PRESENT AND FUTURE APPROACHES TO THE CONTROL OF DYSLIPIDAEMIAS

S.I.Te.C.S.
Società Italiana di Terapia Clinica e Sperimentale

Novel therapeutic approaches

Alberico L. Catapano - University of Milan, Italy

Disclosure of potential conflicts of interest

RESEARCH GRANT / RESEARCH SUPPORT	Sanofi, Sanofi Regeneron, Amgen, Mylan, Menarini, Eli Lilly
SPEAKER BUREAU	Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals, Mylan, Menarini, Merck , Recordati, Regeneron, Daiichi Sankyo, Astrazeneca, Aegerion, Amryt, Sandoz
HONORARIA	Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals,Mylan, Menarini, Merck, Recordati, Regeneron Daiichi Sankyo, Astrazeneca, Aegerion, Amryt, Sandoz
CONSULTANT / ADVISORY BOARD	Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals, Mylan, Menarini, Merck, Recordati, Regeneron Daiichi Sankyo, Genzyme, Aegerion, Sandoz

Alberico L. Catapano - Department of Pharmacological and Biomolecular Sciences, University of Milan, Italy

EMERGING TARGETS FOR LIPID LOWERING

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

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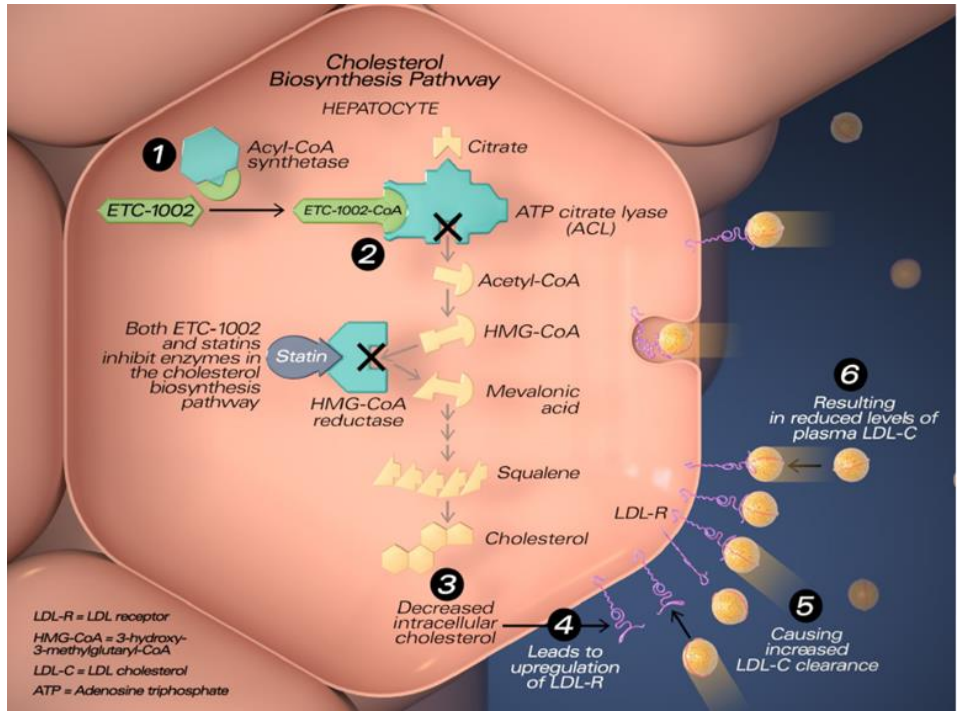
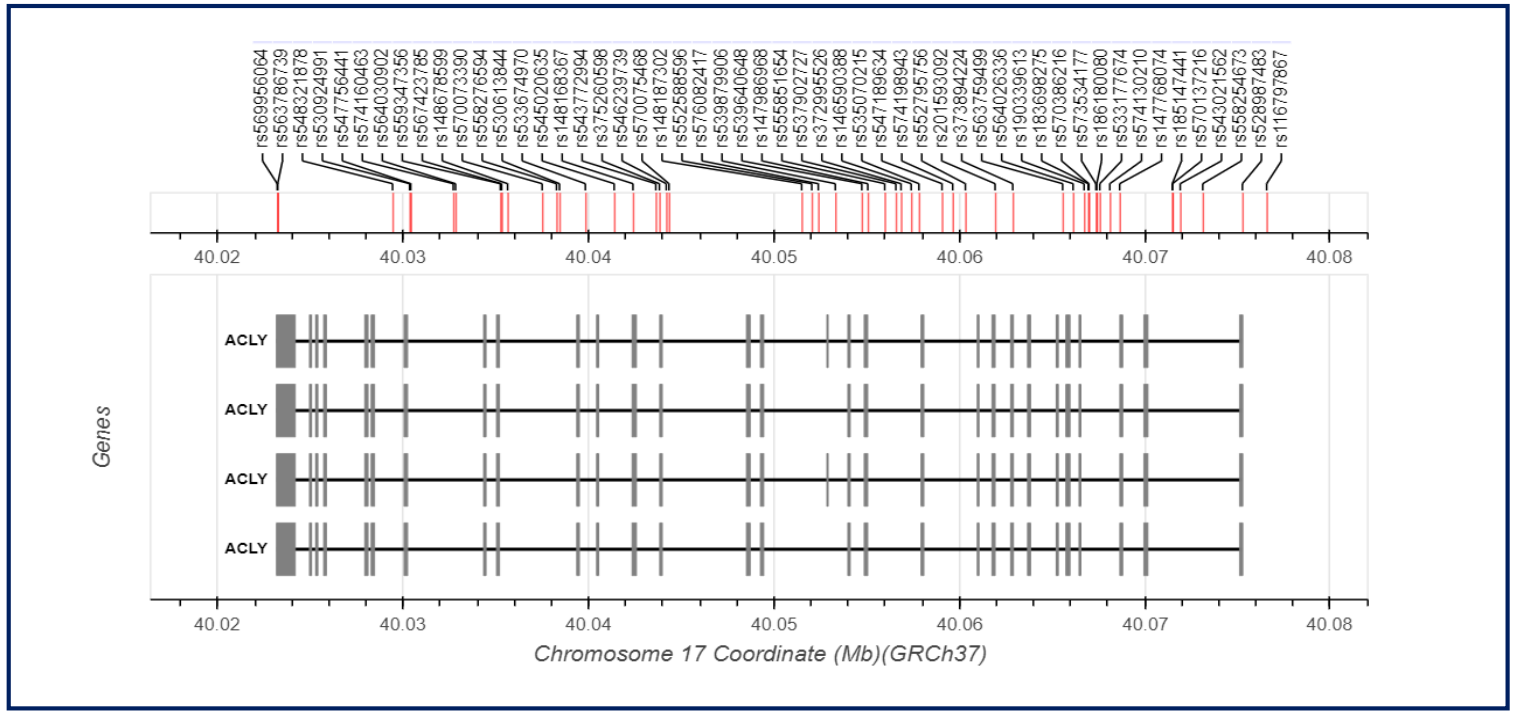
ATP-Citrate Lyase inhibition



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

ACLY genetic score

ACLY genetics consisting of 63 rare variants within ACLY gene: -1.28 mg/dL lower LDL-C (9.4×10^{-10})



Ference BA, et al, 2019 *in progress*

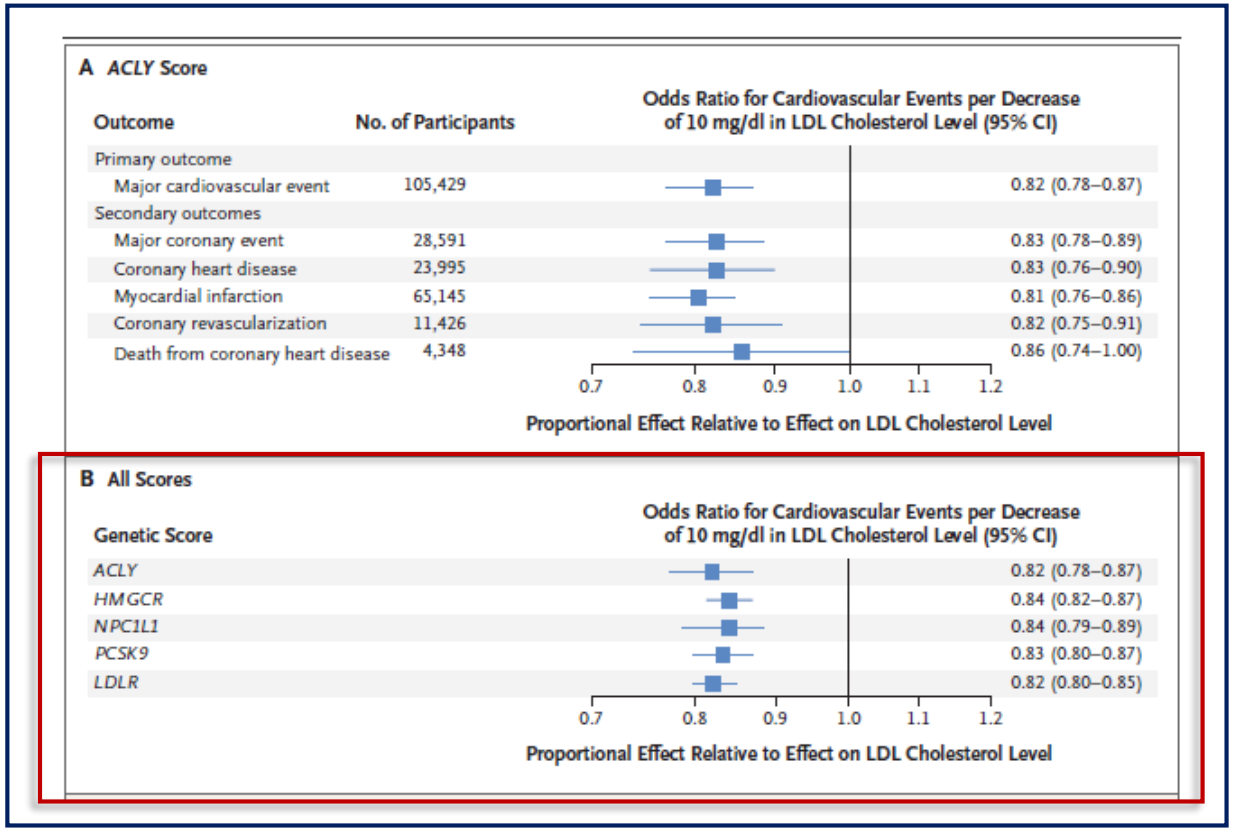
ACLY genetic score mimicking ACL inhibition

Genetic score or therapy	LDL-C	apoB	weight	HbA1C	Diabetes
Bempedoic Acid	↓	↓	↓	↓	↓
ACLY genetic score	↓	↓	↓	↓	↓
Statins	↓	↓	↑	↑	↑
HMGCR genetic score	↓	↓	↑	↑	↑
100 Variant LDL exome score	↓	↓	↑	↑	↑

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

Ference BA, et al, 2019 *in progress*

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

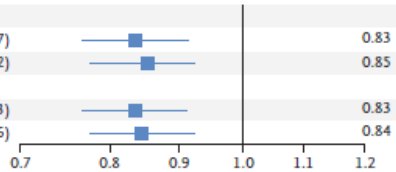
Genetic Score	No. of Participants	Change in Apolipoprotein B Level per Decrease of 10 mg/dl in LDL Cholesterol Level (95% CI)	Odds Ratio for Major Cardiovascular Events per Decrease of 10 mg/dl in LDL Cholesterol Level (95% CI)
		mg/dl per 10 mg/dl	
HMGCR score			
≤Median	245,402	−8.6 (−12.4 to −4.7)	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

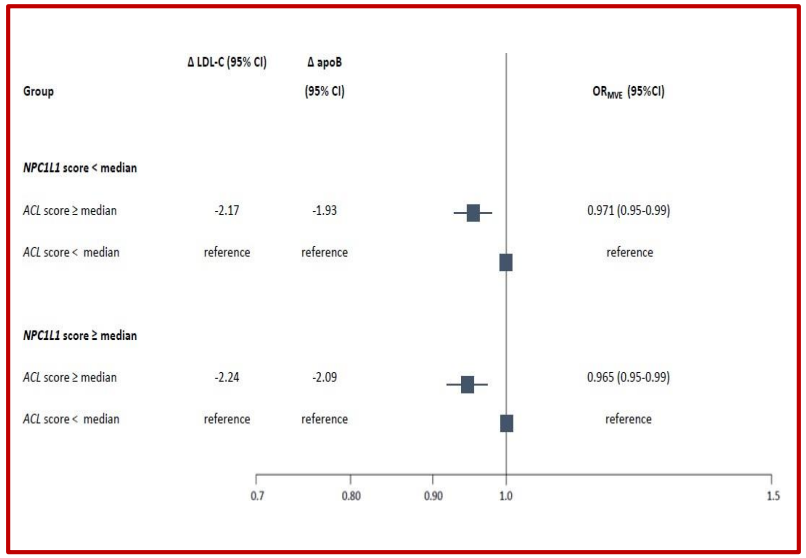


Ference BA, et al, N Engl J Med. 2019 Mar 14;380(11):1033-1042.

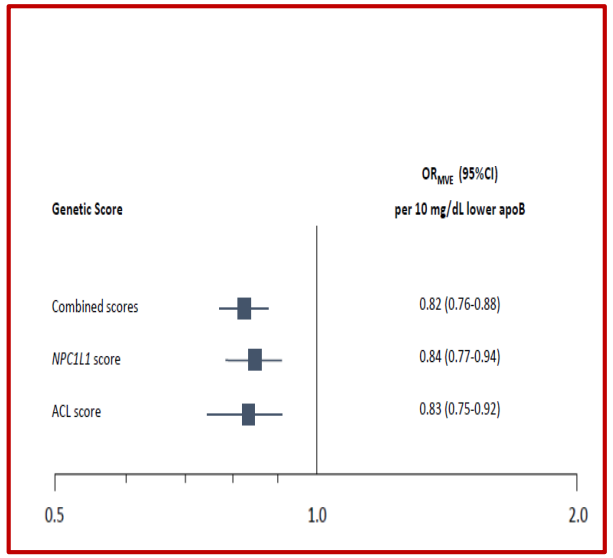
Combined effect of *ACL* and *NPC1L1* inhibition

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

Effect of ACL by NPC1L1 inhibition

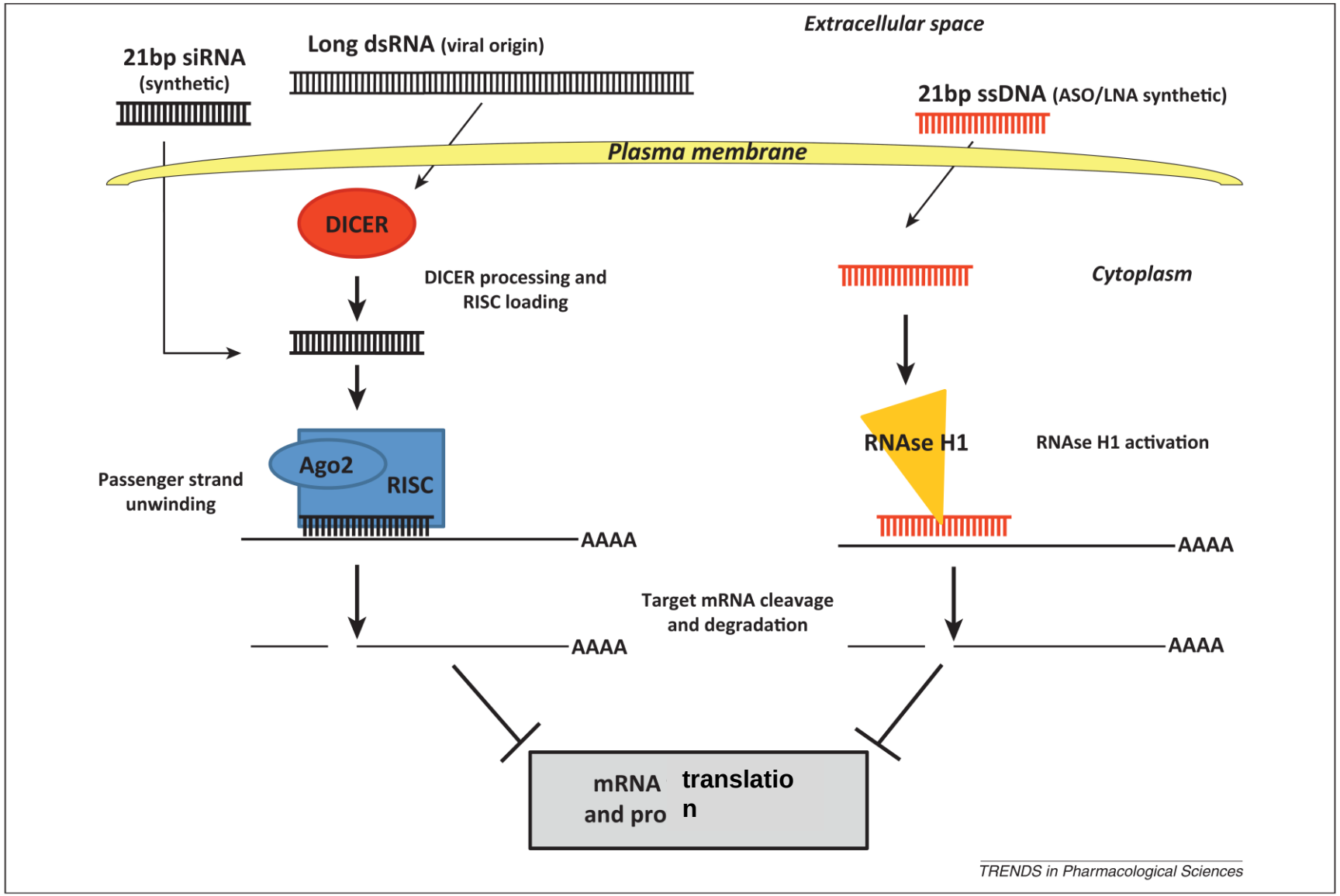


Effect per 10 mg/dl lower LDL-C



Ference BA, et al. 2017

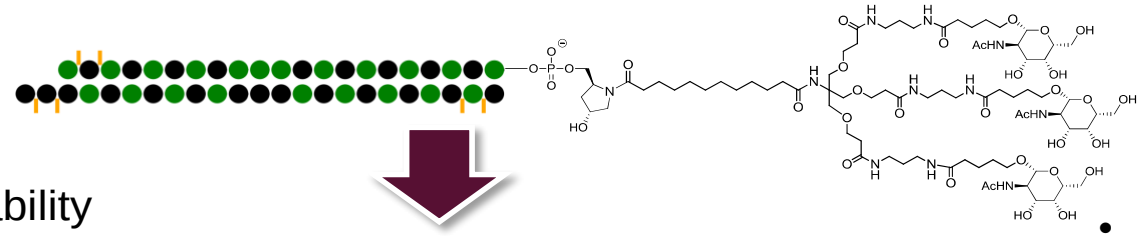
Mechanism of action of short interfering RNA (siRNA) and of antisense oligonucleotides (ASOs)



Imperial College London

Norata GD, *et al.* Trends Pharmacol Sciences 2013

Target delivery to Hepatocytes (GalNAc-chemistry)

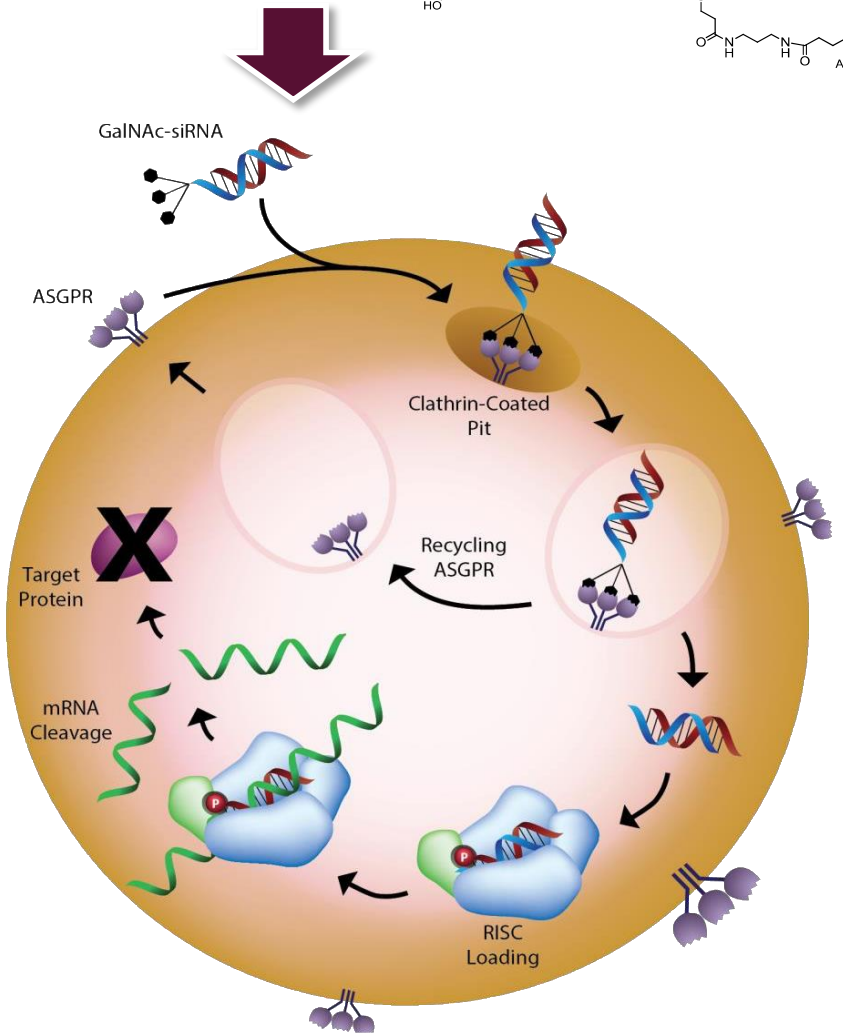


siRNA

- Metabolic stability
- Intrinsic potency

Ligand

- Trivalent GalNAc
- High affinity and specificity



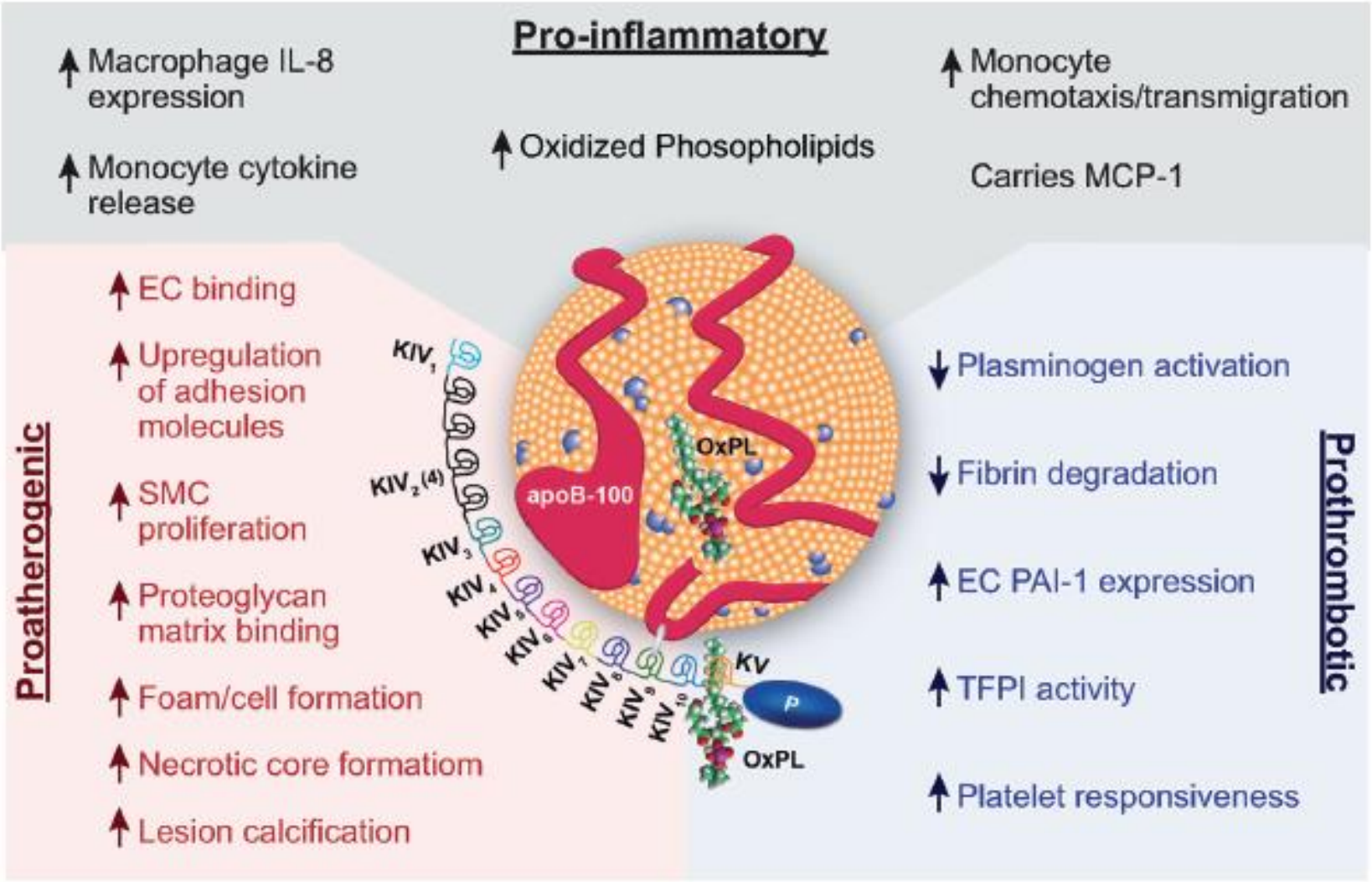
Asialoglycoprotein Receptor (ASGPR)

- Highly expressed in hepatocytes
- High capacity receptor
- Conserved across species

EMERGING TARGETS FOR LIPID LOWERING

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

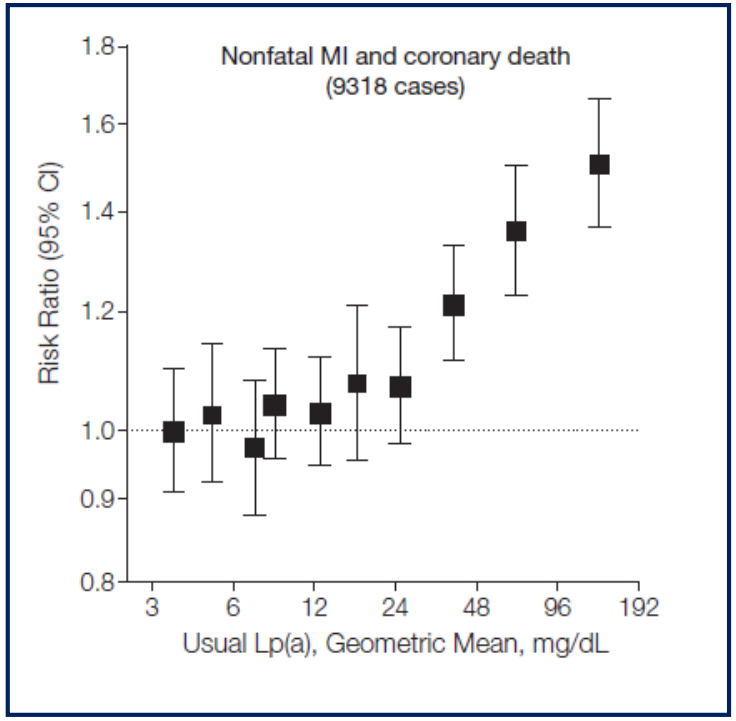
For equal particle concentration, Lp(a) has to be at least as atherothrombotic than LDL



Tsimikas JACC 2017;69:692-711

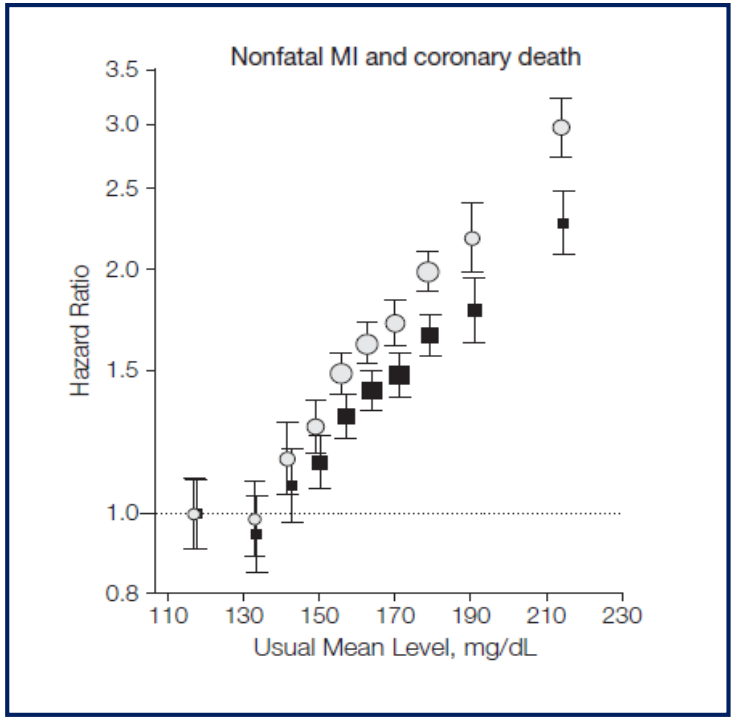
Observational evidence Lp(a) is a weak risk factor for CVD

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



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

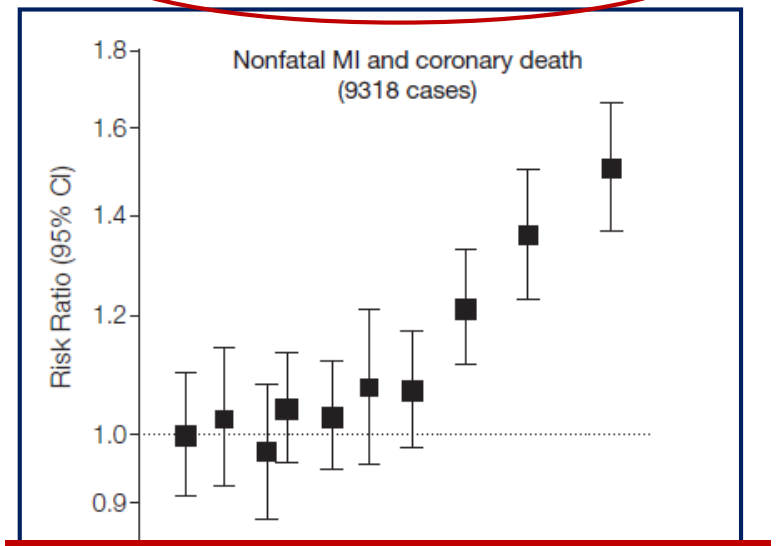
LDL-C OR per 1-SD (33 mg/dl): 1.39



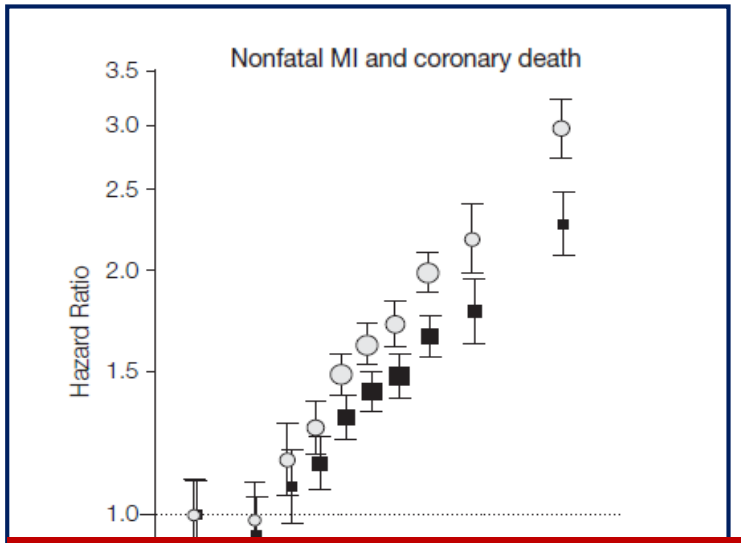
Emerging Risk Factors Collaboration. JAMA. 2009;302:1993-2000

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

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



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



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

Tripling in Lp(a)

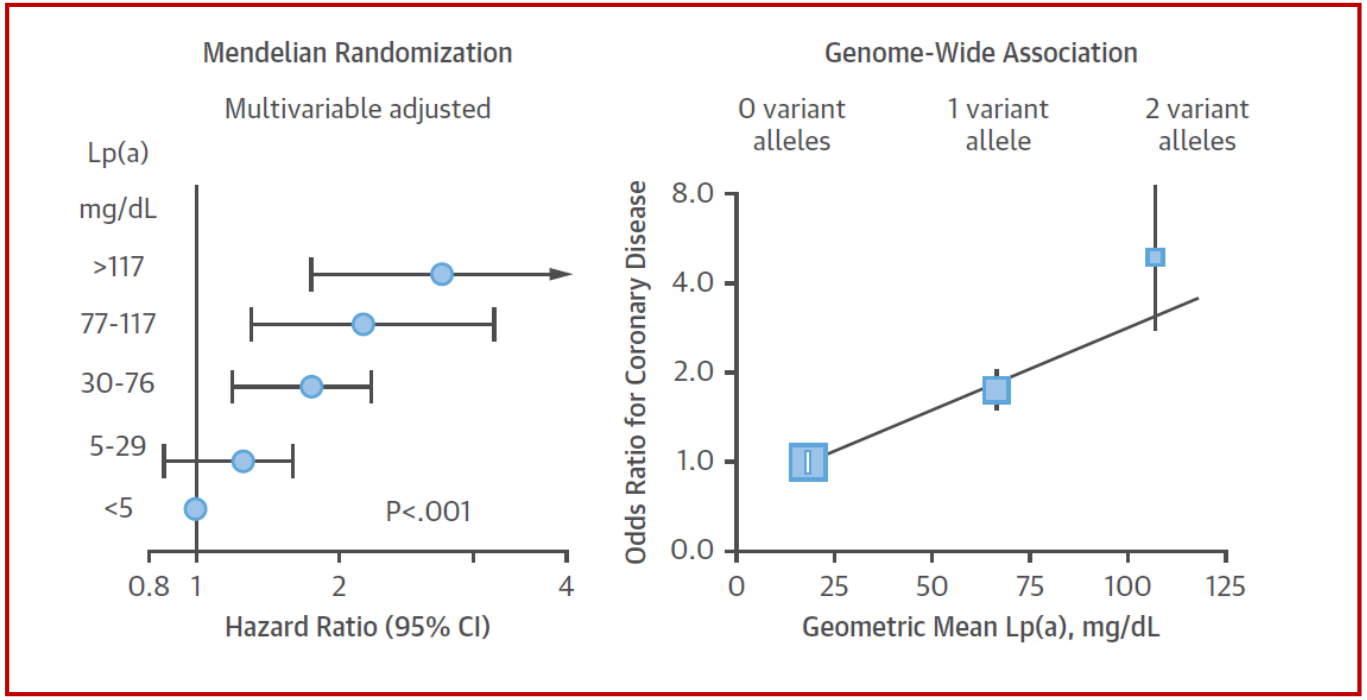
16% increased risk

Mean population LDL-c 3.5 mmol/L

Tripling in LDL-c

386% increased risk

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

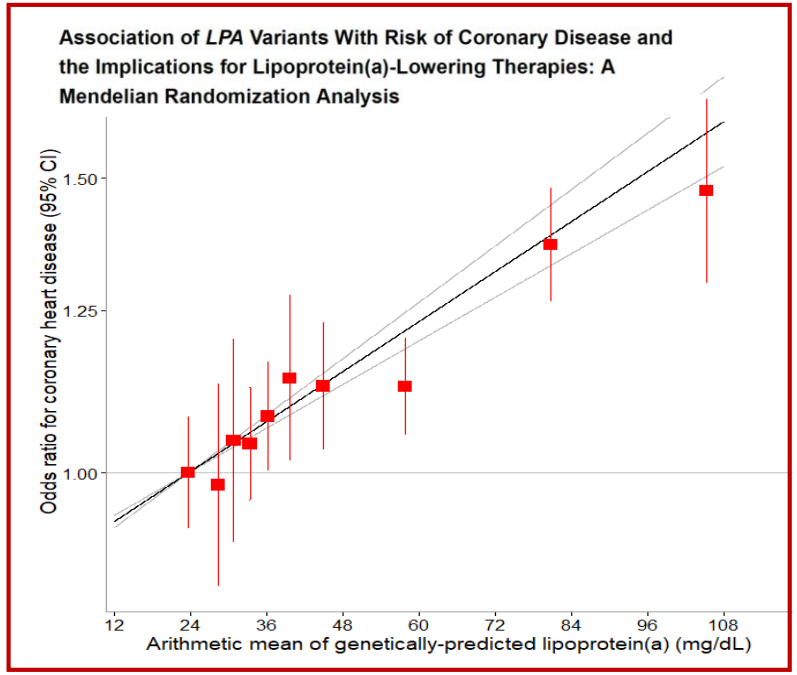


Kamstrup PR, et al. JAMA. 2009;301(22):2331-2339

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

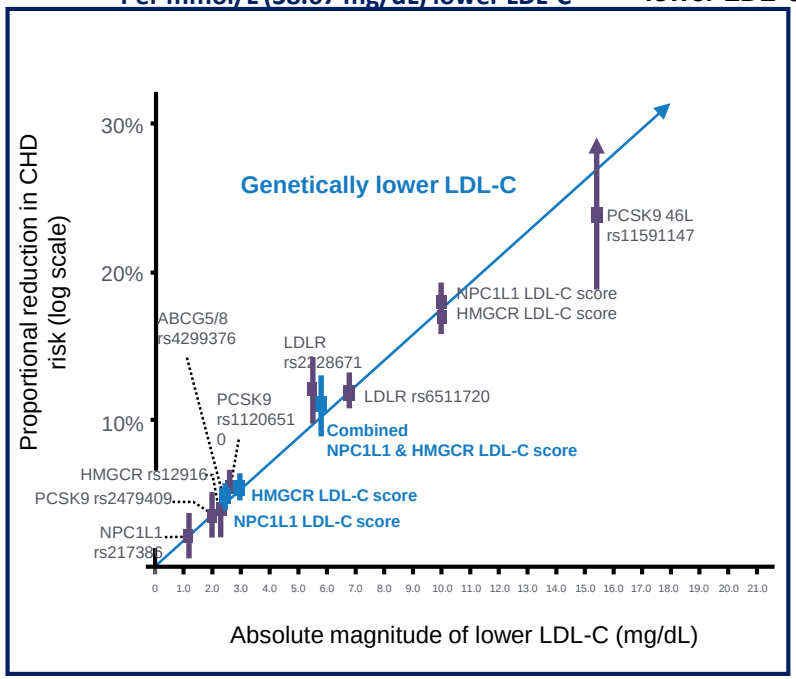
Causal effect of Lp(a) on CHD compared to effect of LDL

OR: 0.942; 95% CI, 0.933–0.951; $p=3\times10^{-37}$
Per 10 mg/dL lower **Lp(a)**



OR: 0.511; 0.417–0.602; $p=2\times10^{-12}$
Per mmol/L (38.67 mg/dL) lower LDL-C

54.5% reduction in CHD risk per 1mmol/L lower LDL-C



Burgess SB, Ference BA, et al. 2018; JAMA Cardiology doi: 10.1001/jamacardio.2018.1470

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Changes in Lp(a) and LDL-C with equivalent effects on CVD

38.7 mg/dl lifetime lower LDL-C

↓

50% reduction in ***lifetime*** risk of CHD

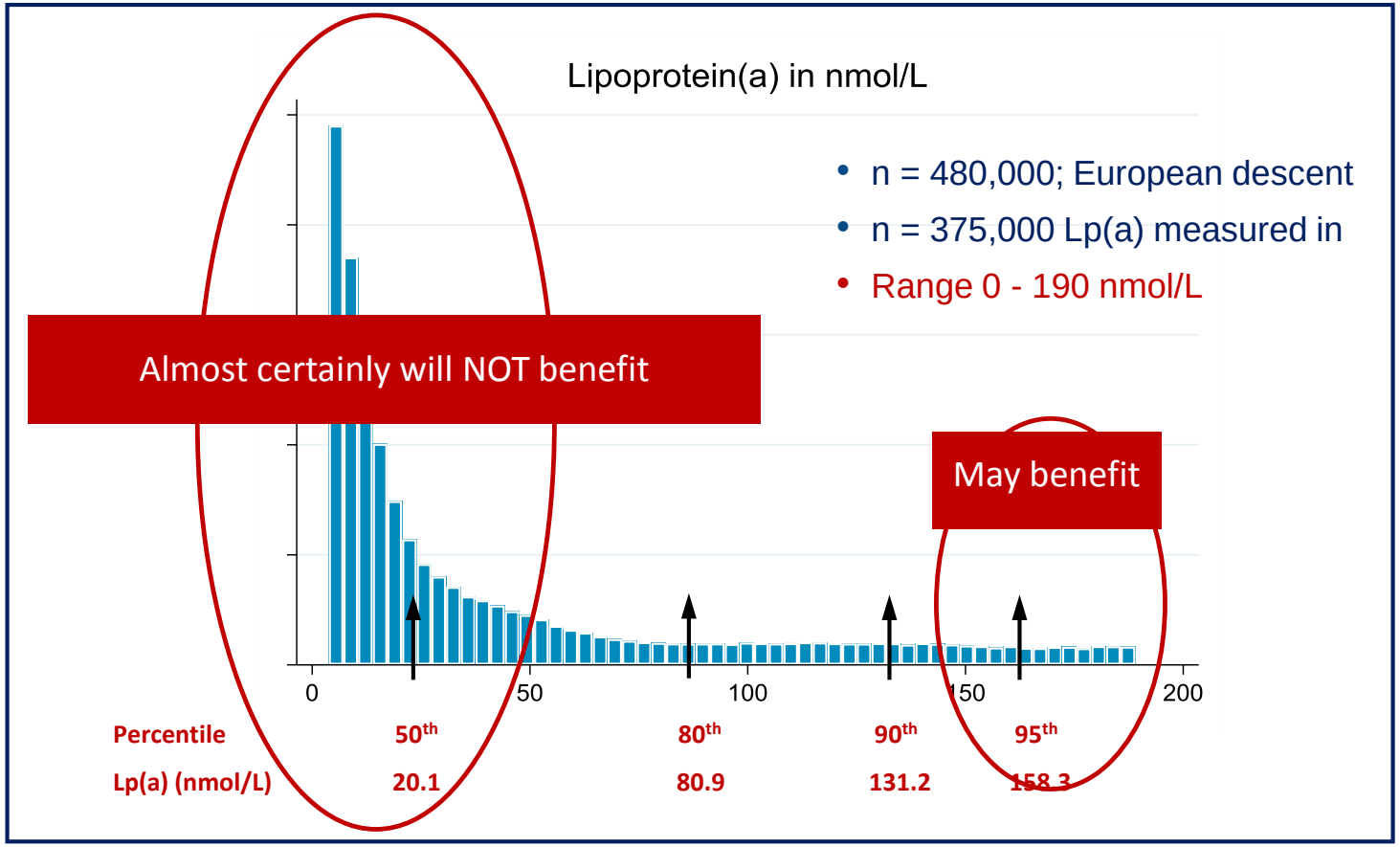
↑

80.4 - 101.5 mg/dl lifetime lower Lp(a)

- *Informs the optimal design of RCTs for potent Lp(a) lowering agents*

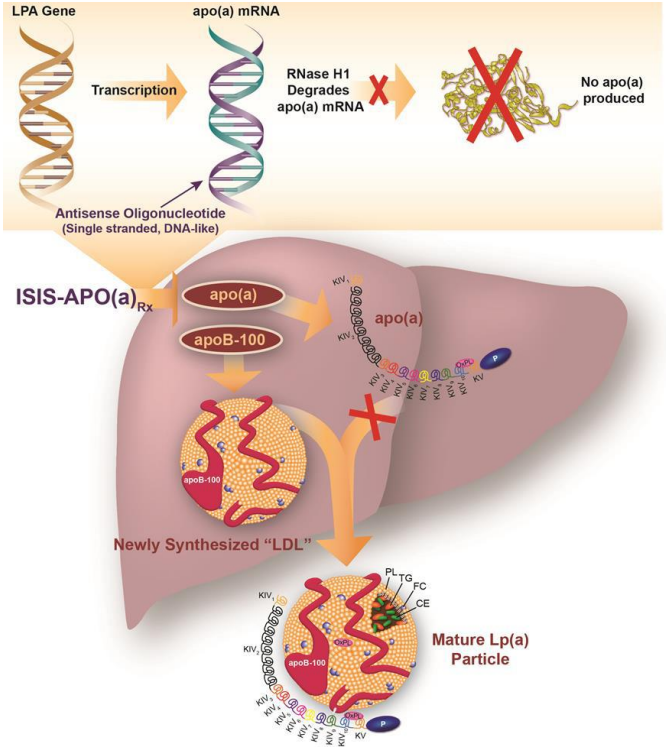
Burgess SB, Ference BA, et al. 2018; JAMA Cardiology doi: 10.1001/jamacardio.2018.1470

Who is likely to benefit from Lp(a) lowering therapies?



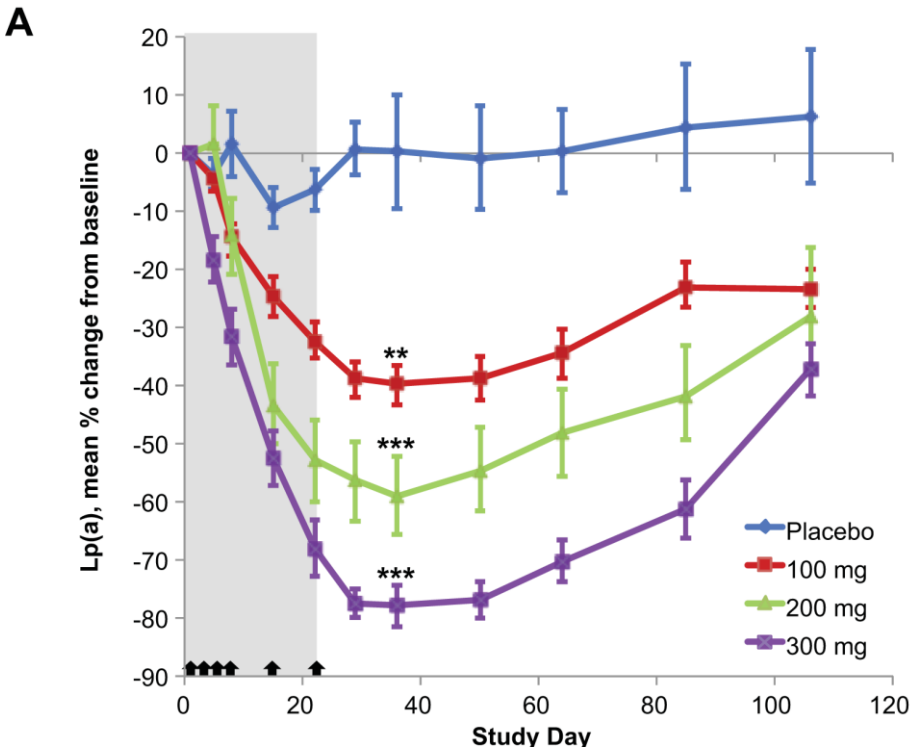
ISIS-APO(a)$_{Rx}$

Mechanism of Action in Reducing Plasma Lp(a)



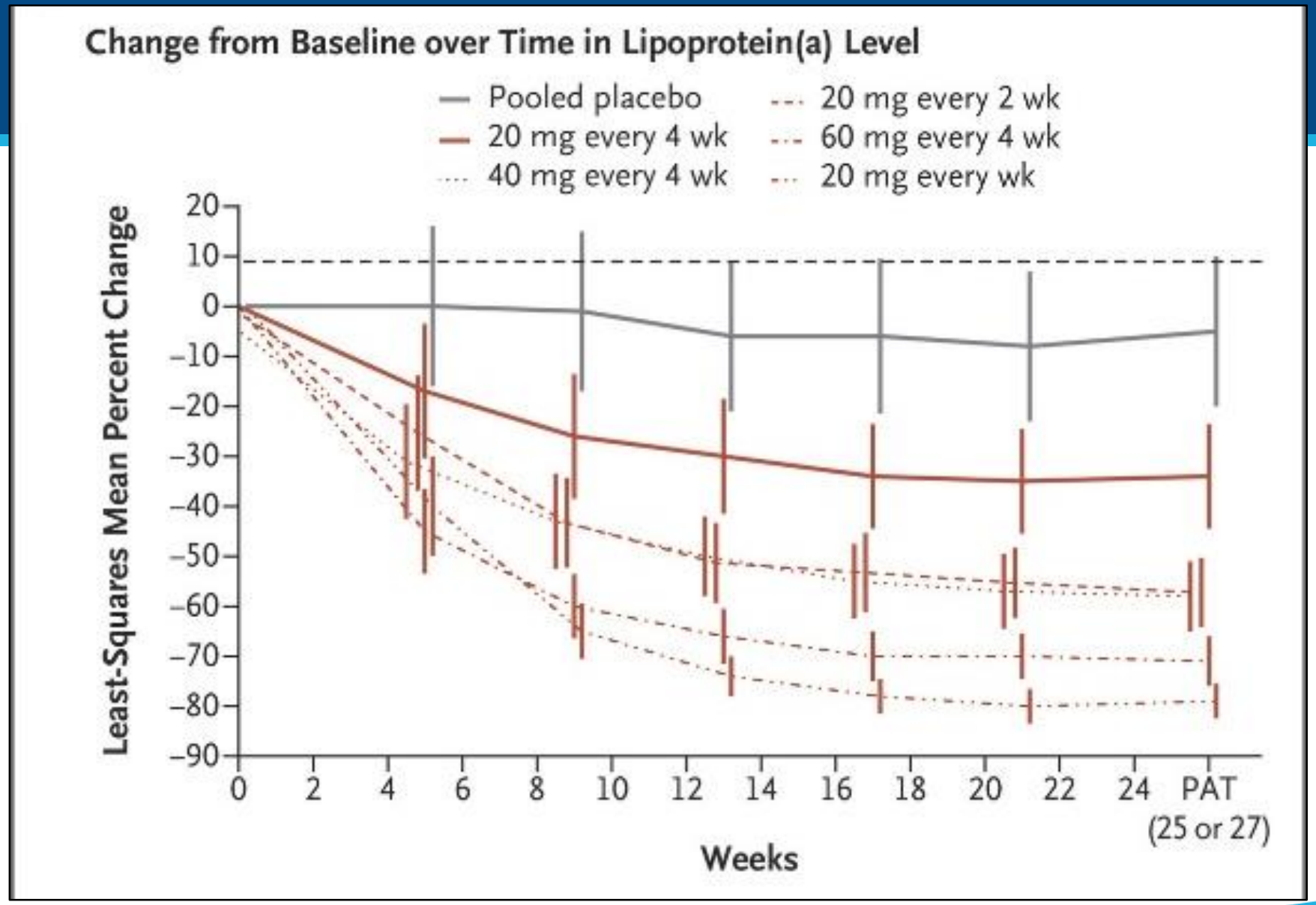
ISIS-APO(a)$_{Rx}$ Phase I Trial

Mean percent change in Lp(a) over time by treatment group in the multiple-dose cohort



Tsimikas et al, Lancet 2015

Effect of APO(a)-LRx on Lipoprotein(a) Level



S. Tsimikas et al. N Engl J Med. 2020;382:244-55

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P2338

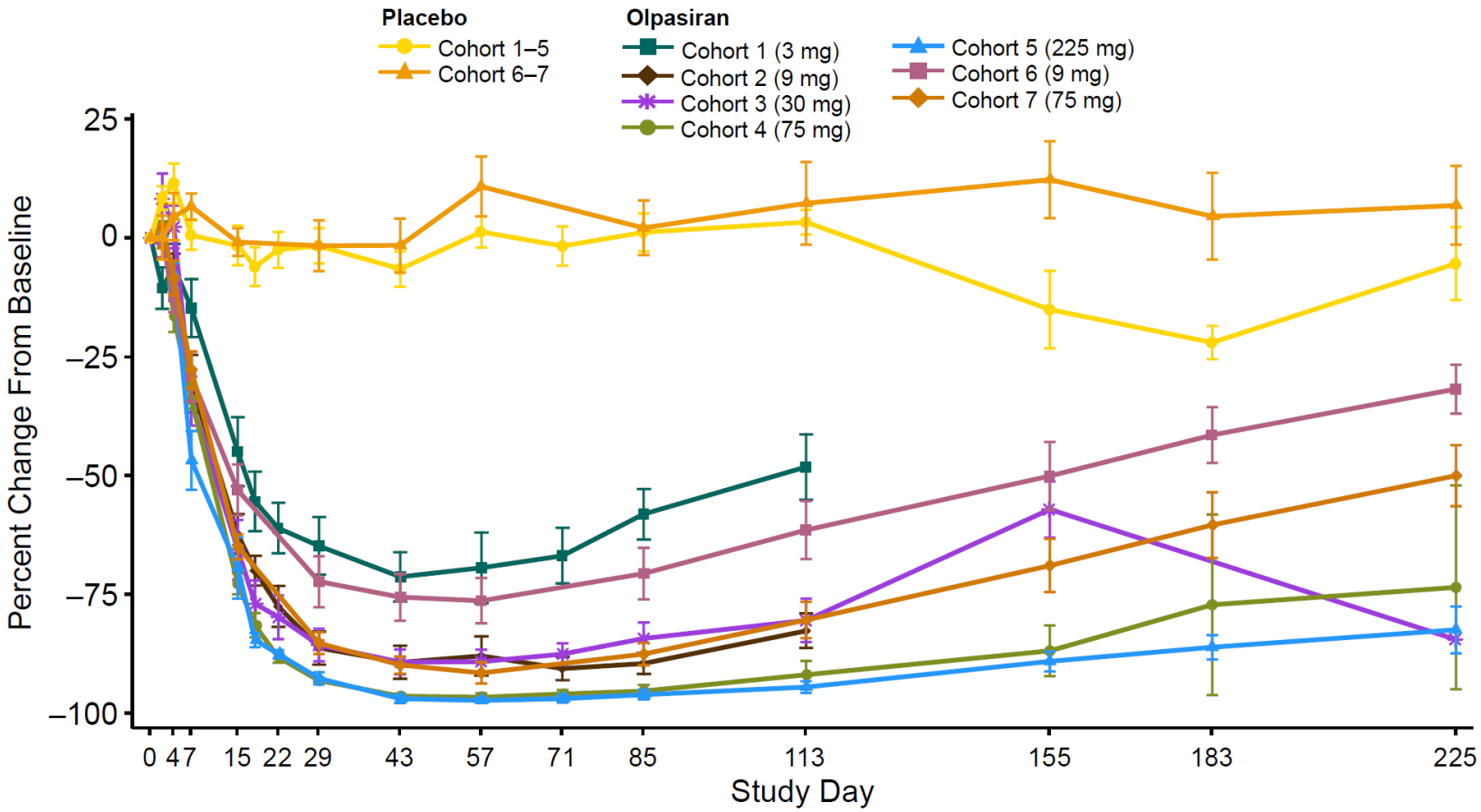
Safety, Tolerability, and Efficacy of Single-dose AMG 890, a Novel siRNA Targeting Lp(a), in Healthy Subjects and Subjects With Elevated Lp(a)

Michael J Koren,[1] Patrick Maurice Moriarty,[2] Joel Neutel,[3] Seth J Baum,[4] Martha Hernandez-Illas,[5] Howard S Weintraub,[6] Jennifer Hellawell,[7] Tracy Varrieur,[8] Winnie Sohn,[9] Huei Wang,[10] Mary Elliott-Davey,[11] Helina Kassahun,[9] Gerald F Watts[12†]

[1]Jacksonville Center for Clinical Research, Jacksonville, FL; [2]University of Kansas Medical Center, Kansas City, KS; [3]Orange County Research Center, Tustin, CA; [4]Excel Medical Clinical Trials, Boca Raton, FL; [5]QPS MRA, Miami, FL; [6]NYU Langone Medical Center, New York, NY; [7]Amgen, South San Francisco, CA; [8]Amgen, Cambridge, MA; [9]Amgen, Thousand Oaks, CA; [10]Amgen, Newbury Park, CA; [11]Amgen Ltd, Cambridge; [12]University of Western Australia, Perth, Australia

[†]Current affiliation, School of Medicine, University of Western Australia, Department of Cardiology, Royal Perth Hospital, Perth, Australia

Lp(a) Percent Change from Baseline After a Single Dose of Placebo or Olpasiran



Baseline values are the mean of screening and day 1 pre-dose values. If only 1 value was available, that value was used as the baseline value.
As-is data snapshot date: 21Oct2020

Koren M.J. e-Poster AHA 2020

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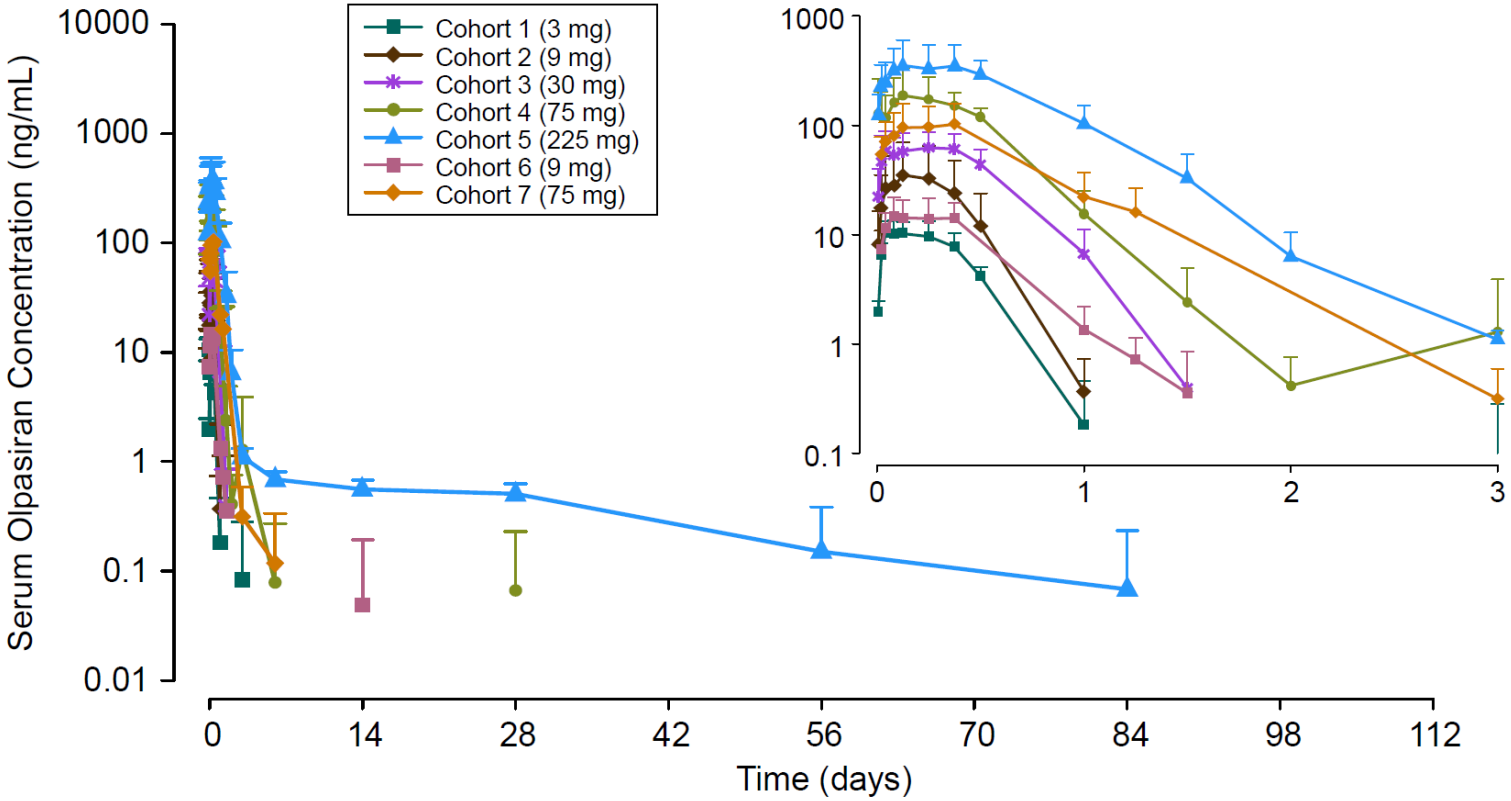
Baseline Characteristics

Baseline Characteristic		Cohorts 1–5 Screening Lp(a) ≥70 to ≤199 nmol/L		Cohorts 6 & 7 Screening Lp(a) ≥200 nmol/L	
		Placebo (N=10)	Olpasiran (N=30)	Placebo (N=6)	Olpasiran (N=18)
Age (years), mean (SD)		46.3 (8.5)	43.9 (13.5)	57.8 (5.8)	52.7 (9.4)
Women, n (%)		3 (30.0)	9 (30.0)	4 (66.7)	6 (33.3)
Ethnicity, n (%)	Hispanic/Latino	5 (50.0)	19 (63.3)	2 (33.3)	5 (27.8)
	Not Hispanic/Latino	5 (50.0)	11 (36.7)	4 (66.7)	13 (72.2)
Race, n (%)	Black	3 (30.0)	9 (30.0)	0	1 (5.6)
	White	7 (70.0)	21 (70.0)	5 (83.3)	16 (88.9)
	Other	0	0	1 (16.7)	1 (5.6)
BMI, kg/m^2, mean (SD)		27.6 (3.5)	27.0 (3.6)	28.1 (2.1)	27.7 (3.3)
Lp(a) nmol/L, median (Q1, Q3)		124 (104, 137)	122 (97, 146)	272 (233, 307)	253 (224, 334)

Koren M.J. e-Poster AHA 2020

Mean (SD) Serum Olpasiran Concentration-Time Profiles Following A Single SC Administration of 3, 9, 30, 75, or 225 mg



Koren M.J. e-Poster AHA 2020

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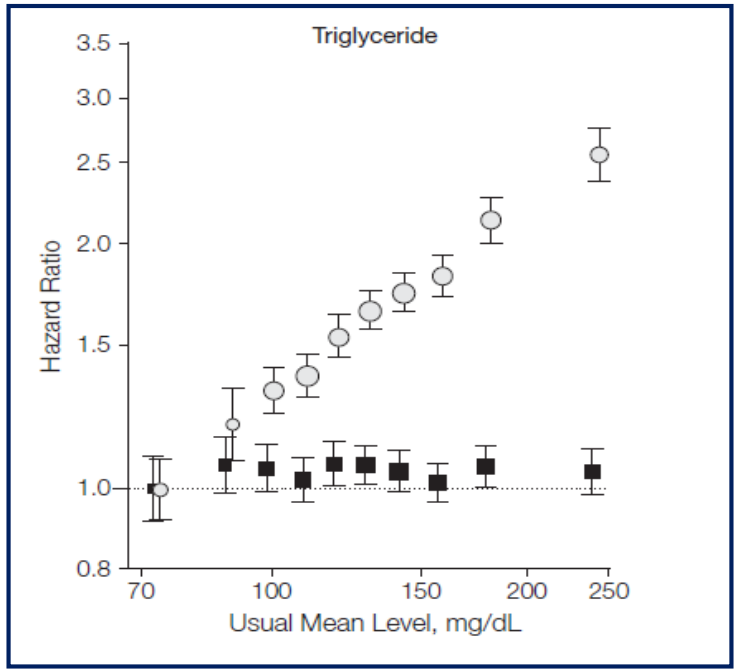
- **Plasma TG (Apo CIII, Angiopoietin Like 3)**

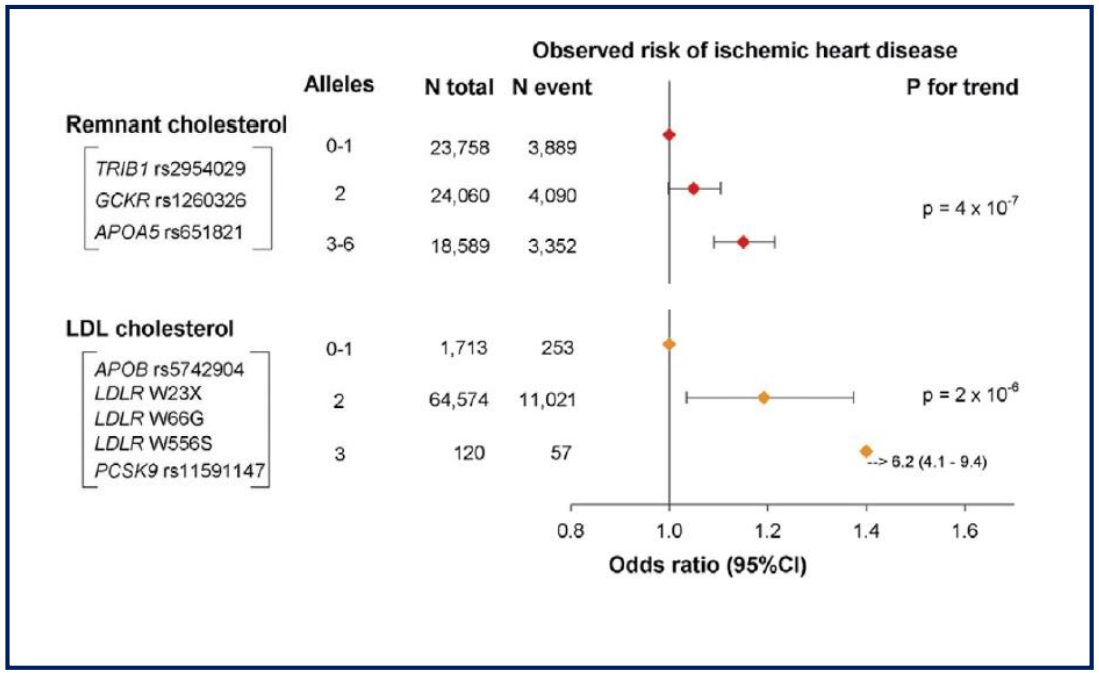
Triglycerides and risk of CHD

Observational epidemiology



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

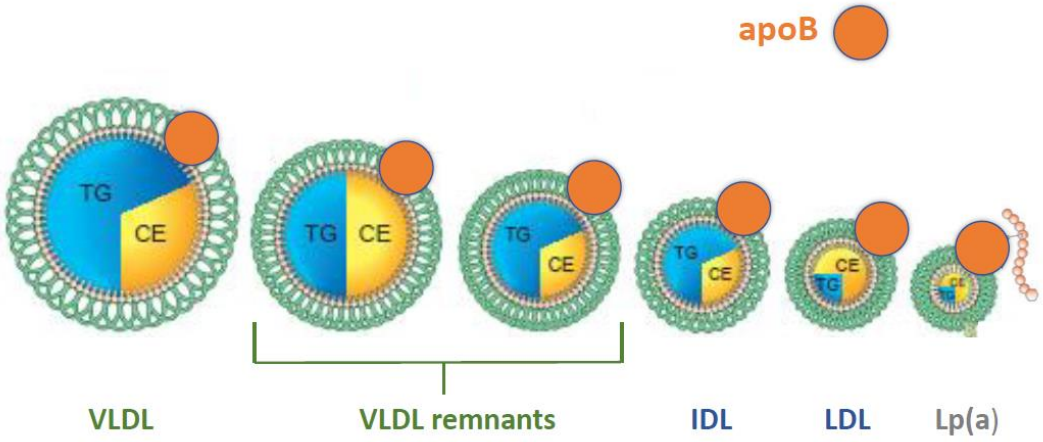
Mendelian Randomization



Varbo A, etal. JACC 2013;61:427–36.

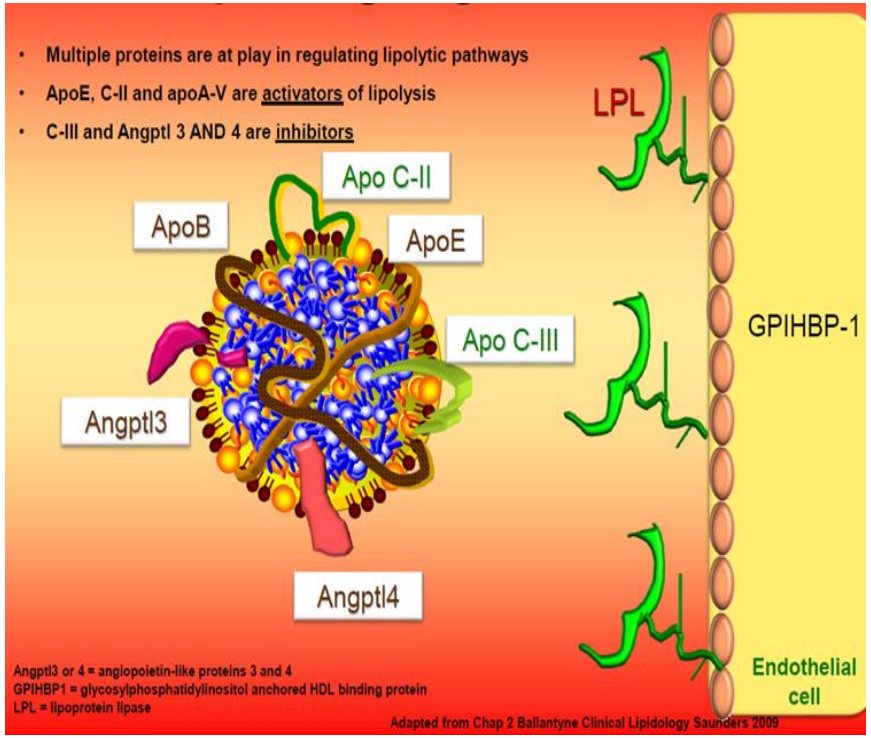
Directly comparing effect of lowering triglycerides and LDL-C on CHD

- 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

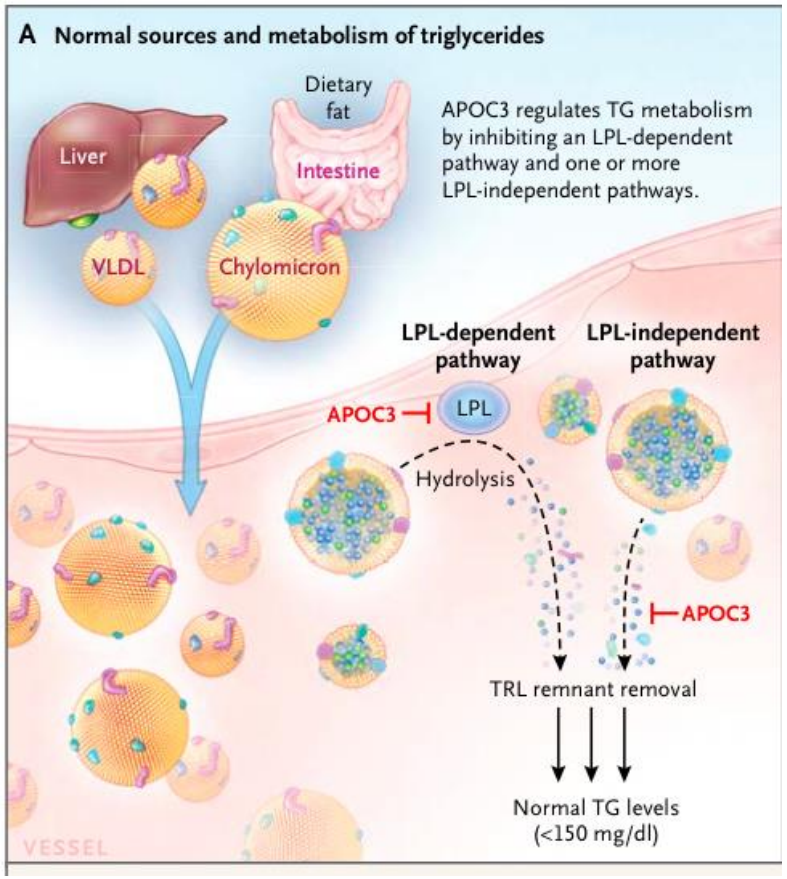
Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, 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

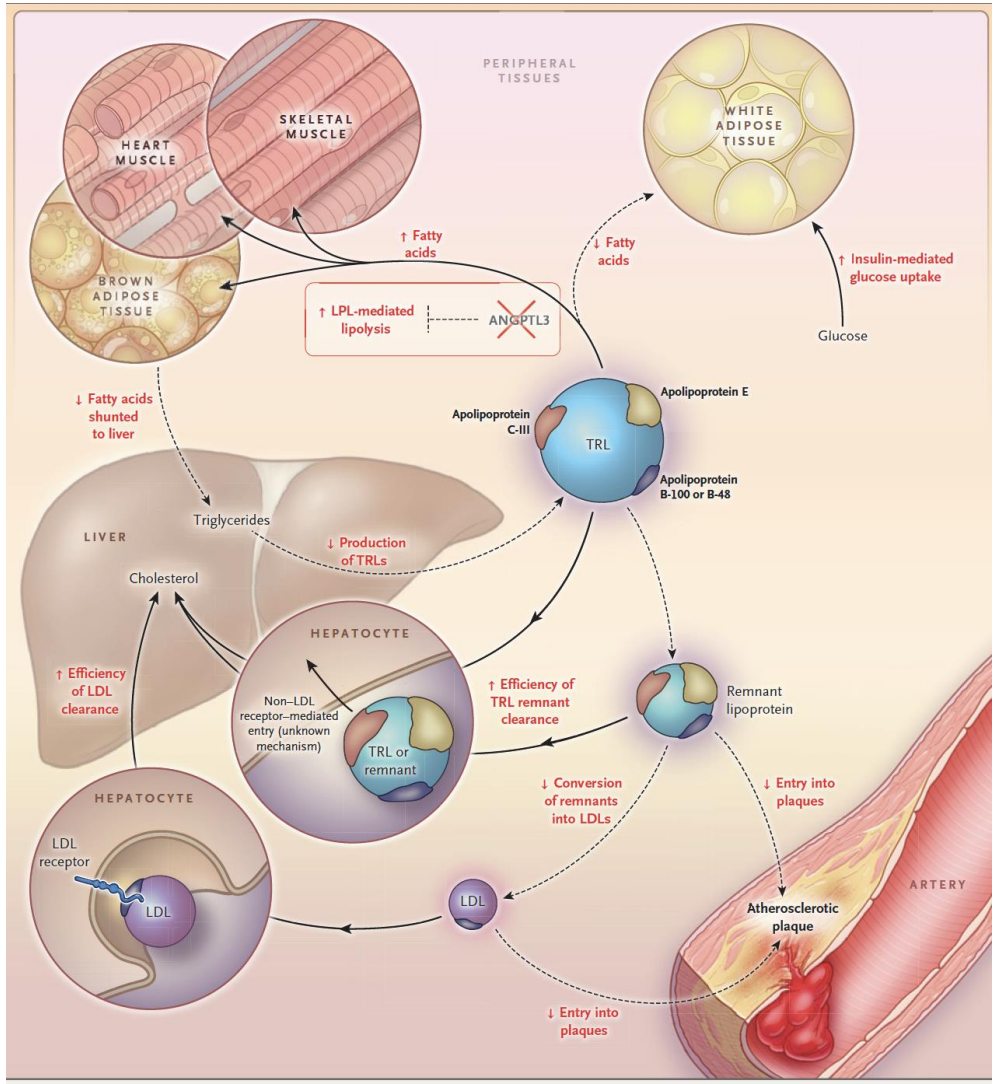


Gaudet, N Engl J Med 2014

- 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 variant associated with LDL, TG or both on risk of CHD

Per 10 mg/dl lower apoB

Table 2. Association of Additional Genetic Scores With Triglycerides, LDL-C, and Risk of CHD per 10-mg/dL Lower Concentration of ApoB-Containing Lipoproteins[a]

Composition of Genetic Score	Δ Triglycerides (95% CI)	Δ LDL-C (95% CI)	Odds Ratio for CHD (95% CI) per 10-mg/dL Lower ApoB
51 Variants associated with triglycerides at $P < 5.0\times10^{-8}$, but not LDL-C ($P > .001$)	−43.1 (−44.5 to −41.7)	−2.1 (−2.6 to −1.6)	0.762 (0.724 to 0.803)
59 Variants associated with LDL-C at $P < 5.0\times10^{-8}$, but not triglycerides ($P > .001$)	−2.1 (−3.0 to −1.1)	−15.5 (−15.8 to −15.1)	0.774 (0.748 to 0.800)
168 Variants associated with either triglycerides or LDL-C at $P < 5.0\times10^{-8}$	−21.6 (−22.1 to −21.1)	−11.8 (−12.0 to −11.6)	0.770 (0.757 to 0.783)
91 Variants associated with triglycerides at $P < 5.0\times10^{-8}$	−35.3 (−35.9 to −34.6)	−9.3 (−9.6 to −9.1)	0.776 (0.758 to 0.795)
100 Variants associated with LDL-C at $P < 5.0\times10^{-8}$	−17.5 (−18.0 to −17.0)	−13.5 (−13.7 to −13.3)	0.776 (0.762 to 0.791)
23 Variants associated with both triglycerides and LDL-C, both at $P < 5.0\times10^{-8}$, in same direction of effect	−32.3 (−33.0 to −31.5)	−12.0 (−12.3 to −11.7)	0.793 (0.771 to 0.815)
10 Variants associated with both triglycerides and LDL-C, both at $P < 5.0\times10^{-8}$, with opposite directions of effect	17.2 (16.0 to 18.4)	−22.5 (−23.0 to −22.1)	0.798 (0.767 to 0.830)
9 Variants associated with both triglycerides and LDL-C, both at $P < 5.0\times10^{-8}$, with opposite directions of effect (excluding *APOE* variant rs7412)	26.0 (23.7 to 28.3)	−20.3 (−21.2 to −19.4)	0.770 (0.711 to 0.833)

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

Multivariable Mendelian randomization

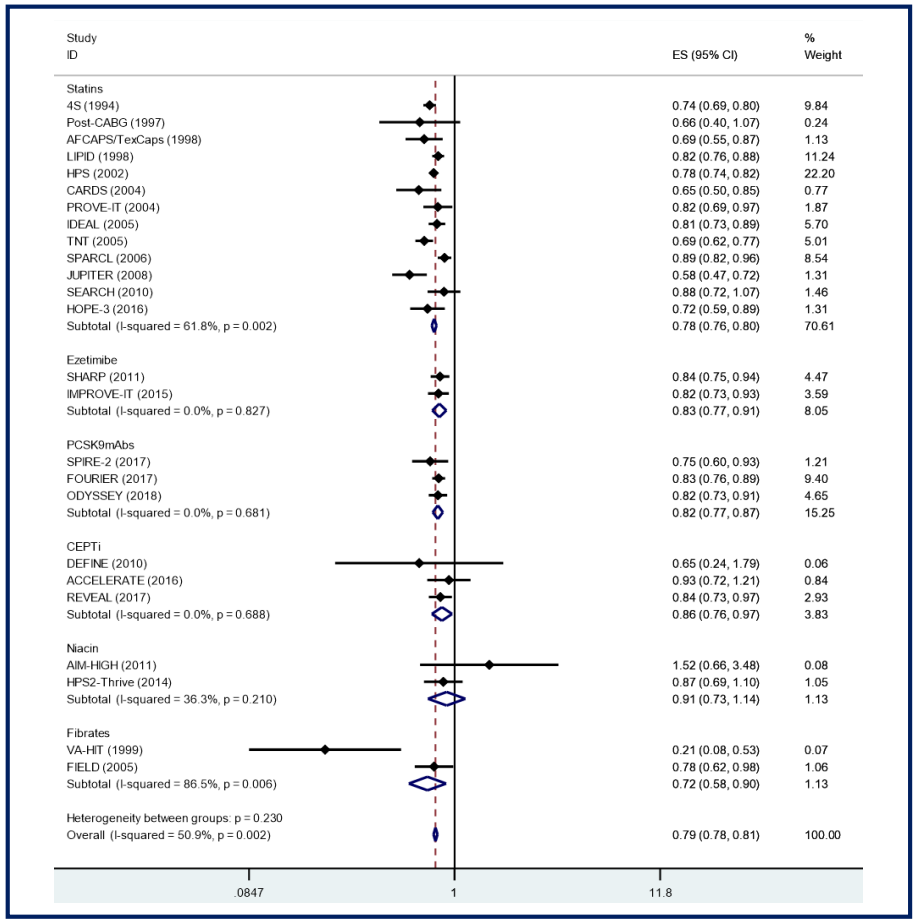
Analysis	variables	OR_{CHD} (95% CI)	p value
Association of apoB with risk of CHD	apoB	0.770 (0.760 - 0.781)	1.42E-170
Association of LDL-C with risk of CHD	LDL-C	0.846 (0.833 - 0.858)	8.16E-77
Association of triglycerides with risk of CHD	Triglycerides	0.815 (0.785 - 0.846)	1.37E-18
Association of LDL-C and triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849 - 0.875)	6.92E-65
	Triglycerides	0.876 (0.850 - 0.902)	1.36E-14
Association of LDL-C, triglycerides and apoB with risk of CHD included in same model	apoB	0.761 (0.723 - 0.798)	7.51E-20
	LDL-C	1.010 (0.967 - 1.055)	0.186
	Triglycerides	1.014 (0.965 - 1.065)	0.189
Association of LDL-C and apoB with risk of CHD included in same model	apoB	0.762 (0.738 - 0.787)	1.27E-36
	LDL-C	1.009 (0.977 - 1.042)	0.140
Association of triglycerides and apoB with risk of CHD included in same model	apoB	0.765 (0.751 - 0.779)	1.20E-105
	triglycerides	1.011 (0.975 - 1.048)	0.161

Ference BA, et al. JAMA. 2019;321(4):1-11. doi:10.1001/jama.2018.20045

Meta-Analysis of Various Lipid lowering Therapies per unit lower apoB

- N = 25 trials (6 classes of lipid lowering therapy)
- N = 285,241 participants (mean age: 63.3 years; female sex: 24.7%)
- N = 40,244 first major cardiovascular events
- mean baseline LDL-C level = 100.7 mg/dL mean baseline apoB level = 93.9 mg/dL
- mean absolute Δ apoB between the treatment and comparison groups at one year was 24.1 mg/dL.
- **overall RR per 30 mg/dL reduction in apoB HR: 0.79 (95% CI 0.77-0.81) for major CV events**

Galimberti F, Ference BA, et al. in progress



S.I.Te.C.S.
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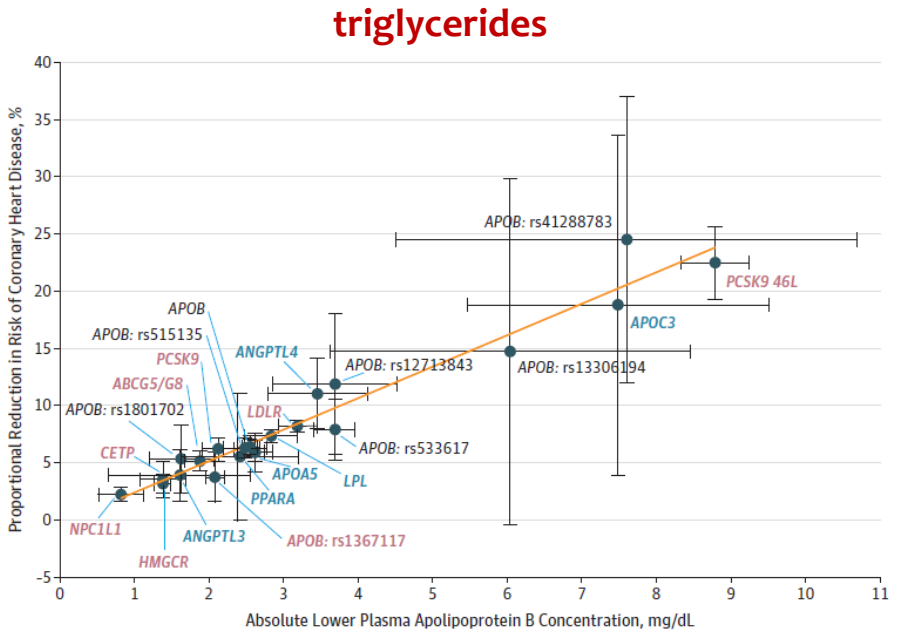
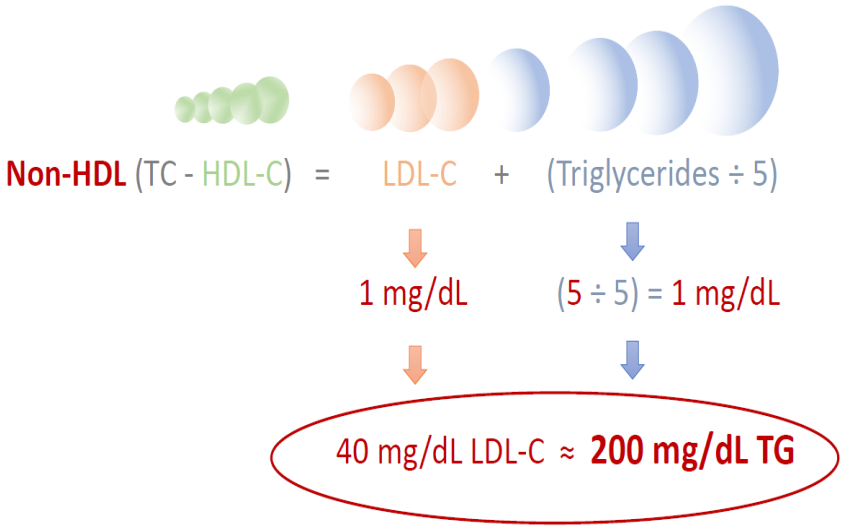
How much to we have to lower triglycerides to reduce risk?



Amount triglycerides must be lowered to reduce apoB by same amount as 1 mmol/L lower LDL



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

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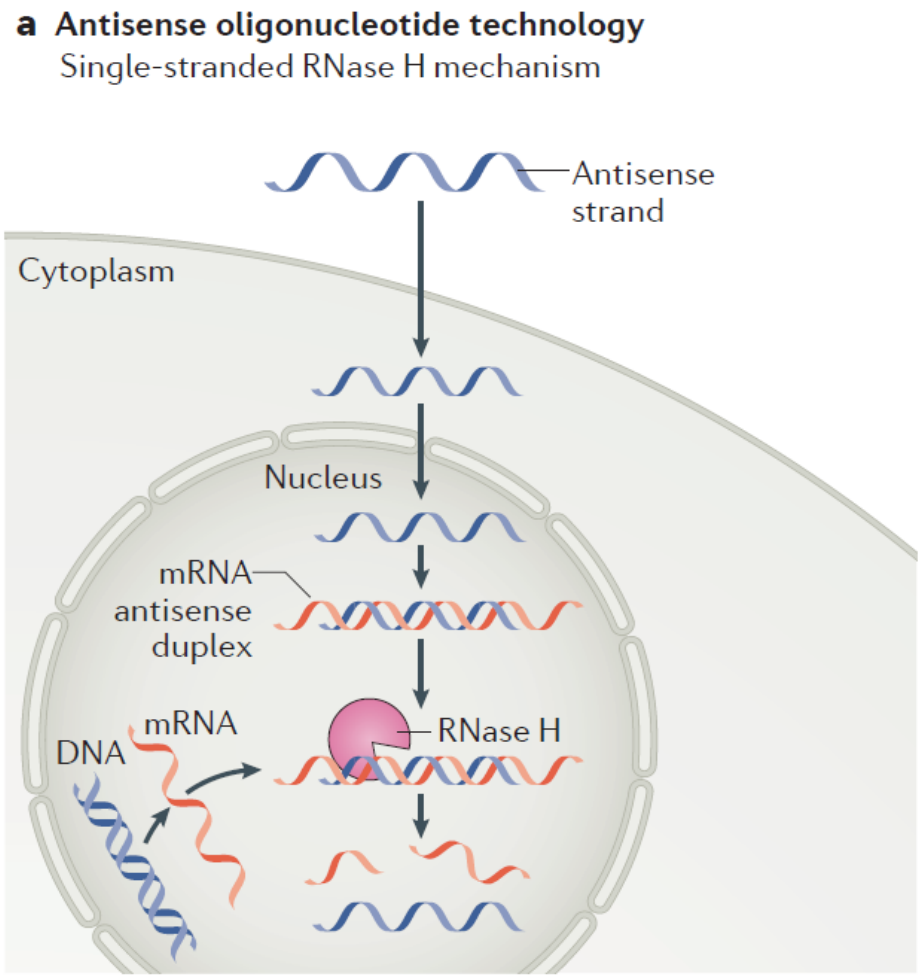
Anti sense oligonutides



<u>Problems to evercome</u>

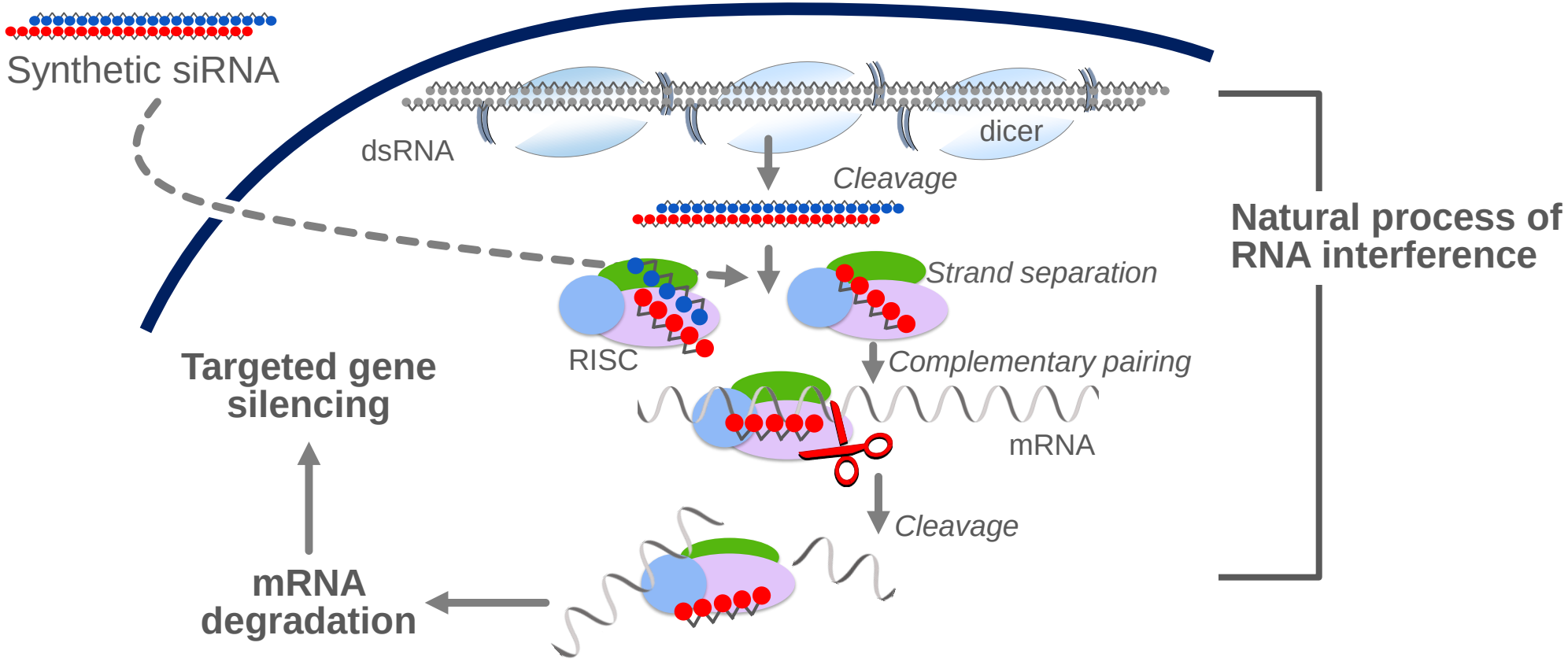
Filtered through the kidney

Immunogenicty

Destruction by endonucleases

Uptake by liver

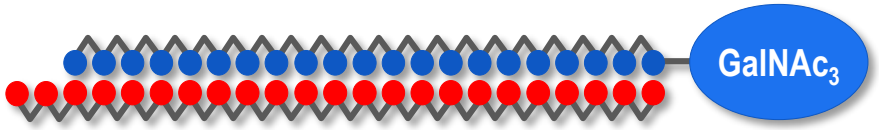
RNAi is an intrinsic process for inhibiting mRNA



GalNAc-siRNA conjugates facilitate rapid hepatic uptake

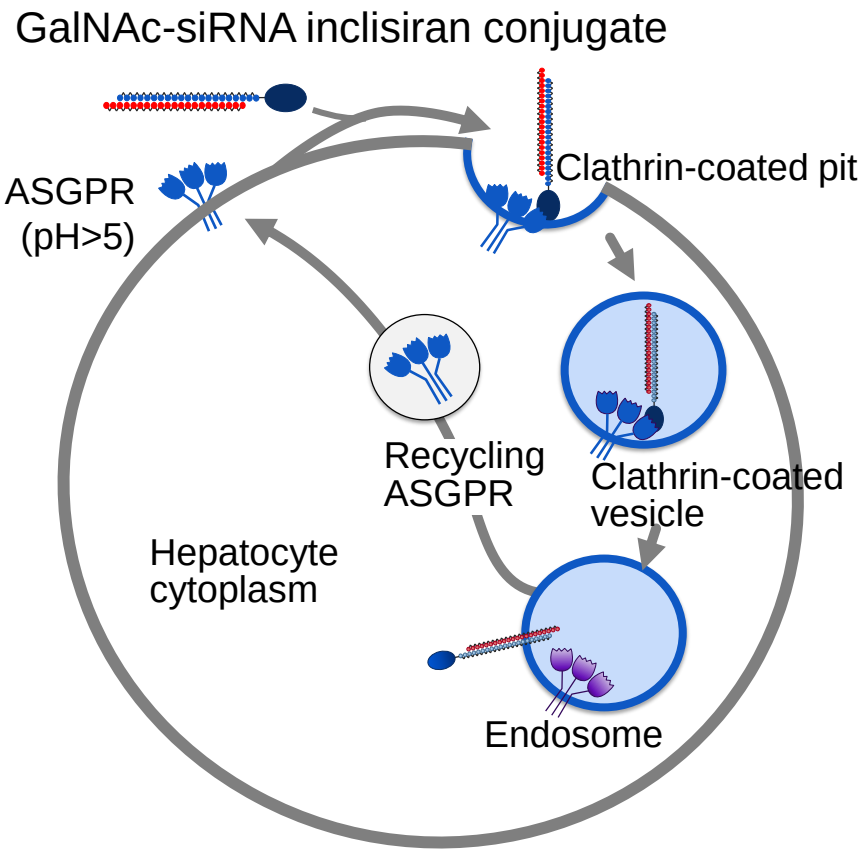
Asialoglycoprotein receptor (ASGPR)

- Highly expressed in hepatocytes only
- High rate of uptake



Inclisiran

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



Emerging ANGPTL3 Blockade Therapies

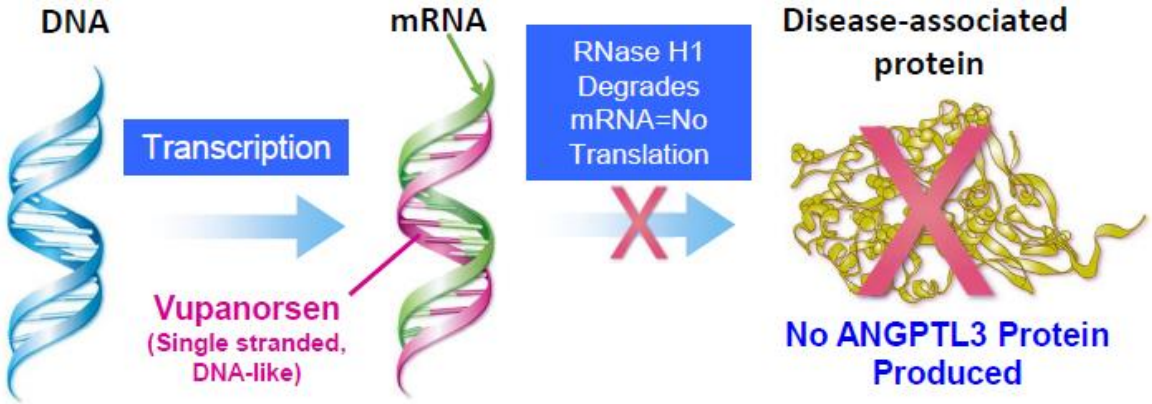
- **ANGPTL3 inhibitors currently in development:**
  - Evinacumab (ANGPTL3 mab) (phase 2-3)
  - IONIS-ANGPTL3-Lx (Galnac ASO) (phase 2-3)
  - ARO-ANG3 (iRNA) (phase 1)

- **Pre-clinical studies**
  - Naturally ANGPTL3 deficient KK/san mouse model
  - ANGPTL3 -/- mouse model
  - Mice of different genetic backgrounds exposed to either evinacumab, Ionis ANGPTL3-Lx or ARO-ANG3:
    - LDLR -/-
    - ApoE -/-
    - LRP -/-
    - Sdn1 -/-
    - apoC3 -/-, apoC3 +/- or -/- and LDLR -/-
    - Mttp -/- apoC3 -/

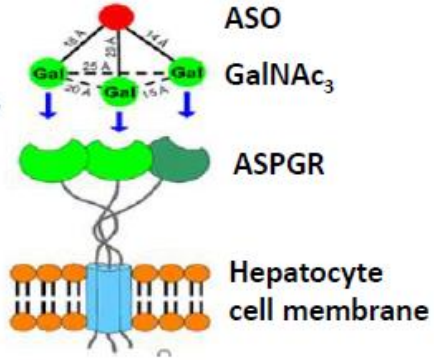
- **Healthy adults (phase 1)**

See Graham MJ et al N Engl J Med, 2017; Wang Y. et al, JLR, 2016

Vupanorsen *(AKCEA-ANGPTL3-L_{Rx} ISIS 703802)*

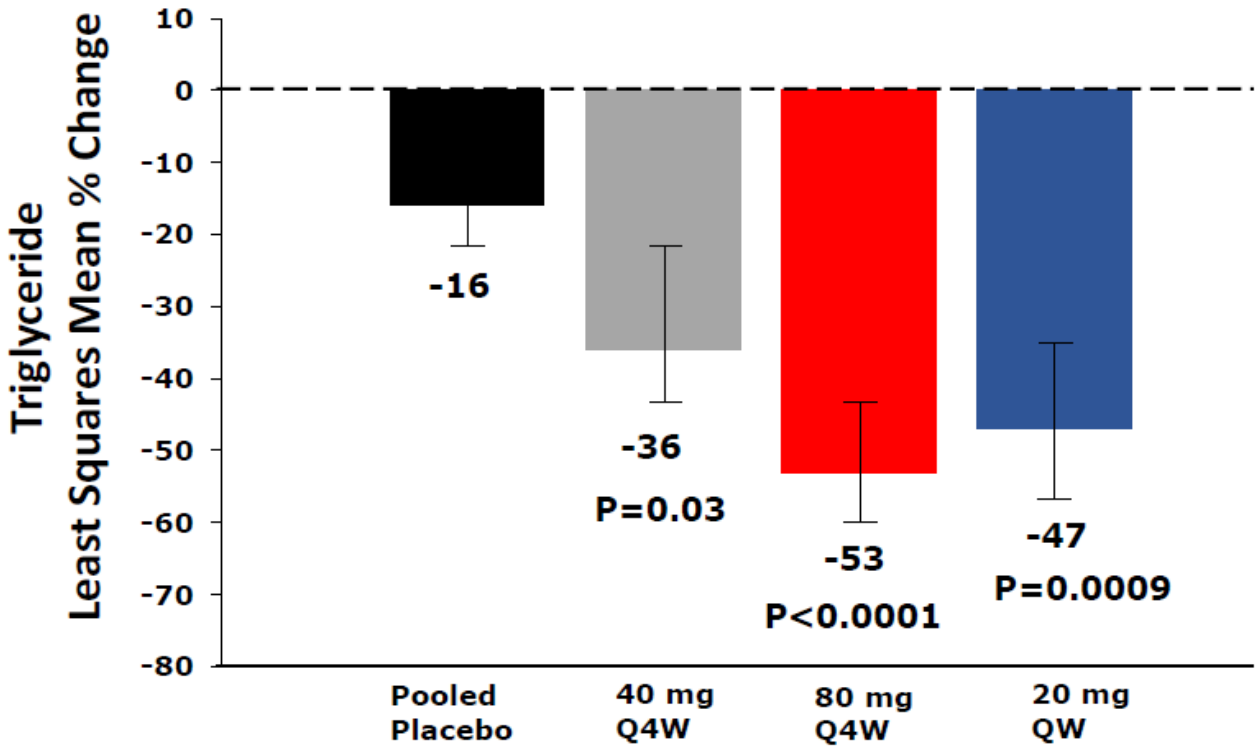


- Vupanorsen is an antisense oligonucleotide (ASO) targeting hepatic *ANGPTL3* mRNA.
- It is a second-generation N-acetyl galactosamine ($GalNAc_3$)-conjugated ASO that binds to the asialoglycoprotein receptor (ASGPR) on hepatocytes leading to enhanced intracellular uptake thus allowing lower dosing to achieve similar therapeutic efficacy as unconjugated ASOs.
- A prior Phase 1 study with vupanorsen in healthy volunteers with elevated triglyceride levels showed dose-dependent reductions in ANGPTL3, triglycerides and atherogenic lipoproteins.



Prakash TP et al. Nucleic Acid Res 2014;42:8796

Primary Endpoint: Percent Change in Triglycerides from Baseline to Month 6



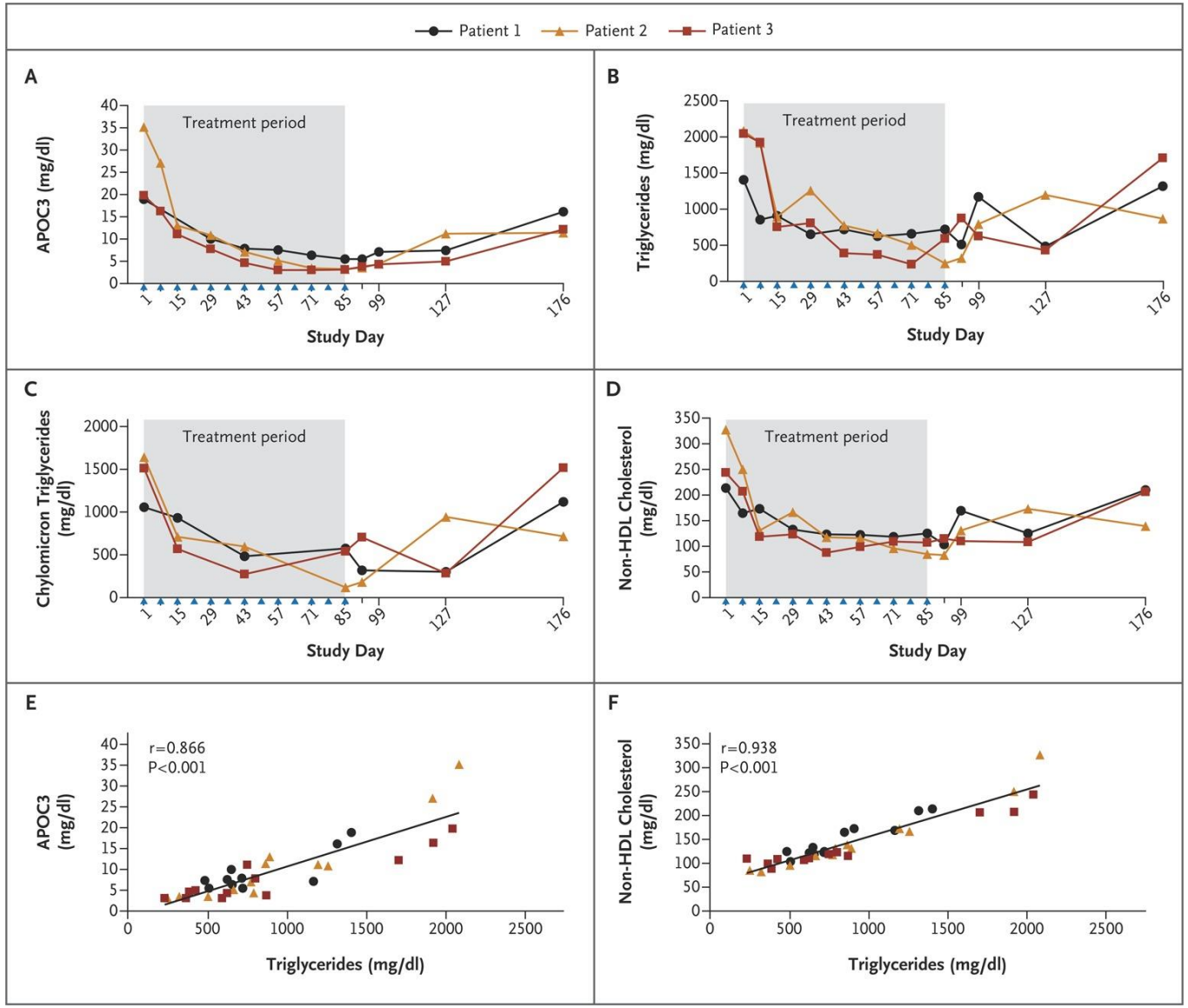
Primary Endpoint Analysis:
Pairwise comparison between each vupanorsen group and pooled placebo group using an ANCOVA model, with treatment group as a fixed factor and log-transformed baseline triglycerides as a covariate.

Missing data imputed by multiple imputation model under assumption of missing at random.

Error bars denote the 95% CI, P-values vs pooled placebo
QW=every week, Q4W=every 4 weeks

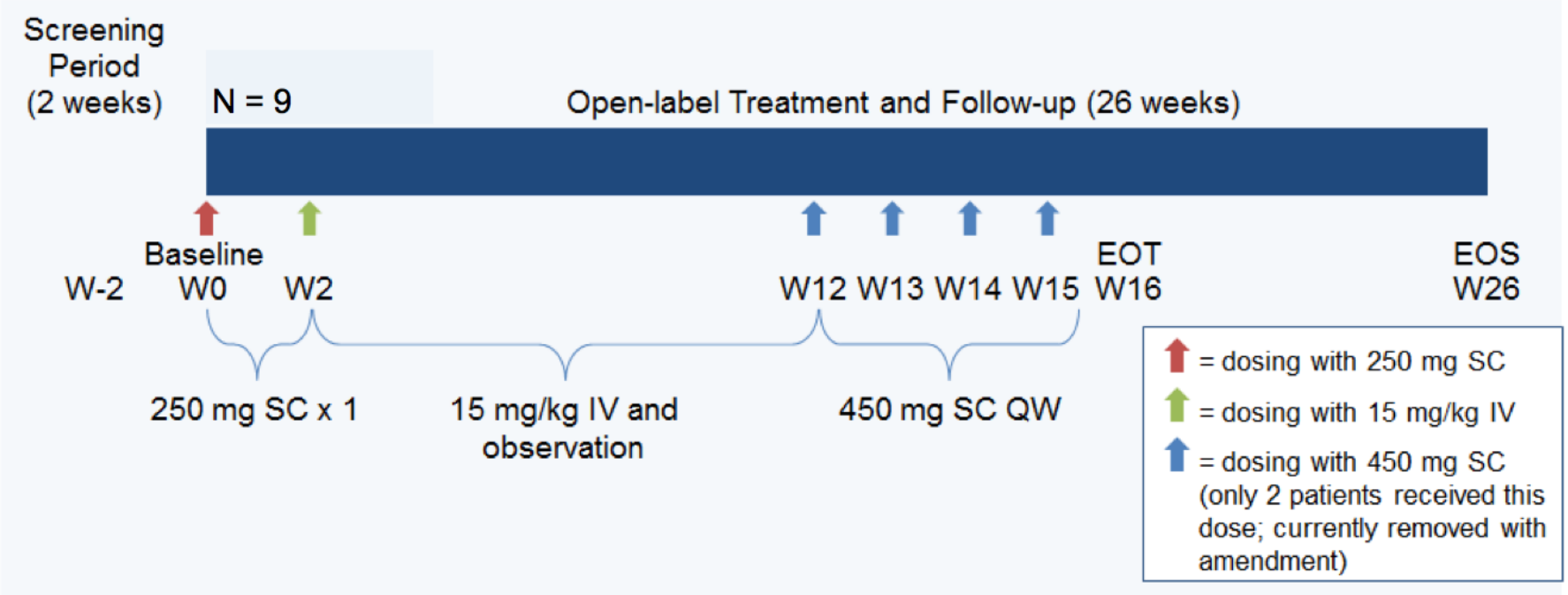
European Heart Journal (2020) 00, 1–10

Volanesorsen in FCS: Lessons from Phase 2 Study



Gaudet D et al. N Engl J Med 2014;371:2200-2206

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

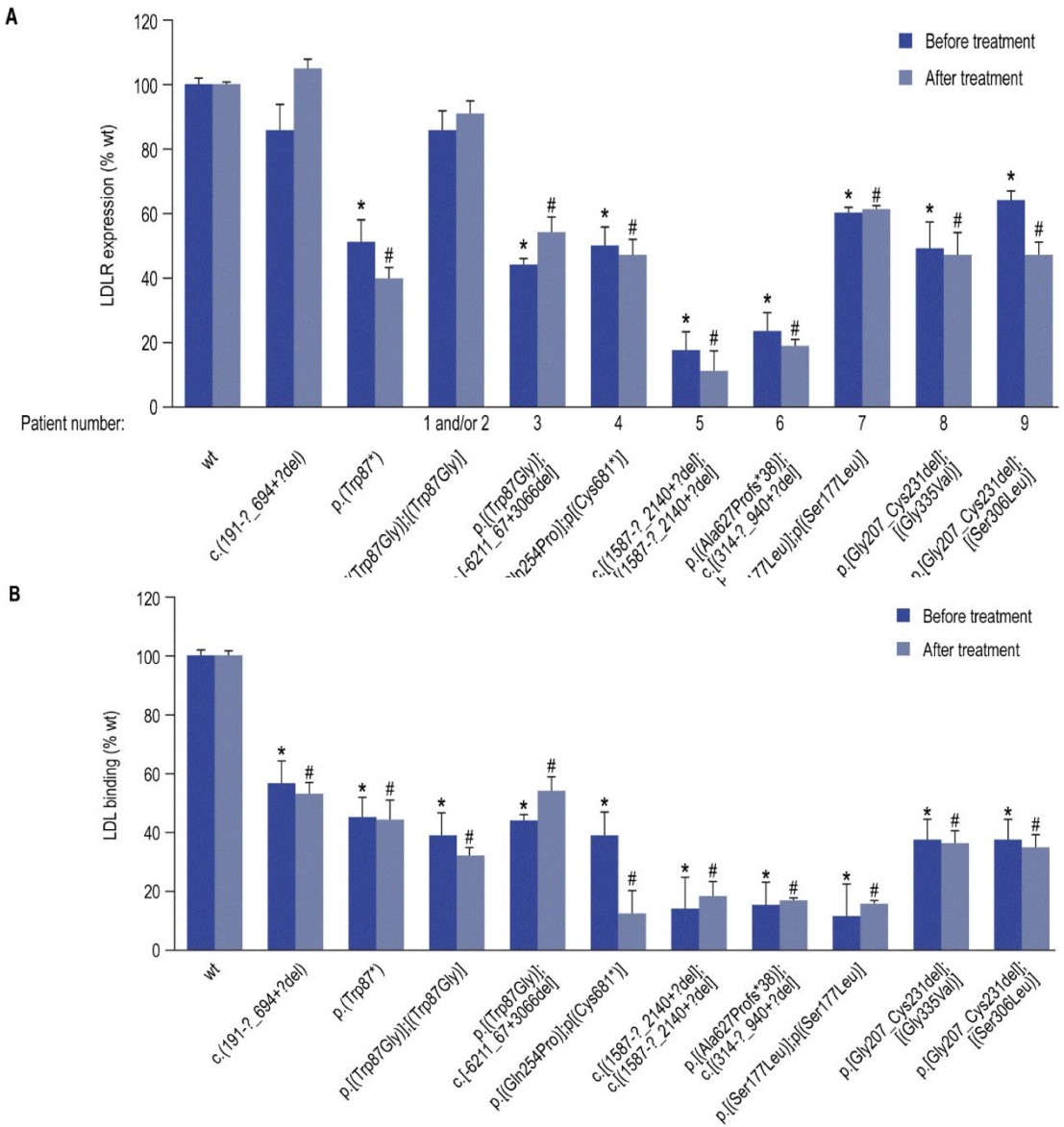


Current LLT was maintained from at least 4 weeks before screening, and through the 26-week treatment and observation period

The Effect of Evinacumab in HoFH was not LDLR Dependent

LDLR expression

LDL binding



Banerjee P, et al 2019

SUMMARY

A number of new pharmacological approaches are currently available including

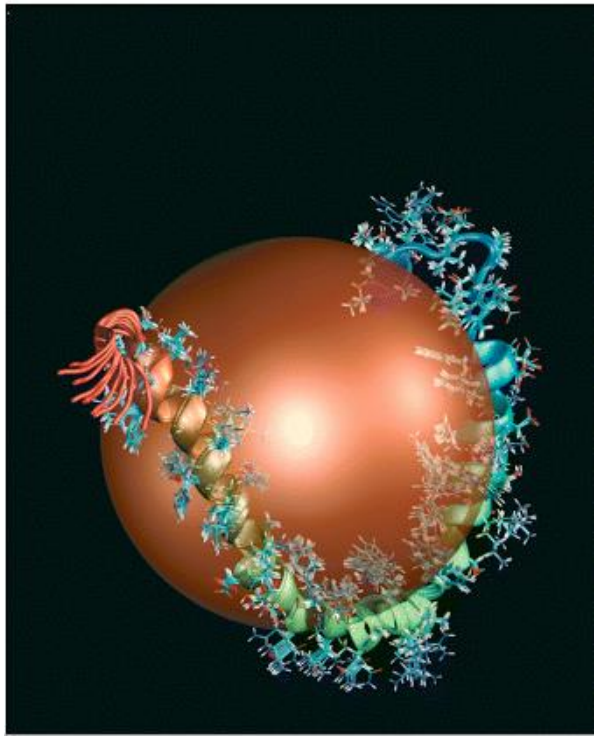
- **Monoclonal antibodies**
- **Oral small molecules**
- **si-RNA**
- **Antisense Oligonuclotides**
- **Vaccination**

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

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

Apolipoprotein C-III

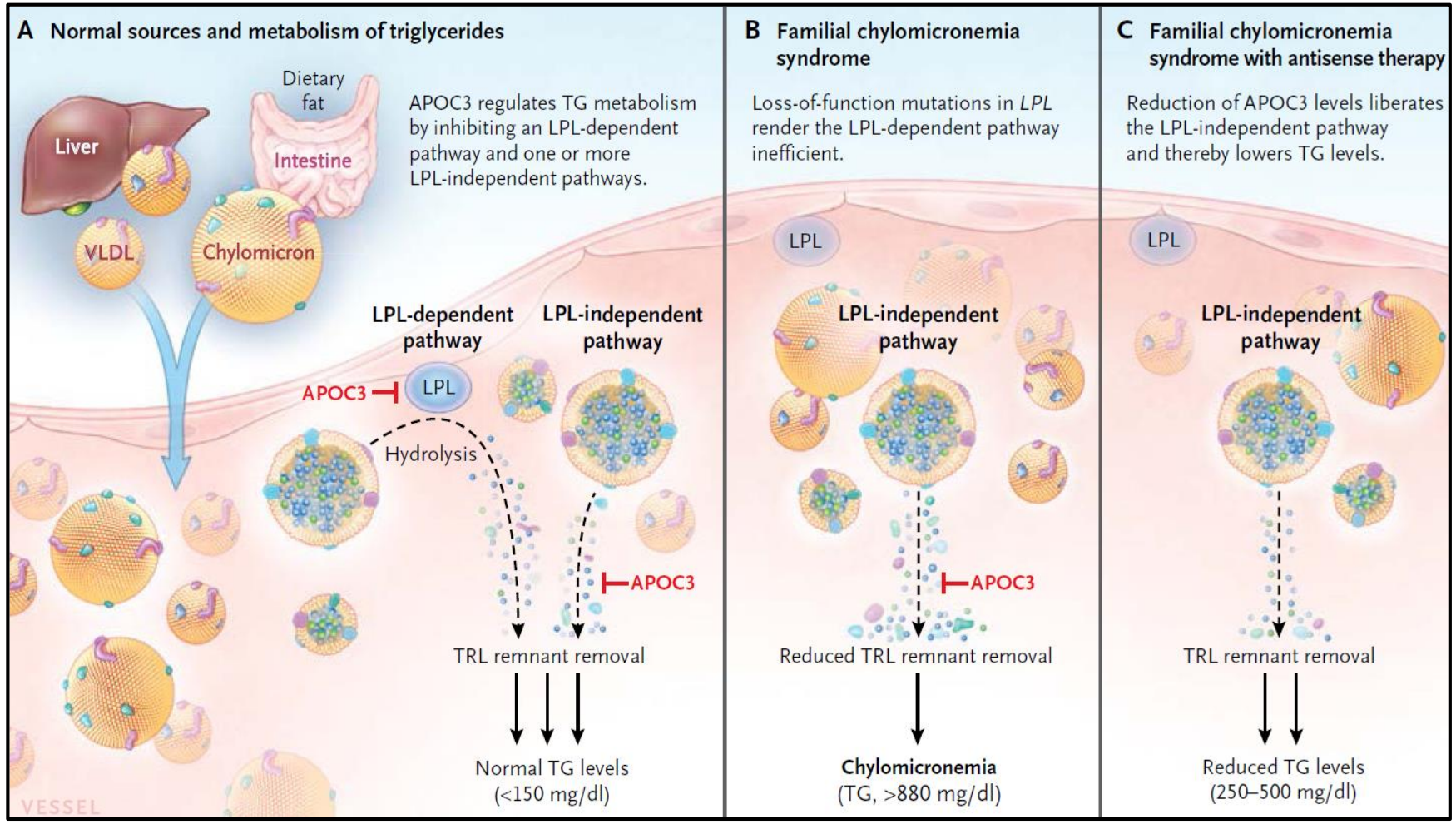
Key Regulator of Serum Triglyceride Levels



ApoC-III in a complex with an SDS micelle as derived by NMR

- **ApoC-III is a 79 amino acid glycoprotein synthesized principally in the liver**
  - Associated with apoB-containing lipoproteins and HDL
- **Plays a key role in determining serum triglyceride levels**
- **Genetically validated target as a causal mediator of CVD-**
  - **Ashkenazi Jews, Lancaster Amish, Exome Sequencing Project, Copenhagen City cohorts**
- **ApoC-III and triglycerides are independent risk factors for cardiovascular disease**

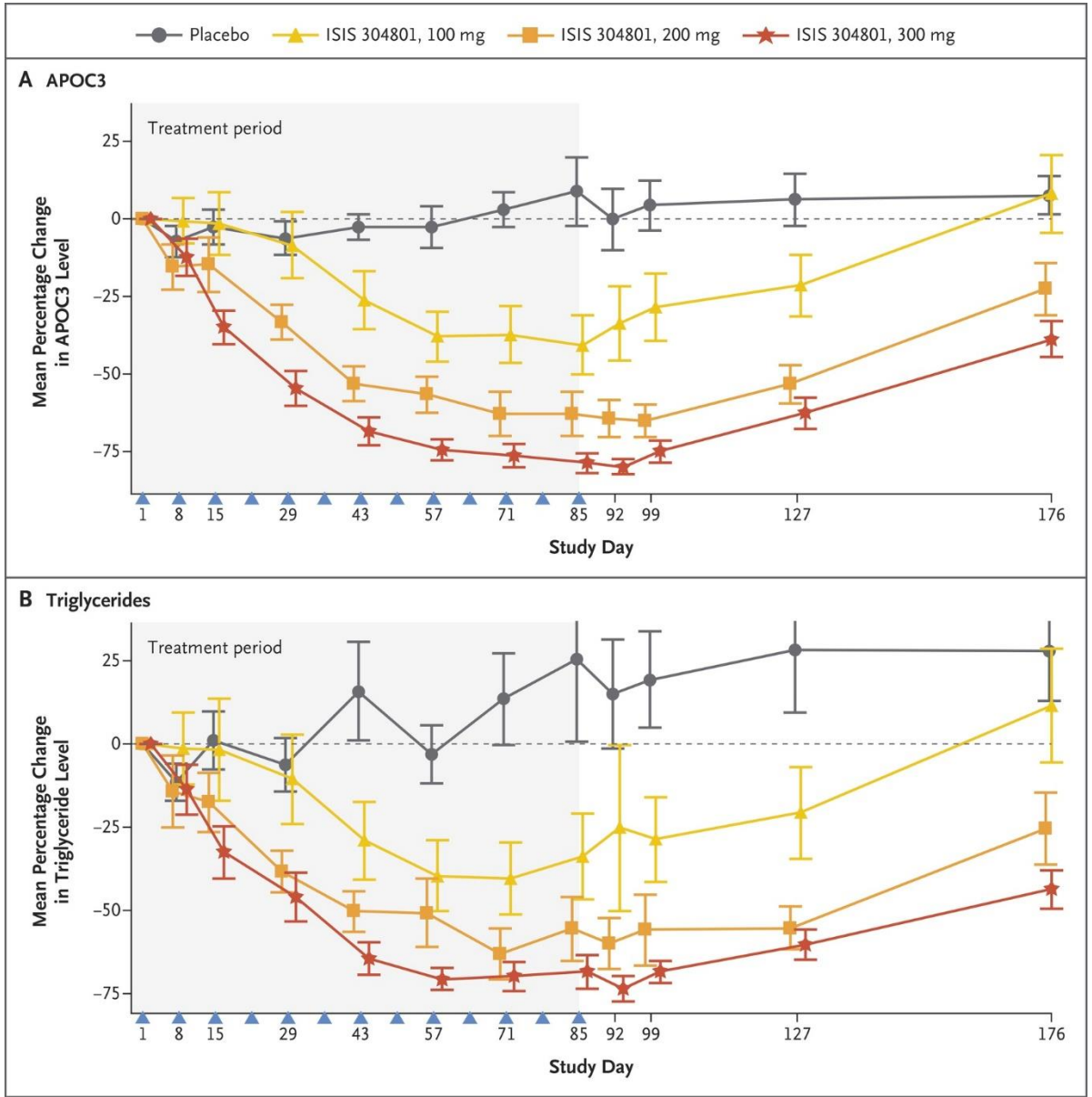
Rationale for APOC-III silencing



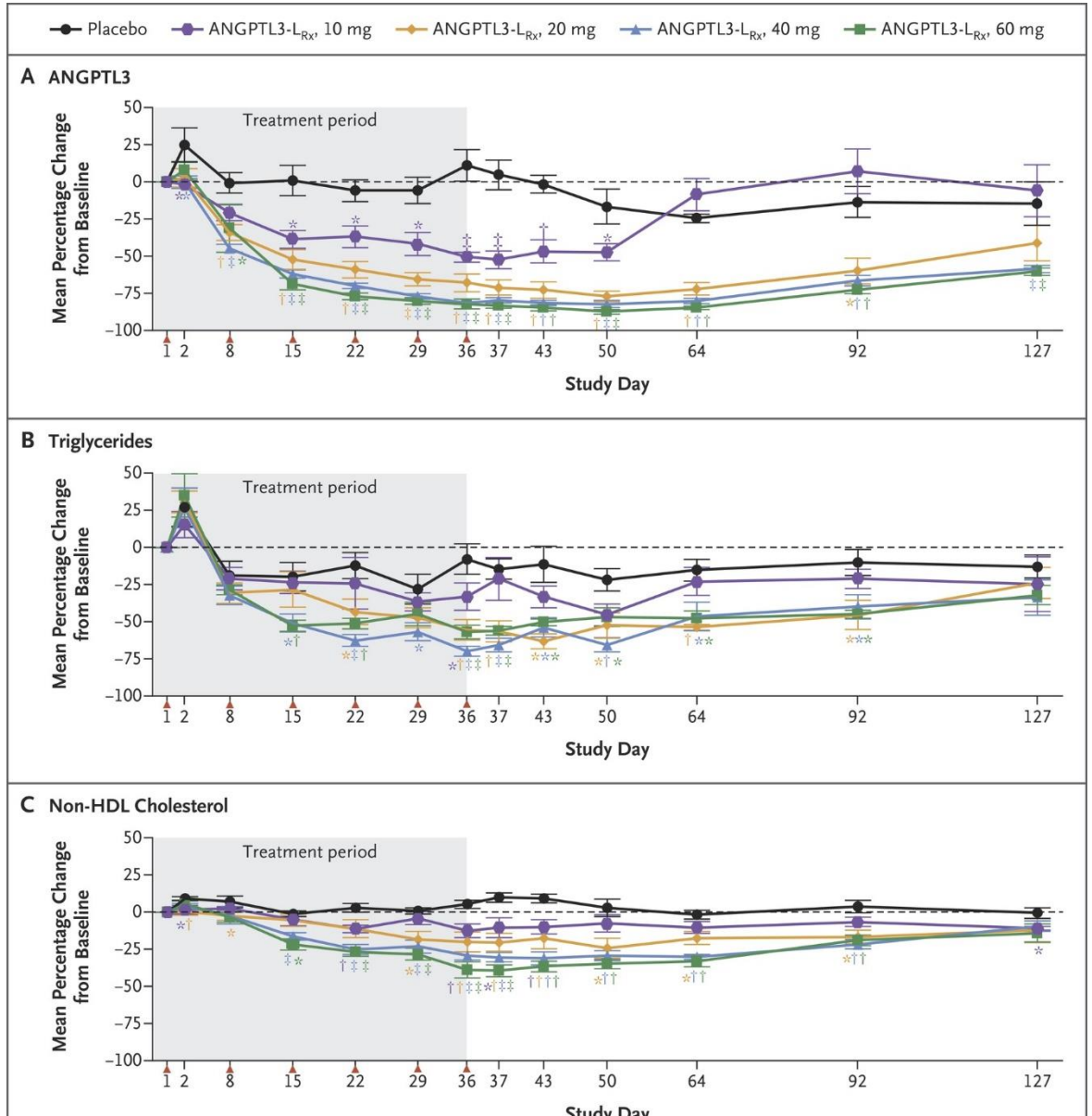
Da: Gaudet, Brisson, Targeting APOC3 in the Familial Chylomicronemia Syndrome, N Eng J Med 2014

Lowering TG through Apo C III inhibition antisense oligo or ANGPTL3 antisense

Gaudet D NEJM 2015 Volaneresen



Graham MJ NEJM 2017



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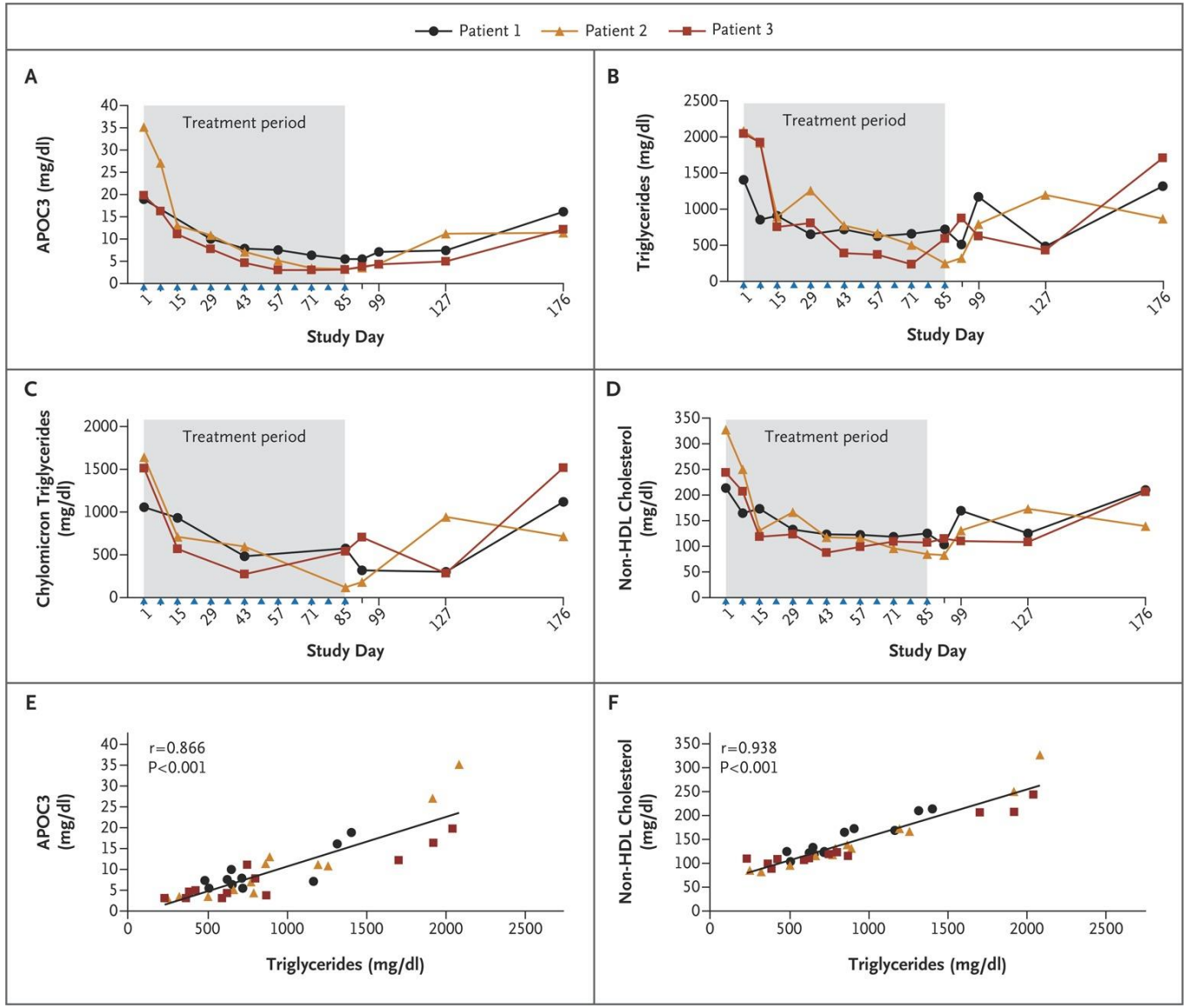

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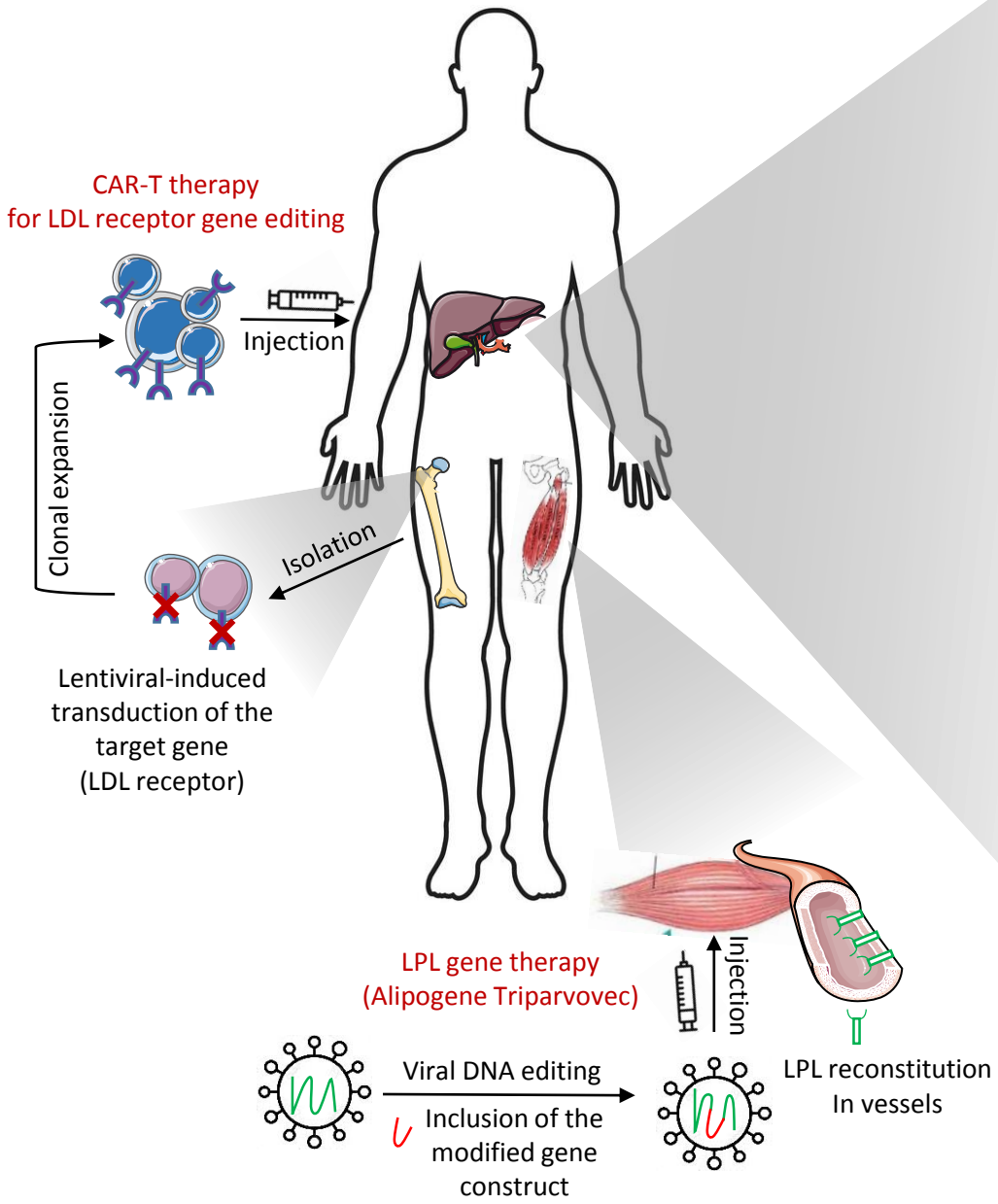

target	*mechanism*	*compound*
PCSK9	**DNA**	CRISPR-Cas9 based «BE-pcsk9 w159»
	RNA	Inclisiran
	Protein	mAb: Alirocumab, Evolocumab
Apo(a)	**RNA**	RNA interfering AMG 890
	RNA	ASOs: IONIS-APO(a)Rx; AKCEA-APO(a)-LRx
ApoCIII	**RNA**	RNAI interfering ISIS 304801
	RNA	ASO Volanesorsen
ANGPTL3	**DNA**	CRISPR-Cas9 based «BE-Angplt3 Gln135»
	RNA	ASO IONIS-ANGPTL3-LRx
	Protein	mAb: Evinacumab
ANGPLT4	**Protein**	mAb: 14D12
LDLR	**DNA**	CRISPR-Cas9 LDLR
	DNA	(AAV8G) vaccination

Figure 1