Lipidology Trials -

What's New and What's in the Pipeline?

Professor Basil S. Lewis, MD, FRCP, FACC, FESC

Past Chairman, WG on Cardiovascular Pharmacotherapy

European Society of Cardiology

SUPPORTED BY AN EDUCATIONAL GRANT FROM AMGEN and NOVARTIS

ESC Working Group Cardiovascular Pharmacotherapy

Declaration of Conflict Of Interest

I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research support:	AstraZeneca, Bayer Healthcare, MSD, Resverlogix, KOWA, Pfizer
Receipt of honoraria or consultation fees:	Bayer Healthcare, MSD, Pfizer, Novo Nordisk
Participation in a company sponsored speaker's bureau:	Pfizer, Novo Nordisk

ESC Working Group Cardiovascular Pharmacotherapy

Challenges in Lipidology Trials

- **What is the pathophysiology?**
  - What are the targets?
    - LDL? HDL? TG? LP(a)?
  - Relation between lipidology, atherosclerosis and CV events?
  - Time discrepancies?

- **What are the end-points?**
  - Surrogate endpoints? Plasma lipids? Plaque volume? Extent of disease?
  - Can these guide in early/late phases of drug development?
  - Outcome events – This is what matters!

- **What is the comparator?**
  - Keeping pace with a rapidly evolving field

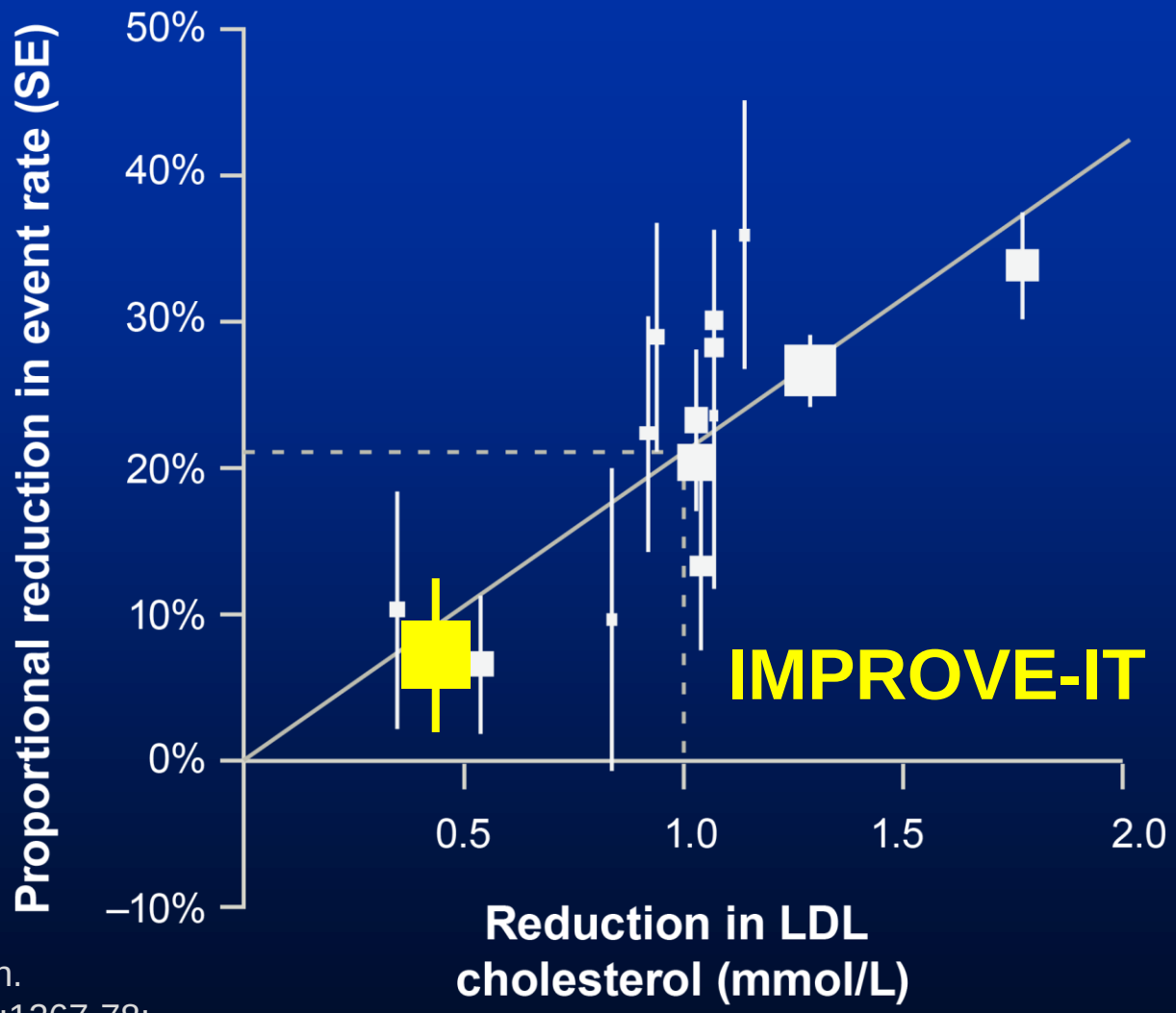
ESC Working Group Cardiovascular Pharmacotherapy

Targets

- **Targeting LDL**
  - PCSK9 Inhibitors (FOURIER, SPIRE, ODYSSEY)
  - RNA interference (RNAi) to reduce PCSK9 (ORION)
  - Decreasing LDL synthesis - Bempedoic acid
- **Targeting HDL**
  - CETP inhibitors
  - Epigenetics - BET on MACE program
  - Apo-A1 infusion – AEGIS program
- **Targeting triglycerides**
  - REDUCE-IT
  - PROMINENT
- **New - Targeting ANGPTL3 (inh of lipoprotein lipase)**

ESC Working Group Cardiovascular Pharmacotherapy

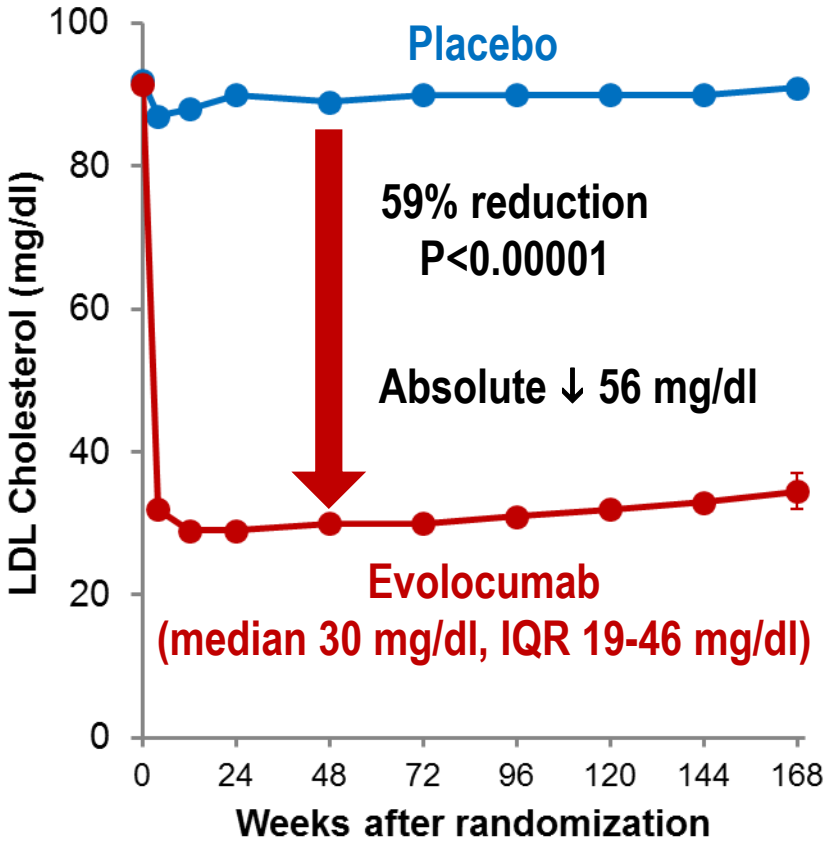
IMPROVE-IT - Proves again the LDL Hypothesis

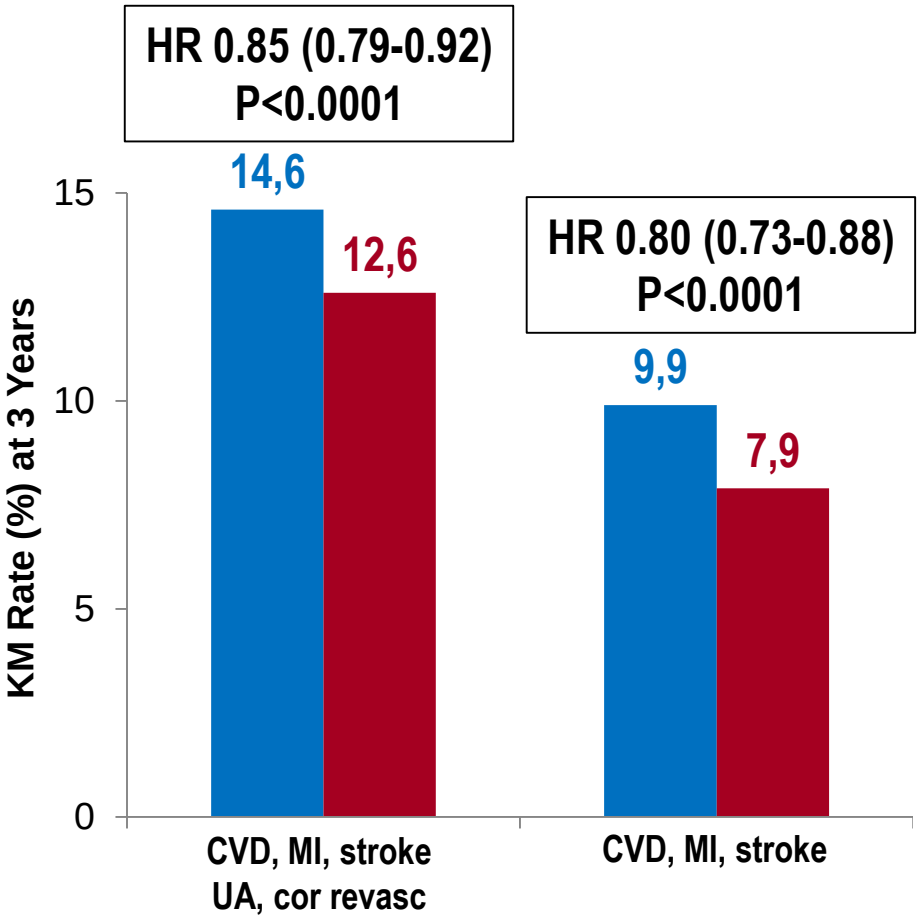


CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

Effects of Evolocumab

- ↓ LDL-C by 59% to a median of 30 mg/dL
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated

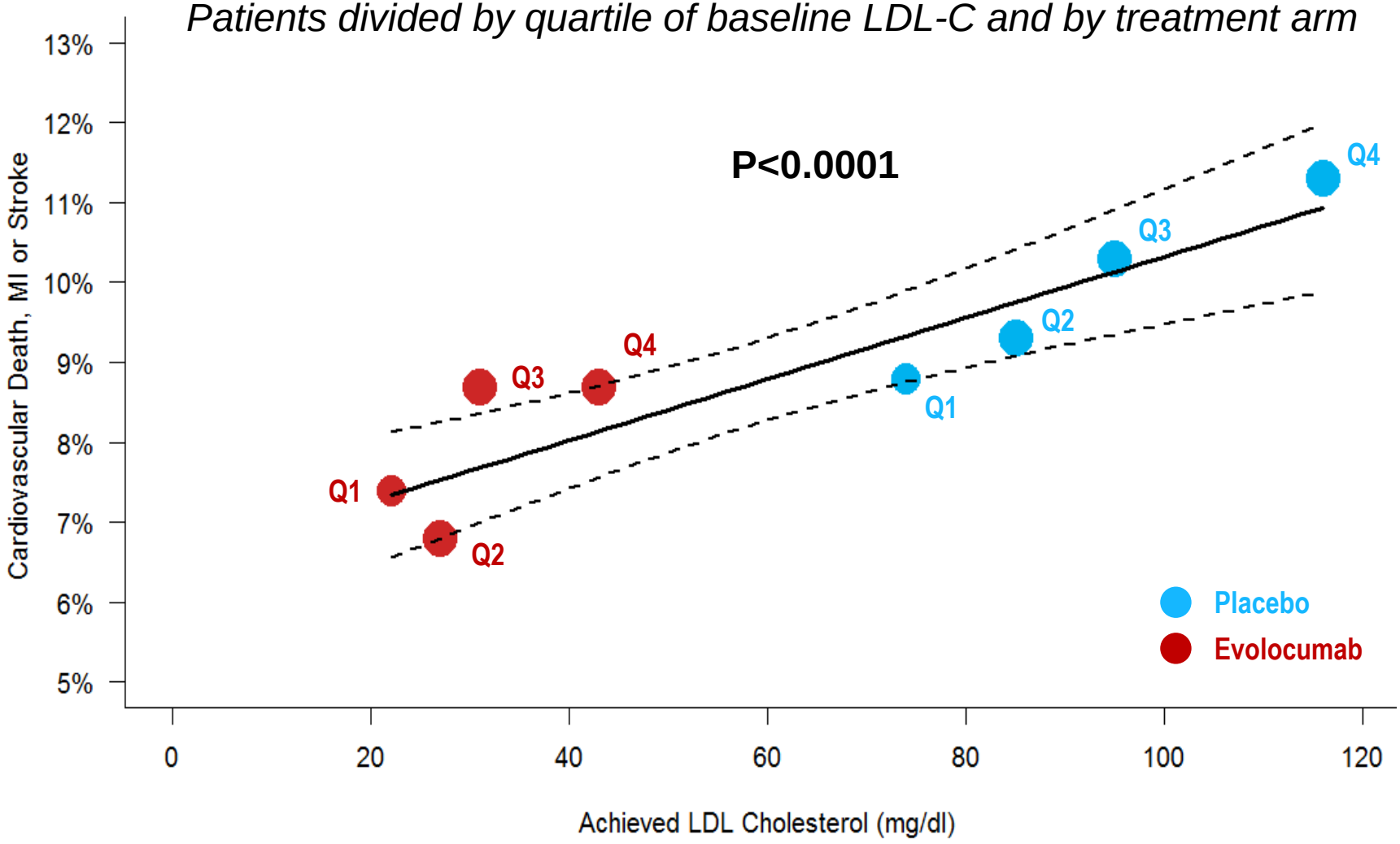




Sabatine MS et al. *NEJM* 2017;376:1713-22

Lower LDL-C Is Better

Patients divided by quartile of baseline LDL-C and by treatment arm



From: **Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events: A Prespecified Analysis From the FOURIER Trial**

JAMA Cardiol. Published online May 22, 2019. doi:10.1001/jamacardio.2019.0886

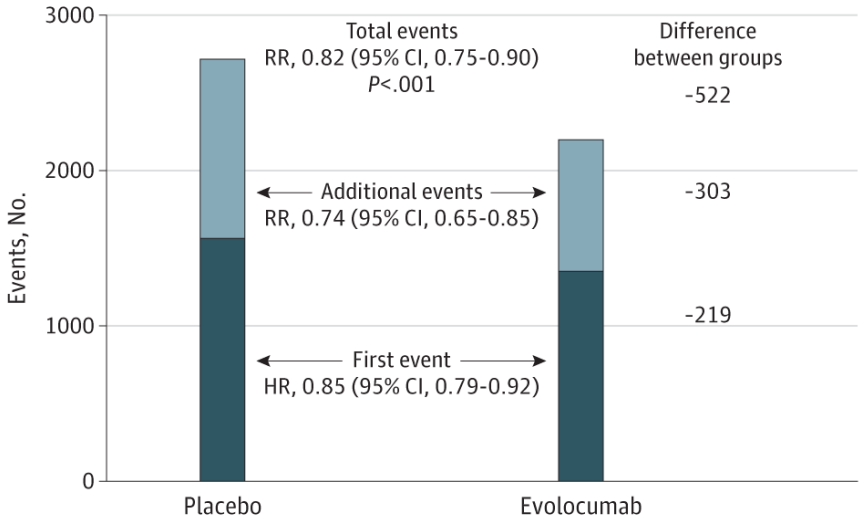


Figure Legend:

First, Additional, and Total Primary End Point Events During Follow-up by Randomization GroupThe first occurrence of the primary end point was significantly reduced in the evolocumab group compared with the placebo group (hazard ratio [HR], 0.85; 95% CI, 0.79-0.92; P < .001), as were additional events (incidence rate ratio [RR], 0.74; 95% CI, 0.65-0.85) and total events (RR, 0.82; 95% CI, 0.75-0.90; P < .001).

From: **Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events in Patients With Cardiovascular Disease: A Prespecified Analysis From the FOURIER Trial**

JAMA Cardiol. Published online May 22, 2019. doi:10.1001/jamacardio.2019.0886

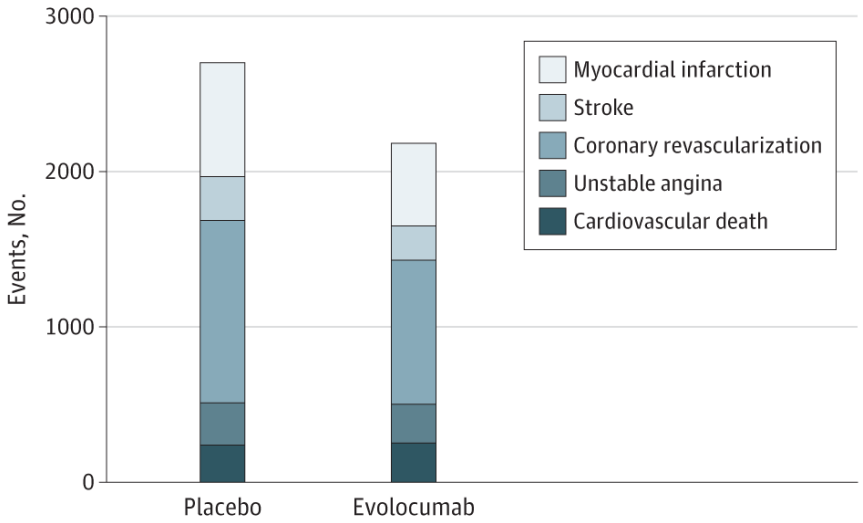
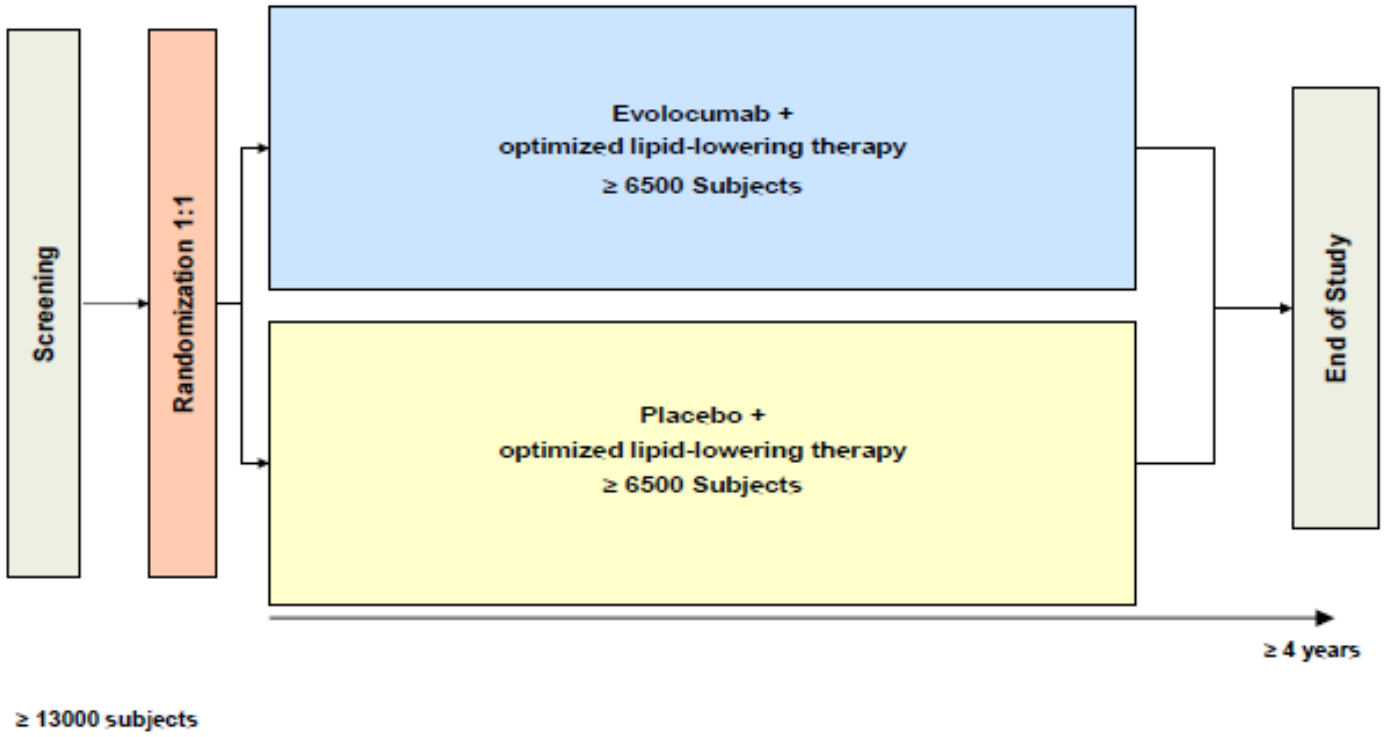


Figure Legend:

Total Events During Follow-up by Randomization Group for Components of the Primary End PointTotal events were significantly reduced with evolocumab vs placebo for the component of myocardial infarction (incidence rate ratio [RR], 0.74; 95% CI, 0.65-0.84; P < .001) and stroke (RR, 0.77; 95% CI, 0.64-0.93; P = .007) and coronary revascularizations (RR, 0.78; 95% CI, 0.71-0.87; P < .001). There was no difference between treatment groups in total hospitalization for unstable angina events or in cardiovascular deaths.

VESALIUS: Effect of Evolocumab in Pts without Previous MI or Stroke



ESC Working Group Cardiovascular Pharmacotherapy

ORION-1

Inclisiran inhibits PCSK9 synthesis by RNA interference

Planned interim analysis of a multi-center randomized controlled dose-finding trial

Kausik K Ray, Ulf Landmesser, Lawrence A Leiter, David Kallend, Peter Wijngaard

Robert Dufour, Timothy Hall, Mahir Karakas, Traci Turner, Frank LJ Visseren,

R Scott Wright, and John JP Kastelein

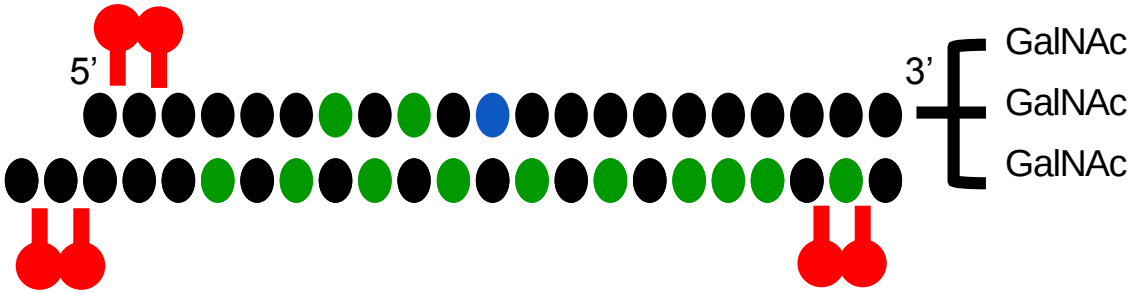
On behalf of the ORION-1 investigators

ESC Working Group Cardiovascular Pharmacotherapy

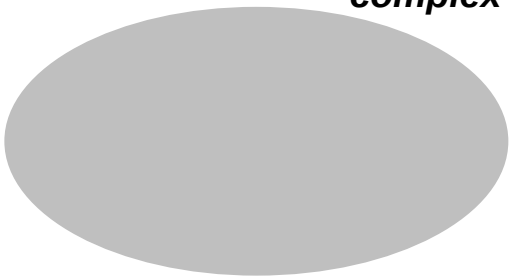
PCSK9 synthesis inhibition via RNA interference

Inclisiran harnesses a natural catalytic process

- Synthetic double strand 21-23mer ***oligonucleotide***
- 3x GalNAc at sense 3' end enables ***hepatic-specific uptake*** via ASGP receptor
- Chemically modified to prevent RNAse degradation
- Dicer separates antisense strand – and incorporates it into RISC
- **RISC degrades PCSK9 mRNA catalytically to halt PCSK9 protein synthesis in the liver**



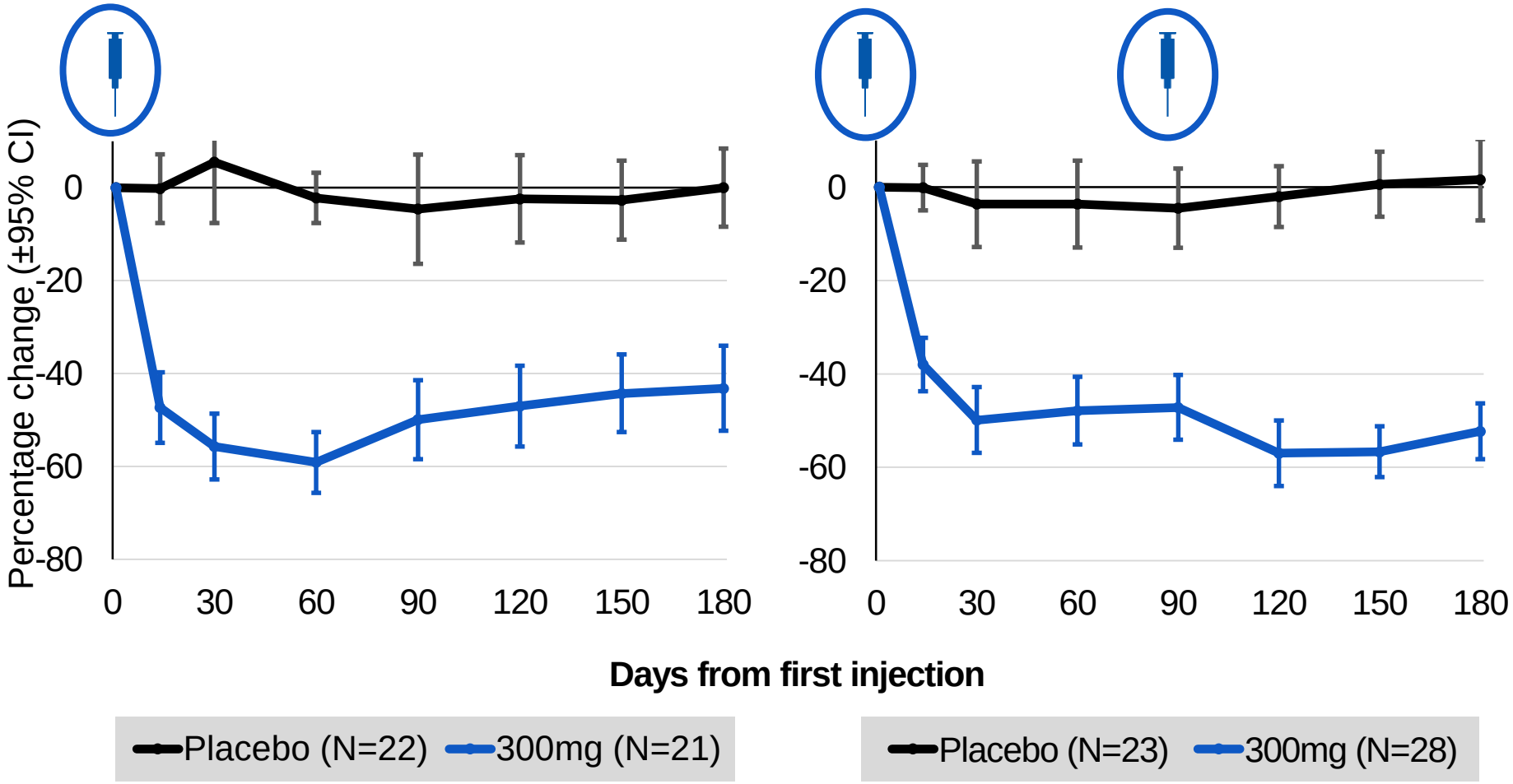
RISC - ***RNA induced silencing complex***



Imperial College London

The Medicines Company

One dose and two doses of inclisiran up to day 180
Efficacy of 300 mg versus placebo on LDL-C



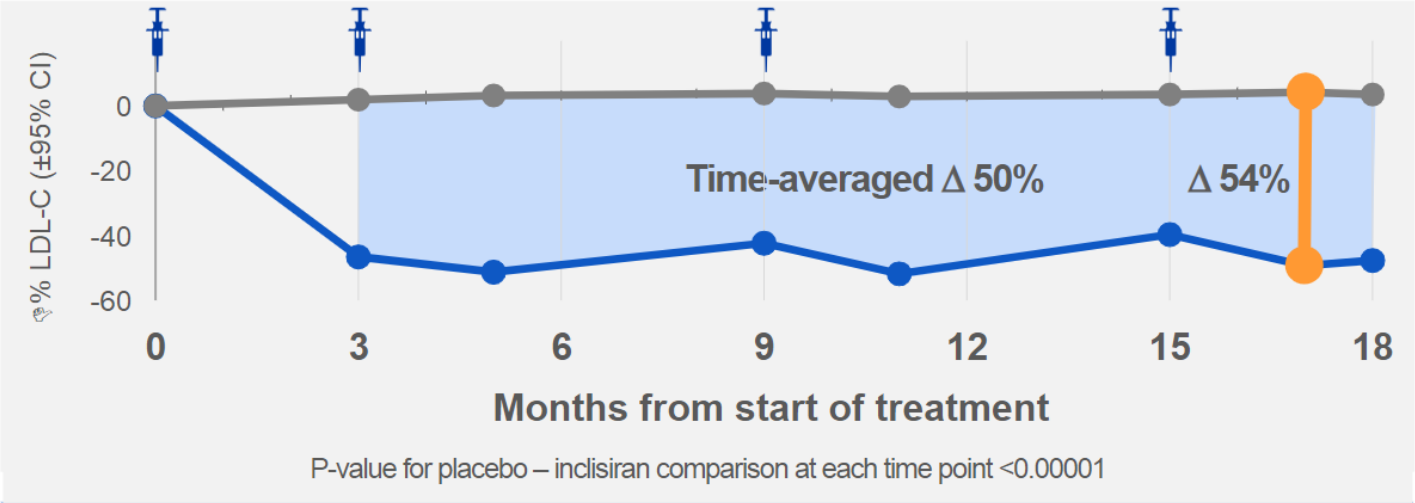
Available data as of 25 Oct 2016

Imperial College London

ORION-11: Efficacy of Inclisiran for Lowering LDL in pts with ASCVD/Risk

ORION-11: Efficacy
Durable, potent and consistent effect over 18 months

Percent change in LDL-C over time – observed values ITT patients



1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

16

ORION-11 ESC 2019 | Late-Breaking Clinical Trial presentation | September 2nd 2019

Ray, ESC, Paris, Aug 2019

ESC Working Group Cardiovascular Pharmacotherapy

Silencing Novel Target Genes: A New Strategy for Lipid Lowering

Advantages of siRNAs

- same molecule can destroy multiple copies of the RNA in a way that provides substantial longevity in terms of duration of effect

- can be targeted directly to the liver

New gene targets – proteins that inhibit the lipoprotein lipase pathway and triglyceride metabolism

apolipoprotein C-III (APOC3)

angiopoietin-like 3 (ANGPTL3)

The siRNA molecules targeting these genes are both in development by Arrowhead Pharmaceuticals. ARO-APOC3 is being developed as a potential treatment for patients with severe hypertriglyceridemia and familial chylomicronemia syndrome, and ARO-ANG3 is being developed for the treatment of dyslipidemias such as familial hypercholesterolemia and other metabolic diseases.

Anti-PCSK9 Fusion Protein

News > Medscape Medical News > Conference News > EAS 2019

Novel Anti-PCSK9 Fusion Protein Slashes LDL-C Levels

Liam Davenport
June 03, 2019

0 Read Comments ADD TO EMAIL ALERTS

MAASTRICHT, The Netherlands — A novel antiproprotein convertase subtilisin/kexin type 9 (PCSK9) recombinant fusion protein that offers a more convenient dosing regimen than anti-PCSK9 monoclonal antibodies substantially decreases low-density-lipoprotein (LDL)-cholesterol levels on patients already taking maximally tolerated statins, results of a phase 2 trial show.

LIB003 combines a PCSK9-binding domain with human serum albumin in a recombinant fusion therapeutic agent derived from a mammalian cell line.

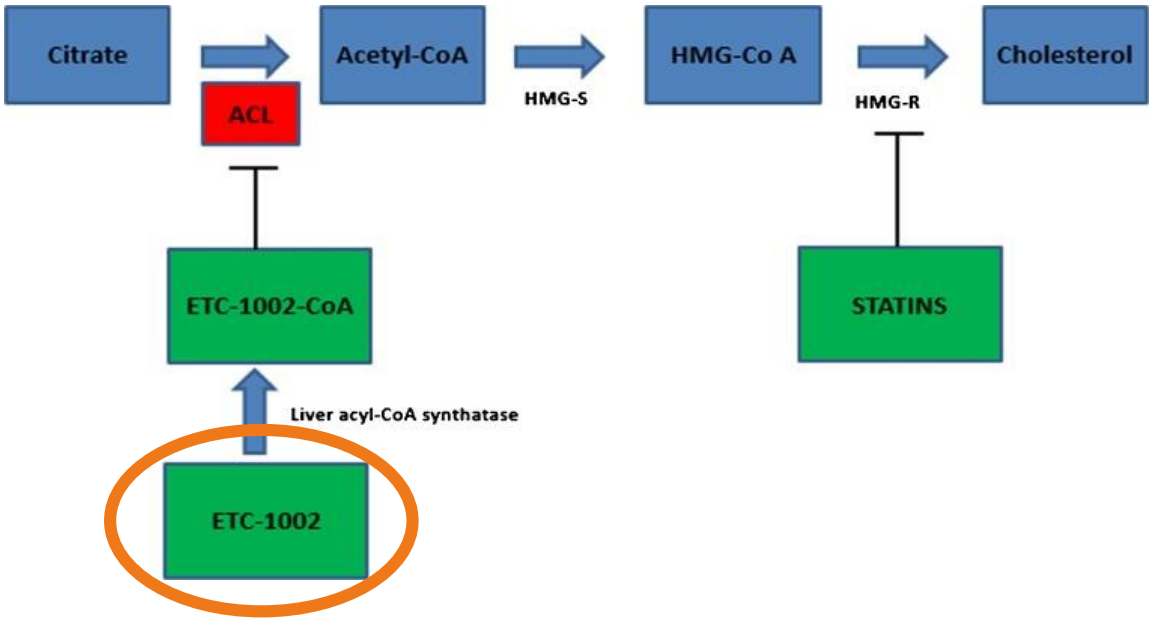
The binding domain blocks the interaction between PCSK9 and the LDL-cholesterol recepto, and the albumin linkage increases the half-life to 12 to 15 days, allowing low-volume injections to be given every 4 weeks.

Following on from promising phase 1 data, the team conducted a phase 2 study in which 81 patients were randomized to 150 mg, 300 mg, or 350 mg of LIB003 or placebo for 12 weeks.

Evan Stein, MD, founder, LIB Therapeutics, and Metabolic & Atherosclerosis Research Center, Cincinnati, presented the results here at the European Atherosclerosis Society 2019 Congress. LIB Therapeutics funded the study.

ESC Working Group Cardiovascular Pharmacotherapy

Targeting LDL: Novel Suppression of Cholesterol Synthesis - Bempedoic acid



- **Bempedoic acid - directly inhibits ATP citrate lyase (ACL), a key enzyme that supplies substrate for cholesterol and fatty acid synthesis; upregulates LDL receptors**

- **Esperion therapeutics - 12,604 patients, 1000 sites, approximately 30 countries**

ESC Working Group Cardiovascular Pharmacotherapy

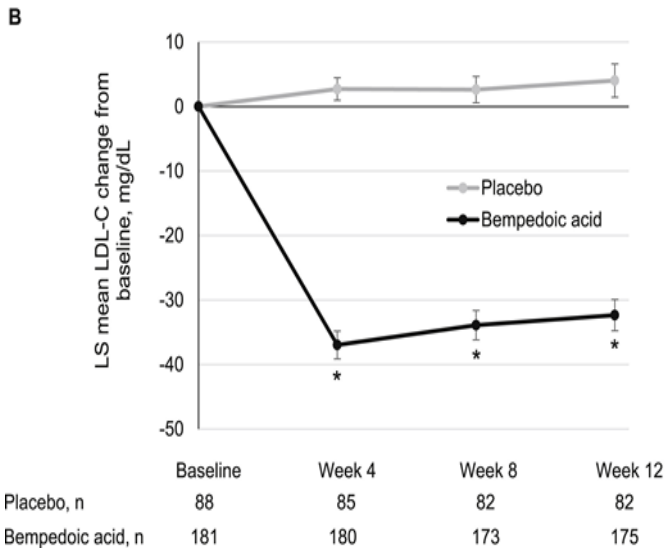
Contents lists available at ScienceDirect

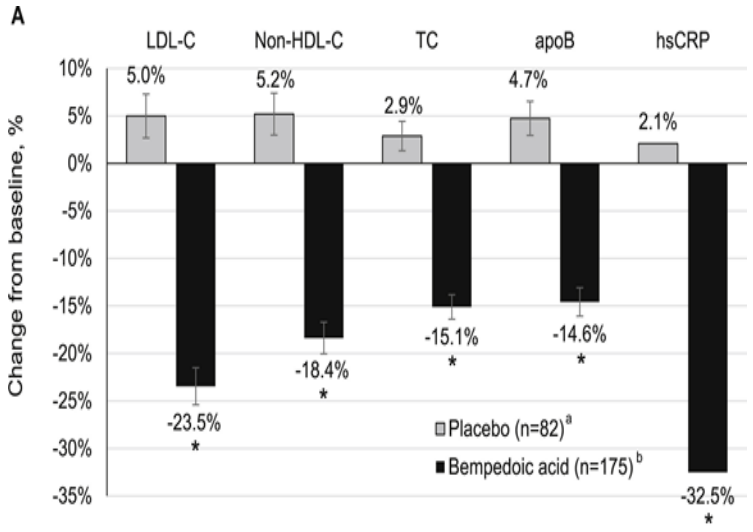
Atherosclerosis

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

Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study

Christie M. Ballantyne [a, *], Maciej Banach [b], G.B. John Mancini [c], Norman E. Lepor [d, e], Jeffrey C. Hanselman [f], Xin Zhao [f], Lawrence A. Leiter [g]





ESC Working Group Cardiovascular Pharmacotherapy

Targets

- **Targeting LDL**
  - Role of PCSK9 Inhibitors (FOURIER, SPIRE, ODYSSEY)
  - RNA interference (RNAi) to reduce PCSK9 (ORION)
  - Decreasing LDL synthesis - Bempedoic acid

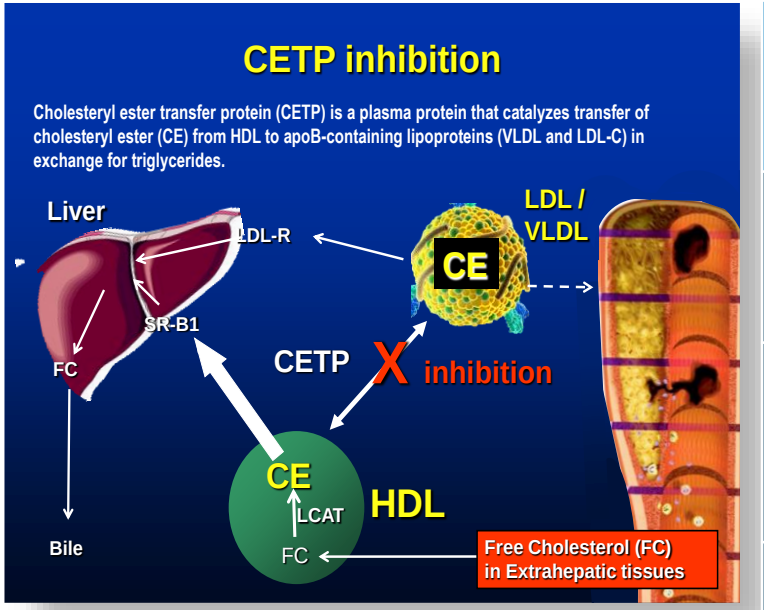
- **Targeting HDL**
  - CETP inhibitors
  - Epigenetics - BET on MACE program
  - Apo-A1 infusion – AEGIS program

- **Targeting triglycerides**
  - REDUCE-IT
  - PROMINENT

- **Other - Targeting ANGPTL3 (inh of lipoprotein lipase)**

ESC Working Group Cardiovascular Pharmacotherapy

Cholesteryl Ester Transfer Protein (CETP) Inhibition



Drug	HDL	LDL	Clinical Outcomes
Torcetrapib (60 mg/d)	+61%	-24%	↑ Mortality
Dalcetrapib (600 mg/d)	+25%	-4%	∅ Benefit
Anacetrapib (100 mg/d)	+140%	~ -30%	REVEAL +
Evacetrapib (130 mg/d)	? +130%	? -30%	Abandoned

Adapted from Rosenson RS et al. *Circulation* 2012;125:1905

AMGEN Cardiovascular

BET on MACE Trial - Epigenetics

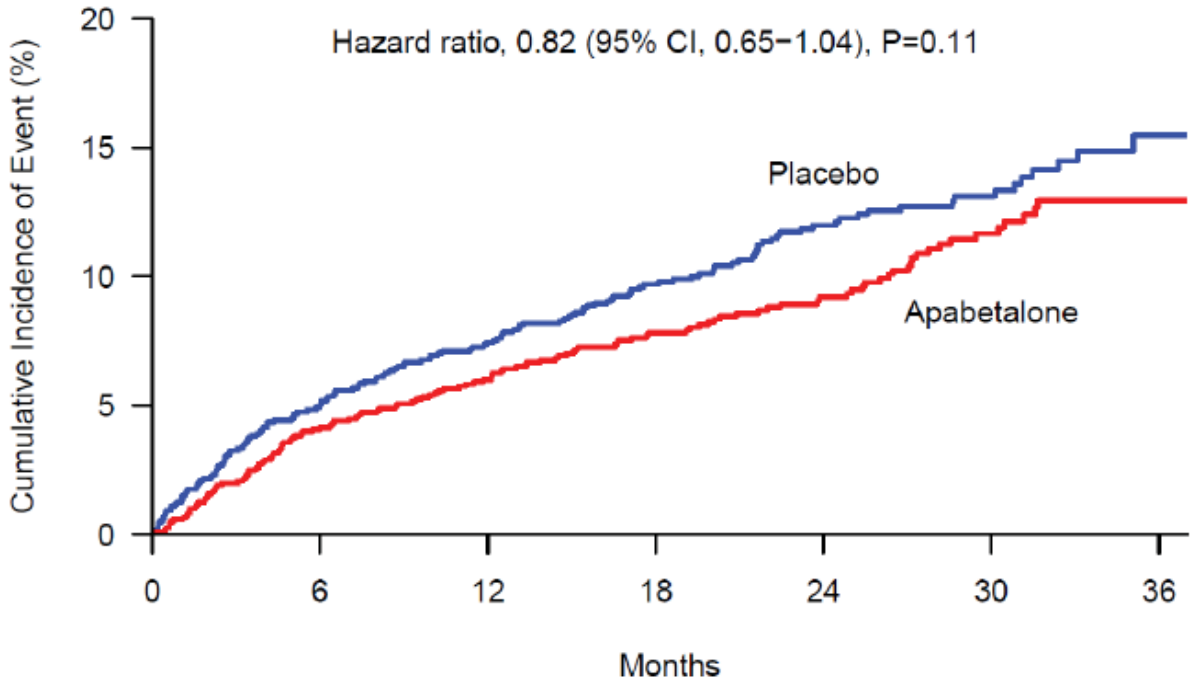
- **RVX-208 (Apabetalone)** is a first-in-class, orally active, small-molecule stimulator of apolipoprotein (APO)A1 gene expression
- Bromodomain and Extra-Terminal (BET) Inhibitor
- RVX-208 increases total HDL as well as the alpha- and pre-beta HDL fractions

BET on MACE – Phase 3 Outcome Study

Primary Efficacy End Point: CV Death, Non-Fatal MI and Stroke (N=274)

Median follow-up
26 months

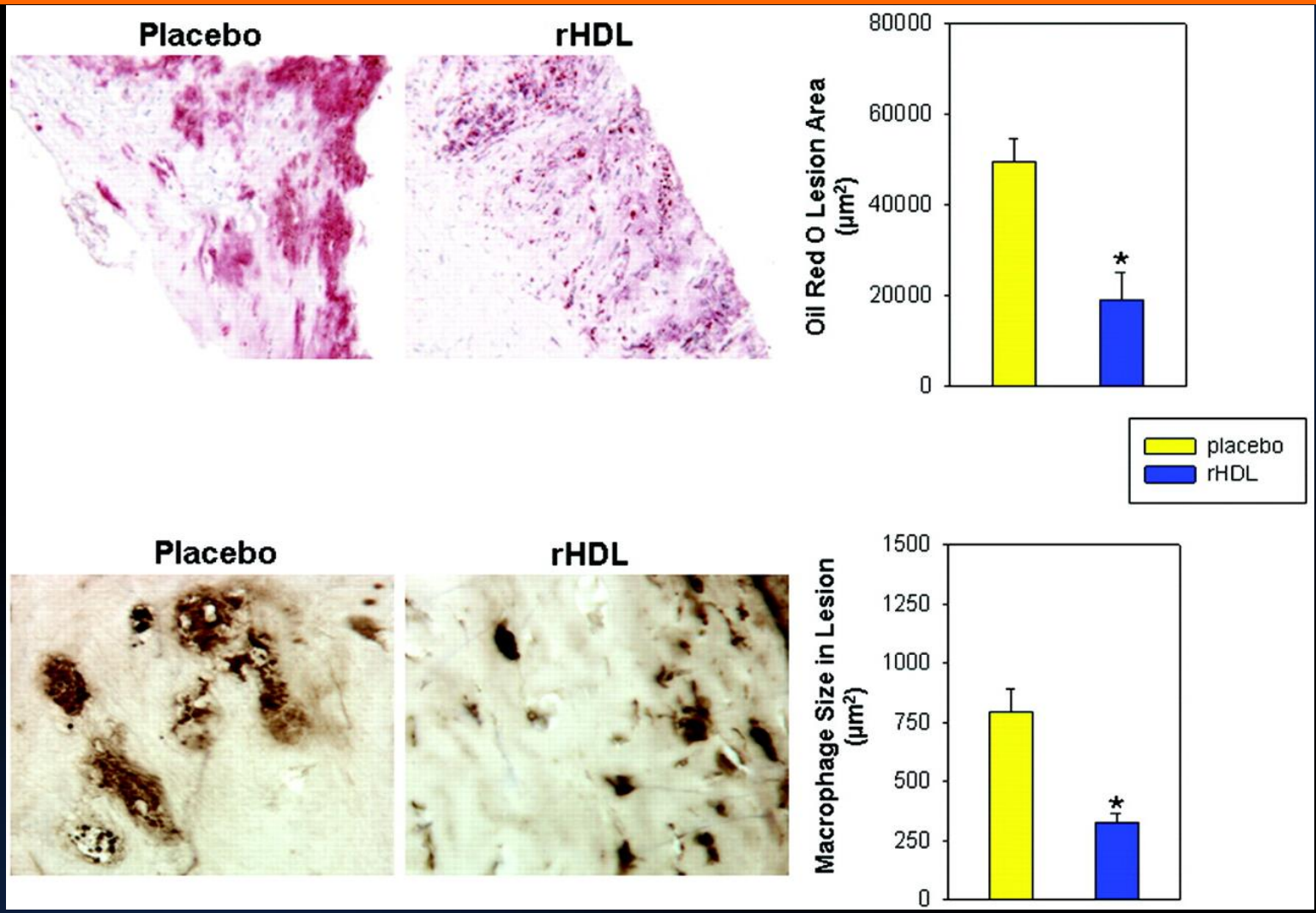
Primary Endpoint:
Placebo 12.4%
Apabetalone 10.3%



No. at Risk							
Placebo	1206	1135	1102	937	641	383	108
Apabetalone	1212	1151	1114	950	672	397	107

Ray et al, AHA, Nov 2019

Single 80 mg/kg Infusion of Reconstituted ApoA-I Reduced Human Femoral Plaque Lipid & Macrophage Size > 50% in 5-7 Days



Gibson et al. AHA 2016

Shaw *et al. Circ Res*. 2008;103:1084-91

AEGIS-II: Study Design

A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study

Interim analysis for efficacy at 70% of the targeted MACE

Interim analyses for futility will be conducted at 30 & 50% of targeted MACE

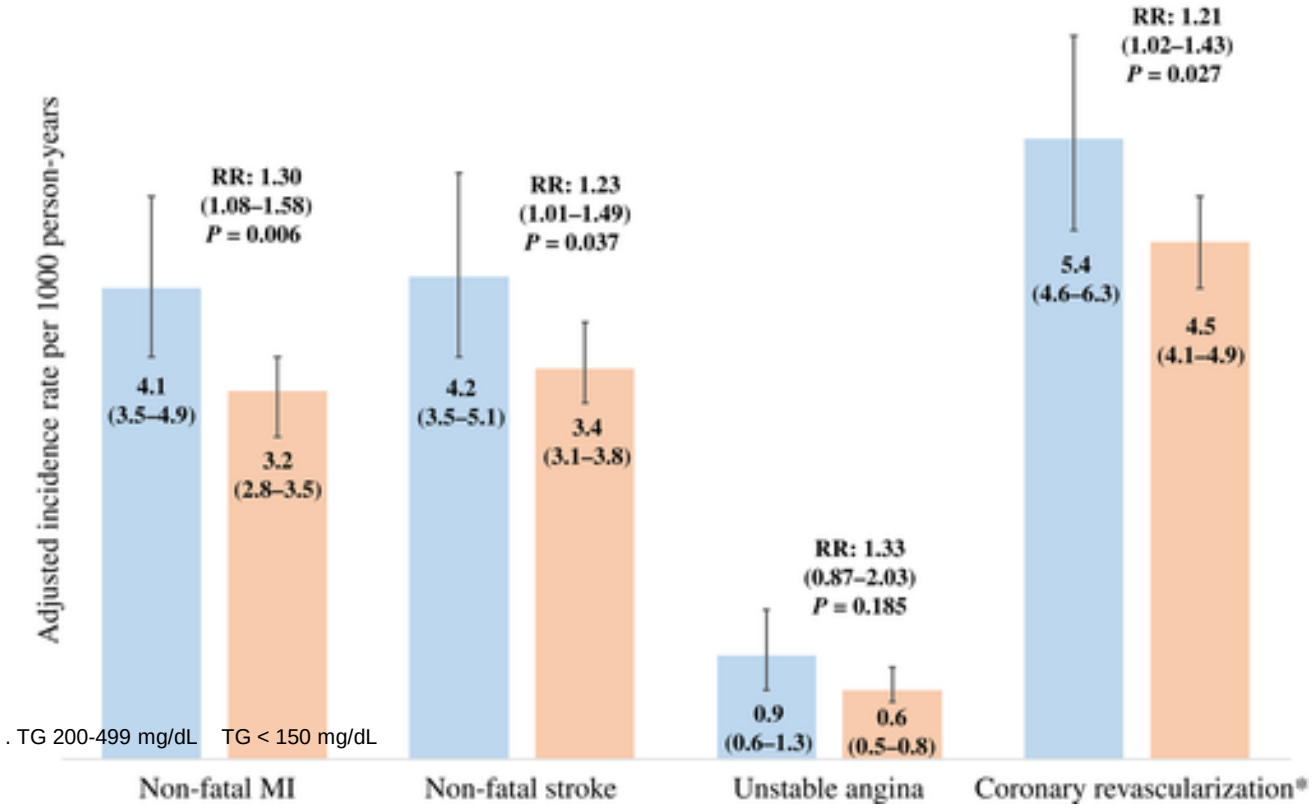
- **Enriched Study Population**: Multi-vessel disease and one of the following: ≥65 years of age, previous MI, peripheral artery disease, or diabetes mellitus
- **Primary endpoint:** Time-to-first occurrence of CVD, MI or stroke through day 90
- **Follow up**: All subjects followed for at least 365 days

Targets

- **Targeting LDL**
  - PCSK9 Inhibitors (FOURIER, SPIRE, ODYSSEY)
  - RNA interference (RNAi) to reduce PCSK9 (ORION)
  - Decreasing LDL synthesis - Bempedoic acid
- **Targeting HDL**
  - CETP inhibitors
  - Epigenetics - BET on MACE program
  - Apo-A1 infusion – AEGIS program
- **Targeting triglycerides**
  - REDUCE-IT
  - STRENGTH
  - PROMINENT
- **Other - Targeting ANGPTL3 (inh of lipoprotein lipase)**

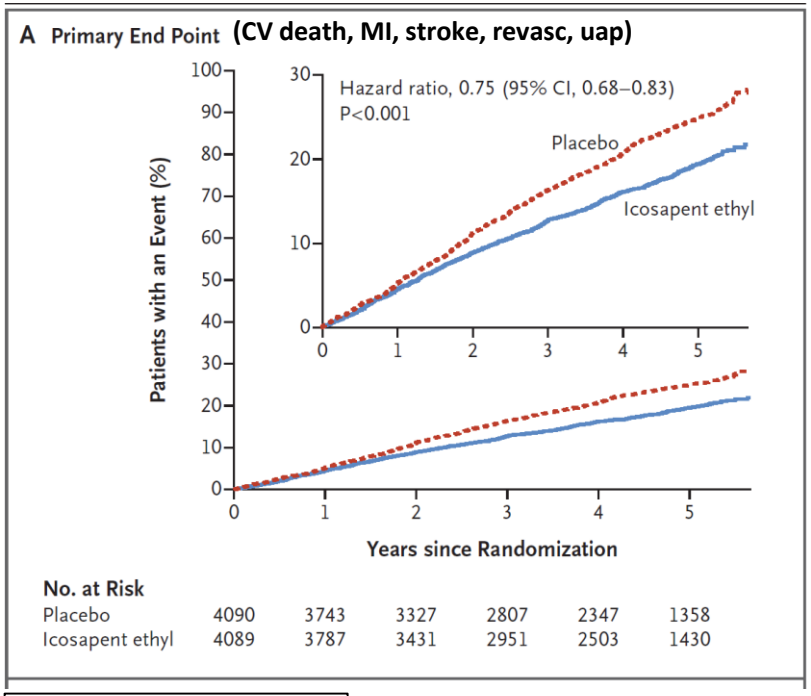
ESC Working Group Cardiovascular Pharmacotherapy

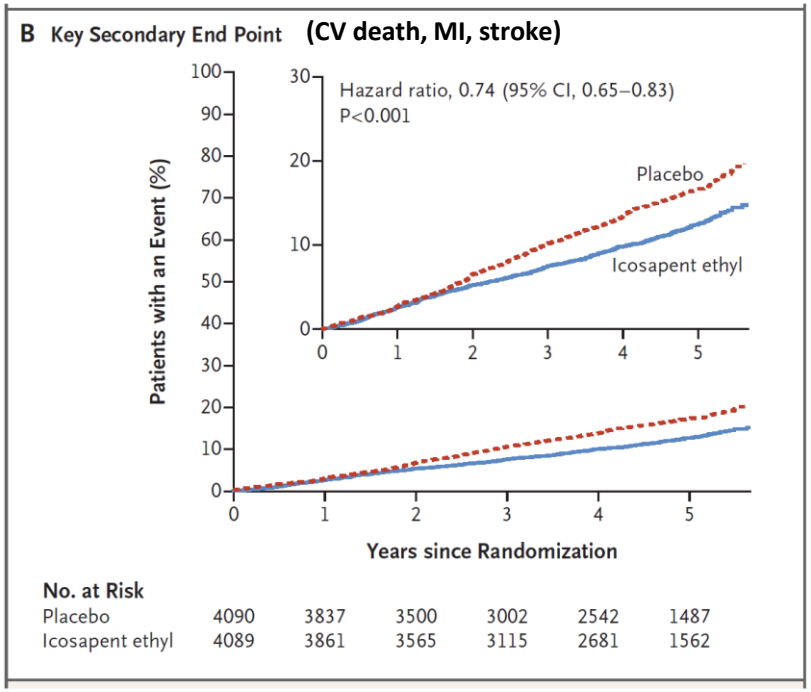
Increased residual CV risk in patients with Diabetes and High (200-499mg%) vs Normal (<150mg%) TG despite statin-controlled LDL cholesterol



Gregory Nichols et al, Diabetes Obes Metab. 2018;1–6

REDUCE IT: CV Risk Reduction with Icosapent Ethyl (Vascepa) For Hypertriglyceridemia (N=8179)





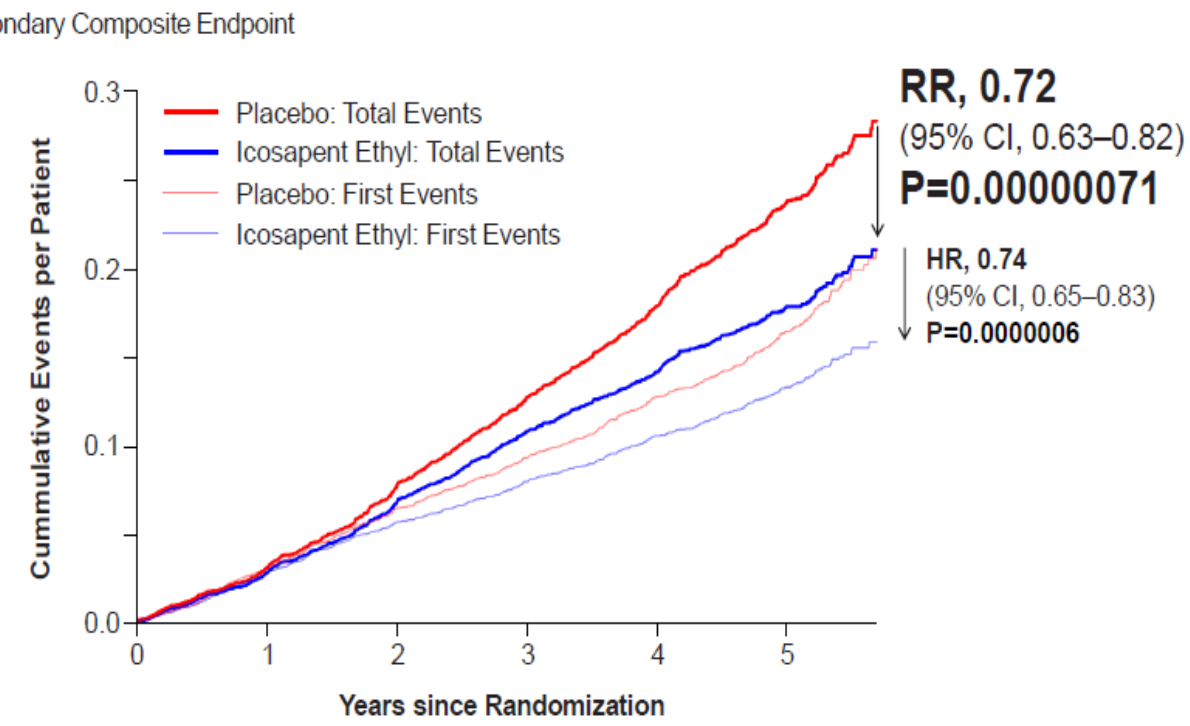
Bhatt et al, NEJM 2018

- **<u>Targeted pts with high TG</u>** (mean 216; range 150-499mg%)
- **<u>High dose (2G bid) purified</u>** product
- 71% sec prevention, 40% DM, Baseline LDL-C 75 mg%

ESC Working Group Cardiovascular Pharmacotherapy

REDUCE-IT

Total (First and Subsequent) Events
Key Secondary: CV Death, MI, Stroke



ACC 2019

ESC Working Group Cardiovascular Pharmacotherapy

STRENGTH (Statin Residual Risk Reduction With Epanova in High CV Risk Patients with Hypertriglyceridemia)

- Double-blind, placebo-controlled (corn oil), parallel group design using Epanova (AZ; n-3 fatty acid)
- 13,000 patients with hypertriglyceridemia, low HDL and high risk for CVD
- Randomized 1:1 to corn oil + statin or Epanova + statin, once daily
- Approximately 3-5 years follow up - MACE outcomes driven trial

Results expected – 2020

ESC Working Group Cardiovascular Pharmacotherapy

PROMINENT

- Test Product: K-877 (pemafibrate) 0.2 mg
- Dose: One tablet twice daily
- Mode of Administration: Oral
- Mechanism of action: new generation selective PPAR-α modulator (SPPARM-α)
- Storage: Room temperature

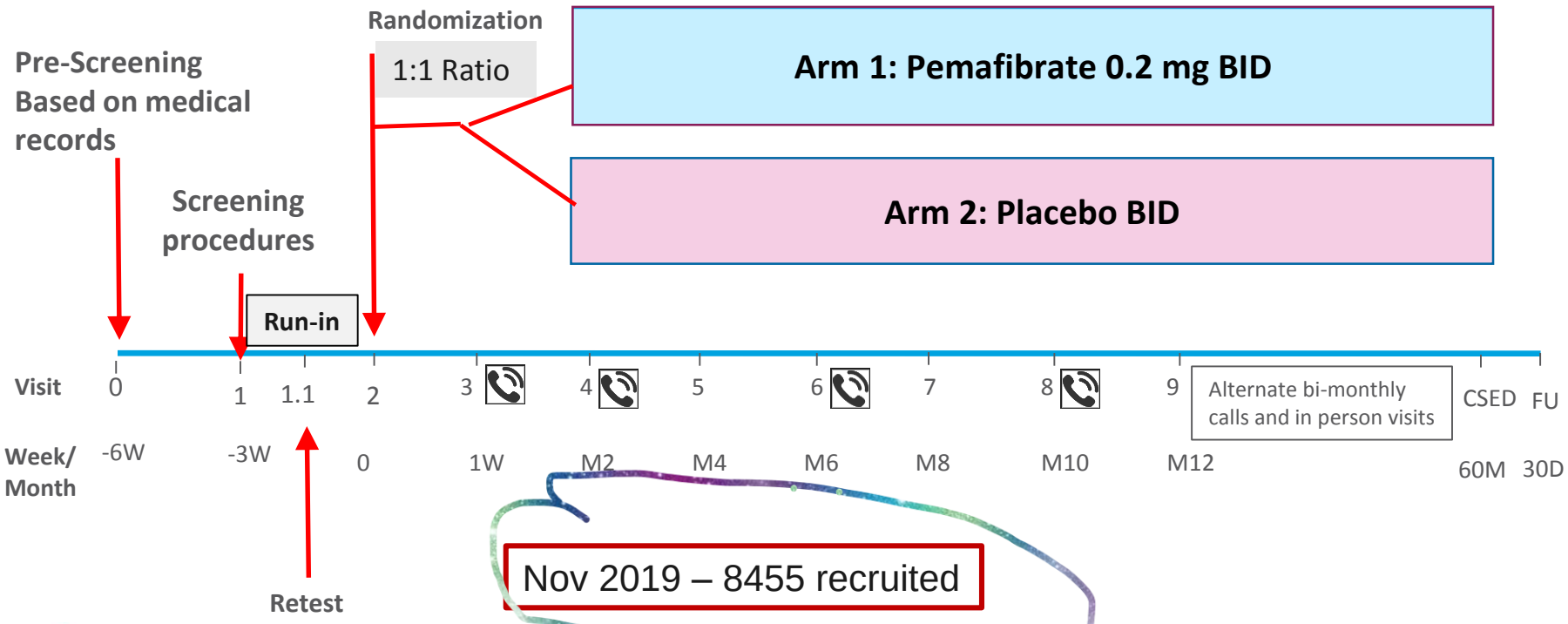
Benefit-Risk Profile
*greater potency and **PPAR-α** selectivity than fenofibrate*
greater TG-lowering efficacy
improved safety and tolerability
minimal inhibitory effects on major drug-metabolizing enzymes and transporters
no impact of renal function on maximum total exposure
no evidence of QTc prolongation
less frequent elevation of liver enzymes than fenofibrate

Triglycerides: PROMINENT Study (N=10,000)

Patient population
- **Adults with T2D with moderate hypertriglyceridemia and low HDL**
- Stable background therapy with statins (or statin intolerant within LDL targets)
  - 2/3 subjects: with documented CVD
  - 1/3 subjects: primary prevention (M≥50y or F≥55y)

Key randomization criteria
- **A1c ≤9.5%**
- **Fasting TG ≥200<500 mg/dL**
- **HDL≤40 mg/dL**

Primary endpoint: MACE+
- **MI**
- **Ischemic Stroke**
- **CVD death**
- **Unstable angina requiring unplanned revascularization**



QUINTILES

Targets

- **Targeting LDL**
  - PCSK9 Inhibitors (FOURIER, SPIRE, ODYSSEY)
  - RNA interference (RNAi) to reduce PCSK9 (ORION)
  - Decreasing LDL synthesis - Bempedoic acid
- **Targeting HDL**
  - CETP inhibitors
  - Epigenetics - BET on MACE program
  - Apo-A1 infusion – AEGIS program
- **Targeting triglycerides**
  - REDUCE-IT
  - PROMINENT
- **New - Targeting ANGPTL3 (inh of lipoprotein lipase)**

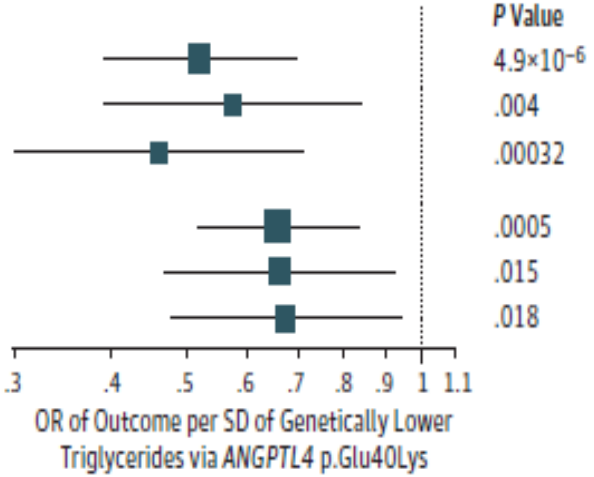
ESC Working Group Cardiovascular Pharmacotherapy

Association of Genetically Enhanced Lipoprotein Lipase–Mediated Lipolysis and LDL Cholesterol–Lowering Alleles With Risk of CAD and Type 2 Diabetes

Figure 4. Associations of Loss-of-Function Alleles With Cardiometabolic Disease Outcomes in *ANGPTL4* and *ANGPTL3*

A Associations of *ANGPTL4* p.Glu40Lys loss-of-function allele with cardiometabolic disease outcomes

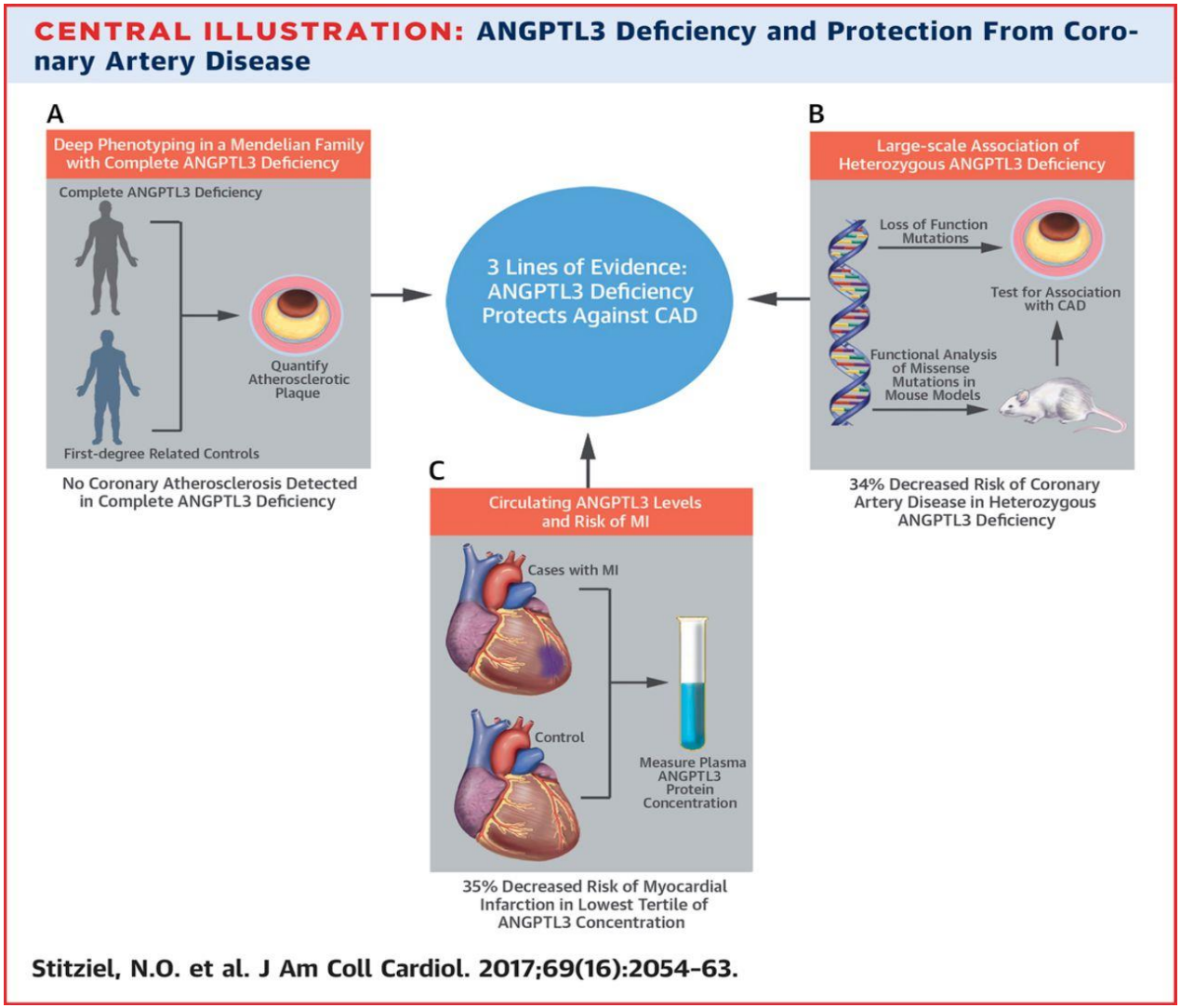
Exposure	Outcome	Stratum	Individuals With Outcome	Individuals Without Outcome	OR (95% CI)	*P* Value
p.Glu40Lys	Coronary artery disease	Whole cohort	22731	348484	0.52 (0.39-0.69)	4.9×10^{-6}
		Genetically higher LDL-C	12429	173178	0.57 (0.39-0.84)	.004
		Genetically lower LDL-C	10302	175306	0.46 (0.30-0.70)	.00032
p.Glu40Lys	Type 2 diabetes	Whole cohort	30873	359597	0.65 (0.52-0.83)	.0005
		Genetically higher LDL-C	15226	180007	0.66 (0.47-0.92)	.015
		Genetically lower LDL-C	15647	179590	0.67 (0.48-0.93)	.018



Lotta et al, JAMA Cardiology 2018;3(10):957-966

ESC Working Group Cardiovascular Pharmacotherapy

ANGPTL3 and Protection from CAD



Nathan O. Stitziel et al. JACC 2017;69:2054-2063

Evinacumab – "FDA Grants Breakthrough Designation"

- **Evinacumab** is a ***monoclonal antibody to angiopoietin-like protein 3 (ANGPTL3)*** - an inhibitor of lipoprotein lipase (LPL) (which is responsible for breakdown of triglycerides and other lipids)

- In Phase I, ***evinacumab reduced TG levels by 64-73%,*** far outperforming current treatments such as fish oils or fibrates which typically reduce TG by 20% to 50%

- In ***Homozygous familial hypercholesterolemia (HoFH)*** -
  - adding the drug to standard cholesterol treatment such as statins improved LDL-cholesterol reduction

ESC Working Group Cardiovascular Pharmacotherapy

Evinacumab – ELIPSE HoFH Trial

ANGPTL3 antibody halves LDL-c levels in HoFH patients in phase 3 trial

NEWS - AUG. 15, 2019

Positive phase 3 results of the ELIPSE HoFH trial have been announced for evinacumab, an investigational angiopoietin-like 3 (ANGPTL3) antibody, in patients with homozygous familial hypercholesterolemia (HoFH). ANGPTL3 acts as an inhibitor of lipoprotein lipase (LPL) and endothelial lipase, and appears to play a central role in lipoprotein metabolism.

On average, patients entered the trial with LDL-c levels of 255 mg/dL, despite treatment with other lipid-lowering therapies, including maximally-tolerated statins, PCSK9 inhibitors, ezetimibe, LDL apheresis and lomitapide. The trial met its primary endpoint, showing that adding evinacumab to other lipid-lowering therapies decreased LDL-c by 49% on average, compared to lipid-lowering therapies alone.

ELIPSE HoFH is an ongoing phase 3 randomized, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy and safety of evinacumab 15 mg/kg administered intravenously every four weeks in 65 patients aged 12 years or older with HoFH (43 evinacumab, 22 placebo). In the evinacumab treatment group, 98% of patients were on statins, 81% were on PCSK9 inhibitors, 75% were on ezetimibe, 33% were on LDL apheresis and 26% were on lomitapide. In addition, 35% of evinacumab patients had the most severe, "null/null" form of HoFH.

The phase 3 trial was designed to assess the effect of evinacumab on LDL-c and other lipid-related endpoints. Results from the evinacumab group at week 24 included:

- 49% reduction in LDL-c from baseline, compared to placebo (47% reduction for evinacumab vs. 2% increase for placebo, P<0.0001), the primary endpoint. LDL-c reductions were observed from the first assessment at week 2, and were maintained throughout the 24-week double-blind treatment period.
- 132 mg/dL absolute change in LDL-c from baseline, compared to placebo (135 mg/dL reduction

ESC Working Group Cardiovascular Pharmacotherapy