Farmacologia dei farmaci innovativi per le dislipidemie (alirocumab, evolocumab, inclisiran, acido bempedoico, pemafibrato, volanesorsen)

Prof Alberto Corsini
Università degli Studi di Milano

Recommended treatment goals for LDL-lowering therapy: main changes from 2016 to 2019

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	**2019**
Very-high-risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8-3.5 (70 - 135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100mg/dL) or >50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50% ↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	< 2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

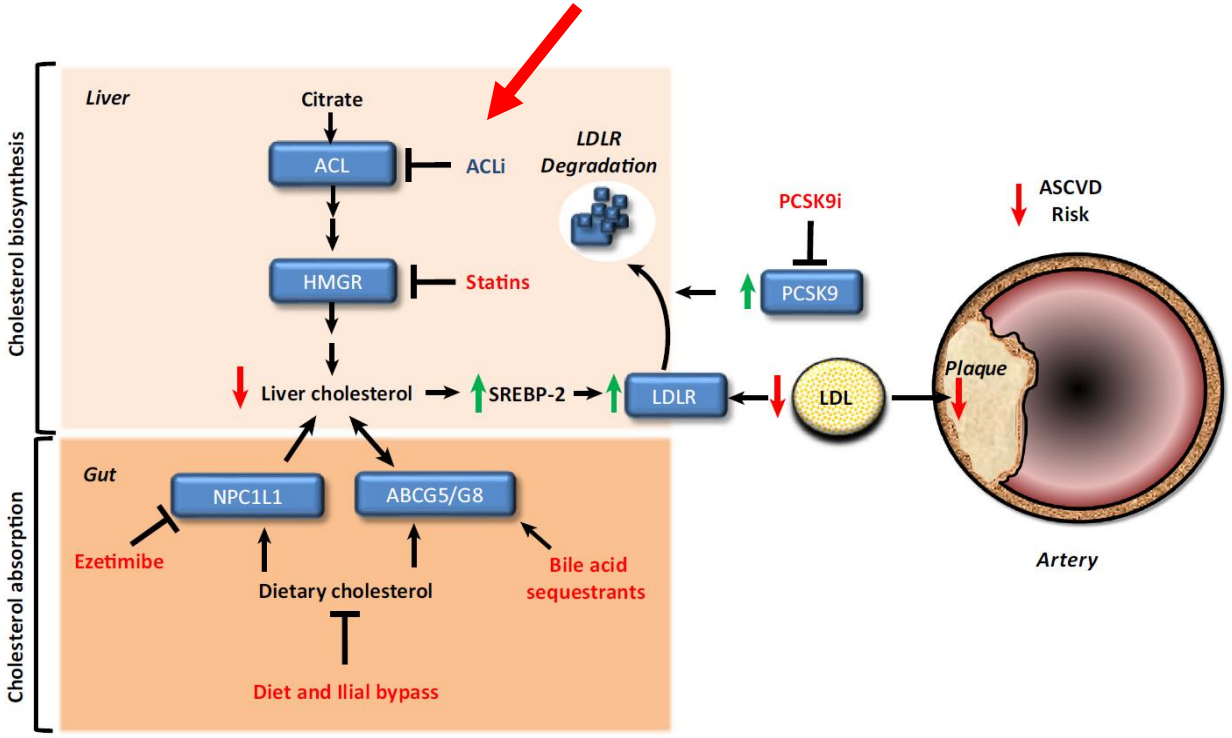
- **acido bempedoico**
- alirocumab, evolocumab
- inclisiran
- Pemafibrato
- volanesorsen

Pharmacological effects of lipid-modification therapies

	Effect on LDL cholesterol	Effect on triglycerides and cholesterol remnants	Effect on lipoprotein(a)	Cardiovascular benefit	Ongoing studies
Antisense and mAbs to ANGPTL3	Moderate decrease	Strong decrease	Neutral	No	NCT02709850 (phase 2), phase 3 trials*
Antisense, mAbs, and siRNA to apolipoprotein C3	Neutral	Strong decrease	Neutral	No	NCT03385239 (phase 2), NCT03783377 (phase 1)
Antisense to apolipoprotein(a)	Neutral	Neutral	Strong decrease	No	NCT03070782 (phase 2)
Bempedoic acid	Moderate decrease	Neutral	Neutral	No	NCT02993406 (phase 3 CVOT)
Bile acid sequestrants	Moderate decrease	Mild decrease	Neutral	No†	No
CETP inhibitors	Moderate decrease	Neutral	Mild decrease	Yes‡	No
Ezetimibe	Moderate decrease	Neutral	Minimal increase	Yes	No
Fibrates: SPPARMs	Neutral	Moderate decrease	Neutral	No†§	NCT03071692 (phase 3 CVOT)
Fish oils: EPA	Neutral	Moderate decrease	Neutral	Yes	No
Fish oils: EPA and DHA	Neutral	Moderate decrease	Neutral	No	NCT02104817 (phase 3 CVOT)
Inclisiran	Strong decrease	Mild decrease	Mild decrease	No	NCT03814187 (phase 3 CVOT)
Lomitapide	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Anti-PCSK9 mAbs	Strong decrease	Mild decrease	Mild decrease	Yes	No
Mipomersen	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Nicotinic acid	Mild decrease	Mild decrease	Mild decrease	No‖	No
Statins	Strong decrease	Mild decrease	Minimal increase	Yes	No

Ray KK et al Lancet 2019; 394: 697–708

ACL Inhibition Can Promote Hepatic LDLR Upregulation and Should Decrease ASCVD Risk



Pinkosky, S.L., et al Trends Mol Med, 2017. **23**(11): p. 1047-1063

ESC European Society of Cardiology
Cardiovascular Research (2018) 114, 1192–1208
doi:10.1093/cvr/cvy045

SPOTLIGHT REVIEW

From genome-wide association studies to Mendelian randomization: novel opportunities for understanding cardiovascular disease causality, pathogenesis, prevention, and treatment

Marianne Benn[1,2,3]* and Børge G. Nordestgaard[2,3,4,5]

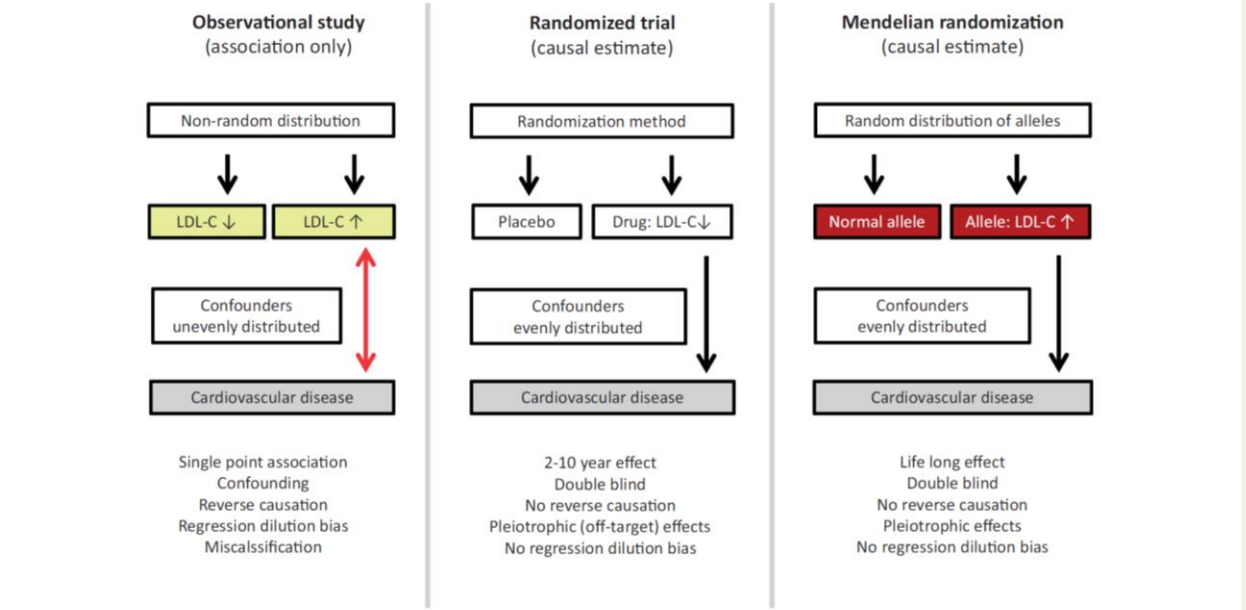


Figure 1 Comparison of observational studies, randomized trials, and Mendelian randomization studies to help understand causality from a risk factor, i.e. high low-density lipoprotein (LDL) cholesterol levels to risk of cardiovascular disease.

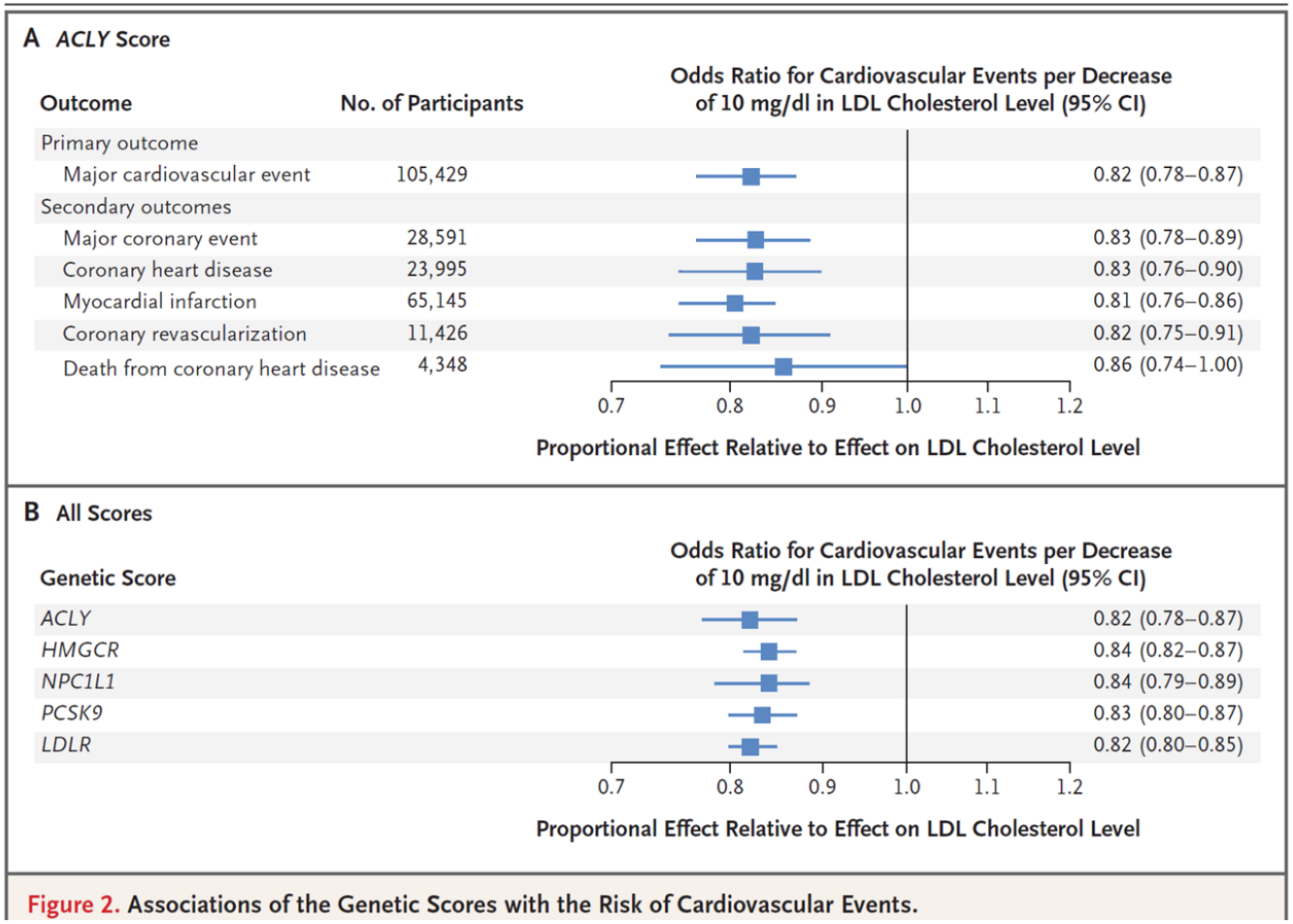
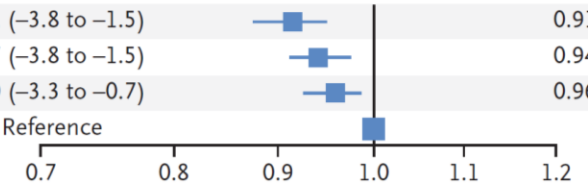


Figure 2. Associations of the Genetic Scores with the Risk of Cardiovascular Events.

N Engl J Med 2019;380:1033-42.

B Combined Effect of *ACLY* and *HMGCR* Scores

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



C Combined Effect of *ACLY* and *NPC1L1* Scores

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

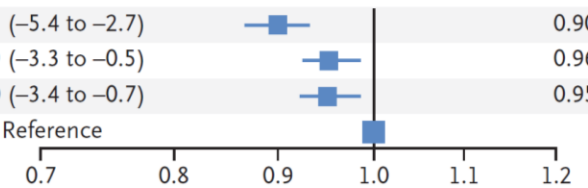


Figure 3. Associations of the *ACLY* Score, Alone and in Combination with the *HMGCR* and *NPC1L1* Scores, with Lipoprotein Levels and the Risk of Major Cardiovascular Events.

N Engl J Med 2019;380:1033-42

Acido Bempedoico

- **Razionale / Premesse**
- **Meccanismo d’azione**
- Farmacologia clinica

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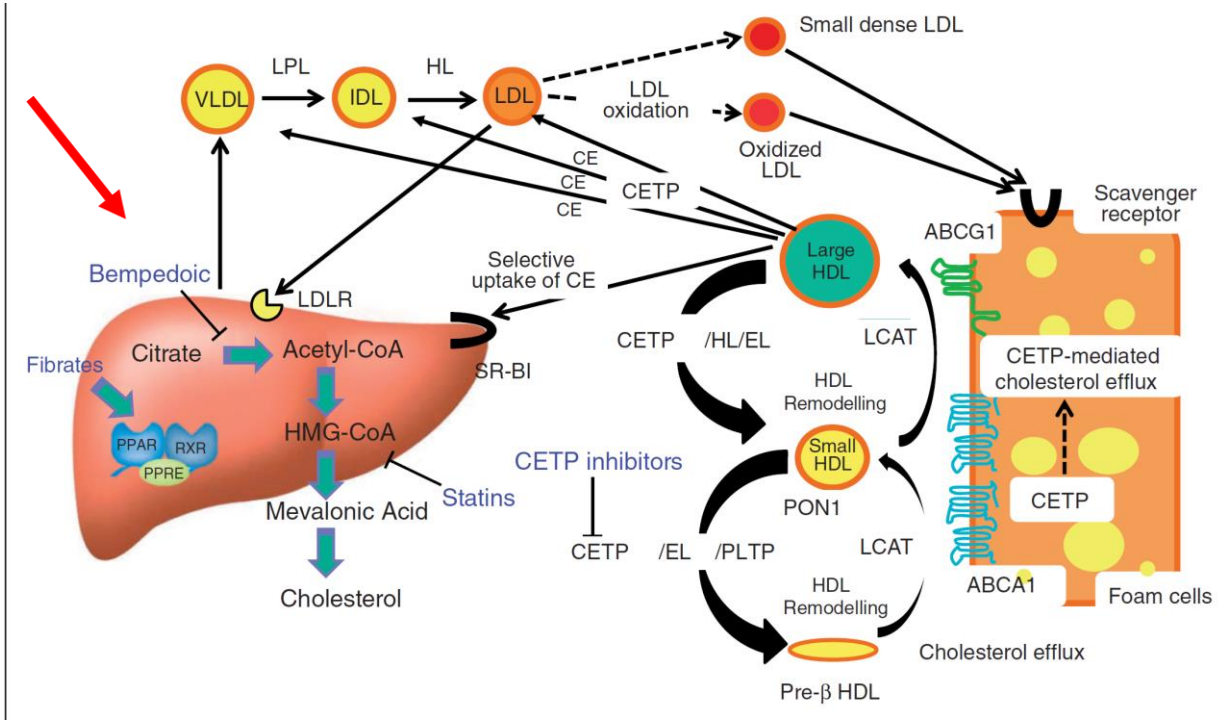
Recent advances in synthetic pharmacotherapies for dyslipidaemias

Cesare R Sirtori[1], Shizuya Yamashita[2,3,4], Maria Francesca Greco[5], Alberto Corsini[5,6], Gerald F Watts[7,8,9] and Massimiliano Ruscica[5]

Mechanisms of action of the proposed synthetic drugs

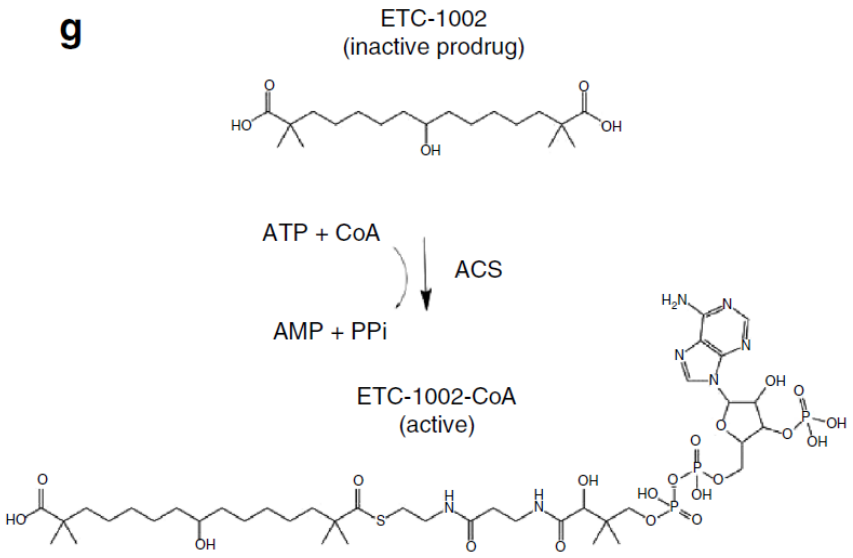


ARTICLE

Received 31 May 2016 | Accepted 6 Oct 2016 | Published 28 Nov 2016

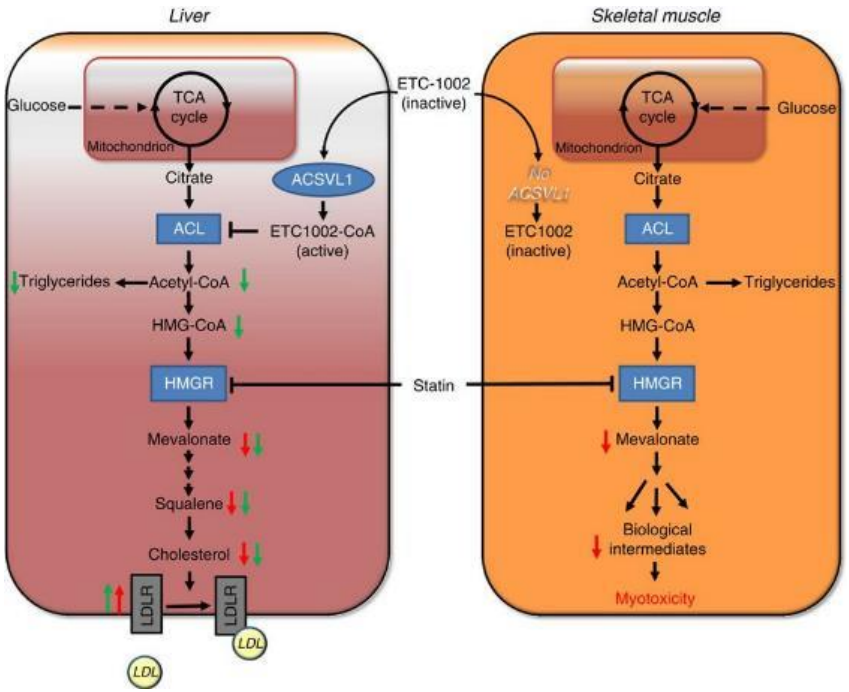
DOI: 10.1038/ncomms13457 OPEN

Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis



- half-life of 15–24 h
- log P of 3.65

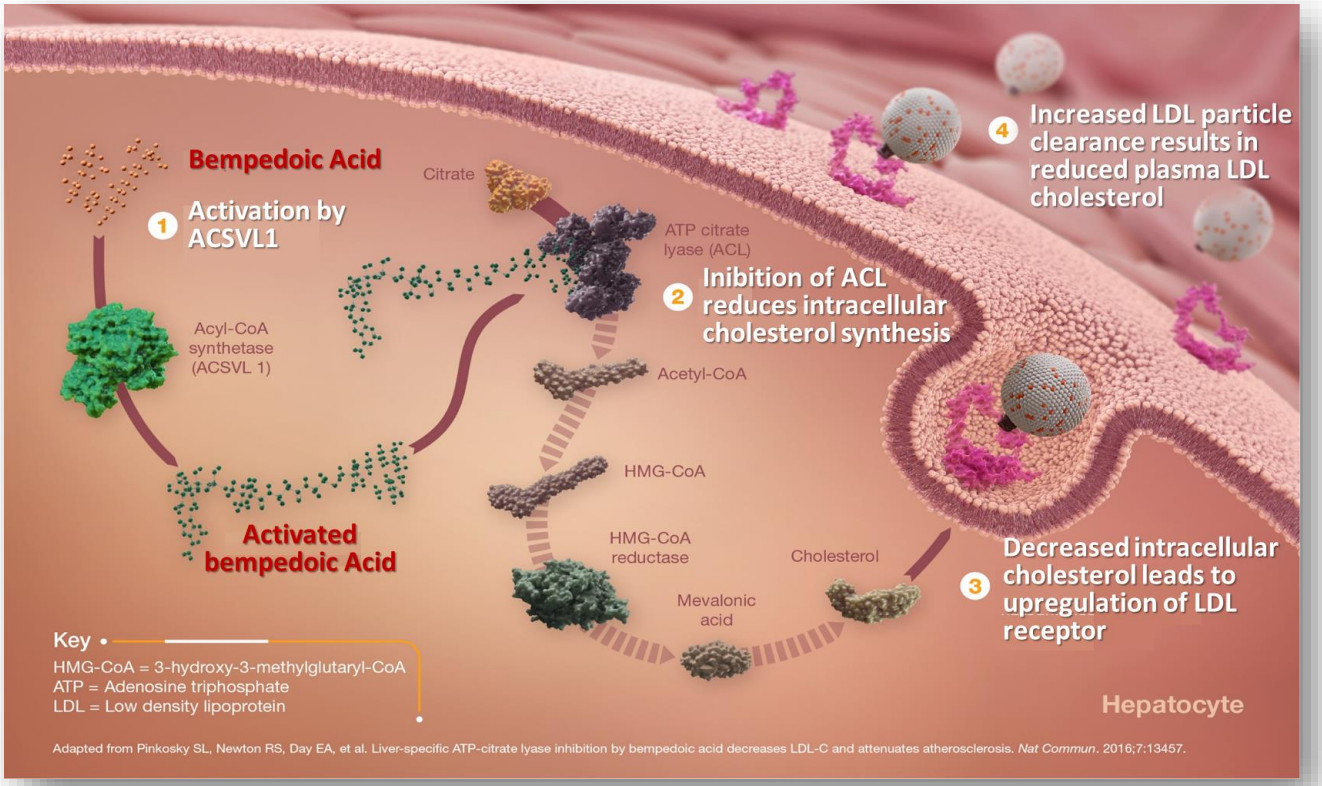
Bempedoic Acid is not Activated in the Skeletal Muscle



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

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

- Activated primarily in the liver, bempedoic acid inhibits the ACL enzyme in the well-known cholesterol synthesis pathway, upstream of the statin target
- Upregulation of the LDL receptor results in an increased uptake and removal of LDL particles by the liver



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

Acido Bempedoico

- **Razionale / Premesse**
- **Meccanismo d’azione**
- **Farmacologia clinica**

Acido bempedoico: meccanismo d'azione

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[1]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi, Milano
[2]Multimedica IRCCS, Milano
[3]U.O.C. Cardiologia-UTIC, Ospedale San Paolo, Bari

Tabella 2. Principali caratteristiche farmacocinetiche dell'acido bempedoico.

Modalità di assunzione	Orale; dose singola (180 mg) giornaliera
Effetto del cibo	Nessuno
Tmax (180 mg)	3.5 h
Volume di distribuzione	18 L
Legame delle proteine plasmatiche	99%
Profarmaco	Si
Metaboliti attivi	Sì. ETC-1002-CoA, ESP15228
Metabolismo	Glucuronidazione UGT2B7
Substrato trasportatori	OATP1B1/3, OAT2, OAT3
Via di eliminazione	Profarmaco: 5% eliminato equamente tra feci e urine Coniugati/metaboliti: 70% rene; 30% fegato
Emivita	15-24 h
Popolazioni speciali	Nessun effetto di età, sesso, etnia sulla farmacocinetica di acido bempedoico
Interazioni farmacologiche	Aumento significativo delle concentrazioni di simvastatina (2 volte) Nessuna inibizione/induzione dei citocromi Acido bempedoico e glucuronide sono deboli inibitori di OATP1B1/3 Acido bempedoico è un debole inibitore di OAT2, OAT3 (aumento acido urico e creatinina)

ATP, adenosin-trifosfato; OAT2/OAT3, organic anion transporter-2/3; OATP1B1/3, organic anion-transporting polypeptide 1B1/3; AUC, area sotto la curva; Tmax, tempo necessario per raggiungere la massima concentrazione plasmatica.

G Ital Cardiol 2021;22(4 Suppl 1):9S-14S

Bempedoic Acid Was Evaluated in a Robust Clinical Development Program in US and Europe

Phase 1

15 studies
bioavailability, PK/PD in different populations, FDI, DDI

Phase 2

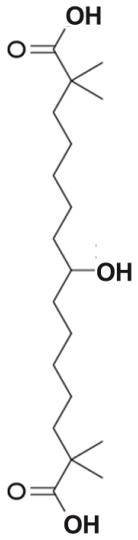
10 studies
1160 patients, most treated for 12 weeks

Phase 3

5 published studies
Efficacy and safety in ~4000 patients

1 completed study
Harmony-OLE: extended safety study, 1462 patients, 1.5 years

1 ongoing study
Cardiovascular Outcomes Trial
14,000 statin intolerant patients with or at high-risk for CVD
Event driven trial → At least 1620 4-component MACE
Estimated median treatment of 3.75 years
Enrolment completed



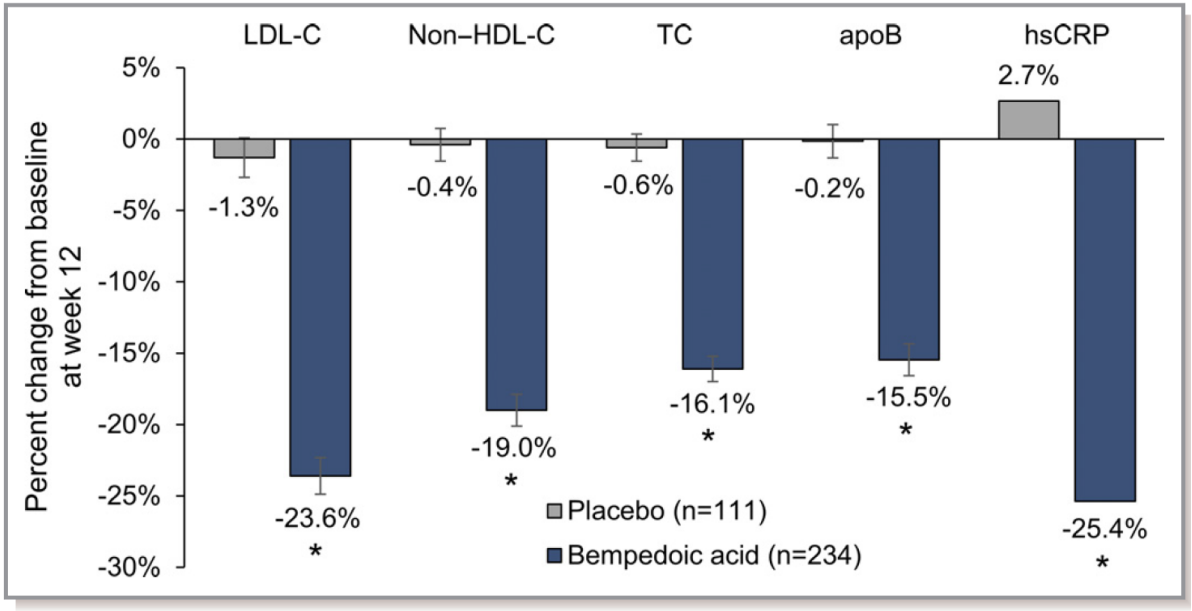


Figure 3. Effect of bempedoic acid in patients with statin intolerance: percent change from baseline to week 12 in lipid parameters and biomarkers. Data for low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (non–HDL-C), total cholesterol (TC), and apolipoprotein B (apoB) are means±standard error. Data are medians for high-sensitivity C-reactive protein (hsCRP). LDL-C, non–HDL-C, TC, and apoB were analyzed using analysis of covariance, with percent change from baseline as the dependent variable, treatment and cardiovascular disease risk category (primary prevention, secondary prevention) as fixed effects, and baseline as a covariate. hsCRP was analyzed using nonparametric Wilcoxon rank sum test. *$P<0.001$ vs placebo.

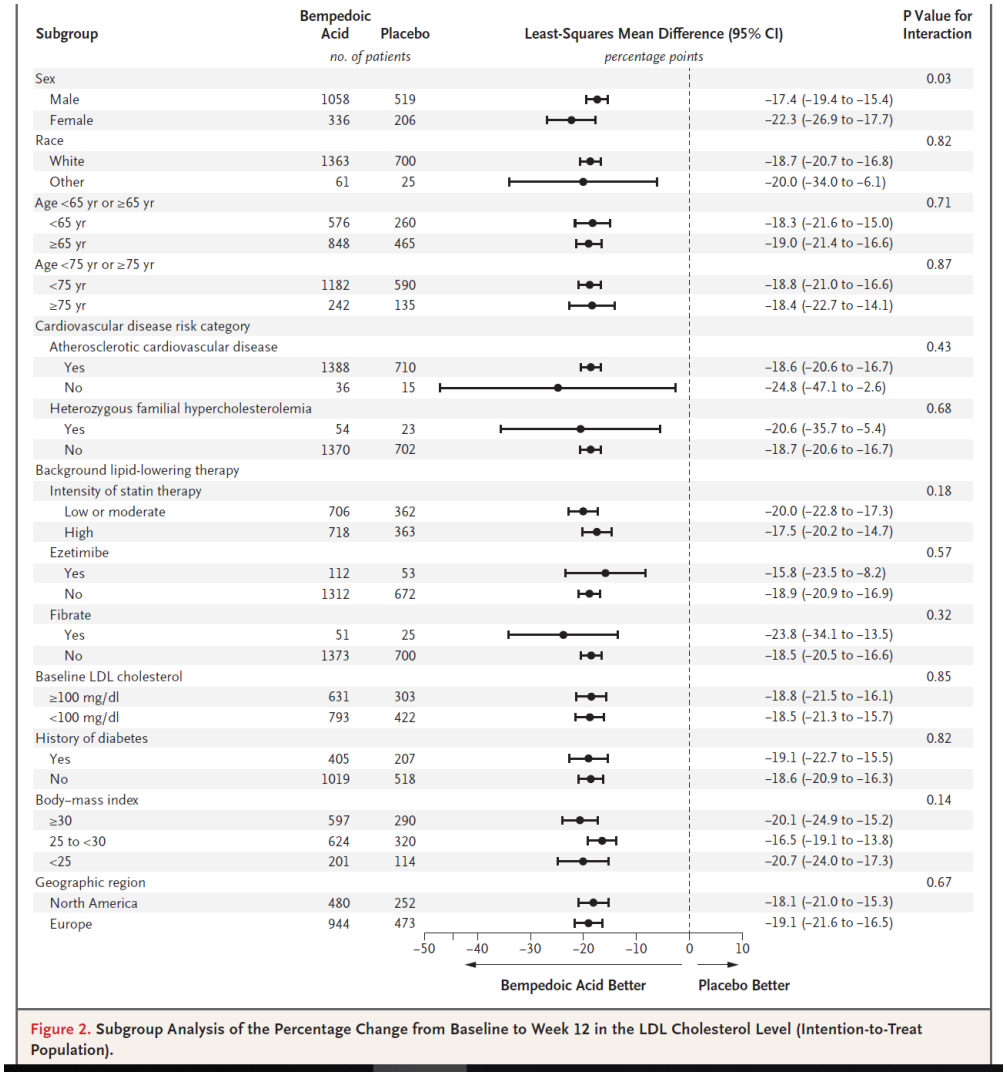
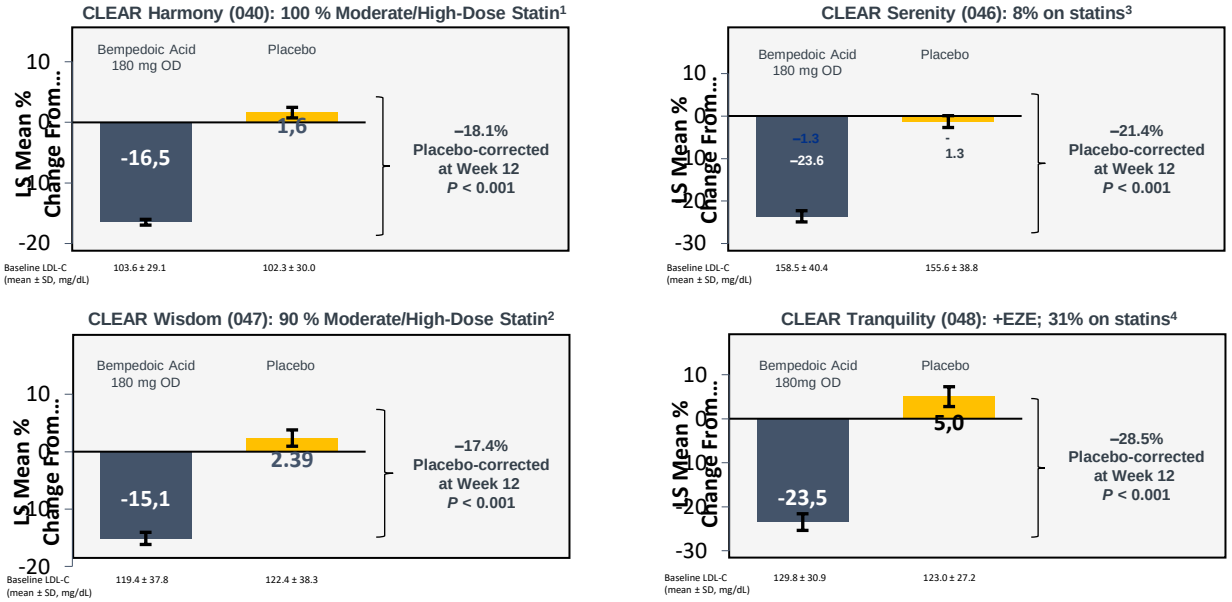


Figure 2. Subgroup Analysis of the Percentage Change from Baseline to Week 12 in the LDL Cholesterol Level (Intention-to-Treat Population).

N Engl J Med 2019;380:1022-32

Phase 3 Efficacy: Consistent LDL-C Lowering



[a]Primary endpoint except for CLEAR Harmony (principal secondary endpoint).
EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; LS = least-squares; MTS = maximally tolerated statin therapy; SD = standard deviation.
1. Ray KK, et al. *N Engl J Med*. 2019;380:1022-32; 2. Goldberg AC et al. JAMA. 2019;322(18):1780-1788. doi:10.1001/jama.2019.16585; 3. Laufs U, et al. *J Am Heart Assoc*. 2019;8:e011662;
4. Ballantyne CM, et al. *Atherosclerosis*. 2018;277:195-203.

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2021) **0**, 1–9
https://doi.org/10.1093/ehjcvp/pvab064
ORIGINAL ARTICLE
Lipids

Pharmacodynamic effect of bempedoic acid and statin combinations: predictions from a dose–response model

Satyawan B. Jadhav[1], Ryan L. Crass[1], Sunny Chapel[1], Michael Kerschnitzki[2], William J. Sasiela[3], Maurice G. Emery[3], Benny M. Amore[3], P. Hugh R. Barrett[4], Gerald F. Watts[5] and Alberico L. Catapano[6,*]

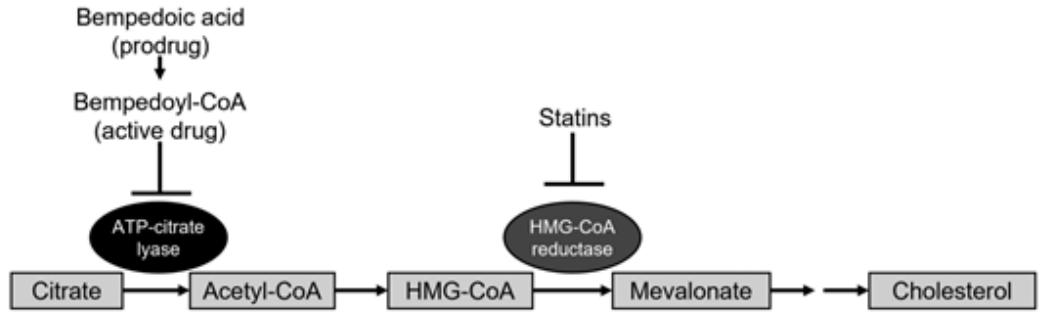
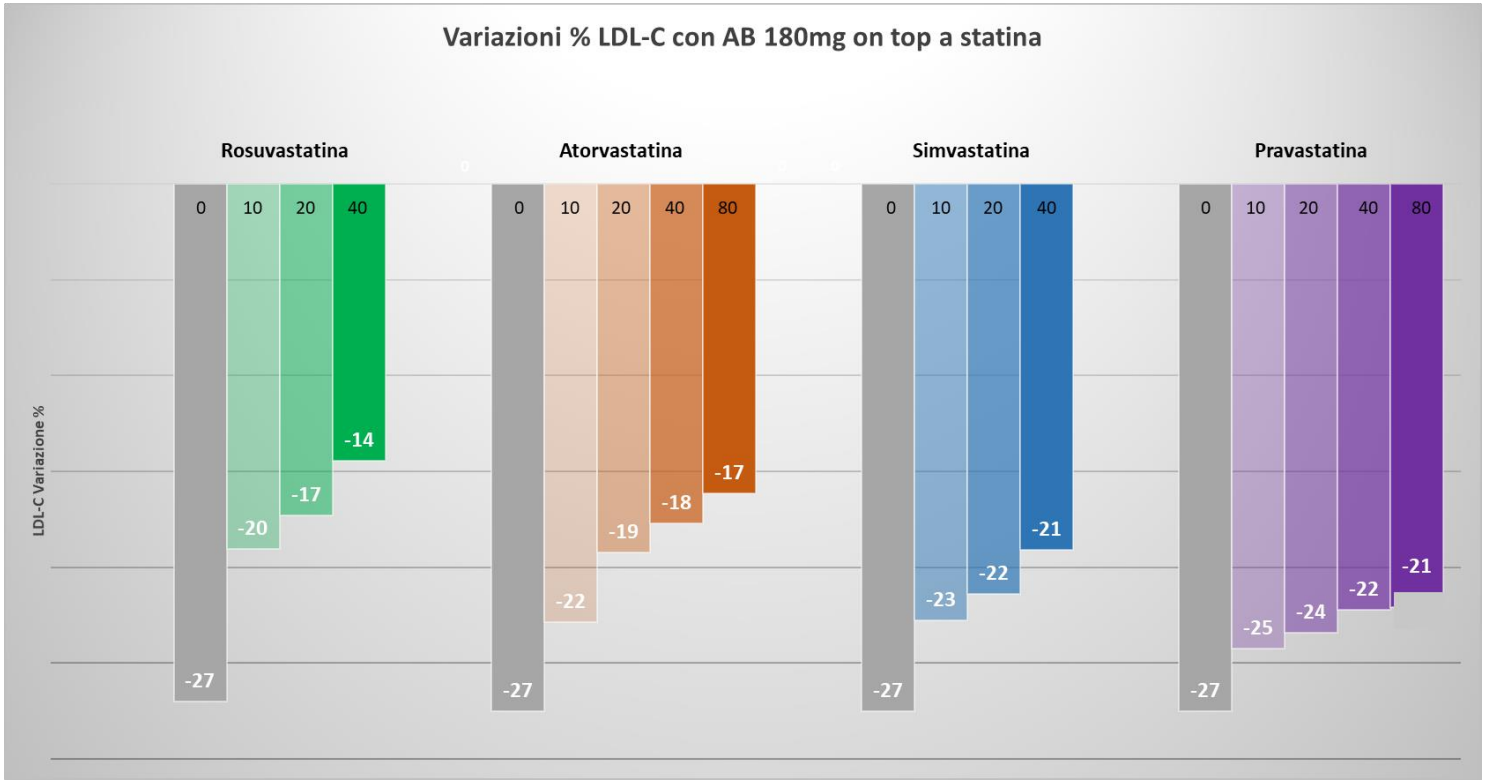


Figure 1 Mechanism of action of bempedoic acid relative to statins. ATP, adenosine triphosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

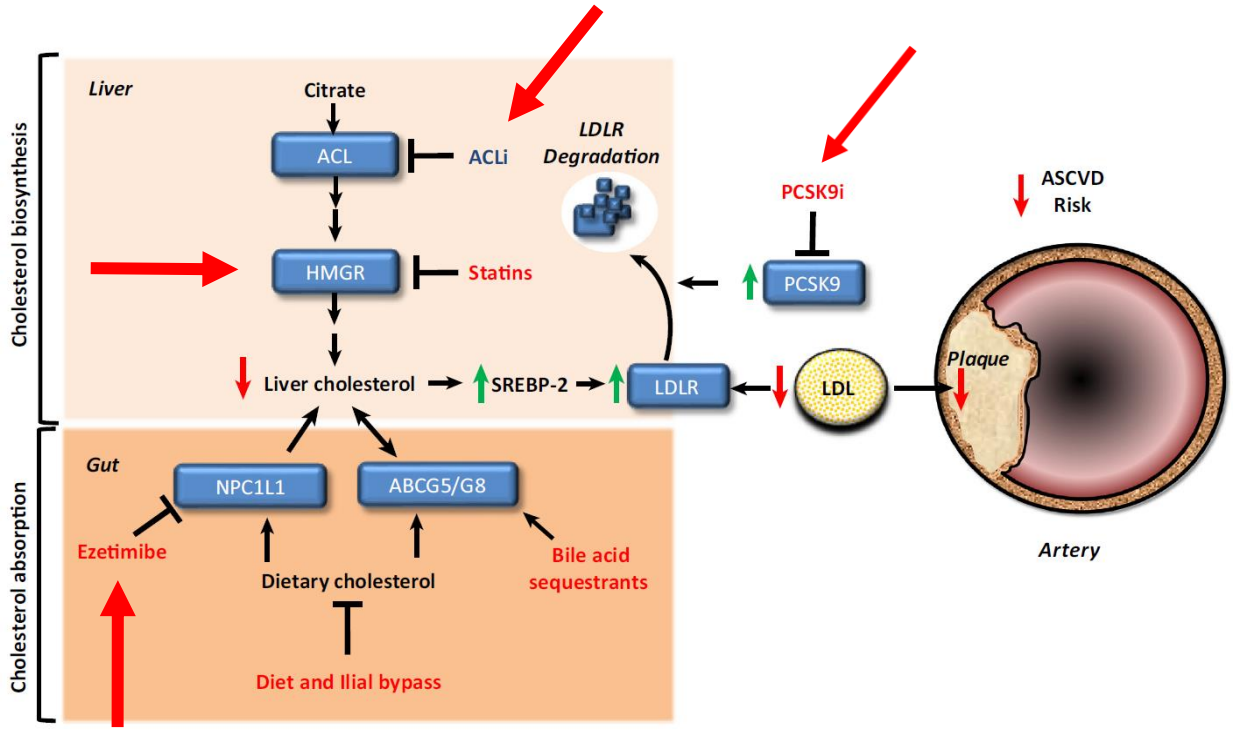
Pharmacodynamic effect of bempedoic acid and statin combinations

Predictions from a dose-response model



Eur Heart J Cardiovasc Pharmacother. 2021 Aug 27;pvab064. doi: 10.1093/ehjcvp/pvab064

ACL Inhibition Can Promote Hepatic LDLR Upregulation and Should Decrease ASCVD Risk



Pinkosky, S.L., et al Trends Mol Med, 2017. **23**(11): p. 1047-1063

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Full research paper

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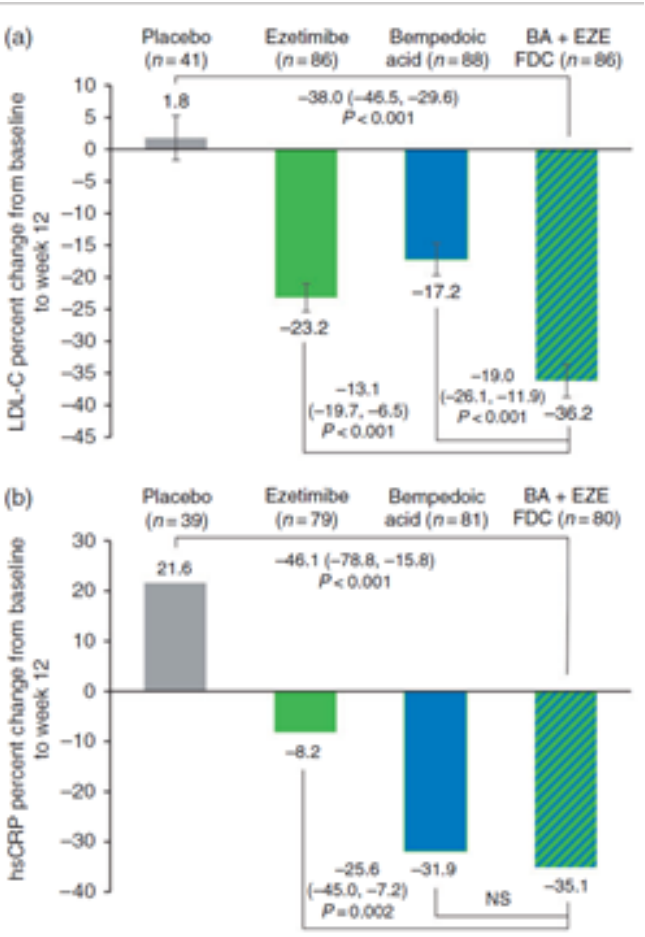
Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy

Christie M Ballantyne[1], Ulrich Laufs[2], Kausik K Ray[3], Lawrence A Leiter[4], Harold E Bays[5], Anne C Goldberg[6], Erik SG Stroes[7], Diane MacDougall[8], Xin Zhao[8] and Alberico L Catapano[9]



ARTICLE IN PRESS

Atherosclerosis xxx (xxxx) xxx

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Atherosclerosis

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Combination of bempedoic acid, ezetimibe, and atorvastatin in patients with hypercholesterolemia: A randomized clinical trial

John Rubino[a], Diane E. MacDougall[b], Lulu R. Sterling[b,1], Jeffrey C. Hanselman[b], Stephen J. Nicholls[c,*]

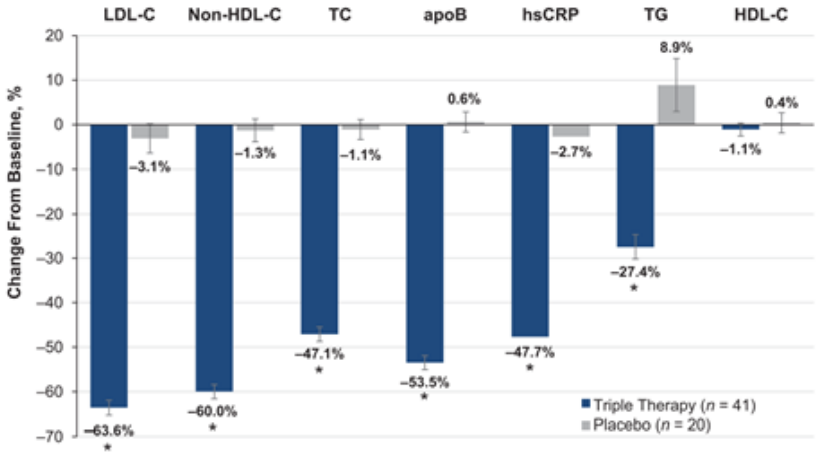


Fig. 2. Change from baseline in primary and secondary endpoints at week 6, modified intention-to-treat population.
Data for low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (apoB), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) are least-squares means ± standard errors. Data for high-sensitivity C-reactive protein (hsCRP) are medians. *$p < 0.001$ for the comparison of triple therapy *vs.* placebo.

Rubino J et al Atherosclerosis. 2021 Mar;320:122-128

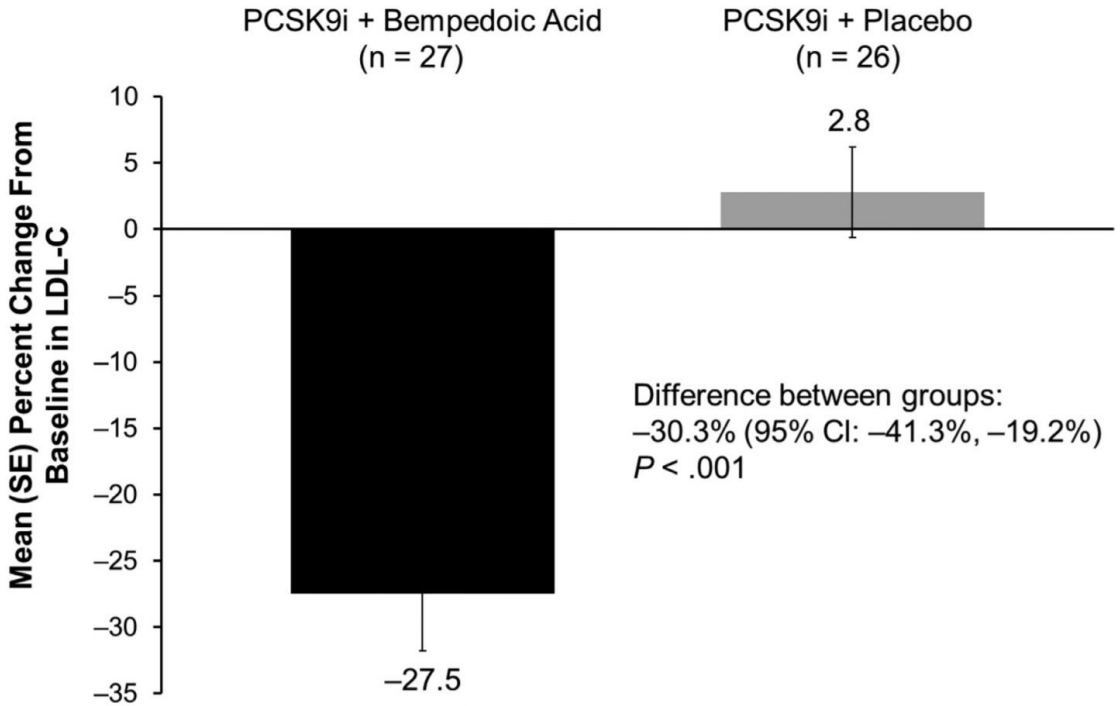


Fig. 2 Percent change from baseline in LDL-C at month 2, mITT population. LDL-C, low-density lipoprotein cholesterol; mITT, modified intent to treat; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; Data are least squares means ± SE.

Please cite this article as: Rubino et al, Lipid lowering with bempedoic acid added to a proprotein convertase subtilisin/kexin type 9 inhibitor therapy: A randomized, controlled trial, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.05.002

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

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

AE – adverse event; LLTs = lipid lowering therapies.

Adverse events of special interest

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

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

Effetti dell'acido bempedoico su altri medicinali

Statine

Le interazioni farmacocinetiche tra acido bempedoico 180 mg e simvastatina 40 mg, atorvastatina 80 mg, pravastatina 80 mg e rosuvastatina 40 mg sono state valutate in studi clinici. La somministrazione di una singola dose di simvastatina 40 mg con acido bempedoico 180 mg allo stato stazionario ha portato a un aumento di 2 volte dell'esposizione all'acido simvastatinico. Innalzamenti da 1,4 a 1,5 volte dell'AUC di atorvastatina, pravastatina e rosuvastatina (somministrate in dosi singole) e/o dei loro metaboliti principali sono stati osservati se le statine sono somministrate in concomitanza con acido bempedoico 180 mg. Sono stati osservati innalzamenti superiori quando queste statine sono state somministrate in concomitanza con una dose di acido bempedoico superiore a quella terapeutica da 240 mg (vedere paragrafo 4.4).

Terapia concomitante con simvastatina

Qualora Nilemdo sia co-somministrato con simvastatina, la dose di simvastatina non deve essere superiore a 20 mg al giorno (o 40 mg al giorno per i pazienti affetti da ipercolesterolemia severa e ad alto rischio di complicanze cardiovascolari, che non hanno raggiunto gli obiettivi di trattamento a dosi più basse e quando si prevede che i benefici siano superiori ai rischi potenziali) (vedere paragrafi 4.4 e 4.5).

RCP

Eliminazione

Acido bempedoico
La clearance allo stato stazionario (CL/F) dell'acido bempedoico determinata da un'analisi farmacocinetica di popolazione in pazienti affetti da ipercolesterolemia era di 12,1 mL/min dopo un dosaggio giornaliero; la clearance renale dell'acido bempedoico immodificato rappresentava meno del 2% della clearance totale. L'emivita media per l'acido bempedoico nell'uomo era di 19 (10) ore allo stato stazionario.

In seguito alla somministrazione orale singola di 240 mg di acido bempedoico (1,3 volte la dose raccomandata approvata), il 62,1% della dose totale (acido bempedoico e i suoi metaboliti) è stato recuperato nelle urine, principalmente sotto forma di coniugato acil glucuronide dell'acido bempedoico, e il 25,4% è stato recuperato nelle feci. Meno del 5% della dose somministrata è stato escreto sotto forma di acido bempedoico immodificato, nelle feci e nelle urine combinate.

RCP

Pazienti con compromissione renale

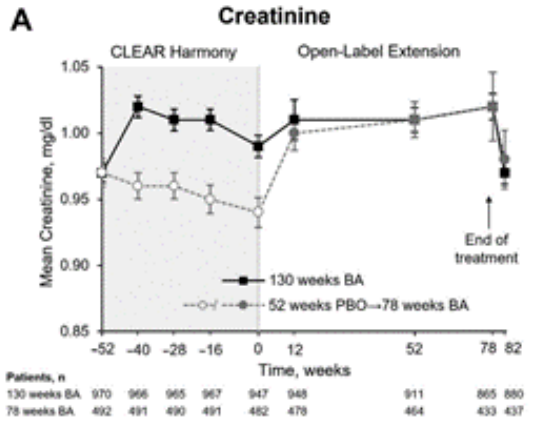
Non è necessario alcun aggiustamento della dose nei pazienti con compromissione renale da lieve a moderata. I dati disponibili sono limitati nei pazienti con grave compromissione renale [definita come velocità di filtrazione glomerulare stimata (eGFR) < 30 mL/min/1,73 m^2]; inoltre, i pazienti con malattia renale allo stadio terminale in dialisi non sono stati studiati. In questi pazienti può essere opportuno un monitoraggio addizionale delle reazioni avverse quando viene somministrato Nilemdo (vedere paragrafo 4.4).

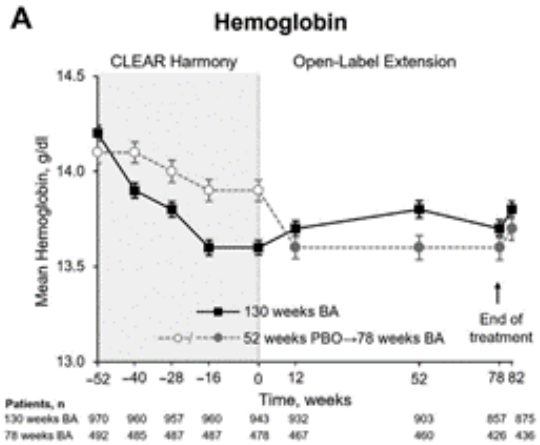
Pazienti con compromissione epatica

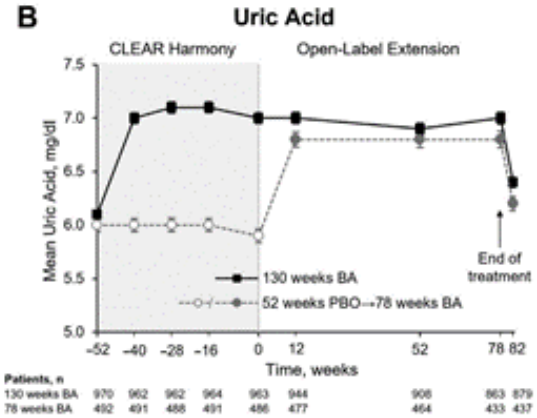
Non è necessario alcun aggiustamento della dose nei pazienti con compromissione epatica lieve o moderata (Child-Pugh A o B). Non sono disponibili dati relativi ai pazienti con compromissione epatica severa (Child-Pugh C). Per i pazienti con compromissione epatica severa si devono considerare prove di funzionalità epatica periodiche (vedere paragrafo 4.4).

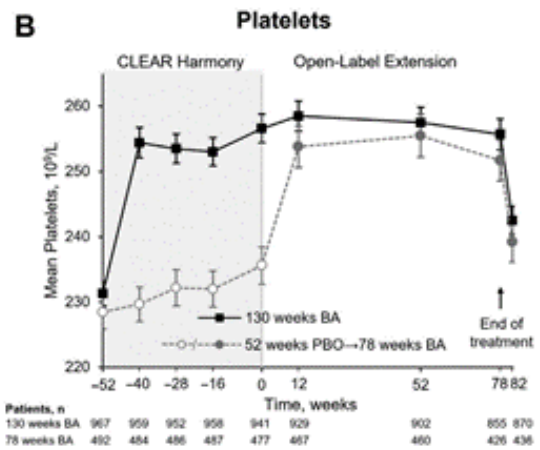
Long-Term Safety and Efficacy of Bempedoic Acid in Patients With Atherosclerotic Cardiovascular Disease and/or Heterozygous Familial Hypercholesterolemia (from the CLEAR Harmony Open-Label Extension Study)

Christie M. Ballantyne, MD[a,*], Maciej Banach, MD, PhD[b,c], Harold E. Bays, MD[d], Alberico L. Catapano, PhD, MD(hc)[e,f], Ulrich Laufs, MD[g], Erik S.G. Stroes, MD, PhD[h], Paula Robinson, MS[i], Lei Lei, PhD[i], and Kausik K. Ray, MD, MPhil[j]









(Am J Cardiol 2022;00:1−11)

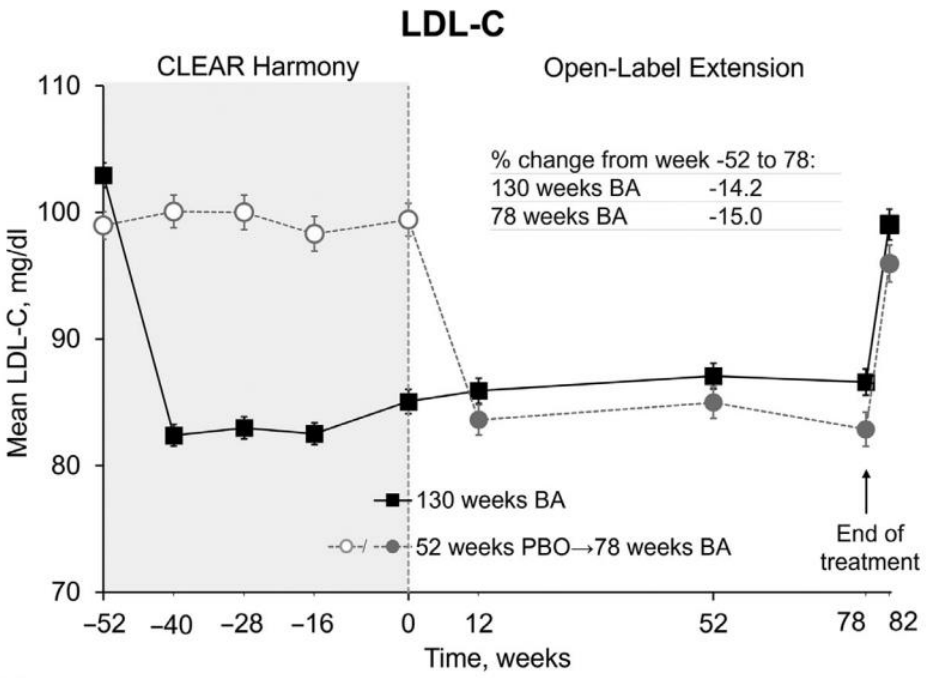
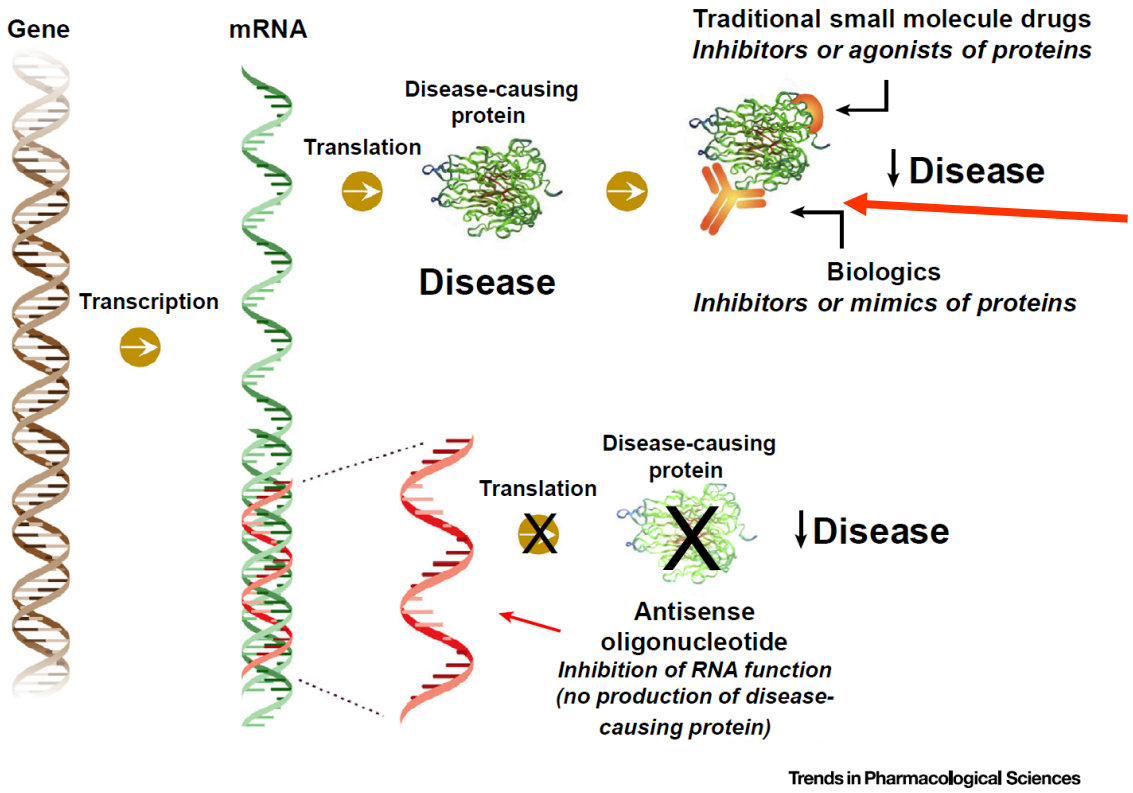


Figure 4. Observed levels of LDL-C over the course of the CLEAR Harmony parent study and the OLE study. Data presented for patients enrolled in the OLE study; not all patients received 130 or 78 weeks of treatment. Dashed line indicates baseline of the OLE study. Error bars represent standard error. Open circles indicate placebo treatment; filled circles indicate bempedoic acid treatment. BA = bempedoic acid; PBO = placebo.

- **acido bempedoico**
- **alirocumab, evolocumab**
- inclisiran
- Pemafibrato
- volanesorsen

Therapeutic Approaches for Managing Dyslipidemia



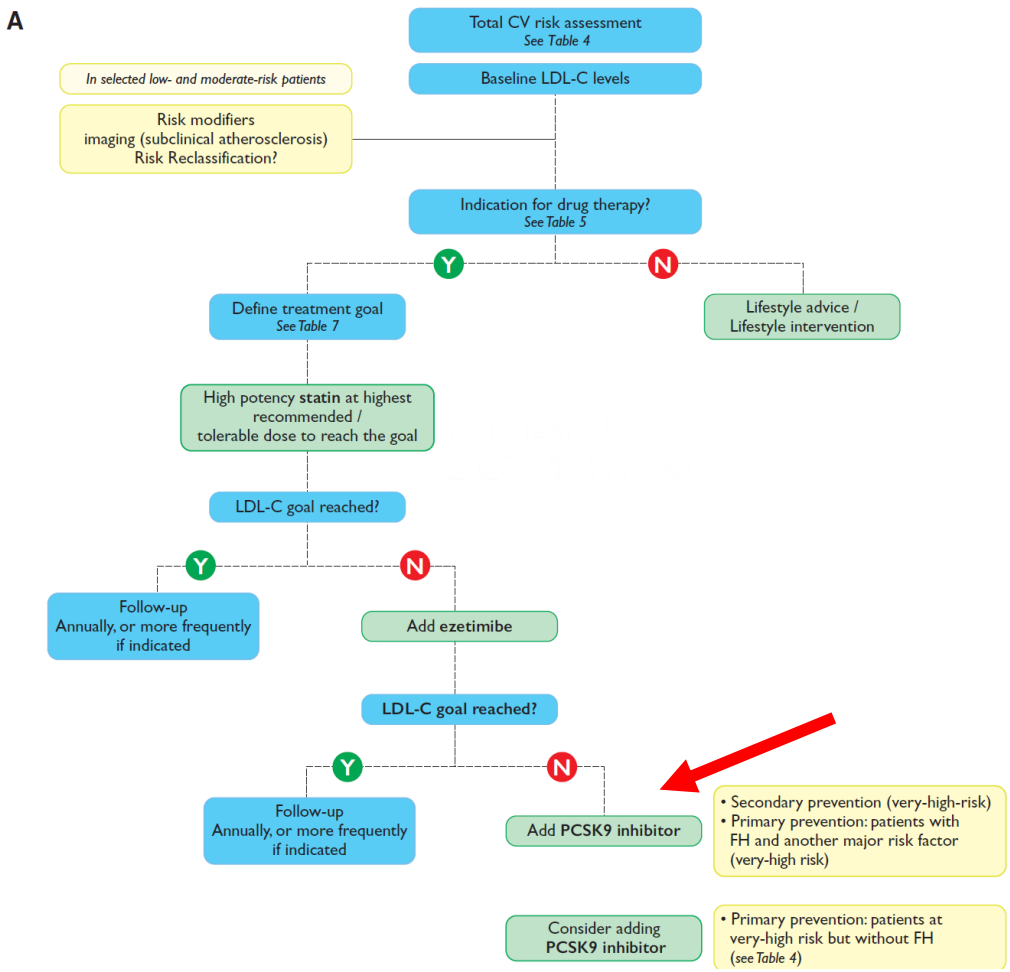
Sathiyakumar V et al Trends Pharmacol Sci. 2018 Aug;39(8):733-747

Pharmacological effects of lipid-modification therapies

	Effect on LDL cholesterol	Effect on triglycerides and cholesterol remnants	Effect on lipoprotein(a)	Cardiovascular benefit	Ongoing studies
Antisense and mAbs to ANGPTL3	Moderate decrease	Strong decrease	Neutral	No	NCT02709850 (phase 2), phase 3 trials*
Antisense, mAbs, and siRNA to apolipoprotein C3	Neutral	Strong decrease	Neutral	No	NCT03385239 (phase 2), NCT03783377 (phase 1)
Antisense to apolipoprotein(a)	Neutral	Neutral	Strong decrease	No	NCT03070782 (phase 2)
Bempedoic acid	Moderate decrease	Neutral	Neutral	No	NCT02993406 (phase 3 CVOT)
Bile acid sequestrants	Moderate decrease	Mild decrease	Neutral	No†	No
CETP inhibitors	Moderate decrease	Neutral	Mild decrease	Yes‡	No
Ezetimibe	Moderate decrease	Neutral	Minimal increase	Yes	No
Fibrates: SPPARMs	Neutral	Moderate decrease	Neutral	No†§	NCT03071692 (phase 3 CVOT)
Fish oils: EPA	Neutral	Moderate decrease	Neutral	Yes	No
Fish oils: EPA and DHA	Neutral	Moderate decrease	Neutral	No	NCT02104817 (phase 3 CVOT)
Inclisiran	Strong decrease	Mild decrease	Mild decrease	No	NCT03814187 (phase 3 CVOT)
Lomitapide	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Anti-PCSK9 mAbs	Strong decrease	Mild decrease	Mild decrease	Yes	No
Mipomersen	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Nicotinic acid	Mild decrease	Mild decrease	Mild decrease	No‖	No
Statins	Strong decrease	Mild decrease	Minimal increase	Yes	No

Ray KK et al Lancet 2019; 394: 697–708

Treatment algorithm for pharmacological LDL-C lowering

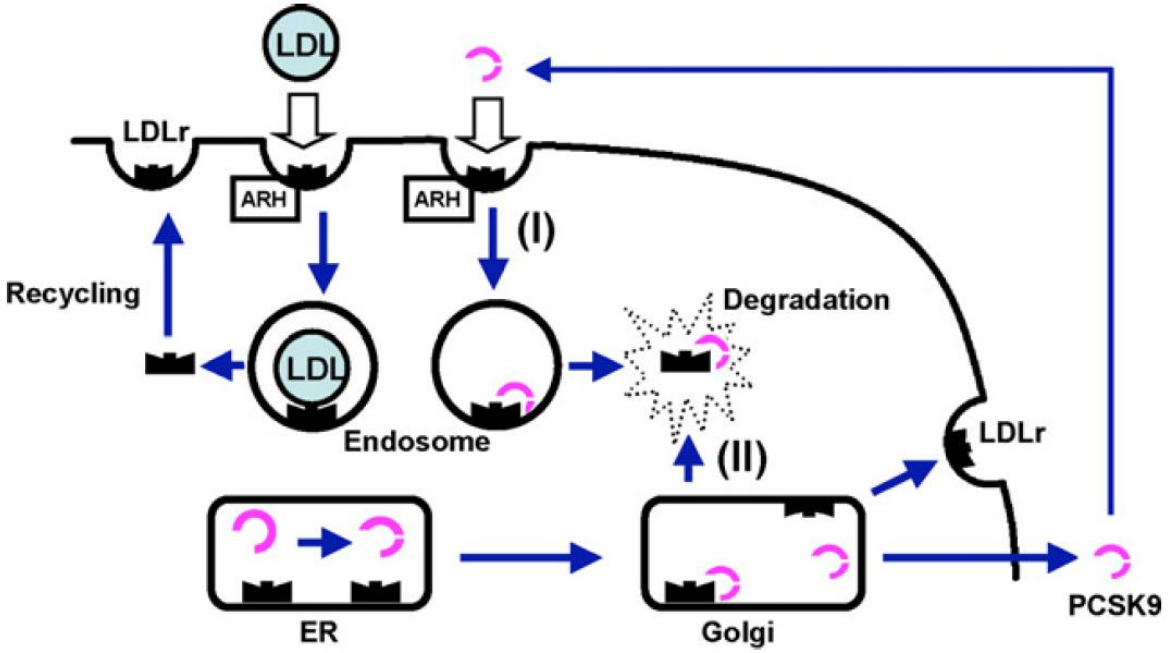


Eur Heart J.
2020 41: 111-188

Perche' un anticorpo monoclonale?

Perche' PCSK9 come bersaglio farmacologico?

Regolazione dell'espressione di LDLR per opera di PCSK9



Lambert G. et *al*, Atherosclerosis 203 (2009) 1–7

Vascular Pharmacology xxx (2014) xxx–xxx

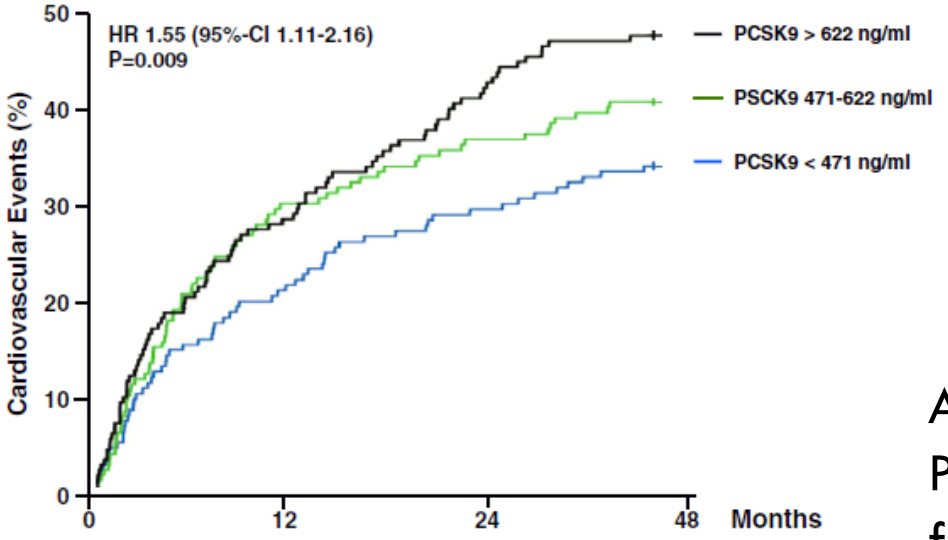
Contents lists available at ScienceDirect

Vascular Pharmacology

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

Risk prediction with proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients with stable coronary disease on statin treatment

Christian Werner [a], Michael M. Hoffmann [b], Karl Winkler [b], Michael Böhm [a], Ulrich Laufs [a,*]



Association of PCSK9 with event-free survival

Atherosclerosis 248 (2016) 117–122

Contents lists available at ScienceDirect

Atherosclerosis

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

PCSK9 in relation to coronary plaque inflammation: Results of the ATHEROREMO-IVUS study

Jin M. Cheng [1], Rohit M. Oemrawsingh [1], Hector M. Garcia-Garcia, Eric Boersma, Robert-Jan van Geuns, Patrick W. Serruys, Isabella Kardys, K. Martijn Akkerhuis*

Erasmus MC, Department of Cardiology, Rotterdam, The Netherlands

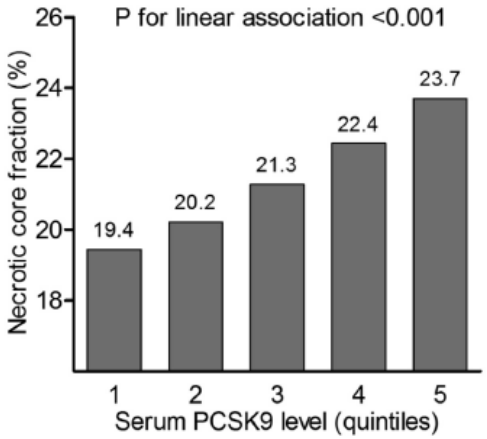
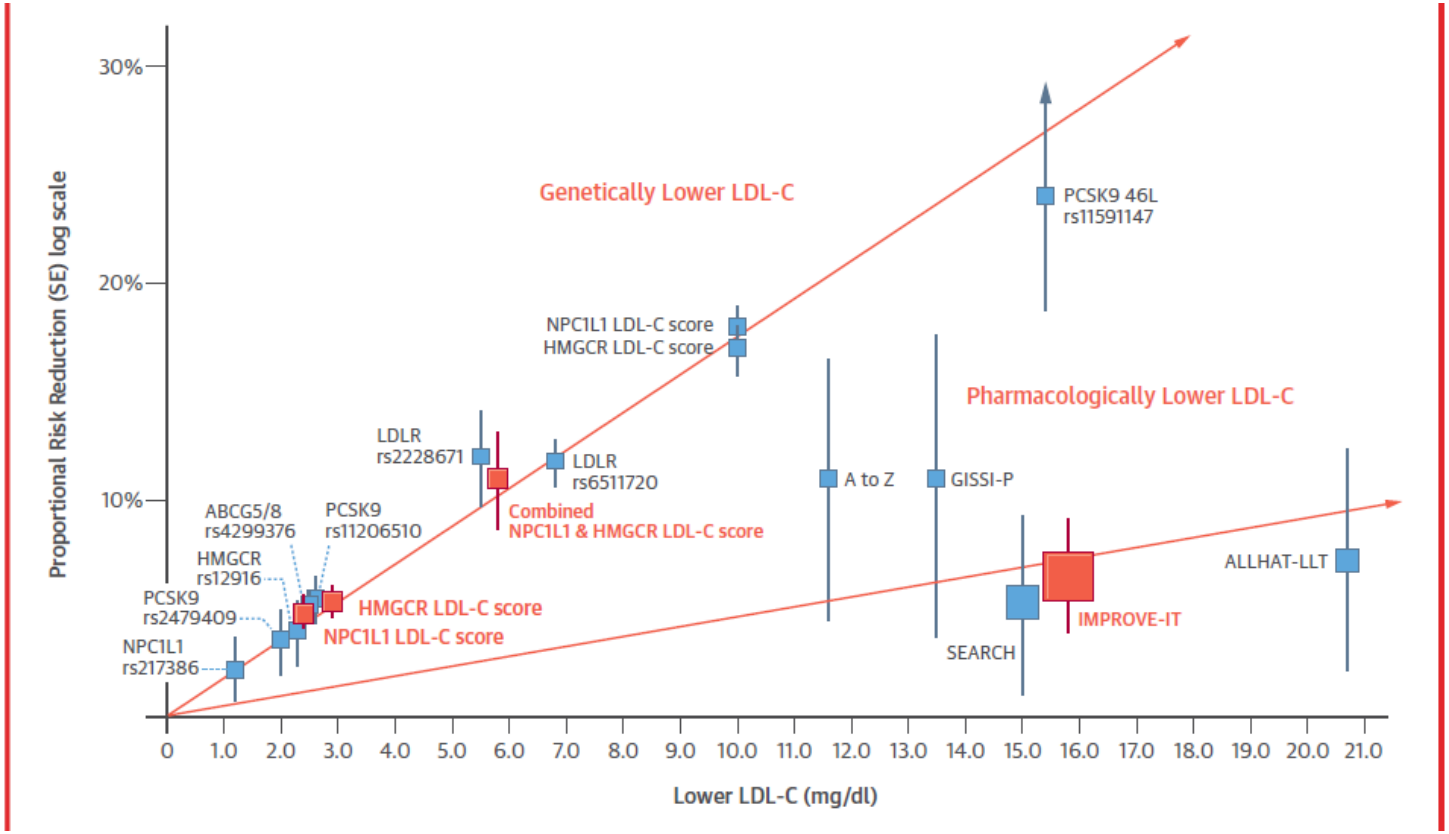


Fig. 2. Association between serum PCSK9 level and fraction of coronary plaque that consists of necrotic core tissue. PCSK9, proprotein convertase substilisin/kexin type 9.

Linear Association Between Genetically and Pharmacologically Mediated Lower LDL and Risk of Coronary Heart Disease

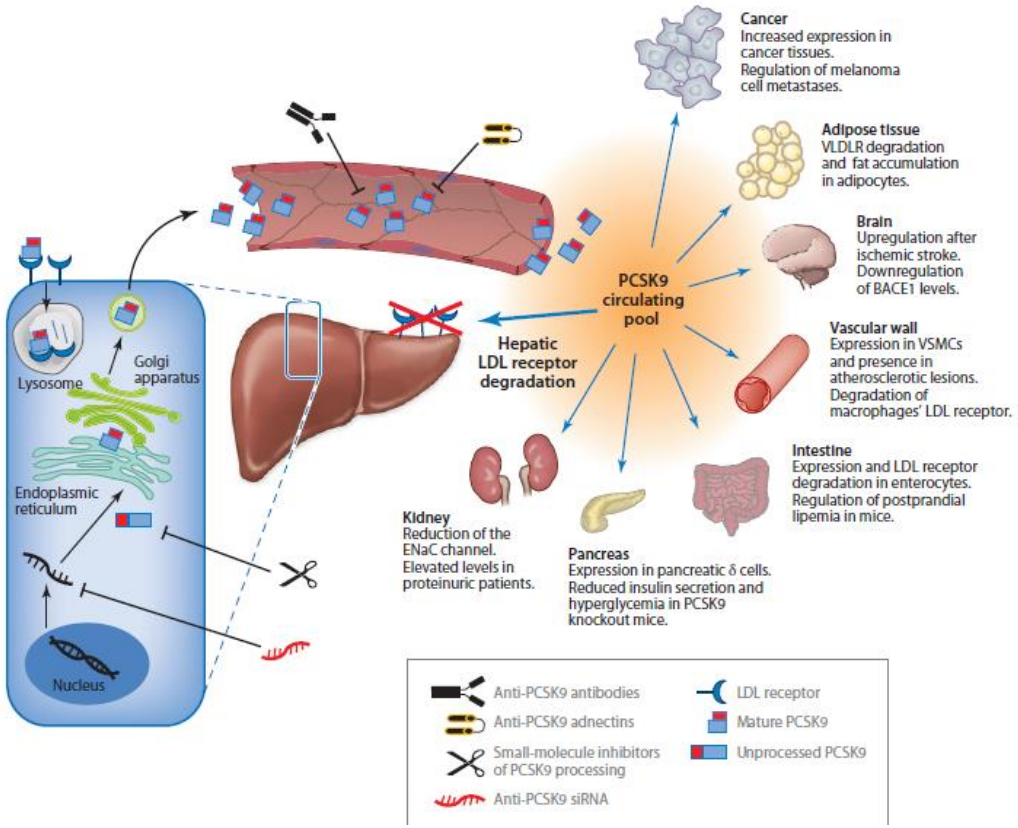


Ference BA et al. J Am Coll Cardiol 2015

Perche' un anticorpo monoclonale?

Perche' PCSK9 come bersaglio farmacologico?

PCSK9: ruolo fisiologico e modulazione farmacologioca



Anti-PCSK9 Therapeutic Approaches

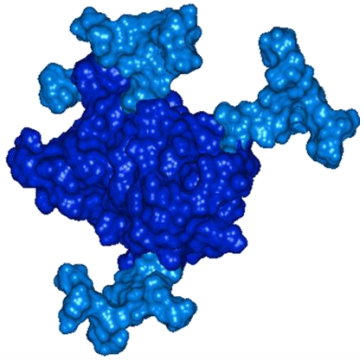
Mechanism of Action	Class	Agent	Company	Phase
PCSK9 binding				
	Human monoclonal antibody	Alirocumab (REGN727/SAR236553)	Regeneron/Sanofi	Approved in USA and EU
	Human monoclonal antibody	Evolocumab (AMG145)	Amgen	Approved in USA and EU
	Humanized monoclonal antibody	Bococizumab (PF-04950615)	Pfizer	3
	Human monoclonal antibody	LY3015014	Eli Lilly	2
	Modified binding protein	Adnectin (BMS962476)	BMS/Adnexus	1
	Small-molecule inhibitor	SX-PCK9	Serometrix	Preclinical
PCSK9 synthesis				
	RNA interference	ALN-PCSsc	Alnylam/The Medicines Company	1

PCSK9, proprotein convertase subtilisin/kexin type 9.

Ito MK et al J Clin Pharmacol. 2016

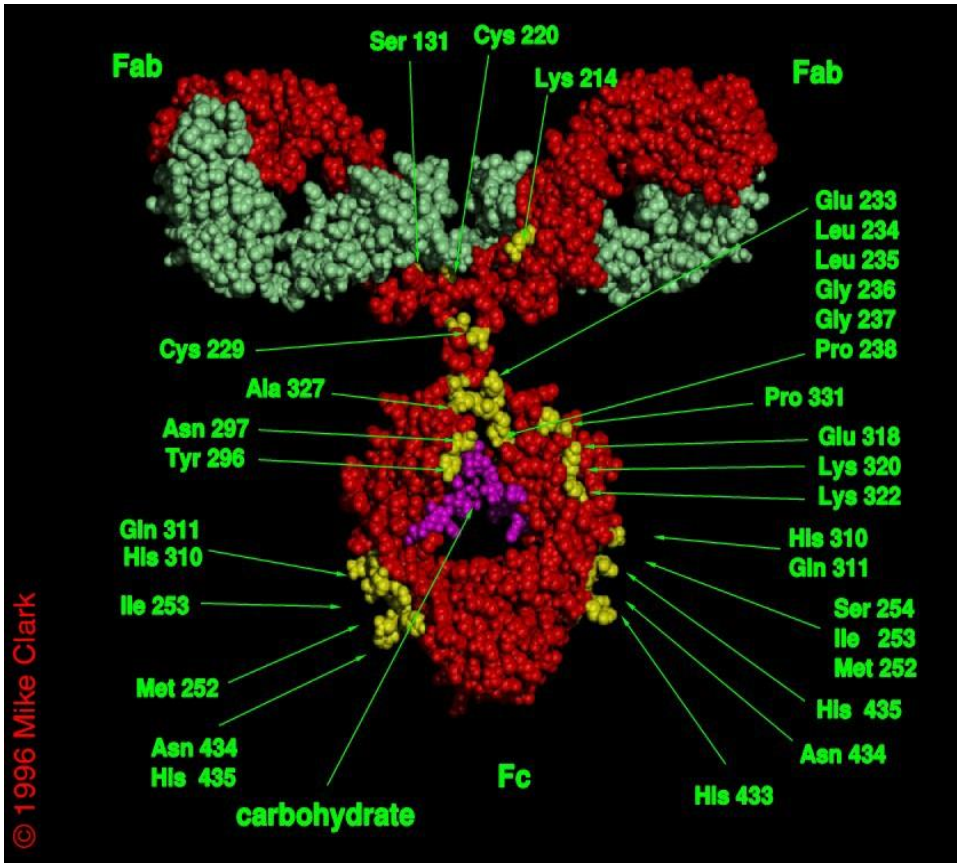
Proteine
Molecular Size and 3-D Structure and Complexity

Aspirin



Erythropoietin

Antibody (IgG) molecule

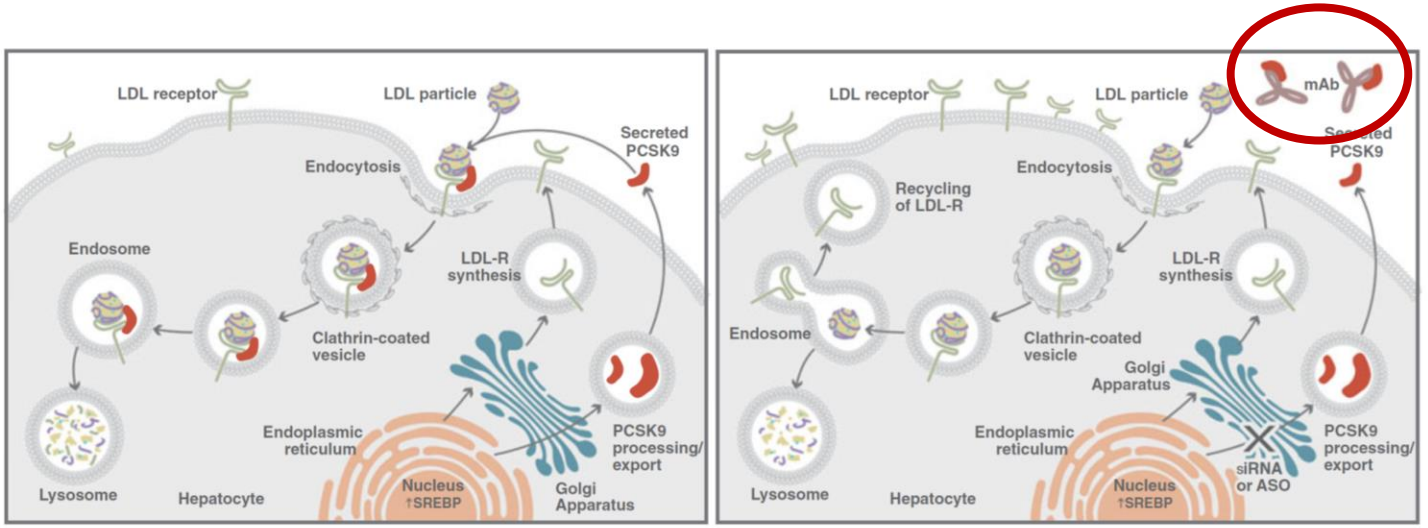


Alirocumab is a human IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology.

Repatha is a human IgG2 monoclonal antibody produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells.

Bococizumab (RN316/PF-04950615) is a humanized IgG2 monoclonal antibody (mAb)

Interaction of PCSK9 and the LDL receptor

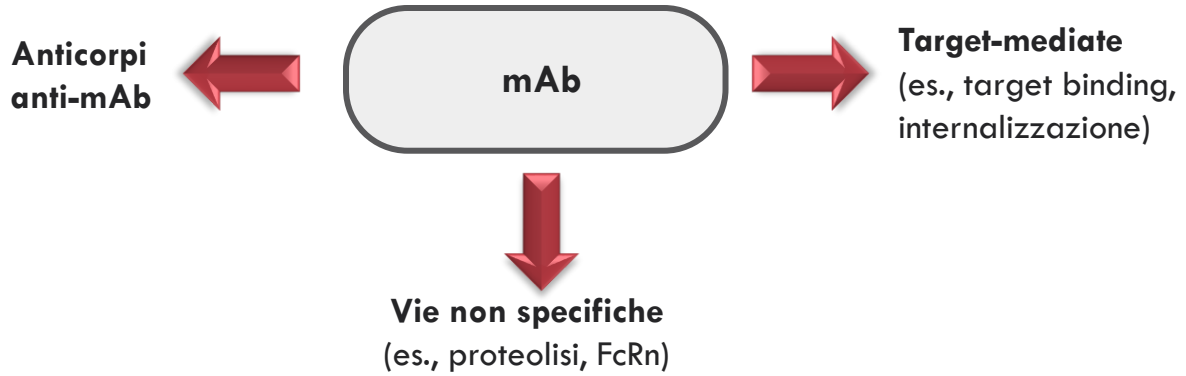


Stein EA and Swergold GD Curr Atheroscler Rep (2013) 15:310

Evolocumab : Pharmacokinetic properties

- Linear / Non linear pharmacokinetics (by RES and hepatocytes)
- Bioavailability 72%
- Tmax 2-7 days
- Vss 3.3 Lt
- T1/2 consistent with other IgG2 Mab (11-17 days)
- In patients with heterozygous familial hypercholesterolemia (HeFH) on high dose statin, the systemic exposure of evolocumab was slightly lower than in subjects on low-to-moderate dose statin (the ratio of AUC_{last} 0.74. An approximately 20% increase in the clearance is mediated by statins increasing the concentration of PCSK9

Vie di eliminazione degli anticorpi monoclonali



- Riduzione e/o stabilizzazione del tumore a seguito della terapia

→ Riduzione espressione antigene → Riduzione clearance

Zhou Z and Mascelli A Annu. Rev. Pharmacol. Toxicol. 2011. 51:359–72

Eliminazione degli anticorpi Monoclonali

- Differente affinità della frazione C dell'anticorpo monoclonale al recettore neonatale (FcRn)

→ l'emivita aumenta a seconda che siano murini (2-3 giorni), chimerici (8-10 giorni) o umanizzati (20-23 giorni)

- L'effetto dell'età, del genere, della funzionalità renale ed epatica sulla farmacocinetica degli anticorpi monoclonali è controversa
  Le differenze tra pazienti, in termini farmacocinetici, sono generalmente modeste
- Auto-antibodies (e.g. rheumatoid factors)

→ esposizione al farmaco consistente nelle diverse tipologie di pazienti

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Population pharmacokinetic analysis of integrated data from the Repatha clinical trials did not reveal a difference in pharmacokinetics of evolocumab in patients with mild or moderate renal impairment relative to non-renally impaired patients. Repatha has not been studied in patients with severe renal impairment (see section 4.4).

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). Single 140 mg subcutaneous doses of Repatha were studied in 8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and 8 healthy subjects. The exposure to evolocumab was found to be approximately 40-50% lower compared to healthy subjects. However, baseline PCSK9 levels and the degree and time course of PCSK9 neutralisation were found to be similar between patients with mild or moderate hepatic impairment and healthy volunteers. This resulted in similar time course and extent of absolute LDL-C lowering. Repatha has not been studied in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.4).

Body Weight

Body weight was a significant covariate in population PK analysis impacting evolocumab trough concentrations, however there was no impact on LDL-C reduction. Following repeat subcutaneous administration of 140 mg every 2 weeks, the 12 week trough concentrations were 147% higher and 70% lower in patients of 69 kg and 93 kg respectively, than that of the typical 81 kg subject. Less impact from body weight was seen with repeated subcutaneous evolocumab 420 mg monthly doses.

Other special populations

Population pharmacokinetic analyses suggest that no dose adjustments are necessary for age, race or gender. The pharmacokinetics of evolocumab were influenced by body weight without having any notable effect on LDL-C lowering. Therefore, no dose adjustments are necessary based on body weight.

Original Manuscript

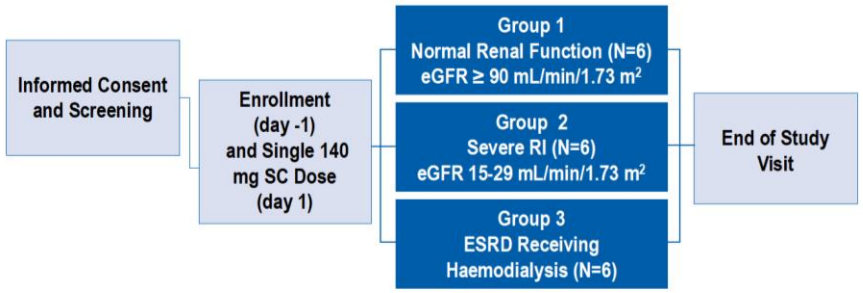
Influence of Renal Function on Evolocumab Exposure, Pharmacodynamics, and Safety

Clinical Pharmacology in Drug Development
2019, 00(0) 1–9
© 2019 The Authors. *Clinical Pharmacology in Drug Development* Published by Wiley Periodicals, Inc. on behalf of The American College of Clinical Pharmacology
DOI: 10.1002/cpdd.650

Edward Lee[1], John P. Gibbs[1,*], Maurice G. Emery[1,*], Geoffrey Block[2], Scott M. Wasserman[1], Lisa Hamilton[3,*], Sreeneeranj Kasichayanula[1,*], Patrick Hanafin[1,*], Ransi Somaratne[1,*], and Ogo Egbuna[1,*]

Figure 1. Study Design and Treatment Schema

Screening	Treatment Phase			End of Study
day -28 to day -2	day -1	day 1	day 2 through day 50	day 57



The Modification of Diet in Renal Disease (MDRD) study equation was used to estimate GFR. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RI, renal impairment; SC, subcutaneous

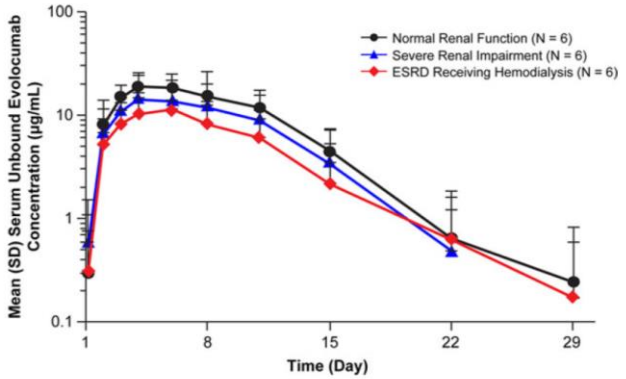


Figure 1. Mean ± standard deviation serum unbound evolocumab concentration-time profiles from normal renal function, severe renal impairment, or ESRD receiving hemodialysis patients after a single 140-mg subcutaneous dose of evolocumab, depicted as a log-linear plot. The lower limit of quantification was 0.8 µg/mL. ESRD, end-stage renal disease; SD, standard deviation.

These results support the use of evolocumab without dose adjustment in patients who have severe RI or ESRD.

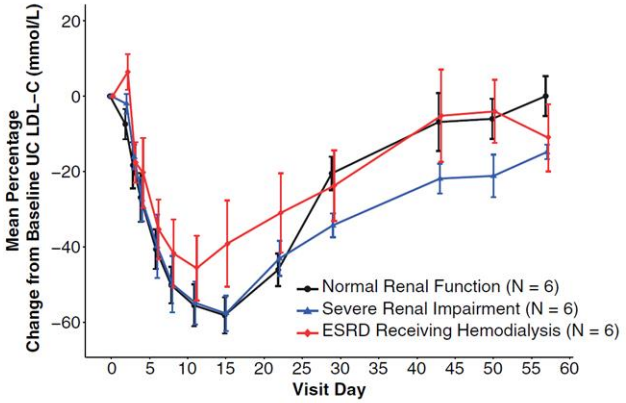


Figure 4. Mean percent change ± standard error from baseline of UC LDL-C (mg/dL) over time by degree of renal impairment. ESRD, end-stage renal disease; LDL-C, low-density lipoprotein cholesterol; UC, ultracentrifugation.

Clin Pharmacol Drug Dev. 2019 Jan 24.

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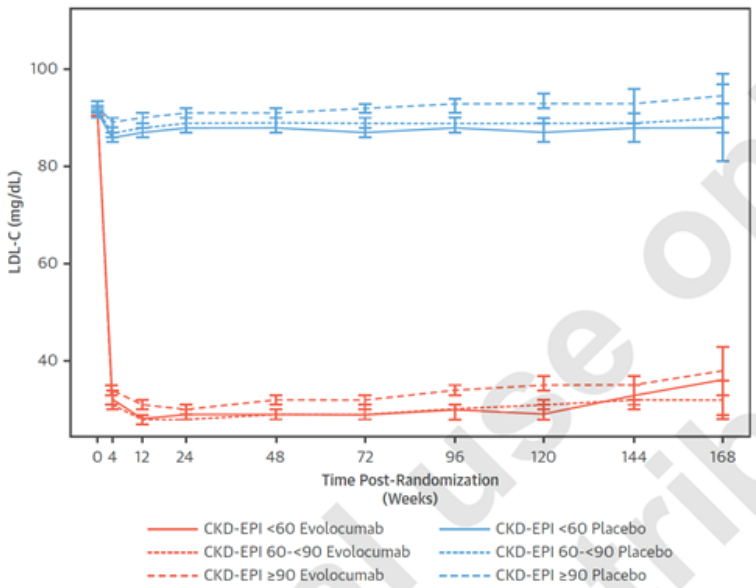
PUBLISHED BY ELSEVIER

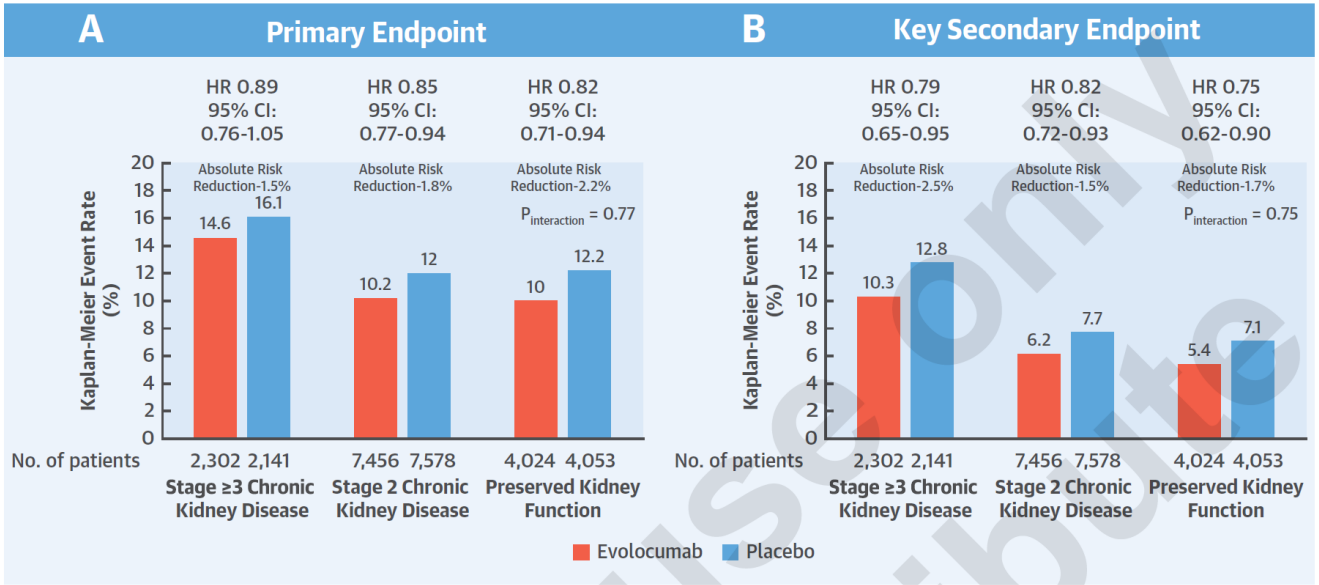
Efficacy and Safety of Evolocumab in Chronic Kidney Disease in the FOURIER Trial

David M. Charytan, MD MSc,[a,b] Marc S. Sabatine, MD, MPH,[b,c] Terje R. Pedersen, MD,[d] KyungAh Im, PhD,[b,c] Jeong-Gun Park, PhD,[b,c] Armando Lira Pineda, MD,[e] Scott M. Wasserman, MD,[e] Prakash Deedwania, MD,[f] Anders G. Olsson, MD, PhD,[g] Peter S. Sever, MD,[h] Anthony C. Keech, MD,[i,j] Robert P. Giugliano, MD, SM,[b,c] on behalf of the FOURIER Steering Committee and Investigators

FIGURE 1 LDL-C Levels Over Time



CENTRAL ILLUSTRATION **PCSK9 Inhibition in Chronic Kidney Disease**



Charytan, D.M. et al. J Am Coll Cardiol. 2019;73(23):2961-70.

Relative and absolute risk of the **(A)** primary endpoint (combined cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) and **(B)** key secondary endpoint (cardiovascular death, myocardial infarction, or stroke), according to CKD stage. Kaplan-Meier event rates at 30 months are provided according to treatment group with placebo in **blue** and evolocumab in **red**. CI = confidence interval; HR = hazard ratio.

Personal use only
Do not distribute

Evaluation of Evolocumab (AMG 145), a Fully Human Anti-PCSK9 IgG2 Monoclonal Antibody, in Subjects With Hepatic Impairment

The Journal of Clinical Pharmacology
2017, 57(4) 513–523
© 2016, The Authors. *The Journal of Clinical Pharmacology* published by Wiley Periodicals, Inc. on behalf of American College of Clinical Pharmacology
DOI: 10.1002/jcph.832

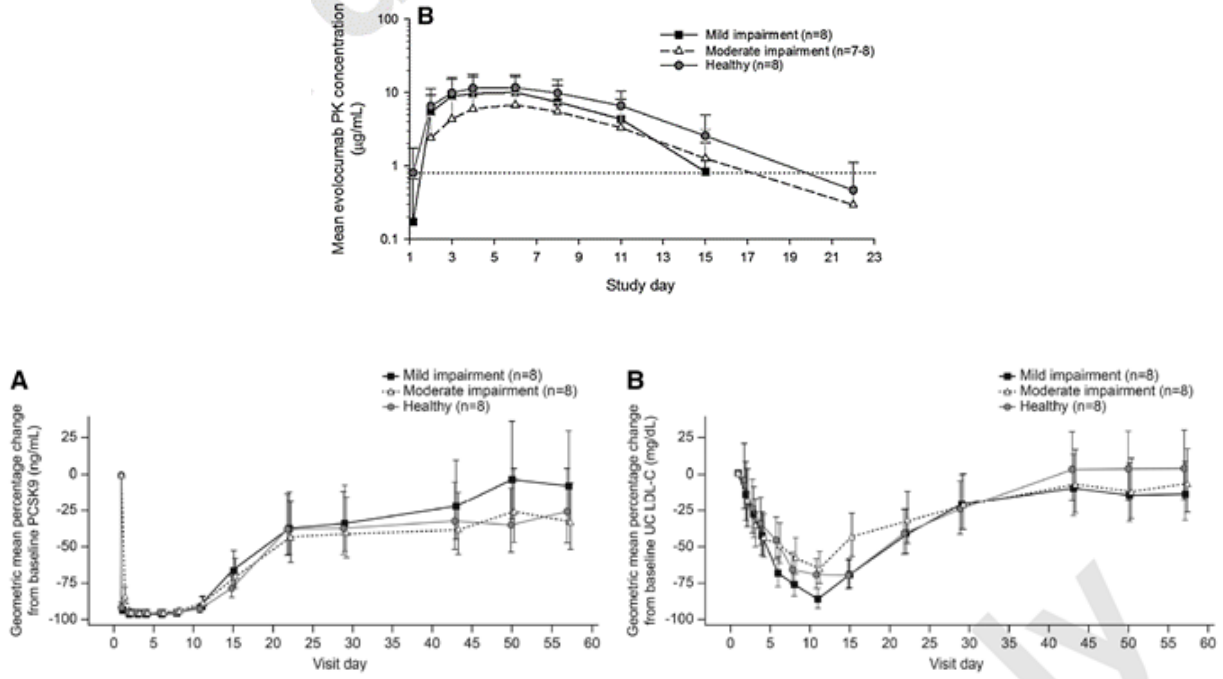


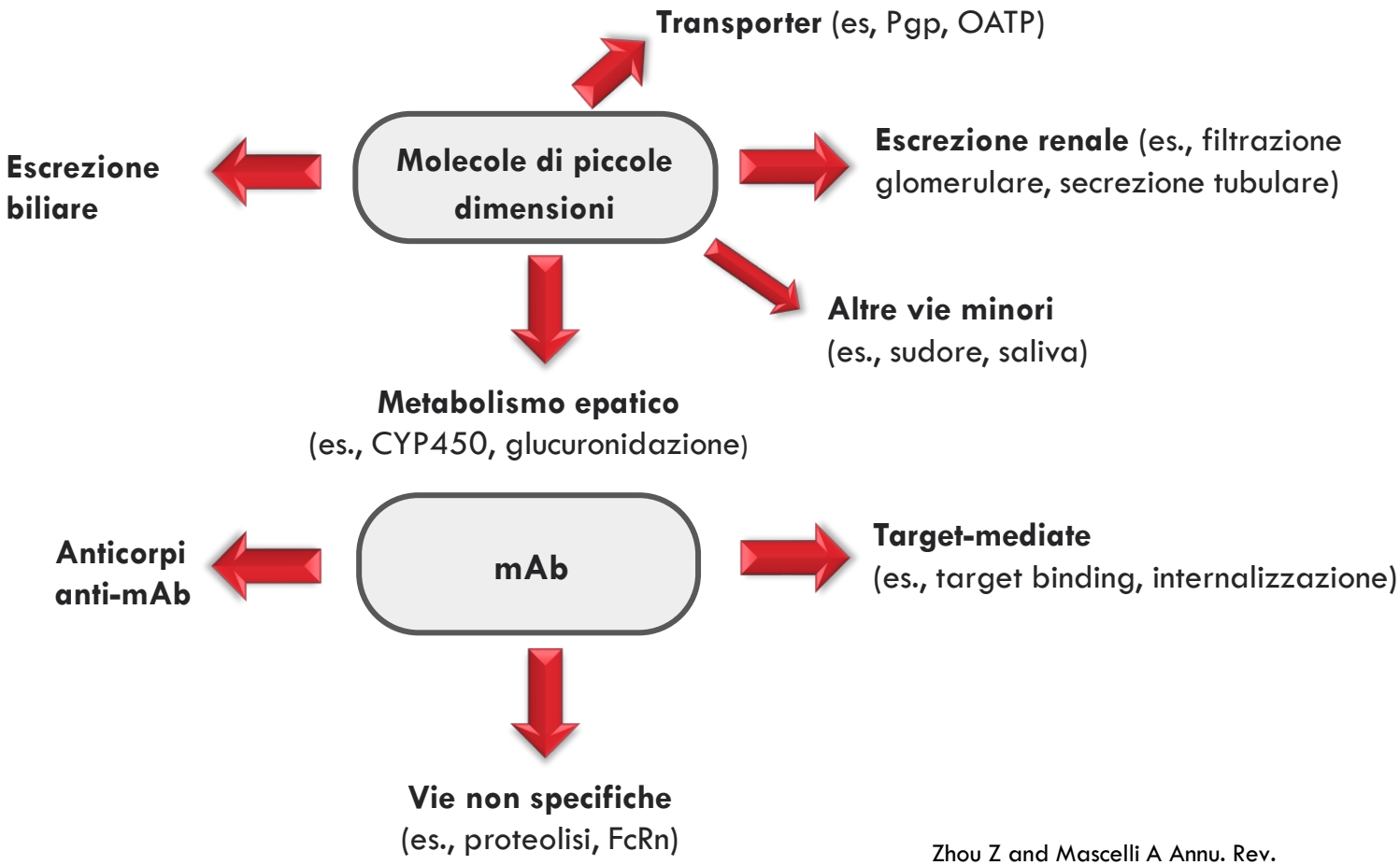
Figure 3. Geometric mean percentage (±95% confidence intervals) changes from baseline in (A) proprotein convertase subtilisin kexin type 9 (PCSK9) and (B) ultracentrifugation (UC) low-density lipoprotein cholesterol (LDL-C) by degree of hepatic impairment.

Eliminazione degli anticorpi monoclonali

- Non vengono metabolizzati attraverso la catalisi indotta dai citocromi
- Non vanno incontro a processi di coniugazione
- Non sono riconosciuti dai trasportatori

→ Fortemente ridotto il rischio di interazione con altri farmaci

Vie di eliminazione degli anticorpi monoclonali



Zhou Z and Mascelli A Annu. Rev. Pharmacol. Toxicol. 2011. 51:359–72

4.5 Interazioni con altri medicinali ed altre forme d'interazione

Non sono stati effettuati studi formali di interazione farmaco-farmaco per evolocumab

Nell'ambito degli studi clinici su evolocumab ta studiata l'interazione farmacocinetica tra statine ed evolocumab. Nei pazienti in trattamento concomitante con statine è stato osservato un aumento di circa il 20% della clearance di evolocumab, in parte mediato dall'aumento della concentrazione della Proproteina Convertasi Subtilisina/Kexina di tipo 9 (PCSK9) indotto dalle statine, senza un impatto negativo dell'effetto farmacodinamico di evolocumab sui lipidi. Non sono necessari aggiustamenti della dose delle statine quando utilizzate in associazione a l evolocumab

Non sono stati effettuati studi di interazione farmacocinetica e farmacodinamica evolocumab farmaci ipolipemizzanti diversi dalle statine e da ezetimibe.

l'Farmaco

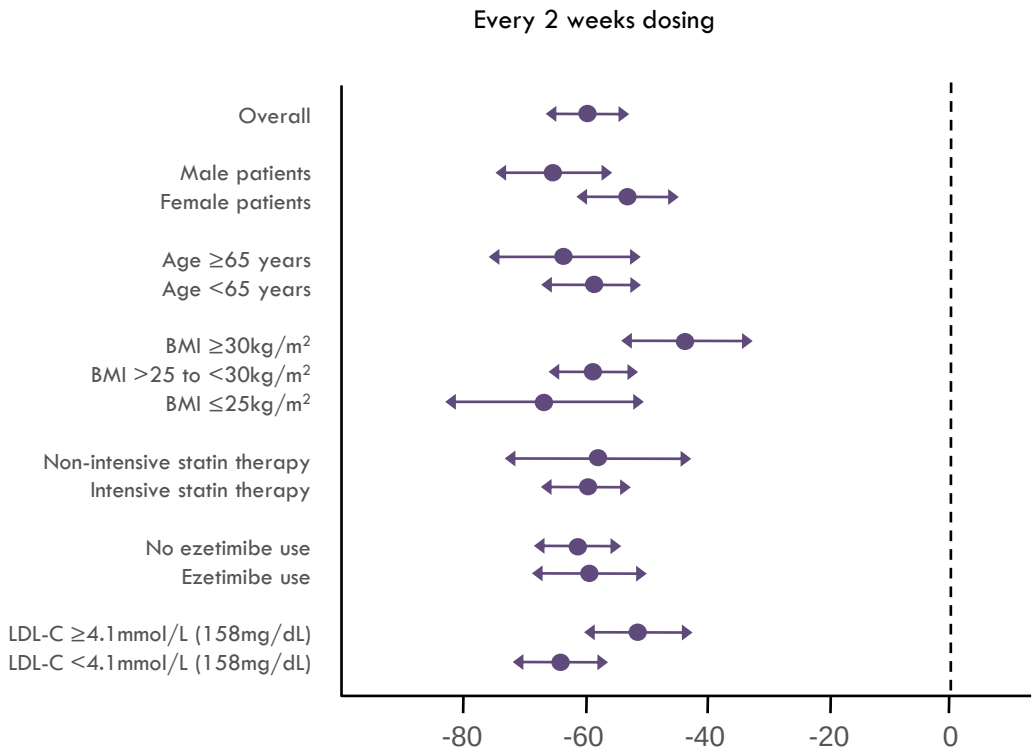
Table 3. Effect of evolocumab compared with placebo on lipid parameters in the Phase III trials.

Background	Without statin		With statin ± ezetimibe				Risk-based therapy	HoFH with statin ± ezetimibe
Study	*MENDEL-2*		*LAPLACE-2*		*RUTHERFORD-2*		*DESCARTES*	*TESLA Part B*
Treatment	140 mg Q2W	420 mg QM	*140 mg Q2W*	420 mg QM	140 mg Q2W	420 mg QM	420 mg QM	420 mg QM
Least square mean percent change from baseline versus placebo at week 12								
LDL-C calc	–59%	–57%	–73%	–64%	–61%	–60%	–58/59%[†]	–32%
Least square mean percent change from baseline versus placebo at mean of weeks 10 and 12								
LDL-C calc	–57%	–60%	–72%	–69%	–61%	–66%	NA	–31%[‡]
TC	–35%	–37%	–41%	–40%	–42%	–44%	–33%	
Non-HDL-C	–49%	–53%	–60%	–60%	–56%	–60%	–50%	
ApoB	–47%	–51%	–56%	–56%	–49%	–55%	–44%	–23%[‡]
Lp(a)	–25%	–26%	–30%	–27%	–31%	–31%	–22%	–11%[‡]
TG	0%	–22%	–17%	–23%	–22%	–17%	–12%	–3.3%[‡]
VLDL-C	0%	–22%	–18%	–22%	–23%	–16%	29%	
HDL-C	6%	9%	6%	8%	8%	9%	5%	1.3%[‡]
ApoA1	3%	5%	3%	5%	7%	5%	3%	

[†]LDL-C percent change from baseline to week 12/52 relative to placebo; week 12 value is based on preparative ultracentrifugation.
[‡]LDL-C percent change from baseline to mean of weeks 6 and 12; week 10 values not available.
References [36,38–41].

Langslet G et al Expert Rev. Cardiovasc. Ther. 13(5), 477–488 (2015)

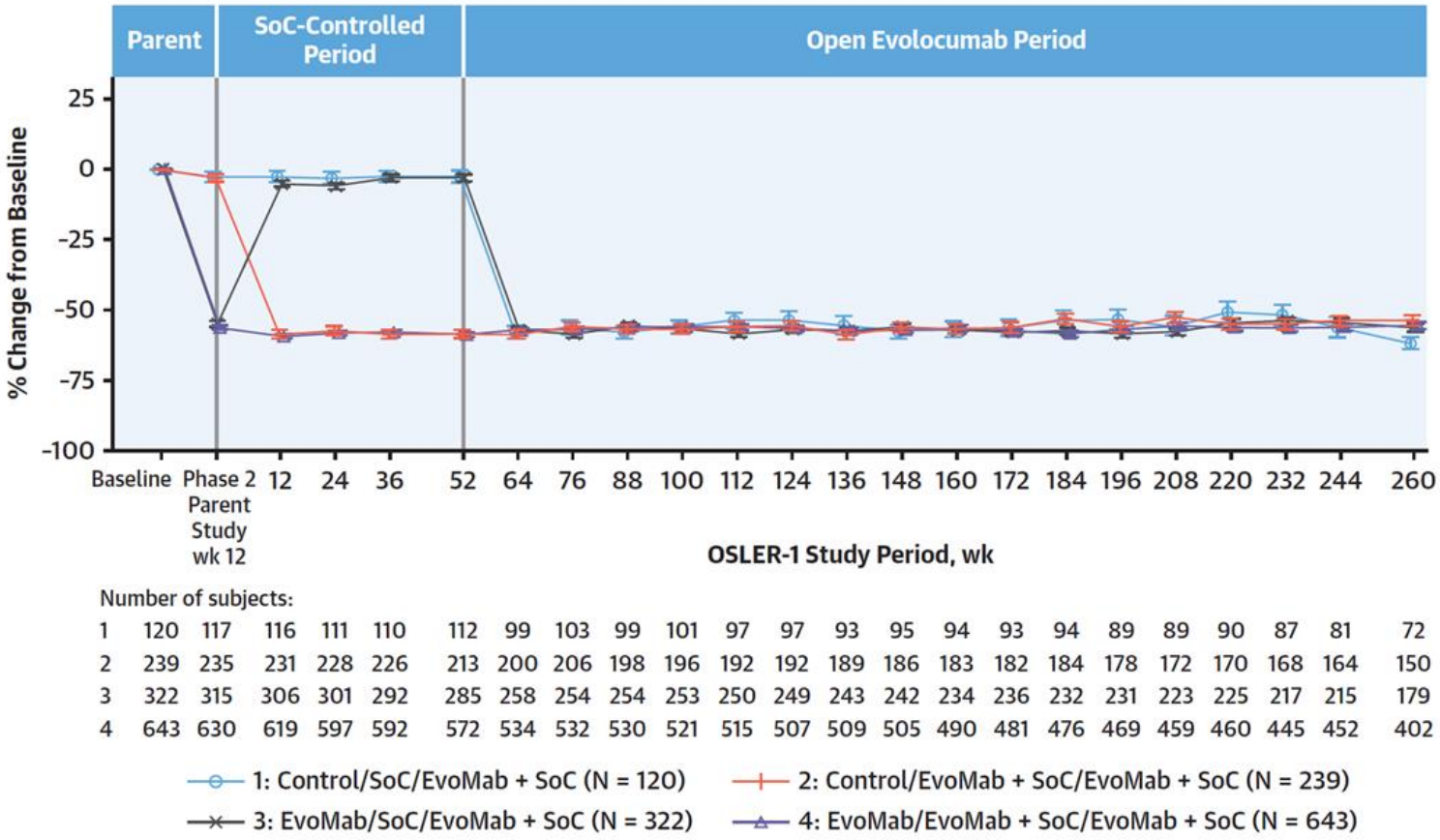
Evolocumab significantly reduces LDL-C irrespective of baseline characteristics



Change from baseline in LDL-C (treatment differences of evolocumab vs placebo)

Raal et al. Lancet 2015;385:331–340.

FIGURE 2 Effects of Evolocumab on LDL-C Levels Over 5 Years



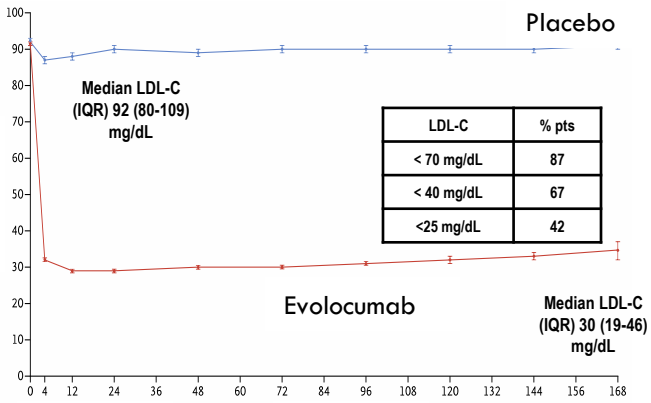
Calculated LDL-C percentage change (mean ± SE) from the phase 2, parent-study baseline to week 260 of OSLER-1 study. The **error bars** represent SEs. Plot is based on observed data with no imputation for missing values. The mean baseline LDL-C level was 140 mg/dl (3.62 mmol/l). The mean week 260 on-treatment LDL-C level was 61 mg/dl (1.47 mmol/l). The **key** shows parent study assignment/year 1 assignment/long-term open-label assignment. To convert LDL-C to millimoles per liter, multiply by 0.0259. LDL-C = low-density lipoprotein cholesterol; other abbreviations as in Figure 1.

The NEW ENGLAND JOURNAL of MEDICINE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

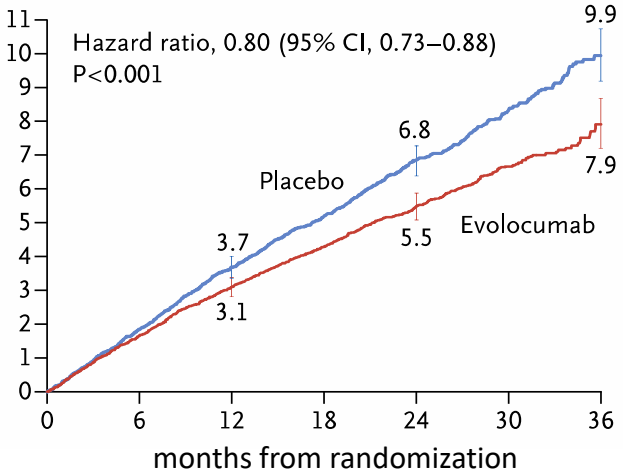
the FOURIER Steering Committee and Investigators*

LDL cholesterol (mg/dL)



59% mean reduction
(95% CI 58-60), p <.00001

CV death, MI, Stroke



20% relative risk reduction
(95% CI .73-.88), p <.001

Cumulative Incidence of Cardiovascular Events

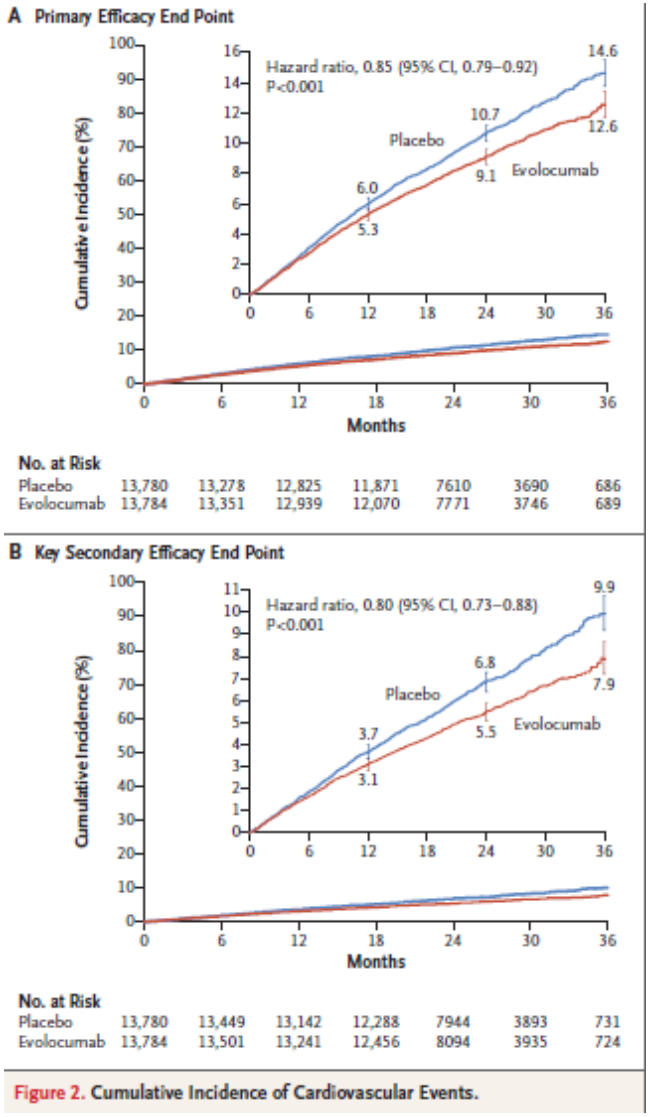
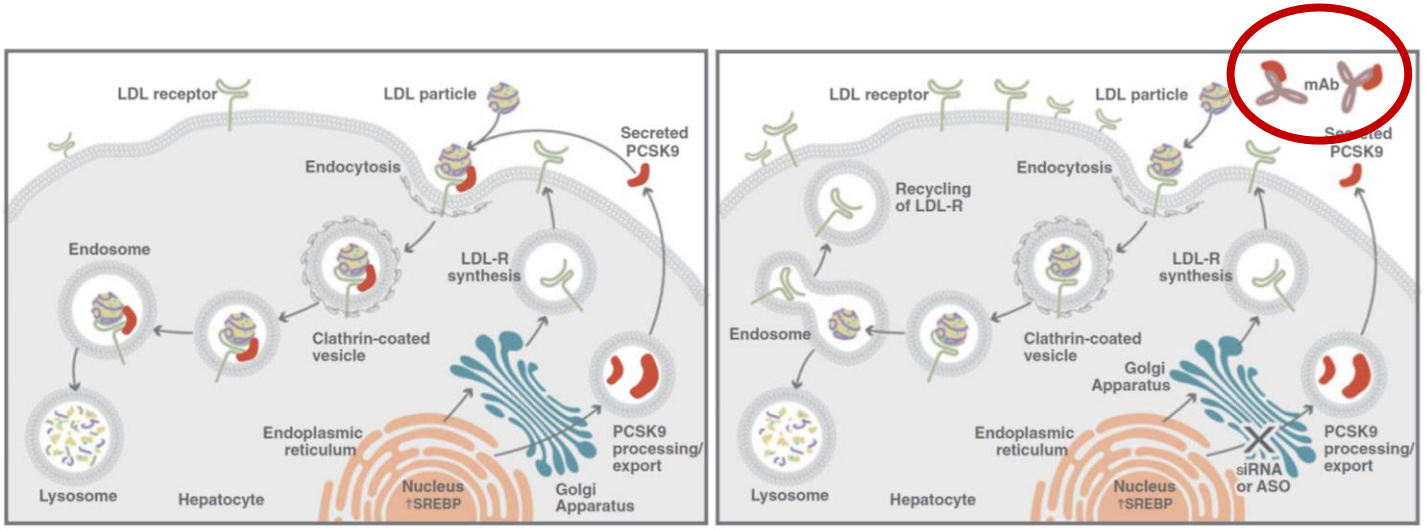


Figure 2. Cumulative Incidence of Cardiovascular Events.

Sabatine MS et al N Engl J Med. 2017 376(18):1713-1722

Interaction of PCSK9 and the LDL receptor



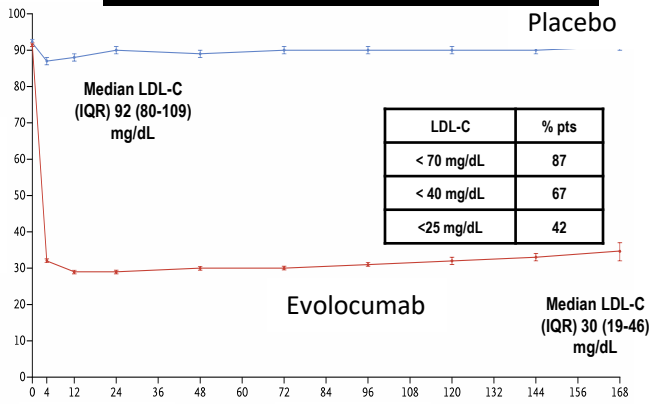
Stein EA and Swergold GD Curr Atheroscler Rep (2013) 15:310

The NEW ENGLAND JOURNAL of MEDICINE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

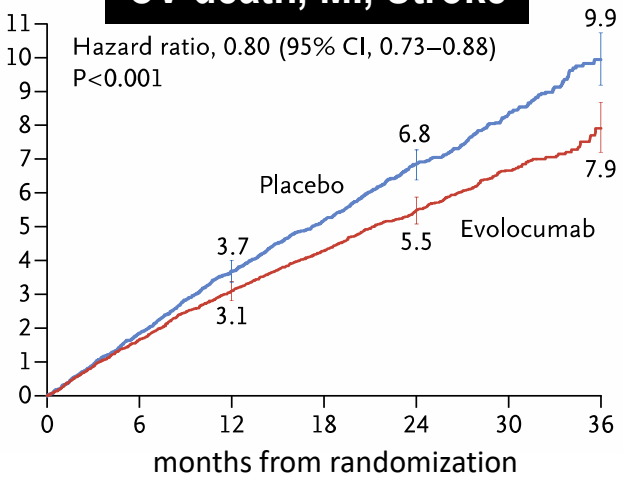
the FOURIER Steering Committee and Investigators*

LDL cholesterol (mg/dL)



59% mean reduction (95% CI 58-60), p <.00001

CV death, MI, Stroke



20% relative risk reduction (95% CI .73-.88), p <.001

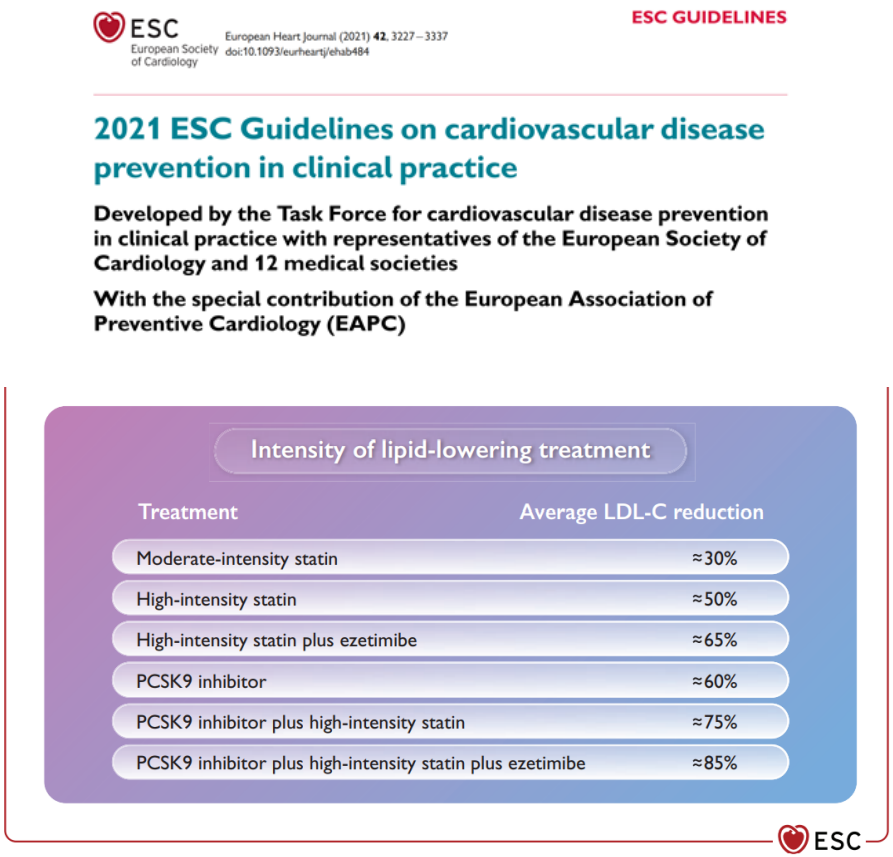
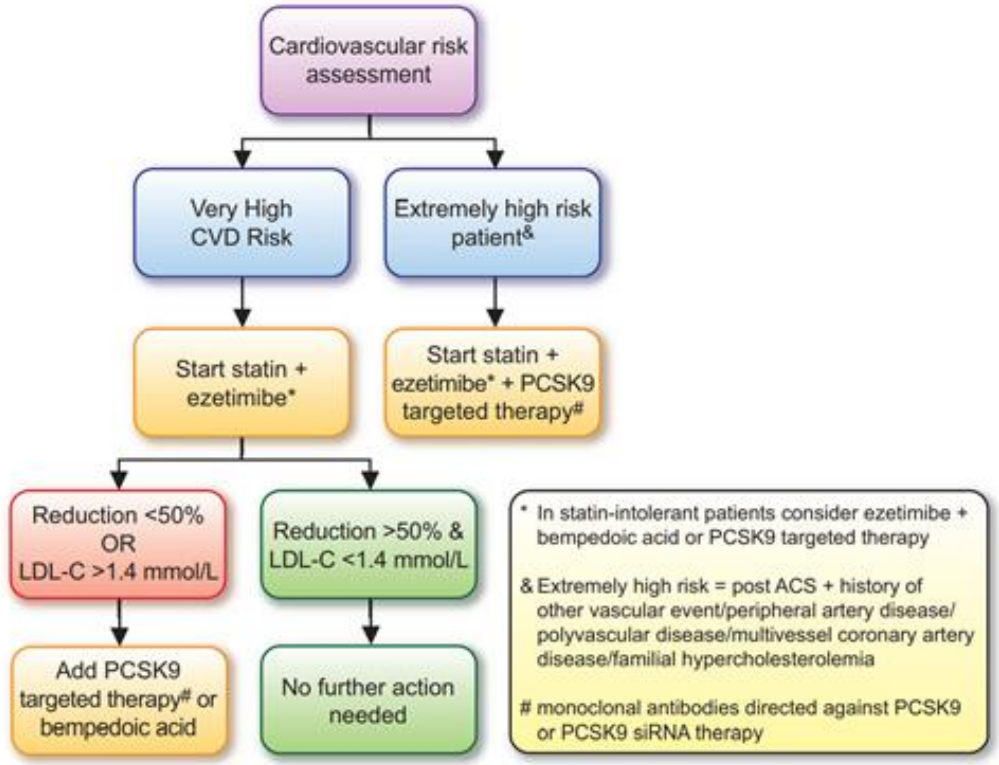


Figure 13 Expected low-density lipoprotein cholesterol reductions for combination therapies. LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9. Adapted from Mach *et al.*[3]

- **acido bempedoico**
- **alirocumab, evolocumab**
- **inclisiran**
- Pemafibrato
- volanesorsen

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



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

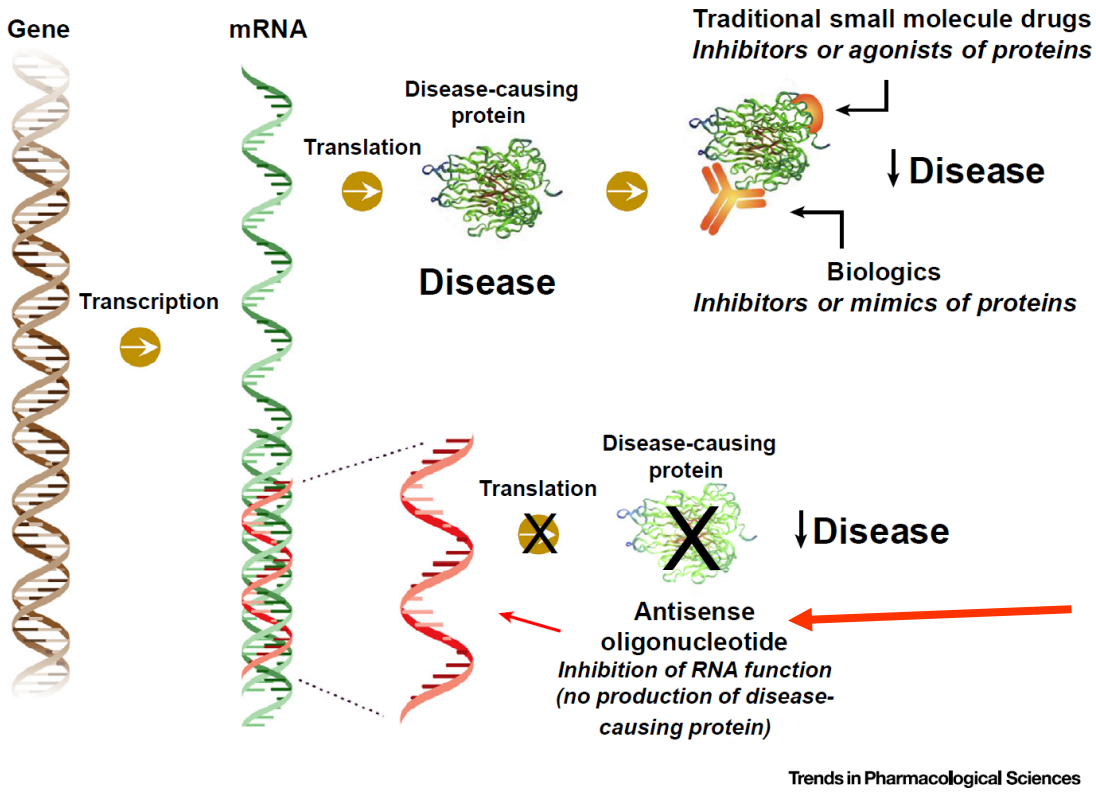
ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–4
doi:10.1093/eurheartj/ehab718

VIEWPOINT
Epidemiology and prevention

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

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

Therapeutic Approaches for Managing Dyslipidemia



Sathiyakumar V et al Trends Pharmacol Sci. 2018 Aug;39(8):733-747

Current Atherosclerosis Reports (2021) 23:17
https://doi.org/10.1007/s11883-021-00918-3

STATIN DRUGS (R. CESKA, SECTION EDITOR)

Lipid Lowering Drugs: Present Status and Future Developments

Massimiliano Ruscica[1] · Nicola Ferri[2] · Raul D. Santos[3,4] · Cesare R. Sirtori[1] · Alberto Corsini[1,5]

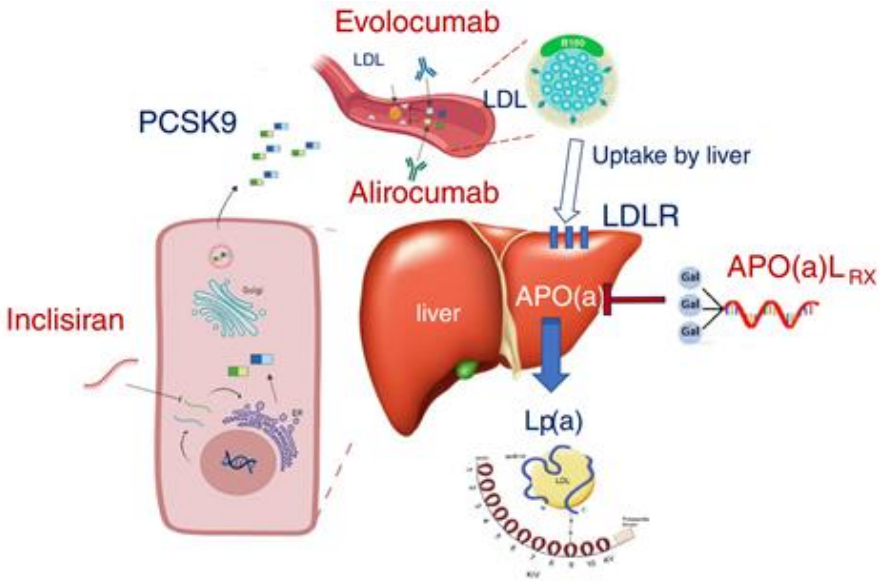


Fig. 1 Molecular mechanisms of PCSK9 and Lp(a) inhibition. PCSK9, mainly derived from the liver, acts by degrading the LDLR expressed on hepatocytes. PCSK9 inhibition leads to higher LDLR expression, thus lowering plasma LDL cholesterol. Inclisiran by inhibiting the transcription of the PCSK9 mRNA reduces the total amount of circulating PCSK9. Conversely, monoclonal antibodies (evolocumab and alirocumab) block PCSK9 interaction with LDLR. Both therapies have shown to strongly reduce the LDL-C levels. Relative to Lp(a) lowering, IONIS-APO(a)Lrx is a ligand-conjugated ASO with a triantennary N-acetylgalactosamine (GalNAc) covalently attached, to allow rapid and specific uptake by hepatocytes. ASO, antisense oligonucleotide; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9. Adapted with permission of Elsevier [40].

Pharmacological Research 150 (2019) 104413

Contents lists available at ScienceDirect

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

Review

A new dawn for managing dyslipidemias: The era of rna-based therapies

C. Macchi[a], C.R. Sirtori[b], A. Corsini[a,c], R.D. Santos[d,e], G.F. Watts[f,g,*], M. Ruscica[a]

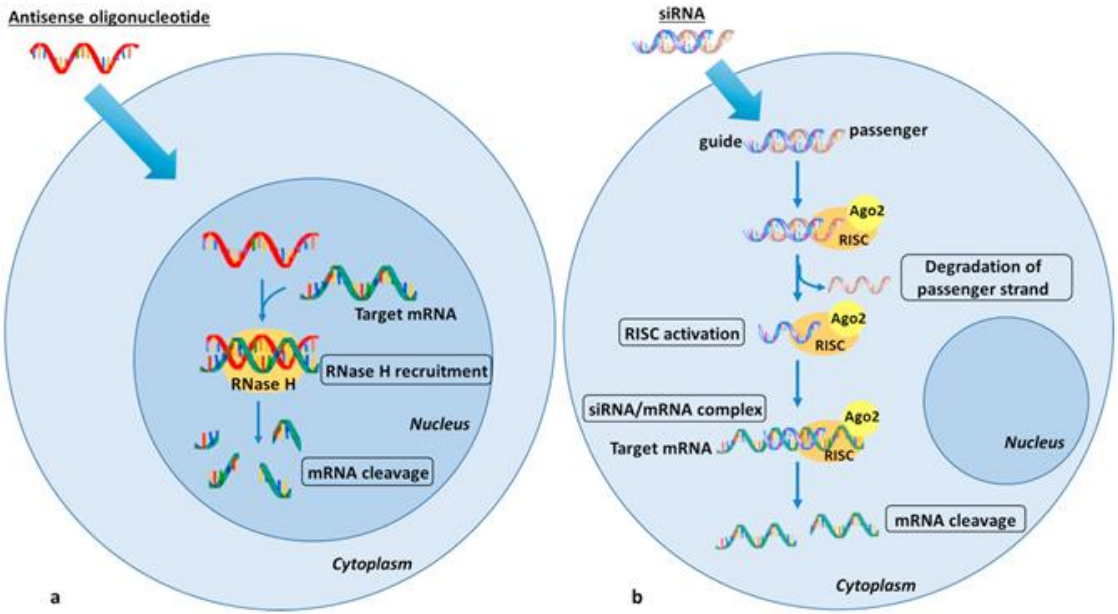
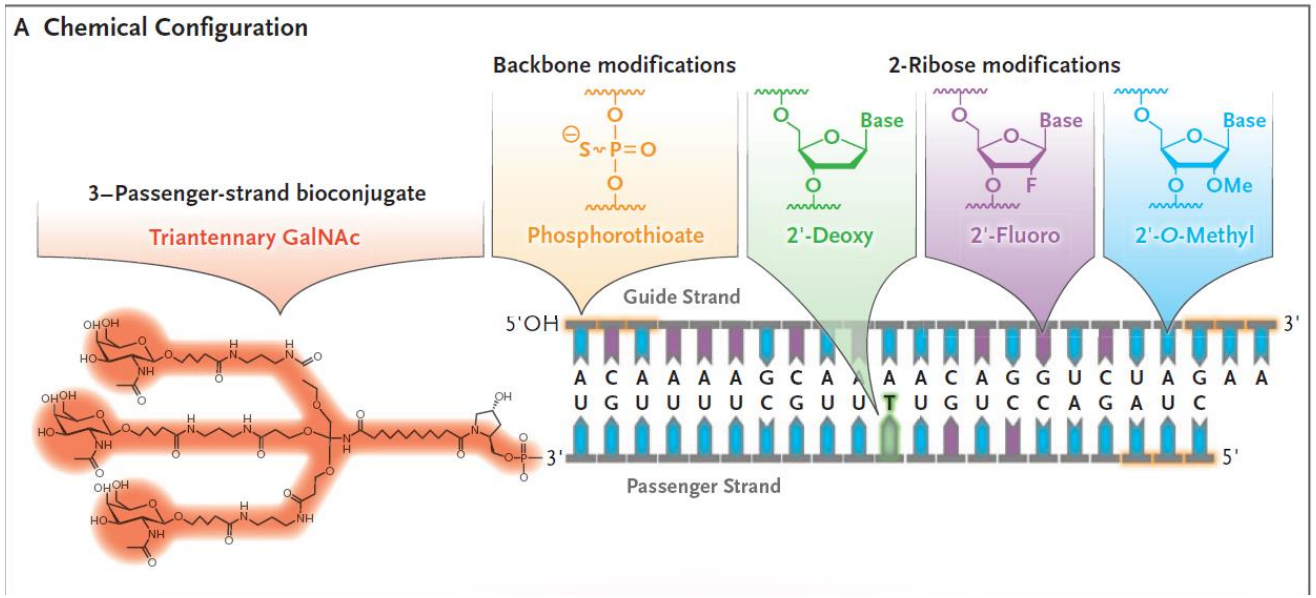


Fig. 1. *RNA-based therapeutic approaches: ASO and siRNA. Panel a)* antisense oligonucleotides (ASOs) control gene expression by the involvement of the RNase H1, an endoribonuclease that preferentially binds to the DNA-RNA hetero-duplex over RNA-RNA and DNA-DNA homo-duplexes. The final result is the selective cleavage of the RNA strand while the synthetic DNA strand remains intact and free to bind additional target mRNAs; *Panel b)* siRNAs are composed of two strands, the guide and the passenger. Once in the cytoplasm the two strands are separated with the guide loaded into the RISC and the passenger removed and degraded. When the complementary target mRNA has hybridized with part of the guide strand, an endonucleolytic cleavage of the mRNA is driven by a component of RISC, the Argonaute 2 (ago 2) protein.

Pharmacological effects of lipid-modification therapies

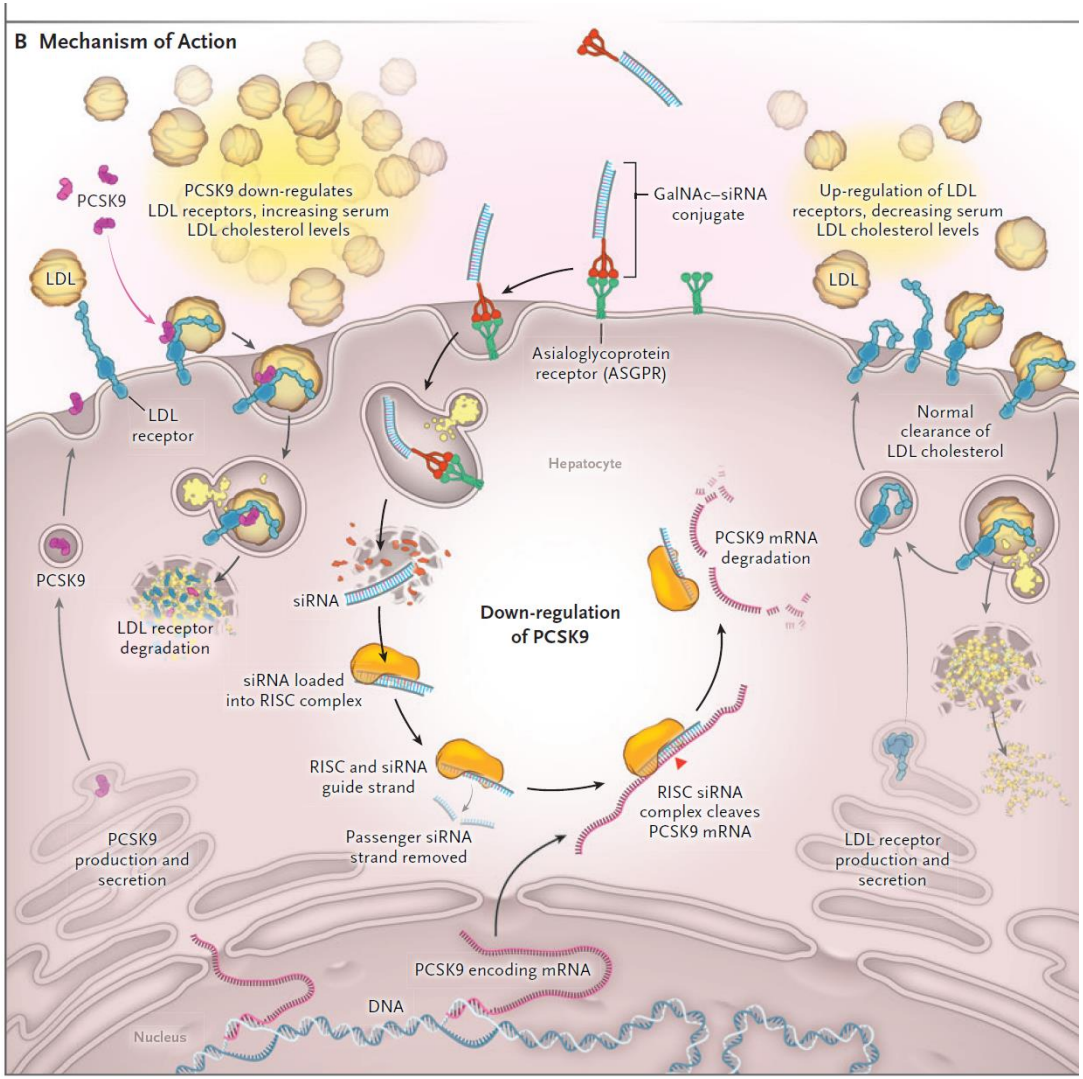
	Effect on LDL cholesterol	Effect on triglycerides and cholesterol remnants	Effect on lipoprotein(a)	Cardiovascular benefit	Ongoing studies
Antisense and mAbs to ANGPTL3	Moderate decrease	Strong decrease	Neutral	No	NCT02709850 (phase 2), phase 3 trials*
Antisense, mAbs, and siRNA to apolipoprotein C3	Neutral	Strong decrease	Neutral	No	NCT03385239 (phase 2), NCT03783377 (phase 1)
Antisense to apolipoprotein(a)	Neutral	Neutral	Strong decrease	No	NCT03070782 (phase 2)
Bempedoic acid	Moderate decrease	Neutral	Neutral	No	NCT02993406 (phase 3 CVOT)
Bile acid sequestrants	Moderate decrease	Mild decrease	Neutral	No†	No
CETP inhibitors	Moderate decrease	Neutral	Mild decrease	Yes‡	No
Ezetimibe	Moderate decrease	Neutral	Minimal increase	Yes	No
Fibrates: SPPARMs	Neutral	Moderate decrease	Neutral	No†§	NCT03071692 (phase 3 CVOT)
Fish oils: EPA	Neutral	Moderate decrease	Neutral	Yes	No
Fish oils: EPA and DHA	Neutral	Moderate decrease	Neutral	No	NCT02104817 (phase 3 CVOT)
Inclisiran	Strong decrease	Mild decrease	Mild decrease	No	NCT03814187 (phase 3 CVOT)
Lomitapide	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Anti-PCSK9 mAbs	Strong decrease	Mild decrease	Mild decrease	Yes	No
Mipomersen	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Nicotinic acid	Mild decrease	Mild decrease	Mild decrease	No‖	No
Statins	Strong decrease	Mild decrease	Minimal increase	Yes	No

Ray KK et al Lancet 2019; 394: 697–708



Inclisiran is a fully chemically modified siRNA conjugated to the triantennary Gal- NAc. Inclisiran is made from one 2’-deoxy, eleven 2’-fluoro, and thirty-two 2’-*O*-methyl modified nucleotides. Termini of the du-plex are modified with phosphorothioates, and the 3’ end of the passenger strand is functionalized with triantennary GalNAc

N Engl J Med. 2017;376:4–7



When inclisiran is delivered to the hepatocytes through GalNAc interactions with the ASGPR receptor, the guide strand of the duplex enters the RISC complex, hybridizes to the PCSK9 mRNA and cleaves it (preventing protein production. Down-regulation of PCSK9, results in the up-regulation of LDLreceptor levels on the surface of the hepatocytes, supporting more efficient clearance of LDL cholesterol from the bloodstream

N Engl J Med. 2017;376:4–7

- The majority of the injected dose is delivered to the liver hepatocytes, and only a relatively small fraction becomes biologically active and is loaded into the RISC immediately

- The loaded RISC has a half-life of weeks, which may be further enhanced in a context of fully stabilized siRNAs.

- In addition, the oligonucleotides trapped in the endosomes may serve as an intracellular depot of the drug, slowly releasing it over time.

N Engl J Med. 2017;376:4–7

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 9, 2021
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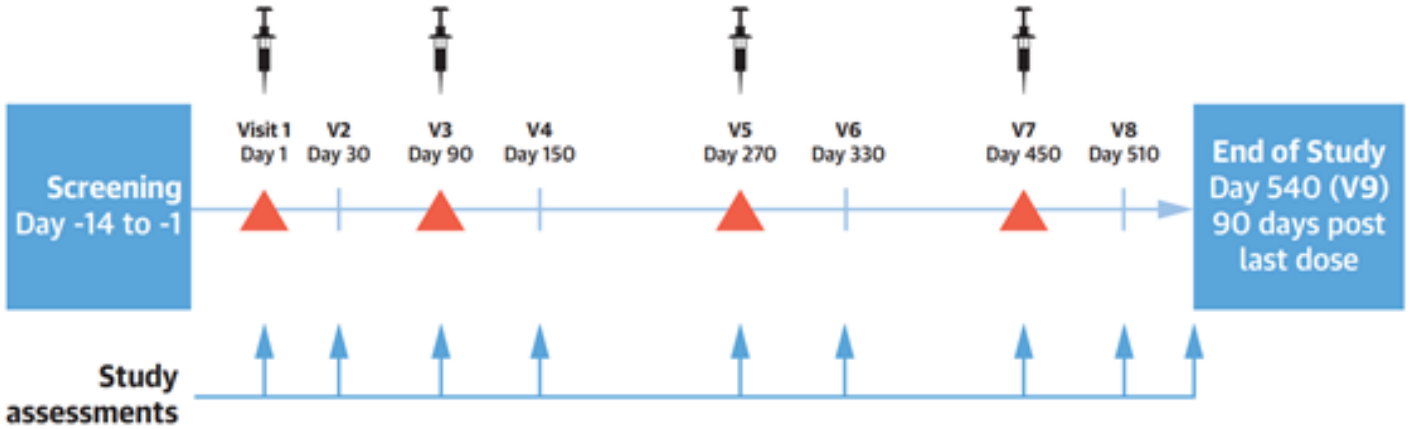
Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis

R. Scott Wright, MD,[a] Kausik K. Ray, MD,[b,*] Frederick J. Raal, MD, PhD,[c,*] David G. Kallend, MBBS,[d] Mark Jaros, PhD,[e] Wolfgang Koenig, MD,[f,g] Lawrence A. Leiter, MD,[h] Ulf Landmesser, MD,[i] Gregory G. Schwartz, MD, PhD,[j] Andrew Friedman, PharmD,[k] Peter L.J. Wijngaard, PhD,[k] Lorena Garcia Conde, MD,[l] John J.P. Kastelein, MD, PhD,[m] for the ORION Phase III Investigators

FIGURE 1 Randomization and Assessment Time Points



Study design and assessment schedule. Participants on maximally tolerated statins and/or other LDL-C-lowering therapies were randomized 1:1 to receive inclisiran sodium 300 mg or placebo.

ORIGINAL ARTICLE

Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Leiter, M.D., Frederick J. Raal, Ph.D., Jenna A. Bisch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., and John J.P. Kastelein, M.D., Ph.D., for the ORION-10 and ORION-11 Investigators*

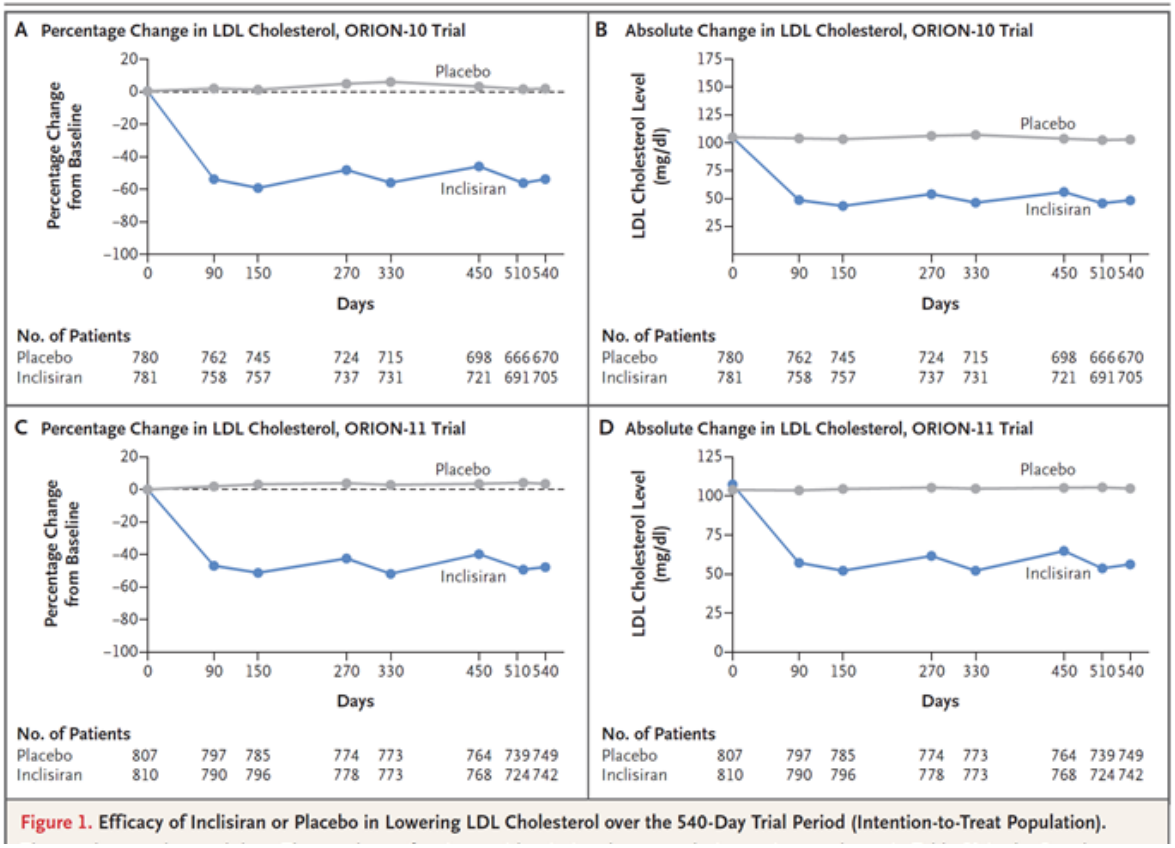
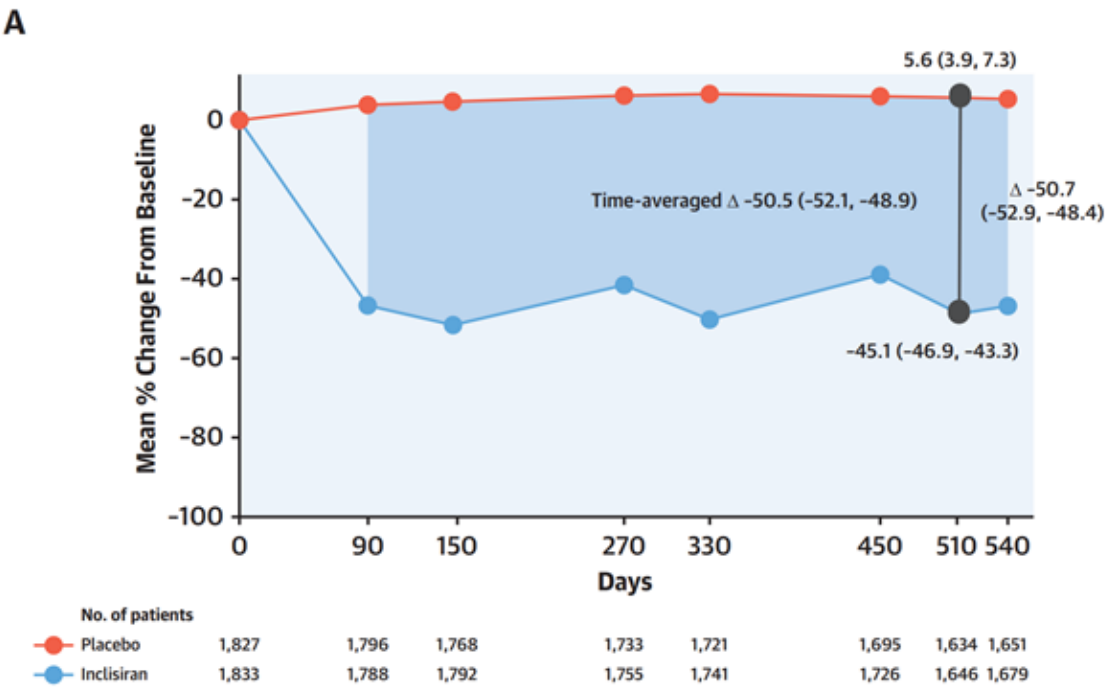


Figure 1. Efficacy of Inclisiran or Placebo in Lowering LDL Cholesterol over the 540-Day Trial Period (Intention-to-Treat Population).

N Engl J Med 2020 Mar18

JACC VOL. 77, NO. 9, 2021
MARCH 9, 2021:1182–93

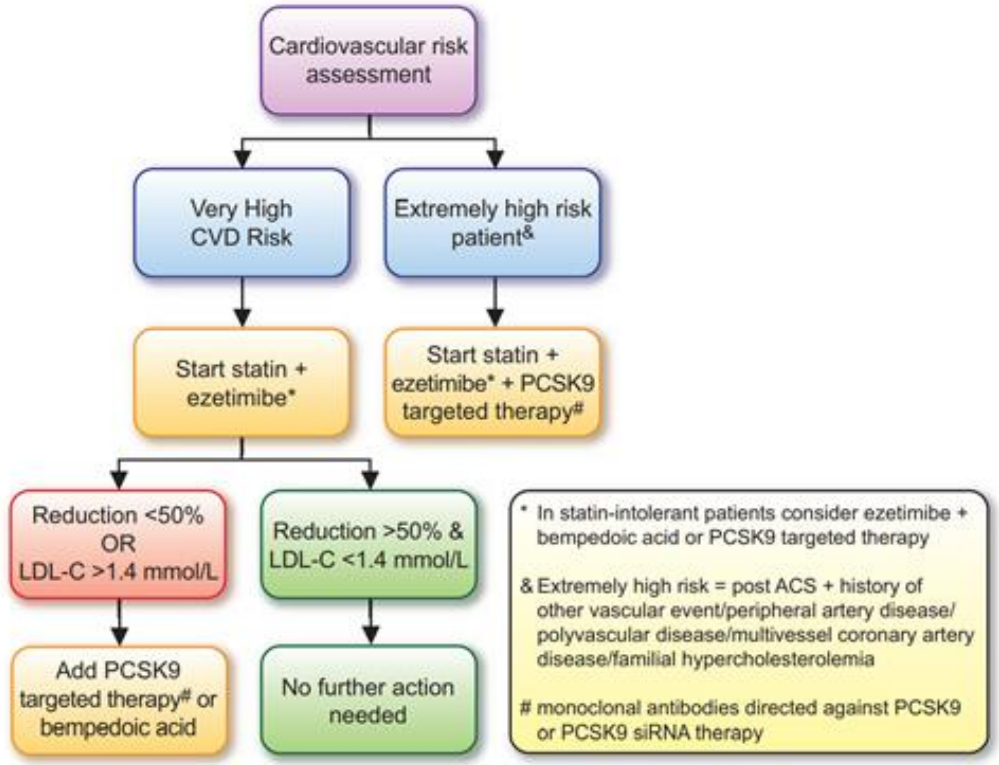
FIGURE 2 LDL-C Changes Over Time



Combined lipid-lowering therapy

Drug class	LDL-C Decrease (%)	Non-HDL-C Decrease (%)	HDL-C Increase (%)	TG Decrease (%)
Statin	+++	+++	+	++
Ezetimibe	++	++	+	+
Acido Bempedoico	++	++	- -	- -
Feno	+	+	++	++++
PCSK9 inhibitor	++++	++++	+	+

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



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

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

VIEWPOINT
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- **acido bempedoico**
- **alirocumab, evolocumab**
- **inclisiran**
- **Pemafibrato**
- volanesorsen

Current Atherosclerosis Reports (2021) 23:17
https://doi.org/10.1007/s11883-021-00918-3

STATIN DRUGS (R. CESKA, SECTION EDITOR)

Lipid Lowering Drugs: Present Status and Future Developments

Massimiliano Ruscica[1] · Nicola Ferri[2] · Raul D. Santos[3,4] · Cesare R. Sirtori[1] · Alberto Corsini[1,5]

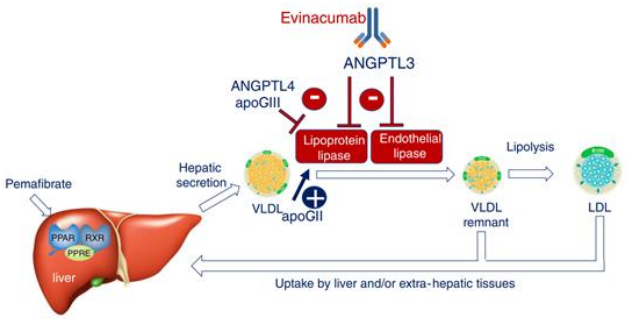


Fig. 2 Molecular mechanism of ANGPTL3 inhibition. ANGPTL3 inhibits both the lipoprotein and endothelial lipases and thus the conversion of VLDL into LDL. A similar effect is determined by ANGPTL4 and apoC-III, while apoC-II is a coactivator of lipoprotein lipase. The monoclonal antibody evinacumab binds and inhibits the ANGPTL3 generating VLDL remnant particles that are efficiently removed from the circulation. Thus, ANGPTL3 inhibition may lower LDL-C by limiting LDL particle production and endothelial lipase could be a key mediator of this novel pathway. ANGPTL, angiopoietin-like; apo, apolipoprotein; LDL, low-density lipoprotein; VLDL, very-low density lipoprotein. Adapted with permission of Elsevier [40].

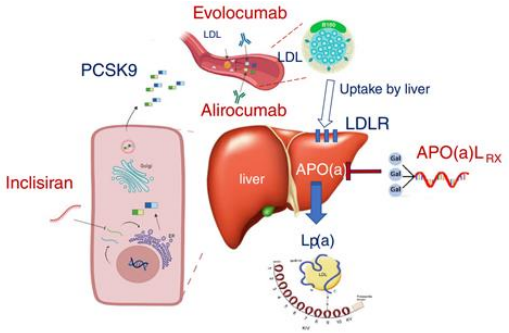
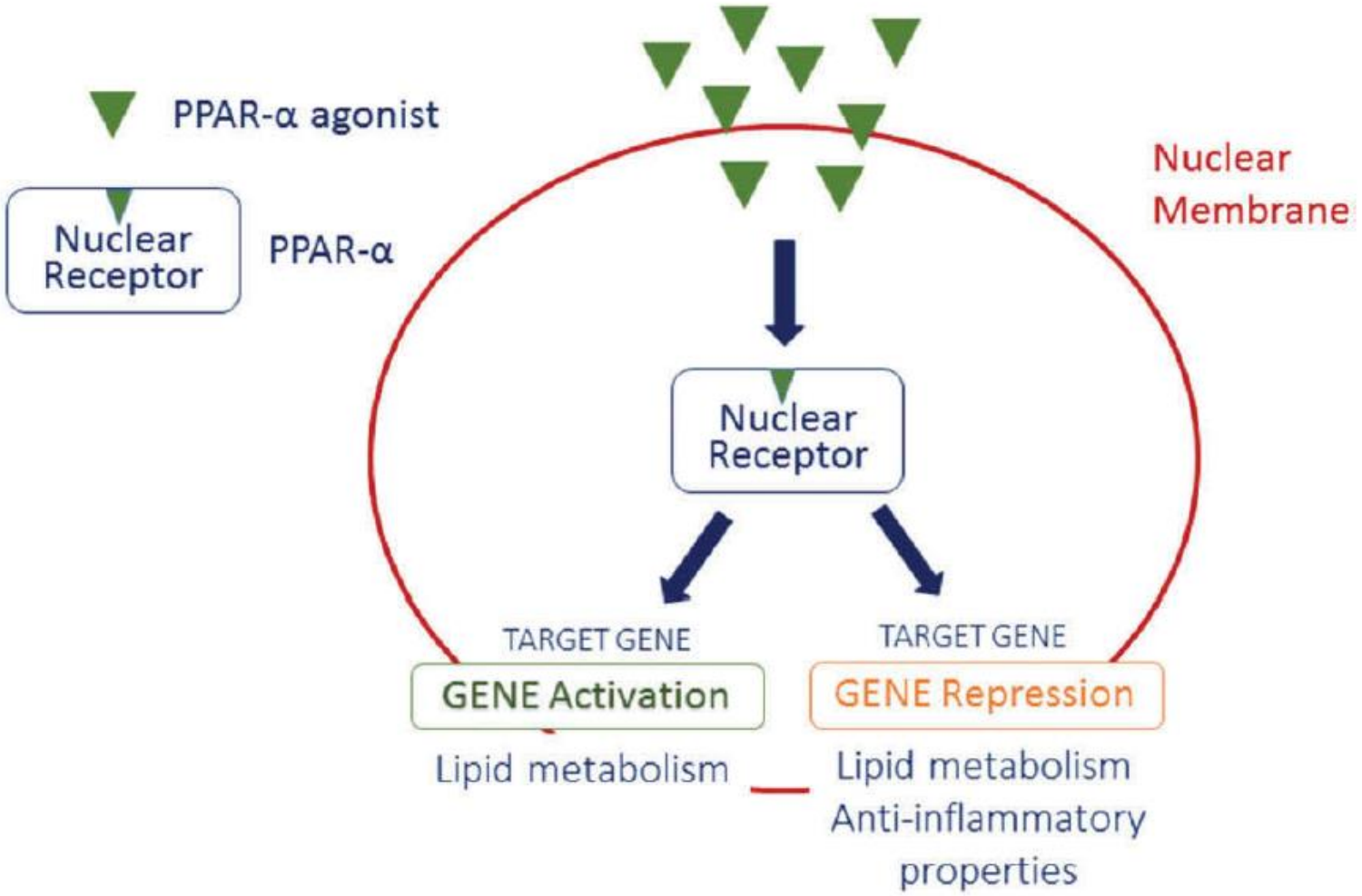


Fig. 1 Molecular mechanisms of PCSK9 and Lp(a) inhibition. PCSK9, mainly derived from the liver, acts by degrading the LDLR expressed on hepatocytes. PCSK9 inhibition leads to higher LDLR expression, thus lowering plasma LDL cholesterol. Inclisiran by inhibiting the transcription of the PCSK9 mRNA reduces the total amount of circulating PCSK9. Conversely, monoclonal antibodies (evolocumab and alirocumab) block PCSK9 interaction with LDLR. Both therapies have shown to strongly reduce the LDL-C levels. Relative to Lp(a) lowering, IONIS-APO(a)Lrx is a ligand-conjugated ASO with a triantennary N-acetylgalactosamine (GalNAc) covalently attached, to allow rapid and specific uptake by hepatocytes. ASO, antisense oligonucleotide; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9. Adapted with permission of Elsevier [40].

Molecular mechanism of PPAR-α agonists



EXPERT OPINION ON INVESTIGATIONAL DRUGS, 2017
http://dx.doi.org/10.1080/13543784.2017.1312339

Taylor & Francis
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REVIEW

Check for updates

PPAR-α agonists are still on the rise: an update on clinical and experimental findings

Nicola Ferri [a], Alberto Corsini [b,c], Cesare Sirtori[d] and Massimiliano Ruscica [b]

Table 1. Chemical structures of peroxisome proliferator-activated receptor-α agonists.

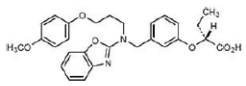
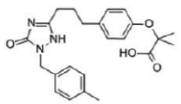
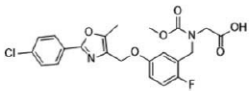
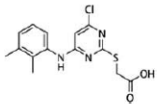
Compound	Chemical structure	Molecular weight	Formula
Pemafibrate		490.55	$C_{28}H_{30}N_2O_6$
LY-518674		409.48	$C_{23}H_{27}N_3O_4$
BMS-711939		462.86	$C_{22}H_{20}ClFN_2O_6$
WY14,643		323.80	$C_{14}H_{14}ClN_3O_2S$

Table 2. Potency and selectivity of peroxisome proliferator-activated receptor (PPAR)α agonists.

Compounds	PPAR-α (EC_{50} nM)	PPAR-γ (EC_{50} nM)	PPAR-δ (EC_{50} nM)
Fenofibrate [48]	14,000 or 22,400	~100,000	Not activated
Pemafibrate [49]	1.0	2300	1000
LY-518674 [50]	45.9	>10,000	>10,000
BMS-711939 [51]	4.0	4511	100,000
WY14,643 [52]	36,300	53,700	100,000

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

Shun Ishibashi, MD, PhD*, Hidenori Arai, MD, PhD, Koutaro Yokote, MD, PhD, Eiichi Araki, MD, PhD, Hideki Suganami, PhD, Shizuya Yamashita, MD, PhD, on behalf of the K-877 Study Group

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

	Baseline (mmol/L)	% Change from baseline	Difference vs fenofibrate
Treatment group	Mean (SD)	LS mean (SE)	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.

Phase 3 CV outcomes study with pemafibrate stopped early

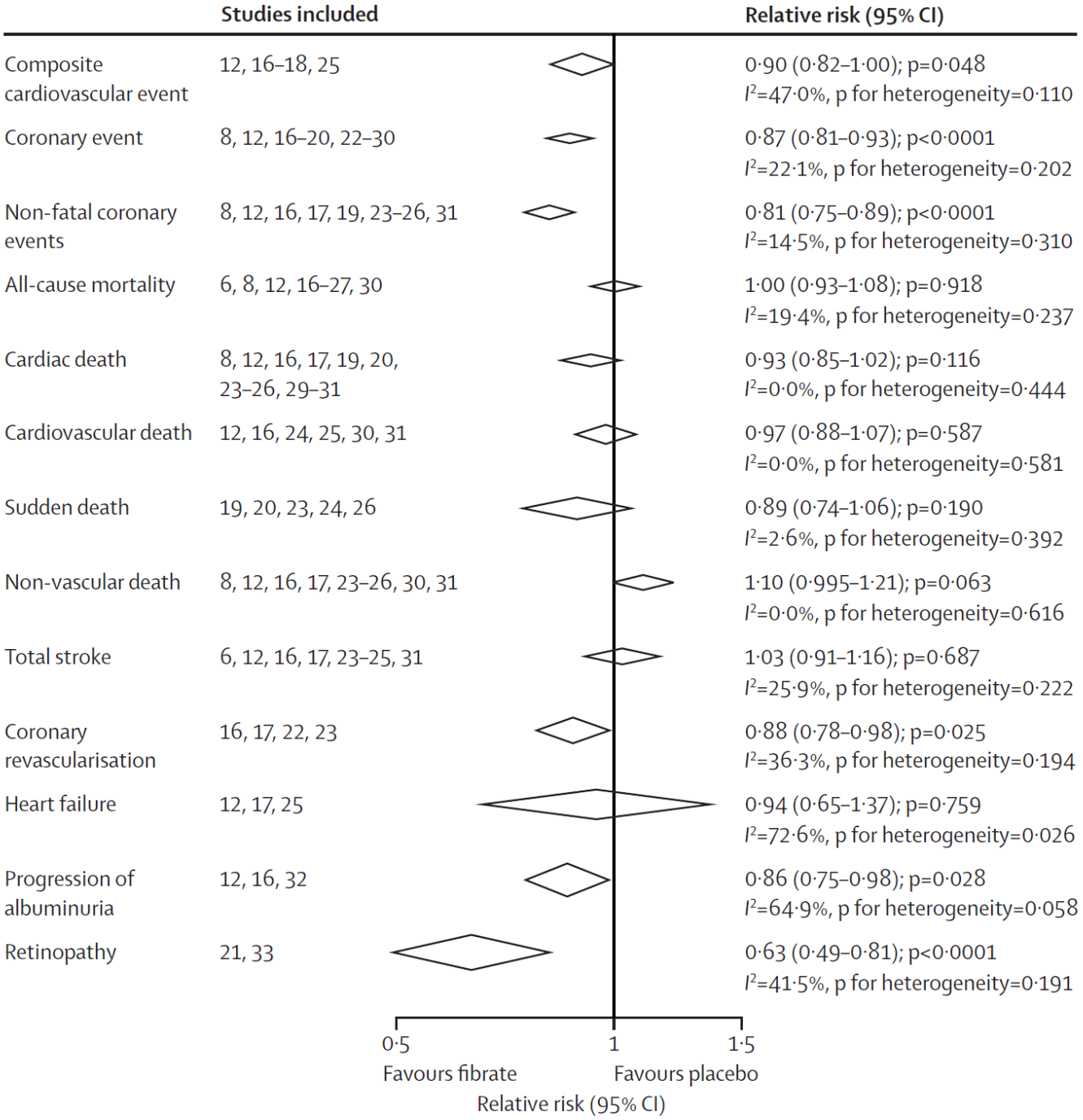
NEWS - APR. 11, 2022

The PROMINENT study, which investigated whether pemafibrate could reduce CV outcomes by reducing triglycerides in patients with T2DM, will be stopped early. This decision follows recommendations of the Data Safety Monitoring Board (DSMB). The DSMB reviewed the results of a planned interim analysis and concluded that it was unlikely that the primary endpoint would be met. There were no notable safety concerns.

The phase 3 PROMINENT study investigated the effects of pemafibrate on risk of CV events in high-risk patients with T2DM, mild-to-moderate hypertriglyceridemia and low levels of HDL-c treated with statins. The primary endpoint is a composite of nonfatal MI, nonfatal ischemic stroke, coronary revascularization and CV death.

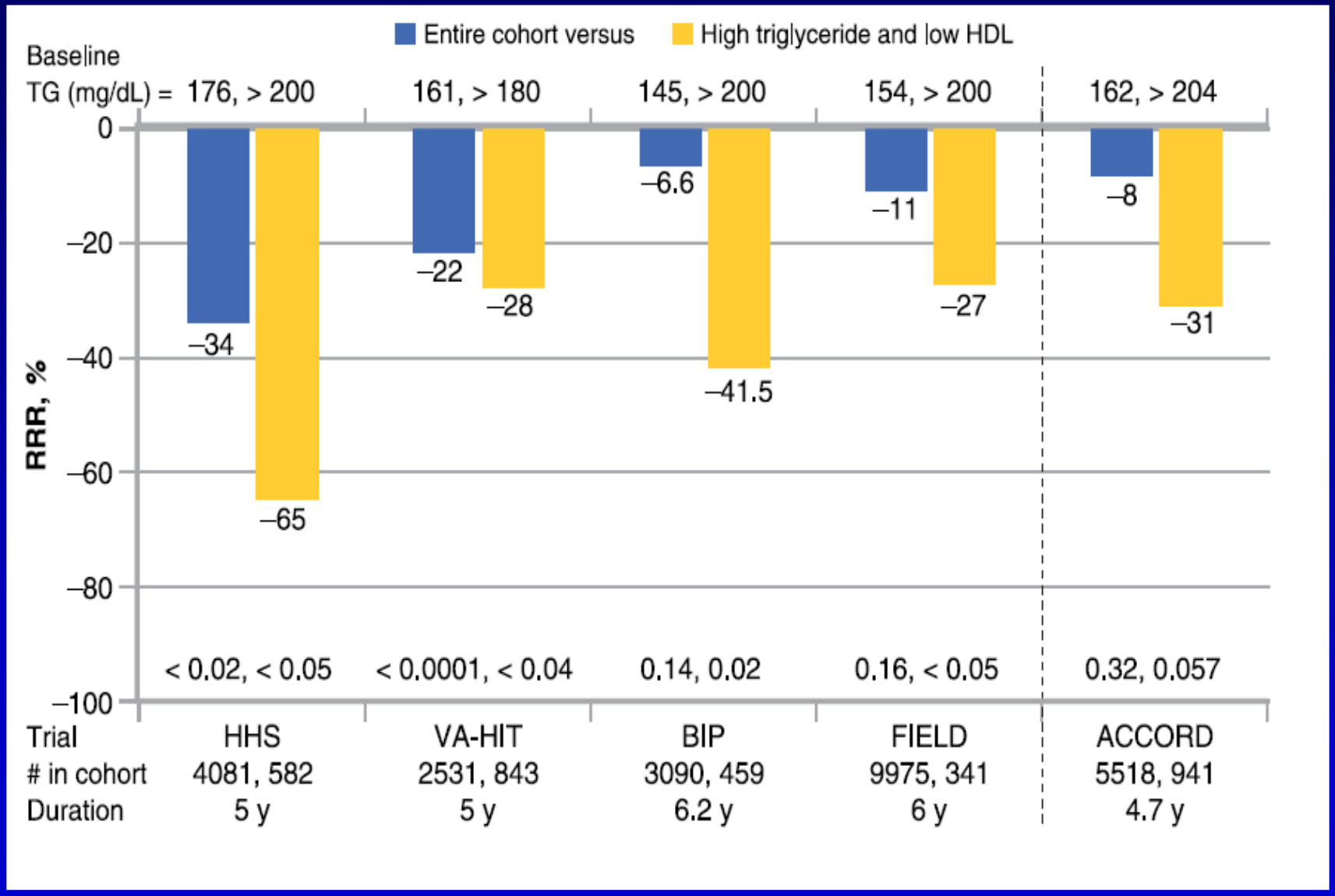
Investigations with pemafibrate will be continued in new therapeutic areas, including nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), as the analysis of the PROMINENT results showed encouraging data in these areas.

Effect of fibrates on clinical outcomes



Jun M et al. Lancet 2010; 375: 1875–84

Cardiovascular event risk reduction in large monotherapy fibrate clinical trials



Rosenblit PD Curr Cardiol Rep (2012) 14:112–124

FIBRATES: SIDE EFFECTS

- mild gastrointestinal distress
- hepatic dysfunction
- muscular syndrome (myalgia)
- impotence
- (cholelithiasis)
- drug interactions

Impact of Existing Drug Therapies on Lipid Parameters

Drug class/agents	HDL-C effect	LDL-C effect	Triglyceride effect
Nicotinic acid	↑ 15–35%	↓ 5–25%	↓ 20–50%
Fibric acids	↑ 10–20%	↓ 5–20%	↓ 20–50%
Statins	↑ 5–15%	↓ 18–55%	↓ 7–30%
Bile acid sequestrants	↑ 3–5%	↓ 15–30%	No change or increase
Ezetimibe	↑ 3%	↓ 19%	↓ 8%
Omega-3 FA*	↑ or neutral	↑ or neutral	↓ 20–50 %

Jacobson et al. Clin Ther 2007; 29: 763-777

- **acido bempedoico**
- **alirocumab, evolocumab**
- **inclisiran**
- **Pemafibrato**
- **volanesorsen**

Pharmacological effects of lipid-modification therapies

	Effect on LDL cholesterol	Effect on triglycerides and cholesterol remnants	Effect on lipoprotein(a)	Cardiovascular benefit	Ongoing studies
Antisense and mAbs to ANGPTL3	Moderate decrease	Strong decrease	Neutral	No	NCT02709850 (phase 2), phase 3 trials*
Antisense, mAbs, and siRNA to apolipoprotein C3	Neutral	Strong decrease	Neutral	No	NCT03385239 (phase 2), NCT03783377 (phase 1)
Antisense to apolipoprotein(a)	Neutral	Neutral	Strong decrease	No	NCT03070782 (phase 2)
Bempedoic acid	Moderate decrease	Neutral	Neutral	No	NCT02993406 (phase 3 CVOT)
Bile acid sequestrants	Moderate decrease	Mild decrease	Neutral	No†	No
CETP inhibitors	Moderate decrease	Neutral	Mild decrease	Yes‡	No
Ezetimibe	Moderate decrease	Neutral	Minimal increase	Yes	No
Fibrates: SPPARMs	Neutral	Moderate decrease	Neutral	No†§	NCT03071692 (phase 3 CVOT)
Fish oils: EPA	Neutral	Moderate decrease	Neutral	Yes	No
Fish oils: EPA and DHA	Neutral	Moderate decrease	Neutral	No	NCT02104817 (phase 3 CVOT)
Inclisiran	Strong decrease	Mild decrease	Mild decrease	No	NCT03814187 (phase 3 CVOT)
Lomitapide	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Anti-PCSK9 mAbs	Strong decrease	Mild decrease	Mild decrease	Yes	No
Mipomersen	Moderate decrease	Mild decrease	Mild decrease	No	No¶
Nicotinic acid	Mild decrease	Mild decrease	Mild decrease	No‖	No
Statins	Strong decrease	Mild decrease	Minimal increase	Yes	No

Ray KK et al Lancet 2019; 394: 697–708

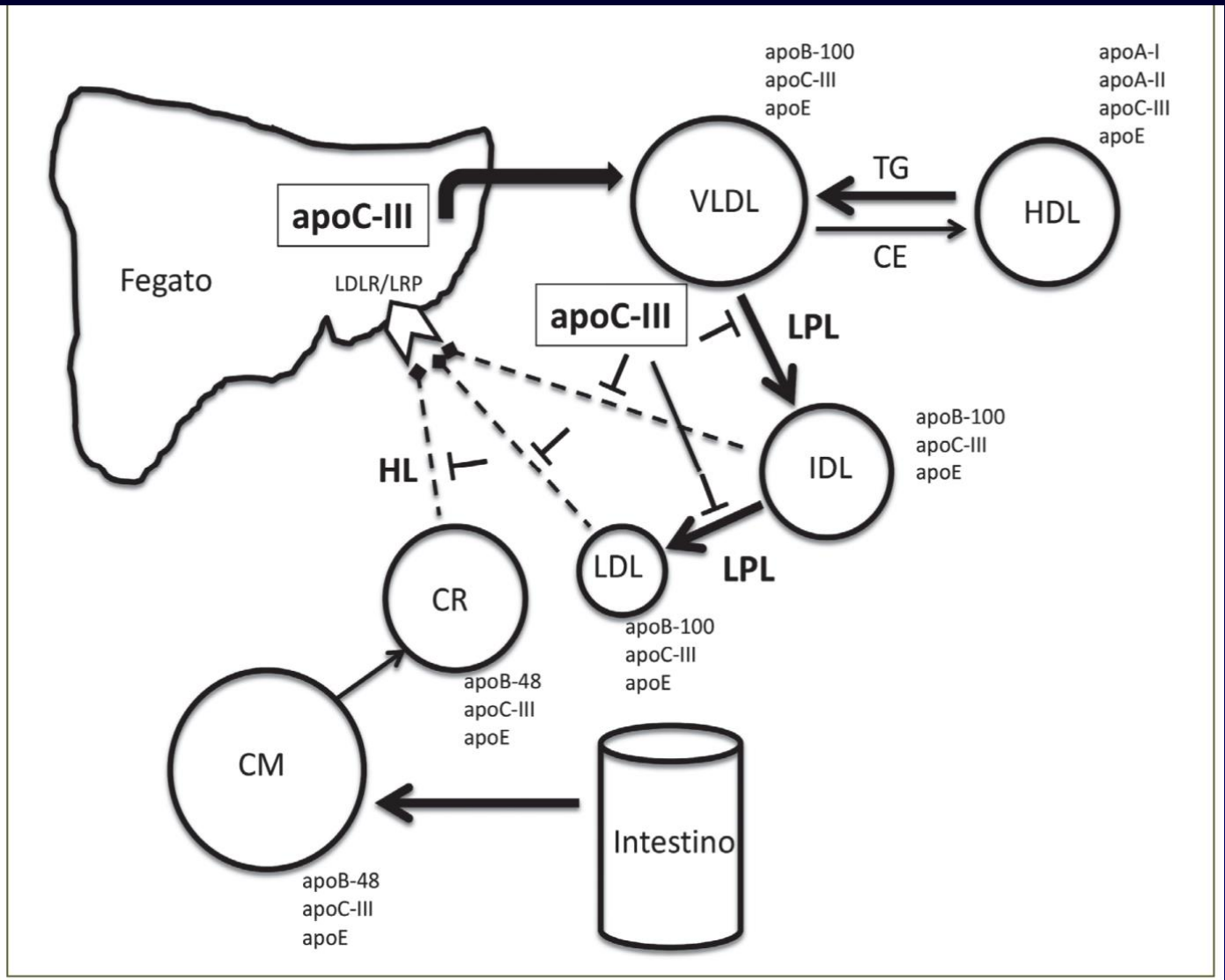


Figura 1 - Ruolo dell'apoC-III nel metabolismo delle lipoproteine. Nel fegato l'apoC-III promuove la lipidizzazione dell'apoB-100 nelle fasi tardive della formazione delle VLDL. Nel compartimento vascolare l'apoC-III inibisce l'attività dell'enzima Lipasi Lipoproteica (LPL). A livello della membrana plasmatica degli epatociti l'apoC-III riduce la cattura delle IDL e dei remnants dei chilomicroni (CR). Il risultato di queste molteplici azioni è l'accumulo nel plasma di lipoproteine ricche in trigliceridi.

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 2785–2796
doi:10.1093/eurheartj/ehz209

N-acetyl galactosamine-conjugated antisense drug to *APOC3* mRNA, triglycerides and atherogenic lipoprotein levels

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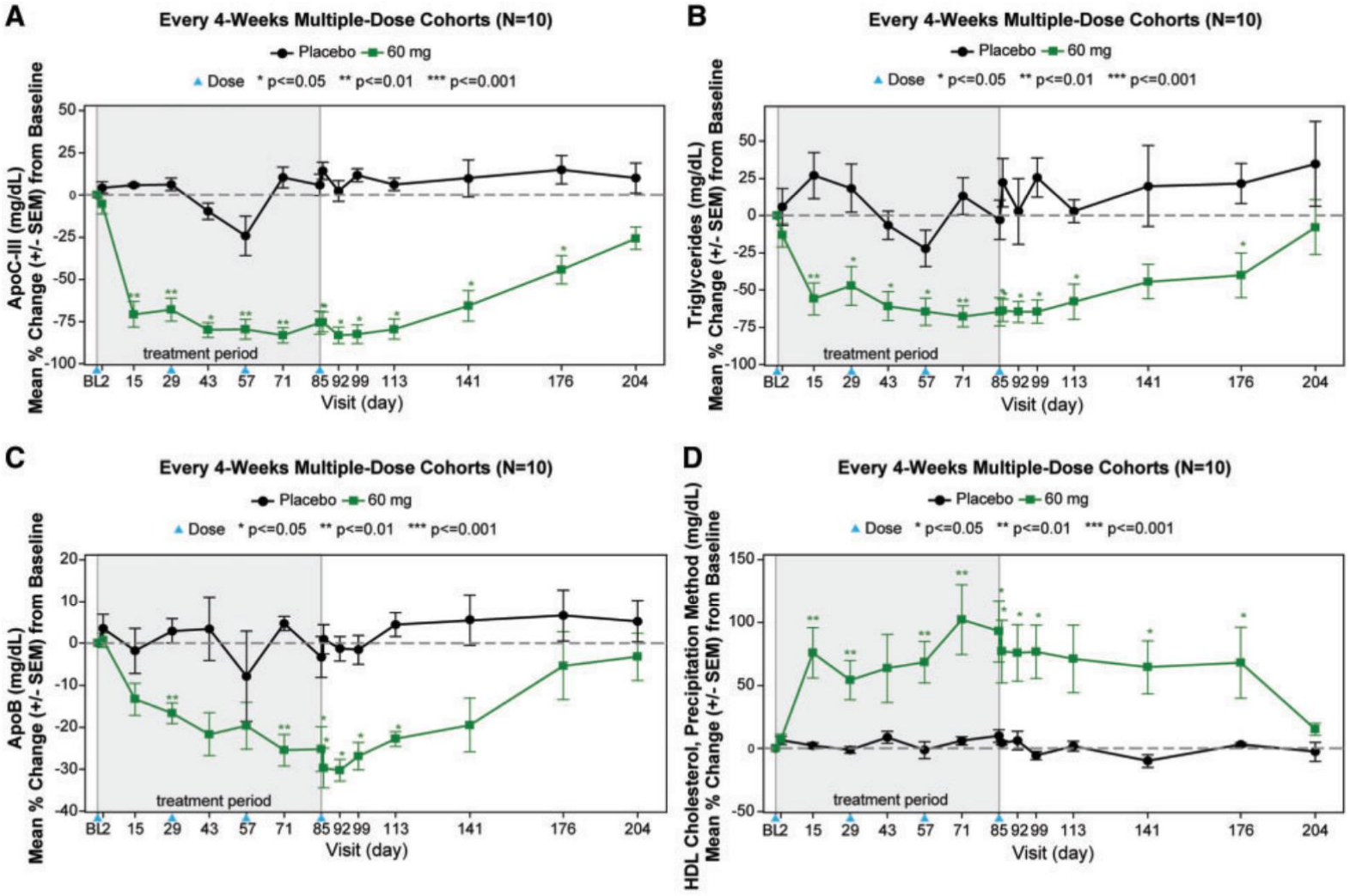

Antisense oligonucleotide approaches to lower triglycerides.

Drug	study	Efficacy	
Volanesorsen (binds the *APOC3* mRNA)	Phase 2[95]: Patients with fasting TG 350 −2000 mg/dL	As a monotherapy (*) **apoC-III** −40% (100 mg), −63.8% (200 mg) and −79.6% (300 mg)	As a monotherapy (*) **TG**: -31.3% (100 mg), −57.7% (200 mg) and −70.9% (300 mg) **HDL-C:** 26.6%(100 mg), +36.2% (200 mg) and +45.7% (300 mg)
		In combination with fibrates (*) **apoC-III** −60.2% (200 mg) and −70.9% (300 mg)	In combination with fibrates (*) **TG**: −51% (200 mg) and -64.0% (300 mg) **HDL-C:** 50.6%(200 mg) and +51.8% (300 mg)
	APPROACH (Phase 3) [97]: 300 mg/once weekly. Patients With FCS (n = 66) and mean fasting TG = 2209 mg/dL	**apoC-III (*)** −84% after 3 months −83% after 6 months	**TG (*)** −76.5% after 3 months −53% after 6 months −40% after 12 months
APOCIII-L_{Rx} (with GalNac modification)	Phase1/2a [103]: Healthy volunteers with TG ≥200 mg/dL	**apoC-III** (*) −4% (10 mg), −32% (30 mg), −65% (60 mg), −78% (90 mg), −91% (120 mg)	**TG(*)** −12% (10 mg), −11% (30 mg), −43% (60 mg), −68% (90 mg), and −77% (120 mg)
		multiple-dose design −65% (15 mg/weekly for six weeks) and −84% (30 mg/weekly for six weeks)	multiple-dose design −61% (15 mg/weekly for six weeks) and −71% (30 mg/weekly for six weeks)
		−83% (60 mg, every 4-week for 3 months)	−65% (60 mg, every 4-week for 3 months)
ANGPTL3-L_{Rx} (with GalNac modification)	Phase 1 [111]:Healthy volunteers (n = 32). multiple-dose design (weekly for 6 weeks)	**ANGPTL3** (*) −46.6% (10 mg), −72.5% (20 mg), −81.3% (40 mg), −84.5% (60 mg)	**TG** (*) −33.2% (10 mg), −63.1% (20 mg), −53.8% (40 mg), −50.4% (60 mg) **LDL-C** (*) −1.3% (10 mg), −4.3% (20 mg), −25.4% (40 mg), −32.9% (60 mg) **apo C-III** (*) −18.9% (10 mg), −57.8% (20 mg), −50.7% (40 mg), −58.8% (60 mg)

**vs baseline mean changes*; APOC3, apolipoprotein C3; ANGPTL3, angiopoietin-like 3; GalNac, triantennary N-acetyl galactosamine; HDL-C, high-density lipoprotein cholesterol; FCS, familial chylomicronemia syndrome; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; VLDL-C, very-low density lipoprotein cholesterol.