Hypocholesterolemia

HOW LOW IS SAFE ?

THE FRONTIER OF VERY LOW LDL CHOLESTEROL

דר' כהן חופית

מרכז הליפידים ע"ש ברוך שטרסבורגר ז"ל, המרכז הרפואי ע"ש שיבא ,תל- השומר

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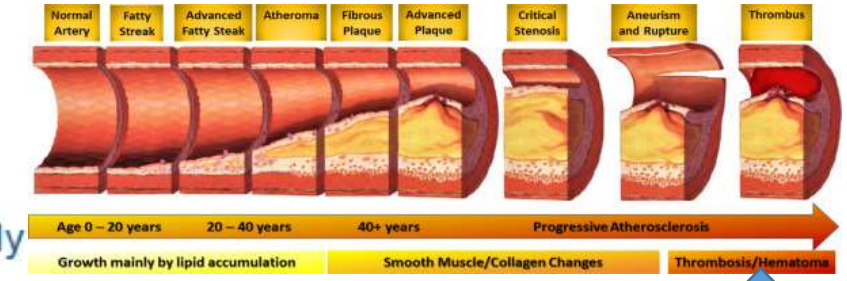
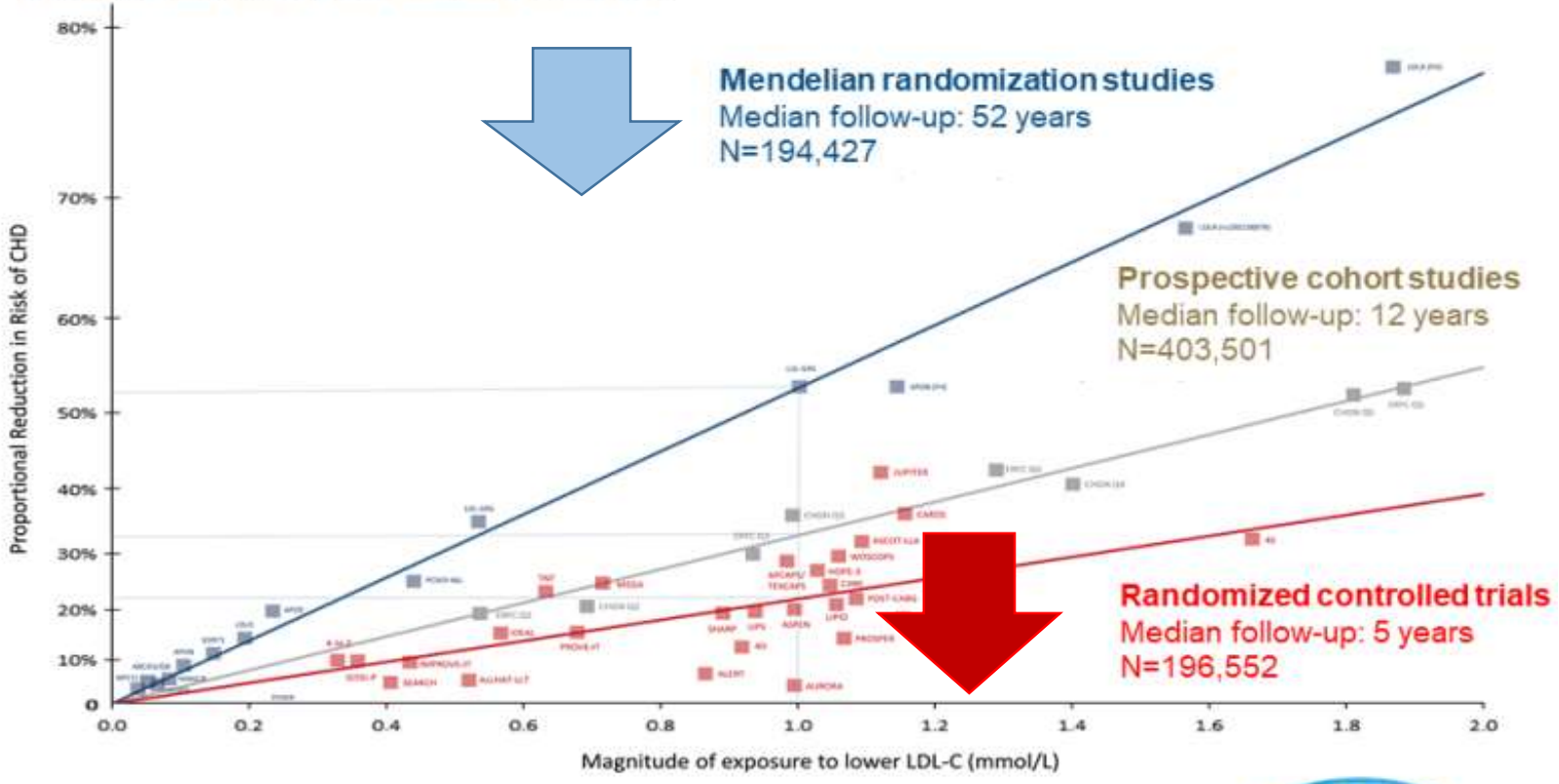
Sackler Faculty Of Medicine, Tel-aviv University, Israel

The lower the LDL-C achieved, the lower the risk of CV events

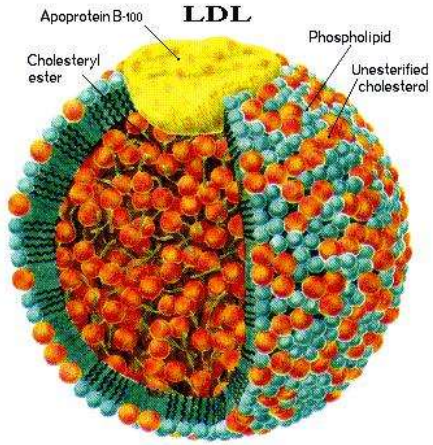


Evidence from meta-analyses of **Mendelian randomization studies**, **prospective cohort studies**, and **randomized controlled trials** unequivocally establishes that LDL causes ASCVD.



Ference BA *et al.*, Eur Heart J. 2017;38(32):2459-2472

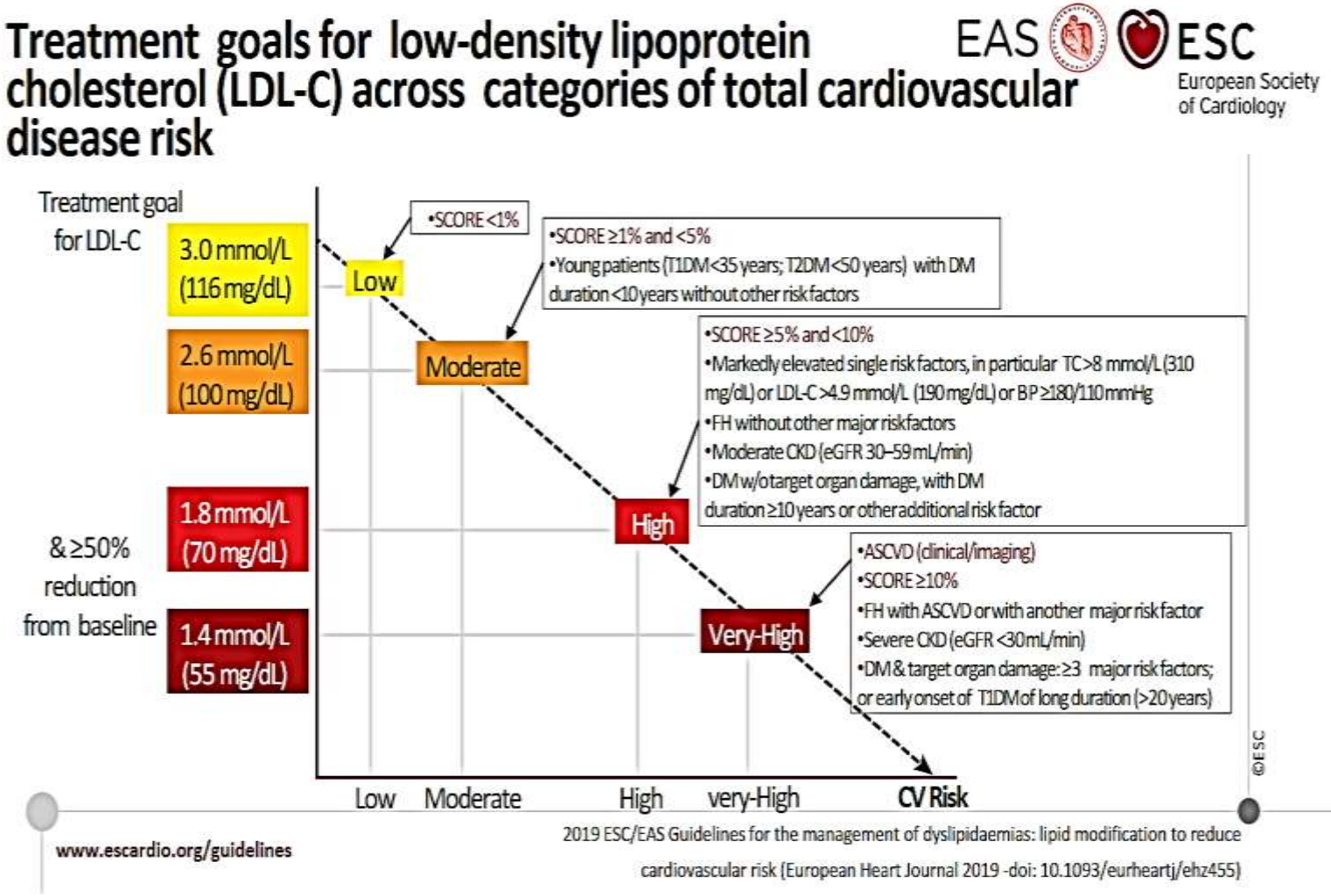
Serum LDL-C is a causative factor for developing atherosclerosis



LOWER Treatment goals for low-density lipoprotein cholesterol

יעדי הטיפול של LDLc

דרגת הסיכון לתמותה ב-10 שנים	% ירידה	יעדי טיפול (מ"ג/ד"ל)			חוזק המלצה	חוזק הוכחה
		LDLc	non-HDLc	apoB		
נמוכה [1] • SCORE < 1%		≤ 140	≤ 170	≤ 130	IIb	B
בינונית [1] • SCORE 1%-5% • חולי סוכרת צעירים עם משך סוכרת יחסית קצר וללא גורמי סיכון נוספים		≤ 100	≤ 130	≤ 100	IIb	A
גבוהה • SCORE 5%-10% • נוכחות גורם סיכון ברמה גבוהה במיוחד • היפרכולסטרולמיה משפחתית ללא גורם סיכון נוסף • סוכרת מעל 10 שנים ו/או עם גורם סיכון נוסף אך ללא פגיעה באיבר מטרה • מחלת כליות כרונית דרגה 3	> 50%	≤ 70	≤ 100	≤ 80	I	A
גבוהה מאוד - מניעה ראשונית • SCORE > 10% • סוכרת עם פגיעה באיבר מטרה ו/או 3 גורמי סיכון • סוכרת מסוג I מגיל צעיר עם משך > 20 שנה • מחלת כליות כרונית דרגה 4 • היפרכולסטרולמיה משפחתית עם גורמי סיכון נוספים	> 50%	≤ 70 ≤ 55	≤ 100 ≤ 85	≤ 80 ≤ 65	I IIb	A B
גבוהה מאוד - מניעה שניונית • עדות ל-ASCVD (קליני או לפי אמצעי הדמייה)	> 50%	≤ 55	≤ 85	≤ 65	I	A
גבוהה במיוחד • חולים עם ASCVD שעברו אירוע וסקולרי נוסף תוך שנתיים למרות טיפול במינון מקסימלי נסבל של סטטין	> 50%	≤ 40	≤70	≤ 50	IIb	B



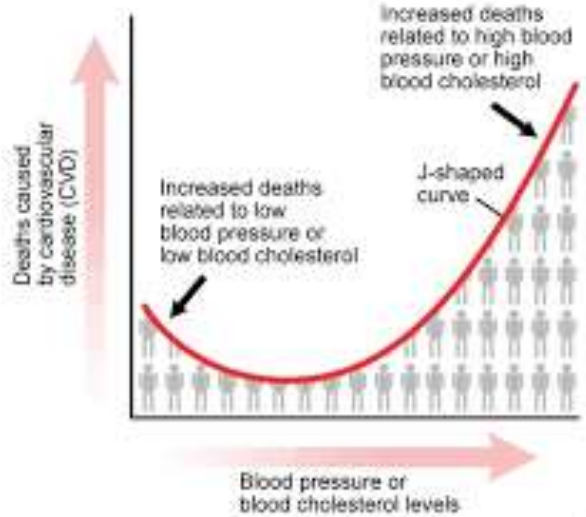
https://www.ima.org.il/medicine/viewnewspaper.aspx?newspaperid=293

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 2154–2169
doi:10.1093/eurheartj/ehaa1080

STATE OF THE ART REVIEW

Dyslipidaemias

How low is safe? The frontier of very low (<30 mg/dL) LDL cholesterol



Cholesterol is an essential component of the cell membrane

Precursor for steroid hormone, vitamin D and bile acid synthesis

Concerns about lowering LDL-C to territory uncommonly before…

European Heart Journal (2021) 42, 2154–2169

Primary

Low Levels Of Circulating LDL Cholesterol

Secondary

Congenital lipid disorders

Acquired disease

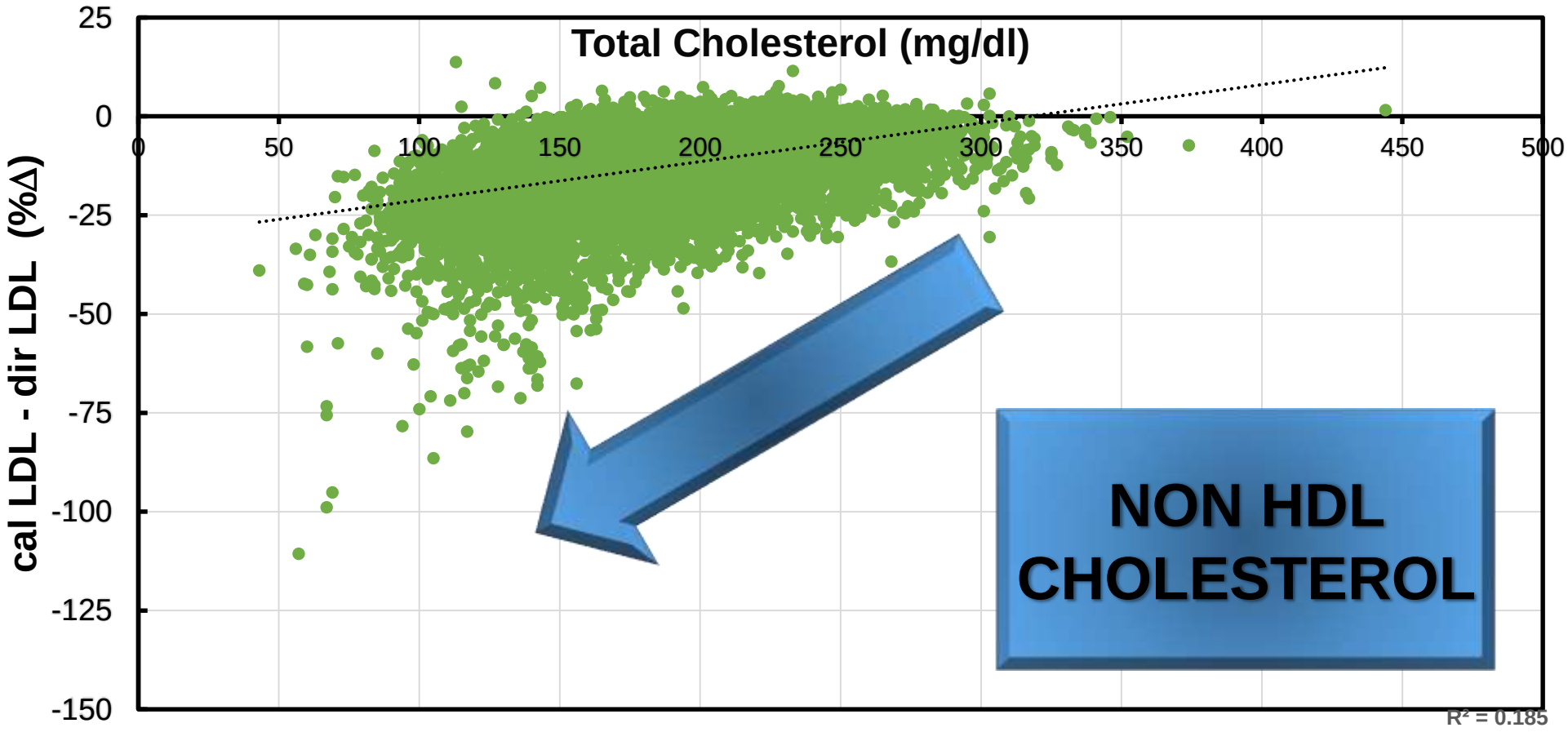
LLT
Lipid Lowering Therapy

Causes of acquired hypocholesteremia

Malignancy **cachexia**	Hypercatabolic state •Colorectal and prostatic carcinoma, leukemias, reticuloses •Myeloma and other monoclonal gammopathies
Malabsorption	•Short-bowel syndrome, blind loop syndrome, celiac disease, pancreatic exocrine insufficiency, giardiasis
Anemia	•Thalassemia, pernicious anemia
Chronic infection & infestations	•Pulmonary tuberculosis, schistosomiasis
Severe illness in hospitalized patients	Aberrant expression of inflammatory cytokines

Durrington P. Dyslipidaemia. Lancet 2003; 362:717.

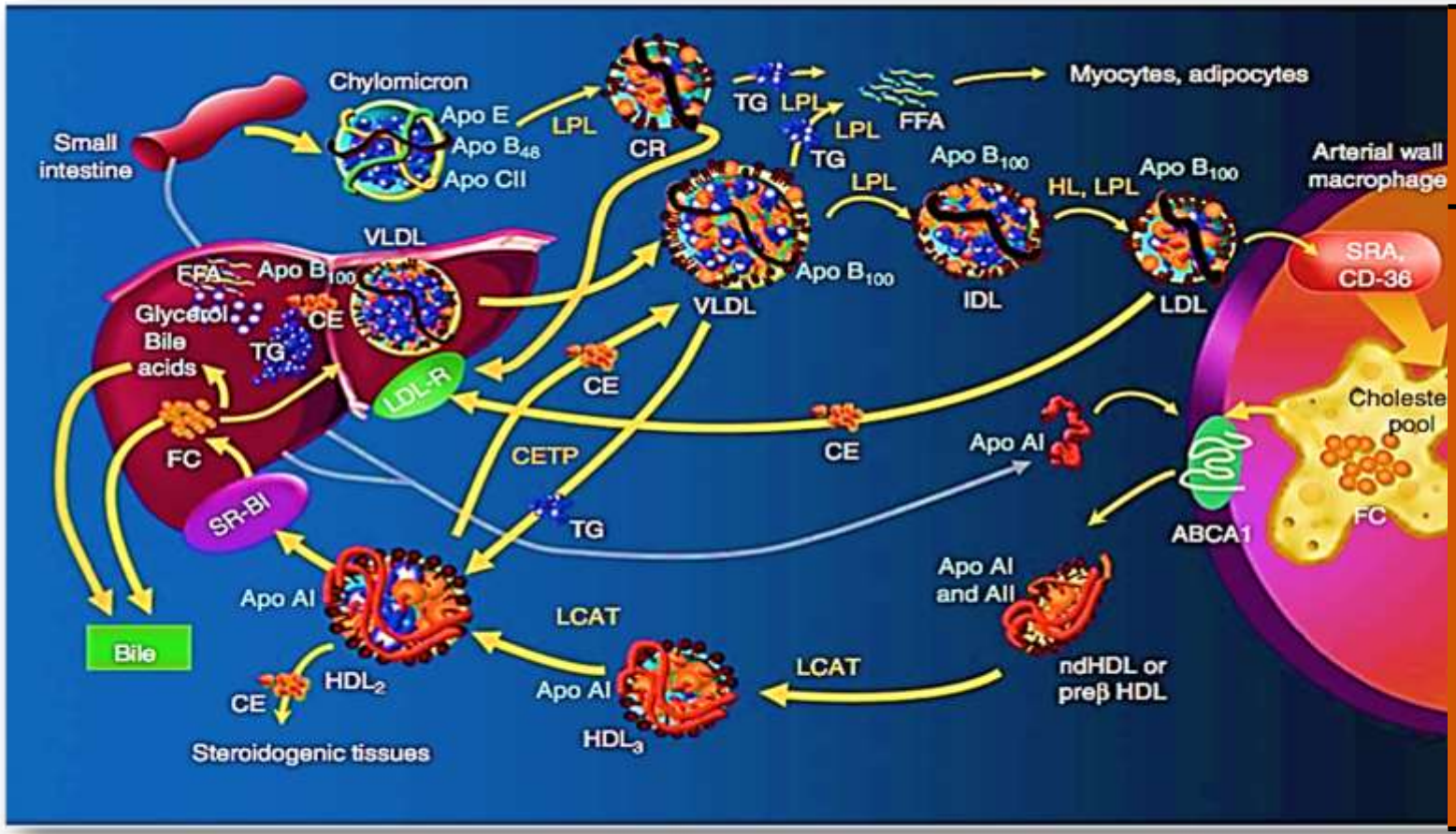
The difference between Friedewald calculated LDL and direct LDL levels is **inversely correlated** to plasma TC levels



H. Cohen,D.Harats,A. Shaish,J. Roitelman.https://doi.org/10.1016/j.atherosclerosis.2019.06.315

Inherited causes of low levels of plasma cholesterol

Life-long exposure to lower LDL-C



Abetalipoproteinemia

Hypobetalipoproteinemia

PCSK9 — Loss-of-function variants in PCSK9

Familial combined hypolipidemia

Genetic Variants of human PCSK9 gene and lower LDL-c Levels

- PCSK9 is a serine protease
- Binds to the LDL-R
- Chaperones the **LDL-R** to the intracellular **degradation**
- **Loss of function** mutations
- 1% to 3% of the population
- **Lower levels of PCSK9**
- **Reduced serum LDL-c**
- Lower incidence of **coronary heart disease events**

LDLR=LDL receptor

Mutations In PCSK9 Lead To **lower LDL-C levels** and a **lower incidence of CVD**

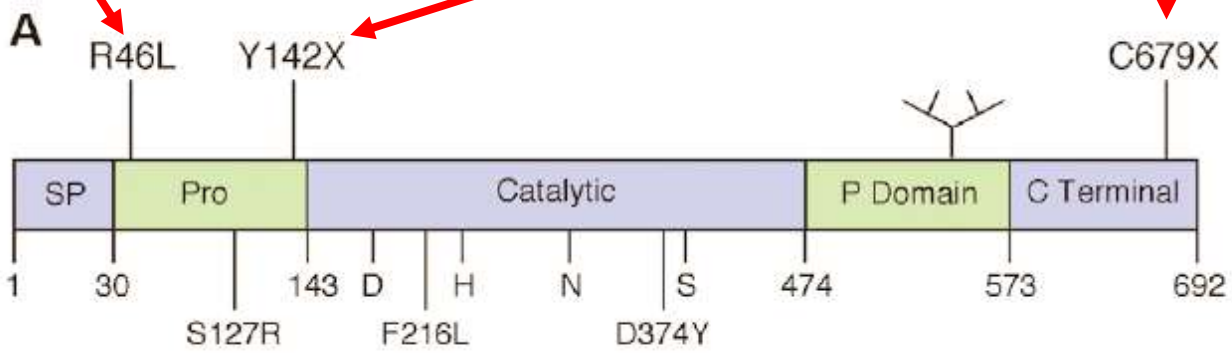
- **3.2% of white subjects**
- **21% reduction in mean LDL-C**

ARIC 16,000pt
15-year interval in the Atherosclerosis Risk in Communities study

- **2% of black subjects**
- **40% reduction in mean LDL-C**

50% risk reduction

88% risk reduction



No 2nd morbidities

- **Compound heterozygosity** for *PCSK9* loss-of-function variants
- **LDL-C levels <5th percentile**
- **No clinical abnormalities**

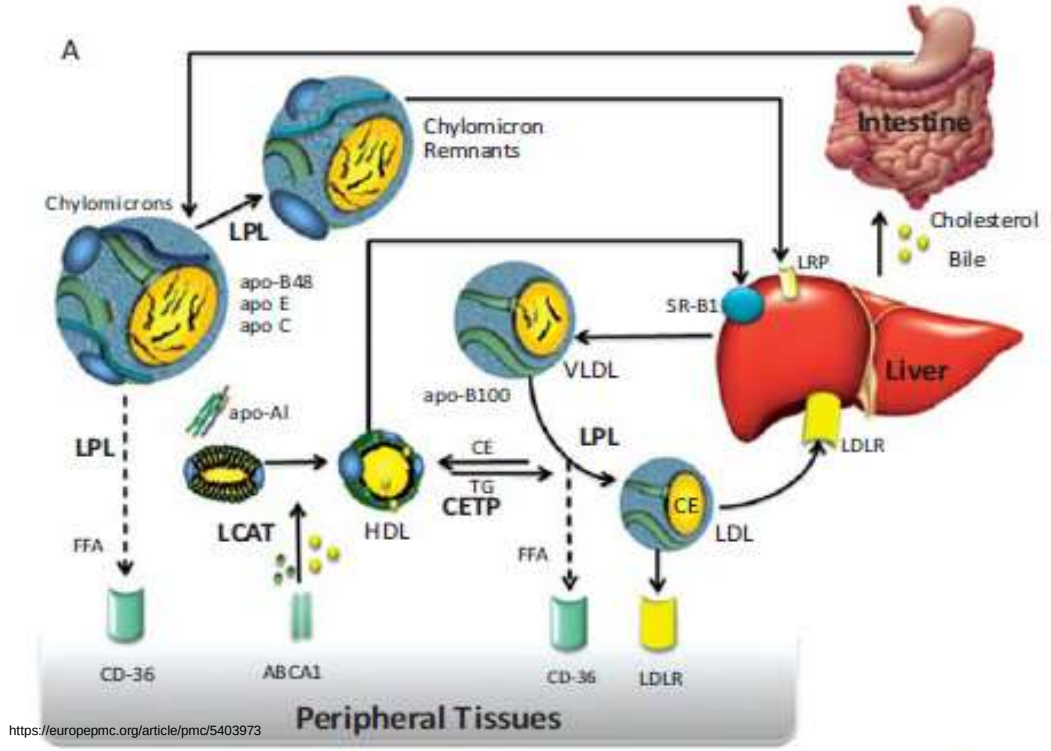
Trends Biochem Sci 2007; 32; 71

N Engl J Med. 2006 Mar;354(12):1264-72

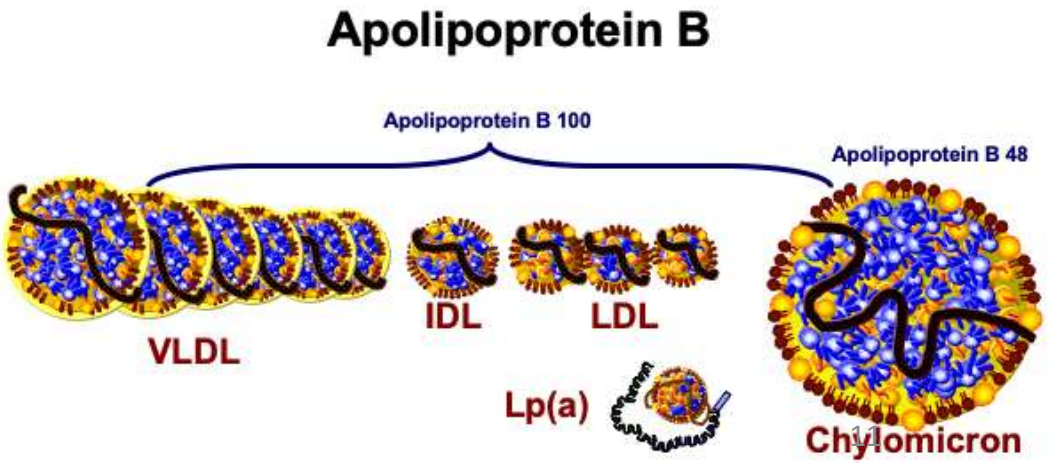
The NEW ENGLAND JOURNAL of MEDICINE

Heterozygous Familial Hypobetalipoproteinemia

- **Dominantly inherited**
- **ApoB** and **LDL-C levels** < 5th percentile
- **LDL = 20 - 50 mg/dl**
- Mutations in *APOB* leading to **truncation of apo B**
- Prevalence in the general population 0.1% to 1.9%
- Patients are entirely ***asymptomatic***
- Increased risk of hepatic steatosis, rare **NAFLD**
- **Reduced risk for cardiovascular diseas**
- **Increased longevity**



https://europepmc.org/article/pmc/5403973



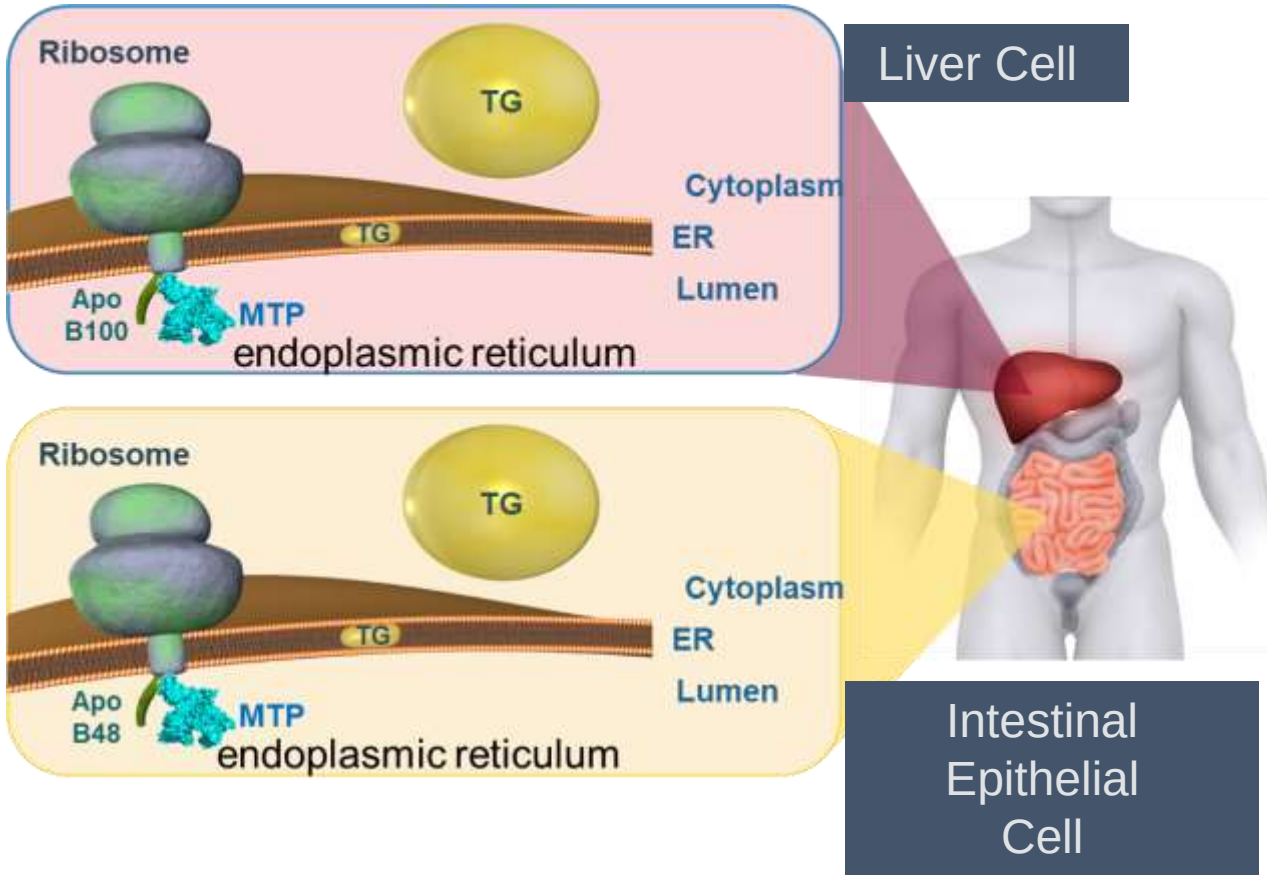
https://peterattiamd.com/wp-content/uploads/2019/12/Slide7.png

Costanzo A, et al J Clin Lipidol. 2017;11(5):1234.

Abetalipoproteinemia

- Rare **autosomal recessive** disorder
- Mutations in the **microsomal triglyceride transfer protein (MTTP) gene**
- **MTP** - essential for the formation and secretion of apolipoprotein B-containing lipoproteins
- **intestine (chylomicrons)+ liver (LDL and VLDL)**
- **No apo B-containing** lipoproteins in the plasma
- **LDL-C levels are near zero**

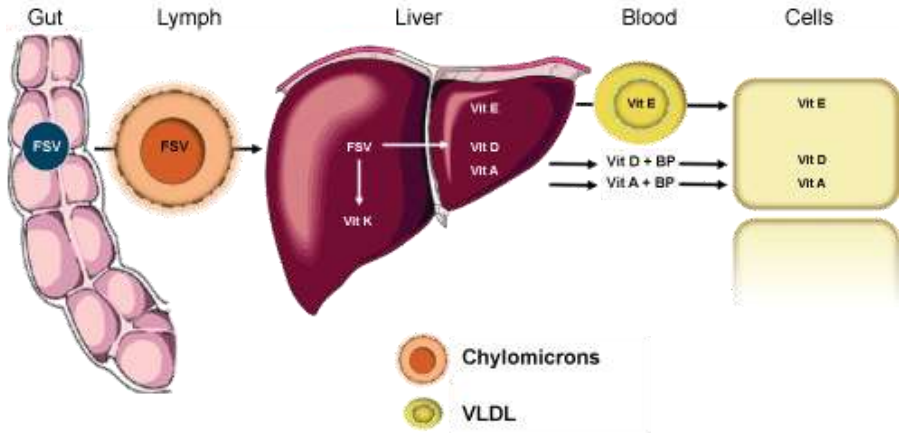
MTP - Microsomal triglyceride transfer protein - responsible for the intracellular assembly of **apolipoprotein B** and **lipids** in the **liver + intestine**



J Atheroscler Thromb. 2021;28(10):1009.
Zamel R, Khan R, Pollex RL, Hegele RA,Orphanet J Rare Dis. 2008;3:19

Abetalipoproteinemia

- Chylomicron formation is necessary for absorption and transport of the **fat-soluble vitamins**.
- **Presents in early childhood** with steatorrhea, abdominal distension, and failure to thrive
- Vitamin A deficiency = **retinal degeneration**
- **Neurologic manifestations** = inability to absorb and transport vitamin E
- Acanthocytes circulating RBC population.
- Impaired cortisol response to ACTH
- **Treatment - administration of vitamin E, A, K, D**

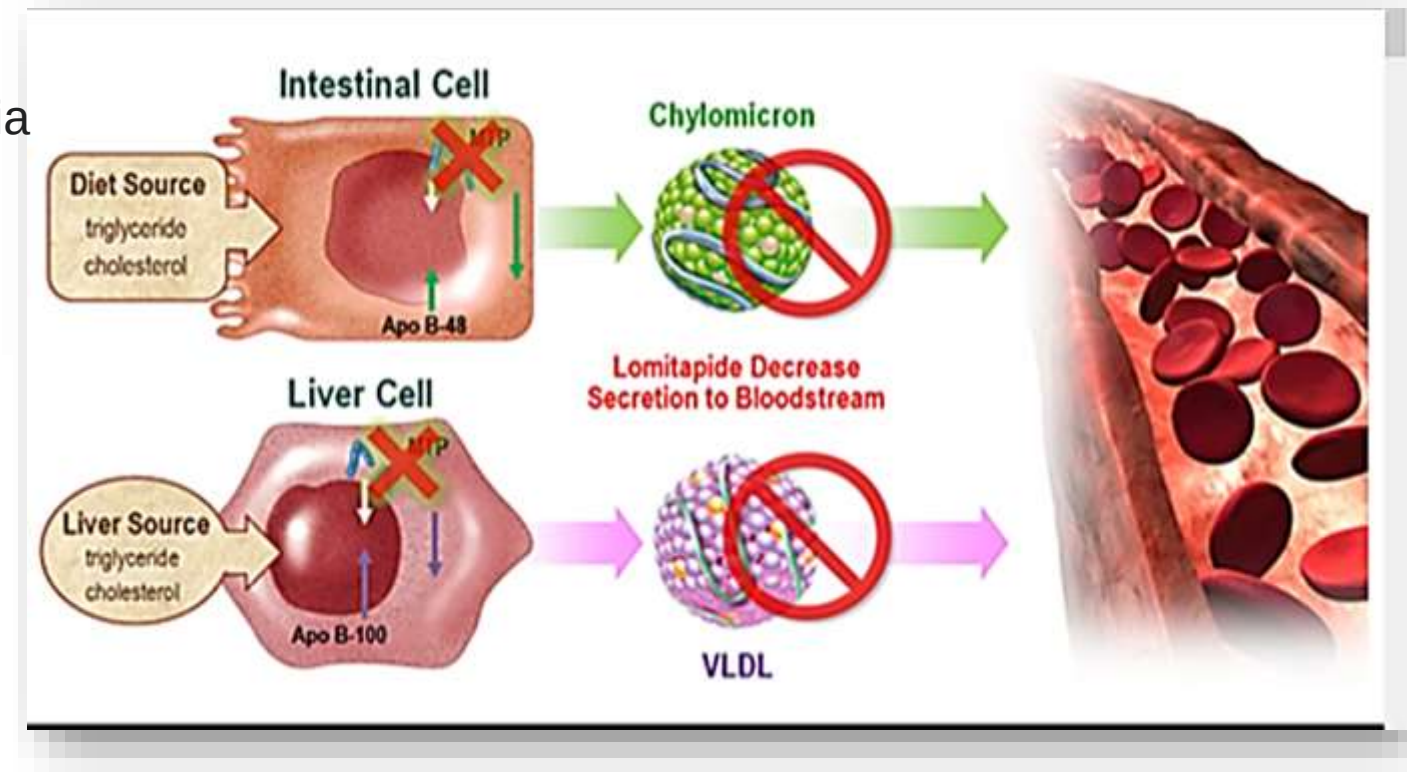


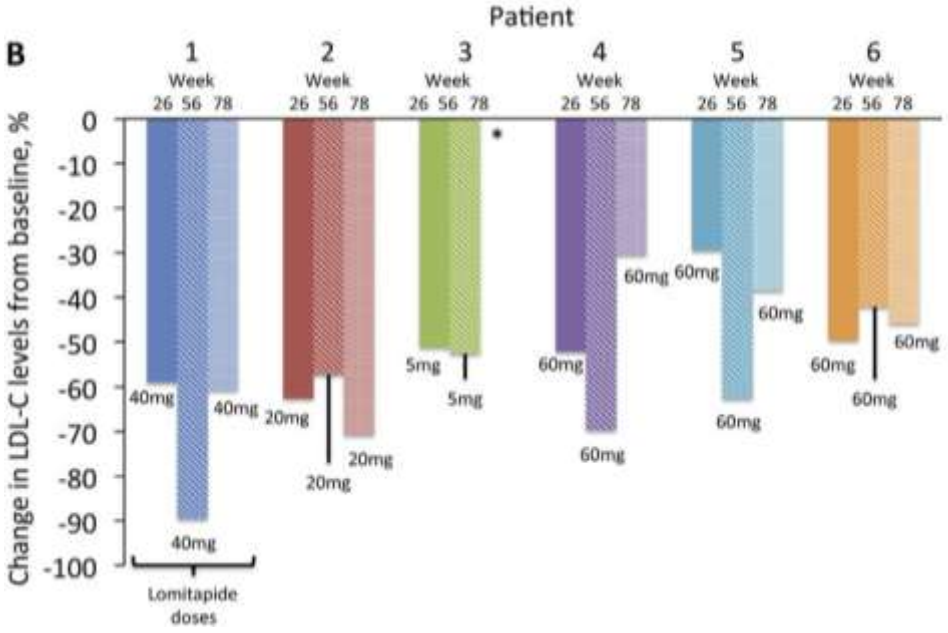
Impaired transport of fat-soluble vitamins (A, D, E, K)

J Atheroscler Thromb. 2021;28(10):1009.

Lomitapide עיכוב של MTP

- The US Food and Drug Administration (FDA) approved lomitapide in 2012
- Reduce plasma LDL cholesterol
- In homozygous familial hypercholesterolemia

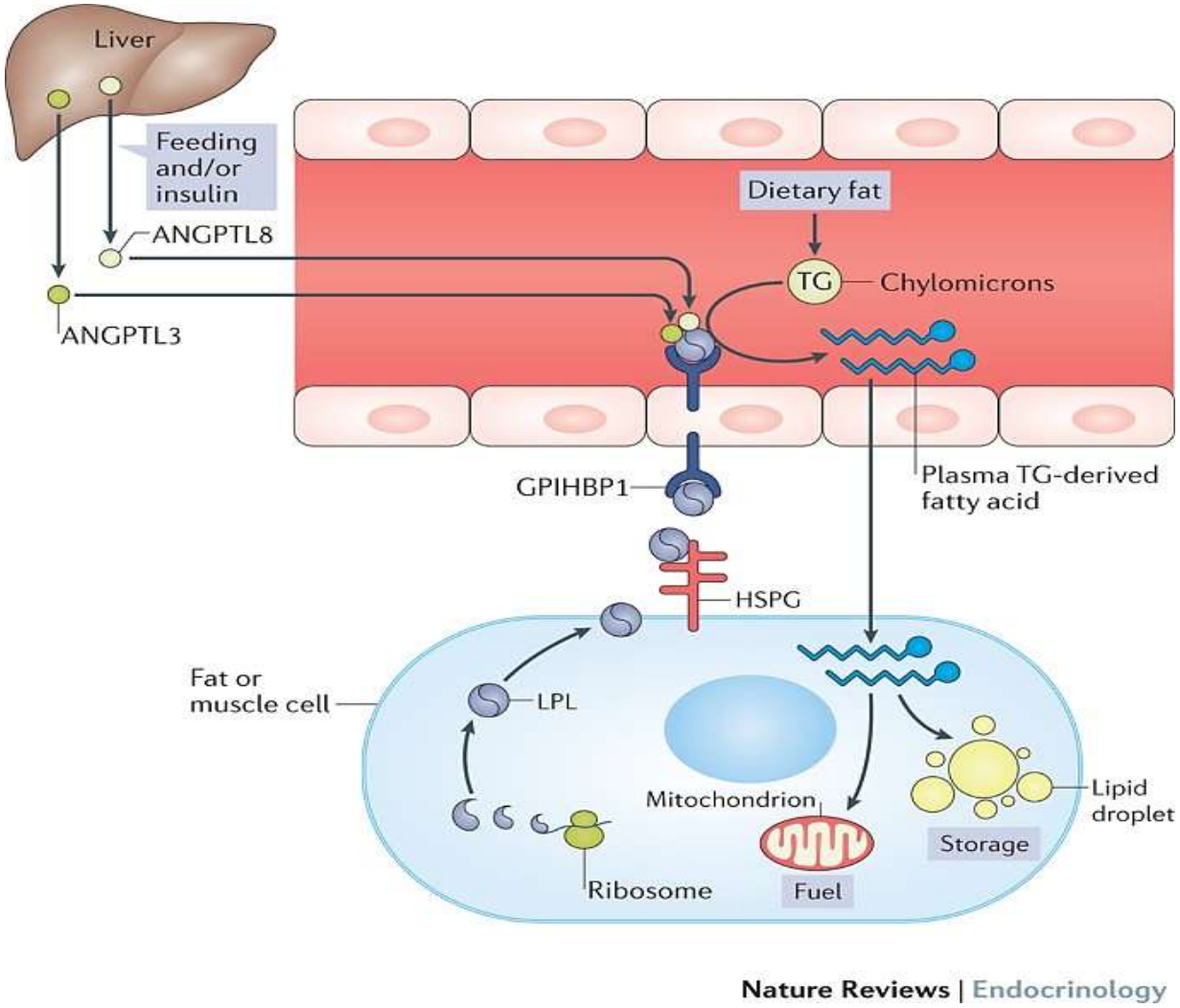




Averna, Maurizio & Cefalu, Angelo & Stefanutti, Claudia & Giacomo, Serafina & Sirtori, C.R. & Vigna, Giovanni. (2015). Nutrition, Metabolism and Cardiovascular Diseases. 26. 10.1016/j.

Angiopoietin-like proteins in lipoprotein metabolism

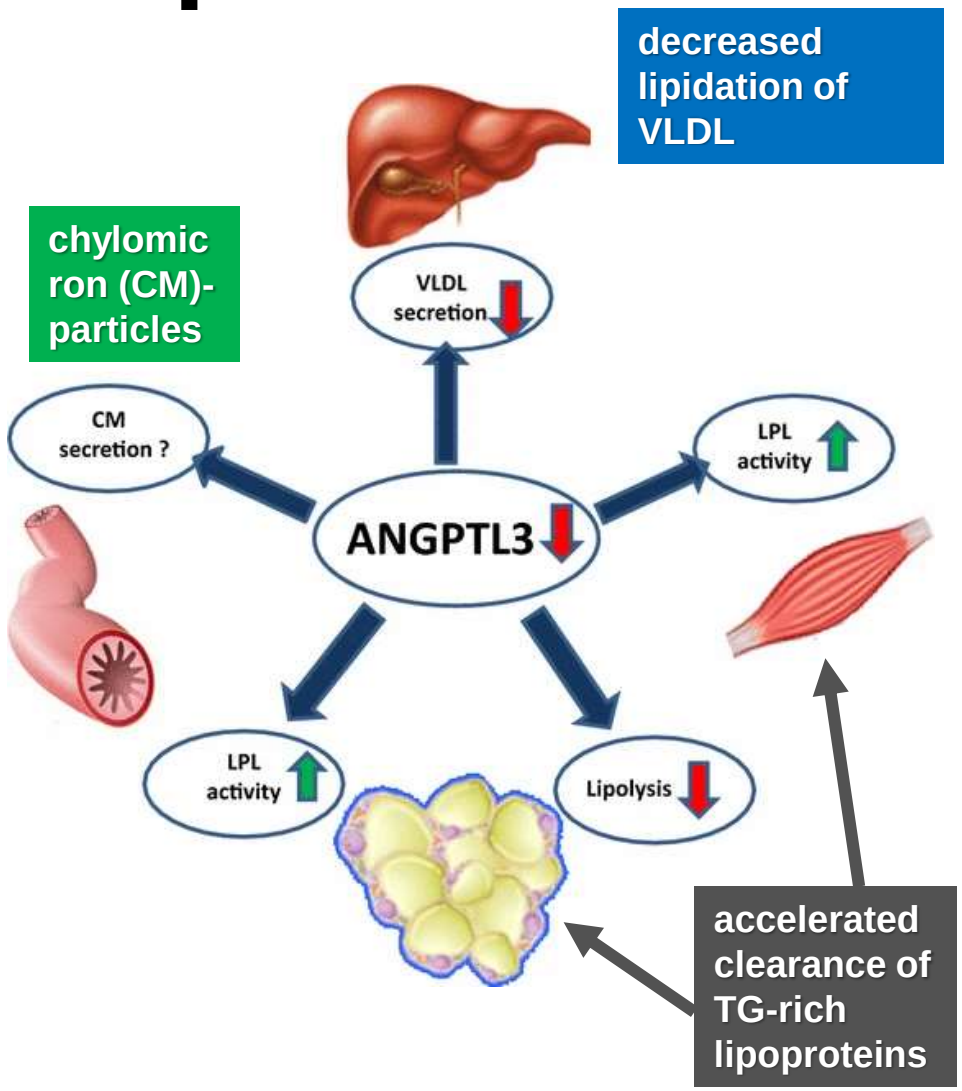
- Three members of the **angiopoietin-like (ANGPTL) protein family** = ANGPTL3, ANGPTL4 & ANGPTL8
- **Regulators of plasma lipoprotein levels**
- **Inhibiting the enzyme lipoprotein lipase**
- ANGPTL3 is exclusively produced in the **liver**



Nat Rev Endocrinol **13**, 731–739 (2017). https://doi.org/10.1038/nrendo.2017.119

Familial Combined Hypolipidemia

- **Loss-of-function mutations** in the gene encoding for ***ANGPTL3***
- **Increased lipoprotein lipase activity**
- **Low levels of plasma LDL-C, HDL-C and triglycerides**
- **Homozygotes** -2 mutant alleles -no detectable *ANGPTL3* protein
- **Heterozygotes** - protein concentrations 34 - 88 % , *depending on the genotype.*
- **Protection from cardiovascular disease**

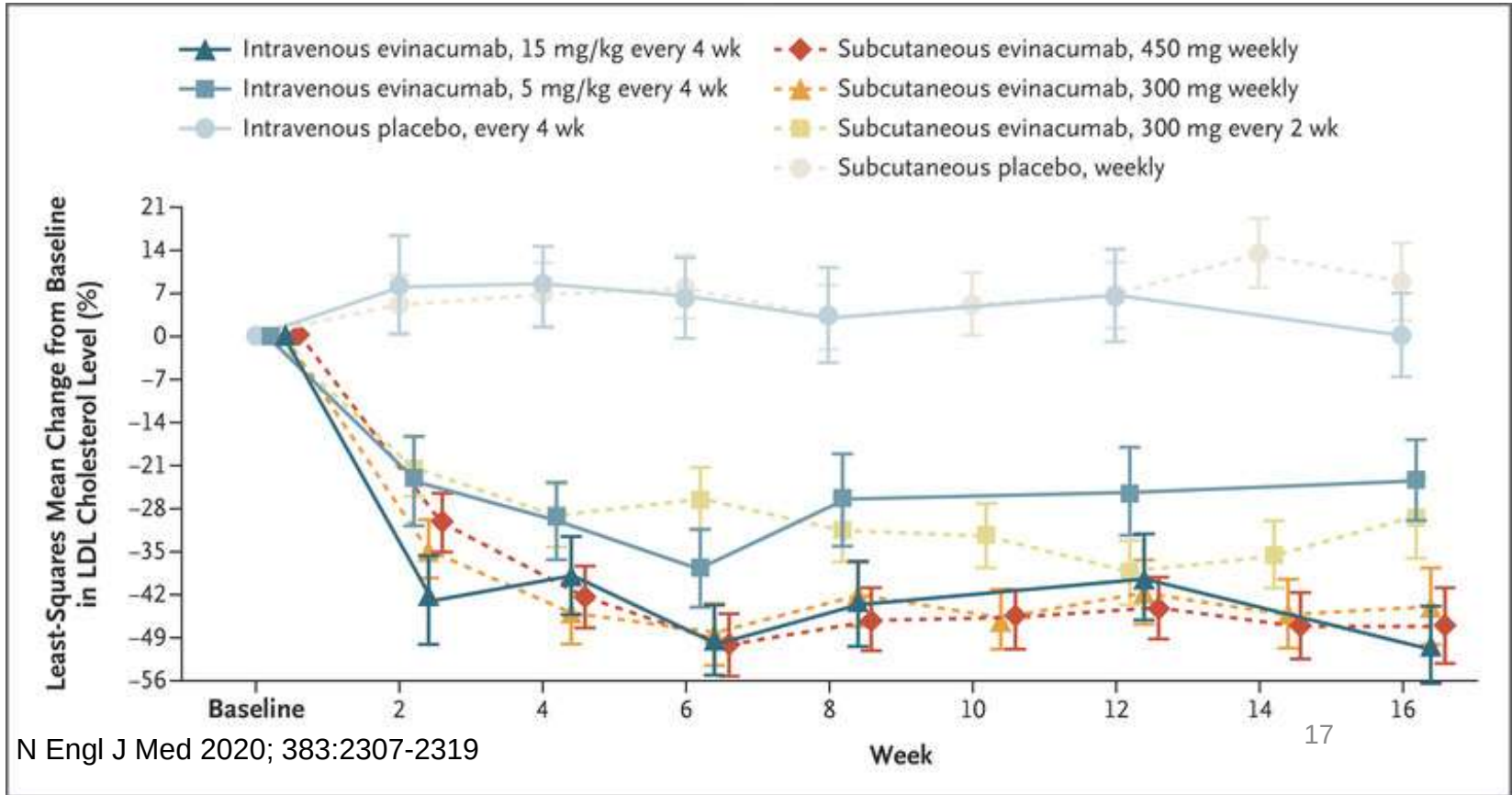


J Lipid Res. 2013;54(12):3481 Endocrine volume 52, pages187–193 (2016)

Evinacumab - human monoclonal antibody against **ANGPTL3**

2021 Approved by the U S Food and Drug Administration for **homozygous familial hypercholesterolemia**

Least-Squares Mean Percent Change from Baseline in the Calculated **Low-Density Lipoprotein Cholesterol** Level at Week 16



N Engl J Med 2020; 383:2307-2319

Genetic conditions of hypocholesterolemia

	LDL-C level	premature coronary heart disease	Adverse effects
		✓	X
I. PCSK9 loss of function mutations *PCSK9*	Varies, can reach as low as 14mg/dL	Healthy Lower rates of cardiovascular events	No comorbidities
II. Abetalipoproteinemia *MTP*	Undetectable	No study to investigate potential cardiovascular benefit among affected individuals	Lipid soluble vitamins (A, D, E, K) deficiency Severe neurological manifestations
III. Familial hypobetalipoproteinemia *ApoB*	Usually 20–50mg/dL	Reduced arterial wall stiffness	Hepatic steatosis and subsequent liver cirrhosis
IV. Familial combined hypolipidemia *ANGPTL3*	Varies, can reach as low as 27mg/dL	Healthy Lower rates of cardiovascular events	No comorbidities

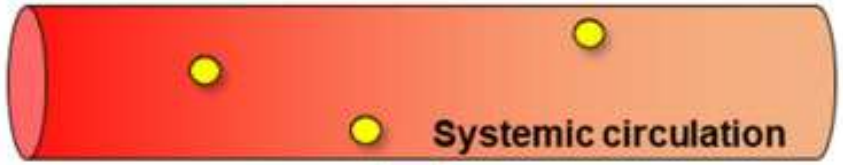
European Heart Journal (2021) 42, 2154–2169

Promotes coronary plaque regression

Efficacy

Reduces composite of
- Cardiovascular death
- Myocardial infarction
- Ischemic stroke
- Coronary revascularization
- Unstable angina

Very low (<30mg/dL) LDL-C



Safety

?

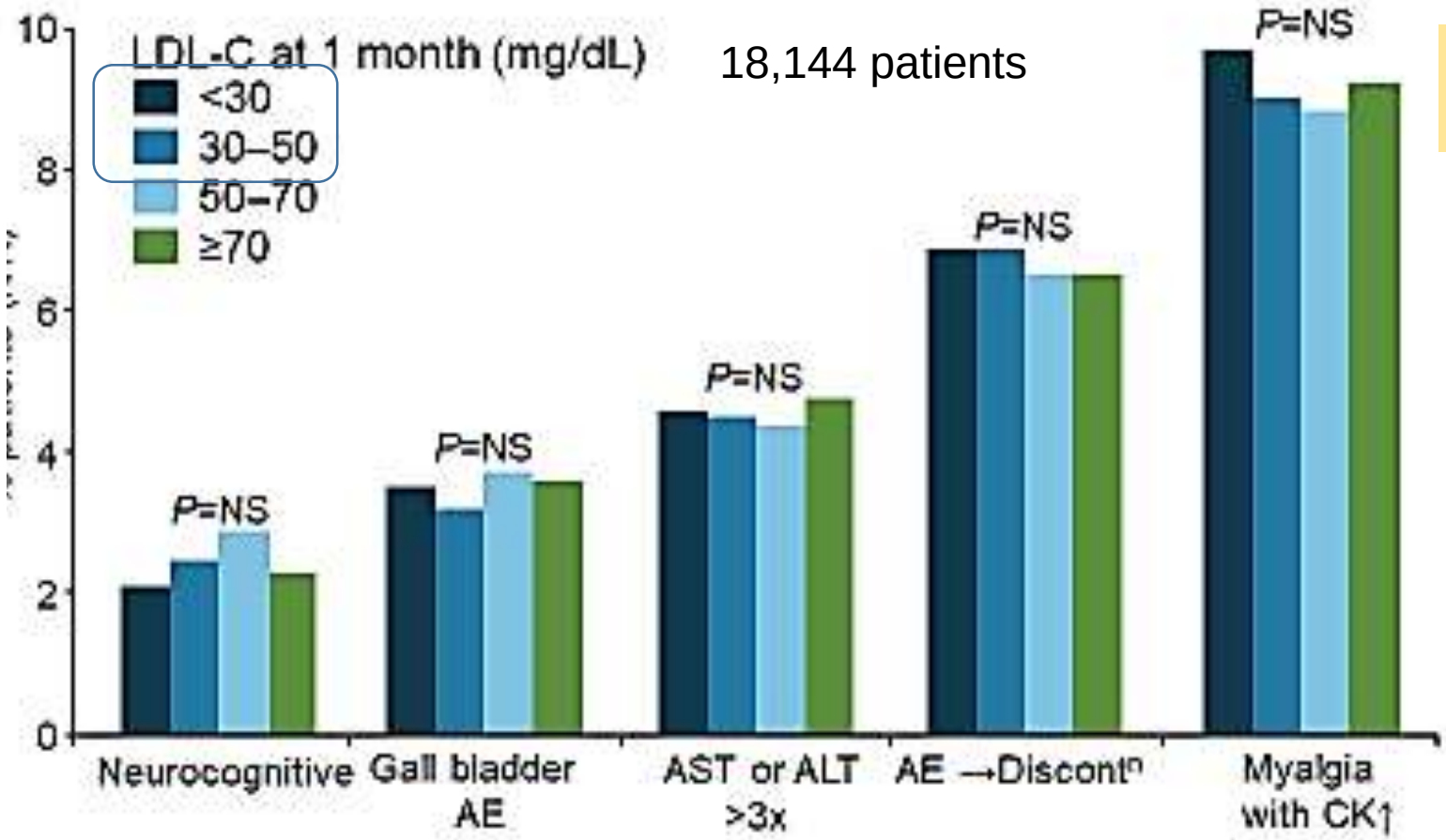
New onset diabetes mellitus

Hemorrhagic stroke

CNS

Regardless of how low the LDL-C level is, there does not appear to be an increase in adverse events in the IMPROVE-IT study

- ACS
- simvastatin 40 mg + ezetimibe 10 mg
- Simvastatin 40 mg
- median FU- six years



- **גיל ממוצע 64±10 שנים**

Giugliano RP, et al. Presented at European Society of Cardiology, London, 2015.

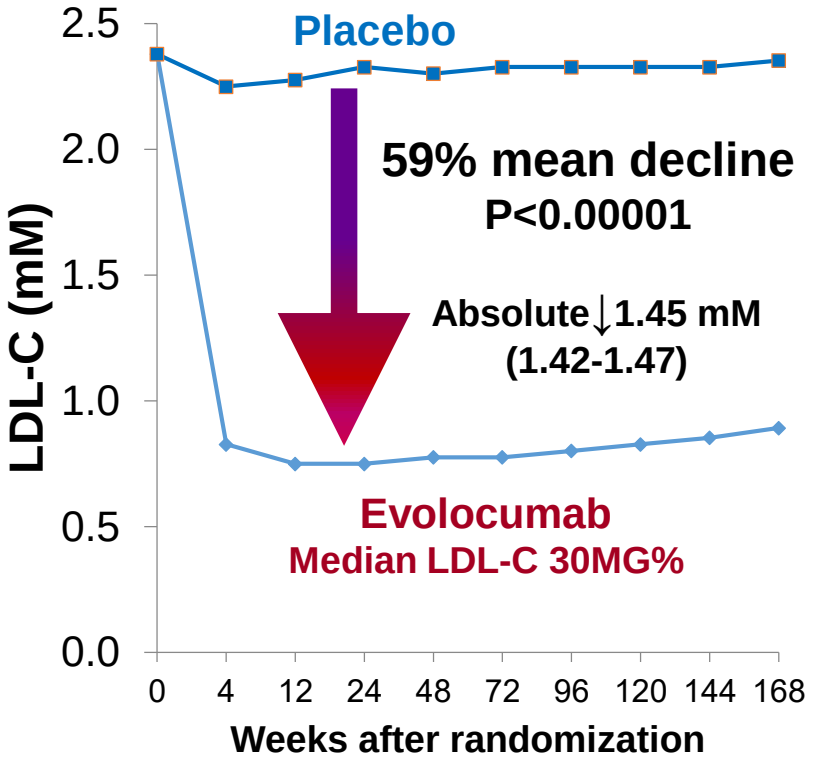
LOW PLASMA CHOLESTEROL

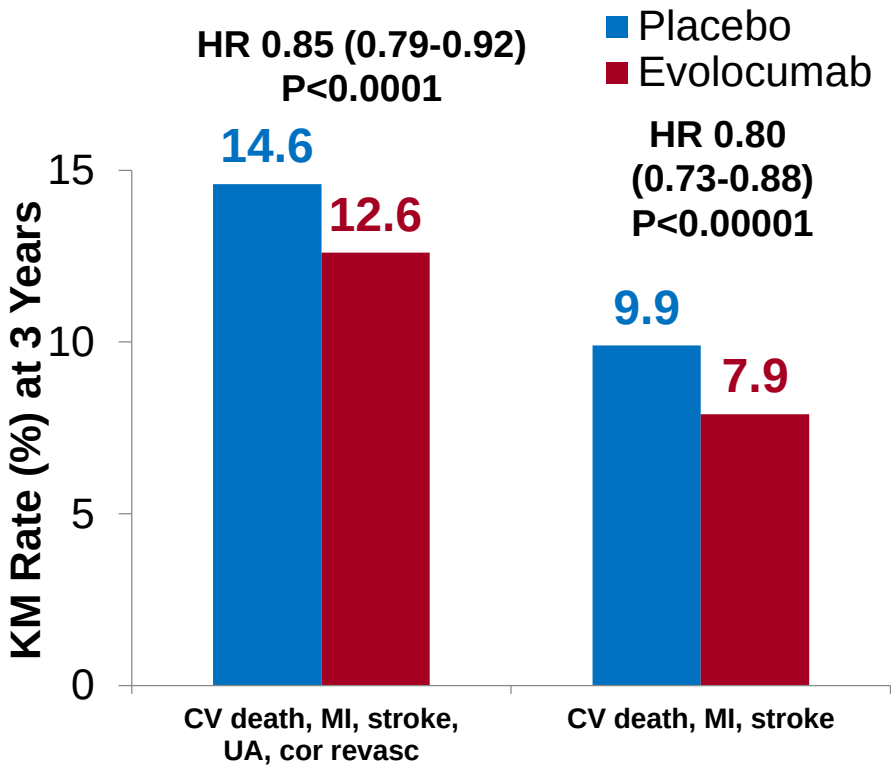
Pcsk9 studies

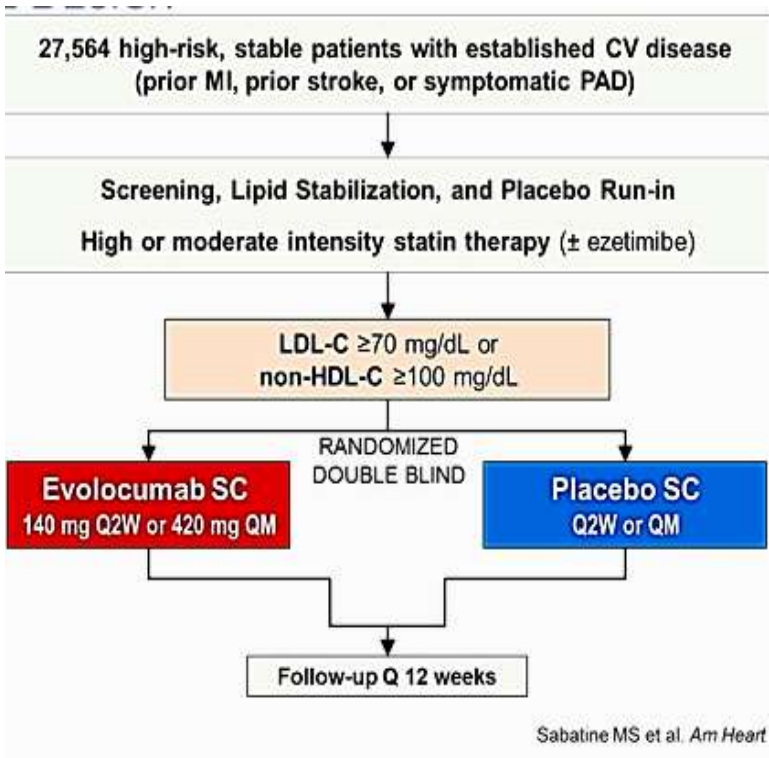
Evolocumab - Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

- ↓ LDL-C by 59% from a median baseline value of 92 mg/dl to 30 mg/dl
- ↓ CV outcomes in patients already on statin therapy
- 15% ↓ primary endpoint *;20% ↓ CV death, MI, or stroke

Median follow-up (years) 2.16







* the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization),

Sabatine MS et al. *New Engl J Med* 2017;376:1713-22

Clinical Efficacy and Safety of Achieving Very Low LDL-C Levels With the PCSK9 Inhibitor Evolocumab in the FOURIER Trial

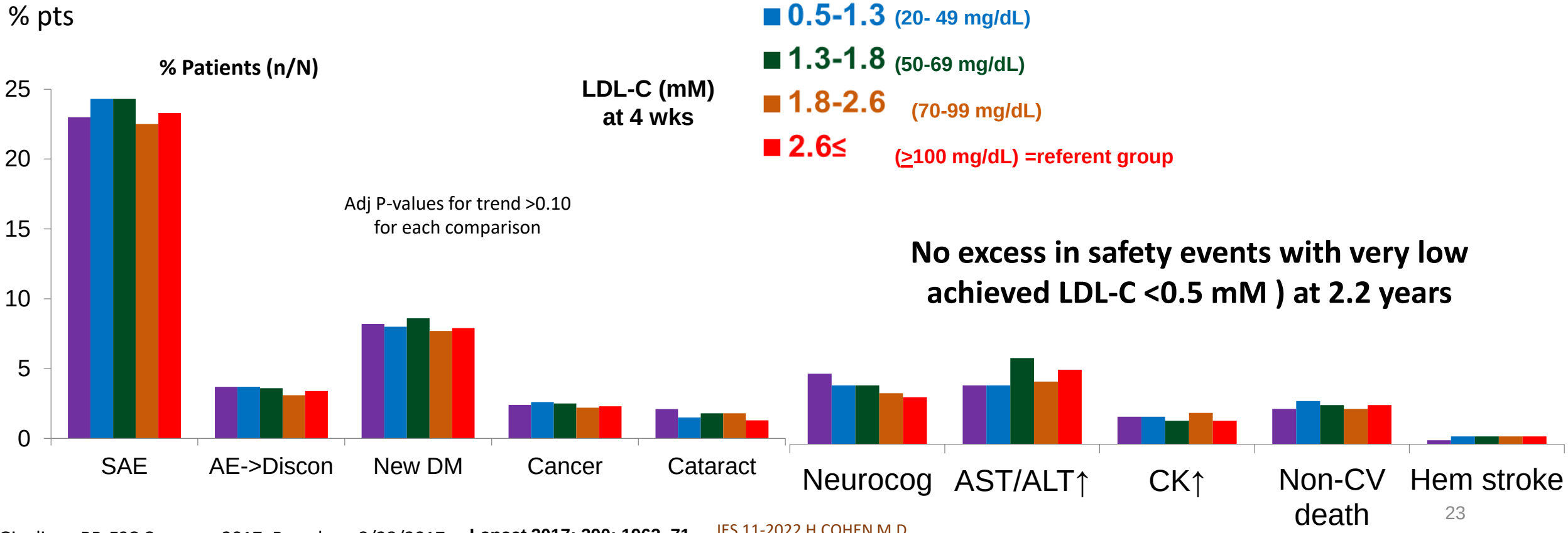
Safety Events

LDL-C assessed at 4 wks (ultracentrifugation if <1 mM)

Analyzed 5 groups by achieved LDL-C at 4 weeks

LDL-C (mM) at 4wks

- **0.5>** (20 mg/dL)
- **0.5-1.3** (20- 49 mg/dL)
- **1.3-1.8** (50-69 mg/dL)
- **1.8-2.6** (70-99 mg/dL)
- **2.6≤** (≥100 mg/dL) =referent group



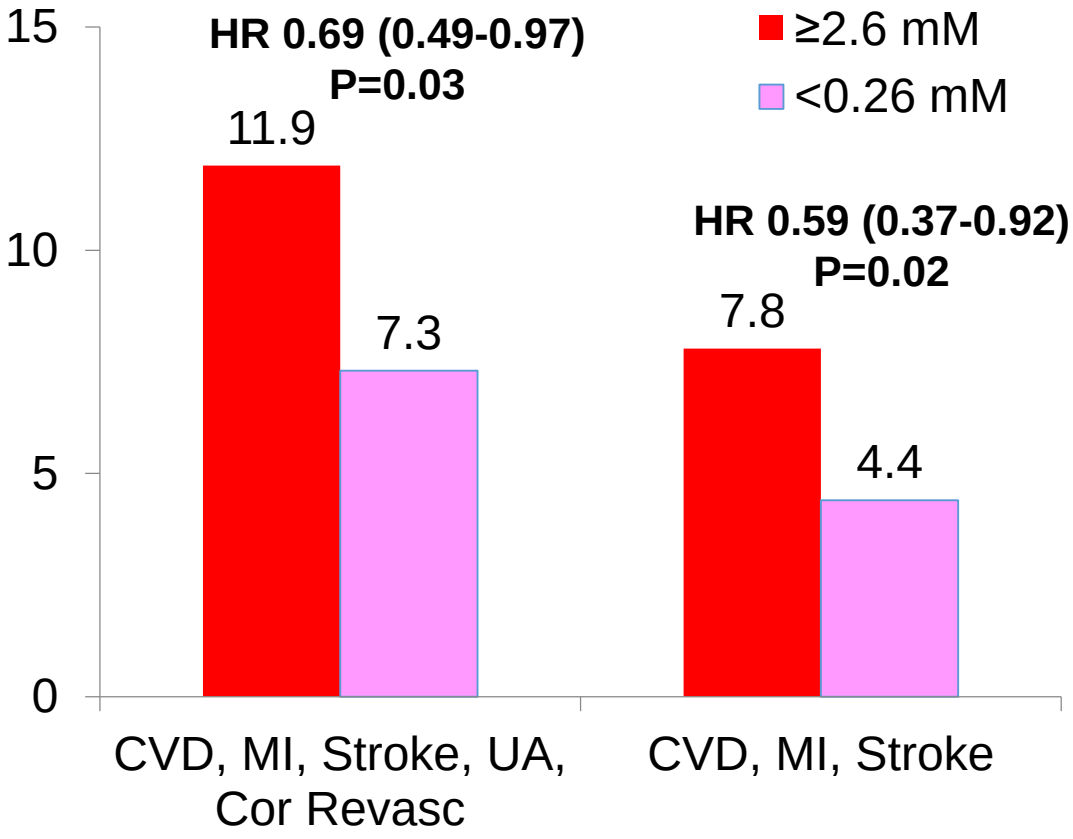
Adj P-values for trend >0.10 for each comparison

No excess in safety events with very low achieved LDL-C <0.5 mM) at 2.2 years

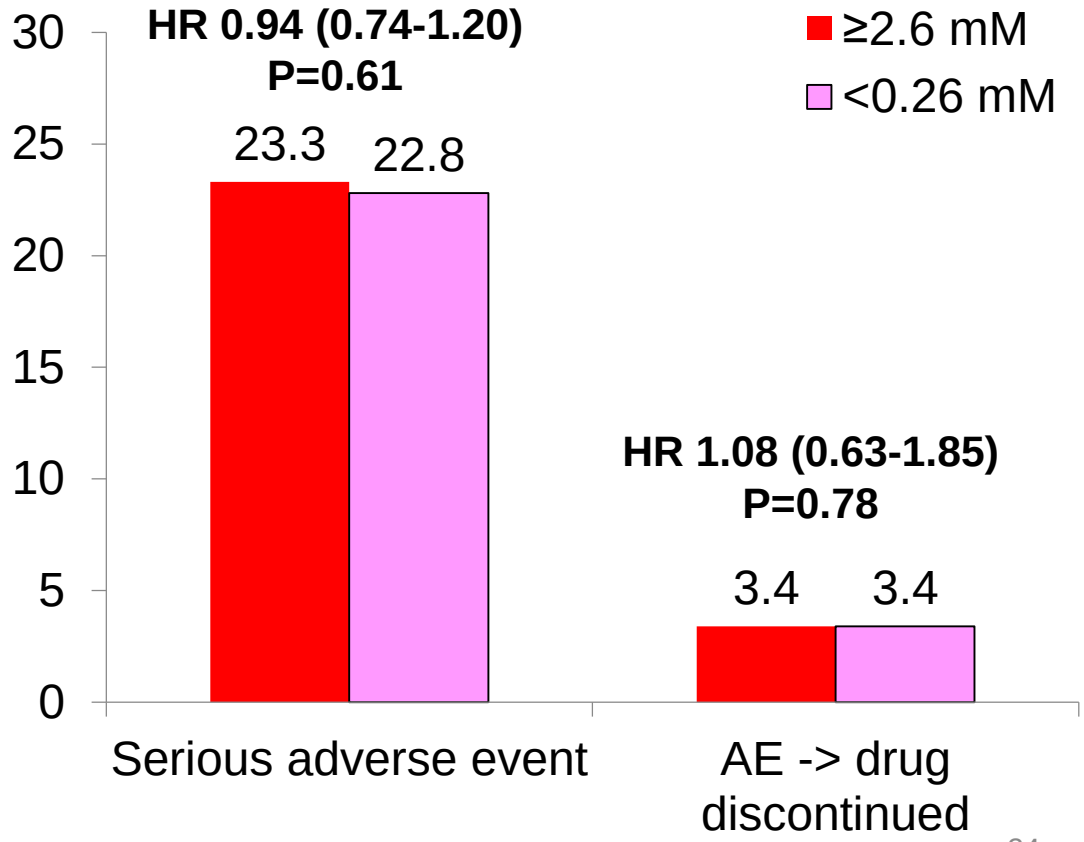
Exploratory Analysis Pts with LDL-C <10 mg/dL at 4 wks

N=504: Median [IQR] LDL-C 7 [5-9] mg/dL

Cardiovascular Efficacy



Safety



Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

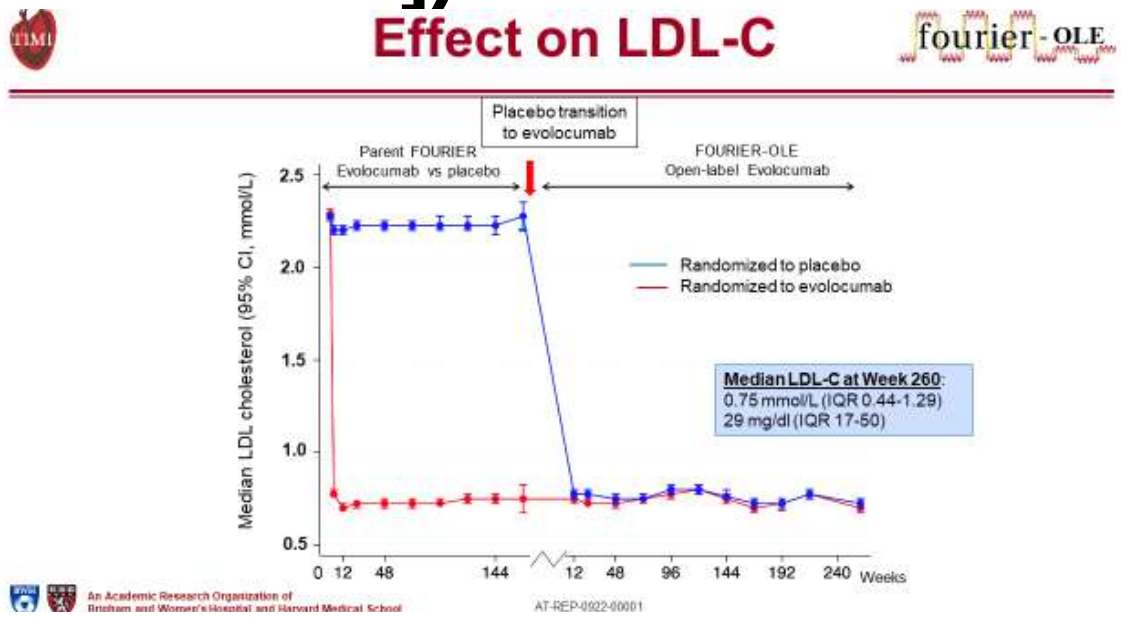
Open-label extension studies (FOURIER-OLE [FOURIER Open-Label Extension])

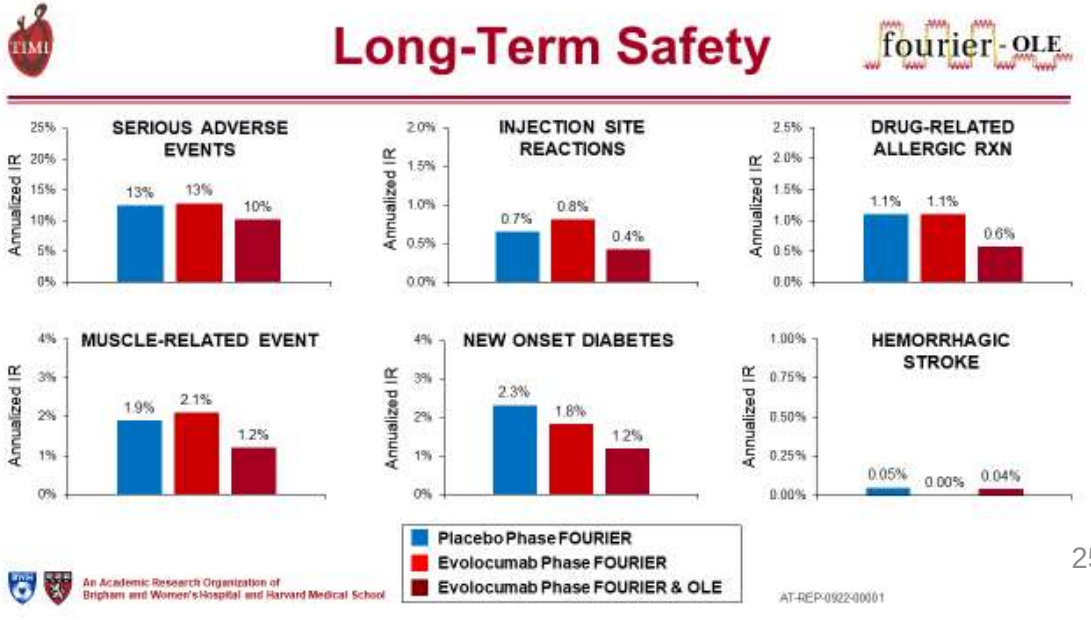
- **Maximum** exposure to evolocumab in parent plus FOURIER-OLE =**8.4 years**

- **Median LDL-C = 30 mg/dL**
- **63.2% of patients = LDL-C <40 mg/dL**

Serious adverse events

- muscle-related events, new-onset diabetes, hemorrhagic stroke, and neurocognitive events
- **did not exceed** those for placebo-treated patients during the parent study and did not increase over time

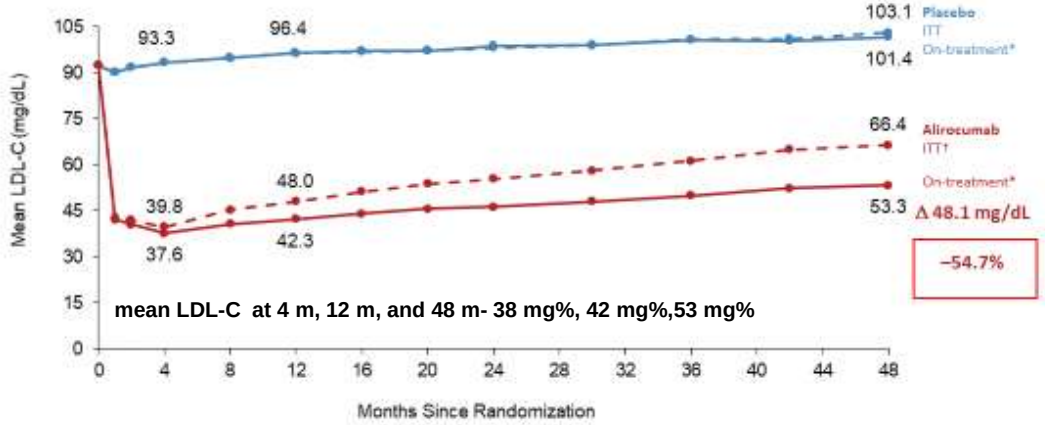




Circulation. 2022 Oct 11;146(15):1109-1119.

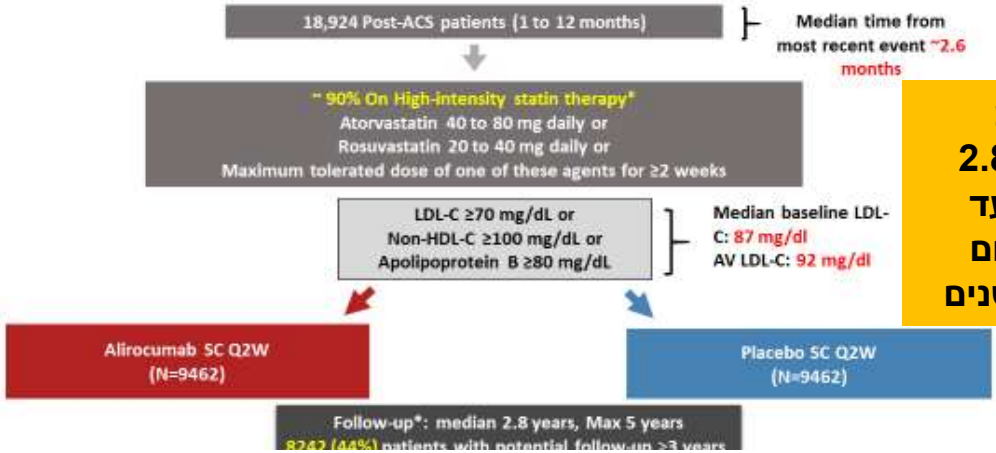
nes after Acute Coronary Syndrome

LDL-C: ITT and On-Treatment Analyses



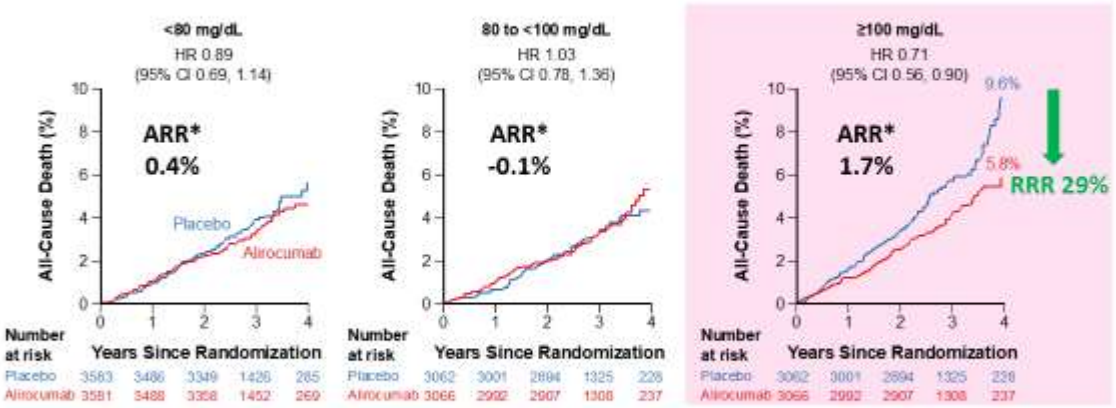
mean LDL-C at 4 m, 12 m, and 48 m- 38 mg%, 42 mg%,53 mg%

*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C



המעקב נמשך 2.8 שנים ועד מקסימום של 5 שנים

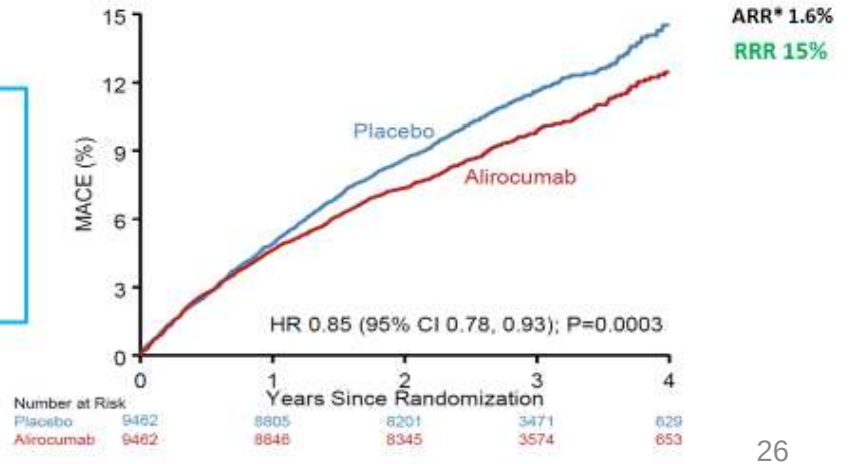
Post Hoc Analysis: All-cause Death in Three Predefined Categories of Baseline LDL-C



Relative risk reduction: Interaction P=0.12
*Absolute risk reduction: Interaction P=0.005

MACE:
- CHD death
- Non-fatal MI
- Ischemic stroke
- unstable angina requiring hospitalization

Primary endpoints: MACE



*Based on cumulative incidence

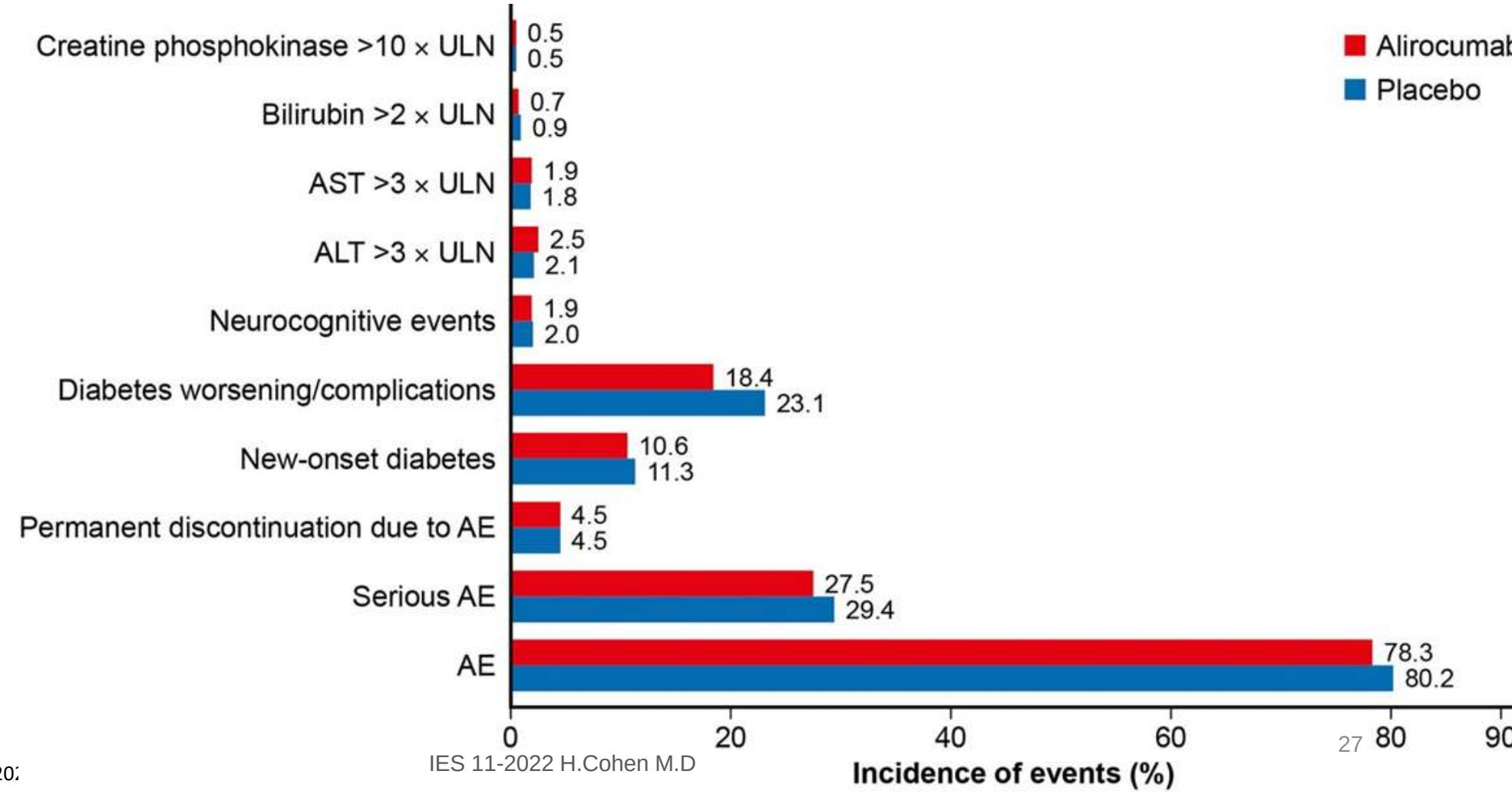
Schwartz GG, et al. NEJM 2018;379(22):2097-2107.

Longer-term safety of alirocumab : Further insights from the ODYSSEY OUTCOMES trial*

Odyssey Outcomes Longer-term Safety

Post hoc analyses of alirocumab vs. placebo in a pre-specified subgroup of patients

- 8,228 patients eligible for **3-5 years f/u.**
- Total 24,610 patient-years of observation;
- median follow-up 3.3 years, max 5 years



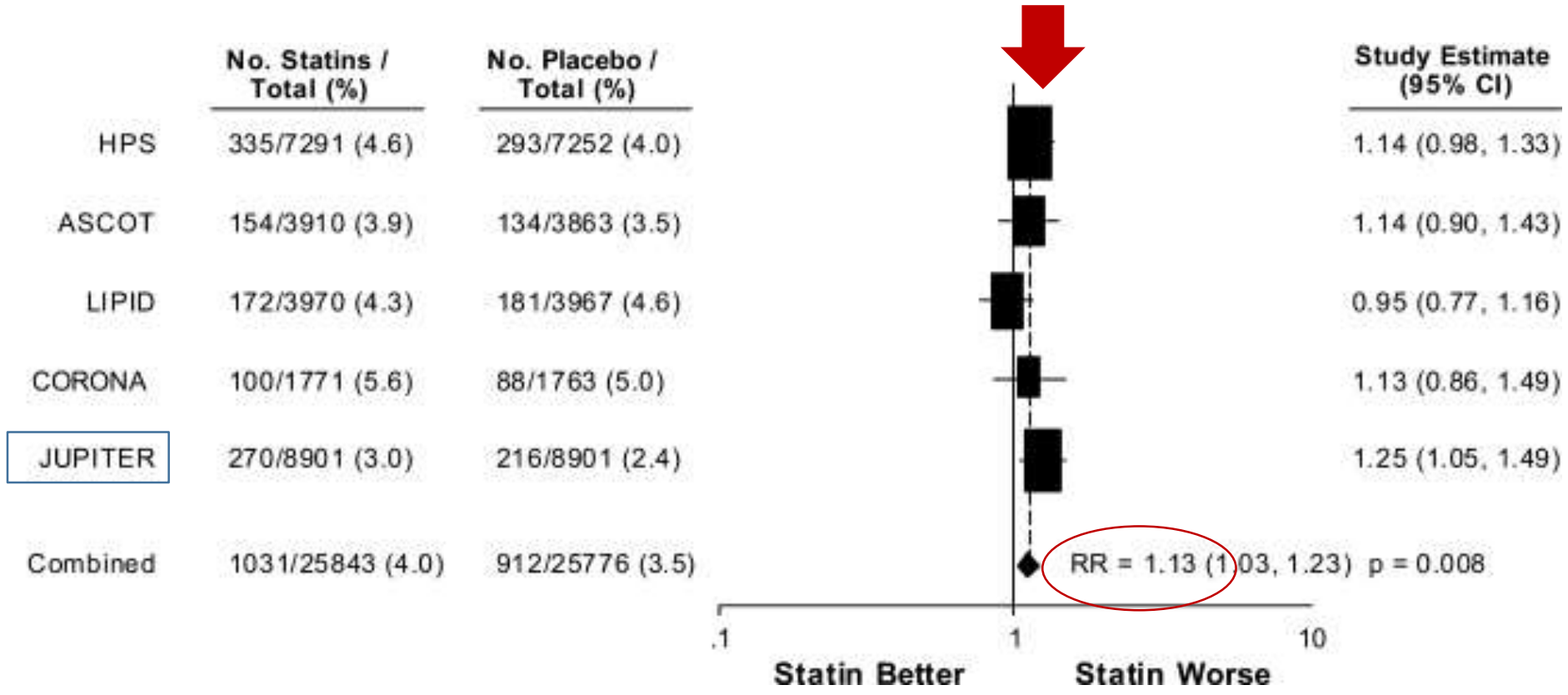
LOW PLASMA CHOLESTEROL

diabetes risk

Insulin resistance and diabetes - **STATINS**

Association between **statin therapy** + risk of **type 2 DM**

Meta-analysis of clinical trials evaluating the effects of statins on diabetes risk



57,593 patients with mean follow-up of 3.9 years

overall HR for statin therapy of 1.1

Diabetes Care. 2009 Oct;32(10):1924-9.

Statins increased the risk for new-onset diabetes and worsening glycemia

- Meta-analysis
- 23 trials > 150,000 participants
- > 4.0 years f/u
- NOT related to the degree of LDL-C lowering

HIGH-INTENSITY STATIN TREATMENT

(atorvastatin at a daily dose of at least 40 mg, or rosuvastatin at a daily dose of at least 20 mg)

INCREASE in A1c

0.08 % among people w/o DM

0.24 % among diabetics

BLOOD GLUCOSE LEVELS elevation

average of <1 mg/d in those without diabetes

average 4 mg/dL in those with diabetes

2022 reported at the American Heart Association scientific sessions

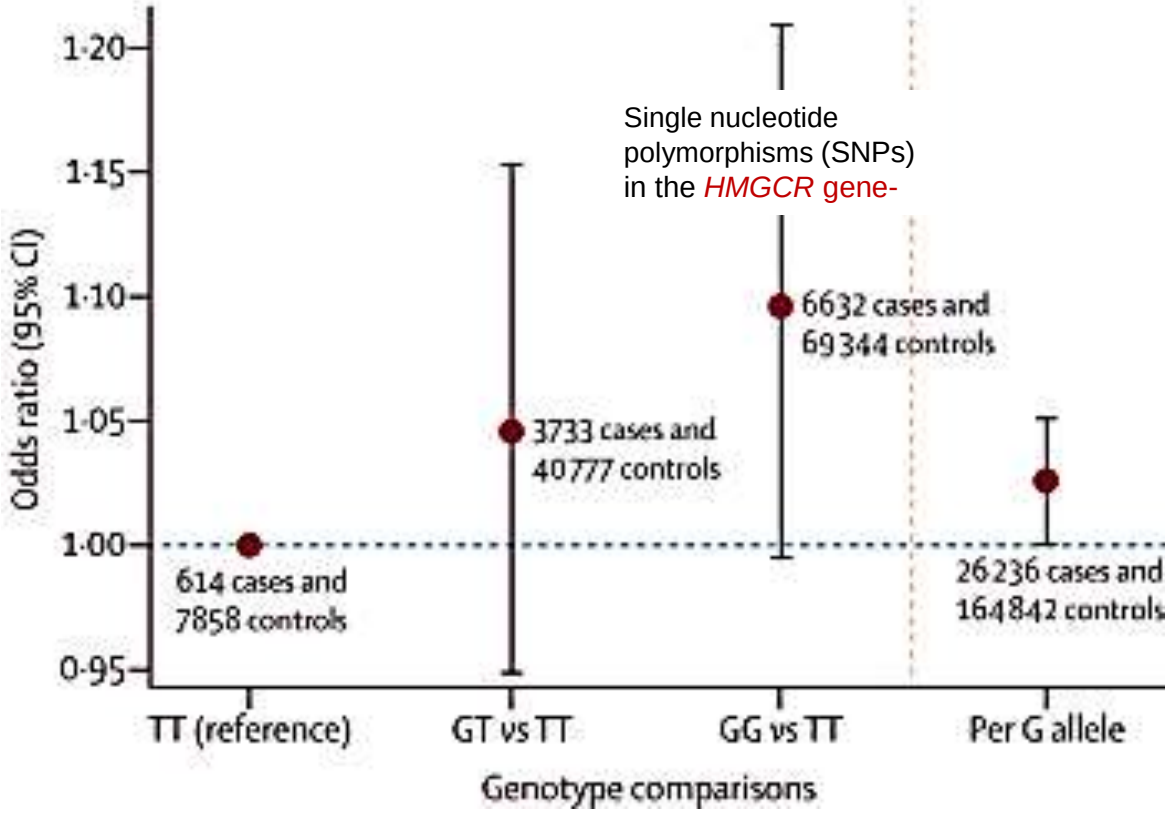
Statins and type 2 diabetes - low cholesterol ? off target effect ?

- Single nucleotide polymorphisms (SNPs) in the *HMGCR* gene-(hydroxy-3-methylglutaryl-coenzyme A reductase)
- 223,463 individuals from 43 genetic studies

Genetic analysis

- **Increased risk of type 2 diabetes** noted with statins is at least partially explained by **HMGCR inhibition**

association of the rs17238484 genotype with **risk of type 2 diabetes**



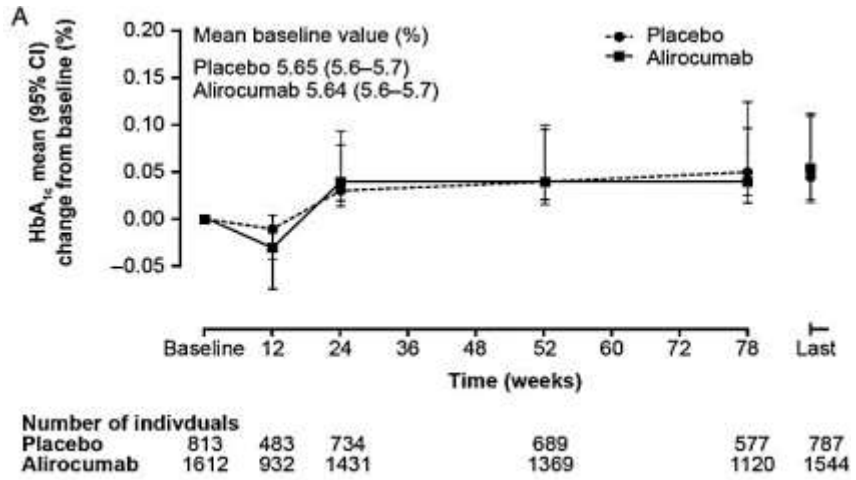
Frayling TM. . Lancet. 2015 Jan 24;385(9965):310-2. Swerdlow DI.Lancet. 2015 24;385(9965):351-61.

Glucose metabolism and PCSK9 INH

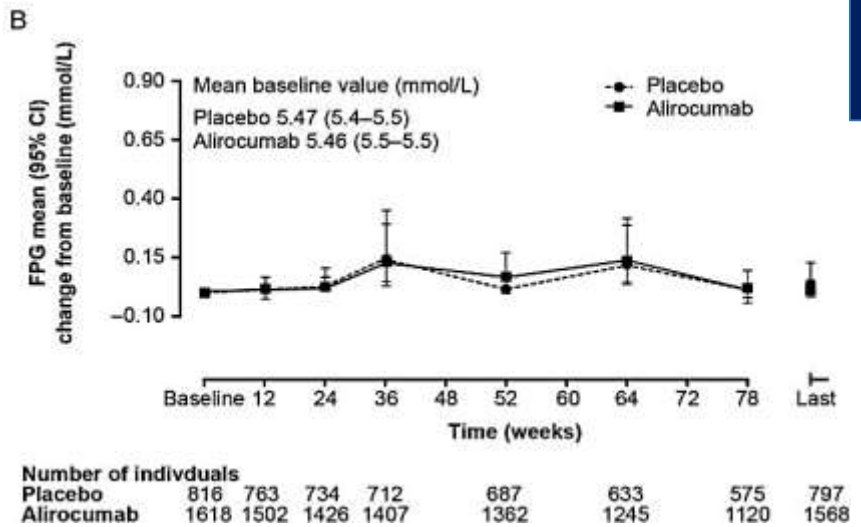
Pooled analysis **of 10 ODYSSEY Phase 3 trials no evidence** of an effect of alirocumab on transition to new-onset diabetes in 3448 individuals without diabetes at baseline with a **follow-up period of 6-18 months**

No correlation

- **insulin resistance**
- **plasma glucose levels**
- **increased rates of diabetes**



A_{1C} (%)



fasting plasma glucose (mmol/L)

Eur Heart J. 2016;37(39):2981

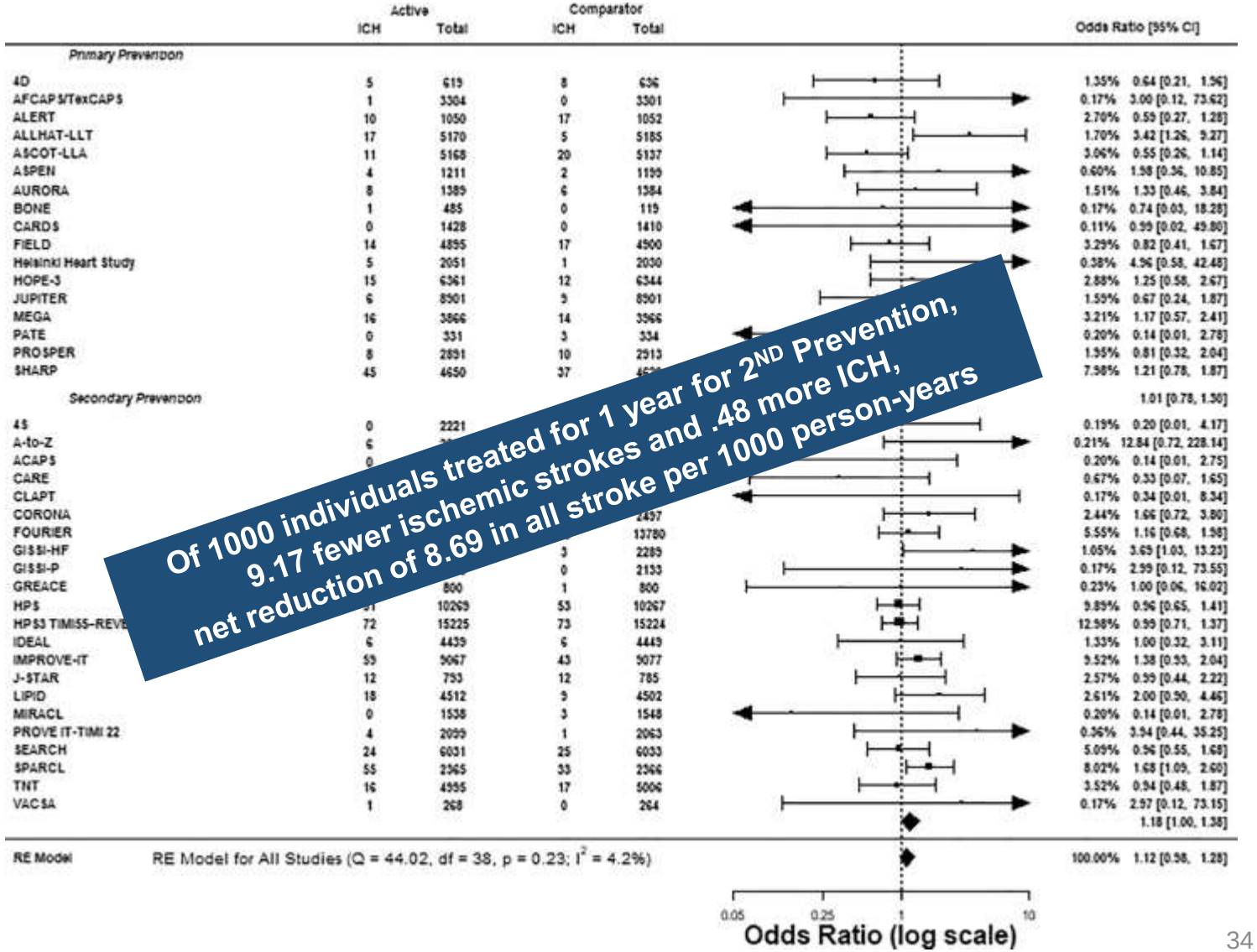
LOW PLASMA CHOLESTEROL &

Intracerebral Hemorrhage

https://healthjade.net/intracerebral-hemorrhage/

Lipid Lowering Therapy, LDL Level and Risk of Intracerebral Hemorrhage - *A Meta-Analysis 2019*

- 39 trials
- 287,651 participants
- **lipid lowering therapy**
- **not associated with a statistically significant increased risk of ICH**
- in primary and secondary prevention trials
- OR, 1.12; 95% confidence interval [CI], .98-1.28)



Stroke Cerebrovasc Dis Actions. 2019;28(6):1703-1709

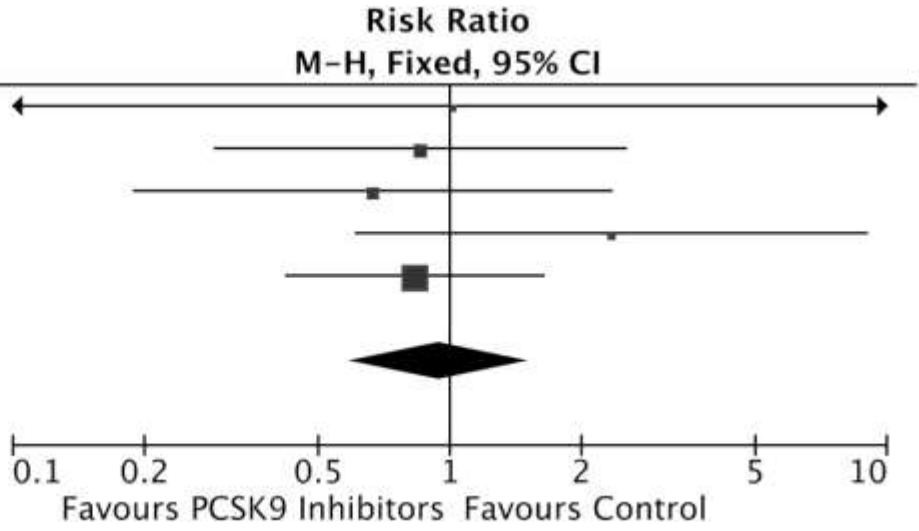
Lipid-Lowering Therapy and Hemorrhagic Stroke Risk: Comparative *Meta-Analysis of Statins and PCSK9 Inhibitors 2021*

Risk of hemorrhagic stroke in PCSK9 inhibitor randomized clinical trials enrolling patients without and with ischemic stroke or transient ischemic attack

Study or Subgroup	PCSK9 Inhibitors Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
ODYSSEY Long Term 2015	2	1550	1	788	3.8%	1.02 [0.09, 11.20]	2015
SPIRE-1 2017	6	8386	7	8374	19.8%	0.86 [0.29, 2.55]	2017
FOURIER 2017	4	13769	6	13756	17.0%	0.67 [0.19, 2.36]	2017
SPIRE-2 2017	7	5276	3	5297	8.5%	2.34 [0.61, 9.05]	2017
ODYSSEY Outcomes 2018	15	9482	18	9462	51.0%	0.83 [0.42, 1.65]	2018
Total (95% CI)		**38463**		**37677**	**100.0%**	**0.94 [0.59, 1.51]**	
Total events	34		35				

Heterogeneity: $Chi^2 = 2.19$, $df = 4$ ($P = 0.70$); $I^2 = 0\%$

Test for overall effect: $Z = 0.24$ ($P = 0.81$)



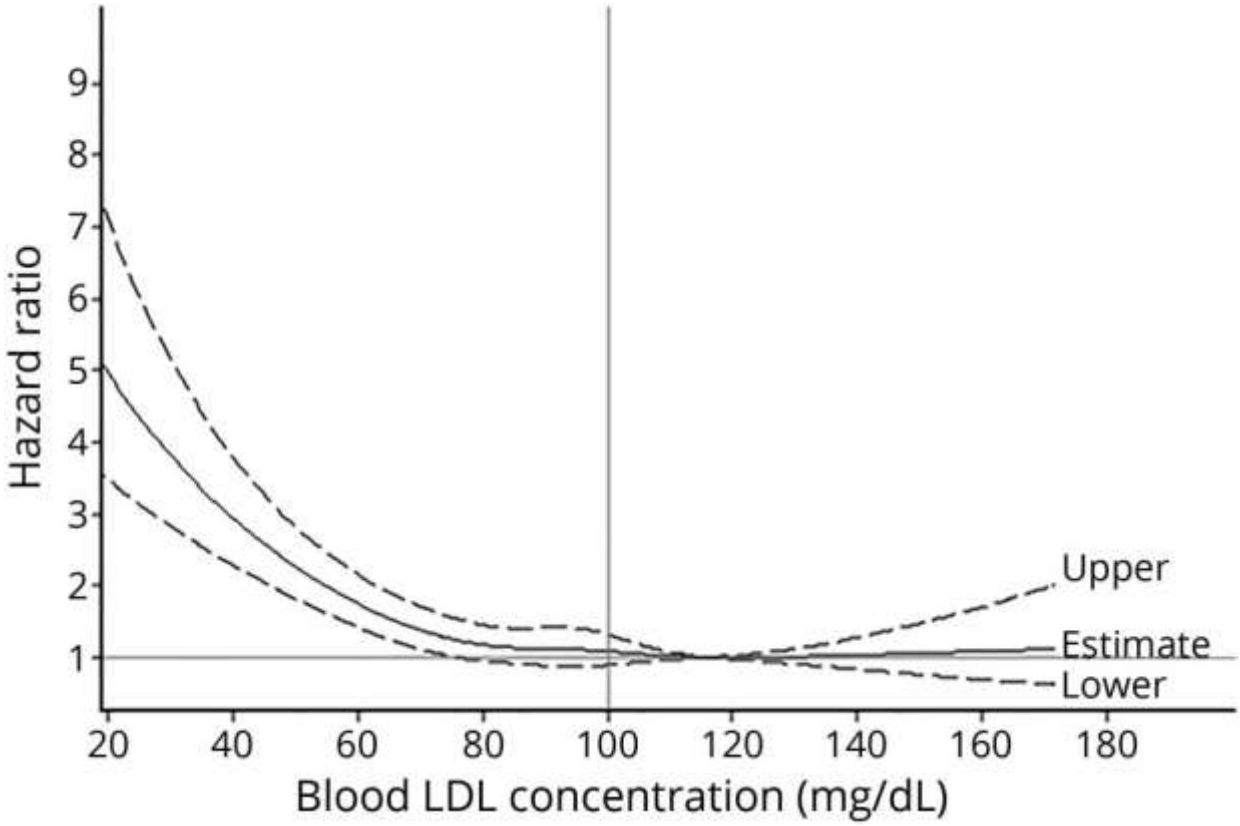
5 RCTs in 76,140 patients = not significant increased risk of hemorrhagic stroke with PCSK9Is added to maximally tolerated statins compared with maximally tolerated statins alone

Stroke .3142-3150:(10)52; 2021 Oct

Association between lower LDL-C and higher risk of intracerebral hemorrhage: *A **prospective study***

- 96,043 participants - mean age 51.3 y
- LDL-C concentrations - 2006, 2008, 2010, 2012
- ICH - review of medical records
- 9 years of follow-up
- **Participants with LDL-C <70 mg/dL = significantly higher risk of developing ICH**
- than those with LDL-C of 70- 99 mg/dl
- Hazard ratio = 1.65 for LDL-C 50 - 69 mg/dL
- Hazard ratio =2.69 for LDL-C <50 mg/dL

Hazard ratios for intracerebral hemorrhage according to updated cumulative average blood LDL cholesterol from 2006 to 2012 among 96,043 participants



Neurology. 2019 Jul 30;93(5):e445-e457.

Cognitive dysfunction and **very low plasma LDL levels**

Relation between plasma and brain lipids

The brain is the most cholesterol-rich organ in the body

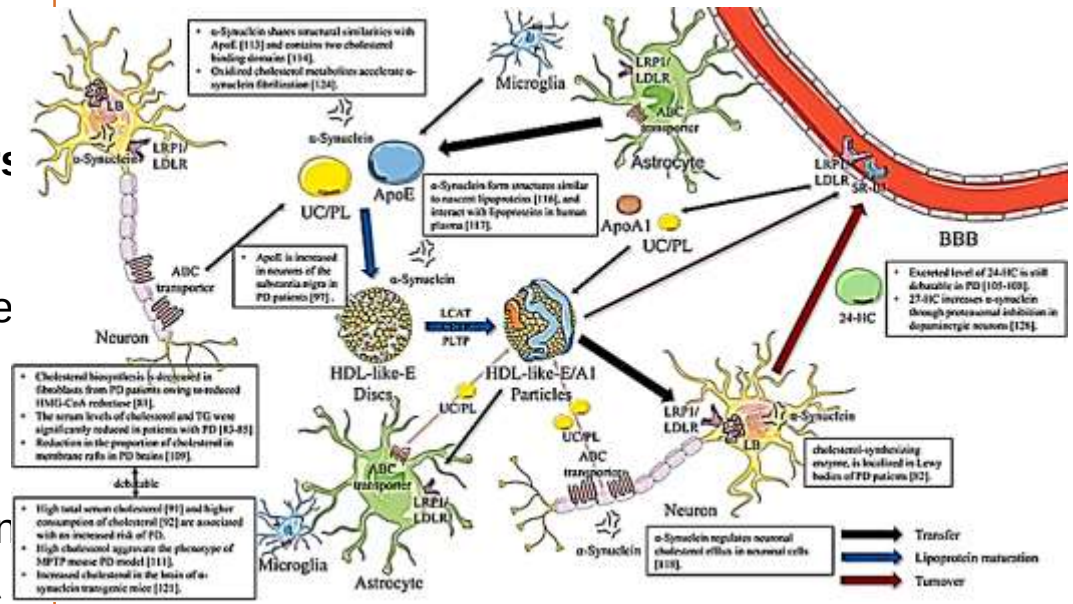
- 25% of the body's total cholesterol

brain cholesterol regulation is dependent upon **local de novo cholesterol synthesis**

Lipoproteins in the CNS : **differs** from that in the **circulation**

Cholesterol or PCSK9 ***Cannot*** cross the **blood-brain barrier**

Pcsk9-inhibitors ***cannot*** cross the **blood-brain barrier** in humans



Concerns have been raised in the media and popular press about **cognitive dysfunction** and **memory loss** associated with **very low plasma LDL levels**

Current Opinion in Lipidology: June 2016 – Vol.27 (3)p 225-232

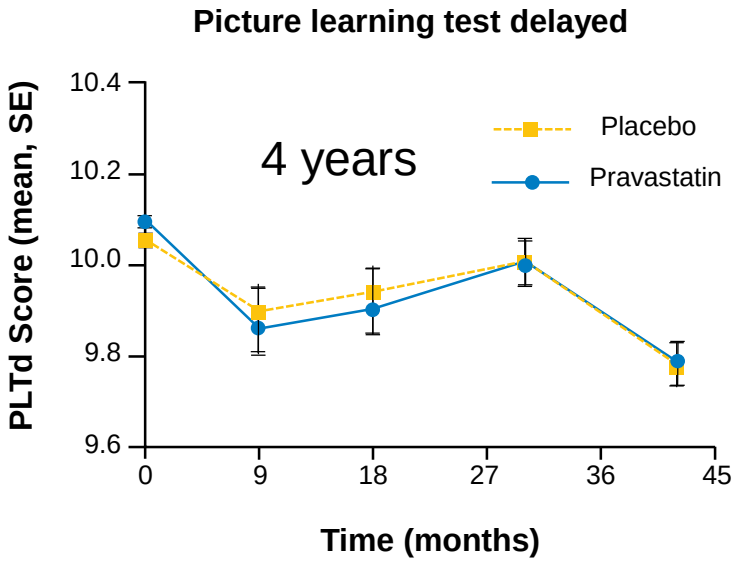
IES 11-2022 H.Cohen M.D

Jin, Uram & Park, Soo Jin & Park, Sang Myun. (2019). Experimental Neurobiology. 28. 554-567.

Cognitive Function in PROSPER and HPS Trials

PROSPER[1]

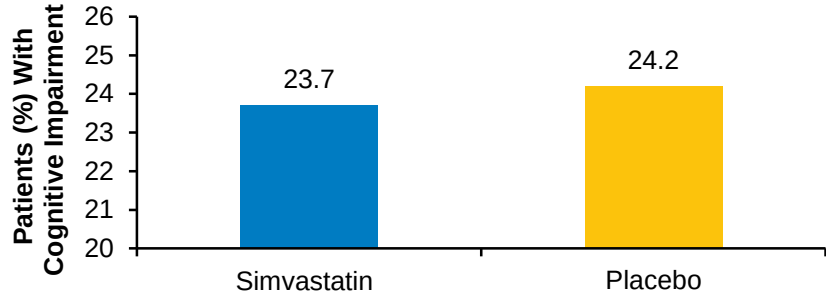
Prospective, multicenter, randomized, placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly people (70–82 y); N = 5,804



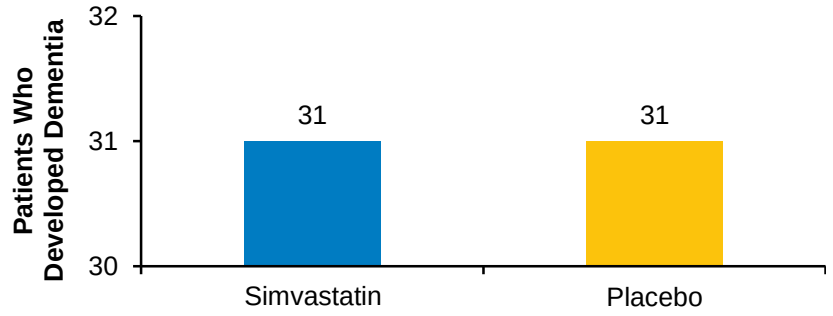
Mean LDL-C:
Pravastatin: (147 mg/dL) ; Control: (147 mg/dL)

HPS[2]

5-year, multicenter, randomized, placebo-controlled study to evaluate the long-term effects of lipid lowering with simvastatin on vascular and nonvascular mortality and major morbidity; N = 20,536 (age 40-80,AVR=65 years)



Mean LDL-C:
Simvastatin: (131 mg/dL) ; Control: (131 mg/dL)



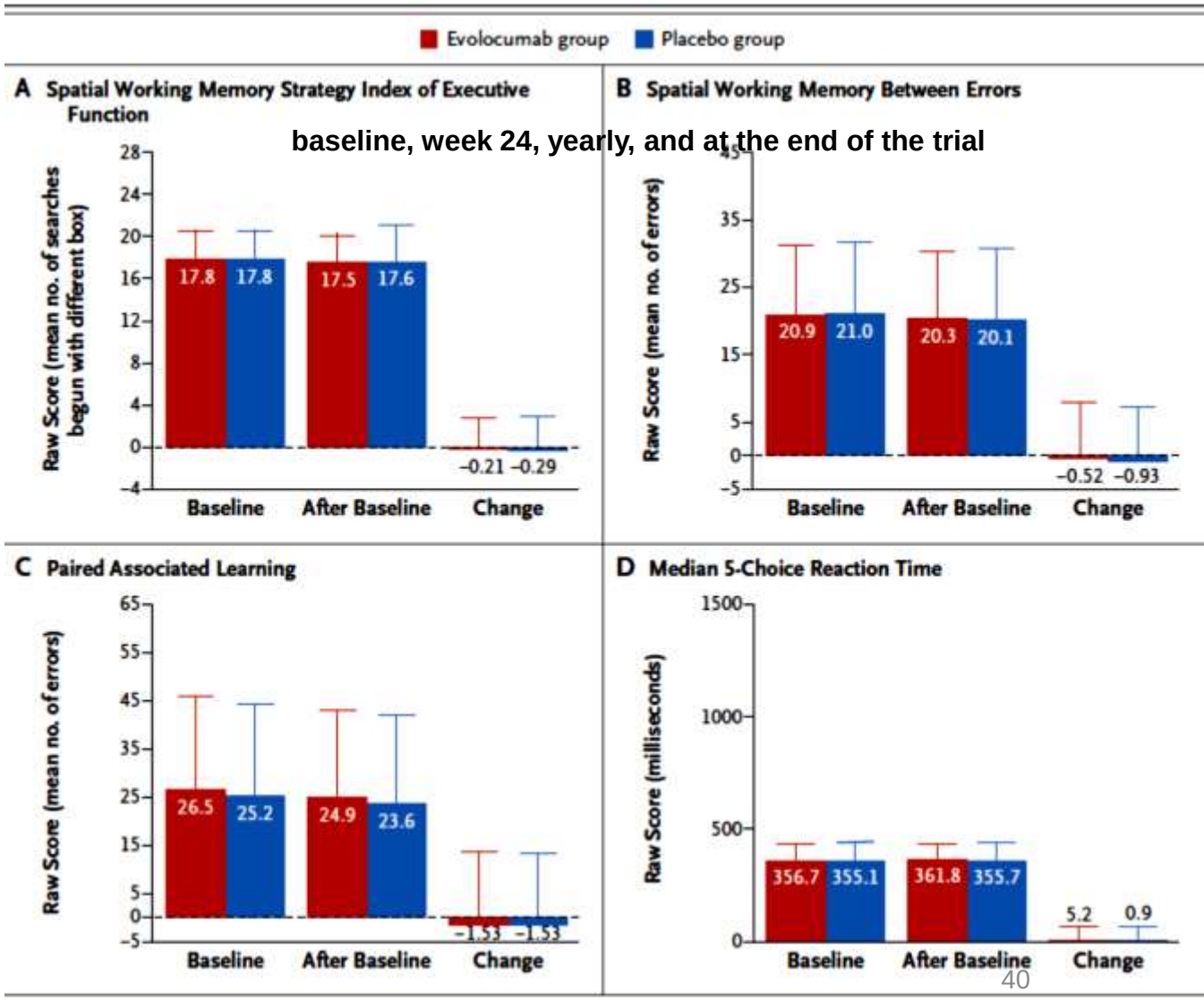
PLTd = picture learning test delayed To convert from 1 mmol/L to mg/dL - multiply by 38.67

1. Trompet S, et al. J Neurol 2010;257:85-90. **2.** Heart Protection Study Collaborative Group. Lancet 2004;363:757-767.

Hypocholesterolemia & Cognition

Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study

- 1204 patients – f/u median **19 months;**
- **NO significant between-group differences**
- End points of scores for working memory ,episodic memory or psychomotor speed
- **No associations** between **LDL-c levels** and **cognitive changes**
- **NO Difference -661 patients whose LDL- c<25 mg /deciliter**
- Entire FOURIER trial



baseline, week 24, yearly, and at the end of the trial

N Engl J Med 2017;377:633-43

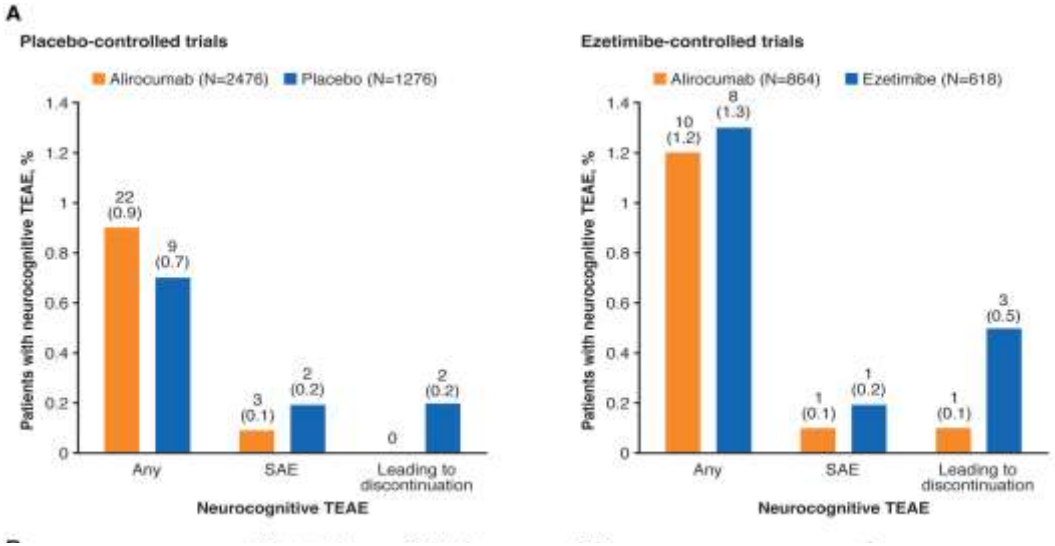
J Am Coll Cardiol. 2020 12;75(18):2283-2293

No evidence of neurocognitive adverse events associated with **alirocumab treatment**

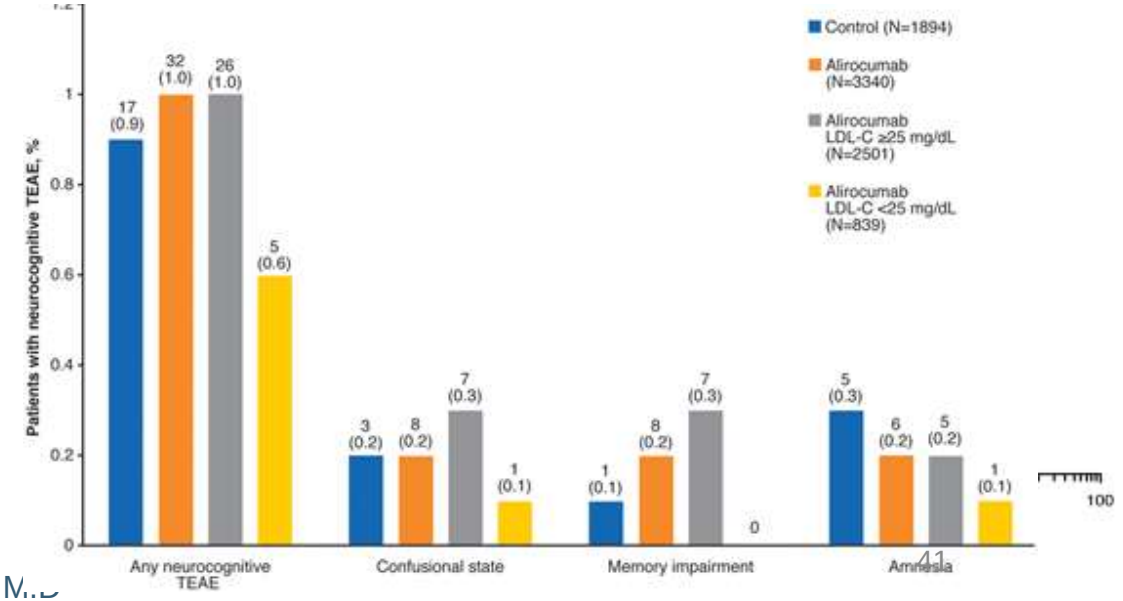
ESC European Society of Cardiology

- 14 Phase 2 and 3 trials of alirocumab.n = 3340
- **Neurocognitive treatment-emergent adverse events** (TEAEs):
- Neurocognitive TEAE incidences were low (≤1.2%)
- 0.9% alirocumab-treated patients vs. 0.7% with placebo and 1.2% with alirocumab vs.1.3% with ezetimibe
- **LDL level :** Rates of neurocognitive TEAEs were similar in patients receiving alirocumab with **LDL-C<25 mg/dL vs. ≥25 mg/dL** .
- **NO sig. differences between alirocumab vs. controls up to 104 weeks**.
- Similar between alirocumab and controls **when stratified by age**

Overall percentage rates of neurocognitive treatment-emergent adverse events



Neurocognitive treatment-emergent adverse events in patients with two consecutive LDL levels <**25 mg/dL**



Harvey PD, Sabbagh MN, Harrison JE, Ginsberg HN, Chapman MJ, Manvelian G, Moryusef A, Mandel J, Farnier M.. Eur Heart J. 2018 Feb 1;39(5):374-381

LOW PLASMA CHOLESTEROL & cancer risk

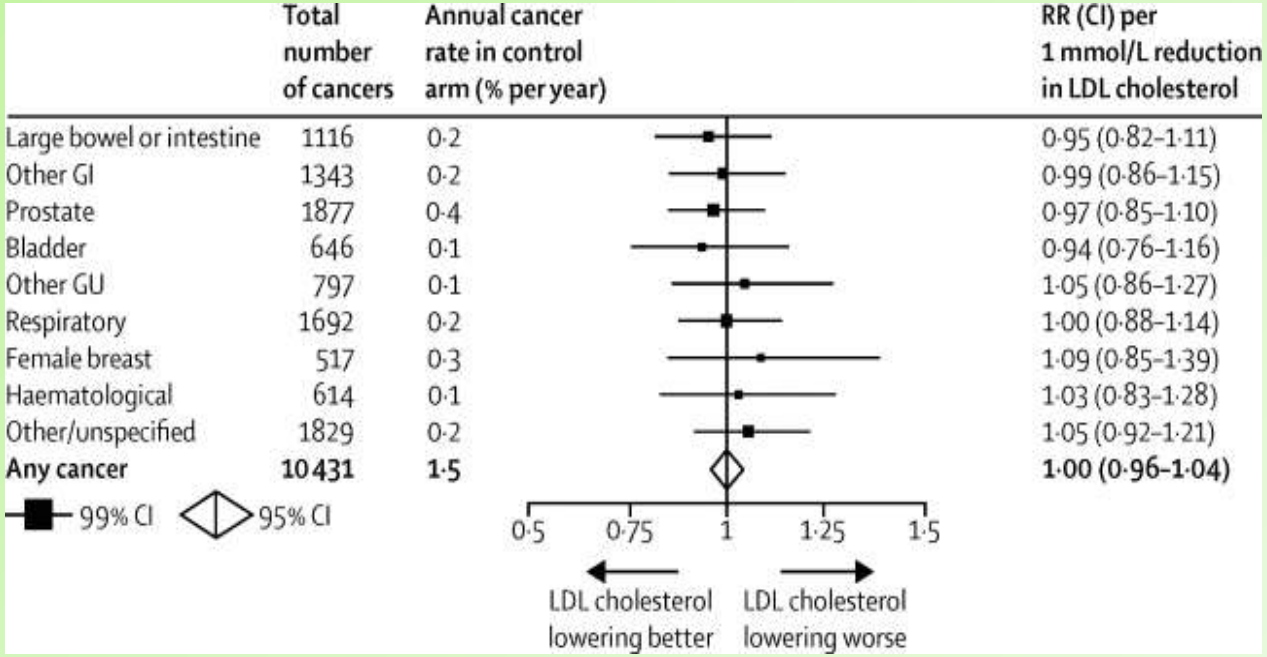
Cancer incidence- low cholesterol

Not increased

Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis –

NO CORRELATION between statin therapy and any **cancer or overall cancer rate-relative risk (RR)1.00**

Collins R et al , Lancet 2016;388:2532–2561.



Additional follow-up studies= no increased cancer incidence

Increased

Mendelian randomization analysis :

Genetically raised LDL cholesterol levels = associated **with lower risks** of endometrial cancer of all histologies combined

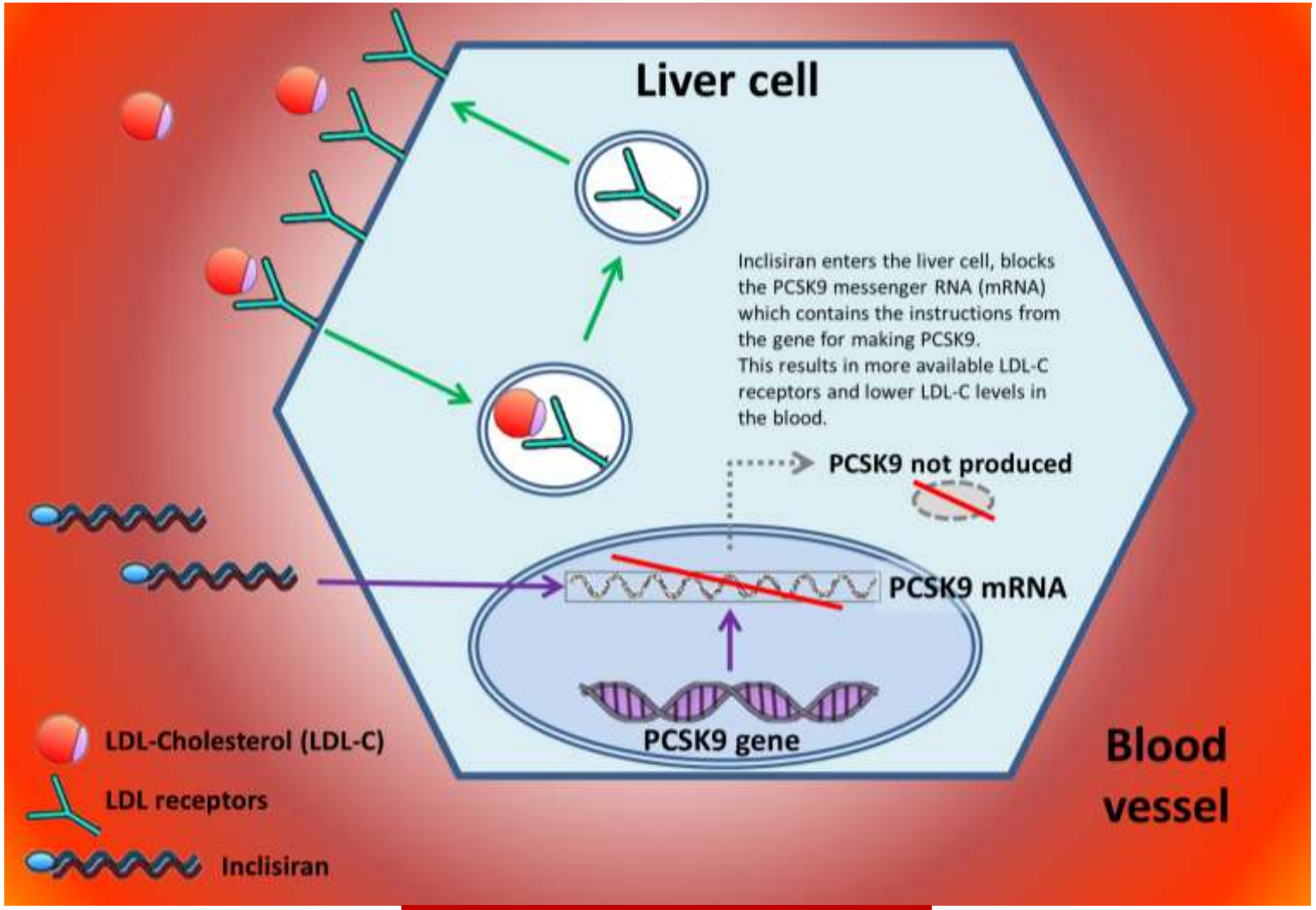
Kho P-F et al ,Int J Cancer 2021;148:307–319.

No sub-studies with long-term safety f/u that have shown association with higher cancer rates

MEDICATIONS :

Prolonged cholesterol lowering

Inclisiran – **siRNA blocks the PCSK9 messenger RNA**



1. אינקליסירן = small interfering RNA (siRNA)
2. חומצה ריבונוקלאית , המחוברת לשייר (GalNAc)
3. בתאי הכבד, אינקליסירן גורם לפירוק של mRNA עבור האנזים (PCSK9)
4. עלייה במספר הקולטנים של LDL
5. עליית UPTAKE של LDL, לתאים
6. וירידה ברמת LDL כולסטרול בפלסמה

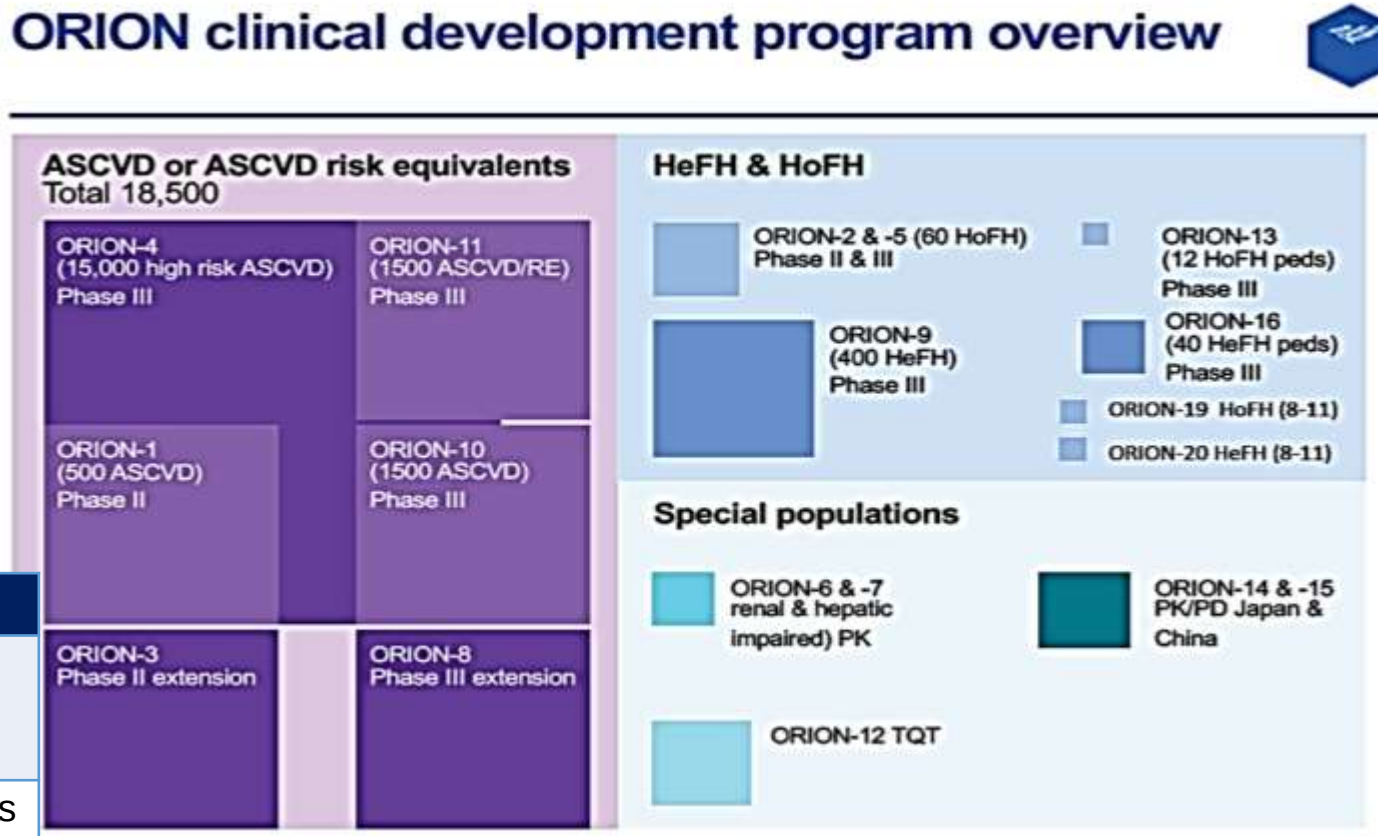
triantennary N- שייר של acetylgalactosamine (GalNAc

https://www.orion4trial.org/faq-1/pcsk9-and-inclisiran-action-diagram

אנליזה של שלושה מחקרים **יעילות ובטיחות פורסמו לאחרונה**

ORION Phase III pooled analysis:
Specific study inclusions

ORION-9	ORION-10	ORION-11
482 HeFH[1]	1561 ASCVD (CHD, CVD, PAD)	1617 ASCVD (CHD, CVD, PAD)
Stable on a low-fat diet		ASCVD risk equivalents • Type 2 diabetes • 10-year risk ≥20% • HeFH[1]
LDL-C ≥100 mg/dL	LDL-C ≥70 mg/dL	LDL-C ≥70 mg/dL / ≥100 mg/dL in risk-equivalent



במסגרת מערכת מחקרי אוריון וכעת מחקרי VictORION נבדקת היעילות

הבטיחות והתוצרים ה-CVO של אינקלסירן

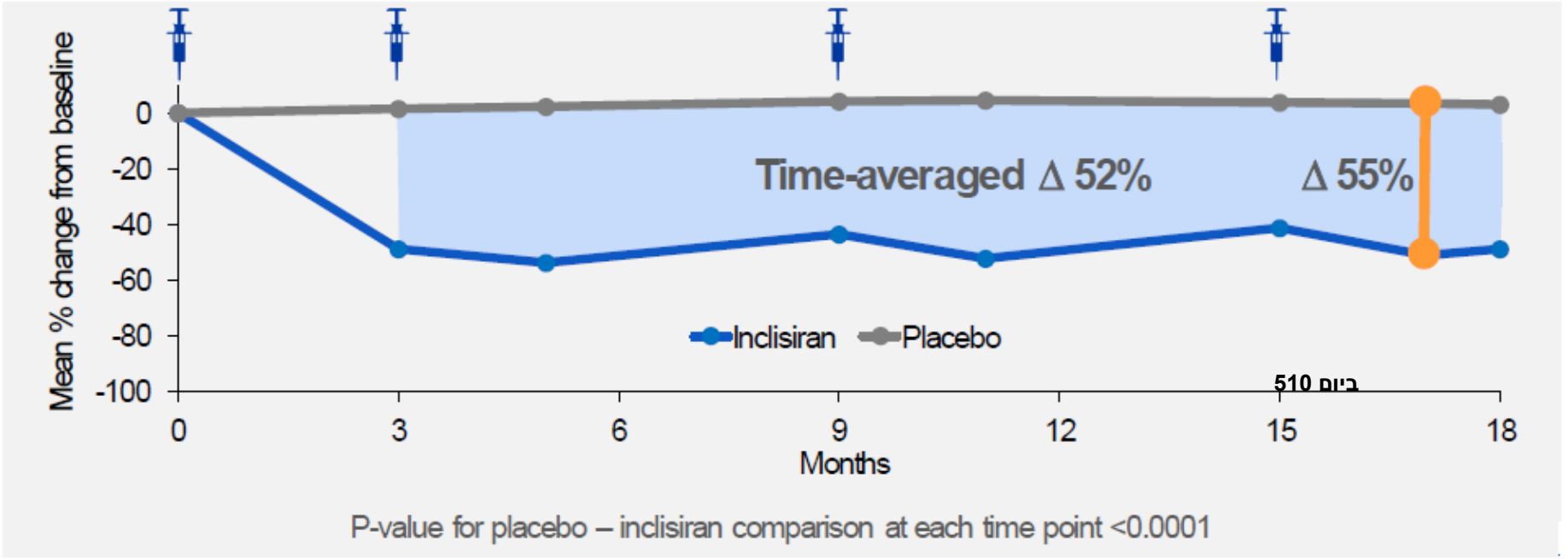
Reference: Wright, R. Scott, and A. ORION. "A pooled analysis of Phase III studies of inclisiran." Data presented at ACC's Scientific Session Together with World Congress of Cardiology, March.Ray, Kausik K., et al. "Two phase 3 trials of Inclisiran in patients with elevated LDL cholesterol." New England Journal of Medicine 382.16 (2020): 1507-1519.Raal, Frederick J., et al. "Inclisiran for the treatment of heterozygous familial hypercholesterolemia." New England Journal of Medicine 382.16 (2020): 1520-1530.

ORION 9, 10, 11 Results

3660 נבדקים

ORION Phase III pooled analysis: Efficacy
Durable and potent with consistent effect over 18 months

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



P-value for placebo – inclisiran comparison at each time point <0.0001

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

תוכנית המחקר זריקה זמן אפס +שלושה חודשים +אחת לחצי שנה מעקב אחרי תגובת LDL 510 ימים

הפחתת רמות LDL בפלסמה בממוצע **בחמישים אחוז**

Wright, R. Scott, and A. ORION. "A pooled analysis of Phase III studies of inclisiran." Data presented at ACC's Scientific Session Together with World Congress of Cardiology, March. Ray, Kausik K., et al. "Two phase 3 trials of Inclisiran in patients with elevated LDL cholesterol." New England Journal of Medicine 382.16 (2020): 1507-1519. Raal, Frederick J., et al. "Inclisiran for the treatment of heterozygous familial hypercholesterolemia." New England Journal of Medicine 382.16 (2020): 1520-1530.

Inclisiran and **cardiovascular events**

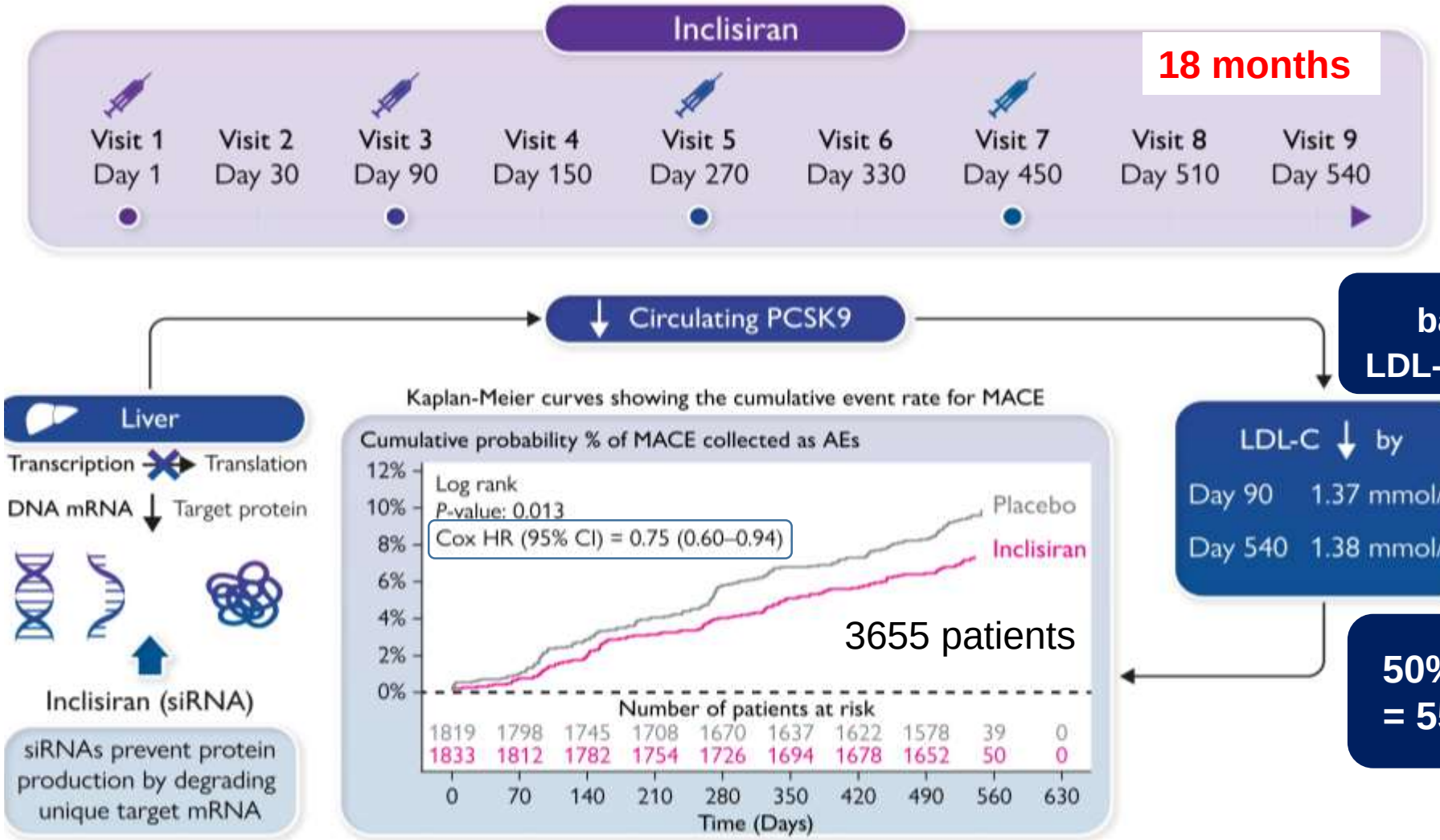
pooled analysis of phase III ORION-9, 10 ,11 trials - ***potential benefits for MACE reduction***

AES

1. Injection site, RR 7.54
2. Bronchitis RR 1.55

3. Liver, renal function, CK

PLTs = similar



Prespecified exploratory endpoint of major cardiovascular events (MACEs)

non-adjudicated CV death, cardiac arrest, non-fatal myocardial infarction (MI), and fatal and non-fatal stroke

Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated low-density lipoprotein cholesterol (ORION-3): Results from the 4-year open-label extension of the ORION-1 trial

American Heart Association.

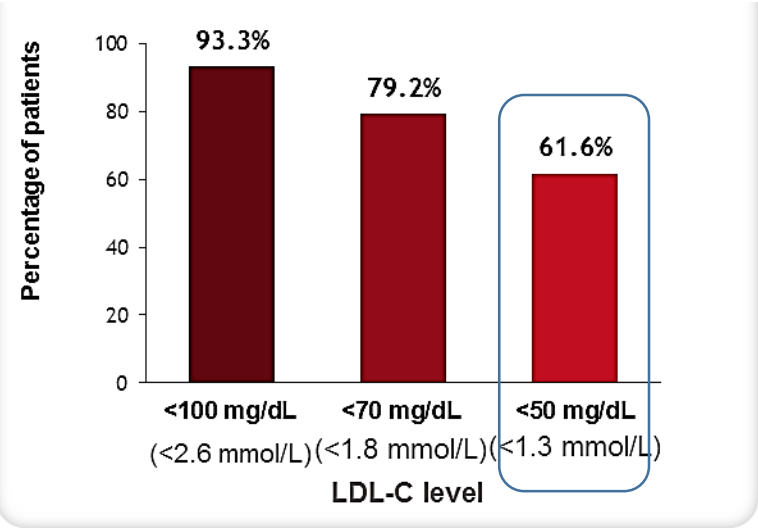
Study population

= **382** patients who completed the **ORION-1 trial + ASCVD or ASCVD risk equivalent** (high-risk primary prevention)

Primary endpoint

= **% change in LDL-c** from baseline of ORION-1 to day 210 of ORION-3 for the inclisiran-only arm

Efficacy outcomes



Mean percentage reduction of **44.2%** with~ 8 injections of inclisiran

Safety outcomes

No safety findings

the most common treatment adverse events observed were **injection site reactions**

Presented at the Nov. 2022 AHA Scientific Sessions Prof. Kausik Ray, MD - London, UK

Very Low plasms cholesterol levels : Worry ? Ignore ? Treat ?

LLT- Statins, ezetimibe, PCSK9 inhibitors ***(MAB, RNA based)***

- **Reduce LDL-C to an unprecedented extent.**

Increasing numbers of patients achieve very low (<30 mg/dl) LDL-C

- **CVD event reduction** increases log linearly in association with **lowering LDL-C**

Without any clear plateau even with very low LDL-C levels

- Potential for cardiovascular **benefit** & **safety profile** of very low LDL-C in **specific high-risk populations**…

Karagiannis AD, Mehta A, Dhindsa DS, Virani SS, Orringer CE, Blumenthal RS, Stone NJ, Sperling LS. Eur Heart J. 2021 Jun 7;42(22):2154-2169.