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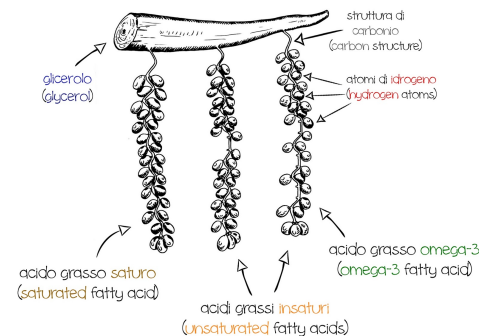
**30 Settembre
1 Ottobre
2022**

Ipertrigliceridemia: quale peso come fattore i rischio e quale terapia?
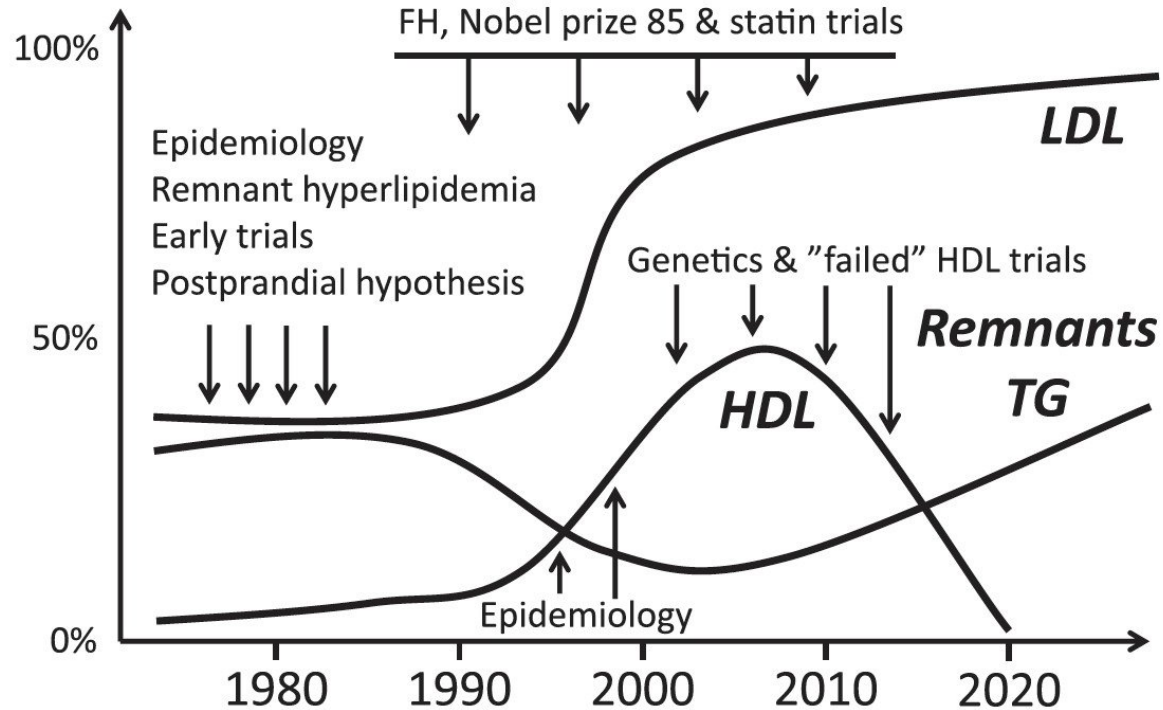
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IL TRIGLICERIDE
(THE TRIGLYCERIDE)

glicerolo
(glycerol)

struttura di
carbonio
(carbon structure)

atomi di idrogeno
(hydrogen atoms)

acido grasso saturo
(saturated fatty acid)

acidi grassi insaturi
(unsaturated fatty acids)

acido grasso omega-3
(omega-3 fatty acid)

Clinical focus on lipoproteins for ASCVD prevention

Nordestgaard BG. Circulation Research. 2016

Available prospective studies of TG and CHD in essentially general populations.

Background—Many epidemiological studies have reported on associations between serum triglyceride concentrations and the risk of coronary heart disease, but this association has not been reliably quantified. In the present study, we report 2 separate nested case-control comparisons in 2 different prospective, population-based cohorts, plus an updated meta-analysis of 27 additional prospective studies in general Western populations.
Methods and Results—Measurements were made in a total of 3582 incident cases of fatal and nonfatal coronary heart disease and 6175 controls selected from among the 44 237 men and women screened in the Reykjavik and the European Prospective Investigation of Cancer (EPIC)-Norfolk studies. Repeat measurements were obtained an average of 4 years apart in 1933 participants in the EPIC-Norfolk Study and an average of 12 years apart in 379 participants in the Reykjavik study. The long-term stability of log-triglyceride values (within-person correlation coefficients of 0.64 [95% CI, 0.60 to 0.68] over 4 years and 0.63 [95% CI, 0.57 to 0.70] over 12 years) was similar to those of blood pressure and total serum cholesterol. After adjustment for baseline values of several established risk factors, the strength of the association was substantially attenuated, and the adjusted odds ratio for coronary heart disease was 1.76 (95% CI, 1.39 to 2.21) in the Reykjavik study and 1.57 (95% CI, 1.10 to 2.24) in the EPIC-Norfolk study in a comparison of individuals in the top third with those in the bottom third of usual log-triglyceride values. Similar overall findings (adjusted odds ratio, 1.72; 95% CI, 1.56 to 1.90) were observed in an updated meta-analysis involving a total of 10 158 incident coronary heart disease cases from 262 525 participants in 29 studies.
Conclusions—Available prospective studies in Western populations consistently indicate moderate and highly significant associations between triglyceride values and coronary heart disease risk. Because these associations depend considerably on levels of established risk factors, however, further studies are needed to help assess the nature of any independent associations. (*Circulation*. 2007;115:450-458.)

Key Words: coronary disease ■ epidemiology ■ lipids ■ meta-analysis ■ triglycerides

Risk ratio (95% CIs) (top third vs. bottom third)

Sarwar N et al. Circulation. 2007;115:450-458

TG-REAL Study: Event Rates and Adjusted Hazard Ratios for All-Cause Mortality and ASCVD Events in the Study Population, According to Triglyceride Levels

Triglyceride Levels (mg/dL)	Events (Number)	Crude Incidence per 1000 person/y	Age and Sex Adjusted HR [CI, *P* Value]	Multivariate Adjusted* HR [CI, *P* Value]
ASCVD events				
Normal TG	2076	6.4	1	1
High TG	459	14.8	2.21 [1.99–2.44, *P*<0.001]	1.61 [1.43–1.82, *P*<0.001]
Very high TG	6	16.2	3.85 [1.72–8.58, *P*=0.001]	2.30 [1.02–5.18, *P*<0.05]
Total	2541	7.2		
Overall mortality				
Normal TG	5346	16.4	1	1
High TG	747	24.2	1.61 [1.49–1.74, *P*<0.001]	1.49 [1.36–1.63, *P*<0.001]
Very high TG	7	18.9	3.15 [1.50–6.61, *P*<0.01]	3.08 [1.46–6.50, *P*<0.01]
Total	6100	17.1		

ASCVD indicates atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; and TG, triglycerides.

Normal Triglyceride Levels and Coronary Artery Disease Events: The Baltimore Coronary Observational Long-Term Study

MICHAEL MILLER, MD, FACC, ALEXANDER SEIDLER, PhD, AZITA MOALEMI, MD,
THOMAS A. PEARSON, MD, PhD, FACC*

Baltimore, Maryland and Rochester, New York
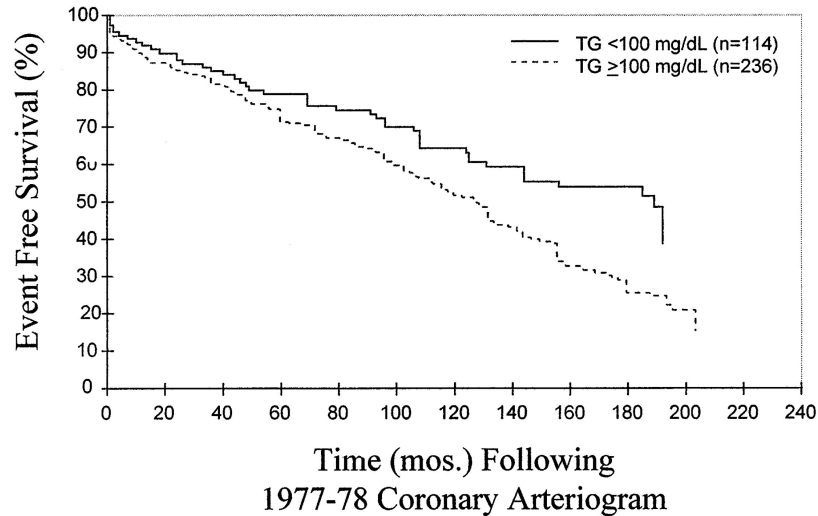
Figure 2. Kaplan-Meier survival analysis comparing patients with CAD stratified by baseline TG level (100 mg/dl) at 1977 to 1978 coronary arteriography. Wilcoxon log-rank test indicates significant differences in event-free survival between the groups (p = 0.008).

URRAH-TG Study-Kaplan-Meier survival curves for CV events
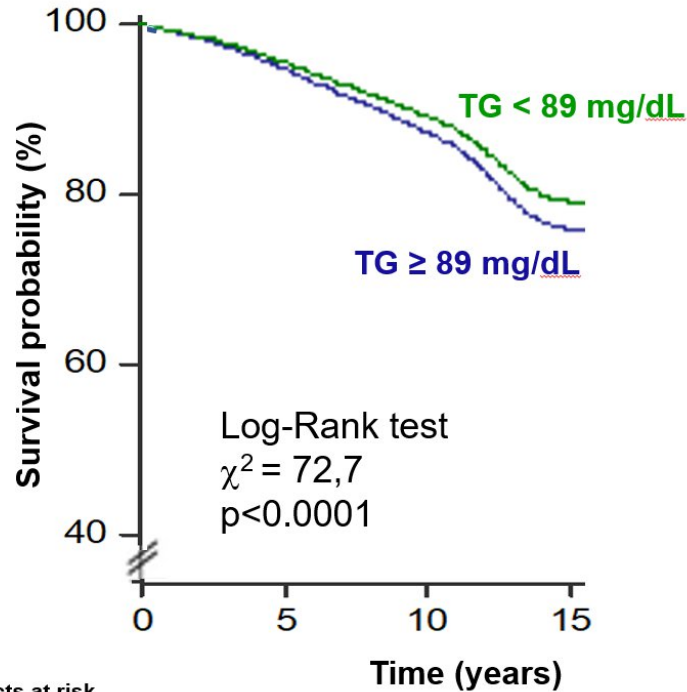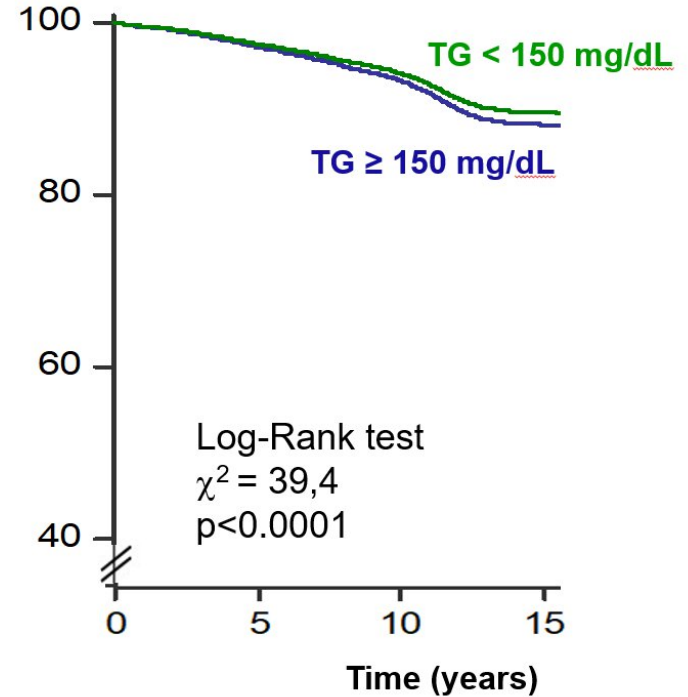
Subclinical Atherosclerosis According to TG Levels

Raposeiras-Roubin S et al. J Am Coll Cardiol 2021;77:3031–41
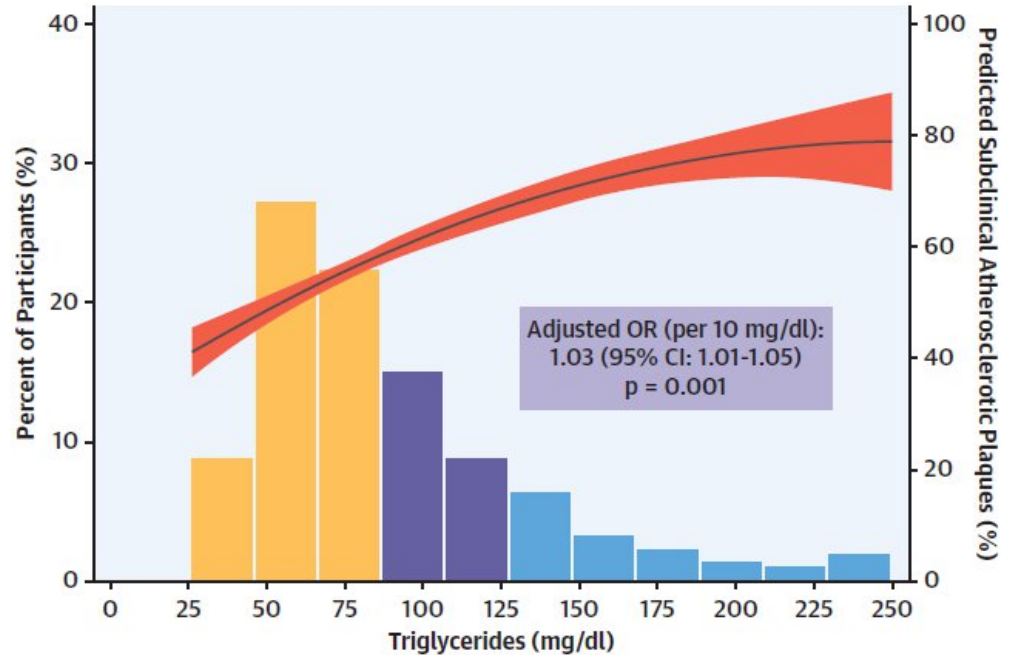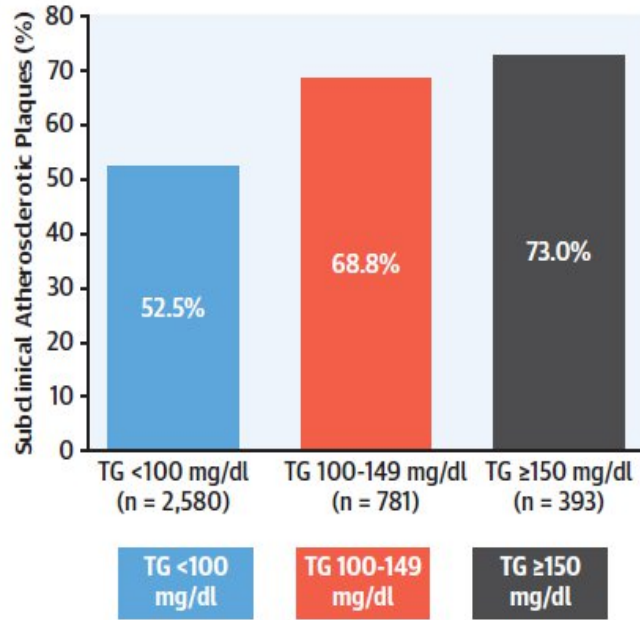
Normal LDL-Cholesterol Levels Are Associated With Subclinical Atherosclerosis in the Absence of Risk Factors

Leticia Fernández-Friera, MD, PhD,[a,b,c] Valentín Fuster, MD, PhD,[a,d] Beatriz López-Melgar, MD, PhD,[a,b]
Belén Oliva, MSc,[a] José M. García-Ruiz, MD,[a,c,e] José Mendiguren, MD,[f] Héctor Bueno, MD, PhD,[a,g]
Stuart Pocock, MSc, PhD,[a,h] Borja Ibáñez, MD, PhD,[a,c,i] Antonio Fernández-Ortiz, MD, PhD,[a,c,j] Javier Sanz, MD[a,d]

CENTRAL ILLUSTRATION Relation Between LDL-Cholesterol Levels and Atherosclerosis
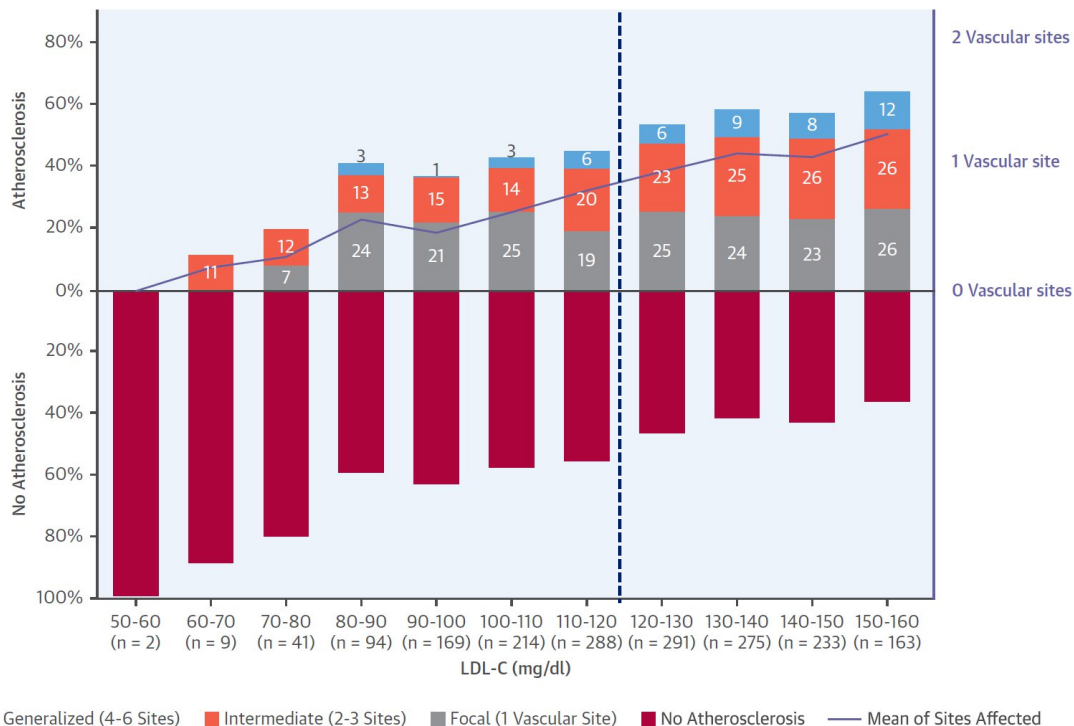
Fernández-Friera, L. et al. J Am Coll Cardiol. 2017;70(24):2979–91.

As LDL-cholesterol levels rise, there is a linear and significant increase in the prevalence of atherosclerosis, ranging from 11% in the 60 to 70 mg/dl category to 64% in the 150 to 160 mg/dl subgroup (p < 0.001). A similar pattern is observed for the multiterritorial extent of atherosclerosis (focal, intermediate or generalized disease) as well as for the mean number of vascular sites affected (blue line). LDL-C = low-density lipoprotein cholesterol.

Explained risk of causal association of CHD by different lipoproteins

EDITORIAL COMMENT

Low-Density Lipoprotein Triglycerides
Widening the Atherogenic Landscape in CVD Risk Assessment*

Michael Miller, MD

	Age and Sex Adjusted	Explained Risk (95% CI)	Multivariable Adjusted	Explained Risk (95% CI)
VLDL Cholesterol		46% (21%-72%)		50% (22%-78%)
VLDL Triglycerides		8% (0%-23%)		8% (0%-24%)
IDL + LDL Cholesterol		25% (10%-39%)		29% (13%-45%)

Explained Risk in the Association of apoB-Containing Lipoproteins with Myocardial Infarction, %

Multivariable adjusted for age, sex, smoking, and systolic blood pressure. The logarithm of apoB, VLDL cholesterol, and VLDL triglycerides, and the square root of IDL + LDL cholesterol were taken to obtain normally distributed variables. The analyses comprised 25,474 individuals from the Copenhagen General Population Study including 1,816 cases of myocardial infarction. Abbreviations as in **Figures 1 and 2**.

Balling M et al, JACC Volume: 76, Issue: 23, Pages: 2725-2735, 2020

Genetic Variants Affecting the Lipoprotein Lipase Pathway and the Risk of Coronary Artery Disease.
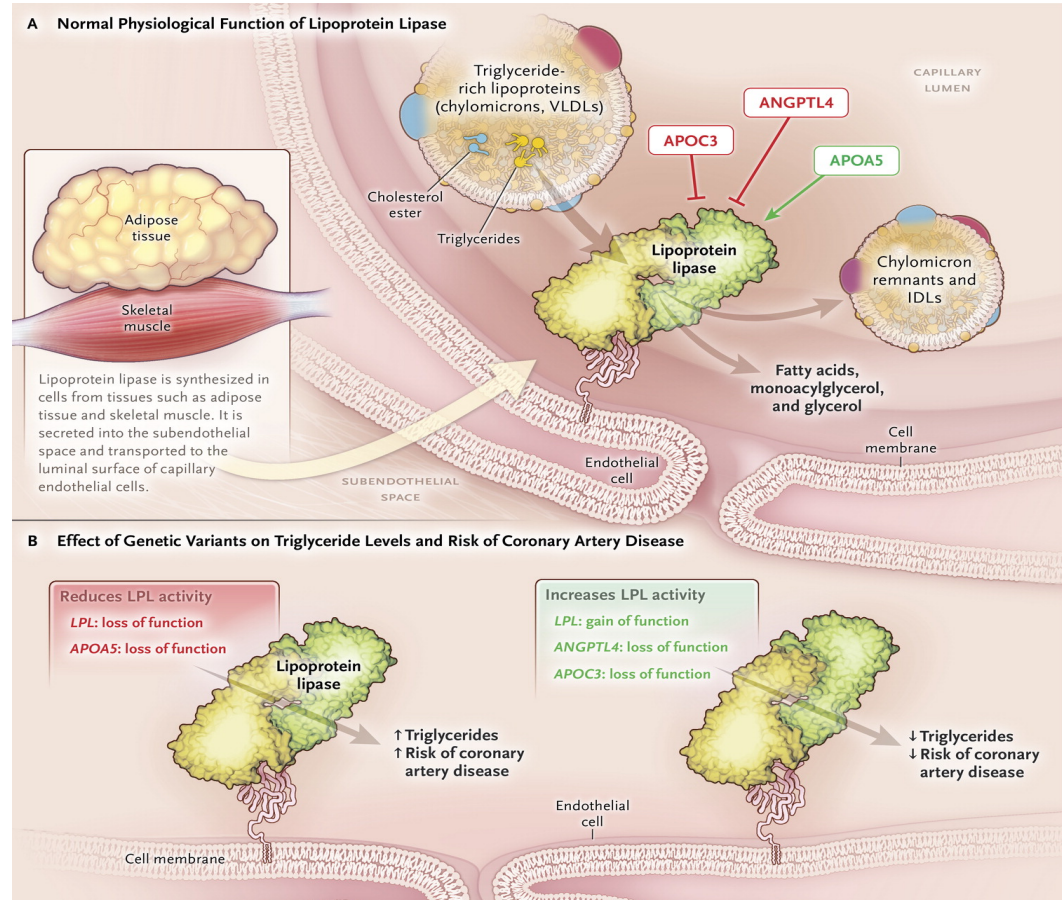
Observational and causal genetic association of high and low concentration of LDL-C, HDL-C and TG with the risk of ischemic heart Disease (IHD)
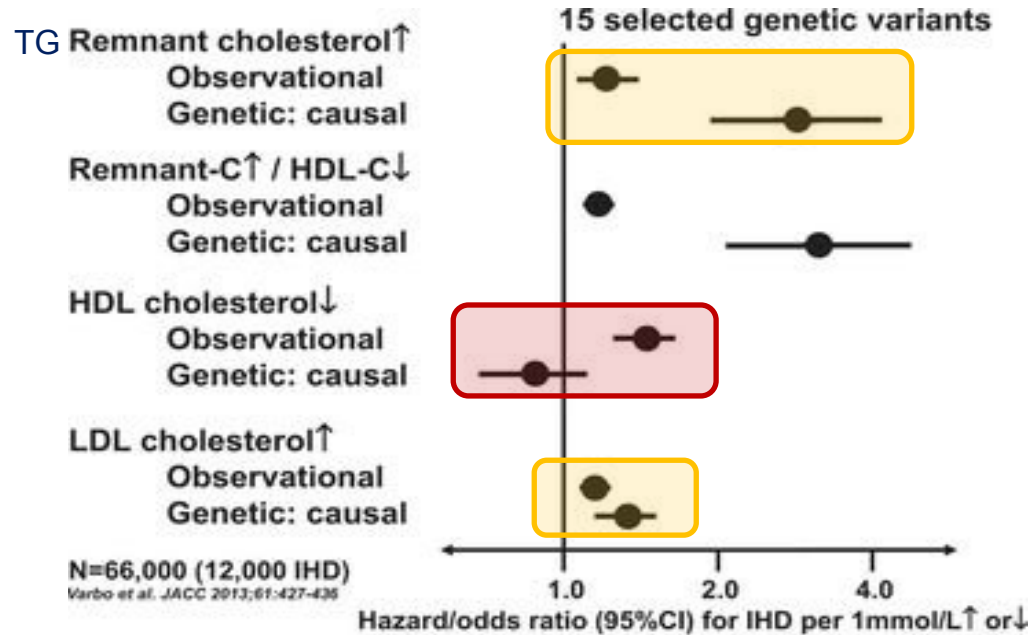
Nordestgaard BG. Circulation Research. 2016

ESC
European Society
of Cardiology

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Recommendations for lipid analyses for cardiovascular disease risk estimation

Recommendations	Class[a]	Level[b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); SCORE = Systematic Coronary Risk Estimation; TC = total cholesterol; TG = triglyceride.

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For most people the horizon is as far as they can see. But for us it represents the threshold to an unseen world of new opportunities. As one of the world's foremost managers of capital and risk, we are constantly searching for solutions that lie beyond the obvious. With financial and intellectual reservoirs of great depth and breadth to draw from, we combine insight, knowledge and original thinking to create new opportunities. We do it for ourselves. We can do it for you.

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So how to manage this problem?

Recommendations for Lifestyle Interventions in Patients With Increasing Levels of Weight Loss and Effects on Triglycerides

Adults with fasting TG ≥150 mg/dL or nonfasting TG ≥175 mg/dL

- Assess nonlifestyle secondary causes
- Assess lifestyle practices (body weight; diet, including amount and type of carbohydrates, alcohol, and long-chain omega-3 fatty acids; and physical activity)

Emphasize healthy dietary pattern* and increased physical activity

Implement shared decision-making intervention	TG <500 mg/dL[†]	TG 500-999 mg/dL[†]	TG ≥1000 mg/dL[‡]
Added sugars (percent calories)	<6%	<5%	Eliminate
Total fat (percent calories)	30%-35%	20%-25%[§]	10%-15%
Alcohol	Restrict	Abstain completely	Abstain completely
Aerobic activity	At least 150 min/wk of accumulated moderate-intensity or 75 min/wk of vigorous-intensity aerobic physical activity (or equivalent combination of both)[∥]		
Weight loss (percent body weight)	Recommended weight loss goal is 5%-10% for all patients with elevated TG		

- Monitor response to intervention
- Consider referral to RDN, exercise trainer, or other supportive services
- Continue intervention or adjust as indicated

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Mach F et al, Eur Heart J 2019

Recommendations for drug treatment of patients with hypertriglyceridaemia

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5—5.6 mmol/L (135—499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305—307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305—307,356]	IIb	C

Fibrates, n-3 PUFA-EPA, Niacin – CV Outcome Trials

Larger Risk Reductions in Hypertriglyceridemia

Trial (drug)	Entire cohort HR (95% CI)	Subgroup	Subgroup HR (95% CI)
HHS (gemfibrozil)	**0.66 (0.47, 0.92)**	TG ≥184 mg/dL BMI >27.5 kg/m^2	**0.30 (0.15, 0.58)**
BIP (bezafibrate)	0.91 (NR)	TG ≥200 mg/dL	0.60 (NR)
VA-HIT (gemfibrozil)	0.78 (0.65, 0.93)	TG ≥151 mg/dL	0.73 (0.58, 0.93)
FIELD (fenofibrate)	**0.89 (0.75, 1.05)**	TG ≥204 mg/dL HDL-C <42 mg/dL	**0.73 (0.58, 0.91)**
ACCORD (fenofibrate)	**0.92 (0.79, 1.08)**	TG ≥204 mg/dL HDL-C ≤34 mg/dL	**0.69 (NR)**
JELIS (ethyl-EPA)	0.81 (0.69, 0.95)	TG >150 mg/dL HDL-C <40 mg/dL	0.47 (0.23, 0.98)
AIM-HIGH (niacin)	1.02 (0.87, 1.21)	TG >198 mg/dL HDL-C <33 mg/dL	0.74 (0.50, 1.09)
PERMANENT (pemafibrate)	**Interrupted**	-	-

Maki et al. J Clin Lipidol. 2012;6:413. Guyton et al. JACC 2013;62:1580.(mod)
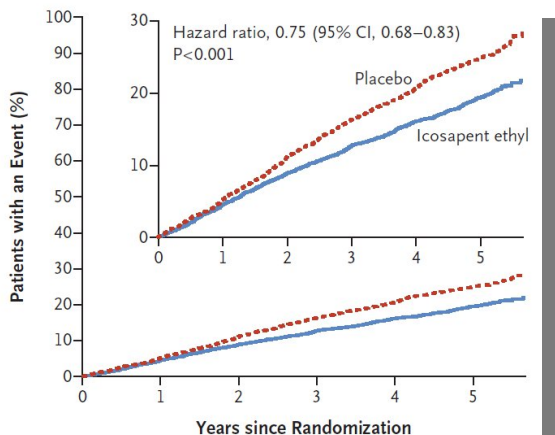
Cumulative Incidence of primary and secondary efficacy composite end-points in the REDUCE-IT trial

CV death, non-fatal MI, non-fatal stroke, PCI/CABG, or unstable angina

CV death, nonfatal MI, or nonfatal Stroke

The NEW ENGLAND JOURNAL of MEDICINE

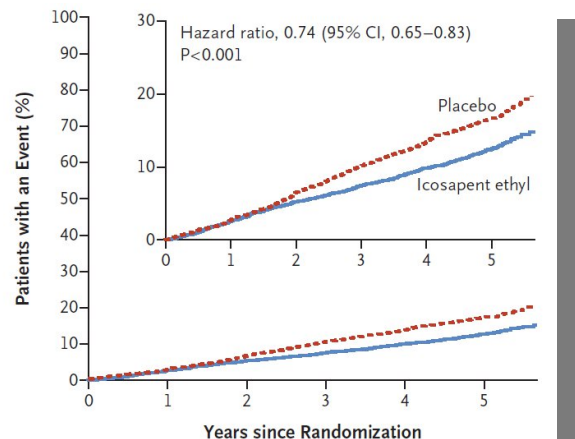ESTABLISHED IN 1812   JANUARY 3, 2019   VOL. 380   NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D.,
Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D.,
Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D.,
for the REDUCE-IT Investigators*

Primary and secondary key end-points by achieved TG levels at 1 year
The REDUCE-IT study

A Primary End Point by Achieved Triglyceride Level at 1 Year

Hazard Ratio (95% CI):

Icosapent Ethyl Triglyceride <150 vs ≥150 mg/dL	0.99 (0.84–1.16)
Icosapent Ethyl Triglyceride ≥150 mg/dL vs Placebo	0.71 (0.63–0.79)
Icosapent Ethyl Triglyceride <150 mg/dL vs Placebo	0.70 (0.60–0.81)

B Key Secondary End Point by Achieved Triglyceride Level at 1 Year

Hazard Ratio (95% CI):

Icosapent Ethyl Triglyceride <150 vs ≥150 mg/dL	1.00 (0.82–1.23)
Icosapent Ethyl Triglyceride ≥150 mg/dL vs Placebo	0.67 (0.56–0.80)
Icosapent Ethyl Triglyceride <150 mg/dL vs Placebo	0.66 (0.57–0.77)

No. at Risk (Panel A)

Placebo	4090	3743	3327	2807	2347	1358
Icosapent Ethyl TG ≥150 mg/dL	2364	2276	2085	1775	1473	803
Icosapent Ethyl TG <150 mg/dL	1325	1277	1179	1040	922	571

No. at Risk (Panel B)
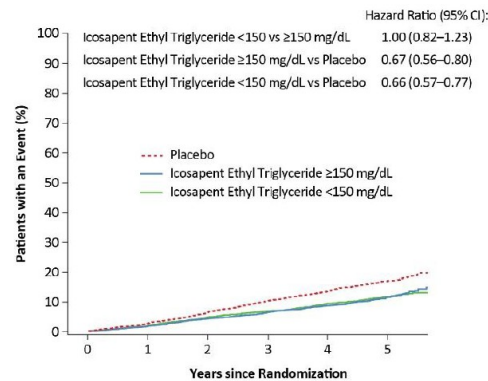
Placebo	4090	3837	3500	3002	2542	1487
Icosapent Ethyl TG ≥150 mg/dL	2364	2319	2171	1875	1579	879
Icosapent Ethyl TG <150 mg/dL	1325	1300	1218	1096	986	620

Bhatt DL et al, New Engl J Med 2019

Mean plaque progression for the different components in patients treated with Icosapent Ethyl or Placebo

Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial

Matthew J. Budoff [1]*, Deepak L. Bhatt [2], April Kinninger [1], Suvasini Lakshmanan[1], Joseph B. Muhlestein[3], Viet T. Le [3,4], Heidi T. May [3], Kashif Shaikh[1], Chandana Shekar[1], Sion K. Roy[1], John Tayek[1], and John R. Nelson[5]

[1]Department of Medicine, Lundquist Institute at Harbor-UCLA Medical Center, 1124 W Carson Street, Torrance, CA 90502, USA; [2]Department of Medicine, Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA; [3]Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, UT, USA; [4]Department of Medicine, Rocky Mountain University of Health Profession, Provo, UT, USA; and [5]California Cardiovascular Institute, Fresno, CA, USA
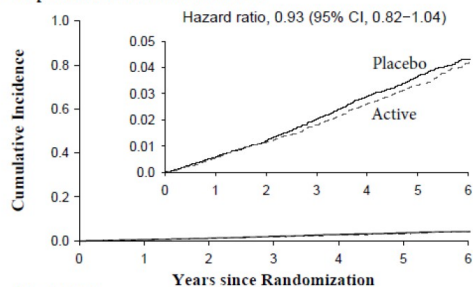
Received 1 July 2020; revised 10 July 2020; editorial decision 26 July 2020; accepted 29 July 2020
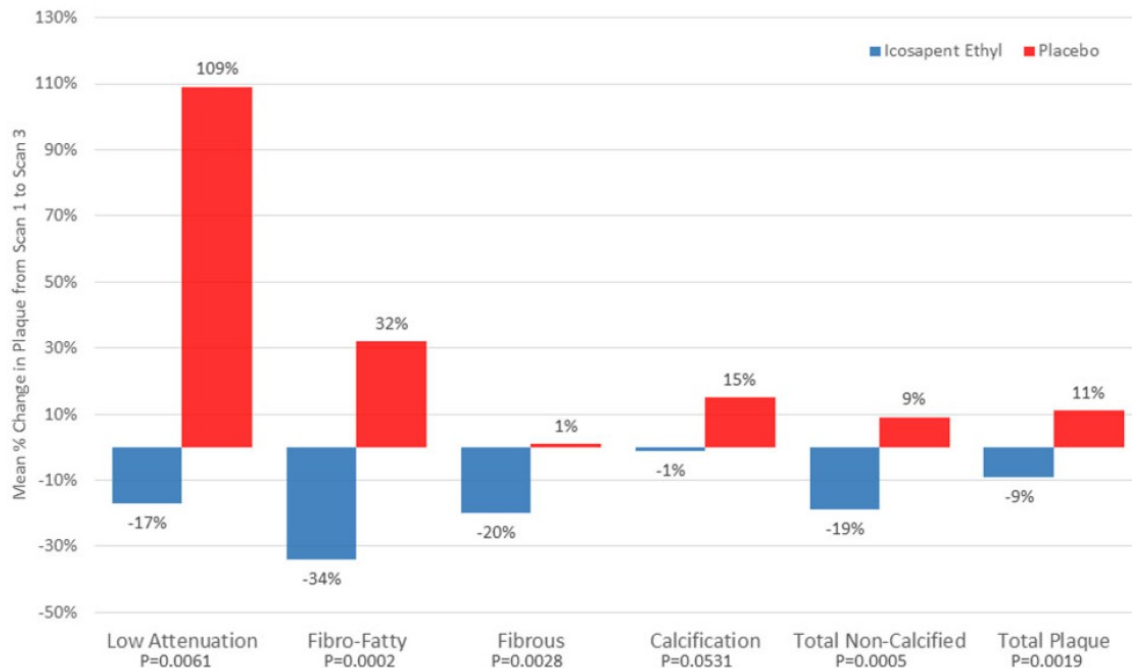
Cumulative Incidence Rates of A) Expanded Cardiovascular Events, B) Total Myocardial Infarction, C) Total Stroke, and D) Cardiovascular Mortality, By Year of Follow-up.
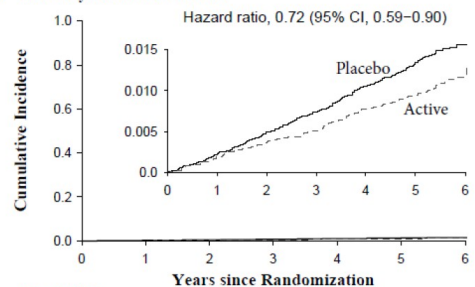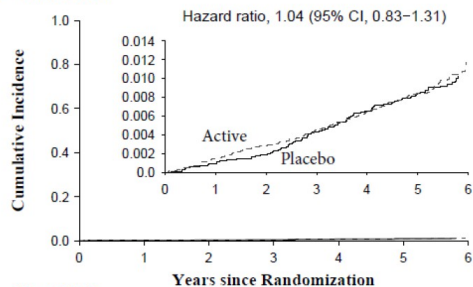## The VITAL study
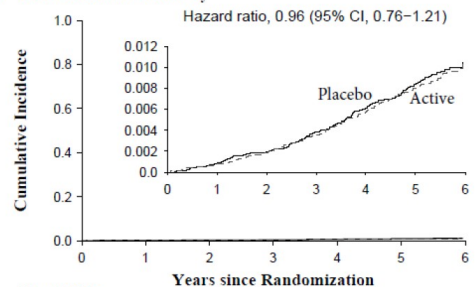
1 gr/day!

Manson JE, et al, N Engl J Med 2019;380

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at **High Cardiovascular Risk**: The **STRENGTH Randomized Clinical Trial**

Time to First Incidence of Any Component of the Primary Composite End Point and Time to Core MACEA, The primary composite end point consisted of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina.

A | Primary MACE, total population

HR, 0.99 (95% CI, 0.90-1.09); *P* = .84

No. at risk
Omega-3 CA	6539	6372	6200	6060	5917	5751	4900	2965	1535	567
Corn oil	6539	6373	6207	6083	5906	5754	4899	2995	1508	562

B | Core MACE

HR, 1.05 (95% CI, 0.93-1.19)

No. at risk
Omega-3 CA	6539	6426	6302	6190	6070	5933	5069	3091	1604	596
Corn oil	6539	6420	6312	6212	6091	5966	5093	3132	1588	595

Nicholls SJ et al, JAMA.2020
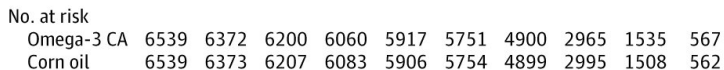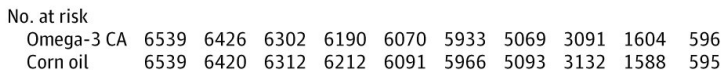
ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D.,
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Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D.,
Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and
Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

ELIGIBILITY

Patients could be enrolled if they were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional risk factor.

Events in Placebo populations
REDUCE-IT: 22% (70.7% pts with ASCVD)
STRENGTH: 12% (56.0 pts with ASCVD)

Research

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk
The STRENGTH Randomized Clinical Trial

Study Population

Details of the study design have been published previously.[16] Adult patients (≥18 years) considered at high risk for a future cardiovascular event were eligible to participate. High cardiovascular risk was defined as (1) the presence of established atherosclerotic cardiovascular disease involving the coronary, peripheral, carotid, or aortic territories (secondary prevention); (2) type 1 or 2 diabetes with age 40 years or older for men and 50 years or older for women with at least 1 additional risk factor including chronic smoking, hypertension, high-sensitivity C-reactive protein (hs-CRP) level of 2 mg/L or higher, or moderately increased albuminuria; or (3) high-risk primary prevention patients aged at least 50 years for men or at least 60 years for women with at least 1 additional risk factor, including a family history of premature coronary artery disease, chronic smoking, hs-CRP level of 2 mg/L or higher, impaired kidney function, or coronary calcium score greater than 300 Agatston units.

Serum TG in RCT of PUFA-3 and CV prevention

Study	TG at baseline	TG changes
Primary prevention		
ASCEND, N Engl J Med 2018	None	None
VITAL, N Engl J Med 2019	None	None
ORIGIN, N Engl J Med 2012	142 mg/dL (99-196 mg/dL)	None
Risk and Prevention Collaborative Group, N Engl J Med 2013	None	None
Secondary prevention		
REDUCE-IT	150-499 mg/dL	-18.3% vs +2.2%
STRENGTH, JAMA 2020	>180/<500 mg/dL	-19% vs.-0.9%

Evinacumab in Patients with Refractory Hypercholesterolemia

Robert S. Rosenson, M.D., Lesley J. Burgess, M.D., Ph.D.,
Christoph F. Ebenbichler, M.D., Seth J. Baum, M.D., Ph.D., Erik S.G. Stroes, M.D., Ph.D.,
Shazia Ali, Pharm.D., Nagwa Khilla, M.S., Robert Hamlin, B.S., Robert Pordy, M.D.,
Yuping Dong, Ph.D., Vladimir Son, Ph.D., and Daniel Gaudet, M.D., Ph.D.

Table 2. Demographics and Clinical Characteristics of the Patients in the Intravenous-Treatment Groups.*

Characteristic	Intravenous Evinacumab		Intravenous Placebo, Every 4 Wk (N=33)	Total (N=106)
	15 mg/kg Every 4 Wk (N=38)	5 mg/kg Every 4 Wk (N=35)		
Total cholesterol — mg/dl	220.9±56.8	228.8±60.2	231.6±50.4	226.8±55.7
Median fasting triglycerides (IQR) — mg/dl	126.5 (89.0–166.0)	102.0 (86.0–156.0)	147.0 (104.0–200.0)	122.0 (92.0–171.0)
Median lipoprotein(a) (IQR) — nmol/liter	34.0 (15.0–157.0)	27.0 (18.0–80.0)	33.0 (16.0–154.0)	31.0 (17.0–127.0)
Lipid-lowering therapy — no. (%)				
Any statin	33 (87)	27 (77)	28 (85)	88 (83)
High-intensity statin¶	23 (61)	17 (49)	15 (45)	55 (52)
Ezetimibe	13 (34)	15 (43)	12 (36)	40 (38)
PCSK9 inhibitor	37 (97)	33 (94)	32 (97)	102 (96)

ORIGINAL RESEARCH ARTICLE

Effect of Vupanorsen on Non–High-Density Lipoprotein Cholesterol Levels in Statin-Treated Patients With Elevated Cholesterol: TRANSLATE-TIMI 70
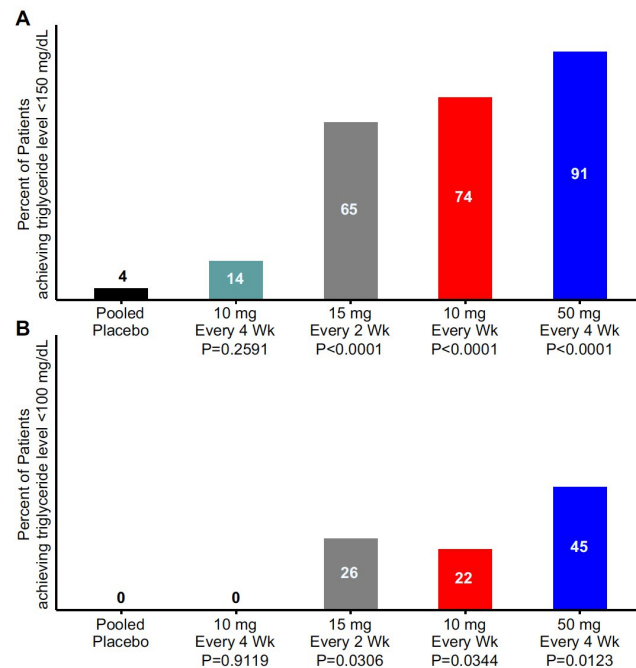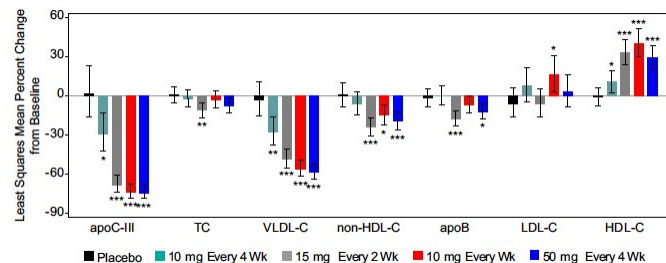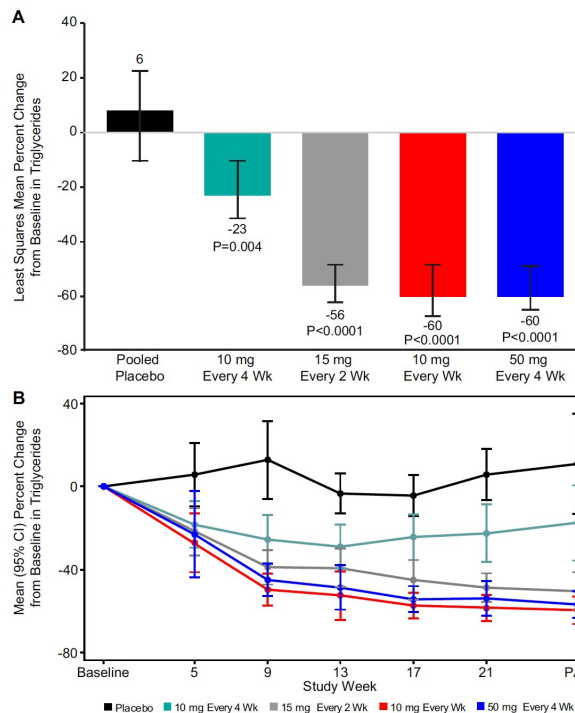
Effect of vupanorsen on lipid parameters at 24 weeks.

Oligonucletide antisense mRNA ANGPLT3

Bergmark PA et al, Circulation 2022
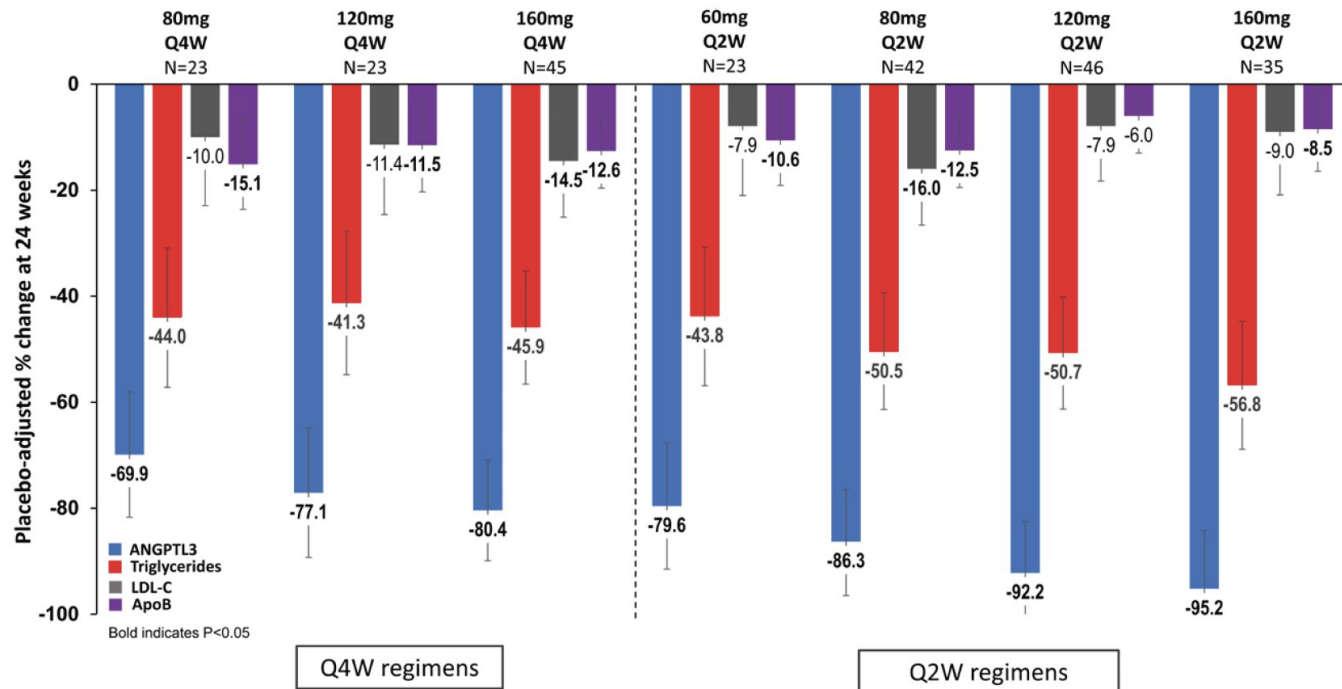
Apolipoprotein C-III reduction in subjects with moderate hypertriglyceridaemia and at high cardiovascular risk

Jean-Claude Tardif[1]*, Ewa Karwatowska-Prokopczuk [2], Eric St. Amour[3],
Christie M. Ballantyne[4], Michael D. Shapiro [5], Patrick M. Moriarty[6],
Seth J. Baum [7], Eunju Hurh [2], Victoria J. Bartlett [2], Joyce Kingsbury[2],
Amparo L. Figueroa[2], Veronica J. Alexander [8], Joseph Tami[8],
Joseph L. Witztum[9], Richard S. Geary[8], Louis St. L. O'Dea[2],
Sotirios Tsimikas [8,10]*, and Daniel Gaudet [11]; for the Olezarsen Study Investigators

Oligonucletide antisense mRNA APO-C3

Clinical focus on lipoproteins for ASCVD prevention

Nordestgaard BG. Circulation Research. 2016