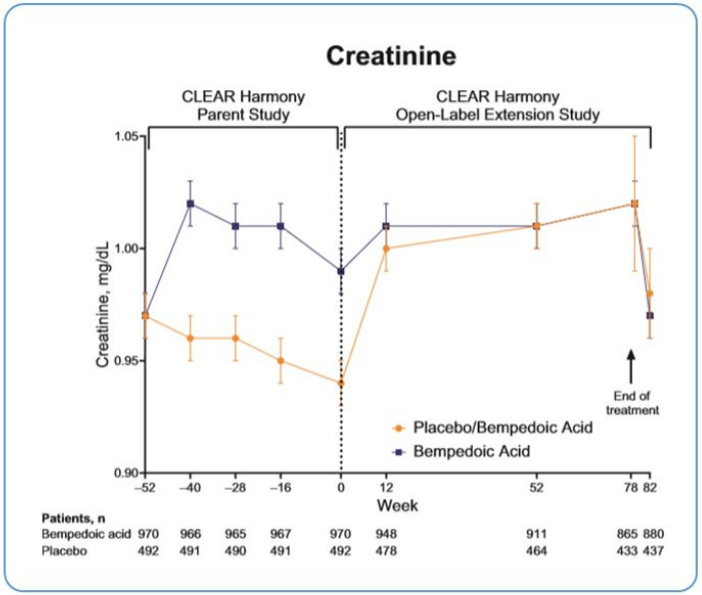
Eventi avversi durante il trattamento	Acido Bempedoico N=2424, % (n)	Placebo N=1197, % (n)	*p*
Debolezza muscolare	0.5 (13)	0.6 (7)	0.82
Nuova insorgenza di diabete/iperglicemia	4.0 (96)	5.6 (67)	0.03
Aumento di acido urico nel sangue	2.1 (51)	0.5 (6)	< 0.001
Iperuricemia	1.7 (40)	0.6 (7)	0.007
Gotta	1.4 (33)	0.4 (5)	0.008
Aumento di creatinina nel s			
Diminuzione della velocità di filtrazi			
Aumento degli enzimi epatici			
> 3 volte rispetto ai limiti superio			
> 5 volte rispetto ai limiti superio			
Disordini neurocognitivi			

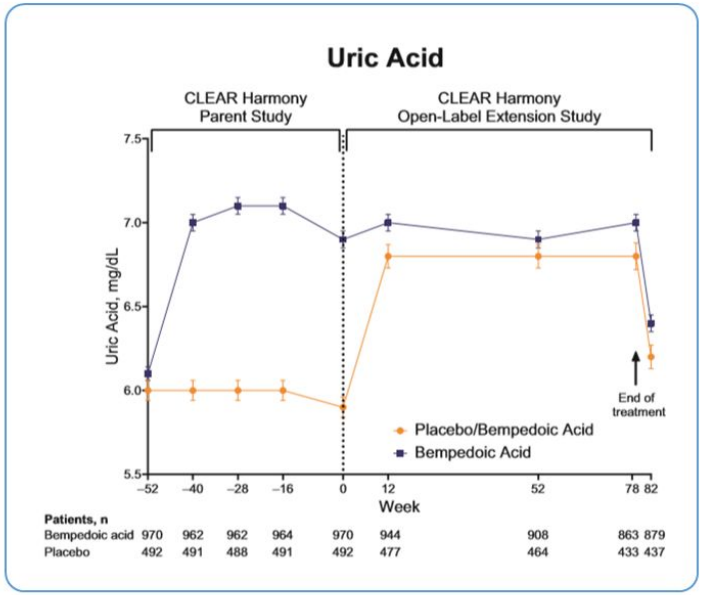
Banach M. et al., JAMA Cardiology, published

Eventi avversi di speciale interesse

- **Modeste variazioni dei livelli ematici di acido urico (0,8mg/dL) e creatinina (0,05mg/dL) 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

Modeste variazioni della creatinina e dell'acido urico si verificano precocemente, si mantengono stabili e sono reversibili dopo l'interruzione del trattamento

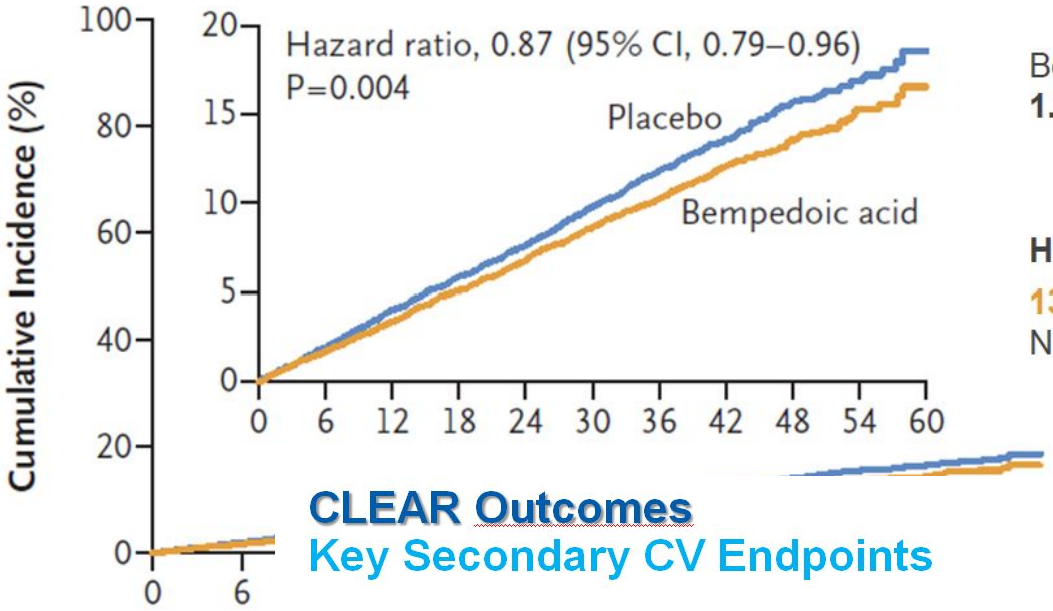




Ballantyne et al. Am J Cardiol 2022 https://doi.org/10.1016/j.amjcard.2022.03.020.

CLEAR Outcomes
Primary CV Endpoint: MACE-4

A Four-Component MACE (Primary End Point)



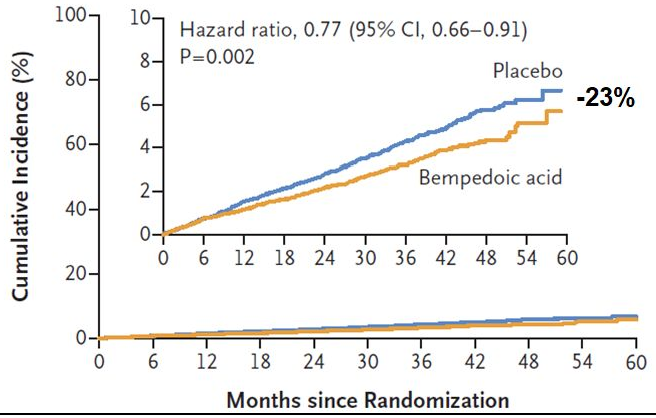
Bempedoic acid (11.7%) vs. placebo (13.3%)[1]
1.6% ARR

HR 0.87, 95% CI: 0.79–0.96, P=0.004[1]
13% RRR†[1]
NNT 63[2]

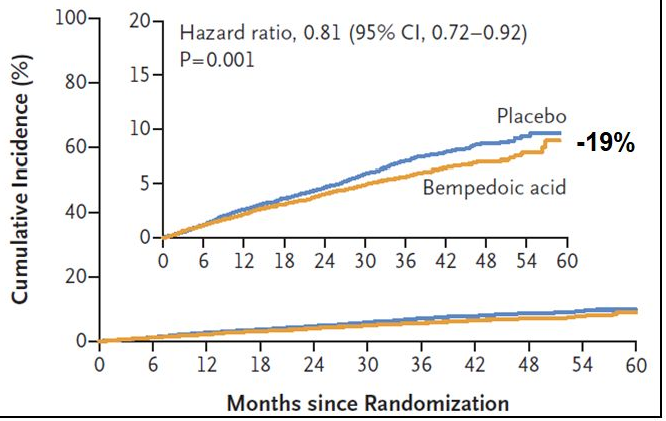
CLEAR Outcomes
Key Secondary CV Endpoints

The primary efficacy endpoint (MACE-4) is t
includes **death from cardiovascular cause**
revascularisation.
†This percentage is from the publicly availa
ARR, absolute risk reduction; **CI**, confidenc
needed to treat; **RRR**, relative risk reductior

C Fatal or Nonfatal Myocardial Infarction



D Coronary Revascularization



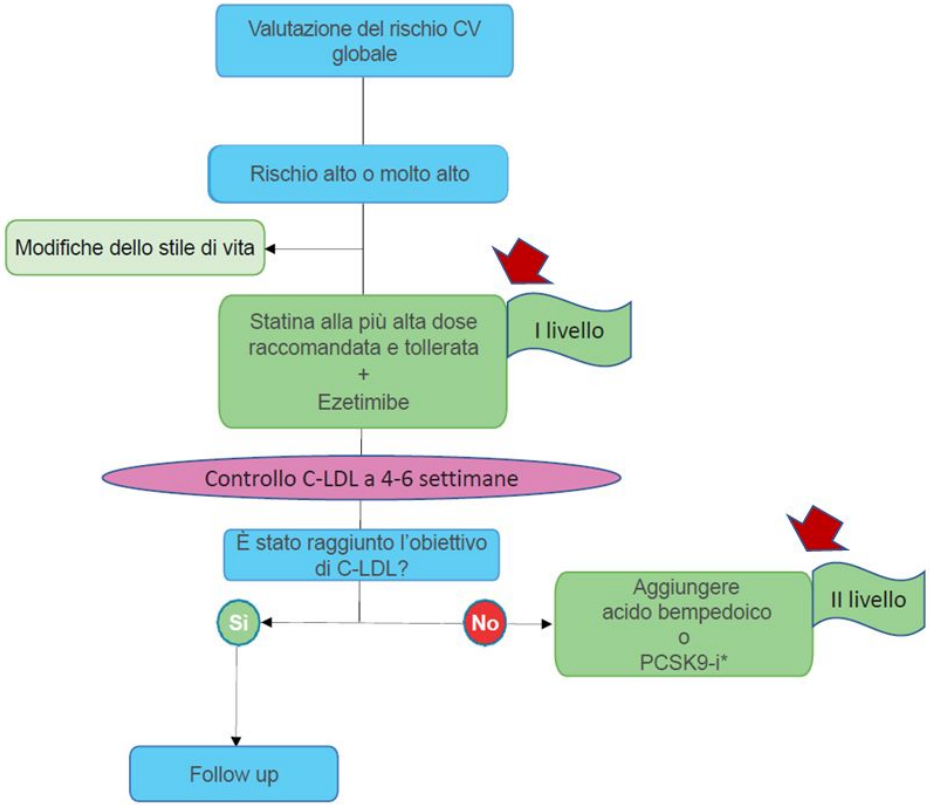
POSITION PAPER

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

Stefania Angela Di Fusco[1], Stefano Aquilani[1], Antonella Spinelli[1], Alessandro Alonzo[1], Lorenzo Castello[1], Pasquale Caldarola[2], Leonardo De Luca[3], Carmine Riccio[4], Michele Massimo Gulizia[5], Domenico Gabrielli[3,6], Fabrizio Oliva[7], Furio Colivicchi[1]

[1]U.O.C. Cardiologia Clinica e Riabilitativa, Presidio Ospedaliero San Filippo Neri - ASL Roma 1, Roma

Acido Bempedoico Position paper ANMCO



«Considerando che le ultime linee guida sulla gestione dei pazienti con dislipidemia hanno reso i target dei pazienti a rischio alto e molto alto ancora più difficili da raggiungere, in questi specifici contesti l'acido bempedoico, **terapia addizionale rispetto a statine ed ezetimibe**, maneggevole e ben tollerata, può facilitare il raggiungimento degli obiettivi terapeutici raccomandati.»

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

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

- **L'acido bempedoico (180 mg) e la sua associazione fissa con ezetimibe (180 mg/10 mg) sono nuove opzioni terapeutiche orali che possono essere utilizzate in aggiunta alle terapie orali esistenti per ottenere un'ulteriore riduzione del C-LDL nei pazienti non controllati**

New treatment options for LDL cholesterol

New strategies

Early combination therapy

Fixed-dose combinations

Population-wide application of PCSK9-siRNA

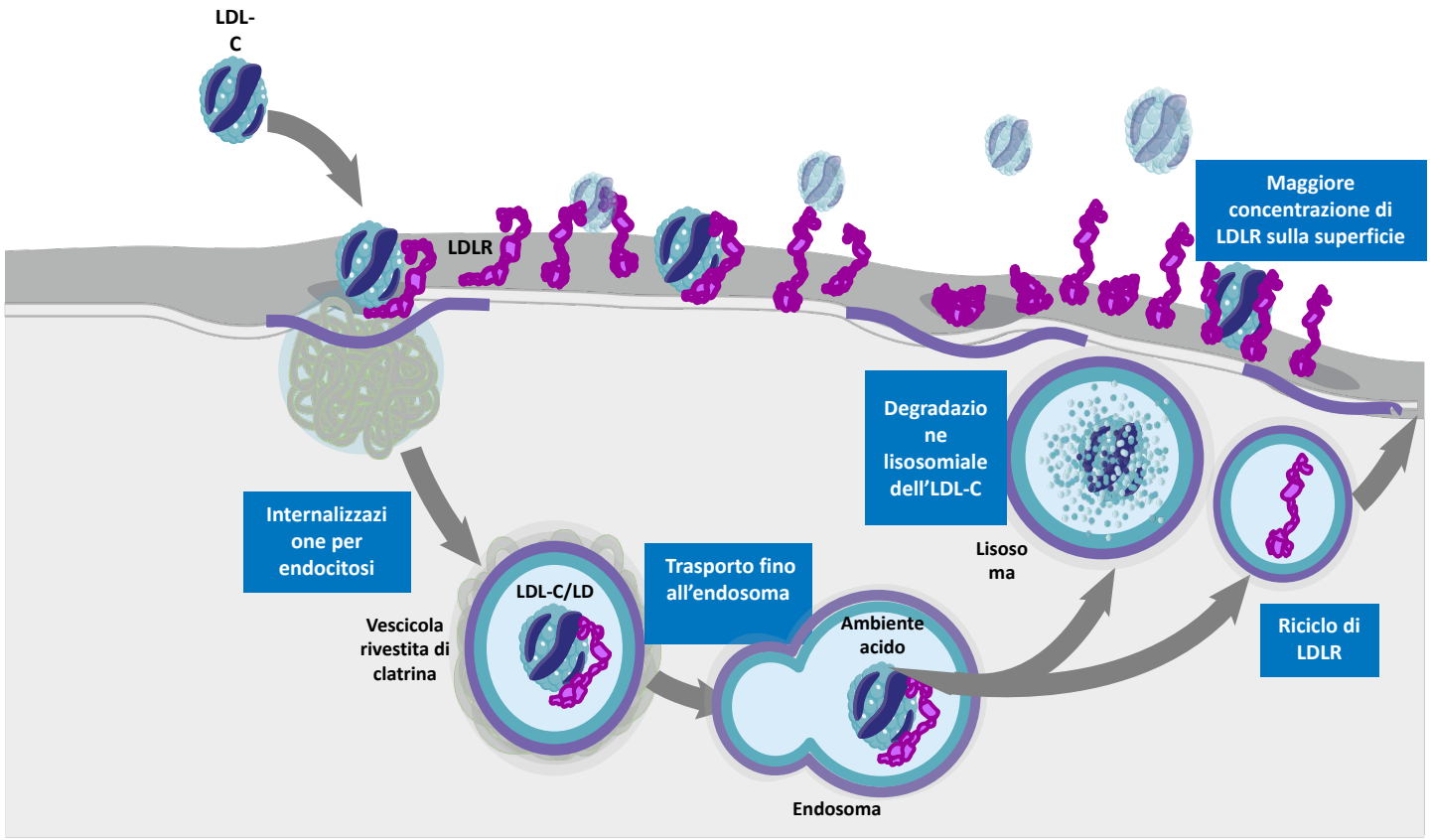
Novel drugs – approved

Bempedoic Acid, Inclisiran

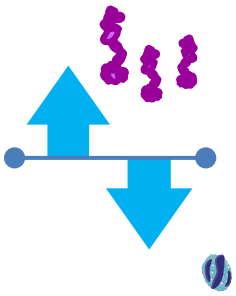
Novel drugs - in development

AngPTLi, CETPi, oral PCSK9i, … , ?PCSK9 gene therapy

La concentrazione di LDL-C è ampiamente regolata dal livello di LDLR espresso sugli epatociti



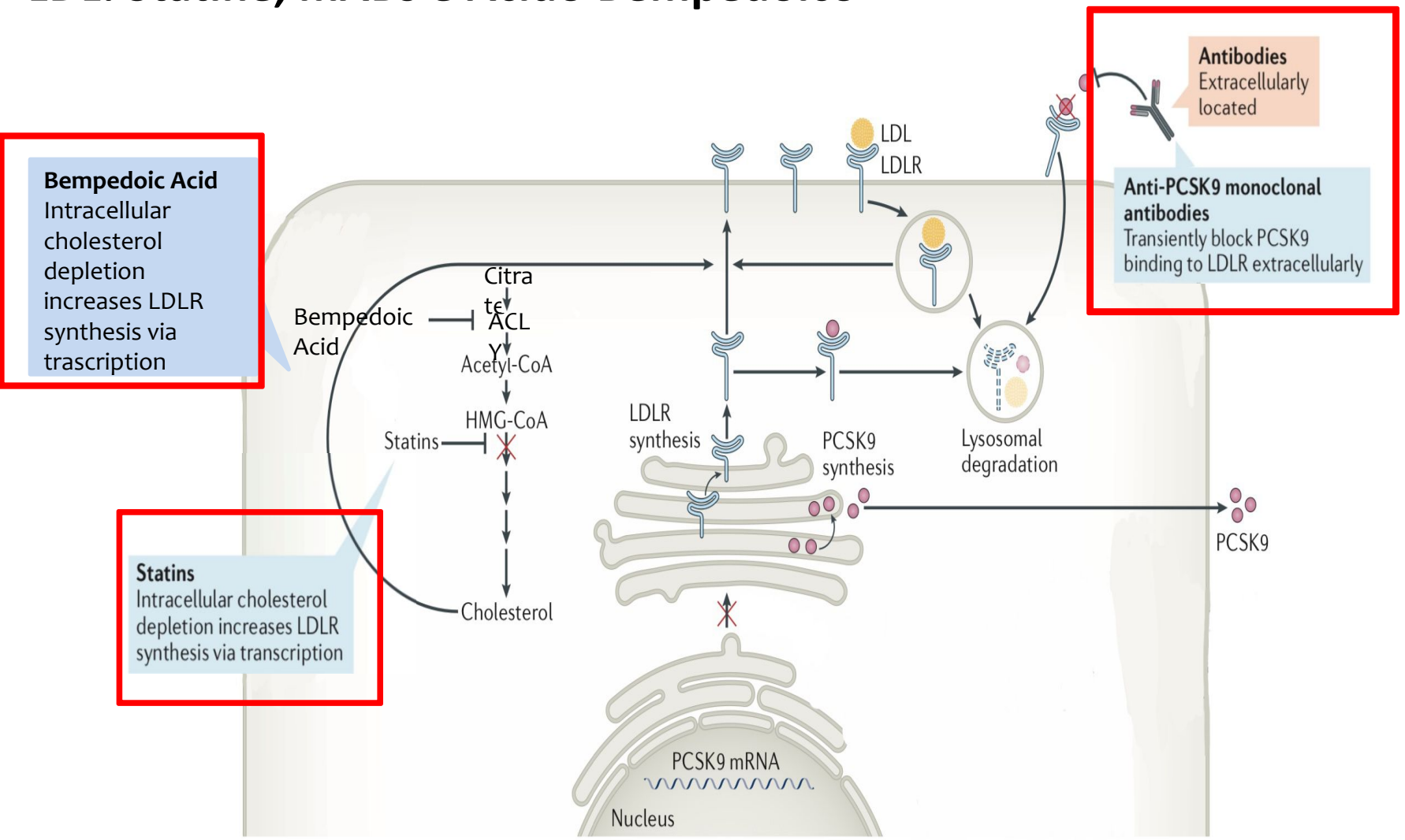
LDLR sulla superficie cellulare



LDL-C nel plasma

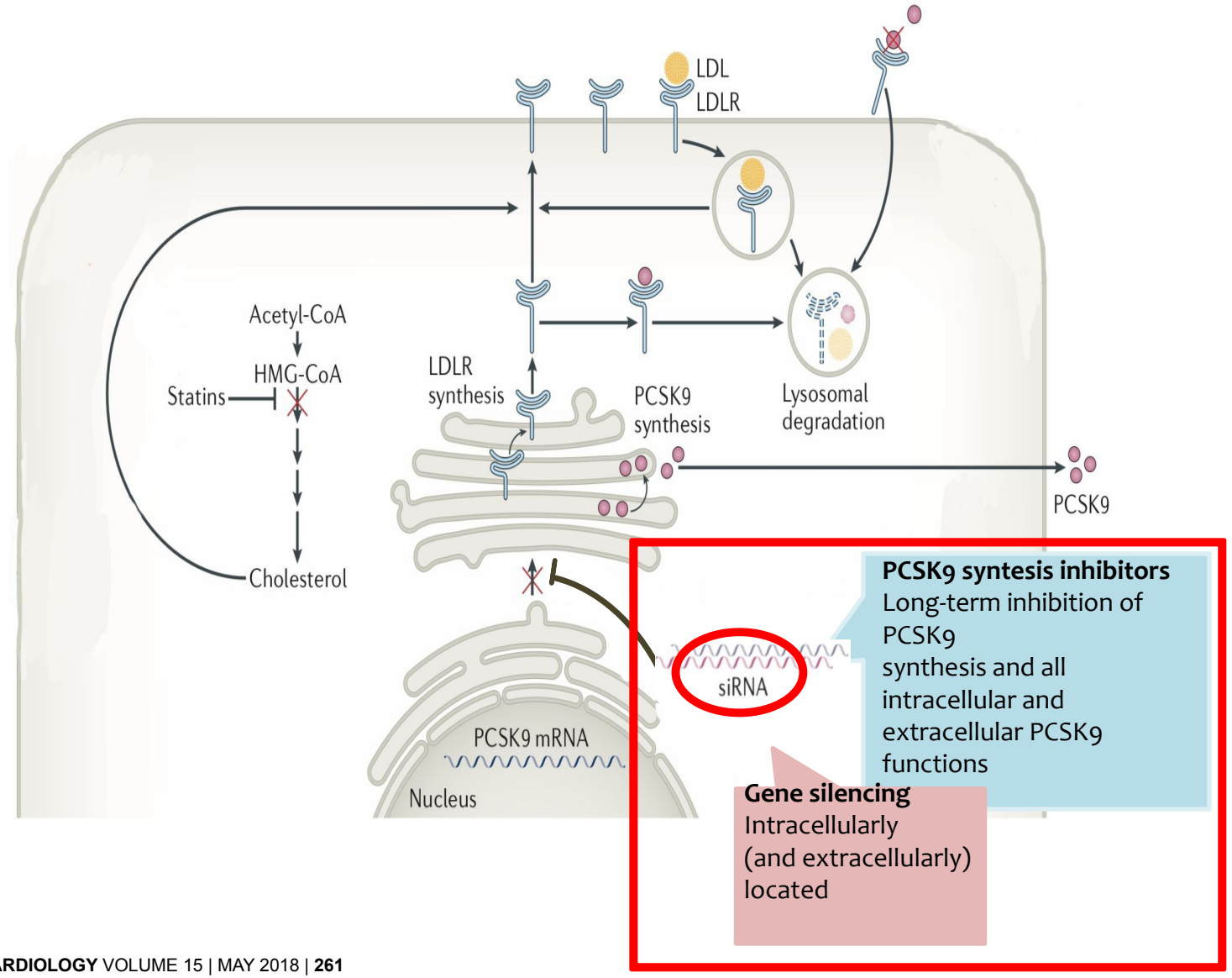
1. Goldstein JL, et al. Aterioscler Thromb Vasc Biol. 2009;29:431-438; 2. Brown MS, et al. Proc Natl Acad Sci. 1979;76:3330-3337; 3. Horton JD, et al. J Lipid Res. 2009;50:S172-S177

Approcci terapeutici per ridurre LDL-C attraverso il recettore per le LDL: Statine, mABs e Acido Bempedoico



ACLY: ATP-Citrate Lyase

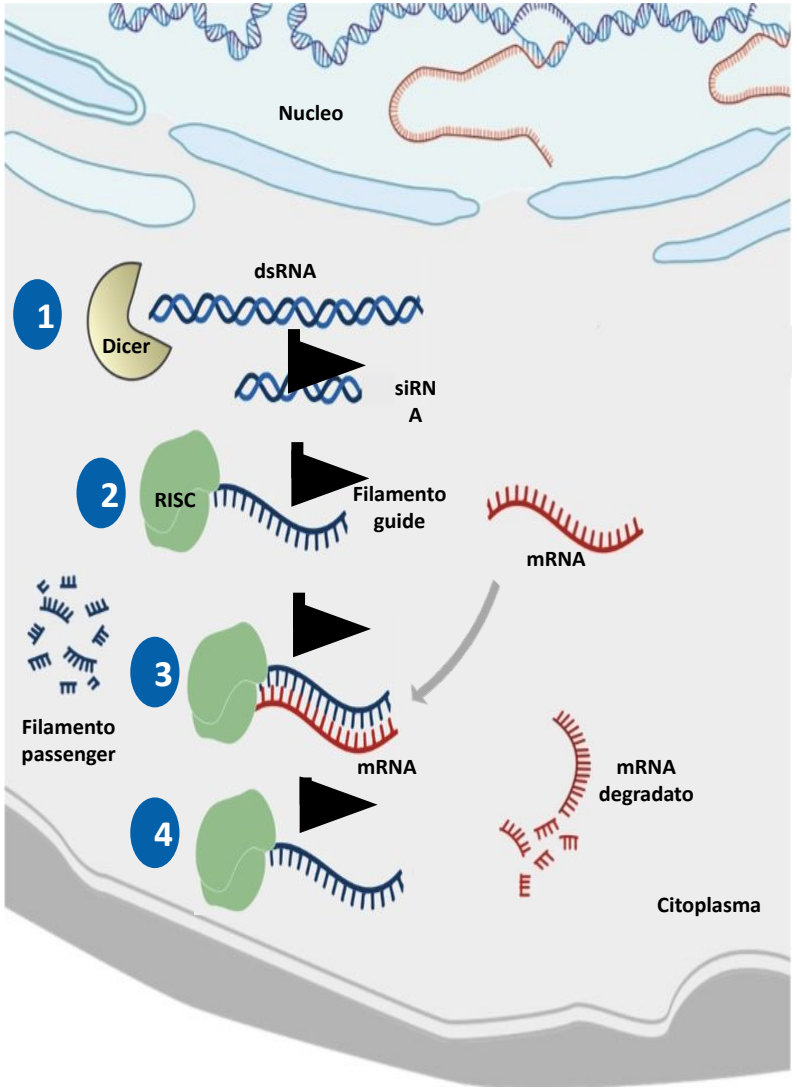
Approcci terapeutici per ridurre LDL-C attraverso il recettore per le LDL: siRNA



siRNA è un meccanismo di controllo dell'espressione genica fisiologico

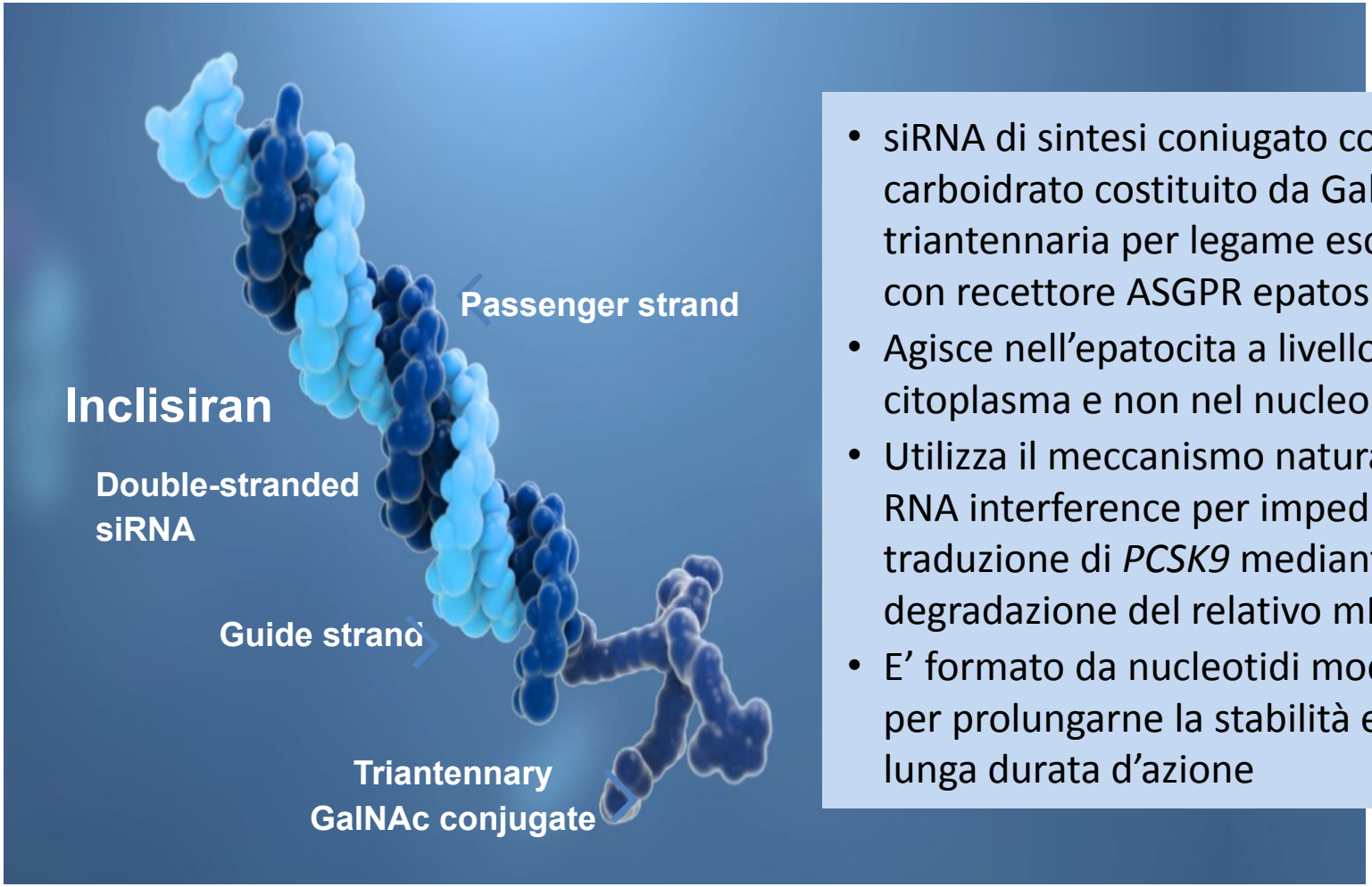
1. Un lungo RNA a doppio filamento (dsRNA), trascritto o esogeno, promuove il silenziamento genico in modo specifico. Viene processato in un piccolo siRNA a doppio filamento dagli enzimi **Dicer** (RNasi) nel citoplasma[1]
2. Il siRNA processato viene legato dal **RISC** (RNA-induced silencing complex)[1,2]

   Argonaute-2, un componente enzimatico del RISC, taglia e degrada il filamento passenger del siRNA[3]
3. Il filamento guide indirizza il RISC verso l'mRNA bersaglio tramite l'accoppiamento complementare delle basi[1]
4. Argonaute-2 nel RISC taglia l'mRNA bersaglio per impedire la traduzione e la sintesi proteica[1,2]



1. Lam JKW, et al. Mol Ther Nucleic Acids. 2015;4:e252; 2. Wilson RC and Doudna JA. Annu Rev Biophys. 2013;42:217-239; 3. Rand TA, et al. Cell. 2005;123:621-629

Inclisiran è un siRNA che mima il processo fisiologico di RNA interference. Aumenta l'espressione dei recettori LDL sulla superficie dell'epatocita grazie al blocco della produzione di PCSK9.



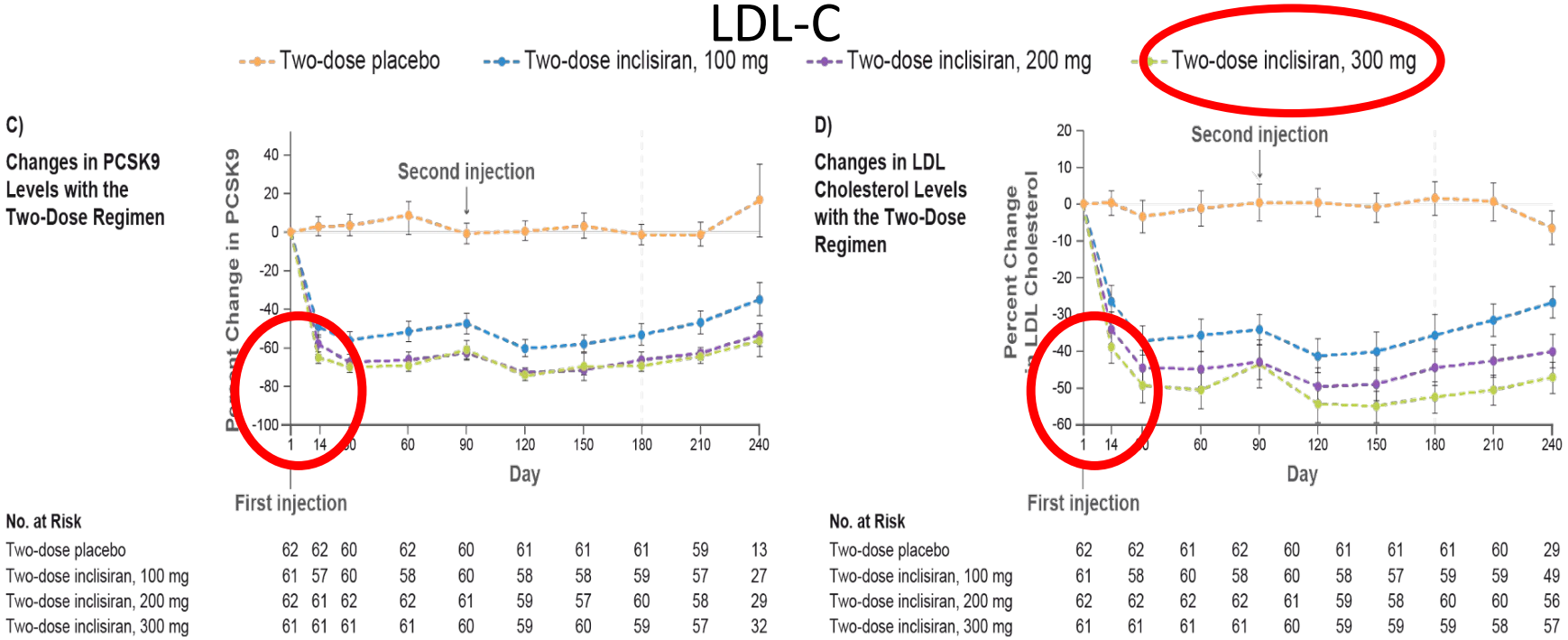
- siRNA di sintesi coniugato con un carboidrato costituito da GalNAc triantennaria per legame esclusivo con recettore ASGPR epatospecifico
- Agisce nell'epatocita a livello del citoplasma e non nel nucleo
- Utilizza il meccanismo naturale del RNA interference per impedire la traduzione di *PCSK9* mediante la degradazione del relativo mRNA
- E' formato da nucleotidi modificati per prolungarne la stabilità e la lunga durata d'azione

Khvorova A, et al. *N Engl J Med*. 2017;376:4-7.
Fitzgerald K, et al. *N Engl J Med*. 2017;376:41-51.
Wang N, et al. Circ Res. 2017;120:1063-1065; 2. Fitzgerald K, et al. N Engl J Med. 2017;376:41-51

ORION-1: trial di fase 2 che ha permesso di identificare il regime di somministrazione associato alla maggiore riduzione di PCSK9 e LDL-C

- At 180 days, LDL cholesterol was significantly lowered among persons at high cardiovascular risk who had elevated levels at baseline.

Già a 14 giorni si ha una consistente riduzione dei livelli di PCSK9 ed LDL-C



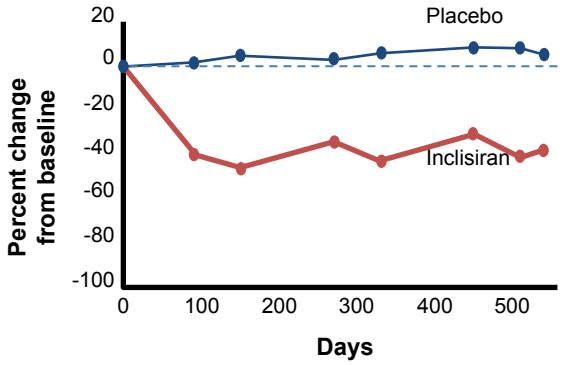
Ray KK et al; New England Journal of Medicine, 2017; 376:1430-1440

Studi ORION 9-10-11: endpoint primario
Inclisiran fornisce un'efficace e prolungata riduzione delle LDL-C per 18 mesi

Variazione percentuale LDL nel tempo (over time)

ORION-9[1]

Change in LDL cholesterol

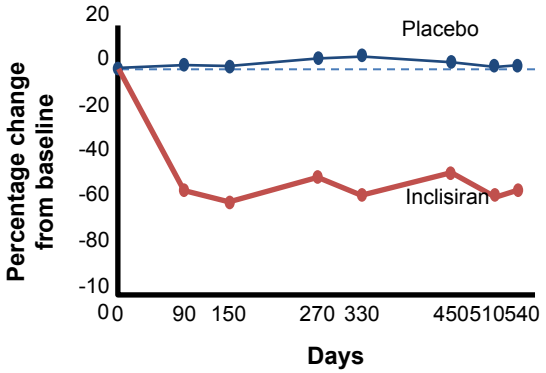


No. of patients								
Placebo	240	237	238	235	233	233	229	232
Inclisiran	242	240	239	240	237	237	231	232

Used with permission. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530.

ORION-10[2]

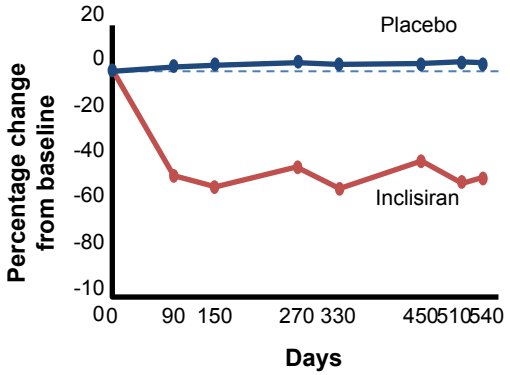
Percentage change in LDL cholesterol



No. of patients								
Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

ORION-11[2]

Percentage change in LDL cholesterol



No. of patients								
Placebo	807	797	785	774	773	764	739	749
Inclisiran	810	790	796	778	773	768	724	742

Used with permission. Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519.

Between group difference	**-47.9%** (*P*<0.001)	**-52.3%** (*P*<0.001)	**-49.9%** (*P*<0.001)

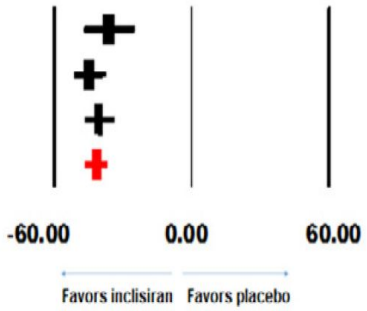
1. Raal FJ, et al. *N Engl J Med.* 2020;382(16):1520-1530.
2. Ray KK, et al. *N Engl J Med.* 2020;382(16):1507-1519.

Metanalisi studi Orion 9-10-11
Riduzione delle LDL-C e Major adverse Cardiovascular Event (MACE)

A: LDL cholestrol Level

Study name	Difference in means	Lower limit	Upper limit	p-Value
ORION-9	-47.90	-53.39	-42.41	0.000
ORION-10	-52.30	-55.75	-48.85	0.000
ORION-11	-49.90	-53.15	-46.65	0.000
Total	-50.53	-52.73	-48.34	0.000

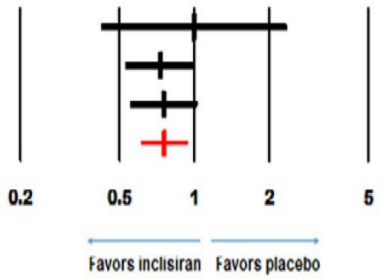
Heterogeneity ($Q = 2.0, P = 0.36; I^2 = 2.0$)



B: MACE

Study name	Risk ratio	Lower limit	Upper limit	p-Value
ORION-9	1.00	0.42	2.35	0.992
ORION-10	0.73	0.53	1.01	0.058
ORION-11	0.75	0.55	1.03	0.075
Total	0.76	0.61	0.94	0.012

Heterogeneity ($Q = 0.4, P = 0.80; I^2 = 0.0$)



Khan SA et al; AM.J Cardiol; 134:69-73

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

AIFA
AGENZIA ITALIANA DEL FARMACO

Indicazioni

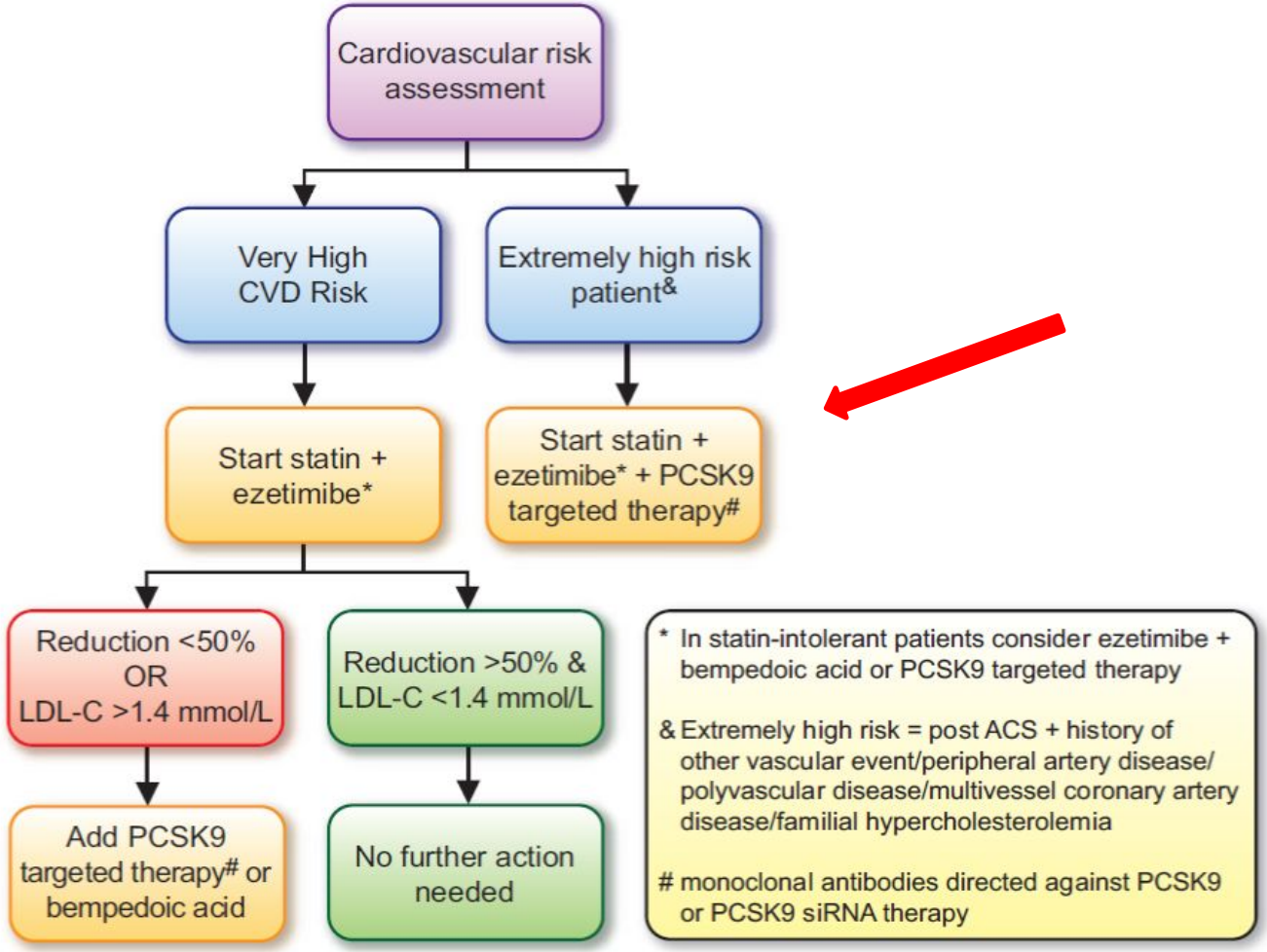
15 October 2020
EMA/CHMP/520993/2020
Committee for Medicinal Products for Human Use (CHMP)

Inclisiran è indicato in adulti con **ipercolesterolemia primaria*** (eterozigote familiare e non familiare) o **dislipidemia mista**, in aggiunta alla dieta:

- in **associazione a una statina** o una statina con altre terapie ipolipemizzanti in pazienti non in grado di raggiungere gli obiettivi per l'LDL-C con la dose massima tollerata di una statina, oppure
- in monoterapia o in associazione ad altre terapie ipolipemizzanti in pazienti **intolleranti** alle statine o per i quali una statina è controindicata.

*per definizione è qualsiasi ipercolesterolemia causata da un disturbo (familiare o non familiare) nel metabolismo lipidico e non causata da un'altra condizione, come l'ipotiroidismo o l'effetto di un farmaco

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



Ray KK. European Heart Journal (2022) **43**, 830–833

New treatment options for LDL cholesterol

New strategies

Early combination therapy

Fixed-dose combinations

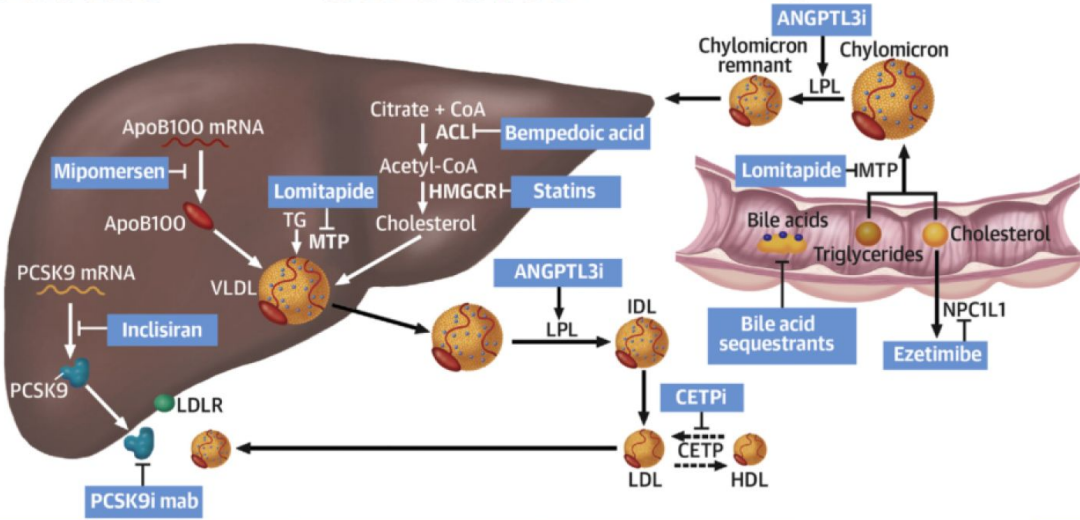
Population-wide application of PCSK9-siRNA

Novel drugs – approved

Bempedoic Acid, Inclisiran

Novel drugs - in development

AngPTLi, CETPi, oral PC

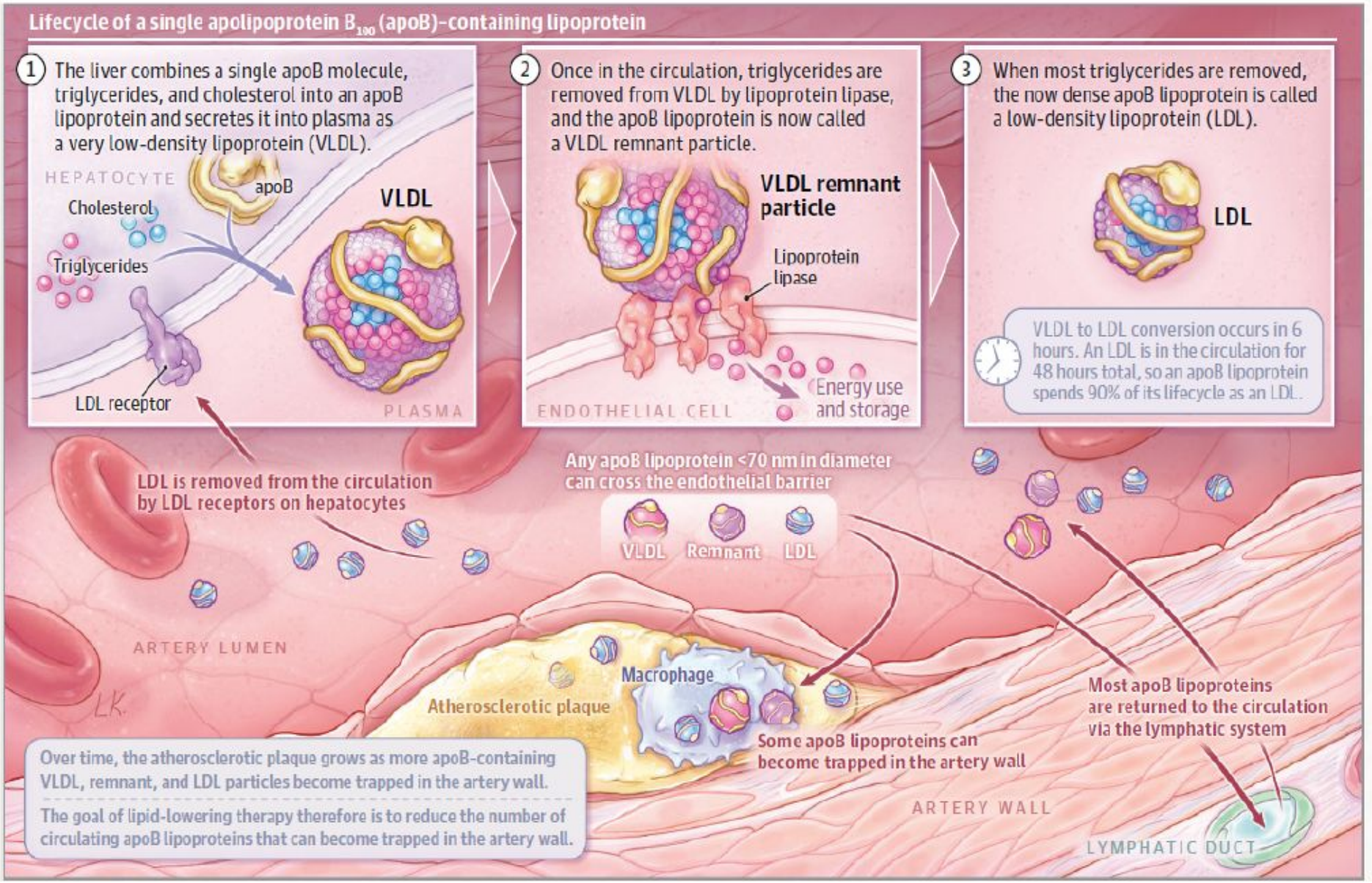


Residual ‘lipid’ risk

There is more than ’LDL-cholesterol’

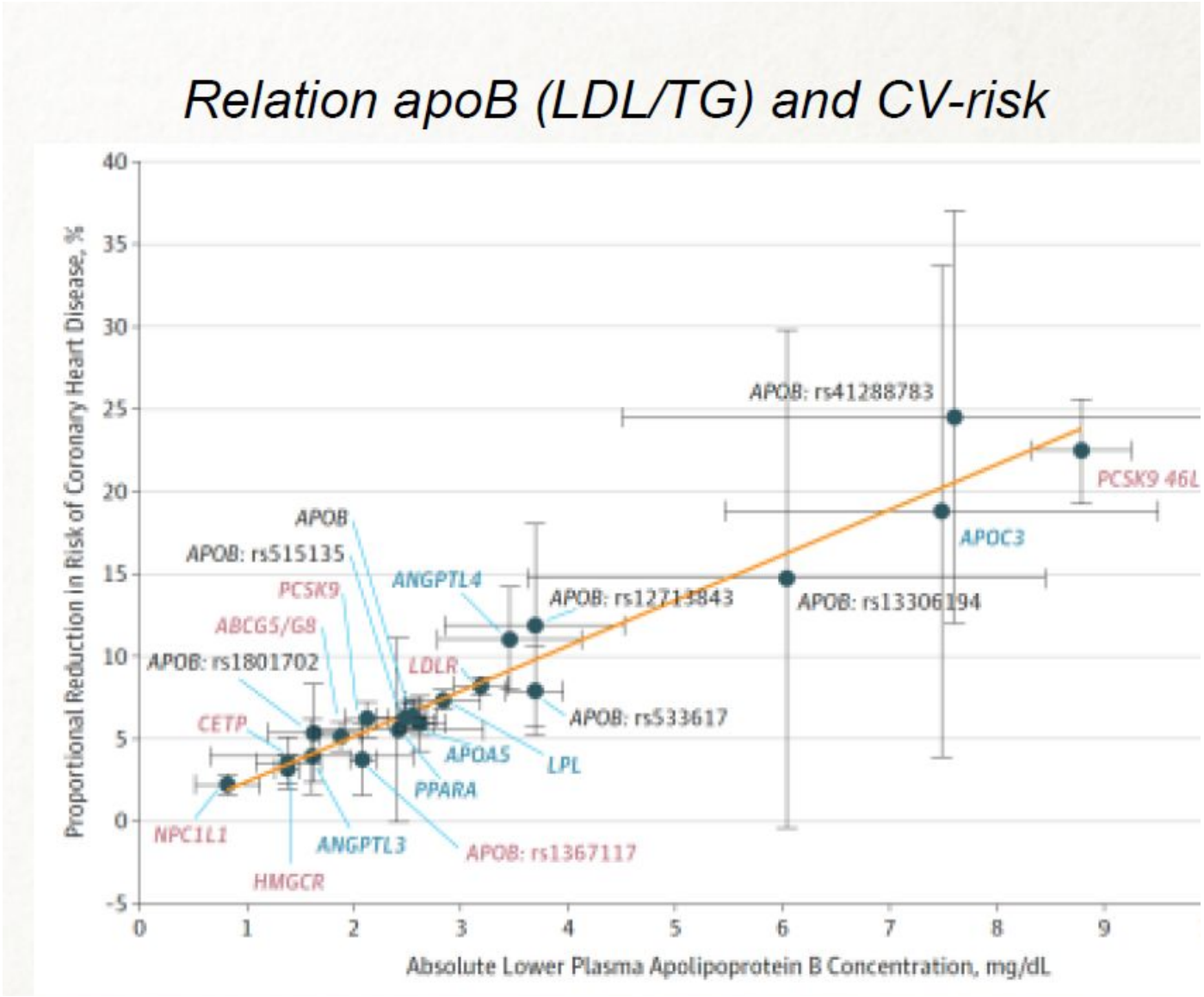
ApoB

Retained apoB-containing lipoproteins initiate atherosclerosis



Ference B, JAMA 2020; Ference B, JAMA 2019

Relation apoB (LDL/TG) and CV-risk



Ference B, JAMA 2020; Ference B, JAMA 2019

Residual ‘lipid’ risk

There is more than ’LDL-cholesterol’

ApoB

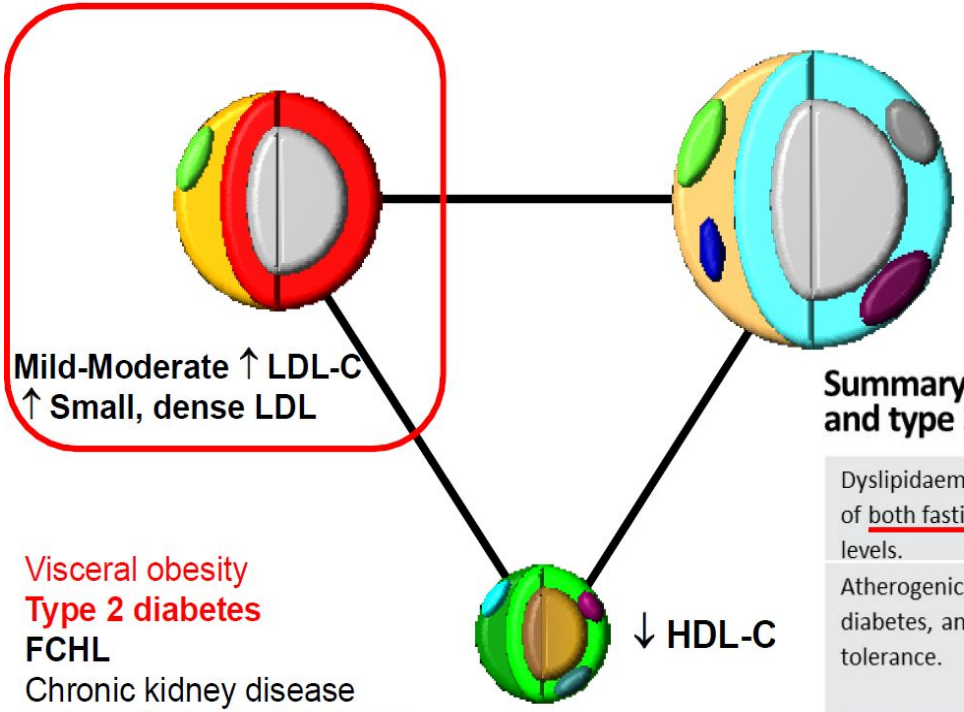
Trigliceridi

Prevalence of hypertriglyceridemia

- Residual CV-risk in high-risk patients on statin therapy:
  - 1.5 – 4.5% MACE / year
- Prevalence of elevated TGs:
  - 14 – 40% of population
  - highest in overweight/obesity and diabetes
- Guideline-based CV-medication ‘modest’ impact on TGs:
  - statins: -20 – -25%
  - PCSK9-ab: -9%

Dyslipidemia in Type 2 Diabetes: a Cluster of Lipid Abnormalities

#1 Lipid target CVD Risk ESC/EAS 2019 - ESC 2021



Visceral obesity
Type 2 diabetes
FCHL
Chronic kidney disease
Polycystic Ovary Syndrome

FCHL: Familial Combined Hyperlipidemial

Austin et al. Circulation 1990

Summary of dyslipidaemia in metabolic syndrome and type 2 diabetes mellitus

EAS ESC European Society of Cardiology

Dyslipidaemia represents a cluster of lipid and lipoprotein abnormalities, including elevation of both fasting and post-prandial TG, ApoB, and small dense LDL, and low HDL-C and ApoA1 levels.

Atherogenic dyslipidaemia is one of the major risk factors for CVD in people with type 2 diabetes, and in people with abdominal obesity and insulin resistance or impaired glucose tolerance.

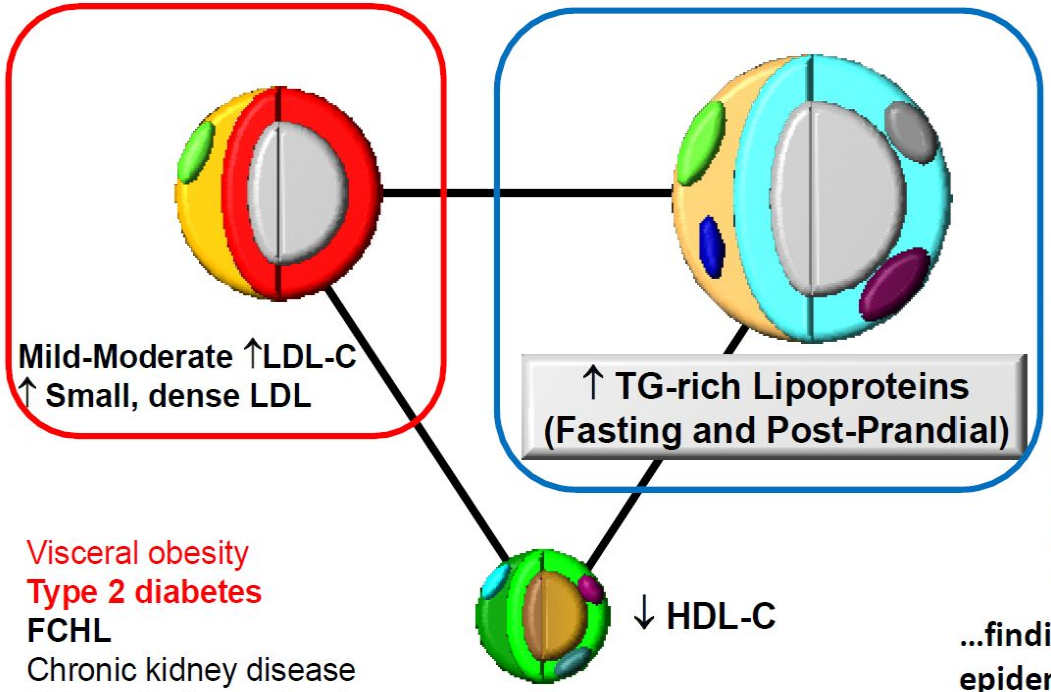
www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Mach F, et al. *Eur Heart J.* 2019;00:1–78

Dyslipidemia in Type 2 Diabetes: Not Only LDL-C....

#1 target CVD Risk ESC/EAS 2019 - ESC 2021



Visceral obesity
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Austin et al. Circulation 1990

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 4791–4806
doi:10.1093/eurheartj/ehab551

Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society

Henry N. Ginsberg[1*†], Chris J. Packard[2†], M. John Chapman[3], Jan Borén[4], Carlos A. Aguilar-Salinas[5,6], Maurizio Averna[7], Brian A. Ference[8], Daniel Gaudet[9], Robert A. Hegele[10], Sander Kersten[11], Gary F. Lewis[12], Alice H. Lichtenstein[13], Philippe Moulin[14], Børge G. Nordestgaard[15,16], Alan T. Remaley[17], Bart Staels[18], Erik S.G. Stroes[19], Marja-Riitta Taskinen[20], Lale S. Tokgözoğlu[21], Anne Tybjaerg-Hansen[22,23,24,25], Jane K. Stock[26], and Alberico L. Catapano[27]

...findings from genetic studies, clinical trials, and epidemiology have provided strong evidence to support the CAUSAL ASSOCIATION of TRL levels (both fasting and post-prandial) WITH ATHEROGENESIS....

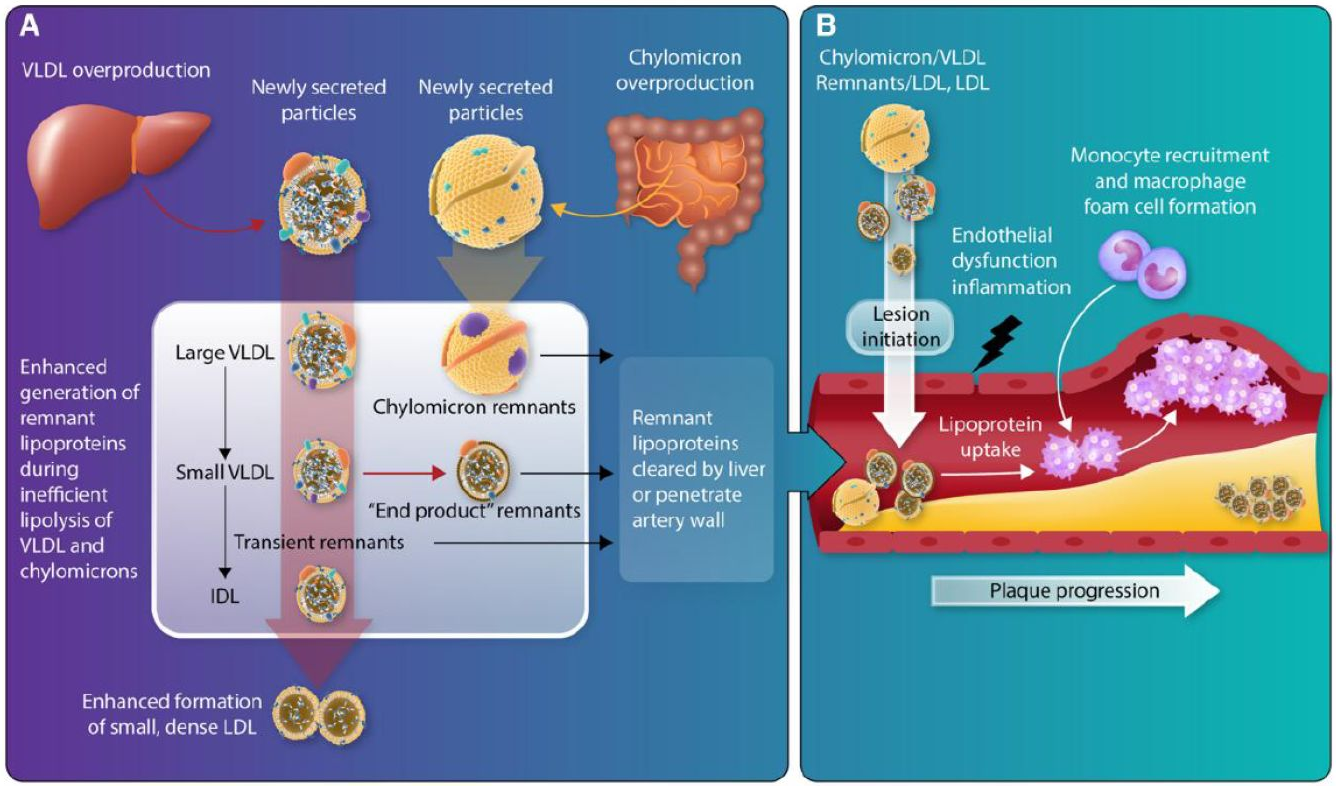
ESC European Society of Cardiology
European Heart Journal (2022) 43, 807–817
https://doi.org/10.1093/eurheartj/ehab875
Lale Tokgozoglu [1]*, Carl Orringer [2], Henry N. Ginsberg [3], and Alberico L. Catapano [4]

The year in cardiovascular medicine 2021: dyslipidaemia

Triglyceride-Rich Lipoprotein (TGRL) are CAUSAL in Promoting The Atherothrombotic Process

1 TG-RICH LIPOPROTEIN IS AS ATHEROGENIC AS 1 LDL PARTICLE

Robust, recent evidence supports a causal association between triglyceride-rich lipoproteins, and TRIGLYCERIDE-RICH LIPOPROTEIN REMNANTS WITH CARDIOVASCULAR EVENTS. Overproduction and inefficient lipolysis, such as in Type 2 diabetes, mainly in the post-prandial phase, of both very low-density lipoprotein and chylomicrons lead to increased remnant formation. Triglyceride-rich lipoprotein remnants contribute to the initiation and progression of atherosclerotic lesions.

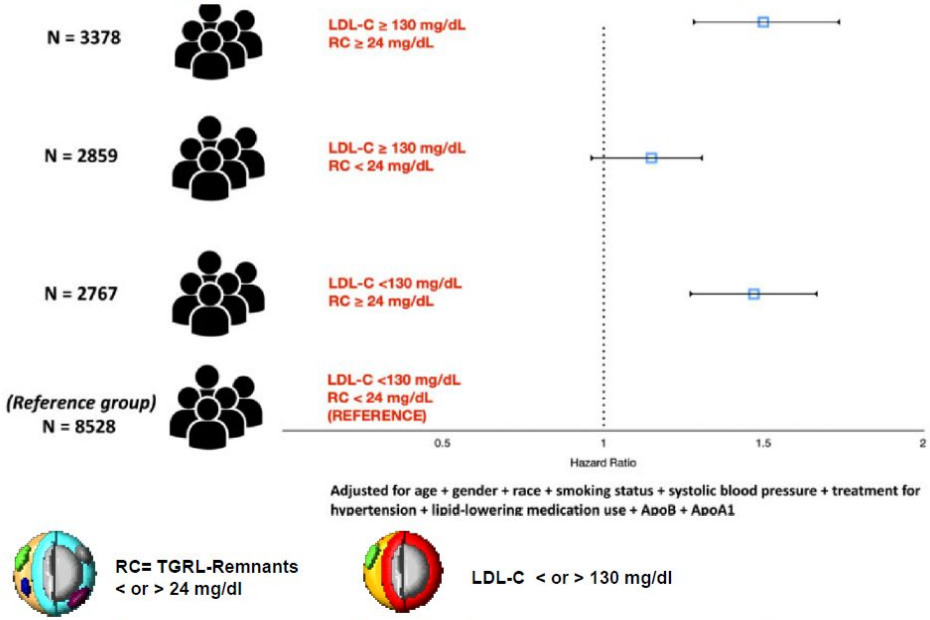


ESC European Society of Cardiology
European Heart Journal (2021) 42, 4324–4332
doi:10.1093/eurheartj/ehab432

CLINICAL RESEARCH
Vascular biology and medicine

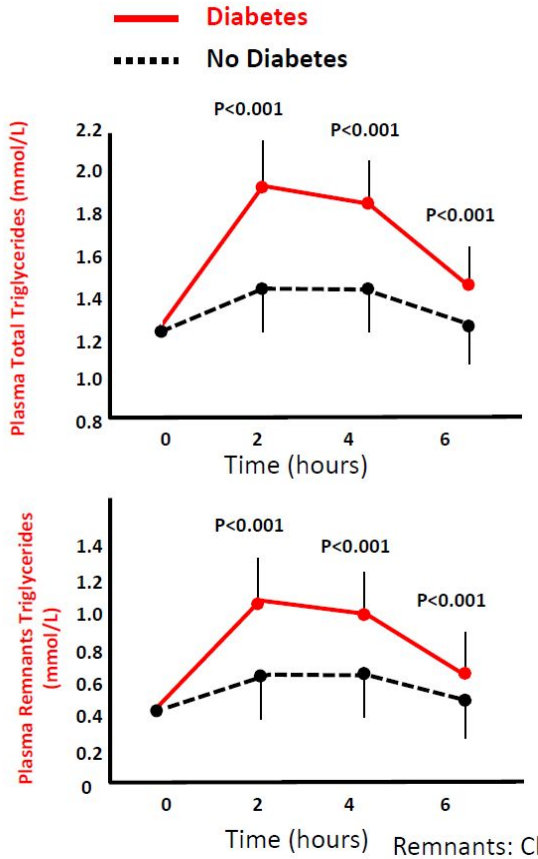
Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study

Renato Quispe[1,2], Seth Shay Martin[1,2], Erin Donelly Michos[1,2], Isha Lamba[3], Roger Scott Blumenthal[1,2], Anum Saeed[4], Joao Lima[2,5], Rishi Puri[6], Sarah Nomura[7], Michael Tsai[7], John Wilkins[8], Christie Mitchell Ballantyne[9], Stephen Nicholls[10], Steven Richard Jones[1,2], and Mohamed Badreldin Elshazly[1,6]*



Elevated TGRL-Remnants (RC) levels were associated with ASCVD independent of traditional risk factors, LDL-C, and apoB levels.

High postprandial triglyceridemia in patients with type 2 diabetes and microalbuminuria



Patients with T2DM show high and prolonged postprandial lipemia after meals.

Epidemiological data suggest that high plasma TG levels, both in the fasting state and post-prandially, are associated with cardiovascular diseases in patients with diabetes

Remnants: Chylomicrons and VLDL remnants

Tentolouris N et al. J. Lipid Res. 2007. 48: 218–225.

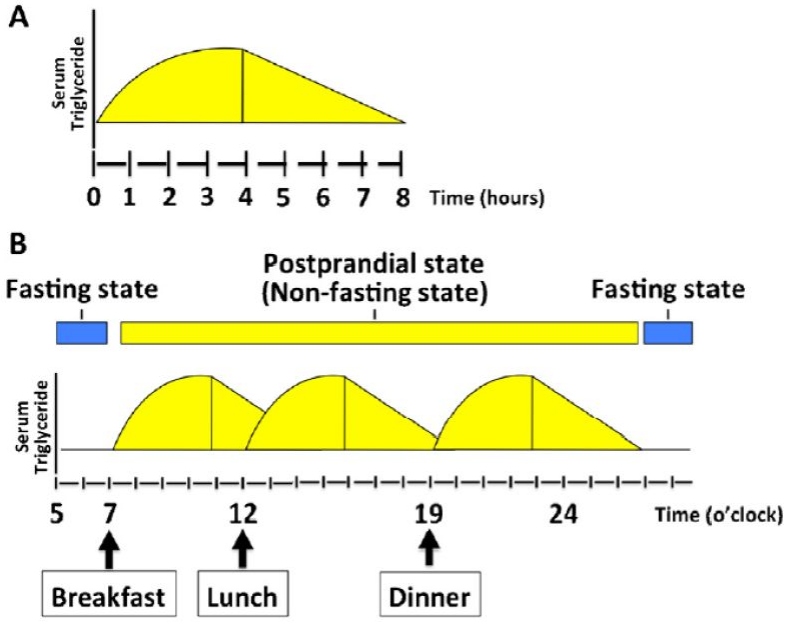
Review

Postprandial hyperlipidemia as a potential residual risk factor

Kazufumi Nakamura (MD, FJCC)[a,*], Toru Miyoshi (MD, FJCC)[a], Kei Yunoki (MD)[b], Hiroshi Ito (MD, FJCC)[a]

[a] Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[b] Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan

Journal of Cardiology 67 (2016) 335–339



A - Serum TG levels reach a peak at 3–4 h after the meal and slowly return to initial levels at 6–8 h after the meal.
B - Most of the day is a nonfasting state (in other words a postprandial state) in people who eat at least three meals a day.

Atherosclerosis 217 (2011) 142–148

Contents lists available at ScienceDirect

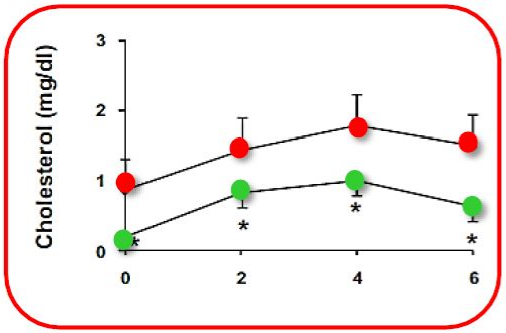
Atherosclerosis

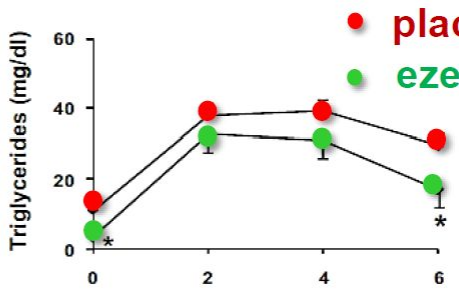
journal homepage: www.elsevier.com/locate/atherosclerosis

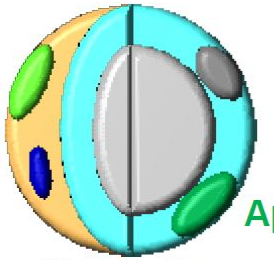
Ezetimibe beneficially influences fasting and postprandial triglyceride-rich lipoproteins in type 2 diabetes

Lutgarda Bozzetto, Giovanni Annuzzi, Giuseppina Della Corte, Lidia Patti, Paola Cipriano, Anna Mangione, Gabriele Riccardi, Angela A. Rivellese*

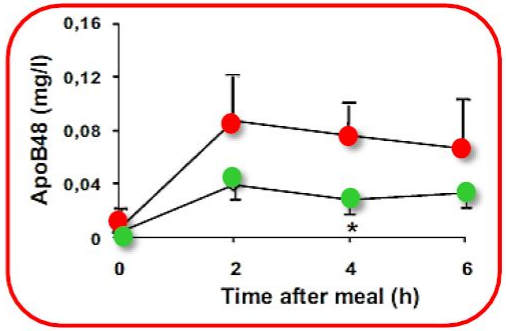
Chylomicrons and VLDL Remnants







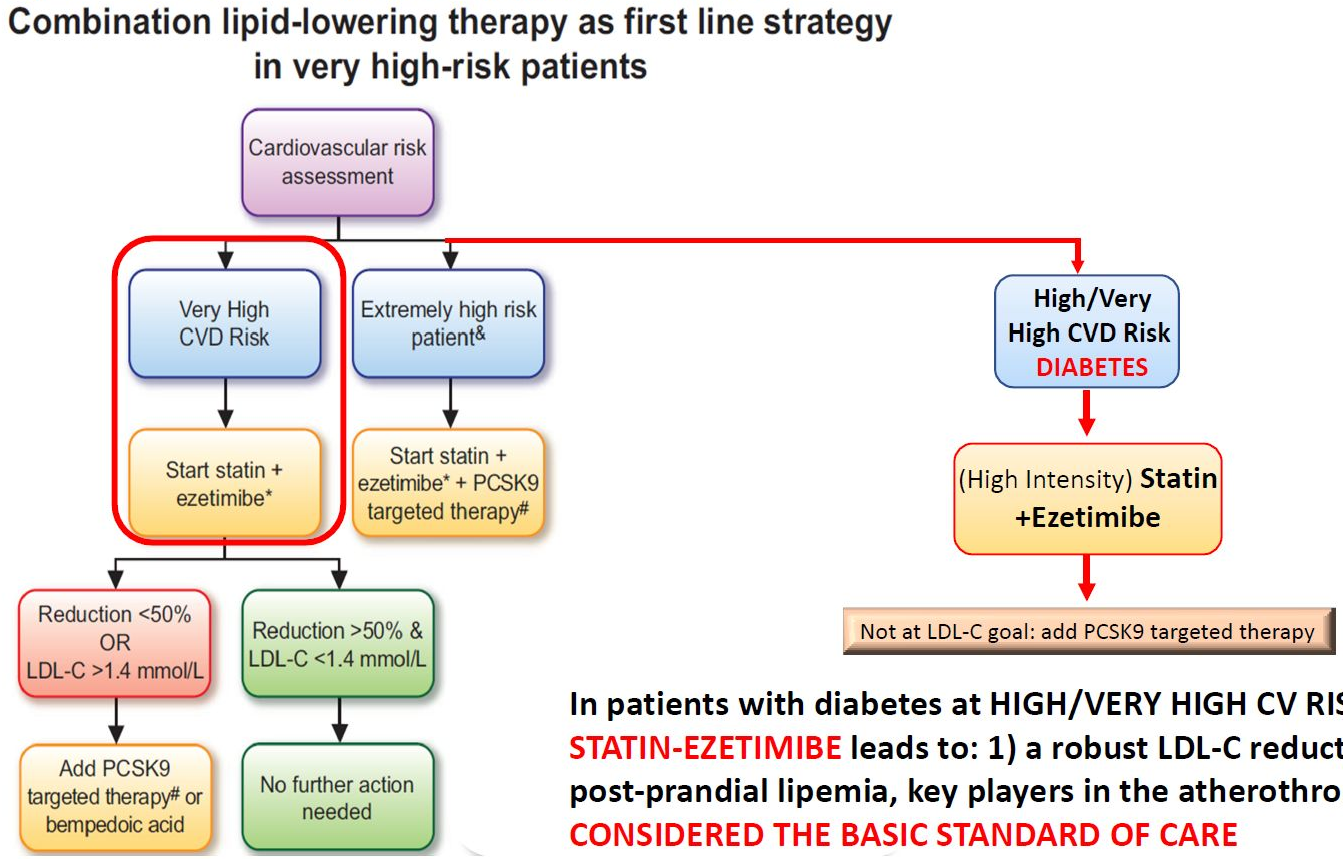
Chylomicrons



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]

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–4
doi:10.1093/eurheartj/ehab718
VIEWPOINT
Epidemiology and prevention



Main Lipid Effect on

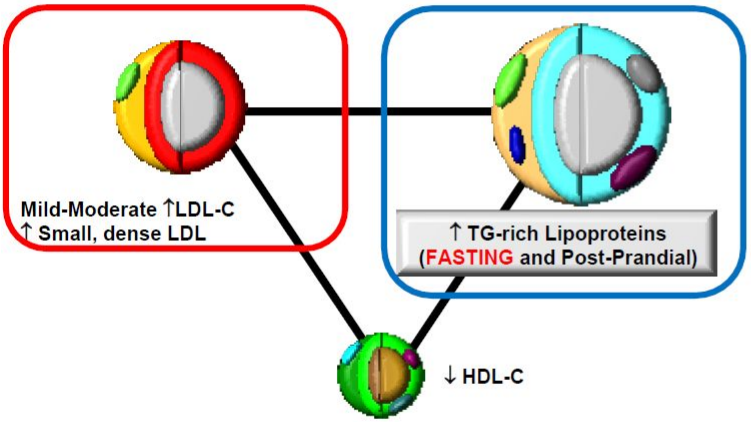
LDL Cholesterol (STATIN, EZETIMIBE)

Post-prandial TGRL and Remnants (EZETIMIBE)

In patients with diabetes at HIGH/VERY HIGH CV RISK, COMBINATION THERPAY STATIN-EZETIMIBE leads to: 1) a robust LDL-C reduction and, 2) improvement in the post-prandial lipemia, key players in the atherothrombotic process and SHOULD BE CONSIDERED THE BASIC STANDARD OF CARE

Dyslipidemia in Type 2 Diabetes: Not Only Post PRandial but <u>also FASTING TG ARE IMPORTANT</u>....

#1 target CVD Risk ESC/EAS 2019 - ESC 2021

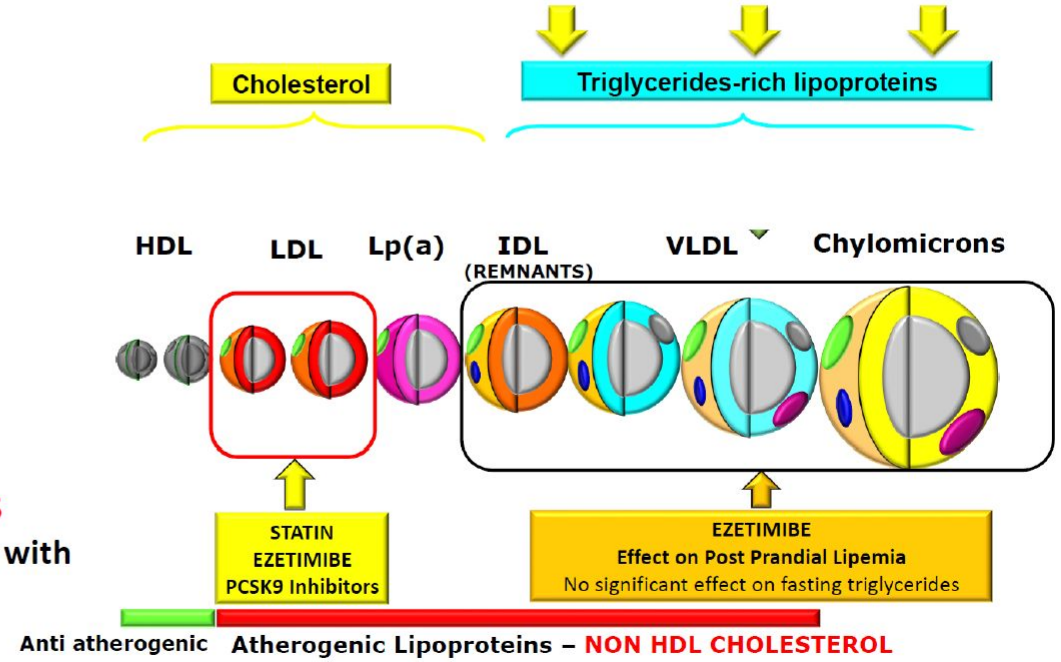


Not only post-prandial but also
FASTING ELEVATED TRIGLYCERIDE-RICH LIPOPROTEINS
NEEDS TO BE ADDRESSED to reduce CV risk in Patients with Diabetes

Austin et al. Circulation 1990

ESC European Society of Cardiology
European Heart Journal (2021) 42, 4791–4806
doi:10.1093/eurheartj/ehab551

Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society



2021 ESC Recommendations for Patients with Hypertriglyceridemia

ESC European Society of Cardiology
European Heart Journal (2021) 42, 3227–3337 doi:10.1093/eurheartj/ehab484

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

European Heart Journal
(2021) 42, 3227-3337

RECOMMENDATIONS FOR DRUG TREATMENT OF PATIENTS WITH HYPERTRIGLYCERIDAEMIA

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)].[533]	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.[534–536]	IIb	B
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 × 2 g/day) may be considered in combination with a statin.[84]	IIb	B

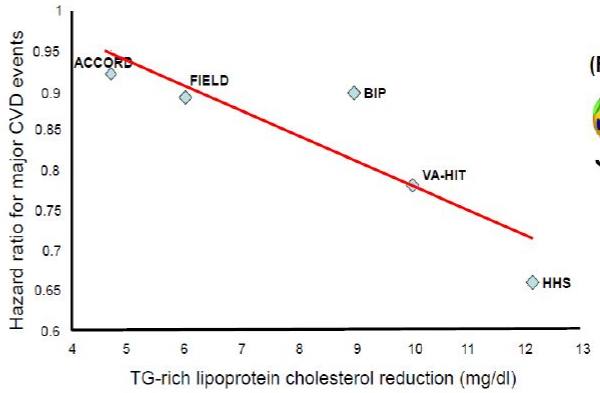
FIBRATE+STATIN → High CV risk patients

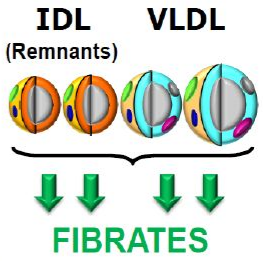
n3 PUFA EPA +STATIN → High-Risk CV or above

FIBRATES AND CARDIOVASCULAR BENEFITS

A. Zambon, A. Pirillo, S. Zambon, G.D. Norata, A.L. Catapano

Association between the magnitude of TG-rich lipoprotein reduction and the risk of cardiovascular events in FIBRATE trials





Current Atherosclerosis Reports (2020) 22:74

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]

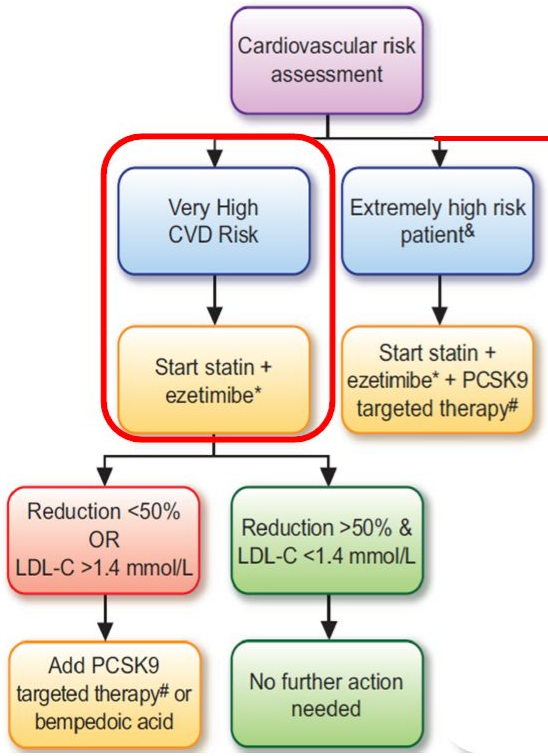
ESC European Society of Cardiology

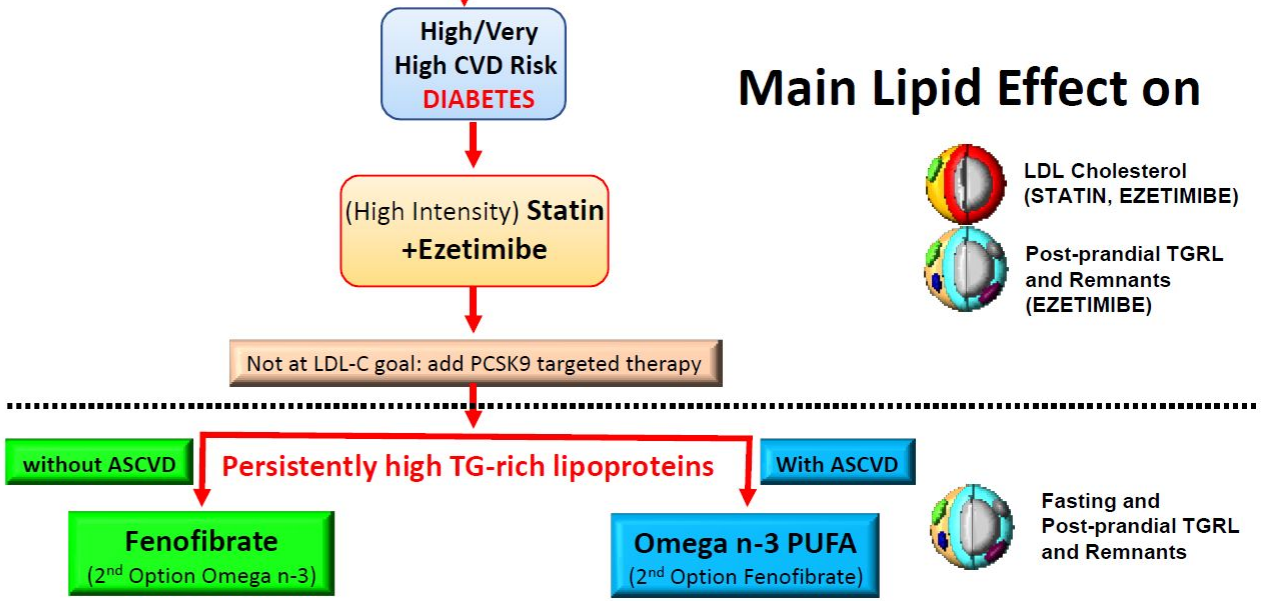
European Heart Journal (2021) **00**, 1–4
doi:10.1093/eurheartj/ehab718

VIEWPOINT
Epidemiology and prevention

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

OPTIMAL CONTROL of both LDL-C and Fasting and PP TG-Rich lipoproteins
KEY STEP in Diabetic Patients
for an **EFFECTIVE RISK MANAGEMENT OF CARDIOVASCULAR EVENTS**





Main Lipid Effect on

LDL Cholesterol (STATIN, EZETIMIBE)

Post-prandial TGRL and Remnants (EZETIMIBE)

Fasting and Post-prandial TGRL and Remnants

Residual ‘lipid’ risk

There is more than ’LDL-cholesterol’

- ApoB
- Trigliceridi
- Lp(a)

ESC European Society of Cardiology

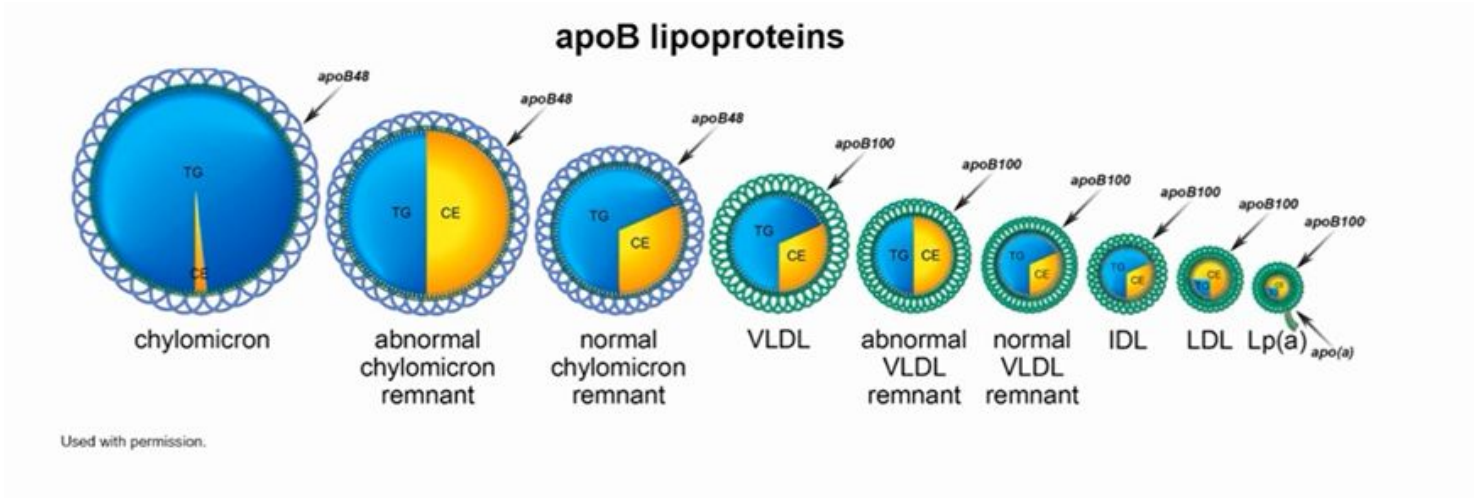
European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

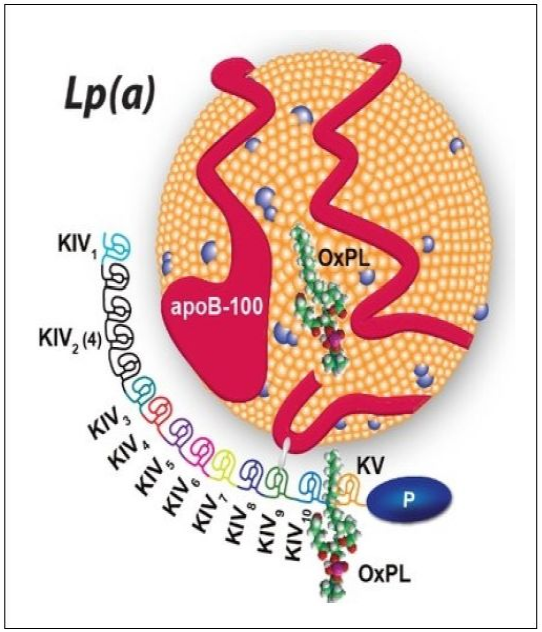
2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

Recommendations for lipid analyses for cardiovascular disease risk estimation

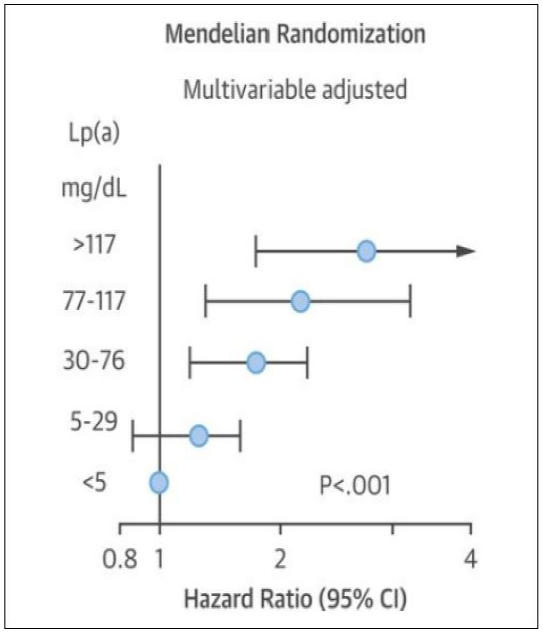
Recommendations	Class[a]	Level[b]
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C



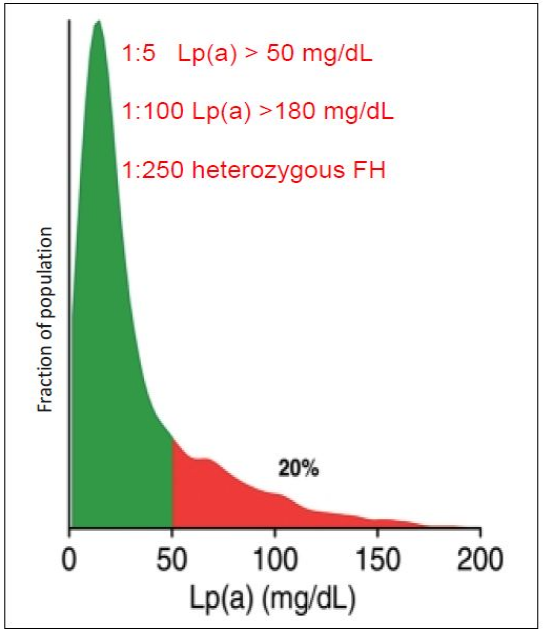
Lp (a)



Tsimikas, JACC, 2017



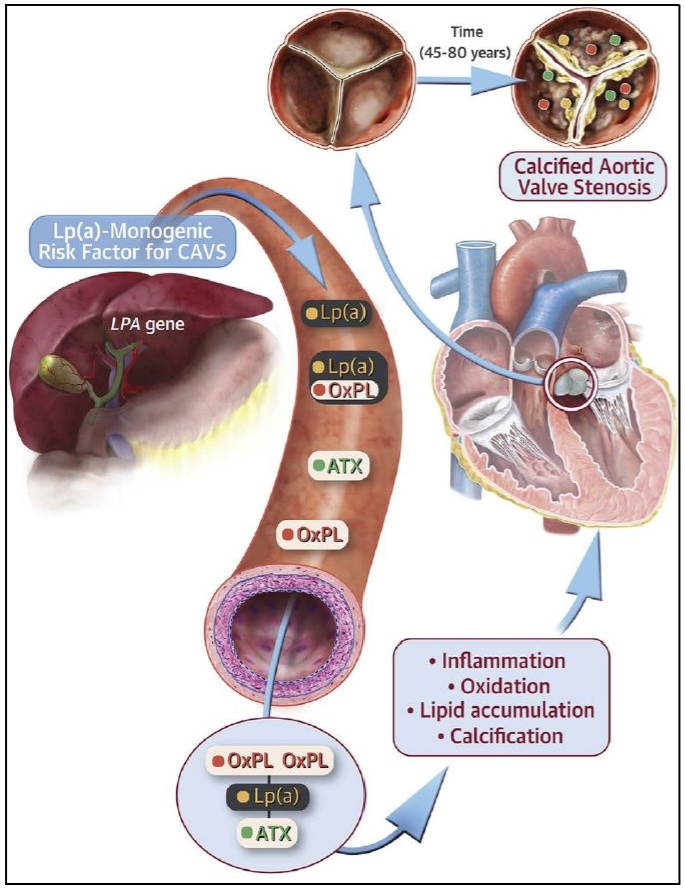
Kamstrup, JAMA, 2009



Nordestgaard, EHJ, 2010

Kamstrup PR, et al. *JAMA*. 2009;301:2331-9; Nordestgaard BG, et al. *Eur Heart J*. 2010 Dec; 31: 2844–2853; Tsimikas S. *J Am Coll Cardiol*. 2017;69:692-711.

Lp(a) is associated with ADCVD and calcific aortic valve stenosis



CV-risk increase for Lp(a) > 99th percentile vs < 20th percentile:

	OR	CI
• **ASCVD**	2.73	1.49 – 5.18
• **MI**	3.33	1.53 – 7.79

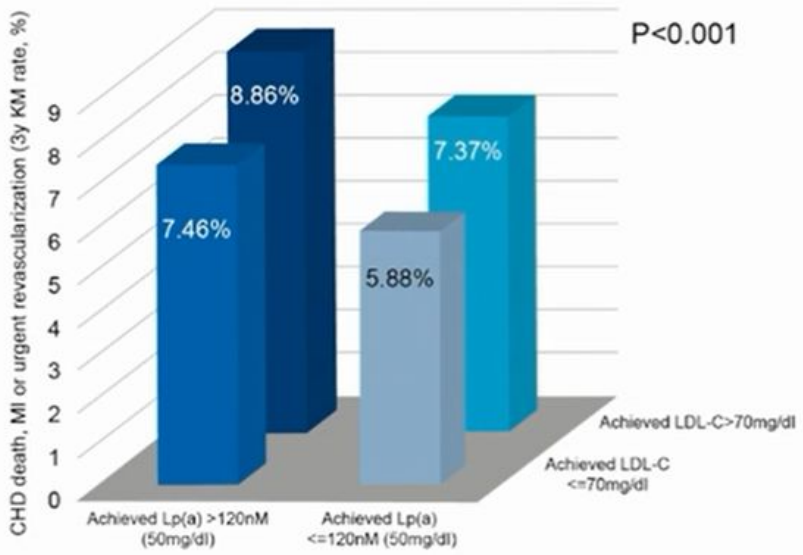
Torzewski, M. et al. J Am Coll Cardiol Basic Trans Science (2017). 2(3):229-41

Elevated Lp(a) is an independent and causal CV risk factor

An exploratory analysis of the FOURIER trial found a stepwise decrease in the risk of **CHD death, MI, or urgent coronary revascularisation** for patients who achieved either an **Lp(a) ≤120 nM (~50 mg/dL)** or **LDL-C value below ≤70 mg/dL.**

The lowest event rate was observed for patients who achieved lower levels of both Lp(a) and LDL-C.

Effect of Lp(a) and LDL-C achieved levels on CHD events



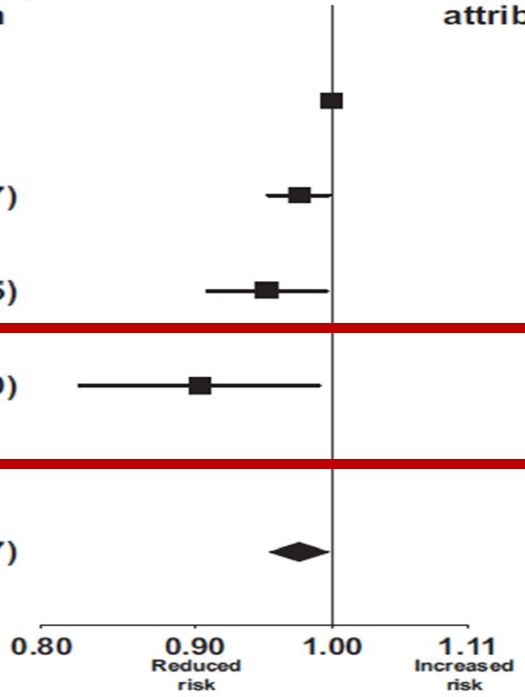
Adapted with permission.

CHD=coronary heart disease; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; KM=Kaplan-Meier; LDL-C=low-density lipoprotein cholesterol.

From: Supplementary materials: O'Donoghue ML et al. *Circulation.* 2019;139(12):1483-1492.

PSCK9 MAbs lower Lp(a) by 20-30%- and this may independent of LDL-C lowering offer additional benefit

Baseline Lp(a) quartile	Month 4 median Lp(a) reduction	HR (95% CI) for Lp(a) median reduction	Joint risk reductio attributable to Lp
Quartile 1 (<6.7 mg/dL)	0 mg/dL	1.00	0%
Quartile 2 (6.7 to <21.2 mg/dL)	5.1 mg/dL	0.975 (0.952, 0.997)	13%
Quartile 3 (21.2 to <59.6 mg/dL)	9.9 mg/dL	0.951 (0.909, 0.995)	23%
Quartile 4 (≥59.6 mg/dL)	20.1 mg/dL	0.903 (0.824, 0.990)	39%
Overall	5.0 mg/dL	0.975 (0.953, 0.997)	13%



Szarek *et al. Eur Heart J.* 2020; 41:4245-55.

Inclisiran a siRNA reducing hepatic synthesis of PCSK9 also lowers Lp(a) –Pooled analyses From ORION 9-11

Percent Change from baseline to day 510		Placebo		Inclisiran	p-value
ITT population[1] Imputed values[2]		N = 1827		N = 1833	
PCSK9	Mean %	+ 14.8	**-83%**	- 68.2	<0.0001
Total cholesterol	Mean %	+ 2.9	**-32%**	- 29.5	<0.0001
Non HDL-C	Mean %	+ 3.6	**-46%**	- 42.8	<0.0001
ApoB	Mean %	+ 1.7	**-42%**	- 40.2	<0.0001
Lp (a) (day 540)	Median %	+ 0.7	**-20%**	- 19.5	<0.0001[3]

1. All patients who were randomized imputed
2. Wright RS, Ray KK JACC 2021

2: Imputed using a mixed model for repeated measures3: Non-parametric test; not

CONCLUSIONI

dislipidemia e rischio cardiovascolare residuo

- LDL-C: più basso e preocemente (indipendentemente dai valori iniziali di LDL)
- Nuovi farmaci: acido bempedoico ed inclisiran
- Residual “lipid” risk: apoB, trigliceridi, lp (a)

Working group

Michele A. Pacilli,

Giuseppe Di Stolfo,

Mauro Salvatori,

Carlo Coli,

Matteo Impagliatelli

Thanks for your

Bempedoic Acid + Ezetimibe FDC

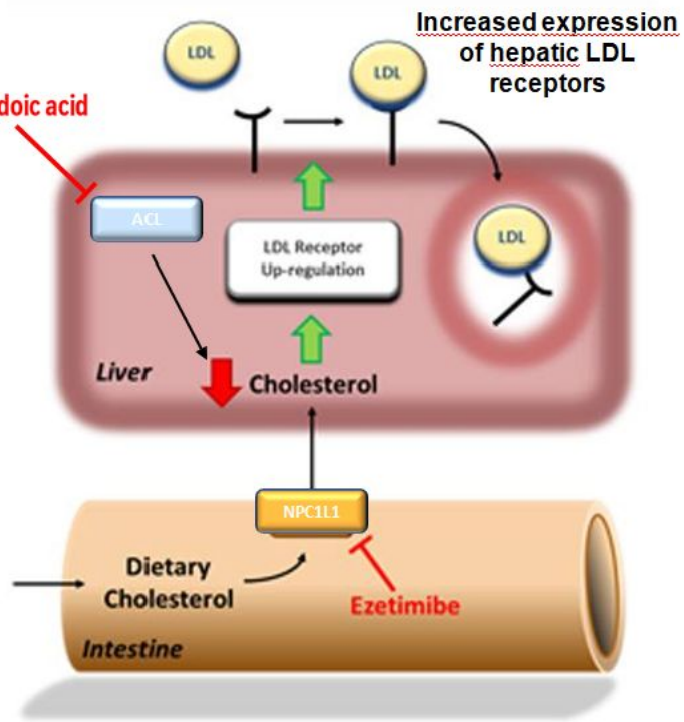
Poiché acido bempedoico ed ezetimibe riducono i livelli di LDL-colesterolo mediante la sovraregolazione dell'espressione dei recettori per le LDL grazie a due diversi meccanismi, esiste un forte razionale per lo sviluppo di una combinazione a dose fissa (FDC) di questi due principi.

Acido Bempedoico

Inibizione della sintesi epatica di colesterolo via ACL

Ezetimibe

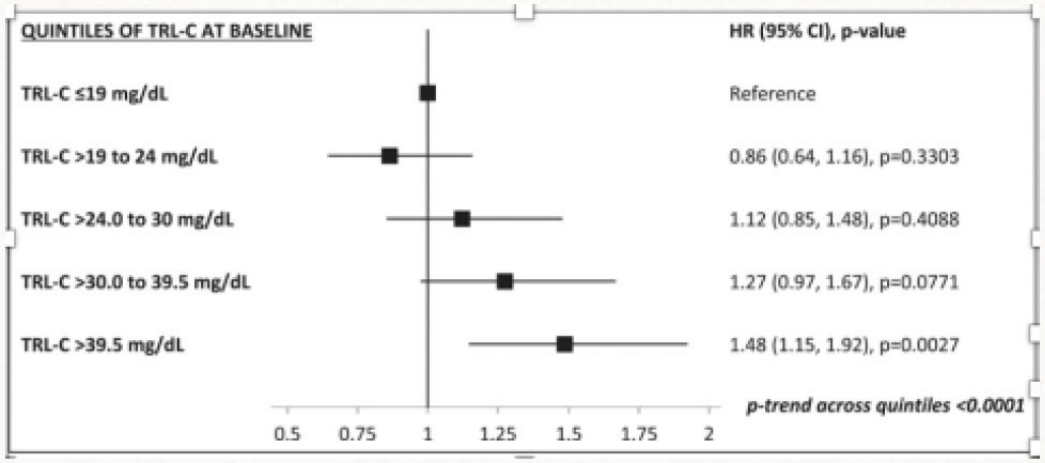
Inibizione dell'assorbimento intestinale di colesterolo



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.

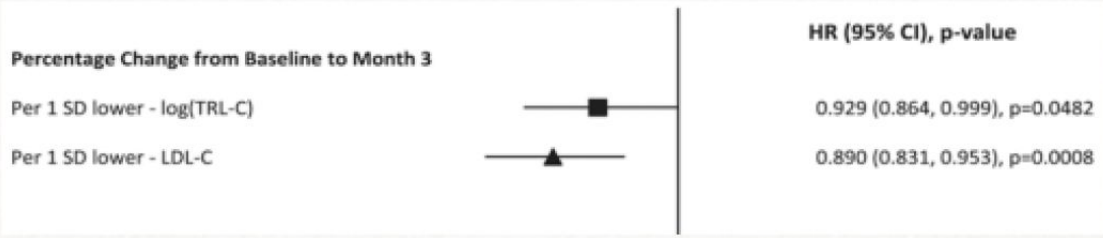
Relevance of TRLs on CV-event rate

TRL-c baseline predicts MACE in pts using atorvastatin



TRL-c = nonHDLc - LDLc

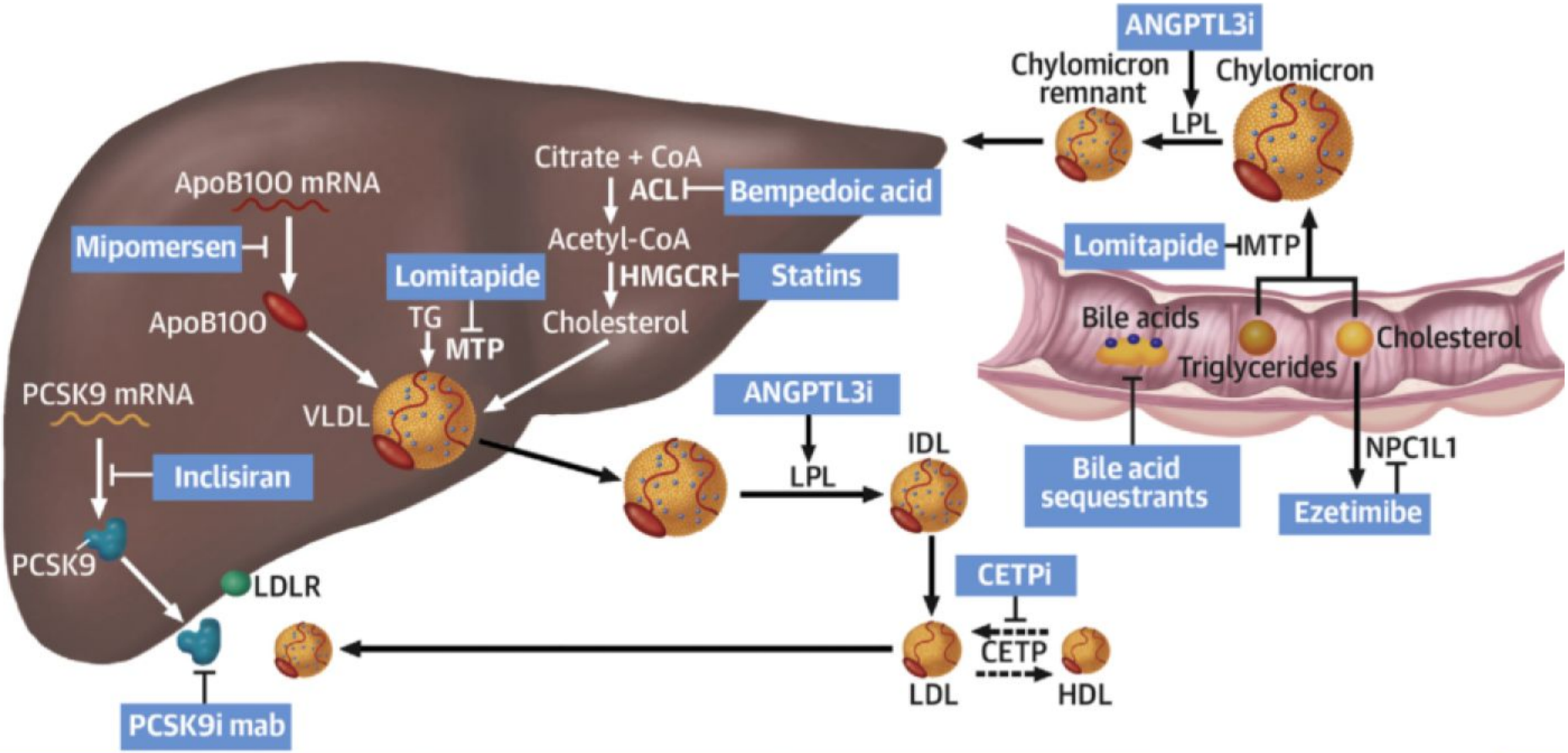
Both TRLc and LDLc change predict MACE risk



TNT study. Vallejo-Vaz et al, Circ 2018

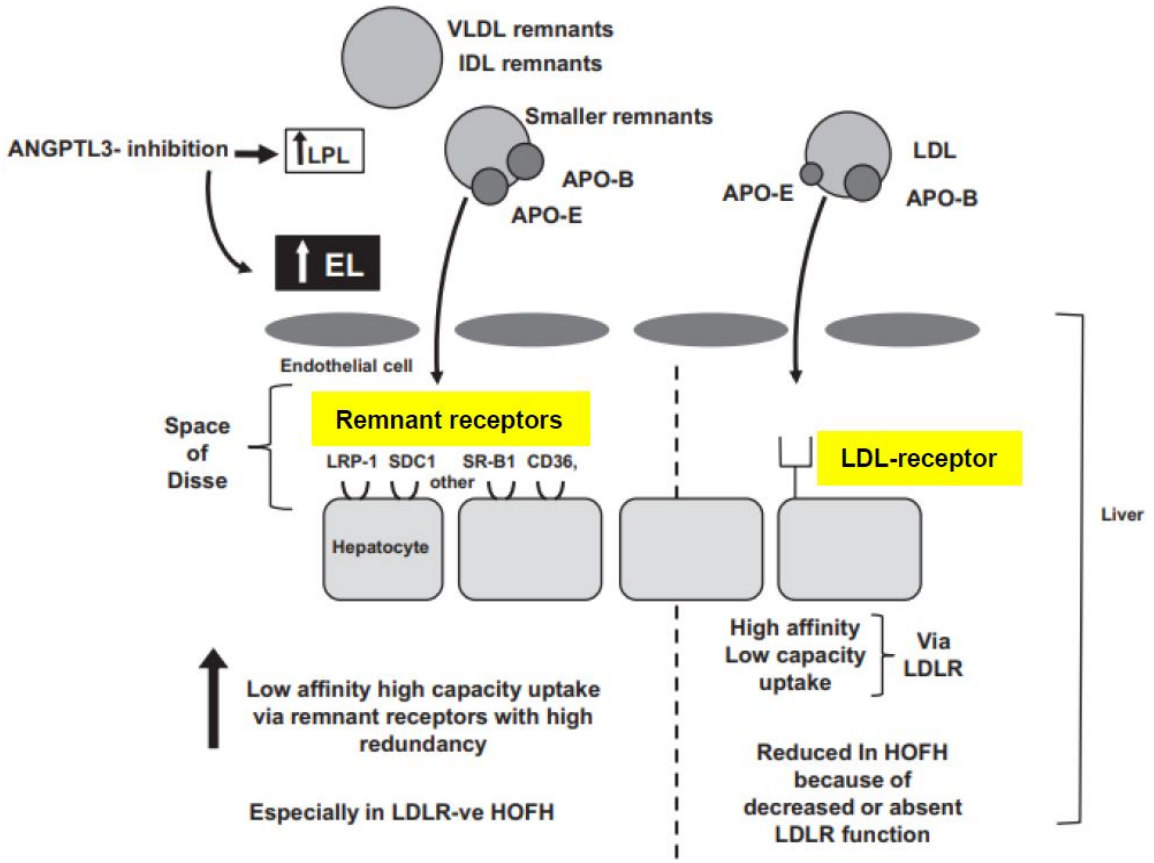
Genetics:

ANGPTL3 deficiency is associated with protection from atherosclerotic cardiovascular disease



Proposed mechanism of LDL-cholesterol reduction with ANGPTL3 inhibition in homozygous familial hypercholesterolaemia

Increased low-affinity but high capacity uptake of remnants by activation of both LPL and EL with ANGPTL3 inhibition



LPL = Lipoprotein lipase; EL = Endothelial lipase; LRP-1 = LDL receptor-related protein -1; SDC-1 = Sydecan-1—the main heparin sulphate proteoglycan (HSPG) receptor
SR-B1 = Scavenger receptor class B, type 1; CD36 = Cluster of differentiation 36

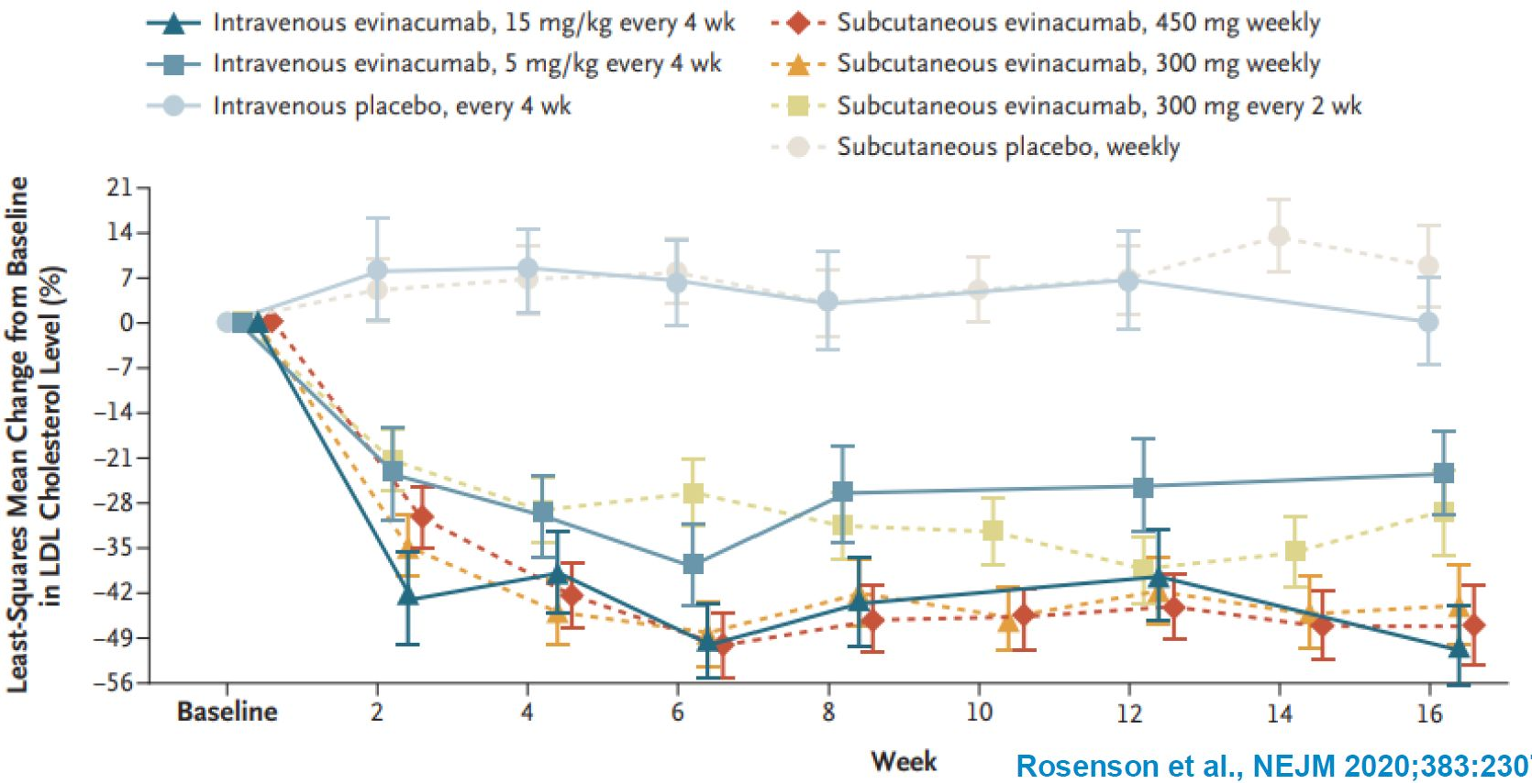
Mohamed et al., Curr Opin Lipidol 2021, 32:213–18

Clinical trials targeting ANGPTL3

Drug	Mechanism	Indication	Study phase	Status
Angptl3-LRx (vupanorsen)	GalNAc3-modified ASO	HyperTG	1	Completed
		FH	2	Completed
		Severe hyperTG	2	Completed
		Partial lipodystrophy	2	Completed
		NAFLD, T2D, HyperTG	2	Completed
		Mixed dyslipidemia	2	Not yet recruiting
Evinacumab	ANGPTL3 monoclonal antibody	Severe hyperTG	2	Completed
		Refractory hypercholesterolemia	2	Completed
		Homozygous FH	3	Completed
		Pediatric homozygous FH	3	Recruiting
ARO-ANG3	RNAi-mediated Angptl3 silencing	Dyslipidemia, FH, HyperTG	1	Completed
		Mixed dyslipidemia	2	Recruiting
Lilly ANGPTL3 siRNA**	ANGPTL3 siRNA	CVD, diabetes	1	n/a

Clinical trials.gov; november 2021

Evinacumab, monoclonal antibody against ANGPTL3 in heFH with refractory hypercholesterolemia

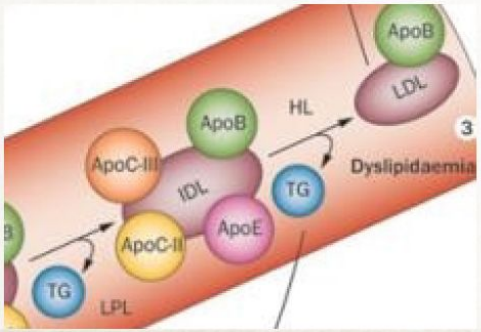


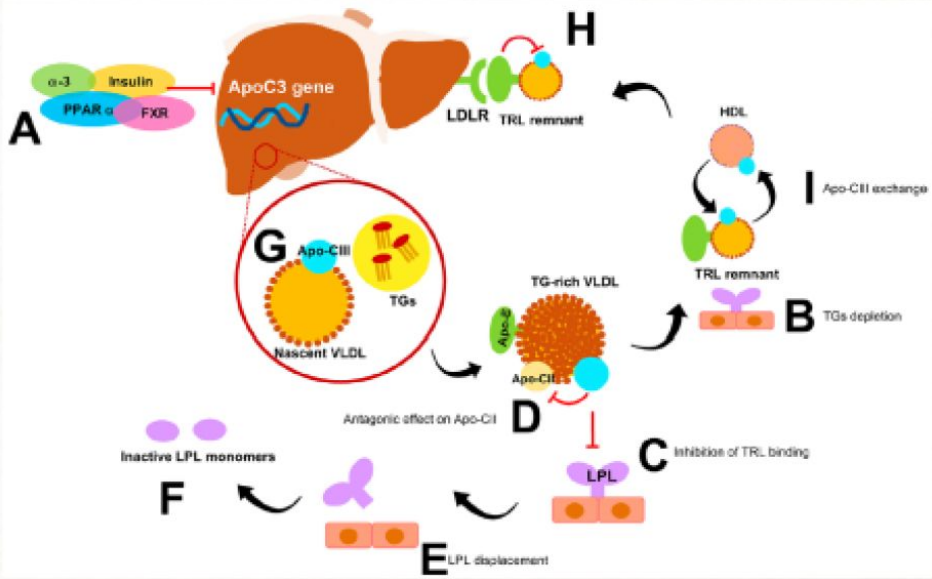
N=272

Rosenson et al., NEJM 2020;383:2307-2319

apoC-III
Effect in Lipids/TRL metabolism

- 8.8 kD – 79 amino-acids
- Synthesized in
  - Predominantly in liver
  - Intestine
- Carried by lipoproteins:
  - Large VLDL 60-90%
  - Small VLDL 40-70%
  - LDL 5-15%

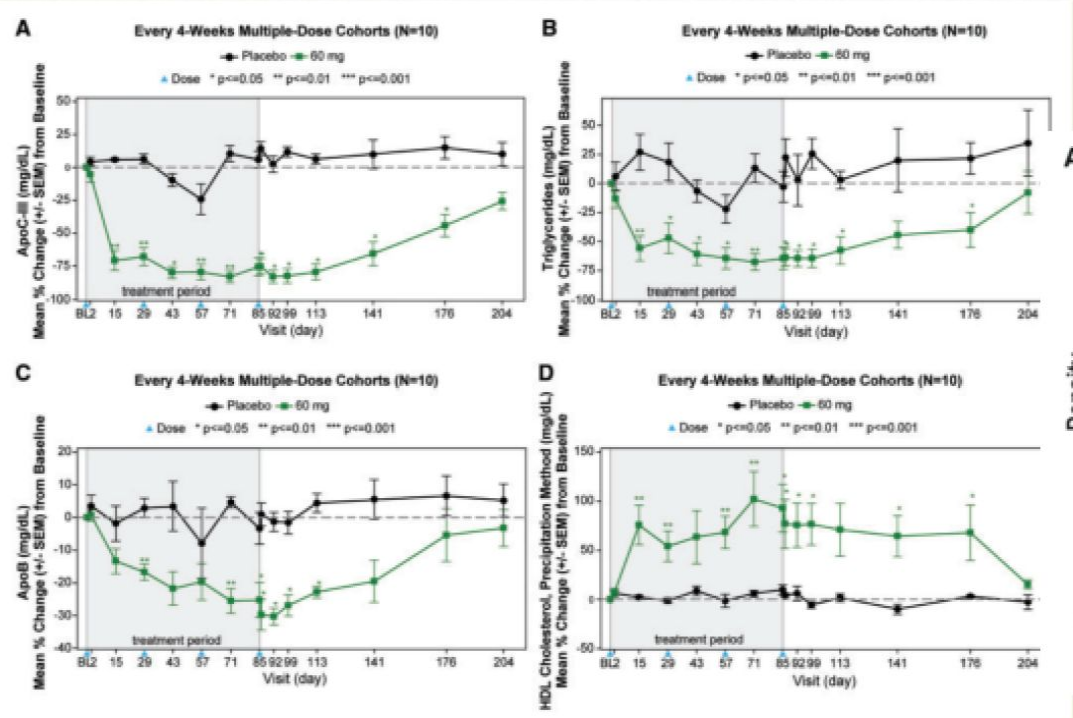




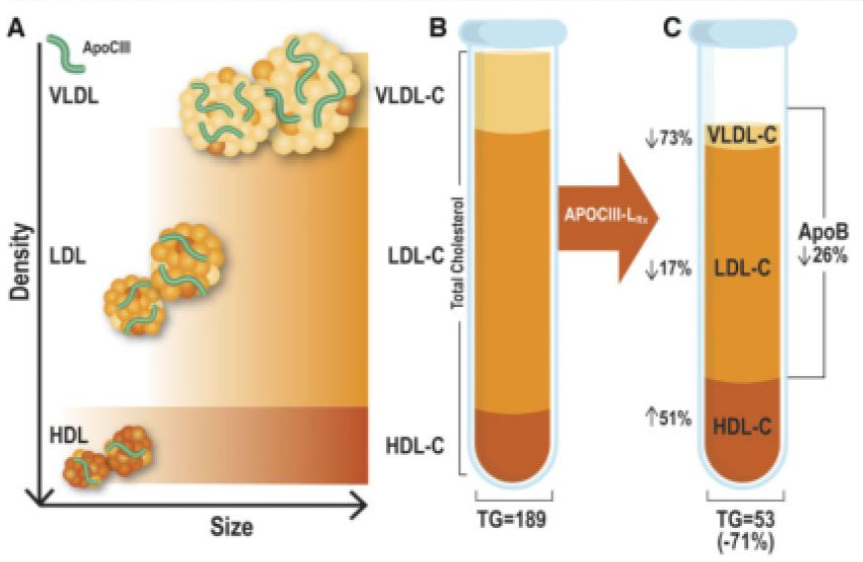
B. Inhibition of LPL activity
C. prevention of LPL binding to TRL
D. reduced apoCII action
E. displacement of LPL from Endothelium
F. conversion of LPL dimer into monomer
G. increased VLDL1 secretion
H. prevention of hepatic TRL uptake

V. Alexander et al. J Am Coll Cardiol 2012; M. Wyler von Ballmoos et al. J Clin Lipidol 2015; De La Parra Sotto, Nutrition Metabolism CV disease 2022

apoCIII galnac-antisense in overweight HTG subjects
potent TG reduction with LDLc/apoB reduction



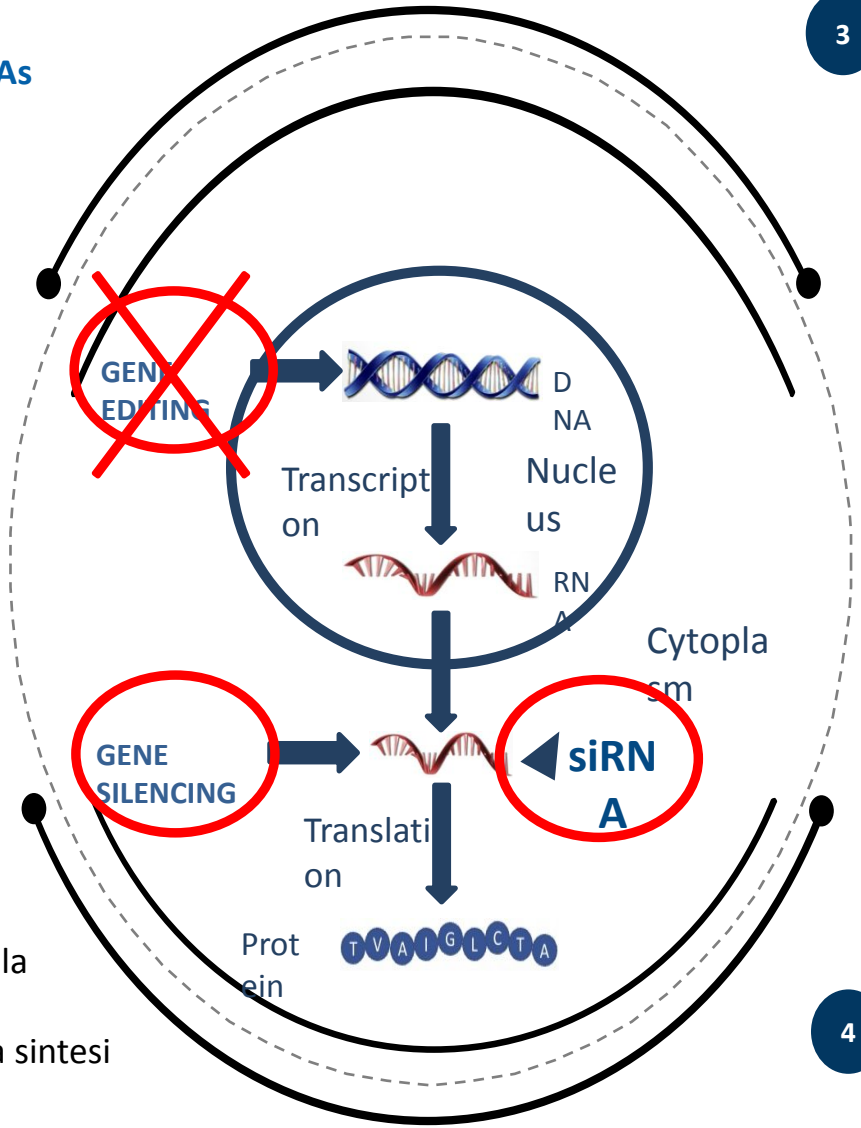
Broad reduction in atherogenic lipids



Alexander V, Eur Heart J 2019

Regolazione dell'espressione genica attraverso RNAi (Gene Silencing)

1 Solo il **~2%** del genoma umano codifica proteine, mentre una parte significativa di esso codifica per **non-coding RNAs** (ncRNA)[1]



3 I **siRNA** sono brevi ncRNA a doppio filamento che **impediscono la sintesi proteica** degradando specifici mRNA bersaglio attraverso un meccanismo naturale chiamato **RNA interference**[2,3]

2 Gli ncRNA sono coinvolti nella **regolazione genica**, nella maturazione del RNA e nella sintesi proteica[1]

4 L'RNAi non è una tecnica di Gene Editing, ma di Gene Silencing. Non si svolge nel nucleo ma nel citoplasma

1. Aryal and Suarez. Vascul Pharmacol. 2019;114:64-75; 2. Wilson RC and Doudna JA. Annu Rev Biophys. 2013;42:217-239