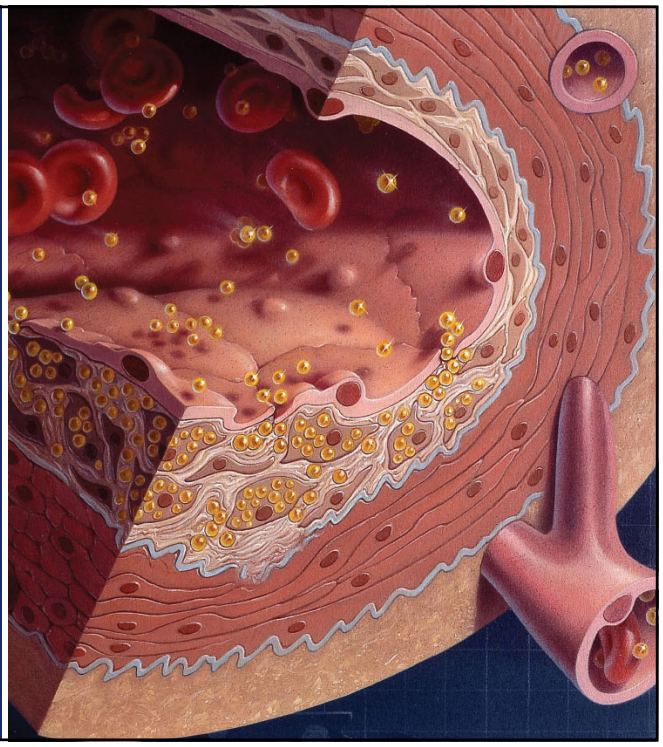
Omega-3 Fatty Acids in Patients with ASCVD Risk- The Role of Icosapent Ethyl (IPE)



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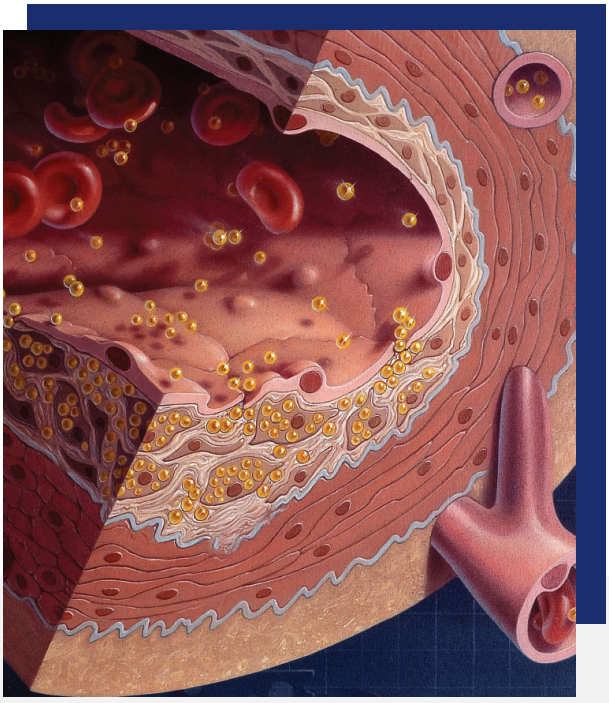
medtelligence℠



2

Clinical Trial Evidence of Omega-3 Fatty Acids in ASCVD

Michel Farnier, MD, PhD

PEC2, EA 7460, University of Bourgogne Franche-Comté, and Cardiology Department, CHU Dijon Bourgogne, Dijon, France

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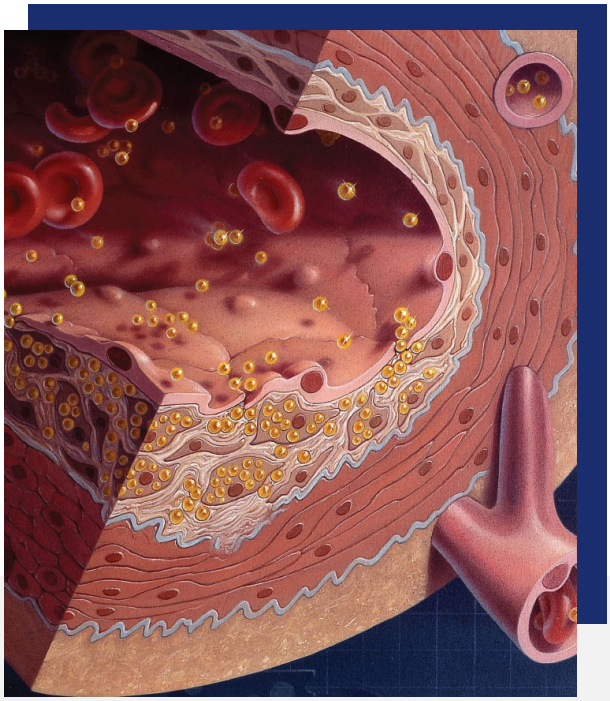

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Disclosure of potential conflicts of interest

Research contracts:	None
Consulting:	Abbott, Akcea/Ionis, Amarin, Amgen, Daïchi-Sankyo, Kowa, Merck and Co, Mylan, Pfizer, Sanofi/Regeneron, and Servier
Participation in Clinical Trials:	ODYSSEY Programme (Sanofi/Regeneron) TESLA/TAUSSIG (Amgen) Evinacumab (Regeneron)

4

ESC European Society of Cardiology

European Heart Journal (2020) **0**, 1–28
doi:10.1093/eurheartj/ehz962

CURRENT OPINION
Translational medicine

Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel

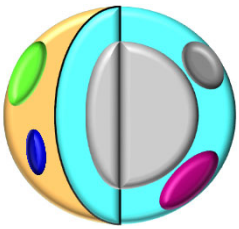
LDL-cholesterol (LDL-C) is the primary target in the management of dyslipidemia

Borén, et al. *Eur Heart J.* 2020:online.
Mach, et al. *Eur Heart J.* 2020;41:111-188.

5

Cardiovascular Risk Reduction: Beyond LDL-C

- Substantial residual risk persists despite significant reductions in LDL-C with high-intensity statins, with or w/o ezetimibe, and PCSK9 inhibitors.
- Particularly among high-risk subjects with elevated levels of serum triglycerides (TG) and increased TG-rich lipoproteins.



TG-rich Lp (TRLs)

Ganda, et al. *J Am Coll Cardiol.* 2018;72:330-43.

6

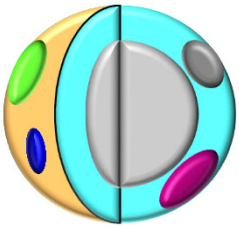
Clinical Trial Evidence of Omega-3 Fatty Acids in ASCVD

- What is the evidence that TRLs contribute to the risk of ASCVD?
- What is the evidence of the role of ω3-FA in ASCVD prevention?
- What is recommended in current guidelines?

ASCVD: atherosclerotic cardiovascular disease
TRLs: TG-rich lipoproteins

Clinical Trial Evidence of Omega-3 Fatty Acids in ASCVD

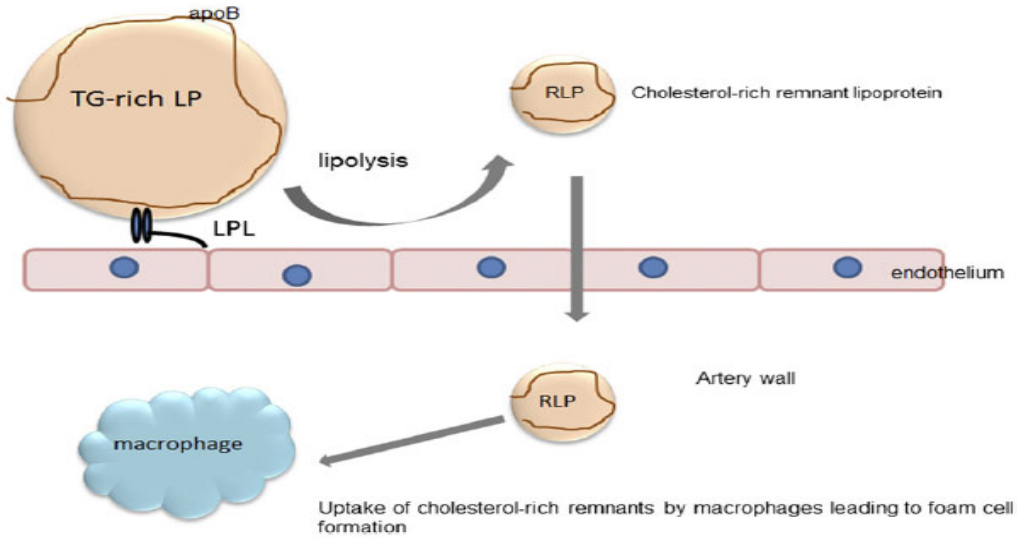
- What is the evidence that TRLs contribute to the risk of ASCVD?
  - Epidemiological data
  - Genetic data
  - Residual risk on statin



TG-rich Lp (TRLs)

Nordestgaard BG, et al. *Circ Res.* 2016;118:547-63.

TG-rich Lipoproteins and Atherosclerosis



McPherson. *J Am Coll Cardiol.* 2013;61:437-39.

9

Cardiometabolic Risk

Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease

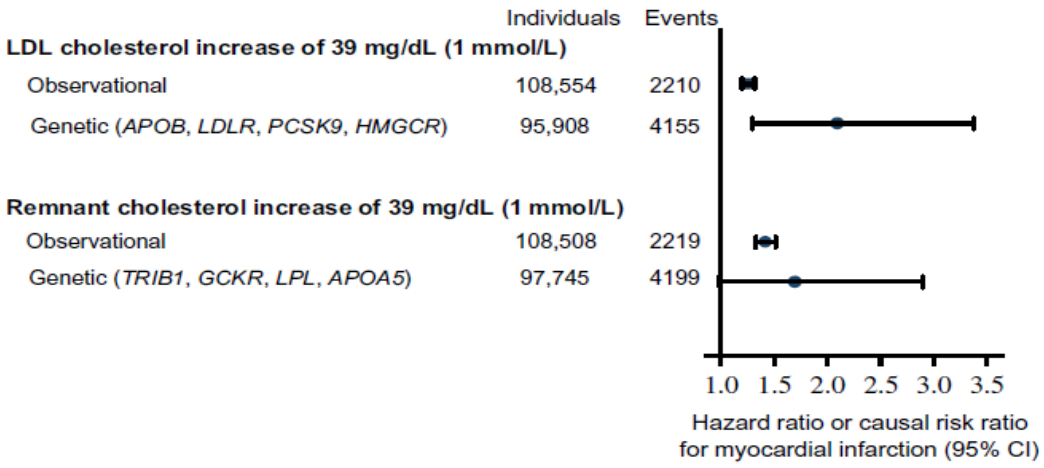
Anette Varbo, MD,*†‡ Marianne Benn, MD, PHD, DMSC,*†‡
Anne Tybjærg-Hansen, MD, DMSC,†‡§‖ Anders B. Jørgensen, MD,†‡§
Ruth Frikke-Schmidt, MD, PHD, DMSC,†‡§ Børge G. Nordestgaard, MD, DMSC*†‡§
Herlev and Copenhagen, Denmark

A nonfasting remnant cholesterol increase of 1 mmol/L (39 mg/dL) is associated with a 2.8-fold causal risk for ischemic heart disease, independent of reduced HDL-C

Varbo, et al. *J Am Coll Cardiol.* 2013;61:427-36.

10

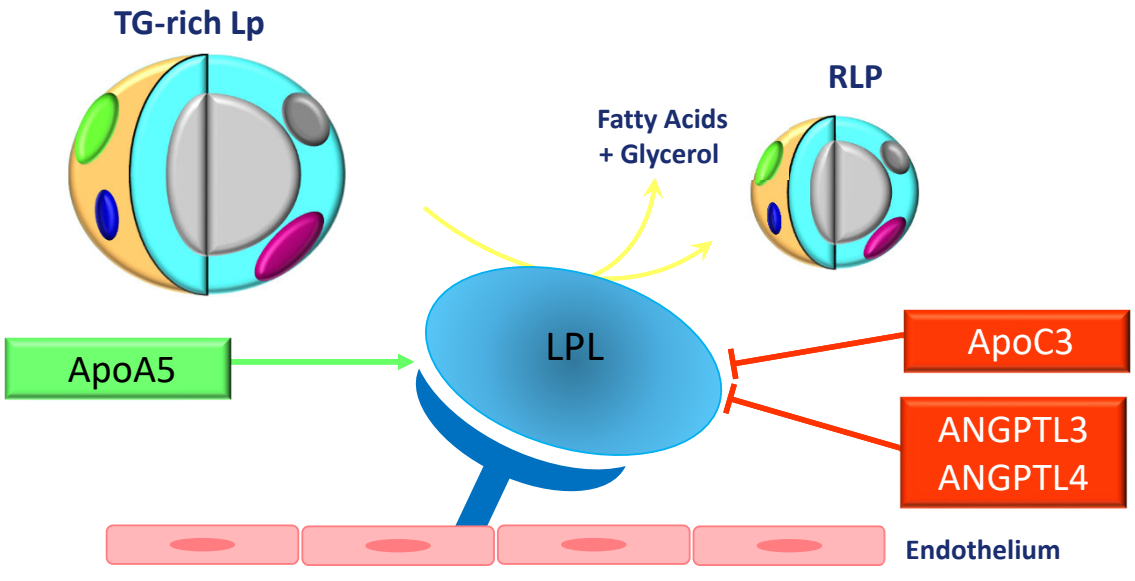
Risk of MI by 1 mmol/L (39 mg/dL) Higher Levels of LDL-C and RLP-C from Observational and Genetic Studies



(data from individuals in the Copenhagen General Population Study)

Borén, et al. *J Am Coll Cardiol.* 2020:online.

11



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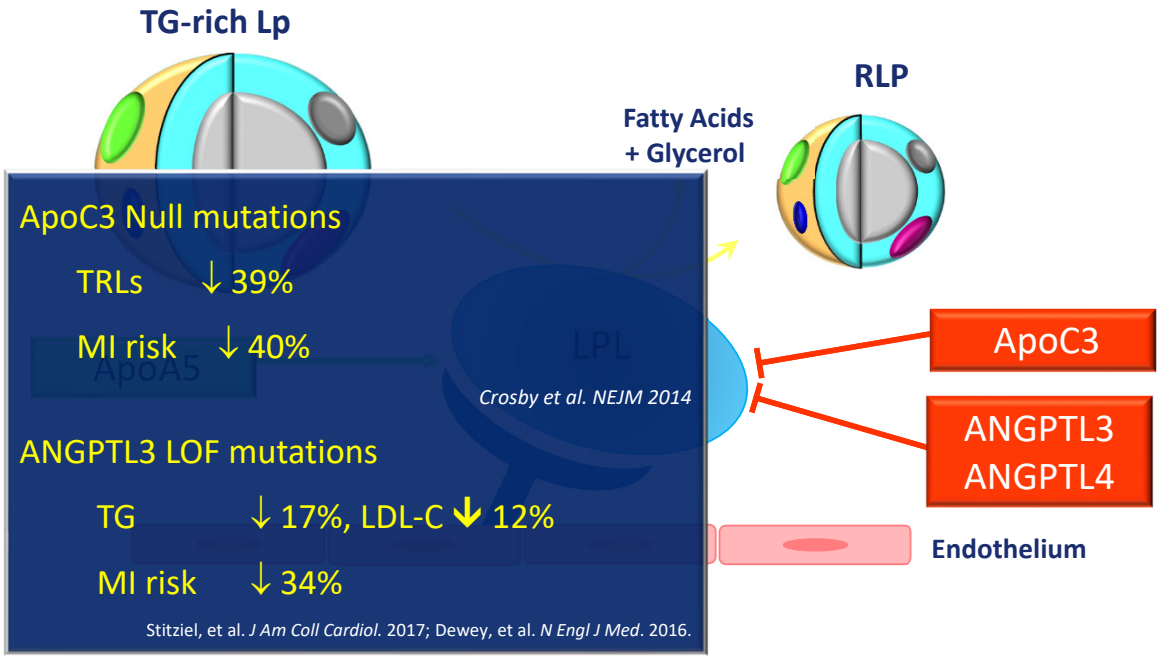


13

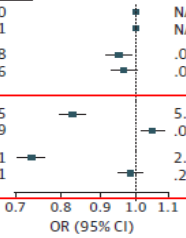
Research

JAMA Cardiology | Original Investigation

Association of Genetically Enhanced Lipoprotein Lipase–Mediated Lipolysis and Low-Density Lipoprotein Cholesterol–Lowering Alleles With Risk of Coronary Disease and Type 2 Diabetes

Figure 1. Associations of Genotype Category With Cardiometabolic Disease Outcomes in 2 × 2 Factorial Genetic Analyses

Genotype Category	Proxy for	Outcome	LDL-C Level, Median (IQR), mg/dL	Triglyceride Level, Median (IQR), mg/dL	OR (95% CI)	Individuals With Outcome	Individuals Without Outcome	*P* Value
Reference	Placebo	Coronary disease Type 2 diabetes	158.3 (135.1-185.3)	150.4 (106.2-212.4)	1 [Reference] 1 [Reference]	6439 7956	87 650 91 321	NA NA
Genetically lower triglyceride levels via *LPL* only	LPL-enhancing therapy only	Coronary disease Type 2 diabetes	158.3 (135.1-185.3)	132.7 (47.4-194.7)	0.95 (0.91-0.99) 0.96 (0.93-1.00)	5990 7270	85 528 88 686	.007 .045
Genetically lower LDL-C levels only	LDL-C–lowering therapy only	Coronary disease Type 2 diabetes	142.4 (114.7-166.0)	141.6 (97.4-144.7)	0.83 (0.79-0.86) 1.05 (1.01-1.08)	5470 8265	88 515 90 939	5.5×10^{-22} .009
Both genetically lower triglyceride and LDL-C levels	LPL-enhancing and LDL-C–lowering therapy	Coronary disease Type 2 diabetes	142.4 (114.7-166.0)	132.7 (88.5-185.8)	0.73 (0.70-0.76) 0.98 (0.95-1.02)	4832 7382	86 791 88 651	2.8×10^{-52} .28



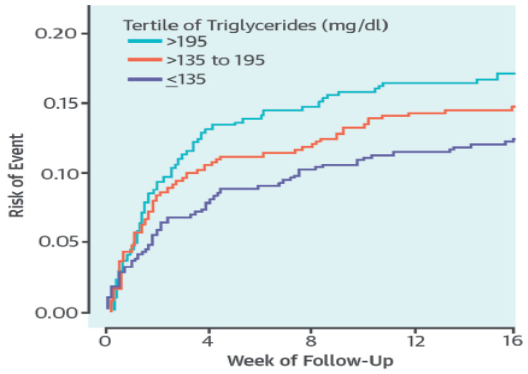
Lotta, et al. *JAMA Cardiol.* 2018;3:957-66.

14

Triglycerides and Risk After ACS

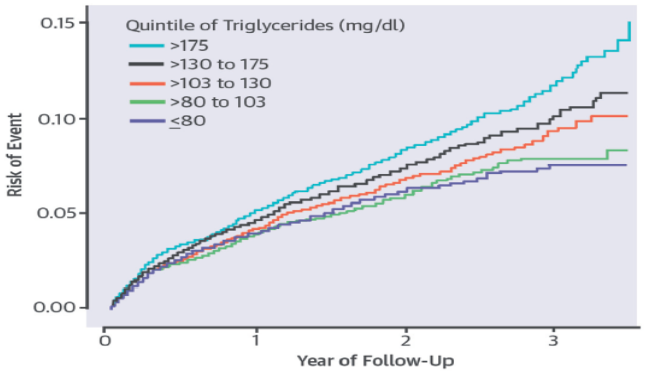
MIRACL

Short-Term Risk After ACS



dal-OUTCOMES

Long-Term Risk After ACS



Kaplan-Meier analysis of CHD death, nonfatal MI, ischemic stroke, cardiac arrest with resuscitation, or hospitalization for UA after ACS.

Schwartz, et al. *J Am Coll Cardiol.* 2015;65:2267-75.

15

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 86–94
doi:10.1093/eurheartj/ehz767

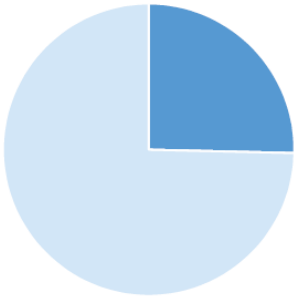
FASTTRACK CLINICAL RESEARCH
Lipids

Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies

Patrick R. Lawler [1,2,3]*, Gynter Kotrri[2], Maria Koh[4], Shaun G. Goodman [2,5], Michael E. Farkouh[1,2], Douglas S. Lee[1,2,3,4], Peter C. Austin[4], Jacob A. Udell [1,2,4,6], and Dennis T. Ko[1,2,4]

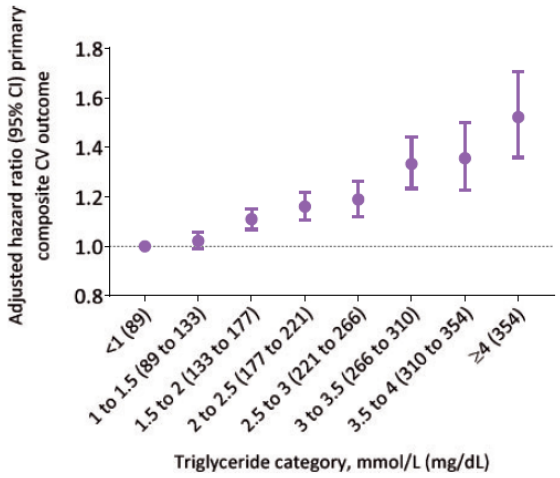
16

Approximately 1 in 4 patients with ASCVD in the general population may have hypertriglyceridemia and controlled LDLc*



*defined as triglyceride 1.52-5.63 mmol/L (135-499 mg/dL) and LDLc 1.06-2.59 mmol/L (41-100 mg/dL)

Risk of ASCVD events associated with triglyceride level among 196,717 patients with prevalent ASCVD in the population



Lawler, et al. *Eur Heart J.* 2020;41:86-94.

17

Clinical Trial Evidence of Omega-3 Fatty Acids in ASCVD

- What is the evidence of the role of ω3-FA in ASCVD prevention?
  - Meta-analysis from Aung et al.
  - Recent trials with EPA + DHA
  - Trials with EPA alone
  - REDUCE-IT

18

Research

JAMA Cardiol. 2018;3(3):225-234.

JAMA Cardiology | Original Investigation

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

Meta-analysis of 10 Trials Involving 77 917 Individuals

Theingi Aung, MBBS, FRCP; Jim Halsey, BSc; Daan Kromhout, PhD; Hertzel C. Gerstein, MD; Roberto Marchioli, MD; Luigi Tavazzi, MD; Johanna M Geleijnse, PhD; Bernhard Rauch, MD; Andrew Ness, PhD, FFPH; Pilar Galan, MD, PhD; Emily Y. Chew, MD; Jackie Bosch, PhD; Rory Collins, FMedSci, FRCP; Sarah Lewington, DPhil; Jane Armitage, FRCP, FFPH; Robert Clarke, MD, FRCP, FFPH; for the Omega-3 Treatment Trialists' Collaboration

CONCLUSIONS AND RELEVANCE This meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events. It provides no support for current recommendations for the use of such supplements in people with a history of coronary heart disease.

19

Meta-analysis of Association of ω-3 Fatty Acids and CV Risk

Study (Year)	Patients, No.	Dose of EPA/DHA (mg/d)	Male, No. (%)	Mean Trial Duration, y	Mean (SD) Age, y	No. (%)			
						Prior CHD	Prior Stroke	Prior Diabetes	Statin Use
DOIT (2010)	563	1150/800	563 (100)	3	70 (3)	133 (23.6)	37 (6.6)	46 (8.2)	NA
AREDS-2 (2014)	4203	650/350	1816 (43.2)	4.5	74 (NA)	405 (9.7)	211 (5.0)	546 (13.0)	1866 (44.4)
SU.FOL.OM3 (2010)	2501	400/200	1987 (79.4)	4.7	61 (NA)	1863 (74.5)	638 (25.5)	440 (17.9)	2079 (83.1)
JELIS (2007)[a,b]	18 645	1800/NA	5859 (31.4)	4.6	61 (8)	NA	NA	3040 (16.3)	18 645 (100.0)
Alpha Omega (2010)	4837	226/150	3783 (78.2)	3.3	69 (6)	4837 (100.0)	345 (7.2)	1014 (21.0)	4122 (85.2)
OMEGA (2010)	3818	460/380	2841 (74.4)	1	64 (NA)	796 (22.5)	192 (5.5)	948 (27.0)	3566 (94.2)
R&P (2013)	12 505	500/500	7687 (61.5)	5	64 (NA)	Not stated (30)	594 (4.8)	7494 (59.9)	12 505 (100.0)
GISSI-HF (2008)	6975	850/950	5459 (78.3)	3.9	67 (11)	3614 (51.8)	346 (5.0)	1974 (28.3)	NA
ORIGIN (2012)	12 536	465/375	8150 (65.0)	6.2	64 (8)	8094 (64.6)	10 877 (86.8)	11 081 (88.4)	6739 (53.8)
GISSI-P[b] (1999)	11 334	850/1700	9658 (85.2)	3.5	59 (11)	11 334 (100.0)	NA	2139 (18.9)	NA
Total	77 917	NA	47 803 (61.4)	4.4	64	31 076/46 767 (66.4)	13 240/47 938 (27.6)	28 722 (36.9)	49 522 (83.4)

Aung, et al. *JAMA Cardiol.* 2018;3:225-34.

20

Regulatory Advisory on Omega-3 Dietary Supplements

- Should not be used in place of prescription medication for the treatment of high TGs because they are not approved by the FDA for this purpose
- The potency, quality, and efficacy of dietary supplements are not reviewed or approved, nor monitored or assured by the FDA

2019 AHA Science Advisory[a]

- EMA has confirmed that omega-3 fatty acid medicines containing a combination EPA and DHA at a dose of 1 g/d are not effective
- Will no longer be authorized for secondary prevention after MI

2019 EMA Press Release[b]

a. Skulas-Ray AC, et al. *Circulation*. 2019;140: e1-e19; b. EMA [press release]. March 2019; c. FDA [press release]. June 2019.

21

Recent Trials with EPA + DHA

	VITAL [1] (n=25,871)	ASCEND [2] (n=15,490)	STRENGTH [3] (n=13,086)
Dose	840 mg/d	840 mg/d	4 g/d*
Population	Primary prevention (diabetes 14%)	Primary prevention in patients with diabetes	Secondary prevention and high-risk primary prevention
Statins	37.5%+	75%	100%
TG at baseline	NR	NR	180-500 mg/dL
Follow-up	5.3 years	7.4 years	3 years
Effect on primary endpoint (vs control)	No significant difference	No significant difference	Stopped 01/2020 for low likelihood of demonstrating benefit

1. Manson, et al. *N Engl J Med*. 2019;380:23-32.
2. Bowman, et al. *N Engl J Med*. 2018;379:1540-50.
3. Nicholls, et al. *Clin Cardiol*. 2018;41:1281-8.

* omega-3 carboxylic acids EPA+DHA
+ cholesterol-lowering drugs
NR: not reported

22

Trials with EPA Alone

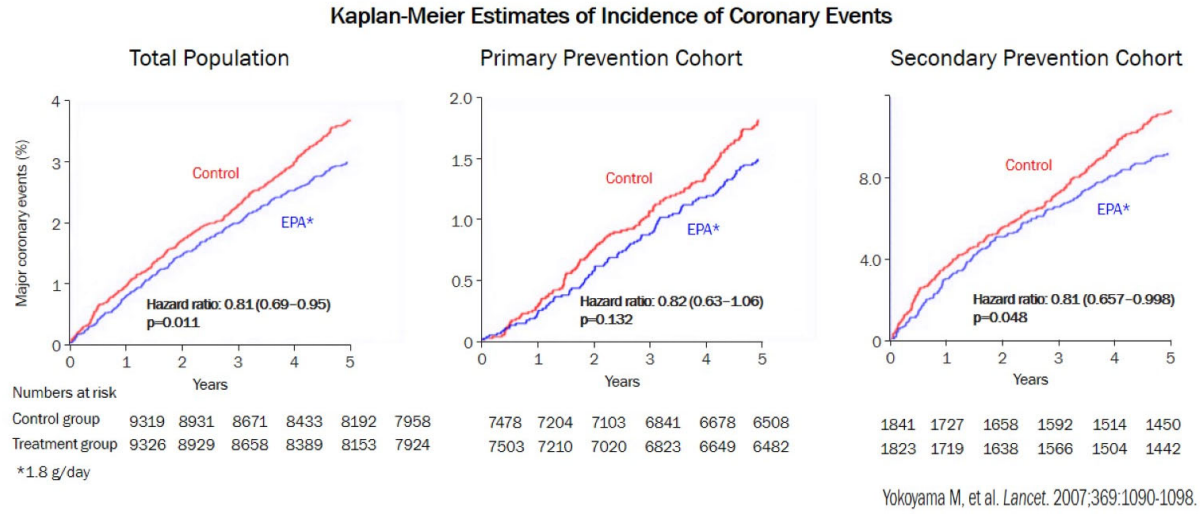
	JELIS [1] (n=18,645)	REDUCE-IT [2] (n=8,179)
Dose	1.8 g/d	4 g/d
Population	Patients with hypercholesterolemia (16% diabetics, 20% CAD)	Patients with ASCVD (70.7%) or with diabetes + other risk factors
Statins	98%*	100%
LDL-C at baseline TG at baseline	182 mg/dL (4.70 mmol/L) 152 mg/dL (1.74 mmol/L)	75 mg/dL (1.94 mmol/L)+ 216 mg/dL (2.47 mmol/L)
Follow-up	4.6 years	4.9 years
Effect on primary endpoint	19% RRR (p=0.011)	25% RRR (p<0.001)

1. Yokoyama, et al. *Lancet.* 2007;369:1090-8.
2. Bhatt, et al. *N Engl J Med.* 2019;380:11-22.

* Pravastatin 10 mg, simvastatin 5 mg; + baseline on statin
RRR: relative risk reduction

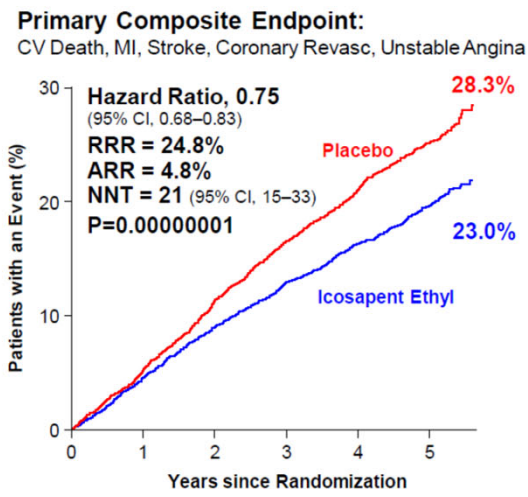
23

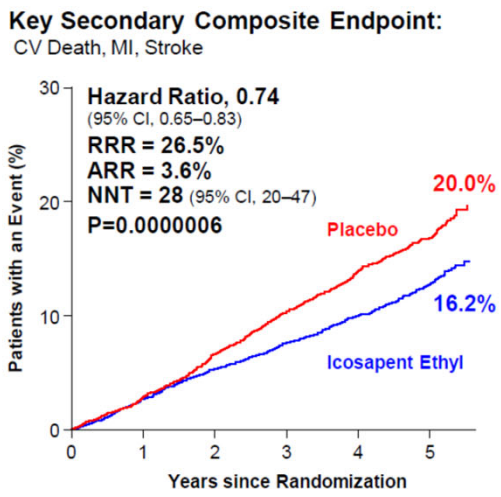
JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients



24

Primary and Key Secondary Composite Endpoints





Bhatt DL, et al. *N Engl J Med.* 2019;380:11-22.
Bhatt DL. AHA 2018, Chicago.

25

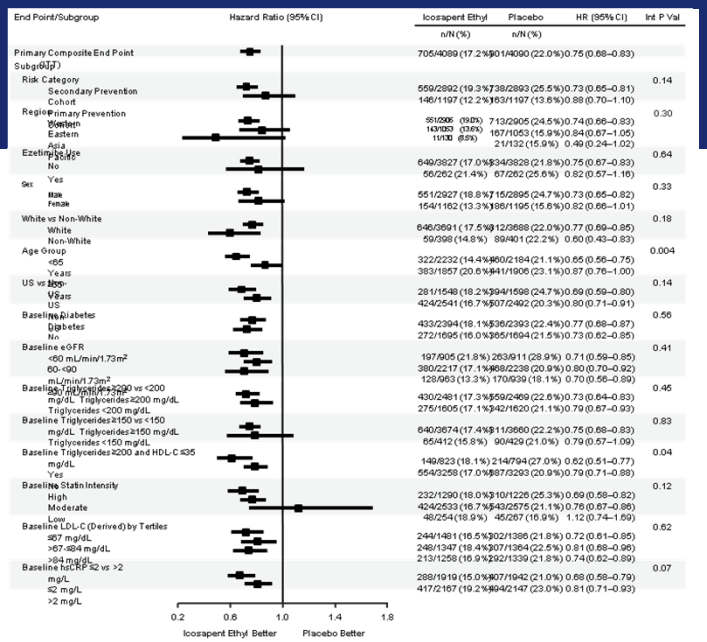
Prespecified Hierarchical Testing

Endpoint	Hazard Ratio (95% CI)	RRR, %	*P* Value
Primary composite (ITT)	0.75 (0.68, 0.83)	25↓	<.001
Key secondary composite (ITT)	0.74 (0.65, 0.83)	26↓	<.001
CV death or nonfatal MI	0.75 (0.66, 0.86)	25↓	<.001
Fatal or nonfatal MI	0.69 (0.58, 0.81)	31↓	<.001
Urgent or emergent revascularization	0.65 (0.55, 0.78)	35↓	<.001
CV death	0.80 (0.66, 0.98)	20↓	.03
Hospitalization for UA	0.68 (0.53, 0.87)	32↓	.002
Fatal or nonfatal stroke	0.72 (0.55, 0.93)	28↓	.01
Total mortality, nonfatal MI, or nonfatal stroke	0.77 (0.69, 0.86)	23↓	<.001
Total mortality	0.87 (0.74, 1.02)	13↓	.09

Broad and clinically meaningful CV effect

Bhatt DL, et al. *N Engl J Med.* 2019;380:11-22.

26

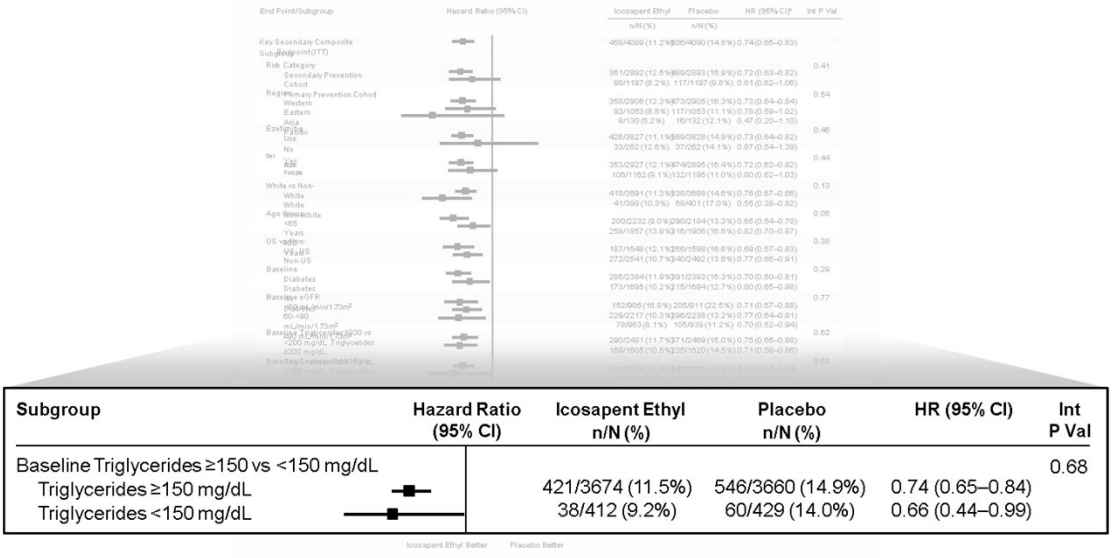


Primary Endpoint in Subgroups

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019;380:11-22.

27

Key Secondary Endpoint in Subgroups



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019;380:11-22.

28

Treatment-Emergent Adverse Events

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Subjects with at Least One TEAE, n (%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

Bhatt DL, et al. *N Engl J Med*. 2019;380:11-22.

29

Safety

	Icosapent Ethyl	Placebo	p
Atrial Fibrillation (AF)	5.3%	3.9%	0.003
Hospitalization for AF	3.1%	2.1%	0.004
Peripheral edema	6.5%	5.0%	0.002
SA bleeding events	2.7%	2.1%	0.06
Diarrhea	9.0%	11.1%	0.002
Constipation	5.4%	3.6%	< 0.001
Anemia	4.7%	5.8%	0.03

Bhatt DL, et al. *N Engl J Med*. 2019;380:11-22.

30

Treatment-Emergent Adverse Event of Interest: Serious Bleeding

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Bleeding related disorders	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke: no significant difference between treatments (13 icosapent ethyl versus 10 placebo; P=0.55)

Bhatt DL, et al. *N Engl J Med*. 2019;380:11-22.

31

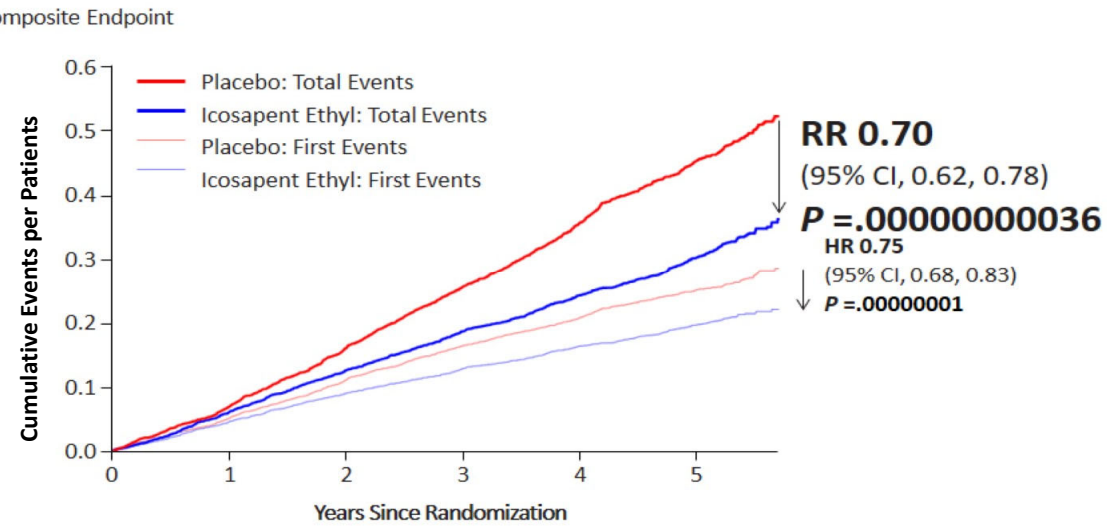
Safety Results

- Over 5 years, icosapent ethyl was well tolerated with no significant differences in rates of SAEs vs placebo
  - Low overall rates; no fatal events in either treatment group
  - Trend toward increased serious bleeding with icosapent ethyl (no significant increases in adjudicated hemorrhagic stroke, serious CNS bleeding, or GI bleeding)
  - Small but significant increase in Afib
- Treatment with icosapenty ethyl averted ischemic events and led to significant reductions in:
  - Fatal and nonfatal stroke (28%)
  - Cardiac arrest (48%)
  - Sudden death (31%)
  - CV death (20%)

Bhatt DL, et al. *J Am Coll Cardiol*. 2019;73:2791-802.
Bhatt DL, et al. *N Engl J Med*. 2019;380:11-22.

32

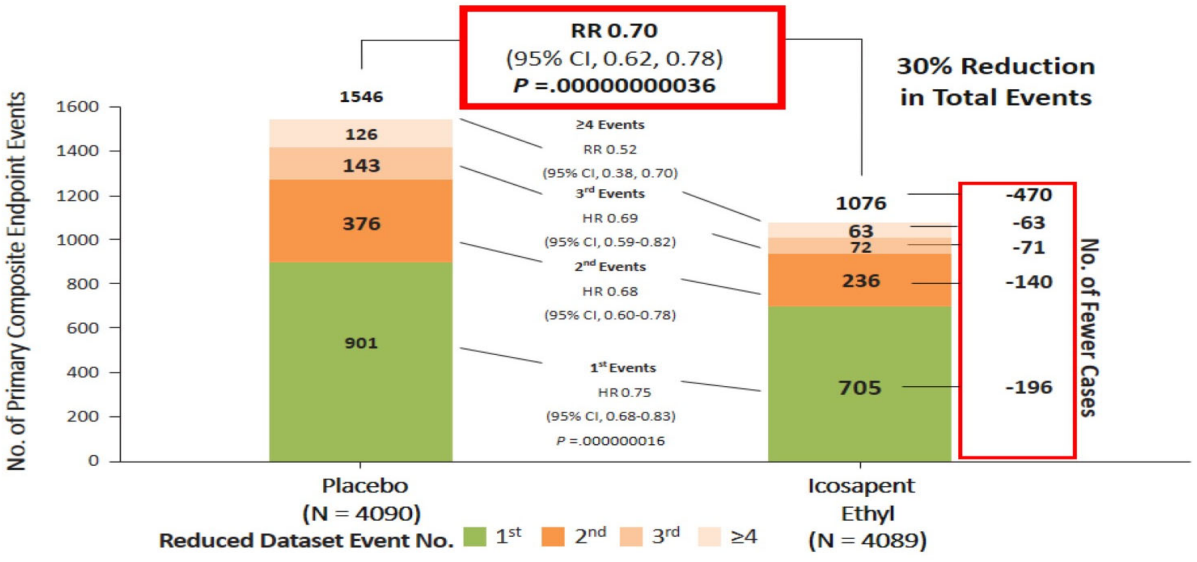
First and Total Events Over the Years



Bhatt DL, et al. *J Am Coll Cardiol.* 2019;73:2791-802.

33

Reduction of First and Subsequent Events

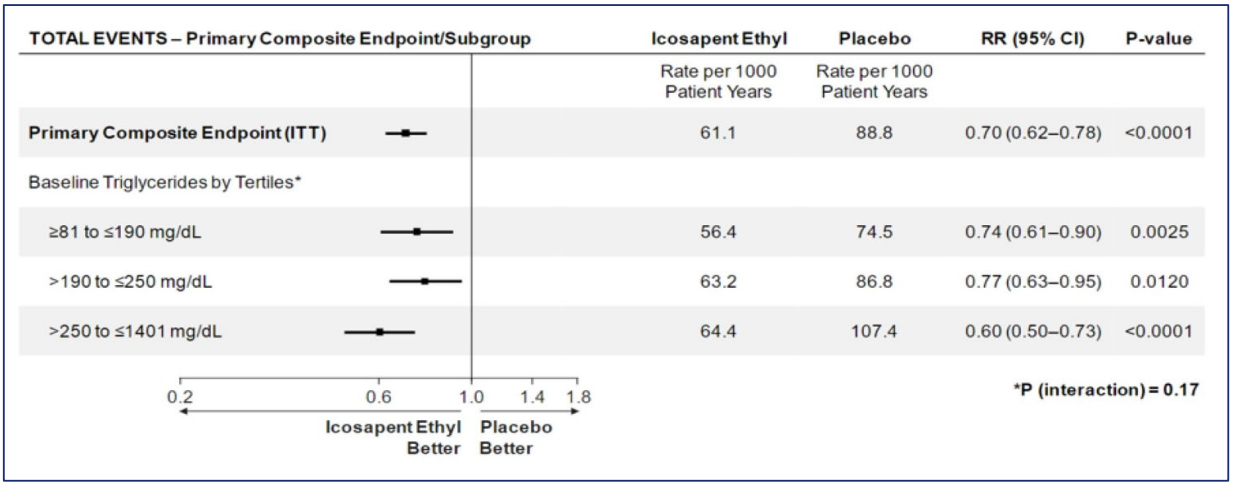


Bhatt DL, et al. *J Am Coll Cardiol.* 2019;73:2791-802.

34

Primary Composite Endpoint

Total endpoint events by baseline TG tertiles



Bhatt DL, et al. *J Am Coll Cardiol.* 2019;73:2791-802.

35

Lipids and Inflammatory Marker

	Icosapent Ethyl 4g/day		Placebo (Mineral oil)		Between Group	
	Median % change	p	Median % change	p	Median % change	p
Triglycerides						
Year 1	-18.3	< 0.001	2.2	< 0.001	-19.7	< 0.001
Non-HDL-C						
Year 1	-3.6	< 0.001	10.4	< 0.001	-13.1	< 0.001
LDL-C (UC)						
Year 1	3.1	< 0.001	10.2	< 0.001	-6.6	< 0.001
Last visit	3.1	< 0.001	10.2	< 0.001	-6.6	< 0.001
hsCRP						
Last visit	-12.6	0.75	29.9	< 0.001	-37.6	< 0.001

Bhatt DL, et al. *N Engl J Med.* 2019;380:11-22.

36

ORIGINAL RESEARCH ARTICLE

Association Between Triglyceride Lowering and Reduction of Cardiovascular Risk Across Multiple Lipid-Lowering Therapeutic Classes

A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials

CONCLUSIONS: In randomized controlled trials, triglyceride lowering is associated with a lower risk of major vascular events, even after adjustment for LDL-C lowering, although the effect is less than that for LDL-C and attenuated when REDUCE-IT is excluded. Furthermore, the benefits of marine-derived omega-3 fatty acids, particularly high-dose eicosapentaenoic acid, appear to exceed their lipid-lowering effects.

Marston, et al. *Circulation*. 2019;140:1308-17.

37

Meta-Regression Analysis: Association Between TG Lowering and Reduction of CV Risk

Lipid Parameters	RR (95% CI) per 1 mmol/L reduction	p-value
Non-HDL-C	0.79 (0.76-0.82)	< 0.0001
LDL-C	0.80 (0.76-0.85)	< 0.0001
TG	0.84 (0.76-0.94)	0.0026
TG (excluding REDUCE-IT)	0.91 (0.81-1.006)	

24 trials of TG-lowering nonstatin therapy (9 fibrate, 3 niacin, and 13 omega-3 fatty acids trials)

Marston, et al. *Circulation*. 2019;140:1308-17.

38

Clinical Trial Evidence of Omega-3 Fatty Acids in ASCVD

- What is recommended in current guidelines?
  - 2019 ESC/EAS guidelines
  - 2020 ADA guidelines
  - FDA indications

39

Recommendations for Drug Treatments of Patients with Hypertriglyceridaemia

ESC/EAS GUIDELINES
European Heart Journal (2019)

Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L [>200 mg/dL]).	I	B
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) should be considered in combination with statin.	IIa	B

Recommendations	Class	Level
In primary prevention patients who are at LDL-C goal with TG >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	B
In high-risk patients who are at LDL-C goal with TG >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	C

Mach, et al. *Eur Heart J.* 2020;41:111-188.

40

ADA Guidelines: Medical Care in Diabetes

In patients with ASCVD or other CV risk factors on a statin with controlled LDL-C but elevated TG (135-499 mg/dL), the addition of icosapent ethyl can be considered to reduce CV risk (Level A)

Diabetes Care. 2020;43:S111-S134.

41

US Indications for EPA

- As an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and
  - Established cardiovascular disease or
  - DM and 2 or more additional risk factors for cardiovascular disease
- As an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia

42

Conclusions

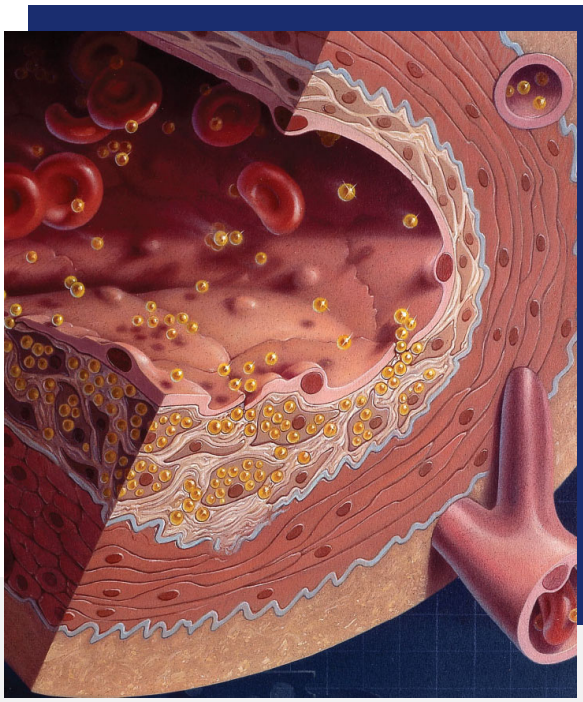
- Despite controlled LDL-C on statins, patients with increased TG remain at high CV residual risk.
- REDUCE-IT trial provides remarkable CVD benefit, safety, and tolerability of pure EPA.
- EPA benefit is not different according to baseline or achieved TG levels.
- Are there other potential mechanisms for benefit of pure EPA?

43

Mechanisms and Comparisons of Omega-3s

Børge G. Nordestgaard, MD, DMSc
Professor, Chief Physician

medtelligence℠



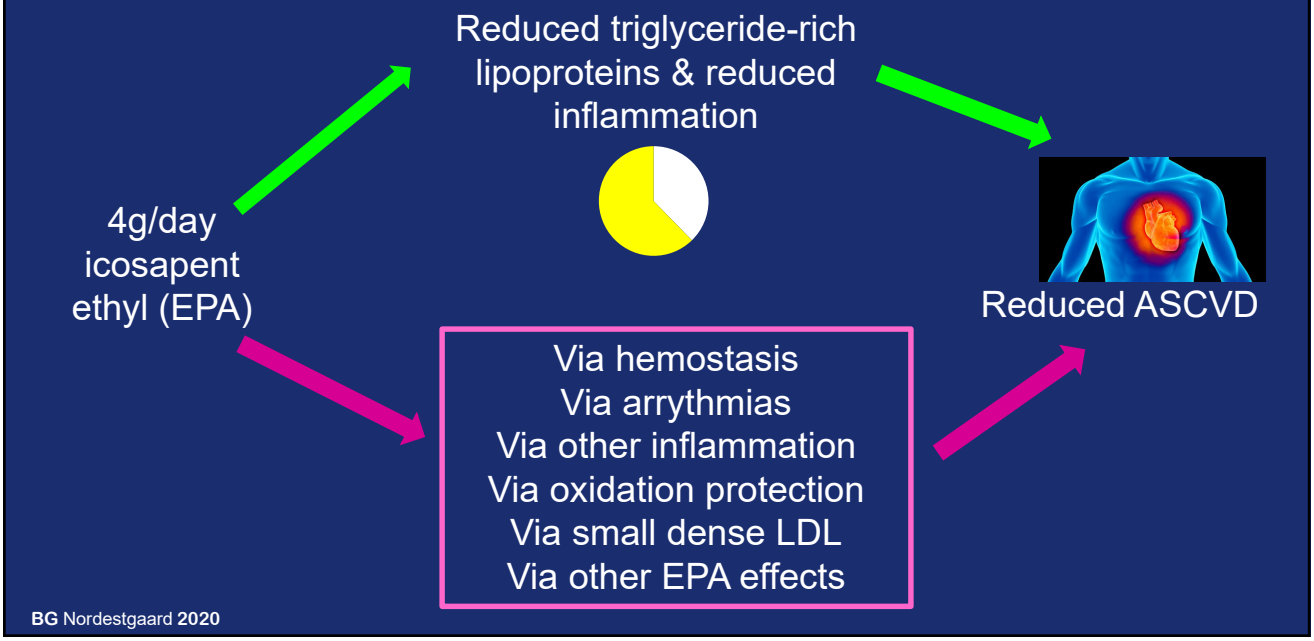
44

Financial Discloure- Børge G. Nordestgaard

Dr. Nordestgaard is a Danish tax payer. He is a consultant for Akcea, Amarin, Amgen, AstraZeneca, Denka Seiken, Kowa, Sanofi, Novartis, Novo Nordisk, Regeneron and Silence Therap.

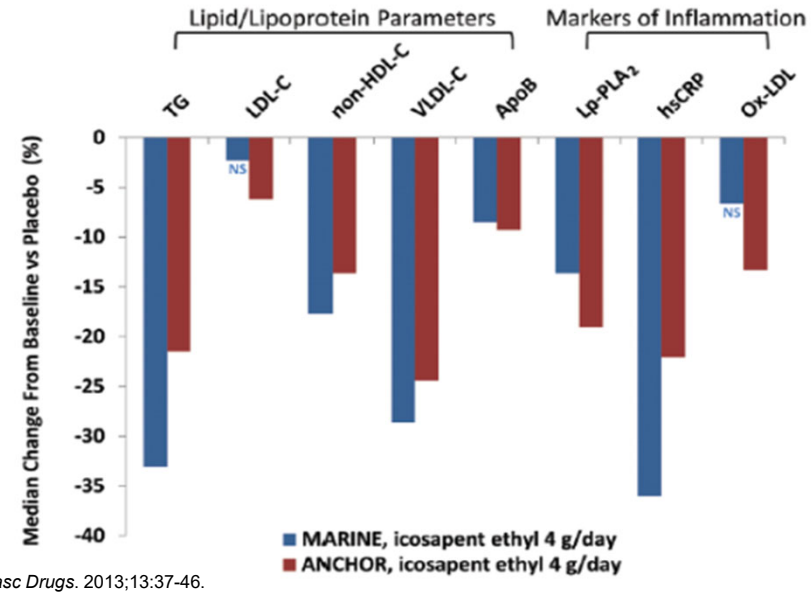
45

Two Different Mechanisms



46

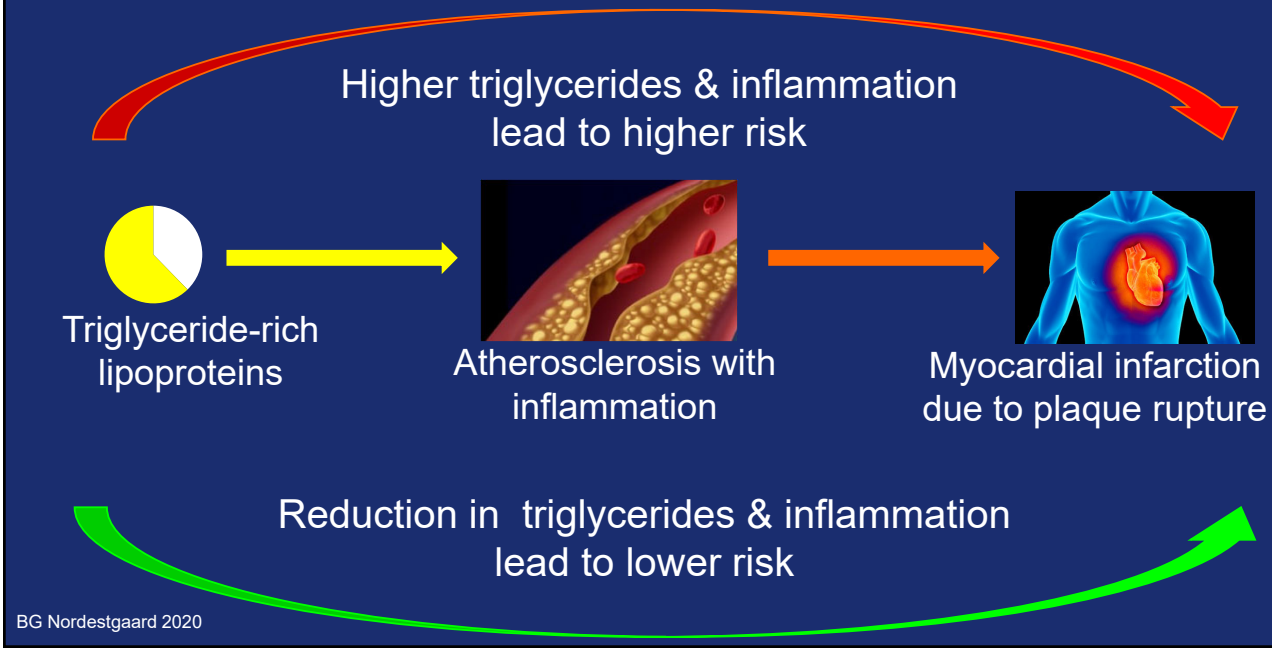
Effects of EPA on Non-HDL-C and Inflammatory Markers in Patients With Elevated TGs at 4 g/d



Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46.

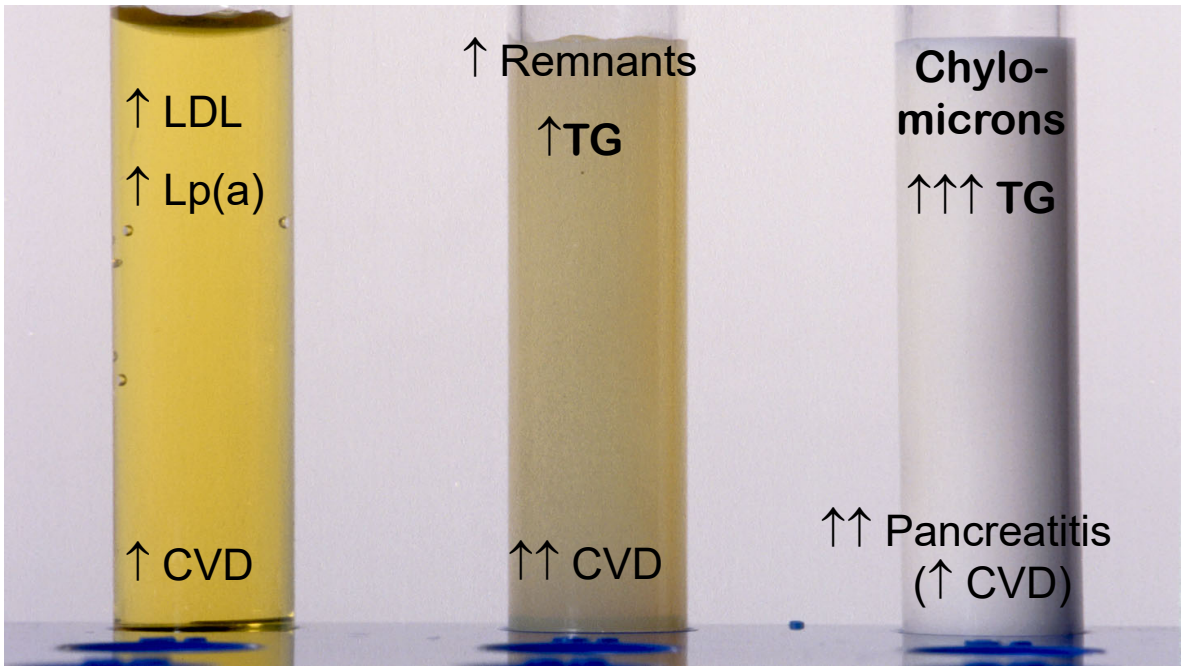
47

The Simplest Chain of Events



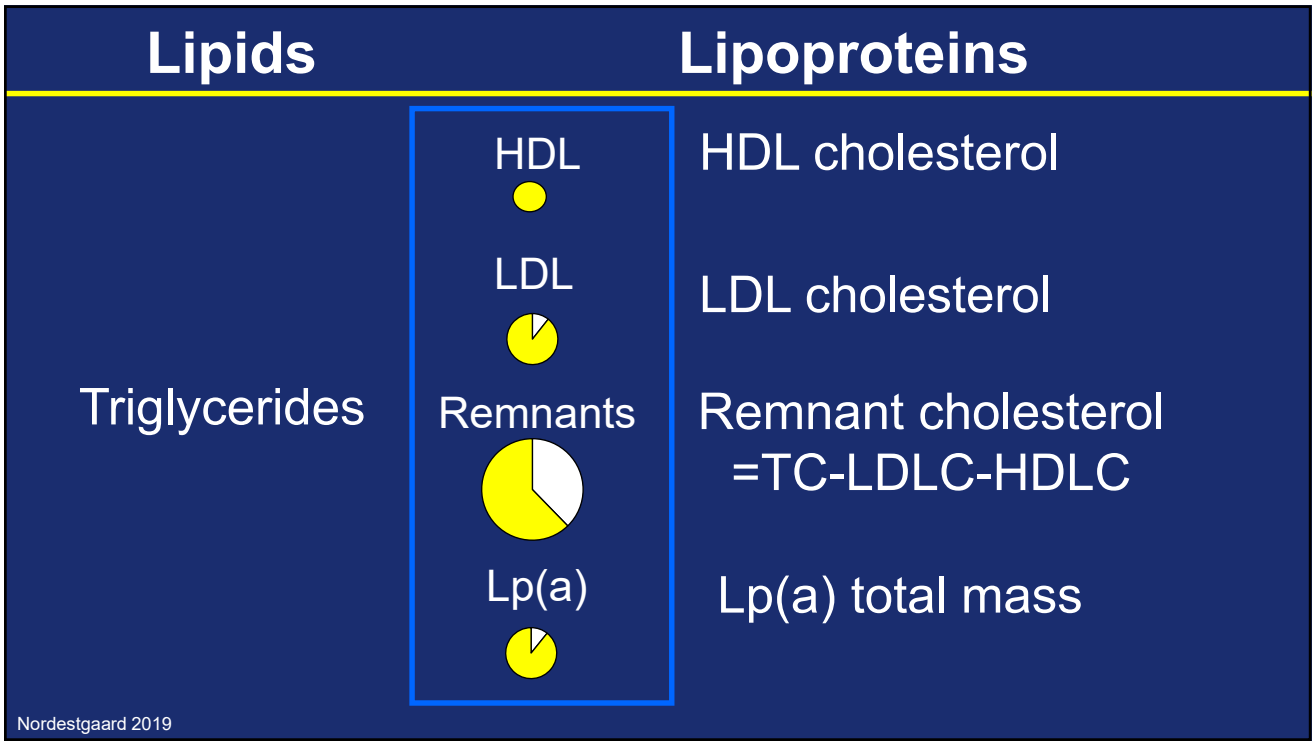
BG Nordestgaard 2020

48



Nordestgaard 2019

49

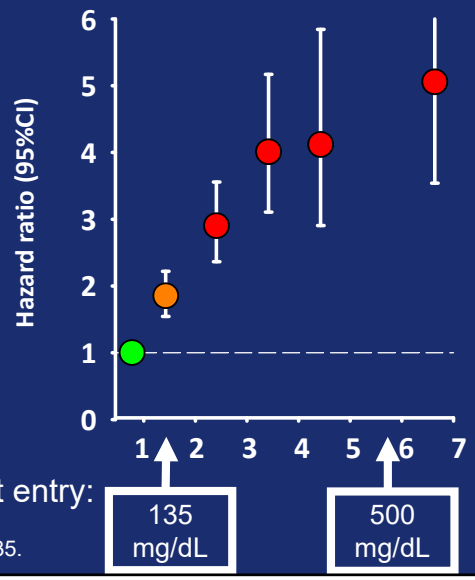


Nordestgaard 2019

50

Copenhagen City Heart Study and Copenhagen General Population Study

Myocardial infarction
N = 96,394 (Events = 3,287)

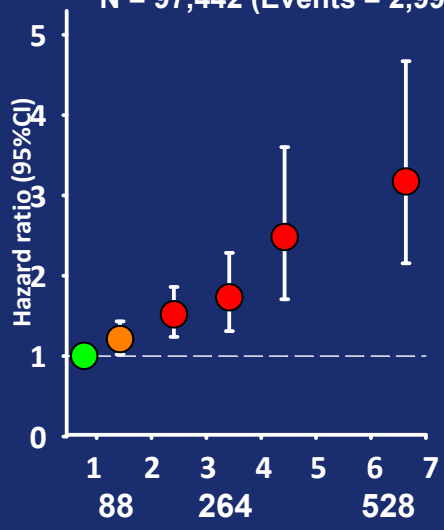


Nordestgaard & Varbo, Lancet 2014; 384: 626-635.

51

Copenhagen City Heart Study and Copenhagen General Population Study

Ischemic stroke
N = 97,442 (Events = 2,994)



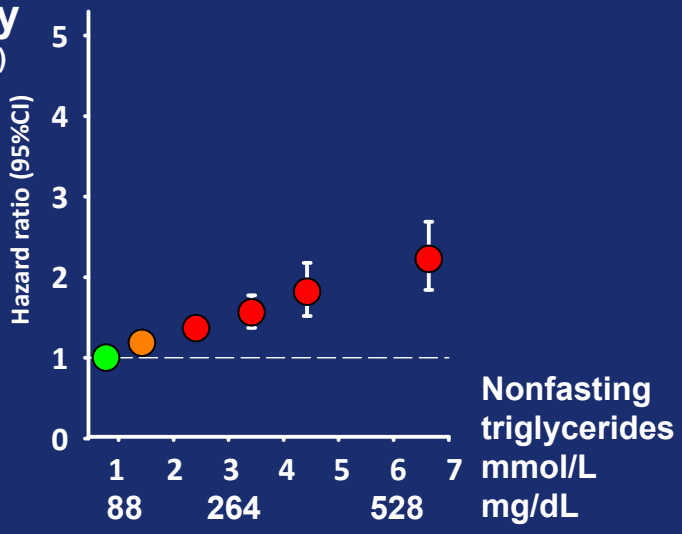
Nordestgaard & Varbo, Lancet 2014; 384: 626-635

52

Copenhagen City Heart Study and Copenhagen General Population Study

All-cause mortality

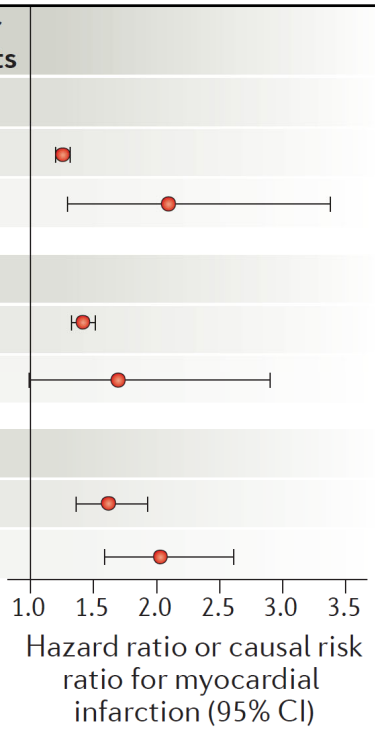
N = 98,515 (Events = 14,547)



Nordestgaard & Varbo, Lancet 2014; 384: 626-635

53

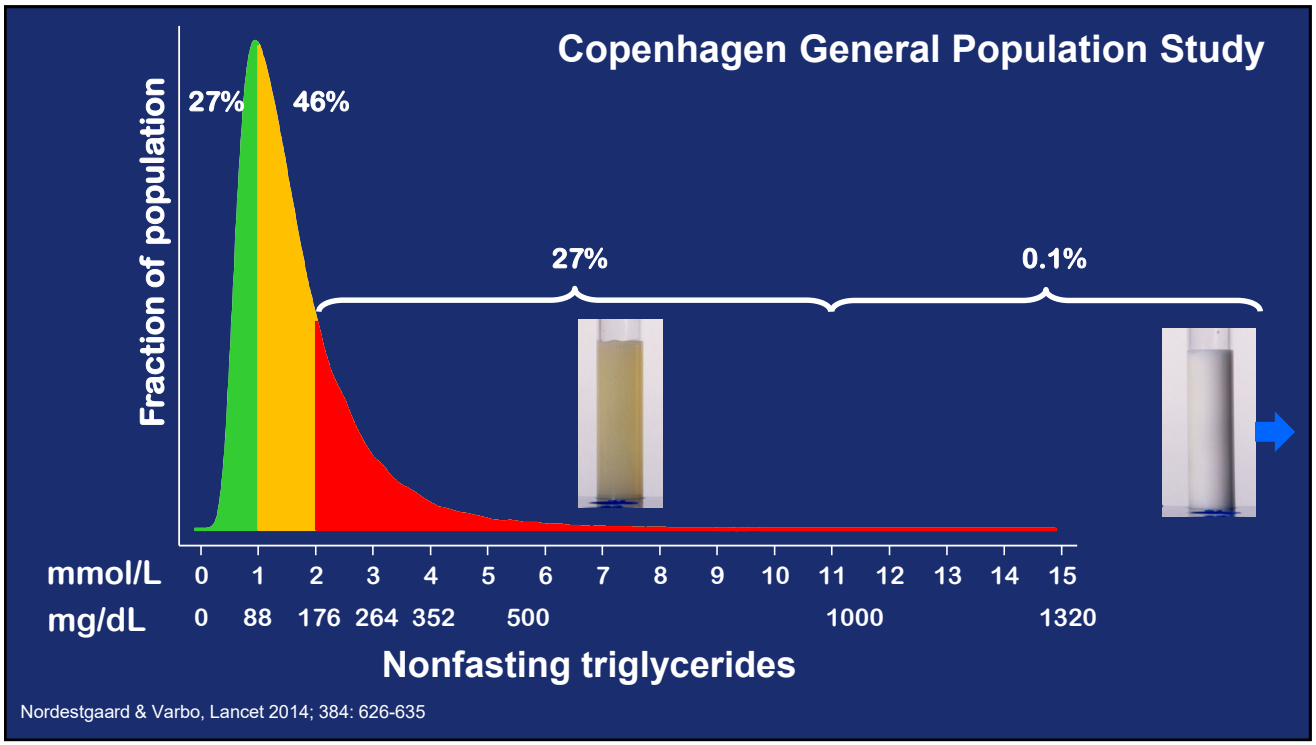
	n	Number of events
LDL cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,554	2,210
Genetic (*APOB, HMGCR, LDLR, PCSK9*)	95,908	4,155
Remnant cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,508	2,219
Genetic (*APOA5, GCKR, LPL, TRIB1*)	97,745	4,199
Lipoprotein(a) cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,550	2,210
Genetic (*LPA*)	103,715	4,425



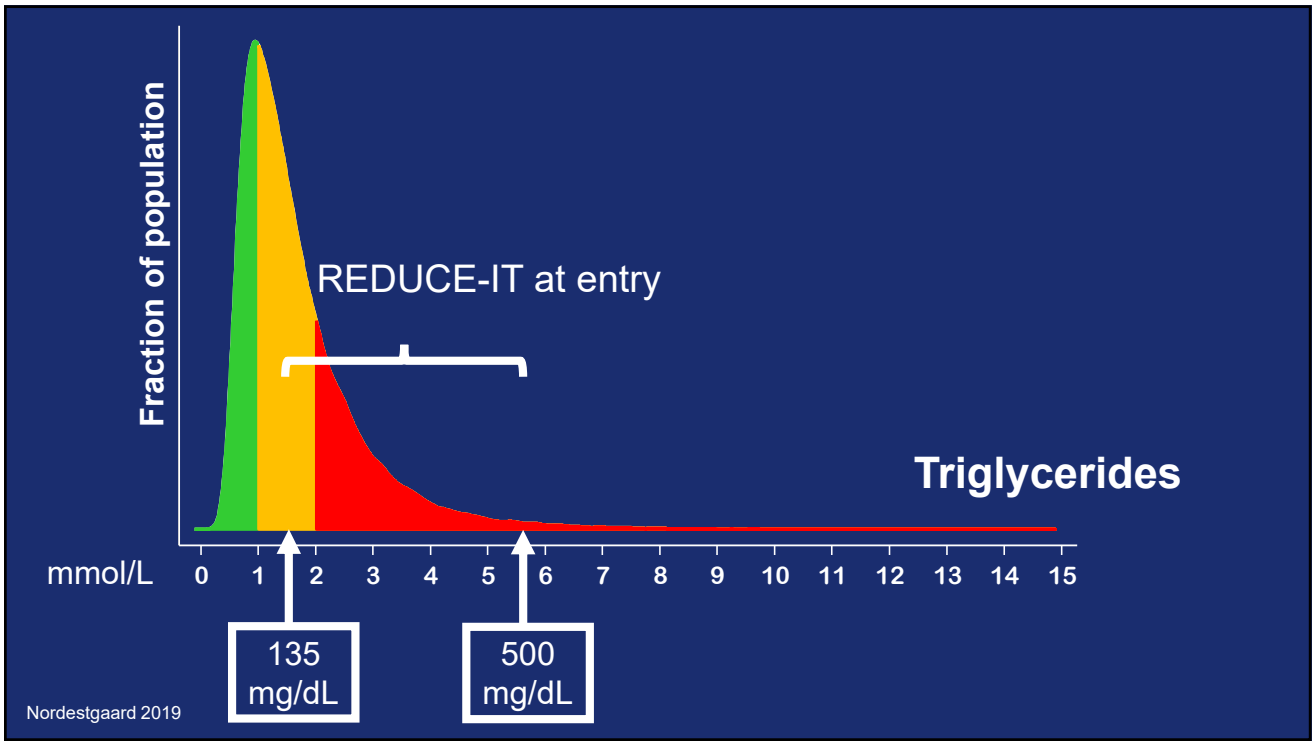
Copenhagen General Population Study

Nordestgaard, Nicholls, Langsted, Ray & Tybjærg-Hansen. Nat Rev Cardiol 2018 2018; 15: 261-272

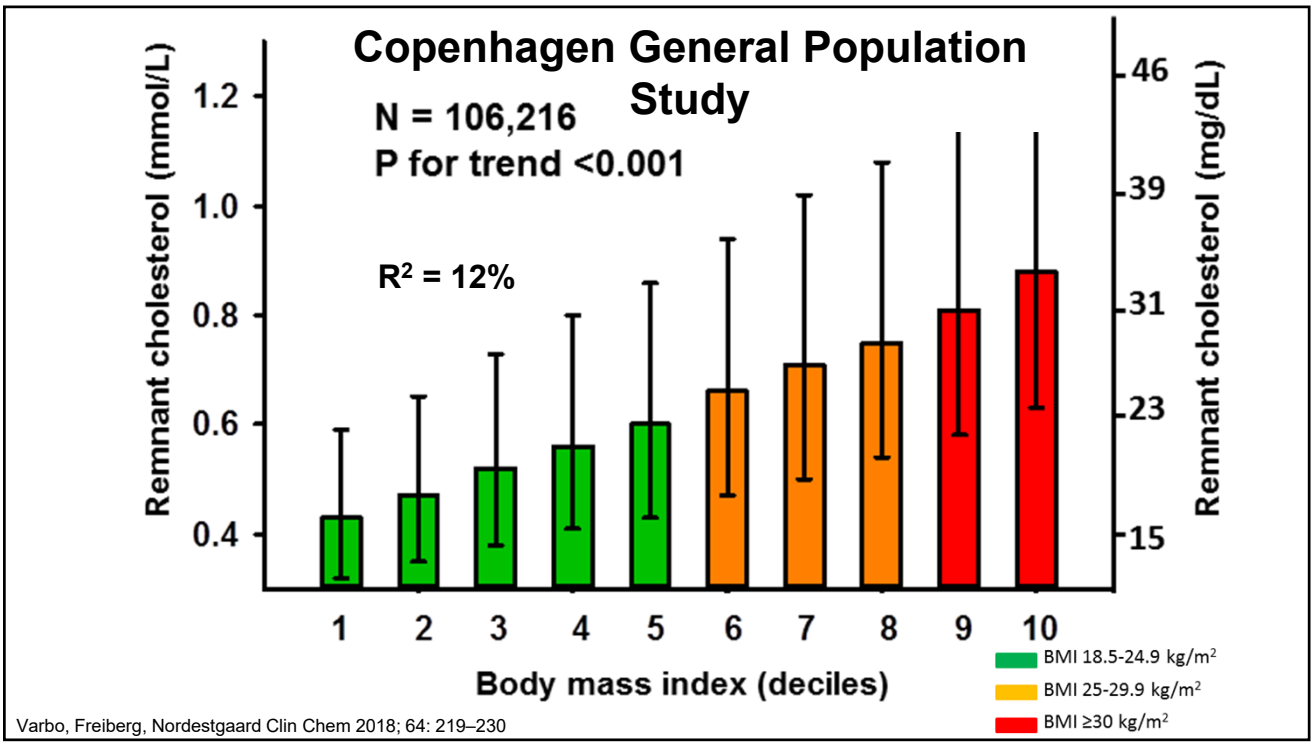
54


Copenhagen General Population Study
Fraction of population
27%
46%
27%
0.1%
mmol/L 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
mg/dL 0 88 176 264 352 500 1000 1320
Nonfasting triglycerides
Nordestgaard & Varbo, Lancet 2014; 384: 626-635

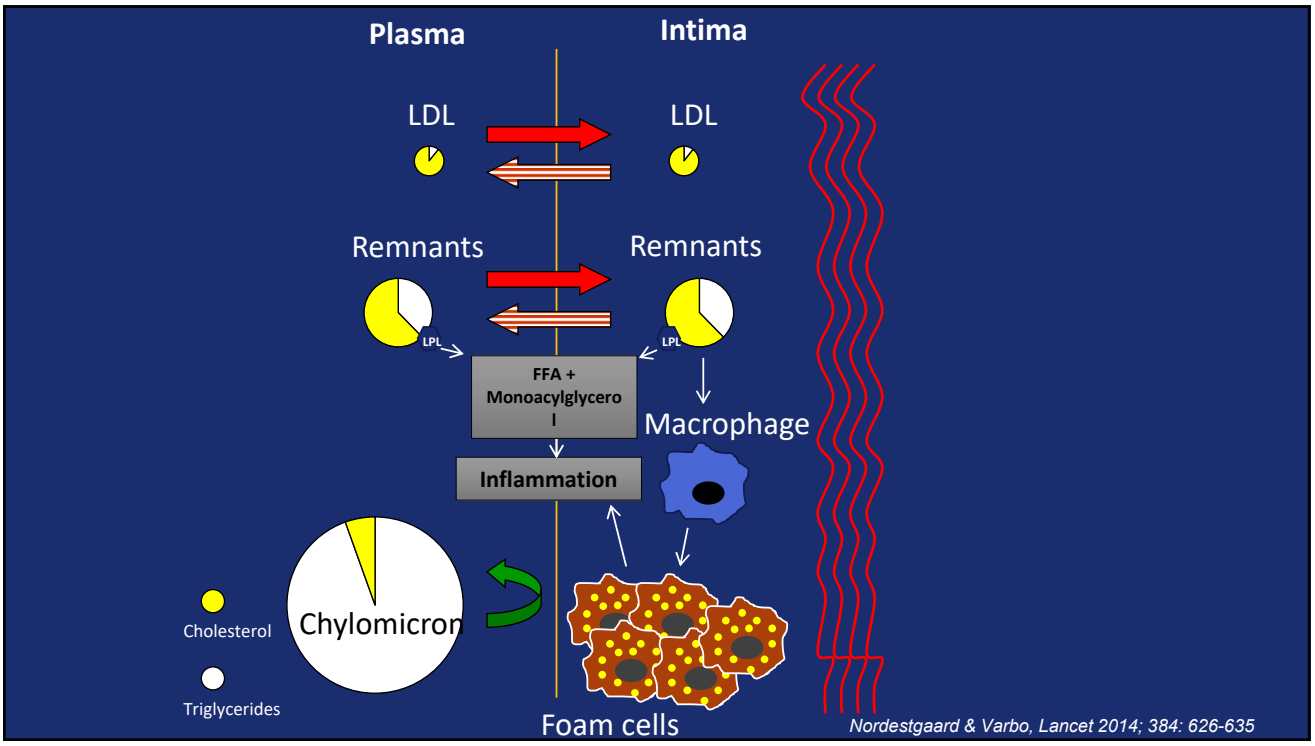
55


Fraction of population
REDUCE-IT at entry
Triglycerides
mmol/L 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
135 mg/dL
500 mg/dL
Nordestgaard 2019

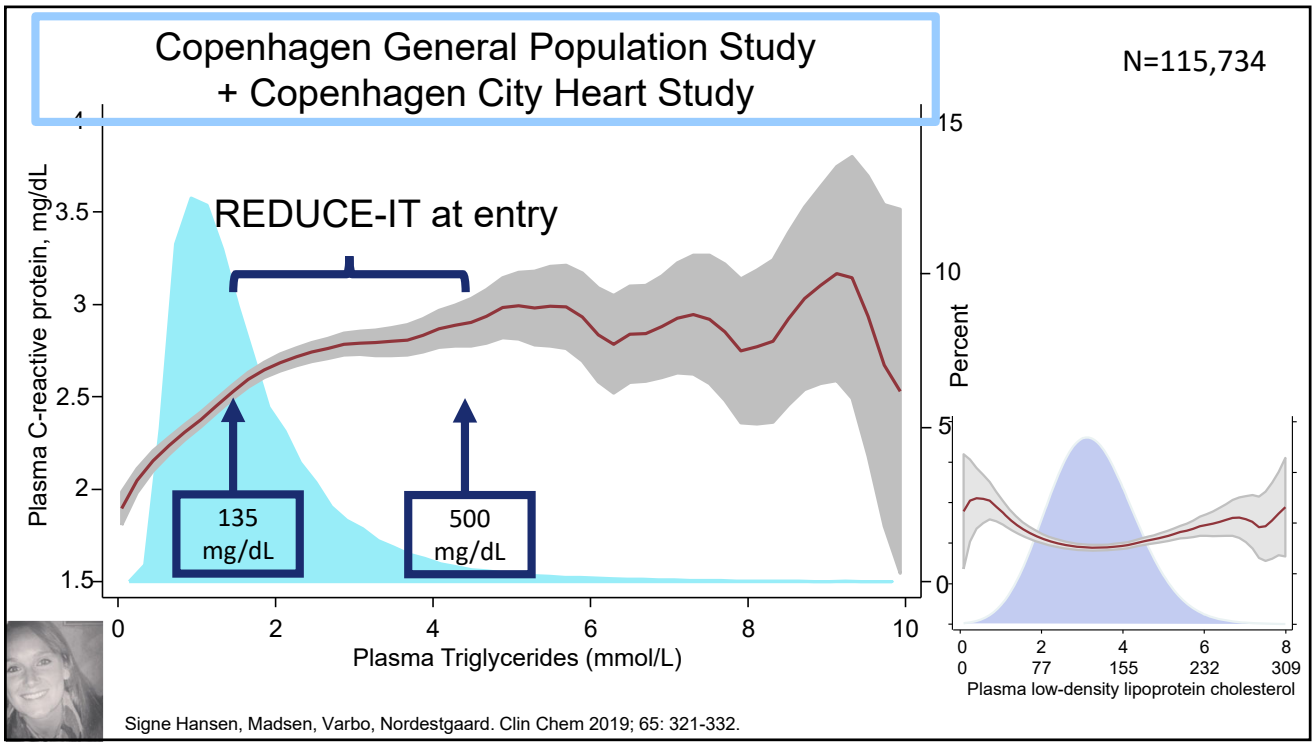
56


Copenhagen General Population Study
N = 106,216
P for trend <0.001
R² = 12%
Remnant cholesterol (mmol/L)
1.2
1.0
0.8
0.6
0.4
Remnant cholesterol (mg/dL)
46
39
31
23
15
1 2 3 4 5 6 7 8 9 10
Body mass index (deciles)
BMI 18.5-24.9 kg/m²
BMI 25-29.9 kg/m²
BMI ≥30 kg/m²
Varbo, Freiberg, Nordestgaard Clin Chem 2018; 64: 219–230

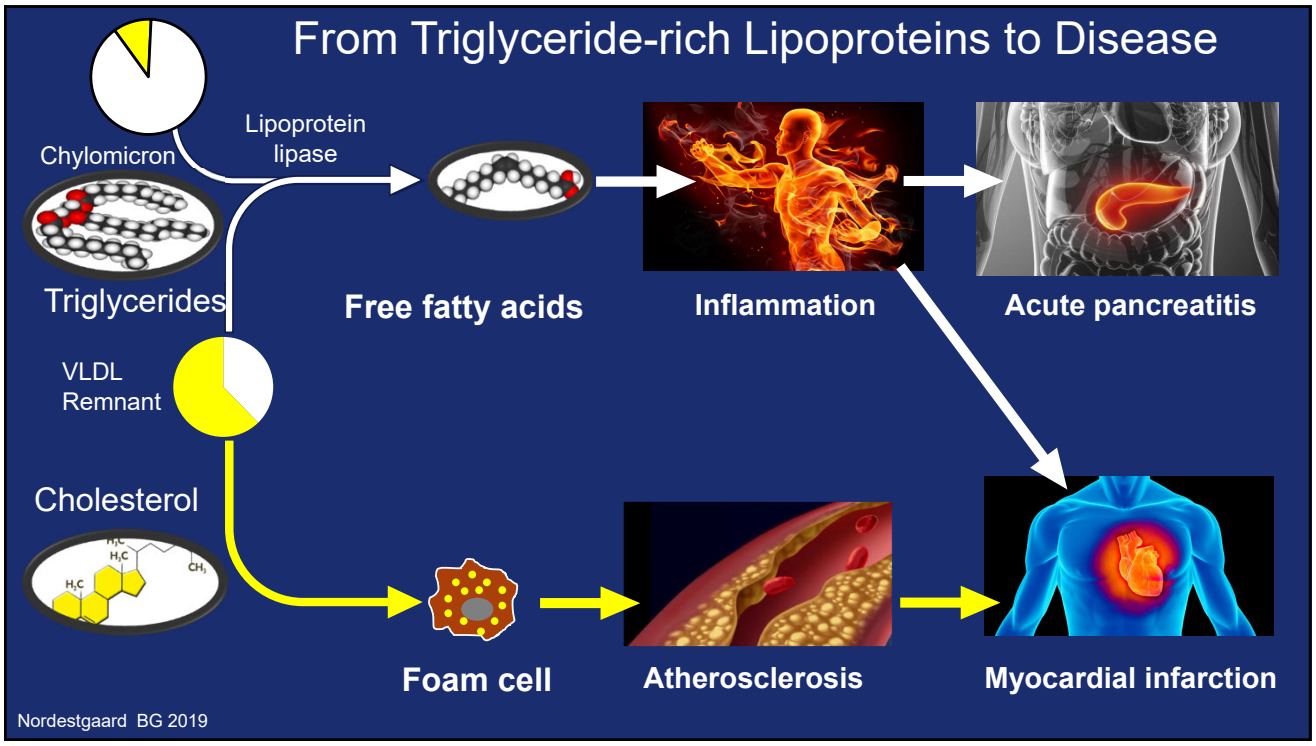
57


Plasma
Intima
LDL
LDL
Remnants
Remnants
LPL
LPL
FFA + Monoacylglycero l
Macrophage
Inflammation
Chylomicron
Cholesterol
Triglycerides
Foam cells
Nordestgaard & Varbo, Lancet 2014; 384: 626-635

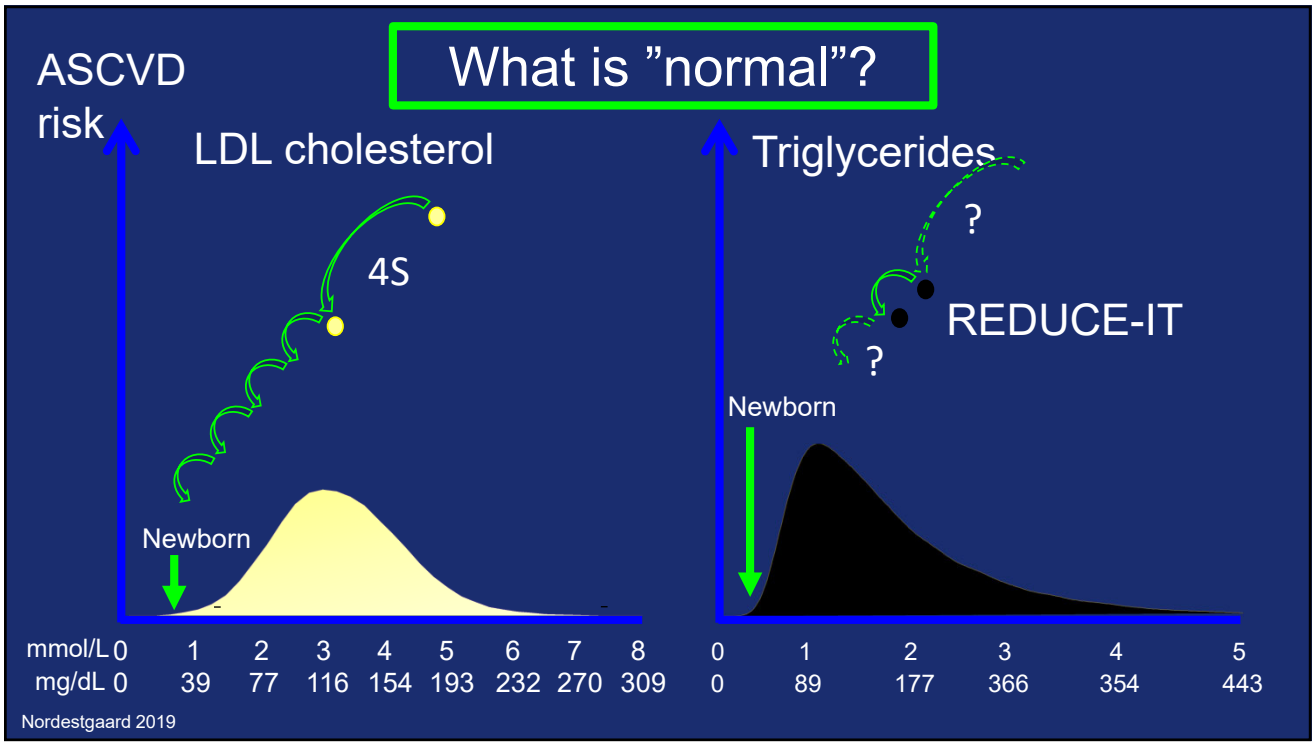
58


Copenhagen General Population Study
+ Copenhagen City Heart Study
N=115,734
REDUCE-IT at entry
135 mg/dL
500 mg/dL
Plasma C-reactive protein, mg/dL
Plasma Triglycerides (mmol/L)
Percent
Plasma low-density lipoprotein cholesterol
Signe Hansen, Madsen, Varbo, Nordestgaard. Clin Chem 2019; 65: 321-332.

59

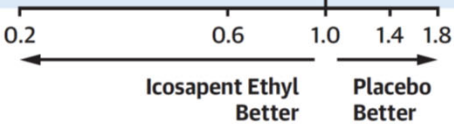

From Triglyceride-rich Lipoproteins to Disease
Chylomicron
Lipoprotein lipase
Triglycerides
Free fatty acids
Inflammation
Acute pancreatitis
VLDL Remnant
Cholesterol
Foam cell
Atherosclerosis
Myocardial infarction
Nordestgaard BG 2019

60



61

TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-Value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62-0.78)	< 0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dl	56.4	74.5	0.74 (0.61-0.90)	0.0025
>190 to ≤250 mg/dl	63.2	86.8	0.77 (0.63-0.95)	0.0120
>250 to ≤1401 mg/dl	64.4	107.4	0.60 (0.50-0.73)	< 0.0001



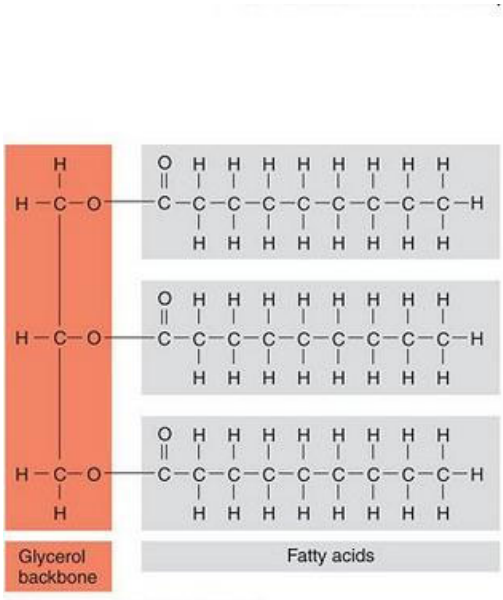
*P (interaction) = 0.17

Bhatt DL JACC 2019 online August 27

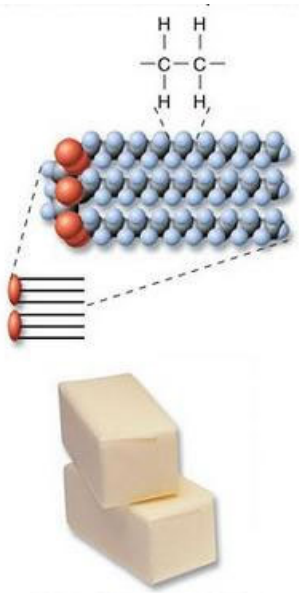
62

Comparison of Omega-3 Fatty Acids

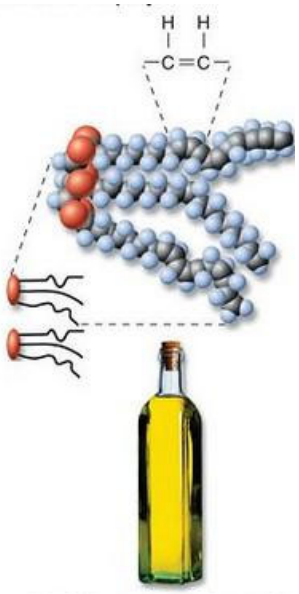
63



(a) Fat molecule (triacylglycerol)



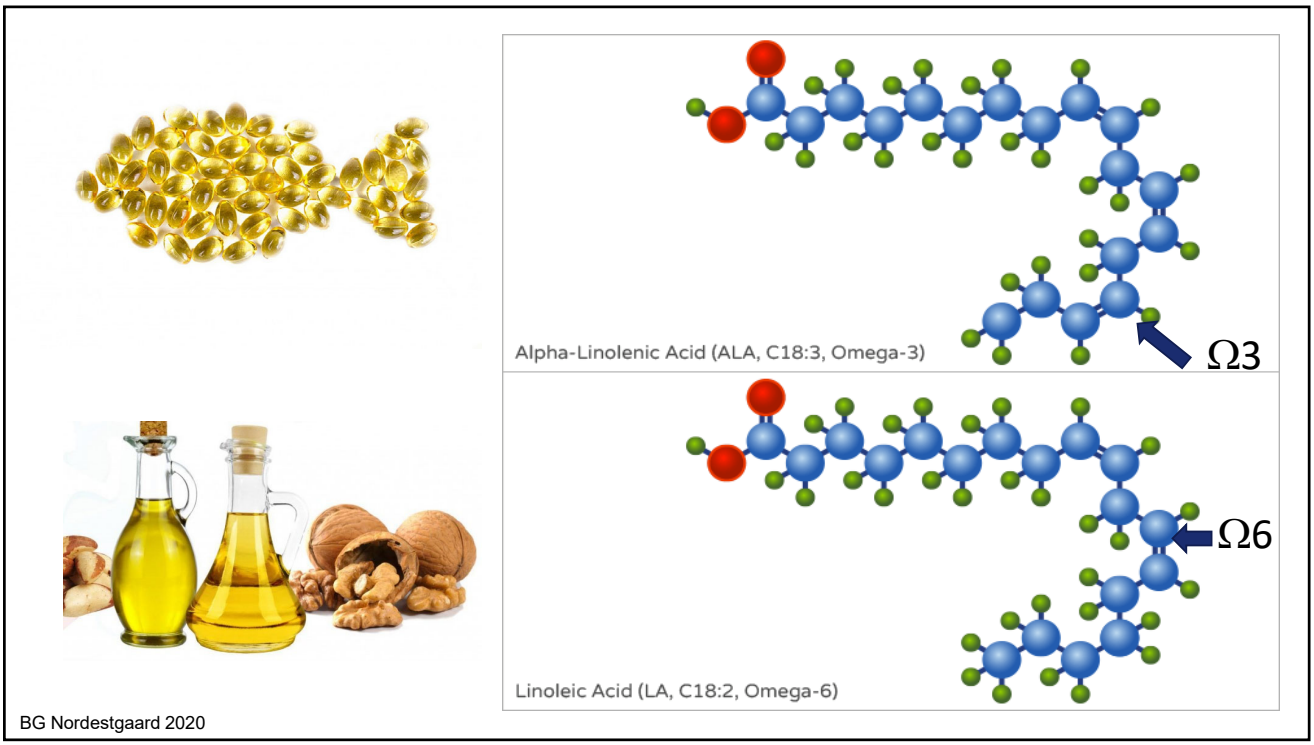
(b) Hard fat (saturated): Fatty acids with single bonds between all carbon pairs



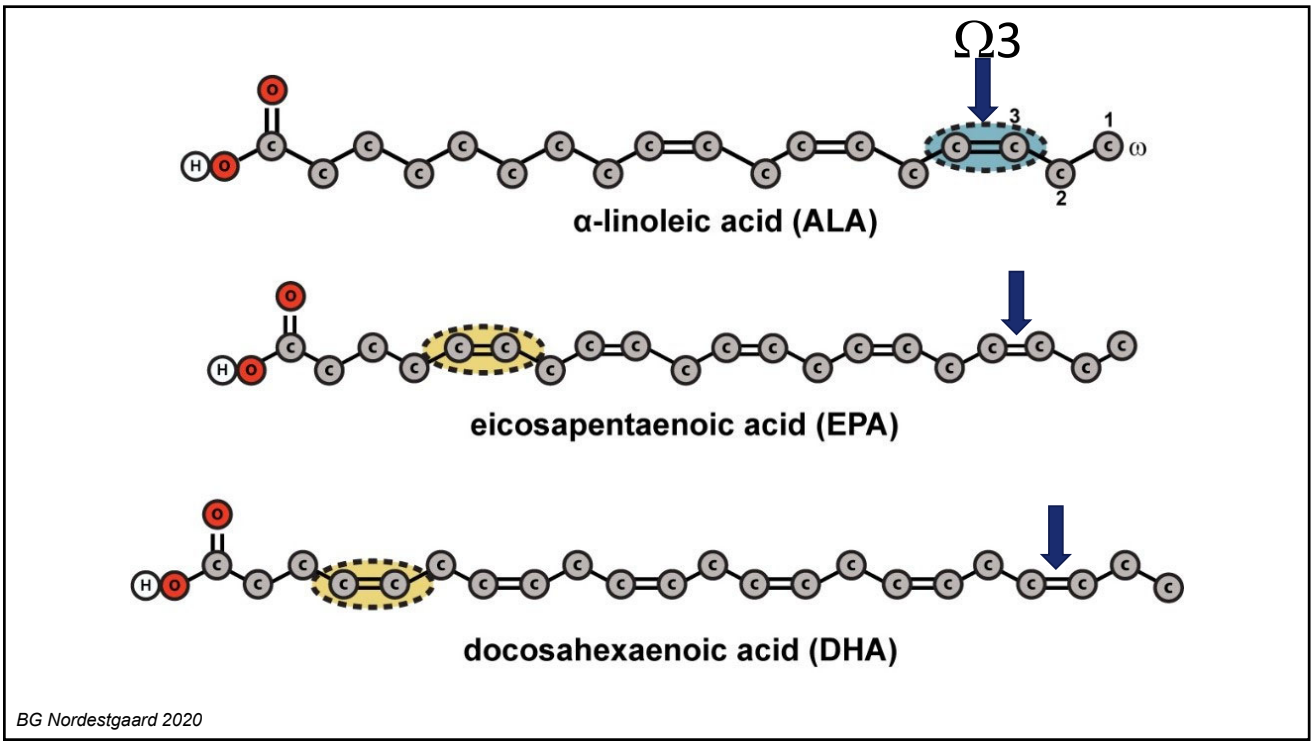
(c) Oil (unsaturated): Fatty acids that contain double bonds between one or more pairs of carbon atoms

BG Nordestgaard 2020

64

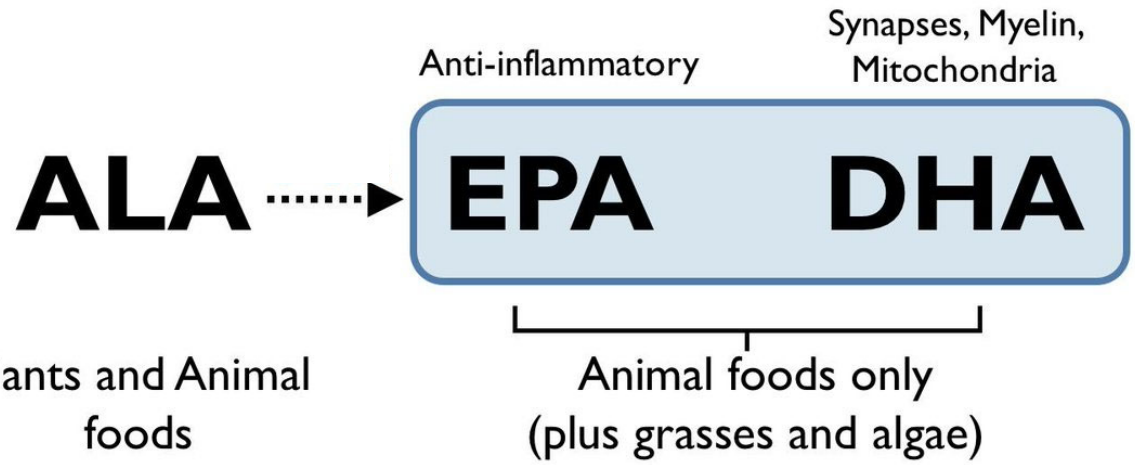

Alpha-Linolenic Acid (ALA, C18:3, Omega-3)
Ω3
Linoleic Acid (LA, C18:2, Omega-6)
Ω6
BG Nordestgaard 2020

65


Ω3
α-linoleic acid (ALA)
eicosapentaenoic acid (EPA)
docosahexaenoic acid (DHA)
BG Nordestgaard 2020

66

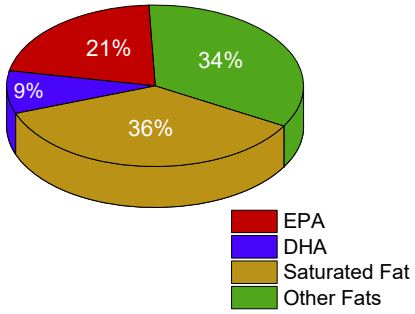
3 Types of Omega-3

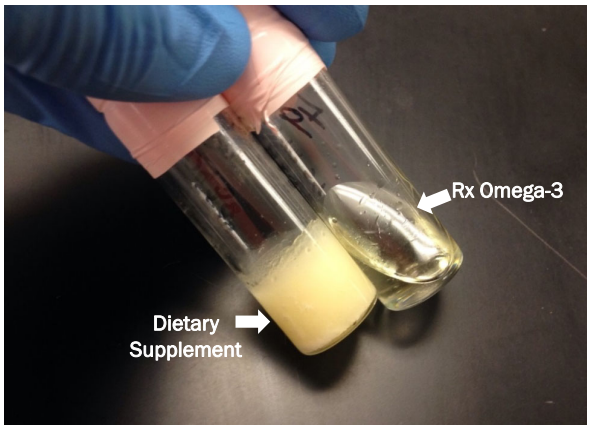


BG Nordestgaard 2020

67

Fatty Acid Content of Leading US Fish Oil Supplement





Saturated fatty acid content in fish oil supplement results in solid mass following isolation

Mason RP, Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483:425-429.

68

Mechanism via Fatty Acid *per se*

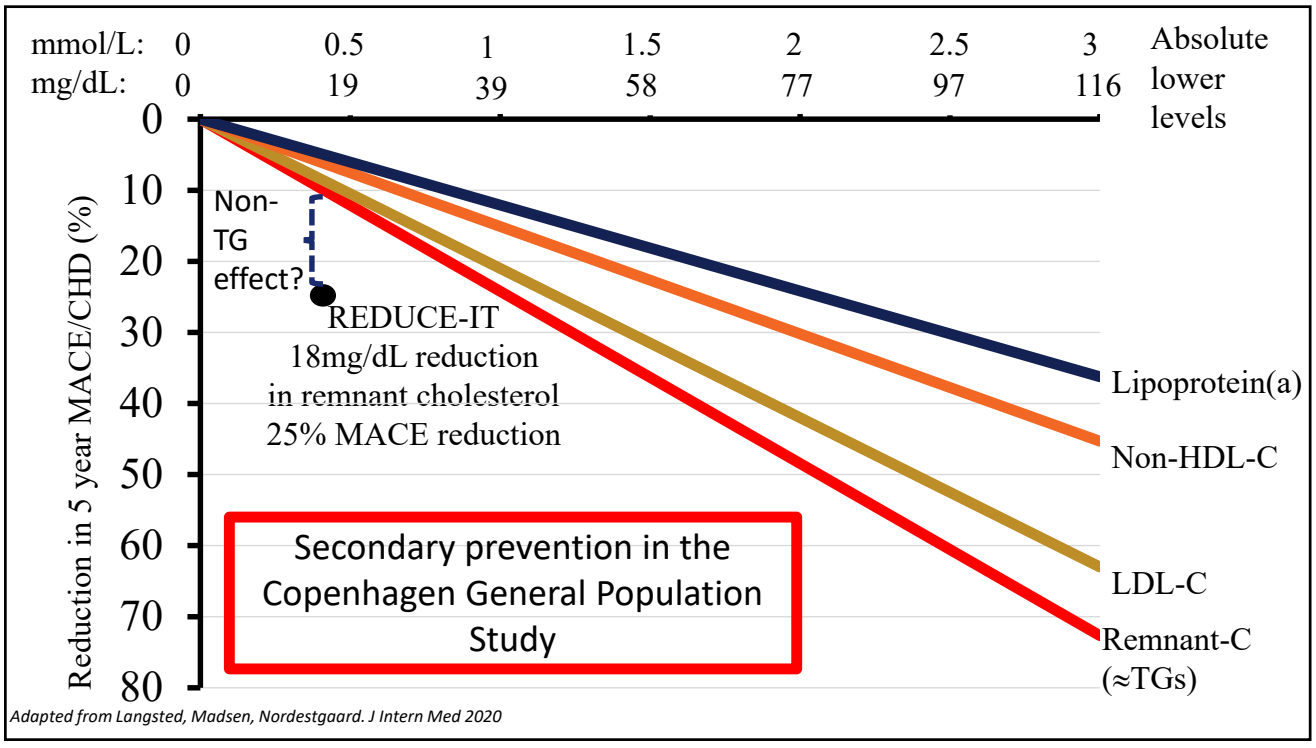
4g/day icosapent ethyl (EPA)

Via hemostasis
Via arrythmias
Via other inflammation
Via oxidation protection
Via small dense LDL
Via other EPA effects

Reduced ASCVD

BG Nordestgaard 2020

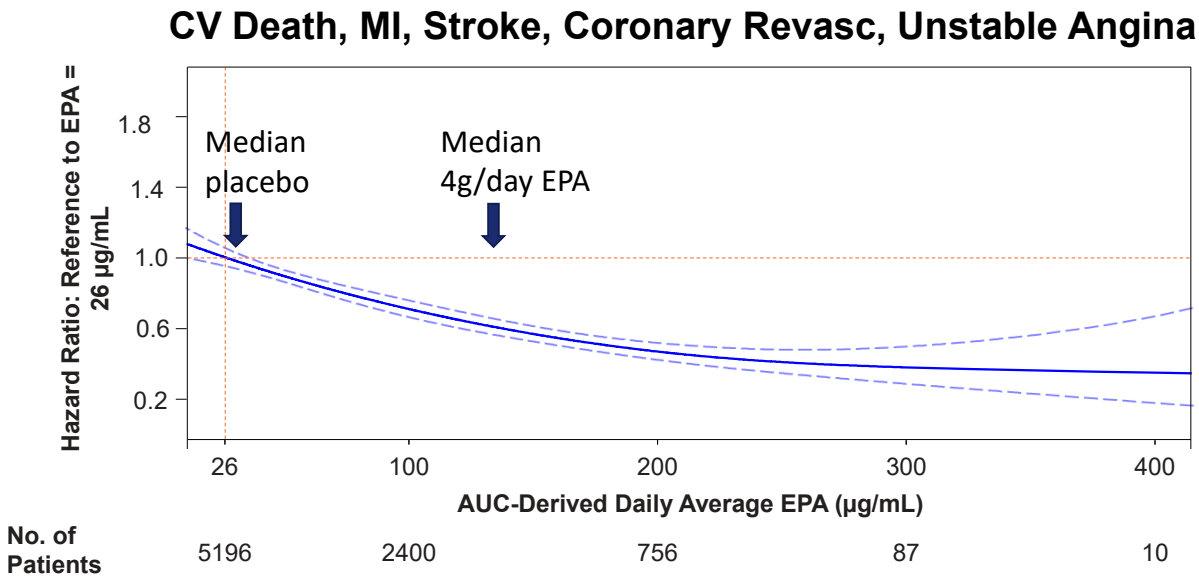
69



Adapted from Langsted, Madsen, Nordestgaard. J Intern Med 2020

70

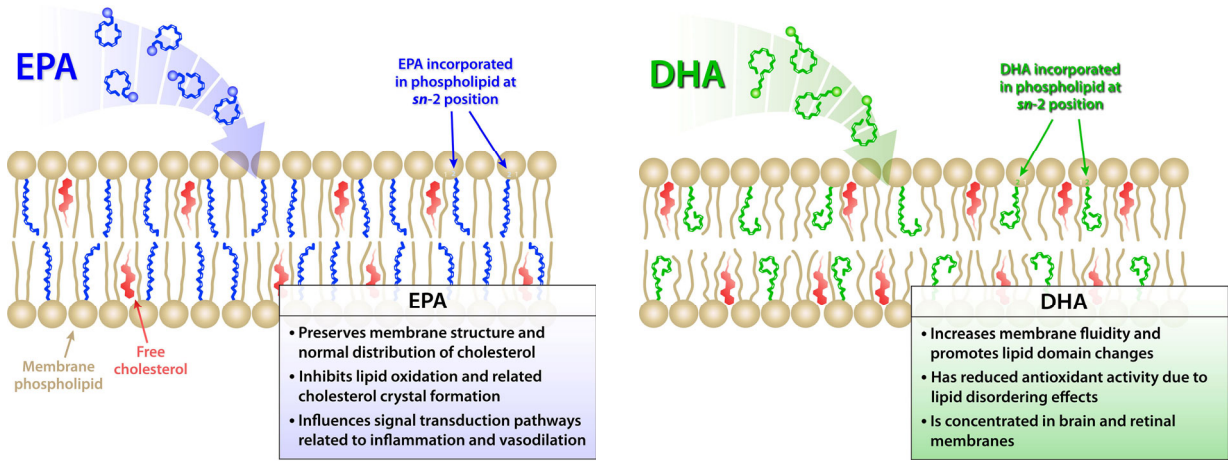
Primary Endpoint by On-treatment Serum EPA



Adapted from Bhatt DL. ACC/WCC 2020, Chicago (virtual).

71

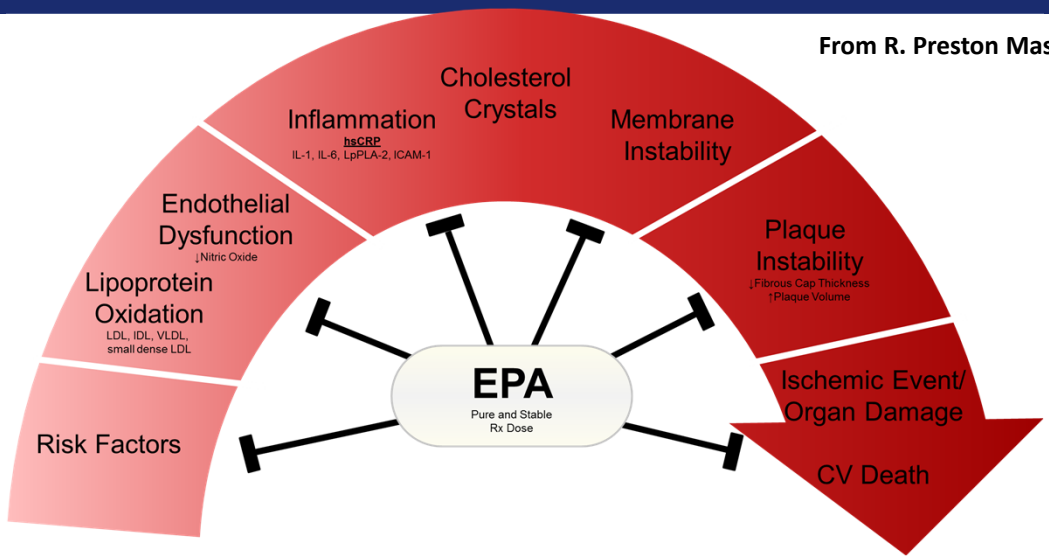
Contrasting Effects of EPA and DHA



Mason RP, Libby P, Bhatt DL. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2020.

72

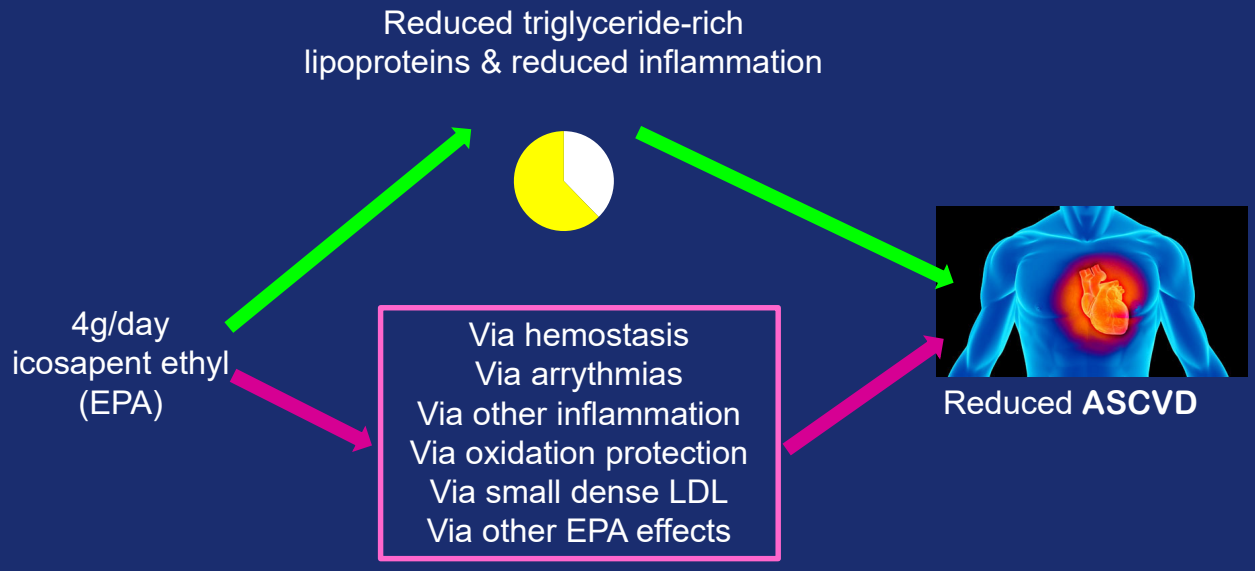
EPA Interferes with the Cardiovascular Disease Continuum at Multiple Points to Reduce CV Events



Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46; Borow KM, Nelson JR, Mason RP. *Atherosclerosis*. 2015;242:357-66; Bhatt DL et al. *N Engl J Med*. 2019;380:11-22; Ganda OP et al. *J Am Coll Cardiol*. 2018;72:330-43; Jia X et al. *Curr Atheroscler Rep*. 2019;21:1; Mason RP et al. *Biomed Pharmacother*. 2018;103:1231-7; Ference BA et al. *JAMA*. 2019;321:364-73. Sherratt SCR and Mason RP. *Biochem Biophys Res Comm*. 2018; 496:335-338.

73

Two Different Mechanisms



BG Nordestgaard 2020

74

Mineral oil as placebo

As a mild relaxant
it could
reduce statin uptake and raise
atherogenic lipoproteins

Kastelein JJP, Stroes ESG. N Engl J Med. 2019 3;380:89-90

75

Lipids and Inflammatory Marker

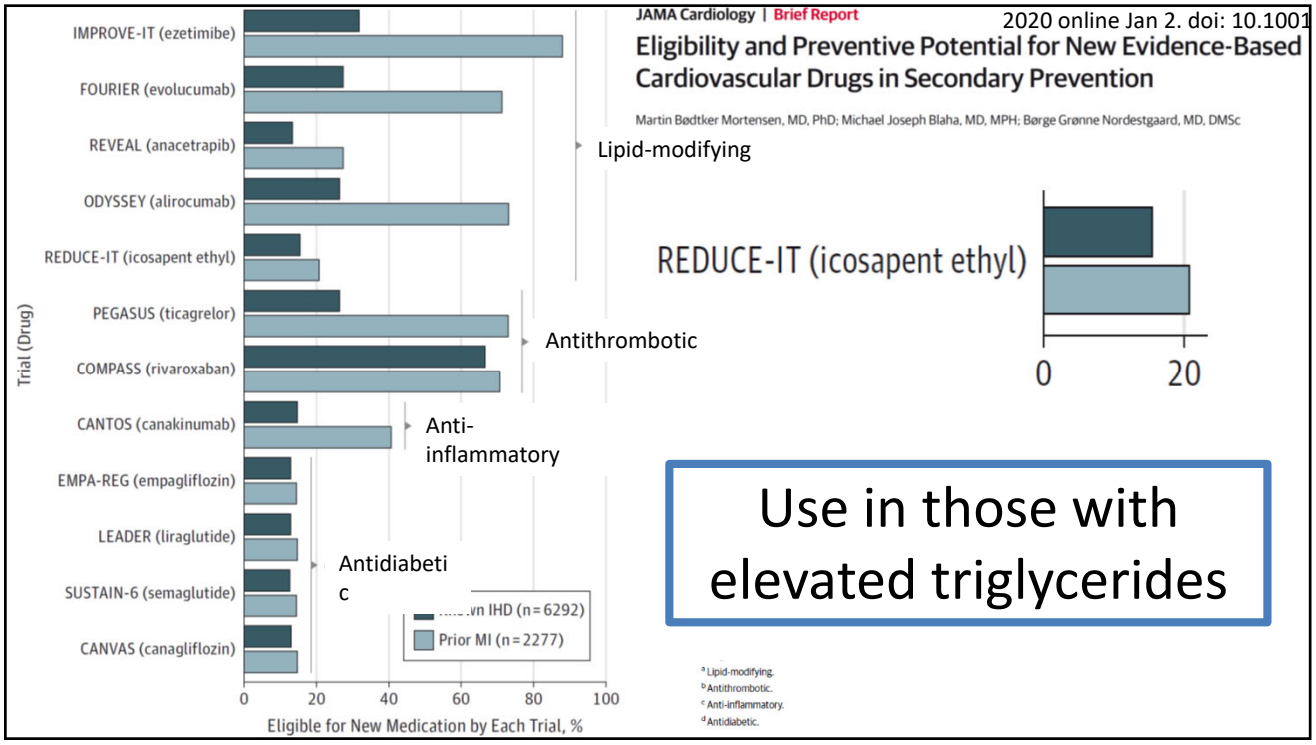
	Icosapent Ethyl 4g/day		Placebo (Mineral oil)		Between Group	
	Median %change	p	Median %change	p	Median % change	p
Triglycerides						
Year 1	-18.3	< 0.001	2.2	< 0.001	-19.7	< 0.001
Non-HDL-C						
Year 1	-3.6	< 0.001	10.4	< 0.001	-13.1	< 0.001
LDL-C (UC)						
Year 1	3.1	< 0.001	10.2	< 0.001	-6.6	< 0.001
Last visit	3.1	< 0.001	10.2	< 0.001	-6.6	< 0.001
hsCRP						
Last visit	-12.6	0.75	29.9	< 0.001	-37.6	< 0.001

Bhatt et al. N Engl J Med 2019; 380: 11-22

76

Clinical use

77



78

Recommendations for Drug Treatments of Patients with Hypertriglyceridaemia

ESC/EAS GUIDELINES
European Heart Journal (2019)

Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (>200 mg/dL)).	I	B
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) should be considered in combination with statin.	IIa	B

Recommendations	Class	Level
In primary prevention patients who are at LDL-C goal with TG >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	B
In high-risk patients who are at LDL-C goal with TG >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	C

Mach et al. Eur Heart J Eur Heart J 2020;41:111-188

79

Conclusions on: Mechanisms and Comparisons of Omega-3s

MECHANISMS
- Lowering of TG-rich lipoproteins explain large part of effect
- This mechanism likely work via reduced inflammation
- Other effects specific to EPA may also contribute

COMPARISONS OF OMEGA-3s
- Over-the-counter fish oils or omega-3s have very little EPA

CLINICAL USE
- Use purified 4g/day icosapent ethyl (EPA) in high-risk individuals with high TGs
- Do not use over-the-counter fish oils or omega-3s as substitute

80