NEW LIPID LOWERING DRUGS

Alberico L. Catapano

Sorrento nov 2019

Prof Catapano has received honoraria, lecture fees, or research grants from:

- Sigma-Tau, Manarini, kowa, Recordati, Eli Lilly, Astrazeneca, Mediolanum, Pfizer, Merck, Sanofi, Aegerion, Amgen, Genzyme, Bayer, Sanofi and Regeneron Daiichi-Sankyo

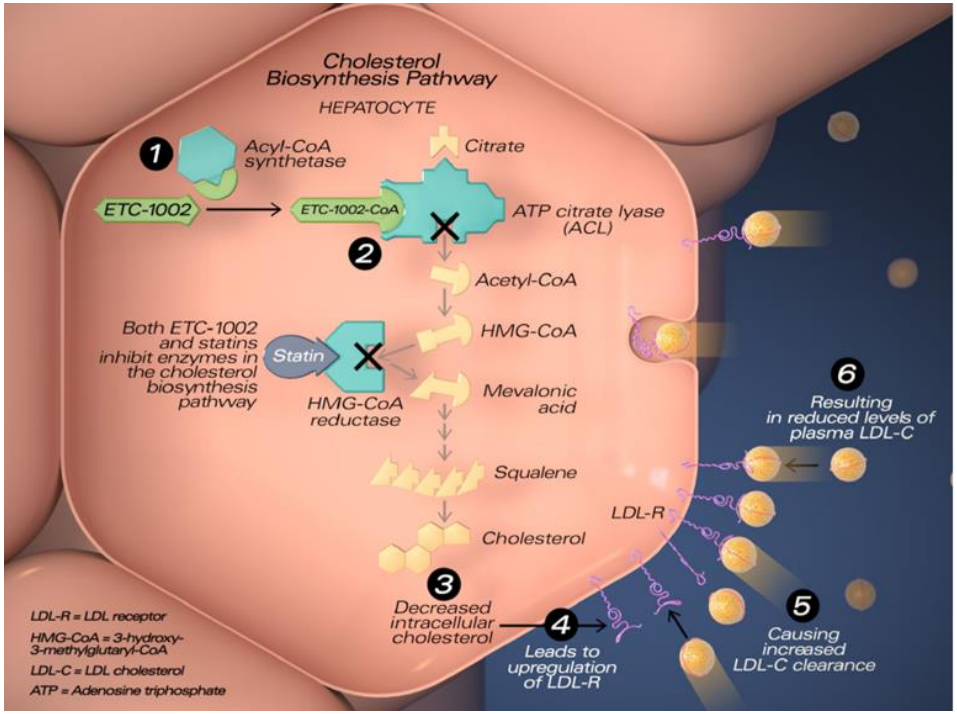
EMERGING TARGETS FOR LIPID LOWERING

- Acid Litrate Lyase (Cholesterol Synthesis)
- Lp(a)
- Plasma TG (Apo CIII, Angiopoietin 3)

EMERGING TARGETS FOR LIPID LOWERING

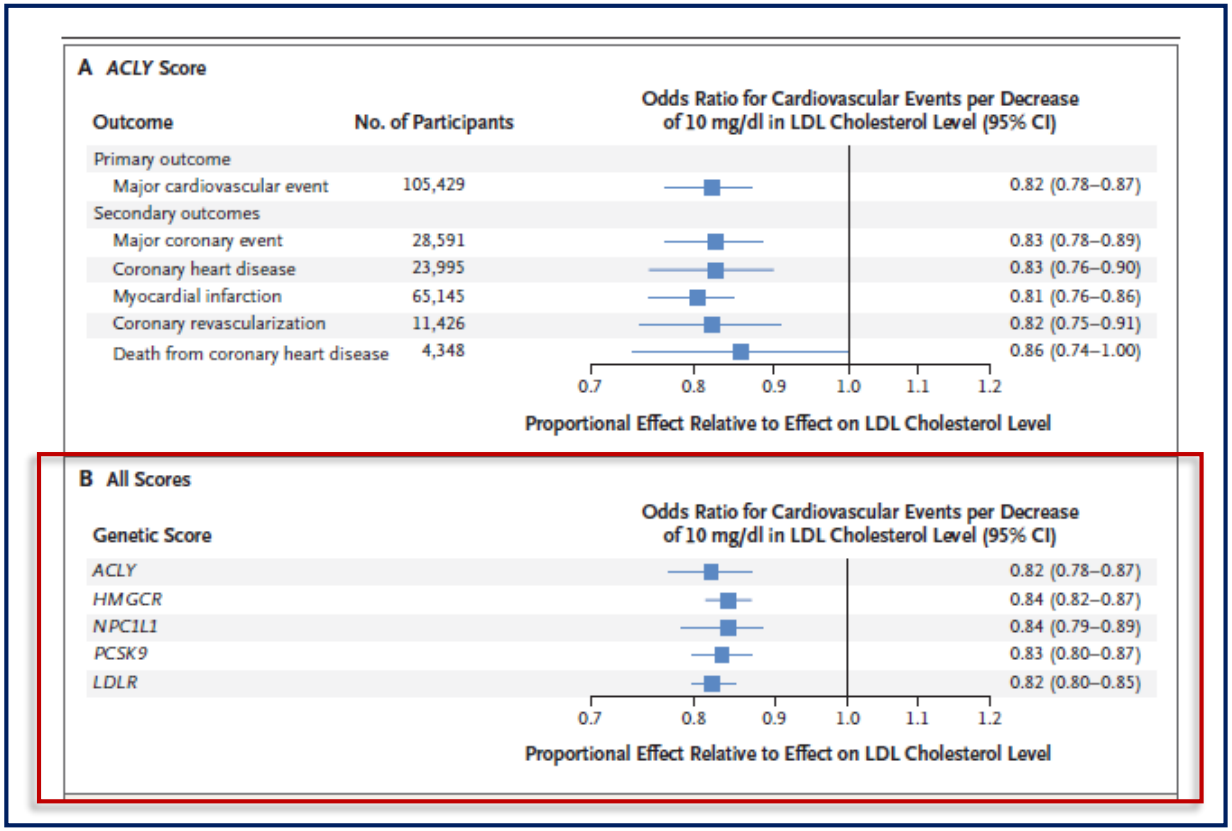
- **Acid Litrate Lyase (Cholesterol Synthesis)**
- **Lp(a)**
- **Plasma TG (Apo CIII, Angiopoietin 3)**

ATP-Citrate Lyase inhibition



Pinkosky SL, et al. Nature Communications volume 7, Article number: 13457 (2016)

ACLY genetic score and risk of CHD

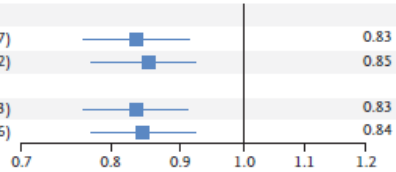


Ference BA, et al, N Engl J Med. 2019 Mar 14;380(11):1033-1042.

Comparing *ACLY, HMGCR & NPC1L1* inhibition on risk of CHD

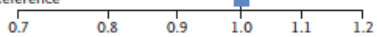
A Effect of *ACLY* Score, Stratified According to *HMGCR* and *NPC1L1* Scores

Genetic Score	No. of Participants	Change in Apolipoprotein B Level per Decrease of 10 mg/dl in LDL Cholesterol Level (95% CI)	Odds Ratio for Major Cardiovascular Events per Decrease of 10 mg/dl in LDL Cholesterol Level (95% CI)
		mg/dl per 10 mg/dl	
HMGCR score			
≤Median	245,402	−8.6 (−12.4 to −4.7)	0.83 (0.77 to 0.91)
>Median	225,076	−7.8 (−11.4 to −4.2)	0.85 (0.78 to 0.92)
NPC1L1 score			
≤Median	237,024	−8.0 (−11.6 to −4.3)	0.83 (0.77 to 0.91)
>Median	233,454	−8.4 (−12.1 to −4.6)	0.84 (0.78 to 0.92)



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



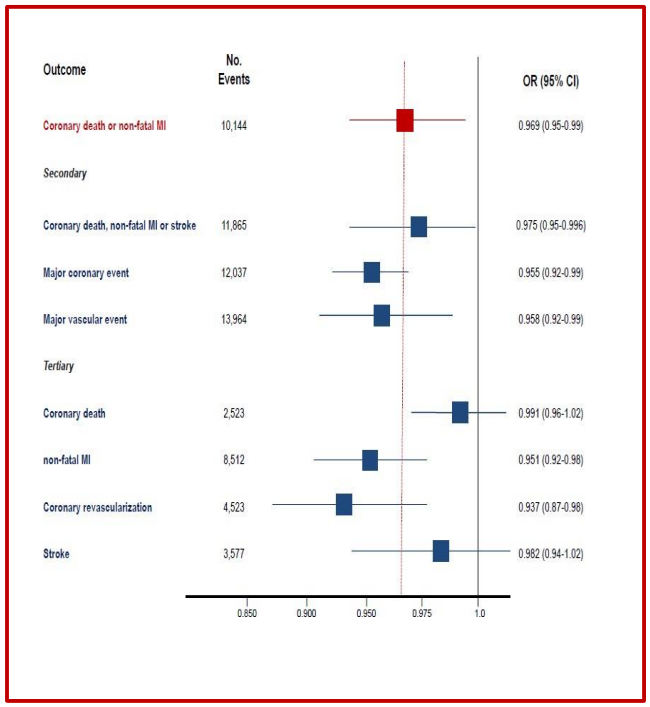
C Combined Effect of *ACLY* and *NPC1L1* Scores

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

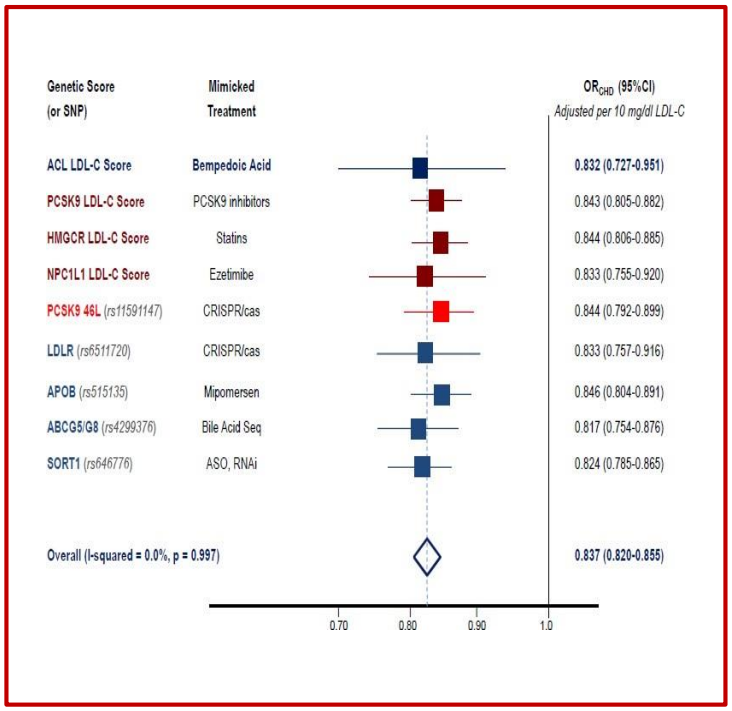
Ference BA, et al, N Engl J Med. 2019 Mar 14;380(11):1033-1042.

Genetic target validation of ACL inhibition

ACL genetic score and risk of cardiovascular events



ACL inhibition comparative effectiveness

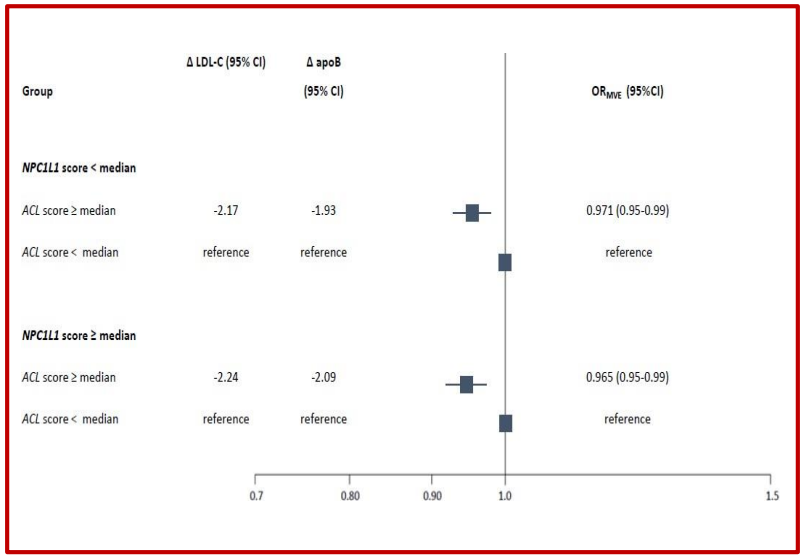


Ference BA, et al. 2017

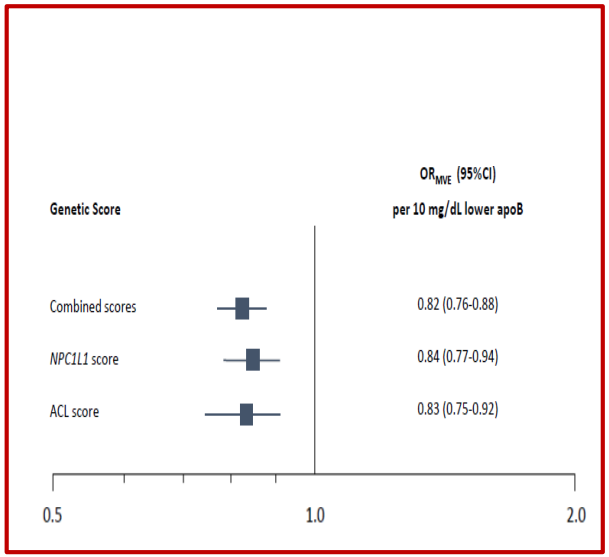
Combined effect of *ACL* and *NPC1L1* inhibition

- Up to 651,356 participants and 91,203 cardiovascular events

Effect of ACL by NPC1L1 inhibition

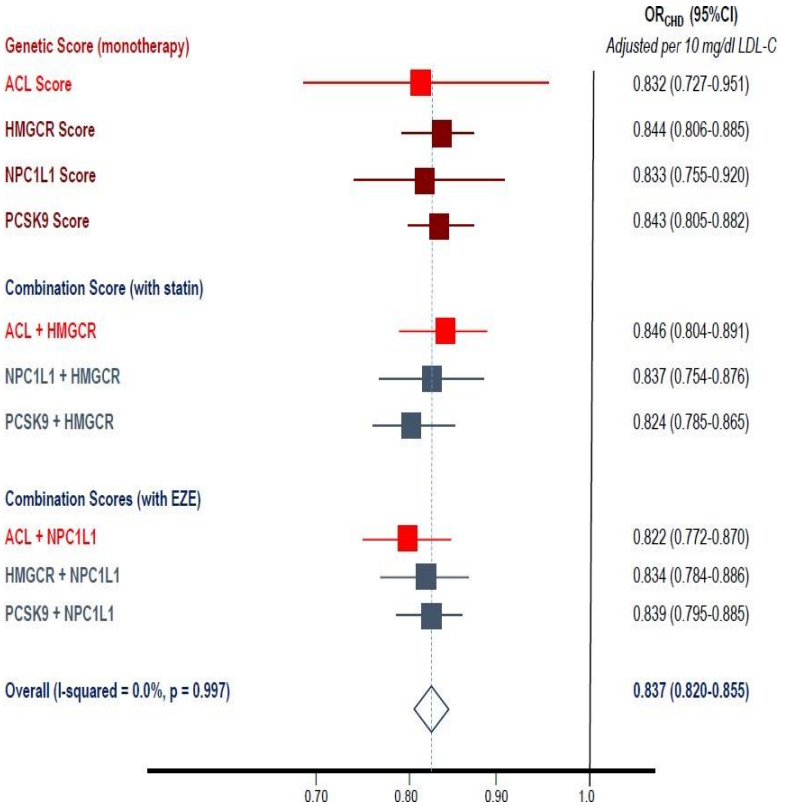


Effect per 10 mg/dl lower LDL-C



Ference BA, et al. 2017

Anticipated clinical effectiveness of *ACL* inhibition therapies



Ference BA, et al. 2017

Long-term Safety, Tolerability, and Efficacy of Bempedoic Acid vs Placebo in High Cardiovascular Risk Patients with LDL-C Above 1.8 mmol/L on Maximally Tolerated Statin Therapy (CLEAR Harmony)

Kausik K Ray, Harold E Bays, Alberico L Catapano, Narendra Lalwani, LeAnne T Bloedon, Lulu Ren Sterling, Christie M Ballantyne
on behalf of the CLEAR Harmony Steering Committee:

Christie M Ballantyne, Maciej Banach, Harold E Bays, Alberico L Catapano, Bart Duell, William Sasiela, Anne Goldberg, Antonio Gotto, Ulrich Laufs, Larry Leiter, John Mancini, Pamela Morris, Kausik K Ray, Erik Stroes

ESC Congress
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CLEAR Harmony: Study Design

- Aim: Assess long-term overall safety and efficacy of BA in patients receiving maximally tolerated statin therapy
- Methods
  - Phase 3, double-blind, placebo-controlled, parallel-group study
  - Patients randomized 2:1 to treatment with BA 180 mg or placebo OD for 52 weeks
  - Key inclusion criteria
    - Pre-existing ASCVD and/or HeFH
    - Baseline LDL-C ≥ 1.8 mmol/L (70 mg/dL) while receiving maximally tolerated statin therapy
- Endpoints
  - Primary endpoint was safety
    - *P* values for safety endpoints were calculated *post hoc* and without adjustment for multiplicity
  - Principle efficacy endpoint: percent change from baseline to week 12 in LDL-C
  - Key secondary endpoints: percent change from baseline to week 24 in LDL-C, and to week 12 in non–HDL-C, total cholesterol, apoB, and hsCRP

apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; HeFH, heterozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol; OD, once daily.

CLEAR Harmony: Baseline Characteristics

Characteristic	Placebo (n=742)	BA (n=1488)
Age, years*	66.8 (8.6)	65.8 (9.1)
Male sex, %	71.3	73.9
CV risk factor, %		
Pre-existing ASCVD	98.0	97.4
HeFH	3.1	3.8
Diabetes	28.6	28.6
Hypertension	80.1	78.9
Concomitant LMT, %		
Statin	100	99.8
Ezetimibe	7.5	7.8
Fibrate	3.5	3.6
None	0	0.1

Characteristic	Placebo (n=742)	BA (n=1488)
Statin intensity, %		
Low	6.5	6.7
Moderate	43.7	43.4
High	49.9	49.9
Baseline lipids, mmol/L*		
Total cholesterol	4.63 (0.92)	4.66 (0.91)
LDL-C	2.65 (0.78)	2.68 (0.75)
Non–HDL-C	3.35 (0.88)	3.39 (0.87)
HDL-C	1.28 (0.30)	1.26 (0.31)
ApoB, mg/dL*	86.8 (21.8)	88.5 (21.6)
hsCRP, mg/dL*	1.51 (0.79–3.33)	1.49 (0.74–3.28)

*Data are means (standard deviations), except high-sensitivity C-reactive protein (hsCRP) values, which are medians (interquartile ranges).
ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy.

CLEAR Harmony: Safety (Primary Endpoint)

Variable*	Patients, %		*P* value†
	Placebo (n=742)	Bempedoic Acid (n=1487)	
Any AE	78.7	78.5	NS
Serious AE	14.0	14.5	NS
AE leading to discontinuation of study drug	7.1	10.9	0.005

*Includes adverse events (AEs) occurring from the first dose through 30 days after the last dose of study drug.
†*P* values are nominal without adjustment for multiplicity and are provided for descriptive purposes only. $P \geq 0.05$ labelled as not significant (NS).

The difference in discontinuation frequency was not driven by any single system organ class or preferred term

CLEAR Harmony: SAEs by System Organ Class

Variable	Patients, %	
	Placebo (n=742)	BA (n=1487)
Cardiac disorders	5.7	5.2
Infections & infestations	1.5	2.6
Nervous system disorders	1.6	1.7
Vascular disorders	1.6	0.8
General disorders & administration site conditions	1.3	1.0
Neoplasms*	0.9	1.2
Gastrointestinal disorders	1.1	1.0
Injury, poisoning & procedural complications	0.9	1.1
Respiratory, thoracic & mediastinal disorders	0.4	0.9
Musculoskeletal & connective tissue disorders	0.7	0.8

Variable	Patients, %	
	Placebo (n=742)	BA (n=1488)
Renal & urinary disorders	0.5	0.4
Hepatobiliary disorders	0.3	0.5
Metabolism & nutrition disorders	0.5	0.3
Reproductive system & breast disorders	0.1	0.5
Blood & lymphatic system disorders	0.1	0.1
Eye disorders	0.1	0.1
Psychiatric disorders	0.1	0.1
Congenital, familial & genetic disorders	0	0.1
Endocrine disorders	0	0.1
Immune system disorders	0	0.1
Investigations	0	0.1

BA, bempedoic acid; SAE, serious adverse event. *Benign, malignant and unspecified (including cysts and polyps)

CLEAR Harmony: AEs of Special Interest

Variable*	Patients, %		*P* value†
	Placebo (n=742)	Bempedoic Acid (n=1487)	
Muscular disorders	10.1	13.1	NS
Leading to discontinuation of study drug	1.9	2.1	NS
Myalgia	6.1	6.0	NS
Muscle spasms	2.7	4.2	NS
Pain in extremity	2.2	3.4	NS
Muscular weakness	0.5	0.6	NS
New-onset or worsening diabetes	5.4	3.3	0.02
Gout	0.3	1.2	0.03
Blood creatinine increased	0.4	0.8	NS
Glomerular filtration rate decreased	0	0.5	NS
Neurocognitive disorders	0.9	0.7	NS

*Includes adverse events (AEs) occurring from the first dose through 30 days after the last dose of study drug.
†*P* values are nominal without adjustment for multiplicity and are provided for descriptive purposes only. $P \geq 0.05$ labelled as not significant (NS).

CLEAR Harmony: Laboratory Results

Variable	Placebo (n=742)	Bempedoic Acid (n=1487)	*P* value*
Patients with ALT and/or AST >3 × ULN†, %	0.1	0.5	NS
Patients with creatine kinase >5 × ULN†, %	0.1	0.5	NS
Change from baseline in uric acid, mg/dL‡	–0.06 (0.87)	0.73 (1.11)	< .001

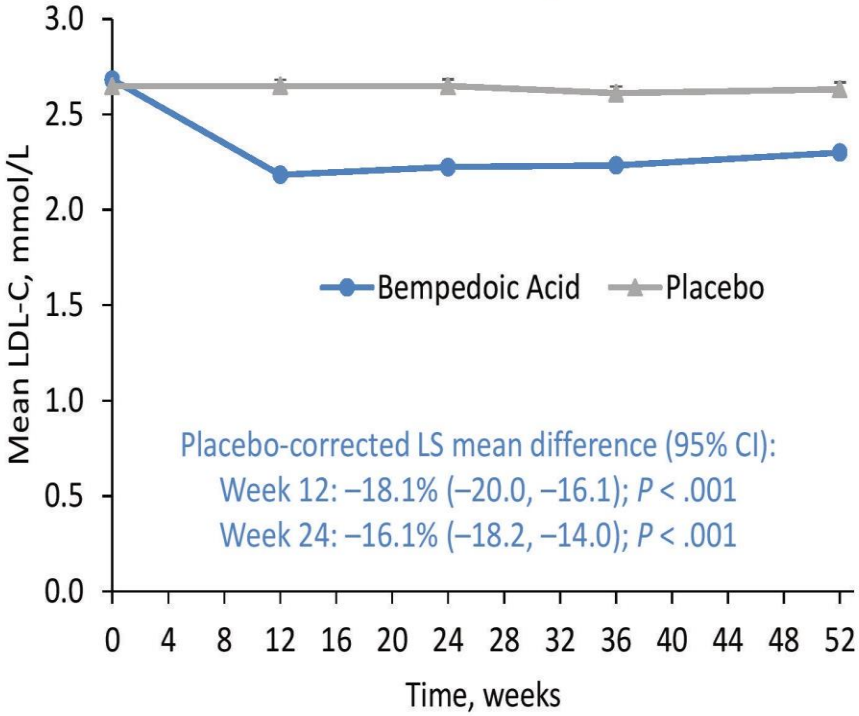
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
**P* values are nominal without adjustment for multiplicity and are provided for descriptive purposes only. $P \geq 0.05$ labelled as not significant (NS).
†Includes elevations of greater than 3 (aminotransferase) or 5 (creatine kinase) times the upper limit of normal (ULN) that have been repeated and confirmed.
‡Data are mean changes (standard deviations) from baseline to week 52 for 680 patients in the placebo group and 1358 patients in the bempedoic acid group.

CLEAR Harmony: AEs by Statin Intensity

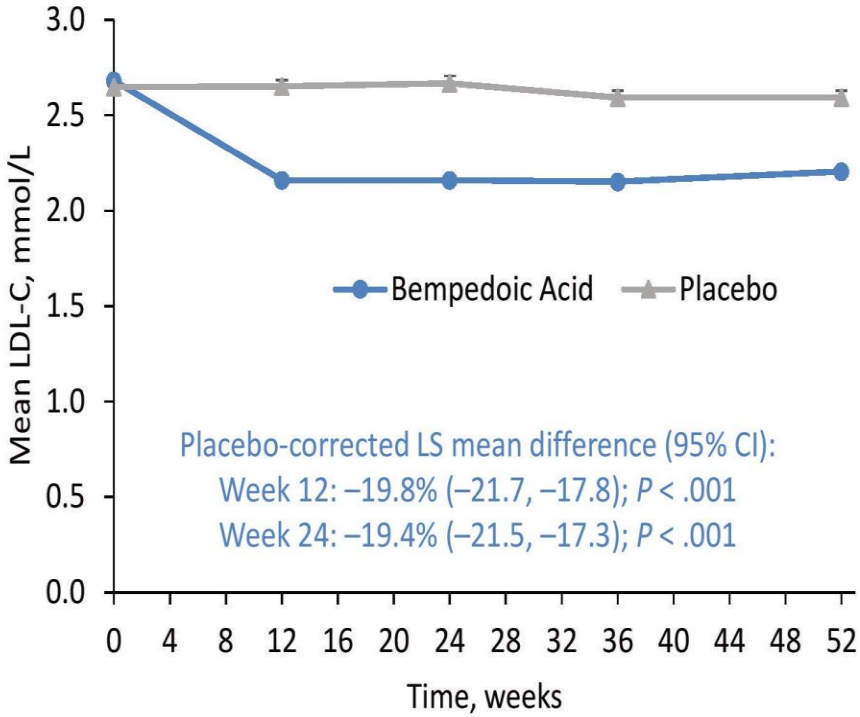
	Patients, %					
	Low-intensity Statin		Moderate-intensity Statin		High-intensity Statin	
Variable	Placebo (n=47)	BA (n=99)	Placebo (n=327)	BA (n=652)	Placebo (n=368)	BA (n=736)
Any AE	78.7	80.8	79.2	78.7	78.3	78.0
Serious AE	10.6	15.2	14.1	13.7	14.4	15.2
Muscle-related AE*	17.0	22.2	11.0	12.9	8.4	12.1
Common AEs†						
Nasopharyngitis	10.6	8.1	12.8	9.0	10.9	10.7
Myalgia	12.8	11.1	6.7	6.6	4.6	4.8
UTI	8.5	11.1	6.4	4.1	6.0	4.5
Pain in extremity	2.1	8.1	2.4	3.5	1.9	2.6
Dizziness	6.4	5.1	4.9	4.6	3.3	4.1
Arthralgia	2.1	5.1	7.0‡	3.8‡	5.4	4.8
URTI	2.1	2.0	2.8	3.1	5.7	6.8
Fatigue	6.4	5.1	5.2‡	2.6‡	1.4	2.2

AE, adverse event; BA, bempedoic acid; URTI, upper respiratory tract infection; UTI, urinary tract infection.
*Muscle-related adverse events were predefined as muscle spasms, myalgia, muscular weakness, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinemia, myoglinuria, myopathy, myopathy toxic, muscle necrosis, necrotizing myositis, pain in extremity, and rhabdomyolysis.
†Treatment-emergent AEs reported by at least 6% of patients in any treatment and statin intensity subgroup.
‡P=0.04 for the comparison of event rates in the bempedoic acid and placebo groups.

CLEAR Harmony: Percent Change in LDL-C



BA, n	1488	1424	1397	1375	1364
Placebo, n	742	725	707	692	685

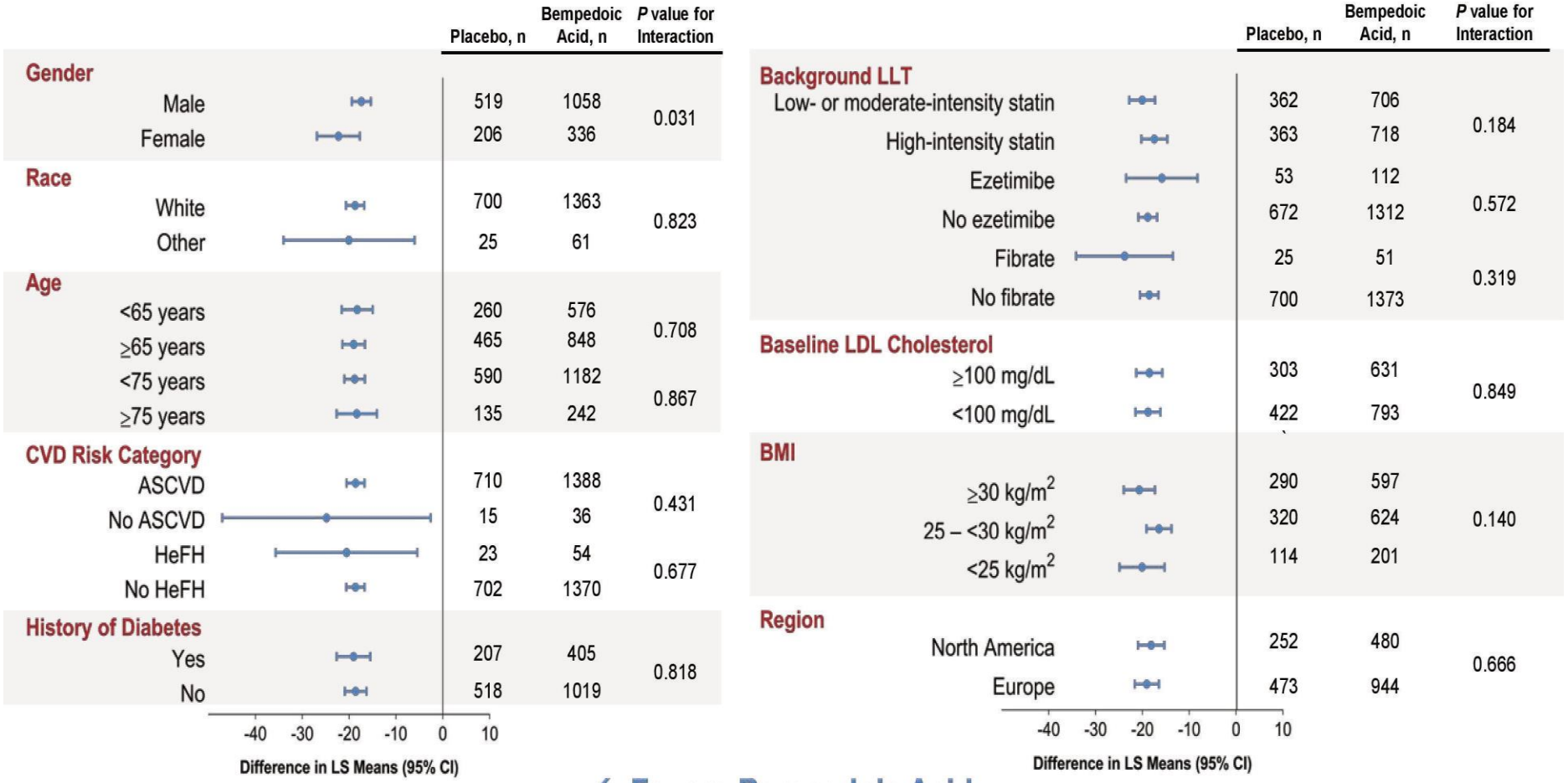


BA, n	1487	1335	1213	1172	1121
Placebo, n	742	695	643	617	589

BA, bempedoic acid; CI, confidence interval; ITT, intention to treat; LDL-C, low-density lipoprotein cholesterol. Data are least-squares (LS) means ± standard errors.

CLEAR Harmony: LDL-C Reduction by Subgroup

Percent Change from Baseline to Week 12



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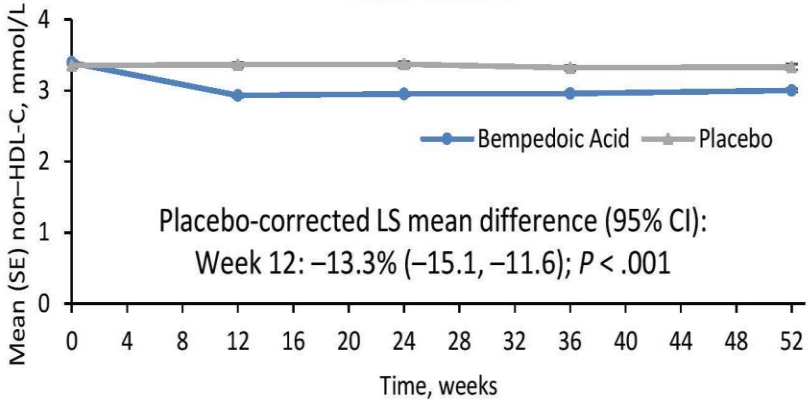
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

CLEAR Harmony: Secondary Efficacy Parameters



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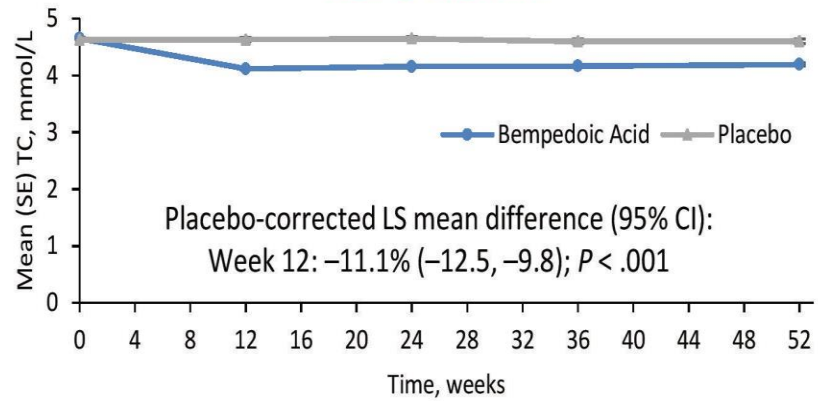

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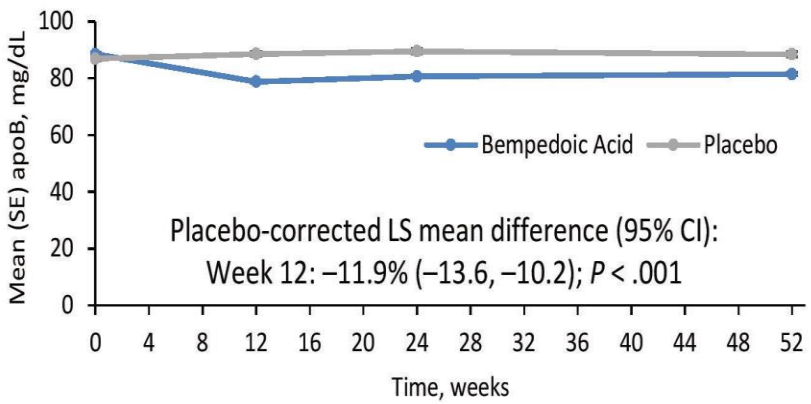
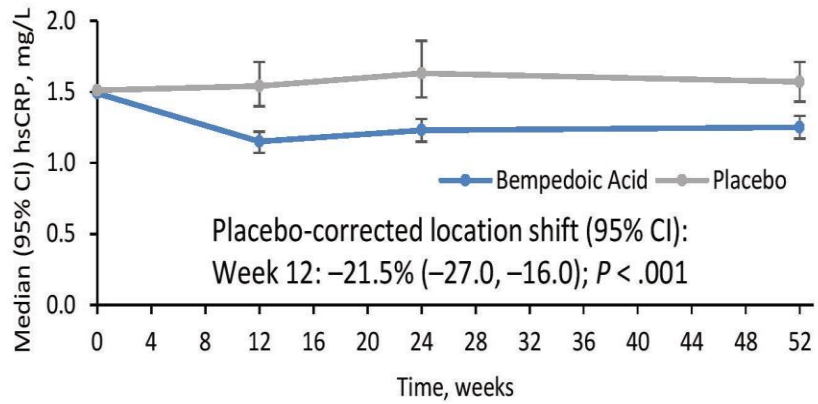


BA, n	1485	1418	1384		1345
Placebo, n	736	723	704		680



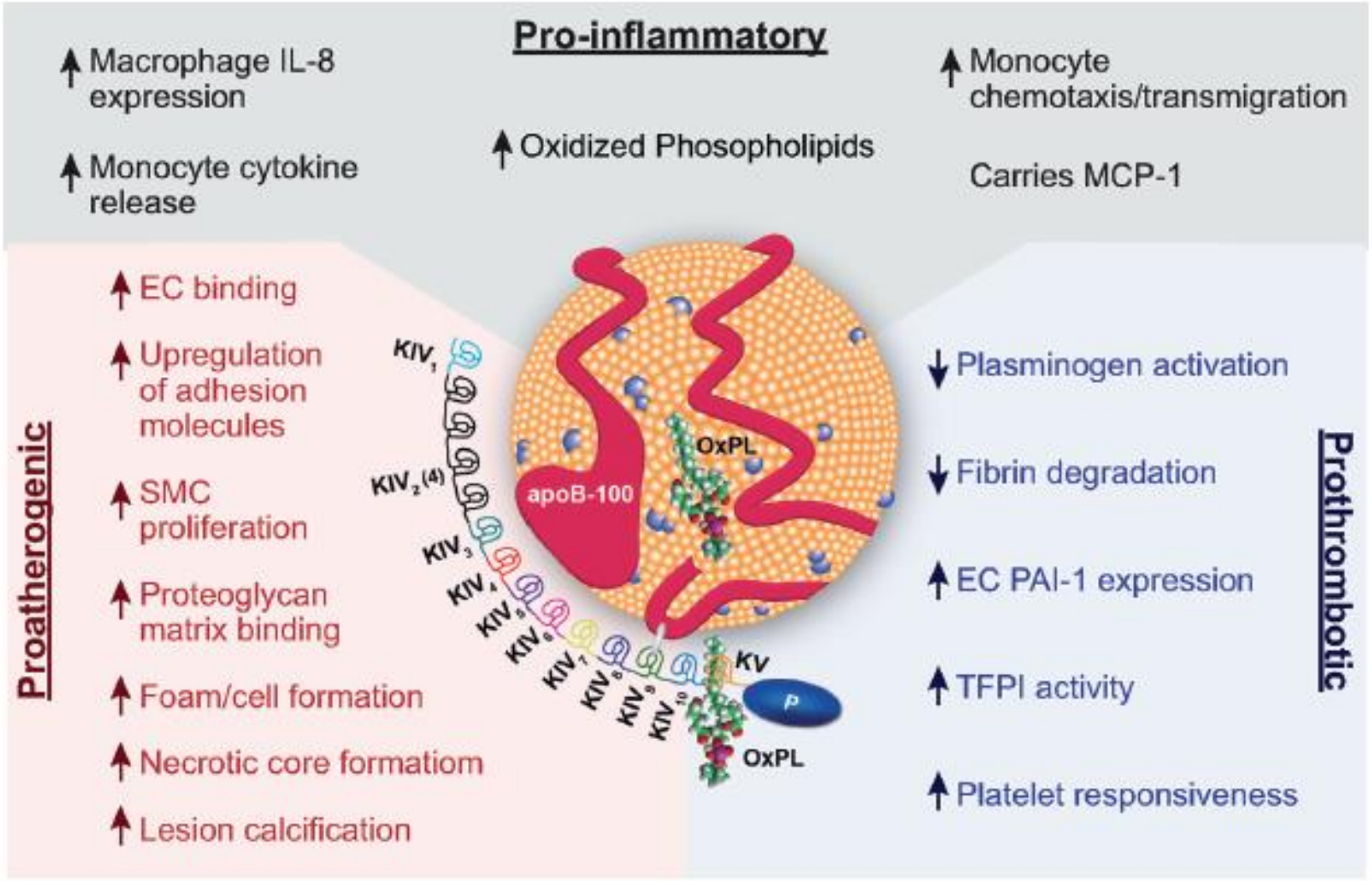
BA, n	1487	1422	1393		1359
Placebo, n	739	726	708		683

apoB, apolipoprotein B; BA, bempedoic acid; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; LS, least-squares; non–HDL-C, non–high-density lipoprotein cholesterol; TC, total cholesterol.

EMERGING TARGETS FOR LIPID LOWERING

- Acid Litrate Lyase (Cholesterol Synthesis)
- **Lp(a)**
- Plasma TG (Apo CIII, Angiopoietin 3)

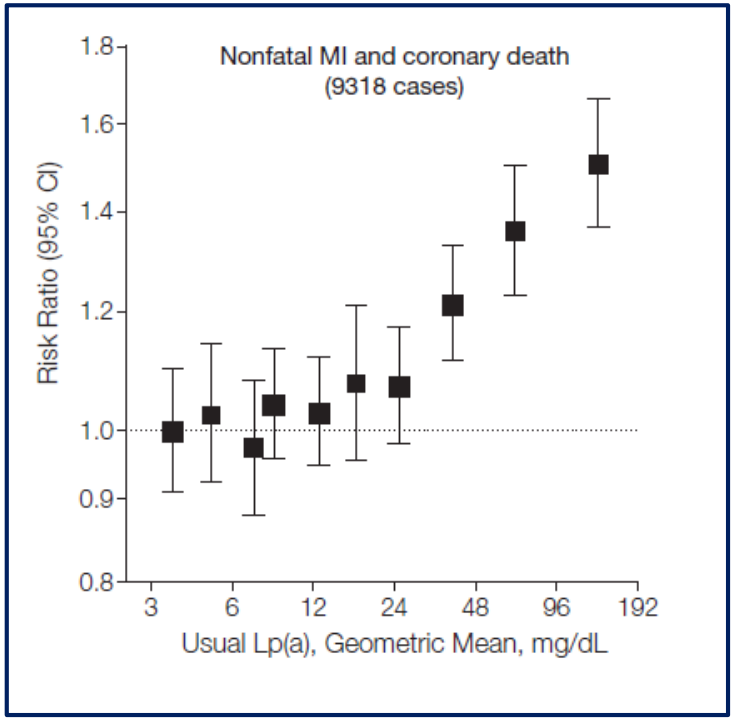
For equal particle concentration, Lp(a) has to be at least as atherothrombotic than LDL



Tsimikas JACC 2017;69:692-711

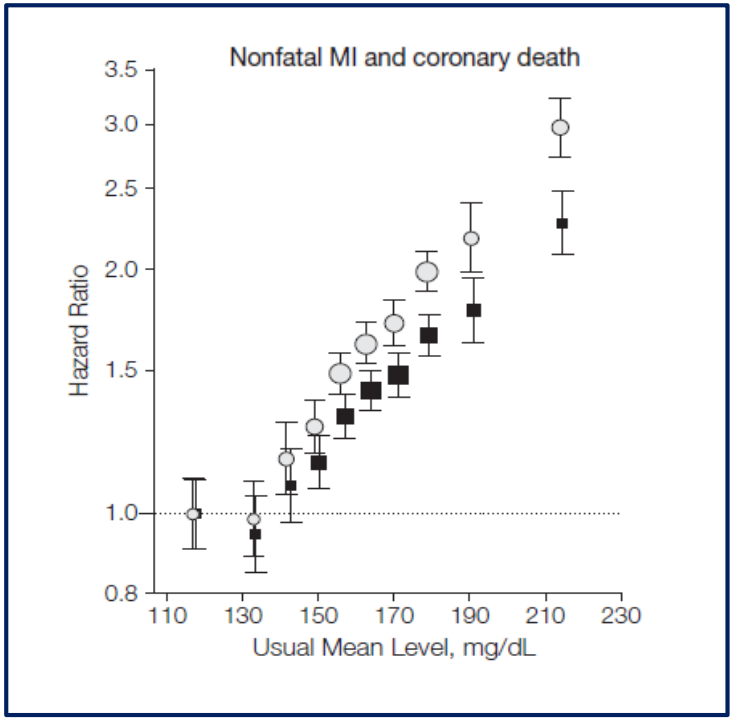
Observational evidence Lp(a) is a weak risk factor for CVD

Lp(a) OR per 1-ln(SD): 1.16



Emerging Risk Factors Collaboration. JAMA. 2009; 302:412-23.

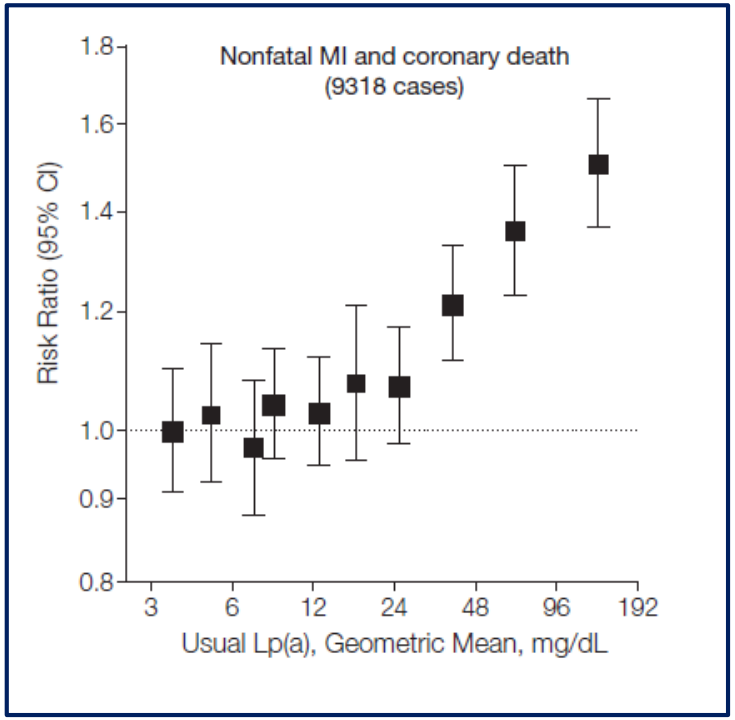
LDL-C OR per 1-SD (33 mg/dl): 1.39



Emerging Risk Factors Collaboration. JAMA. 2009;302:1993-2000

Effect of Lp(a) *compared to effect of LDL-C* on risk of CVD

Lp(a) OR per 1-ln(SD): 1.16



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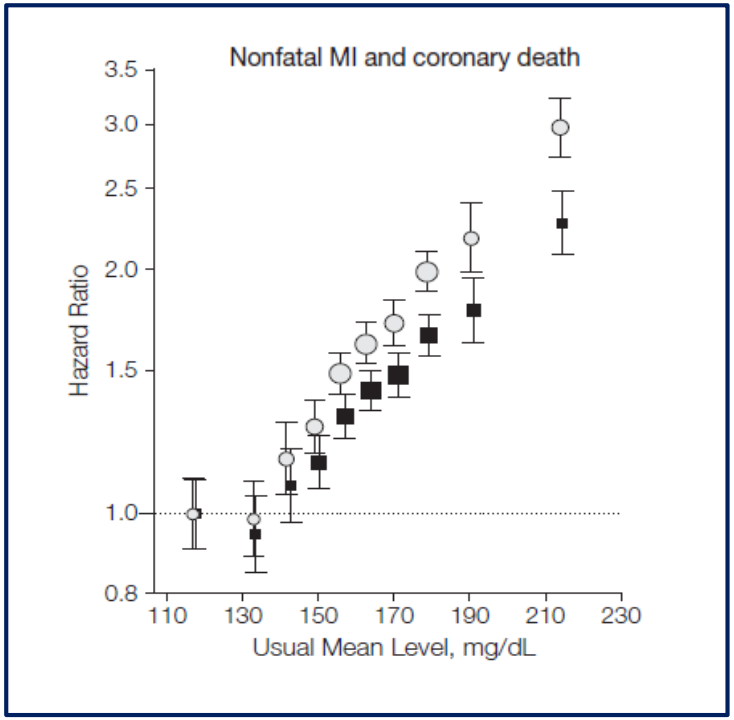

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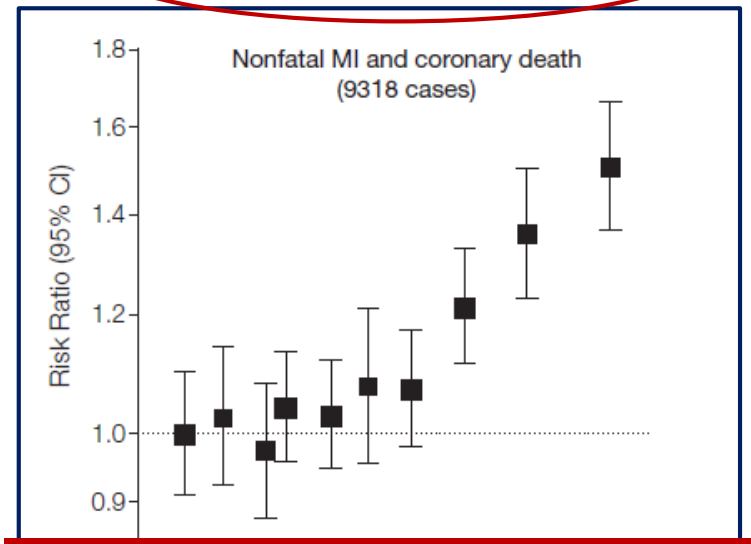

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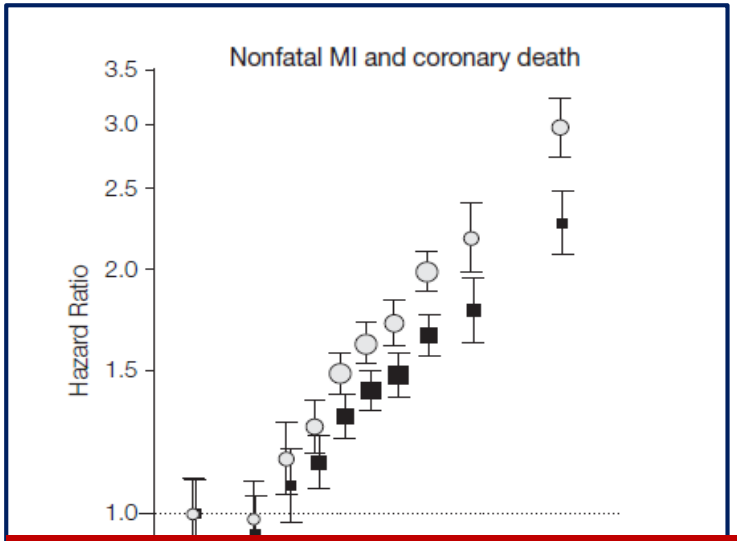


Ln-SD = 1.1 $e^{1.1}$ = 3-fold increase

Tripling in Lp(a)

16% increased risk

Mean population LDL-c 3.5 mmol/L

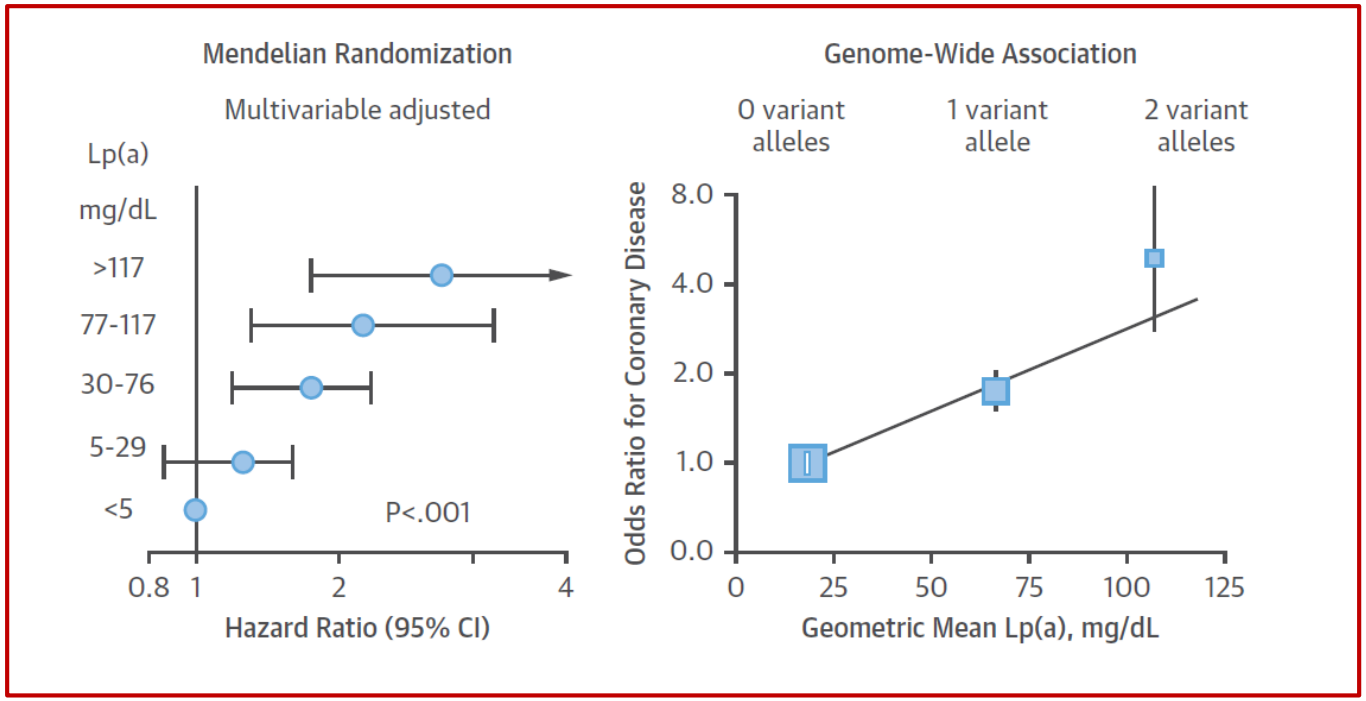
Tripling in LDL-c

386% increased risk

23.

2000

Mendelian randomization: *causal effect of Lp(a)?*

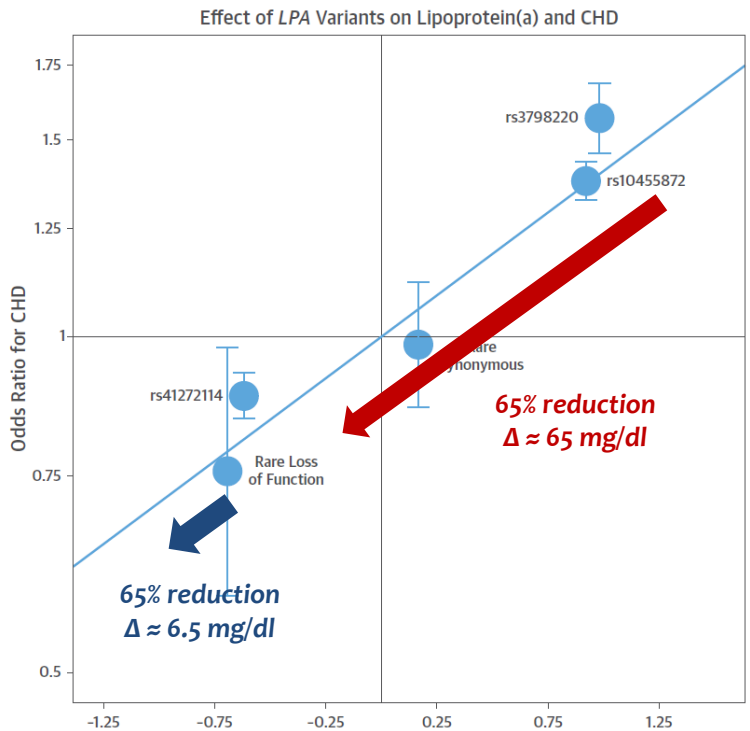


Kamstrup PR, et al. JAMA. 2009;301(22):2331-2339

Clarke R, et al. N Engl J Med 2009;361:2518-28

Beyond causality: estimating the clinical relevance of Lp(a)

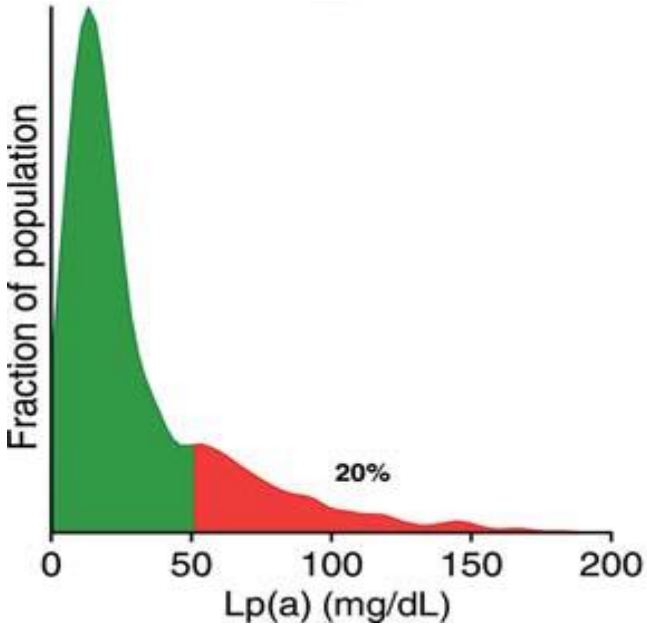
linear association with log-Lp(a)?
not biologically plausible



Conner AE, et al. JACC. 2016; 68:2761–72..

Highly skewed distribution

Median: 12.8 mg/dL



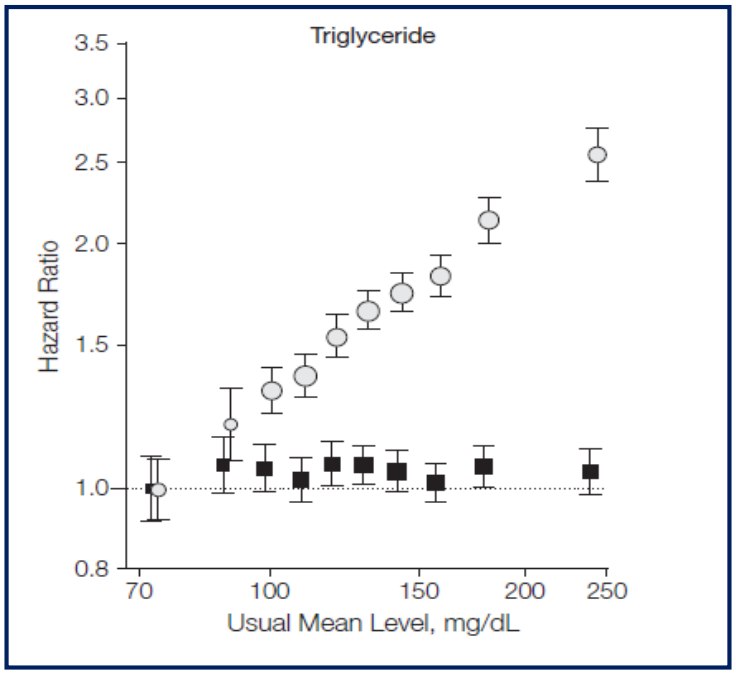
Nordestgaard BG, et al. Eur Heart J. 2010;31:2844-53

EMERGING TARGETS FOR LIPID LOWERING

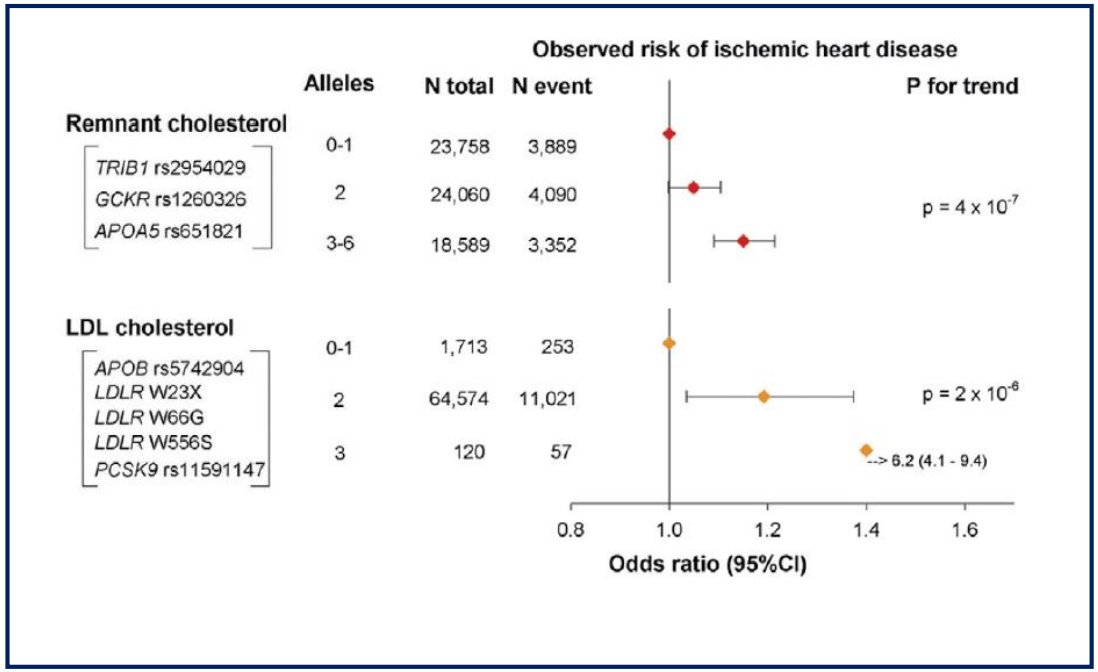
- Acid Litrate Lyase (Cholesterol Synthesis)
- Lp(a)
- Plasma TG (Apo CIII, Angiopoietin 3)

Triglycerides and risk of CHD

Observational epidemiology



Mendelian Randomization

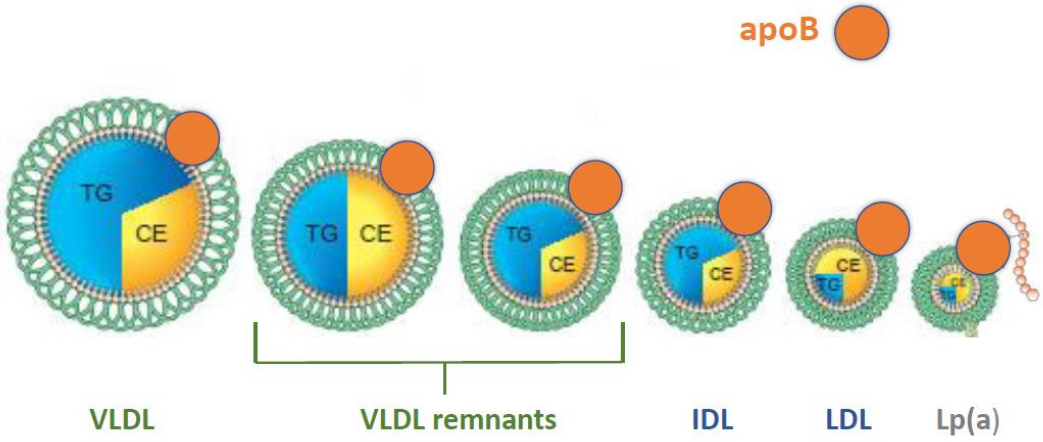


Emerging Risk Factors Collaboration. JAMA. 2009;302(18):1993-2000.

Varbo A, etal. JACC 2013;61:427–36.

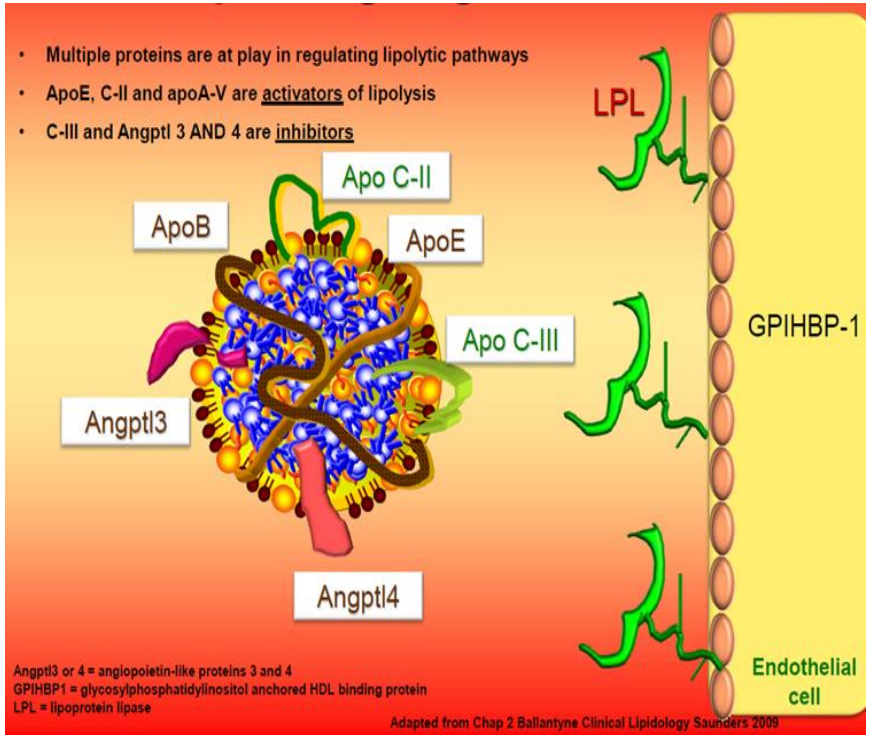
Directly comparing effect of lowering triglycerides and LDL-C on CHD

- Triglyceride-rich VLDL and their remnants particles, and LDL particles each have one apoB100
- Therefore, the effect of lowering triglycerides on the risk of cardiovascular events can be directly compared with the effect of lowering LDL-C by comparing their effects per unit change in apoB



Ference BA, et al. JAMA 2019;321(4):1-11

Lowering triglycerides: genetically validated LPL pathway targets



ORIGINAL ARTICLE

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

F.E. Dewey, V. Gusarova, R.L. Dunbar, C. O'Dushlaine, C. Schurmann, O. Gottesman, S. McCarthy, C.V. Van Hout, S. Bruse, H.M. Dansky, J.B. Leader, M.F. Murray, M.D. Ritchie, H.L. Kirchner, L. Habegger, A. Lopez, J. Penn, A. Zhao, W. Shao, N. Stahl, A.J. Murphy, S. Hamon, A. Bouzelmat, R. Zhang, B. Shumel, R. Pordy, D. Gipe, G.A. Herman, W.H.H. Sheu, I-T. Lee, K.-W. Liang, X. Guo, J.I. Rotter, Y.-D.I. Chen,* W.E. Kraus, S.H. Shah, S. Damrauer, A. Small, D.J. Rader, A.B. Wulff, B.G. Nordestgaard, A. Tybjærg-Hansen, A.M. van den Hoek, H.M.G. Princen, D.H. Ledbetter, D.J. Carey,* J.D. Overton, J.G. Reid, W.J. Sasiela, P. Banerjee, A.R. Shuldiner, I.B. Borecki, T.M. Teslovich, G.D. Yancopoulos, S.J. Mellis, J. Gromada, and A. Baras

ORIGINAL ARTICLE

Inactivating Variants in *ANGPTL4* and Risk of Coronary Artery Disease

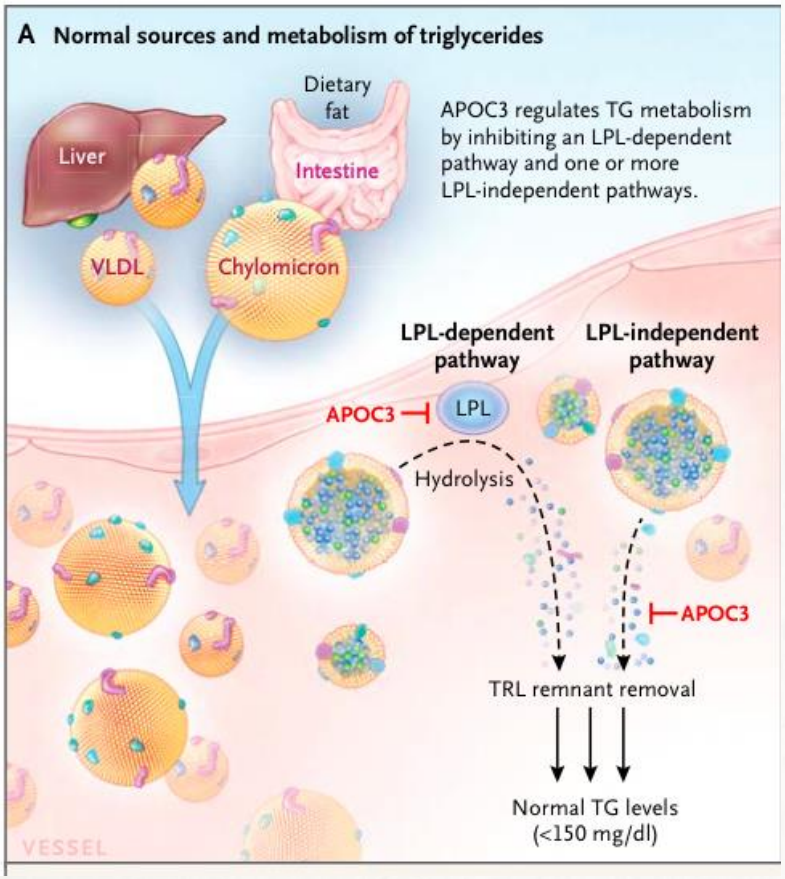
Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, Ph.D., H. Lester Kirchner, Ph.D., David H. Ledbetter, Ph.D., John Penn, M.S., Alexander Lopez, M.S., Ingrid B. Borecki, Ph.D., John D. Overton, Ph.D., Jeffrey G. Reid, Ph.D., David J. Carey, Ph.D., Andrew J. Murphy, Ph.D., George D. Yancopoulos, M.D., Ph.D., Aris Baras, M.D., Jesper Gromada, Ph.D., D.M.Sc., and Alan R. Shuldiner, M.D.

ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

Apolipoprotein C-III

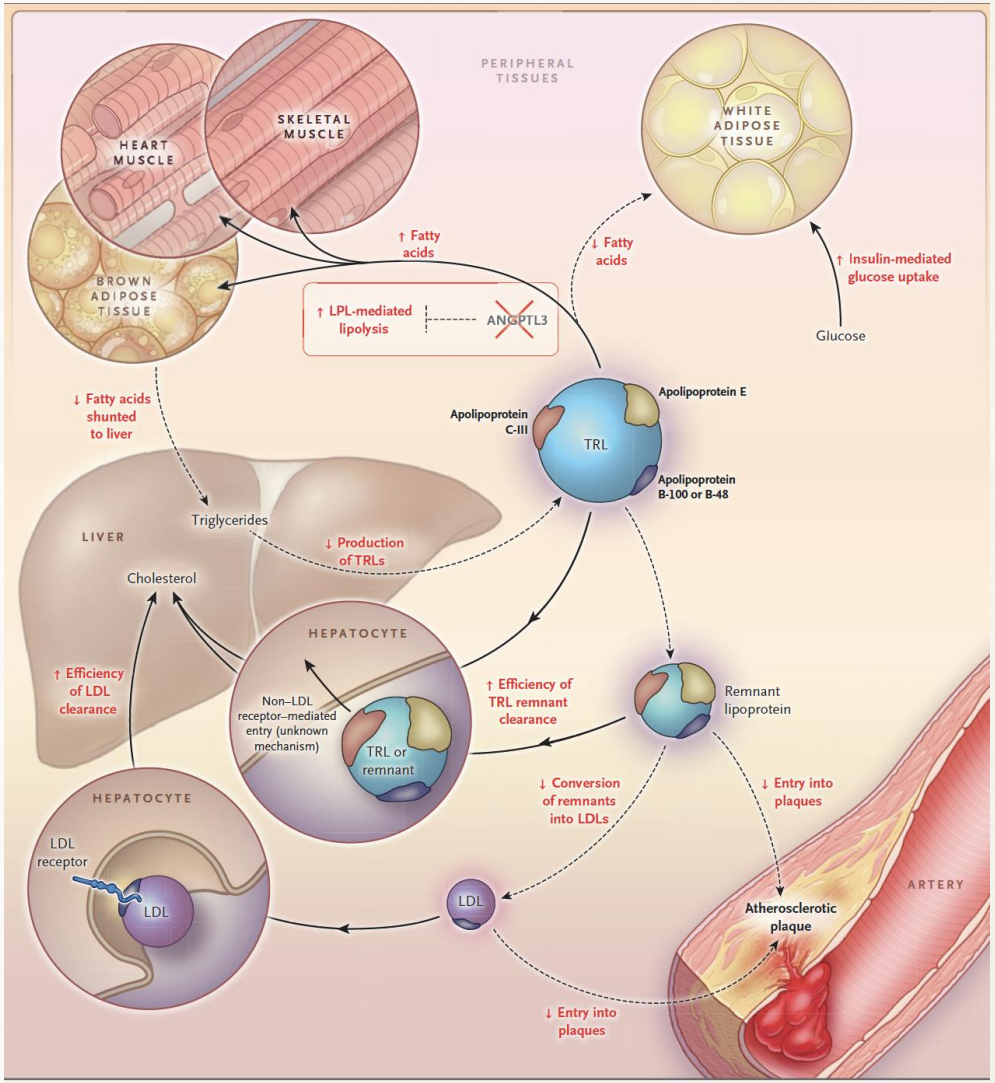


Gaudet, N Engl J Med 2014

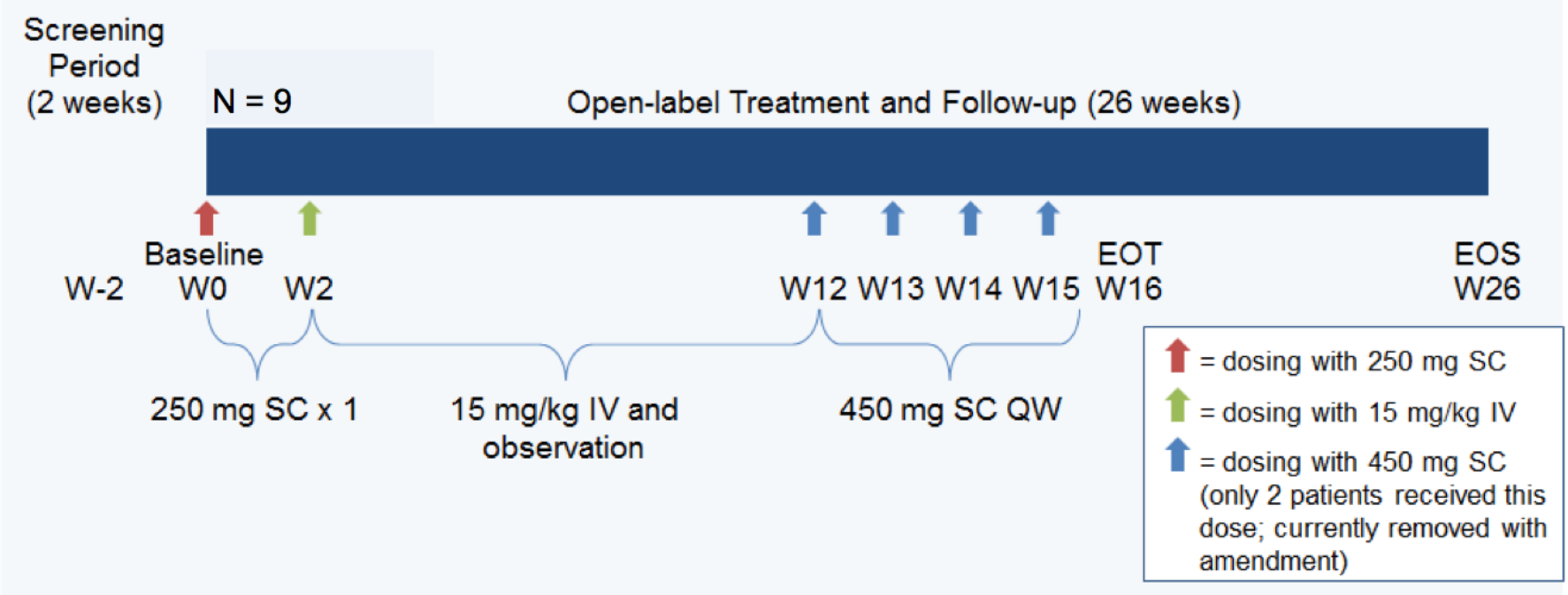
- Inhibits LPL
- Inhibits hepatic lipase
- Inhibits hepatic remnant uptake

ANGPTL3-i lowers all lipoprotein fractions

- Plasma compartment:
  - Increased LPL activity
  - Increased VLDL-conversion
  - Increased (partially LDLr-independent) LDL clearance
- Hepatic
  - Increased remnant clearance
  - Increased LDL clearance
  - Decreased VLDL production (→ less FFA flux)
  - Increased HDL clearance (EL)
- Fat tissue:
  - Increased insulin sensitivity
  - Decreased lipolysis
- Intestines
  - Reduced chylomicron formation



Effect of ANGPTL3 Blockade with Evinacumab (ANGPTL3 mab) in HoFH: Phase 2 Study Design



Current LLT was maintained from at least 4 weeks before screening, and through the 26-week treatment and observation period

LDL-C and lipids/Lipoproteins at Week 4 (N = 9)

Variable	Mean±SD % change	Mean±SD or median (Q1, Q3) absolute change
LDL-C (mmol/L)	–49 ± 23	–4.1 ± 2.3
Non-HDL cholesterol (mmol/L)	–49 ± 22	–4.3 ± 2.4
Apolipoprotein A1 (g/L)	–39 ± 9	–0.4 ± 0.2
Apolipoprotein B(g/L)	–46 ± 18	–1.0 ± 0.6
Total cholesterol (mmol/L)	–47 ± 19	–4.7 ± 2.3
Lipoprotein(a) (nmol/L)	−19 (−27, 1)	−27 (−29, 1)
HDL-cholesterol (mmol/L)	−36 ± 16	−0.4 ± 0.3
Triglycerides (mmol/L)	−47 (−57, −38)	−0.3 (−0.2, −0.6)

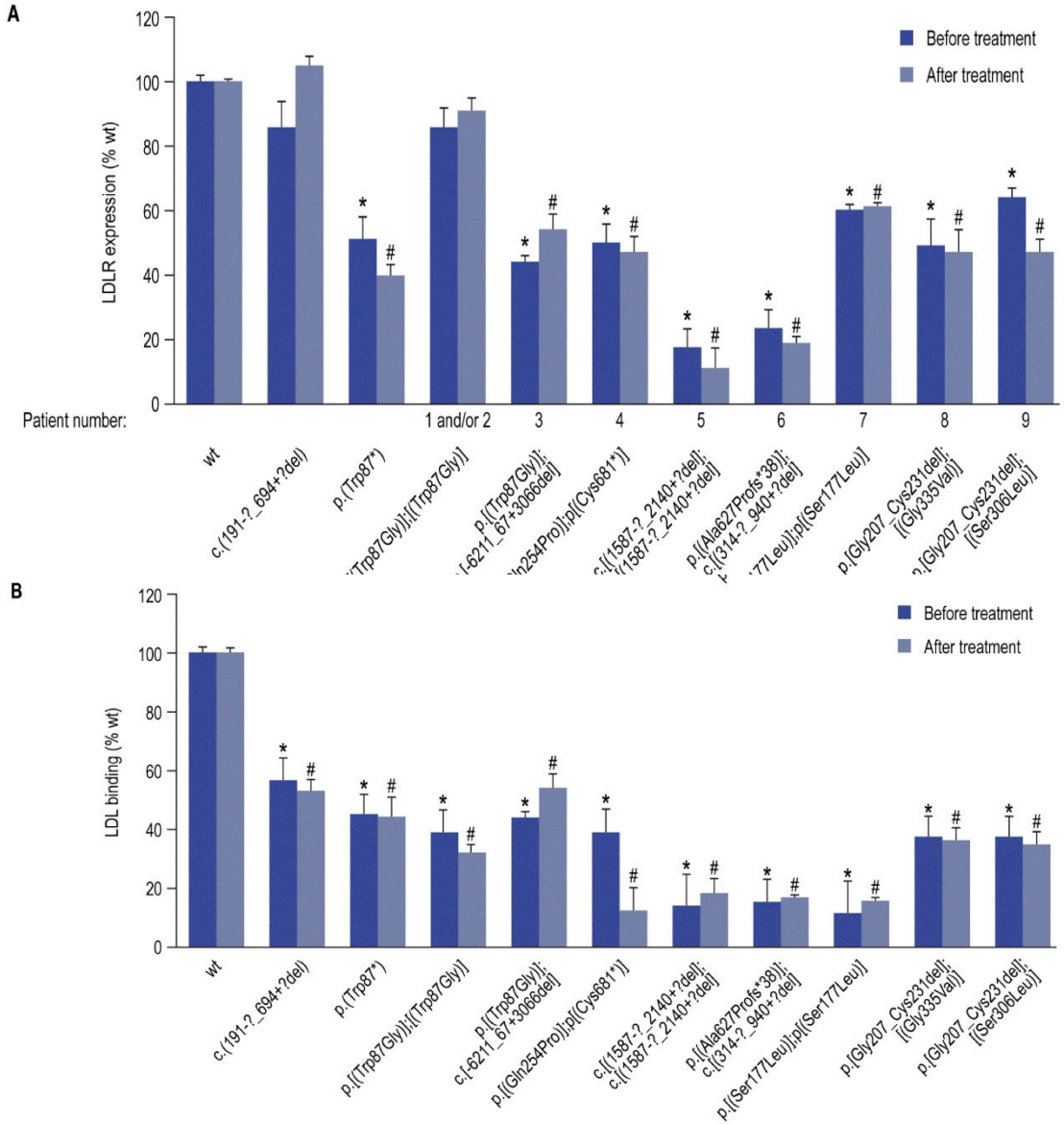
Data given as mean ± SD or median (Q1, Q3)

Adapted from Gaudet D et al. NEJM 2017

The Effect of Evinacumab in HoFH was not LDLR Dependent

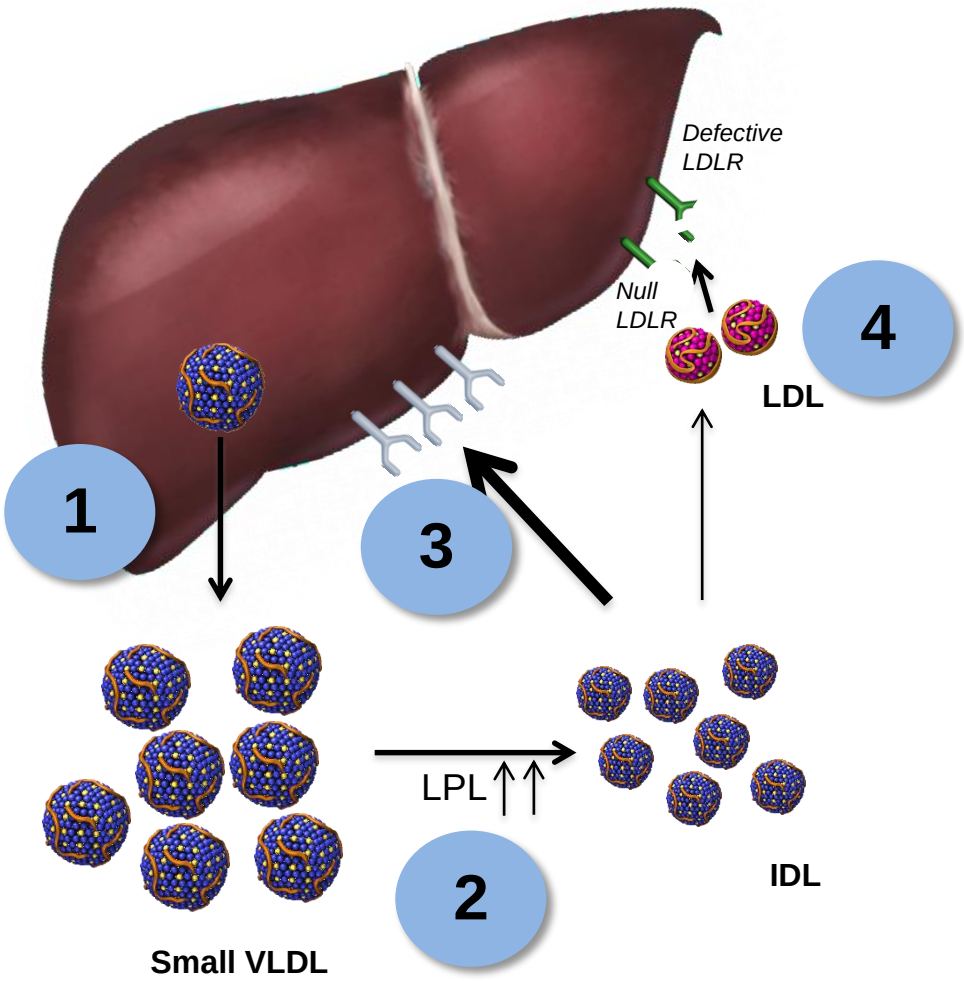
LDLR expression

LDL binding

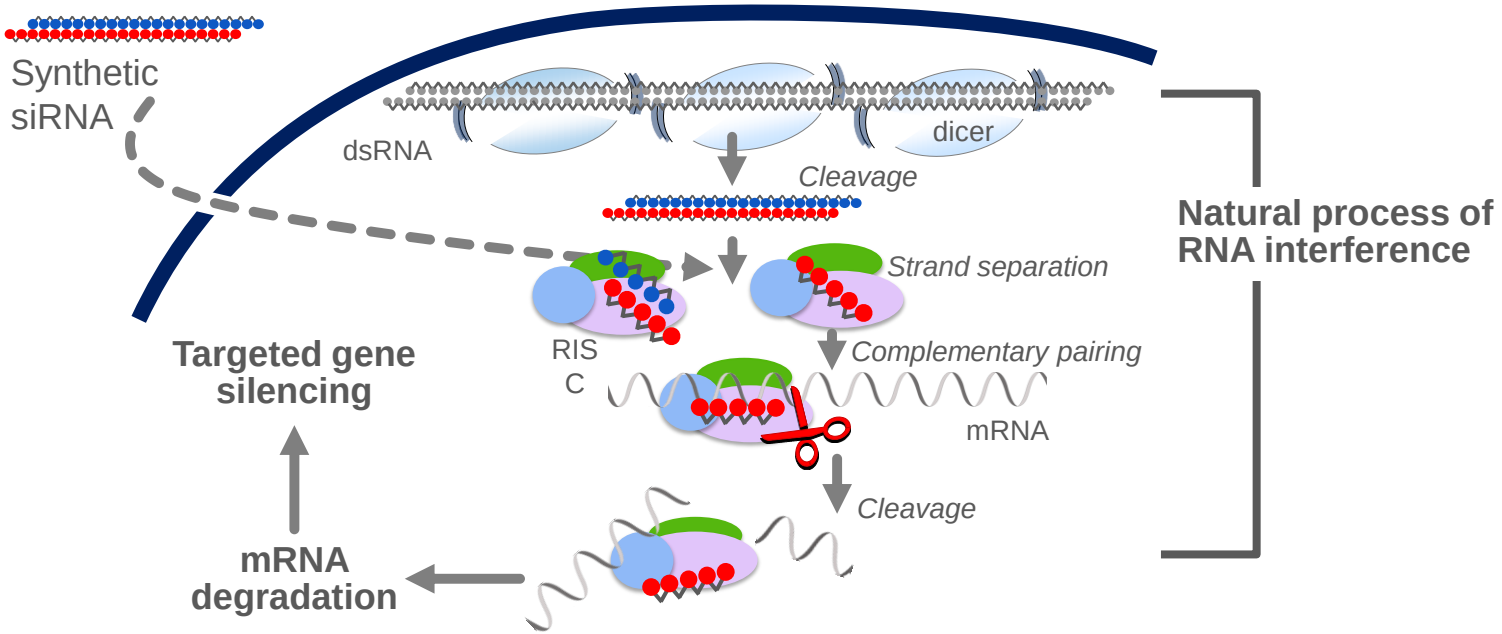


Banerjee P, et al 2019

Results in HoFH are Compatible with the Following Mechanisms of Action



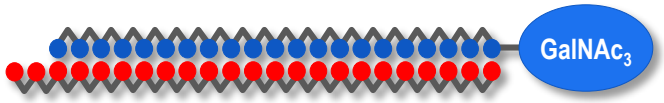
RNAi is an intrinsic process for inhibiting mRNA



GalNAc-siRNA conjugates facilitate rapid hepatic uptake

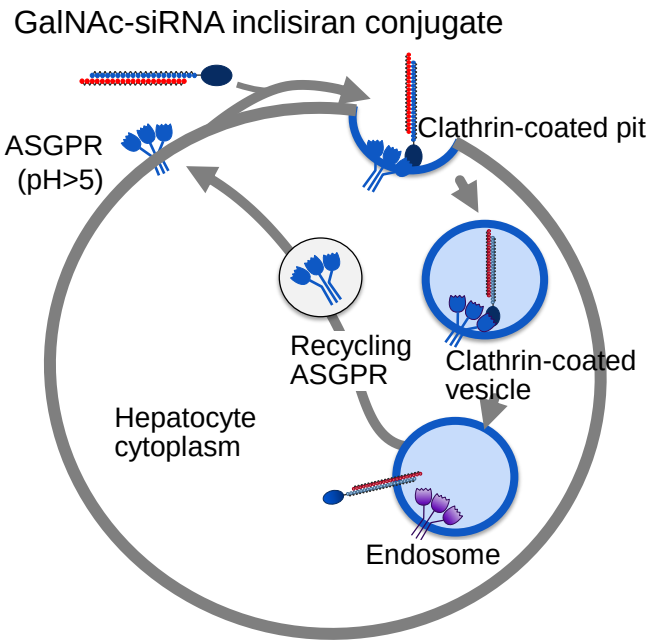
Asialoglycoprotein receptor (ASGPR)

- Highly expressed in hepatocytes only
- High rate of uptake



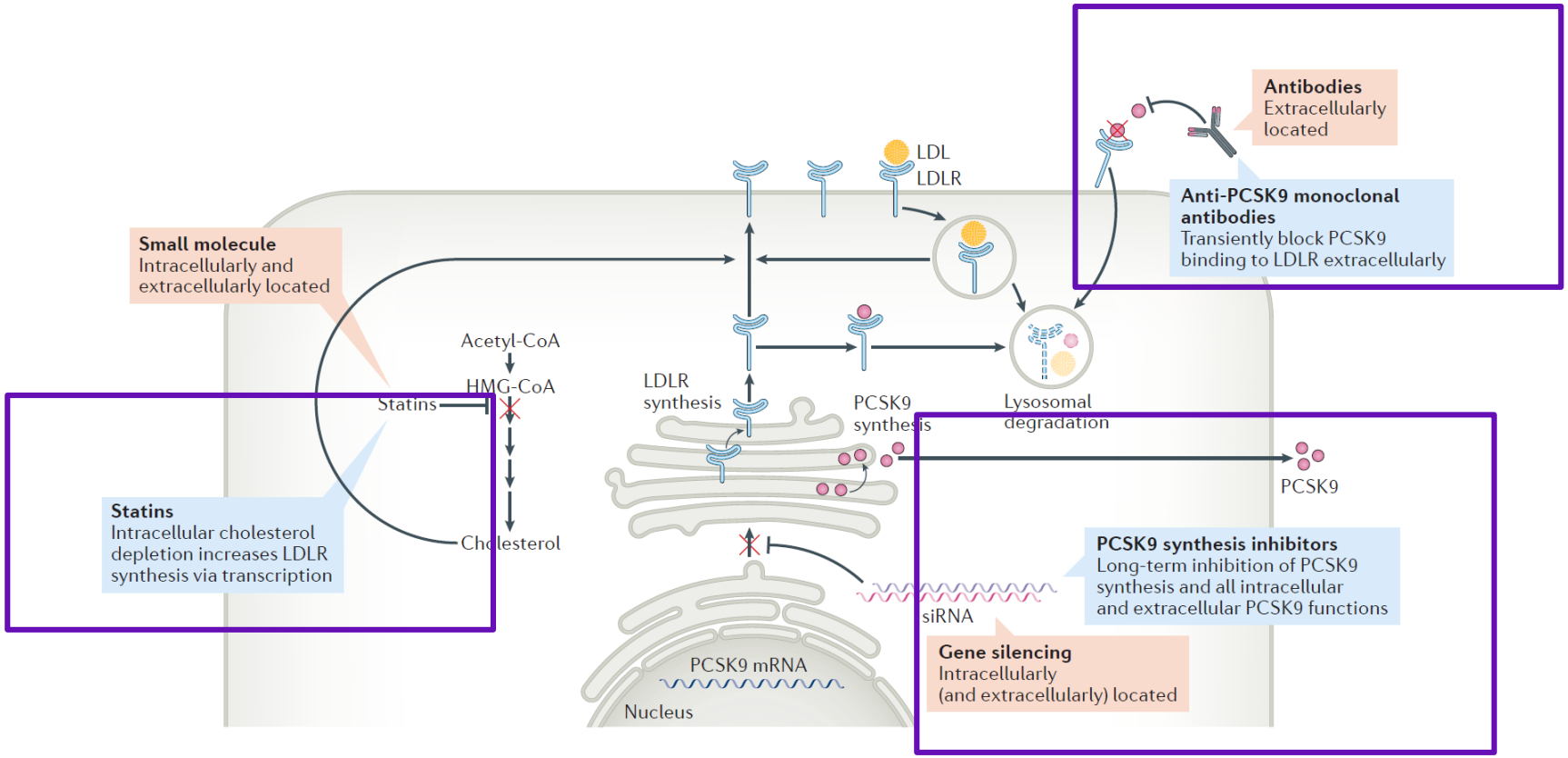
Inclisiran

- siRNA conjugated to N-acetylgalactosamine
- Subcutaneous administration
- Targeted delivery to hepatocytes



Therapeutic approaches to reducing LDL-C via the LDL recptor

Small Molecules, Mabs, siRNA



1. Nordestegaard B, Ray KK Nature Reviews Cardiology Jan 2018

Antisense Drugs for Dyslipidemia: state of the art

Target	Drug	Clinical Development
Apolipoprotein B	Mipomersen (ASO)	Approved in USA not in EU
PCSK9	PCSK9 (siRNA)	Phase III
Apolipoprotein (a)	Apo(a) (ASO)	Phase I-II
Apolipoprotein C-III	Volanerorsen (ASO)	Phase III
ANGPTL3	ANGPLT3	Phase I-II
CRP	CRP (ASO)	Phase I

SUMMARY

A number of new pharmacological approaches are currently available including

- **Monoclonal antibodies**
- **Oral small molecules**
- **si-RNA**
- **Antisense Oligonuclotides**
- **Vaccination**

- **Preliminary trials are ongoing demostrating safety and efficacy**

- **These new agents may provide additional benefit to patients not able to reach their lipid goals**